Application of the Baylis-Hillman Reaction in the Preparation of Quinoline Derivatives

THESIS

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by

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ABSTRACT

The reaction of various 2-nitrobenzaldehyde derivatives with methyl vinyl ketone (MVK) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) has afforded the Baylis-Hillman adducts in moderate to good yield. Dissolution of the catalyst in the solvent before the addition of the aldehyde was observed to improve the yield. Reduction of the Baylis-Hillman adducts was effected by catalytic hydrogenation using a 10% palladium-on-carbon catalyst in ethanol to give quinoline and quinoline-*N*-oxide derivatives and, in some cases, acyclic reduction products. All products were characterised using NMR and, where appropriate, HRMS methods.

Selected quinoline-*N*-oxides were successfully converted to their corresponding quinoline derivatives using phosphorus tribromide (PBr_3) and DMF as solvent. Conjugate addition of the benzylamine and piperidine nucleophiles to the Baylis-Hillman adducts was also investigated but proved problematic, with one of the substrates undergoing a retro-Baylis-Hillman reaction to afford the aldehyde in *ca.* 40% yield, but seemingly only traces of the required product. Perkin-type coupling of two 2-methylquinolines with benzaldehyde was successfully effected to afford the desired styrylquinoline derivatives confirming the potential of the Baylis-Hillman approach to the construction of the analogues of known HIV-1 integrase inhibitors.

Three ^{13}C NMR chemical shift prediction programmes, *viz.*, ChemWindow, neural network and HOSE (hierarchically ordered spherical description of environment) methods were applied to selected representative compounds prepared in the project. The results from the three programmes correlated reasonably well with the experimental carbon-13 chemical shift data for each of the selected compounds.

ACKNOWLEDGEMENTS

First and foremost I would like to thank my supervisor, Professor Perry Kaye for his continued support, guidance and encouragement throughout this project. Without you Prof. this project wouldn't have been possible. I feel both honoured and privileged to have worked under your supervision.

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CONTENTS

1 INTRODUCTION

1.1 Heterocyclic compounds

Heterocyclic compounds can be divided into two groups, *viz.*, heteroaromatic and heteroalicyclic.[1] Heteroaromatic compounds are further grouped according to the number of ring atoms they comprise, typically ranging from three-membered to seven-membered heterocyclic compounds. For example, six-membered monoheteroaromatic compounds **1** can be viewed as being derived from benzene **2** by replacing one of the methyne (CH) groups with S^+, N, O^+ or BH^-, whereas in the five-membered analogues **3**, NH, O or S replaces CH^- in the cyclopentadienyl anion **4**.[1]

1

2

3

4

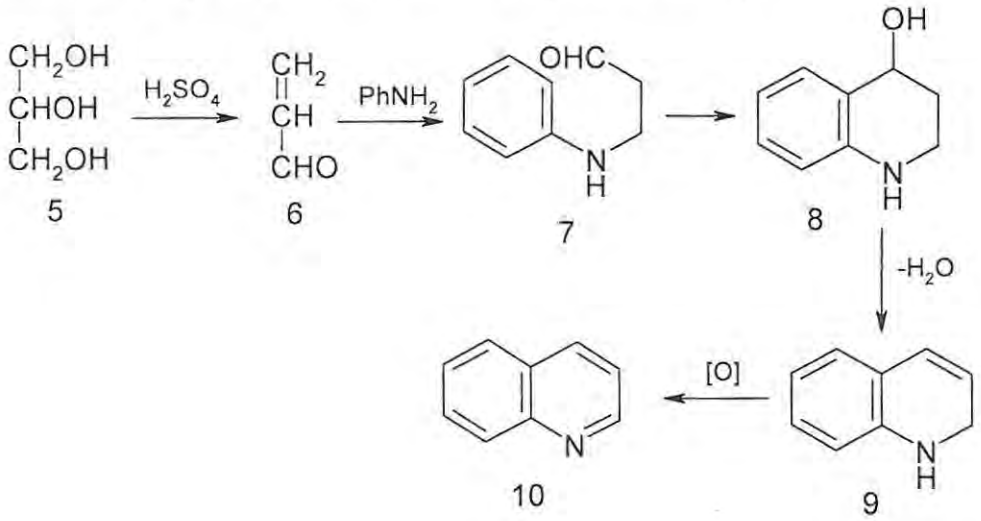
pyridine	X = N	pyrrole	X = NH
pyrylium cation	$X = O^+$	furan	X = O
thiinium cation	$X = S^+$	thiophene	X = S
boratobenzene	$X = BH^-$		

1.1.1 Synthesis of heterocyclic compounds

The chemistry of the heterocyclic compounds is enormously wide, and has been covered in numerous and extensive reviews.[1-7] Given the focus of the present study, only the synthesis of quinoline derivatives will be considered here. Quinoline, which may be viewed as the fusion of a benzene ring to a pyridine ring, is a liquid that boils at 240°C and has a pleasant, characteristic smell.[2,3] Quinoline was first isolated from coal-tar[3,5,7] in 1834 and was later obtained by distillation of the alkaloid, cinchonine, from potash in 1842.[3,5,7] However, the isolation of quinoline from cinchonine and quinine by Gerhardt[6] led to a rigorous search for derivatives containing the quinoline nucleus, and many of these compounds were later found to be important antimalarials,[6] a number of which have been synthesised (see Section 1.3).

1.1.1.1 The Skraup quinoline synthesis[1,2,45]

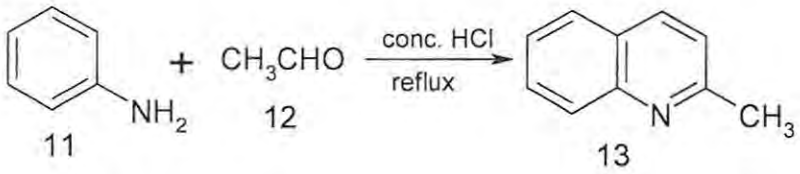
Although there are variations, the classic Skraup quinoline synthesis involves the reaction between an arylamine and glycerol.[3,5,8] Usually, glycerol **5** is treated with a strong acid to afford an α,β-unsaturated carbonyl system **6** which is then reacted with the arylamine to give intermediates **7** - **9** which lead finally to the production of quinoline **10** (or quinoline derivatives, depending on the choice of reagents; Scheme 1).[3,7,9,10]



Scheme 1

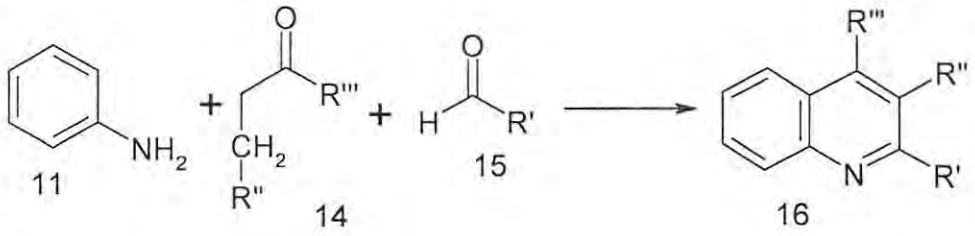
1.1.1.2 The Doebner-von Miller synthesis[1,2,4,5]

This is an example of a modification of the Skraup synthesis. In this reaction, an arylamine **11** is heated with an aldehyde **12** in the presence of hydrochloric acid (Scheme 2).[5] It was observed that better yields were afforded if *m*-nitrobenzenesulfonic acid was used as an oxidant instead of air. Aldehyde precursors may be used instead of the aldehyde itself and zinc chloride is sometimes used as a condensing agent in place of HCl. The mechanism involves formation of an α,β-unsaturated carbonyl intermediate (*e.g.*, crotonaldehyde from acetaldehyde) through an acid-catalysed aldol condensation, followed by conjugate addition, cyclisation and elimination of water to afford the quinoline.[1,2,4,5]



Scheme 2

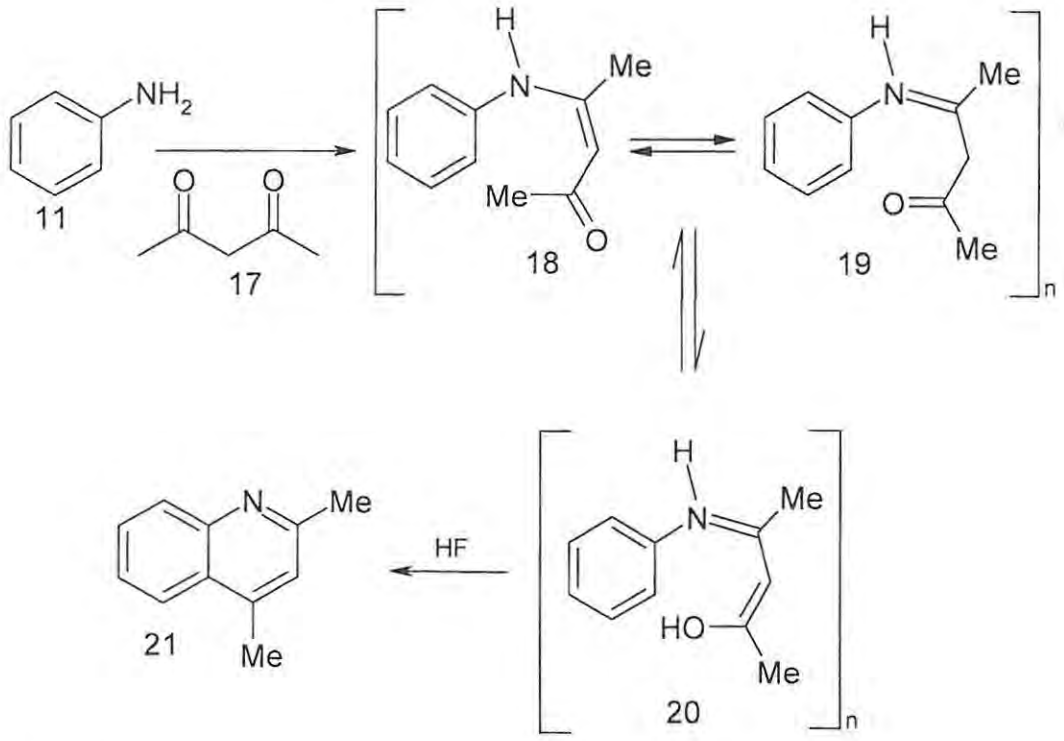
A variation of this reaction is the Bayer synthesis in which a mixture of a ketone **14** and an aldehyde **15** is saturated with hydrogen chloride so that aldolisation and dehydration can occur. The mixture is heated with an arylamine **11** to give the quinoline derivative **16**[3] (Scheme 3).



Scheme 3

1.1.1.3 The Combes synthesis[1,2,4]

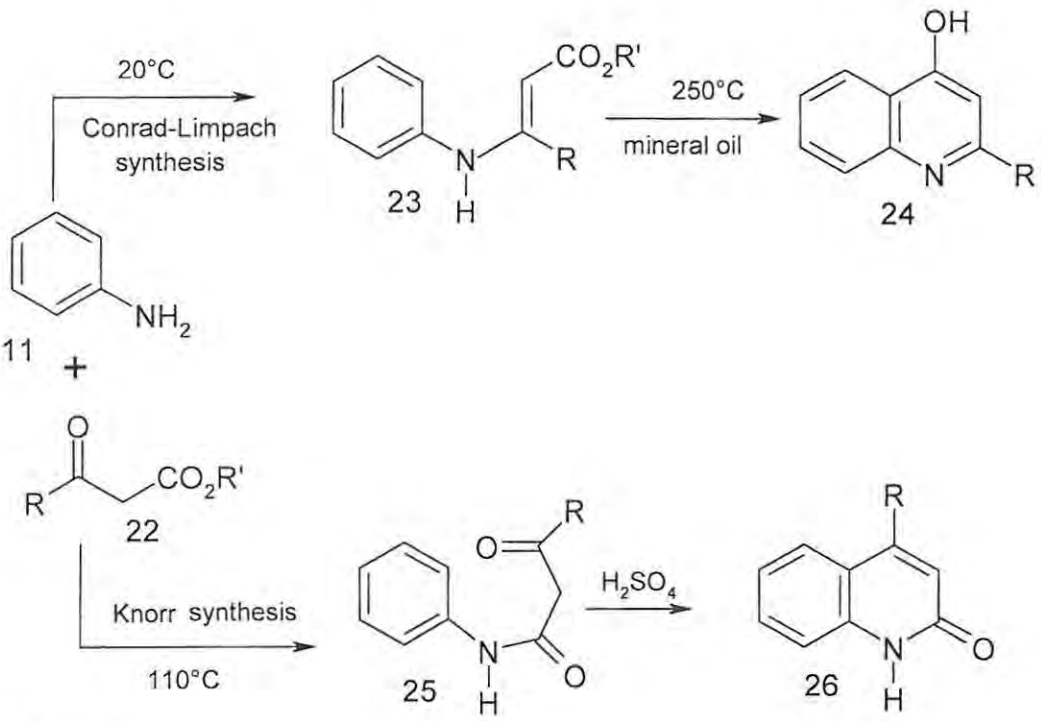
2,4-Disubstituted quinolines are formed as a result of heating mono-anils of 1,3-diketones with sulphuric acid. Thus, acetylacetone **17** (pentan-2,4-dione) and aniline afford the enamine **18**, which is in equilibrium with the imine **19**. The next step is enolization to give the intermediate **20**, followed by cyclization with HF to yield 2,4-dimethylquinoline **21** (Scheme 4).[2] The use of 2-nitrobenzaldehyde affords the corresponding 3-substituted quinolines. Another approach attributed to Combes involves the reaction of 2-substituted malonic esters with an aromatic amine in diphenyl ether under nitrogen; the product which results is a 3-substituted 4-hydroxy-2-quinoline.[1,2,4]



Scheme 4

1.1.1.4 The Conrad-Limpach and the Knorr synthesis[2,4,5,8]

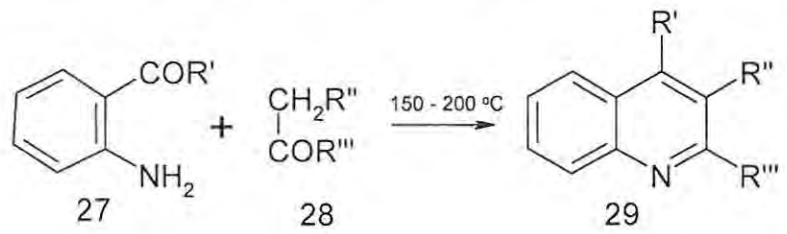
These two reactions involve the same reactants but behave differently at different temperatures. The anilinocrotonoate ester **23** is formed as a result of condensation of analine **11** at the more reactive keto-group of the β-keto ester **22** at low temperatures; the product cyclizes on heating to afford a 4-quinolone, which tautomerises to the hydroxyquinoline **24**. The condensation of the amine **11** at the ester carbonyl, however, is favoured at higher temperatures; ring closure is achieved by heating the intemediate anilide **25** alone or with sulphuric acid to give the 2-quinolone **26.** This product can then be reduced to the quinoline (Scheme 5).[2,4,5,8] Treatment of product **26** with phosphoryl chloride affords 2-chloroquinolines,[5] reduction of which also gives the quinolines.[11]



Scheme 5

1.1.1.5 The Friedlander synthesis[1,2,4,5]

The Friedlander synthesis involves the formation of quinolines *via* condensation, in aqueous alkali, of an *o*-amino aromatic aldehyde or ketone **27** with a carbonyl compound **28** possessing an α-methylene group.[3,4] The procedure involves refluxing an aqueous or alcoholic solution of the reactants in the presence of a base, or simply heating the reactants in the absence of base at 150 – 200°C (Scheme 6).[4] It was later discovered that acids are also very effective catalysts for this reaction, but that the Friedlander synthesis

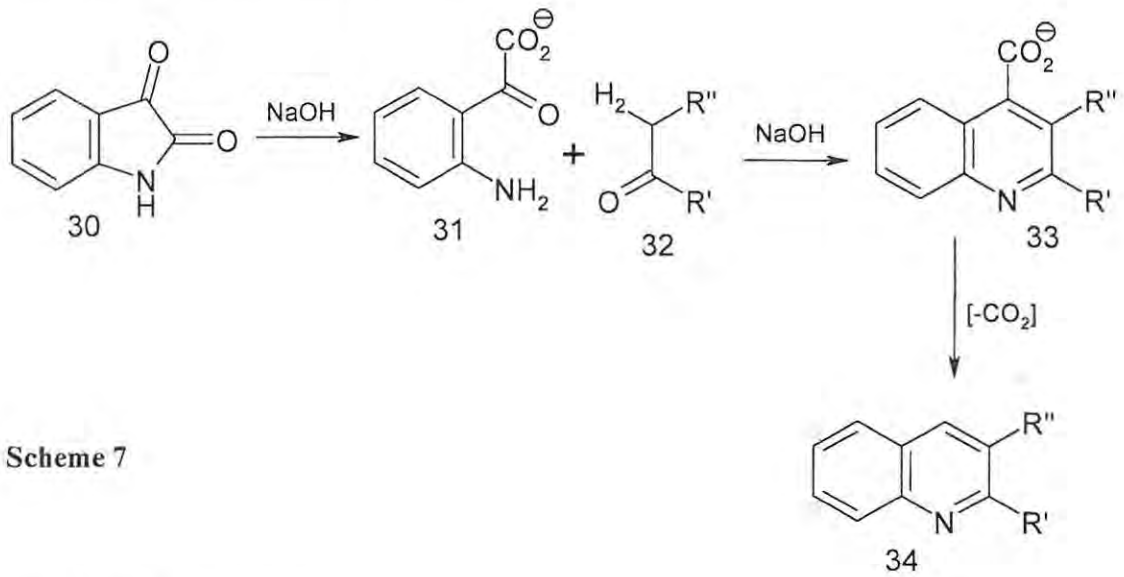


Scheme 6

could not be readily adapted for the preparation of quinoline derivatives bearing substituents on the benzene ring.[4] This drawback can be overcome by use of the Pfitzinger synthesis.

1.1.1.6 The Pfitzinger synthesis[1,2,4,5]

In the Pfitzinger synthesis, the *o*-aminobenzaldehyde employed in the Friedlander synthesis is replaced by an anion of isatinic acid **31**, which is usually obtained from the cleavage of the lactam ring of isatin **30** by base. The isatinic acid reacts with a ketone **32** to give a quinoline-4-carboxylic acid derivative **33**, which can be decarboxylated to the corresponding quinoline **34** (Scheme 7).[2,7]

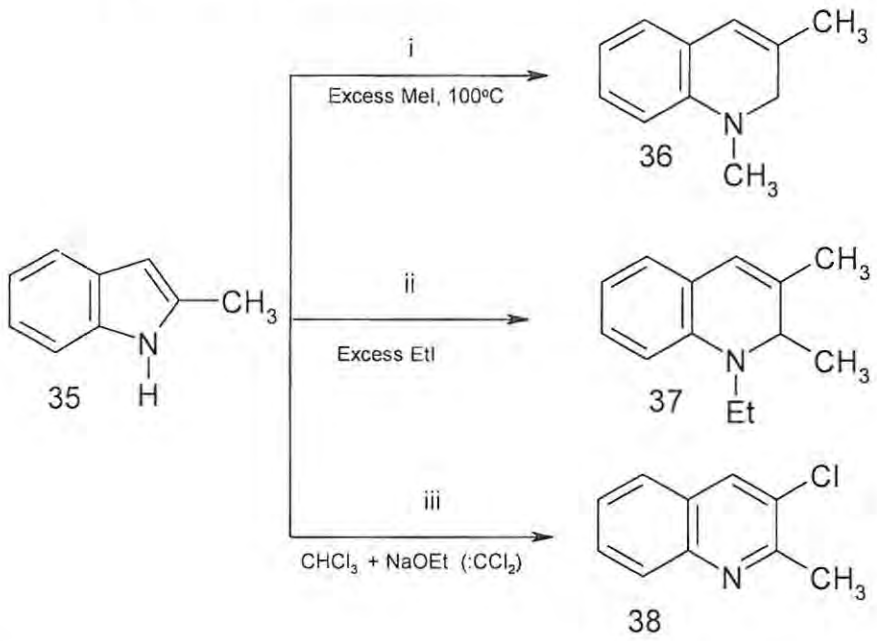


Scheme 7

1.1.1.7 Ring enlargement

Ring enlargement of the indole derivative **35** can lead to three different quinoline compounds.[12] The type of compound formed depends on the conditions of the reaction. As illustrated in Scheme 8, ring enlargement in the presence of excess methyl iodide (route i) yields a quinoline derivative **36** with methyl substituents at positions 1 and 3, but if the reaction is carried out in the presence of excess ethyl iodide (route ii), a quinoline derivative **37** with an ethyl substituent at position 1 and methyl substituents at positions 2

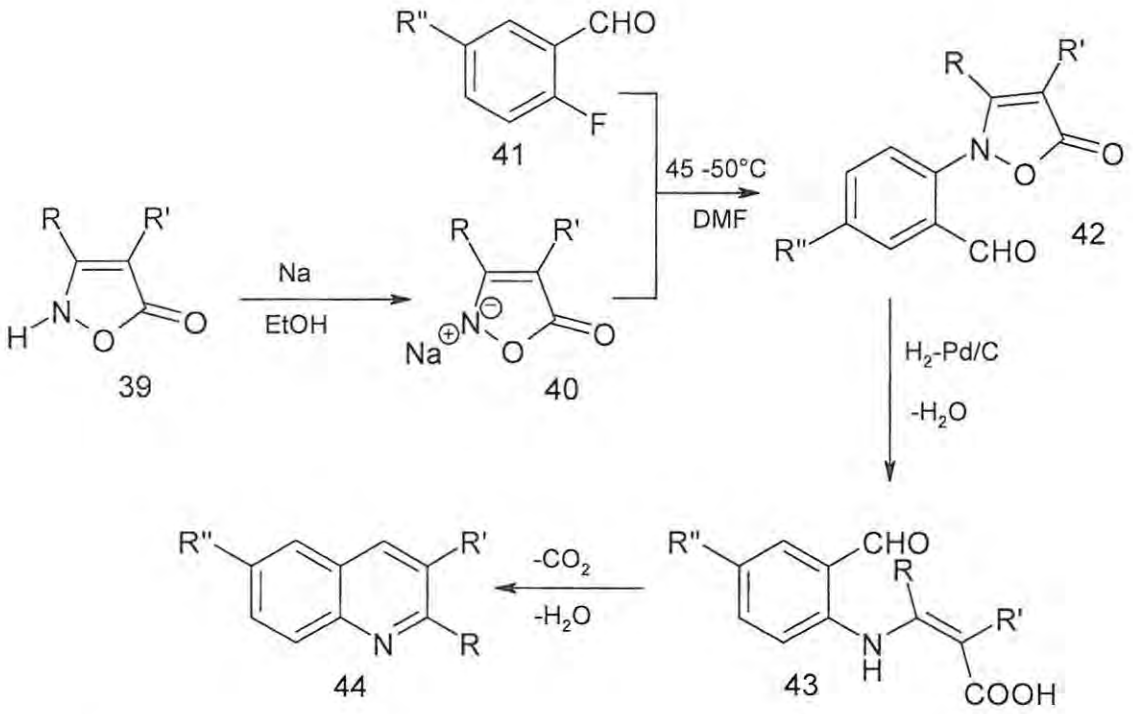
and 3 is obtained. However, a chloroquinoline derivative **38** can be obtained if the ring enlargement is carried out in chloroform under basic conditions (route iii),[12] the reaction involving insertion of dichlorocarbene.



Scheme 8

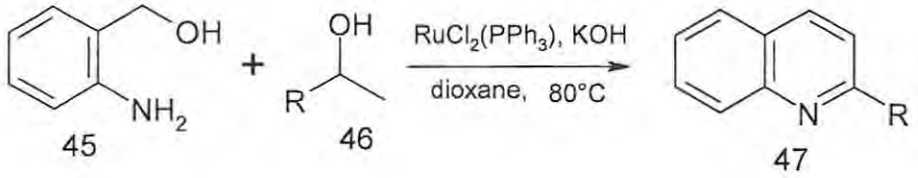
1.1.1.8 Other quinoline syntheses

Recently, Abbiati *et al.*[13] reported the synthesis of quinoline derivatives from isoxazolin-5(*2H*)-ones **39** *via* heterocyclic ring transformation. Their method involves three steps: i) the isolation of the 3,4-disubstituted isoxazolin-5(*2H*)-one salt **40**; ii) nucleophilic displacement of fluoride in 2-fluorobenzaldehyde derivatives **41** by the salt **40**; and iii) hydrogenolysis of the heterocycle using palladium-on-carbon as a catalyst, followed by cyclization, decarboxylation and elimination of water (Scheme 9). These researchers indicated that this method is particularly suitable for highly substituted quinoline systems. They also mentioned the fact that it is possible to make other heterocyclic systems through this method using appropriate suitable substrates.



Scheme 9

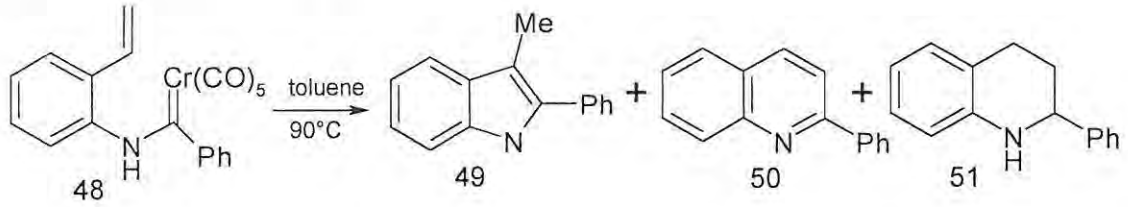
Cho *et al.*[14] have synthesised quinoline derivatives through Ru-catalysed oxidative coupling of 2-aminobenzyl alcohol **45** with a second alcohol **46** followed by cyclization. The reaction mechanism is believed to proceed *via* a series of steps. Firstly, both reactants are oxidised to their corresponding carbonyl compounds. A crossed aldol reaction, catalysed by KOH, then takes place, leading to the formation of an α,β–unsaturated ketone, cyclodehydration of which affords the quinoline derivative **47**.



Scheme 10

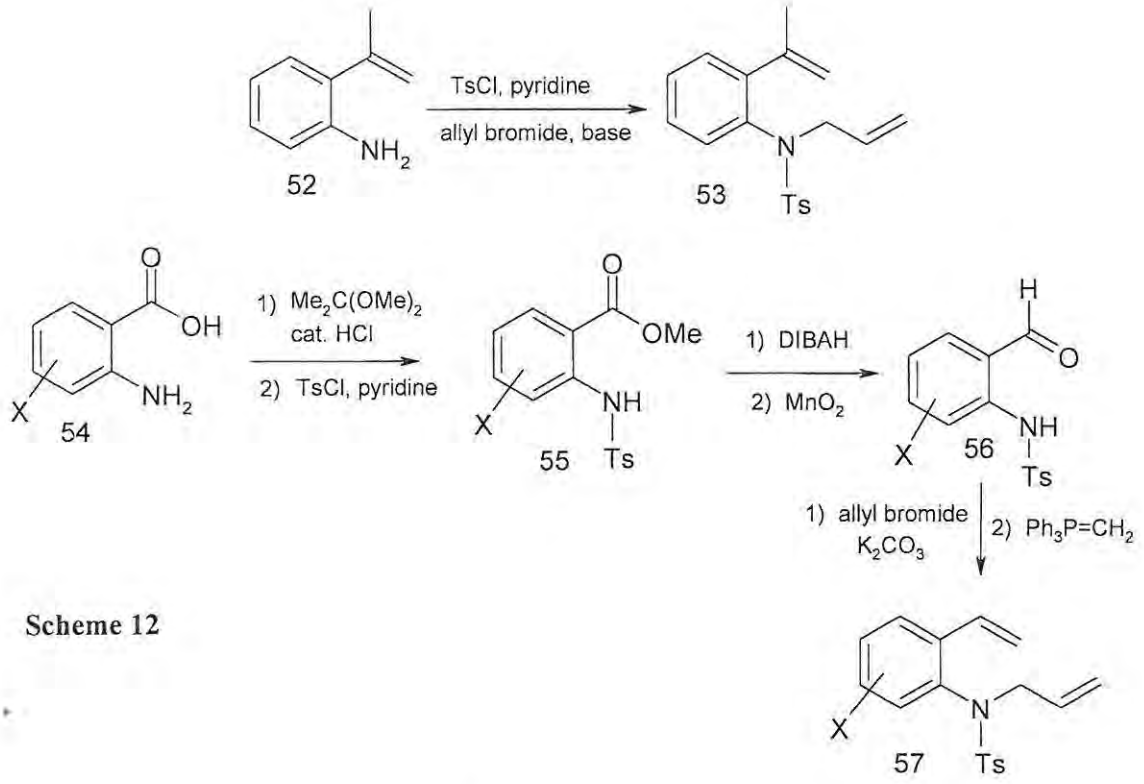
Söderberg *et al.*[15] have demonstrated that the thermal decomposition of *N*-(2-alkenyl-phenyl)amino Fischer chromium carbenes **48** produces quinolines and/or indoles. They also indicated that the ratio and yield of the products depend on electronic and steric

factors, and on the solvent used. One major drawback of this reaction is the isolation of 2-aminostyrenes from which compound **48** is initially synthesised. One example of this approach is shown in Scheme 11.

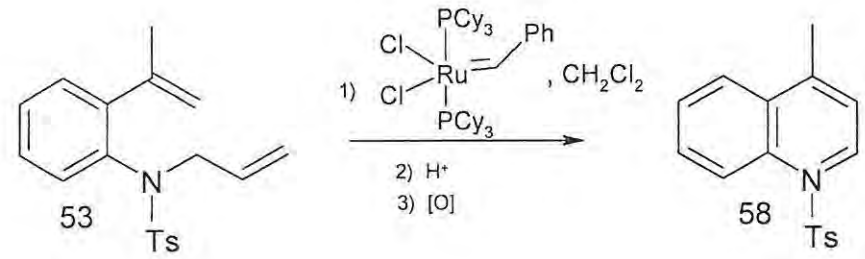


Scheme 11

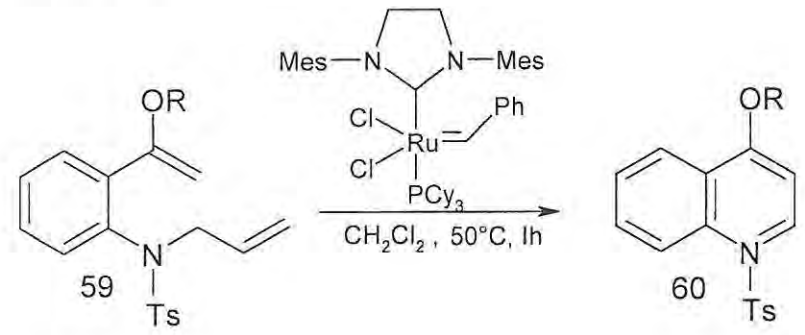
Arisawa and co-workers[16] have communicated how they used the ring-closing olefin metathesis (RCM) and silyl enol ether-ene methods to synthesise quinolines and substituted 1,2-dihydroxyquinoline derivatives. Their work began with the preparation of the dienes **53** and **57** from commercially available 2-isopropenylaniline **52** and anthrinilic acid **54**, respectively (Scheme 12). The dienes were readily transformed to the 1,2-dihydroxyquinoline derivatives in the presence of a ruthenium catalyst (RCM method); these researchers found that protection of nitrogen by tosylation led to quantitative yields of the quinoline derivatives following protonation and air oxidation, as illustrated for the preparation of quinoline derivative **58** in Scheme 13. The synthesis of 4-methoxy- and 4-siloxy-1,2-dihydroxyquinolines by ene-enol metathesis of dienes, prepared from *o*-aminoacetophenone, was also investigated (Scheme 14). Interest in these compounds was prompted by the fact that 4-substituted quinolines are important intermediates for the preparation of cinchona alkaloids, including quinine.



