Some Uses Of Acyliminium Ions In The Synthesis Of Isoquinolones With Potential Biological Activity.

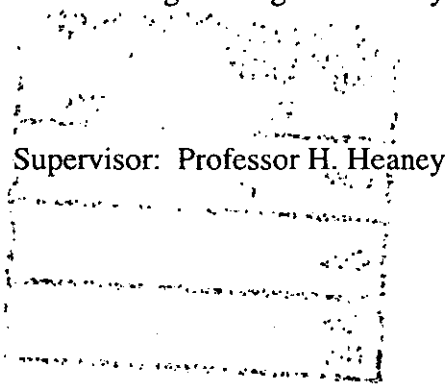
By

Mutasem Omar Taha

A thesis submitted in partial fulfilment of the requirements for the award of:

Doctor of Philosophy

of The Loughborough University

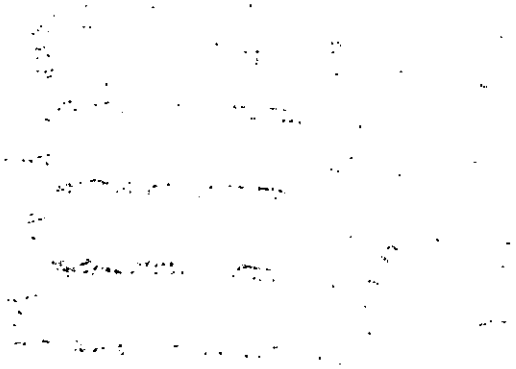


Supervisor: Professor H. Heaney

Certificate Of Originality

This is to certify that I am responsible for the work submitted in this thesis, that the original work is my own except as specified in acknowledgements or in footnotes, and that neither the thesis nor the original work contained therein has been submitted to this or any other institution for a higher degree.

Mutasem Omar Taha April 1998.



To My Parents

Acknowledgements

I would like to express my sincere thanks to the following people for their assistance during this project.

Professor H. Heaney for his excellent guidance, constant enthusiasm and friendship throughout the supervision of this project;

The Jordan University and The British Council for funding this project;

Dr. T. Smith and Mr. J. C. Kershaw for running high field NMR spectra and for technical assistance;

Dr. A. M. Z. Slawin for performing single crystal X-ray structural analysis;

Mr. J. C. Kershaw and Mrs L. Sands for mass spectroscopic services and related technical assistance;

Astra Charnwood for the period I spent in their laboratories (from November to April 1996) and spectroscopic services;

Everybody in the laboratories F0001 and F009 over the last 3 years.

Abstract

The preparation of a number of 2-substituted homophthalimides through the condensation of homophthalic anhydride with different arylalkyl amines is reported. The prepared compounds were alkylated at the 4-position to generate 4-mono-, 4,4-disubstituted and 4-spirocyclic homphthalimides, the analogues of which were reported to have interesting biological activity. Regioselective reduction of the 4-substituted derivatives generated the corresponding carbinolamides. Treating the carbinolamides with mineral or Lewis acids generated *N*-acyliminium ions, which were trapped *in situ* by one of the following: (1) aromatic neucleophiles to generate analogues of the natural product berberine, (2) alkyl chain migration to generate tetrahydrophenanthridones and functionalised isoquinolones, (3) cyclopropane ring-opening to generate 4-alkylisoquinolones, (4) addition to double bond to generate cyclopentaisoquinolones and (5) benzyl or allyl elimination.

The oxidation of 4-monosubstituted homophthalimides with triplet dioxygen in alkaline media was investigated, and it generated 4-hydroxyhomophthalimides and isobenzofurancarboxamides. Treating isobenzofurancarboxamides with $POCl_3$ provided a concise route to analogues of the neuroactive naturally-occurring phthalideisoquinolines.

Contents

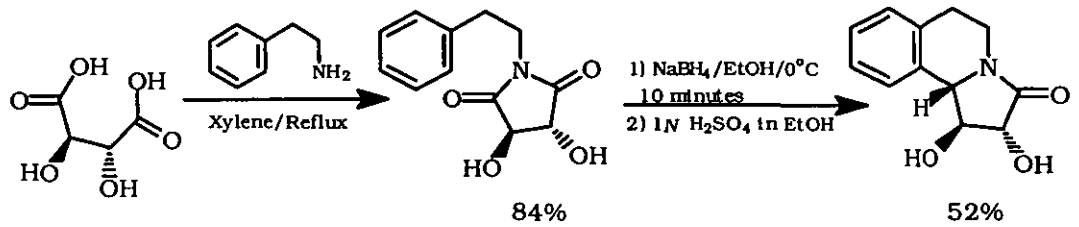
Experimental

Abbreviations

Bn	Benzyl.
t-Bu	*tert*-Butyl.
t-BuLi	*tert*-Butyllithium.
BSA	*N,O*-Bis(trimethylsilyl)acetamide.
CPTC	Chiral Phase Transfer Catalyst.
o-DCB	*o*-Dichlorobenzene.
DCM	Dichloromethane.
DMF	Dimethylformamide.
DMSO	Dimethylsulfoxide.
EA	Ethyl acetate.
KHMDS	Potassium hexamethyldisilazide.
LP	Light petroleum.
Me	Methyl.
NMR	Nuclear magnetic resonance.
Ph	Phenyl.
ppm	Parts per million.
i-Pr	Isopropyl.
Quant.	Quantitative.
r.t.	Room temperature.
TEA	Triethylamine.
TFA	Trifluoroacetic acid.
TES	Triethylsilyl.
TLC	Thin layer chromatography.
TMEDA	*N,N,N',N'*-tetramethylethylenediamine.
TMSOTf	Trimethylsilyl trifluoromethanesulfonate.
Triflate	Trifluoromethanesulfonate.
TMS	Trimethylsilyl.
p-Ts	*para*-Toluenesulfonyl.
THF	Tetrahydrofuran.

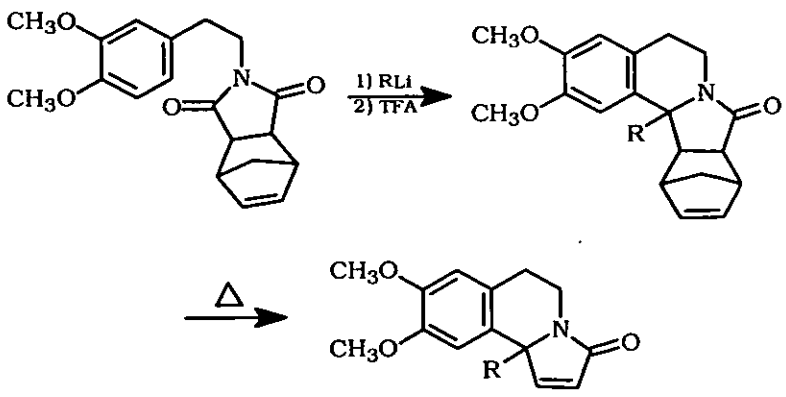
Chapter 1: Introduction.

N-acyliminium ion chemistry was originally introduced to allow Mannich type condensation reactions to be carried out. However, it was quickly realised that the intermediate is of great importance in other synthetic reactions as well.[1, 2] Recently, many research groups around the world have employed *N*-acyliminium ions in their synthetic routes towards naturally occurring alkaloids, or to prepare compounds of potential biological activity, which can be further investigated as potential medicines. Some recent examples on *N*-acyliminium ion chemsitry are now reviewed. However, further discussion and more examples on this cationic species are detailed in chapter 5. Lee *et al.*[3] showed that the cyclisation reactions of chiral carbinol lactams, derived from (L)-tartaric acid and phenylethylamine, afforded one diastereomer under variety of acidic conditions in moderate to good yields. One of their reactions is illustrated in **Scheme 1.1**.



Scheme 1.1

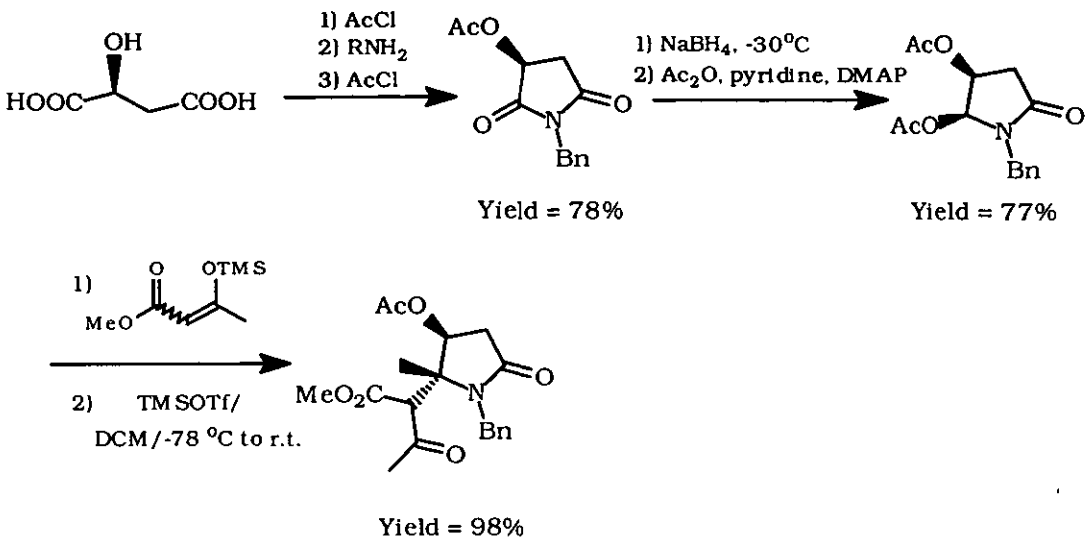
Manteca *et al.*[4] prepared pyrrolo[2,1-a]isoquinolones, in high yields, from the sequential nucleophilic addition of organolithium reagents followed by *N*-acyliminium ion cyclisation. The products are considered to be key intermediates towards *Erythrina*-type alkaloids. The procedure is outlined in **Scheme 1.2**.



Scheme 1.2

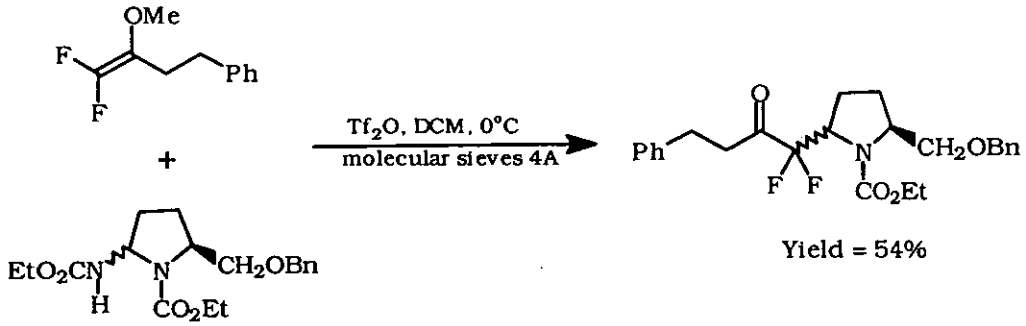
It is important to mention that the authors used *cis*-norbor-5-en-2,3-dicarboximide as a masked α,β-unsaturated imide moiety, since they found that the direct lithiation of the equivalent maleimide led only to polymerisation products. The overall yield is 31%, and no detailed reaction conditions were mentioned.

Louwrier *et al.*[5] reported a highly stereoselective *N*-acyliminium ion coupling of β-ketoester-derived silyl enol ethers with enantiopure lactams derived from (*S*)-malic acid. This reaction type is applied in the synthesis of an enantiopure plausible intermediate in a projected synthesis of ptilomycalin A. One of the reaction sequences reported by this group is shown in **Scheme 1.3**.



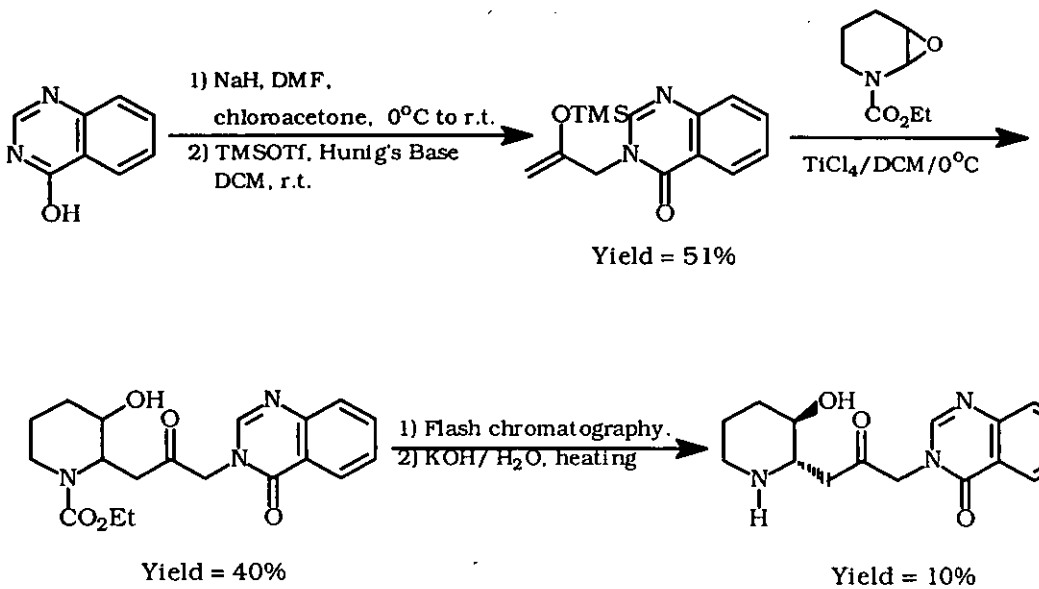
Scheme 1.3

Kodama *et al.*[6] reported an efficient preparation of β-amino-α,α-difluoroketones based on the reaction of 1,1-difluorovinyl methyl ethers with *N*-acyliminium intermediates, generated by treating biscarbamates with trifluoromethane-sulfonic anhydride (Tf_2O) in the presence of molecular sieves. An example of their work is shown in **Scheme 1.4**.



Scheme 1.4

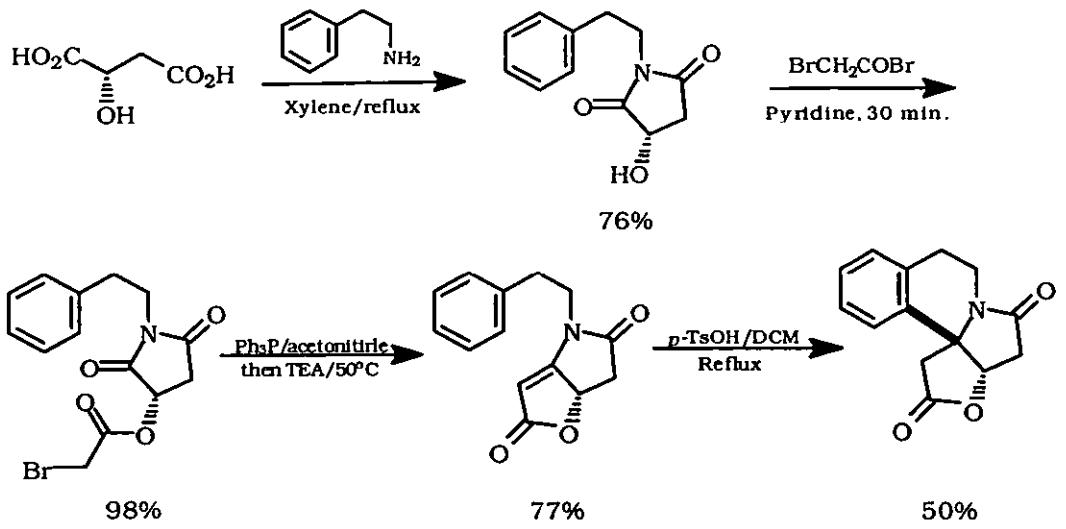
Burgess *et al.*[7] utilised the epoxides generated from cyclic enecarbamates as effective *N*-acyliminium ion precursors. This methodology was utilised to prepare β-hydroxy, α-substituted piperidines and pyrrolidines including the antimalarial agent febrifugine. **Scheme 1.5** illustrates their approach to Febrifugine.



Scheme 1.5

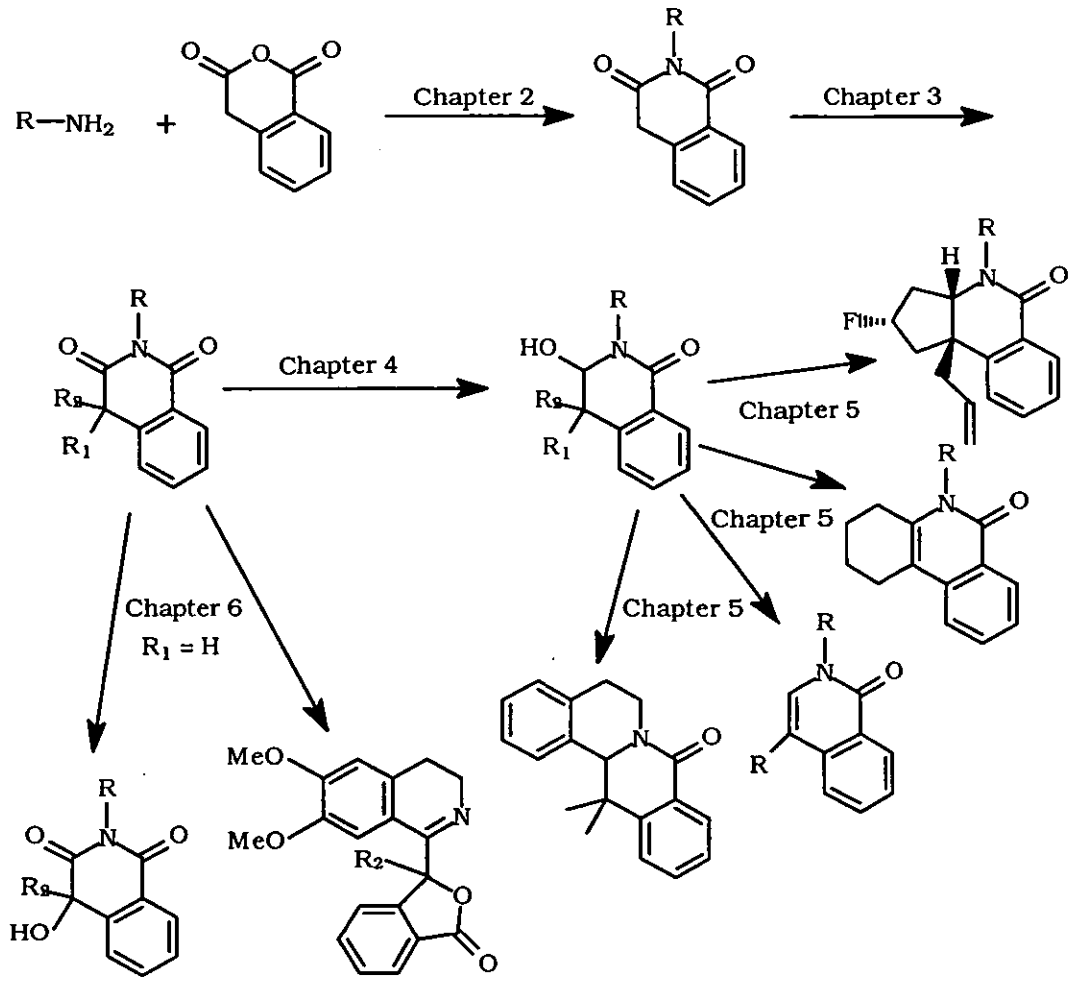
In another example reported by Lee *et al.*,[8] the asymmetric synthesis of furopyrroloisoquinolines was achieved starting from the cheap L-malic acid and

via a diastereoselective *N*-acyliminium ion cyclisation of chiral enamides as show in **Scheme 1.6**.



Scheme 1.6

The research described in this thesis is summarised in **Scheme 1.7**, whereby each step in the scheme represent the research discussed in the corresponding chapter. The central theme of this thesis is chapter 5, which deals with generation and trapping of *N*-acyliminium ions, while chapters 2, 3 and 4 deal the research conducted to prepare the *N*-acyliminium ion precursors. Despite the use of known methodologies for the preparation of the different intermediates discussed in chapters 2,3 and 4, many novel findings are also discussed in these chapters. On the other hand, chapter 6 deals with a somewhat different area, which is the aerial oxidation of homopthalimides and its utilisation in concise routes towards some potentially biologically active alkaloidal analogues.
The research discussed herein already yielded three published articles,[9,10,11] and it contains other novel findings covering at least two more future papers.


R—NH2
+
Chapter 2
Chapter 3
Chapter 4
Chapter 5
Chapter 5
Chapter 5
Chapter 6
R1 = H
MeO
MeO

Scheme 1.7

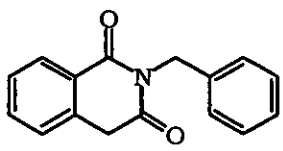
Chapter 2: Preparation of 1,3-Isoquinolinediones from Arylalkyl Amines and Homophthalic anhydride.

2-Substituted 1,2,3,4-tetrahydro-1,3-isoquinolinediones, commonly known as homophthalimides, were reported as early as 1887 by Pulvermacher,[12] when he generated 2-benzylhomophthalimide **2.1** by heating together benzylamine and homophthalic acid.

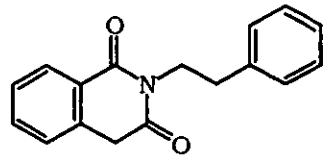
Howarth *et al.*,[13] in their synthetic approaches to oxyberberine, generated 2-(2-phenethyl) homophthalimide **2.2** in 72% by heating homophthalic acid and 2-phenethylamine, at 180 °C for 3 hours. Other related homophthalimides were similarly prepared by the same group.[13]

In their route towards a synthesis of berberine alkaloids, Huffman *et al.*,[14] synthesised 2-(3,4-dimethoxyphenethyl) homophthalimide **2.3** by heating homophthalic anhydride and 3,4-dimethoxyphenethylamine at 180 °C for 2 hours to give the product in 45% yield. D'Sa *et al.*[15] reported the preparation of the same product, following a similar procedure without reporting the yield.

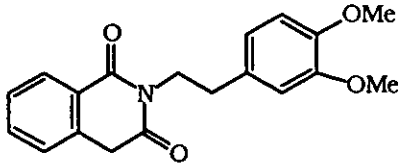
Edwards *et al.*[16] have reported the preparation of 2-[2-(1H-3-indolyl)ethyl] homophthalimide **2.4** by heating tryptamine and homophthalic acid at 180 °C until water elimination ceased to give **2.4** in 86%. Clemo *et al.*[17] reported the same product, from the same starting materials and *via* similar procedure, without reporting a yield.



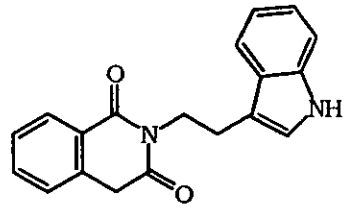
2.1



2.2



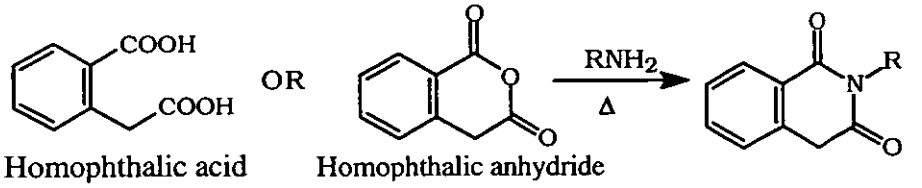
2.3



2.4

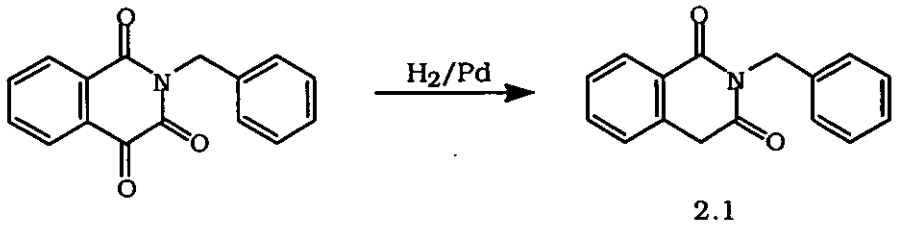
In 1995 Cheng *et al.*[18] generated **2.1** in 80% yield by refluxing homophthalic anhydride and benzylamine in toluene for 24 hours.

The condensation reactions are generally illustrated in **Scheme 2.1**.



Scheme 2.1

Muchowski[19] also prepared **2.1** in 91% yield by palladium catalysed hydrogenation of the readily available 2-benzylhomophthalonimide as in **Scheme 2.2**.

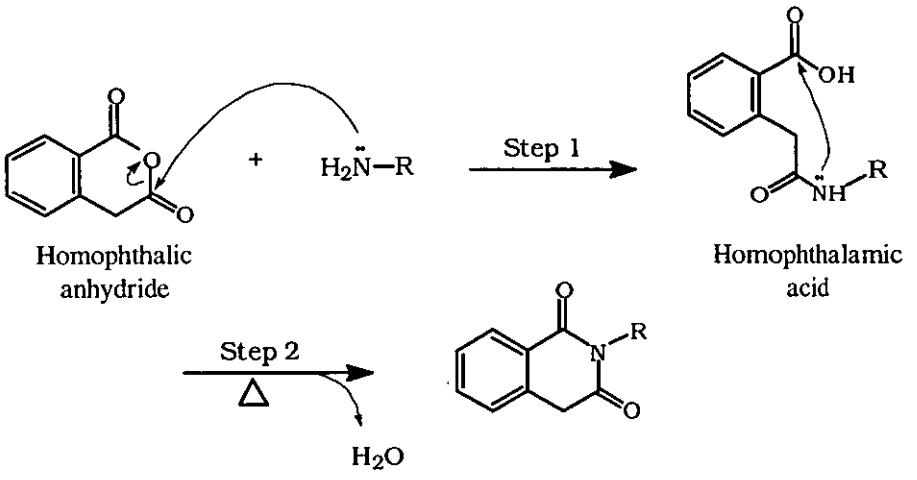


2.1

Scheme 2.2

In the present work we have prepared various 2-substituted homophthalimides as starting materials that could be converted into *N*-acyliminium ion precursors the reactions of which will be discussed later.

The preparation approach we followed is based on heating the particular amine with homophthalic anhydride to 180-185 °C for relatively short period of time (30 to 120 minutes), since we found that longer heating times can result in a reduction of yield. The condensation reaction is expected to proceed *via* the mechanism described in **Scheme 2.3**.



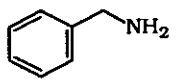
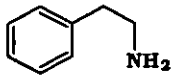
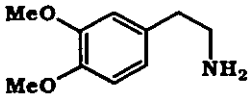
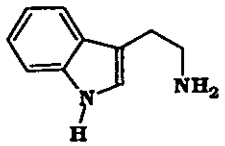
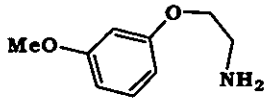
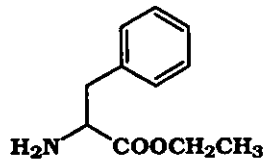
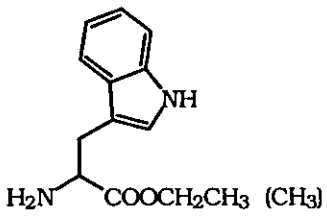
Scheme 2.3

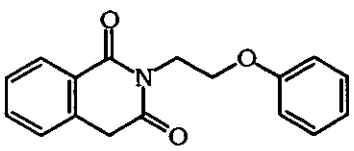
In the proposed mechanism, the first step is the nucleophilic attack of the unshared pair of electrons of the amino group on the electron-deficient unconjugated carbonyl of homophthalic anhydride, to generate N-substituted homophthalamic acid. The second step is the heat facilitated water elimination. Evidence from the work of Clemo *et al.*[17] supports this mechanism. They found that refluxing homophthalic anhydride and tryptamine in benzene, for 3 hours generated N-[2-(1H-3-indolyl) ethyl] homophthalamic acid (**Scheme 2.3**) as the major product.

Optimised reaction conditions and yields of the prepared homophthalimides are summarised in **Table 2.1**. By examining **Table 2.1**, one can quickly see that the yields for the homophthalimides generated from α-amino acid esters, namely **2.6**, **2.7** and **2.8**, are significantly lower than those generated from other arylalkyl amines. This behaviour can be attributed to two possible factors:

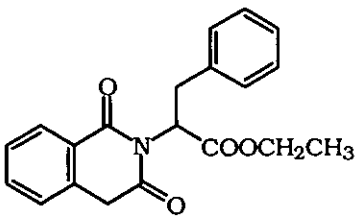
1. Steric hindrance resulting from the α-ester.
2. The deactivating effect of the carbonyl group on the nucleophilicity of the amino group. A measure of the low nucleophilicity caused by the electron withdrawing α-ester is indicated by the pK_b of the α-amino-ester which is *ca.* 10^3 times lower than equivalent amines.[20]

Table 2.1

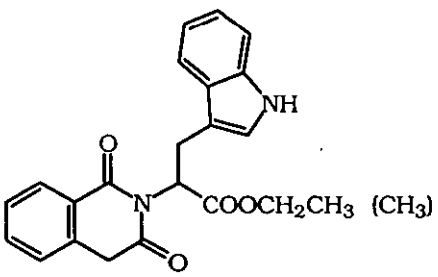
Starting Amine	Reaction Temperature (°C)	Reaction Time (minutes)	Yield (%)	Product
	185	30	100	**2.1**
	185	30	86	**2.2**
	185	30	90	**2.3**
	185	30	85	**2.4**
	175	95	92	**2.5**
	185	95	29	**2.6**
	175 (180)	120 (140)	31 (27)	**2.7 (2.8)**



2.5



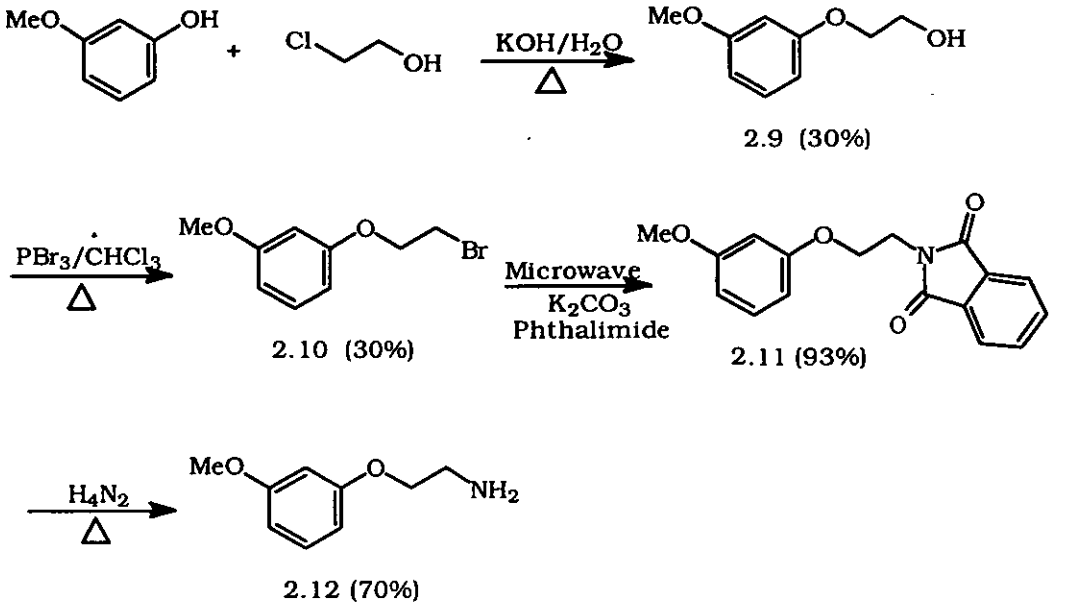
2.6



2.7 (2.8)

The synthetic route to 2-(3-methoxyphenoxy)ethylamine (2.12).

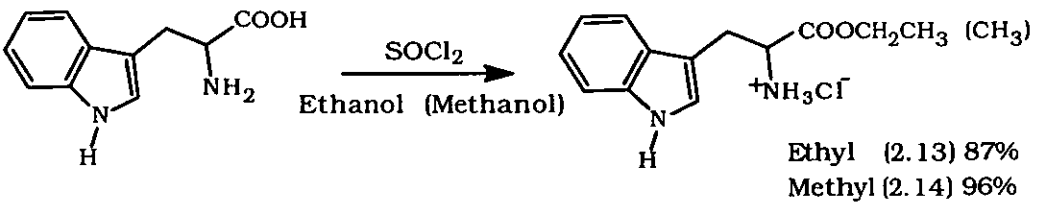
This amine is not available commercially and it was prepared as described in **Scheme 2.4**. In the first step 2-(3-methoxyphenoxy)-1-ethanol **2.9** was prepared from *m*-methoxyphenol and chloroethanol in 30% yield.[21] The product was then treated with phosphorus tribromide in chloroform and yielded 30% of 1-(2-bromoethoxy)-3-methoxybenzene **2.10**,[22] this was then converted to the phthalimide intermediate **2.11** in 93% yield, *via* a recently-described microwave-assisted solid phase reaction.[23] Finally the target amine **2.12** was generated by hydrazinolysis of **2.11** in 70% yield.



Scheme 2.4

Synthesis of tryptophane methyl and ethyl esters.

Tryptophane ethyl and methyl esters, which were used as starting materials in the synthesis of homophthalimides **2.7** and **2.8**, were prepared from the relatively inexpensive tryptophan. The esterification was conducted by treating tryptophan with thionyl chloride in ethanol or methanol to give the ethyl or methyl esters, as described by Biossonnas *et al.*[24] The reaction is illustrated in **Scheme 2.5**.

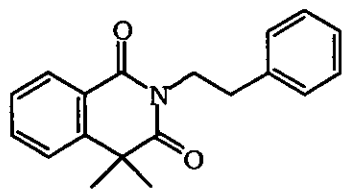


Scheme 2.5

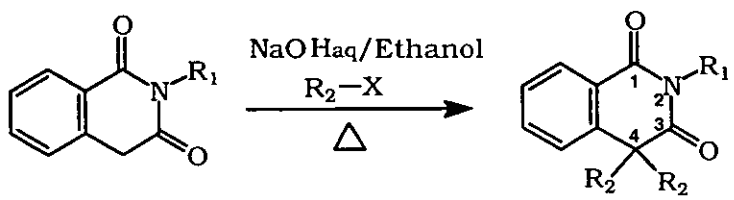
Chapter 3: Formation of 4-Mono- and 4,4-Dialkylhomophthalimides and Related Reactions.

The 4,4-dialkylation of homophthalimides was performed as early as 1887 by Gabriel[25] when he reported the formation of 4,4-dimethyl- and 2,4,4-trimethyl-homophthalimide. In the same year Pulvermacher reported the preparation of 4,4-diethyl, 2,4,4-triethyl and 2,4,4-tribenzylhomophthalimide.[12] In 1925, Haworth *et al.*[13] prepared 2-phenethyl-4,4-dimethylhomophthalimide **3.1** starting from 2-phenethylhomophthalimide. Harriman *et al.*[26] prepared different 4,4-dialkylhomophthalimides for testing as hypnotic agents, they found that the best alkylating agents were iodides except for allyl and benzyl derivatives, for which the chlorides worked best.

All the above alkylation reactions were conducted by refluxing an aqueous ethanolic solution of the starting homophthalimide, sodium hydroxide (2 equivalents) and the particular alkylhalide (2 or more equivalents). The reactions can be generally illustrated in **Scheme 3.1**.



3.1



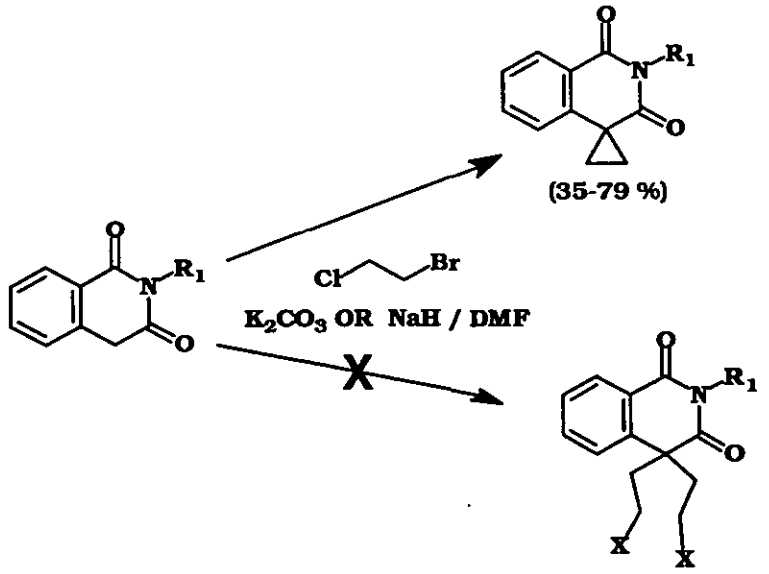
Yields = 18-71%

R_1 Benzyl, Ethyl, H, Allyl, ...
R_2 Methyl, Ethyl, Benzyl
X = Cl, I

Scheme 3.1

Horning *et al.*[27] attempted the preparation of 4,4-dihaloethylhomophthalimides *via* alkylation with large excess of 1-bromo-2-chloroethane, using sodium

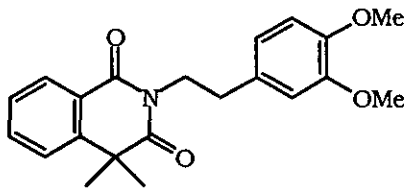
hydride or potassium carbonate in dimethylformamide. However, these conditions generated homophthalimide-4-spirocyclopropanes in medium to good yields as illustrated in **Scheme 3.2**.



R_1= Methyl, Ethyl, Phenyl, Chloroethyl.
X= Cl, Br.

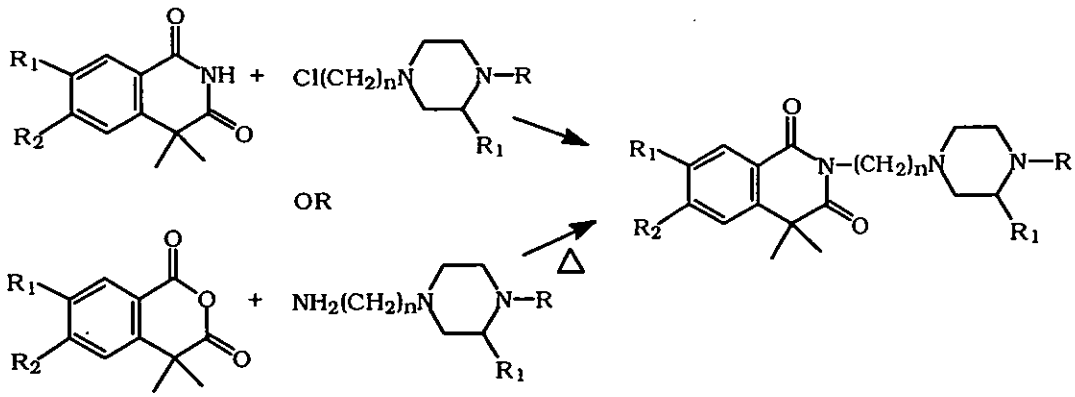
Scheme 3.2

Collado *et al.*[28] prepared 2-(3,4-dimethoxyphenethyl)-4,4-dimethylhomophthalimide (**3.2**) by deprotonating the starting homophthalimide at position 4 with lithium diisopropylamide (LDA) followed by quenching with methyliodide, however the yield was not reported.



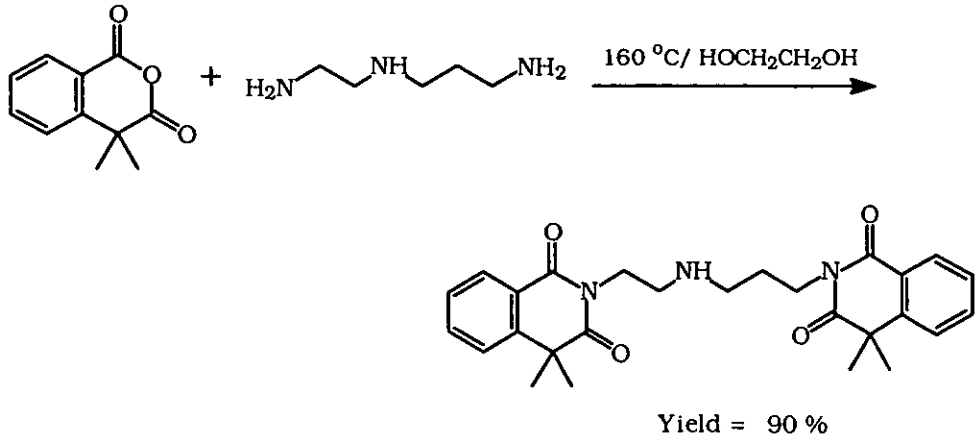
3.2

Kutter *et al.*[29] prepared various 4,4-dimethyl-2-(1-piperazinylalkyl) homophthalimides by condensing 4,4-dimethylhomophthalic anhydride with (1-piperazinyl) alkylamines or by the reaction of 4,4-dimethylhomophthalimide with (1-piperazinyl) alkylchlorides as illustrated in **Scheme 3.3**. These compounds were reported as useful antihypertensives or sedatives or in tachycardia treatment.



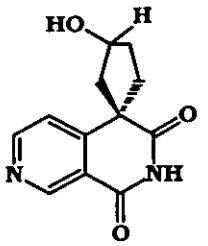
Scheme 3.3

Kutter *et al.*[30] prepared the fumarate salts of 4,4-dialkylated homophthalimide dimers by condensing 4,4-dimethyl homophthalic anhydride and the particular diamine linkage. **Scheme 3.4** illustrates the preparation of one of these compounds. The products were tested on mice as potential antiarrhythmic agents.

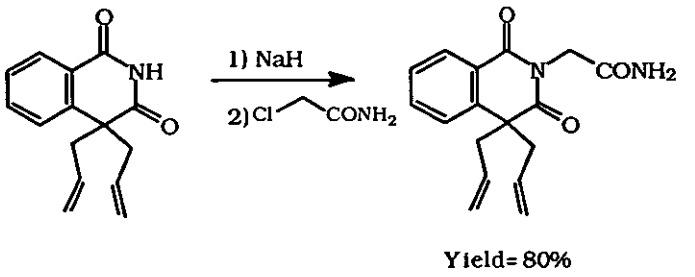


Scheme 3.4

Jonsson *et al.*[31] prepared 2-amidoethyl-4,4-diallylhomophthalimide and found that this product caused 40% reduction in the reserpine-induced depression in mice. This group prepared and tested other homophthalimides, isoindolones and indolones. **Scheme 3.4.**

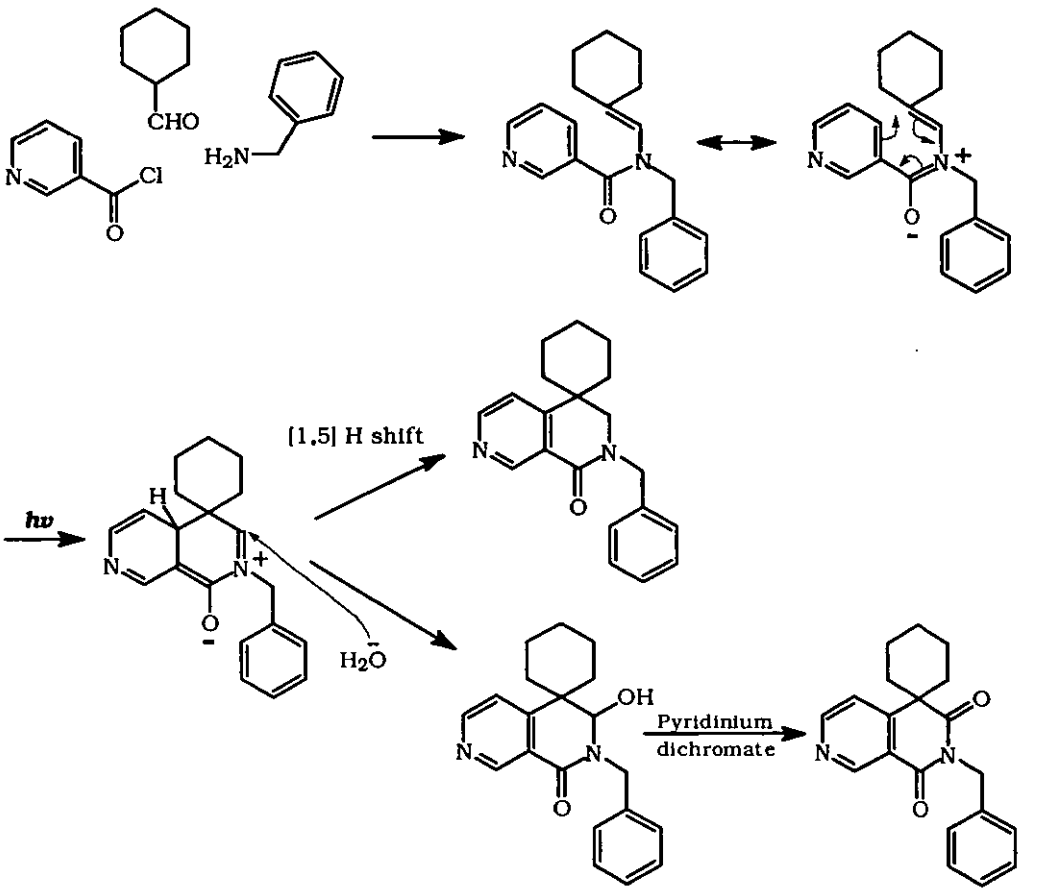


sesbanine



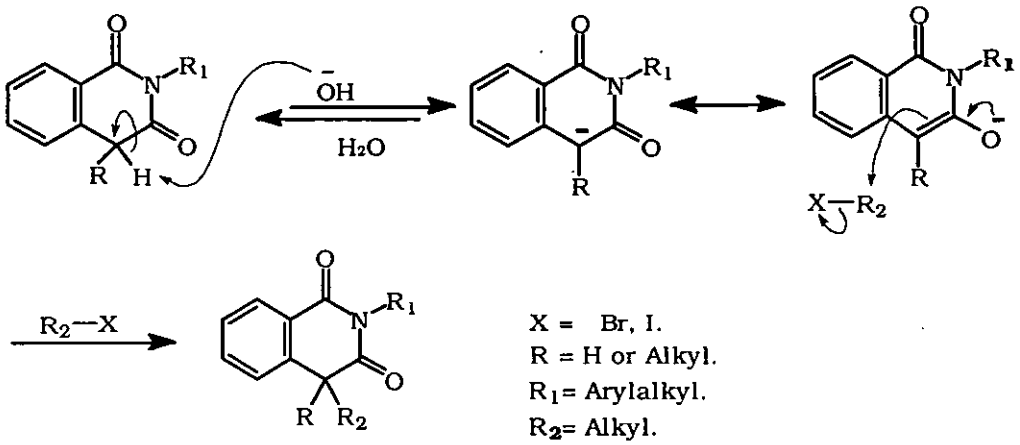
Scheme 3.4

Powell *et al.*[32] have isolated the potent antileukemic 4,4-spirocyclic homophthalimide derivative, sesbanine. Gramain *et al.*[33,34] in their synthetic approaches towards sesbanine, utilised photocyclisation of *N*-benzoylamines followed by oxidation with pyridinium dichromate to generate 4-spirocyclic homophthalimide derivatives as illustrated by **Scheme 3.5**.



Scheme 3.5

In the present work we have prepared various 4-mono and dialkylated homophthalimides, in moderate to excellent yields, as starting materials that could be converted into *N*-acyliminium ion precursors the reactions of which will be discussed later. We followed an alkylation procedure similar to that described by Harriman *et al.*[26] and as illustrated in **Scheme 3.1**, whereby the starting homophthalimide is heated to reflux in aqueous ethanolic (1:1, *ca.* 50 ml) solution of sodium hydroxide (*ca.* 2 equivalents) and the particular alkylating agent (1 or more equivalents). We also applied this procedure for the preparation of 4-spirocyclic homophthalimides as will be discussed later. The expected mechanism for the general alkylation reaction is illustrated in **Scheme 3.6**.



Scheme 3.6

Three points are to be noticed in this suggested mechanism.

1. The enolate form is promoted by the aromatisation of the imide ring. However, under neutral conditions the predominant form seems to be the ketone rather than the enol, since the ^{13}C nmr spectrum of the starting homophthalimides in $CDCl_3$ shows clearly the presence of two carbonyl resonances (165 and 170 ppm) and their infrared spectra show two bands at 1716 and 1670 cm^{-1}. The infrared spectra lack any significant hydroxy bands.
2. In similar alkylation reactions the formation of the enolate anion results from an equilibrium reaction between the carbonyl compound and the base. A competing equilibrium involves the enolate anion and the solvent. Thus, with diethyl malonate (pKa 13) in solvent SolH in the presence of base B^-, we have

$$CH_2(CO_2C_2H_5)_2 + B^- \rightleftharpoons {}^-CH(CO_2C_2H_5)_2 + BH$$

$$^-CH(CO_2C_2H_5)_2 + SolH \rightleftharpoons CH_2(CO_2C_2H_5)_2 + Sol^-$$

to ensure the adequate concentration of the enolate anion at equilibrium clearly both the solvent and the conjugate acid of the base must be much weaker acids than the active methylene compound. The correct choice of base and solvent is thus of great importance if the subsequent alkylation is to be successful. Reactions must normally be affected under anhydrous conditions since water is a much stronger acid than the usual activated methylene compounds and, if present, will instantly protonate any carbanion produced.[35] Based on this and since our alkylation reaction was conducted in aqueous ethanol (in 1:1 ratio, *ca.* 50 ml), it can be concluded that the active methylene in the homophthalimide structure must be of higher acidity (pKa < 14) than water/ethanol.[35] Such improved acidity is probably due to the combined consequence of the electron withdrawing effect of the imide, stabilisation by charge distribution on the carbonyl and aromatisation of the imide ring.

3. The alkylation takes place on the α-carbon rather than the carbonyl oxygen since alkylhalides are soft electrophiles and prefer to form bonds with the softer α-carbon than the harder ionised oxide ion.[36]

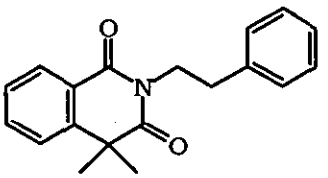
Dimethylation of Homophthalimides at the 4-Position.

Table 3.1 shows the optimised reaction conditions and yields of the 4,4-dimethylation reaction for the different homophthalimides discussed in chapter 2, using methyliodide as the alkylating agent and sodium hydroxide (2 equivalents) for deprotonation.

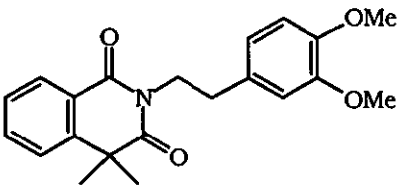
Table 3.1

Starting material.	Methyl iodide (equivalents)	Reaction time. (hours)	Yields. (%)	Products.
2.1	4	3	72	**3.3**
2.2	3	3	92	**3.1**
2.3	3	3	91	**3.2**
2.4	3	3	95	**3.4**
2.5	5	2	80	**3.5**
2.6	5*	20 minutes	93	**3.6**
2.7	4*	3	74	**3.7**
2.8	5**	3	71	**3.8**

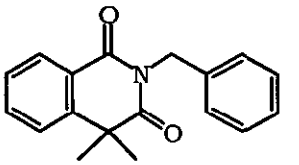
* in absolute ethanol, ** in methanol



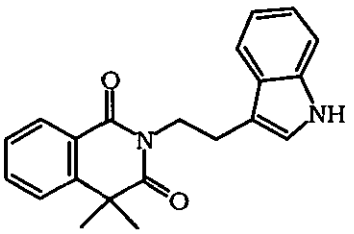
3.1



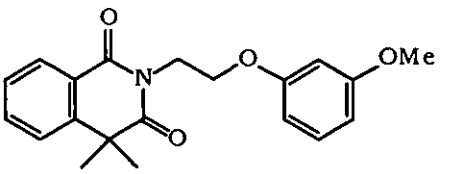
3.2



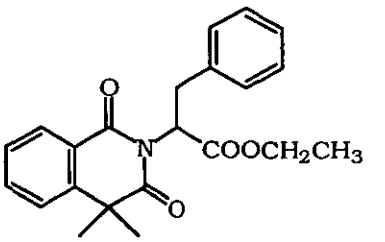
3.3



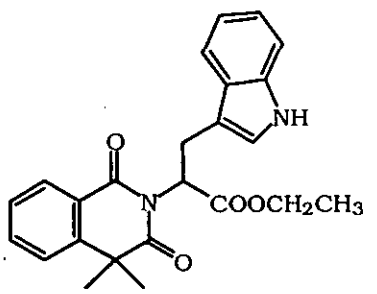
3.4



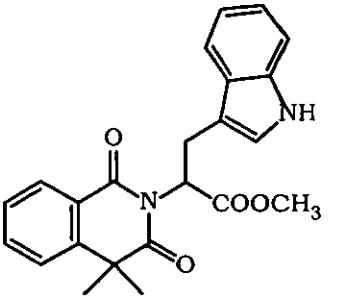
3.5



3.6



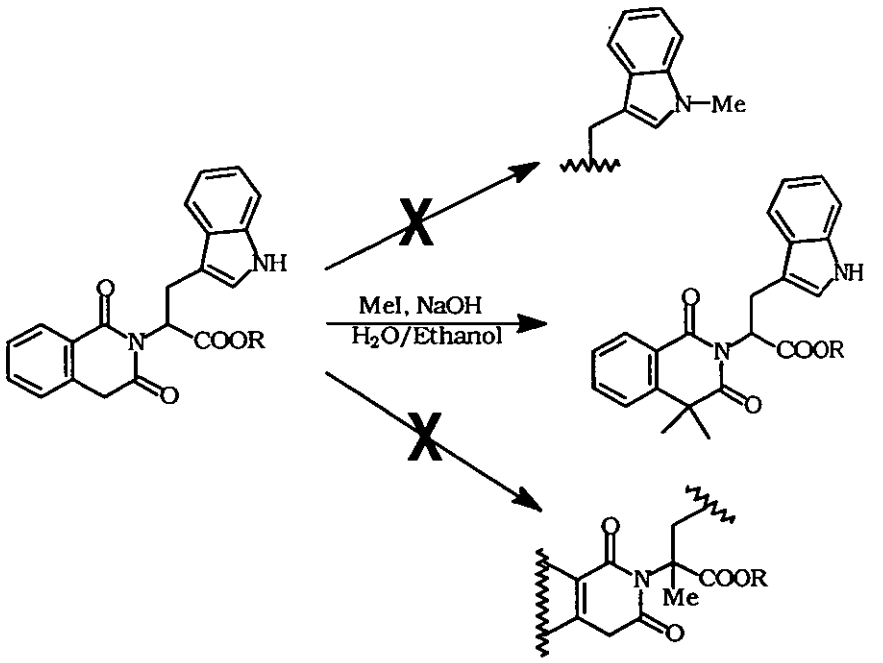
3.7



3.8

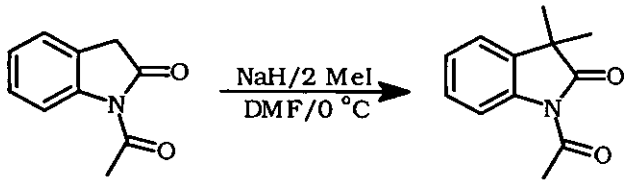
From **Table 3.1** one can note the following points.

1. Absolute ethanol was used as reaction solvent for the methylation of the phenylalanine and tryptophan homophthalimides (**2.6**, **2.7**), while methanol was the reaction solvent in case of **2.8**, as we found that incorporating water in these reactions led to reduced isolated yields, probably due to the hydrolysis of the ester functions. When ethanol was used to generate **3.8** from **2.8**, an inseparable mixture of **3.8** and **3.7** was isolated due to ester-alcohol exchange. In this regard it is worth mentioning that Harriman *et al.*[26] reported that no alkylation of similar homophthalimides took place using sodium ethoxide in absolute ethanol. This finding should be questioned in view of the results reported here.
2. The isolated yields are generally very good (70-95%). There is a correlation between the yield and the reaction scale in each reaction; the larger the scale is associated with a lower yield. However, ^{1}H nmr spectra of the crude products show the exclusive presence of the expected product in each case. Also the alkylation reaction seems to be rapid as 20 minutes reflux was enough to generate **3.6** in 93%.
3. The homophthalimides derived from α-amino acids, namely **2.6**, **2.7** and **2.8**, were methylated without interference from the C-H positioned α- to the ester carbonyl, as illustrated in **Scheme 3.7**. This is as expected because the reaction conditions were not basic enough (due to water presence) to deprotonate the α-carbon (pKa ~ 24).[35]
4. The methylation proceeded without touching the indole nitrogen, despite the relatively acidic indole N-H (pKa 16.2) [37] which clearly indicates the greater acidity of the active methylene hydrogen atoms, within the homophthalimide ring system, over the indolic N-H. **Scheme 3.7**.



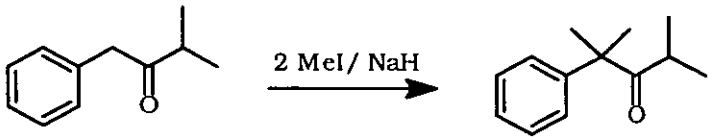
Scheme 3.7

Similar regioselective alkylation reactions were reported before, for example Robertson *et al.*[38] reported the methylation of 1-acetyl-1,3-dihydroindol-2-one, using sodium hydride in DMF, as illustrated in **Scheme 3.8**.



Scheme 3.8

Another example is the reaction described by Semmelhack *et al.*[39] where they prepared 2,4-dimethyl-2-phenylpentan-3-one *via* methylating 3-methyl-1-phenylbutan-2-one, using sodium hydride and methyl iodide. **Scheme 3.9**.



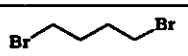
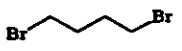
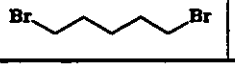
Scheme 3.9

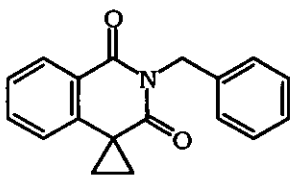
Preparation of 4-Spirocyclic and other 4,4-Dialkylated Homophthalimides.

During the course of this research some 4-spirocyclic-homophthalimides were prepared using a similar procedure to that used for the preparation of 4,4-dimethyl derivatives as shown in **Scheme 3.1**.

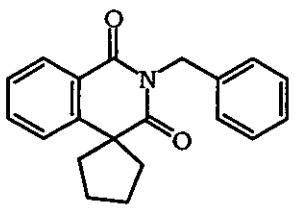
However, only one equivalent (approximately) of the dihaloalkane chain was used in each reaction. **Table 3.2** summarises the products, the reaction conditions and yields for the homophthalimide spiroalkylation reaction.

Table 3.2

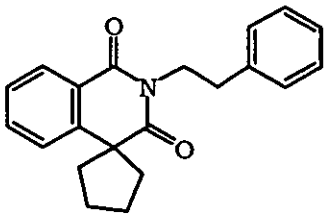
Starting material.	Alkylating agent.	NaOH (equivalents)	Reflux time. (hours)	Yields. (%)	Products.
2.1		2	45 minutes	15	**3.9**
2.1		2	2	73	**3.10**
2.2		10	2	12	**3.11**
2.1		2	3	42	**3.12**



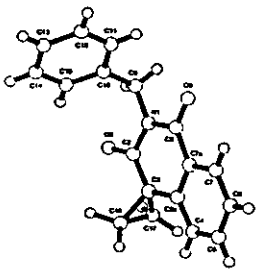
3.9



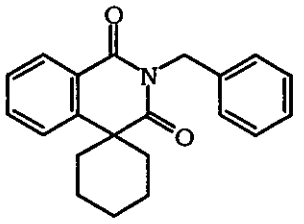
3.10



3.11



X-ray picture of 3.9



3.12

From the results illustrated in **Table 3.2** the following can be noted:

1. The highest isolated yield, under relatively similar reaction conditions, was for the cyclopentane spirocyclic derivative **3.10**, then the cyclohexane **3.12** and the lowest was for the cyclopropane **3.9**, which is not too surprising as the ring formation is expected to be optimum for the 5-membered ring, while the 6-

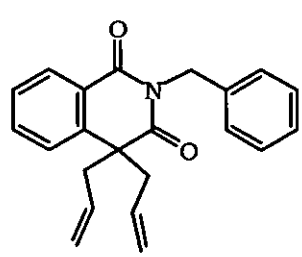
memebered ring precursor will have an additional C-C bond available for rotation, which increases the entropy in the system prior to cyclisation, while the 3-memebered ring is presumably too sterically strained for efficient cyclisation.[40]

In order to improve the yield for **3.9**, we used a similar procedure to that of Horning *et al.*[27] Using 2 equivalents potassium carbonate and 5 equivalents of 1,2-dibromoethane, the homophthalimide **2.1** gave **3.9** in 92%. This result should be compared with the reaction reported by Horning *et al.*[27] who used 1-bromo-2-chloroethane and obtained a similar product (2-phenyl-4-homophthalimide-spirocyclpropane) in 57% yield, as previously illustrated in **Scheme 3.2.**

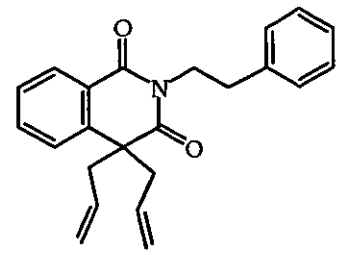
2. By comparing the reactions generating **3.10** and **3.11**, the difference in yields is very clear and is probably due to the large excess of sodium hydroxide used in the second reaction, which was only carried out once. The excess of sodium hydroxide probably leads to the dehydrobromination of 1,4-dibromobutane, which removes the alkylating agent (**Scheme 3.6**).

Reactions of 1,3-dibromopropane with homophthalimides in aqueous alcoholic sodium hydroxide.

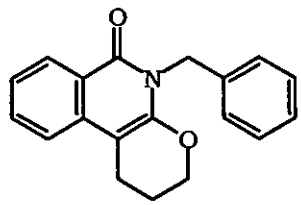
When the homophthalimides **2.1** and **2.2** were heated under reflux with 1,3-dibromopropane in aqueous ethanolic sodium hydroxide (2 equivalents), they gave the 4,4-diallylhomophthalimides **3.13** and **3.14** and the pyrano-isoquinolinones **3.15** and **3.16** without any spirocyclobutane derivatives. The mechanism behind the formation of these compounds is illustrated in **Scheme 3.10**. The absence of the cyclobutane derivatives is not surprising. It is sterically difficult for the HOMO of the enolate C=C bond to attack the LUMO of C-Br bond either because, (a) the HOMO and LUMO orbitals are too far from each other to have any efficient overlap, as in the conformations **B** and **C** in **Figure 3.1** or, (b) the two interacting orbitals are not in the same plain (nearly perpendicular on each other) as in the conformations **A** and **D** in **Figure 3.1**. On the other hand the enolate oxygen has a lone electron pair in the right plain, although not in the precise angle, for effective overlap with C-Br LUMO orbital. As illustrated in conformations **A** and **D** in **Figure 3.10**.



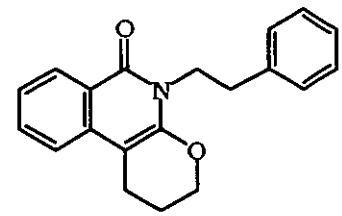
3.13



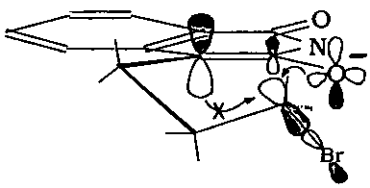
3.14



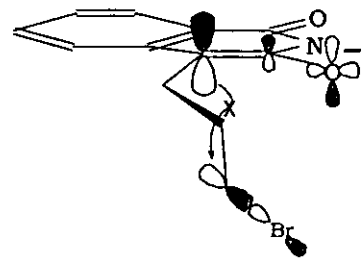
3.15



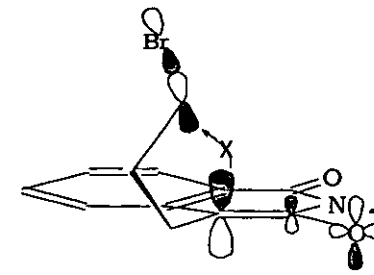
3.16



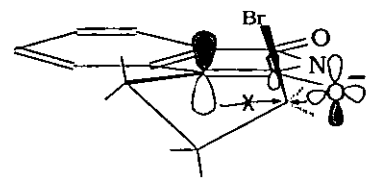
A



B

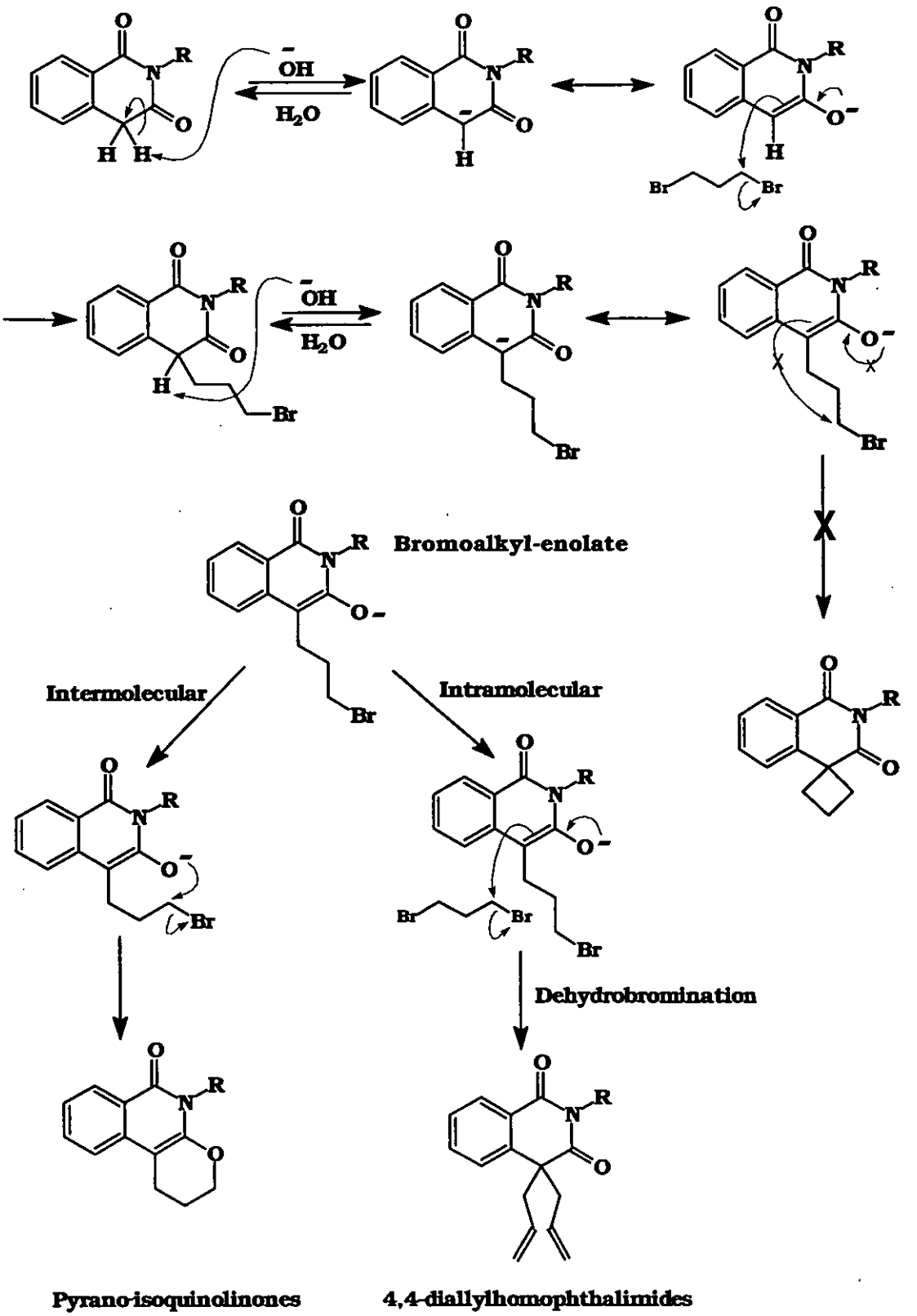


C



D

Figure 3.1 - Different possible conformations for the bromoalkyl-enolate intermediate.


OH
H2O
Bromoalkyl-enolate
Intermolecular
Intramolecular
Dehydrobromination
Pyrano-isoquinolinones
4,4-diallylhomophthalimides

Scheme 3.10

The yields of 4,4-diallylhomophthalimides and pyranoisoquinolinones were found to be dependent on the amount of sodium hydroxide used, as shown in **Table 3.3**. This behaviour can be explained by the fact that excess sodium hydroxide leads to the dehydrobromination of the bromoalkyl-enolate intermediate (**Scheme 3.10**), subsequently removing the alkylating potential of the bromoalkyl side chain.

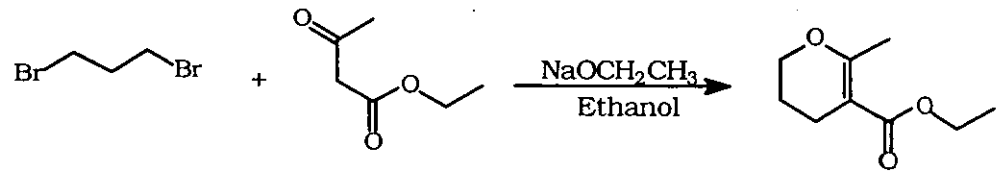
Table 3.3

			Products	
Starting material.	**NaOH (equivalents)**	**Reflux Time.**	**PI (yield)**	**DH (yield)**
2.1	2	90 minutes	**3.15** (26%)	**3.13** (13%)
2.2	10	15 hours	**3.16** (18 %)	**3.14** (22%)

PI: pyrano-isoquinolinones.

DH: 4,4-diallylhomophthalimides.

Synthesis of 5,6-dihydropyrane derivatives *via* alkylation with 1,3-dibromopropane was reported in the literature, for example Anderson *et al.*[41] prepared 2-methyl-3-carbethoxy-5,6-dihydropyran in 65% by heating a mixture of 1,3-dibromopropane, ethyl acetoacetate (2 equivalents) and sodium ethoxide (2 equivalents) in ethanol over 22 hours, as illustrated in **Scheme 3.11**.



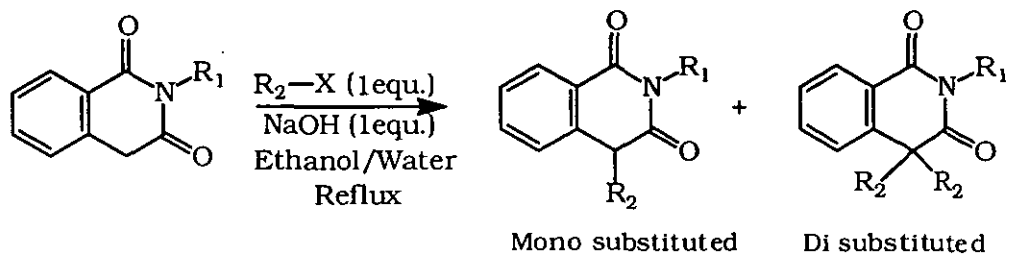
Scheme 3.11

Chan *et al.*[42] and Zefirov *et al.*[43] conducted the same cycloalkylation reaction, shown in **Scheme 3.11**, using potassium carbonate either in acetone (38% yield), or dimethylsulfoxide (76% yield), respectively. According to our best knowledge, we were the first to report the pyranoisoquinolinone system (**3.15** and **3.16**).

In the course of this research, we required 2-benzyl-4,4-diallylhomophthalimide **3.13** as starting material for multiple experiments to study *N*-acyliminium intermediates, for this goal we prepared **3.13** in 91% yield by refluxing 2-benzylhomophthalimide with allylbromide (2 equivalents) in aqueous alcoholic sodium hydroxide (2 equivalents) (**Scheme 3.1**). Harriman *et al.*[26] reported the synthesis of 4,4-diallylhomophthalimide in 38% yield by refluxing homophthalimide with allyl chloride in aqueous alcoholic sodium hydroxide. The yield difference is probably due to the fact that bromide is a better leaving group than chloride.

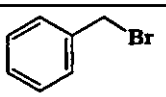
Reactions of 2-Substituted Homophthalimides with 1 equivalent Alkyl or Arylalkyl Halides and 1 equivalent Sodium Hydroxide.

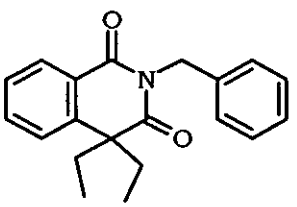
During the course of this research we required 4-monosubstituted homophthalimides for oxidation studies (chapter 6) and for preparing homophthalimides substituted with two different groups at the 4-position.
In this direction we attempted direct alkylation with the particular alkylhalide (1 equivalent) in aqueous ethanolic sodium hydroxide (1 equivalent), as shown in **Scheme 3.12**. In this regard, it is worth mentioning that Howarth *et al.*[13] reported that all their attempts to obtain 4-monomethyl homophthalimide derivatives were unsuccessful. This finding should be questioned in view of the results reported here. **Table 3.4** summarises the reaction conditions and yields of the generated 4-mono and 4,4-disubstituted homophthalimides.



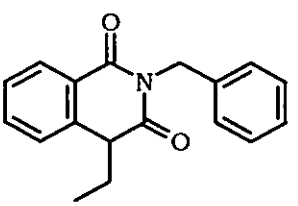
Scheme 3.12

Table 3.4.

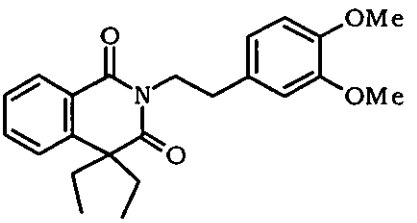
Starting material	Alkylating agent.	Reaction time (hours)	Products	
			Di- (Yield)	Mono- (Yield)
2.1		6	**3.17** (12 %)	**3.18** (26 %)
2.3		3.5	**3.19** (9 %)	**3.20** (29 %)
2.1		3	**3.21** (17 %)	**3.22** (42 %)
2.1		4	-----	**3.23** (42 %)
2.4		3	-----	**3.24** (44 %)



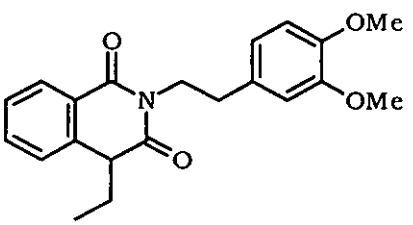
3.17



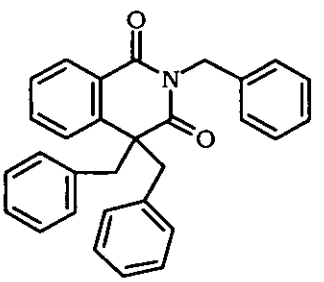
3.18



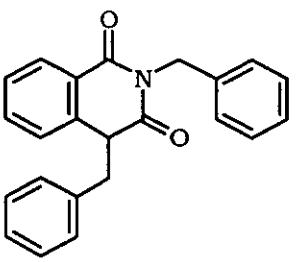
3.19



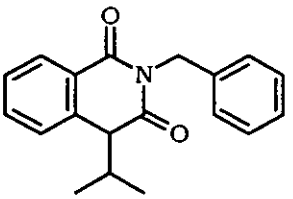
3.20



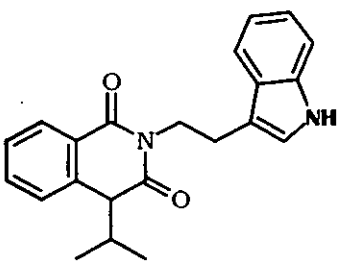
3.21



3.22



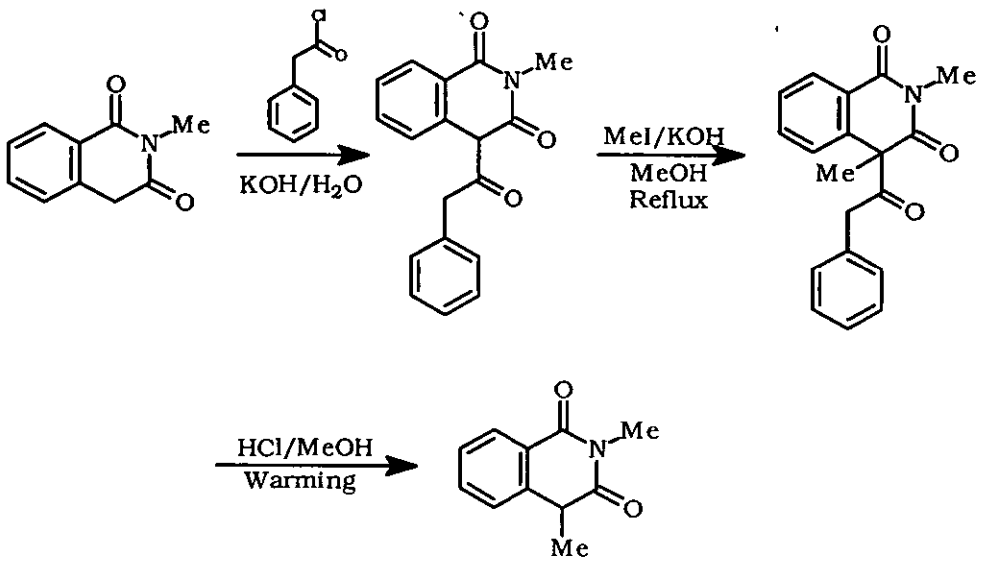
3.23



3.24

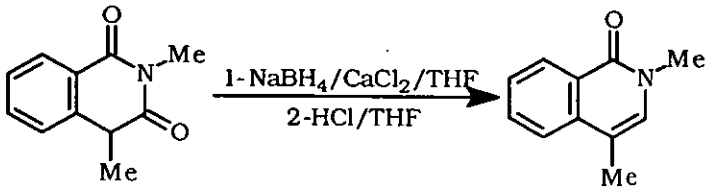
From **Table 3.4** one can notice the following:

1. Compared to other alkylations, ethylation resulted in relatively lower yields, this is probably due to the higher volatility of ethyliodide (bp 71 °C) compared to other alkylating agents (benzyl bromide, bp 199 °C; isopropyl iodide, bp 89 °C).
2. Isopropylation proceeded with the sole formation of 4-monosubstituted derivatives, this behaviour was previously reported by Harriman *et al.*,[26] which is not surprising, as it is expected that the bulky isopropyl group will hinder further alkylation. 4-Monosubstituted homophthalimides were targeted before. For example, Haworth[44] prepared 2,4-dimethylhomophthalimide through conversion to the 4-phenylacetyl derivative followed by methylation with methyliodide then removal of the phenylacetyl group by hydrolysis with methanolic hydrogen chloride as shown in **Scheme 3.13**.



Scheme 3.13

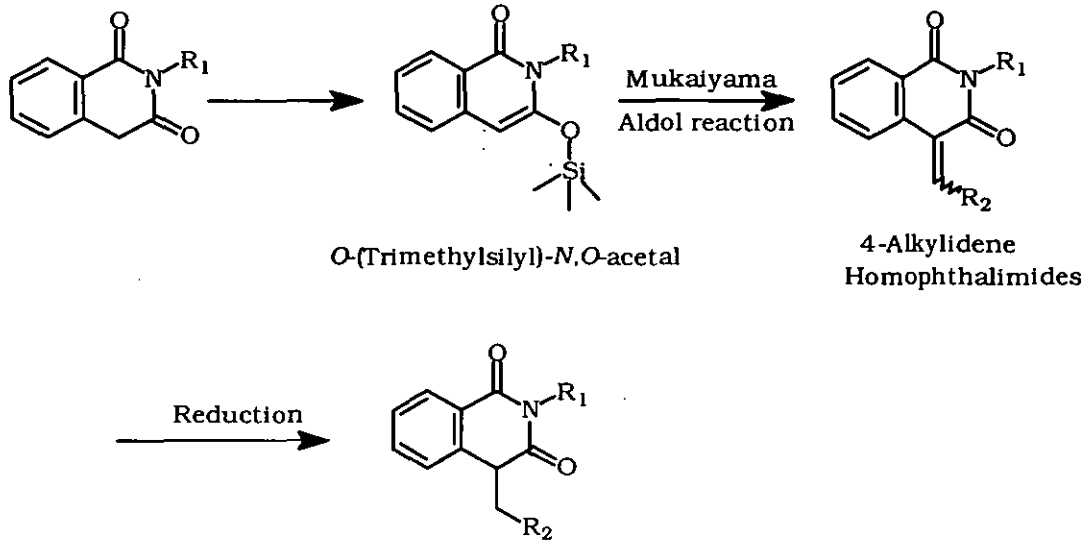
In the above scheme, the author reported 60% yield in the first step, and quantitative yield in the hydrolysis step. However, he did not mention the yield in the methylation step. Helmut *et al.*[45] prepared 2,4-dimethyl-2*H*-isoquinolin-1-one in 64% *via* sodium borohydride reduction of 2,4-dimethylhomophthalimide as in **Scheme 3.14**.



Scheme 3.14

Preparation of the 4-Monoalkylated Homophthalimides *via* the Reduction of 4-Alkylidene or Arylalkylidene Homophthalimides.

We investigated an alternative approach for the preparation of 4-mono substituted homophthalimides. It includes converting the starting materials to *O*-(trimethylsilyl)keten-*O,N*-acetals which are then converted to 4-alkylidene homophthalimides *via* Mukaiyama directed aldol reactions.[46] The resulting products were converted to 4-monoalkylhomophthalimides *via* reduction with sodium borohydride as illustrated in **Scheme 3.15**.



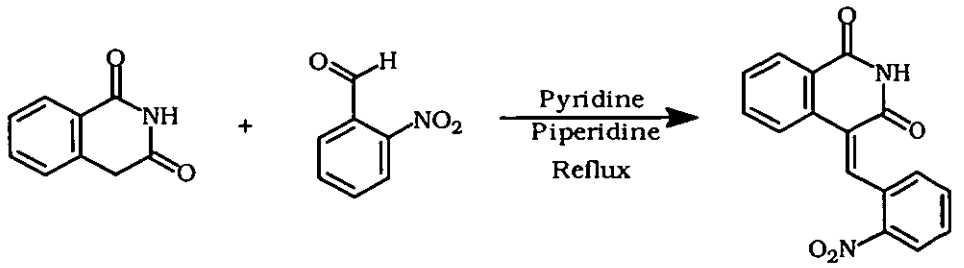
Scheme 3.15

The above scheme can be divided into the following steps:

<u>Step 1:</u> formation of the enolate equivalents, *O*-(trimethylsilyl)keten-*O,N*-acetals, and the following directed aldol condensation reactions.

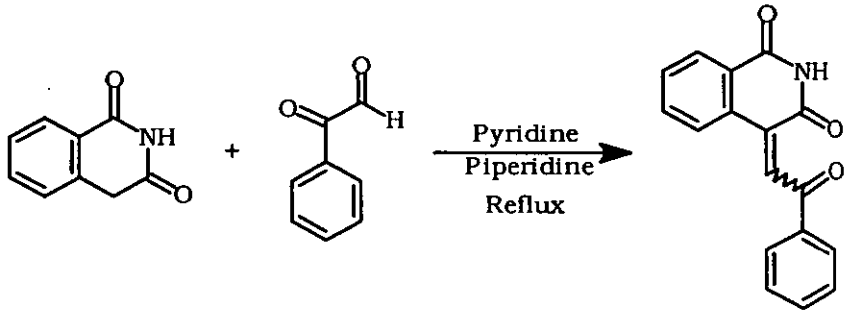
Typical aldol condensation reactions have been utilised before for preparing 4-alkylidene homophthalimides, via base catalysed condensation of a particular aldehyde with a particular homophthalimide, for example, Howarth *et al.*[13] reported that 2-phenethylhomophthalimide, when dissolved in sodium ethoxide / ethanol solution, condensed with aldehydes. However, they did not mention the particular aldehydes, and did not provide any experimental data or yields.

Later, Howarth *et al.*[47] prepared 4-(*o*-nitrobenzylidene)homophthalimide in 88% yield, by reacting homophthalimide with *o*-nitrobenzaldehyde in pyridine solution and in the presence of a trace of piperidine as in **Scheme 3.16**.



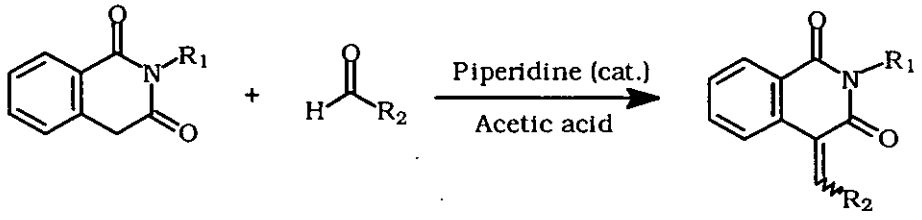
Scheme 3.16

Bailey *et al.*[48] reported that the treatment of 2-methylhomophthalimide with phenylglyoxal in the presence of pyridine as catalyst gave an excellent yield of 2-methyl-4-phenacylidenehomophthalimide as illustrated in **Scheme 3.17**.



Scheme 3.17

Elliott *et al.*[49] prepared different 4-arylidenehomophthalimides by refluxing homophthalimide or its 2-methyl derivative, and different aromatic aldehydes with piperidine as a catalyst as in **Scheme 3.18**.



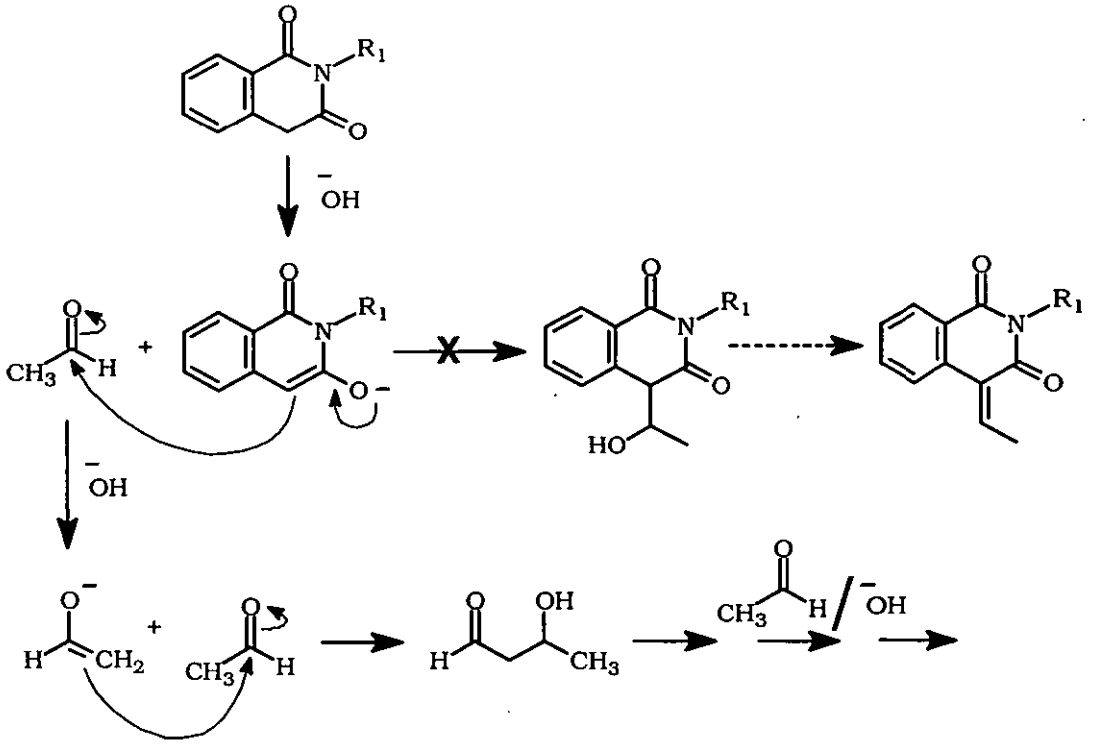
Yields = 75-92 %

R_1= H, Methyl.

R_2= Phenyl, 3,4-$(CH_3O)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 2-Furyl.

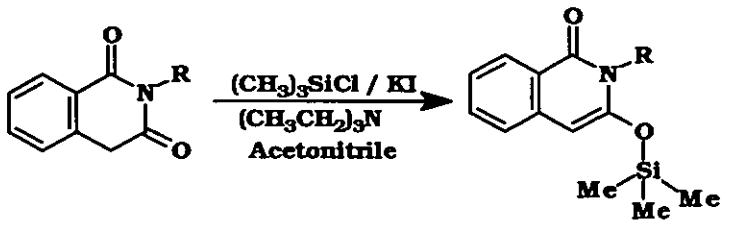
Scheme 3.18

Our attempts to generate 4-ethylidenehomopthalimides, from 2-substituted homophthalimides and acetaldehyde, using typical aldol condensation conditions were fruitless, probably due to acetaldehyde self-condensation. The crude product showed streaks on TLC plates and was impossible to separate. The proposed self-condensation reaction is illustrated in **Scheme 3.19**.

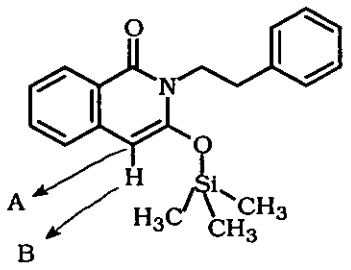


Scheme 3.19

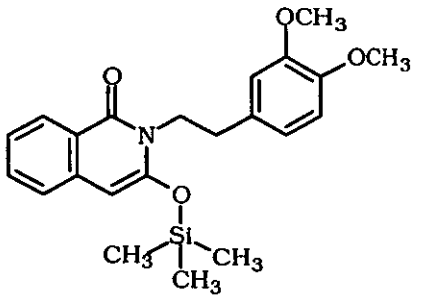
According to our best knowledge, all the previously reported aldol reactions generating 4-alkylidene or 4-arylalkylidene homophthalimides, in alkaline media, were conducted with aldehydes lacking active α-methylene hydrogen atoms (**Schemes 3.16, 3.17, 3.18**), which further supports the acetaldehyde self-condensation theory. To overcome this problem, we switched to directed aldol reactions.[46] The enolate equivalents *O*-(trimethylsilyl)keten-*O,N*-acetals **3.25** and **3.26** were prepared in 89% and 64% yield, respectively, by treating the acetonitrile solutions of the starting homophthalimides with trimethylsilyl iodide in the presence of triethylamine and at room temperature. Trimethylsilyl iodide was generated *in situ* from trimethylsilyl chloride and potassium iodide as described by Cazeau *et al.*[50] **Scheme 3.20** illustrates the reaction conditions.



