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# Synthesis and Pharmacological Studies on a novel series of Mast Cell-stabilising Tetrahydronaphthalenes and related compounds

by

**James William Barlow**

A thesis presented to the University of Dublin for the degree of Doctor of Philosophy

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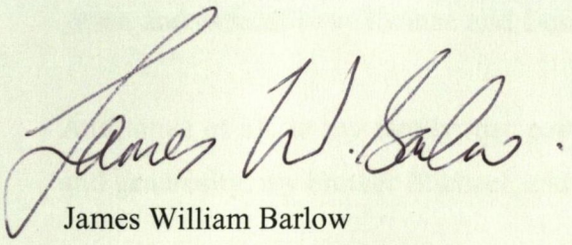
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Trickling water, if not stopped, will become a mighty river.

Confucius

## Summary

The purpose of this thesis was the design, synthesis and pharmacological screening of a novel series of tetrahydronapthalene molecules for mast cell-stabilising activity. The introductory Chapter commences with a discussion of mast cells and basophils as key effectors of the allergic response. The molecular mechanisms through which these cells are activated and degranulated are discussed, together with a synopsis of the chemical mediators of allergy released from them, both upon degranulation and those synthesised *de novo*. The consequences of pathological activation of the allergic cascade are then outlined, with an overview of both currently available and investigational therapies for these conditions, with especial emphasis on molecules derived from natural sources. The rationale for the screening of the target molecules is introduced, with reference to previously tested indan molecules and dimers thereof, and the biological activities of indan and tetrahydronaphthalene molecules reported to date is reviewed. Chapter 1 concludes with a discussion of the various pharmacological models of allergic disease that are utilised in candidate drug screening programmes.

Chapter 2 presents the synthetic strategy developed in the generation of a series of novel 4-(cyclopentylamino)-1,2,3,4-tetrahydro-1-naphthalenones, and the preliminary screening results for mast cell-stabilising activity. The importance of the both the fused hydroaromatic tetralin ring and the cyclopentyl substituent within the molecules was emphasised by the parallel synthesis and testing of two compounds bereft of these key functionalities.

Chapter 3 investigates the effect of expansion of the cyclopentyl ring system contained in the molecules of Chapter 2 to a six-membered carbocycle, and the effect of insertion of a double bond into the cyclohexyl substituent. The synthetic routes to these compounds and the mast cell stabilising results of both the 4-(cyclohexylamino)-1,2,3,4-tetrahydro-1-naphthalenones and the 4-(2-cyclohexenylamino)-1,2,3,4-tetrahydro-1-naphthalenones are discussed. Chapters 2 & 3 also contain the synthesis and preliminary testing of a reduced number of cyclopentyl- and cyclohexenyl-substituted 9-amino-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones.

Chapter 4 contains the synthetic strategies employed in the production of amine-linked dimer compounds of tetrahydronaphthalenes and indanones, investigating the effects of ring size and positioning of the link on pharmacological activity. Of the many ring-substituted derivatives that could be envisaged, development of suitable synthetic routes towards some methoxy-substituted analogues and a chroman analogue were selected for investigation, and the preliminary mast cell-stabilising results for these molecules are also presented.

Chapter 5 details the preparation and testing of a novel group of tetrahydonapthalene-based secondary alcohols and related ring-opened compounds, all lacking the nitrogenous functionality contained in the molecules of Chapters 2-4. The selection of a key acid-catalysed aldol condensation forms the central synthetic focus of the Chapter.

Chapter 6 is concerned with the pharmacological screening of the novel molecules of Chapters 2-5 for anti-allergic activity. The methodological aspects of the mast cell stabilisation assay employed in the preliminary screens of Chapters 2-5 are discussed. The results of dose-response studies for selected compounds using a range of elicitors of mast cell degranulation is presented, followed by the results and discussion of *in vivo* rat studies using the Passive Cutaneous Anaphylaxis (PCA) experimental method. Finally, the results of an anti-inflammatory assay employing Arachidonic acid-induced murine ear oedema are presented.

Chapter 7 details the development of an asymmetric synthetic route for the preparation of individual isomeric forms of the most active series of compounds, as identified in Chapter 6.

The Experimental Section contains the details of all synthetic methods employed in the generation of the novel molecules of this thesis, and complete spectral data.

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**List of abbreviations**

| | |
|---|---|
| AA | Arachidonic acid |
| $Ac_2O$ | Acetic anhydride |
| ACN | 1,1′-Azobis (cyclohexane carbonitrile) |
| ADTN | 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene |
| AND | Anaphylactic degranulation |
| BOC | Butyloxylcarbonyl |
| Btk | Bruton's tyrosine kinase |
| cAMP | Cyclic adenosine monophosphate |
| Con A | Concanavalin A |
| CTMC | Connective tissue mast cell |
| DCM | Dichloromethane |
| DEPT | Distortionless enhancement by polarisation transfer |
| DMAP | 4-Dimethylamino pyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulphoxide |
| DSCG | Disodium cromoglycate |
| ER | Endoplasmic reticulum |
| Fcε | Complement-binding region of Immunoglobulin E |
| Fcγ | Complement-binding region of Immunoglobulin G |
| FcεRI | High-affinity receptor for IgE |
| GCMS | Gas chromatography-mass spectroscopy |
| HBSS | Hepes balanced salt solution |
| HEPES | *N*-2-hydroxy-ethylpiperazine-*N*′-2-ethanesulphonic acid |
| HMBC | Heteronuclear multiple bond correlation |
| HMPA | Hexamethylphosphoric triamide |
| HMQC | Heteronuclear multiple quantum correlation |
| HRMS | High resolution mass spectroscopy |
| IgE | Immunoglobulin E |
| IR | Infrared |
| IL | Interleukin |
| ITAM | Immunoreceptor tyrosine-based activation motif |
| $K^+t$-$BuO^-$ | Potassium *tert*-butoxide |
| LDA | Lithium di-isopropylamide |

| | |
|---|---|
| Lyn | v-yes-1 Yamaguchi sarcoma viral related oncogene homolog |
| M | Molar |
| MAP | Mitogen-activated protein kinase |
| MCM | Mast cell medium |
| MC-SAb | Mast cell-sensitising antibody |
| $MC_T$ | Mast cell, tryptase positive |
| $MC_{TC}$ | Mast cell, tryptase and chymase positive |
| $MGlu_{1a}$ | Group 1 metabotropic glutamate receptors |
| MMC | Mucosal mast cell |
| Moc | Methyl oxy carbonyl |
| NBS | *N*-bromosuccinimide |
| NMR | Nuclear magnetic resonance |
| *N*,*N*-DIPEA | *N*,*N*-Di-isopropylethylamine |
| NOE | Nuclear Overhauser effect |
| 7-OHDPAT | 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin |
| *o*-PT | *ortho*-Phthalaldehyde |
| PAL | Phenylalanine ammonia lyase |
| PCA | Passive cutaneous anaphylaxis |
| $PI_3$ | Phosphoinositol-3-OH-kinase |
| $PIP_3$ | Phosphatidylinositol [3,4,5] triphosphate |
| PLC-γ | Phospholipase gamma |
| PMD | Piecemeal degranulation |
| PPA | Polyphosphoric acid |
| PS | Physiological saline |
| *p*-ToSH | *para*-Toluene sulphonic acid |
| PVG | Phthalimidovinylglycinol |
| RBL-1 | Rat basophilic leukaemia cell line 1 |
| RPMC | Rat peritoneal mast cell |
| R.T. | Room temperature |
| SCF | Stem cell factor |
| SH2 | Src homology domain 2 |
| SIRP | Signal regulatory protein |
| Sl | Murine steel mutation |
| Slg | Surface immunoglobulin |
| SOCC | Store-operated calcium channel |

| | |
|---|---|
| SRS-A | Slow reacting substances of anaphylaxis |
| Syk | Spleen tyrosine kinase |
| TBAT | Tetrabutylammonium (triphenylsilyl)difluorosilicate |
| *t*-BuOH | *tert*-butanol |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMB-8 | 3,4,5,-trimethoxy benzoic acid diethylamino octyl ester |
| TMSOTf | Trimethylsilyltrifluoromethanesulphonate |
| TNFα | Tumour necrosis factor alpha |
| TOCSY | Total correlation spectroscopy |
| TPA | 12-*O*-tetradecanoylphorbol-13-acetate |
| UV | Ultraviolet |
| W | Murine dominant white spotting mutation |

## Introduction

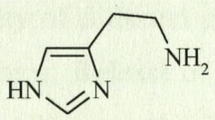
Throughout the ages, manifestation of allergic phenomena has afflicted society. An understanding of the allergic response, and the consequent pathophysiological sequelae, have never been so pertinent as in today's society, as the incidence of allergen-induced disease is increasing at an alarming rate on a global scale. Epidemiological evidence has demonstrated this fact to be true for diseases such as rhinitis[1], atopic dermatitis[2] and asthma[3]. In the case of asthma, it is estimated that more than 150 million people worldwide have the disease, and that 180,000 fatalities result each year from asthmatic attacks[4]. Ireland has one of the top four incidences of asthma in the world, with 15% of children and 5% of adults affected.[5]

The reason for the increase is unknown, although several theories have been proposed. One of these is the so-called 'Hygiene Hypothesis', which proposes that the increase in both autoimmune and allergic diseases is due to a reduction in the prevalence of childhood infections[6]. In support of this theory, it is of interest to note the disproportionate increases in allergic disease in Western society. Factors such as increased use of antibiotics and cleaner dwelling environments may be partly responsible. Two mechanisms have been proposed to explain the Hygiene Hypothesis. The first is that the decrease in childhood infections results in a decrease in immunoregulatory cytokine production, while the second is attributed to the increase to lack of exposure to endotoxin, a potent immunostimulant. Exposure to endotoxin is more frequent in rural environments, and children from farming backgrounds have been shown to develop less allergic pathologies[7]. Another interesting correlation is the lower incidence of allergy in less developed nations where helminthic infections are more prevalent. However, many additional factors may influence the likelihood of an individual developing allergic disease. Some of these may include environmental factors, such as levels of pollution, additional microbial components such as heat-shock protein and beta 1,3-glucan; genetic factors; socio-economic status; climate and dietary factors. Whatever the reason(s), there is a clear need for continued research into both the pathophysiology of allergic disease and the development of new pharmacological agents. Due to the multi-faceted nature of the allergic cascade, many pharmacological targets are available. Of the many participating cells and molecules that play a role in allergy, the focus of this work was primarily the mast cell, and its principal mediator, histamine.

## 1.1 Mast cells and Basophils as key effectors of the allergic response

### 1.1.1 Growth and heterogeneity[8]

Mast cells were originally described in 1878 by Ehrlich, who observed their metachromatism in histological specimens. These cells have a pivotal role in allergic disease. The term 'mast cell' is derived from the German *Mastzellen*, which means 'well-fed', and refers to the abundant granular contents (Figure 1.1), which are not the result of phagocytic behaviour as originally thought, but comprise endogenously synthesised mediators, primarily histamine (**1.1**), stored in association with a proteoglycan matrix.




Histamine (**1.1**)

They are primarily connective tissue cells, and are also found free on serosal and mucosal surfaces, especially in the airways, conjunctiva, dermis, gastrointestinal mucosa and perivascular tissues. A connective tissue mast cell is shown below:

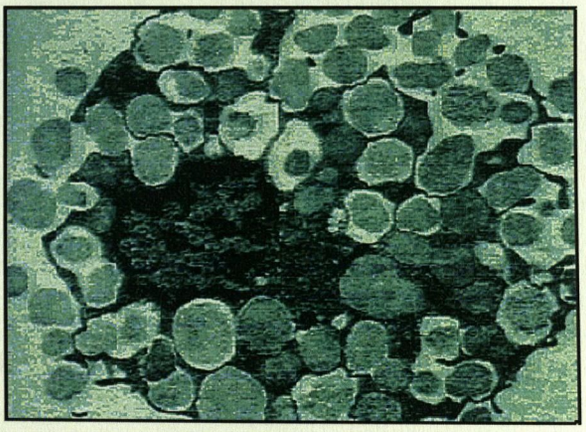


**Figure 1.1 Connective tissue mast cell**

Morphological features of note include the numerous cytoplasmic granules; these granules may be of various patterns, including crystal, scroll, particle and mixed granules, which are clearly visible on electron microscopy.

Indeed, cells from different tissues exhibit differences in preponderance among granule types, and may aid identification of tissue origin[9]. Also present are vesicles, mitochondria, a single-lobed nucleus and non-membrane bound osmiophilic lipid bodies, which may store or generate eicosanoid products, the relative amounts of which can also vary with site of origin. The roles of mast cells may include, apart from generation of inflammatory mediators; regulation of the microcirculation, gastric secretion and part of the IgE-mediated response to helminth infestation.

The basophil (Figure 1.2) is the circulating counterpart of the mast cell, and is the rarest leucocyte, comprising only 0.5% of total leucocytes. Although mast cells circulate in blood, they can also infiltrate tissues. The heterogeneity of mast cells cannot be over-stressed; this is due to their capability of different phenotypic expression. However, all types contain histamine in granular form. Release of this amine following cross-linking of the IgE molecules found on the high-affinity cell surface receptors (FcεRI) is responsible for allergic reactions. Basophils also constitutively express FcεRI. Other cells may participate in IgE-mediated reactions via the FcεRII receptors on their cell surfaces.

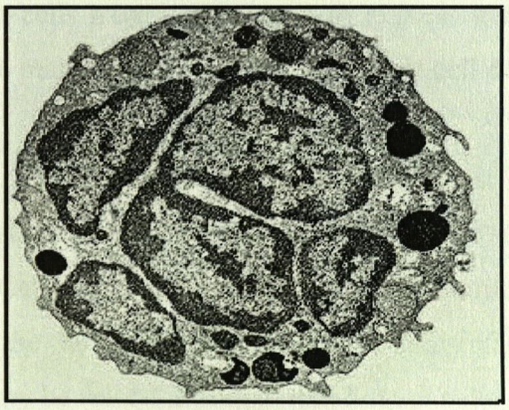


**Figure 1.2 Peripheral blood Basophil**

The prominent features of these cells are the multi-lobed nucleus with extensive chromatin condensation, the granular contents, predominantly particulate in nature, and the multiple broad surface processes. An additional key feature is the presence of Charcot-Leyden crystals within the particulate matrix of the granules[10]. These crystal proteins exhibit lysophospholipase activity, although their biological role has not been defined.

Both mast cells and basophils derive independently from the multipotential haematopoietic stem cell. Although granule content and function of mast cells and basophils are similar, the former resemble macrophages in terms of nuclear characteristics, surface antigens and differentiation, whereas basophils more closely resemble neutrophils[11].

Mast cells complete their differentiation outside the haematological system, in connective or mucosal tissue, and some retain the ability to proliferate, even after degranulation caused by IgE-dependent or independent mechanisms. Regulation of mast cell development varies within species: in mice, T-cell derived cytokines, notably IL-3 and IL-4, have important roles, notably following parasitic infestation. In addition, fibroblasts regulate constitutive development. In humans, fibroblast-dependent mechanisms appear more important. Development of basophils appears T-cell mediated, primarily via IL-3. Mast cell growth factors have been identified from mutant strains of rodents, including the murine W/W (Murine dominant white spotting mutation) and Sl/Sl$^{d}$ (Murine steel mutation), which lack mast cells due to deficiencies at chromosomes 5 and 10 respectively. These loci code for the c-kit proto-oncogene, a transmembrane receptor with tyrosine kinase activity, and the c-kit ligand, stem cell factor (SCF). SCF has been identified in humans, and human mast cells have been shown to express increasing amounts of kit as they mature, reflecting the many functions of SCF on mast cell development and survival.

Phenotypic differences are readily identifiable in rodent mast cells, and this has led to identification of two distinct populations, connective tissue mast cells (CTMCs) and mucosal mast cells (MMCs)[12]. The former are richer in histamine and are present in skin and peritoneum, while the latter are prominent in intestinal mucosa and have less histamine. Phenotypes may be traced in rodent and human cells via protease content. Mast cells have also been classified into two subtypes based on their neutral protease content; those containing tryptase only ($MC_T$), or those containing, (in addition to tryptase), chymase, carboxypeptidase and cathepsin G ($MC_{TC}$).

$MC_T$ and $MC_{TC}$ cells can also be distinguished by ultrastructural means, according to granule morphology, as mentioned above: T mast cells contain granules with discrete scrolls, whereas TC mast cells have more uniform granules with poorly-defined scrolls and lamellae.

Interestingly, patients with AIDS show selective reductions in $MC_T$ populations, whereas $MC_{TC}$ levels are largely unaffected[13]. This may imply different pathways of development for both phenotypes, the former being T-cell dependent.

An alternative hypothesis for the development of heterogenous mast cell populations includes the presence of circulating mast cell precursors that differentiate selectively depending on tissue microenvironment, including cytokines, cells and extracellular milieu. This has been demonstrated by transferring either MMCs or CTMCs to sites rich in the other phenotype, whereby phenotypic change was seen to occur. Heterogeneity is also evidenced by histochemical methods, whereby different mast cell populations display different optimum pH to show granule metachromasia and different stabilities to formalin fixation.

As will be noted later (Chapter 6), mast cell populations also show disparities in reactivities to certain degranulatory stimuli, such as Compound 48/80; for example, rat mucosal mast cells are refractory to this agent, mouse peritoneal mast cells are much less responsive than those of the rat, and guinea pig mast cells are uniformly unresponsive. In humans, only skin mast cells show a significant response to Compound 48/80.

## 1.2 The IgE molecule

The IgE molecule, discovered by Ishizaka in 1966[14], is an immunoglobulin of 190,000 molecular weight, and is heterotetrameric in nature. It consists of two identical heavy and two identical light chains, the heavy chains are both designated $\varepsilon$, while the light chains are either $\kappa$ or $\lambda$, thus the assembled molecule is termed either $\varepsilon_2\ \kappa_2$ or $\varepsilon_2\ \lambda_2$. Disulphide bonds stabilise the dimeric structure. The domains of the antibody variable region are involved in antigen binding, while the constant region domains of the heavy chain are responsible for such biological functions as complement fixation and antibody binding to the Fc$\varepsilon$RI. A schematic diagram of the IgE molecule is shown in Figure 1.3.

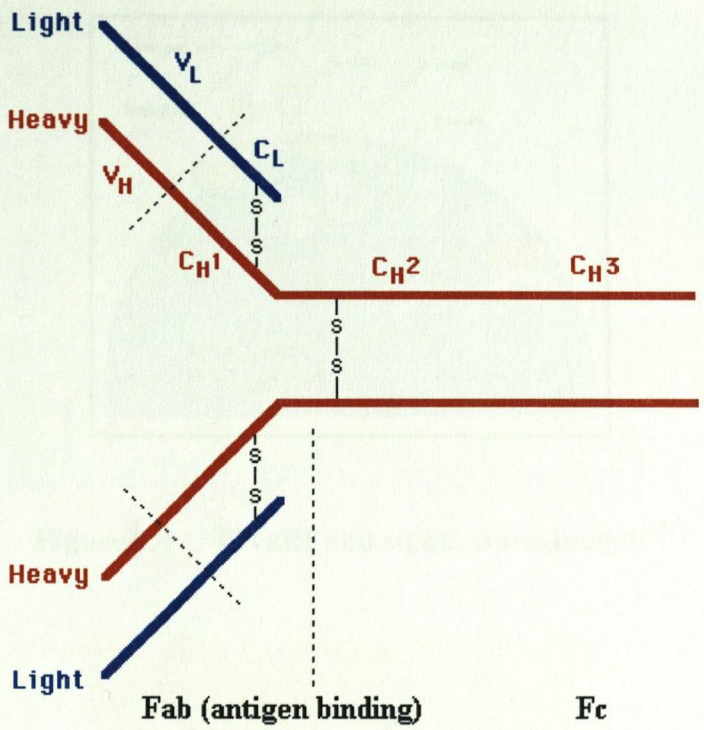



**Figure 1.3 A schematic representation of Immunoglobulin E**

On entering the body, allergens are recognised by slg (surface immunoglobulin) on β-lymphocytes. The β-lymphocyte, under the stimulus of interleukins, proliferates and differentiates into plasma cells that generate and secrete IgE against epitopes of the allergen. The half-life of the IgE molecule is 2.5 days.

## 1.3 The high-affinity FcεRI

Degranulation of mast cells and basophils is mediated through their high-affinity membrane receptors for IgE ($K_d \sim 1 \times 10^{-9}$M). These receptors are tetrameric in composition [$\alpha\beta(\gamma)_2$]. Stabilization within the membrane is primarily via hydrophobic interactions. The two γ units are linked via a disulphide bridge. The FcεRI shows considerable homology with one of the three forms of FcγRI. A diagrammatic representation of the receptor is depicted in Figure 1.4, while a theoretical model of the α-subunit is shown in Figure 1.5.

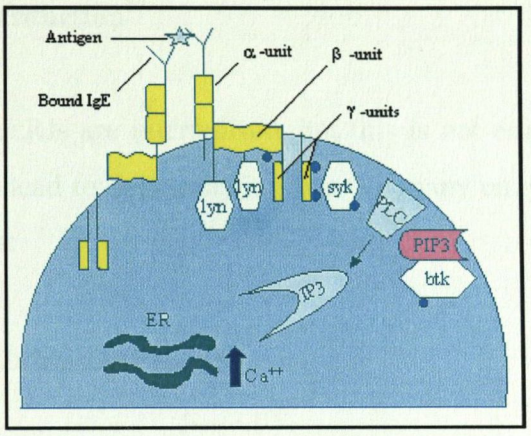



**Figure 1.4 FcεRI and signal transduction**[15]

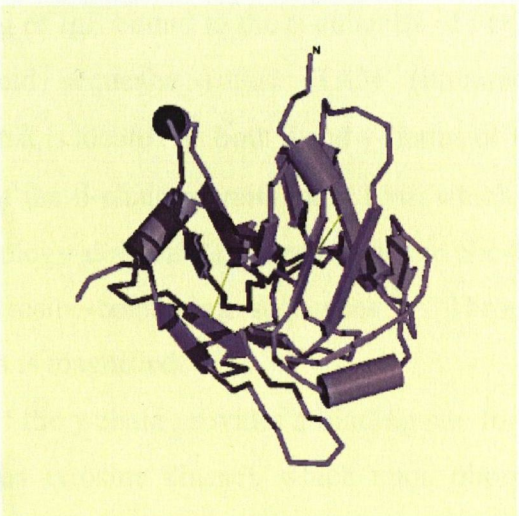



**Figure 1.5 α-subunit of FcεRI**[16]

The α subunit (Figure 1.5) contains the high-affinity binding site for IgE, and several sites for potential *N*-glycosylation. The β unit has four membrane-spanning domains with both termini on the cytoplasmic side of the membrane, while the γ subunits have a single transmembrane domain. The critical event in receptor stimulation is aggregation of the receptors themselves. Only a small proportion of the available receptors, are required, upon aggregation, to induce a maximal response. Using chemically cross-linked IgE, it has been demonstrated that dimeric, trimeric or higher oligomeric forms of IgE can all induce secretion from mast cells[17].

### 1.3.1 FcεRI signal transduction[18]

Upon aggregation, the FcεRIs are internalised, but this is not essential for degranulation. The complex events that lead to degranulation involve many enzymic reactions, and may be summarised as follows:

Steps involved in FcεRI signal transduction

- An enzyme of the Src family of tyrosine kinases, called Lyn (v-yes-1 Yamaguchi sarcoma viral related oncogene homolog), is constitutively associated with the β-chain of the FcεRI.
- Upon cross-linking of IgE bound to the α-subunits of FcεRI, Lyn phosphorylates a special amino acid sequence called ITAM (immunoreceptor tyrosine-based activation motif) that is located on both β and γ-chains of FcεRI.
- Phosphorylation of the β-chain recruits more Lyn, which can associate by its SH2 domain (Src homology domain 2), a region of the Src-family protein that binds phosphorylated tyrosine-containing sequences[19]. Through this mechanism the signal transduction is magnified.
- Phosphorylation of the γ-chain provides a binding site for the cytoplasmic tyrosine kinase, Syk (spleen tyrosine kinase), which upon phosphorylation by Lyn, and possibly through autophosphorylation, becomes activated.
- Inhibitory signals to these processes are also present, in the form of signal regulatory proteins (SIRPs), which cause downregulation through catalysis of dephosphorylation reactions.
- Activated Syk phosphorylates kinases including $PI_3$ (phosphoinositol-3-OH-kinase), which results in generation of $PIP_3$ (phosphatidylinositol [3,4,5] triphosphate), and its association with another tyrosine kinase, Btk (Bruton's tyrosine kinase) allows association of Btk with the plasma membrane. (To date, Btk has been identified in mice, but not human cells.)
- Other enzymes thought to be important following Syk activation include MAP kinase (mitogen-activated protein kinase), protein kinase C and Phospholipase C γ (PLC-γ).

- Upon Btk activation, PLC-γ is phosphorylated by Syk and generates inositol trisphosphate ($IP_3$) which causes $Ca^{2+}$ release from the endoplasmic reticulum (ER).
- Depletion of intracellular $Ca^{2+}$ stores activates store-operated calcium channels (SOCC) and allows $Ca^{2+}$ influx. This is aided by increased membrane fluidity through methylation of phospholipids.
- $Ca^{2+}$ influx promotes activity within the cytoskeleton, causing microtubule assembly and contraction of microfilaments. Disassembly of actin-myosin complexes facilitates granule contact with the cell membrane.
- FcεRI activation also results in a rise in cyclic adenosine monophosphate (cAMP), which mediates phosphorylation of the granule membrane proteins, altering their permeability.
- Swelling of the granules aids fusion of granule and plasma membranes, followed by release of granule contents.

Non-immunological releasers of histamine such as the lectin Concanavalin A (Section 5.2.3.1), are multivalent and cause degranulation of mast cells in a similar manner.

## 1.4 Patterns of degranulation[11]

Degranulation of mast cells occurs via one of two morphological patterns, termed piecemeal degranulation (PMD) and anaphylactic degranulation (AND).

### 1.4.1 Piecemeal Degranulation

This is the most commonly witnessed degranulatory event of mast cells *in vivo* in many diseases, e.g. contact allergies, Crohn's disease and melanoma. It is characterised by the presence of non-fused, partially empty and empty granules in the cytoplasm. It is also apparent in basophils *in vivo* and *in vitro*. Materials are transported from the granules to the cell surface by vesicular transport without granule extrusion. This form of degranulation may evolve into AND if intravesicular channels form. Cells can recover following PMD.

### 1.4.2 Anaphylactic Degranulation[9]

AND involves rapid IgE-stimulated degranulation via degranulation chambers, and/or direct extrusion of the granule contents through multiple plasma membrane pores. Cells following AND possess amplified surface folds. Cells may also recover following AND. To date, this form of degranulation has only been observed in mast cells *in vivo*, and not in basophils.

## 1.5 Mediators of allergy and inflammation

Upon degranulation, both mast cells and basophils secrete a plethora of chemicals into the extracellular environment. These mediators may be sub-divided into two broad classes; the pre-formed mediators and those only synthesised after cellular activation.

### 1.5.1 Pre-formed mediators

Principal among these is histamine (**1.1**), the most important tissue amine. Histidine decarboxylation, catalysed by the enzyme histidine decarboxylase, generates histamine, which is stored at acidic pH in secretory granules. On release, it is rapidly metabolised by histamine *N*-methyltransferase or histaminase, to methylhistamine or imidazole acetic acid, respectively. Further metabolism follows, by conjugation and deamination. The pathways of histamine metabolism in various tissues (with special emphasis on gastric mucosa) and the enzymic differences between species have been highlighted by Lorenz[20]. Histamine exerts its biological actions via $H_1$, $H_2$ and $H_3$ receptors, leading to the following effects: via $H_1$: venule permeabilization via endothelial cell contraction, stimulation of intestinal and bronchial smooth muscle contraction and mucus secretion; via $H_2$: stimulation of gastric parietal acid secretion, immune modulation and endothelial cell stimulation; and via $H_3$, neuromodulation. A pathway depicting the formation and metabolism of histamine is shown in Figure 1.6.

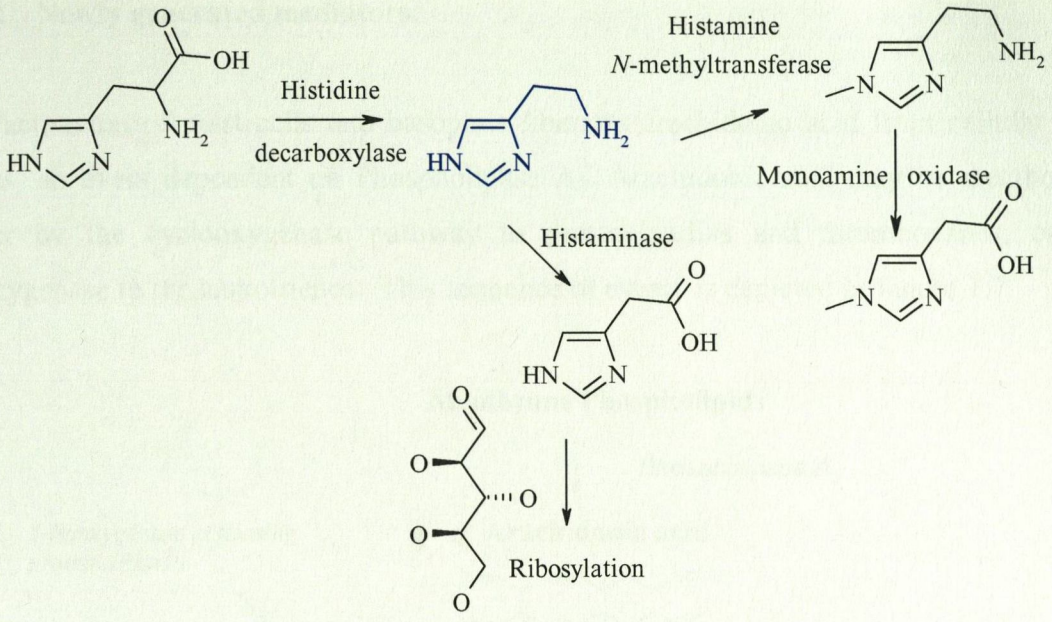



**Figure 1.6 Histamine formation and metabolism**

In addition to histamine, proteoglycans are also present in the granules, of highly sulphated composition. It is the staining of these granules that allows histological identification of these cells. Proteoglycans present include heparin and chondroitin sulphates A and E, and may be important in aiding the sequestration of histamine and the enzymic contents of mast cells and basophils within the granules. Studies with radiolabelled [$^{35}$S] have allowed the isolation of native heparin from rat peritoneal cells, both *in vitro* and *in vivo*[21]. The functions of the proteoglycans may include stabilisation of released tryptase, and expression of their anticoagulant, anticomplement and other activities.

The final important class of preformed mediators are the neutral proteinases, such as tryptase, chymase, carboxypeptidase and cathepsin G. These exist at greater levels than the acid hydrolases also found within human and rodent mast cells, and, as aforementioned, are used as markers to distinguish mast cells from basophils and mast cell subpopulations from each other. The biological importance of tryptase and chymase remains incompletely elucidated, but potential roles include fibrinogen degradation and generation of C3a for the former, and activation of an interleukin-1b precursor for the latter.

### 1.5.2 Newly generated mediators

The activation of mast cells and basophils liberates arachidonic acid from cellular lipid stores, an event dependent on Phospholipase $A_2$. Arachidonic acid may be metabolised either by the cyclooxygenase pathway to prostaglandins and thromboxanes, or via lipoxygenase to the leukotrienes. This sequence of events is depicted in Figure 1.7.

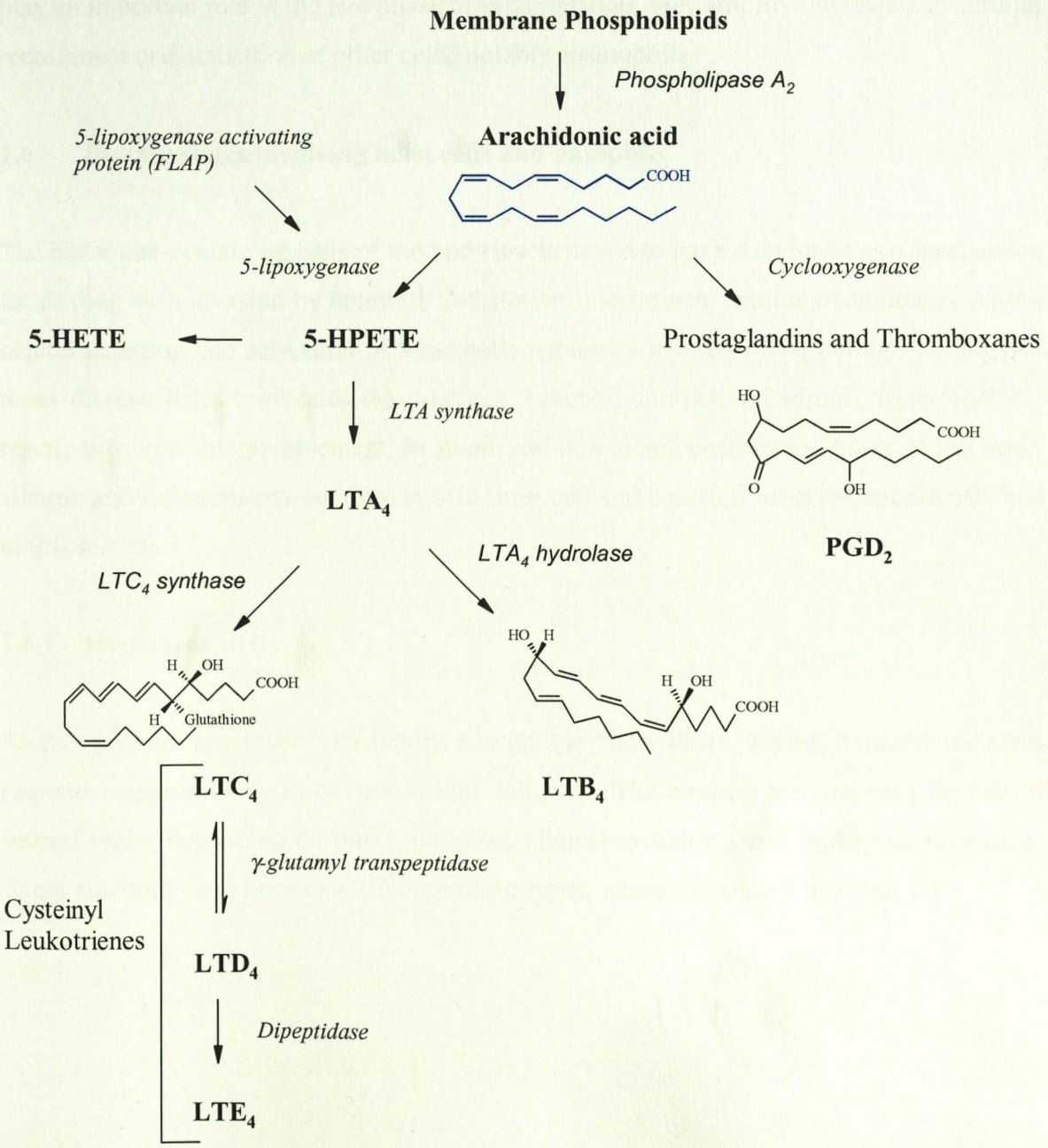



**Figure 1.7 Metabolism of arachidonic acid**

Prostaglandins and thromboxanes are responsible for vasodilation and inhibition of platelet aggregation during the inflammatory response, whereas leukotrienes cause increased venule permeability and contraction of smooth muscle.

Upon activation, mast cells and basophils produce a broad range of cytokines. These include tumour necrosis factor α (TNF-α), interleukins 3, 4, 5, 6, 8, 10, 13 and 16, various growth factors and other peptides. Cytokines released after IgE-mediated cell activation play an important role in the late phase of inflammation; they amplify the response through recruitment and activation of other cells, notably eosinophils.

## 1.6 Disease states involving mast cells and basophils

The histamine-containing cells of the body are believed to have developed as a mechanism for dealing with invasion by helminth and similar infestations, and the evolutionary reason behind inappropriate activation of these cells remains a mystery. The pathophysiology of many disease states implicates the mast cell, basophil and derived stimuli, from localised reactions to systemic involvement, in atopic and non-atopic conditions. Some of the many allergic and inflammatory conditions with mast cell and basophil involvement are outlined in this section.

### 1.6.1 Hypersensitivity

Atopic persons are those genetically susceptible individuals whose immune defences respond inappropriately to environmental antigens. The ensuing reaction may be one of several types, depending on onset, duration, clinical symptoms and biological mediators. These reactions have been classified into four types, which are shown in Table 1.1.

**Table 1.1 Gell and Coombs classification of hypersensitivity reactions**

| Reaction Type | Name | Onset Time | Mechanism | Examples |
|---|---|---|---|---|
| Type I | IgE-mediated | 2-30 min | Cross-linking of IgE bound to mast cells causes mediator release | Systemic anaphylaxis, localised anaphylaxis, e.g. hay fever, asthma, eczema |
| Type II | Antibody-mediated cytotoxic hypersensitivity | 5-8 hr | Cell destruction through complement activation by antibodies targeted against cell surface antigens | Blood transfusion reactions, autoimmune haemolytic anaemia |
| Type III | Immune complex-mediated hypersensitivity | 2-8 hr | Deposition of antigen – antibody complexes in tissue, causing complement activation and inflammation. | Arthus reaction, rheumatoid arthritis, glomerulonephritis, systemic lupus erythematosus. |
| Type IV | Cell-mediated hypersensitivity | 24-72 hr | Sensitised T cells release cytokines that activate macrophages or T cells, causing cellular damage | Contact dermatitis, graft rejection |

The most common reactions, primarily involving histamine as mediator after its release from activated mast cells and basophils, are Type I reactions. Systemic anaphylaxis is the most serious and life-threatening example of this type, and requires adrenaline treatment followed by corticosteroids and antihistamines, to counteract both the dramatic drop in cardiac output and blood pressure, and the massive mucus secretion in gut and lung, caused by systemic histamine release. Both β-tryptase and histamine levels in the blood are markedly elevated in this disorder.

Localized reactions depend on the site of entry of the offending antigen. Cutaneous reactions include urticaria, with itching, wheal and flare and erythema, and atopic dermatitis. Other skin disorders with mast cell involvement include bullous pemphigoid, psoriasis, scleroderma and fibrosis[22]. Seasonal allergic rhinitis is characterised by early degranulation of mast cells in nasal mucosa and epithelium. Asthma is one of the most common diseases of modern society, and is increasing in frequency[3]. It is characterised by variable airflow obstruction and bronchial hyperresponsiveness.



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Initially considered to be a disorder involving primarily bronchoconstriction, the chronic inflammatory nature of the disease is now appreciated. Although mediator release from mast cells contributes significantly to its pathophysiology, the importance of other cell types such as the airway smooth-muscle cell should be recognised. Indeed, these two cell types may act in concert to orchestrate an asthmatic attack[23]. Mast cells and other inflammatory cells are all present in higher levels in asthmatic lung tissue than in normal subjects. A recent report compares the number of tryptase-positive mast cells in airway smooth muscle of patients with asthma and eosinophilic bronchitis; the asthmatic patients had five times the number of tryptase-positive mast cells than either the patients with eosinophilic bronchitis or normal controls[24].

Current therapies for asthma include inhaled corticosteroids and $\beta_2$-agonists; it is interesting to note that apart from their primary action on β-adrenergic receptors in the lung, through which they mediate bronchodilation, $\beta_2$-agonists have other effects. They strongly inhibit the release of histamine and other mediators from human mast cells, including those of lung and skin, and, given orally to rats, can significantly inhibit passive cutaneous anaphylaxis[25].

The relatively recent development of clinically useful leukotriene-receptor antagonists (Section 1.7.4) as adjunctive therapy in asthma also reflects mast cell involvement in this condition. Despite these observations, the exact role of the mast cell in asthma remains a contentious topic. Apart from the conditions in which IgE-mediated degranulation of mast cells play a central role, other diseases involving abnormal proliferation or functioning of mast cells and basophils are known.

### 1.6.2 Mastocytosis

This disease is characterised by the abnormal accumulation of mast cells in skin (cutaneous mastocytosis) and other organs (systemic mastocytosis). It may be indolent or aggressive, and may be associated with a haematological disorder such as leukemia. Diagnostic features include elevated tryptase levels and spindle-shaped mast cells in marrow biopsies[26]. Symptoms include nausea, pruritis and bone pain. Oral therapy with sodium cromoglycate is often useful, despite its poor oral bioavailability; other agents that have been tried include α-interferon.

### 1.6.3 Cutaneous basophil hypersensitivity[11]

This is the term given to the invasion from blood into tissues of basophilic leucocytes during delayed-onset cellular immune reactions. These reactions are erythematous but non-indurated, as compared to classical delayed hypersensivity reactions following adjuvant-containing immunisations, e.g. Freund's complete adjuvant. The histological profile of the two reactions is also markedly different, with a much higher percentage of basophils in the former. Basophil infiltration occurs in many species, under experimental and pathological circumstances, which in humans include a wide variety of illnesses, including contact allergies, eczema, herpes, Crohns disease, ulcerative colitis, conjunctivitis and lymphatic carcinomas. Piecemeal degranulation is a key degranulatory characteristic of these cells.

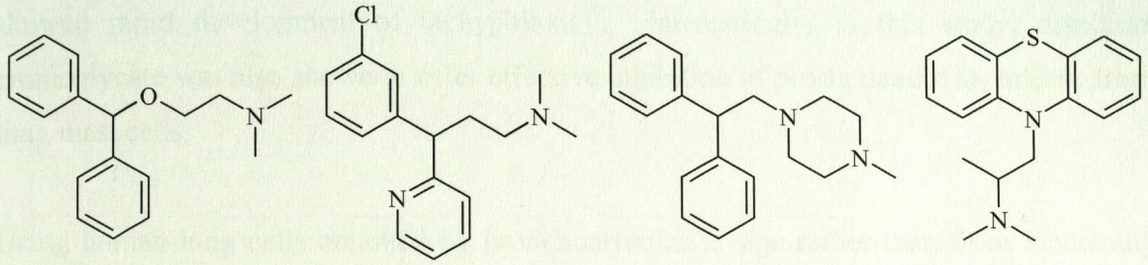
## 1.7 Current therapies for allergic disease

The term 'allergic disease' is a term inclusive of many different pathologies, affecting the organism both at a local and systemic level. The biochemical mechanisms through which allergic reactions are made manifest are discussed in Section 1.9. Treatments are complicated by the heterogeneity of the key cell evoking the allergic response, the mast cell, and development of novel therapies is often hampered by the difficulty of widespread availability of certain mast cell populations. The mast cell is by no means, however, the only cell involved in allergic responses; other key cells include its circulating counterpart, the basophil, and many other leucocytes and tissue cells. Many of the drugs in current use are believed to work at more than one site of action, although there is a trend towards more targeted therapies.

### 1.7.1 Histamine antagonists

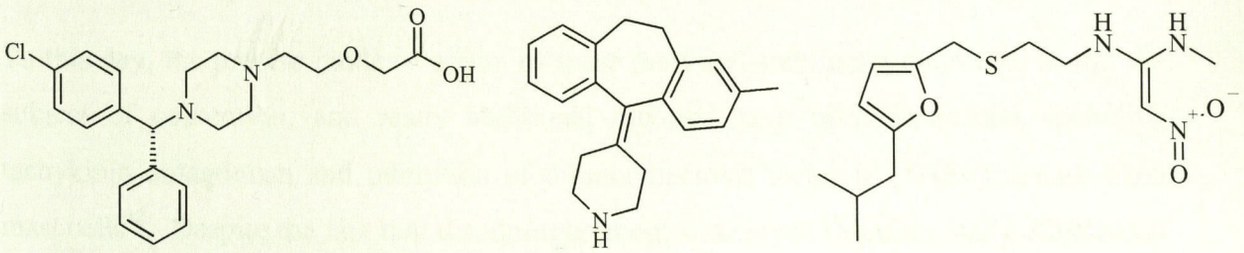
The actions of histamine, one of the earliest recognised mediators of allergy, was an obvious target for pharmacological intervention. Histamine $H_1$-antagonists were easily screened for activity using the guinea pig ileal preparation, and several drug candidates were launched, many of which are still in clinical use.

These include the ethanolamine derivatives, such as diphenhydramine (**1.2**), the alkylamines, typified by chlorpheniramine (**1.3**), the piperazines, such as cyclizine (**1.4**), and the phenothiazines, including promethazine (**1.5**).



Diphenhydramine (**1.2**) Chlorpheniramine (**1.3**) Cyclizine (**1.4**) Promethazine (**1.5**)

Many of the antihistamines continue to be widely used in the treatment of allergic disorders, recent years having seen the launch of more potent derivatives, including levocetirizine (**1.6**, the *R* isomer of cetirizine), and desloratidine (**1.7**), the main active metabolite of loratidine. In recent years, the diversity of histamine receptor subtypes in gastric and brain tissues has led to development of specific antagonists for each receptor subtype; this may explain why the actions of histamine as a mediator of allergy are not fully obliterated by $H_1$ receptor antagonists alone, but require concerted therapy with $H_1$ and $H_2$ antagonists[27]. A typical $H_2$ antagonist, ranitidine (**1.8**), is shown below:



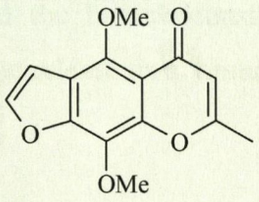
Levocetirizine (**1.6**) Desloratidine (**1.7**) Ranitidine (**1.8**)

### 1.7.2 Mast cell-stabilisers

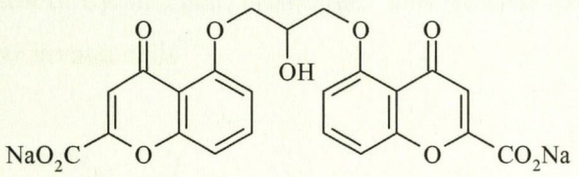
In 1967, following fortuitous studies on compounds with structural similarity to khellin (**1.9**), disodium cromoglycate (DSCG) (**1.10**) was launched as the first of a new therapeutical class, the mast cell-stabilisers[28]. Disodium cromoglycate can inhibit both passive cutaneous anaphylaxis in the rat and the release of histamine from rat peritoneal

cells induced by 48/80[29]. Using enzymatic and mechanical methods of dispersion, Church *et al.* demonstrated that disodium cromoglycate and similar anti-allergic drugs caused weak inhibition (<35% at 100-1000μM) of histamine release from human lung cells, although all anti-allergic drugs tested, unlike the more potent β-agonist, salbutamol, showed rapid development of tachyphlaxis[30]. Interestingly, in this study, disodium cromoglycate was also shown to offer effective inhibition of prostaglandin $D_2$ release from lung mast cells.

Using human lung cells obtained by bronchoalveolar lavage rather than from lobectomy specimens, Leung *et al.* demonstrated a dose-dependent inhibition of anti-IgE-induced histamine release using both disodium cromoglycate and nedocromil[31] (*vide infra*). In a comparison with collagenase-digested parenchymal lung tissue, Leung showed the phenomenon of tachyphylaxis to occur only in the former preparation, which may partly explain the usefulness of these drugs in clinical practice.



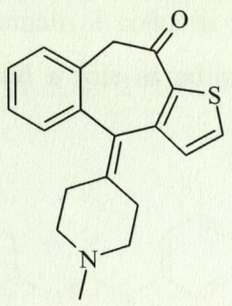

Khellin (**1.9**)




Disodium cromoglycate (DSCG) (**1.10**)

To this day, the precise mode of action of these mast cell-stabilising molecules is still the subject of contention, and many additional theories have been forwarded, including tachykinin antagonism and inhibition of tumour necrosis factor α (TNFα) release from mast cells[32]. Despite the fact that disodium cromoglycate is not therapeutically effective in all patients, and has mainly an adjunctive role in asthma, its excellent safety profile has made it especially useful in this disease, especially in children. It also has a therapeutic role in diseases such as mastocytosis and allergic conjunctivitis.

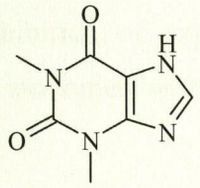
Many newer mast cell-stabilisers have been developed, and although studies *in vitro* have shown consistently higher activity than disodium cromoglycate, results in the clinic have been disappointing. A notable example of this is lodoxamide (**1.9**), a dioxamic acid, which was 2,500 times more active than disodium cromoglycate in rat studies[33], and, despite oral



Ketotifen (**1.13**)

### 1.7.3 Phosphodiesterase inhibitors

The phosphodiesterase inhibitors such as theophylline (**1.14**) remain an adjunctive therapy in asthmatic patients, and do possess some mast cell-stabilising properties, inhibiting both antigen-induced $^{45}Ca$ uptake and histamine release from rat peritoneal cells at a concentration of 1mM[39]. In human experimental models, theophylline (at concentrations up to 2.8mM) has prevented histamine release induced by anti-IgE or Substance P from basophils and chopped lung, and Compound 48/80-induced histamine release from sliced skin[36].

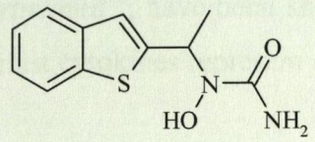


Theophylline (**1.14**)

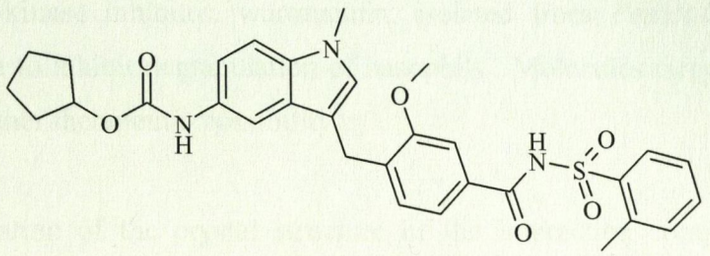
### 1.7.4 Leukotriene antagonists

Among the mediators synthesised following activation of mast cells, and also from neutrophils, eosinophils and alveolar macrophages, are the leukotrienes, formerly termed slow-reacting substances of anaphylaxis (SRS-A). These arachidonic acid metabolites are unsaturated fatty acids, and are formed via the action of 5-lipoxygenase (Figure 1.7). Their actions include chemotaxis, increased mucus secretion and permeability of blood vessels, and bronchoconstriction. Following the realisation of the importance of these inflammatory mediators in asthmatic attacks, molecules to inhibit this cascade were developed, including the 5-lipoxygenase inhibitor, zileuton (**1.15**), and the leukotriene receptor antagonists, including montelukast and zafirlukast (**1.16**)[40].

Although elevated liver enzymes remain a concern with these treatments, notably with zileuton, the latter agents have found a role as adjunctive therapy, notably in the early response to allergen challenge



Zileuton (**1.15**)



Zafirlukast (**1.16**)

### 1.7.5 Corticosteroids

Corticosteroids, such as budesonide, beclomethasone and fluticasone remain a cornerstone of asthmatic and allergic treatment schedules. This is despite their non-specific action, well-documented side-effect profile, especially after oral administration, and their poor patient acceptability. Non-compliance and incorrect use of inhaled medications are additional features that complicate their use. Most of the anti-inflammatory effects of corticosteroids are mediated by inhibition of expression of inflammatory genes, by interaction of glucocorticoid receptor monomers with the relevant transcription factors.

## 1.8 Potential future targets for anti-allergic therapies

In recent years, the many advances in elucidation of the complex mechanistic aspects of the allergic reaction have spawned intense interest in the development of novel therapies.[41] At present, perhaps the most exciting development in anti-allergic treatments is the potential of monoclonal anti-IgE antibodies[42]. One of these, omalizumab, is presently undergoing clinical trials in allergic rhinitis and asthma[43]. It has been shown to reduce free serum IgE, basophil-bound IgE, and the number of basophil receptors, but requires subcutaneous administration. As IgE synthesis is T-cell-dependent, modulated primarily via soluble interleukin-4 (IL-4), prevention of this signalling system by either anti-IL-4 antibodies or IL-4 antagonists may also present a pharmacological target[44].

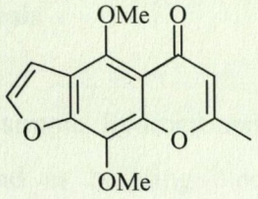
Signal transduction inhibitors to kinases prevent phosphorylation reactions, thus interrupting the allergic cascade, although selectivity may be a problem. Certain molecules, such as the syk inhibitor piceatannol, a stilbene isolated from *Cerbera manghas* (Apocynaceae)[45], and the $PI_3$-kinase inhibitor, wortmannin, isolated from *Penicillium wortmannii*[46], have been shown to inhibit degranulation of basophils. Molecules targeted against cytokines represent another therapeutic possibility.

Following the recent identification of the crystal structure of the interaction complex between IgE and its high-affinity receptor[47], it is hoped that this may lead to rationally designed inhibitor molecules. Another novel idea involves the administration of a bifunctional Fcγ-Fcε fusion protein that cross-links high affinity FcεRI receptor molecules on mast cells and basophils with the FcγRII inhibitory receptor also found on these cells, and thereby inhibits IgE-mediated degranulation[48]. This molecule can inhibit release of histamine from human basophils *in vitro*, and *in vivo* using a chimeric mouse expressing human FcεRIα. It has also been shown to inhibit Syk phosphorylation.

## 1.9 Natural products with anti-allergic properties

A diverse array of naturally occurring molecules has demonstrated anti-allergic activity both *in vitro* and *in vivo*, from simple compounds to complex structures. Lack of complete understanding of the molecular mechanisms at which many of these molecules act has hampered structure-activity studies or molecular modelling approaches, and screening of natural products for novel immunomodulating compounds remains an important focus for many research groups. In addition, many of the established drugs in clinical use for the treatment of allergic diseases are non-specific and have significant side-effect profiles.

One of the prototype drugs in the treatment of allergic disease was the benzo-pyrone khellin (**1.9**), isolated initially from the Egyptian plant *Amni visnaga* and used as an anti-asthmatic[49], and although clinical application was limited due to toxicological considerations, further studies led to the discovery of the synthetic compound disodium cromoglycate.




Khellin (**1.9**)

A wide range of compounds from natural sources possess the ability to inhibit the release of histamine from mast cells, including the microbial-derived immunosuppressants Cyclosporin[50] and Tacrolimus[51]. The ginkgolides, terpenoid molecules isolated from *Ginkgo biloba* (Gingkoaceae), have platelet activating factor antagonist properties, and have been investigated as a standard extract for asthma and other inflammatory and allergic disorders and also in immune disorders such as endotoxic shock and graft rejection[52]. Isocoumarins, phthalides and stilbenes isolated from *Hydrangea macrophylla* SERINGE var. *thunbergii* MAKINO, included in the Japanese Pharmacopoeia XIII have been evaluated for inhibitory activity on histamine release from rat peritoneal mast cells[53]. Six flavonoid glycosides, isolated from the aerial parts of *Mentha piperita* L., have been screened for anti-allergic properties[54]. Of the six, luteolin-7-*O*-rutinoside showed a potent inhibitory effect on Compound 48/80 and antibody-antigen-induced histamine release from rat peritoneal mast cells, and also caused a dose-related inhibition of intranasal provocation with allergen.

Many plant extracts have also been tested with positive results, including the water-soluble fractions of *Terminalia chebula* (Combretaceae)[55], *Rehmannia glutinosa* (Scrophulariaceae)[56] and *Salvia miltiorrhiza* (Labiatae)[57].

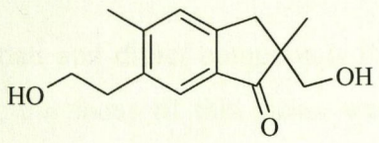


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## 1.10 Rationale and Aims of Thesis

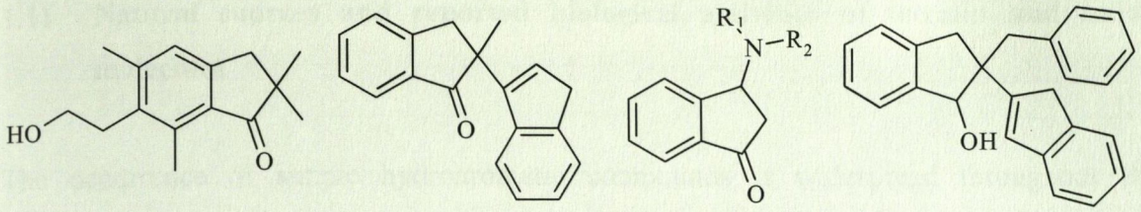
The diversity and abundance of simple hydroaromatic compounds in nature, both as terminally elaborated products and as building blocks for more complex secondary metabolites is ample evidence of the importance of these molecular types. Although many of these molecules have been isolated and characterised to date, there still remains a paucity of information on their potential wealth as pharmacological agents. Based both on the documented ethnopharmacological uses of certain hydroaromatic molecules in the treatment of allergic and inflammatory disorders, and also on previous work in the fields of indanone chemistry and pharmacology, it was decided to embark upon a programme to elucidate the potential of tetralin and tetralone derivatives, and dimers thereof, as novel anti-allergic agents.

The historical exploitation of fern species for their phytomedicinal properties has prompted much interest in their pharmacologically active constituents. Among the metabolites of *Pteridium aquilinum* (Pteridaceae) was isolated a novel group of sesquiterpene indane compounds, termed the pterosins[58]. Since their first isolation, the pterosins have been isolated from many genera of the Pteridophyta, and also from fungi (*Cyathus bulleri*)[59]. Their chemical structure was determined in 1971[60], and an example, Pterosin A (**1.17**), is shown below. The pterosins also occur as glucosides, principally as 2'-*O*-β-D-glucosides; these derivatives are termed pterosides.




Pterosin A (**1.17**)

In light of both the traditional uses of ferns[61], and the reported potential of synthetic anti-spasmodic indane compounds as anti-asthmatic agents[62], a synthetic study to generate a series of novel indanes was performed in the Department[63]. This study yielded several monomeric and dimeric indanes with smooth muscle relaxant properties and mast cell-stabilising activity. Further investigations led to the synthesis and study of aminoindan derivatives, which were evaluated for mast cell-stabilising and anti-inflammatory activity[64]. Several of these indan derivatives have been patented[65]. Some examples of the structural types referred to in references 63-65 are shown below:




$R_1$ = Cyclopentyl or Indanyl
$R_2$ = Alkyl or Acyl

**(1.18)** **(1.19)** **(1.20)** **(1.21)**

Pterosin Z (**1.18**) was found to possess potent smooth muscle relaxant properties, while the dimeric compound (**1.19**) inhibited Compound 48/80-induced histamine release from rat peritoneal mast cells by 18%, when tested at a concentration of 5μg $ml^{-1}$. Several *N*-cyclopentyl and *N*-indanyl derivatives of compound (**1.20**) were potent inhibitors of Compound 48/80-induced histamine release (*N*-alkylated derivatives), whereas some *N*-amido derivatives of the cyclopentyl-substituted indanone showed activity as anti-inflammatory agents in the arachidonic acid-induced mouse ear oedema assay.

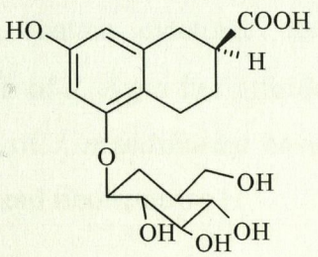
The benzylated indane dimer compound (**1.21**) caused a dose-dependent inhibition of $CaCl_2$-induced contractions of isolated guinea pig ileum, in the concentration range $10^{-7}$-$10^{-4}$M. In addition, it caused 89% inhibition of Compound 48/80-induced histamine release from rat peritoneal mast cells. In an *in vivo* animal model of asthma, the compound protected animals from an asthmatic response following antigen (ovalbumin) challenge.

In view of the potential of indan and dimer compounds thereof as potential anti-allergic and anti-inflammatory agents, the focus of this thesis was the investigation of whether expansion of the alicylic component of the indan nucleus would enhance or reduce the desired pharmacological activity. These aims were addressed via the synthesis of novel monomeric and dimeric hydroaromatic compounds based primarily on the tetralin ring system, and preliminary pharmacological screening of the target compounds using *in vitro* and *in vivo* anti-allergic models.

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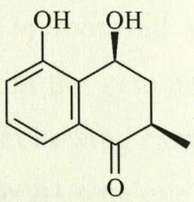
## 1.11 Natural sources and reported biological activities of tetralin and indan molecules

The occurrence of simple hydroaromatic compounds is widespread throughout the botanical spectrum, encompassing representatives from many genera. Of the many hydroaromatics, tetralin and indan derivatives were of especial relevance to this study. As discussed above, the indanes are found in both fern and fungal sources. Tetralin compounds and derivatives thereof are also found in diverse sources throughout the plant kingdom. The Australian rain forest tree *Aceratium megalospermum* (Elaeocarpaceae) contains the cytostatic tetralin glucoside aceratioside (**1.22**)[66].

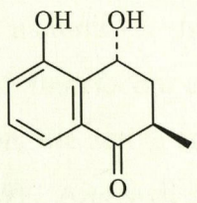



Aceratioside (**1.22**)

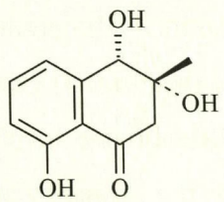
In Vietnamese folk medicine, the leaves of the climbing *Ancistrocladus cochinchinensis* (Ancistrocladaceae) are used traditionally for their diuretic, antifebrile and antiphlogistic actions[67]. The plant has yielded tetralone and naphthoquinone compounds, the former including the hydroxy, methyl-substituted structures (**1.23-1.25**) below:




(**1.23**)



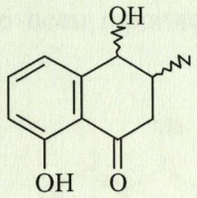

(**1.24**)




(**1.25**)

In addition to these novel compounds, this plant also contains the commonly occurring acetogenic tetralone compound, isoshinanolone (**1.26**), which has been found in numerous plants from five other families; the Iridaceae, Plumbaginaceae, Ebenaceae, Nepenthaceae, and Dioncophyllaceae[68].

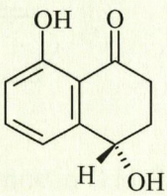
Upon isolation from *Habropetalum dawei* (Dioncophyllaceae), (+-) isoshinanolone was found to possess fish-stunning activity, an effect that is traditionally utilised in Sierra Leone.




Isoshinanolone (**1.26**)

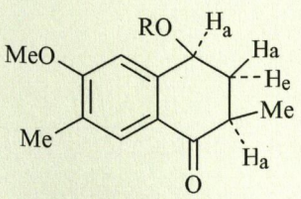
(*cis* and *trans* forms are both found in nature)

Trees of the walnut family, *Juglans* (Juglandaceae) have also yielded tetralone compounds. The roots of *J. mandshurica* contain cytotoxic compounds, including α-tetralone glucosides[69], while the stem-bark of *J. regia* has afforded the α-tetralone derivative (-)-regiolone (**1.27**)[70]. Constituents of *J. mandshurica* have also demonstrated inhibition of HIV type 1 reverse transcriptase and ribonuclease H[71].

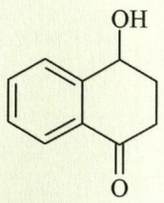



(-)-Regiolone (**1.27**)

The Ghanaese plant *Pararistolochia flos-avis* contains another cytotoxic tetralone, named flossonol (**1.28**), in root and stem material[72]. In Bolivia, the Chimanes Indians use poultices made with the stem bark of *Ampelocera edentula* (Ulmaceae) to treat cutaneous leishmaniasis[73]. Following extraction, the active constituent was identified as the simple tetralone, 4-hydroxy-1-tetralone (**1.29**). Although anti-leishmanial activity was similar to the reference compound antimony (V), the tetralone works via generation of free radicals and is both cytotoxic and carcinogenic.




Flossonol (**1.28**)

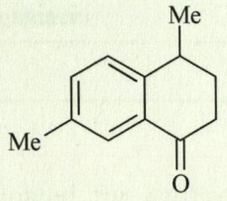



4-hydroxy-1-tetralone (**1.29**)



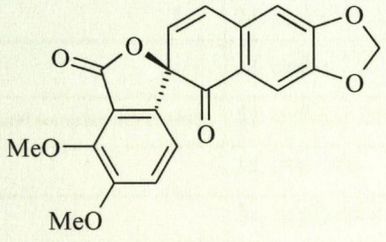
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From amongst the secondary metabolites of *Cyperus rotundus*, a common member of the flora of Thailand and used traditionally to treat malaria, was isolated 4,7-dimethyl-1-tetralone (**1.30**), which had a reported $EC_{50}$ of 8.62 x $10^{-5}$M against *Plasmodium falciparum*[74]. This tetralone has also been reported as a constituent of oil of lavender, *Lavandula angustifolia*.




4,7-dimethyl-1-tetralone (**1.30**)

From the bark of *Xanthoxylum arnottianum* Maxim. (Rutaceae) was isolated the spiro compound arnottin II (**1.31**), composed of a 3,4-dehydro-1-tetralone and a phthalide moiety[75].



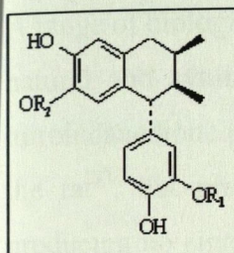

Arnottin II (**1.31**)

Apart from constituting the framework of the isolated tetralin and tetralone compounds discussed above, these six-membered hydroaromatic ring systems form an integral part of an important class of plant secondary metabolites, the lignans. Aryl-tetralin and tetralone lignans are widespread in nature, and cover an impressive spectrum of biological activity. Some of these compounds are contained in Tables 1.2-1.4.



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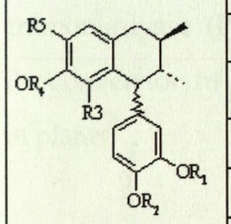
**Table 1.2 Aryltetralins (1.32-1.35) of *Larrea* spp[76,77].**



| Compound Name | Species | $R_1$ | $R_2$ |
|---|---|---|---|
| 4,4',5-trihydroxy-2,7'-cyclolignan (7', 8R, 8'R) | *Larrea tridentata* | H | H |
| 3'-demethoxyisoguaniacin | *Larrea divaricata* | H | Me |
| Di-O-demethylisoguaiacin | *Larrea tridentata* | OH | H |
| Norisoguaicin | *Larrea divaricata* | Me | H |

Norisoguaicin (**1.35**) has been evaluated for antibacterial activity. *Myristica* spp. also contain many aryltetralin lignans, many of which also occur in other genera:

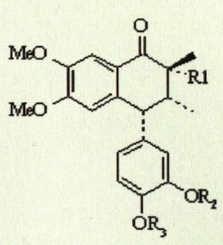
**Table 1.3 Aryltetralins (1.36-1.40) of the Myristicaceae[78,79,80,81].**



| Compound Name | Species | $R_1$ $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| Otobaphenol | *M. otoba* | $-CH_2-$ | H | H | OMe |
| Isogalcatin | *M. otoba* | $-CH_2-$ | H | Me | OMe |
| Otbain (methyls have stereochemistry inverted) | *M. otoba, M. simarum* | $-CH_2-$ | $-OCH_2-$ | | H |
| Guaiacin | *M. fragrans* | Me H | H | H | OMe |
| Cogayanin | *M. cagayensis* | $-CH_2-$ | H | $-OCH_2-$ | |

Of the many aryltetralone lignan-containing plants, certain genera are notably rich sources, including *Aristolochia*, *Schisandra* and *Myristica*, the latter yielding cagayanone (**1.41**) and otobanone (**1.42**), the α-tetralone derivatives of cagayanin and otobain respectively. The aryltetralones of *Aristolochia chilensis* are summarised in Table 1.4.

**Table 1.4 Aryltetralones (1.43-1.48) of *Aristolochia chilensis*[82]**



| Compound Name | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| Aristochilone | H | H | Me |
| Aristoligone | H | Me | Me |
| Aristotetralone | H | $-CH_2-$ | |
| Aristotetralol (benzylic alcohol form) | H | $-CH_2-$ | |
| Aristosynone (methyls have stereochemistry inverted) | H | Me | Me |
| Hydroxyaristotetralone | OH | $-CH_2-$ | |

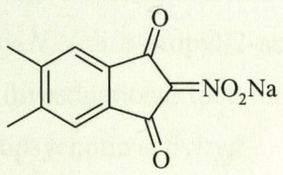


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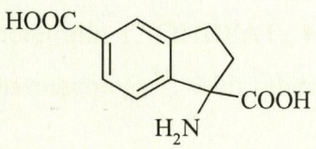
## 1.12 Biological activities of synthetic indan and tetralin compounds

A range of biological activities has been reported for indane compounds. In addition to the natural and synthetic mast cell-stabilising compounds discussed in previous sections, nitroindanedione (**1.49**) has been shown to inhibit immediate hypersensitivity reactions in the rat[83], but proved disappointing in a controlled trial of ulcerative colitis in man, producing no significant improvement in symptoms or sigmoidoscopic findings, although it did improve the histological appearance of rectal biopsies during treatment[84]. The simple amine 2-aminoindan hydrochloride (**1.50**) has been evaluated as an analgesic, and found to have weak activity[85].

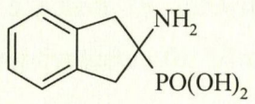
(R,S)-1-aminoindan-1,5-dicarboxylic acid (**1.51**) is a selective antagonist of group 1 metabotropic glutamate receptors ($mGlu_{1a}$) and has neuroprotective properties[86]. The synthetic 2-aminoindan-2-phosphonic acid (**1.52**) is a specific inhibitor of phenylalanine ammonia-lyase (PAL), a key enzyme in the biosynthesis of lignin monomers, catalysing the conversion of phenylalanine to cinnamic acid, and is used in studies of cell wall genesis in plants[87].




**(1.49)**

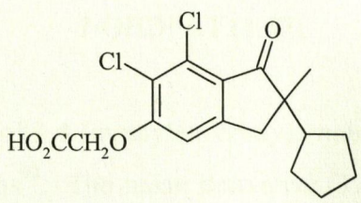



**(1.51)**




**(1.52)**

The cyclopentyl-substituted indanone (**1.53**) has been shown to possess potent salidiuretic and antihypertensive properties, while also causing excretion of uric acid[88].

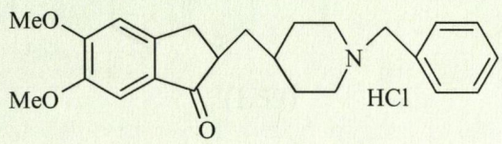



**(1.53)**

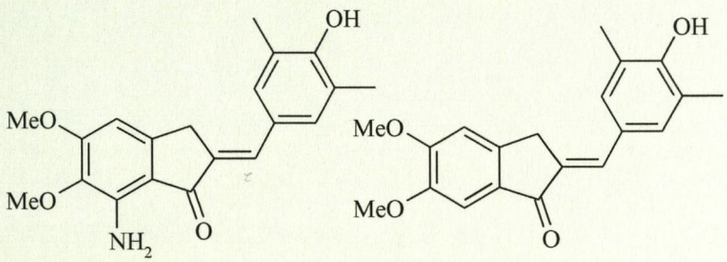


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The reversible acetylcholinesterase inhibitor, donepezil (**1.54**), used as a treatment in Alzheimer's disease, is a 2-alkyl-5,6-dimethoxy-1-indanone[89]. Other dimethoxy indanones and tetralones show promise as cytotoxic agents, notably the indanocine (**1.55**) and indanorine (**1.56**) compounds shown below[90].

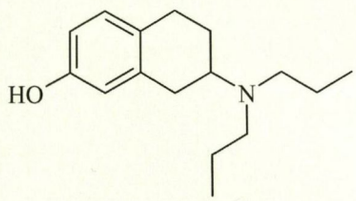



Donepezil (**1.54**)




Indanocine (**1.55**) Indanorine (**1.56**)

Many derivatives of 2-aminotetralin, notably phenol and catechol derivatives, such as 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OHDPAT, **1.57**), a potent $D_3$ agonist, have use as investigational tools in pharmacology[91], with others being evaluated for adrenergic and antipsychotic activity.



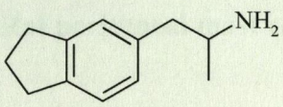

7-OHDPAT (**1.57**)

Indan and tetralin derivatives of 3,4-(methylenedioxy)amphetamine have been prepared for structure-activity investigations[92]. The indan derivative (**1.58**) proved a potent inhibitor at all neuronal uptake sites tested, whereas the tetralin derivative (**1.59**) showed reduced ability to inhibit the uptake at catecholamine sites. Furthermore, the indan derivative gave better results in a drug/saline discrimination test than the tetralin derivative.

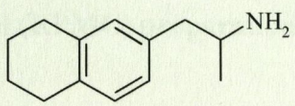


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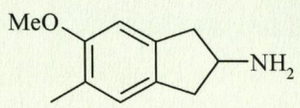
One of the standard drugs employed in these investigations was the 2-aminoindan derivative (**1.60**), which is highly selective in inducing the release of neuronal serotonin but not of catecholamines.




**(1.58)**




**(1.59)**




**(1.60)**

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## 1.13 Pharmacological screens for anti-allergic activity

### 1.13.1 Cell and tissue models (*in vitro*)

#### 1.13.1.1 Rat peritoneal mast cell (RPMC) preparations

A standard model used for initial screening of potential mast-cell stabilising molecules is the rat peritoneal mast cell preparation. Although a defining characteristic of mast cells is heterogeneity, both in and between species, the relative difficulty in obtaining large homogenous mast cell populations from many tissues means that this rodent preparation is still in common use as a preliminary screen. The cells are quite rich in histamine, present in significant numbers, and easily obtained and purified. However, interspecies variation, as illustrated by experience with disodium cromoglycate, should always be remembered when interpreting results of this and similar assays. The development of a chimeric mouse expressing human FcεRI is an important advance in anti-allergic screening[48].

Experimental procedures using mast cell populations have historically been performed using the RPMC preparation, as this was easily attainable and offered consistent results. More recently, as the diversity of mast cell populations has been more fully appreciated, experiments have been reported using mast cells from a vast array of tissues, including nasal mucosa[93], conjunctiva[94], skin[95], trachea and lung[96]. Many of these offer advantages over the traditional RPMC preparation, such as the greater species homology between guinea pig lung cells and those of man. Nevertheless, the RPMC preparation remains an important site for facile harvesting of mast cells for use in preliminary screens. Rat peritoneal mast cells are consistently richer in histamine than other mast cell phenotypes, with an average of 10-30pg $cell^{-1}$ compared to 1-3pg $cell^{-1}$ in human mast cells and basophils[11].

The rat is a useful experimental animal for preliminary assays; interestingly the peritoneal cells of mice do not respond as well to the classical degranulatory agents employed in rat studies[97]. This selective behaviour of mast cell subtypes towards degranulatory agents is widespread and further highlights the heterogeneity of mast cells both within and between species.



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Isolation of RPMCs as described in Section 6.2.3 afforded a cell pellet containing 4-5% mast cells, 15-20% eosinophils and 80-85% mononuclear cells. Use of further purification procedures such as layering over bovine serum albumin[95] or metrizamide[21] allow enrichment of mast cells to over 90% purity. Use of cells in the unpurified state may result in the presence of interfering substances such as proteins, although correction for basal readings reduces this somewhat.

Many degranulating agents have been employed to induce degranulation of mast cell populations; those relevant to our studies (see Chapter 6) are reviewed below.

#### 1.13.1.1.1 Compound 48/80

Release of histamine from mast cells may be effected through several mechanisms, and the agents used have been classified into broad groups, based on dose requirements *in vitro* versus *in vivo* experimentation, and also considering calcium dependence, alteration of metabolic factors and potentiation by lipid[98,99]. Of the many available agents, Compound 48/80 is most commonly used. This molecule is a hypotensive polymer amine obtained as a condensation product of *N*-methyl-*p*-methoxy phenylethylamine with formaldehyde[100], which induces histamine release with similar kinetic characteristics to those caused by antigen, in an energy-dependent process. It preferentially degranulates serosal rather than mucosal mast cells. Studies on peritoneal mast cell suspensions indicate that release of histamine from mast cells by 48/80, or release in response to certain antigen-antibody reactions, involves the following stages[101]:

- rapid attachment of the releasing agent to the cell membrane;
- selective and extremely rapid degranulation of the cell by an energy-dependent 'exocytosis', liberating, without disruption of the cell membrane, only histamine-containing granules;
- liberation of histamine from a histamine-heparin-protein complex by a process of ion exchange with cations of the extracellular fluid.

The activation of G-proteins by Compound 48/80 has been studied by Mousli[102], who demonstrated both increased nucleotide binding and GTPase activity using a purified G protein preparation, stimulated by either Substance P or Compound 48/80.



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The increased GTPase activity was subsequently shown to be due to an interaction between Compound 48/80 and the C-terminus of the α-subunit of the protein[103].

As aforementioned (Section 1.1.1), mast cells from all species do not respond equally to Compound 48/80. In addition, mast cells from different tissues are markedly different in their susceptibility to this and other agents. In one study, repeated injections of Compound 48/80 to rats were shown to degranulate and deplete mast cells from all tissues examined apart from those of the intestinal mucosa, where cell numbers increased by a factor of two over five days of treatment Compound 48/80, and these cells were refractory to the degranulatory effects of Compound 48/80[104].

#### 1.13.1.1.2 Calcium ionophore A23187

The calcium ionophore A23187 acts by altering membrane permeability, and induces the transport of extracellular calcium into the mast cells after forming lipid-soluble complexes with the ion, thus acting as a stimulus for histamine secretion[105]. Cromoglycate has been shown to block $Ca^{2+}$ influx, and IgE-mediated cross-linking of surface receptors alters membrane permeability to calcium. Isolation of a membrane protein, able to exhibit IgE-receptor-dependent $Ca^{2+}$ channel activity, led to a postulation of the mode of action of cromoglycate as an ion channel blocker[106]. In addition, the intracellular calcium antagonist 3,4,5,-trimethoxy benzoic acid diethylamino octyl ester (TMB-8) exerts concentration-dependent inhibition of both antigen-induced histamine release from rat mast cells and release induced by A23187[107]. The fact that higher concentrations are needed to reduce release induced by ionophores suggests that there are different calcium channels involved in the different processes. Although the absolute requirement for $Ca^{2+}$ can be compensated for by certain experimental procedures, under physiological conditions the presence of external $Ca^{2+}$ is crucial for IgE-mediated secretion.

#### 1.13.1.1.3 Concanavalin A

Concanavalin A (Con A) is a lectin obtained from the Jack bean, *Canavalia ensiformis*. It is capable of inducing histamine release from mast cells and basophils[108,109]. It appears to exert its effect via cross-linking of FcεRI receptors on the cell surface, by interaction with saccharides of the IgE glycoprotein.



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Indeed, its action is inhibited by certain sugars, including glucose, and although this is present in the mast cell medium used in assays, at a concentration of 5.6mM it does not prevent release. The concentration of Con A typically employed is 20μg $ml^{-1}$, often with the concomitant use of phosphatidyl serine, which further elevates release[110].

#### 1.13.1.1.4 Vancomycin

Vancomycin is a mixture of related glycopeptides isolated from *Amycolatopsis orientalis*[111], and induces both a time- and dose-dependent release of histamine from RPMCs and RBL-1 cells[112]. Upon microscopical examination, the changes induced by vancomycin include irregularity and reduced density of granules, and granule coalescence. These changes resemble those caused by Compound 48/80. Disodium cromoglycate does not possess the ability to prevent vancomycin-induced degranulation.

#### 1.13.1.1.5 anti-IgE

Antibodies raised against immunoglobulin E molecules induce cross-linking of IgE bound to FcεRI on mast cells and basophils, thus inducing degranulation (Section 1.3.1.).

### 1.13.1.2 Basophils

To investigate the ability of test compounds to inhibit the degranulation of basophils usually requires the partial purification of human blood. Early studies were hampered by the rarity of the basophil in whole blood and the volumes therefore required. Methods of purification generally involve either differential sedimentation in blood-dextran mixtures[113] or the centrifugation of blood over a polymer gradient such as Ficoll-Paque[114]. The latter method allows clear separation of layers; the erythrocytes remain in the base of the tubes and the lymphocytes occupy several overlying bands. Further purification, if required, may be performed by negative selection using immunomagnetic beads[115]. Basophil identification is facile using Alcian blue dye. Rat basophilic leukaemia cell lines such as RBL-1 are also available, which retain the ability to produce histamine and mature granules, and also can express IgE receptors.



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### 1.13.1.3 Guinea pig lung cells

The popularity of guinea pigs as experimental animals in the study of immediate hypersensitivity stems from the fact that they are readily sensitised and respond strongly to antigen challenge. Dispersed lung cells are usually obtained after digestion of the lung tissue with enzymes such as collagenase[116], and further purification may be performed using percoll density gradients. Other isolated cell preparations that have been used in studies of allergy include bronchoalveolar lavage and lung cells of human[117] and animal[118] origin, and cell cultures, e.g. murine haematopoietic cells cultured in the presence of IL-3. The quantitation of released histamine was originally performed using isolated organs, such as guinea pig ileum, but is now commonly determined using a fluorimetric method, originally developed by Shore[119]. As histamine is not inherently fluorescent, the method involves derivatisation with *ortho*-phthalaldehyde (*o*-PT) under alkaline conditions, followed by acidification for reasons of stability. The optimal conditions for fluorometric detection of histamine have been investigated, including the effects of temperature, pH, and interfering substances[120]. The reaction is thought to occur as follows:

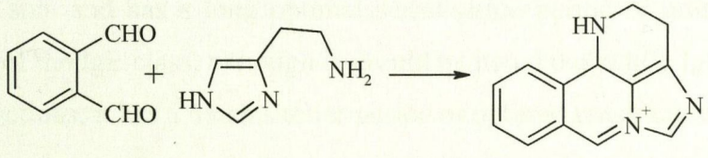



**Figure 1.8 Histamine derivatisation by *o*-PT**

Alternative methods of histamine analysis include HPLC with fluorescence detection[121] (again with *o*-PT derivatisation), and radioimmunoassay.

### 1.13.2 *In vivo* animal models

Many models of allergic, inflammatory and autoimmune pathologies are available to the experimenter[122]. Acute systemic anaphylaxis may be induced by immunization of test animals followed by intravenous challenge, but has the undesirable endpoint of mortality. Alternatives to systemic anaphylactic challenge via the intravenous route include intraperitoneal or subplantar antigen administration[123]. One of the earliest screens for anti-anaphylactic activity was the Schultz-Dale reaction, using ileal strips from sensitised guinea-pigs.



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The method involves measurement of the contractility of the strips on antigenic challenge. The main disadvantage of the method is that it is not very selective; agents such as antispasmodics and local anaesthetics also show activity in the model. Local sensitization with antigens may also be performed, as an attempt to mimic rheumatic conditions, either as an immediate (Arthus) reaction, or a delayed-hypersensitivity reaction. Animal models of asthma include bronchial provocation of guinea pigs and rabbits[124] with inhaled allergens.

#### 1.13.2.1 Passive Cutaneous Anaphylaxis (PCA)

As utilised in Chapter 6, a popular method for the *in vivo* study of allergy is passive cutaneous anaphylaxis (PCA), generally using the rat or mouse, but rabbits or guinea pigs may also be used. Passive cutaneous anaphylaxis is an immediate type hypersensitivity reaction caused by the interaction of antibodies with mast cells of the skin. The technique was developed in 1958 by Ovary[125], and has since been subject to many modifications[126]. Rats immunised with egg albumin or other antigens, with the inclusion of various adjuvants, produce a mast cell-sensitising antibody (MC-SAb), which is heat labile, persistent in the skin and has a long optimal sensitisation period of around 48 hours[127]. This antibody is of the IgE class, although it should be noted that while IgG may also play a role in PCA reactions, it has a much shorter period of optimal sensitisation.

Rats are generally not considered to be good producers of IgE antibodies following immunisation with conventional antigens[128]. In consequence, many studies have evaluated the application of adjuvants and use of booster doses of antigen. Adjuvants that have been used include bacteria such as *Bordetella pertussis*[129], inert materials including aluminium hydroxide and silica gel[130], and Freunds adjuvant[131]. Enhanced titres of IgE have consistently been produced following the use of pertussis, which is believed to act by increasing the rate of cell division of carrier-specific helper T-cells[129]. In addition, impairment of β-adrenergic receptors may play a role[132]. The effect of adrenalectomy has also been studied, and antibody titres in adrenalectomised rats were found to be greater and more reproducible than in intact rats[133].

An alternative to the use of adjuvants is the induction of IgE production following helminth infestation. *Nippostrongylus brasiliensis*[134] and *Ascaris suum*[135] have found



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application in rat and mouse PCA respectively. Many rat strains have been evaluated in PCA, including Wistar, Sprague-Dawley and Hooded Lister rats, the latter having been shown to produce exceptionally high levels of antibody[128]. In the rat, the optimum sensitisation period for IgE is 48 hours. Intradermal injections should not exceed 0.1ml, while up to 1ml may be injected intravenously, via the tail vein, foot vein or the dorsal vein of the penis[126].

### 1.13.2.2 Murine ear oedema assays

Application of arachidonic acid to the murine ear results in immediate erythema, followed by oedema, which is maximal at 1 hour[136]. This phenomenon has been widely used as a screen for anti-inflammatory drugs. Many agents may be used to elicit oedema, including 12-*O*-tetradecanoylphorbol-13-acetate (TPA)[137]. Arachidonic acid has the advantages of a rapid onset of action and being itself a physiological mediator of inflammation. Arachidonic acid metabolites include prostaglandins and leukotrienes, formed via the cyclooxygenase and lipoxygenase enzyme cascades, respectively[138]. There is considerable debate as to whether the mouse ear assay is more selective for lipoxygenase inhibitors than those of cyclooxygenase, as some studies using compounds inhibiting the former enzyme show much greater activity in the model. Nevertheless, the cyclooxygenase inhibitor indomethacin is active in the assay, as was found in the present studies.

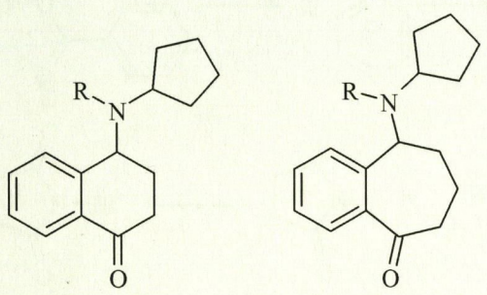
The value of arachidonic acid-induced oedema as a primary screen has been also questioned due to the fact that some compounds e.g. phenobarbitone show activity in the model yet possess no clinically demonstrable anti-inflammatory activity. However, the model is useful as part of a pharmacological profile for a new compound.

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# Synthesis and preliminary screening of novel amino compounds featuring an α-tetralone or benzosuberone nucleus and a benzylic *N*-cyclopentyl moiety

## 2.1 Synthetic targets of Chapter 2

The target compounds of this Chapter shared a key functional group, a tertiary nitrogen function bearing a cyclopentyl group. All target molecules possessed the nitrogen atom on the benzylic position on a fused cyclic system, with a variable number of carbon atoms in the alicyclic portion of the ring system. Of primary interest were the tetralone analogues, based around the key structural type (**A**), where R is an alkyl or acyl substituent. Of secondary importance, a smaller selection of benzosuberone analogues (**B**) were also investigated, thus expanding the scope of the studies with the indanone molecules investigated by earlier workers[64].




**(A)** **(B)**

## 2.2 Synthetic approaches to structural type (A)

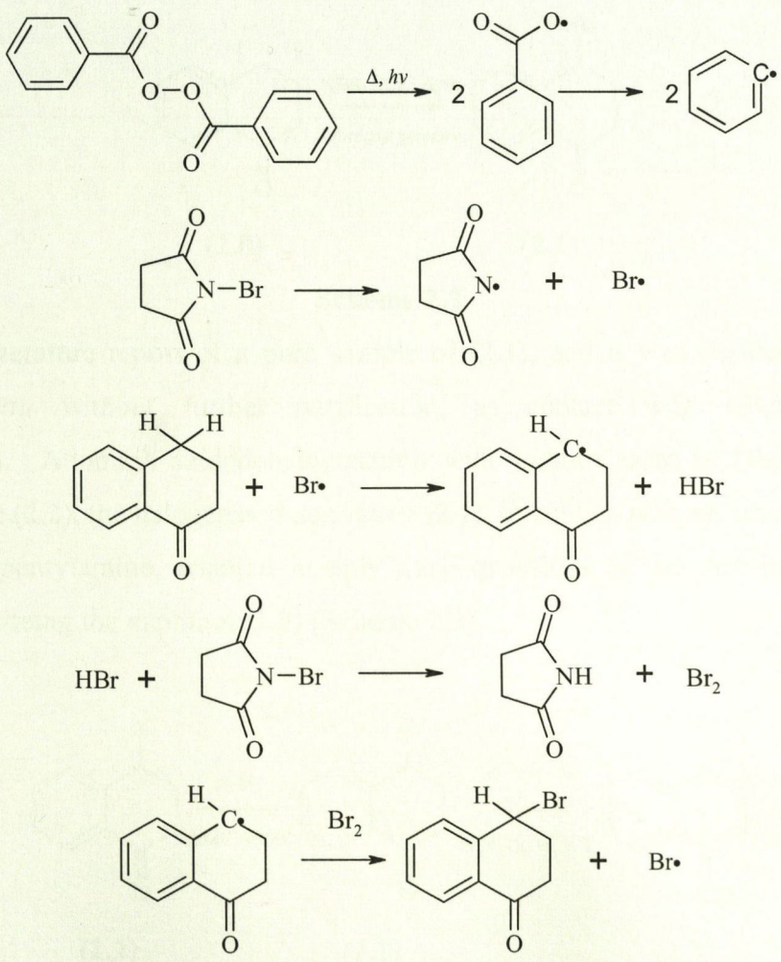
### 2.2.1 Reactions via 4-bromotetralone

Due to the positioning of the amino substituent at the benzylic position, initial attempts to introduce this functionality were centred around the benzylic bromination of the substrate molecule α-tetralone and nucleophilic displacement of the halogen atom with a nitrogen nucleophile or with azide anion. In the case of indanone, this transformation is facile and proceeds with excellent yield, with little competition from elimination reactions. Bromination with *N*-bromosuccinimide (NBS), known as the Wohl-Ziegler reaction[139], was developed in the 1940s as a method of introducing bromine into the α-methylene position of allylic molecules.



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Since then, the scope of the reaction has been greatly extended to include the use of many *N*-bromo-imides and -amides, catalytic modifications[140] and application to a wider range of substrate molecules. In the presence of NBS, bromination at the benzylic position of aromatic molecules was seen to predominate over nuclear bromination[141]. To effect benzylic bromination, the general form of the reaction, using NBS, involves refluxing the reagent in an inert solvent such as carbon tetrachloride ($CCl_4$), with the addition of a catalyst such as 5-10% dibenzoyl peroxide. Photocatalysis may also be employed. The reaction is believed to proceed through a free radical mechanism (Scheme 2.1), involving initial homolytic dissociation of NBS, followed by abstraction of a benzylic proton by the bromine radical. Progress of the reaction is easily monitored by noting the disappearance of the insoluble NBS, and appearance of floating succinimide, often accompanied by a colour change.



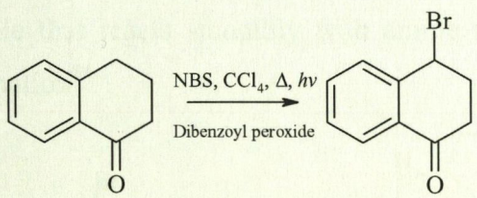

**Scheme 2.1 Possible mechanism of benzylic bromination using NBS**



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The starting material in our proposed synthesis of molecules of structural type (**A**) was α-tetralone. Benzylic bromination of the molecule under Wohl-Ziegler conditions was expected to yield the 4-bromo derivative (**2.1**), although NBS is also known to effect bromination in the alpha position of many carbonyl compounds[139]. Bromination of tetrahydronaphthalene has been previously reported[142]. The reaction product was naphthalene, via 1,4-dibromotetrahydronaphthalene.

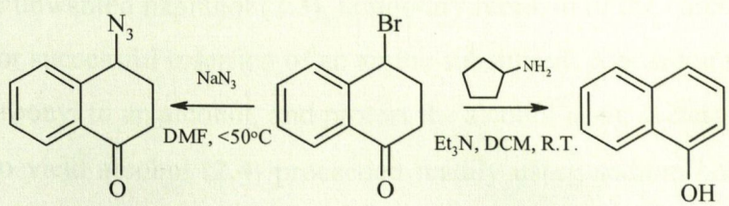
The reaction of α-tetralone proceeded under reflux (Scheme 2.2) but showed a tendency to produce additional products, as judged by TLC. One of these, at higher $R_f$ than the presumed mono-bromo derivative, increased in intensity as the reaction proceeded, and was believed to be the elimination product. On filtration and removal of the solvent, the residue was found to fume and decompose rapidly to a black oil.




**(2.0)** **(2.1)**

**Scheme 2.2**

There is no literature report of a pure sample of (**2.1**), and it was decided to react the residue *in situ* without further purification, as contact with silica accelerated decomposition. Although azidodehalogenation with sodium azide in DMF yielded the expected azide (**2.2**), the halogenated derivative (**2.1**), in contact with an amine nucleophile such as cyclopentylamine, resulted in only trace quantities of the desired product, the major product being the naphthol (**2.3**) (Scheme 2.3).



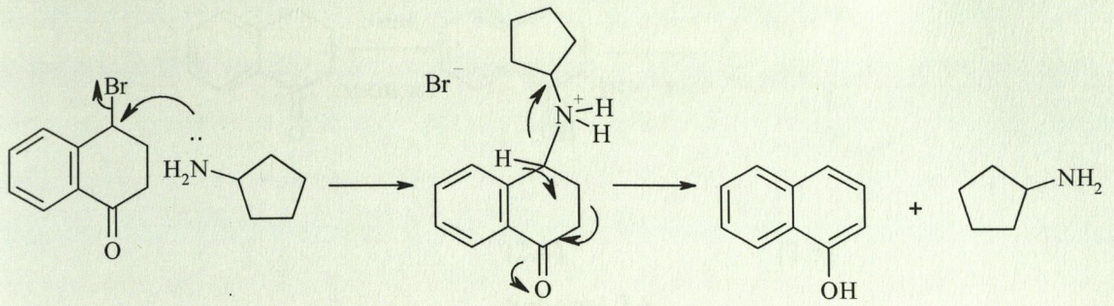

**(2.2)** **(2.1)** **(2.3)**

**Scheme 2.3**

This reaction may be accounted for by the following mechanism (Scheme 2.4):

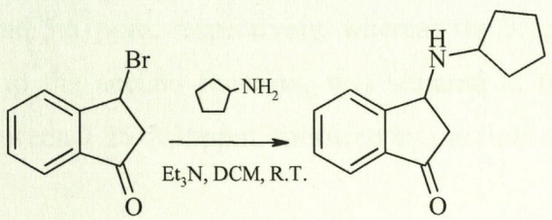


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**Scheme 2.4 Formation of 1-naphthol**

The naphthol was easily identified by $^1$H NMR analysis, showing primarily aromatic character, and agreement with literature data[143]. This preferential formation of (**2.3**) was seen to occur in DCM, DMF or in the absence of any solvent, and at both room temperature and 0°C. This is in stark contrast to the behaviour of 3-bromoindanone, a stable, crystalline molecule that reacts smoothly with amine nucleophiles (Scheme 2.5) without appreciable elimination[64].



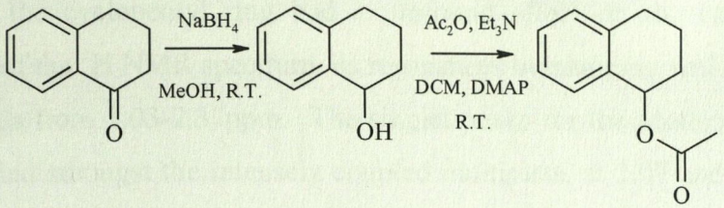
**Scheme 2.5**

### 2.2.2 Reactions via 4-bromo-1,2,3,4-tetrahydro-1-naphthalenyl acetate

Due to the potential for aromatisation in the tetralone series, a different approach was required. As the presence of an unmasked ketone substituent in (**2.1**) contributed to the formation of the unwanted naphthol (**2.3**), temporary removal of the carbonyl functionality was necessary for successful insertion of an amino substituent at position 4. It was decided to reduce the carbonyl to an alcohol, and protect the alcohol as an acetate ester. Reduction of α-tetralone to yield alcohol (**2.4**) proceeded readily using sodium borohydride[144], and acetylation[145] to yield (**2.5**) was performed using acetic anhydride (Scheme 2.6).



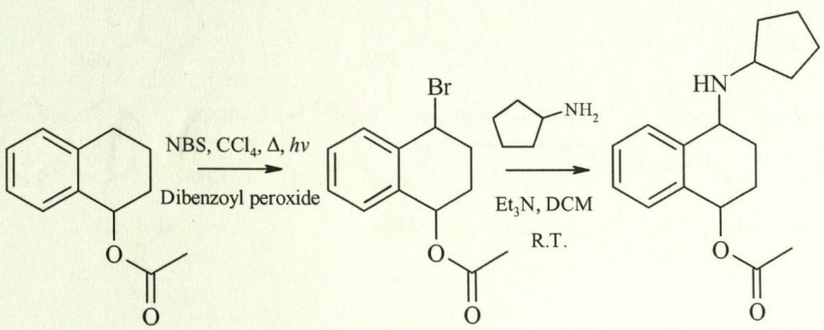
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**(2.4)** **(2.5)**

**Scheme 2.6**

Benzylic bromination of acetate (**2.5**) resulted in acceptable yields (59%) of the bromo derivative (**2.6**), a stable, storable analogue. A literature procedure exists for the preparation of this molecule, using homochiral starting material[146]. The principal bands of interest in the infrared spectrum of the brominated acetate were those of C-$O_{str}$ at 1236cm$^{-1}$ and C=$O_{str}$ at 1732cm$^{-1}$. In the $^1$H NMR spectrum (see Expermental Section for all spectra), a diastereomeric mixture was observed. In the aliphatic region, two sharp singlet peaks for the acetate methyl group dominated the spectrum, at 2.05 and 2.18ppm. These peaks somewhat overlapped with the signals for the two methylene groups, which lay between 2.03-2.52ppm. The signal for the first methine proton was evenly split into two broad signals, at 5.50 and 5.61ppm, respectively, whereas the broad signal for the second methine, that adjacent to the acetate function, was situated at 6.08ppm. Three of the aromatic protons lay between 7.25-7.35ppm, followed by the final proton at 7.42ppm.