Scheme 12



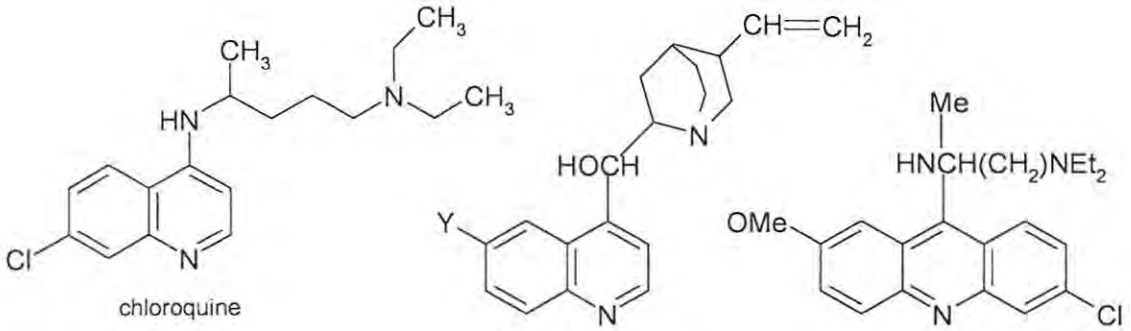
Scheme 13

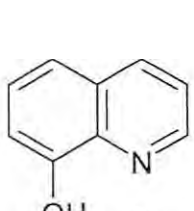


Scheme 14

1.2 Biologically active quinoline derivatives

There are quite a number of quinoline derivatives that are of biological importance. The list includes quinine, chloroquine, plasmoquin, pentaquine, cinchonine and mepacrin (also known as atebrin or quinacrin), all of which are used as antimalarial drugs. Rabe was the first to report the structure of quinine in 1908,[6] and a partial synthesis of this compound was achieved in 1945 by Doering and Woodward.[6] The total synthesis of this compound has recently been achieved by Stork *et. al.*[17] However, due to the undesirable side effects that are produced by these drugs, they have largely been replaced in clinical use.[6] Derivatives of 8-hydroxyquinoline **61** have been found to exhibit bactericidal and fungicidal properties, the former being attributed to the formation of an iron chelate.[18] Vioform (5-chloro-7-iodo-8-hydroxyquinoline), for example, finds use as an amoebocide.[6]





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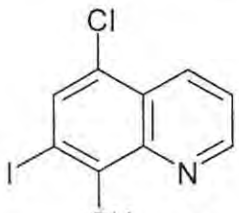


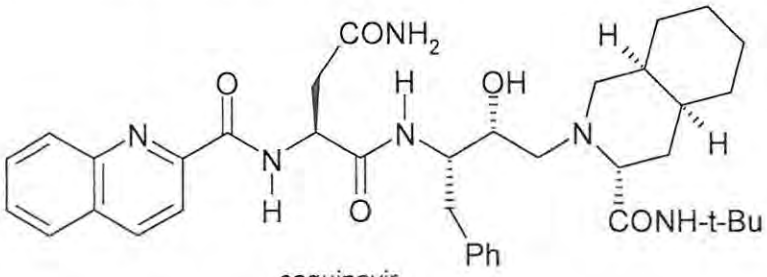
vioform

1.2.1 Anti-HIV-1 agents

Millions of people die from AIDS (acquired immune deficiency syndrome) - a terrible disease for which there is, at present, no complete cure. AIDS is caused by the human immunodeficiency virus (HIV) and attention has been focused on the ways in which this

virus interacts with the host cells by identifying the molecular events in the life cycle of the virus.[18]

There are three enzymes responsible for the replicative life cycle of HIV-1, *viz.*, the HIV-1 protease, reverse transcriptase and the integrase enzymes.[18-25] Several protease inhibitors have been developed which are now in clinical use.[26] These include:- Inverase® (saquinavir mesylate; Hoffman-La Roche); Norvir® (ritonavir; Abbott laboratories); Crixivan® (indinavir sulfate; Merck) and Viracept® (nelfinavir mesylate; Agouron Pharmaceuticals). Recently, amprenavir has entered the market as a fifth HIV-1 protease inhibitor.[19] There are also several reverse transcriptase inhibitors that are available for use in the treatment of AIDS, including AZT (3'-azido-3'-deoxythymidine), which has been used world-wide.[27]



saquinavir

Saquinavir has been shown to be potent against both HIV-1 and HIV-2 protease with IC_{50} values of less than 0.37 nM and 0.8 nM, respectively, but inactive at blocking other mammalian aspartic acid proteins at concentrations below 10 μM. The development of drug resistance has prompted some research groups[20-23] to explore the possibility of using a combination of HIV-1 protease and reverse transcriptase inhibitors. This kind of treatment, known as HAART (Highly Active Anti-Retroviral Therapy), has been shown to halt the replication of the virus to such an extent that the virus becomes undetectable in infected persons.[24] However, replication of the virus can unfortunately continue even at low levels.[24] Researchers have begun to seek HIV-1 integrase inhibitors,[22] which are well tolerated, have low toxicity and ready oral bioavailabilty.[22]

1.2.2 HIV-1 Integrase inhibitors

Much effort has been put into the study of the inhibition of the HIV-1 protease and reverse transcriptase enzymes,[24] and many compounds have been identified as inhibitors.[24,28] Although the HIV-1 integrase enzyme (the third enzyme responsible for the replicative life cycle of the HIV virus)[22,29] has enjoyed relatively little attention, there are a number of compounds that have been shown to inhibit the enzyme *in vitro*.[30] No compounds have yet been released for clinical use,[30] but 5CITEP and L-708,906 have now entered the trial phase in human volunteers.[31]

Both the protease and reverse transcriptase enzymes have been extensively studied because their respective cellular enzymes[24] are known. The integrase enzyme, on the other hand, has not been studied that well since its cellular host is not found in humans.[22,24,28] Its absence from the host cells means that the integrase enzyme is very specific for HIV-1 attack, thereby rendering the enzyme a potential target for the development of highly selective anti-HIV agents.[22,28] Although the integrase enzyme has not been studied that well, there are compounds that have been found to inhibit the enzyme and those compounds are classified according to the groupings; DNA ligands, *C*-terminal domain ligands and compounds that interfere with the catalytic domain of the protein.[24]

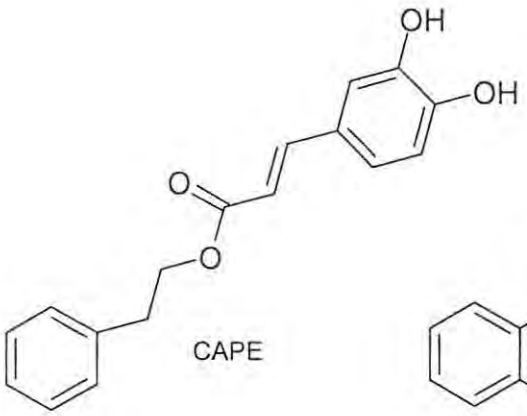
1.2.2.1 HIV-1 Integrase inhibitor design

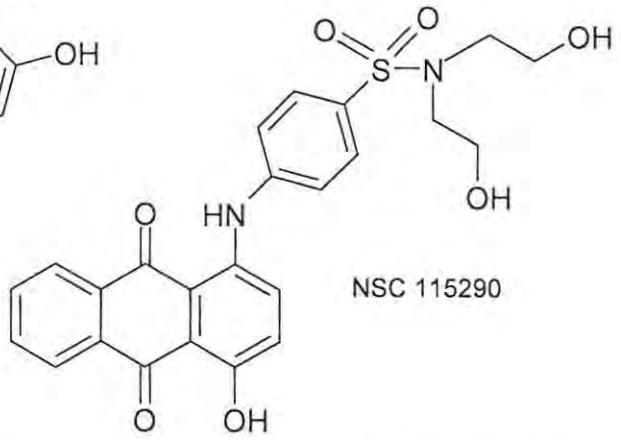
Researchers[21,22,28] have made it clear that the discovery of HIV-1 integrase inhibitors is difficult due to the absence of the integrase enzyme in human cells. Meaning that there are no known counterparts of the HIV-1 integrase enzyme in the host cell.[23] Identification of lead compounds was clearly required,[30] and a three-dimensional data-base search has been used to identify both the possible pharmacophores and lead compounds.[30] Following such a search, a common structural pattern of HIV-1 integrase enzyme inhibition was identified to have *ortho*-polyhydroxylated aromatic units.[21] Nevertheless, compounds which do not correspond to this pattern were also found to inhibit HIV-1 integrase.[21] Following these studies, HIV-1 integrase was described to be a 32kDalton enzyme,[23]

which catalyses transformations in a two-step manner.[21,22] The first step is the "3'-end-processing" which involves removal of a dinucleotide unit from the 3'-end of the viral DNA, while the second step involves "strand transfer" *i.e.*, the transfer of 3'-processed strands from the cytoplasm to the nucleus of the host DNA.[21,22,28] It has also been reported that "strand transfer" takes place just after cleavage of the opposing host strands.[21,22,28] d'Angelo *et al.*[24] have described how both the 3'-end-processing and strand transfer reactions occur. They suggest that both reactions involve nucleophilic attack at a phosphodiester bond by a hydroxyl group and require a divalent metal ion (Mg^{2+} or Mn^{2+}) as a cofactor.[24]

The development of HIV-1 integrase inhibitors has involved the use of radio-labeled oligonucleotide-based assays,[21] which allow *in vitro* determination of IC_{50} values for the inhibition of both 3'-processing and strand transfer. An IC_{50} value determines the concentration that a particular compound needs for 50% inhibition of HIV-1 integrase.

CAPE[22,30] and NSC 115290[30] are the two compounds that were used in the initial stages of the derivation of the integrase inhibitor pharmacophore. CAPE (cafeic acid phenethyl ester) falls within the class of *ortho*-polyhydroxylated aromatic moieties since it contains a catechol substructure and, in addition, an ester functionality. Besides being an average HIV-1 integrase inhibitor, CAPE is a main component of propolis - a substance bees use to minimize the size of the entrance and seal holes in their hives.[30] Moreover, CAPE was found to be cytotoxic to tumor cells and has also been used for the development of other integrase inhibitors.[22,30] However, when CAPE and NCS 115290 were used in a computer search for other possible inhibitors, it was discovered that the pharmacophore should contain atoms that are hydrogen bond acceptors and be able to form complexes with positively charged metals ions. The researchers[22,30] realised that the position or orientation of the carbonyl oxygen was important. Following these discoveries a database of 152 known HIV-1 integrase inhibitors was made and the pharmacophore of 77 of these compounds has been identified.[30] A very similar pharmacophore pattern was identified for 65 out of the 77 active compounds. This pattern consists of an elongated triangle with two sides of the order of 9 Å and a shorter side of the order of 2.5 Å.



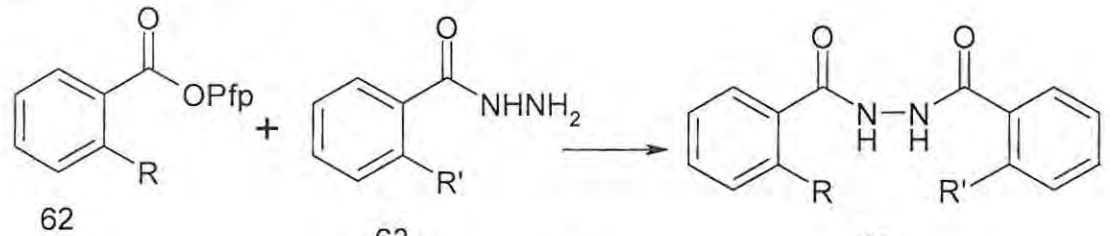


NSC 115290

To date, quercategetin[30], a polyhydroxylated compound, is reported to be the most potent HIV-1 integrase inhibitor known.

Quercategetin

It seems, however, that catechol-containing inhibitors have setbacks, such as cytotoxicity. A search for compounds that do not contain the catechol substructure led to the identification of hydrazide-containing HIV integrase inhibitors (Scheme 15).[21] Zhao *et al.*[21] have further shown that the influence of the substituents R and R' on the activity decreases in the order: OH>SH>>NH_2.

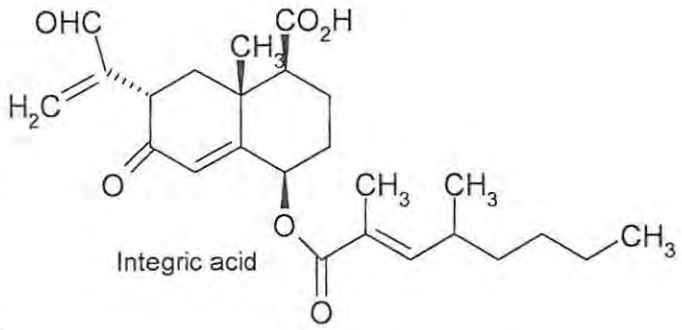


62 63 64

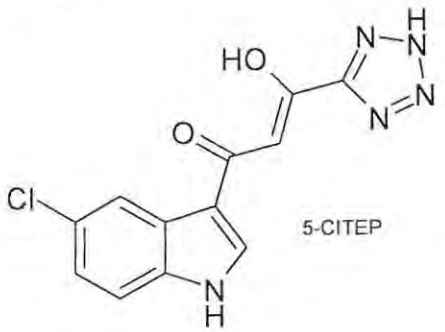
R	R'
OH	OH
OH	H
H	H
OH	NH_2
OH	SH

Scheme 15

There are other compounds, which do not contain the hydrazide linker, that were discovered through library searching and found to inhibit HIV-1 integrase.[28,31] These compounds include:- equisetin,[32,33] phomasetin[32,33] and integric acid.[28] Integric acid was found to inhibit both 3'-end-processing (IC_{50} = 10 μM) and strand transfer (IC_{50} = 10 μM) reactions. In addition, it also inhibited the disintegration reactions that are catalysed by the cut core domain (52-212 amino acids). Integric acid is a member of the eremophilane sesquiterpenoid subfamily produced by *Xylaria sp.* and is a 2,4-dimethyl-2-octenoic acid ester.[28]



Goldgur *et al.*[23] have reported 5-CITEP [1-(5-chloroindol-3-yl)-3-hydroxy-3-(2*H*-tetrazol-5-yl)-propenone] as an HIV-1 integrase core domain inhibitor. These workers claim that the inhibitor binds in the middle of the multifunctional active site of the integrase enzyme, and that this type of binding reduces the capacity of the enzyme to produce other inhibitor-resistant mutants.[23] Furthermore, it was deduced that the amimo and residues with which this inhibitor (5-CITEP) makes contact are Lys 156, Lys 159 and Gln 148.[24]



1.2.2.2 Crystal structure of the core domain of HIV-1 integrase

Maignan and co-workers[26] have reported the catalytic core domain of HIV-1 integrase to consist of a five-stranded β-sheet surrounded by α-helices (Figure 1). However, the active site of the integrase enzyme is considered to contain two carboxylate residues, *viz.*, Asp 64 and Asp 116.[24] Both of these residues appear to be necessary for catalysis and coordination of the metal cation, Mg^{2+} or Mn^{2+}; a third carboxylate residue, Glu 152 (E 152), apparently does not participate in the metal binding.[24] From the structure (Figure 1) it can be noted that residue E 152 is far away from the metal cation, which is why it is not directly involved in the metal binding. Water molecules have also been identified as being responsible for hydrogen bonding interactions at the active site.[26] Figure 1 shows a comparison of the core domain of HIV-1 integrase (green) with the core domain of ASV integrase (avian sarcoma virus) (blue), a turmourous virus related to birds. From the results, Maignan *et al.*[26] were able to conclude that anti-HIV-1 integrase agents could be designed, based on the similarity of the two enzymes. That means if one can be able to design some analogues of the compounds that were used to cure this ASV virus it might be possible that some of them can be important anti-HIV-1 integrase agents.

1.2.2.3 Styrylquinolines as HIV-1 integrase inhibitors

Styryquinolines have been reported as a class of compounds that block the replication of HIV-1 in cell cultures, but which exhibit no cytotoxicity at all.[24] Zouhiri *et al.*[34] have reported that the styrylquinoline **65** is a potent HIV-1 integrase inhibitor *in vitro*, but they also made it clear that the exact mechanism by which this and analogous systems block the enzyme active site was unknown.[24] They[34] also suggest that the possible pharmacophore for these styrylquinoline systems might reside in the salicylic acid moiety - a site that binds with the Mg^{2+} cation.[34] Styrylquinolines **68** can be obtained by Perkin condensation between quinaldines **66** and aromatic aldehydes **67** under strongly basic conditions.[35] Besides their HIV-1 inhibitory potency, styrylquinolines have also been found to be very active in the treatment of leukemia, and to exhibit anti-bacterial, anti-fungicidal and some tumour-inhibiting properties.[6]

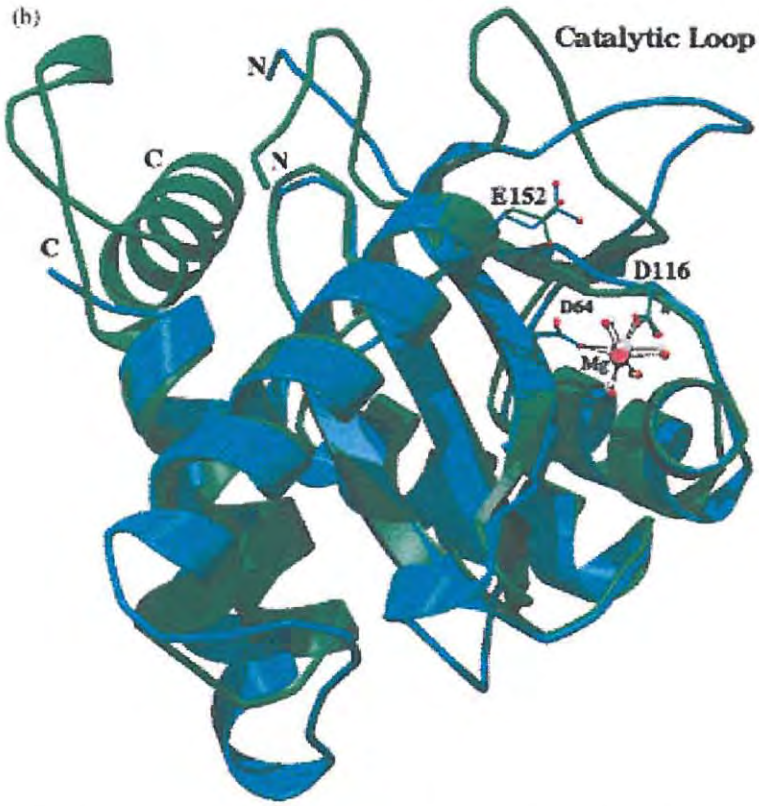
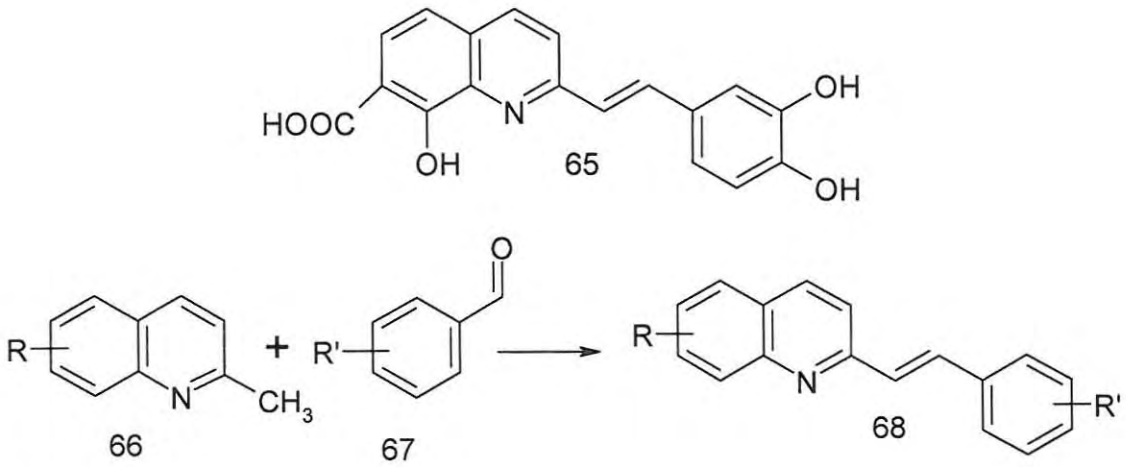


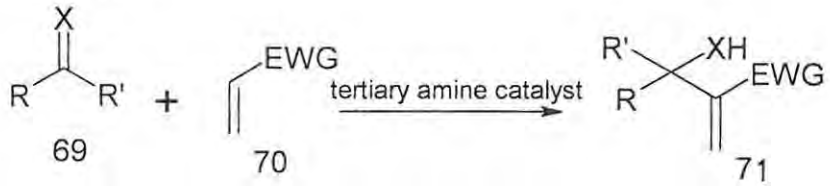
Figure 1. Typical HIV-1 integrase (green) complexed with ASV integrase (blue).[26]



Scheme 16

1.3 The Baylis-Hillman reaction

Over the past few years, the Baylis-Hillman reaction has attracted increasing attention. Testimony to this is the number of reviews that have been published, *viz.*, those by Basavaiah *et al.*,[36-38] Drewes and Roos,[39] and Ciganeck.[40] Our group has also enjoyed some success with applications of the Baylis-Hillman reaction in the preparation of indolizines,[41,42] chromenes,[43] thiochromenes,[43] coumarins[44,45] and quinoline derivatives.[46-48] The basic aspects of the Baylis-Hillman reaction are illustrated in Scheme 17.



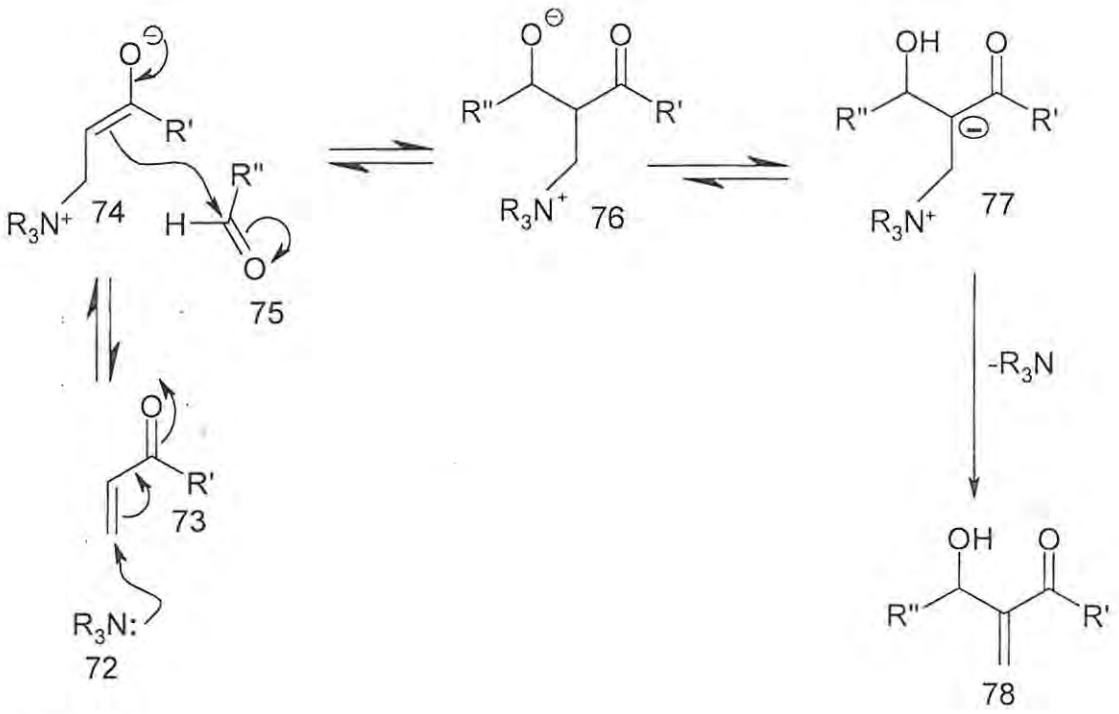
X = O or NR^2

Scheme 17

The Baylis-Hillman reaction leads to the formation of a new carbon-carbon bond between the α-carbon of the activated alkene **70** and the sp^2 carbon of the aldehyde (or aldehyde equivalent) **69**.[36] There are three components that are necessary for a Baylis-Hillman reaction to occur, *viz.*, an electrophile, an activated alkene and a tertiary amine or phosphine catalyst.[36,40,49] A number of such catalysts have been used, including 1,4-diazabicyclo[2,2,2]octane (DABCO),[41,43,45,50,51] triphenylphosphine (PPh_3),[52] diphenylmethylphosphine (Ph_2PMe),[52] 4-dimethylaminopyridine (DMAP),[53] 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)[54,55] and 3-hydroxyquinuclidine (3HQ).[56]

1.3.1 Mechanistic Aspects

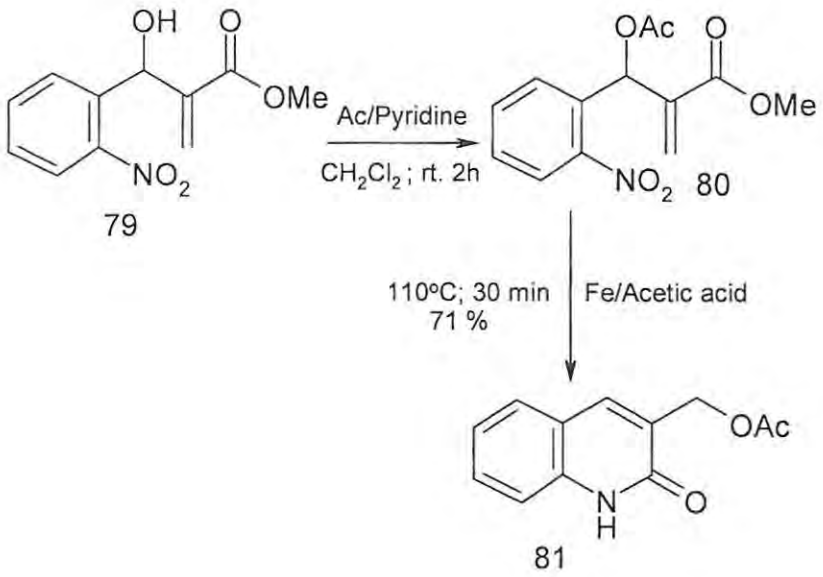
The mechanism[36,46,51] of the Baylis-Hillman reaction is considered to involve several steps (Scheme 18). Initial nucleophilic attack at the vinylic carbon of the activated alkene **73** by a tertiary amine catalyst **72** leads to the formation of a zwitterionic intermediate **74**, which then attacks the carbonyl carbon of the aldehyde **75.** Proton transfer, followed by the elimination of the catalyst, then affords the Baylis-Hillman product **78**.[36,51]



Scheme 18

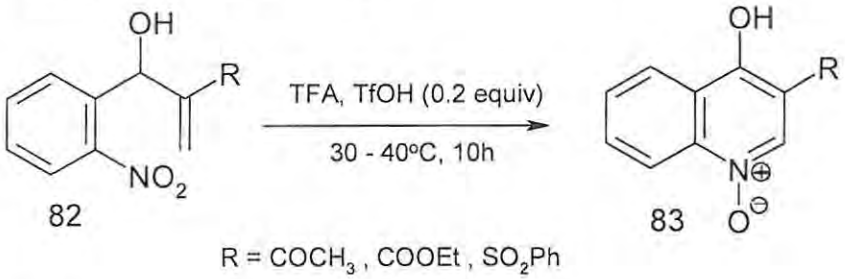
1.3.2 Applications of the Baylis-Hillman reaction in the synthesis of heterocyclic compounds

Since our research group first reported the synthesis of quinoline derivatives from Baylis-Hillman adducts,[46] other groups have also used this approach. Examples include a report by Basavaiah *et al.*[38] who synthesized (1H)-quinol-2-ones **81** and quinoline derivatives *via* the Baylis-Hillman adducts. Different 2-nitrobenzaldehyde substrates were used as starting materials. The method which they used involves acylating the Baylis-Hillman product followed by treatment with Fe/acetic acid at high temperature to afford the required product, as illustrated in Scheme 19.



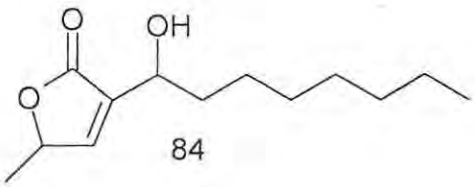
Scheme 19

More recently, Lee and coworkers[49] have used Baylis-Hillman adducts in their preparation of 3-substituted-4-hydroxyquinoline-*N*-oxides. The Baylis-Hillman adducts **82** were treated with triflouroacetic acid in the presence of triflic acid to yield the desired products **83**, as depicted in Scheme 20.



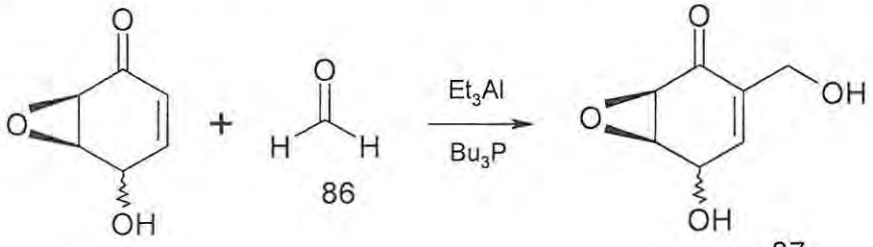
Scheme 20

Other new applications of the Baylis-Hillman reaction continue to be reported. These include preparation of acaterin **84**, an inhibitor of acyl-CoA:cholesterol acyltransferase (ACAT) by Franck and Figadère.[57]



84

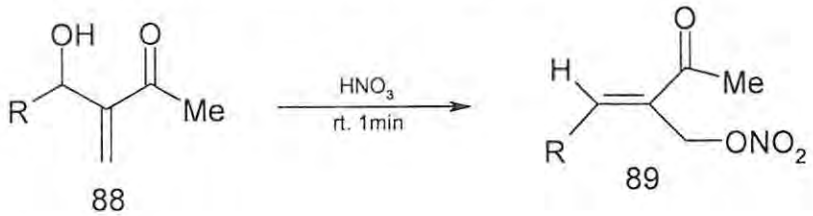
Genski and Taylor[58] have demonstrated (Scheme 21) the application of the Baylis-Hillman reaction in the preparation of *epi*-epoxydon **87** from formaldehyde **86** and the epoxidised hydroxyquinol **85**, using triethylaluminium/tri-butylphosphine as catalyst. *Epi*-epoxidon is believed to exhibit some antibacterial, antifungal and phytotoxic activity.



85 86 87

Scheme 21

Knowing that nitrate esters ($RONO_2$) are therapeutic drugs for the treatment of heart and vascular diseases, Basavaiah *et al.*[59] have prepared (1*R*,2*R*)- and (1*S*,2*S*)-2-nitroxycyclohexan-1-ols in enantiomerically pure form. They[60] later extended their research on nitrate esters by preparing, stereoselectively, (*E*)-3-(nitroxymethyl)alk-3-en-2-ones **89** *via* the reaction of 4-hydroxy-3-methylenealkan-2-ones **88** with concentrated nitric acid. The reaction, which involves allylic rearrangement, was carried out at room temperature for one minute (Scheme 22).

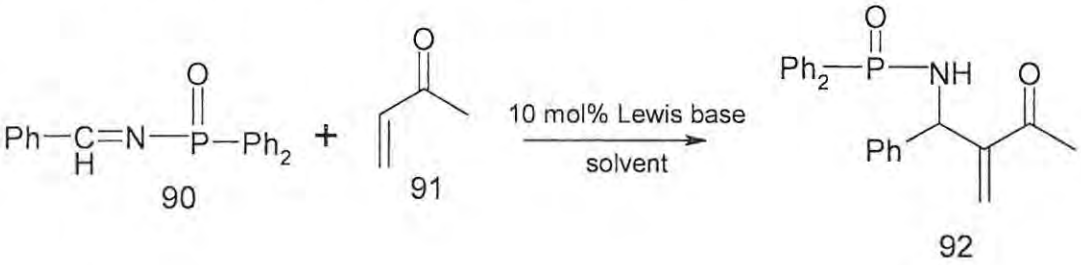


88 89

Scheme 22

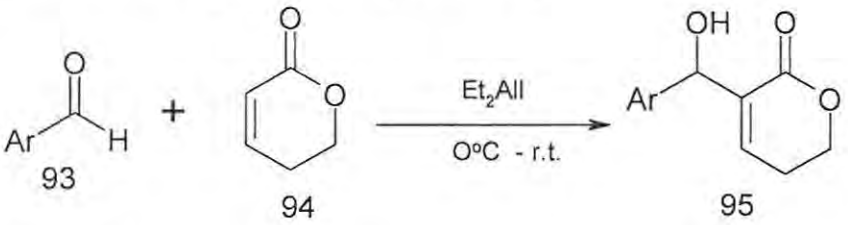
More recently, Baylis-Hillman products have been obtained from the reaction of *N*-arylidenediphenylphosphinamides with methyl vinyl ketone, methyl acrylate and

acrylonitrile (Scheme 23).[52] The authors found that using PPh_3 as a Lewis base and THF, DMF or MeCN as solvents gave high yields. However, they also stated that DABCO was a suitable catalyst when working with acrylonitrile.



Scheme 23

Headley and workers[61] have synthesised Baylis-Hillman adducts by reacting α,β-unsaturated δ-lactones with various aromatic aldehydes. They also report that the use of diethylaluminium iodide promotes reaction with various aldehydes. Furthermore, these researchers have made it clear that their method does not involve the direct use of a Lewis base. Using this approach, moderate to good yields of the Baylis-Hillman products were obtained in just 24 hours (Scheme 24).

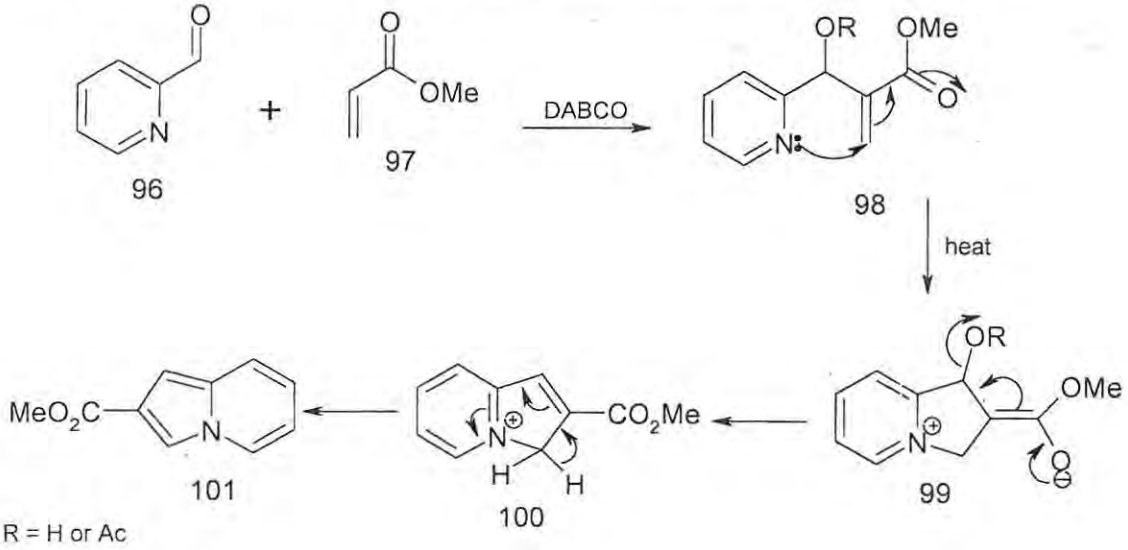


Scheme 24

1.3.2.1 Synthesis of indolizines

Several methods for preparing indolizines have been reported.[42] These include the new methods reported by Goti *et al.*,[62] Druta *et al.*,[63] Acheson and Ansell[64] and Abarca *et al.*[65] Interest in indolizines is due to the fact that these compounds are important intermediates for the preparation of drugs, dyestuffs and light-screening agents in photographic emulsions.[63] In our group,[41,42] indolizine derivatives were obtained by thermal cyclization

of 2-pyridyl derivatives **98**, prepared *via* Baylis-Hillman reactions between pyridine-2-carbaldehyde and activated alkenes, as illustrated in Scheme 25.[41,42]



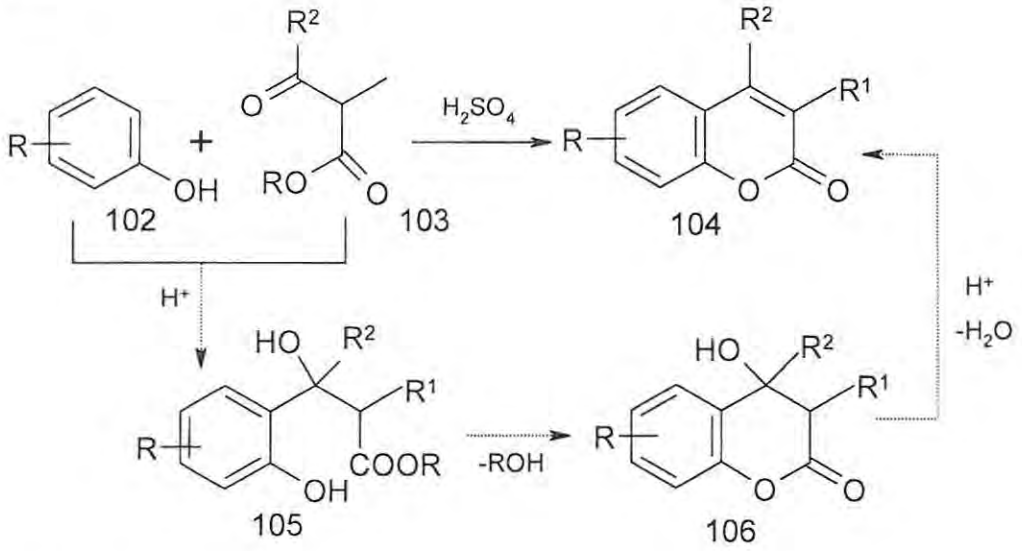
Scheme 25

1.3.2.2 Synthesis of coumarins[1,2,7]

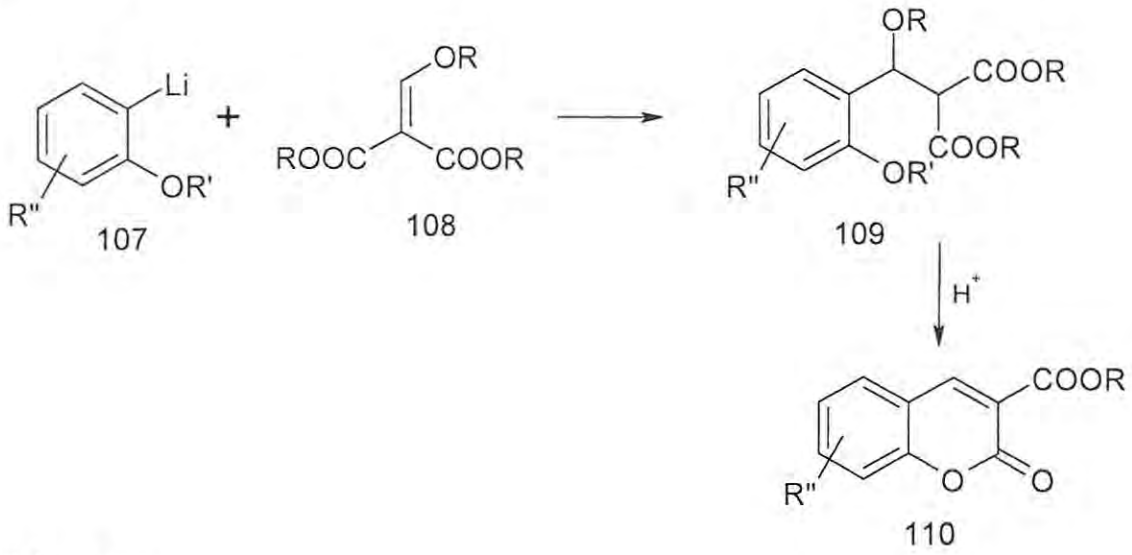
Coumarin derivatives are known to exhibit diverse biological activity and have found use as anticoagulants and antithrombotics.[66] Examples of coumarin derivatives with biological activity include 3-substituted-4-hydroxycoumarins and tricoumarol, both of which possess some HIV inhibitory potency.[66] Numerous methods for the synthesis of these compounds have been developed; these include the preparation of coumarins **104** from the cyclocondensation of phenols **102** with β-keto esters **103** under strongly acidic conditions, as illustrated in Scheme 26.

