KINGSTON
UNIVERSITY

# Synthesis of Bridged Bicyclic Ring Systems using a Novel Variation of the Nicholas Reaction in the Key Cyclisation Step

**Tahmina Bashir**

A thesis submitted in partial fulfilment of the requirements of Kingston University for the Degree of Doctor of Philosophy

**JUNE 1999**

SCHOOL OF APPLIED CHEMISTRY
PENRHYN ROAD
KINGSTON-UPON-THAMES
SURREY
KT1 2EE

***Dedicated to my dearest parents, especially in the loving memory of a very special father.***

# Abstract

This thesis details an investigation into the development of a novel annulation reaction for the synthesis of bridged ring systems. Using the Nicholas reaction, that is, the reaction of a stabilised dicobalt hexacarbonyl propargyl cation with an *intra*molecular nucleophile, cyclisation was achieved to suggest a novel variant of this reaction. In all examples studied, the variant key step involved a double bond isomerisation of the pendant alkenyl nucleophile, that led to the observed novel allylic anion mediated attack onto the cobalt stabilised cation. In addition, the observed incorporation of a halogen atom observed in the cyclised product, further contributed to the novel variance of this reaction.

After the initial discussion, a review of the biological importance and past synthetic approaches for the construction of the bridged ring system in taxane, aphidicolane, stemodane and gibanne families is given. This is followed by a general review of the cobalt-alkyne chemistry, that details the structure and properties of the cobalt-alkyne complex and its chemistry in context with the Nicholas reaction.

The results of these investigations into this novel methodology is then detailed. These studies commenced with the successful cyclisation of a 1,3-difunctionalised cycloalkane. The reaction between the dicobalt hexacarbonyl complexed propynyl alcohol and the pendant pentenyl group, gave in the presence of titanium (IV) chloride, the chloro-substituted bicyclo[3.3.1]nonane ring system.

When conducting preliminary studies into the mechanism for the reaction, that initially involved an investigation into the halogen atom incorporation, additional cyclisation was observed. Using the Lewis acids, titanium (IV) bromide and titanium (IV) fluoride, the successful syntheses of the bromo- and fluoro-substituted bicyclo[3.3.1]nonanes were achieved respectively. In addition to this, the consequence of using other Lewis acids, that included boron trifluoride diethyl etherate, tetrafluoroboric acid, tin (IV) chloride and zinc chloride, is also discussed.

The investigations were continued with optimising the reaction conditions for the cyclisation step. An examination into the effect of changing the solvent, temperature, reaction time, and the stoichiometry of the Lewis acid is included. During the course of these studies, a range of decomplexing agents was also examined.

In extending these investigations, the generality of this protocol was looked into. The consequence of reducing the pendant alkenyl group in the 1,3-difunctionalised cycloalkane, led to the successful synthesis of other bicyclic systems. This included bicyclo[3.2.1]octane and bicyclo[4.3.1]decane. A subsequent study in which the size of the first ring was changed, led to the synthesis of 5,6 and 7,6- bridge ring systems.

In the later stages of the research programme, a stereoselective approach for the synthesis of bicyclo[3.3.1]nonane, using the precursor derived from (*S*)-(+)-carvone was studied, in which no significant stereoselective control was achieved. Additional work involving procedures undertaken to obtain a crystalline derivative to determine the absolute stereochemistry for the bicyclo[3.3.1]nonane system is also included.

In conclusion to these studies, an investigation into the synthesis of the challenging 6,8 membered ring system, present in taxol, is discussed. Preliminary results for this study, show that success may have been achieved.

# CONTENTS

# Acknowledgements

I would first like to express my sincere gratitude towards my supervisor, Dr. Liz Tyrrell, for the help, guidance and encouragement throughout this period of study.

I am also thankful to my second supervisor, Dr. Tony Skinner, for his advice to many things, and especially for proof reading the final draft to this thesis.

My many thanks to Mrs. June Falla for her invaluable help in dealing with the problems that arose with the NMR spectrometer, and to Mr. Fred Quentin for his assistance with the GC-MS instrument.

My special thanks to all my friends. Although restricted space allows me to mention only a few, my sincere thanks goes to you all. In particularly, I am grateful to Dr. Sina Talal, Miss. Jacky Massy and Miss. Naznin Murzumder, whom have constantly been there for me.

And finally, last but not least, I am very grateful to all my family. It was the emotional support and encouragement that you gave me throughout this part of my life, that has made this possible. I therefore thank you all once again.

# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| Ad | 1-adamantyl |
| aq. | aqueous |
| Bn | benzyl |
| Bu | butyl |
| $Bu^t$ | *tert*-butyl |
| $Bu^tOK$ | potassium *tert*-butoxide |
| Bz | benzoyl |
| °C | degrees celsius |
| CAN | ceric ammonium nitrate |
| cat. | catalytic |
| Cbz | carbobenzyloxy |
| Cp | cyclopentadienyl |
| DBN | 1,8-diazobicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| DEAD | diethylazodicarboxylate |
| DME | 1,2-dimethoxyethane |
| DMF | *N*, *N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| eq. | equivalent |
| $Et_2O$ | diethyl ether |
| GC-MS | Gas chromatography-mass spectrometry |
| hrs | hours |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectrometry |
| IMS | industrial methylated spirits |
| IR | Infra-red (spectroscopy) |
| LAH | lithium aluminium hydride |
| LDA | lithium diisopropylamide |

| | |
|---|---|
| LRMS | low resolution mass spectrometry |
| LTA | lead tetraacetate |
| Me | methyl |
| MEM | 2-methoxyethoxymethyl |
| min | minute |
| MOM | methoxymethyl |
| MS | mass spectrometry |
| Ms | mesyl |
| NBS | N-bromosuccinimide |
| p. | page |
| PCC | pyridinium chlorochromate |
| Piv | pivaloyl |
| Pr | propyl |
| $Pr^i$ | *iso*propyl |
| *P*-TSA | *para*-toluenesulfonic acid |
| r.t | room temperature |
| SEM | trimethylsilyethoxymethyl |
| TBAF | tetrabutylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| *tert* | tertiary |
| Tf | triflate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TMS | trimethylsily |
| TLC | Thin layer chromatography |

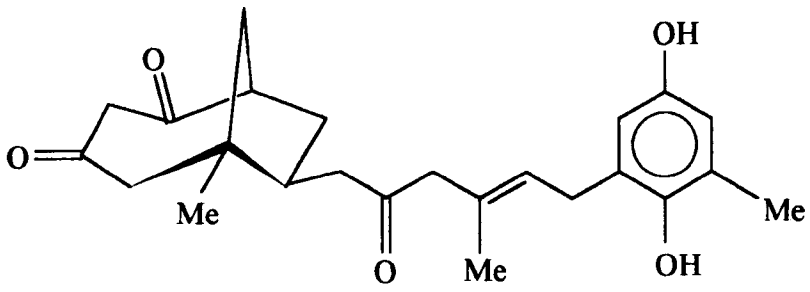
# Chapter One

## Introduction

# 1.0 Introduction

## 1.1 Bridged Bicyclic Ring Systems

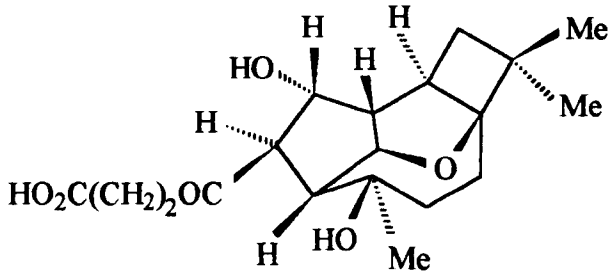
The bridged bicyclic ring system is embodied in many natural products. For example, compounds based upon mediterraneol (1), isolated from the marine brown algae (*Cystoseira mediterranea*), contain the bicyclo[4.2.1]nonane ring system **(Figure 1)**. This compound is found to possess significant anti-leukemic properties.[1]




1

**(Figure 1)**

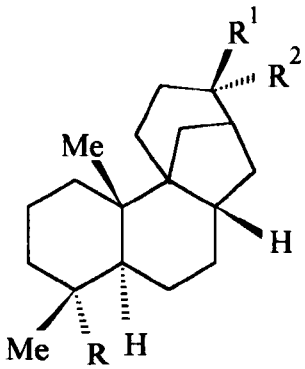
The sesquiterpene (2), obtained from the dung fungus *Poronia punctata*, contains a bicyclo[5.2.1]decane as the major central unit embodied into the framework, and exhibits powerful antibiotic activity.[2]




2

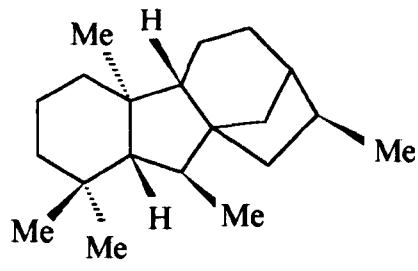
**(Figure 2)**

In addition to the range of the bicyclo compounds that exist in nature, the bridged bicyclo[3.2.1]octane ring itself is prevalent, and has been identified in several natural products including, aphidicolane (3a), stemodane(3b), and in the gibbane (4) family of natural products[3] **(Figure 3)**.




**3a** R, $R^1$=$CH_2OH$, $R^2$=OH

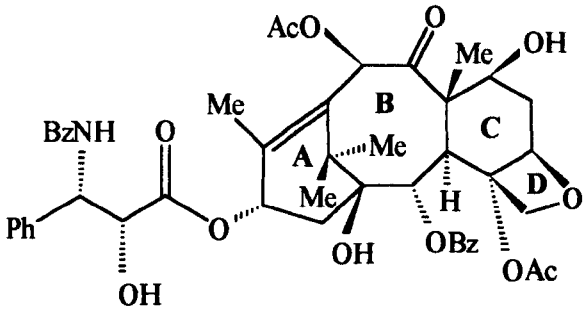
**b** R=Me, $R^1$=OH, $R^2$=Me



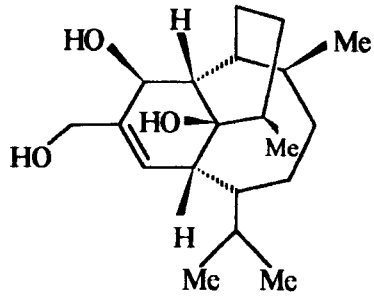

**4**

**(Figure 3)**

Other biologically active natural products such as the taxane diterpene, taxol[4] (5), a potent anticancer drug, and vinigrol[5a] (6), a novel diterpenoid used as an antihypertensive and platelet aggregation inhibiting substance[5b], manifest the bicyclo[5.3.1]undecane ring system, as the central carbocyclic sub-unit **(Figure 4)**.




**5**




**6**

**(Figure 4)**

With such an array of diverse and biologically important natural products, it is not surprising that routes have been investigated to form the bridged bicyclic system. The need to develop short and more flexible routes still remains an ongoing target for the synthesis of many of these natural products.

It was taxol (5), that first initiated our interest in bridged ring systems. Although a large number of synthetic studies towards this remarkable drug have been conducted, efforts for the development of an efficient synthesis of the taxane nucleus are still being made and frequently appear elusive.

In connection with our synthetic studies into the Nicholas reaction,[6] it occurred to us that one eminently attractive entry into the taxanes may be feasible using a novel variation of this reaction that was being developed at Kingston University. This chemistry will be discussed, in part in Chapter Two and more fully in Chapter Three.

For the purpose of this review, the main focus is to illustrate to the reader the biological importance of these natural products, and to provide an overview to the earlier synthetic approaches that have been undertaken to construct the bridged ring system.

The examples chosen have been carefully selected to reflect their importance, with regard to synthetic strategies, and therefore limited to:

**1.2** Taxanes

**1.3** Aphidicolane and Stemodane

**1.4** Gibbanes

Selected members of these families will be discussed in turn under the appropriate section.

## 1.2 Taxanes

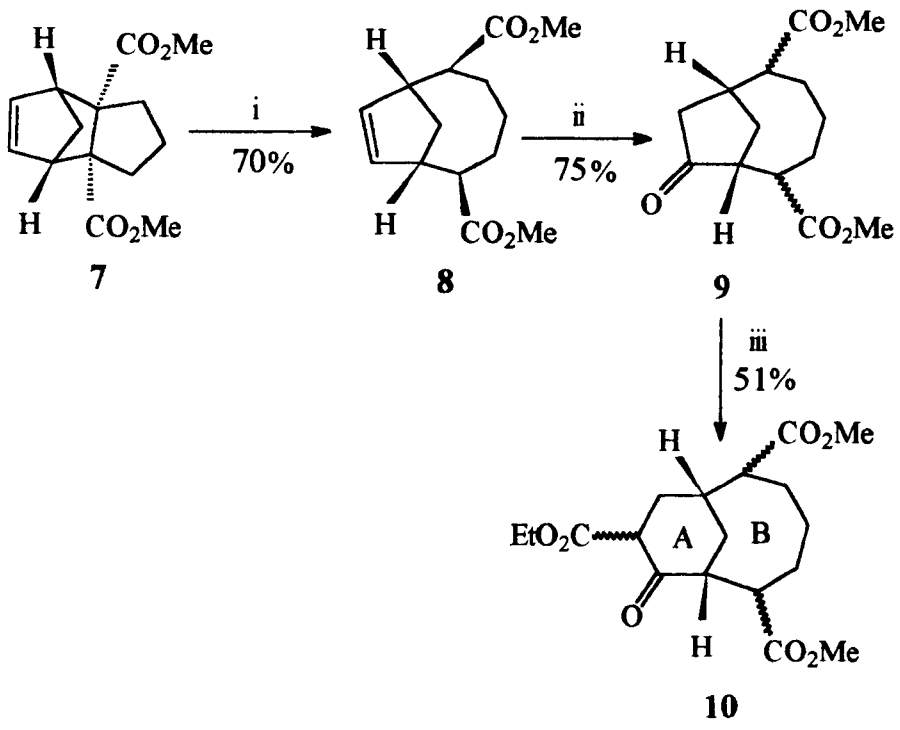
The highly complex tetracyclic diterpene taxol (5), has been the subject of considerable interest. Combined with its structural complexity, unique antimitotic action[7] and limited availability, it has, over the last two decades, attracted intense synthetic interest.[8] To date, four groups[9] have succeeded in the total synthesis of taxol (5). These syntheses have, however, proved non viable on an industrial basis, due to the involvement of many synthetic steps. Thus the search for novel and efficient methods for the synthesis of analogues and advanced intermediary taxanes continues.

One of the important challenges for the synthesis of the taxane skeleton has been in the construction of the A/B ring system bearing suitable functional groups. As a consequence a great deal of work has been undertaken in this area, and is thus well precedented in the literature.[10] Due to the size of the subject, this review will concentrate on providing an overview to the most recent approaches. For a more detailed treatment the reader is referred to the cited references.

### 1.2.1 Synthetic approaches to the A/B ring System

Gosh and coworkers[11] reported a route to the AB ring system of taxanes, in which a reductive fragmentation procedure was first used to establish the eight-membered ring compound (8) **(Scheme 1)**. The reaction was effected by treatment of the diester (7), with sodium in liquid ammonia, that gave the bicyclic adduct (8) in 70% yield.

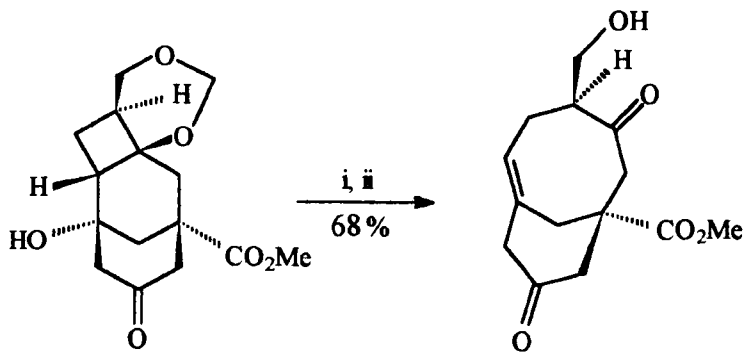
Subsequent modification of the double bond was then achieved *via* hydroboration and Jones oxidation reactions to provide(9) in 75% yield. Following treatment of (9) with ethyl diazoacetate, under $Et_2O^+BF_4^-$ catalysis, ring expansion occurred to form the AB skeleton of the taxane (10) in 51% yield.




***Reagents and conditions*** i, Na(m), liq. $NH_3$, -55°C; ii, (a) $BH_3$, THF; 0°C, then NaOH, $H_2O_2$ (b) $CrO_3$, $H_2SO_4$, acetone; iii, $N_2$=$CHCO_2Et$, $Et_2O^+BF_4^-$, DCM, 0°C.

**(Scheme 1)**

In an approach by Kraus[12], a reductive cleavage process was used as the key step for the synthesis of the AB ring model **(Scheme 2)**.

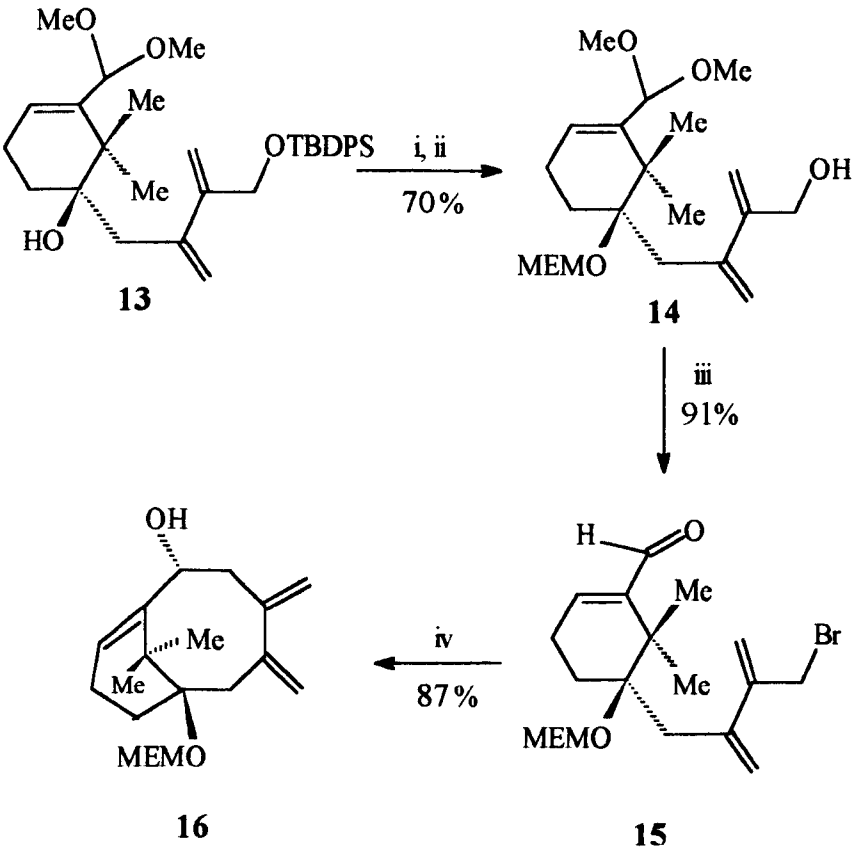



***Reagents and conditions*** i, $PBr_3$, ii, 1.2 eq. $AgBF_4$, (5:1) MeCN:$H_2O$, 0°C.

**(Scheme 2)**

Thus from the tetracycle (11), fragmentation proceeded *via* the generation of the bridgehead bromide, in which subsequent Lewis acid treatment gave the desired bicycle (12) in 68% yield.

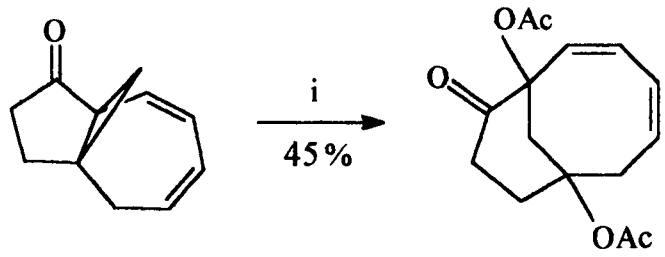
In the approach by Wang,[13] the challenging eight membered ring was constructed *via* an *intra*molecular nucleophilic allylic bromide-aldehyde addition reaction, promoted by a zinc-copper couple **(Scheme 3)**. The key synthetic steps, leading to the cyclisation reaction, involved protection of the tertiary alcohol in (13) and subsequent desilylation to provide compound (14) in 70% yield. Following bromination of (14) and silica gel chromatography, the key cyclisation precursor (15) was achieved in 91% yield. A zinc mediated *intra*molecular cyclisation of (15) was then performed, to afford the desired AB ring system (16) as a single stereoisomer in 87% yield.




***Reagents and conditions*** i, MEMCl, $i$Pr$_2$NEt; ii, $n$-Bu$_4$NF, THF; iii, $CBr_4$, $Ph_3P$, then silica gel; iv, Zn-Cu, THF, reflux.

**(Scheme 3)**

In Kumar's[14] synthetic strategy the key step to the AB framework involved an oxidative cyclopropane ring cleavage of the tricyclic[5.3.1]propellane (17) to form the bicyclo[5.3.1]undec-3,5,7-diene system (18) **(Scheme 4)**. Thus treatment of (17) with lead tetraacetate gave (18) in a modest yield of 45%.

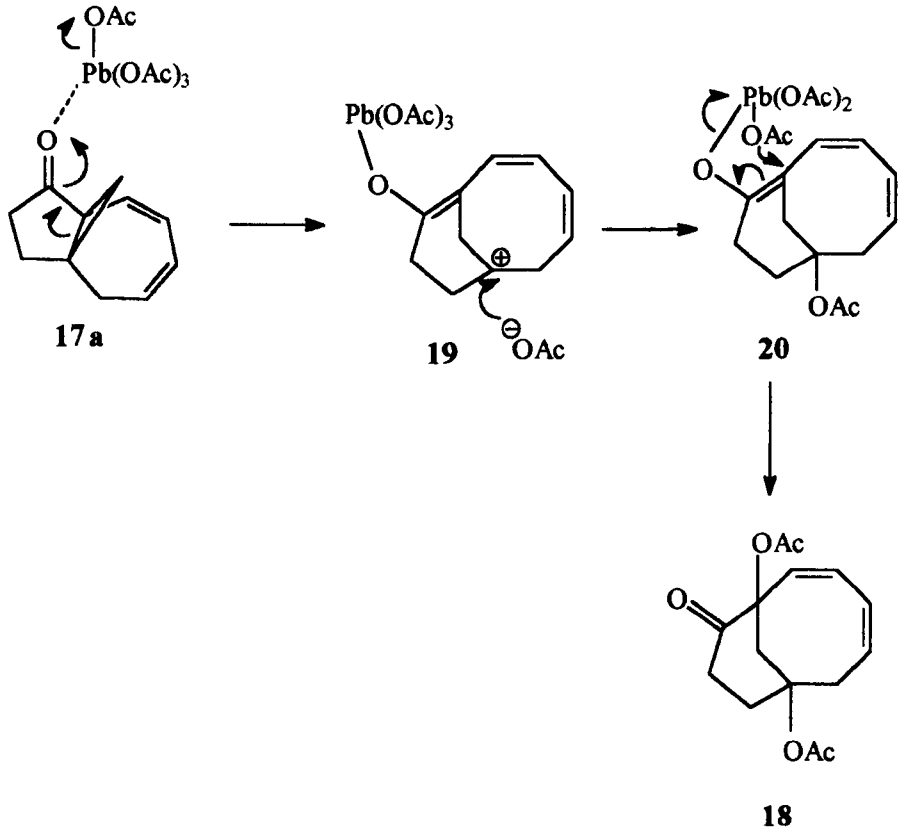



**17** **18**

***Reagents and conditions*** i, LTA, AcOH, $C_6H_6$, reflux.

**(Scheme 4)**

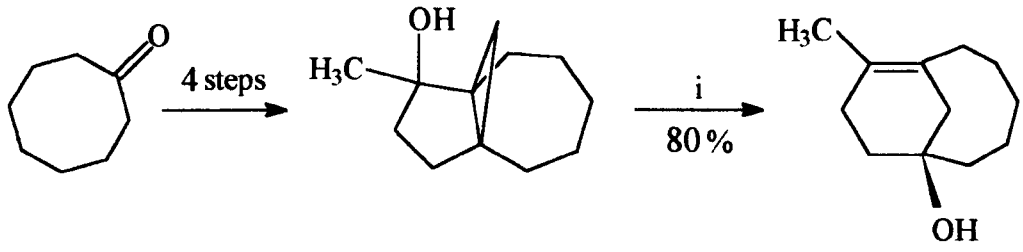
A possible mechanism for the rearrangement is shown **(Figure 5)**.




**(Figure 5)**

It was thought that cleavage proceeds *via* the association of the carbonyl substituent with the ion pair $Pb^{+}(OAc)_3$ $^{-}OAc$. Thus upon the reaction of (17a) with lead tetraacetate, a nucleophilic displacement mechanism occurs with the loss of an acetate ion. This departing acetate ion, then quenches the developing cation (19).

A similar approach was also reported by Schafer[15] **(Scheme 5)**. In this reaction the [5.3.1]propellanol underwent a rearrangement reaction to (23). The reaction is particularly noteworthy due to the high product selectivity observed.



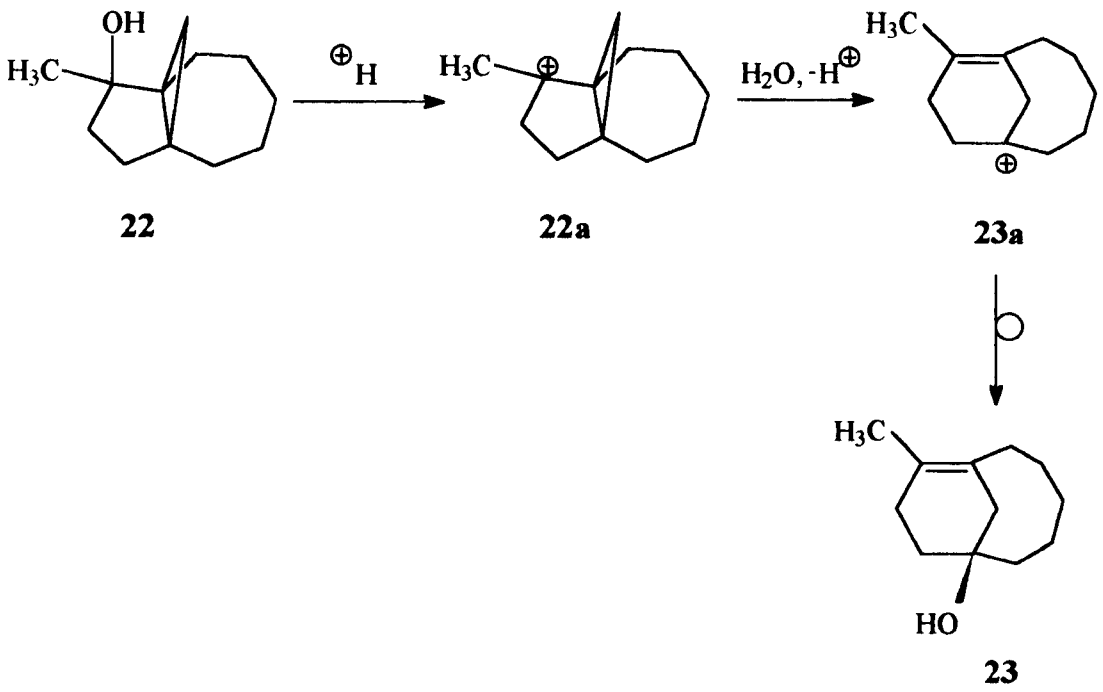

**21** **22** **23**

***Reagents and conditions*** i, 0.05M, $CF_3COOH$, $H_2O$/THF(3:2), r.t.

**(Scheme 5)**

The required precursor (22) was synthesised in four efficient synthetic steps from cycloheptanone (21). Treatment of (22) with dilute trifluoroacetic acid led to the corresponding bicyclo[5.3.1]undecenol (23) in 88% yield.

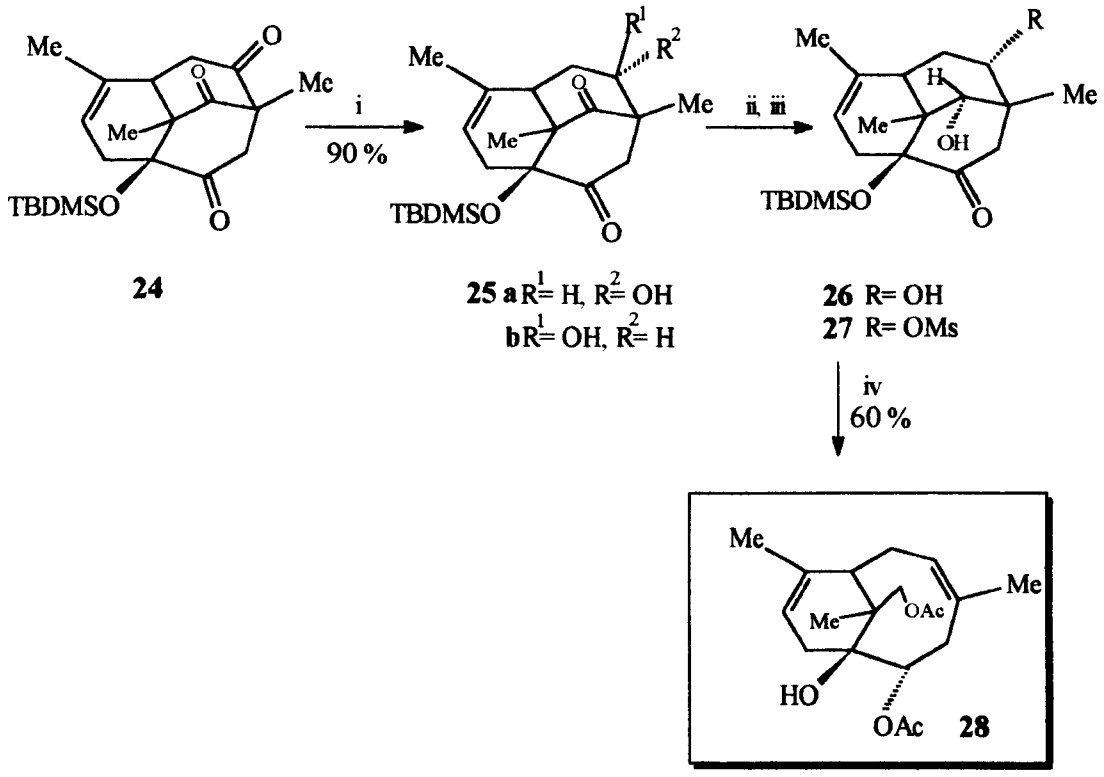
The formation of (23) was explained *via* the tricyclic carbocation (22a), that rearranged by an endocyclic opening of the cyclopropane ring, to provide the bicyclic carbocation (23a), that simultaneously solvolyzes to (23) **(Figure 6)**.




**(Figure 6)**

The Fetizon group[16] have investigated several strategies for the synthesis of taxanes. In their most recent report, a Grob fragmentation process was used as the key step to form the AB ring of the taxane system.

The crucial steps involved a regio- and highly stereoselective reduction of (24), that led to provide, the major compound (25a) in 90% yield, with small amount of the β-isomer (25b) **(Scheme 6)**. Following a further reduction, to afford the single dihydroxyketone (26), facile conversion to the mesylate (27) was achieved in a quantitative yield. The Grob fragmentation reaction was then conducted by treatment of (27) with LAH/DME, followed by acetylation, to afford the corresponding bridged AB taxane ring system (28) in 60% yield.



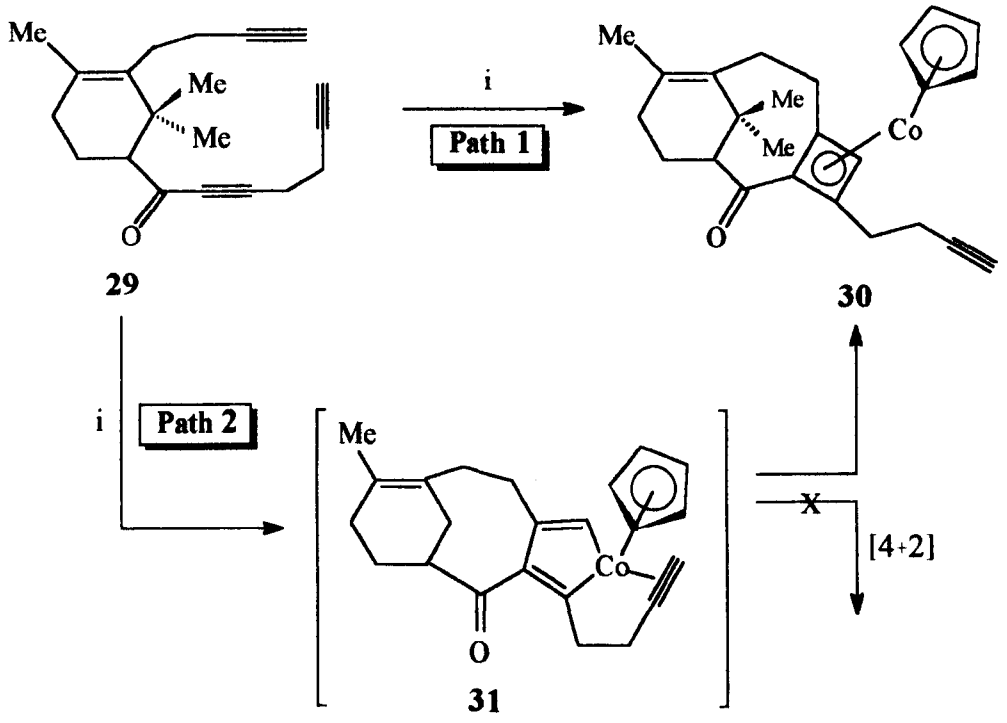

***Reagents and conditions*** i, $NaBH_4$-$CeCl_3$, $7H_2O$-MeOH, 0°C; ii, $NaBH_4$/MeOH, r.t; iii, mesylic anhydride, pyridine, 0°C; iv, (a)LAH/DME, 85°C, (b)AcCl, pyridine.

**(Scheme 6)**

As a final example, Malacria[17] recently reported an interesting construction of the AB taxane ring system that involved a Co(I)-[2+2] cocyclisation, as the major key synthetic step. Thus treatment of the cyclohexenyltriyne (29) with a stoichiometric amount of $CpCo(CO)_2$ ($\eta^5$-cyclopentadienyldicarbonyl cobalt) furnished compound (30) in 32% yield **(Scheme 7)**.

Two plausible pathways were considered to explain the formation of this product. In the first, it was rationalised that a cobalt(I)-mediated [2+2] cycloaddition reaction would afford the complexed cyclobutadiene (30). In the second, it was postulated that the reaction may proceed *via* the intermediate (31), which undergoes a valence tautomerization to (30). The incorporation of the appended alkyne unit was not

observed, probably due to electronic reasons associated with the presence of the carbonyl group conjugated with the cobaltcyclopentadienyl moiety.

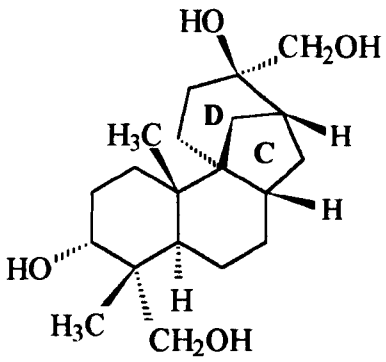



***Reagents and conditions*** i, $CpCo(CO)_2$, $C_6H_6$, hν, reflux.

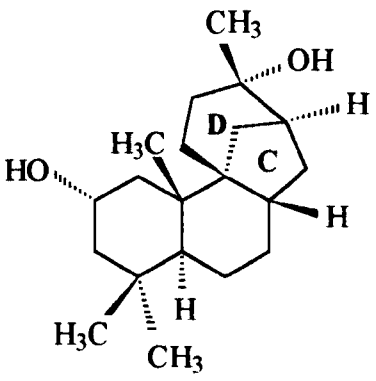
**(Scheme 7)**

## 1.3 Aphidicolane and Stemodane

Due to their unique carbon skeleton, numerous stereocenters and biological activity,[18] the aphidicolane (3a) and stemodane (3b) group of diterpenoids have also received considerable attention as targets for synthesis. Comprising of the bicyclo[3.2.1]octane ring system, members of this select group include, for example, aphidicolin[19] (32) and stemodin[20] (33) respectively **(Figure 7)**.




32




33

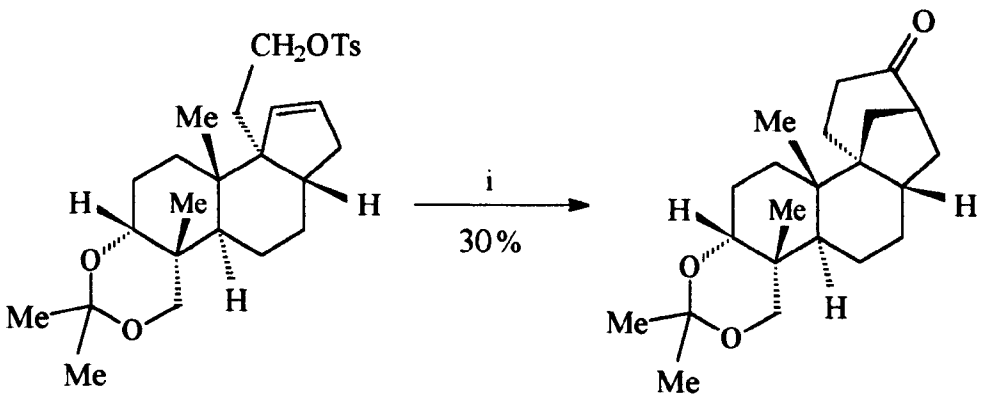
**(Figure 7)**

Stemodin (33), that is obtained from the leaves of the plant *Stemodia maritima L.* (Jamaican "sea mint"), is used in the West Indies for treating venereal disease. Structurally this compound is related to the antiviral and antitumour fungal metabolite aphidicolin (32), differing mainly in the stereorelationship of the C and D ring system as shown **(Figure 7)**. In the past the main problem in devising synthetic routes to these compounds has been the assembly of the tetracyclic ring system, with the appropriate stereochemistry of the C/D-ring moiety. Nevertheless after considerable effort, many elegant approaches have been devised towards the synthesis of these compounds.[21, 22] To continue with the theme of this chapter, this section once again focuses on the chemistry employed for the formation of the bridged ring system that is embodied into these potent diterpenes.

## 1.3.1 Aphidicolin

In the synthesis of aphidicolin by McMurry and co-workers,[23] a carbonylation procedure was used to add the remaining required carbon atom and to affect the closure of the bridge ring.

Thus to the unsaturated tosylate (34), reaction with the reagent disodium tetracarbonylferrate, provided the desired tetracyclic ketone (35) in 30% yield **(Scheme 8)**.

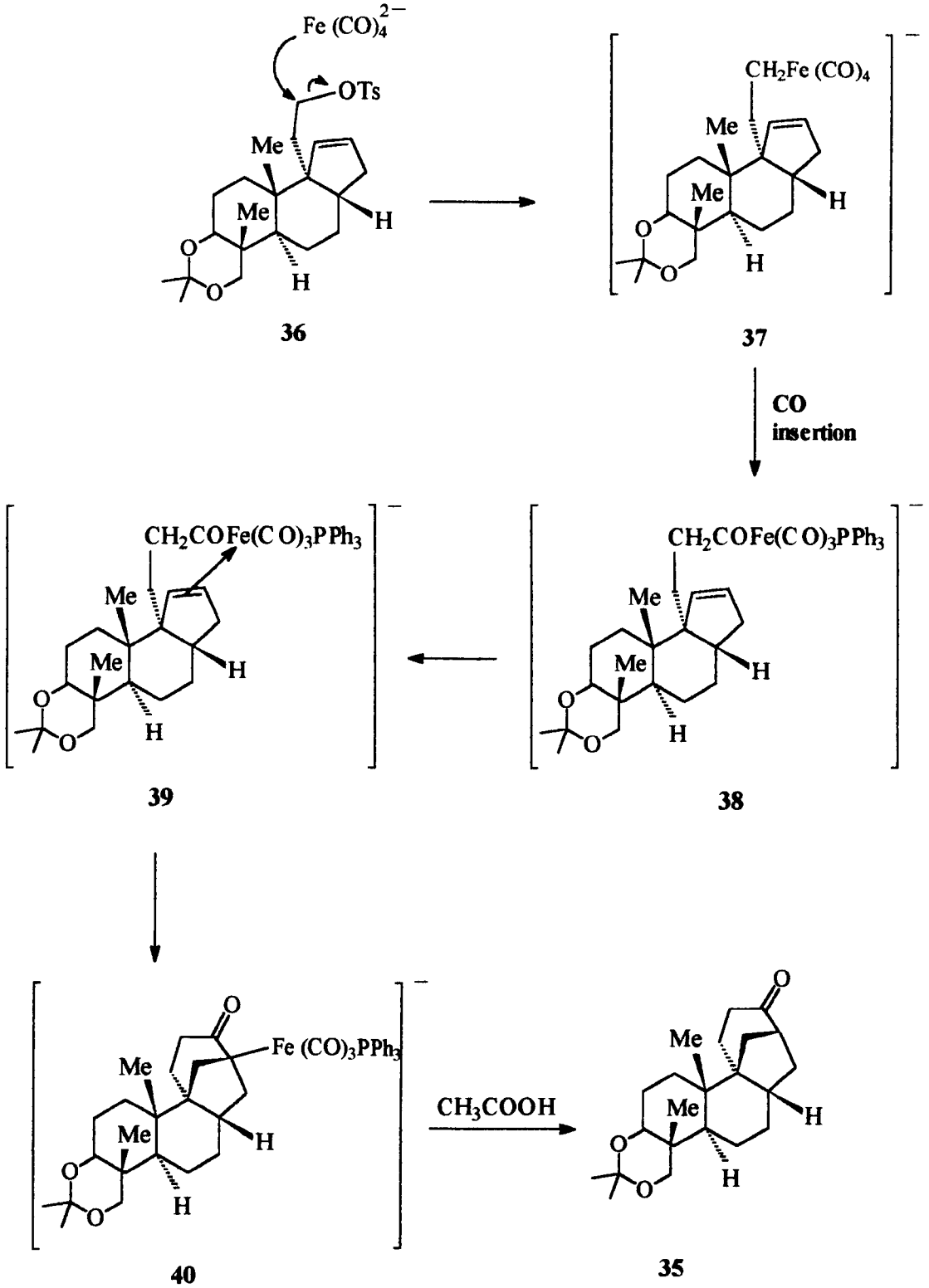



**34** **35**

***Reagents and conditions*** i, $Na_2Fe(CO)_4$, $PPh_3$, $CH_3COOH$, 50°C.

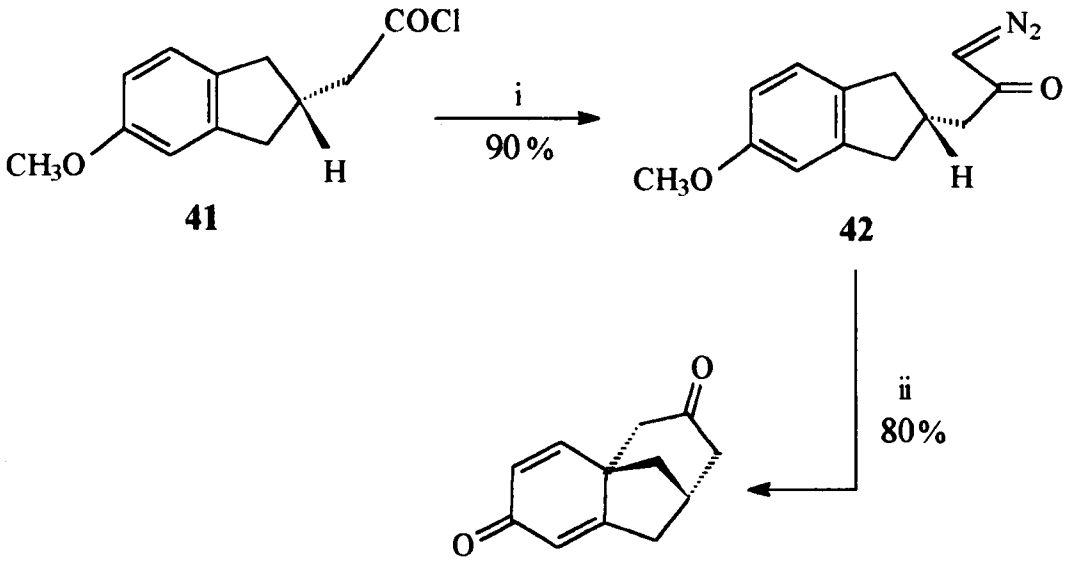
**(Scheme 8)**

The mechanism has been explained in the following way **(Figure 8)**.[24] Nucleophilic attack by the ferrate complex (36), gives the intermediate (37), that undergoes CO incorporation, in the presence of triphenylphosphine, to give the complex (38). Following an insertion of the double bond into the Fe-acyl bond (39), provides the intermediate (40), whereupon a subsequent quench with acetic acid liberates the desired compound (35).


Fe (CO)4 2−
OTs
Me
Me
H
O
O
H
36
CH2Fe (CO)4
Me
Me
H
O
O
H
37
CO
insertion
CH2COFe(C O)3PPh3
Me
Me
H
O
O
H
38
CH2COFe(C O)3PPh3
Me
Me
H
O
O
H
39
O
Fe (CO)3PPh3
Me
Me
H
O
O
H
40
CH3COOH
O
Me
Me
H
O
O
H
35

**(Figure 8)**

An interesting and alternative approach to the bridged system of (32) was illustrated in the work of Nicolaou[25] **(Scheme 9)**.

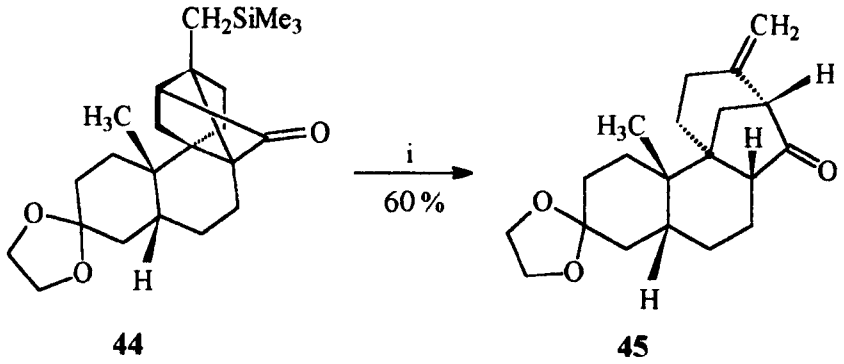



***Reagents and conditions*** i, $CH_2N_2$, ether, -20°C; ii, $CF_3COOH$, DCM, -20°C.

**(Scheme 9)**

In this synthetic route, the bicyclo[3.2.1]octane (43) was obtained using a diazoketone acid-induced cyclisation reaction. Thus upon reacting the acid chloride adduct (41), with diazomethane, the key intermediate (42) was formed in 90% yield. Reaction of this compound with trifluoroacetic acid gave the crystalline dienone (43), which contained the correct BCD ring system of the natural product (32).

In contrast to both the McMurry approach and the Nicolaou approach, the bridged ring system formed in the Ireland[26] synthetic route, was created *via* a mild acid catalysed rearrangement of the pivotal intermediate (44) **(Scheme 10)**. Thus treatment of compound (44) with silica gel, gave the desired bicyclo[3.2.1]octane ring system (45) in 60% yield.

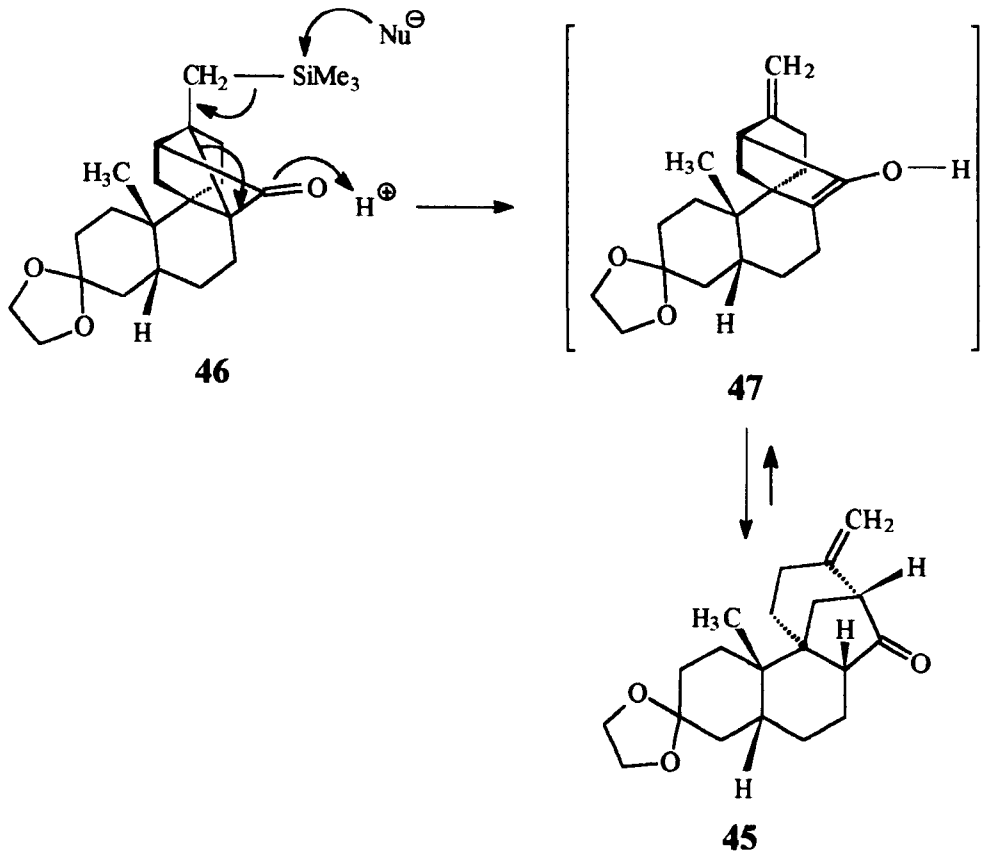



**44** **45**

***Reagents and conditions*** i, $SiO_2$ gel, petroleum ether/$Et_2O$, r.t.

**(Scheme 10)**

The mechanism for the rearrangement is as shown **(Figure 9)**.

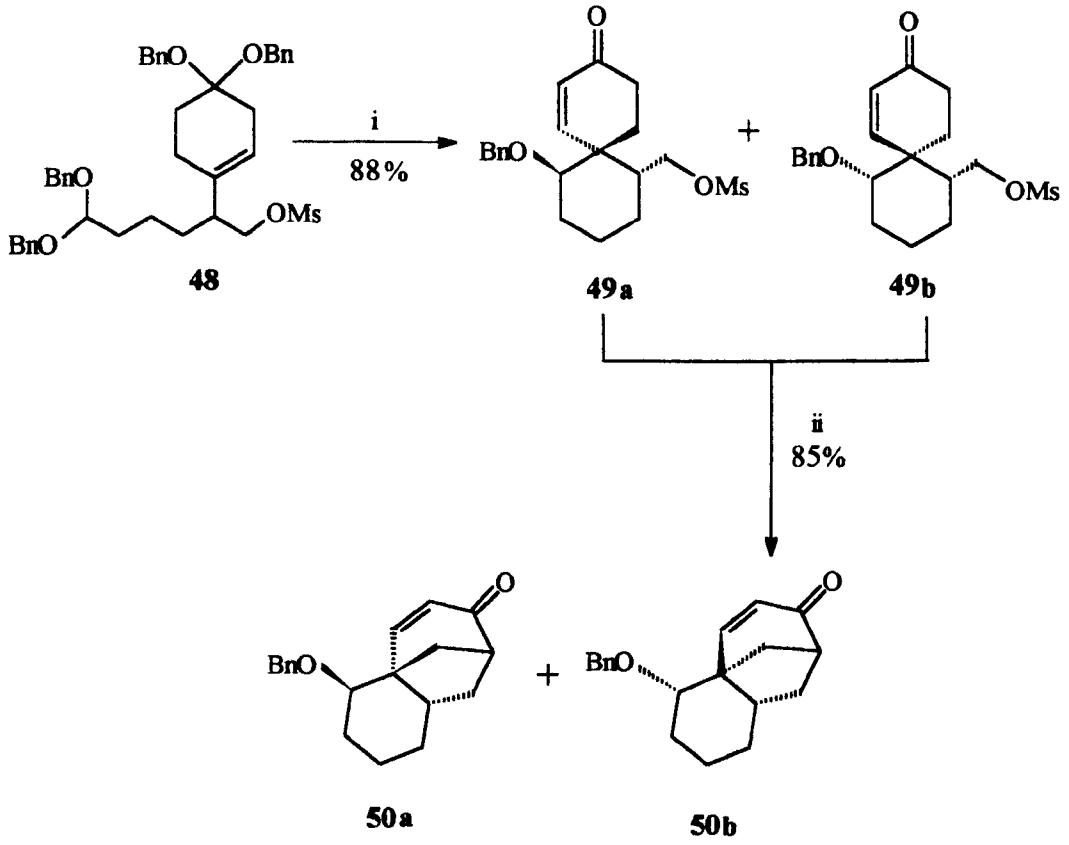



**46** **47** **45**

**(Figure 9)**

Fragmentation of the trimethylsilyl group (46) leads to the development of the double bond, to form the intermediate enol (47). Subsequent tautomerisation then occurs to provide desired compound (45).

More recently Iwata[27] reported a different route to form the aphidicolane structure. In previous synthetic approaches, the construction of the functionalised C/D-ring system had been towards the end of the synthetic approach. However, in this synthetic route, Iwata commenced with the preparation of the B/C/D ring, followed by A-ring cyclisation. Thus treatment of the bis(benzyl acetal) (48) with TMSOTf, gave a 2:1 mixture of the spirocyclic compounds (49a) and (49b) in an excellent yield **(Scheme 11)**. Due to the lability of the compounds on silica gel, separation was not possible, hence subsequent reaction of the mixture with *tert*-butoxide, furnished the tricyclic enones (50a) and (50b) in 85% yield.



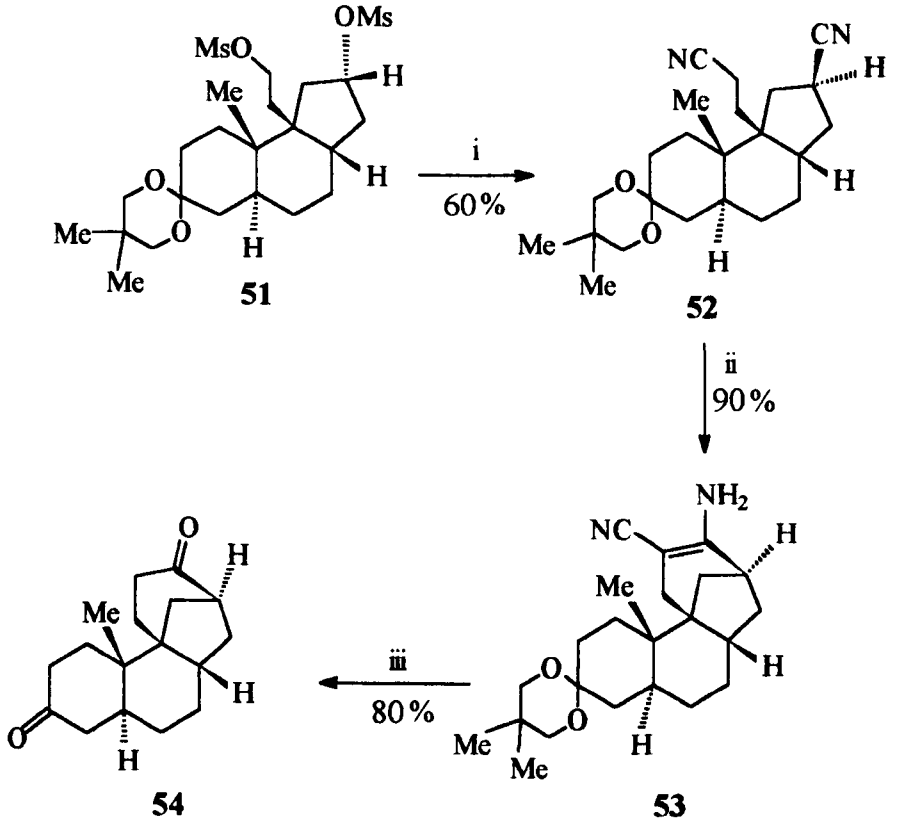

***Reagents and conditions*** i, TMSOTf, $CH_3CN$/DCM, -78°C; ii, *t*-BuOK, $Et_2O$, 0°C.

**(Scheme 11)**

With the isolation of the required bridged intermediate (50a), conversion to the desired natural product (32) was achieved following a previously a reported method.[28]

## 1.3.2 Stemodin

In Piers[29] synthesis of stemodin (33), the C/D structure was constructed using a Thorpe-Ziegler cyclisation reaction **(Scheme 12)**. Thus treatment of the dimesylate (51), with NaCN in warm HMPA, provided the dinitrile (52) in 60% yield. Treatment of (52) with potassium *tert*-butoxide, led to a facile ring closure to afford the enaminonitrile (53) in 90% yield. Following acid hydrolysis of (53), the diketone (54) was formed in 80% yield, that possessed the tetracyclic stemodane carbon skeleton.