Scheme 3.20



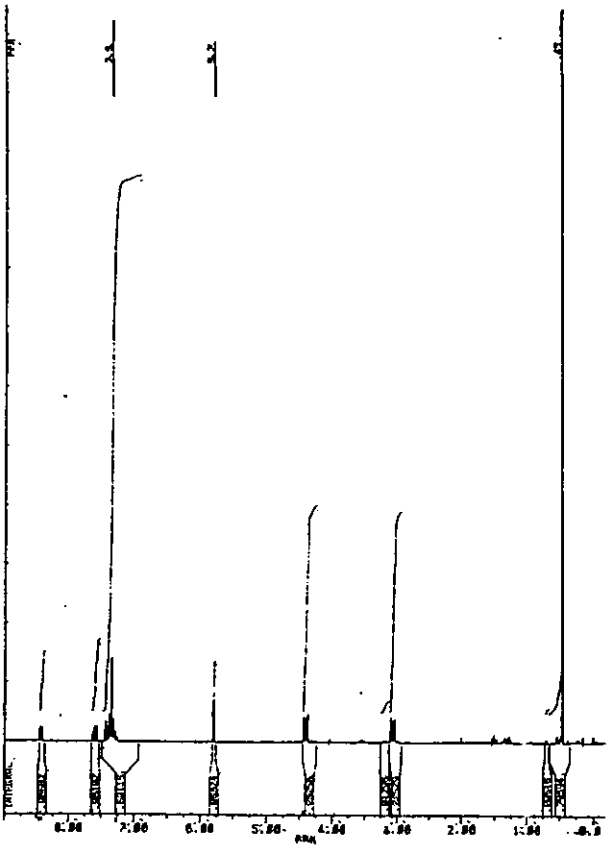
3.25



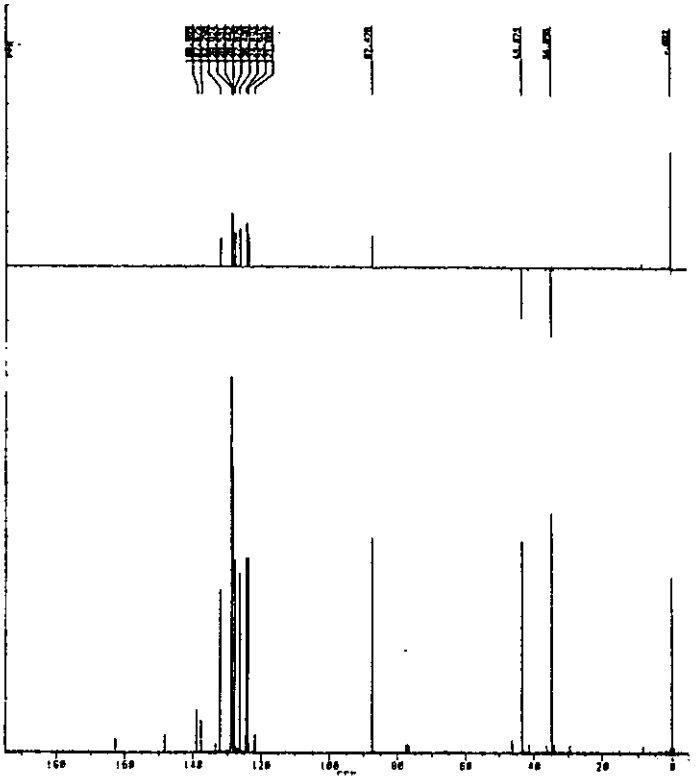
3.26

The following points are to be noticed regarding the above reaction:

1. The generated *O*-(trimethylsilyl)keten-*O,N*-acetals are very moisture-sensitive, as exposure to air moisture for few minutes leads to significant conversion to the starting materials, consequently, the reaction had to be conducted under strictly anhydrous conditions.
2. The key features in the ^{1}H nmr spectra of the products are the singlets at 0.38 and 5.7 ppm, corresponding to the trimethylsilyl protons and the enolate proton (atom B in **3.25**) respectively, as shown in the ^{1}H nmr spectrum for **3.25**.
3. The key feature in the ^{1}H decoupled ^{13}C nmr spectrum of the products are the peaks at 0.0 (3 x CH_3) and 87.5 (CH) ppm, corresponding to trimethylsilyl and the enolate carbon atom (atom A in **3.25**) respectively, as shown in the ^{13}C nmr spectrum for **3.25**.
4. Presumably, the driving forces behind this reaction are (a) the tendency for silicon to form a relatively strong bond with the carbonyl oxygen,[51] (b) aromatisation of the imide ring.

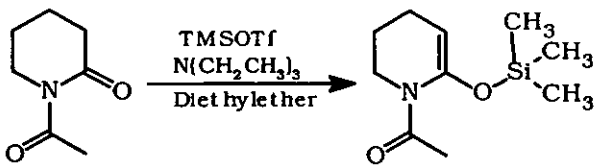


^{1}H nmr spectrum for 3.25



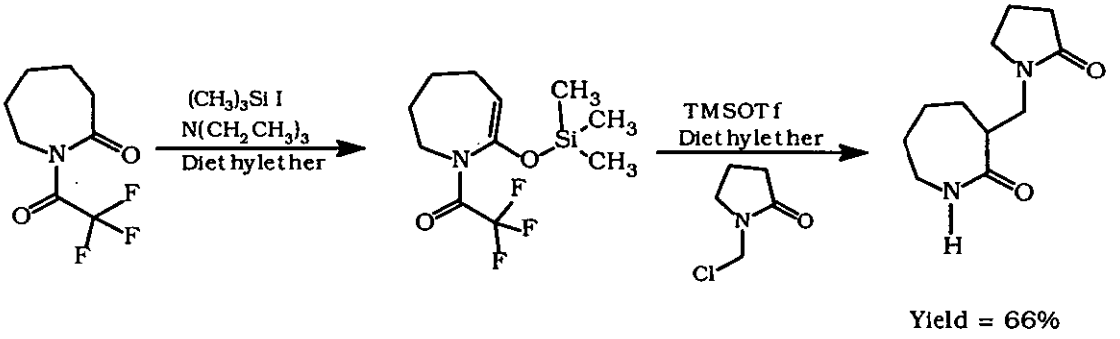
^{13}C nmr chart for 3.25

Similar *O*-(trimethylsilyl)keten-*O,N*-acetals have been targeted before as starting materials in directed aldol reactions or in other alkylation reactions, for example, Frick *et al.*[52] prepared 1-acetyl-1,2,3,4-tetrahydro-6-(trimethylsiloxy)pyridine in 66% by treating the starting material with TMSOTf and triethylamine in diethylether, at ambient temperature, as in **Scheme 3.21**.



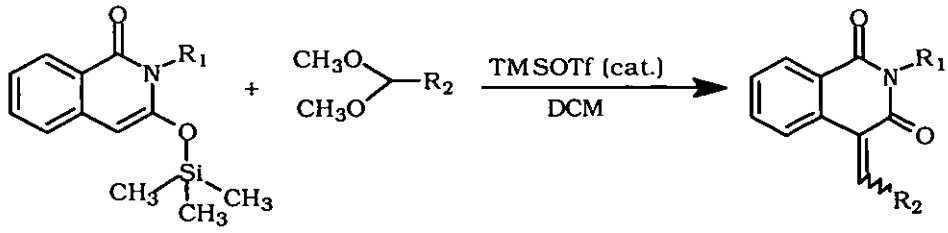
Scheme 3.21

In another example, Kramarova *et al.*[53] prepared 3,5,6,7-tetrahydro-1-(trifluoroacetyl)-2-(trimethylsiloxy)-1H-azepine and its 6-membered ring analogue in 74% and 49%, using trimethylsilyl iodide as silylating agent and at room temperature. They utilised the resulting keten-acetals in a following alkylation reaction as in **Scheme 3.22**.



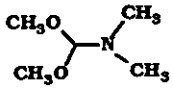
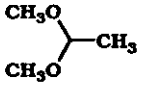
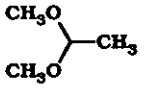
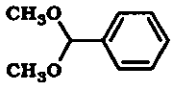
Scheme 3.22

We utilised the enolate equivalents (**3.25** and **3.26**) in the directed aldol reaction to form 4-alkylidenehomophthalimides, which was carried out by injecting catalytic amounts of TMSOTf in a DCM solution of the particular *O*-(trimethylsilyl)keten-*O,N*-acetal and the particular dimethyl acetal as illustrated in **Scheme 3.23**. **Table 3.6** summarises the reaction conditions and yields of the 4-alkylidene products.

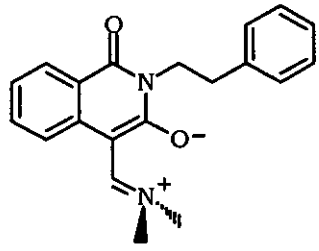


Scheme 3.23

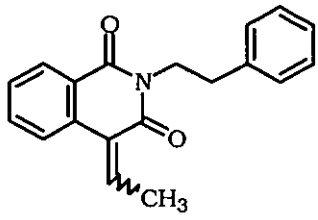
Table 3.6

			Products	
Starting Enolate	**Dimethyl acetal**	**Reaction* time (hours)**	**Product (yield)**	**Ratio *Z:E***
3.25		75 minutes	**3.27** (85%)	-------
3.25		14 - 16	**3.28/3.29** (54%)	56% : 44%
3.26		14 - 16	**3.30/3.31** (26%)	35% : 65%
3.25		14 - 16	**3.32/3.33** (quantitative)	unclear

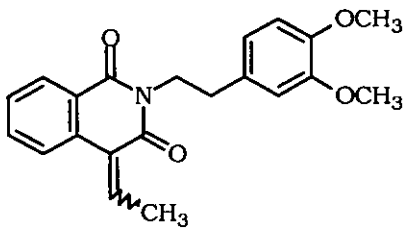
* TMSOTf was injected at -78 °C and after 15 minutes the reaction was warmed to room temperature for the stated period of time.



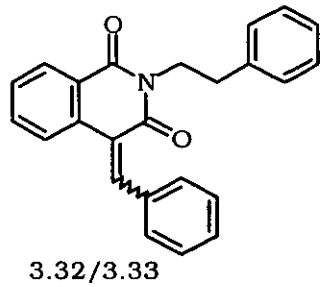
3.27



3.28/3.29



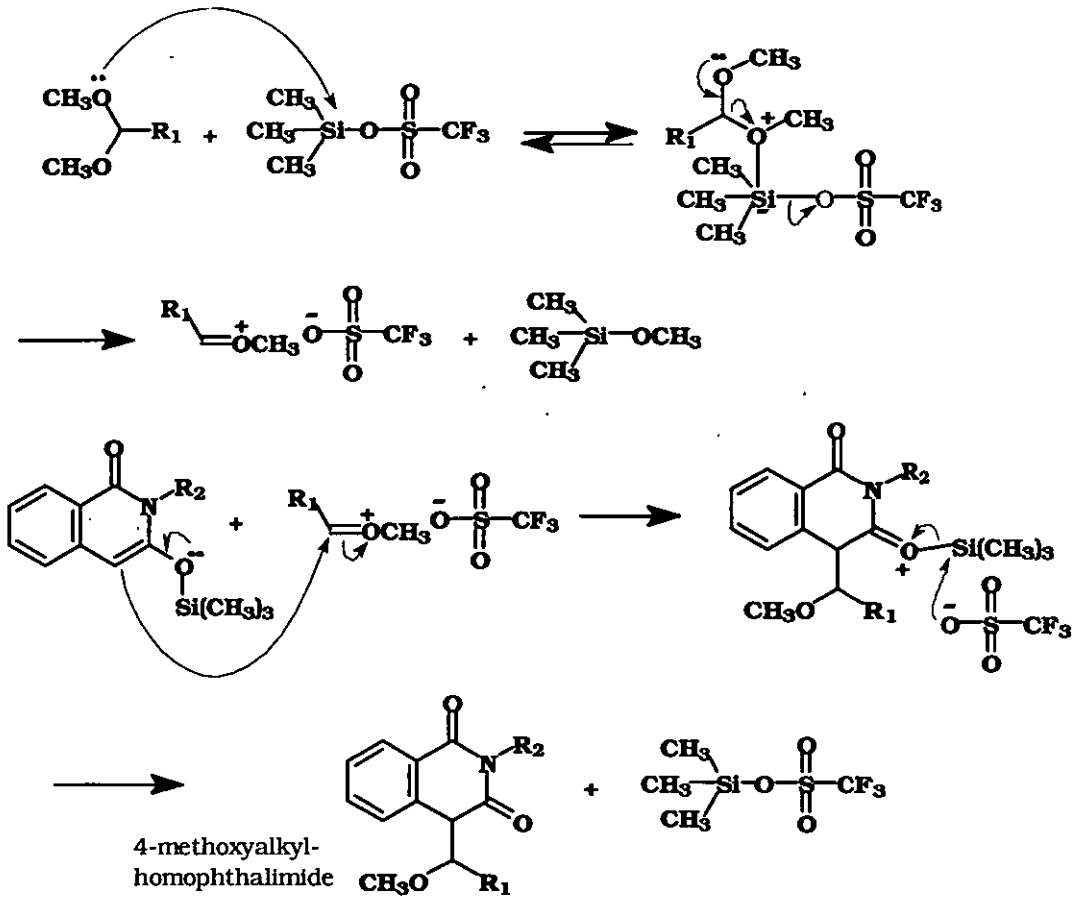
3.30/3.31



3.32/3.33

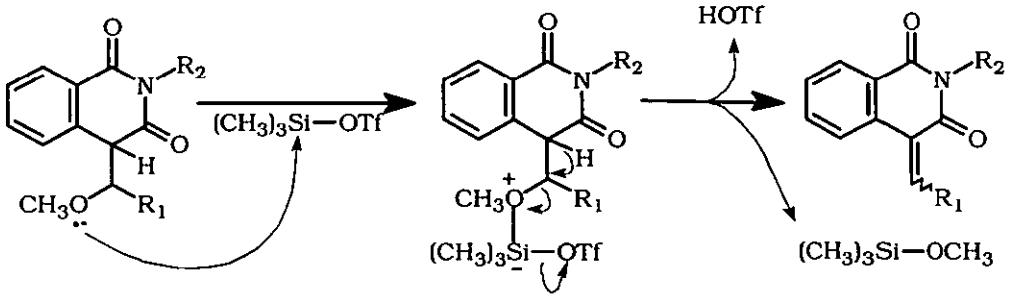
The following are interesting points to be noted regarding this reaction.

1. The reaction is expected to take place through two subsequent steps, the mechanism of the first step, shown in **Scheme 3.24**, is modified from that described by Murata *et al.* in their pioneering work in utilising TMSOTf as a catalyst in directed aldol reactions.[54]



Scheme 3.24.

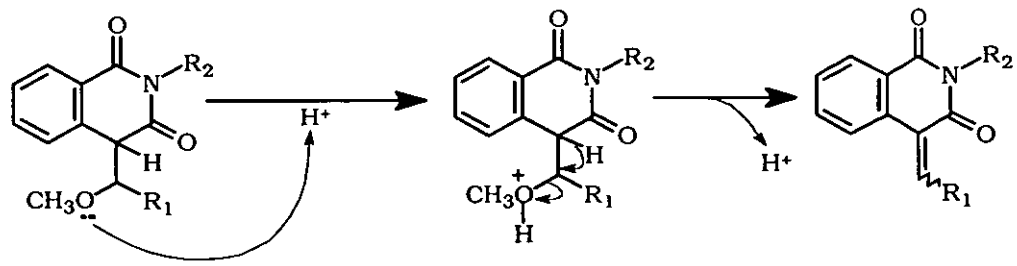
The second step is the β-elimination of methanol and is probably initiated by TMSOTf as in **Scheme 3.25**.



Scheme 3.25

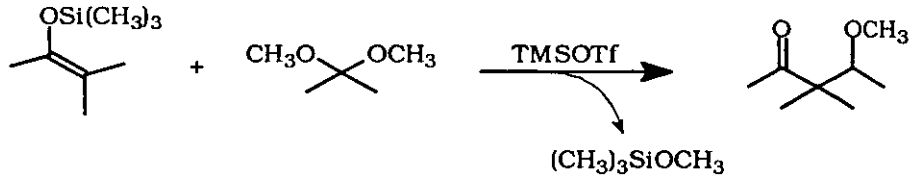
From **Scheme 3.25**, the catalytic amount TMSOTf is expected to be depleted and converted to methoxytrimethylsilane and triflic acid. Consequently, the

reaction is expected to proceed further *via* proton catalysis (triflic acid) as in **Scheme 3.26**.



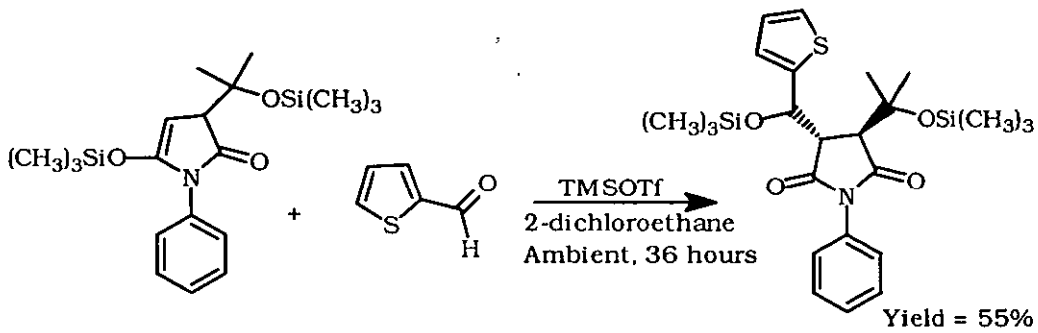
Scheme 3.26

The assumption that the catalytic amount of TMSOTf is not depleted in the first step, i.e. the formation of 4-methoxyalkylhomophthalimide (**Scheme 3.24**) proceeds without significant β-elimination, is based on the findings of Murata *et al.*[54,55] and ElGihani *et al.*[56,57] who showed that the reaction of silylenol ethers and dimethoxyacetals, under low temperatures (-78 °C) and for relatively extended periods of time (14-16 hours), gave excellent yields of the aldol product without β-elimination. **Scheme 3.27**.



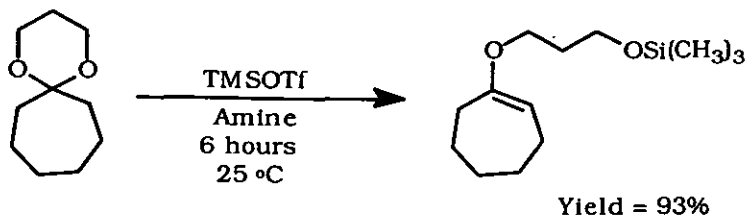
Scheme 3.27

In another example, Zerrer *et al.*[58] reported the use of TMSOTf , under ambient temperature and for 36 hours, to generate stable aldol adducts (without β-elimination) as in **Scheme 3.28**.



Scheme 3.28

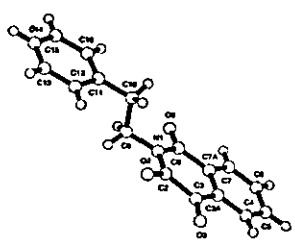
Gassman *et al.*[59] reported the use of TMSOTf (in molar excess) with *N,N*-diisopropylethylamine in the preparation of enol ethers from dimethoxy- and dialkoxy acetals, for example the reaction illustrated in **Scheme 3.29**.

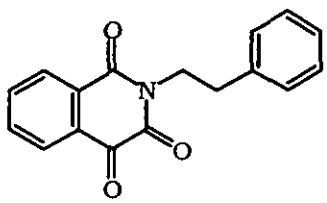


Scheme 3.29

This example supports the assumption that TMSOTf is depleted during the β-elimination step and further demethoxylation is catalysed by the generated triflic acid as in **Scheme 3.26**.

2. The second point, concerning this reaction, is the yield variation between different 4-alkylidene products. The quantitative yield of the 4-benzylidene derivatives **3.32/3.32** can be attributed to the additional conjugation from the phenyl ring, which increases the stability of the product and presumably improves the yield. The relatively low yield of **3.30/3.31** (26%) compared to **3.28/3.29** (54%) is probably due to the aromatic methoxy groups in **3.30/3.31**, which presumably reduce the efficiency of TMSOTf catalysis, by competing with the acetal methoxy groups for coordination with the trimethylsilyl moiety.
3. When a pure sample of 4-benzylidenehomophthalimide derivative **3.32/3.33** was stored for 3 months under ambient conditions, it was partially oxidised (30%) to the tricarbonyl compound **3.34**.



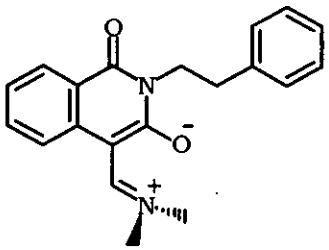


3.34

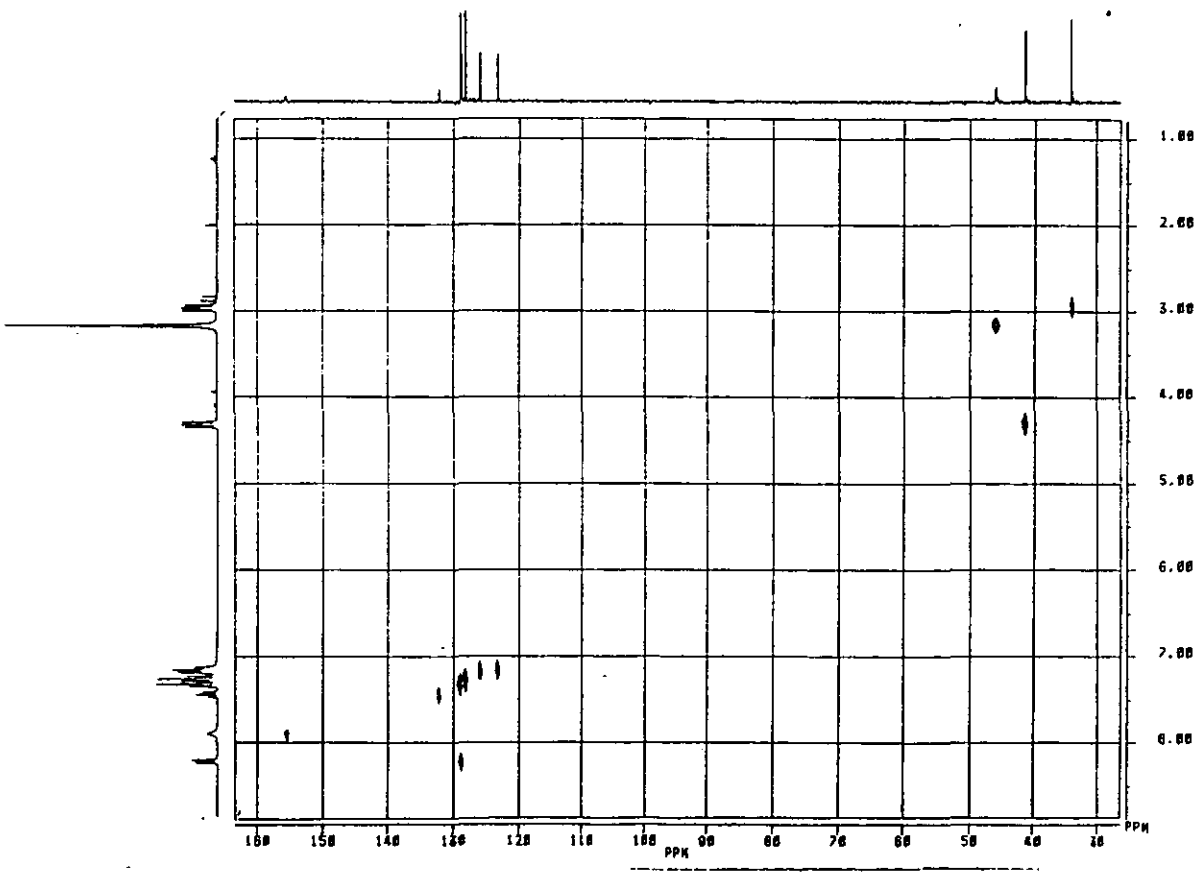
X-ray picture for 3.34

4. Finally, concerning the structure of betaine **3.27**. By inspecting the nmr data one can realise that the following evidence supports the proposed structure. (a) The ^{1}H nmr spectra of both the crude and the pure products show a single isomer, i.e. absence of *Z* and *E* forms in contrast to the other 4-alkylidene derivatives mentioned earlier. (b) In the ^{1}H nmr spectrum at 25 °C the *N,N*-dimethyl protons appear as a broad singlet at 3.2 ppm, which sharpens at 50 °C. Such a chemical shift corresponds to methyl protons bonded to a positively

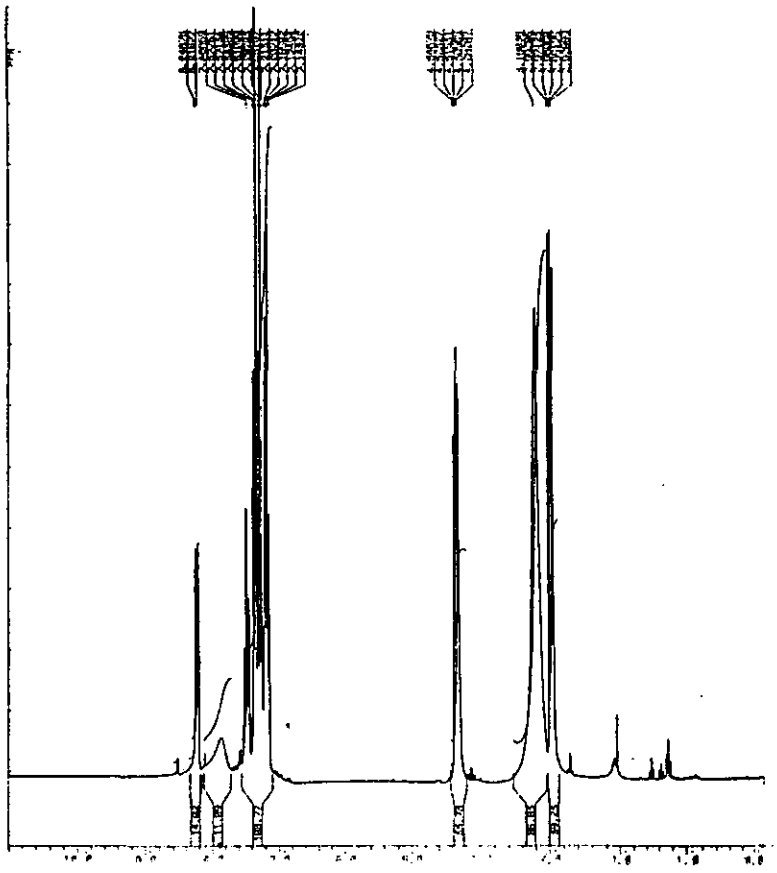
nitrogen (CH_3-N^+).[60] (c) In the ^{13}C nmr spectrum, both at 25 °C and 50 °C, only one carbonyl peak is evident (at 165.4 ppm), despite the fact that accurate molecular ion measurement clearly indicates the presence of two oxygen atoms. (d) At 25 °C the *N*,*N*-dimethyl carbons appear in the ^{13}C nmr spectrum as a broad and short peak at around 45 ppm. However, at 50 °C the peak becomes sharper and more clearly defined in the DEPT spectrum. The peak sharpening at higher temperature indicates improved rotation around a particular single bond within the structure.[61]



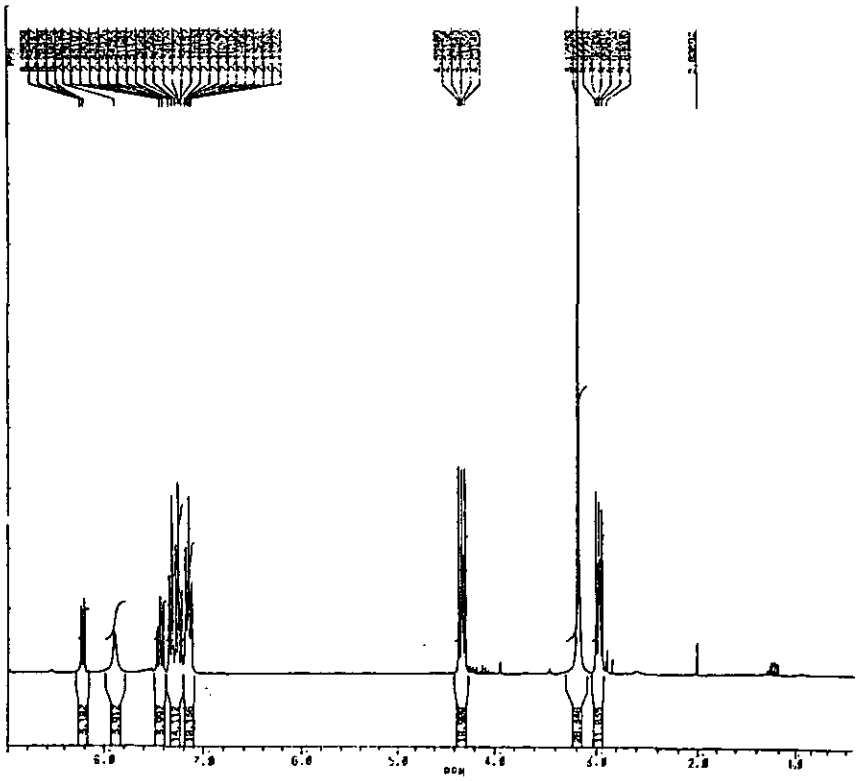
3.27



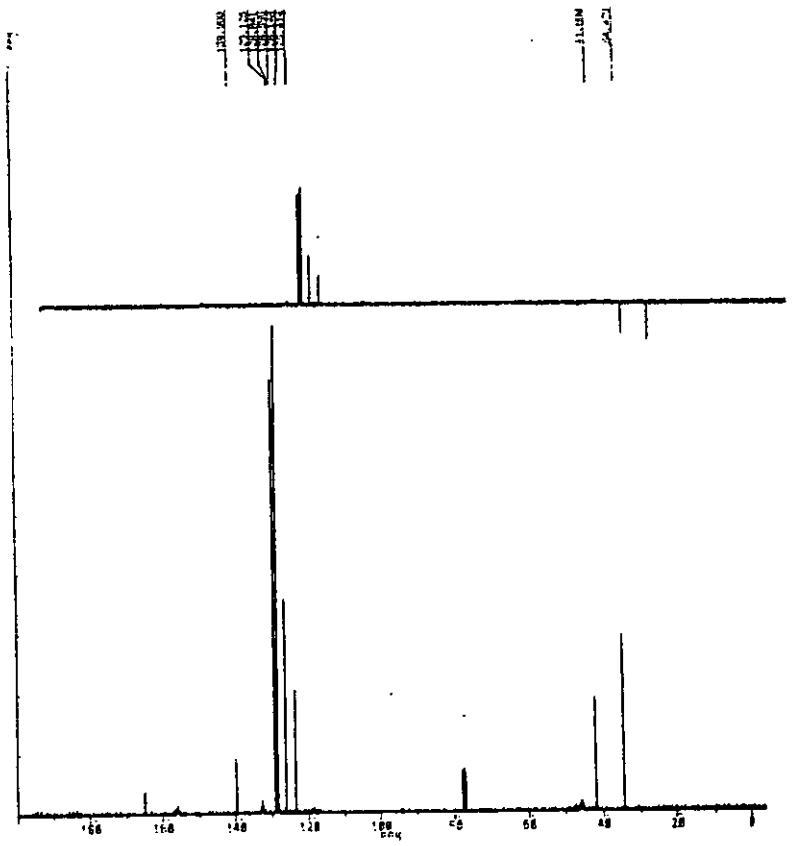
HETCOR experiment at 50 °C to characterise 3.27.



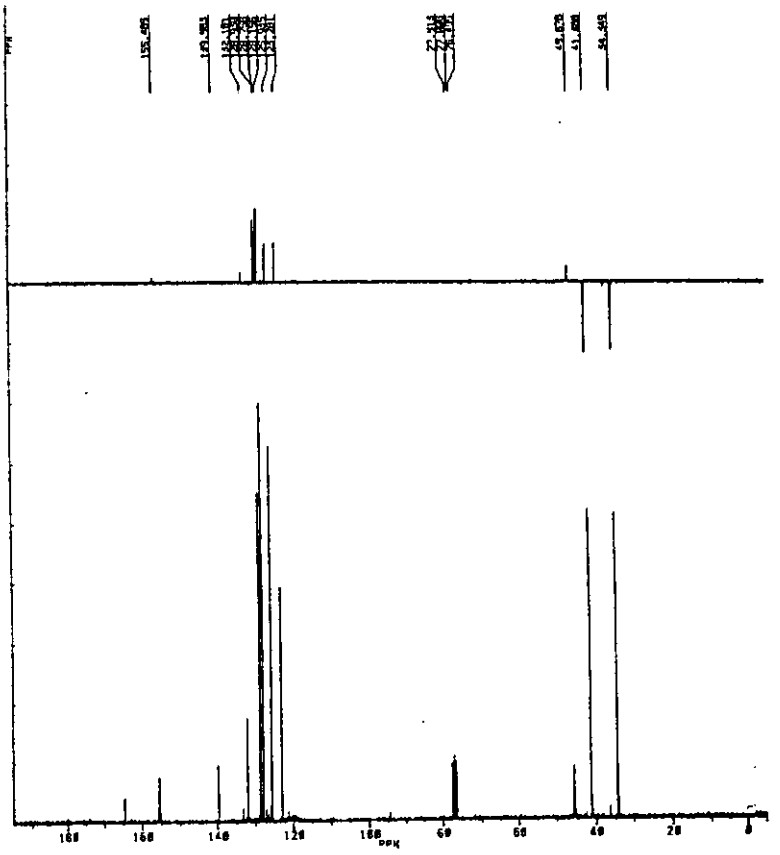
^{1}H nmr spectrum for 3.27 at 25 ^{o}C



^{1}H nmr spectrum for 3.27 at 50 ^{o}C.

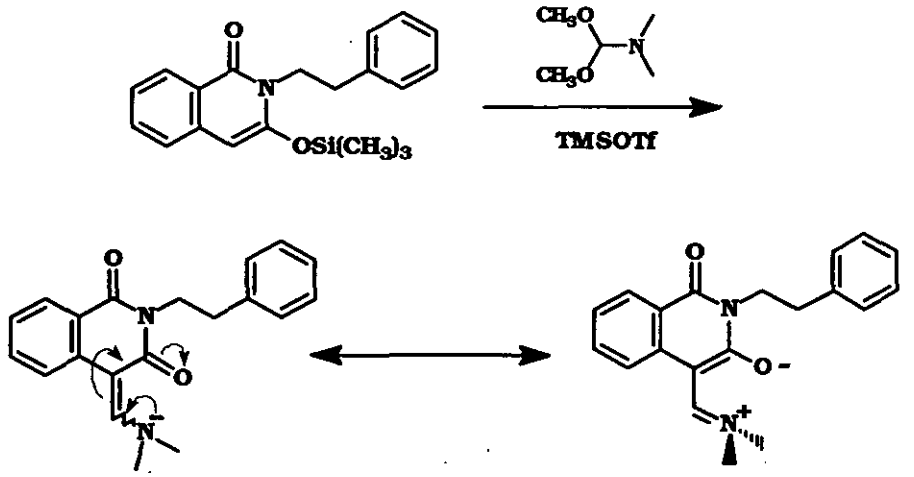


^{13}C nmr spectrum for 3.27 at 25 ^{o}C



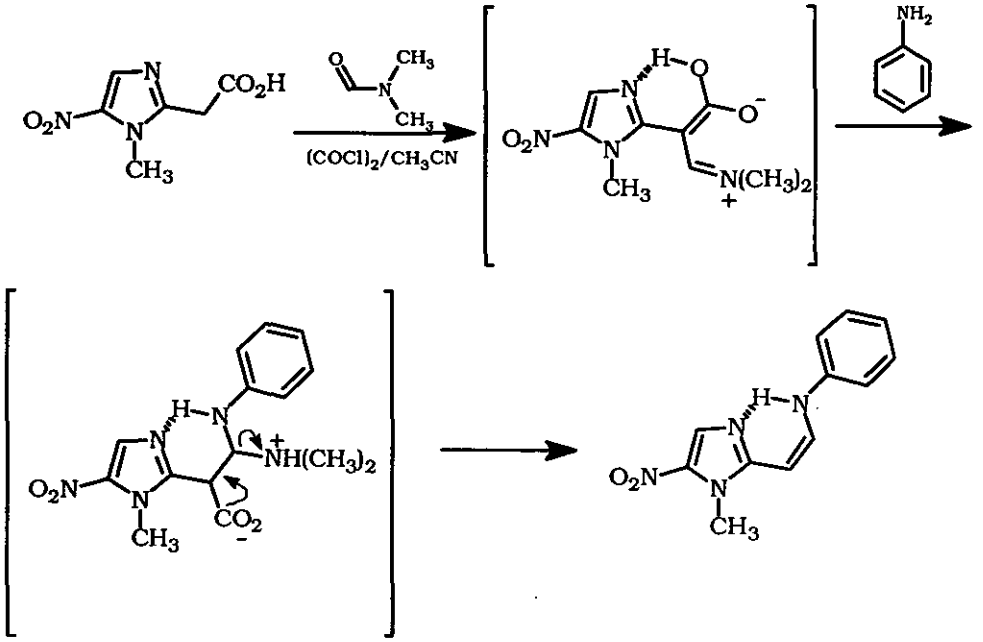
^{13}C nmr spectrum for 3.27 at 50 ^{o}C

The driving force behind the formation of betaine **3.27** is expected to be the following: (a) aromatisation of the imide ring, (b) electrostatic attraction between the positively charged *N,N*-dimethyliminium nitrogen and the negatively charged oxygen, as in **Scheme 3.30**.



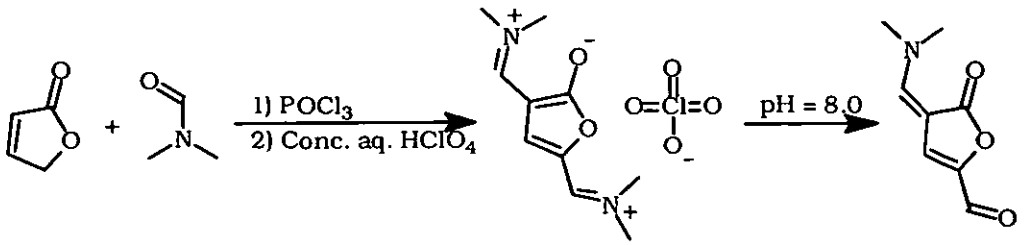
Scheme 3.30

Similar betaines were reported in the literature, for example in 1996 Ramsden *et al.*[62] rationalised the existence of a similar betaine as an intermediate in the route towards the formation of their end product. However, the betaine was not isolated. **Scheme 3.31**.



Scheme 3.31

In another recent example, Kozhina *et al.* [63] generated the perchlorate salt of a similar analogue *via* Vilsmeier-Haak reaction as in **Scheme 3.32**. It is interesting to note that similar betaines are rare in the literature.

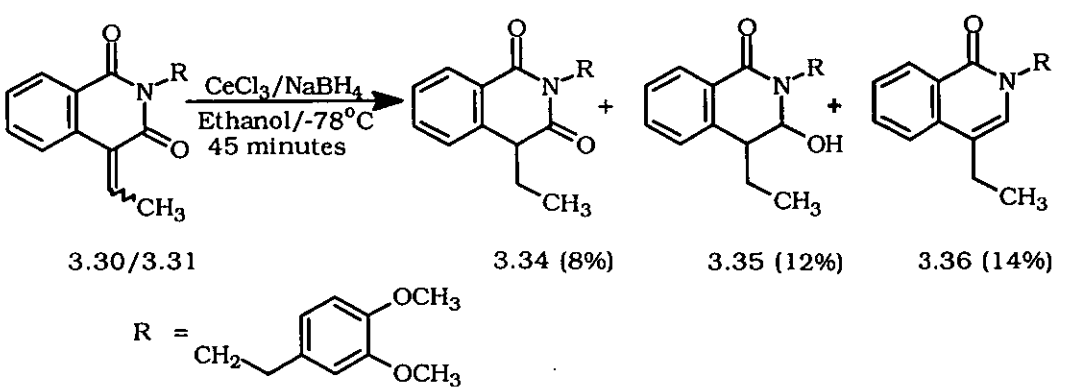


Yield = 75% Yield = 70%

Scheme 3.32

Step 2: Reduction of the 4-Alkylidene Homophthalimides with Sodium Borohydride.

The second step, in the alternative route towards the formation of 4-mono substituted homophthalimides (**Scheme 3.15**), is the reduction of the exocyclic double bond. We decided to achieve this reduction using sodium borohydride for its mild reaction conditions. Towards this we conducted some experiments to increase our understanding of this reaction. In one experiment, we wanted to check the effect of cerium chloride on the reduction reaction so we conducted the following: an ethanolic solution of *Z/E* 2-(3,4-dimethoxy-phenethyl)-4-ethylidenehomophthalimide **3.30/3.31** and 1 equivalent cerium chloride was cooled down to -78 °C and treated with 3 equivalents sodium borohydride. **Scheme 3.33** illustrates the reaction conditions and product yields.

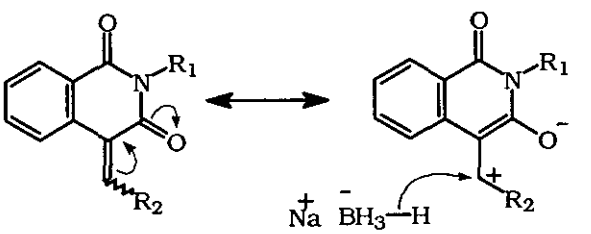


3.30/3.31 3.34 (8%) 3.35 (12%) 3.36 (14%)

Scheme 3.33

The following points are considered regarding this reaction.

1. The ^1H nmr spectrum of the crude reaction product lacks any significant peaks indicating the presence of the 4-ethylisoquinolone derivative **3.36**, while it shows the carbinolamide **3.35** as the major product, which means that **3.36** was mainly generated by silica gel-induced dehydration of the carbinolamide **3.35**.
2. The reaction produced other inseparable mixtures of unidentified compounds.
3. It seems that cerium chloride had no effect on the reduction process, as it is supposed that it will lead to the preferential reduction of the carbonyl group instead of the exocylic double bond,[64] which indicates that the exocyclic double bond is sufficiently reactive to compete with the carbonyl group for the hydride ion. This improved reactivity is probably due to the stabilising effect induced by the imide ring aromatisation as in **Scheme 3.34**.



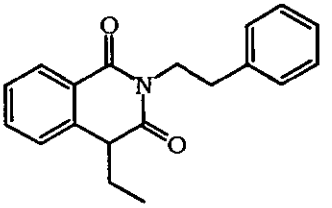
Scheme 3.34.

4. The formation of **3.35** and **3.36** was undoubtedly due to over-reducing the starting material, so that the carbonyl group was also reduced. The regioselective reduction of the imide carbonyl group will be discussed in more details in chapter 4.

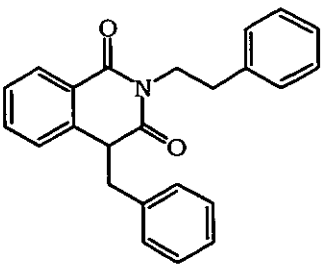
   In an attempt to minimise the over-reduction, we carried out the following optimisation experiments:

   (a) Reduction of the 4-benzylidenehomophthalimides **3.32/3.33** with 0.40 equivalent sodium borohydride and for 1 hour at -78 °C. This gave the 4-benzylhomophthalimide **3.38** in 13% yield, together with a mixture of unidentified compounds.

   (b) Reduction of the 4-ethylidenehomophthalimides **3.28/3.29** with 0.67 equivalent of sodium borohydride for 15 minutes and at -78 °C. This trial yielded the 4-ethylhomophthalimide **3.37** in 28%, together with a mixture of unidentified compounds.

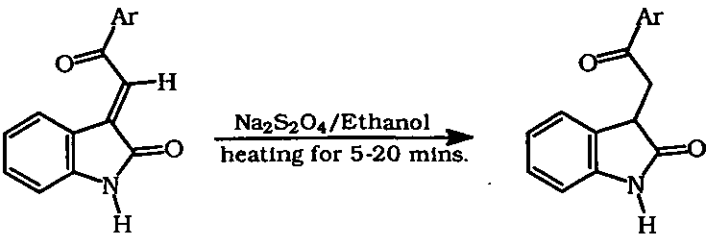


3.37



3.38

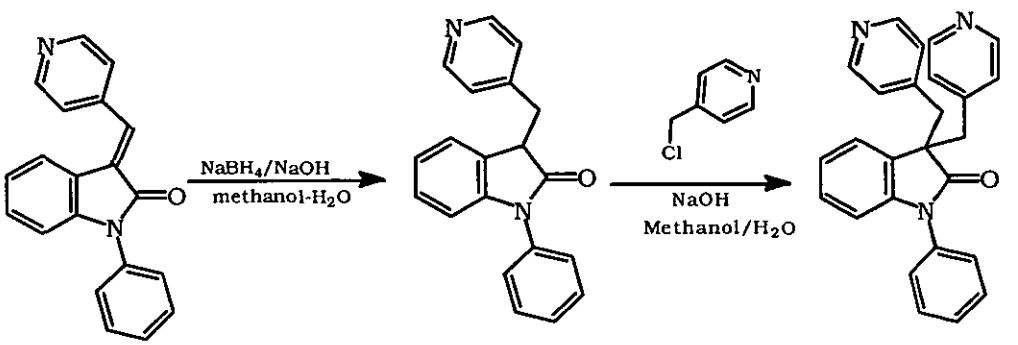
Similar reduction reactions were reported in the literature, for example, Beccalli, *et al.*[65] reported the reduction of an oxindole exocylic double bond using sodium hydrosulfite as in **Scheme 3.35**.



Yield = 57-92%

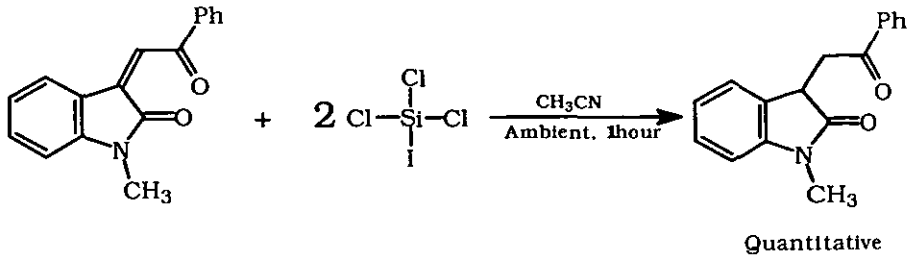
Scheme 3.35

In another example, Bryant *et al.*[66] utilised sodium borohydride reduction of exocyclic oxindole double bond in their proposed commercial manufacturing process of Linopirdine, a potent pharmacological agent for the alleviation of Alzeimer's disease. The reduced intermediate was alkylated *in situ* with overall yield of 85-90%. **Scheme 3.36**.



Scheme 3.36.

In 1996, Elmorsy *et al.*[67] demonstrated that iodotrichlorosilane (ITCS) in acetonitirile selectively reduced the double bond in α-β unstaurated amides as in **Scheme 3.37**.

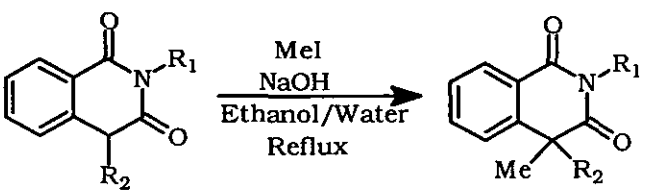


Scheme 3.37

Methylation of 4-Monosubstituted Homophthalimides.

In the course of this research, we required homophthalimides substituted with 2 different groups at C4; to study the behaviour of some interesting *N*-acyliminium ions derived form them as will be discussed later (chapter 5).

To achieve this, we treated 4-alkyl or arylalkyl-homophthalimides with methyl iodide in aqueous ethanolic sodium hydroxide, as illustrated in **Scheme 3.38.**

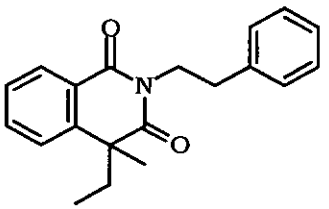


Scheme 3.38

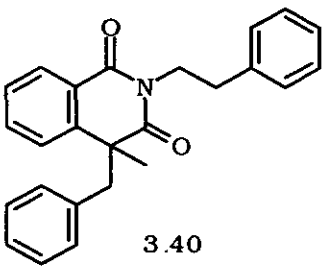
Table 3.5 shows the methylation reaction conditions and yields.

Table 3.5.

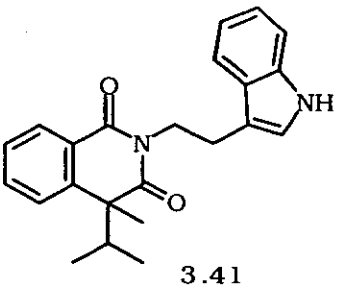
		Products	
Starting material.	**MeI (equ.)**	**Reaction Time.**	**Product (yields).**
3.37	2.6	30 minutes	**3.39** (84%)
3.38	2.2	4 hours	**3.40** (85%)
3.24	10.1	3 hours	**3.41** (28%)



3.39



3.40

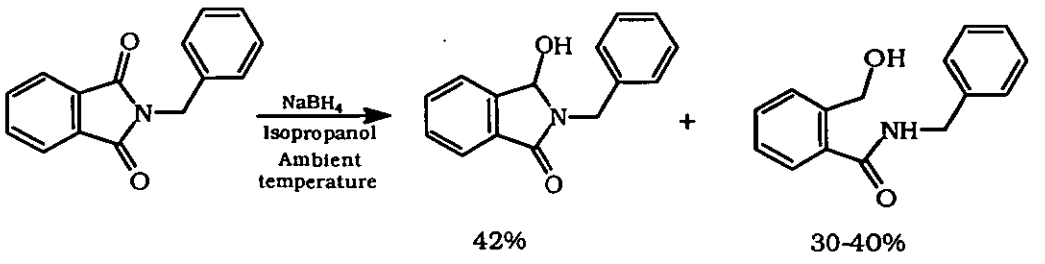


3.41

The most clear point in the above table is the relatively low yield for the methylation of the 4-isopropyl derivative **3.24**, despite the presence of 10 equivalents of methyl iodide, which is understandable based on the steric hindrance resulting from the bulky isopropyl. Harriman *et al.*[13] reported 47% yield of 4-benzyl-4-isopropylhomophthalimide *via* refluxing 4-isopropyl homophthalimide with benzyl chloride in sodium hydroxide aqueous alcoholic solution. This result must be questioned in view of the methylation result reported herein.

Chapter 4: The Sodium Borohydride Regioselective Reduction of 4,4-Dialkyl- and 4-Spirocyclic Homophthalimides.

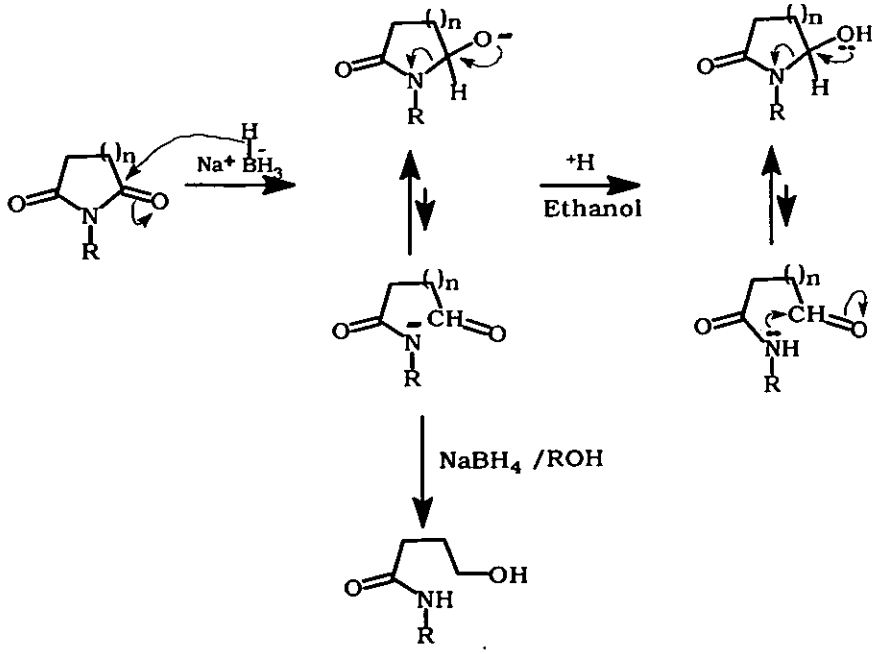
Imide reduction reactions conducted with hydride donors were reported as early as 1961 by Uhle,[68] when he discovered that the reaction of sodium borohydride with a 2-substituted phthalimide produced the corresponding carbinolamide in 42% yield together with the *N*-benzylphthalamidic alcohol as shown in **Scheme 4.1**.



Scheme 4.1

Huang[69] reported the same type of reaction for *N*-phenylphthalimide using methanol as the reaction solvent. The reaction yielded the hydroxyisoindolone in 40% yield. He also reported that treating the starting material with lithium aluminium hydride led to the reduction of both carbonyl groups. Later, many similar imide reduction reactions were reported in the literature, the following are just examples.

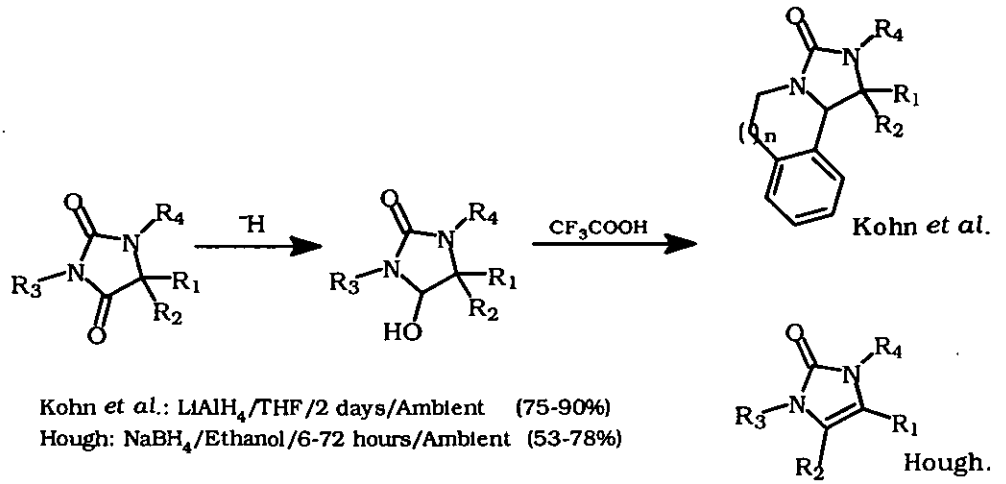
Hurbert *et al.*[70,71,72] reported the reduction of cyclic imides to cyclic carbinolamides using sodium borohydride. The principal problem of these reductions was how to avoid ring cleavage of the carbinolamide to the amide-aldehyde which is further reduced to amide-alcohol. They found that this problem can be solved by conducting the reaction under lower temperartures and by the continuous addition of aliquots of hydrogen chloride to the reaction as in **Scheme 4.2**. The yield of the ring opened products can also be influenced by changing the substituents on the amidic nitrogen. The products were utilised to generate cyclic *N*-acyliminium ion species *via* acid catalysis. The ionic intermediates were trapped with aromatic neucleophiles or addition to double bonds.



Scheme 4.2

Kohn *et al.*[73] used lithium aluminium hydride to reduce 5,5-dimethylhydantoins to 4-hydroxy-2-imidazolidinones and used the products to generate annelated imidazolidinones *via* *N*-amidoyl species as in **Scheme 4.3**.

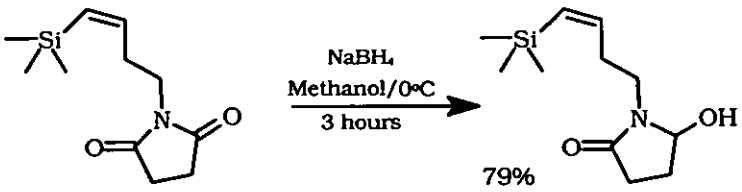
Hough[74] generated similar 4-hydroxyimidazolidinones by treating 5,5-dialkylhydantoins with sodium borohydride. The products were treated with trifluoroacetic acid to generat imidazolin-2-ones *via* alkyl group migration as in **Scheme 4.3**.



Scheme 4.3

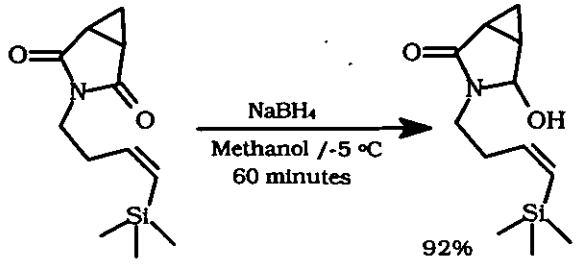
Flann *et al.*[75] generated carbinolamides from corresponding imides, in good yields, *via* sodium borohydride reduction, the products were used to study

acyliminium ion initiated cyclisation reactions of vinylsilanes and the regiocontrolled synthesis of tetrahydropyridines and related heterocycles. One of their reduction reactions is illustrated in **Scheme 4.4**.



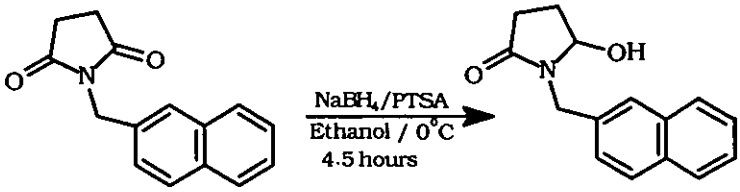
Scheme 4.4

Kim *et al.*[76] conducted the sodium borohydride reduction reaction in their route towards the complete synthesis of (+/-)-indolizomycine, **Scheme 4.5** illustrates the reduction step.



Scheme 4.5

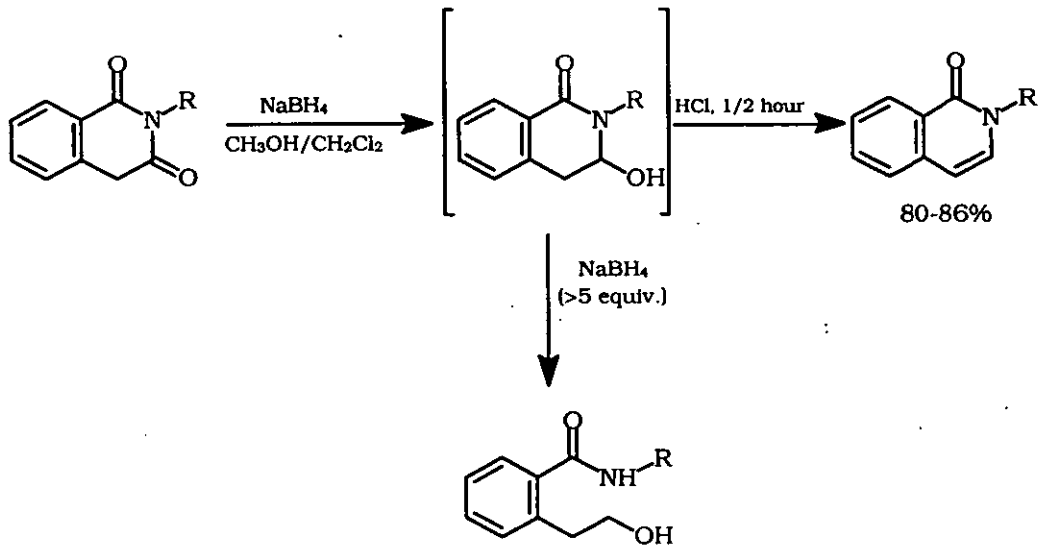
Hitchings *et al.*[77] reduced *N*-(α-naphthylmethyl)succinimide to 5-hydroxy-1-(α-naphthylmethyl)pyrrolidin-2-one in 86% yield using sodium borohydride / toluene-*p*-sulfonic acid (PTSA). **Scheme 4.6.**



Scheme 4.6

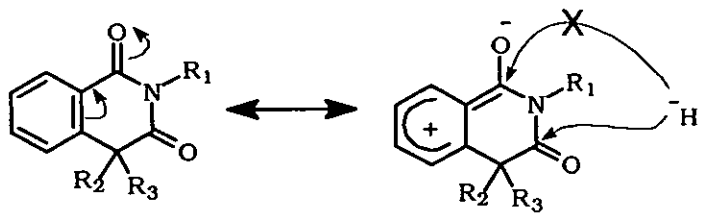
The authors obtained pyrrolo- and pyrido-[1,2-f]phenanthridines and benzo[de]pyrrolo[2,1-a]isoquinolines by acid-catalysed cyclodehydration of appropriate hydroxy lactams and keto amides derived from *N*-substituted succinimide and glutarimide derivatives. Analogous reduction reactions of homophthalimides have been very rarely reported in the literature. However, in 1995 Cheng *et al.*[18] reported sodium borohyride reduction of 2-substituted

homophthalimides, at ambient temperature, to generate the corresponding carbinolamides which, without isolation, were dehydrated upon treatment with hydrochloric acid to afford the isoquinolin-1(2*H*)-ones. The same group also found that when an excess of sodium borohydride (≥ 5 equivalents) was used the carbinolamides intermediate was further reduced to the amide-alcohol as illustrated in **Scheme 4.7**.



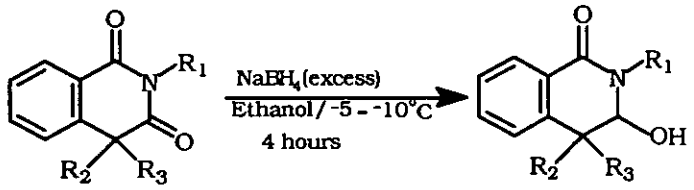
Scheme 4.7

In the present work we have prepared different carbinolamides from 2,4,4-trisubstituted homophthalimides. The generated carbinolamides were utilised to generate *N*-acyliminum ions by treatment with a variety of acids as will be discussed later (in chapter 5). Our reduction procedure is based on treating a cooled ethanolic solution (-5 – -10 °C) of the starting homophthalimide with moderate to large excess of sodium borohydride (5-60 equivalents). The reducing agent was added in two equal lots over a 4 hour period. These reaction conditions yielded the required carbinolamides in moderate to excellent yields. Our aim behind using low temperature was to inhibit further reduction of the generated carbinolamides to the corresponding alcohols as reported by Cheng *et al.*[18] The regioselectivity of the reduction is undoubtedly due to the difference in electron density between the two carbonyl groups. The hydride ion is expected to attack preferentially the more electron deficient nonconjugated carbonyl group as in **Scheme 4.8**.

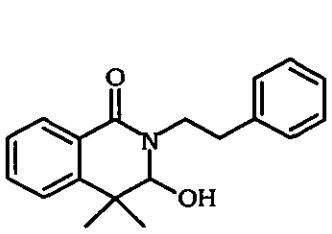


Scheme 4.8

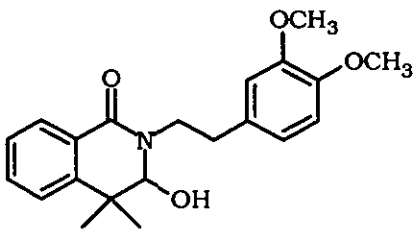
Under our reaction conditions, we did not notice the presence of the over-reduction ring-opened amidic alcohol reported by Cheng *et al.*,[18] neither in the crude product (based on the ^1H nmr spectra) nor after purification. **Scheme 4.9** illustrates our reduction conditions and **Table 4.1** shows the starting materials, reaction conditions and yields.



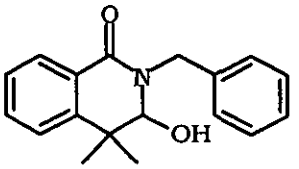
Scheme 4.9



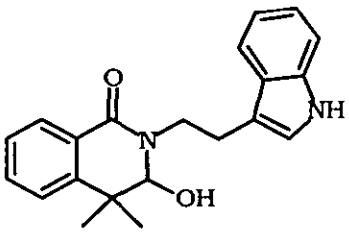
4.1



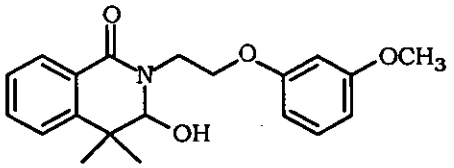
4.2



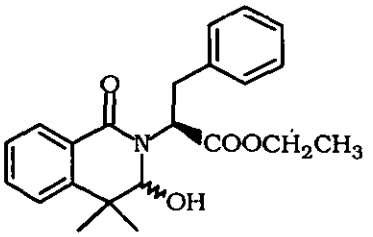
4.3



4.4



4.5



4.6

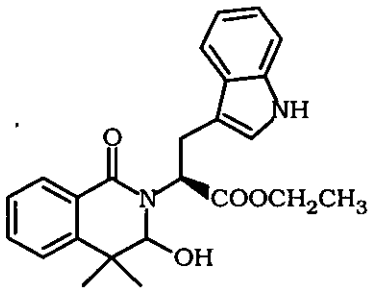
Table 4.1.

Starting Material	Number of Equivalents ($NaBH_4$)	Reaction Time (hours)	Product	Yields (%)
3.1	18	4	**4.1**	83
3.2	17	4	**4.2**	85
3.3	11	4	**4.3**	84
3.4	58	4	**4.4**	43
3.5	33	4	**4.5**	83
3.6	20	4	**4.6**	12*
3.7	44	5.5	**4.7**	21**
3.9	84	6	**4.8**	46†
3.10	20	4	**4.9**	92
3.11	64	4	**4.10**	89
3.12	34	4	**4.11**	87
3.13	20	4	**4.12**	46
3.14	77	4	**4.13**	42
3.39	43	4	**4.14**	73‡
3.40	39	4	**4.15**	91††
3.41	122	6	**4.16**	55‡‡

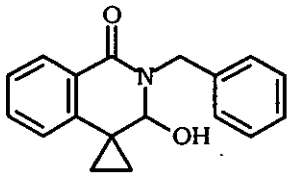
* Diastereomeric ratio 3:1. ** Single diastereomer.

† Reaction temperature is 10 °C. ‡ Diastereomeric ratio 5:12

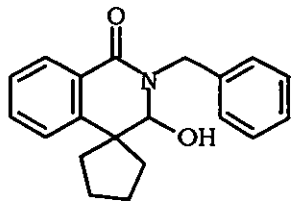
†† Diastereomeric ratio 2:1. ‡‡ Single diastereomer.



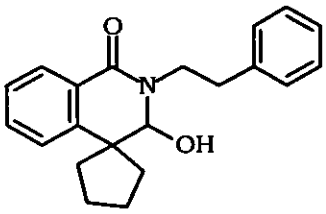
4.7



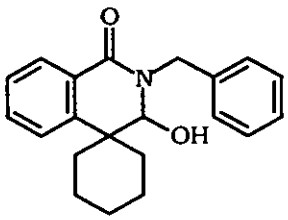
4.8



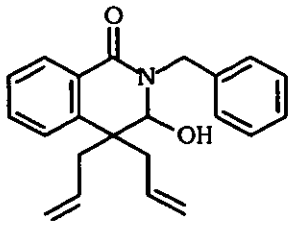
4.9



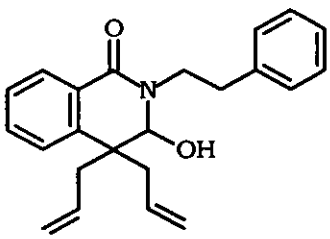
4.10



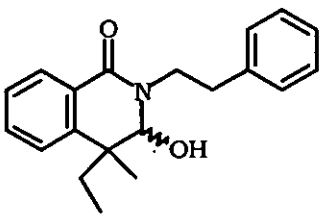
4.11



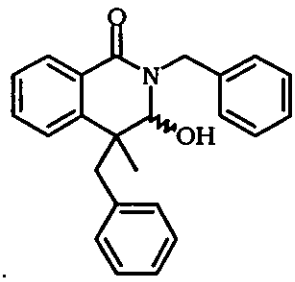
4.12



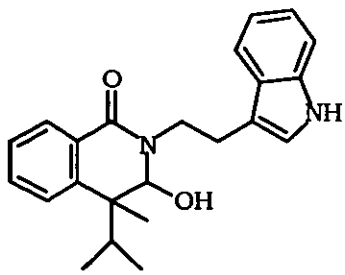
4.13



4.14



4.15

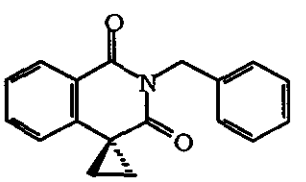


4.16

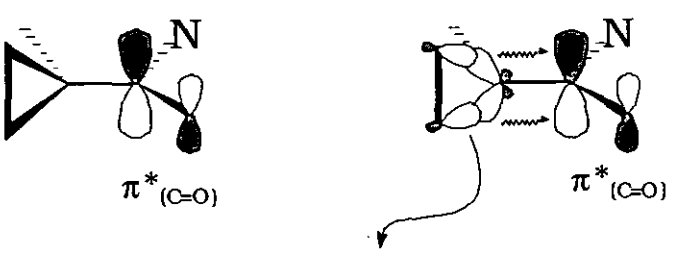
By inspecting the results in **Table 4.1** one can recognise the following points of importance.

1. Under the standard reaction conditions (-5 – -10 °C and for 4 hours), large variations in the amount of sodium borohydride used did not lead to significant differences in the reduction yield for similar compounds. For example, the reduction of the 4-spirocyclopentane derivatives **3.10** and **3.11** gave comparable yields of **4.9** and **4.10** (92 and 89%) despite the fact that **3.11** was treated with 3 times the equivalent amount of sodium borohydride used with **3.10**. A similar trend can be noticed with the 4,4-dimethylhomophthalimides **3.1**, **3.2**, **3.33** and **3.5**, which gave relatively similar yields even though **3.5** was treated with *ca.* double the equivalent amount of sodium borohydride.
2. Reduction of the indole derivatives **3.4** and **3.41** yielded **4.4** and **4.16** in relatively moderate yields in contrast to the excellent yields with other 4,4-dimethyl-homophthalimides. Presumably, this behaviour is due to the poor solubility of the starting material as well as the reduction products in cold ethanol. In the case of **3.41**, steric hindrance by the bulky isopropyl group probably plays an additional role in reducing the reaction efficiency.

3. When our standard reduction conditions (*ca.* 20 $NaBH_4$ equivalents, -5 – -10 °C and for 4 hours) were applied to the 4-spirocyclopropane derivative **3.9**, no reaction took place. A larger excess of sodium borohydride, a higher reaction temperature (10 °C) and a longer reaction time (6 hours) were needed to carry out the reduction. The reaction progress was monitored by TLC and it was terminated when other spots (other than the starting material and the carbinolamide product) started to appear on the TLC plate. The resistance of the imide carbonyl group to the reduction procedure is most probably due to the electron donating effect of the cyclopropane ring. The strained C-C bonds of the cyclopropane ring are of particularly high energy and well-known to be available for delocalisation even with ordinary electron-deficient π-systems. For example, cyclopropane ketone shows low carbonyl stretching frequency in the infrared spectrum.[79] Such delocalisation was described to be the cause for the stabilising effect of cylcopropane ring system on a nearby carbocation.[78] In our case the cyclopropane ring is locked in the "bisected" configuration, whereby two sigma bonds of the cyclopropane ring are suitably aligned to donate electrons to the LUMO of the nearby carbonyl group, as illustrated in **Scheme 4.10**. This leads to increased electron density on the carbonyl carbon thus reducing its reactivity towards the incoming hydride ion.

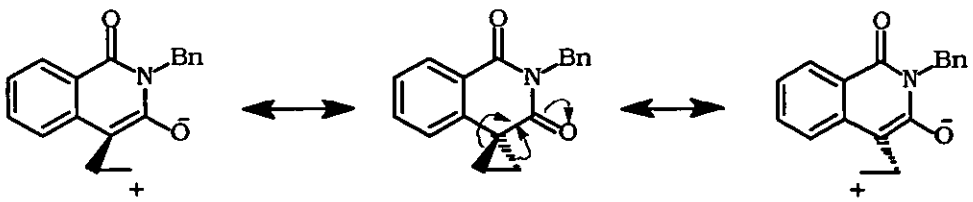


3.9



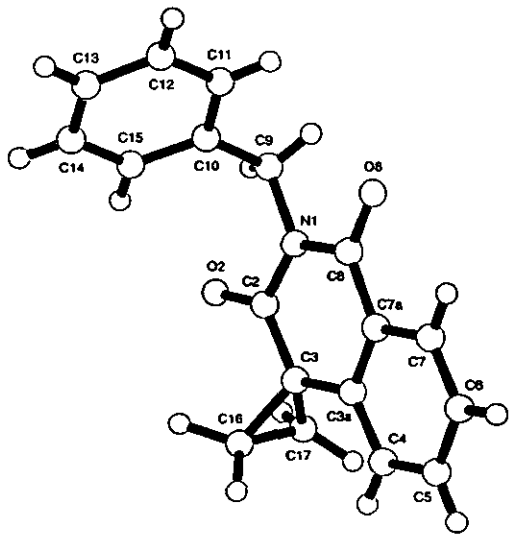
Scheme 4.10

The electron donating effect of the cyclopropane ring is expected to be potentiated by the aromatisation of the imide ring, so that three canonical forms can be drawn for the structure **3.9** as illustrated in **Scheme 4.11**. Resonance stabilisation involving sigma bonds delocalisation is known as hyperconjugation.[80]



Scheme 4.11

At the present time the evidence is against hyperconjugation involving neutral, ground state molecules, since the canonical forms involve charge separation and no bond resonance.[80] Still, in our case we believe that the aromatisation of the imide ring is a powerful factor pushing towards such hyperconjugation.



X-ray picture for **3.9**

The proposed hyperconjugation theory for **3.9** is supported by bond lengths measured using X-Ray crystallography. It is evident that C16-C3 bond (1.542 °A) is longer than other C-C single bonds within the structure. For example, it is 4% longer than C16-C17 (1.480 °A) and 5% longer than N1-C9 (1.468 °A) bond and 2.6% longer than C9-C10 (1.503 °A). Similarly, C3-C17 (1.534 °A) bond is longer than other single bonds. This data indicate that a "no bond" resonance form is contributing to C16-C3 and C17-C3 bonds rendering them somewhat

longer than other single bonds. However, the ^{13}C nmr spectrum of **3.9** in $CDCl_3$ (at 25 °C) clearly shows that the predominant form is the neutral uncharged canonical form (the middle one in **Scheme 4.11**), as two carbonyl groups are evident (at 164.8 and 172.7 ppm).

The electron donating effect of the 4-spirocyclopropane ring and the subsequent reduction in reactivity of the adjacent carbonyl group can be clearly illustrated by comparing the chemical shift of atom A (**Figure 4.1**) in the cyclopropane derivative to the chemical shifts of the analogus atoms in other more reactive homophthalimides. **Table 4.2** shows the ^{13}C nmr chemical shifts of carbon atoms A and B (**Figure 4.1**) in some selected homophthalimides and the corresponding reduction yields under standardised reaction conditions.

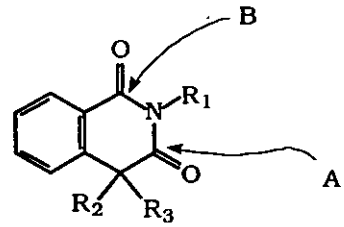


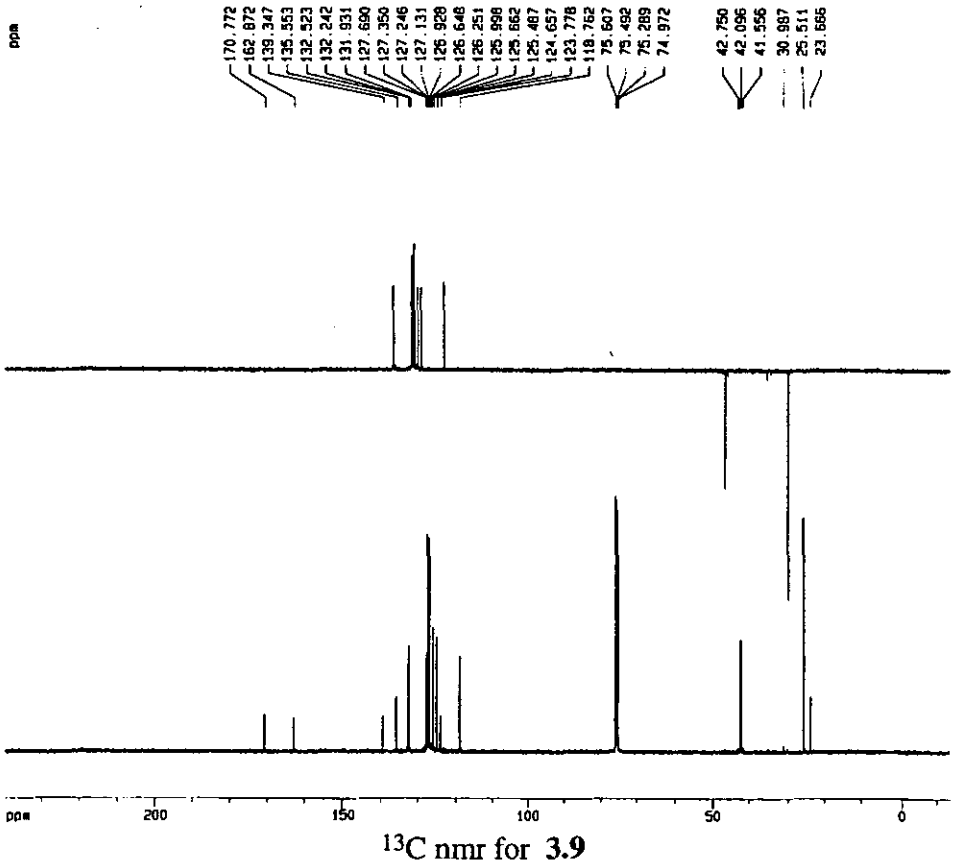
Figure 4.1

Table 4.2

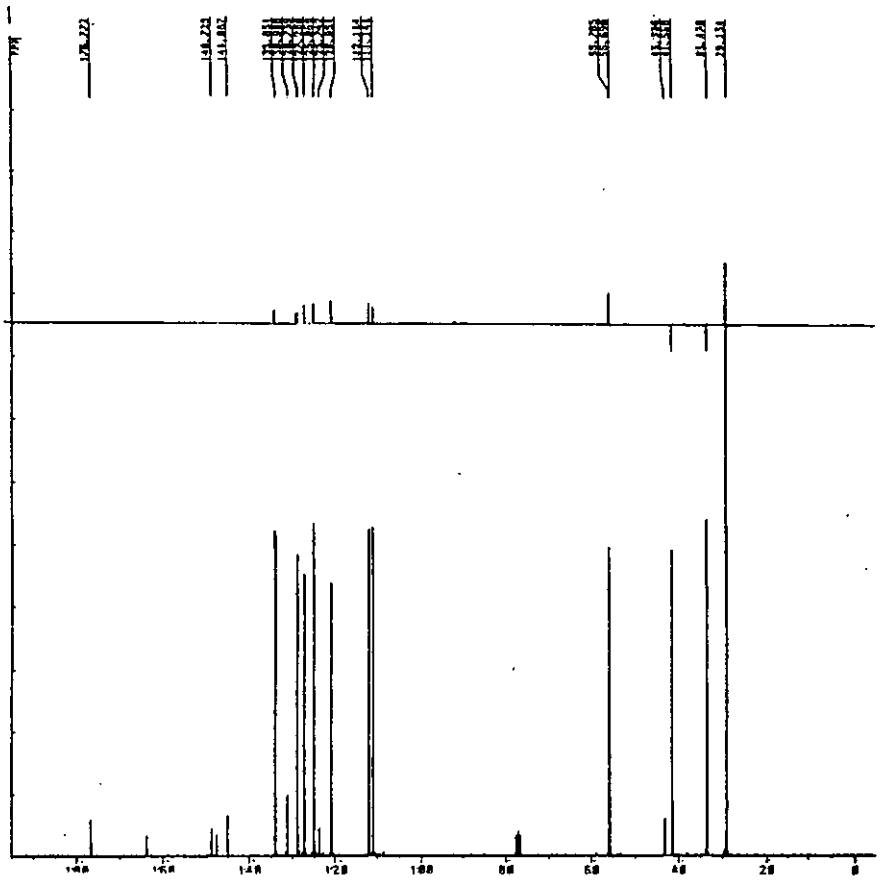
	Chemical Shifts			
Starting Material.	**Carbon A**	**Carbon B**	**Reduction product**	**Reduction Yield %**
3.1	176.7	163.8	**4.1**	83
3.2	176.8	164.7	**4.2**	85
3.10	178.2	164.9	**4.9**	92
3.12	176.8	164.9	**4.11**	87
3.13	175.1	164.4	**4.12**	46
3.39	176.2	164.1	**4.14**	73
3.9	172.7	164.8	**4.8**	40*

* This yield was under our standard reaction conditions (-5 – -10 °C, 4 hours and excess ≥ 20 equivalents), but when the reaction was repeated at higher temperature (10 °C) and longer reaction time (6 hours) the yield was 46%.

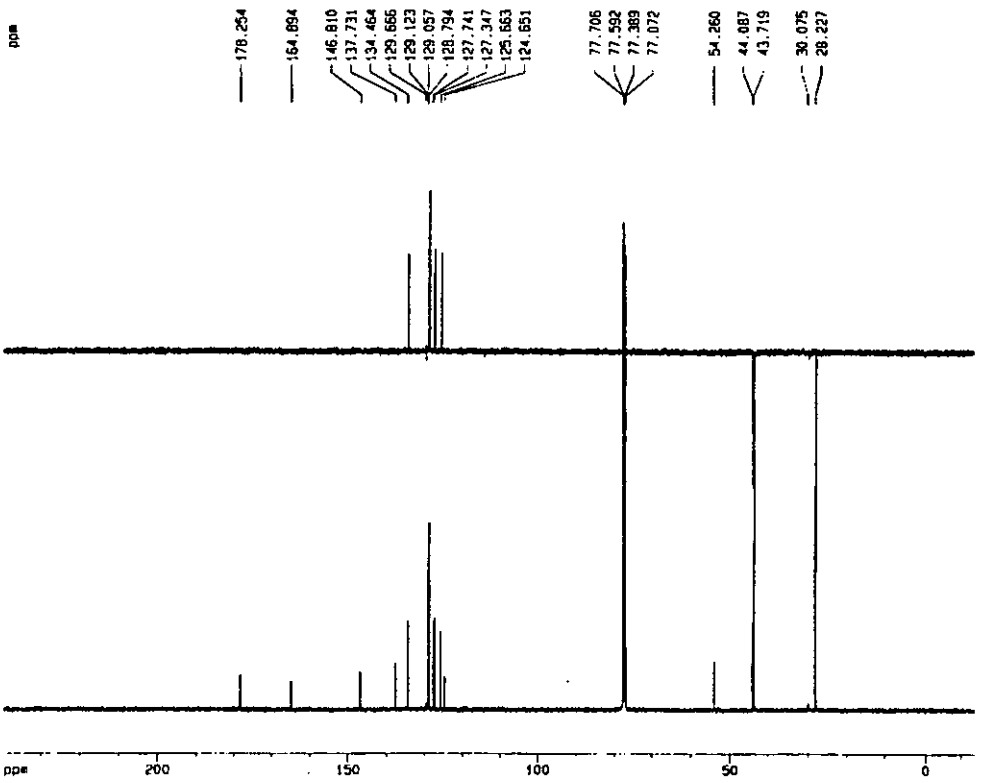
The following points can be recognised from the previous table. (a) There are significant differences in the chemical shifts between the reducible carbonyl carbon (atom A) and the non-reducible conjugated one (carbon B) (8-12 ppm), such differences explain the excellent regioselectivity of the reduction reaction. (b) It seems that the reduction yield is very sensitive to the chemical shift of atom A. For example, excellent yields are seen in the cases where the chemical shifts are 176.7, 176.8 and 178.8 ppm, while when the chemical shift moved to 176.2 ppm (**3.39**) we noticed a moderate decrease in the yield (73%). In the case of 4,4-diallylhomophthalimide **3.13**, a moderate yield of 46% was associated with a chemical shift of 175.1 ppm for carbon A. At 172.7 ppm (**3.9**) there was complete cessation of the reduction under our standard conditions and more forcing conditions were employed to carry out the reaction, which once again clearly ilustrates the electron donating effect of the cyclopropane ring system.



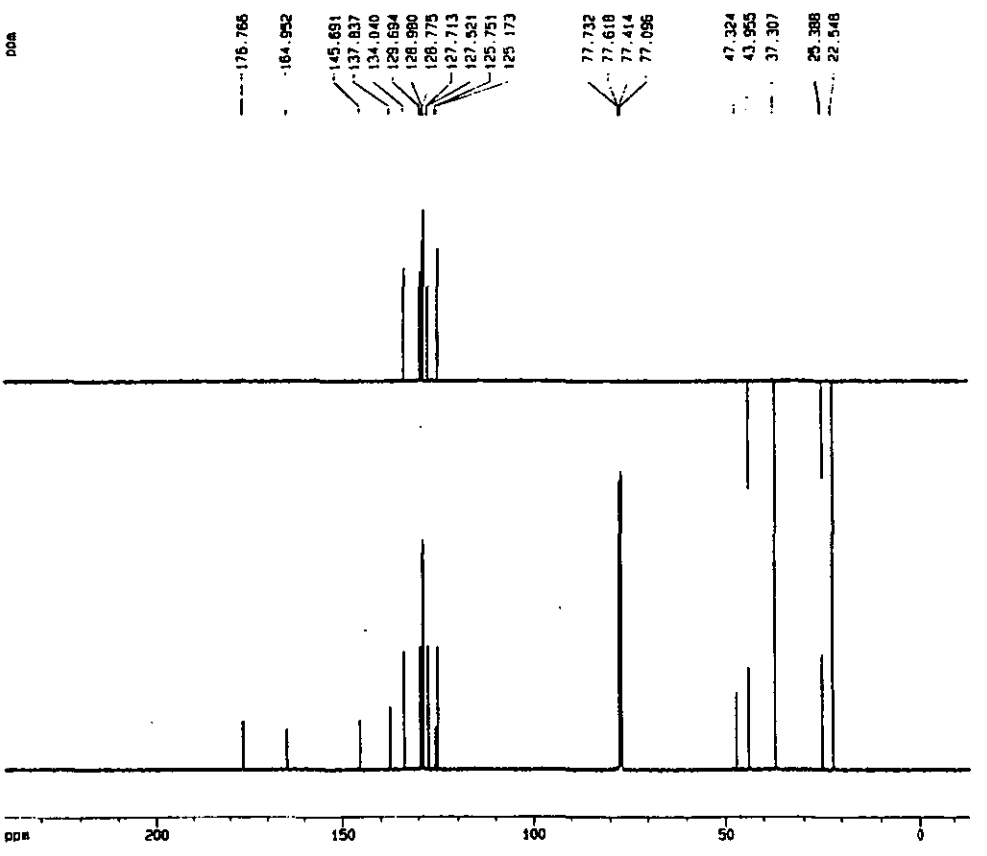
^{13}C nmr for **3.9**



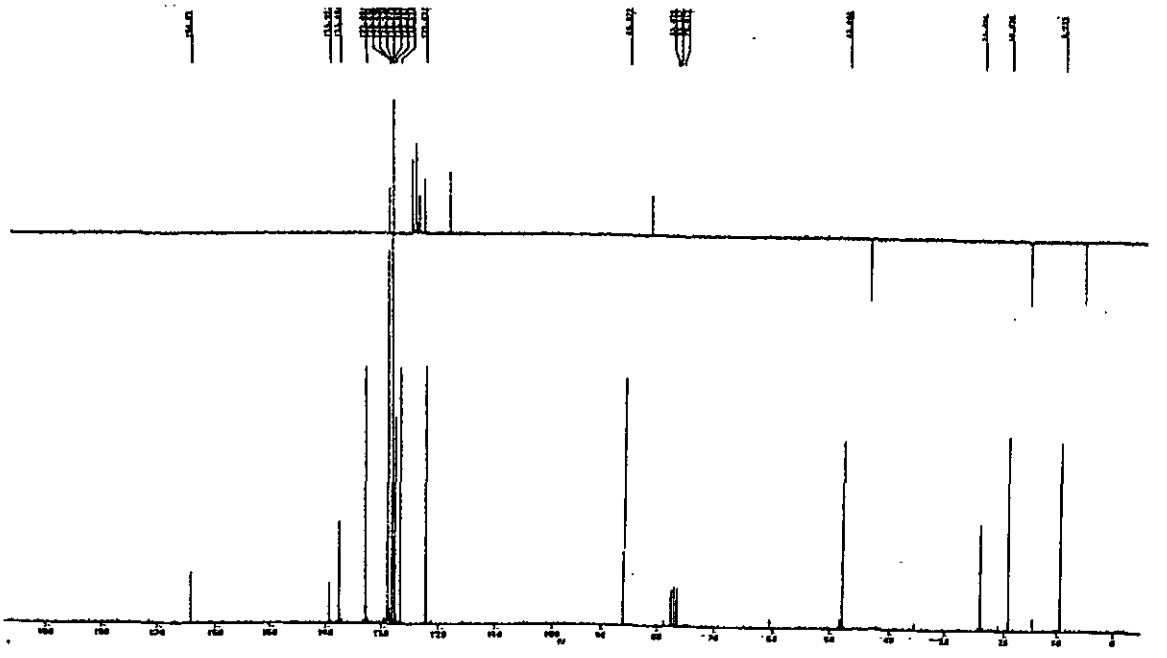
^{13}C nmr for **3.2**



^{13}C nmr for **3.10**

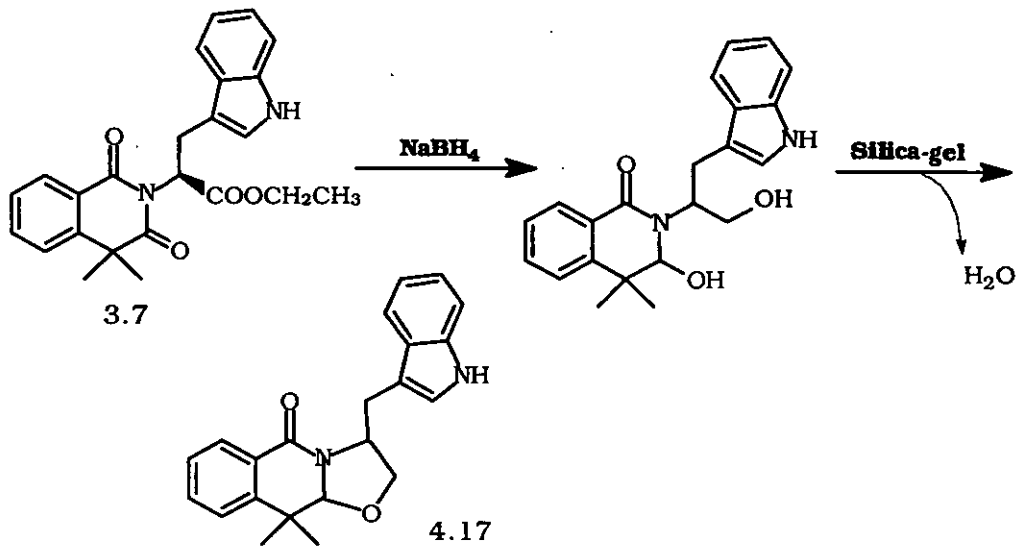


^{13}C nmr for **3.12**



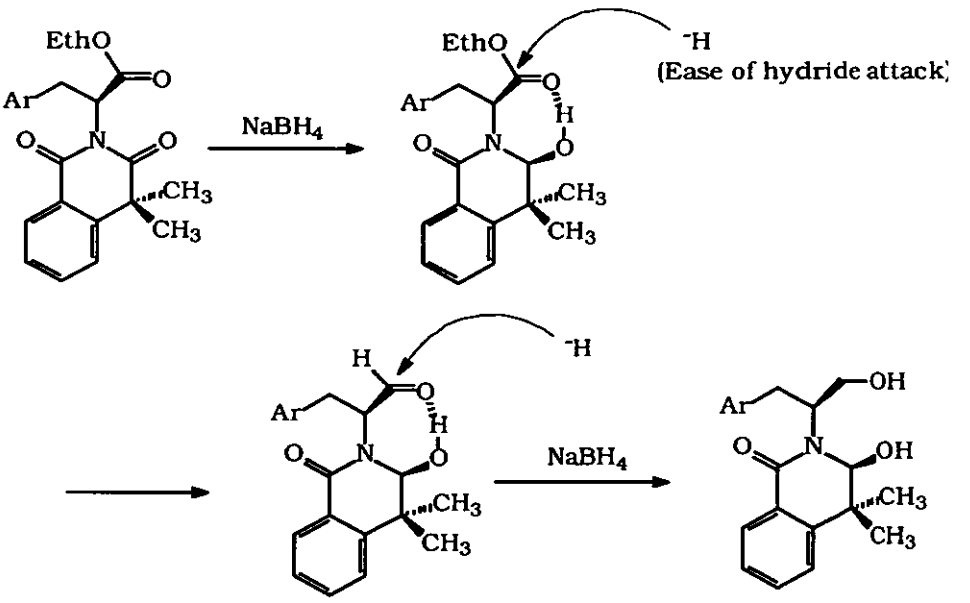
^{13}C nmr for **4.8**

4. The last point in the discussion regarding **Table 4.1** is the poor reduction yield for the amino acid-derived homophthalimides, i.e. **3.6** and **3.7**. In this regard one can note the following interesting points. (a) From the ^{13}C nmr spectra for both **4.6** diastereomers; the chemical shifts for the ester carbonyl groups are 172.2 and 174.4 ppm in contrast to 170.7 ppm for the same group in the starting homophthalimide, this shows that the reduction of the imide carbonyl somehow deshielded the ester carbonyl within the amino acid moiety. (b) Upon purifying **3.7** reduction crude product, two compounds were isolated, namely **4.7** (21 %) and **4.17** (50%, single diastereomer). The later was probably formed from reducing both the imide carbonyl and the ester carbonyl, followed by silica gel-induced dehydration and ether formation, as in **Scheme 4.12**.



