Applications of σ-Organomanganese Compounds in the Synthesis of Potential Antitumour Agents

SAPERE EST IUCUNDUM

A thesis submitted in partial fulfilment
of the requirements of the Degree of
Doctor of Philosophy in Chemistry
at the University of Waikato
by

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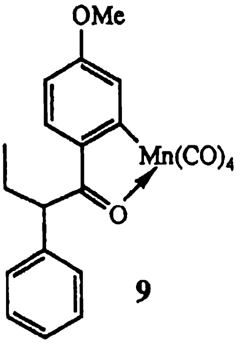
November
1993

Abstract

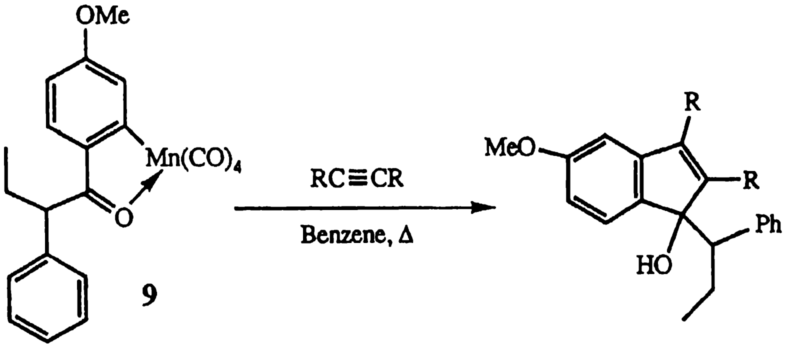
Reported in this thesis are studies exploring the synthetic utility of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** in organic synthesis, in particular, routes to both *ortho*-halogenated derivatives of Tamoxifen, a therapeutic drug for the treatment of hormone dependent breast cancer, and other potentially antiestrogenic compounds which may have therapeutic application.



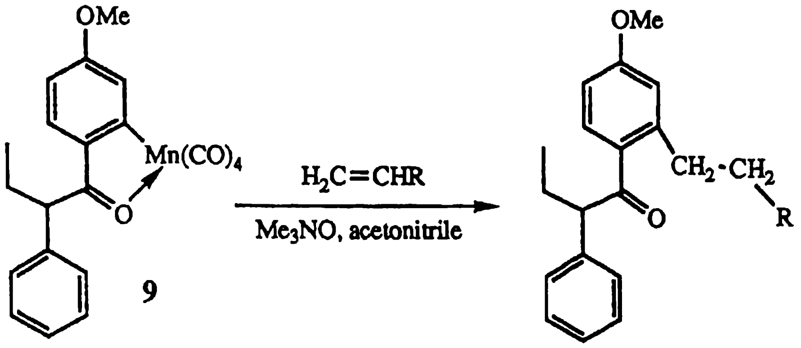
9

Described are the syntheses of the *ortho*-halo-substituted Tamoxifen derivative *Z*-1-(2-bromo-4-(2-(*N*,*N*-dimethylamino)ethoxy)phenyl)-1,2-diphenylbut-1-ene **26** and an analogue *Z*-1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **18**.

The reaction of **9** with phenyl isocyanate gives *E*-6-methoxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **124** which is readily converted upon mild acid hydrolysis to the novel carboxylic acid and Tamoxifen analogue *E*-5-methoxy-2-(2-phenyl-1-phenylamino-1-butenyl)-benzoic acid **125**.



The thermally-activated coupling of **9** in benzene with the alkynes $PhC{\equiv}CPh$, $HC{\equiv}CPh$, $HC{\equiv}CSiMe_3$, $HC{\equiv}CCH_2CH_2OH$, $CH_3C{\equiv}C\text{-}n\text{Pr}$ and $MeO_2CC{\equiv}CCO_2Me$ was undertaken (equation above). An alkyne having a bulky substituent leads to formation of only one of two possible diastereoisomeric inden-1-ol products in benzene and petroleum spirit. In contrast, there is no such stereospecificity for the analogous coupling in the polar solvent acetonitrile. The Pd(II)-mediated coupling of $PhC{\equiv}CPh$ with **9** gives moderate yields of the benzofulvenes *E*- and *Z*-5-methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene **37** and **38** for which the crystal structures of both are reported.



Coupling of the alkenes $H_2C{=}CHCOMe$, $H_2C{=}CHCO_2Me$, $CH_3CH{=}CHCO_2Me$, $H_2C{=}CHOCOMe$, $H_2C{=}CHPh$ and $EtO_2CCH{=}CHCO_2Et$ with **9** was extensively investigated with or without promotion by Pd(II) or trimethylamine *N*-oxide (equation above), employing different solvents and reaction conditions. A development in this area results from the finding that when coupling is carried out in the presence of $NiBr_2(PPh_3)_2$ the yields and specificity of coupled products significantly increase.

In a separate study, titanium-mediated reductive dicarbonyl coupling of halo-substituted benzophenone derivatives with propiophenone gives *ortho*-brominated analogues of Tamoxifen. Titanium-mediated coupling also provides a route to the synthesis of *Z*-1-(2-*N*,*N*-dimethylaminoethyl)-4-(1,2-diphenylbut-1-enyl)pyridinium chloride **121**, a novel Tamoxifen analogue. Some other Titanium-mediated coupling reactions of dicarbonyl compounds previously obtained by coupling of methyl propenoate and 3-buten-2-one with **9** are also studied as potential routes to substituted dihydronaphthalene and tetralone compounds.

Preliminary and tentative investigations are reported toward the synthesis of Tamandron analogues, a potential antitumour agent similar to Tamoxifen. Descibed is the synthesis of 9-hydroxy-6-methoxy-9a-methyl-9-(1-phenylpropyl)-1,2,3,4,4a,9,9a-heptahydro-1-fluorenone **128** a product derived from the coupling of 2-methyl-2-cyclohexenone with **9**.

Acknowledgements

He mihi nui tenei ki nga a tangata katoa i awhina, i manaaki, i tautoko i a au, i aku, mahi rangahau. Ko koutou e whai ake nei, Tena rawa ano koutou katoa.

Assoc. Prof. Lyndsay Main i awhina i a au me aku mahi koreroeo.

Ko te Whare Wananga o Waikato i homaitia e ratou te Post Graduate Scholarship. Te Royal Society of New Zealand i homaitia e ratou he moni awhina. Te New Zealand Institute of Chemistry i homaitia e ratou he moni awhina.

Te Chemistry Department mo a ratou mahi awhina e pa ana ki te hangarau.
- Dr. Ralph Thomson, Dr. Rick Ede, Assoc. Prof.Alistair Wilkins i awhina i a au me aku NMR.
- Janine Sims i awhina i a au me aku mahi GCMS.
- Assoc. Prof. Brian Nicholson i awhina i a au me aku mahi X-ray crystallography, a me aku mahi koreroeo.

He mihi nui ki aku hoa mahi , ko Warren Tully, ko Janine Cooney me tona kanohi whiti, ko Rene deWit te kaimahi tere a ko Ansari Samad. I ngaro a Warreni te pere.

He mihi nui, he tohu aroha hoki ki aku hoa, ki taku whanau. Na ratou i tino tautoko i a au me aku mahi. Ki a koutou Tim, Ross, Anton, Marty me Dave kia ora koutou.

Ko te mea whakamutunga - ki a koe Nyree, tino waimarie ahau ki te mahitahi me tenei wahine tino pai rawa atu.

Noreira
tena koutou, tena koutou
Tena ano koutou katoa.

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Abbreviations

Ac - acetyl
Ar - aromatic or phenyl (Ph)
bp - boiling point
br - broad
Bu - butyl
calcd. - calculated
COSY - Correlated Homonuclear Spectroscopy
Cp - η^5-cyclopentadienyl
δ - chemical shift
d - doublet
DMAD - dimethylacetylene dicarboxylate
DMF - dimethylformamide
ER - estrogen-receptor
Et - ethyl
FAB - fast atom bombardment
GC - gas chromatography
h - hour(s)
IR - infrared spectrum/ spectroscopy
$J_{x\text{-}x}$ - coupling constant (Hz)
lit. - literature value
m - medium (IR)
m - multiplet (NMR)
M^+ - molecular ion
Me - methyl
min - minute(s)
mp - melting point
MS - mass spectrum/ spectroscopy
NBS - *N*-bromosuccinimide
NIS - *N*-iodosuccinimide
NMR - nuclear magnetic resonance
pet. spirit - petroluem spirit (60-80°C)
Ph - phenyl
plc - preparative layer chromatography
PR - progesterone-receptor
Pr - propyl
q - quartet
s - singlet (NMR)
s - strong (IR)
sh - shoulder

t	-	triplet
tol	-	tolyl
THF	-	tetrahydrofuran
THP	-	tetrahydropyranyl
tlc	-	thin layer chromatography
ν	-	stretching frequency (IR)
vs	-	very strong
w	-	weak
$W_{1/2}$	-	width at 1/2 peak height
XH	-	Correlated Hetereonuclear Spectroscopy

CHAPTER ONE

A PERSPECTIVE ON TAMOXIFEN SYNTHESIS

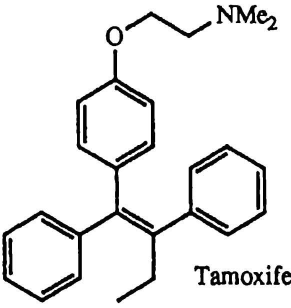
1.1 Introduction.

Breast cancer is by far the most common cancer among women, and following lung cancer it is the most lethal. For advanced breast cancer, masecotomy and radiation are the only treatment. In the United States of America, there are some 46,000 women who die annually as a direct result of breast cancer. It is also a disease with enormous psychosocial ramifications. For a women living in North America, the lifetime odds for getting breast cancer are now 1 in 8. This figure has doubled over the last fifty years. An annual increase in the incidence rate for the disease has been observed over the last fifty years, though importantly the mortality rate has remained relatively constant.[1]

In a minority of cases genes are thought to be responsible for the disease development. Researchers have found[2] that a gene is directly responsible for *ca.* 5% of all breast cancers. This breast cancer susceptibility gene is inherited by 1 in 200 women and of those, 80-90% are at risk of developing the disease. However, there is something inherent in the environment contributing to the increasing cancer rate. The search for environmental causes of breast cancer has held the attention of scientists since the 1960's. Women in North America and Europe have a five times higher chance of developing breast cancer than those of Asia. Geographically, a high fat diet matches up with higher cancer risks. Studies[1] have shown links between fat intake and colon cancer only. Women on a high fat diet had little or no more risk of developing breast cancer than those adhering to a low fat intake. These results show changing lifestyle will not in itself reduce the incidence of breast cancer.

Breast cancer research has refocussed on hormones, especially estrogen. Hormones stimulate cell division in certain target organs. Increased cell division results in a greater risk for abnormal cells to form. It is now thought a woman's total exposure to estrogen may be an important factor to indicate breast cancer risk and may explain the international disparities in risk. Early menarche, age at menopause and age of first childbirth have been identified[2] as critical. Early menarche and late menopause independently correlate with the likelihood of breast cancer, while an early first child reduces it.

As breast cancer is believed to take from three to thirty years to develop, there are three opportunities to stop its development. Firstly by limiting cancer causing exposures, secondly by reversing or containing precancerous cell growth and lastly removing or killing recognisable cancerous lesions. Researchers are now at the stage of preventing breast cancer rather than just treating the disease. Prevention strategies that intervene during the premenopausal period can be expected to have a bigger impact at reducing risk long-term. It is proposed to use the drug Tamoxifen **1** for the hormonal chemoprevention of the disease.

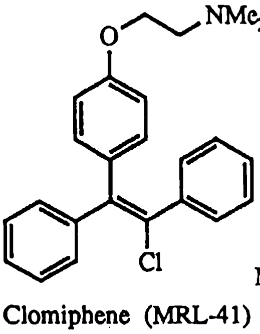


Tamoxifen **1**

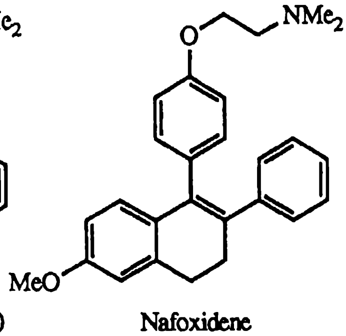
1.2 Tamoxifen.

The most compelling evidence for chemoprevention by Tamoxifen derives from the observation that primary breast cancer patients treated with Tamoxifen appear to have a lower risk of developing the disease in the opposite breast.[3] Tamoxifen has been the mainstay of breast cancer treatment, being used to treat advanced breast cancer since its introduction in the early 1970s. It is an effective treatment,[4] being able to cause regression in advanced tumours, to slow relapse and to cure early cancers.

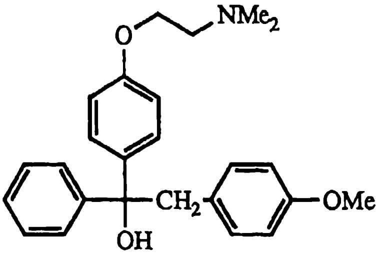
Tamoxifen **1** (ICI-46,474, Nolvadex 1-(4-(2-(*N,N*-dimethylamino)-ethoxy)-phenyl)-1,2-diphenylbut-1-ene) is a triphenylethylene derivative. It was developed[5,6] by Imperial Chemical Industries following research into estrogen antagonists as part of a search for contraceptive agents. The first in a series of anti-estrogen compounds,



Clomiphene (MRL-41)

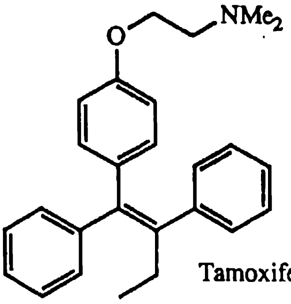


Nafoxidene

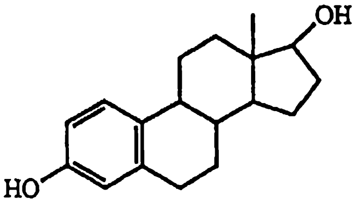


Ethamoxytriphetol (MER 25)

Ethamoxytriphetol (MER-25) was found[7] to be of low potency and its excessive side-effects precluded its use as an antifertility agent. Other triphenylethylene antiestrogens including Clomiphene, Nafoxidene and Tamoxifen were found[7] to have both antagonist and agonist properties in different species and organs. These non-steroidal estrogens are thought[8] to act principally by preventing estradiol 2 from binding to its protein receptor in specific tissues. Although Tamoxifen is classified as an estrogen antagonist because of its predominantly antiestrogenic effects, it also possesses partial estrogenic effects in some tissues.[4] The precise mechanism of Tamoxifen's antiestrogenic activity is uncertain.[4] *In vivo* studies suggest[4] that its antiestrogenic action results from direct binding to the estrogen-receptor proteins, leading to conformational changes in the receptor, altered RNA transcription and decreased cell proliferation. Circulating estrogens are selectively concentrated in estrogen target organs. It is this that has led to effective Tamoxifen treatment for estrogen-dependent, metastatic breast cancer. Overall response to treatment of advanced breast cancers with Tamoxifen vary between 22 and 60 per cent.[9] Presence of estrogen-receptor (ER) and progesterone-receptor (PR) proteins markedly increase the response to treatment. There is a 76 per cent response for patients with ER positive and PR positive tumours, while less than 10 per cent of receptor negative tumours respond.[9]



Tamoxifen **1**



Estradiol **2**

Results of clinical trials[4] suggest Tamoxifen may lower serum cholesterol levels up to *ca.* 20% by working as an estrogen agonist on the liver, thus impeding potential development of cardiovascular diseases. There is no evidence that Tamoxifen working as an antiestrogen decreases bone density promoting osteoporosis. However its partial estrogenic activity may stabilise or lead to a decreased bone density loss. As well as the potential benefits of breast cancer risk, a decrease in cardiovascular disease and bone density stabilisation may also be benefits of Tamoxifen chemoprevention.

1.3 Tamoxifen Synthesis.

Tamoxifen 1 is the Z-isomer. Enigmatically, the *E*-isomer 3, usually referred to as *cis*-Tamoxifen, is estrogenic, would oppose the action of Tamoxifen[10] and has no clinical uses. Pharmaceutical preparations of Tamoxifen need to be isomerically pure and as a consequence, stereoselective syntheses of Tamoxifen are worthwhile. The classical synthesis[5,6] (figure 1.1) gives a mixture of *E*- and Z-isomers from which the Z-isomer is isolated by fractional recrystallisation as the citrate salt.

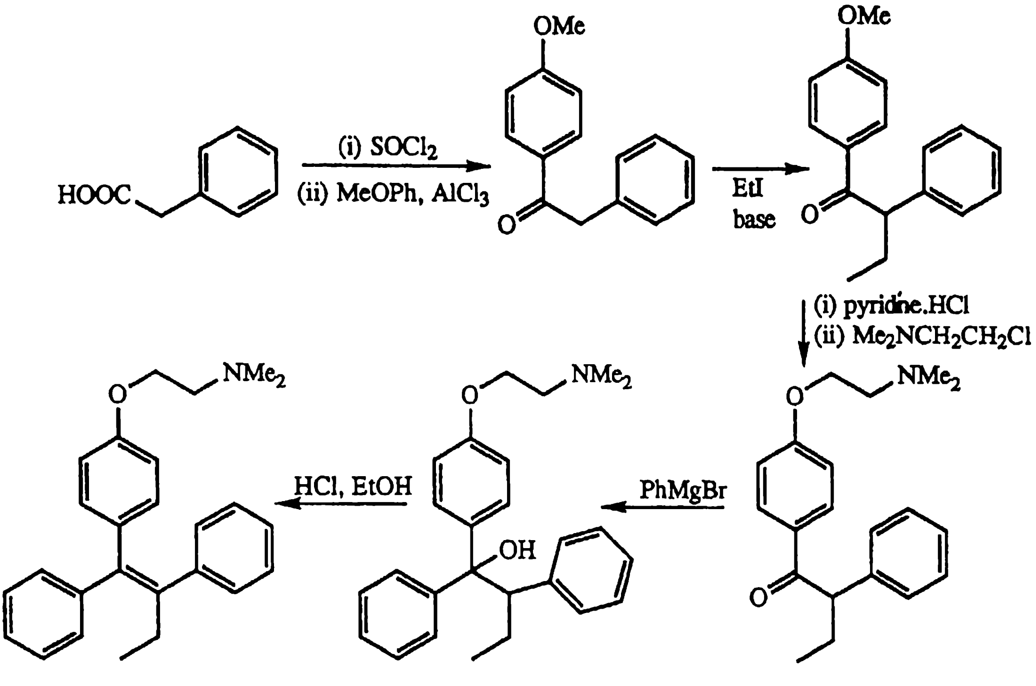


Figure 1.1 Classical Synthesis of Tamoxifen

On an analytical scale, the geometrical isomers of Tamoxifen may be separated[11] by silica gel tlc eluting with benzene/triethylamine. Acid-catalysed dehydration of the tertiary alcohol (as in figure 1.1) gives an isomer ratio of 1:1. This ratio can be improved to 2:1 (*Z*/*E*) by employing milder conditions.[12] However, isomer equilibration to a 1:1 mixture results from extended acid treatment presumably *via* protonation of the central double bond. It appears[12] that the isomer distribution is independent of the stereochemistry of the tertiary alcohol, which can be explained by the dehydration proceeding through a common carbocation intermediate. Treatment[12] of either *Z*- or *E*-Tamoxifen with fluorosulphonic acid regenerates the carbocation and upon quenching gives an 1.4 : 1 (*Z*/*E*) mixture irrespective of the starting isomer.

Although separation of Z-Tamoxifen from the *Z*/*E* mixture is difficult, separation of Tamoxifen precursors is much more straightforward. *Z*- and *E*-isomers derived from the reaction of octafluorotoluene with an *Z*/*E* mixture of 1,2-diphenyl-1-(4-hydroxyphenyl)-but-1-ene are easily separated chromatographically[13]. Cleavage of the ether function of either isomer with sodium methoxide regenerates the phenol of pure configuration and addition of the basic side chain to the pure Z-isomer gives Tamoxifen without isomerisation.[13] Separation of the Z- and *E*-isomers of 1-(4-(2-chloroethoxy)-phenyl)-1,2-diphenylbut-1-ene 4 is possible by recrystallisation of the isomer mixture from propan-2-ol.[14] The chloroethoxy compound 4 can be readily prepared by either of two routes (figure 1.2), by elaboration of the ICI route,[12] or from a titanium-mediated coupling reaction. The latter method[14] gives a crude yield of more than 90% with an *Z*/*E* isomer ratio of 9:1. A convenient precursor, the chloroethoxy compound can be converted to Tamoxifen by substitution of the chlorine with dimethylamine.[8]

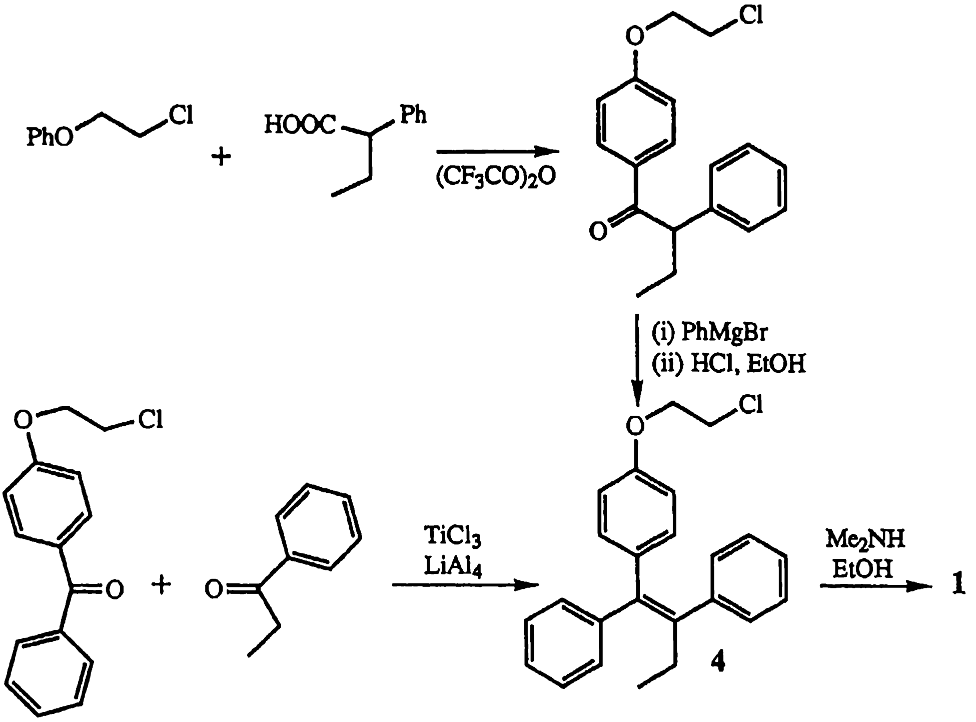


Figure 1.2

A stereospecific synthesis of Tamoxifen has been developed[15] employing the *cis*-selective carbometalation of an alkynylsilane (figure 1.3). The initial step in the synthesis establishes the stereochemistry about the double bond. Stereospecific replacement of the bromo and trimethylsilyl groups with the appropriate aryl groups gives Tamoxifen in 60% yield.

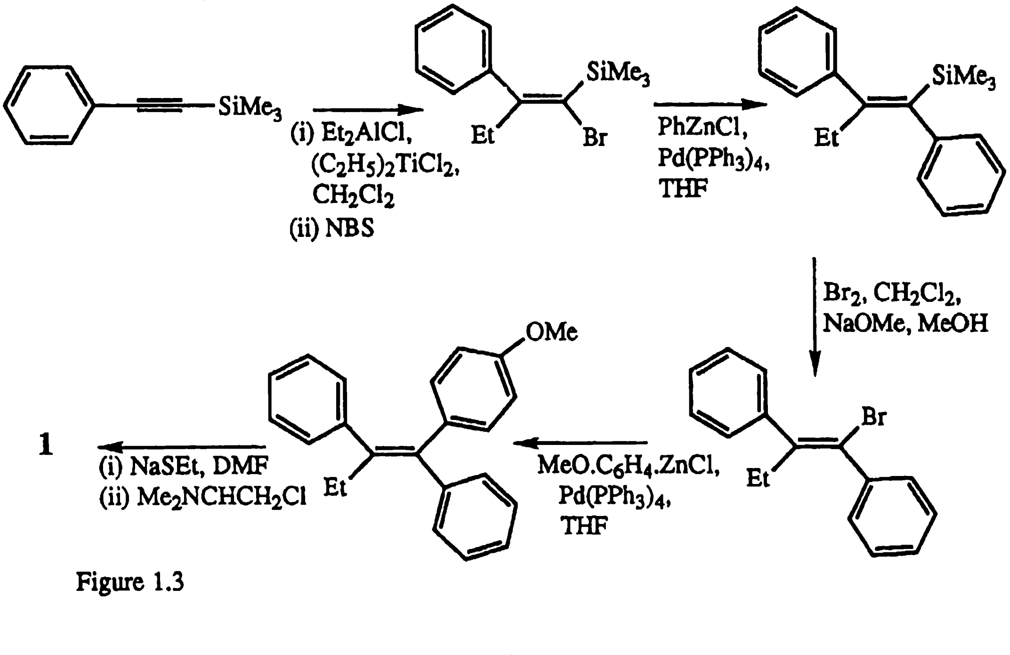


Figure 1.3

Another stereoselective synthesis[16] (figure 1.4) incorporates a similar (*E*) vinyl bromide intermediate to that above (figure 1.3). The vinyl bromide is formed with a high stereoselectivity (20:1 *E/Z*) and the pure *E*-isomer is obtained by crystallisation. The *E*-vinyl bromide is then converted to Tamoxifen with only a minor loss of stereochemical integrity, giving an overall yield of *ca.* 60%. Because 4-hydroxyTamoxifen **5** (1-(4-(2-(*N*,*N*-dimethylamino)-ethoxy)-phenyl)-1-(4-hydroxyphenyl)-2-phenylbut-1-ene) suffers facile geometric isomerisation in the presence of acid or free radical sources[11,17] due to conjugation between the central double bond and the carbocation and radical-stabilising hydroxyl group, any stereospecific synthesis needs to avoid these sources in order to prevent isomerisation. This method[16] (figure 1.4) is the only reported stereospecific synthesis of **5**.

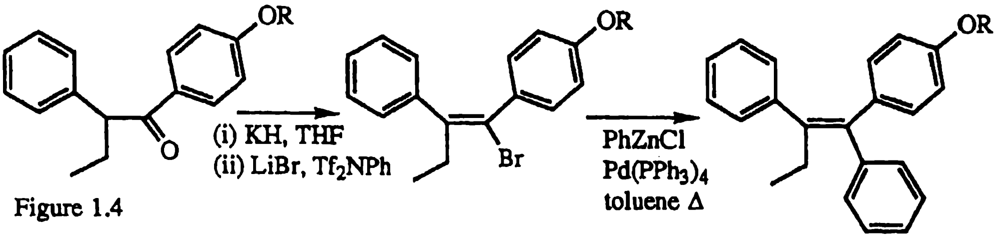
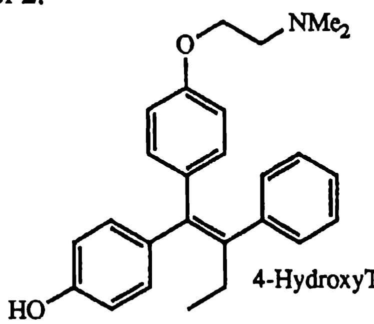


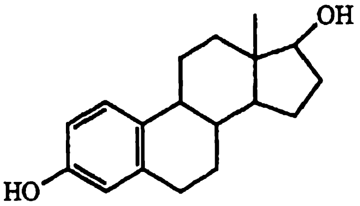
Figure 1.4

1.4 Structure and Activity Relationships.

4-HydroxyTamoxifen **5** has been found to be an important metabolite of Tamoxifen. It has a much higher *in vitro* potency than the parent drug. Binding to the estrogen receptor with 100 times the affinity of Tamoxifen, it perhaps contributes significantly to the overall activity of Tamoxifen.[7] It is thought that in binding to the estrogen receptor the 4-hydroxyl group plays the same role as the 3-hydroxyl group in estradiol **2**.[7]

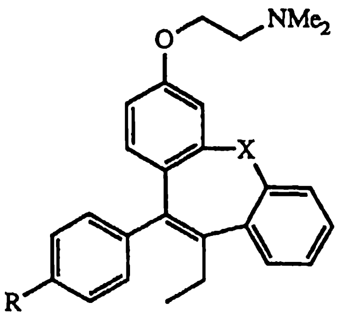


4-HydroxyTamoxifen **5**



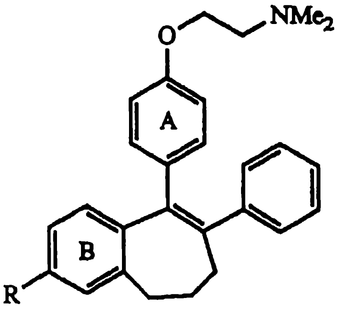
Estradiol **2**

Certain key structural features of Tamoxifen are important for its ability to bind the estrogen-receptor (ER) and block estrogen action. X-ray crystallographic studies of Tamoxifen[18] and its analogues[19,20] show the aryl rings to be non-planar in a "propellor"-type conformation. The importance of the non-planar nature of the triphenylethylene structure for activity has been investigated.[21,22] The degree of planarity is important in determining potency. Increased planarity resulted in a loss of ER binding and a corresponding decrease in potency.[21,22]



X = O, S, CH_2CH_2, SCH_2

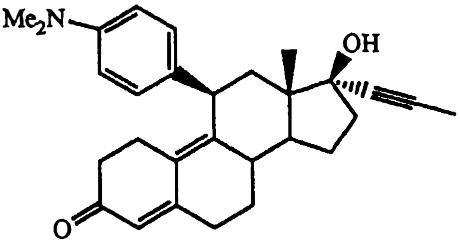
Figure 1.5



R = H or OH

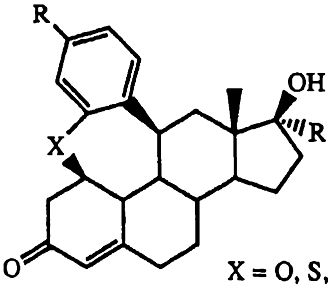
Figure 1.6

It was also found[21,22] that tricyclic fused analogues of the type in figure 1.5 had lower potency than the corresponding Tamoxifen derivatives, probably due to the inclination of the two rings toward one another rather than being in the "propellor" conformation of Tamoxifen.[18] As well as ring planarity, structure activity studies[21] led to the conclusion that the aminoethoxy side chain on the A ring is critical for antiestrogenic activity and the addition of a 4-position hydroxyl group greatly increased potency.[23] The relationship between side chain and hydroxyl positioning and relative antiestrogenic activity have been evaluated[23,24] using non-isomerisable cycloheptene compounds (figure 1.6). Use of a seven-membered ring gives orientations of the aryl rings similar to those of Tamoxifen. Other non-steroidal structures based on triphenylethylene show considerable variation in structure though maintaining antiestrogenicity. These include substituted 2,3-diphenylindoles,[25] 2-phenylindenes[26] and 2,3-diphenylindenes,[27] benzothiophenes[28] and acetoxy-substituted 2-phenylindenes,[29] triphenylethylenes[30] and 1,2-diphenylethanes.[31] More recently, progesterone antagonists have been subject to intensive research.[32] Unlike Tamoxifen derivatives these antiprogestins such as mifepristone (figure 1.7) are substituted steroids and show potential in chemotherapeutic application.[33] The bridged analogues (figure 1.8) are more potent and are currently under investigation.[32]



Mifepristone

Figure 1.7



X = O, S, CH_2

Figure 1.8

1.5 Synthesis with Transition-Metals including Manganese.

For many years organometallic reagents and catalysts have been employed in synthesis. In recent times interest has focused on the synthetically valuable bond activation reactions, for example, the rare case of carbon-carbon, carbon-hydrogen and carbon-oxygen bond activation by an electrophilic ruthenium complex[34] (figure 1.9).

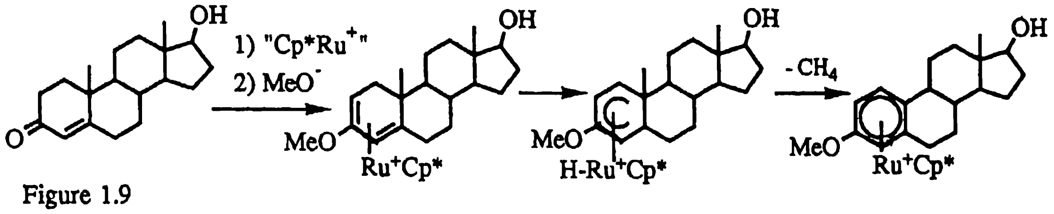


Figure 1.9

Use of transition metal-mediated reactions has proved successful in carbon-carbon bond formation particularly in industrial applications. In the last ten years the metal carbonyl compounds which have generally become useful in synthetic applications are those of nickel, cobalt, chromium and iron. An example is the coupling reaction[35] in figure 1.10 which is followed by oxidation of the tricarbonyliron complex, as part of the sequence for the synthesis of the carbazomycin series of drugs (figure 1.10).

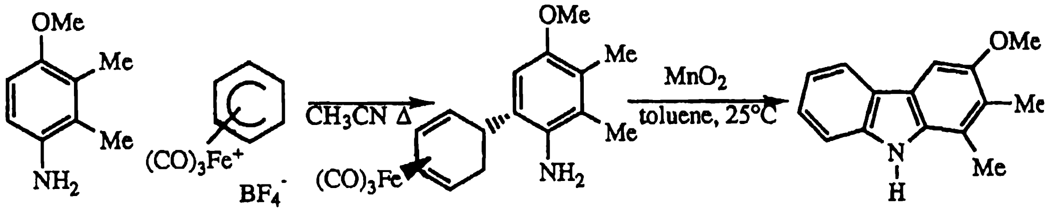


Figure 1.10

Development of syntheses employing manganese carbonyls has been somewhat restricted, with few reports of their use in organic synthesis. An example is the cationic arene complex employed[36] to synthesise stilbene antibiotics (figure 1.11). Few σ-bonded organomanganese compounds have shown synthetic value.

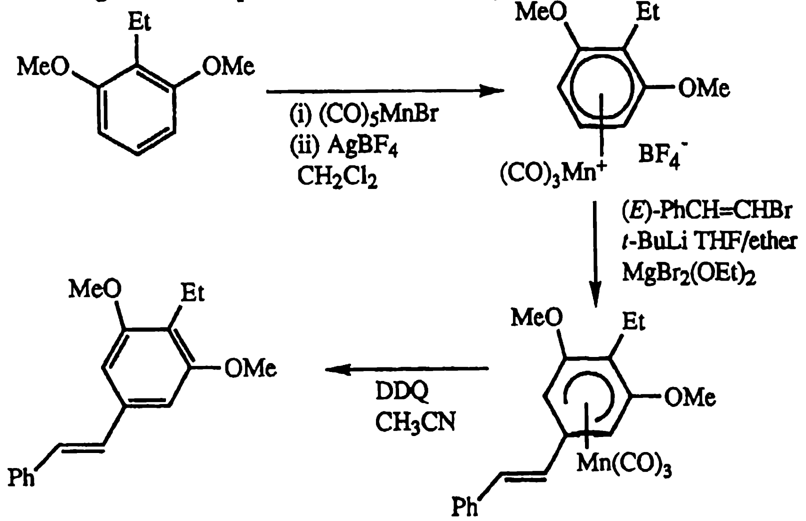


Figure 1.11

The development[38] of simple methods of preparation of cyclometalated compounds of manganese carbonyls has led to recognition of their potential for organic synthesis. It is this which provides the link to Tamoxifen syntheses in this thesis.

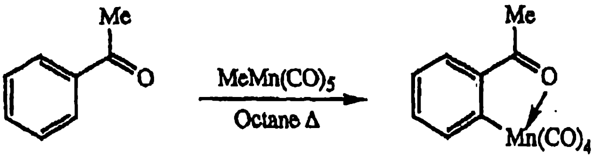


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Figure 1.12

Cyclometalated compounds[37] are organometallic intramolecular coordination compounds in which a chelate ring contains a metal-carbon σ-bond. Orthometalation of aromatic ketones such as acetophenone 6 (figure 1.12) was developed by Kaesz *et al.* [38] in the mid-1970s. Though other metals routinely cyclometalate with other donor substrates (for example nitrogen, phosphorus or sulphur), none, with the exception of rhenium[38], orthometalate to give products with an oxygen donor group. The generality of the reaction has been extended by orthomanganation of aromatic esters.[39] Some[40] substituted benzaldehydes also react, as do *N*,*N*-dialkylbenzamides. Reactivity of the Mn-C σ-bond gives potential for synthesis. Replacement of the manganese leads to orthofunctionalisation, which is important given the carbonyl function is normally *meta* directing in electrophilic aromatic substitution.

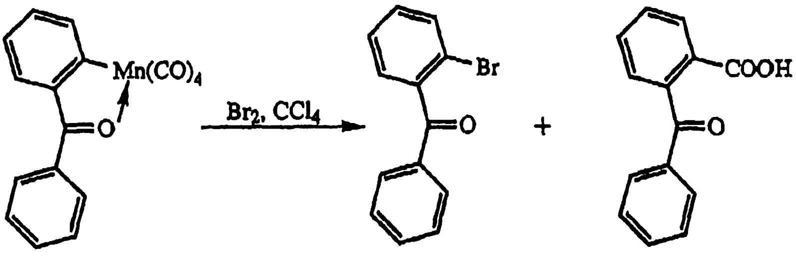


Figure 1.13

The potential synthetic value of these orthomanganated complexes was first shown when a reaction (figure 1.13) with a three-molar excess of Br_2 was reported[41] to give 2-bromobenzophenone and 2-benzoylbenzoic acid, though the analogous acetophenone complex 6 gave no *ortho*-bromination product. Electrophilic substitution by halogen (as in figure 1.13), has been extended to include iodination[42-44] and chlorination[44] for a number of orthomanganated aryl ketone complexes. The reaction of an orthomanganated aryl ketone with Ce(IV) and CD_3COOD is reported to give an *ortho*-mono-deuteriated product[42] amongst others.

There is an increasing tendency to use cyclometalated compounds for directed carbon-carbon bond formation. For example, this is well known with palladium metallacycles. A representative reaction[45] is shown below (figure 1.14).

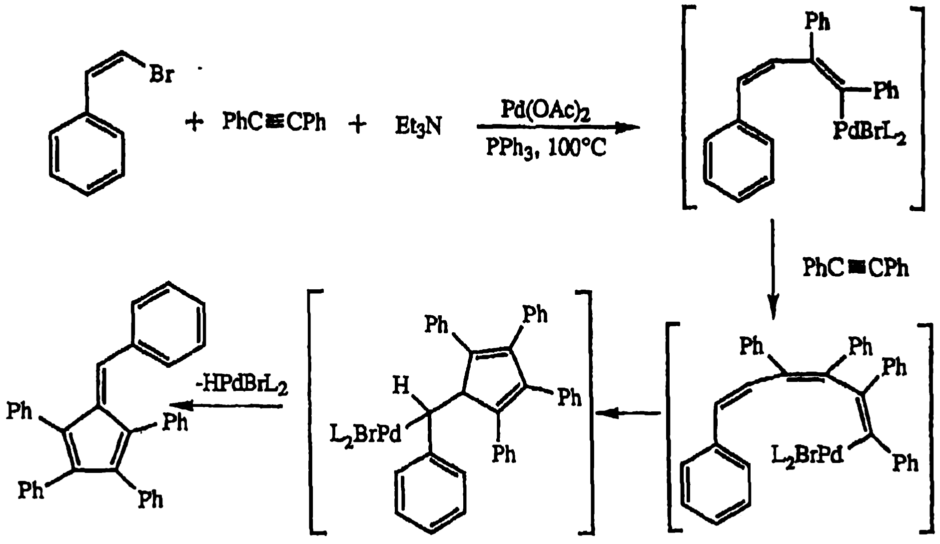


Figure 1.14

However, only more recently has this type of chemistry been extended to the use of orthomanganated aryl ketones as intermediates in the synthesis of organic compounds. Palladium(II)[46] and trimethylamine *N*-oxide[47-49] have been used to promote reactions of orthomanganated ketone complexes with alkenes which give coupled products in moderate to excellent yield. These product types are exemplified in the representative reaction[50] shown below (figure 1.15).

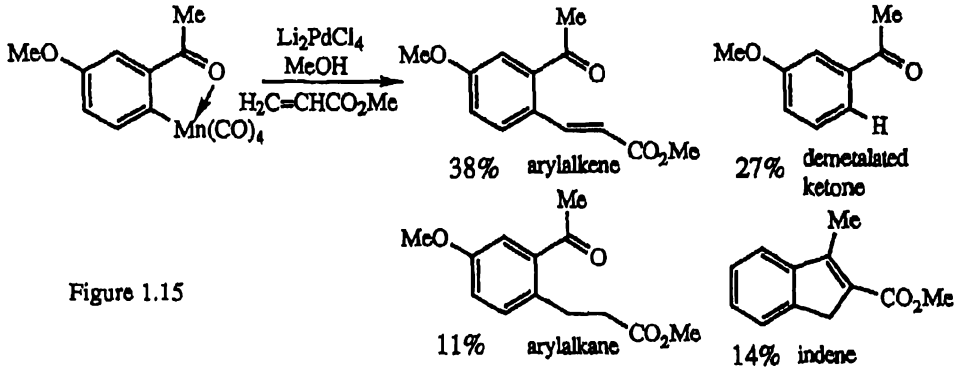


Figure 1.15

Cycloaddition reactions of organometallic compounds with alkynes are well known.[51] Though alkyl manganese carbonyls have been long known[52-54] to react with alkynes, only recently have reactions with orthometalated manganese carbonyl complexes been studied. Two groups have independently reported thermally-[55] and Me_3NO-induced[56] reactions of orthomanganated aryl ketones with alkynes to give cyclopenta-annulated products. The example in figure 1.16 shows alkyne coupling of an orthomanganated *N*-acetylindole complex to give[57] a product having the core unit of the mitomycin series of antibiotic compounds.

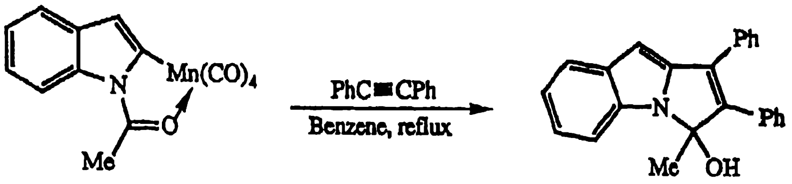
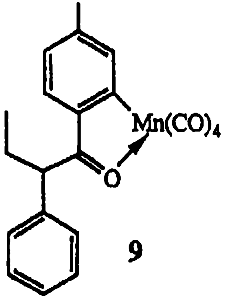


Figure 1.16

1.6 Current Study

It was proposed to develop the chemistry of existing cyclomanganated compounds based mostly on the compound 9 and to incorporate this into synthetic strategies for the preparation of structures analogous to that of Tamoxifen (*cf.* the Grignard step in figure 1.1) and other potentially antiestrogenic compounds.



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In Chapter Two is described attempts to synthesise *ortho*-halogenated Tamoxifen derivatives.

Described in Chapters Three and Four are the development of the coupling of orthomanganated compounds with alkynes and alkenes respectively. Though the topics in these chapters is not related to the theme of Tamoxifen, the structural types formed are sufficently interesting as to be considered as potential ER-binders in their own right.

In Chapter Five is reported an extension of the theme of Chapter Two to titanium-induced reductive coupling in attempts to synthesise substituted Tamoxifen analogues.

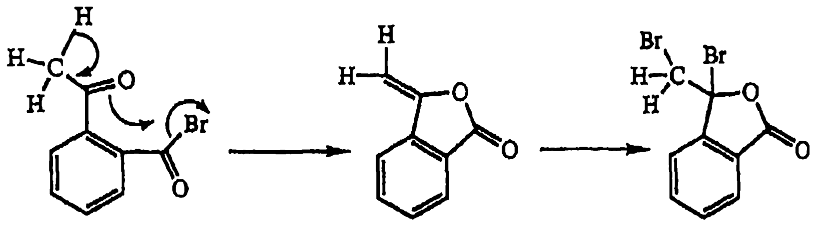
Chapter Six describes tentative attempts to couple substrates containing C=N functions with orthomanganated compounds, and the attempted synthesis of Tamandron analogues.

CHAPTER TWO

SYNTHESIS OF HALOGENATED TAMOXIFEN ANALOGUES

2.1 Introduction.

The ketone function is *meta*-directing in electrophilic aromatic substitution. However, development of orthomanganated aryl ketone chemistry has led to functionalisation of the aromatic ring specifically *ortho* to the ketone function. Electrophilic bromination of orthometalated manganese complexes has been known for a long time[41] (see for example figure 1.13, Chapter One). When orthomanganated acetophenone 6 was reacted with a three-molar excess of Br_2, the major product[41] was the brominated isobenzofuranone compound presumably formed as follows (scheme 2.1).



Scheme 2.1

Repetition of this reaction using only one mole of Br_2 gives[43] both 2-bromoacetophenone and the dibromoisobenzofuranone in poor yield. Further investigations[43,58] showed that electrophilic attack at the manganated aryl carbon could be enhanced by electron-donating substituents such as methoxy groups, leading to good yields of the *ortho*-brominated products (figure 2.1).

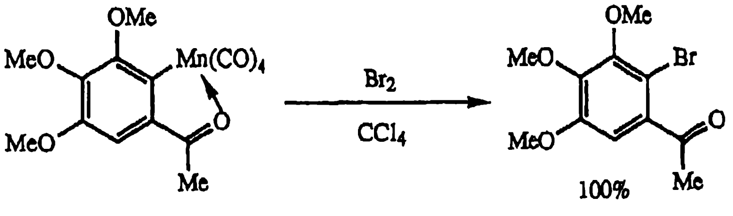


Figure 2.1

Electrophilic iodinations[43,44,58] have also been effected to give iodo-substituted products for example with iodine trichloride (figure 2.2[44]). Both iodine monochloride[43,44] and *N*-iodosuccinimide (NIS)[44] apparently react exclusively at the manganated carbon to give specific *ortho*-iodination products, unlike the case for ICl_3 in figure 2.2 and some other reported cases of bromination.[43,44]

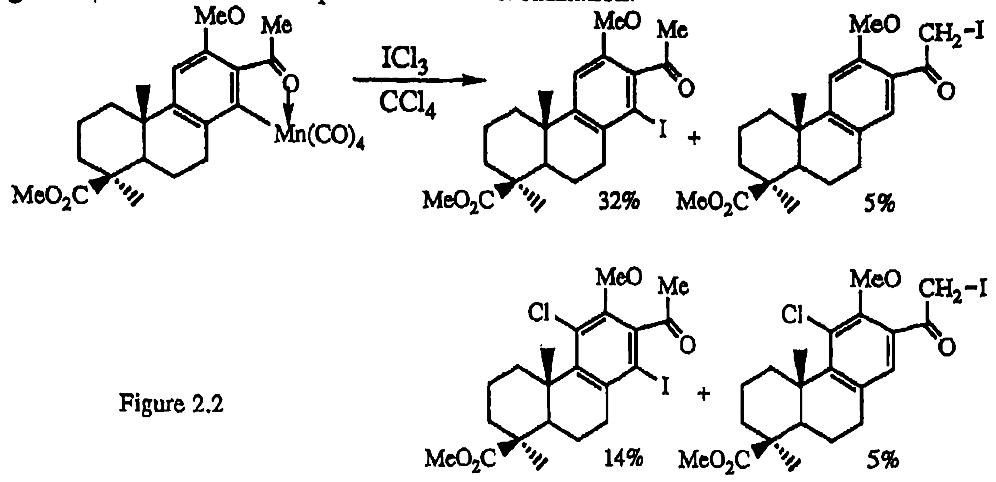


Figure 2.2

2.1.1 Halogenated Tamoxifen Derivatives.

The synthesis of halo-substituted Tamoxifen derivatives has been primarily focused on their potential application for studying breast cancer. Employing radiolabelled pharmaceuticals would be advantageous in characterising breast carcinoma and possibly for monitoring responses to therapy. Radiolabelled iodo-[23,59-64] and fluoro-[61,65] Tamoxifen derivatives have been developed as complexing agents for imaging estrogen-receptor-positive breast cancers. The 4-halo derivatives of Tamoxifen (figure 2.3) are analogous to 4-hydroxyTamoxifen 5 and were found[23,59,60,65] to have higher estrogen-receptor (ER) binding affinities than Tamoxifen. Similarly, the alkyl substituted iodo- and fluoro-derivatives (figure 2.3) were also found[61] to be more potent than Tamoxifen itself.

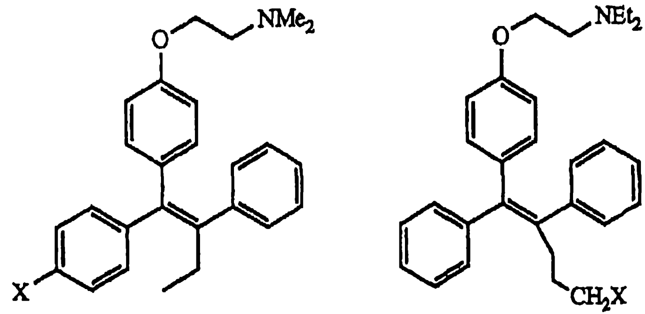


Figure 2.3

X = F or I

Recently a regiospecific *meta*-substitution (*meta* to the butene double bond) of Tamoxifen was reported.[64] Substitution was achieved by employing a trialkylstannyl moiety which was then cleaved with iodine (figure 2.4) to give the iodinated derivative.

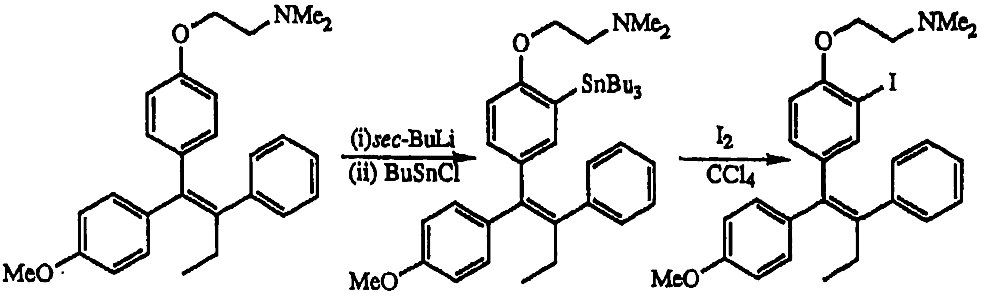


Figure 2.4

It was found[20] that the introduction of a 3-hydroxyl substituent or a methyl or hydroxyl substituent in the 2-position of the B ring (figure 2.5) of Tamoxifen restricts free rotation of the A and B phenyl rings. Both rotational and conformational changes of the phenyl rings in Tamoxifen and in some analogues have been extensively investigated.[20,66-68] One example, the methyl-substituted benzoheptene[69] analogue of Tamoxifen (figure 2.5), was sterically constrained such that the two enantiomers of opposite helicity were resolved at - 5°C.

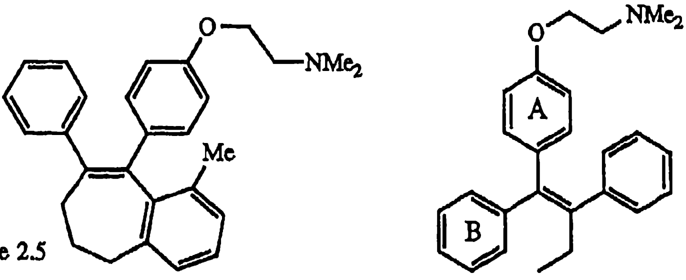


Figure 2.5

Structural studies[20] on Tamoxifen derivatives employing both X-ray crystallography and conformational dynamics (using semi-empirical energy calculations) have shown *ortho* substituents such as hydroxyl or methyl groups significantly increase the non-planarity of the phenyl ring "propellor". This is critical, given that ER binding affinity decreases with increasing planarity of the phenyl rings.[21,22] It is evident from the above results that placement of a halogen on the phenyl ring *ortho* to the double bond has the potential to alter the planarity as well as to inhibit changes in ring conformation of the triphenyl "propellor" system. Though there are reports of substitution in the *para*[11,23,59,60,62,63,65] and *meta*[11,64] positions, there are none on the placement of a halogen in an *ortho* position.

In this study it was proposed to use the specific orthofunctionalisation provided by orthomanganated compounds as a route to *ortho*-halogenated derivatives of Tamoxifen. Not only of interest is the chemotherapeutic potential of these derivatives but also the conformational changes of the phenyl ring "propellor" induced by the *ortho*-halogen. A possible extension to this study, not so far carried out, would be the influence an *ortho*-halogen has on the rate of isomerisation of a derivative of 4-hydroxyTamoxifen, 5. In other studies[20,70] the addition of an *ortho*-substituent, either hydroxyl or methyl, has significantly reduced ease of *cis/trans* isomerisation while still retaining relatively high ER binding affinity. Given the antiestrogenic properties of the *Z*-isomer (Chapter one, section 1.4), any inbuilt limitation to the isomeristaion of the reportedly[7] active Tamoxifen metabolite (4-hydroxyTamoxifen) to the *Z*-isomer of Tamoxifen has potential pharmaceutical importance.

2.2 Results and Discussion

2.2.1 Electrophilic Halogenation

Preparation of the ketone by the procedure in figure 2.6 gives 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** in excellent yield (82%). Using established[38] procedures, orthometalation of **7** with benzylpentacarbonylmanganese **8** gives the manganese carbonyl complex, tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9**, in quantitative yield. Similar high yields of orthomanganated acetophenone derivatives substituted with electron-donating groups are reported.[71]

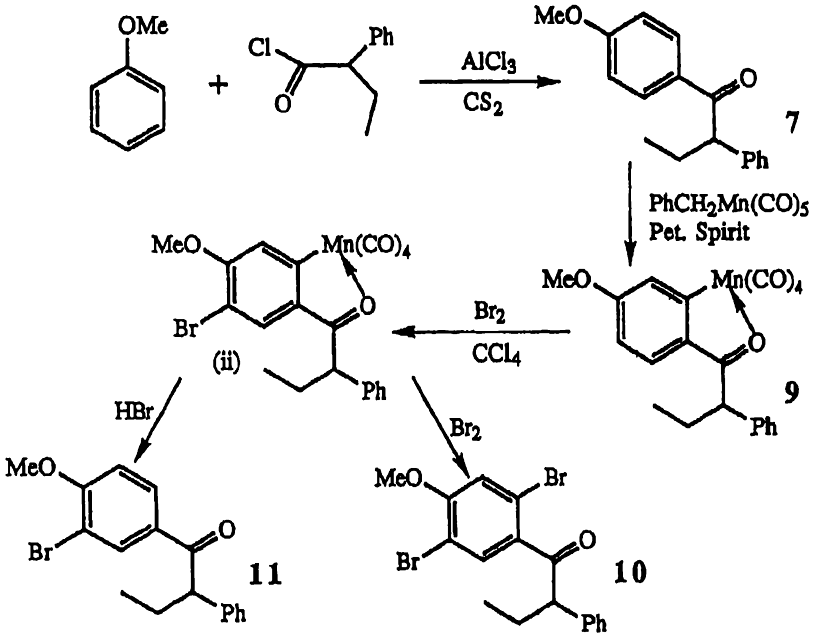
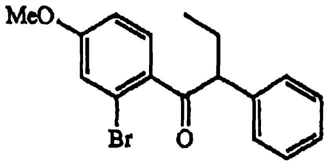


Figure 2.6

Bromination of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** with Br_2 gives the *meta*-brominated product **11** in moderate yield (47%), the demetalated ketone (**7**, 40%) and the minor dibrominated product (**10**, 8%). NOe experiments confirm the bromine to be in the *meta*-position of the phenyl ring of **11**. Bromination at the 3-position rather than at that occupied by the manganese is not unique; it has been reported[43,44] for other similarly substituted orthomanganated acetophenones containing electron-donating *o,p*-directing oxy groups activating aryl C-H centres. A possible route to formation of **11** is shown in figure 2.6. **9** reacts with Br_2 generating HBr and the brominated intermediate (ii) which is then demetalated by HBr to give **11** and $[BrMn(CO)_4]_2$. Isolation of a *meta*-brominated orthomanganated complex from a similar reaction[44] is support for this scheme. Given that no *ortho*-brominated product is formed from this reaction, it is envisaged that the dibrominated product **10** is formed correspondingly (figure 2.6) though Br_2 (and not HBr) reacts with and replaces the manganese at C2 (with bromine, not a proton).

The brominating agent *N*-bromosuccinimide (NBS) has been reported[44] to give high yields of the *ortho*-brominated product with corresponding low yields of the demetalated ketone. Therefore, in an attempt to obtain the desired *ortho*-brominated product, we reacted tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** with NBS. This reaction gives the expected bromination product 1-(2-bromo-4-methoxyphenyl)-2-phenyl-1-butanone **12** in good yield (67%), though the demetalated ketone, **7**, is still obtained in a higher yield (26%) than desired.



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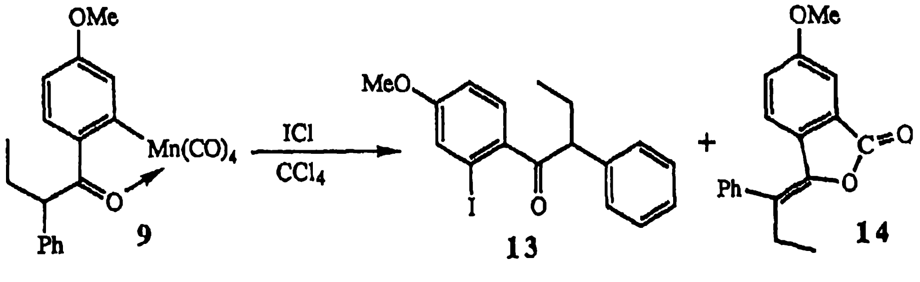
The reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** with iodine monochloride (ICl) is slower than either of the bromination reactions above. After 120 hours, the reaction affords the *ortho*-iodinated product [1-(2-iodo-4-methoxyphenyl)-2-phenyl-1-butanone, **13**, 50%], demetalated ketone (**7**, 24%) and the *Z*-3-alkylidene-1-isobenzofuranone (**14**, 18%). The reaction of **9** with ICl is specific, substituting the metal and not the ring proton. It has been suggested[43] that ICl does not substitute at the ring position due to steric reasons. The yield of the desired 2-iodo-derivative, **13**, is similar to that from other similarly substituted orthomanganated acetophenones.[43]



Formation of the carbonyl insertion product **14**, to the best of our knowledge, is the first example of this type of compound forming from an iodination reaction. These compounds are well known as by-products from bromination reactions[41,43,44] and are particularly favoured in conditions employing a protic solvent.[44] Formation of **14** from an attempted alkene coupling reaction employing Li_2PdCl_4 in acetonitrile (Chapter Four) suggests the base (Cl^-) abstraction of the α-hydrogen may initially lead to the isobenzofuranone product. However, the only products from an attempted reaction of **9** with tetramethylammonium bromide employed to abstract the α-hydrogen (Br^- as base in

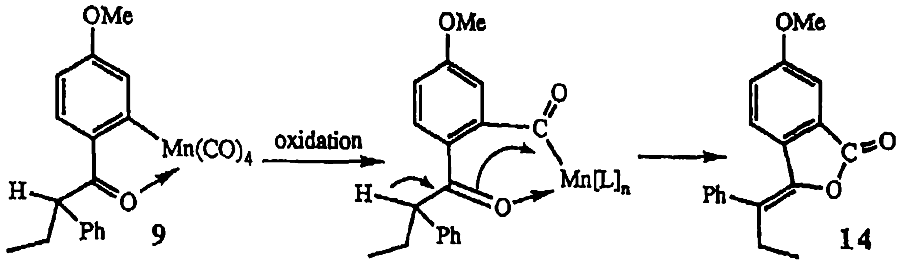


Figure 2.7

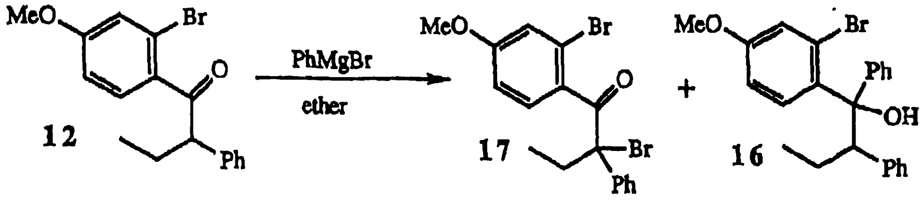
the dipolar aprotic solvent) are the demetalated ketone, **7**, and the tentatively assigned **31** (10%). Benzofuranone compounds analogous to **14** have been formed in low yield from orthomanganated ketones when employing Ce(IV)[43] and $CuCl_2$[72] in protic solvents (glacial acetic acid and methanol respectively). It therefore seems likely that the prerequisite for the formation of the benzofuranone is oxidation at the manganese resulting in carbonyl insertion followed by loss of the α-hydrogen as cyclisation occurs (figure 2.7). This is consistent with the acyl halide intermediate proposed[44,71] in scheme 2.1 which subsequently rearranges to give the isobenzofuranone product. Whether halide on a manganese carbonyl function is substituted at the acyl carbon in the cyclisation step is not clear.

3-Alkylidene-1-(*3H*)isobenzofuran-3-one (phthalides) have recently attracted interest, as some are naturally occurring compounds possessing biological activity.[73,74] Stereospecific syntheses have been reported for Z-(3)-alkylidene-1-(*3H*)isobenzofuran-3-ones either *via* alkylation of benzamides,[75] or metal-catalysed heteroannulation of acetylenic compounds with $Ni(CO)_4$[76] or Pd(II).[77]

The potential exists for the synthesis of 3-alkylidene-1-(*3H*)isobenzofuran-3-one from appropriately substituted orthomanganated aryl ketones and further study may be warranted.

2.2.2 Grignard Coupling

The reaction of the 3-brominated ketone **11** with an excess of phenylmagnesium bromide gives **15** in excellent yield (76%), while that of the 2-brominated compound **12** gives **16** in good yield (60%). Also isolated from the latter reaction are the unreacted ketone (**12**, *ca.* 10%) and the dibrominated compound **17** (*ca.* 15%). The presence of unreacted **12** suggests Grignard coupling may be inhibited to some extent. It is likely that the bromine in the 2-position sterically hinders reaction.



Formation of the α-bromoketone **17** from the Grignard reaction seemed initially to be unlikely. However, **17** is not observed (NMR) in the minor by-products of the initial bromination reaction and with repetition of the Grignard reaction it became obvious that **17** indeed originates from this coupling reaction. The source of positive bromine implicit in the formation of **17** is difficult to imagine, though there is the possibility of bromide oxidation by peroxide impurity in the ether. There is otherwise a problem with the redox chemistry for this reaction. Enolate formation with PhMgBr as base is reasonable[78] (1st step, figure 2.8), but bromination at the α-carbon would require the clearly unlikely reduction of Mg^{2+} to Mg^0!

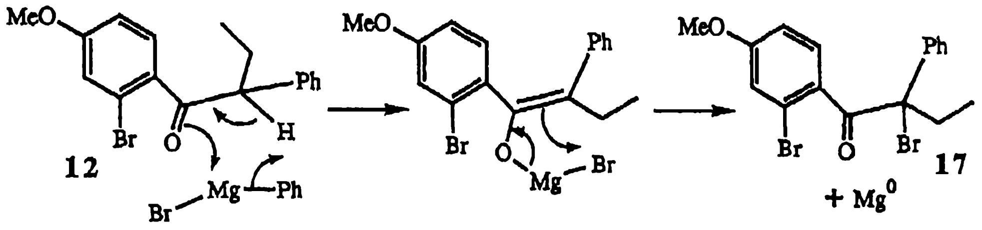
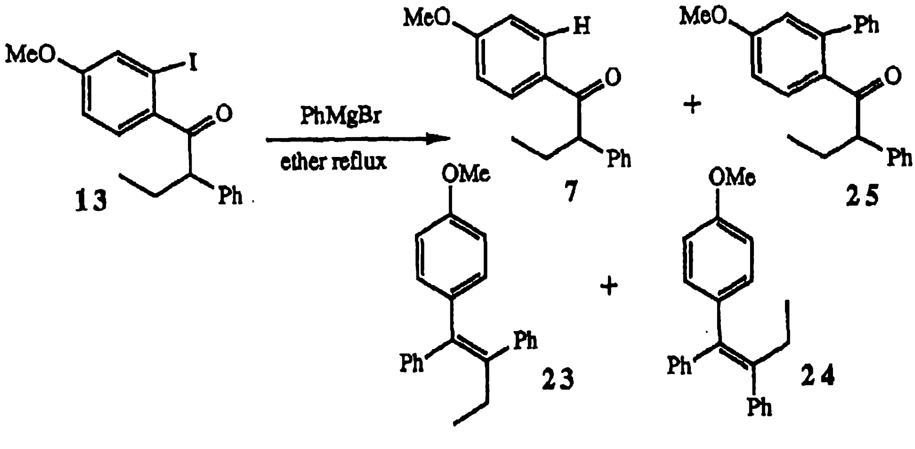


Figure 2.8

When PhMgBr is reacted with the *ortho*-iodinated compound **13** and allowed to stand (18 hours), workup gives **13** (70% recovered) and again the α-bromoketone 22 (6%). When the reaction of **13** and PhMgBr is repeated in ether under reflux for 18 hours it gives only a



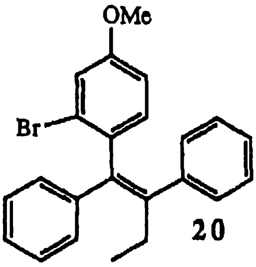
small fraction of unreacted **13** (14%), the butene products **23** and **24** (36%), the dehalogenated ketone **7** (4%) and the tentatively assigned **25** (12%). Clearly formation of **25** results from the coupling reaction of PhMgBr with **13** at the aryl-iodine rather than the carbonyl centre. The coupling reaction is analogous to the common formation of Wurtz[78] (biphenyl) byproduct when preparing phenylmagnesium bromide from bromobenzene and reacting it with carbonyl compounds. Less clear is the route to the coupled products **23** and **24** which result from the reduction of the iodine in the 2-position, Grignard coupling at the carbonyl and dehydration.

2.2.3 Synthesis of a Tamoxifen Derivative.

Dehydration of the substituted 1,1,2-triphenylbutan-1-ol to give the corresponding 1,1,2-triphenylbut-1-ene has been identified as critical in the classical synthesis of Tamoxifen[12] (see section 1.2, Chapter One). Dehydration of the tertiary alcohols **15** and **16** is conducted in acetonitrile using either concentrated sulphuric acid or 4-toluenesulphonic acid. When 1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **15** is dehydrated employing H_2SO_4, the dehydrated products **18** and **19** are obtained in a 2:1 (*Z*/*E*) ratio. A similar isomer ratio has been reported[12] for the dehydration of the corresponding 1-(4-methoxyphenyl)-1,2-diphenylbutan-1-ol in ethanol (employing aqueous HCl, 80°C). Dehydrating **15** using 4-toluenesulphonic acid gives an increased *Z*/*E* isomer ratio of 3:1. This increase is in accord with that found by McCague[12] who obtained the *Z*-isomer of Tamoxifen in greater proportions when utilising milder conditions.

Treatment of 1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **16** with 4-toluenesulphonic acid in acetonitrile for 2 hours gives only a minor amount of dehydrated product. With H_2SO_4, the dehydrated 1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene products **20** and **21** are isolated in a relatively high *Z*/*E* ratio of 4:1 (78%). Repetition of this dehydration at longer reaction times gives a 2.5-3 : 1 (*Z*/*E*) ratio. This result suggests protonation of the double bond gives equilibration of the isomers. A similar result was found[12] when Tamoxifen was similarly treated, isomerisation to a 1:1 mixture occurring with extended reaction time.

Given the initial encouragingly high *Z*/*E* ratio of the butenes **20** and **21** and the desire to synthesise an *ortho*-halogenated Tamoxifen derivative, it was proposed to demethylate **20** and subsequently attach the 2-(*N*,*N*-dimethylamino)ethyl side chain. A number of reagents for demethylation of Tamoxifen precursors have been reported, including the favoured pyridine hydrochloride[22,28,79] and, more recently, sodium ethylthiolate in dimethylformamide[15] (see figure 1.3, Chapter One) and boron tribromide.[80] In this study a mixture of the butenes **20** and **21** (*Z*/*E* 3:1) is demethylated with an excess of boron tribromide in dichloromethane. The ^{13}C NMR spectrum of the extracted crude demethylated product shows no methoxy resonances. From the NMR there is also indication that the 3:1 ratio of isomers is retained. Substitution of 2-(*N*,*N*-dimethylamino)ethyl chloride by the phenoxide ion (employing sodium ethoxide in ethanol[15]) gives the Tamoxifen derivatives **26** and **27** in moderate yield (43%). Direct separation of these isomers by chromatography (plc) could not be effected. The isomer ratio of the Tamoxifen analogues **26** and **27** is 3:1 (*Z*/*E*) which is the same as the initial ratio of the methylated compounds **20** and **21**. This is important, as the isomers **20** and **21** can be separated before demethylation. Therefore, given the result above, the Tamoxifen derivative **26** is likely to be obtained without isomerisation as the pure *Z*-isomer from a pure sample of **20**. Isomeric separation of the perfluorotolyloxy precursors with subsequent cleavage of the ether function and addition of the side chain has similarly given[13] Tamoxifen without isomerisation.



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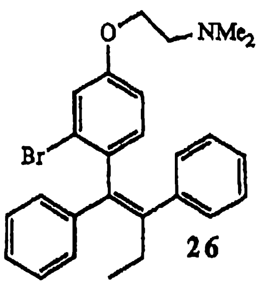

26

Demethylation and the substitution of the 2-(*N*,*N*-dimethylamino)ethyl side chain to the butene compound without isomerisation suggests a 4-hydroxyTamoxifen derivative brominated in the *ortho* position of the A-ring could resist geometric isomerisation. 4-HydroxyTamoxifen is a metabolite of Tamoxifen and has significantly stronger antiestrogenic activity than Tamoxifen itself.[7] However, 4-hydroxyTamoxifen suffers facile geometric isomerisation in the presence of acid or free radical sources.[11,17] *Ortho* substituents on the 4-hydroxy phenyl ring have been shown[20] to reduce the rate of isomerisation. Therefore, synthesis of a 4-hydroxyTamoxifen derivative using the brominated compound **12** was undertaken as outlined in the scheme below (figure 2.9).

Octafluorotoluene was chosen to protect the hydroxyl function of 3-methoxyphenol. Perfluorotolyloxy ethers of 4-hydroxyTamoxifen have been found[81] to readily separate chromatographically to give pure *Z*- and *E*-isomers. The perfluorotolyloxy ether **28** is obtained in moderate yield (50%) from octafluorotoluene and 3-methoxyphenol. Bromination of **28** with Br_2 affords the desired 4-bromo derivative **29** (27%) while the corresponding 2-bromo derivative **30** is obtained in good yield (55%). NOe experiments confirmed the assignment of each isomer. The reason for the preference for substitution in the apparently more sterically crowded 2-position is unknown.

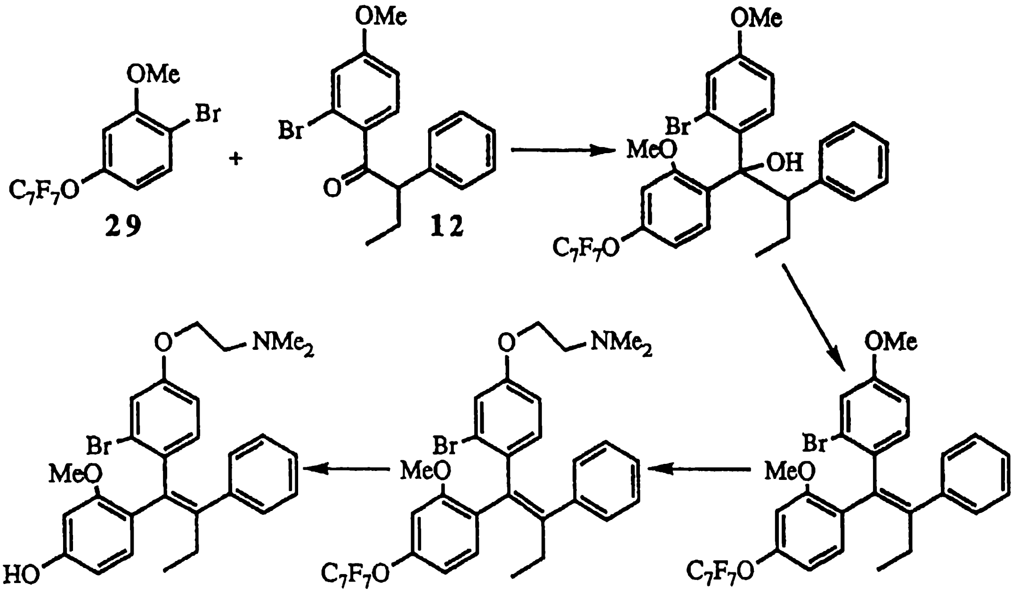

Figure 2.9

Reaction of the 2-brominated ketone **12** with the Grignard reagent of the perfluorotolyl derivative **29** proved unsuccessful. As steric constraints about the carbonyl group of **12** may have contributed to ineffective coupling, the Grignard coupling reaction with **7** was attempted. However, repeated attempts could not induce Grignard coupling*. As the perfluorotolyl group is reported to be stable to Grignard reagents,[81] it is likely that the methoxy group *ortho* to the bromine hinders formation of the Grignard reagent. However, there are known examples of Grignard reagents with an *ortho* methoxy group[32] and with an *ortho* O-tetrahydropyranyloxy group.[70] It is unlikely therefore that the steric effect of the *ortho* methoxy group of **29** is the sole reason Grignard reagent formation could not be induced.

As Grignard coupling with **29** had proved unsuccessful, the sodium and lithium initiated coupling of **29** with the ketone **7** was investigated. However, neither proved successful.

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*Grignard coupling could be initiated using I_2 and CH_3MgI but not sustained.

2.3 NMR Spectroscopy.

The ^1H NMR spectrum of *E*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **14** is relatively uncomplicated. It displays an AB doublet pattern for the monosubstituted phenyl ring as well as the characteristic pattern for the methoxy-substituted benzofuranone ring. The COSY[82] spectrum of **14** is shown in figure 2.10. An obvious starting point for tracing the coupling patterns is the CH_3 resonance, the triplet at high field. The CH_3 resonance (δ 1.06) shows a cross peak to the CH_2 resonance (δ 2.76). At low field, the doublet with $^3J = 8.8$ Hz coupling is H5 and shows a cross peak to the H4 resonance (δ 6.87) which in turn can be traced back to H2 (δ 7.26, $^4J = 2.4$ Hz). The 2D COSY spectrum of 1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **15** (Appendix A.2; figure A.1) shows a more complicated pattern of cross peaks in the aromatic region.

XH[83] 2D NMR techniques are also employed for structural and definitive ^{13}C NMR chemical shift assignments. The XH-correlated spectrum of **14** is shown in figure 2.11. The ^1H NMR CH_3 resonance (δ 1.06) correlates with the ^{13}C NMR resonance at δ 12.4. Likewise the CH_2 and OCH_3 ^1H NMR resonances correlate with the ^{13}C NMR resonances at δ 26.7 and δ 55.8 respectively. The lowfield doublet carbons are similarly assigned. For example the H4 proton shows a correlation with the resonance at δ 123.0. The XH-correlated spectrum for the 1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene products **18** and **19** is shown in Appendix A.2; figure A.2. The crowded aromatic region makes identification of the relative chemical shifts difficult, but these are readily measured by examining vertical and horizontal slices through the spectrum.

The geometry of the isomers **23** and **24** can be empirically deduced[14] for the Z-isomer from ^1H NMR chemical shift values. Due to shielding by adjacent phenyl rings, an upfield shift of δ 0.4-0.8 ppm is observed for the protons of the disubstituted phenyl ring. Assignment of the *Z* (*cis*) stereochemistry for **23** was confirmed by nOe (nuclear Overhauser effect[84]) experiments. NOe experiments were also conducted to determine the geometry of the butene derivatives **18** and **20**. Irradiation of the ethyl group protons of the *E*-isomer, **19**, gives observed nOes to H2, while irradiation of the ethyl group protons for the other isomer, **18**, gives nOes only to the monosubstituted phenyl rings. Similarly, the stereochemical assignment of **14** is based on the results of nOe experiments. For **14** irradiation of the CH_3 and CH_2 protons gives observed nOes into the aromatic region with none observed to the H5 proton. This indicates that the phenyl group lies adjacent to the benzofuranone ring and therefore **14** is assigned the *E* (*trans*) stereochemistry.

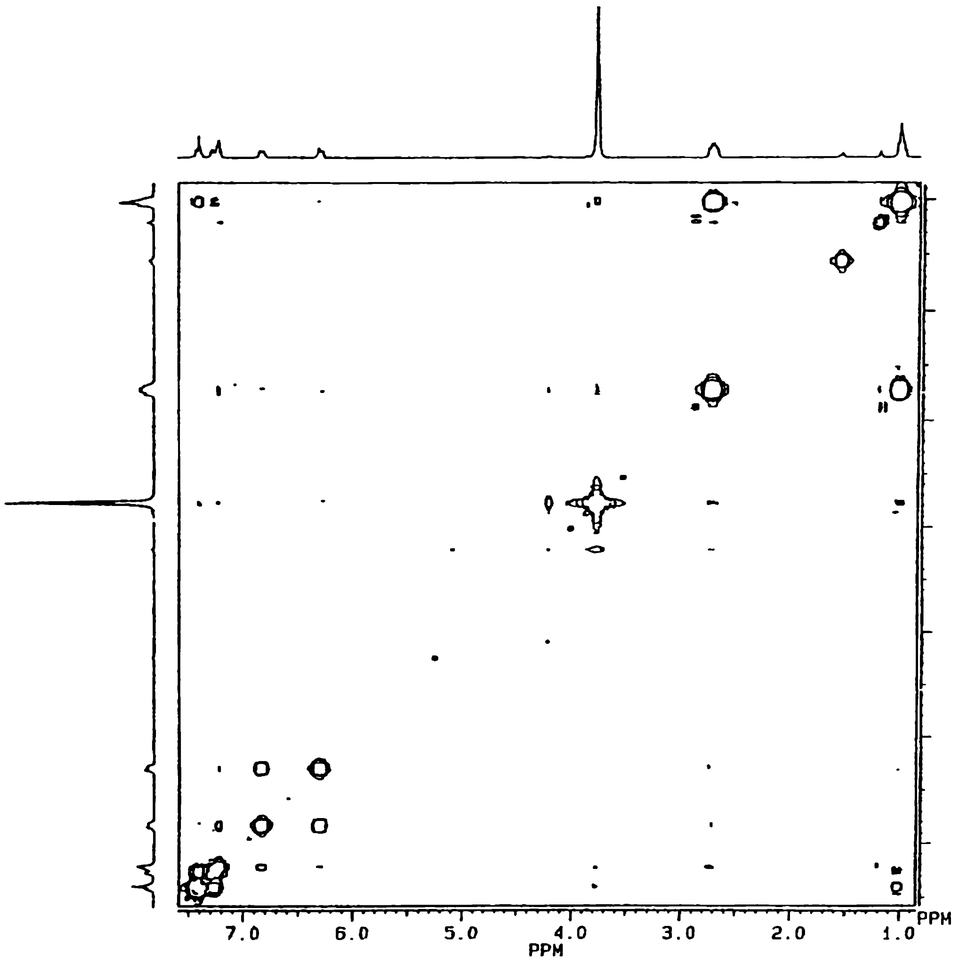


Figure 2.10 COSY spectrum of **14**

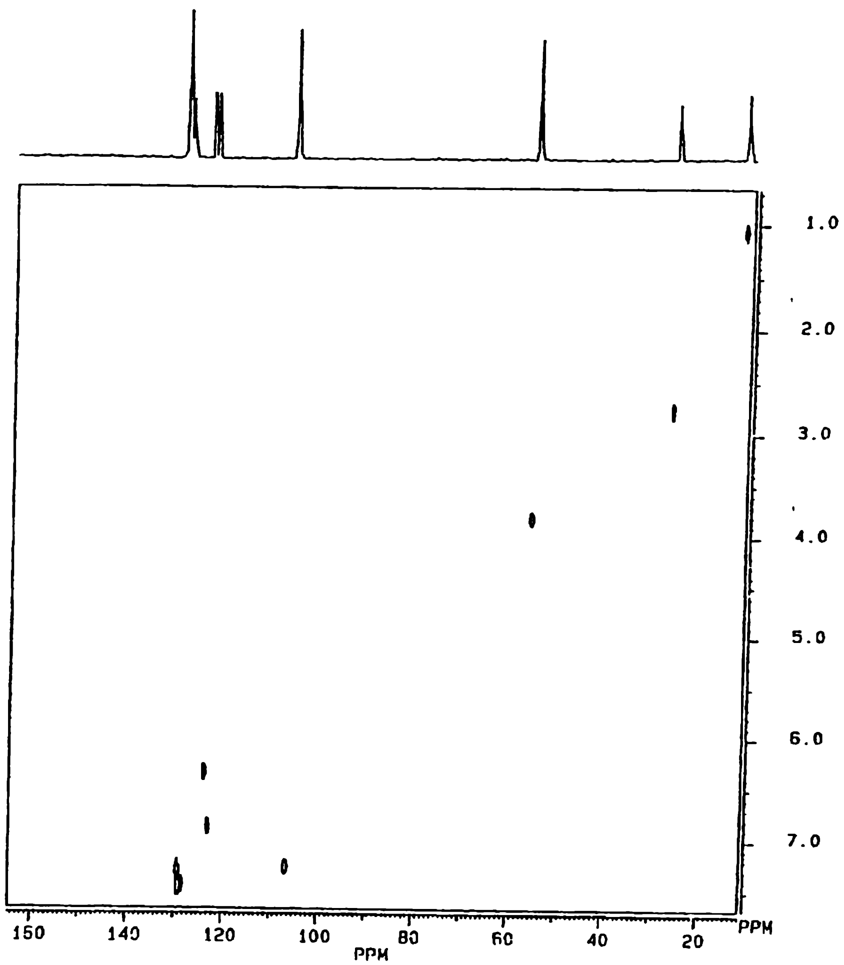


Figure 2.11 XH-correlated spectrum of **14**

2.4 Summary

The ketone **7** is a key compound not only in the classical synthesis[5,6] of Tamoxifen, but also in a variety of Tamoxifen derivatives. To form its orthomanganated complex, **9**, in quantitative yield is encouraging for further work in this and related areas. Bromination of **9** with either NBS or Br_2 gives either *ortho* or *meta* bromination products which can lead to the respective brominated Tamoxifen derivatives. Dehydration of the substituted 1,1,2-triphenylbutan-1-ols, **15** and **16**, gives an *Z/E* isomer ratio of the corresponding dehydrated butene products which is encouragingly high in comparison to those reported in previous studies.[12] The higher *Z/E* ratio may make this preparation of these Tamoxifen derivatives (**18** and **20**) attractive. It was found the Tamoxifen precursors **20** and **21** can be chromatographically (plc) separated and converted to the Tamoxifen derivatives **26** and **27** without isomerisation. Given this result, it is likely that an *ortho*-brominated Tamoxifen derivative can be readily prepared isomerically pure from **20**.

2.5 Experimental

Preparation of 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7.

To 2-phenylbutanoic acid (21.00 g, 0.128 mol) thionyl chloride (11.1 ml) was slowly added from a dropping funnel and the solution was refluxed for 1.5 h. The resulting oil was distilled under reduced pressure (150°C, 40 mmHg) collecting the middle fraction of 2-phenylbutanoyl chloride (19.46 g, 0.107 mol, 83%), obtained as a pale yellow oil.

A general acylation method[85] was followed. 2-Phenylbutanoyl chloride (19.46 g, 0.107 mol) and anisole (13.5 ml, 0.124 mol) were dissolved in carbon disulphide (90 ml, CARE: toxic) and aluminium chloride (14.26 g, 0.107 mol) was added over a 40 min period. The mixture gently refluxes during addition, becoming a deep red colour with a dark red oil sinking to the bottom. The reaction mixture was left at ambient temperature for 2 h, then crushed ice (150 g) and concentrated HCl (20 ml) were added. The carbon disulphide layer was separated and washed with HCl (2 mol l^{-1}, 2 x 40 ml). The solvent was evaporated on a steam bath, water (100 ml) was added, and steam bubbled through for 10 min. After cooling, the solidified product was filtered and washed with water (2 x 10 ml). Recrystallation from pet. spirit yielded fine white crystals of 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (22.33 g, 0.088 mol, 82%), mp 42-43°C (lit.[13] 48-49°C).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.96 (d, J = 8.6 Hz, 2H, H3, H5), 7.26 (s, 5H, ArH), 6.86 (d, J = 8.6 Hz, 2H, H2, H6), 4.39 (t, J = 7.3 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 2.18 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 0.89 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 198.6 (s, C=O), 163.3 (s, C4), 140.2 (s, C1''), 131.1 (d, C2, C6), 130.1 (s, C1), 128.8 (d, C3'', C5''), 128.2 (d, C2'', C6''), 126.1 (d, C4''), 113.7 (d, C3, C5), 55.4 (d, CH), 55.1 (q, OCH_3), 27.2 (t, CH_2), 12.5 (q, CH_3).
MS : 254 (M^+), 135, 92, 77.