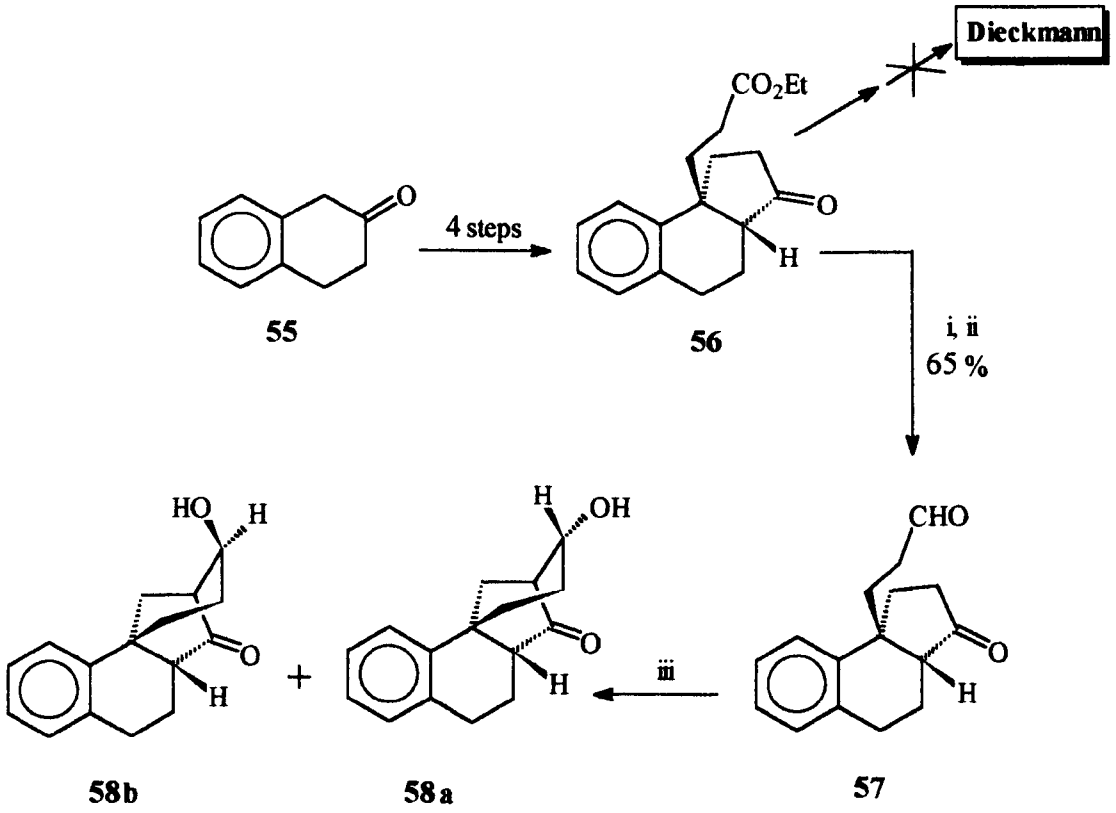



***Reagents and conditions*** i, NaCN, HMPA, 60°C; ii, Bu$^t$OK, Bu$^t$OH, reflux; iii, $H_3PO_4$, HOAc, $H_2O$, reflux.

**(Scheme 12)**

In the approach to the C/D ring system, designed by Mann,[30] 2-tetralone (55), was transformed to the key precursor (56) in four synthetic steps **(Scheme 13)**. With the correct stereochemistry required for the C-ring system, attempts to effect ring closure, to form the D ring, failed using an *intra*molecular Dieckmann cyclisation reaction of the keto ester (56). Instead of the requisite 5,6-ring forming, the undesired 5,5-system was obtained in small quantities.

An alternative method was found using the aldol reaction. Following reduction of the keto ester (56) and subsequent oxidation, the keto-aldehyde (57) was formed in 65% yield. Upon treatment of (57) with *p*-TSA/toluene, an acid catalysed *intra*molecular aldol reaction occurred to provide the epimeric alcohols (58a) and (58b) in 37% and 18% yield respectively.

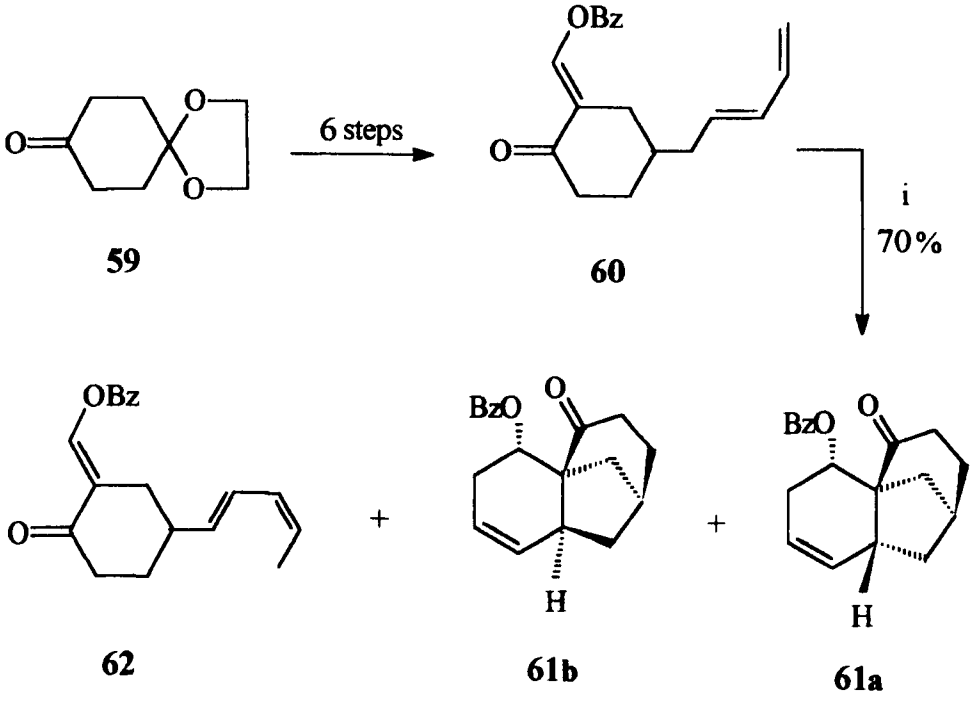



***Reagents and conditions*** i, LAH, ether; ii, PCC, NaOAc, DCM; iii, *p*-TSA, toluene, 60°C.

**(Scheme 13)**

In the Fukumoto[31] approach, the key step for the synthesis of the C/D ring structure of stemodin (33), involved an *intra*molecular Diels-Alder reaction **(Scheme 14)**.

Thus the triene (60) was readily prepared in six synthetic steps from 1,4-cyclohexanedione monoethylene ketal (59). Heating (60) in the presence of a catalytic amount of methylene blue in *o*-dichlorobenzene, afforded a mixture of two tetracyclic compounds (61a) and (61b), along with the isomerisation product (62) in 70% yield, in a ratio of 7:1:0.5. The major product (61a), corresponded to the structure required for the development of the natural product (33).



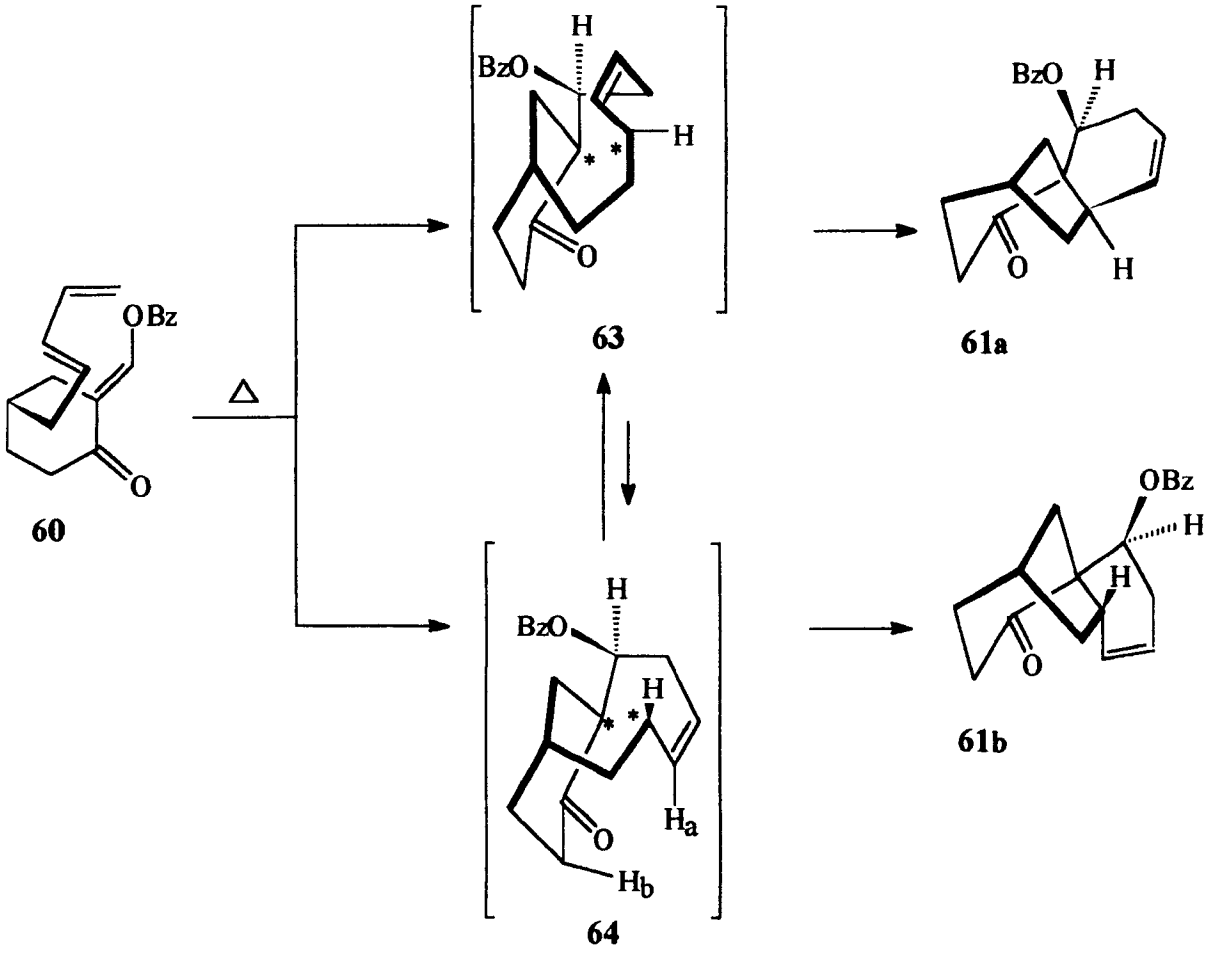

59 60 62 61b 61a

***Reagents and conditions*** i, methylene blue, *o*-dichlorobenzene, 180°C.

**(Scheme 14)**

The preferred formation of (61a) was explained through considering a "concerted but nonsynchronous" transition state for the cyclisation step **(Figure 10)**. Hence steric congestion between the olefinic hydrogen ($H_a$) and the axial hydrogen ($H_b$) in the nine

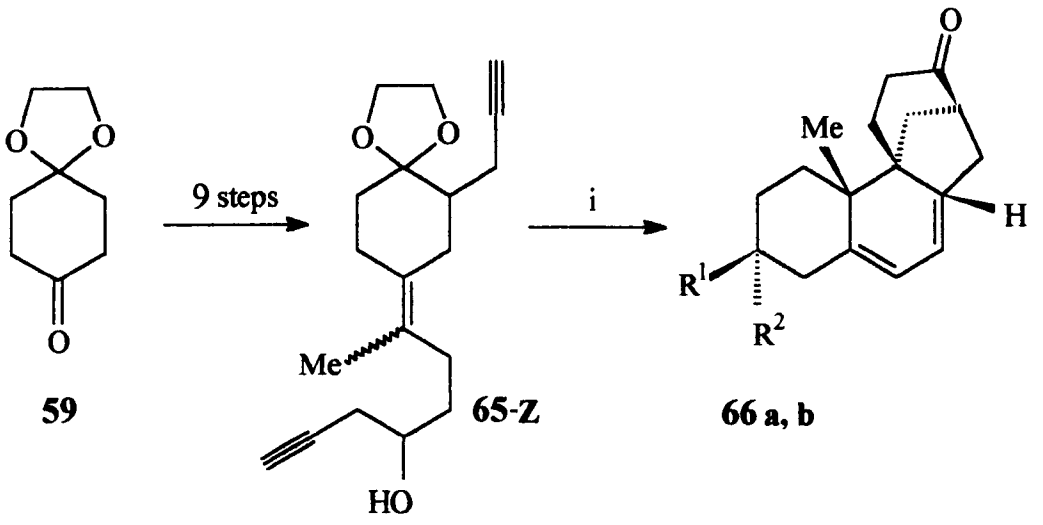
membered ring transition state (64), which is first partially formed, renders it less favourable than the alternative transition state (63) that affords the desired product (61a).




**(Figure 10)**

Finally this section would not be complete without a mention of the approach that was characterised by the work of Vollhardt.[32] In this synthetic route, the bridge ring system was elegantly synthesised with the formation of the entire stemodane nucleus in one step, from the ketal (65) **(Scheme 15)**.

Thus commencing with ethylene glycol monoacetal of cyclohexane 1, 4-dione (59), the crucial intermediate was prepared *via* a nine step synthesis. Upon exposure of the endiyne (65), with 1 equivalent of cyclopentadienylcobaltdicarbonyl, cyclisation occurred to afford the dienes (66a) and (66b) in a 2:1 ratio. This cyclisation was the first example in which an exocyclic alkene was involved.




**59** **65-Z** **66 a, b**

**66a** = $R^1$= H, $R^2$ = OH; 35%

**b** = $R^1$ = OH, $R^2$ = H; 20%

***Reagents and conditions*** i, 1.0 eq $CpCo(CO)_2$, r.t; ii, HCl, $(CH_3)_2CO$.

**(Scheme 15)**

## 1.4 Gibbanes

The bicyclo[3.2.1]octane moiety is also present in the gibbane family of natural products (4). This class of natural compounds contain a fused 6,5 (C/D)-ring system, in contrast to the aphidicolane (3a) and stemodane (3b) that are shown to have a 5,6 (C/D)-ring system.

Since the giberrellins are the most thoroughly studied diterpenes of the gibbane family, as a final example, this group of compounds have been selected for the remaining part of this chapter.

The reader is however, directed to the following fact. As much of the synthetic work in the construction of this framework was conducted over the past two decades, most examples have been taken from this period.

Examining the literature, it would appear that most approaches of today, are formal synthesis that commence with accessible intermediates previously synthesised.[33]

## 1.4.1 Giberrellins

The giberrellins form a group of ~90 highly functionalized diterpenoids, that possess important plant growth regulating properties.[34] With such a wide distribution in nature, coupled with their interesting biological significance, it is not surprising that much synthetic work has been undertaken in this area. In most cases, the bridged ring system in these molecules, have been formed in the last stage of the synthesis. For the purpose of this review, the main strategies that have been involved in the construction of the C/D ring, are placed into the following categories:

**1.4.1.1** Aldol

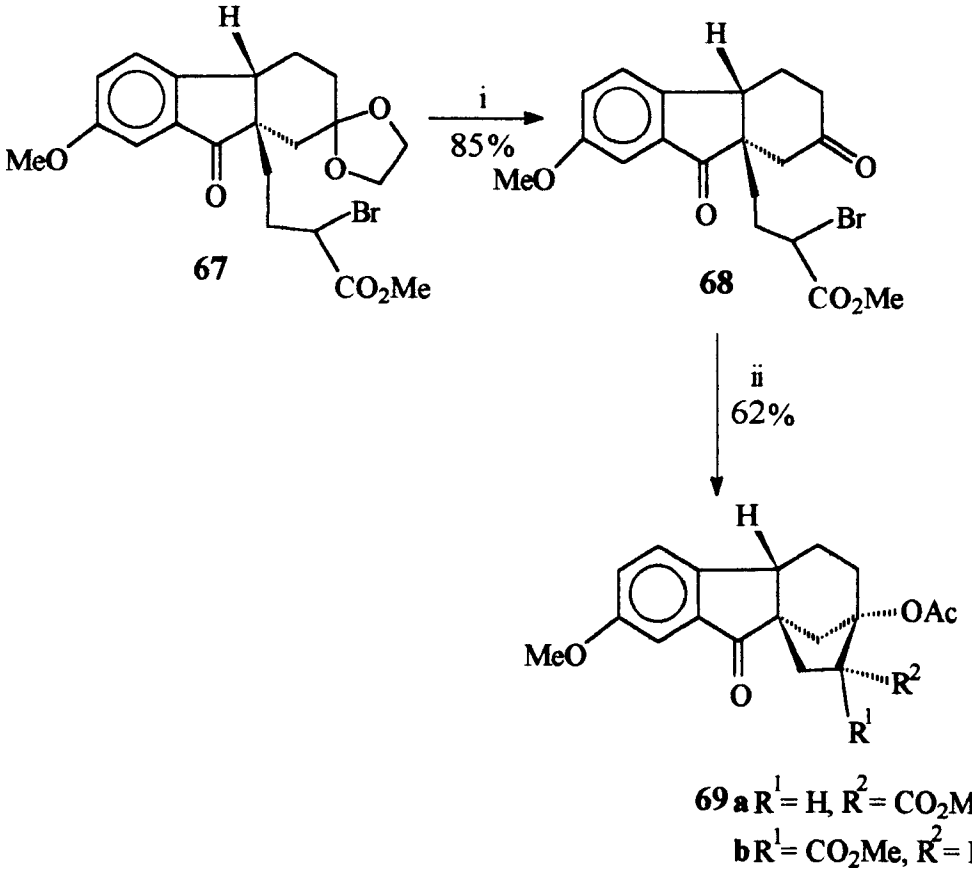
**1.4.1.2** Alkylation

**1.4.1.3** Redox

These class of compounds have been extensively reviewed.[35]

### 1.4.1.1 Aldol Strategy

The *intra*molecular aldol reaction and variants have been a popular method of inducing ring closure to form a bridge ring. For example, Ziegler[36] demonstrated the synthetic utility of an internal Reformatsky reaction, for the creation of the bicyclo[3.2.1]octane C/D ring system **(Scheme 16)**. The key features in this synthesis involved the deketalisation of compound (67), to provide the *cis* bromo ester (68), as a mixture of diastereoisomers about the carbon bearing the ester group. Ring closure was then effected by treatment of this compound with activated zinc. Following the addition of acetic anhydride, a 2:1 mixture of diastereomeric acetoxy esters, (69a) and (69b), were formed in 62% yield.



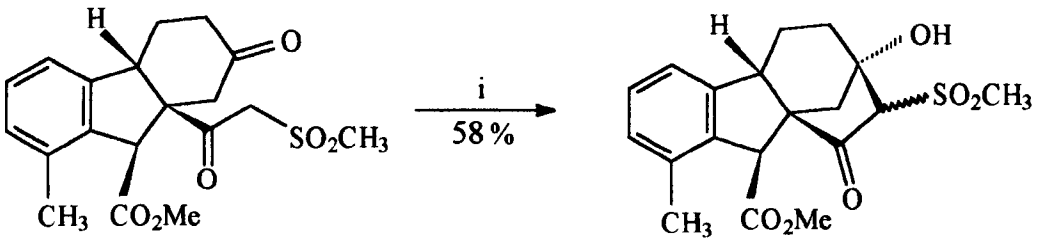

**69 a** $R^1$ = H, $R^2$ = $CO_2Me$

**b** $R^1$ = $CO_2Me$, $R^2$ = H

***Reagents and conditions*** i, 5% HCl, MeOH, reflux; ii, Zn, $C_6H_6$, $(CH_3CO)_2O$, reflux.

**(Scheme 16)**

In an approach by House,[37] an *intra*molecular aldolization reaction was effected using the ketone sulfone compound (70), as the key cyclisation precursor **(Scheme 17)**. Thus following treatment of (70) with the base sodium *t*-amyloxide, a facile cyclisation reaction occurred to afford the tetracycle sulphone (71) in 58% yield.

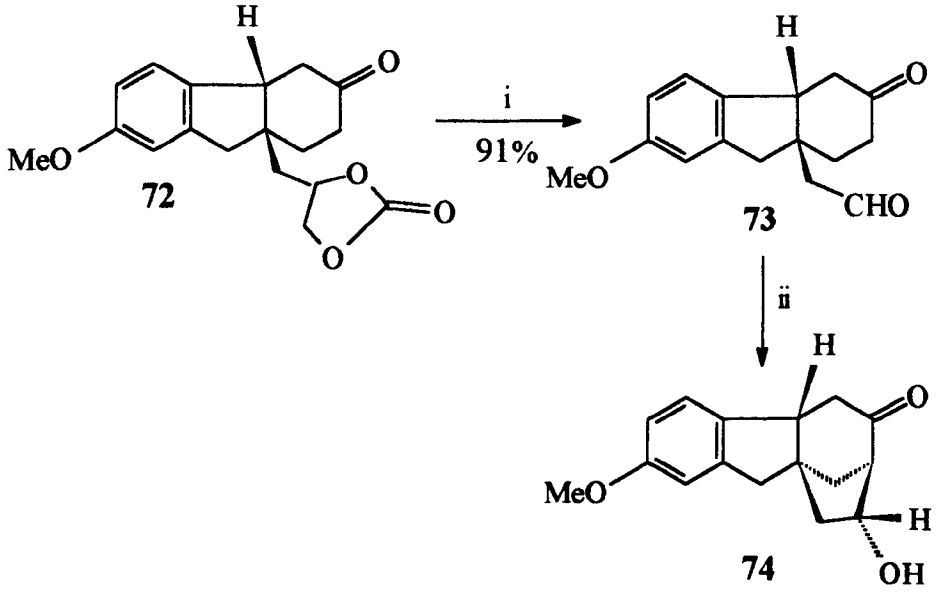



**70** **71**

***Reagents and conditions*** i, *t*-AmO$^-$Na$^+$, $C_6H_6$, dil. HCl, aq. $NaHCO_3$, 0°C.

**(Scheme 17)**

In the first example of an enantioselective synthesis to the gibbane framework, Takano[38] reported the use of an acid induced *intra*molecular aldol reaction to affect ring closure thereby forming the bridge system **(Scheme 18)**.



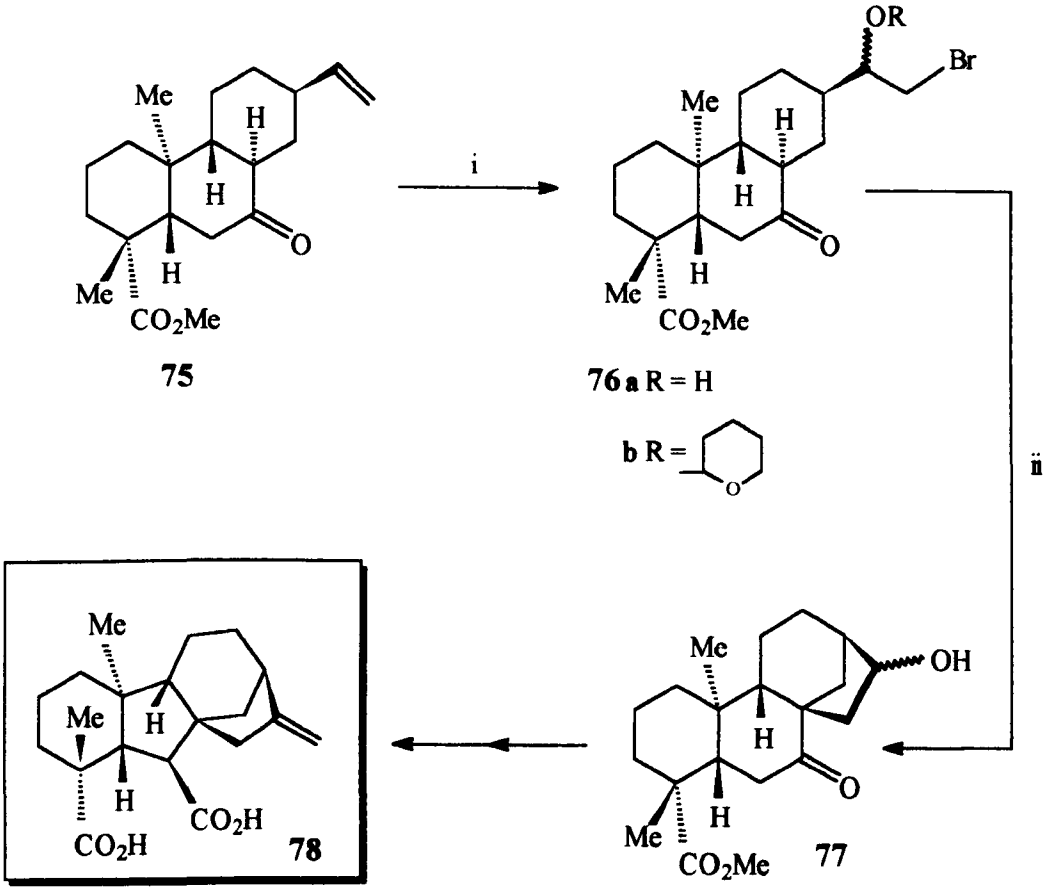

***Reagents and conditions*** i, $NaIO_4$, MeOH, aq.$NaHCO_3$; ii, HCl, acetone, r.t.

**(Scheme 18)**

Thus the required aldehyde (73) was first readily prepared *via* the periodate cleavage of compound (72). Upon the reaction of (73) with hydrochloric acid, in acetone, a 4:1 mixture of α-hydroxy and β-hydroxy isomers, of the tetracyclic ketol (74) were formed in a quantitative yield.

## 1.4.1.2 Alkylation Strategy

In addition to the aldol reactions, alkylation based strategies have also been a well established synthetic route for the generation of the bridged ring system. Mori[39] reported the use of an *intra*molecular alkylation reaction in the synthesis of $GA_{12}$ (78) **(Scheme 19)**.

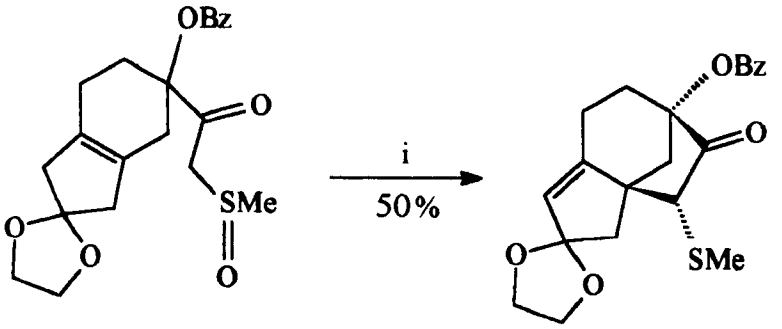



***Reagents and conditions*** i, NBS, aq. DME; ii, NaH in xylene.

**(Scheme 19)**

Thus the key steps to cyclisation involved the conversion of the keto olefin (75) into the corresponding bromohydrin (76a). Protection of the hydroxyl group (76b) and heating with sodium hydride in xylene, led to a rapid *intra*molecular cyclisation to afford (77) after deprotection. This was then transformed over many steps to (78).

In Barco's[40] synthetic work, a Pummerer based cyclisation reaction was used to form the fundamental C/D ring system of the gibbane skeleton **(Scheme 20)**. Thus reaction of (79), with trifluoroacetic anhydride, in the presence of the Lewis acid, tin (IV) chloride, gave the tricyclic ketone (80) in 50% yield.

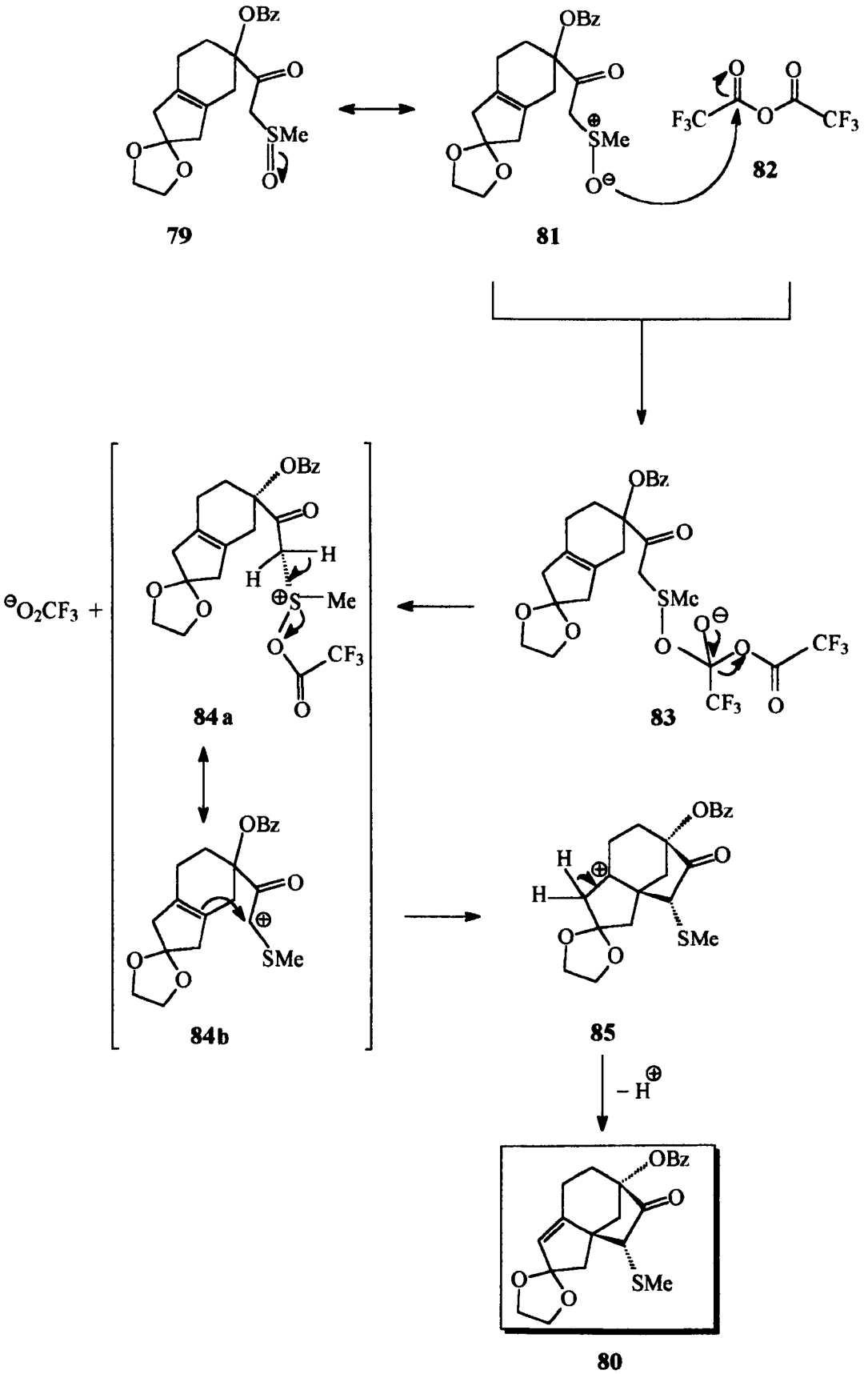



**79** **80**

***Reagents and conditions*** i, $(CF_3CO)_2O$, DCM, $SnCl_4$, 5°C.

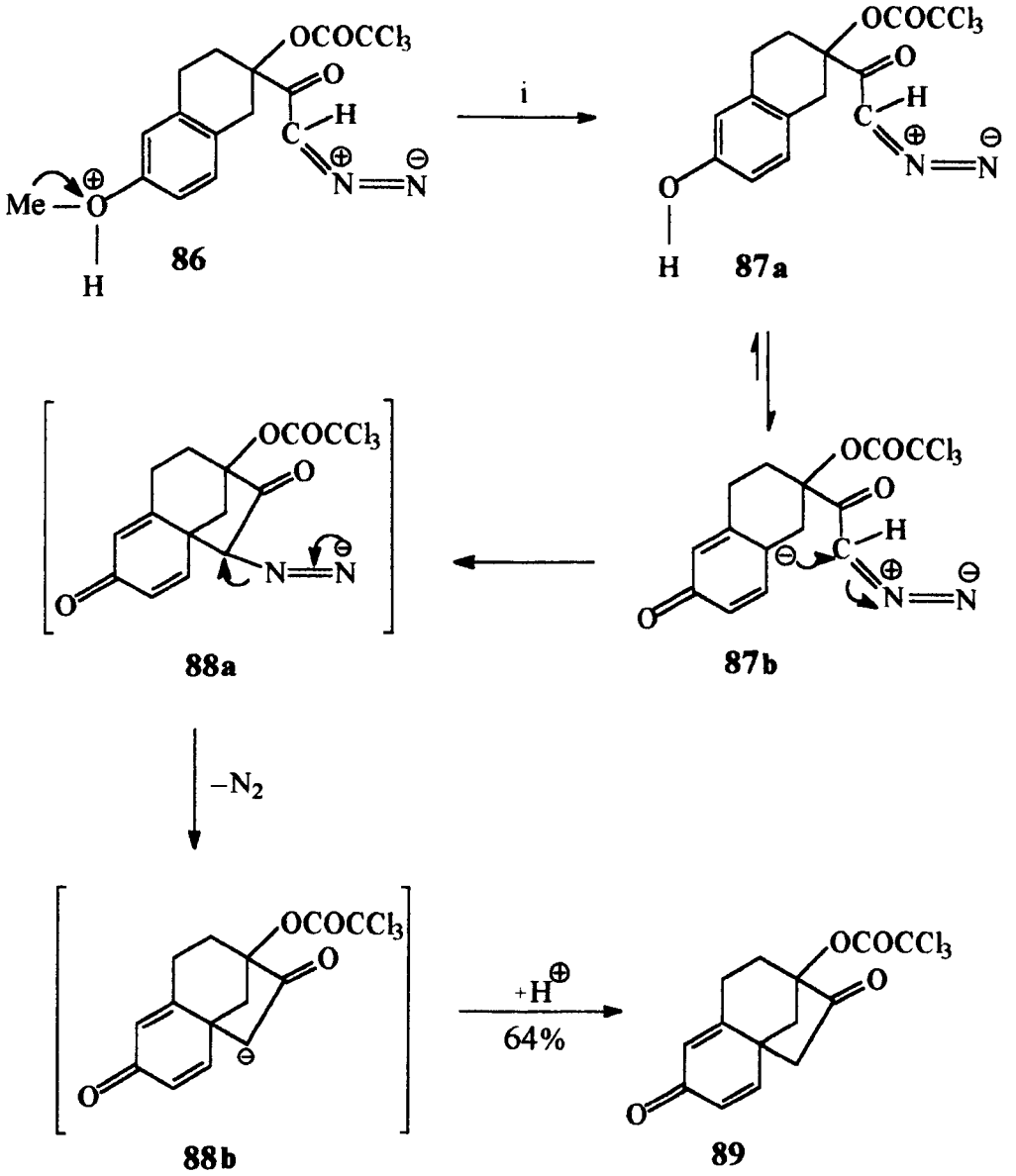
**(Scheme 20)**

The mechanism was explained *via* nucleophilic attack of the sulfoxide ion (81) at the electrophilic carbonyl group in trifluoroacetic acid (82), to form the sulfoxonium intermediate (84a). This then undergoes a Pummerer rearrangement,[41] in which loss of a proton and the trifluoroacetoxy moiety, generates a carbocation (84b), that invokes cyclisation to afford the intermediate (85). Subsequent loss of the ring proton affords the required compound (80) **(Figure 11)**.




**(Figure 11)**

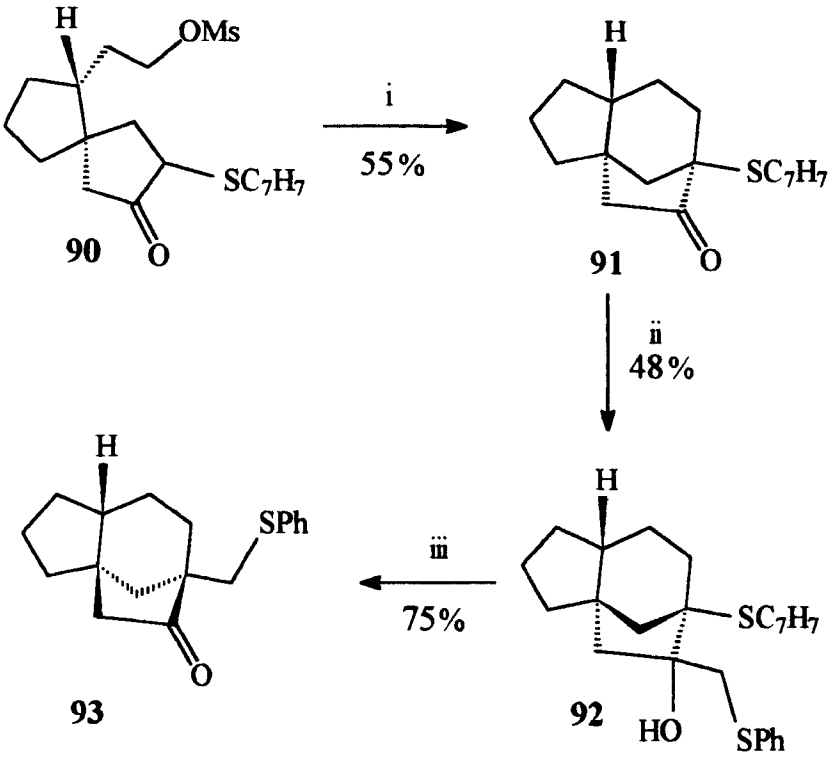
In an alkylation strategy reported by Mander,[42] an acid catalysed diazoketone cyclisation reaction was used as the key step **(Scheme 21)**. Thus treatment of the diazoketone (86) with TFA, led to the intermediate (87b). Following the loss of nitrogen molecule, gave (88a), which upon exposure to acid furnished the desired product (89), in 64% yield.




***Reagents and conditions*** i, $CF_3CO_2H$, DCM, -20°C.

**(Scheme 21)**

An interesting example, based on an alkylation strategy, was also used by Trost[43] **(Scheme 22)**. In this synthetic route, an alkylation process proceeds, upon the treatment of the mesylate (90) with DBN, to afford the tricyclic product (91), in 58% yield. The stereochemistry of this compound was then elegantly modified, following the conversion into the required intermediate (92). Thus, exposure of (92) to TosOH, in refluxing benzene, led to a rapid inversion reaction that gave the desired ketone (93), in 75% yield.

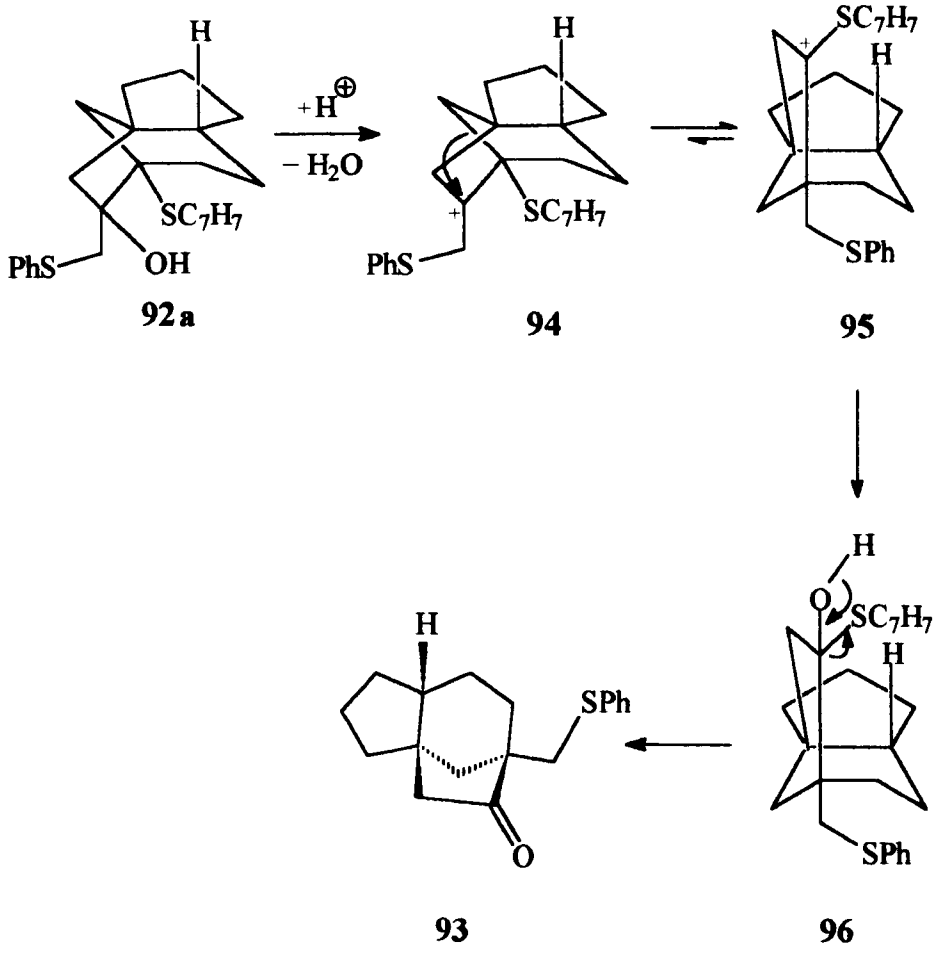



***Reagents and conditions*** i, DBN, DMF-THF, 0°C; ii, lithiothioanisole; iii, TosOH, $C_6H_6$, reflux.

**(Scheme 22)**

The mechanism for the inversion of stereochemistry was explained as follows **(Figure 12)**. Following the loss of $H_2O$ *via* protonation of the hydroxyl group forms the carbocation intermediate (94). A Wagner-Meerwein 1,2 alkyl shift then occurs, allowing the inversion of the stereochemistry, as well as modification of the bridge

substituent, to provide the second carbocation intermediate (95). Subsequent attack by water, affords the alcohol (96), which undergoes an elimination of the *p*-tolyl group to afford the carbonyl moiety, that provides compound (93).

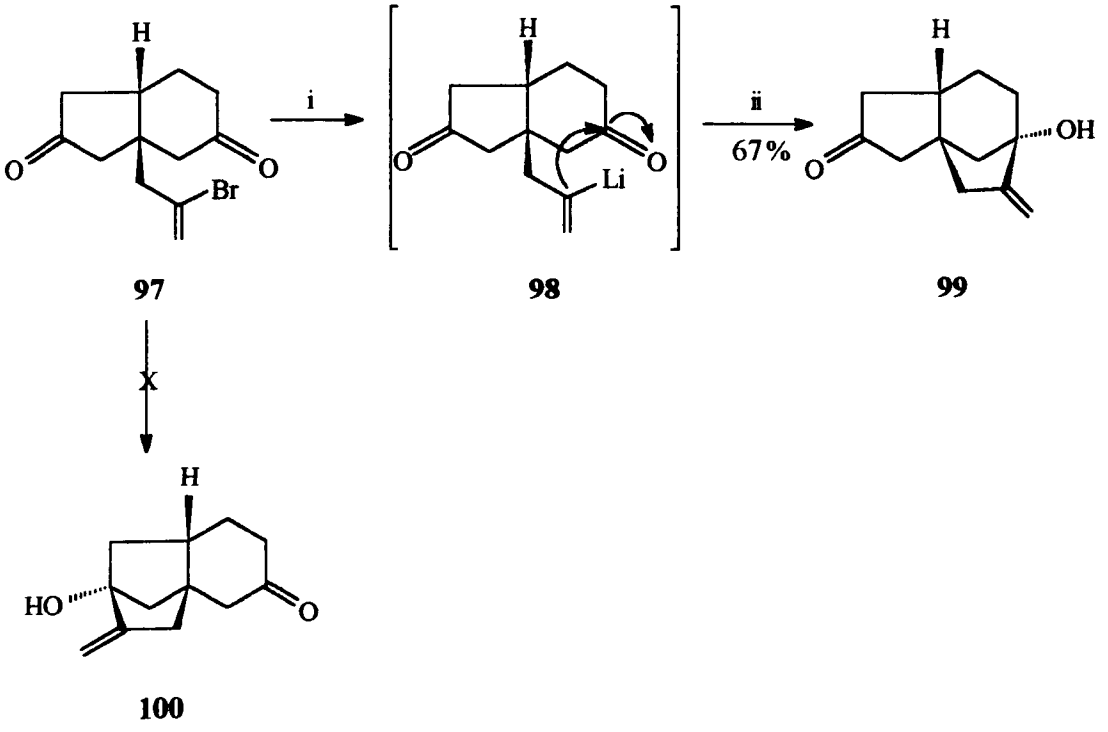



**(Figure 12)**

## 1.4.1.3 Redox Strategy

In addition to these synthetic routes, reductive cyclisation strategies has also been reported. In the approach, reported by Corey,[44] treating the key precursor (97) with lithium-di-*n*-butylcuprate, gave a metal-halogen exchange, to give the required intermediate (98). Subsequent regioselective attack of the nucleophilic carbanionic

centre (C-Li), to the electrophilic carbonyl group, led to cyclisation which upon hydrolysis gave the desired tricyclic alcohol (99) in 67% yield **(Scheme 23)**. The high degree of selectivity observed was rationalised in terms of greater degree of strain in (100), with respect to (99).

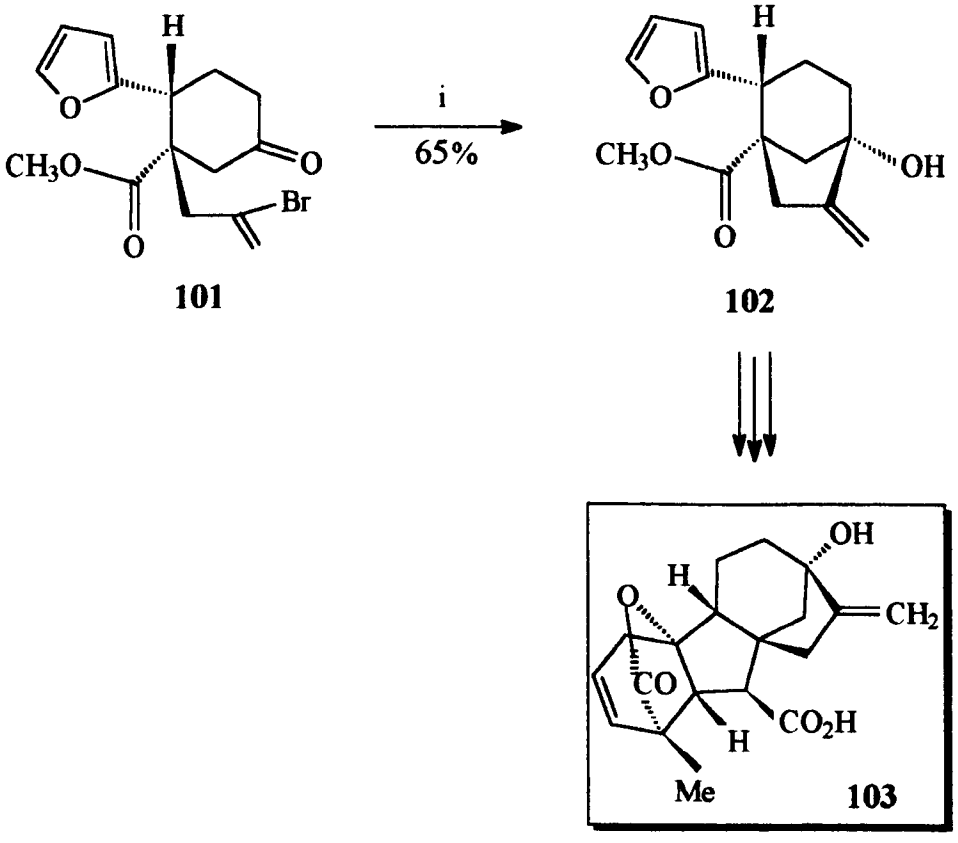



***Reagents and conditions*** i, lithium di-*n*-butylcuprate (11 eq), 33% hexane-diethyl ether, -78°C; ii, $NH_4Cl$.

**(Scheme 23)**

A similar approach was also reported by De Clerq,[45] for the synthesis $GA_5$ (103) **(Scheme 24)**. This reaction was particularly noteworthy as it provided a novel entry into the gibbane skeleton that involved a CD/AB strategy, in contrast to an ABC/D approach. Thus using the same reagent, lithium-di-*n*-butylcuprate, treatment with the ketone (101) gave the desired compound (102) in 65% yield. Consistent with the

original findings,[46] the reaction was found to be critically dependant on both solvent and reaction temperature. Using solvent ratios in favour of hexane, for example ether-hexane, 1:6, or higher temperatures such as 0°C, led to a complex reaction mixture without any considerable amount of the product (102).



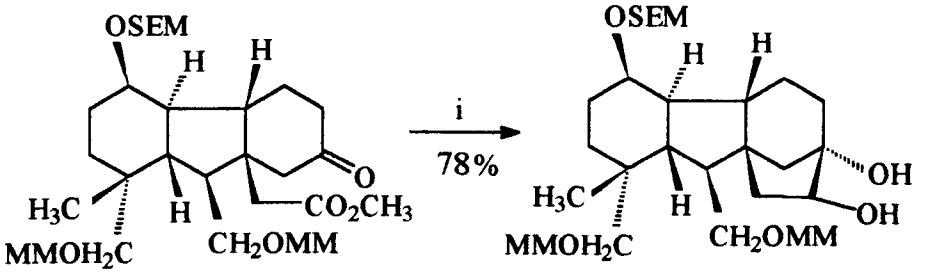

**101** **102** **103**

***Reagents and conditions*** i, lithium di-*n*-butylcuprate (9 eqv), (3:1) THF-hexane, -50°C.

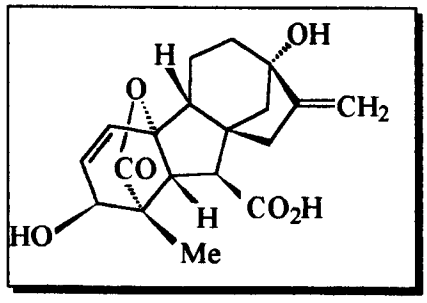
**(Scheme 24)**

In the approach by Yamada[47], a reductive *intra*molecular cyclisation reaction was used to effect ring closure to form the bridge system **(Scheme 25)**. In this synthetic route, treatment of the keto ester (104), with potassium in liquid ammonia, in the presence of

excess ammonium sulphate at -34°C, gave the diol (105), as a 15:1 mixture of diastereoisomers, in 78% yield. Further elaboration of this compound over a number of steps gave the desired natural product $GA_3$ (106).




**104** **105**




**106**

***Reagents and conditions*** i, $K_{(m)}$, $NH_3$ (liq), THF, $(NH)_4SO_4$, -34°C.

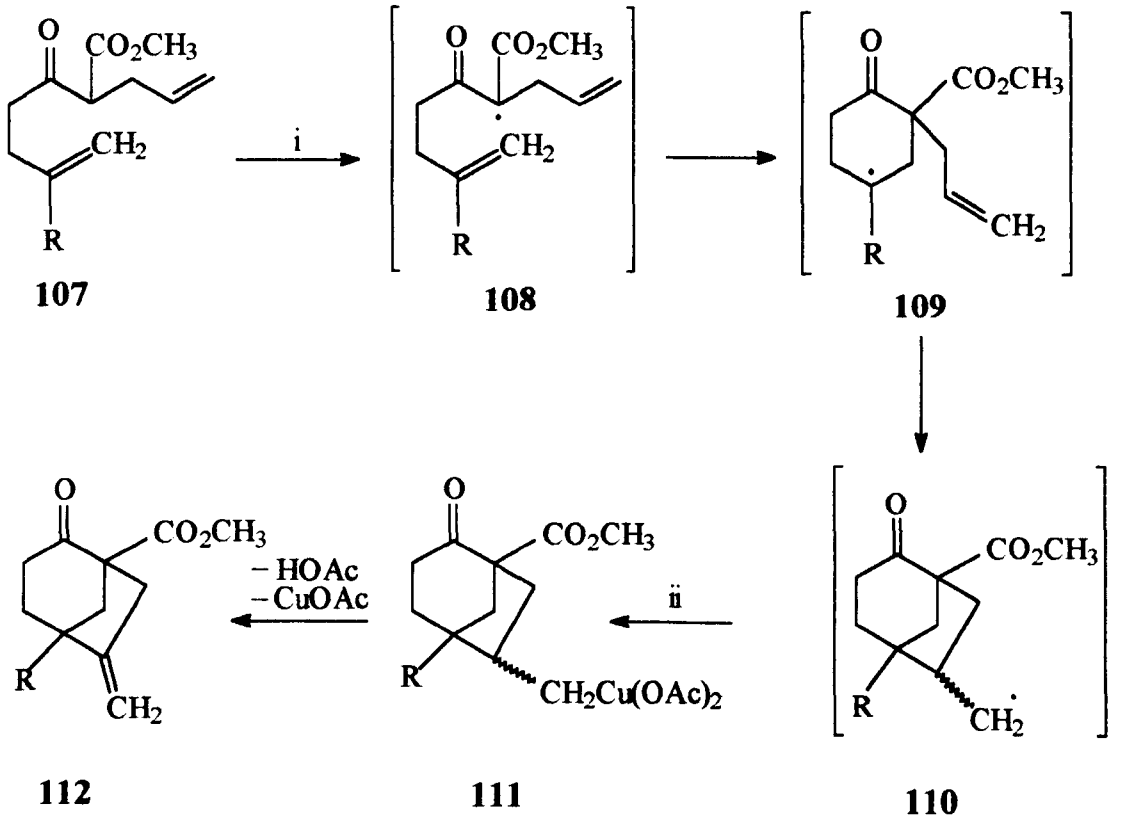
**(Scheme 25)**

## 1.5 Alternative Recent Approaches to the Bridge System

In conclusion to this section, a few examples have recently appeared in the literature for the generation of functionalized bicyclo[3.2.1]octane ring systems.

Snider[48] reported the use of a Mn(III)-based oxidative tandem free-radical cyclization, for the synthesis of substituted bicyclo[3.2.1]octanones. Thus treatment of the keto

ester (107) with manganese (III) acetate in ethanol, led to cyclisation *via* the radical intermediate (108) **(Scheme 26)**. Upon the formation of the cyclohexyl radical (109), resulted in a further tandem reaction to provide the bicyclic intermediate (110). The cyclopentanemethylene radical (110) was oxidised with copper (II) acetate to give, 6-methylenebicyclo[3.2.1]octan-2-one (112) *via* (111), in 52% yield.