The mechanism, indicated by broken lines, is believed to proceed *via* an S_EAr reaction of the phenol with the carbonyl carbon of the presumably protonated β-keto ester **103**,[2] following which, lactonization and elimination of water give the desired coumarin **104**.[1,2,7] Of course, this is not the only method by which coumarins can be synthesised; there are many other methods. These include the addition of *o*-metallated phenolic ethers **107** to alkoxymethylene malonic esters **108**, followed by the removal of the phenolic

protective group, lactonization and elimination of ROH to afford the coumarin system **110**.[2]



Scheme 26



Scheme 27

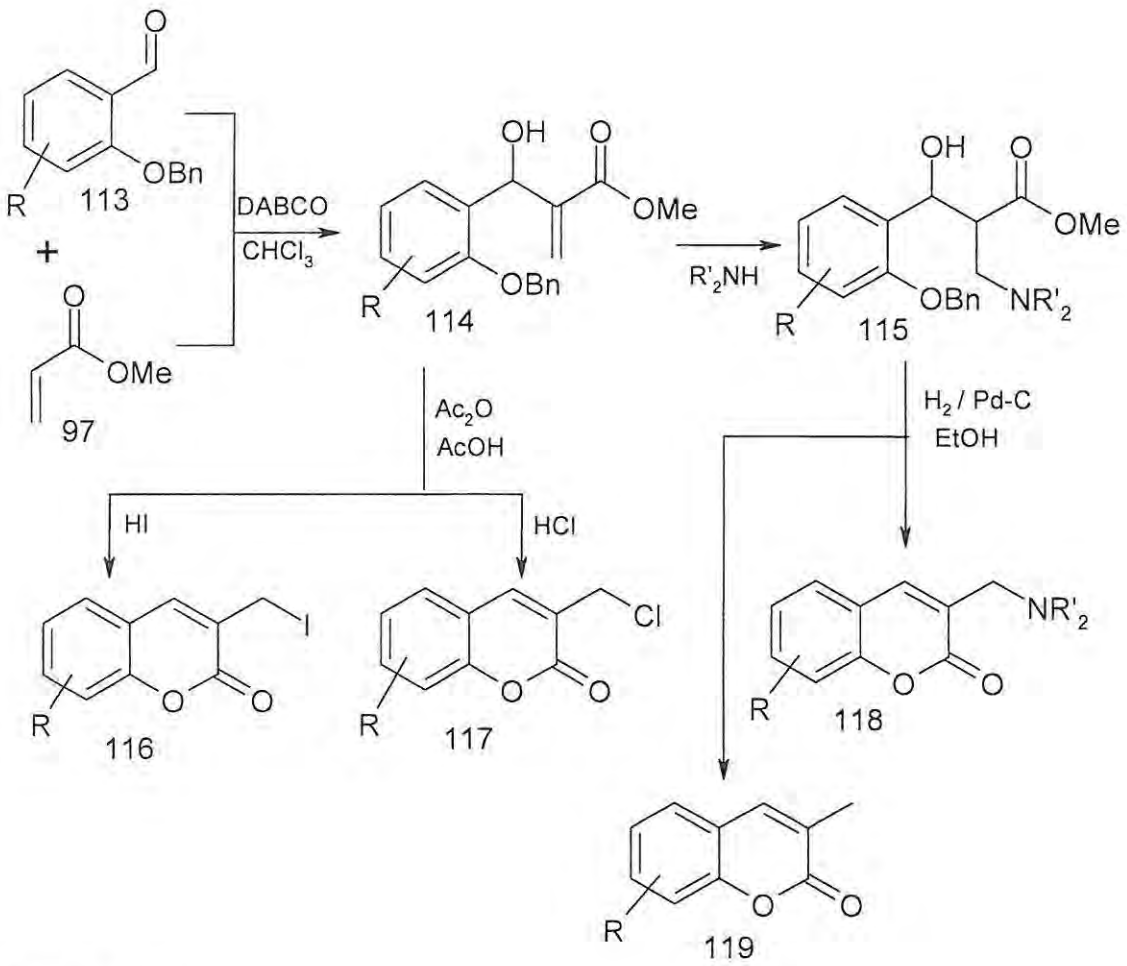
In our group the coumarin derivative **112** was first synthesised *via* the Baylis-Hillman reaction[45,46,48,67] by reacting methyl acrylate **94** with salicylaldehyde **111** in the presence of a tertiary amine (DABCO) (Scheme 28). Subsequent approaches, involving the preparation of coumarins *via* acid-catalysed deprotection and cyclization of *O*-bezylated Baylis-Hillman products, reductive deprotection and cyclization of conjugate addition products, and the direct cyclization of unprotected Baylis-Hillman products were

explored.[45] These latter three methods give 3-substituted coumarin derivatives in moderate to good yields.[45]

Scheme 28

Two of the three methods that were used in our group[45,69] for the synthesis of 3-substituted coumarin derivatives, *i.e.* acid-catalysed deprotection and cyclization of *O*-bezylated Baylis-Hillman products and reductive deprotection and cyclization of conjugate addition products, are illustrated in Scheme 29. The first step involves protection of the phenolic hydroxyl group of the salicylaldehyde precursor by a benzyl protecting group, followed by a Baylis-Hillman reaction between the protected aldehyde and the methyl acrylate. After the isolation of the protected Baylis-Hillman product **114,** conjugate addition of a nucleophile was effected, followed by deprotection and cyclization to afford the coumarin derivatives **116**, **117** or **118** and **119**.[45,69]

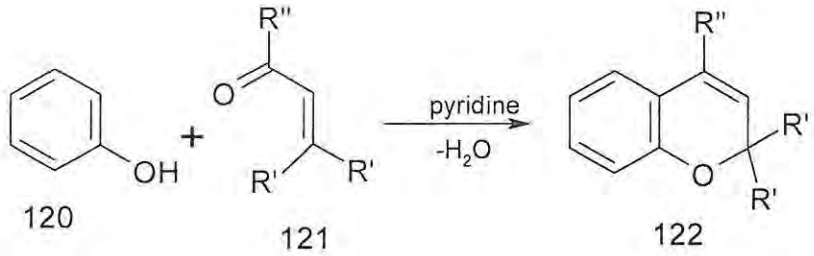
From Scheme 29 it can be noted that the difference between these two methods is that the one (involving acid-catalyzed deprotection) does not require addition of the amine nucleophile whilst the other does. The acid-catalyzed method has the advantage of one less step and affords the coumarins in high yields. In the acid-catalyzed deprotection method the reaction is carried out under reflux for 2 hours using Ac_2O, AcOH and HCl or HI acid as reagents. However, the reductive deprotection method requires the addition of a nucleophile, and the conjugate addition products **115** are then subjected to hydrogenation using 10% palladium on carbon catalyst in ethanol for 6 hours at room temperature.[45,69]



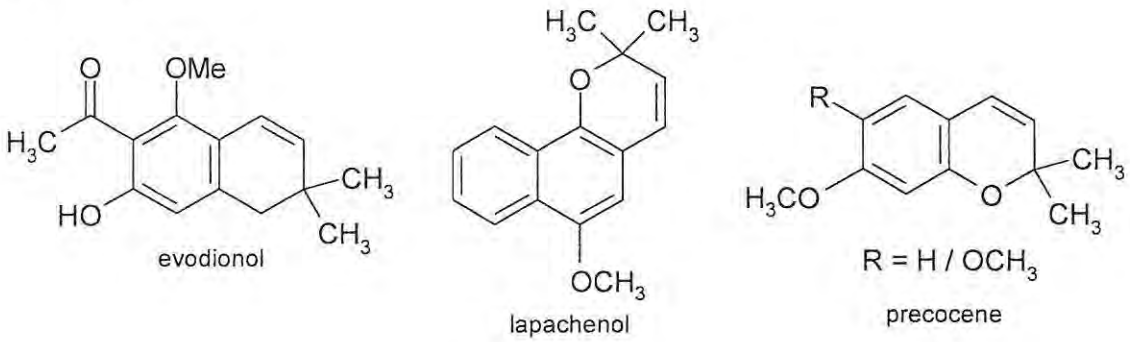
Scheme 29

1.2.2.3 Synthesis of chromenes [1,2]

2-*H*-chromenes can be prepared by cyclization of 2-propynylaryl esters,[2] acid catalysed dehydration of chroman-4-ols[2] or base-catalysed cyclocondensation of phenols **120** with α,β–unsaturated compounds **121**[1] (Scheme 30). 2-*H*-Chromenes form the nucleus of several natural products, *e.g.* the plant constituents, evodionol and lapachenol, and precocene, a juvenile hormone antagonist.[1] 4-*H*-chromenes may also be obtained by treating *o*-acyloxybenzyl bromides with two equivalents of phosphonium ylide.[2]

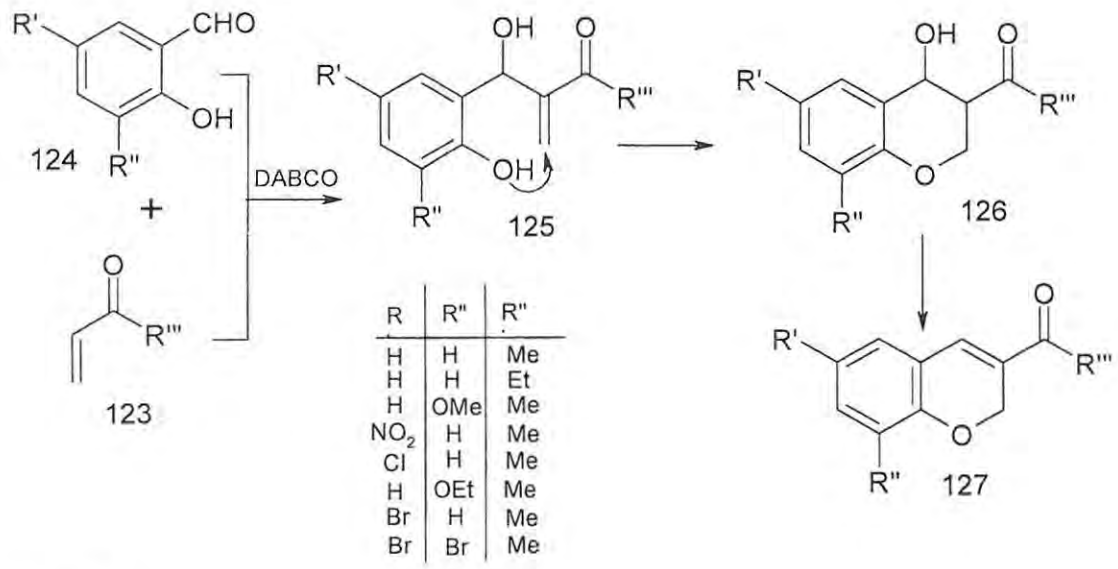


Scheme 30

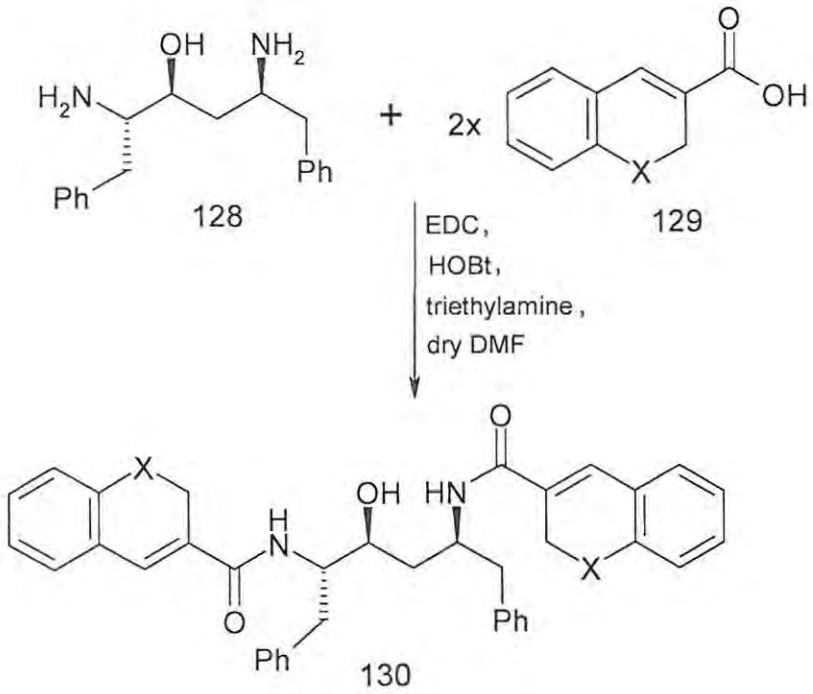


At Rhodes,[70] chromene derivatives have been synthesized *via* the Baylis-Hillman reaction as illustrated in Scheme 31. Chroman-4-ols **126,** which are formed as intermediates, undergo dehydration spontaneously to afford the chromene derivatives **127**. One of these chromene derivatives **127** has been employed in the preparation of a ritonavir analogue, as a potential HIV-1 protease inhibitor[26] by reacting diamine **128** with 2 equivalents of chromene-3-carboxylic acid or thiochromene-3-carboxylic acid (**129**; X = O or S).[71]

The approach requires initial preparation of the diamine "backbone", using a literature procedure,[72] followed by coupling of the diamine to either of the derivatives listed above using a standard coupling procedure[43] as depicted by Scheme 32. These chromone- and thiochromene-containing ritonavir analogues **130** have been subjected to *in vitro* HIV-1 protease enzyme inhibition assays.



Scheme 31

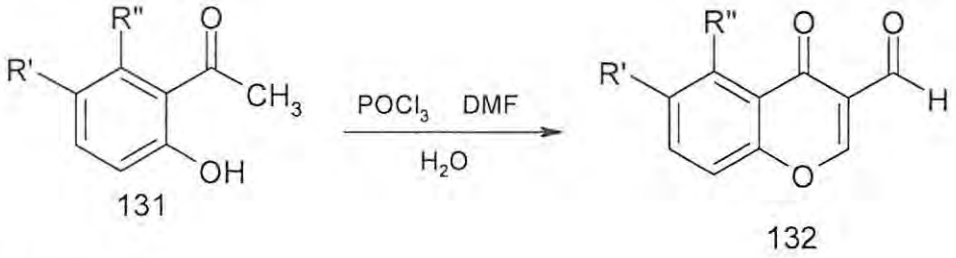


X = S or O

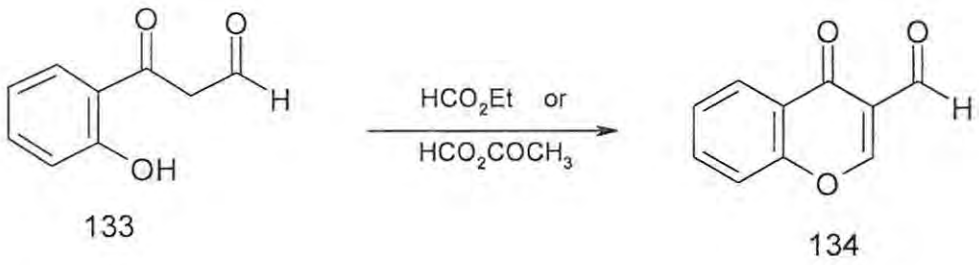
Scheme 32

1.2.2.4 Synthesis of chromone-carbaldehyde derived Baylis-Hillman products

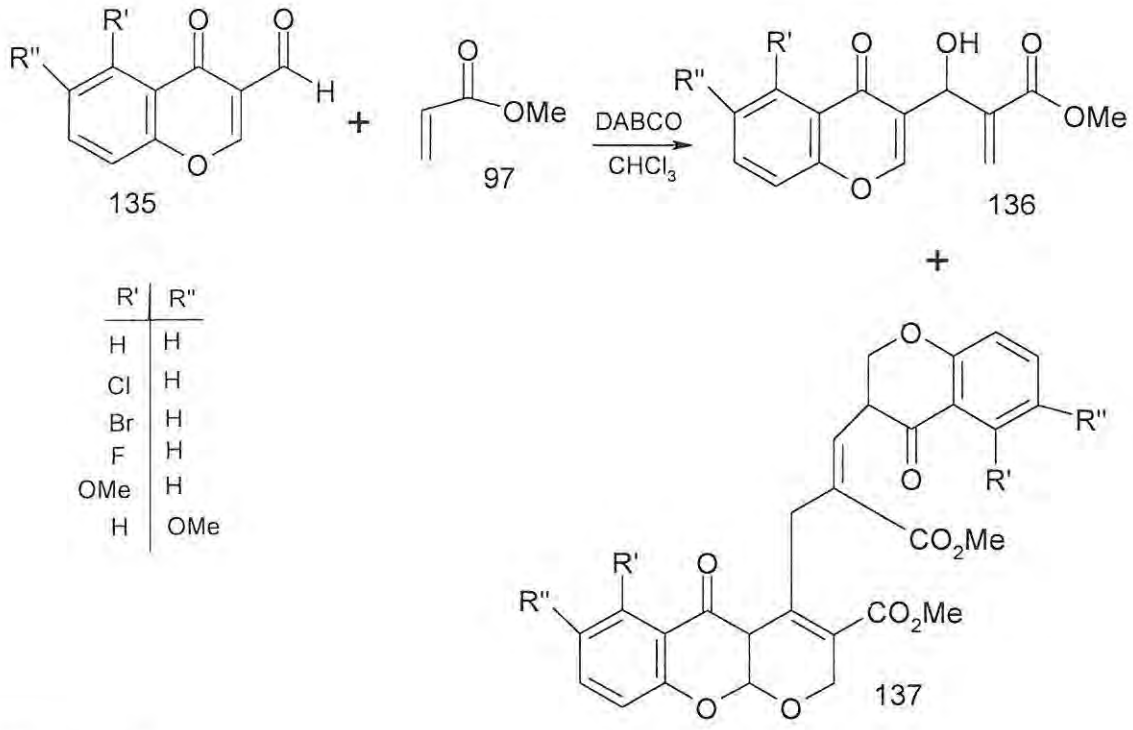
Sabbagh[73,74] used chromone-3-carbaldehydes **132** [prepared from o-hydroxyacetophenones **131** using the Vilsmeier-Haack reaction[5,76] (Scheme 33), or by reacting *o*-hydroxy-*ω*-formylacetophenone **133** and ethyl formate or acetic acid (Scheme 34)] as Baylis-Hillman substrates.[76] The chromone-3-carbaldehydes were treated with methyl acrylate in the presence of DABCO, to afford the Baylis-Hillman products **136**, which were isolated together with novel chromone dimers **137** (Scheme 35).



Scheme 33



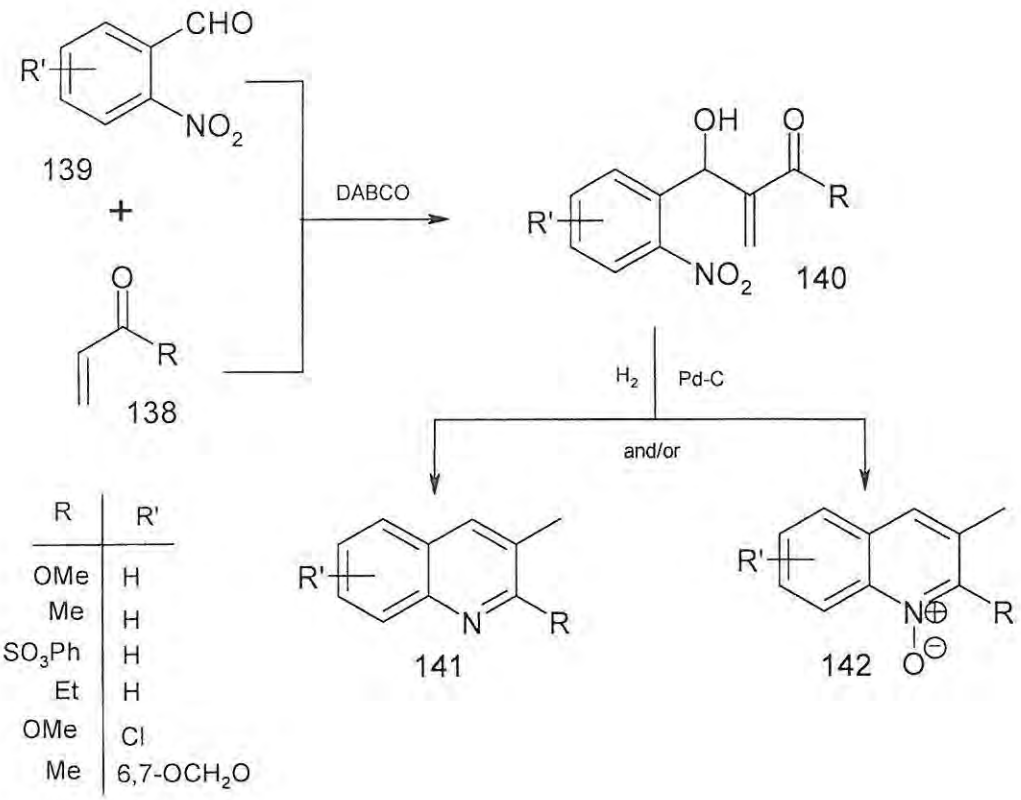
Scheme 34



Scheme 35

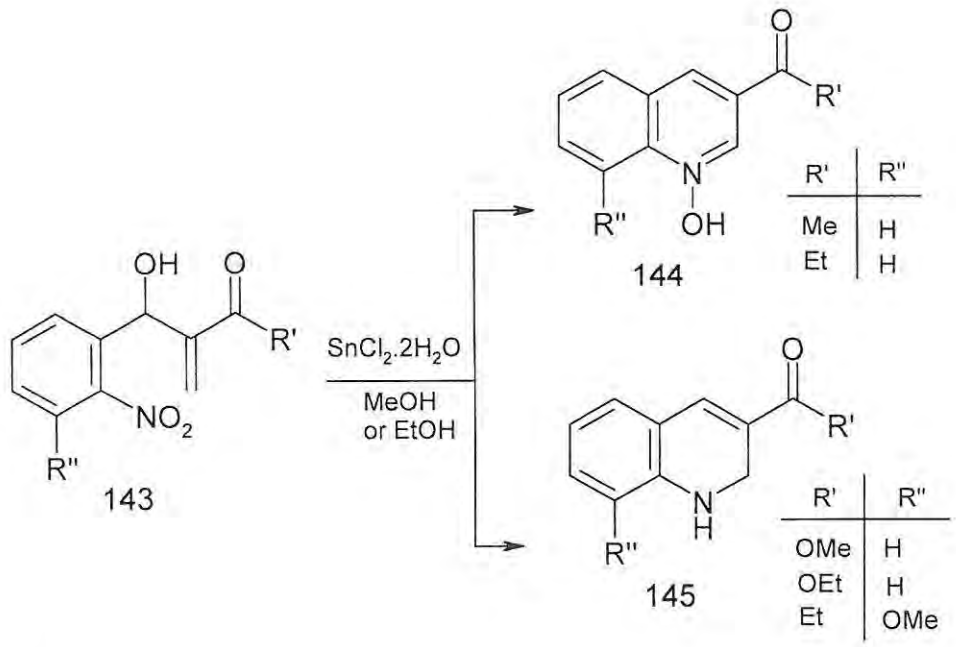
1.2.2.5 Synthesis of quinolines

In our group[46-48] quinoline derivatives have been synthesized *via* the catalytic hydrogenation of the Baylis-Hillman adducts obtained by reacting various *o*-nitrobenzaldehydes with activated alkenes such as methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) (Scheme 36), while acrylates esters lead to the formation of quinolones. Klaas[46] has also demonstrated the use of stannous chloride as a reducing agent with ethanol being used as a solvent. However, reduction of the acrylate ester-derived Baylis-Hillman products with stannous chloride didn't give the expected products resulting from the nucleophilic acyl substitution pathway, observed when palladium-on-carbon is used as a catalyst. Instead, reduction with stannous chloride appeared to favour the formation of dihyhdroquinolines resulting from conjugate addition (Scheme 37).[46,48]



R	R'
OMe	H
Me	H
SO_3Ph	H
Et	H
OMe	Cl
Me	6,7-OCH_2O

Scheme 36



R'	R"
Me	H
Et	H

R'	R"
OMe	H
OEt	H
Et	OMe

Scheme 37

1.4 Aims of the present study

As discussed above, the Baylis-Hillman reaction has been used to prepare various heterocyclic systems, including quinoline derivatives.[46,48] The general aim of the present work has been to extend applications of the Baylis-Hillman reaction in the preparation of quinoline derivatives and explore their elaboration to styrylquinolines. The following specific objectives were identified.

(i) The preparation of a series of Baylis-Hillman adducts from different *o*-nitrobenzaldehyde substrates and methyl vinyl ketone.

(ii) The reductive cyclization of these Baylis-Hillman adducts to afford quinoline derivatives.

(iii) The study of selected quinoline-*N*-oxide - quinoline interconversions.

(iv) The investigation of Perkin-type coupling of selected 2-methylquinolines with benzaldehydes to afford styrylquinolines as potential HIV-1 integrase inhibitors.

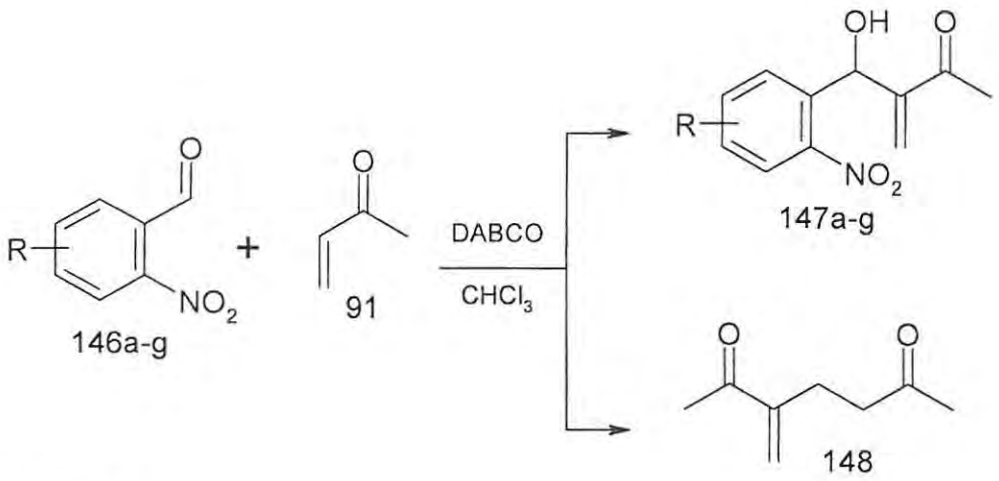
(v) The application of the ^{13}C NMR chemical shift prediction programmes.

2 DISCUSSION

In the discussion, which follows, particular attention will be given to:- i) the preparation of Baylis-Hillman products; ii) reductive cyclisation of these products to quinoline derivatives using a palladium-on-carbon catalyst; iii) the reaction of nucleophiles with the Baylis-Hillman adducts; and iv) the preparation of styrylquinolines as potential HIV-1 integrase inhibitors.

2.1 Synthesis of Baylis-Hillman products

This research represents an extension of previous work in the group.[46,47,48] Amongst the aims of the project, the first involved increasing the yields of the Baylis-Hillman-derived quinoline precursors. The Baylis-Hillman products **147a-g** were prepared by reacting the corresponding 2-nitrobenzaldehydes **146a-g** with methyl vinyl ketone (MVK) **91**, DABCO being used as the catalyst in all cases (Scheme 38). The reaction mixtures were stirred at room temperature for seven days to afford, after separation by column chromatography, the Baylis-Hillman adducts **147a-g** in yields ranging from 24 to 100% as indicated in Table 1. It was noticed that an improvement in yield was obtained when the catalyst was first dissolved in the MVK before the addition of the aldehyde – the approach used to obtain the Baylis-Hillman adduct **147b** in 100% yield. The mechanism for the reaction has already been described in Section 1.3.1, and outlined Scheme 18. In addition to the formation of the normal Baylis-Hillman products **147a-g**, the methyl vinyl ketone dimer **148** was also isolated in some cases. The formation of the dimer **148** can be rationalized as indicated in Scheme 39. Thus, the zwitterionic intermediate, formed by the attack of DABCO on MVK **91**, attacks the vinylic carbon of another MVK molecule, present in the solution, rather than the carbonyl carbon of the aldehyde to form the normal Baylis-Hillman product. Proton transfer, elimination of DABCO and tautomerisation then lead to the MVK dimer **148**.

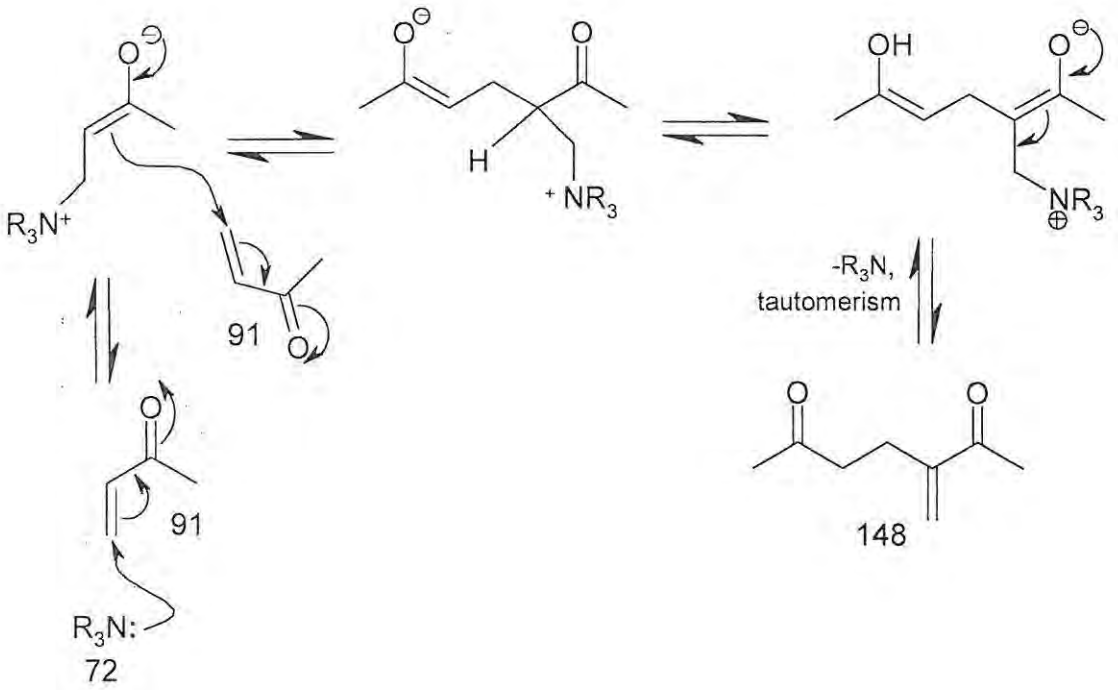


Scheme 38

Table 1. Table showing the yields of the Baylis-Hillman products **147a-g**.

Compound No.	R	% Yield[a]	Mp. / °C
147a	H	75	80 -82
147b	5-Cl	100	72 -74
147c	5-OH	33	131 -133
147d	3-OMe	24	oil
147e	6-Cl	85	oil
147f	4,5-di-OMe	73	oil
147g	4,5-OCH_2O-	60	oil

[a]Chromatographically pure.



Scheme 39

Baylis-Hillman products are generally characterised by the following features in their NMR spectra:- i) the presence of two separate vinylic proton signals in the ^{1}H NMR spectrum which typically resonate as singlets at *ca.* 6 ppm; ii) a methine proton singlet at *ca.* 5.7 ppm; and iii) a ^{13}C NMR methine carbon signal at *ca.* 67 ppm. In some cases, the hydroxylic proton resonates as a broad signal in the ^{1}H NMR spectrum – sometimes so broad as to be unrecognisable. From the spectral data for compound **147a,** illustrated in Figures 2a-c, the general features mentioned above are all evident. Thus, in the ^{1}H NMR spectrum (Figure 2a), the vinylic protons resonate at 6.15 and 6.20 ppm and the methine proton at 5.77 ppm. The broad signal at *ca.* 3.6 ppm integrates for one proton and corresponds to the hydroxyl proton. In the ^{13}C NMR spectrum (Figure 2b), the carbonyl carbon signal appears at 199.0 ppm and the methine carbon signal at 67.2 ppm. The one methylene carbon signal, which can be seen in the DEPT 135 spectrum, resonates at 127.0 ppm (Figure 2c) and corresponds to the terminal vinylic carbon.

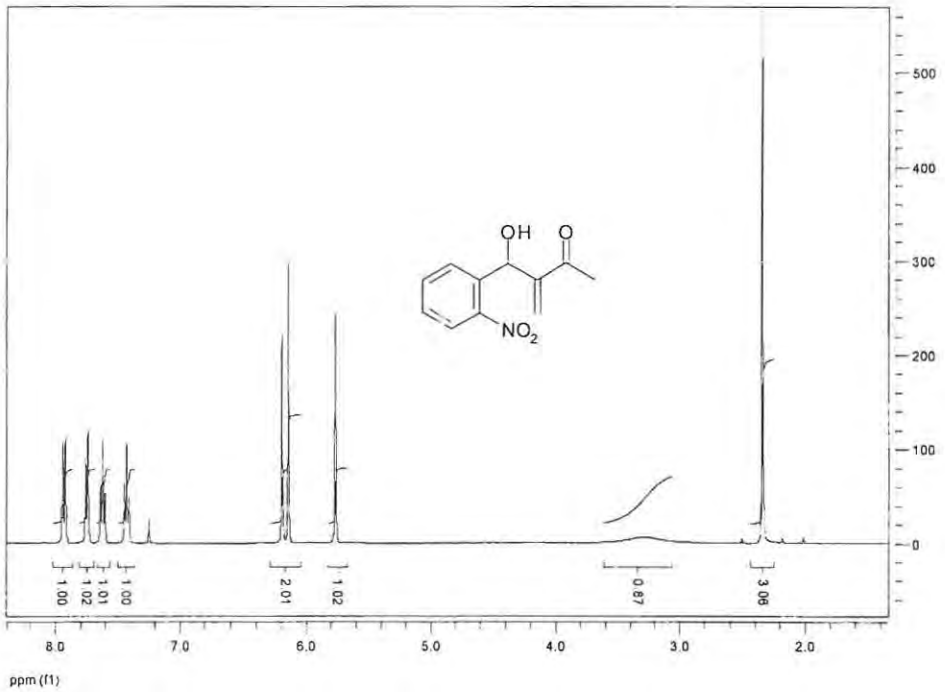


Figure 2a. 400MHz ^{1}H NMR spectrum of compound **147a** in $CDCl_3$.