Preparation of benzylpentacarbonylmanganese 8.

Benzylpentacarbonylmanganese 8 was prepared using the standard method of Closson *et al.*[86] Dried THF (100 ml) was syringed into a Schlenk flask containing sodium amalgam (110g, 1%). The THF was purged with N_2 followed by the addition of manganese carbonyl (4.0 g, 10.3 mmol). The solution was then stirred for 1.5 h under nitrogen at ambient temperature. The green solution of $NaMn(CO)_5$ was decanted from the amalgam under N_2 into a Schlenk flask containing benzyl bromide (2.3 ml, 20.5 mmol). A white precipitate (NaBr) formed immediately and after stirring for 10 min the solution was passed through a short column of silica gel (60-120 mesh) and washed through with further THF (2 x 20 ml). The THF was removed under vacuum to leave a yellow oil which was sublimed (45°C, 1 mm Hg) onto a cold finger yielding pale yellow crystalline benzylpentacarbonylmanganese **8** (5.11 g, 87%), mp 34-35.5°C (lit.[86] 37.5-38.5°C).

^{1}H-NMR (90 MHz) ($CDCl_3$) δ 7.28 (s, H, ArH), 2.46 (s, 2H, CH_2).

IR spectrum ν(CO) (hexane) 2106 (s), 2010 (vs, br) 1990 (vs, br) cm^{-1}.

Pure benzylpentacarbonylmanganese is white. However the pale-yellow product obtained from this route is suitable for further reaction.

Preparation of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9.

Outlined below is the general experimental procedure employed routinuely for the orthomanganation reactions described in this thesis.

Benzylpentacarbonylmanganese $PhCH_2Mn(CO)_5$ **8** (0.137 g, 0.48 mmol) and 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.116 g, 0.46 mmol) were dissolved in pet. spirit (25 ml). The solution was purged with N_2 and heated under reflux for 5 h. The solvent was then removed under reduced pressure and the resulting yellow oil chromatographed (plc) eluting with CH_2Cl_2/pet. spirit (1: 2) this gave one band (R_f = 0.75) which was removed from the plate, placed in a column and extracted with ether. The solvent was removed under reduced pressure to give a yellow oil. This was identified as tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.184 g, 0.44 mmol, 96%). Crystallisation from pet. spirit gave yellow plates, mp 55°C. **9** may also be named η^2-3-methoxy-6-(2-phenylbutanoyl)-phenyltetracarbonylmanganese.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 1H, H5), 7.58 (d, J = 2.7 Hz, 1H, H2), 7.27 (m, 5H, ArH), 6.62 (d of d, J = 2.7 Hz, 8.8Hz, 1H, H4), 4.36 (t, J = 7.9 Hz, 1H, CH), 3.91 (s, 3H, OMe), 2.17 (m, 1H, CH_2), 1.88 (m, 1H, CH_2), 0.88 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 221.2 (s, CO), 215.2 (s, CO), 213.3 (s, CO), 212.0 (s, C=O), 211.4 (s, CO), 198.4 (s, C1), 163.3 (s, C3), 139.5 (s, C1''), 138.4 (s, C6), 133.2 (d, C5), 129.0 (d), 127.7 (d), (C2''-C6''), 127.3 (d, C4''), 124.4 (d, C2), 111.4 (d C4), 55.4 (q, OCH_3), 54.3 (d, CH), 27.0 (t, CH_2), 12.3 (q, CH_3).

IR (CH_2Cl_2) ν(CO) 2083 (s, sh), 1995 (vs, br), 1944 (s, br) cm^{-1}.

FABMS : 616 (2(M^+-4CO)), 378, 336, 308(M^+-4CO).

Found : C, 59.98; H, 4.08%.

$C_{21}H_{17}MnO_6$ calcd : C, 60.06; H, 4.08%.

Bromination of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9.

(a) with Br_2

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.300 g, 0.715 mmol) was dissolved in N_2-saturated carbon tetrachloride (10 ml). Bromine (1.073 mmol; dissolved in N_2-saturated carbon tetrachloride) was added to this solution. The flask was stoppered and the solution stirred at ambient temperature for 3 h then filtered, the residue was found to contain $[Mn(CO)_4Br]_2$ and $BrMn(CO)_5$, identified[87,88] by IR. The solvent was removed under reduced pressure and chromatography (plc) with CH_2Cl_2/pet. spirit (1:9) as eluent yielded five bands. In order of decreasing mobility, they were as follows:

Band one gave **9** (0.018 g, 6% recovered).

Band two gave a pale yellow oil (0.023 g), identified as 1-(2,5-dibromo-4-methoxyphenyl)-2-phenyl-1-butanone **10** (0.056 mmol, 8%). Crystallisation from CH_2Cl_2/pet. spirit gave fine whitish crystals, mp 50.5 °C.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.41 (s, 1H, H6), 7.23 (m, 5H, ArH), 7.01 (s, 1H, H3), 4.26 (t, J = 7.3 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 2.22 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 0.90 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 201.1 (s, C=O), 157.4 (s, C4), 137.9 (s, C1''), 134.5 (s, C1), 133.6 (d, C6), 128.9 (d), 128.7 (d), (C2''-C6''), 127.4 (d, C4''), 119.4 (s, C2), 117.0 (d, C3), 110.4 (s, C5), 59.1 (q, OCH_3), 56.7 (d, CH), 26.1 (t, CH_2), 12.2 (q, CH_3).
MS : 293 (M^+-$CHCH_2CH_3Ph$), 250, 222, 184, 156.
Found : C, 49.49; H, 4.18; Br, 38.81%.
$C_{17}H_{16}Br_2O_2$ calcd : C, 49.54; H, 3.91; Br, 38.78%.

Band three gave orange crystals of $BrMn(CO)_5$, identified[88] by IR.
IR (pet. spirit) ν(CO) 2135 (w), 2052 (vs), 2002 (s) cm^{-1}.

Band four gave 1-(3-bromo-4-methoxyphenyl)-2-phenyl-1-butanone **11** as a colourless oil (0.112 g, 0.336 mmol, 47%). Attempts to crystallise **11** proved unsuccessful.
^1H NMR (300 MHz) ($CDCl_3$) δ 8.21 (d, J = 2.1 Hz, 1H, H2), 7.91 (d of d, J = 2.1, 8.6 Hz, 1H, H6), 7.28 (m, 5H, ArH), 6.80 (d, J = 8.6 Hz, 1H, H5), 4.35 (t, J = 7.2 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 2.19 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 197.4 (s, C=O), 159.3 (s, C4), 139.6 (s, C1''), 134.1 (d, C6), 130.9 (s, C1), 129.8 (d, C2), 128.7 (d), 128.1 (d), (C2''-C6''), 127.0 (d, C4''), 111.9 (s, C3), 111.0 (d, C5), 56.3 (d, CH), 55.1(q, OCH_3), 27.0 (t, CH_2), 12.2 (q, CH_3).
MS : 334, 332 (M^+), 215, 213, 172, 170, 91.

Band five gave demetalated ketone 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.073 g, 0.287 mmol, 40%).

(b) with NBS

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.164 g, 0.390 mmol) and *N*-bromosuccinimide (0.070 g, 0.390 mmol) were dissolved in N_2-saturated carbon tetrachloride (10 ml) and the solution refluxed for 4 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one gave 1-(2-bromo-4-methoxyphenyl)-2-phenyl-1-butanone **12** as large colourless prisms (0.087 g, 0.261 mmol, 67%). Recrystallisation from pet. spirit/diethyl ether gave white chunky crystals, mp 52°C.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.24 (m, 5H, ArH), 7.05 (d, J = 2.4 Hz, 1H, H3), 6.83 (d, J = 8.6 Hz, 1H, H6), 6.70 (d of d, J = 2.4, 8.6 Hz, 1H, H5), 4.31 (t, J = 7.2 Hz, 1H, CH), 3.71 (s, 3H, OCH_3), 2.23 (m, 1H, CH_2), 1.87 (m, 1H, CH_2), 0.92 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.3 (s, C=O), 161.2 (s, C4), 138.5 (s, C1''), 133.5 (s, C1), 130.5 (d, C6), 128.6 (d), 128.5 (d), (C2''-C6''), 127.1 (d, C4''), 120.5 (s, C2), 119.1 (d, C3), 112.8 (d, C5), 59.0 (d, CH), 55.5 (q, OCH_3), 26.3 (t, CH_2), 12.2 (q, CH_3).
MS : 215, 213 (M^+-$PhCHCH_2CH_3$), 172, 170.
Found : C, 61.25; H, 5.14; Br, 22.78%.
$C_{17}H_{17}BrO_2$ calcd : C, 61.28; H, 5.14; Br, 23.98%.

Band two gave demetalated ketone 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.026 g, 0.103 mmol, 26%).
Repetitive plc is required to separate **7** and **12**, though **12** can be readily crystallised from a mixture of both.

Band three gave a mixture (NMR) of several minor components (0.007 g).

Iodination of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9.

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.300 g, 0.715 mmol) was dissolved in N_2-saturated carbon tetrachloride (10 ml). Iodine monochloride (0.715 mmol; dissolved in N_2-saturated carbon tetrachloride) was added to this solution. The flask was stoppered and the solution stirred at ambient temperature for 120 h. The solution was filtered to remove the insoluble orange precipitate, identified[87] (IR) as $[Mn(CO)_4Cl]_2$. Chromatography with CH_2Cl_2/pet. spirit (4:5) yielded four bands.

Band one (R_f = 0.73) gave orange crystals of $IMn(CO)_5$ (0.069 g, 0.214 mmol, 30%), identified[88] by IR.
IR (pet. spirit) ν(CO) 2125 (m, sh), 2043 (vs), 2000 (s) cm^{-1}.

Band two (R_f = 0.50) gave 1-(2-iodo-4-methoxyphenyl)-2-phenyl-1-butanone **13** (0.137 g, 0.360 mmol, 50%) as a colourless oil. Crystallisation from CH_2Cl_2/pet. spirit gave white chunky crystals, mp 44.5°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.39 (d, J = 2.3 Hz, 1H, H3), 7.26 (m, 6H, ArH), 6.78 (d of d, J = 2.3, 8.6 Hz, 1H, H5), 4.25 (t, J = 7.3 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 2.18 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 0.92 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.1 (s, C=O), 161.0 (s, C4), 138.7 (s, C1''), 135.9 (s, C1), 130.0 (d, C6), 128.8 (d), 128.6 (d), (C2''-C6''), 127.1(d, C4''), 126.5 (d, C3), 113.4 (d, C5), 93.6 (s, C2), 58.4 (d, CH), 55.8 (q, OCH_3), 26.6 (t, CH_2), 12.3 (q, CH_3).
MS : <u>261</u>(M^+-$PhCHCH_2CH_3$), 218, 211, 165, 152, 134, 91.
Found : C, 53.53; H, 4.58; I, 33.80%.
$C_{17}H_{17}IO_2$ calcd : C, 53.70; H, 4.51; I, 33.37%.

Band three (R_f = 0.33) gave demetalated ketone 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.046 g, 24%).

Band four (R_f = 0.25) gave white crystals of *E*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **14** (0.036 g, 0.128 mmol, 18%). Recrystallisation from CH_2Cl_2/pet. spirit gave white crystals, mp 152°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.45 (m, 2.5H, ArH), 7.29 (m, 2.5H, ArH), 7.26 (d, J = 2.4 Hz, 1H, H2), 6.87 (d of d, J = 2.4, 8.8 Hz, 1H, H4), 6.34 (d, J = 8.8 Hz, 1H, H5), 3.82 (s, 3H, OCH_3), 2.77 (q, J = 7.5 Hz, 2H, CH_2), 1.06 (t, J = 7.5 Hz, 3H, CH_3).
CH_3 (1.06) and CH_2 (2.77) nOe to 7.29.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 167.3 (s, C1), 160.5 (s, C3), 141.8 (s, C1''), 137.7 (s, C1a), 132.0 (s, C6a), 129.2 (d), 129.0 (d), (C2''-C6''), 128.2 (s), 127.0 (s), (C6, C7), 126.7 (d, C4''), 123.9 (d, C5), 123.0 (d, C4), 106.5 (d, C2), 55.8 (q, OCH_3), 26.7 (t, CH_2), 12.4 (q, CH_3).

IR (CH_2Cl_2) ν(CO) 1763 (s) cm^{-1}.

MS : 280 (M^+), 265, 237, 194, 165.

FABMS : 280 (M^+), 279, 265, 251, 237.

Found : C, 76.91; H, 5.65%.

$C_{18}H_{16}O_3$ calcd : C, 77.12; H, 5.75%.

Preparation of 1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol 15.

1-(3-Bromo-4-methoxyphenyl)-2-phenyl-1-butanone **11** (0.067 g, 0.202 mmol) was reacted with phenyl magnesium bromide (0.45 mmol) in ether (20 ml) and left to stand for 18 h. The mixture was then poured into dilute H_2SO_4 (5%; 50 ml) and the products extracted with ether (3 x 30 ml). The combined ether layers were washed with H_2SO_4 (5%; 1 x 30 ml) and saturated NaCl (1 x 20 ml) and dried ($CaCl_2$). The ether solution was then concentrated under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:3) yielded three bands.

Band one (R_f = 1.00) gave an impure oil (0.020 g), identified (NMR) as biphenyl.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 2H, ArH), 7.48 (t, J = 7.9 Hz, 2H, ArH), 7.38 (m, 1H, ArH).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 141.3 (s, C1), 128.8 (d, C3, C5), 127.3 (d, C4), 127.2 (d, C2, C6).

Band two (R_f = 0.70) gave 1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **15** (0.053 g, 0.129 mmol, 76%) as a pale yellow oil. Attempts to crystallise **15** proved unsuccessful.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.57 (d, J = 7.4 Hz, 1H, ArH), 7.46 (d, J = 2.3 Hz, 1H, H2), 7.41 (t, J = 7.4 Hz, 1H, ArH), 7.27 (m, 4H, ArH), 7.14 (m, 5H, ArH), 6.62 (d, J = 8.7 Hz, 1H, H5), 3.76 (s, 3H, OCH_3), 3.56 (d of d, J = 4.1, 10.2 Hz, 1H, CH), 2.48 (s, br, 1H, OH), 1.82 (m, 2H, CH_2), 0.78 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 154.0 (s, C4), 145.6 (s, C1''), 140.3 (s, C1'), 139.5 (s, C1), 131.1 (d, C6), 130.2 (d), 128.3 (d), 127.9 (d), 126.1 (d), (C2'-C6', C2''-C6''), 126.9 (d, C4''), 126.6 (d, C4'), 125.8 (d, C6), 110.9 (d, C5), 80.5 (s, C-OH), 56.3 (d, CH), 56.1 (q, OCH_3), 23.3 (t, CH_2), 12.5 (q, CH_3).

MS : 293 (M^+-$PhCHCH_2CH_3$), 291, 215, 213, 105.

Band three ($R_f = 0.39$) gave 1-phenylethanol (0.054 g).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.36 (s, 5H, ArH), 4.88 (q, J = 6.5 Hz, 1H, CH), 1.49 (d, J = 6.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 145.8 (s, C1), 128.5 (d, C3, C5), 127.4 (d, C4), 125.4 (d, C2, C6), 70.4 (d, C-OH), 25.1 (q, CH_3).

Preparation of 1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol 16.

1-(2-Bromo-4-methoxyphenyl)-2-phenyl-1-butanone **12** (0.247 g, 0.742 mmol) was dissolved in diethyl ether (5 ml), treated with phenylmagnesium bromide (1.15 mmol in ether) and left to stand for 24 h. The mixture was then poured into dilute H_2SO_4 (4 mol l^{-1}, 20 ml) and extracted with ether (2 x 30 ml). The combined extracts were then washed with H_2SO_4 (20 ml) and sat. NaCl solution (20 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (1:3) yielded four bands.

Band one gave biphenyl (0.090 g).

Band two gave white crystals of 1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **16** (0.184 g, 0.447 mmol, 60%). Recrystallisation from diethyl ether/pet. spirit gave white chunky crystals, mp 106°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.67 (d, J = 8.9 Hz, 1H, H6), 7.32 (m, 6H, ArH), 7.11 (m, 4H, ArH), 6.85 (d, J = 2.7 Hz, 1H, H3), 6.64 (d of d, J = 2.7, 8.9 Hz, 1H, H5), 3.97 (d, J = 10.6 Hz, 1H, CH), 3.67 (s, 3H, OCH_3), 3.01 (s, 1H, OH), 2.03 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 0.84 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.3 (s, C4), 145.1 (s, C1''), 141.4 (s, C1'), 137.3 (s, C1), 129.9 (d, C2', C6'), 129.7 (d, C6), 128.5 (d, C2'', C6''), 127.6 (d), 127.5 (d), (C3', C5', C3'', C5''), 126.9 (d), 126.2 (d), (C4', C4''), 121.8 (s, C2), 119.8 (d, C3), 112.0 (d, C5), 81.4 (s, C-OH), 55.3 (q, OCH_3), 52.7 (d, CH), 25.0 (t, CH_2), 12.6 (q, CH_3).
MS : <u>293</u>, <u>291</u> (M^+-$PhCHCH_2CH_3$), 215, 213, 105.
Found : C, 67.35; H, 5.66; Br, 20.10%.
$C_{23}H_{23}BrO_2$ calcd : C, 67.16; H, 5.64; Br, 19.43%.

Band three gave **12** (0.025 g, *ca.* 10% recovered).

Band four gave a pale yellow oil (0.087 g), identified (NMR ratio 1:1) as a mixture of phenol and 1-(2-bromo-4-methoxyphenyl)-2-bromo-2-phenyl-1-butanone **17** (0.074 mmol, *ca.* 15%). Crystallisation from diethyl ether/pet. spirit (1:10) gave **17** as fine whitish crystals, mp 43°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.54 (d, J = 6.7 Hz, 2H, H2'', H6''), 7.35 (m, 3H, H3'', H4'', H5''), 7.11 (d, J = 2.3 Hz, 1H, H3), 6.77 (d, J = 8.8 Hz, 1H, H6), 6.50 (d of d, J = 2.3, 8.8 Hz, 1H, H5), 3.74 (s, 3H, OCH_3), 2.50 (m, 2H, CH_2), 0.93 (t, J = 7.1 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.2 (s, C=O), 160.8 (s, C4), 138.0 (s, C1''), 131.4 (s, C1), 130.0 (d, C6), 128.7 (d), 127.8 (d), (C2''-C6''), 128.3 (d, C4''), 122.7 (s, C2), 119.5 (d, C3), 111.8 (d, C5), 78.2 (s, C-Br), 55.6 (q, OCH_3), 36.6 (t, CH_2), 10.2 (q, CH_3).

MS : 332, 330 (M^+-Br), 251, 215, <u>213</u>, 172, 170, 115.

Found : C, 50.11; H, 3.96; Br, 38.28%.

$C_{17}H_{17}BrO_3$ calcd : C, 49.54; H, 3.91; Br, 38.78%.

Dehydration of 1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol 15.

(a) <u>with H_2SO_4</u>

1-(3-Bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **15** (0.086 g, 0.210 mmol) was dissolved in acetonitrile (6 ml), 1 drop of concentrated (98%) H_2SO_4 added and the solution stirred for 16 h. The solvent was removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:20) yielded two bands.

Band one gave a pale yellow oil (0.062 g), identified (^{1}H NMR ratio 2:1) as mixture of *Z*- and *E*-1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **18** and **19** (0.158 mmol, 75%). Crystallisation from pet. spirit gave white cystals, mp 81.5-82.5°C.

Found : C, 70.46; H, 5.51%.

$C_{23}H_{21}BrO$ calcd. : C, 70.23; H, 5.38%.

Z-1-(3-Bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **18** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.26 (m, 10H, ArH), 7.07 (d, J = 2.1 Hz, 1H, H2), 6.77 (d of d, 2.1, 8.5 Hz, 1H, H6), 6.53 (d, J = 8.5 Hz, 1H, H5), 3.76 (s, 3H, OCH_3), 2.47 (q, J = 7.4 Hz, 2H, CH_2), 0.95 (t, J = 7.4 Hz, 3H, CH_3).

CH_2 (2.47) nOe to 7.24, 7.15.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 153.8 (s, C4), 143.1 (s), 142.7 (s), 142.0 (s), (C1, C1', C1''), 137.0 (s), 136.9 (s), (C7, C8), 135.4 (d, C2), 130.9 (d, C6), 129.7 (d), 129.5 (d), 128.3 (d), 128.1 (d), (C2'-C6', C2''-C6''), 126.9 (d), 126.4 (d), (C4', C4''), 110.7 (d, C5), 110.6 (s, C3), 56.0 (q, OCH_3), 29.1 (t, CH_2), 13.6 (q, CH_3).

MS : 394, <u>392</u> (M^+), 298, 252, 239.

E-1-(3-Bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **19** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.46 (d, J = 2.2 Hz, 1H, H2), 7.28 (m, 10H, ArH), 7.01 (t, J = 6.6 Hz, 1H, ArH), 6.90 (d, J = 8.5 Hz, 1H, H5), 3.92 (s, 3H, OCH_3), 2.52 (q, J = 7.4 Hz, 2H, CH_2), 0.97 (t, J = 7.4 HZ, 3H, CH_3).
CH_2 (2.52) nOe to 7.15, 7.44.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 154.7 (s, C4), 142.9 (s, C1), 142.7 (s), 142.0 (s), (C1', C1''), 137.4 (s), 137.3 (s), (C7, C8), 134.3 (d, C2), 130.7 (d, C6), 129.7 (d), 129.6 (d), 127.9 (d), 127.5 (d), (C2'-C6', C2''-C6''), 126.3 (d), 126.0 (d), (C4', C4''), 111.6 (d, C5), 111.4 (s, C3), 56.3 (q, OCH_3), 29.1 (t, CH_2), 13.6 (q, CH_3).
MS : 394, 392 (M^+), 238, 199.

Band two gave unreacted **15** (0.015 g, 17% recovered).

(b)with 4-toluenesulphonic acid

1-(3-Bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **15** (0.101 g, 0.246 mmol) was dissolved in THF (6 ml), 4-toluenesulphonic acid (0.015 g, 0.079 mmol) was added and the solution stirred for 22.5 h. The solvent was removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:9) yielded only one band which was removed and identified as a mixture (NMR ratio 3:1) of *Z*- and *E*-1-(3-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **18** and **19** (0.051 g, 0.130 mmol, 52%).

Dehydration of 1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol 16.

(a) with H_2SO_4

1-(2-Bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **16** (0.220 g, 0.535 mmol) was dissolved in acetonitrile (5 ml), one drop of concentrated (98%) H_2SO_4 was added and the solution stirred for 20 h. Chromatography with diethyl ether/pet. spirit (1:20) yielded two bands.

Band one gave *Z*-1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **20** (0.134 g, 0.340 mmol, 64%). Crystallisation from pet. spirit gave fine white crystals, mp 94-95°C.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 1H, H6), 7.25 (m, 7H, ArH), 7.09 (m, 4H, ArH), 6.98 (d of d, J = 2.6, 8.4 Hz, 1H, H5), 3.85 (s, 3H, OCH_3), 2.45 (q, J = 7.4 Hz, 2H, CH_2), 1.00 (t, J = 7.4 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.9 (s, C4), 143.7 (s), 141.6 (s), 141.1 (s), (C1, C1', C1''), 136.7 (s), 136.0 (s), (C7, C8), 131.6 (d, C6), 130.4 (d), 129.6 (d), 127.9

(d), 127.2 (d), (C2'-C6', C2''-C6''), 126.4 (d), 125.8 (d), (C4', C4''), 124.5 (s, C2), 118.0 (d, C3), 113.6 (d, C5),. 55.4 (q, OCH_3), 29.3 (t, CH_2), 12.5 (q, CH_3).
MS : 394, 392 (M^+), 313, 296, 284, 239.
Found : C, 71.57; H, 5.62; Br, 19.49%.
$C_{23}H_{21}BrO$ calcd. : C, 70.23; H, 5.38; Br, 20.32%.

Band two gave *E*-1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **21** (0.029 g, 0.073 mmol, 14%).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.31 (m, 5H, ArH), 7.15 (m, 5H, ArH), 6.95 (d, J = 8.8 Hz, 1H, H6), 6.87 (d, J = 2.2 Hz, 1H, H3), 6.58 (d of d, J = 2.2, 8.8 Hz, 1H, H5), 3.67 (s, 3H, OCH_3), 2.51 (q, J = 7.4 Hz, 2H, CH_2), 1.04 (t, J = 7.4 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.4 (s, C4), 144.2 (s), 142.1 (s), 141.5 (s), (C1, C1', C1''), 137.5 (s), 136.4 (s), (C7, C8), 133.3 (d, C6), 129.6 (d), 128.8 (d), 127.8 (d), 127.3 (d), (C2'-C6', C2''-C6''), 126.6 (d), 126.3 (d), (C4', C4''), 124.7 (s, C2), 117.5 (d, C3), 113.1 (d, C5), 55.3 (q, OCH_3), 28.1 (t, CH_2), 13.6 (q, CH_3).
MS : 394, 392 (M^+), 313, 296, 284, 239.

(b) with 4-toluenesulphonic acid

1-(2-Bromo-4-methoxyphenyl)-1,2-diphenylbutan-1-ol **16** (0.050 g, 0.121 mmol) was dissolved in THF (5 ml). 4-Toluenesulphonic acid (0.010 g, 0.053 mmol) was added and the solution stirred for 2 h. Chromatography with diethyl ether/pet. spirit (1:7) yielded two bands.

Band one (R_f = 0.85) gave a colourless oil (0.006 g), identified (NMR ratio 3:1) as a mixture of Z- and *E*-1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **20** and **21** (0.015 mmol, 12%).

Band two (R_f = 0.58) gave **16** (0.040 g, 80% recovered).

Reaction of 1-(2-iodo-4-methoxyphenyl)-2-phenyl-1-butanone 13 with phenylmagnesium bromide.

(a) in ether

1-(2-Iodo-4-methoxyphenyl)-2-phenyl-1-butanone **13** (0.310 g, 0.816 mmol) was treated with phenylmagnesium bromide (1.54 mmol) in ether (20 ml) and left to stand for 18 h. The mixture was then poured into dilute H_2SO_4 (5%; 50 ml) and extracted with ether (3 x 30 ml). The combined extracts were washed with H_2SO_4 (5%; 2 x 20 ml) and saturated NaCl (1 x 20 ml) and dried ($CaCl_2$). Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded four bands.

Band one ($R_f = 0.95$) gave 1-(2-iodo-4-methoxyphenyl)-2-phenyl-1-butanone **13** (0.217 g, 70% recovered).

Band two ($R_f = 0.83$) gave a pale yellow oil (0.021 g), identified as 2-bromo-1-(2-iodo-4-methoxyphenyl)-2-phenylbutan-1-ol **22** (0.045 mmol, 6%).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.40 (m, 6H, ArH), 6.73 (d, J = 8.7 Hz, 1H, H6), 6.65 (d of d, J = 2.4, 8.7 Hz, 1H, H5), 3.76 (s, 3H, OCH_3), 2.28 (m, 2H, CH_2), 0.94 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 204.6 (s, C=O), 160.9 (s, C4), 140.6 (s, C1''), 133.2 (s, C1), 129.6 (d, C6), 128.7 (d), 126.4 (d), (C2''-C6''), 128.0 (d), 126.6 (d), (C3, C4''), 112.7 (d, C5), 94.6 (s, C2), 83.4 (s, C-Br), 55.8 (q, OCH_3), 31.6 (t, CH_2), 7.8 (q, CH_3).
MS : 381 (M^+-Br), 339, <u>261</u>, 218, 135.

Band three ($R_f = 0.72$) gave an unknown oil (0.011 g).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.96 (d, J = 8.5 Hz, 1H), 7.38 (m, *ca.* 12H), 6.95 (m, 2H), 6.67 (d, J = 7.8 Hz, 2H), 3.96 (s, 3H), 3.77 (m, 2H), 1.76 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H).
MS : 270, 241, 213, 151, <u>135</u>.

Band four ($R_f = 0.30$) gave a colourless oil (0.053 g), identified (NMR and GCMS ratio 1:1) as a mixture of phenol and 1-phenylethanol.

(b) <u>in ether under reflux</u>

1-(2-Iodo-4-methoxyphenyl)-2-phenyl-1-butanone **13** (0.217 g, 0.571 mmol) was dissolved in ether (10 ml), treated with phenylmagnesium bromide (1.14 mmol, in ether) and refluxed for 18 h. The mixture was worked up as above. Chromatography with CH_2Cl_2/pet. spirit (2:3) yields four bands.

Band one ($R_f = 1.0$) gave biphenyl (0.060 g).

Band two ($R_f = 0.82$) gave a pale yellow oil (0.064 g), identified (NMR ratio 5:2) as a mixture of *Z*- and *E*-1-(4-methoxyphenyl)-1,2-diphenylbut-1-ene **23** and **24** (0.204 mmol, 36%). Crystallisation from CH_2Cl_2/pet. spirit (1:15) gave white prisms, mp 116-119°C (lit.[47] 109-111°C, pure Z-isomer[89] 120-121°C).

Z-1,2-diphenyl-1-(4-methoxyphenyl)-but-1-ene **23** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.39 (d, J = 6.7 Hz, 2H, ArH), 7.25 (m, br, 8H, ArH), 6.86 (d, J = 8.6 Hz, 2H, H3, H5), 6.61 (d, J = 8.6 Hz, 2H, H2, H6), 3.71 (s, 3H, OCH_3), 2.53 (q, J = 7.3 Hz, 2H, CH_2), 1.00 (t, J = 7.3 Hz, 3H, CH_3).

CH_2 (2.53) and CH_3 (1.00) nOes to 7.13 and 7.10.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 157.5 (s, C4), 143.9 (s), 142.5 (s), (C1, C1'), 141.3 (s, C1''), 138.3 (s, C8), 135.5 (s, C7), 131.9 (d, C2, C6), 129.7 (d), 129.5 (d), 128.1 (d), 127.9 (d), (C2'-C6', C2''-C6''), 126.5 (d), 126.0 (d), (C4', C4''), 112.8 (d, C3, C5), 55.0 (q, OCH_3), 29.1 (t, CH_2), 13.6 (q, CH_3).

MS : 314 (M^+), 299, 221, 191.

E-1,2-diphenyl-1-(4-methoxyphenyl)-but-1-ene **24** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.22 (m, 10H, ArH), 7.04 (d, J = 8.5 Hz, 2H, H2, H6), 6.96 (d, J = 8.5 Hz, 2H, ArH), 3.86 (s, 3H, OCH_3), 2.57 (q, J = 7.2 Hz, 2H, CH_2), 1.04 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.4 (s, C4), 143.2 (s), 142.1 (s), (C1, C1'), 141.3 (s, C1''), 138.2 (s), 136.1 (s), (C7, C8), 130.8 (d), 130.6 (d), 128.0 (d), 127.8 (d), (C2'-C6', C2''-C6''), 128.3 (d), 125.7 (d), (C4', C4''), 127.3 (d, C2, C6), 113.5 (d, C3, C5), 55.2 (q, OCH_3), 29.1 (t, CH_2), 13.6 (q, CH_3).

MS : 314 (M^+), 299, 221, 191.

Band three (R_f = 0.47) gave **13** (0.029 g, 14% recovered).

Band four (R_f = 0.35) gave a colourless oil (0.023 g), identified (NMR ratio 3:1) as a mixture of 1-(5-methoxy-2-biphenyl)-2-phenyl-1-butanone **25** (0.068 mmol, 12%) and 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.023 mmol, 4%).

1-(5-Methoxy-2-biphenyl)-2-phenyl-1-butanone **25** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.11 (m, br, 12H, ArH), 4.41 (t, J = 7.3 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 1.85 (m, 1H, CH_2), 1.69 (m, 1H, CH_2), 0.58 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 205.8 (s, C=O), 160.9 (s, C4), 142.7 (s), 141.1 (s), (C1', C1''), 139.0 (s, C2), 133.2 (s, C1), 131.0 (d, C6), 128.7 (d), 128.5 (d), 128.4 (d), 128.2 (d), (C2'-C6', C2''-C6''), 127.8 (d, C4'), 126.8 (d, C4''), 115.6 (d, C5), 112.7 (d, C3), 59.1 (d, CH), 55.4 (q, OCH_3), 26.1 (t, CH_2), 12.1 (q, CH_3).

MS : 211 (M^+-$PhCHCH_2CH_3$), 168, 151, 139.

Preparation of *Z*- and *E*-1-(2-bromo-4-(2-(*N*,*N*-dimethylamino)ethoxy)-phenyl)-1,2-diphenylbut-1-ene 26 and 27.

A mixture of *Z*- and *E*-1-(2-bromo-4-methoxyphenyl)-1,2-diphenylbut-1-ene **20** and **21** (ratio by NMR 3:1) (0.163 g, 0.413 mmol) was dissolved in dichloromethane (5 ml) and cooled to -83 °C (employing an ethyl acetate slush bath). Boron tribromide (0.07 ml, 0.74 mmol, in 5 ml CH_2Cl_2) was added and the solution stirred for 1 h then allowed to warm to ambient temperature with stirring for another 3 h. Iced water (40 ml) was added and the solution was extracted with ether (40 ml). The ether layer was washed with water (30 ml) and dried ($CaCl_2$). The solvent was removed under reduced pressure to yield a yellow oil (0.20 g). ^{13}C NMR of the crude oil shows a *Z*/*E* mixture (3:1) of the demethylated product 1-(2-bromo-4-hydroxyphenyl)-1,2-diphenylbut-1-ene.

^{13}C NMR spectrum of *Z*-1-(2-bromo-4-hydroxyphenyl)-1,2-diphenylbut-1-ene.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 156.1 (s, C4), 144.2 (s), 141.8 (s), 141.3 (s), (C1, C1', C1''), 136.9 (s), 135.4 (s), (C7, C8), 131.8 (d, C6), 130.5 (d), 129.7 (d), 127.9 (d), 127.3 (d), (C2'-C6', C2''-C6''), 127.7 (d), 126.5 (d), (C4', C4''), 124.4 (s, C2), 119.9 (d, C3), 114.9 (d, C5), 29.4 (t, CH_2), 12.6 (q, CH_3).

^{13}C NMR spectrum of *E*-1-(2-bromo-4-hydroxyphenyl)-1,2-diphenylbut-1-ene.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 155.4 (s, C4), 143.7 (s), 142.2 (s), 141.7 (s), (C1, C1', C1''), 137.9 (s), 135.9 (s), (C7, C8), 133.5 (d, C6), 129.6 (d), 128.9 (d), 127.9 (d), 125.8 (d), (C2'-C6', C2''-C6''), 126.6 (d), 126.4 (d), (C4', C4''), 124.6 (s, C2), 119.5 (d, C3), 114.4 (d, C5), 29.8 (t, CH_2), 12.6 (q, CH_3).

The crude mixture of 1-(2-bromo-4-hydroxyphenyl)-1,2-diphenylbut-1-ene was added to ethanol (6 ml) containing sodium ethoxide (prepared by adding sodium metal 0.056 g, 2.5 mmol). 2-(*N*,*N*-Dimethylamino)ethyl chloride hydrochloride (0.178 g, 1.24 mmol) in ethanol (10 ml) was then added and the solution refluxed for 21 h. The solution was poured into water (20 ml) and diethyl ether (20 ml) and NaOH (2 mol l^{-1}, 20 ml) added. The aqueous layer was then further extracted with diethyl ether (1 x 30 ml). The combined ether layers were washed with NaOH (3 x 20 ml), dried ($CaCl_2$) and concentrated. Chromatography (plc) with benzene/triethylamine (9:1) yields two bands.

Band one ($R_f = 0.95$) gave 2-(*N*,*N*-dimethylamino)ethyl chloride (0.022 g).

Band two ($R_f = 0.80$) gave a yellow oil (0.066 g), identified (NMR ratio 3:1) as a mixture of *Z*- and *E*-1-(2-bromo-4-(2-(*N*,*N*-dimethylamino)ethoxy)phenyl)-1,2-diphenylbut-1-ene **26** and **27** (0.177 mmol, 43%).

Z-1-(2-Bromo-4-(2-(*N*,*N*-dimethylamino)ethoxy)phenyl)-1,2-diphenylbut-1-ene **26** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.18 (m, 8H, ArH), 6.96 (m, 5H, ArH), 4.07 (t, J = 5.7 Hz, 2H, OCH_2), 2.74 (t, J = 5.7 Hz, 2H, NCH_2), 2.33 (s, 6H, NCH_3), 2.32 (q, J = 7.4 Hz, 2H, CH_2), 0.88 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.2 (s, C4), 143.7 (s), 141.7 (s), 141.1 (s), (C1, C1', C1''), 136.7 (s), 136.1 (s), (C7, C8), 131.6 (d, C6), 130.4 (d), 129.6 (d), 128.4 (d), 127.9 (d), 127.3 (d), (C2'-C6', C2''-C6''), 126.4 (d), 125.8 (d), (C4', C4''), 124.4 (s, C2), 118.7 (d, C3), 114.3 (d, C5), 66.3 (t, OCH_2), 58.2 (t, NCH_2), 45.9 (q, NCH_3), 29.3 (t, CH_2), 12.5 (q, CH_3).

E-1-(2-Bromo-4-(2-(*N*,*N*-dimethylamino)ethoxy)phenyl)-1,2-diphenylbut-1-ene **27** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.18 (m, 8H, ArH), 6.96 (m, 4H, ArH), 6.59 (d of d, J = 2.6, 8.5 Hz, 1H, H5), 3.90 (t, J = 5.7 Hz, 2H, OCH_2), 2.63 (t, J = 5.7 Hz, 2H, NCH_2), 2.33 (q, J = 7.4 Hz, 2H, CH_2), 2.28 (s, 6H, NCH_3), 0.91 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 157.6 (s, C4), 144.3 (s), 142.1 (s), 141.5 (s), (C1, C1', C1''), 137.4 (s), 136.5 (s), (C7, C8), 133.3 (d, C6), 129.5 (d), 128.8 (d), 127.8 (d), 127.6 (d), (C2'-C6'), C2''-C6''), 126.6 (d), 126.3 (d), (C4', C4''), 124.6 (s, C2), 118.2 (d, C3), 113.6 (d, C5), 66.1 (t, OCH_2), 58.2 (t, NCH_2), 45.9 (q, NCH_3), 28.0 (t, CH_2), 13.6 (q, CH_3).

Preparation of 1-(3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene 28.

Octafluorotoluene (1.2 ml, 8.5 mmol), 3-methoxyphenol (0.9 ml, 8.3 mmol) and tetra-*N*-butylammonium hydroxide (0.4 ml) were added to a solution containing CH_2Cl_2 (15 ml) and NaOH (1 mol l^{-1}, 20 ml). The mixture was vigorously stirred for 24 h. The aqueous layer was removed and extracted with CH_2Cl_2 (40 ml). The combined organic layers were washed with NaOH (0.1 mol l^{-1}, 40 ml) and water (30 ml) and then dried ($CaCl_2$). The solution was distilled under vacuum to yield 1-(3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **28** (1.44 g, 4.23 mmol, 51%) as a colourless oil, bp 97-99°C (25 mmHg).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.25 (t, J = 8.3 Hz, 1H, H5'), 6.73 (d of d, J = 2.2, 8.3 Hz, 1H, H6'), 6.62 (t, J = 2.2 Hz, 1H, H2'), 6.56 (d of d, J = 2.3, 8.3 Hz, 1H, H4'), 3.82 (s, 3H, OCH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 161.2 (s, C3'), 157.7 (s, C1'), 141.8 (d of q, $^1J_{F\text{-}C}$ = -245.5 Hz, $^3J_{F\text{-}C}$ = 15.5 Hz, C3, C5), 120.8 (d, $^1J_{F\text{-}C}$ = -273.9 Hz, C2, C6), 130.4 (d, C5'), 109.8 (d, C4'), 107.7 (d, C6'), 102.7 (d, C2'), 55.3 (q, OCH_3).

MS : $\underline{340}$ (M^+), 321, 269, 200, 155.

Bromination of 1-(3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene 28.

1-(3-Methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **28** (1.86 g, 5.48 mmol) was dissolved in carbon tetrachloride (2 ml), bromine (5.50 mmol, in N_2-saturated carbon tetrachloride) was added and the solution stirred for 24 h. Chromatography with ether/pet. spirit (1:9) yielded only one band (R_f = 0.88), identified (^1H NMR ratio 1:2) as a mixture (1.88 g, 4.49 mmol, 82%) of 1-(4-bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **29** and 1-(2-bromo-5-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **30** respectively. Crystallisation from pet. spirit gave white crystals of **29**, mp 79-80°C.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 1H, H5'), 6.70 (d, J = 2.7 Hz, 1H, H2'), 6.38 (d, J = 2.7, 8.6 Hz, 1H, H6'), 3.90 (s, 3H, OCH_3).

OCH_3 (3.90) nOe to 6.70.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 157.2 (C1'), 156.8 (C3'), 143.4 (t of d, $^1J_{F\text{-}C}$ = -268.0 Hz, $^3J_{F\text{-}C}$ = 11.2 Hz, C3, C5), 133.6 (d, C5'), 120.9 (d, $^1J_{F\text{-}C}$ = -276.1 Hz, C2, C6), 108.2 (d, C6'), 101.7 (d, C2), 55.3 (q, OCH_3).

MS : 399 (M^+-F), 375, 373, $\underline{311}$, 270, 268, 217.

Found : C, 40.02; H, 1.38; Br, 19.20; F, 31.62%.

$C_{14}H_6BrF_7O_2$ calcd. : C, 40.12; H, 1.44; Br, 19.07; F, 31.73%.

1-(2-Bromo-5-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **30** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 1H, H3'), 6.63 (d of d, J = 2.7, 8.8 Hz, 1H, H4'), 6.44 (d, J = 2.7 Hz, 1H, H6'), 3.74 (s, 3H, OCH_3).

OCH_3 (3.74) nOe to 6.44, 6.63.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.2 (s, C5'), 153.6 (s, C1'), 141.0 (d of t, $^1J_{F\text{-}C}$ = -245.6, $^3J_{F\text{-}C}$ = 12.5 Hz, C3, C5), 134.1 (d, C3'), 120.9 (d, $^1J_{F\text{-}C}$ = -276.1 Hz, C2, C6), 111.0 (d, C4'), 104.2 (d, C6'), 55.7 (q, OCH_3).

MS : 399 (M^+-F), 375, 373, 340, $\underline{311}$, 270, 268.

Attempted coupling of 1-(4-bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene 29 with 1-(2-bromo-4-methoxyphenyl)-2-phenyl-1-butanone 12.

1-(4-Bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **29** (0.195 g, 0.466 mmol) was dissolved in ether (1.5 ml) and magnesium (0.024 g, 1.00 mmol) added. Initiation with I_2 was followed by refluxing the solution for 1 h. 1-(2-Bromo-4-methoxyphenyl)-2-phenyl-1-butanone **12** (0.160 g, 0.481 mmol) dissolved in ether (5 ml) was added and allowed to stand for 18h. The solution was added to HCl (2 mol l^{-1}, 30 ml), extracted with ether and washed with further portions of HCl (2 x 30 ml) and sat. NaCl solution (20 ml). Chromatography with diethyl ether/pet. spirit (3:7) yielded only two bands.

Band one ($R_f = 1.00$) gave **29** (0.166 g, 85% recovered).

Band two ($R_f = 0.70$) gave **12** (0.139 g, 87% recovered).

Attempted coupling of 1-(4-bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene 29 with 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7.

(a) with magnesium

1-(4-Bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **29** (0.390 g, 0.931 mmol) was dissolved in ether (1.5 ml) and magnesium (0.036 g, 1.50 mmol) added. Initiation (I_2) was followed by refluxing the solution for 1 h. 1-(4-Methoxyphenyl)-2-phenyl-1-butanone **7** (0.228 g, 0.898 mmol) dissolved in ether (5 ml) was added and the solution refluxed for a further 4 h. The solution was added to HCl (2 mol l^{-1}, 40 ml), extracted with ether and washed with further portions of HCl (2 x 40 ml) and sat. NaCl solution (20 ml). Chromatography with diethyl ether/pet. spirit (3:7) yielded only two bands.

Band one ($R_f = 1.00$) gave **29** (0.315 g, 81% recovered).

Band two ($R_f = 0.80$) gave **7** (0.236 g, 103% recovered).

(b) with lithium

1-(4-Bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **29** (0.209 g, 0.499 mmol) was dissolved in ether (1.5 ml) and the flask cooled to -83°C.

Lithium (0.008 g, 1.15 mmol) was added and the solution refluxed for 6 h. 1-(4-Methoxyphenyl)-2-phenyl-1-butanone **7** (0.127 g, 0.301 mmol) dissolved in ether (4 ml) was added and the solution refluxed for a further 13 h. The solution was added to HCl (2 mol l^{-1}, 30 ml), extracted with ether and washed with further portions of HCl (2 x 20 ml). Chromatography with diethyl ether/pet. spirit (3:7) yielded only two bands.

Band one (R_f = 1.00) gave **29** (0.189 g, 90% recovered).

Band two (R_f = 0.80) gave **7** (0.112 g, 88% recovered).

(c) with sodium

1-(4-Bromo-3-methoxyphenoxy)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-benzene **29** (0.189 g, 0.451 mmol) was dissolved in ether (5 ml) and the flask cooled to -83°C. Sodium (0.010 g, 0.434 mmol) was added and the solution warmed to room temperature and then refluxed for 5 h. 1-(4-Methoxyphenyl)-2-phenyl-1-butanone **7** (0.113 g, 0.445 mmol) was added and the solution refluxed for a further 12 h. Ether (8 ml) and ethanol (1 ml) were added and the solution poured into HCl (2 mol l^{-1}, 40 ml) and extracted with ether. The organic layer was washed with HCl (2 x 40 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet spirit (1:4) yielded two bands.

Band one gave **29** (0.161 g, 85% recovered).

Band two gave **7** (0.098 g, 86% recovered).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with tetramethylammonium bromide.

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.193 g, 0.804 mmol) was dissolved in acetonitrile (10 ml). Tetramethylammonium bromide (0.179 g, 1.16 mmol) was added and the solution refluxed for 1 h, turning from yellow to dark orange. The solvent was removed under vacuum to leave an orange residue. Chromatography (plc) with diethyl ether/pet. spirit (1:3) gave (R_f = 0.50) an orange oil (0.034 g), tentatively identified as (acetonitrile-κ*N*)tri(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **31** (0.079 mmol, 10%). **31** is stable for only short periods of time, readily decomposing.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.12 (d, J = 8.8 Hz, 1H, H5), 7.55 (d, J = 2.4 Hz, 1H, H2), 7.30 (m, 5H, ArH), 6.70 (d of d, J = 2.4, 8.8 Hz, 1H, H4), 4.63 (t, J = 7.3 Hz, 1H, CH), 3.96 (s, 3H, OCH_3), 2.23 (m, 1H, CH_2), 1.89 (m, 1H, CH_2), 0.93 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 133.0 (d, C5), 127.9 (d), 126.8 (d), (C2''-C6''), 125.8 (d, C4''), 123.7 (d, C2), 110.0 (d, C4), 54.1 (q, OCH_3), 52.8 (d, CH), 25.8 (t, CH_2), 12.4 (q, CH_3).

IR ($CDCl_3$) ν(CO) 2008 (vs), 1931 (s), 1896 (s, br) cm^{-1}.

CHAPTER THREE

INVESTIGATION OF COUPLING REACTIONS WITH ALKYNES

3.1 Introduction.

Reactions of transition-metal compounds which give alkyne-insertion into a metal-carbon σ-bond have been well studied in recent years. Representative examples include reactions of complexes of Rh[90], Ru[91], Co[92] (figure 3.1[93]), Pd[94], Mn, Mo[95], and W[95]. From these types of reactions, metallacyclic intermediates may be isolated or, of more interest to the synthetic chemist, an organic product may be liberated.

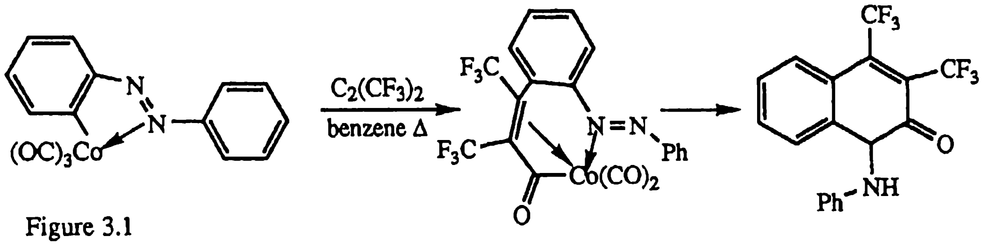


Figure 3.1

The latter case is encompassed in a comprehensive review by Schore[51] on transition metal-mediated cycloaddition reactions of alkynes in the synthesis of cyclic and heterocyclic compounds.

The coupling reaction of an alkyne is of obvious synthetic utility, forming as it does two new carbon-carbon bonds with the preservation of functionality in the form of a double bond. By employing cyclometalated compounds, alkyne coupling can lead to a range of compound types not available from traditional cycloaddition chemistry. Such coupling is well known and advanced for palladium, the wealth of work undertaken[45,96,97,98] including kinetic studies.[94] An illustrative example[96] is shown (figure 3.2). Insertion of an alkyne gives an intermediate which can either liberate an organic product or insert a second alkyne before liberation of a double insertion product.

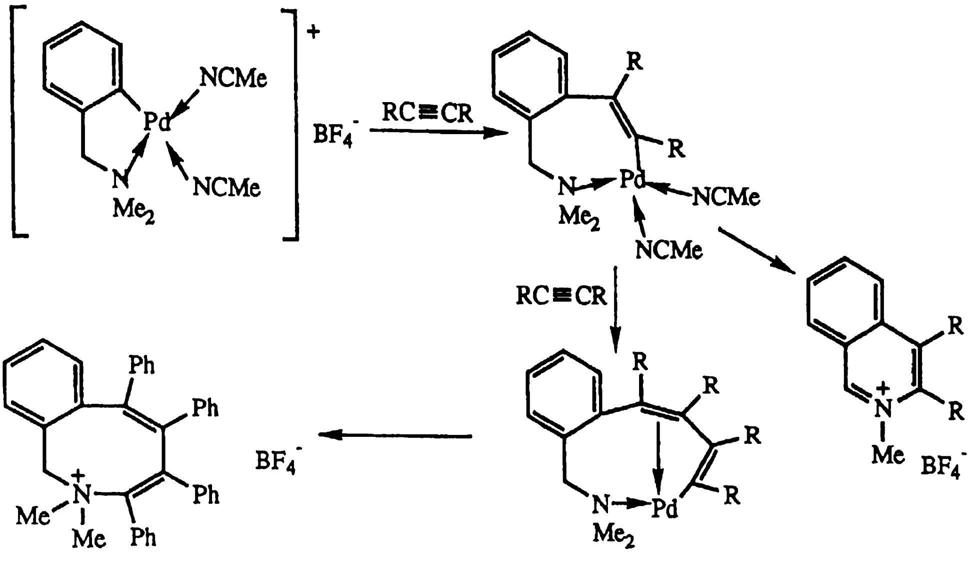


Figure 3.2

3.1.1 Coupling of alkynes with cyclometalated manganese carbonyls.

The synthetic utility of coupling alkynes with manganese carbonyls has been relatively restricted, arguably because organic products are seldom liberated. For example,[99] the addition of the electron-rich ynamine $MeC{\equiv}CNMe_2$ to $Mn_2(CO)_9(NCMe)$ (figure 3.3) yields a vinylidene complex which can undergo further insertion, giving a four-membered carbocyclic intermediate which upon heating gives a complex containing a manganese carbene centre.

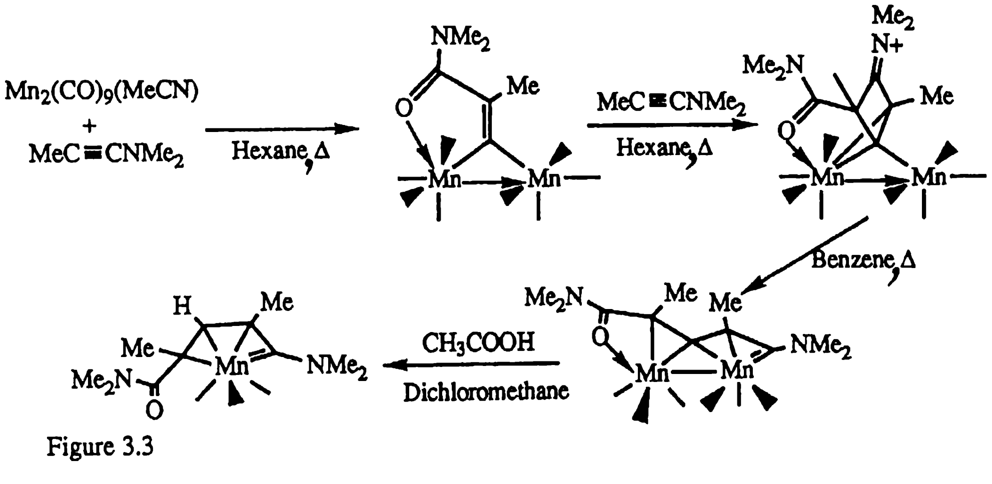


Figure 3.3

Another example in which the metal is retained in the product is alkyne insertion into a Mn-C σ-bond, as has been extensively studied by Booth *et al.*[52-54]. They investigated the reaction of alkynes with $R\text{-}Mn(CO)_5$ complexes (R = H, Me, Ph and COMe) which gave metallacyclic products (figure 3.4). More recently this work was extended by DeShong and co-workers[100-102] who were able isolate butenolides upon reduction with hydride (figure 3.4).

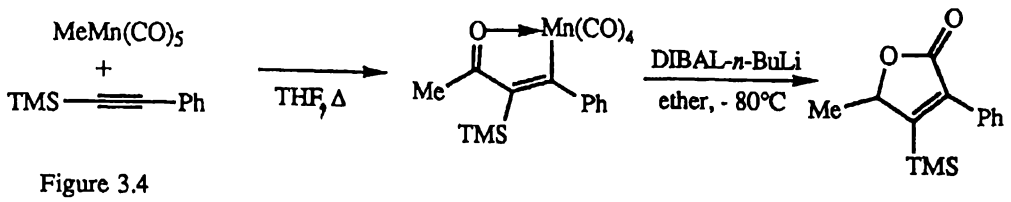


Figure 3.4

However, the potential synthetic utility of alkyne coupling with cyclometalated manganese carbonyls has only recently been developed. Coupling of alkynes with orthomanganated aryl ketones to give substituted inden-1-ols (figure 3.5) was reported

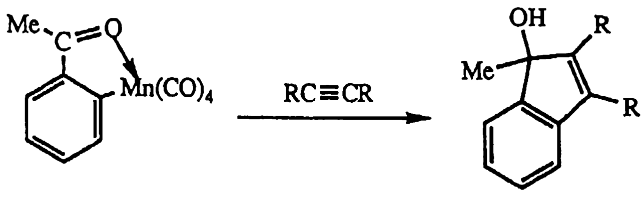


Figure 3.5

independently by Liebeskind and co-workers,[56] and by Robinson.[55] Though similar results were reported, the distinction between the two approaches was the way in which the coupling reactions were initiated. Liebeskind *et al.*[56] employed trimethylamine-*N*-oxide as oxidant to achieve "decarbonylative activation", while Robinson[55,57] used thermal induction. Formation of inden-1-ol products has since been applied to orthomanganated diterpenoid complexes[47,48,103] (figure 3.6[103]).

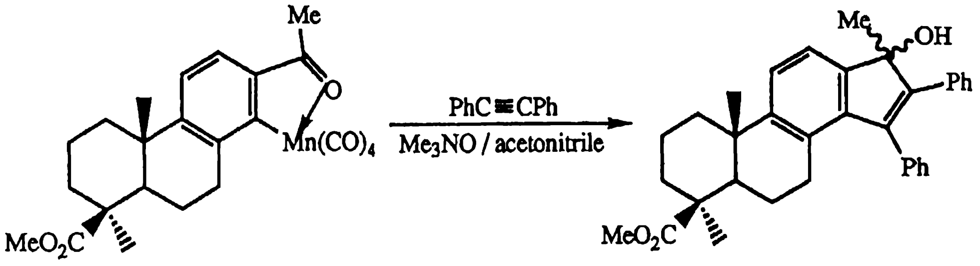


Figure 3.6

The proposed[71] mechanism for alkyne coupling and inden-1-ol formation is shown in figure 3.7. The initial step is the loss of CO to give a 16-electron species (i). This provides a vacant coordination site which allows the alkyne to become η^2-coordinated (ii). A regiospecific migration of the aryl group to the nearest alkyne carbon generates the insertion product (iii), which may exist as a seven-membered metallacyclic ring. Intramolecular addition of the C-Mn bond across C=O gives a manganese alkoxide species (iv) which is subsequently hydrolysed to liberate the inden-1-ol.

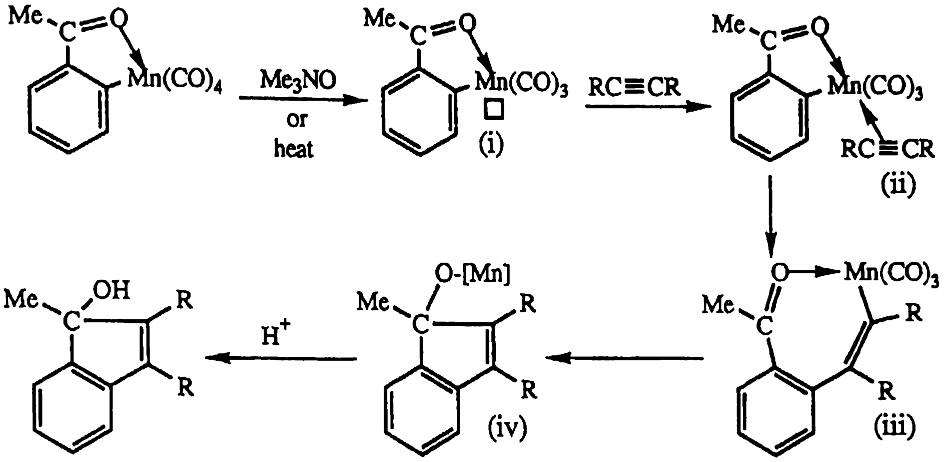


Figure 3.7

Correspondingly, indenone compounds were formed[55,57] from the coupling of alkynes with orthomanganated benzamides, benzaldehydes and benzoate esters. It is thought that indenone products result from the elimination of manganese amide, hydride and alkoxide respectively (figure 3.8) in place of protonation of the alkoxide (iv; inden-1-ol synthesis figure 3.7).

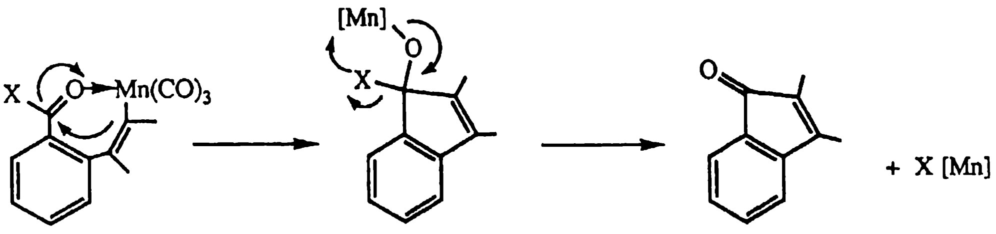


Figure 3.8

X = NMe$_2$, H, OR

Indenones have been similarly synthesised recently using palladium compounds.[104,105] Transmetalation[104] with $PdCl_2$ of mercuriated 3,4,5-trimethoxybenzaldehyde generates the palladium complex (figure 3.9) which

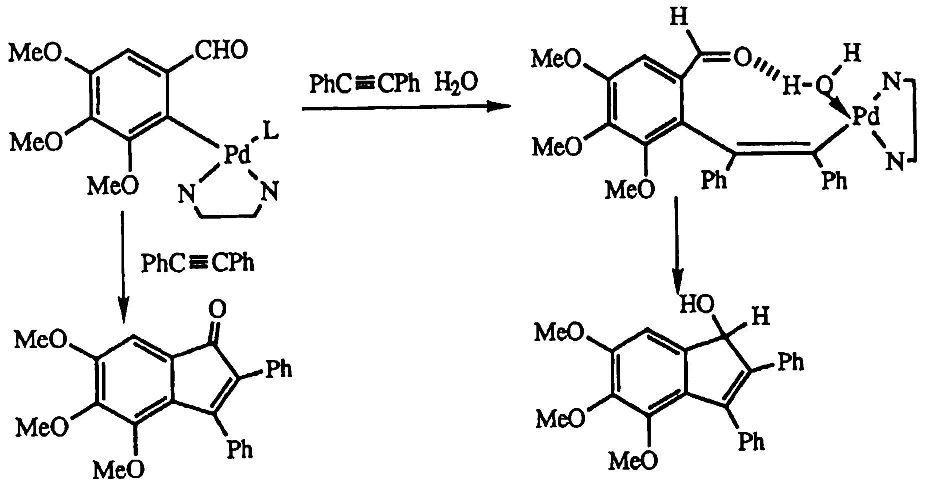
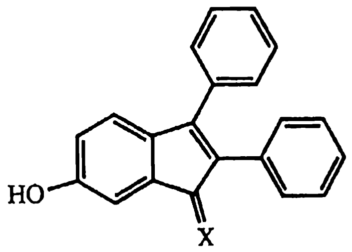


Figure 3.9

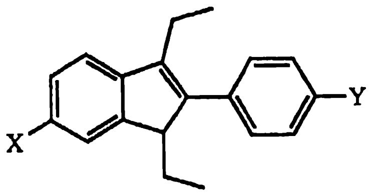
subsequently couples with an alkyne giving the indenone. Catalytic amounts of $PdCl_2$ with $CuCl_2$ as a reoxidant or stoichiometric amounts of a bipyridyl complex with H_2O give the corresponding inden-1-ol (figure 3.9).

3.1.2 Indenyl Estrogen Receptor Ligands.

2-Phenyl-indenes and -indenones have attracted attention[26] as potential ligands for estrogen-receptors (ER) because of their fluorescent properties. The 2-phenylindene system is an ideal structure for a integrated fluorescent estrogen. Like other triphenylethylene ER ligands, the 2-phenylindenes possess a formal *trans*-stilbene chromophore. 2-Phenylindenes are unique in that the 6/5 ring fusion permits a relatively flat disposition of the 2-phenyl group which enhances fluorescent capability. C-1 and C-3 can have a range of diverse substituents which leads to possibilities for ligand design. Such ER-targeted compounds have potential for clinically useful prognostic techniques for the management of breast cancer.



$X = CH_2, O$



if X = OH, Y = H
if X = H, Y = OH

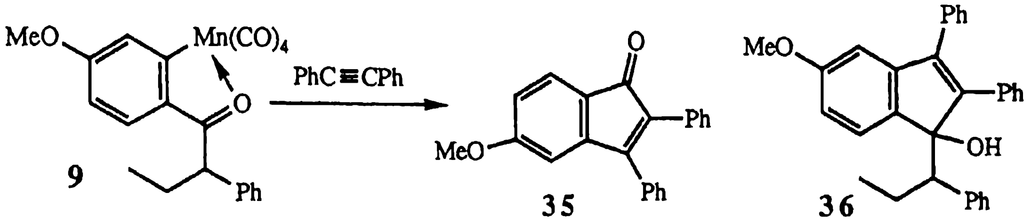
2,3-Diphenyl-indenes and -indenones, though nonfluorescent, have[27] higher ER binding affinity than the corresponding 2-phenylindenes. It was found[27] that with hydroxyl substitution and attachment of a 2-(*N*,*N*-dialkyl)ethoxy side chain, diphenylindenes and indenones may serve as high affinity antiestrogens.

Use of established manganese chemistry could lead to the development of a specific synthesis for ER ligands with high binding affinities. When the work for this chapter was commenced it was proposed not only to extend the understanding and development of alkyne coupling with orthomanganated aryl ketones, but also to synthesise potential antiestrogenic compounds and Tamoxifen analogues containing an indenyl system.

3.2 Results and Discussion.

3.2.1 Alkyne coupling with tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9.

Coupling diphenylethyne and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** in refluxing benzene for five hours gives **36a** in excellent yield (80%). Also isolated are $Mn_2(CO)_{10}$ (9%), the indenone **35** (14%) and unreacted **9** (6%). The results for the coupling of other alkynes with **9** in benzene are shown in table 3.1. These yields are in accord with those reported for other thermally-promoted reactions of tetracarbonylmanganese complexes.[55,57,103] Reaction with 2-hexyne gives the diastereoisomers **43a** and **43b** in a combined yield of 82%. Similarly, coupling 3-butyn-1-ol with **9** gives the diastereoisomeric inden-1-ol products **46a** and **46b** in good yield (65%). This is the first example of a terminal alkynol coupling with an orthomanganated aryl ketone. The major isomer **46a** has comparable ^{1}H NMR chemical shifts to, and is assigned the same stereochemistry as, **33a**.



9

35

36

Table 3.1 Results for the coupling of 9 in refluxing benzene.

alkyne	product	%yield
PhC≡CH	33	41
PhC≡CPh	36	80
$Me_3SiC\equiv CH$	42	10
$CH_3C\equiv C\text{-}nC_3H_7$	43	82
$HC\equiv CC_2H_4OH$	46	65
DMAD	-	-

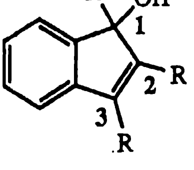
Attempted thermal coupling of dimethyl acetylenedicarboxylate (DMAD) with **9** gives no coupled product. A similar result[57] was observed when DMAD was coupled with orthomanganated acetophenone **6**. It is unclear why this alkyne did not couple. With other aryl-metal centres[93,98] electron-poor alkynes readily couple. Nevertheless, when coupling is oxidatively-induced with trimethylamine *N*-oxide (Me_3NO) a DMAD coupled product, **39**, is formed in good yield (54%).

Results for the other Me_3NO-induced alkyne couplings are shown in table 3.2. The yields for the amine-oxide-induced reactions are higher (10-20%) than those previously reported for the coupling with orthomanganated acetophenone derivatives[56] and acetyl-diterpenoid complexes.[103] The Me_3NO-induced coupling of phenylethyne with **9** gives the demetalated ketone **7** (13%) and the diastereoisomers **33a** and **33b** in a combined yield of 83%. Similarly, reaction with diphenylethyne also gives the coupled product, **36**, as diastereoisomers. The Me_3NO-induced reaction with 2-hexyne gives the diastereoisomers **43a** and **43b** (66%) and a third inden-1-ol **45** (22%). The latter regioisomer has the methyl substituent in the 2-position of the indenyl ring, as confirmed by nOe experiments, and only one diastereoisomer appears to be formed.

Table 3.2 Results for the Me_3NO-induced coupling of 9

alkyne	product	yield%
$PhC\equiv CH$	33	83
$PhC\equiv CPh$	36	87
$CH_3C\equiv C\text{-}n C_3H_7$	43	88
$HC\equiv CC_2H_4OH$	46	63
DMAD	39	54

Previously,[57] the reaction of orthomanganated benzophenone with diphenylethyne gave the corresponding 1,2,3-triphenylinden-1-ol in lower yield (*ca.* 15%) than orthomanganated acetophenone **6** when coupled in similar conditions, suggesting that steric factors influence reactivity. Given the yields of the alkyne coupling reactions above (tables 3.1 and 3.2), which are comparable to those of previous studies,[55-57] it is unlikely that the 1-phenylpropyl substituent impedes the reactivity of the orthomanganated complex **9**.



Both the thermally- and Me_3NO-induced reactions (with the exception of 2-hexyne) give the regioisomer with the bulkier alkyne substituent in the 2-position of the inden-1-ol ring. Steric effects were found[55-57] to control the regiochemistry, with the placement of the bulkier substituent almost exclusively in the 2-position of the inden-1-ol ring. This is consistent with other systems in which the bulkier substituent of the alkyne is inserted adjacent to the metal.[52,100-102] From the range of alkynes investigated,[56] apart from alkynes of the form $RC\equiv CCO_2Et$, only 1-hexyne gave a mixture of regioisomers, that with the bulkier n-C_4H_9 substituent in the 2-position dominating by a 7:1 ratio.

The sterically biased insertion is probably a direct result of the coordination of the alkyne to the manganese intermediate (ii; figure 3.7) prior to insertion. The pre-insertion intermediate requires a coplanar alignment of the alkyne C≡C bond with the Mn-C σ-bond (figure 3.10) to meet the orbital overlap requirement.[106] Steric interactions would be reduced if the bulkier alkyne substituent is positioned over the metal carbonyl group and not over the aromatic ring.

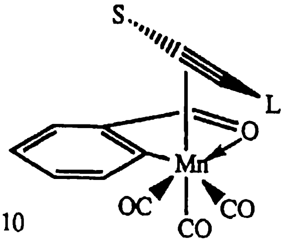


Figure 3.10

For the case of 2-hexyne, the steric restriction associated with the bulk of a group bonded to the alkyne carbon would be little different between $\underline{C}H_3$ and $\underline{C}H_2CH_2CH_3$ (figure 3.10). This results in a more even regioisomer ratio of 3:1. Our results for the coupling of 2-hexyne suggest steric preferences are more dominant for the thermally-induced reaction in comparison to that which is Me_3NO-activated, as only one regioisomer is formed in benzene under reflux.

3.2.2 Solvent Effects.

The thermally-induced reaction of **9** with diphenylethyne was conducted not only in benzene, but also in acetonitrile and petroleum spirit. In refluxing acetonitrile a 2:1 mixture of the inden-1-ols **36a** and **36b** is obtained in quantitative yield. However, in petroleum spirit only **36a** is isolated (60% yield). The reaction of **6** with diphenylethyne in a similar solvent (heptane) has been reported[57] not to give any coupled product. The differing yields of the coupled product, **36**, are consistent with a similar finding by Robinson,[57] that diphenylethyne couples with **6** to give higher yields of the inden-1-ol in benzene than in methanol. Kinetic studies with Pd[94] and Mn[53] complexes have shown that alkyne insertion into the metal-carbon bond is the rate-determining step. The latter study by Booth *et al.*[53] showed this rate of insertion was very solvent dependent. In solvents such as benzene and diethyl ether, insertion was considerably slower than in polar solvents like THF and nitromethane. Intermediate 16-electron species such as (i) in figure 3.7 are more stable in coordinating solvents and as alkyne coordination is an associative process, labile solvent molecules are easily replaced by coordination of an alkyne.

Our results for the coupling of diphenylethyne with **9** in various solvents show a peculiar trend in inden-1-ol formation. Only one diastereoisomer, **36a**, is observed in benzene, a non-polar solvent, while both **36a** and **36b** are formed in the polar coordinating solvent acetonitrile. Similarly when phenylethyne and trimethylsilylethyne are coupled in benzene only one diastereoisomer is observed, each having the same relative stereochemistry as **36a**. In contrast, 2-hexyne and 3-butyn-1-ol which do not have a particularly bulky substituent give two diastereoisomers in benzene. This suggests an alkyne with a bulky substituent leads to only one diastereoisomer in a non-polar solvent.

Consideration of the proposed mechanism (figure 3.7) shows that the diastereoisomerism arises between intermediates (iii) and (iv) when the seven-membered metallacyclic ring collapses to the five-membered manganese alkoxide (figure 3.7). Outlined below are the factors which we have considered when attempting to understand the extent of formation of diastereoisomeric products under different conditions.

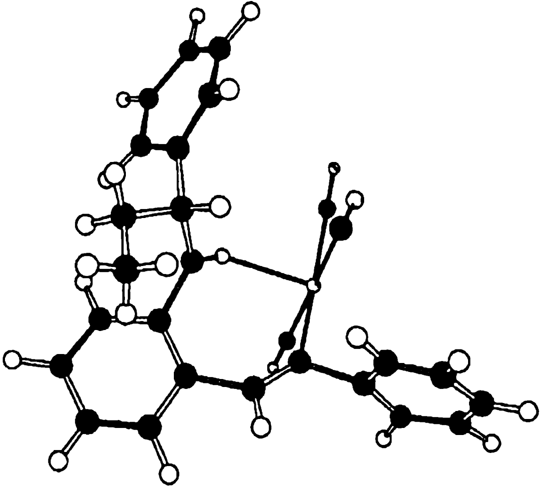
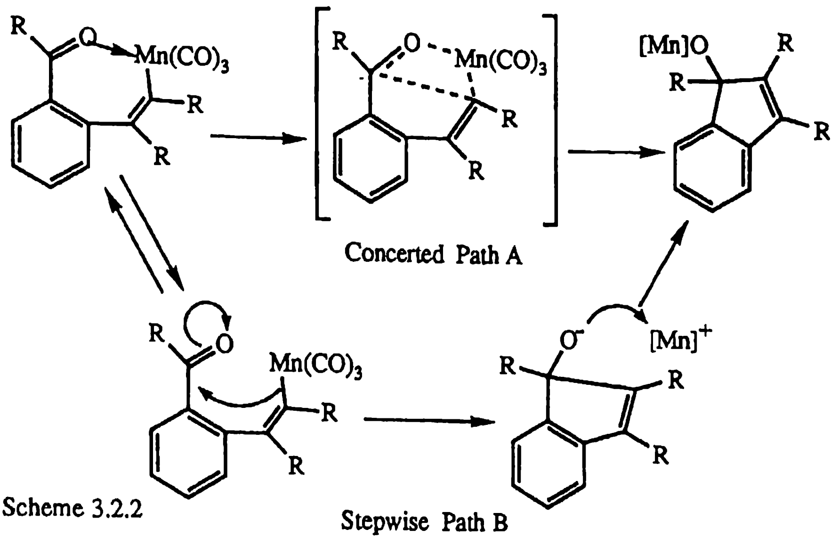


Figure 3.11

In a non-polar solvent, the presence of a bulky alkyne substituent, for example as with phenylethyne, may sterically induce a preferential conformation (figure 3.11) of the proposed 16-electron metallacycle (iii, figure 3.7) irrespective of whether this complex has either octahedral or trigonal bipyramidal geometry. A strong preference for this conformation resulting from the bulk of the alkyne and phenylpropyl groups could lead to a stereospecific reaction giving the product having stereochemistry such as that exhibited by **33a**. Scheme 3.2.2 indicates that both a concerted and stepwise process are possible for the cyclisation step. Figure 3.12a represents a possible transition state for the concerted cyclisation reaction in a non-polar solvent in which the developing Mn cation and alkoxy anion remain associated because of lack of charge stabilisation by solvent. The alkynyl carbon to which the manganese is bonded is pictured as approaching the carbonyl carbon



Scheme 3.2.2

from the top face as required by stereoelectronic considerations for carbonyl addition. When the alkyne substituent is large (phenyl in figure 3.12a), it is clear that the transition state will be favoured by maximum distance between this bulky substituent and the largest

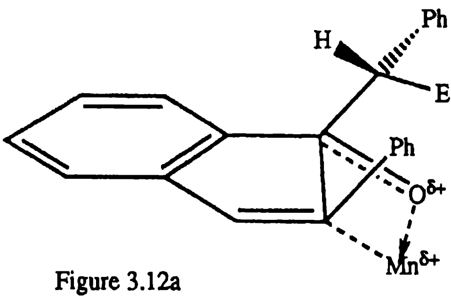


Figure 3.12a

group (phenyl) of the phenylpropyl group, i.e. by the conformation as shown in which the phenyl group is rotated to a rearward position. When the chirality at the phenylpropyl group is as shown (i.e. *S*), the bulkier of the remaining two groups (Et) is in the less sterically crowded position than the smaller group (H) which is in the more crowded environment over the metallacyclic ring. This then appears to be the most favoured transition state for this enantiomer and it would lead to the observed product (defined as 1*S*, 1'*S*). For the other (*R*) enantiomer however the corresponding lowest energy state would be the mirror image of that in figure 3.12a, so in that case Mn and O would prefer to twist up as the transition state is approached and the result would be preferential formation of the (1*R*, 1'*R*) inden-1-ol product (as in **33a**), the other enantiomer of the observed diastereoisomer. The presence of an alkyne substituent which is not particularly bulky, such as the *n*-Pr group of 2-hexyne, may not have such a restriction on the phenylpropyl group. If so, this then leads to either diastereoisomer forming (i.e.1*R**, 1'*S**).

In a polar solvent, effective solvation of the developing charge centres on the O and Mn in the transition state may not require retention of the O-Mn bond (stepwise cyclisation; scheme 3.2.2) and it seems possible that the orientation of attack of the alkynyl carbon at the carbonyl carbon may not be constrained as tightly as that indicated in figure 3.12a in which the phenyl and phenylpropyl groups are forced into rather close proximity. If these groups are more splayed when the O-Mn bond is broken, there may be less rotational constriction at the phenylpropyl centre and less stereo control may result. Alternatively, it may be that a transition state such as that in figure 3.12b is now possible and if, as indicated, the phenyl group of the phenylpropyl group rotates to a rearward position to minimise crowding now not with the alkynyl phenyl group but with the (departing) manganese, the alternative diastereoisomers (1*R*, 1'*S* as in **33b**) can be seen now to be possible.

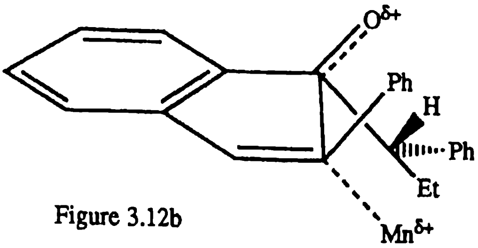
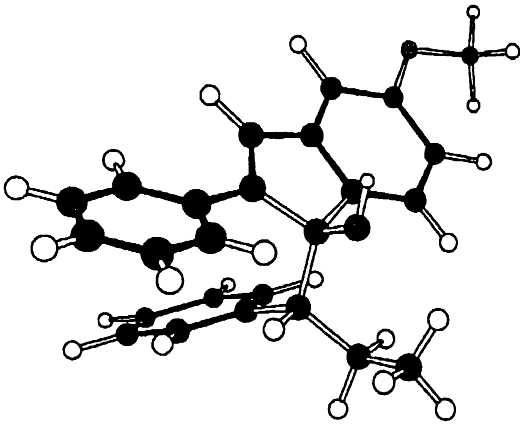
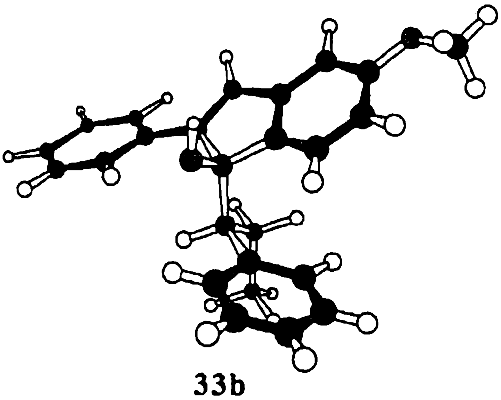


Figure 3.12b



33a



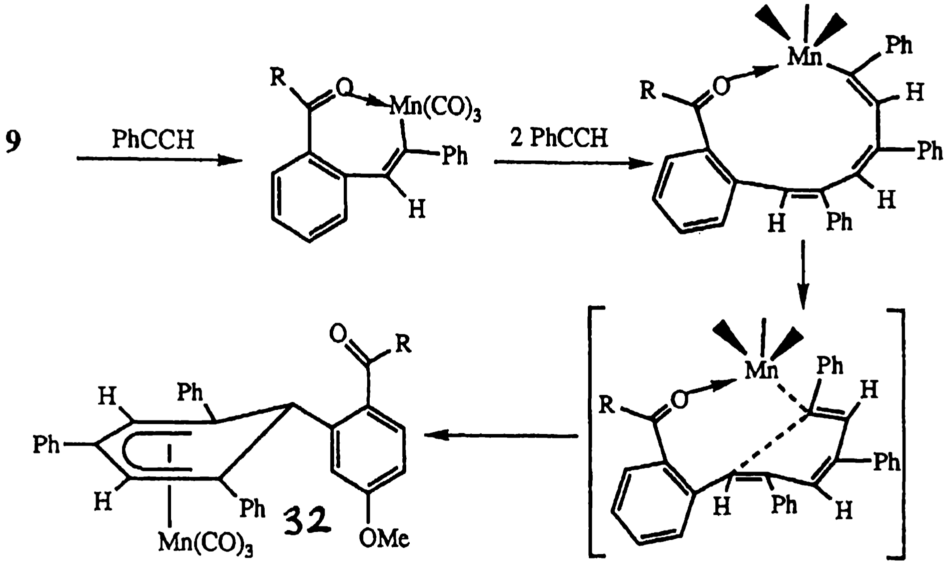
33b

In a polar solvent such as acetonitrile the metallacyclic intermediate (iii, figure 3.7) may be stabilised by having the non-polar phenyl group of the phenylpropyl substituent lying over the non-polar phenyl ring which forms part of the metallacyclic ring. If such stabilisation, analogous to hydrophobic bonding in the polar protic solvent water, operates it could offset any strong preference for the conformation in figure 3.12a and result in more of the product with the stereochemistry exhibited by **33b**. This then could account for the formation of both diastereoisomers in the polar solvent. However, this in itself does not account for the differences observed when coupling alkynes with bulky substituents.

These two mechanisms discussed above for the intramolecular rearrangement of the seven-membered metallacyclic intermediate may rationalise the different degrees of stereospecificity in differing solvent. However, they do not alone account for the differences observed when coupling alkynes with bulky substituents. It is possible therefore, that a combination of the factors discussed above, as well as other unknown factors such as solvent effects, may contribute to the differentiation of product stereospecificity in non-polar and polar solvents and between alkynes.

3.2.3 Formation of Other Alkyne Coupling Products.

The tricarbonyl complex **32**, formed in low yield, may arise from the successive insertion of three alkynes into the Mn-C bond, with subsequent rearrangement (figure 3.13). An analogous product was isolated[57] when **6** was coupled with phenylethyne. An excess of alkyne was found to increase the yield of this product. In a related system, orthomanganated 3-acetylthiophene when coupled with phenylethyne gave[107] the manganese tricarbonyl compound (figure 3.14) whose structure was confirmed by X-ray crystallography. This compound also results from the insertion of three alkynes and a subsequent prototropic rearrangement. No IR spectrum was reported and therefore it cannot be compared to that of **32**. The ^{1}H NMR of **32** shows singlets at δ 5.34 and δ 4.67 which are consistent with the proposed structure and not that exhibited in figure 3.14. No manganese tricarbonyl compounds have been isolated from the Me_3NO-induced reactions.[56,103] Therefore, it may be only in the thermally-induced reactions



R =CH(Ph)CH$_2$CH$_3$

Figure 3.13

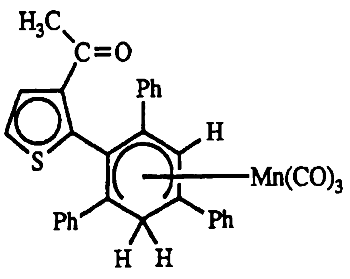


Figure3.14

that there is such a competing reaction. Formation of products such as **32** suggests the proposed metallacyclic intermediate (iii; figure 3.7) may be sufficiently stabilised by internal coordination of Mn to the carbonyl oxygen in non-coordinating solvents that it has sufficent time to insert additional alkynes. It could be speculated therefore that a rate-determining step for inden-1-ol formation in non-polar solvents is the intramolecular rearrangement of the seven-membered ring species (iii) to the alkoxide (iv) (figure 3.7).

Coupling of diphenylethyne and **9** in benzene gives 5-methoxy-2,3-diphenylindenone **35** in 14% yield. GCMS also detected traces (*ca.* <5%) of analogous indenone compounds from the reactions with 2-hexyne and DMAD. This is the first example of indenone formation from the alkyne coupling of an orthomanganated aryl ketone. Indenone products have been formed[55,57] from alkyne coupling with orthomanganated benzoate ester, benzaldehyde and benzamide complexes (see figure 3.8) and rationalised[71] by elimination of X[Mn] rather than protonolysis of the alkoxide (iv; figure 3.7).

Clearly, formation of **35** requires the loss of the phenylpropyl group which necessitates the cleavage of a carbon-carbon bond. When **36** is heated under reflux in benzene (in darkness) for four days **35** is isolated, though in poor yield (9%). This result shows the bond between C1 and CH (of the propyl substituent) can be broken under the conditions employed for alkyne coupling. Though the alkylmanganese entity is not detected, formation of **35** *via* β-elimination may be envisaged as in the scheme below (figure 3.15).