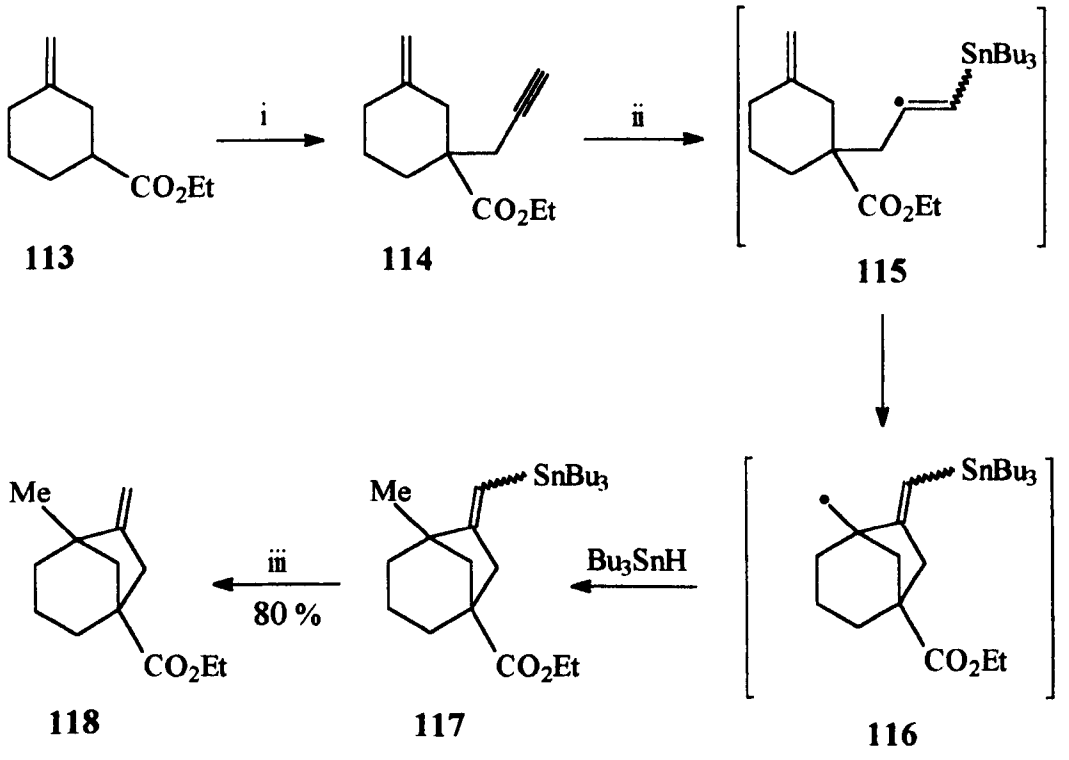



***Reagents and conditions*** i, $Mn(OAc)_3$, EtOH, 60°C; ii, $Cu(OAc)_2$.

**(Scheme 26)**

A radical mediated approach was also reported by Della[49] **(Scheme 27)**. In this synthetic approach, the key propynyl derivative (114) was readily prepared *via* the enolate anion of ester (113). Slow addition of tributyltin hydride, led to the formation of the vinylstannane radical (115), in which upon cyclisation provided the radical intermediate (116). The removal of tributylstannane in (117) was then achieved by

stirring this compound in methylene chloride and silica gel, to afford the unsaturated bicyclo[3.2.1]octyl ester (118) in 80% yield, from (117).

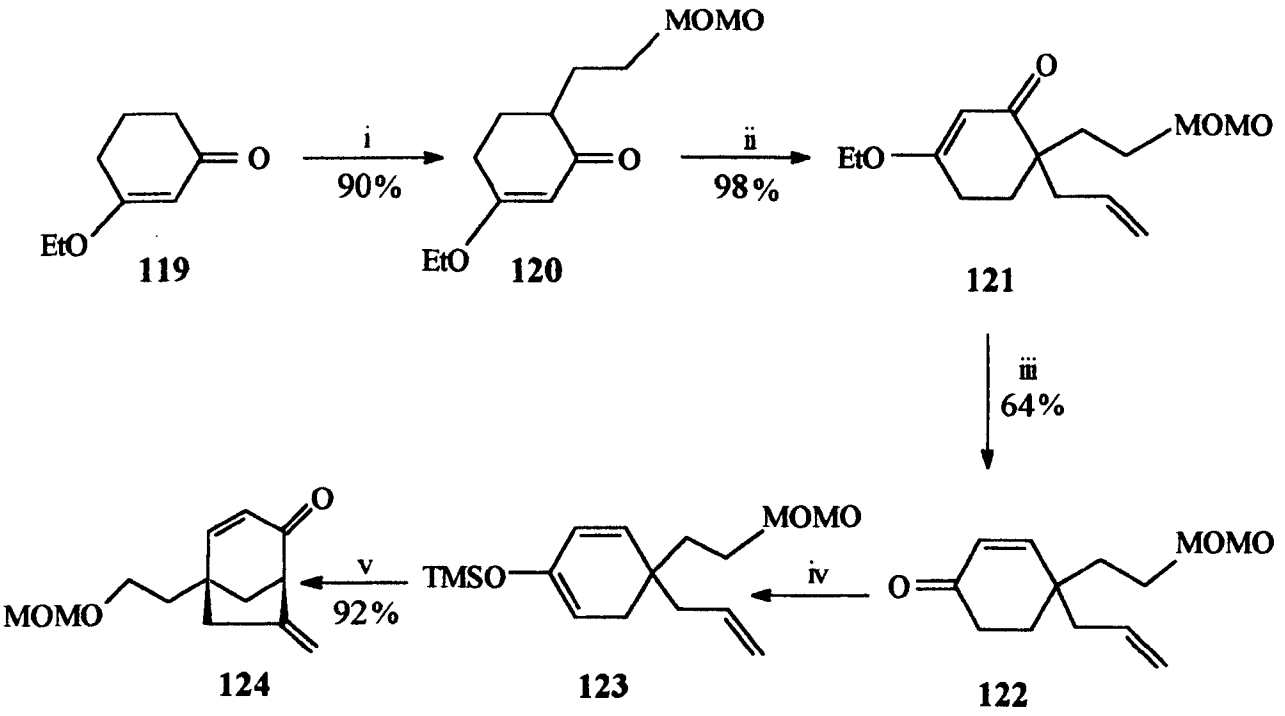



***Reagents and conditions*** i, LDA, Br-$CH_2C{\equiv}CH$, THF, -40°C; ii, $Bu_3SnH$, boiling toluene; iii, DCM, silica gel.

**(Scheme 27)**

In a different approach, Fukamato[50a] reported the use of a $Pd^{2+}$-promoted cycloalkenylation reaction for the development of the bicyclo[3.2.1]octane moiety **(Scheme 28)**. Thus the initial stages of the synthetic route began with the alkylation of 3-ethoxy-cyclohex-2-en-1-one (119) with the iodoethanol derivative, to afford the monoalkylated product (120). Treatment of (120) with the allyl bromide, gave the compound (121), whereupon sequential LAH reduction and acidic treatment led to provide the enone (122) in 64% yield. Upon the conversion of (122), to the silyl enol

ether (123), treatment of this compound with palladium (II) acetate in MeCN, led to a spontaneous cyclisation reaction to afford the desired the bicylic product (124) in 92% yield. This reaction was later incorporated into the synthesis of $GA_{12}$ (78).[50b]




***Reagents and conditions*** i, LDA, THF, HMPA, -30°C, $ICH_2CH_2OMOM$; ii, LDA, THF, -30°C, $CH_2$=$CHCH_2Br$, $Pd(PPh_3)_4$; iii, LAH, THF, 0°C, 5% HCl, THF, 0°C; iv, LDA, THF, -30°C, TMSCl, -78°C→r.t; v, $Pd(OAc)_2$, MeCN.

**(Scheme 28)**

# Chapter Two

## Alkyne-Cobalt Chemistry

# 2.0 Alkyne-Cobalt Chemistry

## 2.1 Introduction

Recently reactivity of transition metal complexes that contain a subsidiary alkyne ligand has been extensively studied by a number of researchers.[51] Although many metal alkyne complexes are known, the most thoroughly studied class have been those derived from the dicobalt hexacarbonyl.[52] The application of such complexes has been extensively exploited in many carbon-carbon bond forming reactions. In particular their use has been highlighted in Pauson-Khand[53] and the Nicholas reactions.[6]

For the purpose of this review, the Nicholas reaction will be discussed as this was the key cyclisation step in these studies. Before proceeding into the discussion a brief outline into the formation and structure of the cobalt alkyne complex is given.

## 2.2 Formation and Structure of the Complex

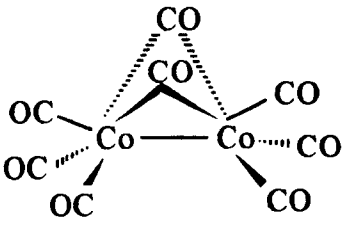
The facile formation of an alkyne hexacarbonyldicobalt complex was revealed in 1956 by Greenfield.[54] Using ambient temperatures and any alkyne, for example terminal ($R^1$=H) or symmetrical disubstituted (R=$R^1$), the complexes of the given formula were formed ***Equation 1.***

$$RC{\equiv}CR^1 + Co_2(CO)_8 \rightarrow (RCCR^1)Co_2(CO)_6$$

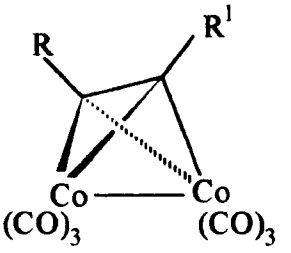
***Equation 1***

The appearances of these complexes were found to have a characteristic deep red brown colour.

From X-ray analysis it was shown that the generation of this complex was accompanied by the displacement of two bridging carbonyls, that are present in the parent dicobalt octacarbonyl (125) **(Figure 13)**.[55]




**125**




**126**

**(Figure 13)**

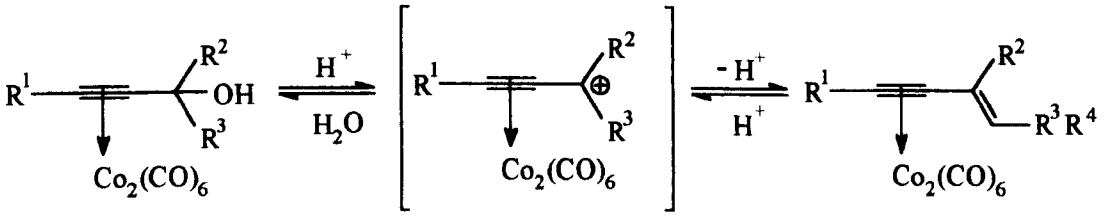
In addition, since the alkyne has two mutually orthogonal orbitals, its potential to bind to two cobalt atoms through π orbital interaction was observed. The geometry about each cobalt and alkyne carbon atoms was found to be essentially a distorted tetrahedron, in which R substituents on the alkyne were bent away as shown (126) **(Figure 13)**.

Direct evidence for the formation of these complexes, could also be obtained through infrared spectroscopy. One distinct difference that is immediately noted, in comparison to the infrared spectrum for dicobalt octacarbonyl, is the absence of the band at 1850cm$^{-1}$ for the bridging carbonyl groups. This further suggests that the complexation occurs *via* displacement of the carbon monoxide ligands at bridging positions and not the terminal, which are shown to be present at 2025, 2050 and 2090 cm$^{-1}$.

In addition, formation of this complex is also evident from the decrease in intensity or complete absence of the sharp band due to the carbon-carbon triple bond that typically occurs at 2100cm$^{-1}$.

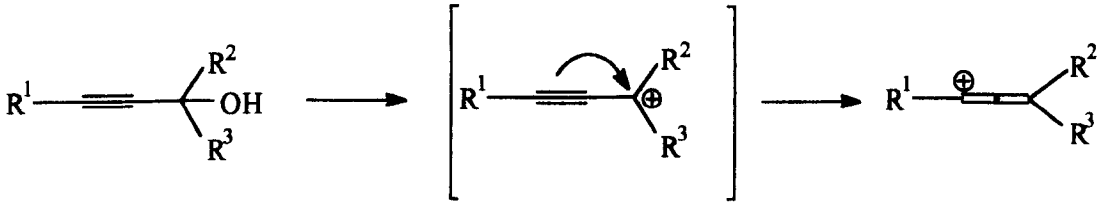
## 2.3 Discovery of the Nicholas Reaction

Having seen, from Greenfield, that complexation of alkynes could be readily achieved, Nicholas[56] embarked on a series of investigations to examine the potential of the hexacarbonyl unit as a protecting group.[56] It was during the course of these studies that the Nicholas cation was discovered and its considerable stability realised. He found that in the presence of a Lewis acid (or a protic solvent), cobalt complexed propargylic alcohols such as (127), readily underwent dehydration to form the corresponding conjugated enyne complex (129) **(Scheme 29)**. The ease of this reaction was attributed to the intermediate metal stabilised carbocation (128), that is now recognised as the Nicholas cation.



**127** **128** **129**

Alternatively this enyne was found to be readily hydrated without the tendency for the intermediate cation to rearrange to form an allene cation (132), that was observed in the absence of the cobalt complex (131) **(Scheme 29)**.



**130** **131** **132**

**(Scheme 29)**

* In this review, $Co_2(CO)_6$ is used to represent the dicobalt hexacarbonyl alkyne complex. For a fully drawn representation see page 39.

The synthetic exploitation of this discovery was later seen. The interaction of the cobalt complex cation was studied with a range of nucleophiles that may be placed into two main categories shown.

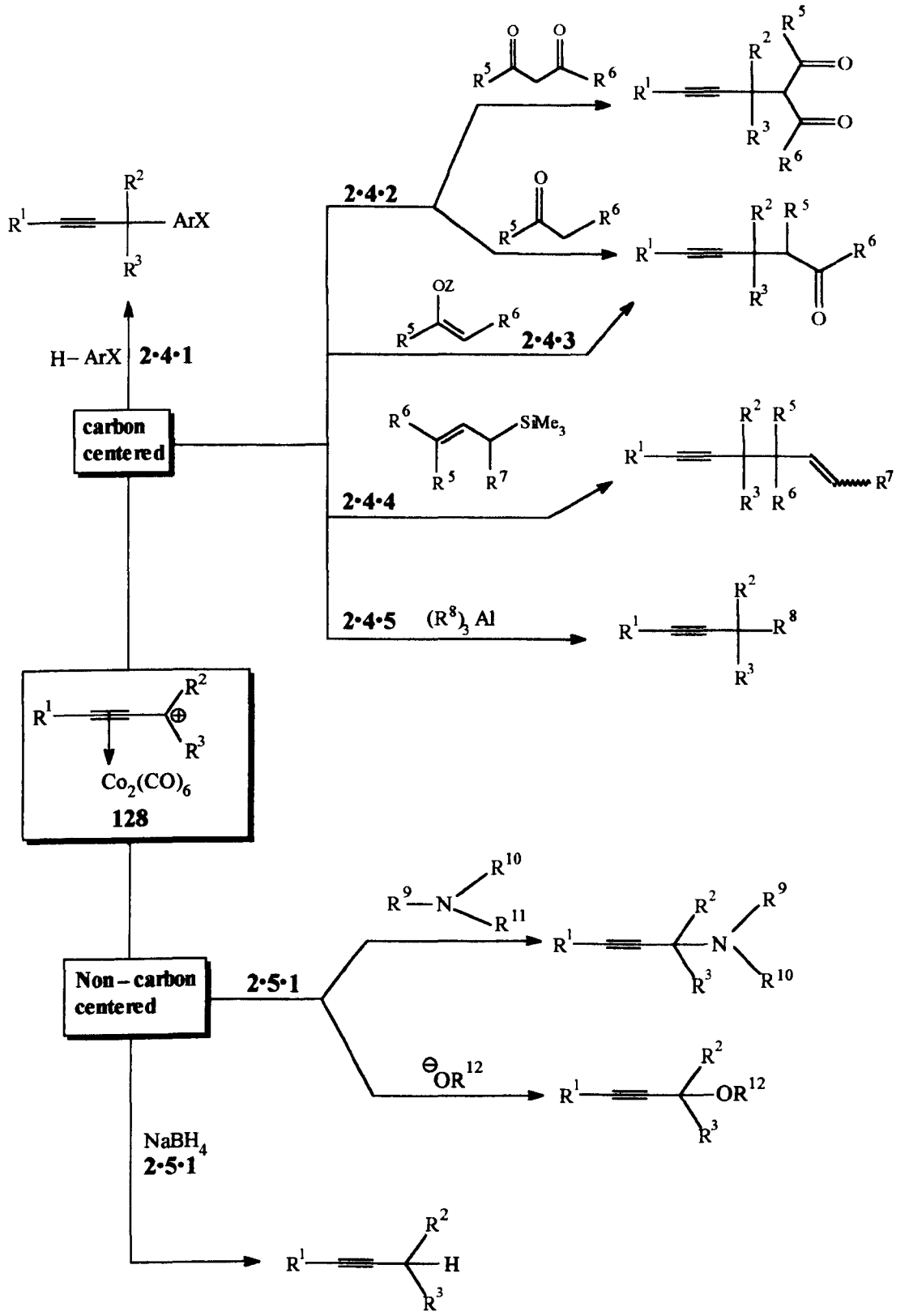
Carbon centred nucleophiles- these included

- aromatics **(2.4.1)**
- β-diketones and ketones **(2.4.2)**
- enol derivatives **(2.4.3)**
- allylsilanes **(2.4.4)**
- organometallics **(2.4.5)**

Non-carbon centred nucleophiles **(2.5.1)**- such as

- nitrogen
- oxygen
- hydride

The addition was shown to occur either through adopting an *inter-* or an *intra*molecular process, that lead to a variety of propargylated derivatives. Facile decomplexation was achieved using oxidising agents such as ceric ammonium (IV) nitrate, ceric (IV) sulphate and iron (III) nitrate nonahydrate.


2•4•2
2•4•3
2•4•4
2•4•5
(R8)3 Al
H– ArX
2•4•1
carbon centered
Co2(CO)6
128
Non – carbon centered
2•5•1
NaBH4
2•5•1

**(Scheme 30)**

where $R^1$=H, Me, or $SiMe_3$

$R^5$, $R^6$, $R^7$, $R^9$, $R^{10}$, $R^{11}$= H, alkyl or aryl

$R^8$=Me

Z = $SiMe_3$, Ac or alkyl

X = OMe, OEt, and so fourth

$OR^{12}$= Me, H

These nucleophiles will now be discussed in turn under the appropriate sections given in **(Scheme 30).**

## 2.4 *Inter*molecular Nicholas Reaction - Reactions with Carbon-Centred Nucleophiles

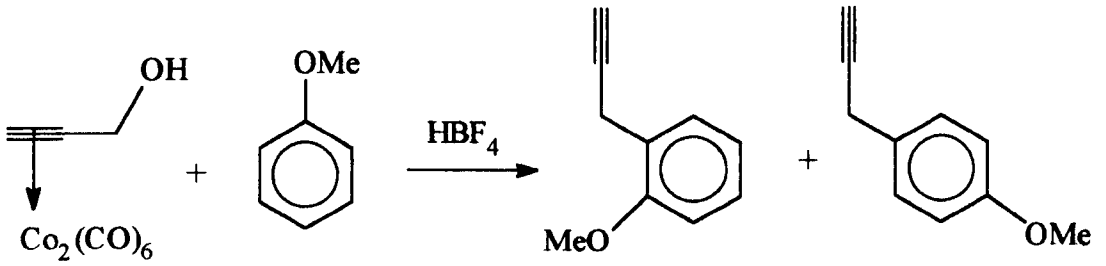
These are the most thoroughly studied class of nucleophiles, since the discovery of the Nicholas reaction. In addition the reader is directed to the fact that most examples given to date (such as aromatics, allylsilanes, enol derivatives) have involved nucleophiles that are classified as activated. This point will be further clarified in section **2.6**.

### 2.4.1 Aromatics

Aromatic compounds such as anisole (134), phenol, N,N-dimethylaniline have been found to react, at ambient temperatures, with a range of cobalt complex propargyl derivatives to provide, after demetallation, the corresponding propargylated products.

For example, by reacting the propargyl cobalt complex (133) with anisole (134) in the presence of tetrafluoroboric acid, provided, upon the removal of the dicobalt hexacarbonyl moiety, 135a and 135b, as a mixture of *ortho* and *para* substituted

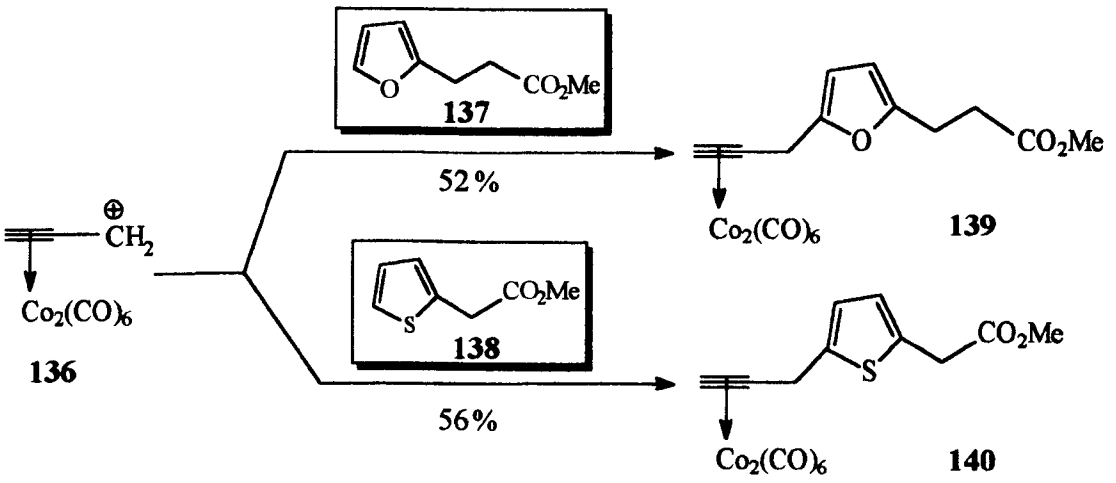
products. The *para* isomer 135b being more favourable due to steric factors **(Scheme 31)**.[57]




**133** **134** **135a** **135b**

**(Scheme 31)**

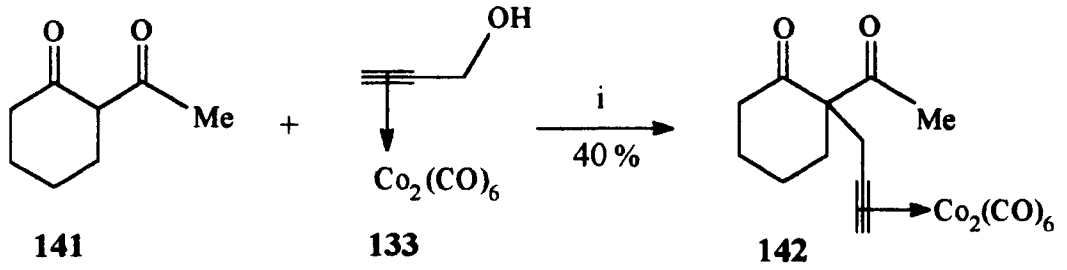
Adopting a similar procedure, Pauson's group[58] showed that facile alkylation could also be achieved using heteroaromatic substrates, for example furans and thiophenes. In these reactions the attack by the Nicholas cation exclusively occurred at the 5-position **(Scheme 32)**. Thus the reaction of (136), with methyl 3-(2-furyl)propanoate (137) and of methyl 2-thienylacetate (138), gave the complexes (139) and (140) in a reasonable yield of, 52% and 56%, respectively. Such reactions were reported to have use in the synthesis of prostaglandin analogues.




**(Scheme 32)**

## 2.4.2 β-Dicarbonyls and Ketones

In these examples, it was seen that the attack occurs *via* the electron rich double bond of the enol tautomer, to provide the product.[59] Thus, the reaction of the β-diketone, 2-acetylcyclohexanone (141), with the cobalt complexed propargyl alcohol (133), gave the diketone (142) in the presence of tetrafluoroboric acid **(Scheme 33)**.

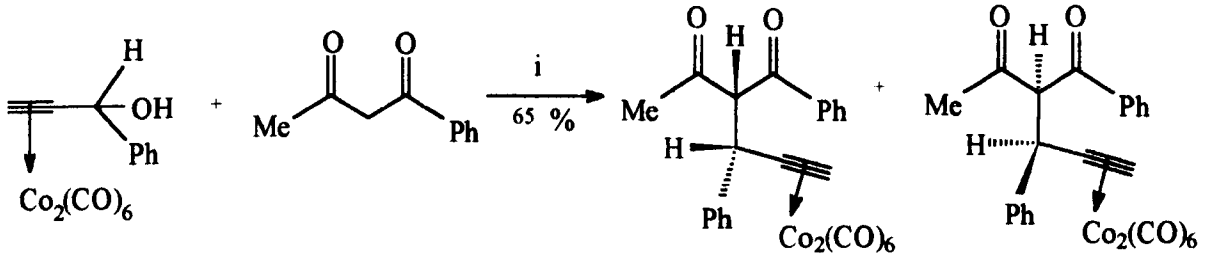



**141** **133** **142**

***Reagents and conditions*** i, $HBF_4$, DCM, -78°C.

**(Scheme 33)**

Similarly a facile alkylation was reported between the cobalt complex (143) and the diketone (144) **(Scheme 34)**.[59] In this reaction significant stereoselectivity was observed in which the ratio of diastereomers formed were 80:20 (145a:145b).




**143** **144** **145a** **145b**

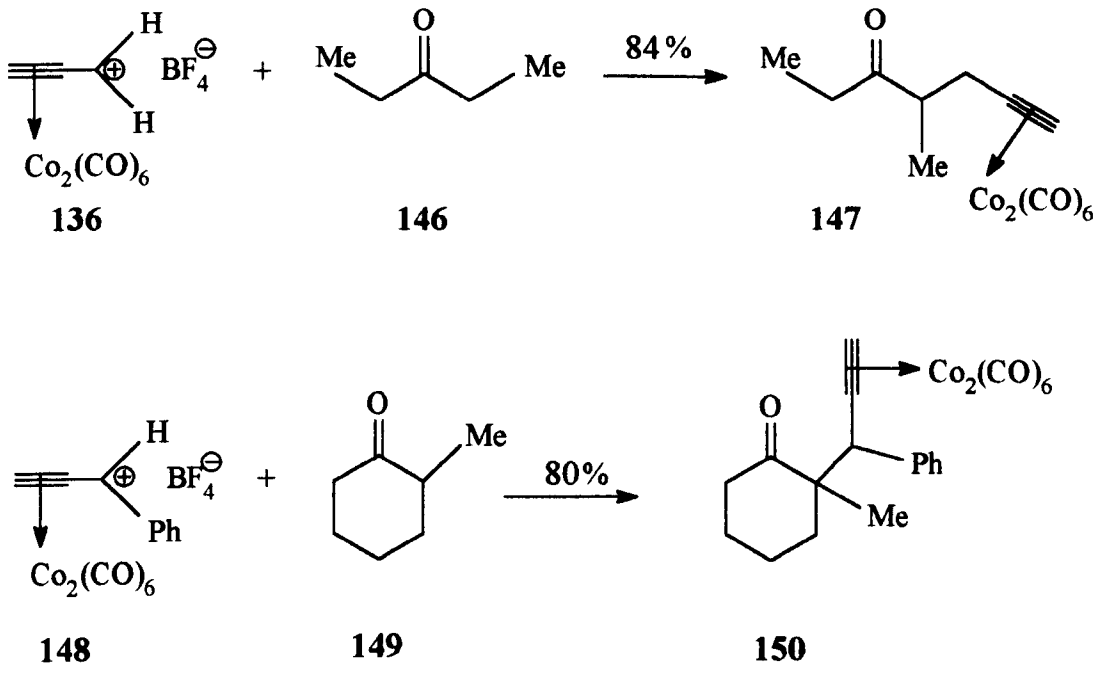
***Reagents and conditions*** i, $HBF_4$, DCM, -78°C.

**(Scheme 34)**

It was found that this ratio dramatically increased to 93:7 if the reaction was stopped after only a few minutes.

A particular interest in the reactions shown in **(Scheme 33)** and **(Scheme 34)**, was the generation of a new asymmetric centre, thus opening a possible path for asymmetric induction.

Under analogous reaction conditions ketones[60] **(Scheme 35)**, (146) and (149), were also seen to react with the cobalt complexed carbocations, (136) and (148), to provide the monocarbon propargylated products (147) and (150) in high yields.

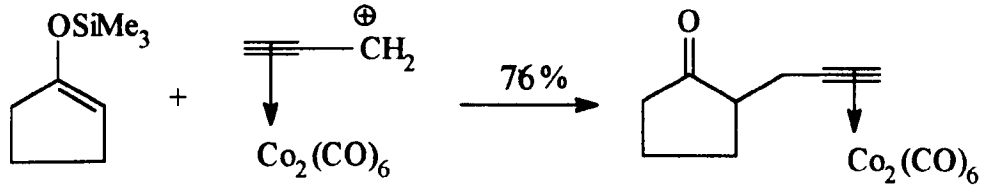



**(Scheme 35)**

The regioselectivity of the alkylation reactions were as expected. Thus, the reaction proceeded *via* attack of the electrophilic complex by the thermodynamically, more highly substituted enol, as illustrated in the formation of compound (150).

## 2.4.3 Enol Derivatives

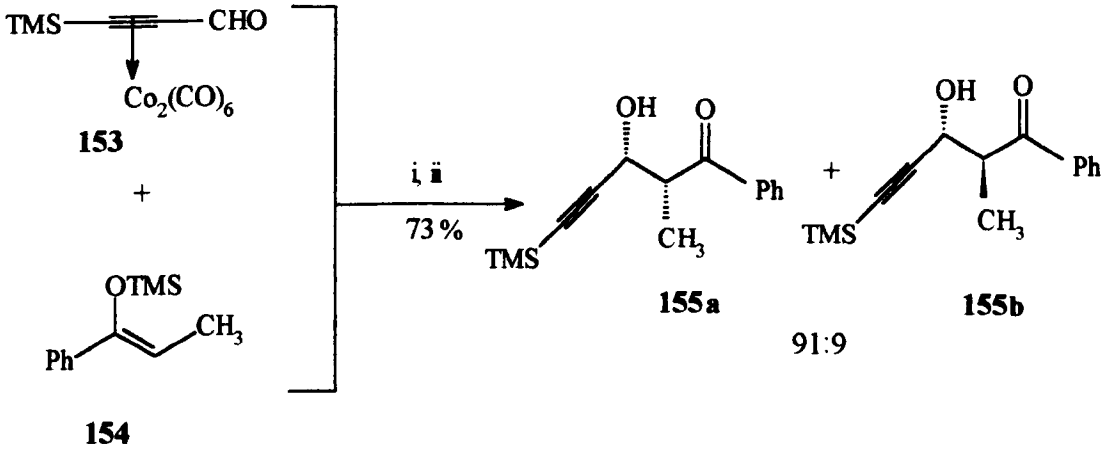
The versatile nature of the carbocation was seen to also include a variety of enol derivatives. In particular, the use of O-silylenol ethers is well documented in the literature.[61] One early example[60] is shown **(Scheme 36)**. In this example the O-silyl enol ether (153), was found to readily react with the cobalt complexed Nicholas cation (138), to afford the α-alkylated product (154), in 76% yield.




**151** **136** **152**

**(Scheme 36)**

Hanaoka[62] reported the first example of a diastereoselective aldol condensation of a cobalt complex propynal with *O*-silyl enol ethers. The reaction was found to proceed with high *syn* selectivity regardless of the stereochemistry of the *O*-silyl enol ether and the Lewis acid employed **(Scheme 37)**.

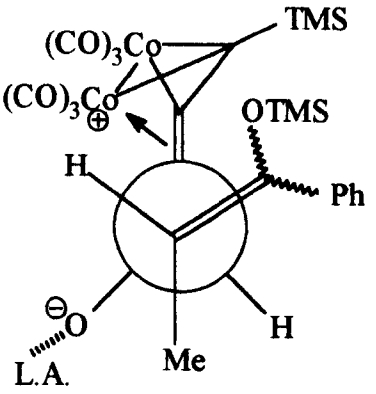



***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, -78°C; ii, CAN, MeOH, 0°C.

**(Scheme 37)**

Thus upon Lewis acid treatment of the *O*-silyl enol ether (154), with the cobalt complexed aldehyde (153), the products (155a) and (155b), were obtained upon decomplexation, in 73% yield. A selectivity ratio of 91:1 (*syn:anti*) was achieved.

The high *syn* selectivity was rationalised in terms of the modified synclinal transition state **(Figure 14)**, previously reported for the reaction between the cobalt-complexed propargyl methyl ether derivative and the *O*-silyl enol ether.[63]

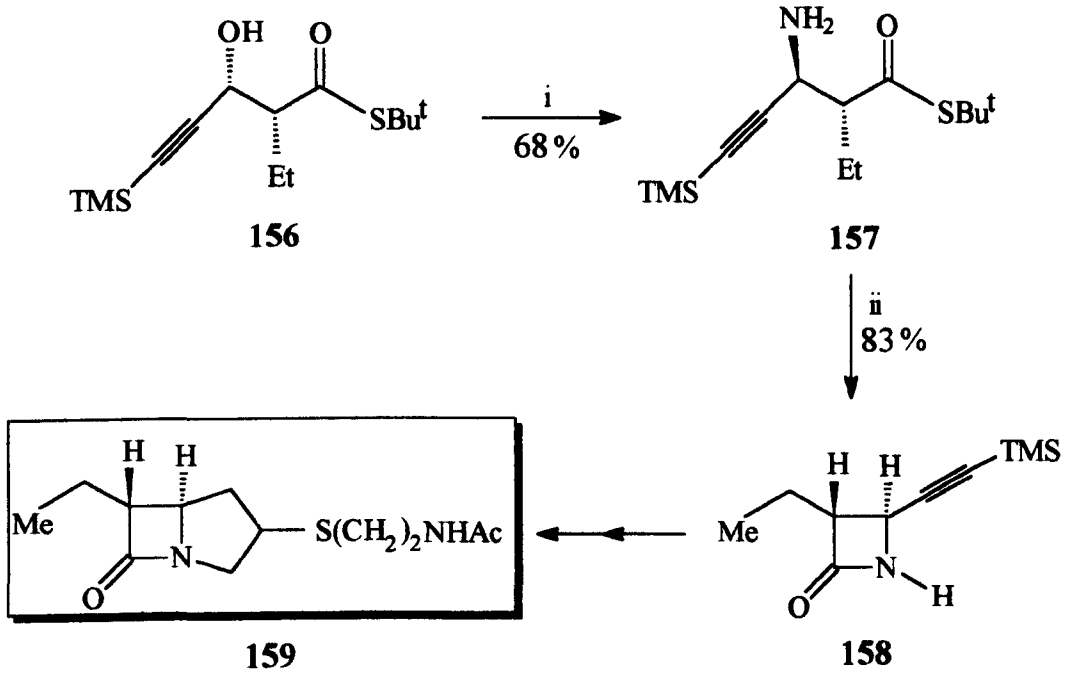



**(Figure 14)**

In this model the hydrogen atom on the double bond of the *O*-silyl enol ether is positioned in the most sterically demanding place of the cationic intermediate, so that minimal interference occurs with the bulky cobalt substituents. Thus, the cobalt complex determines the stereochemical outcome, thereby a high diastereoselective formation of the *syn*-aldol products are observed.

An application of this stereoselective aldol reaction was later shown through the synthesis of some bioactive compounds.[64] For example, the *syn*-aldol product (156) was used for the preparation of the β-lactam antibiotic PS-5 (159) **(Scheme 38)**. Thus following the conversion of (156) into the *anti*-amino derivative (157), the β-lactam ring was next formed by the successive treatment of (157), with trimethylsilyl chloride and *tert*-butylmagnesium chloride, to provide the required compound (158) in 83% yield.

Transformation of this product using a number of synthetic steps led to the desired compound (159).

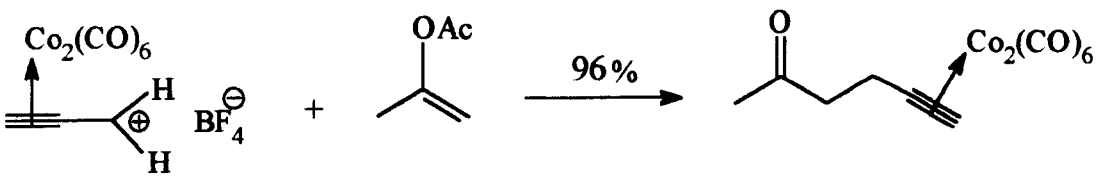



156 157 159 158

***Reagents and conditions*** i, (a) $HN_3$, $PPh_3$, DEAD, (b) $PPh_3$, $H_2O$; ii, (a) TMSCl, $Et_3N$, (b) Bu$^t$MgCl.

**(Scheme 38)**

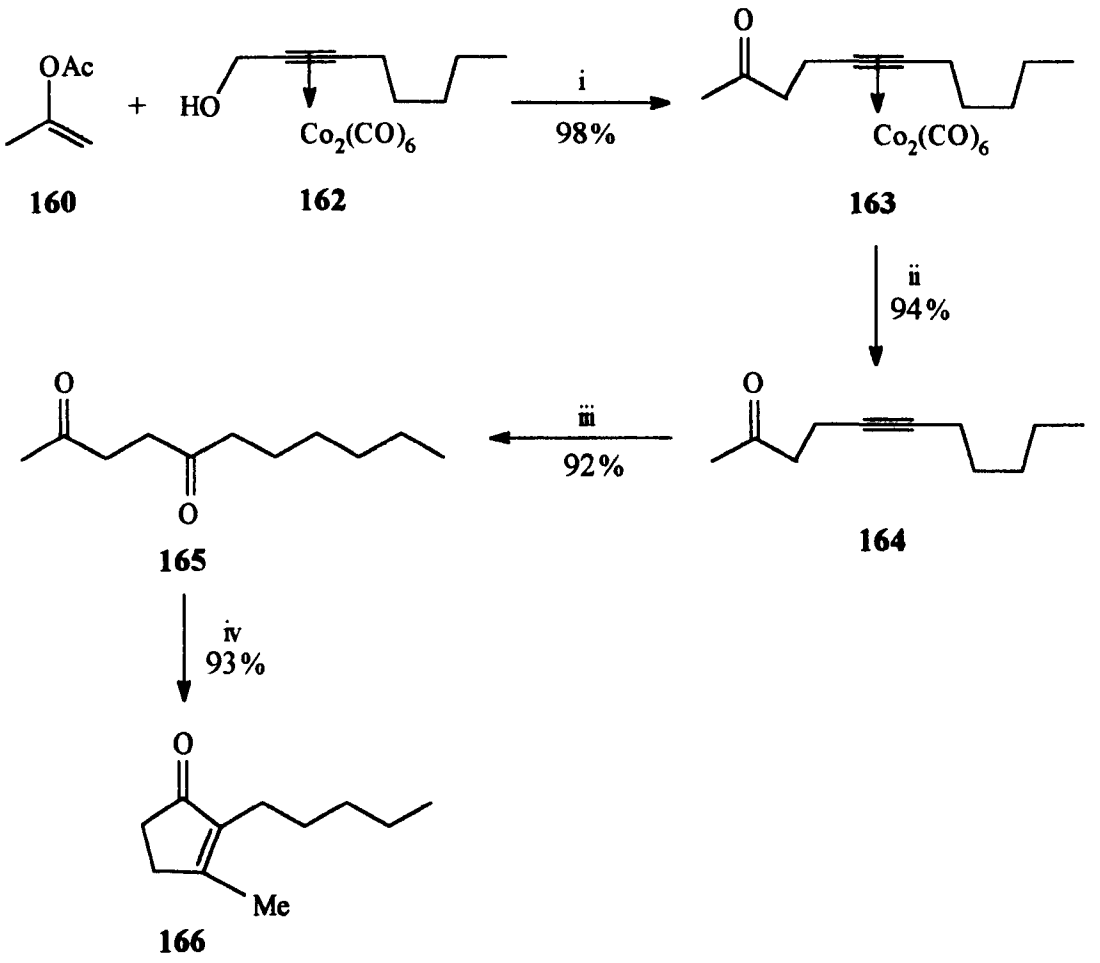
Similiarly, Nicholas[60] showed that enol esters could also be alkylated as shown **(Scheme 39)**. Thus treatment of the enol acetate (160) with (136), gave the hexynone derivative (161) in a high yield.




136 160 161

**(Scheme 39)**

The synthetic application of this work was later seen through the synthesis of dihydrojasmone (166) **(Scheme 40)**.[65] Thus, commencing with an *inter*molecular addition of the enol acetate (160), to the cobalt complexed precursor (162), in the presence of tetrafluoroboric acid, gave the ketone (163) in a quantitative yield. Facile removal of the dicobalt hexacarbonyl moiety with iron (III) nitrate provided compound (164), whereupon subsequent reaction with mercury (II) acetate in acidic methanol furnished the diketone (165). This compound was then subjected to an *intra*molecular aldol condensation reaction, in basic ethanol, in which the desired natural product (166) was isolated in 93% yield.

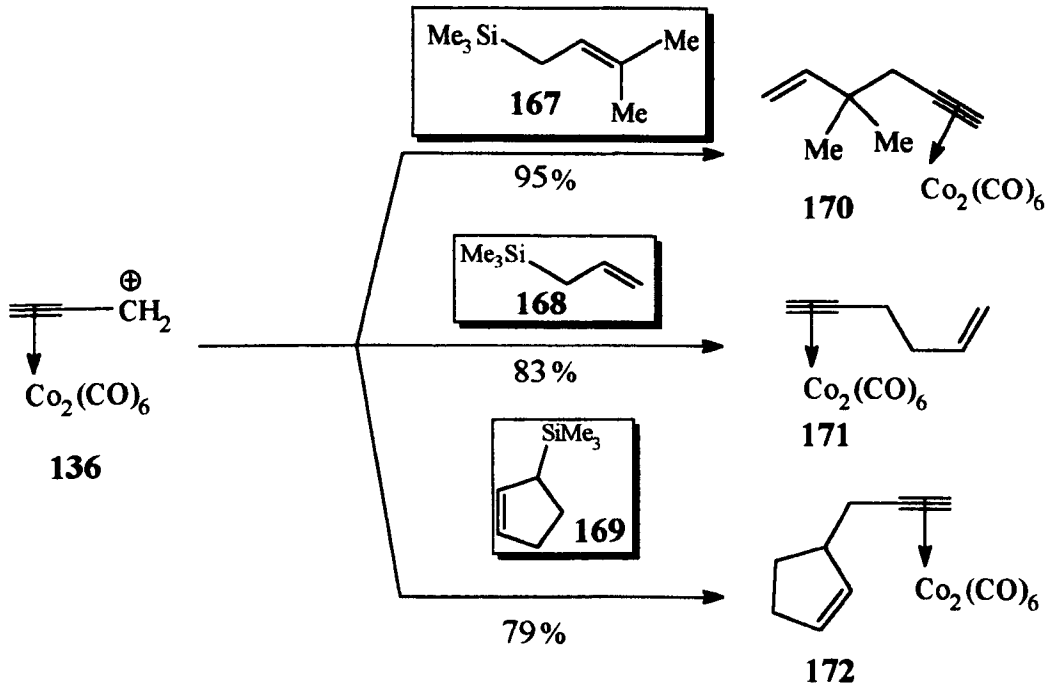



***Reagents and conditions*** i, $HBF_4$, DCM, -78°C; ii, $Fe(NO_3)_3.9H_2O$, ether, 0°C; iii, $(CH_3CO_2)_2Hg$, 5% HCl, MeOH; iv, NaOEt, EtOH, reflux.

**(Scheme 40)**

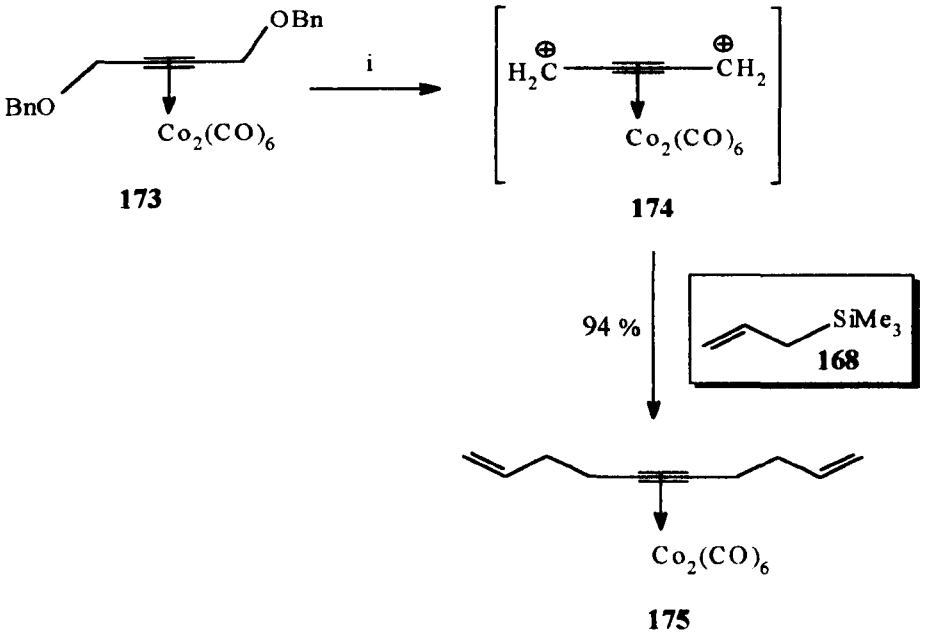
## 2.4.4 Allylsilanes

The interaction between a range of allylsilanes with a cobalt complexed cation has also been reported by Nicholas.[66] Upon studying a range of these nucleophiles, the successful synthesis of the 1,5-enynes (170-172) were achieved in excellent yields and with full regiocontrol **(Scheme 41)**. Such intermediates were seen to be useful in the synthesis of terpenoids.[67]




**(Scheme 41)**

Takano[68] reported an interesting first example of a double Nicholas reaction involving the allylsilane (168) **(Scheme 42)**. Thus upon reacting the bis dibenzylether (173) with the Lewis acid, led to the development of the cobalt stabilised but-2-yne-1,4-dication (174). A double substitution reaction then occurred, in which the nucleophile (168) reacted at carbon atoms 1 and 4 to provide compound (175), in 94% yield.

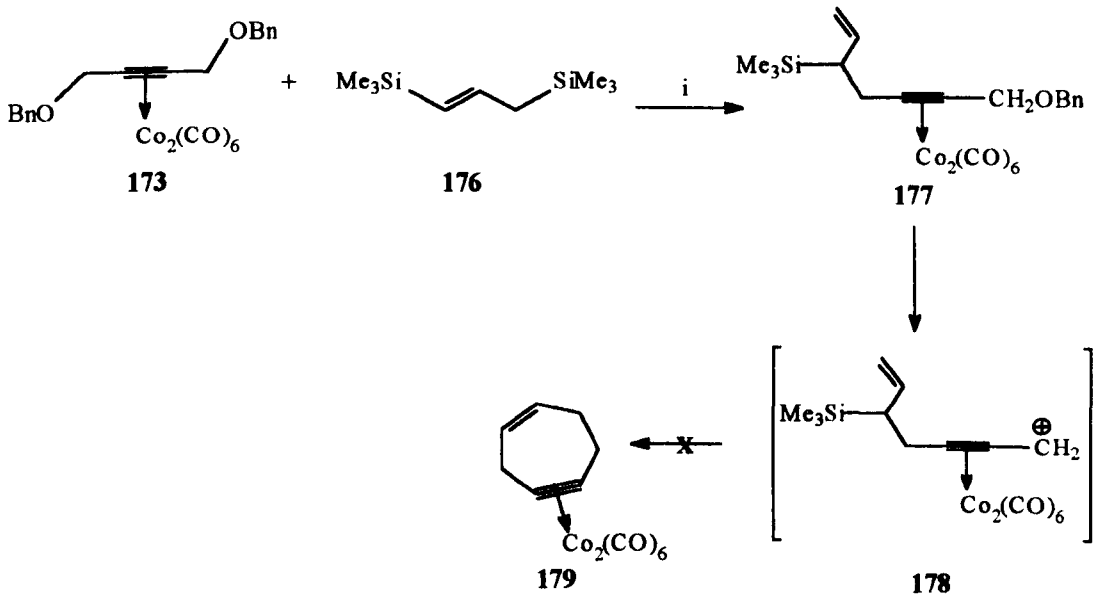



**173** **174** **168** **175**

***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, 0°C.

**(Scheme 42)**

Using a variant of this methodology, Takano then attempted the possible synthesis of seven membered rings **(Scheme 43)**.




**173** **176** **177** **178** **179**

***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, 0°C.

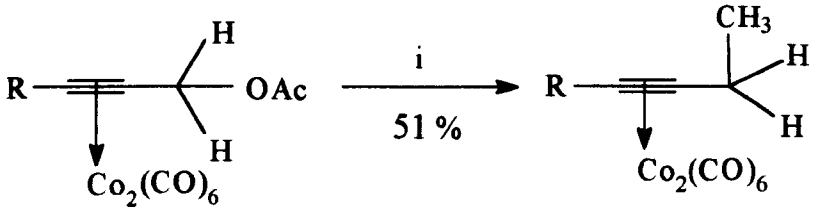
**(Scheme 43)**

Following treatment of (173) with (E)-1,3-bis(trimethylsilyl)propene (176), led to the required precursor (177), in which subsequent reaction with further Lewis acid, gave the cobalt complexed stabilised cation (178). Cyclisation of this cation was then met with no success. Instead of achieving the desired compound (179), a complex mixture of mono- and disubstituted products were obtained.

## 2.4.5 Organometallic Nucleophiles

To broaden the use of the propargyl complex cation, in carbon-carbon bond formation, Nicholas investigated the potential of organomethyl compounds as possible nucleophiles in propargyl/alkyl coupling reactions.[69] After conducting a series of experiments to establish the most efficient methylating agent, it was found that trimethylaluminium was the best.

Thus upon reacting the propargyl acetate (180) with the organometallic nucleophile, a rapid reaction took place, whereupon the desired methylated product (181) was isolated in 51% yield **(Scheme 44)**.



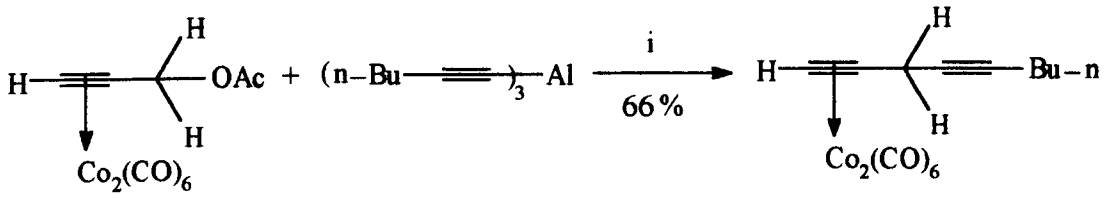

**180** **181**

where R=H

***Reagents and conditions*** i, $(CH_3)_3Al$, DCM, -78°C.

**(Scheme 44)**

The methodology was later extended for the synthesis of a range of 1,4-diynes **(Scheme 45)**.[70] For example, using the propargyl acetate complex (182), it was found that the reaction occurred with ease upon the addition of the trialkynyl aluminium (183) to form the corresponding 1,4-diyne complex (184), in a moderate 66% yield.




**182** **183** **184**

***Reagents and conditions*** i, DCM, 0°C.

**(Scheme 45)**

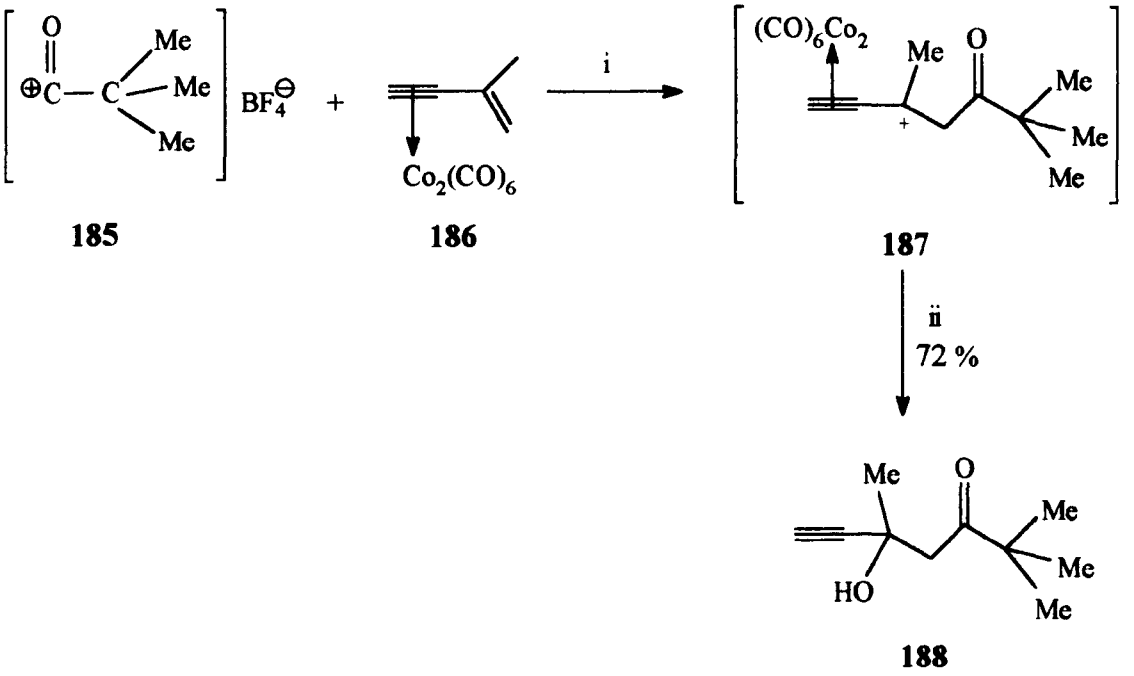
## 2.5 Reaction with Non-Carbon Centered Nucleophiles

Although less studied, non-carbon nucleophiles have been used in the Nicholas reaction. In particular species containing oxygen and nitrogen have shown to be actively involved.

### 2.5.1 Reaction with Oxygen, Nitrogen and Hydride

Smit and Caple[71] have extensively shown the use of oxygen-centered nucleophiles, (such as $^{-}OH$, $^{-}OMe$), to intercept cations generated by the addition of electrophiles to 1,3-enyne cobalt derivatives **(Scheme 46)**.

Thus addition of the eletrophile, (185), to the cobalt complexed isopropenylacetylene (186), generated the cation (187). Nucleophilic attack by a hydroxyl group then proceeded to afford, after demetallation, the adduct (188) in 72% yield. The synthesis of such adducts was seen to open a new method for the formation of isoprenes.