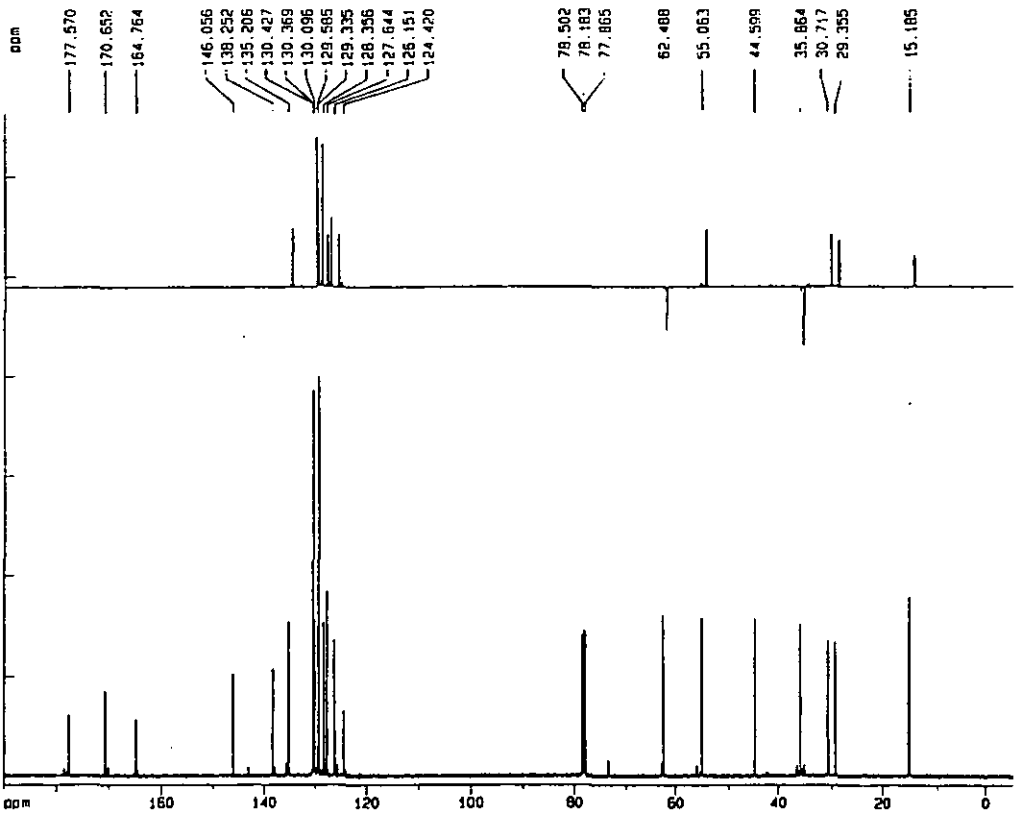
Scheme 4.12

It is known that esters are generally resistant to sodium borohydride/ethanol reduction.[81] However, in this case it seems that the new hydroxy group, formed from the reduction of the imide carbonyl group, forms an intramolecular hydrogen bond with the ester carbonyl group thus causing it to be deshielded in the ^{13}C nmr spectrum (170.7 → 172.2 and 174.4 ppm) and increasing its reactivity towards incoming hydride ions as in **Scheme 4.13**.

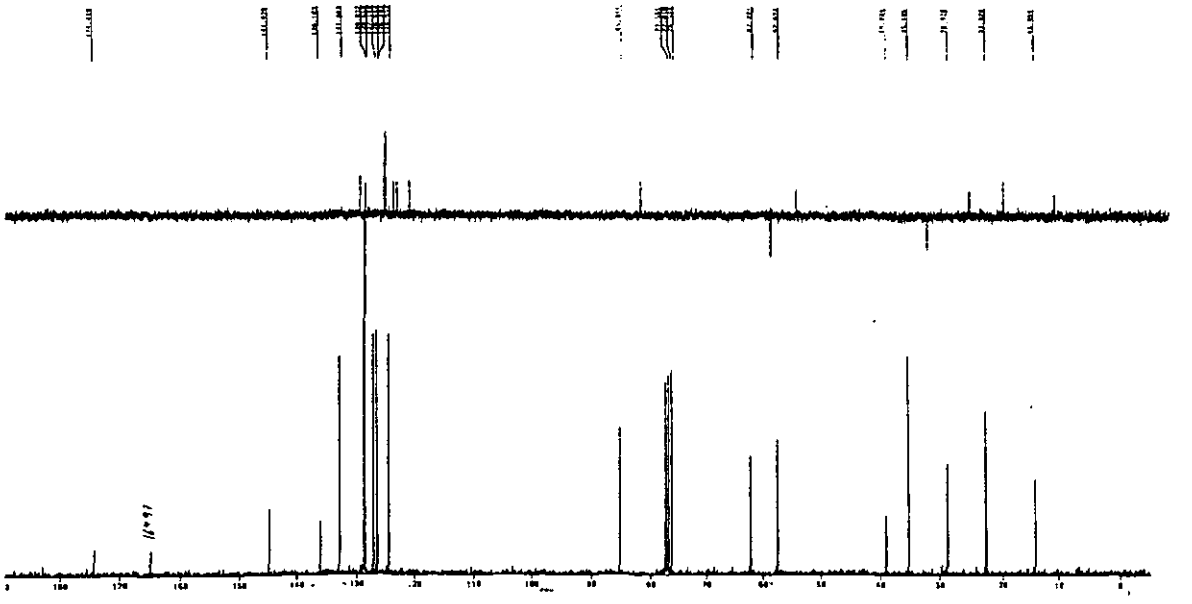


Scheme 4.13

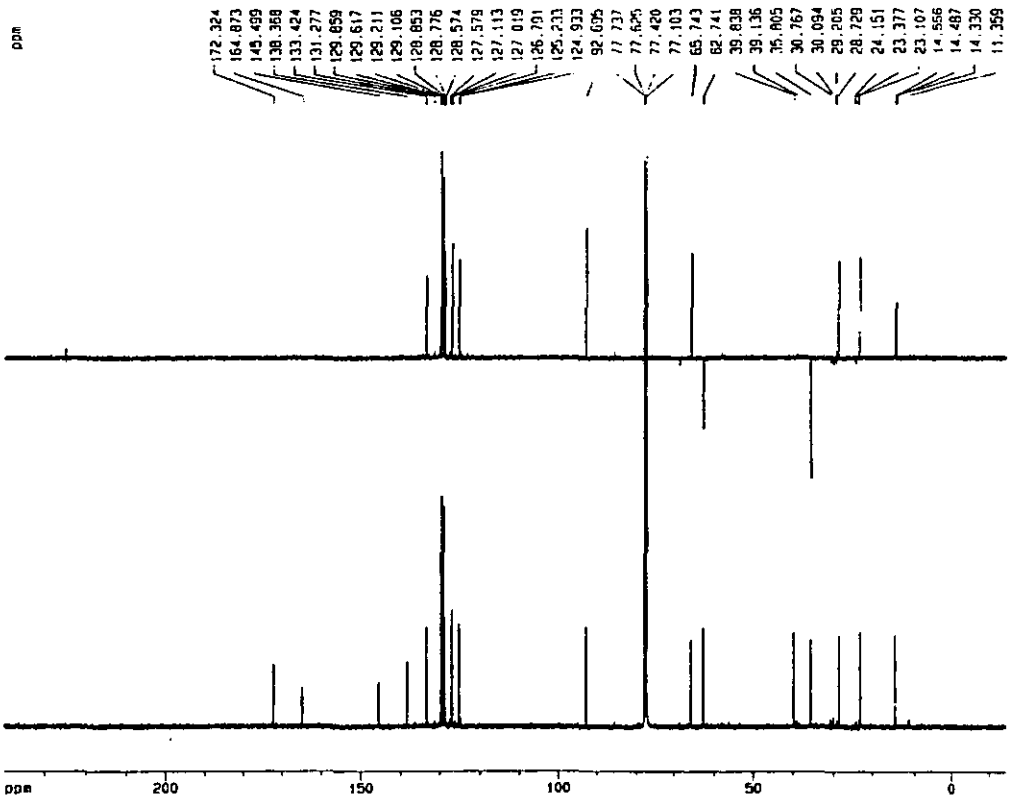
Other evidence on the proposed hydrogen bond comes from the infrared spectrum. The aminoacid derived carbinolamides show their hydroxy bands at around 3420 cm^{-1} and are somehow sharper[82] than the hydroxy bands for other carbinolamides which occur at around 3360 cm^{-1}, also the stretching frequency of the ester carbonyl group is lowered from around 1740 cm^{-1} in the starting materials (**3.6** and **3.7**) to around 1715 cm^{-1} in the corresponding carbinolamides. This suggests that the newly formed hydroxy group forms an intramolecular hydrogen bond and the ester carbonyl group acts as the hydrogen acceptor.[82]



^{13}C nmr for **3.6**



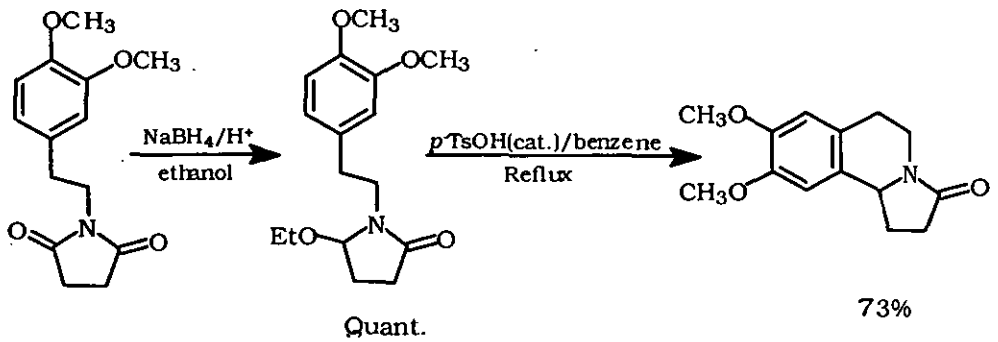
^{13}C nmr for the major diastereomer of **4.6**



^{13}C nmr for the minor diastereomer of **4.6**

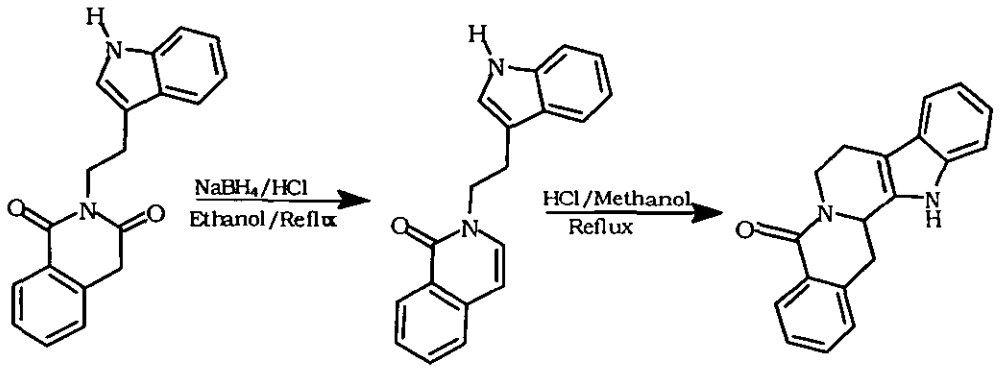
Chapter 5: Generation of *N*-Acyliminium Ions and Their Subsequent Trapping.

The significance of *N*-acyliminium ions has already been briefly discussed in the introductory chapter. Nevertheless, here are more examples with direct relevance to our chemistry with regard to the preparation of the *N*-acyliminium ion precursor, its generation and trapping. One of the early examples illustrating the acid catalysed generation of *N*-acyliminium ions and their subsequent capture with aromatic nucleophiles is reported by Hubert *et al.*[70] when they pioneered the use of this procedure as a more efficient alternative to Bischler-Napieralski cyclisation as in **Scheme 5.1**.



Scheme 5.1

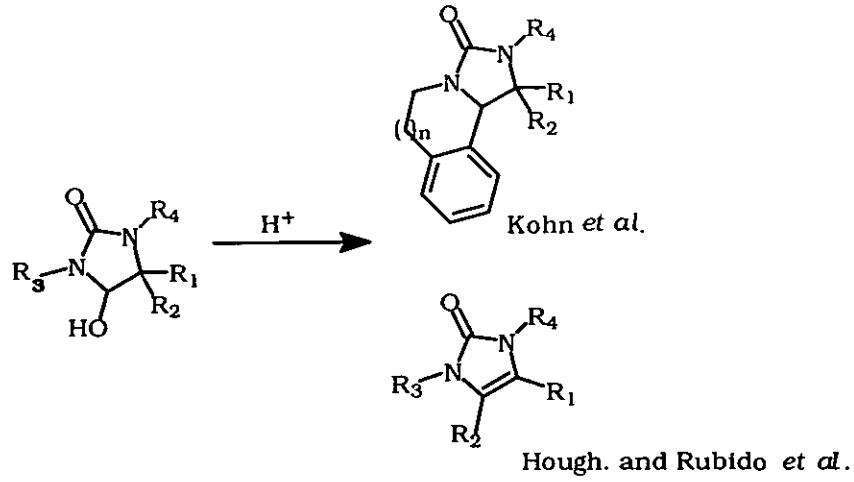
In another example, the same group[71] reported the formation of a β-carboline derivative by refluxing an indoloisoquinolinone in HCl-methanol, the starting material was obtained from the partial reduction of the corresponding homophthalimide as in **Scheme 5.2**.



Scheme 5.2

Kohn *et al.*,[73] Rubido *et al.*[83] and Hough[74] utilised a related ionic intermediate, an *N*-amidoyl species, to prepare annelated imidazolidinones. The ionic

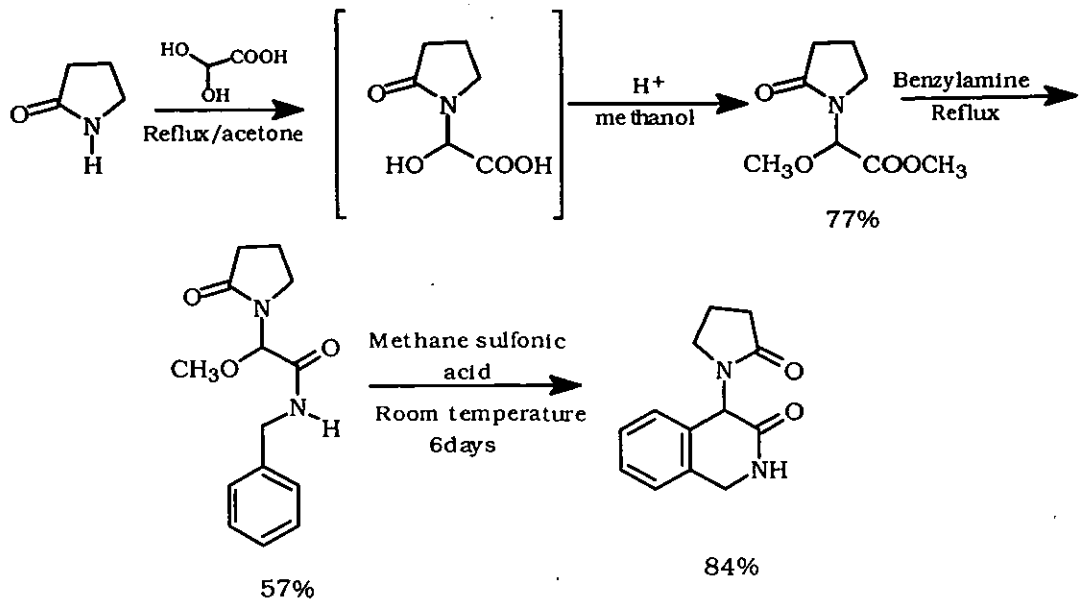
intermediate was generated by treating 4-hydroxy-2-imidazolidinones with acidic reagents as in **Scheme 5.3**.



Scheme 5.3

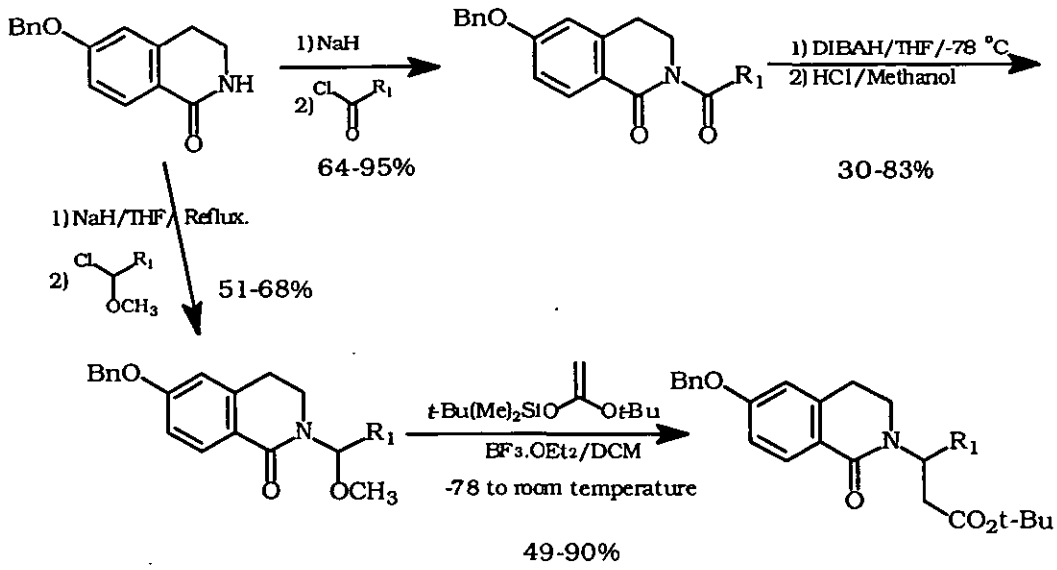
Recently, many research groups utilised *N*-acyliminium ions to generate isoquinolones and related derivatives. The following are some recent examples (1994-1997) on efforts in this direction.

Roth *et al.*[84] showed, as part of their investigation in *N*-acyliminium-mediated Friedel-Crafts amidoalkylation reactions, that the benzylamide of glyoxylic acid-2-pyrrolidinone adduct undergoes intramolecular amidoalkylation to an isoquinolone type compound in good yield, as shown in **Scheme 5.4**.



Scheme 5.4

As part of the efforts to optimise synthetic routes to isoquinolone antagonists of platelet aggregation, Fisher *et al.*[85] treated α-methoxy amides with 1-*t*-butoxy-1-*t*-butyldimethylsiloxyethene in the presence of boron trifluoride etherate providing access to β-substituted isoquinolone propionates in good yields. **Scheme 5.5** illustrates their procedure.



Scheme 5.5

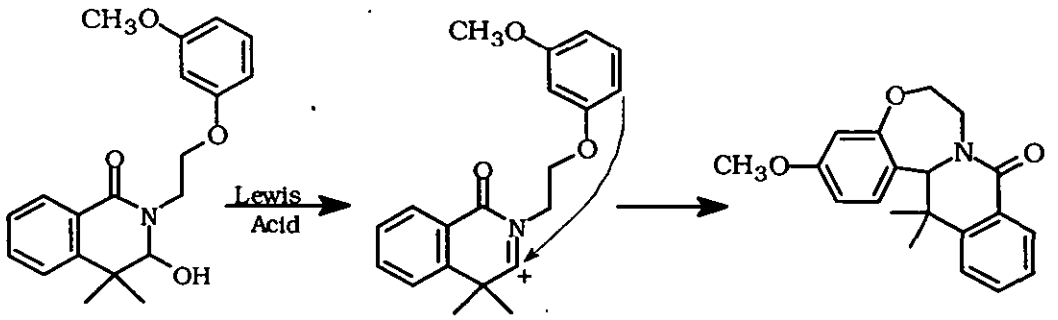
In the current research we have explored the generation and trapping of *N*-acyliminium ions, by treating the starting 4,4-disubstituted carbinolamides with a variety of acids and under different reaction conditions. The nucleophiles used to trap the generated ions, were aromatic rings, migrating alkyl groups or double bonds. The following sections are classified based on the trapped nucleophile.

A- *N*-Acyliminium ions Trapping by Aromatic Nucleophiles.

Trapping *N*-acyliminium ions with aromatic nucleophiles comprises a well known route towards natural products and other interesting heterocycles.[1] The reactions reviewed earlier and outlined in **Schemes 5.1-5.4** are some examples illustrating this point.

In this research we used the following aromatic nucleophiles to trap the generated *N*-acyliminium ions.

1. *m*-Dioxybenzene ring, in this case the carbinolamide **4.5** was treated with three Lewis acids: aluminium bromide, scandium triflate and titanium tetrachloride, and consequently yielded the interesting oxazipinoisoquinolone **5.1**. The reaction time and temperature were varied to explore their effect on the product yield. **Scheme 5.6** outlines the reaction, and **Table 5.1** shows the reaction conditions, reagents and the corresponding yields.



4.5 5.1

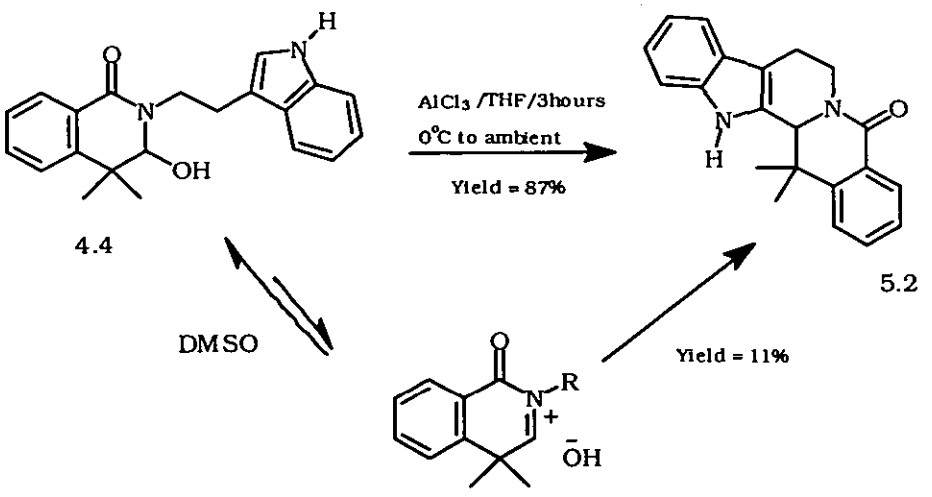
Scheme 5.6

Table 5.1

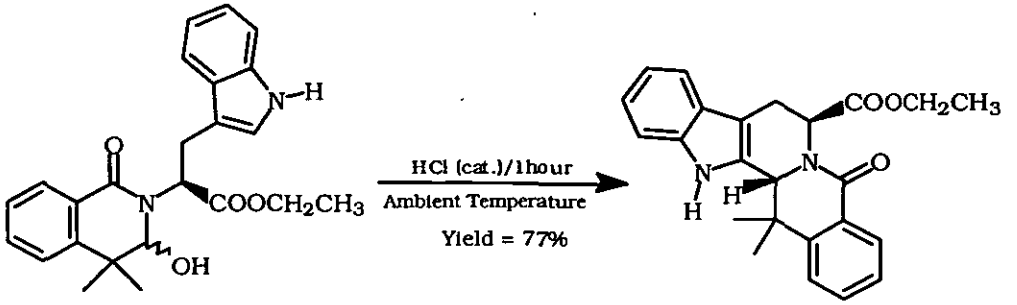
No.	Lewis Acid ** (equi.)	Reaction Temperature (°C)	Reaction Time (hours)	Yield %
1	$AlBr_3$ (1.0)	Ambient	19	6
2	$Sc(OTf)_3$ (0.5)	Ambient	34	0
3	$Sc(OTf)_3$ (0.5)	35	22	7
4	$TiCl_4$ (6.0)	Ambient*	24	32
5	$TiCl_4$ (0.5)	Ambient*	1	23

* $TiCl_4$ was added at -78 °C for 15 minutes then the reaction was warmed up to the mentioned temperature. ** The reactions were conducted in DCM.

2. We also used the indole ring as the trapping nucleophile, in this direction we used the carbinolamides **4.4** and **4.7** as precursors. **Schemes 5.7** and **5.8** illustrate the reaction conditions and yields in each case.



Scheme 5.7



Scheme 5.8

The following are important points for discussion regarding **Table 5.1** and **Schemes 5.6**, **5.7** and **5.8**.

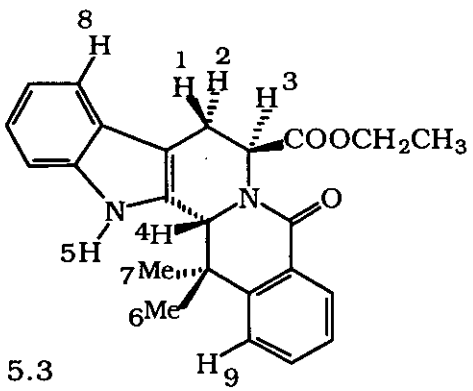
1. It is clear that **5.1** yields are considerably lower than **5.2** and **5.3** yields. Such difference is undoubtedly due to two factors: (a) the higher nucleophilicity of the indole ring, and (b) the faster rate of formation of 6-membered rings (**5.2** and **5.3**) compared to 7-membered ones (**5.1**).[40]
2. After storage in DMSO over 10-day period and under ambient conditions, the carbinolamide **4.4** yielded the corresponding β-carboline **5.2** in *ca.*11%. The yield was estimated from ^{1}H nmr spectroscopy. As DMSO is known to stabilise cations when used as a solvent,[86] the cyclisation suggests the presence of an equilibrium between the carbinolamide **4.4** and its corresponding DMSO-stabilised *N*-acyliminium hydroxide salt. The cation is then captured by the highly nucleophilic indole ring. However, the intermediate ion should have very

short life time, as it is not detected using ^{1}H nmr spectroscopy, also the low yield suggests that the equilibrium is shifted towards the carbinolamide side rather than the *N*-acyliminium hydroxide as illustrated in **Scheme 5.7**.

3. The cyclisation of the tryptophane-derived carbinolamide **4.7** produced **5.3** as the sole detected diastereomer, as illustrated in **Scheme 5.8**. The conclusion of high stereoselectivity is based on ^{1}H nmr spectroscopic data for both the crude reaction product and the purified compound. The elucidation of **5.3** is based on ^{1}H and ^{13}C nmr spectroscopy and mass spectrometry and supported by HETCOR and COSY experiments, while the configuration is established based on ^{1}H nmr spectroscopy and ^{1}H, ^{1}H-NOESY experiments. It was not possible to obtain a crystal that was suitable for X-ray crystallography. Crosspeaks of at least medium strength were considered in the ^{1}H, ^{1}H-NOESY experiment. The following protons show nOe crosspeaks (**Figure 5.1**):

1, 2 and 3.. 4, 5 and 6 (methyl protons). 1 and 8.

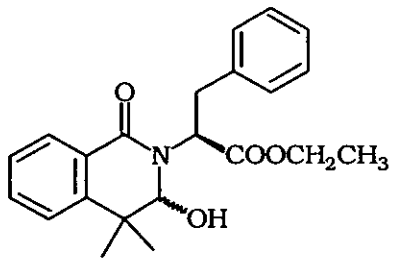
2 and 7 (methyl protons). 9 and 6 (methyl protons).



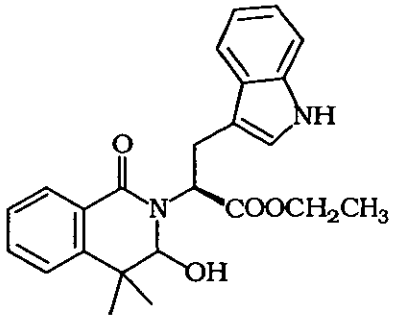
5.3

Figure 5.1

The steric relationship between the hydrogen atoms H1, H2 and H3 is established based on the relevant coupling constants. The coupling constants $J_{1,3}$ and $J_{2,3}$ were found to be 1.8 and 5.4 Hz indicating equatorial-equatorial and axial-equatorial steric relationships.[87] These coupling constants can be compared with their equivalents in the starting material **4.7** (single diastereomer), in which the $J_{1,3}$ and $J_{2,3}$ were found to be 5.7 and 10.3 Hz respectively, corresponding to axial-equatorial and axial-axial steric relationships respectively. Also similar coupling constants are reported for both the major and minor diastereomers of **4.6**.



4.6



4.7

Consequently, in **5.3** the hydrogen atom H3 should be in the equatorial configuration, while the vicinal ester group should be axial. This conclusion was further strengthened by the fact that H3 has equivalent nOe crosspeaks with both H1 and H2 (i.e. intensity wise). This analysis is further supported by conformational energy minimisation conducted with CAChe programme. Relevant interatomic distances calculated by CAChe minimisation are shown in **Table 5.2** and the generated 3-dimensional model is illustrated in **Figure 5.2**. Energy minimisation calculations were conducted without enforcing any constrains on interatomic distances.

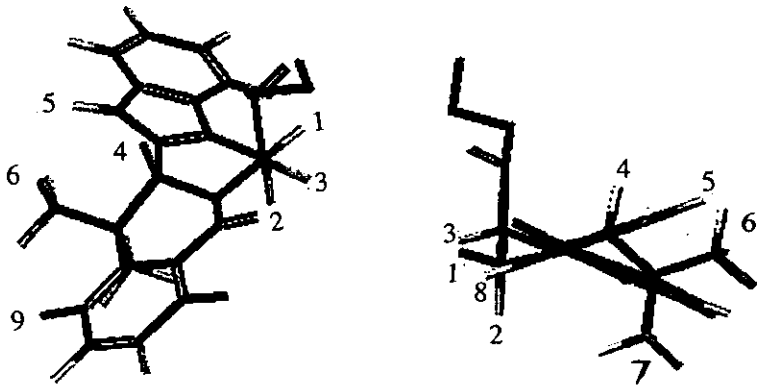
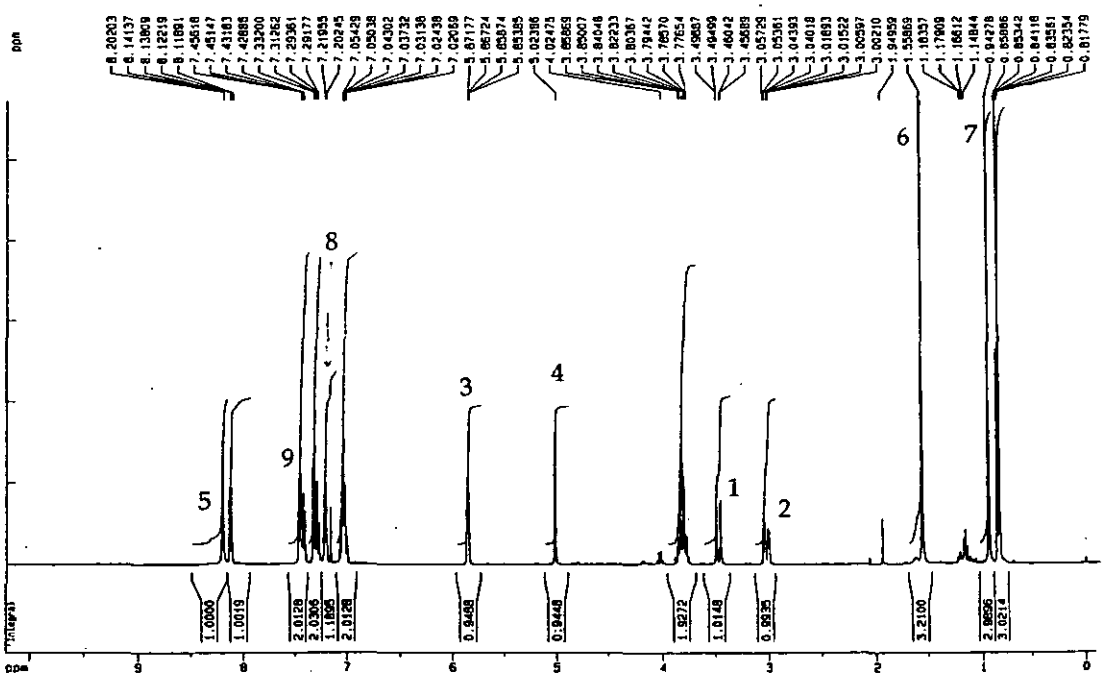


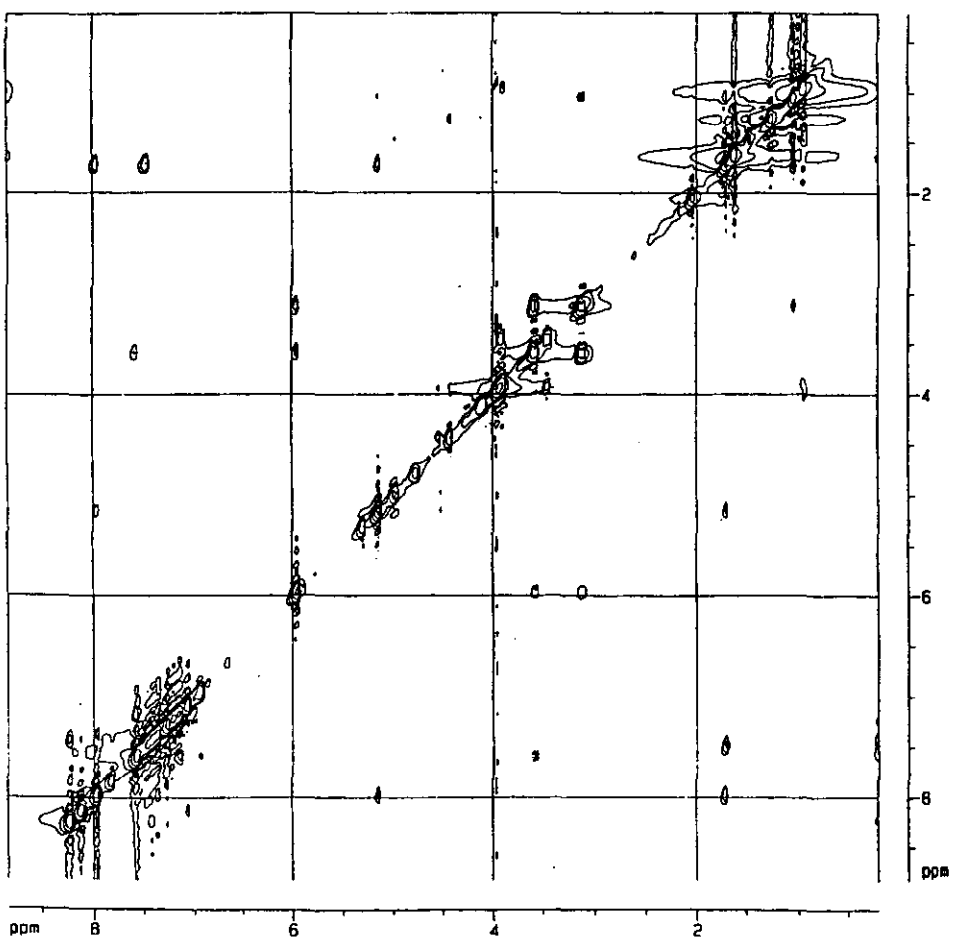
Figure 5.2

Table 5.2

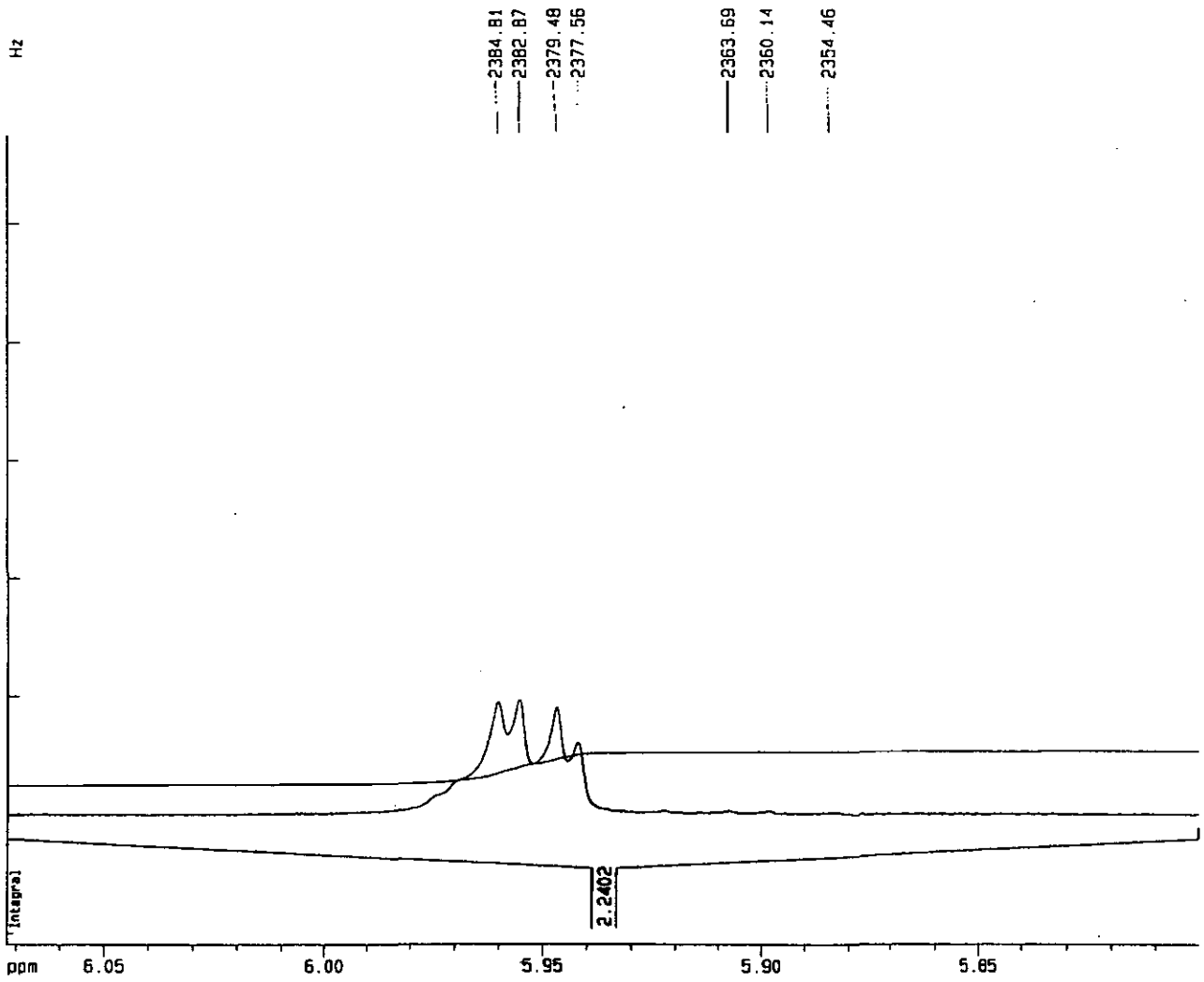
Protons	Distance (°A)
1-2	1.81
2-3	2.50
1-3	2.52
1-8	2.56
2-7 (CH_3)	3.69
4-5	3.04
5-6 (CH_3)	1.94
4-6 (CH_3)	2.52
6-9	3.06



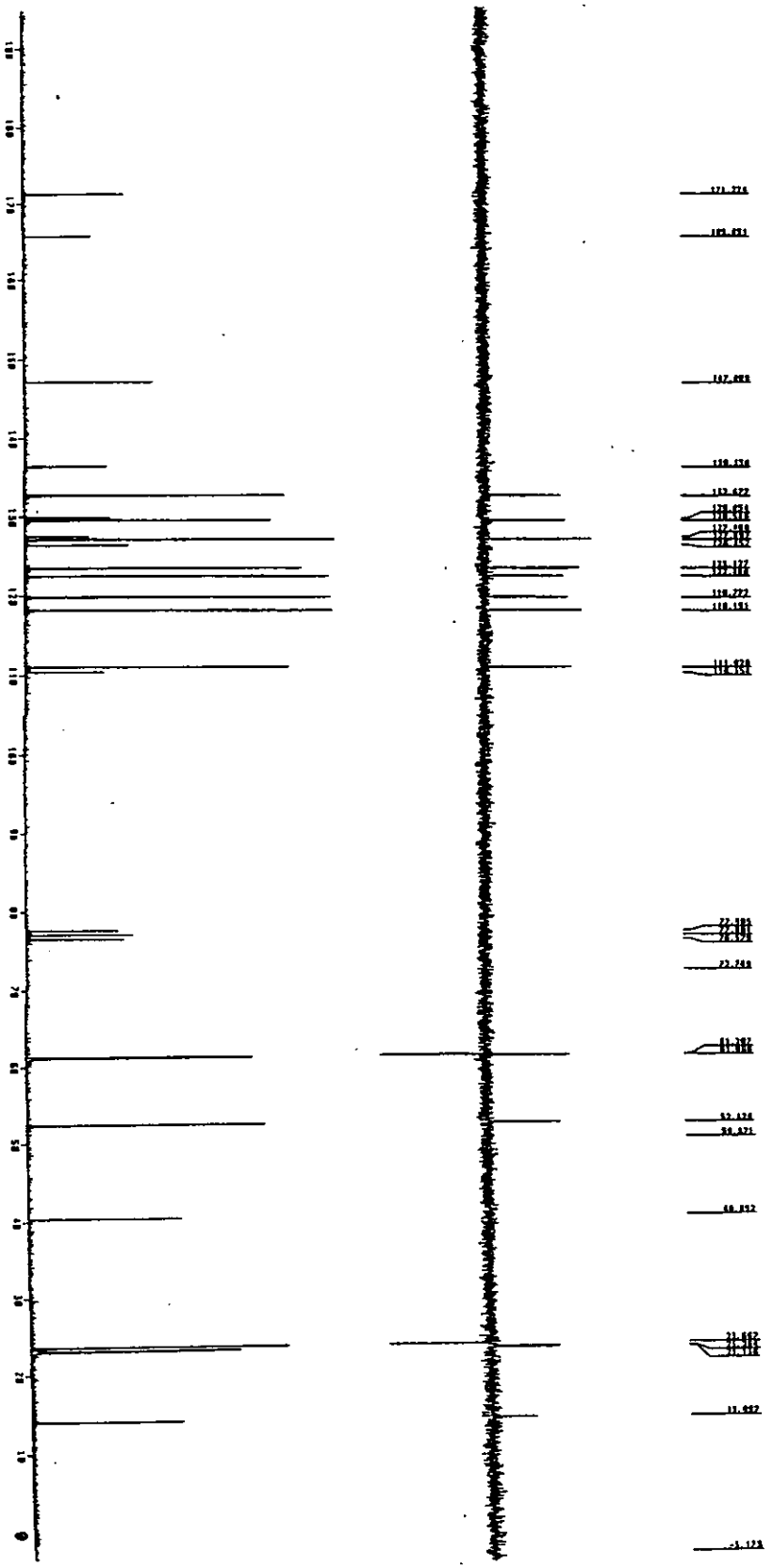
^{1}H nmr spectrum for 5.3.



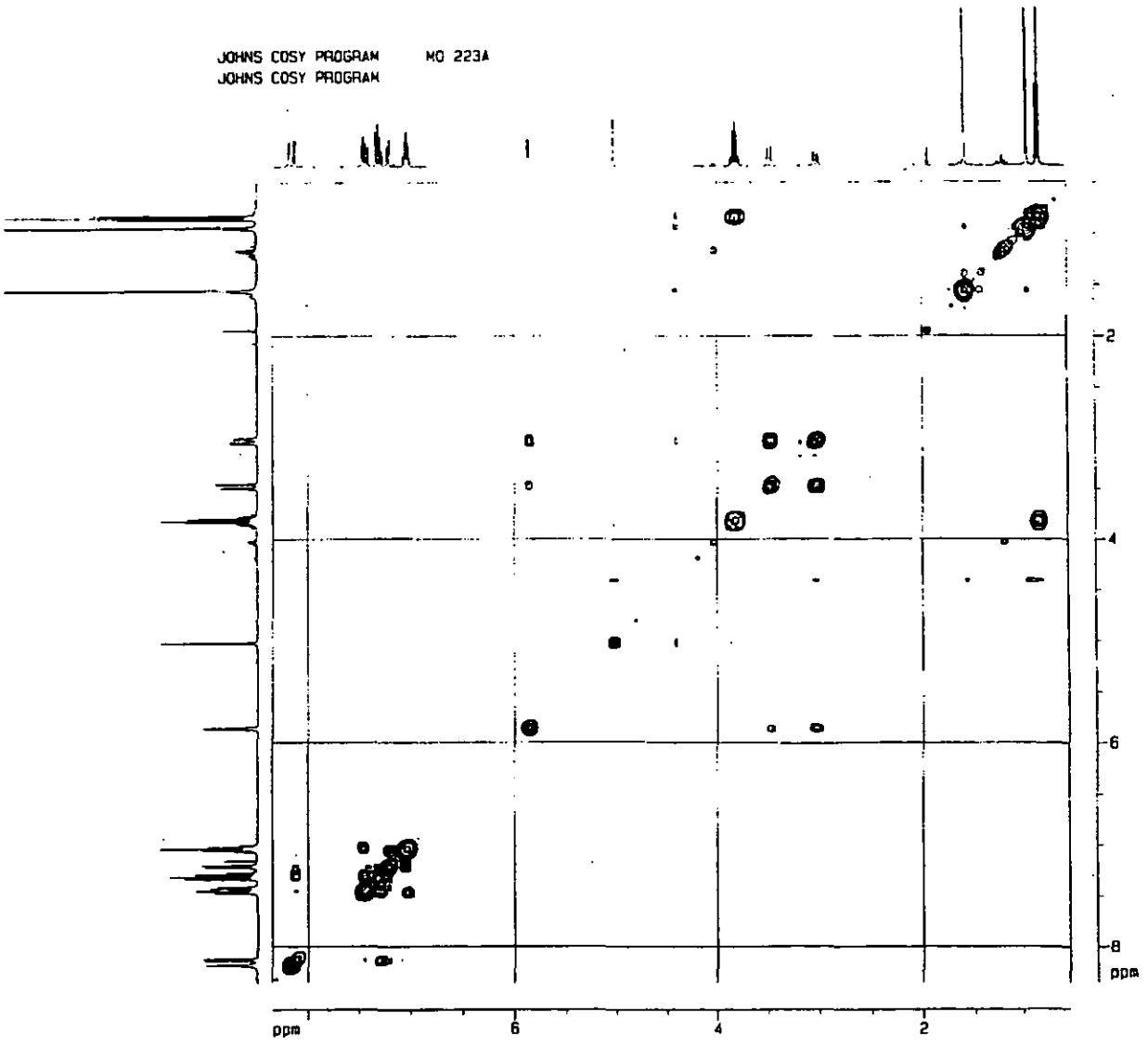
^{1}H, ^{1}H-NOESY experiment for 5.3.



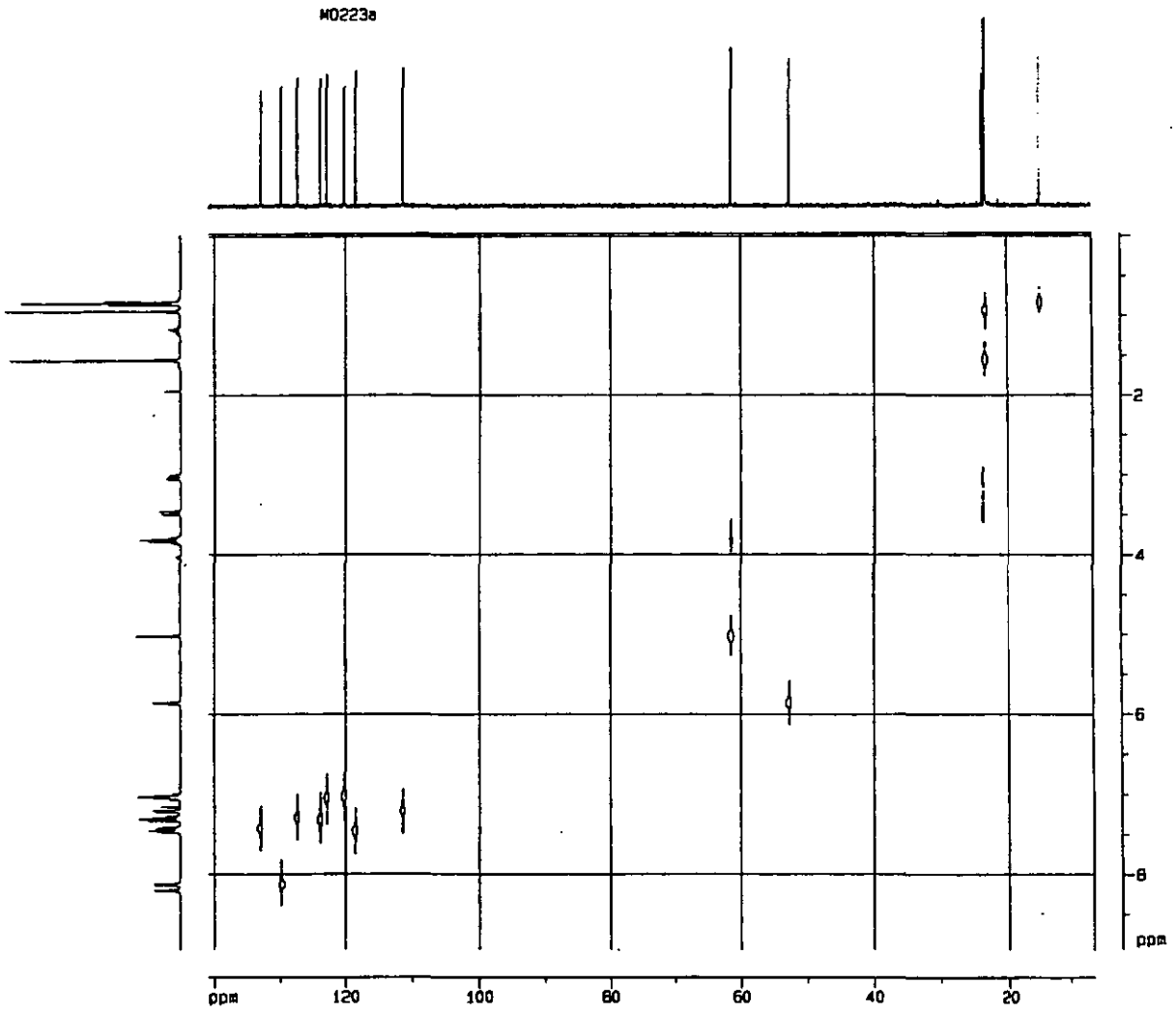
Expansion of ^{1}Hnmr spectrum for 5.3.



^{13}C nmr spectrum for 5.3.

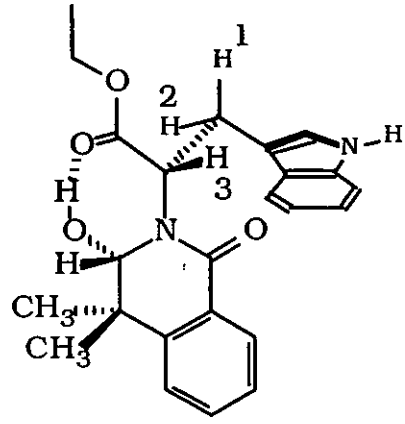


COSY experiment for 5.3.



HETCOR experiment for 5.3.

The driving force behind the formation of **5.3** can be explained as in the following. Initially, the starting material is expected to be in the staggered conformation **A** shown below (most of the time). This conclusion is supported by the following points: (a) the coupling constants $J_{1,3}$ and $J_{2,3}$ measured for **4.7,** which were found to be 5.7 and 10.3 Hz, strongly suggest equatorial-axial and axial-axial steric relationships, as mentioned earlier, (b) the hydrogen bond formed between the ester carbonyl group and the carbinol hydroxy group. The formation of this bond and its supporting evidence were discussed in chapter 4 (pages 61-64), and (c) this conformation provides the maximum distance between the indole moiety and the aromatic carbinolamide and ethyl ester moieties. Even though the starting material is distereomerically pure, the exact configuration of the hydroxy group is unknown, the drawn structure for conformer A shows only one of the possible configurations (the hydroxy is beneath the plane). However, the opposite configuration is still viable regarding hydrogen bond formation with the ester carbonyl function. We are not suggesting that the drawn conformations are exactly the actual ones, rather they are good approximations, based on the available evidence.



Conformer **A** **4.7**

Treating **4.7** with catalytic amounts of hydrogen chloride in DCM is expected to lead to the formation of the corresponding *N*-acyliminium ion, with the concomitant loss of the hydrogen bond in conformer **A**. The generated ion can then take different conformations. **Figure 5.3** illustrates some stable possible conformers for the intermediate ion. The immediate conformer after acid treatment is expected to be **B**. However, the free rotation around the C-N bond

will allow the formation of **C**, **D** and **E** conformers. To minimise the repulsive forces between the bulky indole ring, the ethylester and *N*-acyliminium moieties, the proposed rotation of the C-N bond will be probably associated with conformational change of the central C-C bond from the staggered to the eclipsed forms, as the case in conformers **C** and **D**.

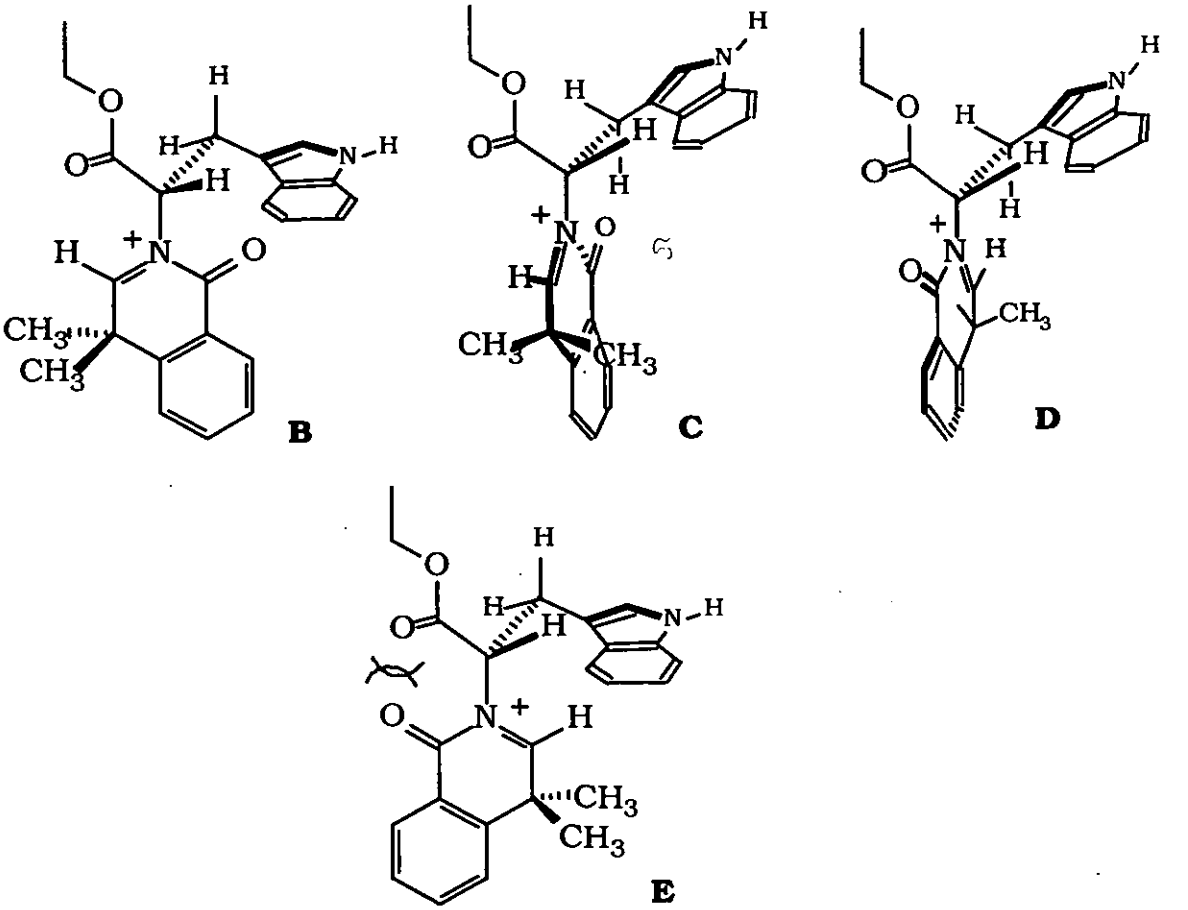
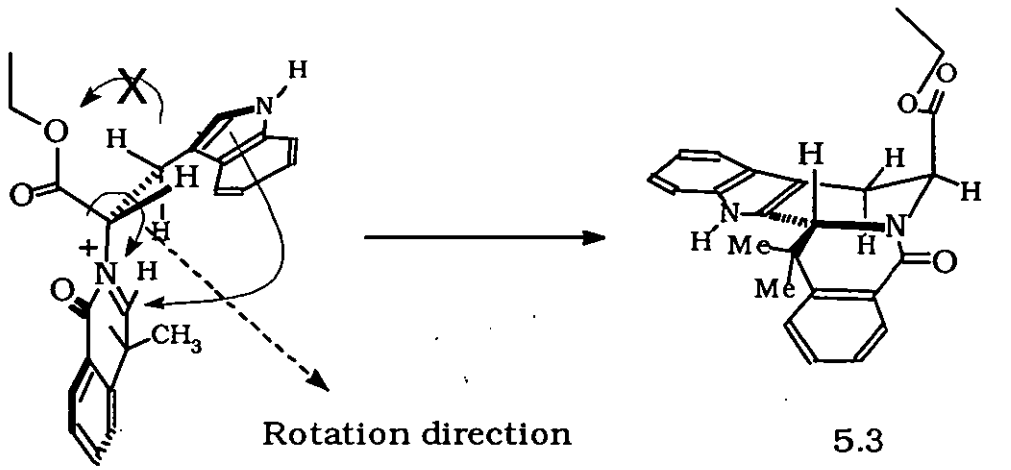


Figure 5.3

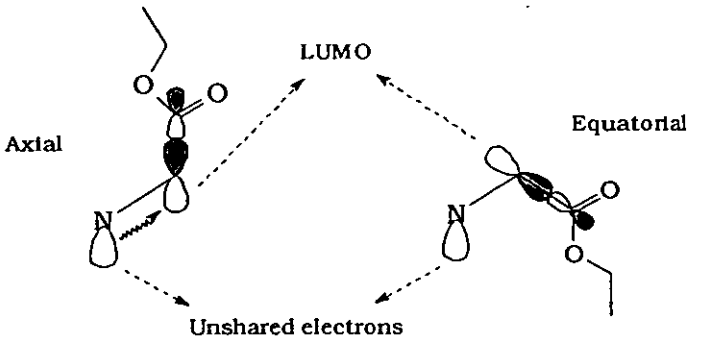
It is expected that **E** conformer will be unfavourable due to the repulsion between the ester and amide carbonyl groups, as illustrated in **Figure 5.3**. By inspecting molecular models of the intermediate ion, we concluded that **C** and **D**, in which the aromatic *N*-acyliminium moiety is aligned parallel with the central C-C bond, are relatively more stable than the other conformers, as they allow improved distances between various bulky moieties within the structure. However, **C** (and other closely related conformers) is fruitless regarding the cyclisation reaction, since the indole ring will be far from the *N*-acyliminium centre. Consequently, the remaining reasonable conformer is **D** (or other closely

related one) both stability wise and in its potential for cyclisation leading to **5.3**. The rotation around the central C-C bond in **D** conformer should be favoured in the opposite direction to the bulky ethyl ester moiety, which means that the indole ring should capture the *N*-acyliminium ion *trans* to the ester moiety, providing good explanation for the formation of **5.3** as the sole diastereomer in this reaction, as illustrated in **Scheme 5.9**.



Scheme 5.9

The axial conformation of the ethyl ester group is somewhat unexpected, since the anticipated conformation for this bulky moiety is the more sterically relaxed equatorial position. Inspection with molecular models shows that the equatorial option for the ethyl ester moiety, when compared to the axial one, is not associated with any significant increase in steric crowding in other parts of the molecule. Consequently, we propose that the axial conformation assumed by the ethyl ester moiety is due to stereoelectronic factors, namely the anomeric effect.[88] Trisubstituted nitrogen atoms are known to be excellent electron donors, for example they are better than oxygen.[89] On the other hand the ethyl ester group is an electron withdrawing moiety. Consequently, a stabilising two-electron interaction is expected between the unshared electron pair of the nitrogen and the antibonding orbital (LUMO) of the C-C bond connecting the ester group, as illustrated in the axial conformation in **Scheme 5.10**.



Scheme 5.10

The equatorial position does not allow proper alignment of the unshared nitrogen electron pair with the antibonding orbital of the relevant C-C bond, thus it disfavours the stabilising two-electron interaction. It remains to be mentioned that the relevant nitrogen is actually amidic, which means that the unshared pair of electrons are supposed to be involved, to some degree, in resonance forms with the amide carbonyl group. However, we assume that the amide carbonyl group is rendered less electron-deficient through resonance with the nearby aryl group, which increases the electron density on the amide nitrogen and improves its sp^3 character, thus allowing effective two-electron interaction as mentioned earlier. This assumption is supported by two pieces of evidence:

(a) The ^{13}C chemical shifts of the two carbonyl groups in various homo-phthalimides. The chemical shifts for the carbon atom **A** (**Figure 5.4**) range between 175.1-178.2 ppm, as previously illustrated in **Table 4.2**, while it ranges between 163.8-164.9 ppm for carbon atom **B**. This difference must be due to the conjugation of the carbonyl group **B** with the adjacent aromatic ring as both carbonyl groups are connected to the same nitrogen atom.

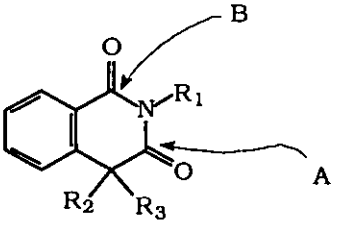


Figure 5.4

(b) Comparing the ^{13}C chemical shifts for the carbon atom **B** before and after reducing **A** (**Figure 5.4**) shows negligible difference, which clearly demonstrates the relative independence of the electron density on carbon **B** from that of the

demonstrates the relative independence of the electron density on carbon **B** from that of the nearby nitrogen, and further supports the assumption that **B** is involved in effective resonance with the aromatic ring leaving the amidic nitrogen with higher electron density. **Table 5.3** illustrates the ^{13}C chemical shifts for carbon **B** (**Figure 5.4**), in some randomly selected homophthalimide derivatives, both before and after reducing the carbonyl group at carbon **A** (**Figure 5.4**).

Table 5.3

	^{13}C chemical shifts for **B**	
Homo-phthalimide	Before Reduction	After Reduction
3.1	163.8	163.9
3.3	164.1	163.8
3.6	164.8	165.0 (164.9)*
3.12	165.0	163.4
3.13	164.5	163.8

* The chemical shift of **B** carbon atom in the minor diastereomer is in brackets.

In addition to the above, the ^{13}C chemical shift for carbon atom **B** within the cyclised products **5.2**, **5.1** and **5.3** (165.6, 163.3 and 165.7 ppm respectively) are close to their starting homophthalimides (164.6, 164.2 and 164.1 ppm, respectively), and the corresponding carbinolamides (161.9- in d_6 DMSO, 164.3 and 165.0 ppm, respectively), which further adds to the evidence on the assumption about the electron density on the amidic nitrogen. Similar anomeric interactions involving ester groups are reported in the literature, for example, the ester group in the dithiane shown in **Figure 5.5** has a clear preference for the axial position due to the anomeric effect.[90]

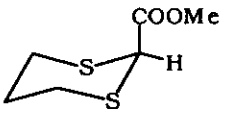


Figure 5.5

Shimizu *et al.*[91] generated the β-carboline derivative shown in **Figure 5.6**, and they proved the axial position of the methyl ester group through ^{1}H nmr

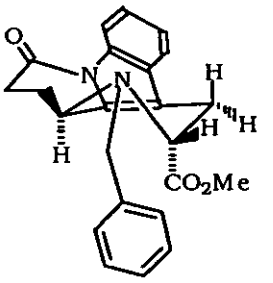
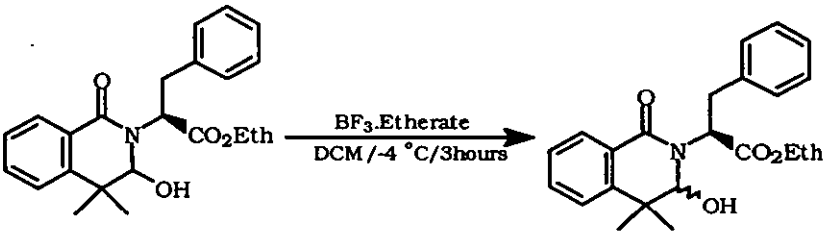


Figure 5.6

Our attempt to carry out the cyclisation reaction starting with the phenyl alanine-derived carbinolamide **4.6** led only to the epimerisation of the starting material. In this attempt, a single diastereomer of **4.6** was treated with boron trifluoride etherate in dry DCM. However, after workup and extraction, no cyclic product was detected in the crude reaction mixture, as judged from ^{1}H nmr spectroscopy. **Scheme 5.11** shows the relevant reaction conditions.

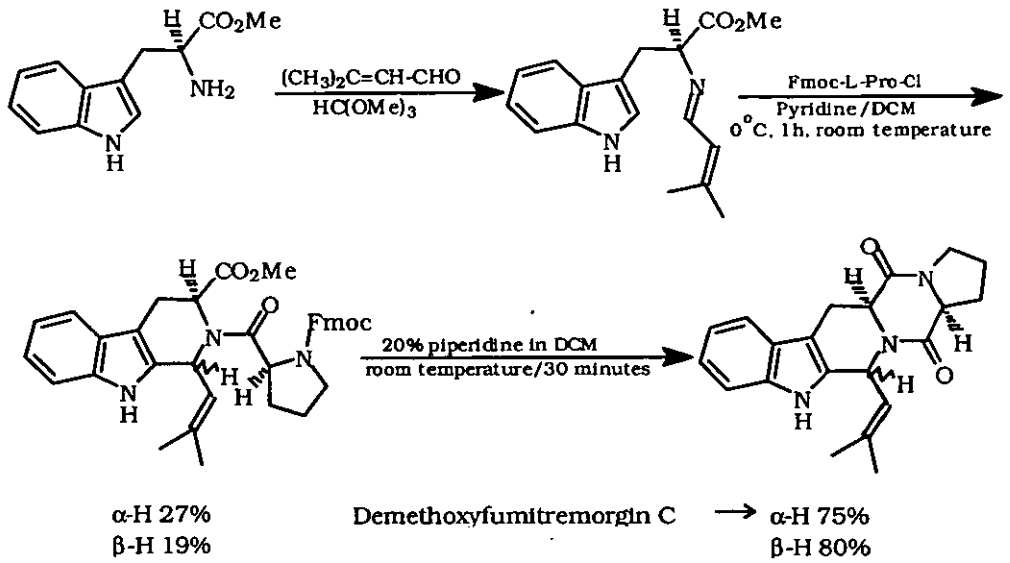


4.6 **Scheme 5.11**

This result clearly indicates the formation of the intermediate *N*-acyliminium ion, as epimerisation occurs only as a result of the formation of the planar cationic intermediate. The lack of cyclisation in this reaction is probably due to the weakly nucleophilic nature of the phenyl ring compared to the indole ring in the case of **4.7**.

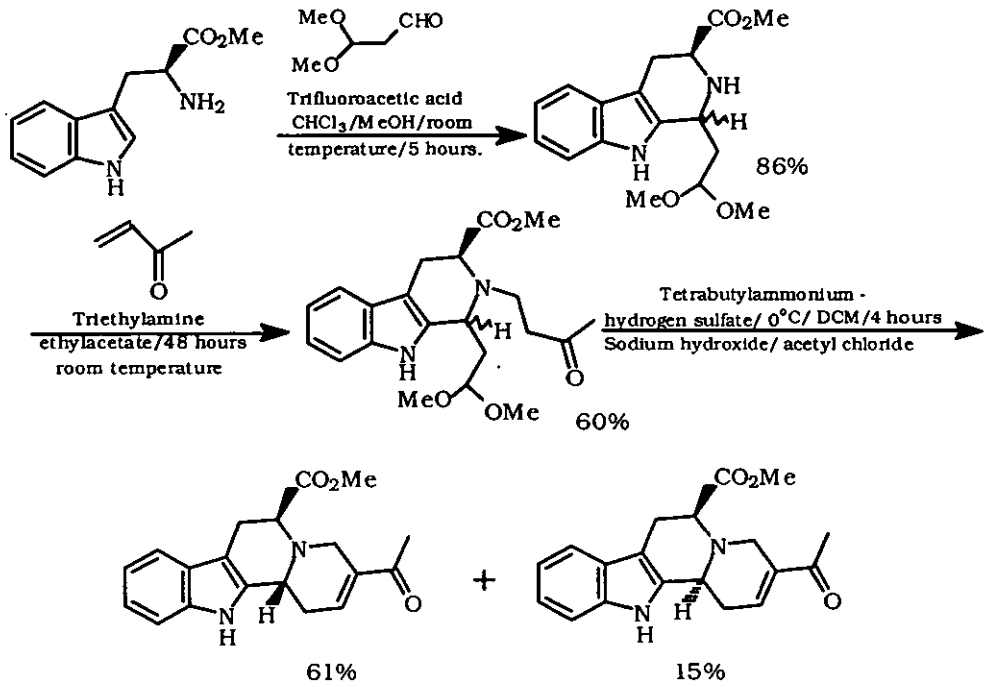
The use of tryptophane esters to affect 1,3-stereochemical induction, involving *N*-acyliminium ion intermediates (as in the reaction leading to **5.3**), is only rarely reported in the literature. These reports dealt mainly with *N*-acyliminium or iminium ions generated from imine-type starting materials. The following are recent examples in this area. Wang *et al.*[92] utilised the imine derived from L-tryptophane methyl ester and senecialdehyde to generate an *N*-acyliminium ion, which was employed in a Pictet-Spengler condensation, yielding a mixture of *cis*- and *trans*-tetrahydro-β-carbolines. This procedure was utilised in the concise

route to the cell cycle inhibitor demethoxyfumitremorgin C, as illustrated in **Scheme 5.12**.



Scheme 5.12

Peng *et al.*[93] synthesised enantiomerically pure indoloquinolizines from tryptophane methyl ester and by employing iminium ion intermediates. **Scheme 5.13** outlines their chemistry.



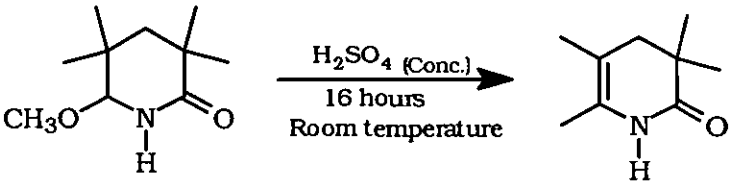
Scheme 5.13

The higher yield of the 1,3-*trans* product in Peng *et al.* chemistry shows similarity to our findings regarding **5.3**.

Other research groups have reported similar examples on related 1,3 - stereochemical induction and these include: De La Figuera *et al.*[94] who investigated 2-amino-3-oxohexahydro-indolizino(8,7-b)indole-5-carboxylate derivatives as new scaffolds for mimicking β-turn secondary structures in proteins, Shimizu *et al.*,[91] Ungemach *et al.*[95] and Konda *et al.*[96]contributed to this area.

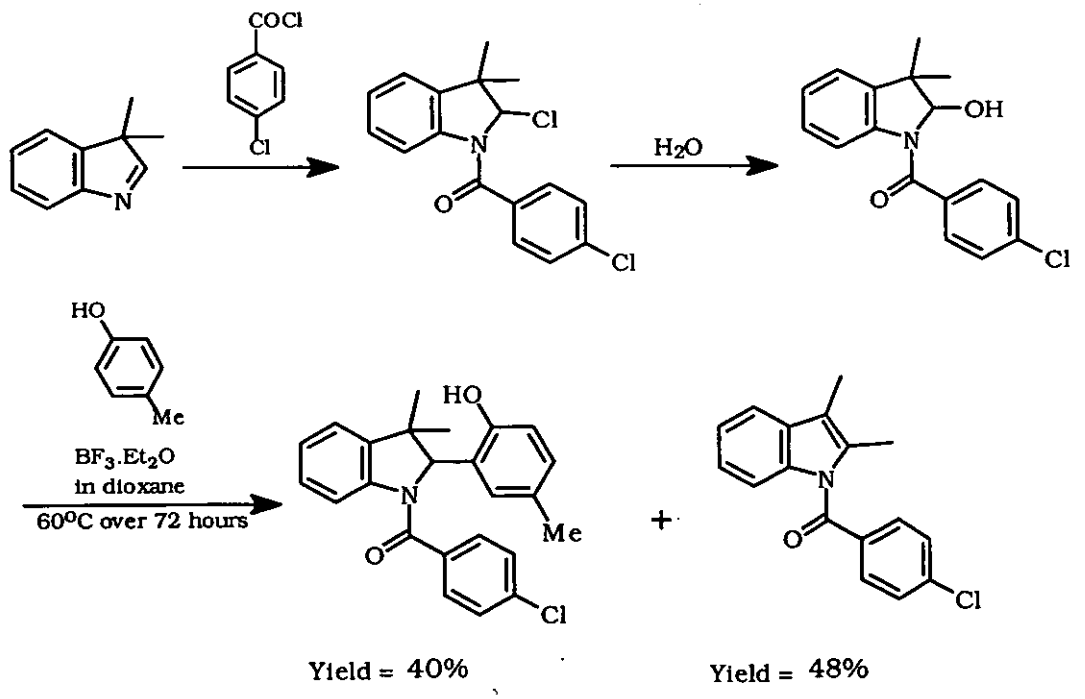
B- Competition between Aromatic Nucleophiles and a Migrating Alkyl group in Trapping *N*-Acyliminium ions.

Trapping iminium and *N*-acyliminium ions with 1,2-alkyl shifts[97] (Wagner-Meerwein type rearrangement reactions) are reported only rarely in the literature. The followings are literature examples in this area. Warshawsky *et al.*[98] showed that treatment of 3,3,5,5-tetramethyl-6-methoxy-2-piperidone with concentrated H_2SO_4, at room temperature and over 16 hours, led to the formation of 1,2,3,4-tetrahydro-3,3,5,6-tetramethyl-2-pyridone, as shown in **Scheme 5.14.**



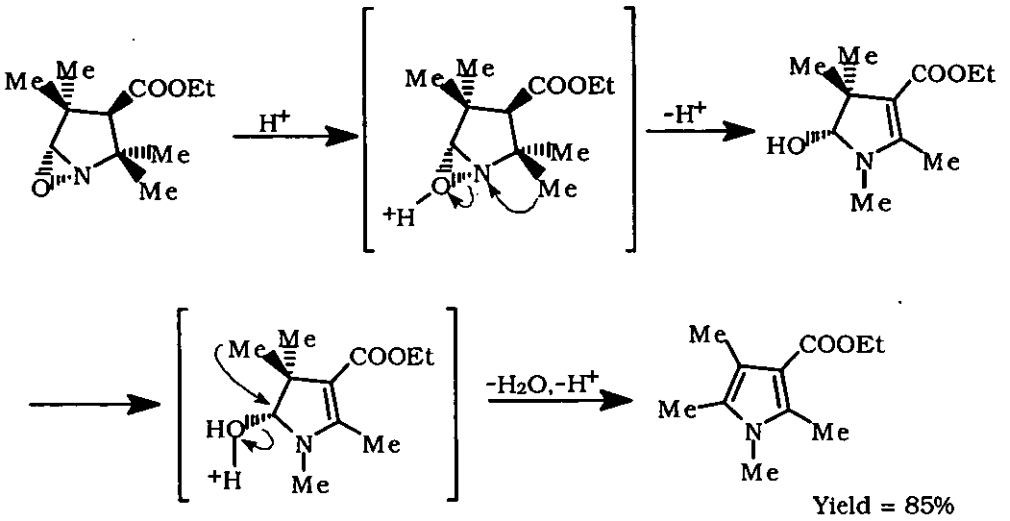
Scheme 5.14

In their work involving the coupling of 2-hydroxyindoline with arenes *via* an *N*-acyliminium ion intermediate, and using boron trifluoride etherate as a Lewis acid, Kitamura *et al.*[99] isolated the Wagner-Meerwein rearrangement product, 1-(4-chlorobenzoyl)-2,3-dimethylindole, as a side product. They also found that the weaker the aromatic nucleophile is, the higher the yield of the 1,2-shift product. **Scheme 5.15** illustrates one of their reactions.



Scheme 5.15

Finally, Dehnel *et al.*[100] found that in the presence of acids, such as HF in pyridine, 3-ethoxycarbonyl-6-oxa-1-azabicyclo[3.1.0]hexanes afforded substituted 3-ethoxycarbonylpyrroles. The second step in this reaction includes the capture of an iminium ion with a migrating alkyl group. **Scheme 5.16** illustrates one of the reactions.



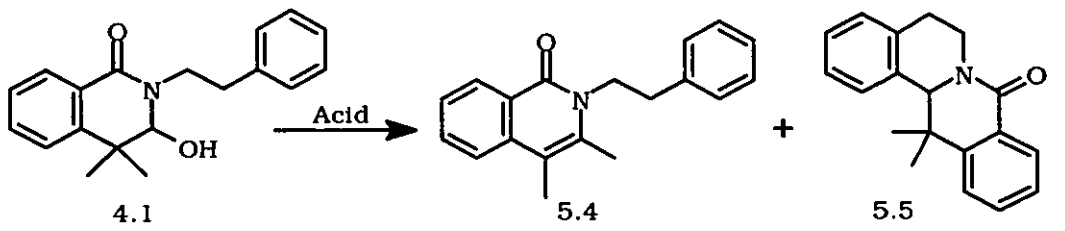
Scheme 5.16

In the research reported in this thesis we have explored the competition between a 1,2-alkyl shift and the intramolecular capture of aromatic nucleophiles,

involved in the neutralisation of the intermediate *N*-acyliminium ion. Different substrates were investigated. In each case, the two competing processes were compared under variable conditions of temperature, solvent, Lewis acid nature and concentration. The following subsections are classified according to the starting substrate.

i) The *N*-acyliminium ion generated from 3-hydroxy-4,4-dimethyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinlinone (4.1).

Treating the carbinolamide (**4.1**) with aluminium chloride or aluminium bromide yielded the 1,2-shift product **5.4** and the cyclisation product **5.5** in different ratios depending on the reaction temperature. The reaction is generally outlined in **Scheme 5.17**. **Table 5.4** shows the different reaction conditions and the corresponding product ratios.



4.1 5.4 5.5

Scheme 5.17

Table 5.4

No.	Reaction Temperature (°C)	Lewis Acid†	Solvent	Reaction Time (hours)	**5.4**†† %	**5.5** %
1	-5	$AlBr_3$	*o*-DCB	6	30	70
2	-5	$AlBr_3$	DCM	6	5	95
3	Ambient	$AlBr_3$	DCM	24	41	59
4	35	$AlBr_3$	DCM	24	44	56
5	180	$AlBr_3$	*o*-DCB	4	94	6
6	35	$AlCl_3$	DCM	24	25‡	9
7	35	$AlCl_3$	DCM	72	73	27
8	180	$AlCl_3$	*o*-DCB	4	93	7

† Quantity =1.5 mmol.

†† Ratios estimated from the average peak areas at 4.81 (s, 1H), 5.01 (m, 1H) and 8.15 (m, 1H) ppm for (**5.5**) compared to peak areas at 2.30 (s, 3H, CH_3), 4.31 (m, 2H) and 8.50 (m, 1H) ppm for (**5.4**) from the ^1H nmr spectra of crude products. Mass balance was maintained.

‡ Starting material accounts for 66 % (based on ^1H nmr).

The results in the above table clearly demonstrate the dependence of product ratios on reaction temperatures, for example, with $AlBr_3$ and in *o*-DCB, the ratio **5.5** to **5.4** changed from 70:30 at -5 °C (reaction no.1) to 6:94 at 180 °C (reaction no.5). A similar trend persists with DCM as the reaction solvent, for example the ratio **5.5** to **5.4** changed from 95:5 at -5 °C (in reaction no.2) to 56:44 at 35 °C (reaction no. 4). The poor solubility of $AlCl_3$ in DCM or *o*-DCB hindered any useful study a low temperature (-5 °C). However, similar temperature-dependent trend was noticed with $AlCl_3$ at higher temperatures, for example, **5.5** to **5.4** ratio changed from 27:73 at 35 °C (reaction 7) to 7:93 at 180 °C (reaction 8). These results strongly suggest that the sterically crowded tetracyclic isoquinolone **5.5** is the kinetically favoured product, while the flat aromatic isoquinolone **5.4** is the thermodynamically preferred one. This conclusion was further supported by global energy calculations conducted using SYBYL programme, which indicate that **5.4** is approximately 10 times more stable that **5.5**. Accordingly, the energy profile of this reaction (**Scheme 5.17**) is expected to be as in **Figure 5.7**.

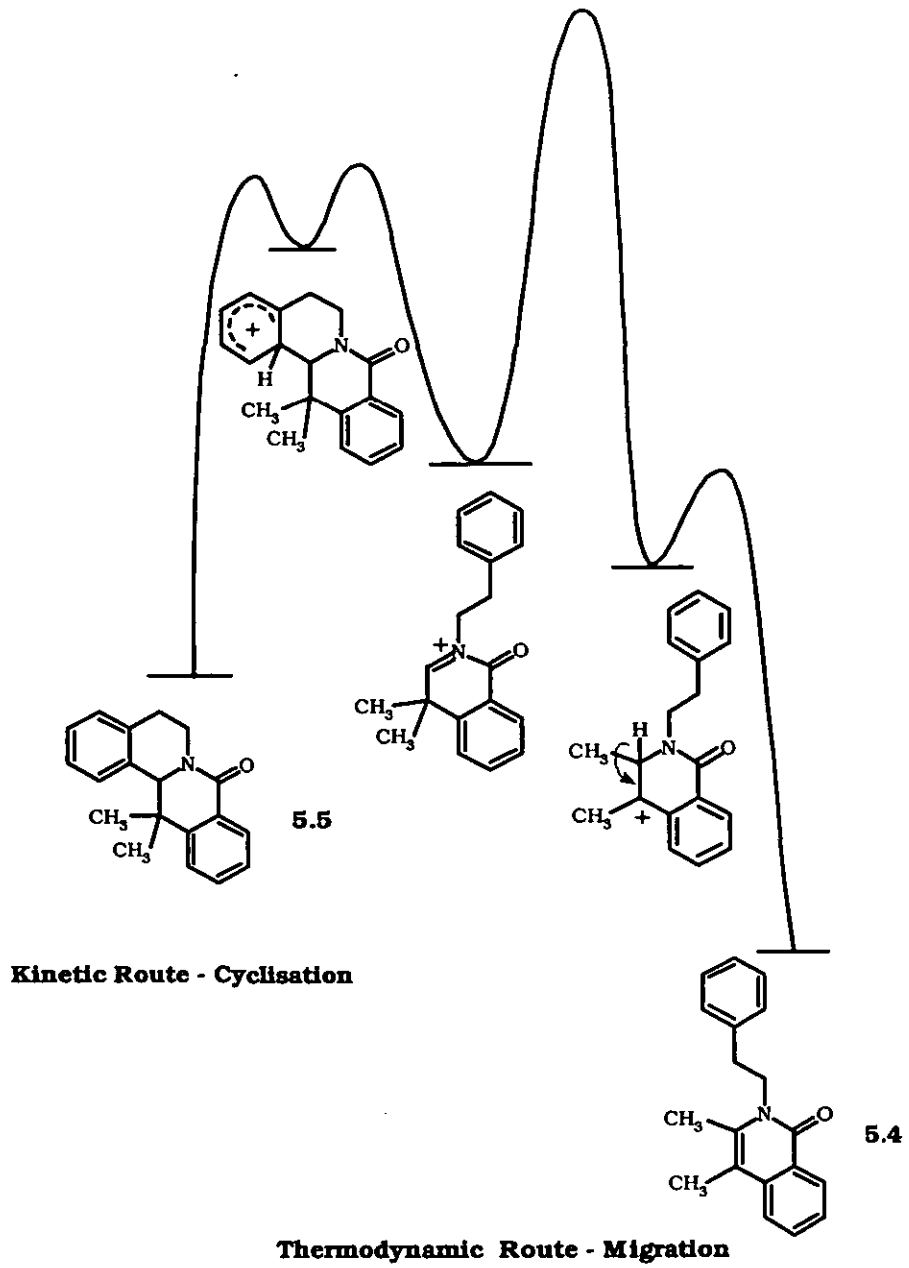
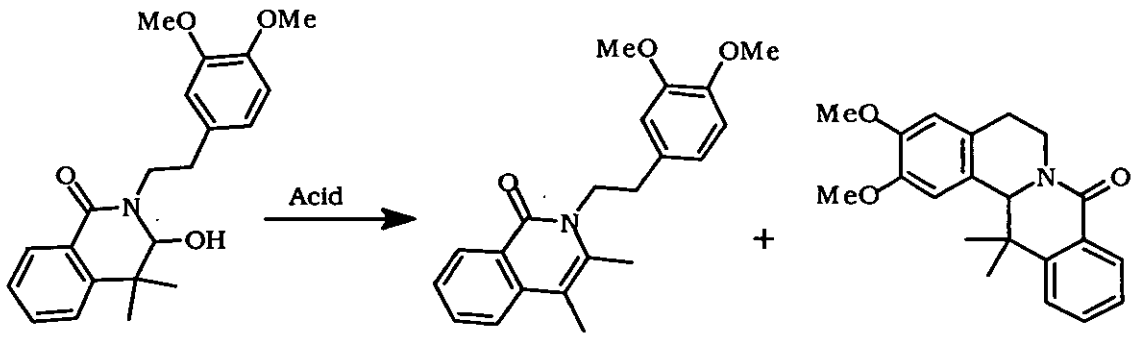


Figure 5.7

Presumably, the driving force behind the methyl migration is attributed to two factors: (a) the formation of a relatively stable benzylic cation, i.e. the intermediate species directly leading to **5.4** shown in **Figure 5.7**, (b) the aromatisation of the isoquinolone ring in the final product **5.4**. However, the energy barrier required for the migration reaction is higher than that needed for the cyclisation reaction as illustrated in **Figure 5.7**. To our best knowledge, there are no reported accounts on similar kinetic/thermodynamic-based

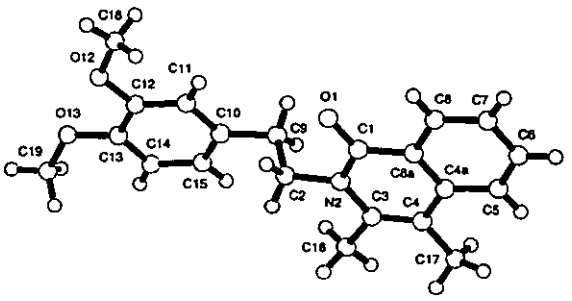
ii) **The *N*-acyliminium ion generated from 2-(3,4-dimethoxyphenethyl)-3-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone (4.2).**

The results of treating the carbinolamide **4.2** with aluminium chloride or bromide showed an opposite trend to that of **4.1**. **Table 5.5** shows the different reaction conditions and the corresponding product ratios, and **Scheme 5.18** outlines the general reaction.



4.2 5.6 5.7

Scheme 5.18



X-ray picture of 5.6

Table 5.5

No.	Reaction Temperature (°C)	Lewis Acid†	Lewis acid equivalents	Reaction Time (hours)	5.6†† %	5.7 %
1	-5	$AlBr_3$	1	2	42‡	0
2	-5	$AlBr_3$	3	2	100	0
3	Ambient	$AlBr_3$	1	24	20‡‡	72
4	Ambient	$AlBr_3$	3	24	100	0
5	180	$AlBr_3$	1	0.5	22	78
6	Ambient	$AlCl_3$	1	24	21+	67
7	Ambient	$AlCl_3$	3	24	29	71

† All the reactions were conducted in *o*-DCB.
†† Ratios estimated from the average peak areas at 4.75 (s, 1H), 5.00 (m, 1H) and 8.13 (m, 1H) ppm for (**5.7**) compared to peak areas at 2.30 (s, 3H, CH_3), 4.31 (m, 2H) and 8.50 (m, 1H) ppm for (**5.6**) from ^1H nmr spectrums of crude products. Mass balance was maintained.
‡ Starting material accounts for 58 % (based on ^1H nmr).
‡‡ Starting material accounts for 8 % (based on ^1H nmr).
+ Starting material accounts for 12 % (based on ^1H nmr).