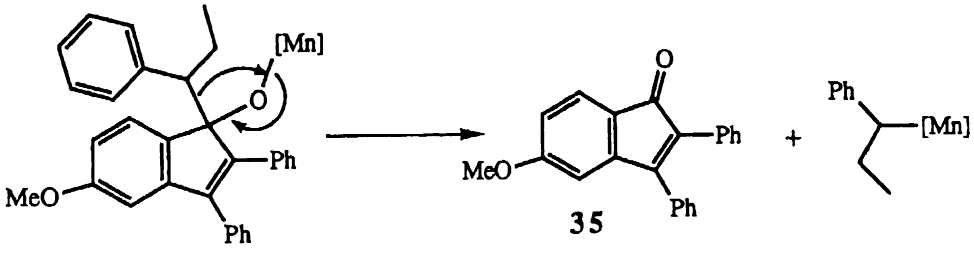


Figure 3.15

Indenone compounds show[26,27] potential as ligands for the estrogen receptor (ER). An analogous compound 6-hydroxy-2,3-diphenylindenone, similar to **35** but having a hydroxyl in the indenone 6-position instead of the 7-methoxy group of **35** has a relatively high ER binding affinity, so hydroxy analogues of **35** and related compounds are of interest as ER binders.

3.2.4 Palladium(II)-assisted coupling.

As indenyl compounds have been synthesised from the coupling of alkynes with palladium complexes[104] (see figure 3.9), and given that Pd(II) reportedly[46,49] transmetalates at the Mn-C σ-bond, it was sought to investigate the coupling of alkynes with **9** mediated with Pd(II) in acetonitrile under reflux. Coupling alkynes with **9** in the presence of $PdCl_4^{2-}$ does not give a clean reaction in comparison to those either thermally or oxidatively induced. The coupling of phenylethyne and **9** gives no coupled product, the only isolated products appeared to be polymerised phenylethyne products. It is not clear whether this results from lack of coupling reactivity or just rapid alkyne polymerisation under the reaction conditions. An attempted Pd(II)-mediated coupling of **9** with diphenylethyne in acetonitrile at ambient temperature gives **36** in poor yield (9%) with most of **9** recovered unreacted (83%). However, the coupling under reflux is more successful giving the inden-1-ol product **36** in 23% yield. Also isolated are tetraphenylcyclopentadienone and the benzofulvene products **37** and **38** (28%). The formation of the cyclopentadienone product arises from the coupling of two alkynes and carbon monoxide and is probably mediated by Pd(II). This method for cyclopentadienone formation is well known for many early and late transition metals.[51]

Though the exact mechanism is not known, a possible sequence leading to the formation of the benzofulvene products **37** and **38** is outlined in figure 3.16. It is likely that transmetalation of the Mn-C σ-bond by Pd(II) with subsequent alkyne insertion leads to the intermediate (ii) as in figure 3.9. Elimination of an HPdOX entity gives the benzofulvene products, **37** and **38**.

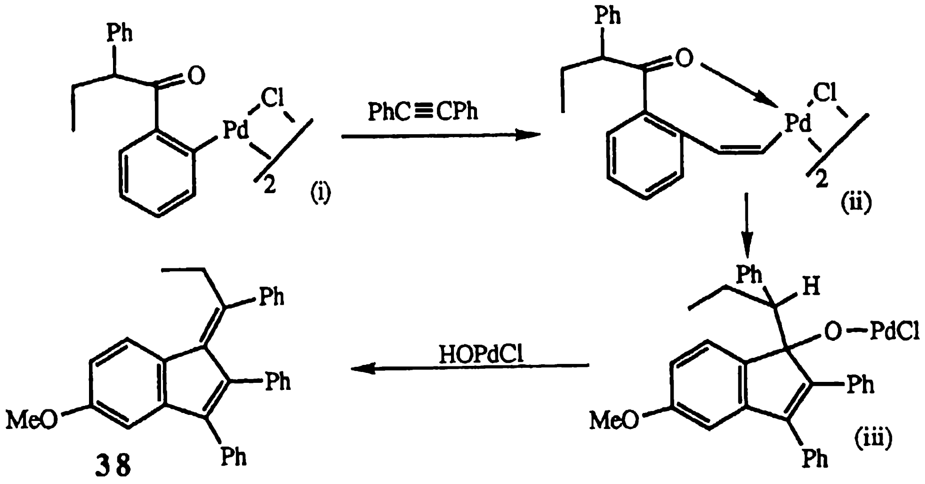


Figure 3.16

3.2.4.1 Crystal Structure of *E*-5-methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene 37.

The crystals of 37 and 38 obtained from solvent diffusion are coloured yellow and orange respectively. Their distinctly different colours suggested differences in the degree of conjugation and possibly of ring coplanarity. X-ray crystallographic studies were undertaken to evaluate bond parameters and shape for the isomeric benzofulvene compounds 37 and 38.

The structure of 37 is depicted in figures 3.17 and 3.18. The propylidene group at the 1-position, is rotated such that the ethyl group is adjacent to the 2-phenyl ring. Although the 5- and 6-membered rings that comprise the indenyl system are not strictly planar, the greatest variation from planarity for ring atoms is only 0.030 Å and 0.020 Å respectively. The angle between these fused rings is 6.8°. The 2- and 3-phenyl rings are twisted out of plane due to non-bonding interactions. The 3-phenyl ring is twisted 53.5° from the plane of the indenyl ring and has a dihedral angle of 104.4° to the adjacent 2-phenyl ring. Non-bonding interactions also cause the phenyl ring attached to the propylidene group to be twisted out of plane . The dihedral angle between this phenyl ring and the indenyl ring is 75.0°.

3.2.4.2 Crystal Structure of *Z*-5-methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene 38.

The structure of 38 in which the phenyl ring attached to the propylidene group is adjacent to the 2-phenyl ring is illustrated in figures 3.19 and 3.20. As found for 37, the 5- and 6-membered rings of the indenyl system also deviate from planarity, but with atoms displaced by a maximum of 0.014 Å and 0.027 Å respectively. The angle between these rings is 3.5° which is less than that for 37 (6.8°). The 3-phenyl ring is twisted 56.7°, from the plane to the indenyl ring. A similar angle is observed for the other isomer 37. However, the dihedral angle between the 2-phenyl ring and the indenyl ring is significantly different. It is twisted only 53.3° compared to 97.6° for 37. Additional non-bonding interactions due to the relatively close proximity of the phenyl ring attached to the propylidene substituent result in a different orientation for the 2-phenyl ring. The dihedral angle between the indenyl ring and the phenyl ring attached to the propylidene substituent is 59.3° which is less than that for 37 (75.0°). This is primarily due to reduced non-bonding interactions caused by the positioning of this ring. There are no significant differences in bond lengths. The bond lengths between O(1)-C(51), C(4)-C(3a), C(2)-C(21) and C(1)-C(8) are all 0.02 Å longer than that found for 37. Though this observation is statistically significant it has no chemical importance.

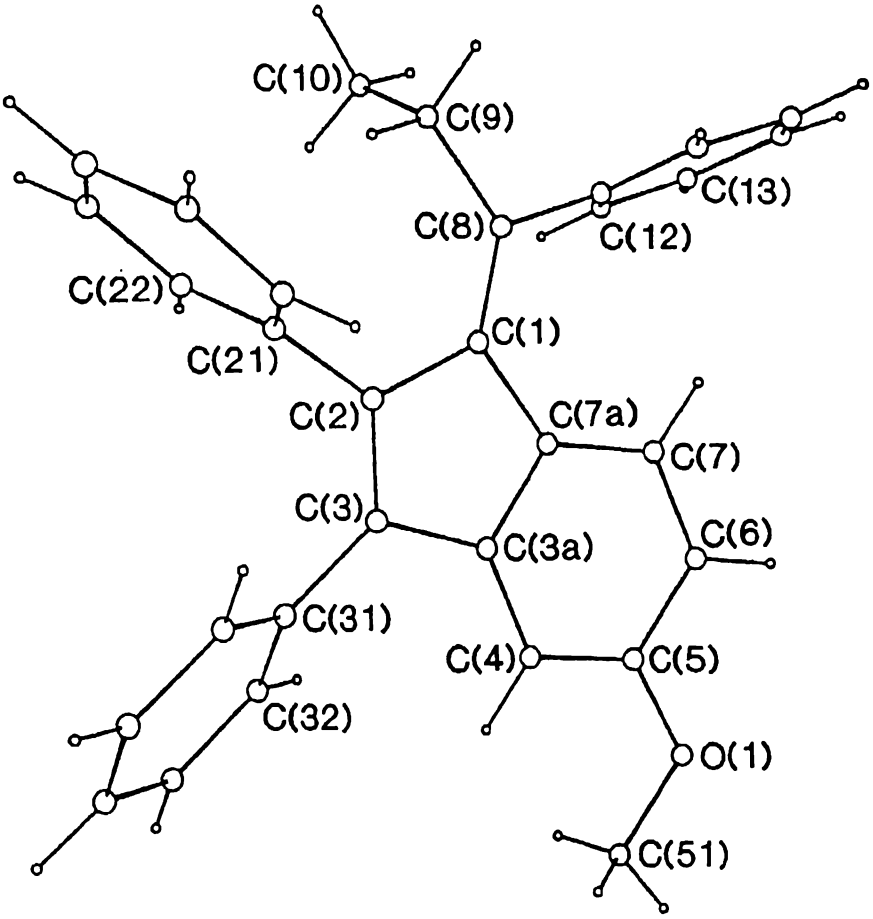


Figure 3.17 Plan view of the structure of 37

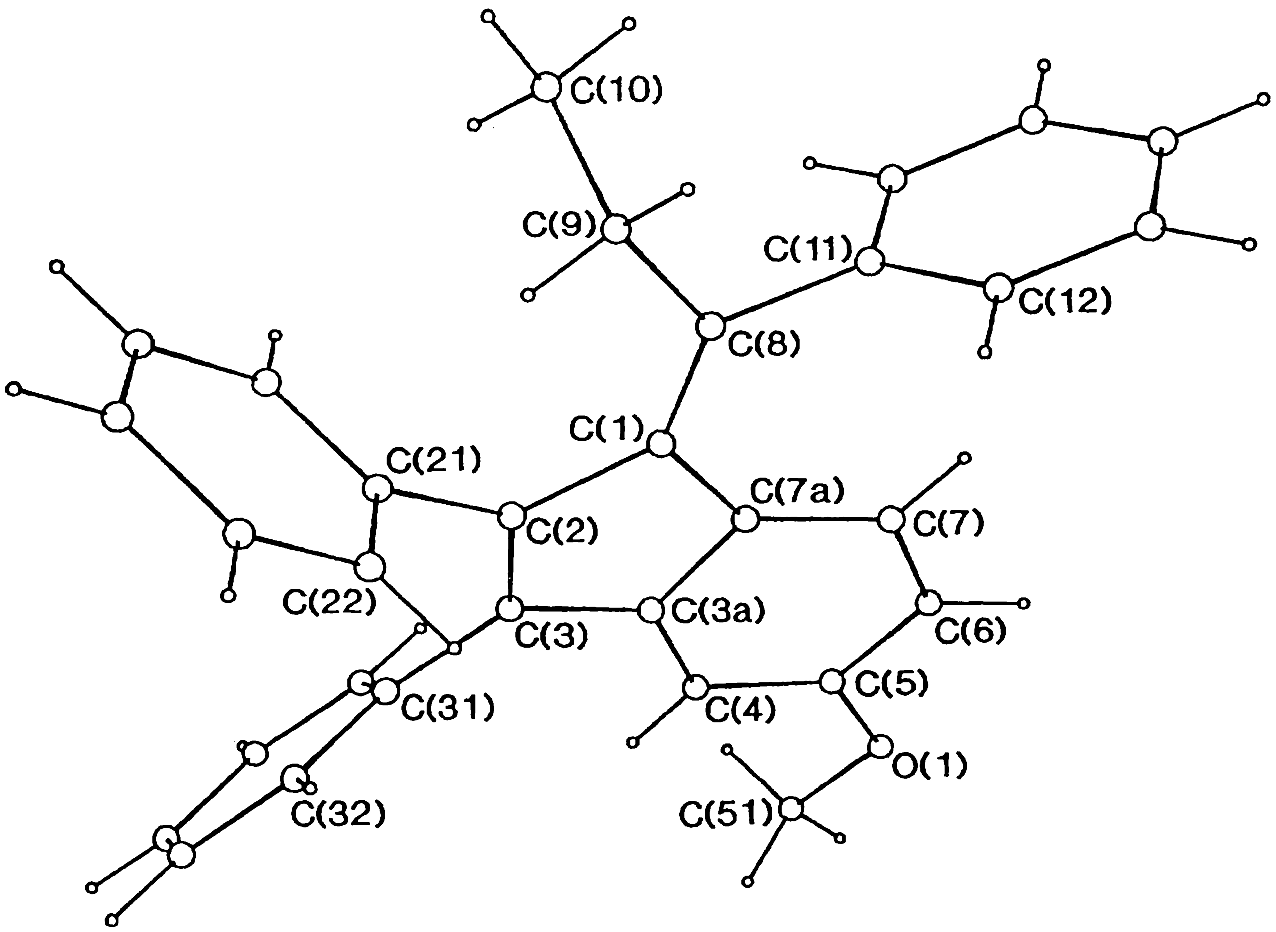


Figure 3.18 Perspective view of the structure of **37**

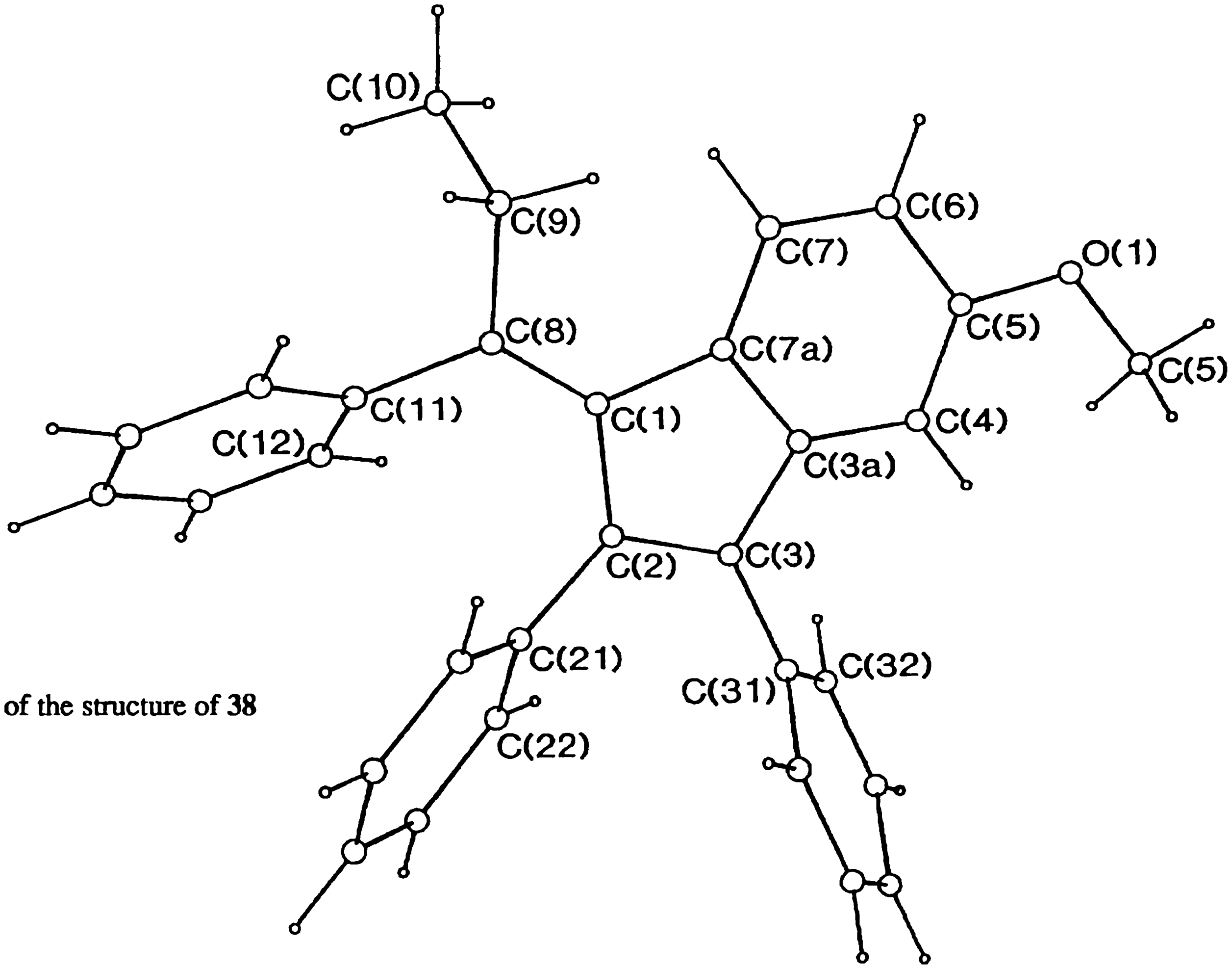


Figure 3.19 Plan view of the structure of 38

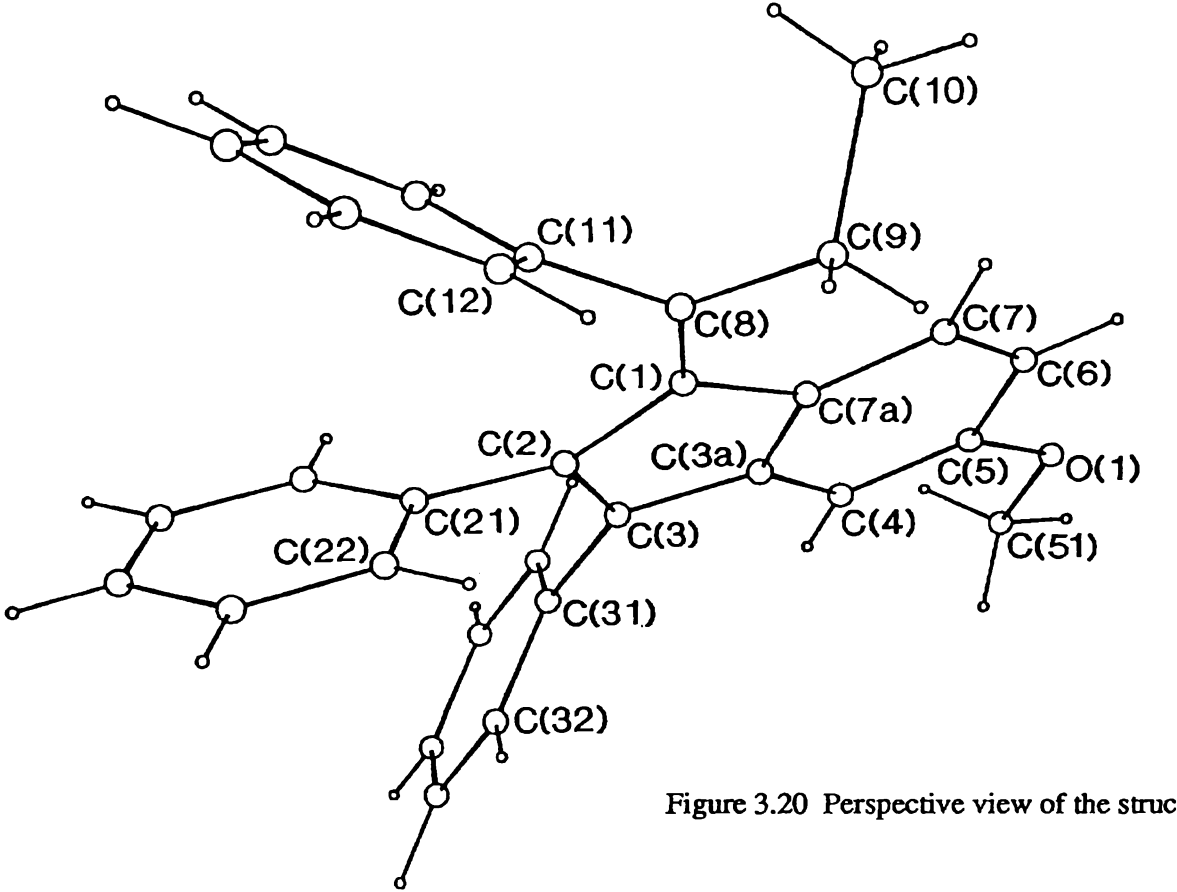


Figure 3.20 Perspective view of the structure of **38**

The crystal structures of **37** and **38** to the best of our knowledge are the first reported for *cis* and *trans* isomers of a 1-phenylbenzofulvene derivative, though analogous structures of 2,3-diphenylbenzofulvene derivatives have been reported.[108,109] An analogous compound to **38**, 1,2-di(pentafluorophenyl)-3-phenylbenzofulvene[108] has similar structural features to those depicted in figures 3.19 and 3.20. The bond lengths for **38** and for the above compound[108] are similar, as is the angle between fused 5- and 6-membered rings. The only significant difference between the two (**38** and that reported[108]) arises from the orientation of the 2-phenyl ring and the phenyl ring of the phenylpropylidene substituent. The dihedral angle between these rings is 33.5° for **38** and only 17° for the fluoro-derivative.[108] This can be simply explained by greater non-bonding interactions for the fluoro derivative.

3.2.5 Synthesis of Tamoxifen Analogues.

The benzofulvene products **37** and **38** are obtained in good yield (70%) from the acid-catalysed dehydration (HCl in acetonitrile) of the corresponding inden-1-ol, **36**. The attempted dehydration of **36** in ethanol is less successful yielding the ethoxy derivative 1-ethoxy-5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-2-indene **47** in moderate yield (58%) and the tentatively-assigned **48**.

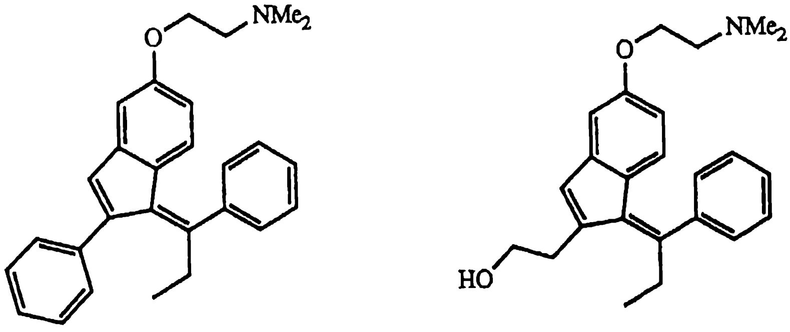


Figure 3.21

The dominance of the *E*-isomer, **37**, when the inden-1-ol **36** is dehydrated, suggested a similar preponderance of this isomer might be observed when the inden-1-ol **33** is dehydrated. Dehydration of **33** followed by demethylation and addition of the *N,N*-dimethylaminoethyl side chain would give a compound with many structural similarities to Tamoxifen (figure 3.21). This is of importance given that 2,3-diphenylindenes have shown[27] significant ER binding affinity, and that the addition of the side chain enhances antiestrogenic activity. An attempted dehydration of **33** (concentrated H_2SO_4 and acetonitrile) gives the inden-1-ol **49**. The likely route to **49** from **33** is outlined in the scheme below (figure 3.22). Initial protonation of the hydroxyl group and loss of H_2O generates the carbocation intermediate. The carbocation is delocalised through the indenyl ring and hydrolysis from adventitious H_2O gives either of the inden-1-ol products **33** or **49**.

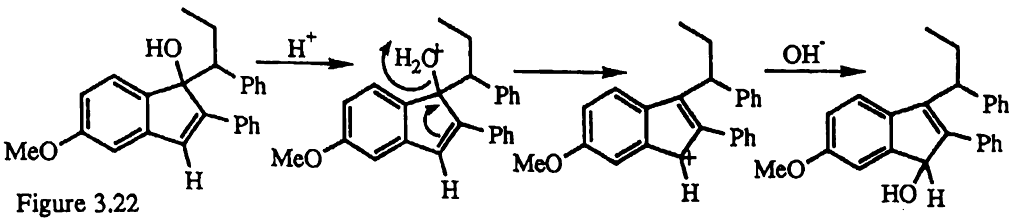


Figure 3.22

An alternative method for dehydration employing mild conditions was sought. Acetylation of **33** (using 4-dimethylaminopyridine and acetic anhydride) gives the desired product **50** in moderate yield (40%). Treatment of the acetylated product **50** with 4-toluenesulphonic acid in acetonitrile under reflux gives the hydrolysis product **33** (7%) and the benzofulvene product 5-methoxy-2-phenyl-1-(1-phenylpropylidene)-indene **52**, though in poor yield (7%). This precluded the attempt to obtain the desired Tamoxifen analogue (figure 3.21) by demethylation and addition of the side chain.

Dehydration of **46**, the product obtained from the coupling of **9** with 3-butyn-1-ol, would give a precursor to a 4-hydroxyTamoxifen analogue. Demethylation of this benzofulvene product and addition of the *N,N*-dimethylaminoethoxy side chain would give a compound having structural similarities to 4-hydroxyTamoxifen **5** (figure 3.21). However repeated attempts using either direct acid-catalysed dehydration of **46** or from the acetylated derivative **51** to obtain a benzofulvene product proved unsuccessful.

3.3 NMR Spectroscopy

The Me_3NO-induced coupling of **9** with phenylethyne gives two isomers **33a** and **33b** of the desired inden-1-ol product. Full structural and stereochemical assignment of each isomer was possible using NMR techniques. NOes from H4 to H3 confirmed the phenyl ring is in the 2-position of the indenyl ring for each isomer. Therefore, the adjacent chiral carbons, C1 and C1' (CH of the 1-phenylpropyl group), give rise to the diastereoisomers. COSY and XH correlated 2D NMR techniques enabled the full assignment of the chemical shift values for **33a**.

Analysis of the ^1H NMR chemical shift values shows the H7 resonance for **33a** at δ 7.54 to be shifted downfield (0.9 ppm) in comparison to that for **33b** (δ 6.65). The difference between the CH_2 proton resonances is also significant. Those for **33a** (δ 2.60, 1.90) are

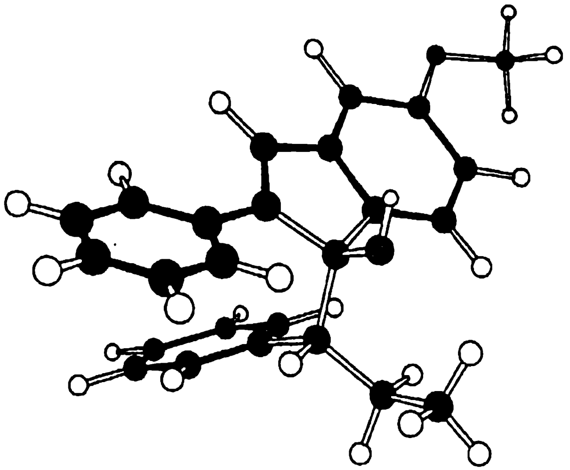


Figure 3.23 Calculated structure of **33a**

downfield and further apart (0.7 ppm) with respect to those of **33b** (δ 1.56, 1.30). These findings suggest for **33a** that the H7 proton is deshielded by the phenyl ring attached to the propyl group and the CH_2 protons deshielded by the indenyl ring. These results enabled the relative stereochemistry about the 1-phenylpropyl group to be deduced. Molecular modelling calculations for **33a** give the minimum energy structure shown in figure 3.23. The structure of the other isomer, **33b**, with *S**-configuration at C1' as depicted in figure 3.24 is similarly determined by employing molecular modelling techniques. An MM2 calculation gives a minimum potential energy of 161.70 kJ mol^{-1} for **33b** (*cf.* 164.10 kJ mol^{-1} for **33a**). Differential nOe experiments confirmed the relative stereochemical assignments for each isomer (results shown in table A.1 and A.2; Appendix A.3). For **33a**, a strong nOe is observed between the H7 proton and the methylene (CH_2) proton at δ 1.90. Other nOes are observed between the H7 proton and H2'' and H6'' and the remaining methylene proton (δ 2.60). For **33b**, there are no observed nOes between these protons. The only nOe observed is between the H22 and CH protons which is consistent with the proposed structure.

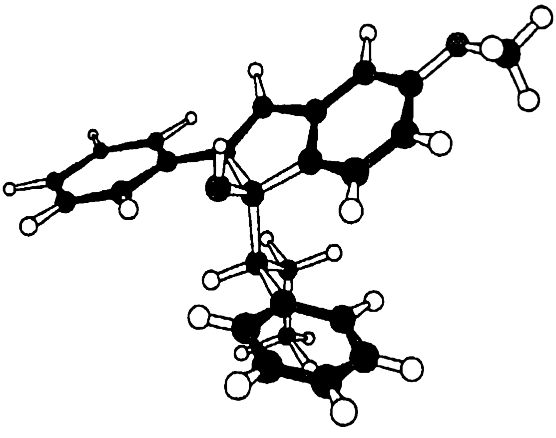


Figure 3.24 Calculated structure of **33b**

The calculated structures shown in figures 3.23 and 3.24 clearly show the dihedral angle between the 2-phenyl and indenyl rings. They suggest that the addition of the 1-phenylpropyl group has caused the normally coplanar rings to twist out of plane with respect to each other by 28.4° for **33a** and 25.2° for **33b**.

Examination of the ^{1}H NMR chemical shifts for the isomers **43a** and **43b** reveal comparable differences for the H7 protons and for the methylene protons (1-phenylpropyl group). Molecular modelling structures for **43a** and **43b** (figures 3.25 and 3.26 respectively) exhibit similar stereochemistry respective to the isomers **33a** and **33b**. The relative stereochemistry for each isomer is consistent with the results obtained from differential nOe experiments (see tables A.3 and A.4; Appendix A.3). The 3-methyl substituent resonance is moved downfield for **43b** (δ 2.02) in comparison to **43a** (δ 1.56). The calculated structure for **43b** shows the phenyl ring is directed away from the methyl substituent, while for the other isomer, **43a**, the calculated structure shows the methyl group is shielded by the phenyl ring resulting in the ^{1}H NMR signal moving upfield.

The above stereochemical assignments for the diastereoisomers of **33** and **43** based on ^{1}H NMR are used as a basis for the assignment of relative stereochemistry for other inden-1-ol compounds.

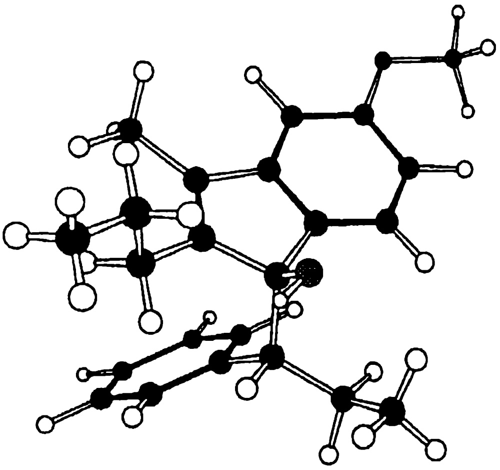


Figure 3.25 Calculated structure of **43a**

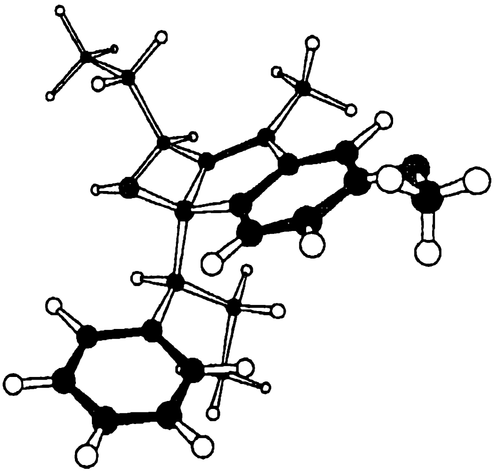


Figure 3.26 Calculated structure of **43b**

The attempted dehydration of **33** in acetonitrile gives a 1:1 mixture of the diastereoisomers of **49**. Full structural assignment was made using long range XH-correlated 2D-NMR and nOe experiments, though definitive stereochemical assignment for each isomer could not be deduced as both have similar chemical shifts. Mass spectroscopy gives a fragment ion of mass 338 (M^+ -H_2O). ^{13}C DEPT NMR shows **49** contains seven singlet resonances and only one triplet resonance, consistent with the structure of **33** or that proposed for **49**. For each isomer the ^{1}H NMR resonance for H1 at *ca.* δ 5.6 is a singlet and correlates with the ^{13}C NMR doublet resonance *ca.* δ 61 (see figures A.3 and A.4, Appendix A.2), the chemical shift indicating the hydroxy group is in fact attached at C1. The long range sequence of the XH-correlated 2D program, which shows the $^{2}J_{C\text{-}H}$ and $^{3}J_{C\text{-}H}$ coupling, enabled unambiguous assignment of singlet resonances and confirms the structure of **49**.

3.4 Summary

The results of coupling **9** with alkynes, both thermally- and oxidatively-induced, are comparable to previous studies.[56,57,103] This indicates that the bulky phenylpropyl substituent does not interfere with the reactivity of the complex, which might have been expected to be the case from the previous[57] result from coupling orthomanganated benzophenone with diphenylethyne.

It was found in our study, that not only does solvent influence the yield of the inden-1-ol, but also it leads to a stereospecific product if the solvent is non-polar and the coupled alkyne has a bulky substituent. The reason for the formation of a stereospecific product is as yet unknown. However, a concerted as opposed to a stepwise mechanism for the intramolecular rearrangement of the seven-membered metallacyclic ring (iii; figure 3.7) to the alkoxide, may lead to differentiation in the stereospecificity of products. The concerted step (path A, scheme 3.2.2) which may be preferred in a non-polar solvent would lead to a stereospecific product. The stepwise process (path B, scheme 3.2.2) is more likely in a polar solvent and would not give a stereospecific product.

The reaction of diphenylethyne with **9** is the first example of indenone formation from an orthomanganated aryl ketone. Formation of the indenone **35** presumably results directly from the alkoxide intermediate (vi, figure 3.7), with β-elimination of the phenylpropyl group giving an alkylmanganese entity not detected as a product.

The coupling of **9** with diphenylethyne in the presence of $PdCl_4^{2-}$ is to the best of our knowledge the first example of this type of reaction. Formation of the benzofulvene products **37** and **38** is an interesting extension to the coupling of alkynes with orthomanganated aryl ketones and this reaction should be investigated further.

Dehydration of the inden-1-ol **33** proved to be difficult, though the products **52** and **53** were eventually obtained from the acetoxy-substituted derivative. The former product, **52**, is structurally analogous to Tamoxifen and may have potential application if its yield can be significantly improved. Not so far carried out is the dehydration of the inden-1-ol **46** derived from the reaction of **9** with 3-butyn-1-ol. This would give a non-isomerisable compound with some of the structural elements of 4-hydroxyTamoxifen.

3.5 Experimental

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with phenylethyne.

The general reaction procedure for the coupling of alkynes with **9** and subsequent workup are outlined in the reaction below.

(a) <u>in benzene</u>

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.200 g, 0.476 mmol) was dissolved in benzene (10 ml) and purged with N_2. Phenylethyne (phenylacetylene) (0.064 g, 0.627 mmol) was then added and the solution refluxed under N_2 for 5 h. The solvent was then removed under reduced pressure and the residual oil extracted with CH_2Cl_2 and chromatographed (plc) eluting with CH_2Cl_2/pet. spirit (1:2) to yield three bands.

Band one (R_f = 0.87) gave $Mn_2(CO)_{10}$ (0.004 g, 0.010 mmol, 2%).

Band two (R_f = 0.66) gave a pale yellow oil (0.0346 g), identified as tri(carbonyl-κ*C*)[6-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-1,3,5-triphenylcyclohexadienyl-η-1,2,3,4,5]-manganese(I) **32** (0.050 mmol, 10%). Crystallisation from CH_2Cl_2 and pet. spirit gave fine pale yellow crystals, mp 107°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.95 (d, J = 8.6 Hz, 2H, ArH), 7.74 (d, J = 7.2 Hz, 2H, ArH), 7.24 (m, 24H, ArH), 6.86 (d, J = 8.6 Hz, 2H, ArH), 5.35 (s, 1H, ArH), 4.67 (s, 1H, H6), 4.39 (t, J = 7.2 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 2.17 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 0.89 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 132.1 (d), 131.0 (d), 129.4 (d), 129.0 (d), 128.8 (d), 127.9 (d), 127.6 (d) (C22-26, C42-46, C52-56, C2''-6''), 126.9 (d, C3'), 113.7 (d, C4', C6'), 96.7 (d, C3, C5), 73.8 (s), (C2, C4, C6), 60.3 (d, C1), 55.4 (q, OCH_3), 55.1 (d, CH), 27.2 (t, CH_2), 12.4 (q, CH_3).

IR (CH_2Cl_2) ν(CO) 2015(s, sh), 1935(s, br) cm^{-1}.

FABMS : 618, 448, 392, 380, <u>363</u>, 256.

Due to a possible calibration error the expected mass for each fragment should be 615 (M^+-3CO+H), 445 (M^+-$C_{17}H_{17}O$), 361 (M^+-$C_{17}H_{17}O$-3CO).

Band three (R_f = 0.37) gave [1R*,1'R*]-5-methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33a** (0.070 g, 0.196 mmol, 41%). Crystallisation from pet. spirit/CH_2Cl_2 gave fine white crystals, mp 91°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.68 (d, J = 6.9 Hz, 2H, H22, H26), 7.54 (d, J = 8.0 Hz, 1H, H7), 7.32 (m, 3H, H23, H24, H25), 6.96 (t, J = 7.3 Hz, 1H, H4''), 6.83 (t, J

= 7.3 Hz, 2H, H3'', H5''), 6.73 (d of d, J = 2.3, 8.0 Hz, 1H, H6), 6.60 (d, J = 2.3 Hz, 1H, H4), 6.38 (s, 1H, H3), 6.20 (d, J = 7.3 Hz, 2H, H2'', H6''), 3.81 (s, 3H, OCH_3), 3.20 (d of d, J = 2.6, 12.0 Hz, 1H, CH), 2.60 (m, 1H, CH_2), 2.13 (s, br, 1H, OH), 1.90 (m, 1H, CH_2), 0.71 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.5 (s, C5), 152.6 (s, C2), 144.4 (s, C1''), 139.8 (s), 139.3 (s), (C3a, C21), 135.4 (s, C7a), 128.4 (d, C2'', C6''), 128.3 (d, C25, C23), 127.8 (d, C24), 127.0 (d, C22, C26), 127.0 (d, C3'', C5''), 126.9 (d, C3), 126.3 (d, C4''), 124.4 (d, C7), 110.1 (d, C6), 107.6 (d, C4), 87.8 (s, C1), 55.5 (q, OCH_3), 54.8 (d, CH), 23.1 (t, CH_2), 12.9 (q, CH_3).

MS : <u>341</u> (M^+-CH_3), 313, 91.

(b) <u>in acetonitrile with Me_3NO</u>

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.541 g, 1.29 mmol) and trimethylamine oxide (0.145 g, 1.93 mmol) were dissolved in N_2-saturated actonitrile (5 ml) and stirred for 5 min with the solution turning a deep orange colour. Phenylethyne (1.0 ml, 9.1 mmol) was added and the solution stirred for a further 26 h. Chromatography with diethyl ether/pet. spirit (1:2) yielded only two bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.042 g, 0.164 mmol, 13%).

Band two gave a pale yellow oil (0.381 g), identified (^1H NMR ratio 1:2) as a diastereoisomeric mixture of 5-methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33a** and **33b** (1.07 mmol, 83%).

[1R*,1'S*]-5-Methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33b** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H, ArH), 7.73 (d of d, J = 1.8, 8.2 Hz, 1H, ArH), 7.37 (m, 7H, ArH), 6.86 (s, 1H, H3), 6.76 (d, J = 2.4 Hz, 1H, H4), 6.65 (d, J = 8.2 Hz, 1H, H7), 6.55 (d of d, J = 2.4, 8.2 Hz, 1H, H6), 3.79 (s, 3H, OCH_3), 3.31 (d of d, J = 3.1, 12.9 Hz, 1H, CH), 2.21 (s, br, 1H, OH), 1.56 (m, 1H, CH_2), 1.30 (m, 1H, CH_2), 0.52 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.3 (s, C5), 152.4 (s, C2), 143.9 (s, C1''), 139.8 (s), 138.2 (s), (C21, C3a), 135.2 (s, C7a), 131.3 (d), 128.6 (d), 127.8 (d), 127.5 (d) (C2''-C6'', C22-C26), 128.5 (d, C24), 128.1 (d, C3), 126.3 (d, C4''), 124.5 (d, C7), 109.7 (d, C6), 107.7 (d, C4), 87.4 (s, C1), 55.4 (q, OCH_3), 53.1 (d, CH), 20.4 (t, CH_2), 12.1 (q, CH_3).

MS : <u>341</u> (M^+-CH_3), 313, 91.

(c) in acetonitrile with Li_2PdCl_4

Li_2PdCl_4 (0.377 mmol) was dissolved in acetonitrile (10 ml) and purged with N_2 (see Chapter Four for method). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.156 g, 0.371 mmol) and phenylethyne (0.12 ml, 1.1 mmol) were added and the solution was stirred for 22 h. Chromatography with CH_2Cl_2/pet. spirit (2:3) yielded several bands, of which four major bands were removed.

Band one (R_f = 0.90) gave **9** (0.044 g, 28% recovered).

Band two (R_f = 0.87) gave an unknown brownish oil (0.043 g).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.40 (m), 4.66 (d, J = 6.7 Hz), 4.18 (d of d, J = 6.7, 19.0 Hz), 3.87 (d, J = 14.6 Hz), 3.50 (d, J = 19.0 Hz), 3.04 (d of d, J = 2.3, 14.6 Hz).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 162.5, 154.7, 154.5, 148.3, 146.6, 144.2, 139.2, 136.6, 135.1, 135.0, 131.5, 130.4, 130.0, 129.4, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.3, 127.1, 126.7, 126.4, 126.1, 125.8, 125.6, 125.3, 124.9, 120.9, 55.1, 42.7, 38.7.

Band three (R_f = 0.45) gave an unknown dark orange oil (0.016 g).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 130.9, 130.4, 129.6, 129.1, 128.6, 128.2, 128.1, 127.0.

Band four (R_f = 0.35) gave an unknown red oil (0.035 g).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.27 (m).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 128.3 (m).

Reaction of Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with diphenylethyne.

(a) in pet. spirit (60-80°C)

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.097 g, 0.231 mmol) was dissolved in N_2-saturated pet. spirit (10 ml), diphenylethyne (diphenylacetylene) (0.071 g, 0.413 mmol) was then added and the solution refluxed for 7 h. Chromatography with CH_2Cl_2/pet. spirit (2:3) yielded six bands.

Band one (R_f = 0.93) gave as $Mn_2(CO)_{10}$ (0.002 g, 2%).

Bands two (R_f = 0.84) and three (R_f = 0.53) give the starting materials diphenylethyne and 9 (0.020 g, 21% recovered) respectively.

Band four (R_f = 0.31) gave a yellow oil (0.002 g). This band was tentatively assigned tri(carbonyl-κ*C*)[6-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-1,2,3,4,5,6-hexaphenylcyclohexadienyl-η-1,2,3,4,5]-manganese(I) **34** (0.002 mmol, 1%), based on IR.

IR (pet. spirit) ν(CO) 2035 (s), 1968 (s), 1938 (s) cm^{-1}.

Band five (R_f = 0.20) gave an orange oil (0.002 g), identified as 5-methoxy-2,3-diphenylindenone **35** (0.006 mmol, 6%). Crystallisation from pet. spirit/CH_2Cl_2 gave orange needle crystals, mp 123-125°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 1H, ArH), 7.39 (m, 4H, ArH), 7.27 (m, 6H, ArH), 6.69 (m, 2H, ArH), 3.84 (s, 3H, OCH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 215 (s, C=O), 164.5 (s, C5), 153.2 (s, C3), 148.0 (s, C3a), 132.8 (s, C21, C31), 130.9 (s, C2), 130.0 (d), 128.8 (d), 128.6 (d), 128.1 (d), (C22-26, C32-36), 129.2 (d), 127.8 (d), (C24, C34), 124.9 (d, C7), 123.5 (s, C7a), 110.5 (d), 110.4 (d), (C4, C6), 55.8 (q, OCH_3).

IR (pet. spirit) ν(CO) 1703 (s, br) cm^{-1}.

MS : <u>312</u> (M^+), 281, 268, 239.

FABMS : <u>313</u> (M^++H), 312 (M^+).

Band six (R_f = 0.17) gave fine white crystals of [1R*,1'R*]-5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36a** (0.060 g, 0.139 mmol, 60%), mp 156°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.65 (m, 5H, ArH), 7.35 (m, 10H, ArH), 6.87 (d, J = 8.0 Hz, 1H, H7), 6.79 (d, J = 2.3 Hz, 1H, H4), 6.67 (d of d, J = 2.3, 8.0 Hz, 1H, H6), 3.77 (s, 3H, OCH_3), 3.11 (d of d, J = 3.3, 10.2 Hz, 1H, CH), 2.29 (s, 1H, OH), 1.79 (m, 1H, CH_2), 1.46 (m, 1H, CH_2), 0.60 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.1 (s, C5), 147.1 (s, C2), 145.3 (s, C1''), 140.7 (s), 138.8 (s), 138.1 (s), (C3a, C21, C31), 135.2 (s), 134.6 (s), (C3, C7a), 131.0 (d), 129.7 (d), 129.2 (d), (C32-C36, C2'', C6''), 128.8 (d, C34), 128.5 (d), 128.0 (d), 127.6 (d), (C22-C26, C3'', C5''), 127.4 (d, C24), 126.9 (d, C4''), 124.5 (d, C7), 110.0 (d, C6), 107.3 (d, C4), 87.3 (s, C-OH), 55.3 (q, OCH_3), 53.1 (d, CH), 20.4 (t, CH_2), 12.1 (q, CH_3).

MS : <u>312</u> (M^+-$HPhCHCH_2CH_3$), 281, 268, 239, 120.

Found : C, 85.82; H, 6.70%.

$C_{31}H_{28}O_2$ calcd : C, 86.08; H, 6.52%.

(b) in benzene

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.121 g, 0.284 mmol) was dissolved in N_2-saturated benzene (10 ml), diphenylethyne (0.056 g, 0.313 mmol) was then added and the solution refluxed for 5 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded five bands.

Band one ($R_f = 0.95$) gave $Mn_2(CO)_{10}$ (0.011 g, 9%).

Bands two ($R_f = 0.81$) and three ($R_f = 0.55$) give the starting materials diphenylethyne (0.034 g) and **9** (0.019 g, 16% recovered) respectively.

Band four ($R_f = 0.13$) gave 5-methoxy-2,3-diphenylindenone **35** (0.012 g, 0.385 mmol, 14%).

Band five ($R_f = 0.10$) gave white crystals of [1R*,1'S*]-5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36a** (0.100 g, 0.231 mmol, 80%).

(c) in acetonitrile

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.107 g, 0.254 mmol) and diphenylethyne (0.047 g, 0.262 mmol) were dissolved in acetonitrile (10 ml), purged with N_2 and the solution refluxed for 6 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded white crystals identified (^1H NMR ratio 2:1) as 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36a** and **36b** (0.110 g, 0.231 mmol, 100%), mp 90-96°C.

[1R*,1'S*]-5-Methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36b** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.59 (d of d, J = 2.3, 8.0 Hz, 1H, H6), 7.30 (m, 15H, ArH), 6.51 (d, J = 2.3 Hz, 1H, H4), 6.30 (d, J = 8.0 Hz, 1H, H7), 3.78 (s, 3H, OCH_3), 3.03 (d of d, J = 3.3, 10.1 Hz, 1H, CH), 2.69 (m, 1H, CH_2), 1.93 (m, 1H, CH_2), 0.73 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.6 (s, C5), 146.8 (s), 146.4 (s), (C2, C1''), 140.0 (s), 139.4 (s), 138.8 (s), (C3a, C21, C31), 135.0 (s), 134.8 (s), (C3, C7a), 130.0 (d), 128.8 (d), 128.5 (d), (C32-C36, C2'', C6''), 127.5 (d), 127.4 (d), 127.2 (d), (C22-C26, C3'', C5''), 127.3 (d), 127.25 (d), (C34, C24), 126.4 (d, C4''), 124.4 (d, C7), 110.4 (d, C4), 107.1 (d, C6), 88.1 (s, C-OH), 55.0 (q, OCH_3), 53.5 (d, CH), 23.6 (t, CH_2), 12.8 (q, CH_3).

GCMS : 312 (M^+-$HPhCHCH_2CH_3$), 281, 268, 239, 120.

(d) in acetonitrile with Me_3NO

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.226 g, 0.537 mmol) was dissolved in N_2-saturated actonitrile (2 ml). Trimethylamine oxide (0.044 g, 0.578 mmol) was dissolved in acetonitrile (1 ml), the solutions combined and stirred for 5 min. Diphenylethyne (0.198 g, 1.12 mmol) was then added and the solution stirred for a further 18.5 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded three bands.

Bands one (R_f = 0.95) and two (R_f = 0.63) give the starting materials diphenylethyne and **9** (0.016 g, 16% recovered) respectively.

Band three (R_f = 0.33) gave a colourless oil, identified as a diastereoisomeric mixture (2:3) of the 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ols **36a** and **36b** (0.202 g, 0.469 mmol, 87%).

(e) in acetonitrile with Li_2PdCl_4 under reflux

Li_2PdCl_4 (0.677 mmol) was dissolved in acetonitrile (10 ml), tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.287 g, 0.682 mmol) and diphenylethyne (0.248 g, 1.39 mmol) were then added and the solution refluxed for 6 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded several bands, with the removal of five major bands.

Band one (R_f = 0.91) gave diphenylethyne.

Band two (R_f = 0.58) gave a yellow oil (0.080 g), crystallisation from CH_2Cl_2/pet. spirit (vapour diffusion, 4°C) gave (^1H NMR ratio 2:1) both *E*- and *Z*-5-methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene **37** and **38** (0.193 mmol, 28%) as yellow crystals, mp 155-156°C.
Found : C, 89.71; H, 6.43%.
$C_{31}H_{26}O$ calcd : C, 89.82; H, 6.32%.
Isomer separation was achieved by recrystallisation using vapour diffusion (diethyl ether/pentane, 4°C) which yielded the *Z*-isomer, **38**, as long orange coloured plates (mp 183°C) and the *E*-isomer, **37**, as yellow chunks (mp 163°C). Both identified by X-ray crystallography.

E-5-Methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene **37** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.31 (m, 11H, ArH), 6.90 (m, 5H, ArH), 6.40 (d of d, J = 2.5, 8.6 Hz, 1H, H6), 5.98 (d, J = 8.6 Hz, 1H, H7), 3.73 (s, 3H, OCH_3), 2.32 (q, J = 7.4 Hz, 2H, CH_2), 0.76 (t, J = 7.4 Hz, 3H, CH_3).

5.98 (H7) has nOe to 7.25, 7.39 (ArH).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.9 (s, C5), 151.3 (s, C2), 144.1 (s, C3a), 143.2 (s, C1''), 142.3 (s), 142.0 (s), (C21, C31), 139.8 (s, C1), 138.8 (s, C8), 136.0 (s, C7a), 134.9 (s, C3), 130.2 (d), 129.6 (d), 128.7 (d), 128.2 (d), 127.9 (d), 127.8 (d), (C22-26, C32-36, C2''-C6''), 126.8 (d), 126.9 (d), 127.0 (d), (C24, C34, C4''), 124.6 (d, C7), 110.6 (d, C6), 105.8 (d, C4), 55.4 (q, OCH_3), 29.6 (t, CH_2), 12.5 (q, CH_3).

MS : <u>414</u> (M^+), 399, 385, 323, 278.

Z-5-Methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene **38** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 1H, H7), 7.20 (m, 11H, ArH), 6.77 (m, 6H, ArH), 3.85 (s, 3H, OMe), 3.24 (q, J = 7.5 Hz, 2H, CH_2), 1.29 (t, J = 7.5Hz, 3H, CH_3).

7.90 (H7) has nOe to 3.24 (CH_2) and 1.29 (CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 159.2 (s, C5), 151.6 (s, C2), 145.0 (s, C3a), 143.2 (s, C1''), 142.3 (s), 141.8 (s), (C21, C31), 140.7 (s, C1), 137.1 (s, C8), 135.8 (s, C7a), 135.2 (s, C3), 130.9 (d), 129.9 (d), 129.8 (d), 127.8 (d), 127.6 (d), 126.6 (d), (C22-26, C32-36, C2''-C6''), 126.8 (d), 126.1 (d), 125.0 (d), (C24, C34, C4''), 124.7 (d, C7), 110.1 (d, C6), 106.3 (d, C4), 55.5 (q, OCH_3), 31.6 (t, CH_2), 12.3 (q, CH_3).

MS : <u>414</u> (M^+), 399, 385, 323, 278.

Band four (R_f = 0.44) gave purple crystals of tetraphenylcyclopentadienone (0.014 g, 0.036 mmol, 5%), mp 209-212°C (lit.[110] 217-220°C).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.23 (m, 15H, ArH), 6.92 (m, 5H, ArH).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 201.0 (s, C=O), 154.5 (s, C3), 133.1 (s, C2), 131.5 (s, C21, C31), 130.2 (d), 129.4 (d), 128.1 (d), 128.0 (d), (C22-26, C32-36), 128.5 (d), 127.5 (d), (C24, C34).

MS : 384 (M^+), 356, 307, 278, <u>178</u> (M^+-C_2Ph_2CO).

Band five (R_f = 0.35) gave a pale yellow oil (0.069 g), identified as a diastereoisomeric mixture (2:1) of 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36a** and **36b** (0.159 mmol, 23%).

(f) <u>in acetonitrile with Li_2PdCl_4 at ambient temperature</u>

Li_2PdCl_4 (0.545 mmol) was dissolved in acetonitrile (10 ml), tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.224 g, 0.554 mmol) and diphenylethyne (0.407 g, 2.287 mmol) were then added and the solution stirred at ambient temperature for 21 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded four major bands.

Band one gave diphenylethyne.

Band two gave **9** (0.185 g, 83% recovered).

Band three gave tetraphenylcyclopentadienone (0.026 g, 0.067 mmol, 12%).

Band four gave a pale yellow oil (0.023 g), identified as a diastereoisomeric mixture (2:1) of 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36a** and **36b** (0.052 mmol, 9%).

(g) in acetonitrile with $NiBr_2(Ph_3P)_2$ under reflux

$NiBr_2(Ph_3P)_2$ (0.240 g, 0.367 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.165 g, 0.392 mmol) were dissolved in acetonitrile (8 ml). Diphenylethyne (0.195 g, 1.10 mmol) was added and the solution refluxed for 6 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded three bands.

Band one (R_f = 0.97) gave diphenylethyne (0.138 g).

Band two (R_f = 0.90) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.003 g, 0.012 mmol, 3%).

Band three (R_f = 0.76) gave a pale yellow oil (0.152 g), identified as a mixture of diastereoisomers (NMR ratio 2:1) of 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ols **36a** and **36b** (0.353 mmol, 90%).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with dimethyl acetylenedicarboxylate.

(a) in benzene

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.161 g, 0.383 mmol) was dissolved in N_2-saturated benzene (10 ml), dimethyl acetylenedicarboxylate (0.124 g, 0.873 mmol) was then added and the solution refluxed for 24 h. Chromatography with CH_2Cl_2/pet. spirit (1:2) gave no coupled product, only starting materials, **9** (0.009 g, 6% recovered).

(b) in acetonitrile with Me_3NO

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.152 g, 0.361 mmol) was dissolved in N_2-saturated acetonitrile (2 ml). Trimethylamine oxide (0.029 g, 0.382 mmol) was dissolved in acetonitrile (1 ml), the solutions combined and stirred for 5 min. Dimethyl acetylenedicarboxylate (0.09 ml, 0.733 mmol) was then added and the solution stirred for a further 18.5 h. Chromatography with CH_2Cl_2/pet. spirit (2:3) yielded four bands.

Bands one (R_f = 0.76) and two (R_f = 0.67) gave 9 (0.064 g, 40% recovered) and dimethyl acetylenedicarboxylate respectively.

Band three (R_f = 0.58) gave an unknown oil (0.005 g).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 3.89 (s), 3.75 (s), 3.71 (s).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 166.3, 164.0, 162.5, 119.7, 107.8, 93.8, 93.2, 70.7, 57.0, 53.0, 51.6.
MS : 366, 309, $\underline{278}$, 219, 187.

Band four (R_f = 0.33) gave an oil (0.077 g), identified (NMR ratio 1:2) as a diastereoisomeric mixture of 5-methoxy-2,3-di(methoxycarbonyl)-1-(1-phenylpropyl)-inden-1-ol **39a** and **39b** (0.195 mmol, 54%). Attempts to crystallise **39** proved unsuccessful.

[1R*,1'R*]-5-Methoxy-2,3-di(methoxycarbonyl)-1-(1-phenylpropyl)-inden-1-ol **39a** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 1H, H7), 7.19 (m, 5H, ArH), 7.07 (d of d, J = 2.3, 8.1 Hz, 1H, H6), 6.69 (d, J = 2.3 Hz, 1H, H4), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.22 (s, br, 1H, CH), 2.34 (m, 1H, CH_2), 1.76 (m, 1H, CH_2), 0.77 (t, J = 7.0 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 165.1 (s, C=O), 160.6 (s, C5), 143.4 (s, C1''), 141.4 (s), 140.6 (s), 139.7 (s), 138.4 (s), (C2, C3, C3a, C7a), 128.1 (d, C2'', C6''), 127.6 (d, C3'', C5''), 126.9 (d, C4''), 125.1 (d, C7), 114.4 (d, C6), 108.2 (d, C4), 86.8 (s, C-OH), 56.0 (q, OCH_3), 53.4 (q, OCH_3), 52.2 (d, CH), 52.0 (q, OCH_3), 22.4 (t, CH_2), 12.7 (q, CH_3).
MS : 338 (M^+-$C_2H_3O_2$), 279, $\underline{220}$, 191, 159.

[1R*,1'S*]-5-Methoxy-2,3-di(methoxycarbonyl)-1-(1-phenylpropyl)-inden-1-ol **39b** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.28 (m, 5H, ArH), 7.10 (m, 1H, H6), 6.72 (d, J = 2.3 Hz, 1H, H4), 6.62 (d, J = 8.0 Hz, 1H, H7), 3.93 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.36 (d, br, J = 10.8 Hz, 1H, CH), 1.76 (m, 1H, CH_2), 1.40 (m, 1H, CH_2), 0.69 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 164.4 (s, C=O), 160.4 (s, C5), 143.4 (s, C1''), 140.0 (s), 138.8 (s), 138.6 (s), 137.7 (s), (C2, C3, C3a, C7a), 130.5 (d, C2'', C6''), 127.6 (d, C3'', C5''), 127.0 (d, C4''), 125.4 (d, C7), 113.5 (d, C4), 108.7 (d, C6), 86.8 (s, C-OH), 55.5 (q, OCH_3), 54.2 (q, OCH_3), 52.4 (d, CH), 52.3 (q, OCH_3), 21.1 (t, CH_2), 12.2 (q, CH_3).

MS : 338(M^+-$C_2H_3O_2$), 279, $\underline{220}$, 191, 159.

GCMS also gave a third minor peak (*ca.* <5%) corresponding to 5-methoxy-2,3-di(methoxycarbonyl)indenone **40**.

MS : 276 (M^+), $\underline{245}$, 217, 186, 158, 116.

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9with trimethylsilylethyne.

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.17 g, 0.404 mmol) was dissolved in benzene (10 ml). Trimethylsilylethyne (0.098 g, 1.00 mmol) added and the solution refluxed for 18 h. Chromatography with CH_2Cl_2/pet. spirit (2:3) yielded five bands.

Band one (R_f = 0.93) gave yellow crystals of $Mn_2(CO)_{10}$ (0.025 g, 0.064 mmol, 16%).

Band two (R_f = 0.65) gave a yellow oil (0.002g), which is tentatively assigned as tri(carbonyl-κ*C*)[6-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-1,3,5-trimethylsilylcyclohexadienyl-η-1,2,3,4,5]-manganese(I) **41** (0.003 mmol, 1%).

IR (CH_2Cl_2) ν(CO) 2017 (s), 1939 (s, br) cm^{-1}.

Band three (R_f = 0.55) gave **9** (0.019 g, 11% recovered).

Band four gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.066 g, 0.266 mmol, 65%).

Band five (R_f = 0.45) gave 5-methoxy-1-(1-phenylpropyl)-2-trimethylsilyl-inden-1-ol **42a** as a yellow oil (0.014 g, 0.040 mmol, 10%). Attempts to crystallise **42a** proved unsuccessful.

5-Methoxy-1-(1-phenylpropyl)-2-trimethylsilylinden-1-ol **42a** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m, 6H, ArH), 6.88 (d of d, J = 2.3, 8.Hz, 1H, H6), 6.72 (s, 1H, H2), 6.52 (d, J = 2.Hz, 1H, H4), 3.82 (s, 3H, OCH_3), 3.28 (d of d, J = 3.3, 10.8 Hz, 1H, CH), 2.18 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 0.65 (t, J = 7.2 Hz, 3H, CH_3), 0.35 (s, 9H, $SiCH_3$).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.2 (s, C5), 158.3 (s, C2), 145.3 (s, C1''), 141.7 (d, C3), 141.4 (s, C3a), 138.1 (s, C7a), 131.2 (d), 127.7 (d), (C2''-C6''), 127.0 (d, C4''), 124.5 (d, C7), 109.9 (d), 107.3 (d), (C4, C6), 90.7 (s, C-OH), 55.4 (q, OCH_3), 53.0 (d, CH), 19.9 (t, CH_2), 11.8 (q, CH_3), -0.3 (q, $SiCH_3$).

MS : 352 (M^+), 337, 323, 307, 278, 233, 218.

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with 2-hexyne.

(a) in benzene

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.232 g, 0.552 mmol) was dissolved in N_2-saturated benzene (10 ml). 2-Hexyne (0.068 g, 0.822 mmol) was added and the solution refluxed for 24 h. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded two bands.

Band one (R_f = 0.90) gave $Mn_2(CO)_{10}$ (0.019 g, 9%).

Band two (R_f = 0.35) gave a yellow oil (0.153 g), identified as a diastereoisomeric mixture (NMR ratio 1:2) of 5-methoxy-2-methyl-1-(1-phenylpropyl)-3-propyl-inden-1-ol **43a** and **43b** (0.455 mmol, 82%). Crystallisation from CH_2Cl_2/pet. spirit (1:15) gave fine yellow crystals of **43b**, mp 89-91°C.

[1R*,1'S*]-5-Methoxy-2-methyl-1-(1-phenylpropyl)-3-propyl-inden-1-ol **43b** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.33 (m, 5H, ArH), 6.67 (d, J = 2.1 Hz, 1H, H4), 6.54 (d, J = 8.2 Hz, 1H, H7), 6.48 (m, 1H, H6), 3.80 (s, 3H, OCH_3), 3.12 (d of d, J = 2.9, 9.1 Hz, 1H, CH), 2.45 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 1.75 (m, 2H, CH_2), 1.45 (m, 1H, CH_2), 1.35 (m, 1H, CH_2), 1.08 (t, J = 7.3 Hz, 3H, CH_3), 0.68 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.3 (s, C5), 148.5 (s, C3), 147.3 (s, C3a), 140.3 (s, C1"), 138.5 (s, C7a), 133.9 (s, C2), 131.1 (d, C2", C6"), 127.6 (d, C3", C5"), 126.9 (d, C4"), 123.9 (d, C7), 108.2 (d, C4), 105.3 (d, C6), 86.5 (s, C-OH), 55.4 (q, OCH_3), 52.7 (d, CH), 27.9 (t, CH_2), 22.5 (t, CH_2), 20.4 (t, CH_2), 15.0 (q, CH_3), 12.2 (q, CH_3), 10.5 (q, CH_3).

MS : 336 (M^+), 318, 289, 261, 246, 233, 217, 188, 145.

[1R*,1'R*]-5-Methoxy-2-methyl-1-(1-phenylpropyl)-3-propyl-inden-1-ol **43a** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.46 (d, J = 8.1 Hz, 1H, H7), 7.33 (m, 5H, ArH), 6.54 (m, 1H, H6), 6.48 (d, J = 2.1 Hz, 1H, H4), 3.84 (s, 3H, OCH_3), 3.03 (d of d, J = 2.3, 9.4 Hz, 1H, CH), 2.55 (m, 1H, CH_2), 2.25 (m, 2H, CH_2), 1.85 (m, 1H, CH_2), 1.60 (m, 2H, CH_2), 1.56 (s, 3H, CH_3), 0.98 (t, J = 7.3 Hz, 3H, CH_3), 0.80 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.6 (s, C5), 149.0 (s, C3), 147.8 (s, C3a), 144.8 (s, C1"), 138.2 (s, C7a), 132.8 (s, C2), 128.1 (d, C2", C6"), 126.9 (d, C3", C5"), 126.1 (d, C4"), 123.7 (d, C7), 108.5 (d, C6), 105.0 (d, C4), 87.6 (s, C-OH), 55.5 (q, OCH_3), 54.6 (d, CH), 28.2 (t, CH_2), 23.6 (t, CH_2), 23.0 (t, CH_2), 14.8 (q, CH_3), 13.1 (q, CH_3), 9.9 (q, CH_3).

MS : 336 (M^+), 318, 289, 261, 246, 233, 217, 188, 145.

GCMS shows a minor peak (*ca.* <5%) of 5-methoxy-2-methyl-3-propylindenone **44**.

MS : 216 (M^+), 201, 187, 159, 144.

(b) in acetonitrile with Me_3NO

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.252 g, 0.600 mmol) was dissolved in N_2-saturated actonitrile (2 ml). Trimethylamine oxide (0.075 g, 0.890 mmol) was dissolved in acetonitrile (1 ml), the solutions combined and stirred for 5 min. 2-Hexyne (0.20 ml, 0.169 mmol) was then added and the solution stirred for 22 h. Chromatography with CH_2Cl_2/pet. spirit (2:3) yielded two bands.

Band one (R_f = 0.80) gave **9** (0.025 g, 10% recovered).

Band two (R_f = 0.31) gave a yellow oil (0.177 g), identified as a mixture (NMR ratio 1:2:1) of 5-methoxy-2-methyl-1-(1-phenylpropyl)-3-propyl-inden-1-ol **43a** and **43b** and 5-methoxy-2-methyl-1-(1-phenylpropyl)-3-propylinden-1-ol **45** (0.528 mmol, 88%).

[1R*,1'R*]-5-Methoxy-2-methyl-1-(1-phenylpropyl)-3-propylinden-1-ol **45** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 1H, H7), 7.32 (m, 5H, ArH), 6.98 (m, 1H, H6), 6.57 (d, J = 2.2 Hz, 1H, H4), 3.79 (s, 3H, OCH_3), 3.65 (d of d, J = 2.1, 8.7 Hz, 1H, CH), 2.42 (m, 2H, CH_2), 2.14 (m, 1H, CH_2), 1.97 (s, 3H, CH_3), 1.75 (m, 2H, CH_2), 1.45 (m, 1H, CH_2), 0.99 (t, J = 7.3 Hz, 3H, CH_3), 0.71 (t, J = 7.3 Hz, 3H, CH_3).

0.97 (2-CH_3) nOe to 2.42.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.2 (s, C5), 147.2 (s, C3), 146.7 (s, C3a), 138.6 (C1''), 137.5 (s, C7a), 131.0 (d), 127.6 (d), (C2''-C6''), 127.3 (s, C2), 127.2 (d, C4''), 124.1 (d, C7), 107.6 (d, C6), 105.7 (d, C4), 85.6 (s, C-OH), 55.4 (q, OCH_3), 52.9 (d, CH), 27.3 (t, CH_2), 21.7 (t, CH_2), 20.6 (t, CH_2), 14.5 (q, CH_3), 12.4 (q, CH_3), 10.0 (q, CH_3).

MS : 336 (M^+), 318, 289, 261, 246, 233, 217, 188, 145.

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with 3-butyn-1-ol.

(a) in benzene

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.207 g, 0.492 mmol) was dissolved in benzene (8 ml). 3-Butyn-1-ol (0.20 ml 2.6 mmol) was added and the solution refluxed for 3 h. Chromatography with diethyl ether/pet. spirit (2:3) yielded two bands.

Band one (R_f = 0.80) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.018 g, 0.071 mmol, 14%).

Band two (R_f = 0.20) gave a pale yellow oil (0.104 g), identified as a diastereoisomeric mixture (NMR ratio 1:3) of 2-(2-hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46a** and **46b** (0.321 mmol, 65%). Crystallisation from pet. spirit/diethyl ether gave fine white crystals, mp 119-120°C.

Found : C, 77.70; H, 7.26%.

$C_{21}H_{24}O_3$ calcd : C, 77.75; H, 7.46%.

[1R*,1'R*]-2-(2-Hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46a** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 1H, H7), 7.30 (m, 2H, H3'', H5''), 7.03 (t, J = 7.0 Hz, 1H, C4''), 6.65 (d of d, J = 2.4 Hz, 8.1 Hz, 1H, H6), 6.58 (d, J = 6.9 Hz, 2H, H2'', H6''), 6.46 (d, J = 2.4 Hz, 1H, H4), 5.87 (s, 1H, H3), 3.79

(s, 3H, OCH_3), 3.76 (m, 1H, CH_2OH), 3.56 (m, 1H, CH_2OH), 2.93 (d of d, J = 2.3, 11.7 Hz, 1H, CH), 2.37 (t, J = 5.5 Hz, 2H, CH_2), 2.50 (m, 1H, CH_2), 1.70 (m, 1H, CH_2), 0.75 (t, J = 7.3 Hz, 3H, CH_3).

5.87 (H3) nOe to 6.46 (H4) and 2.37 (CH_2).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.4 (s, C5), 154.1 (s, C2), 145.1 (s, C1''), 140.0 (s, C3a), 138.7 (s, C7a), 128.1 (d), 127.5 (d), (C2''-C6''), 127.3 (d, C3), 126.4 (d, C4''), 124.5 (d, C7), 109.2 (d, C4), 107.1 (d, C6), 86.3 (s, C-OH), 62.23 (t, CH_2OH), 55.39 (q, OCH_3), 55.0 (d, CH), 31.1 (t, CH_2), 23.9 (t, CH_2), 12.9 (q, CH_3).

MS : 204 (M^+-$HPhCHCH_2CH_3$), 175, <u>174</u>, 173, 141, 131.

[1R*,1'R*]-2-(2-Hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46b** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m, 4H, ArH), 6.98 (t, J = 7.9 Hz, 1H, H4''), 6.64 (d, J = 2.3 Hz, 1H, H4), 6.52 (d, J = 8.2 Hz, 1H, H7), 6.45 (d of d, J = 2.3, 8.2 Hz, 1H, H6), 6.34 (s, 1H, H3), 3.90 (m, 1H, CH_2OH), 3.76 (m, 1H, CH_2OH), 3.74 (s, 3H, OCH_3), 3.07 (d of d, J = 3.1, 12.2 Hz, 1H, CH), 2.60 (t, J = 5.4 Hz, 2H, CH_2), 1.48 (m, 1H, CH_2), 1.29 (m, 1H, CH_2), 0.67 (t, J = 7.3 Hz, CH_3).

6.34 (H3) nOe to 6.64 (H4) and 2.60 (CH_2).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.2 (s, C5), 153.6 (s, C2), 144.5 (s, C1''), 138.4 (s), 137.9 (s), (C3a, C7a), 131.0 (d), 127.7 (d), (C2''-C6''), 128.7 (d, C3), 127.0 (d, C4''), 124.6 (d, C7), 108.8 (d, C6), 107.3 (d, C4), 85.9 (s, C-OH), 62.16 (t, CH_2OH), 55.36 (q, OCH_3), 52.8 (d, CH), 31.6 (t, CH_2), 20.2 (t, CH_2), 12.2 (q, CH_3).

MS : 204 (M^+-$HPhCHCH_2CH_3$), 175, <u>174</u>, 173, 141, 131.

(b) <u>in acetonitrile</u>

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.164 g, 0.390 mmol) was dissolved in acetonitrile (10 ml). 3-Butyn-1-ol (0.40 ml 5.2 mmol) was added and the solution refluxed for 5 h. Chromatography with diethyl ether/pet. spirit (2:3) gave a pale yellow oil (0.060 g), identified as a diastereoisomeric mixture (NMR ratio 2:3) of 2-(2-hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46a** and **46b** (0.184 mmol, 47%).

(c) <u>in acetonitrile with Me_3NO</u>

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.290 g, 0.690 mmol) was dissolved in acetonitrile (5 ml) and purged with N_2. Trimethylamine *N*-oxide (0.090 g, 1.16 mmol) was added and the solution stirred for 5 min. 3-Butyn-1-ol (0.20 ml 2.6 mmol) was added and the solution stirred for a further 45 h. Chromatography with diethyl ether/pet. spirit (2:3) yielded two bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.009 g, 0.035 mmol, 5%).

Band two gave a pale yellow oil (0.142 g), identified as a diastereoisomeric mixture (NMR ratio 1:2) of 2-(2-hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46a** and **46b** , 0.436 mmol, 63%).

Preparation of 5-methoxy-2,3-diphenylindenone 35 from 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol 36.

2,3-Diphenyl-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **36** (0.065 g, 0.150 mmol) was dissolved in benzene (10 ml) and refluxed (in darkness) for four days. Chromatography with ethyl acetate/pet. spirit (3:7) yielded two bands.

Band one ($R_f = 0.90$) gave 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36** (0.055 g, 85% recovered).

Band two ($R_f = 0.80$) gave 5-methoxy-2,3-diphenyl-indenone **35** (0.004 g, 0.013 mmol, 9%).

Attempted Dehydration of 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol 36.

(a) in acetonitrile with HCl

5-Methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36** (0.023 g, 0.054 mmol) was dissolved in acetonitrile (10 ml). Concentrated hydrochloric acid (1 drop) was added and the solution stirred for 66 h. $NaHCO_3$ (0.087 g) was added and the solvent removed under vacuum. Chromatography with CH_2Cl_2/pet. spirit (1:1) yielded two bands.

Band one ($R_f = 0.60$) gave a yellow oil (0.016 g), identified (^1H NMR ratio 2:1) as a mixture of the *E*- and *Z*-2,3-diphenyl-5-methoxy-1-(1-phenylpropylidene)-indene **37** and **38** respectively (0.038 mmol, 70%).

Band two ($R_f = 0.14$) gave **36** (0.008 g, 34 % recovered).

(b) in ethanol with H_2SO_4

5-Methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36** (0.078 g, 0.182 mmol) was dissolved in a solution containing ethanol (12 ml), dioxan (12 ml) and H_2SO_4 (4 mol l^{-1}, 12 ml) and stirred for 65 h. Water (50 ml) was added and the solution extracted with ether (3 x 30 ml) and dried ($MgSO_4$). Chromatography (plc) with CH_2Cl_2/pet. spirit (1:3) yielded three bands.

Band one (R_f = 0.67) gave a colourless oil (0.049 g), identified as a diastereoisomeric mixture (2:1 ratio ^{1}H NMR) of 1-ethoxy-5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-2-indene **47a** and **47b** (0.106 mmol, 58%). Attempts to crystallise **47** proved unsuccessful.

[1R*,1'R*]-1-Ethoxy-5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-2-indene **47a** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 1H, H7), 7.26 (m, 11H, ArH), 6.85 (m, 4H, ArH), 6.49 (d, J = 2.3 Hz, 1H, H4), 6.22 (d, J = 8.3 Hz, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.52 (q, J = 7.0 Hz, 1H, OCH_2), 3.10 (q, J = 7.0 Hz, 1H, OCH_2), 3.10 (d of d, J = 2.7, 11.7 Hz, 1H, CH), 2.80 (m, 1H, CH_2), 2.00 (m, 1H, CH_2), 1.34 (t, J = 7.0 Hz, 3H, CH_3), 0.76 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.4 (s, C5), 147.3 (s, C2), 143.5 (s, C1''), 141.7 (s), 139.4 (s), (C21, C31), 135.6 (s), 135.3 (s), 134.9 (s), (C3, C3a, C7a), 129.6 (d), 128.8 (d), 128.6 (d), 127.5 (d), 126.7 (d), (C2''-C6'', C22-26, C32-36), 127.1 (d), 126.7 (d), 126.2 (d), (C4'', C24, C34), 124.9 (d, C7), 110.3 (d, C6), 106.7 (d, C4), 93.3 (s, C1), 58.9 (t, OCH_2), 55.3 (d, CH), 55.2 (q, OCH_3), 23.6 (t, CH_2), 15.6 (q, CH_3), 12.8 (q, CH_3).
MS : 460 (M^+), 386, 341, 313, 281.

[1R*,1'S*]-1-Ethoxy-5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-2-indene **47b** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.25 (m, 12H, ArH), 6.82 (m, 5H, ArH), 3.77 (s, 3H, OCH_3), 3.50 (q, J = 7.0 Hz, 1H, OCH_2), 3.30 (d of d, J = 2.7, 9.6 Hz, 1H, CH), 3.10 (q, J = 7.0 Hz, 1H, OCH_2), 1.85 (m, 1H, CH_2), 1.41 (m, 1H, CH_2), 1.21 (t, J = 7.0 Hz, 3H, CH_3), 0.54 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.1 (s, C5), 145.9 (s, C2), 143.8 (s, C1''), 142.5 (s), 138.9 (s), (C21, C31), 135.7 (s), 135.5 (s), 135.4 (s), (C3, C3a, C7a), 131.2 (d), 129.2 (d), 128.7 (d), 128.6 (d), 127.9 (d), 127.2 (d), (C2''-C6'', C22-26, C32-36), 126.1 (d, C4''), 125.2 (d, C7), 110.0 (d, C4), 106.7 (d, C5), 92.9 (s, C1), 58.4 (t, OCH_2), 55.3 (q, OCH_3), 53.6 (d, CH), 20.1 (t, CH_2), 15.4 (q, CH_3), 12.2 (q, CH_3).
MS : 460 (M^+), 386, 341, 313, 281.

Band two (R_f = 0.52) gave a colourless oil (0.009 g), tentatively assigned as 1-ethoxy-6-methoxy-1,2-diphenyl-3-(1-phenylpropyl)-2-indene **48** (0.020 mmol, 11%).
^{1}H NMR (90 MHz) ($CDCl_3$) δ 7.16 (m, 11H, ArH), 6.69 (m, 7H, ArH), 3.70 (s, 3H, OCH_3), 3.43 (m, 2H, CH_2), 2.21 (m, 4H, CH_2), 0.87 (t, J = 7.2 Hz, 3H, CH_3).
MS : 460 (M^+), 343, 341, 313, 297.

Band three (R_f = 0.33) gave **36** (0.014 g, 18% recovered).

Attempted dehydration of 5-methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol 33.

(a) in THF with 4-toluenesulphonic acid

5-Methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33** (0.350 g, 0.983 mmol) and 4-toluenesulphonic acid hydrate (0.025 g, 0.132 mmol) were dissolved in THF (5 ml) and stirred for 3 days. Solvent was removed under vacuum. Chromatography with diethyl ether/pet. spirit (1:19) yielded only **33** (0.343 g, 98% recovered).

(b) in THF with H_2SO_4

5-Methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33** (0.094 g, 0.264 mmol) was dissolved in THF (8 ml). Concentrated H_2SO_4 (98%, 4 drops) was added and the solution stirred for 3 days. Chromatography with diethyl ether/pet. spirit (1:9) yielded two bands.

Band one gave an unknown red oil (0.005 g).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.36 (m, 10H), 7.11 (d, J = 2.4 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.64 (d of d, J = 2.4, 8.1 Hz, 1H), 4.30 (d of d, J = 5.7, 9.7 Hz, 1H), 3.79 (s, 3H), 2.27 (m, 1H), 2.13 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 160.5 (s), 141.0 (s), 131.5 (s), 129.6 (d), 128.8 (d), 128.4 (d), 127.8 (d), 127.5 (d), 126.8 (d), 123.5 (d), 116.4 (d), 110.1 (d), 55.7 (q), 44.6 (d), 24.8 (t), 12.6 (q).

Band two gave **33** (0.062 g, 66% recovered).

(c) in acetonitrile with HCl

5-Methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33** (0.280 g, 0.787 mmol) was dissolved in acetonitrile (15 ml) and concentrated HCl (1 drop) added and the solution stirred for 20 h. $NaHCO_3$ was added and the solution volume reduced. Chromatography with diethyl ether/pet. spirit (1:9) yielded two bands.

Band one (R_f = 0.78) gave a pale yellow oil (0.224 g), identified as a diastereoisomeric mixture (NMR 1:1) of 6-methoxy-2-phenyl-3-(1-phenylpropyl)-inden-1-ol **49** (0.630 mmol, 81%). Crystallisation from pet.spirit/diethyl ether gave whitish crystals, mp 111-114°C.

Major isomer:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.33 (m, 10H, ArH), 7.23 (d, J = 2.2 Hz, 1H, H7), 7.17 (d, J = 8.4 Hz, 1H, H4), 6.77 (d of d, J = 2.2, 8.4 Hz, 1H, H5), 5.61 (s, 1H, H1), 4.19 (m, 1H, CH), 3.84 (s, 3H, OCH_3), 2.25 (m, 2H, CH_2), 1.29 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.8 (s, C6), 146.3 (s, C3), 143.1 (s), 141.7 (s), (C21, C1'), 142.1 (s, C1''), 135.2 (s, C2), 134.5 (s, C3a), 129.7 (d), 128.7 (d), 128.6 (d), 127.7 (d), (C22-C26, C2''-C6''), 127.8 (d, C4'), 126.3 (d, C4''), 122.9 (d, C4), 113.8 (d, C5), 111.1 (d, C7), 62.0 (d, C1), 55.6 (q, OCH_3), 43.9 (d, CH), 24.6 (t, CH_2), 13.0 (q, CH_3).

MS : 340 (M^+-CH_3), 221, 207, 178.

Minor isomer:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.33 (m, 10 H, ArH), 7.28 (d, J = 2.0 Hz, 1H, H7), 7.07 (d, J = 8.4 Hz, 1H, H4), 6.75 (d of d, J = 2.0, 8.4 Hz, 1H, H5), 5.77 (s, 1H, H1), 4.25 (m, 1H, CH), 3.86 (s, 3H, OCH_3), 2.19 (m, 2H, CH_2), 0.85 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.9 (s, C6), 146.1 (s, C3), 143.3 (s), 141.9 (s), (C21, C1'), 142.7 (s, C1''), 134.9 (s, C2), 134.5 (s, C3a), 129.2 (d), 128.5 (d), 128.4 (d), 127.6 (d), (C22-C26, C2''-C6''), 127.8 (d, C4'), 126.5 (d, C4''), 123.2 (d, C4), 113.8 (d, C5), 111.2 (d, C7), 61.3 (d, C1), 55.6 (q, OCH_3), 44.1 (d, CH), 25.4 (t, CH_2), 12.7 (q, CH_3).

MS : 338 (M^+-H_2O), 277, 245, 119.

Band two (R_f = 0.28) gave **33** (0.054 g, 19% recovered).

Attempted dehydration of 2-(2-hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol 46.

2-(2-Hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46** (0.142 g, 0.436 mmol) was dissolved in acetonitrile (6 ml). Concentrated H_2SO_4 (98%, 1 drop) was added and the solution stirred for 18 h. Chromatography eluting with diethyl ether/pet. spirit (3:7 and 1:1) proved unsuccessful.

Acetylation of 5-methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol 33.

(a) in pyridine

5-Methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33** (0.110 g, 0.309 mmol) and acetic anhydride (0.05 ml, 0.530 mmol) were dissolved in pyridine (2 ml) and stirred for 42 h. The solution was poured into HCl (2 mol l^{-1}, 50 ml), extracted with ether (30 ml) and washed with further HCl (2 mol l^{-1}, 50 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (1:4) yielded **33** (0.053 g, 48% recovered).

(b) in pyridine with 4-dimethyaminopyridine

5-Methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33** (0.199 g, 0.557 mmol), 4-dimethylaminopyridine (0.045 g, 0.368 mmol) and acetic anhydride (0.05 ml, 0.530 mmol) were dissolved in pyridine (3 ml) and the solution stirred for 70 h. The solution was poured into HCl (2 mol l^{-1}, 50 ml), extracted with ether (30 ml) and washed with further HCl (2 mol l^{-1}, 2 x 50 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (1:6) yielded three bands.

Band one gave **33** (0.022 g, 11% recovered).

Band two gave a yellow oil (0.088 g), identified as a mixture (NMR 4:3) of 1-acetoxy-5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene **50a** and **50b** (0.221 mmol, 40%). Attempts to crystallise **50** proved unsuccessful.

[1R*,1'R*]-1-Acetoxy-5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene **50a** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.53 (d, J = 7.1 Hz, 2H, ArH), 7.38 (m, 4H, ArH), 7.03 (t, J = 7.3 Hz, 1H, H4''), 6.87 (t, J = 7.8 Hz, 2H, H3'', H5''), 6.78 (d of d, J = 2.4, 8.2 Hz, 1H, H6), 6.69 (d, J = 2.4 Hz, 1H, H4), 6.65 (s, 1H, H3), 6.18 (d, J = 7.2 Hz, 2H, H2'', H6''), 3.84 (s, 3H, OCH_3), 3.36 (d of d, J = 2.6, 11.8 Hz, 1H, CH), 2.59 (m, 1H, CH_2), 2.15 (s, 3H, $COCH_3$), 1.99 (m, 1H, CH_2), 0.77 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 168.2 (s, C=O), 160.4 (s, C5), 148.4 (s, C2), 144.8 (s, C1''), 137.6 (s), 136.1 (s), (C21, C3a), 134.4 (s, C7a), 131.5 (d), 128.6 (d), 126.9 (d), 126.1 (d), (C2''-C6'', C22-C26), 127.7 (d), 127.1 (d) (C3, C24), 126.6 (d, C4''),

123.2 (d, C7), 110.3 (d, C6), 107.7 (d, C4), 91.80 (s, C1), 55.4 (q, OCH_3), 54.4 (d, CH), 23.2 (t, CH_2), 22.0 (q, $COCH_3$), 12.9 (q, CH_3).
MS : 398 (M^+), 355, 338, 237.