**(2.5)** **(2.6)** **(2.7)**

**Scheme 2.7**

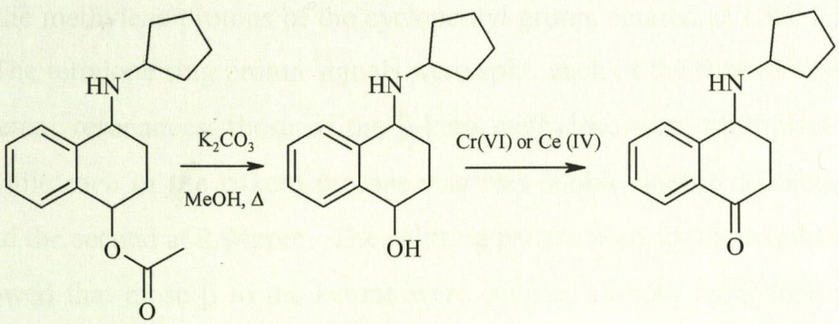
Although the stability of the brominated acetate (**2.6**) resulted in sluggish nucleophilic substitution, reasonable yields of the diastereomeric amine (**2.7**) were isolated. The reaction mechanism for this nucleophilic substitution reaction is known and proceeds with inversion of configuration, thus yielding again a diasteromeric mixture of (**2.7**). Replacement of the halogen by an amine had little effect on the infrared spectrum of (**2.7**); the C-$O_{str}$ at 1240cm$^{-1}$ and the C=$O_{str}$ at 1733cm$^{-1}$.



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Introduction of the cyclopentyl ring had a profound effect on the complexity of the aliphatic region of the $^1$H NMR spectrum, its resonances overlapping with both methyl and methylene signals from 1.03-2.37ppm. The singlet peaks for the acetoxy methyl protons could be identified amongst the intensely coupled multiplets, at 2.07 and 2.09ppm. Each of the three methine peaks were clearly identifiable, that of the cyclopentyl ring showing the expected intense coupling to the other ring protons and perhaps also to the proton of the secondary amine. The methine of position four on the hydroaromatic ring, that bearing the cyclopentylamino group, appeared as two triplets, at 3.75 and 3.86ppm. This was also the case for the third methine, that adjacent to the acetoxy group, whose two pseudo-triplets were located at 5.95 and 6.02ppm. Again, the aromatic region showed three of the protons together, between 7.20-7.30ppm, but in this case the proton nearest the acetoxy group appeared as two distinct doublets, at 7.38 and 7.55ppm. In the GCMS spectrum, the M+1 peak (274) was of medium intensity, with the principal ion cluster (213,214) representing cleavage of the acetoxy group (M-$CH_3COO$).

Restoration of the ketone moiety was accomplished in two steps (Scheme 2.8), namely removal of the acetate by treatment with base[147] (potassium carbonate in methanol proving superior to ammonia in methanol) and subsequent oxidation of the secondary alcohol.




**(2.7)** **(2.8)** **(2.9)**

**Scheme 2.8**

Oxidation of alcohols to ketones may be performed using several oxidising reagents, and two of these were investigated. Use of the Cerium (IV) reagent, ceric ammonium nitrate in acetonitrile[148] was compared with the Chromium (VI) reagent, chromium trioxide, the latter in the form of Jones's reagent[149]. Jones's reagent is a chromium trioxide-acetone-sulphuric acid mixture. A general equation for the oxidation of a benzylic secondary alcohol with Ce (IV) can be written as follows:



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Ce (IV) Oxidation: $RArCHOH + 2\ Ce(IV) \rightarrow RArC{=}O + 2\ Ce(III) + 2\ H^+$

In aqueous media, a single equation is insufficient to explain the Jones oxidation, as several chromium species, including $CrO_4^{2-}$, $HCrO_4^{2-}$ and $HCrO_7^{2-}$ may be present. In addition, oxidation is thought to proceed via an intermediate chromate ester. Both oxidation reactions, as judged by GCMS analysis, gave the desired ketone, yet the latter gave a cleaner product, albeit after considerable clean-up procedures to remove contaminating Cr (III) salts.

The benzylic ketone (**2.9**) was obtained as a pale brown oil, which solidified on standing. Acicular crystals developed slowly on recrystallisation from acetone. GCMS analysis showed a molecular ion cluster at 230 (M+1, 100) and 229 ($M^+$, 44) but no intense fragment ions, and HRMS gave the accurate molecular mass as 230.1561 ($+H^+$, as was noted with all amines examined), calculated 230.1545). The main feature of the infrared spectrum was the sharp ketone band at 1689$cm^{-1}$.

$^1H$ NMR analysis (Figure 2.1) showed a broad signal at 1.09ppm for the proton of the secondary amine, followed by four extremely complex coupled, yet highly symmetrical signals for the methylene protons of the cyclopentyl group, centred at 1.35, 1.53, 1.69 and 1.84ppm. The tetralone ring proton signals were split, each of the four methylene protons having different resonances; those of the β-keto methylene were multiplets at 2.04 and 2.26ppm, while each of the α-keto protons was two double double doublets, the first at 2.49ppm and the second at 2.94ppm. The splitting pattern seen for the tetralone methylene protons showed that those β to the ketone were coupled to both methylene and methine protons to either side, while those α to the ketone were coupled only to the adjacent methylene protons. The methine proton of the cyclopentyl group was coupled equally to both neighbouring methylene groups, the quintet signal reflecting the symmetry of the ring, with a coupling constant of 6.5Hz. The other methine proton, that of the benzylic position, resonated at 3.91ppm and appeared as a double doublet. In the aromatic region of the spectrum, overlapping signals arose for protons 5, 6 and 7, centred at 7.29 and 7.47ppm, whereas the proton of position 8 was a sharp doublet at 7.96ppm. The key feature of the $^{13}C$ NMR spectrum (Figure 2.2) was the carbonyl resonance, at 197.6ppm.

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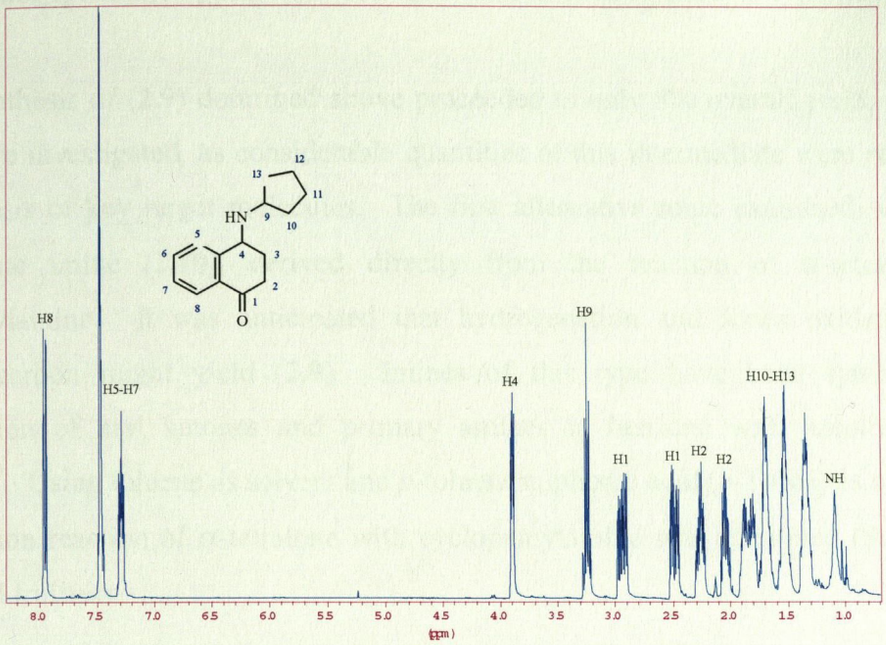



**Figure 2.1** $^{1}$H NMR spectrum of compound (2.9)

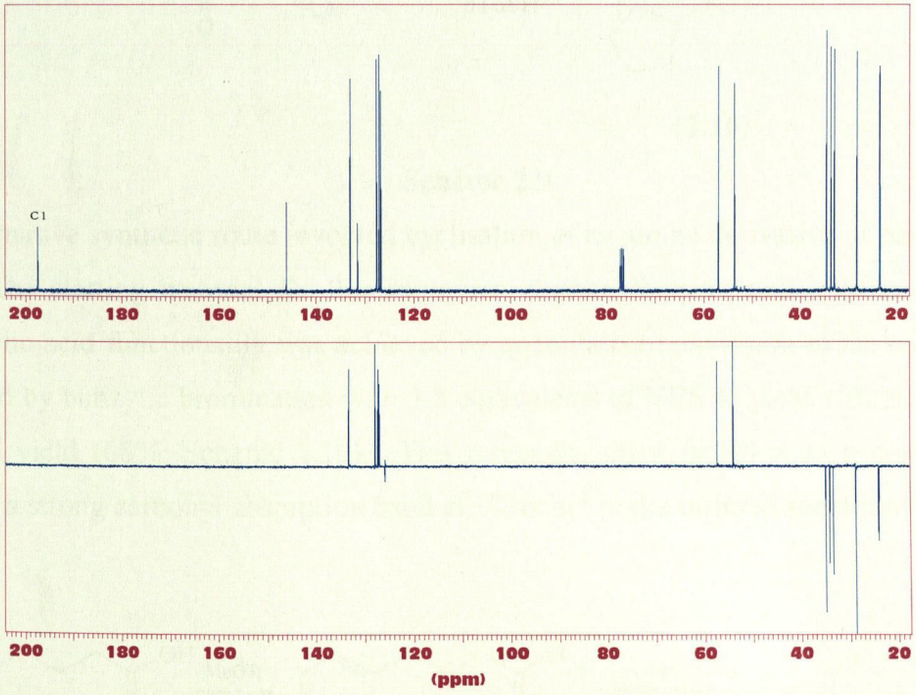
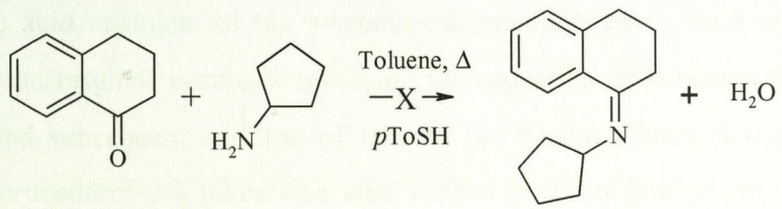



**Figure 2.2** $^{13}$C NMR and DEPT 135 spectra of compound (2.9)

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### 2.2.3 Other synthetic approaches towards molecules of structural type (A)

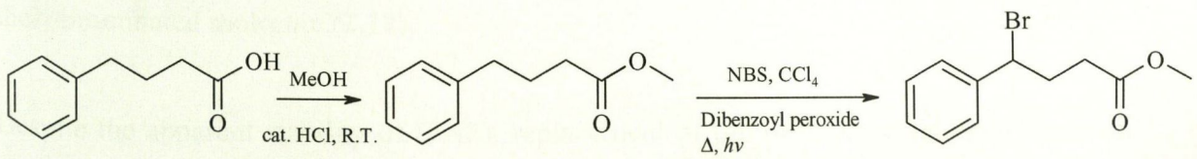
As the synthesis of (**2.9**) described above proceeded to only 8% overall yield, alternative routes were investigated, as considerable quantities of this intermediate were required for the synthesis of key target molecules. The first alternative route examined was via the intermediate imine (**2.10**), derived directly from the reaction of α-tetralone with cyclopentylamine. It was anticipated that hydrogenation and Jones oxidation at the benzylic carbon might yield (**2.9**). Imines of this type have been synthesised by condensation of aryl ketones and primary amines in benzene with azeotropic water removal[150]. Using toluene as solvent and *p*-toluenesulphonic acid (*p*-ToSH) as catalyst, the condensation reaction of α-tetralone with cyclopentylamine was attempted (Scheme 2.9) but proved fruitless.




(**2.10**)

**Scheme 2.9**

An alternative synthetic route involved cyclisation of an amine derivative of phenylbutyric acid. The starting material for this route was 4-phenylbutyric acid. Protection of the carboxylic acid functionality was achieved by quantitative conversion to the methyl ester, followed by benzylic bromination with 1.5 equivalents of NBS to yield a stable derivative in good yield (68%, Scheme 2.10). This molecule, upon isolation as a colourless oil, showed a strong carbonyl absorption band at 1736cm$^{-1}$ in the infrared spectrum.




(**2.11**) (**2.12**)

**Scheme 2.10**

The $^1$H NMR spectrum of (**2.12**) contained a complex multiplet ranging from 2.42–2.51ppm, and the methine proton resonance, at 5.06ppm, was also a multiplet.



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The $^{13}C$ NMR spectrum of (**2.12**) showed both methylene carbons to have very similar resonances, at 32.5 and 35.0 ppm. These characteristics alone did not unequivocally determine the pattern of bromination in the molecule, as it was appreciated that under the conditions employed that bromination could well have occurred at the position α to the ester function, which, as already mentioned, is a frequent side reaction witnessed while employing Wohl-Ziegler conditions on a molecule bearing a carbonyl functionality.

A perusal of the literature reveals the prior preparation of the α- and γ-brominated esters of (**2.11**). The α-brominated compound has been prepared by the free radical addition of benzyl bromide to methyl acrylate, using $Fe(CO)_5$ as catalyst and either HMPA or DMF as initiator[151]. Yields reported approached 87%, and although the authors did not include $^1H$ NMR data, $^{13}C$ NMR, GCMS and elemental analytical evidence supported the structure. The carboxylic acid analogue of the γ-bromo compound is established in the literature since 1889[152], the original synthesis involving the reduction of β-benzoylpropionic acid with $NaBH_4$ and subsequent addition of HBr to the γ-lactone thus formed. In a later paper[153], this procedure was taken one step further by esterification of the acid using diazomethane, and brief $^1H$ NMR data for the isolated product (**2.12**) was reported. An alternative synthesis of (**2.12**) has been reported more recently, and involves the reaction of methyl 2-bromoacetate with styrene under redox catalysis by cuprous chloride in the presence of α-bipyridyl or 1,10-phenanthroline[154].

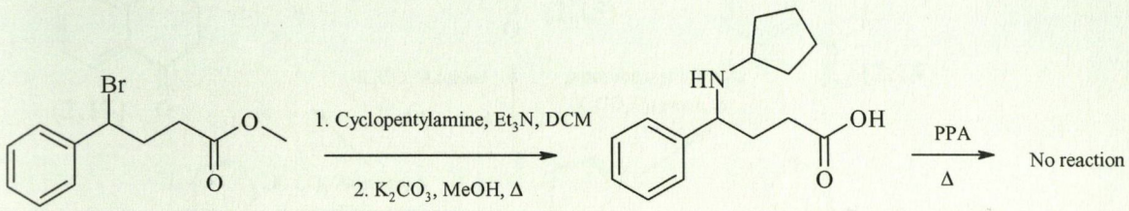
The spectral data reported in Cooks paper[110] following $^1H$ NMR analysis of the methyl ester mirrored that obtained following our reaction of (**2.11**) with NBS, whereas the $^{13}C$ data reported by Vasil'eva[108] for the α-bromo compound was not in agreement with our analysis. These observations suggested that the product obtained was entirely composed of the γ-brominated molecule (**2.12**).

Despite the apparent stability of (**2.12**), replacement of the bromine atom was, however, attempted, and substitution by the cyclopentylamino group under basic conditions resulted in a mixture of the acid and ester. Ester hydrolysis was completed using potassium carbonate in methanol.



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The amino acid thus obtained was added neat to polyphosphoric acid and the mixture heated on a steam bath. No cyclisation was observed to the keto derivative, perhaps reflecting the steric hindrance involved, and the starting material was recovered unchanged (Scheme 2.11).




**(2.12)** **(2.13)**

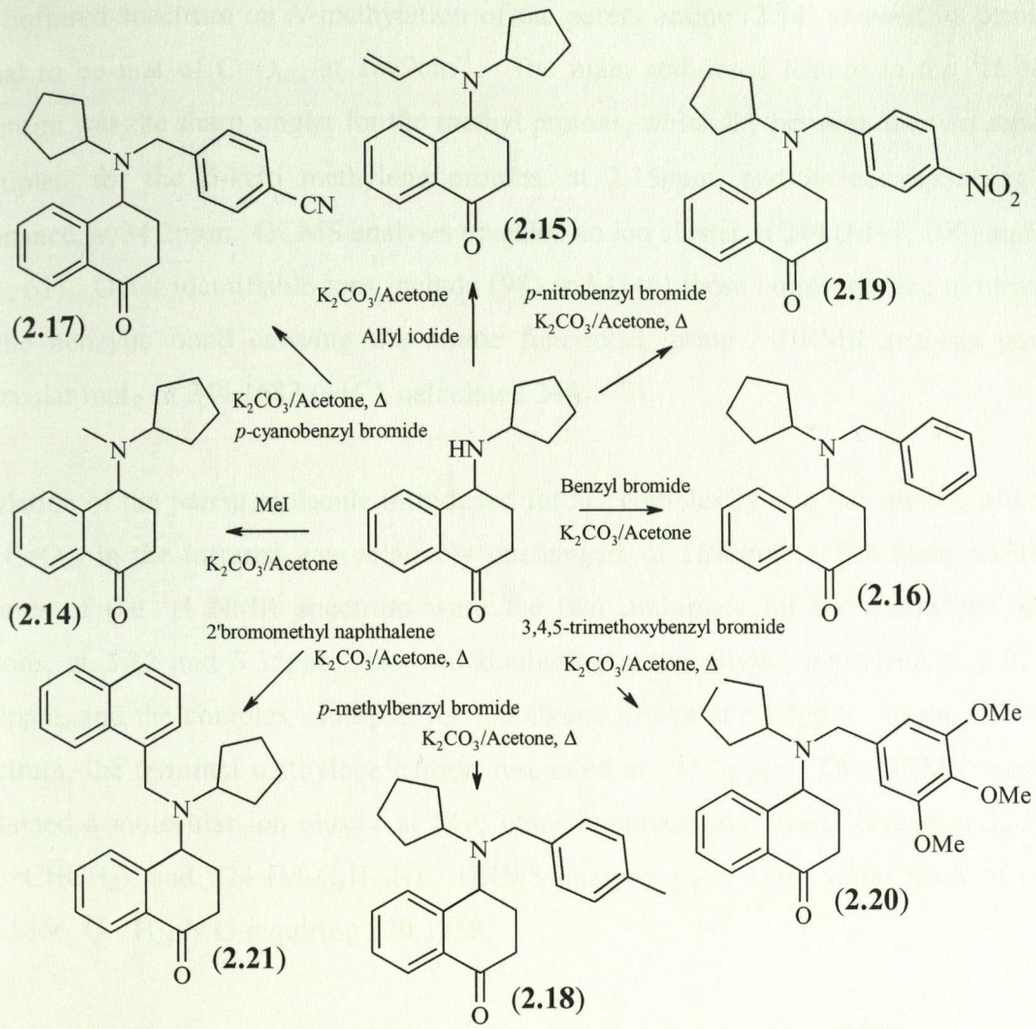
**Scheme 2.11**

## 2.3 *N*-alkylations of the key secondary amine intermediate towards structural types (A)

Despite the reduced yield of the desired secondary amine with the original method, that sequence was chosen to generate quantities of (**2.9**). The final step towards a series of tertiary amine derivatives (**2.14-2.21**) was alkylation of the secondary nitrogen. Common methods of *N*-alkylation utilise a tertiary base such as potassium carbonate ($K_2CO_3$), and, as alkylating agent, a reactive halide, such as a benzylic or allylic bromide or iodide[155]. Reactions usually proceed to good yield within several hours. However, in the alkylation of (**2.9**), a slow rate of reaction was anticipated, due to the relatively hindered position of the nitrogen atom. This premise was seen to hold, as little or no reaction occurred at room temperature overnight, even with very reactive halides such as methyl or allyl iodide. *N*-alkylation of amines may also be performed using methyltrialkoxyphosphonium tetrafluoborate salts[156] or with organocopper reagents[157]. A modification of the reaction, using potassium carbonate as base in acetonic media (instead of the DCM initially used), was found to proceed more rapidly and with improved overall yields. Heating the reactions under reflux was found to be vital for the introduction of bulky groups such as substituted benzyl or naphthalenyl moieties. In some cases these reactions were allowed to proceed for two to three weeks to achieve satisfactory yields. Using the $CO_3^{2-}$/Alkylating agent/ Acetone system, several *N*-alkyl derivatives of (**2.9**) were synthesised, as shown in Scheme 2.12 and in Table 2.1.



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**Scheme 2.12** ***N*-alkyl derivatives of structural type (A)**

**Table 2.1** **Tertiary amine derivatives of compound (2.9)**

| R Group | Compound | Reaction time | % Yield |
|---|---|---|---|
| Methyl | (**2.14**) | 24hr, R.T. | 94 |
| Allyl | (**2.15**) | 4 days,R.T. | 60 |
| Benzyl | (**2.16**) | 4 days,R.T. | 55 |
| *p*-cyanobenzyl | (**2.17**) | 3 days, Δ | 78 |
| *p*-methylbenzyl | (**2.18**) | 7 days, Δ | 80 |
| *p*-nitrobenzyl | (**2.19**) | 14 days, Δ | 53 |
| 3,4,5-trimethoxybenzyl | (**2.20**) | 7 days, Δ | 70 |
| 2'methylnaphthalenyl | (**2.21**) | 7 days, Δ | 27 |



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The infrared spectrum on *N*-methylation of the parent amine (**2.14**) showed its principal signal to be that of $C=O_{str}$, at $1689cm^{-1}$. The main additional feature in the $^{1}H$ NMR spectrum was the sharp singlet for the methyl protons, which lay between the two separate multiplets for the β-keto methylene protons, at 2.15ppm, and its corresponding $^{13}C$ resonance, at 34.2ppm. GCMS analysis revealed an ion cluster at 244 (M+1, 100) and 243 (M+, 61). Other identifiable ions include (98) and (146) those corresponding to cleavage of the benzylic bond carrying the amine functional group. HRMS analysis gave a molecular mass of 244.1682 ($+H^{+}$), calculated 244.1701.

Allylation of the parent molecule introduced further complexity into the spectra, although the $C=O_{str}$ in the infrared was relatively unchanged, at $1691cm^{-1}$. The main additional features of the $^{1}H$ NMR spectrum were the two multiplets for the methylene amino protons, at 3.22 and 3.35ppm, the two doublets for the allylic methylene at 5.07 and 5.22ppm, and the complex multiplet for the alkene proton at 5.92ppm. In the $^{13}C$ NMR spectrum, the terminal methylene carbon resonated at 115.3ppm. The GCMS spectrum contained a molecular ion cluster at 269; other important ions were located at 227 ($M-CH_2=CHCH_2$), and 124 ($M-C_8H_{14}N$). HRMS analysis gave a molecular mass of ($+H^{+}$) 270.1866, $C_{18}\ H_{24}\ N\ O$ requiring 270.1858.

To further aid the structural elucidation of these molecules, a series of NMR experiments was performed on the allyl derivative (**2.15**) as a representative of the series. In addition to the routine $^{1}H$ NMR and $^{13}C$ NMR spectra, the following spectra were obtained: TOCSY, HMQC and NOE spectra. A selection of these spectra is presented in Figures 2.3 and 2.4. The correlations observed in these spectra are used to aid identification of the molecule (see Experimental Section).



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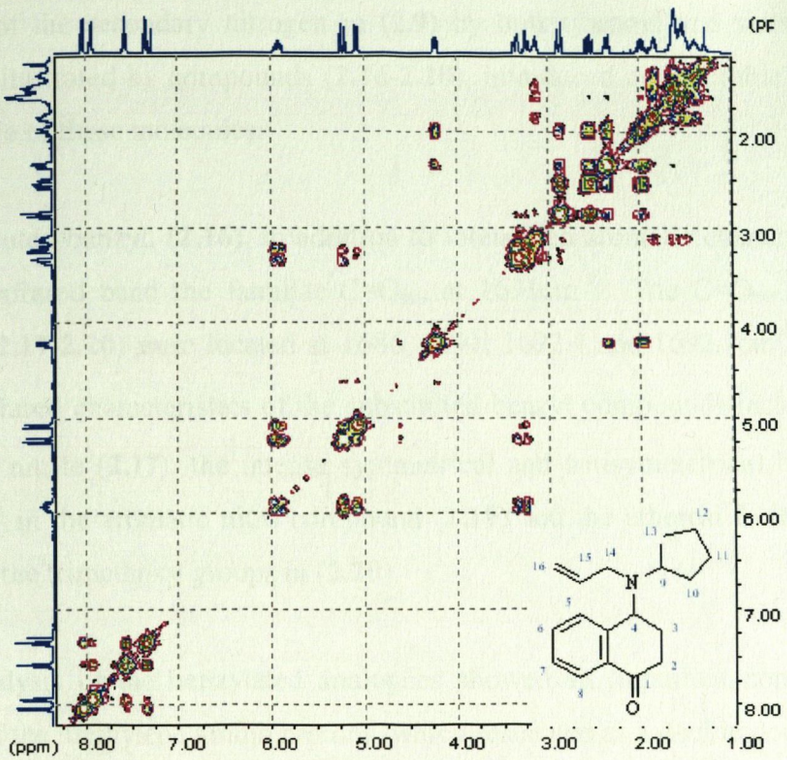



**Figure 2.3 TOCSY spectrum of compound (2.15)**

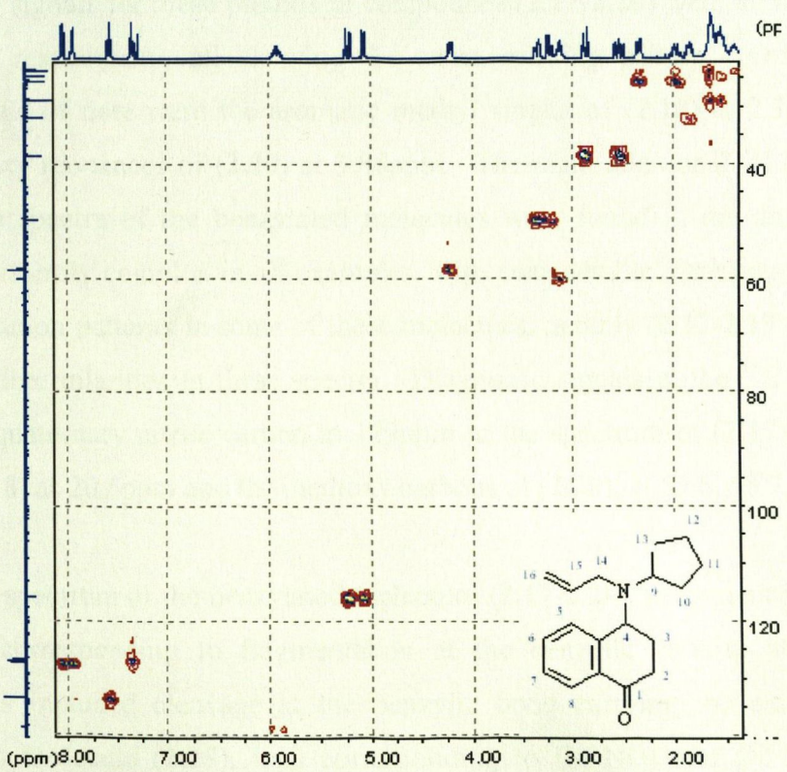



**Figure 2.4 HMQC spectrum of compound (2.15)**

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Substitution of the secondary nitrogen in (**2.9**) by bulky benzyl and substituted benzyl moieties, as illustrated by compounds (**2.16-2.20**), introduced considerable change to the spectral profile of these molecules.

The unsubstituted benzyl, (**2.16**), in addition to intensified aromatic character, showed as its primary infrared band the familiar $C{=}O_{str}$, at $1691cm^{-1}$. The $C{=}O_{str}$ frequencies in compounds (**2.17-2.20**) were located at 1686, 1691, 1692.4 and $1692.7cm^{-1}$, respectively. Important infrared characteristics of the substituted benzyl compounds included $C{\equiv}N_{str}$ at $2227cm^{-1}$ for nitrile (**2.17**), the intense symmetrical and antisymmetrical $N{=}O_{str}$ at 1346 and $1526cm^{-1}$ in the aromatic nitro compound (**2.19**) and the ethereal $C\text{-}O_{str}$ at 1133 and $1228cm^{-1}$ for the trimethoxy groups in (**2.20**).

$^{1}H$ NMR analysis of the benzylated analogues showed an important common aliphatic signal, that of the methylene amino protons, which resonated as a double doublet, and were found at 3.88ppm in the spectrum of the unsubstituted benzylated molecule (**2.16**). The corresponding signals for these protons in compounds (**2.17-2.20**) were at 3.89, 3.84, 3.94 and 3.80ppm respectively, all showing the same splitting pattern. Other individual aliphatic signals of note were the aromatic methyl singlet of (**2.18**) at 2.35ppm and the intense methoxy reonances of (**2.20**) at 3.88ppm. The main additional $^{1}H$ NMR features present in the spectra of the benzylated molecules were found in the aromatic region, which was uniformly complex in all examples, with considerable signal overlap. Despite similar substitution patterns in some of these molecules, notably (**2.17-2.19**), there existed considerable dissimilarities in these spectra. Diagnostic signals in the $^{13}C$ NMR spectra included the quaternary nitrile carbon at 119ppm in the spectrum of (**2.17**), the aromatic methyl of (**2.18**) at 20.6ppm and the methoxy carbons of (**2.20**), at 55.6, 55.7 and 57.9ppm.

In the GCMS spectrum of the benzylated molecules (**2.17-2.20**), prominent ions were seen in all cases corresponding to fragmentation at the benzylic carbon; other important fragmentations included cleavage at the benzylic bond carrying the amine functional group, and in molecule (**2.19**), ions corresponding to (M-NO) and (M-NO-CO) were visible, characteristic of aryl nitro compounds. Cleavage of the aryl ketone was also expected, yet many fragmentation patterns can arise from such a split.

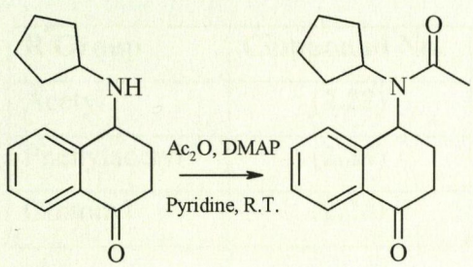


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## 2.4 *N*-acylation of the key secondary amine intermediate towards amides of structural type (A)

Apart from the tertiary amines outlined above, it was of interest to synthesise some *N*-acyl derivatives of (**2.9**), as it was felt that these molecules might possess anti-inflammatory properties, akin to the amides of the aforementioned indanone derivatives[64]. *N*-acylation of amines is usually performed using a reactive acid derivative such as an acid chloride[158,159] or anhydride[160], with the inclusion of a tertiary base such as triethylamine or pyridine, and perhaps an acylation catalyst. Commonly employed catalysts include *N*,*N*-Dimethylamino pyridine (DMAP), cobalt (II) chloride[161], and, in the case of selective acylations, phase-transfer catalysis[162]. *N*-acylation of (**2.9**) proved even more difficult than *N*-alkylation, with very slow reaction rates and scant yields.

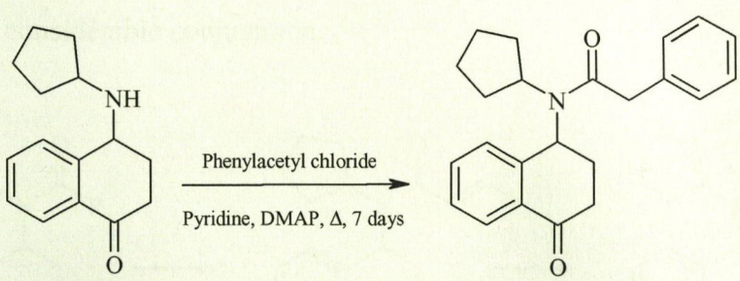
Acetylation of the amino group was accomplished using acetic anhydride in pyridine (Scheme 2.13), the reaction in DCM with triethylamine giving only unchanged starting material. Several equivalents of DMAP were required to accomplish the reaction.




(**2.22**)

**Scheme 2.13**

Using pyridine as both solvent and base, a low yield of the phenylacetyl derivative was obtained (Scheme 2.14), thus allowing contrast with amine (**2.16**).



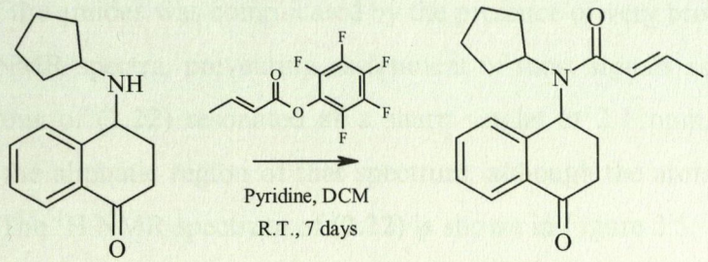

(**2.9**) (**2.23**)

**Scheme 2.14**



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Of four attempted reactions of (**2.9**) with various activated esters, only trace amounts of one derivative, the *N*-crotonyl (**2.24**), were isolated (Scheme 2.15).




**(2.9)** **(2.24)**

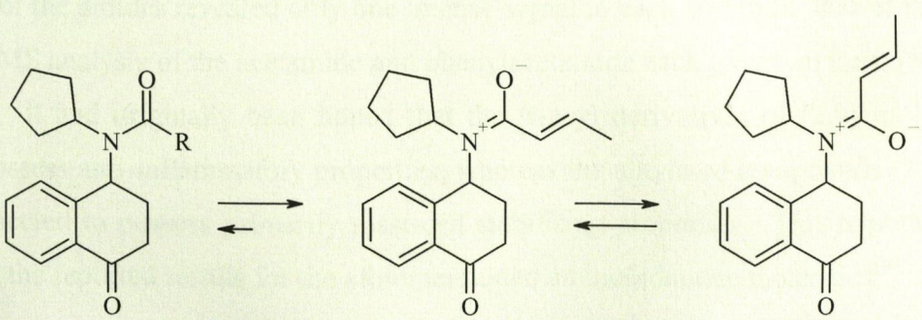
**Scheme 2.15**

One further method of amide synthesis is the *in situ* generation of an acid chloride in refluxing toluene using as substrates the parent acid and 2,6-dichlorobenzoyl chloride, yet this method proved to be of no benefit in the synthesis of *N*-acyl analogues of (**2.9**).

**Table 2.2 *N*-acyl derivatives of compound (2.9)**

| R Group | Compound No. |
|---|---|
| Acetyl | (**2.22**) |
| Phenylacetyl | (**2.23**) |
| Crotonyl | (**2.24**) |

The amides were isolated as crystalline compounds, and infrared analysis showed intense $C{=}O_{str}$ of the amide moiety in the first two cases, at 1644 and 1646cm$^{-1}$. It was postulated that the absence of a strong band in this region for the crotonyl derivative may be due to its almost complete existence as the mesomeric form shown below (Scheme 2.16), which is favoured due to considerable conjugation.




**(2.24)** **Scheme 2.16**



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The $C{=}O_{str}$ of the benzylic ketone followed the amide $C{=}O_{str}$ absorption, at 1688, 1694, and 1738cm$^{-1}$.

NMR analysis of the amides was complicated by the presence of very broad signals in both the $^{1}H$ and $^{13}C$ NMR spectra, preventing assignment of most signals as discrete entities. The methyl protons of (**2.22**) resonated as a sharp singlet at 2.11ppm, the only clearly visible signal in the aliphatic region of that spectrum, although the aromatic signals were better resolved. The $^{1}H$ NMR spectrum of (**2.22**) is shown in Figure 2.5.

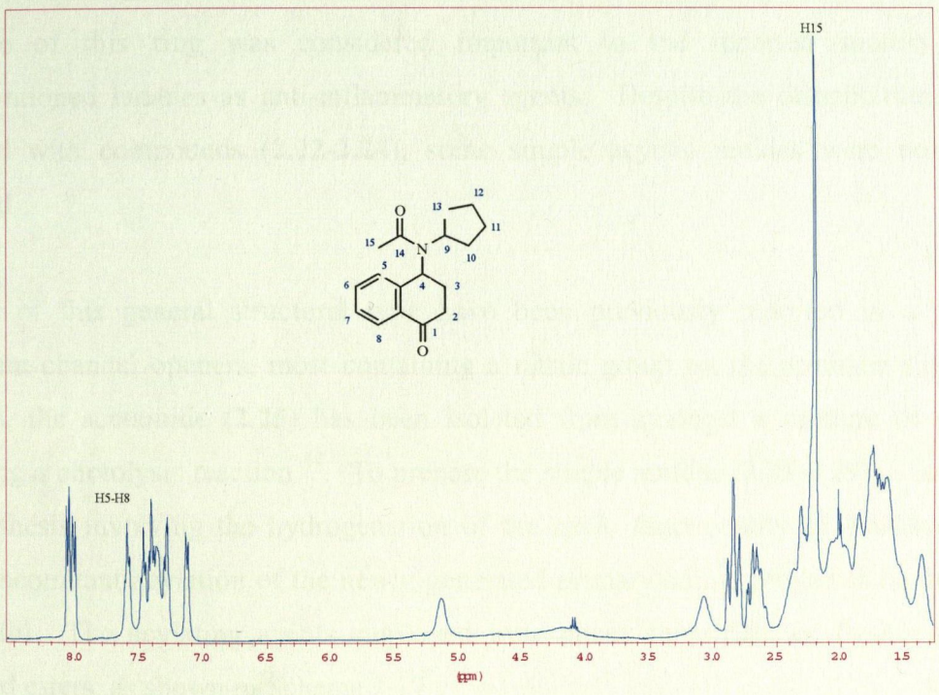



**Figure 2.5 $^{1}H$ NMR spectrum of compound (2.22)**

This was assumed to be due to mesomerism about the amide bond, which can lead to the existence of *cis* and *trans* forms, as illustrated for the crotonyl derivative above. GCMS analysis of the amides revealed only one intense signal in each spectrum, that of the (M+1) ion. HRMS analysis of the acetamide and phenylacetamide each gave two ions, (M+1) and (M+Na). It had originally been hoped that the *N*-acyl derivatives of (**2.9**) in Table 2.2 would possess anti-inflammatory properties, whereas the alkylated compounds (**2.14-2.21**) were expected to possess primarily mast-cell stabilising properties. This hypothesis was based on the reported results for the aforementioned aminoindanone molecules[64].



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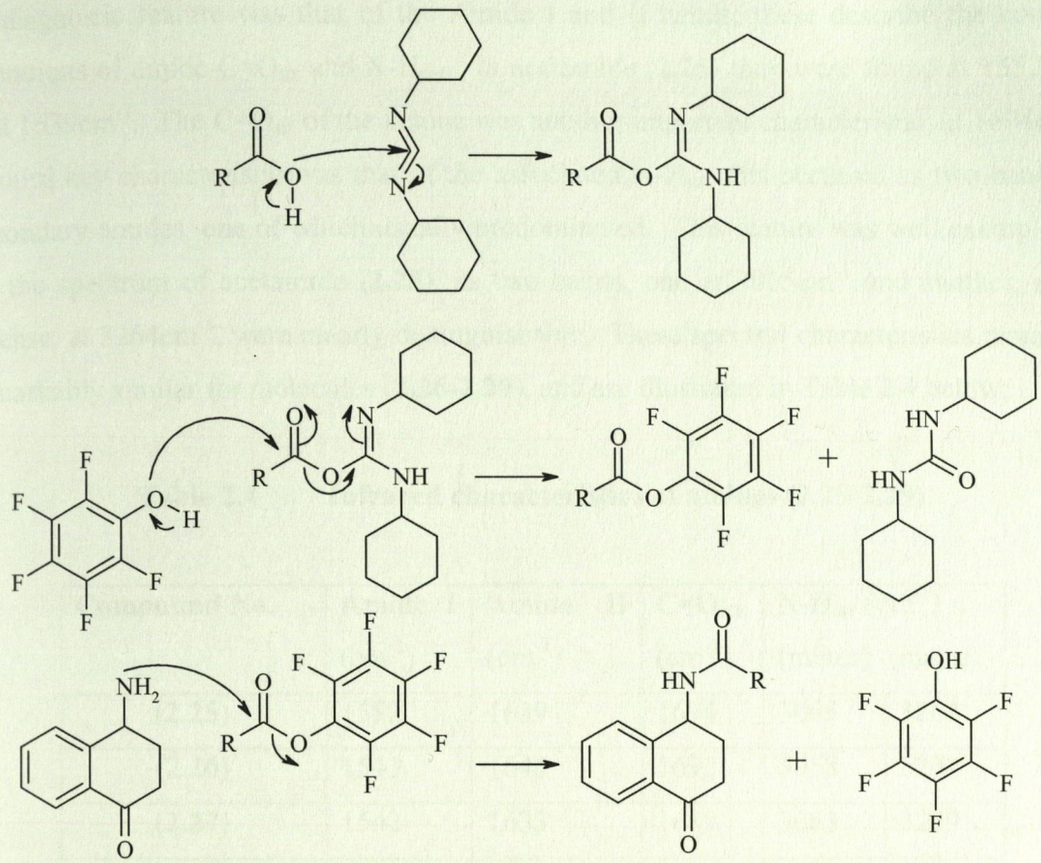
In that series, the *N*-acyl derivatives showed considerable promise as anti-inflammatory agents. When tested (Section 6.3.6, Figure 6.14), the amides (**2.22-2.24**) did not show statistically significant inhibition of arachidonic acid-induced ear swelling in the standard murine model.

## 2.5 *N*-acylations of 4-aminotetralone

In the design of these molecules, it had also been planned to generate a series of simple amides with a 4-amino tetralone nucleus but lacking the cyclopentyl ring system, as the presence of this ring was considered important to the reported success of the aforementioned indanes as anti-inflammatory agents. Despite the disappointing results obtained with compounds (**2.22-2.24**), some simple acyclic amides were nonetheless prepared.

Amides of this general structural type have been previously reported in a study of potassium channel openers, most containing a nitrile group on the aromatic ring[163]. In addition, the acetamide (**2.25**) has been isolated from amongst a mixture of products following a photolysis reaction[164]. To prepare the simple amides (**2.25-2.29**), a facile one-pot synthesis involving the hydrogenation of the azide functionality in 4-azidotetralone with concomitant acylation of the newly generated primary amine proved to be uniformly successful. The acylating agents employed were either anhydrides or freshly prepared activated esters, as shown in Scheme 2.17.

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**Scheme 2.17 General scheme for the preparation of amides (2.25-2.29)**

**Table 2.3 Secondary amides of 4-amino tetralone**

| R group | Compound No. | Reaction time | % Yield |
|---|---|---|---|
| Acetyl | (**2.25**) | R.T, overnight | 50 |
| Propionyl | (**2.26**) | R.T, overnight | 40 |
| Hydrocinnamyl | (**2.27**) | R.T, overnight | 69 |
| Phenylacetyl | (**2.28**) | R.T, overnight | 64 |
| 3,4-Dichlorobenzoyl | (**2.29**) | R.T, overnight | 81 |

These compounds were all isolated as solids in moderate to good yields. Infrared spectroscopy was an important tool in the characterisation of these amides, as they showed several important vibrations.



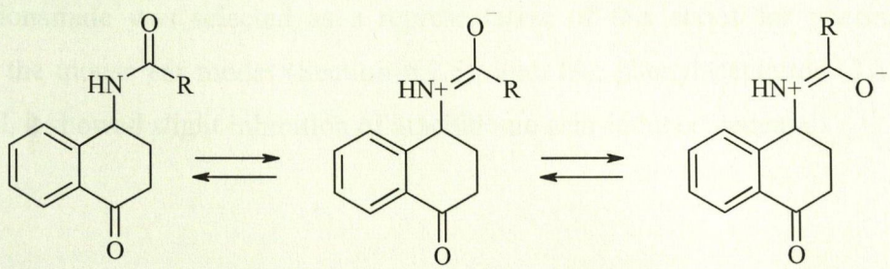
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A diagnostic feature was that of the Amide I and II bands; these describe the coupled vibrations of amide $C=O_{str}$ and $N\text{-}H_{def}$. In acetamide (**2.25**) they were found at 1552cm$^{-1}$ and 1639cm$^{-1}$. The $C=O_{str}$ of the ketone was another important characteristic, at 1694cm$^{-1}$. A third key characteristic was that of the associated $N\text{-}H_{str}$; this occurred as two bands in secondary amides, one of which usually predominated. This feature was well exemplified by the spectrum of acetamide (**2.25**), as two bands, one at 3065cm$^{-1}$ and another, more intense, at 3264cm$^{-1}$, were clearly distinguishable. These spectral characteristics remained remarkably similar for molecules (**2.26-2.29**), and are illustrated in Table 2.4 below:

**Table 2.4 Infrared characteristics of amides (2.25-2.29)**

| Compound No. | Amide I ($cm^{-1}$) | Amide II ($cm^{-1}$) | $C=O_{str}$ ($cm^{-1}$) | $N\text{-}H_{str}$ ($cm^{-1}$) (minor) | (major) |
|---|---|---|---|---|---|
| (**2.25**) | 1552 | 1639 | 1694 | 3065 | 3264 |
| (**2.26**) | 1541 | 1645 | 1692 | 3058 | 3274 |
| (**2.27**) | 1542 | 1633 | 1689 | 3063 | 3279 |
| (**2.28**) | 1542 | 1640 | 1690 | 3063 | 3267 |
| (**2.29**) | 1543 | 1637 | 1689 | 3066 | 3252 |

Analysis of the $^1$H NMR spectra of these compounds revealed the same broadening of signals that was encountered with the *N*-cyclopentyl amides (**2.22-2.24**), as these amides may also exist in more than one mesomeric form. This can be depicted by the following representation (Scheme 2.18):




**Scheme 2.18**

Compound (**2.25**), the acetamide, showed in the $^1$H NMR two broad signals for the methyl protons, at 2.04 and 2.05ppm. These overlapped with one of the β-keto methylene protons, at 2.10ppm. The second β-keto methylene proton was found at 2.32ppm. Two multiplets were also visible for the α-keto methylene protons, at 2.62 and 2.75ppm.



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The methine proton was also very broad, at 5.32ppm. The squat signal at 6.44ppm may be attributed to the proton of the secondary amide, and the aromatic signals were also broadened, with two protons at 7.36ppm, and one each at 7.54 and 7.94ppm. This data agreed well with the reported NMR data for the acetamide.

A very similar spectrum was observed for the propionamide (**2.26**), the two key signals of the side chain being the methyl triplet at 1.24ppm and the methylene quartet at 2.33ppm. Substitution of the amine by a hydrocinnamoyl group resulted in a more resolved spectrum than that of the more simple amides; the β-keto methylene protons resonated at 1.97 and 2.24ppm, followed by a multiplet for the side chain methylenes from 2.56-2.62ppm. The protons of the α-keto methylene appeared as a double doublet at 3.02ppm. Addition of the second benzene ring added complexity to the aromatic region, with a doublet at 7.04ppm integrating as one proton, six protons from 7.21-7.34ppm, what appeared to be two almost superimposed triplets at 7.44ppm, and the final doublet at 7.93ppm. The $^{1}H$ NMR spectrum of (**2.27**) contained four methylene resonances, from 1.97-3.02ppm, while a characteristic feature of the spectrum of (**2.28**) was the side chain methylene protons of the phenacyl moiety, a broad apparent singlet at 3.63ppm, contrasting to the broad double doublet signals of the benzyl side-chain methylene protons of compounds (**2.16-2.20**).

GCMS analysis of the amides showed strong M+1 ions for compounds (**2.25**), (**2.26**), (**2.27**) and (**2.28**); these four spectra contained no other intense ions; compound (**3.29**) also contained an ion cluster around the molecular ion, but had an intense ion at 144.

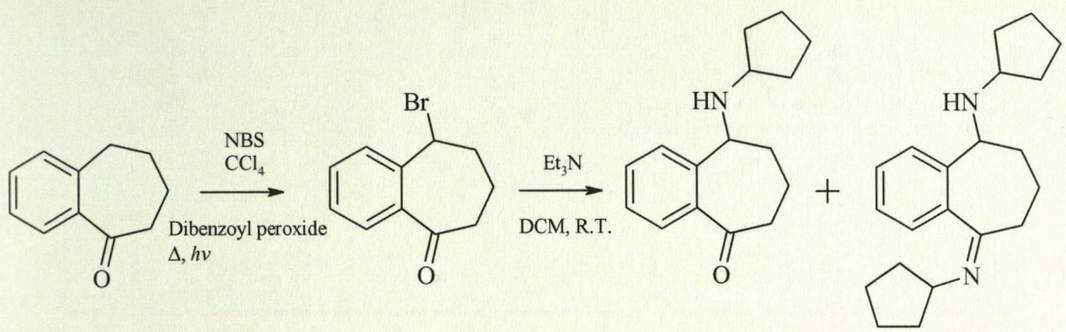
The propionamide was selected as a representative of this series for pharmacological testing in the mouse ear model (Section 6.2.5), and, like phenylacetamide (**2.23**) already mentioned, it showed slight inhibition of arachidonic acid-induced oedema.



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## 2.6 Synthesis of molecules of structural type (B)

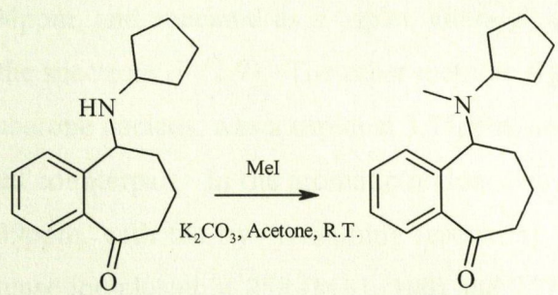
To investigate the effect on mast cell-stabilising activity of extending the ring system in (**2.9**) by one carbon, the benzosuberyl analogue (**2.30**) was synthesised. The brominated derivative of benzosuberone was a stable, isolable molecule, and was formed in good yields under Wohl-Ziegler conditions, although the reaction was difficult to drive to completion. Substitution with cyclopentylamine in this case suffered from competing side-reactions, including that of imine formation through reaction of the primary amino group in cyclopentylamine with the ketone in benzosuberone, forming (**2.31**) (Scheme 2.19).




**(2.30)** **(2.31)**

**Scheme 2.19**

The considerable stability of this imine was exhibited by its lack of degradation on silica and by the molecular ion observed on GCMS analysis. The crude mixture of the desired amine (**2.30**) and imine (**2.31**) was treated with a 1:1 mixture of 2M aqueous HCl and methanol to hydrolyse the imine bond. The secondary amine (**2.30**) was then methylated using methyl iodide in acetone with potassium carbonate as base (Scheme 2.20).




**(2.30)** **(2.32)**

**Scheme 2.20**

The principal infrared absorption of this molecule was the $C{=}O_{str}$, at 1687cm$^{-1}$. $^1$H NMR analysis (Figure 2.6) revealed an intensely coupled spectrum, the first two signals being those of the four cyclopentyl methylene protons; those flanked on either side by the other



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two methylenes occur at 1.42ppm, with the remaining two, those flanking the cyclopentyl methine, at 1.57ppm.

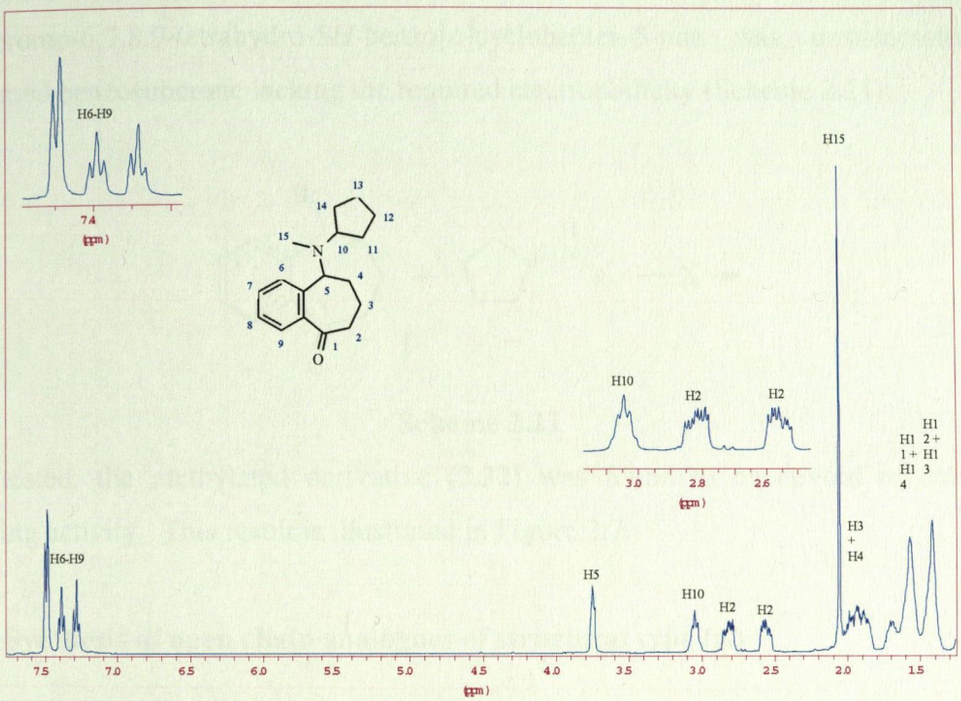



**Figure 2.6** **$^1$H NMR spectrum of compound (2.32)**

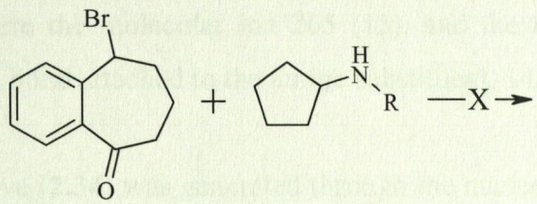
Two of the benzosuberone methylenes occupied the region from 1.67-1.74ppm and 1.85-2.02ppm, immediately followed by the sharp singlet signal for the methyl amino protons, at 2.05ppm. The remaining methylene group, that α to the ketone, was split into two multiple signals, one for each proton, at 2.55 and 2.81ppm. The methine of the cyclopentyl group resonated at 3.04ppm, and appeared as a triplet, although quite broad, and may in fact be a quintet as in the spectrum of (**2.9**). The other methine signal, that of the benzylic position of the benzosuberone nucleus, was a triplet at 3.75ppm, and appeared broader than that of its six-membered counterpart. In the aromatic region, two of the protons appeared singly, at 7.28 and 7.39ppm, with the two remaining resonating from 7.50ppm. GCMS analysis showed an intense ion cluster at 258 (M+1, 100) and 257 ($M^+$, 48). HRMS gave an accurate mass of 258.1873 ($+H^+$), calculated 258.1858.

Although other alkylations of (**2.30**) were planned, the apparent rate of reaction was even slower than in the tetralone series, perhaps reflecting enhanced steric bulk of the benzosuberyl moiety, and no further tertiary amines were isolated.



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A further attempt to react secondary amines bearing a cyclopentyl group (formed quantitatively through the condensation of aromatic aldehydes with cyclopentylamine and subsequent reduction of the Schiff base with borohydride[165,166]) with the benzylic bromine of 9-bromo-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one was unsuccessful, the brominated benzosuberone lacking the required electrophilicity (Scheme 2.21).



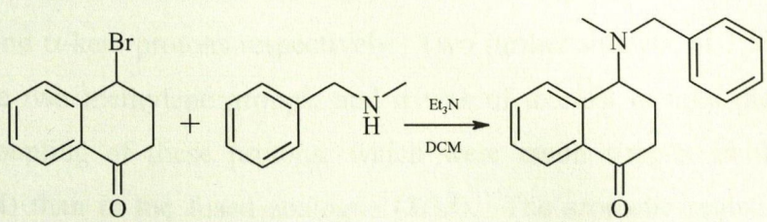

**Scheme 2.21**

When tested, the methylated derivative (**2.32**) was found to be devoid of mast cell-stabilising activity. This result is illustrated in Figure 2.7.

## 2.7 Synthesis of open chain analogues of structural type (A)

To demonstrate the necessity of both the fused tetralone ring and the cyclopentyl ring in derivatives of (**2.9**) for activity, two disassembled molecules were selected for synthesis and testing, namely analogues (**2.33**) and (**2.34**), the former devoid of the cyclopentyl ring but possessing the tetralone nucleus, and the latter a completely open-chain derivative, having neither tetralone nor cyclopentyl substituents.

The first structure, (**2.33**), was synthesised by simply reacting *N*-benzylmethylamine with 4-bromotetralone, using either DCM or acetone as solvent (Scheme 2.22). The amine was isolated in poor yield (25%) due to the aforementioned propensity of 4-bromotetralone to undergo rapid decomposition.




**(2.33)**

**Scheme 2.22**

The main feature of this molecule in the infrared spectrum was the $C{=}O_{str}$, at 1693cm$^{-1}$. In the $^1$H NMR spectrum, the β-keto methylene protons resonated between 2.11-2.39ppm,

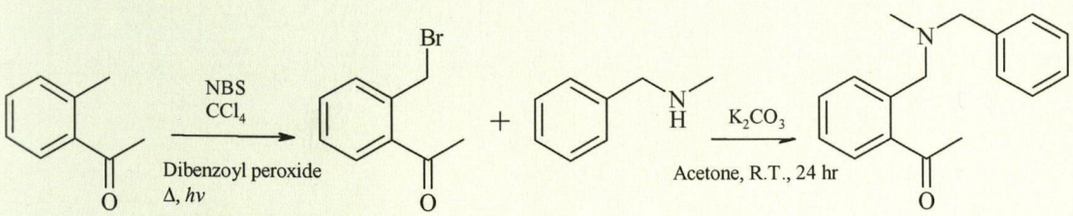


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overlapping with the singlet for the *N*-methyl group, at 2.26ppm. The second methylene of the tetralone ring, that α to the keto group, was split into two multiplets, at 2.55 and 2.93ppm. The third methylene group, that of the benzyl substituent, resonated at 3.75ppm as a double doublet. The methine proton, at 4.08ppm, was double doublet. In the aromatic region, six of the protons resonated between 7.26-7.44ppm, followed by three signals; a multiplet at 7.60ppm and two doublets, at 7.96 and 8.05ppm. In the GCMS spectrum, the three important ions were the molecular ion 265 (15), and the two ions resulting from cleavage of the benzylic bond attached to the amine substituent, 146 (100) and 120 (86).

The open-chain derivative (**2.34**) was generated through the nucleophilic substitution of 1-[2-(bromomethyl)phenyl]-1-ethanone, the latter obtained through benzylic bromination of 2′-methylacetophenone (Scheme 2.23).

Interestingly, this simple brominated molecule also darkened rapidly on removal of the solvent, and fumed considerably. The reaction of this molecule with benzylamine, a primary amine, resulted only in decomposition, yet its combination with *N*-benzylmethylamine, a secondary amine, was successful in the production of (**2.34**), albeit in modest yield (26%).




**(2.34)**

**Scheme 2.23**

The $^1$H NMR spectrum of (**2.34**) was simple, with two singlet peaks at 2.09 and 2.58ppm, for *N*-methyl and α-keto protons respectively. Two further singlets, at 3.53 and 3.79ppm, represented the two methylene groups, and it was of interest to note the effect of ring opening on coupling of these protons, which were much simpler in the ring-opened molecule (**2.34**) than in the fused analogue (**2.33**). The aromatic region was relatively similar to that of (**2.33**), with six protons between 7.25-7.35ppm, followed by a single proton at 7.41 and two condensed terminal proton signals at 7.54ppm.



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The literature does not record the prior preparation of the simple brominated derivative of 2′-methylacetophenone used above, and it may be that although it cannot itself eliminate, it may undergo alternative side-reactions. The results of preliminary screening of molecules (**2.33**) and (**2.34**) are shown in Figure 2.8.

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## 2.8 Initial mast cell-stabilising results for compounds of Chapter 2

Preliminary pharmacological screening of all novel compounds in this thesis for anti-allergic activity was performed using the rat peritoneal mast cell (RPMC) preparation (Section 1.13.1.1). Details of the experimental procedure are included in Section 6.2.3, and the mast cell-stabilising results for molecules (**2.14-2.21**) are shown in Figure 2.7.

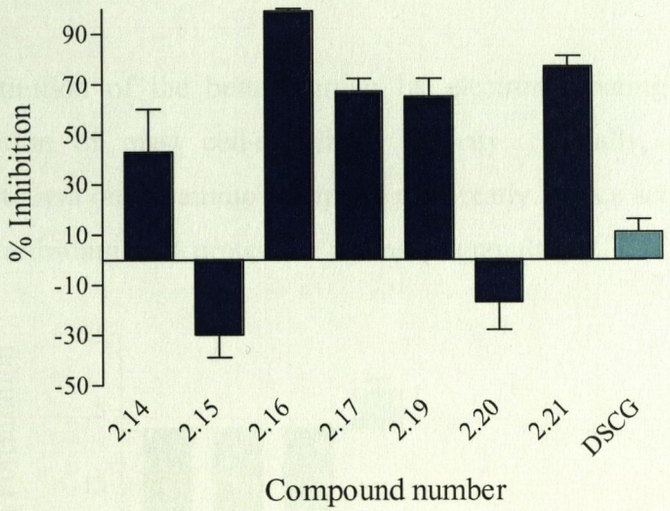



**Figure 2.7 Mast cell-stabilising activity of compounds (2.14-2.21)**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*

**Table 2.5 Summary statistics for compounds (2.14-2.21)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **2.14** | 41 | 25 | 12 | 4 |
| **2.15** | -30 | 19 | 9 | 5 |
| **2.16** | 99 | 1 | 1 | 5 |
| **2.17** | 67 | 9 | 5 | 5 |
| **2.19** | 65 | 15 | 7 | 5 |
| **2.20** | -17 | 24 | 11 | 5 |
| **2.21** | 77 | 12 | 4 | 10 |
| DSCG | 10 | 25 | 3 | 94 |



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Methylation of the amine substituent in (**2.9**) resulted in a compound capable of inhibiting histamine release from rat peritoneal cells by 41%, whereas allylation of the molecule actually had the opposite effect within this series of molecules. Introduction of a bulky planar benzyl had a profound effect on activity, resulting in complete inhibition of histamine release at the concentration tested. Activity was reduced slightly by the presence of electron-withdrawing *para*-substituents such as a nitrile or nitro group on the benzyl ring, although both compounds retained significant activity (67% and 65% inhibition, respectively).

Conversely, substitution of the benzyl group by electron-donating trimethoxy groups resulted in abolition of mast cell-stabilising activity. Finally, a large planar 2'-naphthalenyl substituent on the amino group did not greatly reduce activity as compared to the benzyl group, affording 77% protection against degranulation.

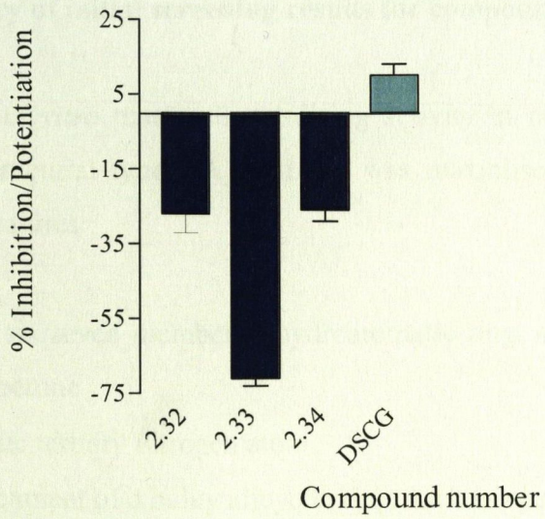



**Figure 2.8 Mast cell-stabilising activity of compounds (2.32-2.34)**
*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*



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**Table 2.6 Summary statistics for compounds (2.32-2.34)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **2.32** | -27 | 11 | 5 | 4 |
| **2.33** | -71 | 2 | 2 | 2 |
| **2.34** | -26 | 6 | 3 | 4 |
| DSCG | 10 | 25 | 3 | 94 |

It is clear from Figure 2.8 that none of these derivatives possessed any mast-cell stabilising activity whatsoever, and in fact were seen to encourage degranulation. These results further corroborated the theory that a conformationally restrained cyclic system as in (**2.9**) and its derivatives was essential for mast cell-stabilising activity among molecules of this type.

## 2.9 Summary of initial screening results for compounds of Chapter 2

To summarise, *in vitro* mast cell-stabilising activity in rat peritoneal mast cells among molecules of structural types (**A**) and (**B**) was maximised in molecules possessing the following key features:

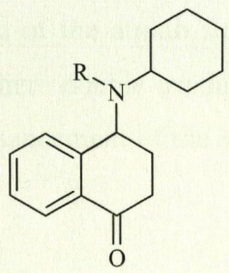
- A fused six/seven membered hydroaromatic ring, as exemplified by tetralone and benzosuberone
- A benzylic tertiary nitrogen atom
- The attachment of a bulky alicyclic ring, such as cyclopentyl, to the amino group
- Additional substitution of the amino group by a bulky benzyl/substituted benzyl group
- Electron withdrawing substituents on the bulky aromatic portion of the molecule resulted in slightly reduced activity, whereas substitution by the highly electron-donating trimethoxy group abolished activity completely.
- The requirement for structural rigidity was emphasised by the abolition of activity among ring-opened derivatives.

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# Synthesis and preliminary screening of novel amino compounds featuring a tetralone or benzosuberone nucleus and a benzylic tertiary *N*-cyclohexyl or *N*-cyclohexenyl moiety

## 3.1 Synthetic targets of Chapter 3

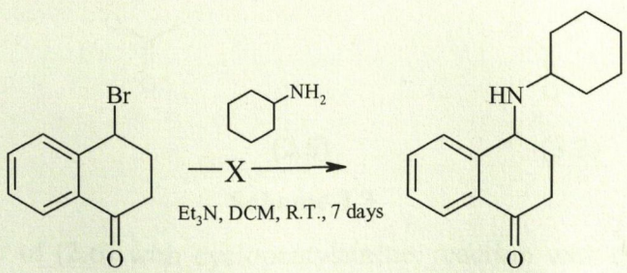
From the initial mast-cell stabilising results obtained from Chapter 2, it became evident that both a fused hydroaromatic ring system and a bulky cyclopentyl group were essential for the desired pharmacological effect, and that activity was greatly enhanced by the presence of a benzyl substituent attached to the amino group. Having determined these apparent pre-requisites for mast cell-stabilising activity, it was decided to investigate the effect of enlarging the cyclopentyl ring by one methylene group. Replacement of the cyclopentyl by a cyclohexyl moiety was the first target, generating compounds of structural type (**C**).




**(C)**

## 3.2 Synthesis of molecules of structural type (C)

Unsurprisingly, all attempts to react cyclohexylamine directly with the highly reactive 4-bromotetralone (**2.1**) met with the same fate as the analogous reactions of cyclopentylamine, namely, swift decomposition of the unstable brominated molecule (Scheme 3.1).



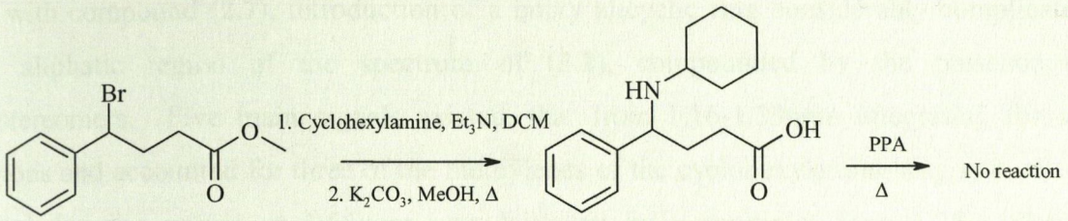

**Scheme 3.1**



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Analogously to the reaction of (**2.12**) with cyclopentylamine, replacement of the bromine atom was also attempted with cyclohexylamine (Scheme 3.2), and again substitution by the amine resulted in a mixture of the acid and ester. Ester hydrolysis was completed using potassium carbonate in methanol, to yield acid (**3.1**).

The amino acid thus obtained was added neat to polyphosphoric acid and the mixture heated gently. Again, no cyclisation to the keto derivative was observed, and the starting material was recovered unchanged.

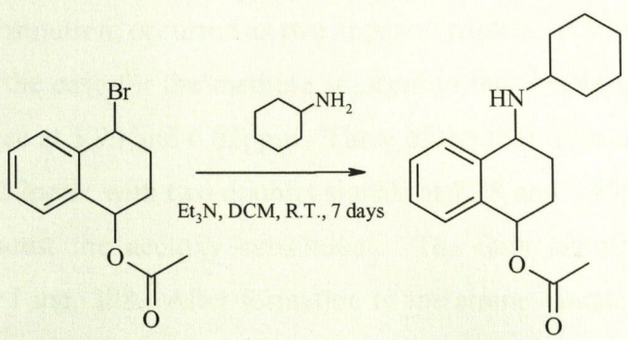



(**2.12**) (**3.1**)

**Scheme 3.2**

To further support the γ-positioning of the amino substituent in the above molecule, an NOE experiment was performed, where double irradiation of the benzylic methine proton at 4.71ppm resulted in emphatic enhancement of the signal for the *ortho*-aromatic protons at 7.25ppm.

Having exhausted the above options, the analogous pathway to the synthesis of (**2.9**) was selected for production of the cyclohexyl derivative (**3.4**). Reaction of the brominated acetate (**2.6**) with cyclohexylamine was performed in DCM with triethylamine as tertiary base (Scheme 3.3).




(**2.5**) (**3.2**)

**Scheme 3.3**

As with the reaction of (**2.6**) with cyclopentylamine, reaction with cyclohexylamine was sluggish, even under reflux conditions, and the reaction was allowed to proceed for seven



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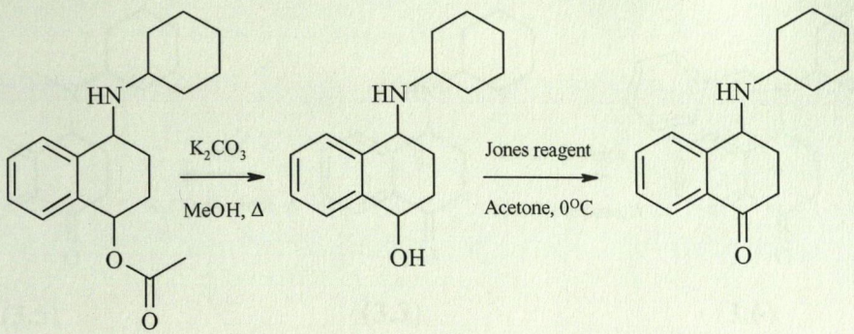
days before work-up, with intermittent addition of additional quantities (2 x 0.5 equivalents) of base and cyclohexylamine; as with all substitution reactions of this nature, salt formation of the amine precursor with liberated hydrogen halide can lower the theoretical yield. The infrared spectrum of the product amine (**3.2**) greatly resembled that of its cyclopentyl-substituted analogue (**2.7**), the two principal absorptions being those of $C\text{-}O_{str}$ at $1240cm^{-1}$ and the ketonic $C{=}O_{str}$ at $1733cm^{-1}$. $^1H$ NMR analysis showed the presence of a 2:1 diastereomeric ratio.

As with compound (**2.7**), introduction of a bulky alicyclic ring considerably complicated the aliphatic region of the spectrum of (**3.2**), compounded by the presence of diastereomers. Five main signals existed, that from 1.16-1.33ppm integrating for six protons and accounted for three of the methylenes of the cyclohexylamino ring system. A signal for one proton at 1.66ppm was followed by a multiplet from 1.78-1.90ppm, integrating for four protons. A complex signal for seven protons lay between 2.01-2.14ppm, and included both methylene and methyl protons, the latter dominating the spectrum as two sharp singlets, at 2.08 and 2.12ppm. The methylene $\alpha$ to the acetate functionality appeared as two separate signals, one for each proton, and in turn showed diastereomeric differences.

Much of one of these protons was engulfed by the aforementioned methylene/methyl signal, although the contribution from the smaller diastereomer was still visible, itself a multiplet at 2.35ppm. Its geminal proton was shifted considerably downfield, and the unequal diastereomeric contributions allowed pinpointing of the centre of these multiplet signals at 2.67 and 2.72ppm. The benzylic methine of position four, that of the cyclohexylamino substitution, occurred as two apparent triplets, at 3.85 and 3.97ppm. This was also seen to be the case for the methine adjacent to the acetate group, the two triplet signals in this instance at 5.96 and 6.02ppm. Three of the four aromatic protons resonated between 7.21 and 7.32ppm, with two doublet signals at 7.38 and 7.55ppm representing the aromatic proton nearest the acetoxy substituent. The only significant ion on GCMS analysis was the M+1 ion, 288. After formation of the amine acetate (**3.2**), the protecting ester group was removed by treatment with potassium carbonate, in methanol/water, under reflux for three hours (Scheme 3.4). Jones oxidation of the residue successfully generated the amine ketone (**3.3**).



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**(3.2)** **(3.3)** **(3.4)**

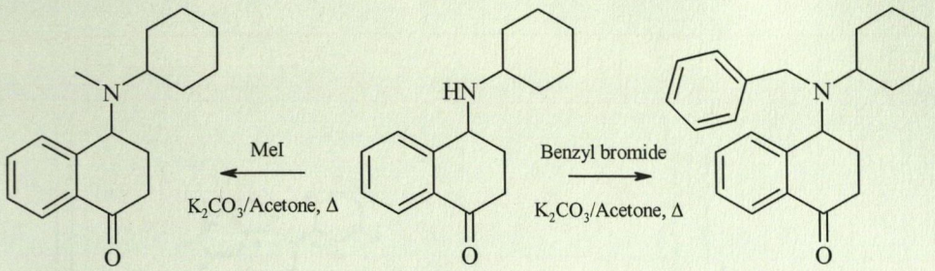
**Scheme 3.4**

The desired ketone was isolated as a pale brown oil, and its infrared spectrum showed characteristic ketonic $C=O_{str}$ at 1690cm$^{-1}$. The $^{1}H$ NMR spectrum was extremely complex in the aliphatic region, with intense coupling within the two ring systems. Three of the methylene groups from the cyclohexyl ring formed a broad multiplet resonating between 1.10-1.39ppm. The remaining two methylenes, those beside the methine proton, occurred further downfield, along with the secondary amine proton; these broad multiplets were located at 1.65, 1.78, 1.91 and 2.01ppm. The complex multiplet for the methine of the cyclohexyl ring was found at 2.09ppm, followed by the four separate signals for each of the protons of the tetralone methylene groups; these were also comprised of intricate multiplets. The resonance values for the β-keto protons were 2.30 and 2.67ppm, and those for the α-keto methylene double double doublets were 2.57 and 3.01ppm. The furthest downfield aliphatic resonance was that of the benzylic methine, which occurred at 4.08ppm. The aromatic region contained two multiplet signals, one representing a proton at 7.37ppm, another accounting for two protons at 7.55ppm, and the final resonance that of the proton nearest the ketone, which was a doublet at 8.03ppm. In the $^{13}C$ spectrum, the carbonyl resonance was at 197.9ppm. As with the cyclopentyl analogue (**2.9**), the GCMS profile of (**3.4**) contained as its main feature the molecular ion cluster, principally 244 (M+1, 100).

The final step in the synthesis of structural types (C) involved the alkylation of the amino substituent (Scheme 3.5). The two derivatives synthesised were the methyl and benzyl analogues. Acylations of the amine were not attempted, due to the reduced activity of derivatives (**2.22-2.24**).



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(3.5) (3.3) (3.6)

**Scheme 3.5**

As in the *N*-alkylations of (**2.9**), conversion of the secondary amine to a tertiary amine had little effect on the infrared spectral characteristics. The main infrared absorptions in molecules (**3.5**) and (**3.6**) were those of $C{=}O_{str}$, which occurred at 1692 and 1691cm$^{-1}$, respectively. The $^1$H NMR spectrum of (**3.5**) contained the complex cyclohexyl resonances between 1.16-1.51, 1.64 and 1.78-1.97ppm. The tetralone methylenes were multiplets at 2.20 (β-keto) and 2.58ppm (α-keto), the former almost obliterated by the methyl singlet at 2.21ppm. The methine signals comprised double doublets at 2.89ppm (cyclohexyl) and an apparent triplet at 4.16ppm (benzylic). In the aromatic region, all four signals were clear; at 7.35ppm, a double doublet; at 7.55ppm, a double doublet; at 7.80ppm, the doublet of position five; and at 8.03ppm, the doublet of position eight. In the $^{13}$C NMR spectrum, the methyl carbon resonated at 32.6ppm. The key features of the benzylated compound were the benzylic methylene group of the side chain, which appeared as a double doublet at 3.85ppm, and the complex aromatic region, which integrated as nine protons; at 7.24ppm, one proton; at 7.33ppm, three protons; at 7.45ppm, two protons; at 7.58, one proton; and at 8.03ppm, two protons.

As a representative of series (**C**), the $^1$H NMR spectrum of compound (**3.6**) is shown in Figure 3.1, showing the distinctive benzylic methylene resonance at 3.86ppm. The GCMS profile of (**3.5**) and (**3.6**) shared many characteristics both with each other and with those of (**2.14**) and (**2.16**); both *N*-methylated compounds showed dominant molecular ion clusters, strong peaks at 214, and peaks represnting cleavage at the benzylic amine bond, while the two benzylated molecules had M-142/143 ions, and compounds (**3.5**) and (**3.6**) had M-43 ions.

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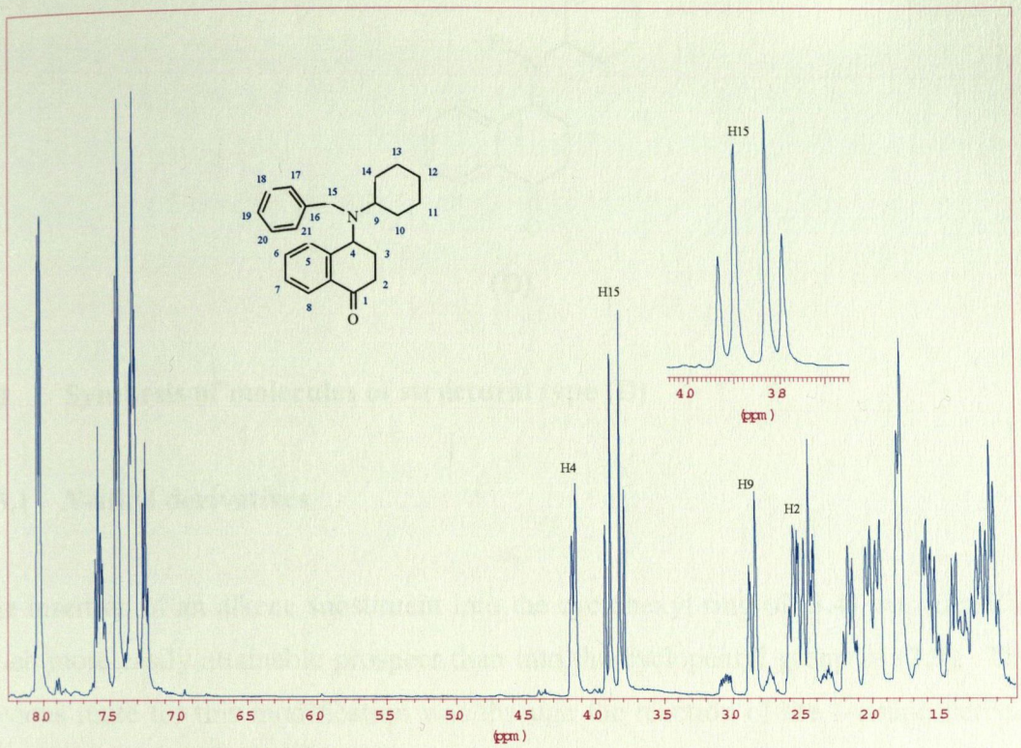



**Figure 3.1** **$^1$H NMR spectrum of compound (3.6)**

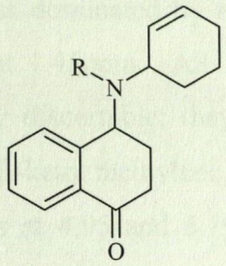
Preliminary screening results for compounds (**3.5**) and (**3.6**) are shown in Figure 3.6, Section 3.5.

From the results shown in Figure 3.4, it was clear that expansion of the alicyclic ring attached to the tertiary nitrogen in (**2.9**) and its derivatives by one carbon did not result in loss of activity. Also, the pattern of amine substitution was seen to affect the mast-cell stabilising activity of the molecule in a similar fashion to that observed with the cyclopentyl-substituted compound (**2.9**), a methyl group proving ineffective in comparison with a bulky, planar, benzylic substituent.

Conformational alterations in the alicyclic ring of the molecule may result in steric interference during the juxtapositioning of the pharmacophore with its site of action. With this in mind, it was decided to impose a degree of structural rigidity upon the relatively flexible alicyclic moiety. The modification chosen was the insertion of a double bond into the ring system, thus imposing both steric and electronic constraints. The targeted structures were of structural type (**D**).



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**(D)**

## 3.3 Synthesis of molecules of structural type (D)

### 3.3.1 *N*-alkyl derivatives

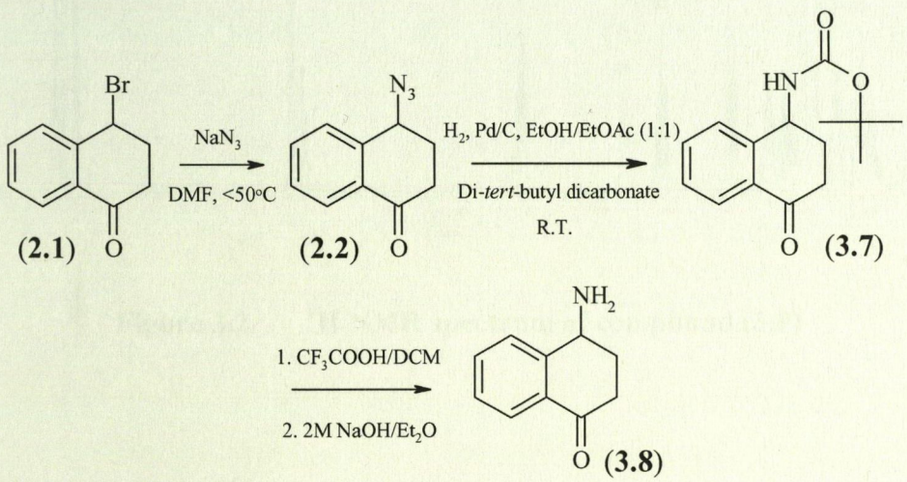
The insertion of an alkene substituent into the cyclohexyl ring of (**3.4**) was identified as a much more easily attainable prospect than into the cyclopentyl group of (**2.9**). The most obvious route for this modification was through the reaction of the 4-amino derivative of α-tetralone with a suitable allylic halide. The usefulness of 3-halocyclopentenes is well documented in the literature[167], as these molecules have been exploited in the synthesis of some important natural products. Unfortunately, the instability of these molecules makes their preparation difficult. Established methods include the addition of hydrogen halides to cyclopentadiene[168] and the vacuum thermolysis of adducts of dihalocarbenes with dicyclopentadiene[169]. The use of NBS to brominate cyclopentene has been documented, yet the resulting halo compound is unstable at temperatures above –30°C[117]. The synthetic difficulties anticipated in both the synthesis and reaction of this compound meant that our attention was focussed solely on the cyclohexenylamino derivative (**3.9**).

The synthesis of (**3.9**) required the 4-amino derivative of α-tetralone as a starting material (Scheme 3.6). As described in the previous chapter, this was obtained through the benzylic bromination of α-tetralone, without isolation of the halide as a pure substance. Instead, it was reacted *in situ* with sodium azide to afford the 4-azido derivative (**2.2**). This stable, storable intermediate was converted to the *BOC*-protected amine (**3.7**) under hydrogenation conditions, employing 10% palladium on activated carbon as hydrogenation catalyst. Characterisation of the amine as its stable *BOC*-protected derivative was facile; the molecule contained broad $C{=}O_{str}$ in the infrared at 1684cm$^{-1}$.



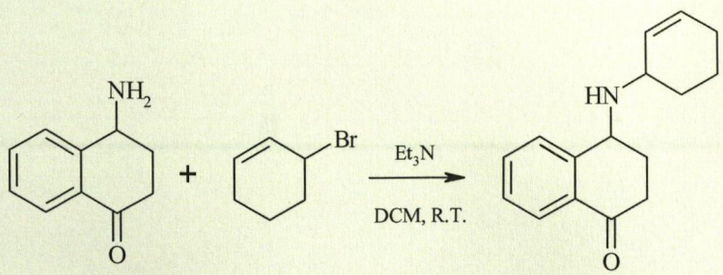
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The $^1$H NMR spectrum of (**3.7**) was dominated by the large singlet of the *BOC* group, which integrated for nine protons at 1.45ppm. All four of the protons in the tetralone methylene groups were individually discernible; they resonated at 2.05, 2.31, 2.57 and 2.74ppm, the former two for the β-keto methylene and the latter two for the α-keto methylene. Two broadened signals at 4.95 and 5.19ppm accounted for the amino and methine protons. In the aromatic region, the four protons were located at 7.31ppm (double doublet), 7.39ppm (doublet of position five), 7.49ppm (double doublet) and 7.92ppm (doublet of position eight). Subsequent removal of the *BOC* group was accomplished using trifluoracetic acid in DCM (1:1). Residual trifluoroacetic acid was removed under high vacuum using toluene to create an azeotrope, to yield the amine trifluoroacetate as a white solid. Washing with aqueous base and partitioning with ether yielded the free amine from the organic layer.




**Scheme 3.6**

Nucleophilic substitution of the commercially available halide 3-bromocyclohexene with (**3.8**), using triethylamine as base, afforded the secondary amine (**3.9**) (Scheme 3.7). Use of potassium carbonate as base in acetone resulted in a reduced yield for this transformation.




(**3.9**)

**Scheme 3.7**



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NMR analysis revealed the secondary amine (**3.9**) to consist of a diasteromeric mixture, complicating the analysis of the spectra, which are shown in Figures 3.2 and 3.3.

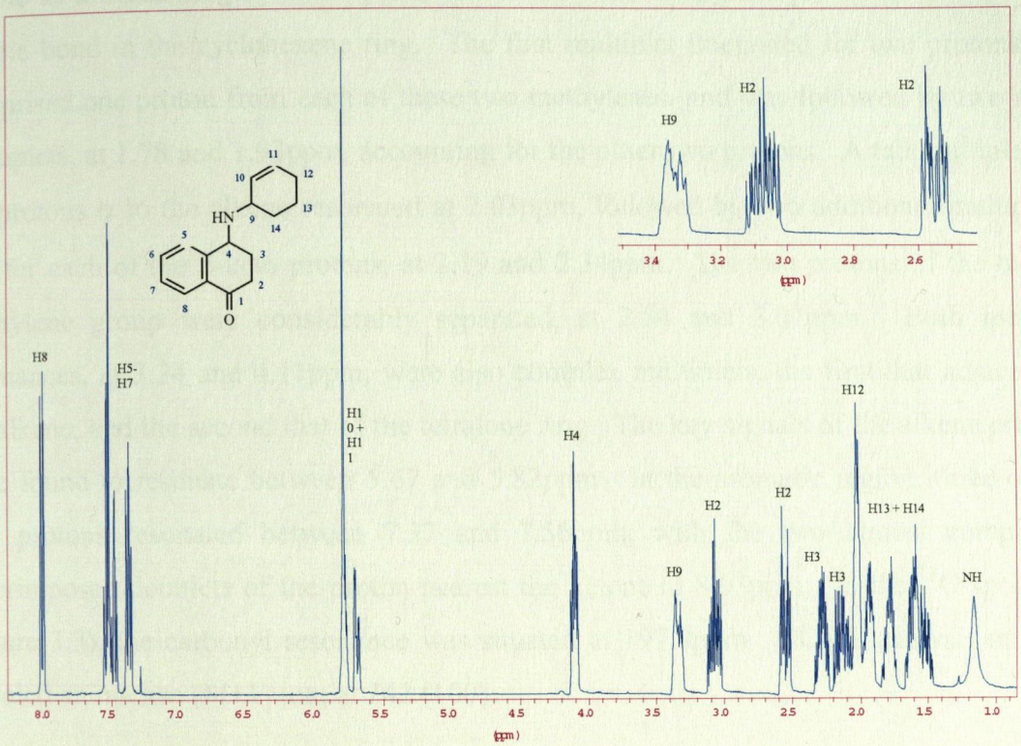



**Figure 3.2** **$^{1}$H NMR spectrum of compound (3.9)**

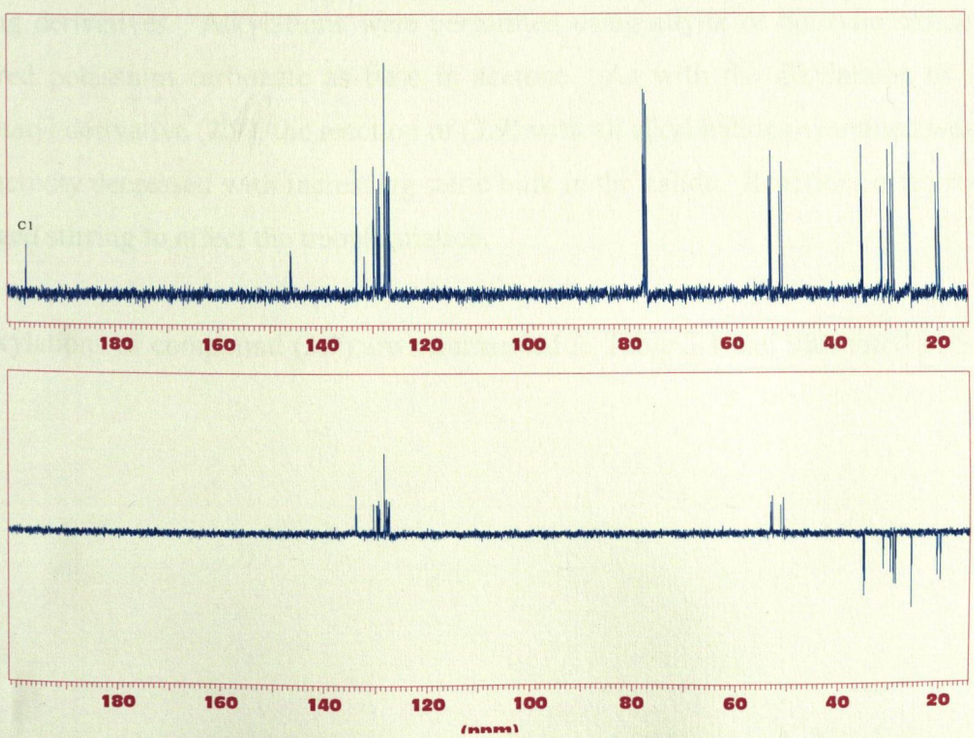



**Figure 3.3** **$^{13}$C NMR and DEPT 135 spectra of compound (3.9)**



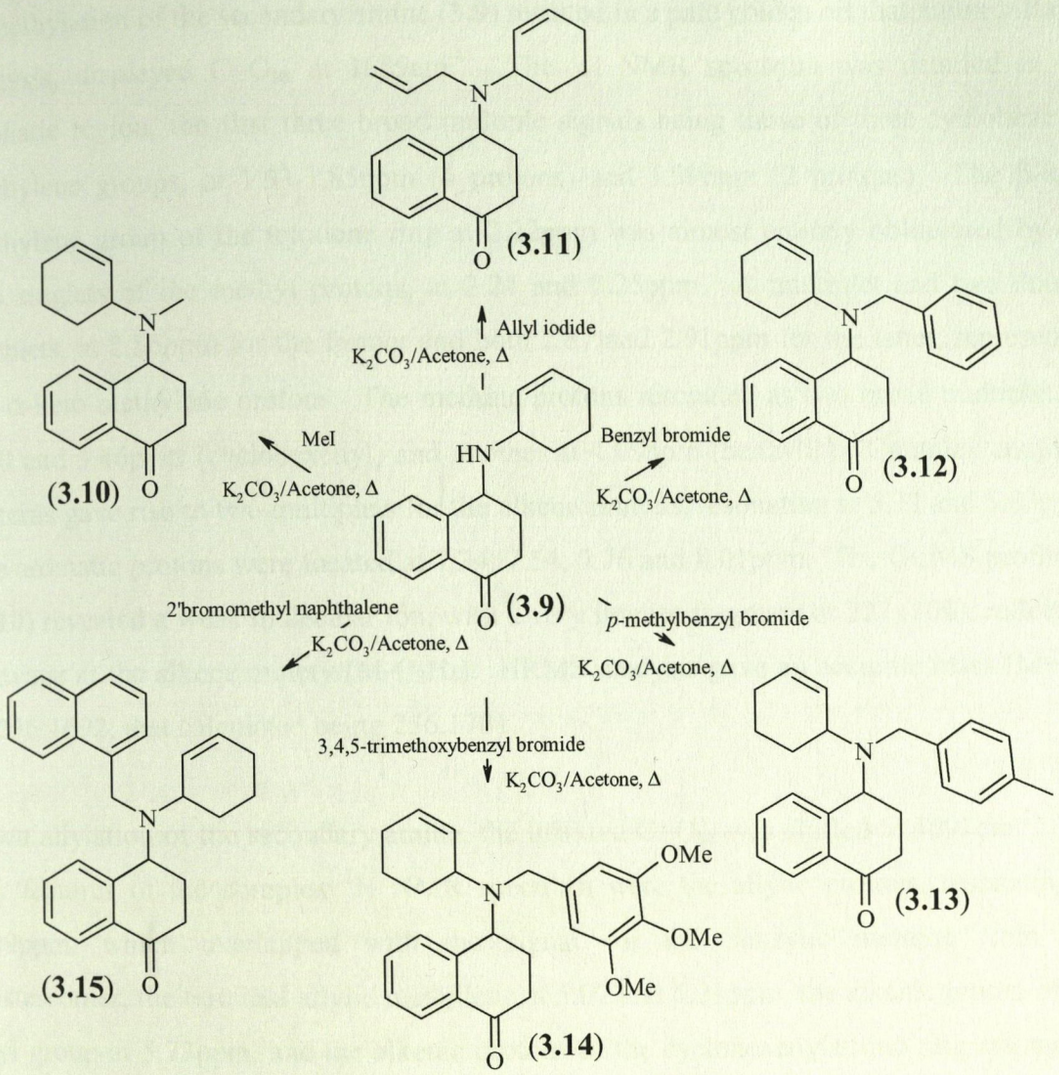
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In the aliphatic region of Figure 3.2, all of the methylene resonances were intense multiplets, and were assignable with the aid of a TOCSY spectrum. The amino proton was visible as a broad singlet at 1.16ppm, followed by the methylene protons β and γ to the double bond in the cyclohexene ring. The first multiplet integrated for two protons and comprised one proton from each of these two methylenes, and was followed by two more multiplets, at 1.78 and 1.93ppm, accounting for the other two protons. A tall multiplet for the protons α to the alkene resonated at 2.03ppm, followed by two additional multiplets, one for each of the β-keto protons, at 2.19 and 2.34ppm. The two protons of the α-keto methylene group were considerably separated, at 2.54 and 3.07ppm. Both methine resonances, at 3.34 and 4.11ppm, were also complex multiplets, the first that adjacent to the alkene, and the second that of the tetralone ring. The key signals of the alkene protons were found to resonate between 5.67 and 5.82ppm. In the aromatic region, three of the four protons resonated between 7.37 and 7.56ppm, with the two almost completely superimposed doublets of the proton nearest the ketone at 8.03ppm. In the $^{13}C$ spectrum (Figure 3.3), the carbonyl resonance was situated at 197.8ppm. GCMS analysis of (**3.9**) revealed an intense (M+1) ion, at 242 (100).

Upon isolation of the secondary amine in preparative quantities, a series of *N*-alkylations and *N*-acylations was planned, to enable quantitation of the effect of the double bond in the resulting derivatives. Alkylations were performed using allylic or benzylic halides, and employed potassium carbonate as base in acetone. As with the alkylations of the *N*-cyclopentyl derivative (**2.9**), the reaction of (**3.9**) with all alkyl halides examined was slow, and reactivity decreased with increasing steric bulk in the halide. Reactions often required prolonged stirring to effect the transformation.

The alkylations of compound (**3.9**) are summarised in Table 3.1 and illustrated in Scheme 3.8.

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**Scheme 3.8** ***N*-alkylations of compound (3.9)**

**Table 3.1** ***N*-alkyl derivatives of compound (3.9)**

| R Group | Compound No. | Reaction time | % Yield |
|---|---|---|---|
| Methyl | (3.10) | 74hr, R.T. | 72 |
| Allyl | (3.11) | 74hr, R.T. | 66 |
| Benzyl | (3.12) | 74hr, R.T. | 63 |
| *p*-methylbenzyl | (3.13) | 14 days, R.T. | 18 |
| 3,4,5-trimethoxybenzyl | (3.14) | 14 days, R.T. | 14 |
| 2'methylnaphthalenyl | (3.15) | 14 days, R.T. | 43 |



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*N*-methylation of the secondary amine (**3.9**) resulted in a pale golden oil that, upon infrared analysis, displayed $C=O_{str}$ at 1689cm$^{-1}$. The $^{1}H$ NMR spectrum was detailed in the aliphatic region, the first three broad multiple signals being those of three cyclohexenyl methylene groups, at 1.53-1.85ppm (4 protons) and 1.99ppm (2 protons). The β-keto methylene group of the tetralone ring at 2.22ppm was almost entirely obliterated by the two singlets of the methyl protons, at 2.24 and 2.25ppm. A multiplet and two double doublets, at 2.56ppm for the former and both 2.87 and 2.91ppm for the latter, represented the α-keto methylene protons. The methine protons resonated as two broad multiplets at 3.30 and 3.46ppm (cyclohexenyl) and another at 4.09ppm (benzylic). Complex coupling patterns gave rise to two multiplets for the alkene protons, resonating at 5.72 and 5.83ppm. The aromatic protons were located at 7.34, 7.54, 7.76 and 8.01ppm. The GCMS profile of (**3.10**) revealed a weak molecular ion, with a very intense fragment at 227 (100), reflecting cleavage at the alkene moiety ($M-C_2H_4$). HRMS analysis gave an accurate mass ($M+H^+$) of 256.1692, that calculated being 256.1701.