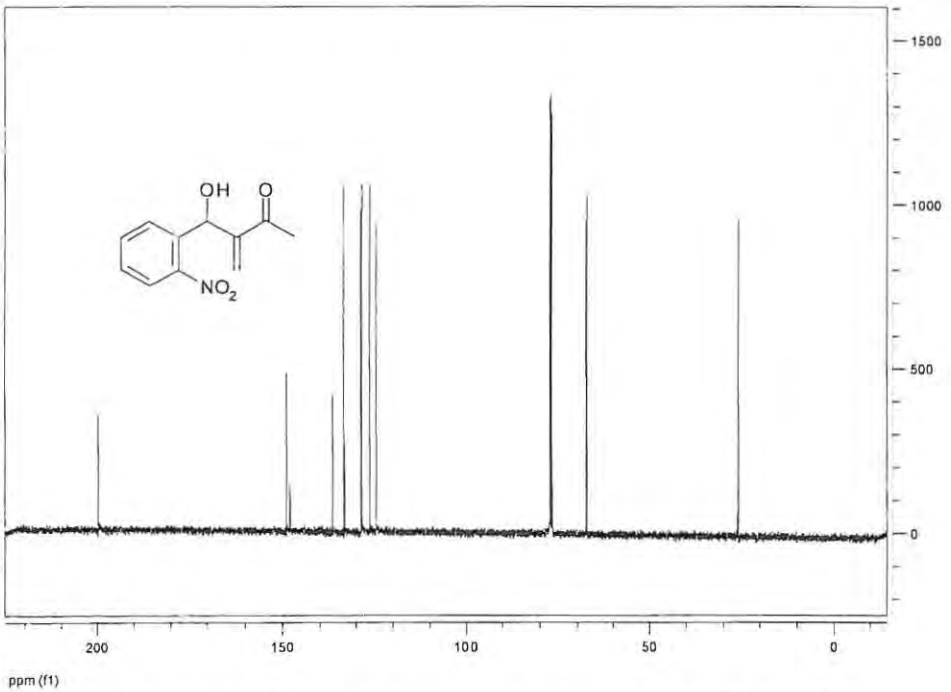


Figure 2b. 100MHz ^{13}C NMR spectrum of compound **147a** in $CDCl_3$.

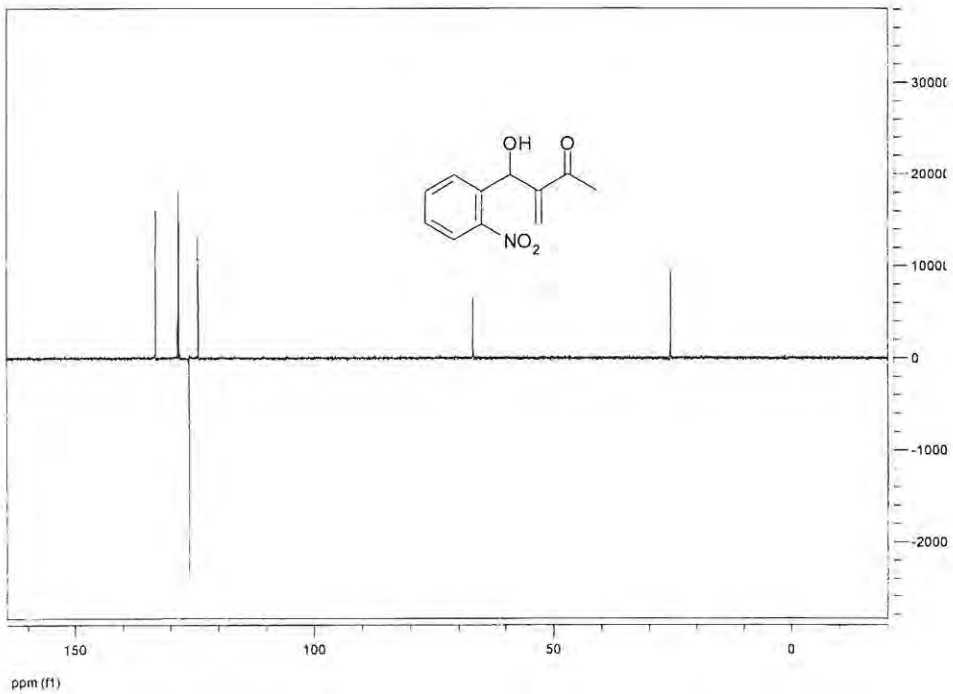


Figure 2c. 100MHz DEPT 135 NMR spectrum of compound **147a** in $CDCl_3$.

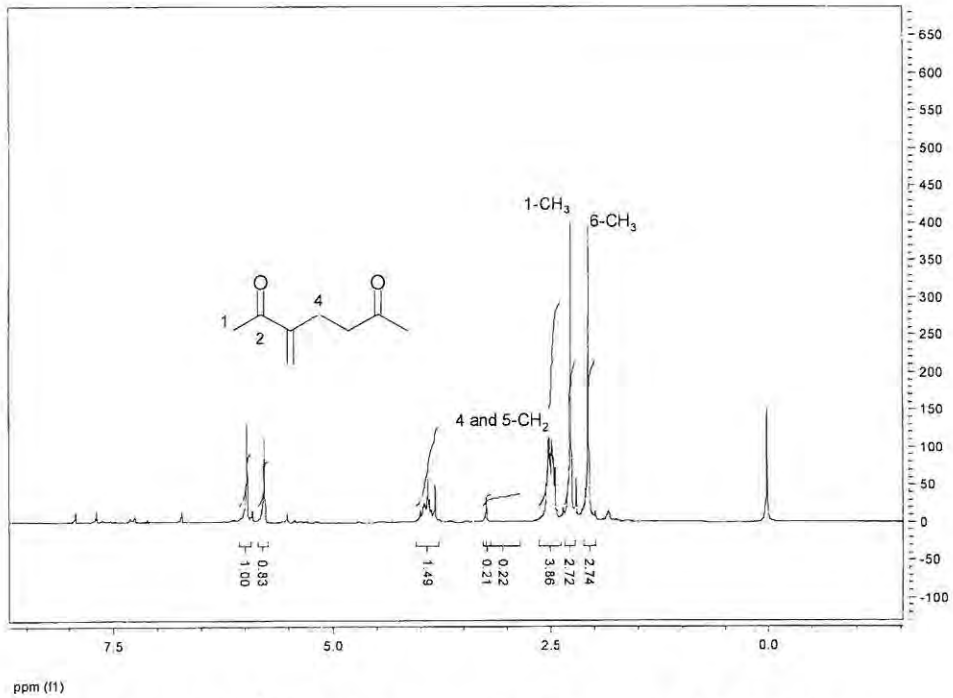
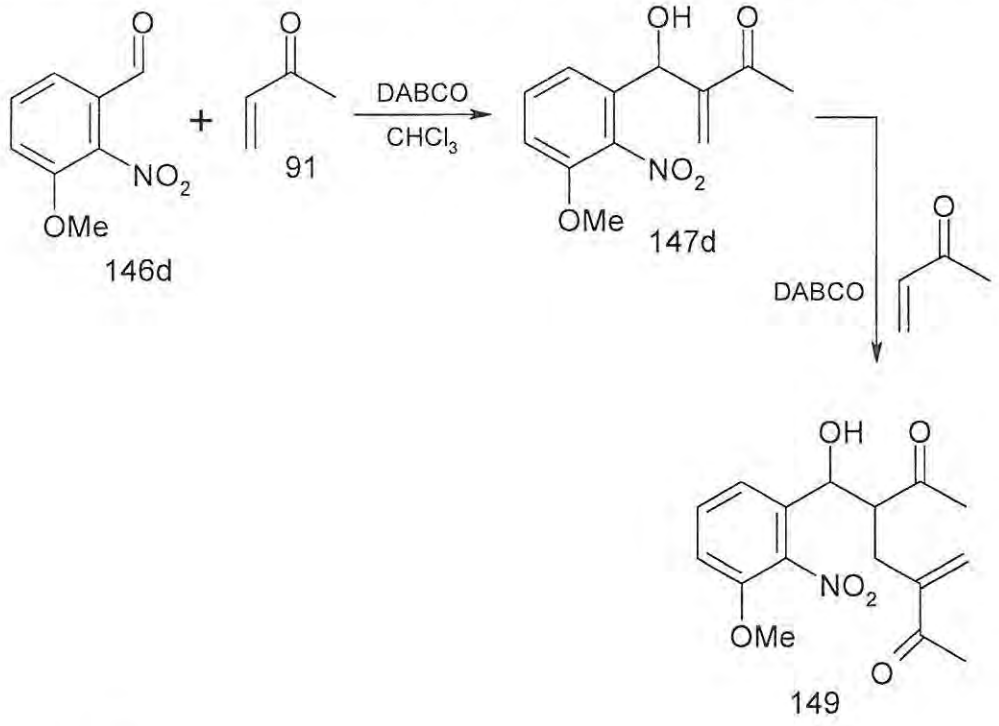


Figure 3. 400MHz ^1H NMR spectrum of compound **148** in $CDCl_3$.

The ^{1}H NMR spectrum (Figure 3) of methyl vinyl ketone dimer **148**, on the other hand, reveals two methyl proton signals resonating at *ca.* 2.3 ppm, each integrating for three protons, and two vinylic proton signals at *ca.* 5.9 ppm. The 4-and 5-CH_2 protons resonate as multiplets at *ca.* 2.5 and 4.0 ppm that integrate for two protons each. In the ^{13}C NMR spectrum, two carbonyl carbons are evident, indicating a lack of symmetry in the dicarbonyl system.

Interestingly, a further Baylis-Hillman product, the bis-MVK adduct **149** was also isolated from the reaction between 3-methoxy-2-nitrobenzaldehyde **146d** and methyl vinyl ketone (Scheme 40). In this case, formation of the Baylis-Hillman adduct **147d** was still incomplete after seven days, and additional MVK and DABCO were added and the reaction mixture stirred for a further three days. After this period, TLC analysis indicated the presence of two products, and chromatography permitted isolation of the normal Baylis-Hillman product **147d** and the di-adduct **149** in yields of 24% and 60%, respectively. Formation of the bis-MVK adduct **149** is attributed to subsequent reaction of the zwitterionic intermediate with the product **147d** in a Michael-type addition.



Scheme 40

The formation of the bis-MVK adduct **149** is supported by three methyl singlets at 2.06, 2.33 and 3.84 ppm (OMe) in the ^{1}H NMR spectrum (Figure 4a), each of which integrates for three protons. The two methylene protons at C-4 resonate as multiplets at 2.31 and 2.50 ppm, which each integrate for one proton. The fact that these two protons are non-equivalent reflects their diastereotopicity. The 6-methine proton resonates as a broad singlet at 4.66 ppm. The broad signal at 4.04 ppm corresponds to the hydroxyl proton, while the 5-methine proton resonates at 3.09 ppm. The two clearly separated signals at 5.83 and 6.04 ppm correspond to the two vinylic protons. And finally, the three aromatic protons resonate downfield around 7 ppm.

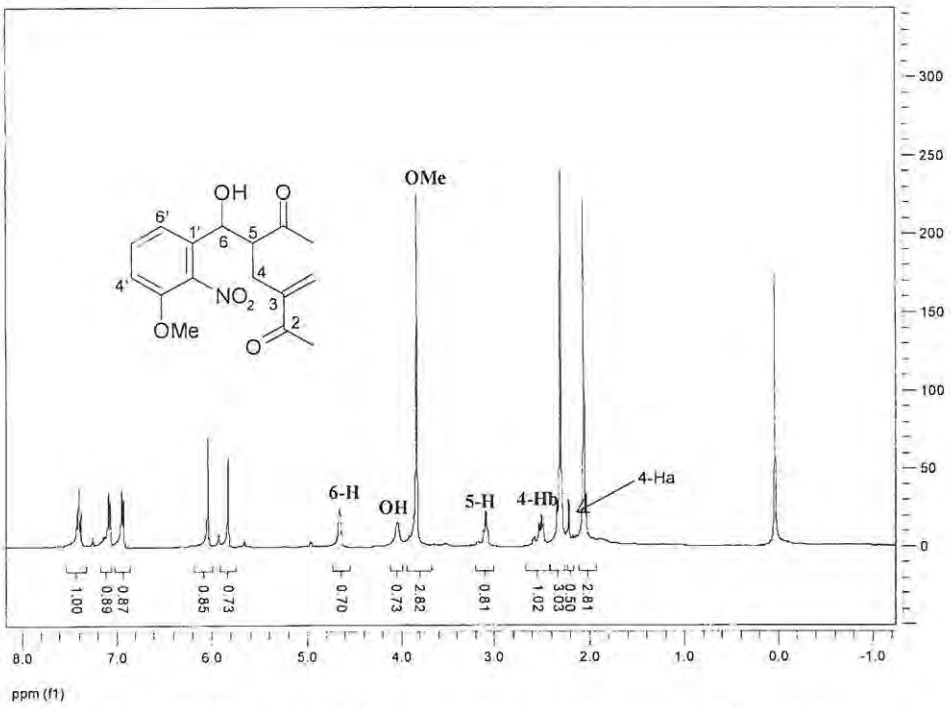


Figure 4a. 400 MHz ^{1}H NMR spectrum of compound **149** in $CDCl_3$.

The ^{13}C NMR spectrum of the bis-MVK adduct **149** (Figure 4b) reveals the expected 16 signals. The two methyl carbons resonate upfield and the deshielded OMe signal at 56.4 ppm, while the two carbonyl carbon signals at *ca.* 211 and 213 ppm supports the formation of the bis-MVK adduct. In the DEPT 135 spectrum (Figure 4c) the two methylene carbon signals resonating at 30.9 ppm and 128.6 ppm correspond to C-4 and C-3a, respectively.

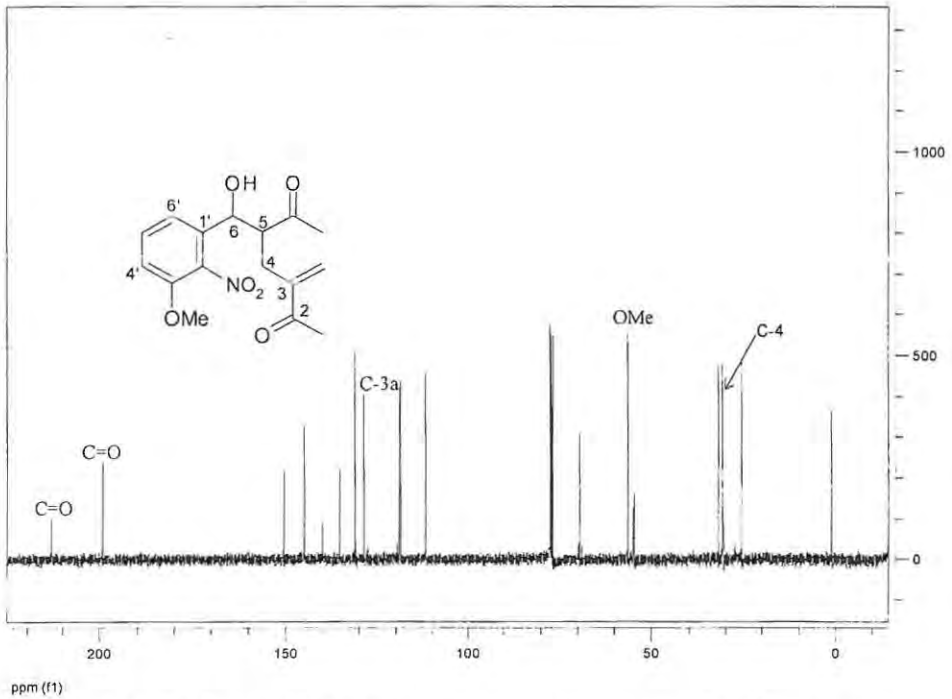


Figure 4b. 100 MHz ^{13}C NMR spectrum of compound **149** in $CDCl_3$.

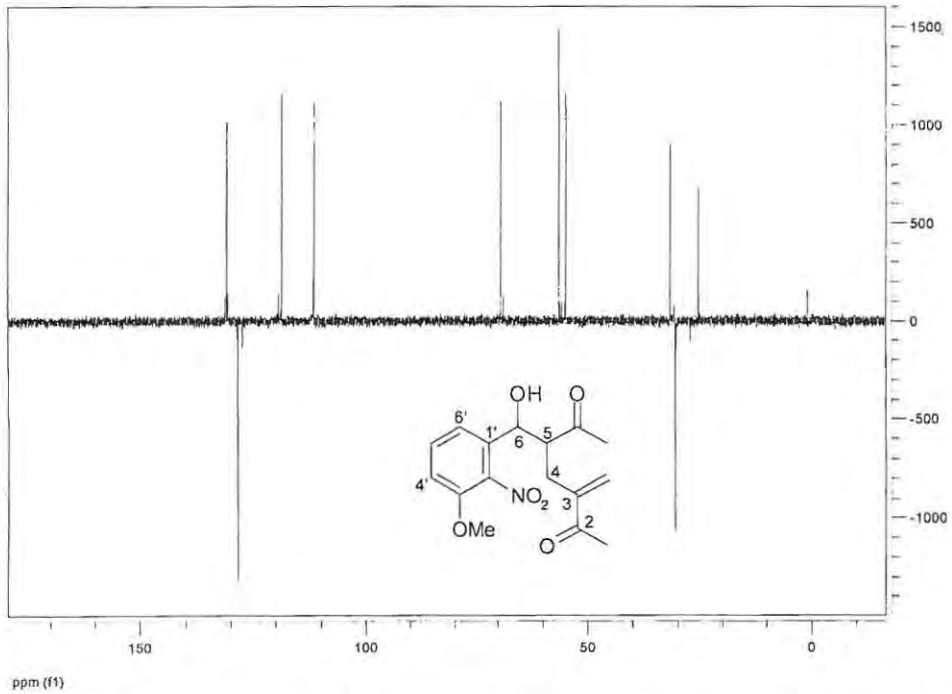
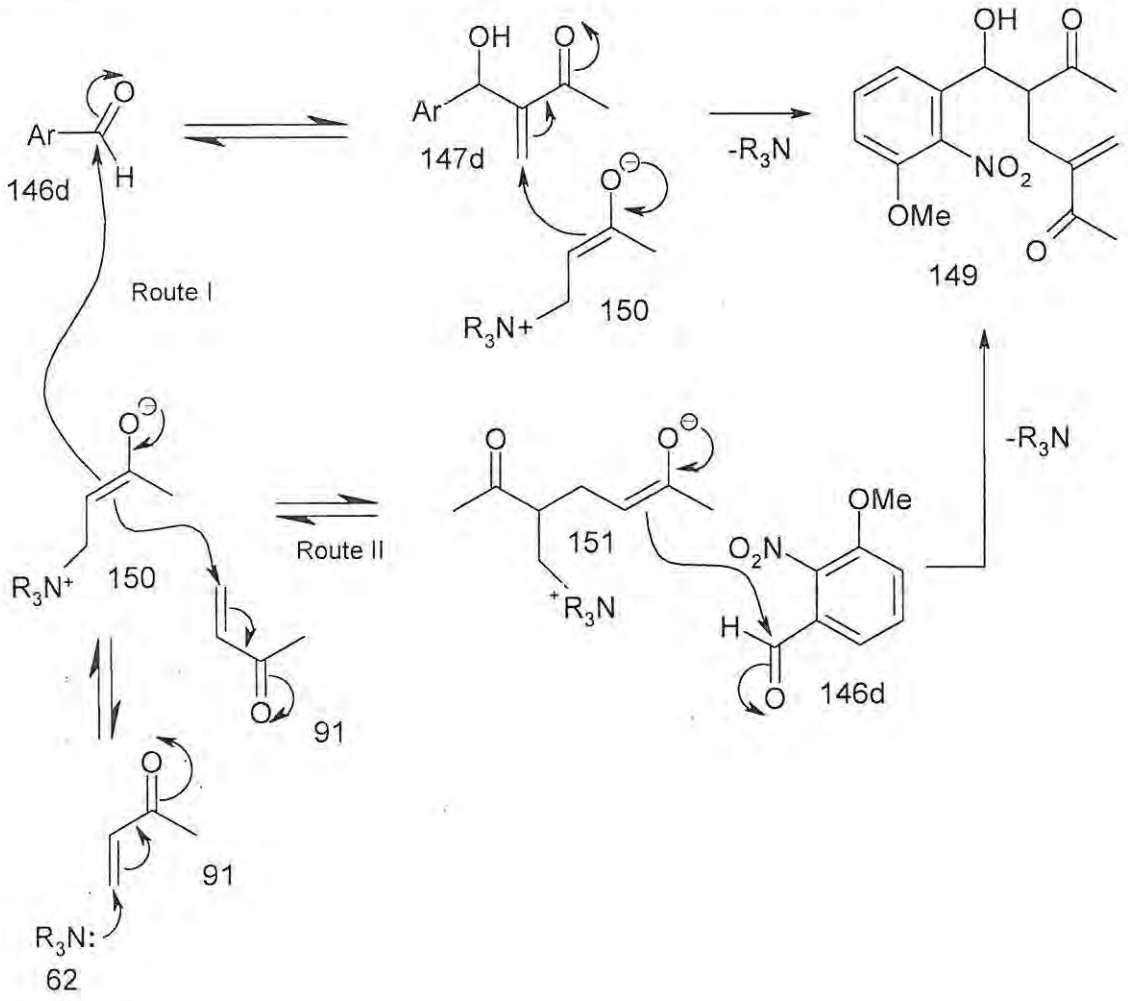


Figure 4c. 100 MHz DEPT 135 NMR spectrum of compound **149** in $CDCl_3$.

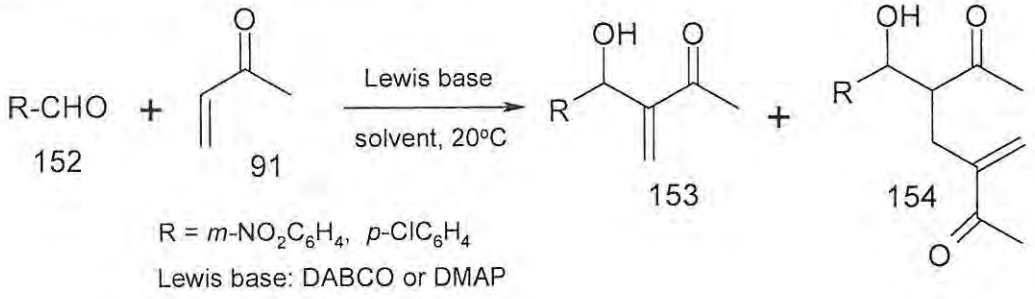
Detailed below, are two possible mechanistic pathways for the formation of the Baylis-Hillman bis-MVK adduct **149** (Scheme 41). In both cases, initial nucleophilic attack of the catalyst (DABCO) at the vinylic carbon leads to the formation of the zwitterionic intermediate **150**. At this point the routes diverge; the zwitterionic intermediate **150** would normally attack the carbonyl carbon of the aldehyde **146d** (Route I) but, since there is an excess of MVK present, the zwitterionic intermediate ion **150** could also attack the MVK carbonyl carbon. This leads (Route II) to the formation of an extended zwitterionic intermediate **151**, which attacks the carbonyl carbon of the aldehyde **146d**. Proton exchange followed by the elimination of the catalyst then yields the bis-MVK adduct **149**. In Route I, however, the bis-MVK adduct is formed *via* attack of the initial zwitterionic intermediate **150** on the normal Baylis-Hillman product **147d**.



Scheme 41

Shi and co-workers[35] have previously reported the isolation of this type of product from the Baylis-Hillman reaction of arylaldehydes with MVK (Scheme 42). Moreover, they state that the yield of such products can be increased by increasing the amount of the MVK, and that the catalysts used [4-dimethylaminopyridine (DMAP) or DABCO] also affect the yields, with DABCO being the most effective. The mechanism which these authors suggest for the formation of the bis-vinyl ketone adducts follows Route I (Scheme 41), *i.e.* attack on the Baylis-Hillman products **153** formed by the zwitterionic intermediate **150,** elimination of the catalyst then affording the bis-vinyl ketone adducts **154.**

Interestingly, Shi *et al.*[35] found that *o*-nitrobenzaldehyde failed to afford the corresponding bis-MVK adduct, the sole product being the normal Baylis-Hillman adduct. It is thus apparent that the 3-methoxy group present in the system examined in the present study (**146d** and / or **147d**) plays an important role in facilitating formation of the bis-MVK adduct **149**. Kinetic and computational studies are now being conducted in the group to explore the mechanistic details.



Scheme 42

In order to explore the rate of transformation to a normal Baylis-Hillman, a reaction was set up using 5-chloro-2-nitrobenzaldehyde, MVK and DABCO (1:1.5:0.05) and $CDCl_3$ as the solvent. The reaction was monitored daily by ^1H NMR analysis, *i.e.* every 24 hours. The ratio of the integrals for the methyl singlets corresponding to the substrate (MVK) and product (Baylis-Hillman adduct) was determined, assuming that the sum of these integrals remains constant. From the ^1H NMR data, acquired from the seven spectra

collected, the rate of formation of the adduct was determined, and a graph of the percentage yield against time was plotted (Figure 5). From the graph it was apparent that

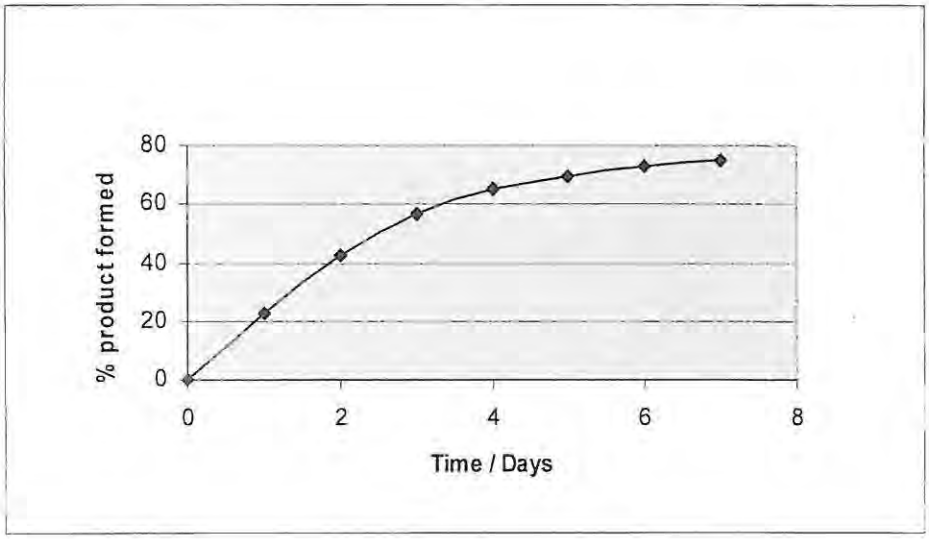
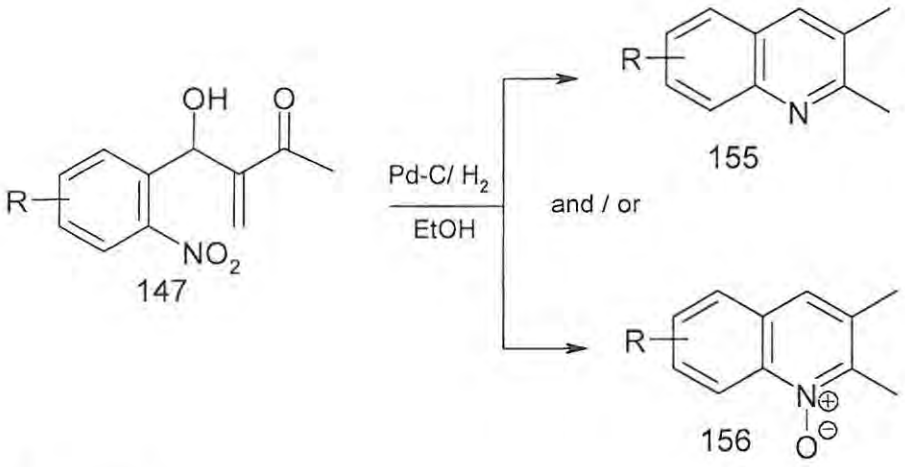


Figure 5. Rate monitoring using the 5-chloro-2-nitrobenzaldehyde substrate.

the reaction proceeded smoothly for the first three or four days, after which the rate decreased markedly affording a yield of *ca.* 75% after seven days. Baylis-Hillman reactions are, typically, quite slow, and we decided the reactant ratio of 1: 1.5: 0.05 for benzaldehyde, MVK and DABCO, respectively, should be maintained. However, it was observed that dissolution of the catalyst in the solvent before the addition of the aldehyde improved the yield.

2.2 Catalytic hydrogenation of Baylis-Hillman products

The Baylis-Hillman adducts, prepared as described above, were then reductively cyclized in the presence of a 10% palladium-on-carbon catalyst. The reactions were carried out at room temperature for periods of *ca.* 1.5 hours. The intention was, of course, to prepare quinoline derivatives but, in the process, quinoline-*N*-oxide derivatives and amino derivatives were also isolated as competition products. Scheme 43 illustrates the general approach adopted.



Scheme 43

When examined in isolation, the proton NMR spectra of the quinolines and the corresponding quinoline-*N*-oxides are not readily differentiated (Figures 6a and 6b). When compared, however, there are a number of features which permit the products to be distinguished from each other. Thus, in the case of the ^{1}H NMR spectrum of the quinoline-*N*-oxide **156b**, there is a doublet which resonates downfield at *ca.* 8.6 ppm that corresponds to the proton on carbon-8. This proton resonates downfield because it is close to the positive nitrogen of the *N*-oxide moiety. In the case of the quinoline **155b**, however, the *N*-oxide oxygen is absent and, as a result, the 8-H nucleus resonates further upfield. Other important distinctions between the quinoline and the quinoline-*N*-oxide proton NMR spectra are the downfield shifts of both the methyl signals of the quinoline-*N*-oxide **156b** and a marked decrease in their chemical shift separation compared to the corresponding signals of the quinoline **155b**. These differences can be seen in Figures 6a and 6b below.

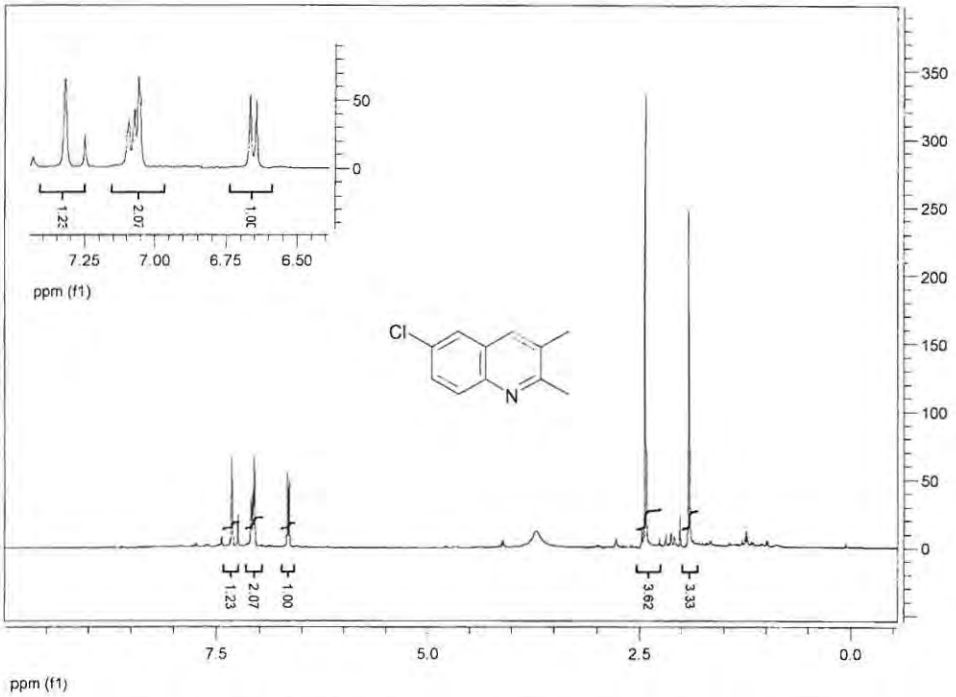


Figure 6a. 400 MHz ^{1}H NMR spectrum of compound **155b** in $CDCl_3$.

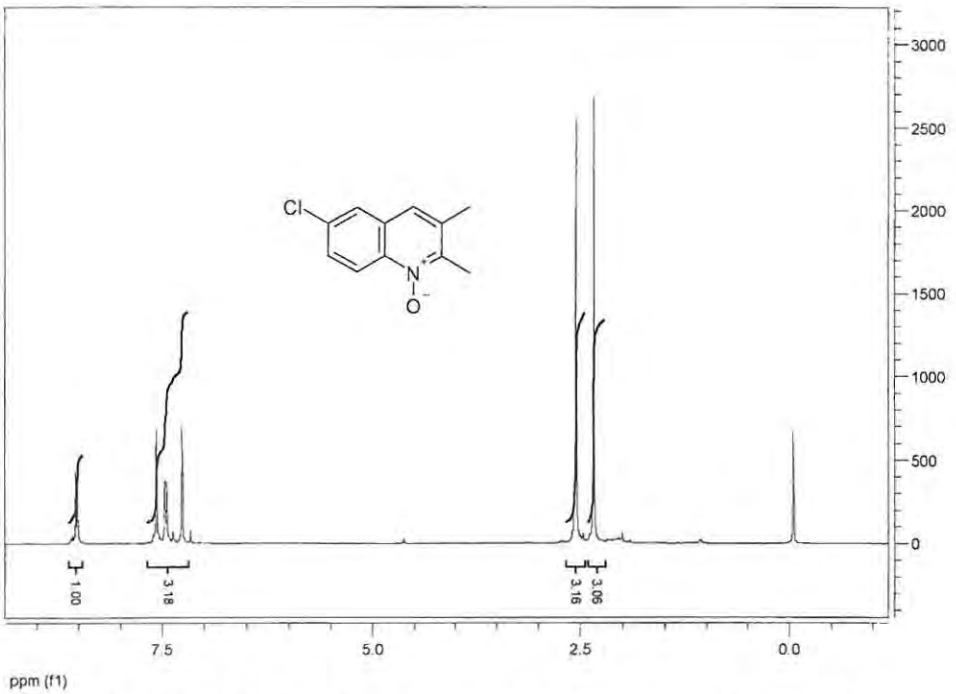


Figure 6b. 400 MHz ^{1}H NMR spectrum of compound **156b** in $CDCl_3$.

Not surprisingly, ^{13}C NMR and DEPT 135 spectra of the quinoline **155b** and quinoline-*N*-oxide **156b**, are rather similar except that in both ^{13}C NMR and DEPT 135 spectra of the quinoline **155b**, the two upfield methyl signals are significantly more separated than those of the quinoline-*N*-oxide **156b**. The aromatic carbons of the quinoline-*N*-oxide **156b** also resonate closer to each other, compared to the corresponding quinoline **155b** (see Figures 6c and 6e). The presence of the oxygen atom in the *N*-oxide is supported by the high resolution mass spectrometric data and by the N-O IR stretch observed at *ca.* 1250 cm^{-1}.

Though the high resolution mass spectrometric data of compounds **155b** and **155e** gave the correct results which matched the given compounds but there were some anomalies in the ^{13}C NMR spectra of both compounds, the signal at *ca.* 200 ppm (see Figure 6c), for example, does not correlate with any of the structures concerned. Also, two methine carbon signals were missing form the DEPT 135 spectrum of compound **155e**. These aspects need to be explored further.