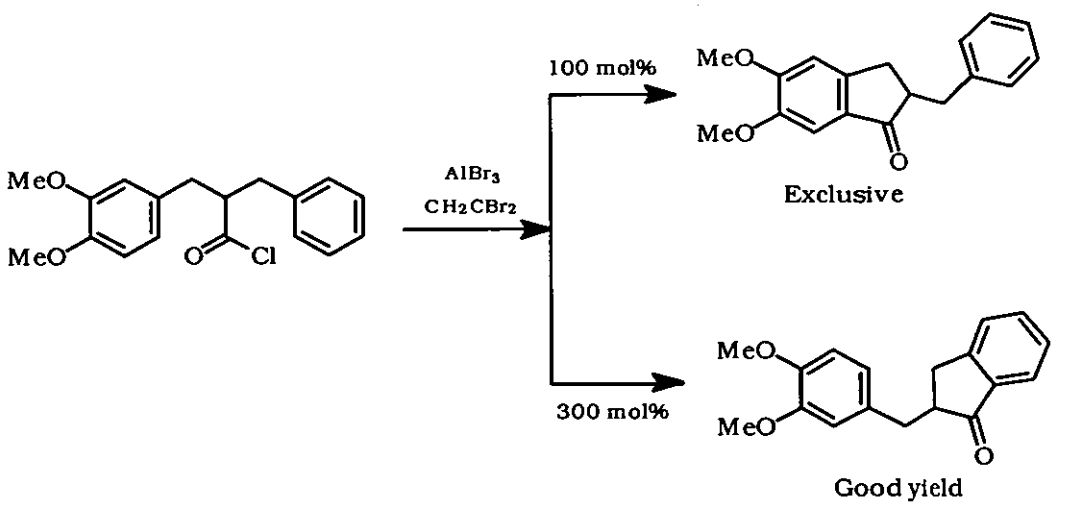
Form the above table, it is clear that the electron releasing effect of the dimethoxy groups led to improved cyclisation yields, i.e. **5.7**, both at room temperature and at 180 °C, provided that only one equivalent of $AlBr_3$ is present (reactions 3 and 5). However, migration was the preferred route, i.e. **5.6**, when the reaction was carried out at low temperature (-5 °C) or with three-fold excess of $AlBr_3$ (reactions 1,2 and 4). This behaviour is most probably attributed to aluminium complexation with oxygen atoms within the aromatic dimethoxy groups. Such complexation will undoubtedly reduce the nucleophilicity of the aromatic ring due to the following reasons: (a) it ties up the pair of unshared electrons on the oxygen, which are otherwise available for donation to the aromatic ring, this leaves the electron-withdrawing effect of oxygen to be the predominant electronic factor. (b) It generates a partial positive charge on the oxygen atom, the value of which is dependent on the relative strength of the coordination bond between aluminium and oxygen atoms. The inactivation of

the aromatic ring nucleophile leaves methyl migration as the only remaining alternative to capture the cationic intermediate.

The proposed coordination bond seems to be relatively weak, since at moderately higher reaction temperatures (room temperature or 180 °C), cyclisation was the predominant reaction, and higher ratios of **5.7** were observed. On the other hand, the lower the temperature, the more stable the complex will be, hence the higher the fraction of aluminium-coordinated molecules within the molecular population, leading to higher **5.6** ratios. Similarly, increasing the abundance of aluminium within the reaction mixture, by increasing the number of $AlBr_3$ equivalents (reactions 2 and 4), will increase the fraction of aluminium-coordinated starting material molecules and thus increase the migration yield.

Cyclisation was the preferred route with aluminium chloride, regardless of its quantity in the reaction mixture (reactions 6 and 7). This result is probably due to the poor solubility of this reagent in *o*-DCB, which leads to reduced complexation with the methoxy functions, and hence, cyclisation will be promoted by the activating effect of the methoxy groups.

Buckley *et al.*[101] illustrated the dependence of the acylation of alkyl aryl ethers on the stoicheiometry of the Friedel-Crafts catalyst. They found that the acylation reaction of oxygenated aromatic rings was completely arrested with large molar excesses of the catalyst. They stated that the most likely explanation for these effects is a total reversal of the electron-donating ability of an aryl ether oxygen in the presence of excess Lewis acid. This results from the essentially complete complexing of oxygen lone pair with the Lewis acid in solution. When this Lewis acid-aromatic complexing was prevented by the steric bulk of an attached highly branched group, the greater electron density and greater reactivity of the oxygenated aromatic nucleus is restored. **Scheme 5.19** illustrates one of the reactions conducted by Buckley *et al.* to support their assumption.

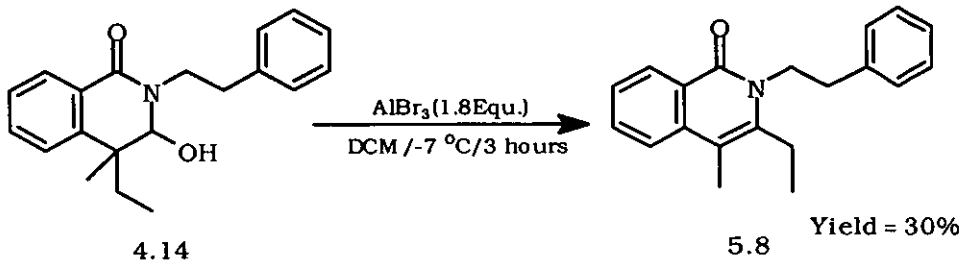


Scheme 5.19

According to our best knowledge, the work conducted by Buckley *et al.* is the only published account regarding the effect of Lewis acid stoicheiometry on the acylation yields of oxygenated aromatic rings.

iii) The *N*-acyliminium ion generated from 4-ethyl-3-hydroxy-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone (4.14).

In an attempt to cyclise the carbinolamide **4.14**, it was treated with aluminium bromide under the optimum cyclisation conditions, which were determined from the previously discussed experimentation with **4.1** (**Table 5.4**). However, the reaction yielded the migration derivative **5.8**, in 30% yield together with 25% remaining staring material. No cyclisation product was detected. The reaction is illustrated in **Scheme 5.20**.



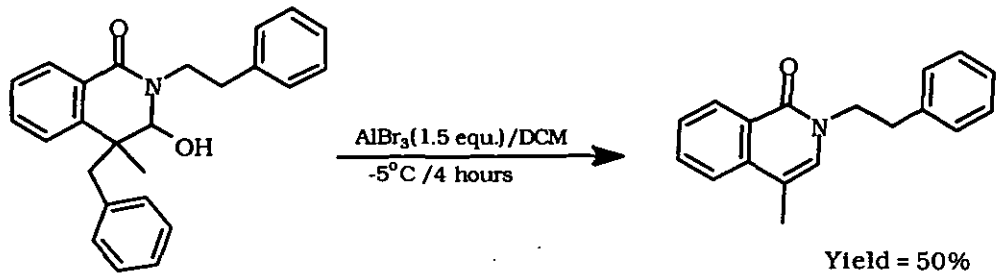
4.14 5.8

Scheme 5.20

The absence of any cyclisation product is probably due to either the ethyl group higher migratory aptitude compared to methyl group,[102] or the increased steric bulk around the *N*-acyliminium ion (before migration), or both factors together.

iv) The *N*-acyliminium ion generated from 4-benzyl-3-hydroxy-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone (4.15).

In an attempt to evaluate the effect of benzyl group substitution at position 4 on the cyclisation product, the carbinolamide **4.15** was treated with $AlBr_3$ in DCM at -5 °C. However, only the isoquinolone **5.9** was isolated in 50 % yield and without detecting any cyclisation products both in the crude reaction mixture and after purification. **Scheme 5.21** shows the reaction.

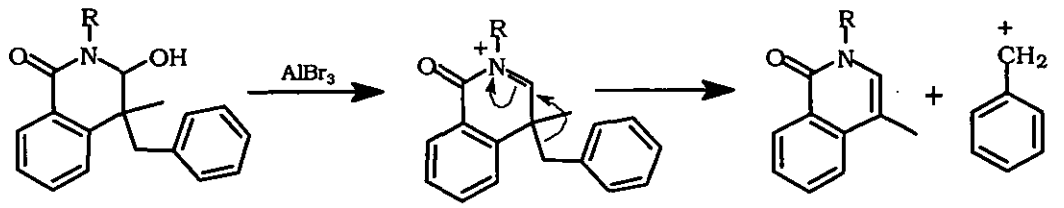


4.15 5.9

Scheme 5.21

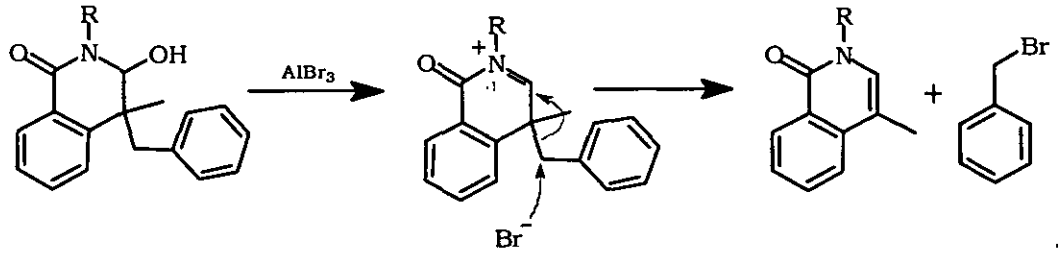
Benzyl group elimination could take place *via* two mechanisms:

A- Through forming stable benzyl cation, as shown in **Scheme 5.22.**



Scheme 5.22

B- Through bromide ion S_N2 attack on the benzylic methylene carbon as in **Scheme 5.23.**



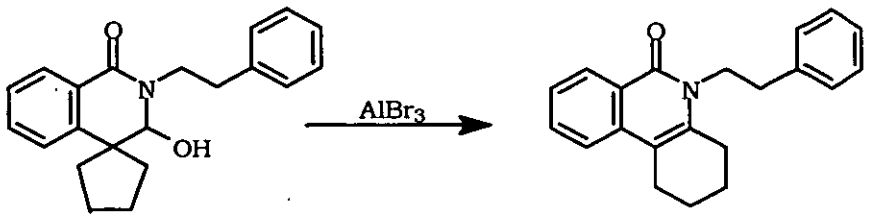
Scheme 5.23

We favour the first mechanism, since the benzylic cation is undoubtedly more stable than the *N*-acyliminium ion, justifying the relatively rapid loss of the benzyl group (i.e. quicker than cyclisation). The absence of any cyclisation product is

expected to be due to either the relatively rapid benzyl elimination process, or the increased steric bulk around the *N*-acyliminium ion (before benzyl elimination), or both factors together.

v) The *N*-acyliminium ion generated from 3-hydroxy-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolin-one-4-spiro-cyclopentane (4.10).

The final attempt to study the competing cyclisation/migration processes was conducted with **4.10**. Two reactions were carried out: (a) under optimum cyclisation conditions, and (b) under optimum migration conditions. **Scheme 5.24** outlines the two reactions and **Table 5.6** shows the reaction conditions and the corresponding product yields.



4.10 5.10

Scheme 5.24

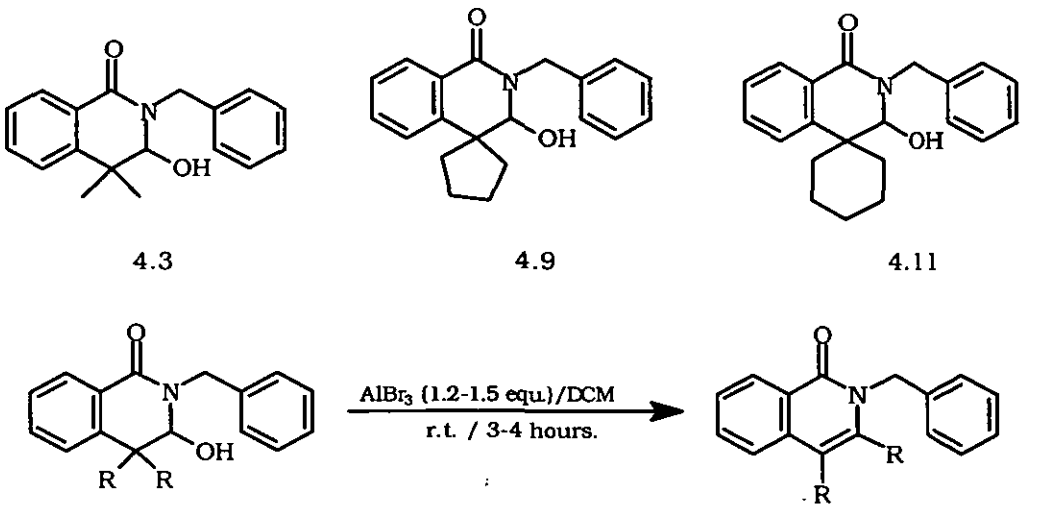
Table 5.6

Reaction Temperature (°C)	$AlBr_3$ equivalents	Solvent	Reaction Time (hours)	**5.10** Yield %
150	1.5	o-DCB	2	96
-7	1.5	DCM	4	80

As illustrated above, the only isolated product from both reactions is the tetrahydrophenanthridinone **5.10**. This result clearly indicate relative ease by which the 5-membered spirocyclic ring undergoes ring expansion to the 6-membered one. No cyclisation product was detected.

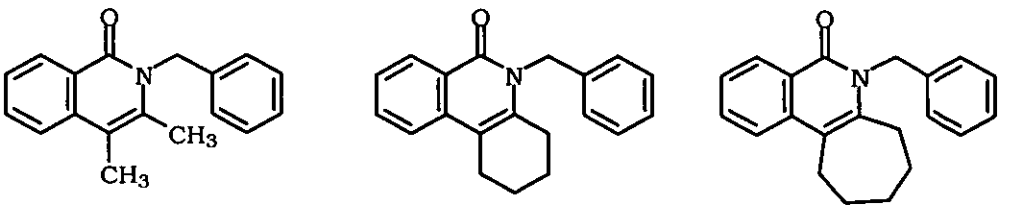
C- *N*-Acyliminium ions Trapping by Migrating Alkyl Groups.

Inorder to investigate the previously mentioned 1,2-alkyl shift under relatively mild conditions and in the absence of any potential cyclisation, the carbinolamides **4.3**, **4.9** and **4.11** were treated with $AlBr_3$ (1.2-1.5 equivalents) at room temperature. The general reaction conditions are illustrated in **Scheme 5.25**.



4.3 4.9 4.11

Scheme 5.25

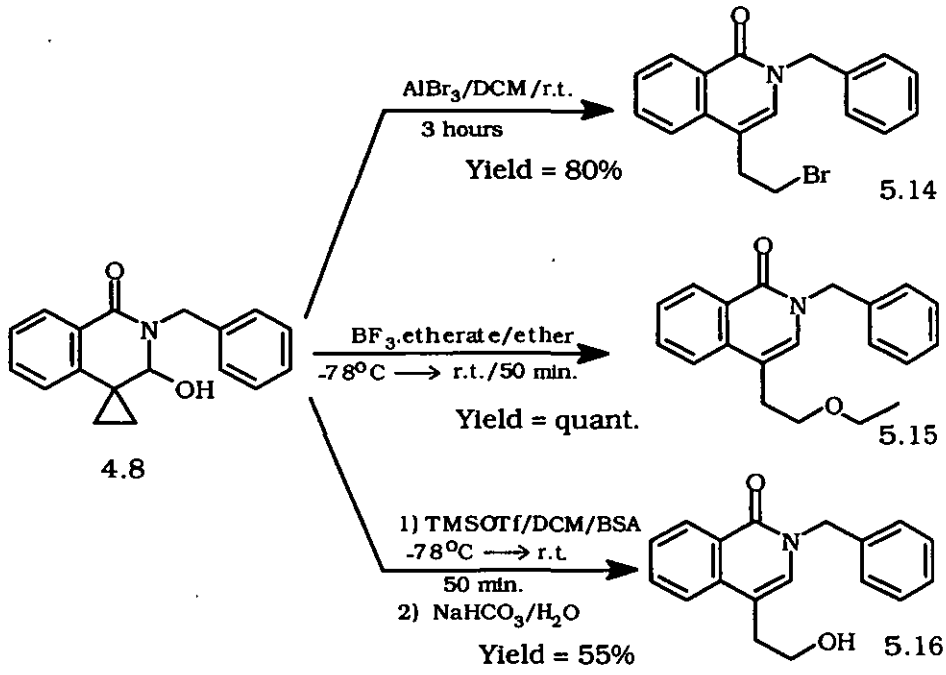


5.11 (Yield = 19%) 5.12 (Yield = 77%) 5.13 (Yield = 53%)

From the experiments discussed in the previous section, one expects the isoquinolones **5.11**, **5.12** and **5.13** will be generated in higher yields if the reactions were conducted at higher temperatures. The choice of the *N*-benzyl substitution has two aims: (a) to avoid the competing cyclisation reaction, which can take place with longer aryl alkyl chains, and (b) the relative ease by which the benzyl group can be removed providing a concise route to isoquinolones and tetrahydrophenanthridinones.[9] These two classes of compounds were reported to have interesting biological activities, which will be discussed later in more detail.

D- *N*-Acyliminium ions Trapping by Cyclopropane Ring Opening.

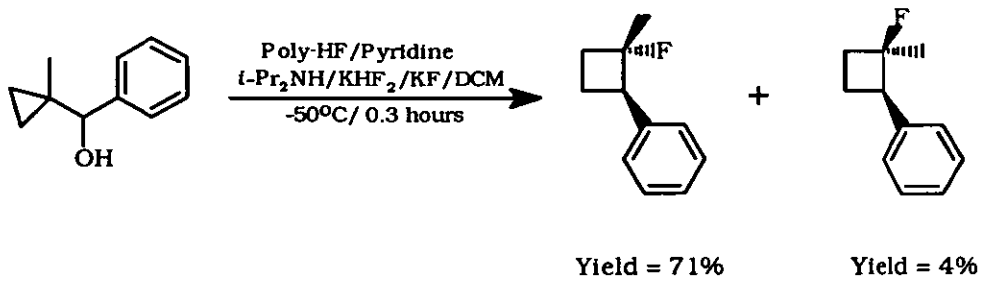
Treating 2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spirocyclopropane **4.8** with three Lewis acids led only to cyclopropane ring-opened products. **Scheme 5.26** illustrates the three reactions and the corresponding products.



Scheme 5.26

The following are important points for discussion regarding the reactions in **Scheme 5.26.**

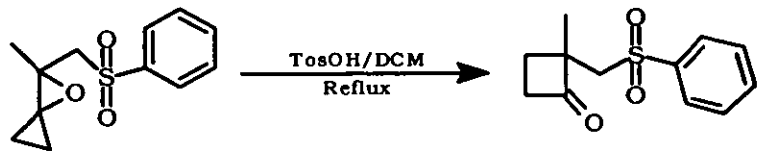
1. None of the above reactions yielded any detectable migration product, i.e. the cyclobutane derivative, despite the fact that similar reactions, involving cyclopropane to cyclobutane ring-expansion, are frequently reported in the literature. For example, Kanemoto *et al.*[103] reported the formation of the fluorinated cyclobutane by treating the hydroxycyclopropyl compound with poly-hydrogenfluoride as shown in **Scheme 5.27**.



Yield = 71% Yield = 4%

Scheme 5.27

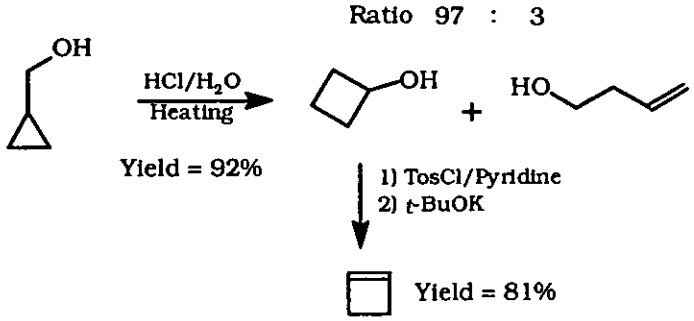
In another example, Bernard *et al.*[104] reported cyclopropane ring-expansion coupled with acid-induced epoxide-ring opening, as shown in **Scheme 5.28**.



Yield = 80%

Scheme 5.28

One of the clear examples that shows the higher tendency of cyclopropyl-methanol to expand to cyclobutanol, under acidic conditions, was illustrated by Fadel *et al.*,[105] when they showed that cyclopropylmethanol ring-expansion to cyclobutanol was the basis of an efficient cyclobutene synthesis. **Scheme 5.29** shows their reaction.

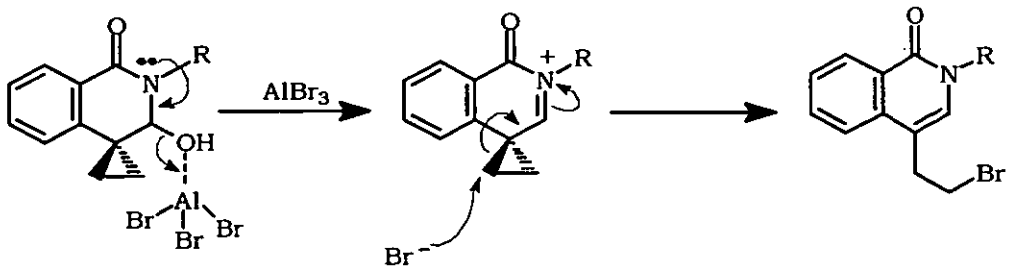


Scheme 5.29

Presumably, in our case (**Scheme 5.26**) the relative ease by which the cyclopropane ring is cleaved is due to the aromatisation of the isoquinolone ring system in the products.

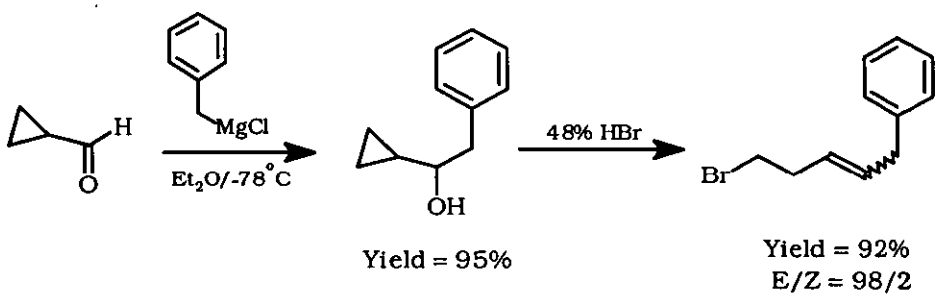
2. The mechanism by which cyclopropane-ring opening takes place is expected to be as in the following:

A) In the case of the bromine containing product **5.14**, the expected mechanism is illustrated in **Scheme 5.30**.



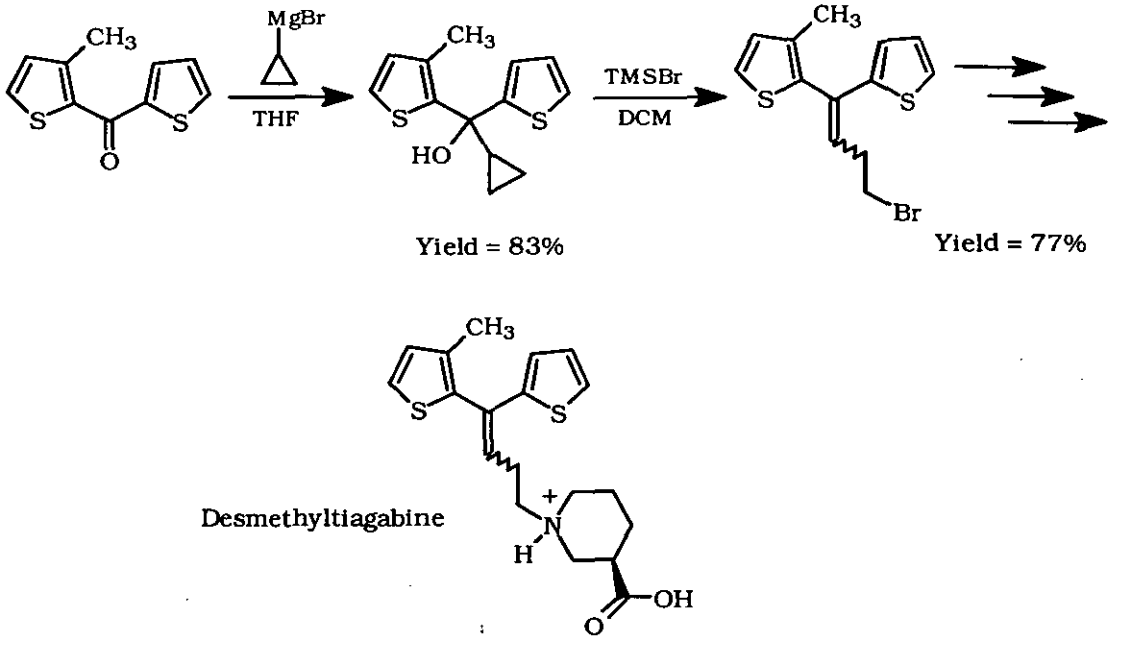
Scheme 5.30

Similar examples of bromide induced cyclopropane ring-opening have been reported in the literature, for example, Ferreri *et al.*[106] reported a facile entry to secondary cyclopropylcarbinols from cyclopropanecarboxaldehyde, the products were further used to generate (*E*)-homoallylic bromides. One of their reactions is illustrated in **Scheme 5.31**.



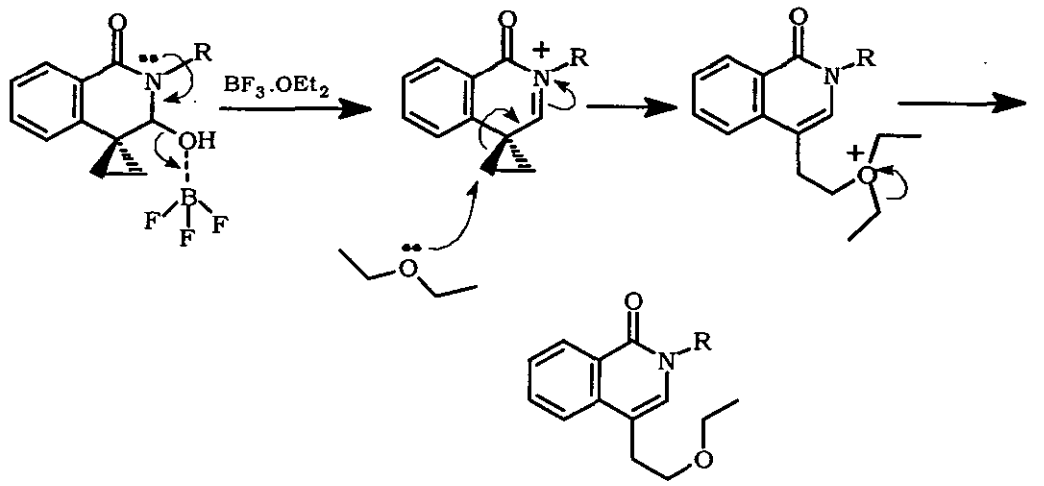
Scheme 5.31

Chorghade *et al.*[107] developed a versatile synthesis for the preparation of the potent anti-convulsant desmethyltiagabine in excellent yields. The key steps in the synthesis were Grignard reaction followed by ring opening with simultaneous dehydration and bromination of a hydroxymethyl cyclopropane with bromotrimethylsilane. **Scheme 5.32** shows the mentioned key steps in the synthesis.



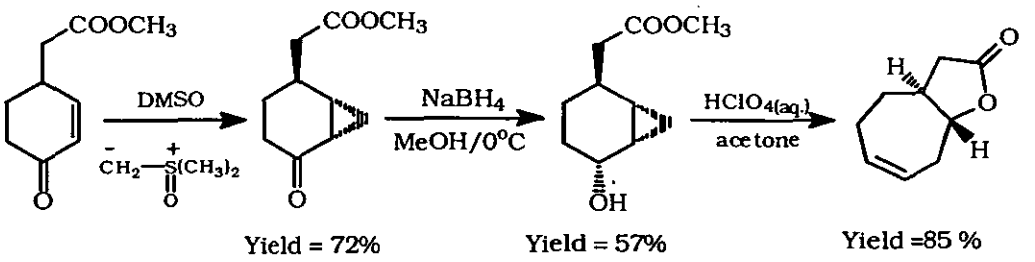
Scheme 5.32

B) The mechanism leading to the formation of the ethylether **5.15** is expected to take place as in **Scheme 5.33**.



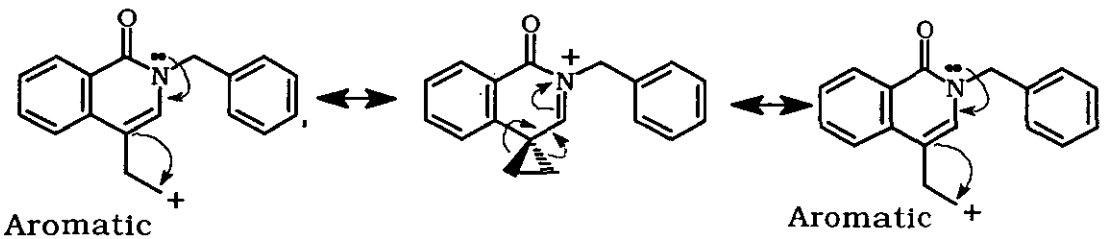
Scheme 5.33

Similar examples of cyclopropane ring-opening associated with capture of dialkyl substituted oxygen nucleophiles have been reported in the literature, for example, Marshall *et al.* [108] reported the intramolecular capture of methyl ester oxygen in the process of cyclopropane ring opening as illustrated in **Scheme 5.34**.



Scheme 5.34

C) Before considering the mechanism leading to the hydroxy isoquinolone **5.16**, it is important to mention two points: (a) BSA (*N,O*-bistrimethylsilyl acetamide), which was added (4 equivalents) as a proton scavenger to the reaction mixture (5-10 minutes before introducing 2 equivalents of TMSOTf), is known to be rapid silylating agent for hydroxy groups,[56, 115] thus it is expected that at least a fraction of the starting material (compound **4.8** in **Scheme 5.26**), is silylated at the free hydroxy group before the introduction of TMSOTf. (b) After reaction workup, *ca.* 20% of the starting material was retrieved from the reaction mixture suggesting good stability for the intermediate *N*-acyliminium ion, particularly in the absence of any effective nucleophile. The improved stability of the *N*-acyliminium ion is expected to be due to two factors (1) hyperconjugation involving the adjacent cyclopropane ring, and (2) the aromatisation of the isoquinolone ring system in the cyclopropane ring-opened canonical forms as in **Scheme 5.35**.

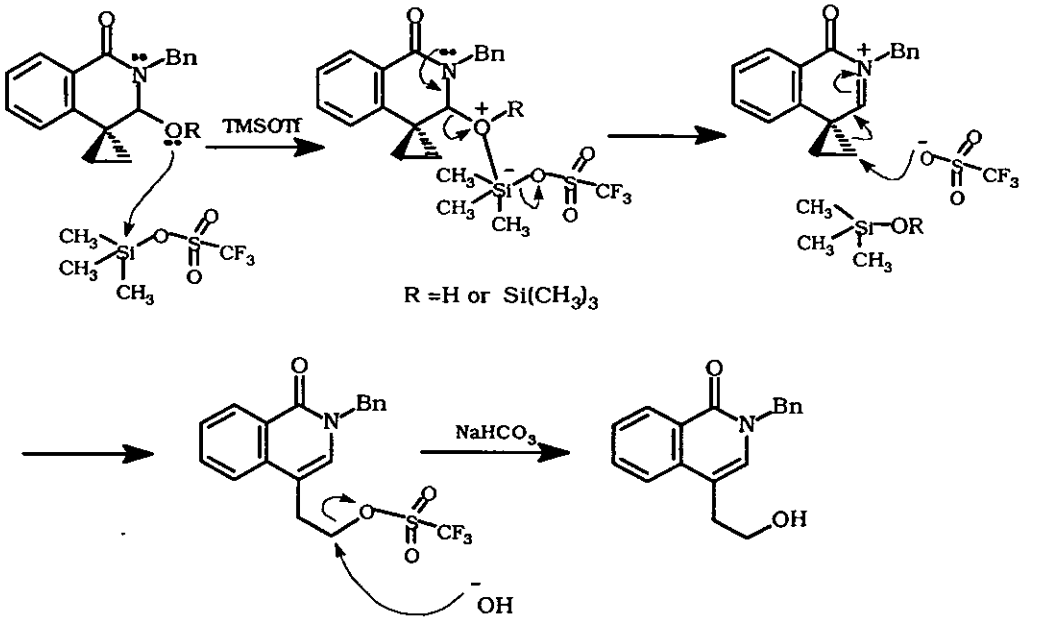


Scheme 5.35

The improved stability of cyclopropylmethyl carbocations is known and has been discussed in the literature.[78]

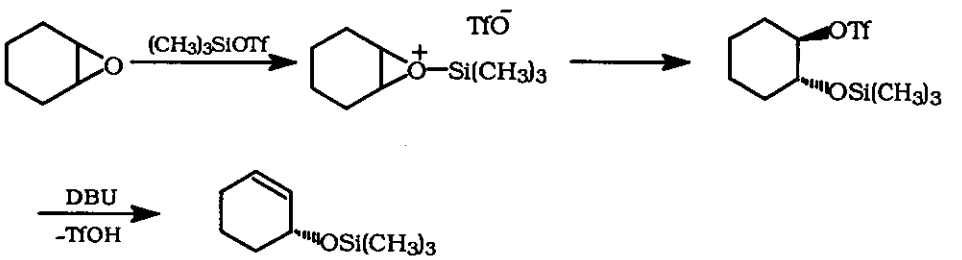
Formation of the hydroxyisoquinolone derivative **5.16** can take place *via* two possible mechanisms:

1- Cyclopropane ring-opening coupled with triflate capture as in **Scheme 5.36**.



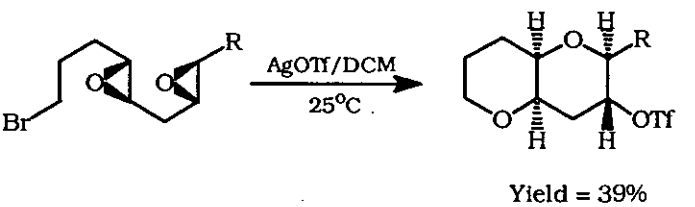
Scheme 5.36

Despite the poor nucleophilicity of triflate ion and its nature as a good leaving group, it has been reported in the literature to be captured by carbocationic centres, albeit rarely. For example, Murata *et al.*[109] reported triflate capture in association with TMSOTf-induced epoxide ring opening as in **Scheme 5.37**.



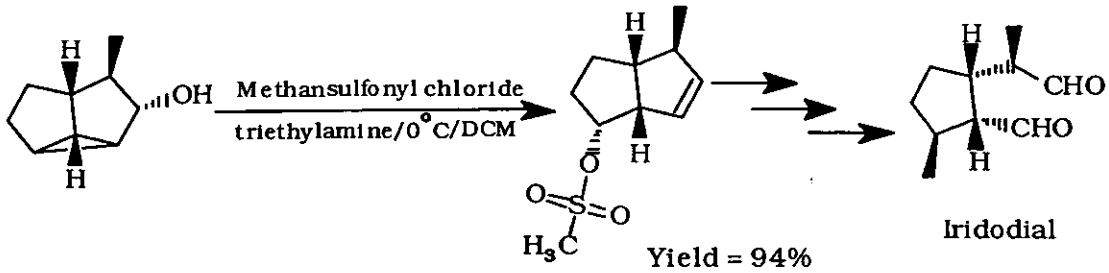
Scheme 5.37

In another example, Hayashi *et al.*[110] reported one-pot successive ring expansion reactions of 1-bromo-9-*t*-butyldiphenylsilyloxy-4,5,7,8-diepoxynonanes. In the course of these reactions, triflate was captured by the cationic intermediates, one of these reactions is shown in **Scheme 5.38**.



Scheme 5.38

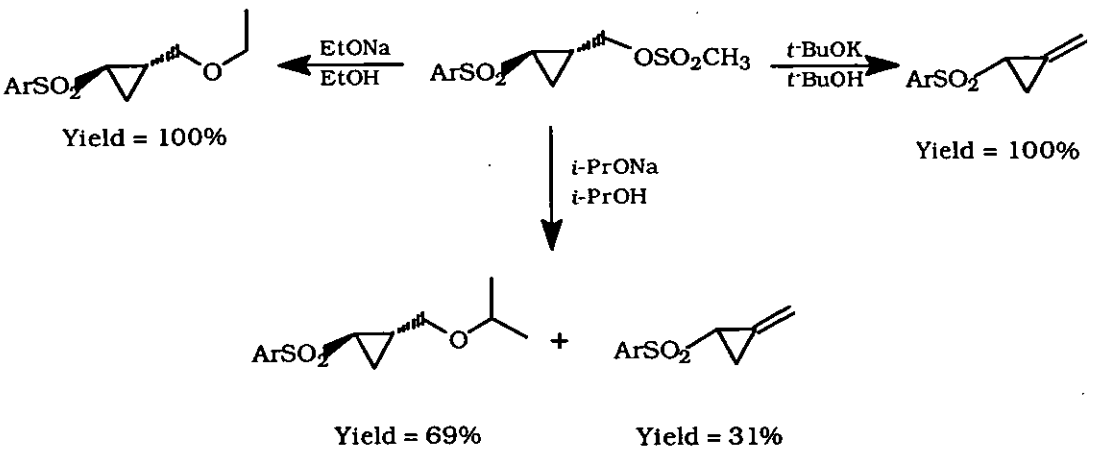
Ritterskamp *et al.*[111] reported the capture of mesylate group in association with cyclopropane ring-opening. This step was utilised in the total synthesis of iridodial, a biologically significant compound, produced in some insects. **Scheme 5.39** shows the cyclopropane ring-opening step.



Scheme 5.39

Earlier examples on the reactivity of cyclopropane-ring system and its utilisation in organic synthesis are sufficiently reviewed in the literature.[112] These examples support the suggested triflate nucleophilic attack on the cyclopropyl group, as in the proposed mechanism shown in **Scheme 5.36**.

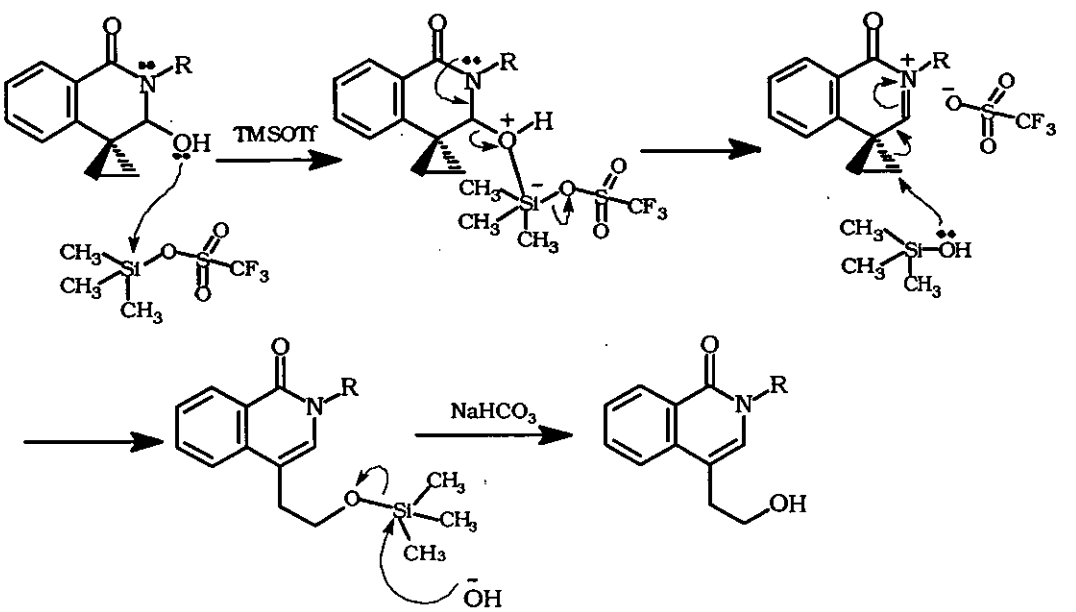
Other literature examples support the suggested conversion of the labile triflate intermediate to the hydroxy end-product (**5.16**) *via* water molecule or hydroxide ion nucleophilic substitution, as in **Scheme 5.36**. The work reported by Roberts *et al.*[113] on cyclopropylmethyl methanesulfonate illustrates the effect of the nucleophile nature on elimination/nucleophilic substitution ratio. **Scheme 5.40** shows the products and their corresponding yields resulting from treating cyclopropylmethyl methanesulfonate with: (a) sodium ethoxide in ethanol (most nucleophilic), (b) sodium isopropoxide in isopropanol (medium nucleophilicity and basicity) and (c) potassium *t*-butoxide in *t*-butanol (most basic).



Scheme 5.40

In another example, Huang *et al.*[114] converted 5′-*O*-tosylthymidine to the hydroxy analogue by treatment with sodium bicarbonate.

2- The second potential mechanism, towards forming **5.16**, is a cyclopropane ring-opening coupled with trimethylsilanol capture as in **Scheme 5.41**.

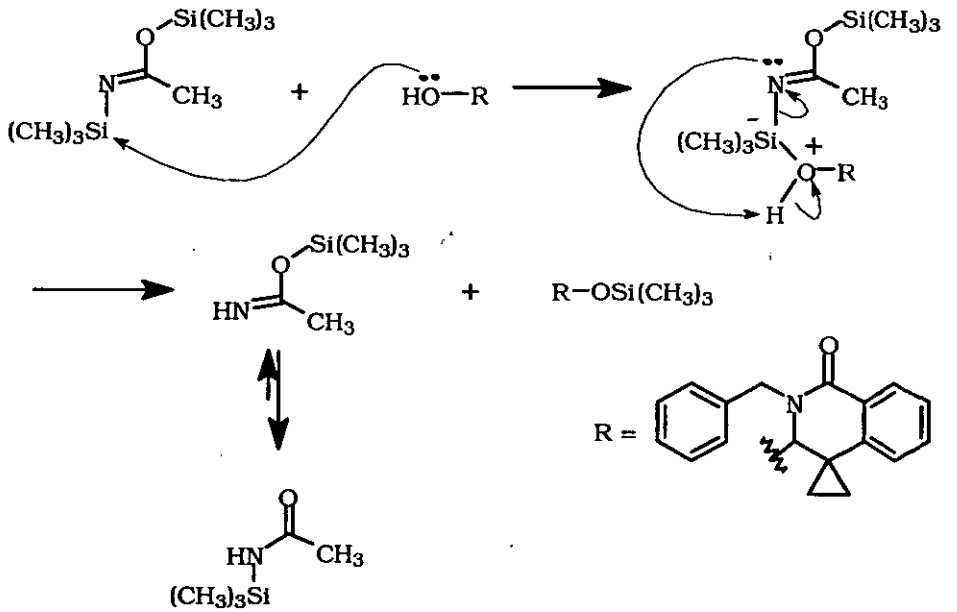


Scheme 5.41

However, the reaction is less likely to take place *via* this mechanism for the following reasons:

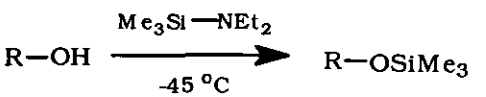
1) The presence of BSA in the reaction mixture is expected to reduce the possibility of this mechanism through two factors:

(a) It will silylate the free hydroxy group in at least a fraction of the starting material **4.8** molecules, as in **Scheme 5.42**.



Scheme 5.42

In this suggested silylation mechanism, the proposed nucleophilic attack of the hydroxy group on the nitrogen-bonded silicon is supported by the following points: (a) the relatively strong Si-O bond,[51] (b) silicon is known to be oxophilic rather than being azaphilic,[115] and (c) the previously reported use of *N*-trimethylsilyldiethylamine (TMSDEA) as a reactive reagent for preparing trimethylsilylethers from hydroxy compounds,[116] as in **Scheme 5.43**.

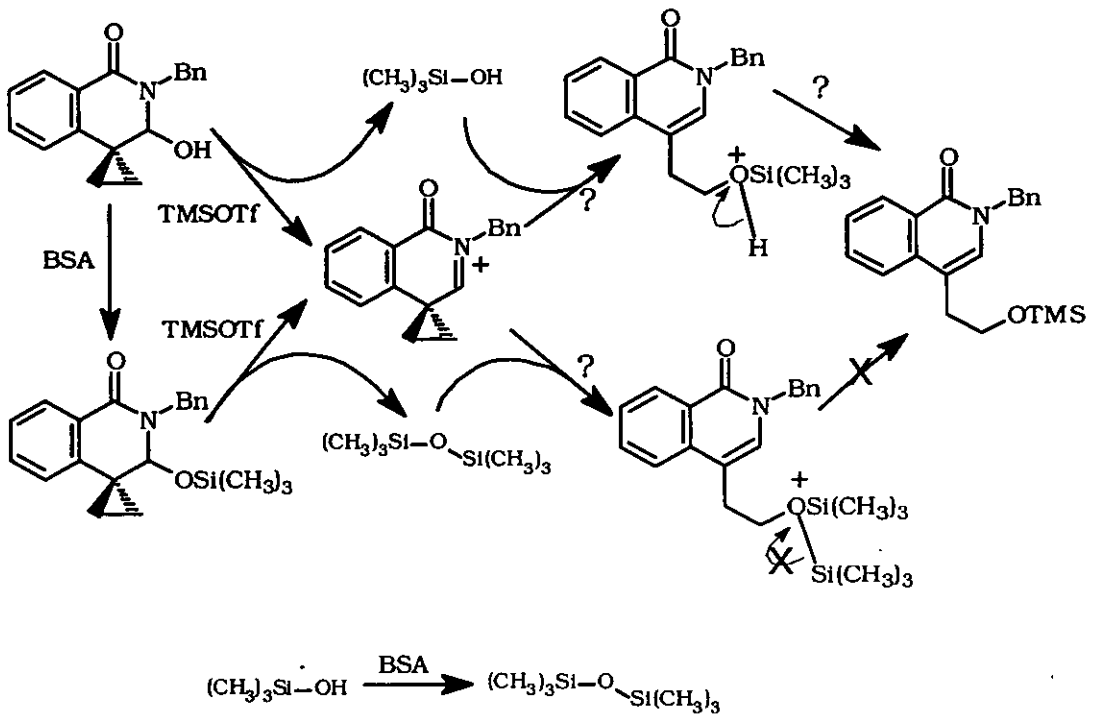


Scheme 5.43

Other silylation reactions involving silicon-substituted amines have been sufficiently reviewed in the literature.[117] Also, it is known that *N*-trimethylsilylacetamide is at lower energy level compared to the *O*-trimethylsilyl form, explaining the biased equilibrium towards the acetamide form as shown in **Scheme 5.42**.[115] Other BSA-induced hydroxy silylation mechanisms have been suggested and discussed in the literature.[115]

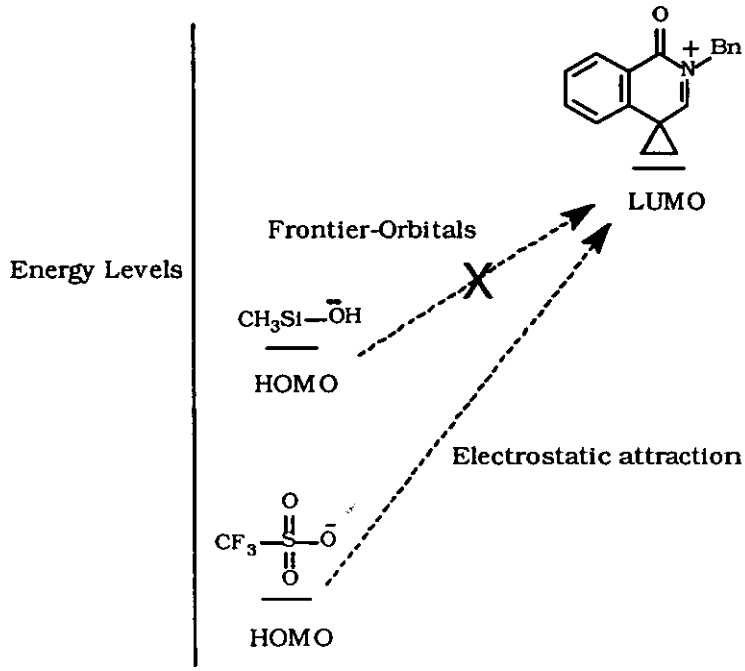
As a consequence for the expected rapid silylation of the starting material **4.8**, a TMSOTf attack on the siloxy group (in the silylated fraction of the starting material) will lead to the formation of hexamethyldisiloxane $[(CH_3)_3Si)]_2O$ as in **Schemes 5.36** and **5.44**. This species is weakly nucleophilic since the unshared pair of electrons on the oxygen atom are involved in an overlap with the vacant *d* orbitals of the adjacent silicon atoms,[118] in fact this factor accounts for the reduced nucleophilicity of the hydroxy group within trimethylsilanol as well. Also, a nucleophilic attack by the oxygen atom within $[((CH_3)_3Si)_2O]$, on the cyclopropane ring, is expected to be fruitless regarding the formation of a siloxy adduct, since Si-O bond is stronger than C-O bond, [51] as shown in lower part of **Scheme 5.44**.

(b) BSA is also expected to silylate the trimethylsilanol generated from the TMSOTf attack on the hydroxy group of the staring material (the non-silylated fraction), leading to the hexamethyldisiloxane mentioned earlier. This silylation reaction will compete with any potential mucleophile attack by trimethylsilanol on the cyclopropane ring as in **Scheme 5.44**.



Scheme 5.44

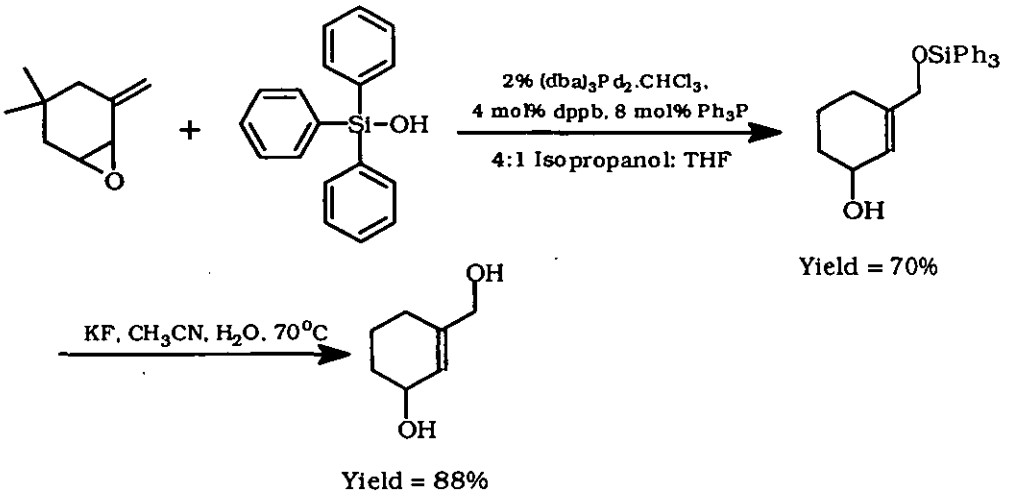
2) Trimethylsilanol is expected to be a softer oxygen nucleophile compared to triflate, as it is neutral, and its oxygen's HOMO electrons are predicted to be in a higher energy level in contrast to their equivalents in the triflate ion (due to the strong electronegative effect of CF_3SO_2 fragment in the triflate ion, which renders the electrons highly stabilised).[119] On the other hand, the generated *N*-acyliminium ion is positively charged, and the charge is concentrated on three atoms (two carbons and a nitrogen), thus it can be described as a hard electrophile.[119] In fact, the hard electrophilic nature of the intermediate cation is evident by the fact that it captured diethylether, which is known as a hard nucleophile[119] (**Scheme 5.33**). Consequently, the reaction of the hard *N*-acyliminium ion is more likely to be with hard triflate ion, due to the expected strong electrostatic attraction between the two ions,[119] and possibly the high energy difference between the silicon-stabilised HOMO hydroxy electrons in trimethylsilanol and the LUMO in the *N*-acyliminium intermediate. **Scheme 5.45** illustrates the anticipated relative energy levels of the relevant orbitals within the interacting molecules.



Scheme 5.45

The soft nucleophilic nature of triphenylsilanol was utilised by Trost *et al.*[120] to generate 2-ene-1,4-diols from palladium catalysed 1,4-opening of vinyl epoxides. This group reported that while water and hydroxide ion did not show

nucleophilic properties in similar palladium catalysed reactions, carboxylic acids, as oxygen nucleophiles, led to high yields of the 1,2-epoxide ring-opened products. On the other hand, triphenylsilanol reacted smoothly with different 1,4-vinyl epoxides and offered, after optimisation, good to excellent yields of the 2-ene-1,4-diols, one of the reactions conducted by this groups is illustrated in **Scheme 5.46**. These results can be compared with the 1,2-epoxide ring opening reported for triflate ions as in **Schemes 5.37** and **5.38**.



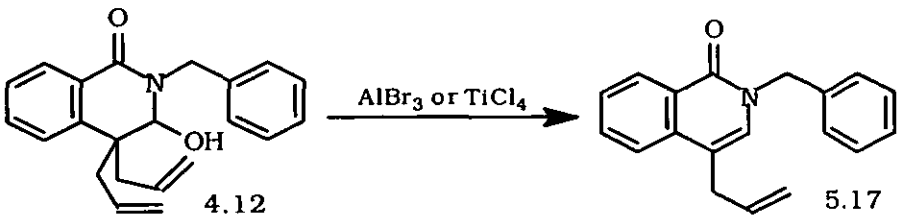
Scheme 5.46.

E- The Trapping of *N*-acyliminium Ion Generated From 4,4-Diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone.

Treating 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone **4.12** with different Lewis acids in different solvents led to different products, extending from double bond addition to 1,2-allyl migration and allyl elimination. The different products and their yields are now discussed. The following subsections are classified according to the Lewis acid and/or the reaction solvent used to generate the *N*-acyliminium ion.

i) Reactions of 4.12 with titanium tetrachloride and aluminium tribromide.

Treating **4.12** with $TiCl_4$ or $AlBr_3$ led to allyl group elimination as in **Scheme 5.47**. The reaction conditions and yields are summarised in **Table 5.7**.



Scheme 5.47

Table 5.7

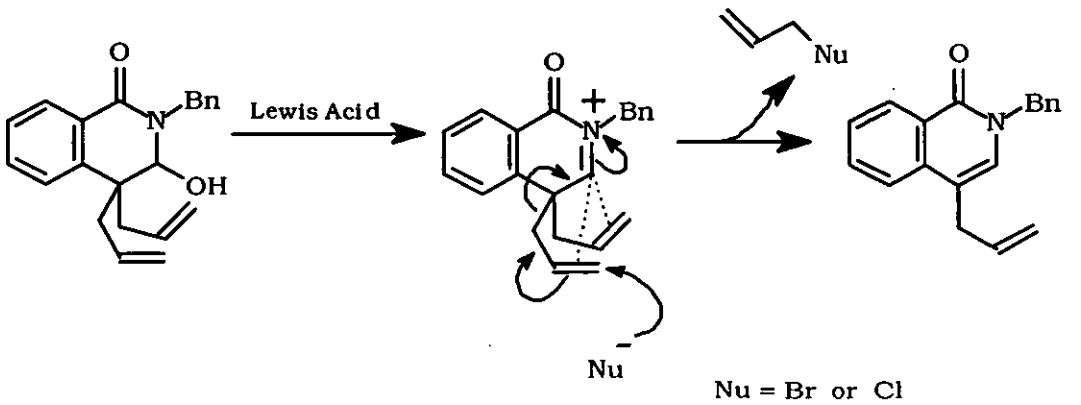
No.	Reaction Temperature (°C)	Lewis Acid** Type	Lewis Acid** Number of Equivalents	Reaction Time (hours)	5.17 Yield %
1	Ambient	$AlBr_3$	1.25	4	42†
2	Ambient*	$TiCl_4$	2.10	4.5	92

* $TiCl_4$ was added at -78 °C for 15 minutes then the reaction was warmed up to the room temperature.

** Solvent = dry DCM.

† *ca.* 34% recovered starting material.

The elimination reaction is expected to take place *via* a bromide or chloride ion nucleophilic attack on the bis-homoallylic-stabilised *N*-acyliminium ion (this cation will be discussed in more details later) as in **Scheme 5.48**.

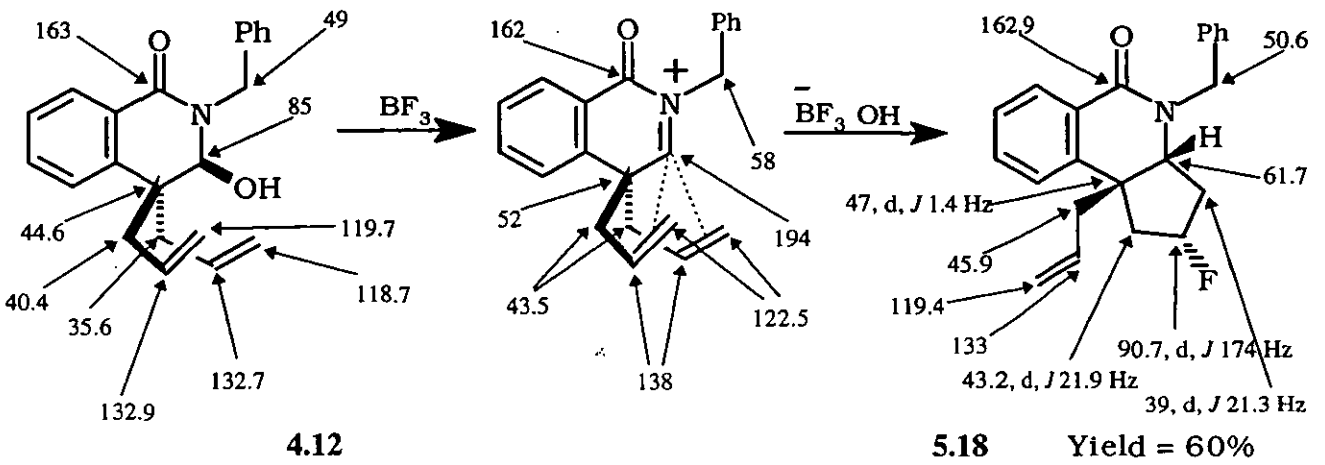


Scheme 4.48

Allyl group elimination is somewhat similar to the benzyl elimination described earlier in **Scheme 5.21**. It was not possible to find similar allyl elimination reactions in the literature.

ii) Reaction of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with boron trifluoride etherate in chloroform.

Treatment of a solution of the carbinolamide **4.12** in $CDCl_3$ with boron trifluoride etherate (1 equivalent) at room temperature resulted in the generation of the bis(homoallyl)-stabilised *N*-acyliminium ion and allowed the collection of the ^{13}C nmr spectrum, the chemical shifts of which are shown against the structure in **Scheme 5.49**. After *ca.* 1 hour, the ^{13}C spectrum showed the nearly exclusive presence of a new compound and after *ca.* 2.5 hours, the reaction was quenched with sodium bicarbonate and extracted with DCM, to give the fluorine containing compound **5.18** in 60% yield and as a single diastereomer (based on ^{13}C and ^{1}H nmr spectroscopic analysis). This result was confirmed by a separate experiment, in which the carbinolamide **4.12** was reacted with boron trifluoride (1 equivalent) in $CHCl_3$ over *ca.* 2.5 hours to give again **5.18** in *ca.* 60% yield. **Scheme 5.49** outlines the reaction and shows the chemical shifts of the directly involved carbon atoms in the starting material, the intermediate cation, and the end product. The changes in the chemical shifts are easily noticed and compared in the three species.



4.12 **5.18** Yield = 60%

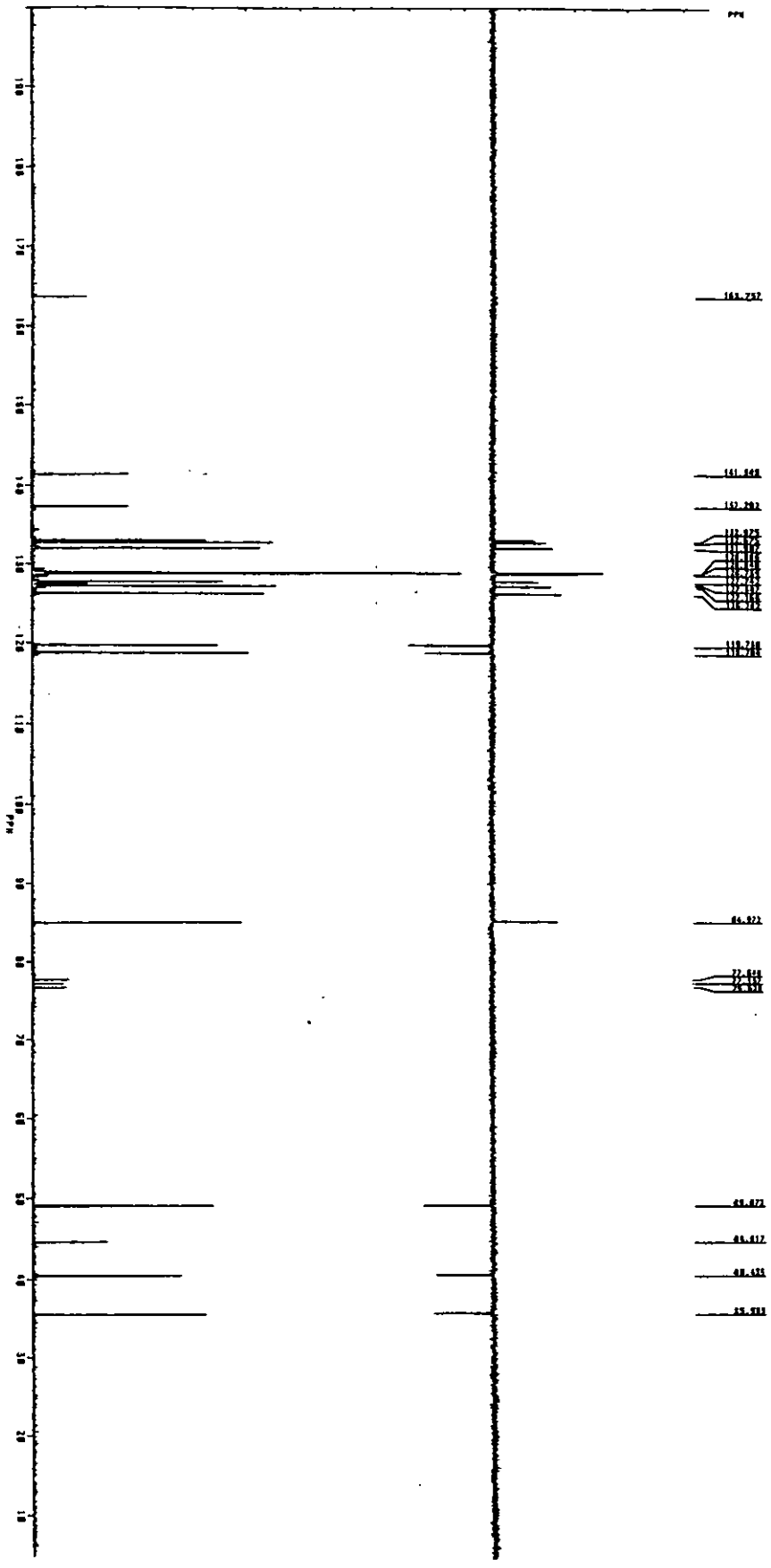
Scheme 5.49

The following are important points for discussion regarding this reaction.

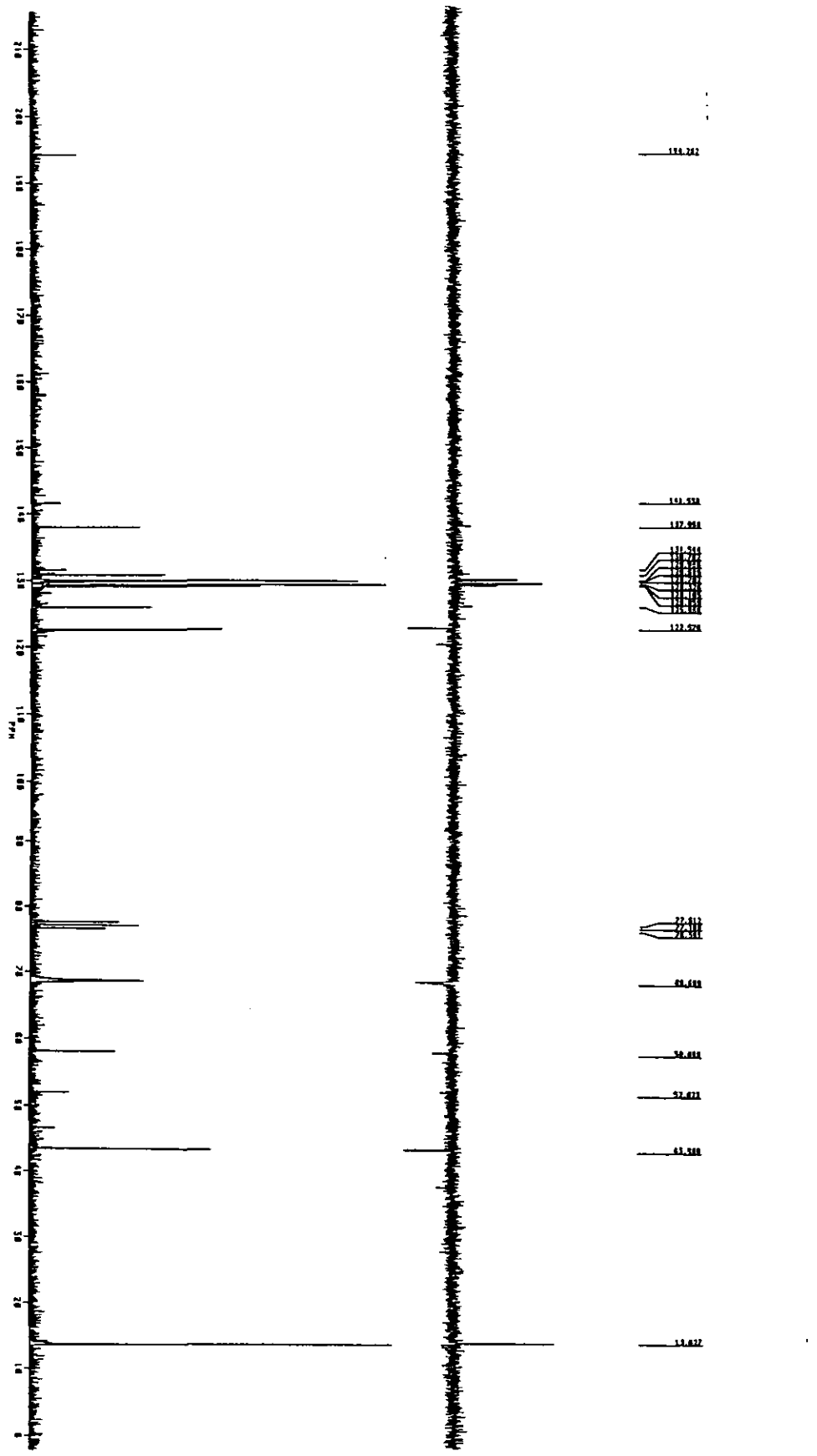
1) As shown in **Scheme 5.49**, two dotted coordination lines are connecting the *N*-acyliminium ion centre with the two allylic double bonds, this assumed

coordination is supported by the following pieces of evidence: (i) the *N*-acyliminium intermediate was found to be stable over *ca.* 20 minutes period in $CDCl_3$ (the time needed for the acquisition of ^{13}C and DEPT spectra.). However, a ^{13}C nmr spectrum taken after *ca.* 1 hour showed the absence of the intermediate cation and the formation of **5.18**. This moderate stability of the cation, at room temperature, is assumed to be due to the demonstrated coordination. (ii) The ^{13}C and DEPT spectra of the intermediate cation show the two allylic chains to have equivalent chemical shifts and to be deshielded from their original chemical shifts in the starting material, for example the allylic double bonds methylene carbons (CH_2) were deshielded from 118.7 and 119.7 ppm in the starting material to 122.5 in the intermediate cation, and the same happened for the allylic double bonds methine carbons (CH), i.e. from 132.7 and 132.9 ppm to 138 ppm. The fact that the allylic carbons have equivalent chemical shifts, and the clear deshielding of the double bonds' carbon atoms clearly demonstrate the coordination. A control experiment was done to ensure that the deshielding of the two allylic double bonds is due to their coordination to the *N*-acyliminium centre rather than boron trifluoride (or other related acidic material). In this experiment, the ^{13}C nmr spectrum of a mixture of 1-hexene and boron trifluoride, in 1:1 molar ratio, was collected and compared with ^{13}C nmr spectrum of pure 1-hexene sample. All the carbon atoms in the 1-hexene molecule, including the double bond atoms, kept their original chemical shifts, i.e. before the addition of boron trifluoride, which clearly rules out the possibility of any contribution by boron trifluoride in the mentioned deshielding of the allylic double bonds.

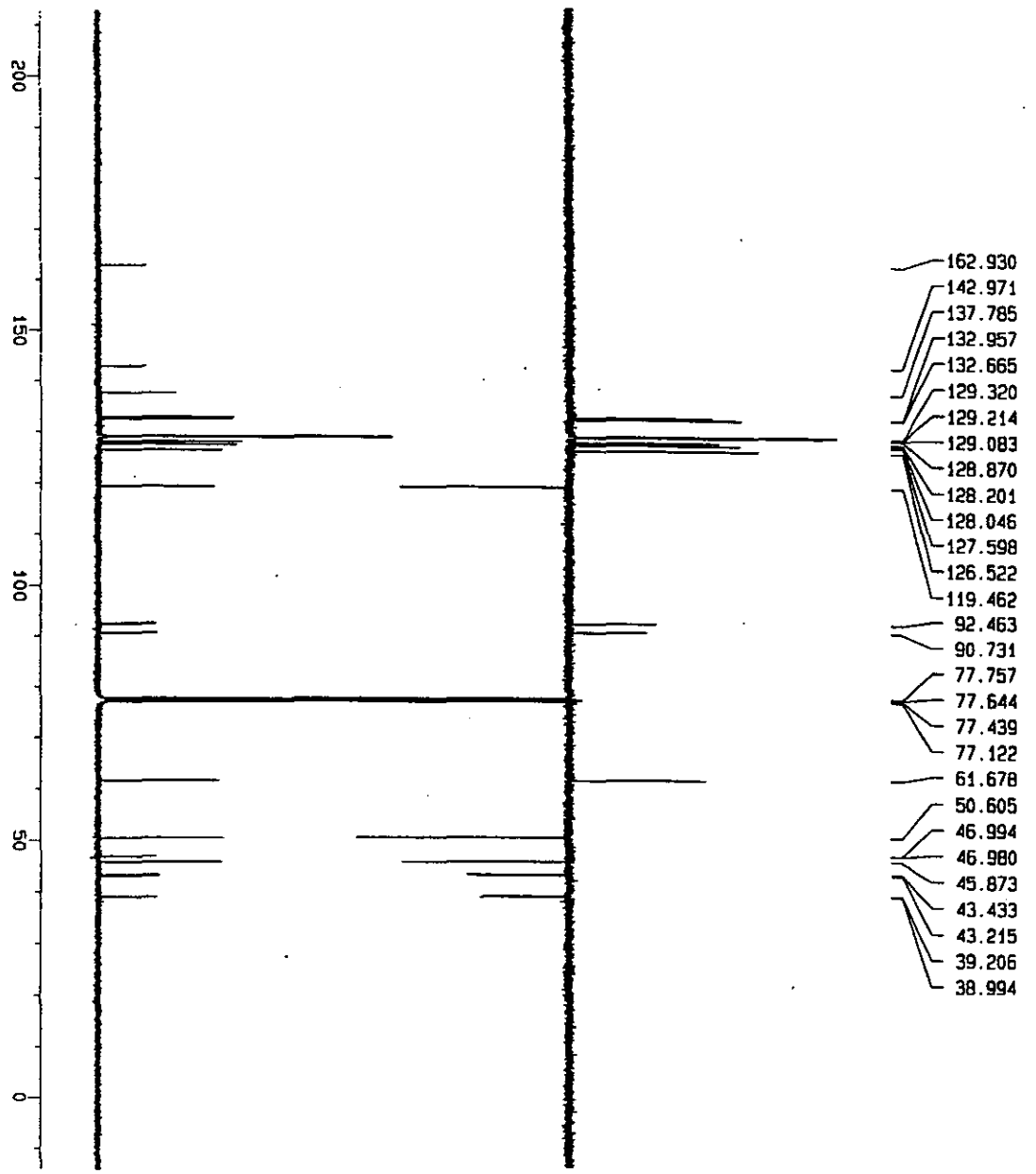
2) The chemical shift of the *N*-acyliminium ion reported in this research (**Scheme 5.49**) is more deshielded compared to the previously reported chemical shifts of



^{13}C nmr spectrum for the starting material **4.12**.



The ^{13}C nmr spectrum for the bis(homoallylic)-stabilised *N*-acyliminium ion, the peaks at 13.6 and 68.7 ppm correspond to BF_3.etherate. (as determined from a separate control experiment.)



^{13}C nmr spectrum for the product **5.18**.

other iminium and *N*-acyliminium ions shown in **Figure 5.8**.[1]

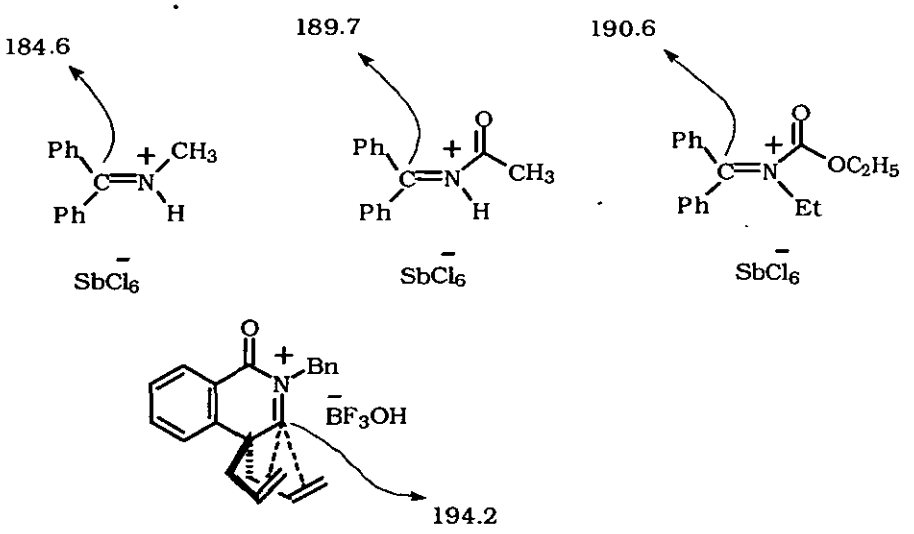
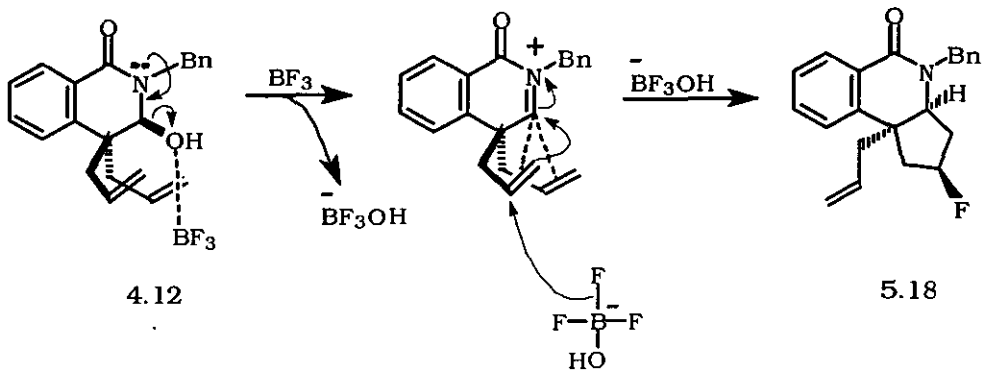


Figure 5.8

It was not possible to find literature examples showing direct evidence on allylic-stabilised *N*-acyliminium ions. However, speculative theories regarding the formation of such complexes were discussed in the earlier literature.[2]

3) The mechanism leading to **5.18** proceeds, most likely, *via* a fluoride ion nucleophilic attack on the less hindered face of one of the cation-coordinated double bonds. This attack is expected to be concerted with the ring closure, resulting in the 5-membered ring formation. The suggested mechanism justifies the high diastereoselectivity of the reaction. The fluoride ion is expected to be mainly donated from the BF_3OH complex. The mechanism is shown in **Scheme 5.50**.



Scheme 5.50

4) The elucidation of **5.18** was based on ^{13}C and ^{1}H nmr spectroscopy aided by COSY and HETCOR experiments, while the configuration was established based

on: (a) ^1H, ^1H-NOESY experiments, (b) the mechanistic evidence regarding the formation of the bis(homoallyl)-stabilised *N*-acyliminium ion intermediate, and (c) the fact that only one diastereomer was formed in the reaction.

Concerning the ^1H, ^1H-NOESY experiment, it was conducted at 25 °C in $CDCl_3$, over two mixing times: 0.55 and 0.70 second and at 400 M Hz. Crosspeaks of at least medium strength were considered. The following protons show nOe crosspeaks, (the numbers of the relevant hydrogen atoms are in bold, and they correspond to the numbered atoms in **Figure 5.9**):

1 (dd, 3.82 ppm) and **2** (m, 2.14 ppm). **2** (m, 2.14 ppm) and **4** (m, 4.83-4.86 ppm).

1 (dd, 3.82 ppm) and **7** (m, 5.37-5.44 ppm). **2** (m, 2.14 ppm) and **8b** (d, 4.47 ppm).

1 (dd, 3.82 ppm) and **8a**(d, 5.12 ppm) and **8b** (d, 4.47 ppm).

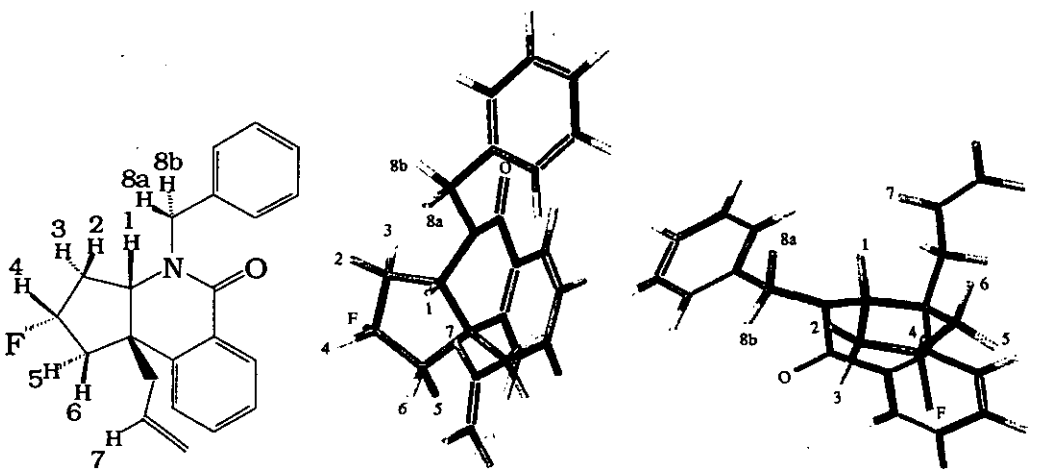
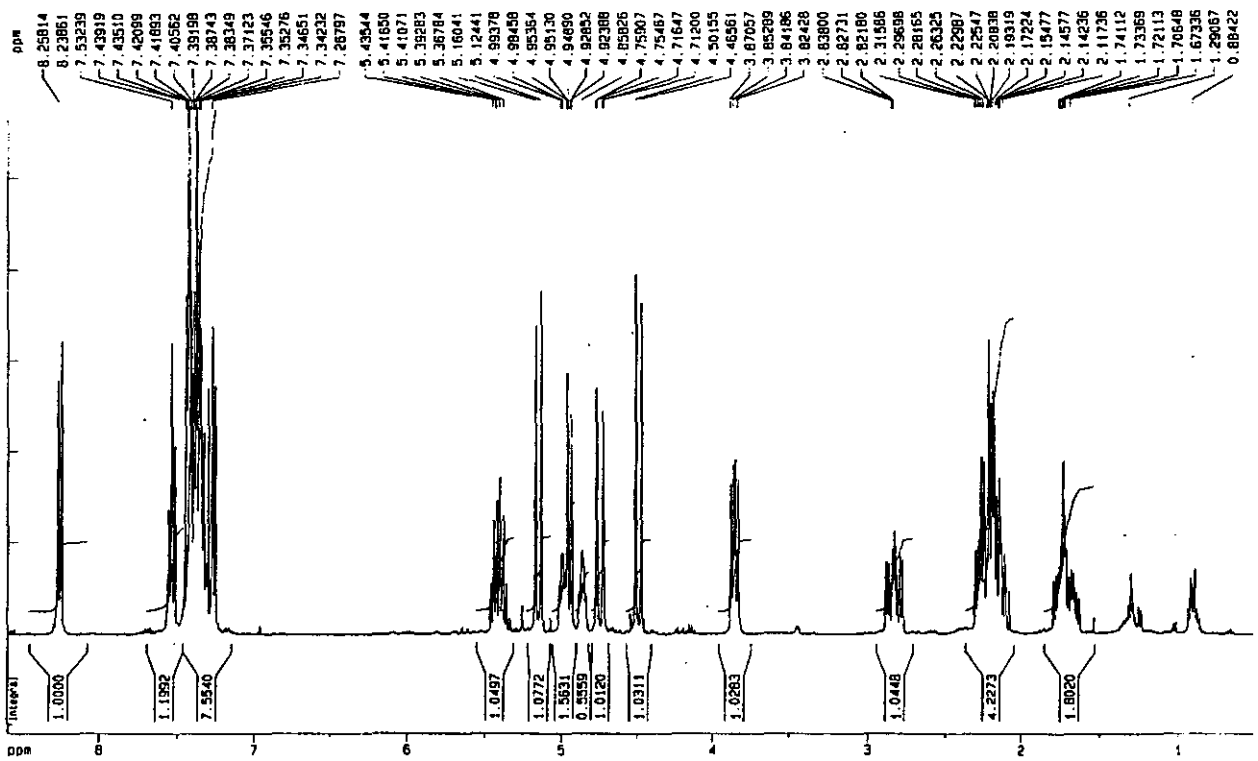


Figure 5.9

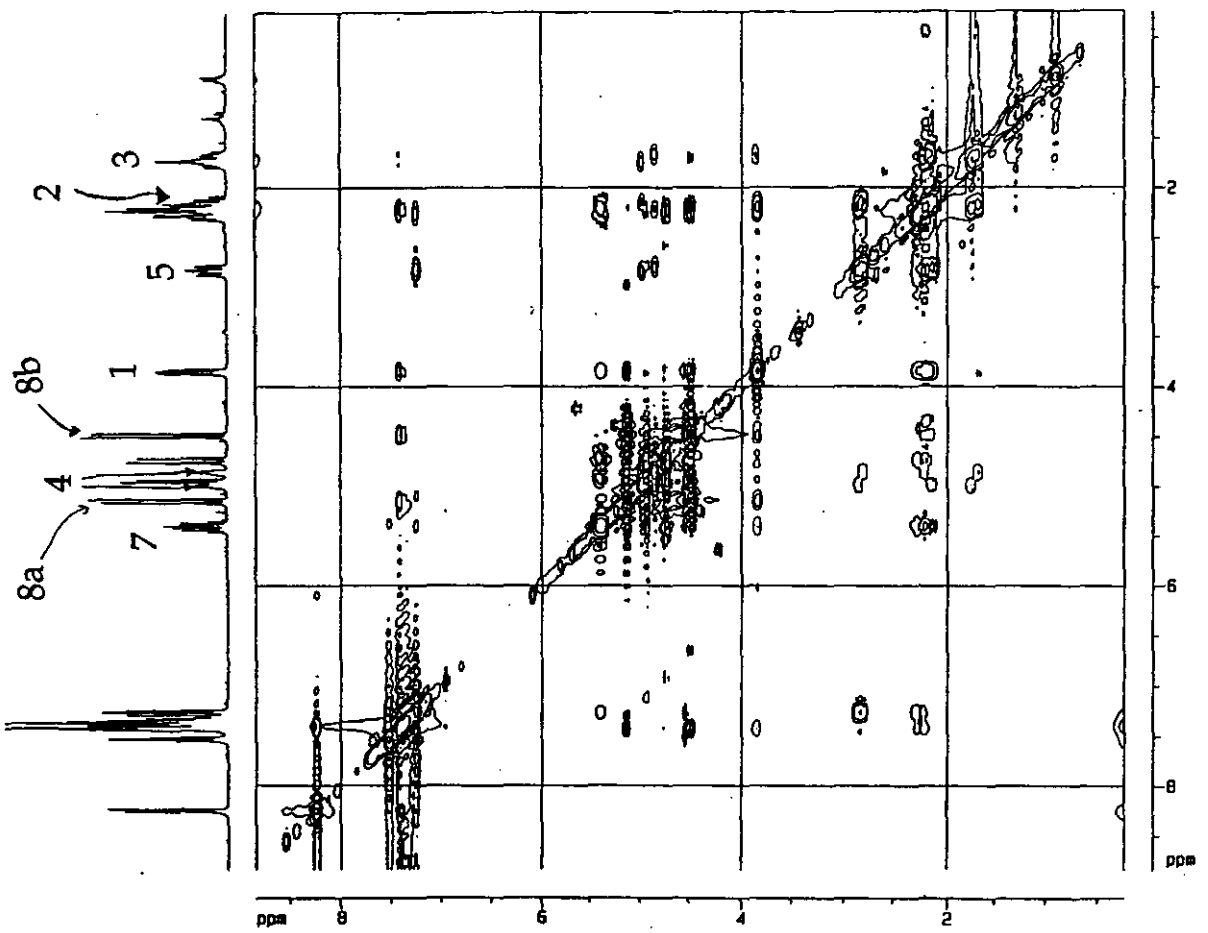
The analysis results were further strengthened by conformational energy minimisation calculations conducted by CAChe programme. Relevant interatomic distances calculated by CAChe minimisation are shown in **Table 5.8** and the three-dimensional model generated by the programme for **5.18** is also shown in **Figure 5.9**.

Table 5.8

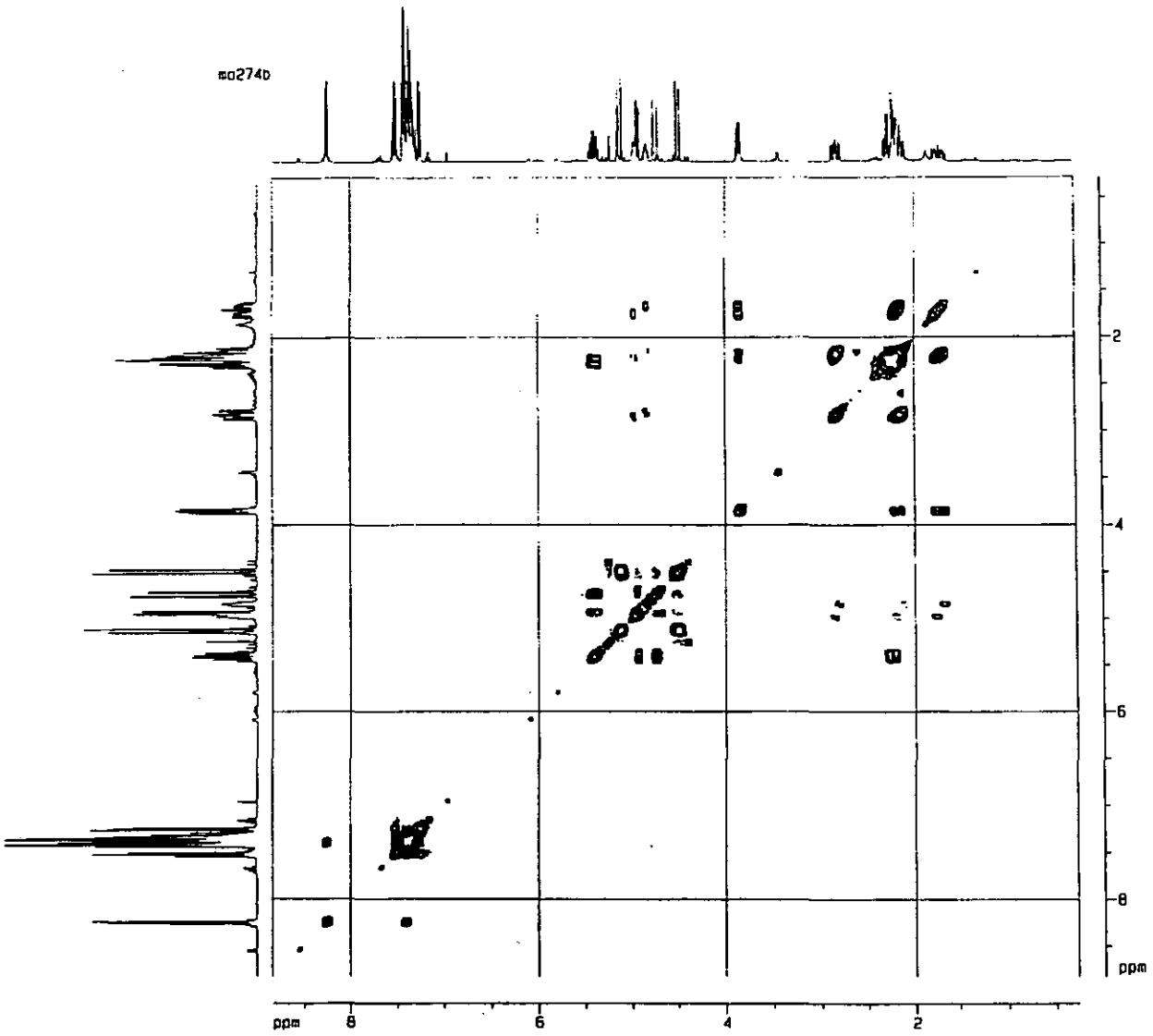
protons	distance (^oA)
1-2	2.38
2-4	2.39
1-7	1.78
2-8b	2.91
1-8a	2.28
1-8b	3.24



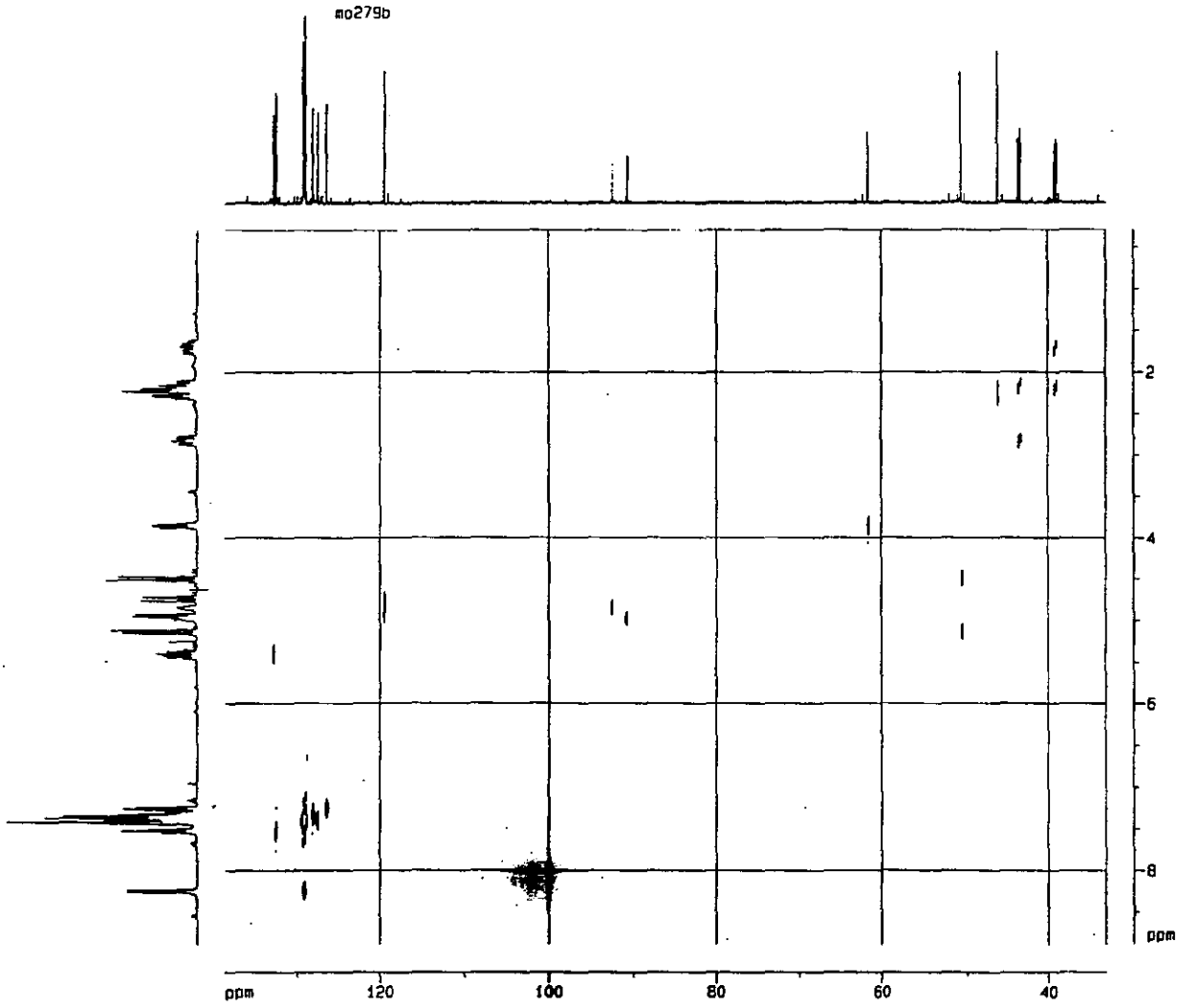
^{1}H nmr spectrum for 5.18



1H,1H NOESY experiment for 5.18.