Upon allylation of the secondary amine, the infrared $C=O_{str}$ was shifted to 1691cm$^{-1}$. The key features of the complex $^{1}H$ NMR spectrum were the allylic protons, resonating at 3.29ppm, which overlapped with the signal for the benzylic methine from one diastereomer, the terminal allylic methylene at 5.07 and 5.21ppm, the alkenic proton of the allyl group at 5.73ppm, and the alkenic protons of the cyclohexenylamino ring resonating between 5.81-5.92ppm. GCMS analysis revealed a moderately intense molecular ion at 281 (34), and also ions at 253 ($M-C_2H_4$), 240 ($M-CH_2=CHCH_2$) and 138 (100). HRMS data yielded a mass of 282.1877 ($+H^+$), calculated 282.1858.

Upon *N*-benzylation, $C=O_{str}$ was also found at 1691cm$^{-1}$ in the infrared spectrum. In the $^{1}H$ NMR spectrum, the *N*-benzyl residue was accounted for by the multiplet at 3.88ppm for the methylene group and by the additional complexity in the aromatic region; one proton at 7.24ppm, three at 7.33ppm, two at 7.45ppm, one at 7.60ppm and the final two at 8.03ppm. The *p*-methylbenzyl derivative (**3.13**) had an identical $C=O_{str}$ in the infrared to the benzylated compound, at 1691cm$^{-1}$. Key signals in the $^{1}H$ NMR were again those of the side chain; the methyl singlets of identical resonance at 2.36ppm and the amino methylene at 3.86ppm. In the $^{13}C$ NMR, the *p*-tolyl carbon signal resonated at 20.6ppm. When substituted by a trimethoxy benzyl group, the infrared spectrum was characterised by the presence of ethereal $C-O_{str}$ at 1132 and 1236cm$^{-1}$, in addition to the $C=O_{str}$ of the ketone at



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1693cm$^{-1}$. The two key signals of the $^{1}$H NMR spectrum, namely the methylene amino and the trimethoxy signals were found to have almost identical resonance values, their signals being considerably overlapped.

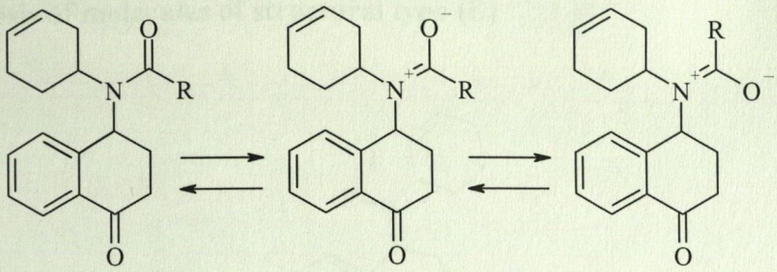
Three separate signals were visible for the trimethoxy protons, at 3.82, 3.84 and 3.85ppm, while the methylene amino multiplet resonated from 3.73-3.94ppm. In the aromatic region of the spectrum, two diagnostic signals for the two unsubstituted positions on the trimethoxybenzyl ring were found at 6.65 and 6.70ppm. In the $^{13}$C NMR spectrum, the trimethoxy carbon resonances were located at 55.6 and 60.3ppm. In the infrared spectrum of the highly hindered naphthalene derivative (**3.15**), the carbonyl group was found at 1692cm$^{-1}$. The $^{1}$H NMR spectrum of this molecule contained the diagnostic amino methylene group at 3.98-4.10ppm, while both alkene protons resonated at almost the same frequency, at 5.90ppm. GCMS analysis of molecules (**3.12-3.15**) revealed many similar characteristics. In all cases, molecular ions were very weak and a dominant (M-28 ion, -$C_2H_4$) revealed fragmentation at the alkene group. Also present in each case were ions representing loss of the benzyl or substituted benzyl groups, cleavage occurring at the benzylic carbon; in the case of compound (**3.14**) the trimethoxy benzyl fragment was the base peak. Also present in most spectra were ions representing sequential losses of benzyl and $C_2H_4$. HRMS analysis in all cases gave acceptably accurate (M+1) molecular masses. The mast cell-stabilising properties of compounds (**3.10-3.15**) are shown in Figure 3.7, section 3.5.)

### 3.3.2 *N*-acyl derivatives

Due to the reduced activity of the *N*-acyl derivatives of (**2.9**) as compared to the *N*-alkyl derivatives, a smaller number of acylations were planned, requiring refluxing conditions in pyridine and several molar equivalents of the acylation catalyst DMAP. As with the *N*-acyl derivatives of (**2.9**), the NMR spectra of these molecules was complex, with many overlapping signals. Both the existence of a diasteromeric mixture and the broadened signals, thought to be attributable to isomerism about the amide bond accounted for the complexities of the NMR spectra (Scheme 3.9).

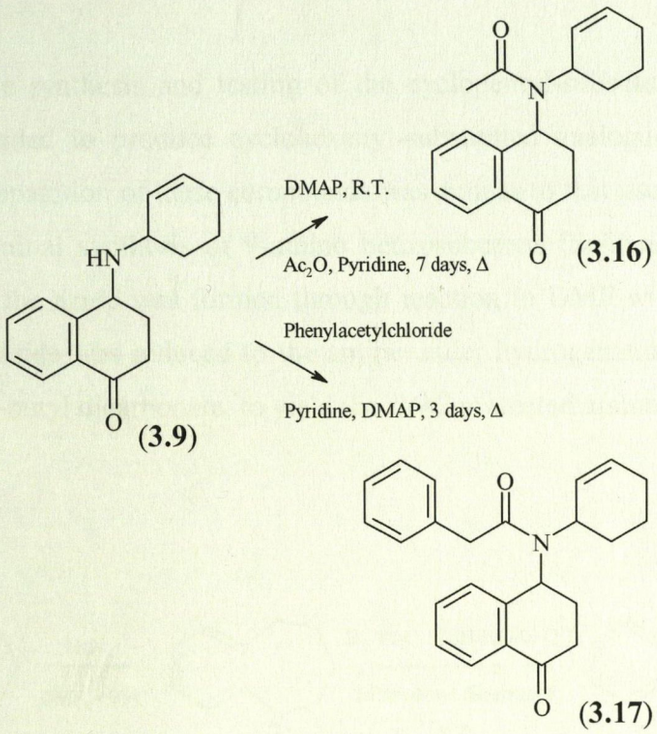


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**Scheme 3.9**

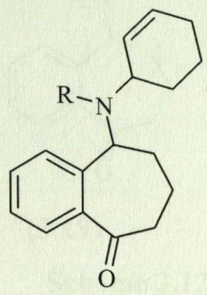
Only two amides were synthesised, the *N*-acetyl and *N*-phenylacetyl derivatives, (**3.16**) and (**3.17**) respectively (Scheme 3.10).




**Scheme 3.10**

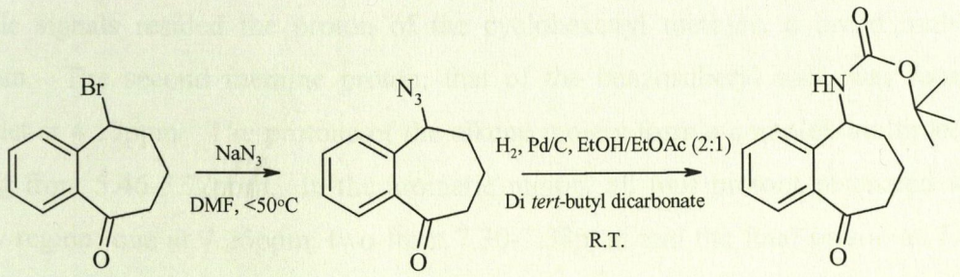
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## 3.4 Synthesis of molecules of structural type (E)



**(E)**

To complement the synthesis and testing of the cyclopentyl-substituted benzosuberone (**2.34**), it was decided to produce cyclohexenyl-substituted analogues. The synthetic rationale for the preparation of these compounds was similar to that used to generate (**3.9**), and involved the initial synthesis of 9-amino benzosuberone (Scheme 3.11). From the bromo compound, the azide was formed through reaction in DMF with sodium azide as nucleophile. The azide was reduced to the amine under hydrogenation conditions in the presence of Di-*tert*-butyl dicarbonate, to yield the *BOC*-protected amine (**3.18**).



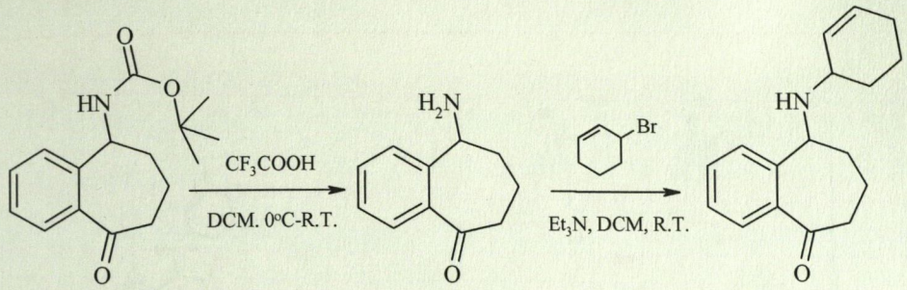

**(3.18)**

**Scheme 3.11**

Liberation of the free amine was accomplished using trifluoroacetic acid, and a base wash afforded the free amine (**3.19**). Reaction of this molecule with 3-bromocyclohexene in DCM, using triethylamine as base yielded a diastereomeric mixture of the secondary amine (**3.20**) (Scheme 3.12).



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**(3.11)** **(3.19)** **(3.20)**

**Scheme 3.12**

This amine was isolated as a golden oil and its infrared spectrum contained $C{=}O_{str}$ at 1685cm$^{-1}$. The $^1$H NMR spectrum (Figure 3.4) was extremely complex in the aliphatic region, due to the presence of six methylene signals, all strongly coupled within their cyclic environments. A broad signal at 1.10ppm was attributable to the secondary amine proton. Five of the six methylene protons resonated from 1.15-1.97ppm; two between 1.15-1.42ppm, one at 1.54ppm, four between 1.61-1.74ppm, two at 1.84ppm and one at 1.97ppm. The remaining methylene protons, those α to the carbonyl group, were visible as two separate pairs of signals; although broadened considerably, they each appeared to take the form of two triplet pairs, with resonance values of 2.45 and 2.49ppm for the first two pairs, and values of 2.85 and 2.90ppm for the second two pairs. In between these two multiple signals resided the proton of the cyclohexenyl methine, a broad multiplet at 2.74ppm. The second methine proton, that of the benzosuberyl unit, was found as a multiplet at 4.17ppm. The protons of the alkene moiety form a complex multiplet signal, ranging from 5.46-5.72ppm. In the aromatic region, all four protons resonated within a narrow region; one at 7.25ppm, two from 7.30-7.38ppm and the final proton at 7.42ppm. GCMS analysis of (**3.20**) showed, akin to the spectrum of (**3.9**), as its only dominant features the molecular ion cluster 256 (M+1, 100) and 255 ($M^+$, 24).

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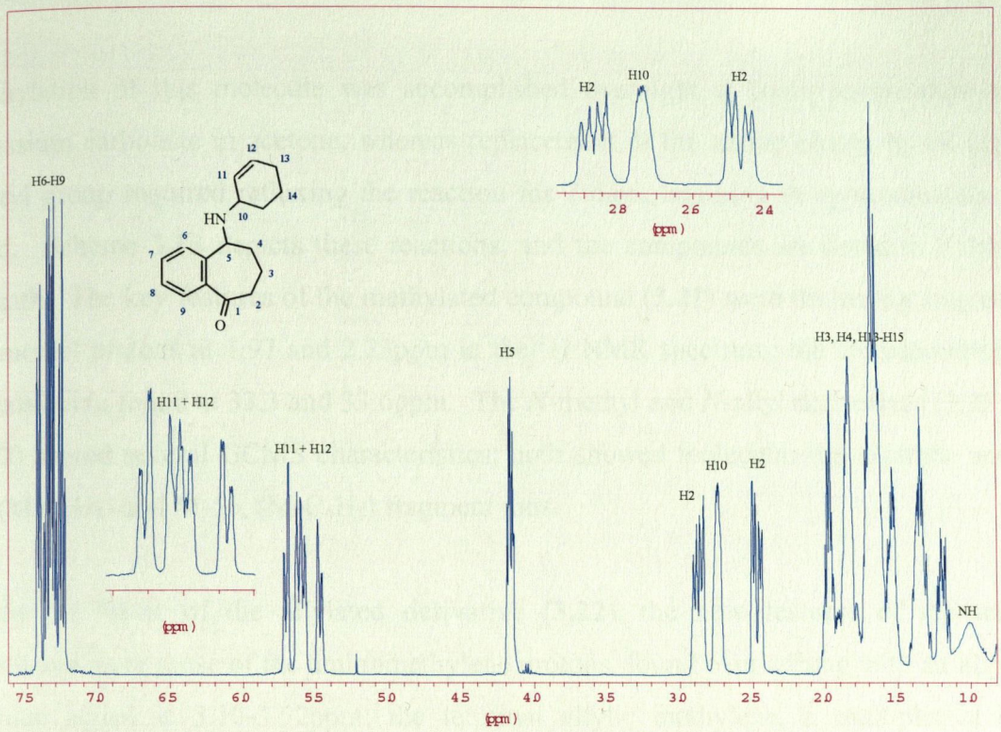



**Figure 3.4** $^{1}$H NMR spectrum of compound (3.20)

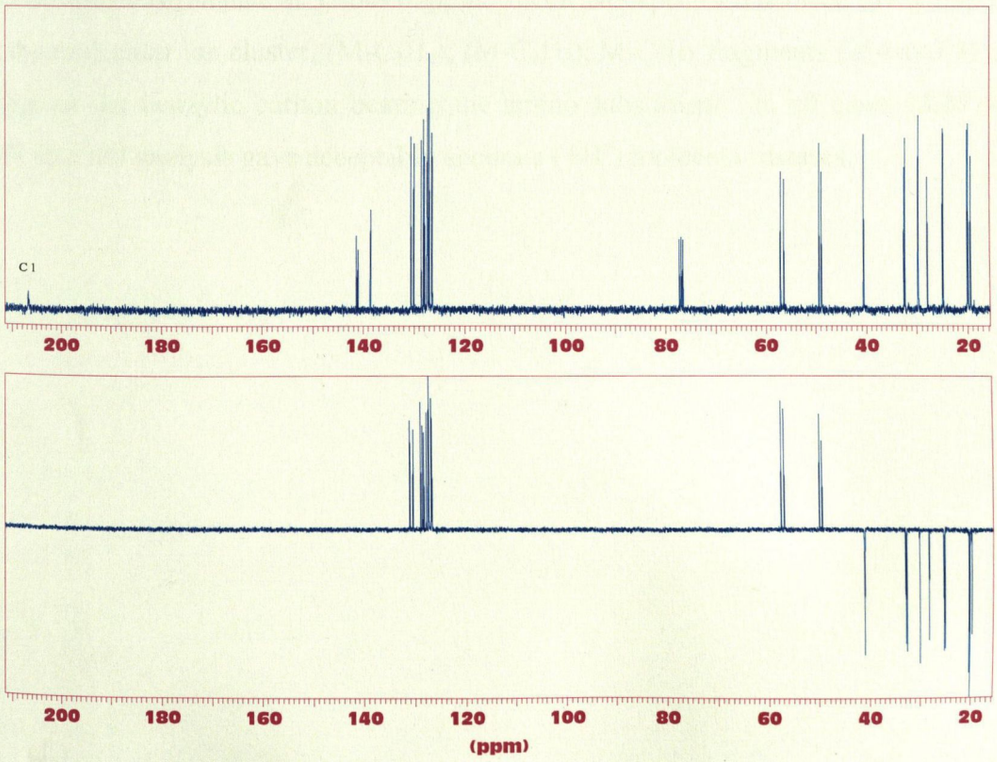



**Figure 3.5** $^{13}$C NMR and DEPT 135 spectra of compound (3.20)



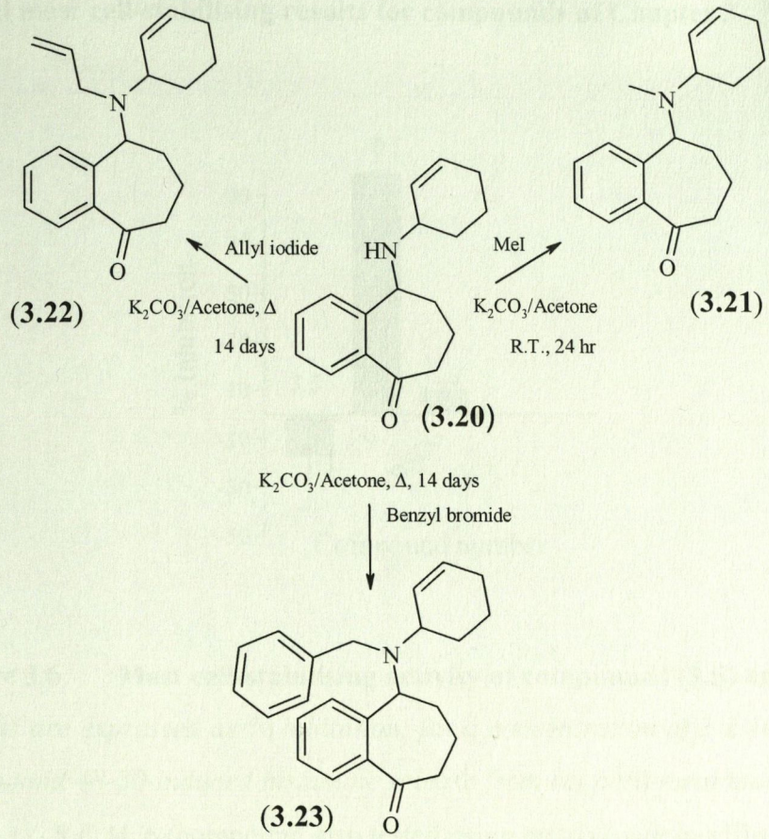
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### 3.4.1 *N*-alkyl derivatives of (3.20)

Methylation of this molecule was accomplished overnight at room temperature using potassium carbonate in acetone, whereas replacement of the amine proton by an allyl or benzyl group required refluxing the reaction for 7 days, resulting in approximately 50% yield. Scheme 3.13 depicts these reactions, and the compounds are listed in Table 3.2 beneath. The key features of the methylated compound (**3.21**) were the strong singlets for the methyl protons at 1.97 and 2.23ppm in the $^{1}H$ NMR spectrum; the corresponding $^{13}C$ signals being found at 33.3 and 33.6ppm. The *N*-methyl and *N*-allyl derivatives (**3.21**) and (**3.22**) shared several GCMS characteristics; both showed molecular ion clusters, and M-28, ($M-C_2H_4$) and M-56, ($M-C_4H_8$) fragment ions.

In the $^{1}H$ NMR of the allylated derivative (**3.22**), the new features of the tertiary substituent were those of the aminomethylene protons, found overlapping with an aliphatic methine signal at 3.10-3.52ppm; the terminal allylic methylene, a multiplet at 4.96-5.13ppm, and the allylic methine, at 5.79-5.98ppm. *N*-benzylation, as in compound (**3.23**), mainly affected the complexity of the aromatic region, with the exception of the distinctive aminomethylene resonance at 3.76-4.02ppm. Its GCMS spectrum showed many important ions; the molecular ion cluster; ($M-C_2H_4$); ($M-C_4H_8$); $M-C_7H_7$ fragments (254 and 91); and cleavage at the benzylic carbon bearing the amino substituent. In all cases (**3.20-3.23**), HRMS spectral analysis gave acceptably accurate ($+H^+$) molecular masses.

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**Scheme 3.13 *N*-alkylations of compound (3.20)**

**Table 3.2 *N*-alkyl derivatives of compound (3.20)**

| R group | Compound | Reaction time | % Yield |
|---|---|---|---|
| Methyl | (**3.21**) | 24 hr, R.T. | 79 |
| Allyl | (**3.22**) | 7 days, Δ | 30 |
| Benzyl | (**3.23**) | 7 days, Δ | 25 |

The mast cell-stabilising potential of molecules (**3.21-3.23**) is illustrated in Figure 3.8, Section 3.5.



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## 3.5 Initial mast cell-stabilising results for compounds of Chapter 3

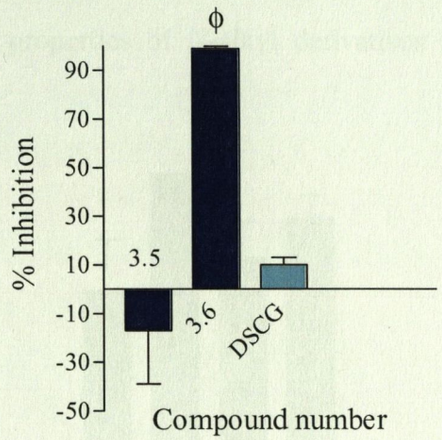



**Figure 3.6 Mast cell-stabilising activity of compounds (3.5) and (3.6).** *Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.* ϕ (compound also tested using metrizamide-purified cells)

**Table 3.3 Summary statistics for compounds (3.5) and (3.6)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **3.5** | -17 | 39 | 22 | 3 |
| **3.6** | 99 | 1 | 1 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

As compared to the standard, DSCG, the cyclohexyl analogues shown in Figure 3.6 possessed dramatically different abilities to inhibit Compound 48/80-induced release of histamine from rat peritoneal mast cells. While the *N*-benzyl analogue was remarkably effective at the dose level tested (99% inhibition, S.E.M. 1%), the *N*-methyl analogue was devoid of any mast cell-stabilising activity, again reflecting the benefit of a planar bulky substituent on the nitrogen atom.

From the results depicted above, it is clear that expansion of the alicyclic ring attached to the tertiary nitrogen in (**2.9**) and its derivatives by one carbon did not result in loss of activity. Also, the pattern of amine substitution was seen to affect the mast cell-stabilising activity of the molecule in a similar fashion to that observed with the cyclopentyl-



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substituted compound (**2.9**), a methyl group proving ineffective in comparison with a benzylic substituent.

The mast-cell stabilising properties of *N*-alkyl derivatives (**3.10-3.15**) are depicted in Figure 3.7.

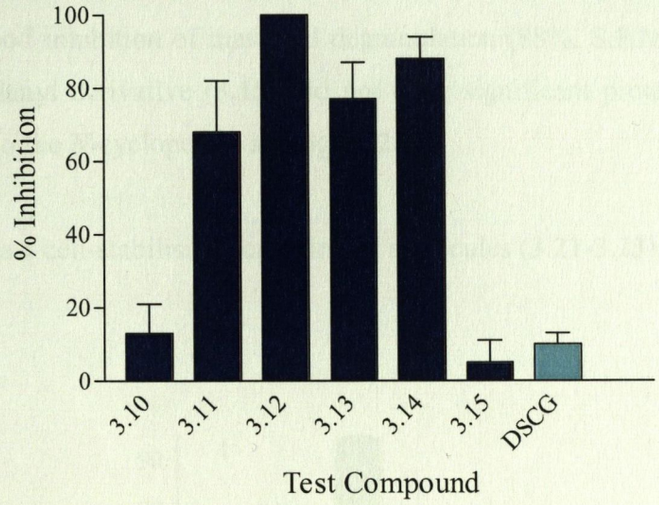



**Figure 3.7 Mast cell-stabilising activity of compounds (3.10-3.15)**
*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*

**Table 3.4 Summary statistics for compounds (3.10-3.15)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **3.10** | 13 | 15 | 8 | 4 |
| **3.11** | 68 | 30 | 14 | 5 |
| **3.12** | 100 | - | - | 5 |
| **3.13** | 77 | 21 | 10 | 5 |
| **3.14** | 88 | 14 | 6 | 5 |
| **3.15** | 5 | 12 | 6 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

The results in Figure 3.7 show that introduction of a double bond into the six-membered ring attached to the amino group did not result in a diminution of activity. Substitution of the nitrogen atom in (**3.9**) by a methyl group resulted in a molecule offering 13% inhibition of Compound 48/80-induced degranulation. Unlike the *N*-cyclopentyl allyl derivative



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(**2.15**), the allyl derivative (**3.11**) offered significant protection (68% inhibition, S.E.M. 14%). As with the benzyl derivative of (**2.9**), a bulky planar benzyl group attached to the nitrogen atom in (**3.12**) resulted in a compound that completely abolished Compound 48/80-induced degranulation at 2 x $10^{-5}$M. With the *p*-methylbenzyl derivative (**3.13**), the inhibition was 77%, S.E.M. 10%. Another difference from the derivatives of (**2.9**) arose in the case of the trimethoxybenzyl derivative (**3.14**), as unlike compound (**2.20**), compound (**3.14**) offered good inhibition of mast cell degranulation (88%, S.E.M. 6%). Finally, the 2'methylnaphthalenyl derivative (**3.15**) did not offer significant protection (5%, S.E.M. 6%), in contrast to the *N*-cyclopentyl analogue (**2.21**).

The results for mast cell-stabilising screening of molecules (**3.21-3.23**) are shown in Figure 3.8.

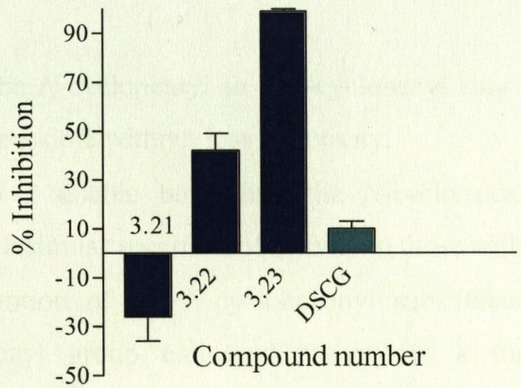



**Figure 3.8 Mast cell-stabilising activity of compounds (3.21-3.23)**
*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*

**Table 3.5 Summary statistics for compounds (3.21-3.23)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **3.21** | -26 | 23 | 10 | 6 |
| **3.22** | 42 | 16 | 7 | 6 |
| **3.23** | 99 | 2 | 1 | 6 |
| DSCG | 10 | 25 | 3 | 94 |



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The results in Figure 3.8 show that expansion of the tetralone ring in (**3.9**) by one carbon atom, to yield benzosuberone analogues (**3.21-3.23**) is possible without significant change in mast cell-stabilising activity.

The tertiary substitution on the benzylic nitrogen bearing the cyclohexenyl ring affected activity in an analogous manner to that of the derivatives of compound (**3.9**). Yet again, the *N*-benzylated derivative (**3.23**) possessed the greatest ability to inhibit Compound 48/80-induced mast cell degranulation (99%, S.E.M. 1%), with the *N*-allyl substituted derivative (**3.22**) retaining some activity (42%, S.E.M. 7%), while the *N*-methylated derivative was wholly inactive.

## 3.6 Summary of mast cell-stabilising results for compounds of Chapter 3

To summarise the mast cell stabilising results in this chapter;

- Expansion of the *N*-cyclopentyl to a *N*-cyclohexyl ring in the tetralone series of molecules was possible without loss of activity.
- Introduction of a double bond into the *N*-cyclohexyl substituent resulted in molecules with a similar spectrum of activity to those without this moiety.
- Tertiary substitution of the *N*-cyclohexenyl substituent by a benzyl group or substituted benzyl group enhanced activity in a manner analogous to the substitution of the *N*-cyclopentyl analogue, with some noteworthy differences: a trimethoxybenzyl substituent within this series of molecules enhanced, rather than abolished activity, and the presence of a naphthalenyl moiety did not protect the cells to as great an extent as in the *N*-cyclopentyl series.
- Expansion of the tetralone nucleus by one methylene group to yield benzosuberone analogues was also permissible without any loss in activity.
- As in the previous structural types (**A**) & (**B**), a benzyl or substituted benzyl was preferable to smaller alkyl substituents (such as methyl and allyl) on the tertiary nitrogen.

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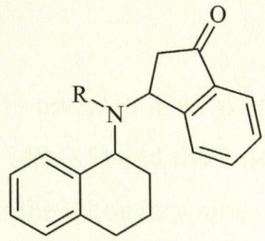
# Synthesis and mast cell-stabilising properties of nitrogen-linked dimer compounds of tetralin and indanone, and related structures

## 4.1 Synthetic targets of Chapter 4

In addition to the novel monomeric α-tetralone compounds of Chapters 2 & 3, it was of interest to generate a series of dimeric derivatives, bearing in mind the potent activities of the indan dimer compounds discussed in Section 1.10. From the starting materials 1- and 2-indanone, and α- and β-tetralone, many possible dimeric combinations are conceivable. Following a perusal of the results already reported for the nitrogen-linked indan homodimers[64], certain structures were identified as more desirable targets than others. The target molecules can be categorised in several ways, depending on the ring position through which the amine link occurs and on whether the molecules are homodimeric or heterodimeric in nature.

## 4.2 Dimers of indan and tetralin, linked via their benzylic carbon atoms

The first target structural type was a combination of tetralin and indanone, with the nitrogen link through benzylic positions on both monomers, as shown below:

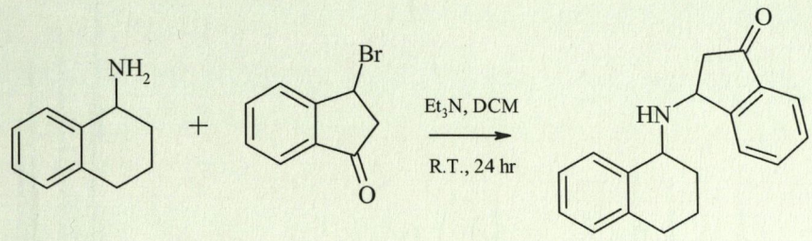



The analogous molecule where the tetralin is replaced by indan has already been shown to possess potent mast-cell stabilising properties[64]. The synthetic strategy adopted for the new target molecule involved nucleophilic attack of 3-bromoindanone by 1-aminotetralin. The benzylic bromination of 1-indanone using NBS yielded the 3-bromo derivative in excellent yield as a yellow crystalline solid, which was stable to silica and could be stored for considerable periods at temperatures <0°C.



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Nucleophilic substitution using triethylamine as tertiary base in DCM as solvent yielded the desired amine (**4.1**) in good yield, as a diasteromeric mixture (Scheme 4.1).




(**4.1**)

**Scheme 4.1**

In the infrared spectrum, compound (**4.1**) showed strong $C{=}O_{str}$ at 1702cm$^{-1}$. The $^{1}$H NMR spectrum (Figure 4.1) of (**4.1**) showed quite broadened signals; the amine proton resonated furthest upfield, at 1.60ppm. This was followed by multiplets at 1.85, 2.02 and 2.20ppm, representing the non-benzylic tetralin methylene protons. Four separate multiple signals followed, at 2.60, 2.79, 2.91 and 3.10ppm, each one a proton of the remaining two methylenes, those of the benzylic position on the tetralin ring and those of the indanone ring. The broadened signals of the methine groups followed, at 4.00 and 4.08ppm for one diastereomeric pair, and 4.57 and 4.64ppm for the second pair. The aromatic region was considerably overlapped; three multiplets at 7.16, 7.32-7.45 and 7.61-7.80ppm accounting for the eight protons. In the $^{13}$C NMR spectrum (Figure 4.2), the carbonyl resonance was located at 204.2ppm.

GCMS analysis of compound (**4.1**) revealed a weak molecular ion of 277 ($M^{+}$, 2). The principal fragments were those at 148 (85) and the base peak at 130. These ions revealed the principal fragmentation to be at the secondary nitrogen, as expected.

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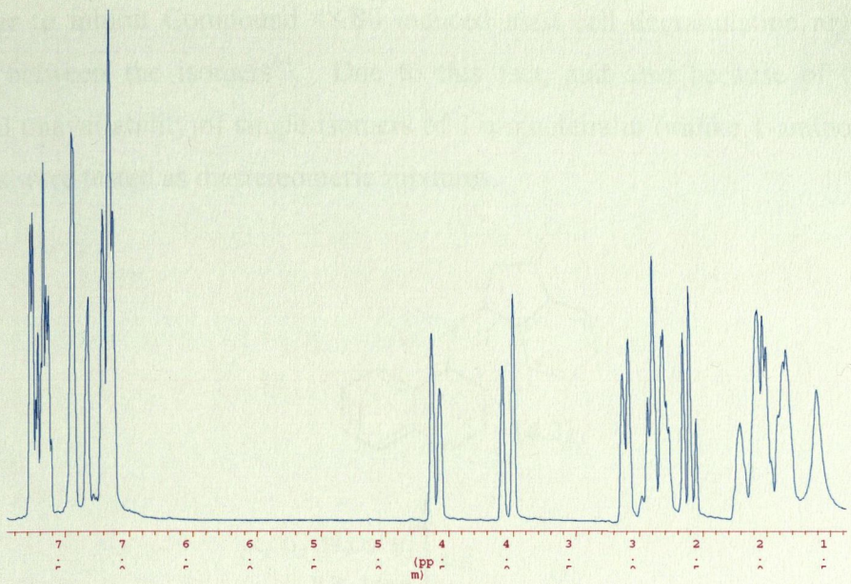



**Figure 4.1** $^{1}$H NMR spectrum of compound (4.1)

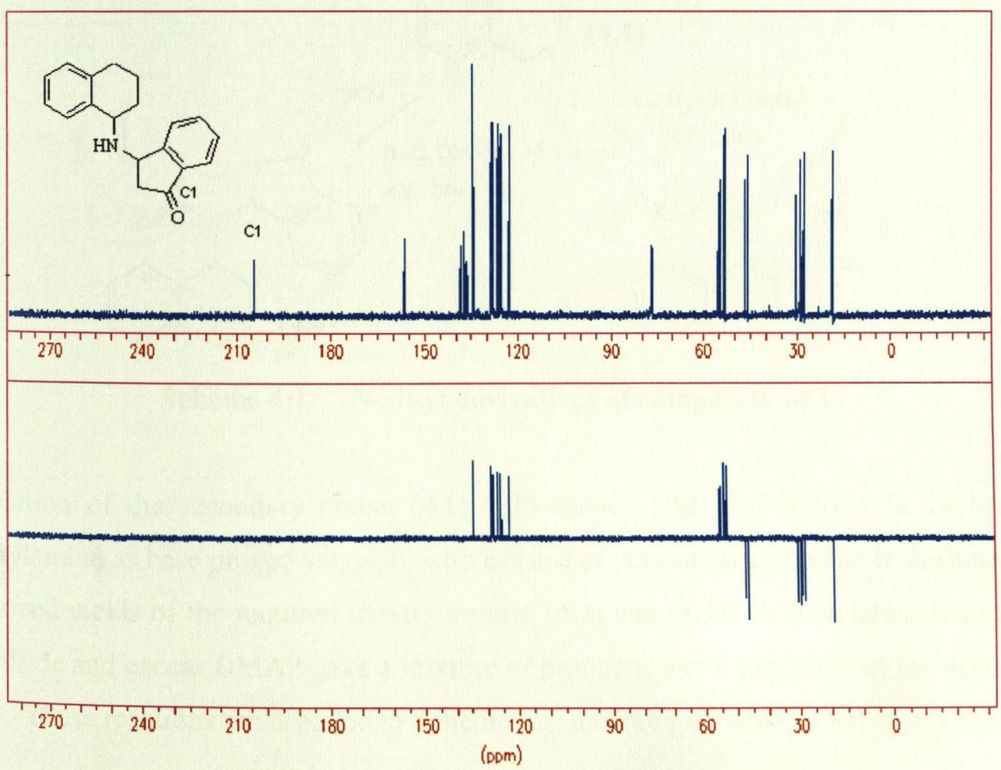
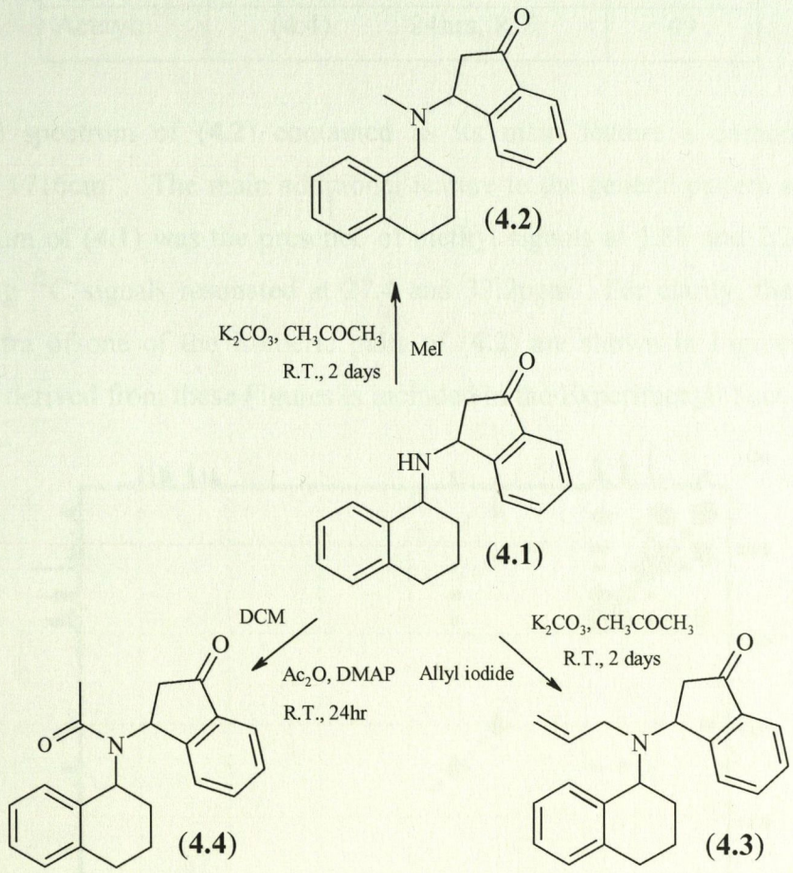



**Figure 4.2** $^{13}$C NMR and DEPT 135 spectra of compound (4.1)

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Previous studies to assess the relative abilities of individual isomers of the aforementioned indan dimer to inhibit Compound 48/80 induced mast cell degranulation revealed little difference between the isomers[64]. Due to this fact, and also because of the general commercial unavailability of single isomers of 1-aminotetralin (unlike 1-aminoindan), the compounds were tested as diastereomeric mixtures.




**Scheme 4.2 *N*-alkyl derivatives of compound (4.1)**

Alkylation of the secondary amine (**4.1**) with methyl and allyl iodides in DCM with triethylamine as base proved sluggish, whereas use of potassium carbonate in acetone gave improved yields of the required tertiary amines (**4.2**) and (**4.3**). *N*-acetylation with acetic anhydride and excess DMAP gave a mixture of products, and a low yield of the acetamide (**4.4**). These reactions are depicted in Scheme 4.2, and the products are listed in Table 4.1.

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**Table 4.1 Tertiary derivatives of compound (4.1)**

| R Group | Compound | Reaction time | % Yield |
|---|---|---|---|
| Methyl | (**4.2**) | 2 days, R.T. | 65 |
| Allyl | (**4.3**) | 2 days, R.T. | 42 |
| Acetyl | (**4.4**) | 24hrs, R.T. | 49 |

The infrared spectrum of (**4.2**) contained as its main feature a carbonyl stretching frequency at 1716cm$^{-1}$. The main additional feature to the general pattern seen in the $^{1}$H NMR spectrum of (**4.1**) was the presence of methyl signals at 1.88 and 2.28ppm, whose corresponding $^{13}$C signals resonated at 27.4 and 33.2ppm. For clarity, the TOCSY and HMQC spectra of one of the isomeric pairs of (**4.2**) are shown in Figures 4.3 and 4.4 below. Data derived from these Figures is included in the Experimental Section.

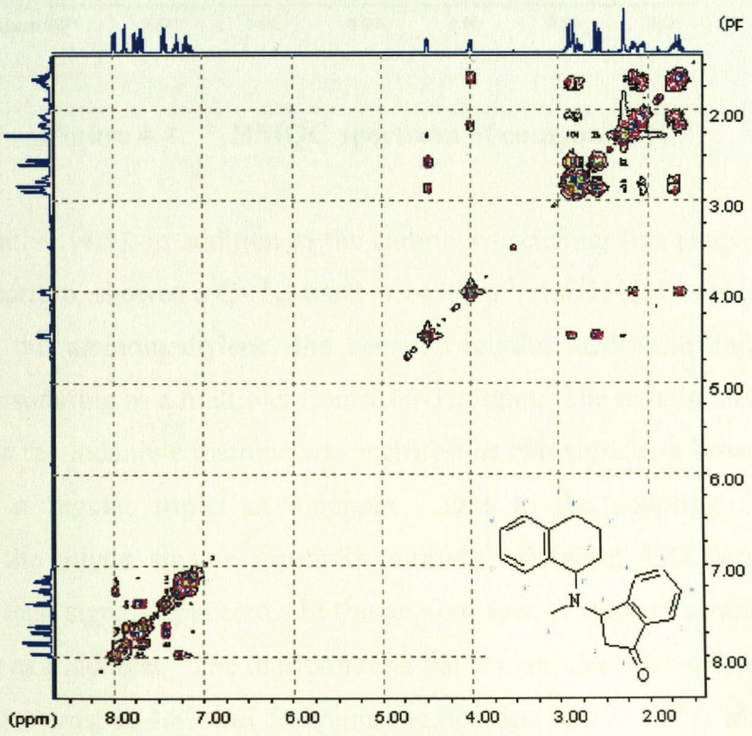



**Figure 4.3 TOCSY spectrum of compound (4.2)**

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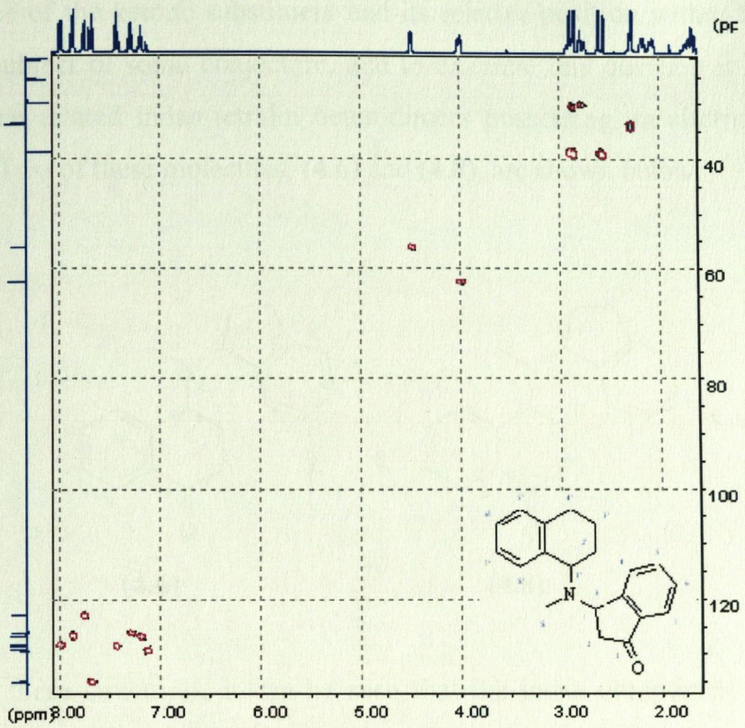


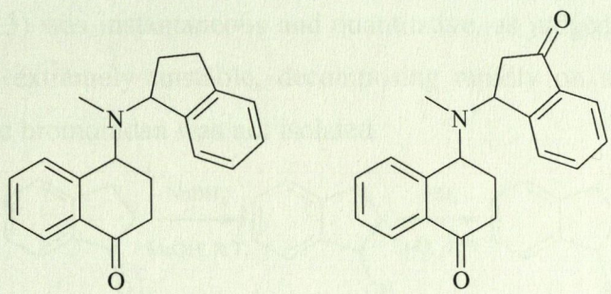

**Figure 4.4 HMQC spectrum of compound (4.2)**

The allyl derivative (**4.3**), in addition to the carbonyl stretching frequency at 1723cm$^{-1}$ in the infrared spectrum, showed a C-$H_{def}$ band at 1438cm$^{-1}$. Its $^{1}$H NMR spectrum was quite complex, with the aminomethylene, the benzylic tetralin methylene and the indanone methylene all resonating as a multiplet from 2.65-3.25ppm. The tetralin methine resonated at 4.16ppm, but the indanone methine was manifest as two signals; a broadened triplet at 4.51ppm, and a regular triplet at 4.66ppm. Due to the coupling of four proton environments, the allylic signals appeared complex. Between 4.82 and 5.25ppm, the terminal methylene signals appeared. In this region, four broadened signals were visible, each appearing as a doublet. The diasteromeric pairs were identifiable by examination of the coupling constants; at 4.83 and 5.09ppm, the doublets had J=10Hz, while at 4.96 and 5.23ppm, the values were J=17.9Hz. The vinylic proton resonated further downfield, as two complicated signals centred at 5.65 and 5.83ppm. Principal fragmentation patterns in the GCMS spectra of the amine derivatives (**4.2**) and (**4.3**) reflect cleavage at the nitrogen atom. The extremely low aqueous solubilities of these compounds, even the hydrochloride salts of (**4.2**) and (**4.3**), required the use of dilutions of stock DMSO solutions prior to testing for mast cell-stabilising properties. Figure 4.18 shows the results of mast cell-stabilising experiments for the compounds of Table 4.1.



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The importance of the ketone substituent and its relative position within these molecules was also the subject of some conjecture, and to examine this question it was decided to synthesise some related indan-tetralin heterodimers possessing an alternative pattern of oxygenation. Two of these molecules, (**4.6**) and (**4.8**), are shown below.



(**4.6**)



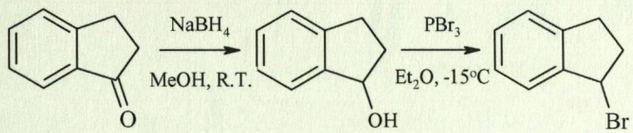
(**4.8**)

In the first of these structures, it can be seen that the indan component is devoid of an oxygen atom, whereas the six-membered ring carries a ketone in the benzylic position, making it a derivative of α-tetralone. The synthesis of this molecule presented the immediate problem posed by the instability of 4-bromotetralone, and indeed attempts to employ this molecule as electrophile were in vain, as contact with base resulted in immediate decomposition. An alternative approach investigated the use of the previously described bromoacetate (**2.6**), and its reaction with 1-aminoindan. Unfortunately, the inherent stability of this brominated derivative, coupled with a seemingly lower nucleophilicity of 1-aminoindan as compared with cyclopentylamine, meant that this reaction was wholly unsuccessful.

Mindful of the reactivity of benzylic halides, the use of 1-bromoindan as electrophile and 4-aminotetralone as nucleophile was considered. The latter amine has been described previously (**3.8**) and is easily attainable in preparative quantities. However, the procurement of 3-bromoindan posed a more challenging prospect. It was decided to reduce 1-indanone to the secondary alcohol, easily accomplished using $NaBH_4$, with subsequent conversion of the alcohol into the required halide.

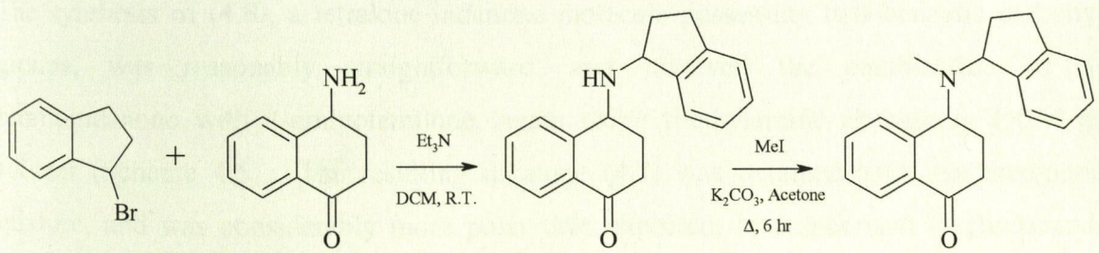
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The conversion of secondary alcohols to halides may be accomplished using one of a number of reagents, including phosphorus tribromide ($PBr_3$),[170,171] phosphorus pentabromide ($PBr_5$),[172] thionyl bromide ($SOBr_2$),[173] and the combination of NBS and triphenylphosphine ($PPh_3$) in DMF[174]. For the bromination of 1-indanol, the starting material in this synthesis, $PBr_3$ was chosen, using diethyl ether as solvent at –15°C. The reaction (Scheme 4.3) was instantaneous and quantitative, as judged by TLC. However, the compound was extremely unstable, decomposing rapidly on silica (presumably to indene), and the pure bromoindan was not isolated.




**Scheme 4.3**

After rapid work-up of the reaction, the residue was immediately reacted with 4-aminotetralone (**3.8**), using triethylamine as base in DCM at room temperature (Scheme 4.4). Purification of the resultant dimer (**4.5**) was hampered by the presence of residual (**3.8**), and the mixture was alkylated overnight with methyl iodide in potassium carbonate/acetone, with subsequent isolation of pure (**4.6**), without any contaminating methylated (**3.8**).




**(3.8)** **(4.5)** **(4.6)**

**Scheme 4.4**

Methylation of dimer (**4.5**) shifted the carbonyl stretching frequency from 1687 to 1692cm$^{-1}$. Interestingly, the $^1$H NMR spectrum (Figure 4.5) contained two well-separated signals for the *N*-methyl group, at 2.11 and 2.32ppm. In the $^{13}$C NMR spectrum, the carbonyl resonances were located at 197.2 and 197.3ppm. The aqueous solubility of this compound was in stark contrast to that of its regioisomer (**4.2**), as the hydrochloride salt of this molecule was readily soluble in water, unlike that of (**4.2**).



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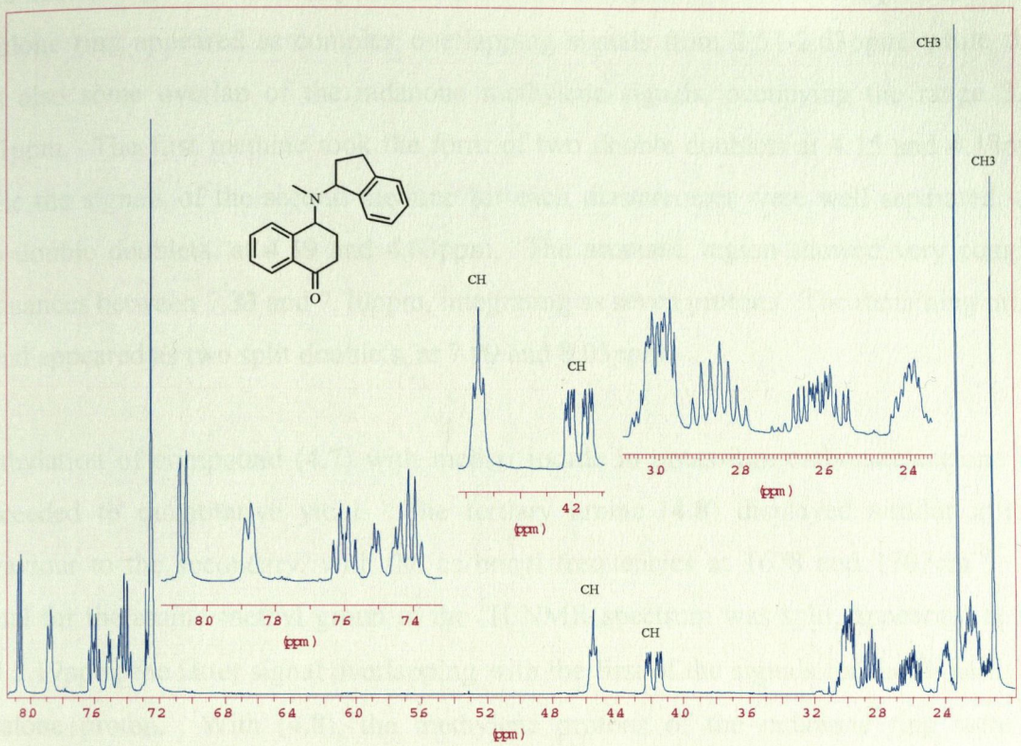
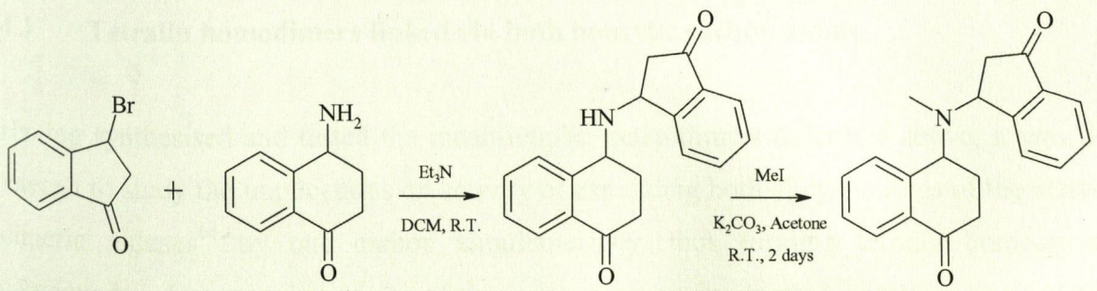



**Figure 4.5** $^{1}$**H NMR spectrum of compound (4.6)**

The synthesis of (**4.8**), a tetralone-indanone molecule possessing two benzylic carbonyl groups, was reasonably straightforward, and involved the combination of 3-bromoindanone with 4-aminotetralone, again using triethylamine as base in DCM as solvent (Scheme 4.5). The resulting diketone (**4.7**) was obtained as a diastereomeric mixture, and was considerably more polar than expected, in comparison to compounds (**4.1**) and (**4.5**)




(**4.7**) (**4.8**)

**Scheme 4.5**

The infrared spectrum of (**4.7**) contained two carbonyl stretching frequencies, at 1676 and 1702cm$^{-1}$. In the $^{1}$H NMR spectrum, the signal for the β-protons on the tetralone ring was



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split, resonating as two multiplets, at 2.15 and 2.35ppm. The α-keto protons of the tetralone ring appeared as complex overlapping signals from 2.51-2.63ppm, while there was also some overlap of the indanone methylene signals, occupying the range 3.02-3.21ppm. The first methine took the form of two double doublets at 4.15 and 4.18ppm, while the signals of the second methine for each diastereomer were well separated, also two double doublets, at 4.39 and 4.63ppm. The aromatic region showed very complex resonances between 7.33 and 7.70ppm, integrating as seven protons. The remaining proton signal appeared as two split doublets, at 7.99 and 8.03ppm.

Methylation of compound (**4.7**) with methyl iodide in potassium carbonate/acetone also proceeded to quantitative yield. The tertiary amine (**4.8**) displayed similar infrared behaviour to the secondary, with the carbonyl frequencies at 1678 and 1707cm$^{-1}$. The signal for the amino methyl group in the $^{1}$H NMR spectrum was split, appearing at 1.99 and 2.19ppm, the latter signal overlapping with the first of the signals for the β-methylene tetralone proton. With (**4.8**), the methylene protons of the indanone ring were not overlapping, but resonated as discrete multiplets at 2.84 and 2.97ppm. The remainder of the proton spectrum largely mirrored that of (**4.7**), although both aromatic protons closest to the keto groups could be clearly discerned.

GCMS analysis of molecules (**4.5**) to (**4.8**) showed, in all cases, moderately intense molecular ion clusters and fragmentation patterns corresponding to cleavage at either side of the nitrogen atom. Both molecules (**4.6**) and (**4.8**) were subject to mast-cell stabilisation studies, and the results are shown in Figure 4.19.

## 4.3 Tetralin homodimers linked via both benzylic carbon atoms

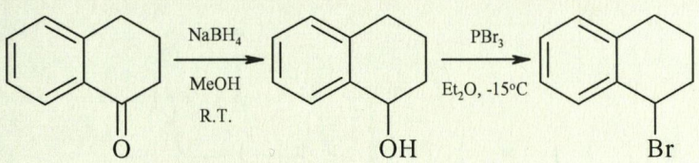
Having synthesised and tested the indan-tetralin heterodimers described above, it was of interest to study the implications on activity of expanding both alicyclic rings of the active dimeric indanes[64] by one carbon simultaneously, thus forming tetralin homodimer compounds. As expansion of one of the indan rings by one methylene group, as in (**4.2**), had little or no effect on activity, it might reasonably be expected that the tetralin homodimer (**4.10**) should retain some mast cell-stabilising properties. Synthesis of this molecule was again approached from various routes, the first reaction being that of 1-aminotetralin with 4-bromotetralone.



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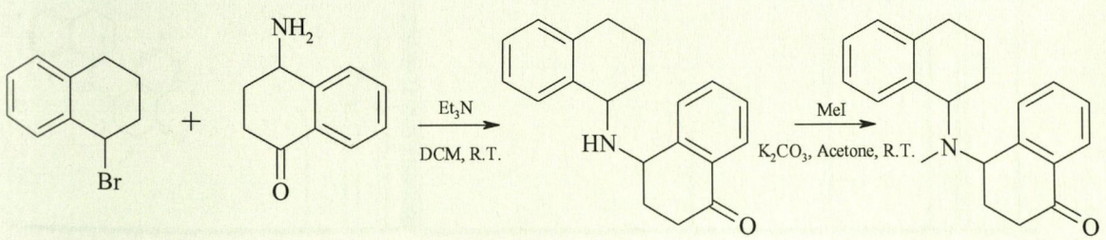
As with all other reactions of 4-bromotetralone with any primary amine examined, the reaction failed to yield the desired product, resulting only in decomposition. An attempt to react the bromo acetate (**2.6**) with 1-aminotetralin was also unsuccessful.

The reaction that eventually proved successful in the synthesis of (**4.10**) was akin to that used to form (**4.6**), employing the reactive benzylic halide 1-bromotetralin. This halide has been previously synthesised from both the reaction of bromine with tetralin[175] and the treatment of α-tetralol with $PBr_3$[176]. The second of these routes was chosen, and reduction of α-tetralone with $NaBH_4$ formed the alcohol in quantitative yield, and substitution of the hydroxyl group with bromine was performed using $PBr_3$ at –15°C (Scheme 4.6).




**Scheme 4.6**

As with the reaction of 1-indanol, this brominated derivative was very unstable, and was not itself isolated in pure form. Instead, it was reacted directly after partial work-up with 4-aminotetralone (Scheme 4.7), to give a poor yield of the required secondary amine (**4.9**), as a diasteromeric mixture.




**(4.9)** **(4.10)**

**Scheme 4.7**

The infrared spectrum of (**4.9**) was dominated by the carbonyl signal at 1689cm$^{-1}$. $^1$H NMR analysis (Figure 4.6) showed a complex aliphatic region; although the amine proton was clearly visible as a broad signal at 1.21ppm. Six broad multiplets for the ten methylene protons followed: at 1.86ppm, one proton; from 1.93-2.27ppm, four protons; at 2.41ppm, one proton; at 2.64ppm, one proton; from 2.74-2.95ppm, two protons, with the terminal methylene proton, one of those α to the keto group, from 3.12-3.26ppm. The first of the two methine signals appeared as two double doublets, at 3.91 and 4.06ppm, followed



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by overlapping diastereomeric signals from the second methine at 4.21ppm. In the aromatic region, seven of the eight protons resonated from 7.13-7.61ppm, with the proton nearest the carbonyl group partially overlapping doublets at 8.10ppm.

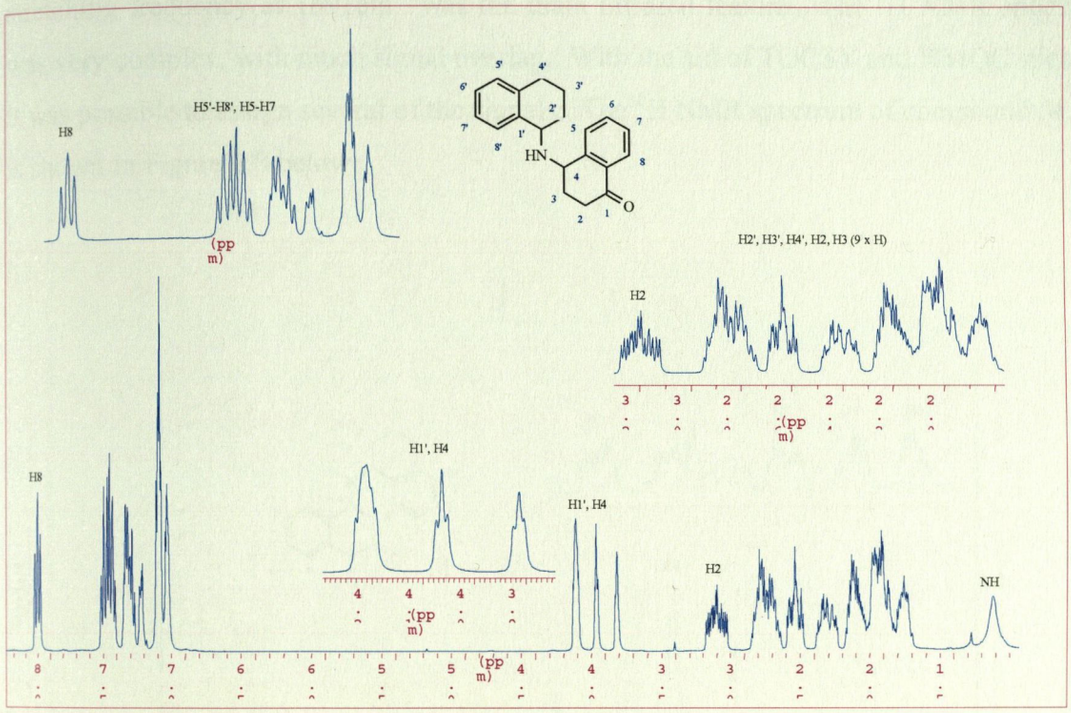



**Figure 4.6** $^{1}$H NMR spectrum of compound (4.9)

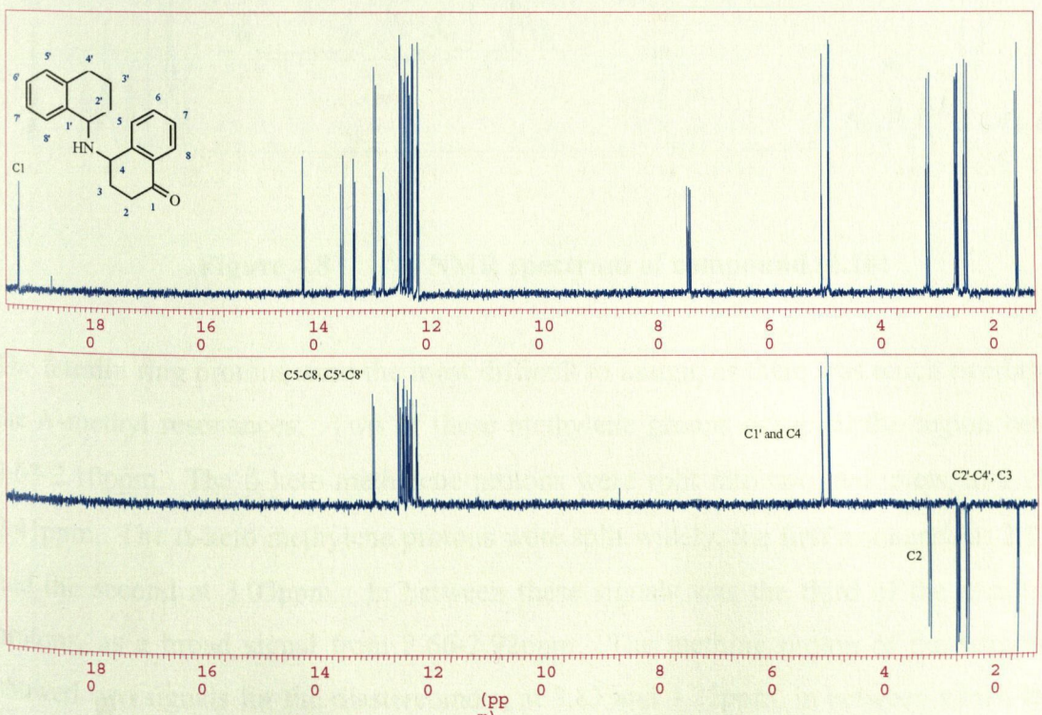



**Figure 4.7** $^{13}$C NMR and DEPT 135 spectra of compound (4.9)



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In the $^{13}C$ NMR spectrum (Figure 4.7), the carbonyl resonances were at 197.8 and 197.9ppm. Methylation of (**4.9**) proved tedious, even with heating under reflux, and only a small quantity of the *N*-methylated tertiary derivative was obtained. A strong carbonyl stretching frequency at 1691cm$^{-1}$ was the main infrared feature. The $^{1}H$ NMR spectrum was very complex, with much signal overlap. With the aid of TOCSY and HMQC spectra, it was possible to assign several of the signals. The $^{1}H$ NMR spectrum of compound (**4.10**) is shown in Figure 4.8 below:

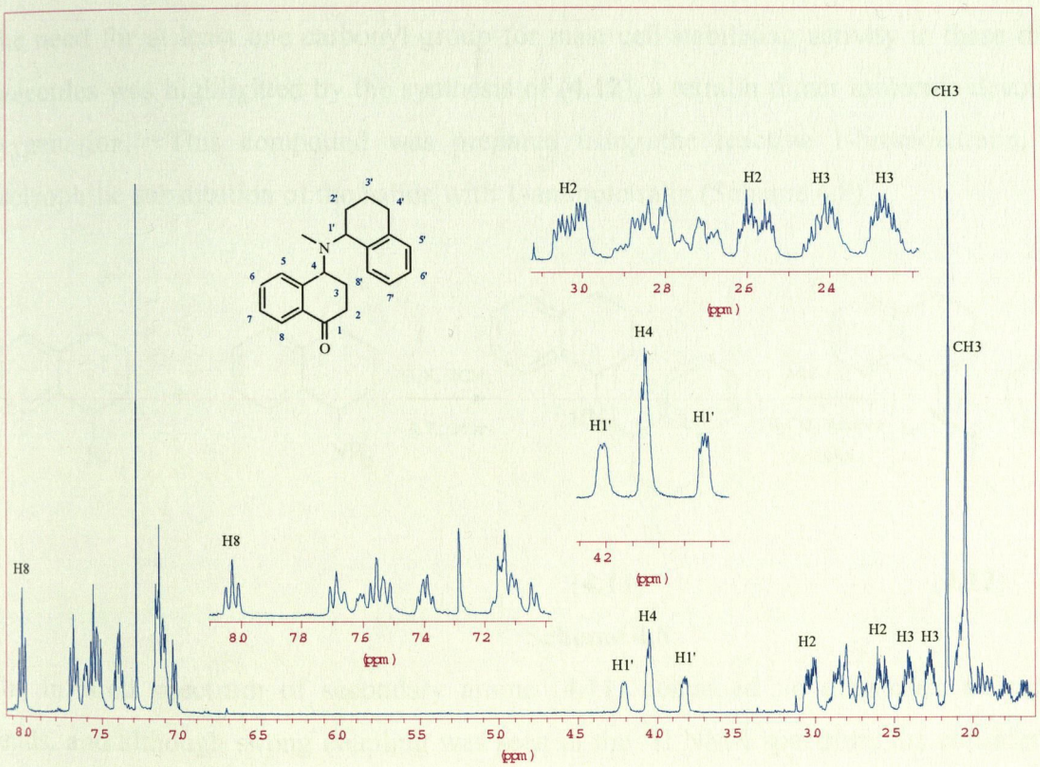



**Figure 4.8 $^{1}H$ NMR spectrum of compound (4.10)**

The tetralin ring protons were the most difficult to assign, as there was much overlap with the *N*-methyl resonances. Two of these methylene groups occupied the region between 1.63-2.10ppm. The β-keto methylene protons were split into two multiplets, at 2.27 and 2.41ppm. The α-keto methylene protons were split widely, the first resonance at 2.57ppm and the second at 3.03ppm. In between these signals was the third of the tetralin ring protons, as a broad signal from 2.66-2.92ppm. The methine proton of the tetralin ring showed two signals for the diastereomers, at 3.83 and 4.21ppm, in between which lay the tetralone methine signal, at 4.05ppm.

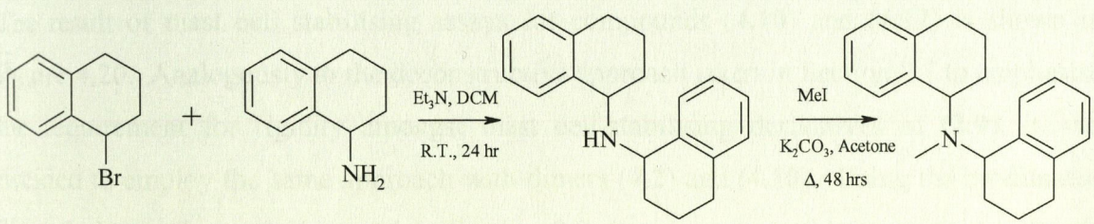


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The aromatic region also contained overlapping signals, with the only clearly identifiable protons belonging to the tetralone ring, at 7.43ppm and 8.03ppm, the latter those nearest the carbonyl group. In the $^{13}C$ NMR spectrum, the carbonyl signal resonated at 198.0ppm.

Although it was of interest to synthesise the dimeric tetralone analogue of (**4.8**), possessing two benzylic carbonyl groups, all attempts to react 4-bromotetralone with 4-aminotetralone resulted in decomposition.

The need for at least one carbonyl group for mast cell-stabilising activity in these dimer molecules was highlighted by the synthesis of (**4.12**), a tetralin dimer molecule devoid of oxygenation. This compound was prepared using the reactive 1-bromotetralin, and nucleophilic substitution of the halide with 1-aminotetralin (Scheme 4.8).




**(4.11)** **(4.12)**

**Scheme 4.8**

The infrared spectrum of secondary amine (**4.11**) contained no diagnostic absorption bands, and although strong coupling was seen in the $^{1}H$ NMR spectrum, the considerable symmetry simplified matters somewhat. Three main multiplets represented the aliphatic character of the molecule; a broad multiplet stretching from 1.92-2.35ppm accounting for eight of the protons, another multiplet from 2.83-3.01ppm for two more methylene groups, and a third centred at 4.14ppm representing the two methine protons. The aromatic region consisted of a multiplet for six protons from 7.19-7.29ppm, and additional resonances from 7.46-7.53ppm for the two remaining aryl protons.

Methylation of this compound was performed using methyl iodide in potassium carbonate/acetone, and the main spectral difference between this tertiary amine (**4.12**) and its precursor was the sharp singlet for the *N*-methyl group at 2.10ppm and its corresponding carbon signals at 29.8 and 33.8ppm in the $^{13}C$ NMR spectrum.

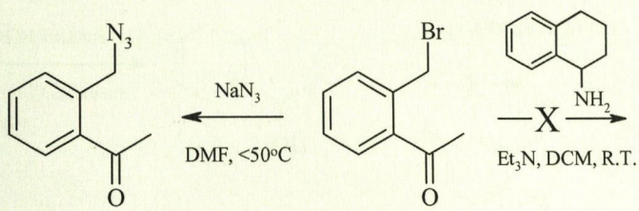


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GCMS analysis of compound (**4.11**) revealed as the only significant peak that of the molecular ion, whereas the spectrum of (**4.12**) contained intense ion fragments corresponding to cleavage at either side of the nitrogen atom.

An attempt to generate the benzylic diketo derivative through Jones oxidation of both benzylic carbon atoms resulted in recovery of starting material. Indeed reaction of 1-aminotetralin itself under Jones oxidation conditions did not result in the formation of any 4-aminotetralone. Using chromium trioxide in acetic acid as oxidant, Burnham *et al.* undertook a study of the effect of alkyl substituents in the chromic acid oxidation of tetralins, demonstrating that *para*-alkyl substituents favoured Jones oxidation at the benzylic methylene position[177]. However, the effect of *para*-amino substitution was not addressed.

The result of mast cell stabilising assays for compounds (**4.10**) and (**4.12**) is shown in Figure 4.20. Analogously to the deconstructive approach taken in Section 2.7 to emphasise the requirement for rigidity amongst mast cell-stabilising derivatives of (**2.9**), it was decided to employ the same approach with dimers (**4.2**) and (**4.10**). Using the brominated 2'-methylacetophenone discussed in Section 2.7, it was attempted to react this molecule with 1-aminotetralin. The reactivity of this halide has already been mentioned, and it was discovered that although it did react with azide ion (Scheme 4.9), it failed to yield any of the expected secondary amine upon reaction with 1-aminotetralin.




**(4.13)**

**Scheme 4.9**

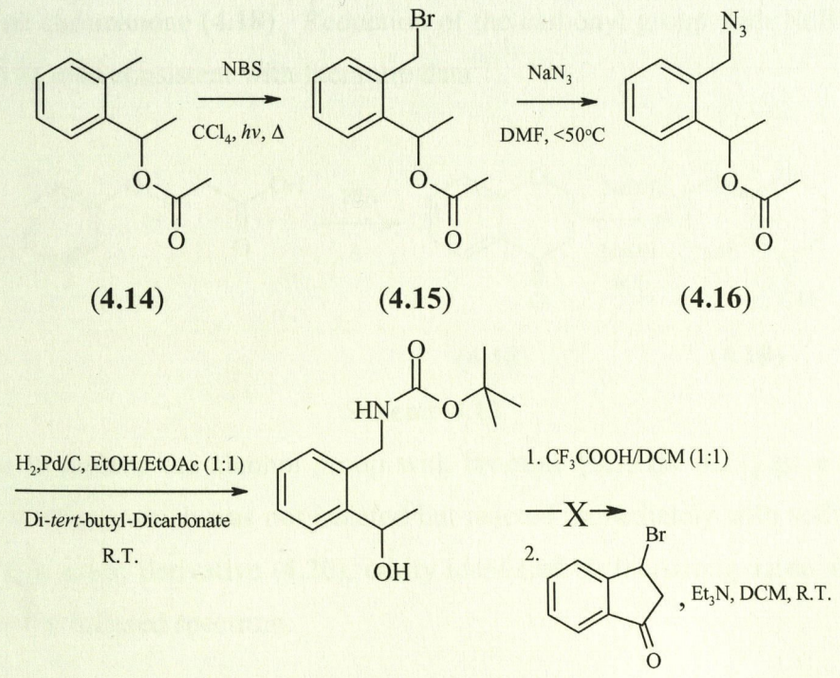
The azide (**4.13**) was isolated as a clear oil, with characteristic infrared absorption at $2104cm^{-1}$. Interestingly, upon reaction under hydrogenation conditions to obtain the primary amine derivative (as its *BOC*-protected carbamate), complete decomposition was observed. Other methods of azide reduction were thus investigated, including treatment with triphenylphosphine in THF[178], sodium borohydride in THF with dropwise addition of methanol[179], and sodium borohydride under phase-transfer catalysis[180].



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In all cases, none of the desired amine was observed. It was postulated that the amine derivative, upon generation, may have reacted immediately with further molecules and underwent polymerisation.

Conversion of the ketone to an acetate functionality was accomplished via the alcohol, using sodium borohydride as reducing agent, and acetic anhydride/DMAP for acylation. Upon reaction of acetate (**4.14**) with NBS, a stable benzylic bromide (**4.15**) was isolable (Scheme 4.11), which, upon reaction with sodium azide in DMF, afforded azide (**4.16**). However, bromide (**4.15**) failed to react with either cyclopentylamine or 1-aminotetralin, using DCM as solvent, and triethylamine as base. Reduction of azide (**4.16**) under hydrogenation conditions in the presence of Di-*tert*-butyl-dicarbonate afforded the *BOC*-derivative of the amine alcohol (**4.17**); however, attempted reaction of the liberated amine with 3-bromoindanone was not successful.




**(4.14)** **(4.15)** **(4.16)**

**(4.17)**

**Scheme 4.11**

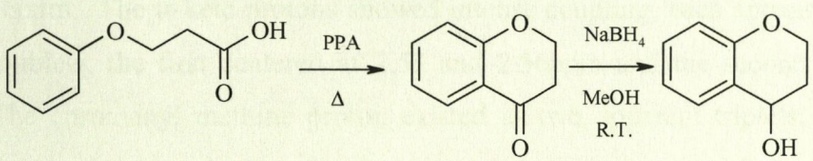
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## 4.4 Dimeric derivatives of compound (4.2)

### 4.4.1 Chroman analogue

Until this juncture, attention has been solely focussed on ring size and presence or absence of one or more benzylic ketone substituents. There is of course an immense range of potential derivatives of these molecules, including substitution both on the aromatic and alicyclic rings, and alternative alkyl groups on the nitrogen atom. Of the myriad possibilities, a few derivatives were selected for synthesis, and all were based on the parent compound (**4.2**), and therefore contained an indanone ring containing a benzylic carbonyl, linked via position 3 to a six membered hydroaromatic ring.

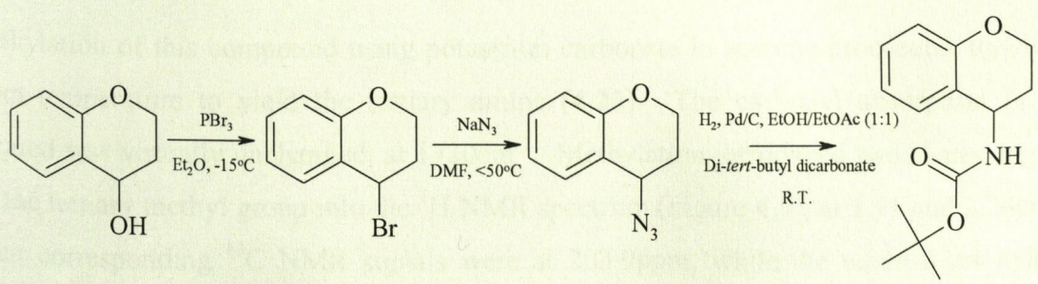
The first of these was the chroman analogue (**4.23**). The starting material for this synthesis was 3-phenoxypropionic acid, which on cyclisation using polyphosphoric acid (Scheme 4.12) yielded chromanone (**4.18**). Reduction of the carbonyl group with $NaBH_4$ gave the alcohol (**4.19**), also consistent with literature data[181].




**(4.18)** **(4.19)**

**Scheme 4.12**

Using $PBr_3$ to replace the alcohol group with bromine (Scheme 4.13) gave an unstable halide intermediate, which was not isolated but reacted immediately with sodium azide to give the stable azido derivative (**4.20**), easily identified by the strong azide absorption at $2105cm^{-1}$ in the infrared spectrum.



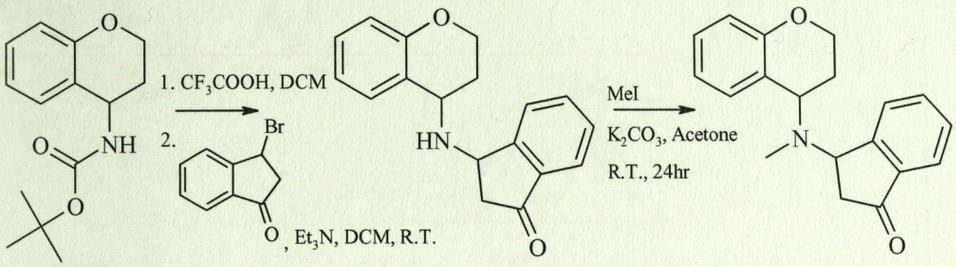

**(4.20)** **(4.21)**

**Scheme 4.13**



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Reduction of the azide under hydrogenation conditions in the presence of Di-*tert*-butyl dicarbonate gave the *BOC*-protected amine (**4.21**), and removal of the protecting group was performed using trifluoroacetic acid. The free amine was reacted with 3-bromoindanone, using triethylamine as base in DCM (Scheme 4.14), to yield the desired dimer (**4.22**), as a diastereomeric mixture. The main feature of this molecule in the infrared spectrum was the carbonyl absorption at 1721cm$^{-1}$.




**(4.22)** **(4.23)**

**Scheme 4.14**

The $^{1}$H NMR spectrum of (**4.22**) was well resolved in the aliphatic region; the first methylene signal being that β to the ether oxygen on the chroman ring, resonating between 1.88 and 2.16ppm. The α-keto protons showed intense coupling, each appearing as a pair of double doublets, the first centered at 2.53 and 2.56ppm and the second at 3.06 and 3.10ppm. The chromanyl methine proton existed as two apparent triplets, at 3.96 and 4.06ppm. A complex signal arose for the ethereal methylene group, between 4.20 and 4.46ppm, slightly overlapping with the superimposed triplets of the indanone methine. As is a feature of many of these molecules, the complexity of the aromatic region was considerable. A particularly noteworthy characteristic of the $^{13}$C NMR spectrum for this molecule was the resonance of the ethereal methylene carbon, at 62.2 and 62.3ppm, one for each diastereomer.

Methylation of this compound using potassium carbonate in acetone proceeded slowly at room temperature to yield the tertiary amine (**4.23**). The carbonyl absorption in the infrared was virtually unchanged, at 1720cm$^{-1}$. Methylation introduced two sharp singlets for the tertiary methyl group into the $^{1}$H NMR spectrum (Figure 4.9), at 1.91 and 2.24ppm. Their corresponding $^{13}$C NMR signals were at 203.9ppm, while the ethereal methylene carbon resonated at 64.0 and 64.7ppm. GCMS analysis of (**4.22**) and (**4.23**) revealed, as with the dimer molecules reported to date in this Chapter, that cleavage occurred primarily at the nitrogen atom.



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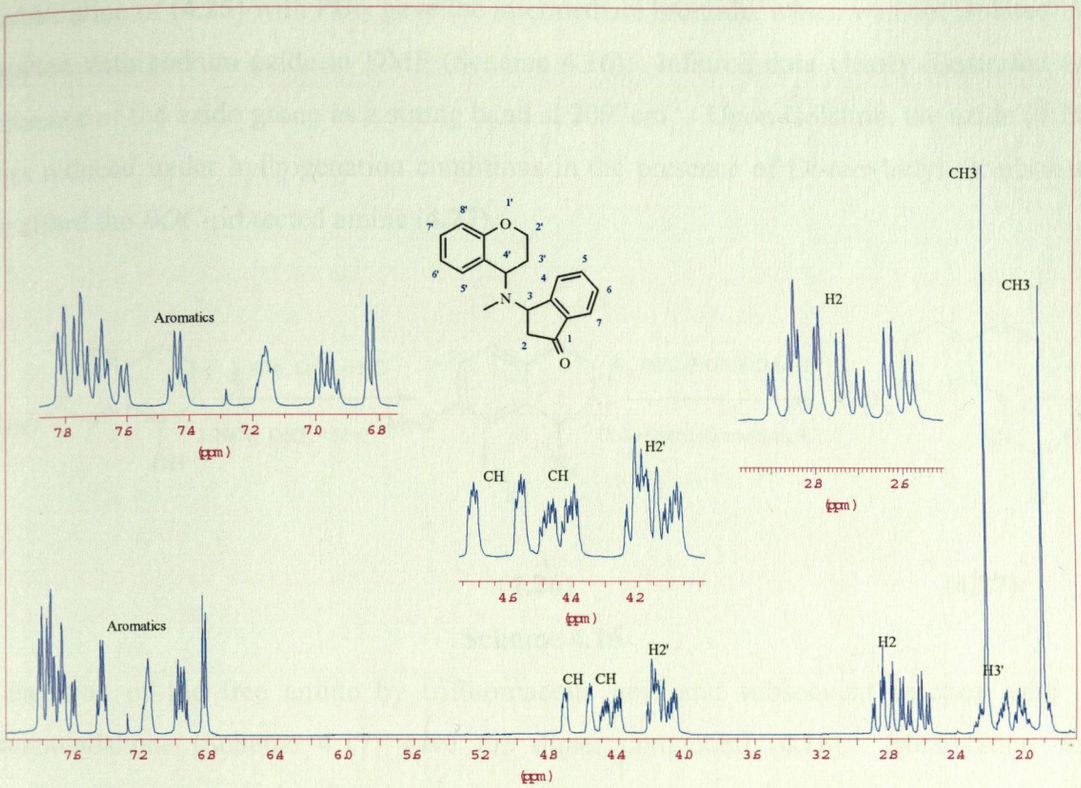
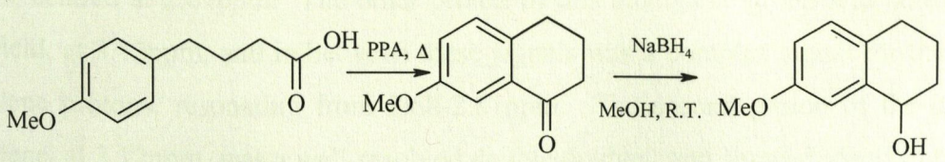



**Figure 4.9 $^1$H NMR spectrum of compound (4.23)**

### 4.4.2 7-methoxy tetralin analogue

Substitution on the aromatic portion of the tetralin ring by an electron-donating methoxy group at position 7 was approached through a similar sequence of reactions to those used for (**4.23**). The starting material in this case was 4-(4-methoxyphenyl)butyric acid, cyclisation of which with polyphosphoric acid (Scheme 4.15) gave 7-methoxytetralone[182] (**4.24**). Alternative literature protocols include cyclisation of the acid using phosphorus (IV) oxide and phosphoric acid[183], or cyclisation using the acid chloride. Reduction of (**4.24**) with $NaBH_4$ gave the secondary alcohol (**4.25**).



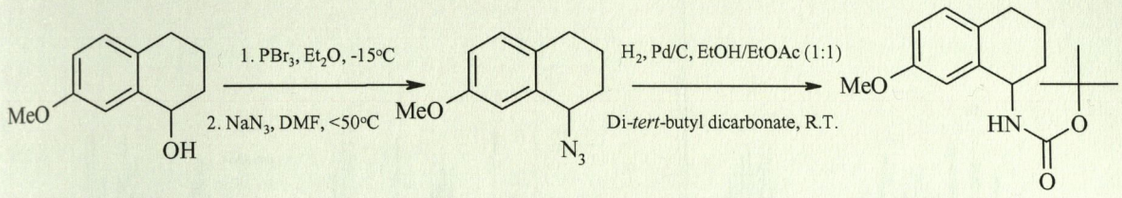

**(4.24)** **(4.25)**

**Scheme 4.15**



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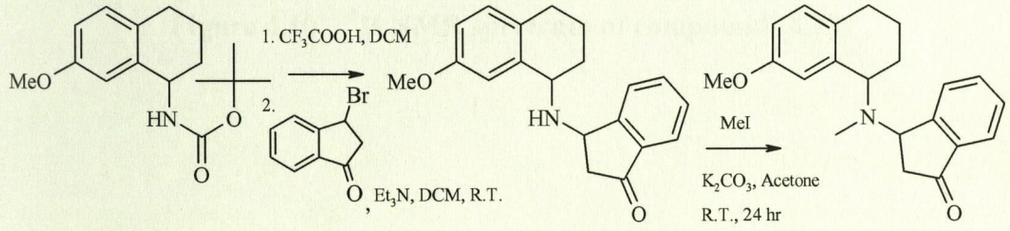
Substitution of (**4.25**) with $PBr_3$ gave the intermediate bromide, which was not isolated but reacted with sodium azide in DMF (Scheme 4.16). Infrared data clearly illustrated the presence of the azido group as a strong band at $2097cm^{-1}$. Upon isolation, the azide (**4.26**) was reduced under hydrogenation conditions in the presence of Di-*tert*-butyl-dicarbonate to afford the *BOC*-protected amine (**4.27**).




(**4.26**) (**4.27**)

**Scheme 4.16**

Liberation of the free amine by trifluoroacetic acid and subsequent reaction with 3-bromoindanone (Scheme 4.17) gave the dimer compound (**4.28**). Methylation was performed using methyl iodide in acetone with potassium carbonate as base, to give the tertiary amine (**4.29**).




(**4.28**) (**4.29**)

**Scheme 4.17**

$^1H$ NMR analysis of compound (**4.28**) (Figure 4.10) revealed an unequal mixture of diastereomers, which aided analysis of the complex spectrum. At 1.51ppm, the amine proton was visible. Two of the tetralin methylenes occupied the region from 1.75-2.21ppm, followed by two overlapping double doublets for one of the indanone methylene protons, centred at 2.61ppm. The other proton of this methylene group was considerably downfield, at 3.12ppm, and in between these signals was a complex signal for the tetralin methylene protons, resonating from 2.68-2.87ppm. The second proton of the indanone methylene, at 3.12ppm, was a well-resolved double doublet, and showed identical coupling constants to the signal at 2.61ppm. The two signals of the aromatic methyl ether were sharp singlets at 3.77 and 3.81ppm, followed by the methine protons, two pairs of double doublets, the first at 3.77 and 3.81ppm, and the second pair at 4.60 and 4.65ppm.



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In the aromatic region, much signal overlap occurred, the seven protons resonating between 6.74-7.98ppm. The $^{13}C$ NMR spectrum (Figure 4.11) contains important signals at 54.8ppm (methoxy resonance) and 204.1ppm (carbonyl group).

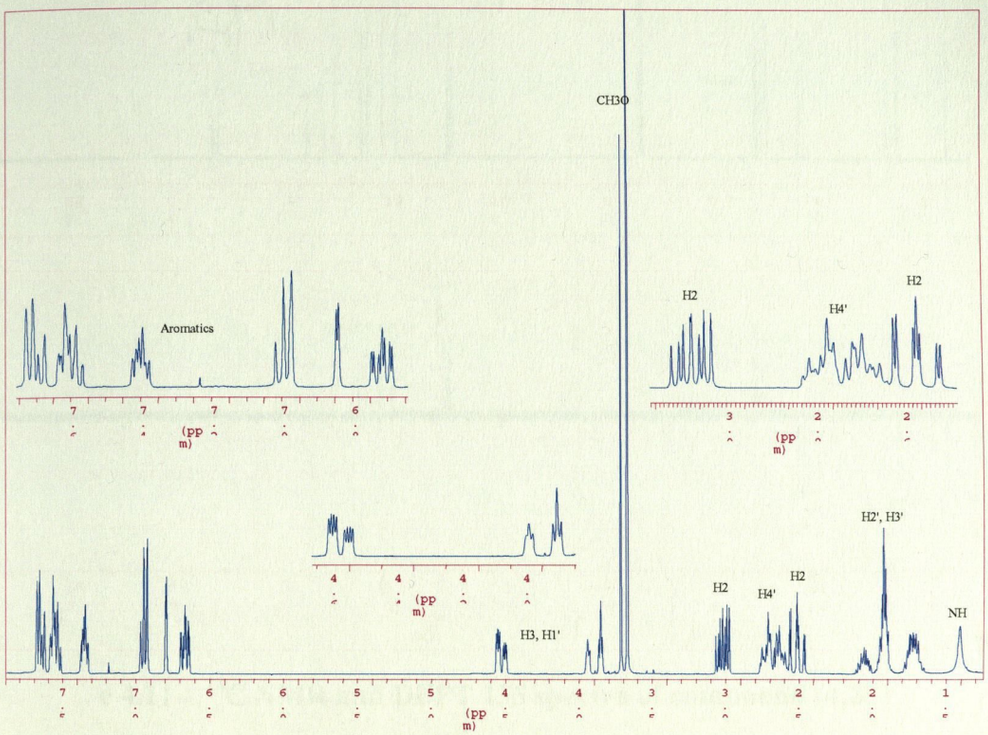



**Figure 4.10 $^{1}H$ NMR spectrum of compound (4.28)**

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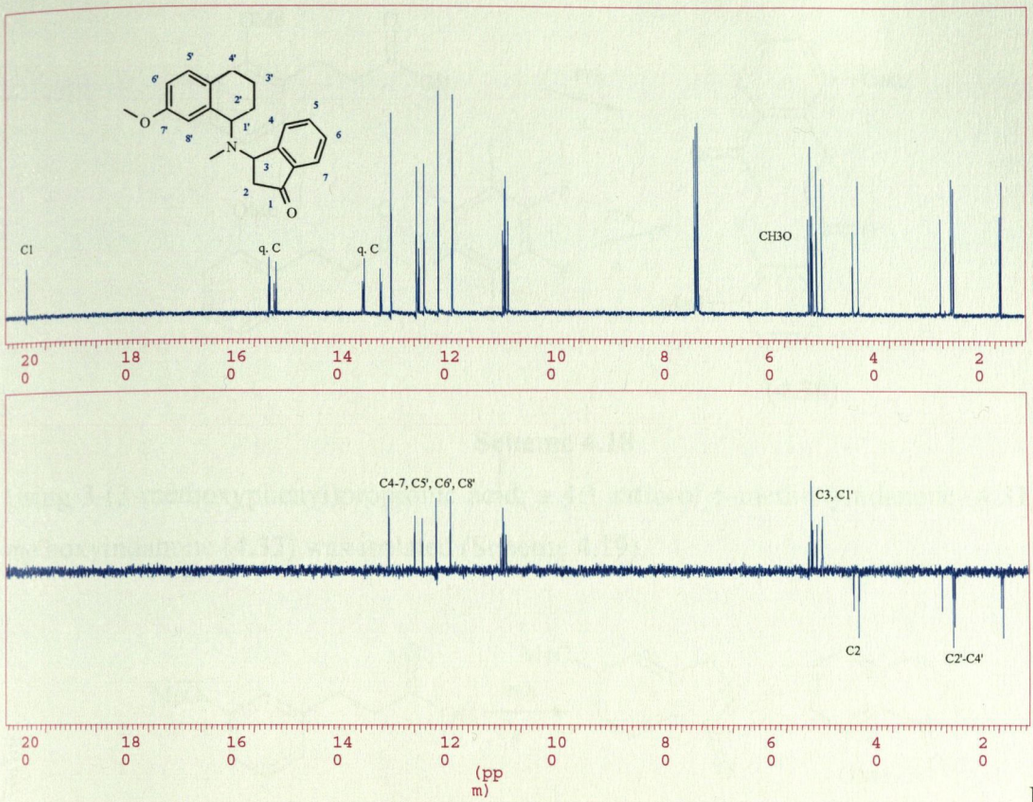



**Figure 4.11 $^{13}$C NMR and DEPT 135 spectra of compound (4.28)**

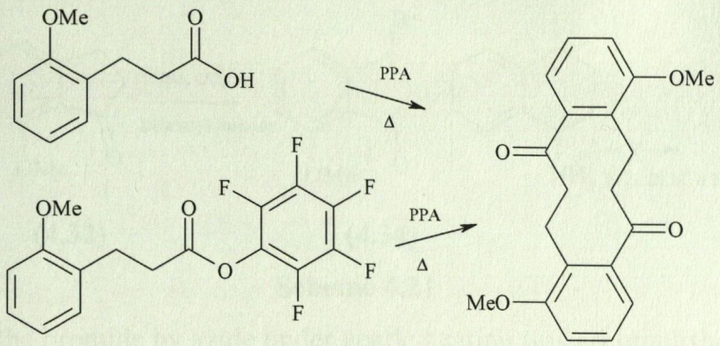
Methylation of the dimer compound (**4.28**) to afford the tertiary amine (**4.29**) did not greatly affect the spectral characteristics; in the infrared spectrum the two important signals, C-$O_{str}$ and C=$O_{str}$, were located at 1244 and 1722cm$^{-1}$, respectively. The $^{1}$H NMR spectrum revealed two sharp *N*-methyl singlets at 1.89 and 2.29ppm. Their corresponding $^{13}$C resonances were at 27.3 and 33.2ppm.

### 4.4.3 Methoxy indanone analogues

The methoxy group was also chosen as a modifying substituent on the aromatic ring of the indanone fragment of (**4.2**), due to the ready availability of 2, 3, and 4-methoxy phenyl propionic acids as starting materials. Cyclisation of these and similar acids is routinely performed using polyphosphoric acid, and there are literature procedures for the cyclisation of both 3-(3-methoxyphenyl)propionic[184] and of 3-(4-methoxyphenyl)propionic[185] acids. Attempted cyclisation of 3-(2-methoxyphenyl)propionic acid with polyphosphoric acid results in the formation of a metacyclophane (**4.30**)[186]. This was also found to be the case for an activated ester of the acid (Scheme 4.18).



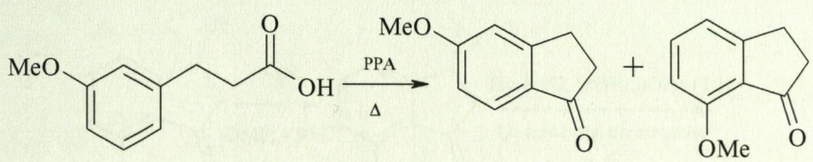
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**(4.30)**

**Scheme 4.18**

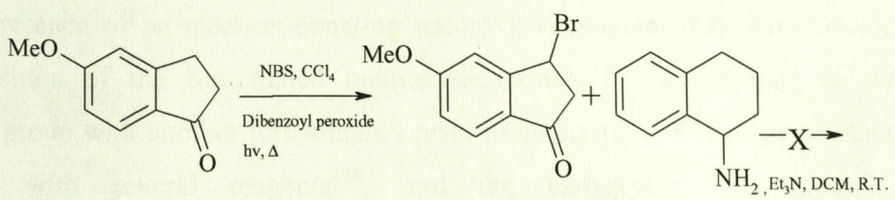
Using 3-(3-methoxyphenyl)propionic acid, a 4:1 ratio of 5-methoxyindanone (**4.31**) to 7-methoxyindanone (**4.32**) was isolated (Scheme 4.19).



**(4.31)** **(4.32)**

**Scheme 4.19**

Upon bromination with NBS, 5-methoxyindanone yielded a mixture of products, and one of these, as judged by NMR to be the 3-bromo derivative (**4.33**), was isolated in low yield. Friedrich and Tam have reported preparation of this compound, yet only as an intermediate without purification, and characterised by $^1$H NMR alone[187]. The bromo compound proved to be quite unstable, and when reaction with 1-aminotetralin was attempted, only decomposition was observed (Scheme 4.20).



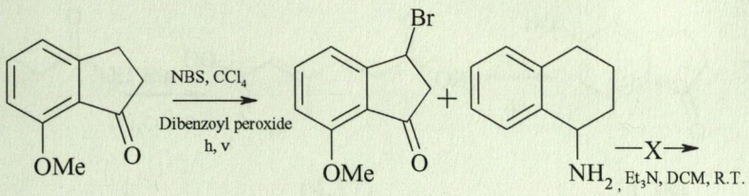
**(4.33)**

**Scheme 4.20**

The bromination of 7-methoxyindanone (**4.32**) yielded a mixture of products, but primarily the required benzylic bromide (**4.34**). However, attempted nucleophilic substitution of this bromide with 1-aminotetralin resulted in complete elimination of the sensitive bromo functionality in the presence of base (Scheme 4.21).