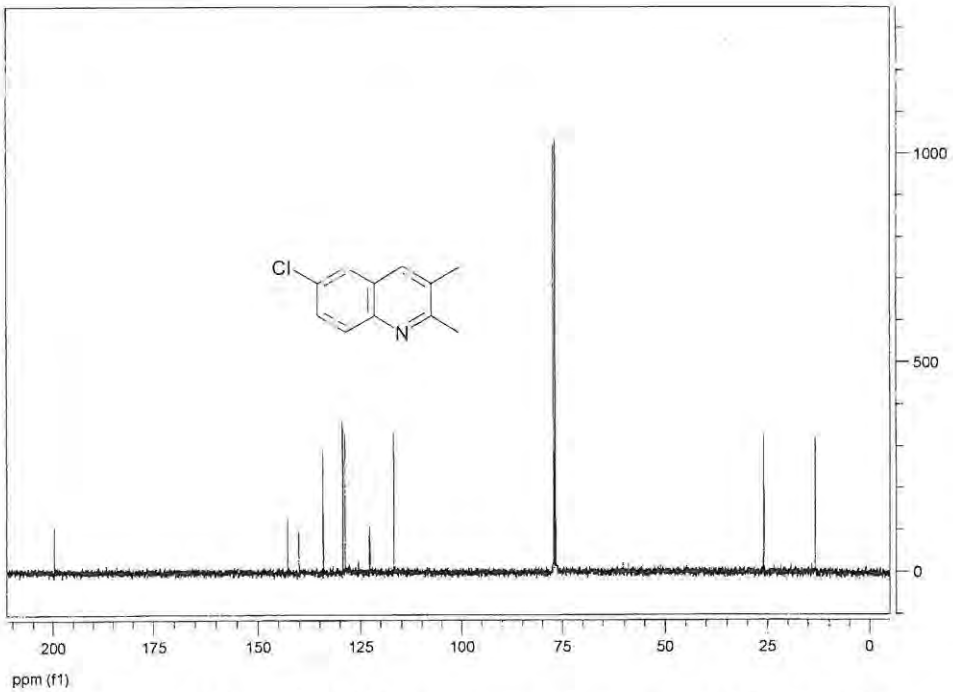


Figure 6c. 100 MHz ^{13}C NMR spectrum of compound **155b** in $CDCl_3$.

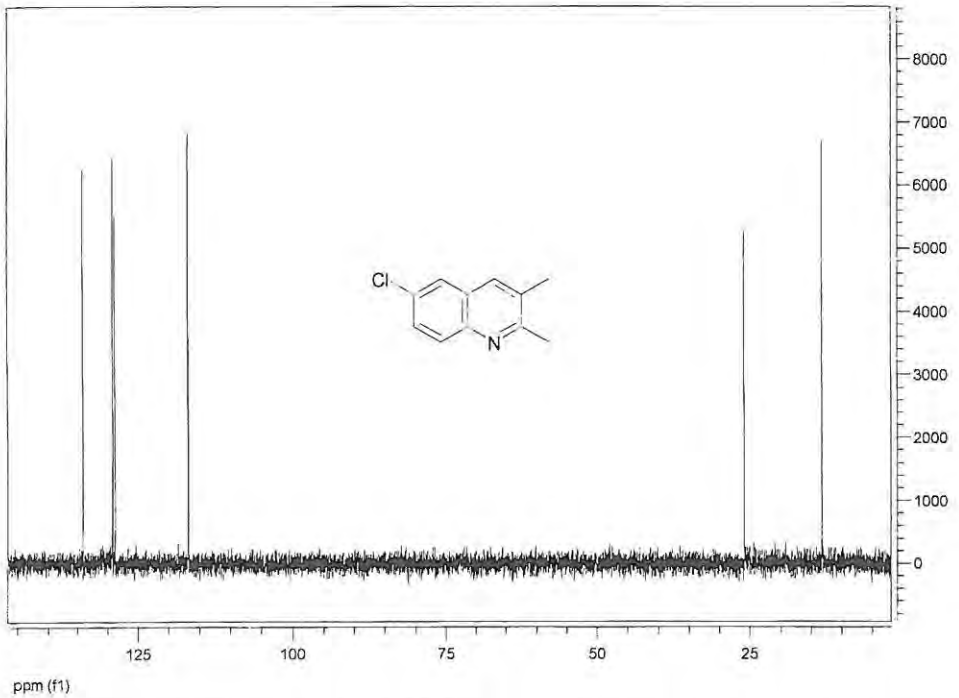


Figure 6d. 100MHz DEPT 135 NMR spectrum of compound **155b** in $CDCl_3$.

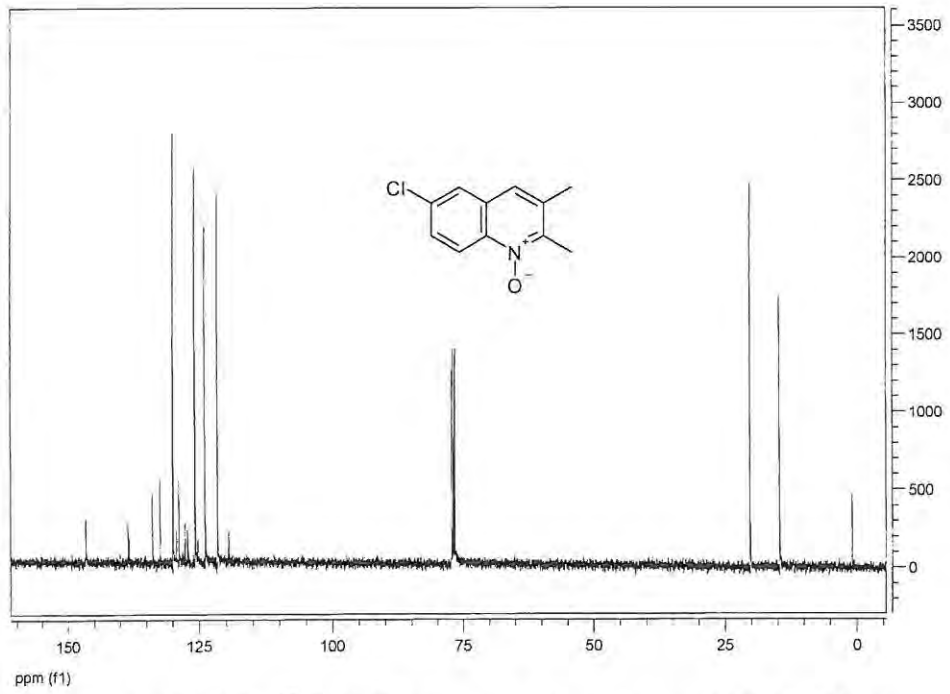


Figure 6e. 100 MHz ^{13}C NMR spectrum of compound **156b** in $CDCl_3$.

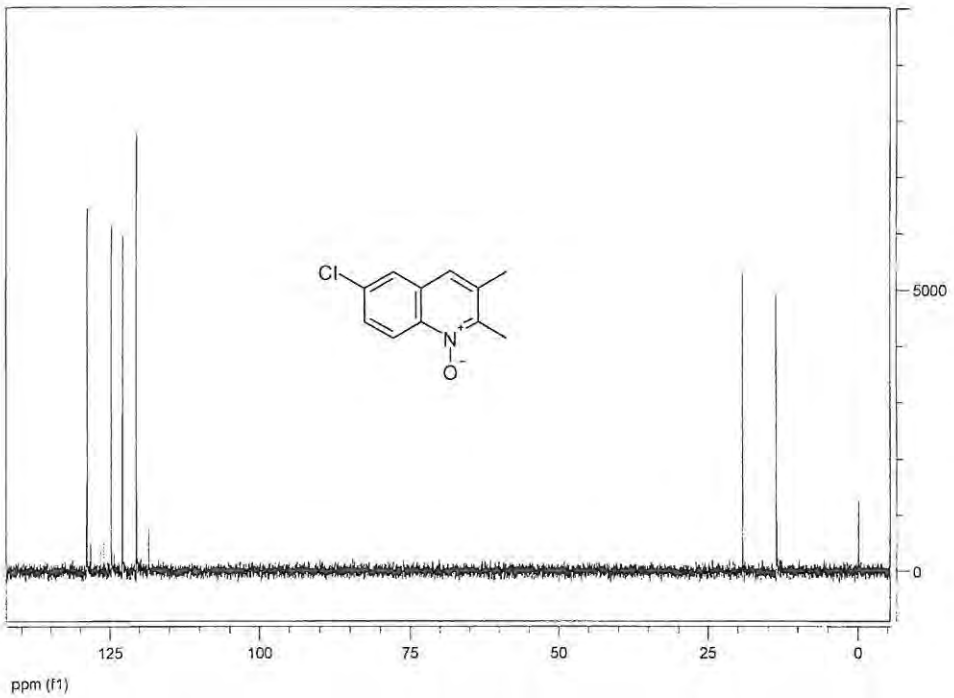
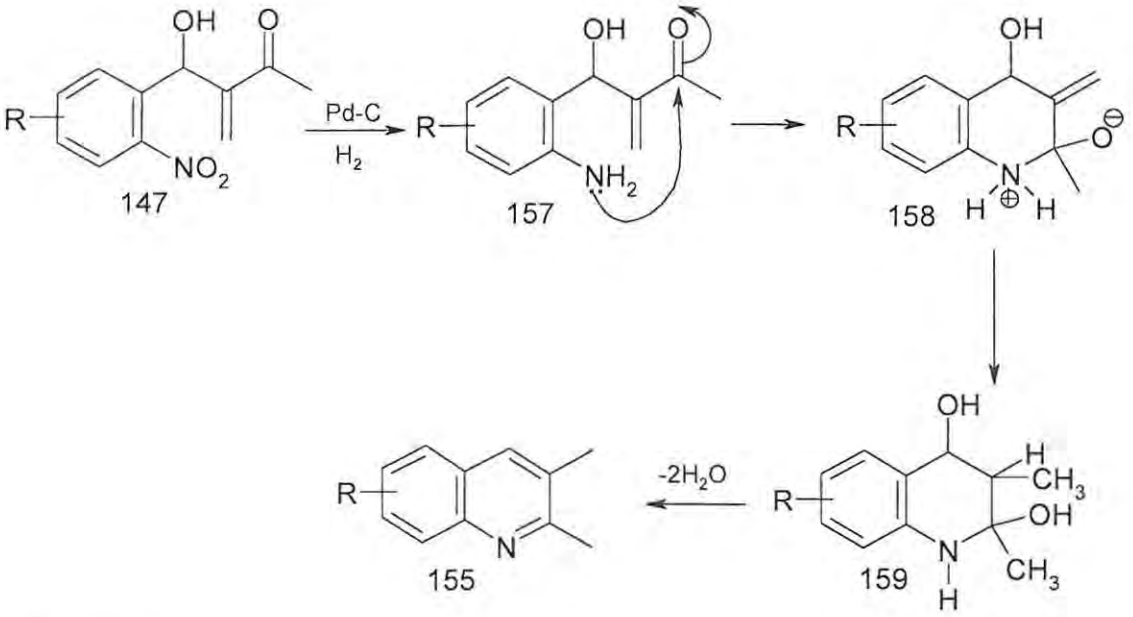


Figure 6f. 100 MHz DEPT 135 NMR spectrum of compound **156b** in $CDCl_3$.

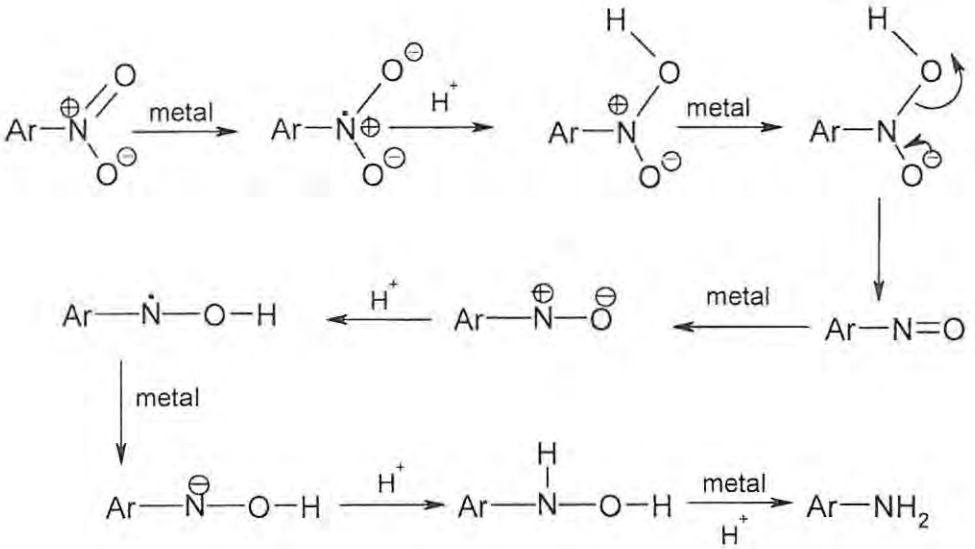
The reaction mechanism which has been proposed[46] for the formation of the quinoline products is illustrated in Scheme 44. Conversion of the nitro group to an amino group is followed by nucleophilic attack on the carbonyl carbon and concomitant cyclization, reduction of the resulting exocyclic double bond in intermediate **158,** proton exchange and, finally, the loss of two water molecules to afford the quinoline derivative **155.**[#]

During the reduction of the nitro group to the amino group, a series of steps take place and a number of the intermediate groups could, conceivably, be sufficiently nucleophilic to attack the carbonyl carbon and thus lead to a cyclic *N*-oxide product. Reduction of the nitro group is known to involve the sequence outlined in Scheme 45,[77] and formation of the corresponding *N*-oxides can thus be attributed to partial reduction of the nitro group.

[#] The order of the reduction and cyclisation phases is, of course, still open to debate.



Scheme 44



Scheme 45

The table below (Table 2) shows the products obtained from the reductive cyclization of the Baylis-Hillman products. It is evident that the products obtained are not the same, or to be precise, not all the same types of products were isolated from each reaction. In fact, four different product types were identified, *viz.*, the expected quinolines **155**, the corresponding *N*-oxides **156**, the partially reduced nitro compounds **161** and, in one case,

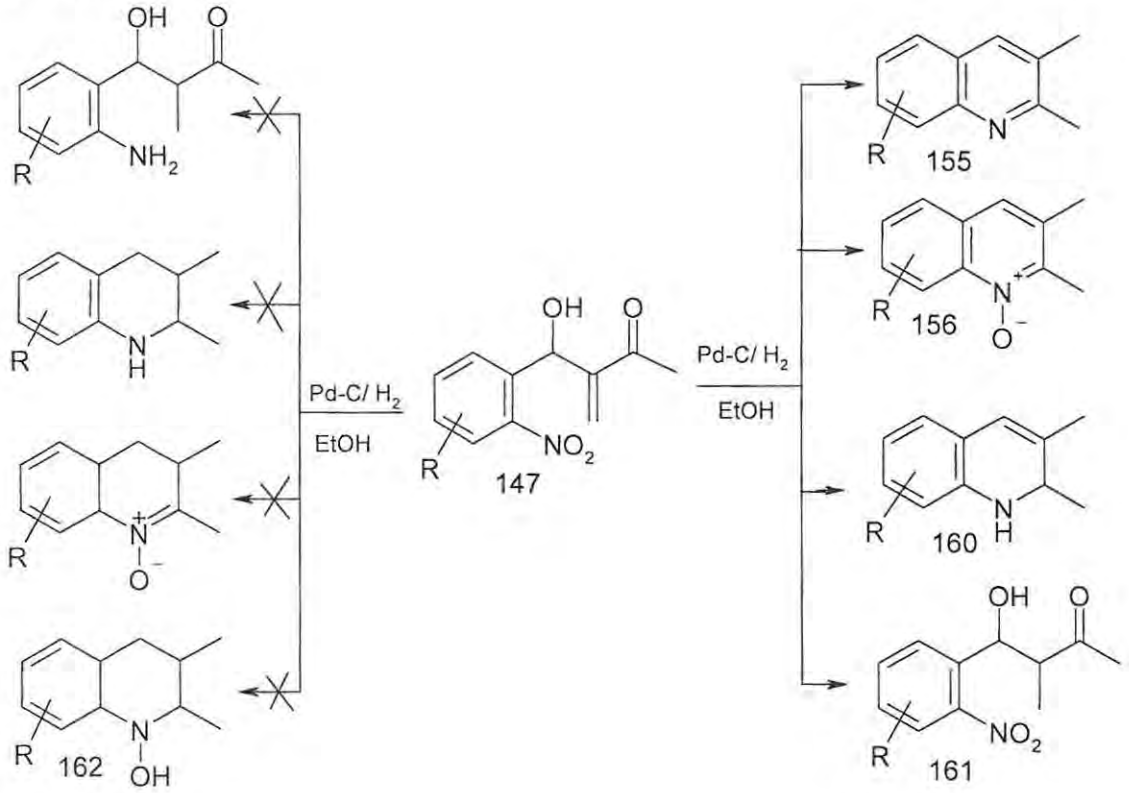
the dihydroquinoline **160**. The reasons for this may vary. As mentioned above, different intermediates are involved (Scheme 45) and can result in different reductively cyclized products. Consequently, different products were obtained, together with the quinoline derivatives, from each individual reaction. The major products were isolated by flash chromatography and then analysed. When the Baylis-Hillman products **147e** and **147g** were hydrogenated, only two spots were visible on the TLC plates with some material remaining on the baseline. The quinoline-*N*-oxides are very polar and tend to stick at the base of the plate or column. In some cases, the quinoline-*N*-oxide was obtained by flushing the column with distilled acetone. In retrospect, the absence of the quinoline-*N*-oxide derivatives in two cases may be due to the competitive formation of the partially reduced "acyclic" products **161a, b** and **c** or to the fact that the corresponding polar *N*-oxides were not washed off the column.

Table 2. Yields obtained from the hydrogenation of the Baylis-Hillman adducts **147a-g**.

Substrate	R								
		Compd.	Yield[a] / %	Compd.	Yield[a] / %	Compd.	Yield[a] / %	Compd.	Yield[a] / %
147a	H	**155a**	14	**156a**	66	**161a**	8	—	—
147b	6-Cl	**155b**	26	**156b**	23	—	—	—	—
147c	6-OH	**155c**	15	**156c**	20	—	—	—	—
147d	8-OMe	**155d**	26	—	—	**161b**	38	—	—
147e	5-Cl	**155e**	29	**156e**	13	—	—	**160**	4
147g	6,7-OCH_2O-	**155f**	12	—	—	**161c**	30	—	—

[a]Chromatographically pure.

The formation of compounds of the type **160** is not surprising, as a number of the intermediates involved in the conversion of nitro to amino could attack the carbonyl carbon of the Baylis-Hillman product to form different products (see Scheme 46), while catalytic hydrogenation of the alkene moiety accounts for the formation of products of type **161**.



Scheme 46

Spectroscopic analysis confirmed the formation of the nitro derivatives **161**. Thus, in the ^{1}H NMR spectrum of compound **161b** (Figure 7a), three methyl signals, each integrating for three protons, are present. The signal at *ca.* 1 ppm, which is a doublet, corresponds to the 3"-methyl protons, which couple with the 3-methine proton. The second methyl signal at *ca.* 2 ppm corresponds to the acetyl methyl group and the third methyl signal at *ca.* 4 ppm corresponds to the methoxy protons. Both the methyl signals at *ca.* 2 ppm and 4 ppm are singlets. The multiplet at 4.78 ppm integrates for one proton and is assigned to the 4-methine proton, while the broad hydroxyl signal is observed at *ca.* 3.26 ppm.

Lastly, the 3-methine signal (3.02 ppm) and the three aromatic proton signals (7.0 – 7.5 ppm) confirm formation of the nitro comopund **161b**.

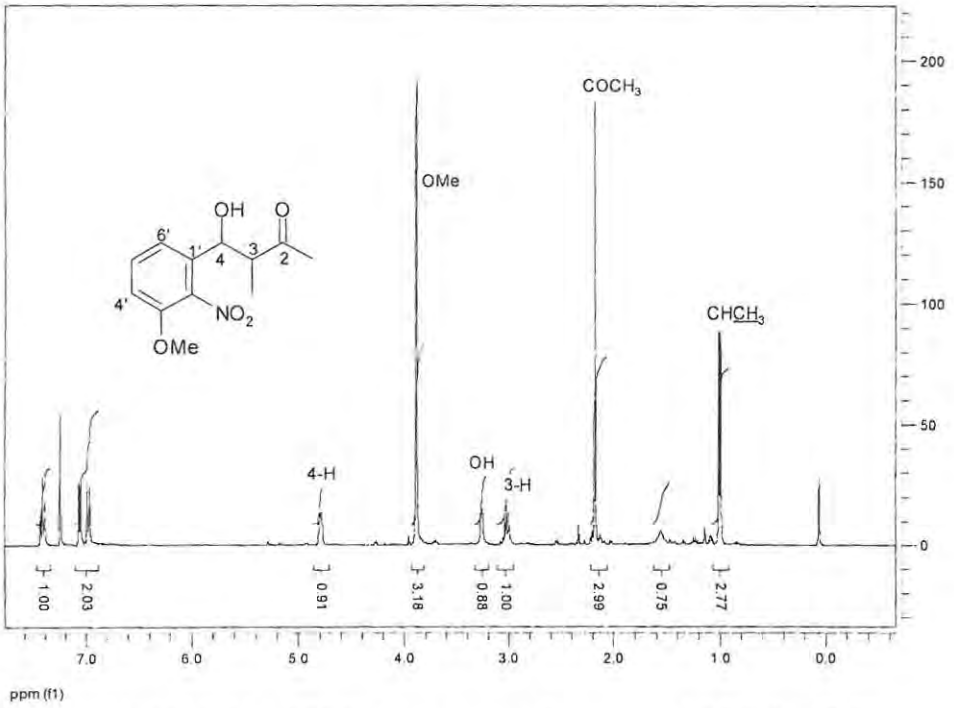


Figure 7a. 400 MHz ^{1}H NMR spectrum of compound **161b** in $CDCl_3$.

In the ^{13}C NMR spectrum (Figure 7b) only eleven carbon signals are immediately apparent instead of the expected twelve, but signals corresponding to two of the quaternary carbons (C-1' and C-2') overlap and resonate at the same chemical shift value (δ134.8 ppm). The DEPT 135 spectrum (Figure 7c) shows eight carbon signals which correspond to all the proton-bearing carbons. The carbonyl carbon signal is evident at *ca.* 210 ppm in the proton noise decoupled spectrum (Figure 7b).

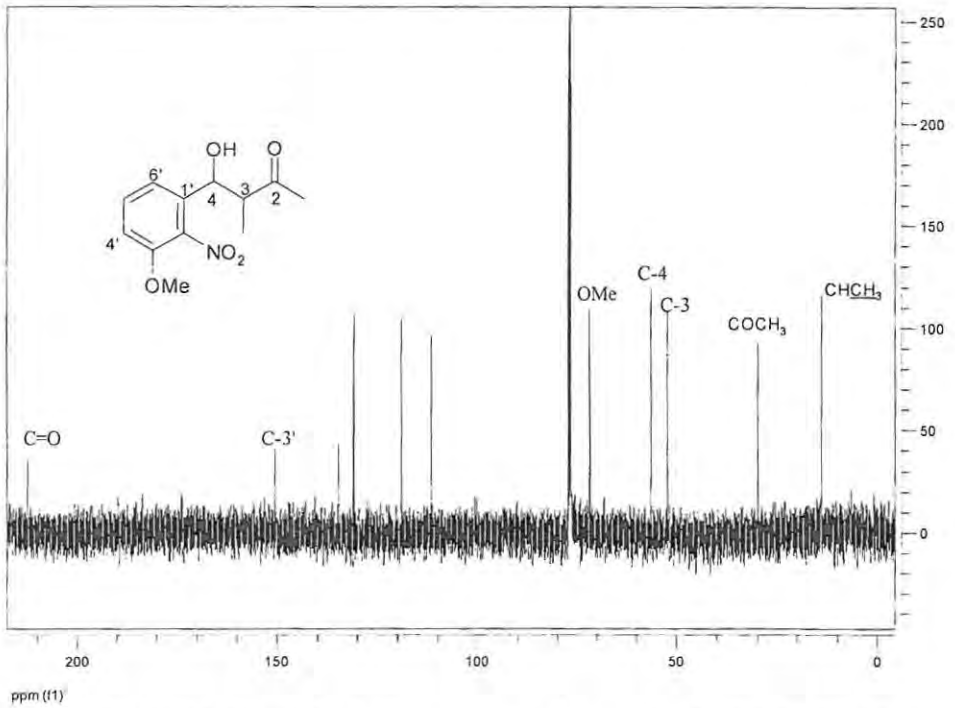


Figure 7b. 100 MHz ^{13}C NMR spectrum of compound **161b** in $CDCl_3$.

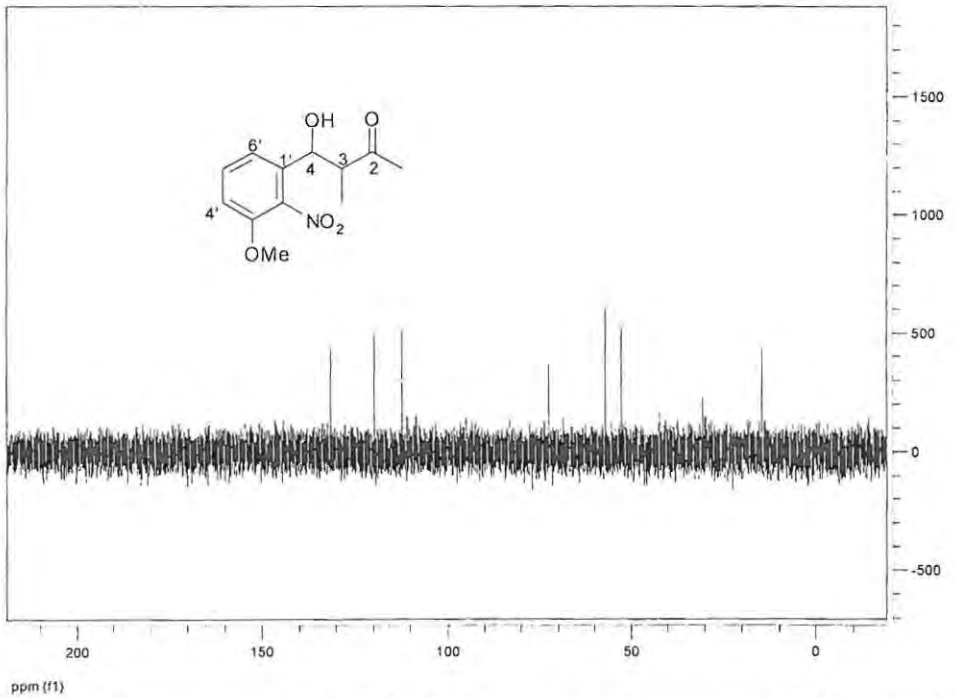


Figure 7c. 100MHz DEPT 135 NMR spectrum of compound **161b** in $CDCl_3$

Although the ^{1}H NMR spectrum (Figure 8a) clearly shows that the compound **160** was not pure, but it was possible from the spectrum to detect some special characteristics that support the formation of the dihydroquinoline derivative **160**, *viz.*, the presence of two methyl signals, each integrating for three protons, at 1.36 and 1.70 ppm, one methine proton and four aromatic protons. The signal at 1.36 ppm is a doublet because it is coupling with the 2-methine proton at 4.35 ppm. When the chemical shifts of the two methyl signals of compound **160** were compared to other *N*-oxide methyl signals prepared in this study, it was evident that the product was not an *N*-oxide. In the ^{13}C NMR spectrum (Figure 8b), eleven carbon signals are consistent with the proposed structure. Furthermore, the DEPT 135 spectrum (Figure 8c), confirms the presence of seven proton-bearing carbons and that there are no methylene carbons. However, when the compound was submitted for HR mass spectrometry analysis a mass of 211.07643 Daltons which correlates to the molecular formula of $C_{11}H_{14}NO^{35}Cl$ was observed. This suggests the presence of a less polar minor component **162** (Scheme 46). No M+ ion at *m/z* 193 (and M+2 at *m/z* 195) was observed for compound **160**.

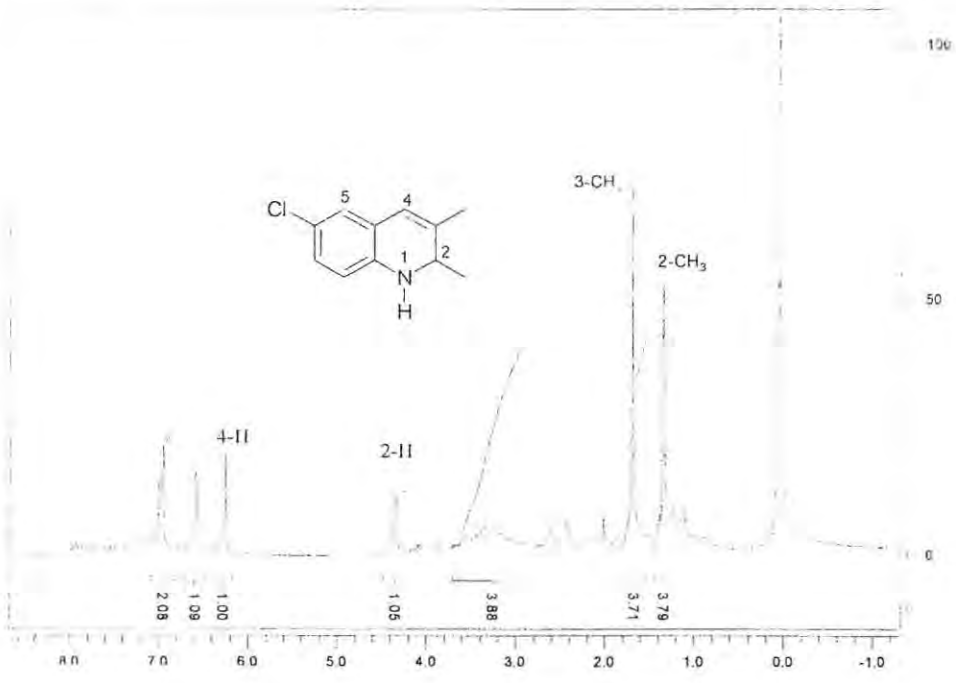


Figure 8a. 400 MHz ^{1}H NMR spectrum of compound **160** in $CDCl_3$.

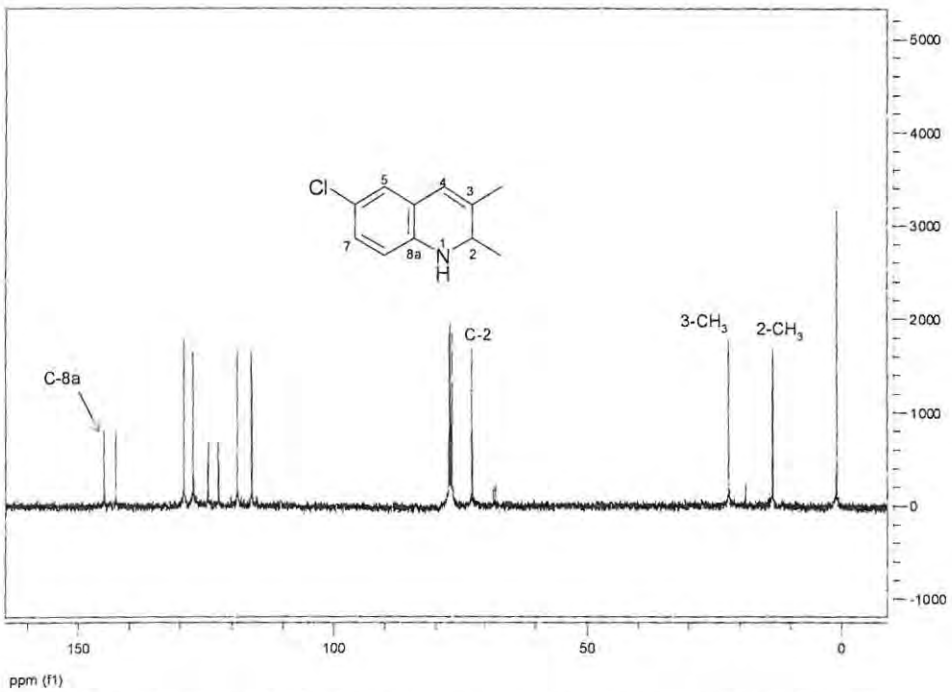


Figure 8b. 100 MHz ^{13}C NMR spectrum of compound **160** in $CDCl_3$.

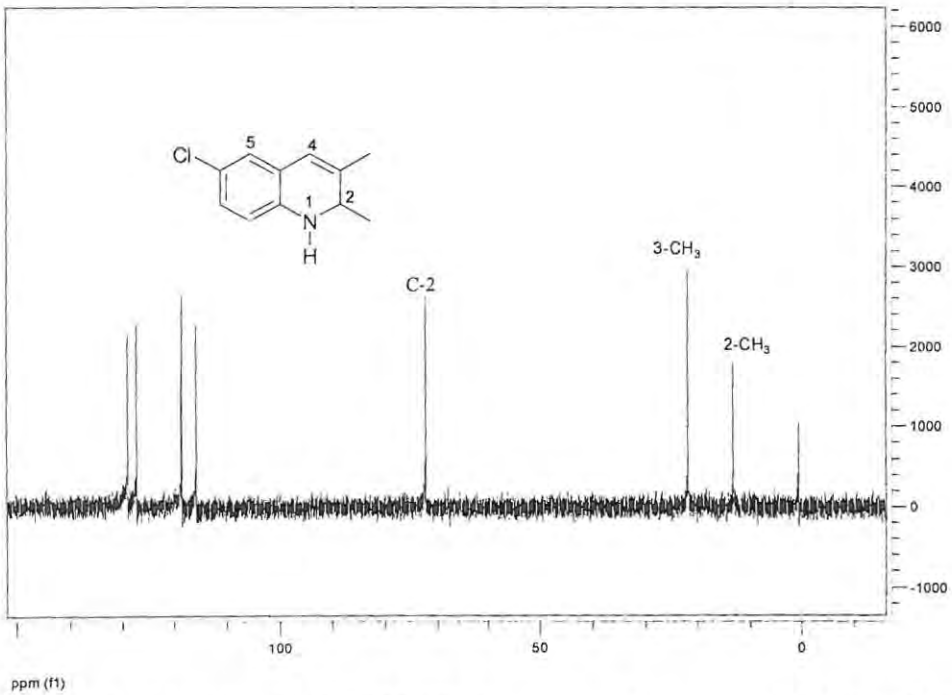
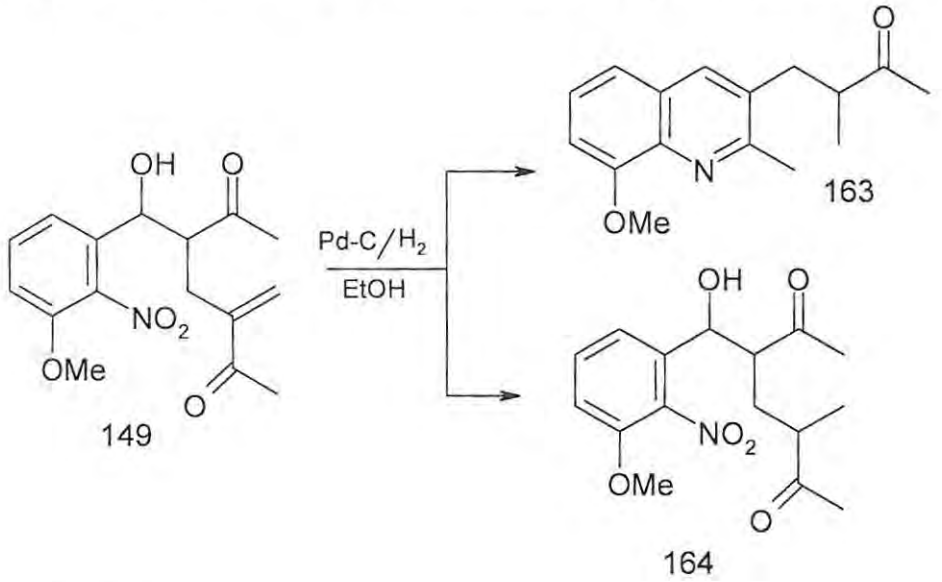


Figure 8c. 100 MHz DEPT 135 NMR spectrum of compound **160** in $CDCl_3$.