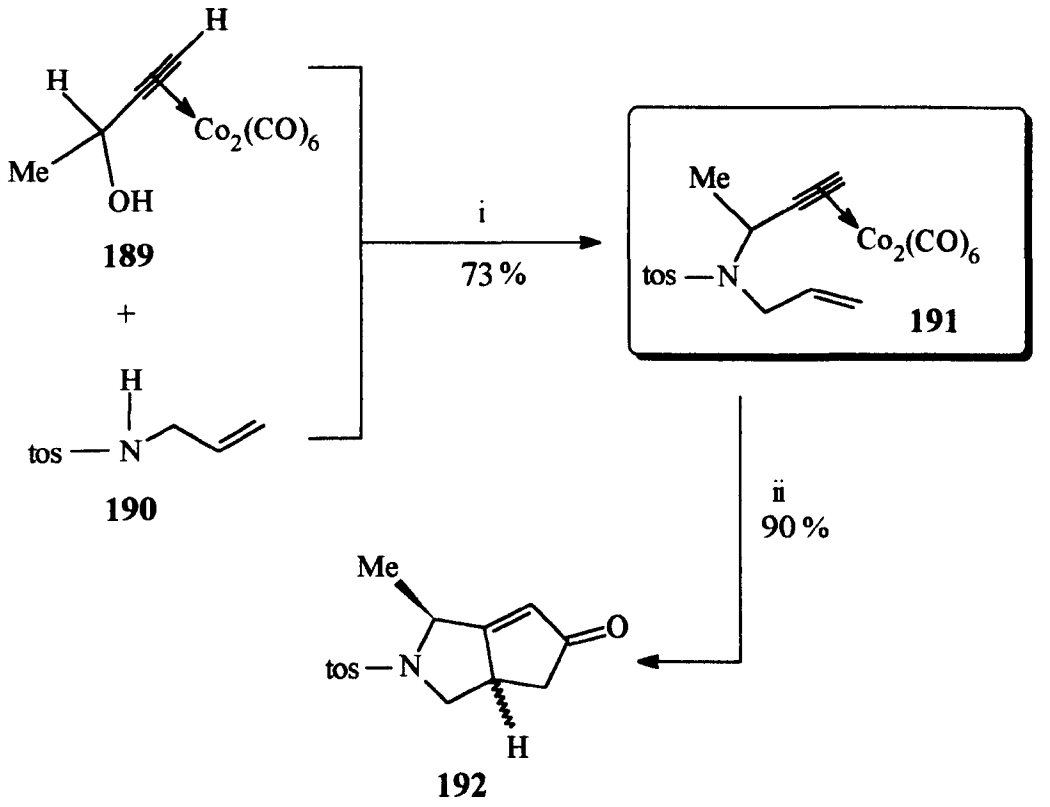

185 186 187 188

***Reagents and conditions*** i, DCM, 0°C; ii, (a) $H_2O$, 0°C, (b) $Fe(NO_3)_3.9H_2O$, ether, -78°C.

**(Scheme 46)**

The first use of a nitrogen nucleophile in a Nicholas reaction was reported by Joeng.[72] In a one pot procedure, an *inter*molecular Nicholas reaction coupled, with a Pauson-Khand reaction was to be used for the synthesis of the 3-azabicyclo[3:3:0]-oct-5-en-7-one (192). Such compounds were seen as useful synthetic intermediates for natural product synthesis.[73] Upon investigating the propargylation reaction of a range of amide functionalities, with the propargyl alcohol-cobalt complex, it was found that the N-tosyl and Cbz groups were efficient as protectors, to conduct propargylation in the presence of the Lewis acid.

This was in contrast to the t-Boc, trifluoroacetamide and benzoyl that formed no propargylated products. An example given is shown **(Scheme 47)**.

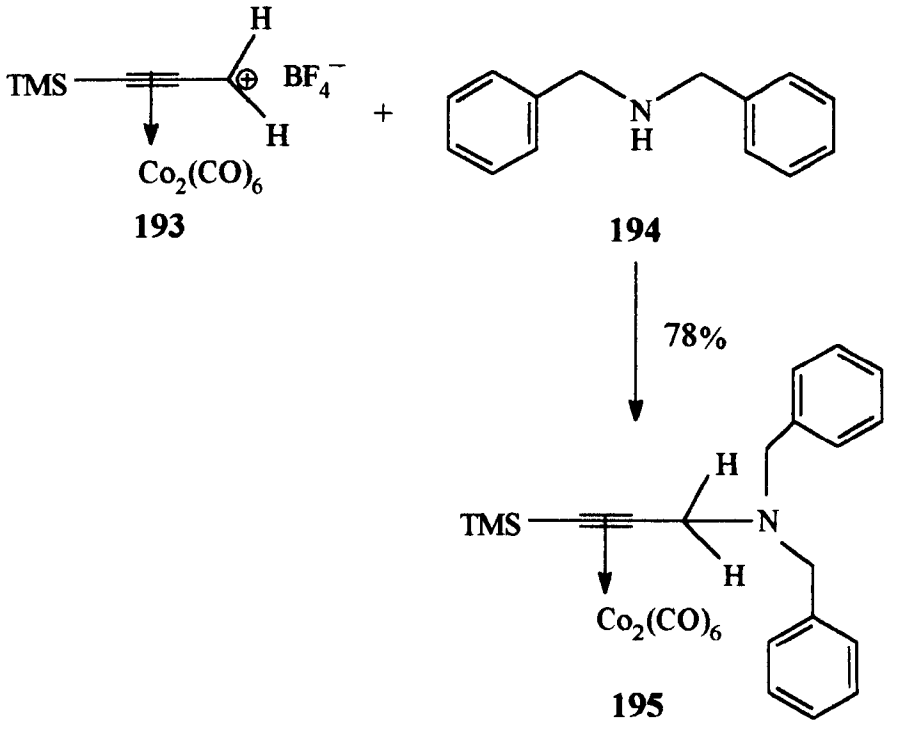



***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, -78°C; ii, triethylamine-N-oxide, $O_2$, DCM, r.t.

**(Scheme 47)**

Thus treatment of the butyn-3-ol cobalt complex (189), with the allyltosylamide (190) gave the enyne (191). Upon quenching this reaction with $Et_3N$, followed by reaction with trimethylamine N-oxide gave the bicyclic compound (192) in 90% yield.

Roth and coworkers[74] have recently developed a simple and efficient procedure for the propargylation of primary and secondary amines by means of the Nicholas cation. The desired tertiary amines were found to be isolated in reasonable to high yields. One example is shown **(Scheme 48)**.



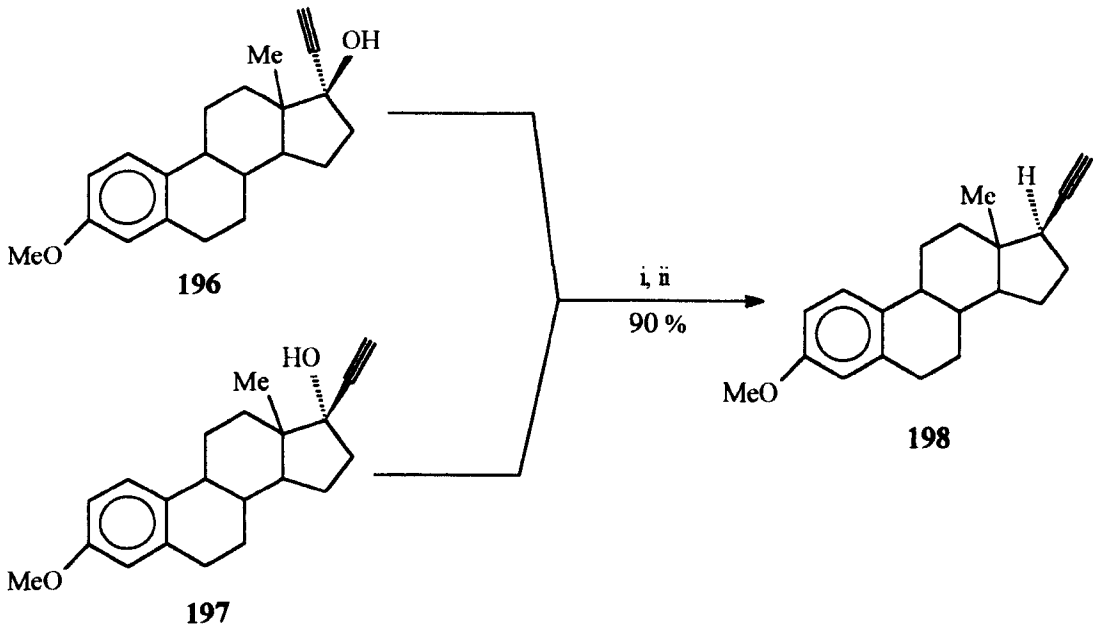

**(Scheme 48)**

Thus treatment of the cobalt complexed propargyl cation (193), with the secondary amine (194), gave the complexed monopropargylated product (195) in 78% yield.

A similar rationale had been previously reported by Roth,[75] in which the Nicholas cation was seen to react with enamines.

Finally, the use of the (propargyl) $Co_2(CO)_6$ cations have also been shown in reduction processes. A useful and interesting example was given by Nicholas and Siegel[76] that involves the epimeric mestranols (196) and (197) **(Scheme 49)**. Upon sequential subjection of either α-ethynyl derivative (196) or β-ethynyl species (197), to complexation, reduction, and demetallation, gave stereoselectively the same β-ethynyl product (198). The result was explained by the formation of a common metal

stabilised carbocation intermediate, that was quenched by $BH_4^-$ from the less hindered α-face.




***Reagents and conditions*** i, (a) $Co_2(CO)_8$, DCM, r.t, (b) $NaBH_4$, TFA, 0°C; ii, $Fe(NO_3)_3.9H_2O$, DCM.

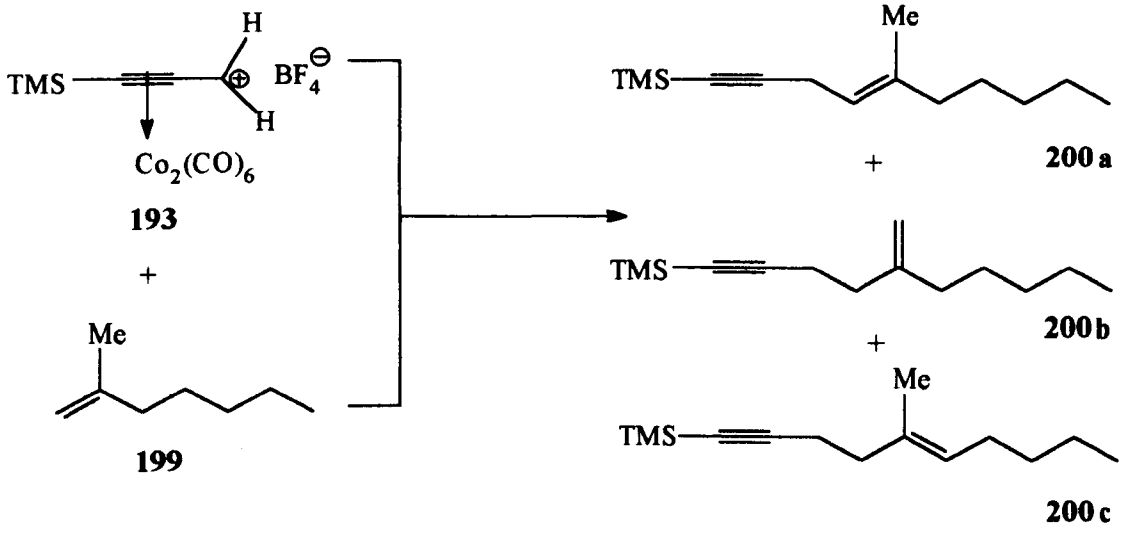
**(Scheme 49)**

The stereoselective conversion to the 17-β-ethynyl-17-deoxy derivatives provided a novel and effective route to these inaccessible compounds[77] that are precursors to many 17-β-side chain steroids.

## 2.6 Non-Activated Carbon Nucleophiles

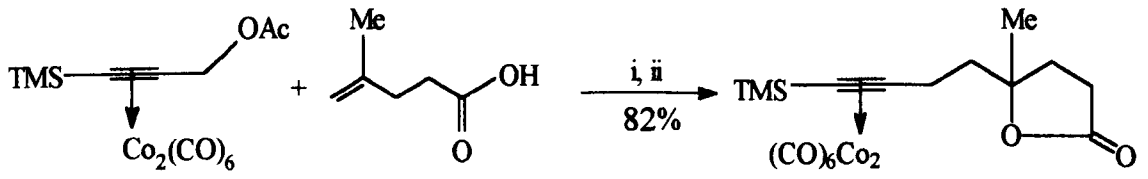
Since the discovery of the Nicholas reaction, most carbon nucleophiles that have been used are activated. This is clearly seen from the previous examples that were discussed. It was not until recently that the first appearance of a non-activated nucleophile appeared in an intermolecular Nicholas reaction.

Krafft[78] showed that although a mixture of regioisomeric products (200a, 200b and 200c) were formed, following demetallation, a simple pendant alkene (199) was sufficient to quench the Nicholas cation (193) **(Scheme 50)**.




**(Scheme 50)**

This rationale was then applied for the synthesis of a series of lactones.[78] One example is illustrated in **(Scheme 51)**.




**201** **202** **203**

***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, 0°C; ii, CAN, ether, 0°C.

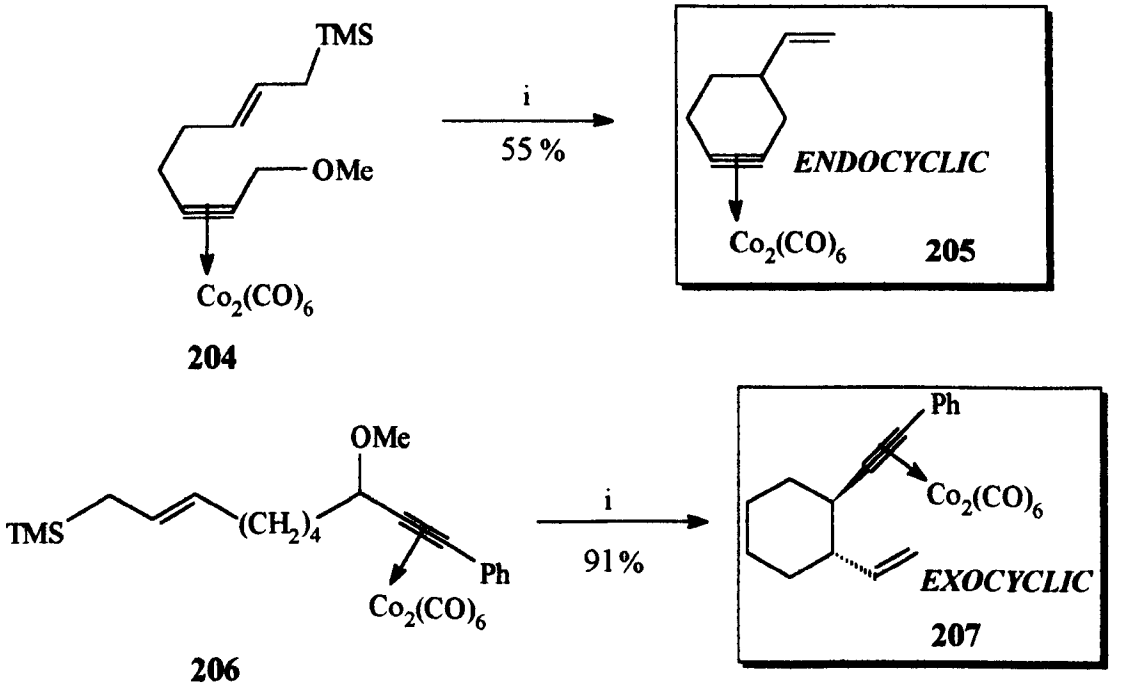
**(Scheme 51)**

Thus upon treatment of cobalt complex (201), with the alkene (202), in the presence of Lewis acid, gave the lactone (203) in 82% yield, upon decomplexation.

The possibility of simple alkenes acting as adequate nucleophiles has been extensively investigated within our research group involving the *intra*molecular addition. This will be discussed in part under *intra*molecular Nicholas reactions and more fully in Chapter 3, since the methodology used in this project to form bridged ring systems has involved this type of nucleophile.

## 2.7 *Intra*molecular Nicholas Reaction

An *intra*molecular Nicholas reaction may be performed readily using the same principles as shown in the *inter*molecular mode. For example, Schreiber[63b] used the allylsilanes (204) and (206) to produce cyclic compounds (205) and (207), in reasonable to high yields. In these reactions it was found that the alkyne group could either be contained within the ring (endocyclic) or allocated outside (exocyclic) **(Scheme 52)**.

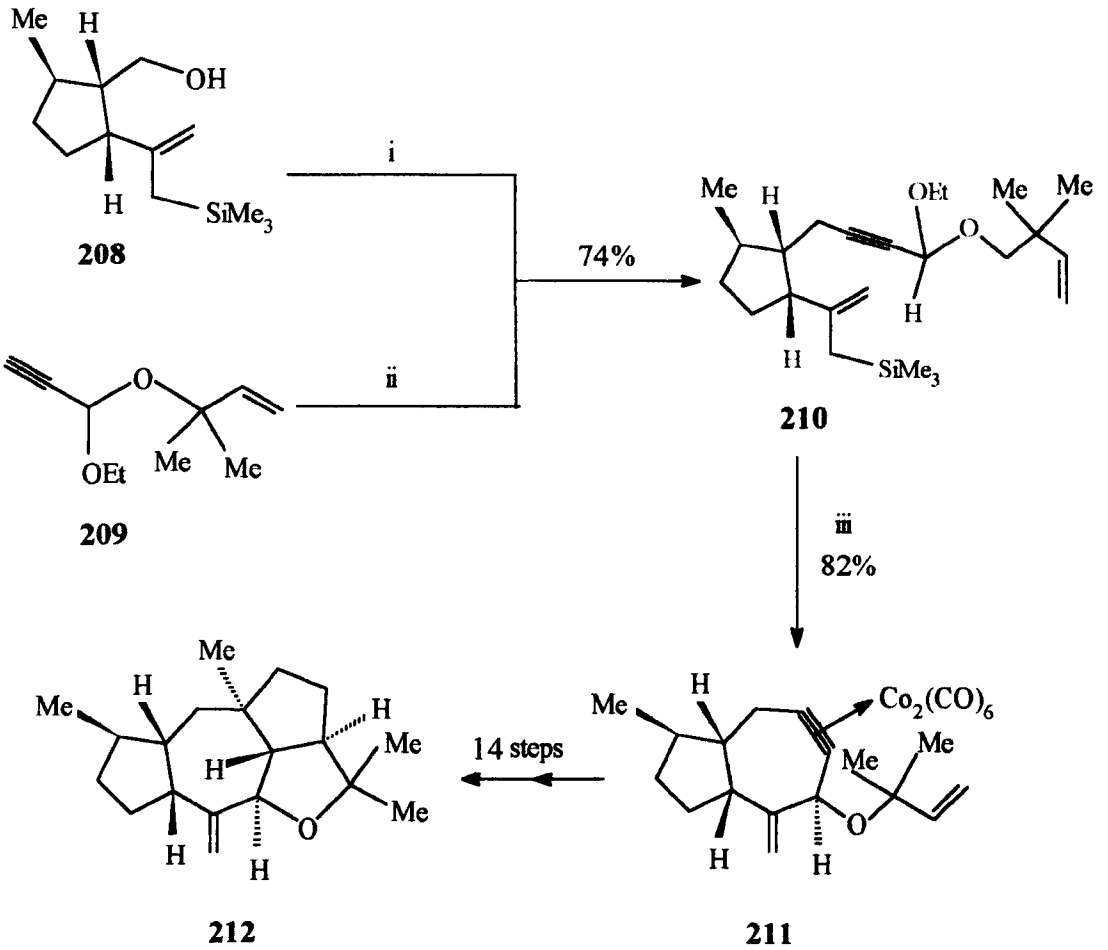



***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, 0°C.

**(Scheme 52)**

The use of the *endo* mode ring closure of allylsilanes was later exploited as key precursors in the synthesis of many natural products.[63b] One example is the formation of diterpene epoxydictoymene (212) **(Scheme 53)**.[79]

In this reaction, the allylsilane (208) was first reacted with the lithium anion derivative of (209), to provide the intermediate precursor (210) in 74% yield.

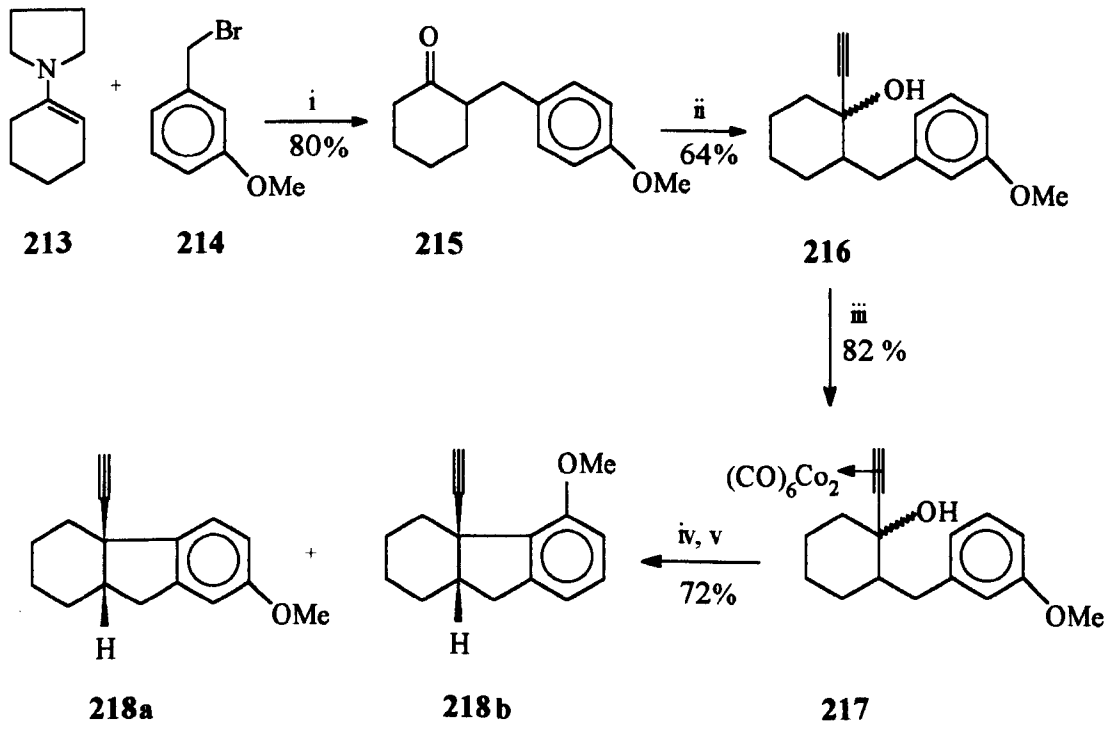



***Reagents and conditions*** i, 4-methyl-2,6-di-tert-butylpyridine, $Tf_2O$, DCM; ii, n-BuLi, THF, HMPA, -78°C; iii, $Co_2(CO)_8$, $Me_3SiOTf$, $Et_2O$.

**(Scheme 53)**

Reaction of this compound with dicobalt octacarbonyl, followed by treatment with the Lewis acid, gave the required 5,7 fused ring system (211) that was isolated in an efficient 82% yield. Further elaboration of this compound *via* 14 synthetic steps, furnished the desired natural product (212).

With the aim of developing a novel methodology for the preparation of alkaloids, Grove[80], and coworkers, exploited the use of electron rich aromatic compound to produce tricyclic ring systems (218a) and (218b) **(Scheme 54)**.

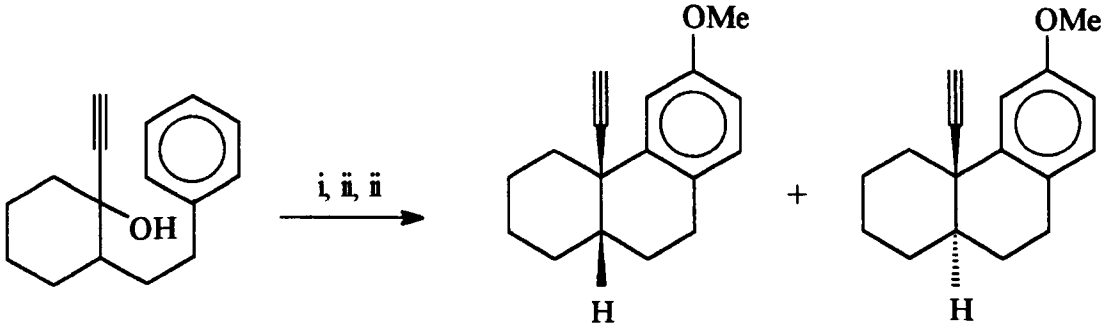



***Reagents and conditions*** i, (a) dioxane, ht; (b) HOAc, ht; ii, $HC{\equiv}C^{-}Na^{+}$, THF; iii, $Co_2(CO)_8$, DCM; iv, $BF_3.OEt_2$, DCM, 0°C; v, $Fe(NO_3)_3.9H_2O$, MeOH.

**(Scheme 54)**

Thus commencing with the enamine (213), the methylene link was obtained upon its reaction with the benzylic halide (214), to provide the ketone (215) in 80% yield. Conversion of this compound to the required propargyl alcohol (216) was next achieved, by the treatment with sodium acetylide. This provided a 7:3 mixture of diastereomers, in a reasonable yield. The corresponding complex was then obtained upon reacting the alcohol with dicobalt octacarbonyl to afford (217). Treatment of this complex with boron trifluoride etherate, followed by demetallation using iron (III) nitrate nonahydrate, gave the fused ring products (218a) and (218b), in a ratio of 85:15. Upon conducting $^1H$ nmr studies, it was revealed that the ring fused products were *cis* with respect to the 6/5 ring junction, thus showing the reaction to be stereoconvergent.

A similar methodology was later used by Grove for the synthesis of the A, B, C ring of morphinan analogues **(Scheme 55)**.[81]




**219** **220a** **220b**

***Reagents and conditions*** i, $Co_2(CO)_8$, ether, r.t; ii, $BF_3.OEt_2$, DCM, 0°C; iii, $Fe(NO_3)_3.9H_2O$, MeOH, 0°C.

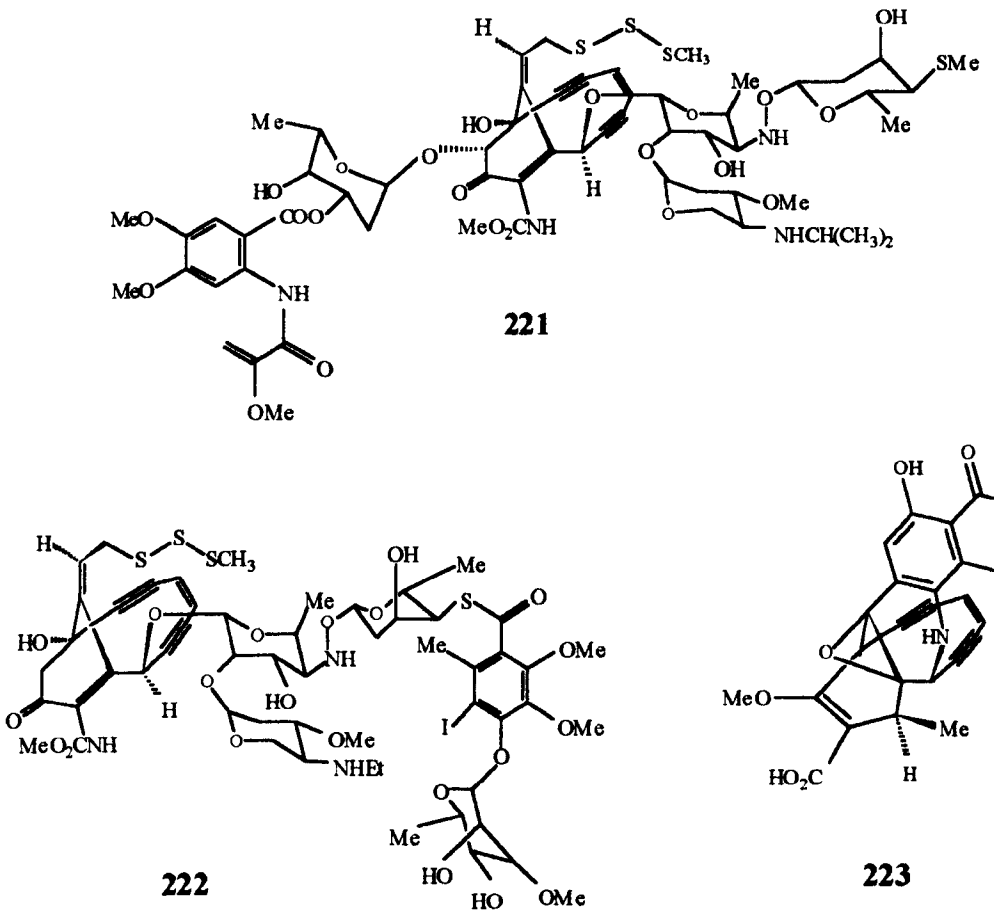
**(Scheme 55)**

Thus treatment of compound (219) with octacarbonyl dicobalt, followed by the addition of the Lewis acid, boron trifluoride diethyl etherate at 0°C, gave after

decomplexation, the desired ethynyloctahydrophenanthrenes (220a) and (220b). These compounds were obtained as a 10:1 mixture of diastereoisomers, in 51% yield.

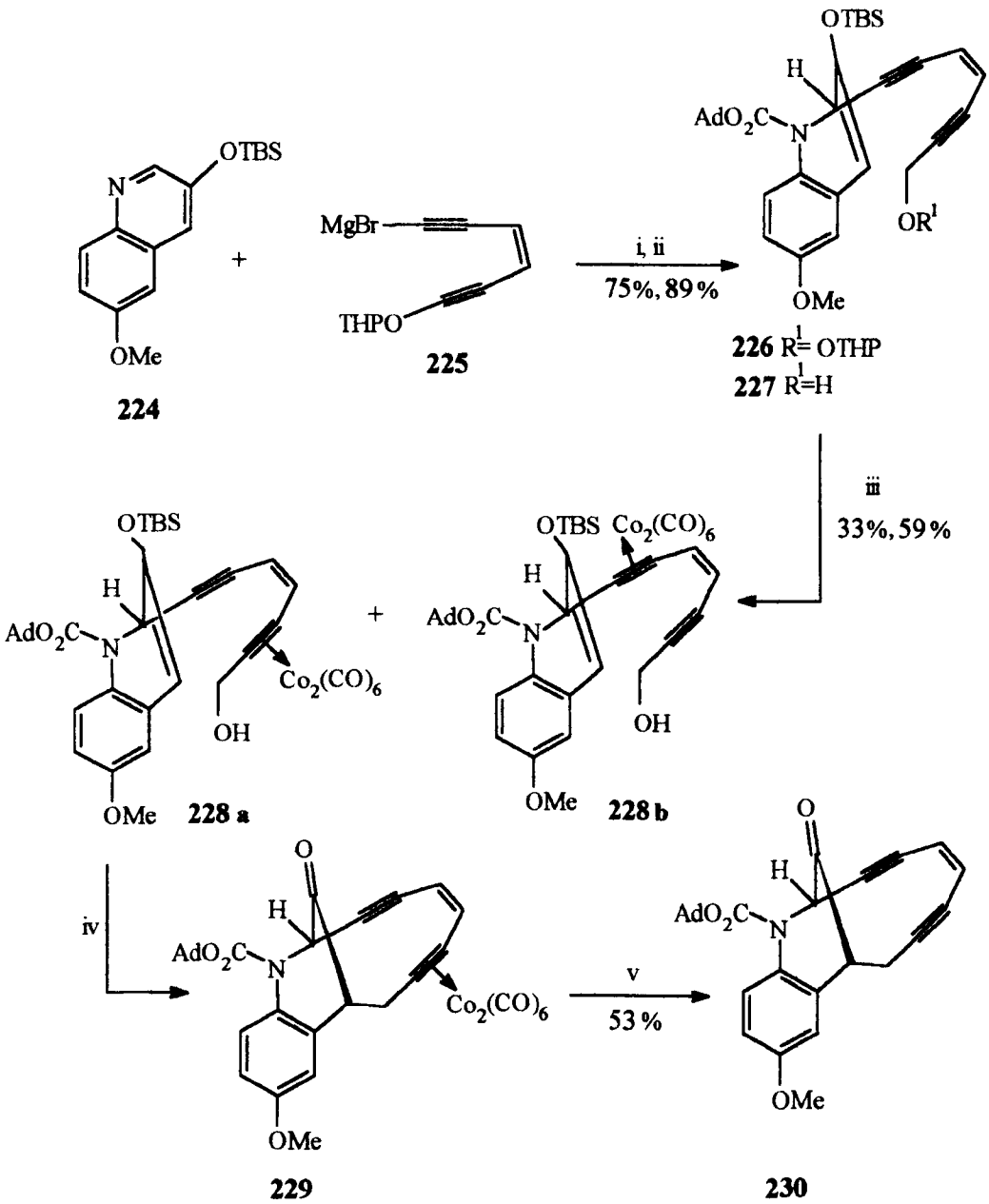
It was found that upon repeating the reaction at -78°C, the compound (220a) was achieved as the sole product in 58% yield.

Recently Magnus[82] reported a general strategy for the construction of the structural core of diynene natural products. These molecules exhibit potent antitumour and/or antimicrobial activity.[83] Using an *intra*molecular Nicholas reaction as the key cyclisation step, the successful synthesis of the nucleus contained in the antibiotics esperamicin (221) and calicheamicin (222) were achieved **(Figure 15)**.




**(Figure 15)**

One of the latest antitumour antibiotics to be added to this list is dynemicin (223).[84] Using 5 efficient synthetic steps, the azabicyclo[7.3.1]enediyne (230) was synthesised **(Scheme 56)**.

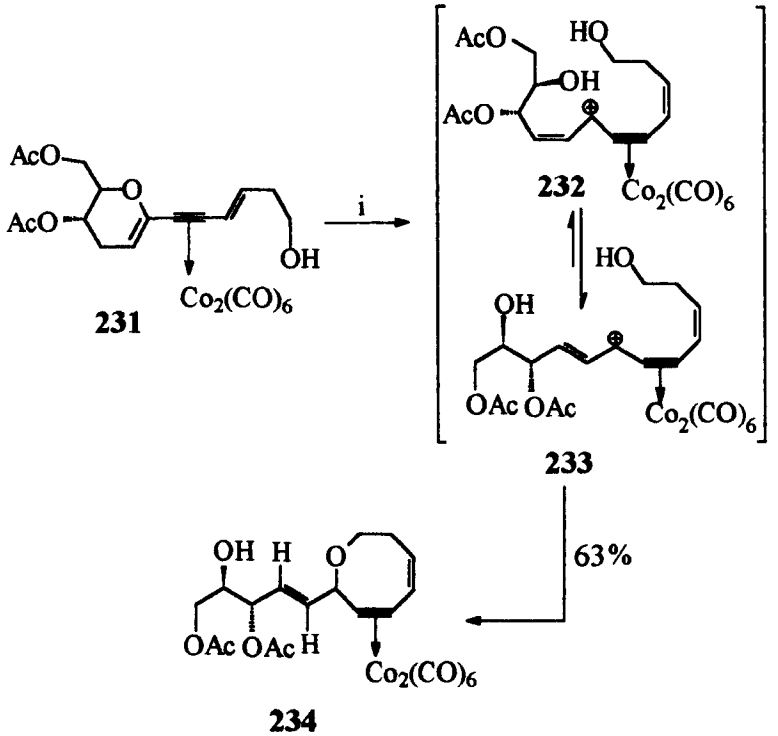



***Reagents and conditions*** i, $AdO_2CCl$; ii, pyridinium tosylate, EtOH; iii, $Co_2(CO)_8$, THF, r.t; iv, $Tf_2O$-2-nitropropane, 2,6-di-*tert*-butyl-4-methylpyridine, -10°C; v, $Ce(NH_4)_2(NO_3)_6$, acetone, 0°C.

**(Scheme 56)**

Treatment of the quinoline (224) with the enediyne Grignard derivative (225), in the presence of 1-adamantyl chloroformate (an amine protecting group), gave the dihydroquinoline (226) in 75% yield. Deprotection of the THP ether, next provided (227), whereupon subsequent complexation of this compound, with dicobalt octacarbonyl, gave the regioisomers (228a) and (228b) in 33% and 59% yield respectively. This was in contrast to that found previously, in which the less sterically hindered acetylene was exclusively converted into the dicobalt hexacarbonyl complex. Upon separating these isomers by chromatography over silica gel, treatment of the cobalt adduct (228a), with triflic anhydride at -10°C for 30 minutes, gave the cyclised product (229), in which direct oxidative decomplexation using CAN, produced the desired enediyne (230), in an efficient 53% yield.

Continuing the theme of the Nicholas reaction, Isobe[85] used an oxygen centred nucleophile to form the challenging eight membered ring that is found in compound (234) **(Scheme 57)**.

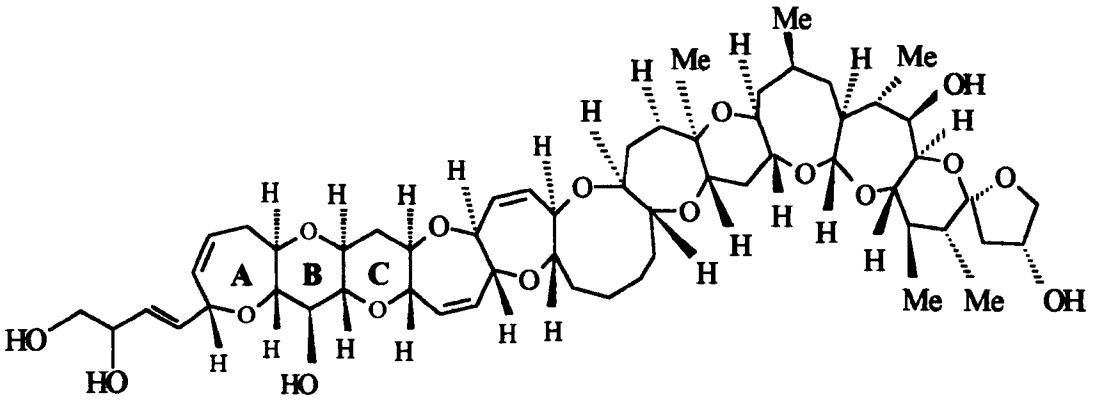



***Reagents and conditions*** i, *p*-TSA, DCM.

**(Scheme 57)**

Thus treatment of the enyne (231) with *p*TSA provided the *trans* allylic cation (233) as the major isomer, that readily cyclised to afford, following decomplexation, the cyclised product (234) in 63% yield.

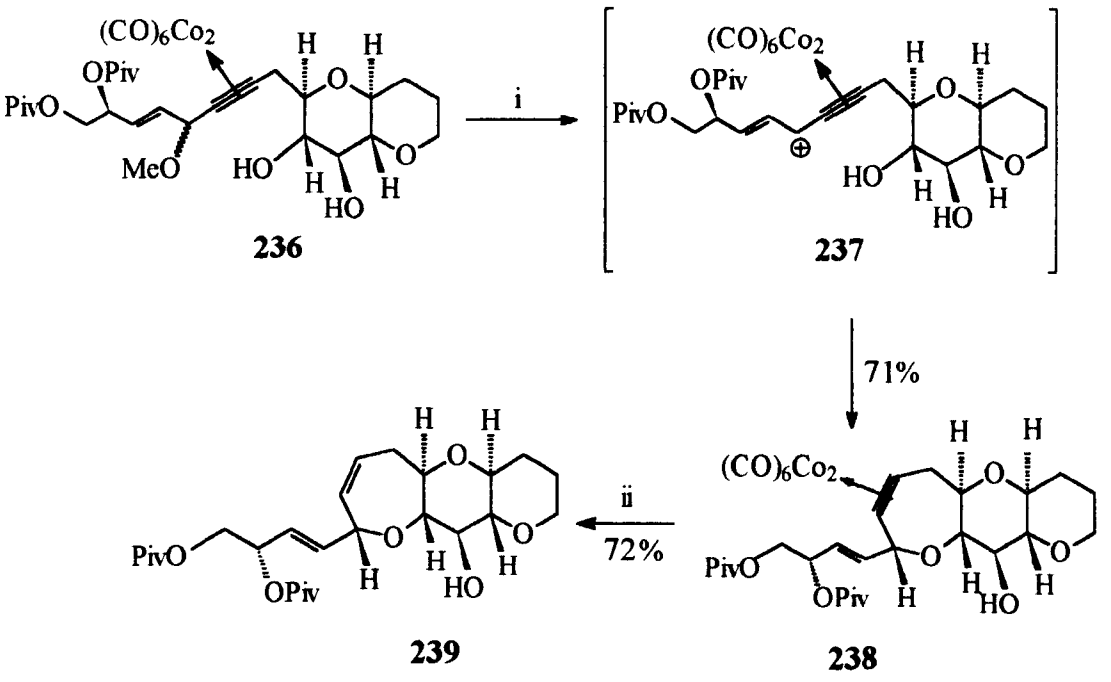
Following a similar rationale, in his most recent report, Isobe[86] synthesised the ABC fragment of ciguatoxin[87] (235) **(Figure 16)**, that is obtained from the moray eel *Gymmothorax javanicus*.




**235**

**(Figure 16)**

Thus from the crucial intermediate (236), treatment of this compound with boron trifluoride diethyl etherate, gave *via* the intermediate cation (237), the tricyclic product (238) in 71% yield **(Scheme 58)**. Following decomplexation of (238) by hydrogenation in the presence of Wilkinson catalyst, afforded the ABC ring (239) of the natural product (235).

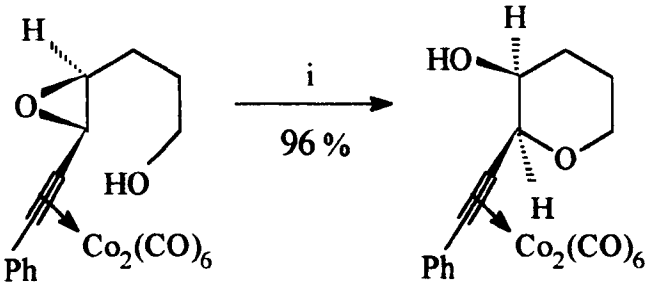



***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, 0°C; ii, $H_2$(100kg/cm$^2$), cat. $RhCl(PPh_3)_3$, PhH, 65°C.

**(Scheme 58)**

The use of oxygen centred nucleophiles was also reported in the work of Hanaoka.[88] Using α-acetylenic epoxides as key intermediates, facile ring closure was achieved to form the required product. For example, exposure of the epoxide (240), to a catalytic amount of $BF_3.OEt_2$ at 0°C, gave the desired compound (241) in 65% yield **(Scheme 59)**.

An important feature of this reaction was that ring construction was occurring with complete retention of configuration at the propynyl position.




**240** **241**

***Reagents and conditions*** i, $BF_3.OEt_2$, DCM, 0°C.

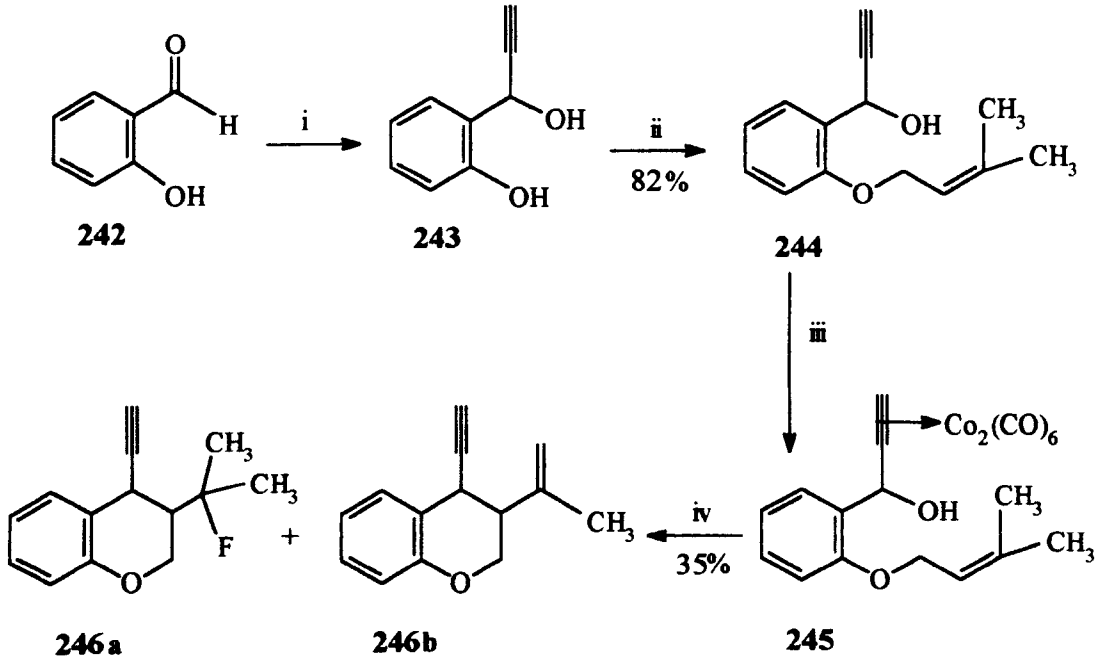
**(Scheme 59)**

Finally many examples of the *intra*molecular Nicholas reaction has been reported within our research group. With the successful synthesis of a diverse array of cyclic[89a] and potential fused bicyclic ring systems,[89b] our recent investigations have embarked upon developing the use of unactivated alkenes in the Nicholas reaction. As mentioned in section **2.6**, the use of such nucleophiles have received very little attention in the literature.

Recently, Tyrrell[90] reported the first example of an *intra*molecular cyclisation reaction, in which the key cyclisation step involved attack of a dicobalt hexacarbonyl complexed propargyl cation with a trisubstituted alkene, to afford the novel benzopyrans (246a) and (246b) **(Scheme 60)**.

Thus commencing with an inexpensive, readily available salicaldehyde (242), treatment of this compound with ethynylmagnesium bromide at 0°C, gave the propargyl alcohol (243) in a quantitative yield. Upon reacting this product with 4-bromo-2-methylbut-2-ene, gave the precursor (244) in 82% yield. Subsequent treatment of (244), with octacarbonyl dicobalt, led to a quantitative conversion to the dicobalt hexacarbonyl complex (245). Upon the reaction of (245) with tetrafluoroboric acid, followed by

decomplexation using ceric ammonium nitrate, furnished the benzopyrans (246a) and (246b) in 35% yield, with a ratio of 1:1 (from 244).

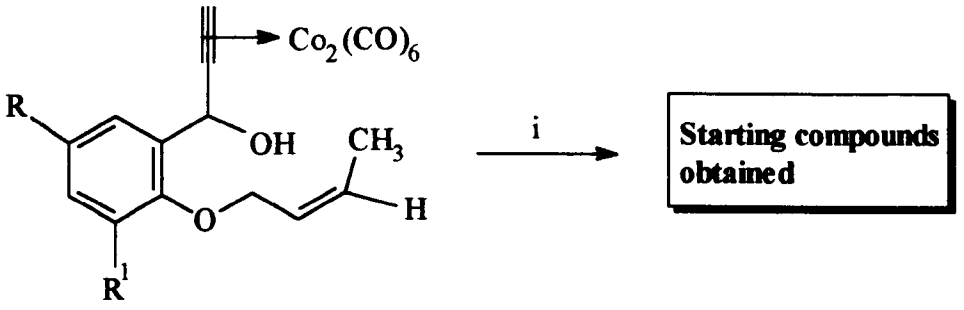



***Reagents and conditions*:** i. ethynylmagnesium bromide; ii, $K_2CO_3$, KI, DMF, 4-bromo-2-methylbut-2-ene; iii, $Co_2(CO)_8$, hexane, r.t; iv, $HBF_4.Et_2O$, $(NH_4)_2Ce(NO_3)_6$, acetone, 0°C.

**(Scheme 60)**

The stereochemical relationship of the ring methine protons were found to be *trans* for both compounds. This reaction was later optimised in which the fluorinated compound (246a) was isolated as the major product, in a one pot procedure.

Upon conducting extensive studies, it was found that the minimum requirement to quench the Nicholas cation was a trisubstituted compound for this reaction, as attempts to effect cyclisation of (247a) and (247b), failed using analogous conditions.




**247a** R=$NO_2$, $R^1$=H

**247b** R=H, $R^1$=H

***Reagents and conditions*** i, $HBF_4.OEt_2$, 0°C, acetone.

**(Scheme 61)**

## 2.8 Concluding Remarks

To conclude this chapter, it can be said that the Nicholas reaction is a versatile method that allows the formation of carbon-carbon and carbon-heteroatom bonds. This can be clearly seen from the variety of nucleophiles discussed. The major advantage of this method are that no propargylic/allenic rearrangement reaction occurs, a problem that has plagued most conventional propargylation reactions.

Thus, it is a reaction that is efficient, and in addition, entirely regioselective and therefore has been, on numerous occasions, employed for the synthesis of natural products.

# Chapter Three

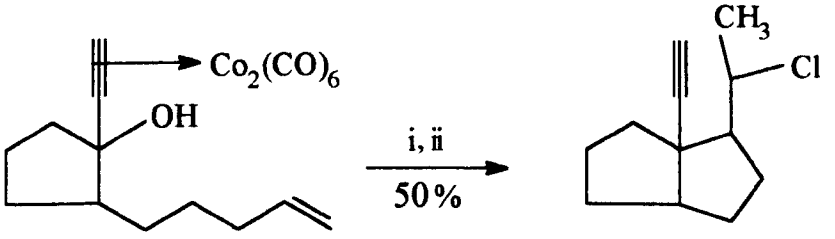
## Results and Discussion

# 3.0 Results and Discussion

## 3.1 Introduction

Part of the ongoing studies into the Nicholas reaction being conducted at Kingston University have been to investigate the nature of the alkenyl group that quenches the dicobalt stabilised cation. To further this aim and to extend these investigations, the methodology was developed for the synthesis of bridged carbocyclic ring systems, that are commonly observed as major components in the framework of many natural products.

Previous work within the research group[89b] showed that the dicobalt hexacarbonyl complexed propynyl alcohol (248) **(Scheme 62)** underwent an intramolecular Nicholas reaction, in the presence of excess titanium (IV) chloride, to afford the 1,2-difunctionalised bicyclo[3:3:0]octane (249) in 50% yield.




**248** **249**

***Reagents and conditions*** i. $TiCl_4$, DCM; ii. $Ce(SO_4)_2$, IMS, $H_2O$.

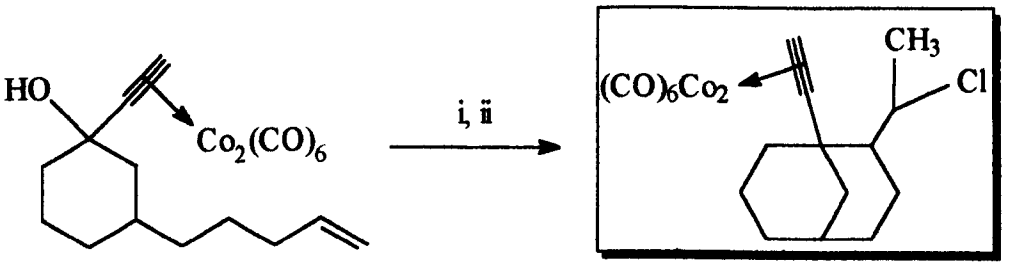
**(Scheme 62)**

On the basis of this observation, it became of interest to investigate the general nature of this reaction. Of particular importance was the fact that this was the first example of an *intra*molecular cyclisation reaction, of this kind, involving an unactivated alkene.

This had hitherto not been observed in the literature of relation to the Nicholas reaction. Furthermore, the incorporation of a chloride ion into the product, further implied that the mechanism involved a novel variant of the Nicholas reaction. Thus herein we describe model studies completed for the development of the bridged ring systems based on this novel annulation reaction.

## 3.2 Synthesis of Bicyclo[3.3.1]nonane

The strategy employed for the synthesis of bridged bicyclic compounds is shown **(Scheme 63).** In this approach the dicobalt hexacarbonyl complexed propynal alcohol (250) was strategically positioned six carbon atoms away from the pendant alkenyl group. By analogy with previous results treatment of (250) with a Lewis acid, should effect the cyclisation reaction to provide the 1,2-difunctionalised bicyclo[3.3.1]nonane (251) ring system **(Scheme 63)**. Success in this strategy would complement the studies into benzopyran syntheses discussed previously.

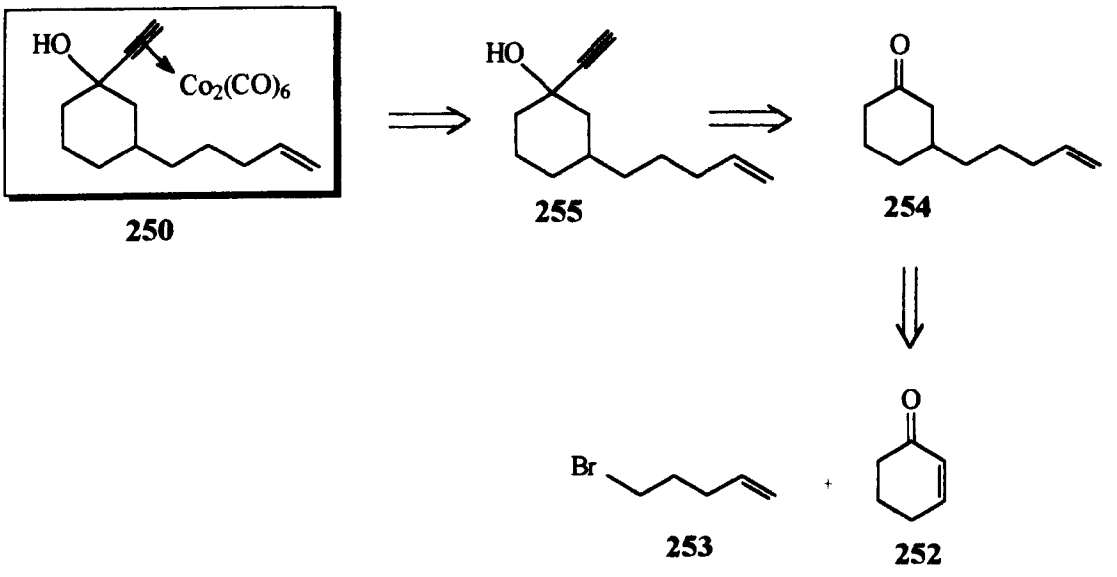



**250** **251**

***Reagents and conditions*** i, $TiCl_4$, DCM, 0°C; ii, $Ce(SO_4)_2$, IMS, $H_2O$.

**(Scheme 63)**

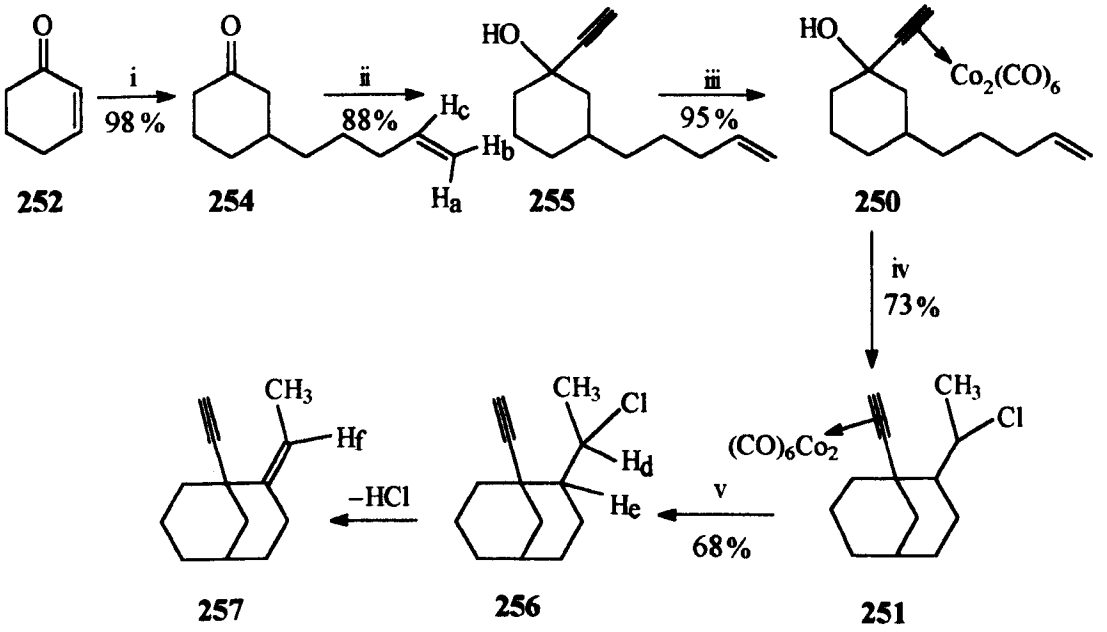
Retrosynthetic[91] analysis performed upon the propargyl alcohol (255), suggested that this cyclisation precursor (250) may be synthesised in three efficient steps from cyclohex-2-en-1-one (252) **(Figure 17)**.