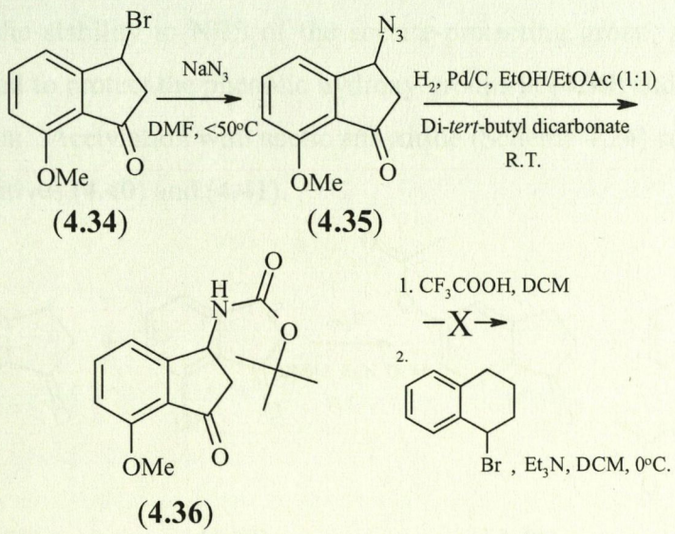
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**(4.32)** **(4.34)**

**Scheme 4.21**

Replacement of the bromide by azide under gentle heating was accomplished in good yield (Scheme 4.22), and hydrogenation in the presence of Di-*tert*-butyl dicarbonate gave the *BOC*-protected amine derivative (**4.36**). Removal of the *BOC* group using trifluoracetic acid gave the free amine, which was added, together with triethylamine, to a freshly prepared solution of 1-bromotetralin in cooled DCM. Unfortunately, no trace of the desired dimer was isolated from the reaction mixture.

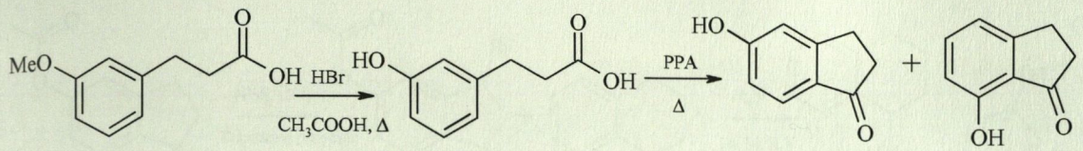



**(4.34)** **(4.35)** **(4.36)**

**Scheme 4.22**

As the presence of an electron-donating methoxy substituent may have accelerated the decomposition of the brominated methoxyindanones, it was decided to replace the methoxy group with another functionality prior to cyclisation. Cleavage of ethers may be achieved with several reagents[188], and the carboxylic acid group in 3-(3-methoxyphenyl)propionic acid is stable to most of these. One of the standard reagents for the cleavage of aromatic ethers is HBr in acetic acid, and indeed this reagent gave quantitative yields of (**4.37**). Cyclisation of this phenolic acid with polyphosphoric acid (Scheme 4.23) gave predominantly the 5-hydroxyindanone (**4.38**), with small amounts of the 7-hydroxyindanone (**4.39**).

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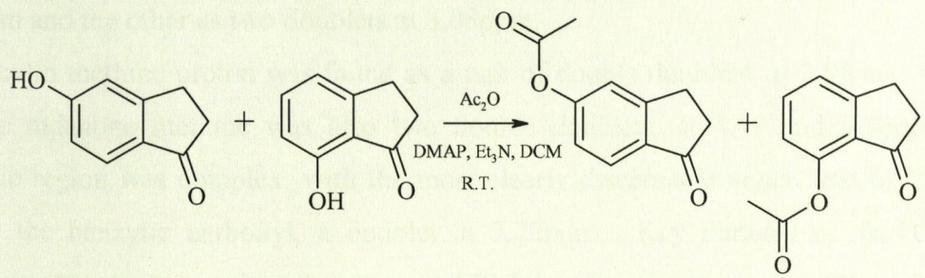



**(4.37)** **(4.38)** **(4.39)**

**Scheme 4.23**

Alternative syntheses of the latter molecule have been reported in the literature, including the fusion of chromanone and aluminium chloride[189], and the cyclisation of an acrylic ester in the eutetic mixture $AlCl_3$-NaCl[190]. These methods effectively block cyclisation to the 5-hydroxy isomer. Benzylic bromination of these hydroxyindanones was also unsuccessful; the polar 5-hydroxy derivative being in any case insoluble in $CCl_4$ and the non-polar 7-hydroxy derivative forming several products, which were found to decompose in contact with silica.

Bearing in mind the stability to NBS of the acetate-protecting group, as exemplified by (**2.6**), it was decided to protect the phenolic hydroxy groups in (**4.38**) and (**4.39**) as acetates prior to bromination. Acetylation with acetic anhydride (Scheme 4.24) smoothly generated both acetate derivatives (**4.40**) and (**4.41**).

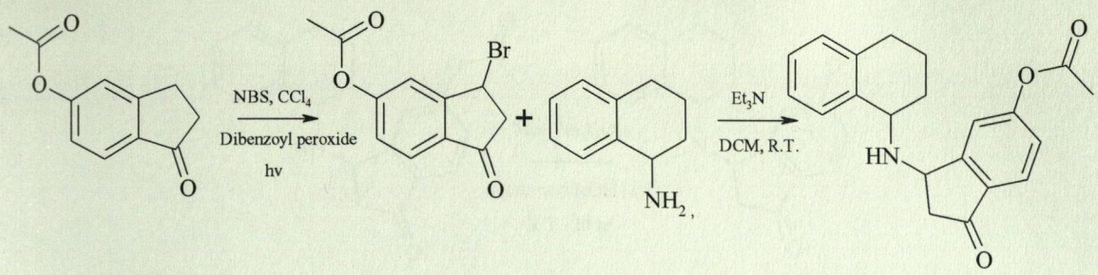



**(4.38)** **(4.39)** **(4.40)** **(4.41)**

**Scheme 4.24**

The benzylic bromination of acetate (**4.40**) with NBS gave good yields of the isolable bromo derivative (**4.42**). Reaction of this halide with 1-aminotetralin in DCM (Scheme 4.25), using triethylamine as tertiary base, gave the secondary amine (**4.43**), as a diasteromeric mixture in good yield (67%).

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**(4.40)** **(4.42)** **(4.43)**

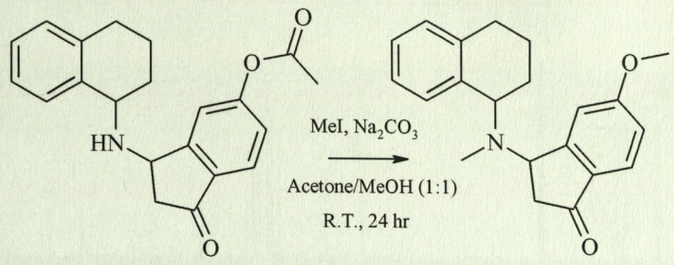
**Scheme 4.25**

IR analysis of dimer (**4.43**) showed prominent C-$O_{str}$ of the ester group at 1198cm$^{-1}$, the ketonic carbonyl at 1719cm$^{-1}$, and the ester carbonyl stretching frequency at 1772cm$^{-1}$. $^{1}$H NMR analysis revealed a diastereomeric mixture, with complex signal overlap in the aliphatic region. Two of the tetralin methylene groups occupied a broad region from 1.76-2.23ppm, followed by two singlets at 2.29 and 3.32ppm, representing the ester methyl protons. The third tetralin methylene, that of the benzylic position, resided between 2.71 and 2.89ppm, separating the two signals for the indanone methylene. The protons of the indanone methylene were widely split, one appearing as a pair of double doublets at 2.57ppm and the other as two doublets at 3.08ppm.

The tetralin methine proton was found as a pair of double doublets, at 3.95 and 4.02ppm, and the indanone methine was also two double doublets, at 4.49 and 4.56ppm. The aromatic region was complex, with the most clearly discernable signal that of the proton nearest the benzylic carbonyl, a doublet at 7.72ppm. Key features of the $^{13}$C NMR spectrum were the two carbonyl groups, at 168.3ppm for the ester carbonyl and 202.6ppm for the ketone.

In a one-pot synthesis, both removal of the acetate protecting group and methylation of both phenolic and secondary amine sites were accomplished using methyl iodide in acetone/methanol, utilising sodium carbonate as base (Scheme 4.26). The product of this synthesis was the tertiary *N*-methylated compound (**4.44**). The three key infrared spectral features of (**4.44**) were largely unaffected by *N*-methylation, at 1197, 1717 and 1772cm$^{-1}$, respectively.

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**(4.43)** **(4.44)**

**Scheme 4.26**

$^1$H NMR analysis of (**4.44**) (Figure 4.12) revealed *N*-methyl singlet resonances at 1.89 and 2.30ppm, their corresponding $^{13}$C NMR resonances (Figure 4.13) being located at 27.4 and 33.3ppm. GCMS analysis of any of the aromatic acetate molecules in this section was hampered by their instability to the conditions used; several peaks of low mass resulted upon injection. In contrast, the methoxy-substituted compound (**4.44**) gave a strong molecular ion cluster and a base peak of 192, corresponding to cleavage of the tetralin moiety. HRMS analysis gave an accurate molecular mass ($+H^+$) of 322.1811, $C_{21}$ $H_{24}$ N $O_2$ requiring 322.1807.

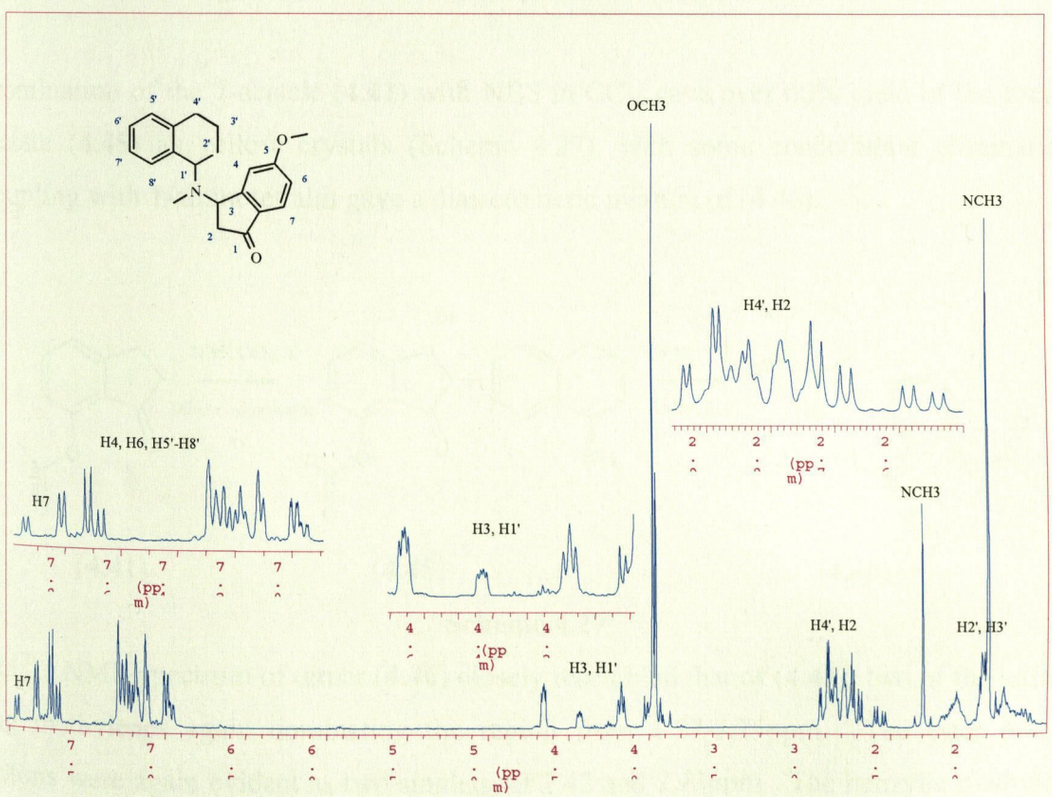



**Figure 4.12** **$^1$H NMR spectrum of compound (4.44)**

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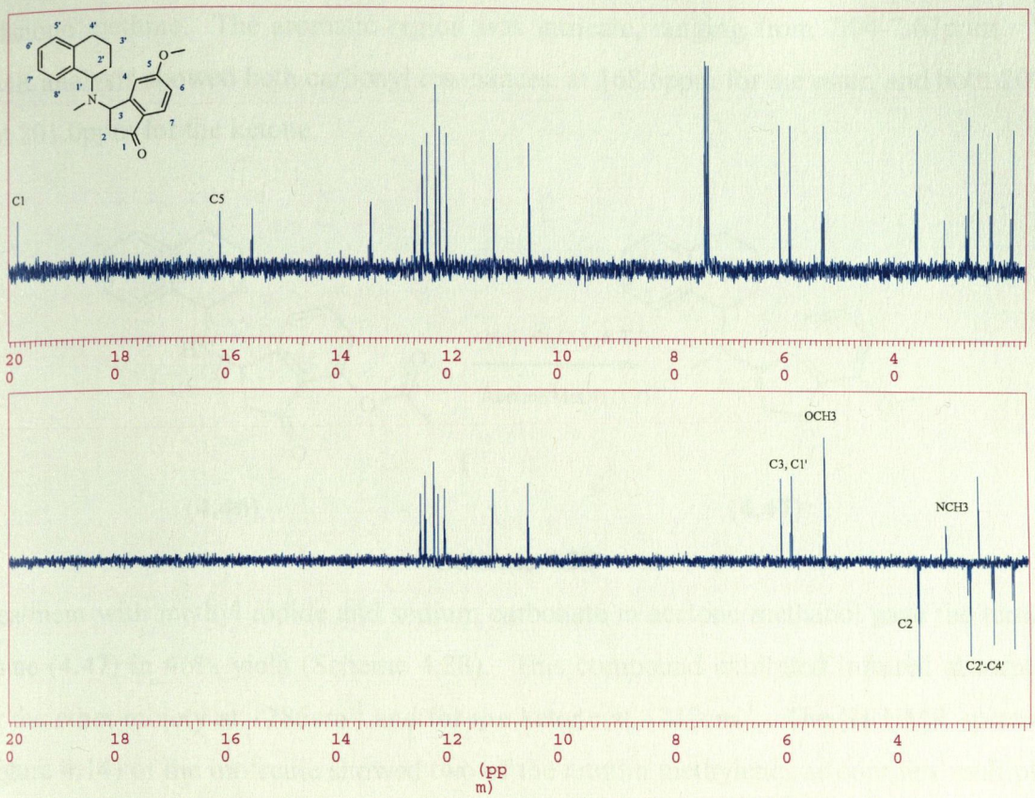
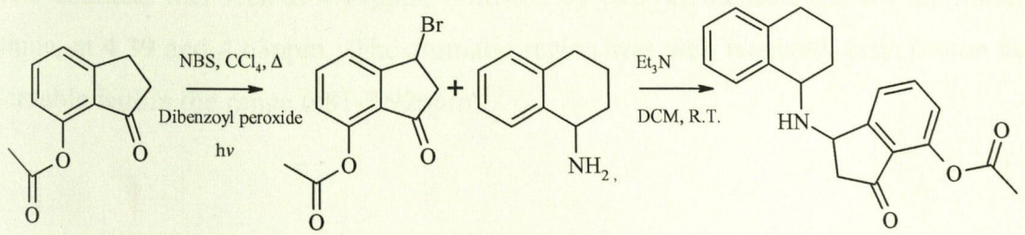



**Figure 4.13** $^{13}$**C NMR spectra of compound (4.44)**

Bromination of the 7-acetate (**4.41**) with NBS in $CCl_4$ gave over 60% yield of the bromo acetate (**4.45**) as yellow crystals (Scheme 4.27), with some concomitant elimination. Coupling with 1-aminotetralin gave a diasteromeric mixture of (**4.46**).




**(4.41)** **(4.45)** **(4.46)**

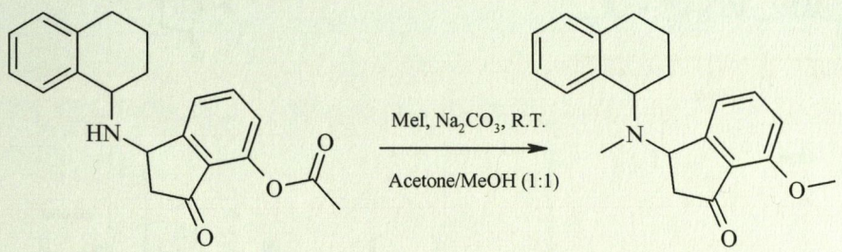
**Scheme 4.27**

The $^1$H NMR spectrum of dimer (**4.46**) closely resembled that of (**4.43**); two of the tetralin ring methylenes again dominating the region from 1.77-2.25ppm. The ester methyl protons were again evident as two singlets, at 2.42 and 2.43ppm. The benzylic methylene centred at 2.85ppm was flanked on either side by a complex indanone methylene signal, at 2.59 and 3.09ppm. Two overlapping double doublets at 3.98 and 4.07ppm represented the tetralin methine, and two double doublets at 4.55 and 4.61ppm reflected the splitting of the



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indanone methine. The aromatic region was intricate, ranging from 7.04-7.67ppm. $^{13}C$ NMR analysis showed both carbonyl resonances: at 168.6ppm for the ester, and both 200.9 and 201.0ppm for the ketone.




**(4.46)** **(4.47)**

**Scheme 4.28**

Treatment with methyl iodide and sodium carbonate in acetone/methanol gave the tertiary amine (**4.47**) in 46% yield (Scheme 4.28). This compound exhibited infrared absorption for the ether moiety at 1286cm$^{-1}$ and for the ketone at 1712cm$^{-1}$. The $^1H$ NMR spectrum (Figure 4.14) of the molecule showed two of the tetralin methylenes as complex multiplets from 1.55-2.14ppm, overlapping with one of the amino methyl singlets at 1.85ppm, and the second of the amino methyl singlets at 2.25ppm.

Considerable overlap between the indanone methylene and benzylic methylene of the tetralin ring meant these signals comprised a broad array of peaks from 2.51-2.92ppm. The methyl ether protons on the indanone ring resonated as two singlets at 3.94 and 3.96ppm, concealing one of the tetralin methine double doublets. The second of these double doublets was seen at 4.14ppm, followed by two double doublets for the indanone methine, at 4.39 and 4.63ppm. The aromatic region was well resolved, each proton being observable within the range 6.81-7.92ppm.

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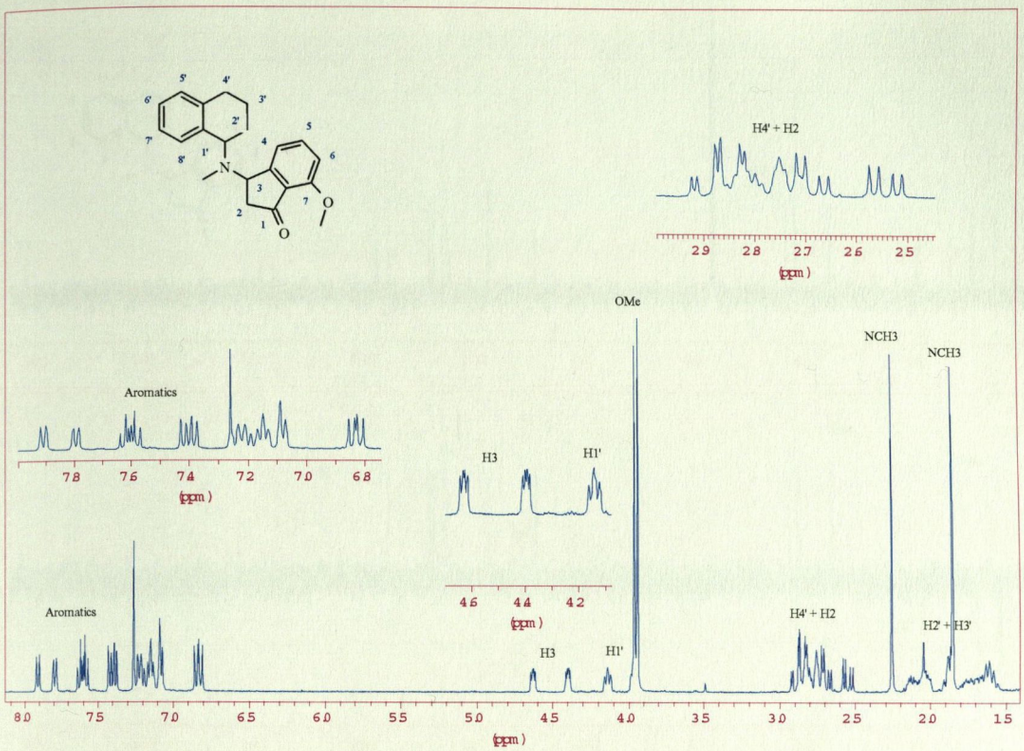



**Figure 4.14 $^{1}$H NMR spectrum of compound (4.47)**

Important features of the $^{13}$C NMR spectrum (Figure 4.15) were the methyl resonances; those of the *N*-methyl carbons at 27.8 and 33.7ppm, and those of the methyl ether carbons at 55.8ppm. HRMS analysis of (**4.47**) gave an accurate molecular mass ($+H^{+}$) of 322.1823, calculated 322.1807.

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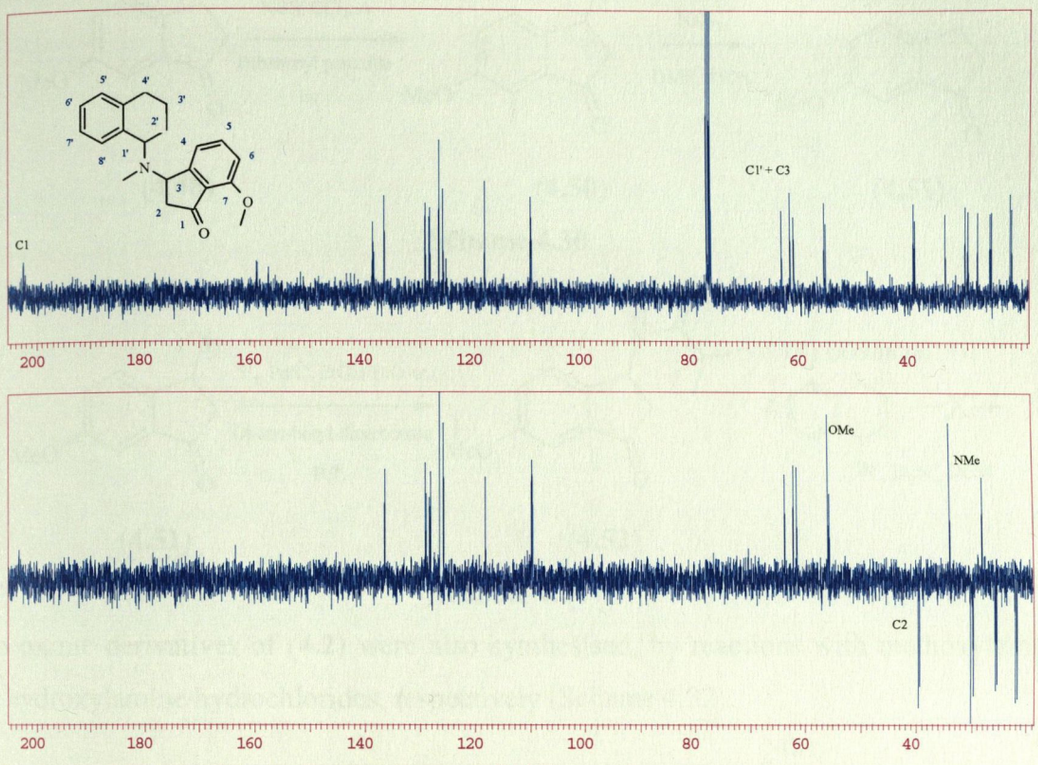
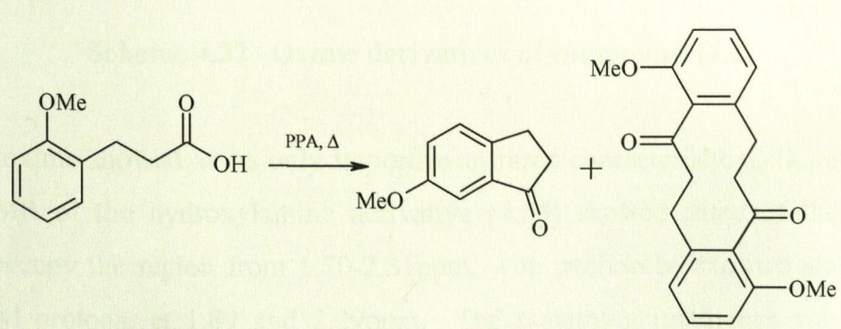



**Figure 4.15** $^{13}$**C NMR and DEPT 135 spectra of compound (4.47)**

Cyclisation of 3-(4-methoxyphenyl)propionic acid (Scheme 4.29) produced a mixture of 6-methoxyindanone (**4.48**) and 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**4.49**), although the ratio seemed to favour the indanone at higher dilutions in polyphosphoric acid. Upon isolation of 6-methoxy indanone, bromination (Scheme 4.30) again proved to yield a reactive intermediate (**4.50**), which was reacted as a crude residue with sodium azide in DMF. The azide (**4.51**), upon reduction and deprotection of carbamate (**4.52**), did not react with 1-bromotetralin (Scheme 4.31).

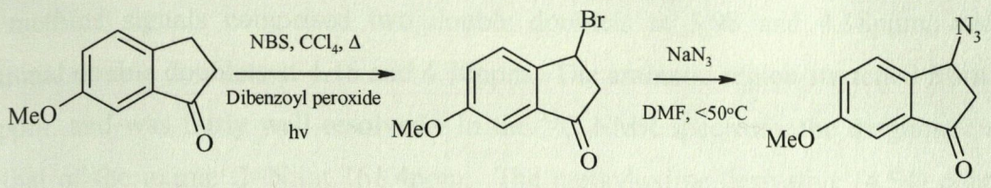



**(4.48)** **(4.49)**

**Scheme 4.29**

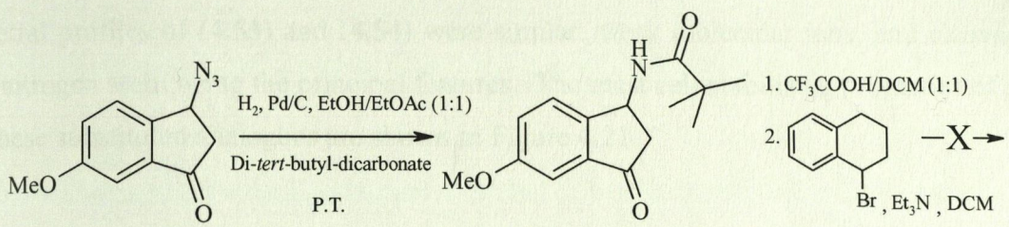


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**(4.48)** **(4.50)** **(4.51)**

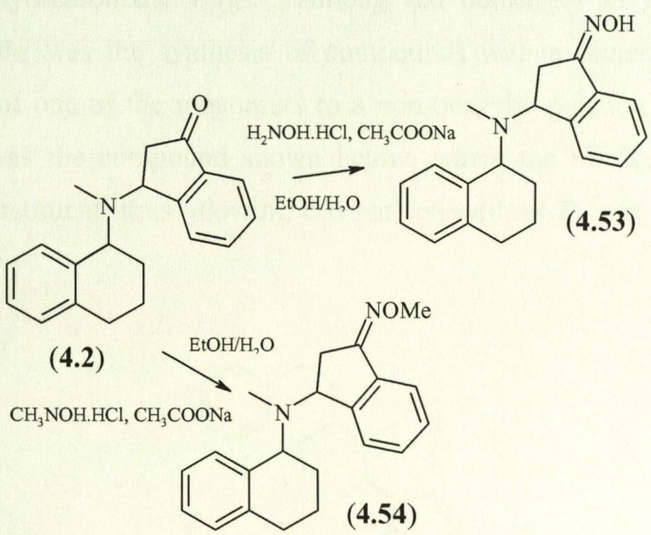
**Scheme 4.30**




**(4.51)** **(4.52)**

**Scheme 4.31**

Two oxime derivatives of (**4.2**) were also synthesised, by reactions with methoxylamine and hydroxylamine hydrochlorides, respectively (Scheme 4.32).




**(4.2)** **(4.53)** **(4.54)**

**Scheme 4.32 Oxime derivatives of compound (4.2)**

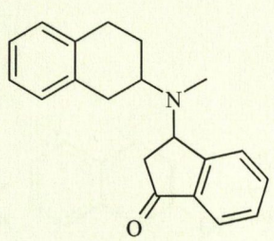
The methyloxime showed as its only important infrared characteristic C-$O_{str}$ at 1050$cm^{-1}$. The $^1H$ NMR of the hydroxylamine derivative (**4.53**) showed three of the methylene groups to occupy the region from 1.70-2.31ppm, with overlap by the two singlets of the aminomethyl protons, at 1.89 and 2.29ppm. The remaining methylene was centred at 2.84ppm, followed by the hydroxyl proton at 3.11ppm.

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The methine signals comprised two double doublets at 3.98 and 4.18ppm, and two additional double doublets at 4.46 and 4.70ppm. The aromatic region stretched from 7.10-7.97ppm, and was fairly well resolved. In the $^{13}C$ NMR spectrum, the diagnostic signal was that of the oxime C=N, at 161.4ppm. The methyloxime derivative (**4.54**) contained diagnostic singlets at 4.01 and 4.04ppm in the $^{1}H$ NMR, corresponding to the methyl protons of the oxime moiety; their carbon counterparts resonated at 61.7ppm. The GCMS spectral profiles of (**4.53**) and (**4.54**) were similar; weak molecular ions, and cleavage at the nitrogen atom being the principal features. The mast cell-stabilising properties of some of these substituted analogues are shown in Figure 4.21.

## 4.5 Dimers of indanone and tetralin, linked via one benzylic, and one non-benzylic carbon atom

All of the molecules reported to date in this Chapter are dimers linked through the benzylic position of two hydroaromatic rings. Among the objectives in our study of these molecules, however, was the synthesis of compounds with a dimeric link through the benzylic position of one of the monomers to a non-benzylic position of the second. Of primary interest was the compound shown below, where the nitrogen atom contains a tertiary methyl substituent, thus allowing comparison with (**4.2**), one of our most active molecules.




**(4.61)**

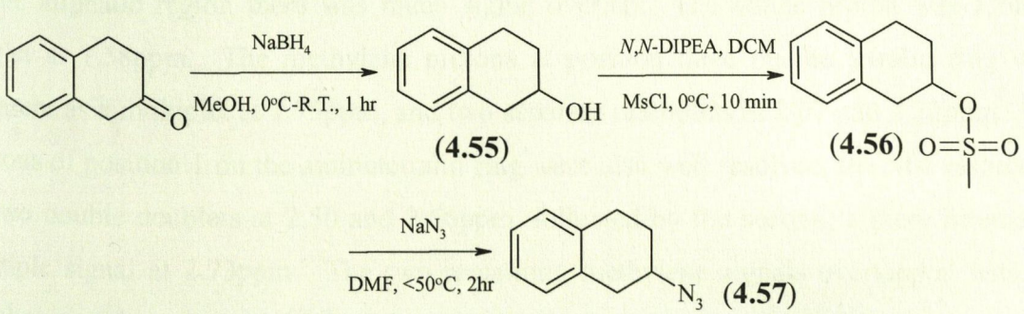
The obvious route to this compound was via the secondary amine, 2-aminotetralin. This amine, unlike its 1-isomer, is not widely available. There has been much interest in the synthesis of 2-aminotetralins, as they possess known pharmacological activity, including dopamine receptor activity[91], and are key precursors in the synthesis of many important structures, including steroids and alkaloids.

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The two most common approaches to this primary amine are via reductive amination of β-tetralone, or reduction of the corresponding oxime. The first of these reactions, reductive amination, is frequently performed using sodium cyanoborohydride, at pH 6-8[191]. This reaction in our hands was slow and did not give a clean product.

The reduction of oximes may be achieved using several reagents, including Diborane-THF[192] and Raney nickel in alkaline solution[193]. Cleavage using the former reagent is reported to proceed at room temperature using oxime ethers, although using 1,2,3,4-tetrahydro-2-naphthalenone *O*2-methyloxime, this procedure proved unsatisfactory. It was therefore decided to pursue an alternative route to 2-aminotetralin, as outlined below.

Using as starting material β-tetralone, reduction with sodium borohydride (Scheme 4.33) gave quantitative yields of the alcohol (**4.55**). Conversion of the hydroxyl to a suitable leaving group was necessary to enable substitution with azide. There were several options in the choice of leaving group at position 2, including halide and sulphonyl moieties. Indeed, the preparation of 1,2,3,4-tetrahydro-2-iodonaphthalene was reported in 1946 by Arbit[194]. We decided to use methane sulphonyl chloride to substitute the hydroxyl for a sulphonyl group, and found that this transformation gave excellent yields of the methane sulphonate (**4.56**), although the reaction was somewhat difficult to monitor, given the identical $R_f$ values observed for both compounds on silica gel. The key feature in the characterisation of the sulphonate ester was the presence of strong $S{=}O_{str}$ in the infrared at 1176 and 1342cm$^{-1}$.



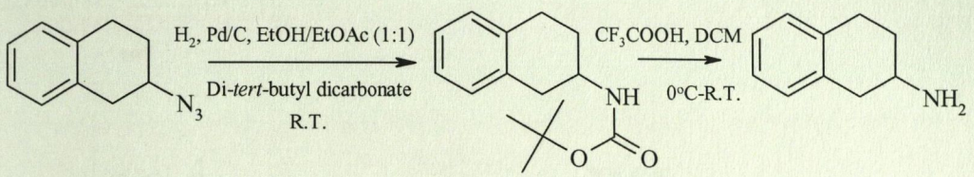

**Scheme 4.33**

After isolation of the pure sulphonate, substitution with azide anion in DMF[195] was followed by reduction of the azide under hydrogenation conditions in the presence of Di-*tert*-butyl dicarbonate (Scheme 4.34) to give the *BOC*-protected amine.



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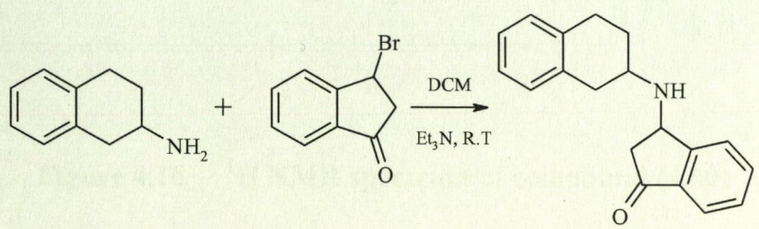
Removal of the protecting group afforded the amine trifluoroacetate, a dark brown oil which solidified on standing.




**(4.57)** **(4.58)** **(4.59)**

**Scheme 4.34**

Reaction of the liberated amine with 3-bromoindanone (Scheme 4.35) gave good yields of the diasteromeric dimer (**4.60**), which was isolated as a pale golden oil. The diastereomers of (**4.60**) were unresolvable by TLC.




**(4.59)** **(4.60)**

**Scheme 4.35**

The only strong feature of this molecule in the infrared spectrum was the stretching frequency of the carbonyl group at 1718cm$^{-1}$. The $^1$H NMR spectrum (Figure 4.16), like many of the molecules in this Chapter, was complicated by the presence of diastereomers. In the aliphatic region there was much signal overlap. The amine proton was a broad singlet at 1.58ppm. The methylene protons at position three on the tetralin ring were apparent as a multiplet at 1.75ppm, and two separate multiplets at 2.07 and 2.22ppm. The protons of position 1 on the aminotetralin ring were also well resolved, the first resonating as two double doublets at 2.50 and 2.56ppm, followed by the second, a more broadened multiple signal at 2.73ppm. The two remaining methylene signals overlapped with the tetralin methine from 2.86-3.26ppm, and the indanone methine resonated as two superimposed signals at 4.64ppm. Again, there was complexity in the aromatic region, with a multiplet centered at 7.13ppm integrating as four protons, and four additional signals further downfield, each integrating as one proton. In the $^{13}$C NMR spectrum (Figure 4.17), the carbonyl signal resonated at 204.1ppm.



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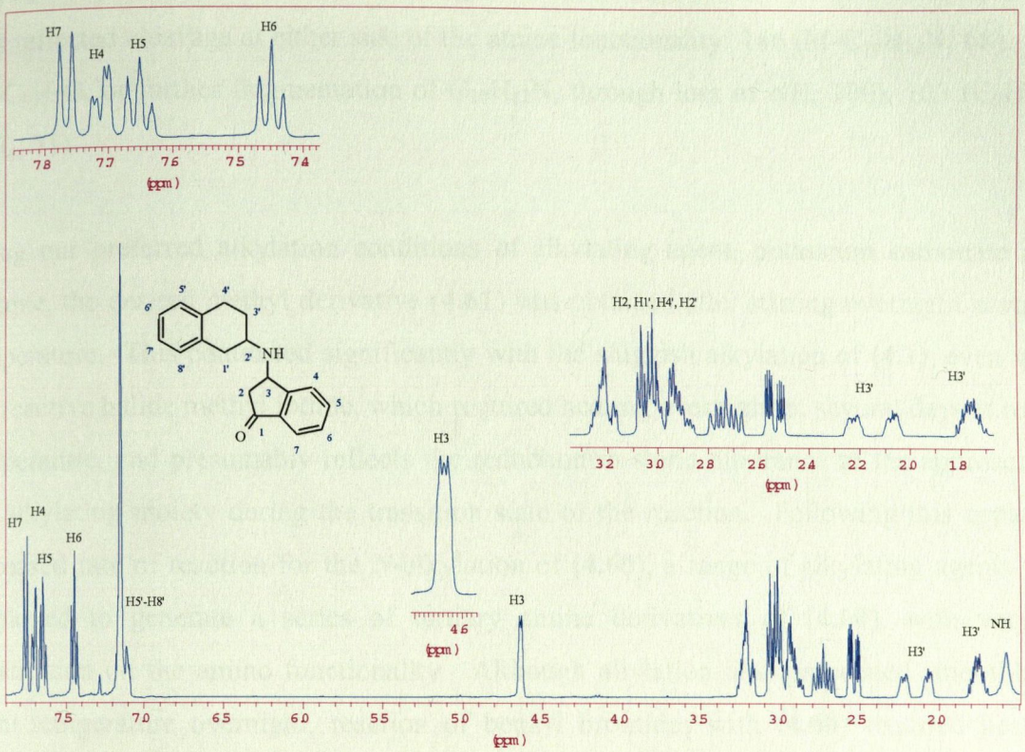



**Figure 4.16** $^{1}$H NMR spectrum of compound (4.60)

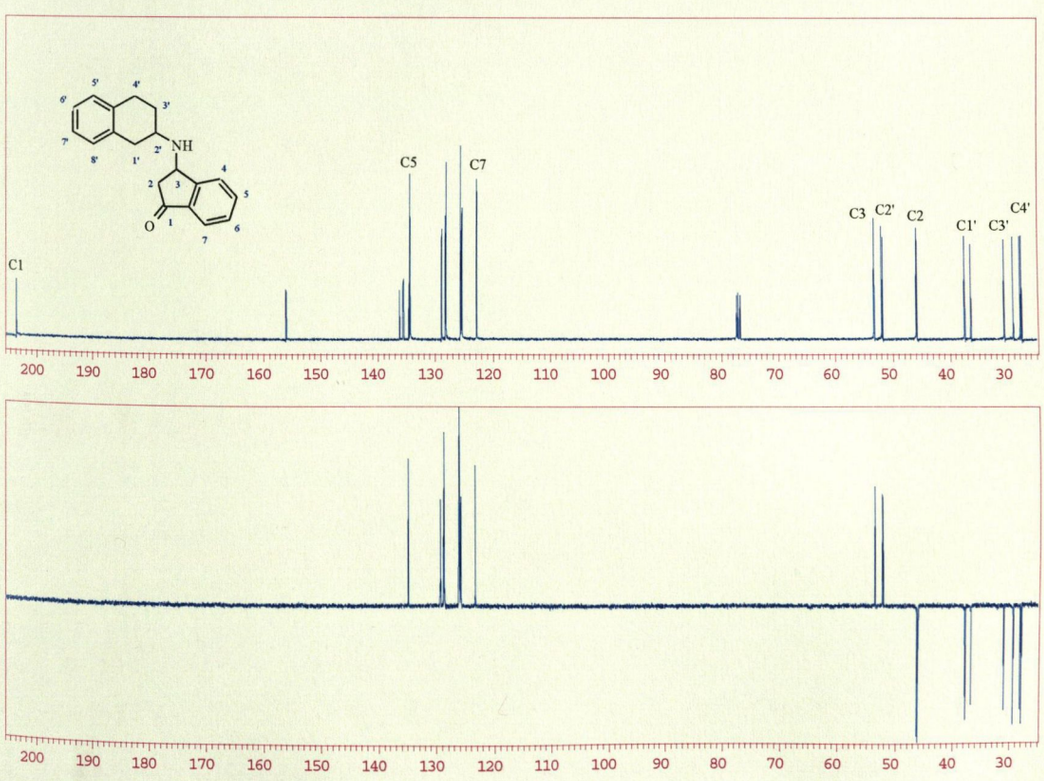



**Figure 4.17** $^{13}$C NMR and DEPT 135 spectra of compound (4.60)

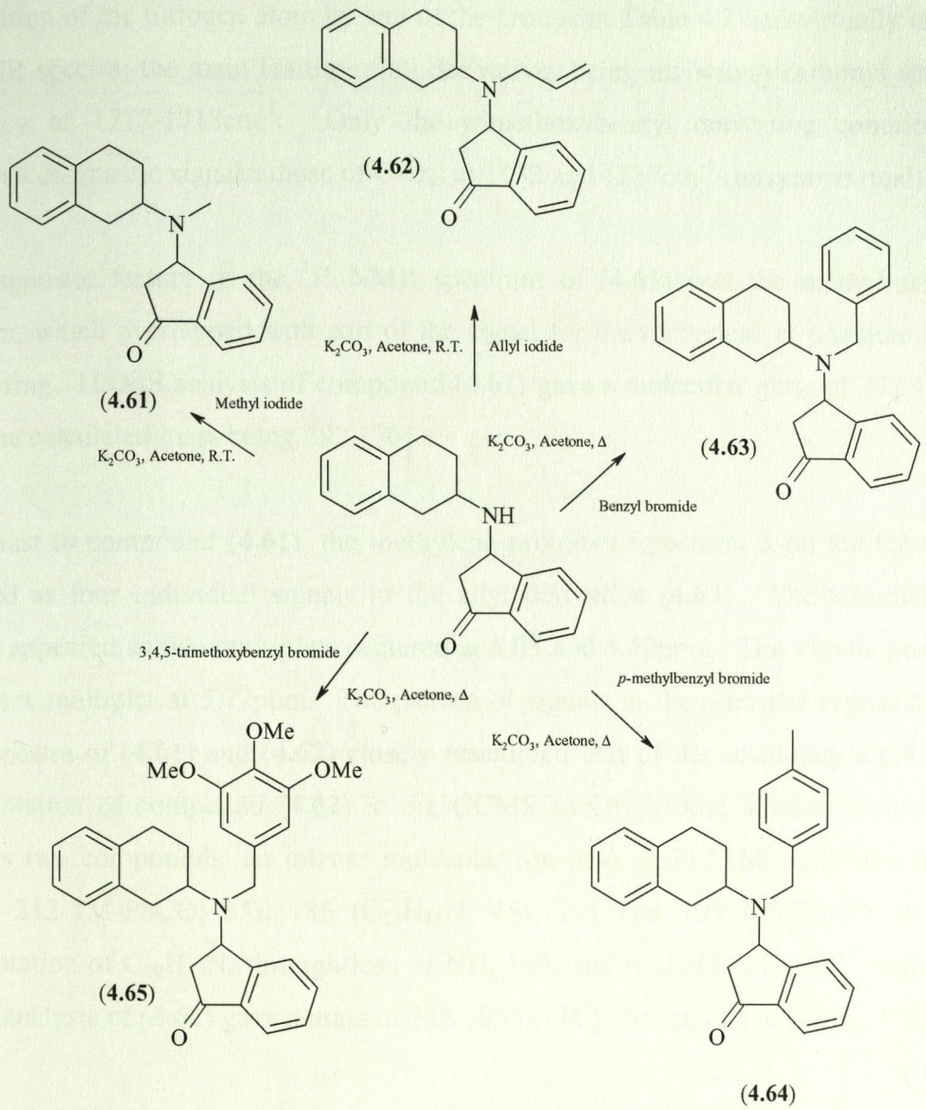


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GCMS analysis of (**4.60**) revealed a strong molecular ion of 277 ($M^+$, 99). Other important ions reflected cleavage at either side of the amine functionality: 146 (M-$C_{10}H_{12}N$, 68), 131 (M-$C_9H_7O$, or further fragmentation of $C_{10}H_{12}N$, through loss of NH, 100), 103 ($C_9H_7O$-$C_2H_4$, 71).

Using our preferred alkylation conditions of alkylating agent, potassium carbonate and acetone, the desired methyl derivative (**4.61**) was obtained after stirring overnight at room temperature. This contrasted significantly with the sluggish alkylation of (**4.1**), even with the reactive halide methyl iodide, which required heating overnight or several days at room temperature, and presumably reflects the reduction in steric hindrance to the approach of the alkylating moiety during the transition state of the reaction. Following this apparent increased rate of reaction for the *N*-alkylation of (**4.60**), a range of alkylating agents was employed to generate a series of tertiary amine derivatives of (**4.60**), with varying substitution on the amino functionality. Although allylation also proceeded smoothly at room temperature overnight, reaction of benzyl bromides with (**4.60**) required heating under reflux for several days. The derivatives synthesised are listed in Table 4.2, and the structures are depicted below.

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**Scheme 4.36** ***N*-alkylations of compound (4.60)**

**Table 4.2 Tertiary amine derivatives of (4.60)**

| R Group | Compound No. | Reaction time | % Yield |
|---|---|---|---|
| Methyl | **(4.61)** | 6hr, R.T. | 34 |
| Allyl | **(4.62)** | 6hr, R.T. | 56 |
| Benzyl | **(4.63)** | 6 days, Δ | 47 |
| *p*-methylbenzyl | **(4.64)** | 6 days, Δ | 15 |
| 3,4,5-trimethoxybenzyl | **(4.65)** | 6 days, Δ | 27 |

Substitution of the nitrogen atom by any of the groups in Table 4.2 had virtually no effect on the IR spectra; the main feature of all derivatives being the strong carbonyl stretching frequency at 1717-1718cm$^{-1}$. Only the trimethoxybenzyl derivative contained any additional diagnostic signals, those of C-$O_{str}$ at 1132 and 1237cm$^{-1}$ (unsymmetrical).

The diagnostic feature in the $^1$H NMR spectrum of (**4.61**) was the methyl singlet at 2.14ppm, which overlapped with part of the signal for the methylene at position 3 on the tetralin ring. HRMS analysis of compound (**4.61**) gave a molecular mass of 292.1678 (M $+H^+$), the calculated mass being 292.1701.

In contrast to compound (**4.61**), the methylene protons of position 3 on the tetralin ring appeared as four individual signals in the allyl derivative (**4.62**). The terminal alkene protons appeared as two multiplets centered at 5.05 and 5.20ppm. The vinylic proton was a complex multiplet at 5.77ppm. The pattern of signals in the aromatic region of the $^1$H NMR spectra of (**4.61**) and (**4.62**) closely resembled that of the secondary amine (**4.60**). Fragmentation of compound (**4.62**) in the GCMS spectrum bore similar features to the previous two compounds: an intense molecular ion peak at 317 ($M^+$, 78), and fragment ions at 212 (M-PhCO, 55), 186 ($C_{13}H_{16}N$, 45), 131 and 103 (M-$C_9H_7O$, or further fragmentation of $C_{10}H_{12}N$, through loss of NH, 100) and ($C_9H_7O$-$C_2H_4$, 71), respectively. HRMS analysis of (**4.62**) gave a mass of 318.1835 ($+H^+$), that calculated being 318.1858.

Introduction of a benzyl or substituted benzyl group onto the amine substituent, as in compounds (**4.63-4.65**), introduced some additional features to the $^1$H NMR spectra. The aliphatic methylene signals for the protons at position 3 on the tetralin ring all appeared reasonably well resolved between 1.60-2.30ppm, although in the case of (**4.64**), there was a slight overlap with the sharp singlet for the *p*-tolyl methyl group. In all three benzylated compounds, a complex multiple signal integrating for seven protons occupied the region between 2.73 and 3.19ppm, which represented both benzylic methylene groups on the tetralin ring in addition to the α-keto methylene group on the indanone ring. One of the key features of these three spectra was the distinctive signal for the amino methylene protons, which appeared as two overlapping signals at 3.66 and 3.69ppm in the spectrum of (**4.63**).

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Substitution on the benzene ring by electron-donating groups, as in (**4.64**) and (**4.65**), had a shielding effect on the aminomethylene protons, as the corresponding resonances for these protons in molecules (**4.64**) and (**4.65**) were at 3.52 and 3.71ppm for the *p*-methylbenzyl, and 3.49 and 3.68ppm for the trimethoxybenzyl derivatives respectively. A further important signal in this region of the spectrum for (**4.64**) was that of the methyl ether groups, resonating at 3.85ppm. The $^{1}H$ NMR spectra of all three structures contained a methine signal for the benzylic indanone proton at 4.80-4.85ppm. The aromatic region of the three derivatives bore similarities only in the downfield region, between 7.65 and 8.00ppm, where each spectrum comprised three signals, each integrating for one proton, the last signal in each case being two doublets, one each for the diasteromeric forms of the aryl proton nearest the benzylic indanone carbonyl. One important feature of the spectrum of (**4.65**) was the signal at 6.63ppm, which accounted for the two remaining protons on the substituted trimethoxy benzyl ring.

GCMS analysis of the unsubstituted benzyl (**4.63**) revealed a similar spectrum to molecules (**4.61**) and (**4.62**); a strong molecular ion at 367 ($M^{+}$, 65), the base peak at 276 corresponding to cleavage of the benzyl group (M-$PhCH_2$), 236 (M-$C_9H_7O$, or further fragmentation of $C_{10}H_{12}N$, through loss of NH, 58), and moderately intense ions at 131 (32) and 103 (25). Interestingly, the only intense ion in the GCMS profile of (**4.65**) was that at 181, corresponding to the trimethoxy benzyl ion. All three benzylated molecules gave satisfactory molecular masses ($+H^{+}$) on HRMS analysis: for (**4.63**), 368.2007 ($+H^{+}$), calculated 368.2014; for (**4.64**), 382.2147 ($+H^{+}$), calculated 382.2171, and for (**4.65**), 458.2336, calculated 458.2331.

*N*-acylations of (**4.60**) using acetic anhydride or phenylacetylchloride, even using several equivalents of DMAP, were uniformly unsuccessful.

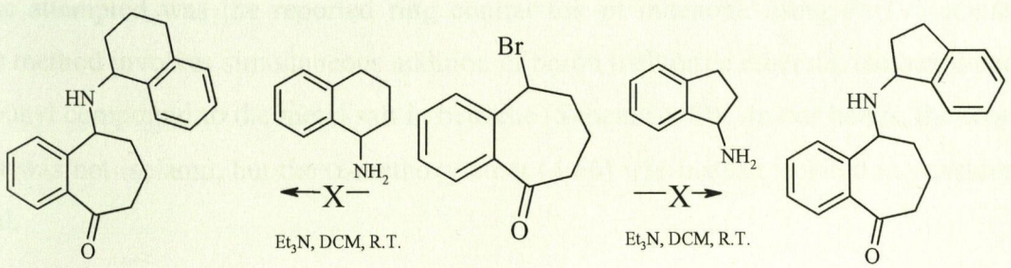
The mast cell-stabilising results of compounds (**4.61-4.65**) are depicted in Figure 4.22.

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## 4.6 Synthetic attempts towards dimer compounds with either a seven or four-membered hydroaromatic ring

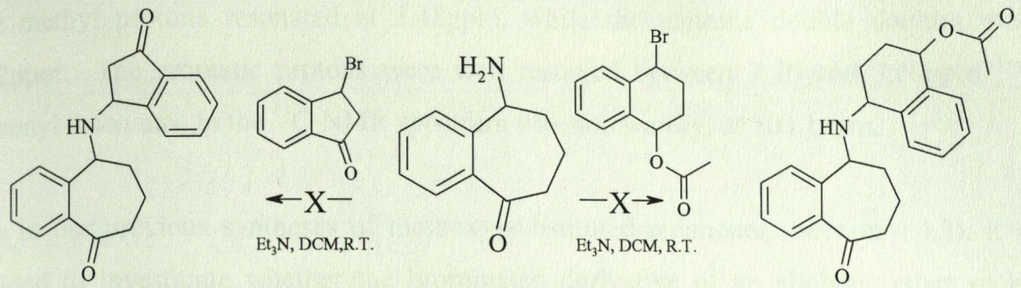
An examination of the *in vitro* data in Section 4.7 revealed that mast cell-stabilising activity was greatest in those molecules with a 1-indanone or α-tetralone ring linked to a tetralin ring. Activity seemed to be retained whether the linkage joined the two ring systems via their benzylic positions or was from one benzylic position to a non-benzylic carbon of the other ring system. Substitution of the ring or amine positions affected activity to some extent, especially the introduction of electron-donating functional groups.

It was anticipated that attempts to probe the importance of configurational restraints within these molecular types would be aided by a study of the effect of further manipulation of the hydroaromatic rings. Expansion of one ring to a seven-membered ring component or contraction to a four-membered ring may well be expected to have a significant impact on activity. The first of these targets, namely use of a benzosuberone unit as one half of a dimer with either a tetralin or indan moiety conjoined, was not realised, as the relatively low reactivity of the benzylic bromide of benzosuberone, as encountered in Chapter 2, precluded its successful use as an electrophile in reactions with either 1-aminotetralin or 1-aminoindan (Scheme 4.37).




**Scheme 4.37**

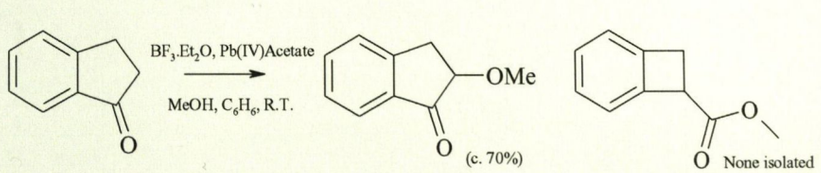
The apparent low nucleophilicity of the benzylic benzosuberylamine meant that attempted reaction with either bromoacetate (**2.6**) or 3-bromoindanone also proved unsatisfactory (Scheme 4.38).




**Scheme 4.38**

Use of a strained ring component, in the form of a benzocyclobutenyl ring, formed an area of considerable focus but failed to yield any dimer molecule. This outcome has been attributed to both the considerable ring strain and well-documented reactivity of four-membered hydroaromatic molecules. Benzocylobutenes and their derivatives have been prepared using many synthetic routes[196], although many of these require special apparatus e.g. flash vacuum pyrolysis[197] and the reaction of benzocyclopropene with dihalocarbenes[198]. Other routes are successful but potentially dangerous e.g. those reactions employing benzenediazonium salts[199], or require specially prepared catalysts such as trimethylsulphonium chloride, used in the epoxidation of aromatic aldehydes prior to cyclisation into benzocyclobutenols[200].

For our purposes simpler methods offering better yields were required, and the first of those attempted was the reported ring contraction of indanone using Pb(IV) acetate[201]. This method involves simultaneous addition of boron trifluoride etherate, methanol and the carbonyl compound to the metal salt in benzene (Scheme 4.39). In our hands, the reported ester was not isolated, but the α-methoxy ether (**4.66**) was instead isolated in considerable yield.




**(4.66)**

**Scheme 4.39**

This molecule exhibited a strong carbonyl absorption at 1725cm$^{-1}$ in the infrared spectrum, and its $^1$H NMR spectrum showed the benzylic methylene split into two double doublets, at 2.82 and 3.34ppm.

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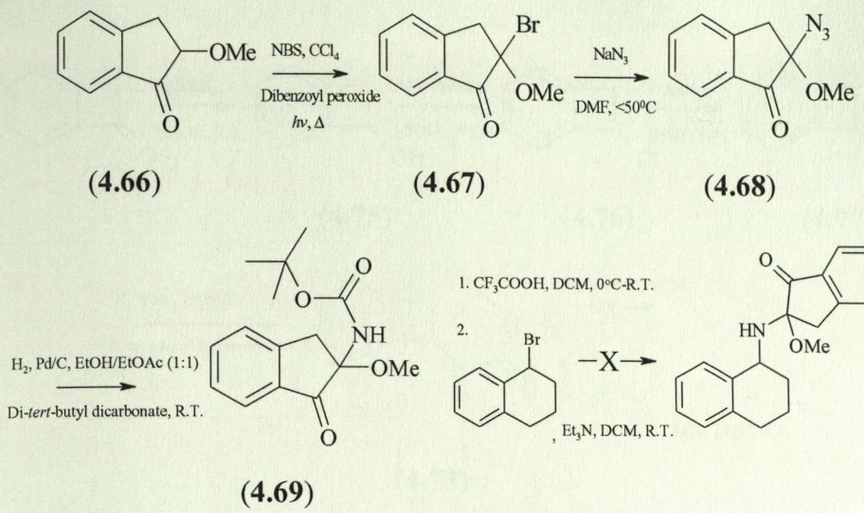
The methyl protons resonated at 3.48ppm, while the methine double doublet was at 4.02ppm. The aromatic protons were well resolved between 7.20 and 7.60ppm. The carbonyl resonance in the $^{13}C$ NMR spectrum was noteworthy, at 203.1ppm.

Due to our previous syntheses of methoxy-substituted indanones (Section 4.4.3), it was decided to investigate whether the brominated derivative of an aliphatic ether such as (**4.66**) would behave similarly to those of the aromatic ether derivatives (**4.31**) and (**4.32**) in coupling reactions with aminotetralin. Bromination of (**4.66**) under Wohl-Ziegler conditions (Section 2.2.1) afforded as the main product an unstable oil that was not isolated, but reacted *in situ* with 1-aminotetralin, using triethylamine as base and DCM as solvent at room temperature (Scheme 4.40). However, only decomposition was observed.

The azide derivative (**4.68**) was isolated following reaction of the brominated residue described above with sodium azide in DMF. $^{1}H$ NMR analysis of the azide revealed that bromination had occurred $\alpha$ to the ketone, rather than in the benzylic position of (**4.66**), affording primarily (**4.67**). This was apparent from the methylene double doublet in the $^{1}H$ NMR spectrum of (**4.68**) and its corresponding $^{13}C$ NMR signal at 37.0ppm. As aforementioned, (Section 2.2.1), reaction of NBS with carbonyl compounds may suffer from this competing side-reaction.

The *BOC*-amino derivative (**4.69**) was isolated following hydrogenation of the intermediate azide in the presence of Di-*tert*-butyl dicarbonate. After liberation of the free amine using trifluoracetic acid, addition of 1-bromotetralin resulted only in decomposition, with no trace of any dimer molecule.

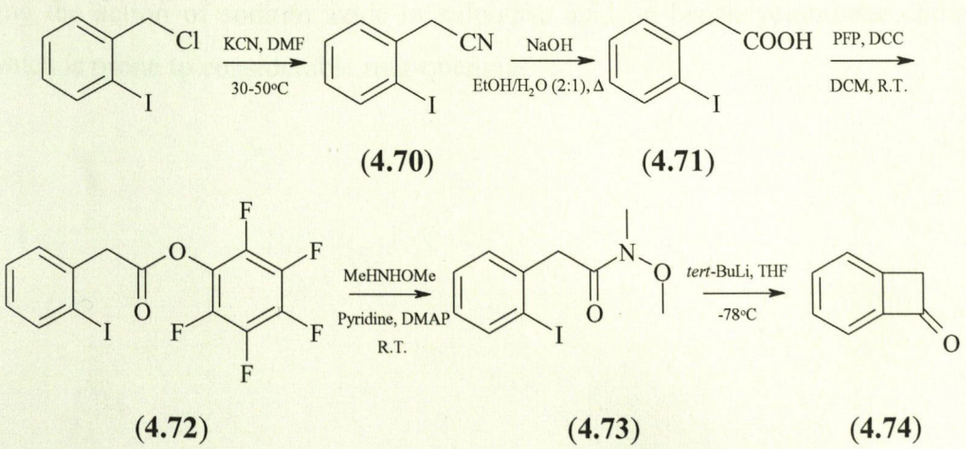
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**Scheme 4.40**

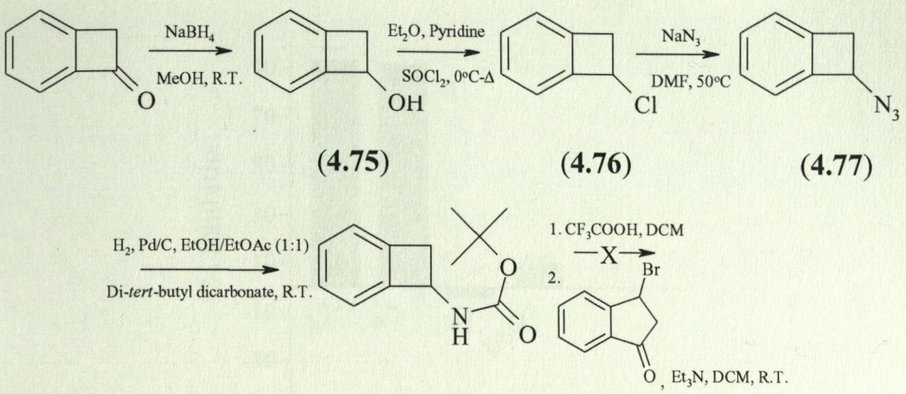
Having abandoned the Pb(IV) acetate route to the benzocyclobutenes, the second route examined was via the use of aryllithium intermediates.

Two reported methods include the lithium-halogen exchange reactions of 2-(2′-halophenyl) ethyl bromides with subsequent cyclisation[202], and the lithium-iodine exchange initiated cyclisation of *o*-iodo-*N*-methoxy-*N*-methyl phenylacetamides[203]. The latter of these approaches proved quite successful (Scheme 4.41), and involved initial substitution of chloro compound with cyanide, followed by hydrolysis and formation of amide (**4.73**)[204]. Cyclisation was mediated using *tert*-butyllithium, affording ketone (**4.74**) in agreement with literature data.




**Scheme 4.41**

The product ketone was reduced (Scheme 4.42) to the alcohol (**4.75**) and converted to the chloride (**4.76**) using thionyl chloride. Substitution of the halogen afforded azide (**4.77**) and subsequent reduction yielded the *BOC*-protected amine (**4.78**).




**Scheme 4.42**

Removal of the protecting group was achieved using trifluoracetic acid, and the free amine (**4.79**) was added to 3-bromoindanone in DCM, with triethylamine as tertiary base. To our great disappointment, the only product isolated from the reaction was an impure, unstable oil that on crude $^1$H NMR analysis, showed that the four-membered ring had opened. This was evident from the large methyl signal at 2.60ppm in the $^1$H NMR spectrum, and the corresponding carbon resonance at 19.4ppm.

$^1$H NMR analysis showed that the deprotection step using trifluoracetic acid had no deleterious effect on the integrity of the ring system, as evidenced by the broad methine signal in the $^1$H NMR at 4.73ppm, and its carbon counterpart at 49.8ppm. Thus this method is superior to the literature method of preparation of the primary amine[205], involving the action of sodium azide in sulphuric acid on benzocyclobutene carboxylic acid, which is prone to considerable ring-opening.

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## 4.7 Initial mast cell-stabilising results for compounds of Chapter 4

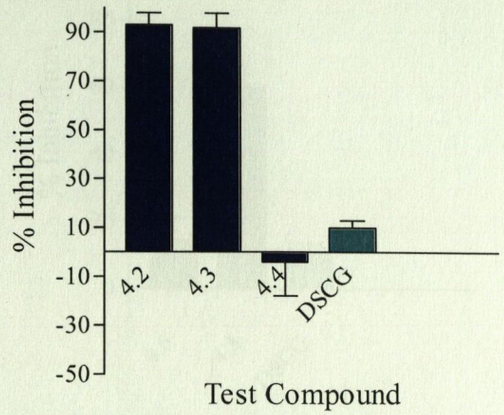



**Figure 4.18 Mast cell-stabilising activity of derivatives of compounds (4.2-4.4)**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*

**Table 4.3 Summary statistics for compounds (4.2-4.4)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **4.2** | 93 | 12 | 5 | 5 |
| **4.3** | 92 | 13 | 6 | 5 |
| **4.4** | -4 | 31 | 14 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

From Figure 4.18, it can be seen that both the methyl and allyl derivatives of (**4.1**) almost completely inhibited the Compound 48/80-induced histamine release (93 and 92% inhibition, respectively) from rat peritoneal mast cells at the concentration examined, while the acetamide (**4.4**) was inactive. These results correlated well with the pattern of results reported for indanone homodimers, and suggested that enlargement by one carbon of one of the alicyclic portions of these molecules had no deleterious effect on mast cell-stabilising activity.

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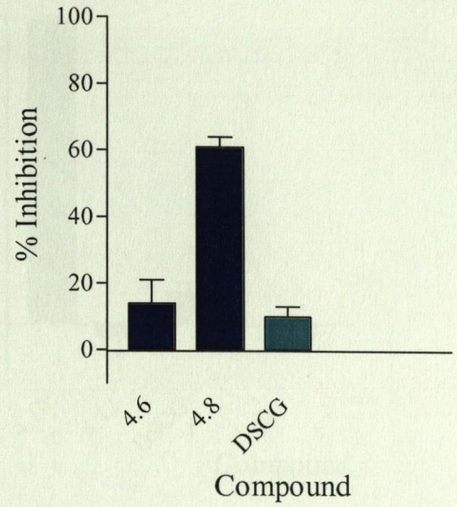



**Figure 4.19 Mast cell-stabilising activity of compounds (4.6) and (4.8)**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*

**Table 4.4 Summary statistics for compounds (4.6) and (4.8)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **4.6** | 14 | 15 | 7 | 5 |
| **4.8** | 61 | 6 | 3 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

It was evident from Figure 4.19 that although addition of a second carbonyl group onto the tetralin ring component, as in (**4.8**) did not have a completely deleterious effect on mast cell-stabilising activity (61% inhibition, S.E.M. 3%). However, removal of the carbonyl from the indenyl component and replacement in the benzylic position of the tetralin ring greatly reduced activity (14%, S.E.M. 7%). The presence of a benzylic indenyl carbonyl seemed central to mast cell-stabilising activity within these molecular types.

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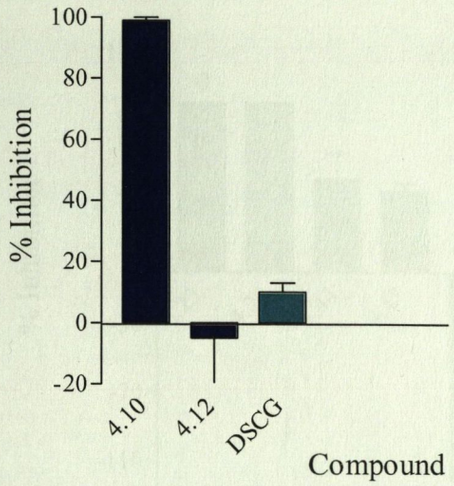



**Figure 4.20 Mast cell-stabilising activity of compounds (4.10) and (4.12)**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.*

**Table 4.5 Summary statistics for compounds (4.10) and (4.12)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | N |
|---|---|---|---|---|
| **4.10** | 99 | 2 | 1 | 5 |
| **4.12** | -5 | 34 | 15 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

It was clear from Figure 4.20 that compound (**4.10**), possessing one benzylic carbonyl group, completely inhibited the Compound 48/80-induced release of histamine from rat peritoneal mast cells, in stark contrast to the second compound, (**4.12**), which offered no protective effect. The importance of at least one benzylic carbonyl in these dimer molecules was underlined by these results, but the need for an indanyl carbonyl did not seem essential, conflicting somewhat with the results of Figure 4.19.

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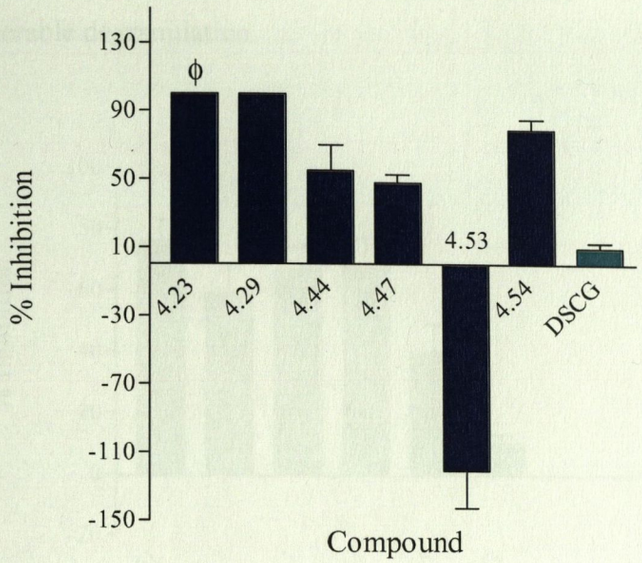



**Figure 4.21 Mast cell-stabilising activity of substituted derivatives of compound (4.2)**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.* ϕ (compound also tested using metrizamide-purified cells).

**Table 4.6 Summary statistics for substituted derivatives of compound (4.2)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | N |
|---|---|---|---|---|
| **4.23** | 100 | - | - | 5 |
| **4.29** | 100 | - | - | 5 |
| **4.44** | 55 | 34 | 15 | 5 |
| **4.47** | 48 | 11 | 5 | 5 |
| **4.53** | -121 | 43 | 22 | 4 |
| **4.54** | 80 | 16 | 6 | 6 |
| DSCG | 10 | 25 | 3 | 94 |

From Figure 4.21 it is obvious that dimer molecules (**4.23**) and (**4.29**) completely inhibited Compound 48/80-induced mast cell degranulation, at the dose level tested. The methoxy indanone molecules (**4.44**) and (**4.47**) showed similar activity (55%, S.E.M. 15%, and 48%, S.E.M. 5%, respectively), and the methyl oxime (**4.54**) also showed considerable inhibitory activity (80%, S.E.M. 6%) as compared to the standard, disodium cromoglycate,

yet interestingly the hydroxylamine derivative (**4.53**) had the opposite effect, and was seen to provoke considerable degranulation.

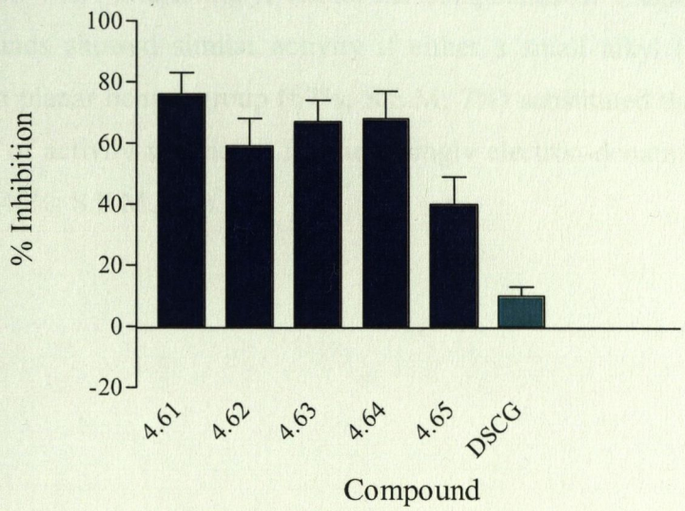



**Figure 4.22 Mast cell-stabilising activity of derivatives of compound (4.60)**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48-80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M*

**Table 4.7 Summary statistics for derivatives of compound (4.60)**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **4.61** | 76 | 16 | 7 | 5 |
| **4.62** | 59 | 20 | 9 | 5 |
| **4.63** | 67 | 16 | 7 | 5 |
| **4.64** | 68 | 20 | 9 | 5 |
| **4.65** | 40 | 20 | 9 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

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It is evident from Figure 4.22 that all of the 2-aminotetralin derivatives tested exhibited considerable mast cell-stabilising activity at the dose level tested, as compared to the standard, disodium cromoglycate. Substitution by a methyl group resulted in 76% inhibition, S.E.M. 7%. Interestingly, unlike the compounds of Chapters 2 and 3, these dimeric compounds showed similar activity if either a small alkyl (e.g. *N*-allyl, 59%, S.E.M. 9%) or a planar benzyl group (67%, S.E.M. 7%) substituted the tertiary nitrogen. Some reduction of activity was noted for the strongly electron-donating 3,4,5-trimethoxy analogue (**4.65**; 40%, S.E.M. 9%).

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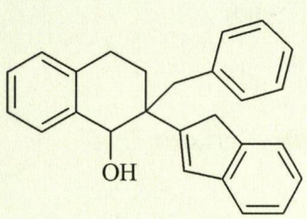
# Synthesis and Preliminary Screening of Carbon-Carbon Dimer Compounds of Tetralol, Indanol and related structures

## 5.1 Synthetic targets of Chapter 5

Following the synthesis and screening of the nitrogenous dimer compounds in the preceding Chapters, it was decided to investigate the effect of removing the electron-rich nitrogen atom, with replacement by direct carbon-carbon attachment, thus probing the relevance of physicochemical factors such as charge and solubility, and their potential contribution to activity. It was anticipated from prior work in the area that this modification would yield derivatives with sustained mast cell-stabilising properties but with enhanced anti-inflammatory activity[63, 64, 65].

## 5.2 Synthesis of a tetralol-inden dimer alcohol and derivatives

The first target compound in this series was identified as 2-benzyl-2-(1*H*-2-indenyl)-1,2,3,4-tetrahydro-1-naphthalenol (**5.9**), a secondary alcohol. The synthetic strategy envisaged for the generation of this compound was the directed aldol condensation of the two parent ketones, followed by enolate alkylation and subsequent reduction.




**(5.9)**

Depending on the method employed to activate the substrate molecules, aldol reactions have been subdivided into various classes[206]. Following the method of Murata *et al.*, selective activation of one carbonyl precursor in a directed aldol reaction can be accomplished by acetalization of the species, and reaction with the enolate of another, the latter trapped as its silyl enol ether. The catalyst employed in this transformation was the super-reagent trimethylsilyl trifluoromethanesulphonate (TMSOTf)[207]. The reaction benefits from the mild conditions employed, affording high yields with minimal side-product formation and shows considerable stereoselectivity.

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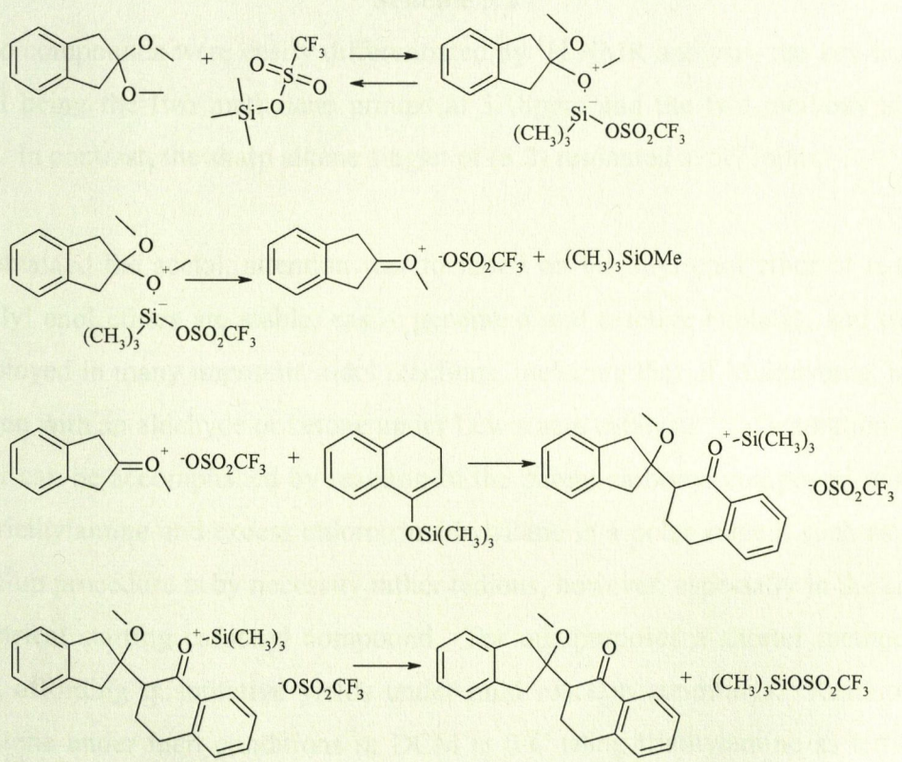
### 5.2.1 TMSOTf-directed approaches

Following the work of Murata, the scope of TMSOTf as a catalyst in the aldol reaction has been extended to the activation of a diverse array of carbonyl groups, in molecules such as carboxylic acid esters, 1,3-dicarbonyl compounds, and lactones[207]. Murata has proposed a reaction mechanism for this aldol reaction[208], which can be described in four steps:

Proposed mechanism for TMSOTf-catalysed aldol condensations

1. Donation of an electron pair by an acetal oxygen atom to the silicon atom of TMSOTf.
2. Fragmentation of the complex thus formed to generate a carboxonium ion pair and alkoxytrimethylsilane.
3. Trapping of the carboxonium ion by the silyl enol ether.
4. Collapse to the β-alkoxy ketone with regeneration of TMSOTf.

This mechanism is illustrated in Scheme 5.1 for our candidate molecules:

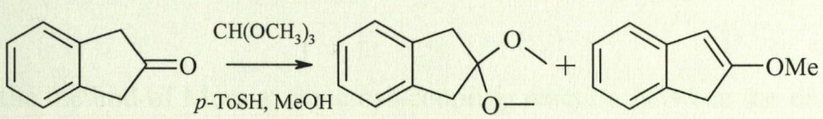



**Scheme 5.1 TMSOTf-catalysed aldol reaction**

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Directed aldol condensation of indanone molecules has been achieved in good yields using the TMSOTf-catalysed reaction, and we sought to extend the scope of this transformation to our combination of tetralone and indanone precursors. The first step involved generation of an acetal of 2-indanone (**5.1**). Acetalization of aldehydes and ketones has traditionally been accomplished in alcoholic media in the presence of an acidic catalyst with azeotropic removal of water[209], or by use of water scavengers such as ortho-formate esters[210].

More recent developments include the use of alkoxysilanes and TMSOTf catalysis[211]. Using *p*-toluenesulphonic acid (*p*ToSH) as catalyst and trimethyl orthoformate as dehydrating agent (Scheme 5.2), the desired dimethylacetal was obtained after 3 hours at room temperature, albeit with considerable decomposition, accelerated on silica, to the enol ether (**5.2**).




**(5.1)** **(5.2)**

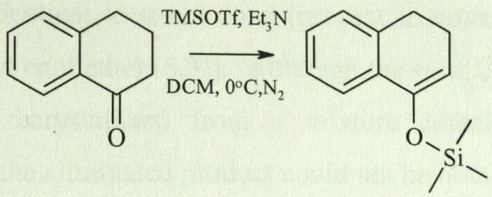
**Scheme 5.2**

These two compounds were easily differentiated by $^1$H NMR analysis, the key features of the acetal being the two methylene groups at 3.18ppm and the two methoxy signals at 3.33ppm. In contrast, the sharp alkene singlet of (**5.2**) resonated at 5.71ppm.

Having obtained the acetal, attention was focussed on the silyl enol ether of α-tetralone (**5.3**). Silyl enol ethers are stable, easily generated and reactive enolates, and have long been employed in many important aldol reactions, including that of Mukaiyama, involving the reaction with an aldehyde or ketone under Lewis acid catalysis[212]. Generation of a silyl enol ether can be accomplished by reaction of the parent carbonyl compound with a base such as triethylamine and excess chlorotrimethylsilane in a polar solvent such as DMF[213]. The work-up procedure is by necessity rather tedious, however, especially in the case of an unsymmetrical starting carbonyl compound. For our purposes a shorter method proved adequate, affording quantitative yields under mild reaction conditions. Reaction of the parent ketone under inert conditions in DCM at 0°C using triethylamine as tertiary base and an equivalent of TMSOTf (Scheme 5.3), with subsequent rapid purification using flash column chromatography gave, in the case of α-tetralone, (3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane (**5.3**).



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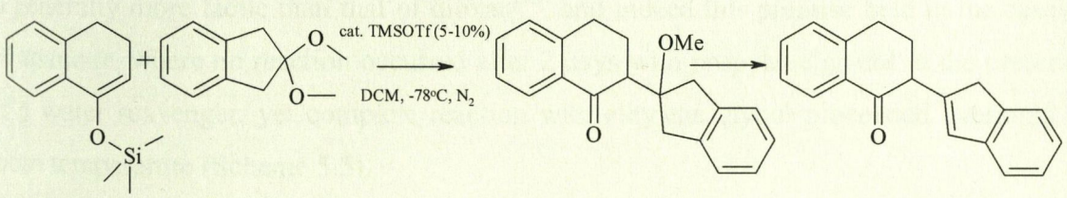



**(5.3)**

**Scheme 5.3**

The $^1H$ NMR spectrum of the silylated tetralone showed an intense singlet integrating as nine protons at 0.51ppm, corresponding to the trimethylsilyl protons. The allylic and benzylic methylene groups appeared as a multiplet and a triplet, at 2.53 and 2.98ppm, respectively. The alkene proton was a triplet at 5.43ppm, and the aromatic protons comprised three signals from 7.30-7.44ppm, and the proton of position eight a doublet at 7.69ppm.

Employing the method of Murata, the cross-coupling reaction between the dimethylacetal (**5.1**) and the silylenol ether (**5.3**) at –78°C in DCM (Scheme 5.4) was expected to afford the aldol product in good yield.




**(5.4)** **(5.5)**

**Scheme 5.4**

Unfortunately, this proved not to be the case. Only traces of the desired product were isolated, even after reaction for 24 hours at –78°C. However, GCMS analysis of the crude reaction mixture over several hours showed the presence of significant quantities of the β, γ-eliminated derivative (**5.5**). Murata quotes the lack of β-elimination of alcohols as one of the advantages of the reaction in his review, however the great potential for conjugation in this system upon elimination may explain the ready degradation.

Although different catalyst concentrations (1-10%) were investigated, little improvement in yield was evident. Elevation of the temperature to -60°C or higher only accelerated decomposition. Despite the fact that the reaction afforded some usable quantities of the β-

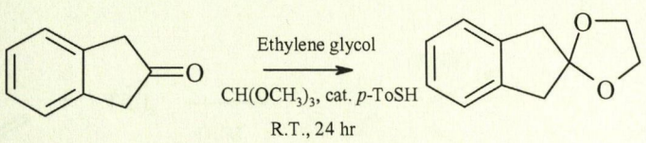


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eliminated product, purification of this was hampered by the fact that its $R_f$ in any solvent system examined was identical to α-tetralone [present in considerable quantity through decomposition of the silyl enol ether (**5.3**)]. Although the solid condensation product (**5.5**) could theoretically be recrystallised from a mixture containing the oily tetralone, preparative quantities of the eliminated product could not be obtained.

Failure to isolate the desired product under various conditions of temperature, reaction time and catalyst concentration in the above sequence led to the investigation of alternative substituents in the activated acetal moiety. It was envisaged that altered polarity in the resultant dimer might lead to more facile isolation and perhaps less degradation to the eliminated product. From attempts to synthesise acyclic acetals of 2-indanone using ethanol and *n*-propanol, only inseparable mixtures were obtained, in each case predominating in the enol ethers.

Murata's work employed acyclic acetals and ortho esters, but information on the use of TMSOTf-catalysed aldol reactions using cyclic acetals as activated carbonyl compounds is scant. Acetalization of 2-indanone using ethylene glycol or propylene glycol to obtain the dioxolan and dioxan derivatives was attempted[214,215]. It is known that dioxolan formation is generally more facile than that of dioxan[209], and indeed this premise held in the case of 2-indanone, where no reaction occurred after 2 days with propylene glycol in the presence of a water scavenger, yet complete reaction with ethylene glycol proceeded overnight at room temperature (Scheme 5.5).




**(5.6)**

**Scheme 5.5**

The dioxolan was identified from the strong cyclic ether C-$O_{str}$ in the infrared at 1104cm$^{-1}$, and the three signals of the simple $^1$H NMR, reflecting the axis of symmetry in the molecule. The indan methylene protons appeared as a singlet at 3.27ppm, the dioxolan methylene protons as another singlet at 4.06ppm, and the four aromatic protons at 7.26ppm.

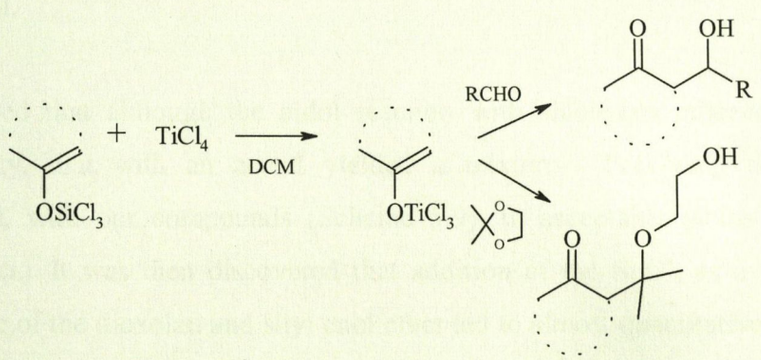
Without the inclusion of trimethyl orthoformate as water scavenger, reaction with ethylene glycol was incomplete after 2 days, and as the starting material and product have approximately identical $R_f$ values, the ortho ester was routinely included. Reaction of the dioxolan derivative of 2-indanone with (**5.3**) was attempted under Murata conditions, again varying the temperature, duration of reaction and catalyst concentration (2.5-5%), yet all efforts to isolate the required dimer in preparative quantities proved futile.

### 5.2.2 Lewis acid-catalysed aldol condensations

#### 5.2.2.1 Titanium tetrachloride ($TiCl_4$)

Following the evident shortcomings of TMSOTf as an aldol condensation catalyst for our molecular entities, it was decided to employ Mukaiyama conditions[212], involving a Lewis acid catalyst. Since the 1970s, the utility of $TiCl_4$ in promoting directed aldol reactions has been exploited, including those of sensitive molecules and encompassing intramolecular reactions[216]. In addition, the combined use of TMSOTf-$TiCl_4$ has led to an interesting synthesis of six and seven-membered rings[217]. Thus, as the preferred catalyst of several groups, titanium tetrachloride ($TiCl_4$) was selected for initial studies.

Titanium tetrachloride is known to form trichlorotitanium enolates upon reaction with silyl enol ethers, which have been isolated in some instances[218]. These species undergo rapid aldol reaction with aldehydes or acetals[219], as shown in Scheme 5.7.



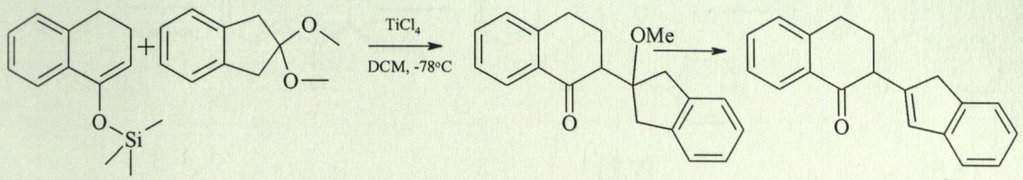

**Scheme 5.7 $TiCl_4$-catalysed aldol reaction**

Using a stoichiometric quantity of $TiCl_4$ in anhydrous DCM, to which acetal (**5.1**) and the silyl enol ether (**5.3**) were sequentially added at -78°C (Scheme 5.8), the reaction afforded a mixture of products. Although GCMS analysis revealed considerable quantities of the correct aldol to be present, isolation was again hampered by not only the presence of α-



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tetralone and the seemingly unavoidable β-elimination, but also by the presence of considerable quantities of an undesired indan dimer, as revealed by GCMS and NMR evidence.




**(5.3)** **(5.1)** **(5.4)** **(5.5)**

**Scheme 5.8**

Despite the fact that most of the published literature dwells on the use of $TiCl_4$, many other Lewis acids and miscellaneous promoters of aldol reactions have found application, including trityl perchlorate, tin, zinc and zirconium salts, and clay montmorillonite[220].

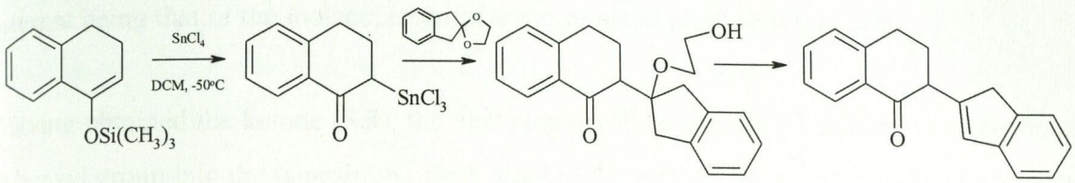
### 5.2.2.2 Tin tetrachloride ($SnCl_4$)

As documented yields with tin tetrachloride ($SnCl_4$) as an aldol catalyst have been promising[221], it was decided to perform our reaction using this Lewis acid. In contrast to the behaviour of $TiCl_4$ with enolate anions as outlined above, $SnCl_4$ reacts to form α-stannyl ketones[222]. This is also observed in analogous reactions of metal chlorides of antimony and tellurium. The method of Nakamura[223] advises the preliminary formation of a stannyl ketone from the silyl enol ether with subsequent addition of an aldehyde or dimethyl acetal.

It was observed that although the aldol reaction with aldehydes proceeded with high stereoselectivity, that with an acetal yielded a mixture. Following the method of Nakamura led, with our compounds (Scheme 5.9), to acceptable yields (54%) of the desired product. It was then discovered that addition of the $SnCl_4$ as a final step to a cooled mixture of the dioxolan and silyl enol ether led to almost quantitative yield, with no undesired product formation. The reaction temperature could be raised to –50°C without appreciable decomposition during the course of the reaction, and although on silica the aldol product (**5.7**) proved quite unstable, recrystallisation of the elimination product afforded good yields of the ketone (**5.5**).

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Quantities of the pure aldol product were obtained enabling partial analysis, but after 24 hours storage at 0°C, had eliminated to the β-elimination product.




**(5.7)** **(5.5)**

**Scheme 5.9**

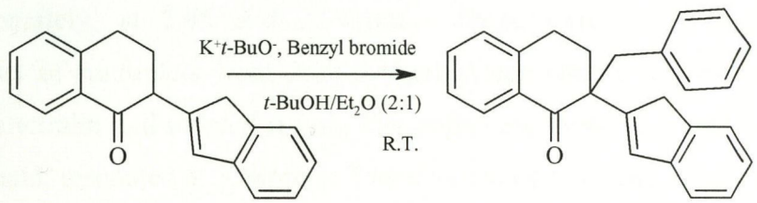
The unstable aldol product (**5.7**) showed many important infrared absorptions, including those of ethereal C-$O_{str}$, coupled alcohol C-$O_{str}$ and O-$H_{def}$ at 1053cm$^{-1}$, 1091cm$^{-1}$ and 1227cm$^{-1}$. These were followed by the strong benzylic C=$O_{str}$ at 1684cm$^{-1}$. The presence of broad O-$H_{str}$ at 3494cm$^{-1}$ indicated hydrogen bonding between molecules. The $^{1}$H NMR spectrum was extremely complex, revealing a diastereomeric mixture, with the only easily discernible methylene signal being that at position three on the tetralone ring, which appeared as two multiplets at 2.20 and 2.40ppm. The eleven remaining methylene and methine protons occupied the region from 2.81-3.60ppm, with considerable signal overlap. The aromatic region was equally complex, with six of the protons resonating closely together from 7.10-7.30ppm. Two protons were individually visible, two almost overlapping double doublets at 7.43ppm, and the two doublets of the proton on position eight of the tetralone ring at 8.01ppm. Important features of the $^{13}$C NMR spectrum included the ethereal methylene carbons at 61.5 and 63.7ppm, and the carbonyl signal at 198.0ppm.

The main infrared spectral feature of the eliminated product (**5.5**) was the C=$O_{str}$ at 1683cm$^{-1}$. $^{1}$H NMR analysis revealed the presence of a multiplet at 2.45ppm for the β-keto methylene group, and another at 3.10ppm for the benzylic tetralone methylene. The indenyl methylene resonated as a singlet at 3.55ppm, followed by a triplet for the methine proton at 3.79ppm. The alkenic proton was a singlet at 6.68ppm, followed by a well resolved aromatic region of seven protons, from 7.16-7.55ppm. The terminal signal was that of the aromatic proton adjacent to the carbonyl group, a doublet at 8.14ppm.

In the $^{13}$C NMR spectrum, the carbonyl group resonated at 198.0ppm. The presence of the alkene singlet in the $^{1}$H NMR spectrum and three methylene carbons in the $^{13}$C NMR

spectrum confirmed that elimination took place β,γ to the ketone, and not to the α,β enone. Injection of either the aldol or its eliminated product into the GCMS resulted in the same spectrum, the former molecule eliminating ethylene glycol, and the only intense peak present being that of the molecular ion of the eliminated product at m/z 260.

Having obtained the ketone (**5.5**), the next step involved enolate alkylation by insertion of a benzyl group into the α-position. Both aldol (**5.7**) and the elimination product (**5.5**) were expected to yield the same product on alkylation. Enolate alkylation was attempted using potassium tert-butoxide ($K^+t$-$BuO^-$) as base and benzyl bromide as electrophile. The reaction was performed in *tert*-butanol/diethylether at room temperature (Scheme 5.10).

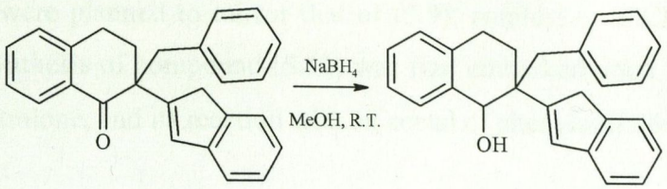



(**5.8**)

**Scheme 5.10**

Benzylation of (**5.5**) had little effect on the infrared $C{=}O_{str}$, at 1684cm$^{-1}$. The $^1$H NMR spectrum was much better resolved in the aliphatic region than that of (**5.5**), with discrete signals for each of the four protons of the tetralone ring, at 2.20 and 2.37ppm for the β-keto protons, and 2.77 and 3.06ppm for the benzylic tetralone protons. The remaining benzylic methylene protons, those of the indenyl ring and the α-benzyl group, resonated at 3.23 and 3.51ppm. The alkenic proton singlet appeared at 6.53ppm, followed by a complex aromatic region, from 7.11-7.45ppm, with the final aryl proton at 8.20ppm. GCMS analysis revealed an intense molecular ion at 350 (100), with the only other intense peak that at 259 (M-$PhCH_2$).

Interestingly, the TLC profile on reaction showed more than one product, and complete exhaustion of starting material. The alkylated product (**5.8**) was obtained in 23% yield and the final step in the sequence remained, reduction of the carbonyl functionality. This was accomplished in almost quantitative yield using sodium borohydride (Scheme 5.11) to afford the desired secondary alcohol as a diasteromeric mixture.




**(5.8)** **(5.9)**

**Scheme 5.11**

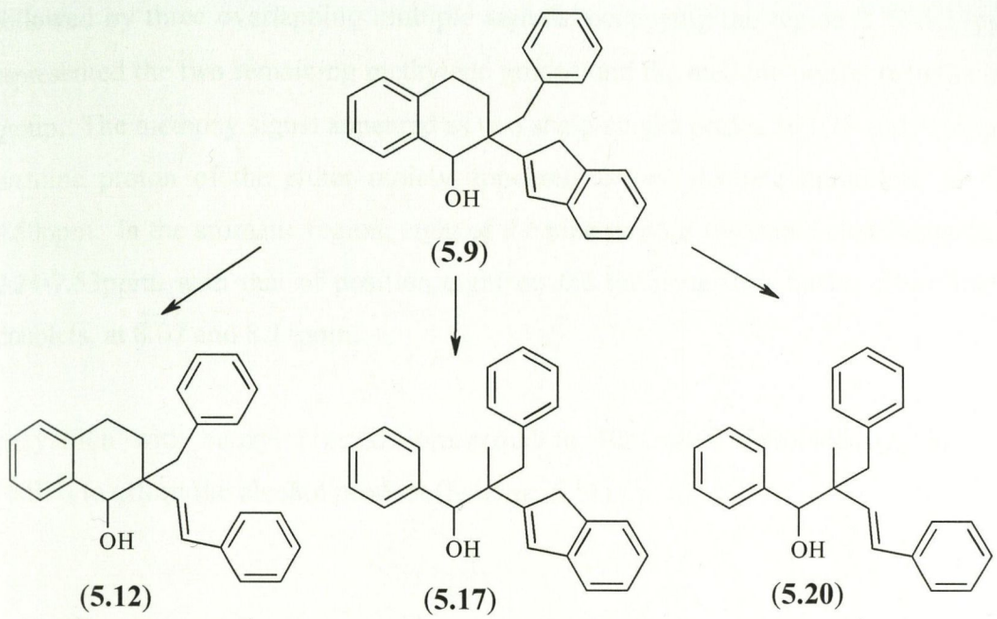
Attempts to alkylate (**5.7**) using α-bromo *p*-tolunitrile and 2-bromoacetophenone as alkylating agents were unsucessful.

$^1$H NMR analysis of the diastereomeric mixture of (**5.9**) revealed complex coupling patterns for the methylene protons; those β to the carbon bearing the alcohol moiety resonated separately, at 2.05 and 2.34ppm. These were followed by a complex overlapping set of multiplets from 2.80-3.40ppm, representing the benzylic methylene protons of the tetralin and indenyl rings. The remaining methylene protons, those of the benzyl side chain, resonated at 3.58ppm. Two singlets were visible for the methine proton of the carbon bearing the secondary alcohol, at 4.73 and 4.80ppm, and also for the alkene proton, at 6.33 and 6.69ppm. The terminal resonances, those of the aromatic protons, comprised four broad multiplets from 7.03-7.54ppm. GCMS analysis of (**5.9**) revealed a molecular ion of 334 ($M^+$, 54). Other important fragments included the base peak at 261 (M-$PhCH_2$), 117 (74) and 91 ($PhCH_2$, 68). HRMS analysis revealed the molecular mass as 375.1713 (+$Na^+$), calculated 375.1725.