Compound **149** was also subjected to catalytic hydrogenation conditions and the products **163** and **164** were isolated in 7% and 43% yield, respectively (Scheme 47).



Scheme 47

From the ^{1}H NMR spectrum of compound **163** (Figure 9a), four methyl signals each integrating for three protons are evident. The furthest upfield of the four signals appears at *ca.* 1 ppm and corresponds to the methyl group attached to C-2'. This methyl signal is a doublet due to coupling with the 2'-methine proton. The diastereotopic methylene protons 1'-H_a and 1'-H_b resonate as well separated multiplets, at 2.71 and 3.19 ppm. These protons couple not only with each other but also with the 2'-methine proton. The four aromatic protons resonate, as expected, in the region δ 7 - 8 ppm. The sixteen signals in the ^{13}C NMR spectrum (Figure 9b) are consistent with the structure and the DEPT 135 spectrum (Figure 9c) confirms that there are ten proton-bearing carbons, one of which is a methylene carbon. High resolution mass spectrometry indicates a molecular mass of 257.14224 Daltons, which is consistent with the molecular formular $C_{16}H_{19}NO_2$.

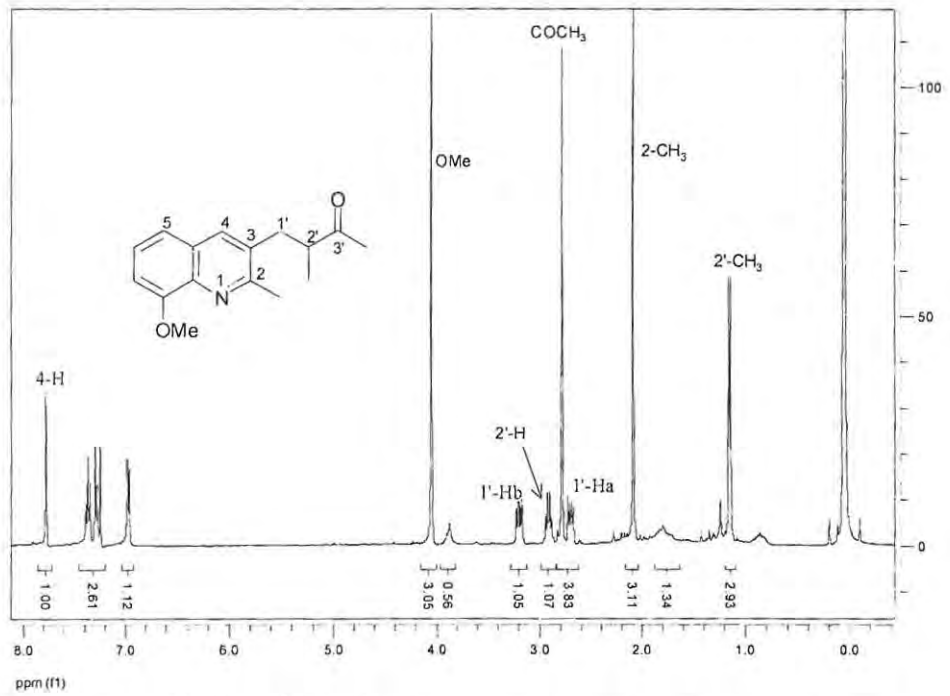


Figure 9a. 400 MHz ^{1}H NMR spectrum of compound **163** in $CDCl_3$.

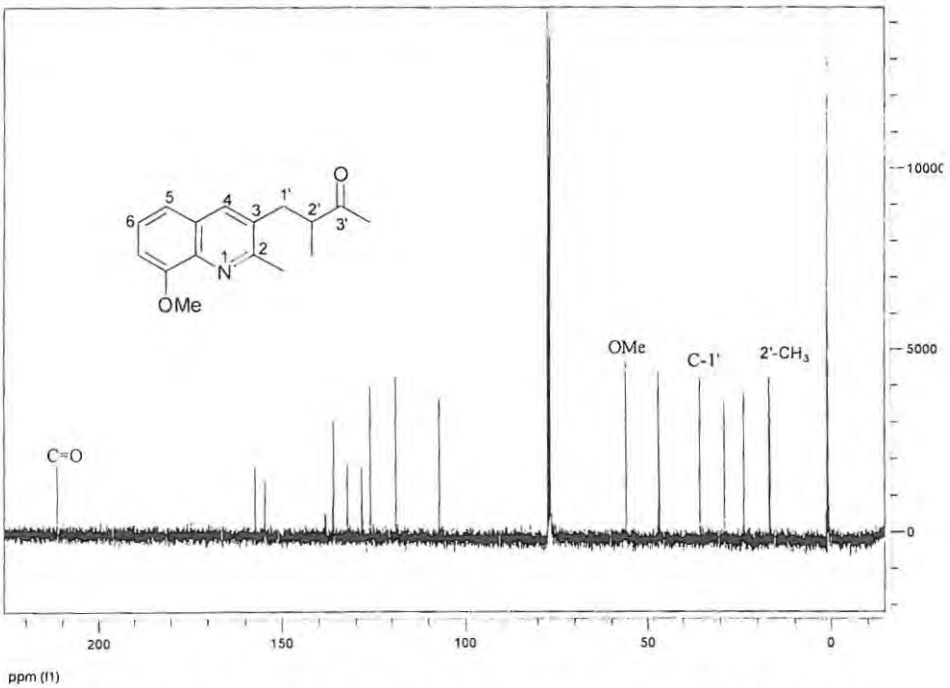


Figure 9b. 100 MHz ^{13}C NMR spectrum of compound **163** in $CDCl_3$.

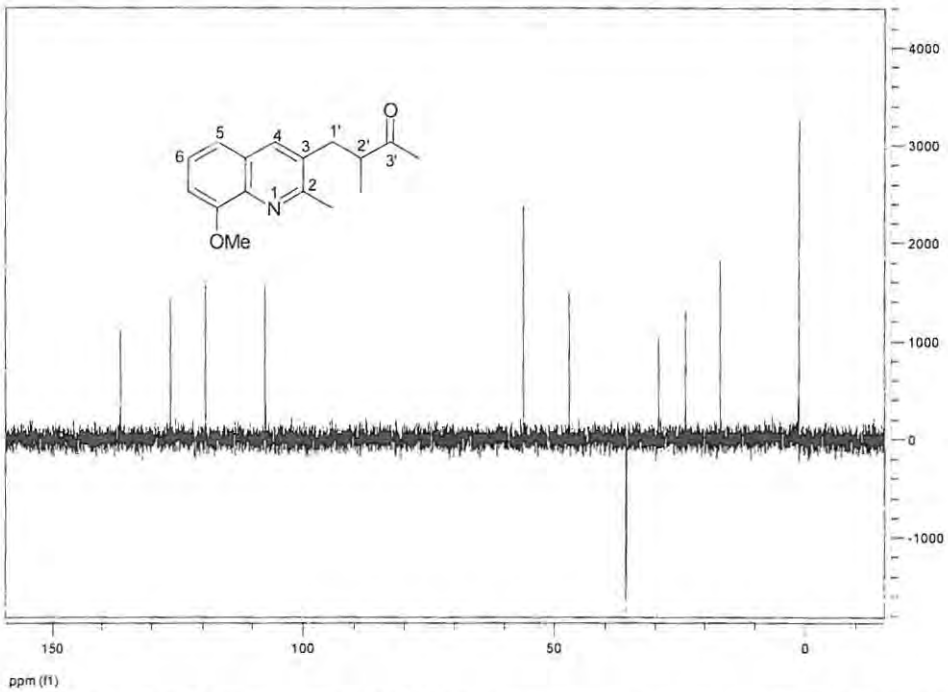


Figure 9c. 100 MHz DEPT 135 NMR spectrum of compound **163** in $CDCl_3$.

From the COSY NMR spectrum (Figure 9d) for compound **163,** it is evident that there is a strong coupling between the methyl protons of the 2'-methyl group (*ca.* 1 ppm) and the 2'-methine proton (2.91 ppm). The two diastereotopic proton multiplets at 2.71 and 3.16 ppm couple with each other and with the 2'-methine proton, while the HMQC spectrum (Figure 9e) reveals that these two protons are definitely on the same carbon (C-1'; at 35.5 ppm).

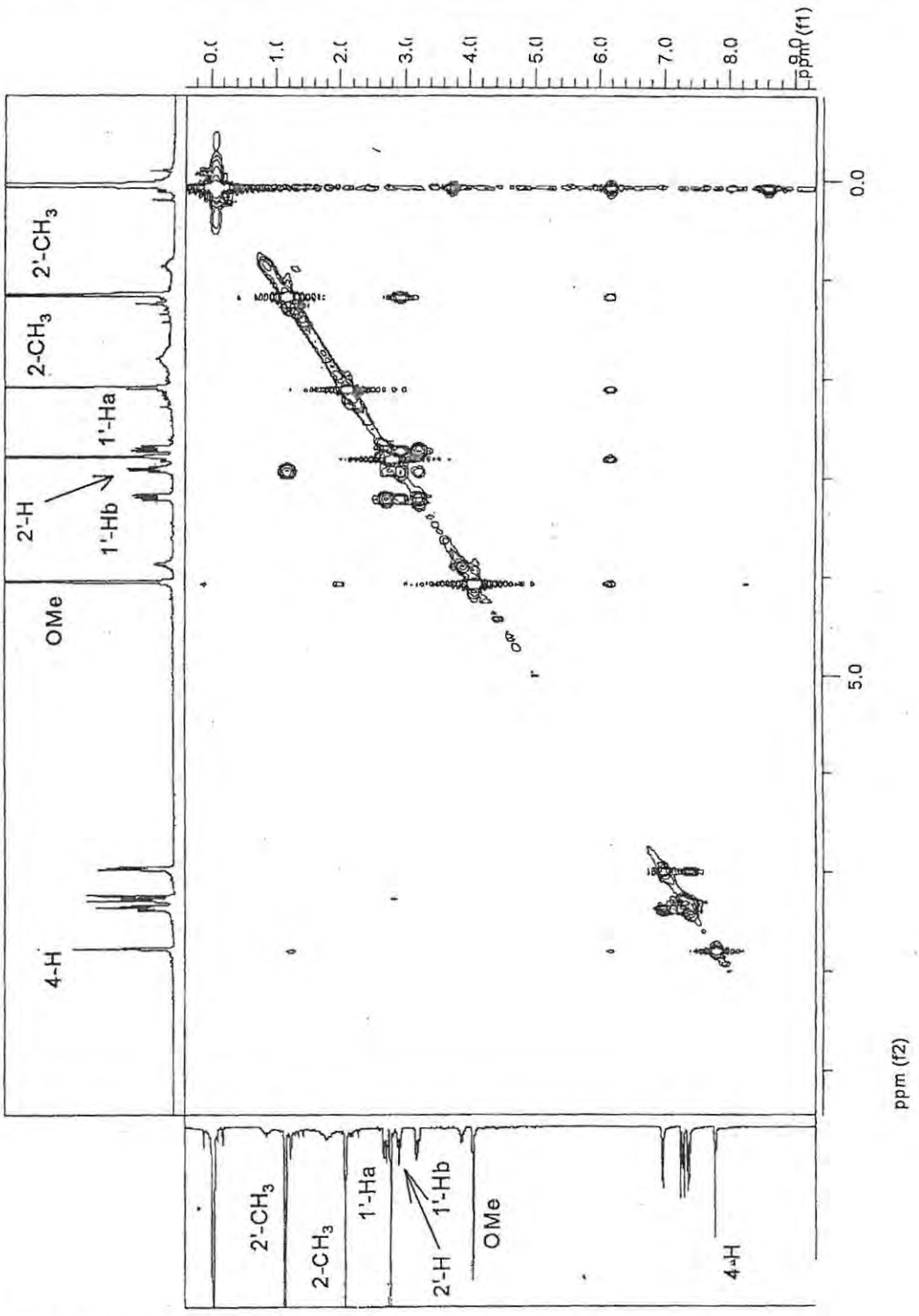


Figure 9d. COSY NMR spectrum of compound **163** in $CDCl_3$.

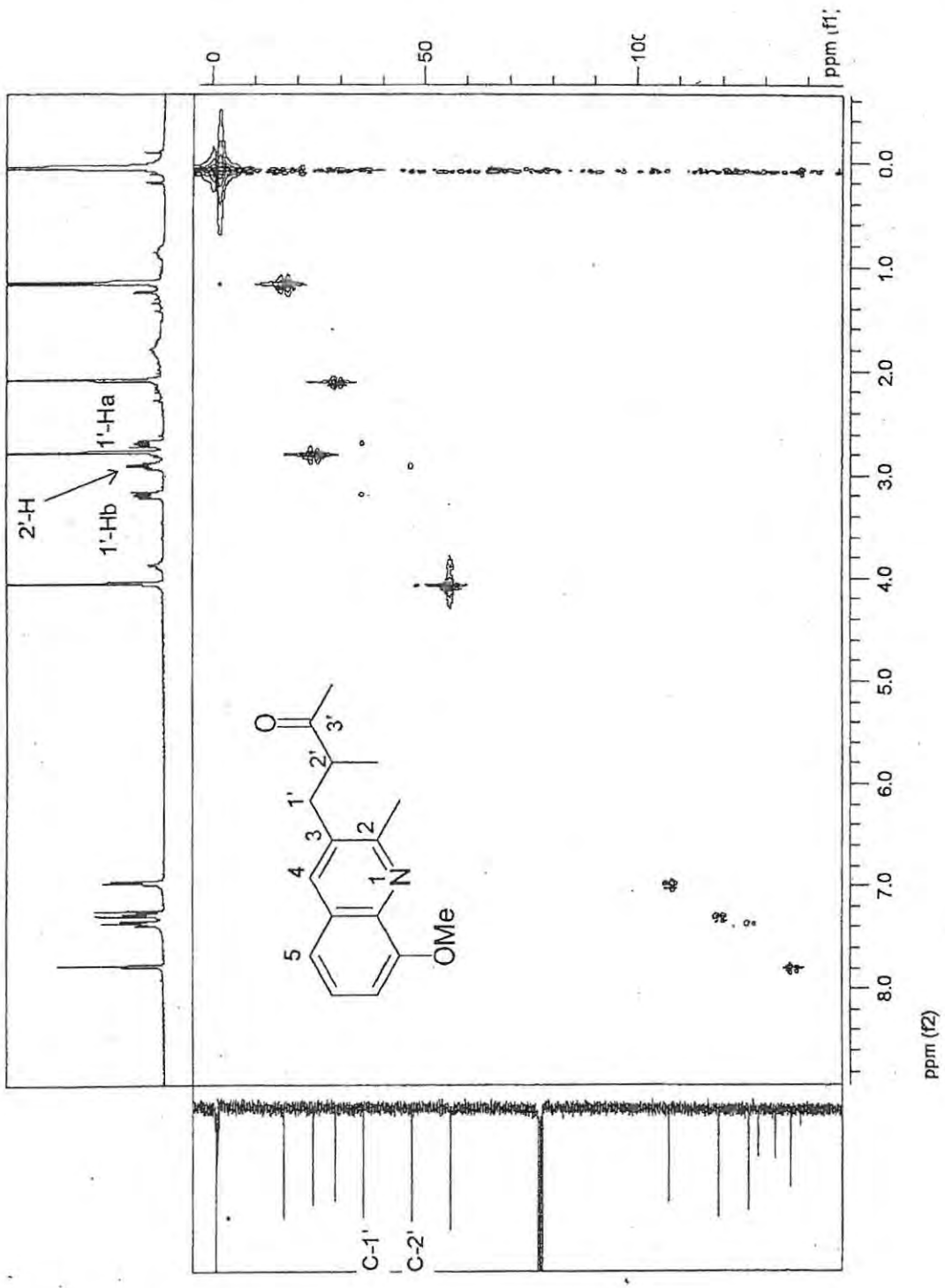


Figure 9e. HMQC NMR spectrum of compound **163** in $CDCl_3$.

From the ^{1}H NMR spectral data for compound **164** (Figure 10a), the three signals in the aromatic region, each integrating for one proton, are consistent with the structure. Four methyl signals, each integrating for three protons, two separate methylene proton signals, each integrating for one proton, and three methine proton signals also correlate with the proposed structure. Again, the methyl signal at *ca.* 1 ppm corresponding to the 3-methyl group appears as a doublet due to coupling with the 3-methine proton. In the ^{13}C NMR spectrum (Figure 10b), the sixteen carbon signals, two of which are carbonyl carbons, are also consistent with the proposed structure. Furthermore, the DEPT 135 spectrum confirms the presence of eleven proton-bearing carbons, only one of which is a methylene carbon. Additional doublet at 1.08 ppm, additional singlets at 2.13 and 2.16 ppm, and methoxyl singlet at 3.88 ppm are attributed to the presence of a diastereomeric product.

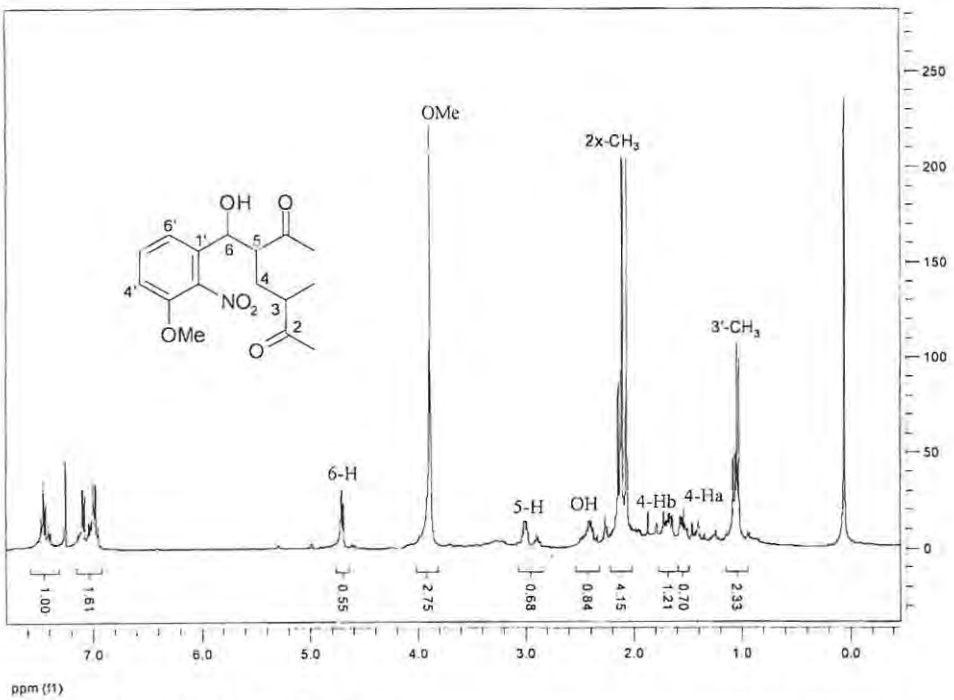


Figure 10a. 400 MHz ^{1}H NMR spectrum of compound **164** in $CDCl_3$.

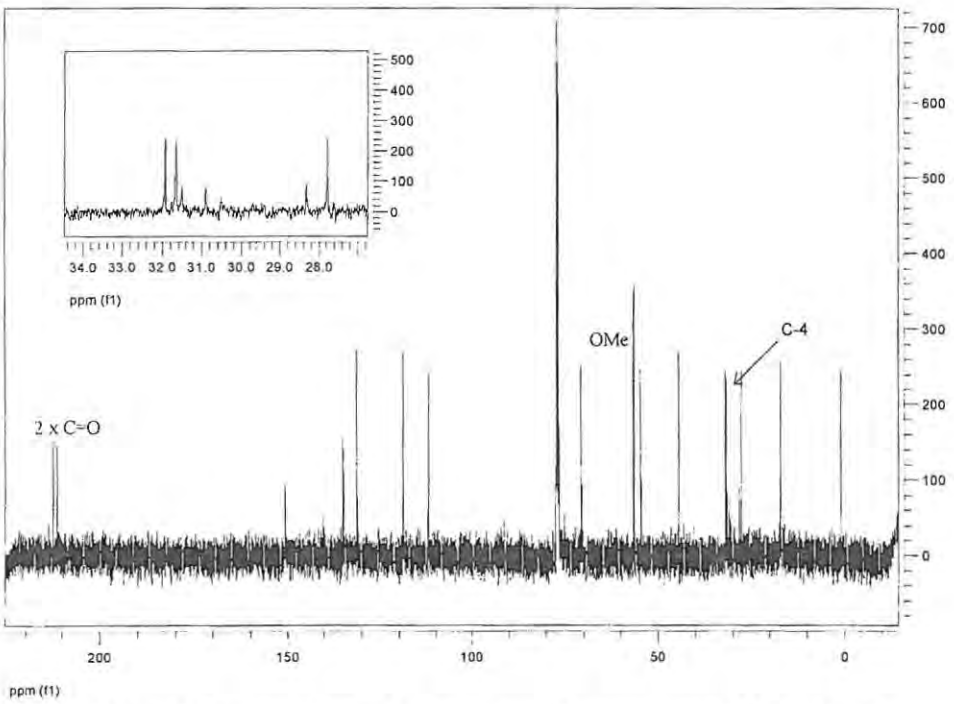
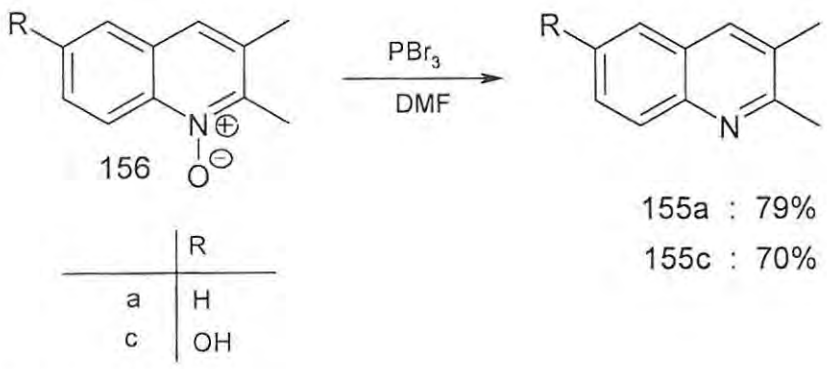


Figure 10b. 100 MHz ^{13}C NMR spectrum of compound **164** in $CDCl_3$.

2.3 The conversion of quinoline-*N*-oxides to quinolines

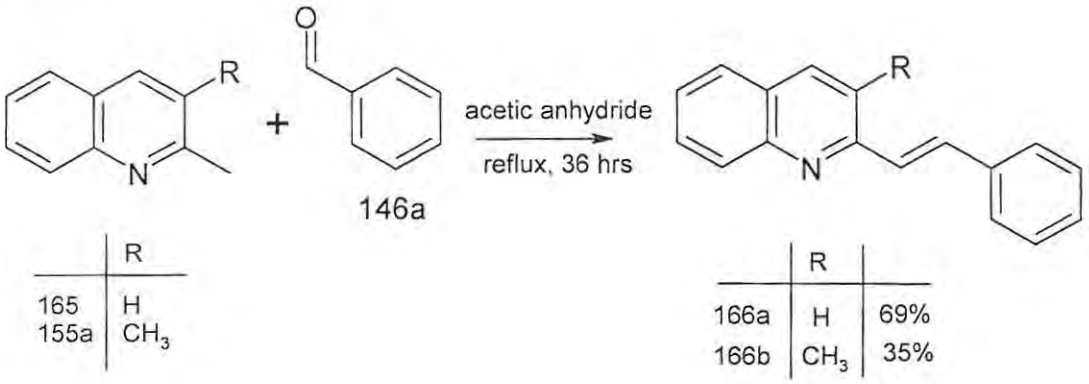
Selected quinoline-*N*-oxide derivatives were successfully converted in reasonable yield to their corresponding quinoline derivatives using phosphorus tribromide in DMF.[46] The anhydrous reaction mixtures were stirred under nitrogen at room temperature for approximately 1 hour (Scheme 48). The NMR spectra of the reduced products matched those of the corresponding quinoline derivatives prepared previously.



Scheme 48

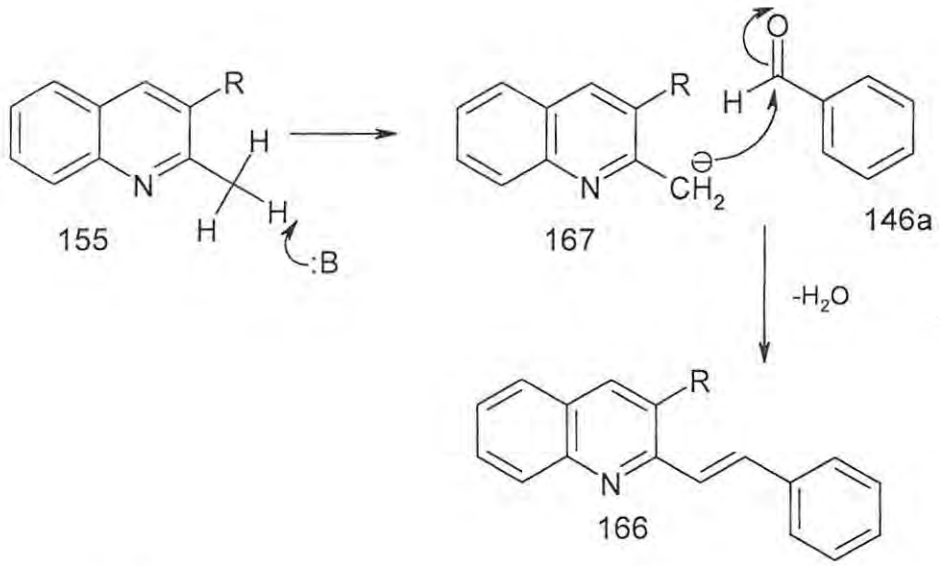
2.4 Preparation of styrylquinoline derivatives

The formation of styrylquinoline derivatives was one the aims of this project. Besides the the HIV-1 integrase inhibitory potency[24,34] associated with these compounds, it has also been reported that compound **166a** inhibits (IC_{50} value of *ca.* 4μM[78]) the growth of trypomastigote forms of *T. brucei* (sleeping sickness), albeit it 20 times less effectivity than the drug in clinical use. Employing the method reported by Mekouar *et al.*[79] for the synthesis of styryquinolines, we reacted the 2-methylquinolines **155a** and **165** respectively, with benzaldehyde in a Perkin-type coupling reaction. The reaction mixtures were boiled under reflux for 36 hours under strongly basic conditions, quinaldine being used initially as a model system. Fortunately, the reaction went well and the styrylquinoline **166a** was obtained in 69% yield (Scheme 49). The reaction was then applied to 2,3-dimethylquinoline **155a** to obtain styrylquinoline **166b** in somewhat lower yield (35%).



Scheme 49

The mechanism for these reactions involves abstraction of one of the acidic hydrogens of the 2-methyl group by a strong base, thus generating the resonance-stabilised carbanion **167**. Nucleophilic attack at the carbonyl carbon of the aldehyde followed by loss of water affords the styrylquinoline derivative **166** (Scheme 50).



Scheme 50

The ^{1}H NMR spectra of these styrylquinolines are characterised by numerous signals in the aromatic region. In the ^{1}H NMR spectrum of **166b** (Figure 11a), for example, this complexity is evident. Thus, apart from the methyl signal at 2.61 ppm integrating for three protons, the remaining signals appear as a series of overlapping signals in the aromatic region, due to aromatic and vinylic protons and integrating, as expected, for 12 protons. The 16 signals in the ^{13}C NMR spectrum correlate with the expected number of different carbons in the compound. Actually, the number of carbon signals is supposed to be 18 but, due to the symmetry of the phenyl ring, the number of signals drops to 16. Therefore, the NMR records one carbon instead of two for the phenyl *ortho*- and *meta*-carbons. Furthermore, the DEPT 135 spectrum confirms the presence of eleven proton-bearing carbons, including one methyl carbon, while the HMQC spectrum shows the expected carbon-hydrogen correlations.

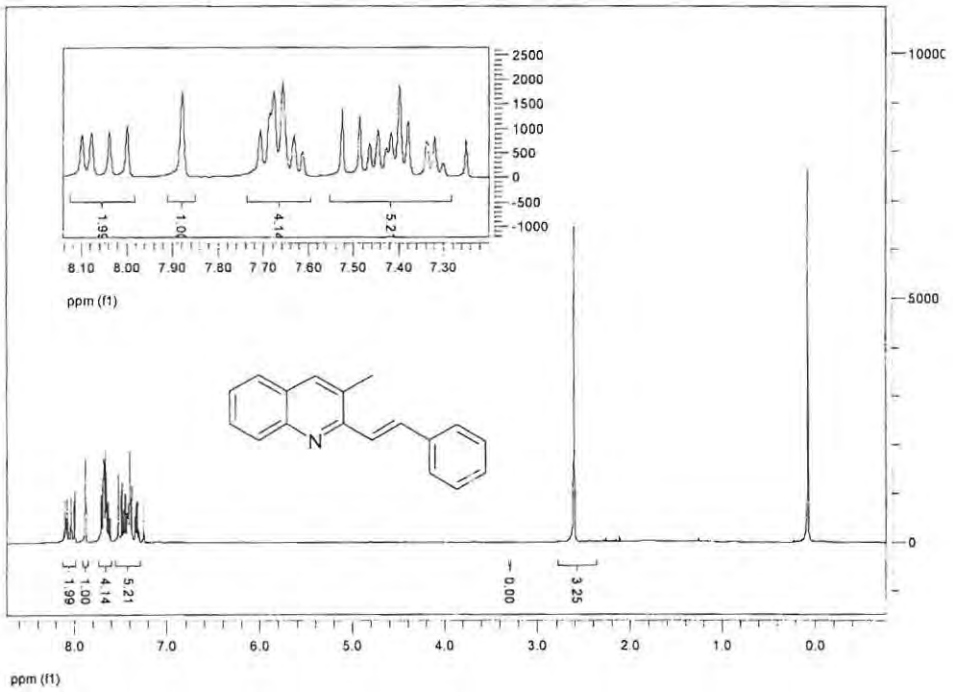


Figure 11a. 400 MHz ^{1}H NMR spectrum of compound **166b** in $CDCl_3$.

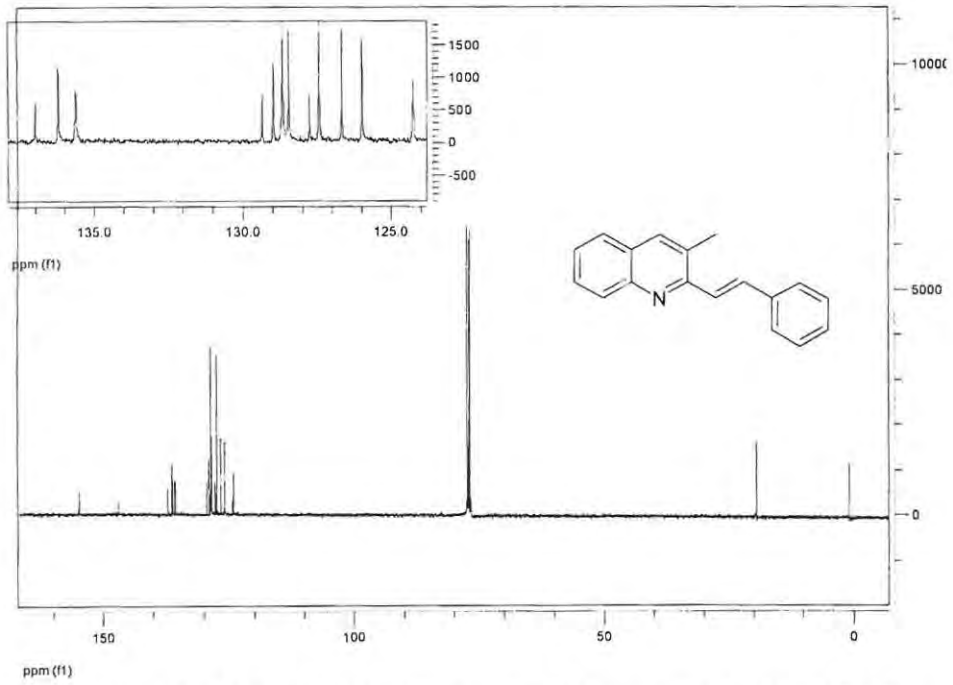


Figure 11b. 100 MHz ^{13}C NMR spectrum of compound **166b** in $CDCl_3$.

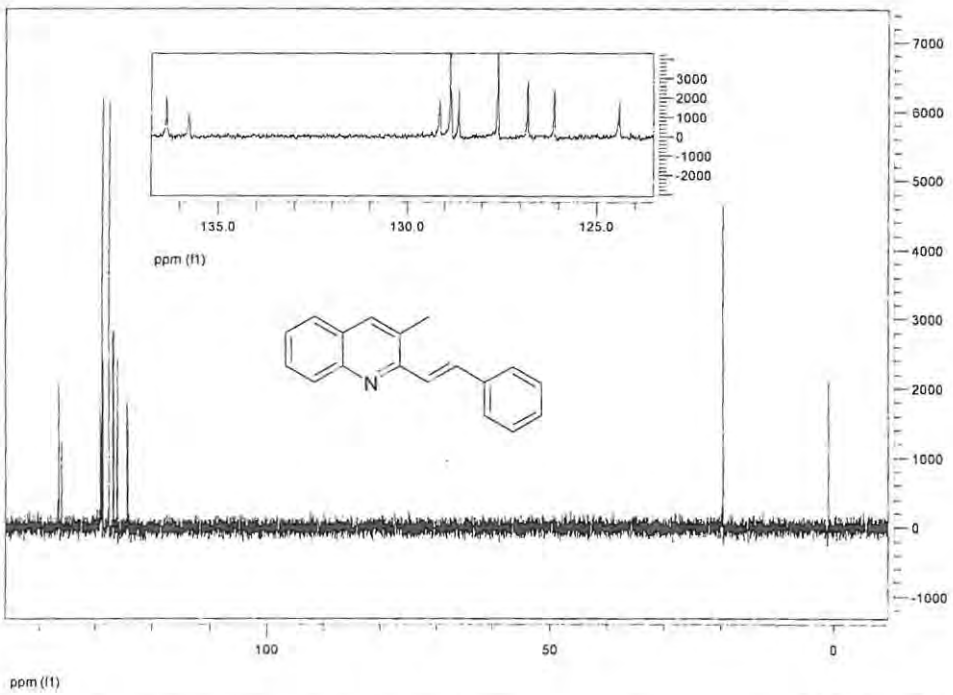
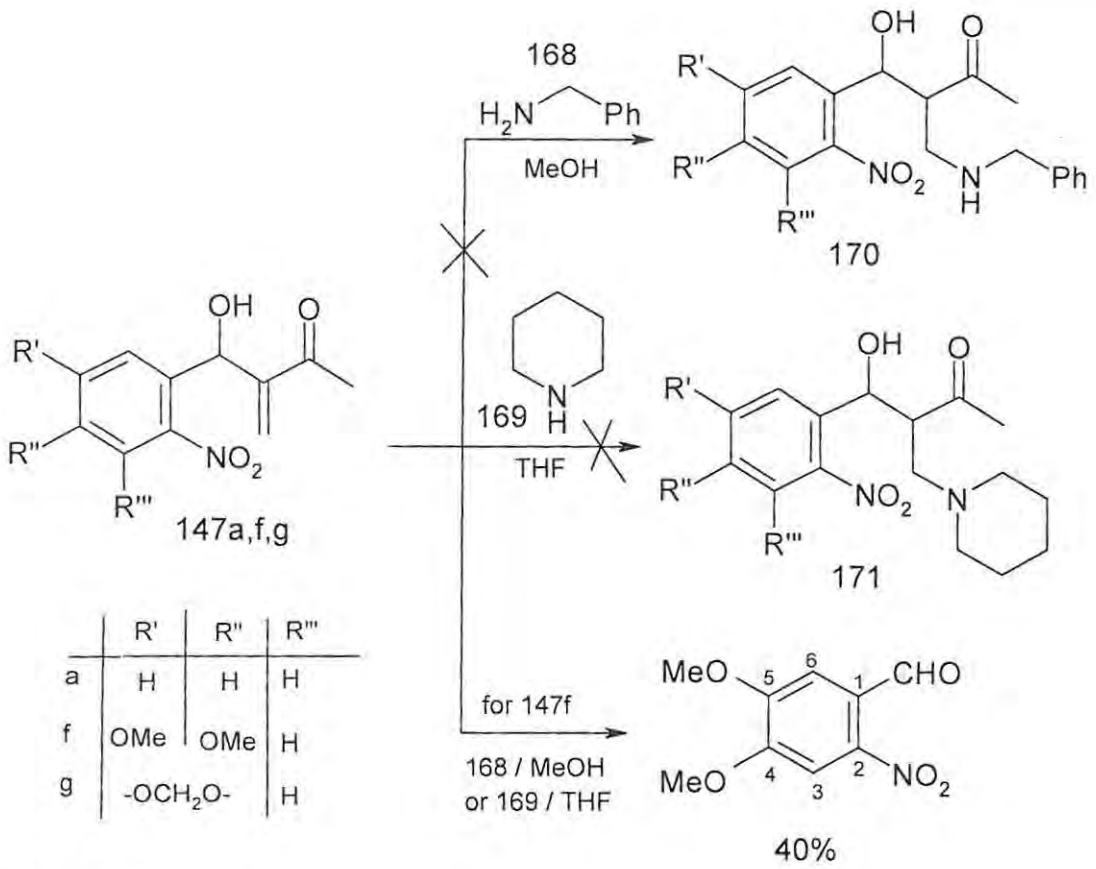


Figure 11c. 100 MHz DEPT 135 NMR spectrum of compound **166b** in $CDCl_3$.