[1R*,1'S*]-1-Acetoxy-5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene **50b** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 2H, ArH), 7.35 (m, 11H, ArH), 7.13 (s, 1H, H3), 6.84 (d, J = 2.3 Hz, 1H, H4), 6.56 (d of d, J = 2.3, 8.2 Hz, 1H, H6), 6.46 (d, J = 8.2 Hz, 1H, H7), 3.81 (s, 3H, OCH_3), 3.46 (d of d, J = 3.2, 12.3 Hz, 1H, CH), 1.99 (s, 3H, $COCH_3$), 1.62 (m, 1H, CH_2), 1.26 (m, 1H, CH_2), 0.53 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 168.0 (s, C=O), 160.2 (s, C5), 148.2 (s, C2), 144.0 (s, C1''), 137.7 (s), 136.0 (s), (C21, C3a), 134.35 (s, C7a), 129.0 (d, C3), 128.8 (d), 128.6 (d), 127.1 (d), 126.8 (d), (C2''-C6'', C22-C26), 128.0 (d, C24), 126.8 (d, C4''), 124.0 (d, C7), 109.8 (d, C6), 107.7 (d, C4), 91.83 (s, C1), 55.3 (q, OCH_3), 52.5 (d, CH), 21.8 (q, $COCH_3$), 19.4 (q, CH_2), 12.0 (q, CH_3).
MS : 398 (M^+), 355, 237.

Acetylation of 2-(2-hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol 46.

2-(2-Hydroxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **46** (0.142 g, 0.436 mmol) and 4-dimethylaminopyridine (0.045 g, 0.368 mmol) were dissolved in pyridine (2 ml). Acetic anhydride (0.05 ml, 0.530 mmol) was added and the solution stirred for 43 h. The solution was poured into HCl (2 mol l^{-1}, 20 ml), extracted with ether (30 ml) and washed with HCl (2 mol l^{-1}, 3 x 30 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (3:7) gave (R_f = 0.39) a yellow oil (0.109 g), identified as a diastereoisomeric mixture (NMR ratio 4:3) of 1-acetoxy-2-(2-acetoxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **51** (0.266 mmol, 61%). Attempts to crystallise **51** proved unsuccessful.

[1R*,1'R*]-1-Acetoxy-2-(2-acetoxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **51a** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m, 4H, ArH), 6.68 (d of d, J = 2.2, 8.4 Hz, 1H, H6), 6.59 (d, J = 2.2 Hz, 1H, H4), 6.49 (m, 2H, H2'', H6''), 6.01 (s, 1H, H3), 4.20 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.01 (d of d, J = 2.3, 11.5 Hz, 1H, CH), 2.56 (m, 2H, CH_2), 2.40 (m, 1H, CH_2), 2.06 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 1.82 (m, 1H, CH_2), 0.76 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 171.0 (s, C=O), 168.1 (s, C=O), 160.4 (s, C5), 148.0 (s, C2), 145.6 (s, C1''), 138.1 (s), 134.7 (s), (C3a, C7a), 128.3 (d), 127.2 (d), (C2''-C6''), 127.5 (d, C3), 126.9 (d, C4''), 123.2 (d, C7), 109.4 (d, C6), 107.4 (d, C4), 92.0 (s, C1), 62.1 (t, OCH_2), 55.4 (q, OCH_3), 53.5 (d, CH), 26.1 (t, CH_2), 23.9 (t, CH_2), 21.7 (q, $COCH_3$), 21.0 (q, $COCH_3$), 12.9 (q, CH_3).
MS : 348 (M^+-CH_3OH), 306, 288, 259, 187.

[1R*,1'S*]-1-Acetoxy-2-(2-acetoxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **51b** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.33-6.97 (m, br, 8H, ArH), 6.69 (d, J = 2.4 Hz, 1H, H4), 4.40 (t, J = 6.9 Hz, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.08 (d of d, J = 2.9, 12.3 Hz, 1H, CH), 2.45 (m, 2H, CH_2), 2.08 (s, 3H, $COCH_3$), 1.92 (s, 3H, $COCH_3$), 1.65 (m, 1H, CH_2), 1.30 (m, 1H, CH_2), 0.66 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 171.0 (s, C=O), 167.9 (s, C=O), 160.2 (s, C5), 148.0 (s, C2), 144.7 (s, C1''), 138.1 (s), 134.8 (s), (C3a, C7a), 131.0 (d), 127.5 (d), (C2''-C6''), 128.0 (d, C3), 126.8 (d, C4''), 124.0 (d, C7), 108.9 (d, C6), 107.4 (d, C4), 91.8 (s, C1), 62.2 (t, OCH_2), 55.3 (q, OCH_3), 52.4 (d, CH), 26.4 (t, CH_2), 21.5 (q, $COCH_3$), 21.0 (q, $COCH_3$), 19.6 (t, CH_2), 12.1 (q, CH_3).
MS : 348 (M^+-CH_3OH), 306, 288, 259, 187.

Reaction of 1-acetoxy-5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene 50 with 4-toluenesulphonic acid.

1-Acetoxy-5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene **50** (0.139 g, 0.349 mmol) and 4-toluenesulphonic acid hydrate (0.010 g, 0.053 mmol) were dissolved in THF (10 ml) and stirred for 12 h. Chromatography with diethyl ether/pet. spirit (1:6) yielded three bands.

Band one (R_f = 0.96) gave a yellow oil (0.008 g), identified (NMR ratio 4:1) as a mixture of the *E*- and *Z*-5-methoxy-2-phenyl-1-(1-phenylpropylidene)-indene **52** and **53** respectively (0.024 mmol, 7%). Attempts to separate by further chromatography and crystallisation proved unsuccessful.

E-5-Methoxy-2-phenyl-1-(1-phenylpropylidene)-indene **52** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.41 (m, 10H, ArH), 6.77 (d, J = 2.5 Hz, 1H, H4), 6.69 (s, 1H, H3), 6.30 (d of d, J = 2.5, 8.5 Hz, 1H, H6), 5.85 (d, J = 8.5 Hz, 1H, H7), 3.75 (s, 3H, OCH_3), 2.35 (q, J = 7.4 Hz, 2H, CH_2), 0.75 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 159.0 (s, C5), 151.2 (s, C2), 145.7 (s, C3a), 143.3 (s), 141.9 (s), (C1'', C21), 138.8 (s, C8), 13.8 (s, C7a), 132.5 (d, C3), 128.7 (d), 128.6 (d), 128.2 (d), 128.0 (d), (C2''-C6'', C22-C26), 127.1 (d), 127.0 (d), (C4'', C24), 124.5 (d, C7), 109.9 (d, C6), 106.1 (d, C4), 55.4 (q, OCH$_3$), 29.7 (t, CH$_2$), 12.5 (q, CH$_3$).
GCMS : 338 (M^+), 223, 248, 245.

Z-5-Methoxy-2-phenyl-1-(1-phenylpropylidene)-indene **53** has the following spectral characteristics.
^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.76 (d, J = 8.6 Hz, 1H, H7), 7.35 (m, 7H, ArH), 6.89 (m, 5H, ArH), 6.67 (s, 1H, H3), 3.88 (s, 3H, OCH$_3$), 3.18 (q, J = 7.4 Hz, 2H, CH$_2$), 1.18 (t, J = 7.4 Hz, 3H, CH$_3$).
^{13}C NMR (300 MHz) (CDCl$_3$) δ 159.3 (s, C5), 151.4 (s, C2), 144.2 (s, C3a), 143.3 (s), 142.8 (s), (C1'', C21), 140.2 (s, C8), 135.5 (s, C7a), 132.2 (d, C3), 130.3 (d), 128.7 (d), 127.1 (d), 127.0 (d), (C2''-C6'', C22-C26), 128.2 (d), 125.3 (d), 124.7 (d), (C7, C4'', C24), 110.6 (d, C6), 106.6 (C4), 55.5 (q, OCH$_3$), 30.9 (t, CH$_2$), 12.4 (q, CH$_3$).
GCMS : 338 (M^+), 223, 248, 245.

Band two (R_f = 0.81) gave 5-methoxy-2-phenyl-1-(1-phenylpropyl)-inden-1-ol **33** (0.008 g, 0.023 mmol, 7%).

Band three (R_f = 0.71) gave **50** (0.120 g, 86% recovered).

Reaction of 1-acetoxy-2-(2-acetoxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol 51 with 4-toluenesulphonic acid.

1-Acetoxy-2-(2-acetoxyethyl)-5-methoxy-1-(1-phenylpropyl)-inden-1-ol **51** (0.101 g, 0.266 mmol) and 4-toluenesulphonic acid (0.031 g, 0.161 mmol) were dissolved in acetonitrile and refluxed for 4 h. Chromatography with diethyl ether/pet. spirit (1:1) proved unsuccessful.

Crystal structure of *E*-5-methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene 37.

Yellow plates were grown by diethyl ether/pentane diffusion (4°C). Preliminary precession photography indicated a monoclinic lattice with a possible space group $P2_1/c$. The intensity data were collected in $P2_1/n$ (non-standard setting of $P2_1/c$).

Crystal Data : $C_{31}H_{26}O$, Mr = 414.548, monoclinic, space group $P2_1/n$, a = 7.927 (3) Å, b = 25.535 (9) Å, c = 11.046 (5) Å, β = 99.38 (3)°, V = 2206.1 (1.5) $Å^3$, D_c = 1.25 g cm^{-3} for Z = 4. F(000) = 880, μ(Mo-K_α) = 0.38 cm^{-1}, T = -90°C, crystal size = 0.28 x 0.68 x 0.31 mm.

A total of 5538 diffraction intensities were collected using Wyckoff scans in the range 4° < 2θ < 55° of these 4249 were unique. No absorption corrections were applied. The 2604 reflections for which $I > 2\sigma(I)$ were employed in all calculations.

The structure was solved by the TREF direct methods routine of SHELXS-86[111] and developed and refined routinely (SHELX-76[112]). In the final cycles of full-matrix least-squares refinement all non-hydrogen atoms were made anisotropic and the hydrogen atoms were included in their calculated positions with isotropic temperature factors. The three mono-substituted phenyl rings were included as rigid hexagons. Refinement converged at R = 0.0689, R_w = 0.0602, where $w = [\sigma^2(F) + 0.00556F^2]^{-1}$ with no parameter shifting more than 0.014σ. The positional parameters were obtained from this refinement cycle. The final difference map showed no peaks or troughs greater than ±0.3 e $Å^{-3}$. The positional and thermal parameters and tables of bond lengths and angles are given in Appendix A.IV. Structure factor tables are archived in the Department of Chemistry.

Crystal structure of *Z*-5-methoxy-2,3-diphenyl-1-(1-phenylpropylidene)-indene 38.

Orange prisms were obtained from diethyl ether/pentane diffusion (4°C). Preliminary precession photography indicated a triclinic lattice with a possible space group $P\bar{1}$.

Crystal Data : $C_{31}H_{26}O$, Mr = 424.548, triclinic, space group $P\bar{1}$, a = 10.654 (6) Å, b = 11.105 (7) Å, c = 11.093 (7) Å, α = 69.67 (4)°, β = 77.64 (5)°, γ = 67.47 (5)°, V = 1131.8 (1.7) $Å^3$, D_c = 1.22 g cm^{-3} for Z = 2. F(000) = 440, (Mo-K_α) = 0.37 cm^{-1}, T = -90°C, crystal size = 0.60 x 0.36 x 0.24 mm.

Intensity data were collected for 3640 unique reflections, for which 4° < 2θ < 50°. Of these 2818 had $I > 2\sigma(I)$ and were employed in all calculations. No absorption corrections were applied.

The solution was obtained using direct methods[111] and developed and refined routinely. In the final cycles of full-matrix least-squares refinement all non-H atoms were made anisotropic and the H atoms included in their calculated positions with isotropic temperature factors. The mono-substituted phenyl rings were treated as rigid hexagons. The refinement converged at $R = 0.0502$, $R_w = 0.0492$ with no parameter shifting more than 0.011σ in the final refinement. Positional parameters were obtained from this refinement cycle. The final difference map showed no peaks greater than ±0.65 e Å^{-3}. The positional and thermal parameters and tables of bond lengths and angles are given in Appendix A.IV. Structure factor tables are archived in the Department of Chemistry.

CHAPTER FOUR

INVESTIGATION OF COUPLING REACTIONS WITH ALKENES

4.1 Introduction.

Coupling reactions of cyclometalated complexes with alkenes have opened up new methods of organic synthesis. For example the orthometalated ruthenium triphenylphosphite complex undergoes alkylation at all *ortho* positions to liberate *o*-dialkyl-phenols[113] (figure 4.1).

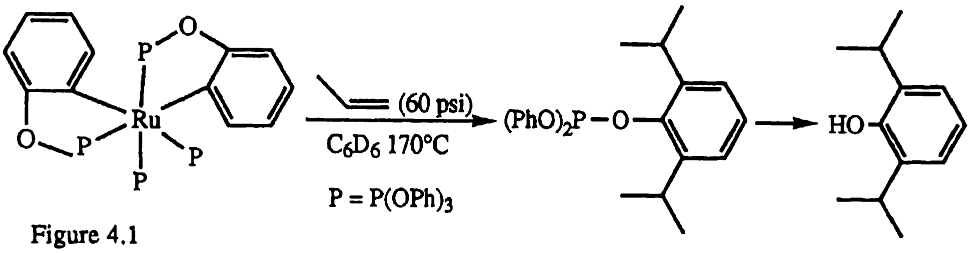


Figure 4.1

Palladium-assisted carbon-carbon bond formation reactions are well known. Formation of an organopalladium salt is thought to be the initial step.[114] Several methods have been established for this step which include direct metalation (equation 1)

(1) direct metalation $RH + PdX_2 \longrightarrow R{-}Pd{-}X + HX$ Equation 1

(2) oxidative addition $RM + PdX_2 \longrightarrow R{-}Pd{-}X + MX$ Equation 2

and oxidative addition (equation 2). The organopalladium salt may form products by disproportionation, alkylation or addition to an unsaturated compound. In the last case, liberation of a coupled product from addition to (insertion of) an alkene, diene or alkyne is followed by either palladium hydride or halide elimination or sometimes by reductive elimination (figure 4.2).

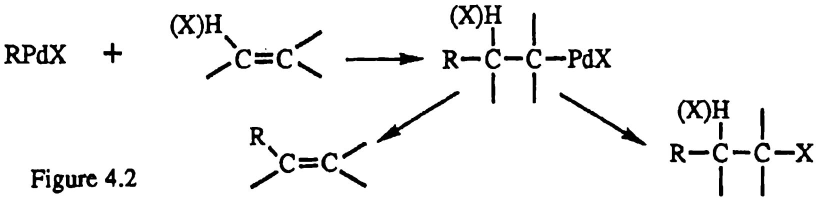


Figure 4.2

Palladium reagents promote an extensive range of synthetically valuable coupling reactions of alkenes at aryl carbons substituted by mercury or halogens.[114]

Similar reactions with other aryl-substituted organometallic compounds[114] involve Tl, B, Mg, Sn and Pb, and the range has recently been extended to Zn[115] (figure 4.3).

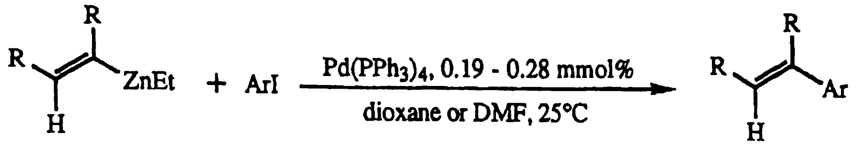
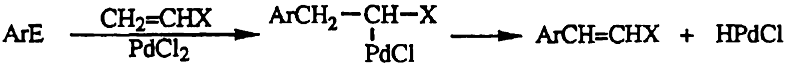


Figure 4.3

4.1.1 Coupling of Alkenes with Orthomanganated Aryl Ketones.

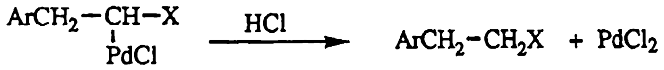
Coupling reactions of orthomanganated aryl carbonyl compounds with alkenes employing palladium(II) have been investigated.[43,46,47,49,116] These reactions afford three main coupled products, an arylalkene, an arylalkane and an indene (Chapter One, figure 1.15). The ratio of these products tends to vary with reaction conditions and substrate. For example,[50] in the above case (Chapter One, figure 1.15), the indene product dominates in refluxing acetonitrile more so than in methanol. The mechanisms which have been proposed for the palladium-mediated formation of arylalkene, arylalkane



$$\mathrm{ArE} \xrightarrow[\mathrm{PdCl_2}]{\mathrm{CH_2{=}CHX}} \mathrm{ArCH_2{-}}\underset{\mathrm{PdCl}}{\underset{|}{\mathrm{CH}}}\mathrm{{-}X} \longrightarrow \mathrm{ArCH{=}CHX} + \mathrm{HPdCl}$$

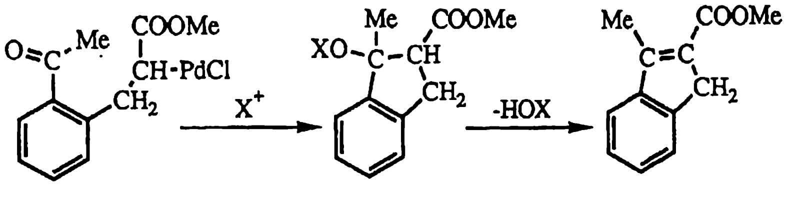
Equation 3

$$\mathrm{PdHCl} \longrightarrow \mathrm{Pd} + \mathrm{HCl}$$



$$\mathrm{ArCH_2{-}}\underset{\mathrm{PdCl}}{\underset{|}{\mathrm{CH}}}\mathrm{{-}X} \xrightarrow{\mathrm{HCl}} \mathrm{ArCH_2{-}CH_2X} + \mathrm{PdCl_2}$$

Equation 4



Equation 5

and indene products are outlined in the generalised equations 3-5. Equations 3 and 4 are those proposed[114] for the arylation of alkenes: syn-elimination of metal hydride gives the *E*-arylalkene while cleavage of the metalated intermediate via protonolysis gives the saturated analogue. A possible[71] route to formation of indene products is shown in equation 5 (where X^+ maybe $PdCl^+$, H^+, or a Mn(I) function); the amount of indene is not limited by the extent of HCl formation (equation 3) as it is in the case for the arylalkane under otherwise aprotic conditions.

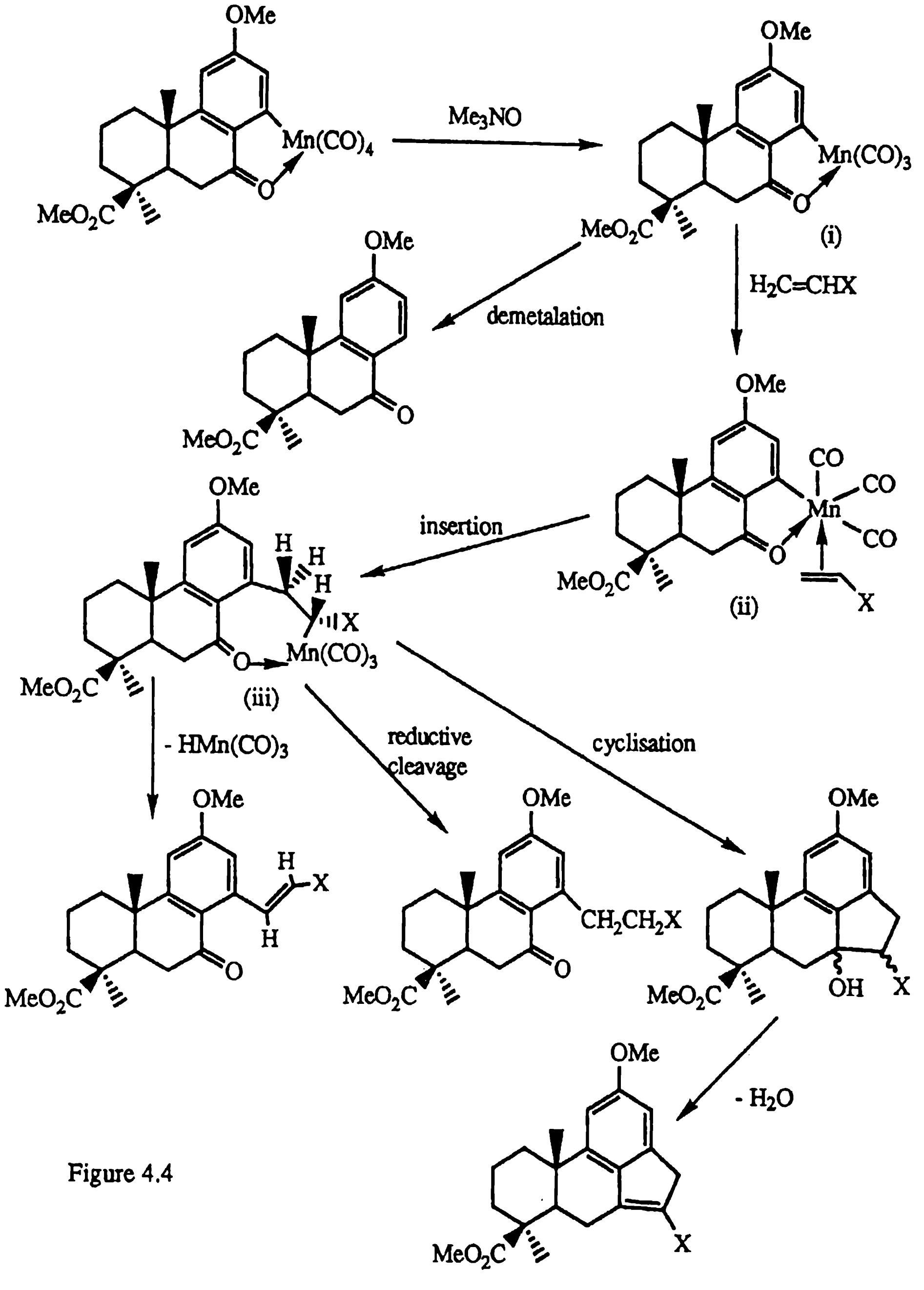


Figure 4.4

Coupling reactions in the absence of palladium(II) have been attempted.[43,49,116] Trimethylamine *N*-oxide, successfully employed[56] for promoting alkyne coupling with orthomanganated aryl ketones, has been applied to induce alkene coupling.[47-49,118] These coupling reactions gave indanol products as well as those previously described. A speculative mechanism,[49] whose initial part is analogous to that proposed by Liebeskind[56] for the insertion of alkynes (Chapter Three), is shown in figure 4.4.

The aims of the research reported in this chapter were two-fold. First, to investigate the reactions of the orthomanganated complex, **9**, with alkenes, examining whether the bulky phenylpropyl substituent would interfere with the reactivity of the complex. Few thermally-induced alkene coupling reactions have been reported[49,116]

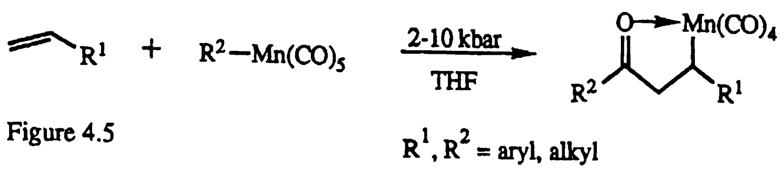
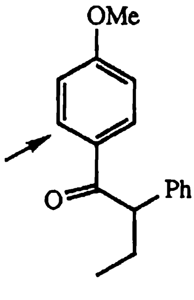
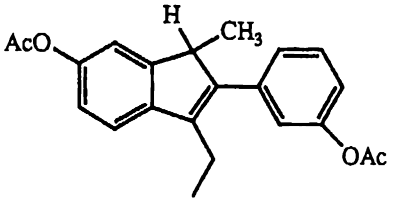


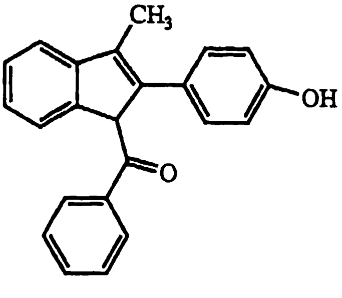
Figure 4.5

and, as DeShong *et al.*[100,101] have shown, alkenes insert into the Mn-C σ-bond uncatalysed (figure 4.5). Therefore the coupling of 9 with alkenes in a range of solvents would be investigated.

Parallel to this theme is the synthesis of potentially antiestrogenic compounds. Specific aims were to introduce an ethenyl group in the *ortho* position (arrowed) of the substituted phenyl ring of 7 and to synthesise substituted indanyl compounds which might have antiestrogenic activity analogous to the substituted acetoxy-indenes[29] and indole compounds.[25]







4.2 Results and Discussion.

4.2.1 Alkene coupling with tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9.

Results for the coupling reactions of tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with the alkenes methyl propenoate (methyl acrylate), 3-buten-2-one (methyl vinyl ketone) and methyl but-2-enoate (methyl crotonate) are displayed in table 4.1.

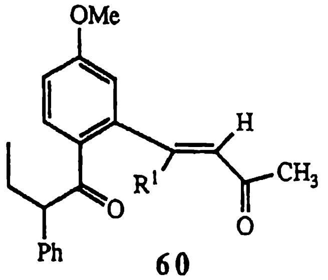
Palladium(II)-promoted reaction of 9 and methyl propenoate in methanol over 18 hours affords the Heck (arylalkene) product, methyl *E*-3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-propenoate **54**, in moderate yield (41%). Also isolated are the demetalated ketone (**7**, 28%) and unreacted **9** (30% recovered). In contrast, coupling with 3-buten-2-one in methanol gives the cyclised indene product **58** in 46% yield, with **7** and **9** obtained in similar quantities to that above. Palladium-assisted coupling with

Table 4.1 Results of the coupling of alkenes with **9**.

Reaction	unreacted 9	demetallated	arylalkene	arylalkane	indene	indanol
with methyl propenoate		**7**	**54**	**56**	**55**	**57**
Pd/methanol ambient	30	28	41			
Pd/THF under reflux	7		13	20	37	
Pd/acetonitrile ambient temperature	28	34	26	13		
Pd/acetonitrile under reflux			13	13	28	
carbon tetrachloride	5			26		11
acetonitrile		64		29		15
Me_3NO/acetonitrile	4	10		85		9
Ni/methanol				75		
Ni/acetonitrile		19		66		12
with 3-buten-2-one	**9**	**7**	**60**	**59**	**58**	**61**
Pd/methanol ambienttemperature	31	31			46	
Pd/THF under reflux	2	4	6	24	32	
Pd/acetonitrile ambient temperature	77	3		14		
Pd/acetonitrile under reflux	1		35	12	16	
carbon tetrachloride under reflux	2			27	43	
acetonitrile under reflux		15		57	30	
Me_3NO/acetonitrile				67		13
Ni/methanol ambient temperature	88	8				
Ni/methanol under reflux	26			30		10
Ni/acetonitrile ambient temperature	75	18				
Ni/acetonitrile under reflux						96
acetonitrile CO atmosphere	1			19	13	65
with methyl but-2-enoate	**9**	**7**	**63**	**65**	**62**	**64**
Pd/acetonitrile under reflux			12		2	
acetonitrile		18				72
Ni/acetonitrile		5		14		35

methyl propenoate in either THF or acetonitrile under reflux gives several products. The major product is the arylalkane **55**. Similarly, coupling with 3-buten-2-one in either THF or acetonitrile gives a number of products. In acetonitrile, the arylalkene (**60**, 35%)

is the major product, with other products isolated in similar quantity to those for the methyl propenoate case.



60

These results (table 4.1) show a tendency for palladium-mediated reactions carried out under reflux, in THF or acetonitrile, to give coupled products with minimal demetalated product formation, unlike the situation when methanol is used as solvent. This may be a result of the ability of the protic solvent methanol to protiodemetalate the manganese complex. In methanol, palladium-promoted couplings of orthomanganated aryl methyl ketones with methyl propenoate have been reported[43,49,50] to give the arylalkene product in excellent yield, while by contrast cyclised indene products predominate in refluxing acetonitrile. Our results with **9** are consistent with these observations. With stirring at ambient temperature in acetonitrile it was found[49] the palladium-promoted reactions did not give any coupled products. However, in our study coupled products are formed with both methyl propenoate and 3-buten-2-one though in relatively poor yield. Palladium-promoted coupling of **9** with methyl but-2-enoate (methyl crotonate) in refluxing acetonitrile gives the coupled products **62** and **63** in low yield (2% and 12% respectively). Similar yields of coupling products for this alkene have been reported[49] for the Me_3NO-induced reaction in acetonitrile. The low reactivity of this alkene might seem to be explained by hindrance by the terminal methyl group on the methylene function. If so, such steric hindrance appears to be overcome by heating: coupling of methyl but-2-enoate with **9** in refluxing acetonitrile without $PdCl_4^{2-}$ present gives the corresponding indanol, **64**, in good yield (72%).

Reaction of **9** with methyl propenoate in refluxing carbon tetrachloride gives the arylalkane, **56**, as the major product (26%). **56** is the predominant product from other methyl propenoate coupling reactions, either thermally- or Me_3NO-induced (see table 4.1). Similarly, coupling of **9** with 3-buten-2-one in various solvents gives the arylalkane **59** in greater yield, except in carbon tetrachloride where the dominant product is the indene **58** (43%). Me_3NO-induced reactions with methyl propenoate tended[49] to give the saturated arylalkane products in high yield with orthomanganated tetralone type precursors, while cyclised indanol products were formed with orthomanganated acetophenone type compounds. Formation of the arylalkanes in preference to the indanol type products, **57** and **61**, suggests the attached 1-phenylpropyl substituent may limit cyclisation, although the formation of the indanol **64** in high yield is an apparent anomaly.

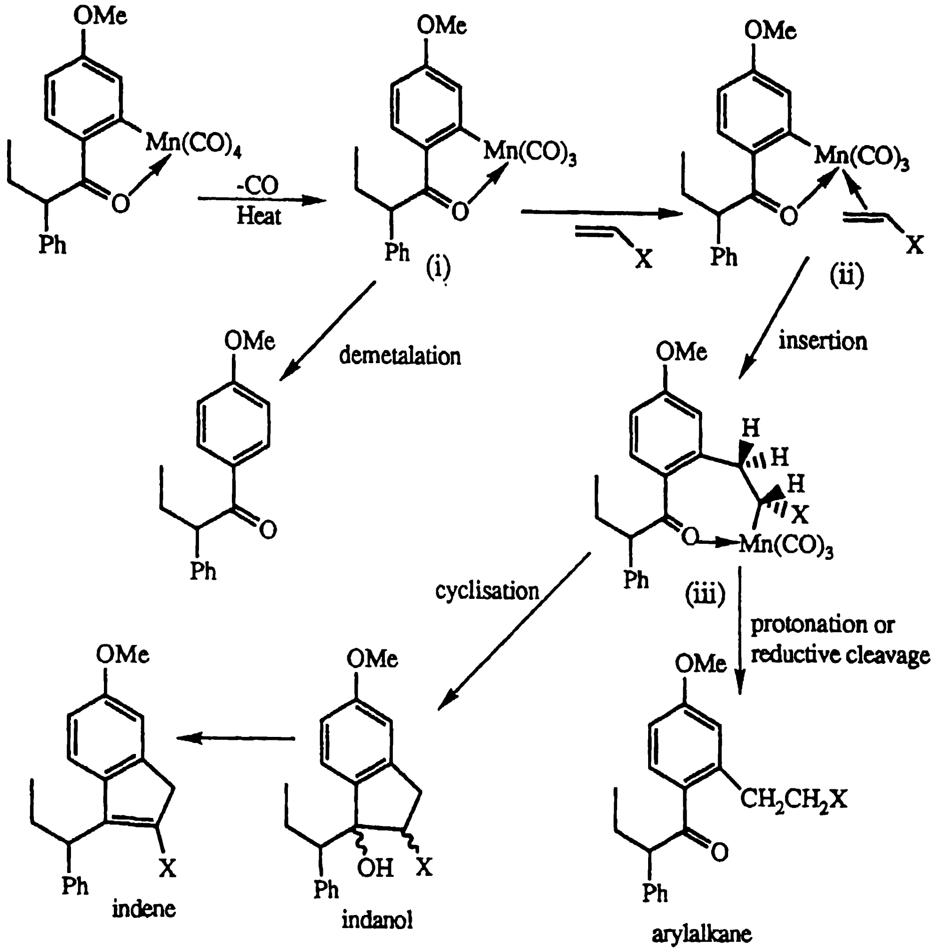


Figure 4.6

Cambie *et al.*[49] have investigated Me_3NO-induced alkene coupling reactions with orthomanganated substrates and have proposed a general reaction scheme (figure 4.4). Investigations[49] of this reaction have included quenching the reaction with CD_3COOD, the lack of deuterium-incorporation indicating cleavage (figure 4.4) must occur during the course of reaction rather than protonation during workup procedures. The source of reducing hydrogen is as yet unknown though a manganese hydride species has been suggested.[49] It would be reasonable to expect the thermally-induced alkene coupling reactions to proceed similarly (figure 4.6). The initial step in the coupling reaction, as with the Me_3NO case (figure 4.4), is loss of CO to give the coordinatively unsaturated 16-electron intermediate (i) which then coordinates the alkene with subsequent insertion. Intramolecular rearrangement of the seven-membered ring species (iii) leads to indanol and indene products. The route to the arylalkane product is not fully understood, with the source of the hydrogen only speculative.

It was found[56,57] that the coupling of orthomanganated aryl ketones with alkynes (Chapter Three) involved regioselective insertion. Coupling with methyl but-2-

enoate could give two regioisomers, though only one is observed, that with the methyl group adjacent to the ring. For the indanol **64**, all diastereoisomers have the ester substituent in the 2-position. This is not unexpected, as with the coupling of carboethoxy substituted alkynes, the ester substituent is always found[56] in the 2-position of the indenyl product. This was rationalised[56] by the coordination of the ester carbonyl to the manganese prior to η^2-alkyne coordination and subsequent insertion into the Mn-C σ-bond. For the coupling of methyl but-2-enoate, only regioisomers with the terminal methyl group adjacent to the aryl ring are isolated. It is probable that similar pre-

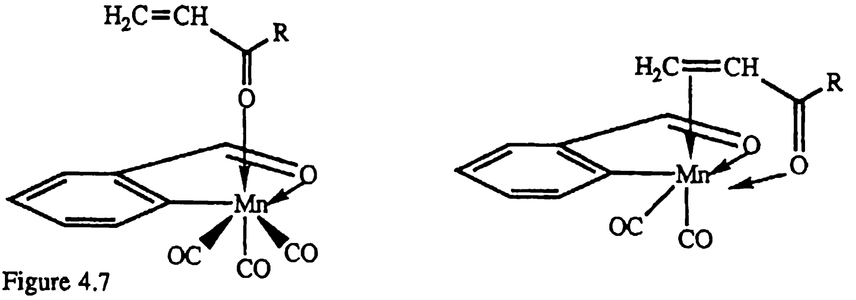


Figure 4.7

coordination of the ester carbonyl to manganese (figure 4.7) leads to this regiospecific alkene insertion. Pre-coordination of the carbonyl group may explain why electron-poor alkenes of this type tend to react quicker than other alkenes (the reaction with methyl propenoate (complete in 2 hours) is quicker than that of phenylethene (16 hours)), though in contrast the diester, diethyl maleate, does not give any coupled product. The latter may be a result of the inability of the electron-poor C=C bond to effectively η^2-coordinate to the manganese a prior requirement for insertion into the Mn-C σ-bond though steric effects may also come into play for this disubstituted ethene.

When a 7:1 mixture of 3-buten-2-one and diphenylethyne is reacted with **9** in refluxing acetonitrile, the predominant products are those derived from alkene insertion, indicating 3-buten-2-one is more reactive than diphenylethyne. This may reflect preferential coordination of the enone over η^2-alkyne coordination, though the insertion rate, implicit for the formation of a metallacyclic intermediate (e.g. ii; figure 4.6), must also be considered.

Insertion of CO plus an alkene into the Mn-CH$_3$ bond of CH$_3$Mn(CO)$_5$ has been reported[100,101] (figure 4.5), as has the insertion of CO and ethene into an orthomanganated aryl-Mn(CO)$_4$ compound.[49] The latter, a Me$_3$NO-induced reaction of a diterpenoid complex with ethene (340 kPa) reportedly gave two products derived from insertion of CO and two molecules of ethene, though in low yield (figure 4.8). In an attempt to promote both CO insertion and alkene coupling, **9** and 3-buten-2-one were coupled in acetonitrile under CO (15 atm). The reaction gives the cyclised products **58** (13%) and **61** (41%), the arylalkane **59** (19%) and Mn$_2$(CO)$_{10}$ (17%), but no product derived from the insertion of CO. Yields of the cyclised products and arylalkane are thus

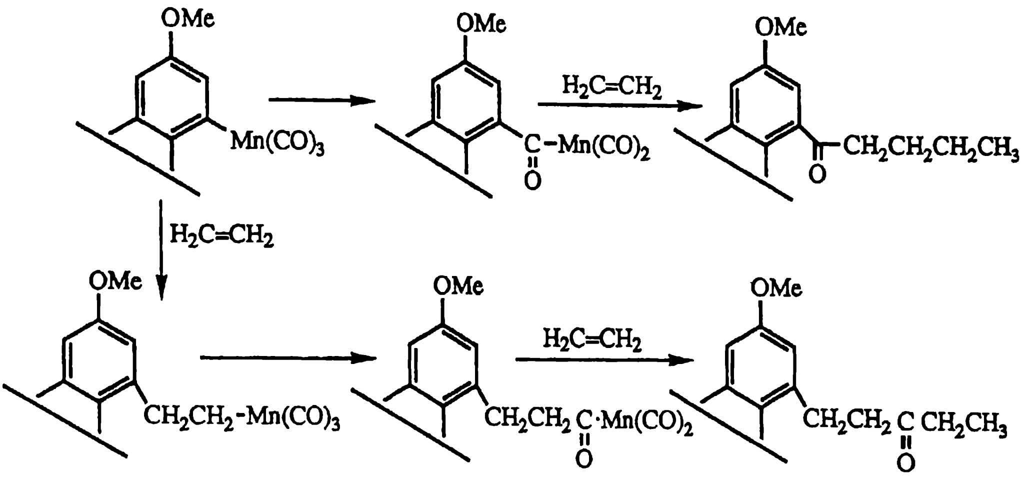


Figure 4.8

reversed in comparison to those obtained in reactions under N_2. With a CO-saturated solution, the reactive 16-electron metallacycle proposed as an intermediate (iii; figure 4.4 and 4.6) may be stabilised as an 18-electron tetracarbonyl by re-coordination of excess CO. This increases the likelihood of cyclisation at the expense of protiodemetalation. The results for this reaction suggest that under these conditions both CO and an alkene can not be inserted into the Mn-C σ-bond to subsequently liberate products of the type in figure 4.9.

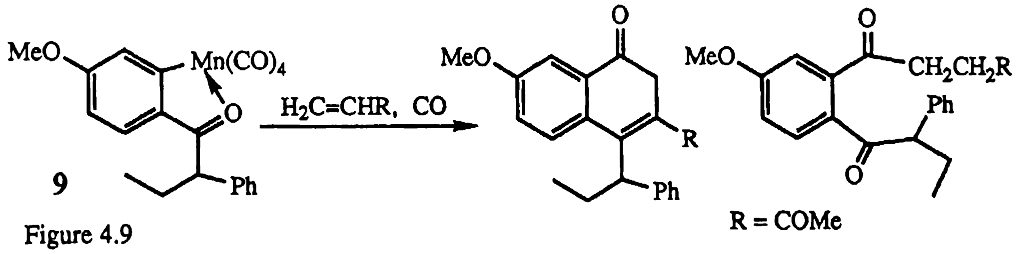
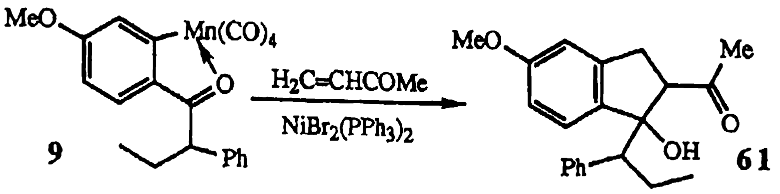


Figure 4.9

4.2.2 Nickel(II)-mediated Coupling.

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κO)-phenyl-κC]-manganese(I) **9** was reacted with methyl propenoate in the presence of dibromobis(triphenylphosphine)nickel(II) ($NiBr_2(PPh_3)_2$) in acetonitrile under reflux for 1.75 h. The initial dark green solution gives a fine bright yellow suspension at reflux temperature after which the solution becomes a clear yellow-brown colour. Methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** is the predominant product (66%). When 3-buten-2-one is similarly coupled, 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol **61** is isolated in quantitative yield after only 30 minutes refluxing.



9 **61**

Dibromobis(triphenylphosphine)nickel(II) and the analogous dichloro complex have been employed as cross-coupling catalysts for the reactions of Grignard reagents with aryl halides.[117] When **9** is reacted with alkenes as described above in the presence of $NiBr_2(PPh_3)_2$, yields dramatically increased. Increased yields suggest there is involvement of the nickel complex in the coupling reaction. For comparison the manganese carbonyl complex of acetophenone, **6**, was coupled in the presence of Ni(II) with the alkenes methyl propenoate and 3-buten-2-one giving excellent to quantitative yields of the indanol products **76** and **79**. The relative stereochemistry of the 1-methyl and 2-acetyl substituents in the indanol product **76a** and the more polar isomer **76b** were deduced by differential nOe experiments. When **6** is coupled with either alkene in the absence of Ni(II) only moderate yields of the corresponding indanols are obtained.

When 3-buten-2-one and **6** were coupled in the presence of PPh_3 the product ratio and yield did not appreciably change in comparison to those of the directly coupled reaction. Therefore, the labile PPh_3 ligands of the nickel complex which could coordinate to manganese do not in themselves contribute to the increased yield of the coupling reaction. The nickel itself must be involved in some way.

A nickel-catalysed reaction of iodofluoroacetates with terminal alkenes employing $NiCl_2.6H_2O$ has been recently reported[118] to give α-fluoroesters. However no mechanism was suggested. Coupling reactions with enone-derived π-allyl nickel reagents have also been reported[119] (figure 4.10). This latter reaction involves the direct conversion of the enone to the [1-(trialkylsilyloxy)allyl]nickel(II) chloride complex, the structure of which was confirmed by crystallographic analysis.

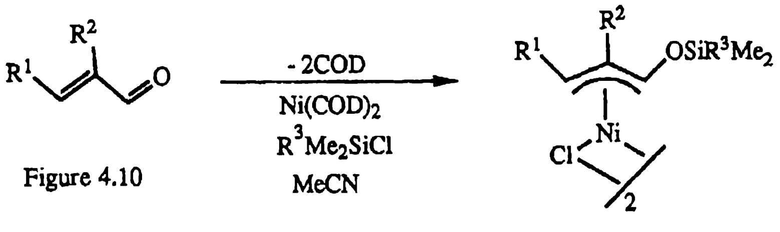
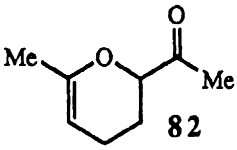


Figure 4.10

Coupling aryl mercury compounds with alkenes in the presence of palladium has been reported to give the corresponding arylalkene in good yield.[114] Coupling the mercuriated compound **80** with methyl propenoate in the presence of $NiBr_2(PPh_3)_2$ gives the biaryl compound **81** (46%) with no alkene-coupled product detected. From this result it can be presumed the nickel species does not transmetalate at the aryl C to replace manganese, in contrast to the reported cases for Hg[120] and Pd.[46] The nickel complex must aid formation of the coordinated η^2-alkene intermediate (ii; figure 4.4 and 4.6) or an analogous complex, promoting insertion to give the seven-membered metallacyclic ring.

As Ni(II)-mediated coupling seems limited to enone-type alkenes it is most likely that the nickel provides a coordination centre for the enone which promotes the coupling reaction in some unknown way. As there is no source of electrons (other than Mn(I) to Mn(II)) it is unlikely $NiBr_2(PPh_3)_2$ forms an allylic ligand upon coupling with the enone such as that in figure 4.10, though such an allylic dianionic complex (analogous to figure 4.10) would readily couple with a coordinatively unsaturated 16-electron manganese entity (i; figure 4.6).



82

When 3-buten-2-one is added to a refluxing solution of $NiBr_2(PPh_3)_2$ in acetonitrile the dark green solution turns emerald in colour. Subsequent workup and chromatography gives the dihydropyranyl compound **82**. Formation of **82** may be promoted by Ni(II) as above. However, nickel(II)-assisted cyclisation reactions of this type to the best of our knowledge are unknown. Further investigation may be warranted.

Palladium(II)-mediated alkene coupling is reported[49] to be catalytic if $Pd(OAc)_2(PPh_3)_2$ is employed. A tentative attempt at coupling **9** with 3-buten-2-one in acetonitrile using a catalytic amount (10 mol%) of $NiBr_2(PPh_3)_2$ gives several coupled products in good yield (**58**, 15%; **59**, 33%; **61**, 48%). The relatively high overall yield of products in comparison to non-Ni(II)-mediated reactions (table 4.1) indicates a catalytic role for Ni(II) but the loss of product specificity as compared to the case for stoichiometric amounts shows that more than one type of Ni(II)-promoted reaction occurs.

Reaction of **9** with 3-buten-2-one at ambient temperature in methanol in the presence of $NiBr_2(PPh_3)_2$ gives no coupled product, though a colour change is observed. However, repetition in refluxing methanol gives the arylalkane **59** in moderate yield (30%). Similarly, coupling methyl propenoate gives **56** in good yield (75%). This result indicates a preference for arylalkane formation with $NiBr_2(PPh_3)_2$ in methanol, while the indanol, **61**, is favoured in acetonitrile. Coupling in methanol with $NiBr_2(PPh_3)_2$ may be complicated by replacement of the PPh_3 ligands with solvent as there is an initial decolourisation of the solution.

4.2.3 Cyclisation.

The proposed mechanisms (equation 5, figure 4.4) suggest that cyclic products are derived from intramolecular nucleophilic attack rather than an aldol-type reaction of the liberated arylalkane, though there is no reported supporting evidence for this. In our work, attempts to promote cyclisation of the arylalkane **59** with Li_2PdCl_4 or Br^- proved unsuccessful. This suggests that neither electrophilic Pd(II) nor base (Br^- in the dipolar aprotic solvent) promotes cyclisation of the liberated arylalkane after the coupling reaction. With acid (4-toluene-sulphonic acid and acetonitrile), cyclisation of **59** gives the indene **58** (40%) and 2-ethyl-7-methoxy-3-methyl-2-phenyl-6,7-benzocyclohept-3-enone **83** (6%) (see figure 4.11). The latter product is not detected in any coupling reactions in the same solvent suggesting acid generation during coupling by elimination of HPdX (HX + Pd) (equation 3, section 4.1) is insufficient to promote arylalkane cyclisation to give either the indene or indanol products. When the ester **56** is similarly treated no cyclised product formed. Given these results, cyclisation probably occurs as an integral part of the coupling reaction. Proposed mechanisms (figures 4.4 and 4.6 and equation 5) have a manganese moiety attached to and polarising the aryl carbonyl function (as part of the seven-membered metallacyclic ring). It is likely that the extent of this polarisation, determined by solvent donor coordination, steric requirements, and position of electron withdrawing groups adjacent to the manganese, determines whether intramolecular rearrangement to give the cyclic products proceeds or not.

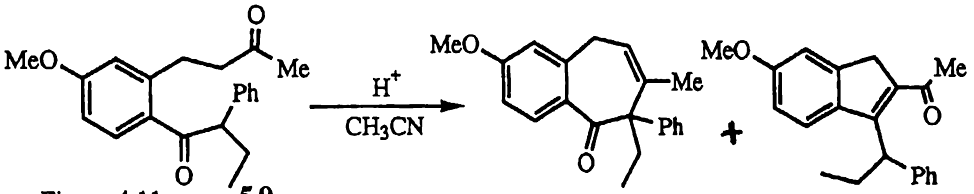
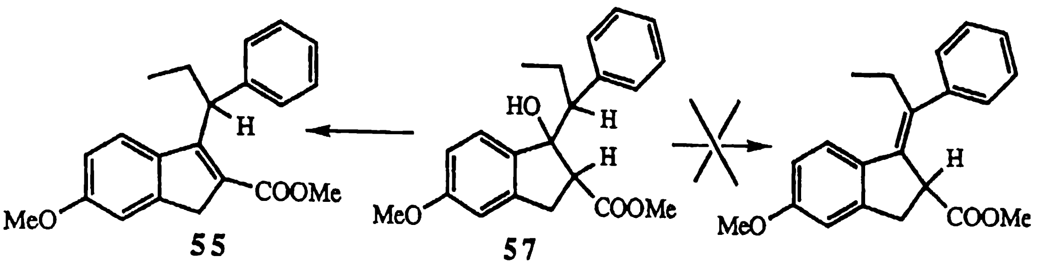


Figure 4.11 **59** **83** (6%) **58** (40%)

It was found[43,107] that the product ratio was altered if the solvent contained water. For wet solvent, the cyclised (indene) product yield decreased and that of the arylalkane increased. From our results above, any adventitious H_2O is unlikely to lead to a higher proportion of cyclised product. From figures 4.4 and 4.6 any adventitious H^+ is likely to protiodemetalate at the manganese leading to either demetalated ketone or more arylalkane product; the latter arising from protonation of the proposed seven-membered metallacyclic intermediate (iii).

As shown in section 4.2.1, there is a preference (in dehydration) for indene formation. Dehydration of **57** with acid (H_2SO_4 and acetonitrile) gives the indene **55** exclusively. This dehydration shows a preference to form the indene rather than to dehydrate across C1-C1' (CH of the propyl group) to form the 1-phenylpropylidene indane compound (figure 4.12).



55 **57**

Figure 4.12

4.2.4 Tamoxifen Analogues.

The cyclised indene and indanol products exhibit structural characteristics similar to antiestrogenic compounds.[25,26,27,29] In an attempt to synthesise Tamoxifen analogues and more antiestrogenic-type indenes, coupling of **9** with ethenyl ethanoate (vinyl acetate) and phenylethene (styrene) was undertaken.

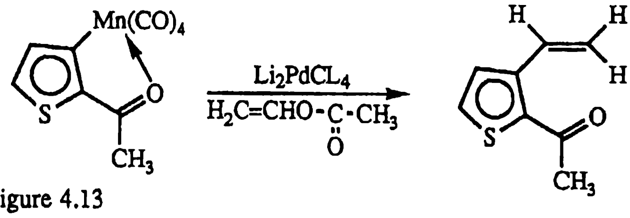


Figure 4.13

Gommans has reported[43] the synthesis of an ethenyl-substituted product in good yield (55%) from the palladium(II)-promoted coupling reaction of η^2-(2-acetylthien-3-yl)tetracarbonylmanganese with ethenyl ethanoate in methanol (figure 4.13). Addition of an *ortho*-ethenyl substituent to **7** would lead to an ethenyl-substituted Tamoxifen derivative. When **9** and ethenyl ethanoate are reacted together under similar conditions, only two coupling products are observed: **67** (4%) and the saturated analogue **66** (2%). The attached methoxy group originates from the solvent. This is confirmed by the formation of the ethoxy derivatives, **68** and **69**, when the reaction is repeated in ethanol. Formation of these products is envisaged as occurring by acid-catalysed vinylic substitution.

In refluxing acetonitrile the desired product **70** is obtained in moderate yield (28%) as well as the isobenzofuranone products **71** (3%) and **14** (7%) and the aldehyde **72** (7%) (figure 4.14). The latter product, **72**, is the hydrolysis product of the saturated arylalkane. Formation of the ethenyl substituted product **70** shown in figure 4.15 is similar to that reported by Heck.[121] Neither the Me_3NO-induced nor the nickel(II)-mediated reactions of **9** with ethenyl ethanoate give any coupled product.

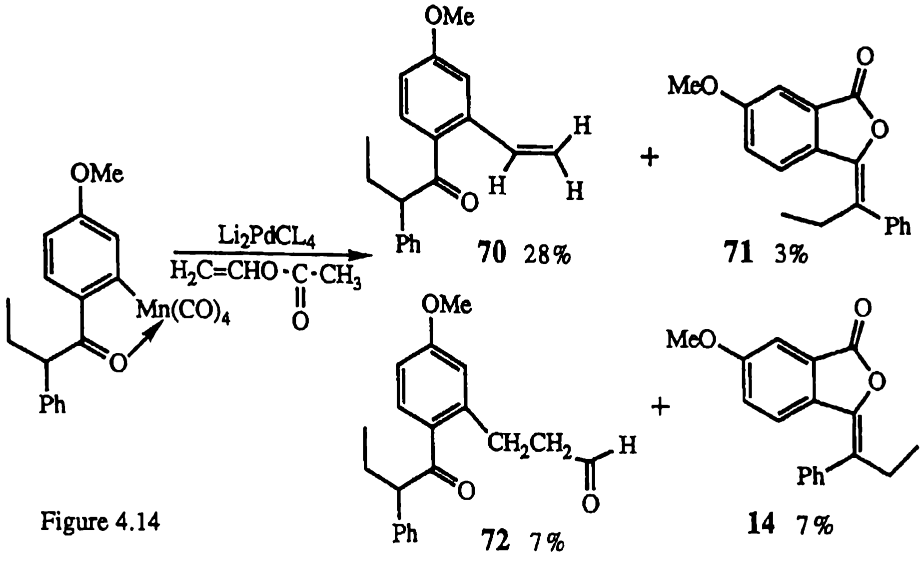


Figure 4.14

Palladium-mediated coupling of 9 with phenylethene gives the Heck (arylalkene) product 73 in excellent yield (75%). Reaction of 9 with phenylethene in acetonitrile in the absence of Pd(II) gives no coupled product after 2 hours, though in benzene the cyclic product 74 is obtained in moderate yield (43%) if reaction time is significantly extended. Formation of 74 probably results from the prototropic rearrangement subsequent to indene formation (figure 4.16).

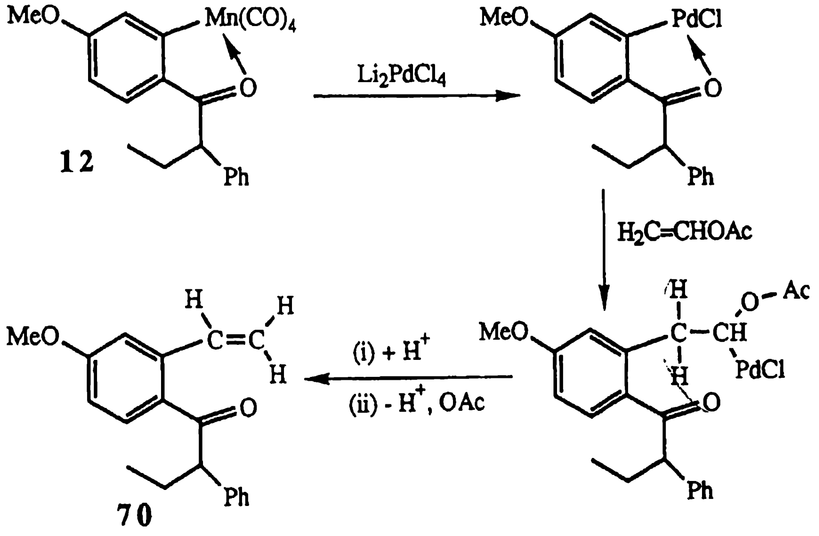


Figure 4.15

74 is an analogous to 52 (Chapter Three) having comparable structural features to the reported antiestrogenic indene compounds.[25,29] Though the C-C bond between the indenyl ring and the phenylpropyl group for 74 is hydrogenated it was found[31] that 1,2-diphenylethanes do exhibit some antiestrogenic activity and a derivative of 74 with the N,N-dialkylaminoethoxy side chain may show potential antiestrogenic activity. No attempt has so far been made to demethylate the methoxy substituent and add this side chain to give a derivative structurally analogous to Tamoxifen.

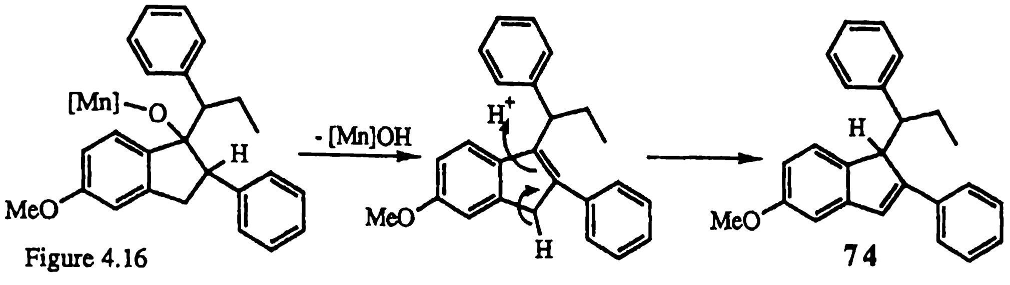


Figure 4.16

4.3 Crystal structure of methyl [1S*,2R*,3R*,1'S*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate 64e.

The crystal structure of **64e** was undertaken to give confirmation of the relative stereochemistry about the indanyl ring and to support the NMR structural assignment. **64e** is one of five diastereoisomers of an indanol produced from the coupling reaction of **9** and methyl but-2-enoate.

Positional parameters for **64e** are listed in Appendix A.IV. The structure is shown in figure 4.17. It is an indanol derivative and shows the unambiguous atom connectivity and relative stereochemistry about the indanyl ring and of the phenylpropyl group. The adjacent 3-methyl and 2-carboxylate substituents are orientated *trans* to each other with the methyl group above the plane of the indanyl ring. The phenyl ring, attached to the propyl group, is twisted out of plane and away from the carboxylate group above the indanyl ring. Due to the poor quality of the analysis (R and R_w *ca.* 0.15) further discussion of the structural features is not warranted.

4.4 NMR Spectroscopy.

4.4.1 Stereochemistry of the diastereoisomers of methyl 1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate 64.

X-Ray crystal structure analysis of **64e** resolved the stereochemistry of the compound. Using this as a basis, definitive stereochemical assignments for the other diastereoisomers of methyl 1-hydroxy-5-methoxy-3-methyl-1-(phenylpropyl)-indane-2-carboxylate, **64**, were achieved using differential nOe experiments. For each isomer, an nOe is observed at the H4-proton when the methyl substituent protons are irradiated.

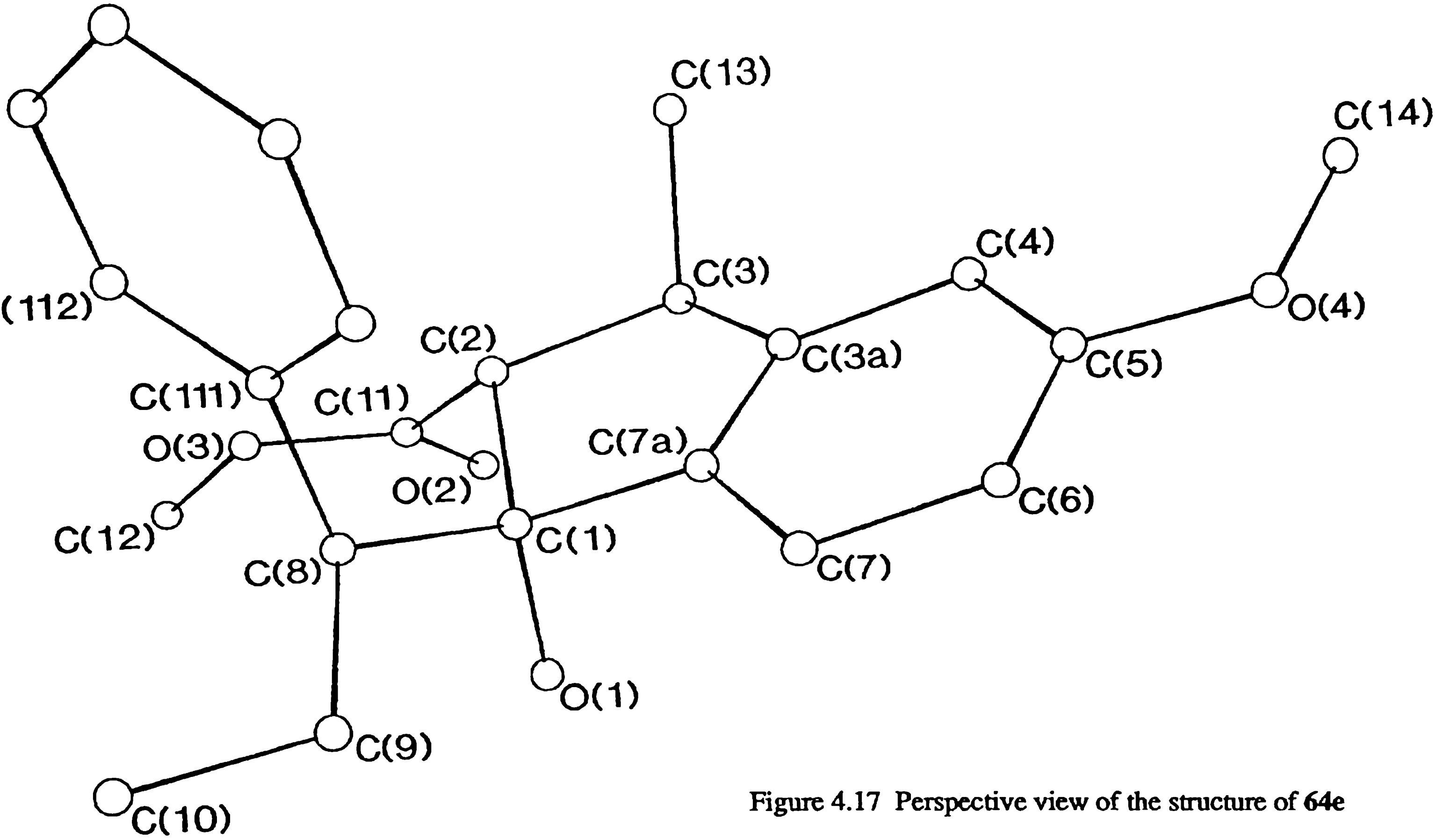
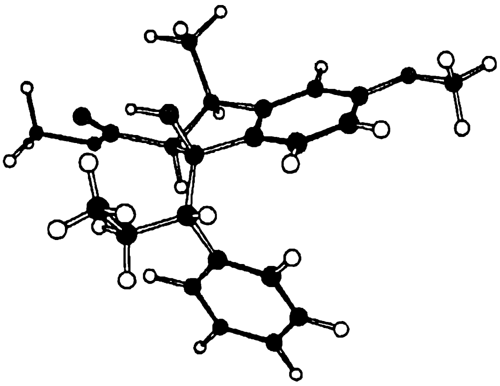


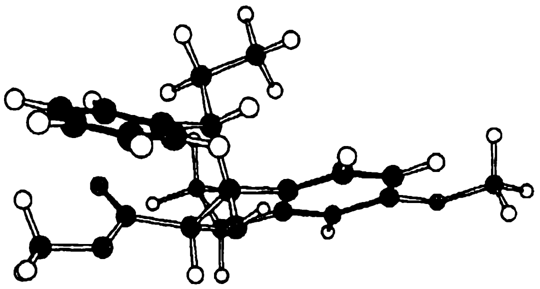
Figure 4.17 Perspective view of the structure of **64e**

This confirms that the methyl substituent is in the 3-position of the indanyl ring for each isomer. For the purpose of defining relative stereochemistry, all the isomers of **64** have C3 assigned the *R** configuration. Results for the differential nOe experiments are displayed in tables A.5 - A.9 (Appendix A.3).

Results of the nOe experiments for **64e** are consistent with the stereochemistry exhibited by the solid state crystal structure determination. Irradiation of the 3-CH_3 gives observed nOes for the H4 and H2 protons, the latter nOe indicating the methyl and adjacent 2-carboxylate groups are *trans* about the indanyl ring. Due to close contacts, strong reciprocal nOes are observed between the H2 and methylene (CH_2) protons. The methylene protons also have nOes into the aromatic region which indicate close contacts with the phenyl ring and H7 protons. The stereochemistry about the methylene group deduced from the nOes is consistent with the crystal structure solution. The CH proton gives no observable nOes other than those to the CH_2 and CH_3 protons of the ethyl group, in accord with the crystal structure.



64a

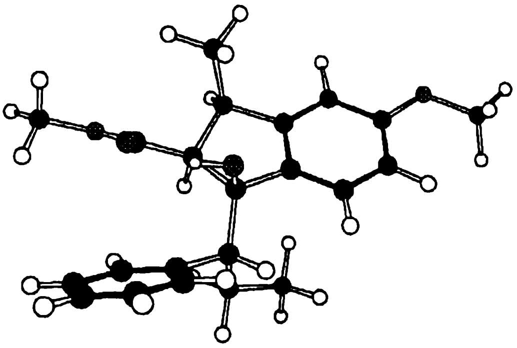


64c

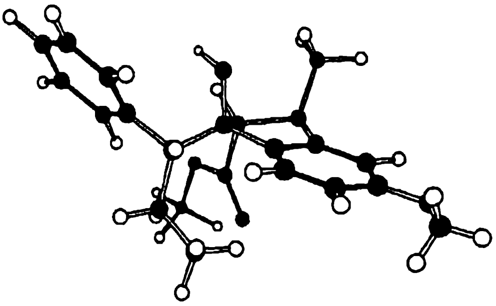
For **64a**, strong reciprocal nOes for the H2 and H3 protons establish that the 2-carboxylate substituent is above the indanyl ring *cis* to the 3-methyl group. Therefore C2 is assigned the *S** configuration. The chemical shift for the H7 proton is downfield compared to **64e** which indicates that this proton undergoes significant deshielding from the monosubstituted phenyl ring. With strong nOes observed between the H3 and CH protons, the phenylpropyl substituent must lie below the indanyl ring, having similar relative stereochemistry to that of the inden-1-ol **33a** (see Chapter Three section 3.3), with the ethyl group directed away from the rest of the molecule. Therefore C1 is assigned the *S** configuration, as is C1' (CH of the phenylpropyl group).

With the H7 resonance deshielded at δ 7.45 ppm and nOes confirming the 3-CH_3 and carboxylate groups are *cis* to each other, **64c** must have similar stereochemistry to **64a**. However, irradiation of the CH proton gives a relatively weaker nOe to H2 and none to H3 which indicates the phenylpropyl group lies in the same plane as the CH_3 group, above the indanyl ring, and as a result C1 is assigned the *R** configuration.

As found with **64a** and **64c**, observed nOes between the H2 and H3 protons confirm the 3-CH_3 and 2-carboxylate substituents are *cis* for **64b**. The CH proton gives comparatively strong nOes to H2 indicating the phenylpropyl group lies below the indanyl ring indicating C1 has *S** configuration. With no significant shielding effects for H7 (δ 7.07) and strong nOes from the methylene protons to H2, the phenylpropyl group must have similar relative stereochemistry to that found for the inden-1-ol **33b** (see Chapter Three, section 3.3). Therefore C1' is assigned the *R** configuration.



64b



64d

As found for **64e**, the methyl and carboxylate substituents are *trans* for **64d**. NOes are observed between H2 and the 3-CH_3 protons. The phenylpropyl group like the carboxylate group lies below the indanyl ring, with only nOes between the H2 proton and methylene protons observed, therefore C2 and C1 are assigned the *R** and *S** configuration respectively. As found above for **64b**, the phenylpropyl group has similar relative stereochemistry to **33b**, confirmed by nOes from the methylene group protons to H7 and the phenyl ring.

4.4.2 2D NMR Techniques.

Full and definitive assignment of ^{13}C NMR resonances of **64e** is achieved using XH correlated NMR (spectra in Appendix A.2). The assignments for **64e** are used as a basis for the assignment of the other diastereoisomers of methyl 1-hydroxy-5-methoxy-3-methyl-1-(phenylpropyl)-indane-2-carboxylate **64**. Similarly, the XH spectrum for another indanol **57b** (Appendix A.2; figure A.10) enabled unambiguous assignment of **57a** and the acetyl derivatives **61a** and **61b**. For the indanols **61a** and **61b** the assignment of each H3 proton is based on vicinal coupling. For **61b** the doublet of doublets at δ 2.82 ppm with ^3J = 2.9 Hz was assigned to the H3 resonance *cis* to 2-$COCH_3$ and the other doublet of doublets at δ 2.30 ppm with ^3J = 8.6 Hz resonance *trans* to 2-$COCH_3$.

A standard $^1J_{C\text{-}H}$ coupling XH spectrum enabled assignment of the protonated carbon signals for **64e**, while assignment of the singlet carbon resonances is achieved by the long-range routine of the XH program. The spectra (appendix A.2) show $^2J_{C\text{-}H}$ coupling between the methoxy protons and the C6 resonance. A $^2J_{C\text{-}H}$ coupling is also shown between methoxy protons and C=O of the carboxylate group. Similarly, a $^3J_{C\text{-}H}$ coupling correlation is observed between the 3-CH_3 protons and C3a. Both H4 and H6 proton resonances show $^3J_{C\text{-}H}$ coupling to the C7a resonance at δ 136.5.

4.5 Summary

The results for the coupling of alkenes with **9** promoted by Pd(II), though varied, show overall similar reactivity to those previously reported.[43,49,50] The thermally-induced reactions in various solvents favour the formation of the arylalkane products over those which are cyclised, indicating that the 1-phenylpropyl substituent may influence the reactivity of **9**. The results from the attempted acid-catalysed aldol condensation reactions suggest acid does not induce cyclisation of arylalkane product subsequent to its formation in the coupling reaction. Rather it seems likely that acid leads to protiodemetalation to give either demetalated ketone or arylalkane products (figure 4.4 and 4.6).

The poor yields of the ethenyl derivative **70** precluded its further use in the synthesis of an *ortho*-ethenyl Tamoxifen derivative. The indenyl compound **74** is structurally analogous to the benzofulvene **52** (and **53**; Chapter Three). Demethylation and attachment of the *N,N*-dimethylaminoethyl side chain would give a compound exhibiting structural features similar to Tamoxifen.

Of importance to the further development of the chemistry of alkene coupling with orthomanganated aryl ketones is the discovery that product specificity and yields dramatically increase with the use of $NiBr_2(PPh_3)_2$. Though initial investigations suggest Ni(II) is apparently not catalytic and its effect has not so far been found to extend beyond enone-type alkenes, further investigation is warranted to investigate the applicability and define the reactivity and mechanisms of the Ni(II)-mediated reactions.

4.6 Experimental.

Preparation of [2-acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) 6.

Benzylpentacarbonylmanganese **8** (0.393 g, 1.37 mmol) and acetophenone (0.170 g, 1.42 mmol) were dissolved in pet. spirit (15 ml) and refluxed for 6 h. Chromatography (plc) with CH_2Cl_2/pet. spirit (1:3) yielded two bands.

Band one gave $Mn_2(CO)_{10}$ (0.053 g, 10%).

Band two gave yellow crystals of [2-acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) **6** (0.356 g, 1.25 mmol, (pure by NMR) 91%). Recrystallisation from pet. spirit gave fine yellow crystals, mp 93.5-95.0°C (lit.[156] 114-116°C).
^1H NMR (300 MHz) ($CDCl_3$) δ 8.10 (d of d, J = 0.3, 7.4 Hz, 1H, H6), 7.85 (d of d, J = 1.5, 7.7 Hz, 1H, H3), 7.43 (d of t, J = 1.5, 7.4 Hz, 1H, H5), 7.18 (d of t, J = 1.2, 7.7 Hz, 1H, H4), 2.62 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 221.1 (s, CO), 216.6 (s, C=O), 212.9 (s), 212.4 (s), 211.5 (s), (CO), 193.5 (s, C1), 145.4 (s, C2), 141.4 (C6), 133.9 (d, C5), 131.6 (d, C3), 123.9 (d, C4), 24.6 (q, CH_3).
IR (pet. spirit) ν(CO) 2084 (s), 1996 (vs), 1948 (s) cm^{-1}.

Preparation of dibromobis(triphenylphosphine)nickel(II).

Nickel bromide ($NiBr_2.3H_2O$) (1.28 g, 4.70 mmol) was dissolved in ethanol (40 ml). Triphenylphosphine (1.23 g, 4.69 mmol) was dissolved in acetone (7 ml) and the solutions combined with immediate precipitation of the green $NiBr_2(Ph_3P)_2$ complex. Filtering yielded $NiBr_2(Ph_3P)_2$ as dark green crystals (1.60 g, 2.16 mmol, 46%), mp 19 °C (decomp)(lit.[127] 222-225°C).

Preparation of methyl but-2-enoate.

2-Butenoic acid (5.93 g, 68.9 mmol) was dissolved in methanol (60 ml). Concentrated H_2SO_4 (3 drops) was added. The solution was refluxed for 19 h, then poured into water (60 ml) and extracted with ether (60 ml). The ether solution was washed with water (3 x 40 ml) and NaOH (0.1 mol l^{-1}, 1 x 30 ml) and then ($CaCl_2$). The solution was distilled yielding methyl but-2-enoate as a colourless oil (2.39 g, 23.9 mmol, (pure by ^1H NMR) 35%), bp 116-117°C (lit.[4] 118-120°C).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 6.91 (m, 1H, H3), 5.78 (d of t, J = 1.6 , 15.5 Hz, 1H, H2), 3.65 (d, J = 4.4 Hz, 3H, OCH_3), 1.81 (d of t, J = 1.6, 6.2 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 166.8 (s, C=O), 144.6 (d, C3), 122.3 (d, C2), 51.2 (q, OCH_3), 17.8 (q, CH_3).

Reactions of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with methyl propenoate.

The general procedures for reactions employing palladium(II) chloride are outlined in the following experiment.

(a) with Li_2PdCl_4 in Methanol

Lithium chloride (0.057 g, 1.34 mmol) and palladium chloride (0.110g, 0.62 mmol) were added to methanol and the solution stirred for 3 h to dissolve Li_2PdCl_4. The solution was then purged with N_2. Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.265 g, 0.63 mmol) and methyl propenoate (0.70 ml, 7.78 mmol) were then added to the Li_2PdCl_4 solution and stirred for a further 18 h. The solution was filtered and the solvent removed under vacuum to leave a yellow-greenish oil. The oil was then chromatographed (plc), eluting with CH_2Cl_2/pet. spirit (1: 2) to yield three bands.

Band one (R_f = 0.90) gave **9** (0.080 g, 30% recovered), identified by IR.

Band two (R_f = 0.67) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.045 g, 0.177 mmol, 28%), identifed by ^{1}H NMR.

Band three (R_f = 0.45) gave a pale yellow oil (0.088 g), identified as methyl *E*-3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-propenoate **54** (0.259 mmol, (pure by ^{1}H NMR) 41%). Attempts to crystallise **54** proved unsuccessful.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.03 (d, J = 15.8 Hz, 1H, H3), 7.72 (d, J = 8.7 Hz, 1H, H5'), 7.25 (m, 5H, ArH), 6.94 (d, J = 2.6 Hz, 1H, H2'), 6.84 (d of d, J = 2.6, 8.7 Hz, 1H, H4'), 6.19 (d, J = 15.8 Hz, 1H, H2), 4.30 (t, J = 7.3 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.20 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 0.89 (t, J = 7.4 Hz, 3H, CH_3).
The H2 and H3 protons of **54** have a $^3J_{H-H}$ coupling constant of 15.8 Hz and are therefore assigned the *trans* configuration.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.0 (s, C=O), 173.6 (s, C=O), 161.7 (s, C3'), 145.0 (d, C3), 144.4 (s, C1''), 139.7 (s, C6'), 131.5 (d, C5'), 130.6 (s, C1'), 128.9 (d, C2'', C6''), 128.2 (d, C3'', C5''), 126.9 (d, C4''), 120.3 (d, C2), 114.3 (d, C4'),

113.8 (d, C2'), 57.8 (d, CH), 55.3 (q, OCH_3), 51.5 (q, OCH_3), 27.0 (t, CH_2), 12.4 (q, CH_3).
MS : 308 (M^+-OCH_3), 219, 175, 150, 91.

(b) with Li_2PdCl_4 in THF

Li_2PdCl_4 (0.62 mmol) was dissolved in THF (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.246 g, 0.59 mmol) and methyl propenoate (0.70 ml, 7.78 mmol) were added and the solution stirred for 17.5 h. Tlc indicated no significant reaction so the solution was then heated under reflux for a further 4.5 h. Chromatography with CH_2Cl_2/pet. spirit (1: 3) yielded three bands.

Band one (R_f = 0.75) gave **9** (0.017 g, 7% recovered).

Band two (R_f = 0.50) gave pale yellow crystals of methyl 6-methoxy-3-(1-phenylpropyl)-indene-2-carboxylate **55** (0.071 g, 0.220 mmol, 37%), mp 102-3°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.41 (d, J = 8.5 Hz, 1H, H4), 7.25 (m, 5H, ArH), 7.00 (d, J = 2.3 Hz, 1H, H7), 6.69 (d of d, J = 2.3, 8.5 Hz, 1H, H5), 5.42 (d of d, J = 5.0, 6.0 Hz, 1H, CH), 3.85 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 3.71 (d, J = 2.7 Hz, 2H, H2), 2.40 (m, 1H, CH_2), 2.20 (m, 1H, CH_2), 0.96 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 166.4 (s, C=O), 159.7 (s, C6), 157.2 (s, C3), 146.5 (s, C2), 142.6 (s, C1''), 135.8 (s, C3a), 128.9 (s, C7a), 128.3 (d, C2'', C6''), 127.8 (d, C3'', C5''), 126.1 (d, C4), 124.8 (d, C4''), 112.5 (d, C5), 109.7 (d, C7), 55.4 (q, OCH_3), 51.2 (q, CO_2CH_3), 43.2 (d, CH), 39.2 (t, C1), 24.7 (t, CH_2), 12.6 (q, CH_3).
MS : 322 (M^+), 275, 233, 204, 91.
Found : C, 78.32; H, 6.69%.
$C_{21}H_{22}O_3$ calcd : C, 78.23; H, 6.88%.

Band three (R_f = 0.20) gave a pale yellow oil (0.021 g), identified (NMR ratio 2:3) as a mixture of methyl *E*-3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-propenoate **54** (0.078 mmol, 13%) and methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.039 g, 0.016 mmol, 20%). This mixture is inseparable by further chromatography or crystallisation.

Methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.72 (d, J = 8.6 Hz, 1H, H5'), 7.25 (m, 5H, ArH), 6.72 (d, J = 2.5 Hz, 1H, H2'), 6.71 (d of d, J = 2.5, 8.6 Hz, 1H, H4'), 4.30 (t, J = 7.3 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.02 (d of d, J = 7.8, 7.9 Hz,

2H, CH_2), 2.57 (d of d, J = 7.8, 7.9 Hz, 2H, CH_2), 2.18 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 0.90 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 201.3 (s, C=O), 167.0 (s, C=O), 161.4 (s, C3'), 139.4 (s), 138.2 (s), (C1', C1''), 131.2 (d, C5'), 130.6 (s, C6'), 128.9 (d, C3'', C5''), 128.2 (d, C2'', C6''), 127.1 (d, C4''), 116.9 (d, C2'), 111.2 (d, C4'), 57.6 (d, CH), 55.5 (q, OCH_3), 51.7 (q, OCH_3), 35.7 (t, CH_2), 30.0 (t, CH_2), 27.1 (t, CH_2), 12.4 (q, CH_3).

MS : 284 (M^+-C_3H_4O), <u>221</u>,193, 189, 161, 133, 91.

(c) <u>with Li_2PdCl_4 in acetonitrile at ambient temperature</u>

Li_2PdCl_4 (0.62 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.265 g, 0.63 mmol) and methyl propenoate (0.70 ml, 7.78 mmol) were added and the solution stirred for 18.5 h. Chromatography with CH_2Cl_2/pet. spirit (1: 2) yielded three bands.

Band one (R_f = 0.73) gave **9** (0.075 g, 28% recovered).

Band two (R_f = 0.36) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.055 g, 0.216 mmol, 34%).

Band three (R_f = 0.20) gave a pale yellow oil (0.084 g), identified (NMR ratio 2:1) as a mixture of methyl *E*-3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-propenoate **54** (0.165 mmol, 26%) and methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.082 mmol, 13%).

(d) <u>with Li_2PdCl_4 in acetonitrile under reflux</u>

Li_2PdCl_4 (0.62 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.261 g, 0.620 mmol) and methyl propenoate (0.70 ml, 7.78 mmol) were added and the solution stirred for 1 h and then refluxed for a further 3 h. Chromatography using CH_2Cl_2/pet. spirit (1:2) yielded two bands.

Band one (R_f = 0.65) gave white crystals of methyl 6-methoxy-3-(1-phenylpropyl)-indene-2-carboxylate **55** (0.056 g, 0.173 mmol, 28%).

Band two (R_f = 0.56) gave a pale yellow oil (0.056 g), identified (NMR ratio 1:1) as a mixture of methyl *E*-3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-propenoate **56**

(0.083 mmol, 13%) and methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.082 mmol, 13%).

(e) in carbon tetrachloride

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κC]-manganese(I) **9** (0.293 g, 0.698 mmol) and methyl acrylate (1.00 ml, 11.1 mmol) were dissolved in carbon tetrachloride (10 ml) and refluxed for 4.25 h. Chromatography with CH_2Cl_2/pet. spirit (2:1) yielded three bands.

Band one (R_f = 0.88) gave **9** (0.014 g, 5% recovered).

The remaining bands were removed from the plate and rechromatographed (plc) eluting with ethyl acetate/pet. spirit (1:1).

Band one gave methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.062 g, 0.181 mmol, 26%).

Band two gave methyl [1S*,1'R*]-1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57b** (0.027 g, 0.081 mmol, 11%) as a colourless oil. Crystallisation from diethyl ether/pet. spirit (1:15) gave whitish crystals, mp 89-90°C.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.20 (m, 4H, ArH), 6.97 (m, 2H, ArH), 6.77 (d of d, J = 2.3, 8.5 Hz, 1H, H6), 6.62 (d, J = 2.3 Hz, 1H, H4), 3.78 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.39 (d of d, J = 3.1, 8.6 Hz, 1H, H2), 2.96 (d of d, J = 2.7, 11.8 Hz, 1H, CH), 2.91 (d of d, J = 3.1, 16.1 Hz, 1H, H3 *cis* to CO_2CH_3), 2.35 (d of d, J = 8.6, 16.1 Hz, 1H, H3 *trans* to CO_2CH_3), 2.10 (d of q, J = 2.7, 7.3 Hz, 1H, CH_2), 1.76 (m, 1H, CH_2), 0.73 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 174.9 (s, C=O), 160.3 (s, C5), 143.7 (s, C1''), 139.8 (s), 136.2 (s), (C3a, C7a), 129.6 (d), 127.9 (d) (C2''-C6''), 126.8 (d, C4''), 125.3 (d, C7), 113.2 (d, C6), 109.1 (d, C4), 86.5 (s, C-OH), 58.4 (d, C2), 55.3 (q, OCH_3), 52.0 (d, CH), 51.7 (q, OCH_3), 34.2 (t, C3), 22.7 (t, CH_2), 12.5 (q, CH_3).
MS : 338 (M^+-H), 322, 221, <u>189</u>.
Found : C, 74.04; H, 7.09%.
$C_{21}H_{24}O_4$ calcd : C, 74.09; H, 6.81%.

(f) in acetonitrile

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κC]-manganese(I) **9** (0.115 g, 0.273 mmol) was dissolved in acetonitrile (8 ml). Methyl propenoate (0.50 ml, 5.56 mmol) was added and the solution refluxed for 1.75 h. Chromatography with CH_2Cl_2/pet. spirit (3:7) yielded three bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.051 g, 0.202 mmol, 74%).

Band two gave methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.027 g, 0.078 mmol, 29%).

Band three gave a colourless oil (0.014 g), identified (NMR ratio 1:2) as a mixture of the diastereoisomers of methyl 1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57a** and **57b** (0.040 mmol, 15%).