Having developed a method to synthesise the primary compound of interest, two main objectives could be addressed, namely (1) the deconstruction of the rigid skeletal framework of (**5.9**) and testing of these disassembled analogues, and (2) to generate similar rigid molecules based on the tetralin and indan ring systems. To investigate the potential effects of (1), the following deconstructions of (**5.9**) were planned, testing each derivative after its point modification (Scheme 5.12).

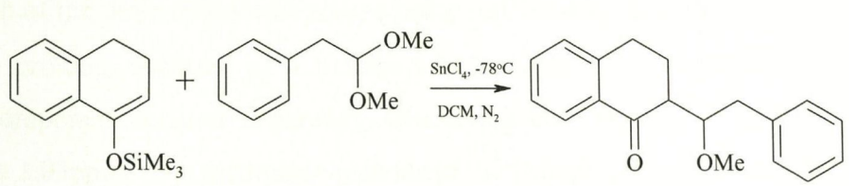
- Synthesis of a phenyl ethenyl analogue (indenyl ring opened)
- Synthesis of an indenyl diphenyl propanol analogue (tetralone ring opened)
- Synthesis of a diphenyl butenol derivative (both fused ring systems opened)

These syntheses were planned to mirror that of (**5.9**), employing $SnCl_4$ in the key aldol condensation. Synthesis of compound (**5.12**) was first embarked upon, requiring the silyl enol ether of α-tetralone, and its reaction with an acetal of phenylacetaldehyde.




**Scheme 5.12**

As phenylacetaldehyde during acetalization may be prone to side reactions such as polymerization of the enol ether, to avoid unnecessary complications it was decided to use the commercially available dimethyl acetal. Reaction of this acetal with (**5.3**) in the presence of $SnCl_4$ (Scheme 5.13) led to smooth generation of the aldol as a diasteromeric mixture without β- elimination in almost quantitative yield.



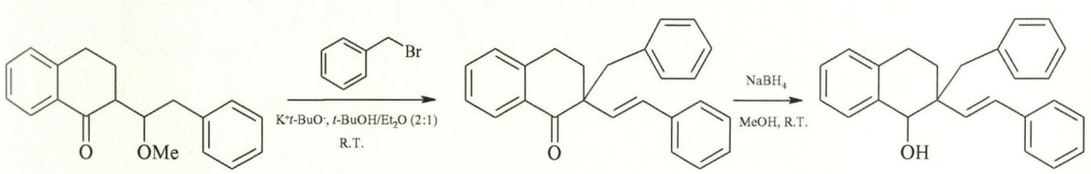

(**5.3**) (**5.10**)

**Scheme 5.13**

The product, although bearing the same $R_f$ as the residual α-tetralone, was obtained as white needles from acetone. Again it was observed that terminal addition of the Lewis acid was necessary for optimal yields.

The two important features of the infrared spectrum of (**5.10**) were the C-$O_{str}$ of the ether moiety at 1098cm$^{-1}$ and the carbonyl C=$O_{str}$ at 1684cm$^{-1}$. The $^1$H NMR spectrum revealed the presence of a diasteromeric mixture. The first aliphatic signal was that of the β-keto methylene, which occurred as two multiplets at 2.13 and 2.38ppm. These signals were followed by three overlapping multiple signals, occupying the region 2.72-3.17ppm, and represented the two remaining methylene groups and the methine proton α to the carbonyl group. The methoxy signal appeared as two sharp singlet peaks, at 3.27 and 3.36ppm. The methine proton of the either moiety appeared as two discrete multiplets, at 4.27 and 4.50ppm. In the aromatic region, eight of the nine protons resonated closely together, from 7.24-7.53ppm, with that of position eight on the tetralone ring further downfield as two doublets, at 8.07 and 8.11ppm.

Alkylation with benzyl bromide proceeded to 40% yield followed by reduction with $NaBH_4$ to afford the alcohol product (Scheme 5.14).



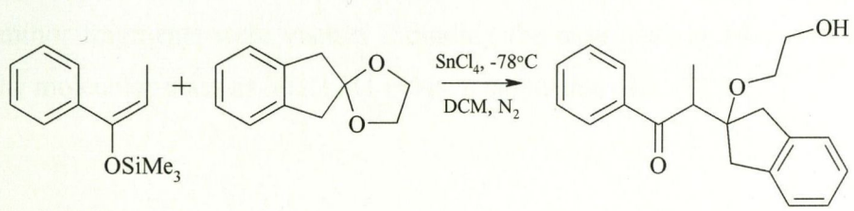

(**5.10**) (**5.11**) (**5.12**)

**Scheme 5.14**

Alkylation of (**5.10**) had little effect on the infrared spectrum, the C=$O_{str}$ at 1682cm$^{-1}$. The aliphatic region of the $^1$H NMR was considerably simpler than that of the parent molecule (**5.10**), each of the three methylene groups being individually discernible. The first, that of the β-keto protons, occurred as a multiplet at 2.14ppm. The benzylic protons of the tetralone component occurred separately, two double doublets at 2.85 and 2.90ppm, and a multiplet at 3.03ppm. The methylene protons of the benzyl side chain occurred as a double doublet at 3.23ppm. The alkenyl proton resonances were two overlapping doublets at 6.28ppm. The aromatic region again showed a complex pattern, all but one of the fourteen protons between 7.17-7.47ppm. The terminal resonance was again that of that nearest the benzylic ketone, at 8.18ppm, although the doublet showed some evidence of *meta* coupling.

Reduction of the ketone in (**5.11**) gave a diastereomeric mixture of (**5.12**). The $^{1}H$ NMR spectrum of (**5.12**) showed overlapping of the aliphatic signals; from 1.83-2.26ppm, a multiplet accounted for the alcohol proton and the sole non-benzylic methylene group. A complex multiplet from 2.87-3.25ppm represented the two benzylic methylene groups, followed by two singlets at 4.58 and 4.63ppm, for the methine proton. Two broad doublet pairs at 6.11 and 6.49ppm accounted for the alkene protons, followed by a large aromatic signal from 7.13-7.56ppm, representing the fourteen aromatic protons. GCMS analysis did not show a molecular ion peak, as is the case with many alcohols. The base peak at 249 represented loss of the benzyl group (M-$PhCH_2$). HRMS analysis revealed the accurate molecular mass (+$Na^+$) as 363.1716, calculated 363.1725.

To generate the indenyl diphenyl propanol analogue (**5.17**), the silyl enol ether of propiophenone (**5.13**) was reacted with dioxan (**5.14**). After 1 hour, 70% of the desired aldol product (Scheme 5.15) was formed.



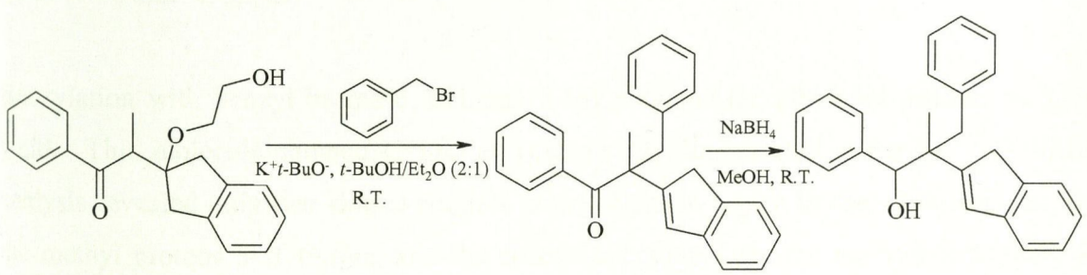

(**5.13**) (**5.14**) (**5.15**)

**Scheme 5.15**

The important infrared absorptions of (**5.15**) included those of ether C-$O_{str}$, coupled alcohol C-$O_{str}$ and O-$H_{def}$ at 1057$cm^{-1}$, 1086$cm^{-1}$ and 1227$cm^{-1}$. These were followed by the strong benzylic C=$O_{str}$ at 1679$cm^{-1}$, and broad O-$H_{str}$ at 3470$cm^{-1}$. A doublet for the methyl protons was the first important characteristic of the $^{1}H$ NMR spectrum, at 1.32ppm. The alcohol proton was visible as a broad singlet at 2.35ppm. The indan methylene signals resonated at 3.14 and 3.28ppm, whereas the side chain methylenes overlapped, in the region from 3.36-3.46ppm. The four aromatic protons of the indanyl moiety were found together at 7.18ppm, followed by the protons of the aryl ring bearing the carbonyl group. These were readily identifiable as *meta* (7.47ppm), *para* (7.56ppm) and *ortho* (8.00ppm) to the keto group. The $^{13}C$ NMR spectrum contained important signals at 61.5 and 63.7ppm for the side chain methylenes, an aliphatic quaternary signal at 87.9ppm, and a carbonyl signal at 203.0ppm.

Despite the potential for conjugation, none of the β-elimination product was isolated, and alkylation (Scheme 5.16) also proved very sluggish, despite reaction over several days and application of heat. The alkylated derivative (**5.16**) contained infrared $C{=}O_{str}$ at 1681cm$^{-1}$. Its $^{1}H$ NMR spectrum contained a signal for the methyl protons at 1.51ppm, and two methylene protons at 3.30 and 3.49ppm. The alkenic proton resonated at 6.72ppm, before a complex aromatic signal from 6.90-7.37ppm. The *ortho* keto protons were visible at 7.85ppm.

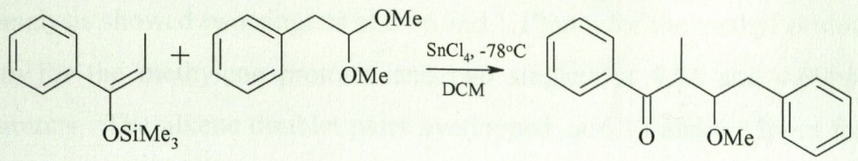
On reduction of the alkylated derivative, two separable pairs of diasteromers were obtained, one predominating as a white solid. This molecule (**5.17**) showed both free and H-bonded $O\text{-}H_{str}$ in the infrared, at 3563 and 3615cm$^{-1}$. Reduction of the carbonyl group shifted the methyl signal upfield, to 1.05ppm. The methylene protons resided at 3.04 and 3.51ppm, while the alkene was found at 6.66ppm. The aromatic region was broad and complex, from 7.04-7.46ppm. GCMS analysis of (**5.17**) did not reveal any molecular ion, and only minor fragments were visible, including the base peak at 144. HRMS analysis revealed the molecular mass as 363.1731 ($+Na^{+}$), calculated 363.1725.




**(5.15)** **(5.16)** **(5.17)**

**Scheme 5.16**

To complete the deconstruction of the rigid framework of (**5.9**), the diphenyl butenol (**5.20**) was synthesised, by combining the silyl enol ether of propiophenone with phenylacetaldehyde dimethyl acetal (Scheme 5.17).



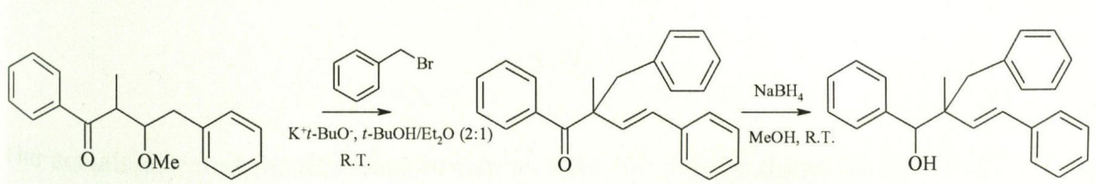

**(5.18)**

**Scheme 5.17**

Coupling of these two precursors also afforded a good yield (70%) of the desired aldol, also without β-elimination, as a diastereomeric mixture. Infrared analysis revealed C-$O_{str}$ at 1100cm$^{-1}$, and C=$O_{str}$ at 1686cm$^{-1}$.

The $^1$H NMR spectrum contained two doublets for the methyl protons at 1.24 and 1.34ppm. The methylene multiplet stretched from 2.72-3.11ppm, followed by the methoxy singlets, at 3.17 and 3.30ppm. Two quintets for one of the methine protons resonated at 3.54 and 3.74ppm, while the other methine, that adjacent to the methoxy group, was a multiplet at 3.86ppm. In the aromatic region, five protons of the phenyl ring overlapped from 7.22-7.35ppm, and, as in the case of compound (**5.15**), the protons of the ring bearing the ketone group could be clearly identified, those *meta* (7.43ppm), *para* (7.54ppm) and *ortho* (7.78 and 7.95ppm).

Benzylation with benzyl bromide (Scheme 5.18) obtained the alkylated product in 33% yield. This molecule showed C=$O_{str}$ at 1685cm$^{-1}$ in the infrared spectrum. $^1$H NMR analysis revealed only two simple singlets in the aliphatic region of the spectrum, one for the methyl protons at 1.49ppm, and the second accounting for the methylene protons at 3.30ppm. The alkenic protons occurred as two doublets, at 6.47 and 6.52ppm. All but two of the fifteen ring protons lay between 7.12-7.50ppm, those *ortho* to the carbonyl resonating further downfield at 7.87ppm.




**(5.18)** **(5.19)** **(5.20)**

**Scheme 5.18**

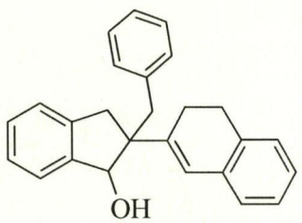
Reduction of the benzylated compound (**5.19**) to yield the alcohol resulted in the isolation of a (**5.20**), a diastereomeric mixture, in 75% yield.

$^1$H NMR analysis showed two singlets at 0.96 and 1.17ppm for the methyl protons, another at 2.20ppm for the methylene protons, and two singlets at 4.61 and 4.69ppm for the methine protons. The alkene doublet pairs overlapped, at 6.13 and 6.35ppm for one pair, and 6.20 and 6.54ppm for the other. All fifteen aromatic protons were tightly bunched together from 7.18-7.42ppm. The base peak on GCMS analysis at 131 represented fragmentation at either side of the quaternary aliphatic carbon, with loss of both benzyl substituents. The only other substantial fragment was that of benzyl itself at 91 ($PhCH_2$, 53). HRMS analysis gave the accurate molecular mass ($+Na^+$) as 351.1709, calculated 351.1725.

## 5.3 Synthesis of an indanol-tetralen dimer alcohol and derivatives

To fulfil our second objective, namely to assess the effect of ring orientation on activity, a series of molecules was designed to probe the configurational restrictions (if any) on mast cell-stabilising activity. The tetralin and indan systems were retained as rigidity was felt to be important (*vide infra*) but the relative positions of the carbonyl functionalities in the precursor molecules were altered. Thus, instead of α-tetralone and 2-indanone, β-tetralone and 1-indanone were selected as primary candidates.

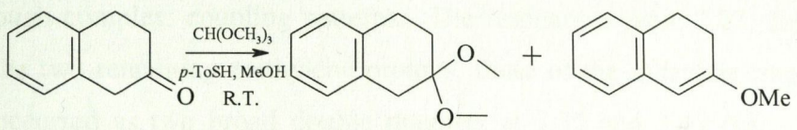
The initial target, (**5.29**) was approached in analogous fashion to the generation of (**5.9**), and thus necessitated the synthesis of the silyl enol ether of 1-indanone and an acetal of β-tetralone.



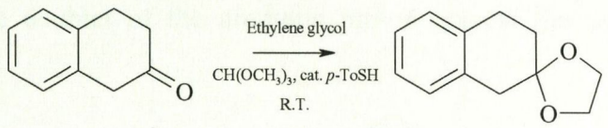

(**5.29**)

The acetals selected for this transformation were the acyclic dimethyl (**5.21**) and diethyl (**5.23**) acetals and the dioxolan (**5.24**). Generation of the dimethyl acetal (**5.22**) was readily accomplished in analogous fashion to the synthesis of (**5.1**), but yields were reduced due to the competitive elimination reaction to form the enol ether (**5.22**). This problem was amplified in the case of the diethyl acetal, yet did not arise in the formation of a dioxolan.

The dioxolan was also favoured through comparative synthetic ease of manufacture and improved stability. This acetal was readily obtained from the parent ketone after overnight reaction with ethylene glycol in the presence of trimethylorthoformate as drying agent (Scheme 5.19).



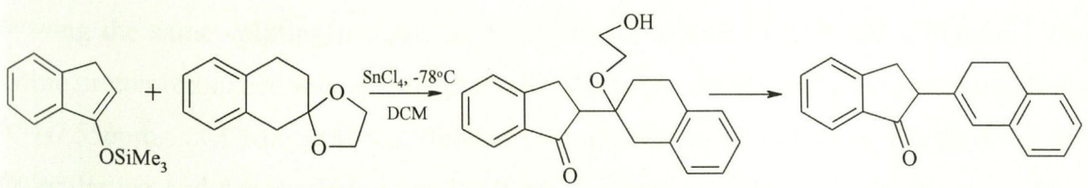

**(5.21)** **(5.22)**




**(5.24)**

**Scheme 5.19**

The important infrared features of (**5.24**) were those of C-$O_{str}$, which were found at 1063, 1099 and 1123$cm^{-1}$. The $^1H$ NMR had four signals, a methylene triplet at 2.05ppm and multiplets at 3.08, 4.09 and 7.16ppm, the two aliphatic signals each corresponding to two methylenes, and the final signal that of the aromatic ring protons. The dioxolan (**5.24**) was reacted with the silyl enol ether of 1-indanone (**5.25**) (Scheme 5.20), analogously to the synthesis of (**5.7**). As expected from the synthesis of (**5.7**), the aldol product decomposed rapidly on silica through β-elimination to generate (**5.27**). Tedious separation from residual 1-indanone afforded the product as a yellow solid in 31% yield.

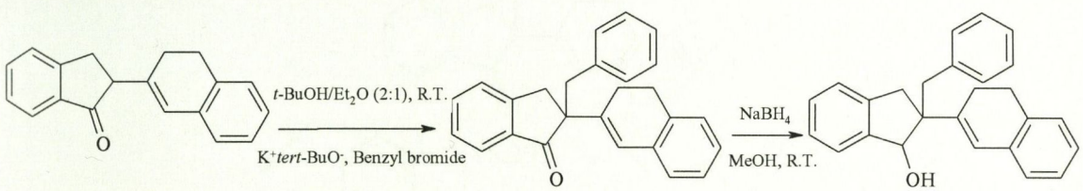



**(5.25)** **(5.24)** **(5.26)** **(5.27)**

**Scheme 5.20**

Infrared analysis of dimer (**5.27**) showed strong C=$O_{str}$ at 1683$cm^{-1}$. $^1H$ NMR analysis showed the resonance positions of the tetralenyl methylene groups at 2.45 and 3.10ppm, with that of the indanone ring at 3.57ppm. The triplet signal at 3.79ppm was that of the α-keto methine. The alkene singlet was located at 6.70ppm, and the aromatic region was well resolved, with seven of the eight protons individually visible. Of the eight, seven were found between 7.19-7.56ppm, with that nearest the ketone at 8.17ppm.

Alkylation with benzyl bromide using $K^+t$-$BuO^-$ (Scheme 5.28) was successful in the formation of (**5.28**). This molecule was little unchanged in the infrared spectrum, its principal absorption again that of the carbonyl stretching absorption, at 1683cm$^{-1}$. The main changes in the $^1$H NMR spectrum related to the aliphatic region. All four of the tetralenyl methylene protons had different resonances, yet two pairs each showed almost identical, though complex, coupling patterns. The resonances were 2.23, 2.38, 2.83 and 3.07ppm. The two remaining methylene protons, those of the indanone ring and benzyl side chain, occurred as two broad double doublets at 3.35 and 3.43 ppm. The alkene singlet arose at 6.54ppm, followed by twelve of the thirteen aromatic protons between 7.12-7.45ppm. The doublet of the aromatic proton nearest the carbonyl resonated at 8.20ppm.




(**5.27**) (**5.28**) (**5.29**)

**Scheme 5.21**

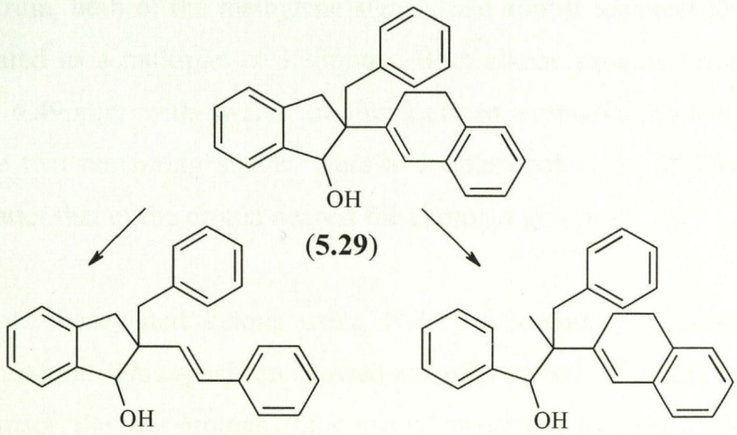
Reduction with $NaBH_4$ proceeded with characteristic smoothness to the alcohol (**5.29**). The main feature of this molecule in the infrared spectrum was the extremely broad O-$H_{str}$, centred at 3408cm$^{-1}$. Analysis of the diasteromeric mixture by $^1$H NMR analysis was hampered by complex coupling patterns and signal overlap. In the aliphatic region, all four methylene groups resonated closely together, from 2.43-3.28ppm. The methine proton of the indan ring occurred as two signals, at 4.96 as a broad singlet and a doublet at 5.30ppm, showing the same splitting patterns as the hydroxyl signals at 1.73 and 2.06ppm. The alkene proton resonance was at 6.16ppm, with all thirteen of the aromatic protons between 6.94-7.55ppm. GCMS analysis showed two dominant ion clusters representing the molecular ion and debenzylation, while HRMS analysis gave the accurate molecular mass ($+Na^+$) as 375.1737, calculated 375.1725.

Attempted alkylation with 2-bromoacetophenone to yield a diketo derivative met with failure, however, yielding a mass of products on TLC.

To complement the mast cell-stabilising data obtained for compound (**5.29**) [see Figure 5.1], and further establish the requirement for a doubly fused ring system in these molecules, it was decided to generate the disassembled analogues (**5.32**) and (**5.34**), akin to (**5.9**) and its simpler derivatives (**5.12**), (**5.17**) and (**5.20**).

These two new targets (Scheme 5.22) represented the following modifications:

- Opening of the tetralin ring to yield a phenyl ethenyl indanol
- Lysis of the indan ring to yield a naphthalenyl propanol

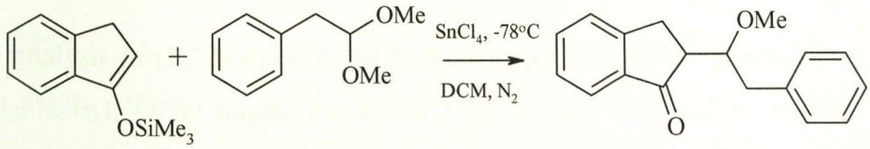



(**5.29**)

(**5.32**) (**5.34**)

**Scheme 5.22**

The synthesis of the former molecule proved much more facile than the latter, and was achieved via the aldol product (**5.30**), formed in 88% yield from the silyl enol ether of 1-indanone and phenylacetaldehyde dimethylacetal (Scheme 5.23).




(**5.25**) (**5.30**)

**Scheme 5.23**

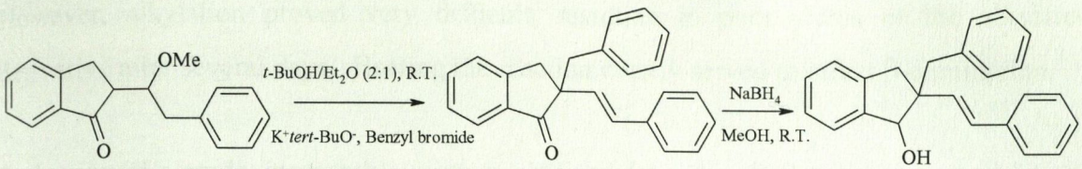
The two diagnostic infrared characteristics of (**5.30**) were the ethereal C-$O_{str}$ at 1109cm$^{-1}$ and the C=$O_{str}$ of the ketone at 1714cm$^{-1}$. $^1$H NMR analysis revealed a diastereomeric mixture. Both methylene groups appeared as intricate multiple signals, the first from 2.63-2.88ppm and the second from 3.09-3.21ppm. The methoxy protons gave rise to two singlet peaks, at 3.25 and 3.33ppm, the latter peak largely obscuring the degenerate signal of the

indanone methine. Two signals also arose for the second methine, that of the ethereal moiety, and these multiplets resonated at 3.97 and 4.27ppm. In the aromatic region, six of the nine protons lay between 7.21-7.37ppm. A one-proton doublet at 7.49ppm followed, and then another, a multiplet at 7.58ppm. The terminal signals were two overlapping doublets at 7.77ppm. In the $^{13}C$ NMR spectra, the signals for the methoxy carbons were located at 57.3 and 57.9ppm, while the carbonyl signals were at 206.3 and 207.1ppm.

Enolate alkylation with benzyl bromide (Scheme 5.24) gave the benzylated ketone (**5.31**), and the $C{=}O_{str}$ for this molecule in the infrared spectrum was located at 1706cm$^{-1}$. In the $^{1}H$ NMR spectrum, both of the methylene signals had almost identical resonance values, and thus appeared as a multiplet at 3.28ppm. Both alkene protons featured as a single sharp peak at 6.49ppm, with twelve of the fourteen aromatic protons between 7.21-7.45ppm. The two remaining signals were a double doublet at 7.59 and a doublet at 7.83ppm, the latter that of the proton nearest the carbonyl group.

Reduction of the benzylated ketone using $NaBH_4$ afforded the desired alcohol as a diasteromeric mixture. This spectrum showed a similar pattern of signal overlap to that of its ketone precursor, the four protons of the methylene groups forming a complex multiplet from 2.78-3.16ppm. The methine proton appeared as two singlets, at 5.06 and 5.16ppm. The resonance for the two alkene protons may have been expected to resemble two pairs of doublets, but due to the non-first order nature of the spectra, were highly unsymmetrical, with four peaks, one predominating over the others. The centre of this multiple signal was at 6.34ppm. In the aromatic region, thirteen of the fourteen protons were closely assembled between 7.17-7.37ppm, with one isolated proton signal at 7.43ppm.

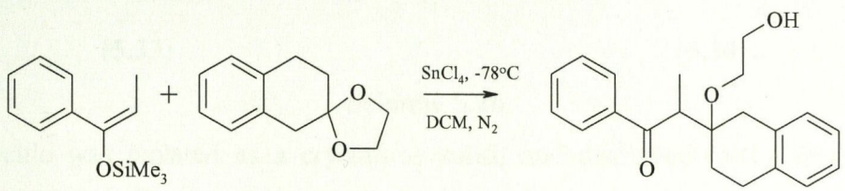
GCMS analysis of (**5.32**) showed the prominent peak to be the debenzylated fragment at 235 (M-$PhCH_2$). Other fragments were at 308 (23), 217 (46) and 91 ($PhCH_2$, 68). HRMS analysis gave the accurate molecular mass (+$Na^+$) as 349.1581, calculated 349.1568.




**(5.30)** **(5.31)** **(5.32)**

**Scheme 5.24**

To generate the second of these ring-opened compounds necessitated the generation of an acetal of 2-tetralone, and subsequent reaction with the silyl enol ether of propiophenone. Mindful of the greater success obtained above using dioxolan derivatives, it was decided to pursue the aldol product using this acetal, and it was reacted with the silyl enol ether (**5.13**) (Scheme 5.25) to generate the aldol product in 25% yield.




**(5.13)** **(5.24)** **(5.33)**

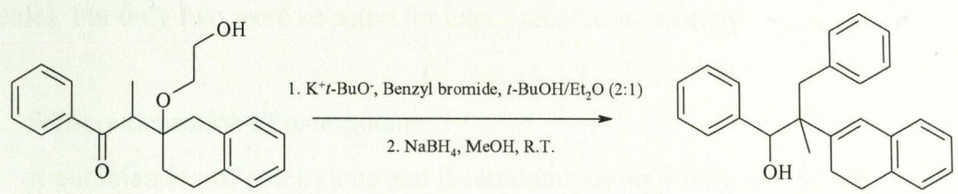
**Scheme 5.25**

As in the synthesis of (**5.15**), no appreciable β-elimination was observed at room temperature. This was confirmed by the presence of strong ethereal C-$O_{str}$ at 1051 and 1095$cm^{-1}$ in the infrared spectrum. The ketonic C=$O_{str}$ was located at 1676$cm^{-1}$, with broad O-$H_{str}$ at 3438$cm^{-1}$. $^{1}H$ NMR analysis revealed a diastereomeric mixture, the methyl group appearing as two doublets at 1.35 and 1.39ppm. The methylene protons of the tetralin ring were visible as four multiplet signals, at 1.67, 2.12, 2.70 and 3.02ppm, the third of these signals overlapping with a broad signal at 2.44ppm, possibly that of the terminal hydroxyl group. The two methylene groups of the side chain resonated as two broad multiplets, at 3.36 and 3.54ppm. The methine proton adjacent to the ketone resonated as two overlapping quartets, at 4.14 and 4.17ppm.

The four aromatic protons of the tetralin ring were found together from 7.02-7.10 ppm, followed by the protons of the aryl ring bearing the carbonyl group. These were identifiable as *meta* (7.49ppm), *para* (7.58ppm) and *ortho* (8.01ppm) to the keto group. In the $^{13}C$ NMR spectrum, two key signals were those of the ethereal methylene carbons, at 61.4 and 61.5ppm for one pair, and 62.3 and 62.8ppm for the other; and the carbonyl signals, at 202.8 and 203.0ppm.

However, alkylation proved very difficult, resulting in poor yields of the alkylated derivative after several days. Heating the reaction merely served to effect β-elimination.

Reduction of a crude, inseparable mixture obtained from the alkylation reaction which, as judged by GCMS appeared to contain some of the desired product, yielded a mixture of compounds, one of which proved to be the desired alcohol, of which only one isomeric pair was isolated (**5.34**).




**(5.33)** **(5.34)**

**Scheme 5.26**

This molecule was isolated as a crystalline solid, and displayed O-$H_{str}$ in the infrared spectrum at 3557$cm^{-1}$. In the $^1H$ NMR spectrum, a singlet at 1.05ppm represented the methyl protons. The three methylene groups were accounted for by two multiplets, at 2.59 and 2.92ppm, integrating for three and two protons respectively, and another at 3.10ppm integrating as a single proton. At 4.86ppm, the methine adjacent to the alcohol group was finely split into a doublet, reflecting coupling to the hydroxyl proton. A singlet at 6.35ppm was attributable to the alkene proton. In the aromatic region, one proton resonated at 7.02ppm, two at 7.08ppm, six between 7.26-7.21ppm, and the remaining five between 7.35-7.46ppm.

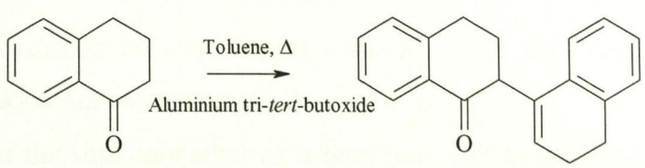
## 5.4 Approaches towards the synthesis of dimeric tetralin alcohols

To complement the tetralin-indan dimer molecules synthesised in the preceeding Sections, it was decided to investigate the effect of increasing the five membered ring of the indan component in (**5.9**) and (**5.29**) to a six membered ring, thus generating tetralin/tetralone dimers. There are several possibilities through which two tetralone molecules can be linked via an aldol reaction, depending on the position of the keto groups in the parent molecules, but only two were selected for experimentation, namely:

- Self-condensation of α-tetralone
- A combination of α-tetralone and β-tetralone, using β-tetralone as acetal precursor

The generation of a silyl enol ether from β-tetralone is complicated by the possible formation of two enolates, and the reactions of α-tetralone are limited by the extreme difficulty encountered when attempting to produce acetals of benzylic ketones. Therefore, to accomplish a self-condensation of α-tetralone, an alternative route was considered. In their study of the alkali fusion of tetralone molecules, Springer *et al.* reported a dimerization of α-tetralone in 25% yield using anhydrous HCl[224].

As an alternative synthesis, it was decided to employ basic conditions and aluminium tri-*tert*-butoxide was chosen. After addition of the base to α-tetralone in dry toluene under reflux, the reaction was heated for several hours (Scheme 5.27), and after workup yielded the requisite dimer (**5.35**).



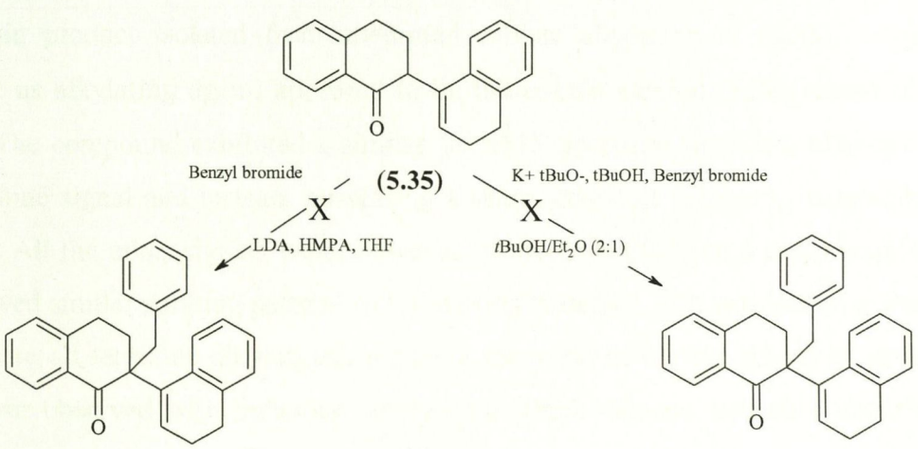

(**5.35**)

**Scheme 5.27**

The main infrared spectral characteristic of dimer (**5.35**) was the $C{=}O_{str}$, at 1679cm$^{-1}$. The $^1$H NMR spectrum contained four multiplets in the aliphatic region, accounting for the four methylene groups. The methine proton, at 3.89ppm, was more complex than the expected triplet. At 5.84ppm, the alkene proton was a fine triplet.

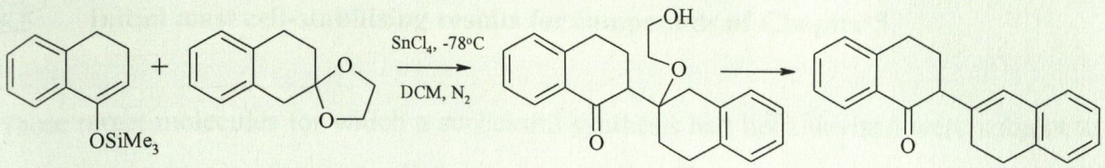
The aromatic region was well resolved, four protons occupying the region from 7.13-7.20ppm, followed by four discrete signals for the remaining four aromatic protons, a doublet at 7.30ppm, two double doublets at 7.38 and 7.53ppm, and a terminal doublet at 8.16ppm, that of position eight on the tetralone ring.

To alkylate dimer (**5.35**) proved a fruitless task (Scheme 5.28); under our standard alkylation conditions of $K^{+}$*tert*-$BuO^{-}$ and benzyl bromide, no benzylated product was detected on GCMS analysis. Instead of $K^{+}$*tert*-$BuO^{-}$, lithium di-isopropyl amide (LDA) was also employed as base but to no avail. As the rate of enolate alkylation can often be slow, coordinating reagents such as HMPA have been used to enhance reactivity. Goto *et al.* have employed a selection of reagents to enhance the alkylation of α-tetralone, and demonstrated significantly improved yields with several of these[225]. HMPA failed to have any impact on the alkylation of (**5.35**). It may be that the considerable steric bulk of the dimer molecule prevented approach of the alkylating agent.




**Scheme 5.28**

Attention was focussed on the other target tetralone dimer molecule, to see whether its behaviour under alkylation conditions would mirror that of (**5.35**). To create this molecule required reaction of the silyl enol ether of α-tetralone with an acetal of β-tetralone. As in the synthesis of (**5.9**), use of the dimethyl acetal and TMSOTf as catalyst were unsuccessful, whereas the use of a dioxolan and $SnCl_4$ (Scheme 5.29) yielded the desired dimer (**5.36**), again very prone to β-elimination, resulting in the isolation of (**5.37**), a yellow solid in 32% yield.

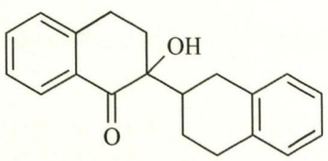



**(5.3)** **(5.24)** **(5.36)** **(5.37)**

**Scheme 5.29**

The aldol condensation product (**5.37**) exhibited $C{=}O_{str}$ at 1679cm$^{-1}$ in the infrared spectrum. $^1$H NMR analysis showed a multiplet integrating as four protons from 2.24-2.44ppm, corresponding to two of the methylene groups. The other two methylene signals were also multiplets, at 2.93 and 3.09ppm. The methine proton, akin to the corresponding signal in (**5.33**), appeared as a multiplet rather than a triplet, at 3.44ppm. The alkene proton resonated as a singlet at 6.32ppm. In the aromatic region of the spectrum, most of the protons were individually visible, at 7.01ppm, three at 7.16ppm, a doublet at 7.29ppm, a double doublet at 7.37ppm, a double triplet at 7.52ppm, and the doublet of position eight on the tetralone ring at 8.13ppm.

The main product isolated from attempted enolate alkylation of (**5.35**), using benzyl bromide as alkylating agent, appeared to be the α-keto alcohol (**5.38**), obtained in 40% yield. The compound exhibited a similar $^1$H NMR spectrum to (**5.35**), although without the methine signal and instead, possessing a sharp singlet at 5.35ppm, integrating as one proton. All the other signals were, however, shifted downfield to a considerable degree, yet showed similar splitting patterns to the starting material. This product type was seen to complicate all tetralone alkylations, reducing the yield of enolate alkylated product, yet was never observed with indanone alkylations, which alkylate smoothly under standard conditions to excellent yield.




**(5.38)**

## 5.5 Initial mast cell-stabilising results for compounds of Chapter 5

Those target molecules for which a successful synthesis had been devised were subject to preliminary screening for mast cell-stabilising activity. The assay was performed using the standard method employed for the previous nitrogenous molecules (Section 6.2.3), although solubility concerns were encountered with the carbon-linked dimer molecules, especially at higher concentrations, necessitating a slightly higher percentage of DMSO as cosolvent, an event that was corrected for in the blank samples. The results of the mast-cell stabilising assay are illustrated in Figure 5.1 below.

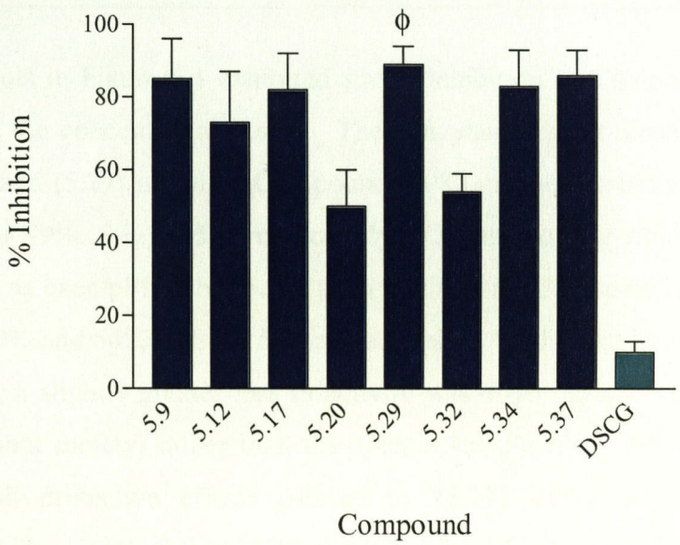



**Figure 5.1 Mast cell-stabilising activity of compounds of Chapter 5**

*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of Compound 48/80-induced histamine release from rat peritoneal mast cells] mean +/- S.E.M.* ϕ (compound also tested using metrizamide-purified cells).

**Table 5.1 Summary statistics for compounds of Chapter 5**

| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **5.9** | 77 | 26 | 11 | 5 |
| **5.12** | 73 | 32 | 14 | 5 |
| **5.17** | 82 | 22 | 10 | 5 |
| **5.20** | 50 | 23 | 10 | 5 |
| **5.29** | 89 | 11 | 5 | 5 |
| **5.32** | 54 | 12 | 5 | 5 |
| **5.34** | 83 | 22 | 10 | 5 |
| **5.37** | 86 | 15 | 7 | 5 |
| DSCG | 10 | 25 | 3 | 94 |

All of the alcohols in Figure 5.1 exhibited strong inhibition of Compound 48/80-induced degranulation at the concentration tested. The benzylated dimer alcohols with rigid ring structures (**5.9**) and (**5.29**) inhibited Compound 48/80-induced histamine release by 77%, S.E.M. 11% and 89%, S.E.M. 5% respectively. Opening of the rigid ring structures of (**5.9**) and (**5.29**), as exemplified by (**5.20**) and (**5.32**), resulted in some reduction in activity (50%, S.E.M. 10% and 54%, S.E.M. 5%, respectively). Of the two hydroaromatic rings in (**5.9**) and (**5.29**), a slightly greater loss in activity was observed upon opening of the ring bearing the alcohol moiety, rather than the alkenic substituent. This was seen from the consistently high protective effects offered by (**5.17**) and (**5.34**), whose respective inhibitory values were 82%, S.E.M. 10% and 83%, S.E.M. 10%. In contrast, the value for (**5.12**), where the alcohol-bearing ring had been opened, was 73%, S.E.M. 14%.

Interestingly, the enone (**5.37**) retained mast cell-stabilising activity (86%, S.E.M. 7%). Either the presence of a rigidly held benzylic carbonyl or a benzylic secondary alcohol functionality seemed important for mast cell-stabilising activity within this novel series of carbon-carbon dimer molecules.

# Pharmacological screening of the novel compounds of Chapters 2-5 for anti-allergic and anti-inflammatory properties

## 6.1 Objectives

The aim of this chapter was the evaluation of the novel compounds described in the preceding chapters for activity in various *in vitro* and *in vivo* pharmacological screens. The initial sections outline the derivation of the mast cell-stabilisation results presented in Chapters 2-5, followed by the use of alternative elicitors of histamine release in dose-response studies, all using the rat peritoneal mast cell preparation (RPMC). Subsequent studies on the ability of the more active compounds to inhibit passive cutaneous anaphylaxis (PCA) in the rat and an evaluation of anti-inflammatory activity in the mouse ear model are also presented.

## 6.2 Materials and Methods

### 6.2.1 Reagents

NaCl, KCl, $CaCl_2.2H_2O$, $NaH_2PO_4.2H_2O$, D-Glucose, HEPES, $MgCl_2.7H_2O$, Gelatin, and Bovine Serum Albumin for use as buffer components were all purchased from Sigma and were of the highest analytical grade possible. Buffers were prepared daily using deionised water. *o*PT, DMSO, Evans Blue, Arachidonic Acid, Compound 48/80, Vancomycin, A23187, Concanavalin A, Metrizamide, Chicken Egg Albumin and Indomethacin were also purchased from Sigma. Intal® Nebules (Fisons) were used as the source of disodium cromoglycate (DSCG). Pentobarbitone sodium (Sagatal®) was obtained from Rhone-Poulenc. Mouse anti-rat IgE was purchased from Zymed Laboratories. *Bordetella pertussis* suspension was a generous gift from Nicole Guiso, Institut Pasteur, Paris.

Buffers

HEPES buffer consisted of 156mM NaCl, 2.7mM KCl, 2.7mM $MgCl_2$, 0.4mM $NaH_2PO_4.2H_2O$, 0.5mM $CaCl_2$, 5.6mM Glucose and 5mM HEPES (*N*-2-hydroxy-ethylpiperazine-*N*'-2-ethanesulphonic acid). Mast cell medium (MCM) consisted of 150mM NaCl, 2.7mM KCl, 0.9mM $CaCl_2$, 5.6mM Glucose and 5mM HEPES, and was adjusted to pH 7.4 using 3M NaOH. Physiological saline (PS) [-] contained 154mM NaCl, 2.7mM KCl, 0.9mM $CaCl_2$, 5mM HEPES, at pH 7.4. (PS) [+] consisted of (PS) [-] with the inclusion of 5.6mM Glucose. Fresh buffers were made daily, always adding calcium lastly (as a 1M solution) to avoid precipitation of insoluble salts.

### 6.2.2 Animals

Female rats of the Wistar strain were employed in preliminary mast cell assays and also in PCA studies *in vivo*. Male Brown Norway rats were used to evaluate the ability of compounds to inhibit anti-IgE induced degranulation of mast cells. Male mice of the Laca strain were employed for arachidonic acid-induced ear oedema studies. All animals were given food and water *ad libitum* before experimentation.

### 6.2.3 Mast Cell Stabilisation Assay Procedures

#### 6.2.3.1 Isolation of RPMC

A 250-300g female Wistar rat was selected, and sacrificed by $CO_2$ inhalation. The animal was immediately injected with 15ml of the appropriate buffer solution (at 37°C) into the peritoneal cavity, and massaged gently in this region for 90 seconds, to facilitate cell recovery. A midline incision was made and the peritoneum exposed. The pale fluid was aspirated using a blunted plastic Pasteur pipette, and collected in a plastic centrifuge tube. The fluid was then centrifuged at 1000rpm for 5 minutes (Heraeus Christ Labofuge$^{GL}$), and the supernatant discarded to reveal a pale cell pellet. Any grossly bloody samples were discarded, and minor erythrocytic impurities were removed by brief (30 second) haemolysis using double-distilled water before reconstitution in buffer. The cell pellets were re-suspended in fresh buffer and re-centrifuged. After resuspension, the volume of fluid was adjusted to 9ml. Cell suspensions of this nature appeared to be relatively consistent, as judged by basal and total readings for histamine content, and were not

routinely purified further. If further purification was required, the method of Yurt *et al.* was adopted[21], and the cell pellet was resuspended in 1ml of buffer, and overlaid on 2ml of metrizamide solution. After centrifugation at 1800rpm for 15 minutes, the cells at the interface were discarded and the pellet resuspended in fresh buffer, a procedure that removes contaminating cells and results in over 90% purity.

### 6.2.3.2 Inhibition of Histamine release

4.5ml of buffer was added to each of sixteen plastic tubes, at 37°C (Julabo U3 metabolic shaker). The tubes were divided into eight pairs, representing the following readings; Basal release, Maximal release, Total histamine content, Blank (maximal adjusted for cosolvent use, if appropriate), Control (disodium cromoglycate, DSCG), Test compounds x 3. The test compounds and control were present at a final concentration of $2 \times 10^{-5}$M. Test compounds not soluble in water were prepared as stock solutions in DMSO or 20% DMSO in water at a concentration of $3 \times 10^{-4}$M before use.

The following table displays the order of addition of various substances to the assay tubes:

**Table 6.1 Experimental protocol for mast cell-stabilisation assay**

| Tube | Time: 0 min | Time: 5min | Time: 15min |
|---|---|---|---|
| Basal | 25µL $H_20$ | 0.5ml cells | 50µL $H_20$ |
| Maximal | 25µL $H_20$ | 0.5ml cells | 50µL releasing agent |
| Total | 25µL $H_20$ | 0.5ml cells | 50µL releasing agent |
| Blank | 25µL Vehicle | 0.5ml cells | 50µL releasing agent |
| Control | 25µL DSCG in $H_2O$ | 0.5ml cells | 50µL releasing agent |
| Test Compounds | 25µL Test in Vehicle | 0.5ml cells | 50µL releasing agent |

Depending on the releasing agent being employed in the assay, slight modifications of buffer systems and incubation times were required. These modifications are outlined in Table 6.2, the assays being otherwise identical in all respects.

**Table 6.2 Variable assay parameters for different histamine-releasing agents**

| Releasing Agent | Concentration | Time of Incubation | Buffer System |
|---|---|---|---|
| Compound 48/80 | 0.2μg $ml^{-1}$ | 5 min | HBSS |
| $Ca^{2+}$ Ionophore A23187 | 1μg $ml^{-1}$ | 10 min | MCM |
| Concanavalin A | 20μg $ml^{-1}$ | 10 min | MCM |

All preliminary studies on the novel compounds, as presented in the preceding chapters, were performed using Compound 48/80 as histamine-releasing agent. After the appropriate incubation time with releasing agent, the reaction was terminated by addition of 0.5ml ice-cold buffer to each of the tubes. The 'Total' tubes were placed in boiling water for two minutes to lyse the cells. All tubes were then centrifuged at 1000rpm for 5 minutes. To 3ml of the supernatant from each tube, 0.6ml of 1M NaOH was added, followed by 150μL of a 0.1%$^{w}/_{v}$ solution of *o*-phthalaldehyde (*o*PT) in methanol. After 4 minutes, 0.3ml of 3M HCl was added to each tube and the fluorescence measured at 350nm excitation, 450nm emission (Turner® Quantech™ Fluorometer or Perkin Elmer 204A spectrophotometer). Linearity of measurement was determined by regular construction of a standard curve for histamine, using concentrations ranging from 5ng $ml^{-1}$ to 800ng $ml^{-1}$.

Mast cell stabilisation studies using either vancomycin or anti-IgE utilised slightly different methods. In the case of vancomycin-induced release of histamine, the method of Williams[112] was used with certain modifications. To 1.5ml of Tyrodes buffer was added 25μL vehicle or test compound, and, after 10 minutes, 0.5ml cell suspension. 0.68ml of vancomycin solution was added to give a final concentration of 2.52mg $ml^{-1}$. This concentration was selected as it was the midpoint of the two values used by Williams, in order to mimic likely plasma concentrations. After 30 minutes incubation, the reaction was terminated by addition of 2.7ml ice-cold buffer and histamine determined as before. The procedure adopted for anti- IgE-induced degranulation was that of Sugimoto *et al.*[226], again with slight modifications. To 1.5ml PS buffer was added 50μL vehicle or test compound, and, after 10 minutes, 0.25ml cells (from 2 animals, pooled to 5ml). After 15 minutes incubation, 50μL of anti-IgE was added to a final concentration of 5.4μg $ml^{-1}$. After a further 10 minutes, the reaction was terminated by addition of 3.15ml ice-cold buffer and analysed as above.

#### 6.2.3.3 Dose-Response Studies

The procedure adopted was identical to that used in the preceding section. Compound 48/80, A23187 and Con A were used as elicitors, and a range of concentrations of selected test compounds was employed.

### 6.2.4 Passive Cutaneous Anaphylaxis assay methodology

#### 6.2.4.1 Preparation of antiserum

An antiserum was raised by means of intraperitoneal inoculation of Wistar rats with 1ml of heat-killed *Bordetella pertussis* suspension ($10^{10}$ organisms per ml) and 0.5ml of chicken egg albumin solution (1mg per animal) in 0.5M NaCl. After 14 days, the animals were exsanguinated by means of cardiac puncture under light halothane anaesthesia, and the blood collected and pooled. The serum was separated by centrifugation at 2000rpm for 10 minutes, and stored in aliquots at –4°C until future use.

#### 6.2.4.2 Assay

The titre of the antiserum was expressed as the lowest dilution capable of producing a wheal of 10mm diameter in the dorsal skin of four out of five test rats. These dilutions were performed using isotonic saline, and inoculation was via the intradermal route, into the shaved dorsal skin of female Wistar rats. The wheal was visualised by intravenous injection of a solution of 2.5mg chicken egg albumin in 0.5ml 1% Evans Blue dye 48 hours after inoculation. Having selected an appropriate dilution of the antiserum for future studies, six injections, three each of diluted antiserum and isotonic saline were performed on each group of rats into the shaved dorsal skin. The volume injected was 100µL per site, and the sites were outlined by means of a water-insoluble red marker.

After 48 hours, the rats were intravenously challenged via the tail vein with 2.5mg albumin in 0.25ml 2% Evans Blue, with simultaneous injection of 0.25ml of vehicle (positive control) or test compound at a dose of 3mg $kg^{-1}$.

Test compounds insoluble in water alone were dissolved with the aid of a pharmaceutically acceptable cosolvent such as propylene glycol or Tween 80. Thirty minutes after intravenous injection, the animals were sacrificed by cervical dislocation and the skin reflected. The vehicle control and test sites were measured and excised, and the tissue segments added to 1ml 1M KOH. Using the method of Katayama[227], the tissue was digested overnight at 37°C, and to each digest was added 2.5ml 0.6M $H_3PO_4$ and 6.5ml acetone.

The tubes were thoroughly shaken, and centrifuged at 3000rpm for 15 minutes. The absorbance of each supernatant was measured using UV spectroscopy at 620nm (Spectronic® Genesys™ 5 spectrometer), and the readings from the tubes containing tissue from the vehicle-only sites subtracted from their companion site inoculated with antiserum. Linearity of absorbance of Evans Blue dye over the range of concentrations encountered was verified by means of a standard curve. In a few experiments, the test compounds were injected intravenously 30 minutes before intravenous challenge with antigen.

### 6.2.5 Arachidonic acid-induced Mouse Ear Oedema

#### 6.2.5.1 Experimental protocol

Male Laca mice weighing 25-30g were divided into groups of five and sedated using sodium pentobarbitone, at a dose of 60mg $kg^{-1}$ via the intraperitoneal route. Additional anaesthetic was administered during the course of the experiment if the mice showed any signs of regaining consciousness. Test compounds, the control (indomethacin), and arachidonic acid (AA) were dissolved in acetone, the latter prepared immediately before use from a stock solution and stored on ice until required.

The following Table outlines the test procedure:

**Table 6.3 Protocol for Arachidonic acid-induced ear oedema**

| Time | Application |
|---|---|
| 0 min | Indomethacin (300μg $ear^{-1}$) to R ears, acetone to L ears Group 1 |
| 10 min | Acetone to R & L ears Group 2 |
| 20 min | Test Compound (300μg $ear^{-1}$) to R ears, acetone to L ears Group 3 |
| 60 min | 1mg AA to R ears, acetone to L ears Group 1 |
| 70 min | 1mg AA to R ears, acetone to L ears Group 2 |
| 80 min | 1mg AA to R ears, acetone to L ears Group 3 |

All individual applications to an ear consisted of a 20μL volume, 10μL of which was applied evenly to each ear surface. The amount of arachidonic acid to be applied was determined from a standard curve. One hour after application of arachidonic acid, the animals were sacrificed by cervical dislocation. Using a 5mm surgical punch (Stiefel Labs), tissue sections were removed from both ears of each animal, and carefully weighed. The weights of the left ears were subtracted from those of the right, and a mean value obtained for the difference in weights in each group. The reduction in swelling was obtained by comparison of the weight differences in the positive control group (AA only), with those in the Indomethacin (Indo) and test groups.

### 6.2.6 Statistical Analysis

Studies using RPMCs were repeated on the cells of 5 rats, unless otherwise stated. Graphical data was obtained from the mean $^{+}/_{-}$ the standard error of the mean (S.E.M.). For PCA experiments, results were analysed using one-way analysis of variance (ANOVA). If a significant difference between treatment groups was detected, the individual group difference was determined by Dunnett's test. A P value of $<0.05$ was considered to be statistically significant. Statistical analysis of arachidonic acid-induced mouse ear oedema was performed using Students t-test when comparing untreated (positive control) groups with treatment groups. P values of $<0.05$ were considered significant.

## 6.3 Results and Discussion

### 6.3.1 Inhibition of histamine release induced by Compound 48/80

Degranulation induced by Compound 48/80 is generally a very fast phenomenon, reflected by the short incubation times required. It has been reported to cause degranulation in the region of 61%[29], when used at a concentration of 0.2μg $ml^{-1}$; the average value over 94 assays in these studies was 33%, S.E.M. 2%. The % inhibition of Compound 48/80-induced histamine release was calculated using the following formula:

$$100 - \frac{(\text{Reading} - \text{Basal})}{(\text{Blank} - \text{Basal})} \times \frac{100}{1}$$

All the raw data utilised in the construction of the Figures of Chapters 2-5 is included in Appendix 1, on the accompanying CD-ROM. The application of the above formula and the mean results of repeated experiments are also summarised in Appendix 1. The % inhibition for the control compound (disodium cromoglycate), and any other compounds soluble in water alone was obtained from the same formula, inserting the maximal reading in the place of the blank. As can be seen from the Figures of Chapters 2-5 (*vide supra*), at the concentrations tested, some compounds exhibited complete inhibition of release. The average basal release of histamine from unstimulated cells was 7%, S.E.M. 0.5% (literature value 6% over 20min incubation)[101]. Literature values for the standard, disodium cromoglycate vary widely; reported values include 7.4% at $10^{-5}M$[29] (using 0.2μg $ml^{-1}$ Compound 48/80), and 47% at 10mM (using 1μg $ml^{-1}$ Compound 48/80 and a 30 minute incubation)[112]. The value obtained over 94 assays in our studies was 10%, S.E.M. 3%, using a concentration of $2 \times 10^{-5}M$. It should be noted that the kinetics of inhibition of histamine release by cromoglycate are often biphasic and difficult to interpret. Time of addition of cromoglycate has also been demonstrated to be important; values reported vary from 14.5% inhibition with 5 min prior incubation with the cells to 40.5% when cromoglycate is added at the same time as challenge with 48/80[29].

### 6.3.2 Vancomycin-induced histamine release

At a concentration of 2.52mg $ml^{-1}$, vancomycin induced considerable degranulation of mast cells (71%, s.d. 12%, S.E.M. 7%). To date, no studies have shown compounds able to inhibit vancomycin-induced degranulation of RPMC's. In the studies of Williams *et al.*, disodium cromoglycate did not inhibit vancomycin-induced degranulation from either RPMC or RBL-1 cells[112]. With compound (**4.2**) as a model compound, inhibition of degranulation was observed, at compound concentrations of $10^{-6}$M or greater. This interesting result is shown in Figure 6.1. The raw data used in the generation of Figure 6.1 is included in Appendix 1.

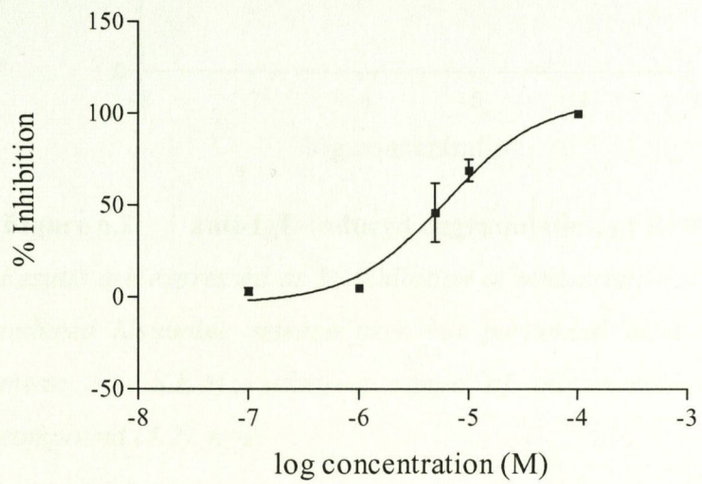



**Figure 6.1 Vancomycin-induced degranulation of RPMCs**

*Results are expressed as % inhibition of Vancomycin-induced histamine release from rat peritoneal mast cells, mean +/- S.E.M., using a range of concentrations of compound (**4.2**).*

### 6.3.3 anti-IgE-induced histamine release

Incubation of RPMC suspensions with 5.4μg $ml^{-1}$ mouse anti-rat IgE caused rapid (within 10 minutes) release of histamine (87%, s.d. 12%, S.E.M. 6%, n=5). Using a range of concentrations of compound (**4.2**), a rather flat dose response curve was obtained, although inhibition was noted at all concentrations examined (see Appendix 1). Employing a range of concentrations of the *N*-benzylated compound (**2.16**) did not result in any inhibition whatsoever. Figure 6.2 shows the results for compound (**4.2**).

Four other structurally diverse molecules were tested at a concentration of 2 x $10^{-5}$M, and these results are presented in Figure 6.3. The raw data used in the generation of Figures 6.2 and 6.3 is included in Appendix 1.

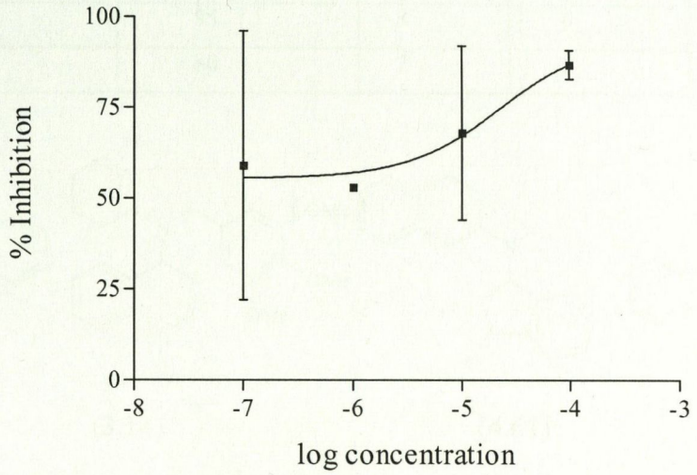



**Figure 6.2 anti-IgE-induced degranulation of RPMCs**

*Results are expressed as % inhibition of mouse anti-rat IgE-induced histamine release from rat peritoneal mast cells, mean +/- S.E.M., using a range of concentrations of compound (**4.2**), n=2.*

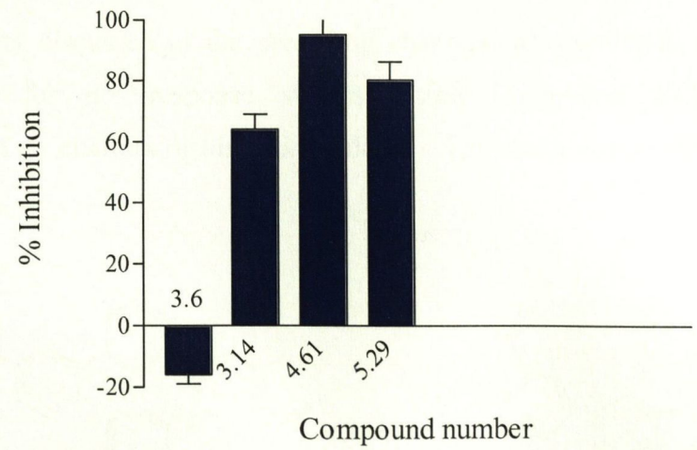
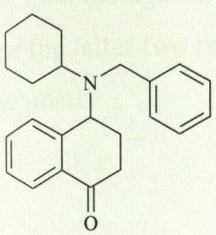



**Figure 6.3 % Inhibition of anti-IgE-induced histamine release from RPMC**

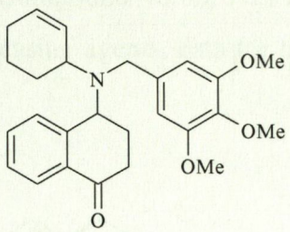
*Results are expressed as % inhibition, [at a concentration of 2 x $10^{-5}$M, of mouse anti-rat IgE-induced histamine release from rat peritoneal mast cells], mean +/- S.E.M., n=2.*

**Table 6.4 Summary statistics for selected compounds vs anti-IgE**

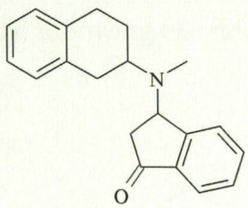
| Compound | % Inhibition | $\sigma_{n-1}$ | S.E.M | n |
|---|---|---|---|---|
| **3.6** | -16 | 13 | 9 | 2 |
| **3.14** | 64 | 4 | 3 | 2 |
| **4.61** | 95 | 8 | 6 | 2 |
| **5.29** | 80 | 7 | 5 | 2 |



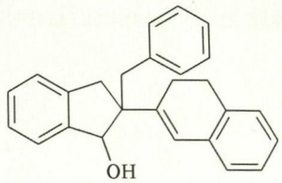

**(3.6)**




**(3.14)**




**(4.61)**

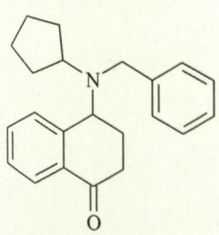



**(5.29)**

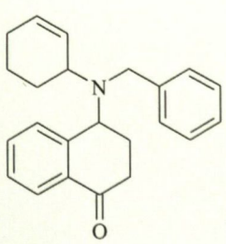
It can be seen from Figure 6.3 and Table 6.4 that excellent inhibition of anti-IgE-induced histamine release was obtained using the nitrogen linked dimer (**4.61**), and that good inhibition was also observed with both the trimethoxybenzyl-substituted amine (**3.14**) and the alcohol (**5.29**), although no inhibition was noted using compound (**3.6**).

### 6.3.4 Dose-response studies

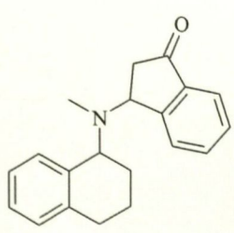
From the results discussed in the preceding chapters, representative active compounds were selected for dose-response studies, using Compound 48/80, A23187 and Concanavalin A as elicitors of histamine release. The structures of these compounds are shown below:



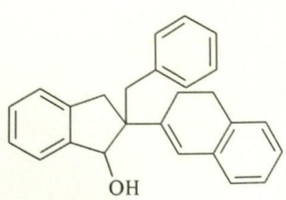

**(2.16)**




**(3.12)**

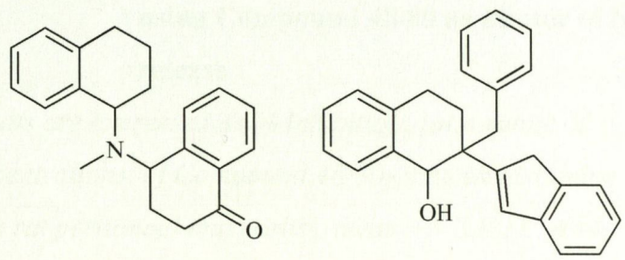



**(4.2)**




**(5.29)**

These compounds were representative of the many active molecules encountered in previous chapters, possessing key structural features within a strained ring system(s). A series of dose-response curves was constructed over the range $10^{-7}$M to $10^{-4}$M using the three aforementioned releasing agents. The raw experimental data and its manipulation in order to construct the dose-response curves of Figures 6.4-6.6 are included in Appendix 1. Maximal release induced by A23187 and Con A was 84%, n=24, S.E.M.=17%; and 62%, n=29, S.E.M.=11%, respectively. The dose-response curves for each of the four selected compounds against Compound 48/80, A23187 and Con A are shown in Figures 6.4-6.6. For the latter two releasing agents, data for the following two additional compounds is also included.




**(4.10)** **(5.9)**

### 6.3.4.1 Dose response curves using Compound 48/80 as histamine-releasing agent

Figure 6.4 shows that all four compounds tested caused dose-dependent inhibition of Compound 48/80-induced mast cell degranulation, and all four profiles were very similar, as illustrated by the $IC_{50}$ values (Table 6.6). In these 16 experiments, the maximal release caused by 0.2μg $ml^{-1}$ Compound 48/80 was 38%, S.E.M. 4%, agreeing well with the value already obtained in previous experiments (see Section 6.3.1).

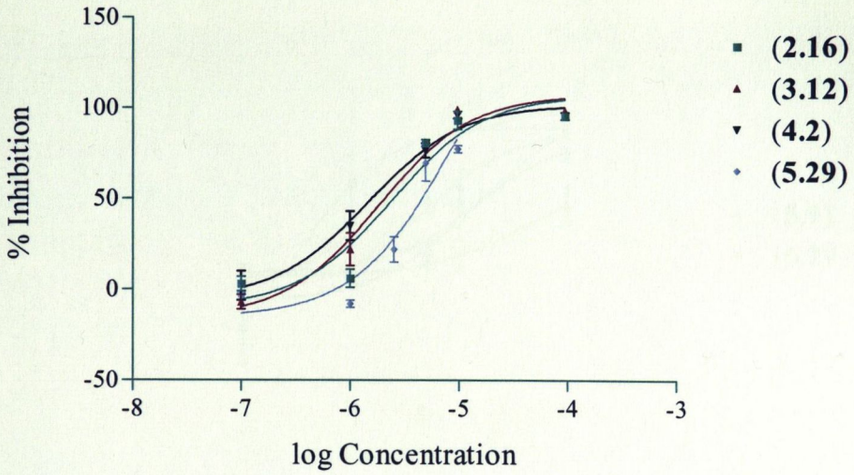



**Figure 6.4 Dose response curves for selected compounds using Compound 48/80 as elicitor of histamine release**

*Results are expressed as % inhibition, [at a range of concentrations, of Compound 48/80-induced histamine release from rat peritoneal mast cells], mean +/- S.E.M., n=4.*

### 6.3.4.2 Dose response curves using A23187 as histamine-releasing agent

All compounds exhibited a dose-dependent reduction of A23187-induced histamine release from RPMCs. The importance of optimal $Ca^{2+}$ concentrations in studies using A23187 was highlighted by the use of different buffer systems, as illustrated in Table 6.5. Use of the low $Ca^{2+}$-containing HEPES buffer resulted in only small amounts of histamine release, whereas complete degranulation was observed using the $Ca^{2+}$-rich Tyrodes buffer, an effect that could not be inhibited by the test compounds. Use of an intermediate $Ca^{2+}$ concentration, as found in MCM, resulted in almost complete release but also good inhibition by the test compounds.

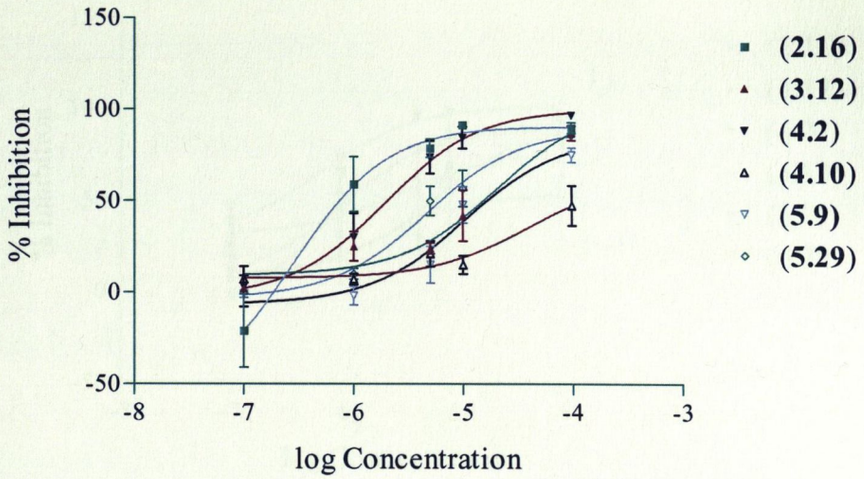



**Figure 6.5 Dose response curves for selected compounds using A23187 as elicitor of histamine release**

*Results are expressed as % inhibition, [at a range of concentrations, of A23187-induced histamine release from rat peritoneal mast cells], mean +/- S.E.M.*

**Table 6.5 The influence of $[Ca^{2+}]$ on A23187-induced histamine release**

| Buffer | $[Ca^{2+}]$ | [A23187] | Incubation time | % Histamine release |
|---|---|---|---|---|
| HEPES | 0.5mM | 1μgml$^{-1}$ | 20 min | 15% |
| Tyrodes | 1.36mM | 1μgml$^{-1}$ | 20 min | 100% |
| MCM | 0.9mM | 1μgml$^{-1}$ | 10 min | 84% |

### 6.3.4.3 Dose response curves using Concanavalin A as histamine-releasing agent

Concanavalin A is reported to induce about 40% histamine release from RPMCs, an effect that is magnified by the concomitant addition of phosphatidylserine[98]. Under the experimental conditions employed in our dose response studies, release of histamine was consistently high, even in the absence of phosphatidylserine. All compounds investigated exhibited dose-dependent inhibition of Concanavalin A-induced mast cell degranulation (Figure 6.5), and the best-fit $IC_{50}$ values are shown in Table 6.6.

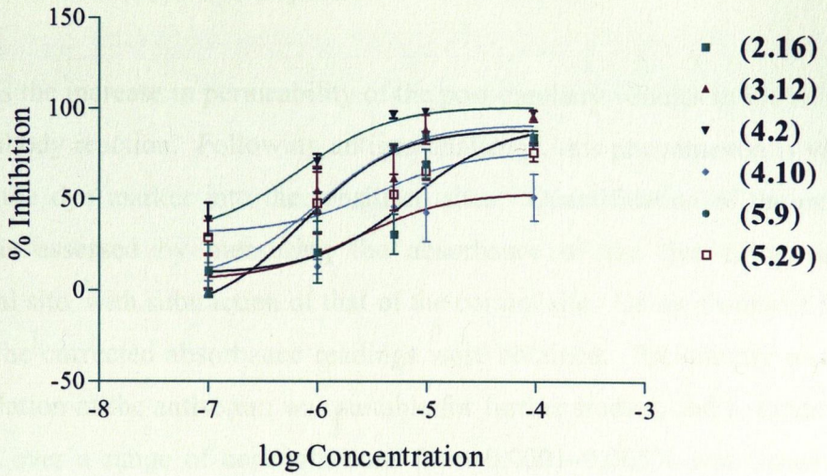



**Figure 6.6 Dose response curves for selected compounds using Con A as elicitor of histamine release**

*Results are expressed as % inhibition, [at a range of concentrations, of Con A-induced histamine release from rat peritoneal mast cells], mean +/- S.E.M., n=4.*

The best-fit $IC_{50}$ values for the tested compounds (using all three releasing agents) are listed in Table 6.6.

**Table 6.6 $IC_{50}$ values for selected compounds**

| Compound | $IC_{50}$ (μM) | | |
|---|---|---|---|
| | 48/80 | Con A | A23187 |
| (**2.16**) | 2.4 | 7.2 | 0.28 |
| (**3.12**) | 1.8 | 1.1 | 20 |
| (**4.2**) | 1.5 | 0.68 | 2.0 |
| (**5.29**) | 7.7 | 3.6 | 4.7 |
| (**5.9**) | Not tested | 0.75 | 10 |
| (**4.10**) | Not tested | 2.4 | 38 |

### 6.3.5 Passive Cutaneous Anaphylaxis

PCA utilises the increase in permeability of the post-capillary venules in the skin following antigen-antibody reaction. Following antigen challenge, this phenomenon is visualised by leakage of the dye marker into the sensitised sites. Quantification of the extent of dye leakage was assessed by measuring the absorbance of the dye extracted from the experimental site, with subtraction of that of the control site. Using groups of 5 rats, mean values for the corrected absorbance readings were obtained. Preliminary results showed that a $^1/_8$ dilution of the antiserum was suitable for further studies, and a standard curve for Evans blue over a range of concentrations from 0.0001–0.005% was linear with an $R^2$ value of 0.9989. This is depicted in Figure 6.7 below:

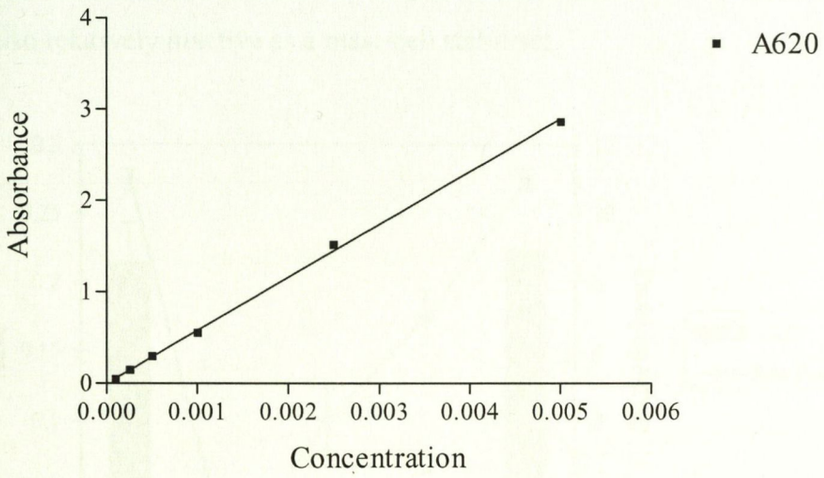



**Figure 6.7 Demonstration of linearity for absorbance of Evans Blue dye at 620nm.**

The results for the compounds tested in the PCA assay are shown in the following Figures, and were divided into three groups depending on their solubility in various vehicles.

Group 1: Compounds soluble in Isotonic Saline

Group 2: Compounds soluble in 5% Propylene Glycol

Group 3: Compounds soluble in 2.5% Tween 80

All raw experimental data used in the construction of Figures 6.7-6.12 is included in Appendix 2 on the attached CD-ROM.

### 6.3.5.1 PCA results for Group 1 compounds

The results for those compounds soluble in isotonic saline are shown in Figure 6.8. The first bar in the Figure represents the positive control, that is, the amount of dye leakage among rats challenged with antigen (ovalbumin) without any concomitant inhibitor. Blueing of the tissue sites was considerable, as assessed either by absorbance or site diameter. Injection of disodium cromoglycate at 3mg $kg^{-1}$ completely abolished the PCA reaction; this was in good agreement with literature data, where values of 80-100% inhibition have been reported[122]. Both *N*-methyl (**4.61**) and *N*-allyl (**4.62**) dimer compounds exhibited considerable inhibition of PCA at the dose level investigated, whereas the indan-tetralone dimer molecule (**4.6**) was entirely inactive. These results correlated well with the relative activity of these compounds *in vitro*, as dimer compound (**4.6**) was also relatively inactive as a mast-cell stabiliser.

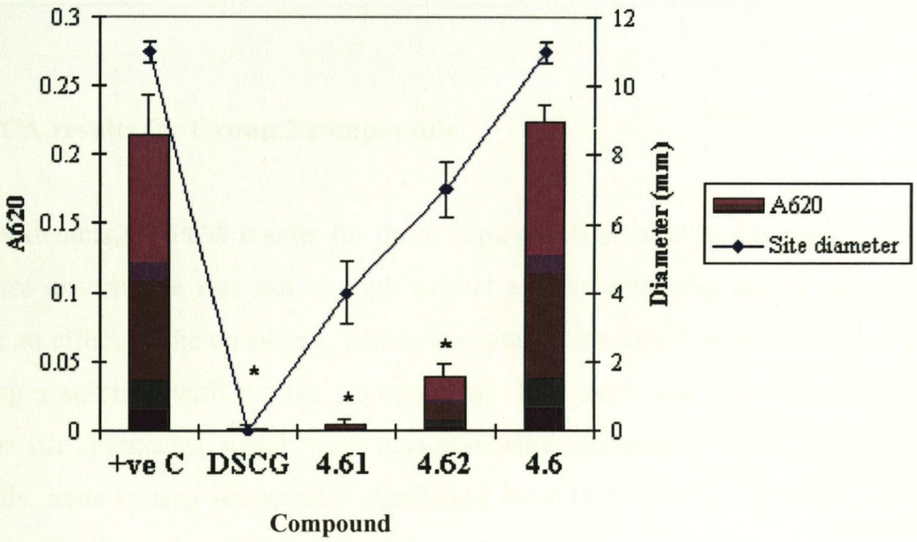
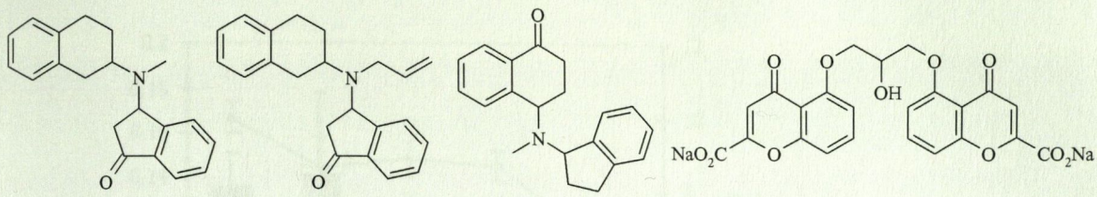



**Figure 6.8 PCA results for compounds soluble in isotonic saline**

*Results are expressed as % inhibition [Mean, $^{+}/_{-}$ S.E.M.] of rat PCA induced by i.v. injection of ovalbumin (1mg $rat^{-1}$). Rats were passively sensitised with i.d. injections of antiserum (0.1ml $site^{-1}$) to ovalbumin and challenged i.v. 48 hours later.* ***** $P<0.001$.



**(4.61)** **(4.62)** **(4.6)** **(DSCG)**

**Table 6.7 Summary statistics for PCA studies, group 1 compounds**

| Compound | Mean $\Delta A_{620}$ | N | $\sigma_{(n-1)}$ | SEM | % Inhibition |
|---|---|---|---|---|---|
| Positive Control | 0.214 | 21 | 0.139 | 0.030 | |
| Cromoglycate | 0.0016 | 15 | 0.0097 | 0.0025 | 99 |
| (**4.61**) | 0.00446 | 15 | 0.013 | 0.0034 | 98 |
| (**4.62**) | 0.039 | 12 | 0.036 | 0.01 | 82 |
| (**4.6**) | 0.224 | 12 | 0.045 | 0.013 | -5 |

### 6.3.5.2 PCA results for Group 2 compounds

Figure 6.9 depicts the PCA results for those compounds soluble in 5% propylene glycol. The control absorbance was not as high as that encountered with saline alone, perhaps reflecting an effect of the cosolvent, which was used at the smallest concentration capable of forming a solution with the test compounds. This trend was also apparent from the values for site diameters, which were also somewhat depressed. Among this group of compounds, none caused statistically significant inhibition of PCA. From a comparison with the *in vitro* data of earlier chapters, the result for compound (**3.5**) was not unexpected. However, the result obtained for the *N*-methylated dimer compound (**4.2**) was disappointing, as this compound did inhibit anti-IgE-induced histamine release, in addition to inhibiting that caused by Compound 48/80, vancomycin, Con A and A23187. The methoxy indanone dimer (**4.44**) was seen to inhibit PCA to some extent, but the result did not achieve statistical significance ($P>0.05$).

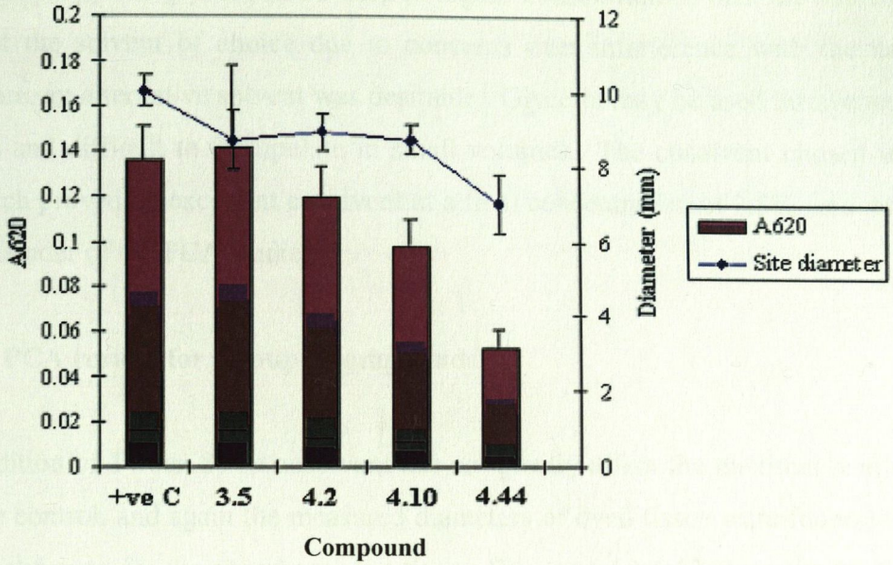
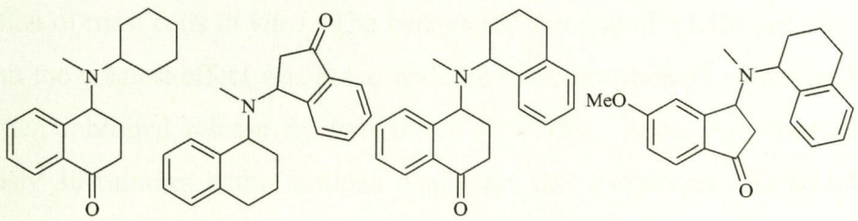



**Figure 6.9 PCA results for compounds soluble in 5% Propylene Glycol**

*Results are expressed as % inhibition [Mean, $^{+}/_{-}$ S.E.M.] of rat PCA induced by i.v. injection of ovalbumin (1mg rat$^{-1}$). Rats were passively sensitised with i.d. injections of antiserum (0.1ml site$^{-1}$) to ovalbumin and challenged i.v. 48 hours later.*




**(3.5)** **(4.2)** **(4.10)** **(4.44)**

**Table 6.8 Summary statistics for PCA studies, Group 2 compounds**

| Compound | Mean Δ $A_{620}$ | n | $\sigma_{(n-1)}$ | SEM | % Inhibition |
|---|---|---|---|---|---|
| Positive Control | 0.136 | 6 | 0.038 | 0.015 | |
| **(3.5)** | 0.142 | 12 | 0.126 | 0.036 | -4 |
| **(4.2)** | 0.119 | 14 | 0.014 | 0.053 | 13 |
| **(4.10)** | 0.097 | 12 | 0.013 | 0.044 | 29 |
| **(4.44)** | 0.052 | 15 | 0.035 | 0.009 | 62 |

Although propylene glycol can be used in higher concentrations than the 5% employed, it was not the solvent of choice due to concerns over interference with the assay itself. Therefore, an alternative solvent was desirable. Glycerin may be used intravenously, yet is viscous and difficult to manipulate in small volumes. The cosolvent chosen was Tween 80, which proved an excellent cosolvent at a final concentration of 2.5%, and was used for the remainder of the PCA studies.

#### 6.3.5.3 PCA results for Group 3 compounds

The addition of Tween 80 as cosolvent did not greatly affect the maximal readings for the positive control, and again the measured diameters of dyed tissue were found to mirror the pattern observed for the absorbance readings. Figures 6.10-6.12 show the PCA results for those compounds solubilised using 2.5% Tween 80. Figure 6.10 shows those compounds from Chapters 2 & 3.

Among the compounds of Figure 6.10, the cyclopentyl-substituted amine (**2.16**) did not inhibit PCA, which was not surprising as neither did it inhibit anti-IgE-induced degranulation of mast cells *in vitro*. The benzylated compound (**3.12**) did show inhibition of PCA, but the greatest effect was noted with the trimethoxybenzyl-substituted compound (**3.14**), which inhibited release by two thirds ($P<0.05$). However, when administered intravenously 30 minutes before antigen challenge, this compound offered no protective effect whatsoever, the absorbance readings being consistently high. This may reflect metabolism of the molecule after injection.

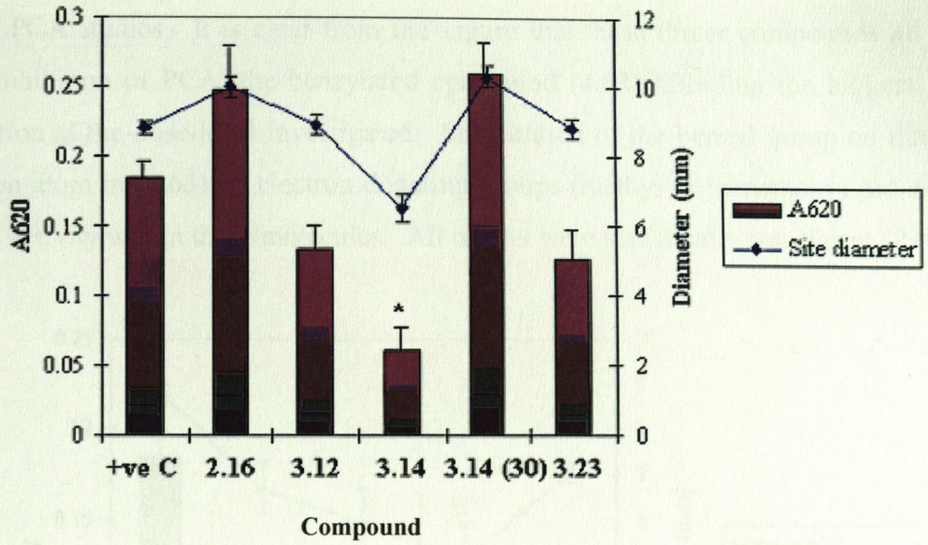
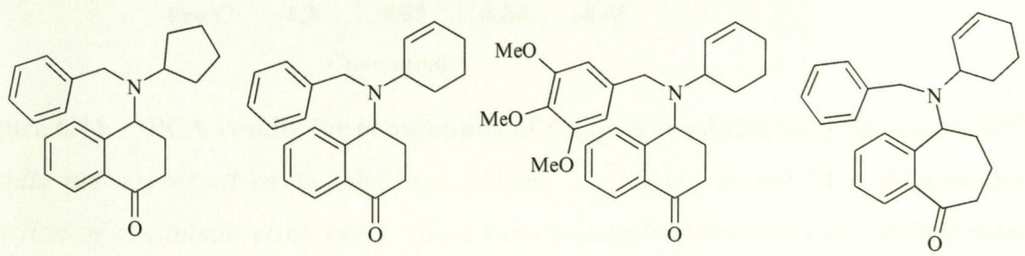



**Figure 6.10 PCA results for compounds of Chapters 2&3 soluble in 2.5% Tween 80**

*Results are expressed as % inhibition [Mean, +/- S.E.M.] of rat PCA induced by i.v. injection of ovalbumin (1mg rat$^{-1}$). Rats were passively sensitised with i.d. injections of antiserum (0.1ml site$^{-1}$) to ovalbumin and challenged i.v. 48 hours later.* ***P<0.05.**




**(2.16)** **(3.12)** **(3.14)** **(3.23)**

**Table 6.9 Summary statistics for PCA studies, group 3 compounds (a)**

| Compound | Mean $\Delta A_{620}$ | n | $\sigma_{(n-1)}$ | SEM | % Inhibition |
|---|---|---|---|---|---|
| Positive Control | 0.184 | 51 | 0.094 | 0.013 | |
| (**2.16**) | 0.248 | 15 | 0.125 | 0.032 | -35 |
| (**3.12**) | 0.133 | 12 | 0.059 | 0.017 | 28 |
| (**3.14**) | 0.060 | 18 | 0.073 | 0.017 | 67 |
| (**3.14**) (30 mins) | 0.260 | 15 | 0.089 | 0.023 | -41 |
| (**3.23**) | 0.127 | 15 | 0.082 | 0.021 | 31 |

Figure 6.11 shows the dimer compounds of Chapter 4 that were solubilised using Tween 80 for PCA studies. It is clear from the Figure that these dimer compounds all showed good inhibition of PCA, the benzylated compound (**4.63**) affording the highest level of protection at the dose level investigated. Substitution of the benzyl group on the tertiary nitrogen atom in (**4.63**) by electron donating groups (methyl or trimethoxy) did not cause loss of activity within these molecules. All results were statistically significant ($P<0.001$).

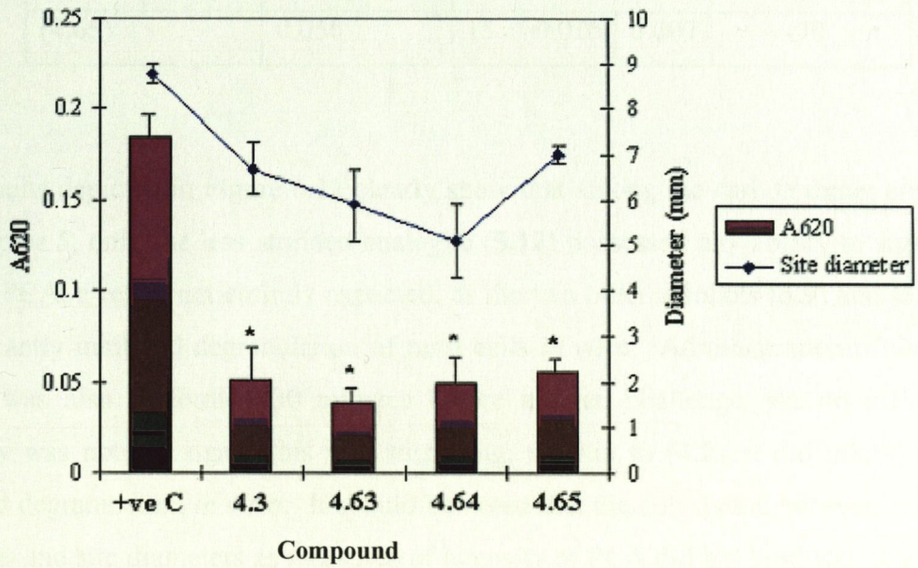
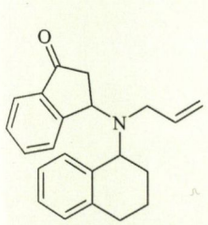
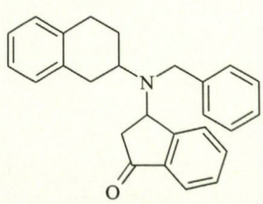



**Figure 6.11 PCA results for compounds of Chapter 4 soluble in 2.5% Tween 80**

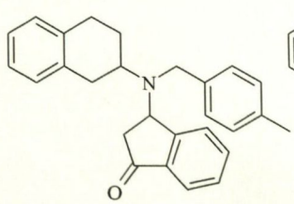
*Results are expressed as % inhibition [Mean, +/- S.E.M.] of rat PCA induced by i.v. injection of ovalbumin (1mg rat$^{-1}$). Rats were passively sensitised with i.d. injections of antiserum (0.1ml site$^{-1}$) to ovalbumin and challenged i.v. 48 hours later.* * *P<0.001.*



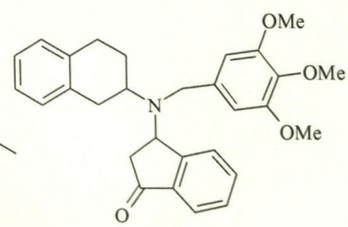

**(4.3)**




**(4.63)**




**(4.64)**




**(4.65)**

**Table 6.10 Summary statistics for PCA studies, group 3 compounds (b)**

| Compound | Mean $\Delta A_{620}$ | n | $\sigma_{(n-1)}$ | SEM | % Inhibition |
|---|---|---|---|---|---|
| Positive control | 0.184 | 51 | 0.094 | 0.013 | |
| (**4.3**) | 0.051 | 11 | 0.060 | 0.018 | 72 |
| (**4.63**) | 0.038 | 15 | 0.036 | 0.009 | 79 |
| (**4.64**) | 0.050 | 15 | 0.054 | 0.014 | 73 |
| (**4.65**) | 0.056 | 15 | 0.026 | 0.007 | 70 |

The results depicted in Figure 6.12 clearly show that among the carbon dimer compounds of Chapter 5, only the less strained analogue (**5.12**) possessed any ability to significantly inhibit PCA, a result not entirely expected, as the two other alcohols (**5.9**) and (**5.29**) both significantly inhibited degranulation of mast cells *in vitro*. Administration of the alcohol (**5.29**) was also performed 30 minutes before antigen challenge, yet no difference in efficacy was noted. Again this was surprising, as akin to (**4.2**), it did inhibit anti-IgE-induced degranulation *in vitro*. It should be noted that the correlation between absorbance readings and site diameters as measures of intensity of PCA did not hold well among these compounds; the sites tended to vary from intense compact sites to paler, more diffuse areas of skin. As these compounds all exhibited poor aqueous solubility, it may be that derivitisation to more soluble derivatives or conversion to pro-drugs may be beneficial in terms of bioavailability.

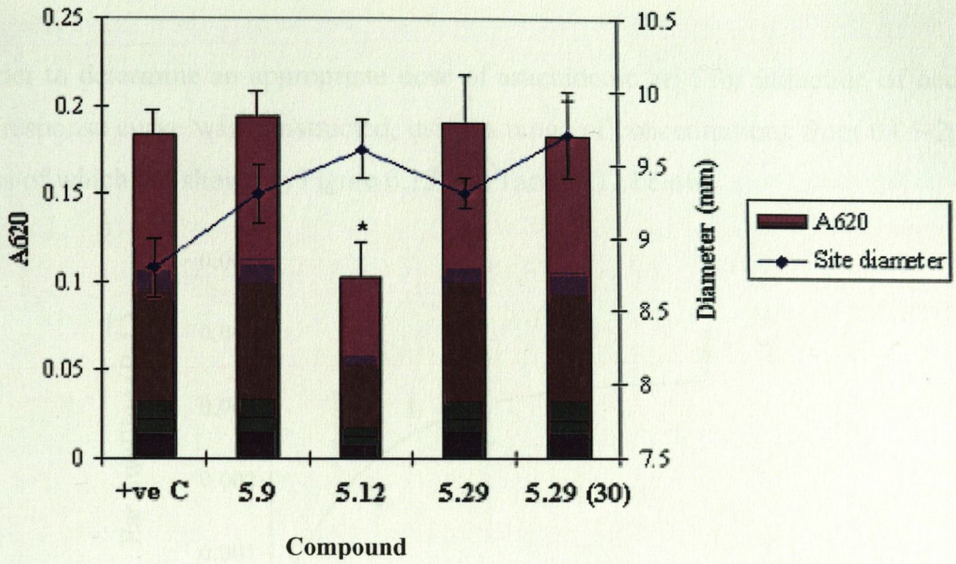
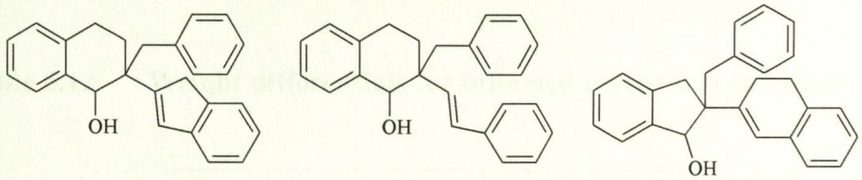



**Figure 6.12 PCA results for compounds of Chapter 5 soluble in 2.5% Tween 80**

*Results are expressed as % inhibition [Mean, +/- S.E.M.] of rat PCA induced by i.v. injection of ovalbumin (1mg rat$^{-1}$). Rats were passively sensitised with i.d. injections of antiserum (0.1ml site$^{-1}$) to ovalbumin and challenged i.v. 48 hours later.* ** P<0.001.*




**(5.9)** **(5.12)** **(5.29)**

**Table 6.11 Summary statistics for PCA studies, group 3 compounds (c)**

| Compound | Mean Δ $A_{620}$ | N | $\sigma_{(n-1)}$ | SEM | % Inhibition |
|---|---|---|---|---|---|
| Positive Control | 0.184 | 51 | 0.094 | 0.013 | |
| (**5.9**) | 0.194 | 15 | 0.053 | 0.014 | -5 |
| (**5.12**) | 0.103 | 15 | 0.073 | 0.019 | 44 |
| (**5.29**) | 0.190 | 12 | 0.097 | 0.028 | -3 |
| (**5.29**) (30 mins) | 0.182 | 12 | 0.077 | 0.022 | 1 |

### 6.3.6 Arachidonic acid-induced Mouse Ear Oedema

In order to determine an appropriate dose of arachidonic acid for induction of oedema, a dose response curve was constructed, using a range of concentrations from 0.05-2mg, the results of which are shown in Figure 6.13 and Table 6.12 below.