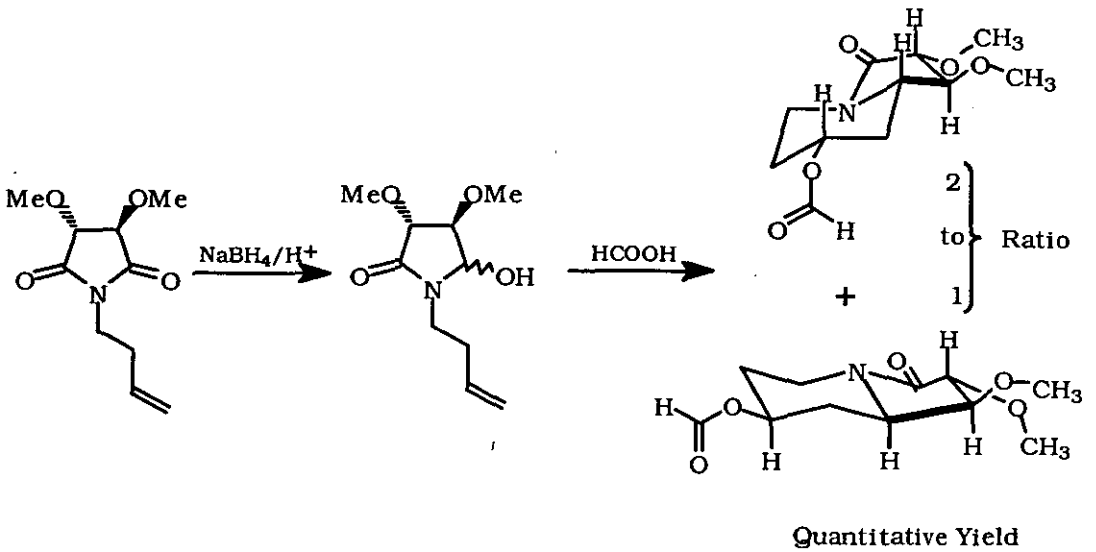


COSY experiment for 5.18.



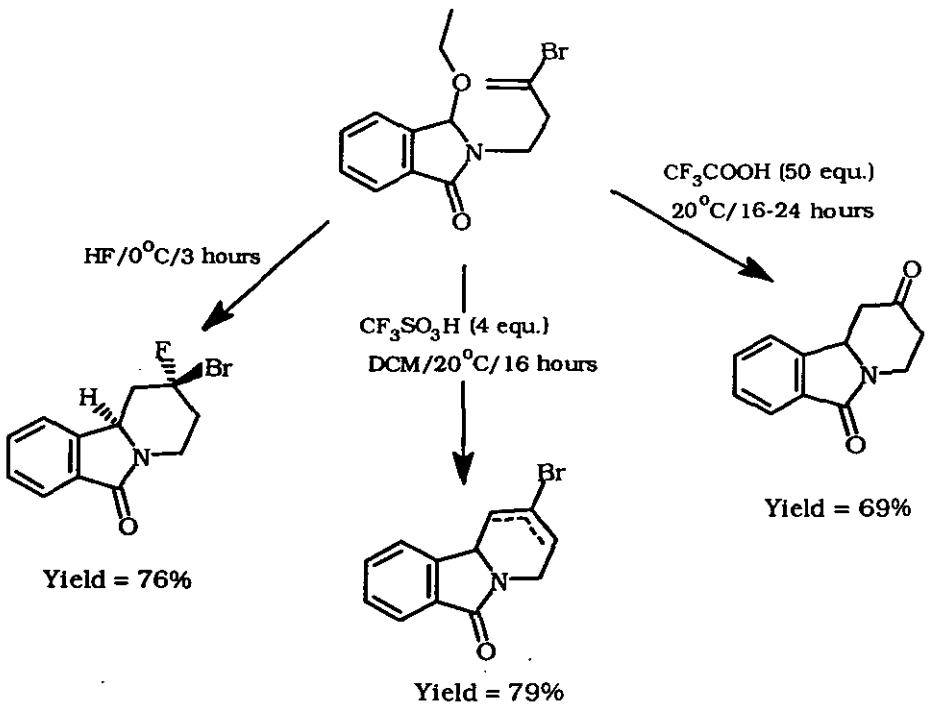
HETCOR experiment for 5.18.

5) The addition of an *N*-acyliminium ion to double bonds is a frequently reported transformation, and it was recently sufficiently reviewed.[2] Nevertheless, some selected interesting reactions, within this class, are outlined in the following. Wijnberg *et al.*[121] converted (R,R)-tartaric acid into (R,R)-dimethoxy-succinimide, then the succinimide was coupled with 3-butenol, or other related alkenols and the products were reduced to the corresponding carbinolamides, which were cyclised by treatment with formic acid. One of their reaction sequences is illustrated in **Scheme 5.51**.



Scheme 5.51

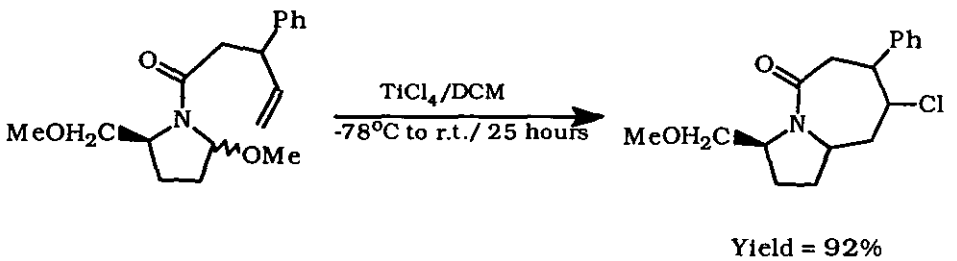
Gesson *et al.*[122] showed that the cyclisation of *N*-acyliminium ions, generated from imide-derived ethoxycarbinolamides, using trifluoroacetic acid, trifluoro-methanesulfonic acid and anhydrous HF, afforded ketones, bromoalkenes and geminal bromofluoro compounds, respectively. **Scheme 5.52** shows the products generated by treating the phthalimide-derived ethoxycarbinolamide with the three acidic reagents.



Scheme 5.52

It is noteworthy to mention that this example is the only literature example we found describing a nucleophilic attack by a fluoride ion in a *N*-acyliminium ion/double bond addition reaction.

In another example, Moeller *et al.*[123] generated an *N*-acyliminium ion intermediate by treating a proline derivative with titanium tetrachloride, the cation was then captured by a tethered double bond to yield a 7-memebered ring. **Scheme 5.53** illustrates the reaction.



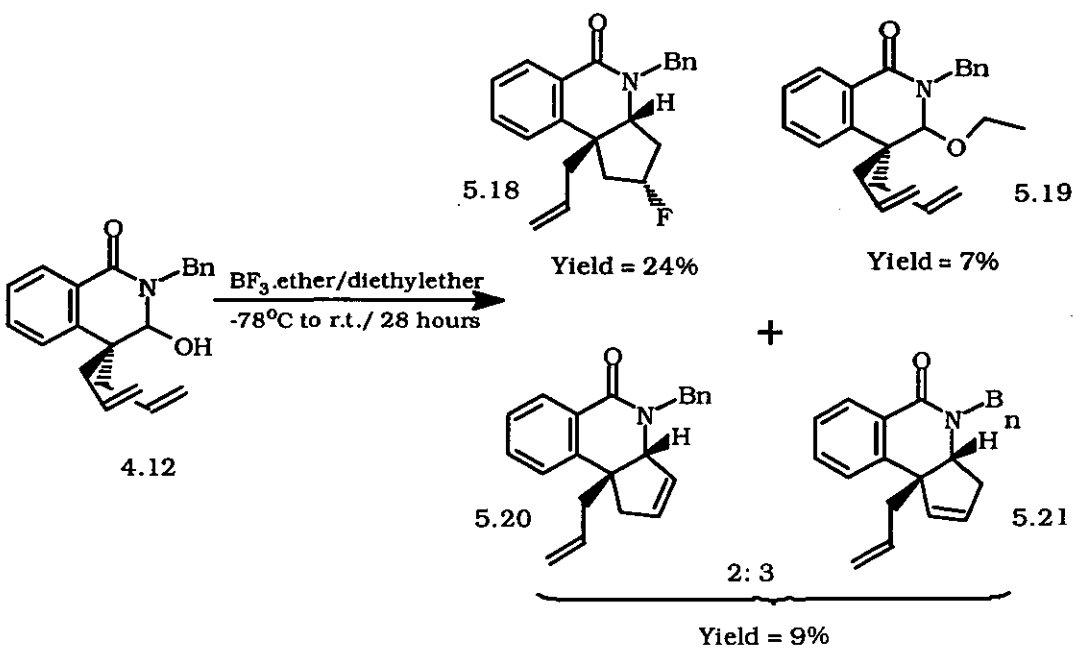
Scheme 5.53

The addition reactions of *N*-acyliminium ions to double bonds have been addressed by many research groups[2] including Chamberlin *et al.*[124] who applied cyclisations of ketene dithioacetals to synthesise pyrrolizidine, indolizidine and quinolizidine alkaloid ring system. Fisher *et al.*[125] reported the addition

of *N*-acyliminium ions to alkynes. Other examples include the work reported by Lessen *et al.*,[126] and Frauenrath *et al.*[127]

iii) Reaction of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with boron trifluoride etherate in diethylether.

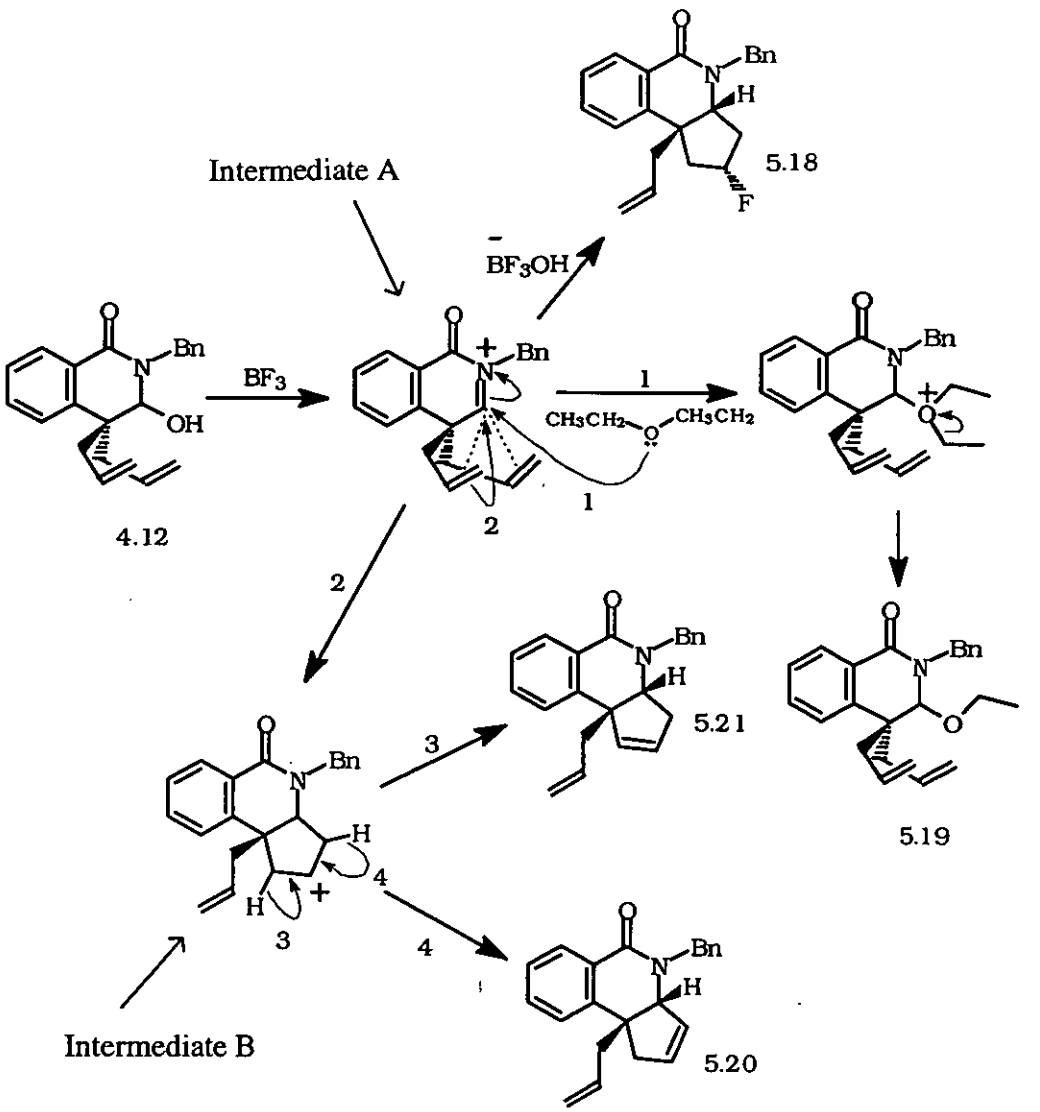
The bis(homoallyl)-stabilised cation, described earlier, seems to live longer when generated in diethylether. This assumption is based on the following experiment. The compound **4.12** was allowed to react with boron trifluoride etherate in diethylether at room temperature for 3 hours and 20 minutes and then an aliquot taken and quenched with aqueous sodium bicarbonate. Analysis using thin layer chromatography showed only the presence of starting material, suggesting an improvement in the stability of the *N*-acyliminium ion intermediate. The reaction therefore was allowed to proceed for 28 hours. The reaction conditions and products and their corresponding yields are illustrated in **Scheme 5.54**. The reaction was initiated at -78 °C for 15 minutes, then it was warmed up to room temperature.



Scheme 5.54

In addition to the products shown in **Scheme 5.54**, *ca.* 2% of the starting material was also recovered from the reaction.

The mechanisms leading to the different products in this reaction are expected to proceed *via* the same double bond-stabilised *N*-acyliminium ion, as shown in **Scheme 5.55**.

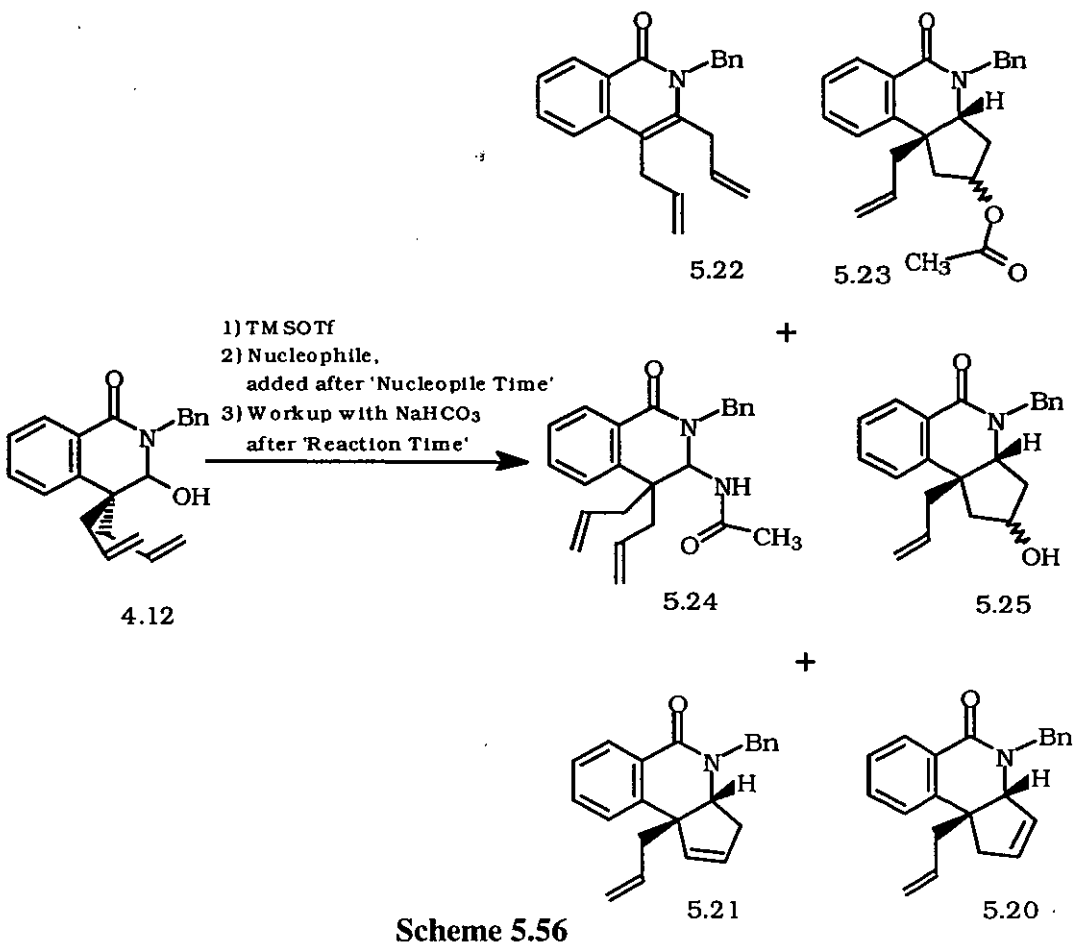


Scheme 5.55

The improved stability of *N*-acyliminium ion (intermediate A) is probably due to the coordination of diethylether molecules to the cationic centre. This assumption is supported by the capture of diethylether to give the ethoxy-carbinolamide **5.19**. Also, it seems that diethylether, by the virtue of its ability to coordinate to cationic centres, is enhancing the formation of another cation, i.e. intermediate B, which led to the formation of the two alkenes **5.20** and **5.19**, albeit in low yields. The formation of the fluorine containing compound **5.18** is expected to take place *via* the same mechanism described in **Scheme 5.50**.

iv) Reactions of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with TMSOTf in the presence and absence of selected nucleophiles.

The previously mentioned reactions of the carbinolamide **4.12** with different Lewis acids did not lead to 1,2-alkyl shift, which was one of our investigation goals. Consequently, we decided to conduct a series of exploration reactions using TMSOTf as a Lewis acid.[11] The low nucleophilicity of the TMSOTf counter ion, i.e. triflate, made it an excellent candidate for the potential migration reaction. Also, the use of this Lewis acid allows the incorporation of external nucleophiles that can be captured by the intermediate *N*-acyliminium ion. **Scheme 5.56** illustrates the generalised reactions that were carried out.



Scheme 5.56

Table 5.9 summarises the detailed conditions and the corresponding products with their yields in each reaction. The nucleophile time is defined as the time

delay between the addition of TMSOTf and the injection of the selected nucleophile to the reaction, while the reaction time is the period between the addition of the selected nucleophile until the reaction termination by workup with sodium bicarbonate solution.

Table 5.9

Reaction No. →	1	2	3	4	5
TMSOTf [@] Equ.[x]	catalytic	1.9	2.1	2.1	2.0
Reaction Temperature in °C [xx]	Ambient	Ambient	Ambient	-10	Ambient
Nucleophile (Equ.[x])	BSA (3.0)	BSA (4.0)	ACN[‡] (10.0)	Non	TMSA[‡] (4.0)
Nucleophile Time in minutes	0[*]	80	60	------	60
Reaction Time in hours	4	10	23	29	25
The Reaction Products and their Yields (%).					
5.22	------	15	7	9	5
5.20/5.21 [**]	------	28[†]	[1:5] 29	[1:3] 40	[1:4] 16
5.23 [#]	------	[3:2] 24	[3:1] 11	------	[4:1] 7
5.25 [††]	------	------	[2:1] 10	------	------
5.24	44	31	------	------	25

[@] The solvent used in these reactions is dry DCM.

[x] The number of equivalents compared to the starting material.

[xx] The reactions were initiated at -78 °C, and after 15 minutes they were warmed up to the indicated temperatures.

‡ ACN = acetonitrile, TMSA = *N*-trimethylsilyl acetamide.

[*] BSA was added to the stirred solution of the starting material in DCM, and after 5 minutes, the reaction was cooled down to -78 °C and TMSOTf was added.

[**] The alkene ratios are shown between square brackets, and are calculated from the average peak hights of comparable carbon atoms in ^{13}C nmr spectroscopy.

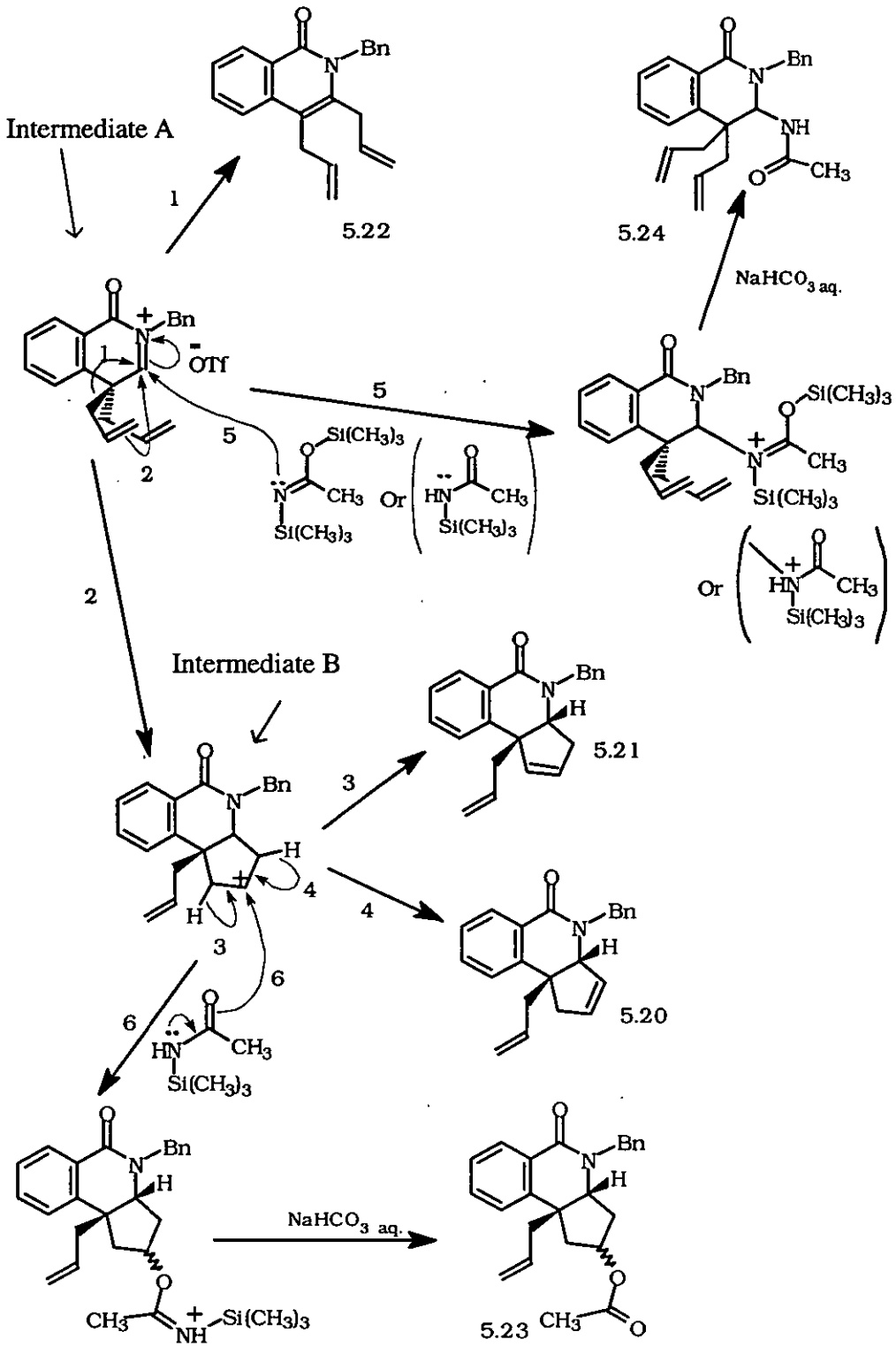
[†] Only **5.21** was isolated.

[#] The diastereomeric ratios of [Major : Minor] are shown in square brackets and are calculated from the peak areas for the comparable protons at 3.44 (dd, 1H, *J* 7.9, 10.5 Hz) ppm for the major diastereomer and 3.67 (dd, 1H, *J* 8.2, 10.4 Hz) ppm for the minor diastereomer.

[††] The diastereomeric ratios [Major : Minor] are shown in square brackets and are calculated from the isolated and purified diastereomers.

The following points are noticed regarding these reactions.

1) It is expected that these reactions take place *via* the same double bond-stabilised *N*-acyliminium ion (intermediate A in **Scheme 5.57**).



Scheme 5.57

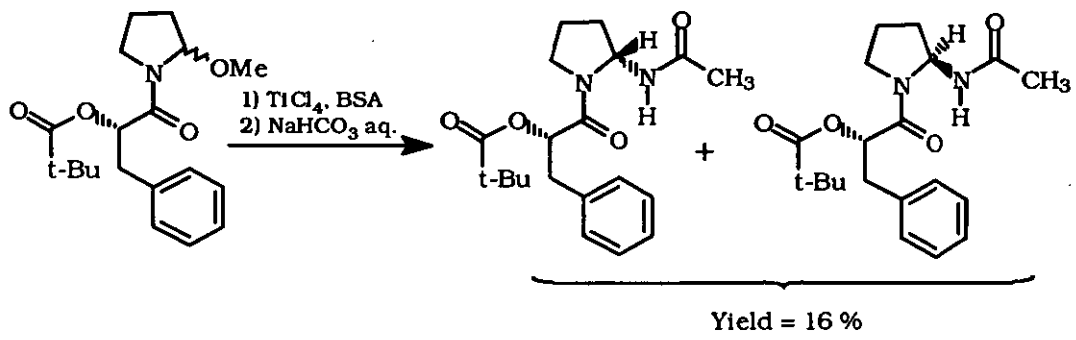
2) It seems that the *N*-acyliminium addition to the double bond occurs at a faster rate than the 1,2-alkyl shift reaction, as it is clearly evident from the yields in reaction number 4 in **Table 5.9**.

3) The expected mechanisms of the different reactions, summarised in **Table 5.9**, are shown in **Scheme 5.57** (except reaction number 3, i.e. when acetonitrile is used as nucleophile).

4) It is important to mention that *N*-trimethylsilylacetamide, which is essential for the production of **5.23** and might contribute in the formation of **5.24** (as in **Scheme 5.57**), can be generated in *situ* from BSA as it was previously illustrated in **Scheme 5.42**.

5) The isolation of **5.24** in reactions 2 and 5 (after 80 or 60 minute of 'nucleophile time' as in **Table 5.9**) illustrates the relatively good stability of the intermediate *N*-acyliminium ion (intermediate A in **Scheme 5.57**). The improved stability is expected to be, once again, due to the double bond-coordination mentioned earlier.

6) An earlier account of an intramolecular reaction between BSA and a *N*-acyliminium ion has been reported by Wanner *et al.*[128] The reaction is shown in **Scheme 5.58**.



Scheme 5.58

7) Approximately 7% starting material was isolated from the crude product in reaction 4 (**Table 5.9**), which is another evidence on the improved stability of the intermediate *N*-acyliminium ion, albeit at -10 °C in this case.

8) The isolation of the acetate **5.23** in reactions 2,3 and 5 (after 80 or 60 minute of 'nucleophile time' as in **Table 5.9**) indicates a relatively good stability of the intermediate cation B (in **Scheme 5.57**), which might be due to a certain degree

of coordination between the cation and the double bond of the nearby allyl group as in **Figure 5.10**.

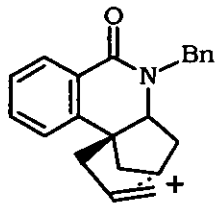
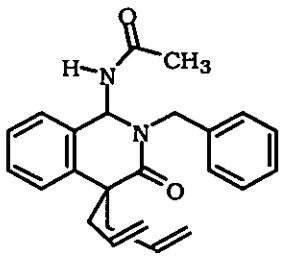
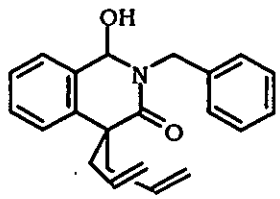


Figure 5.10

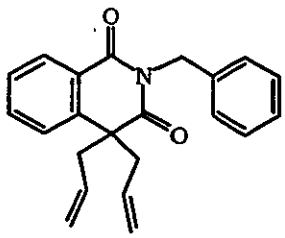
9) The lower yields for the products isolated from reaction 5, in **Table 5.9**, is assumed to be due to the presence of an impurity in the starting material. This assumption is based on the fact that one of the isolated compounds (in *ca.* 20% yield) is believed to be **5.26** according to infrared, spectroscopic and X-ray evidence. The compound was not further characterised. The presence of this product can only mean that the starting material was contaminated with **5.27**, which probably was formed as a side product in the reduction of the starting homopthalimide **3.13**.



5.26

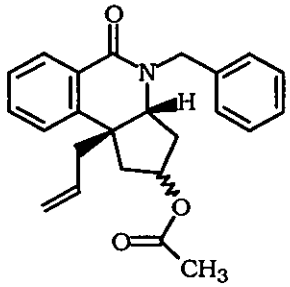


5.27

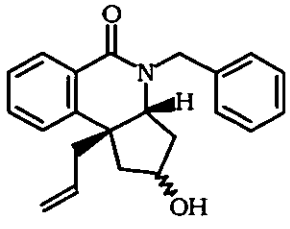


3.13

10) The isolation of **5.23** and **5.25** from reaction 3 (in **Table 5.9**) was unexpected, as the attacking nucleophile in this case is supposed to be acetonitrile. Our theory, regarding the formation of **5.23**, is based on the possibility that BSA was formed *in situ*, as illustrated in **Scheme 5.59**.

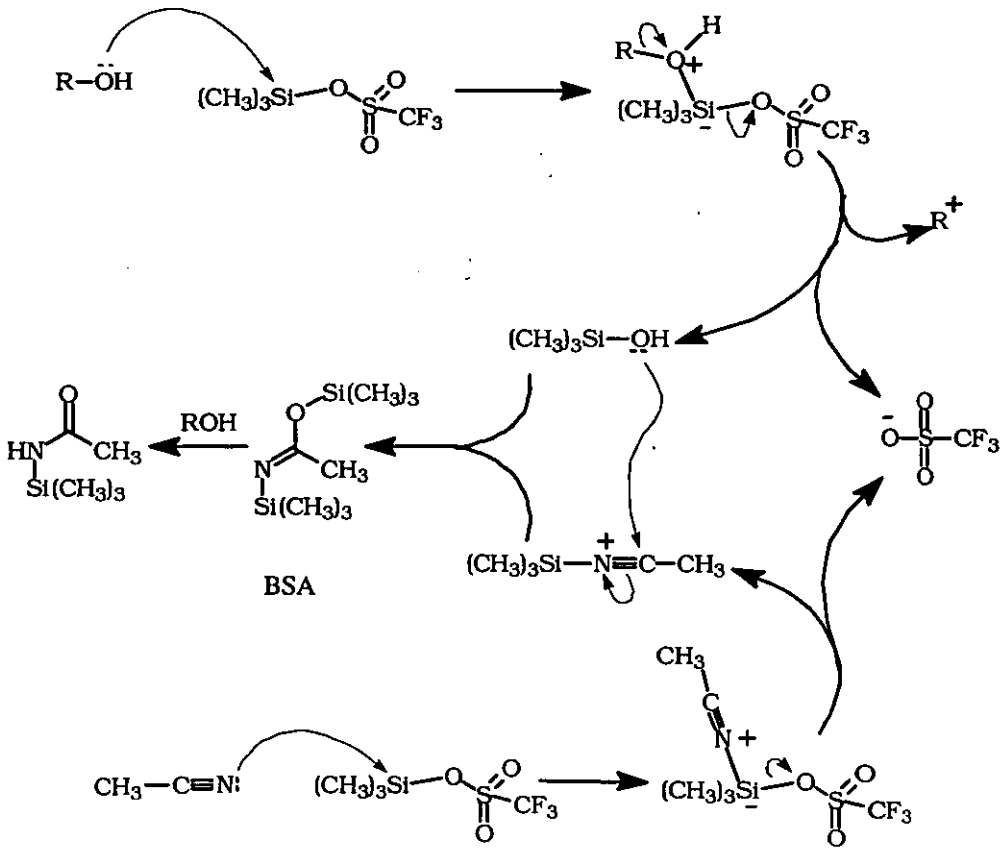


5.23



5.25

BSA is known to generate *N*-trimethylsilylacetamide upon reaction with hydroxy compounds.[115] The generated acetamide will then act as an oxygen nucleophile as in **Scheme 5.57**. On the other hand, **5.25** was possibly formed from capture of water or hydroxide ion by the intermediate cation B (**Scheme 5.57**) during the reaction workup, suggesting an improved stability of this intermediate, which might be due to the presence of acetonitrile. Acetonitrile is expected to stabilise cationic species. However, further experimentation is required to know what is really happening.

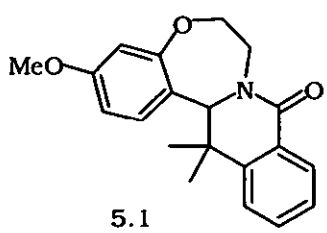


Scheme 5.59

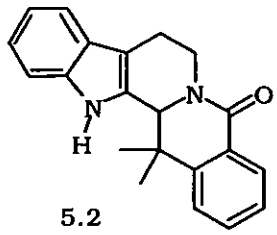
Significance of Berbines, Tetrahydrophenanthridinones and related Isoquinolones.

1) Berberines.

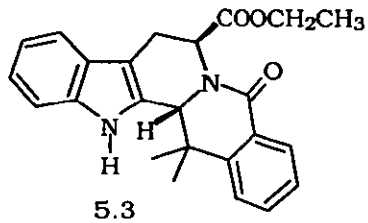
Tetracyclic isoquinolones, analogous to **5.5** and **5.7** and to a lesser degree to **5.1**, **5.2** and **5.3**, are described as having the berbine ring skeleton.[129,130]



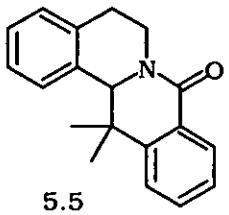
5.1



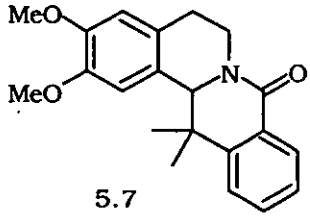
5.2



5.3

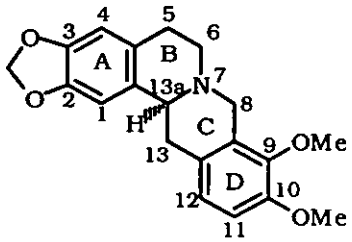


5.5

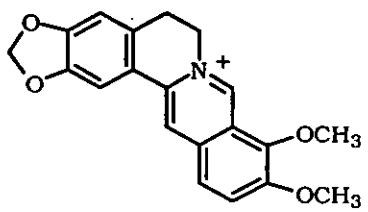


5.7

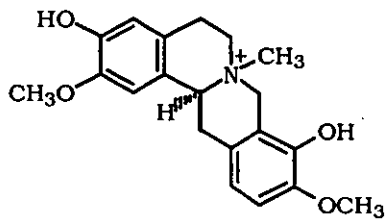
Berbine alkaloids, also known as protoberberine alkaloids, are widely distributed in nature, occurring in at least eight botanical families. They occur most frequently in the various genera of the *papaveraceae* but are also well represented in the *berberaceae*, *menispermaceae*, *rununculaceae*, *rutaceae* and *annonaceae*.[131] **Figure 5.8** shows some Berbine alkaloids of interest. [129]



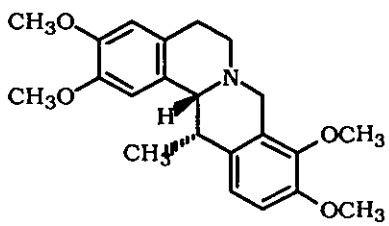
(-) Canadine



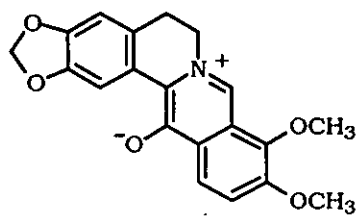
Berberine (Berbine)



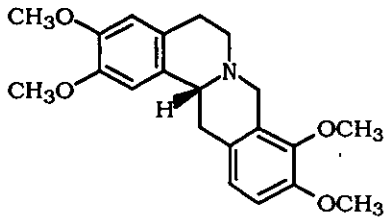
(-) Steporine



(+) Corydaline



Neooxyberberine



(-) Corexirnine

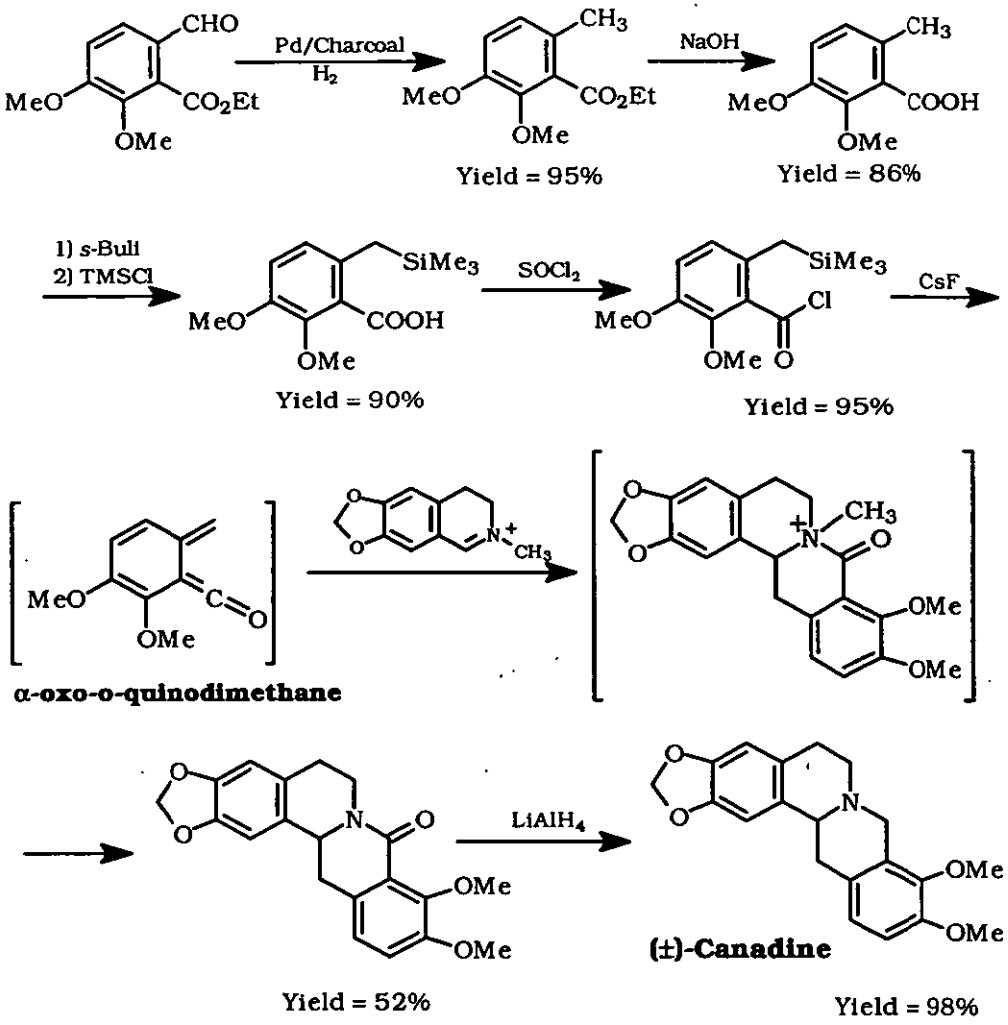
Figure 5.8

Regarding their pharmacological properties, large number of berbine alkaloids substituted in rings A and D have shown tranquillising characteristics in initial tests.[132] Berberine, which was first isolated from *Berberis vulgaris*, is of low toxicity, and was shown to have LD_{50} of 0.275 mg/10 g after intraabdominal administration to mice.[130] It has shown ability to intercalate and form a complex with DNA leading to some antibacterial and antiprotozoal activity. Furthermore it has transient hypotensive activity in rats.[132] 13-Allylberberine bromide may have potential as an antiulcer drug.[132]

Naturally occurring and modified berbine derivatives have shown hypotensive activity and [133] the berbine derivative tetrahydropalmatine has been found to possess antipsychotic, tranquillising and sedative activity.[134] Recently, Schmeller *et al.*[135] showed that berberine and palmatine are active α-2 adrenergic blockers, and good DNA intercalaters. The authors concluded that these biochemical activities may mediate chemical defence against microorganisms, viruses and herbivores in the plants producing these alkaloids. Ckless *et al.*[136] concluded that the anti-inflammatory action of berberine, may arise in part from the inhibition of DNA-synthesis in activated lymphocytes.

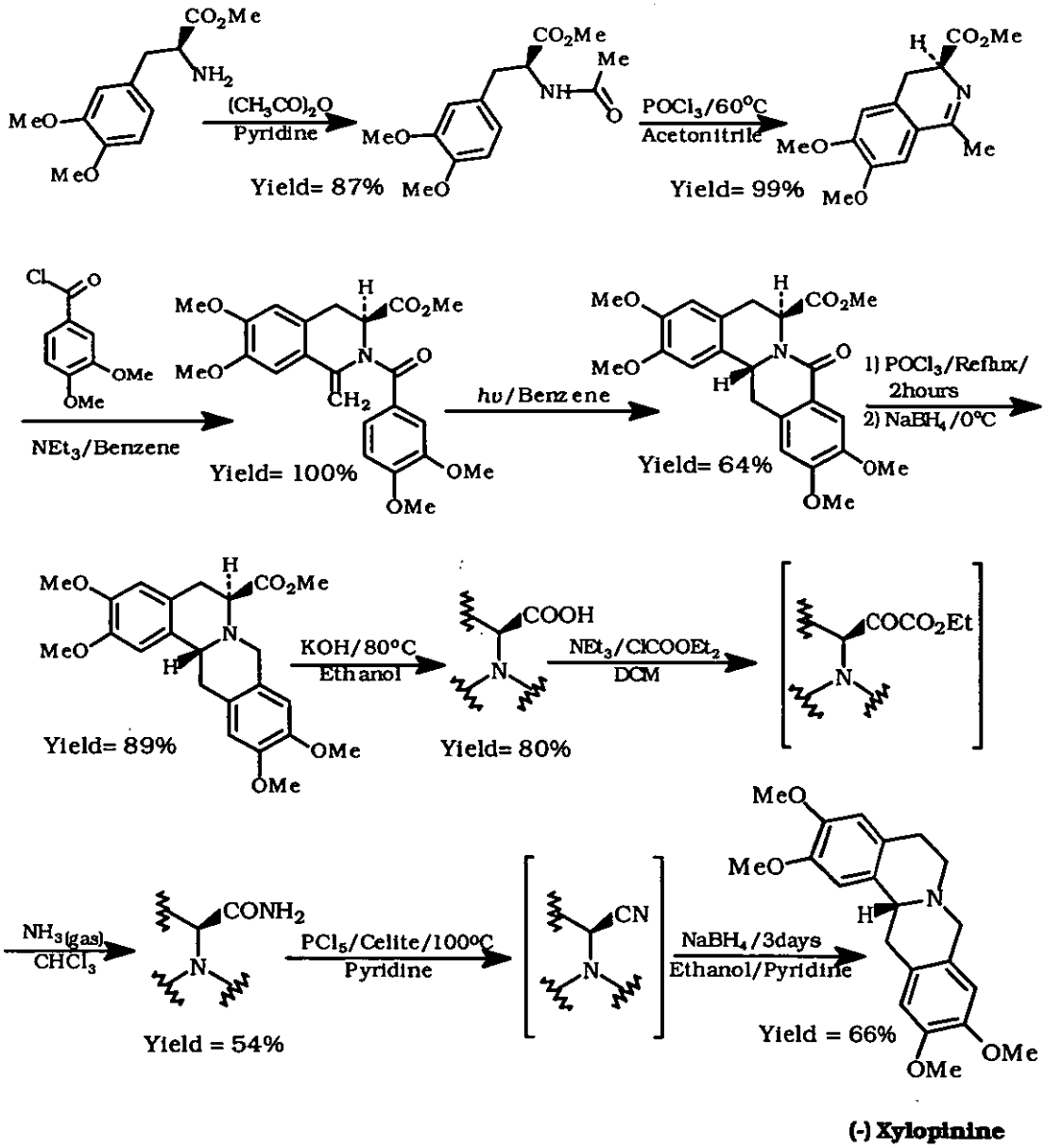
The biosynthesis of berberine and related alkaloids have been studied extensively and it appears that the amino acid tyrosine plays an important role in providing the aromatic moieties, while methionine plays an important role in the biosynthetic pathway as a single carbon atom donor.[137]

The chemical synthesis of the berbine ring system has been achieved in a variety of ways. [129, 131, 138] Some selected recent synthetic routes are now reviewed. Kessar *et al.*[139] synthesised tetrahydropalmatine and canadine and other related analogues, by reacting α-oxo-*o*-quinodimethanes with 3,4-dihydroisoquinolinium salts followed by reducing of the generated 8-oxoberbines to the target berbines. **Scheme 5.60** illustrates their synthetic route.



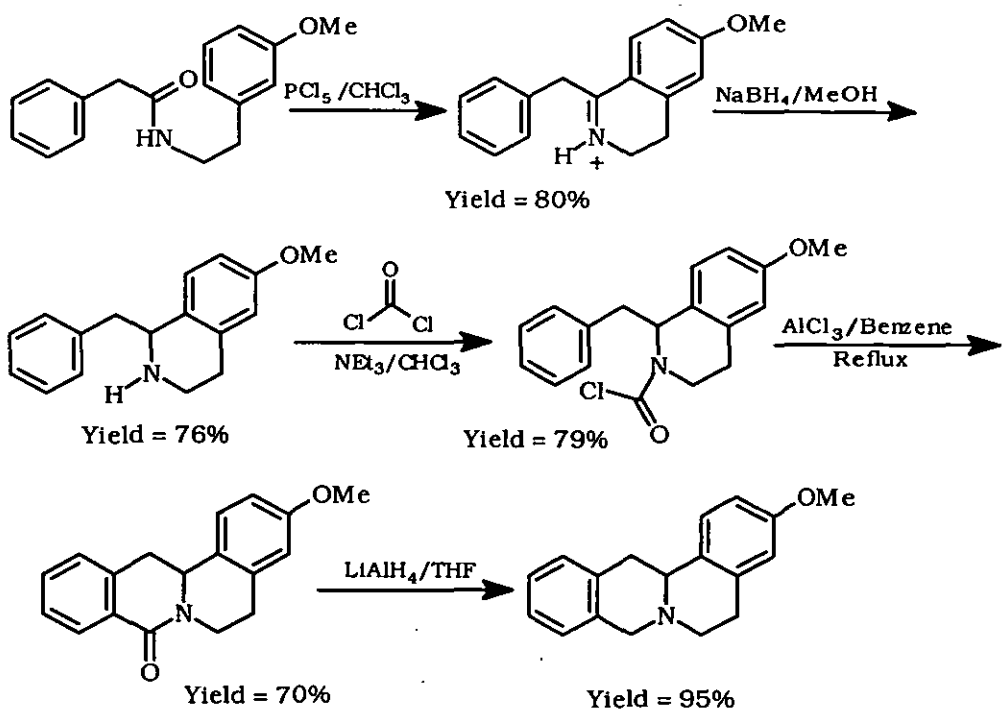
Scheme 5.60

Kametani *et al.*[140] achieved the total synthesis of the protoberberine alkaloid (-) xylopinine by photochemical 1,3-asymmetric induction. **Scheme 5.61** shows their synthetic route.



Scheme 5.61

In another interesting short synthesis, Stambach *et al.*[141] achieved the berbine ring system by treating 1-benzyl-1,2,3,4-tetrahydroisoquinolines with phosgene. The resulting *N*-chloroformyl derivatives were subjected to a variety of Lewis acids to induce intramolecular ring closure yielding berbine-8-ones. The corresponding berbines were prepared by reducing the berbin-8-ones with $LiAlH_4$. **Scheme 5.62** shows an example on this synthetic route.

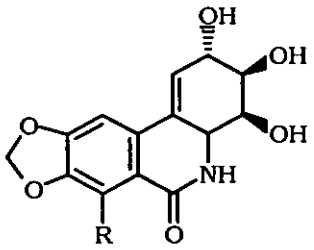


Scheme 5.62

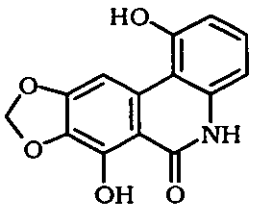
Other synthetic routes to berbine alkaloids and related compounds include: palladium catalysed insertion of carbon monoxide into benzyltetrahydro-isoquinolines, developed by Pandey *et al.*[142], the reaction of phthalide anions with 3,4-dihydroisoquinolines, developed by Marsden *et al.*[143] and electro-reductive annelation reaction, in which controlled potential reduction of iminium salts in the presence of bromo esters, such as *o*-bromomethyl benzoates, afforded berbine-type compounds, this methodology was utilised by Shono *et al.*[144]

2) Tetrahydrophenanthridinones and Related Isoquinolones.

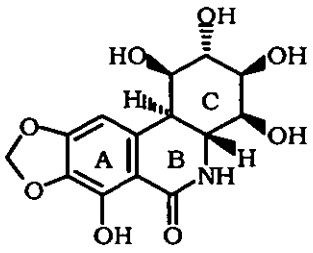
Phenanthridinones are found in a range of natural products, mainly in alkaloids isolated from the *amaryllidaceae* botanical family.[145,146] Some phenanthridin-one alkaloids of interest are illustrated in **Figure 5.9**.



R = OH, (+) Narciclasine.
R = H, Lycoricidine.



Narciprimine.



Pancratistatin

Figure 5.9

Narciclasine and narciprimine have been extracted from daffodil bulbs (*Narcissus incomparabilis.*),[145,146] the structure of narciclasine had been subject to several revisions until an X-ray structure was published.[147] It must be pointed out that narciprimine is an extraction artefact, since avoiding acid treatment during the daffodil extraction, it seemed completely absent.[148] Pettit *et al* have recently isolated and identified pancratistatin from *Pancratium littorale*.[149] Regarding their biological activity, narciclasine and lycoricidine are powerful antimitotic agents that effectively inhibit eukaryotic protein synthesis at the ribosomal level.[150] Competitive binding studies suggest that narciclasine inhibits protein elongation by binding to intact 80S ribosomes at or near the peptidyl transferase centre, a site that appears to be accessible to structurally diverse elongation inhibitors including anisomysine, homoharringtonine, and the biogenetically related *amaryllidaceae* alkaloids haemanthamine and pretazettine. [151] On the other hand, pacratistatin exhibits pronounced *in vivo* antitumor activity in animal models and demonstrates significantly higher therapeutic indices than narciclasine and lycoricidine.[152]

Simpler isoquinolones are also known to have interesting biological activities, for example, 4-aryl-1(2*H*)-isoquinolones (**Figure 5.10**) are reported to be

cholesterol biosynthesis inhibitors,[153] antiulcer,[154] anticholinergic[155] and anticonvulsive agents.[156]

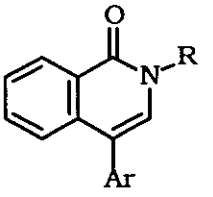
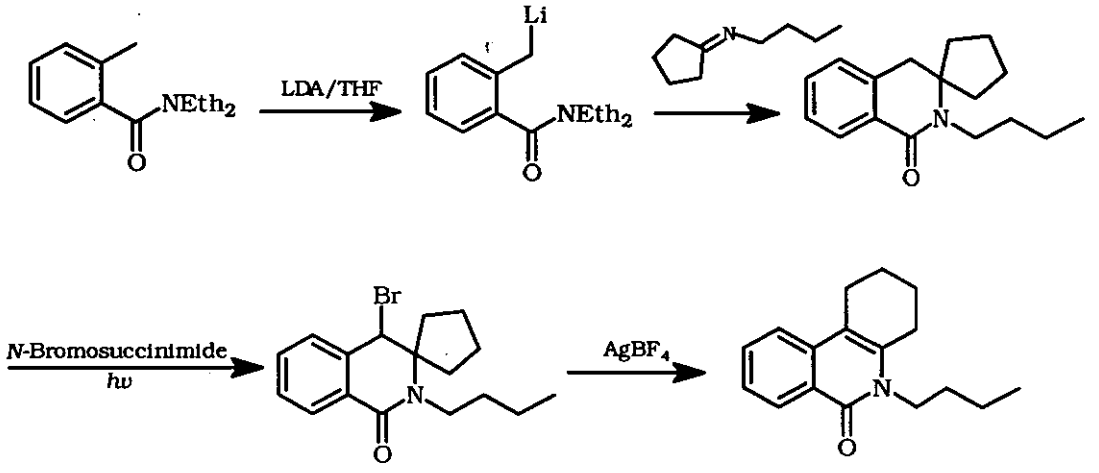


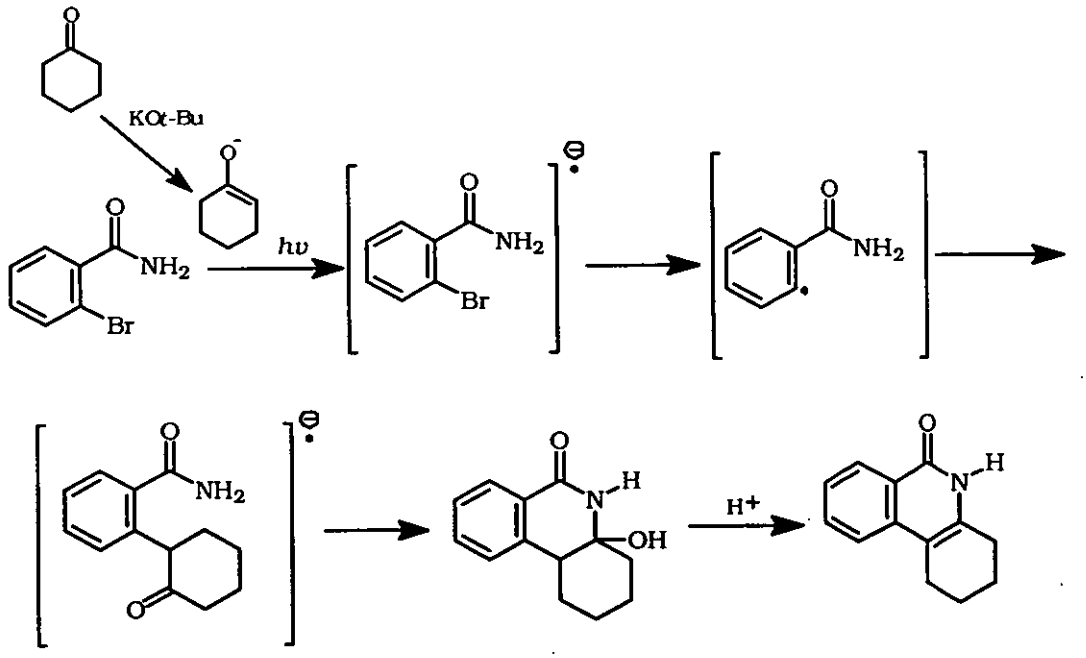
Figure 5.10.

Many synthetic approaches to the phenanthridinone and related isoquinolone ring systems have been reported.[145] Some recent selected approaches are reviewed in the following. Jahangir *et al.*[157] have synthesised *N*-butyl-1,2,3,4-tetrahydrophenanthridinone ring system, in 28% yield, starting from *N,N*-diethyl-*o*-toluamide by a route involving, in the final step, a Lewis acid induced rearrangement to a benzylic position, as in **Scheme 5.63.**



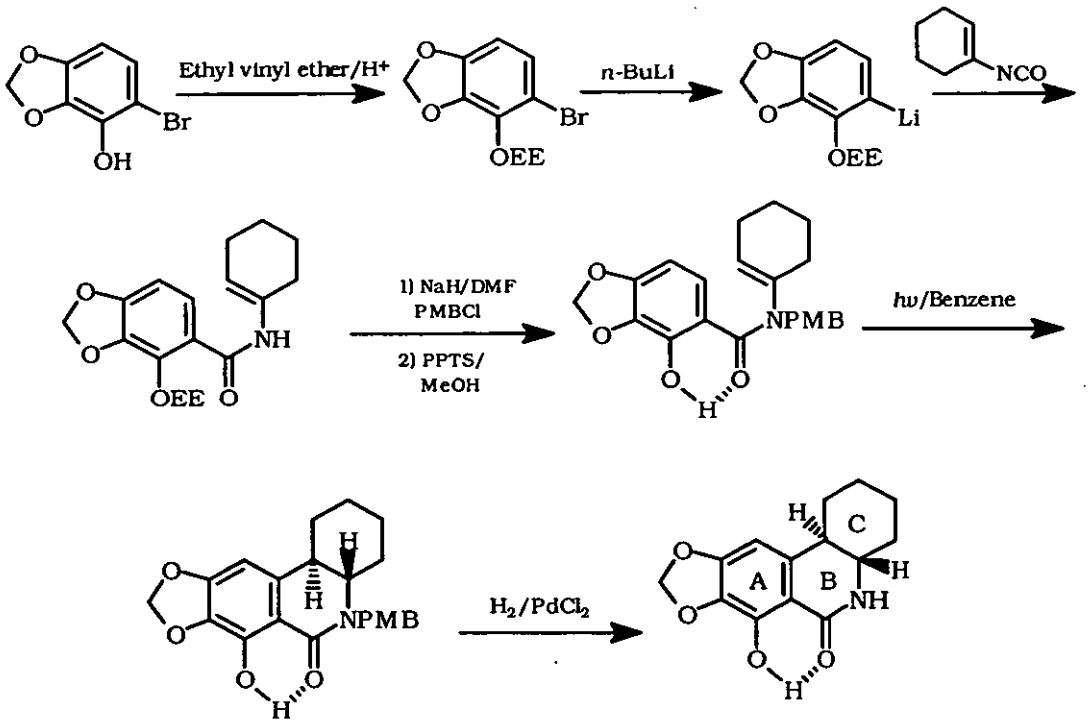
Scheme 5.63

Beugelmans *et al.*[158] utilised aromatic $S_{RN}1$ reactions, in one pot procedures, to generate various 3,4-disubstituted 1-oxo-1,2-dihydroisoquinolines (isocarbostyrils) including tetrahydrophenanthridinone, which was synthesised in 30% yield starting from *o*-bromobenzamide and cyclohexanone. The reaction is outlined in **Scheme 5.64.**



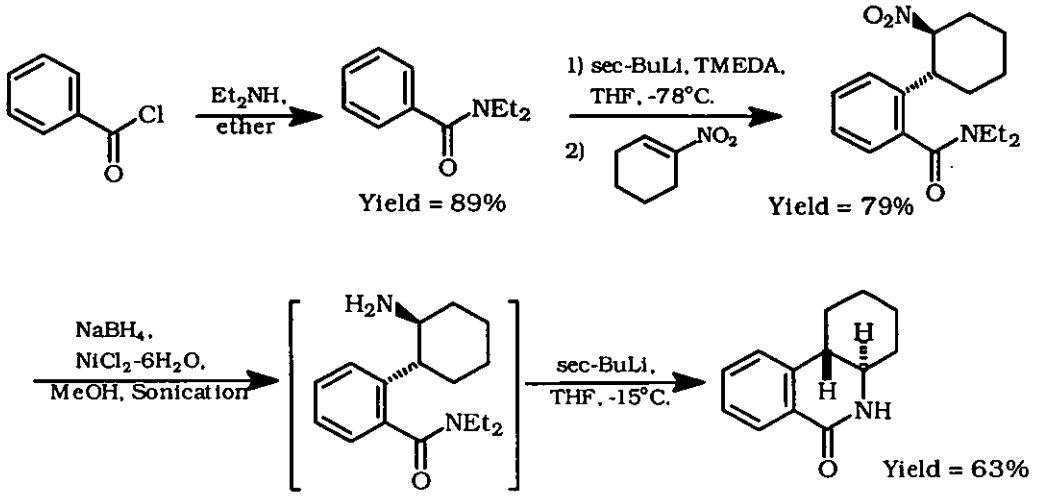
Scheme 5.64

Rigby *et al.*[159] utilised a photocyclisation approach to synthesis the phenanthridinone core of pancratistatin. The regiocontrolled arylamide photocyclisation was the key step to produce *trans*-BC ring junction, the regiocontrol was achieved by allowing hydrogen bond formation between a free A-ring phenol and the adjacent enamide carbonyl. The overall yield of all steps is 18 %. Their synthetic route is outlined in **Scheme 5.65**.



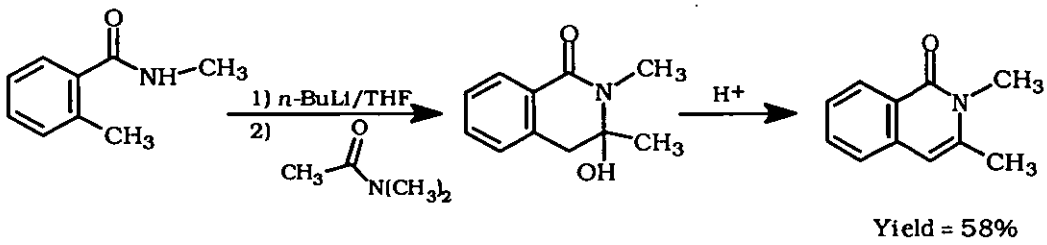
Scheme 5.65

Lopes *et al.*[160] synthesised the phenanthridinone core of the cytotoxic alkaloid pancratistatin. The key manoeuvre in their synthesis is the 1,4-addition of an ortho-lithiated benzamide derivative to 1-nitrocyclohexane. The synthetic steps and their corresponding yields are outlined in **Scheme 5.66**.



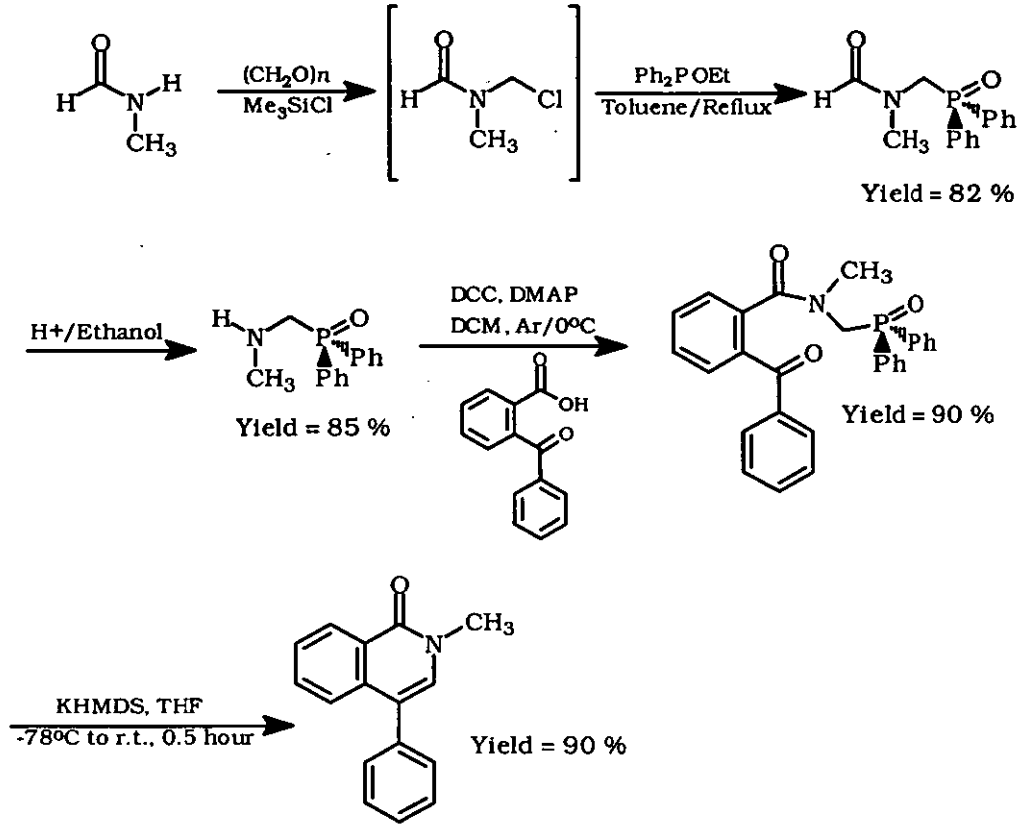
Scheme 5.66

Mali *et al.*[161] reported a general one-step synthesis of 2-methyl-1,2-dihydroisoquinolones from *N*,2-dimethylbenzamide via lithiation followed by reaction of the dilithiated derivative with *N*,*N*-dimethyl-carboxamides. The yields ranged from 58-77%. **Scheme 5.67** illustrates one of their reactions.



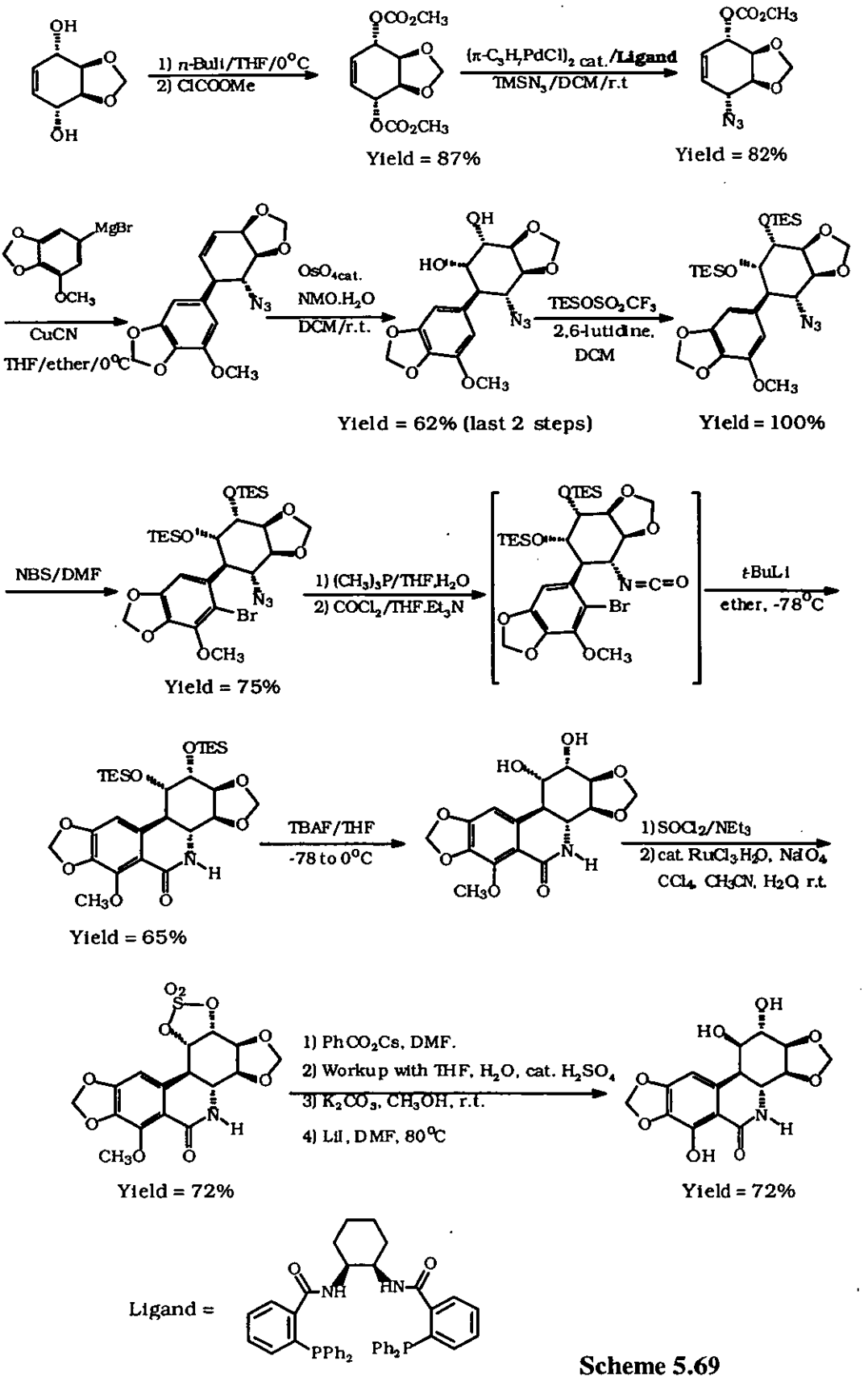
Scheme 5.67

Recently, Couture *et al.*[162] prepared 4-aryl and heteroaryl-1(*2H*)-isoquinolones by base promoted cyclisation of phosphorylated *o*-aroyl and heteroaroyl benzamides. **Scheme 5.68** shows an example of their work.



Scheme 5.68

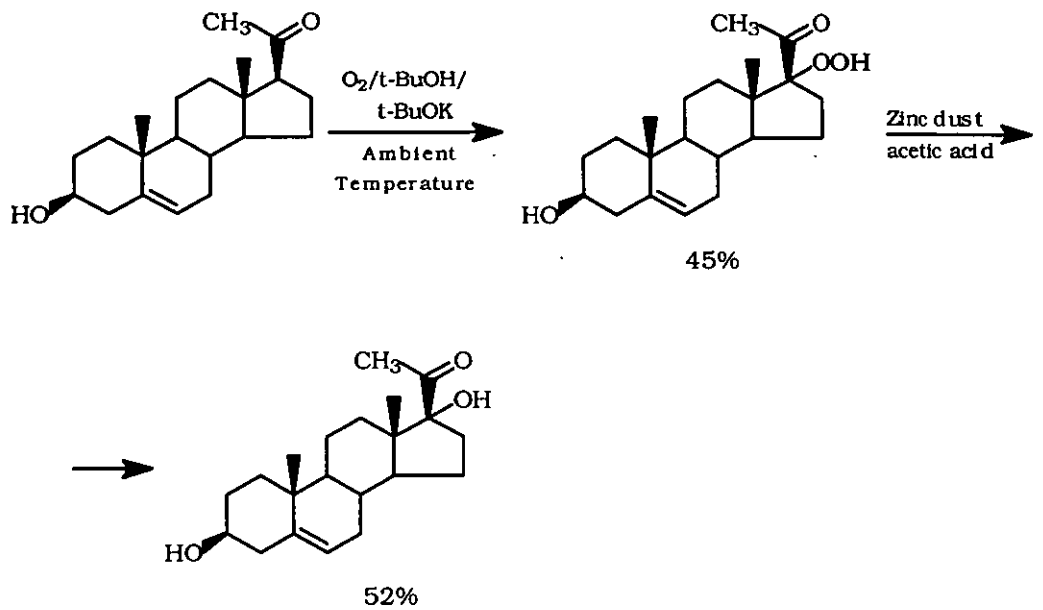
Trost *et al.*[163] reported an elegant asymmetric total synthesis of pancratistatin, in which a palladium-catalysed approach to desymmetrization was utilised to construct rings B and C within the pancratistatin structure. **Scheme 5.69** illustrates their synthesis.


1) n-BuLi/THF/0°C
2) ClCOOMe
(π-C3H7PdCl)2 cat./Ligand
TMSN3/DCM/r.t
Yield = 87%
Yield = 82%
CuCN
THF/ether/0°C
OsO4cat.
NMO.H2O
DCM/r.t.
TESOSO2CF3
2,6-lutidine.
DCM
Yield = 62% (last 2 steps)
Yield = 100%
NBS/DMF
1) (CH3)3P/THF,H2O
2) COCl2/THF.Et3N
t-BuLi
ether, -78°C
Yield = 75%
TBAF/THF
-78 to 0°C
1) SOCl2/NEt3
2) cat. RuCl3.H2O, NaIO4
CCl4, CH3CN, H2O, r.t.
Yield = 65%
1) PhCO2Cs, DMF.
2) Workup with THF, H2O, cat. H2SO4
3) K2CO3, CH3OH, r.t.
4) LiI, DMF, 80°C
Yield = 72%
Yield = 72%
Ligand =

Scheme 5.69

Chapter 6: The Oxidation of 4-Monosubstituted Homophthalimides by Dioxygen in Alkaline Media and The Related Cleavage-Cyclisation Reactions.

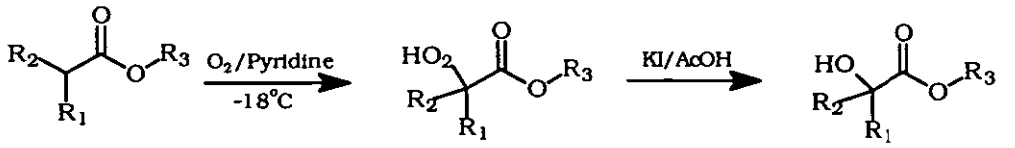
The alkaline-mediated dioxygen oxidation of carbonyl groups is a known reaction.[164] For example, Bailey *et al.* [165,166] found that steroidal ketones, when converted to the enol form, using sodium or potassium alkoxides, can be easily oxidised with dioxygen to the α-hydroperoxyketone derivatives in 40-60% yields. The reaction gave best results with a large excess of the alkoxide. The α-hydroperoxides were either spontaneously dehydrated to the corresponding di-ketones in quantitative yield, or reduced to the hydroxy-ketones with zinc dust/acetic acid in 50-70 % yield. **Scheme 6.1** illustrates one of the reported reactions.



Scheme 6.1

The same group found that only tertiary alkoxides can induce the reaction, while primary or secondary alkoxides failed to do so. Avramoff *et al.*[167] reported the preparation of α-hydroperoxy-esters *via* the autoxidation of esters of diaryl-and (arylalkyl)aryl acetic acids. The reactions were carried out in pyridine in the presence of catalytic amounts of the phase transfer catalyst benzyltrimethyl ammonium hydroxide. The reactions were carried out under low temperatures

(-30 – 0 °C) and the yields ranged from 28-65% depending on the nature of R_1, R_2 and R_3. One of their reactions is illustrated in **Scheme 6.2**.



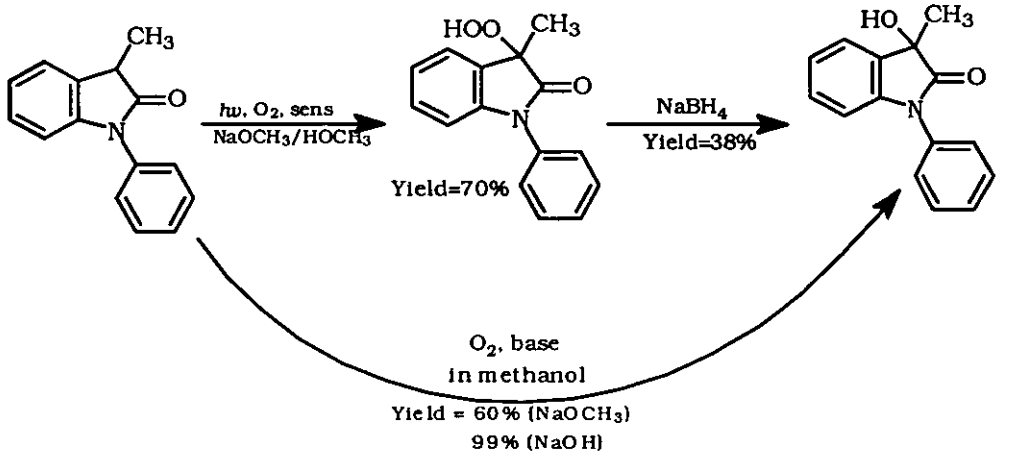
R_1= *p*-$MeOC_6H_4CH_2$

R_2= Phenyl

R_3= Ethy

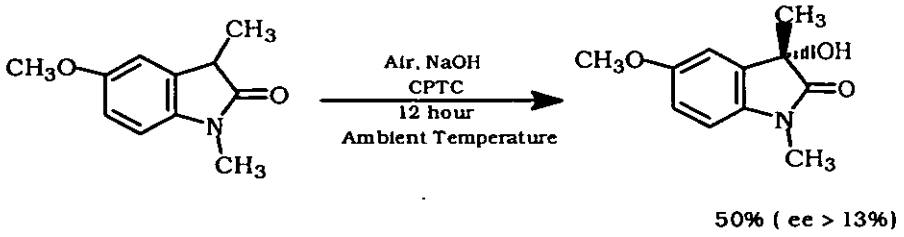
Scheme 6.2

Nishio[168] reported the formation of 3-hydroperoxyindolin-2-one by the dye-sensitised photooxygenation of indolin-2-ones. One of the prepared peroxides was reduced to the corresponding alcohol in 38% yield using sodium borohydride. The author also found that 3-hydroxyindolin-2-one was formed as the sole product from the direct air oxidation (without dye-sensitisation) of indolin-2-ones in the presence of catalytic amounts of sodium hydroxide or sodium methoxide. An example reaction is illustrated in **Scheme 6.3**.



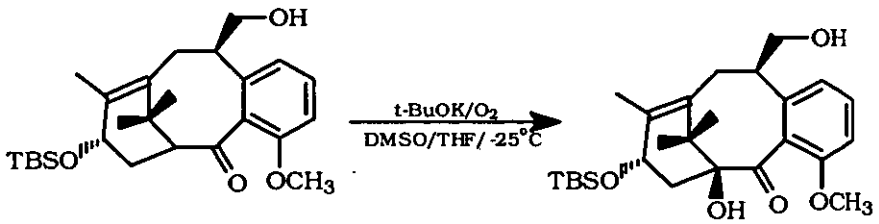
Scheme 6.3

Yu *et al.*[169] reported the preparation of the optically active 1,3-dimethyl-3-hydroxy-5-methoxyoxindole in 50% yield *via* air oxidation of 1,3-dimethyl-5-methoxyoxindole in 50% NaOH aqueous solution and in the presence of the chiral catalyst *N*-[(4-trifluoromethyl) benzyl] cinchonium bromide. The reaction is illustrated in **Scheme 6.4**.



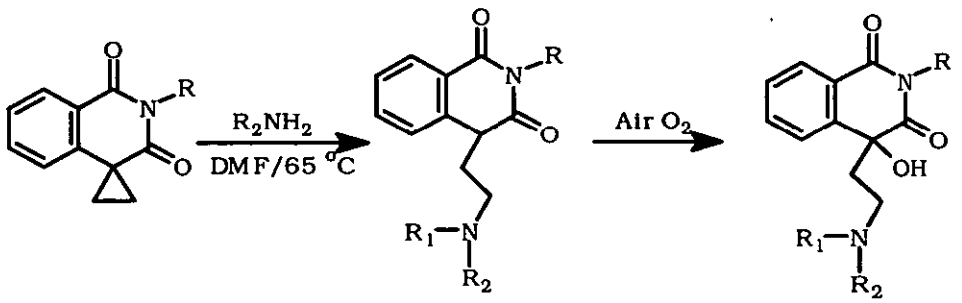
Scheme 6.4

A recent example of the use of this type of oxidation reaction was reported by Wender *et al.*[170] when they utilised the reaction in two steps in their pinene route to taxanes. One of the steps is illustrated in **Scheme 6.5**.



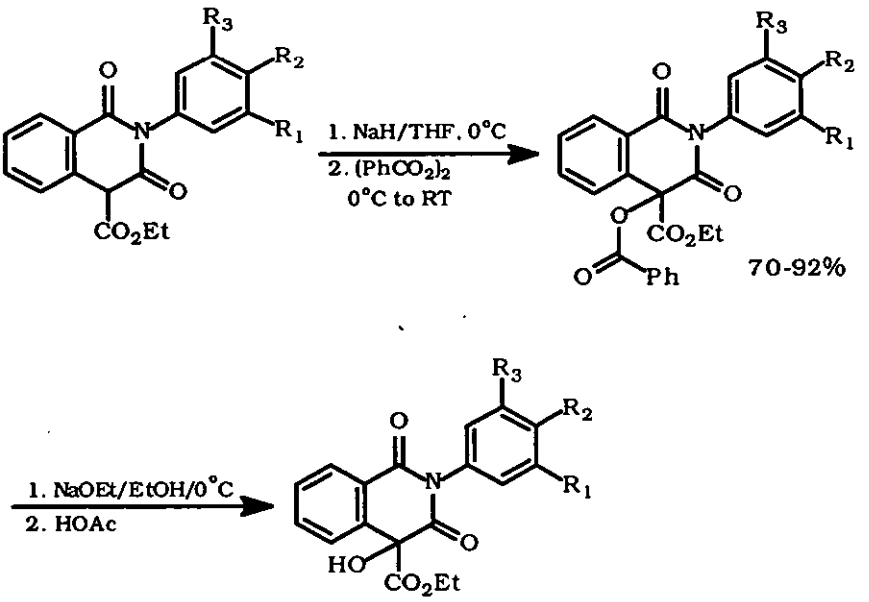
Scheme 6.5

This type of reaction has been reported only rarely using homophthalimide derivatives. According to our best knowledge, the only paper to report the air oxidation of homophthalimide derivatives was by Horning *et al.*,[27] when they reported the oxidation of 4-(*N*,*N*-dialkyl-amino) ethyl homophthalimides in the solid state. They obtained the corresponding hydroxy derivatives upon exposure of the crystalline starting materials to air. Their starting materials were attained from treating the 4-spirocyclopropane derivatives with various amines, as illustrated in **Scheme 6.6** but the yields obtained were not reported.



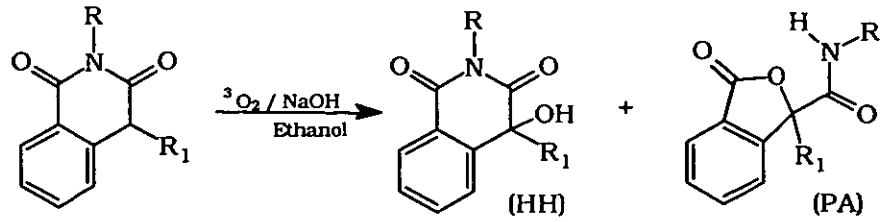
Scheme 6.6

Recently, Semple *et al.*[171] described an efficient route to the preparation of the herbicidal agents ethyl 2-aryl-4-hydroxy-1,3(2*H*, 4*H*)-homophthalimide-4-carboxylates starting form corresponding non-hydroxylated homophthalimides *via* treating the sodium enolates of the starting homophthalimides with benzoyl peroxide followed by the selective alcoholysis of the benzoyl group with sodium ethoxide as in **Scheme 6.7**.



Scheme 6.7

We were interested in exploring the oxygen-induced oxidation of homophthalimides in order to increase our understanding of the mechanism of such reaction, and to explore novel and concise routes to phthalide-isoquinoline alkaloidal analogues. We conducted a number of experiments in which the starting homophthalimide was heated to reflux in oxygen-saturated ethanol (aqueous or anhydrous) and in the absence or the presence of NaOH (catalytic or equivalent amounts), as illustrated in **Table 6.1**. These reactions generally yielded two types of compounds, 4-hydroxy-homophthalimides (HH) and phthalideamides (PA). The transformation is outlined in **Scheme 6.8**.



Scheme 6.8

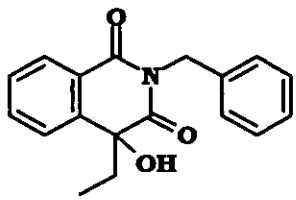
Table 6.1

No.	Starting Material	NaOH†† equiv.	Reaction Time (hours)	HH (Yield%)	PA (Yield%)	SM† %
1	**2.1**	0.15	3 days	non	non	100
2	**3.18**	1.10	4	**6.1** (10)	**6.2** (51)	non
3	**3.18**	0.15	9	(36)	(25)	non
4	**3.20**	1.00	24	**6.3** (10)	**6.4** (51)	---**
5	**3.22**	0.15	17	(33)	(13)	57
6	**3.23**	1.10*	6	non	**6.7** (22)	non
7	**3.23**	1.10	7	non	(quant.)	non
8	**3.23**	1.0	5	non	(quant.)	non
9	**3.23**	0.15	5	non	(89)	non
10	**3.23**	non	5	non	non	100
11	**3.24**	1.1	5	----**	**6.8** (91)	---**

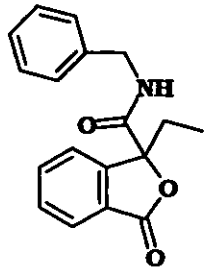
†† Number of sodium hydroxide equivalents used.

* Solvent: ethanol/water [5:8]. †Remaining starting material

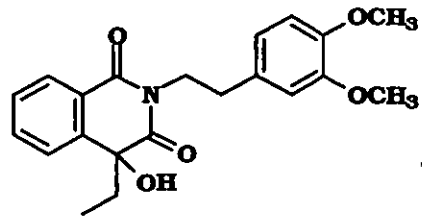
** Isolation was not attempted.



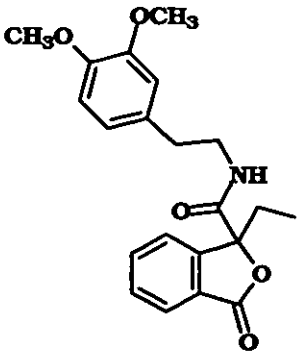
6.1



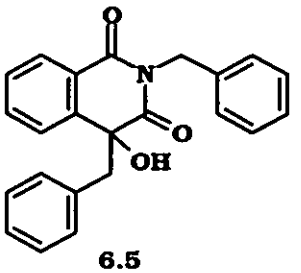
6.2



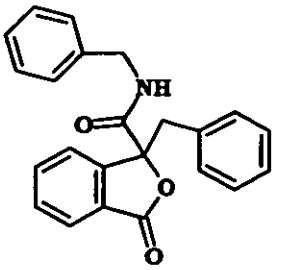
6.3



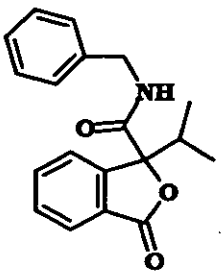
6.4



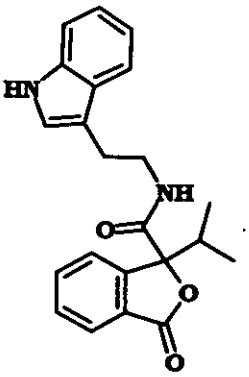
6.5



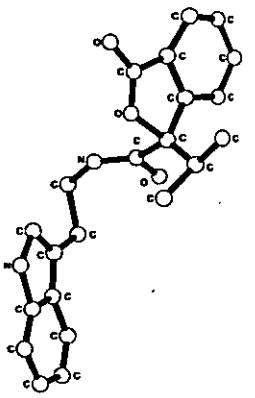
6.6



6.7



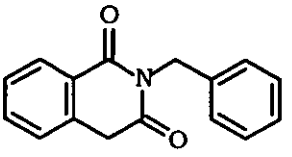
6.8



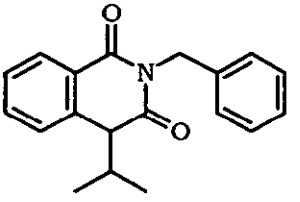
X-ray picture for **6.8**

From **Table 6.1** the following are interesting points for discussion.

1. The presence of sodium hydroxide proved to be essential for the reaction to proceed, as the oxidation of **3.23** to the corresponding phthalideamide **6.7** did not take place under neutral conditions (reaction 10 in **Table 6.1**). However, the reaction proceeded efficiently in the presence of catalytic or equivalent amounts of sodium hydroxide.



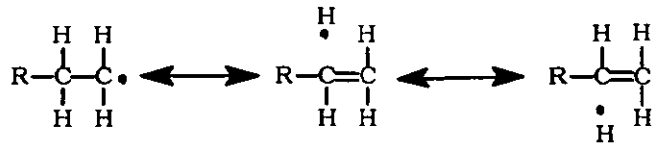
2.1



3.23

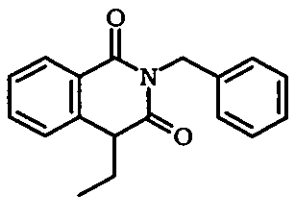
2. When the oxidation was attempted on the nonsubstituted *N*-benzylhomophthalimide **2.1**, no reaction took place and only the starting material was retrieved (reaction 1 in **Table 6.1**). This indicates that substitution at the 4-

position is essential for the oxidation reaction to take place. Presumably, the presence of an alkyl group at position 4 will stabilise radicals generated at that position. Alkyl groups stabilise adjacent radicals through hyperconjugation mechanisms[172] as illustrated in **Scheme 6.9**.