Methyl [1S*,1'S*]-1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57a** has the following spectroscopic properties.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 1H, H7), 7.16 (m, 3H, ArH), 6.96 (m, 3H, ArH), 6.80 (d of d, J = 2.3, 8.7 Hz, 1H, H6), 3.76 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.39 (d of d, J = 3.1, 8.6 Hz, 1H, H2), 2.96 (d of d, J = 2.7, 11.8 Hz, 1H, CH), 2.85 (d of d, J = 3.1, 16.1 Hz, 1H, H3 *cis* to CO_2CH_3), 2.71 (d of d, J = 8.6, 16.1 Hz, 1H, H3 *trans* to CO_2CH_3), 2.15 (d of q, J = 2.7, 7.3 Hz, 1H, CH_2), 1.91 (m, 1H, CH_2), 0.88 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 175.1 (s, C=O), 160.1 (s, C5), 143.7 (s, C1''), 140.1 (s), 139.6 (s), (C3a, C7a), 129.9 (d), 128.2 (d), (C2''-C6''), 126.6 (d, C4''), 125.2 (d, C7), 113.0 (d, C6), 109.3 (d, C4), 86.3 (s, C-OH), 57.4 (d, C2), 55.3 (q, OCH_3), 52.2 (d, CH), 51.4 (q, OCH_3), 33.2 (t, C3), 21.0 (t, CH_2), 12.4 (q, CH_3).
MS : 338 (M^+-H), 322, 221, 189.

(g) with Me_3NO in acetonitile

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.245 g, 0.584 mmol) was dissolved in acetonitrile (5 ml) and purged with N_2. Trimethylamine oxide (0.069 g, 0.908 mmol) was added and the solution stirred for 5 min. Methyl propenoate (0.90 ml, 1.00 mmol) was then added and the solution stirred for a further 18.5 h. Chromatography with ethyl acetate/pet. spirit (1:4) yielded four bands.

Band one (R_f = 0.97) gave **9** (0.009 g, 4% recovered).

Band two (R_f = 0.91) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.015 g, 0.059 mmol, 10%).

Band three (R_f = 0.78) gave methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.168 g, 0.496 mmol, 85%).

Band four (R_f = 0.49) gave methyl 1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57b** as white crystals (0.017 g, 0.05 mmol, 9%).

(h) with $NiBr_2(Ph_3P)_2$ in acetonitrile

$NiBr_2(Ph_3P)_2$ (0.156 g, 0.238 mmol) was dissolved in acetonitrile (13 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.128 g, 0.305 mmol) and methyl propenoate (0.50 ml, 5.56 mmol) were added and the solution refluxed for 1.75 h. Chromatography with CH_2Cl_2/pet. spirit (3:7) yielded four bands.

Band one (R_f = 0.97) gave PPh_3 (0.042 g, 0.159 mmol), identified by ^1H NMR.

Band two (R_f = 0.68) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.015 g, 0.058 mmol, 19%).

Band three (R_f = 0.41) gave methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.068 g, 0.201 mmol, 66%).

Band four (R_f = 0.24) gave a colourless oil (0.012 g), identified as a diastereoisomeric mixture (NMR ratio 1:2) of methyl 1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57a** and **57b** (0.037 mmol, 12%).

(h) with $NiBr_2(Ph_3P)_2$ in methanol under reflux

$(Ph_3P)_2NiBr_2$ (0.165 g, 0.252 mmol) was dissolved in methanol (6 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.104 g, 0.248 mmol) and methyl acrylate (0.70 ml, 7.78 mmol) were added and the solution stirred for 3 h (monitored by tlc) and then refluxed for a further 2.5 h. Chromatography with ethyl acetate/pet. spirit (3:7) yielded three bands.

Band one gave **9** (0.033 g, 32% recovered).

Band two gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.007 g, 0.028 mmol, 11%).

Band three gave methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.037 g, 0.109 mmol, 29%).

$NiBr_2(Ph_3P)_2$ (0.241 g, 0.369 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.156 g, 0.370 mmol) were dissolved in methanol (6 ml). Methyl acrylate (0.70 ml, 7.78 mmol) was added and the solution refluxed for 4 h. Chromatography with ethyl acetate/pet. spirit (1:3) yielded only one band which gave methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.093 g, 0.274 mmol, 75%).

Reactions of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with 3-buten-2-one.

(a) with Li_2PdCl_4 in methanol

Li_2PdCl_4 (0.62 mmol) was dissolved in methanol (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.265 g, 0.63 mmol) and 3-buten-2-one (0.60 ml, 7.21 mmol) were added and the solution stirred for 19 h. Chromatography CH_2Cl_2/pet. spirit (2:1) yielded three bands.

Band one (R_f = 0.90) gave **9** (31% recovered).

Band two (R_f = 0.75) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.049 g, 0.19 mmol, 31%).

Band three (R_f = 0.65) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.078 g, 0.288 mmol, 46%). Crystallisation from diethyl ether/pet. spirit gave fine whitish crystals of **58**, mp 82°C.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.25 (m, 3H, ArH), 7.15 (t, J = 7.3 Hz, 1H, H4") 7.01 (d, J = 2.4Hz, 1H, H7), 6.70 (d of d, J = 2.4Hz, 8.6Hz, 1H, H5), 5.44 (d of d, J = 6.2Hz, 9.7Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.74 (d, J = 3.2Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.35 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 0.94 (t, J = 7.3Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.8 (s, C=O), 159.9 (s, C6), 156.1 (s, C3), 146.1 (s, C2), 142.6 (s, C1"), 136.6 (s, C3a), 135.4 (s, C7a), 128.3 (d, C2", C6"), 127.8 (d, C3", C5"), 126.1 (d, C4), 125.5 (d, C4"), 112.9 (d, C5), 109.7 (d, C7), 55.5 (q, OCH_3), 43.1 (d, CH), 39.9 (t, C1), 30.7 (q, CH_3), 24.9 (t, CH_2), 12.5 (q, CH_3).

MS : 306 (M^+), 291, 263, 236, 215, 203, 189.

(b) with Li_2PdCl_4 in acetonitrile at ambient temperature

Li_2PdCl_4 (0.62 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.268 g, 0.631 mmol) and 3-buten-2-one (1.00 ml, 12.0 mmol) were added and the solution stirred for 18.3 h. Chromatography CH_2Cl_2/pet. spirit (1: 2) yielded three bands.

Band one ($R_f = 0.80$) gave **9** (0.207 g, 77% recovered).

Band two ($R_f = 0.50$) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.005 g, 3%).

Band three ($R_f = 0.40$) gave 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.029 g, 0.090 mmol, 14%) as a pale yellow oil (pure by NMR). Recrystallisation from pet. spirit gave colourless plates, mp 54.5-55.0°C.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.71 (d, J = 9.1 Hz, 1H, H4'), 7.24 (m, 5H, ArH), 6.70 (m, 2H, H3', H5'), 4.30 (t, J = 7.3 Hz, CH), 3.79 (s, 3H, OCH_3), 3.00 (m, 1H, CH_2), 2.86 (m, 1H, CH_2) 2.58 (m, 2H, CH_2), 2.20 (m, 1H, CH_2), 2.05 (s, 3H, CH_3), 2.00 (m, 1H, CH_2), 0.90 (t, J = 7.3Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 207.5 (s, C=O), 202.0 (s, C=O), 161.5 (s, C3'), 144.7 (s, C1''), 139.4 (s, C1'), 131.1 (d, C5'), 130.5 (s, C6'), 128.5 (s), 128.0 (s), (C2'', C3'', C5'',C6''), 126.7 (d, C4''), 116.7 (d, C4'), 110.8 (d, C2'), 57.5 (d, CH), 55.0 (q, OCH_3), 45.1 (t, CH_2), 28.6 (q, CH_3), 28.6 (t, CH_2), 26.6 (t, CH_2), 12.2 (q, CH_3).

MS : 205 (M^+-$PhCHCH_2CH_3$), 161, 91.

Found : C, 78.03; H, 7.41%.

$C_{21}H_{24}O_3$ calcd : C, 77.75; H, 7.46%.

(c) with Li_2PdCl_4 in acetonitrile under reflux

Li_2PdCl_4 (0.62 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.265 g, 0.63 mmol) and 3-buten-2-one (1.00 ml, 12.0 mmol) were added and the solution refluxed for 3.75 h. Chromatography CH_2Cl_2/pet. spirit (1: 2) yielded three bands.

Band one ($R_f = 0.72$) gave **9** (0.003 g, 1% recovered).

Band two ($R_f = 0.47$) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.031 g, 0.101 mmol, 16%).

Band three (R_f = 0.28) gave a pale yellow oil (0.096 g), identified (NMR ratio 1:3) as a mixture of 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.074 mmol, 12%) and *E*-4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-but-3-en-2-one **60** (0.223 mmol, 35%) inseparable by crystallisation or further chromatography.

E-4-(3-Methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-but-3-en-2-one **60** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.88 (d, J = 16.3 Hz, 1H, H4), 7.67 (d, J = 8.7 Hz, 1H, H5'), 7.24 (m, 5H, ArH), 6.98 (d, J = 2.0 Hz, 1H, H2'), 6.87 (d of d, J = 2.0, 8.7 Hz, 1H, H4'), 6.40 (d, J = 16.3 Hz, 1H, H3), 4.35 (t, J = 7.3 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3), 2.22 (m, 1H, CH_2), 1.83 (m, 1H, CH_2), 0.91 (t, J = 7.3 Hz, 3H, CH_3).

The H3 and H4 protons of **60** have a $^3J_{H\text{-}H}$ coupling constant of 16.3 Hz and are therefore assigned the *trans* configuration.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 201.6 (s, C=O), 198.9 (s, C=O), 162.0 (s, C3'), 143.9 (s, C1''), 139.2 (s, C1'), 138.2 (d, C4) 131.3 (d), 130.8 (d), (C3, C6'), 128.9 (d), 128.2 (d), (C2'', C3'', C5'', C6''), 127.2 (d, C4''), 114.6 (d, C4'), 113.5 (d, C2'), 57.6 (d, CH), 55.5 (q, OCH_3), 29.8 (q, CH_3), 26.7 (t, CH_2), 12.4 (t, CH_3).

MS : 322 (M^+), 275, 233, 204, 189, 119.

(d) with Li_2PdCl_4 in THF

Li_2PdCl_4 (0.584 mmol) was dissolved in THF (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.244 g, 0.581 mmol) and 3-buten-2-one (0.70 ml, 8.05 mmol) were added and the solution refluxed for 3 h. Chromatography CH_2Cl_2/pet. spirit (1:3) yielded four bands.

Band one (R_f = 0.85) gave **9** (0.006 g, 2% recovered).

Band two (R_f = 0.68) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.006 g, 0.023 mmol, 4%).

Band three (R_f = 0.50) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.057 g, 0.185 mmol, 32%).

Band four (R_f = 0.33) gave a pale yellow oil (0.057 g), identified (NMR ratio 4:1) as a mixture of 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.141 mmol, 24%) and *E*-4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-but-3-en-2-one **60** (0.035 mmol, 6%).

(e) in carbon tetrachloride

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κO)-phenyl-κC]-manganese(I) **9** (0.135 g, 0.321 mmol) was dissolved in carbon tetrachloride (8 ml) and purged with N_2. 3-Buten-2-one (1.00 ml, 12.0 mmol) was then added and the solution refluxed for 4 h. Chromatography with CH_2Cl_2/pet. spirit (1: 2) yielded three bands.

Band one (R_f = 0.88) gave **9** (2% recovered).

Band two (R_f = 0.67) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.042 g, 0.138 mmol, 43%).

Band three (R_f = 0.58) gave 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.028 g, 0.087 mmol, 27%).

(f) in acetonitrile

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κO)-phenyl-κC]-manganese(I) **9** (0.192 g, 0.457 mmol) was dissolved in acetonitrile (10 ml). 3-Buten-2-one (0.70 ml, 8.4 mmol) was then added and the solution refluxed for 3 h. Chromatography with diethyl ether/pet. spirit (3: 7) yielded four bands.

Band one (R_f = 0.82) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.021 g, 0.083 mmol, 15%).

Band two (R_f = 0.67) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.042 g, 0.138 mmol, 30%).

Band four (R_f = 0.58) gave 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.084 g, 0.259 mmol, 57%).

(g) with Me_3NO in acetonitrile

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κO)-phenyl-κC]-manganese(I) **9** (0.294 g, 0.700 mmol) was dissolved in acetonitrile (3 ml) and purged with N_2. Trimethylamine oxide (0.091 g, 1.199 mmol) was then added and stirred for 5 min. 3-Buten-2-one (0.85 ml, 10.2 mmol) was added and the solution stirred for further 17 h. Chromatography with CH_2Cl_2/pet. spirit (1: 2) yielded three bands.

Band one gave an unknown oil (0.050 g).

^{1}H NMR (300 MHz) (CDCl$_3$) δ 4.50 (s), 4.13 (m), 3.78 (s), 3.65 (m), 3.5 (s, br), 2.44 (m), 2.13 (m), 1.75 (m), 1.58 (m), 1.30 (m), 0.86 (m).
^{13}C NMR (300 MHz) (CDCl$_3$) δ 203.9, 202.1, 202.0, 200.8, 200.2, 142.2, 123.3, 121.1, 120.6, 106.0, 91.9, 88.7, 72.6, 69.9, 69.5, 69.0, 68.8, 35.3, 35.2, 27.8, 24.9, 24.5, 24.4, 24.3, 22.3, 21.7, 20.1, 18.2, 17.6, 16.8, 12.4, 11.5, 11.4, 10.9.

Band two gave 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.0152 g, 0.467 mmol, 67%).

Band three gave [1S*,1'R*]-2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol **61b** (0.030 g, 0.093 mmol, 13%). Attempts to crystallise **61b** proved unsuccessful.
^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.20 (m, 3H, ArH), 7.11 (d, J = 8.5 Hz, 1H, H7), 6.95 (m, 2H, ArH), 6.77 (d of d, J = 2.1, 8.5 Hz, 1H, H6), 6.61 (d, J = 2.1 Hz, 1H, H4), 3.78 (s, 3H, OCH$_3$), 3.53 (d of d, J = 2.9, 8.6 Hz, 1H, H2), 3.30 (s, 1H, OH), 2.92 (d of d, J = 2.5, 11.6 Hz, 1H, CH), 2.82 (d of d, J = 2.9, 16.5 Hz, 1H, H3 *cis* to COCH$_3$), 2.30 (d of d, J = 8.6, 16.5 Hz, 1H, H3 *trans* to COCH$_3$), 2.05 (s, 3H, CH$_3$), 2.00 (m, 1H, CH$_2$), 1.73 (m, 1H, CH$_2$), 0.71 (t, J = 7.3Hz, 3H, CH$_3$).
^{13}C NMR (300 MHz) (CDCl$_3$) δ 211.2 (s, C=O), 160.4 (s, C5), 143.4 (s, C1''), 139.9 (s), 136.7 (s), (C3a, C7a), 129.6 (d), 127.9 (d), (C2''-C6''), 126.8 (d, C4''), 125.2 (d, C7), 113.3 (d, C6), 109.1 (d, C4), 87.1 (s, C-OH), 59.1 (d), 58.3 (d), (CH, C2), 55.3 (q, OCH$_3$), 33.5 (t, C3), 30.7 (q, CH$_3$), 22.4 (t, CH$_2$), 12.4 (q, CH$_3$).
MS : 306 (M$^+$-H$_2$O), 263, 205, 161.

(h) with NiBr$_2$(Ph$_3$P)$_2$ in acetonitrile

NiBr$_2$(Ph$_3$P)$_2$ (0.181 g, 0.276 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.119 g, 0.283 mmol) were dissolved in acetonitrile (6 ml) and purged with N$_2$. 3-Buten-2-one (0.50 ml, 6.01 mmol) was added and the solution stirred for 40 min at ambient temperature during which the solution turned from dark green to yellow in colour. Chromatography with CH$_2$Cl$_2$/pet. spirit (3:7) yielded two bands.

Band one (R$_f$ = 0.85) gave **9** (0.089 g, 75% recovered).

Band two (R$_f$ = 0.58) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.013 g, 0.051 mmol, 18%).

(i) with $NiBr_2(Ph_3P)_2$ in acetonitrile under reflux

$NiBr_2(Ph_3P)_2$ (0.170 g, 0.259 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.117 g, 0.279 mmol) were dissolved in acetonitrile (5 ml), purged with N_2 and then heated. At reflux temperature 3-buten-2-one (0.60 ml, 7.20 mmol) was added and the solution refluxed for further 30 min. Chromatography with CH_2Cl_2/pet. spirit (3:7) yielded a colourless oil (0.0.087 g), identified (NMR ratio 2:3) as a diastereoisomeric mixture of 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol, **61a** and **61b** (0.268 mmol, 96%). Isomer separation was achieved by further chromatography eluting with diethyl ether/pet. spirit (1:4).

[1S*,1'S*]-2-Acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol **61a** crystallised from ether/pet. spirit (1:20) to give clear prisms (pure by NMR), mp 124-126°C.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.26 (d, J = 8.2 Hz, 1H, H7), 7.20 (m, 6H, ArH), 6.77 (d of d, J = 2.2, 8.2 Hz, 1H, H6), 6.62 (d, J = 2.2 Hz, 1H, H4), 3.77 (s, 3H, OCH_3), 3.50 (d of d, J = 2.6, 8.4 Hz, 1H, H2), 3.43 (s, 1H, OH), 2.91 (d of d, J = 2.6, 16.3 Hz, 1H, H3 *cis* to $COCH_3$), 2.73 (d of d, J = 3.3, 11.6 Hz, 1H, CH), 2.61 (d of d, J = 8.4, 16.3 Hz, 1H, H3 *trans* to $COCH_3$), 2.02 (m, 1H, CH_2), 1.96 (s, 3H, $COCH_3$), 1.71 (m, 1H, CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 211.3 (s, C=O), 160.2 (s, C5), 142.2 (s, C1''), 140.4 (s), 138.5 (s), (C3a, C7a), 129.9 (d), 127.9 (d), (C2''-C6''), 128.3 (d, C7), 126.7 (d, C4''), 113.0 (d, C6), 109.3 (d, C4), 87.1 (s, C-OH), 57.9 (d), 57.5 (d), (CH, C2), 55.3 (q, OCH_3), 33.4 (t, C3), 28.9 (q, CH_3), 21.2 (t, CH_2), 12.5 (q, CH_3).

Found : C, 76.84; H, 7.01%.

$C_{21}H_{24}O_3$ calcd : C, 77.75; H, 7.46%.

(j) with 10% mol $NiBr_2(Ph_3P)_2$ in acetonitrile under reflux

$NiBr_2(Ph_3P)_2$ (0.025 g, 0.037 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.155 g, 0.369 mmol) were dissolved in acetonitrile (5 ml) and purged with N_2. 3-Buten-2-one (0.60 ml, 7.20 mmol) was added and the solution refluxed for 2 h. Chromatography with CH_2Cl_2/pet. spirit (3:7) yielded four bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.005 g, 0.020 mmol, 5%).

Band two gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.017 g, 0.056 mmol, 15%).

Band three gave 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.040 g, 0.123 mmol, 33%).

Band four gave a colourless oil (0.057 g), identified (NMR ratio 1:2) as a diastereoisomeric mixture of 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol, **61a** and **61b** (0.176 mmol, 48%).

(k) with $NiBr_2(Ph_3P)_2$ in methanol at ambient temperature

$NiBr_2(Ph_3P)_2$ (0.260 g, 0.474 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.198 g, 0.471 mmol) were dissolved in methanol (8 ml). 3-Buten-2-one (0.70 ml, 8.41 mmol) was added and the solution stirred for 18 h. The solvent was removed under reduced pressure to leave a yellow gelatinous residue. Chromatography with ethyl acetate/pet. spirit (3:7)

Band one (R_f = 0.94) gave **9** (0.174 g, 88% recovered).

Band two (R_f = 0.74) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.010 g, 0.039 mmol, 8%).

(l) with $NiBr_2(Ph_3P)_2$ in methanol under reflux

$NiBr_2(Ph_3P)_2$ (0.310 g, 0.350 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.144 g, 0.343 mmol) were dissolved in methanol (10 ml). 3-Buten-2-one (0.70 ml, 8.41 mmol) was added and the solution refluxed for 2 h. The solvent was removed under reduced pressure to leave a yellow oily residue. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.94) gave a yellow oil (0.056 g), identified (NMR) as **9** (26% recovered).

Band two (R_f = 0.56) gave 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.036 g, 0.103 mmol, 30%).

Band three (R_f = 0.40) gave a colourless oil (0.009 g), identified (NMR ratio 1:2) as a diastereoisomeric mixture of 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol, **61a** and **61b** (0.034 mmol, 10%).

(m) in acetonitrile under CO atmosphere

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.220 g, 0.523 mmol) was dissolved in acetonitrile (10 ml). 3-Buten-2-one (0.60 ml, 7.21 mmol) was then added and the solution heated to 75°C under an atmosphere of CO (15 atm) for 25 h. Chromatography with diethyl ether/pet. spirit (1:4) yielded five bands.

Band one gave $Mn_2(CO)_{10}$ (0.034 g, 0.088 mmol, 17%).

Band two gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.001 g, 0.004 mmol, 1%).

Band three gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.021 g, 0.069 mmol, 13%).

Band four gave a pale yellow oil (0.074 g), identified (NMR) as a mixture of 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.102 mmol, 19%) and 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol **61a** (0.127 mmol, 24%).

Band five gave a colourless oil (0.069 g), identified (NMR ratio 2:3) as a mixture of 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol **61a** and **61b** (0.213 mmol, 41%).

(n) in acetonitrile with diphenylethyne

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.176 g, 0.419 mmol) and diphenylethyne (0.151 g, 0.848 mmol) were dissolved in acetonitrile (8 ml) and purged with N_2. 3-Buten-2-one (0.5 ml, 6.00 mmol) was added and the solution refluxed for 2 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one ($R_f = 0.97$) gave diphenylacetylene (0.009 g).

Band two ($R_f = 0.84$) gave a pale yellow oil (0.009 g), identified by (^{1}H NMR ratio 2:1) as a mixture of 5-methoxy-2,3-diphenyl-1-(1-phenylpropyl)-inden-1-ol **36** (0.010 mmol, 3%) and 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.020 mmol, 4%) respectively.

Band three ($R_f = 0.56$) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.036 g, 0.116 mmol, 28%).

Band four (R_f = 0.44) gave a pale yellow oil (0.049 g), identified (^{1}H NMR 4:3:3) as 4-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-2-butanone **59** (0.063 mmol, 15%) and 2-acetyl-5-methoxy-1-(1-phenylpropyl)-1-indanol **61a** and **61b** (0.092 mmol, 22 %) respectively.

Reactions of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with methyl but-2-enoate.

(a) with Li_2PdCl_4 in acetonitrile

Li_2PdCl_4 (0.624 mmol) was dissolved in acetonitrile (8 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.252 g, 0.600 mmol) and methyl but-2-enoate (methyl crotonate) (0.50 ml, 4.72 mmol) were added and the solution refluxed for 3 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one (R_f = 0.84) gave a pale yellow oil tentatively identified (NMR) as methyl 6-methoxy-1-methyl-3-(1-phenylpropyl)-indene-2-carboxylate **62** (0.005 g, 0.015 mmol, 2%).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.42 (d, J = 7.3 Hz, 2H, H2'', H6''), 7.34 (m, 2H, H3'', H5''), 7.26 (m, 1H, H4''), 7.12 (d, J = 8.6 Hz, 1H, H4), 6.94 (J = 2.3 Hz, 1H, H7), 6.64 (d of d, J = 2.3, 8.7 Hz, 1H, H5), 5.31 (m, 1H, CH), 3.86 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 2.35 (m, 1H, CH_2), 2.18 (m, 1H, CH_2), 1.88 (d of d, J = 1.8, 6.9 Hz, 2H, H1), 1.42 (d, J = 1.8 Hz, 3H, CH_3), 0.98 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 173.2 (s, C=O), 159.8 (s, C6), 152.9 (s, C3), 144.8 (s, C2), 142.6 (s, C1''), 138.1 (s, C3a), 131.2 (s, C7a), 128.2 (d, C2'', C6''), 127.7 (d, C3'', C5''), 126.1 (d, C4), 125.0 (d, C4''), 112.3 (d, C5), 108.9 (d, C7), 55.5 (q, OCH_3), 51.1 (q, CO_2CH_3), 44.8 (d, C1), 43.0 (d, CH), 24.7 (t, CH_2), 18.0 (q, CH_3), 12.4 (q, CH_3).

Band two (R_f = 0.77) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.019 g, 0.076 mmol, 13%).

Band three (R_f = 0.70) gave *E*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **14** (0.012 g, 0.044 mmol, 7%).

Band four (R_f = 0.58) gave a red oil identified as methyl *E*-3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butenoate **63** (0.026 g, 0.073 mmol, 12%).

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.68 (d, J = 8.6 Hz, 1H, H5'), 7.23 (m, 5H, ArH), 6.77 (d of d, J = 2.6, 8.6 Hz, 1H, H4'), 6.62 (d, J = 2.6 Hz, 1H, H2'), 5.56 (d, J = 1.3 Hz, 1H, H2), 4.24 (t, J = 7.3 Hz, 1H, CH), 3.80 (s, 3H, OCH$_3$), 3.72 (s, 3H, CO$_2$CH$_3$), 2.35 (d, J = 1.3 Hz, 3H, CH$_3$), 2.14 (m, 1H, CH$_2$), 1.81 (m, 1H, CH$_2$), 0.87 (t, J = 7.3 Hz, 3H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 200.8 (s, C=O), 166.8 (s, C=O), 161.8 (s, C3'), 159.4 (s, C3), 147.1 (s, C1''), 139.3 (s, C6'), 131.5 (d, C5'), 131.2 (s, C1'), 128.7 (d), 128.2 (d), (C2'', C3'', C5'', C6''), 127.0 (d, C4''), 117.4 (d, C2), 114.6 (d, C2'), 112.6 (C4'), 57.3 (d, CH), 55.5 (q, OCH$_3$), 51.0 (q, CO$_2$CH$_3$), 26.8 (t, CH$_2$), 21.0 (q, CH$_3$), 12.3 (CH$_3$).

MS : 325 (M$^+$), 293, 233, 201, 145.

(b) in acetonitrile

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.148 g, 0.352 mmol) was dissolved in acetonitrile (8 ml). Methyl but-2-enoate (0.50 ml, 4.72 mmol) was added and the solution refluxed for 3 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.016 g, 0.065 mmol, 18%).

Band two gave methyl [1S*,2S*,3R*,1'S*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate **64a** (0.008 g, 0.023 mmol, 6%) as a colourless oil.
^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.35 (d, J = 8.3 Hz, 1H, H7), 7.21 (m, 5H, ArH), 6.81 (d of d, J = 2.3, 8.7 Hz, 1H, H6), 6.56 (d, J = 2.3 Hz, 1H, H4), 3.79 (s, 3H, OCH$_3$), 3.56 (s, 3H, OCH$_3$), 3.41 (d, J = 8.0 Hz, 1H, H2 *trans* to 3-CH$_3$), 3.04 (m, 1H, H3), 2.72 (d of d, J = 3.0, 12.6 Hz, 1H, CH), 2.15 (m, 1H, CH$_2$), 1.90 (m, 1H, CH$_2$), 1.15 (d, J = 7.1 Hz, 3H, 3-CH$_3$), 0.67 (t, J = 7.2 Hz, 3H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 173.8 (s, C=O), 160.3 (s, C5), 146.1 (C3a), 140.6 (s, C1''), 139.0 (s, C7a), 129.9 (d), 127.9 (d), (C2''-C6''), 126.5 (d, C4''), 124.9 (d, C7), 112.6 (d, C6), 108.4 (d, C4), 84.9 (s, C-OH), 58.4 (d, C2), 56.1 (d, CH), 55.4 (q, OCH$_3$), 51.2 (q, OCH$_3$), 38.8 (d, C3), 21.2 (t, CH$_2$), 15.7 (q, 3-CH$_3$), 12.4 (q, CH$_3$).

MS : 336 (M$^+$-H$_2$O), 277, 235, 203, 177.

Band three gave a pale yellow oil (0.025 g), identified (NMR ratio 5:3) as a diastereoisomeric mixture of methyl 1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate **64b** and **64c** (0.071 mmol, 20%).

Methyl [1S*,2S*,3R*,1'R*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate **64b** has the following spectral characteristics.

^{1}H NMR (300 MHz) (CDCl3) δ 7.18 (m, 3H, ArH), 7.07 (d, J = 8.4 Hz, 1H, H7), 6.96 (m, 2H, ArH), 6.75 (d of d, J = 2.3, 8.4 Hz, 1H, H6), 6.57 (d, J = 2.3 Hz, 1H, H4), 3.87 (s, br, 1H, OH), 3.79 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (d, J = 8.7 Hz, 1H, H2 *trans* to 3-CH_3), 2.92 (d of d, J = 2.7, 10.3 Hz, 1H, CH), 2.67 (m, 1H, H3), 2.05 (d of q, J = 2.7, 7.3 Hz, 1H, CH_2), 1.77 (m, 1H, CH_2), 1.09 (d, J = 7.2 Hz, 3H, 3-CH_3), 0.72 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) (CDCl3) δ 173.8 (s, C=O), 160.4 (s, C5), 147.8 (s, C3a), 140.0 (s, C1''), 136.7 (s, C7a), 129.6 (d), 127.8 (d), (C2''-C6''), 126.7 (d, C4''), 125.0 (d, C7), 112.9 (d, C6), 108.2 (d, C4), 85.0 (s, C-OH), 57.6 (d), 57.4 (d), (CH, C2), 55.4 (q, OCH_3), 51.3 (q, OCH_3), 39.2 (d, C3), 22.9 (t, CH_2), 16.6 (q, 3-CH_3), 12.5 (q, CH_3).

MS : 323 (M^+-OCH_3), 277, 235, <u>203</u>, 177.

Methyl [1R*,2S*,3R*,1'S*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate **64c** has the following spectral characteristics.

^{1}H NMR (300 MHz) (CDCl3) δ 7.45 (d, J = 8.5 Hz, 1H, H7), 7.15 (m, 5H, ArH), 6.80 (d of d, J = 2.4, 8.5 Hz, 1H, H6), 6.59 (d, J = 2.4 Hz, 1H, H4), 4.08 (s, br, 1H, OH), 3.78 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.44 (m, 1H, H3), 3.13 (d of d, J = 3.0, 11.8 Hz, 1H, CH), 2.95 (d, J = 7.4 Hz, 1H, H2 *trans* to 3-CH_3), 2.31 (d of q, J = 3.0, 7.3 Hz, 1H, CH_2), 1.91 (m, 1H, CH_2), 1.10 (d, J = 7.0 Hz, 3H, 3-CH_3), 0.78 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) (CDCl3) δ 175.6 (s, C=O), 160.4 (s, C5), 147.7 (s, C3a), 140.1 (s, C1''), 137.8 (s, C7a), 130.4 (d), 127.9 (d), (C2''-C6''), 126.5 (d, C4''), 125.0 (d, C7), 113.2 (d, C6), 108.4 (d, C4), 85.2 (s, C-OH), 57.8 (d), 57.0 (d), (CH, C2), 55.4 (q, OCH_3), 52.0 (q, OCH_3), 41.5 (d, C3), 21.9 (t, CH_2), 18.5 (q, 3-CH_3), 12.7 (q, CH_3).

MS : 336 (M^+-H_2O), 277, 235, <u>203</u>.

Band four gave a yellow oil (0.057 g), identified (NMR ratio 1:2) as a diastereoisomeric mixture of methyl 1-hydroxy-5-methoxy-1-(phenylpropyl)-indane-2-carboxylate **64d** and **64e** (0.161 mmol, 46%). Crystallisation from diethyl ether/pet. spirit gave colourless chunky crystals of methyl [1S*,2S*,3R*,1'R*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate **64e**, mp 117-121°C.

^{1}H NMR (300 MHz) (CDCl3) δ 7.24 (m, 6H, ArH), 6.82 (d of d, J = 2.3, 8.6 Hz, 1H, H6), 6.69 (d, J = 8.6 Hz, 1H, H7), 4.10 (s, br, 1H, OH), 3.80 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.45 (m, 1H, H3), 3.19 (d of d, J = 4.4, 10.1 Hz, 1H, CH), 2.88 (d, J = 8.2 Hz, 1H, H2 *cis* to 3-CH_3), 1.85 (m, 2H, CH_2), 1.22 (d, J = 6.8 Hz, 3H, 3-CH_3), 0.79 (t, 3H, CH_3).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 174.8 (s, C=O), 160.4 (s, C5), 148.2 (s, C3a), 139.6 (s, C1''), 136.5 (s, C7a), 129.9 (d), 127.8 (d), (C2''-C6''),.126.7 (d, C4''), 124.5 (d, C7), 113.5 (d, C6), 108.4 (d, C4), 85.2 (s, C-OH), 56.7 (d, C2), 56.3 (d, CH), 55.3 (q, OCH$_3$), 51.7 (q, OCH$_3$), 41.4 (d, C3), 23.0 (t, CH$_2$), 18.2 (q, 3-CH$_3$), 12.7 (q, CH$_3$).

MS : 336 (M$^+$-H$_2$O), 277, 235, 203, 175.

Found : C, 74.30; H, 7.42%.

$C_{22}H_{26}O_4$ calcd : C, 74.55; H, 7.39%.

Crystals suitable for X-ray crystallography were obtain by employing diethyl ether/pentane solvent diffusion.

Methyl [1S*,2R*,3R*,1'R*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate **64d** has the following spectral characteristics.

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.25 (m, 6H, ArH), 6.80 (d of d, J = 2.3, 8.6 Hz, 1H, H6), 6.55 (d, J = 2.3 Hz, 1H, H4), 3.80 (s, br, 6H, OCH$_3$), 3.03 (d of d, J = 2.5, 11.8 Hz, 1H, CH), 2.92 (d, J = 8.4 Hz, 1H, H2 *cis* to 3-CH$_3$), 2.31 (m, 1H, CH$_2$), 2.06 (m, 1H, H3), 1.62 (m, 1H, CH$_2$), 1.13 (d, J = 6.6 Hz, 3H, 3-CH$_3$), 0.63 (t, J = 7.3 Hz, 3H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 172.6 (s, C=O), 160.4 (s, C5), 147.5 (s, C3a), 139.4 (s, C1''), 134.9 (s, C7a), 129.4 (d, C7), 127.3 (d), 127.0 (d), (C2''-C6''), 125.5 (d, C4''), 112.3 (d, C6), 108.2 (d, C4), 85.1 (s, C-OH), 66.9 (d, C2), 55.5 (d, CH), 55.3 (q, OCH$_3$), 51.4 (q, OCH$_3$), 37.8 (d, C3), 23.5 (t, CH$_2$), 18.8 (q, 3-CH$_3$), 12.2 (q, CH$_3$).

MS : 336 (M$^+$-H$_2$O), 277, 235, 203, 175.

(c) with $NiBr_2(PPh_3)_2$ in acetonitrile

$NiBr_2(PPh_3)_2$ (0.169 g, 0.259 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.120 g, 0.286 mmol) were dissolved in acetonitrile (8 ml). Methyl but-2-enoate (0.50 ml, 4.72 mmol) was added and the solution refluxed for 3 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one (R_f = 0.89) gave PPh_3 (0.009 g).

Band two (R_f = 0.80) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.041 g, 0.162 mmol, 57%).

Band three (R_f = 0.46) gave a yellow oil (0.018 g). Crystallisation from diethyl ether/pet. spirit (1:5) yielded fine white crystals of methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-butanoate **65** (0.014 g, 0.041 mmol, *ca.* 14%), mp 165-166°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.63 (d, J = 8.7 Hz, 1H, H5'), 7.21 (m, 5H, ArH), 6.77 (d, J = 2.3 Hz, 1H, H2'), 6.68 (d of d, J = 2.3, 8.7 Hz, 1H, H4'), 4.23 (d of t, J = 1.6, 7.3 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.50 (m, 1H, H3), 2.69 (d, J = 6.6 Hz, 1H, H3), 2.50 (d, J = 8.4 Hz, 1H, CH_2), 2.20 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 1.03 (d, J = 6.6 Hz, 3H, CH_3), 0.92 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 203.7 (s, C=O), 172.6 (s, C=O), 161.5 (s, C3'), 143.9 (s, C1''), 139.2 (s, C1'), 131.2 (s, C6'), 129.9 (d, C5'), 128.7 (d), 128.5 (d), (C2''-C6''), 126.9 (d, C4''), 133.0 (d, C2'), 110.3 (d, C4'), 59.2 (d, CH), 55.3 (q, OCH_3), 51.4 (q, OCH_3), 42.4 (t, C2), 31.7 (d, C3), 21.7 (q, C4), 12.4 (q, CH_3).
MS : 235 (M^+-$PhCHCH_2CH_3$), 203, 193, 175, 161.

Band four (R_f = 0.34) gave a diastereoisomeric mixture of methyl 1-hydroxy-5-methoxy-1-(phenylpropyl)-indane-2-carboxylate **64** (0.035 g, 0.100 mmol, 35%).

Reactions of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with ethenyl ethanoate.

(a) with Li_2PdCl_4 in methanol

Li_2PdCl_4 (0.610 mmol) was dissolved in methanol (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.249 g, 0.593 mmol) and ethenyl ethanoate (vinyl acetate) (0.85 ml, 9.2 mmol) were added and the solution stirred at ambient temperature for 18 h. Chromatography with (1:3) ethyl acetate/pet. spirit yielded four bands.

Band one (R_f = 0.97) gave **9** (0.154 g, 62% recovered).

Band two (R_f = 0.88) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.021 g, 0.083 mmol, 14%).

Band three (R_f = 0.79) gave a colourless oil (0.003 g), characterised spectroscopically as 1-(2-(2-methoxy-1-ethanyl)-4-methoxyphenyl)-2-phenyl-1-butanone **66** (0.010 mmol, 2%). Attempts to crystallise **66** proved unsuccessful.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.10 (m, 4.5H, ArH), 7.03 (m, 3.5H, ArH), 4.31 (t, J = 7.3 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.08 (m, 1H, CH_2), 2.57 (m, 1H, CH_2), 2.17 (m, 1H, CH_2), 1.82 (m, 1H, CH_2), 0.89 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 161.8 (s, C3'), 139.6 (s, C1''), 130.9 (d, C5'), 128.7 (d), 128.3 (d), (C2''-C6''), 128.0 (d, C4''), 116.9 (d, C4'), 111.2 (d, C2'), 58.1 (d,

CH), 55.7 (q, OCH_3), 53.5 (q, OCH_3), 35.7 (t, CH_2), 30.6 (t, CH_2), 21.1 (t, CH_2), 12.4 (q, CH_3).
MS : 252 (M^+-CH_2CH_2OMe), 225, 193.

Band four (R_f = 0.73) gave a colourless oil (0.007 g), characterised spectroscopically as *E*-1-(2-(2-methoxy-1-ethenyl)-4-methoxyphenyl)-2-phenyl-1-butanone **67** (0.023 mmol, 4%). Attempts to crystallise **67** proved unsuccessful.
^1H NMR (300 MHz) ($CDCl_3$) δ 8.04 (d, J = 15.8 Hz, 1H, H2'), 7.72 (d, J = 8.6 Hz, 1H, H5), 7.26 (m, 5H, ArH), 6.95 (d, J = 2.3 Hz, 1H, H2), 6.85 (d of d, J = 2.3, 8.6 Hz, 1H, H4), 6.19 (d, J = 15.8 Hz, 1H, H1'), 4.30 (t, J = 7.1 Hz, 1H, CH), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.21 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 198.0 (s, C=O), 159.7 (s, C3), 145.1 (d, C1'), 139.4 (s), 138.3 (s), (C1'', C1), 131.2 (d, C5), 128.9 (d), 128.3 (d), (C2''-C6''), 127.1 (d, C4''), 126.8 (s, C6), 120.3 (d, C2'), 114.3 (d, C4), 113.8 (d, C2), 57.6 (d, CH), 55.5 (q, OCH_3), 51.8 (q, OCH_3), 27.1 (t, CH_2), 12.4 (q, CH_3).
MS : 309 (M^+-H), 237, 221, 193, 189, 161, 139.

(b) with Li_2PdCl_4 in ethanol

Li_2PdCl_4 (0.412 mmol) was dissolved in ethanol (5 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.172 g, 0.410 mmol) and ethenyl ethanoate (0.50 ml, 5.4 mmol) were added and the solution stirred at ambient temperature for 21.5 h. Chromatography with (3:7) diethyl ether/pet. spirit yielded three bands.

Band one gave **9** (0.076 g, 44% recovered).

Band two gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.017 g, 0.068 mmol, 16%).

Band three gave a colourless oil (0.006 g), identified as a mixture (NMR ratio 1:2) of (2-(2-ethoxy-1-ethanyl)-4-methoxyphenyl)-2-phenyl-1-butanone **68** (0.006 mmol, 1%) and *E*-(2-(2-ethoxy-1-ethenyl)-4-methoxyphenyl)-2-phenyl-1-butanone **69** (0.012 mmol, 3%).

(2-(2-Ethoxy-1-ethanyl)-4-methoxyphenyl)-2-phenyl-1-butanone **68** has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m, 6H, ArH), 6.73 (d, J = 2.3 Hz, 1H, H2), 6.69 (d of d, J = 2.3, 8.7 Hz, 1H, H4), 4.26 (m, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 3.04 (m,

2H, CH_2), 2.55 (m, 2H, CH_2), 2.23 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.30 (t, J = 7.1 Hz, 3H, CH_3), 0.88 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.1 (s, C=O), 161.7 (s, C3), 144.5 (s, C1''), 139.7 (s, C6), 131.4 (d, C5), 130.7 (s, C1), 128.9 (d), 128.4 (d), (C2''-C6''), 126.9 (d, C4''), 116.8 (d, C4), 111.2 (d, C2), 60.3 (t, OCH_2), 57.8 (d, CH), 55.3 (q, OCH_3), 35.9 (t, CH_2), 32.0 (t, CH_2), 22.7 (t, CH_2), 14.2 (q, CH_3), 12.4 (q, CH_3).

MS : 253 (M^+-C_4H_3O), 164, 163, 119.

E-(2-(2-Ethoxy-1-ethenyl)-4-methoxyphenyl)-2-phenyl-1-butanone **69** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 8.00 (d, J = 16.0 Hz, 1H, H2'), 7.69 (d, J = 8.7 Hz, 1H, H5), 7.30 (m, 5H, ArH), 6.96 (d, J = 2.4 Hz, 1H, H2), 6.85 (d of d, J = 2.4, 8.7 Hz, 1H, H4), 6.18 (d, J = 16.0 Hz, 1H, H1'), 4.28 (m, 2H, OCH_2), 4.11 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 2.23 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.34 (t, J = 7.1 Hz, 3H, CH_3), 0.91 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 201.4 (s, C=O), 161.8 (s, C3), 144.7 (d, C1), 139.3 (s), 138.2 (s), (C1'', C6), 131.1 (d, C5), 131.0 (s, C1), 128.8 (d), 128.3 (d), (C2''-C6''), 127.1 (d, C4''), 120.8 (d, C2'), 114.3 (d, C4), 113.7 (d, C2), 60.6 (t, OCH_2), 57.7 (d, CH), 55.5 (q, OCH_3), 27.0 (t, CH_2), 14.3 (q, CH_3), 12.4 (q, CH_3).

MS : 309 (M^+-CH_3), 227, 235, 189, 163, 161.

(c) with Li_2PdCl_4 in acetonitrile

Li_2PdCl_4 (0.864 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.361 g, 0.860 mmol) and ethenyl ethanoate (1 ml, 10.9 mmol) were added and the solution refluxed for 4 h. Chromatography with (1:2) ethyl acetate/pet. spirit yielded five bands.

Band one (R_f = 0.90) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.076 g, 0.301 mmol, 35%).

Band two (R_f = 0.82) gave 1-(2-ethenyl-4-methoxyphenyl)-2-phenyl-1-butanone **70** (0.067 g, 0.241 mmol, 28%) as a colourless oil. Attempts to crystallise **70** proved unsuccessful.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 1H, H6), 7.26 (m, 5H, ArH), 7.10 (d of d, J = 10.9, 17.3 Hz, 1H, H'), 6.98 (d, J = 2.5 Hz, 1H, H3), 6.76 (d of d, J = 2.5, 8.6 Hz, 1H, H5), 5.57 (d of d, J = 1.2, 17.3 Hz, 1H, H2' *cis* to Ar), 5.29 (d of d, J = 1.2, 10.9 Hz, 1H, H2' *trans* to Ar), 4.31 (t, J = 7.2 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 2.19 (m, 1H, CH_2), 1.87 (m, 1H, CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.5 (s, C=O), 161.7 (s, C4), 141.0 (s, C1''), 136.5 (d, C1'), 130.8 (s, C1), 130.7 (d, C6), 128.6 (d), 128.2 (d) (C2''-C6''), 126.9 (d, C4''), 116.2 (d, C5), 112.8 (t, C2'), 112.5 (d, C3), 58.0 (d, CH), 55.3 (q, OCH_3), 27.1 (t, CH_2), 12.4 (q, CH_3).

MS : 280 (M^+), 250, 223. 207, 189, 161, 133, 118.

Band three (R_f = 0.65) gave white crystals of *E*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **14** (0.017 g, 0.060 mmol, 7%).

Band four (R_f = 0.52) gave a pale yellow oil (0.007 g), characterised (^1H NMR) as *Z*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **71** (0.026 mmol, 3%).

^1H NMR (300 MHz) ($CDCl_3$) δ 7.81 (d, J = 8.7 Hz, 1H, H3), 7.38 (m, 7H, ArH), 3.91 (s, 3H, OCH_3), 2.92 (q, J = 7.4 Hz, 2H, CH_2), 0.88 (t, J = 7.5 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 129.0 (d), 128.2 (d), (C2''-C6''), 127.7 (d, C4''), 124.4 (d, C5), 123.7 (d, C4), 107.2 (d, C2), 55.9 (q, OCH_3), 22.7 (t, CH_2), 14.2 (q, CH_3).

MS : 280 (M^+), 265, 237, 194, 165.

Band five (R_f = 0.39) gave 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanal **72** (0.053 g, 0.172 mmol, 21%) as a pale yellow oil. Attempts to crystallise **72** proved unsuccessful.

^1H NMR (300 MHz) ($CDCl_3$) δ 9.71 (s, 1H, HC=O), 7.72 (d, J = 8.7 Hz, 1H, H5'), 7.20 (m, 5H, ArH), 7.61 (d of d, J = 2.7, 8.6 Hz, 1H, H4'), 6.70 (d, J = 2.7 Hz, 1H, H2'), 4.31 (t, J = 7.3 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.00 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 2.10 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 0.90 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.1 (s, C=O), 201.9 (d, HC=O), 161.8 (s, C3'), 144.4 (s, C1''), 139.6 (s, C1'), 131.6 (d, C5'), 130.3 (s, C6'), 128.8 (d), 128.2 (d), (C2''-C6''), 127.0 (d, C4''), 117.0 (d, C4'), 111.2 (d, C2'), 57.7 (d, CH), 55.4 (OCH_3), 45.6 (t, CH_2), 27.4 (t, CH_2), 26.8 (t, CH_2), 12.4 (q, CH_3).

MS : 191 (M^+-$PhCHCH_2CH_3$), 163, 145, 135, 121.

(d) with Me_3NO in acetonitrile

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.188 g, 0.447 mmol) was dissolved in acetonitrile (3 ml) and purged with N_2. Trimethylamine oxide (0.048 g, 0.628 mmol) was added and the solution stirred for 5 min, ethenyl ethanoate (0.87 ml, 9.44 mmol) was then added and the solution stirred for a further 19 h. Chromatography with ethyl acetate/pet. spirit (3:7) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.0879 g, 0.346 mmol, 77%).

(c) with $NiBr_2(Ph_3P)_2$ in acetonitrile

$(Ph_3P)_2NiBr_2$ (0.326 g, 0.498 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.207 g, 0.493 mmol) were dissolved in acetonitrile (6 ml) and purged with N_2. Ethenyl ethanoate (0.7 ml, 7.61 mmol) was added and the solution refluxed for 5 h. Chromatography with ethyl acetate/pet. spirit (1:3) yielded two bands.

Band one (R_f = 0.97) gave PPh_3 (0.056 g).

Band two (R_f = 0.83) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.109 g, 0.429 mmol, 87%).

Reactions of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with diethyl maleate.

(a) with Li_2PdCl_4 in methanol

Li_2PdCl_4 (0.62 mmol) was dissolved in methanol (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.265 g, 0.63 mmol) and diethyl maleate (1 ml, 6.21 mmol) were added and the solution stirred for 18 h. Chromatography with (1:3) CH_2Cl_2/pet. spirit yielded two bands.

Band one (R_f = 0.75) gave9 (0.109 g, 41% recovered).

Band two (R_f = 0.56) gave white crystals of 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.102 g, 65%).

(b) with Li_2PdCl_4 in methanol under reflux

Li_2PdCl_4 (0.62 mmol) was dissolved in methanol (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.261 g, 0.62 mmol) and diethyl maleate (1 ml, 6.21 mmol) were then added. The solution was stirred for 18 h and then refluxed for a further 3.5 h. Chromatography with (1:2) CH_2Cl_2/pet. spirit yielded two bands.

Band one (R_f = 0.80) gave 9 (0.049 g, 17% recovered).

Band two (Rf = 0.12) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.115 g, 0.454 mmol, 73%).

(c) with Li_2PdCl_4 in acetonitrile

Li_2PdCl_4 (0.62 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.265 g, 0.63 mmol) and diethyl maleate (1 ml, 6.21 mmol) were added and the solution refluxed for 3.5 h. Chromatography with (1:2) CH_2Cl_2/pet. spirit yielded two bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.102 g, 65%).

Band two gave diethyl maleate (0.097 g).

(d) with Me_3NO in acetonitrile

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.170 g, 0.404 mmol) was dissolved in acetonitrile (5 ml) and purged with N_2. Trimethylamine oxide (0.047 g, 0.618 mmol) was added and the solution stirred for 5 min. Diethyl maleate (1.00 ml, 6.21 mmol) was then added and the solution stirred for further 17.5 h. Chromatography with ethyl acetate/pet. spirit (3:7) yielded three bands.

Band one gave **9** (0.009 g, 5% recovered).

Band two gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.079 g, 0.311 mmol, 77%).

Band three gave diethyl maleate (0.080 g).

(e) with $NiBr_2(Ph_3P)_2$ in acetonitrile

$NiBr_2(PPh_3)_2$ (0.303 g, 0.463 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.194 g, 0.462 mmol) were dissolved in acetonitrile (8 ml) and purged with N_2. Diethyl maleate (1.0 ml, 6.21 mmol) was added and the solution refluxed for 10 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded a pale yellow oil (0.179 g), identified as a mixture (NMR ratio 2:1) of diethyl maleate and 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.238 mmol, 55%) respectively.

Reactions of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with phenylethene.

(a) with Li_2PdCl_4 in acetonitrile under reflux

Li_2PdCl_4 (0.400 mmol) was dissolved in acetonitrile (10 ml) and purged with N_2. Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κC]-manganese(I) **9** (0.167 g, 0.398 mmol) and phenylethene (styrene) (0.5 ml 4.36 mmol - freshly distilled) were added and the solution refluxed for 2.5 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 1.00) gave phenylethene (0.015 g), identified by NMR.

Band two (R_f = 0.82) gave *E*-1-(4-methoxy-2-(2-phenyl-ethenyl)-phenyl)-2-phenyl-1-butanone **73** (0.106 g, 0.299 mmol, 75%). Attempts to crystallise **73** proved unsuccessful.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.67 (d, J = 8.7 Hz, 1H, H6), 7.78 (d, J = 16.1 Hz, 1H, H1'), 7.51 (d, J = 7.2 Hz, 2H, H2'', H6''), 7.31 (m, 8H, ArH), 7.13 (d, J = 2.5 Hz, 1H, H3), 6.94 (d, J = 16.1 Hz, 1H, H2'), 6.78 (d of d, J = 2.5, 8.7 Hz, 1H, H3), 4.35 (t, J = 7.3 Hz, 1H, CH), 3.83 (s, 3H, OCH_3), 2.25 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 0.92 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.9 (s, C=O), 161.8 (s, C4), 140.4 (s), 139.6 (s), (C1', C1''), 137.3 (s, C2), 131.3 (d, C2'), 131.0 (d, C6), 128.8 (d), 128.7 (d), 128.4 (d), 128.3 (d), 128.0 (d), (C1', C3'', C5'', C24-C26)128.6 (s, C1), 127.9 (d), (C4'', C24), 127.0 (d, C2'', C6''), 112.5 (d), 112.4 (d), (C3, C5), 58.3 (d, CH), 55.4 (q, OCH_3), 27.3 (t, CH_2), 12.5 (q, CH_3).

MS : 356 (M^+), 281, 237.

Band three (R_f = 0.75) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.020 g, 0.080 mmol, 20%).

(b) in acetonitrile

Tetra(carbonyl-κC)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κC]-manganese(I) **9** was dissolved in acetonitrile (5 ml) and purged with N_2. Phenylethene (0.5 ml, 4.36 mmol) was added and the solution refluxed for 1 h. Chromatography with diethyl ether/pet. spirit (1:3) yielded four bands.

Band one gave phenylethene (0.056 g).

Band two gave **9** (0.023 g, 11% recovered).

Band three gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.014 g, 0.054 mmol, 11%).

Band four gave an unknown yellow oil (0.034 g) which readily decomposed upon work up.

(c) in benzene

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.209 g, 0.497 mmol) was dissolved in benzene (10 ml) and purged with N_2. Phenylethene (0.5 ml, 4.36 mmol) was added and the solution refluxed for 16 h. Chromatography with diethyl ether/pet. spirit (1:4) yielded four bands.

Band one (R_f = 0.97) gave $Mn_2(CO)_{10}$ (0.032 g, 0.082 mmol, 16%), identified by IR.

Band two (R_f = 0.83) gave phenylethene (0.011 g).

Band three (R_f = 0.74) gave a yellow oil (0.105 g), identified (NMR 1:1) as a mixture of 9 (0.156 mmol, 31% recovered) and 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.156 mmol, 31%).

Band four (R_f = 0.37) gave 5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene 74 (0.073 g, 0.214 mmol, 43%) as a pale yellow oil. NMR (ratio 1:1) showed a mixture of diastereoisomers.

^{1}H NMR for 5-methoxy-2-phenyl-1-(1-phenylpropyl)-indene 74 is given for both isomers.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.60-6.77 (m, br, 26H, ArH), 5.12 (d, J = 8.0 Hz. 2H, H1), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.86 (m, 2H, CH), 2.30 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 0.71 (t, J = 7.3 Hz, 3H, CH_3), 0.64 (J = 7.4 Hz, 3H, CH_3).

^{13}C NMR is given for each diastereoisomer.

Major isomer:

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.7 (s, C5), 141.4 (s, C2), 137.7 (s), 137.6 (s), (C1', C1''), 133.6 (C3a), 131.2 (d, C7), 129.1 (s, C7a), 128.8 (d), 128.6 (d), 128.20 (d), 126.7 (d), (C2'-C6', C2''-C6''), 128.1 (d, C3), 127.8 (d, C4'), 127.0 (d, C4''), 113.2 (d, C6), 111.1 (d, C4), 75.0 (d, C1), 55.4 (q, OCH_3), 54.9 (d, CH), 22.1 (t, CH_2), 12.3 (q, CH_3).

MS : 340 (M^+), 311, <u>239</u>, 178, 161.

Minor isomer:

^{13}C NMR (300 MHz) ($CDCl_3$) δ 159.0 (s, C5), 142.1 (s, C2), 137.6 (d), 136.7 (d), (C1', C1''), 132.9 (s, C3a), 130.9 (d, C7), 129.1 (s, C7a), 129.0 (d), 128.8 (d), 128.18 (d), 126.4 (d), (C2'-C6', C2''-C6''), 128.15 (d, C3), 127.9 (d, C4'), 126.1 (d, C4''), 113.6 (d, C6), 111.3 (d, C4), 74.9 (d, C1), 56.1 (d, CH), 55.3 (q, OCH_3), 24.9 (t, CH_2), 12.2 (q, CH_3).
MS : 311 (M^+-C_2H_7O), 298, 239, 178, 161.

Reactions of [2-acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) 6.

(a) with $NiBr_2(PPh_3)_2$ and 3-buten-2-one in acetonitrile

$NiBr_2(PPh_3)_2$ (0.218 g, 0.333 mmol) and [2-acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) **6** (0.086 g, 0.301 mmol) were dissolved in acetonitrile (6 ml). 3-Buten-2-one (0.6 ml, 7.21 mmol) was added and the solution refluxed for 1 h. Chromatography with ethyl acetate/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.99) gave PPh_3 (0.008 g).

Band two (R_f = 0.82) gave [2-acetyl-κ*O*-phenyl-κ*C*]-tri(carbonyl-κ*C*)-(triphenylphosphine-κ*P*)-manganese(I) **75** (0.015 g, 0.029 mmol, 10%). Crystallisation from pet. spirit gave fine yellow-orange needles, mp 163-164 °C (lit. value[126] 167°C).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 1H, ArH), 7.34 (m, 5H, ArH), 7.22 (m, 6H, ArH), 7.11 (m, 6H, ArH), 6.94 (t, J = 7.5 Hz, 1H, ArH), 2.05 (d, J = 2.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 145.5 (s, C2), 141.5 (d, C6), 133.8 (t, $J_{P\text{-}C}$ = 10.2Hz, C2', C6'), 131.7 (d), 130.9 (d), (C3, C5), 128.5 (d, $J_{P\text{-}C}$ = 12.8, C1'), 129.6 (d, C4'), 127.9 (d, $J_{P\text{-}C}$ = 9.2Hz, C3', C5'), 121.9 (d, C4), 23.8 (q, CH_3).
^{31}P NMR (90 MHz) ($CDCl_3$) δ 57.7 ($W_{1/2}$ = 9.4Hz).
IR (pet. spirit) ν(CO) 2014 (vs), 1938 (vs, br), 1905 (vs, br) cm^{-1}.

Band three (R_f = 0.52) gave a colourless oil (0.052 g), identified (^{1}H NMR ratio 7:4) as a mixture of diastereoisomers of 2-acetyl-1-methyl-1-indanol **76a** and **76b** (0.274 mmol, 91%) . Isomer separation was achieved by further chromatography eluting with the same solvent. Attempts to crystallise **76** proved unsuccessful.

[1R*,2S*]-2-Acetyl-1-methyl-1-indanol **76a** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.24 (m, 4H, ArH), 3.24 (m, 2H, CH_2), 3.06 (d of d, J = 7.8, 13.4 Hz, 1H, CH), 2.27 (s, 3H, $COCH_3$), 1.71 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 210.1 (s, C=O), 146.5 (s, C7a), 140.4 (s, C3a), 128.6 (d, C4), 127.2 (d, C5), 124.7 (d, C7), 122.5 (d, C6); 81.2 (s, C-OH), 61.2 (d, C2), 32.5 (q, $COCH_3$), 30.8 (t, C3), 27.5 (q, CH_3).
MS : 172 (M^+-H_2O), 147, 129, 115, 91.

[1S*,2S*]-2-Acetyl-1-methyl-1-indanol **76b** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.24 (m, 4H, ArH), 2.78 (d of d, J = 7.2, 15.8 Hz, 1H, CH), 2.51 (m, 2H, CH_2), 2.30 (s, 3H, $COCH_3$), 1.27 (s, 3H, CH_3).
2.30 ($COCH_3$) nOe to 1.20, 3.30, 7.30.
1.20 (CH_3) nOe to 2.30.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 208.4 (s, C=O), 148.0 (s, C7a), 140.4 (s, C3a), 128.2 (d, C4), 127.1 (d, C5), 124.8 (d, C7), 122.0 (d, C6), 82.6 (s, C-OH), 66.0 (d, C2), 31.0 (q, $COCH_3$), 30.4 (t, C3), 24.4 (q, CH_3).
MS : 172 (M^+-H_2O), 157, 129, 115, 102.

(b) in acetonitrile with 3-but-2-enone

[2-Acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) **6** (0.089 g, 0.310 mmol) was dissolved in acetonitrile (6 ml). 3-Buten-2-one (0.7 ml, 8.41 mmol) was added and the solution refluxed for 4 h. Chromatography with ethyl acetate/pet. spirit (3:7) yielded four bands.

Band one gave a yellow oil (0.019 g) which decomposed before NMR could be performed.

Band two gave 1-(3-methyl-2-indenyl)-ethanone 77 (0.010 g, 0.057 mmol, 18%). Crystallisation from diethyl ether/pet. spirit gave fine whitish crystals, mp 60-80°C (decomp).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.53 (m, 2H, ArH), 7.38 (m, 2H, ArH), 3.70 (q, J = 2.3 Hz, 2H, CH_2), 2.56 (t, J = 2.3 Hz, 3H, CH_3), 2.46 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.9 (s, C=O), 150.1 (s, C3), 145.5 (s, C3a), 143.2 (s, C7a), 137.8 (s, C2), 128.2 (d), 126.9 (d), 121.7 (d), (C4, C5, C6), 124.1 (d, C7), 39.3 (t, CH_2), 30.3 (q, CH_3), 13.1 (q, CH_3).
MS : 172 (M+), 129, 128, 115.

Band three gave [1R*,2S*]-2-acetyl-1-methyl-1-indanol **76a** (0.017 g, 0.092 mmol, 30%).

Band four gave [1S*,2S*]-2-acetyl-1-methyl-1-indanol **76b** (0.014 g, 0.071 mmol, 23%).

(c) with PPh_3 and 3-buten-2-one in acetonitrile

[2-Acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) **6** (0.094 g, 0.328 mmol) and triphenylphosphine (0.128 g, 0.489 mmol) were dissolved in acetonitrile (6 ml). 3-Buten-2-one (0.70 ml, 8.41 mmol) was added and the solution refluxed for 17 h. Chromatography with ethyl acetate/pet. spirit (1:3) yielded two bands.

Band one ($R_f = 0.97$) gave an unknown yellow oil (0.014 g) which readily decomposed.

Band two ($R_f = 0.70$) gave white crystals of 1-(3-methyl-2-indenyl)-ethanone **77** (0.008 g, 0.045 mmol, 14%).

(d) with $NiBr_2(PPh_3)_2$ and methyl propenoate in acetonitrile

$(PPh_3)_2NiBr_2$ (0.114 g, 0.174 mmol) and [2-acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) **6** (0.050 g, 0.175 mmol) were dissolved in acetonitrile (6 ml). Methyl propenoate (0.60 ml, 6.67 mmol) was added and the solution refluxed for 3 h. Chromatography with ethyl acetate/pet. spirit (3:7) yielded four bands.

Band one ($R_f = 1$) gave white cystals of PPh_3 (0.036 g).

Band two ($R_f = 0.94$) gave a yellow oil (0.005 g), identified (NMR) as [2-acetyl-κ*O*-phenyl-κ*C*]tetra(carbonyl-κ*C*)(triphenylphosphine-κ*P*)manganese(I) **75** (0.090 mmol, 5%). ^{1}H NMR shows this oil contains *ca.* 5% acetophenone.

Band three ($R_f = 0.73$) gave methyl 3-(2-acetylphenyl)propanoate **78** (0.005 g, 0.024 mmol, 14%).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.70 (d, J = 7.4 Hz, 1H, ArH), 7.40 (d, J = 8.6 Hz, 1H, ArH), 7.38 (m, 2H, ArH), 3.65 (s, 3H, OCH_3), 3.17 (t, J = 7.7 Hz, 2H, CH_2), 2.66 (t, J = 7.7 Hz, 2H, CH_2), 2.59 (s, 3H, CH_3).
MS : 188 (M^+-H_2O), 175(M^+-OCH_3), 146, 145, 131, 103.

Band four ($R_f = 0.30$) gave a colourless oil (0.028 g), identified (NMR ratio 3:4) as a mixture of diastereoisomers of methyl 1-hydroxy-1-methyl-indane-2-carboxylate **79a** and **79b** (0.136 mmol, 78%). Attempts to crystallise **79** proved unsuccessful.

Methyl [1S*,2S*]-1-hydroxy-1-methyl-indane-2-carboxylate **79a** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.34 (m, 2H, ArH), 7.26 (m, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.20 (d of d, J = 3.8, 8.8 Hz, 1H, CH), 3.09 (m, 2H, CH_2), 2.66 (s, br, 1H, OH), 1.37 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 173.0 (s, C=O), 147.1 (s, C7a), 138.7 (s, C3a), 128.4 (d, C4), 127.3 (d; C5), 124.7 (d, C7), 122.4 (d, C6), 82.7 (s, C-OH), 58.3 (d, C2), 51.9 (q, OCH_3), 31.9 (t, C3), 25.1 (q, CH_3).

MS : 191 (M^+-CH_3), 188, 159, 146, 145, 131, 129, 103.

Methyl [1R*,2S*]-1-hydroxy-1-methyl-indane-2-carboxylate **79b** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.34 (m, 2H, ArH), 7.26 (m, 2H, ArH), 3.77 (s, 3H, OCH_3), 3.42 (d of d, J = 7.7, 15.3 Hz, 1H, CH), 3.30 (m, 2H, CH_2), 2.91 (s, br, 1H, OH), 1.75 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 173.5 (s, C=O), 146.0 (s, C7a), 140.8 (s, C3a), 128.8 (d, C4), 127.3 (d, C5), 124.8 (d, C7), 122.8 (d, C6), 81.1 (s, C-OH), 54.6 (d, C2), 51.9 (q, OCH_3), 32.9 (t, C3), 26.7 (q, CH_3).

MS : 188 (M^+-H_2O), 159, 146, 145, 131, 129, 103.

Preparation of 2-acetylphenylmercuric(II) chloride 80.

[2-Acetyl-κ*O*-phenyl-κ*C*]-tetra(carbonyl-κ*C*)-manganese(I) **6** (0.147 g, 0.514 mmol) and $HgCl_2$ (0.205 g, 0.755 mmol) were dissolved in methanol (10 ml) and refluxed for 4 h. The precipitate was filtered, washed with (cold) methanol and dried to yield 2-acetylphenylmercuric(II) chloride **80** (0.120 g, 0.338 mmol, 67%), mp 155-174 °C decomposition (lit.[120] 214.5-216 °C).

^1H NMR (300 MHz) ($CDCl_3$) δ 8.35 (d of d, J = 1.2, 7.7 Hz, 1H, H6), 7.86 (d of d, J = 1.2, 7.3 Hz, 1H, H3), 7.78 (d of t, J = 1.3, 7.3 Hz, 1H, H4), 7.59 (d of t, J = 1.3, 7.6 Hz, 1H, H5), 2.89 (s, 3H, CH_3).

Reaction of 2-acetylphenylmercuric(II) chloride 80 with methyl propenaote and $(Ph_3P)_2NiBr_2$.

2-Acetylphenylmercuric(II) chloride **80** (0.144 g, 0.405 mmol) and $NiBr_2(Ph_3P)_2$ (0.310 g, 0.417 mmol) were dissolved in acetonitrile (6 ml). Methyl propenoate (0.5 ml, 5.56 mmol) was added and the solution refluxed for 18 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded two bands.

Band one (R_f = 0.80) gave acetophenone (0.010 g, 0.083 mmol, 20%).

Band two (R_f = 0.45) gave 2-(2-acetylphenyl)-acetophenone **81** (0.044 g, 0.185 mmol, 46%). Crystallisation from pet. spirit gave long colourless needle crystals, mp 79-80°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.73 (d of d, J = 1.9 Hz, 7.1 Hz, 1H, H6), 7.46 (m, 2H, ArH), 7.17 (d of d, J = 1.9 Hz, 7.1 Hz, 1H, H3), 2.26 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 216.0 (s, C=O), 140.7 (s), 138.8 (s), (C1, C2), 131.1 (d), 130.8 (d), 128.6 (d), 127.7 (d), (C3, C4, C5, C6), 29.3 (q, CH_3).

MS : 195 (M^+-$COCH_3$), 165, 152.

Found : C, 80.45; H, 5.81%.

$C_{14}H_{14}O_2$ Calcd : C, 80.64; H, 5.92%.

Reaction of $(Ph_3P)_2NiBr_2$ and 3-buten-2-one.

$NiBr_2(Ph_3P)_2$ (0.071 g, 0.096 mmol) was dissolved in acetonitrile (4 ml), purged with N_2 and refluxed for 30 min. 3-Buten-2-one (0.70 ml, 8.41 mmol) was added causing an immediate colour change from dark green to an emerald colour and the solution was further refluxed for 30 min. Chromatography with diethyl ether/pet. spirit (3:7) yielded two bands.

Band one gave PPh_3 (0.005 g, 0.019 mmol, 17%), identified by NMR.

Band two gave a colourless oil (0.025 g), identified as 1-(3,4-dihydro-6-methyl-(2*H*)-pyran-2-yl)-ethanone **82** (0.179 mmol, 184% based on Ni).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 4.51 (s, br, 1H, H5'), 4.25 (d of d, J = 3.5, 7.7 Hz, 1H, H2'), 2.22 (s, 3H, $COCH_3$), 1.93 (m, 4H, CH_2), 1.77 (s, br, 3H, C6'-CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 209.7 (s, C=O), 149.8 (s, C6'), 96.3 (d, C5'), 80.3 (d, C1'), 26.0 (q, $COCH_3$), 23.5 (q, C6'-CH_3), 20.0 (t), 19.1 (t), (C3', C4').

MS : 140 (M^+), 97, 79, 69.

Dehydration of methyl 1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate 57.

Methyl 1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57** (0.011 g, 0.033 mmol) was dissolved in acetonitrile (5 ml), 3 drops of concentrated sulphuric acid added and the solution stirred for 24 h. $NaHCO_3$ (0.09 g) was added and the solvent removed under reduced pressure. Chromatography with CH_2Cl_2/pet. spirit (2:3) yielded a colourless oil (0.010 g), identified as methyl 6-methoxy-3-(1-phenylpropyl)-indene-2-carboxylate **55** (0.030 mmol, 90%).

Attempted aldol condensation of 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone 59.

(a) with 4-toluene-sulphonic acid in acetonitrile

4-(3-Methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.072 g, 0.221 mmol) and 4-toluenesulphonic acid (0.010 g, 0.053 mmol) were dissolved in acetonitrile (4 ml) and stirred for 24 h. Chromatography with diethyl ether/pet.spirit (3:7) yielded four bands.

Band one (R_f = 0.53) gave 2-ethyl-7-methoxy-3-methyl-2-phenyl-6,7-benzocyclohept-3-enone **83** (0.004 g, 0.013 mmol, 6%). Attempts to crystallise **83** proved unsuccessful.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.37 (m, 3H, ArH), 7.15 (m, 2H, ArH), 6.72 (d, J = 2.3 Hz, 1H, H6), 6.37 (d of d, J = 2.3, 8.7 Hz, 1H, H8), 6.02 (d, J = 8.7 Hz, 1H, H9), 4.05 (d of d, J = 1.9, 9.5 Hz, 1H, CH_2 *cis* to CH), 3.72 (s, 3H, OCH_3), 3.37 (d of d, J = 9.5, 17.3 Hz, 1H, CH), 2.94 (d of d, J = 1.9Hz, 17.3Hz, 1H, CH_2 *trans* to CH), 2.42 (d of q, J = 7.3, 20.1 Hz, 2H, CH_2), 2.03 (s, 3H, CH_3), 0.90 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 209.2 (s, C=O), 159.4 (s, C7), 146.7 (s, C4), 142.0 (s, C1''), 138.1 (s), 134.7 (s), (C5a, C9a), 133.4 (s, C3), 129.0 (d), 128.6 (d), (C2''-C6''), 127.1 (d, C4''), 125.6 (d, C9), 112.9 (d), 109.8 (d), (C8, C6), 56.7 (t, C5), 55.3 (q, OCH_3), 53.5 (s, C2), 34.2 (q, CH_3), 25.1 (t, CH_2), 11.9 (q, CH_3).
MS : 306 (M^+), 263, 234, 191, 189, 145.

Band two (R_f = 0.50) gave 1-(6-methoxy-3-(1-phenylpropyl)-2-indenyl)-ethanone **58** (0.027 g, 0.088 mmol, 40%).

Band three (R_f = 0.37) gave **59** (0.027 g, 37% recovered).

Band four (R_f = 0.33) gave *E*-4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-but-3-en-2-one **60** (0.005 g, 0.016 mmol, 7%).

(b) with Li_2PdCl_4 in acetonitrile

Li_2PdCl_4 (0.067 mmol) is dissolved in acetonitrile (5 ml) and purged with N_2. 4-(3-Methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.020 g, 0.062 mmol) was added and the solution stirred for 14 h. Tlc indicated no reaction so the solution was refluxed for an additional 27 h. Chromatography with diethyl ether/pet. spirit gave only one significant band (R_f = 0.28), identified (NMR) as **59** (0.018 g, 89% recovered).

(c) with Et_4NBr in acetonitrile

4-(3-Methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.029 g, 0.090 mmol) and tetraethylammonium bromide (0.015 g, 0.071 mmol) were dissolved in acetonitrile (8 ml) and the solution stirred for 18 h. Chromatography with diethyl ether/pet. spirit (3:7) gave **59** (0.020 g, 70% recovered).

Attempted aldol condensation of methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate 56.

Methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propanoate **56** (0.084 g, 0.247 mmol) and 4-toluenesulphonic acid (0.017 g, 0.089 mmol) were dissolved in acetonitrile (4 ml) and stirred for 4.5 days. The solution was then poured into water (20 ml) and extracted with ether (2 x 20 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (3:7) gave **56** (0.029 g, 35% recovered).

Attempted aldol condensation of methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propenoate 54.

Methyl 3-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-propenoate **54** (0.088 g, 0.260 mmol) and 4-toluenesulphonic acid (0.017 g, 0.089 mmol) were dissolved in acetonitrile (4 ml) and stirred for 7 days. The solution was then poured into water (50 ml) and extracted with ether (2 x 25 ml). The solvent was removed under reduced pressure giving **54** (0.088 g, 100% recovered).

Crystal structure of methyl [1S*,2R*,3R*,1'S*]-1-hydroxy-5-methoxy-3-methyl-1-(1-phenylpropyl)-indane-2-carboxylate 64e.

A colourless chunky crystal was obtained by solvent diffusion (diethyl ether/pet. spirit). Preliminary precession photography indicated a triclinic lattice, with a probable space group $P\bar{1}$.

Crystal Data : $C_{22}H_{26}O_4$, Mr = 354.450, triclinic, space group $P\bar{1}$, a = 7.650 (7) Å, b = 10.535 (10) Å, c = 13.190 (12) Å, α = 111.22 (7)°, β = 100.02 (7)°, γ = 82.51(6)°, V = 973 (1) $Å^3$, D_c = 1.25 g cm^{-3} for Z = 2. F (000) = 380, μ(Mo-K_α) = 0.47 cm^{-1}, T = 290 K, crystal size = 0.24 x 0.16 x 0.12 mm.

Intensity data were collected for 2161 unique reflections for which (2° < 2θ < 40°). Of these 1108 had I > 2σ(I) and were employed in all calculations. Due to the low linear absorption coefficient (μ) the intensity data were used without absorption corrections.

A partial structure was obtained by the direct methods routine of SHELXS-86[111]. Subsequent difference maps located the remaining non-hydrogen atoms. All atoms were refined with anisotropic temperature factors. However least-squares refinement did not give R values below 0.15.

The solution has the correct structural features, though is possibly wrongly located in the unit cell resulting in the high R values. A translational and rotational search using the existing atom coordinates was undertaken employing the PATSEE[152] program. However, from this search the best solution matched the existing solution. Positional coordinates of a partial structure of an analogous indanyl compound[116], dimethyl 17α-hydroxy-12-methoxy-4β,17β-dimethyl-18-nor-5-α-androsta-8,11,13-triene-4β,16α-dicarboxylate, were also employed in a PATSEE search, the results of which gave an incorrect solution. As a result of the translational and rotational search, it appears the original structural solution was correct. It is probable crystal quality and a weak intensity data set may have independently contributed to high final R values. Nevertheless, the solution unequivocally gave the geometry of the compound, although individual bond parameters must be regarded as being low in accuracy. The positional and thermal parameters and tables of bond lengths and angles are given in Appendix A.IV. Structure factor tables are archived in the Department of Chemistry.

CHAPTER FIVE

SYNTHESIS OF TAMOXIFEN ANALOGUES USING LOW-VALENT TITANIUM

5.1 Introduction

Among the variety of reactions induced by low-valent titanium, the reductive coupling of carbonyl compounds to alkenes (figure 5.1), generally referred to as the McMurry reaction,[127] has gained widespread acceptance and use. The potential of this titanium-mediated reaction in organic syntheses is evident from the vast amount of literature published.[127] It not only allows for the formation of strained alkenes, but also gives access to cycloalkenes in good yield[127] (e.g. figure 5.2) when applied to dialdehydes, ketoaldehydes or diketones. The versatility of the method is evident in product ring sizes which range from 3 to 20.[128]

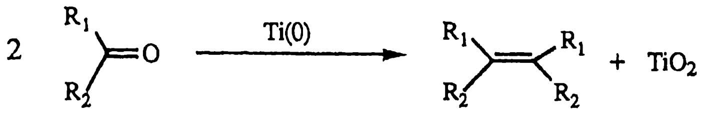


Figure 5.1

R_1,R_2 = H, alkyl, aryl

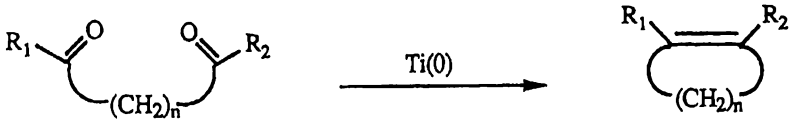


Figure 5.2

The low-valent titanium reagent system first[129] introduced was prepared by reaction of $TiCl_3$ with $LiAlH_4$ (ratio 2:1) which gave a mixture of Ti(II) and Ti(0) oxidation states. This system has been surpassed by more easily prepared reagents such as the $TiCl_3$/Zn-Cu system[127] which give more reproducible results. Variations on this reagent system include those using $TiCl_4$/Zn/pyridine or $TiCl_3$/K/graphite.[127]

It is generally accepted[127] that carbonyl coupling takes place in two steps: (1) reductive dimerization of the starting ketone to form a carbon-carbon bond, and (2) deoxygenation of the 1,2-diolate intermediate to yield the alkene. The first step is simply a pinacol reaction and is not unique to low-valent titanium. Reducing metals are capable

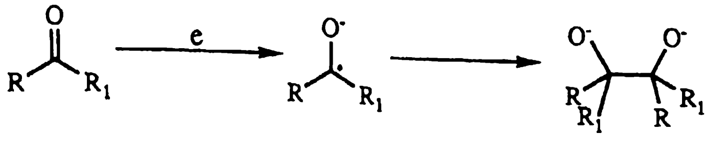


Figure 5.3

of adding an electron to a ketone or aldehyde yielding a radical anion that dimerizes (figure 5.3).[127] In the second step (figure 5.4), titanium-induced deoxygenation of the pinacolates is thought[127] to take place by coordination to a small, zero-valent titanium particle. This is followed by stepwise cleavage of the C-O bonds with the formation of the π-bonded alkene and an oxide-coated titanium surface.[127]

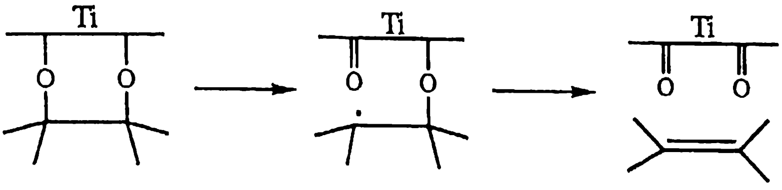


Figure 5.4

Reductive carbonyl coupling has been used as a key step in the synthesis of Tamoxifen 1 and several of its analogues.[14,65,80] The more traditional syntheses[5,6,12] (Chapter One, section 1.2) of Tamoxifen are multi-step and in the final stages usually involve the separation of the *E*/*Z* isomers[5,6]. In seeking a more direct synthesis, Coe and Scriven[14] studied low-valent titanium-mediated coupling between 4-substituted benzophenones and propiophenone. The initial investigation[14] with 4-methoxybenzophenone and propiophenone, employing a $TiCl_3$-Li system, afforded a crystalline product (76% yield) of the crossed-coupling product (*Z*/*E* 8:3). Similarly, the chloroethoxy benzophenone derivative when coupled gave the crossed product in excellent yield with an *Z*/*E* ratio 7-9 : 1 (see Chapter One, figure 1.2). Other titanium-induced reactions that give Tamoxifen derivatives are included in the synthesis[65] of an ^{18}F-labelled 4-fluoro derivative (whose structure is analogous to 4-hydroxyTamoxifen 5) and in the coupling of benzoylpyridine compounds[80] to give Tamoxifen derivatives (figure 5.5). The latter example gives a Tamoxifen analogue with a similar[80] hydrogen-bonding potential to 4-hydroxyTamoxifen.

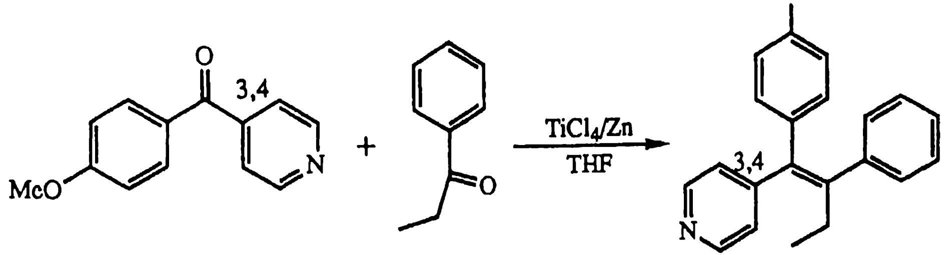


Figure 5.5

In this study, it was proposed to use titanium-induced coupling of benzophenones with propiophenone as a straightforward route to *ortho*-halogenated derivatives of Tamoxifen (for example figure 5.6). With few reports of aryl-halogen reduction by low-valent titanium[127] this was not anticipated as a major problem. Of interest also, was whether the marked preponderance of the Z-isomer found in a previous study[14] would be retained with *ortho*-halo-substituted benzophenone derivatives. As an accompaniment to the Tamoxifen investigation, titanium-induced intramolecular dicarbonyl coupling was attempted with the alkene-coupled products **54**, **56**, and **59** which were synthesised in Chapter Four.

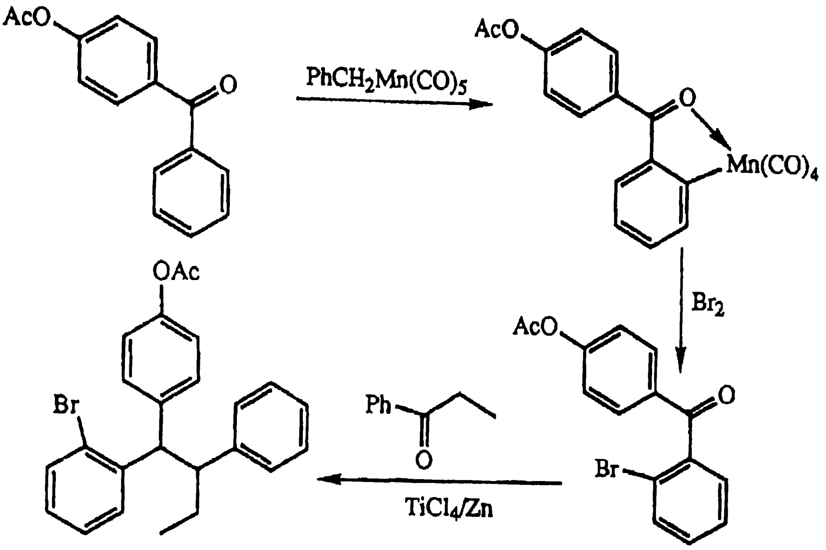


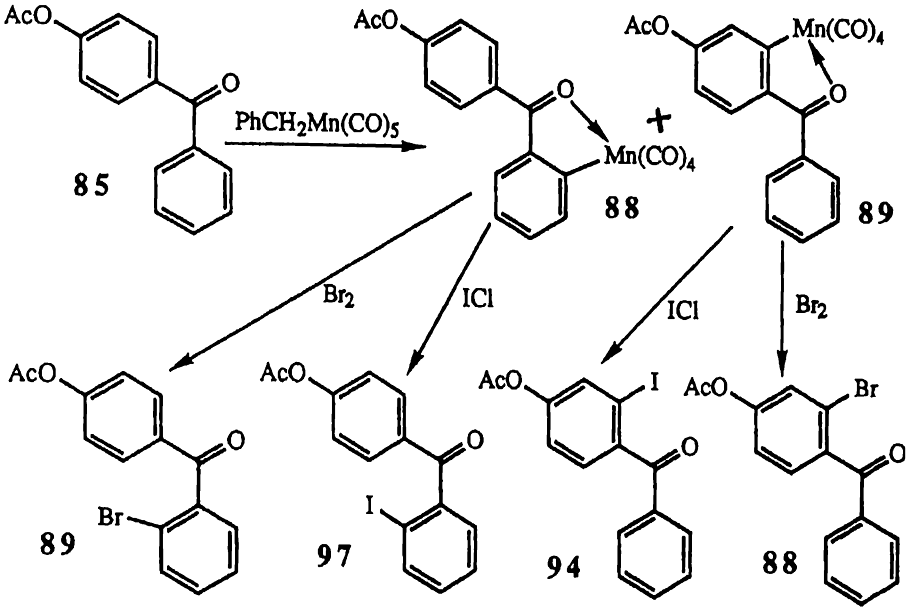
Figure 5.6

5.2 Results and Discussion.

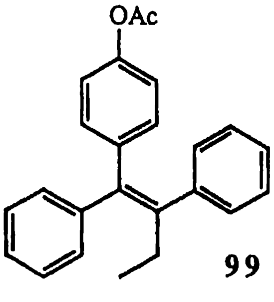
5.2.1 Synthesis and reductive coupling of halogenated benzophenone derivatives.