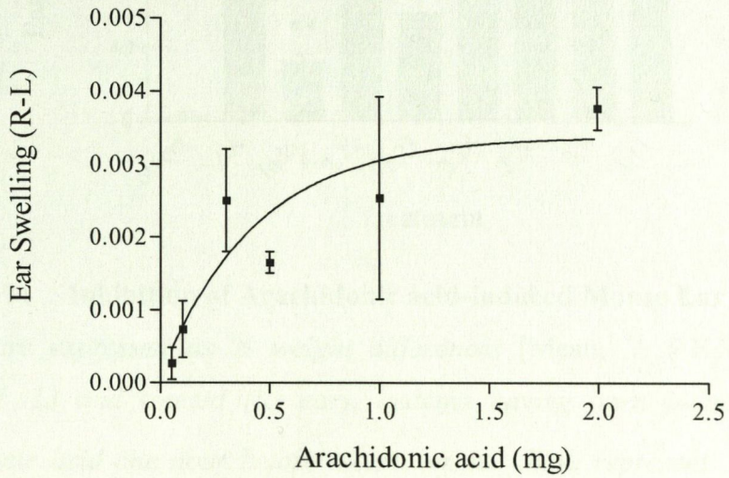



**Figure 6.13 Dose-response curve for Arachidonic acid**

**Table 6.12 Weight differentials for inflamed versus non-inflamed ears**

| Dose (mg) | Increase in Wt (R-L) (g) |
|---|---|
| 0 | 0.00045 |
| 0.05 | 0.0004 |
| 0.1 | 0.0011 |
| 0.3 | 0.0025 |
| 1.0 | 0.00253 |
| 2.0 | 0.00377 |

A dose of 1mg Arachidonic acid was selected to elicit the inflammatory response in the assay. Literature doses[136, 138] vary from 4mg $ear^{-1}$ applied 30 minutes after application of the test compounds to coapplication of drug with 0.5mg arachidonic acid. The raw experimental data used in the generation of Figures 6.14-6.17 and the statistical manipulations thereof are included in Appendix 3 on the accompanying CD-ROM.

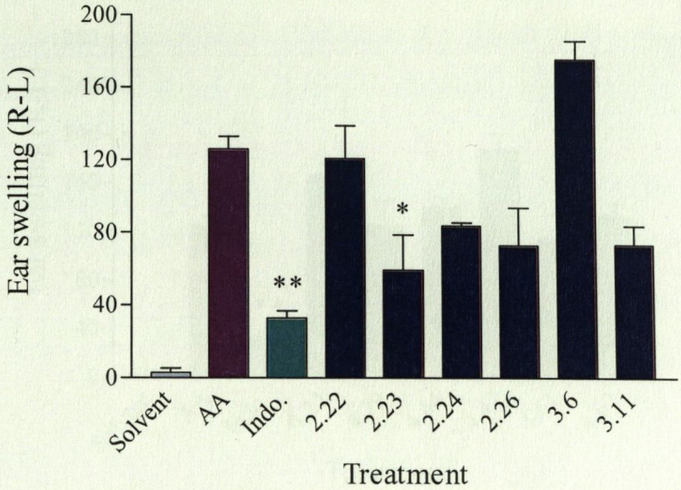



**Figure 6.14 Inhibition of Arachidonic acid-induced Mouse Ear Oedema (1)**

*Results are expressed as % weight differences* [Mean, +/- S.E.M.] *between untreated (L) and treated (R) ears, oedema having been induced by 1mg Arachidonic acid one hour before measurement. Bars represent* $\overline{X}$ *± S.E.M. from 5 animals.* **P<0.0001, *P<0.05.

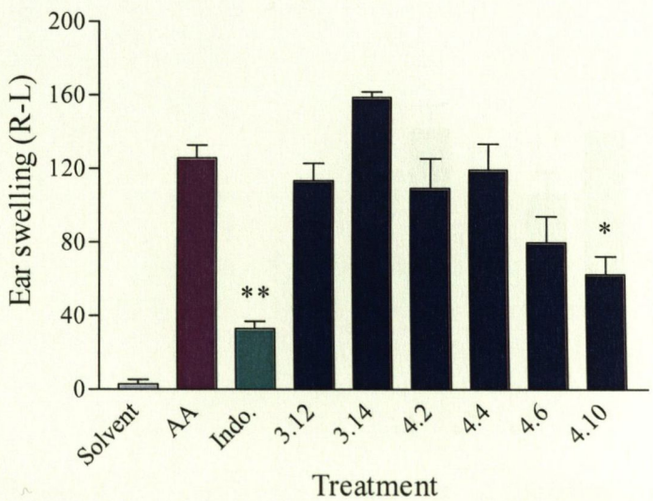



**Figure 6.15 Inhibition of Arachidonic acid-induced Mouse Ear Oedema (2)**

*Results are expressed as % weight differences* [Mean, +/- S.E.M.] *between untreated (L) and treated (R) ears, oedema having been induced by 1mg Arachidonic acid one hour before measurement. Bars represent* $\overline{X}$ *± S.E.M. from 5 animals.* **P<0.0001, *P<0.05.

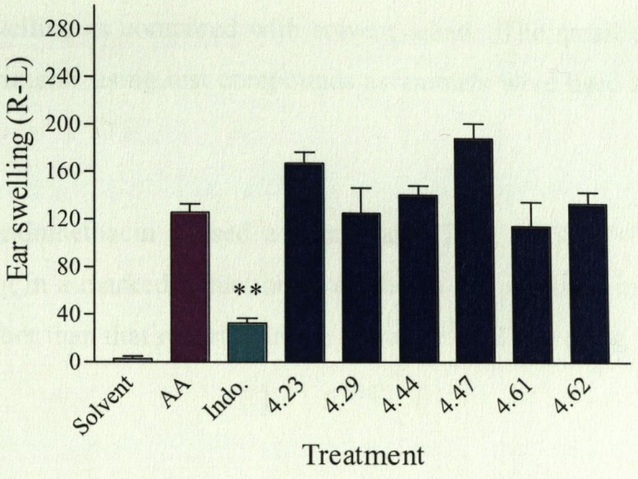



**Figure 6.16 Inhibition of Arachidonic acid-induced Mouse Ear Oedema (3)**

*Results are expressed as % weight differences* [Mean, +/- S.E.M.] *between untreated (L) and treated (R) ears, oedema having been induced by 1mg Arachidonic acid one hour before measurement. Bars represent* $\overline{X}$ *± S.E.M. from 5 animals.* **P<0.0001, *P<0.05.

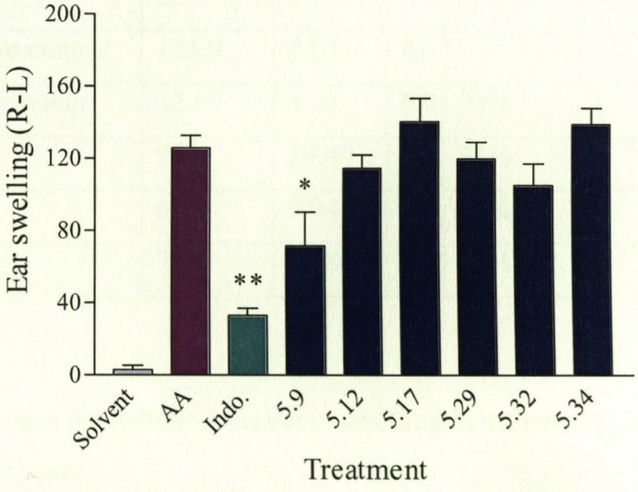



**Figure 6.17 Inhibition of Arachidonic acid-induced Mouse Ear Oedema (4)**

*Results are expressed as % weight differences* [Mean, +/- S.E.M.] *between untreated (L) and treated (R) ears, oedema having been induced by 1mg Arachidonic acid one hour before measurement. Bars represent* $\overline{X}$ *± S.E.M. from 5 animals.* **P<0.0001, *P<0.05.

It is clear from Figures 6.14-6.17 that application of arachidonic acid produced a marked degree of ear swelling as compared with solvent alone. The small effect of solvent was negated in experiments using test compounds as animals were used as their own controls (Section 6.2.5.1).

Application of indomethacin caused a significant (74%, n=68, P<0.0001) inhibition of oedema, resulting in a marked reduction in erythema and swelling index. This value was considerably higher than that reported in the literature[136] (21%, using 3mg arachidonic acid per ear).

Of the compounds tested, only three showed significant (P<0.05) reduction of arachidonic acid-induced oedema. These were the phenylacetamide (**2.23**), the tertiary dimer amine (**4.10**) and the alcohol (**5.9**). These results are summarised in Table 6.13 below.

**Table 6.13 Summary statistics for compounds with anti-inflammatory activity in the mouse ear model**

| Compound | $\overline{X}$* | S.E.M. | n | % Inhibition | P |
|---|---|---|---|---|---|
| Positive control | 125.9 | 7.03 | 61 | | |
| Indomethacin | 32.68 | 4.24 | 68 | 74% | <0.0001 |
| (**2.23**) | 59.4 | 19.49 | 5 | 53% | 0.0135 |
| (**4.10**) | 62.2 | 9.94 | 5 | 51% | 0.0165 |
| (**5.9**) | 71.2 | 18.86 | 5 | 43% | 0.0424 |

* represents the mean percentage increase in swelling in inflamed right ears, as compared to the control (left) ears.

## Synthesis of individual isomeric forms of compound (4.60)

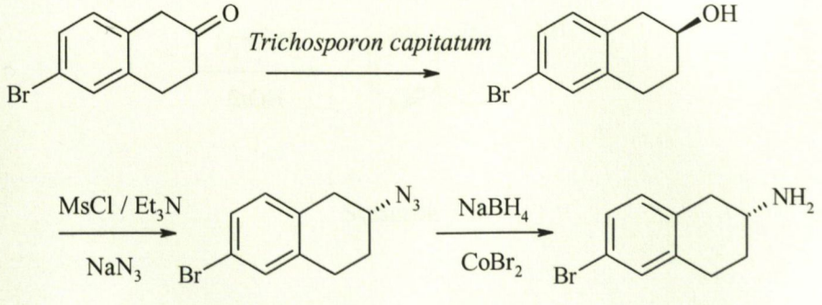
### 7.1 Introduction

As mentioned in Section 4.2, the dimeric compounds of that Chapter were tested as stereoisomeric mixtures, due to the general unavailability of individual enantiomeric forms of the starting materials and the difficulties in separating the product amines. However, on establishment of the promising anti-allergic activity of many of the compounds both *in vitro* (Section 4.7) and *in vivo* (Section 6.3.5), it was decided to attempt to devise a stereoselective synthesis for the most active series of compounds, the dimeric derivatives of 2-aminotetralin and 1-indanone, as discussed in Section 4.5.

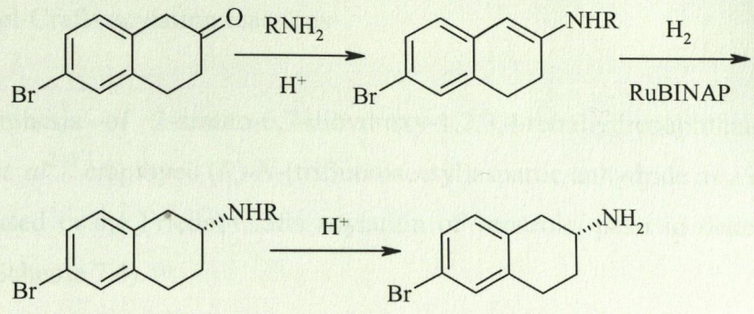
Several literature protocols exist for the synthesis of chiral 2-aminotetralins, notably methoxy-substituted compounds, as these derivatives have well-established neuropharmacological properties, notably activity at dopamine and 5-HT receptors (see Section 1.12). Established syntheses include the following:

1. Hydrogenation of an enamide derived from 2-tetralone

In a synthesis of a potent antiarrhythmic agent, MK-0499, two successful routes to chiral aminotetralins were developed: the first including a microbial reduction of a bromotetralone (Scheme 7.1) in high yield and retaining enantioselectivity; and the second, the hydrogenation of an enamine (Scheme 7.2) using a chiral BINAP catalyst[228]. Both methods afford the chiral amine, however the first requires access to cell cultures of *Trichosporon capitatum* and the second high pressure equipment.



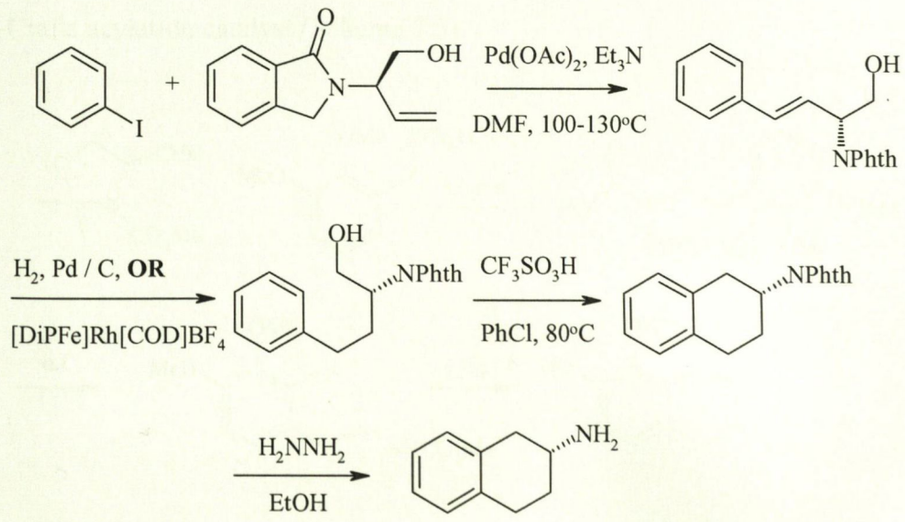

**Scheme 7.1**




**Scheme 7.2**

2. Cyclisation of chiral phthalimidovinylglycinol (PVG) derivatives

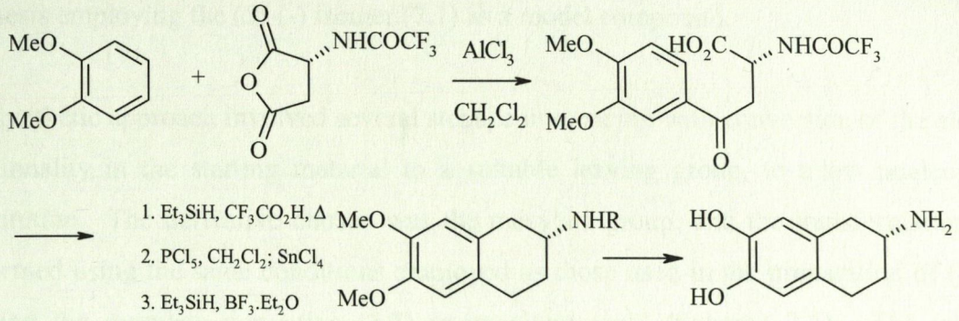
The key features of this synthesis[229] (Scheme 7.3) are the use of a specially prepared PVG derivative and its Heck coupling to an aromatic halide. The method requires special catalysts, however, for the palladium-catalysed allylic substitution reaction involved in the formation of the PVG component, namely, $(\eta^3C_3H_5PdCl)_2$, an (S,S)-diphenylphosphinonaphthoic acid derivative, and a soluble halide additive such as tetrabutylammonium (triphenylsilyl)difluorosilicate (TBAT).




**Scheme 7.3**

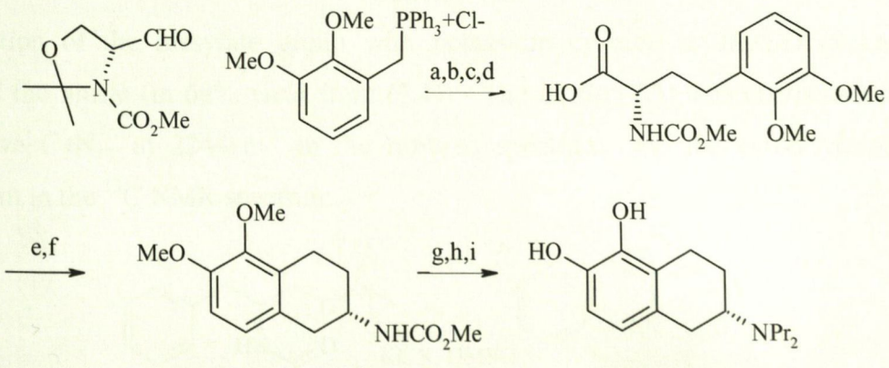
3. Friedel-Crafts acylation reactions

In their synthesis of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN), Nordlander *et. al*[230] employed (*R*)-*N*-(trifluoroacetyl)aspartic anhydride as a chiral synthon, which they used in the Friedel-Crafts acylation of veratrole, prior to deketonisation and cyclisation (Scheme 7.4).




**Scheme 7.4**

A similar approach was utilised by Baxter and co-workers in their synthesis of the potent $D_2$-receptor agonist, 5,6-$(HO)_2$DPAT[231]; however, substitution of veratrole for catechol using the methodology of Nordlander led to the regiosiomer 6,7-$(HO)_2$DPAT, necessitating the use of an alternative synthon. As a solution, Baxter *et. al* employed D- or L-serine to create a chiral aldehyde, a derivative of which was cyclised using $TiCl_4$ as intramolecular Friedel-Crafts acylation catalyst (Scheme 7.5).



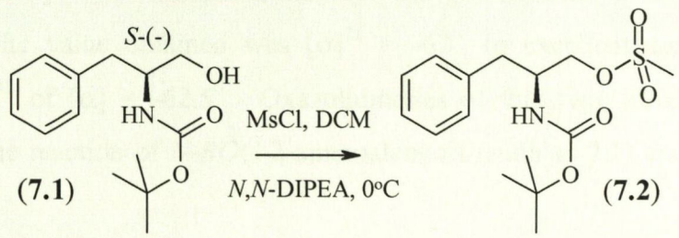

a) $K^+t$-$BuO^-$, THF, 0°C, 2hr, 100%. b) $H_2$, Pd / C, EtOAc, 2hr, 100%. c) TsOH, MeOH, R.T., 18hr, 84%. d) PDC, DMF, R.T., 6hr, 56%. e) $(COCl)_2$, cat. DMF, $CH_2Cl_2$, 0°C; $TiCl_4$, $CH_2Cl_2$, 0°C-R.T., 2hr, 80%. f) $Et_3SiH$, $BF_3.OEt_2$, R.T., 18hr, 59%. g) KOH, MeOH, $H_2O$, Δ, 18hr, 86%. h) $NaBH(OAc)_3$, EtCHO, HOAc, $ClCH_2CH_2Cl$, R.T., 2hr, 92%. i) $BBr_3$, $CH_2Cl_2$, R.T., 18hr, 89%.

**Scheme 7.5**

## 7.2 Synthetic strategy

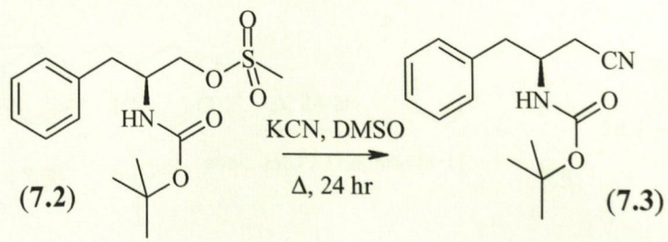
It was decided to adopt an approach exploiting several of the features of the third method outlined above. The starting material of choice was a phenylalanine derivative, 2-(*tert*-Butoxycarbonylamino)-3-phenyl-1-propanol, which is commercially available as the *BOC*-protected amino alcohol, in both (*S*)-(-) and (*R*)-(+) forms. It was decided to pursue the synthesis employing the (*S*)-(-) isomer (**7.1**) as a model compound.

The synthetic approach involved several steps, commencing with conversion of the alcohol functionality in the starting material to a suitable leaving group, to allow nucleophilic substitution. The derivative chosen was the mesylate group, and the transformation was performed using the same conditions employed as those used in the preparation of (**4.56**), yielding the mesylate derivative (**7.2**) in excellent yield (Scheme 7.6). The infrared spectrum of the mesylate contained diagnostic $S{=}O_{str}$ at 1346cm$^{-1}$, and the presence of the *S*-methyl group was noted by the singlet at 3.02ppm in the $^{1}$H NMR spectrum.



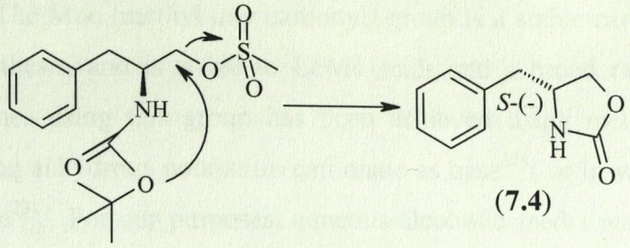

**Scheme 7.6**

Substitution of the mesylate group with potassium cyanide in DMSO (Scheme 7.7) afforded the nitrile (in 68% yield from (**7.1**)). The nitrile (**7.3**) was characterised by the distinctive $C{\equiv}N_{str}$ at 2244cm$^{-1}$ in the infrared spectrum, and the carbon resonance at 117.2ppm in the $^{13}$C NMR spectrum.




**Scheme 7.7**

A second product isolated from the reaction (24% yield) was an oxazolidinone (**7.4**), believed to have been formed through the following mechanism (Scheme 7.8).

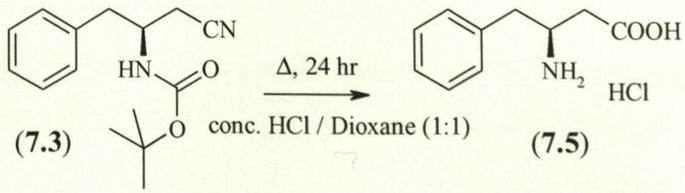



(7.4)

**Scheme 7.8**

Constant Wave decoupling experiments aided the structural elucidation of the oxazolidinone: irradiation of the multiplet at 4.09ppm resulted in simplification of the upfield methylene signal from a pair of double doublets to a pair of doublets, leaving only the geminal coupling; and simplification of the upfield multiplet at 4.35ppm, implying the methine group separated both methylenes. Similarly, irradiation of the amino proton resonance at 6.73ppm simplified the multiplet signal at 4.09ppm, reflecting the adjacent positioning of the amino proton to the methine. The $^{13}C$ NMR spectrum revealed a methylene signal at 69.0ppm, reflecting the downfield shift caused by an oxygen atom. The stereochemistry was confirmed to be the (*S*) isomer from optical rotation measurements; the value obtained was $[\alpha]^{22} = -62^{\circ}$, in excellent agreement with the literature value[232] of $[\alpha] = -62.5^{\circ}$. Oxazolidinones of this type have been previously prepared from the reaction of *N-BOC*-2-aminoalcohols (such as **7.1**) and thionyl chloride in THF[233].

Hydrolysis of the nitrile group was accomplished by refluxing in hydrochloric acid (Scheme 7.9), using dioxane as a cosolvent. Hydrolysis of (**7.3**) was sluggish, requiring 24 hours and concentrated acid, conditions that also cleaved the *BOC* group, thus affording the β-amino acid (**7.5**).




(7.3) (7.5)

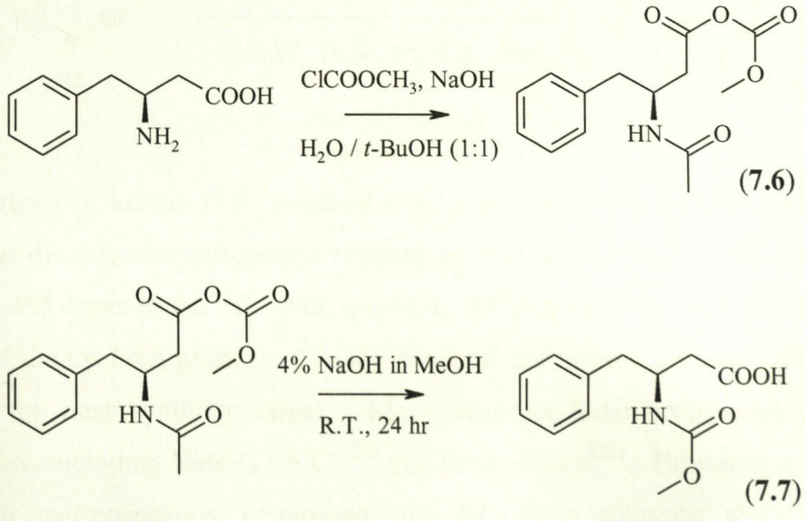
**Scheme 7.9**

The acid was readily identified by the extremely broad singlet of the acid proton at 8.17ppm in the $^{1}H$ NMR spectrum, and the acid carbonyl resonance at 172.3ppm in the $^{13}C$ NMR spectrum. Prior to cyclisation of the acid, the amino group had to be protected with

a suitable group. The Moc (methyl oxy carbonyl) group is a stable carbamate group used in amino acid synthesis, and is stable to Lewis acids and a broad range of pH values. Protection of amines using this group has been achieved using methyl chloroformate, either in THF, using anhydrous potassium carbonate as base[234]; or in water, using sodium bicarbonate as base[231]. For our purposes, aqueous alcoholic media was employed due to solubility considerations, and sodium hydroxide was used as base (Scheme 7.10).

After reaction overnight, TLC analysis showed the presence of two products, with that at higher $R_f$ predominating. Upon isolation of the less polar product, infrared and NMR spectral analysis revealed the presence of three carbonyl groups. These formed a broad band in the infrared spectrum around 1732cm$^{-1}$, while the $^1$H NMR spectrum contained two singlet peaks, each integrating for three protons, at 3.60 and 3.65ppm.

The $^{13}$C NMR spectrum contained a strong quaternary signal at 155.9ppm, corresponding to the degenerate resonances of the two carbonyl groups. The carbonyl of the carbamate moiety resonated downfield at 171.4ppm. The principal product was believed to be the anhydride (**7.6**), and the reaction mixture was treated with 4% methanolic sodium hydroxide overnight, during which time the upper product was gradually seen to disappear. Upon isolation of the lower spot, $^1$H NMR analysis revealed the product to be the desired amine-protected β-amino acid.




(**7.6**)

(**7.7**)

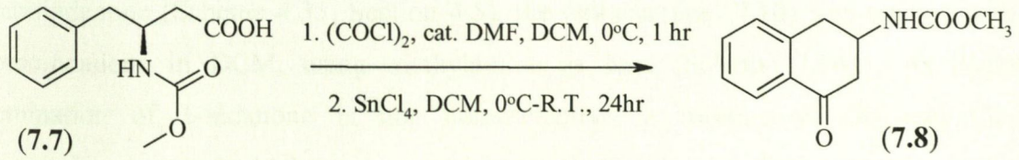
**Scheme 7.10**

The acid (**7.7**) exhibited broad C=O$_{str}$ at 1698cm$^{-1}$ in the infrared spectrum, and characteristic features of the $^1$H NMR spectrum were the singlet at 3.66ppm, corresponding

to the methyl protons of the carbamate moiety, and the broad singlet of the acid protons at 10.64ppm. The key features of the $^{13}C$ NMR spectrum were the two carbonyl groups; that of the carbamate moiety at 156.1ppm, and the carbon of the acid at 176.2ppm.

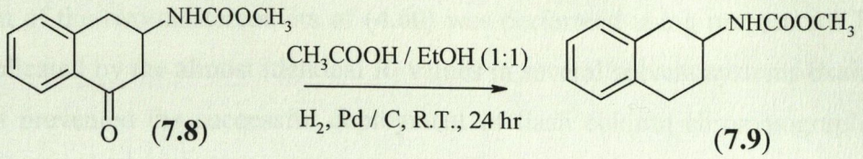
The key step in the synthesis was the Lewis acid-catalysed cyclisation of the acid intermediate (**7.7**). Activation of the acid moiety was accomplished by conversion to the acid chloride, using oxalyl chloride and DMF as catalyst in DCM (Scheme 7.11). Many Lewis acids may be employed in ring closure reactions of this nature, and titanium and tin tetrachlorides have found application in the intramolecular Friedel-Crafts acylation of catechol and veratrole derivatives, such as in the syntheses of ADTN[230] and 6,7-$(HO)_2$DPAT[231].

It was anticipated that cyclisation using a non-activated derivative such as (**7.7**) would prove to be more difficult. This was indeed found to be the case, as after 1 hour only 8% of the desired cyclised product (**7.8**) was obtained, as compared to the 80% reported by Baxter *et. al* after 2 hours. However, if the reaction was allowed to proceed overnight, slowly reaching room temperature, acceptable yields (45%) of the desired ketone were obtainable.




**Scheme 7.11**

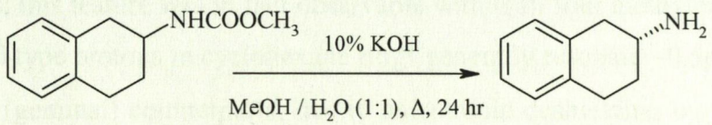
Infrared analysis of ketone (**7.8**) revealed $C{=}O_{str}$ at 1687cm$^{-1}$. The $^1H$ NMR spectrum revealed four discrete aromatic proton resonances, and the carbonyl of the ketone moiety resonated at 195.4ppm in the $^{13}C$ NMR spectrum. GCMS analysis confirmed the structure to be that of the cyclised product. Having obtained the ketone, removal of the carbonyl group was the next synthetic target. Many reagents have been employed for this transformation, including $NaBH_4$ / $AlCl_3$[235] and Raney nickel[236]. However, it was decided to use acidic hydrogenolysis, employing 10% Pd / C in ethanolic glacial acetic acid (Scheme 7.12). The reaction afforded the protected aminotetralin (**7.9**) in 66% yield.




**(7.8)** **(7.9)**

**Scheme 7.12**

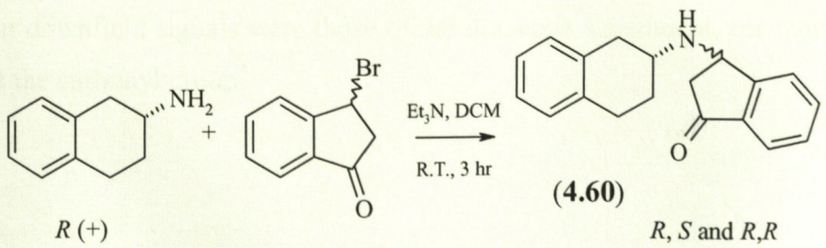
Deprotection of methyl carbamates has been performed using several reagents, including trimethylsilyl iodide[237], hydrogen bromide in acetic acid[238], or potassium hydroxide in methanol / water, the latter reagent being used on a tetralin molecule[239]. Potassium hydroxide in methanol / water was chosen; the reaction requiring reflux for 24 hours to cleave the carbamate (Scheme 7.13). The product, 2-aminotetralin (**7.10**), was isolated as a pale oil, and converted to the hydrochloride salt for analytical purposes.




**(7.9)** **(7.10)**

**Scheme 7.13**

Measurement of the optical rotation of the hydrochloride salt of (**7.10**) confirmed the product to be the (*R*) isomer, as the value of $[\alpha]^{22} = +66°$ was quite consistent with the literature value[240] of $[\alpha]^{17} = +72°$. Akin to the reaction of racemic 2-aminotetralin with 3-bromoindanone (Scheme 4.35, Section 4.5), the chiral amine (**7.10**) was reacted with 3-bromoindanone in DCM, using triethylamine as base (Scheme 7.14). As benzylic bromination of 1-indanone is not stereoselective, a mixture of (*R*) and (*S*) 3-bromoindanone resulted; thus upon reaction with (**7.10**), two diastereomeric forms of (**4.60**) were obtained. Nucleophilic substitution reactions of this nature are subject to complete inversion of stereochemistry in the substrate (in this case, the indanone substituent), due to backside attack of the nucleophile. The analytical data for the diasteromeric mix is presented in the Experimental Section and discussed in Section 4.5.




*R* (+) **(4.60)** *R*, *S* and *R*,*R*

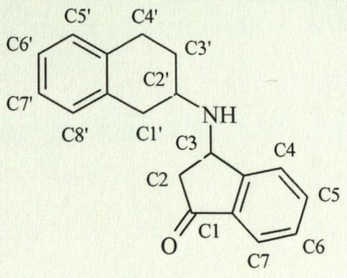
**Scheme 7.14**

Separation of the two diastereomers of (**4.60**) was performed using preparative TLC; this was complicated by the almost identical $R_f$ values in several solvent systems examined, an event that prevented the successful deployment of flash column chromatography. Small quantities of both diastereomers were isolated, and subject to analysis.

Figures 7.1 and 7.2 are the $^1$H NMR and TOCSY spectra of one of the two diastereomers isolated. In comparison with Figure 4.16, the spectra were considerably simplified. In the aliphatic region of Figure 7.1, the first of the four methylene groups resonated as two distinct multiplets, at 1.78 and 2.22ppm. These signals were complex due to coupling with both methylene and methine protons on either side, as illustrated by the TOCSY spectrum (Figure 7.2). It is interesting to note the considerable chemical shift differences of these geminal protons; this feature was in fact observable within all four methylene groups in the molecule. Axial type protons in cyclohexane rings generally resonate ~0.5ppm higher than their equatorial (geminal) counterparts, due to anisotropic deshielding by the $\sigma$–electrons in the $\beta$-$\gamma$ bonds. A broadened peak lying between the first two methylene protons, at 2.03ppm represented the amine proton; no correlation contours being observable for this signal in the HMQC spectra, as expected.

One of the methylene protons of the indanone moiety was considerably more deshielded than the other, the first proton signal of this residue a double doublet at 2.58ppm, and the second forming the most downfield segment of the complex 3-proton signal stretching from 2.98-3.11ppm. This latter signal contained one proton from each of three methylene groups; the two remaining protons of the benzylic methylene positions resonated at 2.72ppm (double doublet) and 2.89ppm (multiplet). The methine proton of the tetralin substituent resonated as a multiplet at 3.24ppm, while the double doublet of the indanone methine was located at 4.69ppm. The aromatic region of the $^1$H NMR spectrum was quite similar to that of (**4.60**), comprising a large signal integrating for four protons stretching from 7.08-7.15ppm, and four discrete downfield signals. Using Figure 7.2, it was evident that the four downfield signals were those of the indanone substituent, the most downfield that nearest the carbonyl group.

In the following discussion, the following numbering system was adopted:



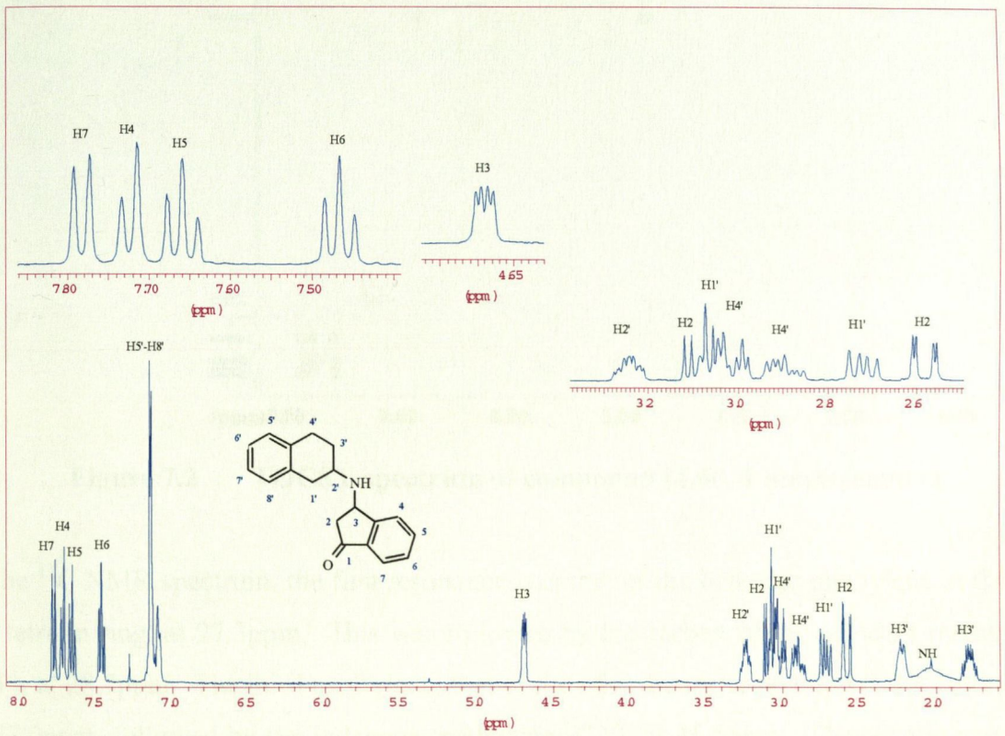




**Figure 7.1 $^{1}$H NMR spectrum of compound (4.60, 1 diastereomer)**

The $^{1}$H NMR spectrum of the second, more polar stereoisomer, generally resembled that of the isomer described above, although in the aliphatic region, the overlapping proton signals of three methylene groups showed slight differences, and in the aromatic region, where two of the indanone protons also overlapped.

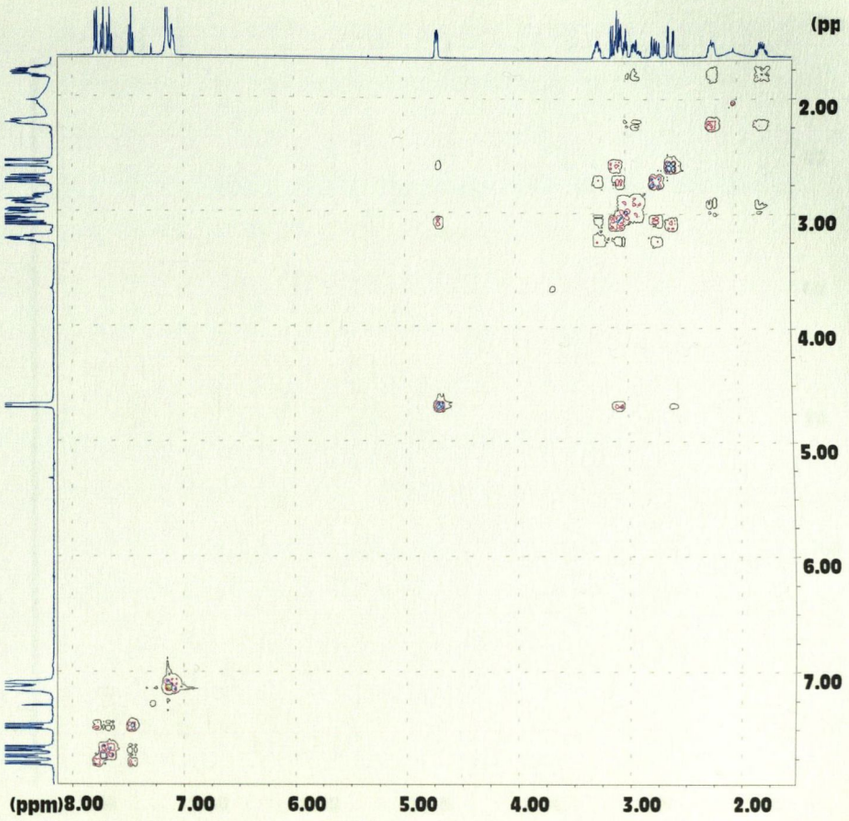



**Figure 7.2 TOCSY spectrum of compound (4.60, 1 diastereomer)**

In the $^{13}C$ NMR spectrum, the first resonance was that of the benzylic methylene at C4′ on the tetralin ring, at 27.3ppm. This was followed by the carbon of the adjacent methylene (C3′), at 28.7ppm. The third methylene, that of the other benzylic position (C1′), resonated at 37.0ppm, followed by the indanone methylene (C2′), at 45.5ppm. The tetralin methine carbon (C2′) resonated at 51.7ppm, while its indanone counterpart (C3) was further downfield, at 53.0ppm. With the aid of the HMQC spectrum (Figure 7.3) and a HMBC spectrum, many of the aromatic signals were assignable (see also Experimental Section). The carbonyl carbon (C1) resonated at 204ppm.

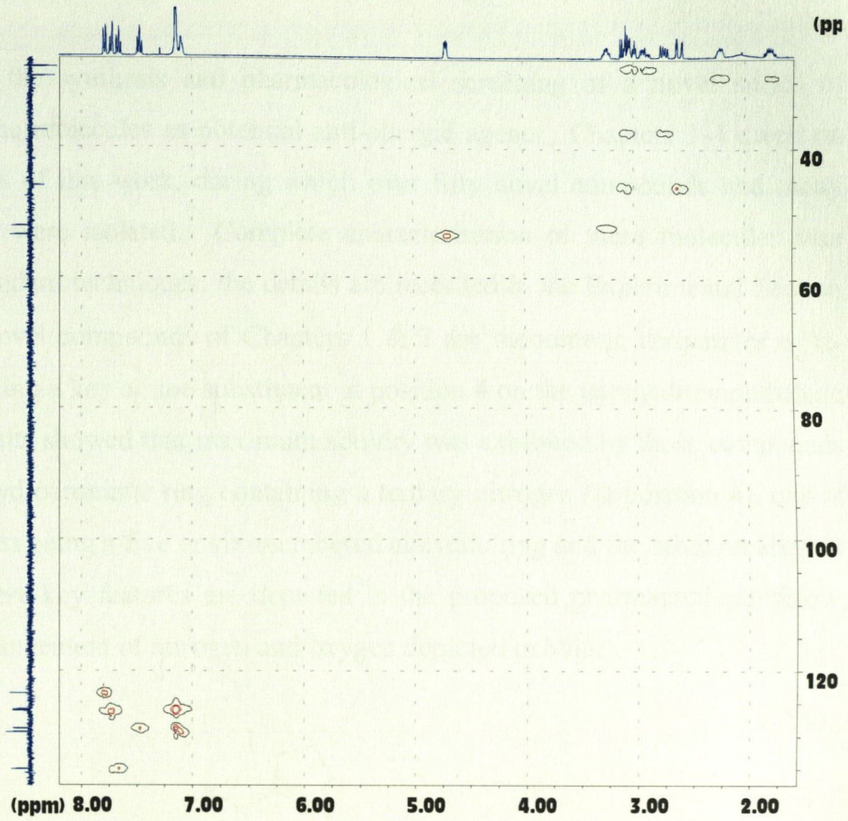
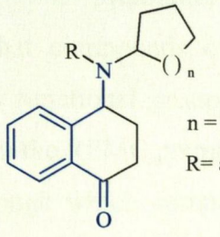



**Figure 7.3 HMQC spectrum of compound (4.60, 1 diastereomer)**

## Summary

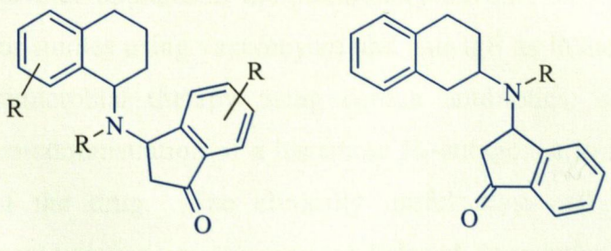
This thesis reports the synthesis and pharmacological screening of a novel series of tetrahydronaphthalene molecules as potential anti-allergic agents. Chapters 1-4 dwell on the synthetic aspects of this work, during which over fifty novel compounds and many novel intermediates were isolated. Complete characterisation of these molecules was performed using standard techniques; the details are recorded in the Experimental Section (*vide infra*). The novel compounds of Chapters 1 & 2 are monomeric derivatives of α-tetralone, all possessing a key amine substituent at position 4 on the tetrahydronaphthalene ring. Screening results showed that maximum activity was exhibited by those compounds possessing a rigid hydroaromatic ring containing a tertiary nitrogen (at position 4), one of the amine substituents being a five or six-membered alicyclic ring and the other an alkyl or benzyl moiety. These key features are depicted in the proposed pharmacophore below, with the key 1, 4 arrangement of nitrogen and oxygen depicted in blue:



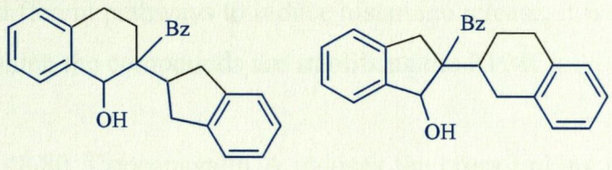

n = 1/2

R= alkyl/benzyl

The dimeric molecules of Chapter 4 further emphasised the importance of the nitrogen and oxygen loci within these novel molecules, but also demonstrated the retention of anti-allergic activity by tetralin-indan dimers. Both ring size and relative positioning of the nitrogen and oxygen atoms within the dimers were amenable to modification without loss of activity. The most active of the many various dimeric derivatives synthesised are shown below, again emphasising the important features by shading.



The novel molecules of Chapter 5 differed from those of preceding Chapters in that they did not possess and nitrogenous centre. The most active of these carbon-carbon bonded dimer compounds of tetralin and indan were those possessing two rigid hydroaromatic rings, one containing a secondary alcohol substituent. Ring-opened analogues exhibited less activity. *In vivo* activity of these compounds was disappointing, but this may be a reflection of their physicochemical properties, notably their poor solubility. The key features of these systems are depicted below:




From the results obtained during preliminary screening of the novel hydroaromatic compounds of Chapters 2-5, it is clear that several show potential as model compounds for further anti-allergic studies. The preliminary screen using Compound 48/80 as degranulating agent showed that compounds of diverse structural characteristics, but generally containing some key functional groups, possessed the ability to significantly inhibit mast cell degranulation in the RPMC preparation. It has been reported that the non-immunological mechanism through which compound 48/80 causes release of histamine from mast cells may be related to an increase in permeability of the lipid bilayer membrane of the cell. Inhibition of this mechanism may be one explanation for compounds exhibiting mast cell-stabilising properties. Substances akin to compound 48/80 are also reported to activate G proteins (see Section 1.13.1.1.1), and additional properties of compound 48/80 are thought to include increases in GTPase activity, cytosolic free calcium and phospholipase C activity.

One of the most active compounds in the preliminary screens, the nitrogen-linked dimer (**4.2**), was chosen for studies using vancomycin and anti-IgE as inducers of degranulation (Chapter 6). Antimicrobial therapy using certain antibiotics, notably vancomycin, routinely involves co-administration of a histamine $H_1$-antagonist to negate the histamine releasing effects of the drug. The clinically useful mast cell stabiliser, disodium cromoglycate, is unable to prevent vancomycin-induced degranulation, yet the nitrogen dimer (**4.2**) exhibited dose-dependent inhibition of release in the RPMC preparation.

In addition, this compound also inhibited mouse anti-rat IgE-induced histamine release, an effect that was demonstrated for three other novel compounds, notably the 2-aminotetralin derivative (**4.61**). Inhibition of anti-IgE-induced histamine release may be related to a reduction in cytokine production by cells participating in the allergic response.

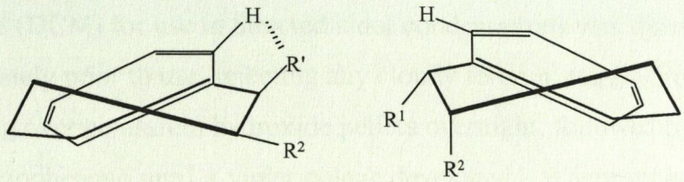
Certain compounds were selected for dose-response studies using the releasing agents Compound 48/80, concanavalin A and the calcium ionophore A23187. All compounds selected exhibited a dose-dependent inhibition of histamine release. As these releasing agents act through different pathways to induce histamine release, it is difficult to speculate on the manner by which the compounds are stabilising the RPMCs.

Unlike Compound 48/80, Concanavalin A induces the cross-linking of IgE molecules on the mast cell membrane, leading to the activation of the adenylate cyclase system, and subsequent histamine release. The intracellular [$Ca^{2+}$] is known to increase following antigen-antibody interactions, and selective ionophores such as A23187 have an important role in mechanistic studies. However, not all compounds capable of inhibiting A23187-induced degranulation, notably the *N*-benzylated compound (**3.9**), were successful inhibitors of anti-IgE-induced degranulation.

In the PCA studies of Chapter 6, several compounds caused statistically significant inhibition of the reaction. It became clear, however, that activity *in vitro* in the RPMC preparation did not necessarily predict usefulness in PCA *in vivo*. Of the many compounds having shown strong inhibitory effects *in vitro*, the one class of compounds that also showed consistent strong inhibition of PCA were the 2-aminotetralin derivatives, all of which were active, with the methylated compound (**4.61**) showing comparable activity to cromoglycate, which is known to produce excellent inhibition in the model.

In general, the results obtained for the arachidonic acid induced ear oedema model (also Chapter 6) were disappointing, especially given the reported success of prior workers with related indanone molecules. Five compounds from twenty-four tested did show significant reduction in erythema and swelling, but none approached the consistently excellent inhibition seen with the cyclooxygenase inhibitor, indomethacin, which showed consistent ability to prevent arachidonic acid-induced oedema.

Studies have shown the tetralin skeleton to exist in a 'twist half-chair' conformation[241], as depicted below. Substitution patterns have an important influence on relative configuration (pseudoaxial/pseudoequatorial). 1-Tetralones are also considered to exist in 'half-chair' conformations.




Greater conformational possibilities obviously exist for the dimeric compounds of this thesis. Many of the novel compounds were assayed as diastereomeric mixtures, and it would be desirable to elucidate the effects of stereochemical constraints on activity. The marked differences between the three dimensional structures of the diastereomers of some of the novel molecules was apparent from the sometimes widely varying chemical shifts in the NMR spectra of the diasteromers (as typified by compound (**4.44**), Figure 4.12). This has obvious significance with regard to interactions with an 'active site' *in vivo*. Therefore, the focus of Chapter 7 was the successful development of an asymmetric synthesis of the most active dimeric series of compounds. Preliminary alkylation experiments with methyl iodide confirmed the application of this asymmetric route towards the generation of single enantiomeric forms of the most active compounds of this study. A similar approach with the corresponding (*R*) (-) isomer of the starting material used in this Chapter would allow generation of the other two diastereomeric forms (*S*, *R* and *S*, *S*). In conclusion, several excellent potential mast cell-stabilising molecules of novel chemical structure have been synthesised and subjected to pharmacological testing. Future work to test individual isomers of the more active compounds and screening in human cells is planned, with emphasis on elucidating potential modes of action of these compounds.

## Chemistry Experimental

All solvents for synthetic work were of general reagent grade unless otherwise specified, and were distilled prior to use. Solvents were dried using standard procedures[242]: dichloromethane (DCM) for use in directed aldol condensations was distilled over calcium hydride immediately prior to use, rejecting any cloudy forerun; tetrahydrofuran (THF) was dried by standing over potassium hydroxide pellets overnight, followed by distillation over sodium and benzophenone until a violet colour developed. Where included in a reaction Scheme, the symbol Δ signifies that the reaction was heated under reflux.

Flash column chromatography was performed using Silica Gel, Grade 9385, 230-400 mesh, 60 • (Merck Laboratories). Typically, a glass column was packed with silica and saturated with hexane, and the crude reaction mixture/extract carefully pipetted onto the levelled silicaceous surface. A gradient elution technique was routinely employed; involving commencement of elution of solvent fractions with 200mls hexane as mobile phase, with gradual inclusion of increasing ethyl acetate concentrations (0.5% in the second 200mls, and thereafter doubling the concentration every 200mls of mobile phase). For Thin Layer Chromatographic (TLC) procedures, aluminium foil plates pre-coated with Silica Gel 60 $F_{254}$ were used (Merck Laboratories). Each collected aliquot from the column was monitored for the presence of reaction products by pipetting a sample (typically 10-20μL) onto a TLC plate, and developing alongside a suitably diluted sample of the crude reaction mixture/extract. TLC plates were visualised under ultraviolet light at 254nm. Aliquots containing the product(s) of interest, as inferred from the chromatographic profile of the reaction mixture, were combined and the solvent evaporated *in vacuo* to isolate the desired product, which was subject to further purification, such as recrystallisation, as necessary.

Data analysis was collected using the following techniques:

**Infrared Spectroscopy** (IR) of test samples was performed on a Perkin Elmer Paragon 1000 FT-IR. Solid samples were analysed using potassium bromide (KBr) discs, while oleaginous samples were analysed as films on sodium chloride (NaCl) plates, having dispersed the sample in carbon tetrachloride ($CCl_4$). Sample readings are recorded in reciprocal centimetres ($\upsilon max/cm^{-1}$).

**Nuclear Magnetic Resonance** (NMR) **Spectroscopy** was performed using a Bruker DPX-400 instrument, at 400.13MHz for proton ($^1$H) magnetic resonance and 100.61MHz for carbon ($^{13}$C) spectra. Spectral analysis was performed using Bruker WIN-NMR software. Samples were prepared in deuterated chloroform ($CDCl_3$) unless otherwise stated. Resonance positions in ppm were assigned relative to the $CHCl_3$ resonance at 7.27ppm for $^1$H spectra and 76.5, 76.8 and 77.2ppm for $^{13}$C spectra. Signal descriptions are abbreviated as follows: (s = singlet; d = doublet; t = triplet; dd = double doublet; dt = double triplet; ddd = double double doublet; q = quartet; m = multiplet; br. signifies a broad signal; Ar-C<u>H</u> signifies a proton attached directly to an aromatic ring; Ar-<u>C</u>H the carbon atom of an aromatic ring bearing a proton; and Ar-<u>C</u> a quaternary carbon of an aromatic ring). Diastereomeric compounds have $^{13}$C NMR data reported as paired signals.

**Melting points** of solid samples we re obtained using an Electrothermal apparatus, and are uncorrected.

**Optical rotations** were measured in an AA-10 Automatic Polarimeter, Optical Activity Ltd. Recordings are expressed as $[\alpha]^{t,}$ (c, solvent), where $\alpha$ is the rotation at temperature t, using a concentration c (g $ml^{-1}$) in a specified solvent.

**Gas chromatographic-Mass Spectral** (GCMS) samples were injected in splitless mode (as dilute solutions in acetonitrile) onto a GC capillary column (30 m x 0.25 mm i.d., Va 35MS) coupled to a Saturn 2000 MSD (EI 70 eV). The injector temperature and the GC-MS transfer line was held at 260°C and the column programmed from 100°C (3 min), rising to 300°C at 15°C per minute. Helium was used as carrier gas at a flow rate of 1ml/min. Data was reported as a fragmentation pattern with ion intensities relative to the most intense fragment ion.

**High Resolution Mass Spectroscopy** (HRMS) was performed using a Micromass LCT instrument, operating in $ES^+$ mode. Data analysis was performed using MassLynx software, Version 3.5. Instrument tolerance was 10ppm, and errors are reported in ppm.

Compounds were named using Advanced Chemical Development (ACD) software, Version 2.51.

**4-azido-1,2,3,4-tetrahydro-naphthalen-1-one (2.2)**

To a solution of α-tetralone (5g, 34.2mmol) in $CCl_4$ (50ml) was added *N*-bromosuccinimide (9.14g, 51.4mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and upon reaching reflux, the heat source was removed and replaced by two 240W lamps, the light from these focussed on the reaction, stirring vigorously all the time. On completion of the reaction a colour change from deep orange to clear was observed. The reaction was then filtered to remove the insoluble *N*-hydrosuccinimide, and the solvent removed *in vacuo*, using the lowest temperature possible. The residue (4-bromo-tetrahydro-naphthalen-1-one) (**2.1**) was very unstable to air and silica, preventing further purification and was used immediately. To a solution of (**2.1**) (3g, 13.3mmol) in DMF (5ml) was added sodium azide (8.6g, 133mmol). The resultant slurry was heated on an oil bath for 2 hours at 50°C, and then partitioned between water and ether. The aqueous layer was washed twice with ether (2 x 20ml portions) and the combined ethereal layers dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the azide as a yellow oil (2.73g, 89%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2944, 2100, 1686, 1600, 1455, 1283 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.20-2.28 (1H, m, 1H of C$\underline{H}_2$), 2.34-2.42 (1H, m, 1H of C$\underline{H}_2$), 2.60 (1H, ddd, $J_1$=11.0Hz, $J_2$=6.5Hz, $J_3$=4.5Hz, 1H of COC$\underline{H}_2$), 2.90 (1H, ddd, $J_1$=10Hz, $J_2$=10.0Hz, $J_3$=4.5Hz, 1H of COC$\underline{H}_2$), 4.75 (1H, dd, $J_1$=6.3Hz, $J_2$=3.8Hz, H of C$\underline{H}N_3$), 7.41-7.46 (2H, m, 2 x Ar-$\underline{H}$), 7.56-7.60 (1H, m, 1 x Ar-$\underline{H}$), 8.03-8.05 (1H, dd, $J_1$= 8.04 Hz, $J_2$ = 1Hz, 1 x Ar-$\underline{H}$); $^{13}$CNMR $\delta_C$ 28.1 ($\underline{C}H_2CHN_3$), 34.0 ($\underline{C}H_2CO$), 58.4 ($\underline{C}HN_3$), 127.2, 127.6, 128.7, 133.5 (4 x Ar-$\underline{C}$H), 131.1, 139.6 (2 x Ar-$\underline{C}$), 195.7 ($\underline{C}$=O).

**1,2,3,4,-Tetrahydro-naphthalen-1-ol (2.4)**

To a stirred solution of α-tetralone (5g, 34.2mmol) in methanol (10ml) at 0°C, was added sodium borohydride (1.9g, 51.4 mmol), over 5 minutes. The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alcohol (4.31g, 85%) as a colourless oil; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.77-1.85 (1H, m, $\underline{H}$ of $CH_2$), 1.88-1.95 (1H, m, $\underline{H}$ of $CH_2$), 1.96-2.06 (2H, m, C$\underline{H}_2$), 2.74-2.81 (1H, m), 2.84-2.93 (3H, m), 4.75-4.77 (1H, dd, J~4.5-

5Hz, C<u>H</u>), 7.14-7.18 (1H, m, Ar-C<u>H</u>), 7.23-7.28 (2H, m, Ar-C<u>H</u>), 7.45-7.49 (1H, m, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 18.6, 28.9, 31.8 (3 x <u>C</u>H$_2$), 67.5 (<u>C</u>H), 125.7, 127.0, 128.3, 128.5 (4 x Ar-<u>C</u>H), 136.7, 138.5 (2 x Ar-<u>C</u>).

**1,2,3,4-tetrahydro-1-naphthalenyl acetate (2.5)**

To a stirred solution of (**2.4**) (2.76g, 18.6mmol) in DCM (10ml) was added triethylamine (7.80ml, 55.9mmol) and acetic anhydride (3.51ml, 37.2mmol). To this solution a crystal of DMAP was added, and the solution stirred for two hours. On completion, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the acetate (3.13g, 88%) as a colourless oil, which slowly solidified on standing and had the following physical properties: IR (film) υmax/cm$^{-1}$ 2943, 1736, 1371, 1240, 1016 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.79-1.88 and 1.98-2.05 (4H, m, 2 x C<u>H</u>$_2$), 2.09 (3H, s, C<u>H</u>$_3$), 2.71-2.79 and 2.84-2.90 (2H, m, C<u>H</u>$_2$), 6.07 (1H, dd, J~4Hz, C<u>H</u>), 7.13 (1H, d, J=7.5Hz, Ar-C<u>H</u>), 7.18-7.26 (2H, m, 2 x Ar-C<u>H</u>), 7.34 (1H, d, J=7.5Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 18.5 (<u>C</u>H$_2$), 20.8 (<u>C</u>H$_3$), 28.5, 28.7 (2 x <u>C</u>H$_2$), 69.4 (<u>C</u>H), 125.6, 127.6, 128.6, 129.0 (4 x Ar-<u>C</u>H), 134.3, 137.4 (2 x Ar-<u>C</u>), 169.9 (<u>C</u>=O); MS, m/z, (RI) 148 (8), 131 (100).

**4-bromo-1,2,3,4-tetrahydro-1-naphthalenyl acetate (2.6)**

The procedure used for bromination of (**2.5**) was identical to that used in the synthesis of (**2.1**) although as catalyst, instead of dibenzoyl peroxide, 1,1'-Azobis (cyclohexane carbonitrile) (ACN) was used, giving better yields. After filtration to remove the insoluble succinimide by-product, the eluant was concentrated *in vacuo* and purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the benzylic bromide (0.83g from 1g (**2.5**), 59%). The bromide was isolated as a pale yellow oil, with the following physical properties: IR (film) υmax/cm$^{-1}$ 2960, 1732, 1438, 1370, 1236, 1025, 964 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.05 and 2.18 (3H, 2 x s, C<u>H</u>$_3$), 2.03-2.12, 2.24-2.34, 2.42-2.52 (4H, m, 2 x C<u>H</u>$_2$), 5.50 and 5.61 (1H, 2 x broad m, BrC<u>H</u>CH$_2$), 6.07 (1H, m, OC<u>H</u>CH$_2$), 7.25-7.35 (3H, m, 3 x Ar-C<u>H</u>), 7.42 (1H, m, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 20.9 x 2 (<u>C</u>H$_3$), 24.4 and 25.2 (<u>C</u>H$_2$), 27.9 and 30.7 (<u>C</u>H$_2$), 49.4 and 49.8 (Br<u>C</u>HCH$_2$), 67.7 and 69.7 (O<u>C</u>HCH$_2$), 127.3, 127.8, 128.3, 128.5, 128.6, 130.1, 130.1, 130.2 (4 x Ar-<u>C</u>H), 132.8 and 134.2, 137.0 and 137.1 (2 x Ar-<u>C</u>), 169.8 and 170.4 (<u>C</u>=O).

**4-(cyclopentylamino)- 1,2,3,4-tetrahydro-1-naphthalenyl acetate (2.7)**

To a solution of (**2.6**) (0.83g, 3.08mmol) in DCM (10ml) was added cyclopentylamine (0.60ml, 6.16mmol) and triethylamine (0.86ml, 6.16mmol). The reaction was refluxed for 9 hours, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the amine (0.25g, 30%) a brown oil, as a diastereomeric mixture, with the following physical properties: IR (film) υmax/$cm^{-1}$ 2954, 2867, 1733, 1452, 1371, 1240 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.27-2.12 (12H, overlapping m, 4 x cyclopentyl C$\underline{H}_2$ and 2 x tetralin C$\underline{H}_2$), 2.07 and 2.09 (3H, 2 x s, overlapping, C$\underline{H}_3$), 3.29 and 3.35 (1H, 2 overlapping quintets, J=6.4Hz, NC$\underline{H}$ cyclopentyl), 3.75 and 3.86 (1H, 2 x t, J=5.3Hz, NC$\underline{H}$Ar), 5.95 and 6.02 (1H, 2 x t, J=5.0Hz, OC$\underline{H}$), 7.20-7.30 (3H, m, 3 x Ar-CH), 7.38 and 7.55 (1H, 2 x d, J=7.5Hz, COOAr-CH); $^{13}$CNMR $\delta_C$ 20.9 (C$\underline{H}_3$), 23.4, 23.5 x 2, 23.8, 24.4, 25.4, 25.6 (4 x cyclopentyl C$\underline{H}_2$), 32.8, 33.8, 33.9 (2 x tetralin C$\underline{H}_2$), 52.9 and 53.4 (NC$\underline{H}$), 56.7 and 56.9 (NC$\underline{H}$Ar), 69.3 and 69.9 (OC$\underline{H}$Ar), 126.5 and 126.7 (Ar-C$\underline{H}$), 127.7, 127.9, 128.2, 128.5, 128.8 (3 x Ar-C$\underline{H}$), 134.1 and 134.4, 140.2 and 140.7 (2 x Ar-C$\underline{}$), 170.1 and 170.2 (C$\underline{}$=O); MS, m/z, (RI) 274 (M+1, 25), 213 (100), 185 (5), 129 (13), 86 (14).

**4-(cyclopentylamino)- 1,2,3,4-tetrahydro-1-naphthalenone (2.9)**

To a solution of the amine acetate (**2.7**) (0.25g, 0.92mmol) in methanol/water (10ml, 1:1) was added excess potassium carbonate (0.25g, 1.83mmol). The reaction was heated under reflux for 1 hour, monitoring by GCMS. On completion, the reaction was filtered and the solvent removed *in vacuo*, using toluene to azeotropically distill any residual water. To the residue containing the alcohol (**2.8**) thus obtained, (0.14g, 60%) was added acetone (10ml) and Jones reagent (1.4ml), the latter added drop-wise over 30 minutes to the ice-cooled reaction. On appearance of the green $Cr_2(SO_4)_3$, anhydrous sodium sulphate (0.30g, 2.12mmol) was added. After 2 hours, the solvent was evaporated, and the reaction separated using ether/water. After three washings with ether (3 x 20ml), the combined organic extracts were filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 1:1) to yield the amine as a brown oil, which crystallised slowly on standing (83mg, 60%). IR (film) υmax/$cm^{-1}$ 2955, 2868, 1689, 1600, 1453, 1284 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$; 1.35 (2H, m, C$\underline{H}_2$), 1.53 (2H, m, C$\underline{H}_2$), 1.69 (2H, m, C$\underline{H}_2$), 1.77-1.92 (2H, m, C$\underline{H}_2$), 2.04 and

2.24 (2H, 2 x m, $COCH_2C\underline{H}_2$), 2.49 (1H, ddd, $J_1$=11.5Hz, $J_2$=7Hz, $J_3$=4.5Hz, 1H of $C\underline{H}_2CO$), 2.94 (1H, ddd, $J_1$=14.5Hz, $J_2$=10.0Hz, $J_3$=4.5Hz, 1H of $C\underline{H}_2CO$), 3.25 (1H, quintet, J=6.5Hz, $CH_2C\underline{H}CH_2$), 3.91 (1H, dd, $J_1$=6.0Hz, $J_2$=3.5Hz, $C\underline{H}CH_2CH_2CO$), 7.29 (1H, m, Ar-C<u>H</u>), 7.47 (2H, m, 2 x Ar-C<u>H</u>), 7.95 (1H, d, J=7.5Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 23.4, 23.5, 28.2, 32.9, 33.6, 34.5 (5 x $\underline{C}H_2$), 53.5, 56.9 (2 x <u>C</u>H), 126.6, 127.0, 127.6 (3 x Ar-<u>C</u>H), 131.4 (Ar-<u>C</u>), 133.0 (Ar-<u>C</u>H), 146.1 (Ar-<u>C</u>), 197.6 (<u>C</u>=O); MS, m/z, (RI) 230 (M+1, 100), 229 ($M^+$, 44), 115 (4); HRMS (+$H^+$) 230.1561, $C_{15}$ $H_{20}$ N O requires 230.1545; error 7.2ppm.

**methyl 4-phenylbutanoate (2.11)**

To a stirred solution of 4-phenylbutyric acid (5g, 30.5mmol) in methanol (50ml) was added a catalytic amount of concentrated HCl. The reaction was stirred at room temperature for two hours. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the methyl ester (4.94g, 91%) as a colourless oil, with the following physical properties: IR (film) υmax/$cm^{-1}$ 3028, 2952, 1740, 1205$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.01 (2H, quintet, J=7.5Hz, $CH_2C\underline{H}_2CH_2$), 2.37 (2H, t, J=7.5Hz, $ArC\underline{H}_2$), 2.70 (2H, t, J=7.5Hz, $C\underline{H}_2CO$), 3.69 (3H, s, $C\underline{H}_3$), 7.24 (3H, m, 3 x Ar-C<u>H</u>), 7.33 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 26.1 ($\underline{C}H_2$), 32.9 ($\underline{C}H_2$), 34.7 ($\underline{C}H_2$), 50.9 ($\underline{C}H_3$), 125.5 (Ar-<u>C</u>H), 127.9 (2 x Ar-<u>C</u>H), 128.0 (2 x Ar-<u>C</u>H), 141.0 (Ar-<u>C</u>), 173.2 (<u>C</u>=O); MS, m/z, (RI) 178 ($M^+$, 3), 147 (100), 104 (12).

**methyl 4-bromo-4-phenylbutanoate (2.12)**

To a solution of (**2.11**) (1.92g, 10.8mmol) in $CCl_4$ (30ml) was added *N*-bromosuccinimide (2.88g, 16.2mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and upon reaching reflux, the heat source was removed and replaced by two 240W lamps, the light from these focussed on the reaction, stirring vigorously all the time. The reaction was filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the brominated product as a yellow oil (1.88g, 68%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 3033, 2953, 1736, 1438, 1254$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.42-2.64 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.68 (3H, s, $C\underline{H}_3$), 5.06 (1H,

m, CHBr), 7.28-7.38 (3H, m, 3 x Ar-CH), 7.42 (2H, m, 2 x Ar-CH); $^{13}$CNMR $\delta_C$ 32.1 ($CH_2$), 34.6 ($CH_2$), 51.2 ($CH_3$), 53.8 (CHBr), 126.8 (2 x Ar-CH), 128.1 (Ar-CH), 128.3 (2 x Ar-CH), 141.0 (Ar-C), 172.3 (C=O); MS, m/z, (RI) 177 (100), 117 (17).

**4-(cyclopentylamino)-4-butanoic acid (2.13)**

To a stirred solution of (**2.12**) (2g, 7.78mmol) in DCM was added cyclopentylamine (1.53ml, 15.6mmol) and triethylamine (2.1ml, 15.1mmol). The reaction was stirred at room temperature for five days, during which time additional triethylamine (1.2ml, 8.6mmol) was added. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield a mixture of the ester and acid. $^1$H NMR analysis revealed only three clearly distinguishable signals among the mixture; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 3.52 (s, $CH_3$ of ester), 3.96 (quintet, J=8.5Hz, $CH_2CHCH_2$ of acid), 4.63 (dd, $J_1$=8.2Hz, $J_2$=3.2 Hz, NCHAr of acid). Due to the unequal composition, all $^{13}$C signals were assignable: $^{13}$CNMR $\delta_C$ (ester) 23.3, 23.3, 30.6, 32.0, 32.6, 33.3 (6 x $CH_2$), 50.9 ($CH_3$), 56.3 (CH), 60.4 (CH), 126.5 (Ar-CH), 126.6 (2 x Ar-CH), 127.9 (2 x Ar-CH), 143.2 (Ar-C), 173.4 (C=O). $^{13}$CNMR $\delta_C$ (acid) 22.8, 23.2, 28.4, 28.9, 28.9, 29.7 (6 x $CH_2$), 54.3, 61.3 (2 x CH), 125.4 (2 x Ar-CH), 127.2 (Ar-CH), 128.3 (2 x Ar-CH), 142.9 (Ar-C), 175.2 (C=O). Upon heating with excess polyphosphoric acid on a steam bath, no cyclisation to the tetralone was observed.

**4-cyano-4-phenylbutanoic acid**

To a stirred solution of (**2.12**) (1g, 3.9mmol) in DMSO (5ml) was added potassium cyanide (1g, 15.4mmol). The reaction was stirred under reflux for two days. The solvent was then removed by partitioning between water and ether, and the ethereal layers concentrated *in vacuo*. Crude $^1$H NMR analysis revealed a mixture of the ester and acid. The mixture was subsequently treated with a 10% solution of sodium bicarbonate and methanol (1:1), and gently heated for two hours. After filtration and removal of the solvent, the residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the acid: IR (film) $\upsilon$max/cm$^{-1}$ 3034, 2942, 2245, 1712, 1456, 1249cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.23 (2H, dd, $J_1$~16Hz, $J_2$=7.3Hz, $CH_2$), 2.54 (2H, m, $CH_2$), 3.99 (1H, t, J=7.5Hz, CH), 7.35-7.40 (5H, m, 5 x Ar-CH), 9.24 (1H, broad s, COOH); $^{13}$CNMR $\delta_C$ 30.0, 30.4 (2 x $CH_2$), 35.8 (CH), 119.8 (C≡N), 126.9 (2 x Ar-CH), 128.0

(Ar-CH), 128.8 (2 x Ar-CH), 134.4 (Ar-C), 177.1 (C=O). Upon heating with excess polyphosphoric acid on a steam bath, no cyclisation to the tetralone was observed.

**4-[cyclopentyl(methyl)amino]- 1,2,3,4-tetrahydro-1-naphthalenone (2.14)**

To a solution of (**2.9**) (50mg, 0.22mmol) in acetone (10ml) was added methyl iodide (0.07ml, 1.1mmol) and anhydrous potassium carbonate (0.15g, 1.1mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (50mg, 94%); IR (film) υmax/cm$^{-1}$ 2958, 2873, 2791, 1691, 1598, 1453, 1285cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.47-1.65 (4H, m, 2 x $CH_2$), 1.74 (2H, m, $CH_2$), 1.89 (2H, m, $CH_2$), 1.97-2.07 (1H, m, 1H of $CH_2CH_2CO$), 2.15 (3H, s, $CH_3$), 2.24-2.30 (1H, m, 1H of $CH_2CH_2CO$), 2.54 (1H, ddd, $J_1$=17.5Hz, $J_2$=14.0Hz, $J_3$=4.5Hz, 1H of $CH_2CO$), 2.86 (1H, irr. ddd, $CH_2CO$), 3.06 (1H, quintet, J=7.5Hz, $CH_2CHCH_2$), 4.21 (1H, dd, $J_1$=11.4Hz, $J_2$=4.0Hz, ArCHN), 7.33 (1H, dd, $J_1$=8.2Hz, $J_2$=7.5Hz, Ar-$C_{(7)}$H), 7.56 (1H, dd, $J_1$=8Hz, $J_2$=7.5Hz, Ar-$C_{(6)}$H), 7.90 (1H, d, J=8.0Hz, Ar-$C_{(5)}$H), 8.02 (1H, d, J=8.0Hz, Ar-$C_{(8)}$H); $^{13}$CNMR $\delta_C$ 21.8, 23.8, 23.9, 30.8, 31.7 (4 x cyclopentyl $CH_2$ and $CH_2CHN$), 34.6 ($CH_3$), 38.1 ($CH_2CO$), 60.1 (CH), 63.0 (CH), 126.3, 126.6, 127.1 (3 x Ar-CH), 132.4 (Ar-C), 133.1 (Ar-CH), 146.3 (Ar-C), 197.5 (C=O); MS, m/z, (RI) 244 (M+1, 100), 243 ($M^+$, 61), 214 (45), 186 (11), 146 (18), 100 (49); HRMS (+$H^+$) 244.1682, $C_{16}$ $H_{22}$ N O requires 244.1701; error -8.0ppm.

**4-[allyl(cyclopentyl)amino]- 1,2,3,4-tetrahydro-1-naphthalenone (2.15)**

To a solution of (**2.9**) (50mg, 0.22mmol) in acetone (10ml) was added allyl iodide (0.10ml, 1.1mmol) and anhydrous potassium carbonate (0.15g, 1.1mmol). The reaction was stirred at room temperature for 4 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (35mg, 60%). IR (film) υmax/cm$^{-1}$ 2957, 2869, 1692, 1598, 1550, 1452, 1284cm$^{-1}$; MS, m/z, (RI) 270 (M+1, 25), 269 ($M^+$, 34), 227 (67), 126 (100); HRMS (+$H^+$) 270.1866, $C_{18}$ $H_{24}$ N O requires 270.1858; error 3.1ppm.

NMR

| Label | $\delta^{13}C$ (ppm) | $\delta^{1}H$ (ppm), mult, J (Hz) | TOCSY (H-H) | HMQC (C-H) | NOE |
|---|---|---|---|---|---|
| 1 | 197.3 | - | | | |
| 2 | 38.2 | 2.54, ddd, 16.5, 14.5, 4.5 / 2.86, irr. ddd | H3 x 2, H2 x 1 H3 x 2, H2 x 1 | H2 x 2 | H2 |
| 3 | 25.0 | 1.98, m / 2.34, m | H3 x 1, H2 x 2, H4 / H3 x 1, H2 x 2, H4 | H3 x 2 | |
| 4 | 58.1 | 4.21, dd, 11.6, 3 | H3 x 2 | H4 | H2, H3 |
| 5 | 126.9 | 7.94, d, 8 | H6, H7 | H5 | H6 |
| 6 | 133.1 | 7.58, dd, 8.2, 7.5 | H7, H5, H8 | H6 | H5, H7 |
| 7 | 126.3 | 7.34, dd, 8, 7.5 | H5, H6, H7 | H7 | |
| 8 | 126.7 | 8.03, d, 8 | H6, H7 | H8 | H7 |
| 9 | 59.7 | 3.13, q, 7.9 | H10-H13 | H9 | |
| 10-13 | 23.2, 24.2 28.3, 31.5 | 1.34-1.67, m, (7H) 1.85, m, (1H) | H10-H13, H9 | H11, H12 H10, H13 | |
| 14 | 49.3 | 3.22, m / 3.35, m | H15, H16 | H15, H16 | H15, H16 |
| 15 | 138.1 | 5.92, m | H14, H16 | H15 | H16 |
| 16 | 115.3 | 5.07, 5.22, 2 x d, 17.3, 10.4 | H14, H15 | H16 | H15 |

**4-[benzyl(cyclopentyl)amino]- 1,2,3,4-tetrahydro-1-naphthalenone (2.16)**

To a solution of (**2.9**) (57mg, 0.25mmol) in acetone (10ml) was added benzyl bromide (0.17ml, 1.25mmol) and anhydrous potassium carbonate (0.17g, 1.25mmol). The reaction was stirred at room temperature for 4 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as brown crystals (44mg, 55%). IR (film) $\upsilon max/cm^{-1}$ 2956, 2869, 1691, 1597, 1452, 1284 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.39 (1H, m, 1H of $C\underline{H}_2$), 1.55-1.73 (6H, m, 6H of 4 x $C\underline{H}_2$), 1.93-2.06 and 2.42-2.52 (2H and 2H, 2 x m, 1H of $C\underline{H}_2$ cyclopentyl, 2H of $C\underline{H}_2CH_2CO$ and 1H of $C\underline{H}_2CO$), 2.88 (1H, m, 1H of $C\underline{H}_2CO$), 3.20 (1H, quintet, J=7-8Hz, $CH_2C\underline{H}CH_2$), 3.80 and 3.97 (2H, dd, J=14.5Hz, $NC\underline{H}_2$), 4.03 (1H, dd, $J_1$=12Hz, $J_2$=3.5Hz, $C\underline{H}CH_2CH_2CO$), 7.26 (1H, dd, $J_1$=8.1Hz, $J_2$=7.5Hz, Ar-C<u>H</u>), 7.33-7.37 (3H, m, 3 x Ar-C<u>H</u>), 7.51 (2H, m, 2 x Ar-C<u>H</u>), 7.62 (1H, ddd, $J_1$=8.5Hz, $J_2$=7.5Hz, $J_3$=1Hz, Ar-C<u>H</u>), 8.03 (2H, m, 2 x Ar-C<u>H</u>); $^{13}C$NMR $\delta_C$ 23.7, 25.1, 25.3, 27.8, 32.1 (4 x $\underline{C}H_2$ cyclopentyl and $\underline{C}H_2CH_2CO$), 38.6 ($\underline{C}H_2CO$), 49.9 ($N\underline{C}H_2$), 58.1, 59.2 (2 x $\underline{C}H$), 126.4, 126.5, 126.8, 127.9, 127.9 (8 x Ar-$\underline{C}H$), 132.6 (Ar-$\underline{C}$), 133.2 (Ar-$\underline{C}H$), 140.5, 146.9 (2 x Ar-$\underline{C}$), 197.3 ($\underline{C}$=O); MS, m/z, (RI) 320

(M+1, 42), 319 ($M^+$, 27), 290 (29), 228 (36), 177 (100); HRMS ($+H^+$) 320.1997, $C_{22}$ $H_{26}$ N O requires 320.2014; error -5.5ppm.

**4-[cyclopentyl(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)amino]methylbenzonitrile (2.17)**

To a solution of (**2.9**) (100mg, 0.44mmol) in acetone (10ml) was added α-bromo-*p*-tolunitrile (0.43g, 2.20mmol) and anhydrous potassium carbonate (0.17g, 1.25mmol). The reaction was heated at reflux for 3 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether: ethyl acetate, 5:1) to yield the amine as a white crystalline solid (117mg, 78%), with the following physical properties: m.p. 186-188°C; IR (KBr disc) υmax/$cm^{-1}$; 2947, 2865, 2227, 1686, 1596 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.38 (1H, m, 1H of C$\underline{H}_2$), 1.49-1.66 (6H, m, 6H of C$\underline{H}_2$ cyclopentyl), 1.93 (1H, m, 1H of C$\underline{H}_2$), 2.02 (1H, m, 1H of C$\underline{H}_2$CH$_2$CO), 2.41-2.50 (2H, m, 1H of C$\underline{H}_2$CH$_2$CO and 1H of C$\underline{H}_2$CO), 2.84 and 2.89 (1H, 2 x m, 1H of C$\underline{H}_2$CO), 3.19 (1H, quintet, J=7.9Hz, CH$_2$C$\underline{H}$CH$_2$), 3.85 and 3.95 (2H, dd, J=15Hz, NC$\underline{H}_2$), 3.94 (1H, dd, $J_2$=3Hz, C$\underline{H}$CH$_2$CH$_2$CO), 7.35 (1H, dd, $J_1$=8.3Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.58-7.63 (5H, m, 5 x Ar-C$\underline{H}$), 7.92 (1H, d, J=8.0Hz, Ar-C$\underline{H}$), 8.01 (1H, dd, $J_1$=7.8Hz, $J_2$=1Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 23.2, 24.6, 24.7, 27.6 and 31.7 (4 x $\underline{C}$H$_2$ cyclopentyl and $\underline{C}$H$_2$CH$_2$CO), 38.0 ($\underline{C}$H$_2$CO), 49.7 (N$\underline{C}$H$_2$), 58.3 ($\underline{C}$H), 59.2 ($\underline{C}$H), 110.2 ($\underline{C}$C≡N), 118.5 (C≡$\underline{N}$), 126.4, 126.7, 127.0 (3 x Ar-$\underline{C}$H), 128.3, 131.8 (4 x Ar-$\underline{C}$H), 132.6 (Ar-$\underline{C}$), 133.3 (Ar-$\underline{C}$H), 145.9, 146.6 (2 x Ar-$\underline{C}$), 196.9 ($\underline{C}$=O); MS, m/z, (RI) 344 ($M^+$, 20), 315 (29), 228 (36), 199 (86), 171 (100), 145 (47), 116 (91), 89 (51); HRMS ($+H^+$) 345.1986, $C_{23}$ $H_{25}$ $N_2$ O requires 345.1967; error 5.6ppm.

**4-[cyclopentyl(4-methylbenzyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (2.18)**

To a solution of (**2.9**) (100mg, 0.44mmol) in acetone (10ml) was added *p*-methyl(benzyl)bromide (0.41g, 2.22mmol) and anhydrous potassium carbonate (0.17g, 1.25mmol). The reaction was heated at reflux for 7 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale golden oil (116mg, 80%), with the following physical properties: IR (HCl salt, KBr disc) υmax/$cm^{-1}$; 3422, 2960, 1691, 1590, 1452, 1421$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.36 (1H, m, 1H of 4 x C$\underline{H}_2$),

1.54-1.73 (6H, m, 6H of 4 x $C\underline{H}_2$), 1.91-2.04 (2H, m, 1H of 4 x $C\underline{H}_2$ and 1H of $C\underline{H}_2CH_2CO$), 2.35 (3H, s, $C\underline{H}_3$), 2.42-2.51 (2H, m, 1H of $C\underline{H}_2CH_2CO$ and 1H of $C\underline{H}_2CO$), 2.87 (1H, m, 1H of $C\underline{H}_2CO$), 3.18 (1H, quintet, J=8Hz, $CH_2C\underline{H}CH_2$), 3.76 and 3.91 (2H, dd, J=14-14.5Hz, $NC\underline{H}_2$), 4.03 (1H, dd, J=3.5Hz, $C\underline{H}CH_2CH_2CO$), 7.16 (2H, m, 2 x Ar-C$\underline{H}$), 7.32-7.39 (3H, m, 3 x Ar-C$\underline{H}$), 7.60 (1H, ddd, $J_1$=8.5, $J_2$=7.5Hz, $J_3$=1.5Hz, Ar-C$\underline{H}$), 8.01 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.6 ($\underline{C}H_3$), 23.3, 24.7, 24.8, 27.4, 31.6 (5 x $\underline{C}H_2$), 38.2 ($\underline{C}H_2CO$), 49.2 ($N\underline{C}H_2$), 57.6, 58.9 (2 x $\underline{C}H$), 126.3, 126.7, 126.8 (3 x Ar-$\underline{C}H$), 127.8 (2 x Ar-$\underline{C}H$), 128.6 (2 x Ar-$\underline{C}H$), 132.6 (Ar-$\underline{C}$), 133.1 (Ar-$\underline{C}H$), 136.0, 137.3, 147.0 (3 x Ar-$\underline{C}$), 197.3 ($\underline{C}$=O); MS, m/z, (RI) 333 (M+, 18), 304 (15), 276 (8), 229 (30), 190 (100), 105 (46); HRMS (+$H^+$) 334.2144, $C_{23}$ $H_{28}$ N O requires 334.2171; error -8.1ppm.

**4-[cyclopentyl(4-nitrobenzyl)amino]- 1,2,3,4-tetrahydro-1-naphthalenone (2.19)**

To a solution of (**2.9**) (100mg, 0.44mmol) in acetone (10ml) was added 4-nitrobenzylbromide (0.47g, 2.18mmol) and anhydrous potassium carbonate (0.17g, 1.25mmol). The reaction was stirred at reflux for 14 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a yellow oil (84mg, 53%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2959, 2871, 1692, 1526, 1346$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.41 (1H, m, 1H of $C\underline{H}_2$), 1.52-1.70 (6H, m, 3 x $C\underline{H}_2$ cyclopentyl), 1.94 (1H, m, 1H of $C\underline{H}_2$), 2.05 (1H, m, 1H of $C\underline{H}_2CH_2CO$), 2.42-2.51 (2H, m, 1H of $C\underline{H}_2CH_2CO$ and 1H of $C\underline{H}_2CO$), 2.86 and 2.90 (1H, 2 x m, 1H of $C\underline{H}_2CO$), 3.23 (1H, quintet, J=7.8Hz, $CH_2C\underline{H}CH_2$), 3.91 and 3.98 (2H, dd, J=15.6Hz, $NC\underline{H}_2$), 3.99 (1H, dd, $J_2$=3Hz, $C\underline{H}CH_2CH_2CO$), 7.36 (1H, dd, $J_1$=8.2Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.59-7.65 (3H, m, 3 x Ar-C$\underline{H}$), 7.93 (1H, d, 8.0Hz, Ar-C$\underline{H}$), 8.02 (1H, dd, $J_1$=7.8Hz, $J_2$=1Hz, Ar-C$\underline{H}$), 8.19 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 23.1, 24.5, 24.8, 27.8, 31.7 (4 x $\underline{C}H_2$ cyclopentyl and $\underline{C}H_2$ tetralin), 37.9 ($\underline{C}H_2CO$), 49.7 ($N\underline{C}H_2$), 58.5 ($\underline{C}H$), 59.5 ($\underline{C}H$), 123.2 x 2, 126.4, 126.7, 127.0, 128.2 x 2 (7 x Ar-$\underline{C}H$), 132.6 (Ar-$\underline{C}$), 133.2 (Ar-$\underline{C}H$), 145.7 (Ar-$\underline{C}$), 148.7 (Ar-$\underline{C}$), 151.4 (Ar-$\underline{C}$), 196.7 ($\underline{C}$=O); MS, m/z, (RI) 364 ($M^+$, 17), 335 (22), 307 (13), 228 (28), 221 (100), 191 (52), 145 (27), 117 (45), 89 (24); HRMS (+$H^+$) 365.1837, $C_{22}$ $H_{25}$ $N_2$ $O_3$ requires 365.1865; error -7.7ppm.

**4-cyclopentyl[3,4-dimethoxy-5-(methoxymethyl)benzyl]amino-1,2,3,4-tetrahydro-1-naphthalenone (2.20)**

To a solution of (**2.9**) (100mg, 0.44mmol) in acetone (10ml) was added 3,4,5-trimethoxybenzyl bromide (0.17g, 0.65mmol) and anhydrous potassium carbonate (0.17g, 1.25mmol). The reaction was stirred at reflux for 7 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (125mg, 70%); IR (film) υmax/$cm^{-1}$ 2957, 2870, 1692, 1593, 1508, 1465, 1228, 1133$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.37 (1H, m, 1H of 4 x C$\underline{H}_2$), 1.54-1.64 (6H, m, 6H of 4 x C$\underline{H}_2$), 1.91-2.05 (2H, m, 1H of 4 x C$\underline{H}_2$ and 1H of C$\underline{H}_2$CH$_2$CO), 2.44-2.51 (2H, m, 1H of C$\underline{H}_2$CH$_2$CO and 1H of C$\underline{H}_2$CO), 2.86 (1H, m, 1H of C$\underline{H}_2$CO), 3.20 (1H, quintet, J=7Hz, CH$_2$C$\underline{H}$CH$_2$), 3.75 (1H, half of dd, J=14.6Hz, 1H of NC$\underline{H}_2$), 3.83-3.93 (10H, m, 3 x Ar-OC$\underline{H}_3$ and 1H of NC$\underline{H}_2$), 4.04 (1H, m, C$\underline{H}$CH$_2$CH$_2$CO), 6.73 (2H, s, 2 x (CH$_3$O)$_3$Ar-C$\underline{H}$, 7.34 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.59 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 8.01 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 23.3, 24.8, 24.8, 27.5, 31.6 (5 x $\underline{C}$H$_2$), 38.1 ($\underline{C}$H$_2$CO), 49.7 (N$\underline{C}$H$_2$), 55.6, 55.7, 57.9 (3 x Ar-O$\underline{C}$H$_3$), 58.8, 60.3 (2 x $\underline{C}$H), 104.3 (2 x (CH$_3$O)$_3$Ar-$\underline{C}$H), 126.4 x 2, 126.9 (3 x Ar-$\underline{C}$H), 132.7 (Ar-$\underline{C}$), 133.0 (Ar-$\underline{C}$H), 136.2, 146.7 (2 x Ar-C), 152.3 (2 x Ar-$\underline{C}$), 197.1 ($\underline{C}$=O); MS, m/z, (RI) 409 ($M^+$, 1), 264 (9), 229 (51), 181 (100), 117 (12); HRMS (+$Na^+$) 432.2114, $C_{25}$ $H_{31}$ N $O_4$ Na requires 432.2151; error -8.6ppm.

**4-[cyclopentyl(2-naphthylmethyl)amino]- 1,2,3,4-tetrahydro-1-naphthalenone (2.21)**

To a solution of (**2.9**) (100mg, 0.44mmol) in acetone (10ml) was added 2-(bromomethyl) naphthalene (0.48g, 2.18mmol) and anhydrous potassium carbonate (0.17g, 1.25mmol). The reaction was stirred at reflux for 7 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (39mg, 27%), which on standing yielded a pale brown solid: IR (film) υmax/$cm^{-1}$ 2957, 2869, 1692, 1550, 1284$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.41 (1H, m, 1H of 4 x C$\underline{H}_2$), 1.58-1.76 (6H, m, 6H of 4 x C$\underline{H}_2$), 1.97-2.08 (2H, m, 1H of 4 x C$\underline{H}_2$ and 1H of C$\underline{H}_2$CH$_2$CO), 2.41-2.53 (2H, m, 1H of C$\underline{H}_2$CH$_2$CO and 1H of C$\underline{H}_2$CO), 2.88 (1H, m, 1H of C$\underline{H}_2$CO), 3.23 (1H, quintet, J=7.5Hz, CH$_2$C$\underline{H}$CH$_2$), 3.97 and 4.10 (2H, dd, J=14Hz, NC$\underline{H}_2$), 4.08 (1H, m, C$\underline{H}$CH$_2$CH$_2$CO),

7.33 (1H, dd, $J_1$=8.5Hz, Ar-C<u>H</u>), 7.47 (2H, m, 2 x Ar-C<u>H</u>), 7.61 (1H, dd, $J_1$=9Hz, Ar-C<u>H</u>), 7.70 (1H, d, J=8Hz, Ar-C<u>H</u>), 7.85 (4H, m, 4 x Ar-C<u>H</u>), 8.03 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 23.3, 24.8, 24.8, 27.5, 31.7, 38.2 (6 x <u>C</u>$H_2$), 49.8 (<u>C</u>$H_2$Ar), 57.6, 59.0 (2 x <u>C</u>H), 125.1, 125.5, 126.3 x 2, 126.4, 126.7, 126.8, 127.1, 127.2, 127.7 (10 x Ar-<u>C</u>H), 132.4, 132.6, 132.9 (3 x Ar-<u>C</u>), 133.1 (Ar-<u>C</u>H), 138.0, 146.8 (2 x Ar-<u>C</u>), 197.1 <u>C</u>=O); MS, m/z, (RI) 370 (M+1, 5), 340 (12), 228 (100), 141 (30), 115 (20); HRMS (+$H^+$) 370.2194, $C_{26}$ $H_{28}$ N O requires 370.2171; error 6.2ppm.

**_N_1-cyclopentyl-_N_1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide (2.22)**

To a solution of (**2.9**) (200mg, 0.87mmol) in pyridine (5ml) was added acetic anhydride (0.42ml, 4.35mmol) and a crystal of DMAP. The reaction was stirred at room temperature for 3 hours. The pyridine was removed by washing the organic phase (diluted with 20ml DCM) three times with 2M HCl (3 x 20ml); the organic layer was then concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the acetamide as a white solid (135mg, 57%): m.p. 131-132°C; IR (KBr disc) υmax/$cm^{-1}$ 2946, 2869, 1688, 1644, 1597, 1434, 1285$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.45-2.48 (br. m), 2.21 (s, COC<u>H</u>$_3$), 2.57-2.75 (m), 2.78-2.91 (m), 3.07 and 5.15 (2 x broad s, C<u>H</u>C$H_2$C$H_2$CO), 7.13 (1H, d, J=7.1Hz, Ar-C<u>H</u>), 7.29 (1H, m, Ar-C<u>H</u>), 7.33-7.44 (2H, m, 2 x Ar-C<u>H</u>), 7.47 (1H, dd, $J_2$=7.1Hz, Ar-C<u>H</u>), 7.60 (1H, dd, $J_2$=7.1Hz, Ar-C<u>H</u>), 8.02 (1H, d, J=7.5Hz, Ar-C<u>H</u>), 8.07 (1H, d, J=7.5Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 23.0 (<u>C</u>$H_3$), 23.3 (br.), 23.4 (br.), 25.0 (br.), 25.3 (br.), 28.0, 28.8 (br.), 29.2 (br.), 30.2 (br.), 37.6 (br.), 38.2 (<u>C</u>$H_2$CO), 53.2 (<u>C</u>H), 57.6 (br.), 58.3 (br.), 126.3 (br.), 127.1, 127.4, 127.5, 133.0 (4 x Ar-<u>C</u>H), 133.5 (br.), 195.4, 196.2 (<u>C</u>=O); MS, m/z, (RI) 272 (M+1, 100), 271 ($M^+$, 15), 160 (12), 115 (13), 84 (9); HRMS (+$H^+$) 272.1646, $C_{17}$ $H_{22}$ N $O_2$ requires 272.1651; (+$Na^+$) 294.1454, $C_{17}$ $H_{21}$ N $O_2$ Na requires 294.1470; errors -1.7ppm, -5.3ppm.

**_N_1-cyclopentyl-_N_1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-2-phenylacetamide (2.23)**

To a solution of (**2.9**) (150mg, 0.66mmol) in pyridine (10ml) was added phenylacetyl chloride (0.41g, 2.64mmol). After the addition of a crystal of DMAP, the reaction was stirred at reflux for 7 days. The solvent was removed *in vacuo*, and the residue purified by

flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the phenylacetamide as yellow crystals (0.15g, 68%); IR (film) υmax/cm$^{-1}$ 2956, 1694, 1646, 1599, 1456, 1284, 1140cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.39, 1.58, 1.71, 1.95 (4 x br m, 4 x C$\underline{H}_2$), 2.19 and 2.40 (2H, 2 x m, C$\underline{H}_2$), 2.67, 2.88, 3.05, 3.37 (2H, 4 x m, 2 x C$\underline{H}_2$), 3.84 (C$\underline{H}$), 5.24 (C$\underline{H}$), 7.25-7.48 (8 x Ar-C$\underline{H}$), 7.56 (1H, dd, $J_1$=8.5, $J_2$=7.5Hz, Ar-C$\underline{H}$), 8.07 (COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.2, 25.5, 28.8, 29.1, 30.1 (5 x $\underline{C}H_2$), 37.4, 43.4 (2 x $\underline{C}H_2CO$), 57.8 ($\underline{C}$H), 126.2, 126.5, 126.6, 127.2. 127.4, 127.5, 127.9, 128.2, 128.3, 128.5 (8 x Ar-$\underline{C}$H), 132.9 (Ar-$\underline{C}$), 133.3 (Ar-$\underline{C}$H), 134.7 (Ar-$\underline{C}$), 169.9 (N$\underline{C}$=O), 195.4, 196.2 ($\underline{C}$=O); MS, m/z, (RI) 348 (M+1, 100), 347 ($M^+$, 7), 115 (11); HRMS (+$H^+$) 348.1950, $C_{23}$ $H_{26}$ N $O_2$ requires 348.1964; error -4.0ppm.

**_N_1-cyclopentyl-_N_1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-2-butenamide (2.24)**

To a solution of (**2.9**) (10mg, 0.044mmol) in DCM (10ml) was added the activated ester of crotonic acid, (0.033g, 0.132mmol) and DMAP (0.021g, 0.176mmol). The reaction was stirred at room temperature for 7 days. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the butenamide as yellow crystals (3.1mg, 24%): IR (film) υmax/cm$^{-1}$ 2956, 1738, 1661, 1620, 1237cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ Unresolved; aliphatics 1.23-2.47; 3.27, 5.13; alkene protons 5.96-6.37; aromatics 7.11-7.42.