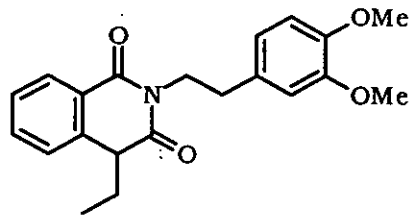


Scheme 6.9

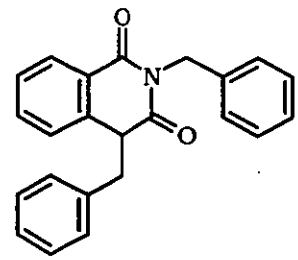
Moreover, the total oxidation yield for each substrate (i.e. the sum of both 4-hydroxyhomophthalimide and phthalideamide yields) is influenced by the nature of the substituent at position 4. The highest oxidation yield is reported for **3.23** with isopropyl group at this position (89-100%, reactions 7, 8 and 9 in **Table 6.1**), while the total oxidation yields for both 4-ethyl derivatives **3.18** and **3.20** are surprisingly the same (61%, reactions 2, 3 and 4), under both catalytic and stoicheiometric amounts of sodium hydroxide. The lowest oxidation yield was for the benzyl derivative **3.22** (46%, reaction 5). The variations in oxidation yields between different substrates are possibly due to the relative stability of the free radical formed at position 4.



3.18



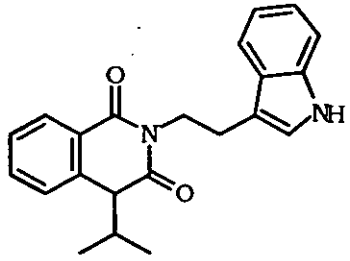
3.20



3.22

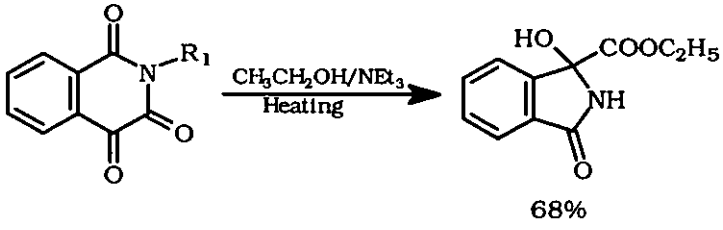
3. When the reaction was conducted in aqueous ethanol (**3.23** in reaction 6 in **Table 6.1**), the isolated oxidation yield suffered a significant decrease (22%). The presence of strong base line spot on the TLC plate suggests that the low yield might be due to the hydrolysis of the starting material by the aqueous sodium hydroxide.
4. Regarding the rearrangement of 4-hydroxyhomophthalimides to phthalideamides, two points are noteworthy: (a) the effect of the 4-alkyl group and (b) effect of the reaction temperature. From **Table 6.1**, it is clear that, under

comparable reflux times, the highest yield of the phthalideamide products were reported for the 4-isopropyl derivatives **3.23** and **3.24** (reactions 7-9 and 11 in **Table 6.1**), then the 4-ethyl derivatives **3.18** and **3.20** (reactions 1, 2 and 3), the least rearrangement yields were for the slowly-oxidised 4-benzyl derivative **3.22** (reaction 5).



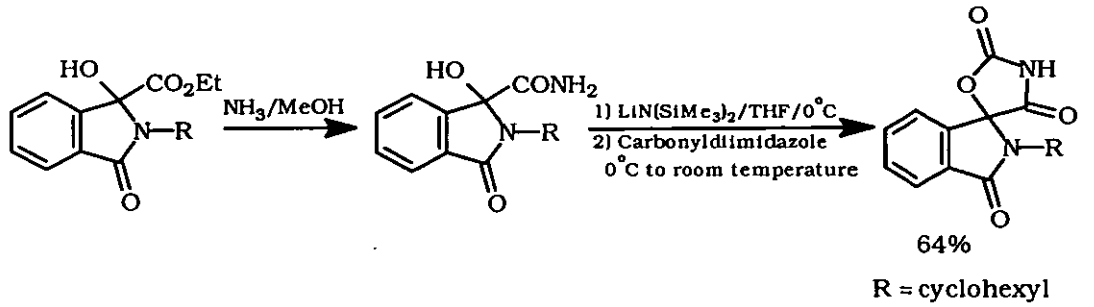
3.24

Such results indicate the dependence of the rearrangement reaction rate on the nature of the 4-substitution. Presumably, differences in the steric strain induced by each of the 3 substituents leads to such variable yields. Regarding the temperature effect, we suspected that the rearrangement reaction is heat-induced, since earlier reports described ring contraction reactions from six-membered to five-membered ring to be heat-induced. For example, the conversion of *N*-substituted isoquinolinetriones into ethyl 3-hydroxyisoindolone-3-carboxylates by heating in ethanol and in the presence of triethylamine,[173] as in **Scheme 6.10**.



Scheme 6.10

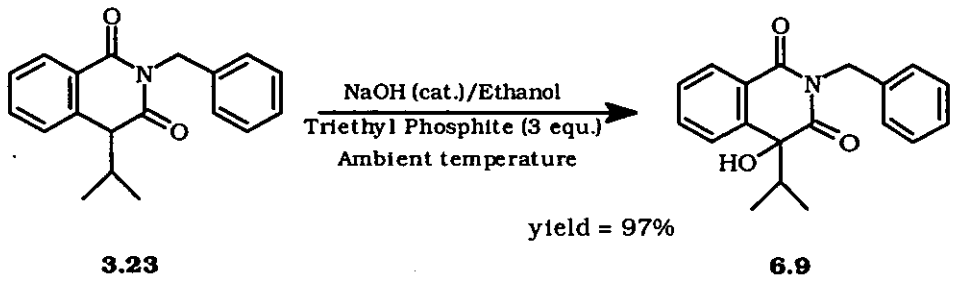
Wrobel *et al.*[174] used this reaction as the key step towards the preparation of the potentially antidiabetic agents, spiro[1H-isoindole-1,5'-oxazolidine] 2',3(2*H*),4'-triones, one of the examples is shown in the **Scheme 6.11**.



Scheme 6.11

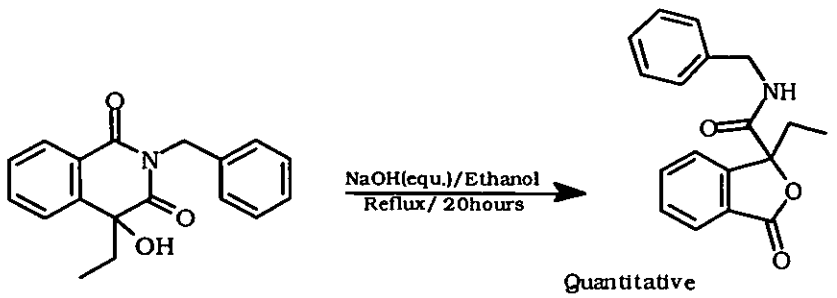
To establish that the formation of the phthalideamides is also heat induced, we conducted two experiments:

1- An ethanolic solution of the homophthalimide **2.23** was treated with a catalytic amount of sodium hydroxide and 3 equivalents of triethyl phosphite (a peroxide reducing agent). The reaction mixture was bubbled with dioxygen gas over 18 hours and at room temperature. Subsequently, the reaction was terminated by extraction with DCM to yield the 4-hydroxy derivative **6.9** in 97% yield as illustrated in **Scheme 6.12.**



Scheme 6.12

2- In the second experiment, an ethanolic solution of the hydroxyhomopthalimide **6.1** was heated under reflux for 20 hours in the presence of an equivalent amount of sodium hydroxide. The reaction was terminated by cooling and extraction with DCM. The ^1H nmr spectrum of the crude reaction mixture showed that the corresponding phthalideamide **6.2** was the sole component. **Scheme 6.13** shows the reaction details.

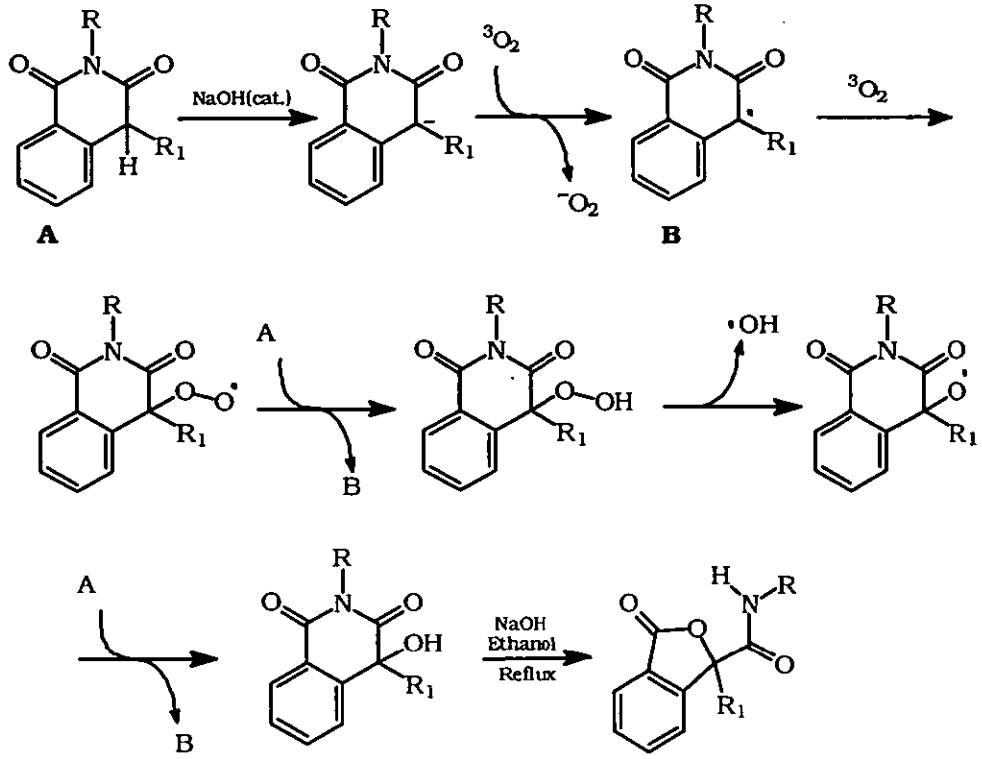


6.1 **6.2**

Scheme 6.13

The two experiments indicate clearly that the ring contraction process is heat-induced.

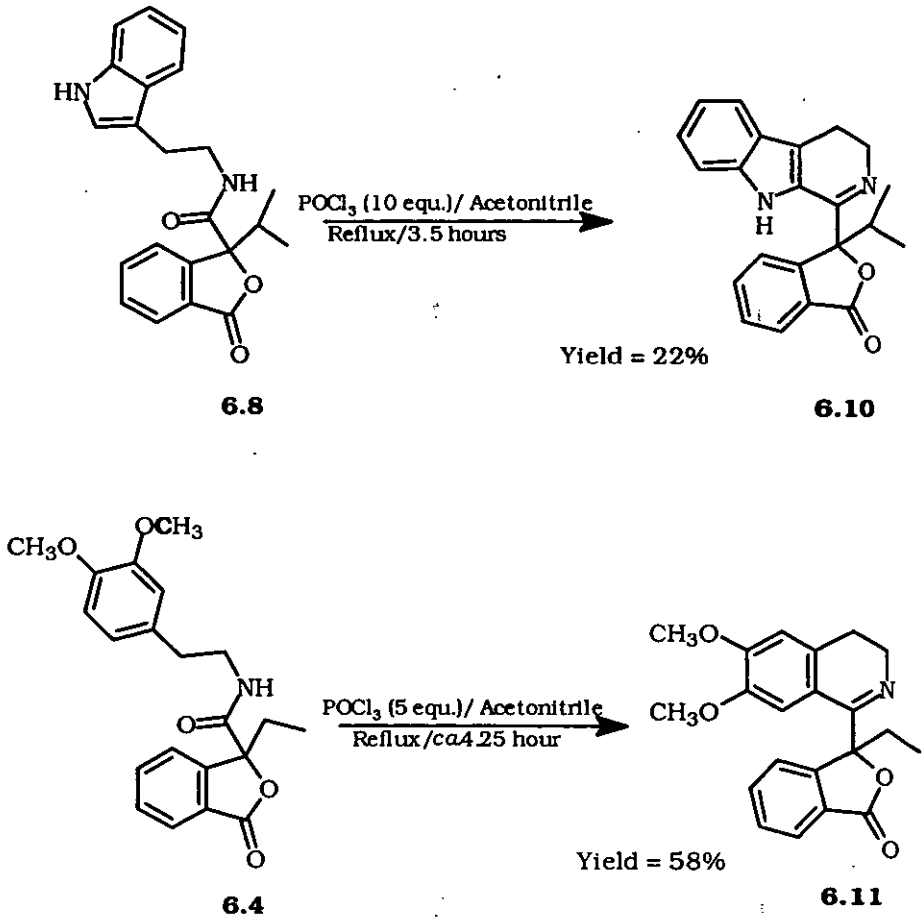
From the results in **Table 6.1** and the other two related reactions (**Schemes 6.12** and **6.13**) it is possible to construct an acceptable mechanistic sequence shown in **Scheme 6.14**. It is clear that a number of alternative routes are available to the initial radical (**B**), for example the involvement of the hydroxy radical in that step would also regenerate hydroxide ion.



Scheme 6.14

After the publishing our results,[10] Ke-Qing *et al.*[178] reported a dye-sensitised photooxygenation of 1,3-isoquinolinediones (homophthalimides).

The preparation of phthalideamide precursors for the Bischler-Napieralski cyclisation reactions that can lead to phthalideisoquinoline alkaloids is frequently troublesome.[175] It is clear that our procedure provides a concise and straight-forward route to phthalideamides. We applied Bischler-Napieralski cyclisation[176] conditions on these products to generate the corresponding phthalideisoquinoline alkaloidal analogues. Such compounds are known to be potent central nervous system active agents.[177] We have prepared two novel phthalide derivatives: the phthalide-β-carboline **6.10** and the phthalide isoquinoline **6.11** using this procedure, **Scheme 6.15** illustrates the products and reaction conditions.



Scheme 6.15

Using one equivalent of phosphoryl chloride and warming to 60 °C were not sufficiently forcing conditions to carry out the cyclisation of **6.8**, as only the starting material was isolated from the reaction mixture.

General Procedures.

Solvents and Reagents - Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction boiling between 40 °C and 60 °C. Light petroleum and ethyl acetate were distilled from anhydrous calcium chloride through a 36 cm vigreux column before use. Dichloromethane was distilled from phosphorus pentoxide.

Chromatographic Procedures - Analytical thin layer chromatography was carried out using glass-backed plates coated in Merck Kieselgel 60 PF_{254}. Plates were visualised by UV light (at 254 and/or 360 nm) or by exposure to an appropriate staining agent. Flash chromatography was carried out using Merck silica gel 60. Pressure was applied at the head of the column with hand bellows. Samples were applied as a concentrated solution in an appropriate solvent.

Spectroscopic Techniques - Infared spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectrometer with internal calibration. Spectra were recorded as thin films or as Nujol mulls. ^{1}H and ^{13}C NMR were recorded using Bruker AC-250 and Bruker DPX-400 instruments. ^{1}H NMR spectra are referenced against residual undeuterated solvent, in the case of deuterio-chlorofom this is 7.260 ppm. Signals are described as singlets (s), doublets (d), double doublet (dd), quartets (q), multiplet (m) *etc.* High and low resolution mass spectra were recorded on a Kratos MS80 instrument.

Other Data and Instrumentation - Melting points were measured on a Electrothermal digital melting point apparatus or using a Kofler hot stage apparatus and are uncorrected. Bulb to bulb distillations were performed on a Buchi GKR-51 Kugelrohr; boiling points refer to air bath temperatures and are uncorrected.

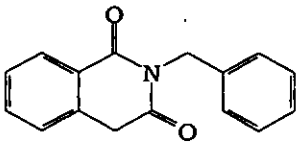
All of the following experimental reactions were carried out under an atmosphere of nitrogen except where it was obviously unnecessary. All coupling constants (*J* values) are quoted in Hertz.

Chapter 2 experimental:

General Method for 1,2,3,4-tetrahydro-1,3-isoquinolinediones Formation.

The amine (1 equivalent) was added to homophthalic anhydride and stirred at 70 °C. The reaction mixture was then heated to the stated temperature for a given length of time.[3, 13, 17] After allowing the mixture to cool to room temperature, the product was purified either by recrystallisation or by flash chromatography on silica gel. The following 1,3-isoquinolinediones were prepared:

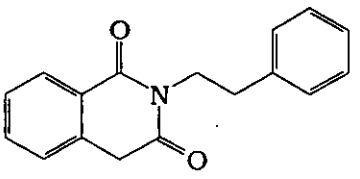
2-Benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.[12, 18, 19, 179,180]



2.1

Benzylamine (1.0g, 9.3 mmol) and homophthalic anhydride (1.5g, 9.3 mmol) were heated at 185 °C for 30 minutes and gave the title compound (**2.1**) (2.3g, 100%), mp 110-112 °C (glass) (lit. [19] 124 - 126 °C) : ν_{max} 3035, 1716 and 1670 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 3.98 (s, 2H), 5.14 (s, 2H), 7.17-7.52 (m, 8H) and 8.15-8.18 (m, 1H) ppm;^{13}C nmr (100.5 M Hz, $CDCl_3$) 37.04 (CH_2), 43.84 (CH_2), 125.95 (C), 127.71 (CH), 128.26 (CH), 128.38 (CH), 128.99 (2 x CH), 129.22 (2 x CH), 129.79 (CH), 134.22 (CH), 134.75 (C), 137.71 (C), 165.25 (C=O) and 170.44 (C=O) ppm; Found: M^+ 251.0950 (88.5%) Calc. for $C_{16}H_{13}NO_2$ 251.0946.

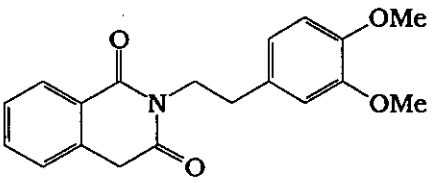
2-Phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.[13,181]



2.2

2-Phenethylamine (0.75g, 6.2 mmol) and homophthalic anhydride (1.0g, 6.2 mmol) were heated at 185 °C for 30 minutes and gave the title compound (**2.2**) after flash chromatography eluting with EA/LP [1:1] (1.4g, 86%), mp 122 - 123.6 °C (lit.[13] 128 - 129 °C) from EA/LP : ν_{max} 3050, 1717 and 1672 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.89- 2.95 (m, 2H), 4.01 (s, 2H), 4.18-4.25 (m, 2H), 7.20-7.62 (m, 8H) and 8.20-8.23 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 34.54 (CH_2), 36.78 (CH_2), 41.92 (CH_2), 125.76 (C), 126.87 (CH), 127.54 (CH), 128.141 (CH), 128.87 (2 x CH), 129.38 (2 x CH), 129.51 (CH), 134.03 (CH), 134.48 (C), 139.00 (C), 165.12 (C=O) and 170.20 (C=O) ppm; Found: C, 76.60, H, 5.53, N, 5.43% Calc. for $C_{17}H_{15}NO_2$ C, 76.98, H, 5.66, N, 5.28%; Found: M^+ 265.1109 (9.2%) Calc. for $C_{17}H_{15}NO_2$ 265.1103.

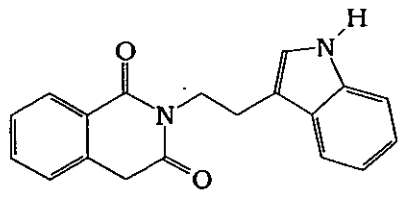
2-(3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydro-1,3-isoquinolinedione.[14,15, 180,181]



2.3

2-(3,4-Dimethoxyphenyl)ethyl amine (1.1g, 6.2 mmol) and homophthalic anhydride (1.0g, 6.2 mmol) were heated at 185 °C for 30 minutes and gave the title compound (**2.3**) after flash chromatography eluting with EA/LP [1:1] (1.8g, 90%), mp 145 - 146.4 °C (lit.[14] 147 - 148 °C) from EA/LP : ν_{max} 3055, 1716 and 1668 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.81-2.87 (m, 2H), 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.99 (s, 2H), 4.13-4.20 (m, 2H), 6.76-6.81 (m, 3H), 7.22-7.56 (m, 3H) and 8.17-8.20 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 33.61 (CH_2), 36.29 (CH_2), 41.53 (CH_2), 55.74 (CH_3, OMe), 55.78 (CH_3, OMe), 111.11 (CH), 111.99 (CH), 120.85 (CH), 125.26 (C), 127.06 (CH), 127.66 (CH), 128.96 (CH), 131.03 (C), 133.54 (CH), 134.01 (C), 147.50 (C), 148.72 (C), 164.64 (C=O) and 169.73 (C=O) ppm; Found: C, 69.51, H, 6.05, N, 4.41% $C_{19}H_{19}NO_4$ requires C, 70.15, H, 5.84, N, 4.31%; Found: M^+ 325.1318 (8.0 %) Calc. for $C_{19}H_{19}NO_4$ 325.1314.

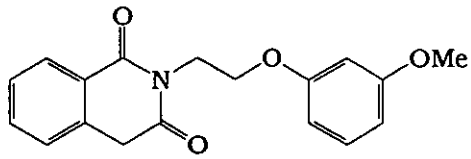
2-[2-(1H-3-Indolyl)ethyl]-1,2,3,4-tetrahydro-1,3-isoquinolinedione. [16,17,182,183]



2.4

Tryptamine (1.0g, 6.2 mmol) and homophthalic anhydride (1.0g, 6.2 mmol) were heated at 185 °C for 30 minutes and gave the title compound (**2.4**) (1.6g, 85%), mp 192-194.5 °C (lit.[182] 195 - 196 °C) from DCM: ν_{max} 3370 (broad), 3154, 1708, and 1655 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.10-3.14 (m, 2H), 4.04 (s, 2H), 4.31-4.35 (m, 2H), 7.13-7.88 (m, 8H), 8.00 (br.s, 1H, N-H) and 8.26-8.28 (m, 1H) ppm; ^{13}C nmr (100.5M Hz, $CDCl_3$) 24.30 (CH_2), 36.85 (CH_2), 41.30 (CH_2), 111.39 (CH), 113.43 (C), 119.58 (CH), 119.89 (CH), 122.44 (CH), 122.45 (CH), 125.92 (C), 127.48 (CH), 128.00 (C), 128.10 (CH), 129.52 (CH), 133.94 (CH), 134.53 (C), 136.64 (C), 165.26 (C=O) and 170.33 (C=O) ppm; Found: M^+ 304.1209 (8.8%) Calc. for $C_{19}H_{16}N_2O_2$ 304.1212.

2-[2-(3-Methoxyphenoxy)ethyl]- 1,2,3,4-tetrahydro-1,3-isoquinolinedione.

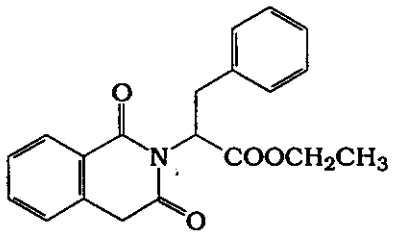


2.5

2-(3-Methoxyphenoxy)ethylamine (**2.12**) (0.7g, 4.2 mmol) and homophthalic anhydride (0.68g, 4.2 mmol) were heated at 175 °C for 95 minutes and gave the title compound (**2.5**) after flash chromatography eluting with EA/LP [1:3] (1.2g, 92%), mp 75-77 °C from EA/LP : ν_{max} 2961, 1717, 1671 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.77 (s, 3H, OMe), 4.05 (s, 2H), 4.21 (t, 2H, *J* 6.2), 4.44 (t, 2H, *J* 6.2), 6.48-6.53 (m, 3H), 7.15 (t, 1H, *J* 8.5), 7.25-7.28 (m, 1H), 7.45 (t, 1H, *J* 7.5), 7.59 (t, 1H, *J* 7.5) and 8.22-8.24 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 36.76 (CH_2), 39.32 (CH_2), 55.64 (CH_3, OMe), 64.89 (CH_2), 101.33

(CH), 107.02 (CH), 107.17 (CH), 125.58 (C), 127.57 (CH), 128.13 (CH), 129.58 (CH), 130.24 (CH), 134.14 (CH), 134.54 (C), 160.15 (C), 161.19 (C), 165.26 (C=O) and 170.45 (C=O) ppm; Found: M^+ 311.1157 (6.3%) $C_{18}H_{17}NO_4$ requires 311.1157.

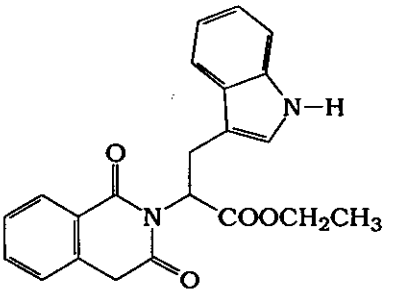
Ethyl 2-(1,3-dioxo-1,2,3,4-tetrahydro-2-isoquiolinyl)-3-phenylpropanoate.



2.6

Phenylalanine ethylester (0.9g, 4.7 mmol) and homophthalic anhydride (0.75g, 4.7 mmol) were heated at 185°C for 95 minutes and gave the title compound (**2.6**) after flash chromatography eluting with EA/LP [1:3] (0.46, 29%), pale yellow oil: ν_{max} 2981, 1741, 1720, 1675 and 1604 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.19 (t, 3H, *J* 7.1), 3.40 (dd, 1H, B of ABX, J_{AB} 14.1, J_{BX} 10.0), 3.62 (dd, 1H, A of ABX, J_{AB} 14.3, J_{AX} 5.7), 3.78 (d, 1H, A of AB, J_{AB} 22.3), 3.93 (d, 1H, B of AB J_{AB} 22.3), 4.21-4.29 (m, 2H), 5.81 (dd, 1H, X of ABX, J_{AX} 5.7, J_{BX} 10.0), 7.13-7.25 (m, 6H), 7.42 (t, 1H, *J* 7.6), 7.57 (t, 1H, *J* 7.5) and 8.15-8.17 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 14.53 (CH_3), 35.18 (CH_2), 36.62 (CH_2), 54.58 (CH), 61.95 (CH_2), 125.28 (C), 127.03 (CH), 127.49 (CH), 128.16 (CH), 128.72 (2 x CH), 129.63 (2 x CH), 134.23 (CH), 134.31 (C), 137.72 (C), 139.00 (C), 164.74 (C=O), 169.86 (C=O) and 169.88 (C=O) ppm; Found: M^+ 337.1315 (12.8%), $C_{20}H_{19}NO_4$ requires 337.1314. COSY and HETCOR experiments support characterisation.

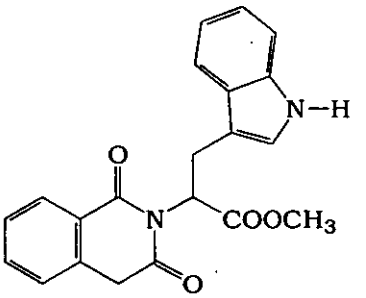
Ethyl 2-(1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl) propanoate.



2.7

Tryptophane ethylester (**2.13**) (1.96g, 8.5 mmol) and homophthalic anhydride (1.37g, 8.5 mmol) were heated at 175 °C for 120 minutes and gave the title compound (**2.7**) after flash chromatography eluting with EA/LP [1:4] (1.0g, 31%), mp 69-72 °C from EA/LP : ν_{max} 3405 (broad), 2982, 1740, 1718, 1670 and 1606 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.25 (t, 3H, *J* 7.1), 3.58-3.88 (m, 4H), 4.20-4.27 (m, 2H), 5.86 (dd, 1H, X of ABX, J_{AX} 5.8, J_{BX} 9.5), 6.98-7.58 (m, 8H), 8.10-8.13 (m, 1H) and 8.15 (br.s, 1H, N-H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 14.20 (CH_3), 24.50 (CH_2), 36.32 (CH_2), 54.05 (CH), 61.47 (CH_2), 111.09 (CH), 111.58 (C), 118.58 (CH), 119.34 (CH), 121.86 (CH), 122.95 (CH), 125.05 (C), 127.01 (CH), 127.56 (C), 127.67 (CH), 129.18 (CH), 133.72 (CH), 134.02 (C), 136.01 (C), 164.52 (C=O), 169.60 (C=O) and 169.80 (C=O) ppm; Found: M^+ 376.1417 (6.5%) $C_{22}H_{20}N_2O_4$ requires 376.1423.

Methyl 2-(1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl) propanoate.

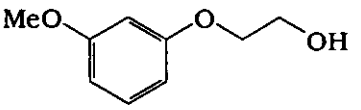


2.8

Tryptophane methylester (**2.14**) (6.1g, 27.7mmol) and homophthalic anhydride (4.5g, 27.7 mmol) were heated at 180 °C for 140 minutes and gave the title compound (**2.8**) after flash chromatography eluting with EA/LP [1:3] (2.7g, 27%), mp 78-80 °C from EA/LP : ν_{max} 3406 (broad), 2951, 1740, 1716, 1670 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.59-4.04 (m, 4H), 3.78 (s, 3H, OMe), 5.88 (dd, 1H, X of ABX, J_{AX} 5.7, J_{BX} 9.5), 7.02-7.60 (m, 8H), 7.99 (br.s, 1H, N-H), 8.15-8.17 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 24.87 (CH_2), 36.65 (CH_2), 52.90 (CH), 54.25 (CH_3, OMe), 111.40 (CH), 111.99 (C), 118.98 (CH), 119.81 (CH), 122.33 (CH), 123.23 (CH), 125.40 (C), 127.39 (CH), 127.92 (C), 128.07 (CH), 129.64 (CH), 134.15 (CH), 134.40 (C), 136.35 (C), 164.86 (C=O), 169.94 (C=O) and 170.65 (C=O) ppm; Found: M^+ 362.1268 (8.1%) $C_{21}H_{18}N_2O_4$ requires 362.1267. COSY and HETCOR experiments support characterisation.

The Intermediates in the Preparation of 2-(3-Methoxyphenoxy)ethylamine.

2-(3-Methoxyphenoxy)-1-ethanol.[21,84,185]

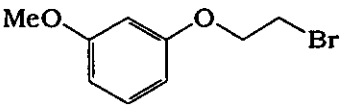


2.9

Procedure modified from that described by Motwani and Wheeler.[21] A magnetically stirred solution of *p*-methoxyphenol (10g, 80.6 mmol), 2-chloroethanol (8g, 99.4mmol) and potassium hydroxide (12 ml, 40% aqueous solution) was heated to reflux for 3 hours. Subsequently the reaction mixture was allowed to cool down to room temperature. The aqueous layer was then extracted with diethyl ether (2 x 200 ml), then the organic layer was washed with potassium hydroxide (40% aqueous solution) until the washings became colourless. The organic extract was then dried over magnesium sulfate and concentrated in *vacuo* and gave the title compound (**2.9**) after vacuum distillation (4.0g, 30%), colourless oil, bp 104 °C/1.0 mmHg (lit.[21] 160 °C/2.0 mmHg) : ν_{max} 3385 (broad), 2940, and 1603 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.60 (br.s, 1H, OH), 3.78 (s, 3H, OMe), 3.91-3.97 (m, 2H), 4.05 (t, 2H, *J* 4.1),

6.48-6.55 (m, 3H) and 7.18(t, 1H, *J* 8.1) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 55.30 (CH_3, OMe), 61.40 (CH_2), 69.29 (CH_2), 101.20 (CH), 106.69 (CH), 106.79 (CH), 129.98 (CH), 159.92 (C) and 160.88 (C) ppm; Found: M^+ 168.0788 (100%) Calc. for $C_9H_{12}O_3$ 168.0786.

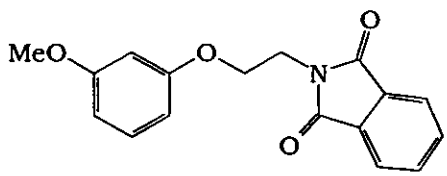
1-(2-Bromoethoxy)-3-methoxybenzene. [22,186,187]



2.10

A scaled-down and modified procedure from that employed by Drain *et al.*[22]
A magnetically stirred solution of 2-(3-methoxyphenoxy)-1-ethanol (**2.9**) (4g, 23.8 mmol) in chloroform (20 ml) was cooled down to 0 °C and phosophorus tribromide (3.4g, 12.6 mmol) added. The reaction mixture was then stirred at the same temperature for 90 minutes then warmed to room temperature and heated to reflux for a further 1 hour. Subsequently, the reaction mixture was cooled down to room temperature and quenched with aqueous saturated sodium bicarbonate solution (100 ml). Extraction of resultant cloudy emulsion with DCM (2 x 100 ml) and drying of the combined organic extracts over magnesium sulfate followed by concentrating in *vacuo* gave the title compound (**2.10**) after flash chromatography eluting with EA/LP [1:2] (1.6g, 30%), colourless oil, lit.[186] bp 95 - 96 °C/0.35 mmHg : ν_{max} 2938, and 1604 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.66 (t, 2H, *J* 6.2), 3.83 (s, 3H, OMe), 4.31 (t, 2H, *J* 6.2), 6.54-6.61 (m, 3H) and 7.24 (t, 1H, *J* 8.2) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 29.32 (CH_2), 55.43 (CH_3, OMe), 67.98 (CH_2), 101.48 (CH), 106.85 (CH), 107.19 (CH), 130.16 (CH), 159.46 (C) and 161.05 (C) ppm; Found: M^+ 229.9948 (84.4%) Calc. for $C_9H_{11}O_2Br$ 229.9943.

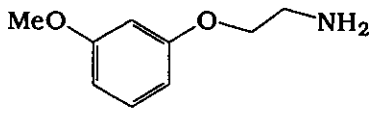
2-[2-(3-Methoxyphenoxy)ethyl]-1,3-isoindolinedione. [187]



2.11

Procedure modified from that of Bogdal *et al.*[23] A mixture of 1,3-isoindoline-dione (1.0g, 6.8 mmol), 1-(2-bromoethoxy)-3-methoxybenzene (**2.10**) (1.5g, 6.5 mmol), tributyl ammonium hydrogen sulfate (0.25g, 0.75 mmol) (lit.[23] tetrabutyl ammonium bromide) and potassium carbonate (2.6g, 18.8 mmol) was heated in a domestic microwave oven (450 W) in an open Erlenmeyer flask for 7 minutes. After cooling down, the reaction mixture was extracted with DCM (2 x 200). Then the extracts were dried over magnesium sulfate, filtered, and the solvent was evaporated to dryness and gave the title compound (**2.11**) (1.8g, 93%), mp 104-105 °C (lit.[187] 114 - 115 °C) from DCM : ν_{max} 1711 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.78 (s, 3H, OMe), 4.13 (t, 2H, *J* 5.7), 4.22 (t, 2H, *J* 5.7), 6.46-6.52 (m, 3H), 7.16 (t, 1H, *J* 8.2), 7.74-7.76 (m, 2H) and 7.88-7.91 (m, 2H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 36.71 (CH_2), 54.65 (CH_3, OMe), 64.10 (CH_2), 100.44 (CH), 106.00 (CH), 106.36 (CH), 122.73 (2 x CH), 129.24 (CH), 131.43 (2 x C), 133.41 (2 x CH), 158.94 (C), 160.17 (C) and 167.55 (2 x C=O) ppm; Found : M^+ 297.1001 (25.6%) Calc. for $C_{17}H_{15}NO_4$ 297.1001.

2-(3-Methoxyphenoxy)ethylamine. [188,189,190,187]



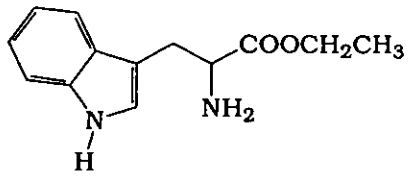
2.12

Procedure modified from that used by Augustin *et al.* to generate 2-(2-methoxyphenoxy) ethylamine from the corresponding 1,3-isoindolinedione.[186] A magnetically stirred solution of 2-[2-(3-methoxyphenoxy)ethyl]-1,3-isoindo-linedione (**2.11**) (1.8g, 6.1 mmol) and hydrazine hydrate (0.33g, 6.5 mmol) in ethanol (15 ml) was heated to reflux for 60 minutes. Subsequently, the reaction mixture was acidified with hydrochloric acid (20 ml, 0.5 M) and further heated

to reflux for 90 minutes Then the reaction was cooled down to room temperature and the white precipitate was filtered and washed with water, the wash water and the filtrate were combined and made strongly basic with sodium hydroxide aqueous solution (20%) and extracted with diethyl ether (2 x 100 ml). Then the extracts were dried with magnesium sulfate, filtered, the solvent was evaporated to dryness to give the title compound (**2.12**) after vacuum distillation (Kugelrohr) (0.71g, 70%), colourless oil, bp 175 °C/0.50 mmHg (lit.[10b] 98 - 100 °C/0.80 mmHg) : ν_{max} 3373 (broad), 2940 and 1604 cm^{-1}; ^1H nmr (250 M Hz,$CDCl_3$) 1.53 (brs, 2H, NH_2), 3.06 (t, 2H, *J* 5.2), 3.78 (s, 3H, OMe), 3.96 (t, 2H, *J* 5.2), 6.48-6.53 (m, 3H) and 7.17 (t, 1H, *J* 8.0) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 41.60 (CH_2), 55.27 (CH_3, OMe), 70.21 (CH_2), 101.07 (CH), 106.43 (CH), 106.73 (CH), 129.91 (CH), 160.19 (C) and 160.86 (C) ppm; Found: M^+ 167.0946 (68.7%) Calc. for $C_9H_{13}NO_2$ 167.0946.

Preparation of Ethyl and Methyl 2-Amino-3-(1H-3-indolyl) propanoate.

Ethyl 2-amino-3-(1H-3-indolyl)propanoate.[194, 195]

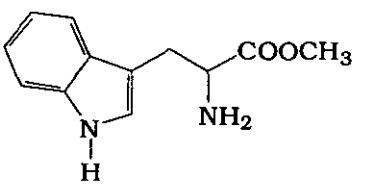


2.13

A scaled down and modified procedure from that employed by Biossonnas *et al* in the formation of tryptophane methylester hydrochloride salt.[24] A magnetically stirred suspension of 2-amino-3-(1H-3-indolyl) propanoic acid (tryptophane) (10g, 49.0 mmol) in absolute ethanol (100 ml) was cooled down to -10 °C and thionyl chloride (8 ml) was added dropwise. The reaction mixture was then stirred at the room temperature for 48 hours. Subsequently, diethyl ether (200 ml) was added to the reaction mixture, the precipitate was filtered and washed with diethyl ether and dried in *vacuo* to give the hydrochloride salt of the title compound (**2.13**) (11.44g, 87%), lit.[194] mp 225 - 226 °C. A solution of the prepared hydrochloride salt (2.6g, 9.7 mmol) in water (50 ml) was treated with

saturated sodium bicarbonate solution (100 ml) and extracted with DCM (2 x 200). The organic layer was dried over magnesium sulfate, filtered and the solvent evaporated to dryness to give the title compound (**2.13**) (2.19g, 97.3%), yellow oil : v_{max} 3365 (broad), 2981 and 1730 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.06 (t, 3H, *J* 7.1), 1.47 (brs, 2H, NH_2), 2.83 (dd, 1H, B of ABX, J_{AB} 14.3, J_{BX} 7.9), 3.09 (dd, 1H, A of ABX, J_{AB} 14.3, J_{AX} 4.6), 3.64 (dd, 1H, X of ABX, J_{AX} 4.6, J_{BX} 7.9), 3.95-4.02 (m, 2H), 6.72-7.45 (m, 5H) and 8.84 (brs, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 12.88 (CH_3), 29.56 (CH_2), 53.68 (CH), 59.75 (CH_2), 109.23 (C), 110.09 (CH), 117.00 (CH), 117.76 (CH), 120.32 (CH), 122.00 (CH), 126.14 (C), 135.07 (C) and 174.10 (C=O) ppm; Found: M^+ 232.1213 (6.2%) Calc. for $C_{13}H_{16}N_2O_2$ 232.1212.

Methyl 2-amino-3-(1H-3-indolyl)propanoate.



2.14

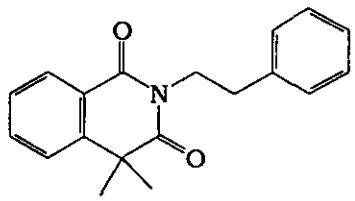
The hydrochloride salt[24, 91, 93, 191, 192, 193] was prepared by treating a methanolic solution of 2-amino-3-(1H-3-indolyl) propanoic acid (tryptophane) with thionyl chloride as described by Biossonnas *et al.*[24] Data for the free base (**2.14**) : yellow oil; v_{max} 3364 (broad), 2981 and 1735 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.65 (brs, 2H, NH_2), 3.08 (dd, 1H, B of ABX, J_{AB} 14.3, J_{BX} 7.7), 3.28 (dd, 1H, A of ABX, J_{AB} 14.3,J_{AX} 4.7), 3.74 (s, 3H, OMe), 3.85 (dd, 1H, X of ABX, J_{AX} 4.7, J_{BX} 7.7), 6.95-7.65 (m, 5H) and 8.86 (brs, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 31.36 (CH_2), 52.62 (CH), 55.49 (OCH_3), 111.15 (C), 111.92 (CH), 119.18 (CH), 119.92 (CH), 122.53 (CH), 123.77 (CH), 127.98 (C), 136.92 (C) and 176.37 (C=O) ppm; Found: M^+ 218.1059 (3.1%) Calc. for $C_{12}H_{14}N_2O_2$ 218.1055.

Chapter 3 Experimental:

General Method for 4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinolinediones Formation.

Procedure modified from that employed by Haworth *et al.*[13] A magnetically stirred solution of the particular 1,3-isoquinolinedione, sodium hydroxide (2 equivalents in *ca.*20 ml water) and methyl iodide (3-5 equivalents) in ethanol (unless otherwise stated, *ca.* 60 ml) was heated to reflux for a given length of time. After allowing the reaction to cool down to room temperature DCM (100 ml) and water (100 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation. The following 4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinolinediones were prepared:

4,4-Dimethyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.[13]

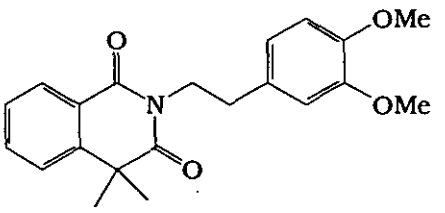


3.1

A stirred solution of 2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.2**) (0.7g, 2.6 mmol), sodium hydroxide (0.2g, 5.3 mmol) and methyl iodide (1.1g, 7.8 mmol) in ethanol (*ca.* 60 ml) heated to reflux for 3 hours gave the title compound[13](**3.1**) (0.7g, 92%), yellow oil : ν_{max} 2975, 1713, 1667 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.56 (s, 6H, 2 x CH_3), 2.91-2.97 (m, 2H), 4.21-4.27 (m, 2H), 7.27-7.46 (m, 8H) and 8.25-8.26 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 29.18 (2 x CH_3), 33.96 (CH_2), 41.52 (CH_2), 43.38 (C), 123.33 (C), 125.11 (CH), 126.36 (CH), 127.23 (CH), 128.34 (2 x CH), 128.81 (CH), 129.00 (2 x CH), 133.90 (CH), 138.47 (C), 144.80 (C), 163.75 (C=O) and

176.67 (C=O) ppm; Found: M^+ 293.1419 (9.4%) Calc. for $C_{19}H_{19}NO_2$ 293.1416.

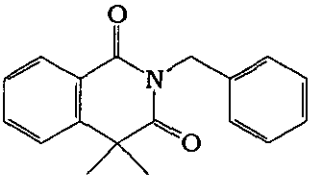
2-(3,4-Dimethoxyphenethyl)-4,4-dimethyl -1,2,3,4-tetrahydro-1,3-isoquinolinedione.



3.2

A stirred solution of 2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.3**) (0.35g, 1.1 mmol), sodium hydroxide (0.09g, 2.2 mmol) and methyl iodide (0.47g, 3.3 mmol) in ethanol (*ca.* 60 ml) heated to reflux for 3 hours gave the title compound (**3.2**) (0.35g, 91%), mp 66-68 °C from DCM : ν_{max} 2977, 1712, 1667 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.55 (s, 6H, 2 x CH_3), 2.85-2.89 (m, 2H), 3.81 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.18-4.22 (m, 2H), 6.75-6.81 (m, 3H), 7.38-7.62 (m, 3H) and 8.19-8.21 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 29.13 (2 x CH_3), 33.48 (CH_2), 41.56 (CH_2), 43.34 (C), 55.69 (CH_3, OMe), 55.79(CH_3, OMe), 111.14 (CH), 112.11 (CH), 120.95 (CH), 123.74 (C), 125.06 (CH), 127.20 (CH), 128.74 (CH), 130.99 (C), 133.85 (CH), 144.97 (C), 147.50 (C), 148.72 (C), 164.66 (C=O) and 176.77 (C=O) ppm; Found: M^+ 353.1621 (7.8%) $C_{21}H_{23}NO_4$ requires 353.1627.

2-Benzyl-4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.

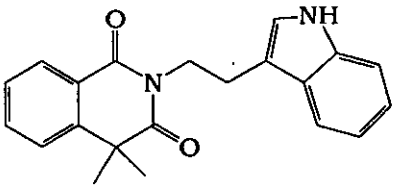


3.3

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g,10 mmol), sodium hydroxide (0.8g, 20 mmol) and methyl iodide (5.7g, 40 mmol) in ethanol (*ca.*60 ml) heated to reflux for 3 hours gave the title compound

(**3.3**) (2.0g, 72%), yellow oil : ν_{max} 2977, 1713 and 1667 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.62 (s, 6H, 2 x CH_3), 5.20 (s, 2H), 7.25-7.62 (m, 8H) and 8.22-8.24 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 29.30 (2 x CH_3), 43.69 (C, CH_2), 124.00 (C), 125.18 (CH), 127.42 (CH),128.47 (CH), 128.65 (2 x CH), 128.92 (2 x CH), 129.55 (CH), 134.07 (CH), 137.35 (C), 145.13 (C), 164.14 (C=O) and 176.95 (C=O) ppm; Found: M^+ 279.1261 (91.9%) $C_{18}H_{17}NO_2$ requires 279.1259.

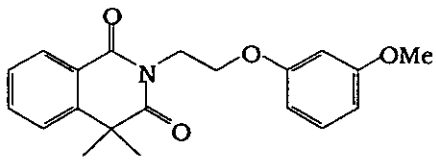
2-[2-(1H-3-Indolyl)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione.



3.4

A stirred solution of 2-[2-(1*H*-3-indolyl)ethyl]-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.4**) (0.35g,1.2 mmol), sodium hydroxide (0.1g, 2.4 mmol) and methyl iodide (0.51g, 3.6 mmol) in ethanol (*ca.* 60 ml) heated to reflux for 3 hours gave the title compound (**3.4**) (0.38g, 95%), mp 148.0 - 149.5 °C from DCM : ν_{max} 3370, 1709, 1656 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.60 (s, 6H, 2 x CH_3), 3.11-3.14 (m, 2H), 4.29-4.35 (m, 2H), 7.11-7.80 (m, 8H), 8.08 (br.s, 1H, N-H) and 8.23-8.24 (m, 1H) ppm;^{13}C nmr (100.5 M Hz, $CDCl_3$) 24.20 (CH_2), 29.64 (2 x CH_3), 41.58 (CH_2), 43.88 (C), 111.38 (CH), 113.32 (C), 119.65 (CH), 119.86 (CH), 122.39 (CH), 122.55 (CH), 124.38 (C), 125.53 (CH), 127.52 (CH), 128.03(C), 129.29 (CH), 134.30 (CH), 136.62 (C), 145.54 (C), 164.58 (C=O) and 177.41 (C=O) ppm; Found: M^+ 332.1520 (15.8%) $C_{21}H_{20}N_2O_2$ requires 332.1525.

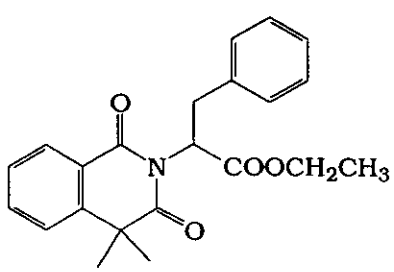
2-[2-(3-Methoxyphenoxy)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



3.5

A stirred solution of 2-[2-(3-methoxyphenoxy)ethyl]-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.5**) (1.14g, 3.7 mmol), sodium hydroxide (0.3g, 7.3 mmol) and methyl iodide (2.6g, 18.5 mmol) in ethanol (*ca.* 60 ml) heated to reflux for 2 hours gave the title compound (**3.5**) (1.0g, 80%), mp 101-102 °C from DCM : ν_{max} 2973, 1715, 1668 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.62 (s, 6H, 2 x CH_3), 3.73 (s, 3H, OMe), 4.16 (t, 2H, *J* 6.1), 4.41 (t, 2H, *J* 6.1), 6.44-6.49 (m, 3H), 7.10 (t, 1H, *J* 8.5), 7.38-7.46 (m, 2H), 7.58 (t, 1H, *J* 7.5) and 8.20-8.23 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 29.26 (2 x CH_3), 39.21 (CH_2), 43.72 (C), 55.24 (CH_3, OMe), 64.59 (CH_2), 101.00 (CH), 106.66 (2 x CH), 124.20 (C), 125.16 (CH), 127.35 (CH), 128.98 (CH), 129.84 (CH), 134.11 (CH), 145.07 (C), 159.83 (C), 160.80 (C), 164.18 (C=O) and 177.09 (C=O) ppm; Found: M^+ 339.1475 (11.1%) $C_{20}H_{21}NO_4$ requires 339.1471.

Ethyl 2-(4,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-phenylpropanoate.

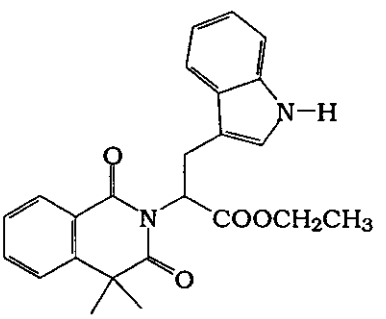


3.6

A stirred solution of ethyl 3-(1,3-dioxo-1,2,3,4-tetrahydro-2-isoquiolinyl)-2-phenylpropanoate (**2.6**) (0.28g, 0.8 mmol), sodium hydroxide (0.07g, 1.6 mmol) and methyl iodide (0.57g, 4.0 mmol) in ethanol (*ca.* 60 ml) heated to reflux for 20 minutes gave the title compound (**3.6**) (0.28g, 93%), yellow oil : ν_{max} 2980,

1742, 1718, 1673 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.19 (t, 3H, *J* 7.1), 1.27 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.39 (dd, 1H, B of ABX, J_{AB} 14.1, J_{BX} 10.4), 3.57 (dd, 1H, A of ABX, J_{AB} 14.1, J_{AX} 5.8), 4.15-4.25 (m, 2H), 5.83 (dd, 1H, X of ABX, J_{AX} 5.8, J_{BX} 10.4), 7.08-7.60 (m, 8H) and 8.12-8.16 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 15.19 (CH_3), 29.36 (CH_3), 30.72 (CH_3), 35.86 (CH_2), 44.60 (C), 55.06 (CH), 62.49 (CH_2), 124.42 (C), 126.15 (CH), 127.64 (CH), 128.36 (CH), 129.34 (2 x CH), 130.10 (CH), 130.37 (2 x CH), 135.21 (CH), 138.25 (C), 146.06 (C), 164.76 (C=O), 170.65 (C=O) and 177.57 (C=O) ppm; Found: M^+ 365.1630 (27.9%) $C_{22}H_{23}NO_4$ requires 365.1627.

Ethyl 2-(4,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl)propanoate.

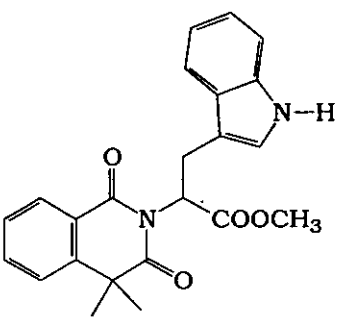


3.7

A stirred solution of ethyl 3-(1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-2-(1*H*-3-indolyl) propanoate (**2.7**) (0.75g, 2.0 mmol), sodium hydroxide (0.16g, 4.0 mmol, anhydrous) and methyl iodide (1.14g, 8.0 mmol) in ethanol (*ca.* 60 ml) heated to reflux for 3 hours gave the title compound (**3.7**) after flash chromatography eluting with EA/LP [1:2] (0.6g, 74%), mp 60-62 °C from EA/LP : ν_{max} 3397, 2979, 1739, 1715, 1669 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.17 (s, 3H, CH_3), 1.24 (t, 3H, *J* 7.1), 1.50 (s, 3H, CH_3), 3.66 (dd, 1H, B of ABX, J_{AB} 15.0, J_{BX} 9.6), 3.74 (dd, 1H, A of ABX, J_{AB} 15.0, J_{AX} 6.0), 4.18-4.35 (m, 2H), 5.95 (dd, 1H, X of ABX, J_{AX} 6.0, J_{BX} 9.6), 7.00-7.61 (m, 8H), 8.17-8.19 (m, 1H) and 8.22 (brs, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 14.45 (CH_3), 24.84 (CH_2), 28.41 (CH_3), 29.72 (CH_3), 43.85 (C), 54.27

(CH), 61.65 (CH_2), 111.31 (CH), 111.63 (C), 119.10 (CH), 119.57 (CH), 122.08 (CH), 123.39 (CH), 123.86 (C), 125.30 (CH), 127.53 (CH), 127.90 (C), 129.25 (CH), 134.35 (CH), 136.36 (C), 145.32 (C), 164.14 (C=O), 170.28 (C=O) and 176.84 (C=O) ppm; Found: M^+ 404.1736 (3.3%) $C_{24}H_{24}N_2O_4$ requires 404.1736.

Methyl 2-(4,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl)propanoate.



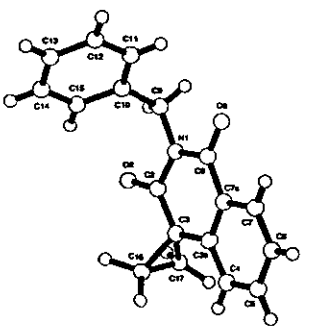
3.8

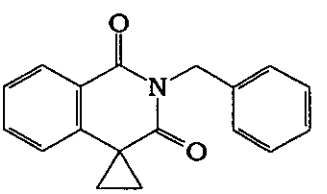
A stirred solution of methyl 3-(1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-2-(1*H*-3-indolyl) propanoate (**2.8**) (0.63g, 1.7 mmol), sodium hydroxide (0.14g, 3.4 mmol, anhydrous) and methyl iodide (1.21g, 8.5 mmol) in methanol (*ca.* 50 ml) heated to reflux for 3 hours gave the title compound (**3.8**) after flash chromatography eluting with EA/LP [1:3] (0.47g, 71%), white foamy oil : v_{max} 3407, 1744, 1712, 1666 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.11 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.67-3.79 (m, 2H, unclear AB of ABX), 3.77 (s, 3H, OMe), 5.96 (dd, 1H, X of ABX, J_{AX} 6.2, J_{BX} 9.5), 7.01-7.60 (m, 8H), 8.17 (brs, 1H, N-H) and 8.18-8.20 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 24.42 (CH_2), 27.94 (CH_3), 29.29 (CH_3), 43.47 (C), 52.30 (CH), 53.68 (CH_3, OMe), 110.89 (CH), 111.14(C), 118.69 (CH), 119.23 (CH), 121.74 (CH), 122.95 (CH), 123.40 (C), 124.91 (CH), 127.14 (CH), 127.44 (C), 128.87 (CH), 134.00 (CH), 135.92 (C), 144.92 (C), 163.73 (C=O), 170.42 (C=O) and 176.48 (C=O) ppm; Found: M^+ 390.1581 (9.2%) $C_{23}H_{22}N_2O_4$ requires 390.1580. COSY experiment supports characterisation.

General Method for 1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cycloalkanes Formation.

A magnetically stirred solution of the particular 1,3-isoquinolinedione, sodium hydroxide (a given number of equivalents) and the appropriate alkylating agent (1 - 1.2 equivalents) in aqueous ethanolic solution [1:1] (*ca.* 100 ml) was heated to reflux for a given length of time. Subsequently, the reaction mixture was allowed to cool down to room temperature then DCM (150 ml) and water (150 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation. The following 1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cycloalkanes were prepared:

2-Benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclopropane.





3.9

Procedure A: following the above mentioned general procedure, a stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10 mmol), sodium hydroxide (0.8g, 20 mmol) and 1,2-dibromoethane (2.25g, 12 mmol) in aqueous ethanol [1:1] (*ca.* 100 ml) heated to reflux for 45 minutes and gave the title compound (**3.9**) after flash chromatography eluting with EA/LP [1:3] (0.42g, 15%).

Procedure B: modified form the procedure described by Horning *et al*,[27] however, 1,2-dibromoethane was used instead of 1-bromo-2-chloroethane. To a stirred mixture of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10 mmol) and potassium carbonate (2.76g, 20 mmol) in 20 ml of dry

dimethylformamide was added 1,2-dibromoethane (9.4g, 50 mmol). The mixture was stirred at room temperature for 24 hours under nitrogen atmosphere. The reaction was terminated by adding DCM (100 ml) and water (100 ml) followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and gave the title compound (**3.9**) after flash chromatography eluting with EA/LP [1:3] (2.55 g, 92%), mp 119-120 °C from EA/LP : ν_{max} 1705, 1663 and 1608 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.64-1.70 (m, 2H), 2.17-2.23 (m, 2H), 5.26 (s, 2H), 6.82 (d, 1H, *J* 7.9), 7.27-7.58 (m, 7H) and 8.29-8.31 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 25.62 (C), 27.47 (2 x CH_2), 44.05 (CH_2), 120.72 (CH), 125.73 (C), 126.62 (CH), 127.62(CH), 128.60 (2 x CH), 129.09 (2 x CH), 129.31 (CH), 134.20 (CH), 137.51 (C), 141.30 (C), 164.83 (C=O) and 172.73 (C=O) ppm; Found: C, 77.28, H, 5.45, N, 4.98 % $C_{18}H_{15}NO_2$ requires C, 77.95, H, 5.41, N, 5.05 %; Found: M^+ 277.1105 (23.0%) $C_{18}H_{15}NO_2$ requires 277.1103. HETCOR experiment supports characterisation.

X-Ray Report (Experimental Details). Carried out by Dr. AMZ Slawin.

A. Crystal Data

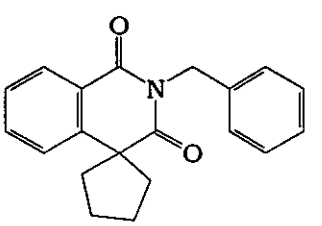
Empirical Formula	$C_{18}H_{15}NO_2$
Formula Weight	277.1103
Crystal Colour, Habit	clear, prism
Crystal Dimensions	0.13 x 0.21 x 0.39 mm
Crystal System	monoclinic
Lattice Type	primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (73.7 - 74.6°)
Omega Scan Peak Width at	
Half -height	0.26°
Lattice Parameters	a = 10.706(1) *°A*

	b = 7.134(2) ^oA
	c = 18.380(1) ^oA
	β = 90.152(7)^o
	V = 1403.7(3) $^oA^3$
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.312g/cm^3
F_{000}	584.00
μ (CuKα)	6.49 cm^{-1}
B. Intensity Measurements	
Diffractometer	Rigaku AFC7S
Radiation	CuKα (λ = 1.54178 ^oA)
	graphite monochromated
Attenuater	Ni foil (factor = 9.42)
Take-off Angle	6.0 ^{o}
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	20.0 ^{o}C
Scan Type	ω
Scan Rate	16.0^o/ min (in ω) (up to 4 scans)
Scan Width	(1.15 + 0.35 tanθ) ^{o}
$2\theta_{max}$	120.1^o
No. of Reflections Measured	Total: 2409
	Unique: 2274 (R_{int} = 0.037)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.7006 - 1.0000)
	Decay (0.60% decline)
	Secondary Extinction
	(coefficient: 6.92481e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function minimised	$\sum w(\|Fo\|-\|Fc\|)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
P-factor	0.0030
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1724
No. Variables	191
Reflection / Parameter Ratio	9.03
Residuals: R; Rw	0.050; 0.047
Goodness of Fit Indicator	5.56
Max Shift/Error in Final Cycle	0.68
Maximum peak in Final Diff. Map	0.19 $e^-/{}^oA^3$
Minimum peak in Final Diff. Map	- 0.16 $e^-/{}^oA^3$

2-Benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclopentane.

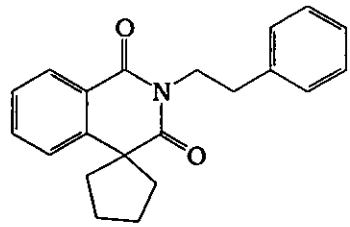


3.10

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10 mmol), sodium hydroxide (0.8g, 20 mmol) and 1,4-dibromobutane (2.6g, 12 mmol) in aqueous ethanol [1:1] (*ca.* 100 ml) heated to reflux for 2 hours and gave the title compound (**3.10**) after flash chromatography eluting with EA/LP [1:3] (2.22g, 73%), mp 89 - 90 °C from EA /LP : ν_{max} 2955, 1711, 1668 and 1604 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.87-2.02 (m, 6H), 2.38-2.42 (m, 2H), 5.12 (s, 2H), 7.15-7.53 (m, 8H) and 8.12-8.14 (m, 1H) ppm; ^{13}C nmr

(100.5 M Hz, $CDCl_3$) 28.22 (2 x CH_2), 43.72 (2 x CH_2), 44.09 (CH_2), 54.26 (C), 124.65 (C), 125.66 (CH), 127.35 (CH), 127.74 (CH), 128.79 (2 x CH), 129.06 (CH), 129.12 (2 x CH), 134.46 (CH), 137.73 (C), 146.81 (C), 164.89 (C=O) and 178.25 (C=O) ppm; Found : M^+ 305.1421 (13.2%) $C_{20}H_{19}NO_2$ requires 305.1416.

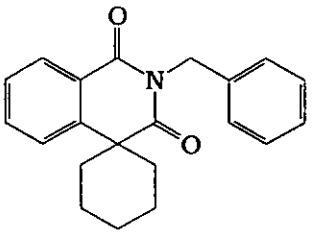
2-Phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclopentane.



3.11

A stirred solution of 2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.2**) (3.0g, 11.3 mmol), sodium hydroxide (4.5g, 113.4 mmol) and 1,4-dibromo butane (2.44g, 11.3 mmol) in aqueous ethanol [1:1] (*ca.* 100 ml) heated to reflux for 2 hours and gave the title compound (**3.11**) after flash chromato-graphy eluting with EA/LP [1:3] (0.44g, 12%), yellow oil : ν_{max} 2956, 1710, 1665 and 1604 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.92-2.07 (m, 6H), 2.38-2.41 (m, 2H), 2.92-2.96 (m, 2H), 4.21-4.25 (m, 2H), 7.19-7.60 (m, 8H) and 8.18-8.21 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 27.81 (2 x CH_2), 34.02 (CH_2), 41.65(CH_2), 43.34 (2 x CH_2), 53.61 (C), 124.03(C), 125.26 (CH), 126.33 (CH), 126.86 (CH), 128.35 (2 x CH), 128.42 (CH), 129.00 (2 x CH), 133.96 (CH), 138.58 (C), 146.40 (C), 164.19 (C=O) and 178.00 (C=O) ppm; Found: M^+ 319.1580 (5.7%) $C_{21}H_{21}NO_2$ requires 319.1572. COSY and HETCOR experiments support characterisation.

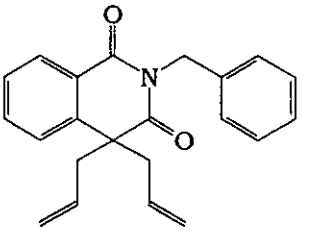
2-Benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclohexane.



3.12

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10 mmol), sodium hydroxide (0.8g, 20 mmol) and 1,5-dibromopentane (2.3g, 10 mmol) in aqueous ethanol [1:1] (*ca.* 100 ml) heated to reflux for 3 hours and gave the title compound (**3.12**) after flash chromatography eluting with EA/LP [1:5] (1:35g, 42%), mp 120 - 121 °C from EA /LP : ν_{max} 2930, 1715, 1671 and 1603 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.26-1.38 (m, 1H), 1.59-1.64 (m, 2H), 1.75-2.02 (m, 7H), 5.15 (s, 2H), 7.22-7.64 (m, 8H) and 8.20-8.23 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 22.55 (2 x CH_2), 25.39 (CH_2), 37.31(2 x CH_2), 43.96 (CH_2), 47.32 (C), 125.17 (CH), 125.75 (C), 127.52 (CH), 127.71 (CH), 128.78 (2 x CH), 128.98 (2 x CH), 129.69 (CH), 134.04 (CH), 137.84 (C), 145.69 (C), 164.95 (C=O) and 176.77 (C=O) ppm; Found: M^+319.1572 (79.0 %) $C_{21}H_{21}NO_2$ requires 319.1572.

Preparation of *2-benzyl-4,4-diallyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (3.13).



3.13

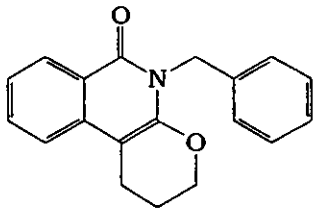
Procedure modified from that described by Harriman *et al.*[26]A magnetically stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10.0 mmol), sodium hydroxide (0.84g, 21.0 mmol in *ca.*20 ml water) and

allyl bromide (2.54g, 21.0 mmol) in ethanol (*ca.* 60 ml) was heated to reflux for 2 hours. Subsequently, the reaction mixture was allowed to cool down to room temperature then DCM (100 ml) and water (100 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate before concentrating in *vacuo* and gave the title compound (**3.13**) (3.01g,91%), brown oil : ν_{max} 3078, 1713, 1668 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.60 (dd, 2H, A of ABX, J_{AB} 13.3, J_{AX} 6.6), 2.97 (dd, 2H, B of ABX, J_{AB} 13.3, J_{BX} 7.9), 4.72-4.85 (m, 4H), 5.05-5.18 (m, 2H), 5.17 (s, 2H), 7.20-7.65 (m, 8H) and 8.23-8.27 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 43.97 (CH_2), 46.78 (2 x CH_2), 53.08 (C), 119.89 (2 x CH_2), 125.99 (CH), 126.66 (C), 127.73 (CH), 127.81 (CH), 128.60 (2 x CH), 129.32 (3 x CH), 131.89 (2 x CH), 134.37 (CH), 137.52 (C), 141.40 (C), 164.45 (C=O) and 175.08 (C=O) ppm; Found: M^+ 331.1571 (19.4%) $C_{22}H_{21}NO_2$ requires 331.1572.

Reactions of 1,3-dibromopropane with 1,2,3,4-tetrahydro-1,3-isoquinoline diones and aqueous alcoholic sodium hydroxide - General Method.

A magnetically stirred solution of the particular 1,3-isoquinolinedione, sodium hydroxide (a given number of equivalents) and 1,3-dibromopropane (1.2 equivalents) in aqueous ethanolic solution [1:1] (*ca.* 50 ml) was heated to reflux for a given length of time. Subsequently, the reaction mixture was allowed to cool down to room temperature then DCM (100 ml) and water (100 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation. The following reactons were conducted:

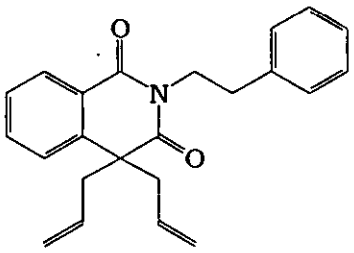
Reaction of 1,3-dibromopropane with 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione and NaOH (2 equivalents).



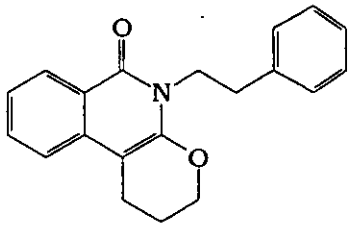
3.15

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10 mmol), sodium hydroxide (0.8g, 20 mmol) and 1,3-dibromopropane (2.4g, 12 mmol) in aqueous ethanol [1:1] (*ca.* 50 ml) heated to reflux for 90 minutes and gave two products after flash chromatography eluting with EA/LP [1:3]. The first product *2-benzyl-4,4-diallyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione* (**3.13**) (0.42g, 13%). The second product *5-benzyl-2,3,5,6-tetrahydro-1H-pyrano[2,3-c]isoquinolin-6-one* (**3.15**) (0.75g, 26%), mp 160.5 -161.5 °C from EA/LP : ν_{max} 2959, 1657, 1616 and 1556 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 2.07-2.16 (m, 2H), 2.72 (m, 2H), 4.31 (m, 2H), 5.39 (s, 2H), 7.25-7.64 (m, 8H) and 8.43-8.45 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 19.94 (CH_2), 22.28 (CH_2), 44.63(CH_2), 68.33 (CH_2), 89.89 (C), 120.82 (CH), 122.40 (C), 124.16 (CH), 127.46 (CH), 128.32 (2 x CH), 128.72 (2 x CH), 128.91 (CH), 132.88 (CH), 137.96 (C), 138.26 (C), 148.02 (C) and 162.34 (C=O) ppm; Found: C, 76.99, H, 5.88, N, 4.65 % $C_{19}H_{17}NO_2$ requires C, 78.32, H, 5.84, N, 4.81 %; Found: M^+ 291.1260 (75.7%) $C_{19}H_{17}NO_2$ requires 291.1259.

Reaction of 1,3-dibromopropane with 2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione and NaOH (10 equivalents).



3.14



3.16

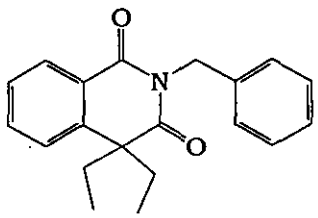
A stirred solution of 2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.2**) (1.5g, 5.6 mmol), sodium hydroxide (2.24g, 56 mmol) and 1,3-dibromopropane (1.36g, 6.7 mmol) in aqueous ethanol [1:1] (*ca.* 50 ml) heated to reflux for 15 hours and gave two products after flash chromatography eluting with EA/LP [1:3]. The first product *4,4-diallyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.14**) (0.43g, 22%), yellow oil : ν_{max} 3078, 1711, 1667 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 2.62 (dd, 2H, A of ABX, J_{AB} 13.5, J_{AX} 6.8), 2.86-2.90 (m, 2H), 3.00 (dd, 2H, B of ABX, J_{AB} 13.5, J_{BX} 7.9), 4.17-4.22 (m, 2H), 4.82-4.93 (m, 4H), 5.15-5.20 (m, 2H), 7.20-7.65 (m, 8H) and 8.23-8.26 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 34.58 (CH_2), 42.16 (CH_2), 46.67 (2 x CH_2), 52.85 (C), 119.71 (2 x CH_2), 125.61 (CH), 126.75 (C), 126.97 (CH), 127.73 (CH), 128.79 (2 x CH), 128.93 (CH), 129.57 (2 x CH), 132.06 (2 x CH), 134.18 (CH), 139.09 (C), 141.32 (C), 164.23 (C=O) and 174.84 (C=O) ppm; Found: M^+ 345.1732 (30.9%) $C_{23}H_{23}NO_2$ requires 345.1729. The second product *5-phenethyl-2,3,5,6-tetrahydro-1H-pyrano[2,3-c]isoquinolin-6-one* (**3.16**) (0.31g, 18%), brown oil : ν_{max} 2959, 1659, 1615 and 1555 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.99-2.05 (m, 2H), 2.63 (m, 2H), 2.93-2.99 (m, 2H), 4.12 (m, 2H), 4.33-4.36 (m, 2H), 7.19-7.60 (m, 8H) and 8.38-8.40 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 19.89 (CH_2), 22.16 (CH_2), 35.17 (CH_2), 42.94 (CH_2), 68.16 (CH_2), 89.61 (C), 120.75 (CH), 122.26 (C), 124.00 (CH), 126.61(CH), 128.57(CH), 128.69 (2 x CH), 129.37 (2 x CH), 132.70 (CH), 137.87 (C), 139.57 (C), 147.90 (C) and 162.04 (C=O) ppm; Found M^+ 305.1416 (15.3%) $C_{20}H_{19}NO_2$ requires 305.1416. COSY experiment supports characterisation.

Reactions of 1,2,3,4-tetrahydro-1,3-isoquinolinediones with alkyl- or arylalkyl halides (1 equivalent) and aqueous alcoholic sodium hydroxide (1 equivalent) - General Method.

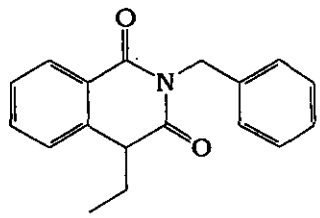
A magnetically stirred solution of the particular 1,3-isoquinolinedione, sodium hydroxide (1 equivalent) and the appropriate alkylating agent (1 equivalent, unless otherwise stated) in aqueous ethanolic solution [1:1] (*ca.* 150 ml) was

heated to reflux for a given length of time. Subsequently, the reaction mixture was allowed to cool down to room temperature then DCM (150 ml) and water (150 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation. The following alkylation reactions were conducted:

Reaction of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione with ethyl iodide and NaOH.



3.17

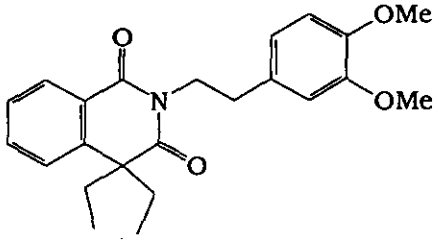


3.18

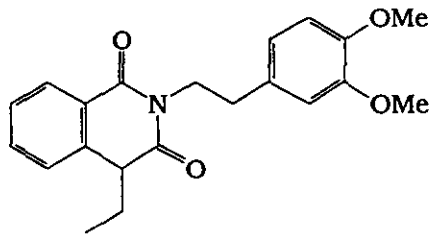
A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (1.5g, 6.0 mmol), sodium hydroxide (0.24g, 6.0 mmol) and ethyl iodide (0.94g, 6.0 mmol) in aqueous ethanol [1:1] (*ca.* 140 ml) heated to reflux for 6 hours and gave two products after flash chromatography eluting with EA/LP [1:5]. The first product *2-benzyl-4,4-diethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.17**) (0.22g, 12%), mp 44-46 °C from EA/LP: ν_{max} 2967, 1712, 1669 and 1606 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.42 (t, 6H, 2 x CH_3, *J* 7.4), 1.81-1.89 (m, 2H), 2.26-2.34 (m, 2H), 5.20 (s, 2H), 7.19-7.63 (m, 8H) and 8.24-8.27 (m, 1H) ppm; ^{13}C nmr (68.2 M Hz, $CDCl_3$) 9.19 (2 x CH_3), 36.19 (2 x CH_2), 43.58 (CH_2), 53.92 (C), 125.04 (CH), 126.81 (C), 127.20 (CH), 127.39 (CH), 128.36 (2 x CH), 128.81 (CH), 128.87 (2 x CH), 134.18 (CH), 137.35 (C), 141.97 (C), 164.37 (C=O) and 175.97 (C=O) ppm; Found: M^+ 307.1581 (56.6 %) $C_{20}H_{21}NO_2$ requires 307.1572. The second product *2-benzyl-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.18**) (0.44g, 26%), yellow oil : ν_{max} 2969, 1715, 1670 and 1603 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.70 (t, 3H, *J* 7.4),

1.98-2.05 (m, 1H), 2.22-2.30 (m, 1H), 3.95 (t, 1H, *J* 5.5), 5.20 (q, 2H, AB, J_{AB} 13.8), 7.24-7.62 (m, 8H) and 8.24-8.26 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 9.77 (CH_3), 30.81 (CH_2), 43.75 (CH_2), 47.63 (CH), 126.16 (C), 127.18 (CH), 127.84 (CH), 127.93 (CH), 128.77 (2 x CH), 129.31 (2 x CH), 129.39 (CH), 134.05 (CH), 137.62 (C), 139.30 (C), 165.13 (C=O) and 173.97 (C=O) ppm; Found: M^+ 279.1257 (100.0 %) $C_{18}H_{17}NO_2$ requires 279.1259.

Reaction of 2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-1,3-isoquinoline dione with ethyl iodide and NaOH.



3.19

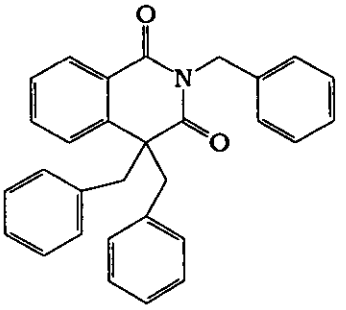


3.20

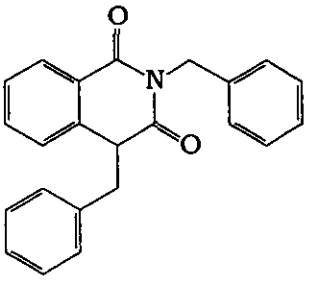
A stirred solution of 2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.3**) (3.3g, 10.0 mmol), sodium hydroxide (0.40g, 10.0 mmol) and ethyl iodide (1.6g, 10.0 mmol) in aqueous ethanol [1:1] (*ca.* 120 ml) heated to reflux for 3.5 hours and gave two products after flash chromatography eluting with EA/LP [1:5]. The first product *2-(3,4-dimethoxy phenethyl)-4,4-diethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.19**) (0.35g, 9%), mp 87-89 °C from EA/LP: ν_{max} 2967, 1711, 1667 and 1607 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.45 (t, 6H, 2 x CH_3, *J* 7.4), 1.80-1.89 (m, 2H), 2.24-2.32 (m, 2H), 2.81-2.88 (m, 2H), 3.81 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.17-4.29 (m, 2H), 6.78-6.83 (m, 3H), 7.23-7.65 (m, 3H) and 8.22-8.25 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 9.19 (2 x CH_3), 33.80 (CH_2), 36.05 (2 x CH_2), 41.86 (CH_2), 53.81 (C), 55.83 (CH_3, OMe), 55.91 (CH_3, OMe), 111.34 (CH), 112.16 (CH), 120.96 (CH), 125.04 (CH), 126.76 (C), 127.20 (CH), 128.53 (CH), 131.22 (C), 134.10 (CH), 141.91 (C), 147.65 (C), 148.91 (C), 164.21 (C=O) and 175.80 (C=O) ppm; Found: M^+ 381.1939 (59.4 %) $C_{23}H_{27}NO_4$ requires 381.1940. The second product *2-(3,4-dimethoxyphenethyl)-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.20**) (1.0g, 29%), yellow oil : ν_{max} 2966,

1713, 1668 and 1608 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.69 (t, 3H, *J* 7.4), 1.92-1.95 (m, 1H), 2.15-2.18 (m, 1H), 2.85-2.92 (m, 2H), 3.79-3.88 (m, 1H), 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.10-4.24 (m, 2H), 6.75-6.84 (m, 3H), 7.25-7.61 (m, 3H) and 8.16-8.20 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 9.52 (CH_3), 30.43 (CH_2), 33.77 (CH_2), 41.60 (CH_2), 47.19 (CH), 55.84 (CH_3, OMe), 55.91 (CH_3, OMe), 111.31 (CH), 112.19 (CH), 121.00 (CH), 125.71 (C), 126.82 (CH), 127.56 (CH), 128.78 (CH), 131.14 (C), 133.62 (CH), 138.92 (C), 147.65 (C), 148.89 (C), 164.70 (C=O) and 173.56 (C=O) ppm; Found: M^+ 353.1627 (16.7 %) $C_{21}H_{23}NO_4$ requires 353.1627. COSY and HETCOR experiments support characterisation.

Reaction of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione with benzyl bromide and NaOH.



3.21

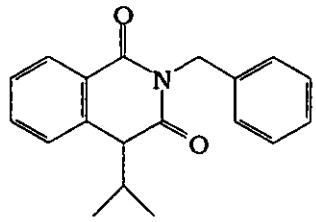


3.22

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (1.0g, 4.0 mmol), sodium hydroxide (0.17g, 4.2 mmol) and benzyl bromide (0.7g, 4.1 mmol) in aqueous ethanol [1:1] (*ca.* 120 ml) heated to reflux for 3 hours and gave two products after flash chromatography eluting with EA /LP [1:4]. The first product *2,4,4-tribenzyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione*[12] (**3.21**) (0.29g, 17%), yellow oil : ν_{max} 3031, 1710, 1667 and 1604 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 3.35 (d, 2H, A of AB, J_{AB} 13.0), 3.78 (d, 2H, B of AB, J_{AB} 13.0), 4.89 (s, 2H), 6.60-6.63 (m, 4H), 6.87-7.40 (m, 12H), 7.76-7.80 (m, 2H) and 7.95-7.98 (m, 1H) ppm; ^{13}C nmr (68.2 M Hz, $CDCl_3$) 43.41 (CH_2), 48.48 (2 x CH_2), 55.94 (C), 126.66 (CH), 126.86 (2 x CH), 127.06 (CH), 127.48 (CH), 127.99 (4 x CH), 128.23 (2 x CH), 128.47 (2 x CH), 128.53

(C), 128.83 (CH), 129.42 (4 x CH), 133.38 (CH), 135.40 (2 x C), 136.61 (C), 140.71 (C), 163.29 (C=O) and 174.44 (C=O) ppm; Found: M^+ 431.1888 (37.0 %) Calc. for $C_{30}H_{25}NO_2$ 431.1885. The second product *2,4-dibenzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.22**) (0.57g, 42%) mp 98-100 °C from EA/LP: ν_{max} 1715, 1669 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.29 (dd, 1H, A of ABX, J_{AB} 13.2, J_{AX} 4.9), 3.42 (dd, 1H, B of ABX, J_{AB} 13.2, J_{BX} 6.1), 4.25 (dd, 1H, X of ABX, J_{AX} 4.9, J_{BX} 6.1), 5.06 (s, 2H), 6.61-6.63 (m, 2H), 7.01-7.59 (m, 11H) and 8.12-8.14 (m, 1H) ppm; ^{13}C nmr (68.2 M Hz, $CDCl_3$) 43.42 (2 x CH_2), 48.16 (CH), 125.87 (C), 127.10 (CH), 127.28 (CH), 127.43 (CH), 127.73 (CH), 128.17 (2 x CH), 128.39 (2 x CH), 128.86 (CH), 129.14 (2 x CH), 129.28 (2 x CH), 133.36 (CH), 135.32 (C), 136.93 (C), 138.09 (C), 164.29 (C=O) and 173.00 (C=O) ppm; Found: M^+ 341.1420 (29.0 %) $C_{23}H_{19}NO_2$ requires 341.1416. COSY and HETCOR experiments support characterisation.

Reaction of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione with isopropyl iodide and NaOH.

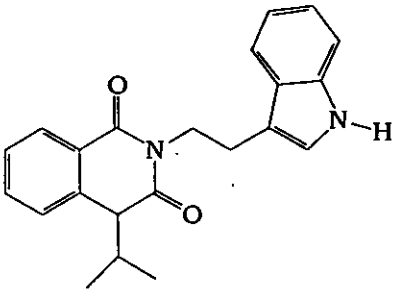


3.23

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.1**) (2.5g, 10.0 mmol), sodium hydroxide (0.44g, 11.0 mmol) and isopropyl iodide (1.7g, 10.0 mmol) in aqueous ethanol [1:1] (*ca.* 140 ml) heated to reflux for 4 hours and gave after flash chromatography eluting with EA/LP [1:8] *2-benzyl-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.23**) (1.23g, 42%), mp 72-74 °C from EA/LP: ν_{max} 2964, 1715, 1671 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.77 (d, 3H, *J* 6.9), 0.91 (d, 3H, *J* 6.9), 2.23-2.31 (m, 1H), 3.79 (d, 1H, *J* 4.2), 5.17 (q, 2H, AB, J_{AB} 13.6), 7.25-7.59 (m, 8H) and 8.22-8.24 (m,

1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 19.04 (CH_3), 19.77 (CH_3), 37.61 (CH), 43.61 (CH_2), 53.38 (CH), 126.15 (C), 127.42 (CH), 127.50 (CH), 127.53 (CH), 128.25 (2 x CH), 128.65 (CH), 129.18 (2 x CH), 133.05 (CH), 137.04 (C), 137.93 (C), 165.45 (C=O) and 173.34 (C=O) ppm; Found: M^+ 293.1410 (32.6 %) $C_{19}H_{19}NO_2$ requires 293.1416.

Reaction of 2-[2-(1H-3-Indolyl)ethyl]-1,2,3,4-tetrahydro-1,3-isoquinolinedione with isopropyl iodide (2 equivalents) and NaOH.



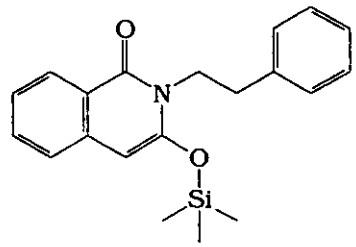
3.24

A stirred solution of 2-[2-(1H-3-Indolyl)ethyl]-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.4**) (1.4g, 4.6 mmol), sodium hydroxide (0.20g, 5.0 mmol) and isopropyl iodide (1.56g, 9.2 mmol) in aqueous ethanol [1:1] (*ca.* 140 ml) heated to reflux for 3 hours and gave after flash chromatography eluting with EA/LP [1:3] *2-[2-(1H-3-Indolyl)ethyl]-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.24**) (0.70g, 44%), mp 135-137 °C from EA/LP: ν_{max} 3370 (broad), 3154, 1714, 1673 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.92 (d, 3H, *J* 6.9), 1.03 (d, 3H, *J* 6.8), 2.34-2.38 (m, 1H), 3.13-3.17 (m, 2H), 3.84 (d, 1H, *J* 4.0), 4.21-4.28 (m, 1H), 4.36-4.44 (m, 1H), 7.13-7.65 (m, 7H) 7.94 (d, 1H, *J* 7.4), 8.25 (br.s, 1H, NH) and 8.28-8.30 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 19.24 (CH_3), 19.86 (CH_3), 24.37 (CH_2), 37.52 (CH), 41.26 (CH_2), 53.42 (CH), 111.39 (CH), 113.11 (C), 119.56 (CH), 119.75 (CH), 122.30 (CH), 122.50 (CH), 126.63 (C), 127.83 (C), 127.92 (CH), 127.96 (CH), 128.88 (CH), 133.38 (CH), 136.60 (C), 138.35 (C), 165.55 (C=O) and 173.50 (C=O) ppm; Found: M^+ 346.1683 (7.9%) $C_{22}H_{22}N_2O_2$ requires 346.1681.

General Method for 3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinones Formation.

Procedure modified from that described by Cazeau *et al*[50] for the preparation of silyl enol ethers from ketones and aldehydes. A solution of sodium iodide (1.5-3 equivalents) in a given volume of dry acetonitrile was added dropwise over 15 minutes, at room temperature, to a solution of the particular 1,3-isoquinolinedione, triethylamine (1.5-3 equivalents) and trimethylchlorosilane (1.5-3 equivalents) in a given volume of dry acetonitrile. Stirring was maintained for 90 minutes at room temperature. Then dry diethyl ether (200 ml) was added to the reaction mixture and stirring was maintained for further 10 minutes. The reaction mixture was then allowed to stand for 10 minutes to permit the suspended solid to settle down. Subsequently, diethyl ether/acetonitrile solution was transferred under nitrogen pressure to a receiving flask *via* canula. diethyl ether and acetonitrile were removed in *vacuo* and fresh dry diethyl ether (150 ml) was added to the residue, the formed suspension was then quickly filtered, and the filtrate was concentrated in *vacuo* to give the title compounds. The products were very sensitive towards atmospheric moisture, consequently, all steps were conducted under tight nitrogen atmosphere and the reaction conditions were optimised to generate the products in sufficiently high purity for characterisation and subsequent reactions. The following 3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinones were prepared:

2-Phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone.

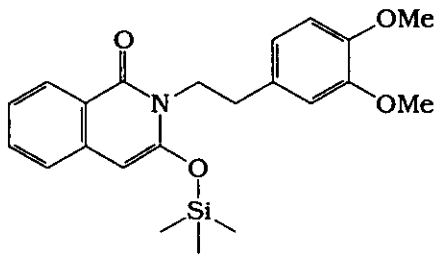


3.25

A solution of sodium iodide (2.55g,17.0 mmol) in dry acetonitrile (20 ml) was added dropwise, at room temperature, to a solution of 2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.2**) (1.50g, 5.7 mmol), triethylamine (2.2 ml,

17.0 mmol) and trimethylchlorosilane (2.2 ml, 17.0 mmol) in dry acetonitrile (20 ml) followed by stirring for 90 minutes and gave the title compound (**3.25**) (1.70g, 89%), brown oil : ν_{max} 1655, 1619 and 1596 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.38 (s, 9H, $Si(CH_3)_3$), 2.92-3.02 (m, 2H), 4.25-4.37 (m, 2H), 5.71 (s, 1H), 7.16-7.54 (m, 8H) and 8.30-8.35 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 0.00 (3 x CH_3, $Si(CH_3)_3$), 34.86 (CH_2), 43.37 (CH_2), 87.48 (CH), 121.88 (C), 123.95 (CH), 124.49 (CH), 126.41 (CH), 127.88 (CH), 128.53 (2 x CH), 128.92 (2 x CH), 132.30 (CH), 137.68 (C), 138.99 (C), 148.33 (C) and 162.50 (C=O) ppm; Found: M^+ 337.1511(0.1%) $C_{20}H_{23}NO_2Si$ requires 337.1498.

2-(3,4-Dimethoxyphenethyl)-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone.

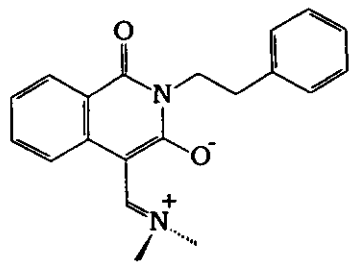


3.26

A solution of sodium iodide (2.55g, 17.0 mmol) in acetonitrile (25 ml) was added dropwise, at room temperature, to a solution of 2-(3,4-dimethoxy phenethyl)-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**2.3**) (3.34g, 10.3 mmol), triethyl amine (2.2 ml, 17.0 mmol) and trimethylchlorosilane (2.2 ml, 17.0 mmol) in acetonitrile (40 ml) followed by stirring for 90 minutes and gave the title compound (**3.26**) (2.60g, 64%), yellow oil : ν_{max} 2961, 1707, 1662, 1620 and 1593 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.38 (s, 9H, $Si(CH_3)_3$), 2.82-2.94 (m, 2H), 3.80 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.15-4.32 (m, 2H), 5.71 (s, 1H), 6.75-6.86 (m, 3H), 7.23-7.34 (m, 2H), 7.48-7.54 (m, 1H) and 8.30-8.33 (m, 1H) ppm;^{13}C nmr (62.8 M Hz, $CDCl_3$) 0.00 (3 x CH_3, $Si(CH_3)_3$), 34.39 (CH_2), 43.57 (CH_2), 55.75 (CH_3, OMe), 55.91 (CH_3, OMe), 87.52 (CH), 111.41 (CH), 112.15 (CH), 120.82 (CH), 121.89 (C), 124.00 (CH), 124.49 (CH), 127.88

(CH), 131.60 (C), 132.34 (CH), 137.67 (C), 147.65 (C), 148.38 (C), 148.93 (C), and 162.77 (C=O) ppm; Found: M^+ 397.1729 (0.1%) $C_{22}H_{27}NO_4Si$ requires 397.1709.