**(Figure 17)**

These preliminary studies commenced with a general investigation into the cyclisation reaction itself. Thus conjugate addition of the Grignard reagent derived from 5-bromo-1-pentene (253) to cyclohex-2-en-1-one (252), provided 3-(4-pentenyl)-cyclohexan-1-one (254) in 98% yield **(Scheme 64)**. Literature evidence[92] suggests that in the presence of trimethylchlorosilane and HMPA, a cuprate 1,4- addition would be favoured over the 1,2 addition reaction. Examination of the relevant part of the $^1H$ NMR spectrum, was found to be consistent with (254). The terminal vinyl protons $H_a$ and $H_b$ were observed as doublet of multiplets. Thus $H_b$ was observed at a chemical shift of δ4.95 ppm, $J_{vic}$=10Hz and $J_{gem}$ 2Hz, plus finer allylic couplings and $H_a$ was observed at δ4.99 ppm as a doublet of multiplets, $J_{vic}$=18Hz, $J_{gem}$ 2Hz, plus fine allylic coupling. The proton, $H_c$, appeared as a multiplet at a chemical shift δ5.80 ppm. The $^{13}C$ NMR spectrum clearly displayed all 13 resonances with the carbonyl carbon atom at δ211.82 ppm and the alkenyl carbon atoms as δ114.55 and 138.52 ppm.

Next, a 1,2-addition reaction was performed upon compound (254) using ethynylmagnesium bromide to provide the propargyl alcohol (255), as a mixture of separable diastereoisomers in a ratio of 4:1. Careful flash chromatography with silica provided the major isomer which was isolated as a pale yellow oil in 88% yield. The presence of an alkyne proton was clearly observable in the $^1H$ NMR spectrum, as a singlet at δ2.48 ppm. The resonance for the hydroxyl group was found to be amongst the overlapping signal that was attributed to the $CH_2$ groups. This was determined by performing a $D_2O$ shake, whereupon the integral in the region δ1.99-2.07 ppm, was reduced from 5 protons to displaying the presence of 4 protons.




***Reagents and conditions*** i, 5-bromo-1-pentene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF; iii, $Co_2(CO)_8$, ether; iv, $TiCl_4$, DCM; v, $Ce(SO_4)_2$, MeOH.

**(Scheme 64)**

The subsequent reaction of propargyl alcohol (255), with octacarbonyl dicobalt in ether provided, the vital cyclisation precursor (250) in 95% yield. Upon treatment of the cobalt cluster (250), with titanium (IV) chloride, a rapid *intra*molecular cyclisation step occurred to provide (251), in 73% yield. Analysis of the infra-red spectrum of the

complex (251), revealed a loss of the absorption bands for, =CH and C=C stretch at 3080cm$^{-1}$ and 1641cm$^{-1}$ respectively, compared to the infra-red spectrum of compound (250), as well as loss of a corresponding -OH stretch.

Decomplexation of the dicobalt hexacarbonyl moiety, using ceric (IV) sulphate in methanol, gave a new product (256) in 68% yield, as an inseparable mixture of diastereoisomers in the ratio of 1.2:1, as ascertained by GC-MS.

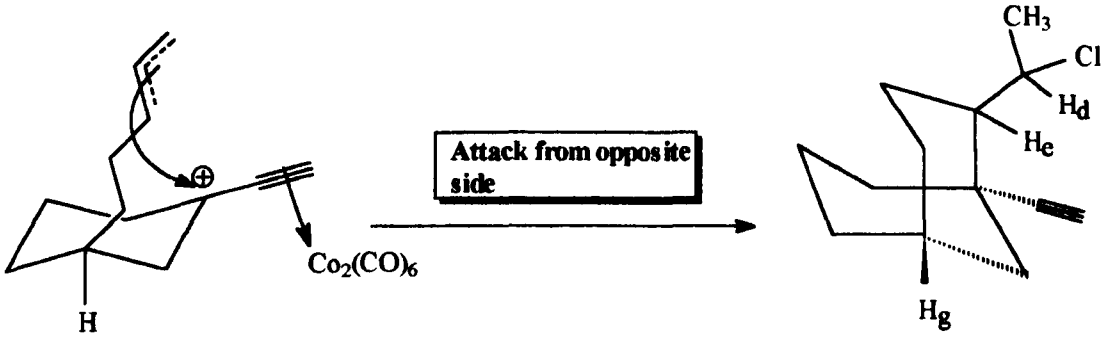
Analysis of the $^1$H NMR spectrum immediately revealed the presence of a methyl group at a chemical shift δ1.49 ppm, as a doublet, $J$=8Hz. The methine proton $H_d$ was found to be a multiplet at a chemical shift of δ4.00-4.06 ppm. The downfield chemical shift was rationalised on the basis of the chlorine atom exerting a deshielding effect upon the proton $H_d$. The proton $H_e$ was found to be in the congested region of the spectrum, that is amongst the methylene hydrogens at δ1.55-1.84 ppm. Due to this an immediate definitive assignment of the stereochemical relationship with regards to the proton $H_d$, was not possible using relevant coupling constants. Thus, the use of molecular modelling experiments and extensive $^1$H NMR studies were later undertaken to obtain a tentative assignment for the relative stereochemistry of these protons. With regards to the corresponding $^{13}$C data, a DEPT experiment showed the methyl carbon atom at a chemical shift δ25.37 ppm and the methine carbon atom for $H_d$ at δ58.72 ppm. Finally, the incorporation of a chlorine atom into the compound was evident from the mass spectrum. Upon examining the mass spectrum, a characteristic splitting pattern of the $M^+$ peak into two signals in the ratio of 3:1 ($^{35}$Cl:$^{37}$Cl) was clearly seen.

It was found that exposure of compound (256) to silica, during flash chromatography, frequently facilitated the loss of HCl to afford a mixture of compound (256) and (257). This was confirmed by $^1$H NMR spectrum, that showed a broad singlet for the proton $H_f$ at 6.17 ppm. In addition the infra-red spectrum also showed the presence of a double bond at 1656cm$^{-1}$. Upon performing gas chromatography analysis, no evidence was shown for the presence of this compound. The separation of this product from the chlorinated compound was found to be impossible at this stage. TLC analysis revealed

that these compounds had a similar $R_f$ value (0.18), and thus were shown as one spot on the plate.

### 3.2.1 A Tentative Assignment of the Relative Stereochemistry of Bicyclo[3.3.1]nonane

It has been shown that *intra*molecular cyclisation of this kind, the nucleophile attacks the stabilised cation from the opposite side to the bulky hexacarbonyl moiety,[80] it was rationalised by analogy therefore, that the bridge, alkynyl group and the ring junction methine proton $H_g$ would be as shown **(Figure 18)**.

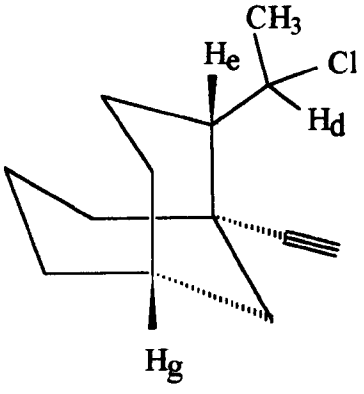



**258** **256a**

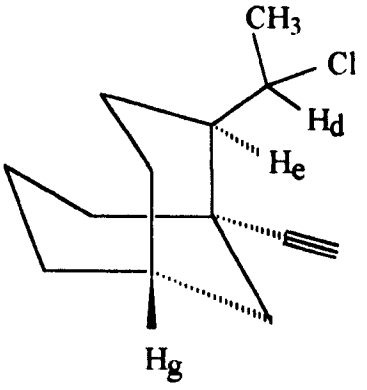
**(Figure 18)**

With this part of the molecule tentatively assigned, the relative stereochemical relationship of methine protons $H_d$ and $H_e$ were then considered. Due to the complexity of the $^1H$ NMR spectrum of compound (256), in terms of overlapping signals, it was found to be difficult to determine the relationship between these methine protons, based upon the magnitude of the coupling constants. Thus with the aid of the molecular modelling program CAche and using a mechanical model of the cycloadduct (256), an attempt has been made to assign the relative stereochemistry of the methine protons $H_d$ and $H_e$.

Using molecular modelling experiments[93] a configurational search was first undertaken, for configurations in which the methine proton, $H_e$, may be depicted as shown (256b) and (256c) **(Figure 19)**.




**256b**

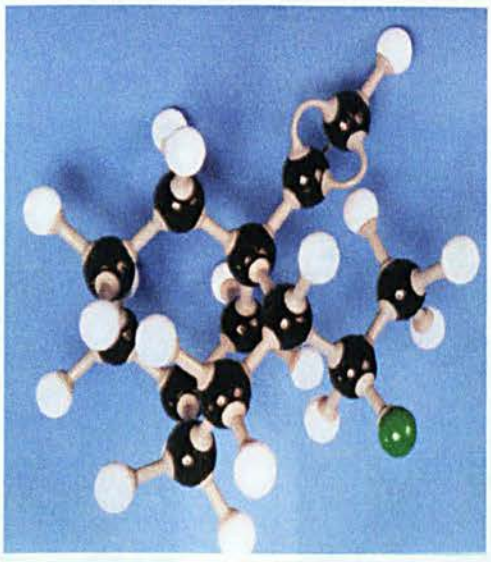



**256c**

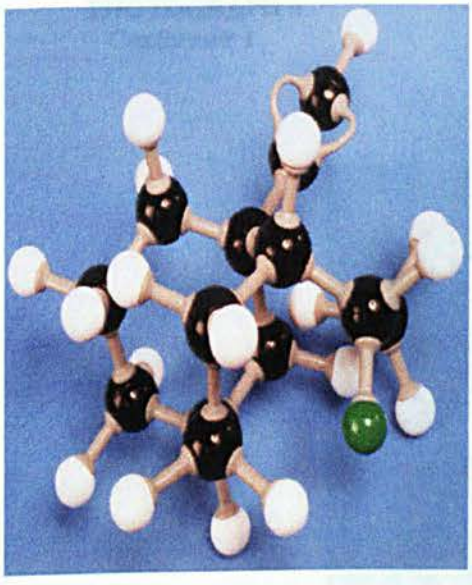
**(Figure 19)**

Analysis of the data from these studies suggested that configuration (256c) was thermodynamically stable by, 6.9 kJ $mol^{-1}$, (using PM3 one label) compared to (256b), suggesting this to be the preferred configuration.

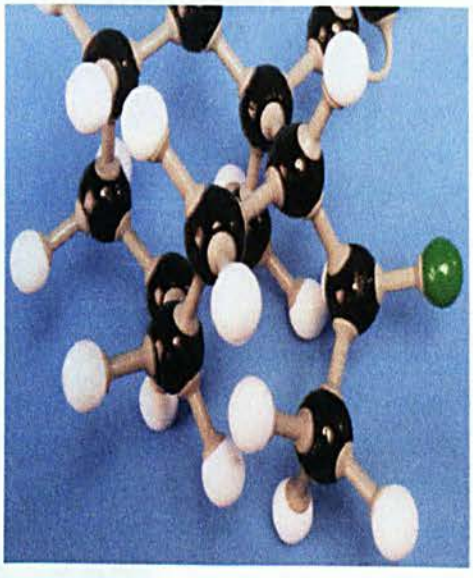
The observed preference can be understood using a ball and stick model constructed for both configurations (256b and 256c). Examining the model with the methine proton, $H_e$, in the orientation of (256b), it was observed that a greater number of steric interactions occurred as the chloroethyl substituent was rotated (photographs1,2 and 3) **(Figure 20)**.



**PHOTOGRAPH 1**
(above) **Steric interactions between the methyl and alkyne substituent**



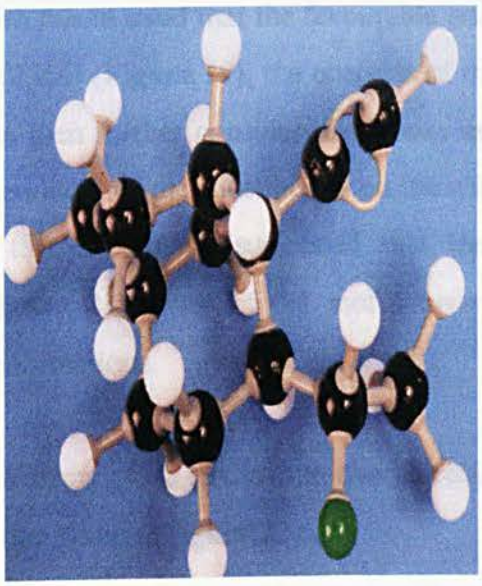
**PHOTOGRAPH 2**
**Steric interactions between the methyl and bridgehead**



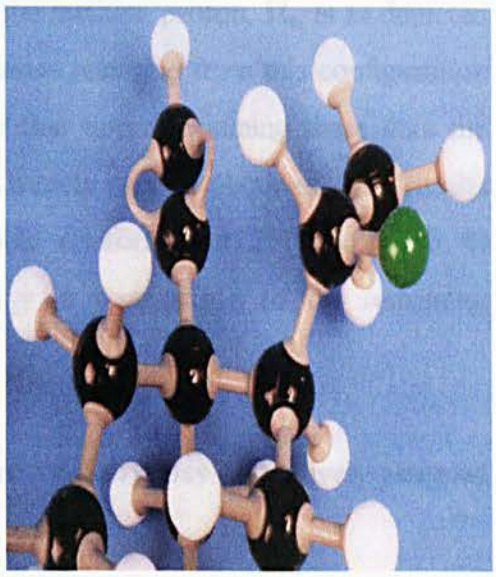
**PHOTOGRAPH 3**
**Severe steric interactions between the methyl and methylene protons**

**(Figure 20)**

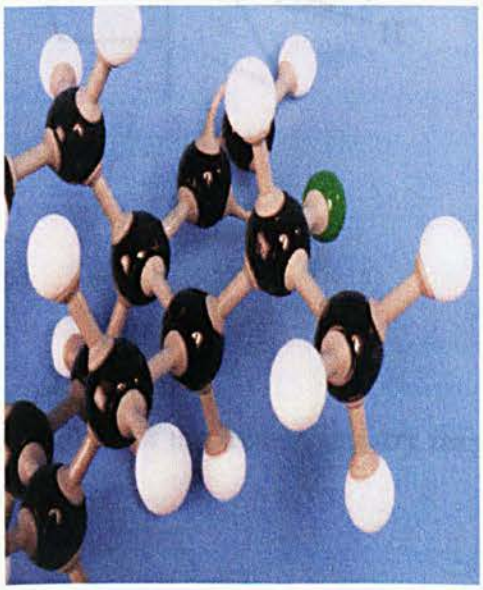
This was in contrast to 256c in which the methine proton, $H_e$, in this orientation showed less unfavourable steric interactions (photographs 4,5 and 6) **(Figure 21)**.



**PHOTOGRAPH 4**
**Conformer 1**



**PHOTOGRAPH 5**
**Conformer 2**



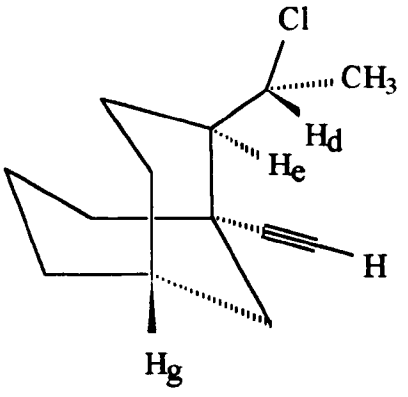
**PHOTOGRAPH 6**
**Conformer 3**

**(Figure 21)**

Thus from these data it was thereby concluded that the configuration 256b is a higher energy configuration compared to 256c.

With this in mind that the favourable position of the methine proton, $H_e$, is as depicted in (256c) **(Figure 19)**, the energies of the conformers resulting from this configuration was then further considered. It was anticipated that upon examining these data the orientation of the substituents on the chloroethyl moiety may be obtained. The results of this experiment suggested that the preferable conformation 1 (photograph 4) **(Figure 21)**, was 3.5 kJ $mol^{-1}$ lower in energy in comparison to the remaining conformations.

Thus from these studies the overall relative stereochemistry may be tentively assigned as that shown **(Figure 22)**.




**(256h)**

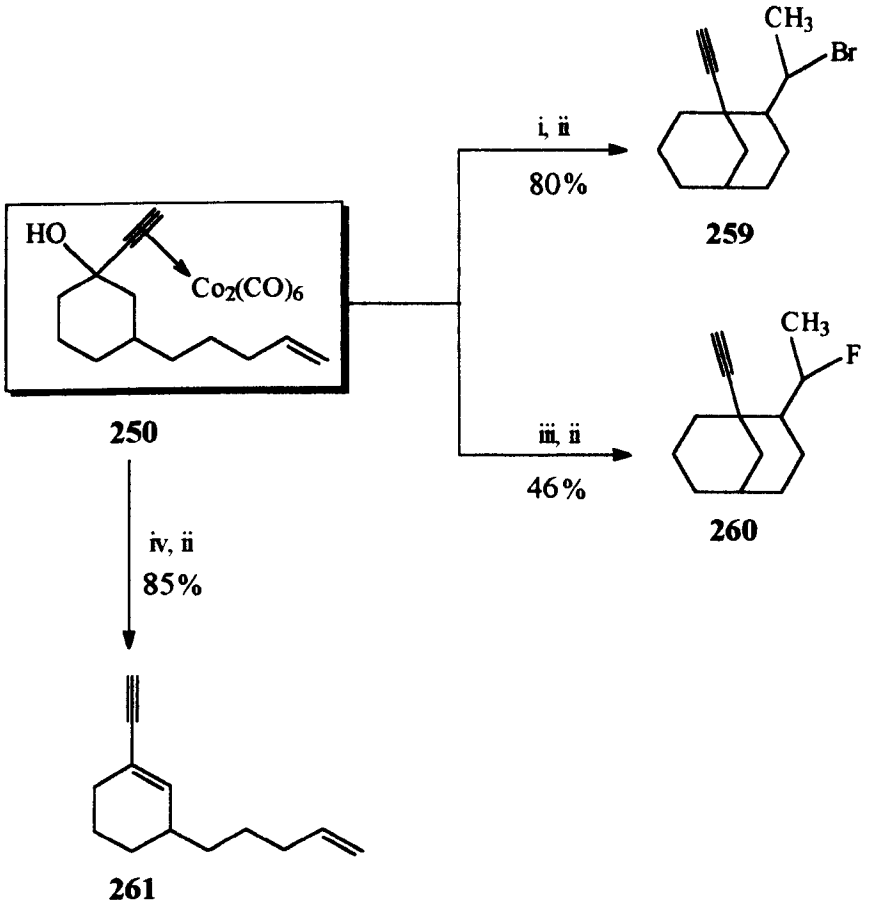
**(Figure 22)**

Clearly an unambiguous assignment of the stereochemistry may only be obtained by a single crystal X-ray crystallography.

## 3.3 Investigation into the Origin of the Halogen Atom

With the desired cyclised compound in hand, the next priority was to focus upon the origin of the halogen incorporated during the cyclisation reaction. It was anticipated, by conducting this study, that a better understanding with regards to the mechanism would begin to emerge. Thus to expand our understanding, it was decided to perform a series of reactions using a range of titanium based Lewis acids.

The reaction conditions were maintained with respect to temperature, reaction time etc. The results found of these studies are shown **(Scheme 65)**.




***Reagents and conditions*** i, $TiBr_4$, DCM, 0°C; ii, $Ce(SO_4)_2$, MeOH, rt; iii, $TiF_4$, DCM, 0°C; iv, $TiI_4$, DCM, 0°C.

**(Scheme 65)**

Hence, treatment of the cyclisation precursor (250), in DCM, with excess titanium (IV) bromide at 0°C, gave a rapid reaction. Analysis by TLC showed a faster moving product ($R_f$ 0.32) had formed within ten minutes. At this time the reaction was quenched, as there was little indication of starting material. Following decomplexation and purification, the corresponding bicyclo compound (259) was isolated in 80% yield. This result clearly suggests that the halogen was originating from the Lewis acid and not the solvent.

Upon careful examination of the $^1$H NMR spectrum, it was found that the same characteristic peaks were present to that reported for compound (256). Thus the methyl group appeared as a doublet at a chemical shift δ1.70 ppm ($J$=8), and the methine proton adjacent to the bromine atom was found, as expected, downfield between δ4.07-4.16 ppm.

The $^{13}$C NMR also showed analogous peak positions to that described for (256). From examination of the mass spectrum, the presence of molecular ion peaks 254 and 256, with an equal intensity, were clearly seen. This verified that a bromine atom had been incorporated into the compound. Significant elimination of HBr was again seen, to provide the cycloadduct (257).

With the successful synthesis of compound (259), the sequence was repeated using the Lewis acid titanium (IV) fluoride. Thus upon reacting the cobalt complexed propargyl alcohol (250) with this Lewis acid, the required bicyclo[3.3.1]nonane (260) with fluorine inclusion was achieved in 46% yield. Although a lower yield was obtained, the result further confirmed that the source of the halogen was the Lewis acid.

Analysis of the relevant sections of the $^1$H NMR and $^{13}$C NMR spectra, again revealed analogous peaks for the methyl group and methylene hydrogens, however it was found, as expected, that the proton adjacent to the fluorine atom was further downfield at δ5.01 ppm, in contrast to the chlorine and bromine cycloadduct spectra.

With these observations in mind, the consequence of using titanium (IV) iodide was then investigated. However, upon reacting (250) with this Lewis acid, the undesired enyne (261) was isolated in 85% yield following decomplexation. The formation of this compound was clearly evident from the $^1$H NMR spectrum, that showed the pendant alkenyl protons at δ4.86 ppm ($J_{gem}$=2Hz, $J_{vic}$=8Hz, and finer allylic coupling), δ4.95 ppm ($J_{gem}$=2Hz, $J_{vic}$=16Hz and finer allylic coupling) and δ5.66 ppm. Additionally, the ring vinyl proton was distinctly seen as a multiplet at δ6.04 ppm.

The formation of the enyne may be rationalised by considering the electronegativity of halogens, which decreases down a group. Literature evidence[94] suggested that the more electron withdrawing the substituent, the more it enhances Lewis acidity and thereby diminishes Lewis basicity. Thus, on simple electronegativity grounds the following order may be predicted: $TiF_4$>$TiCl_4$>$TiBr_4$>$TiI_4$. Hence one can possibly rationalise that cyclisation failed to occur with $TiI_4$ due to the reduced acidity of the Lewis acid.

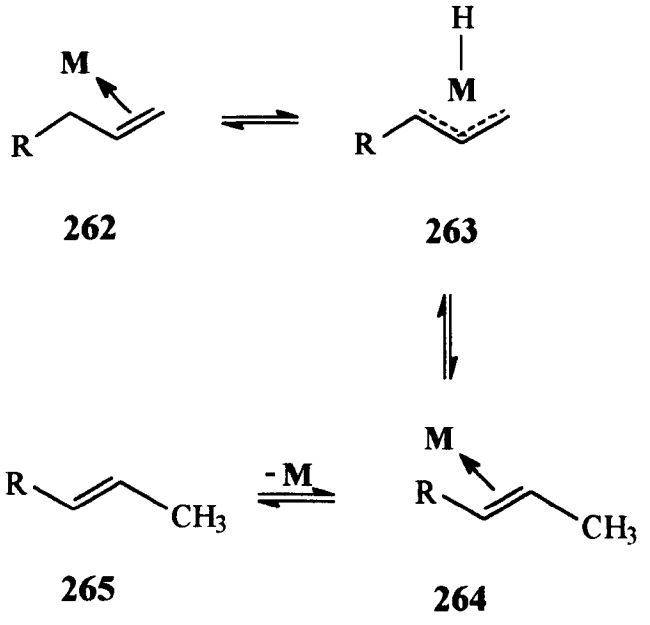
With these observations the study continued, by examining the effect upon the cyclisation reaction when the solvent was changed to dibromomethane. Thus, reacting the cyclisation precursor (250) with titanium (IV) chloride in dibromomethane, it was found that the 2-(1-chloroethyl)-1-(1-ethynyl)bicyclo[3.3.1]nonane (256) was isolated. This further provided evidence that the addition of the halogen was *via* the Lewis acid.

## 3.4 Mechanism for the Reaction

At this moment in time, a conclusive explanation cannot be given with regards to the mechanism involved for the cyclisation. However, one factor is certain that indicates the need for the cobalt hexacarbonyl moiety, since the absence of this group has led to

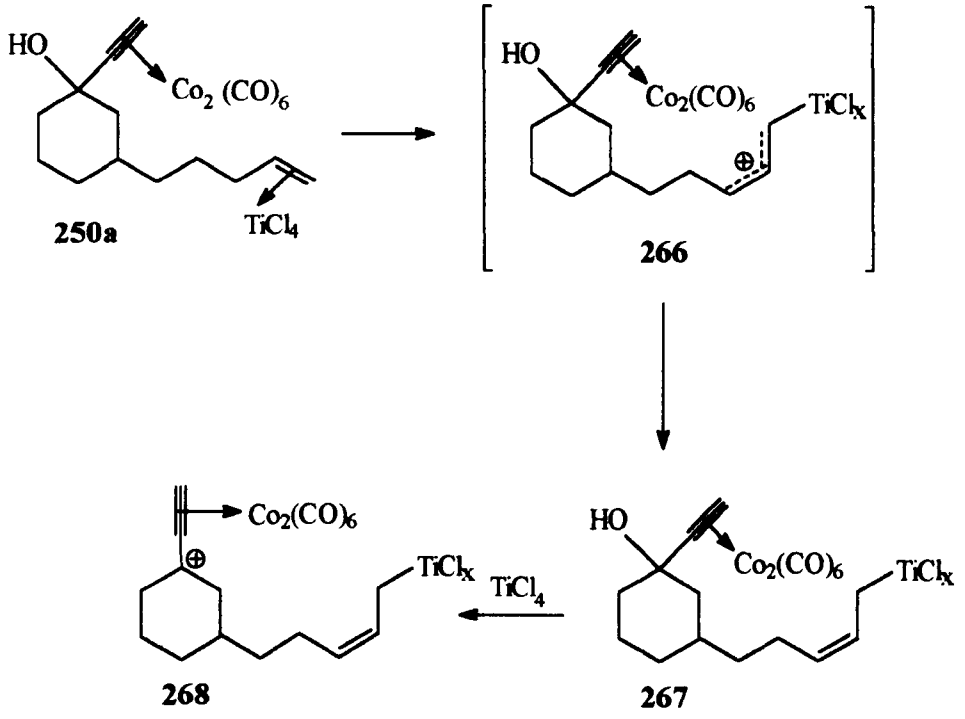
a number of products. Bearing this in mind, two plausible paths may then be considered, in which both mechanisms implicate the titanium species in a regioselective double bond isomerisation reaction.

From a survey of the literature,[95] it may be speculated that this arises *via* co-ordination of the titanium species following a π-allyl mechanism **(Figure 23)**. In this reaction, isomerisation proceeds with the interaction of the metal with the alkene (262) to afford the hydrido-π-allylic complex intermediate (263). Re-addition of the hydride shifts the double bond one step along the carbon skeleton to provide (264). Once formed this reverts to the metal releasing the isomerised olefin (265). Interestingly this isomerisation occurs regioselectively, as no occasion was translocation along the chain observed.




**(Figure 23)**

In this process **(Figure24)** metal-alkene insertion (250a) leads to formation of the most stable disubstituted alkene (267) *via* reaction at the stabilised allylic position of (266). Further reaction with the Lewis acid, then generates the cobalt stabilised cation (268).



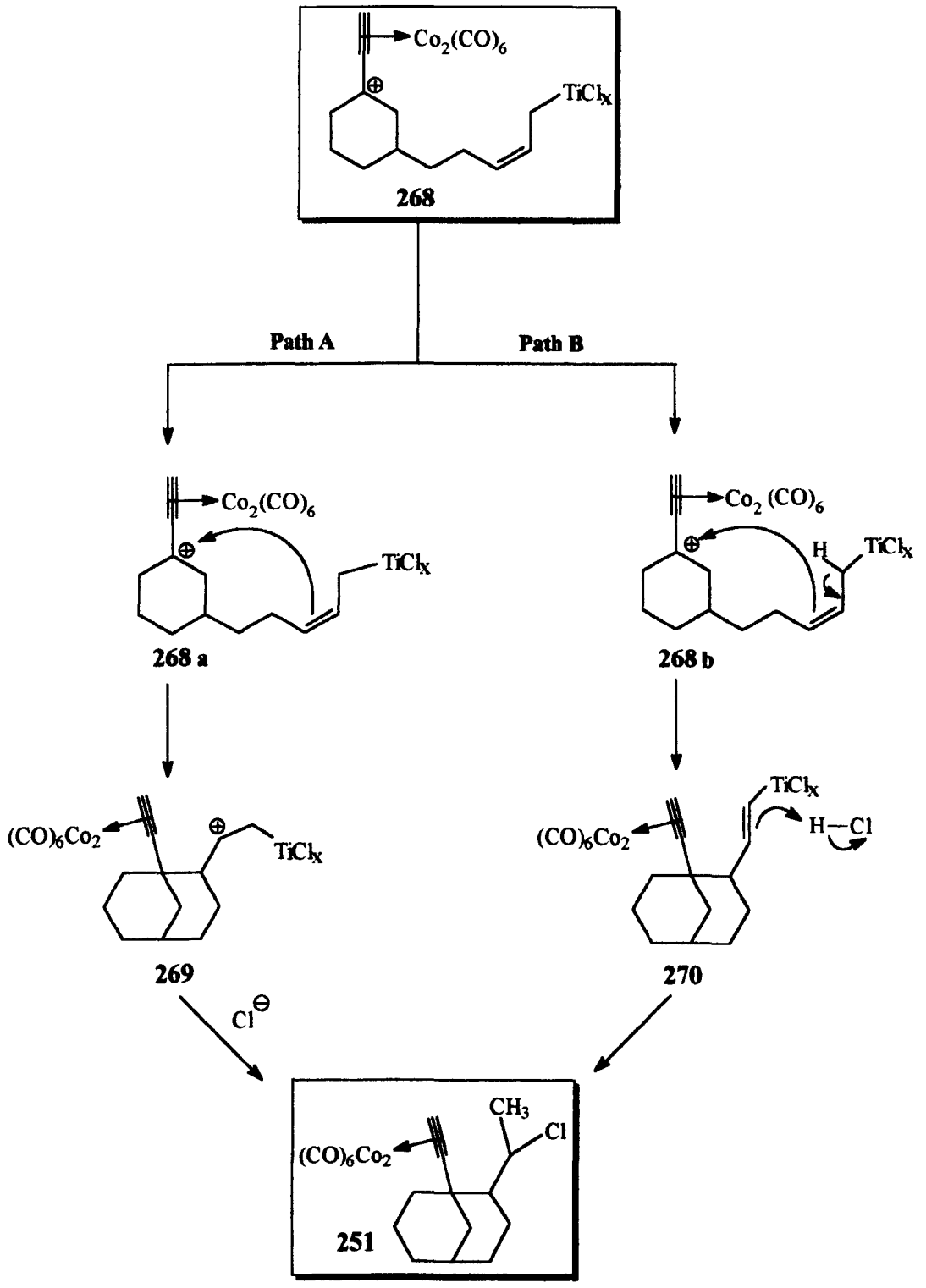

**(Figure 24)**

With the formation of the cation (268), two pathways are then suggested for the synthesis of compound (251) **(Figure 25)**.

Examining path A, electrophilic addition reaction with the dicobalt stabilised cation (268a) will form a second cation (269). This appears to be quenched by a chloride ion, derived from the Lewis acid. Subsequent loss of a $^{\dagger}$titanium species then affords the cycloadduct (251).

If the mechanism is considered *via* path B, then an *intra*molecular ene-type[96] reaction of (268b) would cyclise to form (270). From this, it is possible that electrophilic addition of HCl, then occurs with the loss of $^{\dagger}TiCl_x$, to afford (251).

$^{\dagger}$ It should be noted that as no mechanistic studies were undertaken, the fate of the titanium species at this stage is unknown, and therefore has not been detailed.

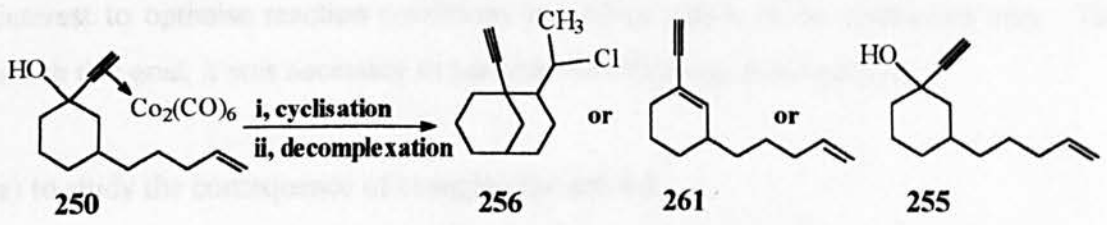

Co2(CO)6
TiClx
268
Path A
Path B
Co2(CO)6
TiClx
268 a
Co2 (CO)6
H
TiClx
268 b
(CO)6Co2
TiClx
269
TiClx
H—Cl
(CO)6Co2
270
Cl⊖
CH3
Cl
(CO)6Co2
251

**(Figure 25)**

The actual mechanism that leads to the synthesis of compound (251) still remains speculative, however unlike most double bond isomerisation processes,[97] this process is regioselective about the positioning of the double bond in the carbon chain.

## 3.5 Investigation into possible Cyclisation using other Lewis Acids

With the success of using titanium Lewis acids to effect the cyclisation reaction, it became of interest to examine the consequence of reacting the organocobalt complex (250) with other Lewis acids. The solvent dichloromethane was to be used, as a survey of the literature[98] suggested that this is the most frequently used solvent for the Nicholas reaction. In addition, as most cyclisations appear to occur at low temperatures,[99] it was decided to perform each experiment at 0°C. Hence, the only factor that was varied for these studies was the type and the stoichiometry of the Lewis acid. The results obtained are shown in **(Table 1)**.




**(Figure 26)**

**Table 1.**

**Reaction of the dicobalt hexacarbonyl complex (250) with other Lewis acids**

| entry | Lewis Acid | 1.1eq | 10eq |
|---|---|---|---|
| 1 | $BF_3.OEt_2$ | 83(261) | 78(261) |
| 2 | $HBF_4$ | 68(261) | 72(261) |
| 3 | $SnCl_4$ | 75(261) | 81(261) |
| 4 | $ZnCl_2$ | 62(255) | 70(255) |

[a]. % yield of product after demetallation

Thus, treatment of compound (250) with boron trifluoride diethyl etherate (entry 1), led to the formation of the enyne (261) using both a stoichiometric and excess Lewis acid. A similar result was observed, upon reacting the cobalt complexed propargyl alcohol (250), with tetrafluoroboric acid and tin (IV) chloride, again only the enyne (261) was isolated (entries 2 and 3). It was then decided to investigate the mild Lewis acid zinc chloride[100] (entry 4). Hence, upon treating compound (250) with $ZnCl_2$, followed by decomplexation, the propargyl alcohol (255) was recovered (entry 4). Thus from these studies, it was concluded that titanium is the major contributing factor in effecting the cyclisation reaction. Lewis acidity appears to operate in a minor role, as shown in the reaction of $TiI_4$ with compound (250).

## 3.6 Optimising Reaction Conditions

With the successful synthesis of the bridged bicyclic compound (256), it became of interest to optimise reaction conditions and hence yields of the cyclisation step. To reach this goal, it was necessary to perform the following investigations:

a) to study the consequence of changing the solvent
b) to examine the effect of cyclisation at different reaction times
c) to determine a temperature nearest to the optimum to effect the reaction
d) to examine the stoichiometry of titanium (IV) chloride
e) to examine other decomplexing agents

These will now be discussed in turn under the appropriate section.

The reader should note that in all investigations performed the dicobalt complexed products obtained for the entries given, were decomplexed and the product spectroscopically analysed.

## 3.6.1 Solvent Effect

Based upon the dielectric constants, that provide a measure of the polarity of the solvent,[101] the effect of using highly polar to non-polar solvents was examined. It was decided that upon conducting this study all other factors would remain unchanged. i.e temperature, reaction time and quantity of Lewis acid. The results were compared with the yield of the cobalt complexed bicyclo [3.3.1]nonane (251) that was isolated in 73% using the solvent dichloromethane. The data obtained is shown in **(Table 2)**.

**Table 2.**

**The effect of cyclisation using different solvents**

| entry | Solvent | Dielectric constant[(a)] | % yield of 251 |
|---|---|---|---|
| 1 | Acetone | 20.7 | 21 |
| 2 | THF | 7.58 | 43 |
| 3 | Ethyl acetate | 6.02 | 23 |
| 4 | Ether | 4.34 | 15 |
| 5 | Hexane | 1.88 | 7 |

[(a)]. values for dielectric constants are quoted from reference 99(b)

* dielectric constant for DCM is 9.08

From these results it is clearly seen that a solvent effect is observable and the yield of the cobalt complexed bicyclo compound is dependant upon the choice of solvent, being optimum with DCM and low with hexane (entry 5).

## 3.6.2 Reaction Time of Cyclisation

Having determined the best solvent for the reaction, our investigations then continued to examine the consequence of using different reaction times for the cyclisation step. From previous experiments the reaction was quenched upon the first indication of product. Thus in order to establish whether employing a shorter or a longer period of reaction time, would possibly lead to better yields of the desired product (251), an investigation was conducted using the times indicated in **(Table 3)**.

**Table 3.**

**The effect of cylisation at variant times**

| entry | Reaction time (min)[a] | % yield of 251[b] |
|---|---|---|
| 1 | 3 | 51 |
| 2 | 5 | 60 |
| 3 | 20 | 84 |
| 4 | 30 | 58 |
| 5 | 60 | 36 |

[a]. TLC analysis was used to monitor the progress of reaction in which, after the required time, the reaction was stopped and the same work-up procedure was undertaken

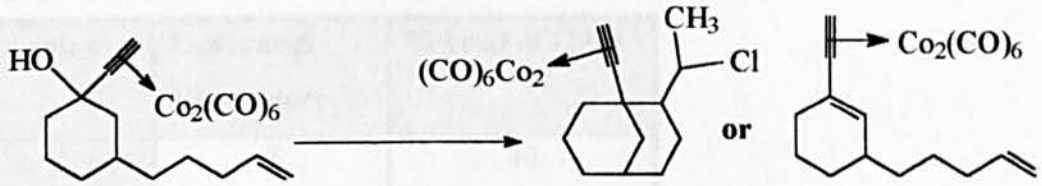
[b]. data was compared with the first yield obtained for (251), that being 73%.

These data suggests that the optimum reaction time is near to 20 minutes (entry 3), with shorter reaction time giving reduced yields (entries 1 and 2). In contrast longer reaction time (entries 4 and 5) gave lower yield of cyclised product (251) and more decomposition products.

### 3.6.3 Temperature Effect

Initially the cyclisation experiment was conducted at 0°C to provide the dicobalt hexacarbonyl bicyclic compound (251) in 73% yield. Thus this result, again formed the basis of comparison.

In these experiments, it was decided that the reaction time of 20 minutes would not be used, simply to ensure that the temperature factor was responsible for the outcome of the result. The data obtained is tabulated **(Table 4)**.




**250** **251** **271**

**(Figure 27)**

**Table 4. The effect of cyclisation at different temperatures**

| entry | T °C | product | %yield of 251 |
|---|---|---|---|
| 1 | rt | 271 + 251 | 11 |
| 2 | -10 | 251 | 82 |
| 3 | -20 | 251+ by-products | 42 |
| 4 | -30 | 251+by-products | 31 |

Upon performing the reaction at ambient temperature (entry 1) it was found that the formation of the enyne (271) was favoured over the cycloadduct (251). As the temperature was lowered (entries 2), the cycloadduct (251) was formed exclusively, with a an increase in yield. At -20°C and -30°C (entries 3 and 4), the yield of the cycloadduct decreased as by-products were beginning to form, and were becoming difficult to separate from the desired product. Thus from these studies it was concluded that the reaction could be performed at -10°C, to achieve a better yield of product.

## 3.6.4 Stoichiometry of the Lewis acid

These studies were based upon the reaction of compound (250) with titanium (IV) chloride. The yields were recorded for the formation of the dicobalt hexacarbonyl substituted bicyclo[3.3.1] nonane (251).

These results are tabulated as shown **(Table 5)**.

**Table 5.**

**Cyclisation and the effect of using stoichiometric amounts of Lewis acid**

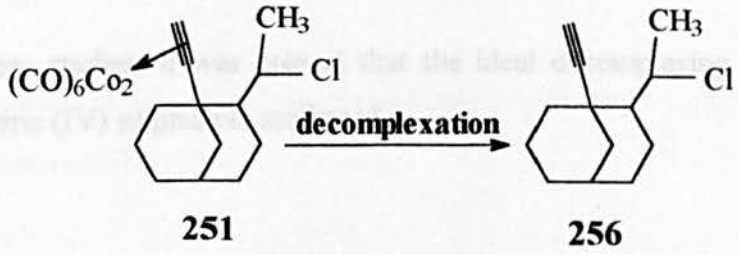
| entry | Lewis acid equivalence | % yield of (251) |
|---|---|---|
| 1 | 2 | 40 |
| 2 | 4 | 58 |
| 3 | 6 | 64 |
| 4 | 8 | 69 |
| 5 | 10 | 75 |

Upon analysing these data, it is clearly observed that as the amount of Lewis acid used is increased there is an accompanying increase in the percentage yield. The attempt to use stoichiometric amounts of the Lewis acid provided a low yield of the bicyclic compound (251) (entry 1) in comparison to the yield obtained using 10 equivalents (entry 5). Increasing the amount of Lewis acid (entries 2,3,4) showed a steady increase in yields. The result can be rationalised by considering the following. As Lewis acid is required for double bond migration as well as in the production of the Nicholas cation, then an increase in yield is expected with increasing stoichiometric amounts of Lewis acid.

Thus it was concluded from these studies to achieve maximum yield an excess amount of the Lewis acid is required.

## 3.6.5 Decomplexing Agents

The removal of dicobalt hexacarbonyl complex of substituted bicyclo-compounds, using ceric (IV) sulphate, was providing yields in the range of 68-84%. Thus in an effort to obtain an efficient system that would possibly allow quantitative recovery of the bicyclo compound, a study of a range of oxidising reagents were undertaken. The results obtained are presented in **(Table 6)**.




**251** **256**

**(Figure 28)**

**Table 6.**

**Decomplexation of Dicobalt Hexacarbonyl Complex (251)**

| entry | oxidising reagent | equivalents | solvent | T (°C) | % yield of 256 |
|---|---|---|---|---|---|
| 1 | $Fe(NO_3)_3.H_2O$ | 10 | $C_2H_5OH$ | 0 | 26 |
| 2 | $I_2$ | 1 | THF | RT | 21 |
| 3 | $(CH_3)_3NO$ | 5 | $C_2H_6O$ | 0 | 33 |
| 4 | $Ce(NH_4)_2(NO_3)_6$ | 1 | $C_2H_6O$ | -78 | 30 |
| 5 | $(KSO_3)_2NO$ | 10 | $C_2H_6O$/THF | -78 | 19 |
| 6 | TBAF | 10 | THF | -10 | 54 |

Conventional methods using oxidising reagents such as ferric nitrate,[57] trimethylamine *N*-oxide[102] and iodine[85] were all found to provide low yields of compound (9) (entries 1,2 and 3). Ceric ammonium nitrate[103] was also found to be inefficient (entry 4), even at low temperatures and the use of potassium nitrosodiosulfonate was ineffective despite the use of ten equivalents (entry 5). In all these cases, it was noted that upon examining the $^1$H NMR spectrum of the decomplexed cycloadduct, the presence of the desired compound was observed with contamination by impurities that were impossible to separate. Finally upon inducing decomplexation with a recently introduced oxidising agent TBAF[104] (entry 6), it was anticipated that a quantitative yield of the product may be obtained. However, the required bicyclic compound was isolated in a modest, 56% yield, in which the absence of undesirable impurities was observed.

Thus from these studies, it was proved that the ideal decomplexing agent for this reaction was ceric (IV) sulphate in methanol.

## 3.7 Summary of Reaction Conditions

Thus to summarise, these studies show that the conditions to use for the cyclisation step are as follows:

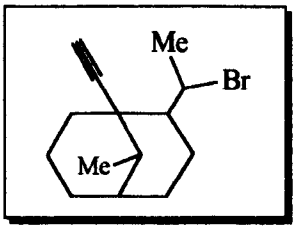
I) the solvent for the reaction should be DCM.
II) the reaction time that is providing a better yield of product is 20 minutes.
III) the reaction should be performed at a temperature -10$^0$C.
IV) 10 equivalents of Lewis acid is required.
V) the ideal decomplexing agent for the reaction is ceric (IV) sulphate in methanol

## 3.8 Extension of Investigations

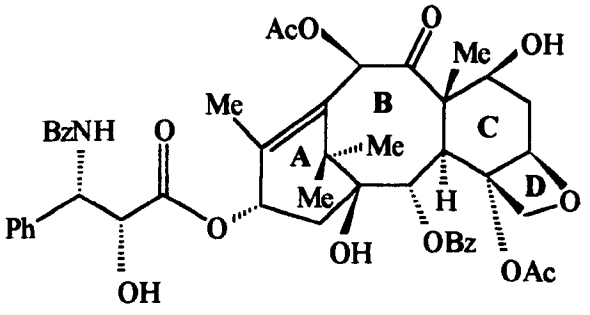
Having examined the consequence of changing the reaction conditions, these investigations then continued by examining the generality of this reaction, for the synthesis of other bridged bicyclic ring systems. It was anticipated that through these studies, model precursors may be developed to the type of bridged systems that were contained in the natural products given in Chapter One. Thus the discussion to follow outlines these investigations.

### 3.8.1 Synthesis of 2-(1-Bromoethyl)-1-ethynyl-9-methyl bicyclo[3.3.1]nonane

The studies commenced with the preparation of 2-(1-bromoethyl)-1-ethynyl-9-methyl bicyclo[3.3.1]nonane (272).




**272**

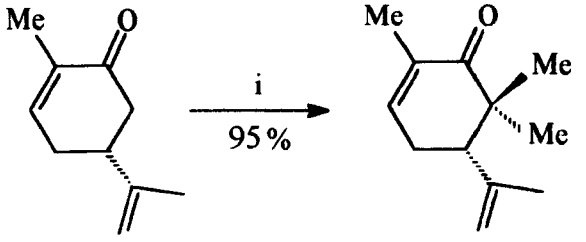



**5**

**(Figure 29)**

Our interest in this particular system was a) examine the effect that such a substituent may have on the cyclisation reaction and b) such system contained one of the geminal dimethyl groups that are present in taxol (5).

It was envisaged that with one methyl group in place, the introduction of the other could be performed following a similar methodology to that described by Srikrishna.[105] In this report alkylation of (*R*)-(-)-carvone (273) with LDA and methyl iodide gave the required dimethylcarvone (274) in 95% yield **(Scheme 66)**.

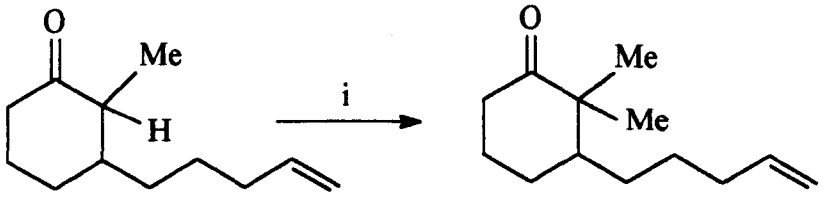



**273** **274**

***Reagents and conditions*** i, (a) LDA, THF, 0°C, (b) MeI, 0°C → r.t

**(Scheme 66)**

Thus by analogy to this observation, using modified reaction conditions, compound (275) should afford the desired product (276) **(Scheme 67)**.

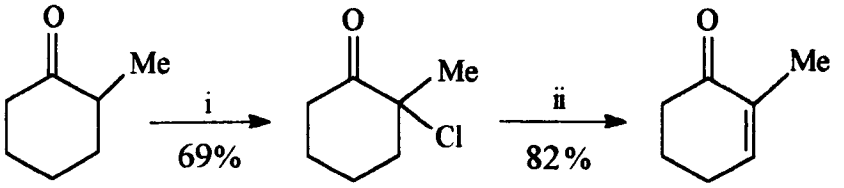



**275** **276**

***Reagents and conditions*** i, TEA, MeI, DMF, 0°C.

**(Scheme 67)**

A survey of the literature[106] showed that the desired starting material, 2-methyl-cyclohex-2-en-1-one (279), could be obtained from 2-methylcyclohexan-1-one (277) **(Scheme 68)**.




**277** **278** **279**

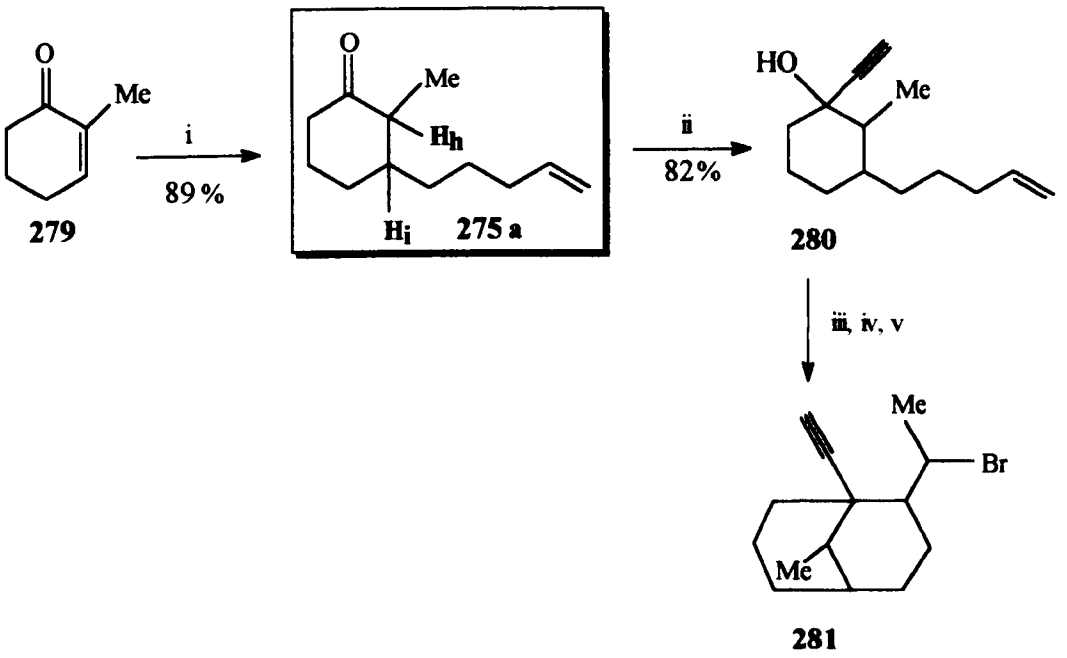
***Reagents and conditions*** i, $SO_2Cl_2$, DCM; ii, LiCl, DMF, 2.5% $H_2SO_4$.

**(Scheme 68)**

Thus, treatment of 2-methylcyclohexan-1-one (277) with sulfuryl chloride provided 2-chloro-2-methylcyclohexan-1-one (278) in 69% yield. Upon reacting compound (278) with LiCl the desired enone (279) was achieved in 82% yield. The formation of the enone (279) was immediately apparent from the infra-red spectrum. A sharp signal at 1721 $cm^{-1}$ (for the carbonyl group) with a shoulder at 1681 $cm^{-1}$, indicated the presence of a carbon-carbon double bond.

Upon analysis of the $^1H$ NMR spectrum, further confirmation for the presence of the alkene double bond was obtained, that showed a broad signal for the ring vinyl proton at δ6.67 ppm. Further inspection of the spectrum revealed the methyl substituent as a doublet at δ1.70 ppm ($J$=2) and the methylene protons adjacent to the carbonyl were shown as a triplet at a chemical shift of δ2.33 ppm. The signals appearing as a multiplet in the region δ2.19 ppm, attributed to the methylene protons at C4 and C5 respectively.

With the key enone prepared, a 1,4-cuprate addition reaction led to the required product (275) in 89% yield, as a mixture of inseparable diastereoisomers in a ratio of 4:1. This ratio was based tentatively on the presence of two methyl doublets resonating at δ1.00 ppm (minor isomer, $J$=7Hz) and at δ1.03 ppm (major isomer, $J$=6.6Hz) in the $^1$H NMR spectrum, with the remaining spectral signals apparently overlapping.



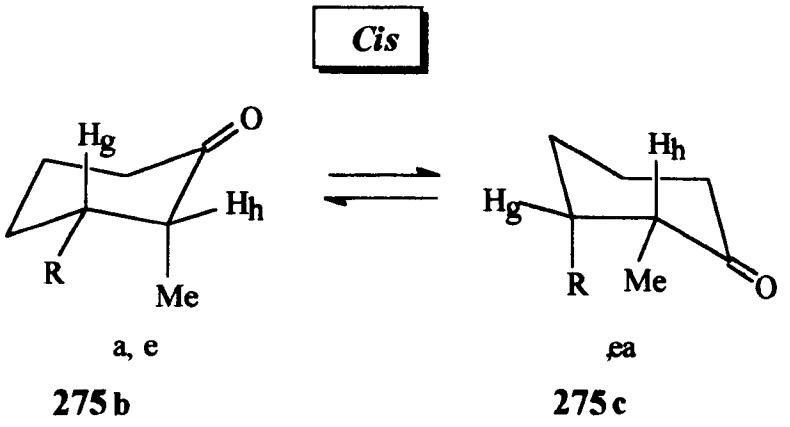

***Reagents and conditions*** i, 5-bromo-1-pentene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF; iii, $Co_2(CO)_8$, ether; iv, $TiCl_4$, DCM; v, $Ce(SO_4)_2$, MeOH.

**(Scheme 69)**

The methine proton $H_h$, α to the carbonyl group appeared as an apparent quintet. Interestingly the quintet for the major isomer was found upfield at δ2.16 ppm, in contrast to the minor isomer at δ2.55 ppm. The chemical shift for proton $H_i$ was located using carbon-proton correlation NMR studies, at a chemical shift of δ1.90 ppm, amongst the ring methylene hydrogen atoms.

At this point an attempt was made to assign the stereochemistry of the methine protons $H_h$ and $H_i$ in 2-methyl-3-(4-pentenyl)-cyclohexan-1-one (275a). It was foreseen that if we could ascertain the relative stereochemistry of these protons within this precursor, then upon cyclisation, the stereochemistry would remain unchanged and thus the relative assignment of these protons within the bicyclic compound would be achieved.

Examining the consequence of the conjugate addition, it was first postulated that attack would give rise to both *cis* (275b and 275c) and *trans* (275d and 275e) conformers shown **(Figure 30)**.




where R = $C_5H_6$

**(Figure 30)**

From a survey of the literature,[107] it was suggested that the *trans*-2,3-disubstituted cyclohexan-1-one (275d) would be more thermodynamically stable than the *trans* conformer (275e), in which the bulky **R** and methyl substituents are diaxially orientated. In contrast, the *cis*-2,3-disubstituted conformers (275b) and (275c) both contain a bulky substituent in the axial position.

Thus, with these thoughts in mind the magnitude of the coupling constant of $H_h$ with $H_i$ was then determined. Based on proton decoupling experiments,[108] it was observed that upon irradiation of the methyl group derived from the major isomer at δ1.03 ppm, the corresponding quintet for this diastereoisomer collapsed to a doublet, with a vicinal coupling constant of ${}^3J_{hi}$=10Hz.

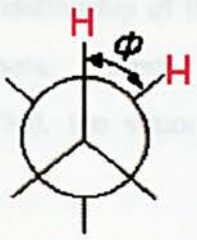
Similarly, irradiation of the methyl group derived for the minor isomer at δ1.00 ppm, a broad doublet was observed at δ2.16 ppm with a coupling vicinal coupling constant of ${}^3J_{hi}$=5Hz.

With these findings the Karplus[109] relationship between the vicinal coupling constant, ${}^3J_{ab}$, and the dihedral angle $\phi$ (equations 2 and 3) (and plotted as in **Figure 31b**), was considered.