**N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide (2.25)**

To a solution of the azide (**2.2**) (0.5g, 2.67mmol) in EtOH/EtOAc (10ml, 1:1), was added acetic anhydride (0.25ml, 2.67mmol) and a catalytic amount of 10% Pd/C. The reaction was stirred at room temperature overnight under an atmosphere of hydrogen, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the acetamide as a white solid (0.27g, 50%): m.p. 138-139°C; IR (film) υmax/cm$^{-1}$ 3252, 2929, 1689, 1637, 1543cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.05-2.05 (3H, 2 x s, C$\underline{H}_3$), 2.10 and 2.32 (2H, 2 x broad m, C$\underline{H}_2$), 2.62 and 2.75 (2H, 2 x m, C$\underline{H}_2$CO), 5.32 (1H, C$\underline{H}$), 6.38 and 6.50 (N$\underline{H}$), 7.35 (2H, broad m, 2 x Ar-C$\underline{H}$), 7.54 (1H, Ar-C$\underline{H}$), 7.94 (1H, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 22.8 ($\underline{C}H_3$), 29.2 ($\underline{C}H_2$), 35.7 ($\underline{C}H_2CO$), 46.9 ($\underline{C}$H), 126.8 (Ar-$\underline{C}$H), 126.9 (Ar-$\underline{C}$H), 127.6 (Ar-$\underline{C}$H),

131.5 (Ar-C), 133.6 (Ar-CH), 142.9 (Ar-C), 169.5 (NHC=O), 196.5 (C=O); MS, m/z, (RI) 204 (M+1, 100), 203 ($M^+$, 21), 144 (70), 115 (25).

**N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide (2.26)**

To a solution of the azide (**2.2**) (0.6g, 3.21mmol) in EtOH/EtOAc (10ml, 1:1), was added propionic anhydride (0.83ml, 6.42mmol) and a catalytic amount of 10% Pd/C. The reaction was stirred at room temperature overnight under an atmosphere of hydrogen, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the propanamide as a white solid (0.2g, 40%): m.p. 142-143°C; IR (film) υmax/$cm^{-1}$ 3274, 1692, 1645, 1541$cm^{-1}$ ; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.24 (3H, t, J=7.5Hz, $CH_3$), 2.12-2.17 (1H, m, 1H of $CHCH_2$), 2.33 (2H, q, J=7.5Hz, $CH_2CH_3$), 2.38 (1H, m, 1H of $CHCH_2$), 2.70-2.82 (2H, m, $CH_2CO$), 5.41 (1H, broad s, CH), 5.92 (NH), 7.38-7.39 (2H, m, 2 x Ar-CH), 7.57 (1H, dd, $J_2$=7.5Hz, Ar-CH), 8.03 (1H, broad s, COAr-CH); $^{13}$CNMR $\delta_C$ 9.4 ($CH_3$), 29.4 (2 x $CH_2$), 35.8 ($CH_2CO$), 46.8 (CH), 126.7 (Ar-CH), 126.9 (Ar-CH), 127.7 (Ar-CH), 131.6 (Ar-C), 133.6 (Ar-CH), 143.0 (Ar-C), 173.1 (NHC=O), 196.3 (C=O); MS, m/z, (RI) 218 (M+1, 100), 217 ($M^+$, 18), 144 (16), 115, (17).

**N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-3-phenylpropanamide (2.27)**

To an ice cold solution of hydrocinnamic acid (0.4g, 2.67mmol) in DCM (10ml) was added pentafluorophenol [PFP] (0.5g, 2.67mmol) and dicyclohexylcarbodiimide [DCC] (0.5g, 2.67mmol). The reaction was stirred for 30 minutes, filtered, and eluted through a silica plug to yield the activated ester of hydrocinnamic acid (0.8g, 95%) as white crystals. To a solution of the ester in EtOH/EtOAc (10ml, 1:1), was added the azide (**2.2**) (0.47g, 2.53mmol), and a catalytic amount of 10% Pd/C. The reaction was stirred at room temperature overnight under an atmosphere of hydrogen, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the phenylpropanamide (0.51g, 69%) as white crystals: m.p. 110-112°C; IR (film) υmax/$cm^{-1}$ 3279, 2929, 1689, 1633, 1542$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.97 and 2.24 (2H, 2 x m, $CH_2$), 2.56-2.62 (4H, m, 2 x $CH_2$), 3.02 (1H, dd, $J_1$=8.2Hz, $J_2$=7.4Hz, $CH_2$), 5.30 (1H, m, CH), 6.05 (NH), 7.04 (1H, d,

J=8Hz, Ar-CH), 7.21-7.34 (6H, m, 6 x Ar-CH), 7.44 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-CH), 7.93 (1H, d, J=7.5Hz, Ar-CH), 7.93 (1H, d, COAr-CH); $^{13}$CNMR $\delta_C$ 29.2 ($CH_2$), 31.3 ($CH_2$), 35.7 ($CH_2CO$), 38.1 ($CH_2CO$), 46.8 (CH), 125.9 (Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-CH), 127.5 (Ar-CH), 128.0 (2 x Ar-CH), 128.1 (2 x Ar-CH), 131.4 (Ar-C), 133.5 (Ar-CH), 140.0 (Ar-C), 142.8 (Ar-C), 171.4 (NHC=O), 196.5 (C=O); MS, m/z, (RI) 294 (M+1, 100), 293 ($M^+$, 43), 249 (23), 218 (27), 249 (23), 160 (20), 128 (25).

**N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-2-phenylacetamide (2.28)**

To a solution of the azide (**2.2**) (0.5g, 2.67mmol) in EtOH/EtOAc (10ml, 1:1), was added the activated ester of phenylacetic acid (2.67mmol), prepared using the method outlined in the synthesis of (**2.28**). After addition of a catalytic amount of 10% Pd/C, the reaction was stirred at room temperature overnight under an atmosphere of hydrogen, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the phenylacetamide (0.48g, 64%) as white crystals: IR (film) υmax/cm$^{-1}$ 3267, 2929, 1690, 1640, 1542cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.97 and 2.28 (2H, 2 x m, $CH_2CH_2CO$), 2.58 and 2.68 (2 x m, $CH_2CO$), 3.63 (1H, s, $PhCH_2CO$), 5.32 (1H, m, NHCH), 6.24 (1H, br. s, NH), 7.21 (1H, d, J=7.7Hz, Ar-CH), 7.26-7.36 (6H, m, 6 x Ar-CH), 7.48 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-CH), 7.94 (1H, d, J=8Hz, Ar-CH); $^{13}$CNMR $\delta_C$ 29.3 ($CH_2CH_2CO$), 35.9 ($CH_2CO$), 43.3 ($CH_2CO$), 47.0 (CH), 126.4, 126.9, 127.0, 127.5, 128.6 (2), 128.7 (2) (8 x Ar-CH), 131.5 (Ar-C), 133.5 (Ar-CH), 134.3, 142.9 (2 x Ar-C), 170.5 (NHC=O), 196.3 (C=O); MS, m/z, (RI) 280 (M+1, 100), 279 ($M^+$, 40), 115 (16), 89(15).

**N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-3,4-dichlorobenzamide (2.29)**

To a solution of the azide (**2.2**) (0.5g, 2.67mmol) in EtOH/EtOAc (10ml, 1:1), was added the activated ester of 3,4-dichlorobenzoic acid (2.67mmol), prepared using the method outlined in the synthesis of (**2.28**). After addition of a catalytic amount of 10% Pd/C, the reaction was stirred at room temperature overnight under an atmosphere of hydrogen, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the 3,4-dichlorobenzamide as white crystals (0.72g, 81%): m.p. 165-167°C; IR (film) υmax/cm$^{-1}$ 3252, 2929, 1689, 1637, 1543cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.75 and 2.45 (2H, 2 x

m, C<u>H</u>$_2$), 2.70 and 2.83 (2H, 2 x m, C<u>H</u>$_2$CO), 5.55 (1H, m, C<u>H</u>), 6.94 (N<u>H</u>), 7.40 (2H, m, 2 x Ar-C<u>H</u>), 7.48-7.59 (2H, m, 2 x Ar-C<u>H</u>), 7.67 (1H, m, Ar-C<u>H</u>), 7.97 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 29.2 (<u>C</u>H$_2$), 35.7 (<u>C</u>H$_2$CO), 47.7 (<u>C</u>H), 125.9, 126.8, 127.0, 127.9, 128.8, 130.2 (6 x Ar-<u>C</u>H), 131.6, 132.7, 133.3 (3 x Ar-<u>C</u>), 133.8 (Ar-<u>C</u>H), 135.9, 142.4 (2 x Ar-<u>C</u>), 164.7 (NH<u>C</u>=O), 196.3 (<u>C</u>=O); MS, m/z, (RI) 334 (M+1, 15), 333 ($M^+$, 10), 144 (100), 115 (25).

**9-[cyclopentyl(methyl)amino]-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (2.32)**

To a solution of 9-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (**2.30**) (1g, 4.12mmol) [prepared from benzosuberone via the benzylic bromide and azide] in acetone (10ml) was added methyl iodide (2.92g, 20.6mmol) and anhydrous potassium carbonate (2g, 14.5mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (0.92g, 87%); IR (film) υmax/cm$^{-1}$ 2957, 2869, 2790, 1687, 1451, 1279, 1246cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.42 (4H, broad m, 4H of $(CH_2)_4$), 1.57 (4H, broad m, 4H of $(CH_2)_4$), 1.69 and 1.85-2.02 (1H and 3H, 2 x m, C<u>H</u>$_2$C<u>H</u>$_2$CH$_2$CO), 2.05 (3H, s, C<u>H</u>$_3$), 2.55 and 2.81 (2H, 2 x m, C<u>H</u>$_2$CO), 3.04 (1H, quintet, J=7.5Hz, CH$_2$C<u>H</u>CH$_2$), 3.75 (1H, dd, $J_1$=6.5Hz, $J_2$=3.5Hz, NC<u>H</u>Ar), 7.28 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C<u>H</u>), 7.39 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C<u>H</u>), 7.50 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 20.3 (CH$_2$<u>C</u>H$_2$CH$_2$CO), 24.1 (<u>C</u>H$_2$), 24.2 (<u>C</u>H$_2$), 26.2 (<u>C</u>H$_2$), 26.7 (<u>C</u>H$_2$CH$_2$CH$_2$CO), 27.9 (<u>C</u>H$_2$), 33.3 (<u>C</u>H$_3$), 40.5 (<u>C</u>H$_2$CO), 61.3 (CH$_2$<u>C</u>HCH$_2$), 65.2 (N<u>C</u>HAr), 127.0, 127.7 x 2, 130.7 (4 x Ar-<u>C</u>H), 139.4 (Ar-<u>C</u>), 143.0 (Ar-<u>C</u>), 205.9 (<u>C</u>=O); MS, m/z, (RI) 258 (M+1, 100), 257 ($M^+$, 48), 200 (28); HRMS (+$H^+$) 258.1873, $C_{17}$ $H_{24}$ N O requires 258.1858; error 5.8ppm.

**4-[benzyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (2.33)**

To compound (**2.2**) (obtained from 1g α-tetralone); was immediately added acetone (10ml), benzylmethylamine (1.76ml, 13.7mmol) and anhydrous $K_2CO_3$ (4.7g, 34.2mmol). The reaction was stirred overnight at room temperature, and separated by sequential acid (2M HCl) and base (2M NaOH) washings, extracting the organic phase three times in each

**4-(cyclohexylamino)-4-phenylbutanoic acid (3.1)**

To a stirred solution of (**2.12**) (0.94g, 3.67mmol) in DCM was added cyclopentylamine (0.72ml, 7.32mmol) and triethylamine (1ml, 7.17mmol). The reaction was stirred at room temperature for five days, during which time additional triethylamine (1.2ml, 8.6mmol) was added. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield a brown oil, which upon $^1$H NMR analysis revealed a mixture of ester and acid. The prominent methyl singlet of the ester resonated at 3.54ppm. Hydrolysis of the mixture with NaOH afforded the acid alone, enabling complete data to be obtained: IR (film) υmax/cm$^{-1}$ 2935, 2857, 1686, 1453, 1414, 1274, 1236cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 0.92 (2H, m, C$\underline{H}_2$), 1.11-1.32 (2H, m, C$\underline{H}_2$), 1.51-1.67 (4H, m, 2 x C$\underline{H}_2$), 1.72 (2H, m, C$\underline{H}_2$), 1.84 (1H, m, 1H of C$\underline{H}_2$), 2.33-2.48 (2H, m, C$\underline{H}_2$), 2.65 (1H, m, 1H of C$\underline{H}_2$), 3.79 (1H, m, $CH_2C\underline{H}CH_2$), 4.71 (1H, dd, $J_1$=8.5Hz, $J_2$=3Hz, NC$\underline{H}$Ar), 7.23-7.36 (5H, m, 5 x Ar-C$\underline{H}$). $^{13}$C signals were assignable for both ester and acid: $^{13}$CNMR $\delta_C$ (ester) 24.2, 24.5, 25.7, 30.5, 32.4, 33.0, 34.1 (7 x $\underline{C}H_2$), 50.8 ($\underline{C}H_3$), 52.7 ($\underline{C}$H), 58.4 ($\underline{C}$H), 126.4 ( 3 x Ar-$\underline{C}$H), 127.9 (2 x Ar-$\underline{C}$H), 143.7 (Ar-$\underline{C}$), 173.4 ($\underline{C}$=O). $^{13}$CNMR $\delta_C$ (acid) 24.9, 25.4 (2), 29.0, 29.8, 29.9, 30.8 (7 x $\underline{C}H_2$), 52.7, 60.6 (2 x $\underline{C}$H), 125.7 (2 x Ar-$\underline{C}$H), 127.2 (Ar-$\underline{C}$H), 128.3 (2 x Ar-$\underline{C}$H), 143.3 (Ar-$\underline{C}$), 174.9 ($\underline{C}$=O). Upon heating with excess polyphosphoric acid on a steam bath, no cyclisation to the tetralone was observed.

**4-(cyclohexylamino)-1,2,3,4-tetrahydro-1-naphthalenyl acetate (3.2)**

To a solution of (**2.6**) (3g, 11.15mmol) in DCM (10ml) was added cyclohexylamine (2.54ml, 22.3mmol) and triethylamine (2.33ml, 16.72mmol). The reaction was refluxed for 9 hours, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the amine (1.66g, 52%) as a brown oil, a diastereomeric mixture, with the following physical properties: IR (film) υmax/cm$^{-1}$ 2929, 2853, 1733, 1450, 1371, 1240, 1020cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.10-1.39, 1.65, 1.72-1.92, 1.98-2.40 (17H, 4 x m, 7 x C$\underline{H}_2$, and $CH_3$, 2 x s at 2.08 and 2.12), 2.66 and 2.72 (1H, 2 x m, $CH_2C\underline{H}CH_2$), 3.85 and 3.97 (1H, 2 x t, J=4-6Hz, NC$\underline{H}$ Ar), 5.96 and 6.02 (1H, 2 x t, J=5.5Hz and 4.3Hz, OC$\underline{H}$), 7.21-7.33 (3H, m, 3 x Ar-C$\underline{H}$), 7.39 and 7.55 (1H, 2 x d, J=7.5Hz and 6.5Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.0 x 2 ($\underline{C}H_3$), 24.1, 24.2, 24.4, 24.5, 24.7, 24.8, 25.4, 25.8 x 2 (5 x $\underline{C}H_2$), 33.0, 33.1, 34.5 (2 x

$\underline{C}H_2$), 51.0, 51.7, 53.7 (2 x N$\underline{C}$H), 69.3 and 70.0 (O$\underline{C}$H), 126.5 and 126.7 (Ar-$\underline{C}$H), 127.8, 127.9, 128.0, 128.1, 128.5, 128.9 (3 x Ar-$\underline{C}$H), 134.1 and 134.4 (Ar-$\underline{C}$), 140.6 and 141.0 (Ar-$\underline{C}$), 170.2 and 170.3 ($\underline{C}$=O); MS, m/z, (RI) 288 (M+1, 100), 287 ($M^+$, 18), 229 (13), 100 (13).

**4-(cyclohexylamino)-1,2,3,4-tetrahydro-1-naphthalenone (3.4)**

To a solution of the amine acetate (**3.2**) (1.5g, 5.23mmol) in methanol/water (10ml, 1:1) was added excess potassium carbonate (5.0g, 36.2mmol). The reaction was heated under reflux for 1 hour, monitoring by GCMS. On completion, the reaction was filtered and the solvent removed *in vacuo*, using toluene to azeotropically distill any residual water. To the residue containing the alcohol (**3.3**) thus obtained, (0.91g, 71%) was added acetone (10ml) and Jones reagent (5ml), the latter added drop-wise over 30 minutes to the ice-cooled reaction. On appearance of the green $Cr_2(SO_4)_3$, anhydrous sodium sulphate (1.5g, 10.6mmol) was added. After 2 hours, the solvent was evacuated, and the reaction separated using ether/water. After three washings with ether (3 x 50ml), the combined organic extracts were filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 1:1) to yield the amine (**3.4**) as a brown oil (0.49g, 54%); IR (film) $\upsilon max/cm^{-1}$ 2930, 2855, 1690, 1451, 1283$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.10-1.39 (5H, m, 5H of C$\underline{H}_2$), 1.65 (1H, m, 1H of C$\underline{H}_2$), 1.78 (2H, m, C$\underline{H}_2$), 1.91 (1H, m, 1H of C$\underline{H}_2$), 2.01 (1H, m, 1H of C$\underline{H}_2$), 2.09 (1H, m, $CH_2C\underline{H}CH_2$), 2.30 (1H, m, C$\underline{H}_2CH_2CO$), 2.57 (1H, ddd, $J_1$=11.0Hz, $J_2$=7.0Hz, $J_3$=4.5Hz, 1H of C$\underline{H}_2$CO), 2.67 (1H, m, 1H of C$\underline{H}_2CH_2CO$), 3.01 (1H, ddd, $J_1$=14.5Hz, $J_2$=10.0Hz, $J_3$=4.5Hz, 1H of C$\underline{H}_2$CO), 4.08 (1H, dd, J=3.5Hz, NC$\underline{H}$Ar), 7.37 (1H, m, Ar-C$\underline{H}$), 7.53-7.57 (2H, m, 2 x Ar-C$\underline{H}$), 8.03 (1H, d, J=8.0Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 24.5 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 28.4 ($\underline{C}H_2$), 33.1 ($\underline{C}H_2$), 34.3 ($\underline{C}H_2$), 34.5 ($\underline{C}H_2$), 51.7 ($\underline{C}$H), 53.7 ($\underline{C}$H), 126.7 (Ar-$\underline{C}$H), 127.0 (Ar-$\underline{C}$H), 127.5 (Ar-$\underline{C}$H), 131.5 (Ar-$\underline{C}$), 133.2 (Ar-$\underline{C}$H), 146.4 (Ar-$\underline{C}$), 197.9 ($\underline{C}$=O); MS, m/z, (RI) 244 (M+1, 100), 100 (10).

**4-[cyclohexyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.5)**

To a solution of (**3.4**) (50mg, 0.20mmol) in acetone (10ml) was added methyl iodide (0.06ml, 0.96mmol) and anhydrous potassium carbonate (0.15g, 1.1mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in*

*vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (46mg, 88%); IR (film) υmax/cm$^{-1}$ 2933, 2856, 1692, 1598, 1452, 1284cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.16-1.51 (5H, m, 5H of 5 x C$\underline{H}_2$), 1.64 (1H, m, 1H of 5 x C$\underline{H}_2$), 1.78-1.97 (4H, m, 4H of 5 x C$\underline{H}_2$), 2.14-2.24 (5H, m, C$\underline{H}_2$CH$_2$CO and C$\underline{H}_3$, a singlet at 2.21), 2.53-2.62 (2H, m, C$\underline{H}_2$CO), 2.89 (1H, 2 x dd, $J_1$=5.5Hz, $J_2$=4.5Hz, CH$_2$C$\underline{H}$CH$_2$), 4.16 (1H, t, J=6.5Hz, NC$\underline{H}$Ar), 7.35 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.55 (1H, ddd, $J_1$=8.4Hz, $J_2$=7.5Hz, $J_3$=1.5Hz, Ar-C$\underline{H}$), 7.80 (1H, d, J=7.6Hz, Ar-C$\underline{H}$), 8.03 (1H, d, J=7.4Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 24.9 (C$\underline{H}_2$), 25.3 (2 x C$\underline{H}_2$), 25.8, 30.4, 30.9 (3 x C$\underline{H}_2$), 32.6 (C$\underline{H}_3$), 37.1 (C$\underline{H}_2$CO), 58.4, 59.9 (2 x C$\underline{H}$), 126.5, 126.7, 127.4 (3 x Ar-C$\underline{H}$), 132.5 (Ar-C$\underline{}$), 132.9 (Ar-C$\underline{H}$), 197.7 (C$\underline{}$=O); MS, m/z, (RI) 258 (M+1,), 257 ($M^+$, 100), 214 (71), 144 (10), 114 (50); HRMS (+H$^+$) 258.1864, $C_{17}$ $H_{24}$ N O requires 258.1858; error 2.3ppm.

**4-[benzyl(cyclohexyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.6)**

To a solution of (**3.4**) (50mg, 0.20mmol) in acetone (10ml) was added benzyl bromide (0.12ml, 1mmol) and anhydrous potassium carbonate (0.15g, 1.1mmol). The reaction was stirred at reflux for 5 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (24mg, 36%): IR (film) υmax/cm$^{-1}$ 2932, 2855, 1691, 1599, 1495, 1452, 1284, 1101cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.06-1.45 (4H, m, 4H of 5 x C$\underline{H}_2$), 1.51-1.63 (2H, m, 2H of 5 x C$\underline{H}_2$), 1.80 (2H, m, 2H of 5 x C$\underline{H}_2$), 1.95-2.04 (2H, m, 2H of 5 x C$\underline{H}_2$), 2.16 (1H, m, 1H of C$\underline{H}_2$), 2.40-2.61 (3H, m, 3H of 2 x C$\underline{H}_2$, 2.84 and 2.88 (1H, 2 x dd, $J_1$=4.5Hz, $J_2$=3Hz, 1H of CHC$\underline{H}_2$CH), 3.82 and 3.90 (2H, dd, J=14.2Hz, NC$\underline{H}_2$), 4.16 (1H, m, NC$\underline{H}$Ar), 7.24 (1H, dd, $J_1$=8.3Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.30-7.36 (3H, m, 3 x Ar-C$\underline{H}$), 7.45 (2H, m, 2 x Ar-C$\underline{H}$), 7.59 (1H, dd, $J_1$=8.0Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 8.03 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.7, 25.8, 26.1, 26.5, 30.6, 32.7 (6 x C$\underline{H}_2$), 38.1 (C$\underline{H}_2$CO), 49.8 (NC$\underline{H}_2$), 56.5, 57.2 (2 x C$\underline{H}$), 126.3, 126.4, 126.7, 127.1 (4 x Ar-C$\underline{H}$), 127.8 (2 x Ar-C$\underline{H}$), 127.9 (2 x Ar-C$\underline{H}$), 132.8 (Ar-C$\underline{}$), 133.0 (Ar-C$\underline{H}$), 140.6, 147.0 (2 x Ar-C$\underline{}$), 197.2 (C$\underline{}$=O); MS, m/z, (RI) 334 (M+1,), 333 ($M^+$, 63), 290 (38), 242 (45), 190 (100), 146 (33); HRMS (+H$^+$) 334.2184, $C_{23}$ $H_{28}$ N O requires 334.2171; error 3.8ppm.

**_tert_-butyl N-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)carbamate (3.7)**

To a solution of the azide (**2.2**) (3.19g, 17.1mmol) in 10ml of a mixture of EtOH/EtOAc (1:1) was added Di-*tert*-butyl dicarbonate (3.74g, 17.1mmol) and a catalytic quantity of 10% Pd/C. The reaction was stirred overnight under an atmosphere of hydrogen. On completion, the reaction was filtered to remove the catalyst, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the BOC-protected amine as a white crystalline solid: IR (KBr disc) υmax/$cm^{-1}$ 2974, 1684, 1508, 1166$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.45 (9H, s, 9H of $(CH_3)_3$), 2.01-2.10 (1H, m, 1H of C$\underline{H}_2$), 2.28-2.35 (1H, m, 1H of C$\underline{H}_2$), 2.57 (1H, ddd, $J_1$=15.5Hz, $J_2$=11.1Hz, $J_3$=4.5Hz, 1H of C$\underline{H}_2$CO), 2.74 (1H, ddd, $J_1$=10.5Hz, $J_2$=6.0Hz, $J_3$=4.5Hz, 1H of C$\underline{H}_2$CO), 4.95 (1H, broad s, CH), 5.19 (1H, broad s, NH), 7.31 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, 1 x Ar-C$\underline{H}$), 7.39 (1H, broad d, J=7.4Hz, 1 x Ar-CH), 7.49 (1H, dd, $J_1$=8.5Hz, $J_2$=7.4Hz, Ar-C$\underline{H}$), 7.92 (1H, d, J=7.5Hz, 1 x COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 27.9 (3 x $\underline{C}H_3$), 29.8 ($\underline{C}H_2$CHNH), 35.9 (CO$\underline{C}H_2$), 48.4 ($\underline{C}$HNH), 79.3 ($\underline{C}(CH_3)_3$), 126.6, 126.7, 127.4, 133.4 (4 x Ar-$\underline{C}$H), 131.3, 143.6 (2 x Ar-$\underline{C}$), 155.2 (O$\underline{C}$O), 196.4 (Ar-$\underline{C}$O); MS, m/z, (RI) 206 (100), 162 (71), 144, (93), 115 (30).

**4-(2-cyclohexenylamino)-1,2,3,4-tetrahydro-1-naphthalenone (3.9)**

To a solution of (**3.7**) (3.84g, 14.7mmol) in DCM (5ml) at 0°C was added 5ml of trifluoroacetic acid (TFA). The reaction was stirred for one hour, allowing the reaction to reach room temperature. When TLC analysis showed completion of the reaction, the solvent was removed *in vacuo*, removing any remaining TFA using toluene to create an azeotrope. After washing with base, extracting with ether and removing the solvent to the free amine (**3.8**) as a dark oil, DCM (10ml) was added. To this stirred solution was added triethylamine (4.1ml, 29.4mmol) and 3-bromocyclohexene (3.4ml, 29.4mmol). The reaction was stirred overnight at room temperature, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the secondary amine, a diastereomeric mixture, as a brown oil, which on standing formed dark crystals (2.11g, 60%): IR (film) υmax/$cm^{-1}$ 2936, 2863, 1690, 1601, 1450$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.16 (1H, br, N$\underline{H}$), 1.47-1.66 (2H, m, C$\underline{H}_2$), 1.78 (1H, m, 1H of C$\underline{H}_2$), 1.93 (1H, m, 1H of C$\underline{H}_2$), 1.99-2.06 (2H, m, CH=CHC$\underline{H}_2$), 2.07-2.19 (1H, m, 1H of C$\underline{H}_2$CH$_2$CO), 2.23-2.33 (1H, m, 1H of

$C\underline{H}_2CH_2CO$), 2.55 and 3.07 (2H, 2 x m, $C\underline{H}_2CO$), 3.34 (1H, m, $C\underline{H}CH=CH$), 4.11 (1H, m, $C\underline{H}CH_2CH_2CO$), 5.67-5.82 (2H, m, $C\underline{H}=C\underline{H}$), 7.37 (1H, m, Ar-$C_5\underline{H}$), 7.46-7.56 (2H, m, 2 x Ar-$C\underline{H}$), 8.03 (1H, m, Ar-$C_8\underline{H}$); $^{13}$CNMR $\delta_C$ 19.2 and 19.8 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 28.0 and 28.4 ($\underline{C}H_2$), 29.0 and 30.3 ($\underline{C}H_2$), 34.1 and 34.3 ($\underline{C}H_2CO$), 49.8 and 50.3 ($\underline{C}H$), 52.0 and 52.3 ($\underline{C}H$), 126.7 and 126.8, 127.1 and 127.2, 127.6, 128.6 and 128.8, 129.1 and 129.7 (3 x Ar-$\underline{C}H$ and $\underline{C}H=\underline{C}H$), 131.6 x 2 (Ar-$\underline{C}$), 133.1 x 2 (Ar-$\underline{C}H$), 145.8 and 146.0 (Ar-$\underline{C}$), 197.8 ($\underline{C}$=O); MS, m/z, (RI) 242 (M+1, 100), 98 (15).

**4-[2-cyclohexenyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.10)**

To a solution of (**3.9**) (150mg, 0.62mmol) in acetone (10ml) was added methyl iodide (0.23ml, 3.73mmol) and anhydrous potassium carbonate (0.43g, 3.1mmol). The reaction was stirred at room temperature for 76 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (114mg, 72%), with the following physical properties: IR (film) $\upsilon max/cm^{-1}$ 2933, 1689, 1598, 1452, 1329, 1284, 1041 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.50-1.78 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.84 (2H, m, $CH_2CH_2C\underline{H}_2CHN$), 2.00 (2H, m, $COCH_2C\underline{H}_2$), 2.19-2.25 (5H, m, $C=CC\underline{H}_2$ and $C\underline{H}_3$), 2.52-2.61 (1H, m, $COC\underline{H}_2$), 2.87 and 2.91 (1H, 2 x dd, $J_1$=5.5, $J_2$=5Hz, $COC\underline{H}_2$), 3.30 and 3.46 (1H, 2 x broad m, $NC\underline{H}C=C$), 4.09 (1H, m, $NC\underline{H}Ar$), 5.72 (1H, m, $C\underline{H}=CH$), 5.83 (1H, m, $CH=C\underline{H}$), 7.34 (1H, m, 1 x Ar-$\underline{H}$), 7.54 (1H, m, 1 x Ar-$\underline{H}$), 7.76 (1H, m, 1 x Ar-$\underline{H}$), 8.01 (1H, m, 1 x Ar-$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.0 and 21.1, 24.7 and 24.8, 25.5 and 25.8, 25.9 and 26.2 (4 x $\underline{C}H_2$), 32.0 and 33.0 ($\underline{C}H_3$), 36.7 and 36.8 ($\underline{C}H_2CO$), 56.9 and 57.1 ($\underline{C}H$), 58.4 and 59.7 ($\underline{C}H$), 126.6 x 2, 126.7 x 2, 127.3 and 127.6, 129.5 and 129.7, 130.1 and 130.7, 132.8 and 132.9 (4 x Ar$\underline{C}H$ and $\underline{C}=\underline{C}$), 132.4 x 2 (Ar-$\underline{C}$), 146.3 and 146.4 (Ar-$\underline{C}$), 197.6 ($\underline{C}$=O); MS, m/z, (RI) 256 (M+1, 8), 255 ($M^+$, 8), 227 (100), 112 (17), 68 (23); HRMS ($+H^+$) 256.1692, $C_{17}$ $H_{22}$ N O requires 256.1701; error -3.6ppm.

**4-[allyl(2-cyclohexenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.11)**

To a solution of (**3.9**) (150mg, 0.62mmol) in acetone (10ml) was added allyl iodide (0.34ml, 3.73mmol) and anhydrous potassium carbonate (0.43g, 3.1mmol). The reaction was stirred at room temperature for 76 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet

ether:ethyl acetate, 10:1) to yield the amine as a pale oil (116mg, 66%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2933, 2863, 1691, 1598, 1452, 1286$cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.48-1.67 (2H, m, 2H of 3 x $C\underline{H}_2$), 1.79 (1H, m, 1H of 3 x $C\underline{H}_2$), 1.89-2.06 (3H, m, 3H of 3 x $C\underline{H}_2$), 2.12 (1H, m, 1H of $CH_2C\underline{H}_2CO$), 2.29 and 2.38 (1H, 2 x m, 1H of $C\underline{H}_2CH_2CO$), 2.51-2.62 (1H, m, 1H of $C\underline{H}_2CO$), 2.83 and 2.88 (1H, 2 x m, 1H of $C\underline{H}_2CO$), 3.23-3.37 and 3.54 (3H, 2 x m, $NC\underline{H}_2$ and $NC\underline{H}C{=}C$), 4.23 (1H, m, $C\underline{H}CH_2CH_2CO$), 5.07 (1H, m, $CH{=}C\underline{H}_2$), 5.21 (1H, m, $CH{=}C\underline{H}_2$), 5.73 and 5.80-5.92 (3H, 2 x m, $C\underline{H}{=}C\underline{H}$ and $C\underline{H}{=}CH_2$), 7.34 (1H, m Ar-C$\underline{H}$), 7.57 (1H, m, Ar-C$\underline{H}$), 7.94 (1H, m, Ar-C$\underline{H}$), 8.03 (1H, m, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.5 and 21.8, 24.6 and 24.7, 26.2 and 26.4, 27.9 and 29.1, 38.1 x 2 (5 x $\underline{C}H_2$), 48.8 and 49.0 ($\underline{C}H_2CO$), 53.7 and 54.2 ($\underline{C}H$), 56.4 and 57.5 ($\underline{C}H$), 115.5 and 115.8 ($\underline{C}H_2{=}C$), 126.4 x 2, 126.7 and 126.8, 127.0 and 127.1, 129.8 and 130.0, 129.9 and 132.1, 133.0 and 133.1, 137.8 and 138.0 (4 x Ar$\underline{C}$H, 1 x $CH_2{=}\underline{C}H$ and $\underline{C}{=}\underline{C}$), 132.7 x 2 (2 x Ar$\underline{C}$), 147.4 x 2 (2 x Ar$\underline{C}$), 197.3 ($\underline{C}{=}O$); MS, m/z, (RI) 282 (M+1, 34), 281 ($M^+$, 34), 253 (83), 225 (37), 138 (100); HRMS ($+H^+$) 282.1877, $C_{19}$ $H_{24}$ N O requires 282.1858; error 6.7ppm.

**4-[benzyl(2-cyclohexenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.12)**

To a solution of (**3.9**) (150mg, 0.62mmol) in acetone (10ml) was added benzyl bromide (0.49ml, 3.73mmol) and anhydrous potassium carbonate (0.43g, 3.1mmol). The reaction was stirred at room temperature for 76 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (130mg, 63%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2934, 1691, 1598, 1453, 1285$cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.54 (1H, m, 1H of 3 x $C\underline{H}_2$), 1.64-1.86 (2H, m, 2H of 3 x $C\underline{H}_2$), 1.91-2.09 (3H, m, 3H of 3 x $C\underline{H}_2$), 2.17 (1H, m, 1H of $C\underline{H}_2CH_2CO$), 2.41-2.58 (2H, m, 1H of $C\underline{H}_2$ and 1H of $C\underline{H}_2CO$), 2.85 and 2.90 (1H, 2 x m, 1H of $C\underline{H}_2CO$), 3.36 and 3.47 (1H, 2 x broad m, $NC\underline{H}C{=}C$), 3.81-3.95 (2H, m, $NC\underline{H}_2$), 4.12 and 4.19 (1H, 2 x dd, $J_1$=11Hz, $J_2$=3.5Hz, $C\underline{H}$ $CH_2CH_2CO$), 5.84 (2H, m, $C\underline{H}{=}C\underline{H}$), 7.24 (1H, m, Ar-C$\underline{H}$), 7.31-7.36 (3H, m, 3 x Ar-C$\underline{H}$), 7.43 (1H, m, Ar-CH), 7.47 (1H, m, Ar-C$\underline{H}$), 7.60 (1H, m, Ar-C$\underline{H}$), 8.03 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.5 and 21.9, 24.6, 25.3, 26.3, 27.2, 29.5 (4 x $\underline{C}H_2$), 38.0 and 38.1 ($\underline{C}H_2CO$), 49.7 and 49.9 ($N\underline{C}H_2$), 53.2 and 53.5 ($\underline{C}H$), 56.6 and 57.7 ($\underline{C}H$), 126.4, 126.5, 126.8 x 2, 127.0, 127.8 x 2, 128.0 (8 x Ar-$\underline{C}$H), 129.7, 130.2, 130.3, 132.1 (2 x $\underline{C}H{=}\underline{C}H$), 132.7 and 132.8 (Ar-$\underline{C}$), 133.0 and 133.1 (Ar-$\underline{C}$H), 140.7,

146.6 (2 x Ar-C), 197.2 x 2 (C=O); MS, m/z, (RI) 303 (100), 212 (19), 188 (42), 158 (19), 144 (15); HRMS ($+H^+$) 332.2007, $C_{23}$ $H_{26}$ N O requires 332.2014; error -2.2ppm.

**4-[2-cyclohexenyl(4-methylbenzyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.13)**

To a solution of (**3.9**) (150mg, 0.62mmol) in acetone (10ml) was added *p*-methylbenzyl bromide (0.57g, 3.11mmol) and anhydrous potassium carbonate (0.43g, 3.1mmol). The reaction was stirred at room temperature for 14 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine (39mg, 18%), as a pale oil: IR (film) υmax/$cm^{-1}$ 2934, 1691, 1598, 1514, 1453, 1330, 1284, 1150, 1022 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.54 (1H, broad m, 1H of C$H_2$), 1.66-1.81 (2H, m, 2H of C$H_2$), 1.99-2.23 (4H, m, 4H of C$H_2$), 2.36 (3H, s, C$H_3$), 2.44-2.57 (2H, m, 2H of C$H_2$, 2.89 (1H, 2 x m, 1H of COC$H_2$), 3.36 and 3.49 (1H, 2 x broad m, NCHC=C), 3.79-3.93 (2H, m, NC$H_2$), 4.14 and 4.20 (1H, 2 x m, ArCHN), 5.85 (2H, m, CH=CH), 7.17 (2H, m, 2 x Ar-CH), 7.34-7.39 (3H, m, 3 x Ar-CH), 7.62 (1H, m, 1 x Ar-CH), 8.05 (2H, m, 2 x Ar-CH). $^{13}$CNMR $\delta_C$ 20.6 (C$H_3$), 21.5 and 22.0, 2 x 24.7, 25.3 and 26.3, 27.3 and 29.5 (4 x C$H_2$), 38.1 and 38.2 (COC$H_2$), 49.4 and 49.6 (NC$H_2$), 53.1 and 53.4, 56.5 and 57.6 (2 x CH), 126.4 x 2, 126.8 x 2, 127.1 x 2, 127.8 x 2, 128.0 x 2, 128.6 x 4, 129.9 and 130.1, 130.2 and 132.3, 133.0 and 133.2 (8 x Ar-CH and CH=CH), 132.7 and 132.8, 135.9 x 2, 136.9 and 137.6, 146.7 and 147.1 (4 x Ar-C), 197.1 and 197.2 (C=O); MS, m/z, (RI) 346 (M+1, 5), 317 (100), 202 (44), 105 (26); HRMS ($+H^+$) 346.2146, $C_{24}$ $H_{28}$ N O requires 346.2171; error -7.3ppm.

**4-(2-cyclohexenyl-3,4,5-trimethoxyanilino)-1,2,3,4-tetrahydro-1-naphthalenone (3.14)**

To a solution of (**3.9**) (100mg, 0.42mmol) in DCM (10ml) was added 5-(bromomethyl)-1,2,3-trimethoxybenzene (0.21g, 0.84mmol, prepared in quantitative yield from 3,4,5-trimethoxybenzyl alcohol) and anhydrous potassium carbonate (0.5g, 3.6mmol). The reaction was stirred for 14 days at room temperature. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the trimethoxybenzamide as a pale oil (24mg, 14%). IR (film) υmax/$cm^{-1}$ 2935, 1693, 1591, 1505, 1464, 1419, 1329, 1236, 1132, 1011$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.52 (1H, m, 1H of C$H_2$), 1.67 (1H, m, 1H of C$H_2$), 1.80 (1H,

m, 1H of C$\underline{H}_2$), 1.89-2.06 (3H, m, 3H of C$\underline{H}_2$), 2.13 (1H, m, 1H of C$\underline{H}_2$), 2.38-2.53 (2H, m, 2H of C$\underline{H}_2$), 2.86 (1H, m, 1H of C$\underline{H}_2$CO), 3.35 and 3.49 (1H, 2 x broad m, NC$\underline{H}$C=C), 3.77-3.94 (5H, m, 3 x OC$\underline{H}_3$ and NC$\underline{H}_2$, with 3 x s for $OCH_3$ at 3.82, 3.84 and 3.85), 4.10-4.19 (2H, m, C$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$CO), 5.80 (2H, m, C$\underline{H}$=C$\underline{H}$), 6.65 (1H, s, $(CH_3O)_3$Ar-C$\underline{H}$), 6.70 (1H, s, $(CH_3O)_3$Ar-C$\underline{H}$), 7.32 (1H, m, Ar-C$\underline{H}$), 7.56 (1H, m, Ar-C$\underline{H}$), 7.97-8.05 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.4 and 21.9 (C$\underline{H}_2$), 24.6 x 2 (C$\underline{H}_2$), 25.4 and 26.3 (C$\underline{H}_2$), 27.2 and 29.4 (C$\underline{H}_2$), 37.9 x 2 (C$\underline{H}_2$CO), 50.0 x 2 (NC$\underline{H}_2$), 53.3 and 53.6 (C$\underline{H}$), 55.6 (3 x OC$\underline{H}_3$), 56.8 and 57.8 (C$\underline{H}$), 104.3 and 104.5 (2 x $(CH_3O)_3$-ArC$\underline{H}$), 126.6, 126.7, 126.9 x 2 (3 x Ar-C$\underline{H}$), 129.6, 130.2, 130.5, 131.8 (C$\underline{H}$=C$\underline{H}$), 132.8 (Ar-C$\underline{}$), 132.9 x 2 (Ar-C$\underline{H}$), 135.9, 136.3, 136.5 (3 x Ar-C$\underline{}$), 146.4 and 146.6, 152.7 x 2 (2 x Ar-C$\underline{}$), 197.0 x 2 (C$\underline{}$=O); MS, m/z, (RI) 422 (M+1, 1), 421 ($M^+$,1), 240 (75), 181 (100), 117 (8); HRMS (+$H^+$) 422.2329, $C_{26}$ $H_{32}$ N $O_4$ requires 422.2331; error -0.5ppm.

**4-[2-cyclohexenyl(2-naphthylmethyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (3.15)**

To a solution of (**3.9**) (100mg, 0.42mmol) in DCM (10ml) was added 2' bromomethyl naphthalene (0.18g, 0.81mmol). The reaction was stirred for 14 days at room temperature. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the tertiary amine, a diastereomeric mixture, as a pale oil (68mg, 43%). IR (film) υmax/$cm^{-1}$ 2935, 1692, 1598, 1285$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.46-2.02 (6H, m, 3 x C$\underline{H}_2$), 2.19 (1H, m, 1H of C$\underline{H}_2$), 2.46-2.62 (2H, m, C$\underline{H}_2$), 2.88 (1H, m, 1H of C$\underline{H}_2$), 3.45 (1H, m, C$\underline{H}$), 3.98-4.10 (2H, m, NC$\underline{H}_2$), 4.16 and 4.23 (1H, 2 x dd, $J_1$~11Hz, C$\underline{H}$), 5.90 (2H, br., C$\underline{H}$=C$\underline{H}$), 7.34 (1H, m, Ar-C$\underline{H}$), 7.47 (2H, m, 2 x Ar-C$\underline{H}$), 7.59-7.69 (2H, m, 2 x Ar-C$\underline{H}$), 7.83 (4H, m, 4 x Ar-C$\underline{H}$), 8.01 (1H, m, Ar-C$\underline{H}$), 8.07 and 8.10 (1H, 2 x d, J=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.5 and 21.9 (C$\underline{H}_2$), 24.6, 25.3, 26.4 (2) (2 x C$\underline{H}_2$), 27.2 and 29.5 (C$\underline{H}_2$), 38.1 x 2 (C$\underline{H}_2$CO), 50.0 and 50.1 (NC$\underline{H}_2$), 53.2 and 53.6, 56.6 and 57.6 (2 x C$\underline{H}$), 125.0, 125.5, 126.2, 126.3, 126.4, 126.5, 126.6, 126.8, 126.9, 127.0, 127.1, 127.2, 127.6, 129.7, 130.3, 130.4, 132.1 (C$\underline{H}$=C$\underline{H}$ and 10 x Ar-C$\underline{H}$), 132.3, 132.7, 132.9 (3 x Ar-C$\underline{}$), 133.0 and 133.2 (Ar-C$\underline{H}$), 137.5, 138.1 (2 x Ar-C$\underline{}$), 197.1 (C$\underline{}$=O); MS, m/z, (RI) 382 (M+1, 2), 381 ($M^+$, 2), 353 (83), 240 (72), 208 (43), 141 (100), 115 (69).

***N*1-(2-cyclohexenyl)-*N*1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide (3.16)**

To a solution of (**3.9**) (100mg, 0.42mmol) in pyridine (10ml) was added acetic anhydride (0.14ml, 0.84mmol) and a crystal of DMAP. The reaction was stirred for 7 days at room temperature with further addition of acetic anhydride (0.14ml) every 2 days. The reaction mixture was subjected to sequential acid (2M HCl) and base (2M NaOH) washings, and the organic layer (ether, 2 x 30ml), removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 1:1) to yield the acetamide (28mg, 24%): IR (film) υmax/$cm^{-1}$ 2941, 1692, 1648, 1426, 1286$cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.52-1.87, 1.98-2.41, 2.66 and 2.83 (m, 6 x C<u>H</u>$_2$, C<u>H</u>), 2.23 and 2.25 (3H, 2 x s, C<u>H</u>$_3$), 4.47 and 4.84 (m, C<u>H</u>), 5.71 and 5.95 (2H, 2 x m, C<u>H</u>=C<u>H</u>), 7.21-7.63 (3H, m, 3 x Ar-C<u>H</u>), 8.05 and 8.10 (1H, 2 x d, J=8Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 22.9 (<u>C</u>H$_3$), 23.8, 23.9, 28.3, 28.8 (4 x <u>C</u>H$_2$), 38.1 (<u>C</u>H$_2$CO), 53.9, 54.1 (<u>C</u>H), 127.2 x 4, 132.9, 133.1 (4 x Ar-<u>C</u>H and <u>C</u>H=<u>C</u>H), 170.7 (N<u>C</u>=O), 196.3, 196.4 (<u>C</u>=O); MS, m/z, (RI) 284 (M+1, 29), 160 (21), 138 (31), 115 (23), 96 (100); HRMS (+$H^+$) 284.1627, $C_{18}$ $H_{22}$ N $O_2$ requires 284.1651, (+$Na^+$) 306.1460, $C_{18}$ $H_{21}$ N $O_2$ Na requires 306.1470; errors -8.4ppm, -3.2ppm.

***N*1-(2-cyclohexenyl)-*N*1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-2-phenylacetamide (3.17)**

To a solution of (**3.9**) (20mg, 0.084mmol) in DCM (10ml) was added phenylacetyl chloride (100mg, 0.65mmol) and a crystal of DMAP. The reaction was stirred for 3 days at reflux. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the phenylacetamide as an off-white solid (11mg, 36%). M.p. 205-207°C; IR (film) υmax/$cm^{-1}$ 2931, 1690, 1654, 1640, 1560, 1543$cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.61 (2H, m, C<u>H</u>$_2$), 1.79 (2H, m, C<u>H</u>$_2$), 1.95-2.45 (4H, m, 2 x C<u>H</u>$_2$), 2.63 (1H, m, 1H of C<u>H</u>$_2$CO), 2.84 (1H, m, 1H of C<u>H</u>$_2$CO), 3.83 (2H, m, PhC<u>H</u>$_2$CO), 4.20-5.45 (2H, br. m, 2 x C<u>H</u>), 5.63 and 5.94 (C<u>H</u>=C<u>H</u>), 7.17-7.56 (8 x Ar-C<u>H</u>), 8.06 and 8.15 (1H, 2 x d, J=7.5Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 21.1, 24.0, 28.0, 28.5 (4 x <u>C</u>H$_2$), 38.1 (<u>C</u>H$_2$CO), 42.4 (Ph<u>C</u>H$_2$CO), 57.8, 59.9 (2 x <u>C</u>H), 124.6, 126.5, 127.2, 127.7, 128.3 x 2, 132.8, 134.6, 143.7, 144.9 (9 x Ar-<u>C</u>H, <u>C</u>H=<u>C</u>H, 3 x Ar-<u>C</u>), 169.4 (N<u>C</u>=O), 196.4 (<u>C</u>=O); MS, m/z, (RI) 360 (M+1,

100), 278 (19), 214 (39), 115 (22), 96 (88); HRMS (+$Na^+$) 382.1770, $C_{24}$ $H_{25}$ N $O_2$ Na requires 382.1783; error -3.3ppm.

**9-(2-cyclohexenylamino)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.20)**

To a solution of 9-amino-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (**3.19**) [prepared from the bromo precursor via the azide and BOC-protected amine] (2.4g, 13.7mmol) in DCM (10ml) was added 3-bromocyclohexene (1.57ml, 13.7mmol), and, dropwise, triethylamine (3.83ml, 27.4mmol). The reaction was stirred at room temperature for two hours, before partitioning between acid and base, and the rebasified organic extract columned on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine, a diastereomeric mixture, as a pale yellow oil (1g, 29%): IR (film) υmax/$cm^{-1}$ 2933, 2862, 1685, 1601, 1449, 1244, 1103$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.01 (1H, NH), 1.15-1.23 and 1.27-1.42 (2H, m, $CH_2$), 1.54 (1H, m, $CH_2$), 1.60-1.74 (4H, m, 4H of $CH_2$), 1.84 (2H, m, 2H of $CH_2$), 1.98 (1H, m, 1H of $CH_2$), 2.45 and 2.49 (1H, dd, $J_1$~4.5Hz, 1H of $CH_2CO$), 2.74 (1H, broad m, NCHC=C), 2.87 (1H, m, 1H of $CH_2CO$), 4.17 (1H, m, NCHAr), 5.46-5.72 (1H, m, CH=CH), 7.25 (1H, m, Ar-CH), 7.30-7.38 (2H, m, 2 x Ar-CH), 7.42 (1H, 2 x d, J=7.5Hz, 1 x Ar-CH); $^{13}$CNMR $\delta_C$ 19.3, 19.7, 19.8, 19.9 (2 x $CH_2$), 24.7 and 24.8 ($CH_2$), 27.8 and 29.6 ($CH_2$), 32.2 and 32.4 ($CH_2$), 40.5 and 40.6 ($CH_2$), 48.8 and 49.3 (CH), 56.3 and 56.9 (CH), 126.4 and 126.5 (Ar-CH), 127.1, 127.4 (2 x Ar-CH), 128.0, 128.2, 128.6, 130.1, 130.7 x 2 (CH=CH and Ar-CH), 138.7 (Ar-C), 141.1 and 141.5 (Ar-C), 206.9 (C=O); MS, m/z, (RI) 256 (M+1, 100), 255 ($M^+$, 24); HRMS (+$H^+$) 256.1677, $C_{17}$ $H_{22}$ N O requires 256.1701; error -9.4ppm.

**9-[2-cyclohexenyl(methyl)amino]-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.21)**

To a solution of (**3.20**) (0.35g, 1.37mmol) in acetone (10ml) was added methyl iodide (0.5ml, 8.03mmol) and anhydrous potassium carbonate (0.5g, 3.62mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a clear oil (0.29g, 79%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2934, 1686, 1450, 1278, 1245, 1008$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.38-2.29 (10H, m, 5 x $CH_2$), 1.97 and 2.23 (3H, 2 x s, $CH_3$),

2.50 and 2.54 (1H, 2 x dd, $J_1$~7.5Hz, $J_2$~3Hz, 1H of C$\underline{H}_2$CO), 2.86-2.94 (1H, m, 1H of C$\underline{H}_2$CO), 2.98 and 3.53 (1H, m, C$\underline{H}$), 3.84 (1H, m, C$\underline{H}$), 5.38 and 5.56 (1H, m, 1H of C$\underline{H}$=CH), 5.70 and 5.79 (1H, m, 1H of CH=C$\underline{H}$), 7.30-7.36 (2H, m, 2 x Ar-C$\underline{H}$), 7.41 (Ar-C$\underline{H}$), 7.47 (1H, m, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 19.6 x 2, 20.0 and 21.1, 21.4 and 22.1, 24.6 and 24.7, 26.5 and 26.8 (5 x $\underline{C}H_2$), 33.3 and 33.6 ($\underline{C}H_3$), 39.7 and 39.8 ($\underline{C}H_2$CO), 54.6 and 54.8 ($\underline{C}$H), 63.9 and 64.3 ($\underline{C}$H), 126.8, 127.0, 127.1 x 2, 127.4 x 2, 128.6, 128.8, 129.2, 130.3, 130.4, 130.8 (4 x Ar-$\underline{C}$H and $\underline{C}$H=$\underline{C}$H), 139.0 and 139.2 (Ar-$\underline{C}$), 141.2 and 141.9 (Ar-$\underline{C}$), 206.1 and 206.4 ($\underline{C}$=O); MS, m/z, (RI) 270 (M+1, 37), 269 ($M^+$, 16), 241 (67), 213 (100); HRMS (+$H^+$) 270.1850, $C_{18}$ $H_{24}$ N O requires 270.1858; error -3.0ppm.

**9-[allyl(2-cyclohexenyl)amino]-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.22)**

To a solution of (**3.20**) (0.25g, 0.98mmol) in acetone (10ml) was added allyl iodide (0.5ml, 5.5mmol) and anhydrous potassium carbonate (0.5g, 3.62mmol). The reaction was stirred at reflux for 7 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a clear oil (0.09g, 30%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2934, 2865, 1686, 1458, 1280, 1242$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.31-1.53 (2H, m, C$\underline{H}_2$), 1.69-2.00 (7H, m, 4H of 4 x C$\underline{H}_2$), 2.01-2.14 (1H, m, 1H of C$\underline{H}_2$), 2.53-2.67 and 2.81-2.95 (2H, 2 x m, C$\underline{H}_2$CO), 3.10-3.52 (3H, m, NC$\underline{H}_2$ and C$\underline{H}$CH=CH), 4.13 (1H, m, NC$\underline{H}$Ar), 4.96-5.13 (2H, m, C$\underline{H}_2$=CH), 5.57 and 5.75 (2H, 2 x m, C$\underline{H}$=C$\underline{H}$), 5.79-5.98 (1H, m, $CH_2$=C$\underline{H}$), 7.30 (1H, m, Ar-C$\underline{H}$), 7.43 (1H, m, Ar-C$\underline{H}$), 7.51 (1 diasteromer H, dd, $J_1$=7.5, $J_2$=1.5Hz), 7.57 (1H, m, Ar-CH), 7.69 (1 diasteromer H, d, J=7.5Hz, 1 diasteromer of COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.0 and 21.0 ($\underline{C}H_2$), 21.5 and 21.6 ($\underline{C}H_2$), 24.7 and 24.8 ($\underline{C}H_2$), 25.1 and 25.5 ($\underline{C}H_2$), 28.2 and 29.3 ($\underline{C}H_2$), 40.1 and 40.2 ($\underline{C}H_2$CO), 49.7 and 50.3 ($\underline{C}H_2$N), 55.1 and 55.3 ($\underline{C}$H), 60.3 and 61.3 ($\underline{C}$H), 114.8 and 115.0 ($\underline{C}H_2$=CH), 126.5 and 126.7 (Ar-$\underline{C}$H), 127.2, 127.4 x 2, 127.7 (2 x Ar-$\underline{C}$H), 129.2 and 129.8, 130.2, 130.6 and 130.7, 138.6 and 139.0 (Ar-$\underline{C}$H, $\underline{C}$H=$\underline{C}$H and $CH_2$=$\underline{C}$H), 138.0 (Ar-$\underline{C}$), 142.6 and 143.8 (Ar-$\underline{C}$), 205.5 and 206.3 ($\underline{C}$=O); MS, m/z, (RI) 296 (M+1, 100), 295 ($M^+$, 18), 267 (22), 211 (24), 131 (19); HRMS (+$H^+$) 296.2006, $C_{20}$ $H_{26}$ N O requires 296.2014; error -2.8ppm.

**9-[benzyl(2-cyclohexenyl)amino]-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.23)**

To a solution of (**3.20**) (0.25g, 0.98mmol) in acetone (10ml) was added benzyl bromide (0.58ml, 4.88mmol) and anhydrous potassium carbonate (0.5g, 3.62mmol). The reaction was stirred at reflux for 7 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a clear oil (85mg, 25%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2933, 2864, 1686, 1599, 1495, 1453, 1280, 1124$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.37-1.57 (2H, m, C$\underline{H}_2$), 1.61-1.90 (5H, m, 5H of C$\underline{H}_2$), 1.91-2.06 (2H, m, C$\underline{H}_2$), 2.10-2.28 (1H, m, 1H of C$\underline{H}_2$), 2.60 and 2.75 (2H, 2 x m, C$\underline{H}_2$CO), 3.35 and 3.42 (1H, 2 x broad m, C$\underline{H}$CH=CH), 3.76-4.02 (2H, m, NC$\underline{H}_2$), 4.20 (NC$\underline{H}$Ar), 5.69-5.87 (2H, m, C$\underline{H}$=C$\underline{H}$), 7.25 (1H , m, Ar-C$\underline{H}$), 7.32-7.38 (3H, m, 3 x Ar-C$\underline{H}$), 7.44-7.63 (4H, m, 4 x Ar-C$\underline{H}$), 7.86 and 7.96 (1H, 2 x d, J=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.0 and 20.3 (C$\underline{H}_2$), 21.6 and 21.7 (C$\underline{H}_2$), 24.7 and 24.8 (C$\underline{H}_2$), 25.0 and 26.5 (C$\underline{H}_2$), 29.1 and 29.9 (C$\underline{H}_2$), 40.2 and 40.3 (C$\underline{H}_2$CO), 50.8 and 51.6 (NC$\underline{H}_2$), 55.2 and 55.3 (C$\underline{H}$), 60.9 and 61.5 (C$\underline{H}$), 126.1 x 2 (Ar-C$\underline{H}$), 126.5 and 126.6 (Ar-C$\underline{H}$), 127.2, 127.3, 127.4, 127.5, 127.7 x 2, 127.8 (6 x Ar-C$\underline{H}$), 129.8 and 129.9, 130.2, 130.9 x 2 (C$\underline{H}$=C$\underline{H}$ and Ar-C$\underline{H}$), 138.8 and 138.9 (Ar-C), 141.1 and 141.8 (Ar-C), 142.7 and 143.7 (Ar-C), 205.6 and 206.5 (C=O); MS, m/z, (RI) 346 (M+1, 100), 345 ($M^{+\cdot}$ 28), 317 (61), 289 (47), 266 (54), 246 (24), 186 (100), 158 (21); HRMS ($+H^+$) 346.2186, $C_{24}$ $H_{28}$ N O requires 346.2171; error 4.4ppm.

**3-(1,2,3,4-tetrahydro-1-naphthalenylamino)-1-indanone (4.1)**

To a stirred solution of 3-bromoindanone [formed in 56% yield from 5g 1-indanone] (4.5g, 21.3mmol) in DCM (30ml) was added triethylamine (5.58ml, 42.6mmol) and 1-aminotetralin (3.14g, 21.3mmol). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine as a diastereomeric mixture, (4.3g, 72%): IR (KBr disc) υmax/$cm^{-1}$ 2933, 1702, 1602, 1467, 1280, 1132$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.60 (1H, br. s, N$\underline{H}$), 1.85, 2.02, 2.20 (4H, 3 x m, ArCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 2.60 (1H, m, 1H of C$\underline{H}_2$), 2.79 (1H, m, 1H of C$\underline{H}_2$), 2.91 (1H, m, 1H of C$\underline{H}_2$), 3.10 (1H, m, 1H of C$\underline{H}_2$), 4.00 and 4.08 (C$\underline{H}$), 4.57 and 4.64 (C$\underline{H}$), 7.16 (3H, m, 3

x Ar-C<u>H</u>), 7.32-7.45 (2H, m, 2 x Ar-C<u>H</u>), 7.61-7.80 (3H, m, 3 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 18.3 and 18.5 (<u>C</u>$H_2$), 27.6 and 28.6 (<u>C</u>$H_2$), 29.0 and 30.0 (<u>C</u>$H_2$), 45.8 and 46.7 (<u>C</u>$H_2$CO), 52.9, 53.5, 54.6, 55.0 (2 x <u>C</u>H), 122.8, 125.3 and 125.5, 125.5 and 125.6, 126.5 and 126.6, 128.1 x 2, 128.3 and 128.4, 128.7 and 128.8, 134.4 (8 x Ar-<u>C</u>H), 136.0 and 136.4, 137.0 and 137.1, 138.4 and 138.6, 156.2 and 156.5 (4 x Ar-<u>C</u>), 204.2 (C=O); MS, m/z, (RI) 278 (M+1, 4), 277 ($M^+$, 2), 148 (85), 130 (100), 103 (26).

**3-[methyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone (4.2)**

To a stirred solution of (**4.1**) (0.5g, 1.81mmol) in acetone (10ml) was added methyl iodide (0.56ml, 9.05mmol) and anhydrous potassium carbonate (0.38ml, 2.72mmol). The reaction was stirred for 2 days at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a yellow solid, with the following physical characteristics (0.34g, 65%): IR (film) υmax/cm$^{-1}$ 2937, 2864, 1718, 1603, 1277, 1040cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.56-2.21 (4H, m, 2 x C<u>H</u>$_2$), 1.88 and 2.28 (3H, 2 x s, C<u>H</u>$_3$), 2.57-2.95 (4H, m, C<u>H</u>$_2$ and C<u>H</u>$_2$CO), 4.01 and 4.09 (1H, 2 x dd, $J_1$=9.5Hz, $J_2$=5Hz, NC<u>H</u>CH$_2$CH$_2$), 4.51 and 4.74 (1H, 2 x dd, $J_1$=7Hz, $J_2$=3.7Hz, NC<u>H</u>CH$_2$CO), 7.10-7.27 (3H, m, 3 x Ar-C<u>H</u>), 7.45 (1H, m, Ar-C<u>H</u>), 7.66-7.79 (2H, m, 2 x Ar-C<u>H</u>), 7.83-7.97 (2H, m, 2 x Ar-C<u>H</u>). $^{13}$CNMR $\delta_C$ 18.6 and 18.8, 27.9 and 29.0, 29.3 and 30.3 (3 x <u>C</u>$H_2$), 30.8 (<u>C</u>$H_3$), 46.1 and 47.1 (<u>C</u>$H_2$CO), 53.3 and 53.9, 54.9 and 55.4 (2 x <u>C</u>H), 122.8 x 2, 125.3 and 125.5, 125.5 and 125.6, 128.1 x 2, 128.3 and 128.4, 128.7 and 128.8, 134.4 x 2 (8 x Ar-<u>C</u>H), 136.0 and 136.3, 137.0 and 137.1, 138.3 and 138.5, 156.1 and 156.4 (4 x Ar-<u>C</u>), 204.2 x 2 (<u>C</u>=O); MS, m/z, (RI) 292 (M+1, 100), 291 ($M^+$, 27), 221 (16), 198 (15), 162 (79); HRMS (+$H^+$) 292.1729, $C_{20}$ $H_{22}$ N O requires 292.1701; error 9.5ppm.

Data for one diasteromer of (**4.2**), aliphatic protons only: (cf Figures 4.3 and 4.4)

| Label | $\delta^{13}C$ (ppm) | $\delta^{1}H$ (ppm), mult, J (Hz) | TOCSY (H-H) | HMQC (C-H) | HMBC |
|---|---|---|---|---|---|
| 1 | 204.3 | - | - | - | H2 |
| 2 | 38.5 | 2.57, dd, 18.6, 7<br>2.87, dd, 18.6, 3.5 | H2 x 1, H3<br>H2 x 1 | H2 | |
| 3 | 55.7 | 4.48, dd, 7, 3.5 | H2 | H3 | H2, H8 |
| 8 | 33.2 | 2.28, s | - | H8 | H3 |
| 1' | 61.9 | 4.00, dd, 9, 4.5 | H2' | H1 | H2', H3, H8 |
| 2' | 25.1 | 1.63, m<br>2.17, m | H3' x 1, H2' x 1<br>H2' x 1, H3' x 1 | | H1', H3'. H4' |
| 3' | 21.5 | 1.71, m<br>2.07, m | H4<br>H3' x 1, H4 | | H2', H4' |
| 4' | 29.5 | 2.76, m<br>2.87, m | H3'<br>H3' | H4' | H2', H3' |

**3-[allyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone (4.3)**

To a stirred solution of (**4.1**) (0.5g, 1.81mmol) in acetone (10ml) was added allyl iodide (0.83ml, 9.05mmol) and anhydrous potassium carbonate (0.38ml, 2.72mmol). The reaction was stirred for 2 days at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a yellow oil (0.24g, 42%): IR (KBr disc, HCl salt) $\upsilon max/cm^{-1}$ 2937, 2523, 1602, 1438, 1278$cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.59, 1.72, 1.84, 1.92-2.22, 2.64-2.98 (9H, 5 x m, 9H of 5 x $C\underline{H}_2$), 3.23 (1H, m, 1H of 5 x $C\underline{H}_2$), 4.16 (1H, m, $C\underline{H}CH_2CH_2$), 4.51 and 4.66 (1H, broad m and t, $J_t$=5Hz, $C\underline{H}CH_2CO$), 4.83 and 4.96, 5.09 and 5.23 (2H, 2 x dd, J=10Hz and 17.9Hz, $CH=C\underline{H}_2$), 5.65 and 5.85 (1H, 2 x m, $C\underline{H}=CH_2$), 7.09 (1H, m, Ar-C$\underline{H}$), 7.15-7.31 (2H, m, 2 x Ar-C$\underline{H}$), 7.43 (1H, m, Ar-C$\underline{H}$), 7.64-7.82 (3H, m, 3 x Ar-C$\underline{H}$), 7.90 and 8.08 (1H, 2 x d, J=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.5 and 21.9, 25.1 and 27.6, 29.2 and 29.6 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2$), 40.1 and 41.5 ($N\underline{C}H_2$), 47.8 and 49.4 ($\underline{C}H_2CO$), 55.0, 57.0, 58.1, 59.7 (2 x $\underline{C}H$), 115.4 and 116.4 ($CH=\underline{C}H_2$), 122.3 and 122.6, 125.3 and 125.5 (2 x Ar-$\underline{C}H$), 125.9, 126.0, 126.1, 126.4 (2 x Ar-$\underline{C}H$), 127.1, 127.8, 128.0 (2) (2 x Ar-$\underline{C}H$), 128.5 and 128.6, 133.9 and 134.5 (2 x Ar-$\underline{C}H$), 136.6 and 137.4 (Ar-$\underline{C}H$), 136.6 and 136.8 (Ar-$\underline{C}$), 138.1, 138.5, 138.5 (2) (2 x Ar-$\underline{C}$), 156.3 and 156.6 (Ar-$\underline{C}$), 204.3 and 204.4 ($\underline{C}$=O) [One 'Ar-$\underline{C}$H') signal is the $\underline{C}H=CH_2$]; MS, m/z, (RI) 318 (M+1, 5), 188 (100), 131 (61), 103 (22); HRMS (+$Na^+$) 340.1671, $C_{22}$ $H_{23}$ N O Na requires 340.1677; error -1.9ppm.

**_N_1-(3-oxo-2,3-dihydro-1H-1-indenyl)-_N_1-(1,2,3,4-tetrahydro-1-naphthalenyl)acetamide (4.4)**

To a stirred solution of (**4.1**) (150mg, 0.54mmol) in DCM (10ml) was added triethylamine (0.15ml, 1.08mmol), acetic anhydride (0.10ml, 1.08mmol) and a crystal of DMAP. The reaction was stirred overnight at room temperature, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 3:1) to yield the acetamide (separable diastereomers) as white crystals (85mg, 49%): IR (KBr disc) υmax/$cm^{-1}$ 2946, 1706, 1645, 1449, 1427, 1307$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.94 (2H, m, C$\underline{H}_2$), 2.08-2.28 (5H, m, C$\underline{H}_2$ and C$\underline{H}_3$), 2.47 (2H, m, C$\underline{H}_2$), 2.85 (2H, m, C$\underline{H}_2$), 3.20 (1H, m, C$\underline{H}$), 4.38 and 5.17 (1H, 2 x m, C$\underline{H}$), 7.16 (1H, m, Ar-C$\underline{H}$), 7.21-7.26 (3H, m, 3 x Ar-C$\underline{H}$), 7.38 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.48 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.60 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.73 (1H, d, J=7.5Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.7 (C$\underline{H}_2$), 23.7 (C$\underline{H}_3$), 29.0, 30.7 x 2 (3 x C$\underline{H}_2$), 42.3, 53.8 (2 x C$\underline{H}$), 123.0 (3), 126.0, 127.3, 129.2, 134.0 (2) (8 x Ar-C$\underline{H}$), 154.3 (NC$\underline{=}$O), 202.6 (C$\underline{=}$O). HRMS (+$Na^+$) 342.1441, $C_{21}$ $H_{22}$ N $O_2$ requires 342.1470; error -8.4ppm.

**4-(2,3-dihydro-1_H_-1-indenylamino)-1,2,3,4-tetrahydro-1-naphthalenone (4.5)**

To a solution of 1-indanol (1g, 7.46mmol) in ether (5ml) at –15°C was slowly added phosphorus tribromide ($PBr_3$, 0.28ml, 2.98mmol). The reaction was stirred for 30 minutes, and poured into ice/water. The organic layer was separated and the aqueous layer washed twice with ether (2 x 10ml). The combined organic layers were quickly washed with aqueous sodium bicarbonate (2.5%), dried over sodium sulphate, and concentrated. To the flask was then added acetone (10ml), 4-amino-1,2,3,4-tetrahydro-1-naphthalenone (1.20g, 7.46mmol) and triethylamine (2.08ml, 14.92mmol). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield a diastereomeric mixture of the amine as a brown oil (0.52g, 25%): IR (film) υmax/$cm^{-1}$ 2946, 2851, 1687, 1600, 1477, 1452, 1285$cm^{-1}$; $^{13}$CNMR $\delta_C$ 29.4 and 29.5 (C$\underline{H}_2$), 29.9 and 30.0 (C$\underline{H}_2$), 34.1 and 34.3 (C$\underline{H}_2$), 35.1 and 35.5 (C$\underline{H}_2$CO), 53.0 and 53.9 (C$\underline{H}$CH$_2$CH$_2$CO), 60.5 and 61.3 (ArCH$_2$CH$_2$C$\underline{H}$Ar), 123.6 and 123.7, 124.2 and 124.4, 125.9 and 126.0, 126.8 and 126.9, 127.1 x 2, 127.3 and 127.4, 127.6 and 127.8 (7 x Ar-C$\underline{H}$), 131.7 and 131.8 (Ar-C$\underline{}$),

133.0 and 133.3 (Ar-CH), 142.8 and 142.9, 145.0 and 145.3, 145.7 x 2 (3 x Ar-C), 197.8 and 198.0 (C=O); MS, m/z, (RI) 277 ($M^+$, 80), 160 (44), 145 (21), 132 (100), 117 (72).

**4-[2,3-dihydro-1*H*-1-indenyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (4.6)**

To a stirred solution of (**4.5**) (100mg, 0.36mmol) in acetone (10ml) was added methyl iodide (0.04ml, 0.72mmol) and anhydrous potassium carbonate (0.25g, 1.80mmol). The reaction was refluxed for 6 hours at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale brown oil (91mg, 87%): IR (film) υmax/$cm^{-1}$ 2947, 1692, 1284$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.14 and 2.25 (3H, 2 x m, 3H of $CH_2$), 2.11 and 2.32 (3H, 2 x s, $CH_3$), 2.40 (1H, m, 1H of $CH_2$), 2.61 (1H, m, 1H of $CH_2$), 2.85 (1H, m, 1H of $CH_2$), 2.96-3.06 (2H, m, $CH_2$), 4.15 and 4.22 (1H, 2 x dd, $J_1$~9Hz, $J_2$~4Hz, CH), 4.55 (1H, m, CH), 7.25-7.27 (3H, m, 3 x Ar-CH), 7.38-7.52 (2H, m, 2 x Ar-CH), 7.60 (1H, m, Ar-CH), 7.87-7.88 (1H, m, Ar-CH), 8.07 (1H, 2 x d, J=8Hz, Ar-CH); $^{13}$CNMR $\delta_C$ 25.9 and 26.0, 26.1 and 26.7 (2 x $CH_2$), 30.1 and 30.3 ($CH_2$), 33.9 ($CH_3$), 36.1 and 36.7 ($CH_2CO$), 60.3 and 61.7, 64.8 and 68.4 (2 x CH), 124.2, 124.4, 124.6, 125.9, 126.0, 127.0 x 2, 127.1, 127.2, 127.4, 127.8 (7 x Ar-CH), 132.5, 132.6 (2 x Ar-C), 132.9 and 133.0 (Ar-CH), 197.2 and 197.3 (C=O); MS, m/z, (RI) 291 ($M^+$, 31), 174 (23), 146 (100); HRMS (+$H^+$) 292.1695, $C_{20}$ $H_{22}$ N O requires 292.1701; error -2.1ppm.

**4-[(3-oxo-2,3-dihydro-1*H*-1-indenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (4.7)**

To a stirred solution of 3-bromoindanone [formed in 63% yield from 1g 1-indanone] (0.68g, 3.23mmol) in DCM (10ml) was added triethylamine (0.90ml, 6.46mmol) and 4-amino-1,2,3,4-tetrahydro-1-naphthalenone (0.52g, 3.23mmol, liberated from (**3.7**) by treatment with trifluoracetic acid). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield a diastereomeric mixture of the amine as a green-brown oil (0.39g, 42%). IR (film) υmax/$cm^{-1}$ 2955, 1702, 1676, 1600, 1462, 1340, 1285$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.68 (1H, broad s, NH), 2.14 and 2.30-2.41 (2H, 2 x m, $CH_2CH_2CO$), 2.51-2.63 (2H, m, $CH_2CH_2CO$), 3.02-3.21 (2H, m, $CHCH_2CO$), 4.15 and 4.18 (1H, 2 x dd, $J_1$=5Hz, $J_2$=3.5Hz, CH), 4.40 and 4.64 (1H, 2 x

dd, $J_1$=6.7Hz, $J_2$=3.5Hz, C<u>H</u>), 7.33-7.70 (7H, m, 7 x Ar-C<u>H</u>), 7.99 and 8.03 (1H, 2 x dd, $J_1$=7.5Hz, $J_2$=1Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 26.9 and 29.5 (<u>C</u>$H_2CH_2CO$), 33.8 x 2 ($CH_2$<u>C</u>$H_2CO$), 45.4 and 45.7 (CH<u>C</u>$H_2CO$), 53.3 and 53.5 (<u>C</u>H), 53.9 and 54.1 (<u>C</u>H), 122.7 and 122.8, 125.6 x 2, 126.8 and 127.2 (3 x Ar-<u>C</u>H), 127.6, 127.7 x 2, 127.9 (2 x Ar-<u>C</u>H), 128.3 and 128.4 (Ar-<u>C</u>H), 131.7 and 131.8 (Ar-<u>C</u>), 132.9 and 133.4, 134.5 x 2 (2 x Ar-<u>C</u>H), 136.0 and 136.2, 144.4 and 144.7, 155.4 and 155.7 (3 x Ar-<u>C</u>), 197.4 (<u>C</u>=O), 203.6 (<u>C</u>=O); MS, m/z, (RI) 292 (M+1, 23), 291 ($M^+$, 86), 160 (42), 146 (93), 132 (100), 115 (69), 103 (73), 77 (62), 51 (29).

**4-[methyl(3-oxo-2,3-dihydro-1*H*-1-indenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (4.8)**

To a stirred solution of (**4.7**) (100mg, 0.34mmol) in acetone (10ml) was added methyl iodide (0.11ml, 1.70mmol) and anhydrous potassium carbonate (0.24g, 1.72mmol). The reaction was stirred for 2 days at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as an off-white solid (71mg, 68%): IR (film) υmax/cm$^{-1}$ 2949, 2791, 1707, 1678, 1597, 1332, 1284, 1040cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.99 and 2.19 (3H, 2 x s, C<u>H</u>$_3$), 2.16 and 2.34 (2H, 2 x m, C<u>H</u>$_2$C$H_2$CO), 2.51-2.72 (2H, m, C<u>H</u>$_2$CO), 2.81 and 2.86 (1H, 2 x dd, $J_1$=12Hz, $J_2$~4Hz, 1H of C<u>H</u>$_2$CO), 2.92-3.02 (1H, m, 1H of C<u>H</u>$_2$CO), 4.05 and 4.10 (1H, 2 x dd, $J_1$~9Hz, $J_2$=3.5Hz, C<u>H</u>C$H_2$CH2), 4.52 and 4.64 (1H, 2 x dd, $J_1$=7Hz, $J_2$=4Hz, C<u>H</u>C$H_2$CO), 7.37-7.45 (2H, m, 2 x Ar-C<u>H</u>), 7.57-7.75 (4H, m, 4 x Ar-C<u>H</u>), 7.82 and 7.93 (1H, 2 x d, J=7.5 and 8Hz, COAr-C<u>H</u>), 8.03 (1H, 2 x irr. dd, $J_1$=8Hz, $J_2$=1.5Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 25.6 and 25.7 (<u>C</u>$H_2CH_2CO$), 29.3 and 33.2 (<u>C</u>$H_3$), 35.2 and 36.5 (<u>C</u>$H_2$), 36.9 and 37.8 (<u>C</u>$H_2$), 56.6 and 60.3 (<u>C</u>H$CH_2CO$), 60.9 and 61.9 <u>C</u>H$CH_2CH_2$), 122.6 and 122.7 (Ar-<u>C</u>H), 125.8 and 125.9 (Ar-<u>C</u>H), 127.1, 127.2 x 2, 127.5, 127.7 (3 x Ar-<u>C</u>H), 128.2 and 128.3 (Ar-<u>C</u>H), 132.5 and 132.6 (Ar-<u>C</u>), 132.9 and 133.0 (Ar-<u>C</u>H), 134.5 x 2 (Ar-<u>C</u>H), 136.5 and 136.7 (Ar-<u>C</u>), 144.4 and 144.6 (Ar-<u>C</u>), 155.2 and 155.4 (Ar-<u>C</u>), 196.9 and 197.3 (<u>C</u>=O), 203.5 and 203.6 (<u>C</u>=O); MS, m/z, (RI) 306 (M+1, 15), 305 ($M^+$, 23), 174 (20), 161 (100), 146 (68), 131 (15); HRMS (+$H^+$) 306.1508, $C_{20}$ $H_{20}$ N $O_2$ requires 306.1494; error 4.6ppm.

**4-(1,2,3,4-tetrahydro-1-naphthalenylamino)-1,2,3,4-tetrahydro-1-naphthalenone (4.9)**

To a solution of α-tetralol (**2.4**) (1g, 6.76mmol) in ether (10ml) at –15°C was added $PBr_3$ (0.73g, 2.70mmol), dropwise over 5 minutes. The reaction was stirred for 30 minutes, and poured into ice/water. The organic layer was separated and the aqueous layer washed twice with ether (2 x 10ml). The combined organic layers were quickly washed with aqueous sodium bicarbonate (2.5%), dried over sodium sulphate, and concentrated, to yield the bromide. To the flask was then added acetone (10ml), 4-amino-1,2,3,4-tetrahydro-1-naphthalenone (1.08g, 6.76mmol) and, dropwise, triethylamine (1.87ml, 13.42mmol). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, the residue extracted with acid, the aqueous acid layer removed and re-extracted with base and DCM, and the re-basified organic extract concentrated and purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield a diastereomeric mixture of the amine as a pale golden oil (0.41g, 21%). IR (film) υmax/$cm^{-1}$ 2937, 2863, 1689, 1601, 1451, 1283$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.21 (NH), 1.86 (1H, m, 1H of $CH_2$), 1.92-2.28 (4H, m, 2 x $CH_2$), 2.41 (1H, m, 1H of $CH_2$), 2.64 (1H, m, 1H of $CH_2$), 2.74-2.95 (2H, m, $CH_2$), 3.19 (1H, m, 1H of $CH_2$), 3.91 and 4.06 (1H, 2 x dd, $J_1$~5.5Hz, $J_2$~4Hz, CH), 4.21 (1H, m, CH), 7.13 (1H, m, Ar-CH), 7.20 (2H, m, 2 x Ar-CH), 7.31-7.44 (2H, m, 2 x Ar-CH), 7.56 (2H, m, Ar-CH), 8.10 (1H, 2 x d, J=8Hz, COAr-CH); $^{13}$CNMR $\delta_C$ 18.4 and 18.6 ($CH_2$), 27.3 and 27.7 ($CH_2$), 28.9 and 29.1 ($CH_2$), 29.4 x 2 ($CH_2$), 34.0 and 34.5 ($CH_2CO$), 52.0 and 52.1 (CH), 53.3 x 2 (CH), 125.4 and 125.5 (Ar-CH), 126.4 x 2 (Ar-CH), 126.7 and 127.0 (Ar-CH), 127.2 and 127.4 (Ar-CH), 127.8 and 127.9 (Ar-CH), 128.4 and 128.7 (Ar-CH), 128.7 x 2 (Ar-CH), 131.6 and 131.8 (Ar-C), 133.1 and 133.3 (Ar-CH), 136.8 and 137.0 (Ar-C), 138.8 and 139.2 (Ar-C), 145.8 and 146.1 (Ar-C), 197.8 and 197.9 (C=O); MS, m/z, (RI) 292 (M+1, 26), 213 (15), 162 (61), 131 (100).

**4-[methyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (4.10)**

To a stirred solution of (**4.9**) (100mg, 0.34mmol) in acetone (10ml) was added methyl iodide (0.11ml, 1.70mmol) and anhydrous potassium carbonate (0.24g, 1.70mmol). The reaction was refluxed for 6 hours, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate,

10:1) to yield the amine as a pale oil (92mg, 88%). IR (film) υmax/$cm^{-1}$ 2936, 2361, 2342, 1691, 1550, 1283$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.58 (NH), 1.63-2.10 (4H, m, 2 x $CH_2$), 2.05 and 2.16 (3H, 2 x s, $CH_3$), 2.27 and 2.41 (2H, 2 x m, $CH_2CH_2CO$), 2.57 (1H, m, 1H of $CH_2CO$), 2.66-2.92 (2H, m, $CH_2$), 3.03 (1H, m, 1H of $CH_2CO$), 3.83 and 4.21 (1H, 2 x irr. dd, $J_1$~9Hz, $J_2$~4.5Hz, $CHCH_2CH_2CH_2$), 4.05 (1H, m, $CHCH_2CH_2CO$), 7.03-7.17 (3H, m, 3 x Ar-CH), 7.39 (1H, m, Ar-CH), 7.51-7.62 (2H, m, 2 x Ar-CH), 7.67 and 7.70 (1H, 2 x d, J=7.8Hz, Ar-CH), 8.03 (1H, m, Ar-CH); $^{13}$CNMR $\delta_C$ 20.9 and 21.1, 23.3, 26.0 and 26.1, 29.0 and 29.2 (4 x $CH_2$), 31.7 and 33.9 ($CH_3$), 34.9 and 35.3 ($CH_2CO$), 57.8 and 58.9 (CH), 59.4 and 59.7 (CH), 125.4, 125.8, 127.0, 127.1, 127.2 (4 x Ar-CH), 127.5, 127.7, 128.0, 128.3, 128.5 (3 x Ar-CH), 132.5 (Ar-CH), 137.8 (2 x Ar-C), 138.7 and 145.7 (2 x Ar-C), 198.0 (C=O); MS, m/z, (RI) 306 (M+1, 5), 176 (76), 162 (100), 131 (100); HRMS (+$H^+$) 306.1884, $C_{21}$ $H_{24}$ N O requires 306.1858; error 8.7ppm.

**_N,N_-di(1,2,3,4-tetrahydro-1-naphthalenyl)amine (4.11)**

To a solution of 1-bromotetralin (0.76g, 3.6mmol), in DCM (10ml) was added 1-aminotetralin (0.65g, 3.6mmol) and triethylamine (1ml, 7.2mmol). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine as a brown oil (0.17g, 17%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2932, 2859, 1489, 1449, 1155, 1091$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.37 (NH), 1.92 (2H, m, $CH_2$), 2.04-2.15 (4H, m, 2 x $CH_2$), 2.15-2.35 (2H, m, $CH_2$), 2.83-2.94 (2H, m, $CH_2$), 2.97 and 3.01 (1H, 2 x dd, $J_1$=6.5Hz, $J_2$=5.3Hz, 1H of $CH_2$), 4.14 (2H, m, 2 x NCH), 7.19-7.29 (6H, m, 6 x Ar-CH), 7.47 and 7.52 (1H, 2 x irr. dd, $J_1$=5.5Hz, Ar-CH); $^{13}$CNMR $\delta_C$ 18.4, 18.5, 27.8, 28.9, 29.2, 30.0 (6 x $CH_2$), 51.9, 54.1 (2 x CH), 125.3, 125.4, 126.1, 126.3, 128.4, 128.5, 128.7, 128.9 (8 x Ar-CH), 136.9, 137.2, 139.6, 139.9 (4 x Ar-C); MS, m/z, (RI) 278 (M+1, 100), 277 ($M^+$, 25), 247 (10), 214 (17).

***N*-methyl- *N,N*-di(1,2,3,4-tetrahydro-1-naphthalenyl)amine (4.12)**

To a solution of N,N-di(1,2,3,4-tetrahydro-1-naphthalenyl)amine (**4.11**) (0.17g, 0.61 mmol) in acetone (10ml) was added methyl iodide (0.19ml, 3.05mmol) and finely ground,

anhydrous potassium carbonate (0.42g, 3.05mmol). The reaction was refluxed for 48 hours, with the 12 hourly addition of methyl iodide (0.19ml, 3.05mmol). On completion, the reaction was filtered, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (89mg, 50%): IR (film) υmax/$cm^{-1}$ 2933, 2862, 1679, 1550, 1488, 1450$cm^{-1}$. $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.75-1.87 (2H, m, C$\underline{H}_2$), 1.99-2.20 (6H, m, 3 x C$\underline{H}_2$), 2.10 (3H, s, C$\underline{H}_3$), 2.75-2.84 (2H, m, C$\underline{H}_2$), 2.90-3.02 (2H, m, C$\underline{H}_2$), 4.08 (2H, m, 2 x NC$\underline{H}$), 7.13 (2H, m, 2 x Ar-C$\underline{H}$), 7.18-7.28 (4H, m, 4 x Ar-C$\underline{H}$), 7.68 and 7.81 (2H, 2 x d, J=7.8Hz, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.4, 20.9, 24.9, 25.3, 29.0 x 2 (6 x $\underline{C}H_2$), 29.8, 33.8 ($\underline{C}H_3$), 58.7, 61.4 (2 x $\underline{C}$H), 125.0, 125.1, 125.8 x 2, 128.0, 128.3 x 2, 128.4 (8 x Ar-$\underline{C}$H), 137.9 x 2, 138.9, 139.7 (4 x Ar-$\underline{C}$); MS, m/z, (RI) 292 (M+1, 100), 291 ($M^+$, 46), 278 (45), 223 (18), 160 (33), 132 (82); HRMS ($+H^+$) 292.2078, $C_{21}$ $H_{26}$ N requires 292.2065; error; error 4.2ppm.

**1-(2-acetylbenzyl)-1,2-triazadien-2-ium (4.13)**

To a solution of 2′-methylacetophenone (4.87ml, 37.3mmol) in $CCl_4$ (50ml) was added *N*-bromosuccinimide (9.94g, 55.9mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and monitored by TLC. When TLC analysis showed exhaustion of the starting material, the crude reaction mixture was filtered, and the solvent removed *in vacuo*. The residue thus obtained, a dark, fuming oil, was not further purified but reacted immediately with sodium azide (5g, 76.9mmol) in DMF (5ml) at 40°C. After four hours, the reaction mixture was partitioned between ether and water (3 x 50ml each) and the ethereal fractions combined. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the azide as a colourless oil (2.37g, 36%): IR (film) υmax/$cm^{-1}$ 2943, 2104, 1685, 1253$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.62 (3H, s, C$\underline{H}_3$), 4.75 (2H, s, C$\underline{H}_2$), 7.43 (1H, m, Ar-C$\underline{H}$), 7.53 (2H, m, 2 x Ar-C$\underline{H}$), 7.83 (1H, d, J=8Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 28.5 ($\underline{C}H_3$), 52.7 ($\underline{C}H_2$), 127.5, 129.4, 129.7, 131.9 (4 x Ar-$\underline{C}$H), 135.7, 135.9 (2 x Ar-$\underline{C}$), 200.3 ($\underline{C}$=O). Upon reaction under hydrogenation conditions in the presence of Di-*tert* butyl dicarbonate, only decomposition was observed.

**1-[2-(bromomethyl)phenyl]ethyl acetate (4.15)**

To a stirred solution of 2′-methylacetophenone (5g, 37.3mmol) in methanol (10ml) at 0°C was added sodium borohydride (1.65g, 44.8mmol). The solution was stirred for two hours, allowing the reaction to reach room temperature. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the alcohol, which was reacted with acetic anhydride (7.03ml, 74.5mmol) in DCM (10ml), with the inclusion of triethylamine (15.6ml, 0.12mol) and a crystal of DMAP. After three hours at room temperature, the solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield acetate (**4.14**) (6.03g, 91%) as a colourless oil. To a solution of (**4.14**) (3g, 16.8mmol) in $CCl_4$ (50ml) was added *N*-bromosuccinimide (4.5g, 25.3mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and upon reaching reflux, the heat source was removed and replaced by two 240W lamps, the light from these focussed on the reaction, stirring vigorously all the time. The reaction was filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the brominated product, a diastereomeric mixture, as a colourless, lachrymatory oil that slowly crystallised on standing (3.67g, 85%); $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.63 (3H, m, $C\underline{H}_3CH$), 2.07 and 2.12 (3H, 2 x s, $C\underline{H}_3CO$), 4.50 and 4.95 (2H, 2 x d, J=10Hz, $C\underline{H}_2$), 6.10 and 6.19 (1H, 2 x q, J=6.5Hz, C$\underline{H}$), 7.26-7.39 (3H, m, 3 x Ar-C$\underline{H}$), 7.49 and 8.01 (1H, 2 x d, J=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.8 and 20.9 ($\underline{C}H_3$), 21.3 and 21.5 ($\underline{C}H_3$), 37.5 ($\underline{C}H_2$), 68.1 and 69.2 ($\underline{C}H$), 126.1 and 126.5, 127.8 and 128.6, 128.9 and 129.5, 130.0 and 130.3 (4 x Ar-$\underline{C}$H), 134.5 and 135.4, 138.9 and 140.3 (2 x Ar-$\underline{C}$), 169.6 and 169.9 ($\underline{C}$=O). Upon attempted reaction with either cyclopentylamine or 1-aminotetralin in DCM/$Et_3N$, only decomposition was observed.

**1-2-[1-(acetyloxy)ethyl]benzyl-1,2-triazadien-2-ium (4.16)**

To a solution of (**4.15**) (2.5g, 9.73mmol) in DMF (10ml) was added sodium azide (2g, 30.8mmol). The resultant slurry was heated on an oil bath for 2 hours at 50°C, and then partitioned between water and ether. The aqueous layer was washed twice with ether (2 x 50ml portions) and the combined ethereal layers dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica

gel (eluant: pet ether:ethyl acetate, 10:1) to yield the azide as a clear oil (1.06g, 50%), with the following physical properties: IR (film) vmax/$cm^{-1}$ 2986, 2097, 1734, 1372, 1243$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.57 (3H, d, J=6.5Hz, $C\underline{H}_3CH$), 2.03 (3H, s, $C\underline{H}_3CO$), 4.51 (2H, dd, $J_2$=13.5Hz, $C\underline{H}_2$), 6.07 (1H, q, J=6.5Hz, C<u>H</u>), 7.29 (2H, m, 2 x Ar-C<u>H</u>), 7.38 (1H, m, Ar-C<u>H</u>), 7.52 (1H, d, J=7.6Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 20.6 ($\underline{C}H_3$), 21.6 ($\underline{C}H_3$), 51.9 ($\underline{C}H_2$), 68.2 (<u>C</u>H), 126.2, 127.6, 128.6, 129.4 (4 x Ar-<u>C</u>H), 131.9, 140.5 (2 x Ar-<u>C</u>), 169.6 (<u>C</u>=O).

**_tert_-butyl _N_-[2-(1-hydroxyethyl)benzyl]carbamate (4.17)**

Di-*tert*-butyl dicarbonate (0.82g, 3.76mmol) was added to a solution of the azide (**4.16**) (0.75g, 3.42mmol) in EtOH:EtOAc (1:1, ml). After addition of 10% Pd/C the reaction was stirred under an atmosphere of hydrogen overnight at room temperature. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the BOC-protected amine alcohol as a white crystalline solid (0.33g, 38%), with the following NMR characteristics: 1.26 (3H, m, $C\underline{H}_3$), 1.50 (9H, s, $(C\underline{H}_3)_3$), 2.70 (2H, br. m, $C\underline{H}_2$), 4.36 and 4.96 (3H, 2 x br., C<u>H</u>, N<u>H</u> and O<u>H</u>), 7.16-7.29 (4H, m, 4 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 14.8 ($\underline{C}H_3CH$), 24.9 ($\underline{C}H_2$), 28.0 (($\underline{C}H_3)_3$), 78.8 ($\underline{C}(CH_3)_3$), 125.6, 127.2, 127.9, 128.8 (4 x Ar-<u>C</u>H), 135.6, 141.7 (2 x Ar-<u>C</u>), 155.3 (<u>C</u>=O). Upon liberation of the free amine (alcohol), reaction with 3-bromoindanone in DCM using $Et_3N$ as tertiary base was unsuccessful.

**4-chromanol (4.19)**

To an evaporating dish containing polyphosphoric acid (10g) was added 3-phenoxypropanoic acid (5g, 30.1mmol). The mixture was stirred using a glass rod over a water bath, until the solid material had dissolved. The reaction was heated thus for 30 minutes, stirring constantly. The coloured raw reaction mixture was quenched using ice water and partitioned between ether and water. The combined ethereal layers (3 x 50ml) were concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the chromanone (**4.18**) (4.1g, 92%) as a white solid, in agreement with literature data, MS, m/z, (RI) 149 (M+1, 21), 148 ($M^+$, 100), 92 (42). To a stirred solution of the ketone (4g, 27mmol) in methanol (20ml) was slowly added $NaBH_4$ (1.4g, 40mmol). After one hour of stirring, the solvent was removed

and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the chromanol (**4.19**) as a pale colourless oil (3.6g, 89%). $^1$H NMR analysis showed homology with literature data: $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.93 and 2.04 (2H, 2 x m, $OCH_2C\underline{H}_2$), 3.13 (1H, broad s, O<u>H</u>), 4.19 (2H, m, $OC\underline{H}_2$), 4.66 (1H, t, J=4Hz, C<u>H</u>), 6.84 (1H, d, J=8.6Hz, Ar-C<u>H</u>), 6.91 (1H, dd, $J_1$=8.3Hz, $J_2$=7Hz, Ar-C<u>H</u>), 7.20 (1H, dd, $J_1$=8.5Hz, $J_2$=7.8Hz, $J_3$=1Hz, Ar-C<u>H</u>), 7.27 (1H, d, J=7.5Hz, Ar-C<u>H</u>); MS, m/z, (RI) 150 ($M^+$, 57), 134 (100).

**3,4-dihydro-2*H*-4-chromenyl azide (4.20)**

To a stirred solution of 4-chromanol (**4.19**) (2g, 13.3mmol) in ether (10ml) at –15°C was added $PBr_3$ (1.44g, 5.3mmol), drop-wise over 5 minutes. The reaction was stirred for 15 minutes, and poured into ice/water. The organic layer was separated and the aqueous layer washed twice with ether (2 x 40ml). The combined organic layers were quickly washed with aqueous sodium bicarbonate (2.5%), dried over sodium sulphate, and concentrated. To the flask was immediately added sodium azide (4g, 61.5mmol) and DMF (10ml), and the reaction stirred at 45°C on an oil bath for 2 hours. To the residue was added water (50ml) and the aqueous mixture extracted with ether (3 x 25ml). The combined organic extracts were concentrated *in vacuo*, and purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the azide as a pale colourless oil (1.86g, 80%): IR (film) υmax/cm$^{-1}$ 2968, 2008, 2105, 1610, 1585, 1490, 1457cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.05 (1H, m, 1H of $OCH_2C\underline{H}_2$), 2.18 (1H, m, 1H of $OCH_2C\underline{H}_2$), 4.24-4.34 (2H, m, $OC\underline{H}_2$), 4.62 (1H, t, J=3.8Hz, C<u>H</u>), 7.01 (2H, m, 2 x Ar-C<u>H</u>), 7.31 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 27.7 ($\underline{C}H_2$), 54.3 (<u>C</u>H), 61.7 ($O\underline{C}H_2$), 117.1 (Ar-<u>C</u>H), 118.9 (Ar-<u>C</u>), 120.0, 129.5, 129.8 (3 x Ar-<u>C</u>H), 154.3 (Ar-<u>C</u>).

***tert*-butyl *N*-(3,4-dihydro-2*H*-4-chromenyl)carbamate (4.21)**

Di-*tert*-butyl dicarbonate (0.16g, 0.73mmol) was added to a solution of the azide (**4.20**) (0.12g, 0.67mmol) in EtOH:EtOAc (1:1, 4ml). After addition of 10% Pd/C the reaction was stirred under an atmosphere of hydrogen overnight at room temperature. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the BOC-protected amine as a white crystalline solid (42mg, 25%) with the following physical

properties: M.p. 106-108°C; IR (KBr disc) υmax/cm$^{-1}$ 2964, 1679, 1523, 1250, 1104, 1066cm$^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.50 (9H, s, (($C\underline{H}_3)_3C$), 2.08 and 2.20 (2H, br. m, $C\underline{H}_2CH$), 4.17 and 4.25 (2H, br. m, $C\underline{H}_2CO$), 4.86 (2H, br. m, C<u>H</u> and N<u>H</u>), 6.82 (1H, d, J=8.5Hz, OAr-C<u>H</u>), 6.91 (1H, dd, $J_1$=8.3Hz, $J_2$=7Hz, Ar-C<u>H</u>), 7.18 (1H, dd, $J_1$=8.8Hz, $J_2$=7.5Hz, Ar-C<u>H</u>), 7.28 (1H, d, J=7.4Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 28.0 ($\underline{C}H_3$), 29.0 ($\underline{C}H_2$), 44.3 (<u>C</u>H), 62.7 ($O\underline{C}H_2$), 79.2 (($CH_3)_3\underline{C}$), 116.6, 120.2 (2 x Ar-<u>C</u>H), 122.0 (Ar-<u>C</u>), 128.7, 128.9 (2 x Ar-<u>C</u>H), 154.5 and 154.7 (Ar-<u>C</u> and <u>C</u>=O); MS, m/z, (RI) 194 (95), 148 (100), 133 (55), 131 (44).