In a previous study it was found[130] that a hydroxyacetophenone substrate would not undergo orthomanganation. Therefore, in this study it was not a surprise that the orthomanganation of 4-hydroxybenzophenone proved to be unsuccessful. The reaction does give an unidentified unstable product but this does not survive chromatography. The tetrahydropyranyl group (THP) was the initial choice for the protection of the hydroxyl group. However, low yields of the THP-protected orthomanganated products **86** and **87**, and subsequent formation of only deprotected, demetallated ketone on their attempted bromination precluded the use of THP. Perhaps bromination of the THP ring is preferential and HBr formed either cleaves the ether linkage or the aryl-manganese bond leading to the 4-hydroxybenzophenone and the tetrahydropyranyloxy product **84** respectively.

With acetylated 4-hydroxybenzophenone, the corresponding orthomanganated complexes, **88** and **89**, are produced in comparatively higher yields (52% and 39% respectively) than for tetrahydropyranylated starting compound. When **88** and **89** are reacted with iodine monochloride, the iodinated compounds **94** and **97** are produced in good yield (59% and 62% respectively). Similarly, bromination with either Br_2 or *N*-bromosuccinimide (NBS) gives **90** and **92** in good to excellent yield. For **88** with Br_2 the *ortho*-substituted product **90** is isolated in good yield (59%), unlike the case for tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** which gives only the *meta*-brominated compound **11** (Chapter Two). It is likely that the reduced electron-donating ability of the acetate group in **88** compared to that of the methoxy group of **9** results in preferential bromination at the site occupied by the manganese rather than the adjacent *meta* position.



$TiCl_4$ added to a suspension of powdered zinc metal in THF or dimethoxyethane is reported[14] to be more reactive than $TiCl_3$/Li. In our study, $TiCl_4$/Zn in THF was employed in all reductive coupling reactions due to its comparative ease of handling. The mixed coupling reaction between 4-benzoylphenyl acetate **85** and propiophenone after three hours gives a mixture of the butenes **99** and **100** in good yield (63%), though it is somewhat lower than those reported[14] for other 4-substituted benzophenone cross-coupling reactions. ^1H NMR shows the acetoxy proton integrals to be in a 7:4 ratio. NOes between the ethyl group protons and those of the 4-substituted ring could not unambiguously define the stereochemistry of either isomer. ^1H NMR studies[14,65] have established the distinctive pattern of protons constituting the A_2B_2 system of the 4-substituted ring of the *Z*-isomer to be well separated from the remaining aryl protons, usually lying upfield δ 0.4 - 0.7 ppm, while those of the *E*-isomer coincide with the remaining aryl protons. This is primarily due to shielding by adjacent phenyl rings. On



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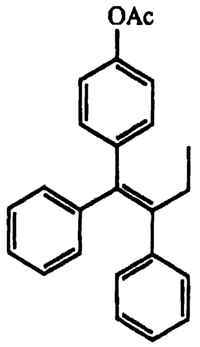


100

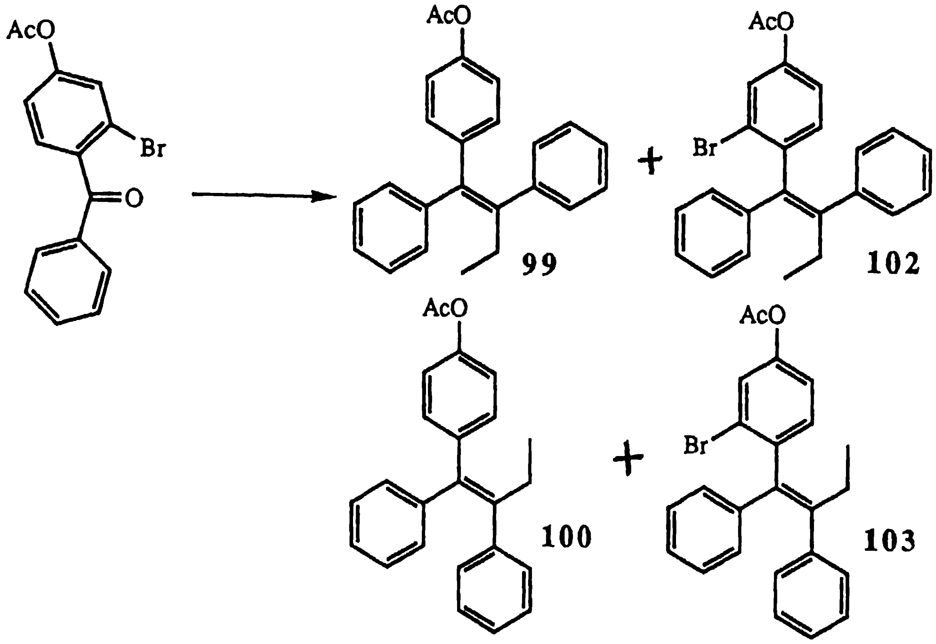
the basis of this result, the dominant isomer, **99**, having the H3,5 and H2,6 proton resonances at δ 6.87 and δ 6.75 respectively, is assigned the *cis* (*Z*) geometry. The other isomer, **100**, assigned as *trans* (*E*), has the corresponding resonances at δ 7.03 and δ 6.87. Preferential formation of the Z-isomer, **99**, is in accord with the selectivity reported by Coe and Scriven[14], though the *Z*/*E* ratio (7:4) is somewhat lower than that found in their work. Also isolated from the coupling reaction are the stilbene **98** and the pinacol **101** resulting from the dimerization of propiophenone. Both of these products are expected as propiophenone is used in excess. What is surprising, however, is the quantity of the pinacol product, **101**, in comparison to **98**. Under similar conditions Coe and Scriven[14] report no isolation of either product from their reactions. The titanium(IV) chloride and zinc system was not favoured by McMurry[129] due to pinacol formation. This, and short reaction time, may be an explanation for the unexpected high proportion of **101**. At longer reaction times (see table 5.1) for the coupling between **90** and propiophenone, **98** does in fact dominate over **101**.

Table 5.1 Yields for the coupling of **90** with propiophenone.

Ratio of **90** to PhCOEt	(time)	**99**	**100**	**102**	**103**	**104**	**105**	**106**	**98**	**101**
1 : 3	(2 h)	13%	7%	20%	19%				10%	40%
1 : 3	(3 h)	15%	6%	2%	5%	8%	6%	3%	17%	2%
1 : 1	(2 h)	5%	3%	9%	4%				15%	27%
1 : 1.4	(5 h)	8%	5%	3%	4%	4%	11%	6%	25%	4%

After two hours the coupling of 4-benzoyl-2-bromophenyl acetate **90** and propiophenone (ratio 1:1) gives unreacted **90** (25%), as well as the dimerized products, **98** and **101**, and a mixture of four compounds not separable by further chromatography. The mixture was analysed by GCMS and NMR and found to contain the isomers **99** and **100** and their respective *ortho*-brominated derivatives **102** and **103**. From the observed reciprocal nOes between the H7 and ethyl group protons, **103** is assigned the *trans* (*E*) geometry. The *Z*-isomers **99** and **102** are obtained in low yields of 5% and 9%

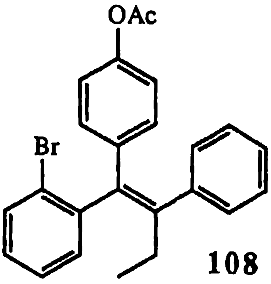
respectively, though greater than the *E*-isomers (**100**, 3% and **103**, 4%), retaining the stereochemical preference observed in a previous study.[14]



McMurry found[131] that employing an excess of one component resulted in good yields of the unsymmetrical alkene. When the ratio of propiophenone to **90** is increased to 3:1 and reacted for a similar length of time, the yields of the cross-coupled products do increase though the *E*/*Z* ratio differs (see table 5.1). Though the ratio between the isomers **99** and **100** remained similar, that for **102** and **103** significantly changes such that equal quantities of each are obtained.

Extended reaction time results in lower yields of the butene isomers **99** and **100** and their respective brominated compounds **102** and **103** (table 5.1). Poorer yields of these compounds may be attributed to the formation of the hydroxyl compounds **104**, **105** and **106**. Extended reaction time seems not only to result in the reduction of the halogen but also the cleavage of the ester linkage with loss of the acetyl group. The loss of the acetyl group may result from reductive cleavage under these conditions.

Reacting 4-(2-bromobenzoyl)-phenyl acetate **92** with propiophenone (ratio 1:3) for three hours gives the dimerized propiophenone products **98** and **101** in similar yields (*ca.* 30%). Also isolated are the diphenylmethanol product, **109**, and a mixture of the butene products **99**, **100** and **108**. NMR data suggest **108** has *cis* (*Z*) stereochemistry. The ^{13}C NMR spectrum for **108** has the resonance for the *meta* carbons, C3 and C5, at δ 120.3 which is identical to that found for **99**, while the corresponding resonance for the *E*-isomer, **100**, is at δ 121.2. ^{1}H NMR shows H3 and H5 at δ 6.99 which is downfield with respect to the isomers, **99** and **100**, but within the region expected[14] for the *Z*-isomer. The most polar product, the substituted diphenylmethanol **109**, has ^{13}C NMR resonances in the aromatic region which show a pattern similar to that for **92**. However the ^{13}C DEPT NMR sequence shows the resonance at δ 74.2 to be a doublet signal, indicating the product to be the diphenylmethanol, rather than the possible dimerized pinacol.



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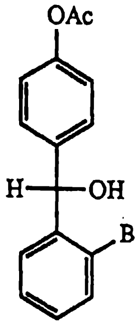

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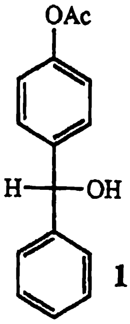


110

Coupling 4-(2-iodobenzoyl)-phenyl acetate **97** with propiophenone gives a mixture of the butenes **99** and **100** in moderate yield (43%, *Z*/*E* 3:2) and the dimerized products **98** and **101**. By contrast, coupling 4-benzoyl-2-iodophenyl acetate **94** with propiophenone gives no butene product. Only the dimerized products, **98** and **101**, and a mixture of the direct-reduction 4-substituted-diphenylmethanol compounds, **110** and **111**, are formed.

We have found that the high reduction potential of titanium(0) has led to some aryl halide reduction. McMurry[127] suggests that organohalides with the exception of 1,2-dihalides and α-haloketones, are not reduced by low-valent titanium reagents. A group studying the synthesis of hetereocyclic compounds found[128] that an excess of titanium reagent does reduce aryl iodide on prolonged exposure, though at a slower rate than the cyclisation reaction being studied. In our studies over extended reaction time, the aryl bromide is reduced at a moderate rate by excess titanium reagent, while the corresponding iodide is reduced relatively rapidly. The *ortho* halogen because of its position adjacent to the carbonyl group may be susceptible to reduction at a greater rate due to electronic effects than that reported elsewhere.[128]

The yields of coupled products from the halo-substituted benzophenone reactions with propiophenone are relatively poor in comparison to those with **85** and other reported elsewhere,[14,80] though formation of the dimerized products **98** and **101** is not diminished in any way. It is obvious that a halogen in the *ortho* position decreases the extent of cross-coupling and it seems likely (figure 5.7) that the *ortho* halogen may impede the radical anion coupling. This is evident in the cross-coupling reactions of **90**

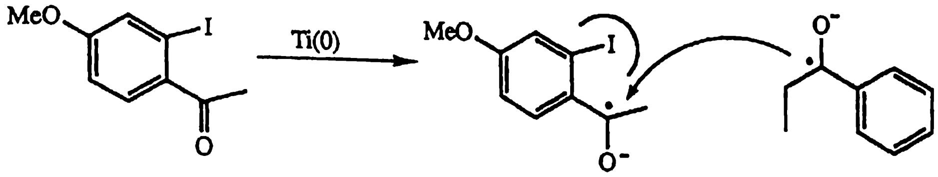


Figure 5.7

with propiophenone (table 5.1). When the ratio of propiophenone is increased, the greater concentration of the corresponding radical anion enables more cross-coupled product to form. It seems an *ortho*-iodo substituent inhibits coupling to a greater degree than a bromo-substituent and this is most likely derived from the relative size of each halogen. Though the diphenylmethanol products, **110** and **111**, are formed from a common radical anion, no cross-coupled product is observed when coupling with **94**. Formation of the butenes **99** and **100** in moderate yield (26% and 17% respectively) from the coupling reaction with **97** is an apparent anomaly which may be rationalised by the initial reduction of the iodine with subsequent coupling of the protio-ketone.

The results for coupling the brominated compounds **90** and **92** would indicate that the reduction of the bromine on the acetoxy-substituted ring (**90**) is retarded in comparison to that for the case of bromine on the corresponding ring (**92**). More brominated product is observed for the reactions employing **90** than for **92**. Similar results for the iodinated compounds **94** and **97** are also observed. Other than a distant steric factor, the only other possible reason why the halogen on the 4-substituted ring is less susceptible to reduction than on the corresponding phenyl ring is an electronic effect.

5.2.2 Synthesis of a Pyridinium Tamoxifen Analogue.

As part of the strategy to synthesise Tamoxifen analogues, it was proposed to attempt the synthesis of a novel pyridinium Tamoxifen analogue (outlined in figure 5.7). However, the titanium-mediated coupling of 4-benzoylpyridine and propiophenone (ratio 1:1) gives only 4-benzylpyridine and the dimerized products **98** and **101**. An investigation[80] into the effect of reactant ratios of pyridine compounds (figure 5.5) for similar coupling using the $TiCl_4/Zn$ reagent indicated that only moderate yields (14 - 43%) of the crossed products could be obtained if ratios were increased. In our study,

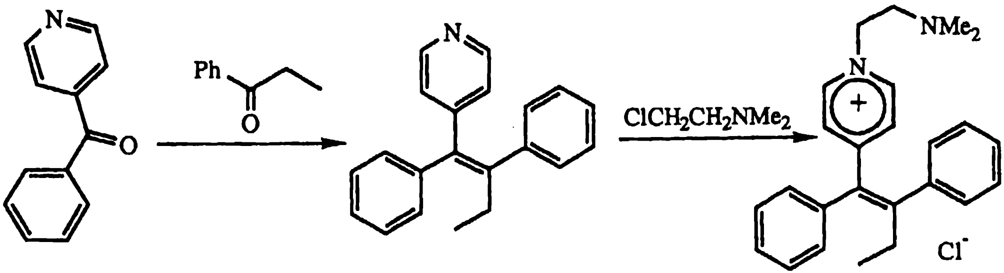


Figure 5.7

when the reactant ratio of propiophenone and 4-benzoylpyridine is improved (2:1) the desired cross-coupled products **113** and **114** (ratio 4:1) are obtained in moderate yield (45%). The dominant isomer **113**, obtained pure by crystallisation from acetonitrile, is assigned the *cis* (*Z*) geometry based on the results of nOe experiments. Also formed in the above reaction are the reduced products **112** and **115**. It is reported by McMurry[127] that strongly coordinating solvents such as pyridine can inhibit titanium reagents. Our results suggest coordination of the pyridyl nitrogen of our reagent to the titanium reagent may in some way inhibit radical anion coupling and contribute to the lower yields of cross-coupled product at the expense of formation of the reduced products **112** and **115**.

Given the preponderance of the Z-isomer of 1,2-diphenyl-1-pyridylbut-1-ene, **113**, though formed in low yield, it was decided to proceed with the synthesis outlined in figure 5.7. Given the availability of 2-(*N*,*N*-dimethylamino)ethyl chloride as the hydrochloride salt, the reaction was conducted in acetonitrile. This gives **113** unreacted (25%) and the desired *N*-alkylated products 1-(2-(*N*,*N*-dimethylamino)-ethyl)-4-(1,2-diphenylbut-1-enyl)pyridinium chloride as the amine hydrochlorides **121** (38%) and **122** (28%) which are tentatively assigned the *Z*- and *E*- stereochemistry respectively based on NMR.

In the latter stages of writing up it was noted Ag_2O had been employed[132] to facilitate a mild *N*-alkylation of pyridine carboxylic acids with alkyl halide. In an attempt to obtain a greater yield of the pyridinium compound **121**, this general preparation was followed. NMR of the crude oil obtained indicated the product may in fact be the dihydropyridine **123** in which hydroxide has added to the electron-deficient pyridinium 2-position rather than the desired pyridinium compound **121**. However, further investigation of this route to **121** is warranted.

It is obvious this initial investigation should be developed to fully investigate the potential of both the synthesis and therapeutic effect of pyridinium Tamoxifen analogues.

5.2.3 Low-Valent Titanium-Induced Intramolecular Coupling: Cyclisation Reactions.

The reaction of the dicarbonyl compound 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** with the $TiCl_4$/Zn reagent in THF under reflux for three hours gives the (intramolecular) crossed-coupled dihydronaphthalene product **116** in quantitative yield (figure 5.8). However, when the keto ester methyl 3-(3-methoxy-6-(2-

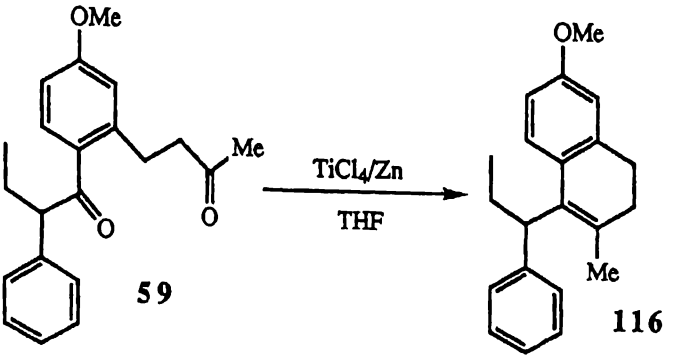


Figure 5.8

phenylbutanoyl)-phenyl)-propanoate **56** is similarly reacted, the 3,4-dihydronaphthalene product (**117**, 7%) and the tetralone (cyclic alkanone) product (**119**, 26%) are isolated. As with **116**, formation of **117** and **119** result from the titanium-induced intramolecular reductive dicarbonyl coupling (figure 5.9). Formation of the tetralone product, **119**, probably results from the hydrolysis of the enol ether **117** (figure 5.9) during workup

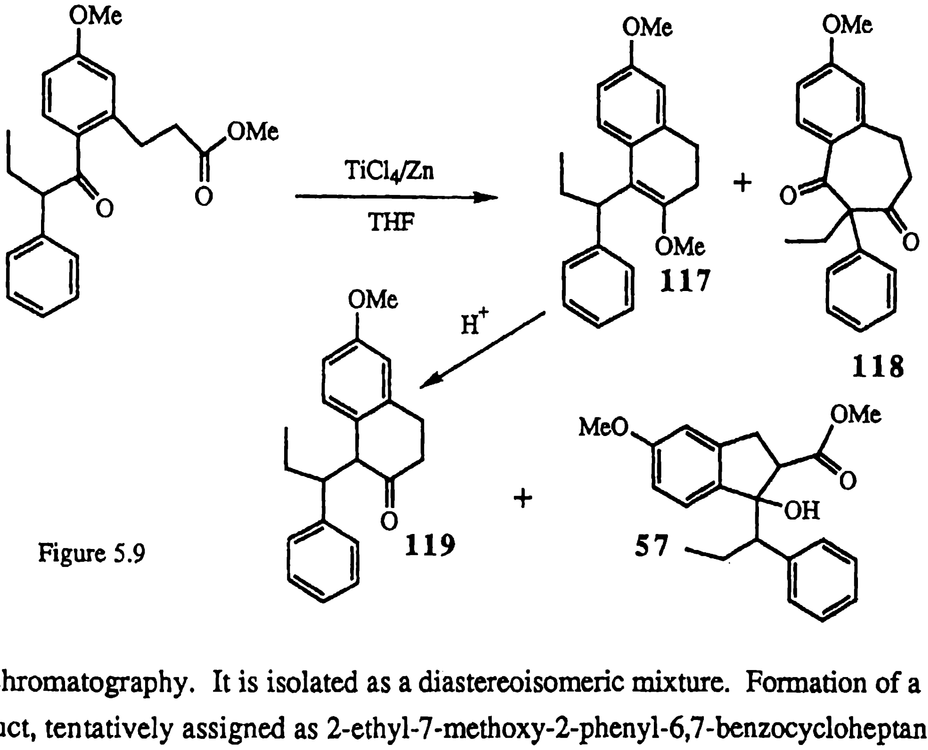


Figure 5.9

and chromatography. It is isolated as a diastereoisomeric mixture. Formation of a third product, tentatively assigned as 2-ethyl-7-methoxy-2-phenyl-6,7-benzocycloheptan-1,3-dione (**118**, 4%), is simply explained as a Claisen-like condensation (figure 5.9). The remaining indanol product (**57**, 18%) is formed most likely *via* an aldol reaction. Titanium-mediated coupling of keto esters has been shown[127,131,133,134] to be a good method for the formation of cyclic alkanone products. If workup conditions are kept basic, the enol ether product can be isolated.[131] In our work the conditions are kept basic, yet the intramolecular coupling of **56** gives both the 3,4-dihydronaphthalene and tetralone products.

When the arylalkene methyl 3-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-propenoate **54** is refluxed with $TiCl_4/Zn$ only two products, the indene (**55**, 23%) and the naphthalene (**120**, 25%), are isolated. The naphthalene, **120**, is the dicarbonyl coupling product. Isomerisation about the original arylalkene double bond may occur at the radical anion stage (see figure 5.10). Due to aromatisation, hydrolysis of the 2-methoxy ether linkage is inhibited so no carbonyl compound analogous to **119** is formed.

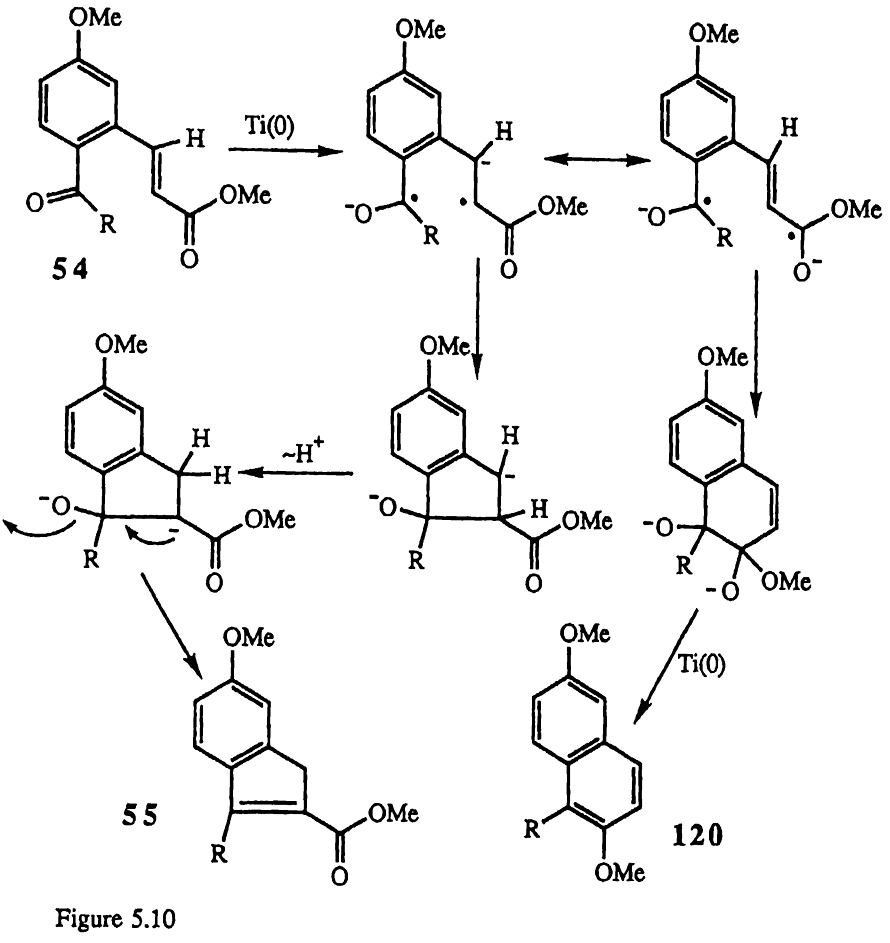


Figure 5.10
R = $PhCHCH_2CH_3$

Though there are no reports of aldol-type reaction products forming from titanium-induced reactions, intramolecular alkylidation of alkanoates (ketoesters) are reported[134] to be more capricious than other McMurry-type reactions, necessitating a modified titanium reagent. It may be that the $TiCl_4/Zn$ system specifically results in indanol and indene formation from the keto ester compounds **56** and **54** respectively. Nevertheless, with optimisation, the yields of the dicarbonyl coupled products could possibly be increased at the expense of the aldol-type products if a suitable titanium reagent is employed. Alkene coupling of the appropriate orthomanganated precursor and subsequent titanium-induced dicarbonyl coupling may prove to be a useful simple route to the synthesis of substituted 3,4-dihydronaphthalenes and tetralone products.

5.3 Summary

Though the *ortho*-halogenated derivatives of **85** could be synthesised in good yield, the titanium-induced coupling reactions tend to give unsatisfactory results: bromine *ortho* to the carbonyl significantly reduces reductive coupling, and iodine eliminates it altogether. By increasing the ratio of propiophenone to **90** an increase in the yield of the crossed products **102** and **103** is observed in the Br case. From the reaction of **90** with propiophenone it is also evident that significant reduction of the halogen occurs over extended reaction time. For the bromo-derivatives, **90** and **92**, the yields show reductive coupling is less hindered if the bromine is positioned on the acetoxy-substituted ring.

Though the titanium-mediated reductive coupling may not prove to be an accessible route to *ortho* halogenated Tamoxifen derivatives it does however provide a convenient route to the novel pyridinium Tamoxifen analogue **121** and further investigation of this system may be warranted.

The cyclic products formed from the reductive coupling of the dicarbonyl compounds show a potential exists for a direct route from acetophenone compounds to substituted dihydronaphthalenes and tetralone products. Further development to try and reduce the extent of aldol and Claisen-type byproducts is warranted.

5.4 Experimental

Preparation of 4-(tetrahydropyran-2-yloxy)-benzophenone 84.

4-Hydroxybenzophenone (4.34 g, 21.9 mmol) was dissolved in THF (20 ml). 4-Toluenesulphonic acid (0.032 g, 0.168 mmol) and 2*H*-dihydropyran (3 ml, 33.1 mmol) were added and the solution stirred for 4 h. The solution was extracted with diethyl ether (100 ml) and washed (3 x 30 ml) with 5% K_2CO_3 solution and dried ($CaCl_2$). The solvent was removed under reduced pressure to give a colourless oil (6.03 g), identified as 4-(tetrahydropyran-2-yloxy)-benzophenone **84** (21.3 mmol, pure by NMR 97%).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.75 (m, 4H, ArH), 7.51 (d, J = 7.1 Hz, 2H, ArH), 7.43 (t, J = 7.1 Hz, 2H, ArH), 7.09 (t, J = 8.7 Hz, 1H, ArH), 5.50 (t, J = 3.0 Hz, 1H, H2''), 3.84 (m, 1H, H6''), 3.62 (m, 1H, H6''), 1.80 (m, 6H, H3'', H4'', H5'').
^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.2 (s, C=O), 160.9 (s, C4), 138.3 (s, C1'), 132.5 (d, C2, C6), 132.1 (d, C4'), 130.7 (s, C1), 129.8 (d), 128.2 (d), (C2', C3', C5', C6'), 115.9 (d, C3, C5), 96.1 (d, C2''), 62.1 (t, C6''), 30.1 (t, C3''), 25.1 (t, C5''), 18.5 (t, C4'').
MS : 198 (M^+-C_5H_9O), 169, 141, <u>121</u>, 105, 77.

Acetylation of 4-hydroxybenzophenone.

4-Hydroxybenzophenone (3.066 g, 15.5 mmol) and acetic anhydride (1.75 ml, 18.6 mmol) were dissolved in pyridine (9 ml) and the solution stirred at ambient temperature for 24 h. The solution was then poured into water (50 ml) and extracted with ether (50 ml). The ether layer was washed with water (4 x 50 ml) and HCl (2 mol l^{-1}, 1 x 30 ml) and NaOH (0.01 mol l^{-1}, 2 x 20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to leave white crystals of 4-benzoylphenyl acetate **85** (3.62 g, 15.1 mmol, 98%). Recrystallisation from pet. spirit gave white crystals of **85**, mp 78-79°C. Elemental analysis (below) indicated some impurity, but the material was considered satisfactory for orthomanganation which gave products (see below) for which accurate elemental analyses were obtained.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.85 (d, J = 8.7 Hz, 2H, H3, H5), 7.79 (d of d, J = 1.3, 8.2 Hz, 2H, H2', H6'), 7.58 (t, J = 7.5 Hz, 1H, H4'), 7.48 (d of t, J = 1.3, 7.1 Hz, 2H, H3', H5'), 7.22 (d, J = 8.7 Hz, 2H, H2, H6), 2.34 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 195.3 (s, C=O), 168.7 (s, C=O), 153.8 (s, C4), 137.3 (s, C1'), 134.8 (s, C1), 132.3 (d, C4'), 131.5 (d, C2, C6), 129.7 (d), 128.2 (d), (C2'-C6'), 121.4 (d, C3, C5), 20.9 (q, CH_3).
MS : 240 (M^+), 198, <u>121</u>, 77.
Found :- C, 73.83; H, 5.19%.

$C_{15}H_{12}O_3$ calcd : C, 74.99; H, 5.03%.

Attempted orthomanganation of 4-hydroxybenzophenone.

Benzylpentacarbonylmanganese **8** (0.238 g, 0.832 mmol) and 4-hydroxybenzophenone (0.157 g, 0.793 mmol) were dissolved in pet. spirit (10 ml) and purged with N_2. The solution was heated under reflux for 8 h. Chromatography with CH_2Cl_2 yielded two bands.

Band one (R_f = 1.00) gave a yellow oil (0.036 g), identified (IR) as a mixture (1:3) of **8** and $Mn_2(CO)_{10}$.

Band two (R_f = 0.55) gave a yellow oil (0.073 g), identified as 4-hydroxybenzophenone.

Orthomanganation of 4-(tetrahydropyran-2-yloxy)-benzophenone 84.

Benzylpentacarbonylmanganese **8** (0.882 g, 3.08 mmol) and 4-(tetrahydropyran-2-yloxy)-benzophenone **84** (0.853 g, 3.02 mmol) were dissolved in pet. spirit (30 ml) and refluxed for 7.5 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.77) gave a yellow oil (0.546 g), identified (NMR ratio 4:1) as tetra(carbonyl-κ*C*)[5-(tetrahydropyran-2-yloxy)-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **86** (0.986 mmol, 32%) and tetra(carbonyl-κ*C*)[2-(4-(tetrahydropyran-2-yloxy)-benzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) **87** (0.246 mmol, 8%). Isomer separation was achieved by crystallisation from pet. spirit.

Tetra(carbonyl-κ*C*)[5-(tetrahydropyran-2-yloxy)-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **86** was obtained as fine yellow crystals, mp 111-112°C. **86** may also be named η^2-(2-benzoyl-5-(tetrahydropyran-2-yloxy)-phenyl)-tetracarbonylmanganese.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.88 (d, J = 8.7 Hz, 1H, H3), 7.79 (d, J = 2.3 Hz, 1H, H6), 7.66 (d, J = 6.9 Hz, 2H, H2', H6'), 7.58 (t, J = 7.2 Hz, 1H, H4'), 7.50 (t, J = 6.9 Hz, 2H, H3', H5'), 6.85 (d of d, J = 2.3, 8.7 Hz, 1H, H4), 5.66 (t, J = 2.9 Hz, 1H, H2''), 3.95 (d of t, J = 2.9, 8.0 Hz, 1H, H6''), 3.71 (m, 1H, H6''), 1.93 (m, br, 6H, H3'', H4'', H5'').
^{13}C NMR (300 MHz) ($CDCl_3$) δ 221 (s, CO), 213.2 (s, CO), 211.5 (s, C=O), 209.2 (s, CO), 199.2 (s, C1), 161.0 (s, C5), 138.2 (s, C1'), 136.8 (s, C2), 136.6 (d, C3), 132.2

(d, C6), 129.1 (d), 128.6 (d), (C2'-C6'), 128.2 (d, C4'), 112.1 (d, C4), 96.0 (d, C2''), 62.3 (t, C6''), 30.2 (t, C3''), 25.1 (t, C5''), 18.6 (t, C4'').
IR (pet. spirit) ν(CO) 2081 (w, sh), 1995 (vs), 1945 (s).
Found : C, 58.83; H, 3.96%.
$C_{22}H_{17}MnO_7$ calcd : C, 58.94; H, 3.82%.

Tetra(carbonyl-κ*C*)[2-(4-(tetrahydropyran-2-yloxy)-benzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) **87** was obtained as chunky dark orange prisms, mp 86°C. **87** may also be named η^2-(2-(4-(tetrahydropyran-2-yloxy)-benzoyl)phenyl)-tetracarbonylmanganese.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.17 (d, J = 7.3 Hz, 1H, H6), 7.98 (d, J = 7.8 Hz, 1H, H3), 7.73 (d, J = 8.9 Hz, 2H, H2', H6'), 7.42 (d of t, J = 1.3, 7.3 Hz, 1H, H5), 7.17 (m, 3H, H4, H3', H5'), 5.55 (t, J = 2.7 Hz, 1H, H2'), 3.86 (d of t, J = 2.8, 8.0 Hz, 1H, H6''), 3.65 (m, 1H, H6''), 1.92 (m, br, 6H, H3'', H4'', H5'').
^{13}C NMR (300 MHz) ($CDCl_3$) δ 221 (s, CO), 213.2 (s, CO), 211.5 (s, C=O), 209.2 (s, CO), 195.2 (s, C1), 161.0 (s, C4'), 144.5 (s, C2), 141.8 (d, C6), 134.4 (d, C5), 133.2 (d, C3), 131.6 (d, C2', C6'), 129.7 (s, C1'), 123.7 (d, C4), 116.3 (C3', C5'), 96.2 (d, C2''), 62.1 (t, C6''), 30.1 (t, C3''), 25.1 (t, C5), 18.5 (t, C4).
IR ($CDCl_3$) ν(CO) 2082 (m, sh), 1998 (vs), 1938 (s).

Band two (R_f = 0.50) gave 4-(tetrahydropyran-2-yloxy)-benzophenone **84** (0.182 g, 22% recovered).

Band three (R_f = 0.20) gave 4-hydroxybenzophenone (0.018 g, 0.010 mmol, 3%).

Orthomanganation of 4-benzoylphenyl acetate 85.

Benzylpentacarbonylmanganese **8** (0.625 g, 2.19 mmol) and 4-benzoylphenyl acetate **85** (0.523 g, 2.18 mmol) were refluxed in pet. spirit (30 ml) for 8 h. Chromatography with CH_2Cl_2/pet. spirit (1:4) yielded one band (R_f = 0.55). This gave a dark orange oil (0.814 g), identified as a mixture (^{1}H NMR ratio 4:3) as tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **88** and tetra(carbonyl-κ*C*)[2-(4-acetoxybenzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) **89** respectively. Isomer separation was achieved by crystallisation (diethyl ether/pentane vapour diffusion).

Tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **88** was obtained as orange needles, mp 100-102°C. **88** may also be named η^2-(5-acetoxy-2-benzoylphenyl)-tetracarbonylmanganese.

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.97 (d, J = 8.5 Hz, 1H, H3), 7.87 (d, J = 2.1 Hz, 1H, H6), 7.70 (d, J = 7.5 Hz, 2H, H2', H6'), 7.63 (t, J = 7.4 Hz, 1H, H4'), 7.53 (t, J = 7.5 Hz, 2H, H3', H5'), 6.97 (d of d, J = 2.1, 8.5 Hz, 1H, H4), 2.37 (s, 3H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 214.4 (s, CO), 210.9 (s, CO), 210.7 (s, C=O), 199.6 (s, C1), 169.0 (s, C=O), 154.3 (s, C5), 141.8 (s, C1'), 135.6 (d, C3), 133.6 (d, C6), 132.7 (d, C4'), 130.9 (s, C2), 129.2 (d), 128.7 (d), (C2'-C6'), 117.8 (d, C4), 21.4 (q, CH$_3$).

IR (pet. spirit) ν(CO) 2084 (m, sh), 1999 (vs), 1949 (s).

mp 100-102°C.

Found : C, 56.18; H, 2.75%.

C$_{19}$H$_{11}$MnO$_7$ calcd : C, 56.18; H, 2.73%.

Tetra(carbonyl-κC)[2-(4-acetoxybenzoyl-κO)-phenyl-κC]-manganese (I) **89** obtained as chunky dark orange prisms, mp 116-120°C. **89** may also be named η^2-(2-(4-acetoxybenzoyl)-phenyl)-tetracarbonylmanganese.

^{1}H NMR (300 MHz) (CDCl$_3$) δ 8.20 (d, J = 7.2 Hz, 1H, H6), 7.96 (d, J = 7.4 Hz, 1H, H3), 7.78 (d, J = 8.6 Hz, 2H, H2', H6'), 7.45 (d of t, J = 0.7, 7.3 Hz, 1H, H5), 7.28 (d, J = 8.6 Hz, 2H, H3', H5'), 7.20 (t, J = 7.3 Hz, 1H, H4), 2.35 (s, 3H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 221.2 (s, CO), 212.9 (s, CO), 211.2 (s, CO), 210.7 (s, C=O), 196.7 (s, C1), 168.8 (s, C=O), 154.1 (C4'), 144.1 (s, C1'), 141.9 (d, C6), 134.7 (d, C5), 133.6 (d, C3), 130.9 (d, C2', C6'), 129.2 (s, C2), 123.9 (d, C4), 122.0 (d, C3', C5'), 21.2 (q, CH$_3$).

IR (pet. spirit) ν(CO) 2083 (m, sh), 1997 (vs), 1948 (s).

Found : C, 56.28; H, 2.77%.

C$_{19}$H$_{11}$MnO$_7$ calcd : C, 56.18; H, 2.73%.

Bromination of tetra(carbonyl-κC)[5-(tetrahydropyran-2-yloxy)-2-(benzoyl-κO)-phenyl-κC]-manganese(I) 86.

(a) with NBS

Tetra(carbonyl-κC)[5-(tetrahydropyran-2-yloxy)-2-(benzoyl-κO)-phenyl-κC]-manganese(I) **86** (0.368 g, 0.824 mmol) and *N*-bromosuccinimide (0.148 g, 0.830 mmol) were dissolved in N$_2$-saturated carbon tetrachloride (10 ml). The solution was refluxed for 5 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded only two major bands.

Band one (R$_f$ = 0.72) gave 4-(tetrahydropyran-2-yloxy)-benzophenone **84** (0.188 g, 0.667 mmol, 81%).

Band two (R_f = 0.24) gave 4-hydroxybenzophenone (0.011 g, 0.053 mmol, 6%).

(b) with Br_2

Tetra(carbonyl-κ*C*)[5-(tetrahydropyran-2-yloxy)-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **86** (0.359 g, 0.801 mmol) was dissolved in N_2-saturated carbon tetrachloride. Bromine (0.801 mol, in N_2-saturated carbon tetrachloride) was added and the solution stirred for 1 h then filtered, the residue identified[87] as $[ClM(CO)_4]_2$. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.75) gave $BrMn(CO)_5$ (0.021 g), identified[88] by IR.

Band two (R_f = 0.55) gave 4-(tetrahydropyran-2-yloxy)-benzophenone **84** (0.044 g, 0.156 mmol, 43%).

Band three (R_f = 0.25) gave 4-hydroxybenzophenone (0.103 g, 0.520 mmol, 65%).

Bromination of tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 88.

(a) with NBS

Tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **88** (0.170 g, 0.419 mmol) and *N*-bromosuccinimide (0.075 g, 0.421 mmol) were dissolved in N_2-saturated carbon tetrachloride (10 ml) and the solution refluxed for 5.5 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded two bands.

Band one gave 4-benzoyl-2-bromophenyl acetate **90** (0.086 g, 2.70 mmol, 64%). Crystallisation from diethyl ether/pet. spirit gave large chunky colourless crystals, mp 104-106°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.82 (m, 2H, H2', H6'), 7.61 (d of t, J = 1.3, 7.4 Hz, 1H, H4'), 7.47 (m, 3H, H3, H3' , H5'), 7.38 (d, J = 8.3 Hz, 1H, H6), 7.18 (d of d, J = 2.2, 8.3 Hz, 1H, H5), 2.33 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 195.1 (s, C=O), 168.8 (s, C=O), 151.8 (s, C4), 137.9 (s, C1'), 136.0 (s, C1), 133.8 (d, C6), 129.8 (d, C3), 130.2 (d), 128.6 (d), (C2'-C6'), 126.5 (d, C4'), 120.6 (d, C5), 119.9 (s, C2), 21.0 (q, CH_3).

MS : 320, 318 (M^+), 278, 276, 210, 199, 139.

Found : C, 56.74; H, 3.54; Br, 24.84%.

$C_{15}H_{11}BrO_3$ calcd : C, 56.45; H, 3.47; Br, 25.04%.

Band two gave a colourless oil (0.008 g), tentatively assigned as 4-benzoyl-3-bromophenyl acetate **91** (0.025 mmol, 6%).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.64 (d, J = 7.1 Hz, 2H, H2', H6'), 7.38 (m, 2H, H5, H4'), 7.25 (t, J = 7.1 Hz, 2H, H3', H5'), 7.14 (d, J = 2.2 Hz, 1H, H2), 7.10 (d of d, J = 2.2 Hz, 1H, H6), 2.29 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.2 (s, C=O), 168.8 (s, C=O), 151.8 (s, C4), 141.5 (s, C1'), 137.2 (s), 135.5 (s), (C3, C1), 132.8 (d, C5), 131.0 (d, C4'), 130.3 (d, C2', C6'), 128.0 (d, C3', C5'), 124.6 (d, C2), 120.1 (d, C6), 21.2 (q, CH_3).
MS : 320, 318 (M^+), <u>278</u>, 276, 201, 199, 139, 105.

(b) <u>with Br_2</u>

Tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **88** (0.049 g, 0.121 mmol) was dissolved in N_2-saturated carbon tetrachloride. Bromine (0.121 mmol, dissolved in N_2-saturated carbon tetrachloride) was added and the solution stirred for 4.5 h. The solution was filtered and solvent removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:4) yielded two bands.

Band one gave a yellow oil (0.011 g), identified[88] (IR) as $BrMn(CO)_5$ and **88**.

Band two gave 4-benzoyl-2-bromophenyl acetate **90** (0.023 g, 0.072 mmol, 59%).

Bromination of tetra(carbonyl-κ*C*)[2-(4-acetoxybenzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) 89.

(a) <u>with NBS</u>

Tetra(carbonyl-κ*C*)[2-(4-acetoxybenzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) **89** (0.210 g, 0.517 mmol) and *N*-bromosuccinimide (0.099 g, 0.556 mmol) were dissolved in N_2-saturated carbon tetrachloride (10 ml) and the solution refluxed for 5 h. Chromatography with CH_2Cl_2/ethyl acetate/pet. spirit (4:1:7) yielded two bands.

Band one gave 4-(2-bromobenzoyl)-phenyl acetate **92** (0.137 g, 0.429 mmol, 83%). Crystallisation from diethyl ether/pet. spirit (1:15) gave fine white crystals, mp 62°C.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H, H2', H6'), 7.65 (d of d, J = 1.7, 7.8 Hz, 1H, H6), 7.38 (m, 3H, ArH), 7.20 (d, J = 8.5 Hz, 2H, H3', H5'), 2.33 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 194.3 (s, C=O), 168.4 (s, C=O), 154.6 (s, C4), 140.1 (s, C1'), 133.3 (s, C1), 133.1 (d, C4'), 131.8 (d, C2, C6), 131.2 (d, C3'), 128.8 (d, C6'), 127.2 (d, C5'), 121.8 (d, C3, C5), 119.3 (s, C2'), 20.7 (q, CH_3).

MS : 320, 318 (M+), 278, 276, 121.
Found : C, 57.07; H, 3.54; Br, 25.07%.
$C_{15}H_{11}BrO_3$ calcd : C, 56.45; H, 3.47; Br, 25.04%.

Band two gave a pale yellow oil (0.014 g), tentatively assigned as 4-(3-bromobenzoyl)-phenyl acetate **93** (0.044 mmol, 9%).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.72 (m, 2H, ArH), 7.36 (m, 3H, ArH), 6.99 (d, J = 8.4 Hz, 2H, ArH), 6.85 (d, J = 8.4 Hz, 2H, ArH), 2.28 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.5 (s, C=O), 168.8 (s, C=O), 154.2 (s, C4'), 140.1 (s), 138.0 (s), (C1, C1'), 134.8 (s, C3), 133.0 (d, C4), 132.0 (d, C2', C6'), 131.6 (d, C2), 130.3 (d, C5), 121.3 (d, C3', C5'), 115.6 (d, C6), 21.2 (q, CH_3).
MS : 320, 318 (M+), 278, 276, 157, 155, 121.

(b) with Br_2

Tetra(carbonyl-κ*C*)[2-(4-acetoxybenzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) **89** (0.068 g, 0.168 mmol) was dissolved in N_2-saturated carbon tetrachloride. Bromine (0.168 mmol, dissolved in N_2-saturated carbon tetrachloride) was added and the solution stirred for 4.5 h. The solution was filtered and solvent removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:4) yielded two bands.

Band one gave a yellow oil (0.003 g), identified[88] (IR) as a mixture of $BrMn(CO)_5$ and **89**.

Band two gave 4-(2-bromobenzoyl)-phenyl acetate **92** (0.041 g, 0.127 mmol, 76%).

Iodination of tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 88.

Tetra(carbonyl-κ*C*)[5-acetoxy-2-(benzoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **88** (0.092 g, 0.227 mmol) was dissolved in N_2-saturated carbon tetrachloride. Iodine monochloride (0.227 mmol in N_2-saturated carbon tetrachloride) was added and the solution stirred for 2.5 days. The solution was filtered and chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one gave orange crystals identified[88] (IR) as $ClMn(CO)_5$ (0.013 g, 0.040 mmol, 18%).

Band two gave pale white crystals of 4-benzoyl-2-iodophenyl acetate **94** (0.049 g, 0.134 mmol, 59%). Recrystallisation from ether/pet. spirit (1:15) gave chunky colourless crystals, mp 126°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.80 (m, 2H, ArH), 7.70 (d, J = 2.2 Hz, 1H, H3), 7.61 (t of t, J = 1.3, 7.4 Hz, 1H, H4'), 7.47 (t, J = 1.8, 7.8 Hz, 2H, ArH), 7.31 (d, J = 8.3 Hz, 1H, H6), 7.21 (d of d, J = 2.2, 8.3 Hz, 1H, H5), 2.32 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 196.6 (s, C=O), 168.7 (s, C=O), 151.5 (s, C4), 141.7 (s, C1'), 135.6 (s, C1), 133.8 (d, C6), 132.9 (d, C3), 130.5 (d), 129.3 (d), (C2'-C6'), 129.3 (d, C4'), 121.3 (d, C5), 92.1 (s, C2), 21.1 (q, CH_3).

MS : 366 (M^+), 324, 247, 197, 168, 139, 105.

Found : C, 49.36; H, 3.26; I, 34.56%.

$C_{15}H_{11}IO_3$ calcd : C, 49.20; H, 3.03; I, 34.66%.

Band three gave a colourless oil (0.005 g), tentatively assigned as 4-benzoyl-3-iodophenyl acetate **95** (0.14 mmol, 6%). Crystallisation from diethyl ether/pet. spirit gave small whitish prisms, mp 151°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.65 (d of d, J = 1.2, 8.4 Hz, 2H, H2', H6'), 7.38 (m, 2H, ArH), 7.25 (m, 2H, ArH), 7.14 (d, J = 2.1 Hz, 1H, H5), 7.09 (d of d, J = 2.3, 8.4 Hz, 1H, H6), 2.29 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 168.5 (s, C=O), 151.8 (s, C4), 141.5 (s, C1'), 137.2 (s, C1), 132.8 (d), 131.0 (d), (C2, C6), 130.3 (d), 128.0 (d), (C2'-C6'), 124.6 (d, C4'), 120.1 (d, C5), 92.5 (s, C3), 21.2 (q, CH_3).

MS : 324 (M^+-$COCH_3$), 121.

Band four gave a colourless oil (0.005 g), tentatively assigned as 4-hydroxy-2-iodobenzophenone **96** (0.015 mmol, 7%).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.80 (d of d, J = 1.5, 6.8 Hz, 2H, H2', H6'), 7.58 (t, J = 8.2 Hz, 1H, H4'), 7.45 (m, 3H, ArH), 7.21 (d, J = 8.5 Hz, 1H, H6), 6.88 (d of d, J = 2.3, 8.5 Hz, 1H, H5).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.0 (s, C4), 136.5 (s, C1'), 133.4 (d, C6), 130.9 (d, C3), 130.5 (d), 128.6 (d), (C2'-C6'), 127.3 (d, C4'), 114.9 (d, C5), 107.8 (s, C1), 93.7 (s, C2).

Iodination of tetra(carbonyl-κ*C*)[2-(4-acetoxybenzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) 89.

Tetra(carbonyl-κ*C*)[2-(4-acetoxybenzoyl-κ*O*)-phenyl-κ*C*]-manganese (I) **89** (0.092 g, 0.227 mmol) was dissolved in N_2-saturated carbon tetrachloride. Iodinechloride (0.227 mmol in N_2-saturated carbon tetrachloride) was added and the solution stirred for 2.5 days. The solution was filtered and chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one gave orange crystals identified[88] (IR) as $ClMn(CO)_5$ (0.013 g, 0.040 mmol, 18%).

Band two gave **89** (0.007 g, 8% recovered), identified by IR.

Band three gave 4-(2-iodobenzoyl)-phenyl acetate **97** (0.052 g, 0.141 mmol, 62%). Crystallisation from diethyl ether/pet. spirit (1:10) gave fine white crystals, mp 67°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.93 (d of d, J = 1.0, 7.2 Hz, 1H, H3), 7.84 (d, J = 8.8 Hz, 2H, H2', H6'), 7.45 (d of t, J = 1.0, 7.5 Hz, 1H, H5), 7.29 (d of d, J = 1.6, 7.6 Hz, 1H, H6), 7.20 (d, J = 8.8 Hz, 2H, H3', H5'), 7.18 (d of t, J = 1.6, 7.2 Hz, 1H, H4), 2.33 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 195.9 (s, C=O), 168.7 (s, C=O), 154.9 (s, C4'), 144.1 (s, C1), 139.7 (d, C3), 133.1 (s, C1'), 132.1 (d, C2', C6'), 131.2 (d, C4), 128.4 (d), 127.8 (d), (C5, C6), 121.9 (d, C3', C5'), 92.9 (s, C2), 21.2 (q, CH_3).

MS : 324 (M^+-C_2H_2O), 140, 121.

Found : C, 49.11; H, 2.98; I, 34.37%.

$C_{15}H_{11}IO_3$ calcd : C, 49.20; H, 3.03; I, 34.66%.

Reductive coupling of 4-benzoylphenyl acetate 85 with propiophenone.

All titanium mediated reactions were performed under an N_2 atmosphere. The general procedure is outlined in the reaction below.

To a solution containing powdered zinc metal (0.500 g, 7.65 mmol) suspended in dry N_2-saturated THF (20 ml) (cooled to -30°C) $TiCl_4$ (0.42 ml, 7.65 mmol) was added by syringe through a septum seal. The solution was refluxed for 1 h. The solution was then cooled to 20°C and a solution with 4-benzoylphenyl acetate **85** (0.170 g, 0.708 mmol) and propiophenone (0.10 ml, 1.14 mmol) in THF (2 ml) added. The solution was then refluxed for a further 3 h. A solution of 10% K_2CO_3 (100 ml) was added to the reaction mixture which was then extracted with ether (2 x 50 ml) and dried ($CaCl_2$). The solvent volume was reduced under vacuum and chromatography (plc) with diethyl ether/pet. spirit (1:9) yielded three bands.

Band one gave 3,4-diphenylhex-3-ene **98** (0.050 g, 0.211 mmol, 10%) which crystallised from pet. spirit to give fine white crystals, mp 27°C.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.06 (m, 5H, ArH), 2.02 (q, J = 7.5 Hz, 2H, CH_2), 1.07 (t, J = 7.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 143.3 (s, C1'), 139.3 (s, C3), 129.9 (d), 127.5 (d), (C2'-C6'), 125.6 (d, C4'), 27.4 (t, CH_2), 13.4 (CH_3).

Band two gave as a colourless oil 1-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene (0.153 g, 0.449 mmol, 63%), identified as a *Z*/*E* mixture (NMR ratio 7:4, based on acetyl ^{1}H integrals) of **99** and **100** respectively.

Z-1-(4-Acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** has the following spectral characteristics.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.33 (m, 4H, ArH), 7.18 (m, 6H, ArH), 6.87 (d, J = 8.7 Hz, 2H, H2, H6), 6.75 (d, J = 8.7 Hz, 2H, H3, H5), 2.48 (q, J = 7.5 Hz, 2H, CH_2), 2.20 (s, 3H, $COCH_3$), 0.95 (t, J = 7.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.3 (s, C=O), 148.6 (s, C4), 143.3 (s), 142.7 (s), 142.0 (s), (C1, C1', C1''), 140.5 (s), 139.0 (s), (C7, C8), 131.7 (d, C2, C6), 129.7 (d), 129.6 (d), 128.3 (d), 128.0 (d), (C2'-C6', C2''-C6''), 126.8 (d), 126.4 (d), C4', C4''), 120.4 (d, C3, C5), 29.1 (t, CH_2), 21.3 (q, $COCH_3$), 13.6 (q, CH_3).
MS : 342 (M^+), 300, 239, 207.

E-1-(4-Acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** has the following spectral characteristics
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.33 (m, 4H, ArH), 7.18 (m, 6H, ArH), 7.03 (m, 2H, H2, H6), 6.87 (d, J = 8.7 Hz, 2H, H3, H5), 2.51 (q, J = 7.5 Hz, 2H, CH_2), 2.31 (s, 3H, $COCH_3$), 0.94 (t, J = 7.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.5 (s, C=O), 149.4 (s, C4), 142.9 (s), 142.8 (s), 142.1 (s), (C1, C1', C1''), 141.1 (s), 138.9 (s), (C7, C8), 130.8 (d), 130.5 (d), 129.7 (d), 127.9 (d), 127.4 (d), (C2, C6, C2'-C6', C2''-C6''), 126.3 (d), 125.9 (d), (C4', C4''), 121.2 (d, C3, C5), 29.0 (t, CH_2), 21.2 (q, $COCH_3$), 13.6 (q, CH_3).
MS : 342 (M^+), 300, 239, 207.

Band three gave a colourless oil (0.152 g), identified as 3,4-diphenyl-hexan-3,4-diol **101** (0.638 mmol, 55%). Crystallisation from diethyl ether/pet. spirit (1:2) gave colourless prisms, mp 68°C.
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.28 (m, 10H, ArH), 2.75 (s, br, 1H, OH), 2.06 (m, 1H, CH_2), 1.73 (m, 1H, CH_2), 0.62 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 140.4 (s, C1'), 128.4 (d), 127.1 (d), (C2'-C6'), 126.9 (d, C4'), 82.1 (s, C3), 27.8 (t, CH_2), 7.6 (q, CH_3).
MS : 136 (M^+-$C_9H_{10}O$), 135, 108, 106.

Reductive coupling of 4-benzoyl-2-bromophenyl acetate 90 with propiophenone.

(a) with a 3-mole excess of propiophenone under reflux for 2 h

Zinc powder (0.500 g, 7.65 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.42 ml, 3.83 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-benzoyl-2-bromophenyl acetate **90** (0.223 g, 0.697 mmol) and propiophenone (0.18 ml, 2.09 mmol) in THF (2 ml) was added and the solution refluxed for a further 2 h. 10% K_2CO_3 (100 ml) was added and the mixture extracted with ether (3 x 50 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (1:9) yielded three bands.

Band one ($R_f = 0.88$) gave 3,4-diphenylhex-3-ene **98** (0.050 g, 0.211 mmol, 10%).

Band two ($R_f = 0.55$) gave a pale yellow oil (0.162 g), identified by NMR as a mixture (ratio 3:3:2:1) of *Z*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **102** (0.138 mmol, 20%), *E*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **103** (0.131 mmol, 19%), Z-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.091 mmol, 13%) and *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.052 mmol, 7%) respectively.

Z-(4-Acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **102** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m, 13H, ArH), 2.50 (q, J = 7.0 Hz, 2H, CH_2), 2.28 (s, 3H, $COCH_3$), 0.93 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.0 (s, C=O), 149.5 (s, C4), 141.7 (s), 141.2 (s), 141.15 (s), (C1, C1', C1''), 134.8 (s), 133.8 (s), (C7, C8), 131.7 (d, C6), 129.7 (d), 128.0 (d), 127.9 (d), 127.89 (d), (C2'-C6', C2''-C6''), 126.4 (d), 126.35 (d), 125.9 (d), (C3, C4', C4''), 124.1 (s, C2), 120.8 (d, C5), 32.0 (t, CH_2), 21.7 (q, $COCH_3$), 14.2 (q, CH_3).

MS : 422, 420 (M^+), 397, 395, 300, 284, 270, 239.

E-(4-Acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **103** has the following spectral characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.43 (d, J = 2.1 Hz, 1H, H3), 7.36 (d, J = 8.3 Hz, 1H, H6), 7.18 (m, 7H, ArH), 6.99 (m, 4H, ArH), 2.32 (q, J = 7.5 Hz, 2H, CH_2), 2.31 (s, 3H, $COCH_3$), 0.88 (t, J = 7.5 Hz, 3H, CH_3).

CH_3 (0.88) and CH_2 (2.32) nOe to 7.43 and 7.18.

H3 (7.43) nOe to 0.88.

H6 (7.36) nOe to 2.31 and 0.88.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.0 (s, C=O), 149.7 (s, C4), 144.0 (s), 141.2 (s), (C1, C1'), 141.2 (C1''), 140.5 (s), 136.3 (s), (C7, C8), 131.5 (d, C5), 130.8 (s), 130.5 (d), 129.6 (d), 127.9 (d), 127.4 (d), (C2'-C6', C2''-C6''), 126.5 (d), 126.1 (d), 126.0 (d), (C3, C4', C4''), 124.1 (s, C2), 120.7 (d, C5), 29.3 (t, CH_2), 21.2 (q, CH_3), 12.5 (q, CH_3).
MS : 422, 420 (M^+), 397, 395, 300, 284, 270, 239.

Band three (R_f = 0.30) gave 3,4-diphenylhexan-3,4-diol **101** (0.110 g, 0.836 mmol, 40%).

(b) with a 3-mole excess of propiophenone under reflux for 3 h

Zinc powder (1.00 g, 15.3 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.84 ml, 7.66 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-benzoyl-2-bromophenyl acetate **90** (0.362 g, 1.13 mmol) and propiophenone (0.30 ml, 3.41 mmol) in THF (5 ml) was added and the solution refluxed for a further 3 h. 10% K_2CO_3 (75 ml) was added and the mixture extracted with ether (3 x 50 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (1:9) yielded five bands.

Band one (R_f = 0.98) gave 3,4-diphenylhex-3-ene **98** (0.139 g, 0.588 mmol, 17%).

Band two (R_f = 0.63) gave a pale yellow oil (0.126 g), identified by NMR as a mixture (ratio 1.3 : 1 : 3.3 : 2.6) of Z-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **102** (0.020 mmol, 2%), *E*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **103** (0.014 mmol, 1%), Z-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.061 mmol, 5%) and *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.049 mmol, 4%) respectively. Crystallisation from pet. spirit gave fine white crystals of **99** and **100** (*ca.* 0.015 g, mp 68-72°C NMR ratio 1:1).

Band three (R_f = 0.58) gave a pale yellow oil (0.068 g), identified as a mixture (NMR ratio 2.2 : 4 : 1) of *E*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **103** (0.049 mmol, 4%), Z-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.111 mmol, 10%) and *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.027 mmol, 2%) respectively. Crystallisation from pet. spirit gave colourless chunky crystals of **103** (*ca.* 0.010 g, mp 82-85°C, pure by NMR).

Band four (R_f = 0.32) gave a colourless oil (0.081 g), identified as a mixture (NMR ratio 1 : 1 : 1 : 0.4) of 3,4-diphenyl-hexan-3,4-diol **101** (0.075 mmol, 2%), Z-(2-bromo-4-hydroxyphenyl)-1,2-diphenyl-but-1-ene **104** (0.090 mmol, 8%), Z-(4-hydroxyphenyl)-

1,2-diphenyl-but-1-ene **105** (0.071 mmol, 6%) and *E*-(4-hydroxyphenyl)-1,2-diphenyl-but-1-ene **106** (0.029 mmol, 3%) repectively.

Z-(2-Bromo-4-hydroxyphenyl)-1,2-diphenyl-but-1-ene **104** has the following spectral characteristics.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 154.7 (s, C4), 143.3 (s, C1), 141.8 (s), 141.3 (s), (C1’, C1”), 137.1 (s), 135.9 (s), (C7, C8), 130.9 (d, C6), 130.4 (d), 129.5 (d), 127.7 (d), 127.6 (d), (C2’-C6’, C2”-C6”), 126.6 (d), 126.4 (d), (C4’, C4”), 121.1 (s, C2), 119.9 (d, C5), 114.9 (d, C3), 31.8 (t, CH_2), 12.7 (q, CH_3).

Z-(4-Hydroxyphenyl)-1,2-diphenyl-but-1-ene **105** has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.25 (m, 10H, ArH), 6.74 (d, J = 6.7 Hz, 2H, H2, H6), 6.47 (d, J = 7.6 Hz, 2H, H3, H5), 4.05 (s, 1H, OH), 2.50 (q, J = 7.3 Hz, 2H, CH_2), 0.93 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 153.9 (s, C4), 143.9 (s, C1), 142.5 (s), 141.8 (s), (C1’, C1”), 141.3 (s), 135.3 (s), (C7, C8), 132.1 (d, C2, C6), 129.6 (d), 128.1 (d), 127.0 (d), 126.1 (d), (C2’-C6’, C2”-C6”), 126.4 (d), 125.8 (d), (C4’, C4”), 114.5 (d, C3, C5), 29.4 (t, CH_2), 12.7 (q, CH_3).

E-(4-Hydroxyphenyl)-1,2-diphenyl-but-1-ene **106** was tentatively assigned by ^{13}C NMR.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 155.7 (s, C4), 143.7 (s, C1), 141.9 (s), 141.2 (s), (C1’, C1”), 138.7 (s), 135.1 (s), (C7, C8), 131.9 (d), 129.6 (d), 128.4 (d), 128.3 (d), 127.2 (d), 126.8 (d), (C2, C6, C2’-C6’, C2”-C6”), 126.3 (d), 125.7 (d), (C4’, C4”), 115.1 (d, C3, C5), 29.1 (t, CH_2), 13.6 (q, CH_3).

Band five (R_f = 0.18) gave 4-(1-hydroxy-1-phenylmethyl)-3-bromophenyl acetate **107** (0.060 g, 0.187 mmol, 16%) as a pale yellow oil. Attempts to crystallise **107** proved unsuccessful.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 1H, H6), 7.29 (m, 7H, ArH), 6.15 (s, 1H, CH), 2.27 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.2 (s, C=O), 150.4 (s, C4), 142.1 (s), 140.4 (s), (C1, C1’), 130.1 (d, C6), 129.1 (d), 127.9 (d), (C2’-C6’), 125.9 (d, C4’), 122.5 (d), 121.1 (d), (C3, C5), 120.9 (s, C2), 74.3 (d, HC-OH), 21.1 (q, CH_3).
MS : 322, 320 (M^+), 280, 278, 203, 201, 199.

(c) with a 1-mole of propiophenone under reflux for 2 h

Zinc powder (1.13 g, 17.3 mmol) was added to dry THF (15 ml). $TiCl_4$ (0.95 ml, 8.66 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-benzoyl-2-bromophenyl acetate **90** (0.138 g, 0.431 mmol) and propiophenone (0.06 ml, 0.431 mmol) in THF (10 ml) was added and the solution refluxed for a further 2 h. 10% K_2CO_3 (100 ml) was added and the mixture extracted with ether (3 x 40 ml) and dried ($MgSO_4$). Chromatography with diethyl ether/pet. spirit (1:9) yielded three bands.

Band one (R_f = 1.00) gave 3,4-diphenylhex-3-ene **98** (0.015 g, 0.065 mmol, 15%).

Band two (R_f = 0.66) gave a colourless oil (0.035 g), identified as a mixture (NMR ratio 4:2:2:1) of *Z*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **102** (0.037 mmol, 9%), *E*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **103** (0.019 mmol, 4%), *Z*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.023 mmol, 5%) and *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.011 mmol, 3%) respectively.

Band three (R_f = 0.46) gave a colurless oil (0.065 g), identified (NMR ratio 1:2) as 4-benzoyl-2-bromophenyl acetate **90** (0.103 mmol, 24% recovered) and 3,4-diphenylhexan-3,4-diol **101** (0.119 mmol, 27%).

(d) with 1-mole of propiophenone under reflux for 5 h

Zinc powder (1.17 g, 17.9 mmol) was added to dry THF (25 ml). $TiCl_4$ (0.98 ml, 8.94 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-benzoyl-2-bromophenyl acetate **90** (0.248 g, 0.778 mmol) and propiophenone (0.142 g, 1.06 mmol) in THF (5 ml) was added and the solution refluxed for a further 5 h. 10% K_2CO_3 (150 ml) was added and the mixture extracted with ether (3 x 40 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (1:9) yielded three bands.

Band one (R_f = 1.00) gave 3,4-diphenylhex-3-ene **98** (0.064 g, 0.271 mmol, 25%).

Band two (R_f = 0.65) gave a yellow oil (0.060 g), identified as a mixture (NMR ratio 1 : 1.3 : 2 : 1.3) of *Z*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **102** (0.025 mmol, 3%), *E*-(4-acetoxy-2-bromophenyl)-1,2-diphenyl-but-1-ene **103** (0.033 mmol, 4%), *Z*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.062 mmol, 8%) and *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.041 mmol, 5%) respectively.

Band three (R_f = 0.38) gave a pale yellow oil (0.061 g), identified as a mixture (NMR ratio 1 : 1 : 2.2 : 1.2) of 3,4-diphenyl-hexan-3,4-diol **101** (0.042 mmol, 4%), *Z*-(2-bromo-4-hydroxyphenyl)-1,2-diphenyl-but-1-ene **104** (0.031 mmol, 4%), *Z*-(4-hydroxyphenyl)-1,2-diphenyl-but-1-ene **105** (0.088 mmol, 11%) and *E*-(4-hydroxyphenyl)-1,2-diphenyl-but-1-ene **106** (0.048 mmol, 6%) repectively.

Reductive coupling of 4-(2-bromobenzoyl)-phenyl acetate 92 with propiophenone.

Zinc powder (0.500 g, 7.65 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.42 ml, 3.83 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-(2-bromobenzoyl)-phenyl acetate **92** (0.124 g, 0.389 mmol) and propiophenone (0.15 ml, 1.13 mmol) in THF (2 ml) was added and the solution refluxed for a further 3 h. A solution of 10% K_2CO_3 (70 ml) was added and the mixture extracted with ether (3 x 50 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one gave 3,4-diphenylhex-3-ene **98** (0.077 g, 0.325 mmol, 29%).

Band two gave a colourless oil (0.033 g), identified as a mixture (NMR ratio 2:1:1.3) of *Z*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.045 mmol, 12%), *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.022 mmol, 6%) and *Z*-(4-acetoxyphenyl)-1-(2-bromophenyl)-2-phenyl-but-1-ene **108** (0.024 mmol, 6%) respectively.

Z-(4-Acetoxyphenyl)-1-(2-bromophenyl)-2-phenyl-but-1-ene **108** has the following characteristics.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.35 (m, 2H, ArH), 7.18 (m, 9H, ArH), 6.99 (d, J = 8.5 Hz, 2H, H3, H5), 2.55 (q, J = 7.3 Hz, 2H, CH_2), 2.20 (s, 3H, $COCH_3$), 0.90 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.2 (s, C=O), 148.6 (s, C4), 143.5 (s), 141.4 (s), (C1, C1', C1''), 137.9 (s), 137.8 (s), (C7, C8), 133.1 (d, C4'), 131.4 (d, C2, C6), 131.3 (d, C3'), 128.9 (d, C6'), 128.4 (d), 128.1 (d), 127.9 (d), 127.8 (d), (C2'-C6', C2''-C6''), 126.9 (d), 126.6 (d), (C4', C4''), 124.3 (s, C2'), 120.3 (d, C3, C5), 28.2 (t, CH_2), 22.8 (q, $COCH_3$), 14.2 (q, CH_3).

Band three gave 3,4-diphenyl-hexan-3,4-diol **101** (0.093 g, 0.346 mmol, 31%).

Band four gave white crystals of 4-(1-(2-bromophenyl)-1-hydroxy-methyl)-phenyl acetate **109** (0.031 g, 0.097 mmol, 25%), mp 145°C.

^1H NMR (300 MHz) ($CDCl_3$) δ 7.55 (m, 2H, H3', H6'), 7.40 (d, J = 8.6 Hz, 2H, H2, H6), 7.33 (d of t, J = 1.1, 7.7 Hz, 1H, H4'), 7.13 (m, 1H, H5'), 7.05 (d, J = 8.6 Hz, 2H, H3, H5), 6.18 (s, CH), 2.28 (s, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.5 (s, C=O), 150.1 (s, C4), 142.5 (C1'), 139.9 (s, C1), 132.9 (d, C4'), 129.3 (d), 128.5 (d), 127.9 (d), (C3', C5', C6'), 128.2 (d, C2, C6), 121.6 (d, C3, C5), 121.1 (s, C2'), 74.2 (d, HC-OH), 21.2 (q, CH_3).

Reductive coupling of 4-benzoyl-2-iodophenyl acetate 94 with propiophenone.

Zinc powder (0.500 g, 7.65 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.42 ml, 3.83 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-benzoyl-2-iodophenyl acetate **94** (0.312 g, 0.853 mmol) and propiophenone (0.12 ml, 0.90 mmol) in THF (2 ml) was added and the solution refluxed for a further 3.5 h. 10% K_2CO_3 (100 ml) was added and the mixture extracted with ether (3 x 50 ml). Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one (R_f = 0.97) gave 3,4-diphenylhex-3-ene **98** (0.020 g, 0.084 mmol, 9%).

Band two (R_f = 0.80) gave propiophenone (0.007 g, 6%).

Band three (R_f = 0.71) gave 3,4-diphenyl-hexan-3,4-diol **101** (0.089 g, 0.326 mmol, 36%).

Band four (R_f = 0.31) gave a pale yellow oil (0.062 g), identified as a mixture (NMR ratio 2:1) of 4-(1-hydroxy-1-phenylmethyl)-phenyl acetate **110** (0.172 mmol, 20%) and 1-(4-hydroxyphenyl)-1-phenylmethanol **111** (0.104 mmol, 12%) respectively. Crystallisation from diethyl ether gave fine pinkish crystals of **111**, mp 159°C.
^1H NMR (300 MHz) (CD_3COCD_3) δ 8.18 (s, 1H, OH), 7.39 (d, J = 7.5 Hz, 2H, H2', H6'), 7.28 (t, J = 7.1 Hz, 1H, H4'), 7.20 (m, 4H, ArH), 6.76 (d, J = 8.6 Hz, 2H, H3, H5), 2.90 (s, 1H, CH).
^{13}C NMR (300 MHz) (CD_3COCD_3) δ 157.3 (C4), 146.8 (s, C1'), 137.5 (s, C1), 128.8 (d), 127.2 (d), (C2'-C6), 128.6 (C2, C6), 127.4 (C4'), 115.7 (d, C3, C5), 75.8 (d, HC-OH).
MS : 200 (M^+), 182, <u>121</u>, 105.

4-(1-Hydroxy-1-phenylmethyl)-phenyl acetate **110** has following spectral characteristics.
^1H NMR (300 MHz) (CD_3COCD_3) δ 7.30 (m, br, 7H, ArH), 5.83 (s, 1H, CH), 2.27 (s, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.8 (s, C=O), 150.0 (s, C4), 143.6 (s, C1'), 141.5 (s, C1), 128.6 (d), 128.5 (d), 127.6 (d), (C2, C6, C2'-C6'), 126.1 (d, C4'), 121.6 (d, C3, C5), 68.0 (d, CHOH), 21.1 (q, CH_3).
MS : 242 (M^+), <u>200</u>, 184, 163.

Reductive coupling of 4-(2-iodobenzoyl)-phenyl acetate 97 with propiophenone.

Zinc powder (0.511 g, 7.81 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.44 ml, 4.01 mmol) was added and the solution refluxed for 1 h. After cooling (20°C) a solution of 4-(2-iodobenzoyl)-phenyl acetate **97** (0.113 g, 0.309 mmol) and propiophenone (0.10 ml, 0.753 mmol) in THF (2 ml) was added and the solution refluxed for a further 3 h. A solution of 10% K_2CO_3 (50 ml) was added and the mixture extracted with ether (3 x 50 ml) and dried ($CaCl_2$). Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one gave 3,4-diphenylhex-3-ene **98** (0.070 g, 0.295 mmol, 39%).

Band two gave a colourless oil (0.064 g), identified as a mixture (NMR ratio 3:2) of Z-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **99** (0.080 mmol, 26%) and *E*-(4-acetoxyphenyl)-1,2-diphenyl-but-1-ene **100** (0.053 mmol, 17%).

Band three gave 3,4-diphenyl-hexan-3,4-diol **101** (0.084 g, 0.236 mmol, 31%).

Reductive coupling of 4-benzoylpyridine and propiophenone.

(a) with 1-mole of propiophenone

Zinc powder (0.999 g, 15.3 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.84 ml, 7.66 mmol) added and the solution refluxed for 1 h. A solution of 4-benzoylpyridine (0.386 g, 2.11 mmol) and propiophenone (0.28 ml, 2.11 mmol) in THF (2 ml) was added and the solution refluxed for a further 3 h. 10% K_2CO_3 (150 ml) was added and the mixture extracted with ether (3 x 50 ml) . Chromatography with diethyl ether/pet. spirit (1:9) yielded four bands.

Band one gave 3,4-diphenylhex-3-ene **98** (0.108 g, 0.457 mmol, 22%).

Band two gave propiophenone (0.003 g, 1% recovered).

Band three gave 3,4-diphenylhexan-3,4-diol **101** (0.106 g, 0.392 mmol, 19%).

Band four gave 4-benzylpyridine **112** (0.211 g, 0.125 mmol, 59%). Crystallisation from diethyl ether gave pale yellowish crystals, mp 79°C to 133°C (decomp).
^1H NMR (300 MHz) ($CDCl_3$) δ 8.55 (s, br, 1H, H6), 7.29 (m, 7H, ArH), 3.99 (s, 2H, CH_2).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 152.2 (s, C2), 149.4 (d, C6), 138.3 (s, C1'), 129.1 (d, C3', C5'), 128.9 (d, C2', C6'), 126.9 (d, C4'), 124.9 (C3, C5), 41.3 (t, CH_2).

(b) with a 2-mole excess of propiophenone

Zinc powder (0.510 g, 7.80 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.42 ml, 3.83 mmol) added and the solution refluxed for 1 h. A solution of 4-benzoylpyridine (0.420 g, 2.30 mmol) and propiophenone (0.60 ml, 4.52mol) in THF (2 ml) was added and the solution refluxed for a further 5 h. 10% K_2CO_3 (100 ml) was added and the mixture extracted with ether (3 x 40 ml). Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one gave 3,4-diphenylhex-3-ene **98** (0.100 g. 0.424 mmol, 9%).

Band two gave a pale yellow oil (0.295 g), identified as a mixture (NMR ratio 4:1) of *Z*- and *E*-1,2-diphenyl-1-(4-pyridyl)-but-1-ene **113** and **114** (1.04 mmol, 45%). Crystallisation from acetonitrile gave colourless chunky crystals of **113** (pure by NMR), mp 84-86°C.
Found : C,88.08; H, 6.81; N, 5.02%.
$C_{21}H_{19}N$ calcd : C, 88.38; H, 6.71; N, 4.91%.

Z- 1,2-Diphenyl-1-(4-pyridyl)-but-1-ene **113** has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 8.22 (d, J = 6.1 Hz, 2H, H2, H6), 7.34 (m, 6H, ArH), 7.16 (m, 4H, ArH), 6.76 (d, J = 6.1 Hz, 2H, H3, H5), 2.48 (q, J = 7.5 Hz, 2H, CH_2), 0.94 (t, J = 7.5 Hz, 3H, CH_3).
CH_3 (0.94) and CH_2 (2.48) nOes to 7.24, 7.09.
H3,5 (6.76) nOes to 7.24, 7.12.
^{13}C NMR (300 MHz) ($CDCl_3$) δ 150.8 (s, C4), 149.0 (d, C2, C6), 145.3 (s), 142.0 (s), 141.2 (s), 136.5 (d), (C1', C1'', C7, C8), 129.5 (d), 129.4 (d), 128.5 (d), 128.2 (d), (C2'-C6', C2''-C6''), 127.2 (d), 127.0 (d), (C4', C4''), 125.5 (d, C3, C5), 29.3 (t, CH_2), 13.4 (q, CH_3).

E-1,2-Diphenyl-1-(4-pyridyl)-but-1-ene **114** has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 8.58 (d, J = 6.0 Hz, 2H, H2, H6), 7.34 (m, 6H, ArH), 7.16 (m, 4H, ArH), 6.76 (d, J = 6.0 Hz, 2H, H3, H5), 2.48 (q, J = 7.5 Hz, 2H, CH_2), 0.95 (t, J = 7.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 151.3 (s, C4), 149.9 (d, C2, C6), 144.1 (s), 141.6 (s), 141.3 (s), 136.5 (s), C1', C1'', C7, C8), 130.7 (d), 129.5 (d), 128.0 (d), 127.7 (d), (C2'-C6', C2''-C6''), 126.7 (d), 126.4 (d), (C4', C4''), 124.6 (d, C3, C5), 29.0 (t, CH_2), 13.6 (q, CH_3).

Band three gave benzylpyridine **112** (0.045 g, 0.26 mmol, 12%).

Band four crystallised from CH_2Cl_2 to give pale chunky crystals of 1-phenyl-1-(4-pyridine)-methanol **115** (0.127 g, 0.69 mmol, 30%), mp 116°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 8.28 (d, J = 6.1 Hz, 2H, H2, H6), 7.28 (m, 7H, ArH), 5.72 (s, 1H, CH).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 153.8 (s, C1), 149.1 (d, C2, C6), 143.2 (s, C1'), 128.7 (d, C3', C5'), 128.0 (d, C4'), 126.9 (d, C2', C6'), 121.5 (d, C3, C5), 74.6 (d, CH).

Reductive coupling of 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone 59.

Zinc powder (1.81 g, 27.7 mmol) was added to dry THF (30 ml). $TiCl_4$ (1.54 ml, 14.0 mmol) was added and the solution refluxed for 1 h. A solution of 4-(3-methoxy-6-(2-phenyl-1-butanoyl)-phenyl)-2-butanone **59** (0.090 g, 0.278 mmol) in THF (6 ml) was added and the solution refluxed for a further 3 h. The solution was then poured into 10% K_2CO_3 (100 ml) and the mixture extracted with ether (3 x 30 ml) and dried ($MgSO_4$). Chromatography with ethyl acetate/pet. spirit (1:9) yielded only one major band (R_f = 0.88) which gave 3,4-dihydro-6-methoxy-2-methyl-1-(1-phenylpropyl)-naphthalene **116** (0.082 g, 0.280 mmol, 100%) as a colourless oil. Crystallisation (4°C) from pet. spirit gave white chunky crystals. However, **116** is an oil at ambient temperature.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.36 (m, 4H, ArH), 7.22 (t, J = 7.4 Hz, 1H, H4''), 6.85 (d, J = 8.6 Hz, 1H, H8), 6.73 (d, J = 2.7 Hz, 1H, H5), 6.50 (d of d, J = 2.7, 8.6 Hz, 1H, H7), 4.24 (d of d, J = 5.1, 10.5 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 2.75 (m, 2H, CH_2), 2.31 (m, 3H, CH_2), 2.03 (m, 1H, CH_2), 2.01 (s, 3H, CH_3), 0.93 (t, J = 7.3 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 157.6 (s, C6), 144.6 (s, C1''), 138.8 (s, C4a), 133.4 (s, C2), 130.8 (s, C1), 128.1 (s, C8a), 128.4 (d), 126.9 (d), (C2''-C6''), 125.7 (d, C4''), 125.4 (d, C8), 113.3 (d, C5), 110.1 (d, C7), 55.1 (q, OCH_3), 44.7 (d, CH), 31.9 (t, C3), 29.4 (t, C4), 23.9 (t, CH_2), 20.9 (q, CH_3), 12.9 (q, CH_3).
MS : 292 (M^+), 263, 248, 202, 173.

Reductive coupling of methyl 3-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-propanoate 56.

Zinc powder (0.803 g, 12.3 mmol) was added to dry THF (15 ml). $TiCl_4$ (0.67 ml, 6.11 mmol) was added and the solution refluxed for 1 h. A solution of methyl 3-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-propanoate **56** (0.200 g, 0.588 mmol) in THF (6 ml) was added and the solution refluxed for a further 3 h. The solution was poured into 10% K_2CO_3 (160 ml) and extracted with ether (2 x 50 ml) and dried ($MgSO_4$). Chromatography eluting with diethyl ether/pet. spirit (1:9) yielded three bands.

Band one (R_f = 0.67) gave a pale yellow oil (0.020 g), identified (NMR ratio 3:2) as a mixture of 3,4-dihydro-2,6-dimethoxy-1-(1-phenylpropyl)-naphthalene **117** (0.039 mmol, 7%) and a compound tenatively assigned as 2-ethyl-7-methoxy-2-phenyl-6,7-benzocycloheptan-1,3-dione **118** (0.026 mmol, 4%). No attempt was made to further separate these compounds.

3,4-Dihydro-2,6-dimethoxy-1-(1-phenylpropyl)-naphthalene **117** has the following spectral characteristics

^1H NMR (300 MHz) ($CDCl_3$) δ 7.26 (m, 5H, ArH), 7.08 (d, J = 2.6 Hz, 1H, H5), 6.91 (d, J = 8.6 Hz, 1H, H8), 6.51 (d of d, J = 2.6, 8.6 Hz, 1H, H7), 4.34 (d of d, J = 5.5, 9.6 Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.84 (m, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.20 (m, 1H, CH_2), 2.02 (m, 1H, CH_2), 0.84 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 155.6 (s, C6), 145.3 (s, C1''), 136.1 (s, C4a), 128.4 (s, C8a), 128.1 (d), 127.4 (d), (C2''-C6''), 127.1 (d, C8), 126.1 (s, C2), 125.4 (d, C4''), 113.5 (d, C7), 110.4 (d, C5), 55.2 (q, OCH_3), 55.1 (q, OCH_3), 42.5 (d, CH), 29.9 (t, CH_2), 24.0 (t, CH_2), 23.5 (t, CH_2), 12.9 (q, CH_3).

MS : 308 (M^+), <u>277</u>.

2-Ethyl-7-methoxy-2-phenyl-6,7-benzocycloheptan-1,3-dione **118**, tentatively assigned, has the following spectral characteristics

^1H NMR (300 MHz) ($CDCl_3$) δ 7.65 (d, J = 8.9 Hz, 1H, H9), 7.21 (m, 5H, ArH), 7.08 (d, J = 2.6 Hz, 1H, H6), 6.99 (d of d, J = 2.6, 8.9 Hz, 1H, H8), 3.87 (s, 3H, OCH_3), 2.46 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 1.80 (m, 1H, CH_2), 1.65 (m, 2H, CH_2), 0.84 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 154.3 (s, C7), 145.5 (s, C1''), 131.0 (s), 128.7 (s), (C5a, C9a), 127.9 (d), 127.6 (d), (C2''-C6''), 127.1 (C4''), 125.3 (d, C9), 118.5 (d, C8), 106.7 (d, C6), 57.1 (s, C2), 55.2 (q, OCH_3), 31.9 (t, CH_2), 29.4 (CH_2), 25.2 (t, CH_2), 12.9 (q, CH_3).

MS : <u>308</u> (M^+), 280, 247.

Band two (R_f = 0.48) gave a colourless oil (0.064 g), identified as 6-methoxy-1-(1-phenylpropyl)-2-tetralone **119** (0.218 mmol, 26%). The relative stereochemistry of the diastereoisomers (NMR ratio 2:1) was not determined.