Reaction of 2-phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone with *N,N*-dimethyl dimethoxyformamide and TMSOTf.



3.27

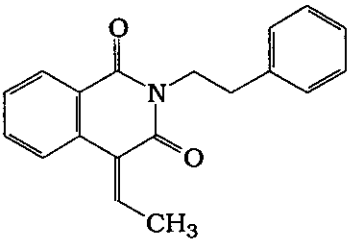
A magnetically stirred solution of 2-phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone (**3.25**) (1.5g, 4.45 mmol) and *N,N*-dimethyldimethoxy formamide (1.80g, 15.1mmol) in dry DCM (*ca.* 50 ml) was cooled down to -78 °C and TMSOTf (catalytic quantity) injected, under tight nitrogen atmosphere. The reaction was then stirred at the same temperature for 15 minutes then warmed gradually to room temperature over 1 hour. The reaction changed colour from yellow to deep red. Subsequently, saturated sodium bicarbonate solution (*ca.* 50 ml) was added to the reaction mixture. Extraction of resultant cloudy emulsion with DCM (2 x 100 ml) and drying of the combined organic extracts over magnesium sulfate followed by concentrating in *vacuo* gave after flash chromatography eluting with EA *4-[(1,1-dimethyl ammonio)methyl]-1-oxo-2-phenethyl-1,2-dihydro-3-isoquinolinolate* (**3.27**) (1.21g, 85%), mp 154.5 - 155.5 °C from EA : ν_{max} 2953, 1672, 1626 and 1604 cm^{-1}; ^1H nmr (298 K, 250 M Hz, $CDCl_3$) 2.93-2.99 (m, 2H), 3.18 (br.s, 6H), 4.28-4.35 (m, 2H), 7.15-7.47 (m, 8H) , 7.91 (br.s, 1H) and 8.22-8.25 (m, 1H) ppm; ^1H nmr (323 K, 250 M Hz, $CDCl_3$) 2.89-3.00 (m, 2H), 3.18 (s, 6H), 4.29-4.35 (m, 2H), 7.12-7.44 (m, 8H) , 7.89 (s, 1H) and 8.20-8.24 (m, 1H) ppm;^{13}C nmr (323 K, 62.8 M Hz, $CDCl_3$) 34.35 (CH_2), 41.39 (CH_2), 45.68 (2 x CH_3), 120.00 (br.s, C), 121.67 (br.s, C), 123.28 (CH), 125.94 (2 x CH), 126.03 (C), 128.16 (2 x CH), 128.76

(CH), 128.93 (2 x CH), 132.18 (CH), 133.33 (C), 139.59 (C), 155.49 (CH) and 165.42 (C=O) ppm; Found: M^+ 320.1532 (100%) $C_{20}H_{20}N_2O_2$ requires 320.1525. HETCOR experiment at 323 K supports characterisation.

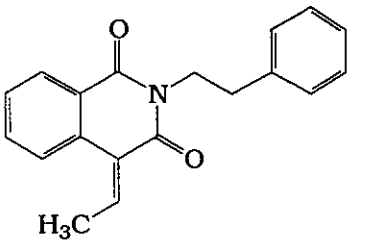
Reactions of 3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinones with dimethyl acetals and TMSOTf -General Method.

A magnetically stirred solution of the particular 3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone, the particular dimethyl acetal (1-1.3 equivalents) and BSA (few drops) in dry DCM (*ca.* 50 ml) was cooled to -78 °C and TMSOTf (catalytic quantity) injected, under tight nitrogen atmosphere. The reaction was then stirred at the same temperature for 15 minutes, then warmed to room temperature and stirred for 14-16 hours. The reaction changed colour from brown to black. Subsequently, saturated aqueous sodium bicarbonate (*ca.* 50 ml) was added to the reaction mixture. The organic layer was then collected and the aqueous layer was further extracted with DCM (2 x 50 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel. The following reaction were conducted:

Reaction of 2-phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone with acetaldehyde dimethylacetal and TMSOTf.



3.28

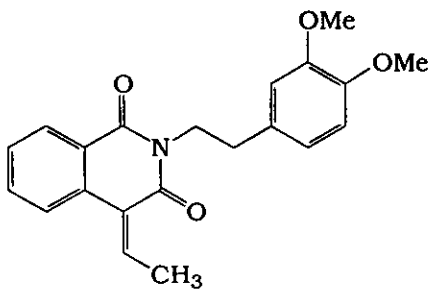


3.29

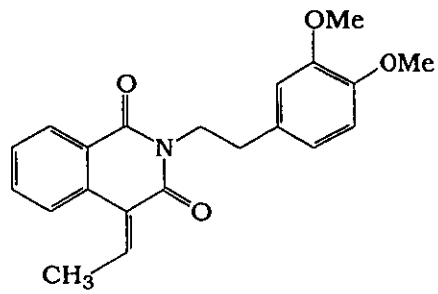
A stirred solution of 2-phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone (**3.25**) (3.03g, 9.0 mmol), acetaldehyde dimethylacetal (1.0g, 11.0 mmol) in dry DCM (50 ml) was cooled to -78 °C and TMSOTf (catalytic quantity) injected and gave after flash chromatography eluting with EA/LP [1:5] mixture of *Z* and *E* [56% : 44%] *4-(ethylidene)-2-phenethyl-1,2,3,4-tetrahydro-*

1,3-isoquinolinedione (**3.28/3.29**) (1.41g, 54%). Fraction of *4-[(Z)ethylidene]-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione* (**3.28**) was isolated (0.11g), yellow oil : ν_{max} 2925, 1703, 1661 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 2.31 (d, 3H, *J* 7.5), 2.82-2.86 (m, 2H), 4.14-4.18 (m, 2H), 7.10-7.56 (m, 9H) and 8.12-8.14 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 17.58 (CH_3), 34.68 (CH_2), 41.95 (CH_2), 122.15 (CH), 124.29 (C), 126.32 (C), 126.76 (CH), 128.42 (CH), 128.83 (2 x CH), 129.32 (CH), 129.42 (2 x CH), 133.82 (CH), 135.00 (C), 139.27 (C), 145.42 (CH), 164.47 (C=O) and 164.68 (C=O) ppm; Found: M^+ 291.1269 (33.5%) $C_{19}H_{17}NO_2$ requires 291.1259. HETCOR and COSY experiments support characterisation. Data for **3.28/3.29** mixture : ^1H nmr (400 M Hz, $CDCl_3$) 2.21 (d, 3H, *J* 7.9), 2.31 (d, 3H, *J* 7.5), 2.82-2.86 (m, 4H), 4.14-4.18 (m, 4H), 7.10-7.56 (m, 18H) and 8.12-8.14 (m, 2H) ppm; mixture ^{13}C nmr (250 M Hz, $CDCl_3$) 17.03 (CH_3), 17.20 (CH_3), 34.14 (CH_2), 34.21 (CH_2), 41.49 (CH_2), 42.06 (CH_2), 121.70 (2 x CH), 123.60 (2 x C), 125.20 (C), 125.6 (C), 126.34 (CH), 126.61 (CH), 127.20 (C), 127.94 (CH), 128.08 (CH), 128.39 (4 x CH), 128.78 (2 x CH), 128.93 (4 x CH), 132.84 (CH), 133.37 (CH), 134.58 (C), 138.80 (2 x C), 144.06 (CH), 145.10 (CH), 164.64 (C=O), 164.88 (C=O), 65.20 (C=O) and 165.76 (C=O) ppm.

Reaction of 2-(3,4-dimethoxyphenethyl)-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone with acetaldehyde dimethylacetal and TMSOTf.



3.30

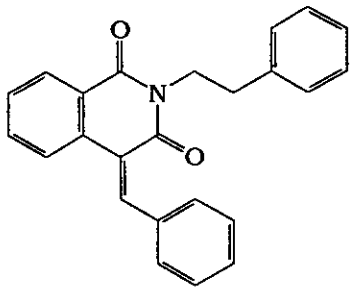


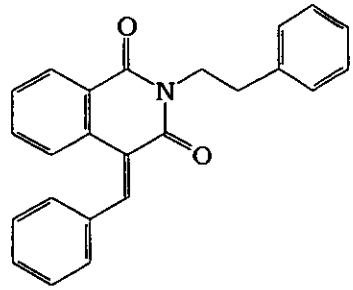
3.31

A stirred solution of 2-(3,4-dimethoxyphenethyl)-3-[(1,1,1-trimethylsilyl) oxy]-1,2-dihydro-1-isoquinolinone (**3.26**) (3.20g, 8.0 mmol), acetaldehyde dimethyl acetal (0.90g, 10.0 mmol) in dry DCM (50 ml) was cooled to -78 °C and

TMSOTf (catalytic quantity) injected and gave after flash chromatography eluting with EA/LP [1:3] mixture of *Z* and *E* [65% : 35%] *2-(3,4-dimethoxy phenethyl)-4-(ethylidene)-1,2,3,4-tetrahydro-1,3-isoquinoline dione* (**3.30/3.31**) (0.72g, 26%). Fraction of *2-(3,4-dimethoxy phenethyl)-4-[(Z)ethylidene]-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.30**) was isolated (0.02g), mp 62 - 64 °C from EA/LP : ν_{max} 2950, 1702, 1660 and 1609 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 2.45 (d, 3H, *J* 7.5), 2.90-2.94 (m, 2H), 3.86 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.24-4.28 (m, 2H), 6.81-6.90 (m, 3H), 7.36 (q, 1H, *J* 7.5), 7.45-7.71 (m, 3H) and 8.24-8.26 (m, 1H) ppm;^{13}C nmr (100.5 M Hz, $CDCl_3$) 17.56 (CH_3), 34.21 (CH_2), 42.05 (CH_2), 56.22 (CH_3, OMe), 56.31 (CH_3, OMe), 111.76 (CH), 112.65 (CH), 121.40 (CH), 122.14 (CH), 124.26 (C), 126.30 (C), 128.43 (CH), 129.27 (CH), 131.83 (C), 133.84 (CH), 134.96 (C), 145.42 (CH), 148.02 (C), 149.27 (C), 164.48 (C=O) and 164.67 (C=O) ppm; Found: M^+ 351.1466 (1.6%) $C_{21}H_{21}NO_4$ requires 351.1471. HETCOR and COSY experiments support characterisation. Data for **3.28/3.29** mixture: ^1H nmr (400 M Hz, $CDCl_3$) 2.33 (d, 3H, *J* 7.8), 2.45 (d, 3H, *J* 7.5), 2.90-2.94 (m, 4H), 3.86 (s, 6H, OMe), 3.87 (s, 6H, OMe), 4.24-4.28 (m, 4H), 6.81-6.90 (m, 6H), 7.28-7.71 (m, 8H) and 8.24-8.26 (m, 2H) ppm; ^{13}C NMR (250 MHz, $CDCl_3$) of the mixture 17.16 (CH_3), 17.31 (CH_3), 33.83 (CH_2), 33.90 (CH_2), 41.74 (CH_2), 42.30 (CH_2), 55.87 (CH_3, OMe), 55.90 (2 x CH_3, 2 x OMe), 55.98 (CH_3, OMe), 111.40 (2 x CH), 112.25 (CH), 112.30 (CH), 121.06 (CH), 121.09 (CH), 121.86 (CH), 123.88 (2 x C), 125.88 (2 x C), 126.76 (CH), 128.11 (2 x CH), 128.25 (CH), 128.90 (CH), 131.52 (2 x C), 132.99 (CH), 133.54 (CH), 134.60 (2 x C), 144.16 (CH), 145.22 (CH), 147.69 (C), 148.92 (3 x C), 164.16 (C=O), 164.31 (C=O), 165.60 (C=O) and 166.20 (C=O) ppm.

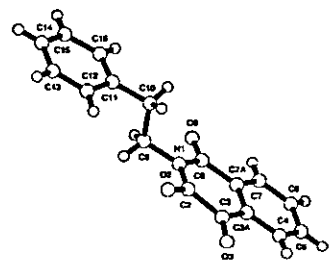
Reaction of 2-phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone with benzaldehyde dimethylacetal and TMSOTf.

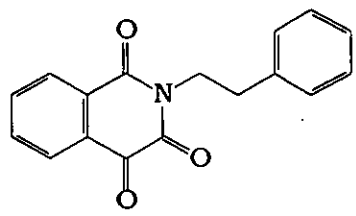




3.32 **3.33**

A stirred solution of 2-phenethyl-3-[(1,1,1-trimethylsilyl)oxy]-1,2-dihydro-1-isoquinolinone (**3.25**) (1.68g, 5.0 mmol), benzaldehyde dimethylacetal (0.76g, 5.0 mmol) in dry DCM (50 ml) was cooled to -78 °C and TMSOTf (catalytic quantity) injected and gave after flash chromatography eluting with EA/LP [1:2] mixture of *Z* and *E* *2-phenethyl-4-(1-phenyl methylidene)-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.32/3.33**) (1.76g, 100%), yellow oil : ν_{max} 3027, 1704, 1662 and 1604 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.92-3.02 (m, 2H), 4.23-4.33 (m, 2H), 7.25-7.55 (m, 15H) and 8.20-8.25 (m, 1H) ppm; Found: M^+ 353.1383 (43.3%) $C_{24}H_{19}NO_2$ requires 353.1416. Upon storing under ambient conditions for 3 months, **3.32/3.33** yielded *2-phenethyl-1,2,3,4-tetrahydro-1,3,4-isoquinoline trione* (**3.34**) (0.42g, 30%) after flash chromatography eluting with EA/LP [1:2].





3.34

Data : mp 126 - 127 °C from EA/LP : ν_{max} 2925, 1709, 1677 and 1597 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.95-3.01 (m, 2H), 4.26-4.32 (m, 2H), 7.19-7.38 (m, 5H), 7.80-7.94 (m, 2H), 8.20-8.24 (m, 1H) and 8.33-8.37 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 34.45 (CH_2), 42.83 (CH_2), 127.17 (CH), 128.23 (CH),

129.04 (2 x CH), 129.36 (2 x CH), 130.23 (CH), 130.33 (C), 131.29 (C), 134.85 (CH), 136.46 (CH), 138.30 (C), 157.29 (C=O), 162.45 (C=O), 175.01 (C=O) ppm; Found: M^+ 279.0901 (17.2%) $C_{17}H_{13}NO_3$ requires 279.0895. HETCOR and COSY experiments support characterisation.

X-Ray Report (Experimental Details). Carried out by Dr. AMZ Slawin.

A. Crystal Data

Empirical Formula	$C_{17}H_{13}NO_3$
Formula Weight	279.09
Crystal Colour, Habit	yellow, block
Crystal Dimensions	0.15 x 0.23 x 0.32 mm
Crystal System	orthorhombic
Lattice Type	primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (74.0 - 75.0°)
Omega Scan Peak Width at	
Half -height	0.27°
Lattice Parameters	a = 6.371(2) °A
	b = 15.476(2) °A
	c = 13.989(2) °A
	V = 1379.1(3) °A^3
Space Group	$Pna2_1$ (#33)
Z value	4
D_{calc}	1.345 g/cm^3
F_{000}	584.00
μ (CuKα)	7.62 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuKα (λ = 1.54178 °A)
	graphite monochromated
Attenuater	Ni foil (factor = 9.42)

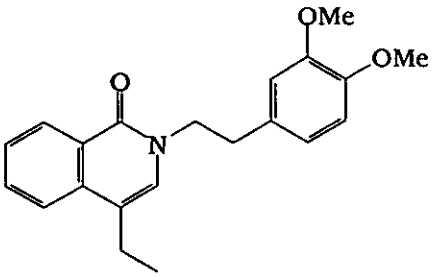
Take-off Angle	6.0 °
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	20.0 °C
Scan Type	ω
Scan Rate	16.0°/ min (in ω) (up to 4 scans)
Scan Width	(1.15 + 0.35 tanθ) °
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 2480
	Unique: 1240 (R_{int} = 0.085)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.4618 - 1.0000)
	Decay (0.26% decline)

C. Structure Solution and Refinement

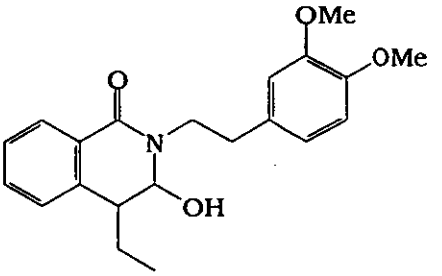
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function minimised	$\sum w(\|Fo\|-\|Fc\|)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
P-factor	0.004
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>2.00σ(I))	1058
No. Variables	191
Reflection / Parameter Ratio	5.54
Residuals: R; Rw	0.000; 0.000
Goodness of Fit Indicator	0.00
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	1.27 e^- / $°A^3$
Minimum peak in Final Diff. Map	- 1.35 e^- / $°A^3$

Sodium borohydride Reduction of 4-(phenylmethylidene)- and 4-(ethylidene)-1,2,3,4-tetrahydro-1,3-isoquinolinediones.

Reduction of 2-(3,4-dimethoxyphenethyl)-4-(ethylidene)-1,2,3,4-tetrahydro-1,3-isoquinoline.



3.36

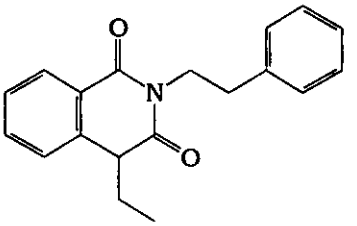


3.35

A magnetically stirred solution of 2-(3,4-dimethoxyphenethyl)-4-(ethylidene)-1,2,3,4-tetrahydro-1,3-isoquinoline (**3.30/3.31**) (0.60g, 1.71 mmol) and cerium chloride heptahydrate (0.64g, 1.71 mmol) in dry ethanol (10 ml) was cooled down to -78 °C and sodium borohydride (0.20g, 5.3 mmol) added. The reaction was then stirred at the same temperature for 45 minutes. Subsequently, the reaction was terminated by quenching with saturated aqueous sodium bicarbonate (*ca.*10 ml). Extraction of resultant cloudy emulsion with DCM (2 x 50 ml) and drying of the combined organic extracts over magnesium sulfate followed by concentrating in *vacuo* gave three products after flash chromatography eluting with EA/LP [1:1]. The first product *2-(3,4-dimethoxy phenethyl)-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.20**) (0.05g, 8%). The second product *2-(3,4-dimethoxyphenethyl)-4-ethyl-1,2-dihydro-1-isoquinolinone* (**3.36**) (0.08g, 14%), yellow oil, ν_{max} 2963, 1652, 1624 and 1594 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.14 (t, 3H, *J* 7.4), 2.59 (q, 2H, *J* 7.4), 3.00 (t, 2H, *J* 7.2), 3.72 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.15 (t, 2H, *J* 7.2), 6.56 (s, 1H), 6.66 (d, 1H, *J* 1.8), 6.72-6.79 (m, 2H), 7.47-7.51 (m, 1H), 7.62-7.67 (m, 2H) and 8.49-8.51 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 14.25 (CH_3), 22.64 (CH_2), 35.15 (CH_2), 51.95 (CH_2), 56.14 (CH_3, OMe), 56.34 (CH_3, OMe), 111.88 (CH), 112.71 (CH), 117.79 (C), 121.31 (CH), 122.97 (CH), 126.58 (C), 126.84 (CH), 128.69 (CH), 129.40 (CH), 131.39 (C), 132.30

(CH), 137.02 (C), 148.19 (C), 149.44 (C) and 162.11 (C=O) ppm; Found: M^+ 337.1690 (0.6 %) $C_{21}H_{23}NO_3$ requires 337.1678. COSY and HETCOR experiments support characterisation. The third product *2-(3,4-dimethoxy phenethyl)-4-ethyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone* single diastereomer (**3.35**) (0.07g, 12%), mp 128-129 °C from EA/LP: ν_{max} 3351, 2936, 1635 and 1603 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.90 (t, 3H, *J* 7.3), 1.47-1.66 (m, 1H), 1.97-2.15 (m, 1H), 2.72-2.83 (m, 1H), 2.92-2.97 (m, 2H), 3.12 (d, 1H, D_2O ex., *J* 8.1), 3.47-3.60 (m, 1H), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.06-4.18 (m, 1H), 4.61 (dd, 1H, J_1 3.3, J_2 7.3), 6.76-6.77 (m, 3H), 7.25-7.49 (m, 3H) and 8.02-8.06 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 11.02 (CH_3), 20.10 (CH_2), 34.58 (CH_2), 42.86 (CH), 48.84 (CH_2), 55.82 (CH_3, OMe), 55.88 (CH_3, OMe), 81.98 (CH), 111.34 (CH), 112.16 (CH), 120.85 (CH), 125.15 (CH), 126.97 (CH), 127.49 (C), 127.87 (CH), 131.77 (C), 132.15 (CH), 137.86 (C), 147.50 (C), 148.97 (C) and 163.93 (C=O) ppm; Found: M^+ 355.1744 (0.1 %) $C_{21}H_{25}NO_4$ requires 355.1784.

Reduction of 4-(ethylidene)-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.

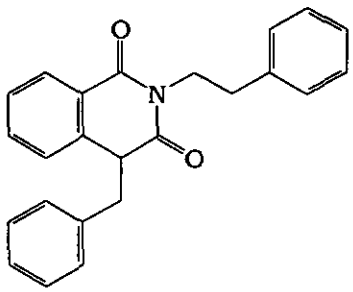


3.37

A magnetically stirred solution of 4-(ethylidene)-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.28/3.29**) (2.0g, 6.90 mmol) in dry ethanol (30 ml) was cooled down to -78 °C and sodium borohydride (0.18g, 4.7 mmol) added. The reaction was then stirred at the same temperature for 15 minutes. Subsequently, the reaction was terminated by quenching with saturated aqueous sodium bicarbonate (*ca.* 10 ml). Extraction of resultant cloudy emulsion with DCM (2 x 50 ml) and drying of the combined organic extracts over magnesium sulfate followed by concentrating in *vacuo* gave after flash chromatography eluting with

EA/LP [1:5] *4-ethyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**3.37**) (0.56g, 28%), oil : ν_{max} 1713, 1669 and 1607 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.70 (t, 3H, *J* 7.4), 1.90-2.01 (m, 1H), 2.16-2.27 (m, 1H), 2.91-2.99 (m, 2H), 3.86-3.91 (m, 1H), 4.09-4.35 (m, 2H), 7.20-7.64 (m, 8H) and 8.21-8.24 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 9.47 (CH_3), 30.36 (CH_2), 34.20 (CH_2), 41.43 (CH_2), 47.14 (CH), 126.15 (C), 126.37 (CH), 126.73 (CH), 127.47 (CH), 128.38 (2 x CH), 128.83 (CH), 128.93 (2 x CH), 133.52 (CH), 138.52 (C), 138.86 (C), 164.95 (C=O) and 173.44 (C=O) ppm; Found: M^+ 293.1416 (12.9 %) $C_{19}H_{19}NO_2$ requires 293.1416.

Reduction of 2-phenethyl-4-(1-phenylmethylidene)-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



3.38

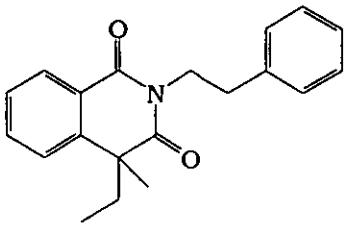
A magnetically stirred solution of 2-phenethyl-4-(1-phenylmethylidene)-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.32/3.33**) (0.69g, 1.95 mmol) in dry ethanol (40 ml) was cooled down to -78 °C and sodium borohydride (0.030g, 0.78mmol) added. The reaction was then stirred at the same temperature for 1 hour. Subsequently, the reaction was terminated by quenching with saturated aqueous sodium bicarbonate (*ca.* 15 ml). Extraction of resultant cloudy emulsion with DCM (2 x 50 ml) and drying of the combined organic extracts over magnesium sulfate followed by concentrating in *vacuo* gave after flash chromatography eluting with EA/LP [1:5] *4-benzyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquin olinedione* (**3.38**) (0.092g, 13%), pale oil : ν_{max} 3028, 1713, 1669 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.68-2.85 (m, 2H), 3.23 (dd, 1H, A of ABX, J_{AB} 13.1, J_{AX} 4.7), 3.34 (dd, 1H, B of ABX, J_{AB} 13.1, J_{BX} 6.3), 3.90-4.14 (m, 2H), 4.19 (dd, 1H, X of ABX, J_{AX} 4.7, J_{BX} 6.3), 6.66-6.70 (m, 2H), 7.09-7.60 (m,

11H) and 8.07-8.11 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 34.16 (CH_2), 41.67 (CH_2), 43.65 (CH_2), 48.18 (CH), 126.05 (C), 126.53 (CH), 127.41 (CH), 127.55 (CH), 128.15 (CH), 128.40 (2 x CH), 128.57 (2 x CH), 128.64 (CH), 128.73 (2 x CH), 129.46 (2 x CH), 133.37 (CH), 135.55 (C), 138.21 (C), 138.85 (C), 164.22 (C=O) and 173.01 (C=O) ppm; Found: M^+ 355.1573 (24.3 %) $C_{24}H_{21}NO_2$ requires 355.1572. COSY and HETCOR experiments support characterisation.

General Method for 4-methylation of 4-alkyl-1,2,3,4-tetrahydro-1,3-isoquinolinediones.

A magnetically stirred solution of the particular 4-alkyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione, sodium hydroxide aqueous solution (a given number of equivalents) and methyl iodide (5 equivalents) in ethanol (*ca.* 60 ml) was heated to reflux for a given length of time. After allowing the reaction to cool down to room temperature DCM (50 ml) and water (50 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (50 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel.

4-Ethyl-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.

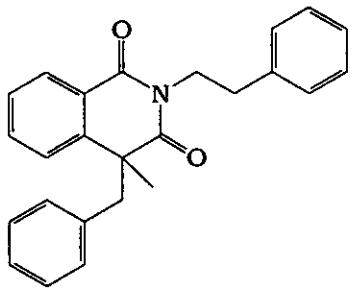


3.39

A stirred solution of 4-ethyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinoline-dione (**3.37**) (0.56g, 1.91 mmol), sodium hydroxide (0.46g, 11.5 mmol) and methyl iodide (0.71g, 5.0 mmol) in aqueous ethanol [1:1] (*ca.* 100 ml) heated to

reflux for 30 minutes and gave the title compound (**3.39**) (0.49g, 84%), oil : ν_{max} 2969, 1711, 1665 and 1606 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.49 (t, 3H, *J* 7.4), 1.57 (s, 3H), 1.80-1.94 (m, 1H), 2.22-2.36 (m, 1H), 2.90-2.97 (m, 2H), 4.21-4.28 (m, 2H), 7.22-7.64 (m, 8H) and 8.23-8.27 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 9.43 (CH_3), 28.62 (CH_3), 34.15 (CH_2), 36.44 (CH_2), 41.71 (CH_2), 48.26 (C), 125.22 (C), 125.26 (CH), 126.43 (CH), 127.29 (CH), 128.45 (2 x CH), 128.92 (CH), 129.08 (2 x CH), 133.96 (CH), 138.57 (C), 143.53 (C), 164.14 (C=O) and 176.24 (C=O) ppm; Found: M^+ 307.1579 (28.9%) $C_{20}H_{21}NO_2$ requires 307.1572.

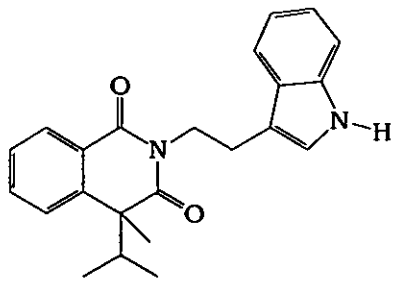
4-Benzyl-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



3.40

A stirred solution of 4-benzyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinoline-dione (**3.38**) (0.80g, 2.25 mmol), sodium hydroxide (0.64g, 16.0 mmol) and methyl iodide (0.71g, 5.0 mmol) in aqueous ethanol [1:1] (*ca.* 100 ml) heated to reflux for 4 hours and gave the title compound (**3.40**) (0.71g, 85%), pale oil : ν_{max} 1710, 1665 and 1604 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.82 (s, 3H), 2.59-2.81 (m, 2H), 3.07 (d, 1H, A of AB, J_{AB} 12.9), 3.44 (d, 1H, B of AB, J_{AB} 12.9), 3.96 (m, 2H), 6.53-6.55 (m, 2H), 6.96-7.73 (m, 11H) and 8.08-8.11 (m, 1H) ppm;^{13}C nmr (68.2 M Hz, $CDCl_3$) 27.02 (CH_3), 33.91 (CH_2), 41.78 (CH_2), 49.18 (C), 50.71 (CH_2), 125.52 (C), 125.86 (CH), 126.34 (CH), 127.08 (CH), 127.41 (CH), 127.85 (2 x CH), 128.40 (2 x CH), 128.91 (CH), 129.29 (4 x CH), 133.60 (CH), 135.37 (C), 138.81 (C), 142.66 (C), 163.42 (C=O) and 175.42 (C=O) ppm; Found: M^+ 369.1728 (31.8%) $C_{25}H_{23}NO_2$ requires 369.1729.

2-[2-(1H-3-Indolyl)ethyl]-4-isopropyl-4-methyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



3.41

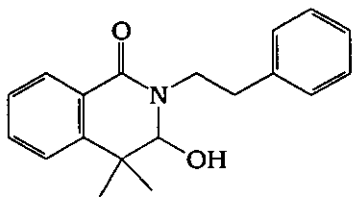
A stirred solution of 2-[2-(1H-3-indolyl)ethyl]-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.24**) (0.48g, 1.39 mmol), sodium hydroxide (0.061g, 1.53 mmol) and methyl iodide (2.0g, 14.1 mmol) in aqueous ethanol [1:1] (*ca.* 50 ml) heated to reflux for 3 hours and gave the title compound (**3.41**) after flash chromatography eluting with EA/LP [1:3] (0.14g, 28%), foamy oil : ν_{max} 3378 (broad), 2968, 1708, 1658 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.76 (d, 3H, *J* 6.8), 0.90 (d, 3H, *J* 6.8), 1.69 (s, 3H), 2.07 (h, 1H), 3.08-3.12 (m, 2H), 4.20-4.27 (m, 1H), 4.31-4.38 (m, 1H), 7.12-7.47 (m, 7H) 7.89 (d, 1H, *J* 7.4), 8.04 (br.s, 1H, NH) and 8.27-8.29 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 18.06 (CH_3), 18.32 (CH_3), 22.54 (CH_3), 24.36 (CH_2), 41.70 (CH_2), 42.12 (CH), 51.20 (C), 111.36 (CH), 113.53 (C), 119.73 (CH), 119.90 (CH), 122.44 (CH), 122.46 (CH), 126.37 (C), 126.47 (CH), 127.61 (CH), 128.00 (C), 128.91 (CH), 133.60 (CH), 136.68 (C), 143.50 (C), 165.06 (C=O) and 176.07 (C=O) ppm; Found: M^+ 360.1844 (3.3%) $C_{23}H_{24}N_2O_2$ requires 360.1838.

Chapter 4 Experimental.

Preparation of 3-hydroxy-4,4-disubstituted-1,2,3,4-tetrahydro-1-isoquinolinones - General Method.

Procedure modified from that employed by Speckamp *et al* in the ragioselective reduction of imides.[70, 71, 72] The following procedure was followed, unless otherwise stated in each individual case. A magnetically stirred solution of the particular 4,4-disubstituted-1,2,3,4-tetrahydro-1,3-isoquinolinedione in ethanol (*ca.* 100 ml, unless otherwise stated) was cooled down to $^{-}5$ °C - $^{-}10$ °C (unless otherwise stated), then sodium borohydride (5-50 equivalents) was added. After 2 hours more sodium borohydride was added (5-50 equivalents), the reaction was stirred at the same temperature for further 2 hours. Subsequently, the reaction was terminated by quenching with aqueous sodium bicarbonate. The resulting cloudy emulsion was extracted with DCM (2 x 100 ml) and the combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation.

3-Hydroxy-4,4-dimethyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinlinone.

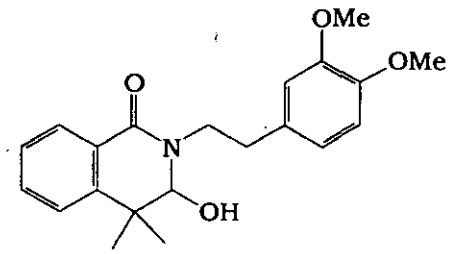


4.1

A stirred solution of 4,4-dimethyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.1**) (0.88g, 3.0 mmol) in ethanol was cooled down and sodium borohydride (1.0g, 26.3 mmol) was added. After two hours more sodium borohydride was added (1.0g, 26.3 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.1**) (0.73g, 83%), mp 157.0 - 159.0 °C from ethanol : ν_{max} 3353 (broad), 2969, 1633 and 1603 cm^{-1}; ^{1}H nmr (250 M Hz, $CDCl_3$) 1.15 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.95 (d, 1H, OH, D_2O ex., *J* 8.0), 3.00-3.13 (m, 2H), 3.78-3.84 (m, 1H),

3.96-4.02 (m, 1H), 4.53 (d, 1H, *J* 8.0), 7.27-7.51 (m, 8H) and 8.10-8.13 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 23.11 (CH_3), 29.95 (CH_3), 34.98 (CH_2), 39.74 (C), 49.18 (CH_2), 90.36 (CH), 125.18 (CH), 126.97 (CH), 127.39 (CH), 127.58 (C), 128.53 (CH), 128.79 (2 x CH), 129.04 (2 x CH), 133.00 (CH), 139.40 (C), 144.31 (C) and 163.86 (C=O) ppm; Found: M^+ 295.1572 (3.8%) $C_{19}H_{21}NO_2$ requires 295.1572.

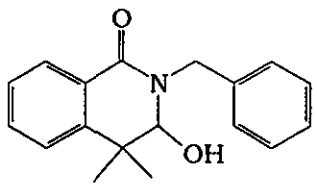
2-(3,4-Dimethoxyphenethyl)-3-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone.



4.2

A stirred solution of 2-(3,4-dimethoxyphenethyl)-4,4-dimethyl -1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.2**) (1.1g, 3.1 mmol) in ethanol was cooled down and sodium borohydride (1.0g, 26.3 mmol) was added. After two hours more sodium borohydride was added (1.0g, 26.3 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.2**) (0.92g, 85%), mp 204.0 - 205.5 °C from ethanol : ν_{max} 3374 (broad), 2962, 1627 and 1604 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.18 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.96 (d, 1H, OH, *J* 8.00), 2.90-3.06 (m, 2H), 3.78-3.84 (m, 1H), 3.86 (s, 3H, MeO), 3.88 (s, 3H, MeO), 3.94-4.06 (m, 1H), 4.55 (d, 1H, *J* 8.00), 6.82-6.83 (m, 3H), 7.27-7.51 (m, 3H) and 8.09-8.12 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 23.12 (CH_3), 29.98 (CH_3), 34.71 (CH_2), 39.82 (C), 49.41 (CH_2), 56.29 (2 x CH_3, 2 x OMe), 90.51 (CH), 111.77 (CH), 112.45 (CH), 121.11 (CH), 125.24 (CH), 127.51 (CH), 127.62 (C), 128.83 (CH), 131.88 (C), 133.06 (CH), 144.08 (C), 148.10 (C), 149.48 (C) and 163.70 (C=O) ppm; Found: C, 68.49, H, 6.79, N, 3.79 % $C_{21}H_{25}NO_4$ requires C, 70.95, H, 7.04, N, 3.94 %; Found: M^+ 355.1783 (1.8%) $C_{21}H_{25}NO_4$ requires 355.1784.

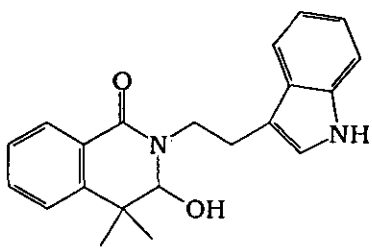
2-Benzyl-3-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone.



4.3

A stirred solution of 2-benzyl-4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinoline-dione (**3.3**) (2.0g, 7.20 mmol) in ethanol was cooled down and sodium borohydride (1.5g, 39.5 mmol) was added. After two hours more sodium borohydride was added (1.5g, 39.5 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.3**) (1.7g, 84%), mp 109-111 °C from ethanol: ν_{max} 3360 (broad), 2971, 1634 and 1604 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.96 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.75 (br.s, 1 H, OH), 4.27 (d, 1H, A of AB, *J* 14.5), 4.56 (s, 1H), 5.33 (d, 1H, B of AB, *J* 14.5), 7.25-7.50 (m, 8H) and 8.07-8.11 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 22.55 (CH_3), 29.56 (CH_3), 38.91 (C), 48.49 (CH_2), 87.57 (CH), 124.73 (CH), 126.84 (CH), 126.97 (C), 127.55 (CH), 128.55 (3 x CH), 128.83 (2 x CH), 132.62 (CH), 137.21 (C), 144.50 (C) and 163.75 (C=O) ppm; Found: M^+ 281.1410 (4.2%) $C_{18}H_{19}NO_2$ requires 281.1416.

3-Hydroxy-2-[2-(1H-3-indolyl)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinlinone.

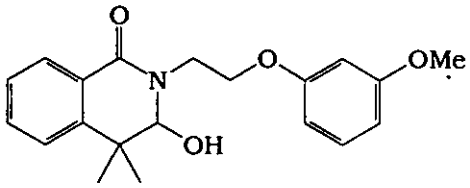


4.4

A stirred solution of 2-[2-(1H-3-indolyl)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione (**3.4**) (0.30g, 0.90 mmol) in ethanol was cooled down and sodium borohydride (1.0g, 26.3 mmol) was added. After two hours more

sodium borohydride was added (1.0g, 26.3 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.4**) after flash chromatography eluting with EA/LP/ethanol [1:1: few drops] (0.13g, 43%), mp 176 - 178 °C from EA/LP : ν_{max} 3336 (broad), 3055, 1616 and 1598 cm^{-1}; ^1H nmr (250 M Hz, d_6 DMSO) 1.11 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.00-3.04 (m, 2H), 3.36-3.40 (m, 1H), 4.04-4.14 (m, 1H), 4.74 (d, 1H, *J* 5.45), 6.17 (d, 1H, OH, *J* 5.40), 7.01-7.56 (m, 5H), 7.27-7.51 (m, 3H), 7.71 (br.s, 1H, N-H) and 8.01-8.04 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, d_6 DMSO) 21.87 (CH_3), 23.39 (CH_2), 28.60 (CH_3), 37.95 (C), 45.29 (CH_2), 86.81 (CH), 110.77 (CH), 110.85 (C), 117.60 (CH), 118.04 (CH), 120.34 (CH), 122.12 (CH), 124.10 (CH), 125.52 (CH, C), 126.59 (CH), 126.90 (C), 131.35 (CH), 135.67 (C), 144.76 (C) and 161.92 (C=O) ppm; Found: M^+ 334.1686 (2.7%) $C_{21}H_{22}N_2O_2$ requires 334.1681.

3-Hydroxy-2-[2-(3-methoxyphenoxy)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone.

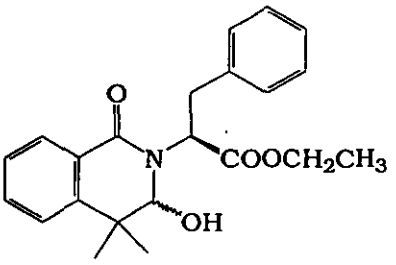


4.5

A stirred solution of 2-[2-(3-methoxyphenoxy)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.5**) (0.80g, 2.4 mmol) in ethanol was cooled down and sodium borohydride (1.5g, 39.5 mmol) was added. After two hours more sodium borohydride was added (1.5g, 39.5 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.5**) after flash chromatography eluting with EA/LP [1:2] (0.68g, 83%), oil : ν_{max} 3419 (broad), 1637 and 1603 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.27 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.63-3.66 (m, 1H), 3.76 (s, 3H, OMe), 3.94 (d, 1H, OH, *J* 3.7), 4.12-4.17 (m, 1H), 4.34-4.41 (m, 2H), 4.80 (d, 1H, *J* 3.7), 6.45-6.54 (m, 3H), 7.14 (t, 1H, *J* 8.2), 7.32-7.35 (m, 2H), 7.48-7.50 (m, 1H) and 8.05-

8.08 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 23.17 (CH_3), 29.94 (CH_3), 39.48 (C), 48.33 (CH_2), 55.73 (CH_3, OMe), 67.37 (CH_2), 91.12 (CH), 101.34 (CH), 107.11 (CH), 107.69 (CH), 124.98 (CH), 127.18 (CH), 127.27 (C), 128.75 (CH), 130.57 (CH), 133.11 (CH), 145.16 (C), 159.31 (C), 161.34 (C) and 164.30 (C=O) ppm; Found: M^+ 341.1626 (1.3%) $C_{20}H_{23}NO_4$ requires 341.1627. COSY experiment supports characterisation.

Ethyl 2-(3-hydroxy-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-phenylpropanoate.

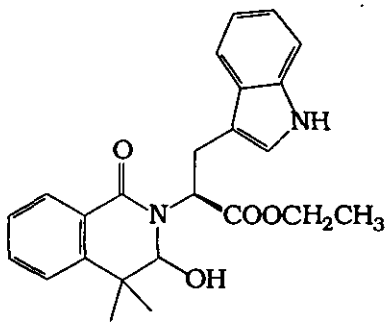


4.6

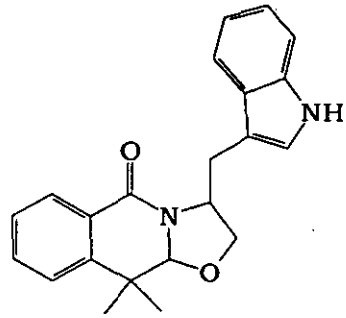
A stirred solution of ethyl 2-(4,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-phenylpropanoate (**3.6**) (0.28g, 0.75 mmol) in ethanol (50 ml) was cooled down and sodium borohydride (0.29g, 7.5 mmol) was added. After two hours more sodium borohydride was added (0.29g, 7.5 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.6**) after flash chromatography eluting with EA/LP [1:3] (0.032g, 12%), diastereomeric ratio [3:1], the major diastereomer (0.025g, 9%): foamy oil, ν_{max} 3420 (broad), 2971, 1719, 1656 and 1604 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.77 (s, 3H, CH_3), 1.20 (t, 3H, *J* 7.1, CH_3), 1.46 (s, 3H, CH_3), 3.16 (dd, 1H, B of ABX, J_{AB} 15.0, J_{BX} 10.5), 3.46 (dd, 1H, A of ABX, J_{AB} 15.0, J_{AX} 6.3), 4.16 (q, 2H, *J* 7.1), 4.38 (d, 1H, OH, D_2O ex., *J* 1.4), 4.81 (d, 1H, *J* 1.9), 5.62 (dd, 1H, X of ABX, J_{AX} 6.3, J_{BX} 10.5), 7.20-7.52 (m, 8H) and 8.07-8.11 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 13.95 (CH_3), 22.98 (CH_3), 28.83 (CH_3), 35.41 (CH_2), 39.22 (C), 57.67 (CH), 62.27 (CH_2), 85.31 (CH), 124.55 (CH), 126.49 (C), 126.63 (CH), 127.20 (CH), 128.67 (3 x CH), 128.83 (2 x CH), 133.00 (CH), 136.10 (C), 144.93 (C), 164.97 (C=O) and 174.43

(C=O) ppm; Found: M^+ 367.1793 (1.1%) $C_{22}H_{25}NO_4$ requires 367.1784. COSY experiment supports characterisation. The minor diastereomer (0.007g, 3%): foamy oil, ν_{max} 3424 (broad), 2968, 1736, 1656 and 1604 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.57 (s, 3H, CH_3), 1.24 (t, 3H, *J* 7.1, CH_3), 1.39 (s, 3H, CH_3), 3.53 (dd, 1H, A of ABX, J_{AB} 14.3, J_{AX} 5.4), 3.65 (dd, 1H, B of ABX, J_{AB}14.3, J_{BX} 10.5), 3.88 (d, 1H, OH, *J* 3.1), 4.30 (q, 2H, *J* 7.1), 4.36 (dd, 1H, X of ABX, J_{AX} 5.4, J_{BX} 10.5), 4.42 (d, 1H, *J* 3.0), 7.16-7.51 (m, 8H) and 8.10-8.12 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 14.56 (CH_3), 23.11 (CH_3), 28.73 (CH_3), 35.81 (CH_2), 39.84 (C), 62.74 (CH_2), 65.74 (CH), 92.70 (CH), 125.23 (CH), 126.79 (C), 127.02 (CH), 127.11 (CH), 128.57 (CH), 129.11 (2 x CH), 129.62 (2 x CH), 133.42 (CH), 138.37 (C), 145.50 (C), 164.87 (C=O) and 172.32 (C=O) ppm; Found: M^+ 367.1755 (33.8%) $C_{22}H_{25}NO_4$ requires 367.1784. COSY and HETCOR experiments support characterisation.

Ethyl 2-(3-hydroxy-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl)propanoate.



4.7

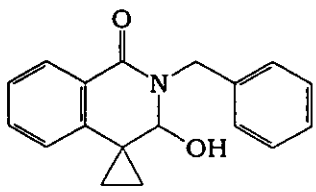


4.17

A stirred solution of ethyl 2-(4,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl)propanoate (**3.7**) (0.74g, 1.8 mmol) in ethanol (50 ml) was cooled down and sodium borohydride (1.5g, 39.5 mmol) was added. After two hours more sodium borohydride was added (1.5g, 39.5 mmol). After further 3.5 hours (at the same temperature) the reaction was quenched with sodium bicarbonate and gave after flash chromatography eluting with EA/LP [1:3] two products. The first product is the title compound (**4.7**) (0.15g, 21%), single diastereomer, mp 78 - 80 °C from EA/LP: ν_{max} 3406, 3300 (broad), 2973,

1715, 1644 and 1603 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.80 (s, 3H, CH_3), 1.16 (t, 3H, *J* 7.1, CH_3), 1.41 (s, 3H, CH_3), 3.40 (dd, 1H, B of ABX, J_{AB} 15.4, J_{BX} 10.3), 3.55 (dd, 1H, A of ABX, J_{AB}15.4, J_{AX} 5.7), 4.13-4.24 (m, 2H), 4.30-4.33 (m, 1H, OH), 4.86-4.87 (m, 1H), 5.62 (dd, 1H, X of ABX, J_{AX}5.7, J_{BX}10.3), 6.98 (d, 1H, *J* 1.9), 7.11-7.65 (m, 7H), 8.11-8.14 (m, 1H) and 8.56 (br.s, 1H, N-H) ppm; Found: M^+ 406.1846 (1.7%) $C_{24}H_{26}N_2O_4$ requires 406.1892. The second product *3-hydroxy-2-[2-hydroxy-1-(1H-3-indolyl methyl)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone* (**4.17**) (0.33g, 50%), single diastereomer, mp 85-86 °C from EA/LP: v_{max} 3412, 3297 (broad), 2974, 1647 and 1604 cm^{-1};^1H nmr (400 M Hz, $CDCl_3$) 1.12 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.08 (dd, 1H, B of ABX, J_{AB}14.0, J_{BX} 9.8), 3.63 (dd, 1H, A of ABX, J_{AB}14.0, J_{AX} 3.1), 3.97-3.40 (m, 1H), 4.09-4.12 (m, 1H), 4.79-4.85 (m, 1H), 5.02 (s, 1H), 7.05-7.57 (m, 7H), 7.85-7.88 (m, 1H), 8.17-8.19 (m, 1H) and 8.66 (br.s, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 22.49 (CH_3), 23.32 (CH_3), 27.34 (CH_2), 39.79 (C), 56.39 (CH), 71.21 (CH_2), 92.57 (CH), 111.57 (C, CH), 119.32 (CH), 119.85 (CH), 122.39 (CH), 123.05 (CH), 124.36 (CH), 127.51 (CH), 127.95 (C), 128.13 (CH), 129.16 (C), 132.89 (CH), 136.60 (C), 144.87 (C) and 161.78 (C=O) ppm; Found: M^+ 346.1680 (1.0%) $C_{22}H_{22}N_2O_2$ requires 346.1681.

2-Benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spiro-cyclopropane.

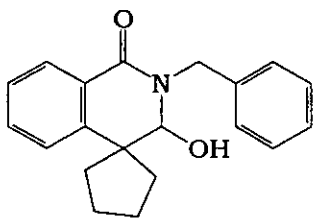


4.8

The usual procedure (sodium borohydride = 2 x 13 equivalents, -5 °C) didn't yield any detectable reduced product. The following is the optimised reduction procedure. A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione-4-spiro-cyclopropane (**3.9**) (0.26g, 0.94 mmol) in ethanol (50 ml) was cooled down to 10 °C, then sodium borohydride was added (0.70g, 18.4 mmol).

After two hours, more sodium borohydride was added (1.0g, 26.3 mmol). After further two hours more sodium borohydride was added (1.3g, 34.2 mmol). Two hours later, the reaction was terminated by quenching with aqueous sodium bicarbonate. The resulting cloudy emulsion was extracted with DCM (2 x 100ml) and the combined organic extracts were dried over magnesium sulfate and concentrated in *vacuo* and gave the title compound (**4.8**) after flash chromatography eluting with EA/LP [1:3] (0.12g, 46%), mp 130-133 °C (glass): ν_{max} 3355 (broad), 3067, 1632 and 1605 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.58-0.74 (m, 2H), 0.96-1.05 (m, 1H), 1.48-1.57 (m, 1H), 3.95 (d, 1H, OH, *J* 6.5), 4.03 (d, 1H, *J* 6.5), 4.18 (d, 1H, A of AB, *J* 15.1), 5.44 (d, 1H, B of AB, *J* 15.1), 6.83 (d, 1H, *J* 7.7), 7.24-7.45 (m, 7H) and 8.08-8.11 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 9.34 (CH_2), 19.04 (CH_2), 24.45 (C), 47.95 (CH_2), 85.97 (CH), 122.03 (CH), 126.52 (CH), 127.48 (CH), 127.98 (2 x CH), 128.04 (C), 128.66 (2 x CH), 128.70 (CH), 132.69 (CH), 137.46 (C), 139.23 (C) and 164.04 (C=O) ppm; Found: M^+ 279.1258 (9.4%) $C_{18}H_{17}NO_2$ requires 279.1259.

2-Benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spiro-cyclopentane.

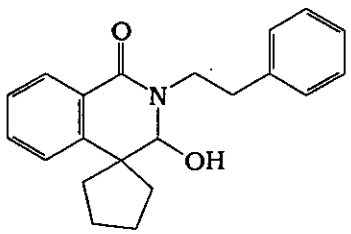


4.9

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclopentane (**3.10**) (1.2g, 3.9 mmol) in ethanol was cooled down and sodium borohydride (1.5g, 39.5 mmol) was added. After two hours more sodium borohydride was added (1.5g, 39.5 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.9**) (1.1g, 92%), mp 139-140 °C from ethanol : ν_{max} 3378 (broad), 2954, 1634 and 1601 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.25-1.60 (m, 4H), 1.72-2.0 (m, 3H), 2.18-

2.28 (m, 1H), 2.53 (d, 1 H, OH, *J* 8.1), 4.32 (d, 1H, A of AB, *J* 14.5), 4.55 (d, 1H, *J* 8.1) , 5.33 (d, 1H, B of AB, *J* 14.5), 7.24-7.48 (m, 8H) and 8.13-8.16 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 24.23 (CH_2), 25.28 (CH_2), 32.76 (CH_2), 40.01 (CH_2), 48.49 (CH_2), 51.31 (C), 86.83 (CH), 125.21 (CH), 126.84 (CH), 127.29 (C), 127.61 (CH), 128.61 (2 x CH), 128.69 (CH), 128.78 (2 x CH), 132.34 (CH), 137.25 (C), 143.48 (C) and 163.64 (C=O) ppm; Found: M^+ 307.1573 (44.4%) $C_{20}H_{21}NO_2$ requires 307.1572.

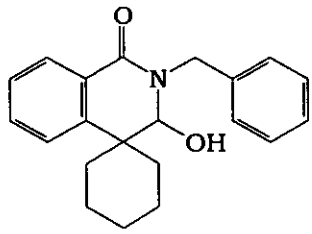
3-Hydroxy-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone-4-spiro-cyclopentane.



4.10

A stirred solution of 2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclopentane (**3.11**) (0.44g, 1.4 mmol) in ethanol was cooled down and sodium borohydride (1.7g, 44.5 mmol) was added. After two hours more sodium borohydride was added (1.7g, 44.5 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.10**) (0.4g, 89%), mp 172-173 °C from ethanol : ν_{max} 3355 (broad), 2954, 1633 and 1602 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.39-1.46 (m, 1H), 1.59-1.75 (m, 3H), 1.89-1.97 (m, 3H), 2.21-2.23 (m, 1H), 2.43 (d, 1 H, OH, *J* 8.0), 2.99-3.09 (m, 2H), 3.68-3.77 (m, 1H), 3.96-4.05 (m, 1H), 4.54 (d, 1H, *J* 8.0), 7.22-7.50 (m, 8H) and 8.06-8.10 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 24.70 (CH_2), 25.67 (CH_2), 33.03 (CH_2), 34.80 (CH_2), 39.97 (CH_2), 48.90 (CH_2), 51.64 (C), 89.39 (CH), 125.22 (CH), 126.51 (CH), 126.92 (CH), 127.45 (C), 128.49 (CH), 128.65 (2 x CH), 128.90 (2 x CH), 132.33 (CH), 139.05 (C), 143.54 (C) and 163.70 (C=O) ppm; Found: M^+ 321.1728 (9.2%) $C_{21}H_{23}NO_2$ requires 321.1729. HETCOR and COSY experiments support characterisation.

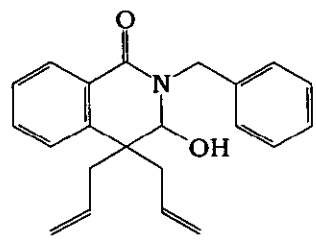
2-Benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spiro-cyclohexane.



4.11

A stirred solution of 2-benzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione-4-spiro-cyclohexane (**3.12**) (1.0g, 3.1 mmol) in ethanol was cooled down and sodium borohydride (2.0g, 52.6 mmol) was added. After two hours more sodium borohydride was added (2.0g, 52.6 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.11**) (0.87g, 87%), mp 191-192 °C from ethanol : ν_{max} 3347 (broad), 2927, 1635 and 1599 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.48-0.73 (m, 1H), 1.05-1.28 (m, 3H), 1.40-1.75 (m, 4H), 1.98-2.03 (m, 2H), 2.22 (d, 1H, OH, *J* 8.9), 4.32 (d, 1H, A of AB, *J* 14.5), 5.12 (d, 1H, *J* 8.9) , 5.39 (d, 1H, B of AB, *J* 14.5), 7.26-7.51 (m, 8H) and 8.15-8.18 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 21.25 (CH_2), 21.30 (CH_2), 25.44 (CH_2), 29.80 (CH_2), 37.96 (CH_2), 41.76 (C), 48.68 (CH_2), 81.84 (CH), 124.55 (CH), 127.04 (CH), 127.53 (C), 127.79 (CH), 128.79 (2 x CH), 128.86 (CH), 129.00 (2 x CH), 132.74 (CH), 137.64 (C), 144.31 (C) and 163.43 (C=O) ppm; Found: M^+ 321.1729 (28.3%) $C_{21}H_{23}NO_2$ requires 321.1729.

4,4-Diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone.

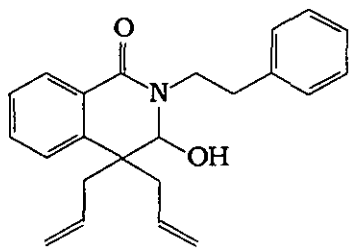


4.12

A stirred solution of 2-benzyl-4,4-diallyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.13**) (2.71g, 8.2 mmol) in ethanol was cooled down and sodium borohydride (3.1g, 81.6 mmol) was added. After two hours more

sodium borohydride was added (3.1g, 81.6 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.12**) after flash chromato-graphy eluting with EA/LP [1:4] (1.24g, 46%), mp 109-112 °C from EA/LP : v_{max} 3363 (broad), 2928, 1634 and 1602 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.97-2.04 (m, 2H), 2.50 (dd, 1H, A of ABX, J_{AB} 13.6, J_{AX} 7.3), 2.72 (dd, 1H, B of ABX, J_{AB} 13.6, J_{BX} 7.4), 3.38 (d, 1H, OH, *J* 7.1), 4.41 (d, 1H, A of AB, *J* 14.6), 4.72-4.79 (m, 2H), 4.92-4.97 (m, 1H), 5.19 (d, 1H, B of AB, *J* 14.6), 5.14-5.32 (m, 3H), 5.82-5.93 (m, 1H), 7.20-7.51 (m, 8H) and 8.12-8.16 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 35.56 (CH_2), 40.44 (CH_2), 44.62 (C), 49.07 (CH_2), 84.97 (CH), 118.79 (CH_2), 119.73 (CH_2), 126.24 (CH), 127.17 (CH), 127.45 (C), 127.74 (CH), 128.74 (2 x CH), 128.85 (CH), 128.89 (2 x CH), 131.99 (CH), 132.68 (CH), 132.98 (CH), 137.29 (C), 141.35 (C) and 163.76 (C=O) ppm; Found: M^+ 333.1729 (43.8%) $C_{22}H_{23}NO_2$ requires 333.1729.

4,4-Diallyl-3-hydroxy-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone.

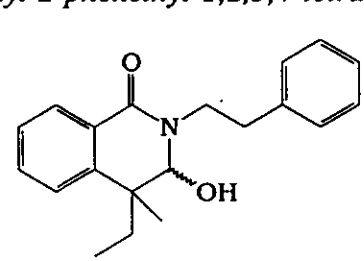


4.13

A stirred solution of 4,4-diallyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinoline-dione (**3.14**) (0.14g, 0.41 mmol) in ethanol was cooled down and sodium borohydride (0.60g, 15.8 mmol) was added. After two hours more sodium borohydride was added (0.60g, 15.8 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.13**) after flash chromatography eluting with EA/LP [1:3] (0.060g, 42%), mp 118-119 °C from EA/LP : v_{max} 3351 (broad), 2928, 1636 and 1601 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.15-2.18 (m, 2H), 2.20 (d, 1H, OH, *J* 7.4), 2.49 (dd, 1H, A of ABX, J_{AB} 13.3, J_{AX} 7.1), 2.74 (dd, 1H, B of ABX, J_{AB} 13.3, J_{BX} 7.3), 2.99-3.10 (m,

2H), 3.78-3.82 (m, 1H), 3.88-3.94 (m, 1H), 4.62 (d, 1H, *J* 7.4), 4.82-5.02 (m, 2H), 5.23-5.32 (m, 3H), 5.86-6.00 (m, 1H), 7.19-7.49 (m, 8H) and 8.11-8.15 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 34.80 (CH_2), 35.63 (CH_2), 40.66 (CH_2), 43.61 (C), 49.09 (CH_2), 86.96 (CH), 118.81 (CH_2), 119.90 (CH_2), 126.17 (CH), 126.59 (CH), 127.26 (CH), 127.67 (C), 128.63 (CH), 128.69 (2 x CH), 128.91 (2 x CH), 131.91 (CH), 132.71 (CH), 132.93 (CH), 139.05 (C), 141.05 (C) and 163.52 (C=O) ppm; Found: M^+ 347.1889 (15.0%) $C_{23}H_{25}NO_2$ requires 347.1885. HETCOR experiment supports characterisation.

4-Ethyl-3-hydroxy-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone.

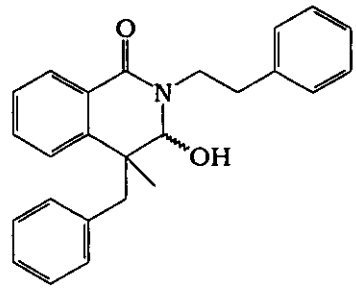


4.14

A stirred solution of 4-ethyl-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.39**) (0.45g, 1.47 mmol) in ethanol was cooled down and sodium borohydride (1.20g, 31.6mmol) was added. After two hours more sodium borohydride was added (1.20g, 31.6mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.14**) after flash chromatography eluting with EA/LP [1:3] (0.33g, 73%), oil, diasteomeric ratio [5:12]. Data for the major diastereomer: ν_{max} 3356 (broad), 2968, 1634 and 1602 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.02 (t, 3H, CH_3, *J* 7.3), 1.08 (s, 3H, CH_3), 1.95-2.00 (m, 2H), 2.46 (d, 1H, OH, *J* 8.0), 2.97-3.00 (m, 1H), 3.05-3.09 (m, 1H), 3.73-3.77 (m, 1H), 4.01-4.10 (m, 1H), 4.66 (d, 1H, *J* 8.0), 7.21-7.46 (m, 8H) and 8.05-8.07 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 7.72 (CH_3), 25.43 (CH_3), 27.58 (CH_2), 34.64 (CH_2), 41.17 (C), 48.73 (CH_2), 86.68 (CH), 124.41 (CH), 125.10 (C), 126.45 (CH), 126.81 (CH), 128.41 (CH), 128.58 (2 x CH), 128.80 (2 x CH), 132.46 (CH), 138.99 (C), 144.90 (C), 163.80 (C=O) ppm; Found: M^+ 309.1727 (1.6%) $C_{20}H_{23}NO_2$ requires 309.1729. HETCOR experiment supports characterisation. Data for the minor

diastereomer, oil : ν_{max} 3356 (broad), 2968, 1634 and 1602 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.66 (t, 3H, CH_3, *J* 7.5), 1.35-1.40 (m, 1H), 1.39 (s, 3H, CH_3), 1.48-1.52 (m, 1H), 2.46 (d, 1H, OH, *J* 8.0), 2.97-3.00 (m, 1H), 3.05-3.09 (m, 1H), 3.73-3.77 (m, 1H), 3.89-3.93 (m, 1H), 4.58 (d, 1H, *J* 8.0), 7.21-7.46 (m, 8H) and 8.05-8.07 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 8.46 (CH_3), 18.64 (CH_3), 33.17 (CH_2), 34.73 (CH_2), 42.77 (C), 49.10 (CH_2), 89.20 (CH), 126.22 (CH), 126.45 (CH), 126.94 (CH), 127.20 (C), 128.32 (CH), 128.58 (2 x CH), 128.80 (2 x CH), 131.90 (CH), 138.99 (C), 142.24 (C), 163.80 (C=O) ppm; Found: M^+ 309.1727 (1.6%) $C_{20}H_{23}NO_2$ requires 309.1729. HETCOR experiment supports characterisation.

4-Benzyl-3-hydroxy-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone.

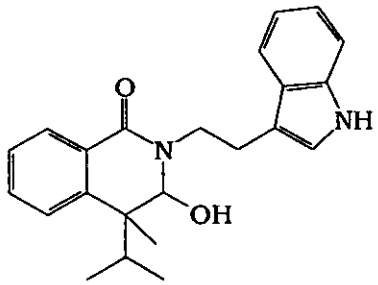


4.15

A stirred solution of 4-benzyl-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.40**) (0.35, 0.95 mmol) in ethanol was cooled down and sodium borohydride (0.70g, 18.4 mmol) was added. After two hours more sodium borohydride was added (0.70g, 18.4 mmol). Two hours later the reaction was quenched with sodium bicarbonate and gave the title compound (**4.15**) (0.32g, 91%), diasteomeric ratio [1:2]. Data for the diastereomeric mixture : ν_{max} 3354 (broad), 2924, 1635 and 1602 cm^{-1}; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 19.51 (CH_3, major), 25.85 (CH_3, minor), 34.67 (CH_2, minor), 34.94 (CH_2, major), 40.11 (CH_2, minor), 42.53 (C, minor), 43.89 (C, major), 47.07 (CH_2, major), 48.85 (CH_2, minor), 49.93 (CH_2, major), 86.44 (CH, minor), 89.70 (CH, major), 124.29-141.39 (Aromatic Cs and CHs), 162.22 (C=O,

minor) and 163.47 (C=O, major) ppm; Found: M^+ 371.1889 (3.6%) $C_{25}H_{25}NO_2$ requires 371.1885.

3-Hydroxy-2-[2-(1H-3-indolyl)ethyl]-4-isopropyl-4-methyl-1,2,3,4-tetrahydro-1-isoquinlinone.



4.16

A stirred solution of 2-[2-(1H-3-Indolyl)ethyl]-4-isopropyl-4-methyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.41**) (0.14g, 0.39 mmol) in ethanol (50 ml) was cooled down and sodium borohydride (0.60g, 15.8 mmol) was added. After two hours more sodium borohydride was added (0.60g, 15.8 mmol). Two hours later a third amount (0.60g, 15.8 mmol) was added. The reaction was quenched with sodium bicarbonate after further two hours (overall 6 hours reaction time) and gave the title compound (**4.16**) after flash chromatography eluting with EA/LP [2:5] (0.078g, 55%), single diastereomer, foamy oil : ν_{max} 3411 (broad), 3323 (broad), 2973, 1634 and 1601 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.10 (d, 3H, *J* 6.8, CH_3), 1.12 (s, 3H, CH_3), 1.13 (d, 3H, *J* 6.8, CH_3), 2.38 (p, 1H, *J* 6.8), 2.76 (d, 1H, OH, *J* 7.6), 3.15-3.22 (m, 2H), 3.85-3.90 (m, 1H), 4.13-4.19 (m, 1H), 4.83 (d, 1H, *J* 7.6), 6.98 (d, 1H, *J* 2.3), 7.14-7.51 (m, 6H), 7.73-7.75 (m, 1H), 8.16-8.19 (m, 1H) and 8.28 (br.s, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 18.28 (CH_3), 20.15 (CH_3), 24.82 (CH_2), 26.18 (CH), 32.87 (CH_3), 45.01 (C), 47.26 (CH_2), 87.68 (CH), 111.76 (CH), 113.34 (C), 119.24 (CH), 119.80 (CH), 122.43 (CH), 122.78 (CH), 126.34 (CH), 126.98 (CH), 127.68 (C), 128.56 (C), 129.16 (CH), 132.39 (CH), 136.84 (C), 144.17 (C) and 164.23 (C=O) ppm; Found: M^+ 362.1985 (0.2%) $C_{23}H_{26}N_2O_2$ requires 362.1994. HETCOR experiment supports characterisation.

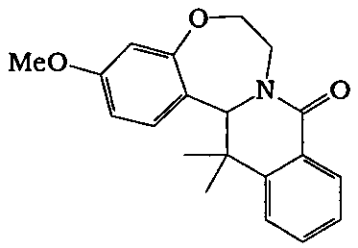
Chapter 5 experimental:

Generation of *N*-acyliminium ions from the corresponding 3-hydroxy-4,4-disubstituted-1,2,3,4-tetrahydro-1-isoquinolinones and their subsequent capture - General Method.

A magnetically stirred solution of the particular 3-hydroxy-4,4-disubstituted-1,2,3,4-tetrahydro-1-isoquinolinone in a given volume of DCM (unless otherwise stated) and under nitrogen atmosphere, was adjusted to the stated temperature, and the particular acid was injected. The reaction was allowed to proceed for a given length of time. Subsequently, the reaction was terminated by quenching with aqueous sodium bicarbonate. The resulting cloudy emulsion was extracted with DCM (2 x 100 ml) and the combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation.

A- *N*-Acyliminium ions Trapping by Aromatic Nucleophiles.

3-Methoxy-14,14-dimethyl-6,7,14,14a-tetrahydro-9H-benzo[6,7][1,4]oxazepino [4,5-b]isoquinolin-9-one.



5.1

A stirred solution of 3-hydroxy-2-[2-(3-methoxyphenoxy)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone (**4.5**) in dry DCM was adjusted to the stated temperature and the particular Lewis acid was added. After the stated reaction time, the reaction was allowed to re-adjust to room temperature and terminated, and gave the title compound (**5.1**) after flash chromatography eluting with EA/LP [1:2] (reaction conditions and yields are listed in **Table Exp. 5.1**),

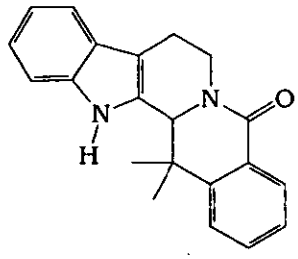
mp 188-190 °C from EA/LP : ν_{max} 2971, 1648 and 1611 cm^{-1}; ^1H nmr (323 K, 400 M Hz, $CDCl_3$) 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.28-3.35 (m, 1H), 3.79 (s, 3H, MeO), 4.07-4.20 (m, 2H), 4.70 (s, 1H), 4.86-4.90 (m, 1H), 6.51 (dd, 1H, *J* 2.6, 8.5), 6.67 (d, 1H, *J* 2.6), 6.81 (d, 1H, *J* 8.5), 7.35-7.56 (m, 3H) and 8.10-8.12 (m, 1H); ^{13}C nmr (323 K, 100.5 M Hz, $CDCl_3$) 24.37 (CH_3), 27.88 (CH_3), 38.79 (C), 44.01 (CH_2), 55.34 (s, 3H, MeO), 68.17 (CH), 71.44 (CH_2), 108.61 (CH), 109.31 (CH), 123.10 (CH), 123.19 (C), 126.75 (CH), 128.21 (C), 128.89 (CH), 130.28 (CH), 132.36 (CH), 146.98 (C), 158.21 (C), 160.68 (C) and 163.27 (C=O) ppm; Found: C, 72.23, H, 6.41, N, 4.15 % $C_{20}H_{21}NO_3$ requires C, 74.27, H, 6.50, N, 4.33 %; Found: M^+ 323.1522 (58%) $C_{20}H_{21}NO_3$ requires 323.1521. HETCOR experiment at 323 K supports characterisation.

Table Exp. 5.1

No.	Starting Material g	mmol	Reaction Temperature (°C)	Lewis Acid (g, mmol)	DCM (ml)	Reaction Time (hours)	Yield mg	%
1	0.34	1.0	Ambient	$AlBr_3$ (0.27, 1.0)	25	19	20	6
2	0.16	0.47	Ambient	$Sc(OTf)_3$ (0.12, 0.24)	15	34	0	0
3	0.16	0.47	35	$Sc(OTf)_3$ (0.12, 0.24)	30	22	10	7
4	0.20	0.59	Ambient*	$TiCl_4$ (0.40 ml, 3.54)	15	24	60	32
5	0.28	0.82	Ambient*	$TiCl_4$ (0.05 ml, 0.41)	20	1	60	23

* $TiCl_4$ was added at -78 °C for 15 minutes then the reaction was warmed up to the mentioned temperature.

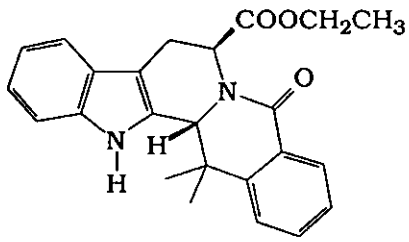
14,14-Dimethyl-5,7,8,13,13b,14-hexahydroisoquino[3,2-a]β-carbolin-5-one.



5.2

A stirred solution of 3-hydroxy-2-[2-(1H-3-indolyl)ethyl]-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinlinone (**4.4**) (0.11g, 0.33 mmol) in dry THF (*ca.* 50 ml) was cooled to 0 °C and aluminium chloride (0.044g, 0.33 mmol) was added. After two hours, the reaction was allowed to warm up to room temperature. One hour later, the reaction was terminated and gave the title compound (**5.2**) (0.091g, 87%), mp 214 - 215 °C from DCM / THF : ν_{max} 3290 (broad), 2924, 1635 and 1600 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.94 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 2.82-2.90 (m, 3H), 4.79 (s, 1H), 5.06-5.09 (m, 1H), 7.09-7.42 (m, 7H), 8.12-8.15 (m, 1H) and 8.21 (br.s, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 21.16 (CH_2), 23.46 (CH_3), 23.72 (CH_3), 40.65 (CH_2), 40.82 (C), 61.97 (CH), 111.36 (CH), 114.35 (C), 118.76 (CH), 120.21 (CH), 122.80 (CH), 123.61 (CH), 126.67 (C), 127.47 (CH), 128.34 (C), 129.68 (CH), 130.17 (C), 132.69 (CH), 136.49 (C), 147.13 (C) and 165.62 (C=O) ppm; Found: M^+ 316.1580 (100%) $C_{21}H_{20}N_2O$ requires 316.1576.

Ethyl (7S/7R, 13bR/13bS)-14,14-dimethyl-5-oxo-5,7,8,13,13b,14-hexahydro isoquino[3,2-a]β-carboline-7-carboxylate.



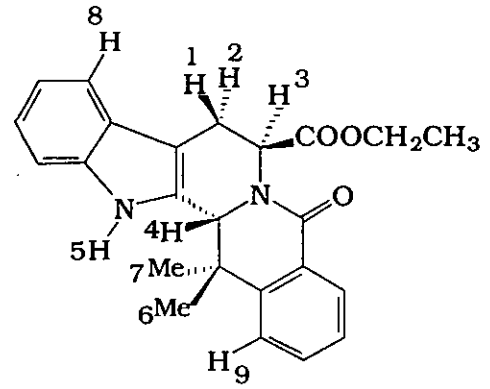
5.3

A stirred solution of ethyl 2-(3-hydroxy-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-2-isoquinolinyl)-3-(1H-3-indolyl)propanoate (**4.7**) (0.15g, 0.37 mmol) in DCM (*ca.* 15 ml), at room temperature, was injected with concentrated hydrogen chloride solution (few drops). After one hour, the reaction was terminated and gave the title compound (**5.3**) after flash chromatography eluting with EA/LP [1:2] (0.11g, 77 %), single diastereomer, mp 239-241°C from EA/LP: ν_{max} 3302 (broad), 2978, 1734, 1638 and 1602 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$)

0.82 (t, 3H, *J* 7.1), 0.94 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.00 (dd, 1H, B of ABX, J_{AB}15.2, J_{BX} 5.4), 3.45 (dd, 1H, A of ABX, J_{AB}15.2 , J_{AX}1.8), 3.77-3.86 (m, 2H), 5.02 (s, 1H), 5.85 (dd, X of ABX, J_{AX} 1.8, J_{BX} 5.4), 7.02-7.47 (m, 7H), 8.12-8.14 (m, 1H) and 8.18 (br.s, 1H, N-H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 14.00 (CH_3), 23.14 (CH_3), 23.26 (CH_3), 23.67 (CH_2), 40.35 (C), 52.32 (CH), 61.10 (CH), 61.21 (CH_2), 110.35 (C), 111.03 (CH), 118.15 (CH), 119.78 (CH), 122.41 (CH), 123.43 (CH), 126.35 (C), 127.09 (CH), 127.47 (C), 129.54 (CH), 129.85 (C), 132.68 (CH), 136.34 (C), 147.09 (C), 165.65 (C=O) and 171.22 (C=O) ppm; Found: M^+ 388.1784 (57.9%) $C_{24}H_{24}N_2O_3$ requires 388.1787. HETCOR and COSY experiments support characterisation. The structural configuration and conformation in $CDCl_3$ at 25 °C was analysed by $^1H,^1H$-NOESY at 400 M Hz over mixing time of 0.70 second.

Crosspeaks of at least medium strength were considered. The following protons show nOe crosspeaks:

1, 2 and 3.	4, 5 and 6 (methyl protons).	1 and 8.
2 and 7 (methyl protons).	9 and 6 (methyl protons).	



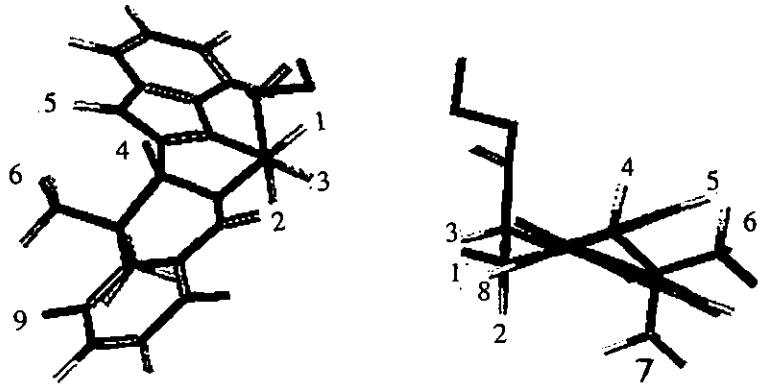


Figure Exp. 5.1

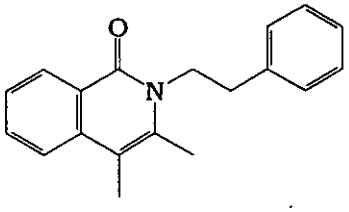
The analysis results were further strengthen by conformational energy minimisation conducted by CAChe programme (**Figure Exp. 5.1**). Relevant interatomic distances calculated by CAChe minimisation are shown in **Table Exp. 5.2**.

Table Exp. 5.2.

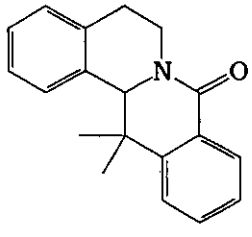
protons	distance ($^{\circ}A$)
1-2	1.81
2-3	2.50
1-3	2.52
1-8	2.56
2-7 (CH_3)	3.69
4-5	3.04
5-6 (CH_3)	1.94
4-6 (CH_3)	2.52
6-9	3.06

B- Competition between Aromatic Nucleophiles and Migrating methyl group in Trapping *N*-Acyliminium ions.

Reactions of 3-hydroxy-4,4-dimethyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinlinone with aluminium tribromide and aluminium trichloride.



5.4



5.5

A stirred solution of 3-hydroxy-4,4-dimethyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinlinone (**4.1**) (0.30g, 1.0 mmol) in the particular solvent (30 ml) was adjusted to the stated temperature and the particular Lewis acid was added (1.5 equivalents). After the stated reaction time the reaction was re-adjusted to room temperature and terminated. Reaction conditions and product ratios are illustrated in **Table Exp. 5.3**.

Table Exp. 5.3

No.	Reaction Temperature (°C)	Lewis Acid†	Solvent	Reaction Time (hours)	**5.4**†† %	**5.5** %
1	-5	$AlBr_3$	o-DCB	6	30	70
2	-5	$AlBr_3$	DCM	6	5	95
3	Ambient	$AlBr_3$	DCM	24	41	59
4	35	$AlBr_3$	DCM	24	44	56
5	180	$AlBr_3$	o-DCB	4	94	6
6	35	$AlCl_3$	DCM	24	25‡	9
7	35	$AlCl_3$	DCM	72	73	27
8	180	$AlCl_3$	o-DCB	4	93	7

† $AlBr_3$ (400mg , 1.5 mmol), $AlCl_3$ (200mg, 1.5 mmol).

†† Ratios estimated from the average peak areas at 4.81 (s, 1H), 5.01 (m, 1H) and 8.15 (m, 1H) ppm for (**5.5**) compared to peak areas at 2.30 (s, 3H, CH_3), 4.31 (m, 2H) and 8.50 (m, 1H) ppm for (**5.4**) from the ^1H nmr spectra of crude products. Mass balance was maintained.

‡ Starting material accounts for 66 % (based on ^1H nmr).

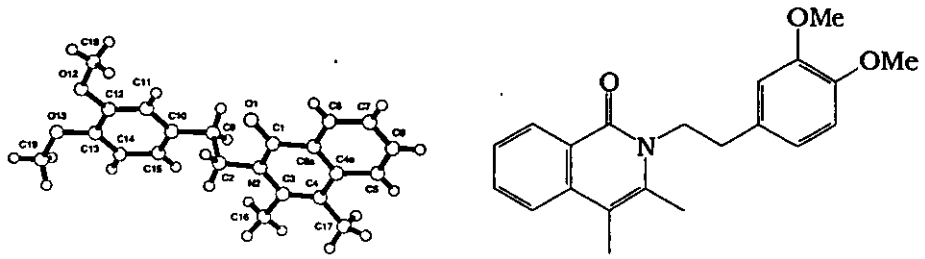
Data for compounds (**5.5**) and (**5.4**).

3,4-Dimethyl-2-phenethyl-1,2-dihydro-1-isoquinolinone (**5.4**), first eluted with EA/LP [1:3], yellow oil : ν_{max} 3050, 1645, 1614 and 1592 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.01-3.07 (m, 2H), 4.33-4.40 (m, 2H), 7.27- 7.69 (m, 8H) and 8.49-8.52 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 13.75 (CH_3), 16.22 (CH_3), 34.79 (CH_2), 46.34 (CH_2), 109.01 (C), 122.41 (CH), 124.39 (C), 125.52 (CH), 126.37 (CH), 127.81 (CH), 128.33 (2 x CH), 128.41 (2 x CH), 131.90 (CH), 134.82 (C), 136.95 (C), 138.48 (C) and 162.18 (C=O) ppm; Found: M^+ 277.1458 (14.6%) $C_{19}H_{19}NO$ requires 277.1467. HETCOR and COSY experiments support characterisation.

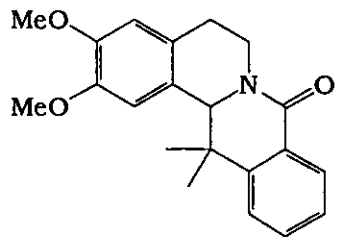
13,13-Dimethyl-5,8,13,13a-tetrahydro-6H-isoquino[3,2-a]isoquinolin-8-one (**5.5**), second eluted with EA/LP [1:3], mp 122-125 °C from EA/LP : ν_{max} 2955, 1647 and 1602 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.90 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.72-3.00 (m, 3H), 4.81 (s, 1H), 4.97-5.04 (m, 1H), 7.17 - 7.48 (m, 7H) and 8.12-8.16 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 23.07 (CH_3), 23.79 (CH_3), 29.97 (CH_2), 39.56 (CH_2), 40.70 (C), 64.88 (CH), 123.35 (CH),

125.23 (CH), 126.84 (CH), 127.27 (CH), 128.24 (C), 128.47 (CH), 128.98 (CH), 130.13 (CH), 131.76 (C), 132.01(CH), 138.61 (C), 147.68 (C) and 164.38 (C=O) ppm; Found: M^+ 277.1468 (29.5%) $C_{19}H_{19}NO$ requires 277.1467. HETCORE and COSY experiments support characterisation

Reactions of 2-(3,4-dimethoxyphenethyl)-3-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone with aluminium tribromide and aluminium trichloride.



5.6



5.7

A stirred solution of 2-(3,4-dimethoxyphenethyl)-3-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone (**4.2**) (0.30g, 0.85 mmol) in *o*-DCB (45 ml) was adjusted to the stated temperature and the particular Lewis acid was added (1 or 3 equivalents). After the stated reaction time the reaction was re-adjusted to room temperature and terminated. Reaction conditions and product ratios are illustrated in **Table Exp. 5.4**.

Table Exp. 5.4

No.	Reaction Temperature (°C)	Lewis Acid (mg, mmol)	Reaction Time (hours)	**5.7** %	**5.6**†† %
1	-5	$AlBr_3$ (227, 0.85)	2	0	42‡
2	-5	$AlBr_3$ (680, 2.55)	2	0	100
3	Ambient	$AlBr_3$ (227, 0.85)	24	72	20‡‡
4	Ambient	$AlBr_3$ (680, 2.55)	24	0	100
5	180	$AlBr_3$ (227, 0.85)	0.5	78	22
6	Ambient	$AlCl_3$ (113, 0.85)	24	67	21+
7	Ambient	$AlCl_3$ (340, 2.55)	24	71	29

†† Ratios estimated from the average peak areas at 4.75 (s, 1H), 5.00 (m, 1H) and 8.13 (m, 1H) ppm for (**5.7**) compared to peak areas at 2.30 (s, 3H, CH_3), 4.31 (m, 2H) and 8.50 (m, 1H) ppm for (**5.6**) form ^1H nmr spectrums of crude products. Mass balance was maintained.

‡ Starting material accounts for 58 % (based on ^1H nmr).

‡‡ Starting material accounts for 8 % (based on ^1H nmr).

+ Starting material accounts for 12 % (based on ^1H nmr).

Data for compounds (**5.6**) and (**5.7**).

2-(3,4-Dimethoxyphenethyl)-3,4-dimethyl-1,2-dihydro-1-isoquinolinone (**5.6**), first eluted with EA/LP [1:2], mp 117.0 - 118.0 °C from EA/LP : ν_{max} 2936, 1643, 1614 and 1590 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.30 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.92-3.01 (m, 2H), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.27-4.37 (m, 2H), 6.78 (s, 1H), 6.81 (d, 2H, *J* 0.6), 7.42-7.48 (m, 1H), 7.63-7.67 (m, 2H) and 8.47-8.51 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 14.00 (CH_3), 16.53 (CH_3), 34.58 (CH_2), 46.74 (CH_2), 55.85 (CH_3, OMe), 55.96 (CH_3, OMe), 109.17 (C), 111.38 (CH), 112.14 (CH), 120.73 (CH), 122.64 (CH), 124.66 (C), 125.77 (CH), 128.05 (CH), 131.36 (C), 132.16 (CH), 135.20 (C), 137.20 (C), 147.79 (C), 149.05 (C) and 162.44 (C=O) ppm; Found: M^+ 337.1680 (6.4%) $C_{21}H_{23}NO_3$ requires 337.1678.

X-Ray Report (Experimental Details). Carried out by Dr. AMZ Slawin.

A. Crystal Data

Empirical Formula	$C_{21}H_{23}NO_3$
Formula Weight	337.1678

Crystal Colour, Habit	clear, block
Crystal Dimensions	0.20 x 0.20 x 0.34 mm
Crystal System	monoclinic
Lattice Type	primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (70.3 - 74.5°)
Omega Scan Peak Width at	
Half -height	0.36°
Lattice Parameters	a = 8.210(2) °A
	b = 13.229(4) °A
	c = 16.372(2) °A
	β = 97.89(2)°
	V = 1761.3(6) °A^3
Space Group	$P2_1/n$ (#14)
Z value	4
D_{calc}	1.272 g/cm^3
F_{000}	720.00
μ (CuKα)	6.42 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuKα (λ = 1.54178 °A)
	graphite monochromated
Attenuater	Ni foil (factor = 9.42)
Take-off Angle	6.0 °
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0 °C
Scan Type	ω
Scan Rate	16.0°/ min (in ω) (up to 4 scans)
Scan Width	(1.37 + 0.35 tanθ) °

$2\theta_{max}$	120.2°
No. of Reflections Measured	Total: 2987
	Unique: 2772 (R_{int} = 0.089)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.7594 - 1.0000)
	Decay (0.62% increase)
	Secondary Extinction
	(coefficient: 5.08129e-06)

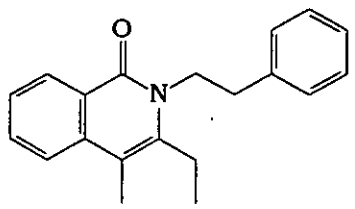
C. Structure Solution and Refinement

Structure Solution	Direct Methods (SAPI91)
Refinement	Full-matrix least-squares
Function minimised	$\sum w(\|Fo\|-\|Fc\|)^2$
Least Squares Weights	$\omega = \frac{1}{\sigma^2(Fo)} = \left[\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2\right]^{-1}$
P-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>2.00σ(I))	1688
No. Variables	227
Reflection / Parameter Ratio	7.44
Residuals: R; Rw	0.040; 0.028
Goodness of Fit Indicator	3.03
Max Shift/Error in Final Cycle	0.05
Maximum peak in Final Diff. Map	0.14 $e^-/{}^oA^3$
Minimum peak in Final Diff. Map	- 0.13 $e^-/{}^oA^3$

2,3-Dimethoxy-13,13-dimethyl-5,8,13,13a-tetrahydro-6H-isoquino[3,2-a]isoquinolin-8-one (**5.7**)[196], second eluted with EA/LP [1:2], mp 165.0 - 167.0 °C from EA/LP: ν_{max} 3056, 1652 and 1634 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.92 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.66-2.90 (m, 3H), 3.86 (s, 3H, MeO), 3.91 (s, 3H, MeO), 4.75 (s, 1H), 4.96-5.01 (m, 1H), 6.67 (s, 1H), 6.72 (s, 1H),

7.36-7.46 (m, 3H) and 8.12-8.15 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 23.41(CH_3), 24.37 (CH_3), 29.89 (CH_2), 40.14 (CH_2), 41.35 (C), 56.28 (CH_3, OMe), 56.51 (CH_3, OMe), 65.08 (CH), 111.66 (CH), 113.97 (CH), 123.73 (CH), 123.97 (C), 127.27 (CH), 128.69 (C), 129.43 (CH), 131.65 (C), 132.52 (CH), 146.75 (C), 148.10 (C), 148.55 (C) and 164.96 (C=O) ppm; Found: M^+ 337.1679 (13.2%) Calc. for $C_{21}H_{23}NO_3$ 337.1678. HETCOR and COSY experiments support characterisation.

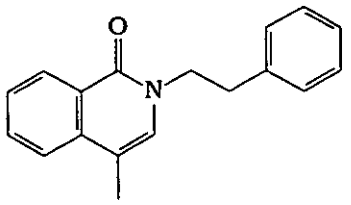
3-Ethyl-4-methyl-2-phenethyl-1,2-dihydro-1-isoquinolone.



5.8

A stirred solution of 4-ethyl-3-hydroxy-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone (**4.14**) (0.18g, 0.58 mmol) in dry DCM (*ca.* 50 ml) was cooled to -7 °C and aluminium bromide (0.29g, 1.05 mmol) was added. After 3 hours the reaction was terminated and gave the title compound (**5.8**) after flash chromatography eluting with EA/LP [1:6] (0.05g, 30%), yellow oil: ν_{max} 2973, 1645, 1613 and 1593 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$) 1.19 (t, 3H, CH_3, *J* 7.5), 2.33 (s, 3H, CH_3), 2.75 (q, 2H, *J* 7.5), 3.01-3.08 (m, 2H), 4.32-4.38 (m, 2H), 7.32- 7.68 (m, 8H) and 8.48-8.52 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 13.45 (CH_3), 13.75 (CH_3), 22.99 (CH_2), 35.63 (CH_2), 46.24 (CH_2), 108.84 (C), 122.78 (CH), 124.94 (C), 125.94 (CH), 126.76 (CH), 128.21 (CH), 129.00 (2 x CH), 129.19 (2 x CH), 132.24 (CH), 137.51 (C), 138.90 (C), 140.70 (C) and 162.69 (C=O) ppm; Found: M^+ 291.1625 (25.8%) $C_{20}H_{21}NO$ requires 291.1623.