2.5 Reaction of the Baylis-Hillman adducts with nitrogen nucleophiles

It was expected that the reaction between Baylis-Hillman adducts and nucleophiles would proceed *via* conjugate addition at the vinylic β-carbon to produce compounds such as **170** and **171** (Scheme 42).[47] Consequently, several Baylis-Hillman products were treated with benzylamine or piperidine, in the THF or MeOH, respectively. The reactions seemed to work because the vinylic protons of the Baylis-Hillman products were absent in the ^1H NMR spectra of the crude products. However, when purification of the crude products was attempted using flash chromatography, it was observed that only traces of what appeared to be the expected products were isolated. In the reaction of 4-(4,5-dimethoxy-2-nitrophenyl)-4-hydroxy-3-methylene-butan-2-one **147f** 4,5-dimethoxy-2-nitrobenz-aldehyde was isolated in 40% yield in both reactions (*i.e.* the benzylamine and piperidine reactions). This means that the Baylis-Hillman product **147f** reverts to the aldehyde **146f** and methyl vinyl ketone **91** under these conditions. Furthermore, when 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was use as the starting material, none of the expected product was isolated (Scheme 42).



	R'	R''	R'''
a	H	H	H
f	OMe	OMe	H
g	$-OCH_2O-$		H

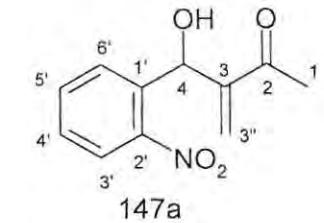
Scheme 42

It was then decided to exclude the added solvent, and 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **147g** was reacted with excess piperidine and with excess benzylamine, the nucleophilic amine acting as solvent in both cases. The Baylis-Hillman product **147g** was stirred with benzylamine or piperidine at room temperature for 24 hours. TLC analysis showed that the reactions were complete within 24 hours – an observation supported by the ^1H NMR spectra of the crude products. However, when the crude products were purified on the chromatotron none of the expected products were isolated. Due to time constraints these reactions could no be explored further.

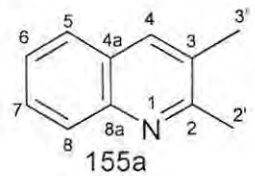
2.6 Application of NMR shift prediction programmes

An investigation of the carbon-13 chemical shifts for selected compounds (**147a**, **155a**, **156a**, **160**, **161c** and **166b**) synthesised in this study was conducted using three different prediction programmes *viz.*, the ChemWindow,[83] and the MODGRAPH neural network and HOSE (hierarchically ordered spherical description of environment) methods.[84] The purpose of using these prediction methods was to further support the ^{13}C signal assignments for the compounds and also to assess whether these methods could differentiate the quinoline and quinoline-*N*-oxide derivatives and clarify the ambiguity encountered with compound **160**, *i.e.* is it a dihydroquinoline or an *N*-oxide.

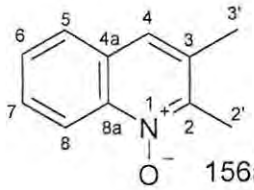
Tables 3 – 8 show the experimental ^{13}C NMR chemical shift data values and the predicted ChemWindow, neural network and HOSE ^{13}C NMR chemical shift values for the selected compounds. Comparison of the predicted data values with the experimental values reveals reasonable correlations and hence supports the formation of the selected compounds. Moreover, the predicted values correlate reasonably well with the experimental data for the dihydroquinoline substrate **160**, the identity of which had been of some concern. The predicted ^{13}C NMR chemical shifts (both experimental and predicted) for C-4 also supports the formation of the dihydroquinoline **160** (Table 6) rather than a tetrahydroquinoline derivative. It was also interesting to note that ChemWindow cannot predict the carbon-13 chemical shifts for the quinoline-*N*-oxide derivative.



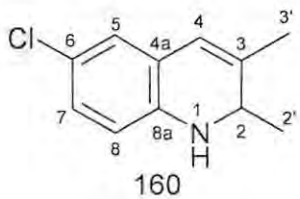
147a



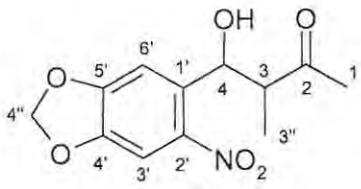
155a



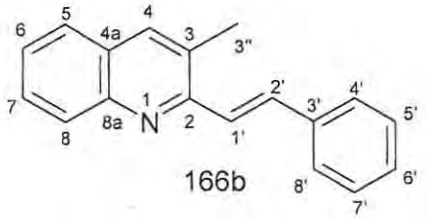
156a



160



161c

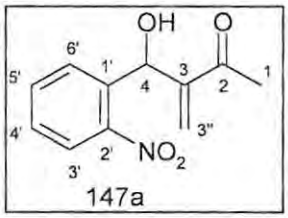


166b

In order to understand how well the experimental ^{13}C NMR chemical shift data correlate with the predicted values using the three prediction methods, root mean square values (RMS) were calculated. (The lower the root mean square value the better the correlation.) The root mean square values in Tables 3 and 8 suggest that the ChemWindow prediction method correlated best with the experimental values for compound **147a** and **166b** giving RMS values of 3.6 and 1.8 respectively, followed by the neural network data, while the HOSE method was the least accurate for these compounds. However, Table 4 for compound **155a** reveals that both the neural network and HOSE prediction methods were the best for this compound.

Table 3. Experimental (100MHz) and Predicted ^{13}C NMR Chemical Shift Data (δ/ppm) for 4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** in $CDCl_3$.

Nucleus	**A**	**B**	**C**	**D**
4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one 147a				
C1	26.4	25.1	27.0	26.1
C2	199.8	196.5	203.0	199.3
C3	148.9	151.8	143.0	149.7
C4	67.9	69.4	69.0	74.9
C1'	136.4	134.5	135.0	135.4
C2'	148.1	148.2	157.0	140.1
C3'	124.6	123.4	122.0	121.5
C4'	128.9	126.6	129.0	127.8
C5'	133.8	134.4	127.0	125.9
C6'	129.3	129.2	127.0	126.8
C3"	126.8	119.8	119.0	126.4
RMS values		3.6	3.8	5.1



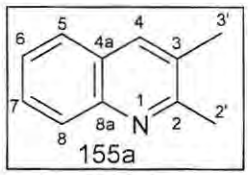
147a

A: Experimental data; B: ChemWindow Predictions; C: Modgraph neural network predictions; D: Modgraph HOSE predictions.

Comparing the RMS values in Table 5 it is evident that the neural network prediction method worked better for **156a** giving lower RMS value of 2.8. Nevertheless, Table 7 reveals that the HOSE prediction method was the best for **161c** as it gave a lowest RMS value of 3.1. The neural network prediction method was the least accurate for this compound, giving the highest RMS value of 6.2. From the results it is evident that no single method of prediction should be used alone. That is, to get the best results from the prediction methods all three should be used as there is no clear pattern as to which method is best.

Table 4. Experimental (100MHz) and Predicted ^{13}C NMR Chemical Shift Data (δ/ppm) for 2,3-dimethylquinoline **155a** in $CDCl_3$.

Nucleus	**A**	**B**	**C**	**D**
2,3-Dimethylquinoline 155a				
C2	159.1	160.1	157.0	160.7
C3	130.4	129.2	128.0	131.7
C4	135.8	136.3	138.0	125.8
C4a	124.9	124.2	127.0	124.2
C5	126.8	126.5	126.0	128.3
C6	125.8	125.0	126.0	125.8
C7	128.7	127.9	129.0	128.8
C8	128.5	128.1	127.0	128.1
C8a	146.2	145.4	144.0	147.7
C2'	24.2	18.4	22.0	22.2
C3'	19.7	18.4	18.0	18.7
RMS values		3.2	1.8	1.8

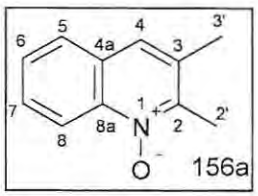


155a

A: Experimental data; B: ChemWindow Predictions; C: Modgraph neural network predictions; D: Modgraph HOSE predictions.

Table 5. Experimental (100MHz) and Predicted ^{13}C NMR Chemical Shift Data (δ/ppm) for 2,3-dimethylquinoline-*N*-oxide **156a** in $CDCl_3$.

Nucleus	A	B	C	D
2,3-Dimethylquinoline-*N*-oxide 156a				
C2	146.6		150.0	156.2
C3	130.9		134.0	131.7
C4	127.8		136.0	125.8
C4a	128.2		129.0	124.2
C5	125.5		128.0	128.3
C6	119.7		133.0	125.8
C7	127.2		128.0	127.8
C8	129.4		116.0	126.0
C8a	140.1		134.0	140.1
C2'	20.3		15.0	20.4
C3'	14.8		17.0	18.7
RMS values			2.8	4.3

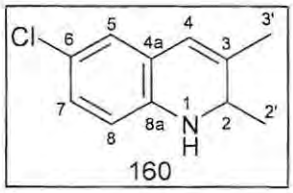


156a

A: Experimental data; C: Modgraph neural network predictions; D: Modgraph HOSE predictions.

Table 6. Experimental (100MHz) and Predicted ^{13}C NMR Chemical Shift Data (δ/ppm) for 6-chloro-2,3-dimethyl-1,2-dihydroquinoline **160** in $CDCl_3$.

Nucleus	A	B	C	D
6-Chloro-2,3-dimethyl-1,2-dihydroquinoline 160				
C2	72.6	61.1	51.0	53.2
C3	142.7	132.7	132.0	138.1
C4	118.9	120.0	119.0	119.7
C4a	122.5	120.1	122.0	127.8
C5	127.5	127.4	127.0	126.7
C6	124.6	122.1	124.0	125.1
C7	129.3	128.9	128.0	125.4
C8	116.2	113.6	115.0	117.2
C8a	144.9	139.3	145.0	141.7
C2'	14.1	18.8	18.0	19.4
C3'	22.1	15.3	18.0	21.8
RMS values		10.8	10.9	5.8

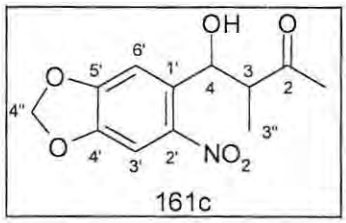


160

A: Experimental data; B: ChemWindow Predictions; C: Modgraph neural network predictions; D: Modgraph HOSE predictions.

Table 7. Experimental (100MHz) and Predicted ^{13}C NMR Chemical Shift Data (δ/ppm) for 4-(2-nitro-4,5-methylenedioxyphenyl)-4-hydroxy-3-methylbutan-2-one **161c** in $CDCl_3$.

Nucleus	A	B	C	D
4-(2-Nitro-4,5-methylenedioxyphenyl)-4-hydroxy-3-methylbutan-2-one 161c				
C1	30.1	22.6	29.0	29.7
C2	212.7	210.2	231.0	209.8
C3	52.3	55.1	50.0	33.1
C4	70.3	68.7	74.0	75.0
C1'	134.4	127.8	133.0	135.4
C2'	141.1	141.5	146.0	140.4
C3'	106.8	110	103.0	116.4
C4'	147.4	145.7	148.0	147.4
C5'	151.2	153.5	149.0	146.7
C6'	104.5	115.8	110.0	106.8
C3"	13.5	6.8	13.0	13.7
C4"	102.3	91.3	102.0	101.3
RMS values		5.1	6.2	3.1

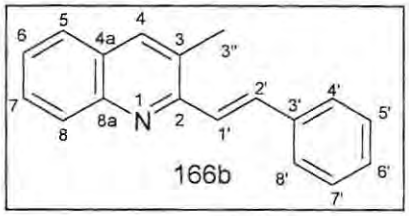


161c

A: Experimental data; B: ChemWindow Predictions; C: Modgraph neural network predictions; D: Modgraph HOSE predictions.

Table 8. Experimental (100MHz) and Predicted ^{13}C NMR Chemical Shift Data (δ/ppm) for (*E*)-3-methyl-2-styrylquinoline **166b** in $CDCl_3$.

Nucleus	A	B	C	D
(*E*)-3-methyl-2-styrylquinoline 166b				
C2	154.8	157.2	132.0	130.7
C3	129.3	127.4	132.0	136.6
C4	136.2	136.9	125.0	125.8
C4a	127.8	126.0	144.0	140.1
C5	126.0	127.0	136.0	127.2
C6	124.3	126.1	123.0	122.6
C7	127.5	128.1	149.0	147.2
C8	128.9	128.7	131.0	124.2
C8a	146.9	145.6	126.0	124.9
C1'	128.5	128.3	126.0	135.9
C2'	135.6	130.5	127.0	128.5
C3'	137.0	134.9	135.0	137.7
C4'/8'	127.4	126.2	127.0	126.3
C5'/7'	128.7	128.4	129.0	128.9
C6'	126.7	127.7	129.0	129.4
C3"	19.5	18.8	20.0	19.4
RMS values		1.8	3.5	4.9



A: Experimental data; B: ChemWindow Predictions; C: Modgraph neural network predictions; D: Modgraph HOSE predictions.

2.7 Conclusions

In conclusion, it is apparent that the objectives of this project have been achieved. Various Baylis-Hillman products were produced from different 2-nitrobenzaldehyde substrates and methyl vinyl ketone in moderate to good yield, with one of the adducts being obtained in 100% yield. Reductive cyclisation of the Baylis-Hillman products was found to result in the formation of the expected quinoline and quinoline-*N*-oxide as well as several unexpected reduction products. Interconversion of quinoline and quinoline-*N*-oxide was achieved and Perkin-type coupling of two 2-methylquinolines with benzaldehyde was successfully effected to afford the desired styrylquinoline derivatives.

When a conjugate addition reaction was effected between selected Baylis-Hillman adducts and a nitrogen nucleophile, such as benzylamine or piperidine in methanol or ethanol, 40% of the aldehyde substrate was recovered, but only traces of the expected product seemed to be present. In the absence of added solvent, mixtures of unexpected products were obtained but, due to time constraints, these products were not identified. The application of three ^{13}C NMR chemical shift prediction programmes was explored to support ^{13}C signal assignments for selected compounds. Results obtained from these three programmes correlated reasonably well with the experimental values of the selected compounds, confirming their usefulness.

Although there is room for further optimisation, it is clear that the application of Baylis-Hillman methodology provides reasonable access to styrylquinoline systems as potential HIV-1 integrase inhibitors. Possibilities for future research arising from this project include the following.

i) Extending the range of quinoline derivatives prepared from Baylis-Hillman products to permit access to additional styrylquinolines.

ii) The use of computer-modelling studies to explore possible docking of the styrylquinolines into the HIV-1 integrase receptor site.

iii) Integrase inhibition assays to evaluate the inhibition activity of the synthesised styrylquinolines to guide the design of further ligands.

3 EXPERIMENTAL

3.1 General

The reagents used in this project were used as supplied by Aldrich, without further purification. Thin layer chromatography and preparative layer chromatography were conducted using Merck silica gel 60 PF_{254} (pre-coated plates for TLC), whereas flash chromatography was conducted using Merck silica gel 60 (particle sizes 0.040 – 0.063 mm).

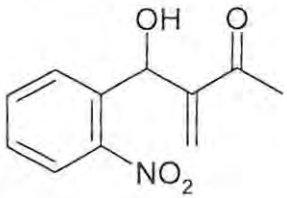
Low resolution mass spectra were obtained at Rhodes on a Finnegan Mat GCQ spectrometer. High resolution mass spectra were acquired by Dr Phillip Boshoff (Cape Technikon Mass Spectral Unit) and by Mr Tommie van der Merwe (University of the Witwatersrand). NMR spectra were recorded on a Bruker 400 MHz AVANCE spectrometer for solutions in $CDCl_3$ or DMSO-d_6, and referenced using solvent signals (δ_H : 7.25 ppm for $CDCl_3$ and 2.50 ppm for DMSO-d_6; δ_C : 77.0 ppm for $CDCl_3$ and 39.43 ppm for DMSO-d_6).

A Perkin-Elmer FT-IR spectrum 2000 spectrometer was used to record all the IR spectra using KBr dics or nujol mulls. Melting points were determined using the Reichert 281313 hot-stage apparatus, and are uncorrected.

Table 9: List of compounds prepared.

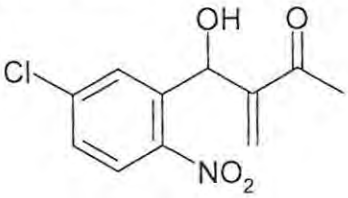
3.2 Synthesis of Baylis-Hillman products

4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a**



A solution of 2-nitrobenzaldehyde **146a** (10.0g, 66.0mmol), methyl vinyl ketone (6.99g, 99.0mmol), DABCO (0.37g, 3.3mmol) in $CHCl_3$ (2mL) was stirred in a stoppered flask at room temperature for 7 days. The solvent was evaporated from the resulting mixture *in vacuo*, and the crude product was purified by flash chromatography on silica [using EtOAc-hexane (1:3)] to afford, as yellow-brown crystals, 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** (11.2g, 75%), m.p. 80 – 81 °C (lit.[38] 94 – 95 °C) (Found, $\mathbf{M}^+$: 221.06672. $C_{11}H_{11}NO_4$ requires *M*, 221.06881); ν_{max}(KBr)/cm^{-1} 3361 (OH) and 1665 (C=O); δ_H (400MHz; $CDCl_3$) 2.34 (3H, s, CH_3), 3.29 (1H, br s, OH), 5.77 (1H, s, CH), 6.15 and 6.20 (2H, 2 x s, CH_2), 7.43 (1H, t, *J* 7.2Hz, 4'-H), 7.62 (1H, t, *J* 7.2Hz, 5'-H), 7.74 (1H, d, *J* 8.0Hz, 6'-H) and 7.92 (1H, d, *J* 8.0Hz, 3'-H); δ_C (100MHz; $CDCl_3$) 26.4 (C-1), 67.9 (C-4), 124.6 (C-3'), 126.8 (C=$\underline{C}H_2$), 128.9 (C-4'), 129.3 (C-6'), 133.8 (C-5'), 136.4 (C-1'), 148.1 (C-2'), 148.9 ($\underline{C}$=CH_2) and 199.8 (C-2); *m/z* 221 ($\mathbf{M}^+$, 0.2%) and 43 (100).

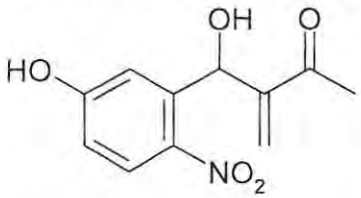
4-(5-Chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147b**



The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was followed, using 5-chloro-2-nitrobenzaldehyde **146b** (1.00g, 5.4mmol), methyl vinyl ketone (0.57g, 8.1mmol), DABCO (0.03g, 0.27mmol) and $CHCl_3$ (2mL). The crude product was purified by flash chromatography on silica [elution with hexane-EtOAc (1:1)] to afford, as a reddish-brown oil, which slowly

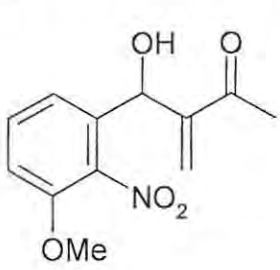
crystallized, 4-(5-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147b** (1.40g, 100%), m.p. 72 – 74°C (lit.[49] cited as oil) (Found, **M-NO_2^+**: 209.03621. $C_{11}H_{10}NO_4{}^{35}Cl$ requires *M-NO_2*, 209.03693); ν_{max}(KBr)/cm^{-1} 3441 (OH), 1676 (C=O) and 752 (C-Cl); δ_H (400MHz; $CDCl_3$) 2.38 (3H, s, CH_3), 3.48 (1H, br s, OH), 5.76 (1H, s, CH), 6.21 and 6.23 (2H, 2 x s, CH_2), 7.41 (1H, d, *J* 8.8Hz, 3'-H), 7.78 (1H, s, 6'-H) and 7.94 (1H, d, *J* 8.8Hz, 4'-H); δ_C (100MHz; $CDCl_3$) 25.9 (C-1), 67.2 (C-4), 126.2 (C-4'), 126.6 (C=$\underline{C}H_2$), 128.6 (C-3'), 129.1 (C-1'), 138.7 (C-6'), 140.3 (C-2'), 146.1 (C-5'), 148.6 ($\underline{C}$=CH_2) and 199.7 (C-2); *m/z* 255 [**M^+(^{35}Cl)**; 13%] and 210 (100).

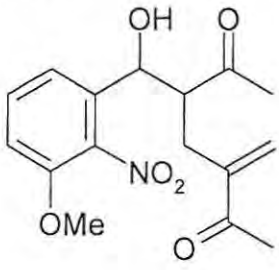
4-hydroxy-4-(5-hydroxy-2-nitrophenyl)-3-methylenebutan-2-one **147c**



The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was followed, using 5-hydroxy-2-nitrobenzaldehyde **146c** (0.40g, 2.4mmol), methyl vinyl ketone (0.43g, 6.12mmol), DABCO (0.057g, 0.51mmol) and $CHCl_3$ (2mL). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane (1:1)] to afford, as brown crystals, 4-hydroxy-4-(5-hydroxy-2-nitrophenyl)-3-methylenebutan-2-one **147c** (0.25g, 33%), m.p. 131 – 133°C (lit.[46] 133 – 134°C) (Found, **M^+-NO_2**: 191.10242. $C_{11}H_{11}NO_5$ requires *M-NO_2*, 191.06925); ν_{max}(KBr)/cm^{-1} 3358 (OH) and 1626 (C=O); δ_H (400MHz; DMSO-d_6) 2.34 (3H, s, CH_3), 3.33 (1H, br s, OH), 5.63 (1H, s, CH), 6.19 and 6.22 (2H, 2 x overlapping s, CH_2), 6.84 (1H, d, *J* 8.4Hz, 3'-H), 7.17 (1H, s, 6'-H), 7.99 (1H, d, *J* 8.4Hz, 4'-H) and 10.85 (1H, br s, Ar-OH); δ_C (100MHz; DMSO-d_6) 26.01 (C-1), 64.6 (C-4), 114.4 (C-4'), 114.9 (C=$\underline{C}H_2$), 124.9 (C-6'), 127.7 (C-3'), 138.9 (C-5'), 142.3 (C-1'), 150.4 (C-2'), 162.3 ($\underline{C}$=CH_2) and 198.0 (C-2); *m/z* 191 (**M^+-NO_2**, 100%).

4-Hydroxy-4-(3-methoxy-2-nitrophenyl)-3-methylenebutan-2-one **147d** ***and 5-acetyl-6-hydroxy-6-(3-methoxy-2-nitrophenyl)-3-methylene-2-hexanone*** **149**





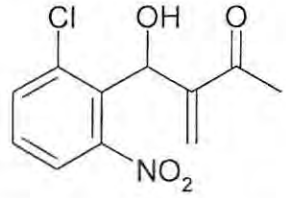
The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was followed, using 3-methoxy-2-nitrobenzaldehyde **146d** (1.60g, 8.00mmol), methyl vinyl ketone (1.60g, 6.4mmol), DABCO (0.10g, 0.80mmol) and $CHCl_3$ (2mL). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (1:1:3)] to afford two fractions.

Fraction 1: as a reddish-brown oil (lit.[81] cites as oil), 4-hydroxy-4-(3-methoxy-2-nitrophenyl)-3-methylenebutan-2-one **147d** (0.48g, 24%) (Found, **M-NO_2^+**: 205.08196. $C_{12}H_{13}NO_5$ requires *M-NO_2*, 205.08647); ν_{max}(KBr)/cm^{-1} 3449 (OH) and 1712 (C=O); δ_H (400MHz; $CDCl_3$) 2.32 (3H, s, CH_3), 3.46 (1H, br s, OH), 3.87 (3H, s, OCH_3), 5.64 (1H, s, CH), 5.94 and 6.22 (2H, 2 x s, CH_2), 6.98 (1H, d, *J* 8.4Hz, 6'-H), 7.13 (1H, d, *J* 7.6Hz, 4'-H) and 7.43 (1H, t, *J* 8Hz, 5'-H); δ_C (100MHz; $CDCl_3$) 26.2 (C-1), 56.5 (OCH_3), 68.7 (C-4), 112.1 (C-5'), 119.5 (C-6'), 127.9 (C-4'), 131.2 (C=$\underline{C}H_2$), 136.4 (C-1'), 147.4 (C-2'), 150.9 ($\underline{C}$=CH_2), 191.2 (C-3') and 199.8 (C-2); *m/z* 251 (**MH^+**, 0.74%) and 205 (100).

Fraction 2: as a reddish-brown oil, *5-acetyl-6-hydroxy-6-(3-methoxy-2-nitrophenyl)-3-methylene-2-hexanone* **149** (1.21g, 60%) [Found (FAB): **MH^+**, 322.2. $C_{16}H_{19}NO_6$; ν_{max}(KBr)/cm^{-1} 3433 (OH) and 1624 (C=O); δ_H (400MHz; $CDCl_3$), 2.06 and 2.30 (6H, 2 x s, 2 x CH_3), 2.31 (1H, m, overlapping CH_3 singlet, 4-H_a), 2.50 (1H, m, 4-H_b), 3.09 (1H, dd, *J* 6.4Hz, 6-H), 3.84 (3H, s, OCH_3), 4.04 (1H, br s, OH), 4.66 (1H, br s, 5-H), 5.83 and 6.04 (2H, 2 x s, CH_2=C), 6.94 (1H, d, *J* 8Hz, 6'-H), 7.14 (1H, d, *J* 8Hz, 4'-H) and 7.41 (1H, t, *J* 8.2Hz, 5'-H); δ_C (100MHz; $CDCl_3$); 25.6 (C-1), 30.9 (C-4), 31.9 (5-$\underline{C}H_3CO$), 54.9 (C-6), 56.4 (OMe), 69.4 (C-5), 111.8 (C-5'), 118.9 (C-6'), 128.6 (C=$\underline{C}H_2$), 131.1 (C-

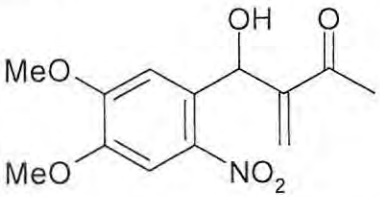
4'), 135.2 (C-2'), 140.0 (C-1'), 144.9 (C-3'), 150.4 (C-3), 211.3 (5-$CH_3\underline{C}O$) and 213.1 (C-2); *m/z* 321 ($\mathbf{MH^+}$, 0.68%) and 200 (100).

4-(6-Chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147e**



The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was followed, using 6-chloro-2-nitrobenzaldehyde **146e** (0.200g, 1.08mmol), methyl vinyl ketone (0.113g, 0.13mmol), DABCO (0.006g, 0.054mmol) and $CHCl_3$ (1mL). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (2:1:1)] to afford, as a reddish-brown oil, *4-(6-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one* **147e** (0.36g, 85%) (Found, $\mathbf{M^+}$: 255.02984. $C_{11}H_{10}NO_4{}^{35}Cl$ requires *M*, 255.02984); ν_{max}(KBr)/cm^{-1} 3490 (OH), 1687 (C=O) and 724 (C-Cl); δ_H (400MHz; $CDCl_3$) 2.33 (3H, s, CH_3), 3.68 (1H, s, OH), 5.92 (1H, s, CH), 6.17 and 6.29 (2H, 2 x s, CH_2), 7.35 (1H, t, *J* 8.2Hz, 4'-H), 7.45 (1H, d, *J* 8Hz, 5'-H) and 7.55 (1H, d, *J* 8Hz, 3'-H); δ_C (100MHz; $CDCl_3$) 26.0 (C-1), 68.5 (C-4), 122.6 (C-4'), 128.2 (C=$\underline{C}H_2$), 129.2 (C-3'), 131.8 (C-1'), 133.1 (C-5'), 135.4 (C-2'), 146.1 (C-6'), 151.4 ($\underline{C}$=CH_2) and 199.7(C-2); *m/z* 255 [$\mathbf{M^+}$(**^{35}Cl**), 0.1%] and 43 (100).

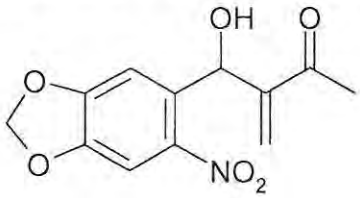
4-(4,5-Dimethoxy-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147f**



The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was followed, using 4,5-dimethoxy-2-nitrobenzaldehyde **146f** (1.00g, 4.7mmol), methyl vinyl ketone (0.50g, 7.1mmol), DABCO (0.027g, 0.24mmol) and $CHCl_3$ (2mL). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (1:1:3)] to afford, as a yellowish-brown oil (lit.[49] m.p 97 – 98°C); 4-hydroxy-3-methylene-4-(4,5-dimethoxy-2-nitrophenyl)butan-2-

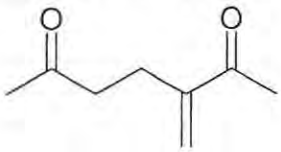
one **147f** (1.24g, 73%) (Found, $\mathbf{M}^+$: 281.08877. $C_{13}H_{15}NO_6$ requires *M*, 281.08994); ν_{max}(KBr)/cm^{-1} 3449 (OH) and 1712 (C=O); δ_H (400MHz; $CDCl_3$) 2.38 (3H, s, CH_3), 3.91 (1H, s, OH), 3.94 and 3.99 (6H, 2 x s, 4-OCH_3 and 5-OCH_3), 5.57 (1H, s, 4-H), 6.05 and 6.31 (2H, 2 x s, CH_2), 7.30 (1H, s, 3'-H) and 7.64 (1H s, 6'-H); δ_C (100MHz; $CDCl_3$) 26.0 (C-1), 56.8 and 56.9 (2 x OCH_3), 68.1 (C-4), 108.4 (C-6'), 110.5 (C-3'), 126.1 (C=$\underline{C}H_2$), 134.8 (C-1'), 144.9 (C-2'), 147.9 (C-5'), 149.5 (C-4'), 153.6 ($\underline{C}$=CH_2) and 200.4 (C-2); *m/z* 281 ($\mathbf{M}^+$, 13.2%) and 43 (100).

4-Hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **147g**



The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** was followed, using 4,5-methylenedioxy-2-nitrobenzaldehyde **146g** (1.00g, 5.1mmol), methyl vinyl ketone (1.1g, 1.3mmol), DABCO (0.07g, 0.80mmol) and $CHCl_3$ (2mL). The crude product was purified by a flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (1:1:3)] to afford, as a reddish-yellow oil, 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **147g** (0.82g, 60%) (lit.[46] cites as yellow crystals m.p. 100 – 103°C) (Found, $\mathbf{M}^+$: 267.07429. $C_{12}H_{11}NO_6$ requires *M*, 267.18570); ν_{max}(KBr)/cm^{-1} 3461 (OH) and 1620 (C=O); δ_H (400MHz; $CDCl_3$) 2.33 (3H, s, CH_3), 3.67 (1H, s, OH), 5.72 (1H, s, CH), 6.09 (4H, overlapping signals, CH_2=C and OCH_2O), 7.16 (1H s, 6'-H) and 7.46 (1H s, 3'-H); δ_C (100MHz; $CDCl_3$) 25.8 (C-1), 67.2 (C-4), 105.4 (C-6'), 107.6 (C-3'), 103.0 (-O$\underline{C}H_2$O-), 125.8 (C=$\underline{C}H_2$), 134.2 (C-1'), 141.7 ($\underline{C}$=CH_2), 147.2 (C-5'), 149.2 (C-4'), 152.2 (C-2') and 199.7 (C-2); *m/z* 266 ($\mathbf{M}^+$, 0.9%) and 43 (100).

3-Methyleneheptan-2,6-dione **148**



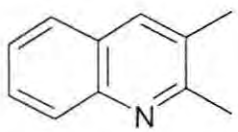
The dimer **148** was also isolated in some of the Baylis-Hillman reactions as a reddish-brown oil in yields ranging from 5 – 12%. (Found, $\mathbf{M}^+$: 140.08679. $C_8H_{12}O_2$ requires *M*, 140.08684); ν_{max}(KBr)/cm^{-1} 1698 (C=O); δ_H (400MHz; $CDCl_3$) 2.07 (3H, s, 7-CH_3), 2.27 (3H, s, 1-CH_3), 2.50 (4H, m, 2 x CH_2), 5.78 and 5.98 (2H, 2 x s, C=C$\underline{H_2}$); δ_C (100MHz; $CDCl_3$) 25.1 (C-7), 42.3 (C-1), 56.3 and 56.4 (C-4 and C-5), 126.1 (C-3a), 139.8 (C-3), 198.8 and 207.4 (2 x C=O).

3.3 Catalytic hydrogenation reactions

Selected Baylis-Hillman products were dissolved in EtOH and then hydrogenated at atmospheric pressure in the presence of 10 % Pd-C catalyst.

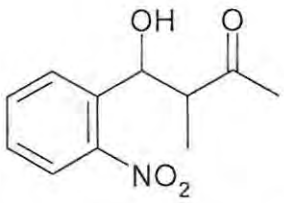
***Hydrogenation of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one* 147a.**

4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** (1.00g, 4.50mmol) was dissolved in ethanol (50 mL), a 10 % Pd-C (0.16g) catalyst was added, and the reaction mixture was stirred vigorously under hydrogen at atmospheric pressure for 1.5hours. The solvent was evaporated off *in vacuo*, and the crude product was dissolved in CH_2Cl_2, dried (anhyd. $MgSO_4$) and finally purified by flash chromatography on silica [elution with hexane-EtOAc (3:1)] to afford three fractions.