Major isomer:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 1H, H8), 7.25 (m, 5H, ArH), 6.82 (d of d, J = 2.2, 8.8 Hz, 1H, H7), 6.65 (d, J = 2.2 Hz, 1H, H5), 3.83 (s, 3H, OCH_3), 3.68 (d of t, J = 4.4, 7.3 Hz, 1H, CH), 3.13 (m, 1H, H1), 2.71 (m, 2H, CH_2), 2.06 (m, 2H, CH_2), 1.70 (m, 1H, CH_2),1.60 (m, 1H, CH_2), 0.73 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 198.8 (s, C2), 163.4 (s, C6), 146.0 (s, C8a), 142.5 (s, C1''), 130.3 (d, C8), 128.8 (d), 128.3 (d), (C2''-C6''), 128.1 (s, C4a), 126.3 (d, C4''), 113.2 (d), 112.43 (d), (C5, C7), 55.4 (q, OCH_3), 52.4 (d, CH), 45.5 (d, C1), 27.5 (t), 27.0 (t), (C3, C4), 25.7 (t, CH_2), 12.3 (q, CH_3).

MS : 265 (M^+-CH_2CH_3), 237, 202, 176, 151, 148.

Minor isomer:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.02 (d, J = 8.8 Hz, 1H, H8), 7.24 (m, 5H, ArH), 6.80 (d of d, J = 2.2, 8.8 Hz, 1H, H7), 6.65 (d, J = 2.2 Hz, 1H, H5), 3.83 (s, 3H, OCH_3), 3.03 (m, 1H, H1), 2.92 (m, 2H, CH_2), 2.82 (m, 2H, CH_2), 1.72 (m, 1H, CH_2),1.62 (m, 1H, CH_2), 0.83 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 197.6 (s, C2), 163.4 (s, C6), 146.5 (s, C8a), 143.5 (s, C1''), 130.3 (d, C8), 128.7 (d), 128.4 (d), (C2''-C6''), 127.8 (s, C4a), 126.1 (d, C4''), 113.2 (d), 112.38 (d), (C5, C7), 55.4 (q, OCH_3), 54.5 (d, CH), 45.6 (d, C1), 29.6 (t), 23.7 (t), (C3, C4), 22.0 (t, CH_2), 12.9 (CH_3).

MS : 265 (M^+-CH_2CH_3), 237, 202, 176, 151, 148.

Band three (R_f = 0.24) gave a colourless oil (0.036 g), identified as a diastereoisomeric mixture (NMR ratio 1:2) of methyl 1-hydroxy-5-methoxy-1-(1-phenylpropyl)-indane-2-carboxylate **57a** and **57b** (0.106 mmol, 18%).

Reductive coupling of methyl 3-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-propenoate 54 .

Zinc powder (1.00 g, 15.3 mmol) was added to dry THF (20 ml). $TiCl_4$ (0.84 ml, 15.3 mmol) was added and the solution refluxed for 1 h. A solution of methyl 3-(3-methoxy-6-(2-phenylbutanoyl)-phenyl)-propenoate **54** (0.094 g, 0.278 mmol) in THF (2 ml) was added and the solution refluxed for a further 2 h. 10% K_2CO_3 (150 ml) was added and the mixture extracted with ether (3 x 50 ml) and dried ($CaCl_2$). Chromatogaphy with diethyl ether/pet. spirit (1:9) gave (R_f = 0.66) a colourless oil (0.041 g), identified as a mixture (NMR ratio 1:1) of methyl 6-methoxy-3-(1-phenylpropyl)-indene-2-carboxylate **55** (0.065 mmol, 23%) and 2,6-dimethoxy-1-(1-phenylpropyl)-naphthalene **120** (0.069 mmol, 25%) respectively.

2,6-Dimethoxy-1-(1-phenylpropyl)-naphthalene **120** has the following spectral characteristics.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.61 (d, J = 1.8 Hz, 1H, ArH), 7.30 (m, 5H, ArH), 6.94 (m, 2H, ArH), 6.74 (d, J = 2.1 Hz, 1H, H5), 6.58 (d of d, J = 2.1, 8.7 Hz, 1H, H7), 4.00 (d of d, J = 1.9, 3.1 Hz, 1H, CH), 3.90 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 1.75 (m, 1H, CH_2), 1.20 (m, 1H, CH_2), 0.75 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 165.4 (s, C2), 159.1 (s, C6), 143.4 (s, C1''), 142.7 (s, 4a), 141.7 (d, C8), 141.0 (s, C1), 139.6 (s, C8a), 128.8 (d), 128.2 (d), (C2''-C6''), 127.7 (d, C4), 126.3 (d, C4''), 125.4 (d, C3), 113.6 (d), 108.2 (d), (C5, C7), 55.8 (q, OCH_3), 46.6 (d, CH), 19.4 (t, CH_2), 12.5 (q, CH_3).

MS : 261 ($M^+-C_2H_{55}O$), 233, 204, 145, 120, 91.

Reaction of 1,2-diphenyl-1-(4-pyridyl)-but-1-ene 113 with 2-(*N*,*N*-dimethylamino)ethyl chloride.

1,2-Diphenyl-1-(4-pyridyl)-but-1-ene **113** (mixture of **113** and **114** NMR ratio 2:1) (0.292 g, 1.02 mmol) and 2-(*N*,*N*-dimethylamino)ethyl chloride hydrochloride (0.140 g, 0.972 mmol) were dissolved in acetonitrile (10 ml) and refluxed for 24 h. The solvent was removed under reduced pressure to leave an orange coloured residue (0.383 g), NMR indicated a mixture (NMR ratio 4:3:2) of 1-(2-(*N*,*N*-dimethylamine)-ethyl)-4-(1,2-diphenylbut-1-enyl)pyridinium chloride hydrochloride **121** (0.383 mmol, 38%), **122** (0.285 mmol, 28%) and **113** (25% recovered).

Major isomer : tentatively assigned as *Z*-1-(2-(*N*,*N*-dimethylamine)-ethyl)-4-(1,2-diphenylbut-1-enyl)pyridinium chloride hydrochloride **121**, has the following spectral characteristics.

^{1}H NMR (300 MHz) (d^6-DMSO) δ 8.69 (s, br, 2H, H2, H6), 7.49-7.11 (m, br, 12H, ArH), 4.13 (t, J = 6.8 Hz, 2H, CH_2), 3.65 (t, J = 6.8 Hz, 2H, CH_2), 2.88 (s, 6H, NCH_3), 2.45 (q, J = 7.2 Hz, 2H, CH_2), 0.95 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 155.7 (s, C4), 151.4 (d, C2, C6), 148.9 (s), 145.1 (s), 144.4 (s), 139.8 (s), (C1', C1'', C7, C8), 134.0 (d, C3, C5), 133.0 (d), 132.9 (d), 131.9 (d), 131.6 (d), (C2'-C6', C2''-C6''), 130.9 (d), 130.6 (d), (C4', C4''), 60.6 (t, NCH_2), 46.1 (q, NCH_3), 41.5 (t, NCH_2), 32.6 (t, CH_2), 16.9 (q, CH_3).

Minor isomer : tentatively assigned as *E*-1-(2-(*N*,*N*-dimethylamine)-ethyl)-4-(1,2-diphenylbut-1-enyl)pyridinium chloride hydrochloride **122**, has the following spectral characteristics.

^{1}H NMR (300 MHz) (d^6-DMSO) δ 8.35 (s, br, 2H, H2, H6), 7.49-7.11 (m, br, 12H, ArH), 6.96 (m, 2H, ArH), 4.13 (t, J = 6.8 Hz, 2H, CH_2), 3.65 (t, J = 6.8 Hz, 2H,

NCH_2), 2.47 (q, J = 7.3 Hz, 2H, CH_2), 2.14 (s, 6H, NCH_3), 0.93 (t, J = 7.3 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 155.3 (s, C4), 152.9 (d, C2, C6), 147.5 (s), 145.2 (s), 144.7 (s), 137.3 (s), (C1', C1'', C7, C8), 133.0 (d), 132.8 (d), 132.1 (d), 131.8 (d), (C2'-C6', C2''-C6''), 131.3 (d), 131.0 (d), 129.4 (d), (C3, C5, C4', C4''), 60.6 (t, NCH_2), 46.1 (q, NCH_3), 41.5 (t, NCH_2), 32.4 (t, CH_2), 17.0 (q, CH_3).

Reaction of 1,2-diphenyl-1-(4-pyridyl)-but-1-ene 113 with 2-(*N*,*N*-dimethylamino)ethyl chloride using Ag_2O.

1,2-Diphenyl-1-(4-pyridyl)-but-1-ene **113** (0.065 g, 0.229 mmol) was dissolved in water (5 ml) and THF (10 ml). Silver oxide (0.098 g, 0.426 mmol) was added and the solution stirred for 3 h. 2-(*N*,*N*-Dimethylamino)ethyl chloride (0.040 g, 0.276 mmol) and Ag_2O (0.150 g, 0.652 mmol) were then added and the solution stirred for 4 days. The solution was filtered and washed with ethanol (2 x 10 ml). The filtrate and washings were combined and the solvent removed under reduced pressure to leave a light brown oil. Attempts to crystallise from ethanol proved unsuccessful. The crude oil obtained from the attempted crystallisation was tentatively assigned as *N*-(2-(*N*,*N*-dimethylamino)-ethyl)-2-hydroxy-1,2-dihydropyrid-4-yl-1,2-diphenylbut-1-ene **123**. Chromatography (plc) of the crude oil eluting with triethylamine/benzene (1:3) proved unsuccessful.

^1H NMR (300 MHz) (d^6-DMSO) δ 8.25 (s, br, 2H,), 7.48-7.16 (m, br), 6.85 (d, J = 6.0 Hz, 1H), 5.47 (d of d, J = 2.1, 6.0 Hz), 3.89 (t, J = 6.3 Hz, 2H, CH_2), 3.58 (t, J = 6.3 Hz, 2H, CH_2), 3.49 (s, 6H, NCH_3), 2.27 (q, J = 7.5 Hz, 2H, CH_2), 0.95 (t, J = 7.5 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) (d^6-DMSO/$CDCl_3$) δ 148.6 (s), 146.9 (d), 142.7 (s), 139.6 (s), 138.9 (s), 134.3 (s), 127.3 (d), 127.2 (d), 126.6 (d), 126.2 (d), (C2'-C6', C2''-C6''), 125.3 (d), 125.0 (d), 123.3 (d), 63.7 (t, CH2), 56.7 (q, NCH3), 54.4 (t, CH2), 50.2 (d), 27.1 (t, CH2), 11.2 (q, CH3). Referenced to $CDCl_3$.

CHAPTER SIX

SYNTHESIS OF TAMOXIFEN AND TAMANDRON ANALOGUES

This is a report on some tentative exploratory studies which do not fit easily with the topics in preceding chapters. The aims of the research presented in this chapter were two-fold. First, to synthesise a Tamoxifen analogue by coupling phenyl isocyanate with **9**, with the possible extention of this chemistry to the imine substrate, *N*-benzylidenemethylamine. Secondly, to synthesise Tamandron analogues incorporating both orthomanganated aryl ketone coupling and Diels-Alder reactions.

6.1 Reaction of Orthomanganated Aryl Ketones With Substrates Containing C=N Functions.

6.1.1 Introduction

As alkynes and alkenes readily insert into the Mn-C σ-bond of orthomanganated aryl ketones, it is expected that other unsaturated substrates may show similar reactivity. Isocyanates have been found[135] to react with orthomanganated acetophenone, **6**, to give 3-methylidene-(*3H*)-isobenzopyrrolidinone (phthalimine) derivatives (figure 6.1). These compounds constitute the core unit of a number of isoindole derived alkaloid families[136] and this route from orthomanganated aryl ketones to alkylidene isobenzopyrrolidinones may prove synthetically valuable.

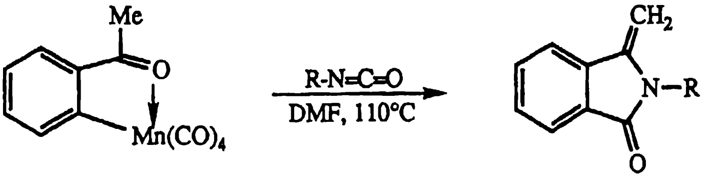


Figure 6.1

Though the insertion of isocyanides into the Mn-C and Mn-N bonds of manganese carbonyls has been investigated[137] (figure 6.2), to the best of our knowledge, other than alkenes,[46-49] alkynes[55,56] and isocyanates,[135] only acetonitrile has been reported[49] (in one case) to undergo insertion into the Mn-C σ-bond of an orthomanganated complex to liberate an organic product (figure 6.3). It was proposed to

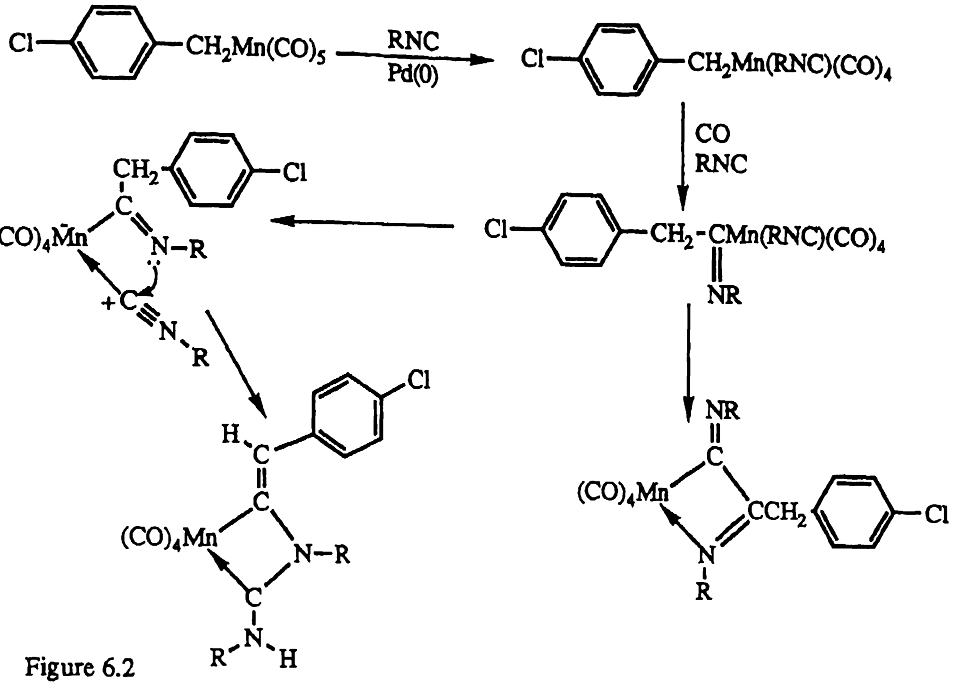


Figure 6.2

study the isocyanate reaction with tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** and to investigate whether this coupling provided a route to carboxylic acid derivatives of aryl ketones. As an extension to this study the ability of an imine to undergo insertion into the Mn-C bond was investigated.

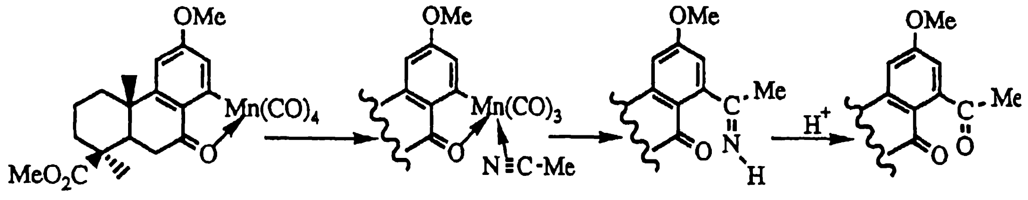


Figure 6.3

6.1.2 Coupling of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with C=N substrates.

The reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** and a three-mole excess of phenyl isocyanate in benzene under reflux after 2.75 hours affords the expected coupled product, 6-methoxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **124**, which is obtained as pure crystals of the *E*-isomer (60%). The stereochemistry of this compound was confirmed by nOe experiments. The mechanism proposed by Liebeskind *et al.*[135] (figure 6.4) for the formation of 3-alkylidene-(*3H*)-isobenzopyrrolidinones suggests that facile elimination of

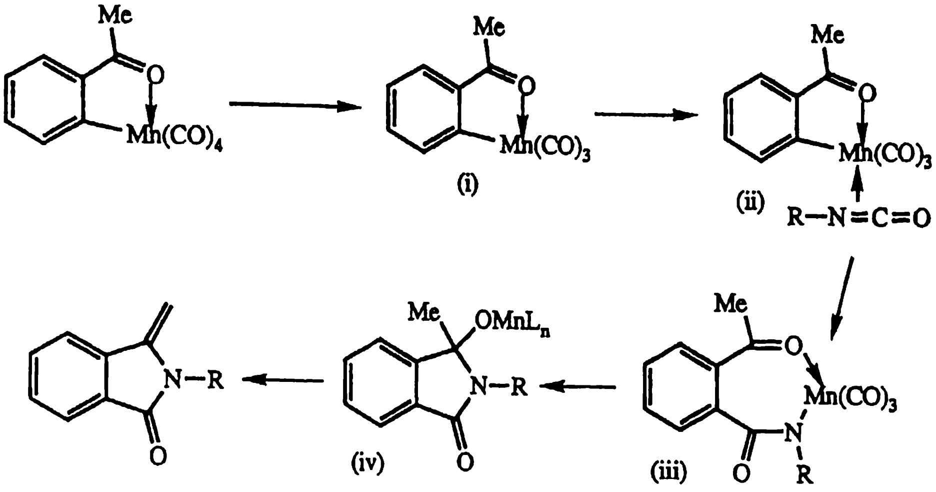


Figure 6.4

"HOMnL$_n$" leads to the observed products. However in this study, the ^{13}C NMR spectrum of the oil obtained from initial chromatography (plc) indicates a significant proportion to be the corresponding hydrated product (figure 6.5). This result suggests that, under our conditions, hydrolysis of the manganese alkoxide (iv; figure 6.4) occurs, with subsequent dehydration leading to the observed product.

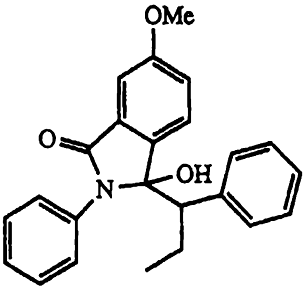
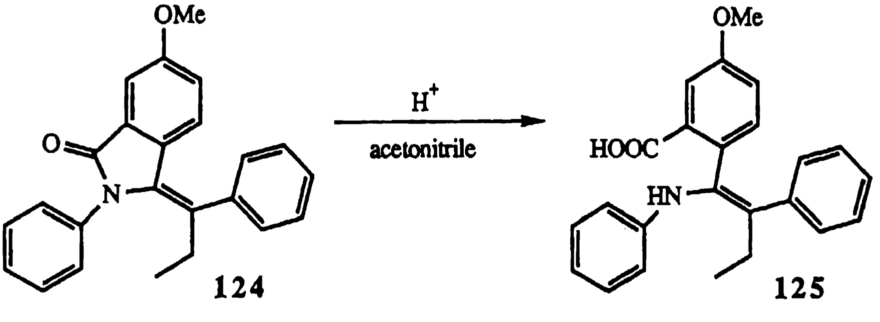


Figure 6.5

The alkylidene isobenzofuranone product **14** (Chapter Two) would upon hydrolysis regenerate the ketone function giving a carboxylic acid function in the *ortho* position of the aryl ring. As the formation of alkylidene isobenzofuranones from orthomanganated precursors (see Chapter Two) is capricious, the reaction of orthomanganated aryl ketones with isocyanates may provide a direct route to the introduction of a carboxylic acid functionality. Hydrolysis of the carbon-nitrogen bond of the resulting alkylidene isobenzopyrrolidinone product would give a carboxylic acid function in the *ortho* position of the aryl ring with regeneration of the ketone. Hydrolysis



of **124** (2 mol l^{-1} HCl and acetonitrile) at ambient temperature gives the benzoic acid derivative **125** in excellent yield (75%). Further reaction would hydrolyse the remaining enamine to regenerate the ketone function, but this reaction has not been attempted so far. *E*-5-Methoxy-2-(2-phenyl-1-phenylamino-1-butenyl)-benzoic acid **125** is a novel Tamoxifen analogue, having an aminophenyl group and an *ortho* carboxylic acid function. It is doubtful whether the enamine would survive the reaction conditions required for demethylation and *N*,*N*-dialkylamino side chain attachment to form a Tamoxifen analogue, but with prior attachment of the side chain this should still be a feasible reaction. Carboxylic acid derivatives of Tamoxifen are known[138] though the acid functions are substituted for the *N*,*N*-dialkylamino function on the side chain. **124** also exhibits similar structural features to Tamoxifen and might have the potential with the dialkylamino side chain of Tamoxifen to possess antiestrogenic activity, as do structurally similar substituted 2-phenylindoles[25] and acetoxy-substituted 2-phenylindenes[29] (see section 4.1.1, Chapter Four). Given the preponderance and easy separation of the *E* isomer, **124**, demethylation using boron tribromide and subsequent base-catalysed reaction with 2-(*N*,*N*-dimethylamino)ethyl chloride was attempted. The only product from this reaction is **126**, the demethylated derivative of **124**. This reaction has not so far been pursued further. If attachment of the *N*,*N*-dimethylaminoethyl side chain to **126** had been successful this would have given a Tamoxifen analogue. Subsequent hydrolysis of this analogue could then lead to a Tamoxifen-like derivative of **125** (figure 6.6).

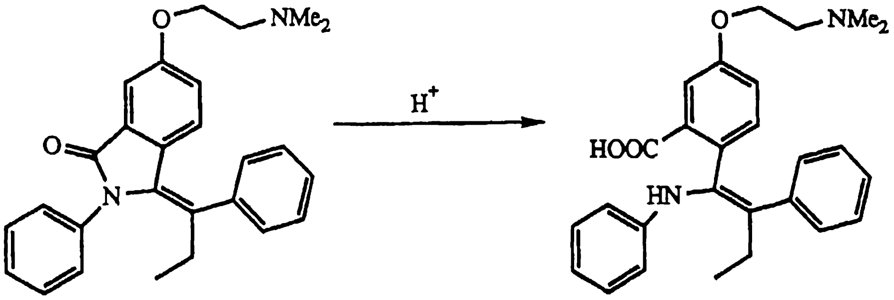


Figure 6.6

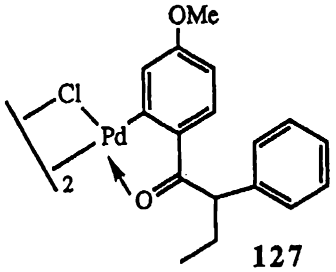
Given that isocyanates readily couple with orthomanganated aryl ketones[135] and that nitriles[139] and isocyanides[137,139] undergo insertion into metal-carbon bonds, it was proposed to attempt the coupling of another CN substrate with **9** which could give a liberated compound having potential to be antiestrogenic. Coupling with *N*-benzylidenemethylamine was undertaken. However the reaction of **9** with *N*-benzylidenemethylamine in acetonitrile under reflux did not give any coupled product after ten hours, only demetalated ketone (**7**, 40%). Palladium(II)-assisted coupling of **9** with *N*-benzylidenemethylamine in acetonitrile similarly proved unsuccessful. Given these results, the attempted coupling of *N*-benzylidenemethylamine was not pursued further. It may be that steric crowding by the phenyl group limits bond formation to the imine carbon, and further study with other imines is required.

Nevertheless the latter reaction above does afford a compound with low mobility (plc). Mass spectrometry confirms the presence of palladium and the fragmentation pattern supports the structure di-μ-chloro-di(5-methoxy-2-(2-phenylbutan-1-oyl)phenyl)dipalladium(II) **127**. NMR data for **127** are consistent with the proposed structure. Differences in both ^1H and ^{13}C NMR data (see table 6.1) for the cyclometalated phenyl ring compared to the "free ligand", **7**, show similar changes for the protonated carbons to those found[140] upon cyclopalladiation. The carbonyl resonance is shifted downfield with respect to the free ligand, consistent with coordination of the carbonyl oxygen to palladium. At δ 212.1, the carbonyl resonance is upfield in comparison to that found for the corresponding orthomanganated compound **9** (δ 215.2).

Table 6.1 Chemical shift changes upon cyclopalladiation.

	C1	C2	C3	C4	C5	C6
δ ppm for **7**	131.1	130.1	131.1	113.7	163.3	113.7
δ ppm for **127**	165.4	139.8	132.6	110.0	163.2	120.2
difference	+ 34.3	+ 9.7	+ 1.5	- 3.7	- 0.1	+ 6.5

Similarly, the chemical shift of the metalated carbon, C1 (δ 165.4), is much further upfield than in the corresponding orthomanganated compound **9** (δ 198.4). The differences in these chemical shifts must be primarily due to the different extents of bond polarisation by the manganese and palladium.



127

Isolation of **127**, though in low yield (7%), is the first direct evidence that Pd(II) can transmetalate at the Mn-C σ-bond of an orthomanganated aryl ketone. This provides some support for the possiblity that the Pd(II)-promoted coupling of alkenes with orthomanganated aryl ketones involves such a transmetalation.[46] Following the precedent above, the coupling of **9** with $PdCl_4^{2-}$ in acetonitrile was undertaken. From this reaction the principal products, though in low yield, are the demetalated ketone (**7**, 12%), the isomeric alkylidene isobenzofuranone compounds **14** and **71** (11% and 6% respectively) and the transmetalated product **127** (6%). Formation of **127** is indeed confirmatory evidence for the transmetalation of the Mn-C σ-bond by palladium. The low yield of **127** may be an indication of the relative instability of this complex. Analogous complexes (see figure 6.7) were found[142] to be stable only with the presence of electron-donating substituents. **127**, to the best of our knowledge is the first isolated orthopalladiated aryl ketone. A palladium metallacycle containing a carbonyl group is not unique, however; the structure of a cyclopalladiated complex has been reported[142] from the insertion of norbornylene into a palladium acyl bond (figure 6.7).

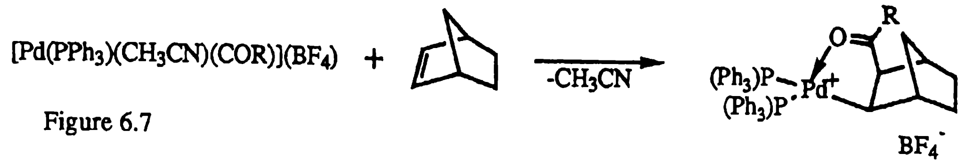
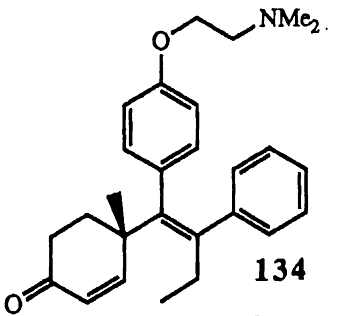


Figure 6.7

6.2 Synthesis of Tamandron Analogues.

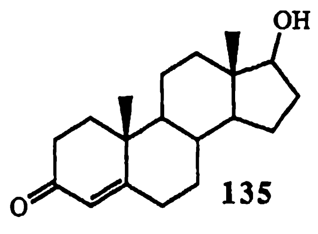
6.2.1 Tamandron.

As with breast cancer, cell growth in prostate tumours is stimulated by normal hormones, and in men, these compounds are known as androgens. Reducing the levels of androgens is known[143] to reduce the incidence of cancer. Currently, the methods to reduce androgen levels such as castration or treatment with estrogen result in a number of serious problems[143] including cardiovascular complications and impotence. In an attempt to minimise side effects and with the consideration of long-term therapy, McCague *et al.* have recently reported[144] the synthesis of a compound dubbed "Tamandron" **134**. Tamandron, based on the design strategy of Tamoxifen, is hoped to inhibit the growth of prostate cancer cells in a similar action to Tamoxifen. The structure in part resembles testosterone **135** and it is this that should cause it to bind specifically to androgen-receptor proteins. Preliminary testing suggests[144] Tamandron exhibits androgen-receptor binding affinity which substantiates the prospect of developing an antiandrogenic Tamoxifen analogue for the treatment of prostate cancer.



134

Tamandron

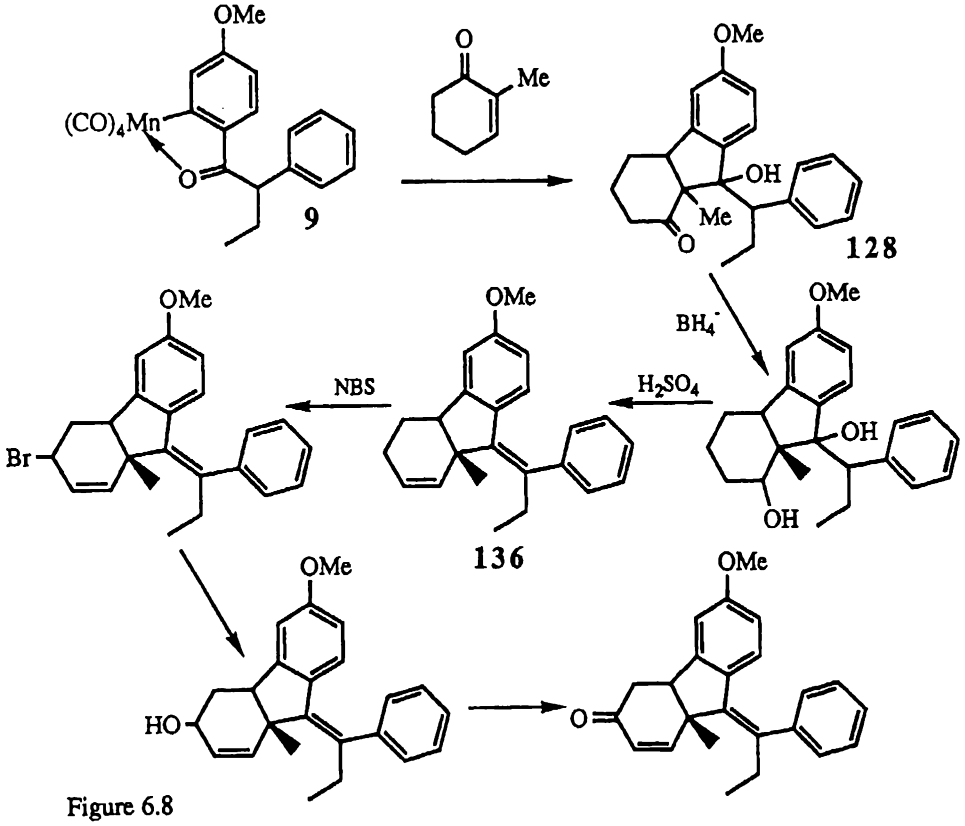


135

Testosterone

6.2.2 Coupling 2-methyl-2-cyclohexenone with tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9.

Isolation of the indanol compound **64** (Chapter Four) in good yield from the coupling of **9** with methyl but-2-enoate shows 1,2-disubstituted alkenes can readily be coupled with orthomanganated complexes. DeShong *et al.* have inserted the cycloalkenes cyclopentene[101] and norbornylene[100,101] into the Mn-CH_3 σ-bond of $CH_3Mn(CO)_5$ to give cyclomanganated complexes analogous to that in figure 6.7. This substantiates the prospect of reacting an orthomanganated aryl ketone with a cycloalkene. In an attempt to synthesize a Tamandron analogue, tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** was reacted with 2-methyl-2-cyclohexenone using the alkene coupling methods described in Chapter Four. It was hoped a coupled tricyclic product could then be readily converted (figure 6.8) to give a compound with structurally similar features to Tamandron. However, the coupling of **9** with 2-methyl-2-cyclohexenone in either benzene or acetonitrile under reflux gives no coupled product, affording only demetalated ketone (**7**, 70% and 90% respectively). Similarly, Pd(II)-mediated coupling gives only demetalated ketone (57%). This result is in accord with those found[49] for the Me_3NO-induced coupling of cyclohexene and 2-cyclohexenone with an orthomanganated diterpenoid complex.



9

128

136

Figure 6.8

Given the precedent that employing one equivalent of $NiBr_2(PPh_3)_2$ increases the yield of alkene coupled product (Chapter Four), the nickel(II)-mediated coupling of **9** with 2-methyl-2-cyclohexenone was undertaken. From this reaction the desired fluorenone product **128** is obtained, though in poor yield (15%). NMR indicates five diastereoisomers of this product. These diastereoisomers are not separable chromatographically (plc), so no attempt was made to determine the relative stereochemistry of each. Treatment of the mixture **128** with 4-toluenesulphonic acid in acetonitrile does not catalyse dehydration to give the desired phenylpropylidene structure analogous to **136** (figure 6.8), the reasons for this lack of reactivity being unknown.

The poor yield of **128** precludes the synthetic approach to a Tamandron analogue outlined in figure 6.8. However, this is the first example of the coupling of an orthomanganated aryl ketone with a cyclic alkene, such alkenes having previously been reported[49] not to undergo coupling. That a coupled product is observed between **9** and 2-methyl-2-cyclohexenone when $NiBr_2(PPh_3)_2$ is employed substantiates the prospect of developing this chemistry as an approach to the synthesis of polycyclic products from orthomanganated derivatives.

6.2.3 Tamandron Analogues Using Diels-Alder Chemistry.

One approach considered was coupling of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** with a substituted diene derivative and the subsequent use of Diels-Alder chemistry to allow a direct route to Tamandron type analogues (figure 6.9), that is if the Diels-Alder reaction with an unactivated dienophile could be made to proceed. To the best of our knowledge coupling of dienes

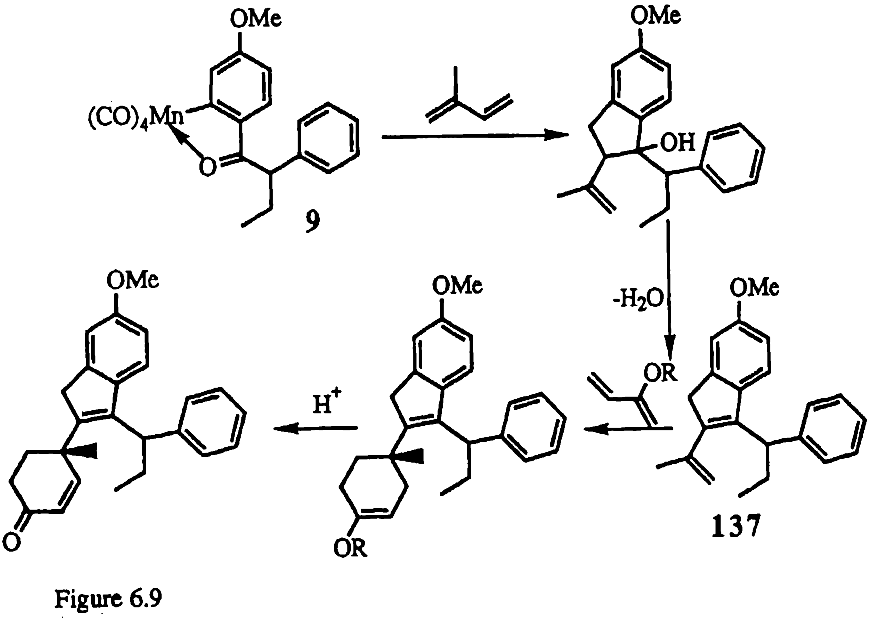


Figure 6.9

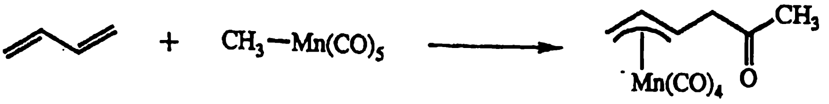


Figure 6.10

with orthomanganated aryl ketones has not been reported, though the reaction of alkyl- and aryl-manganese carbonyl compounds with butadiene has been shown^{145,146} to give π-allyltetracarbonyl manganese complexes (figure 6.10). Coupling of 9 with 2-methyl-1,3-butadiene (isoprene) in benzene under reflux does not afford a liberated organic coupled product. Chromatography (plc) gives an orange oil which readily decomposes, complicating the identification of this product. The IR spectrum shows three carbonyl stretches at 2060, 1992 and 1955 cm^{-1} indicating the compound contains a manganese tricarbonyl moiety. Its structure may be tentatively assigned as **129**. Analogous complexes of the type in figure 6.11,^{147,148} however, have ν(CO) typically at 2013,

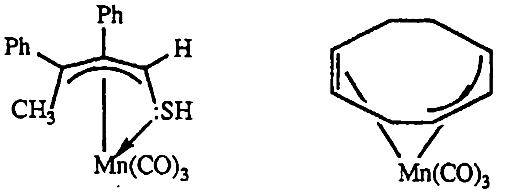
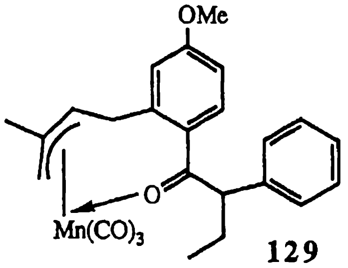
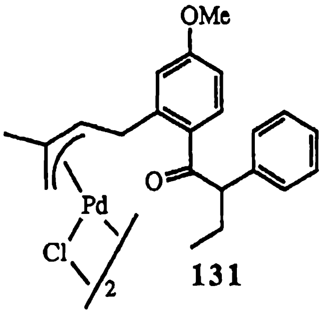


Figure 6.11



129

1935 and 1910 cm^{-1}. A second minor product is also isolated from the above reaction and has been tentatively assigned as **130**. The nickel(II)-mediated coupling reaction with 9 and 2-methyl-1,3-butadiene is unsuccessful, as is the exploratory coupling reaction between 9 and cyclopentadiene. Coupling of 9 with 2-methyl-1,3-butadiene in the presence of palladium(II) is more successful affording 7 (24%), **131** (36%) and a third unknown product. Characterisation of the latter product is complicated by decomposition subsequent to workup with the precipitation of palladium metal.



131

The structure of the π-allyl complex, di-μ-chloro-di(4-(5-methoxy-2-(2-phenyl-1-butanoyl)-phenyl)-2-methyl-1-butenyl)-dipalladium(II) **131**, was deduced by NMR and confirmed by the results of microanalysis and mass spectrometry. Both ^{1}H and ^{13}C NMR indicated a partial structure of the diphenylbutanone fragment, while the rest of the structure was elucidated using 2D-NMR and nOe techniques. Irradiation of the H6' proton at δ *ca.* 6.96 gives an observed nOe signal to the H4 methylene protons at δ 3.10 - 2.85. The H4 methylene proton signal correlates (XH spectrum, Appendix A.2; figure A.13) with the triplet ^{13}C NMR resonance at δ 34.1. From the COSY spectrum (Appendix A.2; figure A.12), the H4 methylene protons show cross peaks to the resonance at δ *ca.* 3.4, which is assigned to H3. The H3 proton correlates with the doublet carbon resonance at δ *ca.* 82. This confirms the regiochemistry of the inserted 2-methyl-1,3-butadiene fragment. Irradiation of the 2-methyl protons gives observed nOes at the expected H3 proton and also to the methylene proton, H1, at δ *ca.* 3.6. 2D NMR shows the H1 geminal proton resonances at δ *ca.* 3.6 and δ *ca.* 2.5 to be mutally coupled (COSY) though they appear as singlets due to a small coupling constant, common among π-allyl complexes. A notable feature of the ^1H and ^{13}C NMR spectra (Appendix A.2) of **131** is that each resonance is doubled indicating a 1:1 ratio of isomers. It was found in a previous study[149] of π-allyl palladium complexes that the preferred stereochemical arrangement of the bulky substituent to the central π-allyl substituent is *syn*. Given the ratio of isomers for **131**, it is apparent there is neither a *syn* nor *anti* stereochemical preference for this structure.

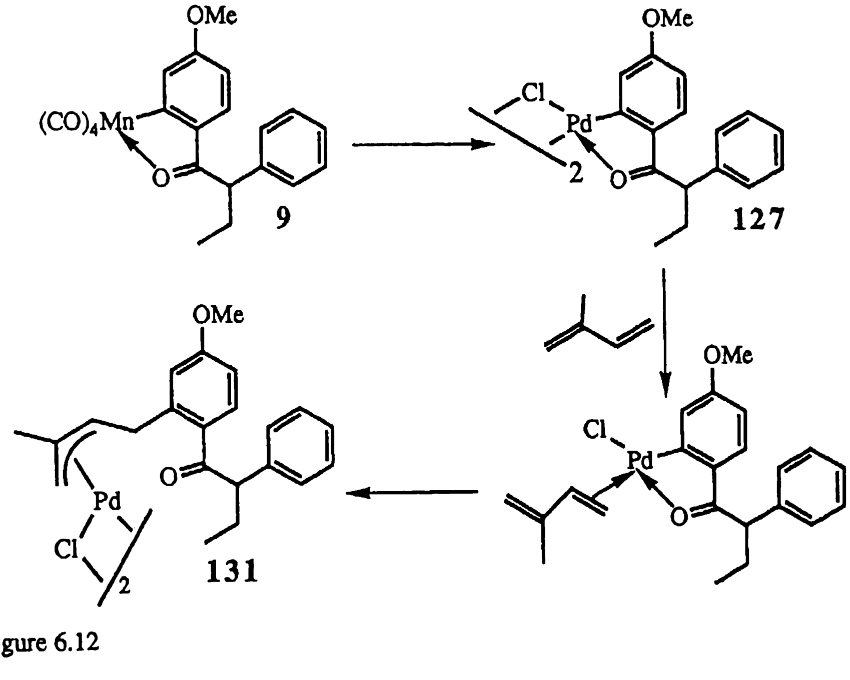


Figure 6.12

π-Allyl palladium complexes are well known[114] and, for example, have previously have been prepared[149] from the coupling of arylmercurials and $PdCl_2$ with dienes which generates the palladium complex *in situ*. Formation of the π-allyl complex **131** may be envisaged as in figure 6.12. Given the formation of **127** in a previous reaction, the initial step is the transmetalation of **9** followed by coordination and insertion of the diene[149] to give the observed product **131**.

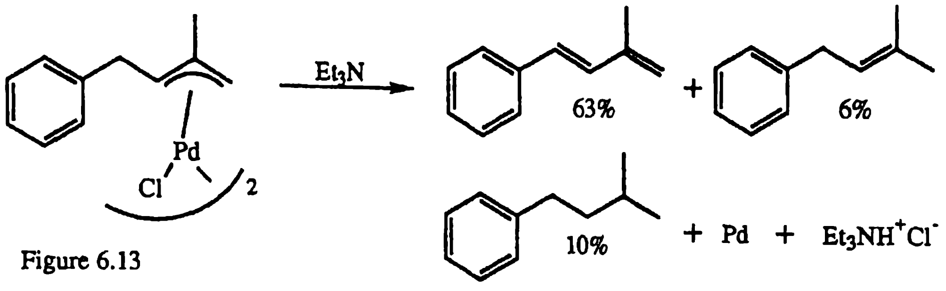


Figure 6.13

Triethylamine is known[150] to demetalate π-allyl palladium complexes giving the corresponding diene (e.g. figure 6.13). As demetalation[150] with Et$_3$N proceeds *via* palladium hydride elimination, **131** was reacted with H$^+$ in an attempt to protiodemetalate the complex. It was hoped protiodemetalation might lead to the compound **137** (figure 6.9). However, the reaction with H$^+$ gives several minor products, though not the desired aldol product **137**.

As the above synthetic approaches to a Tamandron analogue (figures 6.8 and 6.9) had proved unsuccessful a simpler approach was undertaken (figure 6.14).

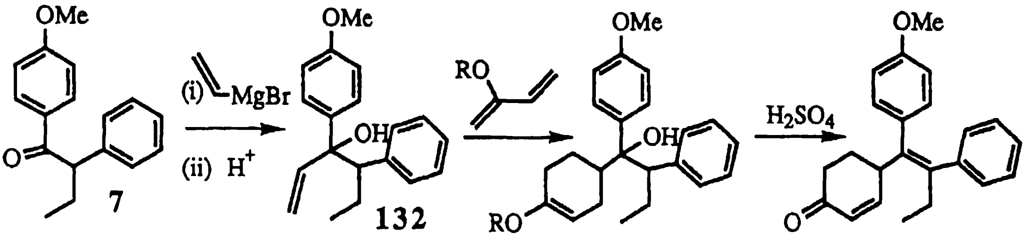


Figure 6.14

Coupling of phenylmagnesium bromide with **7** proceeds[12] in accordance with Cram's rule,[151] as do the couplings with the brominated analogues **11** and **12** (Chapter Two) which give exclusively (by NMR) one diastereoisomer. The reaction of vinylmagnesium bromide with **7** also affords a coupled product, **132** (74%), of which only one diastereoisomer is observed by NMR. However, coupling allylmagnesium bromide with **7** is apparently less stereoselective than the reactions above as both possible diastereoisomers are observed. The coupling of **7** with allylmagnesium bromide gives the corresponding product, **133**, as diastereoisomers (6:1) in similar yield (77%) to that of **132**. Use of allyl bromide instead of the chloride requires the immediate coupling of **7** with the Grignard reagent to overcome[178] the competing self-coupling reaction with excess allylic reagent. Formation of **133** as diastereoisomers (6:1) is expected, given that the carbonyl group in **7** is adjacent to a chiral carbon. The major isomer, **133a**, is that predicted to dominate using Cram's rule (figure 6.15). This result was confirmed by nOe experiments: the α-proton (CH) of the major isomer gives an observed nOe of the *ortho* protons to the substituted ring.

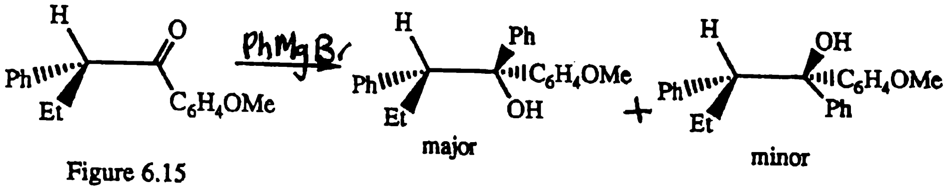


Figure 6.15

Coupling **132** with 2-trimethylsilyloxy-1,3-butadiene in refluxing benzene does not give the expected Diels-Alder cycloaddition product, returning **132** (97%) after 3 hours. Successful coupling would have given a Tamandron type precursor **138**. The coupling of **132** with 2-methyl-1,3-butadiene was attempted using the same conditions. However this also gives no cycloaddition product after 6 hours. Given this result, it is questionable whether **132** is reactive enough to act as a dienophile so the analogous coupling with **133** and 2-methyl-1,3-butadiene was undertaken. However this reaction, after 8 hours, also gives no cycloaddition product. This initial result deterred further attempts to couple **133** to give a Diels-Alder adduct.

Though the attempted Diels-Alder coupling with both **132** and **133** proved unsuccessful, this route to Tamandron should not be abandoned. With further study, perhaps employing an appropriate Diels-Alder catalyst , this may prove a simple and inexpensive route to a variety of Tamandron analogues.

6.3 Summary.

The reaction of phenylisocyanate with **9** gives **124** which has structural similarities to Tamoxifen. Hydrolysis of this compound gives the novel carboxylic acid analogue of Tamoxifen **125**. This result also suggests the orthomanganation of aryl ketones and subsequent coupling with isocyanates may provide a general route for the introduction of an *ortho* carboxylic acid function to an aryl ketone.

Isolation of the palladium complexes **127** and **131** provides support for the possiblity of a transmetalation step in the palladium(II)-promoted coupling of alkenes with orthomanganated aryl ketones for which previously there has been no tangible evidence. **127**, to the best of our knowledge, is the first example of an isolated orthopalladiated aryl ketone.

Formation of the fluorenone **128** indicates cycloalkenes can be coupled with orthomanganated aryl ketones and this increases the prospects of developing nickel(II)-promoted coupling of both alkenes and cycloalkenes.

Use of Diels-Alder chemistry in the preparation of Tamandron derivatives still requires substantial development and may necessitate the use of a suitable catalyst to promote the dienophile coupling of compounds such as **132** with dienes.

6.4 Experimental

Preparation of 2-methyl-2-cyclohexenone.

2-Methyl-2-cyclohexenone was prepared by the standard method[153] as follows. 2-Methylcyclohexanone (20 ml, 0.165 mol) was added to carbon tetrachloride (50 ml). Sulphuryl chloride (14.6 ml, 0.182 mol) was added dropwise over 2 h and the solution stirred for a further 2 h. The solution was first washed with water (3 x 100 ml) then saturated $NaHCO_3$ (1 x 50 ml) and finally saturated NaCl (1 x 25 ml). After drying ($MgSO_4$), the carbon tetrachloride was removed by distillation. The crude 2-chloro-2-methylcyclohexanone was combined with LiCl (4.3 g) and DMF (50 ml) and heated (100°C) for 30 min. Diethyl ether (50 ml) and H_2SO_4 (2 mol l^{-1}, 50 ml) were added and the solution stirred for a further 4 h. The aqueous layer was separated and washed with ether (4 x 25 ml), the extracts combined with the original ether layer and washed with saturated NaCl (40 ml), then saturated $NaHCO_3$ (40 ml) and dried ($CaCl_2$). Vacuum distillation affords 2-methyl-2-cyclohexenone (3.46 g, 0.031 mol, 19%) as a colourless liquid (bp 104°C, 77 mmHg; lit.[153] 99-101°C, 77 mmHg).

^1H NMR (300 MHz) ($CDCl_3$) δ 6.60 (s, br, 1H, H3), 2.28 (m, 2H, CH_2), 2.18 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.62 (t, J = 1.6 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 200.0 (s, C1), 145.6 (d, C3), 135.3 (s, C2), 38.1 (t, CH_2), 25.8 (t, CH_2), 23.1 (CH_2), 15.8 (q, CH_3).

Preparation of *N*-benzylidenemethylamine.

Benzaldehyde (7.6 ml, 75 mmol) and methylamine (83 mmol in ethanol) were dissolved in toluene (100 ml) and heated (*ca.* 40°C) for 2 h. The solution was then refluxed for a further 2 h removing water by Dean-Stark apparatus. The solvent was removed under reduced pressure and the remaining solution distilled to yield *N*-benzylidenemethylamine (4.04 g, 34 mmol, 45%) bp 62°C 10 mmHg lit.[110] 75-80°C 18 mmHg).

^1H NMR (300 MHz) ($CDCl_3$) δ 8.26 (s, 1H, CH), 7.70 (m, 2H, H2, H6), 7.39 (m, 3H, H3, H4, H5), 3.50 (s, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 162.5 (d, CH), 136.3 (s, C1), 130.5 (d, C4), 128.6 (d), 127.9 (d), (C2, C3, C5, C6), 48.2 (q, CH_3).

Preparation of 2-trimethylsilyloxy-1,3-butadiene.

2-Trimethylsilyloxy-1,3-butadiene was prepared following the standard procedure.[154-156] 3-Buten-2-one (5.0 ml, 60 mmol) and triethylamine (20 ml, 140 mmol) were added to DMF (30 ml) in a three neck flask fitted with a reflux condenser and drying tube. Trimethylsilyl chloride (9.2 ml, 72 mmol) was added over 10 min and the solution refluxed for 45 h. The mixture was poured into pentane (80 ml) and washed with $NaHCO_3$ (5%, 3 x 50 ml). The $NaHCO_3$ solution was extracted with pentane (50 ml). The pentane extracts were combined and rapidly washed with cold HCl (2 mol l^{-1}, 30 ml) and $NaHCO_3$ (50 ml) and dried ($CaCl_2$). 2-Trimethylsilyloxy-1,3-butadiene is separated by vacuum distillation, collecting the middle fraction (*ca.* 45% yield).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with phenyl isocyanate.

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.347 g, 0.825 mmol) was dissolved in benzene (10 ml) and purged with N_2. Phenyl isocyanate (0.27 ml, 2.48 mmol) was added and the solution refluxed for 2.8 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded four bands.

Band one gave $Mn_2(CO)_{10}$ (0.009 g, 0.022 mmol, 3%).

Band two gave demetalated ketone 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.011 g, 0.043 mmol, 5%).

Band three gave an unknown orange oil (0.034 g). Crystallisation from diethyl ether/pet. spirit (1:10) gave fine white crystals, mp 145°C.
^1H NMR (300 MHz) ($CDCl_3$) δ 8.92 (s, br), 7.58 (m), 7.38 (m), 7.11 (t, J = 7.2 Hz).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 153.3 (s), 137.3 (s), 136.6 (s), 130.5 (d), 129.9 (d), 129.1 (d), 124.5 (d), 120.7 (d).
MS : 135.

Band four gave a pale yellow oil (0.210 g). Crystallisation from diethyl ether/pet. spirit (1:3) gave *E*-6-methoxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone 124 (0.493 mmol, 60%) as fine white crystals, mp 175°C (decomp).
^1H NMR (300 MHz) ($CDCl_3$) δ 7.45 (m, 5H, ArH), 7.27 (m, 4H, ArH), 6.98 (m, 1H, ArH), 6.72 (d of d, J = 2.5, 8.8 Hz, 1H, H5), 5.92 (d, J = 8.8 Hz, 1H, H4), 3.81 (s, 3H, OCH_3), 2.07 (q, J = 7.3 Hz, 2H, CH_2), 0.60 (t, J = 7.3 Hz, 3H, CH_3).
CH_2(2.07) and CH_3(0.60) nOe to 7.26, 7.45.
H5(6.72) nOe to 5.92.

^{13}C NMR (300 MHz) ($CDCl_3$) δ 168.3 (s, C=O), 159.9 (s, C6), 141.1 (s, C1'), 138.7 (s, C1'), 132.7 (s, C8), 130.7 (s), 130.5 (s), (C3, C7a), 128.1 (s, C3a), 129.3 (d), 128.7 (d), 128.3 (d), 127.9 (d), (C2'-C6', C2''-C6''), 127.6 (d), 127.5 (d), (C4', C4''), 124.8 (d, C4), 120.3 (d, C5), 105.5 (d, C7), 55.7 (q, OCH_3), 27.6 (t, CH_2), 11.6 (q, CH_3).
MS : 355 (M^+), 340, 262.

Hydrolysis of *E*-6-methoxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone 124.

E-6-Methoxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **124** (0.022 g, 0.063 mmol) was dissolved in acetonitrile (15 ml). Hydrochloric acid (2 mol l^{-1}, 5 ml) was added and the solution stirred for 28 h. The solution was poured into water (30 ml) and extracted with ether (40 ml). The ether solution was washed with aqueous HCl (2 mol l^{-1}, 40 ml), water (30 ml) and dried ($CaCl_2$). The solution volume was then reduced. Crystallisation gave small white needles of *E*-5-methoxy-2-(2-phenyl-1-phenylamino-1-butenyl)-benzoic acid **125** (0.018 g, 0.047 mmol, 75%), mp 213°C (decomp).
^{1}H NMR (300 MHz) (d^6-DMSO/$CDCl_3$) δ 8.33 (s, 1H, NH), 7.58 (m, 8H, ArH), 7.43 (m, 2H, ArH), 7.29 (d, J = 2.0 Hz, 1H, H6), 6.89 (d of d, J = 2.0, 9.0 Hz, 1H, H4), 5.97 (d, J = 9.0 Hz, 1H, H3), 3.88 (s, 3H, OCH_3), 2.15 (q, J = 7.4 Hz, 2H, CH_2), 0.62 (t, J = 7.4 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) (d^6-DMSO/$CDCl_3$) δ 165.2 (s, C=O), 157.8 (s, C4), 138.7 (s, C1'), 136.7 (C1''), 128.4 (s), 128.1 (s), 125.6 (s), (C2, C3, C7, C8), 127.4 (d), 127.2 (d), 127.1 (d), (C3', C5', C2'', C3'', C5'', C6''), 126.0 (C4''), 122.6 (C6), 177.8 (d, C4'), 115.8 (d, C5), 103.7 (d, C3), 53.7 (q, OCH_3), 25.2 (t, CH_2), 9.3 (q, CH_3).
^{1}H and ^{13}C NMR referenced to d^6-DMSO and $CDCl_3$ respectively.

Attempted preparation of *E*-6-(2-(*N*,*N*-dimethylamino)-ethoxy)-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone.

E-6-Methoxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **124** (0.101 g, 0.284 mmol) was dissolved in dichloromethane (5 ml) and the flask cooled -83°C ethyl acetate slush bath). Boron tribromide (0.085 g, 0.339 mmol) dissolved in dichloromethane (5 ml) was added to the solution. The solution was allowed to warm with stirring. Ice (20 g) was added to the flask and the contents then poured into HCl (2 mol l^{-1}, 40 ml) and rapidly extracted with ether (40 ml). The organic layer was separated and washed with HCl (2 mol l^{-1}, 40 ml) and dried ($CaCl_2$). The solvent was removed under reduced pressure to give a pale orange oil, identified (^{1}H NMR) as *E*-6-hydroxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **126**.

E-6-Hydroxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **126** (0.090 g, 0.264 mmol) was dissolved in ethanol (8 ml) containing sodium ethoxide (prepared by adding sodium metal 0.010 g, 0.42 mmol). 2-(*N*,*N*-Dimethylamino)ethyl chloride hydrochloride (0.097 g, 0.669 mmol) in ethanol (8 ml) was then added and the solution refluxed for 24 h. The solution was poured into a mixture of NaOH (2 mol l^{-1}, 40 ml) and diethyl ether (40 ml). After shaking, the ethereal layer was washed with NaOH (2 mol l^{-1}, 3 x 40 ml) and dried ($CaCl_2$). Chromatography with ethyl acetate/pet. spirit (2:3) yielded only *E*-6-hydroxy-2-phenyl-3-(1-phenylpropylidene)-(*3H*)-isobenzopyrrolidinone **126** (0.012 g, 0.035 mmol, 13%).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.58 - 6.87 (m, 11H, ArH), 6.60 (d of d, J = 2.2, 8.7 Hz, 1H, H5), 5.84 (d, J = 8.7 Hz, 1H, H4), 2.06 (q, J = 7.4 Hz, 2H, CH_2), 0.60 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 129.4 (d), 129.3 (d), 129.0 (d), 121.0 (d), (C2'-C6', C2''-C6''), 128.3 (d), 124.1 (d), (C4', C4''), 120.1 (d, C4), 115.2 (d, C5), 108.9 (d, C7), 27.6 (t, CH_2), 11.6 (q, CH_3).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with *N*-benzylidenemethylamine.

(a) <u>in acetonitrile</u>

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.188 g, 0.448 mmol) and *N*-benzylidenemethylamine (0.4 ml, 3.3 mmol) were dissolved in acetonitrile (10 ml) and purged with N_2. The solution was then refluxed for 10.5 h. Chromatography with diethyl ether/pet. spirit (1:6) yielded two bands.

Band one (R_f = 0.84) gave a pale yellow oil (0.063 g), identified (NMR ratio 1:1) as a mixture of benzaldehyde and 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (*ca.* 40%).

Band two (R_f = 0.71) gave *N*-benzylidenemethylamine (0.168 g).

(b) <u>with Li_2PdCl_4</u>

Li_2PdCl_4 (0.373 mmol) was dissolved in acetonitrile (8 ml) and purged with N_2. Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.157 g, 0.373 mmol) and *N*-benzylidenemethylamine (0.3 ml, 3.3 mmol) were added and the solution refluxed for 2 h. Chromatography with diethyl ether/pet. spirit (1:4) yielded four bands.

Band one ($R_f = 0.90$) gave benzaldehyde (0.100 g).

Band two ($R_f = 0.73$) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.081 g, 0.317 mmol, 85%).

Band three ($R_f = 0.40$) gave *N*-benzylidenemethylamine (0.016 g).

Band four ($R_f = 0.17$) gave di-μ-chloro-di(5-methoxy-2-(2-phenylbutan-1-oyl)phenyl)-dipalladium(II) **127** (0.011 g, 0.014 mmol, 7%). Crystallisation from diethyl ether/pet. spirit proved unsuccesful giving a viscous yellow oil.

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.64 (d, J = 8.6 Hz, 1H, H3), 7.31 (m, 6H, ArH), 6.55 (d, J = 2.2, 8.6 Hz, 1H, H4), 4.39 (t, J = 7.3 Hz, 1H, CH), 3.85 (s, 3H, OCH_3), 2.34 (m, 1H, CH_2), 2.02 (m, 1H, CH_2), 0.97 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 212.1 (s, C=O), 165.4 (s, C1), 163.2 (s, C5), 140.4 (s, C1''), 139.8 (s, C2), 132.6 (d, C3), 128.9 (d), 128.4 (d), (C2''-C6''), 127.1 (d, C4''), 120.2 (d, C6), 110.0 (d, C4), 55.3 (q, OCH_3), 54.1 (d, CH), 26.9 (t, CH_2), 12.5 (q, CH_3).

MS : 763 (M^+-C_2H_5), 719 (M^+-2Cl), 612, 507, 465.

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with Li_2PdCl_4.

Li_2PdCl_4 (0.565 mmol) was dissolved in acetonitrile (10 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.226 g, 0.538 mmol) was added and the solution refluxed for 1 h. Chromatography with diethyl ether/pet. spirit (4:6) yields four bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.016 g, 0.065 mmol, 12%).

Band two gave *E*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **14** (0.016 g, 0.592 mmol, 11%).

Band three gave *Z*-6-methoxy-3-(1-phenylpropylidene)-1-(3*H*)-isobenzofuranone **71** (0.007 g, 0.025 mmol, 5%).

Band four gave a yellow oil (0.012 g), identified (NMR) as di-μ-chloro-di(5-methoxy-2-(2-phenylbutan-1-oyl)phenyl)-dipalladium(II) **127** (0.015 mmol, 6%).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with 2-methyl-2-cyclohexenone.

(a) in benzene

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.312 g, 0.743 mmol) and 2-methyl-2-cyclohexenone (0.3 ml, 3.0 mmol) were dissolved in benzene (10 ml) and purged with N_2. The solution was refluxed for 12 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.94) gave $Mn_2(CO)_{10}$ (0.062 g, 0.159 mmol, 21%).

Band two (R_f = 0.80) gave **9** (0.094 g, 30% recovered).

Band three (R_f = 0.69) gave a pale yellow oil (0.274 g), identified (NMR ratio 2:5) as a mixture of 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (*ca.* 70%) and 2-methyl-2-cyclohexenone.

(b) in acetonitrile

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.192 g, 0.457 mmol) and 2-methyl-2-cyclohexenone (0.2 ml, 2.0 mmol) were dissolved in acetonitrile (10 ml) and the solution purged with N_2. The solution was refluxed for 12 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.91) gave an unknown colourless oil (0.003 g).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 1H), 7.26 (m, 5H), 6.71 (s, 2H), 6.70 (d of d, J = 2.5, 8.3 Hz, 1H), 5.86 (m, 1H), 4.95 (m, 2H), 4.28 (t, J = 7.3 Hz, 1H), 3.79 (s, 3H), 3.53 (t, J = 6.5 Hz, 2H), 2.20 (m, 1H), 1.82 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H).

Band two (R_f = 0.85) gave a pale yellow oil (0.224 g), identified (NMR ratio 1:1) as a mixture of 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (*ca.* 90%) and 2-methyl-2-cyclohexenone.

Band three (R_f = 0.42) gave an orange oil (0.021 g), IR indicated this oil to be (acetonitrile-κ*N*)tri(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **31**.
IR (pentane) ν(CO) 2008 (vs), 1931 (s), 1896 (s).

(c) with Li_2PdCl_4 in acetonitrile

Li_2PdCl_4 (0.418 mmol) was dissolved in acetonitrile (8 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.176 g, 0.419 mmol) and 2-methyl-2-cyclohexenone (0.30 ml, 3.0 mmol) were added and the solution refluxed for 2.5 h. Chromatography with diethyl ether/pet. spirit (3:7) gave a pale yellow oil (0.122 g), identified (NMR ratio 1:1) as 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (*ca.* 57%) and 2-methyl-2-cyclohexenone.

(d) with $NiBr_2(PPh_3)_2$ in acetonitrile

$NiBr_2(PPh_3)_2$ (0.101 g, 0.136 mmol) and **9** (0.058 g, 0.138 mmol) were dissolved in acetonitrile (10 ml) and purged with N_2. 2-Methyl-2-cyclohexenone (0.20 ml, 2.0 mmol) was added and the solution refluxed for 4 h. Chromatography with diethyl ether/pet. spirit (3:7) yields five bands.

Band one (R_f = 0.97) gave PPh_3 (0.006 g).

Band two (R_f = 0.85) gave an orange oil (0.017 g), identified (IR) as (acetonitrile-κ*N*)tri(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **31** (0.039 mmol, 28%).

Band three (R_f = 0.81) gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.016 g, 0.062 mmol, 45%).

Band four (R_f = 0.73) gave 2-methyl-2-cyclohexenone (0.069 g).

Band five (R_f = 0.30) gave a yellow oil (0.007 g), identified as 9-hydroxy-6-methoxy-9a-methyl-9-(1-phenylpropyl)-1,2,3,4,4a,9,9a-heptahydro-1-fluorenone **128** (0.021 mmol, 15%). Attempts to cyrstallise **128** proved unsuccessful. NMR indicated at least four isomers of **128**.
The major diastereoisomer has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.10 (m, 6H, ArH), 6.69 (d, J = 2.1 Hz, 1H, H5), 6.99 (d of d, J = 2.1, 8.6 Hz, 1H, H7), 4.02 (d of d, J = 2.3, 12.5 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 3.62 (s, 3H, CH_3), 2.92 (m, 2H, 1H, H4), 2.19 (m, 1H, CH_2), 1.89

(m, 1H, H4a), 1.61 (m, 3H, H3, CH_2), 0.86 (t, J = 7.3 Hz, 3H, CH_3), 0.30 (t, J = 7.3 Hz, 2H, H2).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 169.9 (s, C1), 160.0 (s, C6), 141.7 (s, C1''), 139.9 (s, C8a), 137.0 (s, C4b), 133.9 (d, C8), 128.0 (d), 127.2 (d), (C2''-C6''), 126.7 (d, C4''), 121.7 (d, C7), 107.1 (d, C5), 91.1 (s, C1), 55.5 (q, OCH_3), 53.7 (d, CH), 51.9 (d, C4a), 25.3 (t, CH_2), 24.4 (t, CH_2), 24.3 (t, CH_3), 22.4 (t, CH_2), 12.6 (q, CH_3), 12.0 (q, CH_3).

MS : 220 (M^+-$C_{10}H_8O$), 206, <u>205</u>, 177, 145.

Attempted dehydration of 9-hydroxy-6-methoxy-9a-methyl-9-(1-phenylpropyl)-1,2,3,4,4a,9,9a-heptahydro-1-fluorenone 128.

9-Hydroxy-6-methoxy-9a-methyl-9-(1-phenylpropyl)-1,2,3,4,4a,9,9a-heptahydro-1-fluorenone **128** (0.087 g, 0.239 mmol) and 4-toluenesulphonic acid (0.010 g, 0.053 mmol) were dissolved in acetonitrile (10 ml) and stirred for 16.7 h. Chromatography with diethyl ether/pet. spirit (2:3) gave **128** (0.042 g, 48% recovered).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with 2-methyl-1,3-butadiene.

(a) <u>in benzene</u>

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.253 g, 0.602 mmol) was dissolved in benzene (10 ml) and the solution purged with N_2. 2-Methyl-1,3-butadiene (isoprene) (0.9 ml, 6.1 mmol) was added and the solution refluxed for 4 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded two bands.

Band one (R_f = 0.88) gave an orange oil (0.236 g), tentatively assigned as tri(carbonyl-κ*C*)-[4-(5-methoxy)-2-(2-phenyl-1-butanoyl-κ*O*)-phenyl)-2-methyl-butenyl-η-1,2,3]-manganese(I) **129** (0.513 mmol, 85%). Though stable under N_2 for short a period of time, **129** readily decomposed before NMR could be performed.

IR (pentane) ν(CO) 2060 (vs, sh), 1992 (vs, br), 1955 (s, br), 1670 (w, br).

Band two (R_f = 0.12) gave a colourless oil (0.005 g), tentatively assigned by spectroscopically as bis-1,8-di-(5-methoxy-2-(2-phenylbutan-1-oyl)-phenyl)-3,6-dimethylocta-1,7-diene **130** (0.007 mmol, *ca.* 1%).

^1H NMR (300 MHz) ($CDCl_3$) δ 7.57 (d, J = 8.7 Hz, 1H, H3'), 7.24 (m, 5H, ArH), 6.92 (d, J = 2.5 Hz, 1H, H6'), 6.88 (d, J = 15.9 Hz, 1H, H2, H7), 6.74 (d of d, J =

2.5, 8.7 Hz, 1H, H4'), 6.12 (d, J = 15.9 Hz, 1H, H1, H8), 4.28 (t, J = 7.3 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 2.20 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 1.40 (s, 3H, CH_3), 1.30 (s, 2H, H4), 0.90 (t, J = 7.5 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 202.9 (s, C=O), 161.6 (s, C5), 140.0 (d, C1, C8), 139.4 (s, C1'), 131.1 (s, C2'), 130.6 (d, C3), 128.8 (d), 128.3 (d), (C2"-C6"), 127.0 (d, C4"), 125.9 (d, C2, C7), 112.8 (d), 112.3 (d), (C4, C6), 71.1 (C3, C6), 58.3 (d, CH), 55.4 q, OCH_3), 29.8 (t, CH_2), 29.7 (q, CH_3), 26.9 (t, CH_2), 12.4 (q, CH_3).

(b) with $NiBr_2(PPh_3)_2$ in acetonitrile

$NiBr_2(PPh_3)_2$ (0.260 g, 0.350 mmol) and tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.147 g, 0.349 mmol) were dissolved in acetonitrile (10 ml) and purged with N_2. 2-Methyl-1,3-butadiene (0.9 ml, 6.1 mol) was added and the solution refluxed for 3 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded two major bands.

Band one gave PPh_3 (0.011 g).

Band two gave an unknown orange oil (0.107 g) which readily decomposed before NMR could be performed.

(c) with Li_2PdCl_4 in acetonitrile

Li_2PdCl_4 (0.313 mmol) was dissolved in acetonitrile (8 ml). Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) **9** (0.131 g, 0.312 mmol) and 2-methyl-1,3-butadiene (0.9 ml, 6.1 mmol) were added and the solution refluxed for 4.3 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one gave 1-(4-methoxyphenyl)-2-phenyl-1-butanone **7** (0.019 g, 0.076 mmol, 24%).

Band two gave an unknown yellow oil (0.017 g).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 9.71 (s, 1H), 7.75 (m, 2H), 7.25 (m, 5H), 6.71 (m, 3H), 4.31 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 3.05 (m, 3H), 2.60 (m, 2H), 2.19 (m, 1H), 1.85 (m, 1H), 0.91 (t, = 7.4 Hz, 3H).

Band three gave di-μ-chloro-di(4-(5-methoxy-2-(2-phenyl-1-butanoyl)-phenyl)-2-methyl-1-butenyl)-dipalladium(II) **131** (0.052 g, 0.056 mmol, 36%). Crystallisation from diethyl ether/pet. spirit gave fine pale yellow crystals, mp 109-110°C.

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 1H, H3'), 7.69 (d, J = 8.7 Hz, 1H, H3'), 7.23 (m, 10H, ArH), 6.98 (d, J = 2.4 Hz, 1H, H6'), 6.94 (d, J = 2.4 Hz, 1H, H6'), 6.75 (d of d, J = 2.4, 8.7 Hz, 1H, H4'), 6.73 (d of d, J = 2.4, 8.7 Hz, 1H, H4'), 4.31 (t, J = 7.5 H, 1H, CH), 4.28 (t, J = 7.5 Hz, 1H, CH), 3.803 (s, 3H, OCH$_3$), 3.798 (s, 3H, OCH$_3$), 3.66 (s, 1H, H1), 3.64 (s, 1H, H1), 3.51 (m, 1H, H3), 3.35 (d of d, J = 6.2, 25.9 Hz, 1H, H3), 3.10 (d of d, 7.1 Hz, 1H, H4), 2.97 (d of d, J = 4.6, 15.8 Hz, 1H, H4), 2.85 (d of d, J = 3.5, 14.9 Hz, 2H, H4), 2.52 (s, 1H, H1), 2.44 (s, 1H, H1), 2.20 (m, 2H, CH$_2$), 2.13 (s, CH$_3$), 2.08 (s, 3H, CH$_3$), 1.83 (m, 2H, CH$_2$), 0.89 (m, 6H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 202.0 (s, C=O), 201.1 (s, C=O), 161.8 (s, C5'), 161.7 (s, C5'), 142.3 (s, C1''), 142.1 (s, C2'), 131.3 (d, C3'), 131.1 (d, C3'), 130.7 (s, C1'), 130.5 (s, C1'), 128.9 (d), 128.8 (d), 128.3 (d), (C2'', C3'', C5'', C6''), 127.0 (d, C4''), 123.9 (s, C2), 123.7 (s, C2), 117.2 (d, C6'), 117.2 (d, C6'), 111.9 (d, C4'), 111.7 (d, C4'), 82.2 (d, C3), 82.1 (d, C3), 60.1 (t, C1), 60.0 (t, C1), 57.9 (d, CH), 57.7 (d, CH), 55.5 (q, OCH$_3$), 34.1 (t, C4), 34.0 (t, C4), 26.7 (t, CH$_2$), 26.7 (t, CH$_2$), 19.1 (q, CH$_3$), 19.0 (q, CH$_3$), 12.4 (q, CH$_3$), 12.4 (q, CH$_3$).

MS : 891 (M$^+$-Cl), 570, 427, 354, 321.

Found : C, 57.72; H, 5.62%.

$C_{44}H_{50}O_4Cl_2Pd_2$ calcd. : C, 57.04; H, 5.44%.

Reaction of di-μ-chloro-di(4-(5-methoxy-2-(2-phenyl-1-butanoyl)-phenyl)-2-methyl-1-butenyl)-dipalladium(II) 131 with 4-toluenesulphonic acid.

Di-μ-chloro-di(4-(5-methoxy-2-(2-phenyl-1-butanoyl)-phenyl)-2-methyl-1-butenyl)-dipalladium(II) **131** (0.055 g, 0.059 mmol) and 4-toluenesulphonic acid were dissolved in acetonitrile (10 ml). The solution was stirred for 18 h with a colour change from pale to dark yellow. The solvent was removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (3:7) yielded three bands.

Band one (R_f = 0.94) gave a colourless oil (0.004 g), identified (^{1}H NMR ratio 3:2) as a mixture of two unknown compounds.

Major:

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.21 (m, 5H), 6.73 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.6 Hz, 1H), 6.30 (d of d, J = 2.5, 8.6 Hz, 1H), 5.14 (s, br, 1H), 4.97 (s, br, 1H), 4.34 (t, J = 7.6 Hz, 1H), 3.72 (s, 3H), 2.83 (m, 4H), 2.45 (m, 1H), 1.89 (s, 3H), 1.45 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

Minor:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 1H), 7.21 (m, 5H), 6.75 (d of d, J = 2.4, 8.6 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 5.03 (s, br, 1H), 4.84 (s, br, 1H), 4.28 (m, 1H), 3.81 (s, 3H), 2.80 (m, 1H), 2.30 (m, 1H), 1.68 (s, 3H), 1.40 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H).

Band two (R_f = 0.58) gave a colourless oil (0.003 g), identified (^{1}H NMR ratio 6:5) as a mixture of two unknown compounds.

Major:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.45 (d, J = 8.6 Hz, 1H), 7.31 (m, 5H), 6.75 (d, J = 2.7 Hz, 1H), 6.73 (d of d, J = 2.7, 8.6 Hz, 1H), 5.09 (s, br, 1H), 4.91 (s, br, 1H), 4.30 (t, J = 7.4 Hz, 1H), 3.82 (s, 3H), 3.07 (d of d, J = 3.0, 11.6 Hz, 1H), 2.91 (d, J = 3.0 Hz, 1H), 2.88 (s, 1H), 1.88 (m, 1H), 1.84 (s, 3H), 1.30 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H).

Minor:

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 6.9 Hz, 2H), 7.30 (m, 5H), 6.86 (d of d, J = 2.5, 8.4 Hz, 1H), 5.02 (s, br, 1H), 4.87 (s, br, 1H), 4.40 (d of d, J = 3.0, 9.0 Hz, 1H), 3.81 (s, 3H), 2.80 (d, J = 11.5 Hz, 1H), 2.71 (d, J = 2.6 Hz, 1H), 2.66 (d, J = 3.0 Hz, 1H), 2.41 (s, 1H), 2.13 (m, 1H), 1.88 (m, 1H), 1.85 (s, 3H), 0.57 (t, J = 7.4 Hz, 3H).

Band three (R_f = 0.44) gave an unknown pale yellow oil (0.003 g).
^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 1H), 7.23 (m, 5H), 6.74 (m, 2H), 5.03 (s, 1H), 4.85 (s, 1H), 4.34 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 2.74 (d, J = 3.4 Hz, 1H), 2.67 (d, J = 9.9 Hz, 1H), 2.32 (m, 1H), 1.82 (s, 3H), 1.63 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H).

Reaction of tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 with cyclopentadiene.

Tetra(carbonyl-κ*C*)[3-methoxy-6-(2-phenyl-1-butanoyl-κ*O*)-phenyl-κ*C*]-manganese(I) 9 (0.148 g, 0.352 mmol) was dissolved in acetonitrile (10 ml) and the solution purged with N_2. Cyclopentadiene (0.5 ml, 7.5 mmol - freshly distilled) was added and the solution refluxed for 5 h. Chromatography with diethyl ether/pet. spirit (3:7) yielded only 1-(4-methoxyphenyl)-2-phenyl-1-butanone 7 (0.065 g, 0.257 mmol, 74%).

Preparation of 3-(4-methoxyphenyl)-5-phenyl-1-hepten-3-ol 132.

1-(4-Methoxyphenyl)-2-phenyl-1-butanone **7** (0.200 g, 0.787 mmol) dissolved in THF (5 ml) was treated with vinylmagnesium bromide (1.00 mmol in THF) and allowed to stand for 18 h. The solution was then poured into HCl (2 mol l^{-1}, 30 ml) and extracted with ether (40 ml). The solution was washed with HCl (2 mol l^{-1}, 30 ml) and saturated NaCl solution (20 ml) and dried (CaCl$_2$). Chromatography with diethyl ether/pet. spirit (1:4) yielded two bands.

Band one (R_f = 0.91) gave 3-(4-methoxyphenyl)-5-phenyl-1-hepten-3-ol **132** as a colourless oil (0.164 g, 0.582 mmol, 74%). Attempts to crystallise **132** proved unsuccessful.

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.36-7.13 (m, 7H, ArH), 6.83 (d, J = 8.9 Hz, 2H, H3', H5'), 6.58 (d of d, J = 10.8, 17.1 Hz, 1H, H2), 5.34 (d of d, J = 1.3, 17.1 Hz, 1H, H1 *trans* to H2), 5.29 (d of d, J = 1.3, 10.8 Hz, 1H, H1 *cis* to H2), 3.77 (s, 3H, OCH$_3$), 2.99 (d of d, J = 3.2, 11.8 Hz, 1H, H4), 1.85 (m, 2H, CH$_2$), 0.73 (t, J = 7.3 Hz, 3H, CH$_3$).

^{13}C NMR (300 MHz) (CDCl$_3$) δ 158.4 (s, C4'), 142.3 (d, C2), 139.6 (s, C1''), 137.7 (s, C1'), 130.2 (d, C2', C6'), 127.8 (d, C2'', C6''), 127.4 (d, C3'', C5''), 126.7 (d, C4''), 113.6 (t, C1), 113.2 (d, C3', C5'), 79.0 (s, C3), 59.6 (d, C4), 55.2 (q, OCH$_3$), 22.8 (t, CH$_2$), 12.7 (q, CH$_3$).

Band two (R_f = 0.82) gave **7** (0.040 g, 20% recovered).

Preparation of 4-(4-methoxyphenyl)-5-phenyl-1-hepten-4-ol 133.

Magnesium (0.06 g, 2.5 mmol) and allyl bromide (0.28 ml, 3.0 mmol) were added to ether (5 ml). 1-(4-Methoxyphenyl)-2-phenyl-1-butanone **7** (0.501 g, 1.97 mmol) was added. The Grignard reaction initiated and the solution refluxed for 1 h. The mixture was poured into HCl (2 mol l^{-1}, 40 ml) and extracted with ether (2 x 25 ml) and further washed with HCl (2 mol l^{-1}, 2 x 20 ml) and dried (CaCl$_2$). Chromatography with diethyl ether/pet. spirit (2:5) gave a colourless oil (0.447 g), identified as a diastereoisomeric mixture (NMR ratio 2:5) of 4-(4-methoxyphenyl)-5-phenyl-1-hepten-4-ol **133a** and **133b** (1.51 mmol, 77%). Attempts to crystallise **133** proved unsuccessful.

[4R*,5S*]-4-(4-Methoxyphenyl)-5-phenyl-1-hepten-4-ol **133a** has the following spectral characteristics.

^{1}H NMR (300 MHz) (CDCl$_3$) δ 7.18 (m, 3H, H3'', H4'', H5''), 7.13 (d, J = 8.8 Hz, H2', H6'), 6.94 (m, 2H, H2'', H6''), 6.80 (d, J = 8.8 Hz, 2H, H3', H5'), 5.54 (m, 2H, H1), 5.11 (m, 1H, H2), 3.79 (s, 3H, OCH$_3$), 2.84 (d of d, J = 3.2, 11.9 Hz, 1H, CH), 2.79 (m, 1H, H3), 2.54 (d of d, J = 8.8, 14.0 Hz, 1H, H3), 2.19 (s, 1H, OH), 2.13 (m, 1H, CH$_2$), 1.54 (m, 1H, CH$_2$), 0.68 (t, J = 7.3 Hz, 3H, CH$_3$).

^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.3 (s, C4'), 140.1 (s, C1''), 135.7 (s, C1'), 134.1 (d, C2), 130.3 (d, C2'', C6''), 128.4 (d, C2', C6'), 127.6 (d, C3'', C5''), 126.5 (d, C4''), 119.7 (t, C1), 112.7 (d, C3', C5'), 77.4 (C4), 59.5 (d, CH), 55.2 (q, OCH_3), 44.3 (t, C3), 21.9 (t, CH_2), 12.6 (q, CH_3).
MS : 278 (M^+-H_2O), 263, 249.

[4S*,5S*]-4-(4-Methoxyphenyl)-5-phenyl-1-hepten-4-ol **133b** has the following spectral characteristics.
^1H NMR (300 MHz) ($CDCl_3$) δ 7.30 (m, 3H, H3'', H4'', H5''), 7.18 (m, 4H, H2', H6', H2'', H6''), 6.94 (d, J = 8.9 Hz, 2H, H3', H5'), 5.35 (m, 2H, H1), 4.94 (m, 1H, H2), 3.83 (s, 3H, OCH_3), 2.84 (d of d, J = 3.2, 11.9 Hz, 1H, CH), 2.79 (m, 1H, H3), 2.67 (d of d, J = 5.4, 14.0 Hz, 1H, H3), 2.10 (m, 1H, CH_2), 2.01 (s, 1H, OH), 1.78 (m, 1H, CH_2), 0.58 (t, J = 7.4 Hz, 3H, CH_3).
^{13}C NMR (300 MHz) ($CDCl_3$) δ 158.3 (s, C4'), 141.1 (s, C1''), 137.9 (s, C1'), 133.9 (d, C2), 130.3 (d), 128.0 (d), 127.0 (d), (C2', C6', C2''-C6''), 126.6 (d, C4'), 119.2 (t, C1), 113.2 (d, C3', C5'), 77.8 (s, C4), 59.2 (d, CH), 55.2 (q, OCH_3), 46.2 (t, C3), 22.6 (t, CH_2), 12.7 (q, CH_3).
MS : 278 (M^+-H_2O), 263, 249.

Coupling of 3-(4-methoxyphenyl)-5-phenyl-1-hepten-3-ol 132 and 2-trimethylsilyloxy-1,3-butadiene.

3-(4-Methoxyphenyl)-5-phenyl-1-hepten-3-ol **132** (0.154 g, 0.546 mmol) and 2-trimethylsilyloxy-1,3-butadiene (0.118 g, 0.831 mmol) were dissolved in benzene and refluxed for 3 h. The solvent was removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:6) gave **132** (0.151 g, 97% recovered).

Coupling of 3-(4-methoxyphenyl)-5-phenyl-1-hepten-3-ol 132 and 2-methyl-1,3-butadiene.

3-(4-Methoxyphenyl)-5-phenyl-1-hepten-3-ol **132** (0.151 g, 0.535 mmol) and 2-methyl-1,3-butadiene (0.7 ml, 7.0 mmol) were dissolved in benzene and refluxed for 6 h. The solvent was removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (1:9) gave **132** (0.147 g, 97% recovered).

Coupling of 4-(4-methoxyphenyl)-5-phenyl-1-hepten-4-ol 133 and 2-methyl-1,3-butadiene.

4-(4-Methoxyphenyl)-5-phenyl-1-hepten-4-ol **133** (0.187 g, 0.632 mmol) and 2-methyl-1,3-butadiene (0.8 ml, 8.0 mmol) were dissolved in benzene (6 ml) and refluxed for 8 h. The solvent was removed under reduced pressure. Chromatography with diethyl ether/pet. spirit (3:7) gave **133** (0.166 g, 89% recovered).

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A.1 General Experimental Procedures.

All air-sensitive reactions were performed under an atmosphere of dry nitrogen using Schlenk techniques.