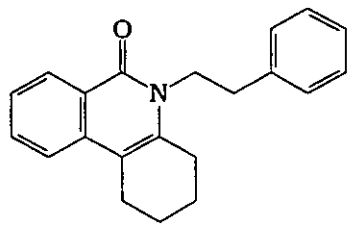
4-Methyl-2-phenethyl-1,2-dihydro-1-isoquinolinone.



5.9

A stirred solution of 4-benzyl-3-hydroxy-4-methyl-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolinone (**4.15**) (0.35g, 0.94 mmol) in dry DCM (*ca.* 50 ml) cooled to -5 °C and aluminium bromide (0.40g, 1.5 mmol) was added. After 4 hours, the reaction was allowed to warm up to room temperature and terminated and gave the title compound (**5.9**) after flash chromatography eluting with EA/LP [1:3] (0.12g, 50%), colourless oil : ν_{max} 2941, 1653, 1623 and 1603 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 2.19 (d, 3H, CH_3, *J* 1.1), 3.01-3.09 (m, 2H), 4.12-4.19 (m, 2H), 6.66 (d, 1H, *J* 1.1), 7.20- 7.68 (m, 8H) and 8.49-8.51 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 15.66 (CH_3), 35.81 (CH_2), 51.58 (CH_2), 112.09 (C), 123.41 (CH), 126.49 (C), 126.99 (2 x CH), 128.55 (CH), 128.99 (2 x CH), 129.37 (2 x CH), 130.04 (CH), 132.35 (CH), 137.74 (C), 138.79 (C) and 162.20 (C=O) ppm; Found: M^+ 263.1311 (17.3%) $C_{18}H_{17}NO$ requires 263.1310. HETCOR and COSY experiments support characterisation.

5-Phenethyl-1,2,3,4,5,6-hexahydro-6-phenanthridinone.



5.10

A stirred solution of 3-hydroxy-2-phenethyl-1,2,3,4-tetrahydro-1-isoquinolin-one-4-spiro-cyclopentane (**4.10**) in the particular solvent was adjusted to the stated temperature and aluminium bromide added. After the stated reaction time, the reaction was allowed to re-adjust to room temperature and terminated, and gave the title compound (**5.10**) (reaction conditions and yields are listed in

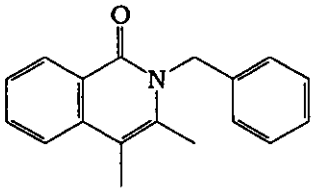
Table Exp. 5.5.), mp 89-92 °C from DCM: ν_{max} 2935, 1645, 1614 and 1597 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.79-1.82 (m, 4H), 2.59-2.62 (m, 2H), 2.73-2.76 (m, 2H), 2.99-3.05 (m, 2H), 4.26-4.32 (m, 2H), 7.26- 7.66 (m, 8H) and 8.49-8.52 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 21.76 (CH_2), 22.78 (CH_2), 24.31 (CH_2), 27.08 (CH_2), 34.86 (CH_2), 45.06 (CH_2), 110.68 (C), 121.44 (CH), 124.54 (C), 125.75 (CH), 126.49 (CH), 127.91 (CH), 128.53 (2 x CH), 128.85 (2 x CH), 131.98 (CH), 136.64 (C), 136.80 (C), 138.79 (C) and 162.70 (C=O) ppm; Found: M^+ 303.1626 (22.8%) $C_{21}H_{21}NO$ requires 303.1623.

Table Exp. 5.5

No.	Starting Material g	mmol	Reaction Temperature (°C)	$AlBr_3$ g	mmol	Solvent (ml)	Reaction Time (hours)	Yield g	%
1	0.14	0.44	150	0.18	0.66	25 (o-DCB)	2	0.13	96
2	0.14	0.44	-7	0.18	0.66	15 (DCM)	4	0.11	80

C- <u>*N*-Acyliminium ions Trapping by Migrating Alkyl Groups.</u>

2-Benzyl-3,4-dimethyl-1,2-dihydro-1-isoquinolinone

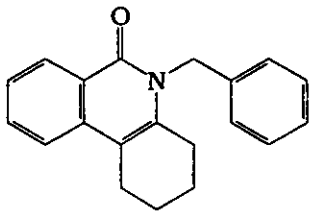


5.11

A stirred solution of 2-benzyl-3-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolinone (**4.3**) (1.20g, 4.3 mmol) in dry DCM (50 ml) at room temperature was injected with aluminium bromide (1.73g, 6.4 mmol). After four hours, the reaction was terminated and gave the title compound (**5.11**) after flash chromatography eluting with EA/LP [1:2] (0.32g, 19%), mp 110-111 °C from EA/LP : ν_{max} 3030, 1647, 1614 and 1595 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 2.28

(s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.49 (br.s, 2H), 7.14-7.69 (m, 8H) and 8.52-8.55 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 13.82 (CH_3), 16.67 (CH_3), 47.55 (CH_2), 109.50 (C), 122.62 (CH), 124.60 (C), 125.72 (CH), 126.17 (2 x CH), 126.98 (CH), 128.47 (CH), 128.67 (2 x CH), 132.23 (CH), 136.20 (C), 137.20 (C), 137.44 (C) and 162.50 (C=O) ppm; Found: M^+ 263.1309 (56.0%) $C_{18}H_{17}NO$ requires 263.1310.

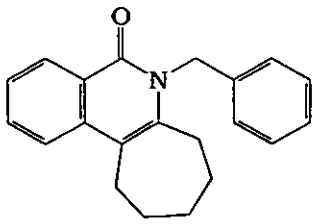
5-Benzyl-1,2,3,4,5,6-hexahydro-6-phenanthridinone.



5.12

A stirred solution of 2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spiro-cyclopentane (**4.9**) (1.0g, 3.26 mmol) in dry DCM (50 ml) at room temperature was injected with aluminium bromide (1.08g, 4.0 mmol). After four hours, the reaction was terminated and gave the title compound (**5.12**) after flash chromatography eluting with EA/LP [1:2] (0.72g, 77%), mp 145-146 °C (lit.[197] 156 - 157 °C) from EA/LP : ν_{max} 2944, 1644, 1615 and 1596 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.77-1.80 (m, 4H), 2.61-2.64 (m, 2H), 2.75-2.77 (m, 2H), 5.45 (br.s, 2H), 7.13- 7.69 (m, 8H) and 8.51-8.54 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 22.22 (CH_2), 23.13 (CH_2), 24.69 (CH_2), 27.54 (CH_2), 46.63 (CH_2), 111.32 (C), 121.91 (CH), 124.93 (C), 126.25 (CH), 126.53 (2 x CH), 127.35 (CH), 128.87 (CH), 129.08 (2 x CH), 132.60 (CH), 137.40 (C), 137.68 (C), 137.93 (C) and 163.22 (C=O) ppm; Found: M^+ 289.1468 (71.1%) Calc. for $C_{20}H_{19}NO$ 289.1467.

6-Benzyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]isoquinolin-5-one.

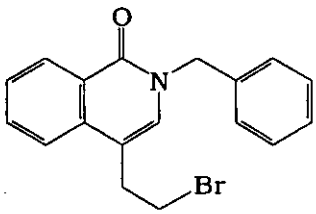


5.13

A stirred solution of 2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spirocyclohexane (**4.11**) (0.60g, 1.87 mmol) in dry DCM (40 ml) at room temperature was injected with aluminium bromide (0.76g, 2.85 mmol). After three hours, the reaction was terminated and gave the title compound (**5.13**) after flash chromatography eluting with EA/LP [1:3] (0.30g, 53%), mp 160-161 °C from EA/LP : ν_{max} 2925, 1642, 1610 and 1590 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.39-1.40 (m, 2H), 1.64-1.67 (m, 2H), 1.76-1.79 (m, 2H), 2.89-2.97 (m, 4H), 5.58 (br.s, 2H), 7.19- 7.80 (m, 8H) and 8.58-8.60 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 25.47 (CH_2), 26.28 (CH_2), 26.46 (CH_2), 30.61 (CH_2), 31.65 (CH_2), 47.89 (CH_2), 117.33 (C), 122.39 (CH), 124.96 (C), 125.96 (CH), 126.79 (2 x CH), 127.48 (CH), 129.11 (2 x CH), 129.37 (CH), 132.73 (CH), 136.80 (C), 138.20 (C), 143.70 (C) and 163.23 (C=O) ppm; Found: M^+ 303.1625 (20.6%) $C_{21}H_{21}NO$ requires 303.1623. HETCOR experiment supports characterisation.

D- <u>*N*-Acyliminium ions Trapping by Cyclopropane Ring Opening.</u>

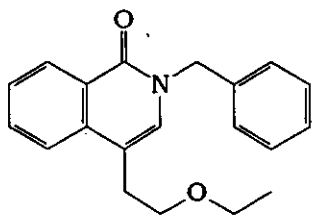
2-Benzyl-4-(2-bromoethyl)-1,2-dihydro-1-isoquinolinone.



5.14

A stirred solution of 2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spirocyclopropane (**4.8**) (0.09g, 0.32 mmol) in dry DCM (15 ml) at room temperature was injected with aluminium bromide (0.76g, 2.85 mmol). After three hours, the reaction was terminated and gave the title compound (**5.14**) after flash chromatography eluting with EA/LP [1:3] (0.087g, 80%), mp 143-144 °C from EA/LP : ν_{max} 3040, 1654, 1619 and 1600 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.20 (t, 2H, *J* 7.5), 3.57 (t, 2H, *J* 7.5), 5.26 (s, 2H), 7.05 (s, 1H), 7.30-7.73 (m, 8H) and 8.56-8.58 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 31.95 (CH_2), 33.57 (CH_2), 52.09 (CH_2), 113.62 (C), 122.48 (CH), 126.90 (C), 127.38 (CH), 128.27 (CH), 128.35 (2 x CH), 129.24 (2 x CH), 129.40 (CH), 131.20 (CH), 132.84(CH), 136.22 (C), 137.15 (C) and 162.26 (C=O) ppm; Found: M^+ 341.0398 (3.4%) $C_{18}H_{16}NOBr$ requires 341.0416. HETCOR experiment support characterisation.

2-Benzyl-4-(2-ethoxyethyl)-1,2-dihydro-1-isoquinolinone.

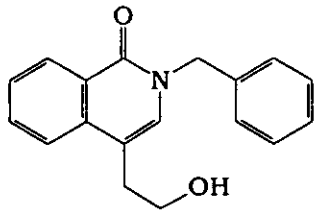


5.15

A stirred solution of 2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spiro-cyclopropane (**4.8**) (0.03g, 0.11 mmol) in dry diethyl ether (25 ml) was cooled to -78 °C and boron trifluoride etherate (0.23g, 1.60 mmol) was injected. After 25 minute the reaction mixture was warmed to room temperature, 25 minutes later the reaction was terminated and gave the title compound (**5.15**) after flash chromatography eluting with EA/LP [1:3] (0.035g, quantitative), oil : ν_{max} 2866, 1655, 1626 and 1602 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.13 (t, 3H, *J* 7.0), 2.90 (t, 2H, *J* 6.9), 3.42 (q, 2H, *J* 7.0), 3.60 (t, 2H, *J* 6.9), 5.21 (s, 2H), 7.01 (s, 1H), 7.26-7.69 (m, 8H) and 8.50-8.54 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 15.55 (CH_3), 30.27 (CH_2), 52.06 (CH_2), 66.75 (CH_2), 70.07 (CH_2), 113.79 (C), 123.08 (CH), 126.74 (C), 127.09 (CH), 128.17 (CH), 128.36 (2 x

CH), 129.10 (CH), 129.18 (2 x CH), 130.44 (CH), 132.55 (CH), 137.05 (C), 137.36 (C) and 162.35 (C=O) ppm; Found: M^+ 307.1573 (6.6%) $C_{20}H_{21}NO_2$ requires 307.1572.

2-Benzyl-4-(2-hydroxyethyl)-1,2-dihydro-1-isoquinolinone.

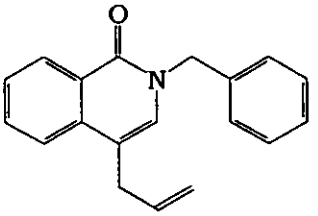


5.16

A stirred solution of 2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone-4-spirocyclopropane (**4.8**) (0.03g, 0.11 mmol) and BSA (0.086g, 0.43 mmol) in dry DCM (25 ml) was cooled to -78 °C and TMSOTf (0.047g, 0.21 mmol) was added. After 25 minute the reaction mixture was warmed to room temperature, 25 minutes later the reaction was terminated and gave the title compound (**5.16**) after flash chromatography eluting with EA/LP [1:3] (0.017g, 55%), mp 133-135 °C from DCM : ν_{max} 3407 (broad), 1651, 1620 and 1599 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 2.16 (br.s, 1H), 2.88 (t, 2H, *J* 6.4), 3.85 (t, 2H, *J* 6.4), 5.06 (s, 2H), 6.98 (s, 1H), 7.26-7.68 (m, 8H) and 8.48-8.50 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 33.18 (CH_2), 51.95 (CH_2), 62.05 (CH_2), 113.38 (C), 123.14 (CH), 126.73 (C), 127.26 (CH), 128.24 (CH), 128.32 (2 x CH), 129.14 (CH), 129.21 (2 x CH), 130.77 (CH), 132.67 (CH), 136.88 (C), 137.21 (C) and 162.28 (C=O) ppm; Found: M^+ 279.1262 (43.1%) $C_{18}H_{17}NO_2$ requires 279.1259. COSY experiment support characterisation.

E- Trapping of *N*-acyliminium Generated from 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone.

Reactions of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with titanium tetrachloride and aluminium tribromide.



5.17

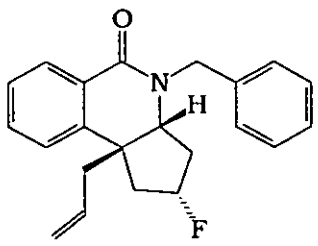
A stirred solution of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone (**4.12**) in dry DCM was adjusted to the stated temperature and the particular Lewis acid was added. After the stated reaction time, the reaction was terminated and gave *4-allyl-2-benzyl-1,2-dihydro-1-isoquinolinone* (**5.17**) after flash chromatography eluting with EA/LP [1:4] (reaction conditions and yields are listed in **Table Exp. 5.6**.), oil : ν_{max} 3062, 1656, 1624 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.31 (d, 2H, *J* 6.1), 5.00-5.05 (m, 2H), 5.13 (s, 2H), 5.84-5.91 (m, 1H), 6.85 (s, 1H), 7.18-7.59 (m, 8H) and 8.43-8.45 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 33.65 (CH_2), 51.71 (CH_2), 114.61 (C), 117.07 (CH_2), 123.18 (CH), 126.34 (C), 126.79 (CH), 127.78 (CH), 127.87 (2 x CH), 128.59 (CH), 128.81 (2 x CH), 129.68 (CH), 132.10 (CH), 135.71 (CH), 136.60 (C), 137.01(C) and 162.04 (C=O) ppm; Found: M^+ 275.1309 (49.7%) $C_{19}H_{17}NO$ requires 275.1310. HETCOR experiment supports characterisation.

Table Exp. 5.6

No.	Starting Material		Reaction Temperature	Lewis Acid	DCM	Reaction Time	Yield	
	mg	mmol	(°C)	(g, mmol)	(ml)	(hours)	mg	%
1	300	0.90	Ambient	$AlBr_3$ (0.30, 1.12)	30	4	103	42
2	200	0.60	Ambient*	$TiCl_4$ (0.24, 1.26)	20	4.5	160	92

* $TiCl_4$ was added at -78 °C for 15 minutes then the reaction was warmed up to the mentioned temperature.

Reaction of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with boron trifluoride etherate in chloroform.



5.18

A solution of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone (**4.12**) (0.130g, 0.38 mmol) in chloroform (2ml) at room temperature, was injected with boron trifloride etherate (54mg, 0.38 mmol). After 2.5 hours, the reaction was terminated, and gave after flash chromatography eluting with EA/LP [1:4] *(2S/2R, 3aR/3aS, 9bR/9bS)-9a-allyl-4-benzyl-2-fluoro-2,3,3a,4,5,9b-hexahydro -1H-cyclopenta[c]isoquinolin-5-one* (**5.18**) (76mg, 60%), single diastereomer, oil : ν_{max} 2977, 1648 and 1601 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.67-1.74 (m, 1H), 2.12-2.32 (m, 4H), 2.77-2.84 (m, 1H), 3.82 (dd, 1H, *J* 7.0, 11.4), 4.47 (d, 1H, *J* 14.4), 4.71 (dd, 1H, *J* 1.8, 17.0), 4.83-4.86 (m, 0.5H), 4.92 (dd, 1H, *J* 1.8, 10.0), 4.97-4.99 (m, 0.5H), 5.12 (d, 1H, *J* 14.4), 5.37-5.44 (m, 1H), 7.27-7.53 (m, 8H) and 8.24-8.26 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 38.99 (d, CH_2, *J* 21.3), 43.22 (d, CH_2, *J* 21.9), 45.87 (CH_2), 46.98 (d, C, *J* 1.4), 50.61 (CH_2), 61.68 (CH), 90.73 (d, CH, *J* 174.1), 119.46 (CH_2), 126.52 (CH), 127.60 (CH), 128.05 (C), 128.20 (CH), 129.08 (2 x CH), 129.21 (CH), 129.32 (2 x CH), 132.67 (CH), 132.96 (CH), 137.79 (C), 142.97 (C) and 162.93 (C=O) ppm; Found: M^+ 335.1685 (92.6%) $C_{22}H_{22}FNO$ requires 335.1685. HETCOR annd COSY experiments support characterisation. The structural conformation and configuration in $CDCl_3$ at 25 °C were analysed by $^1H,^1H$-NOESY at 400 M Hz over two mixing times: 0.55 and 0.70 second. Crosspeaks of at least medium strength were considered. The following protons show nOe crosspeaks (the numbers of the relevant hydrogen atoms are in bold and they correspond to the numbered atoms in **Figure Exp. 5.2**) :

1 (dd, 3.82 ppm) and **2** (m, 2.14 ppm).

2 (m, 2.14 ppm) and **4** (m, 4.83-4.86 ppm).

1 (dd, 3.82 ppm) and **7** (m, 5.37-5.44 ppm).

2 (m, 2.14 ppm) and **8b** (d, 4.47 ppm).

1 (dd, 3.82 ppm) and **8a** (d, 5.12 ppm) and **8b** (d, 4.47 ppm).

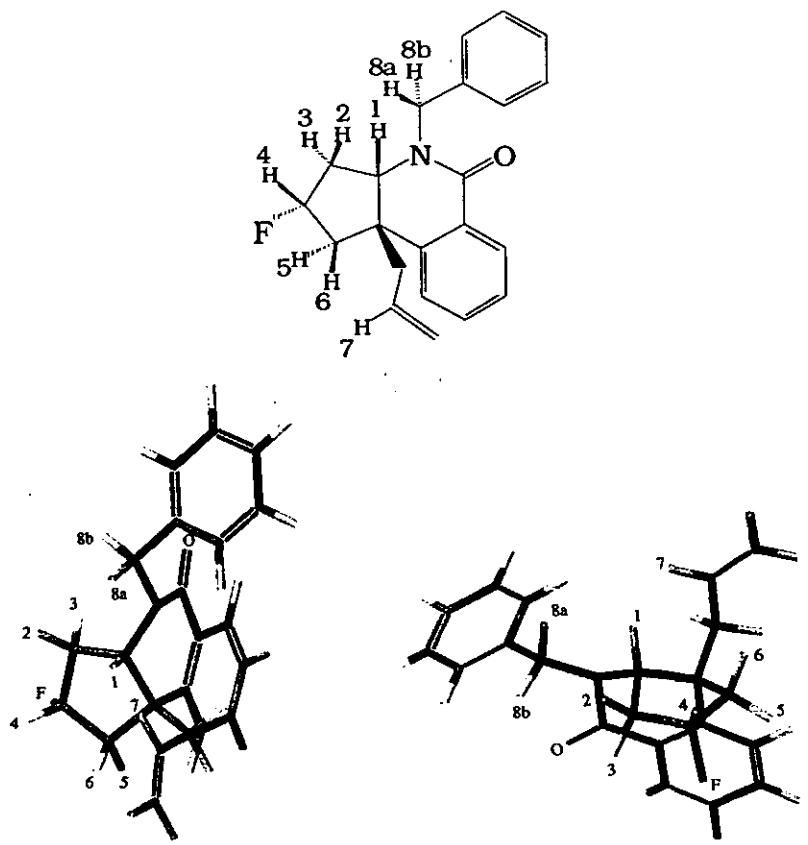


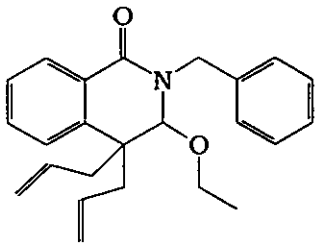
Figure Exp. 5.2.

The analysis results were further strengthened by conformational energy minimisation conducted by CAChe programme (**Figure Exp. 5.2**). Relevant interatomic distances calculated by CAChe minimisation are shown in **Table Exp. 5.7**.

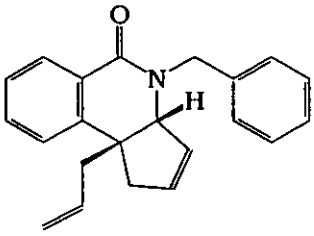
Table Exp. 5.7

protons	distance (^{o}A)
1-2	2.38
2-4	2.39
1-7	1.78
2-8b	2.91
1-8a	2.28
1-8b	3.24

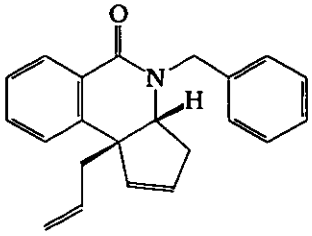
Reaction of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with boron trifluoride etherate in diethyl ether.



5.19



5.20

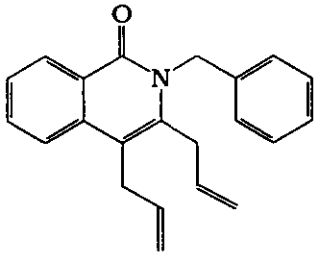


5.21

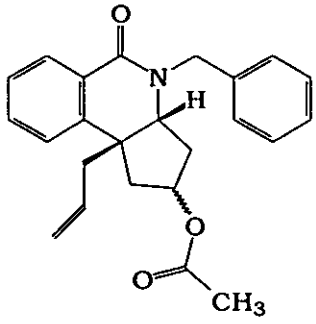
A stirred solution of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone (**4.12**) (0.30g, 0.90 mmol) in dry diethyl ether (30ml) was cooled down to -78 °C and boron trifloride etherate (0.16g, 1.13 mmol) was added. After 15 minutes, the reaction was warmed up to room temperature. After 28 hours the reaction was terminated, and gave after flash chromatography eluting with EA/LP [1:7] four identifiable compounds. The first one *4,4-Diallyl-2-benzyl-3-ethoxy-1,2,3,4-tetrahydro-1-isoquinolinone* (**5.19**)(22mg, 7%), oil : ν_{max} 2978, 1655 and 1603 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.03 (t, 3H, *J* 6.9), 1.82-1.86 (m, 2H), 2.48 (dd, 1H, *J* 7.9, 13.3), 2.69 (dd, 1H, *J* 6.8, 13.3), 3.34-3.40 (m, 1H), 3.54-3.60 (m, 1H), 4.14 (d, 1H, A of AB, *J* 14.4), 4.49 (s, 1H), 4.74-4.94 (m, 2H), 5.16-5.29 (m, 3H), 5.57 (d, 1H, B of AB, *J* 14.4), 5.75-5.82 (m, 1H), 7.12-7.48 (m, 8H) and 8.14-8.17 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 15.36 (CH_3), 35.38 (CH_2), 40.17 (CH_2), 44.36 (C), 51.42 (CH_2), 64.64 (CH_2), 91.45 (CH), 118.59 (CH_2), 119.31 (CH_2), 125.37 (CH), 126.73 (CH), 127.76 (CH), 128.31 (C), 128.58 (CH), 128.60 (2 x CH), 129.23 (2 x CH), 131.58 (CH), 132.72 (CH), 133.08 (CH), 137.25 (C), 142.49 (C) and 164.40 (C=O) ppm; Found: M^+ 361.2043 (0.9%) $C_{24}H_{27}NO_2$ requires 361.2042. The second product is a mixture of two regioisomers *(3aS/3aR, 9bS/9bR)-9b-Allyl-4-benzyl-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]isoquinolin-5-one* (**5.20**) and *(3aS/3aR, 9bS/9bR)-9b-Allyl-4-benzyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]isoquinolin-5-one* (**5.21**) (27mg, 9%), data for the isomeric mixture (**5.20/5.21**) [2:3], oil : ν_{max} 2919, 1647 and 1602 cm^{-1}; ^1H nmr (for **5.21**) (400 M Hz, $CDCl_3$) 2.02-2.07 (m, 1H), 2.12 (dd, 1H, *J* 8.5, 13.9), 2.27 (dd, 1H, *J* 6.3, 13.9), 2.45-2.51 (m, 1H), 3.69 (dd, 1H, *J* 7.6, 9.3), 4.26 (d, A of AB, *J*

14.4), 4.41 (dd, 1H, *J* 1.5, 17.0), 4.74 (dd, 1H, *J* 1.5, 10.1), 5.15 (d, 1H, 14.4), 5.35-5.43 (m, 1H), 5.68-5.70 (m, 1H), 5.97 (dd, 1H, *J* 2.2, 6.2), 7.05 (dd, 1H, *J* 0.7, 8.7), 7.20-7.39 (m, 7H) and 8.11-8.15 (m, 1H) ppm; ^{13}C nmr (for **5.21**) (100.5 M Hz, $CDCl_3$) 38.74 (CH_2), 45.26 (CH_2), 50.07(CH_2), 50.97 (C), 62.31 (CH), 119.08 (CH_2), 127.02 (CH), 127.17 (CH), 127.27 (C), 128.08 (CH), 128.43 (CH), 128.99 (2 x CH), 129.33 (2 x CH), 130.52 (CH), 132.70 (CH), 133.31 (CH), 136.16 (CH), 138.12 (C), 142.19 (C) and 163.26 (C=O) ppm; ^{13}C nmr (for **5.20**) (100.5 M Hz, $CDCl_3$) 44.29 (CH_2), 45.45 (CH_2), 50.30 (C), 50.67 (CH_2), 68.24 (CH), 118.68 (CH_2), 126.46 (CH), 127.25 (CH), 128.11 (CH), 128.60 (CH), 128.75 (C), 129.03 (2 x CH), 129.43 (2 x CH), 130.69 (CH), 131.18 (CH), 132.30 (CH), 133.99 (CH), 137.78 (C), 143.99 (C) and 163.05 (C=O) ppm; Found: M^+ 315.1624 (11.2%) $C_{22}H_{21}NO$ requires 315.1623. The third compound is *(2S/2R, 3aR/3aS, 9bR/9bS)-9a-allyl-4-benzyl-2-fluoro-2,3,3a,4,5,9b-hexahydro -1H-cyclopenta[c]isoquinolin-5-one* (**5.18**) (72 mg, 24%).

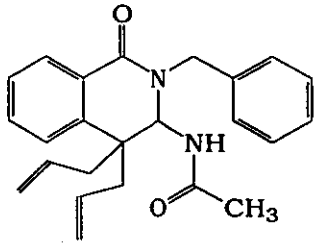
Reactions of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone with TMSOTf in the presence and absence of selected nucleophiles.



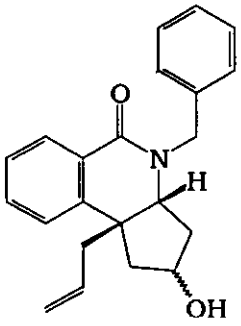
5.22



5.23



5.24



5.25

A stirred solution of 4,4-diallyl-2-benzyl-3-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinone (**4.12**) in a given volume of dry DCM and under nitrogen atmosphere was cooled down to -78 °C and TMSOTf was added. After 15 minutes the reaction was warmed to the stated reaction temperature. After a given period of time, the reaction was quenched with the particular nucleophile (nucleophile time). After the stated reaction time the reaction was terminated. Reaction conditions and yields are illusterated in **Table Exp. 5.8**.

Table Exp. 5.8

Reaction No.	1	2	3	4	5
Starting mg	300	113	200	200	190
material mmol	0.90	0.34	0.60	0.60	0.57
Solvent ml	20	15	20	20	20
TMSOTf mg		152	280	280	250
mmol	catalytic	0.68	1.26	1.26	1.14
Reaction Temperature (°C)	Ambient	Ambient	Ambient	-10	Ambient
Nucleophile mg	BSA 540	BSA 276	ACN‡‡ 260	Non	TMSA‡‡ 340
mmol	2.66	1.36	6.0		2.28
Nucleophile Time minutes	0*	80	60	------	60
Reaction Time hours	4	10	23	29	25
Chromatographic elution system+	1:1	1:6 →1:3‡	1:10→ 1:1‡	1:10→1:4‡	1:10→1:2‡
Products (in elution order).					
5.22 mg	------	16	14	17	9
%	------	15	7	9	5
5.20/5.21 mg	------	30	55	76	28
[**5.20:5.21**]** %	------	28†	[1:5] 29	[1:3] 40	[1:4] 16
5.23 mg	------	31	25	------	15
[Dias. Ratio]# %	------	[3:2] 24	[3:1] 11	------	[4:1] 7
5.25 mg	------	------	19	------	------
[Dias. Ratio]†† %	------	------	[2:1] 10	------	------
5.24 mg	147	40	------	------	53
%	44	31	------	------	25

* BSA was added to the stirred solution of the the starting material in DCM, after 5-10 minutes, the reaction was cooled down to -78 °C and TMSOTf was added.

‡‡ ACN = acetonitrile, TMSA = *N*-trimethylsilyl acetamide.

\+ Solvent system ratio: EA/LP.

‡ Gradient elution.

** The alkene ratios are shown in square brackets and are calculated from the average peak hights of comparable carbon atoms in ^{13}C nmr spectroscopy.

† Only **5.21** was isolated.

The diastereomeric ratios [Major : Minor] are shown in square brackets, and are calculated from the peak areas for the comparable protons at 3.44 (dd, 1H, *J* 7.9, 10.5 Hz) ppm for the major diastereomer and 3.67 (dd, 1H, *J* 8.2, 10.4 Hz) ppm for the minor diastereomer.

†† The diastereomeric ratios [Major : Minor] are shown in square brackets and are calculated from the isolated and purified diastereomers.

Data for compounds (**5.22**), (**5.23**), (**5.25**) and (**5.24**).

3,4-Diallyl-2-benzyl-1,2-dihydro-1-isoquinolinone (**5.22**), oil : ν_{max} 3035, 1648, 1612 and 1600 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 3.36-3.38 (m, 2H), 3.47-3.49 (m, 2H), 4.93-5.27 (m, 4H), 5.46 (br.s, 2H), 5.90-6.05 (m, 2H), 7.10-7.70 (m, 8H) and 8.52-8.55 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 31.83 (CH_2), 33.70 (CH_2), 47.65 (CH_2), 113.02 (C), 116.39 (CH_2), 117.51 (CH_2), 123.56 (CH), 125.52 (C), 126.29 (2 x CH), 126.67 (CH), 127.52 (CH), 129.09 (CH), 129.28 (2 x CH), 132.86 (CH), 133.96 (CH), 135.95 (CH), 137.06 (C), 138.09 (C), 138.17 (C) and 163.45 (C=O) ppm; Found: M^+ 315.1621 (40.2%) $C_{22}H_{21}NO$ requires 315.1623.

N1-[(3aR/3aS, 9bR/9bS)-9b-Allyl-4-benzyl-5-oxo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]isoquinolin-2-yl]acetate (**5.23**), data for the diastereomeric mixture, oil : ν_{max} 2978, 1736, 1645 and 1602 cm^{-1}; ^1H nmr (for the major diastereomer) (400 M Hz, $CDCl_3$) 1.50-1.62 (m, 1H), 1.70 (s, 3H, CH_3), 2.04-2.14 (m, 2H), 2.17-2.21 (m, 1H), 2.36-2.52 (m, 2H), 3.44 (dd, 1H, *J* 7.9, 10.5), 4.39 (d, 1H, A of AB, *J* 14.4), 4.64-4.73 (m, 1H), 4.88-4.94 (m, 2H), 5.09 (d, 1H, B of AB, *J* 14.4), 5.30-5.41 (m, 1H), 7.22-7.51 (m, 8H) and 8.19-8.25 (m, 1H) ppm; ^1H nmr (for the minor diastereomer) (400 M Hz, $CDCl_3$) 1.77-1.85 (m, 1H), 1.88-1.95 (m, 1H), 2.00 (s, 3H, CH_3), 2.04-2.14 (m, 2H), 2.17-2.21 (m, 1H), 2.79 (dd, 1H, *J* 7.3, 13.9), 3.67 (dd, 1H, *J* 8.2, 10.4), 4.36 (d, 1H, A of AB, *J* 14.4), 4.82-4.86 (m, 1H), 4.88-4.94 (m, 2H), 5.12 (d, 1H, B of AB, *J* 14.4), 5.30-5.41 (m, 1H), 7.22-7.51 (m, 8H) and 8.19-8.25 (m, 1H) ppm; ^{13}C nmr (for the major diastereomer) (100.5 M Hz, $CDCl_3$) 21.33 (CH_3), 38.53 (CH_2), 41.31 (CH_2), 45.61 (CH_2), 46.68 (C), 50.44 (CH_2), 62.18 (CH), 71.58 (CH), 119.52 (CH_2), 126.97 (CH), 127.33 (CH), 127.81 (C), 128.22 (CH), 129.09 (2 x CH), 129.24 (3 x CH), 132.74 (CH), 132.97 (CH), 137.76 (C), 142.98 (C), 163.19 (C=O), and 171.10 (C=O) ppm; ^{13}C nmr (for the minor diastereomer) (100.5 M Hz, $CDCl_3$) 21.53 (CH_3), 38.09 (CH_2), 41.46 (CH_2), 45.06 (CH_2), 47.34 (C), 50.51 (CH_2), 61.69 (CH), 71.78 (CH), 119.43 (CH_2), 126.15 (CH), 127.73 (CH), 127.81 (C), 128.19 (CH), 129.09 (2 x CH), 129.29

(3 x CH), 132.08 (CH), 132.74 (CH), 137.79 (C), 142.13 (C), 163.13 (C=O) and 170.98 (C=O) ppm; Found: M^+ 375.1836 (9.0%) $C_{24}H_{25}NO_3$ requires 375.1834. HETCOR, COSY and NOESY (in $CDCl_3$ at 25 °C over 0.70 second mixing time) experiments support characterisation.

(3aR/3aS, 9bR/3aS)-9b-Allyl-4-benzyl-2-hydroxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]isoquinolin-5-one (**5.25**), data for the minor diastereomer (isolated, 7 mg), oil, v_{max} 3394 (broad), 1641 and 1603 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.74-1.87 (m, 3H), 2.22-2.29 (m, 3H), 2.75-2.85 (m, 1H), 3.86 (dd, 1H, *J* 8.2, 10.4), 4.10-4.16 (m, 1H), 4.50 (d, 1H, *J* 14.3), 4.77 (dd, 1H, *J* 1.8, 17.0), 4.92 (dd, 1H, *J* 1.8, 10.0) 5.07 (d, 1H, *J* 14.3), 5.40-5.50 (m, 1H), 7.27-7.50 (m, 8H) and 8.24-8.26 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 41.62 (CH_2), 45.32 (CH_2), 45.81 (CH_2), 47.59 (C), 50.69 (CH_2), 62.16 (CH), 69.16 (CH), 118.82 (CH_2), 126.03 (CH), 127.31 (CH), 127.99 (CH), 128.73 (C), 128.91 (2 x CH), 129.19 (CH), 129.36 (2 x CH), 132.34 (CH), 133.35 (CH), 138.07 (C), 143.40 (C) and 163.15 (C=O) ppm; Found: M^+ 333.1725 (55.0%) $C_{22}H_{23}NO_2$ requires 333.1729. Data for the major diastereomer (eluted after the minor diastereomer, 12 mg), oil, v_{max} 3402 (broad), 1637 and 1600 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 1.37-1.52 (m, 1H), 1.73 (br.s, 1H, OH), 2.00-2.25 (m, 3H), 2.37-2.48 (m, 2H), 3.38 (dd, 1H, *J* 7.7, 11.0), 4.10-4.16 (m, 1H), 4.39 (d, 1H, *J* 14.5), 4.63 (dd, 1H, *J* 1.8, 17.0), 4.88 (dd, 1H, *J* 1.8, 10.0), 5.08 (d, 1H, *J* 14.5), 5.30-5.41 (m, 1H), 7.28-7.55 (m, 8H) and 8.22-8.25 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 42.31 (CH_2), 44.40 (CH_2), 45.81 (CH_2), 46.70 (C), 50.45 (CH_2), 62.52 (CH), 69.29 (CH), 119.38 (CH_2), 127.03 (CH), 127.63 (CH), 127.95 (C), 128.19 (CH), 129.02 (2 x CH), 129.19 (2 x CH), 129.52 (CH), 132.55 (CH), 133.18 (CH), 137.88 (C), 143.32 (C) and 163.15 (C=O) ppm; Found: M^+ 333.1728 (10.0 %) $C_{22}H_{23}NO_2$ requires 333.1729.

N1-(4,4-Diallyl-2-benzyl-1-oxo-1,2,3,4-tetrahydro-3-isoquinolinyl)acetamide (**5.24**), mp 139-142 °C from EA/LP : v_{max} 3288 (broad), 1652, 1645 and 1602 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 1.82-1.86 (m, 1H), 1.87 (s, 3H, CH_3), 2.01-

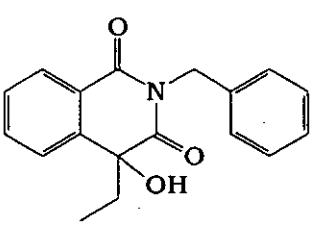
2.04 (m, 1H), 2.33 (dd, 1H, *J* 5.0, 14.8), 2.73 (dd, 1H, *J* 8.3, 14.8), 4.14 (d, 1H, A of AB, *J* 14.0), 4.65-4.69 (m, 1H), 4.89-4.92 (m, 1H), 5.10-5.20 (m, 3H), 5.42 (d, 1H, B of AB, *J* 14.0), 5.47 (d, 1H, *J* 10.2), 5.50-5.70 (m, 1H), 5.89 (d, 1H, *J* 10.2), 7.22-7.54 (m, 8H) and 8.19-8.21 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 23.28 (CH_3), 36.11 (CH_2), 41.09 (CH_2), 43.50 (C), 48.34 (CH_2), 65.81 (CH), 119.12 (CH_2), 119.67 (CH_2), 126.19 (CH), 127.68 (CH), 127.73 (CH), 127.82 (C), 128.56 (2 x CH), 129.25 (CH), 129.56 (2 x CH), 131.95 (CH), 132.08 (CH), 132.22 (CH), 136.79 (C), 140.67 (C), 162.87 (C=O) and 169.96 (C=O) ppm; Found: M^+ 374.1994 (13.4%) $C_{24}H_{26}N_2O_2$ requires 374.1994. HETCOR experiment supports characterisation.

Chapter 6 experimental:

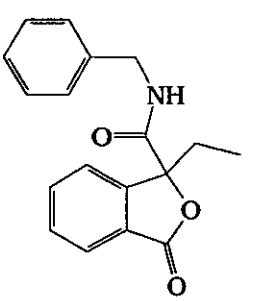
The oxidation of 4-monosubstituted-1,2,3,4-tetrahydro-1,3-isoquinoline-diones by dioxygen in alkaline media and cleavage-cyclisation reactions - General Method.

A magnetically stirred solution of the particular 1,3-isoquinolinedione, sodium hydroxide (1 equivalent or catalytic) in a given volume of oxygen-saturated ethanol was heated to reflux for a given length of time. Subsequently, the reaction mixture was allowed to cool down to room temperature. The reaction was then adjusted to neutral pH using diluted hydrochloric acid. Then DCM (150 ml) and water (150 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation. Oxygen-saturation of ethanol was done by bubbling oxygen gas in the particular volume of ethanol for 5-10 minutes prior to dissolving the particular 1,3-isoquinolinedione. The following oxidation reactions were conducted:

Oxidation of 2-benzyl-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



6.1



6.2

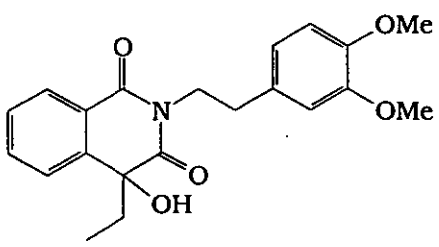
A stirred solution of 2-benzyl-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.18**) and sodium hydroxide in ethanol heated to reflux for the stated period and gave two products after flash chromatography eluting with EA/LP [1:4] (reaction conditions and yields are listed in **Table Exp. 6.1**). The first product *2-benzyl-4-ethyl-4-hydroxy-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**6.1**), oil :

ν_{max} 3464 (broad), 2972, 1722, 1674 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.65 (t, 3H, *J* 7.5), 1.77-1.93 (m, 2H), 3.85 (br.s, 1H, OH), 5.14 (d, 1H, A of AB, J_{AB} 13.9), 5.19 (d, 1H, J_{AB} 13.9), 7.28-7.72 (m, 8H) and 8.18-8.20 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 8.06 (CH_3), 40.70 (CH_2), 44.43 (CH_2), 75.77 (C), 124.71 (C), 125.51 (CH), 128.12 (CH), 128.73 (CH), 128.88 (2 x CH), 129.03 (CH), 129.35 (2 x CH), 134.37 (CH), 136.97 (C), 141.22 (C), 164.37 (C=O) and 177.36 (C=O) ppm; Found: M^+ 295.1211 (14.5%) $C_{18}H_{17}NO_3$ requires 295.1208. The second product *N1-benzyl-1-ethyl-3-oxo-1,3-dihydro-1-isobenzofurancarboxamide* (**6.2**), mp 127-129 °C from EA/LP: ν_{max} 3365 (broad), 2974, 1772, 1675 and 1600 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.88 (t, 3H, *J* 7.4), 2.01-2.10 (m, 1H), 2.46-2.55 (m, 1H), 4.25 (dd, 1H, *J* 5.2, 14.7), 4.56 (dd, 1H, *J* 6.6, 14.7), 7.10 (br.s, 1H, N-H), 7.22-7.31 (m, 5H), 7.56-7.59 (m, 1H), 7.71-7.75 (m, 1H) and 7.83-7.90 (m, 2H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 8.33 (CH_3), 32.09 (CH_2), 43.93 (CH_2), 89.88 (C), 123.91 (CH), 124.61 (C), 125.88 (CH), 128.06 (CH), 128.14 (2 x CH), 129.12 (2 x CH), 130.24 (CH), 135.31 (CH), 137.77 (C), 149.36 (C), 169.25 (C=O) and 169.58 (C=O) ppm; Found: C, 72.55, H, 5.75, N, 4.77 % $C_{18}H_{17}NO_3$ requires C, 73.22, H, 5.76, N, 4.74 %; Found: M^+ 295.1210 (22.8%) $C_{18}H_{17}NO_3$ requires 295.1208.

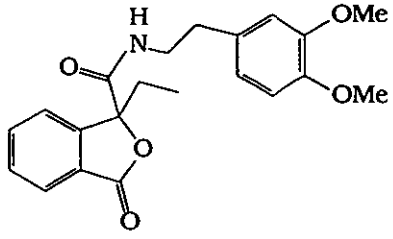
Table Exp. 6.1

No	Starting Material		NaOH		Reaction Time (hours)	Solvent Volume (ml.)	Product yields			
							6.1		**6.2**	
	mg	mmol	mg	mmol			mg	%	mg	%
1	210	0.75	33	0.83	4	70	22	10	113	51
2	210	0.75	5	0.11	9	70	80	36	55	25

Oxidation of 2-(3,4-dimethoxyphenethyl)-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



6.3

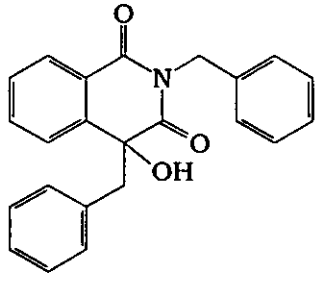


6.4

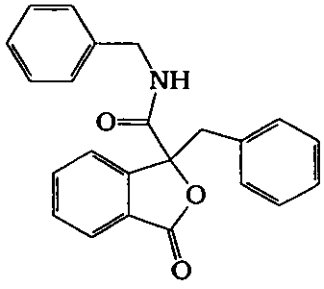
A stirred solution of 2-(3,4-dimethoxy phenethyl)-4-ethyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.20**) (1.0g, 2.83 mmol) and sodium hydroxide (0.11 g, 2.83 mmol) in ethanol (70 ml) was heated to reflux for 24 hours and gave two products after flash chromatography eluting with EA/LP [1:4]. The first product *2-(3,4-dimethoxyphenethyl)-4-ethyl-4-hydroxy-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**6.3**) (0.10g, 10%), oil : ν_{max} 3464 (broad), 2967, 1718, 1671 and 1606 cm^{-1}; ^1H nmr (250 M Hz, $CDCl_3$) 0.70 (t, 3H, *J* 7.5), 1.75-1.88 (m, 2H), 2.88 (t, 2H, *J* 7.8), 3.76 (br.s, 1H, OH), 3.85 (3H, CH_3, OMe), 3.86 (3H, CH_3, OMe), 4.08-4.17 (m, 1H), 4.23-4.32 (m, 1H), 6.78-6.83 (m, 3H), 7.46-7.53 (m, 1H), 7.67-7.70 (m, 2H) and 8.13-8.16 (m, 1H) ppm; ^{13}C nmr (62.8 M Hz, $CDCl_3$) 7.87 (CH_3), 33.78 (CH_2), 40.22 (CH_2), 42.21 (CH_2), 55.78 (CH_3, MeO), 55.93 (CH_3, MeO), 75.25 (C), 111.33 (CH), 112.14 (CH), 121.00 (CH), 124.63 (C), 125.18 (CH), 128.34 (CH), 128.43 (CH), 130.70 (C), 133.93 (CH), 140.81 (C), 147.78 (C), 148.94 (C), 163.98 (C=O) and 177.01 (C=O) ppm; Found: M^+ 369.1574 (4.5%) $C_{21}H_{23}NO_5$ requires 369.1576. The second product *N1-(3,4-dimethoxyphenethyl)-1-ethyl-3-oxo-1,3-dihydro-1-isobenzo furan carboxamide* (**6.4**) (0.53g, 51%), oil : ν_{max} 3369 (broad), 2938, 1771, 1674 and 1592 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.84 (t, 3H, *J* 7.4), 1.98-2.05 (m, 1H), 2.39-2.45 (m, 1H), 2.72 (t, 2H, *J* 7.0), 3.42-3.57 (m, 2H), 3.84 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.60-6.75 (m, 4H), 7.54-7.58 (m, 1H), 7.69-7.73 (m, 1H) and 7.82-7.85 (m, 2H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 8.25 (CH_3), 31.82 (CH_2), 35.54 (CH_2), 41.09 (CH_2), 56.18 (CH_3, OMe), 56.29 (CH_3, OMe), 89.83 (C), 111.86 (CH), 112.22 (CH), 121.00 (CH), 123.85 (CH),

124.52 (C), 125.76 (CH), 130.16 (CH), 131.08 (C), 135.22 (CH), 148.18 (C), 149.37 (C), 149.46 (C), 169.22 (C=O) and 169.49 (C=O) ppm; Found: M^+ 369.1573 (32.7%) $C_{21}H_{23}NO_5$ requires 369.1576.

Oxidation of 2,4-dibenzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



6.5



6.6

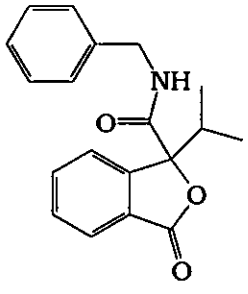
A stirred solution of 2,4-dibenzyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.22**) and sodium hydroxide in ethanol heated to reflux for the stated period and gave two products after flash chromatography eluting with EA/LP [1:7] (reaction conditions and yields are listed in **Table Exp. 6.2**). The first product *2-dibenzyl-4-hydroxy-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**6.5**), mp 109-111 °C ether: ν_{max} 3459 (broad), 3032, 1719, 1673 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.09 (d, 1H, A of AB, J_{AB} 12.9), 3.19 (d, 1H, B of AB, J_{AB} 12.9), 3.95 (br.s, 1H, OH), 4.96 (d, 1H, A of AB, J_{AB} 13.8), 5.08 (d, 1H, J_{AB} 13.8), 6.51-6.52 (m, 2H), 7.04-7.70 (m, 11H) and 8.08-8.10 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 44.50 (CH_2), 54.11 (CH_2), 76.18 (C), 125.17 (C), 125.78 (CH), 127.86 (CH), 128.16 (CH), 128.41 (2 x CH), 128.61 (CH), 128.90 (2 x CH), 128.94 (CH), 129.82 (2 x CH), 130.38 (2 x CH), 133.45 (C), 134.37 (CH), 136.75 (C), 140.25 (C), 163.76 (C=O) and 176.43 (C=O) ppm; Found: M^+ 357.1365 (11.5 %) $C_{23}H_{19}NO_3$ requires 357.1365. COSY experiment supports characterisation. The second product *N1,1-dibenzyl-3-oxo-1,3-dihydro-1-isobenzofurancarboxamide* (**6.6**), mp 96-98 °C from EA/LP: ν_{max} 3364 (broad), 3031, 1774, 1676 and 1600 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 3.26 (d, 1H, A of AB, J_{AB} 14.0), 3.75 (d, 1H, B of AB, J_{AB} 14.0), 4.10 (dd, 1H, *J* 4.7, 14.7), 4.50 (dd, 1H, *J* 6.9, 14.7), 6.70 (br.s, 1H, N-H), 6.95-6.97 (m, 2H), 7.22-7.30 (m, 8H), 7.58-7.60 (m, 1H), 7.79-7.81 (m, 2H) and 8.06-8.08

(m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 43.83 (CH_2), 44.88 (CH_2), 89.17 (C), 124.23 (CH), 124.68 (C), 125.92 (CH), 127.72 (CH), 128.00 (2 x CH), 128.66 (2 x CH), 129.05 (CH), 130.37 (CH), 130.91 (2 x CH), 133.96 (C), 135.26 (CH), 137.23 (C), 149.00 (C), 168.51 (C=O) and 169.10 (C=O) ppm; Found: M^+ 357.1366 (4.1%) $C_{23}H_{19}NO_3$ requires 357.1365. COSY experiment supports characterisation.

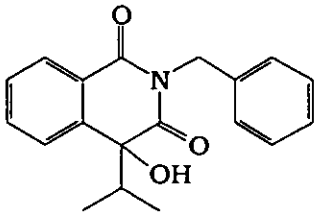
Table Exp. 6.2

Starting Material		NaOH		Reaction Time (hours)	Solvent Volume (ml.)	Product yields			
						6.5		**6.6**	
mg	mmol	mg	mmol			mg	%	mg	%
230	0.67	4	0.10	17	70	80	33	30	13

Oxidation of 2-benzyl-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



6.7



6.9

Procedure A:

A stirred solution of 2-benzyl-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinoline dione (**3.23**) (0.20g, 0.68 mmol), sodium hydroxide (4.1 mg, 0.10 mmol) and triethyl phosphite (0.34g, 2.04 mmol) in ethanol (70 ml) was bubbled with oxygen gas over 18 hours at room temperature. Subsequently, the reaction was terminated by adding DCM (150 ml) and water (150 ml) followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and gave after flash chromatography eluting with EA/LP [1:4] *2-benzyl-4-hydroxy-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione* (**6.9**) (0.20g, 97%), oil : ν_{max} 3482 (broad), 2969, 1719,

1673 and 1605 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.68 (d, 3H, *J* 6.7), 0.73 (d, 3H, *J* 6.7), 1.87 (h, 1H, *J* 6.7), 3.83 (br.s, 1H, OH), 5.12 (d, 1H, A of AB, J_{AB} 13.8), 5.19 (d, 1H, J_{AB} 13.8), 7.30-7.70 (m, 8H) and 8.17-8.19 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 16.78 (CH_3), 17.04 (CH_3), 42.99 (CH), 44.52 (CH_2), 78.03 (C), 125.45 (C), 126.34 (CH), 128.18 (CH), 128.60 (CH), 128.71 (CH), 128.81 (2 x CH), 129.65 (2 x CH), 133.62 (CH), 136.83 (C), 140.26 (C), 164.77 (C=O) and 177.31 (C=O) ppm; Found: M^+ 309.1366 (6.0%) $C_{19}H_{19}NO_3$ requires 309.1365.

Procedure B:

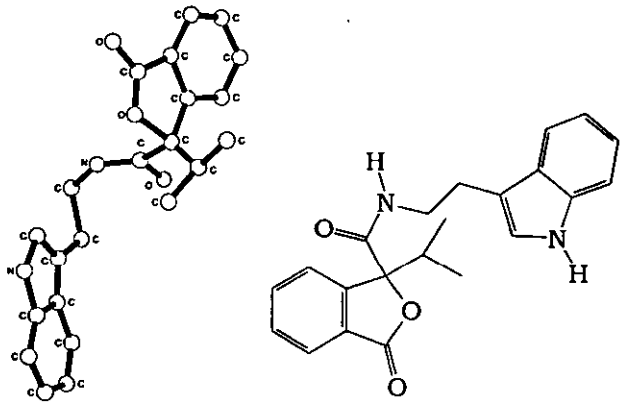
In accordance with the oxidation general method, a stirred solution of 2-benzyl-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.23**) and sodium hydroxide in ethanol (hydrous or anhhydrous) was heated to reflux for a given period of time and gave two products after flash chromatography eluting with EA/LP [1:6] (reaction conditons and yields are listed in **Table Exp. 6.3**). The first product *2-benzyl-4-hydroxy-4-isopropyl-1,2,3,4-tetra hydro-1,3-isoquinoline dione* (**6.9**). The second product *N1-benzyl-1-isopropyl-3-oxo-1,3-dihydro-1-isobenzofurancarboxamide* (**6.7**), mp 143-145 °C from EA/LP : ν_{max} 3366 (broad), 2971, 1773, 1676 and 1598 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.55 (d, 3H, *J* 6.8), 1.13 (d, 3H, *J* 6.8), 2.83 (h, 1H, *J* 6.8), 4.22 (dd, 1H, *J* 5.1, 14.7), 4.57 (dd, 1H, *J* 6.6, 14.7), 7.06 (br.s, 1H, N-H), 7.22-7.31 (m, 5H), 7.56-7.58 (m, 1H), 7.71-7.74 (m, 1H) and 7.83-7.88 (m, 2H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 15.35 (CH_3), 17.76 (CH_3), 35.52 (CH), 43.77 (CH_2), 92.06 (C), 123.71 (CH), 124.61 (C), 125.65 (CH), 128.04 (CH), 128.22 (2 x CH), 128.96 (2 x CH), 130.02 (CH), 135.16 (CH), 137.60 (C), 149.06 (C), 169.30 (C=O) and 169.76 (C=O) ppm; Found: M^+ 309.1363 (12.2%) $C_{19}H_{19}NO_3$ requires 309.1365. HETCOR and COSY experiments support characterisation.

Table Exp. 6.3

No	Starting Material		NaOH		Reaction Time (hours)	Solvent Volume (ml.)	Product yields			
							6.9		**6.7**	
	mg	mmol	mg	mmol			mg	%	mg	%
1	620	2.10	92	2.30	6	65*	non		140	22
2	550	1.90	83	2.10	7	70	non		600	quant.
3	230	0.74	non		5	50	non		non	
4	380	1.30	8	0.20	5	50	non		358	89
5	230	0.74	30	0.75	5	60	non		240	quant.

* Solvent: ethanol/water [5:8]

Oxidation of 2-[2-(1H-3-indolyl)ethyl]-4 -isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione.



6.8

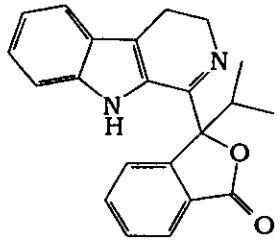
A stirred solution 2-[2-(1H-3-indolyl)ethyl]-4-isopropyl-1,2,3,4-tetrahydro-1,3-isoquinolinedione (**3.24**) (0.20g, 0.58 mmol) and sodium hydroxide (25mg, 0.63 mmol) in ethanol (40 ml) was heated to reflux for 5 hours and gave *N1-[2-(1H-3-indolyl)ethyl]-1-isopropyl-3-oxo-1,3-dihydro-1-isobenzofuran carboxamide*[10, 198] (**6.8**) (0.19g, 91%), mp 187-189 °C from EA/LP: ν_{max} 3406 (broad), 2970, 1771 and 1669 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.56 (d, 3H, *J* 6.8), 1.11 (d, 3H, *J* 6.8), 2.81 (h, 1H, *J* 6.8), 2.94 (t, 2H, *J* 6.9), 3.50-3.69 (m, 2H), 6.72 (br.s, 1H, N-H), 6.91 (d, 1H, *J* 2.0), 7.10-7.13 (m, 1H), 7.19-7.23 (m, 1H), 7.36-7.38 (m, 1H), 7.55-7.60 (m, 2H), 7.71-7.75 (m, 1H), 7.86-7.88 (m, 2H) and 8.17 (br.s, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 15.49 (CH_3), 17.89 (CH_3), 25.70 (CH_2), 35.48 (CH), 40.00 (CH_2), 92.29 (C), 111.67 (CH), 112.77 (C), 118.92 (CH), 119.91 (CH), 122.37 (CH), 122.59 (CH), 123.89 (CH), 124.75 (C), 125.75 (CH),

127.44 (C), 130.12 (CH), 135.30 (CH), 136.82 (C), 149.30 (C), 169.38 (C=O) and 169.95 (C=O) ppm; Found: M^+ 362.1636 (14.0%) $C_{22}H_{22}N_2O_3$ requires 362.1630. HETCOR and COSY experiments support characterisation.

Bischler-Napieralski cyclisation of isobenzofuran carboxamides -General Method.

A magnetically stirred solution of the particular isobenzofuran carboxamide and phosphorus oxychloride (5-10 equivalents) in a given volume of dry acetonitrile was heated to reflux for a given length of time. Subsequently, the reaction mixture was allowed to cool down to room temperature. The reaction was then quenched carefully with diluted ammonia aqueous solution. Then DCM (100 ml) and water (100 ml) were added to the reaction mixture followed by vigorous shaking. The organic layer was then collected and the aqueous layer was further extracted with DCM (100 ml). The combined organic extracts were dried over magnesium sulfate, concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel and/or recrystallisation.

3-(4,9-Dihydro-3H-β-carbolin-1-yl)-3-isopropyl-1,3-dihydro-1-isobenzo furanone.

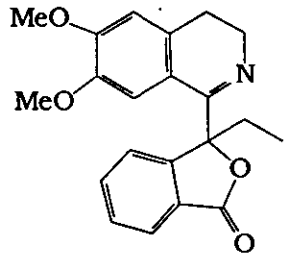


6.10

A stirred solution of N1-[2-(1H-3-indolyl)ethyl]-1-isopropyl-3-oxo-1,3-dihydro-1-isobenzofuran carboxamide (**6.8**) (0.15g, 0.41 mmol) and phosphorus oxychloride (0.61g, 4.0 mmol) in dry acetonitrile (5 ml) was heated to reflux for 3 hours and 30 minutes and gave the title compound (**6.10**) after flash chromatography eluting with EA/LP [1:4] (31mg, 22%), mp 148-149 °C from EA/LP : ν_{max} 3473, 3350 (broad), 2969, 1769 and 1601 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$)

0.77 (d, 3H, *J* 6.8), 1.04 (d, 3H, *J* 6.8), 2.84-2.93 (m, 3H), 3.93-4.05 (m, 2H), 7.16-7.96 (m, 8H) and 9.20 (br.s, 1H, N-H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 16.43 (CH_3), 17.56 (CH_3), 19.40 (CH_2), 37.77 (CH), 48.97 (CH_2), 95.37 (C), 112.75 (CH), 118.66 (C), 120.04 (CH), 120.59 (CH), 125.05 (C), 125.27 (CH), 125.47 (2 x CH), 125.59 (C), 127.00 (C), 129.66 (CH), 134.54 (CH), 136.86 (C), 150.69 (C), 159.67 (C=N) and 170.37 (C=O) ppm; Found: C, 77.27, H, 6.12, N, 7.99 % $C_{22}H_{20}N_2O_2$ requires C, 76.71, H, 5.81, N, 8.14 %; Found: M^+ 344.1524 (1.4%) $C_{22}H_{20}N_2O_2$ requires 344.1525.

3-(6,7-Dimethoxy-3,4-dihydro-1-isoquinolinyl)-3-ethyl-1,3-dihydro-1-isobenzo furanone.



6.11

A stirred solution of N1-(3,4-dimethoxyphenethyl)-1-ethyl-3-oxo-1,3-dihydro-1-isobenzofuran carboxamide (**6.4**) (0.49g, 1.32 mmol) and phosphorus oxychloride (1.0g, 6.54 mmol) in dry acetonitrile (10 ml) was heated to reflux for 4 hours and 20 minutes and gave the title compound (**6.11**) after flash chromato-graphy eluting with EA/LP [1:5] (0.27g, 58%), oil : ν_{max} 2939, 1765 and 1606 cm^{-1}; ^1H nmr (400 M Hz, $CDCl_3$) 0.75 (t, 3H, *J* 7.5), 2.22-2.27 (m, 1H), 2.51-2.60 (m, 3H), 3.58-3.62 (m, 1H), 3.70-3.75 (m, 1H), 3.85 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.66 (s, 1H), 7.39 (s, 1H), 7.49-7.53 (m, 1H), 7.66-7.67 (m, 2H) and 7.86-7.89 (m, 1H) ppm; ^{13}C nmr (100.5 M Hz, $CDCl_3$) 7.91 (CH_3), 26.54 (CH_2), 32.89 (CH_2), 47.72 (CH_2), 56.20 (CH_3, MeO), 56.46 (CH_3, MeO), 93.28 (C), 110.49 (CH), 110.75 (CH), 120.22 (C), 124.96 (CH), 125.40 (CH), 126.20 (C), 129.47 (CH), 133.23 (C), 134.14 (CH), 147.47 (C), 151.01 (C), 151.89 (C), 164.53 (C=N) and 170.64 (C=O) ppm; Found: M^+ 351.1468 (80.5%) $C_{21}H_{21}NO_4$ requires 351.1471. COSY experiment supports characterisation.

References

1. For a review on *N*-acyliminium ions see: Speckamp, W.N.; Hiemstra, H. *Tetrahedron*, **1985**, *41*, 4367-4416.
2. Hiemstra, H.; Speckamp, W.N. In *Comprehensive Organic Synthesis*; Trost, B.M., Flemming, I. Eds; Pergamon, Oxford, **1991**, vol.2, pp 1047-1082.
3. Lee, Y.S.; Kang, D.W.; Lee, S.J.; Park, H. *J. Org. Chem.*, **1995**, *60*, 7149-7152.
4. Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.*, **1996**, *37*, 7841-7844.
5. Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron*, **1996**, *52*, 2603-2628.
6. Kodama, Y.; Okumura, M.; Yanabu, N.; Taguchi, T. *Tetrahedron Lett.*, **1996**, *37*, 1061-1064.
7. Burgess, L.E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.*, **1996**, *37*, 3255-3258.
8. Lee, Y.S.; Lee, J.Y.; Park, H. *Synth. Commun.*, **1997**, *27*, 2799-2812.
9. Heaney, H.; Taha, M.O. *Synlett*, **1996**, 820-822.
10. Heaney, H.; Taha, M.O.; Slawin, A.M.Z. *Tetrahedron Lett.*, **1997**, *38*, 3051- 3054.
11. Heaney, H.; Taha, M.O. *Tetrahedron Lett.*, **1998**, *39*, 3341-3344.
12. Pulvermacher, G. *Chem. Ber.*, **1887**, *20*, 2492-2499.
13. Haworth, R.D.; Perkin, W.H.; Pink, H.S. *J. Chem. Soc.*, **1925**, *127*, 1709-1723.
14. Huffman, J.W.; Miller, E.G. *J. Org. Chem.*, **1960**, *25*, 90-92.
15. D'Sa, A.S.; Deodhar, K.D. *Indian J. Chem. sect.B*, **1980**, *19*, 999-1000.
16. Edwards, O.E.; Marion, L. *J. Am. Chem. Soc.*, **1949**, *71*, 1694-1696.
17. Clemo, G.R.; Swan, G.A. *J. Chem. Soc.*, **1946**, 617-621.
18. Cheng, C.; Tsai, H.; Lin, M. *J. Heterocyclic Chem.*, **1995**, *32*, 73-77.
19. Muchowski, J.M. *Can. J. Chem.*, **1969**, *47*, 857-859.

20. Bowman, R.W.; Coghlan, D.R. *Tetrahedron*, **1997**, *53*, 15787-15798.

21. Motwani, D.C.; Wheeler, T.S. *J. Chem. Soc.*, **1935**, 1098-1101.

22. Drain, D.J.; Howes, J.G.B.; Lazare, R.; Salaman A.M., Shadbolt, R.; Williams, H.W.R. *J. Med. Chem.*, **1963**, *6*, 63-69.

23. Bogdal, D.; Pielichowski, J.; Boroñ, A. *Synlett*, **1996**, 873-874.

24. Biossonnas, R.A.; Guttmann, St.; Huguenin, R.L.; Jaquenoud, P.-A. *Helv. Chim. Acta*, **1958**, *41*, 1867-1875.

25. Gabriel, S. *Chem. Ber.*, **1887**, 1198-1205; Gabriel, S. *Chem. Ber.*, **1886**, 2363-2367.

26. Harriman, B.R.; Shelton, R.S.; Van Campen, M.G.; Warren, M.R. *J. Am. Chem. Soc.*, **1945**, *67*, 1481-1482.

27. Horning, D.E.; Lacasse, G.; Muchowski, J. M. *Can. J. Chem.*, **1971**, *49*, 246-254.

28. Collado, M.I.; Sotomayor, N.; Villa, M-J.; Lete, E. *Tetrahedron Lett.*, **1996**, *37*, 6193-6196.

29. Kutter, E.; Austel, V.; Eberlein, W.; Heider, J. to: Thomae G.m.b.H., Ger. Offen. 2345422 (**1975**), *Chem. Abs.*, **1975**, *83*, 43207d.

30. Kutter, E.; Austel, V.; Eberlein, W.; Heider, J.; Kobinger, W.; Lillie, C. to: Dr. Karl Thomae G.m.b.H., Ger. Offen. 2622690 (**1977**), *Chem. Abs.*, **1978**, *88*, 121001b.

31. Jonsson, N.; Mikiver, L.; Moses, P. to: Aktiebolaget Kabi, Ger. Offen. 2245159, *Chem. Abs.*, **1973**, *78*, 159460g.

32. Powell, R.G.; Smith, C.R.Jr.; Weisleder, D.; Muthard, D.A.; Clardy, J. *J. Am. Chem. Soc.*, **1979**, *101*, 2784-2785.

33. Gramain, J-C.; Troin, Y.; Vallée-Goyet, D. *Tetrahedron*, **1991**, *47*, 7301-7308.

34. Gramain, J-C.; Troin, Y.; Mavel, S.; Vallée-Goyet, D. *Tetrahedron*, **1991**, *47*, 7287-7300.

35. *Some Modern Methods of Organic Synthesis*; Carruthers, W., Cambridge University Press, Cambridge, **1987**, pp 2-3.

36. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, pp 7-8.

37. *Heterocyclic Chemistry*; Joule, J.A.; Mills, K.; Smith, G.F., Chapman and Hall, London, **1995**, p 318.

38. Robertson, D.W.; Krushinski, J.H.; Beedle, E.E.; Wyss, V.; Pollock, G.D.; Wilson, H.; Kauffman, F.; Hayes, J. S. *J. Med. Chem.*, **1986**, *29*, 1832-1840.

39. Semmelhack, M.F.; Bargar, T. *J. Am. Chem. Soc.*, **1980**, *102*, 7765-7774.

40. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, pp 27-28.

41. Anderson, E.P.; Crawford, J.V.; Sherrill, M.L. *J. Am. Chem. Soc.*, **1946**, 68, 1294-1296.

42. Chan, Y.Y.; Li, X.Y.; Zhu, C.; Liu, X.; Zhang, Y.; Leung, H.K. *J. Org. Chem.*, **1990**, *55*, 5497-5504.

43. Zefirov, N.S.; Kuznetsova, T.S.; Kozhushkov, S.I.; Surmina, L.S.; Rashchupkina, Z.A. *J. Org. Chem. USSR (Engl. Transl.)*, **1983**, *19*, 474-480.

44. Haworth, R.D. *J. Chem. Soc.*, **1937**, 1312-1314.

45. Helmut, D.; Kaiser, M. *Spectrochim. Acta*, **1985**, *41a*, 913-924.

46. Review on directed aldol condensation: Mukaiyama, T. *Org. React.*, **1982**, *28*, 203-331.

47. Howarth, R.D.; Pink, H.S. *J. Chem. Soc.* **1927**, 2345-2349.

48. Bailey, A.S.; Swallow, D.L. *J. Chem. Soc.* **1956**, 2477-2482.

49. Elliot, I.W.; Takekoshi, Y. *J. Heterocyclic. Chem.*, **1976**, *13*, 597-599.

50. Cazeau, P.; Duboudin, F.; Moulines, O.; Babot, O.; Dunogues, J. *Tetrahedron*, **1987**, *43*, 2075-2088.

51. *Organic Synthesis: The Role of Boron and Silicon*, Thomas, S.E.; Oxford University Press, Oxford, **1991**, pp 47-48.

52. Frick, U; Simchen, G. *Liebigs Ann. Chem.*, **1987**, 839-845.

53. Kramarova, E.P; Shipov, A.G.; Artamkina, O.B.; Baukov, Y.I. *J. Gen. Chem. USSR (Engl. Transl.)*, **1984**, *54*, 1712-1713.

54. Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron*, **1988**, *44*, 4259-4275.

55. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem Soc.*, **1980**, *102*, 3248-3249.

56. ElGihani, M.; Heaney, H. *Synlett*, **1993**, 433-434.

57. ElGihani, M.; Heaney, H. *Synlett*, **1993**, 583-584.

58. Zerrer, R.; Simchen, G. *Synthesis*, **1992**, *10*, 922-924.

59. Gassman, P. G.; Burns, S. J. *J. Org. Chem.*, **1988**, *53*, 5574-5576.

60. *Spectroscopic Methods in Organic Chemistry*; Williams, D.H; Fleming, I., McGraw-Hill Book Company Europe, London, **1989**, p 135.

61. *Spectroscopic Methods in Organic Chemistry*; Williams, D.H; Fleming, I., McGraw-Hill Book Company Europe, London, **1989**, pp 102-103.

62. Ramsden, C.A.; Sargent, B.J.; Wallett, D. *Tetrahedron Lett.* **1996**, *37*, 1901-1904.

63. Kozhina, N.D.; Krapivin, G.D.; Zavodink, V.E.; Graztsa, T.; Vegh, D.; Chernousenko, L.A.; Badovskaya, L.A. *Khim. Geterotsikl. Soedin.*, **1995**, 135-136.

64. Elliott, J.; Hall, D.; Warren, S. *Tetrahedron Lett.*, **1989**, *30*, 601-604.

65. Beccalli, E.M.; Marchesini, A.; Pilati, T. *Tetrahedron*, **1993**, *49*, 4741-4758.

66. Bryant, W.M.; Huhn, G.F.; Jensen, J.H.; Pierce, M.E. Stammbach, C. *Synth. Commun.*, **1993**, *23*, 1617-1625.

67. Elmorsy, S.S.; El-Ahl, A.A.S; Soliman, H.; Amer, F.A. *Tetrahedron Lett.*, **1996**, *37*, 2297-2298.

68. Uhle, F.C. *J. Org. Chem.*, **1961**, *26*, 2998-3001.

69. Huang, S.J. *J. Chem. Soc., Chem Commun.*, **1968**, 245.

70. Hurbert, J.C.; Steege, W.; Speckamp, W.N.; Huisman, H.O. *Synth. Commun.*, **1971**, *1*, 103-109.

71. Hurbert, J.C.; Speckamp, W.N.; Huisman, H.O. *Tetrahedron Lett.*, **1972**, 4493-4496.

72. Hurbert, J.C.;Wijnberg, B.P.A.; Speckamp, W.N. *Tetrahedron*, **1975**, *31*, 1437-1441.

73. Kohn, H.; Liao, Z.K. *J. Org. Chem.*, **1982**, *47*, 2787-2789.

74. Hough, T.L. *J. Heterocyclic Chem.*, **1989**, *26*, 1523-1525.

75. Flann , C.; Malone, T.; Overman, L.E. *J. Am. Chem .Soc.*, **1987**, *109*, 6097-6107.

76. Kim, G.; Chu-Moyer, M.Y.; Danishefsky, S.J.; Schulte, G.K. *J. Am. Chem. Soc.*, **1993**, *115*, 30-39.

77. Hitchings, G.J.; Thomas, M.D.; Vernon, J.M. *J. Chem. Soc., Perkin. Trans. 1*, **1992**, 895-898.

78. *Advanced Organic Chemistry*; March, J., John Wiley & Sons Inc., New York, **1992**, p 169.

79. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, pp 44-45.

80. *Advanced Organic Chemistry*; March, J., John Wiley & Sons Inc., New York, **1992**, pp 68-69.

81. *Advanced Organic Chemistry*; March, J., John Wiley & Sons Inc., New York, **1992**, p 1208.

82. *Spectroscopic Methods in Organic Chemistry*; Williams, D.H; Fleming, I., McGraw-Hill Book Company Europe, London, **1989**, pp 42-43.

83. Rubido, J.; Pedregal, C.; Espada, M. *Synthesis*, **1985**, 307-309.

84. Roth, E.; Altman, J.; Kapon, M.; Ben-Ishai, D. *Tetrahedron*, **1995**, *51*, 801-810.

85. Fisher, M.; Gunn, B.P.; Um, S.; Jakubowski, A. *Tetrahedron Lett.*, **1997**, *38*, 5747-5750.

86. Traynelis, V.J.; Hergenrother, W.L.; Hanson, H.T.; Valicenti, J.A. *J. Org. Chem.*, **1962**, *27*, 2377-2383; Traynelis, V.J.; Hergenrother, W.L.; Hanson, H.T.; Valicenti, J.A. *ibid.*, **1964**, *29*, 123-129; Traynelis, V.J.; Hergenrother, W.L. *ibid.*, **1964**, *29*, 221-222.

87. *Spectroscopic Methods in Organic Chemistry*; Williams, D.H; Fleming, I., McGraw-Hill Book Company Europe, London, **1989**, pp 92-93.

88. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, pp 14-23.

89. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, p 21.

90. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, p17.

91. Shimizu, M.; Ishikawa, M.; Komoda, Y.; Nakajima, T.; Yamaguchi, K.; Sakai, S.-I. *Chem. Pharm. Bull.*, **1984**, *32*, 1313-1325.

92. Wang, H.; Ganesan, A. *Tetrahedron Lett.*, **1997**, *38*, 4327-4328.

93. Peng, S.; Winterfeldt, E. *Liebigs Ann. Chem.*, **1990**, 313-318.

94. De La Figuera, N.; Alkorta, I.; Garcia-Lopez, M. T.; Herranz, R.; Gonzalez-Muniz, R. *Tetrahedron*, **1995**, *51*, 7841-7856.

95. Ungemach, F.; DiPierro, R. W.; Cook, J. M. *J. Org. Chem.*, **1981**, *46*, 164-168.

96. Konda, M.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.*, **1975**, *23*, 1025-1063.

97. For reviews on 1,2-alkyl shifts in general see: Pocker, Y. in *Molecular Rearrangements*; DeMayo, P. Ed., Interscience Publishers, John Wiley and Sons Inc., New York, **1963**, pp 1-25; Kaupp, G. *Top. Curr. Chem.*, **1988**, *146*, pp 57-98.

98. Warshawsky, A.; Ben-Ishai, D. *J. Heterocyclic. Chem.*, **1970**, 917-921.

99. Kitamura, T.; Harano, K.; Hisano, T. *Chem. Pharm. Bull.*, **1992**, *40*, 2255-2261.

100. Dehnel, A.; Kanabus-Kaminska, J. M. *J. Heterocyclic Chem.*, **1991**, *28*, 317-320.

101. Buckley, T.F.; Rapoport, H. *J. Am. Chem. Soc.*, **1980**, *102*, 3056-3062.

102. *Guidebook to Mechanisms In Organic Chemistry*; Sykes, P., Longman Scientific & Technical, Harlow, **1986**, p 114.

103. Kanemoto, S.; Shimizu. M.; Yoshioka, H. *Tetrahedron Lett.*, **1987**, *28*, 663-666.

104. Bernard, A.M.; Cocco, M.T.; Congiu, C.; Franzone, G.L.; Piras, P.P. *Synthesis*, **1996**, 361-366.

105. Fadel, A.; Salaun, J.; Conia, J.M. *Tetrahedron*, **1983**, *39*, 1567-1574.

106. Ferreri. C.; Ambrosone, M. *Synth. Commun.*, **1995**, *25*, 3351-3356.

107. Chorghade, M.S.; Ellegaard, P.; Lee, E.C.; Petersen, H.; Sørensen, P.O. *Heterocycles*, **1994**, *37*, 783-792.

108. Marshall, J. A.; Ellison, R. H. *J. Org. Chem.*, **1975**, *40*, 2070-2073.

109. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.*, **1979**, *101*, 2738-2739.

110. Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.*, **1996**, *37*, 6173-6176.

111. Ritterskamp, P.; Demuth, M.; Schaffner, K. *J. Org. Chem.*, **1984**, *49*, 1155-1158.

112. For a review on the chemistry of the cyclopropyl group see: Reissig, H-U. in *The chemistry of Cyclopropyl Group* (Part 1); Rappoport, Z. Ed., John Wiley & Sons Ltd., Chichester, **1987**, pp 375-442.

113. Roberts, S.W.; Stirling, C.J.M. *J. Chem. Soc., Chem Commun.*, **1991**, 170-171.

114. Huang, J.J.; Ragouzeos, A.; Rideout, L. *J. Heterocyclic Chem.*, **1995**, *32*, 691-695.

115. For a review on the use of BSA for protection and as reagents in synthesis see: ElGihani, M.T.; Heaney, H. *Synthesis*, **1998**, 357-375.

116. *Organic Synthesis, The Role of Boron and Silicon*; Thomas, S.E., Oxford University Press, Oxford, **1991**, p 51.

117. Lalonde, M.; Chan, T.H. *Synthesis*, **1985**, 817-845.

118. *Organic Synthesis, The Role of Boron and Silicon*; Thomas, S.E., Oxford University Press, Oxford, **1991**, pp 48-49.

119. *Stereoelectronic Effects*; Kirby, A.J., Oxford University Press, Oxford, **1996**, pp 8-9; *Frontier Orbitals and Organic Chemical Reactions*; Fleming, I., John Wiley & Son, London, **1976**, pp 34-41.

120. Trost, B.M.; Ito, N.; Greenspan, P.D. *Tetrahedron Lett.*, **1993**, *34*, 1421-1424.

121. Wijnberg, B.P.; Speckamp, W.N. *Tetrahedron Lett.*, **1980**, *21*, 1987-1990.

122. Gesson, J-P.; Jacquesy, J-C.; Rambaud, D. *Tetrahedron*, **1993**, *49*,

2239-2248.

123. Moeller, K.D.; Rothfus, S.L. *Tetrahedron Lett.*, **1992**, *33*, 2913-2916.

124. Chamberlin, A.R.; Nguyen, H.D.; Chung, Y.L. *J. Org. Chem.*, **1984**, *49*, 1682-1688.

125. Fisher, M.J.; Overman, L.E. *J. Org. Chem.*, **1990**, *55*, 1447-1459.

126. Lessen, T.A.; Demko, D.M.; Weinreb, S.M. *Tetrahedron Lett.*, **1990**, *31*, 2105-2108.

127. Frauenrath, H.; Arenz, T.; Raabe, G.; Zorn, M. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 83-85.

128. Wanner, K. T.; Hofner, G. *Arch. Pharm. (Weinheim)*, **1990**, *323*, 977-986.

129. For reviews and leading references see: *The Isoquinoline Alkaloids*; Shamma, M., Academic Press, New York, **1972**, pp 268-314.

130. V. Preininger in *The Alkaloids*; Manske, R.H.F. Ed., Academic Press, New York, **1975**, *15*, pp 231-236.

131. Jeffs, P.W. in *The Alkaloids*; Manske R. H. F. Ed., Academic Press, New York, **1967**, *9*, pp 41-115.

132. *The Isoquinoline Alkaloids*; Shamma, M., Academic Press, New York, **1972**, pp 305-306.

133. Fukuda, H.; Watanabe, K.; Kudo, Y. *Chem. Pharm. Bull.*, **1970**, *18*, 1299-1304.; Patel, D.G.; Tye, A.; Patil, P.N.; Burkman, A.M.; Beal, J.L. *Lloydia*, **1970**, *33*, 36-42.

134. Chin, K.C.; Chu, H.Y.; Tiang, H.T.; Hsu, P. *Sheng Li Hsuch Pao*, **1962**, *25*, 182-190, *Chem. Abs.*, **1963**, *59*, 13249g.; Hsu, P.; Chin, K.C. *Formakol. Neirotropnykh. Sredstv.*, **1963**, 126-137., *Chem. Abs.*, **1964**, *60*, 13741g.

135. Schmeller, T.; LatzBruning, B.; Wink, M. *Phytochem.*, **1997**, *44*, 257-266.

136. Ckless, K.; Schlottfeldt, J.L.; Pasquak, M.; Moyna, P.; Henriques, J.A.P. *J. Pharm. Pharmacol.*, **1995**, *47*, 1029-1031.

137. McDonald, E. in *Heterocyclic compounds, Isoquinolines*, Grethe, G.

Ed., John Wiley & Sons, New York, **1981**, *38* (Part 1), pp 297-299.

138. McDonald, E. in *Heterocyclic compounds, Isoquinolines*, Grethe, G. Ed., John Wiley & Sons, New York, **1981**, *38* (Part 1), pp 139-274.
139. Kessar, S.V.; Singh, P.; Vohra, R.; Kaur, P.N.; Venugopal, D. *J. Org. Chem.*, **1992**, *57*, 6716-6720.
140. Kametani, T.; Takagi, N.; Toyota, M.; Honda, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2830-2834.
141. Stambach, J.F.; Jung, L. *Tetrahedron*, **1985**, *41*, 169-172.
142. Pandey, G.D.; Tiwari, K. *Tetrahedron*, **1981**, *37*, 1213-1214.
143. Marsden, R.; Maclean, D.B. *Tetrahedron Lett.*, **1983**, *24*, 2063-2066.
144. Shono, T.; Usui, Y.; Mizutani, T.; Hamaguchi, H. *Tetrahedron Lett.*, **1980**, *21*, 3073-3076.
145. Fuganati, C. in *The Alkaloids*; Manske, R.H.F. Ed., Academic Press, New York, **1975**, *15*, pp 83-164.
146. Wildman, W. C. in *The Alkaloids*; Manske R. H. F. Ed., Academic Press, New York, **1968**, *11*, pp 307-405.
147. Fuganati, C.; Mazza, M. *J. Chem. Soc., Chem. Commun.*, **1972**, 239.; Immirzi, A.; Fuganati, C. *J. Chem. Soc., Chem. Commun.*, **1972**, 240.
148. Mondon, A.; Krohn, K. *Chem. Ber.*, **1972**, *105*, 3726-3747.
149. Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc.,Chem. Commun.*, **1984**, 1693-1694.
150. Barbacid, M.; Vazquez, D. *J. Mol. Biol.*, **1974**, *84*, 603-623.; Carrasco, L.; Frenso, M.; Vazquez, D. *FEBS Lett.*, **1975**, *52*, 236-239.
151. Jimenez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.*, **1975**, *60*, 66-70.; Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochim. Biophys. Acta.*, **1976**, *425*, 342-348.; Baez, A.; Vazquez, D. *Biochim. Biophys. Acta.*, **1978**, *518*, 95-103.; Rivera, G.; Gosalbez, M.; Ballesta, J. *Biochem. Biophys. Res. Commun.*, **1980**, *94*, 800-806.

152. Pettit, G.R.; Gaddamidi, V.; Herald, D.L.; Cragg, G.M.; Singh, S. B.; Schmidt, J. M.; Boettner, F.E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.*, **1986**, *49*, 995-1002.

153. Natsukari, H.; Ikeda, H. to: Takeda Chemical Industries Ltd., JPN 03 112967, (**1991**), *Chem. Abs.*, **1991**, *115*, 158988f.

154. Senda, S.; Ohtani, O.; Katho, E.; Nagasaka, M.; Miyake, H.; Fujiwara, K.; Tanaka, M. to: Maruko Pharmaceutical Co. Ltd., FR 2502619, (**1982**), *Chem. Abs.*, **1983**, *98*, 71955.

155. Senda, S.; Ohtani, O.; Katho, E.; Nagasaka, M.; Miyake, H.; Fujiwara, K.; Tanaka, M. to: Maruko Pharmaceutical Co. Ltd., Ger. Offen. 3 211501, (**1982**), *Chem. Abs.*, **1983**, *98*, 198048.

156. Unverferth, K.; Dörre, R.; Körner, B.; Scheibe, H.; Morgenstern, E. *Arch. Pharm. (Weinheim)*, **1991**, *324*, 809-814.

157. Jahangir; Fisher L.E.; Clark, R.D.; Muchowski, J. M. *J. Org. Chem.*, **1989**, *54*, 2992-2996.

158. Beugelmans, R.; Bois-Choussy, M. *Synthesis*, **1981**, 729-731.

159. Rigby, J.H.; Gupta, V. *Synlett*, **1995**, 347-348.

160. Lopes, R.S.C.; Lopes, C.C.; Heathcock, C.H. *Tetrahedron Lett.*, **1992**, *33*, 6775-6778.

161. Mali, R.S.; Kulkarni, B.K.; Shankaran, K. *Synthesis*, **1982**, 329-330.

162. Couture, A.; Deniau, E.; Grandclaudon, P.; Woisel, P. *Tetrahedron*, **1996**, *52*, 4433-4448.

163. Trost, B.M.; Pulley, S. R. *J. Am. Chem. Soc.*, **1995**, *117*, 10143-10144.

164. *Advanced Organic Chemistry*; March, J., John Wiley & Sons Inc., New York, **1992**, p 699.

165. Bailey, E.J.; Elks, J.; Barton, D.H.R. *Proc. Chem. Soc.*, **1960**, 214-215.

166. Bailey, E.J.; Barton, D.H.R.; Elks, J.; Templeton, J.F. *J. Chem. Soc.*, **1962**, 1578-1591.

167. Avramoff, M.; Spinzak, Y. *Proc. Chem. Soc.*, **1962**, 150.

168. Nishio, T. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1717-1720.

169. Yu, Q-S.; Li, Y-Q.; Luo, W-M.; Brossi, A. *Heterocycles*, **1993**, *36*, 1791-1794.

170. Wender, P.A.; Glass, T.E.; Krauss, N.E.; Mühleback, M.; Peschke, B.; Rawlins, D.B. *J. Org. Chem.* **1996**, *61*, 7662-7663.

171. Semple, J. E.; Rydzewski, R. M.; Gardner, G. *J. Org. Chem.*, **1996**, *61*, 7967-7972.

172. *Advanced Organic Chemistry*; March, J., John Wiley & Sons Inc., New York, **1992**, pp 188-189.

173. Peterson, S.; Heitzer, H. *Liebigs Ann. Chem.*, **1978**, 283-288.

174. Wrobel, J.; Dietrich, A. *Heterocycles*, **1994**, *38*, 1823-1837.

175. Flack, J.R; Manna, S. *Tetrahedron Lett.*, **1981**, *22*, 619-620.

176. For a review on Bischler-Napieralski reaction see: Fodor, G.; Nagubandi, S. *Tetrahedron*, **1980**, *36*, 1279-1300.

177. Prager, R.H.; Tippett, J.M.; Ward, A.D. *Austral. J. Chem.*, **1981**, *34*, 1085-1093; Clark, S.I.; Kasum, B.; Prager, R.H.; Ward, A.D. *Austral. J. Chem.*, **1983**, *36*, 2493-2498.

178. Ke-Qing, L.; Gang, J.; Hu, C.; Jian-Hua, X. *Tetrahedron Lett.*, **1998**, *39*, 2381-2384.

179. Bettoni, G.; Carbonara, G.; Franchini, C.; Tortorella, V. *Tetrahedron*, **1981**, *37*, 4159-4164.

180. Iida, H.; Kawano, K.; Kikuchi, T.; Yoshimizu, F. *Yakugaku Zasshi*, **1976**, *96*, 176-179., *Chem. Abs.*, **1976**, *84*, 135898d.

181. Viel, C. *Ann. Chim.*, **1963**, *8*, 515-544.

182. Solomina, L.P.; Grigoryan, R.T.; Markaryan, E.A. *Arm. Khim. Zh.*, **1978**, *31*, 345-348., *Chem. Abs.*, **1978**, *89*, 197265g.

183. Scholz, C. *Helv. Chim. Acta*, **1935**, *18*, 923-933.

184. Perkin, W.H.; Ray, J.N.; Robinson, R. *J. Chem. Soc.*, **1926**, 941-953;

185. Sonn, A; Patschke, E. *Chem. Ber.*, **1925**, *58*, 96-98.

186. Augustin, J.; Austin, W.C.; Boscott, R.J.; Green, S.M.; Worthing, C.R. *J. Med. Chem.*, **1965**, *8*, 356-367.

187. Copp, F.C.; Hodson, H.F. to: Burroughs Wellcome and Co. (U.S.A.) Inc., US 3474134, (**1969**), *Chem. Abs.*, **1970**, *72*, 31478c.; Patent to: Wellcome Foundation Ltd., NL 6508754, (**1966**), *Chem. Abs.*, **1966**, *65*, 2181c.

188. Waefelaer, A.; Pecher, J.; Dubois, A.; Semet, J.; Poultier, P. *Bull. Soc. Chim. Belg.*, **1976**, *85*, 421-425.

189. Bremner, J.B.; Browne, E.J.; Gunawardana, I.W.K. *Austral. J. Chem.*, **1984**, *37*, 129-141.

190. Kuroda, S.; Koyama, S. *Yakugaku Zasshi*, **1943**, *63*, 382-387.

191. Brenner, M.; Sailer, E.; Kocher, V. *Helv. Chim. Acta*, **1948**, *31*, 1908-1914.

192. Holland, D.O.; Nayler, J.H.C. *J. Chem. Soc.*, **1953**, 285-287.

193. Brunner, H.; Kroiss, R.; Schmidt, M. *Eur. J. Med. Chem. - Chim. Ther.*, **1986**, *21*, 333-338.

194. Spies, J.R. *J. Am. Chem. Soc.*, **1948**, *70*, 3717-3719.

195. Berg, C.P.; Rose, W.C.; Marvel, C.S. *J. Biol. Chem.*, **1930**, *85*, 207-218.

196. Lenz, G.R. *J. Org. Chem.*, **1976**, *41*, 2201-2207.

197. Ninomiya, I.; Naito, T.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2257-2260.

198. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited in the Cambridge Crystallographic data centre.