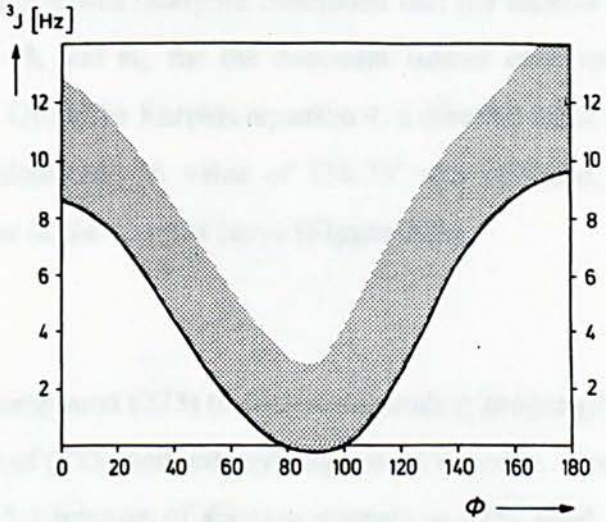
$$ {}^3J_{ab} = J^0 \cos^2\phi - 0.28 \qquad (0^\circ \leq \phi \leq 90^\circ) \qquad \textit{Equation 2} $$

$$ {}^3J_{ab} = J^{180} \cos^2\phi - 0.28 \qquad (90^\circ \leq \phi \leq 180^\circ) \qquad \textit{Equation 3} $$

where $J^0 = 8.5$ and $J^{180} = 9.5$ and the dihedral angle is defined as the angle between, for example, proton $H_x$ and $H_y$ **(Figure 31a)**.




**(Figure 31a)**




**(Figure 31b)** The Karplus Curve for the dependence of vicinal H-H coupling on the dihedral angle: line, theoretical curve; shaded area, range of empirical results.

From this relationship, literature evidence had suggested that in the chair conformation of cyclohexane, the coupling between two axial protons is larger ($J_{aa}$=9-13Hz, as the dihedral is near to 180°) than that between two equatorial protons or between an equatorial and an axial proton ($J_{aa} \approx J_{ea}$= 2-5Hz, as the dihedral angles are nearer to 60°).

Thus by analogy to this observation, the coupling constant for the proton $H_h$ for the major isomer, $J$=10Hz, indicated that the protons $H_h$ and $H_i$ were *trans* to one another. If this is the case, then the only conformer in which these protons are so orientated would be found as the *trans* disubstituted derivative (275d) **(Figure 30)**, which was previously predicted to be the most thermodynamically stable conformation. With

regards to the minor isomer, the coupling constant of $J$=5Hz suggests an axial/equatorial or equatorial/axial relationship of the methine protons $H_h$ and $H_i$, that is seen within the *cis* conformers. Since the conformer (275b) is more thermodynamically stable than (275c), the minor isomer is thought to be the *cis* disubstituted derivative (275b).

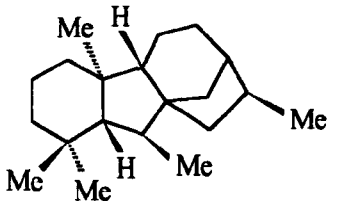
Thus from these studies it was therefore concluded that the relative stereochemistry of the methine protons $H_h$ and $H_i$, for the dominant isomer observed in the $^1$H NMR spectrum was *trans*. Using the Karplus equation 4, a dihedral angle between these two protons was then calculated. A value of 158.73° was obtained, which was found within the shaded area of the Karplus curve **(Figure 31b)**.

Next conversion of compound (275) to the corresponding propargyl alcohol (280) was effected by treatment of (275) with ethynylmagnesium bromide. Compound (280) was formed as separable 5:1 mixture of diastereoisomers in 82% yield. Inspection of the relevant part of the $^1$H NMR spectrum revealed the required alkynyl proton at δ2.30 ppm and the hydroxyl group was located amongst the methylene hydrogens within the region δ1.72-1.95 ppm of the spectrum.

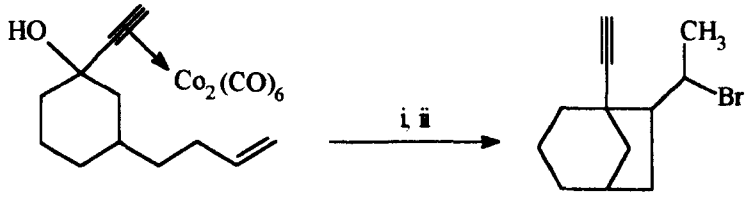
Following isolation of the major isomer of (280), complexation, cyclisation and demetallation led to the desired product (281) in 83% yield (from cyclisation step), as an inseparable mixture of diastereoisomers in the ratio of 3:1. This was confirmed by the integration of the two alkyne peaks at δ2.72 ppm and δ2.99 ppm in the $^1$H NMR spectrum. In addition, the expected characteristic peaks for the two methyl groups were observed at δ1.03 ppm and δ1.63 ppm, as doublets ($J$=8Hz for both) and the proton adjacent to the bromine atom was seen at a chemical shift of δ4.06 ppm as a multiplet. The isotopic effect of bromine was again observed in the mass spectrum.

## 3.8.2 Synthesis of Bicyclo[3.2.1]octane

With the successful synthesis of bicyclo[3.3.1]nonanes, the studies continued by investigating the consequence of reducing the length of the alkyl group upon the subsequent cyclisation step. By analogy with our previous observations, we then reasoned that cyclisation of the precursor hexacarbonyl[1-ethynyl-3-(4-butenyl)cyclohexan-1-ol]dicobalt (282) should afford 7-(1-bromoethyl)-1-ethynylbicyclo[3.2.1]octane (283) **(Scheme 70)**.




**4**




**282** **283**

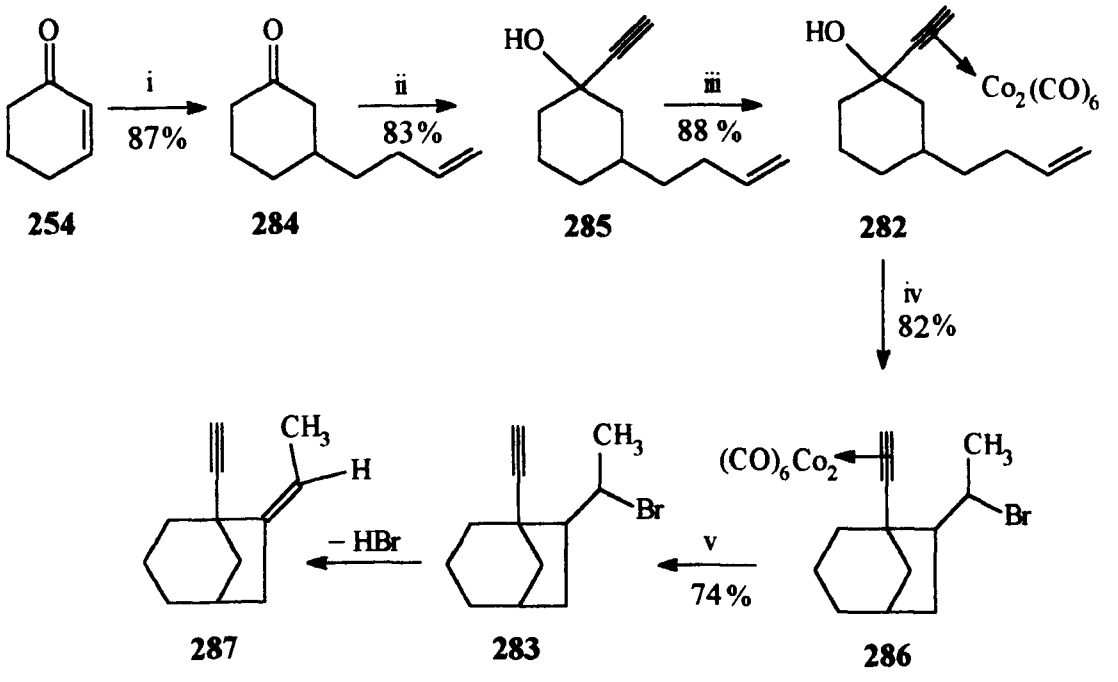
***Reagents and conditions*** i, $TiBr_4$, DCM, -10°C; ii, $Ce(SO_4)_2$, MeOH.

**(Scheme 70)**

The interest in these ring systems was that it would provide a useful model for the CD ring system present in the natural products such as the gibbanes (4).

The cyclisation precursor (282) was synthesised from cyclohex-2-en-1-one (254) *via* conjugate addition to afford (284) and propargylation to provide (285) **(Scheme 71)**. The propargyl alcohol (285) was formed as a single isomer, as ascertained by NMR

studies, with the hydroxyl group at 2.98 ppm and the alkynyl proton at δ2.38 ppm. Treatment of the propargyl alcohol (285) with octacarbonyl dicobalt gave complex (282), which upon reaction with titanium (IV) bromide, effected the cyclisation reaction to afford the cobalt complexed bicyclo[3.2.1]octane (286) in an excellent 82% yield.




***Reagents and conditions*** i, 4-bromo-1-butene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF; iii, $Co_2(CO)_8$, ether; iv, $TiBr_4$, DCM, -10°C; v, $Ce(SO_4)_2$, MeOH.

**(Scheme 71)**

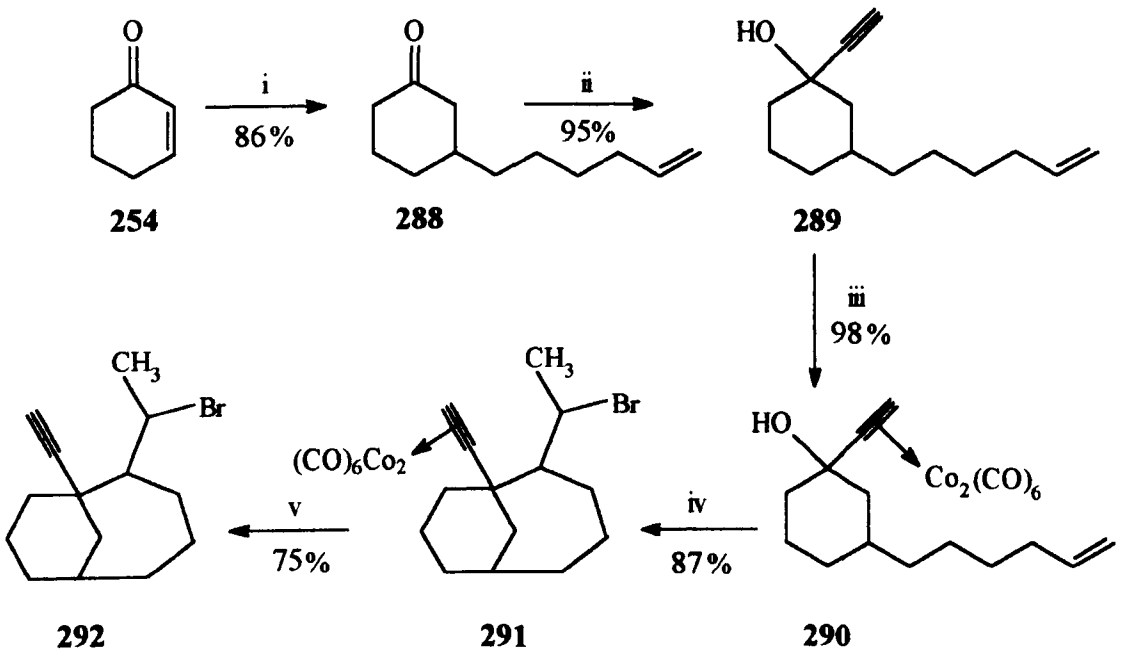
Decomplexation with ceric (IV) sulphate in methanol gave, after purification, the desired product (283), in 74% yield, as an inseparable mixture of diastereoisomers in the ratio of 4:1. The ratio was determined by GC-MS analysis.

Examination of the $^1$H NMR spectrum revealed the expected methyl doublet at δ1.58 ppm ($J$=8Hz), the alkynyl proton at δ2.79 ppm and the methine proton, next to the bromine atom, was found to be a multiplet at a chemical shift of δ4.07 ppm. The presence of the alkene isomer (287) was also clearly observable from the spectrum, that showed a broad singlet at δ6.18 ppm.

## 3.8.3 Synthesis of Bicyclo[4.3.1] decane

The generality of the cyclisation protocol had been established, as a result the studies were extended to the synthesis of larger ring systems such as bicyclo[4.3.1]decanes. This system would be only one carbon atom less than that required of taxol (5). The yields obtained in this synthesis were comparable with those previously obtained.

Thus, cuprate addition occurred in 86% yield, to provide 3-(6-hexenyl)-cyclohexan-1-one (288) **(Scheme 72)**. Treatment of (288) with ethynylmagnesium bromide, gave the propargyl alcohol in a total yield of 95%, as a separable mixture of diastereoisomers in a ratio of 5:1. Addition of octacarbonyl dicobalt to (289) gave the complex (290) in 98% yield, in which following the reaction of the cobalt cluster of (290), with $TiBr_4$, gave the cycloadduct (291), in 87% yield. Decomplexation, with cerium (IV) sulphate in methanol and purification, furnished the desired product (292), as a mixture of inseparable isomers in the ratio of 2:1.



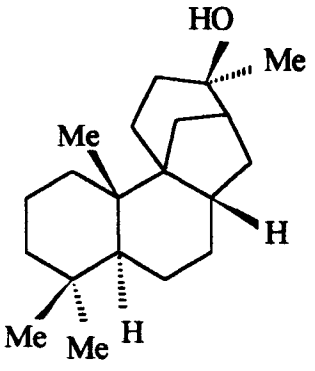

***Reagents and conditions*** i, 6-bromo-1-hexene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF; iii, $Co_2(CO)_8$, DCM; iv $TiBr_4$, DCM, -10°C; v, $Ce(SO_4)_2$, MeOH.

**(Scheme 72)**

The synthesis of the compound was evident from the spectral data. From the $^1H$ NMR spectrum, the characteristic peaks found in the previous investigations were present within the spectra for compound (290). The $^{13}C$ NMR and mass spectra were also found to be in agreement with the desired molecule.

## 3.9 Investigation into the Effect of Changing the Size of the Enone

Having investigated the effect of the alkenyl chain length on the crucial cyclisation reaction, it became of interest to examine the consequence of studying changes in the size of the enone. Of particular interest was to examine the possibility of devising a synthetic route for the synthesis of a 5,6 bridge ring system that is contained, for example, in the stemodanes (3b) **(Figure 32)**. Thus investigations began with the preparation of the 5,6 bicyclic ring system.

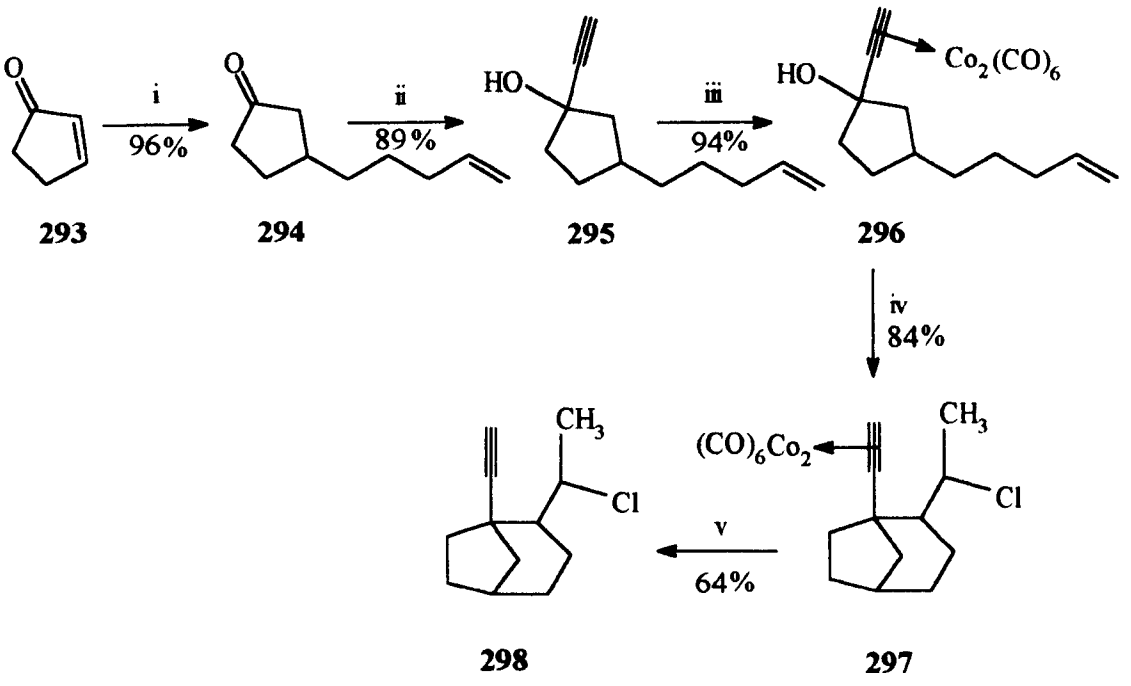



**3b**

**(Figure 32)**

### 3.9.1 Synthesis of 5,6-Bicyclic Ring System

Commencing with cyclopent-2-en-1-one (293), it was found generally that the yields of each synthetic step was similar to those reported in the previous investigations, with the pivotal cyclisation step proceeding to afford the product (297) in an efficient 84% yield **(Scheme 73)**. Upon removal of the hexacarbonyl moiety, the required cycloadduct (298) was formed in 64% yield.




***Reagents and conditions*** i, 5-bromo-1-pentene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, -78°C → r.t, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF, reflux; iii, $Co_2(CO)_8$, DCM; iv, $TiCl_4$, DCM, -10°C; v, $Ce(SO_4)_2$, MeOH.

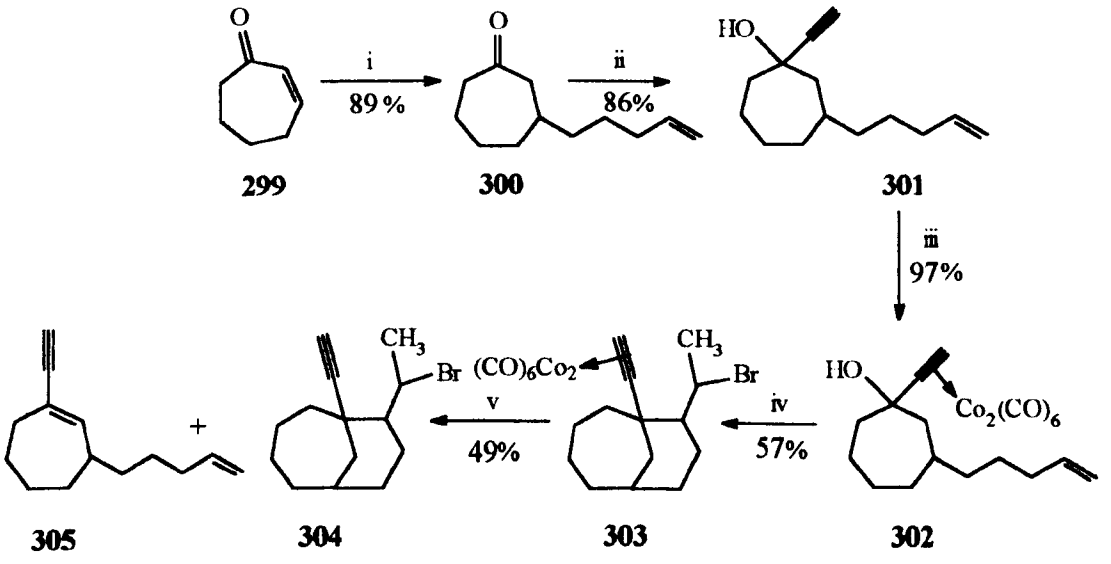
**(Scheme 73)**

Analysis of the $^1H$ NMR spectrum for the compound (296), showed the expected peaks for the methyl group, alkynyl and methine protons at 1.48 ppm ($J$=6Hz), δ2.95 ppm and δ3.96 ppm, respectively. The $^{13}C$ NMR also showed the characteristic peaks expected and the mass spectrum was also found to be consistent with the compound.

## 3.9.2 Synthesis of 7,6-Bicyclic Ring System

With the success in the synthesis of (298), an investigation commencing with cyclohept-2-en-1-one (299), was next undertaken for the possible preparation of a 7,6-bicyclic ring system.

Thus conjugate addition reaction of the Grignard reagent derived from 5-bromopent-1-ene (253) to compound (299), provided 3-(4-pentenyl)cycloheptan-1-one (300) in 89% yield **(Scheme 74)**.




***Reagents and conditions*** i, 5-bromo-1-pentene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, -78°C → r.t, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF; iii, $Co_2(CO)_8$, DCM; iv, $TiBr_4$, DCM, -10°C; v, $Ce(SO_4)_2$, MeOH.

**(Scheme 74)**

Propargylation of the ketone (300) to (301), occurred in 86% yield, as a 2:1 mixture of inseparable isomers. These were subsequently separated however, *via* complexation[110] with octacarbonyl dicobalt, to afford (302) in 97% yield. Upon isolation of the major isomer, *intra*molecular cyclisation occurred, following treatment with titanium (IV)

bromide, to provide the dicobalt hexacarbonyl bicyclic compound (303) in 57% yield. Subsequent demetallation and purification gave the desired product (304) as a yellow oil in 49% yield.

The observed decrease in yield for the cyclisation step, to that obtained from previous experiments, was due to formation of the enyne (305). This showed that the size of the initial ring had some influence upon the cyclisation step. This suggests that if the reaction was to be repeated with an eight membered ring, the formation of the corresponding enyne may be observed.

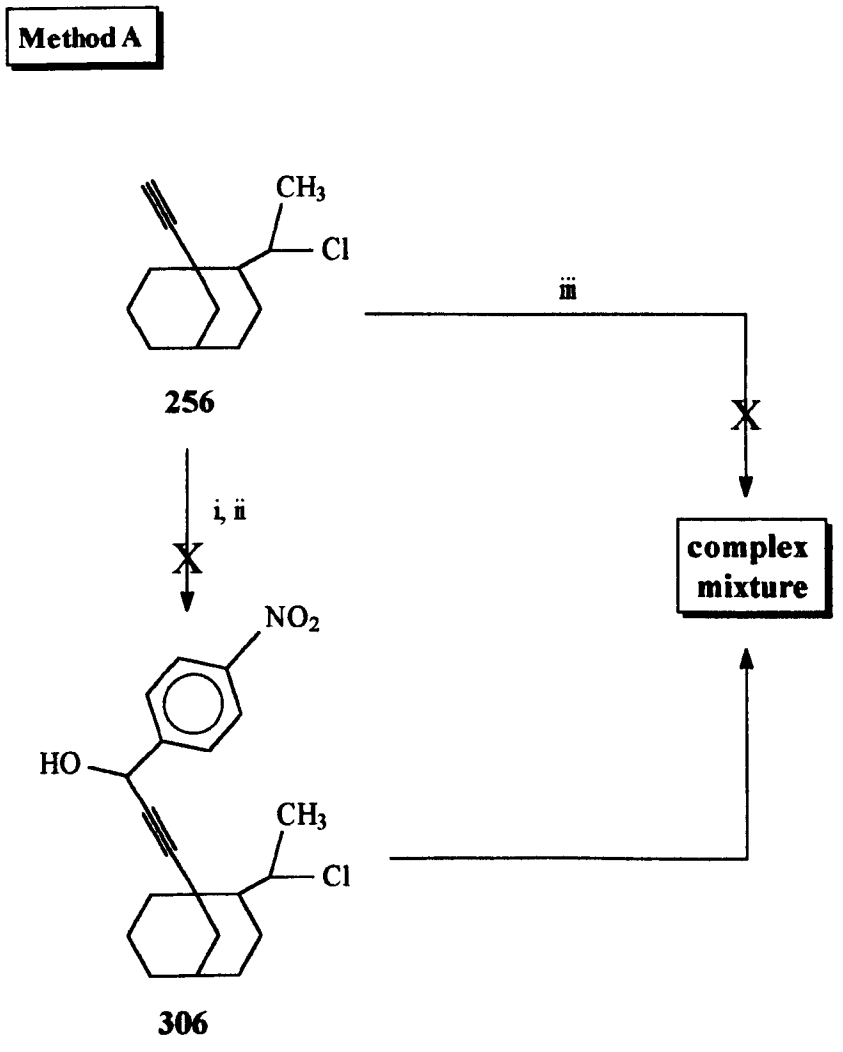
As anticipated the spectral data for compound (304) was consistent to that described for the previous bridged compounds.

## 3.10 Derivative Studies

Having determined the versatility of this novel methodology, attention was then focused upon the possibility of preparing a crystalline derivative of (256) for X-ray analysis. To achieve this, the need to increase the polarity and molecular weight of the cycloadduct was foreseen. Thus in order to define the absolute stereochemistry, the following approaches (A) and (B) were first considered..

(A) base removal of the alkynyl hydrogen atom followed by nucleophilic addition of an aldehyde or ketone.[111]
(B) ozonolysis and subsequent reaction of the alkyne functionality in the cycloadduct (256).[112]

Unfortunately both these reactions were met with limited success. Investigating method A, it was anticipated that treatment of the cyclised product (256) with an excess of *n*-butyllithium, followed by the addition of 4-nitrobenzaldehyde, would lead to the formation of (306) **(Scheme 75)**.

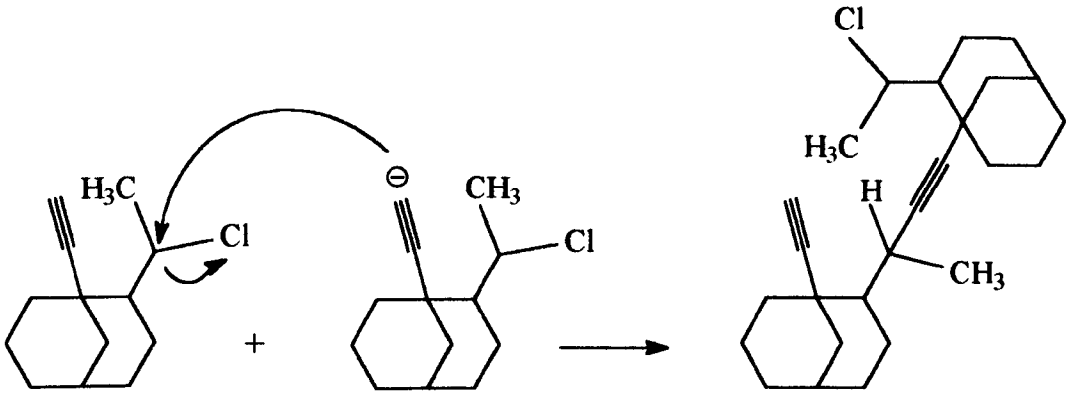



***Reagents and conditions*** i, *n*-BuLi (1.1 eqv), THF, -78°C, $O_2NC_6H_4CHO$, 6 hrs; iii, $NaNH_2$ (1.1 eqv), THF, -50°C, 3hrs.

**(Scheme 75)**

However, upon conducting the experiment it was found that after 6 hours, starting material was still visible by TLC. It was then decided to use a stronger base

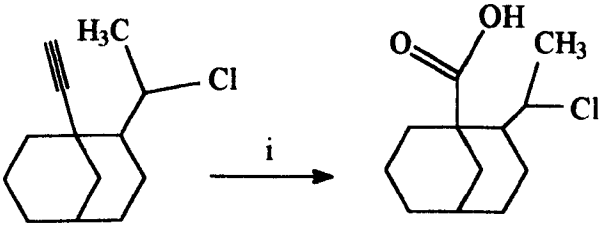
sodamide.[113] Thus the reaction of (256) with this base, followed by the attack of the aldehyde, gave an inseparable mixture of products. A rational explanation for this, could be that base removal of the alkyne hydrogen atom is subsequently attacking another molecule of (256) as shown **(Figure 33)**.




**256** **307** **308**

**(Figure 33)**

Investigating method (B), an attempt was then made to ozonolyse the triple bond **(Scheme 76)**. Literature evidence[112b] had suggested that ozonolysis of an alkyne group does proceed less easily, to that observed with a double bond, since ozone is an electrophilic agent. However, triple bonds can be ozonolysed generally to give carboxylic acids, though sometimes ozone oxidizes them to α-dicarbonyls. Thus, it was expected, if the reaction proceeded efficiently, the major compound would be (309).




**256** **309**

***Reagents and conditions*** i, (a) $O_3$, DCM, -78°C.

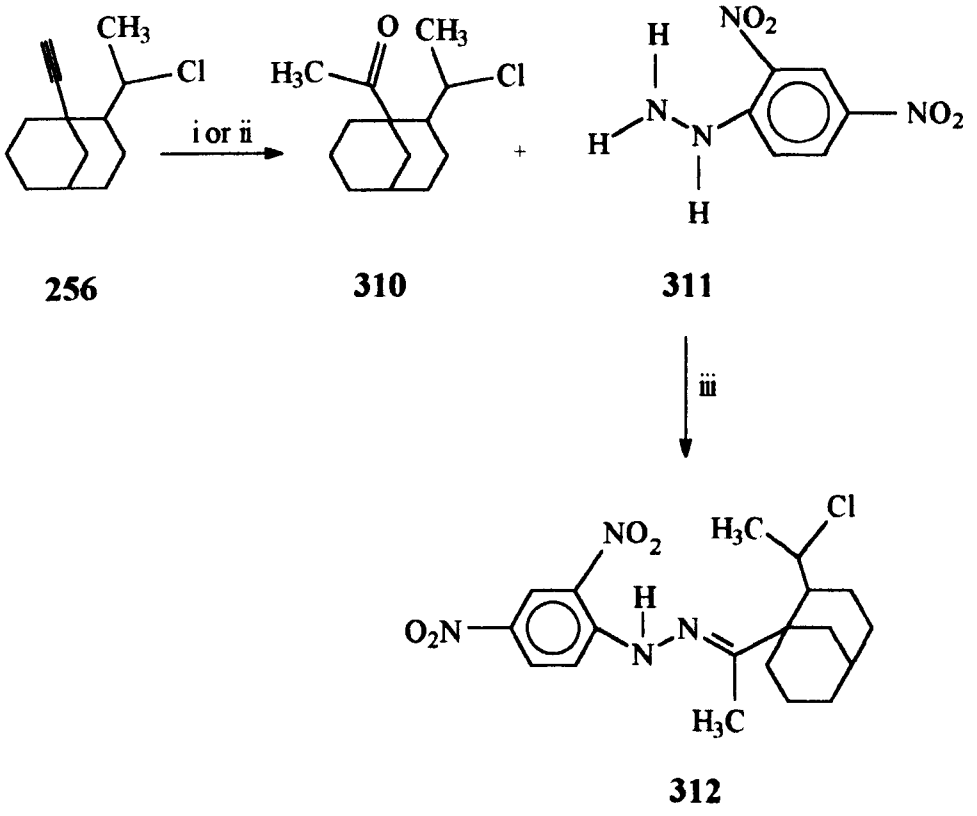
**(Scheme 76)**

It was envisaged, that with the successful conversion of the alkyne (256) to the carboxylic acid (309), subsequent reaction with a suitable alcohol to afford an ester, may provide the desired crystalline compound. However, all attempts proved unsuccessful, with multiple product formation, indicating the product was unstable to the reaction conditions. In addition, ozonolysis of the dehalogenation product, compound (257), could also be occurring to contribute to this mixture of products.

Additional, alternative approaches were then considered. A survey of the literature had suggested that hydration of alkynes could be performed using the approaches (C) and (D), to provide exclusively methyl ketones.

(C) formic acid[114]
(D) mercuric ion salts (such as mercuric sulphate)[115]

It was foreseen, that if successful conversion of the alkyne in (256), to the methyl ketone (310) was achieved, then following treatment with 2,4-dinitrophenylhydrazine (311),[116] may provide the crystalline product (312) **(Scheme 77)**. However, upon conducting these experiments, none of the desired product (312) was obtained. The conditions of method (C) appeared too harsh which led to destruction of (256), whereas in method (D), the terminal alkyne appeared unreactive to the conditions, thus providing starting material.




**256** **310** **311**

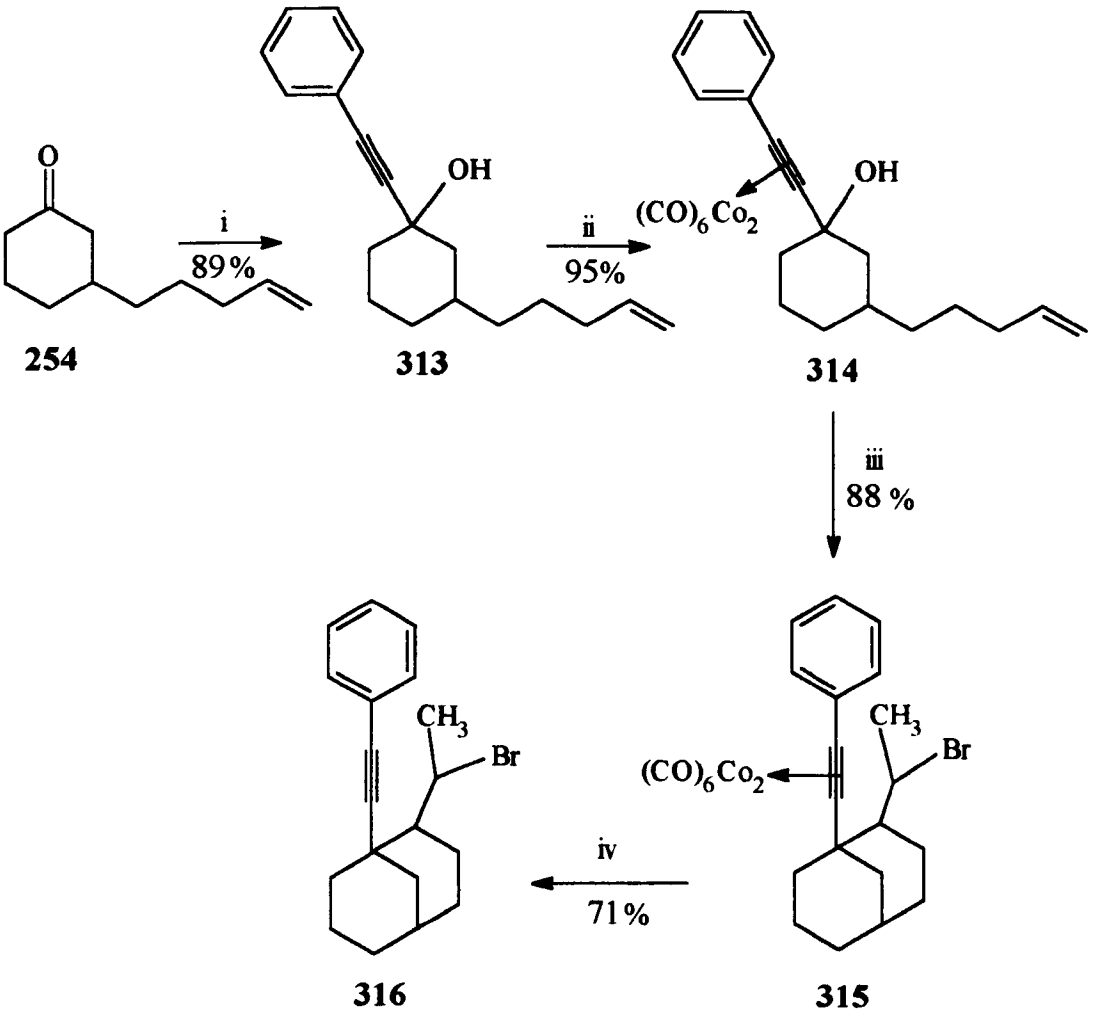
**312**

***Reagents and conditions*** i, HCOOH; ii, mercuric sulphate, $H_2SO_4$, 70% methyl alcohol; iii, c.$H_2SO_4$, MeOH.

**(Scheme 77)**

With no success in these procedures, it was then decided to approach the studies from a different angle. It was envisaged that by reacting the ketone (254) with the Grignard reagent, 0.5M phenylethynylmagnesium bromide, additional chemistry upon the terminal aromatic ring may be performed to provide a crystalline derivative. Thus using analogous conditions to that stated for the synthesis of the propargyl alcohol (255), the required 1-phenylethynyl-3-(4-pentenyl)cyclohexan-1-ol (313) was achieved in 89% yield **(Scheme 78)**. Analysis of the $^1H$ NMR spectrum clearly revealed the

presence of phenyl protons, as multiplets at δ7.26 ppm. The hydroxyl group was observed at δ2.09 ppm, that disappeared following a $D_2O$ shake.



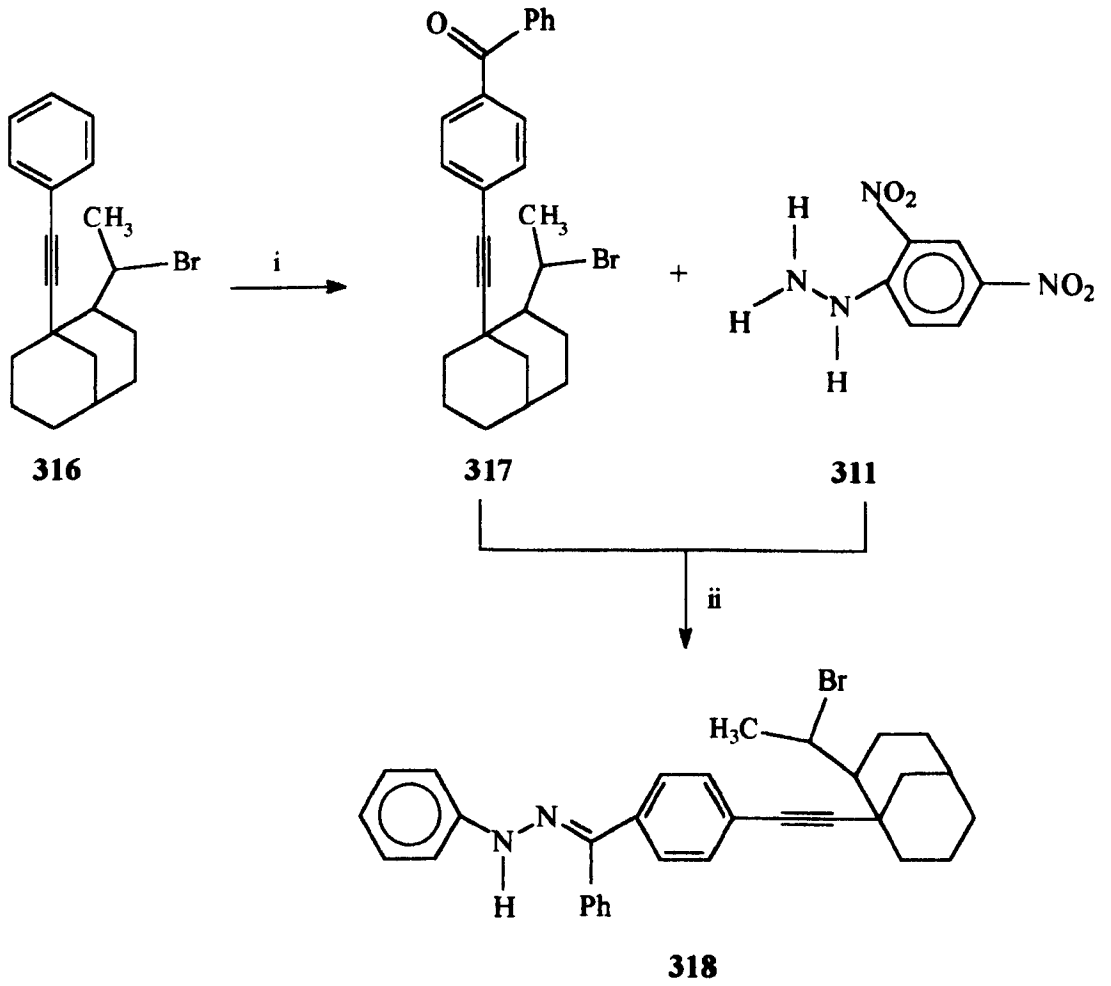

***Reagents and conditions*** i, 1.0M phenylethynylmagnesium bromide, THF, reflux; ii, $Co_2(CO)_8$, DCM; iii, $TiBr_4$, DCM, -10°C; iv, $Ce(SO_4)_2$, MeOH.

**(Scheme 78)**

Subsequent reaction of (313) with octacarbonyl dicobalt in DCM provided, the cyclisation precursor (314) in 95% yield, whereupon treatment with titanium (IV) bromide gave the desired product (315) in 88% yield. Upon performing demetallation, and purification the cycloadduct (316) was achieved in 71% yield, in the form of a

yellow oil. Examination of the $^{1}H$ NMR and $^{13}C$ NMR spectra, showed the anticipated characteristic peaks as found in the previous investigations.

The next aim was to functionalise the aromatic ring in (316) *via* a Friedel-Crafts[117] acylation reaction. This transformation would provide a ketone moiety, predominantly in the *para* position (317), for derivatisation with 2,4-dinitrophenylhydrazine (311). Success in this reaction would possibly afford a crystalline DNP-derivative (318) for X-ray analysis.




318

***Reagents and conditions*** i, PhCOCl, $AlCl_3$; ii, $H_2SO_4$, MeOH.

**(Scheme 79)**

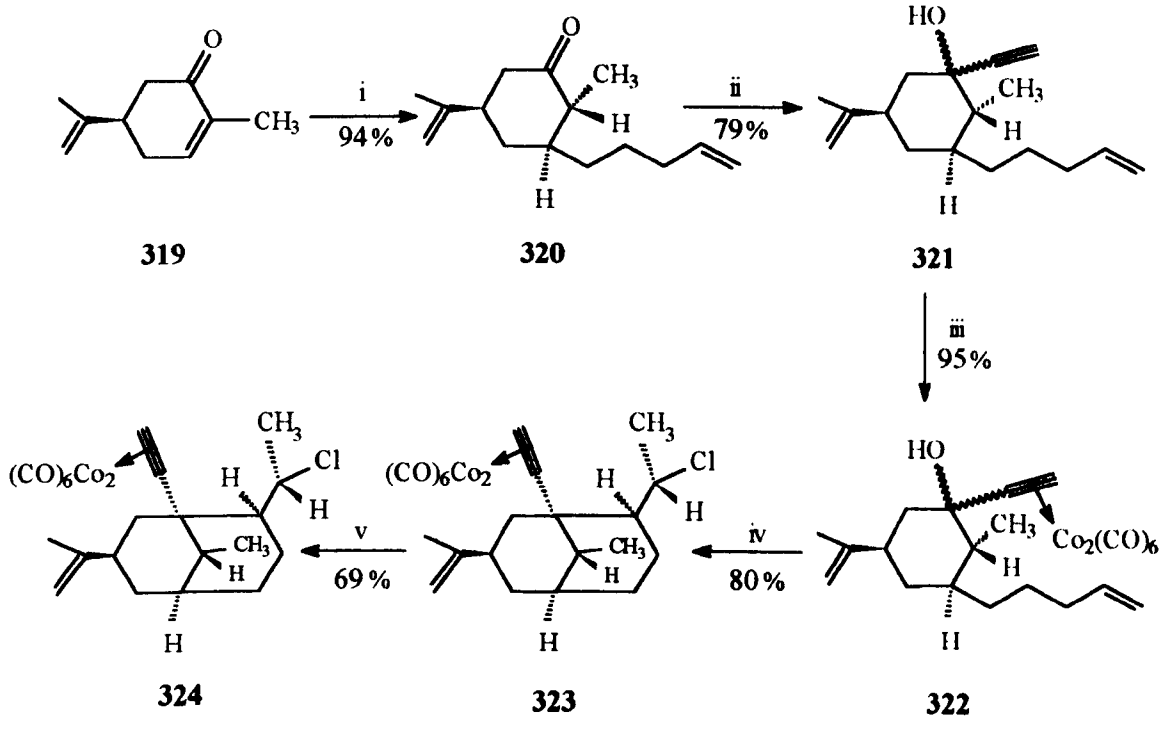
As part of the future endeavours, this chemistry should therefore be investigated.

Nevertheless, the successful synthesis of compound (316) had provided an extension to these studies confirming the generality of this methodology.

## 3.11 A Chiral Approach to the Synthesis of Bicyclo[3.3.1]nonanes

As part of the final investigations, the possibility of extending this approach to develop a stereoselective synthesis for bicyclo[3.3.1]nonane was attempted. It was decided that the readily available monoterpene *(S)*-(+)-carvone (319), derived from the chiral pool of natural products, could be used as a chiral template. The use of carvone as a chiral starting material has been extensively reviewed.[118] If success was achieved using this reagent, it was foreseen that this could later be developed into a stereoselective approach to the AB ring system of taxol. Consequently, the same synthetic route reported for the synthesis of 2-(1-chloroethyl)-1-ethynylbicyclo[3.3.1]nonane (256) was undertaken to form the cycloadduct.

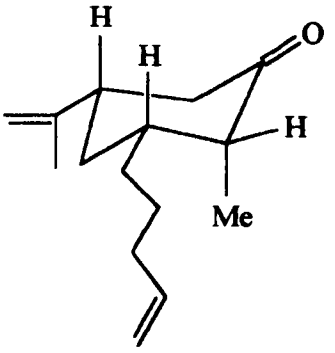
Thus conjugate addition to (*S*)-(+)-carvone (319) provided (320) as an inseparable 5:1 mixture of diastereoisomers, in 94% yield **(Scheme 80)**. This selectivity was disappointing, as a 4:1 selectivity had previously been observed with the conjugate addition using 2-methylcyclohex-2-ene-1-one (275).




***Reagents and conditions*** i, 5-bromo-1-pentene, Mg turnings, THF, $(CH_3)_2S.CuBr$, $(CH_3)_3SiCl$, HMPA, 1M HCl; ii, 0.5M ethynylmagnesium bromide, THF; iii, $Co_2(CO)_8$, DCM; iv, $TiCl_4$, DCM, -10°C; v, $Ce(SO_4)_2$, MeOH.

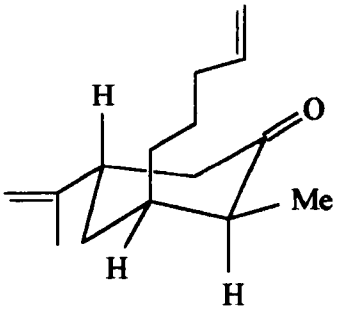
**(Scheme 80)**

Identification of the diastereoisomers were determined by following similar extensive $^1H$ NMR investigations to that described for the compound 2-methyl-3-(4-pentenyl)-cyclohexan-1-one (275). However, upon performing proton decoupling experiments[108] it was not immediately apparent from the magnitude of coupling constants $J$=7Hz (major isomer) and $J$=5.5Hz (minor isomer) in deciding between the configurations given **(Figure 34)**.



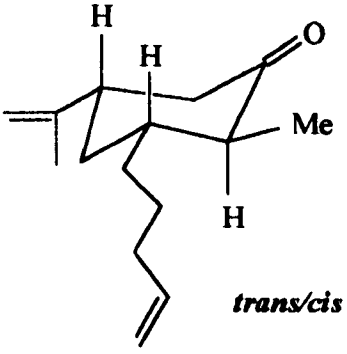

*cis/cis*

**320a**




*cis/trans*

**320b**




*trans/cis*

**320c**

**(Figure 34)**

To elucidate the problem further an NaOD experiment was then conducted. Since the ratios remained unchanged, it was thereby suggested that the mixture of the diastereoisomers were *trans/cis* (320c) (major isomer) and *cis/trans* (320b) (minor isomer).

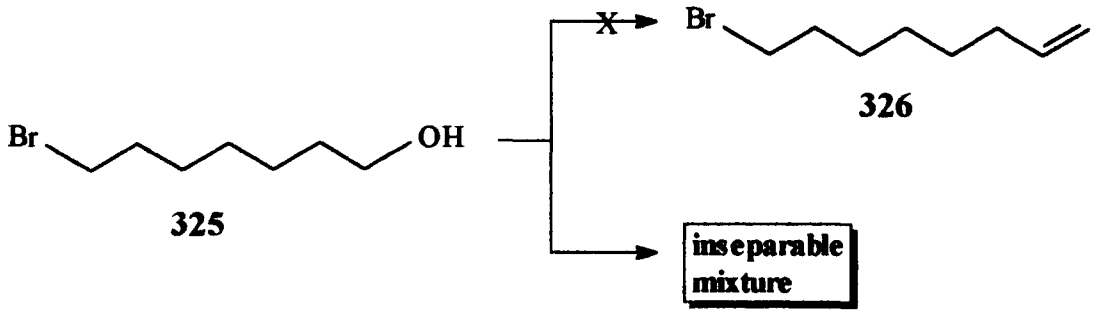
Next, the propargylation step was achieved in 79% yield to provide (321) as a 10:1 mixture of inseparable diastereoisomers. It was anticipated that these isomers maybe separated *via* cobalt complexation.[110] However, one spot was again observed by TLC analysis.

Reaction of (322), with the Lewis acid, led to a rapid *intra*molecular Nicholas cyclisation reaction, that showed two faster moving compounds by TLC analysis ($R_f$ 0.75 and 0.76) (323). Several attempts to separate these compounds, by column chromatography were made, however this procedure proved unsuccessful. Thus, with the removal of the cobalt complex moiety a major product was isolated. Spectroscopic analysis showed the compound to be (324), obtained in 69% yield. Although the $^1$H NMR spectrum showed one set of signals for the three methyl groups, the $^{13}$C NMR revealed all the signal resonances to be duplicate, suggesting that a mixture of diastereoisomers had been isolated.

Interestingly the elimination of HCl was not observed in this reaction.

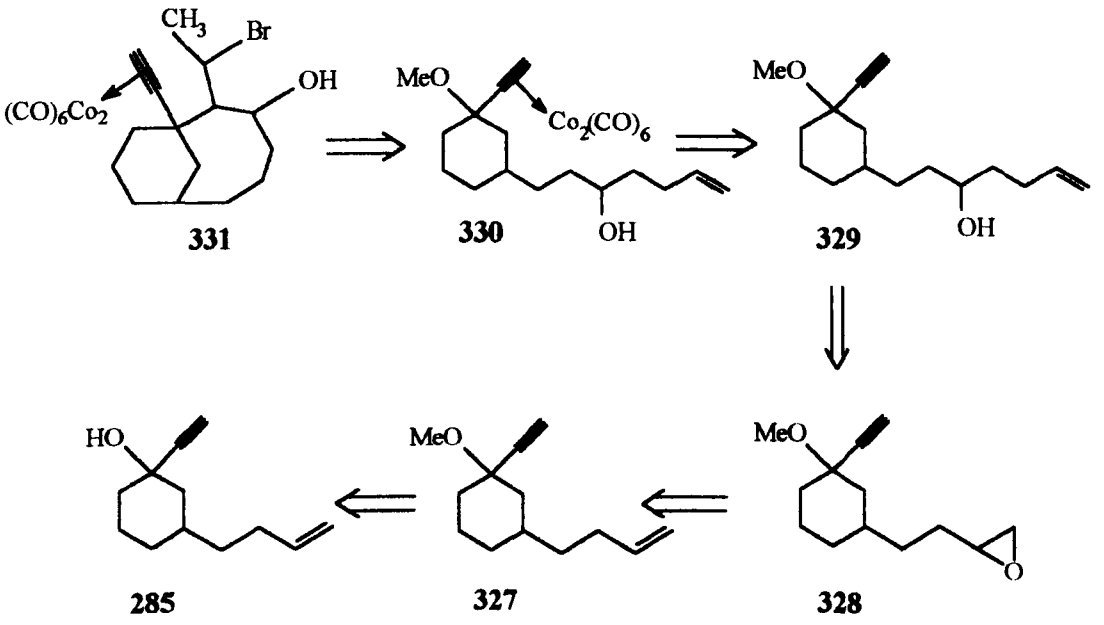
## 3.12 Synthesis of Bicyclo[5.3.1]undecane

To conclude these investigations into this novel methodology, an attempt to synthesise bicyclo[5.3.1] undecane, that is found in taxol (5) and vinigrol (6), was made. Since the reagent 7-bromohept-1-ene (326) was not commercially available, it was first undertaken to prepare this compound. Literature evidence had suggested that one possible route could be *via* dehydration of the corresponding alcohol using phosphorus oxychloride ($POCl_3$).[119] However, the reaction proved unsuccessful. Upon treatment of the bromoalcohol (325) with $POCl_3$, a significant number of products were formed. A possible explanation is that, in addition to the loss of the hydroxyl group, the elimination of HBr could also be occurring **(Scheme 81)**.




**(Scheme 81)**

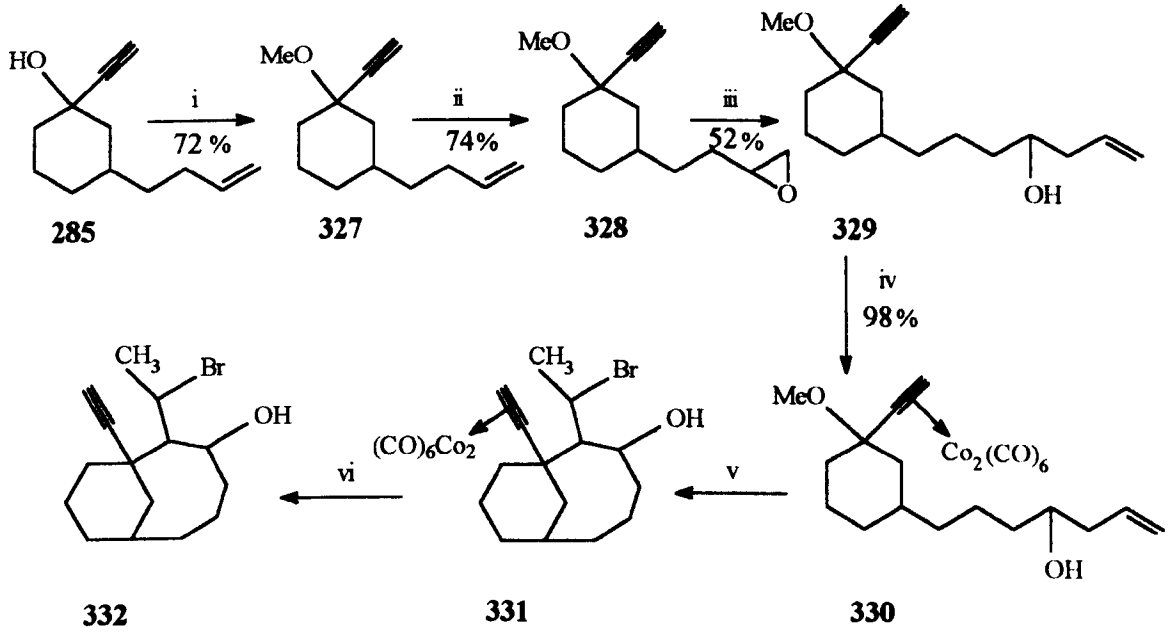
With this in mind, it was then decided to use a different approach to obtain the required seven carbon pendant alkene. Thus, the following retrosynthetic analysis **(Figure 35)** was proposed.




**(Figure 35)**

Commencing with the propargyl alcohol (285) previously synthesised, the required key precursor (330) could be efficiently made within 3 synthetic steps. It was envisaged that the use of the precursor (330), would have the advantage of the hydroxyl group, which could possibly allow subsequent chemistry to be performed if cyclisation to (331) was achieved.

Thus, methylation of the hydroxyl group, using iodomethane and finely ground potassium hydroxide in DMSO, gave the desired methyl ether (327) in 72% yield, following the removal of excess DMSO by reduced pressure distillation **(Scheme 82)**.




***Reagents and conditions*** i, MeI, KOH, DMSO; ii, *m*CPBA, DCM, 0°C→r.t; iii, 1.0M allylmagnesium bromide, CuI, THF, -20°C; vi, $Co_2(CO)_8$, DCM; iv, $TiBr_4$, DCM, -10°C; v, $Ce(SO_4)_2$, MeOH.

**(Scheme 82)**

This conversion was necessary to prevent acid attack at the hydroxyl group, following the transformation of the alkene to the epoxide.[120] Analysis of the $^1H$ NMR spectrum

showed the presence of the required *OMe* functionality as a sharp singlet at δ3.39 ppm that integrated for 3 protons.