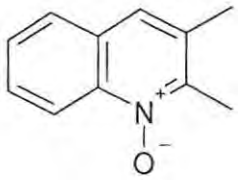


Fraction 1: as light yellow crystals, 2,3-dimethylquinoline **155a** (0.13g, 14%) m.p. 69 – 70 °C (lit.[46] m.p 39 – 43°C) (Found, $\mathbf{M}^+$: 157.08826. $C_{11}H_{11}N$ requires M^+, 157.08915);

ν_{max}(KBr)/cm^{-1} 1663 (N=C); δ_H (400MHz; $CDCl_3$) 2.42 (3H, s, 3-CH_3), 2.67 (3H, s, 2-CH_3), 7.43 (1H, t, *J* 7.6Hz, 6-H), 7.58 (1H, t, *J* 7.6Hz, 7-H), 7.68 (1H, d, *J* 8.0Hz, 5-H), 7.80 (1H, s, 4-H) and 7.99 (1H, d, *J* 8.0Hz, 8-H); δ_C (100MHz; $CDCl_3$) 19.7 (3-CH_3), 24.2 (2-CH_3), 124.9 (C-4a), 125.8 (C-6), 126.8 (C-5), 128.4 (C-7), 128.5 (C-8), 130.4 (C-3), 135.8 (C-4), 146.2 (C-8a) and 159.1 (C-2); *m/z* 157 ($\mathbf{M}^+$, 100%).



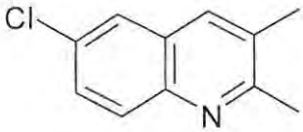
Fraction 2: as reddish-brown oil, 4-(2-nitrophenyl)-4-hydroxy-3-methylbutan-2-one **161a** (0.108g, 8%) (lit.[81] not detailed); ν_{max}(KBr)/cm^{-1} 3390 (OH) and 1715 (C=O); δ_H (400MHz; $CDCl_3$) 1.18 (3H, d, *J* 7.2Hz, C<u>H</u>$_3$CH), 2.12 (3H, s, CH_3CO), 3.09 (1H, m, 3-H), 3.83 (1H, br s, OH), 5.39 (1H, d, *J* 6.0Hz, 4-H), 7.43 (1H, t, *J* 7.2Hz, 5'-H), 7.61 (1H, t, *J* 7.6Hz, 4'-H), 7.67 (1H, d, *J* 6.8Hz, 3'-H) and 7.91 (1H, d, *J* 8.4Hz, 6'-H); δ_C (100MHz; $CDCl_3$) 14.6(<u>C</u>H$_3$CH), 30.3 (<u>C</u>H$_3$CO), 51.9 (C-3), 71.4 (C-4), 124.5 (C-5'), 128.5 (C-4'), 128.7 (C-6'), 133.3 (C-3'), 137.4 (C-1'), 139.9 (C-2') and 213.5 (C=O).



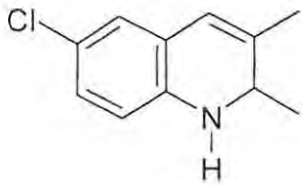
Fraction 3: as brown crystals, 2,3-dimethylquinoline-*N*-oxide **156a** (0.59g, 66%), m.p. 86 – 88°C (lit.[46] m.p. 111 – 114°C) (Found, $\mathbf{M}^+$: 173.08338. $C_{11}H_{11}NO$ requires *M*, 173.08406); ν_{max}(KBr)/cm^{-1} 1650 (N=C) and 1318 (N-O); δ_H (400MHz; $CDCl_3$) 2.45 (3H, s, 3-CH_3), 2.69 (3H, s, 2-CH_3), 7.49 (1H, s, 4-H), 7.56 (1H, t, *J* 7.6Hz, 6-H), 7.67 (1H, t, *J* 7.6Hz, 7-H), 7.71 (1H, d, *J* 8.0Hz, 5-H) and 8.69 (1H, d, *J* 8.8Hz, 8-H); δ_C (100MHz; $CDCl_3$) 14.8 (3-CH_3), 20.3 (2-CH_3), 119.7 (C-6), 125.5 (C-5), 127.2 (C-7), 127.8 (C-4), 128.2 (C-4a), 129.4 (C-8), 130.9 (C-3), 140.0 (C-8a) and 146.6 (C-2); *m/z* 173 ($\mathbf{M}^+$, 70%) and 156 (100).

***Hydrogenation of 4-(5-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one* 147b.**

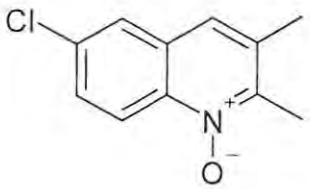
The general procedure described for the synthesis of 2,3-dimethylquinoline **155a** was followed, using 4-(5-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147b** (1.6g, 6.1mmol), ethanol (50 mL) and 10 % Pd-C catalyst (0.22g). Work-up and flash chromatography on silica [elution with hexane-EtOAc(3:1)] afforded two fractions.



Fraction 1: as a brown oil, 6-chloro-2,3-dimethylquinoline **155b** (0.32g; 26%) (Found, $\mathbf{M}^+$: 191.04777. $C_{11}H_{10}N^{35}Cl$ requires *M*, 191.05018); ν_{max}(KBr)/cm^{-1} 1603 (N=C) and 803 (C-Cl); δ_H (400MHz; $CDCl_3$) 1.92 (3H, s, 3-CH_3), 2.43 (3H, s, 2-CH_3), 6.65 (1H, d, *J* 8.4Hz, 7-H), 7.06 (1H, s, 4-H), 7.09 (1H, d, *J* 8.4Hz, 8-H) and 7.32 (1H, s, 5-H); δ_C (100MHz; $CDCl_3$) 13.3 (2-CH_3), 20.0 (3-CH_3), 116.9 (C-4), 122.6 (C-4a), 122.9 (C-3), 128.9 (C-8), 129.3 (C-7), 134.1 (C-5), 140.0 (C-6), 142.7 (C-8a) and 199.7 (C-2); *m/z*191 ($\mathbf{M}^+$, 100%).



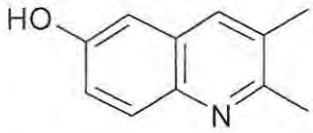
Fraction 2: as a brown oil, *6-chloro-2,3-dimethyl-1,2-dihydroquinoline* **160** (0.313g, 4%) (Found, $\mathbf{M}^+$: 211.07643. $C_{11}H_{14}NO^{35}Cl$ requires M^+, 211.07639); ν_{max}(KBr)/cm^{-1} 3010 (N-H) and 760 (C-Cl); δ_H (400MHz; $CDCl_3$) 1.36 (3H, d, *J* 6.4Hz, 2-CH_3), 1.70 (3H, s, 3-CH_3), 4.35 (1H, d, *J* 6.4Hz, 2-H), 6.26 (1H, s, 4-H), 6.60 (1H, d, *J* 7.2Hz, 7-H), 6.65 (1H, s, 5-H) and 6.69 (1H, d, *J* 8.4Hz, 8-H); δ_C (100MHz; $CDCl_3$) 14.1 (2-CH_3), 22.1 (3-CH_3), 72.6 (C-2), 116.2 (C-8), 118.9 (C-4), 122.5 (C-4a), 124.6 (C-6), 127.5 (C-5), 129.3 (C-7), 142.7 (C-3) and 144.9 (C-8a); *m/z* 211 [$\mathbf{M}^+$(^{35}**Cl**), 98%] and 194 (100).



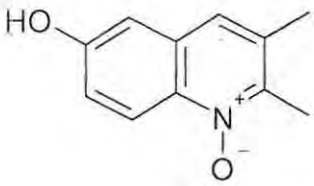
Fraction 3: as a brown solid, 6-chloro-2,3-dimethylquinoline-*N*-oxide **156b** (0.30g; 23%) (Found, $\mathbf{M}^+$: 207.04608. $C_{11}H_{10}N^{35}Cl$ requires *M*, 207.04509); ν_{max}(KBr)/cm^{-1} 1251 (N-O) and 764 (C-Cl); δ_H (400MHz; $CDCl_3$) 2.43 (3H, s, 3-CH_3), 2.64 (3H, s, 2-CH_3), 7.35 (1H, s, 4-H), 7.54 (1H, d, *J* 9.2Hz, 7-H), 7.66 (1H, s, 5-H) and 8.61 (1H, d, *J* 9.2Hz, 8-H); δ_C (100MHz; $CDCl_3$) 13.7 (3-CH_3), 19.3 (2-CH_3), 120.6 (C-4), 122.9 (C-7), 124.8 (C-5), 127.9 (C-4a), 128.9 (C-8), 131.4 (C-3), 132.8 (C-6), 137.5 (C-8a) and 145.6 (C-2); *m/z* 207 [$\mathbf{M}^+$(**^{35}Cl**); 43.9%] and 190 (100).

***Hydrogenation of 4-hydroxy-4-(5-hydroxy-2-nitrophenyl)-3-methylenebutan-2-one* 147c.**

The general procedure described for the synthesis of 2,3-dimethylquinoline **155a** was followed, using 4-hydroxy-4-(5-hydroxy-2-nitrophenyl)-3-methylenebutan-2-one **147c** (1.00g, 4.8mmol), ethanol (50 mL) and 10 % Pd-C catalyst (0.083g). Work-up and flash chromatography on silica [elution with hexane-EtOAc(3:1)] afforded two fractions.



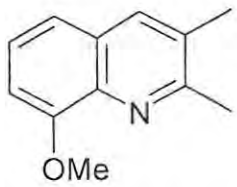
Fraction 1: as yellow crystals, *6-hydroxy-2,3-dimethylquinoline* **155c** (0.165g, 15%), m.p. 260 – 262 °C (Found, $\mathbf{M}^+$: 173.08338 $C_{11}H_{11}NO$ requires *M*, 173.08406); ν_{max}(KBr)/cm^{-1} 3412 (OH) and 1462 (N=C); δ_H (400MHz; $CDCl_3$) 2.32 (3H, s, 3-CH_3), 2.46 (3H, s, 2-CH_3), 6.97 (1H, s, 4-H), 7.13 (1H, d, *J* 8.8Hz, 7-H), 7.69 (1H, d, *J* 8.8Hz, 8-H), 7.75 (1H, s, 5-H) and 9.71 (1H, s, Ar-OH); δ_C (100MHz; $CDCl_3$) 22.7 (2-CH_3), 30.6 (3-CH_3), 107.5 (C-4), 120.4 (C-7), 128.2 (C-4a), 129.2 (C-8), 129.9 (C-3), 133.2 (C-5), 141.0 (C-8a), 154.6 (C-2) and 154.9 (C-6); *m/z* 173 ($\mathbf{M}^+$, 100%).



Fraction 2: as cream crystals, *6-hydroxy-2,3-dimethylquinoline*-N-*oxide* **156c** (0.22g, 20%) m.p. 266 – 268 °C (Found, $\mathbf{MH^+}$: 190.22136 requires $C_{11}H_{11}NO_2$, MH^+, 190.22084); ν_{max}(KBr)/cm^{-1} 3435 (OH), 1462 (N=C) and 1230 (N-O); δ_H (400MHz; DMSO-d_6) 2.39 (3H, s, 3-CH_3), 2.51 (3H, s, 2-CH_3), 7.10 (1H, s, 4-H), 7.23 (1H, dd, *J* 4.0Hz, 7-H), 7.52 (1H, d, *J* 2.4Hz, 5-H), 8.36 (1H, d, *J* 9.6Hz, 8-H) and 10.2 (1H, br s, Ar-OH); δ_C (100MHz; DMSO-d_6) 14.8 (3-CH_3), 20.5 (2-CH_3), 118.8 (C-4), 121.7 (C-7), 126.2 (C-5), 127.9 (C-8), 128.8 (C-4a), 131.1 (C-3), 131.9 (C-6), 141.1 (C-8a) and 147.0 (C-2); *m/z* 190 ($\mathbf{MH^+}$, 100%).

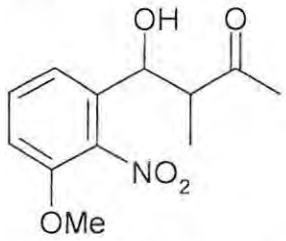
***Hydrogenation of 4-hydroxy-4-(3-methoxy-2-nitrophenyl)-3-methylenebutan-2-one* 147d.**

The general procedure described for the synthesis of 2,3-dimethylquinoline **155a** was followed, using 4-hydroxy-4-(3-methoxy-2-nitrophenyl)-3-methylenebutan-2-one **147d** (0.48g, 1.9mmol), ethanol (50 mL) and 10 % Pd-C catalyst (0.07g). Work-up and flash chromatography on silica [elution with hexane-EtOAc (1:1)] afforded two fractions.



Fraction 1: as yellowish crystals, *8-methoxy-2,3-dimethylquinoline* **155d** (0.09g, 26%) m.p. 140 – 142 °C; ν_{max}(KBr)/cm^{-1}) 1710 (N=C); δ_H (400MHz; $CDCl_3$) 2.39 (3H, s, 3-CH_3), 2.69 (3H, s, 2-CH_3), 4.02 (3H, s, OMe), 6.93 (1H, d, *J* 9.0Hz, 5-H), 7.23 (1H, d, *J* 9.5Hz, 6-H), 7.34 (1H, t, *J* 9.3Hz, 7-H) and 7.76 (1H, s, 4-H); δ_C (100MHz; $CDCl_3$) 19.4 (2-CH_3), 23.8 (3-CH_3), 55.8 (OCH_3), 106.5 (C-4), 118.6 (C-6), 125.6 (C-5), 128.4 (C-3),

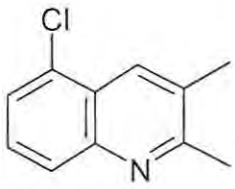
130.5 (C-4a), 135.2 (C-7), 138.1 (C-8) 154.6 (C-2) and 157.9 (C-8a); *m/z* 186 (**MH**$^+$, 100%).



Fraction 2: as yellow crystals, *4-(2-nitro-3-methoxyphenyl)-4-hydroxy-3-methylbutan-2-one* **161b** (0.15g, 38%) m.p. 154 – 156°C (Found, FAB MS: **MH**$^+$: 254.2. $C_{12}H_{15}NO_5$ requires *MH*, 254.10207); ν_{max}(KBr)/cm^{-1} 1712 (C=O) and 3449 (OH); δ_H (400MHz; $CDCl_3$) 1.01 (3H, d, *J* 7.2Hz, C<u>H</u>$_3$CH), 2.18 (3H, s, CH_3CO), 3.02 (1H, m, 3-H), 3.26 (1H, br s, 4-H), 3.90 (3H, s, OMe), 4.78 (1H, br s, OH), 6.97 (1H, d, *J* 8.4Hz, 6'-H), 7.05 (1H, d, *J* 8Hz, 4'-H) and 7.42 (1H, t, *J* 7Hz, 5'-H); δ_C (100MHz; $CDCl_3$) 14.1 (<u>C</u>H$_3$CH), 29.9 (C-3), 52.3 (<u>C</u>H$_3$CO), 56.5 (OCH_3), 71.9 (C-4), 111.9 (C-5'), 119.3 (C-6'), 131.1 (C-4'), 134.8 (C-1') overlapping with (C-2'), 150.6 (C-3') and 212.7 (C-2); *m/z* 223 (**MH**$^+$, 0.44%) and 165 (100).

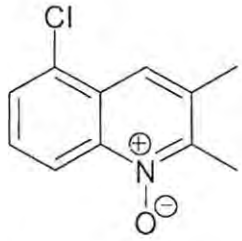
***Hydrogenation of 4-(6-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one* 147e.**

The general procedure described for the synthesis of 2,3-dimethylquinoline **155a** was followed, using 4-(6-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147e** (0.30g, 1.8mmol), ethanol (30 mL) and 10 % Pd-C catalyst (0.042g). Work-up and flash chromatography on silica [elution with hexane-EtOAc (1:1)] afforded two fractions.



Fraction 1: as a brownish oil, *5-chloro-2,3-dimethylquinoline* **155e** (0.087g, 29%) (Found, **M**$^+$: 191.04614. $C_{11}H_{10}N^{35}Cl$, requires *M*, 191.05018); ν_{max}(KBr)/cm^{-1} 1712 (N=C) and 799 (C-Cl); δ_H (400MHz; $CDCl_3$) 1.89 (3H, s, 3-CH_3), 2.46 (3H, s, 2-CH_3),

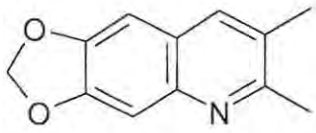
7.03 (1H, overlapping t, 7-H), 7.04 (1H, overlapping s, 4-H), 7.23 and 7.24 (2H, 2 x overlapping d, 6-H and 8-H); δ_C (100MHz; $CDCl_3$) 9.54 (2-CH_3), 32.7 (3-CH_3), 107.4 (C-7), 110.5 (C-4), 113.7 (C-8), 118.4 (C-4a), 122.8 (C-6), 124.7 (C-3), 134.4 (C-5), 138.5 (C-8a) and 201.2 (C-2); *m/z* 191 [$\mathbf{M^+(^{35}Cl)}$, 19.8%] and 43 (100).



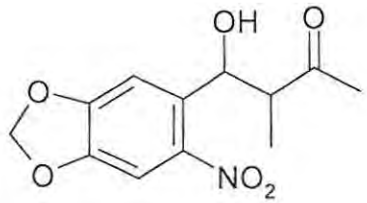
Fraction 2: as a brown oil, *5-chloro-2,3-dimethylquinoline-N-oxide* **156e** (0.04g, 13%) (Found, $\mathbf{M^+}$: 207.04475. $C_{11}H_{10}NO^{35}Cl$, requires *M*, 207.04509); ν_{max}(KBr)/cm^{-1} 1712 (N=C), 1283 (N-O) and 799 (C-Cl); δ_H (400MHz; $CDCl_3$) 2.49 (3H, s, 3-CH_3), 2.68 (3H, s, 2-CH_3), 7.55 (1H, t, *J* 8Hz, 7-H), 7.61 (1H, d, *J* 7.2Hz, 6-H), 7.84 (1H, s, 4-H) and 8.63 (1H, d, *J* 8.8Hz, 8-H); δ_C (100MHz; $CDCl_3$) 14.8 (2-CH_3), 20.5 (3-CH_3), 118.8 (C-7), 121.7 (C-4), 126.2 (C-8), 127.9 (C-4a), 128.8 (C-6), 131.1 (C-3), 131.9 (C-5), 141.1 (C-8a) and 147.0 (C-2); *m/z* 207 [$\mathbf{M^+(^{35}Cl)}$, 71.6%] and 190 (100).

***Hydrogenation of 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one* 147g.**

The general procedure described for the synthesis of 2,3-dimethylquinoline **155a** was followed, using 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **147g** (0.76g, 2.9mmol), ethanol (38 mL) and 10 % Pd-C catalyst (0.103g). Work-up and flash chromatography on silica [elution with hexane-EtOAc-$CHCl_3$ (1:1:3)] afforded two fractions.



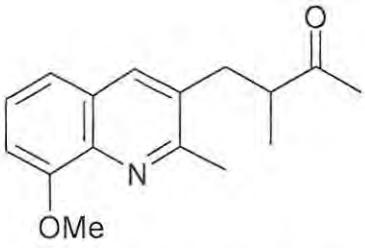
Fraction 1: as yellow crystals, 2,3-dimethyl-6,7-methylenedioxyquinoline **155g** (0.12g, 21%), m.p. 148 – 150°C (lit.[46] m.p 120 – 124°C) (Found, $\mathbf{MH^+}$: 203.07088. $C_{12}H_{11}NO_2$ requires *M*, 203.07082); ν_{max}(KBr)/cm^{-1} 1240 (N=C); δ_H (400MHz; $CDCl_3$) 1.82 (3H, s, 3-CH_3), 2.46 (3H, s, 2-CH_3), 6.16 (2H, s, CH_2), 6.72 (1H, s, 4-H), 7.67 (1H, s, 5-H) and 7.73 (1H, s, 8-H); δ_C (100MHz; $CDCl_3$) 12.9 (3-CH_3), 25.8 (2-CH_3), 136.9 (CH_2), 103.3 (C-4), 105.7 (C-5), 127.1 (C-8), 129.8 (C-4a), 136.9 (C-3), 138.1 (C-8a), 147.3 (C-6), 150.4 (C-7) and 198.9 (C-2); *m/z* 203 ($\mathbf{MH^+}$, 79%) and 43 (100).



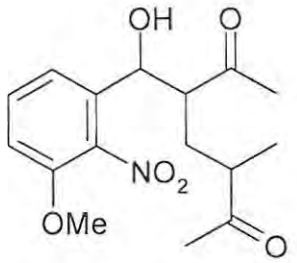
Fraction 2: as a reddish-brown oil, *4-(2-nitro-4,5-methylenedioxyphenyl)-4-hydroxy-3-methylbutan-2-one* **161c** (0.23g, 30%); ν_{max}(KBr)/cm^{-1} 3449 (OH) and 1647 (C=O); δ_H (400MHz; $CDCl_3$) 1.16 (3H, d, *J* 7.2Hz, $C\underline{H}_3CH$), 2.12 (3H, s, CH_3CO), 2.98 (1H, m, 3-H), 3.93 (1H, br s, OH), 5.42 (1H, d, *J* 6.0Hz, 4-H), 6.09 (2H, s, CH_2), 7.08 (1H, s, 3'-H) and 7.43 (1H, s, 6'-H); δ_C (100MHz; $CDCl_3$) 13.5 ($\underline{C}H_3CH$), 30.1 ($\underline{C}H_3CO$), 52.3 (C-3), 70.3 (C-4), 102.3 (CH_2), 104.5 (C-6'), 134.4 (C-1'), 141.1 (C-2'), 106.8 (C-3'), 147.4 (C-4'), 151.2 (C-5') and 212.7 (C=O).

***Hydrogenation of 5-acetyl-6-hydroxy-6-(3-methoxy-2-nitrophenyl)-3-methylene-2-hexanone* 149.**

The general procedure described for the synthesis of 2,3-dimethylquinoline **155a** was followed, using 5-acetyl-6-hydroxy-6-(3-methoxy-2-nitrophenyl)-3-methylene-2-hexanone **149** (0.43g, 1.5mmol), ethanol (50 mL) and 10 % Pd-C catalyst (0.053g). Work-up and flash chromatography on silica [elution with hexane-EtOAc (1:3)] afforded two fractions.



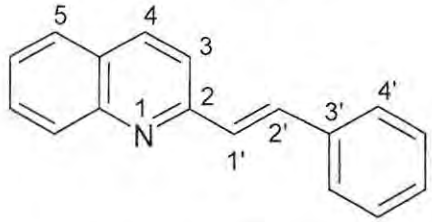
Fraction 1: as yellowish oil, *8-methoxy-2-methyl-3-(2-methyl-3-oxobutyl)quinoline* **163** (0.025g, 7%) (Found, $\mathbf{M}^+$: 257.14224. $C_{16}H_{19}NO_2$ requires *M*, 257.14158); ν_{max}(nujol)/cm^{-1} 1608 (C=O); δ_H (400MHz; $CDCl_3$) 1.16 (3H, d, *J* 6.8Hz, CH-C<u>H</u>$_3$), 2.09 (3H, s, CH_3CO), 2.71 and 3.19 (2H, 2 x m, CH_2), 2.79 (3H, s, 2-CH_3), 2.91 (1H, dq, *J* 7.2Hz, 2'-H), 4.06 (3H, s, OCH_3), 6.98 (1H, d, *J* 7.6Hz, 5-H), 7.28 (1H, d, *J* 8Hz, 7-H), 7.39 (1H, t, *J* 8Hz, 6-H) and 7.78 (1H, s, 4-H); δ_C (100MHz; $CDCl_3$) 16.6 (CH<u>C</u>H$_3$), 23.6 (2-CH_3), 28.9 (CH_3CO), 35.5 (C-1'), 46.8 (C-2'), 55.9 (OCH_3), 107.1 (C-6), 118.9 (C-4), 126.0 (C-5), 128.2 (C-3), 132.2 (C-4a), 136.1 (C-7), 138.2 (C-8a), 154.6 (C-8), 157.3 (C-2) and 211.2 (C=O).



Fraction 2: as a reddish oil, *5-acetyl-6-(2-nitro-3-methoxyphenyl)-6-hydroxy-3-methyl-2-hexanone* **164** (0.18g, 43%); ν_{max}(KBr)/cm^{-1} 1687 (C=O); δ_H (400MHz; $CDCl_3$) 1.07 (3H, d, *J* 7.2Hz, CHC<u>H</u>$_3$), 1.71 (1H, m, 3-H), 2.09 and 2.14 (6H, 2 x s, 2 x C<u>H</u>$_3$CO), 3.02 (1H, m, 5-H), 3.15 and 3.89 (2H, 2 x s, 4-CH_2), 3.25 (1H, br s, OH), 3.90 (3H, s, OCH_3), 4.74 (1H, br t, *J* 5.4Hz, 6-H), 6.98 (1H, t, *J* 9.8Hz, 5'-H), 7.10 (1H, d, *J* 8.0Hz, 6'-H) and 7.48 (1H, d, *J* 8.0Hz, 4'-H); δ_C (100MHz; $CDCl_3$) 17.2 (CH<u>C</u>H$_3$), 27.8 and 31.7 (2 x <u>C</u>H$_3$CO), 44.5 (C-4), 54.8 (C-5), 56.5 (OCH_3), 70.7 (C-3), 112.1 (C-6), 118.9 (C-5'), 131.4 (C-6'), 134.9 (C-4'), 140.4 (C-1'), 140.5 (C-3'), 150.6 (C-2'), 211.5 and 212.5 (2 x C=O).

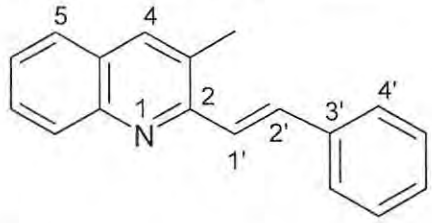
3.4 Synthesis of styrylquinoline derivatives

***(E)-2-styrylquinoline* 166a**



To a solution of quinaldine **165** (0.50g, 3.7mmol) in acetic anhydride (6 mL) was added benzaldehyde **146a** (0.79g, 7.5mmol).[79] The mixture was boiled under reflux for 16 hours and concentrated *in vacuo*. Flash chromatograghy on silica [elution with hexane-EtOAc (9:1)] and recrystalisation from hexane-$CHCl_3$ (3:1) gave, as yellow crystals, (*E*)-2-styrylquinoline **166a** (0.90g, 69%) m.p. 98 – 100°C; (Found $\mathbf{M}^+$: 231.10486. $C_{17}H_{13}N$ requires *M*, 231.10480); ν_{max}(KBr)/cm^{-1} 1594 (N=C); δ_H (400MHz; $CDCl_3$) 7.32 (1H, d, *J* 7.2 Hz, 2'-H), 7.39 - 7.71 (9H, series of overlapping multiplets, Ar-H and C<u>H</u>=C), 7.78 (1H, d, *J* 8.0Hz, 3-H) and, 8.10 and 8.13 (2H, overlapping d, 1'-H and 8-H); δ_C (100MHz; $CDCl_3$) 119.7 (C-2'), 126.6 (C-6'), 127.4 (C-4'), 127.9 (C-5'), 129.1 (C-6), 129.2 (C-5), 129.3 (C-7), 129.6 (C-4), 130.2 (C-3), 127.7 (C-3'), 134.9 (C-1'), 136.5 (C-8), 136.8 (C-4a), 148.2 (C-8a) and 155.9 (C-2); *m/z* 231 ($\mathbf{M}^+$, 96.5%) and 230 (100).

***(E)-3-methyl-2-styrylquinoline* 166b**

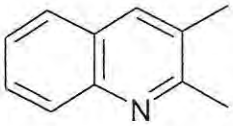


The general procedure described for the synthesis of (*E*)-2-styrylquinoline **166a** was followed, using 2,3-dimethylquinoline **155a** (0.13g, 0.83mmol), acetic anhydride (4mL) and benzaldehyde **146a** (0.18g, 1.7mmol). The mixture was boiled under reflux for 36 hours and concentrated *in vacuo*. Flash chromatograghy on silica [elution with hexane-EtOAc (3:1)] and recrystalisation from hexane-EtOAc (7:1) gave, as colourless crystals,

(*E*)-3-methyl-2-styrylquinoline **166b** (0.11g, 35%) m.p. 112 – 114°C (lit.[82] cites as oil); (Found $\mathbf{M}^+$: 245.12150. $C_{18}H_{15}N$ requires *M*, 245.12045); ν_{max}(KBr)/cm^{-1} 1620 (N=C); δ_H (400MHz; $CDCl_3$) 2.61 (3H, s, CH_3), 7.30 –7.49 (4H, series of overlapping multiplets Ar-H), 7.51 (1H, d, *J* 15.6Hz, 2'-H), 7.68 – 7.75 (4H, series of overlapping multiplets Ar-H), 7.88 (1H, s, 4-H), 8.04 (1H, d, *J* 15.6Hz, 1'-H) and 8.10 (1H, d, *J* 8.4Hz, 8-H); δ_C (400MHz; $CDCl_3$) 19.5 (3-CH_3), 124.3 (C-6), 126.0 (C-5), 126.7 (C-6'), 127.4 (C-4'), 127.5 (C-7), 127.8 (C-4a), 128.5 (C-1'), 128.7 (C-5'), 128.9 (C-8), 129.3 (C-3), 135.6 (C-2'), 136.2 (C-4), 137.0 (C-3'), 146.9 (C-8a) and 154.8 (C-2); *m/z* 245 ($\mathbf{M}^+$, 100).

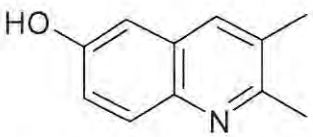
3.5 Conversion of the quinoline *N*-oxides to quinolines

2,3-Dimethylquinoline **155a**



To a stirred solution of the quinoline *N*-oxide **156a** (0.27g; 1.6mmol) and DMF (8mL) at room temperature under nitrogen was added PBr_3 (0.69mL; 2.4mmol) and the stirring continued for 1 hour. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (40mL) ice (10g) and the resulting mixture extracted with EtOAc (3 x 20mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (10mL) and brine (10mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the quinoline **155a** in 79% yield.

6-Hydroxy-2,3-dimethylquinoline **155c**

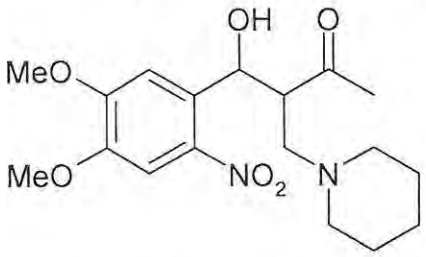


The general procedure described for the conversion of the quinoline *N*-oxide **156a** to 2,3-dimethylquinoline **155a** was followed, using 2,3-dimethyl-6-hydroxyquinoline *N*-oxide

156c (0.22g; 1.13mmol), DMF (8mL) and PBr_3 (0.49mL; 1.72mmol) to give the quinoline **155c** in 70% yield.

3.6 Reaction of the Baylis-Hillman adducts with piperidine

Reaction of 4-(4,5-dimethoxy-2-nitrophenyl)-4-hydroxy-3-butan-2-one **147g**.

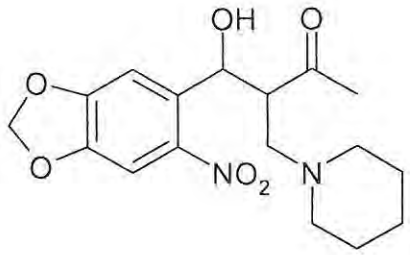


A mixture of 4-(4,5-dimethoxy-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **147g** (0.40g, 2mmol) and piperidine (0.5mL, 2mmol) in THF (5mL) was stirred in a stoppered reaction flask for 3 days.[45] Excess piperidine was evaporated off *in vacuo* to give a dark brown oil which was purified by flash chromatography on silica gel [elution with hexane-EtOAc-$CHCl_3$ (1:2:3)] to afford:-

Fraction 1: as yellow solid, 4,5-dimethoxy-2-nitrobenzaldehyde **146f** (0,24g, 40%).

Fraction 2: as a reddish oil, traces of 4-hydroxy-3-methylene-4-(4,5-methoxy-2-nitrophenyl)-3-piperidinomethylbutan-2-one **171g** (4mg, 1%).

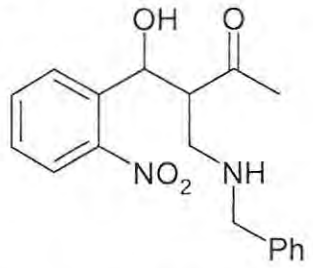
Attempted synthesis of 4-hydroxy-4-(4,5-methylenedioxy-2-nitrophenyl)-3-piperidinomethylbutan-2-one **155g**.



The general procedure used for the synthesis of 4-(4,5-dimethoxy-2-nitrophenyl)-4-hydroxy-3-piperidinomethylbutan-2-one **171f** was followed, using 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one (0.53g, 2mmol) and piperidine (0.5mL, 2mmol) in THF (5mL) to afford a brownish oil which contained traces of the expected product **171f**.

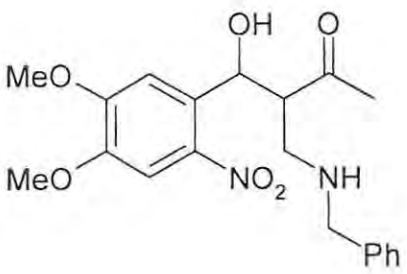
3.7 Reaction of the Baylis-Hillman adducts with benzylamine

***Attempted synthesis of 3-(benzylaminomethyl)-4-hydroxy-4-(2-nitrophenyl)butan-2-one* 170a.**



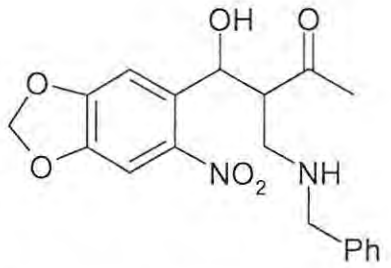
A mixture of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **147a** (0.41g, 2mmol) and benzylamine (0.22mL, 2mmol) in methanol (4mL) was stirred in a stoppered flask for 3 days.[45] Excess benzylamine was evaporated off *in vacuo* to give a dark brown oil which was purified by flash chromatography on silica [elution with hexane-MeOH-EtOAc (3:0.1:1)] to afford, as a pale green oil, benzylamine **168** (0.24g, 40%) and some traces of the expected product **170a**.

***Attempted synthesis of 3-(benzylaminomethyl)-4-(4,5-dimethoxy-2-nitrophenyl)-4-hydroxybutan-2-one* 170g.**



The general procedure used for the synthesis of 3-(benzylaminomethyl)-4-hydroxy-4-(2-nitrophenyl)butan-2-one **170a** was followed, using 4-hydroxy-3-methylene-4-(4,5-dimethoxy-2-nitrophenyl)butan-2-one **147g** (0.60g, 2mmol) and benzylamine (0.22mL, 2mmol) in methanol (4mL) to afford a brown oil which was purified by flash chromatography on silica gel [elution with hexane-$CHCl_3$-EtOAc (3:3:1)] to give, as yellow solid, 4,5-dimethoxybenzaldehyde (0.25g, 40%).

Attempted synthesis of 3-(benzylaminomethyl)-4-(4,5-methylenedioxy-2-nitrophenyl)-4-hydroxybutan-2-one **170f.**



The general procedure used for the synthesis of 3-(benzylaminomethyl)-4-hydroxy-4-(2-nitrophenyl)butan-2-one **170a** was followed, using 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **147f** (0.53g, 2mmol) and benzylamine (0.22mL, 2mmol) in methanol (4mL) to afford a dark brown oil (0.5g). Purification by flash chromatography did no give the expected product.

3.8 Reaction of the Baylis-Hillman adducts with piperidine and with benzylamine without a solvent

The reactions were set up as in the previous sections **3.6** and **3.7** but now without the added solvent, that is, the piperidine and the benzylamine were acting as a solvent. Again the reactions were found to be unsuccessful as none of the expected products were isolated. However, due to time limits we could not work out what were the collected fractions though.

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