THF was dried by distillation from sodium/benzophenone under N_2 as was the diethyl ether used for Grignard reagent preparations. Petroluem spirit (60-80°C) (pet. spirit) used for chromatography purposes was dried with CaH_2 and distilled drum grade X4. All other solvents used were analytical reagent grade.

Infrared spectra were recorded on a Digilab FTS-45 FTIR instrument using a solution cell (KBr windows; CH_2Cl_2 or hexane solvent) and observed routinely for the carbonyl region, 2200 - 1600 cm^{-1}.

^1H-NMR spectra were recorded on either a JEOL FX-90Q (89.55 MHz) or Bruker AC300 (300.13 MHz) instrument. ^1H chemical shifts are reported in δ ppm and referenced downfield from TMS.

^{13}C-NMR spectra were recorded on the JEOL FX-90 (22.5 MHz) and Bruker AC300 (75.47 MHz). Chemical shifts are reported in δ ppm with reference to the central peak of $CDCl_3$ (77.06 ppm). Standard DEFT pulse techniques were used in ^{13}C assignment ambiguities.

2D-NMR techniques and nOe experiments were conducted using the Bruker AC300 instrument employing standard programmes. Homonuclear shift correlation spectroscopy (COSY) was conducted using the Bruker COSY.AU program for ^1H correlations. Hetereonuclear shift correlation spectroscopy (XH) was conducted using the Bruker XHCORR.AU program for ^{13}C correlations. NOe difference spectra were conducted using the Bruker NOEMULT.AU program.

All ^{31}P-NMR were recorded on a JEOL FX-90Q (36.23 MHz) instrument with all spectra referenced to 85% H_3PO_4 using the low field positive convention.

FAB mass spectrometry was carried out at the University of Adelaide using a VG ZAB 2HF instrument. Electron impact ionization mass spectrometry was carried out at the University of Auckland using a VG 70-SE instrument. All GCMS was carried out using a Hewlett Packard HP5890 gas chromatograph connected to a Hewlett Packard HP5970 series mass selective detector.

All chromatography, unless otherwise stated was preparative layer chromatography (plc). The product band(s) was removed from the plate, packed in a column and eluted with diethyl ether. The solvent was then removed under reduced pressure to leave the residual product(s). All bands are recorded in decreasing mobility.

Preparative layer chromatography (plc) was carried out on Merck Kieselgel $60PF_{254+366}$ silica gel coated glass plates poured to a thickness of 1 mm.

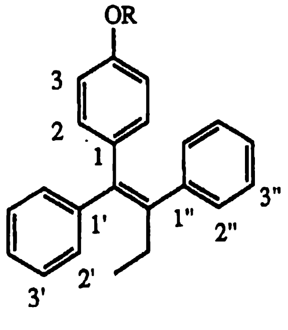
Thin layer chromatography (tlc) was carried out on Merck Kieselgel $60F_{254}$ silica gel backed by aluminium sheets (layer thickness 0.2 mm).

Melting points were recorded on a Reichert Thermovar instrument and are uncorrected.

Elemental analyses were performed by the University of Otago Campbell Microanalytical Laboratory.

A common method employed for recrystallisation was solvent diffusion. This involved the dissolving of the sample in a polar solvent (e.g. CH_2Cl_2) in a small vial and placing it inside a larger vial, the larger vial containing a non-polar solvent (e.g. pentane). The temperatures employed for recrystallisation ranged from -20° to 4°C.

The atom numbering scheme commonly used throughout this thesis is outlined in the figure below. The atoms of the phenyl ring of the phenylpropyl group are always labelled 1''-6''.



A.II 2-D NMR Spectra.

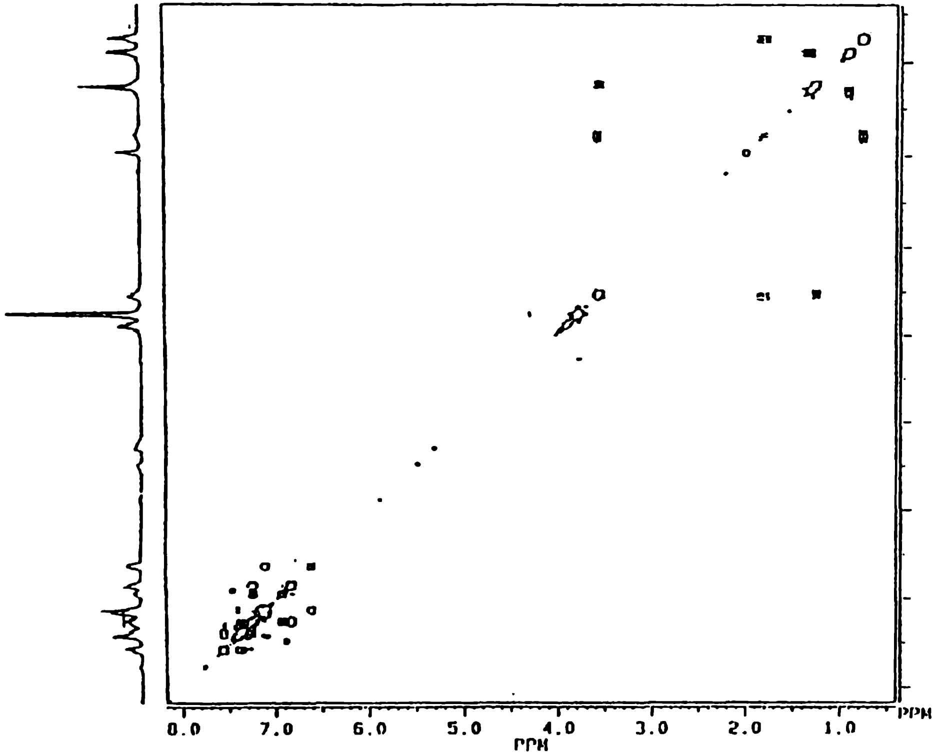


Figure A.1 COSY spectrum of 15

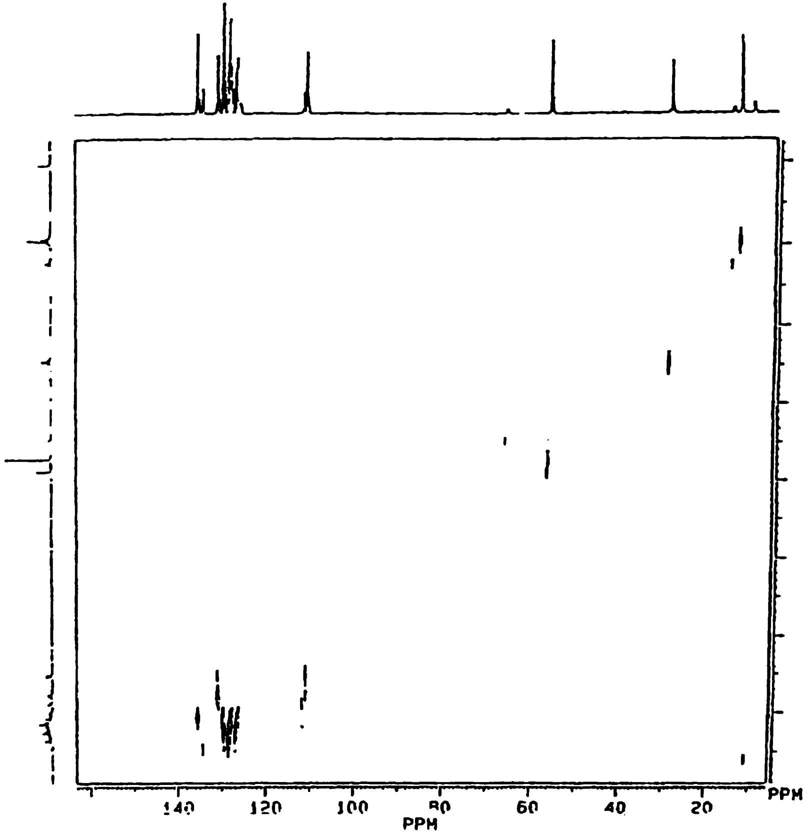


Figure A.2 XH-correlated spectrum of 19 and

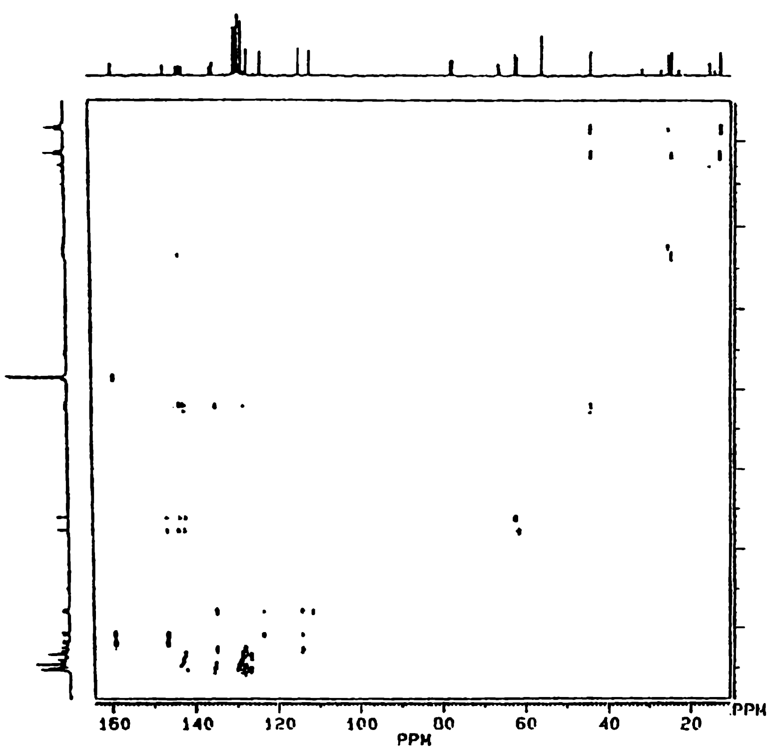


Figure A.4 long range XH-correlated spectrum of 49

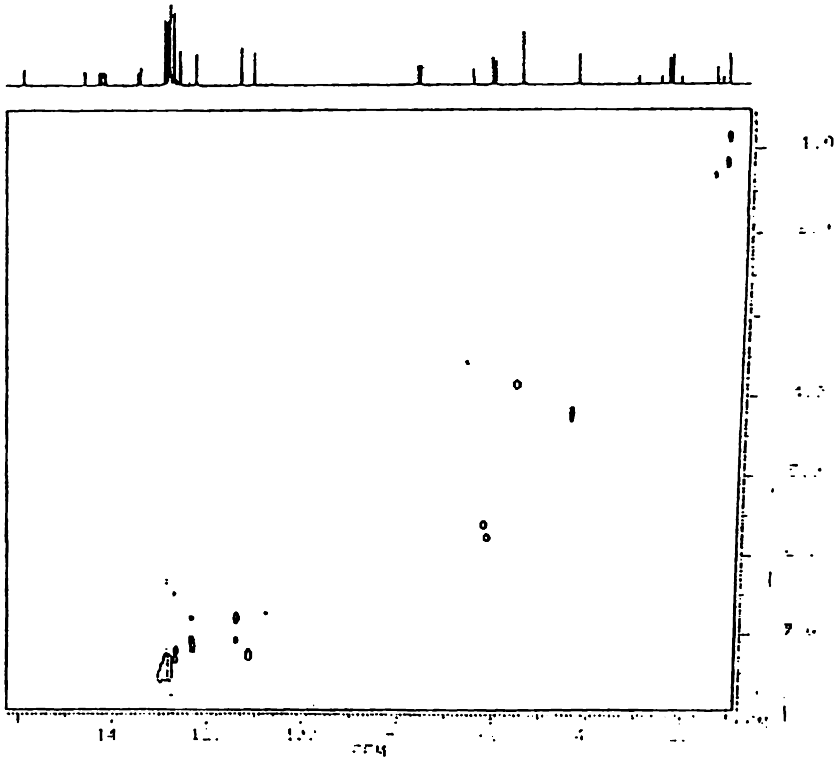


Figure A.3 XH-correlated spectrum of 49

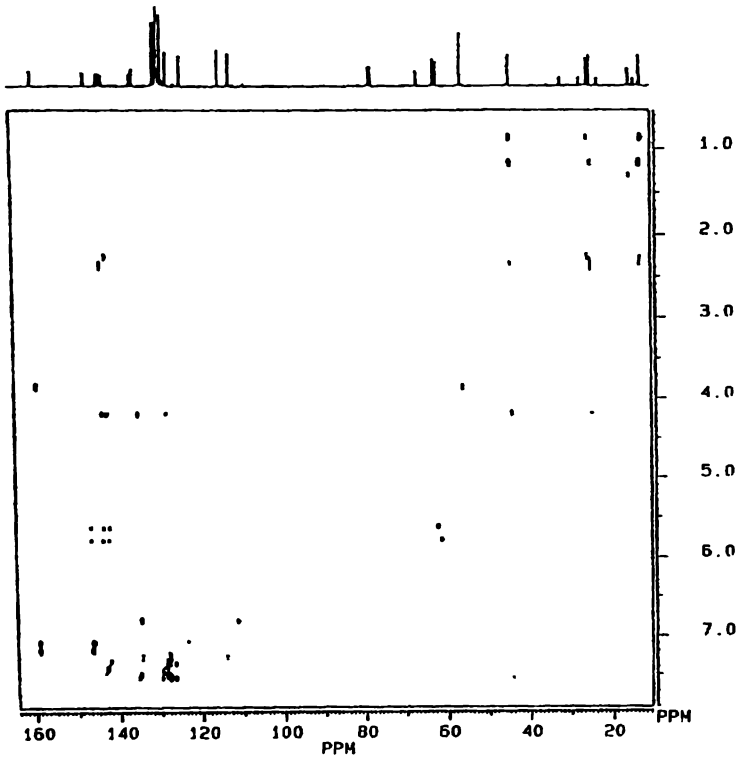


Figure A.5 long range XH-correlated spectrum of 49

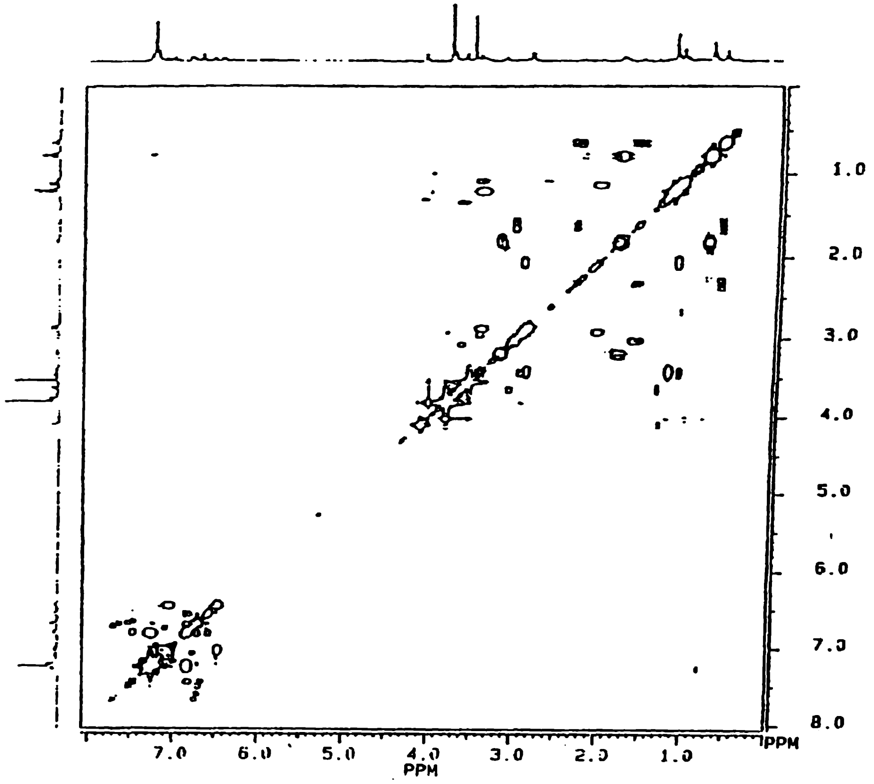


Figure A.6 COSY spectrum of **64d** and **64e**

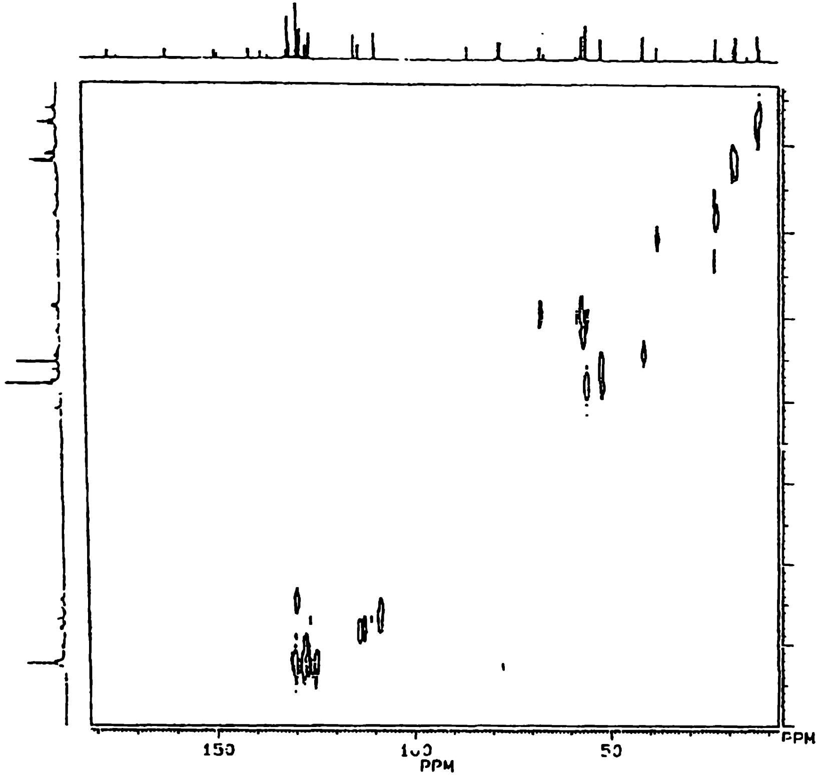


Figure A.7 XH-correlated spectrum of **64d** and **64e**

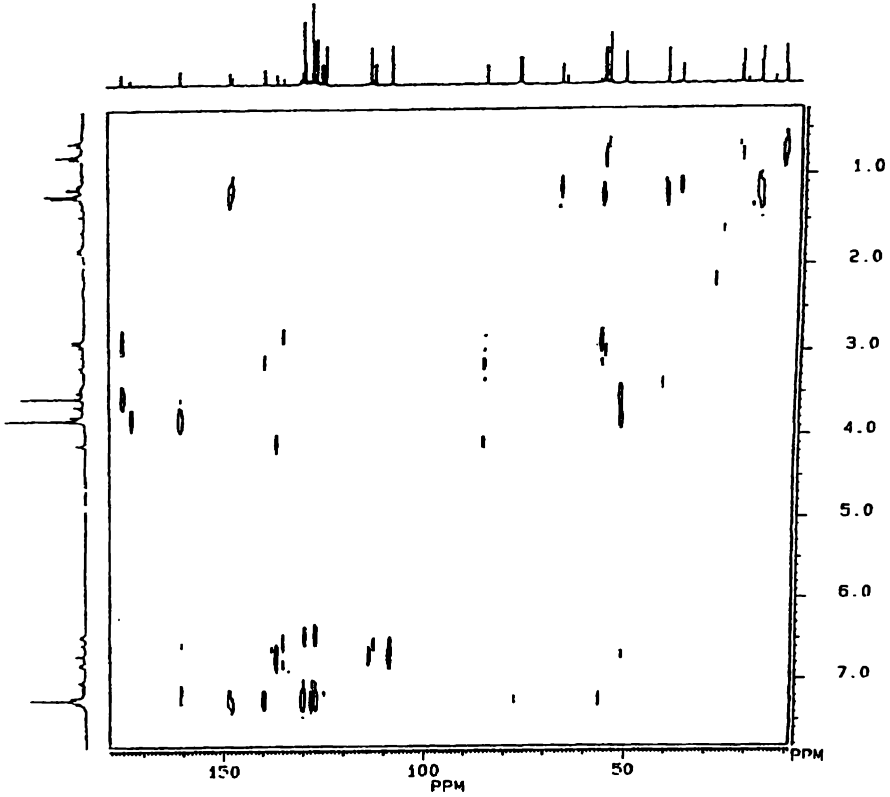


Figure A.8 long range XH-correlated spectrum of **64d** and **64e**

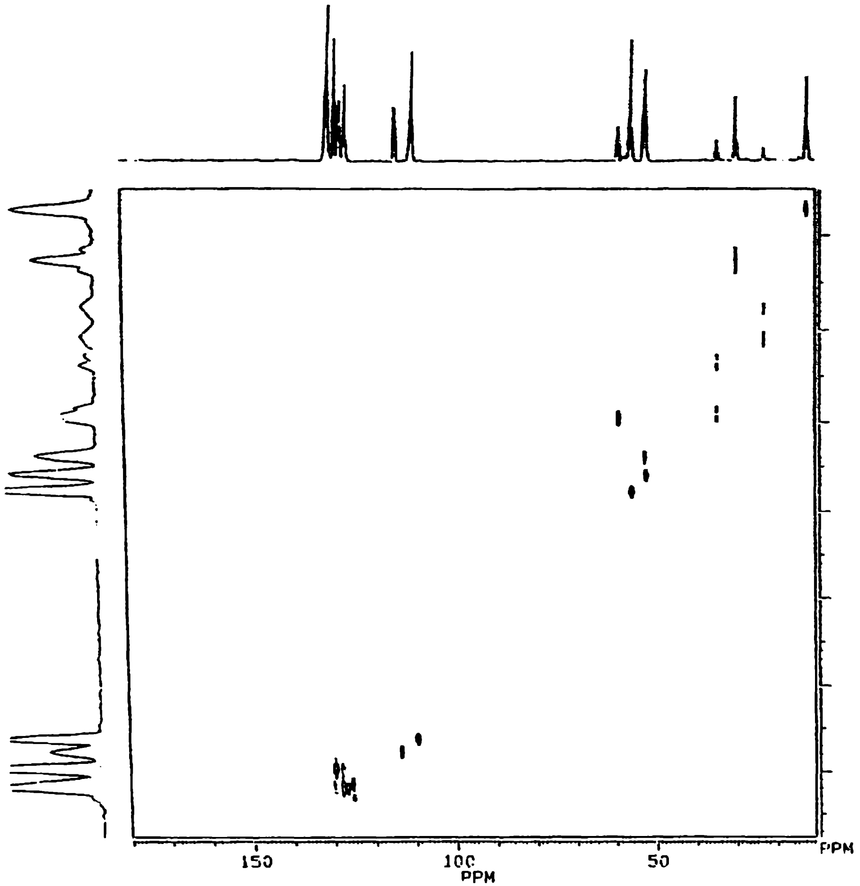


Figure A.10 XH-correlated spectrum of **57b**

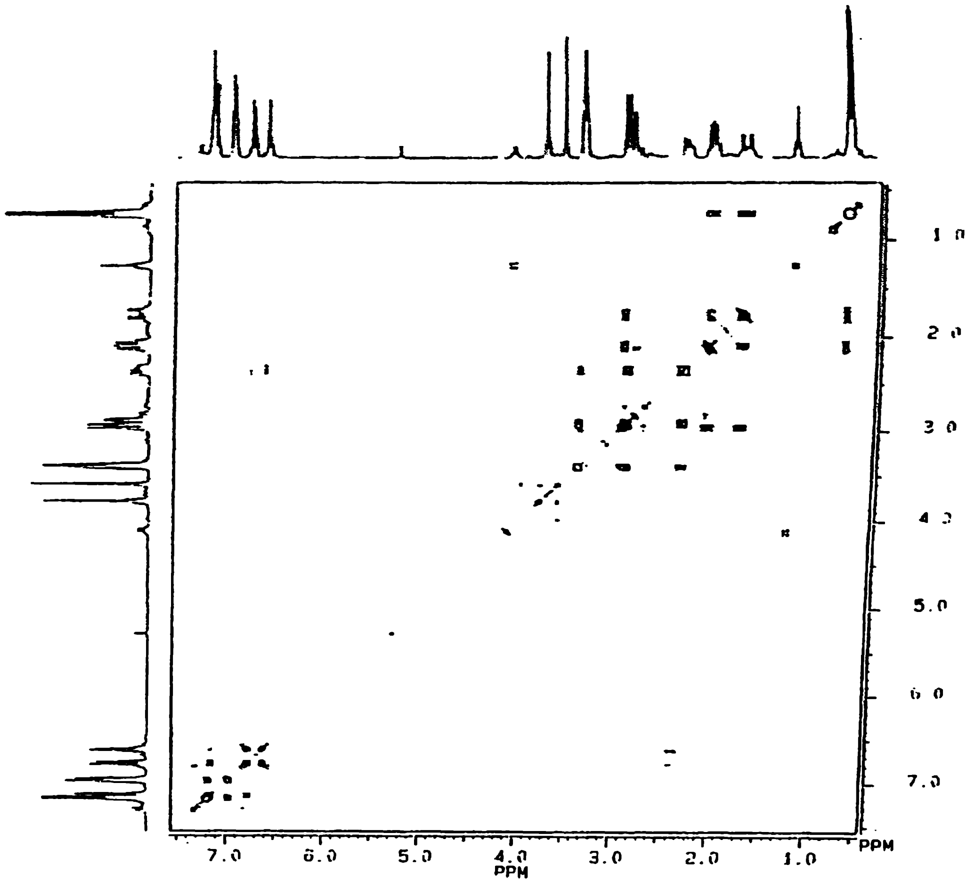


Figure A.9 COSY spectrum of **57b**

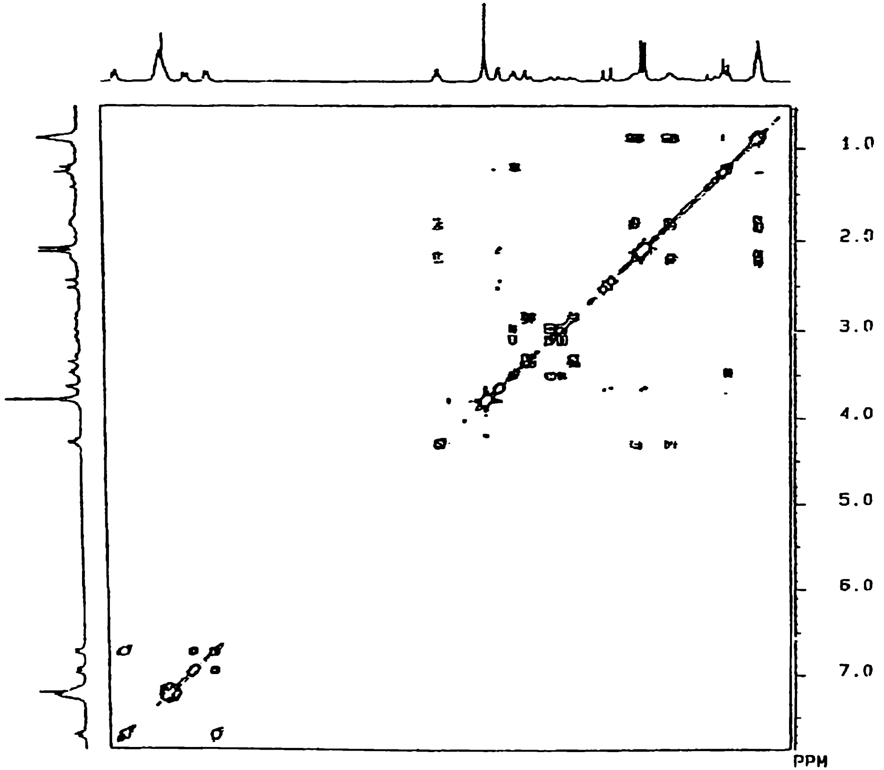


Figure A.11 COSY spectrum of **131**

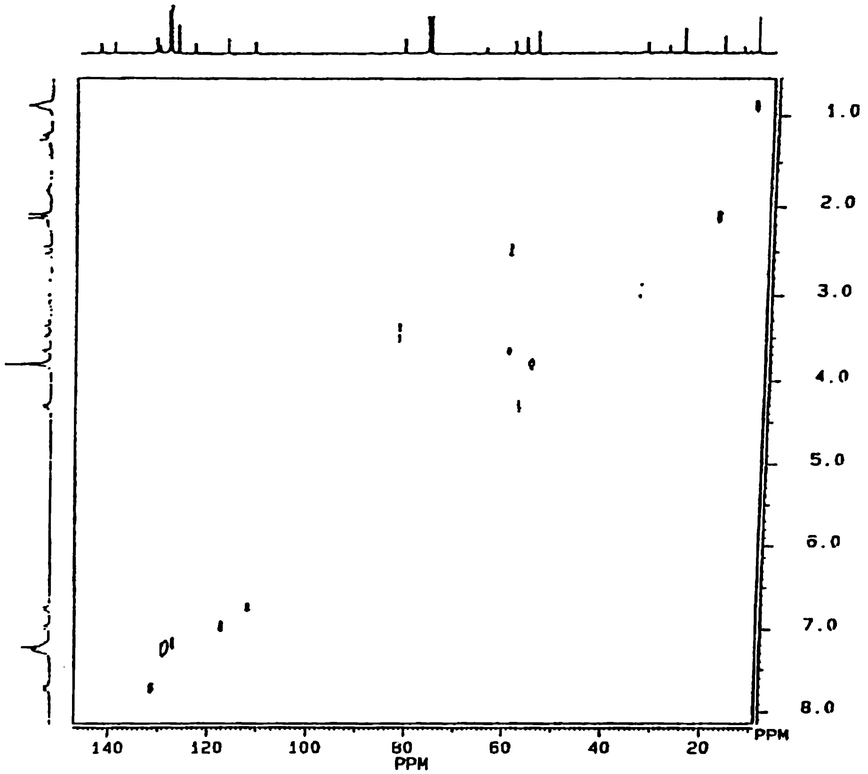


Figure A.12 XH-correlated spectrum of **131**

A.III Results of Differential nOe Experiments.

Table A.1 Differential nOe results for **33a**.

	H3	H4	H7	H22, H26	CH	CH$_2$	CH$_2$	CH$_3$	H2'', H6''
H3	•	4.0		12.0					
H4	2.4	•							
H7			•			3.4	1.6		1.3
H22, H26	6.1			•	3.3				
CH				8.4	•				
CH$_2$						•			
CH$_2$							•		
CH$_3$								•	
H2'', H6''								0.4	•

Table A.2 Differential nOe results for **33b**.

	H3	H4	H7	H22, H26	CH	CH$_2$	CH$_2$	CH$_3$	H2'', H6''
H3	•			1.6					
H4	2.2	•							
H7			•						
H22, H26	5.5			•	2.6				
CH				5.4	•				

Table A.3 Differential nOe results for **43a**.

	H4	3-CH$_3$	H7	2-CH$_2$	CH	CH$_2$	CH$_2$	CH$_3$	H2'', H6''
H4	•	2.4							
3-CH$_3$	2.4	•							
H7			•	3.0		5.6	2.7		
2-CH$_2$				•					
CH				2.3	•		1.6	6.0	3.1

Table A.4 Differential nOe results for **43b**.

	H4	3-CH_3	H7	2-CH_2	CH	CH_2	CH_2	CH_3	H2'', H6''
H4	•	1.6							
3-CH_3	2.6	•		3.1					
H7			•						
2-CH_2				•					
CH			2.3		•				10.0

Table A.5 Differential nOe results for **64a**

	3-CH_3	3-H	2-CO_2CH_3	2-H	CH	CH_2	CH_2	CH_3
3-CH_3	•	2.5	0.4	0.2				
3-H	4.5	•		8.7	4.6			
2-CO_2CH_3			•					
2-H		6.3		•	2.3			
CH		4.6		1.3	•			2.8
CH_2					2.7	•	10.5	1.9
CH_2				1.6		8.9	•	2.0
CH_3					1.8	1.4	0.9	•

Table A.6 Differential nOe results for **64b**

	3-CH_3	3-H	2-CO_2CH_3	2-H	CH	CH_2	CH_2	CH_3
3-CH_3	•	2.9						
3-H	5.6	•		8.6	0.6			
2-CO_2CH_3			•					
2-H		7.7		•	3.8	1.9	0.9	
CH	0.6			4.2	•	2.1		3.1
CH_2				3.4	4.8	•	17.4	5.2
CH_2				2.8		18.6	•	4.7
CH_3					1.9	2.0	1.7	•

Table A.7 Differential nOe results forr **64c**

	$3\text{-}CH_3$	3-H	$2\text{-}CO_2CH_3$	2-H	CH	CH_2	CH_2	CH_3
$3\text{-}CH_3$	•	1.5		0.7				
3-H		•						
$2\text{-}CO_2CH_3$			•					
2-H	2.8	3.5		•		1.7	2.2	4.5
CH				1.8	•			5.5
CH_2					4.0	•	23.6	5.0
CH_2				2.5		17.3	•	4.9
CH_3				0.6	1.9	1.9	2.0	•

Table A.8 Differential nOe results for **64d**

	$3\text{-}CH_3$	3-H	$2\text{-}CO_2CH_3$	2-H	CH	CH_2	CH_2	CH_3
$3\text{-}CH_3$	•	3.7		2.9				
3-H	4.2	•		1.6	1.0			
$2\text{-}CO_2CH_3$			•					
2-H	2.7	1.6		•		0.4		
CH				0.1	•	3.5	1.5	3.0
CH_2					2.8	•	13.8	3.1
CH_2				1.8	0.8	12.3	•	2.2
CH_3					1.7	1.5	1.0	•

Table A.9 Differential nOe results for **64e**

	$3\text{-}CH_3$	3-H	$2\text{-}CO_2CH_3$	2-H	CH	CH_2	CH_3
$3\text{-}CH_3$	•	4.5		2.6			
3-H	3.4	•		1.2			
$2\text{-}CO_2CH_3$			•				
2-H	3.1	2.4		•	1.5	4.2	
CH				1.4	•	2.5	2.8
CH_2				6.0	3.0	•	6.1
CH_3					2.0	2.7	•

A.IV X-ray Crystallographic Data

Table A.10 Final positional and equivalent thermal parameters for 37

Atom	X/A	Y/B	Z/C	Ueq
O(1)	0.3719(3)	0.0233(1)	0.7294(2)	0.034
C(1)	-0.1080(4)	-0.1387(1)	0.6257(3)	0.020
C(2)	-0.0699(4)	-0.1502(1)	0.5004(3)	0.020
C(3)	0.0428(4)	-0.1146(1)	0.4688(3)	0.021
C(3a)	0.0945(4)	-0.0796(1)	0.5745(3)	0.019
C(4)	0.2158(4)	-0.0402(1)	0.5890(3)	0.023
C(5)	0.2569(5)	-0.0166(1)	0.7033(3)	0.025
C(6)	0.1794(5)	-0.0331(1)	0.8016(3)	0.026
C(7)	0.0560(5)	-0.0720(1)	0.7864(3)	0.024
C(7a)	0.0093(4)	-0.0949(1)	0.6708(3)	0.020
C(8)	-0.2277(5)	-0.1597(1)	0.6842(3)	0.021
C(9)	-0.3533(5)	-0.2027(1)	0.6368(3)	0.027
C(10)	-0.5260(5)	-0.1800(2)	0.5794(4)	0.040
C(11)	-0.2548(3)	-0.1398(1)	0.8071(2)	0.022
C(12)	-0.3457(3)	-0.0936(1)	0.8165(2)	0.031
C(13)	-0.3709(3)	-0.0755(1)	0.9313(2)	0.039
C(14)	-0.3052(3)	-0.1037(1)	1.0368(2)	0.041
C(15)	-0.2144(3)	-0.1499(1)	1.0274(2)	0.037
C(16)	-0.1892(3)	-0.1680(1)	0.9126(2)	0.030
C(21)	-0.1411(3)	-0.1953(1)	0.4239(2)	0.020
C(22)	-0.2909(3)	-0.1908(1)	0.3386(2)	0.027
C(23)	-0.3625(3)	-0.2350(1)	0.2760(2)	0.034
C(24)	-0.2843(3)	-0.2838(1)	0.2988(2)	0.035
C(25)	-0.1345(3)	-0.2883(1)	0.3840(2)	0.031
C(26)	-0.0629(3)	-0.2441(1)	0.4466(2)	0.024
C(31)	0.1081(3)	-0.1104(1)	0.3501(2)	0.021
C(32)	0.1717(3)	-0.1539(1)	0.2962(2)	0.025
C(33)	0.2308(3)	-0.1488(1)	0.1845(2)	0.030
C(34)	0.2261(3)	-0.1001(1)	0.1268(2)	0.033
C(35)	0.1625(3)	-0.0566(1)	0.1807(2)	0.032
C(36)	0.1034(3)	-0.0617(1)	0.2924(2)	0.027
C(51)	0.4386(5)	0.0460(2)	0.6302(4)	0.037

Table A.11 Final positional and thermal parameters of calculated hydrogen atoms for 37.

Atom	X/A	Y/B	Z/C	U11
H(1)	0.2714(4)	-0.0291(1)	0.5202(3)	0.041
H(2)	0.2131(5)	-0.0170(1)	0.8824(3)	0.041
H(3)	0.0018(5)	-0.0832(1)	0.8557(3)	0.041
H(4)	-0.3068(5)	-0.2231(1)	0.5747(3)	0.043
H(5)	-0.3694(5)	-0.2256(1)	0.7052(3)	0.043
H(6)	-0.6023(5)	-0.2098(2)	0.5559(4)	0.043
H(7)	-0.5159(5)	-0.1592(2)	0.5064(4)	0.043
H(8)	-0.5729(5)	-0.1582(2)	0.6389(4)	0.043
H(12)	-0.3918(3)	-0.0739(1)	0.7424(2)	0.041
H(13)	-0.4347(3)	-0.0431(1)	0.9379(2)	0.041
H(14)	-0.3229(3)	-0.0909(1)	1.1175(2)	0.041
H(15)	-0.1683(3)	-0.1696(1)	1.1015(2)	0.041
H(16)	-0.1254(3)	-0.2004(1)	0.9060(2)	0.041
H(22)	-0.3458(3)	-0.1566(1)	0.3226(2)	0.041
H(23)	-0.4677(3)	-0.2318(1)	0.2161(2)	0.041
H(24)	-0.3346(3)	-0.3148(1)	0.2548(2)	0.041
H(25)	-0.0795(3)	-0.3226(1)	0.4000(2)	0.041
H(26)	0.0423(3)	-0.2473(1)	0.5065(2)	0.041
H(32)	0.1750(3)	-0.1881(1)	0.3368(2)	0.041
H(33)	0.2755(3)	-0.1794(1)	0.1466(2)	0.041
H(34)	0.2676(3)	-0.0966(1)	0.0483(2)	0.041
H(35)	0.1592(3)	-0.0224(1)	0.1402(2)	0.041
H(36)	0.0587(3)	-0.0311(1)	0.3303(2)	0.041
H(9)	0.5091(5)	0.0757(2)	0.6642(4)	0.043
H(10)	0.3456(5)	0.0586(2)	0.5675(4)	0.043
H(11)	0.5092(5)	0.0211(2)	0.5932(4)	0.043

Table A.12 Thermal parameters for 37

Atom	U11	U22	U33	U23	U13	U12
O(1)	0.035(2)	0.035(2)	0.034(2)	-0.014(1)	0.012(1)	-0.015(1)
C(1)	0.025(2)	0.017(2)	0.017(2)	0.002(1)	0.003(2)	0.004(2)
C(2)	0.021(2)	0.023(2)	0.016(2)	0.001(2)	0.002(2)	0.003(2)
C(3)	0.023(2)	0.020(2)	0.021(2)	-0.004(1)	0.003(2)	0.002(2)
C(3a)	0.015(2)	0.022(2)	0.020(2)	-0.001(2)	0.001(2)	0.006(2)
C(4)	0.024(2)	0.023(2)	0.025(2)	-0.002(2)	0.010(2)	-0.001(2)
C(5)	0.020(2)	0.025(2)	0.030(2)	-0.006(2)	0.003(2)	0.002(2)
C(6)	0.031(2)	0.027(2)	0.019(2)	-0.005(2)	0.001(2)	0.001(2)
C(7)	0.025(2)	0.024(2)	0.022(2)	0.001(2)	0.003(2)	0.001(2)
C(7a)	0.018(2)	0.021(2)	0.020(2)	-0.001(1)	0.002(2)	0.001(2)
C(8)	0.021(2)	0.020(2)	0.022(2)	0.003(2)	0.003(2)	0.001(2)
C(9)	0.035(2)	0.026(2)	0.023(2)	-0.003(2)	0.013(2)	-0.009(2)
C(10)	0.033(2)	0.052(3)	0.034(2)	-0.003(2)	0.007(2)	-0.013(2)
C(11)	0.019(2)	0.023(2)	0.024(2)	0.001(2)	0.006(2)	-0.003(2)
C(12)	0.031(2)	0.028(2)	0.035(2)	-0.005(2)	0.010(2)	-0.002(2)
C(13)	0.036(3)	0.035(2)	0.049(3)	-0.018(2)	0.019(2)	-0.004(2)
C(14)	0.044(3)	0.053(3)	0.030(2)	-0.019(2)	0.020(2)	-0.015(2)
C(15)	0.036(2)	0.049(3)	0.027(2)	0.000(2)	0.007(2)	-0.014(2)
C(16)	0.030(2)	0.037(2)	0.025(2)	0.002(2)	0.011(2)	-0.002(2)
C(21)	0.022(2)	0.027(2)	0.014(2)	-0.001(2)	0.007(2)	-0.002(2)
C(22)	0.027(2)	0.031(2)	0.022(2)	0.001(2)	0.004(2)	0.003(2)
C(23)	0.026(2)	0.048(3)	0.029(2)	-0.010(2)	0.002(2)	-0.003(2)
C(24)	0.034(3)	0.033(2)	0.042(2)	-0.015(2)	0.015(2)	-0.012(2)
C(25)	0.033(2)	0.023(2)	0.041(2)	-0.004(2)	0.016(2)	-0.002(2)
C(26)	0.024(2)	0.025(2)	0.025(2)	0.001(2)	0.009(2)	0.002(2)
C(31)	0.015(2)	0.026(2)	0.020(2)	-0.001(2)	0.000(2)	-0.003(2)
C(32)	0.025(2)	0.026(2)	0.024(2)	-0.002(2)	0.005(2)	-0.001(2)
C(33)	0.031(2)	0.035(2)	0.025(2)	-0.004(2)	0.009(2)	0.002(2)
C(34)	0.028(2)	0.051(3)	0.022(2)	0.002(2)	0.010(2)	-0.002(2)
C(35)	0.035(2)	0.033(2)	0.027(2)	0.004(2)	0.007(2)	0.001(2)
C(36)	0.026(2)	0.029(2)	0.026(2)	0.001(2)	0.004(2)	0.001(2)
C(51)	0.039(3)	0.035(2)	0.038(2)	-0.006(2)	0.014(2)	-0.014(2)

Table A.13 Bond Lengths and Angles for 37.

Bond Lengths	(Å)		
O(1)---C(5)	1.365(4)	C(4)---C(3a)	1.383(5)
O(1)---C(51)	1.416(4)	C(4)---C(5)	1.389(5)
C(1)---C(2)	1.493(4)	C(3a)---C(7a)	1.405(4)
C(1)---C(8)	1.344(4)	C(5)---C(6)	1.397(5)
C(1)---C(7a)	1.486(4)	C(6)---C(7)	1.383(5)
C(2)---C(3)	1.359(4)	C(7)---C(7a)	1.399(4)
C(2)---C(21)	1.486(4)	C(8)---C(9)	1.518(5)
C(3)---C(3a)	1.475(4)	C(8)---C(11)	1.496(4)
C(3)---C(31)	1.490(4)	C(9)---C(10)	1.526(5)

Bond Angles (degrees)

C(5)-O(1)-C(51)	117.6(3)	C(4)-C(5)-C(6)	120.5(3)
C(2)-C(1)-C(7a)	104.4(3)	C(5)-C(6)-C(7)	120.9(3)
C(2)-C(1)-C(8)	129.2(3)	C(6)-C(7)-C(7a)	119.2(3)
C(8)-C(1)-C(7a)	126.2(3)	C(1)-C(8)-C(9)	126.8(3)
C(1)-C(2)-C(3)	110.3(3)	C(1)-C(8)-C(11)	121.2(3)
C(1)-C(2)-C(21)	124.4(3)	C(9)-C(8)-C(11)	112.0(3)
C(3)-C(2)-C(21)	125.3(3)	C(8)-C(9)-C(10)	111.2(3)
C(2)-C(3)-C(3a)	108.2(3)	C(1)-C(7a)-C(3a)	107.9(3)
C(2)-C(3)-C(31)	127.7(3)	C(1)-C(7a)-C(7)	132.8(3)
C(3a)-C(3)-C(31)	124.1(3)	C(3a)-C(7a)-C(7)	119.1(3)
C(3a)-C(4)-C(5)	118.4(3)	C(8)-C(11)-C(12)	120.4(1)
C(3)-C(3a)-C(4)	129.1(3)	C(8)-C(11)-C(16)	119.6(1)
C(3)-C(3a)-C(7a)	108.9(3)	C(2)-C(21)-C(22)	121.5(2)
C(4)-C(3a)-C(7a)	121.7(3)	C(2)-C(21)-C(26)	118.3(2)
O(1)-C(5)-C(4)	124.4(3)	C(3)-C(31)-C(32)	121.3(1)
O(1)-C(5)-C(6)	115.1(3)	C(3)-C(31)-C(36)	118.7(1)

Table A.14 Final positional and equivalent thermal parameters for **38**.

Atom	X/A	Y/B	Z/C	Ueq
O(1)	0.1432(2)	0.8031(2)	0.5690(2)	0.029
C(1)	0.2975(2)	0.5150(2)	1.0754(2)	0.020
C(2)	0.2687(2)	0.3905(2)	1.0853(2)	0.020
C(3)	0.2287(2)	0.4048(2)	0.9709(2)	0.019
C(3a)	0.2227(2)	0.5393(2)	0.8814(2)	0.020
C(4)	0.1822(2)	0.5987(2)	0.7556(2)	0.020
C(5)	0.1810(2)	0.7316(2)	0.6923(2)	0.022
C(6)	0.2172(3)	0.8025(2)	0.7529(2)	0.026
C(7)	0.2572(3)	0.7419(2)	0.8773(2)	0.025
C(7a)	0.2659(2)	0.6064(2)	0.9422(2)	0.020
C(8)	0.3438(2)	0.5407(2)	1.1664(2)	0.021
C(9)	0.4071(3)	0.6510(2)	1.1329(2)	0.025
C(10)	0.3195(3)	0.7736(3)	1.1814(3)	0.033
C(11)	0.3338(2)	0.4654(1)	1.3080(1)	0.022
C(12)	0.4435(2)	0.4215(1)	1.3806(1)	0.028
C(13)	0.4315(2)	0.3551(1)	1.5126(1)	0.034
C(14)	0.3099(2)	0.3325(1)	1.5720(1)	0.034
C(15)	0.2002(2)	0.3764(1)	1.4994(1)	0.030
C(16)	0.2121(2)	0.4429(1)	1.3674(1)	0.025
C(21)	0.2944(1)	0.2594(1)	1.1938(1)	0.021
C(22)	0.4211(1)	0.1912(1)	1.2436(1)	0.025
C(23)	0.4443(1)	0.0663(1)	1.3397(1)	0.031
C(24)	0.3408(1)	0.0094(1)	1.3861(1)	0.035
C(25)	0.2140(1)	0.0775(1)	1.3364(1)	0.032
C(26)	0.1908(1)	0.2025(1)	1.2402(1)	0.025
C(31)	0.2003(1)	0.3016(1)	0.9339(1)	0.019
C(32)	0.2997(1)	0.1743(1)	0.9389(1)	0.025
C(33)	0.2717(1)	0.0787(1)	0.9037(1)	0.031
C(34)	0.1444(1)	0.1105(1)	0.8635(1)	0.035
C(35)	0.0450(1)	0.2378(1)	0.8586(1)	0.032
C(36)	0.0729(1)	0.3333(1)	0.8938(1)	0.025
C(51)	0.0978(3)	0.7374(3)	0.5051(2)	0.035

Table A.15 Final positional and thermal parameters of calculated hydrogen atoms for 38

Atom	X/A	Y/B	Z/C	U11
H(1)	0.1556(2)	0.5486(2)	0.7138(2)	0.035
H(2)	0.2144(3)	0.8964(2)	0.7072(2)	0.035
H(3)	0.2795(3)	0.7941(2)	0.9199(2)	0.035
H(4)	0.4944(3)	0.6106(2)	1.1708(2)	0.036
H(5)	0.4231(3)	0.6836(2)	1.0387(2)	0.036
H(6)	0.3713(3)	0.8353(3)	1.1626(3)	0.036
H(7)	0.2962(3)	0.7427(3)	1.2748(3)	0.036
H(8)	0.2356(3)	0.8217(3)	1.1376(3)	0.036
H(12)	0.5290(2)	0.4374(1)	1.3389(1)	0.035
H(13)	0.5086(2)	0.3243(1)	1.5636(1)	0.035
H(14)	0.3014(2)	0.2858(1)	1.6647(1)	0.035
H(15)	0.1147(2)	0.3606(1)	1.5411(1)	0.035
H(16)	0.1351(2)	0.4737(1)	1.3164(1)	0.035
H(22)	0.4939(1)	0.2312(1)	1.2110(1)	0.035
H(23)	0.5334(1)	0.0184(1)	1.3747(1)	0.035
H(24)	0.3571(1)	-0.0784(1)	1.4536(1)	0.035
H(25)	0.1413(1)	0.0375(1)	1.3689(1)	0.035
H(26)	0.1018(1)	0.2503(1)	1.2053(1)	0.035
H(32)	0.3891(1)	0.1520(1)	0.9671(1)	0.035
H(33)	0.3415(1)	-0.0107(1)	0.9072(1)	0.035
H(34)	0.1248(1)	0.0434(1)	0.8388(1)	0.035
H(35)	-0.0445(1)	0.2601(1)	0.8304(1)	0.035
H(36)	0.0031(1)	0.4227(1)	0.8903(1)	0.035
H(9)	0.0731(3)	0.8054(3)	0.4218(2)	0.036
H(10)	0.0177(3)	0.7136(3)	0.5527(2)	0.036
H(11)	0.1703(3)	0.6555(3)	0.4906(2)	0.036

Table A.16 Thermal parameters for 38.

Atom	U11	U22	U33	U23	U13	U12
O(1)	0.042(1)	0.0254(9)	0.0226(9)	-0.0009(7)	-0.0082(8)	-0.0156(8)
C(1)	0.020(1)	0.019(1)	0.020(1)	-0.007(1)	0.002(1)	-0.008(1)
C(2)	0.018(1)	0.018(1)	0.022(1)	-0.007(1)	0.002(1)	-0.006(1)
C(3)	0.020(1)	0.017(1)	0.020(1)	-0.0052(9)	0.001(1)	-0.007(1)
C(3a)	0.020(1)	0.020(1)	0.020(1)	-0.008(1)	0.002(1)	-0.007(1)
C(4)	0.023(1)	0.018(1)	0.021(1)	-0.006(1)	-0.002(1)	-0.007(1)
C(5)	0.023(1)	0.020(1)	0.019(1)	-0.003(1)	-0.001(1)	-0.007(1)
C(6)	0.034(2)	0.018(1)	0.026(1)	-0.004(1)	0.000(1)	-0.012(1)
C(7)	0.030(2)	0.022(1)	0.026(1)	-0.010(1)	0.001(1)	-0.012(1)
C(7a)	0.018(1)	0.019(1)	0.022(1)	-0.008(1)	0.002(1)	-0.007(1)
C(8)	0.018(1)	0.021(1)	0.025(1)	-0.009(1)	0.001(1)	-0.006(1)
C(9)	0.027(1)	0.029(1)	0.024(1)	-0.009(1)	-0.001(1)	-0.014(1)
C(10)	0.043(2)	0.031(1)	0.033(2)	-0.012(1)	0.002(1)	-0.021(1)
C(11)	0.027(1)	0.020(1)	0.023(1)	-0.010(1)	-0.002(1)	-0.008(1)
C(12)	0.030(2)	0.025(1)	0.033(1)	-0.010(1)	-0.007(1)	-0.009(1)
C(13)	0.042(2)	0.030(1)	0.032(2)	-0.008(1)	-0.016(1)	-0.009(1)
C(14)	0.057(2)	0.027(1)	0.022(1)	-0.006(1)	-0.006(1)	-0.016(1)
C(15)	0.040(2)	0.029(1)	0.024(1)	-0.009(1)	0.003(1)	-0.017(1)
C(16)	0.030(2)	0.024(1)	0.023(1)	-0.010(1)	-0.001(1)	-0.009(1)
C(21)	0.026(1)	0.020(1)	0.016(1)	-0.006(1)	0.002(1)	-0.008(1)
C(22)	0.026(1)	0.025(1)	0.022(1)	-0.009(1)	-0.001(1)	-0.006(1)
C(23)	0.034(2)	0.025(1)	0.026(1)	-0.004(1)	-0.005(1)	-0.004(1)
C(24)	0.050(2)	0.023(1)	0.025(1)	0.000(1)	-0.003(1)	-0.011(1)
C(25)	0.041(2)	0.026(1)	0.030(1)	-0.006(1)	0.002(1)	-0.016(1)
C(26)	0.027(1)	0.023(1)	0.025(1)	-0.007(1)	0.000(1)	-0.011(1)
C(31)	0.025(1)	0.017(1)	0.015(1)	-0.0041(9)	0.001(1)	-0.009(1)
C(32)	0.030(2)	0.021(1)	0.024(1)	-0.005(1)	-0.002(1)	-0.009(1)
C(33)	0.041(2)	0.019(1)	0.031(1)	-0.008(1)	-0.002(1)	-0.007(1)
C(34)	0.049(2)	0.026(1)	0.039(2)	-0.016(1)	-0.004(1)	-0.016(1)
C(35)	0.033(2)	0.032(1)	0.038(2)	-0.013(1)	-0.006(1)	-0.015(1)
C(36)	0.026(1)	0.023(1)	0.028(1)	-0.009(1)	0.001(1)	-0.011(1)
C(51)	0.049(2)	0.036(2)	0.024(1)	-0.007(1)	-0.005(1)	-0.019(1)

Table A.17 Bond Lengths and Angles for **38**.

Bond Lengths (Å).

O(1)---C(5)	1.378(3)
O(1)---C(51)	1.431(3)
C(1)---C(2)	1.491(3)
C(1)---C(8)	1.366(3)
C(1)---C(7a)	1.495(3)
C(2)---C(3)	1.363(3)
C(2)---C(21)	1.505(2)
C(3)---C(3a)	1.464(3)
C(3)---C(31)	1.490(2)
C(4)---C(3a)	1.403(3)
C(4)---C(5)	1.393(3)
C(3a)---C(7a)	1.403(3)
C(5)---C(6)	1.390(3)
C(6)---C(7)	1.388(3)
C(7)---C(7a)	1.399(3)
C(8)---C(9)	1.518(3)
C(8)---C(11)	1.504(2)
C(9)---C(10)	1.528(3)

Bond Angles (degrees)

C(5)-O(1)-C(51)	117.3(2)
C(2)-C(1)-C(7a)	104.7(2)
C(2)-C(1)-C(8)	128.1(2)
C(8)-C(1)-C(7a)	127.1(2)
C(1)-C(2)-C(3)	109.2(2)
C(1)-C(2)-C(21)	128.0(2)
C(3)-C(2)-C(21)	122.3(2)
C(2)-C(3)-C(3a)	109.6(2)
C(2)-C(3)-C(31)	127.6(2)
C(3a)-C(3)-C(31)	122.7(2)
C(3a)-C(4)-C(5)	117.6(2)
C(3)-C(3a)-C(4)	129.1(2)
C(3)-C(3a)-C(7a)	108.3(2)
C(4)-C(3a)-C(7a)	122.6(2)
O(1)-C(5)-C(4)	124.1(2)
O(1)-C(5)-C(6)	115.1(2)
C(4)-C(5)-C(6)	120.8(2)
C(5)-C(6)-C(7)	120.8(2)
C(6)-C(7)-C(7a)	120.2(2)
C(1)-C(8)-C(9)	122.4(2)
C(1)-C(8)-C(11)	123.4(2)
C(9)-C(8)-C(11)	114.2(2)
C(8)-C(9)-C(10)	114.4(2)
C(1)-C(7a)-C(3a)	108.1(2)
C(1)-C(7a)-C(7)	133.7(2)
C(3a)-C(7a)-C(7)	117.8(2)
C(8)-C(11)-C(12)	120.6(1)
C(8)-C(11)-C(16)	119.3(1)
C(2)-C(21)-C(22)	121.2(1)
C(2)-C(21)-C(26)	118.7(1)
C(3)-C(31)-C(32)	120.6(1)
C(3)-C(31)-C(36)	119.4(1)

Table A.18 Final positional and equivalent thermal parameters for **64e**

ATOM	X/A	Y/B	Z/C	Ueq
O(1)	0.101(2)	0.865(1)	0.853(1)	0.055
O(2)	-0.065(2)	1.166(1)	0.955(1)	0.083
O(3)	-0.022(2)	1.143(1)	0.787(1)	0.067
O(4)	-0.495(2)	0.511(1)	0.854(1)	0.074
C(1)	-0.051(3)	0.847(2)	0.768(2)	0.045
C(2)	-0.187(2)	0.980(1)	0.796(2)	0.041
C(3)	-0.321(2)	0.962(1)	0.869(2)	0.039
C(31)	-0.307(2)	0.804(2)	0.830(2)	0.040
C(4)	-0.431(3)	0.738(2)	0.863(2)	0.048
C(5)	-0.390(3)	0.592(2)	0.826(2)	0.050
C(6)	-0.248(3)	0.527(2)	0.778(2)	0.055
C(7)	-0.129(3)	0.599(2)	0.748(2)	0.063
C(71)	-0.168(2)	0.747(2)	0.781(2)	0.037
C(8)	0.013(3)	0.818(2)	0.660(2)	0.043
C(9)	0.163(3)	0.702(2)	0.634(2)	0.067
C(10)	0.261(4)	0.699(2)	0.540(2)	0.092
C(11)	-0.086(3)	1.111(2)	0.857(2)	0.046
C(12)	0.098(3)	1.266(2)	0.842(2)	0.104
C(13)	-0.506(3)	1.023(2)	0.843(2)	0.057
C(14)	-0.643(3)	0.574(2)	0.907(2)	0.084
C(111)	-0.132(2)	0.804(1)	0.563(1)	0.052
C(211)	-0.217(2)	0.684(1)	0.512(1)	0.059
C(311)	-0.349(2)	0.670(1)	0.422(1)	0.063
C(411)	-0.395(2)	0.778(1)	0.382(1)	0.083
C(511)	-0.309(2)	0.899(1)	0.433(1)	0.094
C(611)	-0.177(2)	0.912(1)	0.523(1)	0.067

Table A.19 Thermal parameters for **64e**

ATOM	U11	U22	U33	U23	U13	U12
O(1)	0.052(9)	0.022(7)	0.08(1)	-0.007(7)	0.010(8)	-0.015(6)
O(2)	0.13(2)	0.034(8)	0.08(1)	-0.012(9)	0.04(1)	-0.049(9)
O(3)	0.09(1)	0.023(7)	0.10(1)	0.016(8)	0.05(1)	-0.019(7)
O(4)	0.09(1)	0.025(7)	0.11(1)	0.013(8)	0.04(1)	-0.033(8)
C(1)	0.05(1)	0.02(1)	0.06(2)	0.00(1)	0.01(1)	-0.006(9)
C(2)	0.05(1)	0.007(8)	0.06(1)	0.000(9)	0.03(1)	-0.008(8)
C(3)	0.03(1)	0.003(8)	0.08(2)	0.003(9)	0.03(1)	-0.004(8)
C(31)	0.03(1)	0.011(9)	0.07(2)	-0.001(9)	0.01(1)	-0.014(9)
C(4)	0.08(2)	0.03(1)	0.04(1)	0.02(1)	0.01(1)	-0.02(1)
C(5)	0.05(1)	0.03(1)	0.07(2)	0.02(1)	0.02(1)	-0.01(1)
C(6)	0.06(1)	0.03(1)	0.08(2)	0.01(1)	0.02(1)	-0.02(1)
C(7)	0.07(2)	0.02(1)	0.08(2)	0.01(1)	0.01(1)	0.01(1)
C(71)	0.03(1)	0.015(9)	0.06(1)	0.000(9)	0.01(1)	-0.004(8)
C(8)	0.06(1)	0.019(9)	0.05(1)	0.01(1)	0.02(1)	-0.010(9)
C(9)	0.08(2)	0.03(1)	0.08(2)	0.00(1)	0.04(1)	0.00(1)
C(10)	0.14(2)	0.04(1)	0.11(2)	0.01(1)	0.07(2)	-0.03(1)
C(11)	0.06(1)	0.02(1)	0.05(1)	-0.02(1)	0.04(1)	-0.009(9)
C(12)	0.11(2)	0.03(1)	0.16(3)	0.00(1)	0.03(2)	-0.06(1)
C(13)	0.07(2)	0.02(1)	0.09(2)	0.01(1)	0.04(1)	0.00(1)
C(14)	0.08(2)	0.05(1)	0.14(2)	0.02(1)	0.05(2)	-0.02(1)
C(111)	0.09(2)	0.03(1)	0.04(1)	-0.01(1)	0.03(1)	-0.02(1)
C(211)	0.08(2)	0.04(1)	0.05(1)	-0.01(1)	0.03(1)	-0.03(1)
C(311)	0.10(2)	0.04(1)	0.05(2)	0.02(1)	0.03(1)	-0.01(1)
C(411)	0.10(2)	0.08(2)	0.06(2)	0.02(2)	0.01(2)	-0.03(2)
C(511)	0.14(3)	0.06(2)	0.08(2)	0.02(2)	0.01(2)	-0.03(2)
C(611)	0.10(2)	0.06(2)	0.05(2)	0.02(1)	0.01(2)	-0.02(1)

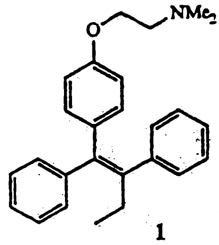
Table A.20 Bond Lengths and Angles for **64e**

Bond Lengths (Å)

O(1)---C(1)	1.44(2)	C(5)---C(6)	1.33(3)
O(3)---C(11)	1.28(2)	C(6)---C(7)	1.45(3)
O(3)---C(12)	1.56(2)	C(7)---C(71)	1.47(2)
O(4)---C(5)	1.42(2)	C(8)---C(9)	1.55(3)
O(4)---C(14)	1.40(3)	C(8)---C(111)	1.52(2)
C(1)---C(2)	1.61(2)	C(9)---C(10)	1.54(3)
C(1)---C(8)	1.50(3)	C(31)---C(71)	1.30(2)
C(1)---C(71)	1.54(2)	O(2)---C(11)	1.19(2)
C(2)---C(3)	1.59(2)	C(3)---C(31)	1.54(2)
C(2)---C(11)	1.55(2)	C(4)---C(5)	1.44(2)
C(3)---C(13)	1.52(3)	C(4)---C(31)	1.46(3)

Bond Angles (degrees)

C(11)-O(3)-C(12)	112(2)	C(1)-C(8)-C(111)	115(2)
C(5)-O(4)-C(14)	118(2)	C(9)-C(8)-C(111)	112(2)
O(1)-C(1)-C(2)	110(1)	C(8)-C(9)-C(10)	113(2)
O(1)-C(1)-C(71)	107(2)	O(3)-C(11)-O(2)	127(2)
O(1)-C(1)-C(8)	109(2)	O(3)-C(11)-C(2)	108(2)
C(2)-C(1)-C(71)	98(1)	C(2)-C(11)-O(2)	123(2)
C(2)-C(1)-C(8)	111(2)	C(3)-C(31)-C(4)	118(2)
C(8)-C(1)-C(71)	120(1)	C(3)-C(31)-C(71)	113(1)
C(1)-C(2)-C(3)	107(1)	C(4)-C(31)-C(71)	127(2)
C(1)-C(2)-C(11)	110(2)	C(1)-C(71)-C(31)	115(1)
C(3)-C(2)-C(11)	111(1)	C(1)-C(71)-C(7)	124(2)
C(2)-C(3)-C(31)	98(1)	C(7)-C(71)-C(31)	120(2)
C(2)-C(3)-C(13)	110(2)	C(8)-C(111)-C(211)	120.0(8)
C(13)-C(3)-C(31)	113(1)	C(8)-C(111)-C(611)	120.0(8)
C(5)-C(4)-C(31)	110(2)	C(5)-C(6)-C(7)	121(2)
O(4)-C(5)-C(4)	118(2)	C(6)-C(7)-C(71)	115(2)
O(4)-C(5)-C(6)	115(2)	C(1)-C(8)-C(9)	113(2)
C(4)-C(5)-C(6)	125(2)		



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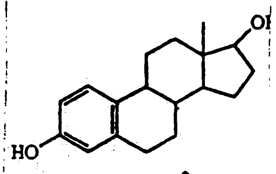

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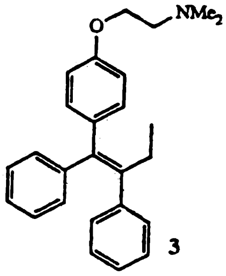

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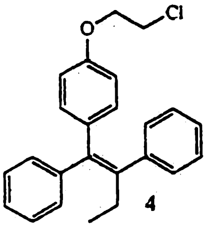

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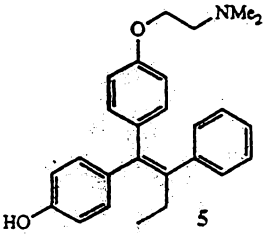

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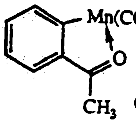

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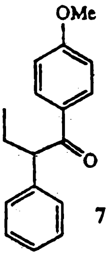

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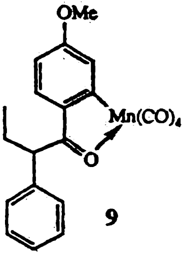

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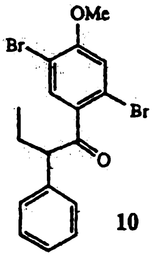

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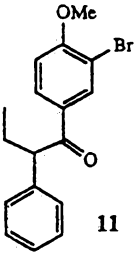

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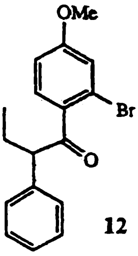

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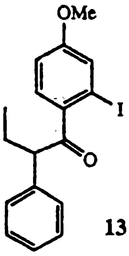

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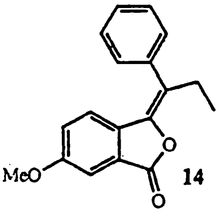

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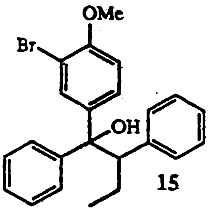

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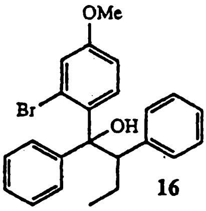

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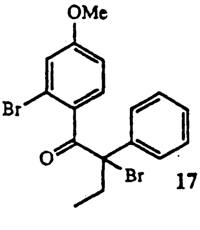

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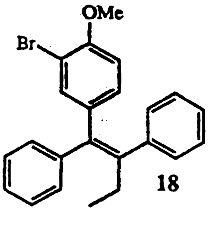

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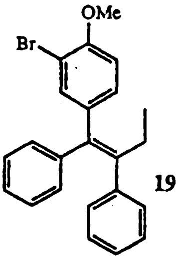

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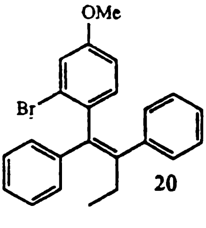

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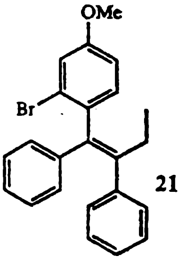

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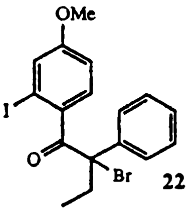

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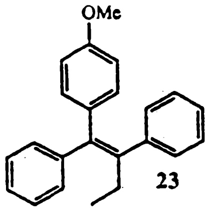

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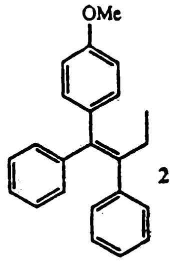

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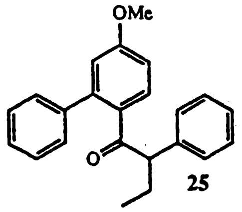

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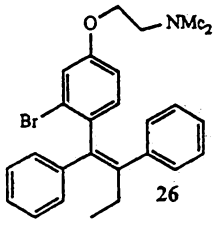

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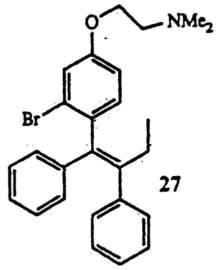

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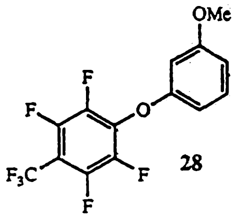

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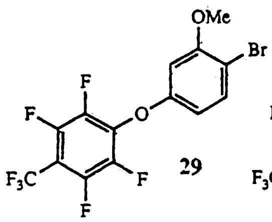

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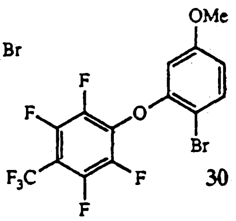

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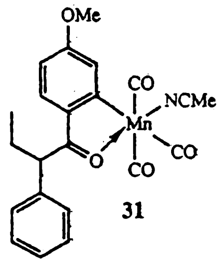

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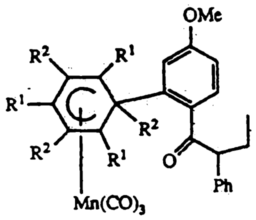
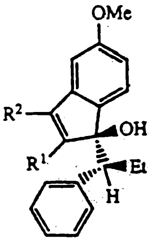


32 : R^1 = Ph, R^2 = H

34 : R^1 = Ph, R^2 = Ph

41 : R^1 = $SiMe_3$, R^2 = H



33a : R^1 = Ph, R^2 = H

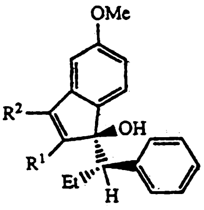
36a : R^1 = Ph, R^2 = Ph

39a : R^1 = R^2 = CO_2Me

42a : R^1 = $SiMe_3$, R^2 = H

43a : R^1 = n-Pr, R^2 = CH_3

46a : R^1 = CH_2CH_2OH
R^2 = H



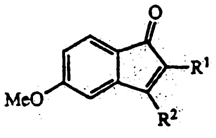
33b : R^1 = Ph, R^2 = H

36b : R^1 = Ph, R^2 = Ph

39b : R^1 = R^2 = CO_2Me

43b : R^1 = n-Pr, R^2 = CH_3

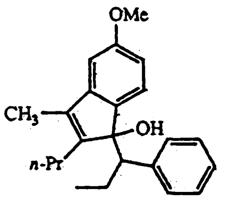
46b : R^1 = CH_2CH_2OH
R^2 = H



35 : R^1 = Ph, R^2 = Ph

40 : R^1 = R^2 = CO_2Me

44 : R^1 = n-Pr, R^2 = CH_3



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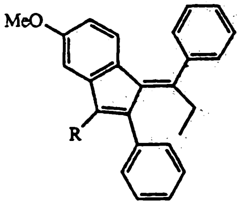
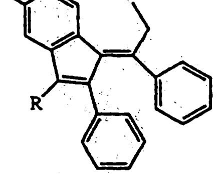


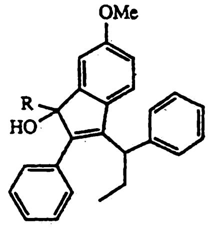
37 : R = Ph

52 : R = H



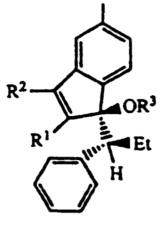
38 : R = Ph

53 : R = H



48 : R = Ph

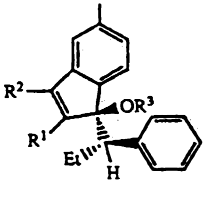
49 : R = H



47a : R^1 = Ph, R^2 = Ph
R^3 = OEt

50a : R^1 = Ph, R^2 = H
R^3 = OAc

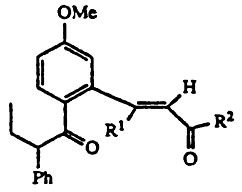
51a : R^1 = CHCHOAc,
R^2 = H, R^3 = OAc



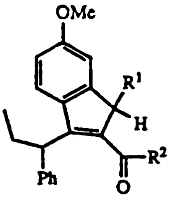
47b : R^1 = Ph, R^2 = Ph
R^3 = OEt

50b : R^1 = Ph, R^2 = H
R^3 = OAc

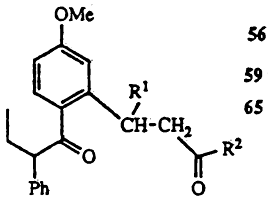
51b : R^1 = CHCHOAc,
R^2 = H, R^3 = OAc



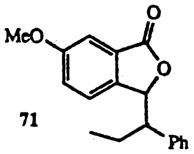
54 : $R^1 = H, R^2 = OCH_3$
60 : $R^1 = H, R^2 = CH_3$
63 : $R^1 = CH_3, R^2 = OCH_3$



55 : $R^1 = H, R^2 = OCH_3$
58 : $R^1 = H, R^2 = CH_3$
62 : $R^1 = CH_3, R^2 = OCH_3$



56 : $R^1 = H, R^2 = OCH_3$
59 : $R^1 = H, R^2 = CH_3$
65 : $R^1 = CH_3, R^2 = OCH_3$



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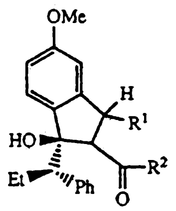
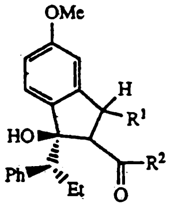
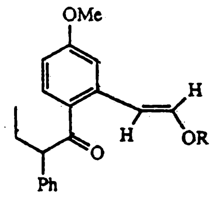


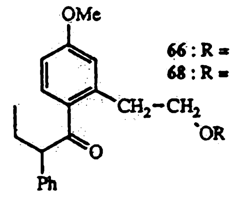
57a : $R^1 = H, R^2 = OCH_3$
61a : $R^1 = H, R^2 = CH_3$



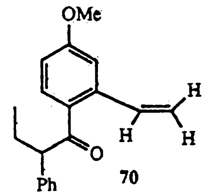
57b : $R^1 = H, R^2 = OCH_3$
61b : $R^1 = H, R^2 = CH_3$



67 : R = Me
69 : R = Et



66 : R = Me
68 : R = Et



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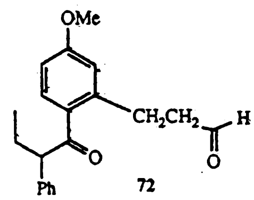

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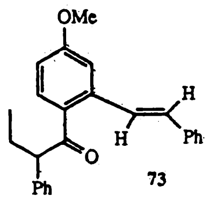

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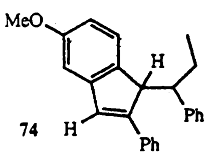

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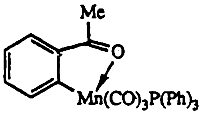

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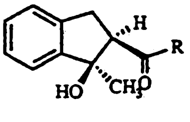
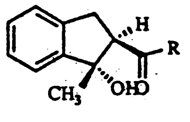
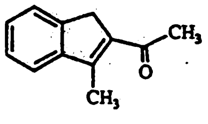


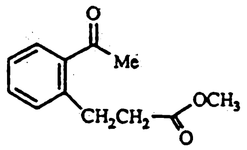




76a : $R = CH_3$
79a : $R = OCH_3$

76b : $R = CH_3$
79b : $R = OCH_3$

77



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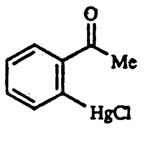

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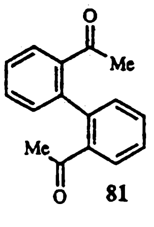

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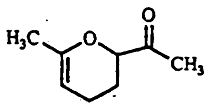

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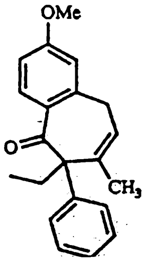

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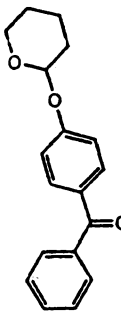
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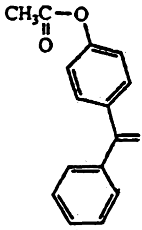
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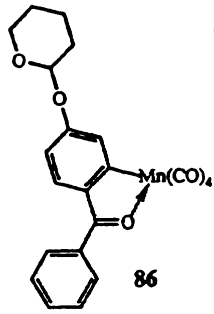
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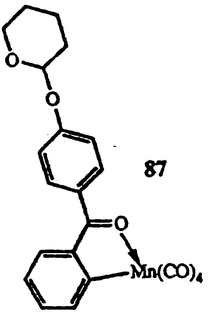
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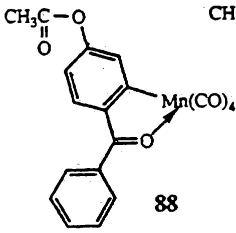
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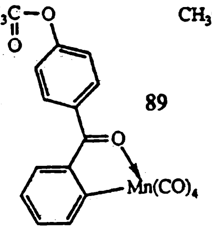
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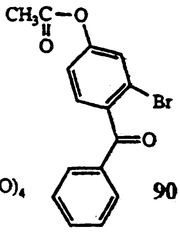
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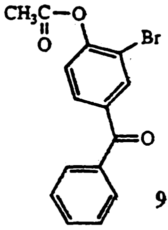
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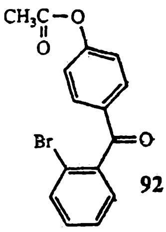
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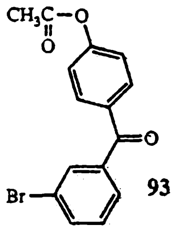
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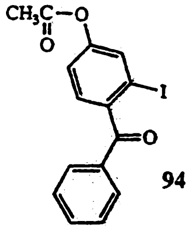
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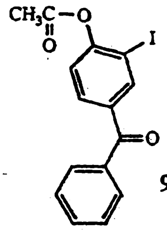
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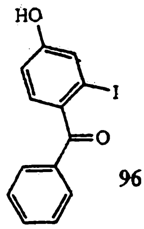
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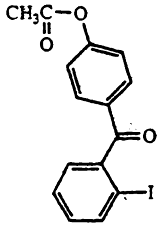
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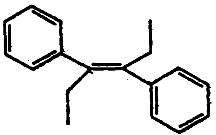
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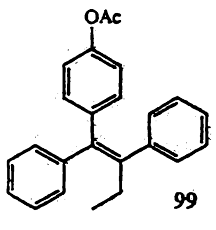
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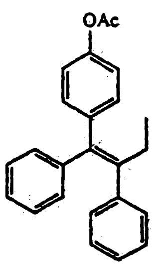
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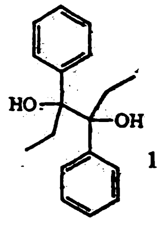
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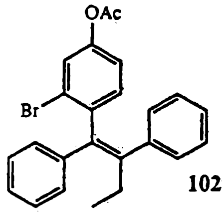
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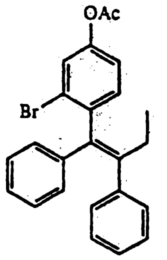
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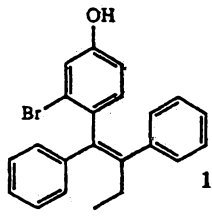
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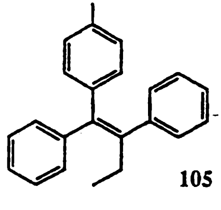
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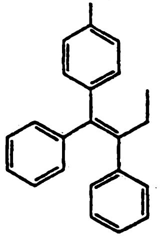
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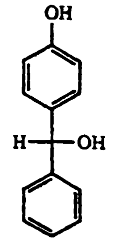
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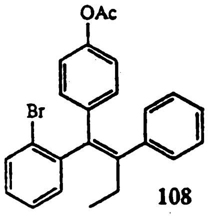
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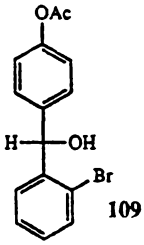
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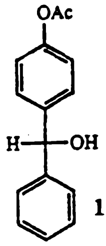
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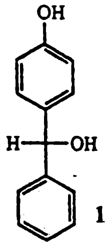
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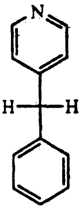
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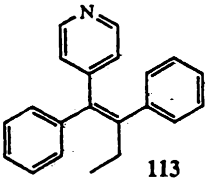
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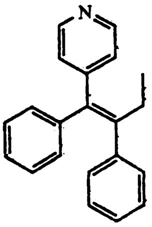
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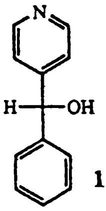
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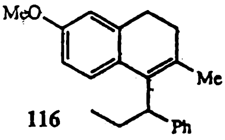
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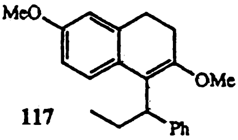
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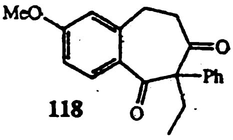
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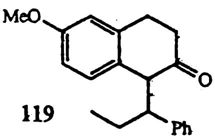
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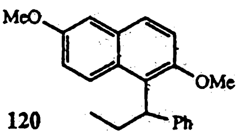
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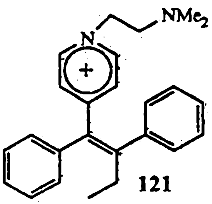
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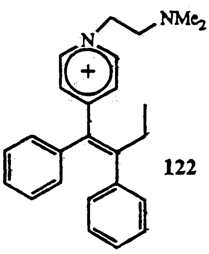
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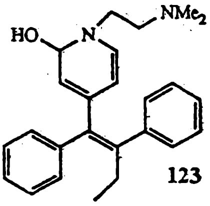
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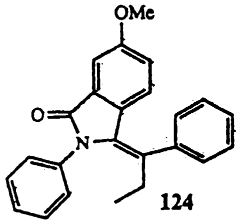
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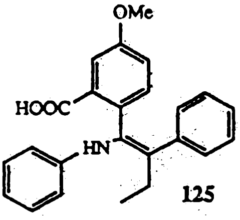
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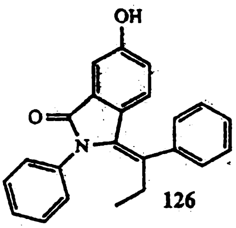
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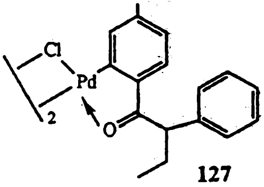
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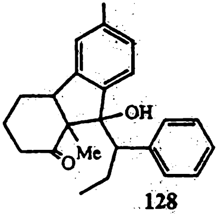
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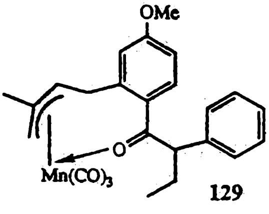
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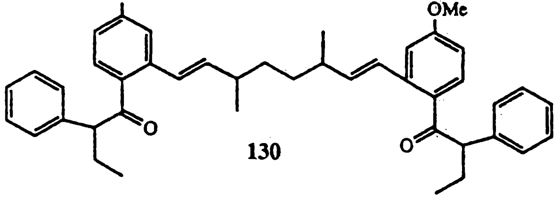
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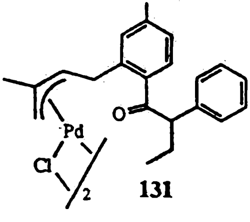
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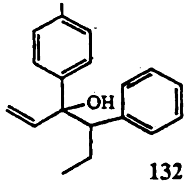
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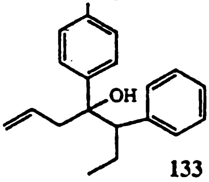
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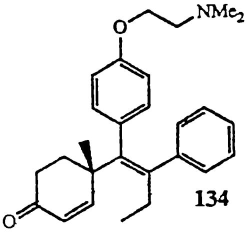

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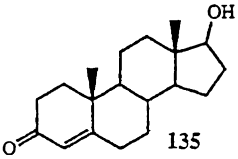

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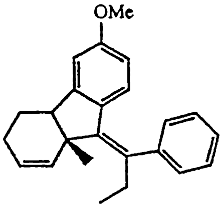

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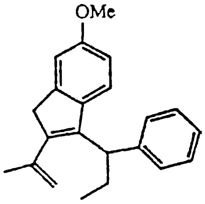

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