Next the reaction of (327) with *meta*-chloroperoxybenzoic acid (*m*CPBA) in DCM furnished the epoxide (328) in 74% yield, as a pale yellow oil, after purification. It was found that the *meta*-chlorobenzoic acid by-product, could be easily removed by column chromatography, as it is was clearly observed by UV examination of the reaction mixture by TLC. Upon inspection of the $^{1}H$ NMR spectrum of compound (328), the absence of the vinyl protons at δ4.91-5.03 ppm and δ5.73 ppm were seen. The addition of the methine proton of the epoxide, was as expected, found to be a multiplet with a chemical shift of δ2.85-2.91 ppm.

The copper catalysed ring opening of the epoxide (328) with the Grignard reagent allylmagnesium bromide[121] was next achieved in 52% yield as an inseparable 1:1 mixture of diastereoisomers (329). Thorough examination of the $^{1}H$ NMR and $^{13}C$ NMR was found to be consistent with the desired molecule. From the $^{1}H$ NMR spectrum, the alkenyl protons were found to resonate at δ4.91 ppm and δ5.49 ppm and the hydrogen atom adjacent to the hydroxyl group was found as a multiplet at δ3.55 ppm. The $^{13}C$ NMR showed this methine carbon to be downfield as expected at δ71.66 ppm. In addition the vinyl carbon atoms were seen at δ114.73 ppm and δ138.97 ppm.

Following cobalt complexation to provide (330) in a quantitative yield, the *intra*molecular cyclisation was then attempted using the Lewis acid, titanium (IV) bromide. Analysis of the crude reaction mixture showed the presence of a new compound consistent with the cyclised product ($R_f$ 0.85). The crude material was then subjected to decomplexation procedures. Unfortunately the NMR spectrometer was non-functioning during this important time as my project was concluding. As a result the purified product had somewhat decomposed whilst retained in storage.

Nevertheless $^1$H NMR spectrum showed characteristic resonances, such as the methyl doublet at δ1.28 ppm, the methine proton adjacent to the bromine at δ4.91 ppm and the methine proton (next to the -OH), as a multiplet at δ3.80 ppm.

Further investigation would elucidate the success of this cyclisation reaction.

## 3.13 Conclusion

The results of this programme of research have shown how versatile this novel methodology is for the production of bridged bicyclic compounds. These studies have shown that the reaction is noteworthy in terms of efficiency and conciseness of the synthetic route. The formation of an allyl silane or an *O*-silylenol derivative, which introduces further steps into the procedure, are avoided by using a simple, accessible alkene that allows rapid entry into the desired bicyclic compound.

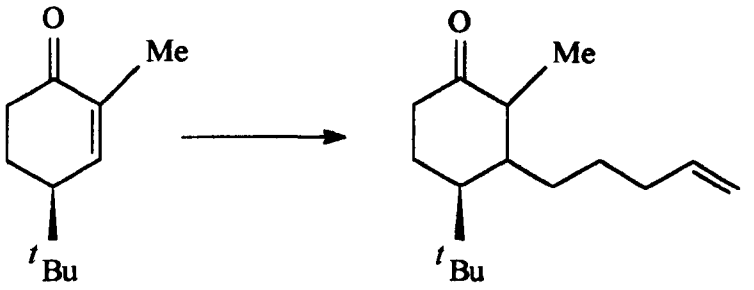
## 3.14 Future Investigations

Future directions could be:

1) initially as an accurate structural analysis was not obtained for the bicyclo[5.3.1]undecane (332) ring system, the synthesis of this compound should be repeated.

2) to perform additional chemistry with the compound 2-(1-bromoethyl)-1-phenylethynylbicyclo[3.3.1]nonane (316), in order to secure a crystalline derivative for X-ray analysis.

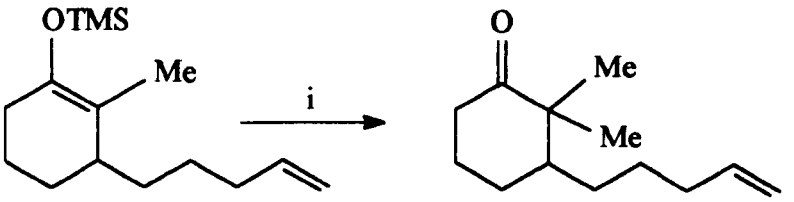
3) to continue with the stereoselective approach for the synthesis of the bicyclo[3.3.1]nonane system. Conjugate addition of 5-bromo-pent-1-ene (253) to 4-*tert*-butyl-2-methyl-cyclohex-2-en-1-one (333)[122] may lead to the isolation of only one isomer which was not observed using *(S)*-(+)-carvone **(Scheme 83)**.




**333** **334**

**(Scheme 83)**

4) to investigate the chemistry for the introduction of the second methyl substituent for compound 2-methyl-3-(4-pentenyl)-cyclohexan-1-one (275) (**section 3.8.1**). This reaction is important as taxol (5) contains two geminal dimethyl groups. A previous study had been conducted earlier on in the project that involved the trimethylsilyl enol ether (335) **(Scheme 84)**. In this synthetic route compound (335) was treated with lithium amide and methyl iodide, following the literature procedure.[123] However, the reaction met with limited success. Analysis of the crude material by $^1$H NMR showed very little of the desired alkylated product (276).




**335** **276**

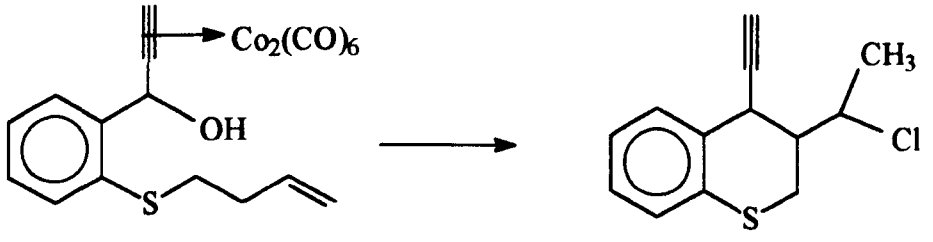
**(Scheme 84)**

Since, at the time other important investigations were being performed, this reaction was not studied further. It is possible that a modification of the reaction conditions may have resulted in success to form the compound (276) in a good yield. Thus this reaction should be repeated. In addition to this investigation, the alternative route involving the alkylation of the ketone, 2-methyl-3-(4-pentenyl)-cyclohexan-1-one (275) (**section 3.8.1**), should be investigated.

5) to extend the generality of the reaction by examining the consequence of the two following changes:

a) aromatic ring systems

b) the addition of a sulphur atom into the pendant alkenyl group.




**336** **337**

**(Scheme 85)**

The successful cyclisation of compound (336) to afford the fused ring system (337), may open a path to sulphur containing natural products **(Scheme 85)**.

6) and finally to incorporate this novel methodology for the possible synthesis of natural products, such as the aphidicolanes (3a), stemodanes (3b) and gibannes (4).

# Chapter Four

## Experimental

# 4.0 Experimental

## 4.1 General Procedure

All reactions were conducted under a nitrogen atmosphere unless otherwise stated. Extractions were performed using unpurified organic solvents and the extracts obtained were dried over anhydrous magnesium sulphate or fused calcium chloride, filtered and the reagents removed under reduced pressure using a rotary evaporator (20mmHg).

Thin layer chromatographic separations were performed on silica gel precoated plastic plates with a fluorescent indicator $UV_{254}$, in which visualisation was achieved through either using short wave ultraviolet radiation, immersion in iodine vapour, or by heating after immersion in aqueous potassium permanganate.

Flash chromatography was performed according to the Still method[124] using 240-400 mesh silica gel. The solvents in use were unpurified diethyl ether, petroleum spirit b.pt 40-60°C and hexane b.pt 67-70°C.

## 4.2 Instrumentation

Infra-red spectra were recorded using Perkin-Elmer (1600 series) Fourier Transform Infra-red spectrophotometer as a liquid film between two sodium chloride discs, unless otherwise stated, and are quoted in wavenumbers ($cm^{-1}$). Proton Nuclear Magnetic Resonance ($^1H$ NMR) spectra and Carbon-13 Nuclear Magnetic Resonance spectra, were recorded using the Bruker AC-300 Fourier Transform Spectrometer at 300 MHz and 75.45 MHz respectively. The solvent deuterochloroform was used as the internal standard in which peak positions are quoted on the $\delta$ scale relative to this solvent, unless otherwise stated. Low resolution mass spectra were recorded using a VG TRIO-2-mass spectrometer under Electron Impact (EI) conditions, whereas the high

resolution data was provided by EPSRC, using a VG-ZAB-E spectrometer. Microanalyses were conducted and reported by Medac Ltd (Uxbridge, Middlesex) using a CEC 240XA. Optical activities were measured using an AA-10 polarimeter. The following standard conventions have been adopted for quoting physical data:[125]

$[\alpha]_D^{20}$: values are recorded in $10^{-1}$ deg $cm^2$ $g^{-1}$ and the concentration in chloroform is quoted in parenthesis.

**$\nu_{max}$ (neat)/$cm^{-1}$** : major bands are expressed in wavenumbers.

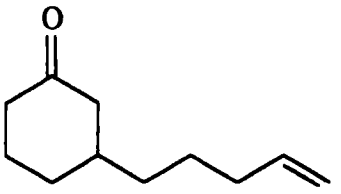
**$\delta_H$ (MHz; solvent)**: $^1H$ NMR data represents s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, br = broad. Coupling constants *J* are given in Hz.

**$\delta_c$ (MHz; solvent)**: Carbon-13 ($^{13}C$) NMR data.

**EI , m/z** where $M^+$ refers to the parent ion and the number in parenthesis the relative intensity and base peak relative intensities are represented as (100%).

# 4.3 Experimental Procedures

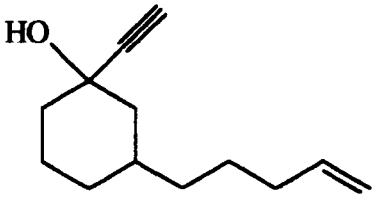
- **Synthesis of 3-(4-pentenyl)-cyclohexan-1-one (254)**



To a dry three necked flask, were added oven dried magnesium turnings (0.88g, 36.90mmol, 1.1eq) and anhydrous THF (5ml). A crystal of iodine was then added to the contents of the flask and was followed by the dropwise addition of 5-bromopent-1-ene (5.0g, 33.55mmol) (253) in THF (10ml). The formation of the Grignard reagent was indicated by the disappearance of the iodine colouration, production of cloudiness and gentle boiling of the THF. The rate was adjusted so that the THF boiled gently from the heat of the reaction alone, without the application of external heat over a period of 5-10 mins. The mixture was then heated to reflux gently, for a further 30 mins to complete the reaction, whereupon it was cooled to -78°C. Upon cooling additional THF (60ml) was added. To this solution was added $(CH_3)_2S.CuBr$ (0.25g, 1.21mmol) and HMPA (10ml, 57.37mmol, 1.71 eq) and stirred for 10 mins, whereupon a mixture of cyclohex-2-en-1-one (252) (2.25g, 23.48mmol) and trimethylchlorosilane (4ml, 47.30mmol, 1.41 eq) in THF (5ml) over a 30 min period. Slow addition was required for high geometrical purity of the silyl enol ether. The solution was then allowed to stir for 2 hrs at -78°C and 1hr at an ambient temperature. After this time, 1M HCl (60ml) was added and the mixture was diluted with hexane (50ml). The mixture was then filtered through Celite and the filtrate was washed with water (3x10ml) (to remove HMPA). The water layer was then extracted with hexane (4x20ml). The organic layer was washed once with saturated $NH_4Cl$, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by column chromatography on silica (eluant hexane:diethyl ether, 90:10, $R_f$ 0.59) gave compound (257) as a yellow oil (3.81g, 98%), (Found: C, 75.46; H, 10.34; $C_{11}H_{18}O$ requires C, 79.47; H,

10.91), $\upsilon_{max}$ **(neat/cm$^{-1}$)** 3075, 2927, 2858, 1713, 1640; $\delta_H$**(300 MHz; CDCl$_3$)** 1.28-2.46(15H, m, 7x$CH_2$+$CH$), 4.95(1H, dm, *J*2 and 10 HC=$CH$), 4.99(1H, dm, *J*2 and 18, HC=$CH$), 5.80(1H, m $HC$=$CH_2$); $\delta_c$**(75.45 MHz; CDCl$_3$)** 25.24(t), 25.88(t), 31.53(t), 33.68(t), 35.96(t), 38.90 (d), 41.45(t), 48.11(t), 114.55(t), 138.52(d), 211.82(s); **HRMS EI m/z** 166.1358 ($M^+$) $C_{11}H_{18}O$ requires 166.1358, **LRMS** 151, 124, 97, 42(100%), 54.

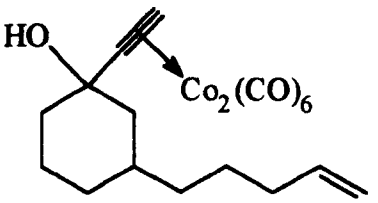
- **Synthesis of 1-ethynyl-3-(4-pentenyl)-cyclohexan-1-o1 (255)**




To a solution of compound (254) (3.81g, 22.95mmol), in anhydrous THF (30ml), under a nitrogen atmosphere was added dropwise ethynyl magnesium bromide (55ml, 27.54mmol, 1.2 eq). The mixture was left to stir at an ambient temperature for 30 mins and then refluxed for 8hrs. Analysis by T.L.C showed the presence of slower moving product (hexane:diethyl ether, 80:20, $R_f$ 0.15). The reaction mixture was quenched by the addition of a saturated ammonium chloride solution (40ml) and the mixture was then extracted with diethyl ether (3x20ml). The recombined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford the crude product. Purification by column chromatography on silica eluted with hexane:diethyl ether (85:15, $R_f$ 0.18) furnished the desired compound (255) as a yellow oil (3.87g, 88%), (Found: C, 80.59; H, 10.41; $C_{13}H_{20}O$ requires C, 81.20; H, 10.48); $\upsilon_{max}$**(neat)/ cm$^{-1}$** 3470, 3309, 3077, 2930, 2850, 1642; $\delta_H$ **(300 MHz; CDCl$_3$)** 1.08-1.73(11H, m, 6x$CH_2$), 1.99-2.07(5H, m, 2x$CH_2$ + O$H$), 2.48(1H, s, C≡$CH$), 4.92(1H, dm, *J*2 and 10 HC=$CH$), 5.02(1H, dm, *J*2 and 16, HC=$CH$), 5.73-5.87(1H, m, $HC$=$CH_2$); $\delta_c$**(75.45 MHz; CDCl$_3$)** 26.05(t), 31.83(t),

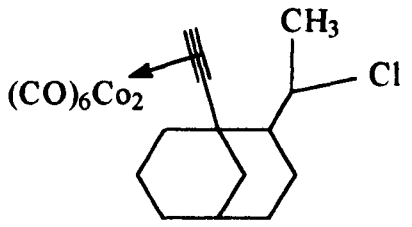
33.90(t), 35.19(t), 36.06(d), 38.93(t), 39.95(t), 46.47(t), 70.04(s), 72.69(d), 87.45(s), 114.35(t), 138.90(d); **HRMS EI m/z** 192.1486($M^+$) $C_{13}H_{20}O$ requires 192.1486, 191.1486($M^+$-1), **LRMS** 56, 68, 82(100%), 95, 135, 149, 177.

- **Synthesis of hexacarbonyl[1-ethynyl-3-(4-pentenyl) cyclohexan-1-ol]dicobalt (250)**



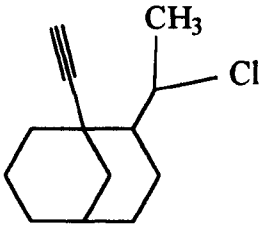

To a solution of the propargyl alcohol (255) (3.87g, 20.16mmol), in anhydrous diethyl ether (30 ml), was added octacarbonyl dicobalt (7.58g, 22.17mmol, 1.1 eq). The reaction mixture was allowed to stir for 1hr at ambient temperature under an nitrogen atmosphere. Analysis by T.L.C. (hexane:diethyl ether 80:20) showed the presence of a faster moving product ($R_f$ 0.91). The solvent was then removed *in vacuo*. Following purification on silica eluted with hexane:diethyl ether (70:30), gave compound (250) (9.14g, 95%) as a red oil, $\upsilon_{max}$**(neat)/cm**$^{-1}$ 3472, 3080, 2932, 2850, 2093, 2050, 2022, 1641.

- **Synthesis of hexacarbonyl[2-(1-chloroethyl)-1-ethynylbicyclo[3.3.1]nonane]dicobalt (251)**




To a solution of hexacarbonyl[1-ethynyl-3-(4-pentenyl)cyclohexan-1-ol]dicobalt (1.04g, 2.18mmol) (250) in anhydrous dichloromethane (20ml), was added $TiCl_4$ (2.40ml, 21.80mmol), and the reaction allowed to stir at 0°C. T.L.C analysis after 10mins showed the presence of a faster moving product ($R_f$ 0.96, hexane 100%). Saturated $NaHCO_3$ (20ml) was then added and the mixture was partitioned. The aqueous layer was extracted with DCM (4 x 20ml) and the organic layers were dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* to afford compound (251) as a brown oil (0.79g, 73%), $\upsilon_{max}$**(neat)/cm$^{-1}$** 2933, 2847, 2091, 2052, 2025.

- **Synthesis of 2-(1-chloroethyl)-1-ethynylbicyclo[3.3.1]nonane (256)**

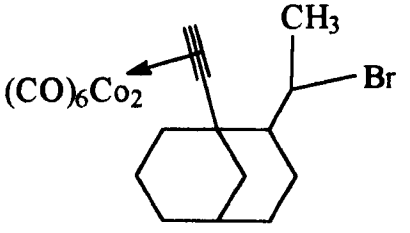



To compound (251) (0.79g, 1.60mmol) was added cerium (IV) sulphate (2.13g, 6.40mmol) in methanol (15ml) and the reaction mixture allowed to stir at an ambient

temperature under a nitrogen atmosphere until the brown solution turned yellow. After 3 hours, TLC analysis showed the presence of a slower moving compound ($R_f$ 0.23, hexane 100%). The reaction mixture was passed through a plug of silica (to remove excess cerium (IV) sulphate) and washed with diethyl ether (3x10ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to provide a dark yellow oil. Purification by column chromatography on silica (eluant hexane 100%) gave the product (256) as a 1.2:1 mixture of †diastereoisomers (0.23g, 68%), $\nu_{max}$**(neat)/cm**$^{-1}$ 3310, 2967, 2860, 2091; $\delta_H$**(300 MHz; CDCl$_3$)** 1.07-1.43(5H, m, 2x$CH_2$+$CH$), 1.49(3H, d, *J*8, $CH_3$), 1.55-1.84(9H, m, 4x$CH_2$+$CH$), 2.80(1H, s, C≡$CH$), 4.00-4.06(1H, dm, ClC$H$CH$_3$), $\delta_c$**(75.45 MHz; CDCl$_3$)** 23.88(t), 25.37(q), 25.59(t), 27.63(t), 27.91(t), 33.11(d), 35.09(t), 35.61(d), 40.45(t), 58.72(d), 74.37(d), 85.53(s); **HRMS EI m/z** 210.1175($M^+$) $C_{13}H_{19}Cl$ requires 210.1175, **LRMS** 175, 105(100%), 91, 77, 55.

† The $^1$H NMR spectrum showed only one set of resonance for these diastereoisomers. Upon the analysis of the $^{13}$C NMR, signals that maybe attributed to the other diastereoisomer were visible. These resonances however overlapped with the major diasteroisomer, therefore have not been recorded.

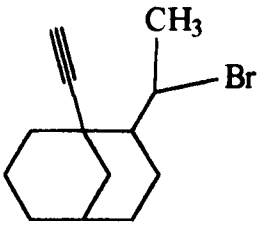
- **Synthesis of hexacarbonyl[2-(1-bromoethyl)-1-ethynylbicyclo[3.3.1]nonane]dicobalt (338)**




The procedure for the synthesis compound (338) was the same as the method used for the synthesis of (251) (p.135) using the following changes: compound (250) (3.0g,

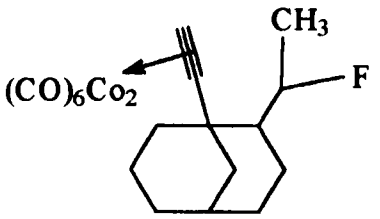
6.30mmol) in DCM (40ml), was reacted with $TiBr_4$ (23.16g, 63.02mmol) to afford (337) (2.56g, 76%), $\nu_{max}$**(neat)/cm$^{-1}$** 2959, 2864, 2092, 2054, 2025.

- **Synthesis of 2-(1-bromoethyl)-1-ethynylbicyclo[3.3.1]nonane (259)**



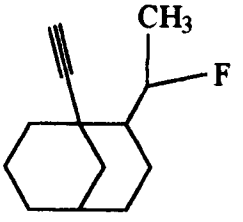

The above compound was achieved adopting the similar method to that given for the formation of (256) using the following quantities: Compound (338) (2.56g, 4.76mmol), cerium (IV) sulphate (6.32g, 19.02mmol), methanol (30ml) to provide compound (259), following purification on silica eluted with petrol (100%, $R_f$ 0.32), in a yield of (0.96g, 80%), $\nu_{max}$**(neat)/cm$^{-1}$** 3298, 2960, 2866, 2094; $\delta_H$**(300 MHz; $CDCl_3$)** 1.10-1.56(9H, m, 4x$CH_2$+$CH$), 1.70(3H, d, *J*8, $CH_3$), 1.75-1.85(5H, 2x$CH_2$+$CH$), 2.79(1H, s, C≡$CH$), 4.07-4.16(1H, m, $CH$Br); $\delta_c$**(75.45MHz; $CDCl_3$)** 25.12(t), 26.50(q), 27.85(t), 27.94(d), 35.40(t), 35.47(t), 35.53(t), 39.61(d), 41.26(t), 51.73(d), 74.42(d), 85.51(s); **HRMS EI m/z** 254.0670($M^+$) $C_{13}H_{19}Br$ requires 254.0670, **LRMS** 185, 151, 133, 119, 105(100%), 91, 67.

- **Synthesis of hexacarbonyl[1-ethynyl-2-(1-fluoroethyl) bicyclo[3.3.1]nonane]dicobalt (339)**




The formation of (339) was undertaken using the same procedure as described for the synthesis of (251) but with the following changes: Compound (250) (3.0g, 6.30mmol), was reacted with $TiF_4$ (7.79g, 62.88mmol, 10eq), in DCM (30ml), to afford product (339) (1.60g, 53%), $\nu_{max}$**(neat)/cm**$^{-1}$ 2979, 2874, 2092 2085, 2051.

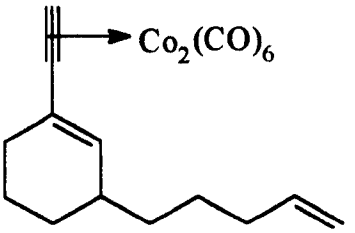
- **Synthesis of 1-ethynyl -2-(1-fluoroethyl)bicyclo[3.3.1]nonane (260)**




The isolation of compound (260) was achieved using the method given for (256) using compound (339) (1.60g, 3.35mmol), cerium (IV) sulphate (4.45g, 13.42mmol), methanol (25ml) to provide compound (260), after purification on silica (eluant hexane

100%, $R_f$ 0.28) in a yield of (0.30g, 46%), **$\nu_{max}$(neat)/cm$^{-1}$** 3311, 2969, 2866, 2094; **$\delta_H$(300 MHz; $CDCl_3$)** 1.13(3H, d, *J*8, C*H*$_3$), 1.19-1.96(14H, m, 6xC*H*$_2$+3xC*H*), 2.80(1H, s, C≡C*H*), 5.01(1H, m, C*H*F); **$\delta_c$(75.45 MHz; $CDCl_3$)** 22.70(q), 25.65(t), 27.76(t), 29.37(t), 31.93(d), 34.22(t), 36.92(t), 38.13(d), 41.33(t), 73.28(d), 87.33(s); **LRMS EI m/z** 193($M^+$), 146, 102(100%), 89, 83, 76.

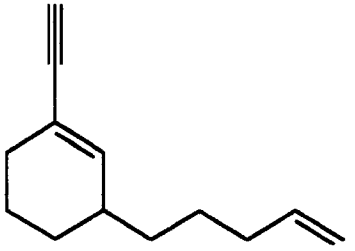
- **Synthesis of hexacarbonyl[1-ethynyl-3-(4-pentenyl)-cyclohex-1-ene] dicobalt (271)**




Compound (271) was formed when an attempt was made to effect the cyclisation reaction using $TiI_4$.

**Spectroscopic data for compound (271): $\nu_{max}$(neat/cm$^{-1}$)** 3303, 3076, 2970, 2880, 2077, 2047, 2028, 1640.

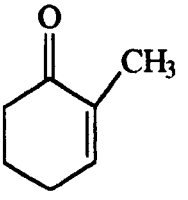
- **Synthesis of 1-ethynyl-3-(4-pentenyl)-cyclohex-1-ene (261)**



Decomplexation of the compound (271) was performed using the procedure described for compound (256).

**Spectroscopic data for compound (261):** $\nu_{max}$**(neat/cm$^{-1}$)** 3311, 3075, 2972, 2880, 2094, 1640; $\delta_H$**(300 MHz; CDCl$_3$)** 1.14-2.01(13H, m, 6x$CH_2$ + $CH$), 2.72(1H, s, C≡$CH$), 4.86(1H, dm, *J*2 and 8, HC=$CH$), 4.95(1H, dm, *J*2 and 16, HC=$CH$), 6.04-6.11(1H, m, C=$CH$); $\delta_c$**(75.45 MHz; CDCl$_3$)** 25.66(t), 27.74(t), 27.92(d), 33.11(t), 33.93(t), 35.14(t), 35.64(t), 74.30(s), 74.47(d), 81.45(s), 114.37(t), 136.29(d), 141.05(d); **LRMS EI m/z** 174($M^+$), 159, 145, 131, 103, 91(100%), 77.

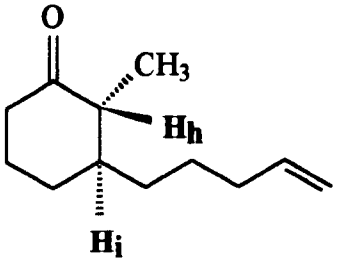
- **Synthesis of 2-methyl-cyclohex-2-en-1-one (279)**



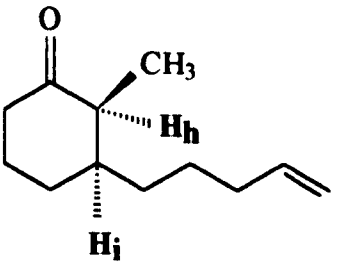

To a three-necked flask, was added 2-methyl-cyclohexan-1-one (277) (15g, 131.36mmol) in DCM (30ml) and the solution was cooled to 0°C. To the solution was added, dropwise, sulfuryl chloride (11.82ml, 147mmol) over a period of 30mins. Upon the completion of the addition, the solution was allowed to stir for a further 2hrs. The yellow solution was then washed with water (3x20ml), once with a saturated solution of NaCl (20ml) and the aqueous layer was extracted with DCM (2x20ml). The extracts were combined and the organic layers were dried over fused calcium chloride. The solvent was removed *in vacuo* to afford 2-chloro-2-methyl-cyclohexan-1-one (278) (9.92g, 69%). The unpurified compound (278) was added to a flask charged with LiCl (2.36g, 55.71mmol) in DMF (30ml) and allowed to stir for 4hrs. To this solution was added diethyl ether (12ml) and 2.5M $H_2SO_4$ (12ml), and the solution was then further stirred for 1hr. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (20ml), and the aqueous layer was extracted with diethyl ether (4x20ml). The organic layers were combined, dried over fused calcium chloride and the solvent was removed *in vacuo*. Purification by distillation through a Vigreux

column provided the required compound (279) as a pale yellow oil (6.15g, 82%), b.p. 98-101°C, (77 mm Hg), $\nu_{max}$**(neat)/cm**$^{-1}$ 3042, 2950, 2873, 1721, 1681; $\delta_H$**(300 MHz; CDCl$_3$)** 1.70(3H, d, *J*2, C*H*$_3$), 1.88-1.98(2H, dt, C*H*$_2$), 2.19-2.30(2H, m, C*H*$_2$), 2.33-2.37(2H, t, C*H*$_2$), 6.67-6.70(1H, br, =C*H*); $\delta_c$**(75.45 MHz; CDCl$_3$)** 15.94(q), 23.25(t), 25.97(t), 38.27(t), 145.61(d); **LRMS EI m/z** 110($M^+$), 83, 82(100%), 67, 54, 41, 39.

- **Synthesis of 2-methyl-3-(4-pentenyl)-cyclohexan-1-one (275)**
  **(Showing the relative stereochemistry for H$_h$ and H$_i$)**




**(275f)**



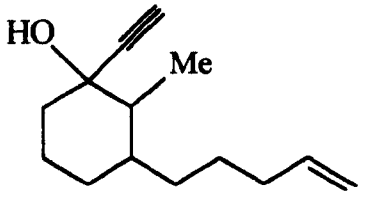

**(275g)**

The synthesis of compound (275) was achieved using the same method described for the formation of (254) but using magnesium turnings (0.71g, 29.52mmol), 5-bromo-1-pentene (4.0g, 26.84mmol) within THF (10ml). Upon cooling THF (50ml), $(CH_3)_2S.CuBr$ (0.20g, 0.97mmol), HMPA (8ml, 45.89mmol), $ClSiMe_3$ (3.22ml, 37.84mmol), 2-methyl-2-cyclohex-2-en-1-one (2.07g, 18.82mmol), 1M HCl (50ml) and hexane (40ml) to furnish the product (275) after purification on silica (eluant petrol: diethyl ether, 80:20, $R_f$ 0.34) as a 4:1 mixture of diastereoisomers (3.01g, 89%), (Found: C, 79.92; H, 11.13; $C_{12}H_{20}O$ requires C, 79.94; H, 11.18); **Spectroscopic data for the *trans* diastereoisomer (275f):** $\nu_{max}$**(neat)/cm**$^{-1}$ 3076, 2949, 2870, 1713, 1640; $\delta_H$**(300 MHz; CDCl$_3$)** 1.03(3H, d, *J*6.6, C*H*$_3$), 1.17-2.33(13H, m, 6×C*H*$_2$+2×C*H*), 2.16(1H, qt, *J*10, C*H*), 4.83(1H, dm, *J*2 and 8, HC=C*H*), 4.94(1H, dm, *J*2 and 14, HC=C*H*), 5.62-5.78(1H, m, *H*C=CH$_2$); $\delta_c$**(75.45**

**MHz; $CDCl_3$)** 11.41(q), 23.89(t), 25.37(t), 26.33(t), 28.37(t), 33.31(t), 33.93(t), 41.46(d), 48.89(d), 114.59(t), 138.63(d), 212.43(s); **HRMS EI m/z** 180.1514 $C_{12}H_{20}O$ requires 180.1514 **LRMS** 137, 111(100%), 97, 55.

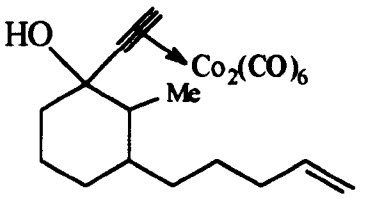
**Spectroscopic data for the *cis* diastereoisomer (275g):** 1.00(3H, d, *J*7, C*H*$_3$), 2.51(1H, qt, *J*5, C*H*), with remaining signals coalescing with the *trans* isomer; **$\delta_c$(75.45 MHz; $CDCl_3$)** 11.98(q), 24.03(t), 25.88(t), 26.99(t), 30.26(t), 33.74(t), 39.75(t), 41.97(d), 49.96(d), 114.59(t), 138.63(d), 212.43(s).

- **Synthesis of 1-ethynyl-2-methyl-3-(4-pentenyl)-cyclohexan-1-ol (280)**



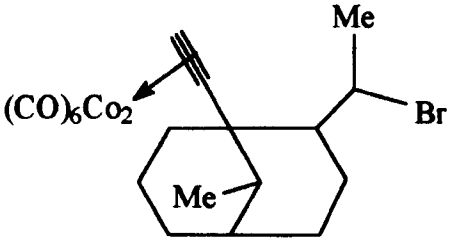

The compound (280) was prepared using the method given for the synthesis for (255) with (275) (2.98g, 16.56mmol), ethynylmagnesium bromide (40ml, 19.87mmol) in THF (35ml). Purification on silica eluted with petrol:diethyl ether (95:05, $R_f$ 0.08) gave the product (280) in a yield of (2.81g, 82%); (Found; C, 79.90; H, 10.53; $C_{14}H_{22}O$ requires C, 81.50; H, 10.75), **$\nu_{max}$(neat)/cm$^{-1}$** 3410, 3307.9, 3076.4, 2944, 2869, 1641; **$\delta_H$(300 MHz; $CDCl_3$)** 0.64-0.67(3H, *J*7, d, C*H*$_3$), 0.80-1.95(15H, 6xC*H*$_2$ + 2xC*H* + OH), 2.30(1H, s, C≡C*H*), 4.73(1H, dm, *J*2 and 14, HC=C*H*), 4.84(1H, dm, *J*2 and 8, HC=C*H*), 5.61-5.66(1H, m, *H*C=CH$_2$); **$\delta_c$(75.45 MHz; $CDCl_3$)** 6.22(q), 23.07(t), 25.40(t), 31.02(t), 33.10(t), 33.91(t), 37.88(d), 40.32(t), 42.74(d), 72.35(s), 73.97(d), 86.04(s), 114.34(t), 139.01(d); **HRMS EI m/z** 206.1671($M^+$) $C_{14}H_{22}O$ requires 206.3272, **LRMS** 191, 81, 56(100%), 42.

- **Synthesis of hexacarbonyl [1-(ethynyl)-2-methyl-3-(4-pentenyl)-cyclohexan-1-ol]dicobalt(340)**



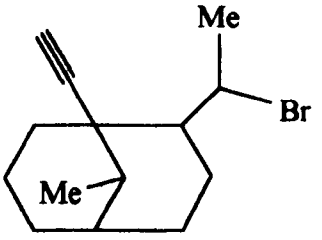

The synthesis of (340) was achieved using the procedure described for the formation of (250), but with (280) (2.0g, 9.71mmol), octacarbonyl dicobalt (3.65g,10.68mmol), diethyl ether (30ml) to furnish, after purification on silica eluted with (petrol:diethyl ether, 85:15, $R_f$ 0.12) (340) (4.31g, 91%), $\nu_{max}$**(neat)/cm**$^{-1}$ 3376, 2945, 2870, 2090, 2049, 2018, 1642.

- **Synthesis of hexacarbonyl[2-(1-bromoethyl)-1-ethynyl-9-methylbicyclo[3.3.1]nonane]dicobalt (341)**




The method was identical to that described for the synthesis of compound (338) (p. 136), except the reaction was performed at a temperature of -10°C and a reaction time of 20 mins was used. Hence to compound (340) (1.0g, 2.04mmol) in DCM (25ml), was added $TiBr_4$ (7.50g, 20.41mmol) to provide the desired product (341) in a yield of (0.97g, 86%), $\nu_{max}$**(neat)/cm**$^{-1}$ 3470, 2939, 2873, 2090, 2050, 2022.

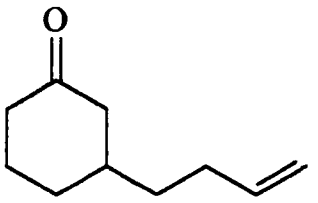
- **Synthesis of 2-(1-bromoethyl)-1-ethynyl-9-methylbicyclo[3.3.1] nonane (281)**




Preparation of the above compound was performed using the same method as that given for (256). To (341) (0.97g, 1.76mmol) in methanol (20ml), cerium (IV) sulphate (2.12g, 6.38mmol) was added to provide (281) as a 3:1 mixture of †diastereoisomers in a yield of (0.39g, 83%), $\nu_{max}$**(neat)/cm$^{-1}$** 3315, 2095, 2940, 2870; $\delta_H$**(300 MHz; $CDCl_3$)** 0.98-1.03(3H, d, *J*7, C*H*$_3$), 1.27-1.58(9H, m, 4×C*H*$_2$+C*H*), 1.63-1.65(3H, d, *J*8, C*H*$_3$), 1.66-1.76(4H, m, C*H*$_2$+2×C*H*), 2.72(1H, s, C≡C*H*), 4.03-4.10(1H, m, C*H*Br); $\delta_c$**(75.45 MHz; $CDCl_3$)** 19.37(q), 20.43(q), 23.71(t), 25.56(t), 26.59(d), 30.00(t), 30.31(d), 32.37(t), 34.02(s), 39.47(d), 41.32(t), 51.64(d), 74.50(d), 87.37(s); **LRMS EI m/z** 268(M$^+$), 255, 241, 199, 133, 119(100%), 105, 91, 77.

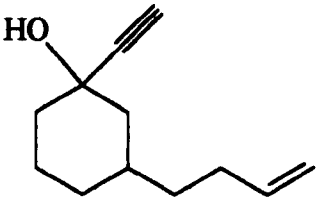
†The $^1$H NMR spectrum showed the alkynyl proton for the minor diastereoisomer at δ2.99 ppm, with the remaining signals in overlap. Upon the analysis of the $^{13}$C NMR, as observed previously with compound (256), signals that maybe attributed to the minor diastereoisomer were found in coalescence with the major diastereoisomer, and therefore have not been recorded.

- **Synthesis of 3-(3-butenyl)-cyclohexan-1-one (284)**



The procedure adopted was identical to that given for the formation of compound (254) but using the following quantities: magnesium turnings (1.17g, 48.89mmol), 4-bromo-1-butene (6.0g, 44.44mmol) in THF (15ml), THF (70ml) upon cooling the solution, $(CH_3)_2S.CuBr$ (0.33g, 1.60mmol), HMPA(13.20ml, 75.89mmol), $ClSiMe_3$(5.3ml, 62.66mmol), cyclohex-2-en-1-one (2.99g, 31.11mmol), HCl (70ml), to provide compound (284) after purification on silica eluted with petrol:diethyl ether (80:20, $R_f$ 0.44) in a yield of (4.12g, 87%), $\nu_{max}$**(neat/cm$^{-1}$)** 3075, 2950, 2866, 1742, 1641; $\delta_H$**(300 MHz; $CDCl_3$)** 1.25-2.44(16H, m, 6x$CH_2$+$CH$), 4.92(1H, dm, *J*2 and 10, HC=C*H*), 5.02(1H, dm, *J*2 and 18, HC=C*H*), 5.69-5.82(1H, m, *H*C=$CH_2$); $\delta_c$**(75.45 MHz; $CDCl_3$)** 25.19(t), 30.81(t), 31.15(t), 35.66(t), 38.38(d), 41.46(t), 48.01(t), 114.77(t), 138.25(d), 214.59(s); **LRMS EI m/z** 152($M^+$), 137, 110, 97(100%), 81, 67, 55.

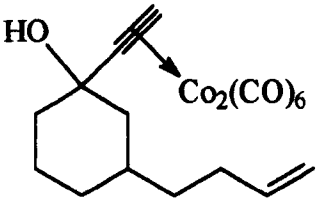
- **Synthesis of 3-(3-butenyl)-1-ethynyl-cyclohexan-1-ol (285)**



The method used was identical to that given for the synthesis of compound (255). Hence using compound (284) (4.0g, 26.32mmol), ethynylmagnesium bromide (68.4ml, 34.21mmol, 1.3eq) in THF (30ml) furnished after purification on silica using the eluant

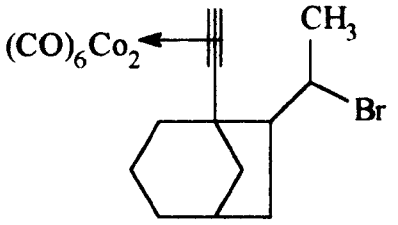
petrol:diethyl ether (70:30, $R_f$ 0.28) product (285) (3.90g, 83%), $\nu_{max}$**(neat/cm$^{-1}$)** 3412, 3303, 3074, 2951, 2868, 1640; $\delta_H$**(300 MHz; CDCl$_3$)** 1.06-2.06(13H, m, 6x$CH_2$+C*H*), 2.38(1H, s, C≡C*H*), 2.98(1H, br, O*H* disappears on $D_2O$ shake), 4.86(1H, dm, *J*2 and 10, HC=C*H*), 5.08(1H, dm, *J*2 and 16, HC=C*H* ), 5.68-5.81(1H, m, *H*C=$CH_2$); $\delta_c$**(75.45 MHz; CDCl$_3$)** 23.29(t), 31.00(t), 31.72(t), 34.82(d), 35.78(t), 39.91(t), 46.33(t), 69.35(s), 72.77(d), 87.40(s), 114.34(t), 138.85(d); **LRMS EI m/z** 177($M^+$-1), 163, 149, 108, 95, 81(100%), 67, 55.

- **Synthesis of hexacarbonyl[3-(3-butenyl)-1-ethynyl-cyclohexan-1-ol]dicobalt (282)**



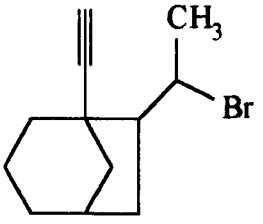

The procedure described for the preparation of (250) was used for the synthesis of (280), but using the propargyl alcohol (285) (1.50g, 8.43mmol) and octacarbonyl dicobalt (3.17g, 9.27mmol), diethyl ether (20ml) to provide after purification on silica eluted with hexane:diethyl ether (75:25, $R_f$ 0.43) compound (282) (3.42g, 88%), $\nu_{max}$**(neat/cm$^{-1}$)** 3481, 3082, 2950, 2870, 2092, 2049, 2026, 1641.

- **Synthesis of hexacarbonyl[7-(1-bromoethyl)-1-ethynyl bicyclo[3.2.1]octane]dicobalt (286)**




The synthesis of compound (286) was achieved using a similar method to that given for the formation of (338). Hence, treatment of (282) (2.0g, 4.33mmol) with $TiBr_4$ (16.0g, 43.53mmol) in DCM (30ml), gave the desired product (286). Purification on silica eluted with petrol:diethyl ether (60:30, $R_f$ 0.60) gave (286) in (1.87g, 82%) yield, $\nu_{max}$**(neat/cm$^{-1}$)** 2951, 2870, 2093, 2054, 2027.

- **Synthesis of 7-(1-bromoethyl)-1-ethynylbicyclo[3.2.1]octane (283)**

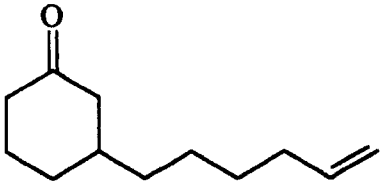



The preparation of compound (283) was performed using the same method as that given for (256). Using compound (286) (1.87g, 3.57mmol), cerium (IV) sulphate (4.74g, 14.27mmol) in methanol (20ml), gave after purification on silica eluted with petrol:diethyl ether (80:20, $R_f$ 0.35) the product (281) (0.64g, 74%) as a 4:1 mixture of diastereoisomers, $\nu_{max}$**(neat/cm$^{-1}$)** 3302, 2954, 2872, 2091; $\delta_H$**(300 MHz; $CDCl_3$)** 1.05-1.56(7H, m, 2x$CH_2$+$CH$), 1.58(3H, d, *J*8, $CH_3$), 1.72-2.27(5H, m, 2x$CH_2$+$CH$), 2.79(1H, s, C≡C*H*), 4.07-4.15(1H, m, C*H*Br) $\delta_c$**(75.45 MHz; $CDCl_3$)** 25.50(t),

126.47(q), 27.94(t), 29.37(t), 30.04(d), 31.04(s), 33.71(t), 35.26(d), 38.31(t), 51.63(d), 76.59(d), 85.39(s) **HRMS EI m/z** 240.0938($M^+$) $C_{12}H_{17}Br$ requires 240.0938, **LRMS** 133, 118, 105(100%), 91, 77.

†As with compound (256), the $^1H$ NMR spectrum showed only one set of resonance for these diastereoisomers. Upon examining the $^{13}C$ NMR, signals that maybe attributed to the other diastereoisomer, were overlapping with the major diasteroisomer and therefore have not been recorded.

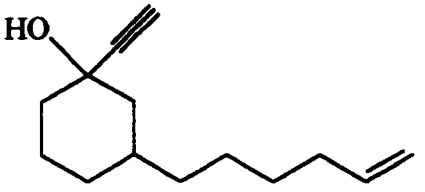
- **Synthesis of 3-(5-hexenyl)-cyclohexan-1-one (288)**



The method was identical to that described for the synthesis of compound (254) using magnesium turnings (0.32g, 13.49mmol), 6-bromo-1-hexene (2.0g, 12.27mmol) in THF (5ml). Upon cooling THF (25ml), $(CH_3)_2S.CuBr$ (0.091g, 0.44mmol), HMPA (3.7ml, 20.97mmol), $ClSiMe_3$ (1.5ml, 17.29mmol), cyclohex-2-en-1-one (0.82g, 8.59mmol), 1M HCl (30ml) and hexane (15ml). This provided the desired compound (288), after purification on silica eluted with petrol:diethyl ether (80:20, $R_f$ 0.61) as a yellow oil (1.33g, 86%), (Found: C, 79.34, H, 11.18; $C_{12}H_{20}O$ requires C, 79.94; H, 11.08); **$\nu_{max}$(neat)/cm$^{-1}$** 3078, 2970, 2861, 1746, 1642; **$\delta_H$(300 MHz; $CDCl_3$)** 1.32-1.94(9H, m, 4×C*H*$_2$+C*H*), 1.99-2.43(8H, m, 4×C*H*$_2$), 4.91(1H, dm, *J*2 and 10, HC=C*H*) 5.01(1H, dm, *J*2 and 16, HC=C*H*), 5.71-5.85(1H, m, *H*C=CH$_2$); **$\delta_c$(75.45 MHz; $CDCl_3$)** 25.30(t), 26.09(t), 28.87(t), 31.31(t), 33.66(t), 36.43(t), 39.04(d),

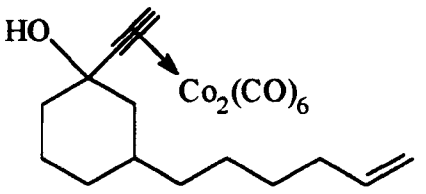
41.52(t), 48.21(t), 114.41(t), 138.83(d), 213.16(s); **HRMS EI m/z** 180.1514 ($M^+$) $C_{12}H_{20}O$ requires 180.1514, **LRMS** 151, 124, 97(100%), 67, 56, 42.

- **Synthesis of 1-ethynyl-3-(5-hexenyl)-cyclohexan-1-ol (289)**



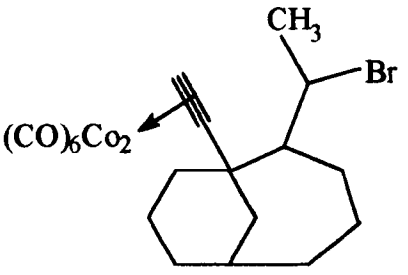

The formation of this compound was achieved in the similar manner to that given for the synthesis of (255) but using a reflux time of 3hrs and using compound (288) (1.0g, 5.56mmol), ethynylmagnesium bromide (13.3ml, 66.67mmol) in THF (18ml), to yield following purification on silica eluted with hexane:diethyl ether (80:20, $R_f$ 0.43), compound (289) (1.08g, 95%), $\nu_{max}$**(neat)/cm$^{-1}$**3411, 3309, 2960, 2880, 3076, 1640; $\delta_H$**(300 MHz; $CDCl_3$)** 1.02-1.68(13H, 6x$CH_2$+$CH$), 1.91-2.05(5H, 2x$CH_2$+$OH$), 2.41(1H, s, C≡$CH$), 4.84(1H, dm, *J*2 and 10, HC=$CH$), 4.95(1H, dm, *J*2 and 18, HC=$CH$), 5.67-5.80(1H, m, $HC$=$CH_2$); $\delta_c$**(75.45 MHz; $CDCl_3$)** 23.42(t), 26.25(t), 29.09(t), 31.86(t), 33.76(t), 35.35(d), 36.50(t), 40.04(t), 46.57(t), 69.54(s), 72.69(d), 87.37(s), 114.25(t), 139.08(d); **LRMS EI m/z** 206($M^+$), 191, 135, 81(100%), 55.

- **Synthesis of hexacarbonyl[1-ethynyl-3-(5-hexenyl)-cyclohexan-1-ol]dicobalt (290)**



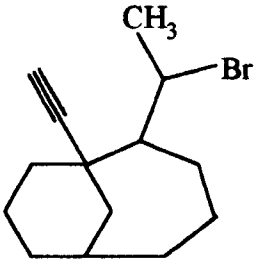

The synthesis of the above compound was conducted using the following changes to that described for the formation of (250). The complexation was carried out in DCM (20ml). Thus, isolation of compound (290) was achieved using compound (289) (1.08g, 5.24mmol), octacarbonyl dicobalt (1.97g, 5.77mmol), to provide a brown oil in (2.52g, 98%), $\nu_{max}$**(neat)/cm**$^{-1}$ 3425, 3045, 2965, 2879, 2092, 2052, 2018, 1642.

- **Synthesis of hexacarbonyl[2-(1-bromoethyl)-1-ethynyl bicyclo[4.3.1]decane]dicobalt (291)**




The formation of (291) occurred using the procedure given for (338). To compound (290) (2.52g, 5.14mmol) was added $TiBr_4$ (18.90g, 51.43mmol) in DCM (30ml), to afford (291) in a yield of (2.47g, 87%), $\nu_{max}$**(neat)/cm**$^{-1}$ 2964, 2880, 2090, 2049, 2017.

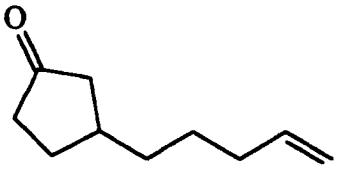
- **Synthesis of 2-(1-bromoethyl)-1-ethynylbicyclo[4.3.1]decane (292)**




The preparation of (292) was undertaken using the method as that reported for the synthesis of (256). Using compound (291) (2.47g, 4.47mmol), cerium (IV) sulphate (5.94g, 17.90mmol) in methanol (25ml) gave after purification on silica, eluted with hexane 100%, ($R_f$ 0.29), the product (292) (0.82g, 75%) as a 2:1 mixture of †diastereoisomers, $\nu_{max}$**(neat)/cm$^{-1}$** 3311.0, 2960, 2879, 2094; $\delta_H$**(300 MHz; $CDCl_3$)** 1.01-1.52(13H, m, 6x$CH_2$+$CH$), 1.69(3H, d, *J*8, $CH_3$), 2.11-2.24(3H, $CH_2$+$CH$), 2.79(1H, s, C≡$CH$), 4.07-4.16(1H, m, $CH$Br); $\delta_c$**(75.45 MHz; $CDCl_3$)** 26.63(t), 26.14(q), 26.47(t), 27.95(t), 30.94(d), 33.11(t), 33.10(t), 35.50(t), 35.99(d), 41.12(t), 51.88(d), 74.33(d), 86.04 (s); **HRMS EI m/z** 268.0827($M^+$) $C_{14}H_{21}Br$ requires 268.0827, **LRMS** 163, 159, 131, 105(100%), 91, 79.

† The data given is for the major diastereoisomer.

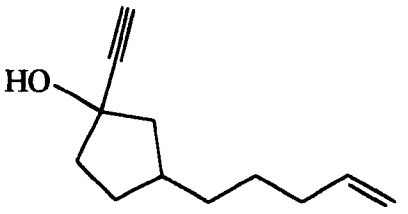
- **Synthesis of 3-(4-pentenyl)-cyclopentan-1-one (294)**




The synthesis of this compound was identical to that described for the formation of (254) but using the following quantities for the reagents: magnesium turnings (0.35g,

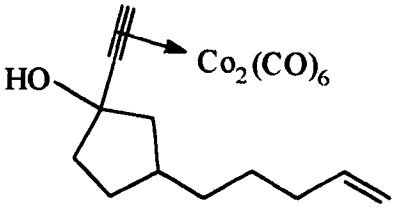
14.76mmol), 5-bromo-1-pentene (2.0g, 13.42mmol) with THF (5ml), THF (30ml) upon cooling the solution, $(CH_3)_2S.CuBr$ (0.10g, 0.49mmol), HMPA (4ml, 22.95mmol), cyclopent-2-en-1-one (0.77g, 9.39mmol), $ClSiMe_3$ (2ml, 18.92mmol), HCl (30ml), hexane (20ml) to yield (294) (1.37g, 96%) as a yellow oil ($R_f$ 0.63, using eluant petrol:diethyl ether, 90:10), $\upsilon_{max}$ **(neat)/cm$^{-1}$** 3076, 2964, 2859, 1743, 1643; $\delta_H$**(300 MHz; $CDCl_3$)** 1.38-1.59(6H, m, 3x$CH_2$), 1.72-1.83(1H, m, C*H*), 2.05-2.41(6H, m, 3×$CH_2$), 4.93(1H, dm, *J*2 and 8, HC=C*H*), 5.03(1H, dm, *J*2 and 17, HC=C*H*), 5.72-5.86 (1H, m, *H*C=$CH_2$); $\delta_c$ **(75.45 MHz; $CDCl_3$)** 27.13(t), 29.50(t), 33.76(t), 35.10(t), 37.09(d), 38.51(t), 45.26(t), 114.64(t), 138.58(d), 219.85(s); **HRMS EI m/z** 152.1201($M^+$) $C_{10}H_{16}O$ requires 152.1201, **LRMS** 137, 123, 109, 96, 83(100%), 55.

- **Synthesis of 1-ethynyl-3-(4-pentenyl)-cyclopentan-1-o1 (295)**



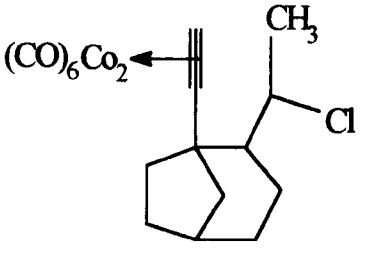

The method employed was identical to that given for (255) using compound (294) (1.37g, 9.01mmol), ethynyl magnesium bromide (22ml, 10.82mmol), THF (20ml) and saturated $NH_4Cl$ (40ml) to afford after purification on silica eluted with hexane:diethyl ether (80:20, $R_f$ 0.15) compound (295) (1.42g, 89%), $\upsilon_{max}$**(neat)/cm$^{-1}$** 3307, 3075, 2964, 2860, 1642; $\delta_H$**(300 MHz; $CDCl_3$)** 1.21-1.44(6H, m, 6x$CH_2$), 1.56-1.58(1H, m, C*H*), 1.91-2.25(7H, m, 3×$CH_2$+O*H*), 2.47(C≡C*H*), 4.90(1H, dm, *J*2 and 7, HC=C*H*), 5.01(1H, dm, *J*2 and 16, HC=C*H*), 5.71-5.85(1H, m, *H*C=$CH_2$), $\delta_c$ **(75.45 MHz; $CDCl_3$)** 27.72(t), 30.37(t), 33.86(t), 35.50(t), 37.58(d), 41.77(t), 48.75(t), 71.05(s), 74.05(d), 87.93(s), 114.35 (t), 138.95 (d); **LRMS EI m/z** 178($M^+$), 135, 121, 109(100%), 95, 81.

- **Synthesis of hexacarbonyl[1-ethynyl-3-(4-pentenyl)-cyclopentan-1-ol] dicobalt (296)**



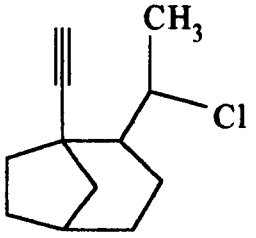

The synthesis of (296) was conducted in a similar manner to that given for (290), using compound (295) (1.42g, 7.98mmol) and octacarbonyl dicobalt (3.0g, 8.78mmol), DCM (20ml), to provide (296), after purification on silica eluted with hexane:diethyl ether (90:10, $R_f$ 0.38), as a brown oil (3.45g, 94%), $\upsilon_{max}$**(neat)/cm$^{-1}$** 3406, 3075, 2965, 2861, 2092, 2049, 2022, 1641.

- **Synthesis of hexacarbonyl[2-(1-chloroethyl)-1-ethynyl bicyclo[3.2.1]octane]dicobalt (298)**



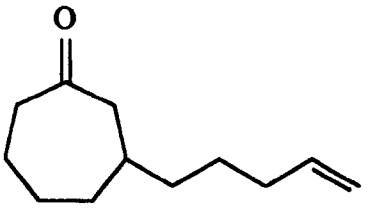

The method described for the preparation of (251) was used for the synthesis of compound (298). Using (296) (1.10g, 2.38mmol), $TiCl_4$ (2.60ml, 23.81mmol) in DCM (25ml) gave the desired product (297) (0.96g, 84%), $\nu_{max}$**(neat/cm$^{-1}$)** 2963, 2860, 2094, 2051, 2025.

- **Synthesis of 2-(1-chloroethyl)-1-ethynylbicyclo[3.2.1]octane (298)**




The preparation of compound (298) was performed using the same method as that given for (256). Using compound (297) (0.96g, 8mmol), cerium (IV) sulphate (2.66g, 2mmol) in methanol (20ml), gave after purification on silica eluted with petrol (100%, $R_f$ 0.26), product (298) (0.25g, 64%), $\upsilon_{max}$**(neat)/cm**$^{-1}$ 3315, 2963, 2861, 2093; $\delta_H$**(300 MHz; CDCl$_3$)** 1.24-1.46(5H, m, 2×C*H*$_2$+C*H*), 1.48(3H, d, *J*8, C*H*$_3$), 1.66-2.61(7H, m, 3×C*H*$_2$+C*H*), 2.95(1H, C≡C*H*), 3.96-4.07 (1H, m, C*H*Cl); $\delta_c$ **(75.45 MHz; CDCl$_3$)** 24.87(t), 25.19(q), 30.00(t), 34.72(t), 35.71(d), 39.45(t), 42.39(t), 46.09(d), 58.69(d), 78.07(d), 81.12(s); **HRMS EI m/z** 196.1019($M^+$) $C_{12}H_{17}Cl$ requires 196.1019, **LRMS** 161, 149, 133, 105, 91(100%), 77, 56.

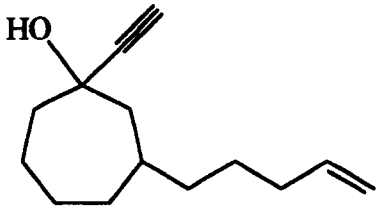
- **Synthesis of 3-(4-pentenyl)-cycloheptan-1-one (300)**




The synthesis of this compound was identical to that described for the formation of (254) but using the following quantities of reagents: magnesium turnings (0.53g, 22.14mmol), 5-bromo-1-pentene (3g, 20.12mmol) in THF (10ml), THF (35ml) upon cooling the solution, $(CH_3)_2S.CuBr$ (0.15g, 0.72mmol), HMPA (6ml, 34.42mmol),

cyclohept-2-en-1-one (1.55g, 14.07mmol), $ClSiMe_3$(2.42ml, 28.38mmol), HCl (35ml), petrol (30ml) to yield (300) (2.24g, 89%), $\nu_{max}$**(neat/cm$^{-1}$)** 3073, 2948, 2868, 1715, 1641; $\delta_H$**(300 MHz; $CDCl_3$)** 1.17-2.02(13H, m, 6x$CH_2$+$CH$), 2.30-2.46(4H, m, 2x$CH_2$), 4.88(1H, dm, *J*2 and 8, HC=C*H*), 4.98(1H, dm, *J*2 and 14, HC=C*H*), 5.69-5.78(1H, m, *H*C=$CH_2$); $\delta_c$**(75.45 MHz; $CDCl_3$)** 24.39(t), 26.20(t), 28.49(t), 33.75(t), 35.96(d), 36.67(t), 36.82(t), 43.89(t), 49.89(t), 114.54(t), 138.64(d), 210.13(s); **LRMS EI m/z** 180($M^+$), 151, 137, 111, 55(100%), 41.

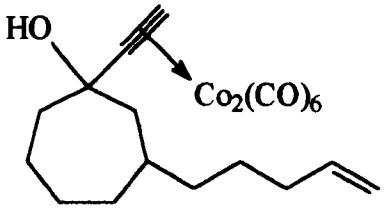
- **Synthesis of 1-ethynyl-3-(4-pentenyl)-cycloheptan-1-ol (299)**




The method undertaken was identical to that given for (255) but using compound (300) (1.0g, 5.56mmol), ethynyl magnesium bromide (13ml, 6.67mmol), THF (20ml) and saturated $NH_4Cl$ (20ml) to yield following purification on silica eluted with petrol:diethyl ether, (90:10, $R_f$ 0.28) (301) (0.98g, 86%), as a 2:1 mixture of diastereoisomers, $\nu_{max}$**(neat/cm$^{-1}$)**; 3328, 3075, 2990, 2878, 2094, 1642; **spectroscopic data for the major diastereoisomer** $\delta_H$**(300 MHz; $CDCl_3$)** 1.18-2.16(18H, 8x$CH_2$+$CH$+$OH$), 2.42(1H, s, C≡C*H*), 4.90(1H, dm, *J*2 and 8, HC=C*H*), 5.01(1H, dm, *J*2 and 16, HC=C*H* ), 5.72-5.84(1H, m, *H*C=$CH_2$); $\delta_c$**(75.45 MHz; $CDCl_3$)** 21.92(t), 26.21(t), 28.61(t), 33.52(d), 33.89(t), 34.57(t), 37.60(t), 42.56(t), 48.63(t), 69.92(s), 71.41(d), 88.26(s), 114.31(t), 139.01(d); **HRMS EI m/z** 206.2014($M^+$) $C_{14}H_{22}O$ requires 206.2014, **LRMS** 161, 149, 133, 105, 91(100%), 77, 56.

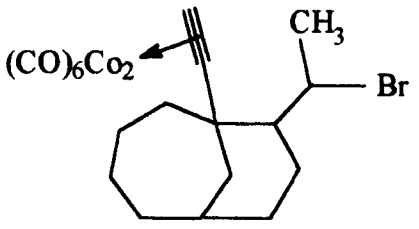
**Spectroscopic data for the minor diastereoisomer:** $\delta_H$**(300 MHz; CDCl$_3$)** 2.40 (1H, s, C≡C*H*), with remaining signals coalescing with the major isomer; $\delta_c$**(75.45 MHz; CDCl$_3$)** 22.33(t), 26.36(t), 32.53(t), 33.68(d), 33.95(t), 35.73(t), 37.70(t), 43.39(t), 49.27(t), 70.17(s), 71.84(d), 90.14(s), 114.63(t), 139.27(d).

- **Synthesis of hexacarbonyl[1-ethynyl-3-(4-pentenyl)-cycloheptan-1-ol] dicobalt (302)**




Using the method reported for the formation of (290), the compound (302) was isolated using (0.98g, 4.76mmol, DCM (20ml), octacarbonyl dicobalt (1.79g, 5.23mmol) to afford after purification on silica eluted with petrol:diethyl ether (80:20, $R_f$ 0.34), the desired product in a yield of (2.25g, 97%), $\nu_{max}$**(neat/cm$^{-1}$)** 3476, 2990, 2879, 2093, 2052, 2029, 1642.

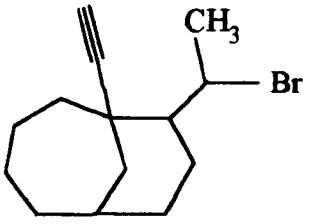
- **Synthesis of hexacarbonyl[9-(1-bromoethyl)-1-ethynyl bicyclo[4.3.1]decane]dicobalt (303)**




The synthesis of the compound (303) was achieved using the same procedure to that described for (338). Using compound (302) (2.25g, 4.59mmol), $TiBr_4$ (16.88g,

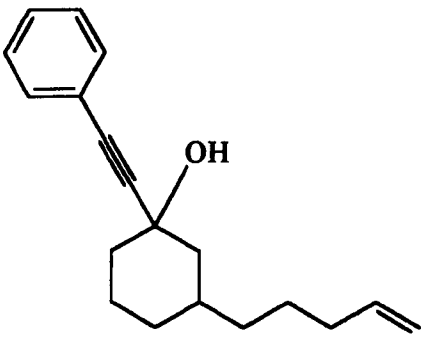
45.92mmol), DCM (30ml), furnished the desired product (303) (1.43g, 57%), $\nu_{max}$**(neat/cm$^{-1}$)** 2988, 2880, 2093, 2052, 2030.

- **Synthesis of 9-(1-bromoethyl)-1-ethynylbicyclo[4.3.1]decane (304)**



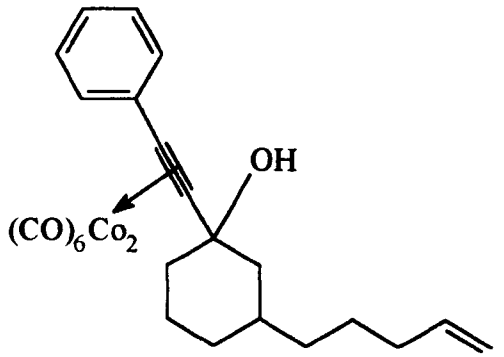

Preparation of the compound (304) was performed using the same method as that given for (256). To the cobalt complex (303) (1.43g, 2.59mmol) in methanol (25ml) was added cerium (IV) sulphate (3.44g, 10.36mmol) to provide the product (304) (0.34g, 49%), $\nu_{max}$**(neat/cm$^{-1}$)** 3307, 2989, 2878, 2090; $\delta_H$**(300 MHz; $CDCl_3$)** 1.02-1.46(9H, m, 4x$CH_2$+C*H*), 1.51(3H, d, *J*8, C$H_3$), 1.55(7H, m, 3x$CH_2$+C*H*), 2.65(1H, s, C≡C*H*), 3.94(1H, m, C*H*Br); $\delta_c$**(75.45 MHz; $CDCl_3$)** 25.49(t), 26.46(q), 28.89(t), 30.86(d), 33.69(t), 35.47(t), 36.01(t), 37.93(t), 41.20(t), 51.61(d), 74.22(s), 76.60(d), 87.21(s); **LRMS EI m/z** 268($M^+$), 189, 173, 147, 119, 105, 91(100%), 79, 55, 41.

- **Synthesis of 3-(4-pentenyl)-1-phenylethynyl-cyclohexan-1-ol (313)**



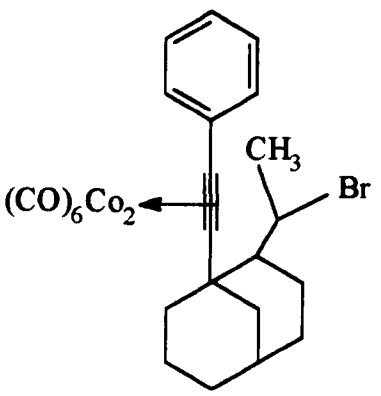

The preparation of this compound was achieved in the similar manner to that given for the formation of (255), but using the following changes. To compound (254) (2.0g, 12.05mmol) was added phenylethynylmagnesium bromide (16ml, 15.67mmol, 1.3 eq) in THF (20ml). A reflux period of 5hrs was allowed, whereupon subsequent work-up and purification on silica eluted with petrol:diethyl ether (75:25, $R_f$, 0.23), gave the desired product (313) (2.87g, 89%), $\nu_{max}$**(neat/cm$^{-1}$)** 3475, 3081, 2980, 2875, 2092, 1642; $\delta_H$**(300 MHz; CDCl$_3$)** 1.17-2.11(16H, 7x*CH*$_2$+*CH*+O*H*), 4.92(1H, dm, *J*2 and 12, HC=C*H* ), 5.03(1H, dm, *J*2 and 18, HC=C*H*), 7.26-7.44(5H, m, phenyl ring); $\delta_c$**(75.45 MHz; CDCl$_3$)** 23.68(t), 26.13(t), 31.96(t), 33.96(t), 35.50(d), 36.13(t), 40.32(t), 46.84(t), 70.04(s), 84.94(d), 92.47(s), 114.34(t), 122.86(s), 128.86(d), 131.67(d), 139.00(d); **LRMS EI m/z** 267($M^+$-1), 239, 199, 146, 129(100%), 115, 102, 91, 55.

- **Synthesis of hexacarbonyl[3-(4-pentenyl)-1-phenylethynyl-cyclohexan-1-ol]dicobalt (314)**




The formation of (314) occurred using the procedure given for (290). Thus to (313) (2.0g, 7.46mmol) was added octacarbonyl dicobalt (2.80g, 8.20mmol) in DCM (30ml) to provide following purification on silica eluted with petrol:diethyl ether (70:30, $R_f$ 0.34), product (314) (3.92g, 95%), $\nu_{max}$**(neat/cm$^{-1}$)** 3479, 3082, 2983, 2876, 2093, 2054, 2024, 1642.

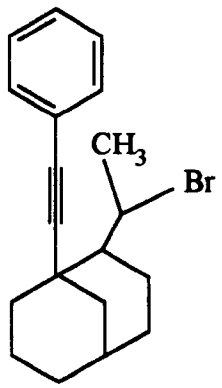
- **Synthesis of hexacarbonyl[2-(1-bromoethyl)-1-phenylethynylbicyclo[3.3.1]nonane]dicobalt (315)**




The synthesis of the compound (315) was achieved using the same procedure to that described for (338), using (338) (1.60g, 2.90mmol), $TiBr_4$ (10.65g, 28.98mmol), DCM

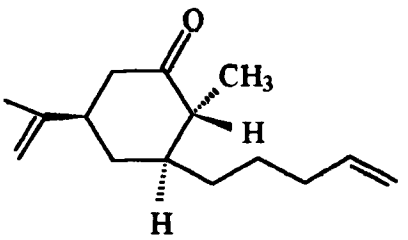
(30ml), to afford compound (315) (1.57g, 88%), $\nu_{max}$**(neat/cm$^{-1}$)** 2983, 2876, 2094, 2051, 2023.

- **2-(1-bromoethyl)-1-phenylethynylbicyclo[3.3.1]nonane (316)**




Adopting a similar procedure as that described for the synthesis of compound (256), isolation of (316) was achieved using the following quantities of reagent: cobalt compound (315) (1.37g, 2.23mmol), cerium (IV) sulphate (2.97g, 8.92mmol), methanol (20ml), to afford (316) (0.72g, 71%), $\nu_{max}$**(neat/cm$^{-1}$)** 2981, 2876, 2091; $\delta_H$**(300 MHz; $CDCl_3$** 1.25-1.60(7H, m, 3x$CH_2$+$CH$), 1.68(3H, d, *J*6, $CH_3$), 1.71-2.06(7H, m, 3x$CH_2$+$CH$), 4.06-4.15(1H, m, $CH$Br), 7.26-7.54(5H, m, phenyl ring); $\delta_c$**(75.45 MHz; $CDCl_3$)** 25.04(t), 26.46(q), 28.16(t), 32.31(t), 34.62(d), 35.85(t), 37.08(d), 38.06(t), 41.32(t), 56.92(d), 70.04(s), 84.92(s), 92.43(s), 128.14(d), 131.66(d); **LRMS EI m/z**. 330($M^+$), 251, 236, 209, 182, 105(100%), 77, 52.

- **Synthesis of 5-isopropenyl-2-methyl-3-(4-pentenyl)-cyclohexan-1-one (320)**

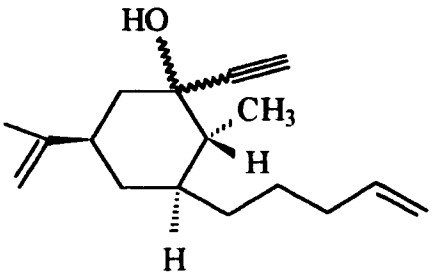



The synthesis of compound (320) was achieved using the method described for compound (254) but with the following quantities: Magnesium turnings (1.77g, 73.81mmol), 5-bromo-1-pentene (10g, 67.10mmol) in THF (25ml). Upon cooling THF (80ml) was added. $(CH_3)_2S.CuBr$ (0.50g, 2.42mmol), HMPA (20ml, 114.73mmol), $ClSiMe_3$ (8.1ml, 94.61mmol), (*S*)-(+)-carvone (7.05g, 46.97mmol), 1M HCl (90ml), hexane (125ml). TLC analysis of the crude reaction mixture showed one major product. Following purification of the crude product on silica eluted with petrol:diethyl ether (80:20, $R_f$ 0.34) gave the required product (9.71g, 94%) as an inseparable 5:1 mixture of diastereoisomers, (Found: C, 80.96; H, 10.82; $C_{15}H_{24}O$ requires C, 81.76; H, 10.98); extensive $^1H$ NMR studies[108] suggested that the products consist of a 5:1 mixture of a *trans/cis* and *cis/trans* diastereoisomers, **$\nu_{max}$(neat)/cm$^{-1}$** 3077, 2972, 2884, 1711, 1642; **spectroscopic data for the *trans/cis*: $\delta_H$(300 MHz; $CDCl_3$)** 0.93-0.95(3H, d, *J*8, C*H*$_3$), 1.20-1.42(4H, m, C*H*$_2$+2xC*H*), 1.68(3H, s, C*H*$_3$), 1.89-2.46(8H, m, 4×C*H*$_2$), 2.16(1H, qt, *J*8, C*H*), 4.64-4.75(2H, m, C=C*H*$_2$), 4.86(1H, dm, *J*2 and 8, HC=C*H*), 4.95(1H, dm, *J*2 and 12, HC=C*H*), 5.64-5.77(1H, m, *H*C=CH$_2$); **$\delta_c$ (75.45 MHz; $CDCl_3$)** 11.40(q), 20.32(q), 25.19(t), 31.13(t), 32.99(t), 33.77(d), 39.86(d), 43.64(t), 46.17(t), 48.62(d), 109.60(t), 114.64(t), 138.40(d), 146.89(s), 212.61(s); **HRMS EI m/z** 220.1830($M^+$) $C_{15}H_{24}O$ requires 220.1830, **LRMS** 205, 191, 149, 110, 96, 68, 56, 42(100%).

**Spectroscopic data for the *cis/trans* diastereoisomer: $\delta_H$(300 MHz; $CDCl_3$)** 2.64(1H, qt, *J*8, C*H*), 2.61(3H, d, *J*6, C*H*$_3$), 1.71(3H, s, C*H*$_3$), with remaining signals

coalescing with the *trans/cis* isomer; $\delta_c$**(75.45 MHz; $CDCl_3$)** 11.64(q), 21.43(q), 26.93(t), 31.98(t), 33.04(t), 34.01(d), 44.26(t), 46.88(t), 49.59(d), 109.85(t), 115.11(t), 138.46(d), 147.42(s), 213.07(s).

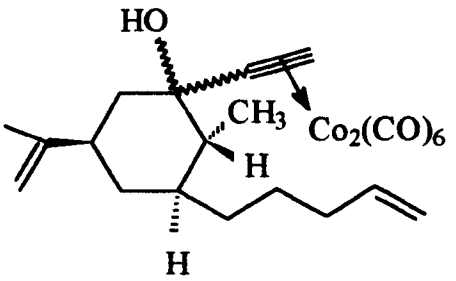
- **Synthesis of 1-ethynyl-5-isopropenyl-2-methyl-3-(4-pentenyl)-cyclohexan-1-ol (321)**




The isolation of the above compound was achieved with the method described for the synthesis of (255), but using the following quantities: (320) (4.0g, 18.18mmol), ethynylmagnesium bromide (47ml, 23mmol), THF (25ml). Purification on silica using eluant hexane:diethyl ether, (85:15, $R_f$ 0.24), gave the desired product (321) as a 10:1 mixture of diastereoisomers (3.95g, 79%), $[\alpha]_D^{20}$ = +19° (*c*1 in $CHCl_3$); $\nu_{max}$**(neat)/cm$^{-1}$** 3446, 3076, 2970, 2879, 3305, 1640; **spectroscopic data for the major diastereoisomer:** $\delta_H$**(300 MHz; $CDCl_3$)** 1.03 (3H, d, *J*8, C$H_3$), 1.40(17H, m, 5xC$H_2$+3xC$H$+C$H_3$+OH), 2.40(1H, C≡C$H$), 4.65(2H, m, C=C$H_2$), 4.89(1H, dm, *J*4 and 10), 5.05(1H, dm, *J*4 and *J*14, HC=C$H$), 5.72-5.88 (1H, m, $H$C=CH$_2$); $\delta_c$**(75.45 MHz; $CDCl_3$)** 11.47(q), 22.05(q), 26.55(t), 31.49(t), 32.49(d), 33.91(t), 34.08(t), 36.08(d), 37.64(t), 43.49(d), 70.06(s), 71.54(d), 80.13(s), 109.57(t), 114.39(t), 138.96(d), 149.13(s); **LRMS EI m/z** 246($M^+$), 228, 213, 157, 122, 107, 91(100%), 82, 67, 56.

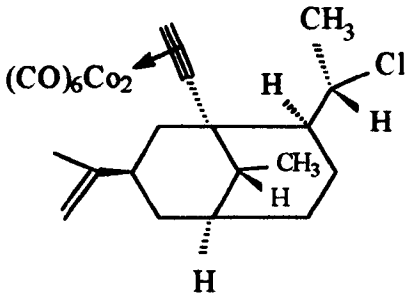
**Spectroscopic data for the minor diastereoisomer:** 0.97 (3H, d, *J*8, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 2.30(1H, C≡C*H*), with the remaining signals in overlap with the major diastereoisomer; $\delta_c$**(75.45 MHz; CDCl$_3$)** 12.01(q), 22.56(q), 26.93(t), 32.51(t), 33.49(d), 34.03(t), 35.16(t), 36.42(d), 38.17(t), 43.79(d), 71.01(s), 71.98(d), 83.46(s), 111.23(t), 114.90(t), 139.09(d), 149.32(s).

- **Synthesis of hexacarbonyl[1-ethynyl-5-isopropenyl-2-methyl-3-(4-pentenyl)-cyclohexan-1-ol]dicobalt (322)**



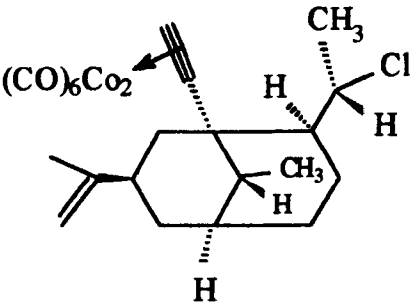

Using the method reported for the formation of (290), the compound (322) was prepared using (321) (3.95g, 16.06mmol), DCM (30ml), octacarbonyl dicobalt (6.04g, 17.66mmol) to provide (322) (8.11g, 95%), $\nu_{max}$**(neat)/cm$^{-1}$** 3489, 3080, 2969, 2873, 2091, 2051, 2020, 1640.

- **Synthesis of hexacarbonyl[2-(1-chloroethyl)-1-ethynyl -(7-isopropenyl)bicyclo[3.3.1]nonane]dicobalt (323)**




The synthesis of the compound (323) was achieved using the same procedure to that described for (251). Using (322) (3g, 5.66mmol), $TiCl_4$ (6.20ml, 56.60mmol), DCM (20ml) gave compound (323) (2.49g, 80%), $\nu_{max}$**(neat)/cm**$^{-1}$ 3074, 2971, 2879, 2089, 2048, 2018, 1640.

- **Synthesis of 2-(1-chloroethyl)-1-ethynyl-(7-isopropenyl) bicyclo[3.3.1]nonane (324)**

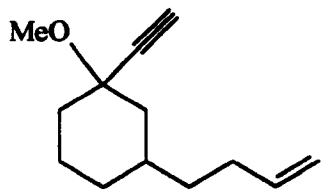



The synthesis of compound (324) was achieved using the method described for compound (256). Using (323) (2.49g, 4.54mmol), cerium (IV) sulphate (6.04g, 18.17mmol) in methanol (30ml) gave the desired compound (324) (0.83g, 69%), $[\alpha]_D^{20} = +10°$ (*c*1 in $CHCl_3$); $\nu_{max}$**(neat)/cm**$^{-1}$ 3310, 3074, 2976, 2881, 2029, 1641; $\delta_H$ **(300 MHz; $CDCl_3$)** 1.04-1.48(8H, m, 3x$CH_2$+2C*H*), 1.51(3H, d, *J*8, C$H_3$), 1.54 (3H,

d, *J*6, $CH_3$), 1.68 (7H, m, $CH_2$+2x$CH$+$CH_3$), 3.06 (1H, s, C≡$CH$), 4.00-4.07 (1H, m, $CH$Cl), 4.95-5.05 (2H, m, C=$CH_2$); **$\delta_c$(75.45 MHz; $CDCl_3$)** 20.54(q), 29.42(q), 25.53(t), 27.07(q), 28.64(d), 29.44(t), 29.71(t), 30.78(s), 31.23(d), 31.51(t), 36.02(d), 38.12(d), 58.60(d), 77.41(d), 87.43(s), 112.97(t), 146.60 (s); **LRMS EI m/z** 264($M^+$), 220, 185, 159, 143, 129(100%), 105, 91, 69.

† $^1H$ NMR spectrum showed only one set of signals for the three methyl groups. The $^{13}C$ NMR revealed all the signal resonances of the minor diastereoisomer to be in overlap with the major diastereoisomer.

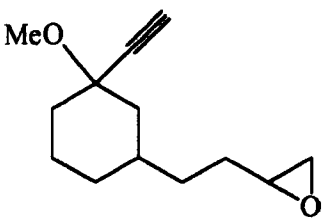
- **Synthesis of 3-(3-butenyl)-1-ethynyl-1-methoxycyclohexane (327)**




Under a nitrogen atmosphere, finely ground potassium hydroxide (0.68g, 12.11mmol) was stirred in DMSO (5ml). Freshly distilled methyl iodide (0.86g, 6.06mmol) was added, followed by the rapid addition of the acetylenic alcohol (285) (0.54g, 3.03mmol) dissolved in DMSO (5ml). The reaction mixture was then allowed to stir at an ambient temperature. TLC analysis after 4hrs, showed the presence of a faster moving product (petrol:diethyl ether, 70:30, $R_f$ 0.75), whereupon the reaction mixture was poured into water. The aqueous layer was extracted with dichloromethane (3×5ml). The organic layers were combined, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to afford the crude product as a yellow oil. Purification by column chromatography on silica eluted with hexane:diethyl ether, 70:30, gave the desired product (327) as a clear oil (0.42g, 72%), **$\nu_{max}$(neat/$cm^{-1}$)** 3308, 3050, 2920, 2860, 2120, 1641; **$\delta_H$(300 MHz; $CDCl_3$)** 1.01-2.19(13H, m,

6x$CH_2$+$CH$), 2.48(1H, s, C≡$CH$), 3.39(1H, s, O$Me$), 4.91(1H, dm, $J$2 and 7, HC=$CH$ ), 5.03(1H, dm, $J$2 and 16, HC=$CH$), 5.73(1H, m, $HC$=$CH_2$); **$\delta_c$(75.45 MHz; $CDCl_3$)** 23.01(t), 31.04(t), 32.09(t), 34.49(d), 35.95(t), 36.91(t),43.44(t), 50.71(q), 74.54(d), 74.94(s), 84.37(s), 114.28(t), 138.94(d); **HRMS EI m/z** 191.1430($M^+$-1) $C_{13}H_{20}O$ requires 191.1430, **LRMS EI m/z** 191($M^+$-1), 178, 163, 149, 121, 95(100%), 79, 53.

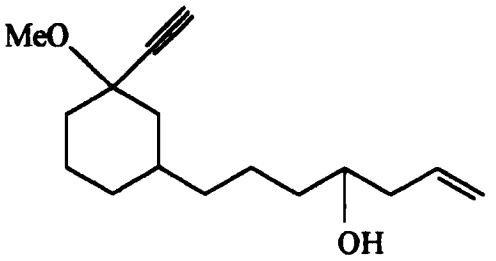
- **Synthesis of 3-(3,4-epoxybutyl)-1-ethynyl-1-methoxycyclohexane (328)**




The alkene (327) (0.42g, 2.19mmol) was dissolved in dichloromethane (5mls) and the solution was cooled to 0°C. Metachloroperoxybenzoic acid (0.45g, 2.60mmol, 1.2eq) was added and the reaction mixture was stirred under a nitrogen atmosphere. TLC analysis after 24hrs showed the presence of a slowing moving product (petrol:diethyl ether, 60:40, $R_f$ 0.43). The reaction was quenched with saturated sodium bicarbonate solution (10mls) and the reaction mixture was stirred until the dichloromethane layer was clear. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×15ml). The organic layers were combined dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to give a crude oil. Purification by column chromatography (petrol:diethyl ether, 60:40) gave the desired epoxide (328) as a clear oil (0.34g, 74%), **$\nu_{max}$(neat/cm$^{-1}$)** 3260, 2920, 2860, 2120, 1460, 1020; **$\delta_H$(300 MHz; $CDCl_3$)** 1.17-1.78(15H, m, 7x$CH_2$+$CH$), 2.46(1H, s, C≡$CH$), 2.85-2.91(1H, m, $CH$(epoxide), 3.38(3H, s, O$Me$); **$\delta_c$(75.45 MHz; $CDCl_3$)** 22.94(t), 29.71(t), 32.04(t), 32.69(t), 34.66(d), 36.82(t), 43.37(t), 47.13(t), 50.73(q), 52.39(d),

74.67(d), 74.85(s), 84.26(s); **LRMS EI m/z** 193($M^+$-15), 177, 165, 137, 121, 95(100%), 79, 65, 55.

- **Synthesis of 3-{[4-hydroxy]-6-pentenyl}-1-ethynyl-1-methoxycyclohexane (329)**

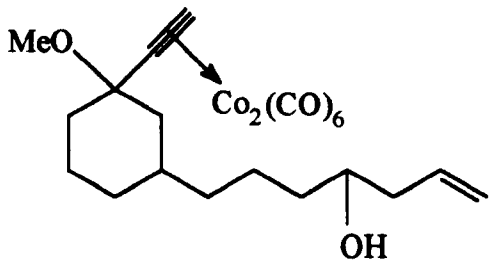



The epoxide (328) (0.34g, 1.63mmol) was dissolved in anhydrous diethyl ether (5ml) and the solution cooled to -25°C. Copper (I) iodide (0.06g, 0.32mmol, 0.2eq) was then added and the reaction mixture was allowed to stir for 10min. Upon the dropwise addition of allylmagnesium bromide (3.3ml, 3.27mmol, 2eq) the solution turned from yellow to black. The reaction mixture was then allowed to stir for a further 1hr at -25°C, whereupon TLC analysis showed the presence of a slower moving compound (petrol:diethyl ether, 60:40, $R_f$ 0.27). The reaction mixture was then quenched by the addition of a solution of saturated ammonium chloride. The aqueous phase was extracted with diethyl ether (3x5ml) and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo*. Subsequent purification on silica using eluant petrol:diethyl ether (60:40), gave compound (329) (0.21g, 52%) as a 1:1 mixture of $^+$diastereoisomers, $\nu_{max}$**(neat/cm$^{-1}$)** 3400, 3320, 3080, 2920, 2840, 1641; $\delta_H$**(300 MHz; CDCl$_3$)** 1.04-1.94(14H, m, 6x$CH_2$+C*H*+O*H*), 2.03-2.27(4H, m, 2x$CH_2$), 2.39(1H, s, C≡C*H*), 3.36(3H, s, O*Me*), 3.55-3.61(1H, m, C*H*), 4.91(1H, dm, *J*2 and 8), 5.03(1H, dm, *J*2 and 18), 5.49(1H, m, *H*C=$CH_2$); $\delta_c$**(75.45 MHz; CDCl$_3$)** 22.97(t), 30.03(t), 32.11(t), 32.57(t), 34.59(t), 35.01(d), 36.44(t), 36.88(d), 43.42(t), 43.58(t), 50.68(s), 71.52(s), 74.66(d), 84.31(s),

114.73(t), 136.97(d); **LRMS EI m/z** 235($M^+$-15), 217, 203, 189, 175, 137, 118, 95(100%), 84, 67, 55, 41.

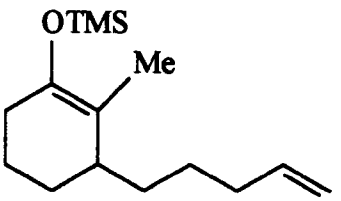
† Only one set of data has been recorded from the $^1H$ NMR and $^{13}C$ NMR spectra, as signals that may be attributed for the other diastereoisomer were in coalesce.

- **Synthesis of hexacarbonyl[3-{(4-hydroxy)-6-pentenyl}-1-ethynyl-1-methoxycyclohexane]dicobalt (330)**




The synthesis of the above compound was achieved using the same procedure to that given for (290), using (329) (0.21g, 0.84mmol), DCM (10ml), octacarbonyl dicobalt (0.32g, 0.92mmol) to afford the product (330) in (0.44g, 98%), $\nu_{max}$**(neat/cm$^{-1}$)** 3350, 3076, 2925, 2843, 2077, 2047, 2028, 1640.

- **Synthesis of 2-methyl-3-(4-pentenyl)-1-[(trimethylsilyl)oxy]-1-cyclohexene (335)**




The synthesis of compound (335) was achieved using the same method and quantity of reagents to that given for the synthesis of (254). However, instead of quenching the reaction with 1.0M HCl, triethylamine (40ml) was added, to afford the desired product (335) in (4.91g, 90%), $\nu_{max}$**(neat/cm$^{-1}$)** 3076, 2890, 2798, 1640, 1251, 1187; $\delta_H$**(300 MHz; $CDCl_3$)** 0.00(9H, s, OSi($CH_3$)$_3$, 0.99(4H, m, 2x$CH_2$), 1.32(3H, s, $CH_3$), 1.34(9H, m, 4x$CH_2$+$CH$), 4.61(1H, dm, *J*2 and 10), 4.85(1H, dm, *J*2 and 16), 5.56(1H, m, $HC$=$CH_2$); $\delta_c$**(75.45 MHz; $CDCl_3$)** 0.306(q), 14.39(q), 21.71(t), 23.88(t), 29.05(t), 30.26(t), 31.40(d), 33.62(t), 36.21(t), 114.17(t), 139.09(d),150.3(s); **LRMS EI m/z** 252($M^+$), 217, 209, 195, 182, 169(100%), 73, 69.

# References and Notes

# References and Notes

1. (a) J.R. Hanson, *Nat. Prod. Rep.*, 1988, **3**, 225 (b) C. Francisco; B. Bernaigs; J. Teste, *J. Org. Chem.*, 1986, **51**, 1115.
2. J. R. Anderson; R. L. Edward; A. J. S. Whalley, *J. Am. Chem. Soc. Perkin Trans.1.*, 1988, 823.
3. D. Goldsmith, *The Total synthesis of Natural products*; John Wiley: New York, 1992, **8**, 101.
4. M. C. Wani; H. L. Taylor; M. E. Wall; P. Coggon; A. T. *J. Am. Chem. Soc.* 1971, **93**, 2325.
5. (a) I. Uchida; T. Ando; N. Fukami; K. Yoshida; M. Hashimato; T. Tada; S. Koda; Y. Morimoto, *J. Org. Chem.*, 1987, **52**, 5292 (b) T. Ando; Y. Tsurumi; N. Ohata; I. Uchida; K. Hoshida; M. Okuhara., *J. Antibiot.*, 1988, **41**, 25.
6. K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207.
7. (a) P. B. Schiff; J. Fant; S. Horwitz, *Nature*, 1979, **277**, 665-667 (b) J. J. Manfredi and P. B. Horwitz, *Pharmac. Ther.*, 1984, **25**, 83-125.
8. For a recent review of synthetic studies from over 35 groups, see P. A Wender; M. G. Natchus; A. J. Shuler, in Taxol Science and Applications; M. Suffness, Ed. *CRC Press* New York, 1995, 123.
9. (a) R. A Holton; C. Somaza; H. B. Kim; F. Liang; R. J. Biediger; P. D. Boatman; M. Slimdo; C. C Smith; H. Nadizadeh; Y. Suzuki; C. Tao; P. Vu; S. Tang; P. Zang; K. K. Murthi; L. N. Gentile; J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1597 (b) K. C. Nicolaou; Z. Zang; H. Ueno; P. G. Nantermet; R. K. Guy; C. F. Claireboume; J. Renaud; E. A. Couladouros; K. Paulvannan; E. J. Sorensen, *Nature.*, 1994, 367 (c) S. J Danishefsky; J. J. Masters; W. B. Young; J. T. Link; L. B. Snyder; T. V. Magee; D. K. Jung; R. C. A. Isaacs; W. G. Bornmann; C. A. Alaimo; C. A. Coburn; M. J. Di Grandi, *J. Am. Chem. Soc.*, 1996, **118**, 2843 (d) P. A. Wender, N. F. Badham; S. P. Conway; P. E. Floreancig; T. E. Glass; J. B. Houze; N. E. Krauss; d. Lee; D. G. Marquess; P. L. McGrane; W. Meng; M. G. Natchus; A. J. Shuker; J. C. Sutton; R. E. Taylor, *J. Am. Chem. Soc.*, 1997, **119**, 2757.

10.(a) C. S. Swindel, *Org. Prep. Proced. Int.* 1991, 23, 465 (b) D. G. I. Kingston; A. A. Molinero; J. M. Rimoldo, The Taxane Diterpenoids *in* Progress in the Chemistry of Natural products, 1993, **36**, 1 (c) K. C. Nicolaou; W. Dai; R. Guy, *Angew. Chem. Int. Ed. Engl.* 1994, **33**, 15.

11.S. Gosh; S. S. Roy; A. Bhattacharya; G. Saha, *Tetrahedron Lett.*, 1990, **31**, 1483

12.G. A. Kraus and D. Zheng, *Synlett.*, 1993, 71.

13.S. Wang; S. E. Warder; H. Perrier; E. L. Grimm; M. A. Bernstein, *J. Org. Chem.*, 1993, **58**, 2931.

14.P. Kumar; A. T. Rao; K. Saravanan; B. Pandey, *Tetrahedron Lett.*, 1995, **36**, 3397.

15.H. A. Schafer; W. Thielemann; S. Kotila, *Tetrahedron Lett.*, 1995, **51**, 12027.

16.M. Fetizon; B. Kerkar; D. D. Khac; F. Guir, *Tetrahedron Lett.*, 1997, **38**, 3223.

17.M. Malacria; C. Aubert; P. Phansavath, *Tetrahedron Lett.*, 1998, **39**, 1561.

18.R. A. Bucknall; H. Moores; R. Simms; B. Hesp. *Antimicrob. Agents. Chemother.*, 1973, **4**, 294.

19.W. Dalziel; B. Hesp; K. M. Stevenson; J. A. Jarvis, *J. Chem. Soc.*, Perkin Trans. 1 1973, 2841.

20.P. S. Manchand; J. D. White; H. Wright; J. Clardy, *J. Am. Chem. Soc.*, 1973, **95**, 2705.

21.Aphidicolin total or formal syntheses: (a) B. M Trost; Y. Nishimura; K. Yamamoto, *J. Am. Chem. Soc.*, 1979, **101**, 1328 (b) E. J. Corey; M. Tius; J. Das, *J. Am. Chem. Soc.*, 1980, **102**, 1742; S.K Maity; D. Mukherjee, *Tetrahedron* 1984, **40**, 757 (c) R.E Ireland; J. D Godfrey; S. Thaisrivongs, *J. Am. Chem. Soc.*, 1981, **103**, 2446; (d) H. Koyama; H. Okawara; S. Kobayashi; M. Ohno, *Tetrahedron Lett.*, 1985, **26**, 2685.

22.Stemodanes: (a) S. Chatterjee, *J. Chem. Soc., Chem. Commun.*, 1979, 622 (b) R. M. Bettolo; P. Tagliatesta; A. Lupi; D. Bravetti, *Helv. Chim.,. Acta* 1983, **66**, 760 (c) R. B. Kelly; S. Lal; G. Gowda; R. N. Rej; *Can. J. Chem.*, 1984, **61**, 1930 .

23.J. E. McMurry; A. Andrus; G. M. Ksander; J. H. Musser; M. A. Johnson, *Tetrahedron.*, 1981, **37**, 319.

24.(a) J. Y. Merour; J. L. Roustan; C. Charrier; J. Collin; J. Benaim, *J. Organomet. Chem.*, 1973, **51**, C24 (b) J. P. Collmann, *Acc. Chem. Res.*, **8**, 342 (c) P. M. Cooke; R. M. Parlman, *J. Am. Chem. Soc.*, 1975, **97**, 6863.

25.K. C. Nicolaou; R. E. Zipkin, *Angew. Chem. Int. Ed. Engl.* 1981, **20**, 785.

26.R. E. Ireland; W. C. Dow; J. D. Godfrey; S. Thaisrivongs, *J. Org. Chem.*, 1984, **49**, 1001.

27.C. Iwata; T. Tanaka; O. Okuda; K. Murakami; H. Yoshino; H. Mikamiyama; A. Kanda; S. W. Kim, *Chem. Pharm. Bull.*, 1995, **43**, 1407.

28.C. Iwata; T. Tanaka; O. Okuda; K. Murakami; H. Yoshino; T. Inoue; T. Kuroda; K. Kamei; T. Murata; T. Imanishi; H. Yoshino, *Chem. Pharm. Bull.*, 1995, **43**, 193

29.E. Piers; B. F. Abeysekera; D. J. Herbert; I. D. Suckling, *J. Chem. Soc., Chem. Commun.*, 1982, 404.

30.J. Mann; P. Hergarty, *Synlett.*, 1993, 553.

31.K. Fukumoto; C. Kabuto; M. Yokoyama; T. Seishi; M. Toyota; *Tetrahedron Lett.*, 1992, **33**, 4581.

32.K. P. C. Vollhardt; C. Aubert; J. Germanas, *J. Am. Chem. Soc.*, 1983, **105**, 142.

33.(a) L. N. Mander; P. K. Klaunzer; M. Furber; B. Twitchin, *Tetrahedron Lett.*, 1990, **31**, 6235 (b) L. N. Mander; G. L. Patrick, *Tetrahedron Lett.*, 1990, **31**, 423 (c) B. M. Fraga; J. A. Hanson; M. G. Hernandez; F. G. Tellado, *Tetrahedron Lett.*, 1994, **30**, 6899.

34.H. N. Krishnamurthy, *Gibberellins and Plant Growth*, Wiley, New York, 1975.

35.L. N. Mander, *Chem. Rev.*, 1992, **92**, 573.

36.F. E. Ziegler; M. E. Condon, *J. Org. Chem.*, 1971, **36**, 3707.

37.H. O. House; D. G. Melillo, *J. Org. Chem.*, 1973, **38**, 1398.

38.S. Takano; C. Kasahara; K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1981, 637.

39.K. Mori; I. Takemoto; M. Matsui, *Tetrahedron* 1976, **32**, 1497.

40.A. Barco; S. Benetti; A. Casolari; S. Manfredini; G. Pllini; E. Polo; V. Zanirato, *Tetrahedron* 1989, **45**, 3935.

41.For reviews, see (a)D. Lucchi; M. Miotti; S. Modena, *Org. React.*,. 1991, **40**, 157-405 (b) Warren, *Chem. Ind.* (London), 1980, **5**, 45-102.

42.L. N. Mander; J. M. Hook; R. Urech, *J. Org. Chem.*, 1984, **49**, 3250.

43.B. M. Trost; L. H. Latimer, *J. Org. Chem.*, 1978, **43**, 1031.

44.E. J. Corey; J. E. Munroe, *J. Am. Chem. Soc.*, 1982, **104**, 6129.

45.(a) P. J. De Clercq; W. M. Grootaert, *Tetrahedron Lett.*, 1986, **27**, 1731.

46.E. J. Corey and I. Kuwajima, *Ibid.*, 1970, **92**, 395 (b) see reference 44.

47.Y. Yamada; M. Shimano; H. Nagaoka, *Tetrahedron Lett.*, 1989, **30**, 971.

48.B. B. Snider; J. E. Merritt; M. A. Dombroski; B. O. Buckman, *J. Org. Chem.*, 1991, **56**, 5544.

49.E. W. Della; A. M. Knill, *J. Org. Chem.*, 1995, **60**, 3518.

50.(a) K. Fukumoto; K. Yanai; Y. Nishikawa; T. Wada; M. Toyota, *Synlett* 1994, 597 (b) K. Fukumoto; K. Yanai; Y. Nishikawa; T. Wada; M. Toyota; C. Kabuto, *Tetrahedron* 1995, **51**, 692.

51.(a) D. Nuel; F. Dahan; R. Mathieu, *J. Am. Chem. Soc.* 1985, **107**, 1658. (b) J. Wang; M. Sabat; L. J Lyons; D. F. Shriver, *Inorg. Chem.* 1991, **30**, 382. (c) R. D. Adams; J. E. Babin; M. Tasi; T. A. Wolfe, *Organometallics* 1987, **6**, 2228. (d) R. D. Adams; I. T. Horvath, *Prog. Inorg. Chem.* 1985, **32**, 127. (e) J. L. Templeton, *Adv. Organomet. Chem.* 1989, **29**, 1.

52.R. S. Dickson; P. Fraser, *J. Adv. Organomet. Chem.* 1974, **12**, 323

53.(a) I. U. Khand; G. R. Knox; P. L. Pauson; W. E. Watts, *J. Chem. Soc., Perkin Trans. 1*, 1973, 975 (b) For an extensive review of the Pauson-Khand reaction, see N. E. Schore, *Org. React.*, 1991, **40**, 1.

54.H. Greenfield; R. A. Sternberg; J. H. Wotiz; R. Markby; I. Wender, *J. Am. Chem. Soc.*, **1956**, 78, 120.

55.(a) R. K. Sheline, J. W. Cable; R. S. Nyholm, *J. Am. Chem. Soc.*, 1954, **76**, 3373 (b) R. A. Friedel; I. Wender, S. L. Shufler; H. W. Sterberg, *J. Am. Chem. Soc.*, 1955, **77**, 3951.

56.K. M. Nicholas; R. Pettit, *Tetrahedron Lett.*, 1971, 3475.

57.K. M. Nicholas; R. F. Lockwood, *Tetrahedron Lett.*, 1977, 4163.

58.H. J. Jaffer; P. L. Pauson, *J. Chem. Res. Synop.*, 1983, 244.

59.K. M. Nicholas; H. D. Hodes, *Tetrahedron Lett.*, 1978, 4349.

60.K. M. Nicholas; M. Mulvaney; M. Bayer, *J. Am. Chem. Soc.*, 1980, **102**, 2508.

61.(a) K. M. Nicholas; M. Khan; A. M. Montana; V. Varghese; R. Tester, *J. Org. Chem.*, 1990, **55**, 186 (b) K. M. Nicholas; A. M. Montana, *J. Org. Chem.*, 1990, **55**, 1569.

62.(a) M. Hanaoka; K. Nagami; C. Mukai, *Tetrahedron Lett.*, 1989, **30**, 5623 (b) M. Hanaoka; C. Mukai, *Synlett*, **1996**, No.1, 11.

63.(a) S. L. Schreiber; M. T. Klimas; T. Sammakia, *J. Am. Chem. Soc.*, 1987, **109**, 5749 (b) S. L. Schreiber; T. Sammakia; W. E. Crowe, *J. Am. Chem. Soc.*, 1986, **108**, 3128.

64. M. Hanaoka; O. Kataoka; C. Mukai, *Tetrahedron Lett.*, 1991, **32**, 7553.

65.K. M. Nicholas; S. Padmanabhan, *Synth. Commun.*, 1980, **10**, 503.

66.K. M. Nicholas; J. E. Boyle; *Tetrahedron Lett.*, 1980, **21**, 1595.

67. (a) E. J. Corey; H. A. Kirst, *Tetrahedron Lett.*, 1968, 5041 (b) E. J. Corey; A. Achiwa, *Tetrahedron Lett.*, 1970, 2245.

68.S. Takano; T. Sugihara; K. Ogasawara, *Synlett*, 1992, 70.

69.K. M. Nicholas; S. Padmanabhan, *J. Organometal. Chem.*, 1981, 115.

70.K. M. Nicholas; S. Padmanabhan, *Tetrahedron Lett.*, 1983, **24**, 2239.

71.W. A. Smit; R. Caple; W. A. Kalyan; A. A. Schegolev, *Tetrahedron Lett.*, 1982, **23**, 4419.

72.N. Jeong; S. Yoo; S. J. Lee; Y. K. Chung, *Tetrahedron Lett.*, 1991, **32**, 2137.

73.(a) N. E. Schore; M. C. Croudace, *J. Org. Chem.*, 1981, **46**, 5436 (b) R. Caple; E. D. Swanson, *Tetrahedron Lett.*, 1986, **27**, 1241 (c) P. Magnus; L. M. Principle; M. J. Slater, *J. Org. Chem.*, 1987, **52**, 1483.

74.K. D. Roth; U. Muller, *Tetrahedron Lett.*, 1993, **34**, 2919

75.K. D. Roth, *Synlett.*, 1992, 435.

76.K. M. Nicholas; J. Siegel, *J. Am. Chem. Soc.*, 1985, **107**, 4999.

77.A. M. Krubiner; N. Grottfried; E. P. Oliveto, *J. Org. Chem.*, 1969, **34**, 3502.

78.M. E. Krafft; Y. Y. Cheong; C. Wright; R. Cali, *J. Org. Chem.*, 1996, **61**, 3912.

79.S. L. Schreiber; T. F. Jamison; S. Shambayati; W. E. Crowe, *J. Am. Chem. Soc.*, 1994, **116**, 5505.

80.D. D. Grove; F. Miskevich; C. C. Smith; J. R. Corte, *Tetrahedron Lett.*, 1990, **31**, 6277.

81.D. D. Grove; J. R. Corte; R. P. Spencer; M. E. Pauly; N. P. Rath, *J. Am. Chem. Soc., Chem. Commun.*, 1994, 49.

82.P. Magnus; P. Carter; J. Elliott; R. Lewis; J. Harling; T. Pitterna; W. E. Bauta; S. Fortt, *J. Am. Chem. Soc.*, 1992, **114**, 2544.

83.M. D.Lee; F. E. Durr; L. H. Hinman;P. R. Haman; G. A. Ellestad, *Advances in Medicinal Chemistry*, JAI Press: Greenwich, 1993, **2**.

84.P. Magnus; D. Parry; T.Lliadis; S. A. Eisenbeis; R. A. Fairhurst, *J. Am. Chem. Soc., Chem. Commun.*, 1994, 1543.

85.M. Isobe; C. Yenjai; S. Tanaka, *Synlett*, 1994, 916.

86.M. Isobe and S. Hosokawa, *J. Org. Chem.*, 1999, **64**, 37.

87.T. Yasumoto; M. Murata; *Chem Rev.*, 1993, **93**, 1897.

88.M. Hanaoka; C. Mukai; Y. Ikeda; Y. Sugimoto, *Tetrahedron Lett.*, 1994, **35**, 2179

89.(a)E. Tyrrell; P. Heshmati; *Synlett*, 1993, 713 (b) E. Tyrrell; S. Claridge; R. Davies; J. Lebel; J. Berge, *Synlett*, 1995, 714.

90.(a)E. Tyrrell; C. Muller; S. Claridge; A. Mann; J. Berge, *Tetrahedron Lett.*, 1997, **38**, 685 (b) E. Tyrrell; C. Muller; A. Mann, *J. Chem. Soc., Perkin Trans.* 1., 1998, 1427.

91. (a) E. J. Corey; W. T. Wipke, *Science* 1969, **166**, 178 (b) E. J. Corey; X. Cheng, *The Logic of Chemical Synthesis*; Wiley-Interscience: New York, 1989

92.S. Matsuzawa; Y. Horiguchi, E. Nukamura; I. Kuwajina, *Tetrahedron.*, 1989, **45**, 349.

93.We would like to thank Dr Richard Singer for his assistance with this study.

94.M. B. Smith, *Organic Synthesis, McGraw Hill Inc.*, 1994, p.106.

95.(a) H. Khan; L. Martell, *Homogeneous Catalsis by metal complexes*; Academic Press: New York, 1974, p. 9 (b) P. Heck, *Organotransition Metal Chemistry*; Academic Press: New York, 1974, p76 (c) F. A. Cotton; G. Wilkinson; P. L. Gaus, *Basic Inorganic Chemistry*, third edition, p. 647.

96.H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl*, 1969, **8**, 556.

97.J. March, *Advanced Organic Chemistry*, fourth edition, p. 583.

98.refer to references 56, 57, 59, 63 and 69.

99.refer to references 57-81, 84-86, and 88-89.

100.D. P. N. Satchell; R. S. Satchell, *Chemical Reviews*, **69**, 251.

101.(a) A. J. Parker, *Quart. Rev. Chem. Soc.*, 1962, **16**, 163; (b) A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

102.R. S. Dickson; P. J. Fraser, *Adv. Organomet. Chem.*, 1974, **12**, 323.

103.D. Seyferth; A. T. Wehman, *J. Am. Chem. Soc.*, 1970, **92**, 5520.

104.B. Jones; M. J. Wright, *J. Org. Chem.*, 1997, **62**, 9379.

105.A. Srikrishna; T. Jagadeeswar; P. Reddy; P. Kumar, *Chem. Commun.*, 1996, 1369.

106.E. W. Warnhoff; D. G. Martin; S. W. Johnson, *Organic Syntheses*, p.162-165.

107.P. Y. Bruice, *Organic Chemistry*, p. 96.

108.We are extremely grateful to a very caring person (who wishes to remain anonymous) at Manchester University for conducting these studies.

109.D. H. Williams; I. Fleming, *Spectroscopic methods in organic chemistry*, p. 91-94.

110.Mioskowski reported the resolution of a pair of propynyl diastereoisomers via complexed to octacarbonyl dicobalt- C. Mioskowski; C. Alayrac; J. P. Salaun; F. Durst, *Synlett*, 1992, 73.

111.M. M. Midland., *J. Org. Chem.*, 1975, **40**, 2250.

112.(a) A. W Pryor; C. K. Govindan; D. F. Church, *J. Am. Chem. Soc.*, 1982, **104**, 7563 (b) J. March, *Advanced Organic Chemistry*, fourth edition p. 1177.

113.W. H. Watson; I. Tavanaiepour, *J. Org. Chem.*,1975, **40**, 2250.

114.N. Menashe; D. Reshef; Y. Shvo, *J. Org. Chem.*, 1991, **56**, 2912.

115.R. T. Thomas, *J. Am. Chem. Soc.*, 1938, **60**, 718.

116.W. Kemp, *Qualitative and Quantitative Organic Analysis*, p. 57.

117.(a) For reviews of Friedel-Crafts acylation: i) P. Gore, *Chem. Ind. (London)*, 1974, 727 ii) G. Baddeley, *Quart. Rev. Chem. Soc.*, 1954, **8**, 355. b) For a list of reagents, with references, see N. Larock, Ref. 171, p. 703-704.

118.(a) S. Hanessian; J. Franco; B. Larouche, *Pure Appl. Chem.*, 1990, **62**, 1887 (b) K. Weinges; H. Reichert; H. P. Ursula; H. Ingartinger, *Liebigs Ann. Chem.*, 1993, 403 (c) A. Anja; B. J. Jansen; A. D. Groot, *Tetrahedron*, 1994, **50**, 10095.

119.S. Kreevoy; H. Thomas, *J. Org. Chem.*, 1977, **42**, 3979.

120.H. Ziffer and M. Imuta, *J. Org. Chem.*, 1979, **44**, 1351.

121.G. Linstrumelle; R. Lorne; H. P. Dang; *Tetrahedron Lett.*, 1978, **42**, 4069.

122.B. J. Bunn; P. J. Cox; N. S. Simpkins, *Tetrahedron.*, 1993, **49**, 207.

123.H. C. Heathcock and E. S Binkley, *J. Org. Chem.*, 1975, **40**, 2156.

124.W. Still; M. Khan; A. Mitra., *J. Org. Chem.*, 1978, **43**, 2923.

125.R. E. J. Smith, *J. Chem. Soc., Perkin Trans 1*, 1996, ix.

# Publications

# List of Publications

- **The Synthesis of Bridged Bicyclic Ring Systems using a Novel Variation of the Intramolecular Nicholas Reaction.**

  Paper in the process of completion.