**3-(3,4-dihydro-2*H*-4-chromenylamino)-1-indanone (4.22)**

A 1:1 mixture of DCM:TFA was added to the BOC-protected amine (**4.21**) (0.5g, 2.01mmol) and the reaction mixture stirred at 0°C for 30 minutes. The solvent was removed *in vacuo*, using toluene as azeotrope (3 x 20ml), to yield the amine trifluoroacetate. Washing with base and extracting the organic layer with DCM afforded 3,4-dihydro-2*H*-4-chromenylamine, a brown oil. To the flask was added 3-bromoindanone (0.42g, 2mmol), triethylamine (0.42ml, 3mmol) and acetone (10ml). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine, a diastereomeric mixture, as a yellow oil (0.24g, 44%): IR (film) υmax/cm$^{-1}$ 2955, 1721, 1490, 1270, 1226cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.55 (1H, broad s, N<u>H</u>), 1.86 and 2.16 (2H, 2 x m, $OCH_2C\underline{H}_2$), 2.53 and 2.56 (1H, 2 x dd, $J_1$=18.5Hz, $J_2$=3Hz, $C\underline{H}_2CO$), 3.06 and 3.10 (1H, 2 x dd, $J_1$=18.5Hz, $J_2$=6.5Hz, $C\underline{H}_2CO$), 3.96 and 4.06 (1H, 2 x t, J=3.5Hz, C<u>H</u>), 4.20 and 4.46 (2H, 2 x m, $OC\underline{H}_2$), 4.56 (1H, m, C<u>H</u>), 6.81-6.90 (2H, m, 2 x Ar-C<u>H</u>), 7.11-7.18 and 7.27 (2H, m, 2 x Ar-C<u>H</u>), 7.41 (1H, m, Ar-C<u>H</u>), 7.58-7.67 (2H, m, 2 x Ar-C<u>H</u>), 7.71 (1H, m, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 26.8 and 29.1 ($CH_2\underline{C}H_2CH$), 45.8 and 46.2 ($\underline{C}H_2CO$), 49.2 and 50.2 (<u>C</u>H), 52.7 and 54.0 (<u>C</u>H), 61.8 and 61.9 ($O\underline{C}H_2$), 116.5 and 116.6 (Ar-<u>C</u>H), 119.6 and 119.9 (Ar-<u>C</u>H), 122.7 and 122.8 (Ar-<u>C</u>H), 123.5 and 123.6 (Ar-<u>C</u>), 125.5 and 125.8 (Ar-<u>C</u>H), 128.2 and 128.3 (Ar-<u>C</u>H), 128.4 and 128.5 (Ar-<u>C</u>H), 129.1 and 129.3 (Ar-<u>C</u>H), 134.4 x 2 (Ar-<u>C</u>H), 136.1 and 136.4 (Ar-<u>C</u>), 154.3 and 154.5 (Ar-<u>C</u>), 155.6 and 156.1 (Ar-<u>C</u>), 203.6 and 203.8 (<u>C</u>=O); MS, m/z, (RI) 280 (M+1, 9), 251 (98), 148 (81), 133 (100), 105 (25); HRMS (+H$^+$) 280.1348, $C_{18}$ $H_{18}$ N $O_2$ requires 280.1338; error 3.8ppm.

**3-[3,4-dihydro-2*H*-4-chromenyl(methyl)amino]-1-indanone (4.23)**

To a solution of (**4.22**) (0.2g, 0.72mmol) in acetone (10ml) was added methyl iodide (0.22ml, 3.58mmol) and anhydrous potassium carbonate (0.20g, 1.45mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (0.20g, 94%), with the following physical properties: IR (KBr disc, HCl salt) υmax/$cm^{-1}$ 2926, 1720, 1609, 1492, 1460, 1228, 1056$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.89, 2.03, 2.14, 2.26 (2H, 4 x m, $OCH_2C\underline{H}_2$), 1.91 and 2.24 (3H, 2 x s, $C\underline{H}_3$), 2.57-2.90 (2H, m, $C\underline{H}_2CO$), 4.06-4.24 (2H, m, $OC\underline{H}_2$), 4.41 and 4.48 (1H, 2 x m, C<u>H</u>), 4.57 and 4.72 (1H, 2 x m, $C\underline{H}CH_2CO$), 6.83 (1H, m, Ar-C<u>H</u>), 6.96 (1H, m, Ar-C<u>H</u>), 7.16 (1H, m, Ar-C<u>H</u>), 7.44 (1H, m, Ar-C<u>H</u>), 7.60-7.77 (3H, m, 3 x Ar-C<u>H</u>), 7.81 (1H, m, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 24.2 and 24.5 ($OCH_2\underline{C}H_2$), 28.0 and 33.0 ($N\underline{C}H_3$), 37.8 and 38.1 ($\underline{C}H_2CO$), 55.6 and 57.1 (<u>C</u>H), 58.4 and 60.9 (<u>C</u>H), 64.0 and 64.7 ($O\underline{C}H_2$), 116.5 x 2, 119.8 and 120.0, 122.5 x 2 (3 x Ar-<u>C</u>H), 123.1 and 123.4 (Ar-<u>C</u>), 125.9 (Ar-<u>C</u>H), 128.0, 128.1, 128.1, 128.2, 128.8 (3 x Ar-<u>C</u>H), 134.4 and 134.5 (Ar-<u>C</u>H), 136.4 and 136.6 (Ar-<u>C</u>), 155.3, 155.7, 155.8 (2 x Ar-<u>C</u>), 203.9 (<u>C</u>=O); MS, m/z, (RI) 294 (M+1, 6), 293 ($M^+$, 4), 265 (18), 248 (15), 160 (73), 133 (100), 105 (93), 77 (54), 51 (17); HRMS ($+H^+$) 294.1470, $C_{19}$ $H_{20}$ N $O_2$ requires 294.1494; error -8.2ppm.

**7-methoxy-1,2,3,4-tetrahydro-1-naphthalenone (4.24)**

To an evaporating dish containing polyphosphoric acid (10g) was added 4-(4-methoxyphenyl)butyric acid (5g, 25.7mmol). The mixture was stirred using a glass rod over a water bath, until the solid material had dissolved. The reaction was heated thus for 30 minutes, stirring constantly. The coloured raw reaction mixture was quenched using iced water and partitioned between ether and water. The combined ethereal layers (3 x 50ml) were concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the ketone product as white needles (3.4g, 75%), with the following physical properties: IR (KBr disc) υmax/$cm^{-1}$ 2944, 1682, 1611, 1497, 1424, 1328, 1279, 1235$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.12 (2H, quintet, J=6.3Hz, $CH_2C\underline{H}_2CH_2$), 2.65 (2H, t, J=6.5Hz, $C\underline{H}_2$), 2.90 (2H, t, J=6Hz, $C\underline{H}_2$), 3.83 (3H, s, $OC\underline{H}_3$), 7.06 (1H, dd, $J_1$=8.3Hz, $J_2$=2.8Hz, Ar-C<u>H</u>),

7.16 (1H, d, J=8Hz, Ar-C<u>H</u>), 7.51 (1H, d, J=3Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 23.0 ($CH_2\underline{C}H_2CH_2$), 28.4 ($\underline{C}H_2Ar$), 38.4 ($\underline{C}H_2CO$), 55.0 ($\underline{C}H_3O$), 108.8 (Ar-<u>C</u>H), 121.5 (Ar-<u>C</u>H), 129.5 (Ar-<u>C</u>H), 132.7 (Ar-<u>C</u>), 136.9 (Ar-<u>C</u>), 157.9 (Ar-<u>C</u>), 198.8 (<u>C</u>=O); MS, m/z, (RI) 176 ($M^+$, 100), 120 (19).

**4-azido-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenone (4.26)**

To a solution of the alcohol (**4.25**) [obtained from ketone (**4.24**) through $NaBH_4$ reduction, MS, m/z, (RI) 178 ($M^+$, 38), 161 (100)] (3g, 17.0mmol) in ether (10ml) at –15°C was added $PBr_3$ (1.82g, 6.8mmol), drop-wise over 5 minutes. The reaction was stirred for 15 minutes, and poured into ice/water. The organic layer was separated and the aqueous layer washed twice with ether (2 x 20ml). The combined organic layers were quickly washed with aqueous sodium bicarbonate (2.5%), dried over sodium sulphate, and concentrated. To the flask was immediately added sodium azide (5.5g, 85mmol) and DMF (5ml), and the reaction was stirred at 45°C on an oil bath for 2 hours. To the residue was added water (50ml) and the aqueous mixture extracted with ether (3 x 25ml). The combined organic extracts were concentrated *in vacuo*, and purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the azide as a pale colourless oil (2.11g, 62%): IR (film) υmax/cm$^{-1}$ 2939, 2097, 1613, 1505cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.84 (1H, m, 1H of C<u>H</u>$_2$), 1.94-2.06 (3H, m, 3H of C<u>H</u>$_2$), 2.67-2.85 (2H, m, C<u>H</u>$_2$), 3.84 (3H, s, OC<u>H</u>$_3$), 4.55 (1H, t, J=4.6Hz, C<u>H</u>), 6.83-6.87 (2H, m, 2 x Ar-C<u>H</u>), 7.08 (1H, d, J=8Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 18.9 ($\underline{C}H_2$), 27.5 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 54.9 ($\underline{C}H_3$), 59.3 (<u>C</u>H), 112.9 (Ar-<u>C</u>H), 114.4 (Ar-<u>C</u>H), 128.8 (Ar-<u>C</u>), 129.9 (Ar-<u>C</u>H), 134.3 (Ar-<u>C</u>), 157.4 (Ar-<u>C</u>).

**3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone (4.28)**

Di-*tert*-butyl dicarbonate (1.93g, 8.84mmol) was added to a solution of the azide (**4.27**) (1.63g, 8.03mmol) in EtOH:EtOAc (1:1, 4ml). After addition of 10% Pd/C the reaction was stirred under an atmosphere of hydrogen overnight at room temperature. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield BOC-protected amine (**4.27**) as a white crystalline solid. A 1:1 mixture of DCM:TFA was added to the BOC-protected amine (0.47g, 1.70mmol) and the reaction mixture stirred at 0°C for 30

minutes. The solvent was removed *in vacuo*, using toluene to create an azeotrope (3 x 20ml), to yield the amine trifluoroacetate. Washing with base and extracting the organic layer with DCM afforded 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine, as a brown oil. To the flask was added 3-bromoindanone (0.36g, 1.71mmol), triethylamine (0.47ml, 3.37mmol) and DCM (10ml). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine, a diastereomeric mixture, as a yellow oil (0.36g, 69%): IR (film) υmax/$cm^{-1}$ 2937, 1719, 1503, 1465, 1271, 1252, 1233$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.50 (1H, br. s, NH), 1.82, 2.02, 2.16 (4H, 3 x m, 2 x $CH_2$), 2.61 (1H, 2 x dd, 1H of $CH_2$), 2.68-2.87 ($CH_2$), 3.12 (1H, dd, $J_1$~11Hz, $J_2$~7Hz, 1H of $CH_2$), 3.77 and 3.81 (3H, 2 x s, $OCH_3$), 3.95 and 4.04 (1H, 2 x dd, $J_1$=5.5Hz, $J_2$=4.5Hz, CH), 4.60 and 4.65 (1H, 2 x dd, $J_1$=6.5Hz, $J_2$=3Hz, CH), 6.77 (1H, m, Ar-CH), 6.89-7.07 (2H, m, 2 x Ar-CH), 7.45 (1H, m, Ar-CH), 7.62-7.78 (3H, m, 3 x Ar-CH); $^{13}$CNMR $\delta_C$ 18.6 and 18.9 ($CH_2$), 27.8 x 2 ($CH_2$), 28.1 and 30.2 ($CH_2$), 45.8 and 46.8 ($CH_2CO$), 52.8, 53.8, 54.6, 55.3 (2 x CH), 54.8 ($OCH_3$), 112.3 and 112.8 (Ar-CH), 113.1 and 113.4 (Ar-CH), 122.8 (Ar-CH), 125.5 (Ar-CH), 128.1 x 2 (Ar-CH), 129.1 and 129.2 (quat. C), 129.6 x 2 (Ar-CH), 134.4 (Ar-CH), 136.1 and 136.4, 139.4 and 139.7, 156.1 and 156.4, 127.2 and 157.4 (4 x quat. C), 204.1 and 204.1 (C=O); MS, m/z, (RI) 308 (M+1, 3), 160 (100), 148 (47), 103 (18).

**3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)(methyl)amino]-1-indanone (4.29)**

To a stirred solution of (**4.28**) (0.36g, 1.17mmol) in acetone (10ml) was added methyl iodide (0.37ml, 5.85mmol) and anhydrous potassium carbonate (0.16g, 1.17mmol). The reaction was stirred overnight at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine as a golden oil (0.30g, 81%): IR (KBr disc, HCl salt) υmax/$cm^{-1}$ 2939, 1722, 1612, 1508, 1465, 1244, 1034$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.54-1.92 (2H, m, $CH_2$), 1.89 and 2.29 (3H, 2 x s, $NCH_3$), 2.05-2.16 (2H, 2 x m, $CH_2$), 2.55-2.94 (4H, m, $CH_2$ and $CH_2CO$), 3.87 and 3.88 (3H, 2 x s, $OCH_3$), 3.97 and 4.15 (1H, 2 x dd, $J_1$~10Hz, $J_2$=5 and 7.5Hz, CH), 4.52 and 4.74 (1H, 2 x irr. dd, $J_1$=7.5Hz, CH), 6.76 (1H, m, Ar-CH), 7.01 and 7.03 (1H, 2 x s, Ar-CH), 7.41-7.57 (2H, m, 2 x Ar-CH), 7.66-7.78 (2H, m, 2 x Ar-CH), 7.88 (1H, 2 x d, J=3.5Hz, COAr-CH); $^{13}$CNMR $\delta_C$ 21.5 and 21.8, 24.7 and 25.0 (2 x $CH_2$), 27.3 and 33.2 ($NCH_3$), 28.2 and 28.7 ($CH_2$), 38.5 and

38.6 ($\underline{C}H_2CO$), 54.8 x 2 ($O\underline{C}H_3$), 55.7 and 61.7 ($\underline{C}H$), 62.2 and 63.5 ($\underline{C}H$), 112.0 x 2, 112.6 and 112.8, 122.4 x 2, 125.8 and 126.0, 127.9 and 128.0, 129.3 and 129.5 (6 x Ar-$\underline{C}H$), 130.1 and 130.3 (Ar-$\underline{C}$), 134.3 and 134.4 (Ar-$\underline{C}H$), 136.4 and 136.5, 139.2 x 2, 156.2 and 156.4, 157.6 x 2 (4 x Ar-$\underline{C}$), 204.2 and 204.3 ($\underline{C}$=O).

**5-methoxy-1-indanone** and **5-methoxy-1-indanone**

To an evaporating dish containing polyphosphoric acid (10g) was added 3-(3-methoxyphenyl)propanoic acid (10g, 55.6mmol). The mixture was stirred using a glass rod over a water bath, until the solid material had dissolved. The reaction was heated thus for 30 minutes, stirring constantly. The coloured raw reaction mixture was quenched using ice water and partitioned between ether and water. The combined ethereal layers (3 x 50ml) were concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the two isomeric ketones as a 4:1 ratio favouring the 5-substituted derivative. Both isomers were obtained as white solids, with the following physical properties:

**5-methoxy-1-indanone (4.31)**

IR (KBr disc) υmax/$cm^{-1}$ 2942, 1708, 1602, 1304, 1257$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.63 (2H, t, J=6Hz, C$\underline{H}_2$), 3.05 (2H, t, J=6Hz, C$\underline{H}_2$CO), 3.86 (3H, s, OC$\underline{H}_3$), 6.87 (2H, m, 2 x Ar-C$\underline{H}$), 7.66 (1H, d, J=9Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.4 ($\underline{C}H_2$), 35.9 ($\underline{C}H_2CO$), 55.1 ($O\underline{C}H_3$), 109.3 (Ar-$\underline{C}H$), 114.8 (Ar-$\underline{C}H$), 124.8 (Ar-$\underline{C}H$), 129.9 (Ar-$\underline{C}$), 157.7 (Ar-$\underline{C}$), 164.8 (Ar-$\underline{C}$), 204.7 ($\underline{C}$=O); MS, m/z, (RI) 163 (M+1, 100), 115 (7).

**7-methoxy-1-indanone (4.32)**

IR (KBr disc) υmax/$cm^{-1}$ 2926, 1695, 1592, 1484, 1299, 1279, 1238, 1203$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.65 (2H, t, J=5-6Hz, C$\underline{H}_2$), 3.06 (2H, t, J=5-6Hz, C$\underline{H}_2$CO), 3.93 (3H, s, OC$\underline{H}_3$), 6.76 (1H, d, J=8Hz, Ar-C$\underline{H}$), 6.99 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.50 (1H, dd, $J_1$=8.3Hz, $J_2$=7.7Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.1 ($\underline{C}H_2$), 36.3 ($\underline{C}H_2CO$), 55.2 ($O\underline{C}H_3$), 108.4 (Ar-$\underline{C}H$), 118.0 (Ar-$\underline{C}H$), 124.7 (Ar-C), 135.9 (Ar-$\underline{C}H$), 157.5 (Ar-$\underline{C}$), 157.7 (Ar-$\underline{C}$), 204.4 ($\underline{C}$=O); MS, m/z, (RI) 163 (M+1, 100), 162 ($M^+$, 20), 133 (26), 91 (20).

**3-bromo-5-methoxy-1-indanone (4.33)**

To a solution of (**4.31**) (1.51g, 9.32mmol) in $CCl_4$ (30ml) was added *N*-bromosuccinimide (1.66g, 9.32mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and on reaching reflux careful monitoring by TLC showed the progress of the reaction. On completion, the reaction was filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the unstable brominated product as a yellow oil (1.12g, 50%): $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 3.04 and 3.35 (2H, 2 x dd, $J_1$=19.7Hz, $J_2$=3.2 and 7.5Hz, C$\underline{H}_2$), 3.94 (3H, s, OC$\underline{H}_3$), 5.54 (1H, dd, $J_1$=7.5Hz, $J_2$=2.5Hz, C$\underline{H}$Br), 7.01 (1H, dd, $J_1$=8.4Hz, $J_2$=2.2Hz, Ar-C$\underline{H}$), 7.11 (1H, d, J=2Hz, Ar-C$\underline{H}$), 7.69 (1H, d, J=8.6Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 40.2 (C$\underline{H}_2$), 47.8 (C$\underline{H}_3$), 55.4 (C$\underline{H}$), 109.8, 117.5, 124.6 (3 x Ar-C$\underline{H}$), 128.9, 156.7, 165.4 (3 x Ar-$\underline{C}$), 199.0 ($\underline{C}$=O).

**3-bromo-7-methoxy-1-indanone (4.34)**

To a solution of (**4.32**) (0.27g, 1.67mmol) in $CCl_4$ (30ml) was added *N*-bromosuccinimide (0.33g, 1.83mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and on reaching reflux careful monitoring by TLC showed the progress of the reaction. On completion, the reaction was filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the brominated product as a bright yellow solid (0.16g, 41%): IR (film) υmax/cm$^{-1}$ 2938, 1725, 1597, 1483, 1295, 1277, 1023cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.99 and 3.29 (2H, 2 x dd, $J_1$=19.5Hz, $J_2$=2 and 7.3Hz, C$\underline{H}_2$), 3.94 (3H, s, OC$\underline{H}_3$), 5.50 (1H, dd, $J_1$=7.5Hz, $J_2$=2Hz, C$\underline{H}$), 6.86 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.21 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.61 (1H, dd, $J_1$=9Hz, $J_2$=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 40.0 (C$\underline{H}$), 48.0 (C$\underline{H}_2$), 55.5 (OC$\underline{H}_3$), 110.7 (Ar-C$\underline{H}$), 118.7 (Ar-C$\underline{H}$), 124.0 (Ar-$\underline{C}$), 136.9 (Ar-C$\underline{H}$), 156.1 (Ar-$\underline{C}$), 157.0 (Ar-$\underline{C}$), 198.6 ($\underline{C}$=O).

**3-azido-7-methoxy-1-indanone (4.35)**

To a constantly stirring mixture of sodium azide (5g, 76.9mmol) in DMF (5ml) at 40°C was added, dropwise, bromo compound (**4.34**) (0.12g, 0.50mmol). The resultant slurry was heated gently at this temperature for 2 hours, and partitioned between water and ether.

The aqueous layer was washed twice with ether (2 x 10ml portions) and the combined ethereal layers dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the azide as a pale oil (55mg, 54%), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2939, 1718, 1597, 1482, 1293, 1230$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.57 and 2.98 (2H, 2 x dd, $J_1$=18-19Hz, $J_2$=3 and 7.6Hz, C$\underline{H}_2$), 3.88 (3H, s, OCH3), 4.95 (1H, dd, $J_1$=7.5Hz, $J_2$=3.3Hz, C$\underline{H}$), 6.88 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.14 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.58 (1H, dd, $J_1$=8.5Hz, $J_2$=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 43.2 (C$\underline{H}$2), 55.4 (O$\underline{C}H_3$), 56.9 (C$\underline{H}$), 111.1 (Ar-C$\underline{H}$), 117.1 (Ar-C$\underline{H}$), 124.0 (Ar-$\underline{C}$), 136.8 (Ar-C$\underline{H}$), 153.1 (Ar-$\underline{C}$), 157.3 (Ar-$\underline{C}$), 198.6 ($\underline{C}$=O).

**_tert_-butyl _N_-(4-methoxy-3-oxo-2,3-dihydro-1_H_-1-indenyl)carbamate (4.36)**

Di-*tert*-butyl dicarbonate (0.44g, 2mmol) was added to a solution of the azide (**4.35**) (0.37g, 1.82mmol) in EtOH:EtOAc (1:1, 10ml). After addition of 10% Pd/C the reaction was stirred under an atmosphere of hydrogen overnight at room temperature. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the BOC-protected amine (0.36g, 71%) with the following physical properties: IR (film) υmax/$cm^{-1}$ 2979, 1714, 1598, 1482, 1289, 1172$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.43 (9H, s, (C$\underline{H}_3$)$_3$), 2.43 and 3.02 (2H, d and irr. dd, $J_d$ and $J_{1dd}$=18.5Hz, C$\underline{H}_2$), 3.87 (3H, s, O$\underline{C}H_3$), 5.19 (2H, broad s, N$\underline{H}$ and C$\underline{H}$), 6.78 (1H, d, J=7Hz, Ar-C$\underline{H}$), 7.11 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.51 (1H, dd, $J_1$=9.6Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 27.9 ((C$\underline{H}_3$)$_3$), 44.9 (C$\underline{H}_2$), 47.7 (C$\underline{C}$(CH$_3$)$_3$), 55.3 (C$\underline{H}$), 110.0 (Ar-C$\underline{H}$), 116.8 (Ar-$\underline{C}$), 116.9 (Ar-CH), 124.1 (Ar-$\underline{C}$), 136.5 (Ar-C$\underline{H}$), 157.0 (N$\underline{C}$=O), 200.3 ($\underline{C}$=O). Upon liberation of the free amine with TFA/DCM and addition to 1-bromotetralin and triethylamine, only decomposition was observed.

**3-(3-hydroxyphenyl)propanoic acid (4.37)**

To a 50ml round-bottomed flask was added 3-(3-methoxyphenyl)propanoic acid (15g, 83.3mmol), 48% hydrobromic acid (11.6ml) and glacial acetic acid (10ml). The reaction was refluxed for two days, before extraction with ether (2 x 100ml) and DCM (2 x 100ml). The organic extracts were combined and concentrated *in vacuo*, and the residue purified by

flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the phenol as a white solid (6.6g, 48%): IR (film) υmax/cm$^{-1}$ 3405, 2966, 1684, 1600, 1461, 1310, 1225, 1158cm$^{-1}$; $^{1}$H NMR ($CD_3OD$, 400Hz) $\delta_H$ 2.58 (2H, broad t, C$\underline{H}_2$), 2.85 (2H, broad t, C$\underline{H}_2$CO), 4.94 (1H, broad s, COO$\underline{H}$), 6.63 (1H, d, J=8Hz, Ar-C$\underline{H}$), 6.69 (2H, m, 2 x Ar-C$\underline{H}$), 7.09 (1H, m, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 30.1 (C$\underline{H}_2$), 34.8 (C$\underline{H}_2$CO), 112.3 (Ar-C$\underline{H}$), 114.3 (Ar-C$\underline{H}$), 118.7 (Ar-C$\underline{H}$), 128.6 (Ar-C$\underline{H}$), 141.8 (Ar-C$\underline{C}$), 156.6 (Ar-C$\underline{C}$OH), 175.0 (C$\underline{C}$=O); MS, m/z, (RI) 146 (100), 131 (16), 117 (26), 104 (83).

**5-hydroxy-1-indanone** and **7-hydroxy-1-indanone**

To an evaporating dish containing polyphosphoric acid (10g) was added (**4.37**) (5g, 30.1mmol). The mixture was stirred using a glass rod over a water bath, until the solid material had dissolved. The reaction was heated thus for 30 minutes, stirring constantly. The coloured crude reaction mixture was quenched using ice water and partitioned between ether and water. The combined ethereal layers (3 x 50ml) were concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the two isomeric ketones as a 5:1 ratio favouring the 5-substituted derivative. Both isomers were obtained as white solids, with the following physical properties:

**5-hydroxy-1-indanone (4.38)**

$^{13}$CNMR $\delta_C$ 24.7 (C$\underline{H}_2$), 35.5 (C$\underline{H}_2$CO), 111.2 (Ar-C$\underline{H}$), 115.2 (Ar-C$\underline{H}$), 124.7 (Ar-C$\underline{H}$), 155.8 (Ar-C$\underline{C}$), 158.9 (Ar-C$\underline{C}$), 164.0 (Ar-C$\underline{C}$), 206.4 (C$\underline{C}$=O).

**7-hydroxy-1-indanone (4.39)**

IR (film) υmax/cm$^{-1}$ 3352, 2931, 1685, 1468, 1298cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.72 (2H, irr. t, C$\underline{H}_2$), 3.11 (2H, t, J=5.5Hz, C$\underline{H}_2$CO), 6.76 (1H, d, J=8Hz, Ar-C$\underline{H}$), 6.95 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.47 (1H, dd, $J_1$=8.5Hz, $J_2$=8Hz Ar-C$\underline{H}$), 9.05 (1H, broad s, O$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.4 (C$\underline{H}_2$), 35.5 (C$\underline{H}_2$CO), 113.0 (Ar-C$\underline{H}$), 117.0 (Ar-C$\underline{H}$), 122.2 (Ar-C$\underline{C}$), 137.2 (Ar-C$\underline{H}$), 154.9 (Ar-C$\underline{C}$), 157.0 (Ar-C$\underline{C}$), 209.7 (C$\underline{C}$=O).

**1-oxo-2,3-dihydro-1*H*-5-indenyl acetate (4.40)**

To a solution of (**4.38**) (0.50g, 3.38mmol) in DCM (5ml) was added acetic anhydride (0.64ml, 6.76mmol), triethylamine (1.41ml, 10.12mmol), and a crystal of DMAP. The reaction was stirred at room temperature for 3 hours. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the acetate as a white solid: IR (KBr disc) υmax/$cm^{-1}$ 2919, 1761, 1702, 1590, 1370, 1206$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.26 (3H, s, C$\underline{H}_3$), 2.63 (2H, m, C$\underline{H}_2$), 3.07 (2H, t, J=6Hz, C$\underline{H}_2$CO), 7.02 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.16 (1H, s, Ar-C$\underline{H}$), 7.68 (1H, d, J=8.5Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.6 ($\underline{C}H_3$), 25.2 ($\underline{C}H_2$), 35.9 ($\underline{C}H_2CO$), 119.2 (Ar-$\underline{C}$H), 120.9 (Ar-$\underline{C}$H), 124.4 (Ar-$\underline{C}$H), 134.2 (Ar-$\underline{C}$), 155.3 (Ar-$\underline{C}$), 156.4 (Ar-$\underline{C}$), 168.4 O$\underline{C}$=OCH$_3$), 205.0 ($\underline{C}$=O).

**3-oxo-2,3-dihydro-1*H*-4-indenyl acetate (4.41)**

To a solution of (**4.39**) (0.30g, 2.03mmol) in DCM (5ml) was added acetic anhydride (0.38ml, 4.06mmol), triethylamine (0.85ml, 6.09mmol), and a crystal of DMAP. The reaction was stirred at room temperature for 3 hours. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the acetate as yellow crystals (0.29g, 75%): IR (film) υmax/$cm^{-1}$ 2930, 1776, 1716, 1612, 1472, 1368, 1244, 1188$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.38 (3H, s, C$\underline{H}_3$), 2.63 (2H, t, J=6Hz, C$\underline{H}_2$), 3.10 (2H, t, J=5.5Hz, C$\underline{H}_2$CO), 6.95 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.31 (1H, d, J=7.6Hz, Ar-C$\underline{H}$), 7.56 (1H, dd, $J_1$=8.9Hz, $J_2$=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.3 ($\underline{C}H_3$), 25.0 ($\underline{C}H_2$), 36.2 ($\underline{C}H_2CO$), 120.0 (Ar-$\underline{C}$H), 123.9 (Ar-$\underline{C}$H), 128.2 (Ar-$\underline{C}$), 135.3 (Ar-$\underline{C}$H), 147.2 (Ar-$\underline{C}$), 156.4 (Ar-$\underline{C}$), 168.6 (O$\underline{C}$OCH$_3$), 203.1 ($\underline{C}$=O).

**3-bromo-1-oxo-2,3-dihydro-1*H*-5-indenyl acetate (4.42)**

To a solution of (**4.40**) (1.46g, 7.68mmol) in $CCl_4$ (30ml) was added *N*-bromosuccinimide (2.05g, 11.53mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and on reaching reflux the heat source was removed and replaced by two 240W lamps, the light from these focussed on the reaction, stirring vigorously all the time. On completion, the reaction was filtered, and the solvent removed *in vacuo*. The

residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the brominated product as a yellow oil (1.32g, 64%): IR (film) υmax/$cm^{-1}$ 1770, 1722, 1607, 1370, 1194, 1095, 1011$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.27 (3H, s, C<u>H</u>$_3$), 2.96 and 3.30 (2H, 2 x dd, $J_1$=19.6Hz, $J_2$=2.8 and 7Hz, C<u>H</u>$_2$), 5.50 (1H, dd, $J_1$=7.5Hz, $J_2$=2.5Hz, C<u>H</u>Br), 7.14 (1H, dd, $J_1$=8.5Hz, $J_2$=1.5Hz, Ar-C<u>H</u>), 7.39 (1H, s, Ar-C<u>H</u>), 7.66 (1H, d, J=8.5Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 20.6 (<u>C</u>H$_3$), 39.6 (<u>C</u>H), 47.7 (<u>C</u>H$_2$), 120.0 (Ar-<u>C</u>H), 123.3 (Ar-<u>C</u>H), 124.1 (Ar-<u>C</u>H), 132.9 (Ar-<u>C</u>), 155.5 (Ar-<u>C</u>), 155.9 (Ar-<u>C</u>), 168.0 (O<u>C</u>OCH$_3$), 199.4 (<u>C</u>=O).

**1-oxo-3-(1,2,3,4-tetrahydro-1-naphthalenylamino)-2,3-dihydro-1*H*-5-indenyl acetate (4.43)**

To a stirred solution of (**4.42**) (1.32g, 4.91mmol) in DCM (10ml) was added triethylamine (1.37ml, 9.82mmol) and 1-aminotetralin (0.9g, 4.91mmol. The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield a diastereomeric mixture of the amine as a pale brown oil (1.1g, 67%). IR (film) υmax/$cm^{-1}$ 2937, 1772, 1719, 1608, 1370, 1198$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.58 (1H, broad s, NH), 1.75-2.24 (4H, m, 2 x $CH_2$, $CH_2$C<u>H</u>$_2$C<u>H</u>$_2$CH), 2.29 and 2.32 (3H, 2 x s, C<u>H</u>$_3$), 2.57 (1H, m, 1H of C<u>H</u>$_2$), 2.71-2.89 (2H, C<u>H</u>$_2$), 3.08 (1H, dd, $J_1$~19Hz, $J_2$=6.5Hz, 1H of C<u>H</u>$_2$CO), 3.95 and 4.02 (1H, 2 x dd, $J_1$=5.5Hz, $J_2$=4.5Hz, C<u>H</u>CH$_2$CH$_2$), 4.49 and 4.56 (1H, 2 x dd, $J_1$~7Hz, $J_2$~3Hz, C<u>H</u>CH$_2$CO), 7.07-7.19 (4H, m, 4 x Ar-C<u>H</u>), 7.27 and 7.44 (2H, m, 2 x Ar-C<u>H</u>), 7.72 (1H, m, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 18.1 and 18.5 (CH$_2$<u>C</u>H$_2$CH$_2$), 20.6 and 20.7 (<u>C</u>H$_3$), 27.4 and 28.6 (<u>C</u>H$_2$), 28.9 and 30.1 (<u>C</u>H$_2$), 45.9 and 46.9 (<u>C</u>H$_2$CO), 52.8 and 53.4 (<u>C</u>H), 54.2 and 54.9 (<u>C</u>H), 118.7 and 118.8 (Ar-<u>C</u>H), 122.2 x 2 (Ar-<u>C</u>H), 124.0 x 2 (Ar-<u>C</u>H), 125.3 and 125.5 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 128.4 x 2 (Ar-<u>C</u>H), 128.7 (Ar-<u>C</u>H), 133.6 and 133.9 (Ar-<u>C</u>), 137.0 and 137.1 (Ar-<u>C</u>), 138.2 and 138.4 (Ar-<u>C</u>), 158.1 and 158.5 (Ar-<u>C</u>), 168.3 x 2 (O<u>C</u>OCH$_3$), 202.6 x 2 (<u>C</u>=O).

**5-methoxy-3-[methyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone (4.44)**

To a stirred solution of (**4.43**) (0.4g, 1.19mmol) in methanol/acetone (1:1) (5ml) was added methyl iodide (0.74ml, 11.9mmol) and potassium carbonate (0.25g, 1.81mmol). The reaction was stirred overnight at room temperature, filtered, and the solvent removed *in*

*vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a yellow oil, a diastereomeric mixture with the following physical characteristics (0.29g, 76%): IR (KBr disc, HCl salt) υmax/cm$^{-1}$ 2923, 1709, 1598, 1266cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.60-2.30 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH$), 1.89 and 2.30 (3H, 2 x s, $NC\underline{H}_3$), 2.53-2.94 (4H, m, $ArC\underline{H}_2$ and $C\underline{H}_2CO$), 3.96 and 3.98 (3H, 2 x s, $OC\underline{H}_3$), 4.02 and 4.17 (1H, 2 x dd, $J_1$=8.8Hz, $J_2$=7.4Hz, C$\underline{H}$), 4.43 and 4.66 (1H, 2 x dd, $J_1$=7-8Hz, $J_2$~4Hz, C$\underline{H}$), 6.96 and 6.99 (1H, m, Ar-C$\underline{H}$), 7.11 (1H, m, Ar-C$\underline{H}$), 7.18 (1H, m, Ar-C$\underline{H}$), 7.22-7.29 (2H, m, 2 x Ar-C$\underline{H}$), 7.67 and 7.72 (1H, m, Ar-C$\underline{H}$), 7.81 and 7.94 (1H, 2 x d, J=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.1 and 21.5 ($\underline{C}H_2$), 24.8 and 25.1 ($\underline{C}H_2$), 27.4 and 33.3 ($N\underline{C}H_3$), 29.0 and 29.5 ($\underline{C}H_2$), 38.4 and 38.6 ($\underline{C}H_2CO$), 55.2 and 55.3 ($O\underline{C}H_3$), 55.6 and 61.4 ($\underline{C}H$), 61.7 and 63.3 ($\underline{C}H$), 109.1 and 109.3 (Ar-$\underline{C}H$), 115.6 and 115.7 (Ar-$\underline{C}H$), 124.1 and 124.2 (Ar-$\underline{C}H$), 125.3 and 125.4 (Ar-$\underline{C}H$), 126.1 (Ar-$\underline{C}H$), 127.5 and 127.7 (Ar-$\underline{C}H$), 128.5 and 128.7 (Ar-$\underline{C}H$), 129.9 and 130.0 (Ar-$\underline{C}$), 137.9, 138.0, 138.1, 138.3 (2 x Ar-$\underline{C}$), 159.4 and 159.6 (Ar-$\underline{C}$), 165.1 and 165.2 (Ar-$O\underline{C}H_3$), 202.6 ($\underline{C}$=O); MS, m/z, (RI) 322 (M+1, 58), 192 (100); HRMS (+H$^+$) 322.1811, $C_{21}$ $H_{24}$ N $O_2$ requires 322.1807; error 1.3ppm.

**1-bromo-3-oxo-2,3-dihydro-1*H*-4-indenyl acetate (4.45)**

To a solution of (**4.41**) (0.29g, 1.53mmol) in $CCl_4$ (30ml) was added *N*-bromosuccinimide (0.41g, 1.68mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux, and on reaching reflux the heat source was removed and replaced by two 240W lamps, the light from these focussed on the reaction, stirring vigorously all the time. On completion, the reaction was filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the brominated product as yellow crystals (0.25g, 61%): IR (film) υmax/cm$^{-1}$ 1776, 1720, 1608, 1178, 1010cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.42 (3H, s, $C\underline{H}_3$), 3.05 and 3.36 (2H, 2 x dd, $J_1$~19-20Hz, $J_2$=3 and ~7Hz, $C\underline{H}_2$), 5.57 (1H, dd, $J_1$=7.5Hz, $J_2$=2.5Hz, C$\underline{H}$), 7.12 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.60 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.73 (1H, dd, $J_1$~9Hz, $J_2$=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 20.2 ($\underline{C}H_3$), 39.4 ($\underline{C}H$), 47.9 ($\underline{C}H_2$), 122.4 (Ar-$\underline{C}H$), 124.7 (Ar-$\underline{C}H$), 127.2 (Ar-$\underline{C}$), 136.3 (Ar-$\underline{C}H$), 146.4 (Ar-$\underline{C}$), 155.3 (Ar-$\underline{C}$), 168.3 ($O\underline{C}OCH_3$), 197.8 ($\underline{C}$=O).

**3-oxo-1-(1,2,3,4-tetrahydro-1-naphthalenylamino)-2,3-dihydro-1*H*-4-indenyl acetate (4.46)**

To a stirred solution of (**4.45**) (0.25g, 0.93mmol) in DCM (10ml) was added triethylamine (0.26ml, 1.86mmol) and 1-aminotetralin (0.17g, 0.93mmol. The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield a diastereomeric mixture of the amine as a pale brown oil (0.16g, 51%), with the following NMR characteristics: $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.77-2.26 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH$), 2.42 and 2.43 (3H, 2 x s, $C\underline{H}_3$), 2.59 (1H, m, 1H of $C\underline{H}_2$), 2.75-2.94 (2H, m, $C\underline{H}_2$), 3.09 (1H, m, 1H of $C\underline{H}_2$), 3.98 and 4.07 (1H, 2 x dd, $J_1$=5.5Hz, $J_2$=4.5Hz, $C\underline{H}CH_2CH_2$), 4.55 and 4.61 (1H, 2 x dd, $J_1$=7Hz, $J_2$=3.5Hz, C$\underline{H}$), 7.06 (1H, m, Ar-C$\underline{H}$), 7.11-7.23 (3H, m, 3 x Ar-C$\underline{H}$), 7.30 and 7.44 (1H, 2 x m, Ar-C$\underline{H}$), 7.52-7.67 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 18.2 and 18.5 ($CH_2\underline{C}H_2CH_2$), 20.3 ($\underline{C}H_3$), 27.5 and 28.6 ($\underline{C}H_2$), 28.9 and 30.1 ($\underline{C}H_2$), 46.2 and 47.2 ($\underline{C}H_2CO$), 52.6 and 53.5 ($\underline{C}H$), 54.2 and 55.1 ($\underline{C}H$), 121.3 (Ar-$\underline{C}H$), 123.2 and 123.3 (Ar-$\underline{C}H$), 125.3 and 125.5 (Ar-$\underline{C}H$), 126.6 x 2 (Ar-$\underline{C}H$), 127.6 and 127.9 (Ar-$\underline{C}$), 128.3 and 128.4 (Ar-$\underline{C}H$), 128.7 and 128.8 (Ar-$\underline{C}H$), 135.5 (Ar-$\underline{C}H$), 137.0 and 137.1 (Ar-$\underline{C}$), 138.2 and 138.4 (Ar-$\underline{C}$), 146.6 (Ar-$\underline{C}$), 157.9 and 158.3 (Ar-$\underline{C}$), 168.6 ($O\underline{C}OCH_3$), 200.9 and 201.0 ($\underline{C}$=O).

**7-methoxy-3-[methyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone (4.47)**

To a stirred solution of (**4.46**) (0.21g, 0.63mmol) in methanol/acetone (1:1) (5ml) was added methyl iodide (0.45g, 3.13mmol) and potassium carbonate (0.43g, 3.13mmol). The reaction was stirred overnight at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a yellow oil, a diastereomeric mixture with the following physical characteristics (93mg, 46%): IR (film) υmax/cm$^{-1}$ 2941, 1712, 1595, 1483, 1286cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.55-1.80 (2H, m, $C\underline{H}_2$), 1.85 and 2.25 (3H, 2 x s, $C\underline{H}_3$), 1.87 and 1.99-2.17 (2H, 2 x m, $C\underline{H}_2$), 2.51-2.92 (4H, m, $C\underline{H}_2$ and $C\underline{H}_2CO$), 3.94 and 3.96 (3H, 2 x s, $OC\underline{H}_3$), 3.96 and 4.14 (1H, 2 x irr. dd, C$\underline{H}$), 4.39 and 4.63 (1H, 2 x dd, $J_1$=7.3Hz, $J_2$=4Hz, C$\underline{H}$), 6.81 and 6.85 (1H, 2 x d, J=8.1Hz, Ar-C$\underline{H}$), 7.08 (1H, m, Ar-C$\underline{H}$), 7.15 (1H, m, Ar-C$\underline{H}$), 7.22 (1H, m, Ar-C$\underline{H}$), 7.38 and 7.42 (1H, 2 x d, J=7.5Hz, Ar-C$\underline{H}$), 7.60 (1H, m, Ar-C$\underline{H}$), 7.80 and 7.91 (1H, 2 x d, J=7.5Hz, Ar-C$\underline{H}$);

$^{13}$CNMR $\delta_C$ 21.6 and 21.9, 25.2 and 25.5 (2 x $\underline{C}H_2$), 27.8 and 33.7 ($N\underline{C}H_3$), 29.5 and 29.9 ($\underline{C}H_2$), 39.2 and 39.5 ($\underline{C}H_2CO$), 55.6 and 61.5 ($\underline{C}H$), 55.8 x 2 ($O\underline{C}H_3$), 62.2 and 63.8 ($\underline{C}H$), 109.7 x 2, 118.2 (2 x Ar-$\underline{C}H$), 125.2 (Ar-$\underline{C}$), 125.8 x 2, 126.5, 128.1 and 128.3, 128.9 and 129.0, 136.4 (5 x Ar-$\underline{C}H$), 138.3, 138.5, 138.7 (2 x Ar-$\underline{C}$), 157.5 x 2 (Ar-$\underline{C}$), 159.6 and 159.7 (Ar-$\underline{C}$), 202.6 and 202.7 ($\underline{C}$=O); HRMS (+$H^+$) 322.1823, $C_{21}$ $H_{24}$ N $O_2$ requires 322.1807; error 4.8ppm.

**6-methoxy-1-indanone (4.48)**

To an evaporating dish containing polyphosphoric acid (10g) was added 3-(4-methoxyphenyl)propionic acid (5.5g, 30.5mmol). The mixture was stirred using a glass rod over a water bath, until the solid material had dissolved. The reaction was heated thus for 30 minutes, stirring constantly. The coloured crude reaction mixture was quenched using ice water and partitioned between ether and water. The combined ethereal layers (3 x 50ml) were concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield ketone (**4.48**) as a white solid (3.62g, 73%): IR (film) υmax/cm$^{-1}$ 2930, 1713, 1493, 1276cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.73 (2H, dd, $J_1$=5.9Hz, $J_2$=5.5Hz, $ArCH_2$), 3.09 (2H, dd, $J_1$=6.9Hz, $J_2$=5.5Hz, $CH_2CO$), 3.86 (3H, s, $ArOC\underline{H}_3$), 7.21 (2H, m, 2 x Ar-C$\underline{H}$), 7.38 (1H, d, J=8Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 24.6 ($Ar\underline{C}H_2$), 36.5 ($\underline{C}H_2CO$), 55.1 ($\underline{C}H$), 104.5, 123.5, 126.9 (3 x Ar-$\underline{C}H$), 137.8, 147.5, 159.0 (3 x Ar-$\underline{C}$), 206.4 ($\underline{C}$=O).

***tert*-butyl *N*-(5-methoxy-3-oxo-2,3-dihydro-1*H*-1-indenyl)carbamate (4.52)**

Di-*tert*-butyl dicarbonate (1.98g, 9.07mmol) was added to a solution of azide (**4.51**, recognised by its characteristic azide absorption in the IR at 2098cm$^{-1}$), [prepared from (**4.48**) via (**4.50**), analogously to the synthesis of (**4.36**), via (**4.34**) and (**4.35**)] (1.67g, 8.23mmol) in EtOH:EtOAc (1:1, 10ml). After addition of 10% Pd/C the reaction was stirred under an atmosphere of hydrogen at room temperature overnight. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the BOC-protected amine (1.64g, 72%) with the following physical properties: IR (film) υmax/cm$^{-1}$ 2979, 1719, 1492, 1166cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.40 (9H, s, $(C\underline{H}_3)_3C$), 2.44 (2H, br. d, J=19Hz, $ArC\underline{H}_2$), 3.07 (2H, dd, $J_1$~19Hz, $J_2$=7Hz, $C\underline{H}_2CO$), 3.75 (3H, s, Ar-

$OC\underline{H}_3$), 5.22 and 5.17 (2H, 2 x br s, C$\underline{H}$ and N$\underline{H}$), 7.01 (1H, s, Ar-C$\underline{H}$), 7.12 (1H, br. d, Ar-C$\underline{H}$), 7.44 (1H, dd, $J_1$=8.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 27.9 (($\underline{C}H_3)_3C$), 45.2 ($\underline{C}H_2$), 47.7 ($\underline{C}$H), 55.1 (Ar-$O\underline{C}H_3$), 79.3 ($(CH_3)_3\underline{C}$), 104.0, 123.8, 126.3 (3 x Ar-$\underline{C}$H), 137.4, 146.5, 155.2 (3 x Ar-$\underline{C}$), 160.1 (NH$\underline{C}$=O), 202.7 ($\underline{C}$=O). Upon liberation of the free amine with TFA/DCM (1:1, 10ml. R.T., 1 hour) and addition to 3-bromoindanone in DCM/$Et_3N$, only decomposition was observed.

**3-[methyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone oxime (4.53)**

To a stirred solution of (**4.2**) (0.45g, 1.55mmol) in EtOH/$H_2O$ (2:1, 10ml) was added sodium acetate (0.13g, 1.55mmol) and hydroxylamine hydrochloride (0.12g, 1.70mmol). The reaction was stirred for three hours at 60°C, after which time the residue was filtered, the filtrate washed with ethanol (2 x 20ml), and the solvent removed under high vacuum. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the oxime as an off-white solid, a diastereomeric mixture with the following physical characteristics (0.21g, 44%): IR (KBr disc) υmax/cm$^{-1}$ 2937, 1550, 1464, 1049cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.70-2.31 (4H, m, 2 x C$\underline{H}_2$), 1.89 and 2.29 (3H, 2 x s, N$\underline{C}H_3$), 2.73-3.07 (2H, m, C$\underline{H}_2$), 3.11 (1H, 2 x s, O$\underline{H}$), 4.00 and 4.18 (1H, 2 x dd, $J_1$=7.5Hz, $J_2$=4.5Hz, C$\underline{H}$), 4.46 and 4.70 (1H, 2 x dd, $J_1$=7.5Hz, $J_2$~4.5Hz, C$\underline{H}$), 7.11 (1H, m, Ar-C$\underline{H}$), 7.18 (1H, m, Ar-C$\underline{H}$), 7.24 (1H, m, Ar-C$\underline{H}$), 7.35 (1H, m, Ar-C$\underline{H}$), 7.47 (1H, m, Ar-C$\underline{H}$), 7.68 (2H, m, 2 x Ar-C$\underline{H}$), 7.86 and 7.96 (1H, 2 x d, J=7.5Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.2 and 21.6 ($\underline{C}H_2$), 25.0 and 25.3 ($\underline{C}H_2$), 27.4 and 33.7 ($\underline{C}H_3$), 27.9 and 28.0 ($\underline{C}H_2$), 29.1 and 29.2 ($\underline{C}H_2$), 58.7 and 61.7 ($\underline{C}$H), 63.2 and 64.7 ($\underline{C}$H), 120.4 and 120.5 (Ar-$\underline{C}$H), 125.4, 125.5 x 2, 126.0 (3 x Ar-$\underline{C}$H), 127.6, 127.7, 127.8, 127.9 (4 x Ar-$\underline{C}$H), 128.4 and 128.5 (Ar-$\underline{C}$H), 130.2 (Ar-$\underline{C}$H), 137.9, 138.3, 149.5 (3 x Ar-$\underline{C}$), 161.4 ($\underline{C}$=N); MS, m/z, (RI) 288 (56), 158 (41), 131 (100), 91 (31); HRMS (+H$^+$) 307.1834, $C_{20}H_{22}N_2O$ requires 307.1810; error 7.7ppm.

**3-[methyl(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-indanone *O*1-methyloxime (4.54)**

To a stirred solution of (**4.2**) (0.35g, 1.20mmol) in EtOH/$H_2O$ (2:1, 10ml) was added sodium acetate (0.17g, 2.07mmol) and methoxylamine hydrochloride (0.12g, 1.44mmol). The reaction was stirred for three hours at 60°C, after which time the residue was filtered,

the filtrate washed with ethanol (2 x 20ml), and the solvent removed under high vacuum. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the oxime as a yellow solid, a diastereomeric mixture with the following physical characteristics (0.29g, 75%): M.p. 138-140°C; IR (KBr disc) υmax/cm$^{-1}$ 2936, 1463, 1110, 1036cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.67-2.22 (4H, m, $C\underline{H}_2C\underline{H}_2$), 1.92 and 2.31 (3H, 2 x s, $NC\underline{H}_3$), 2.73-3.10 (4H, m, 2 x $C\underline{H}_2$), 4.01 and 4.04 (3H, 2 x s, $OC\underline{H}_3$), 4.00 and 4.17 (1H, 2 x dd, $J_2$~7Hz, C$\underline{H}$), 4.46 and 4.69 (1H, 2 x dd, $J_1$=8Hz, $J_2$=6.2Hz, C$\underline{H}$), 7.11, 7.17, 7.25, 7.35, 7.49 (5H, 5 x m, 5 x Ar-C$\underline{H}$), 7.68 and 7.71 (1H, 2 x d, J=7.5Hz, Ar-C$\underline{H}$), 7.85 and 7.93 (1H, 2 x d, J=7.9Hz, Ar-C$\underline{H}$), 8.27 and 8.31 (1H, 2 x d, J=7.8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 21.3 and 21.6 ($\underline{C}H_2$), 25.0 and 25.3 ($\underline{C}H_2$), 27.5 and 33.2 ($N\underline{C}H_3$), 29.1 and 29.5, 31.1 x 2 (Ar$\underline{C}H_2$ and $\underline{C}H_2C$=N), 58.4 and 61.7 ($\underline{C}H$), 61.7 ($O\underline{C}H_3$), 63.2 and 64.4 ($\underline{C}H$), 125.3, 125.4, 126.0 (3 x Ar-$\underline{C}H$), 127.3 and 127.4, 127.6 and 127.9, 128.3 and 128.4, 128.4 and 128.5 (4 x Ar-$\underline{C}H$), 130.7 (Ar-$\underline{C}H$), 132.6 and 132.8 (Ar-$\underline{C}$), 137.9, 138.1, 138.3 (2 x Ar-$\underline{C}$), 150.8 x 2, 156.9 x 2 (2 x Ar-$\underline{C}$); MS, m/z, (RI) 321 (M+1, 29), 191 (100), 160 (77), 131 (78); HRMS (+H$^+$) 321.1948, $C_{21}H_{25}N_2O$ requires 321.1953; error -1.6ppm.

**Methanesulphonic acid 1,2,3,4-tetrahydro-naphthalen-2-yl ester (4.56)**

To a stirred solution of β-tetralone (5g, 34.2mmol) in methanol (10ml), at 0°C, was added sodium borohydride (1.9g, 51.4 mmol), over 5 minutes. The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alcohol (4.87g, 96%) as a colourless oil. The reaction product (**4.55**) was analysed by GCMS: MS, m/z, (RI) 130 (100), 115 (16), 104 (34). To a solution of the alcohol (3.2g, 21.6mmol) in dry DCM under an atmosphere of nitrogen was added methane sulphonyl chloride (3.94g, 34.6 mmol). To the resultant solution, cooled to 0°C, was added *N,N*,-diisopropylethanolamine (4.2g, 32.4mmol), drop-wise by syringe, over 5 minutes. After 5 minutes stirring at this temperature, 5% aqueous $NaHCO_3$ was added and the reaction allowed to return to room temperature. The reaction mixture was partitioned, and the organic layer removed, washed sequentially with water, 2M HCl and water, then the combined organic layers were dried over anhydrous sodium sulphate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 8:1) to yield a pale yellow oil

(4.40g, 90%), with the following physical properties: IR (film) υmax/cm$^{-1}$ 2933, 1341, 1175, 1046, 953 cm$^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.19 (2H, m, J=6.5Hz, $CH_2C\underline{H}_2CH$), 2.87 and 2.92 (1H, 2 x dd, $J_1$=7.5Hz, $J_2$=6.8Hz, 1H of $ArC\underline{H}_2CH_2$), 2.99-3.07 (1H, m, 1H of $ArC\underline{H}_2CH_2$), 3.03 (3H, s, $C\underline{H}_3$), 3.11 (1H, dd, $J_1$~16Hz, $J_2$=6.5Hz, 1H of $ArC\underline{H}_2CH$), 3.25 (1H, dd, $J_1$~16Hz, $J_2$=5Hz, 1H of $ArC\underline{H}_2CH$), 5.18 (1H, quintet, J~5.7Hz, C$\underline{H}$), 7.10-7.19 (4H, m, 4 x Ar-C$\underline{H}$). $^{13}$CNMR $\delta_C$ 25.5, 28.4, 35.0 (3 x $\underline{C}H_2$), 38.2 ($\underline{C}H_3$), 77.4 ($\underline{C}H$), 125.8, 126.0, 128.2, 128.8 (4 x Ar-$\underline{C}H$), 132.0, 134.5 (2 x Ar-$\underline{C}$).

**2-Azido-1,2,3,4-tetrahydro-naphthalene (4.57)**

To a solution of the mesylate (**4.56**) (4g, 17.7mmol) in DMF was added sodium azide (5.75g, 88.5mmol). The resultant slurry was heated on an oil bath for 2 hours at 50°C, and then partitioned between water and ether. The water layer was washed twice with ether (2 x 20ml portions) and the combined ethereal layers dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the azide as a yellow oil (2.73g, 89%), with the following physical properties: IR (film) υmax/cm$^{-1}$ 2931, 2094, 1496, 1498, 1248, 1112 cm$^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.93-2.02 (1H, m, 1H of $CH_2C\underline{H}_2CH$), 2.18-2.25 (1H, m, 1H of $CH_2C\underline{H}_2CH$), 2.91-2.98 (2H, m, $C\underline{H}_2$), 3.05 and 3.09 (1H, 2 x dd, $J_1$=6.5Hz, $J_2$=5.5Hz, 1H of $CH_2$), 3.18 (1H, 2 x irr. dd, $J_2$~5.5Hz, 1H of $C\underline{H}_2$), 3.91-3.98 (1H, m, C$\underline{H}$), 7.18-7.28 (4H, m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 26.7, 27.7, 34.3 (3 x $\underline{C}H_2$), 56.7 ($\underline{C}H$), 125.7, 126.0, 128.4, 128.9 (4 x Ar-$\underline{C}H$), 133.0, 134.8 (2 x Ar-$\underline{C}$).

***tert*-butyl *N*-1,2,3,4-tetrahydro-2-naphthalenyl)carbamate (4.58)**

Di-*tert*-butyl dicarbonate (0.15g, 0.69mmol) was added to a solution of the azide (**4.57**) (0.12g, 0.69mmol) in EtOH:EtOAc (1:1, 10ml). After addition of 10% Pd/C the reaction was stirred under an atmosphere of hydrogen overnight at room temperature. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the BOC-protected amine as a white crystalline solid (0.12g, 79%) with the following physical properties: IR (KBr disc) υmax/cm$^{-1}$ 2982, 2936, 1689, 1522, 1178cm$^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.49 (3H, s, $C\underline{H}_3$), 1.77 (1H, m, 1H of $CH_2C\underline{H}_2CH$), 2.10 (1H, m, 1H of $CH_2C\underline{H}_2CH$), 2.64 and 2.68 (1H, dd, $J_1$~16Hz, $J_2$=8.3Hz, 1H of $ArC\underline{H}_2CH_2$), 2.90 (2H, m,

ArC$\underline{H}_2$CH), 3.12 and 3.16 (1H, dd, $J_1$~16Hz, $J_2$=5Hz, 1H of ArC$\underline{H}_2$CH$_2$), 4.00 and 4.62 (each 1H, 2 x broad s, C$\underline{H}$ and N$\underline{H}$), 7.07-7.15 (4H, m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 26.8 ($\underline{C}H_2$), 28.0 ($\underline{C}H_3$ and $\underline{C}$H), 28.7, 35.6 (2 x $\underline{C}H_2$), 78.8 ($\underline{C}(CH_3)_3$), 125.4, 125.6, 128.3, 130.0 (4 x Ar-$\underline{C}$H), 133.8, 135.1 (2 x Ar-$\underline{C}$), 154.9 ($\underline{C}$=O); MS, m/z, (RI) 192 (100), 148 (97).

**3-(1,2,3,4-tetrahydro-2-naphthalenylamino)-1-indanone (4.60)**

To a stirred solution of 3-bromoindanone (0.3g, 1.42mmol, obtained in 63% yield from 1-indanone) was added 2-amino-1,2,3,4-tetrahydro-naphthalene (**4.59**) (0.21g, 1.42mmol, obtained in quantitative yield from its BOC derivative), and triethylamine (0.40ml, 2.84mmol). The reaction was stirred overnight at room temperature, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine as a diastereomeric mixture, as a golden brown oil (0.05g, 13%). IR (film) υmax/cm$^{-1}$ 2926, 1718, 1604, 1465, 1279, 1237cm$^{-1}$. $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.58 (1H, N$\underline{H}$), 1.76 (1H, m, 1H of $CH_2C\underline{H}_2CH_2$), 2.07 and 2.22 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH_2$), 2.50 and 2.56 (1H, 2 x dd, $J_1$=6.5Hz, $J_2$~3Hz, 1H of C$\underline{H}_2$), 2.73 (1H, m, 1H of C$\underline{H}_2$), 2.86-2.96, 2.98-3.08, 3.16-3.26 (5H, 3 x m, C$\underline{H}_2$, C$\underline{H}_2$CO and C$\underline{H}$), 4.64 (1H, m, C$\underline{H}$CH$_2$CO), 7.09-7.18 (4H, m, 4 x Ar-C$\underline{H}$), 7.45 (1H, m, Ar-C$\underline{H}$), 7.65 (1H, m, Ar-C$\underline{H}$), 7.70 and 7.72 (1H, 2 x d, J=2.5 Hz, Ar-C$\underline{H}$), 7.77 (1H, m, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 27.3 and 27.6 ($\underline{C}H_2$), 28.8 and 30.4 ($\underline{C}H_2$), 36.2 and 37.2 ($\underline{C}H_2$), 45.6 and 45.7 ($\underline{C}H_2$CO), 51.6 and 51.8 ($\underline{C}$H), 53.1 x 2 ($\underline{C}$H), 122.8 (Ar-$\underline{C}$H), 125.4 x 2 (Ar-$\underline{C}$H), 125.5 x 2, 125.7 (2 x Ar-$\underline{C}$H), 128.2, 128.3 x 2 (2 x Ar-$\underline{C}$H), 128.9 and 129.0 (Ar-$\underline{C}$H), 134.4 (Ar-$\underline{C}$H), 134.5 and 134.6 (Ar-$\underline{C}$), 135.7 x 2 (Ar-$\underline{C}$), 136.3 x 2 (Ar-$\underline{C}$), 156.1 x 2 (Ar-$\underline{C}$), 204.1 ($\underline{C}$=O); MS, m/z, (RI) 277 ($M^+$, 99), 146 (68), 131 (100), 103 (71), 77 (31); HRMS (+$H^+$) 278.1526, $C_{19}$ $H_{20}$ N O requires 278.1545; error -6.6ppm.

**3-[methyl(1,2,3,4-tetrahydro-2-naphthalenyl)amino]-1-indanone (4.61)**

To a stirred solution of (**4.60**) (50mg, 0.18mmol) in acetone (10ml) was added methyl iodide (0.06ml, 0.90mmol) and anhydrous potassium carbonate (0.12g, 0.90mmol). The reaction was stirred for 6 hours at room temperature, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a golden oil (18mg, 34%): IR (film)

υmax/cm$^{-1}$ 2930, 1718, 1276, 1044cm$^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.36-1.93 and 2.14-2.24 (2H, 2 x m, $CH_2C\underline{H}_2CH$), 2.14 and 2.15 (3H, 2 x s, $C\underline{H}_3$), 2.67 and 2.71 and 2.81-3.13 (1H, 2 x dd and m, $J_{1dd}$=7Hz, $J_{2dd}$=4Hz, C$\underline{H}$, 3 x $C\underline{H}_2$ and C$\underline{H}$), 4.84 (1H, 2 x t, J~3.7Hz, $C\underline{H}CH_2CO$), 7.14 (4H, m, 4 x Ar-C$\underline{H}$), 7.45 (1H, m, Ar-C$\underline{H}$), 7.64-7.79 (3H, m, 3 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 27.2 and 27.6 ($\underline{C}H_2$), 28.7 and 28.9 ($\underline{C}H_2$), 31.0 and 31.3 ($\underline{C}H_3$), 33.4 and 33.7 ($\underline{C}H_2$), 37.2 and 37.5 ($\underline{C}H_2CO$), 58.0 and 58.3 ($\underline{C}H$), 58.6 and 58.7 ($\underline{C}H$), 122.5 x 2 (Ar-$\underline{C}H$), 125.3 (Ar-$\underline{C}H$), 125.4 x 2 (Ar-$\underline{C}H$), 126.0 (Ar-$\underline{C}H$), 128.0 (Ar-$\underline{C}H$), 128.1 x 2 (Ar-$\underline{C}H$), 128.9 and 129.0 (Ar-$\underline{C}H$), 134.4 x 2 (Ar-$\underline{C}H$), 135.2 and 135.3 (Ar-$\underline{C}$), 135.7 and 135.8 (Ar-$\underline{C}$), 136.6 and 136.7 (Ar-$\underline{C}$), 156.0 (Ar-$\underline{C}$), 204.3 x 2($\underline{C}$=O); HRMS (+H$^+$) 292.1678, $C_{20}$ $H_{22}$ N O requires 292.1701; error -8.2ppm.

**3-[allyl(1,2,3,4-tetrahydro-2-naphthalenyl)amino]-1-indanone (4.62)**

To a stirred solution of (**4.60**) (50mg, 0.18mmol) in acetone (10ml) was added allyl iodide (0.08ml, 0.90mmol) and anhydrous potassium carbonate (0.12g, 0.90mmol). The reaction was refluxed for 6 hours, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a colourless oil (32mg, 56%). IR (film) υmax/cm$^{-1}$ 2928, 1717, 1550, 1273cm$^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.63 and 1.97 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.11 and 2.19 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.75-3.25 (7H, 3 x m, 2 x $C\underline{H}_2$, $C\underline{H}_2CO$, C$\underline{H}$ and $NC\underline{H}_2$), 4.78 (1H, 2 x t, J=5.5Hz, $C\underline{H}CH_2CO$), 5.05 and 5.20 (2H, 2 x m, $C=C\underline{H}_2$), 5.77 (1H, m, $C\underline{H}=CH_2$), 7.14-7.17 (4H, m, 4 x Ar-C$\underline{H}$), 7.45 (1H, m, Ar-C$\underline{H}$), 7.69 (1H, m, Ar-C$\underline{H}$), 7.77-7.83 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 26.5, 29.3, 29.4, 29.6 (2 x $\underline{C}H_2$), 32.7 and 35.0 ($\underline{C}H_2$), 40.2 and 40.3 ($\underline{C}H_2CO$), 48.5 and 48.6 ($N\underline{C}H_2$), 54.8 and 54.9 ($\underline{C}H$), 55.4 and 55.5 ($\underline{C}H$), 115.7 ($C=\underline{C}H_2$), 122.4 and 122.5 (Ar-$\underline{C}H$), 125.2 and 125.3 (Ar-$\underline{C}H$), 125.3 and 125.5 (Ar-$\underline{C}H$), 125.9 and 126.0 (Ar-$\underline{C}H$), 128.0 (Ar-$\underline{C}H$), 128.2 x 2 (Ar-$\underline{C}H$), 128.9 and 129.0 (Ar-$\underline{C}H$), 134.4 x 2 and 137.2 x 2 (2H, Ar-$\underline{C}H$ and $CH_2=\underline{C}H$), 135.5 and 135.6 (Ar-$\underline{C}$), 135.8 and 135.9 (Ar-$\underline{C}$), 136.8 (Ar-$\underline{C}$), 156.5 and 156.6 (Ar-$\underline{C}$), 204.2 ($\underline{C}$=O); MS, m/z, (RI) 317 (M$^+$, 78), 302 (62), 212 (56), 186 (42), 131 (100), 103 (98); HRMS (+H$^+$) 318.1835, $C_{22}$ $H_{24}$ N O requires 318.1858; error -7.3ppm.

**3-[benzyl(1,2,3,4-tetrahydro-2-naphthalenyl)amino]-1-indanone (4.63)**

To a stirred solution of (**4.60**) (0.47g, 1.70mmol) in acetone (10ml) was added benzyl bromide (1.01ml, 8.5mmol) and anhydrous potassium carbonate (0.24g, 1.80mmol). The reaction was refluxed for 6 days, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale yellow oil (0.29g, 47%). IR (film) υmax/$cm^{-1}$ 2928, 1717, 1603, 1495, 1274$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.64 and 2.02 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.14 and 2.31 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.75-3.19 (7H, m, 3 x $C\underline{H}_2$ and C<u>H</u>), 3.66 and 3.69 (2H, 2 x dd, J~14Hz, $NC\underline{H}_2$), 4.81-4.83 (1H, m, $C\underline{H}CH_2CO$), 7.10-7.18 (4H, m, 4 x Ar-C<u>H</u>), 7.28 (1H, m, Ar-C<u>H</u>), 7.37 (2H, m, 2 x Ar-C<u>H</u>), 7.42-7.50 (3H, m, 3 x Ar-C<u>H</u>), 7.75 (1H, m, Ar-C<u>H</u>), 7.84 (1H , m, Ar-C<u>H</u>), 7.96 and 7.99 (1H, 2 x d, J~8Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 25.8, 29.4, 29.5, 29.7, 32.2, 34.9, (3 x $\underline{C}H_2$), 39.7 and 39.9 ($\underline{C}H_2CO$), 49.5 ($N\underline{C}H_2$), 54.2 and 54.3 (<u>C</u>H), 55.0 and 55.2 (<u>C</u>H), 122.5 and 122.6 (Ar-<u>C</u>H), 125.3 x 2, 125.4, 125.6 (2 x Ar-<u>C</u>H), 126.0 and 126.1 (Ar-<u>C</u>H), 126.5 and 126.6 (Ar-<u>C</u>H), 127.7, 127.8, 127.9, 128.2 (6 x Ar-<u>C</u>H), 128.9 and 129.1 (Ar-<u>C</u>H), 134.6 and 134.7 (Ar-<u>C</u>H), 135.4 and 135.6 (Ar-<u>C</u>), 135.8 and 135.9 (Ar-<u>C</u>), 136.9 (Ar-<u>C</u>), 139.6 (Ar-<u>C</u>), 156.4 and 156.5 (Ar-<u>C</u>), 204.4 x 2 (<u>C</u>=O); MS, m/z, (RI) 368 (M+1, 60), 367 ($M^+$, 65), 276 (100), 236 (58), 131 (32), 103 (25); HRMS 368.2007, $C_{26}$ $H_{26}$ N O requires 368.2014; error -1.9ppm.

**3-[(4-methylbenzyl)(1,2,3,4-tetrahydro-2-naphthalenyl)amino]-1-indanone (4.64)**

To a stirred solution of (**4.60**) (0.5g, 1.81mmol) in acetone (10ml) was added *p*-methylbenzyl bromide (0.5g, 2.70mmol) and anhydrous potassium carbonate (0.5g, 3.6mmol). The reaction was refluxed for 6 days, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale yellow oil (0.10g, 15%). IR (film) υmax/$cm^{-1}$ 2927, 1718, 1546$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.63 and 2.00 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.10 and 2.28 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.35 (3H, s, $C\underline{H}_3$), 2.73-2.97 and 2.99-3.17 (7H, 2 x m, 3 x $C\underline{H}_2$ and C<u>H</u>), 3.60 and 3.63 (2H, 2 x dd, J~14Hz, $NC\underline{H}_2$), 4.83 (1H, m, $C\underline{H}CH_2CO$), 7.07-7.14 (6H, m, 6 x Ar-C<u>H</u>), 7.29 (2H, m, 2 x Ar-C<u>H</u>), 7.46 (1H, m, Ar-C<u>H</u>), 7.72 (1H, m, Ar-C<u>H</u>), 7.79 (1H, m, Ar-C<u>H</u>), 7.92 and 7.96 (1H, 2 x d, J=8Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 20.6 ($\underline{C}H_3$), 25.8, 29.4, 29.5, 29.7, 32.1, 34.9

(3 x $\underline{C}H_2$), 39.7 and 40.0 ($\underline{C}H_2CO$), 49.1 and 49.2 ($N\underline{C}H_2$), 53.9 and 54.0 ($\underline{C}H$), 54.9 and 55.2 ($\underline{C}H$), 122.5 x 2 (Ar-$\underline{C}H$), 125.2 and 125.3 (Ar-$\underline{C}H$), 125.3-125.5 (Ar-$\underline{C}H$), 126.0 and 126.1 (Ar-$\underline{C}H$), 127.6, 127.7, 128.1, 128.2, 128.6 (6 x Ar-$\underline{C}H$), 128.9 and 129.0 (Ar-$\underline{C}H$), 134.6 x 2 (Ar-$\underline{C}H$), 135.4 and 135.6 (Ar-$\underline{C}$), 135.8 and 135.9 (Ar-$\underline{C}$), 136.0 and 136.1 (Ar-$\underline{C}$), 136.4 x 2 (Ar-$\underline{C}$), 136.8 (Ar-$\underline{C}$), 156.5 and 156.6 (Ar-$\underline{C}$), 204.5 x 2 ($\underline{C}$=O); MS, m/z, (RI) 251 (66), 129 (39), 120 (38), 105 (100), 103 (32), 91 (21); HRMS ($+H^+$) 382.2147, $C_{27}$ $H_{28}$ N O requires 382.2171; error -6.3ppm.

**3-[1,2,3,4-tetrahydro-2-naphthalenyl(3,4,5-trimethoxybenzyl)amino]-1-indanone (4.65)**

To a stirred solution of (**4.60**) (0.5g, 1.81mmol) in acetone (10ml) was added 5-bromomethyl)-1,2,3-trimethoxybenzene (0.5g, 1.91mmol) and anhydrous potassium carbonate (0.5g, 3.6mmol). The reaction was refluxed for 6 days, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amine as a pale oil (0.22g, 27%). IR (film) $\upsilon max/cm^{-1}$ 2936, 2837, 1717, 1592, 1506, 1464, 1420, 1329, 1237, 1132, 1012$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.68 and 2.04 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.13 and 2.27 (1H, 2 x m, 1H of $CH_2C\underline{H}_2CH$), 2.76-3.18 (7H, m, 3 x $C\underline{H}_2$ and $C\underline{H}$), 3.57 and 3.60 (2H, 2 x dd, J~14.5Hz, $NC\underline{H}_2$), 3.83 (3H, s, $OC\underline{H}_3$), 3.87 (6H, s, 2 x $OC\underline{H}_3$), 4.84 (1H, m, $C\underline{H}CH_2CO$), 6.62 and 6.63 (2H, 2 x s, 2 x $(CH_3O)_3Ar\text{-}C\underline{H}$), 7.07-7.13 (4H, m, 4 x Ar-$\underline{C}H$), 7.45 (1H, m, Ar-$\underline{C}H$), 7.69 (1H, m, Ar-$\underline{C}H$), 7.77 (1H, m, Ar-$\underline{C}H$), 7.86 and 7.89 (1H, 2 x d, J=8Hz, COAr-$\underline{C}H$); $^{13}$CNMR $\delta_C$ 25.9, 29.3, 29.4, 29.5, 32.3, 35.0 (6 x $\underline{C}H_2$), 39.6 and 39.9 ($\underline{C}H_2CO$), 49.8 x 2 ($N\underline{C}H_2$), 54.6 and 54.7 ($\underline{C}H$), 55.0 and 55.2 ($\underline{C}H$), 55.6 and 60.4 (3 x $O\underline{C}H_3$), 104.1 and 104.4 (2 x $(CH_3O)_3Ar\text{-}\underline{C}H$), 122.6 x 2 (Ar-$\underline{C}H$), 125.3 x 2 (Ar-$\underline{C}H$), 125.4 and 125.6 (Ar-$\underline{C}H$), 125.8 and 125.9 (Ar-$\underline{C}H$), 128.2 and 128.3 (2 x Ar-$\underline{C}H$), 128.8 and 129.0 (Ar-$\underline{C}H$), 134.5 x 2 (Ar-$\underline{C}H$), 135.3, 135.4 x 2, 135.5, 135.6, 135.7, 136.2 x 2, 136.9 (6 x Ar-$\underline{C}$), 156.2, 156.3 (2 x Ar-$\underline{C}$), 204.3 ($\underline{C}$=O); MS, m/z, (RI) 328 (8), 181 (100), 147 (13); HRMS ($+H^+$) 458.2336, $C_{29}$ $H_{32}$ N $O_4$ requires 458.2331; error 1.0ppm.

**2-methoxy-1-indanone (4.66)**

To a stirred suspension of lead (IV) acetate (3.35g, 7.6mmol) in dry benzene (100ml) at room temperature was added, in one lot, 1-indanone (1g, 7.6mmol), boron trifluoride etherate (4.65ml, 37.9mmol) and methanol (10ml). The reaction was stirred overnight at room temperature, diluted with cold water, and extracted with benzene (200ml). The organic layer was sequentially washed with saturated sodium bicarbonate solution (150ml) and water (150ml), before drying over anhydrous sodium sulphate. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the a mixture of products, the main product (c. 70%) a yellow oil with the following physical characteristics (~0.8g,~70 %): IR (film) υmax/$cm^{-1}$ 2930, 2828, 1725, 1610, 1466, 1212, 1127$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.82 (1H, dd, $J_1$~17Hz, $J_2$=4.5Hz, 1H of C$\underline{H}_2$), 3.35 (1H, dd, $J_1$~17Hz, $J_2$=7.5Hz, 1H of C$\underline{H}_2$), 3.48 (3H, s, C$\underline{H}_3$), 4.02 (1H, dd, $J_1$=7.5Hz, $J_2$=4.5Hz, C$\underline{H}$), 7.22 (1H, dd, $J_1$=8.2Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.25 (1H, br. d, J~6.6Hz, Ar-C$\underline{H}$), 7.46 (1H, m, Ar-C$\underline{H}$), 7.57 (1H, d, J=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 32.7 (C$\underline{H}_2$), 57.5 (C$\underline{H}_3$), 80.7 (C$\underline{H}$), 123.5, 126.2, 127.3 (3 x Ar-C$\underline{H}$), 134.3 (Ar-C$\underline{}$), 135.0 (Ar-C$\underline{H}$), 150.1 (Ar-C$\underline{}$), 203.1 (C$\underline{}$=O).

**2-azido-2-methoxy-1-indanone (4.68)**

To a solution of (**4.66**) (0.8g, 4.9mmol) in $CCl_4$ (20ml) was added *N*-bromosuccinimide (1.3g, 7.4mmol) and a catalytic amount of dibenzoyl peroxide. The reaction mixture was heated under reflux for 30 minutes. On completion, the reaction was filtered, and the solvent removed *in vacuo*. To a constantly stirring mixture of sodium azide (2g, 30.8mmol) in DMF (10ml) at 40°C was added, dropwise, the unpurified bromo compound (**4.67**). The resultant slurry was heated gently at this temperature for 2 hours, and partitioned between water and ether. The aqueous layer was washed twice with ether (2 x 20ml portions) and the combined ethereal layers dried over sodium sulphate before concentration *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the azide as an orange oil (0.4g, 40% yield from (**4.66**)), with the following physical properties: IR (film) υmax/$cm^{-1}$ 2109, 1734, 1611, 1230$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 3.23 (2H, dd, J~17Hz, C$\underline{H}_2$), 3.59 (3H, s, OC$\underline{H}_3$), 7.41 (2H, m, 2 x Ar-C$\underline{H}$), 7.65 (1H, m, Ar-C$\underline{H}$), 7.81 (1H, d, J=7.6Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 37.0

($\underline{C}H_2$), 52.0 ($O\underline{C}H_3$), 92.8 ($N_3\underline{C}OCH_3$), 125.0, 126.1, 127.9 (3 x Ar-$\underline{C}H$), 132.4 (Ar-$\underline{C}$), 136.0 (Ar-$\underline{C}H$), 148.8 (Ar-$\underline{C}$), 195.6 ($\underline{C}$=O).

**_tert_-butyl _N_-(2-methoxy-1-oxo-2,3-dihydro-1_H_-2-indenyl)carbamate (4.69)**

Di-*tert*-butyl dicarbonate (0.25g, 1.14mmol) was added to a solution of azide (**4.68**) (0.21g, 1.03mmol) in EtOH:EtOAc (1:1, 10ml). After addition of 10% Pd/C, the reaction was stirred under an atmosphere of hydrogen overnight at room temperature. The reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the BOC-protected amine (0.14g, 49%) with the following physical properties: IR (film) υmax/$cm^{-1}$ 3428, 2980, 1720, 1494, 1167$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.47 and 1.50 (12H, 2 x s, ($C\underline{H}_3$)$_3$ and $OC\underline{H}_3$), 3.05 (2H, dd, $J_1$=16.6Hz, $J_2$=5.5Hz, $C\underline{H}_2$), 5.26 (1H, br. s, N$\underline{H}$), 7.41 (1H, dd, $J_1$=8.6Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.47 (1H, d, J=8.1Hz, Ar-$C_4\underline{H}$), 7.64 (1H, dd, $J_1$=8.0Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.79 (1H, d, J=7.5Hz, Ar-$C_7\underline{H}$); $^{13}$CNMR $\delta_C$ 27.9 x 2 ($\underline{C}H_3$)$_3$, 34.6 ($\underline{C}H_2$), 56.8 ($O\underline{C}H_3$), 81.4 (quat. $\underline{C}$), 123.8, 126.2, 127.4 (3 x Ar-$\underline{C}$H), 134.3 (Ar-$\underline{C}$), 135.1 (Ar-$\underline{C}$H), 150.8 (Ar-$\underline{C}$), 159.8 (N$\underline{C}$=O), 202.6 ($\underline{C}$=O).

**2-(2-iodophenyl)acetonitrile (4.70)**

To a stirred solution of 1-(chloromethyl)-2-iodobenzene (10g, 39.6mmol) in DMF (50ml) was added potassium cyanide (5g, 76.9mmol). The reaction was heated at 50°C for three hours, and stirred at room temperature overnight. The reaction was quenched by addition of water, and extracted with ether (3 x 100ml). The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the nitrile (9.45g, 98%), an oil with the following physical properties: IR (film) υmax/$cm^{-1}$ 3063, 2929, 2248, 1568, 1466, 1439, 1414, 1015$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 3.84 (2H, s, $C\underline{H}_2$), 7.07 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.42 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.56 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.90 (1H, d, J=7.5Hz, Ar-CH); $^{13}$CNMR $\delta_C$ 29.5 ($\underline{C}H_2$), 98.6 ($\underline{C}C\equiv N$), 116.6 ($\underline{C}\equiv N$), 128.6 x 2, 129.4 (3 x Ar-$\underline{C}$H), 132.8 (Ar-$\underline{C}$), 139.4 (Ar-$\underline{C}$H).

**2-(2-iodophenyl)acetic acid (4.71)**

To 9.45g (38.9mmol) of cyanide (**4.70**) in EtOH/H2O (300ml, 2:1) was added sodium hydroxide (15.5g, 0.39mol). The reaction was refluxed for six hours, the ethanol removed in vacuo, and the aqueous residue extracted with DCM (3 x 200ml). The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 4:1) to yield the acid (7.92g, 78%), a solid with the following physical properties: IR (KBr disc) υmax/$cm^{-1}$ 1700, 1664, 1230$cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 3.90 (2H, s, C$\underline{H}_2$), 7.02 (1H, m, Ar-C$\underline{H}$), 7.35 (2H, m, 2 x Ar-C$\underline{H}$), 7.90 (1H, d, J=8Hz, Ar-C$\underline{H}$), 11.65 (1H, br s, COO$\underline{H}$); $^{13}$CNMR $\delta_C$ 45.7 ($\underline{C}H_2$), 100.8 (Ar-$\underline{C}$), 128.1, 128.8, 130.4 (3 x Ar-$\underline{C}$H), 136.7 (Ar-$\underline{C}$), 139.2 (Ar-$\underline{C}$H), 176.4 ($\underline{C}$=O).

**2,3,4,5,6-pentafluorophenyl 2-(2-iodophenyl)acetate (4.72)**

To a stirred solution of acid (**4.71**) (10.68g, 40.8mmol) in DCM at 0°C was added DCC (8.4g, 44.8mmol) and PFP (7.5g, 44.8mmol). The reaction was stirred at this temperature for one hour, and then allowed to reach room temperature. After filtration to remove the insoluble dicyclohexylurea, the filtrate was washed with dichloromethane (2 x 50ml) and the organic extracts combined. The organic solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 20:1) to yield the pentafluorophenyl ester (14.7g, 84%), a viscuous oil with the following physical properties: IR (film) υmax/$cm^{-1}$ 1792, 1521, 1092, 1002$cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 4.18 (2H, s, C$\underline{H}_2$), 7.05 (1H, m, Ar-C$\underline{H}$), 7.39 (2H, m, 2 x Ar-C$\underline{H}$), 7.93 (1H, d, J=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 44.9 ($\underline{C}H_2$), 100.3 (Ar-$\underline{C}$), 128.2, 129.1, 130.2 (3 x Ar-$\underline{C}$H), 135.4 (Ar-$\underline{C}$H), 139.3 (Ar-$\underline{C}$), 166.0 ($\underline{C}$=O).

***N*1-methoxymethyl-*N*1-methyl-2-(2-iodophenyl)acetamide (4.73)**

To a stirred solution of (**4.72**) (10.06g, 23.5mmol) in pyridine (20ml) was added *N,O*-dimethyl hydroxylamine (2.5g, 25.9mmol) and a few crystals of DMAP. The reaction was stirred at room temperature overnight, before partitioning between and ether. The organic layers were combined, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the amide (6.93g, 97%), a colourless oil with the following physical properties: IR (film) υmax/$cm^{-1}$ 2938, 1674, 1466, 1437, 1410, 1381, 1015$cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$

3.19 (3H, s, $NC\underline{H}_3$), 3.68 (3H, s, $OC\underline{H}_3$), 3.91 (2H, s, $C\underline{H}_2$), 6.91 (1H, m, Ar-C<u>H</u>), 7.28 (2H, m, 2 x Ar-C<u>H</u>), 7.81 (1H, d, J=8.5Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 32.1 ($N\underline{C}H_3$), (44.0 ($\underline{C}H_2$), 61.0 ($O\underline{C}H_3$), 101.0 (Ar-<u>C</u>), 127.9, 128.2, 130.1 (3 x Ar-<u>C</u>H), 138.1 (Ar-<u>C</u>), 138.9 (Ar-<u>C</u>), 170.8 (<u>C</u>=O).

**Benzocyclobutenone (4.74)**

To a solution of amide (**4.73**) (4.79g, 15.7mmol) in dry THF (10ml) under a nitrogen atmosphere at –78°C was added, dropwise, *tert*-butyllithium (18.5ml, 1.7M solution in pentane). The reaction was stirred four four hours at this temperature, and carefully quenched at –10°C with saturated ammonium chloride solution. After extraction with DCM (3 x 30ml), the residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the ketone (1.04g, 56%), a yellow liquid; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 4.00 (2H, s, $CH_2$), 7.36 (1H, m, Ar-C<u>H</u>), 7.42 (1H, m, Ar-C<u>H</u>), 7.52-7.57 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 51.9 ($\underline{C}H_2$), 120.1, 123.2, 128.2, 134.7 (4 x Ar-<u>C</u>H), 147.5, 150.8 (2 x Ar-<u>C</u>), 188.1 (<u>C</u>=O).

**Benzocyclobutenol (4.75)**

To a stirred solution of ketone (**4.74**) (0.46g, 3.9mmol) in methanol (10ml), at 0°C, was added sodium borohydride (0.22g, 5.8mmol), over 5 minutes. The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alcohol (0.29g, 62%) as white needles, with the following physical properties: M.p. 60-62°C; IR (KBr disc) $\upsilon$max/cm$^{-1}$ 3297, 3206, 2918, 1454, 1111, 1054cm$^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.65 (1H, br s, OH), 3.04 (1H, dd, $J_1$~14Hz, $J_2$=1Hz, 1H of $C\underline{H}_2$), 3.62 (1H, dd, $J_1$~14Hz, $J_2$=4.5Hz, 1H of $C\underline{H}_2$), 5.28 (1H, br. d, J~3Hz, C<u>H</u>), 7.17 (1H, d, J~7Hz, Ar-C<u>H</u>), 7.25 (2H, m, 2 x Ar-C<u>H</u>), 7.32 (1H, m, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 42.0 ($\underline{C}H_2$), 70.6 (<u>C</u>H), 121.8, 123.2, 126.8, 129.0 (4 x Ar-<u>C</u>H), 141.9, 147.4 (2 x Ar-<u>C</u>).

**_tert_-butyl _N_-bicyclo[4.2.0]octa-1(6),2,4-trien-7-ylcarbamate (4.78)**

To a stirred solution of alcohol (**4.75**) (0.3g, 2.5mmol) in ether (5ml) containing pyridine (0.2g, 2.5mmol) at –10°C was added, dropwise, thionyl chloride (300mg, 2.5mmol). The ether was then removed *in vacuo* and the reaction refluxed for one hour. The reaction was then cooled in ice, and water added to destroy the thionyl chloride. The mixture containing the chloride (**4.76**) was extracted with ether (3 x 20ml), the extract washed with water and dried over sodium sulphate. The crude residue was added to a suspension of sodium azide (2g, 30.8mmol) in DMF (10ml), and stirred for one hour at 30-50°C, before partitioning between ether and water, and concentrating the ethereal layers. The azide (**4.77**) was isolated after flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) as a colourless oil, with the following infrared spectral characteristics: IR (film) $\upsilon max/cm^{-1}$ 2932, 2102, 1458, 1251$cm^{-1}$. Due to the apparent volatility of the azide, it was immediately hydrogenated in the presence of Di-*tert*-butyl dicarbonate (0.60g, 2.7mmol) using 10% Pd/C as catalyst in EtOH/EtOAc (1:1, 10ml). After reaction overnight, the *BOC*-protected amine was isolated following flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1). The amide was a white solid with the following physical properties: IR (film) $\upsilon max/cm^{-1}$ 3347, 2981, 2930, 1719, 1498, 1367, 1247, 1168$cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.50 (9H, s, $C(\underline{C}H_3)_3$), 2.99 (1H, d, J~14Hz, 1H of $C\underline{H}_2$), 3.68 (1H, d, J~14Hz, 1H of $C\underline{H}_2$), 5.27 (1H, s, C<u>H</u>), 7.11 (1H, d, J=7Hz, Ar-C<u>H</u>), 7.17-7.29 (3H, m, 3 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 28.0 (3 x $\underline{C}H_3$), 40.4 ($\underline{C}H_2$), 50.8 (<u>C</u>H), 79.1 ($(\underline{C}(CH_3)_3$), 122.0, 122.8, 126.9, 128.6 (4 x Ar-<u>C</u>H), 142.6, 145.5 (2 x Ar-<u>C</u>), 154.9 (N<u>C</u>=O).

**1-aminobenzocyclobutene (4.79)**

To the *BOC*-protected amine (**4.78**) (0.6g, 2.7mmol) was added TFA/DCM (1:1, 10ml) at 0°C. The reaction was stirred for one hour, allowing the reaction to reach room temperature. The amine trifluoroacetate was isolated by removal of the solvent *in vacuo*, a dark oil with the following NMR characteristics: $^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 3.28 (1H, d, J=15Hz, 1H of $C\underline{H}_2$), 3.58 (1H, dd, $J_1$~15Hz, $J_2$=4.5Hz, 1H of $C\underline{H}_2$), 4.73 (C<u>H</u>), 7.12 (1H, d, J=7.5Hz, Ar-C<u>H</u>), 7.18-7.25 (2H, m, 2 x Ar-C<u>H</u>), 7.54 (1H, dd, $J_1$=8Hz, $J_2$=7.5Hz, Ar-C<u>H</u>), 12.7 (1H, br s, $NH_3^+$); $^{13}$CNMR $\delta_C$ 36.1 ($\underline{C}H_2$), 49.8 (<u>C</u>H), 122.6, 123.0, 127.6, 130.4 (4 x Ar-<u>C</u>H), 139.4, 141.4 (2 x Ar-<u>C</u>).

**2,2-dimethoxyindane (5.1)**

To a solution of 2-indanone (2g, 15.2mmol) in methanol (5ml) was added trimethylorthoformate $CH(OCH_3)_3$, 2.5ml) and a crystal of *p*-toluenesulphonic acid (*p*-ToSH). The reaction was stirred at room temperature for 3 hours, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the dimethyl acetal (1.37g, 69%), with the remainder of the product mixture consisting of 1*H*-2-indenyl methyl ether. The dimethyl acetal was isolated as a pale yellow oil: $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 3.18 (4H, s, 2 x C$\underline{H}_2$), 3.33 (6H, s, 2 x OC$\underline{H}_3$), 7.16-7.21 (4H, m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 40.8 (C$\underline{H}_2$ x 2), 49.1 (C$\underline{H}_3$ x 2), 111.1 (C$\underline{(OMe)}_2$), 124.2 (Ar-C$\underline{H}$ x 2), 126.1 (Ar-C$\underline{H}$ x 2), 139.4 (Ar-C$\underline{}$ x 2); MS, m/z, (RI) 176 (100), 104 (10).

**(3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane (5.3)**

To a solution of α-tetralone (1g, 6.84mmol) in dry DCM (10ml) at 0°C was added triethylamine (0.76g, 7.52 mmol) and trimethylsilyltrifluoromethanesulphonate (TMSOTf, 1.52g, 6.84mmol). The reaction was stirred at 0°C for 30 minutes, and immediately columned on silica that had been pre-treated with ethyl acetate and petroleum ether, in that order, to remove any moisture from the silica. The eluant used was petroleum ether, and the silyl enol ether (1.34g, 95%) was obtained as a colourless oil, and stored in a dry flask under nitrogen at 0°C until future use. IR (film) υmax/cm$^{-1}$; 2961, 2835, 1339, 1253, 1189, 1094cm$^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 0.51 (9H, s, Si(C$\underline{H}_3$)$_3$, 2.54 (2H, m, C$\underline{H}_2$), 2.98 (2H, t, 7.9Hz, ArC$\underline{H}_2$), 5.43 (1H, t, J=4.5Hz, C=C$\underline{H}$), 7.30 (1H, Ar-C$\underline{H}$), 7.36 (1H, ddd, $J_1$=8Hz, $J_2$=7.2Hz, $J_3$=1Hz, Ar-C$\underline{H}$), 7.42 (1H, dd, $J_1$=8Hz, $J_2$=7.3Hz, Ar-C$\underline{H}$), 7.70 (1H, d, J=7.6Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 0.06 (C$\underline{H}_3$), 22.0 (C$\underline{H}_2$), 28.0 (C$\underline{H}_2$), 104.8 (C=C$\underline{H}$), 121.6 (Ar-C$\underline{H}$), 125.9 (Ar-C$\underline{H}$), 126.7 (Ar-C$\underline{H}$), 127.0 (Ar-C$\underline{H}$), 133.3 (Ar-C$\underline{}$), 136.7 (Ar-C$\underline{}$), 148.0 (OC$\underline{}$=C).

**1',3'-Dihydro-spiro[[1,3]dioxolane-2,2'-indene] (5.6)**

To a solution of 2-indanone (2g, 15.2mmol) in ethylene glycol (10ml) was added triethylorthoformate (5ml) and a crystal of *p*ToSH. The reaction was stirred at room temperature for 3 hours, and the solvent removed *in vacuo*. The residue was purified by

flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the dioxane, (2.4g, 90%), a colourless oil with the following physical properties: IR (film) υmax/$cm^{-1}$ 2955, 2885, 1403, 1331, 1292, 1226, 1104, 1030 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 3.27 (4H, s, 2 x $C\underline{H}_2$), 4.06 (4H, s, 2 x $OC\underline{H}_2$), 7.23-7.28 (4H, m, 4 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 48.2 (2 x $\underline{C}H_2$), 64.1 (2 x $O\underline{C}H_2$), 117.1 (O<u>C</u>O), 124.1 (2 x Ar-<u>C</u>H), 126.3 (2 x Ar-<u>C</u>H), 139.5 (2 x Ar-<u>C</u>); MS, m/z, (RI) 177 (M+1, 28), 176 ($M^+$, 100), 117 (12), 104 (42).

**2-[2-(2-hydroxyethoxy)-2,3-dihydro-1*H*-2-indenyl]-1,2,3,4-tetrahydro-1-naphthalenone (5.7)**

To a solution of (3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane (**5.3**) (2.13g, 9.77mmol) in anhydrous DCM at –78°C was added 1',3'-Dihydro-spiro[[1,3]dioxolane-2,2'-indene] (1.72g, 9.77mmol) and tin tetrachloride (2.55g, 9.77mmol). The reaction was stirred at –78°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the aldol product, a yellow oil (1.62g, 51%), with the following characteristics: IR (film) υmax/$cm^{-1}$ 3494, 2932, 2873, 1740, 1684, 1601, 1484, 1456, 1227 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.15-2.25 (1H, m, 1H of $CH_2C\underline{H}_2CH$), 2.37-2.44 (1H, m, 1H of $CH_2C\underline{H}_2CH$), 2.81-3.10 and 3.19-3.60 (5 x $C\underline{H}_2$, C<u>H</u> and O<u>H</u>), 7.14-7.28 (6H, m, 6 x Ar-C<u>H</u>), 7.43 (1H, ddd, $J_1$=8.4Hz, $J_2$=7.52Hz, $J_3$=1Hz, Ar-C<u>H</u>), 8.01 (1H, dd, $J_1$=8Hz, $J_2$=1Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 24.8 ($ArCH_2\underline{C}H_2$), 28.7 ($Ar\underline{C}H_2CH_2$), 42.2, 42.6 (2 x $Ar\underline{C}H_2CH$), 54.8 (<u>C</u>H), 61.5 ($HO\underline{C}H_2$), 63.7 ($O\underline{C}H_2CH_2OH$), 86.7 (ArCO<u>C</u>), 123.6, 123.7, 126.1 x 2, 126.2, 126.9, 128.2, 132.8 (8 x Ar-<u>C</u>H), 133.4, 140.5, 141.6, 143.5 (4 x Ar-<u>C</u>); MS, m/z, (RI) 260 (35), 146 (100), 103 (13).

Decomposition rapidly led to the β,γ eliminated derivative (**5.5**), a pale crystalline solid: M.p. 113-115°C; IR (film) υmax/$cm^{-1}$ 3072, 2936, 1687, 1601, 1550, 1460, 1222$cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.43-2.48 (2H, m, $ArCH_2C\underline{H}_2$), 3.08-3.12 (2H, m, $ArC\underline{H}_2CH_2$), 3.55 (2H, s, $C\underline{H}_2$ indenyl), 3.77-3.81 (1H, t, J=7.02Hz, C<u>H</u>), 6.68 (1H, s, C=C<u>H</u>), 7.16-7.20 (1H, dd, $J_2$=7.28Hz, Ar-C<u>H</u>), 7.25-7.39 (4H, m, 4 x Ar-C<u>H</u>), 7.45 (1H, d, J=7.5Hz,

Ar-C<u>H</u>), 7.51-7.55 (1H, ddd, $J_2$=7.52Hz, $J_3$=1.52Hz, Ar-C<u>H</u>), 8.13-8.16 (1H, dd, $J_1$=8.04Hz, $J_2$=1Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 27.7 (<u>C</u>$H_2$), 28.9 (<u>C</u>$H_2$), 39.9 (<u>C</u>$H_2$CO), 49.6 (<u>C</u>H), 120.1 (C=<u>C</u>H), 123.1, 123.8, 125.8, 126.3, 127.3 (5 x Ar-<u>C</u>H), 128.3 (2 x Ar-<u>C</u>H), 132.1 (quat. <u>C</u>), 133.0 (Ar-<u>C</u>H), 142.9, 143.5, 144.3, 146.0 (4 x quat. <u>C</u>), 197.1 (<u>C</u>=O); MS, m/z, (RI) 261 (M+1, 58), 260 ($M^+$, 100), 232 (6); HRMS (+$H^+$) 261.1282, $C_{19}$ $H_{17}$ O requires 261.1279; error 1.1ppm.

**2-benzyl-2-(1*H*-2-indenyl)1,2,3,4-tetrahydro-1-naphthalenone (5.8)**

To a solution of the aldol (**5.7**) (0.54g, 1.68mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (1.0ml, 8.40mmol). To this solution was added potassium *tert*-butoxide as a solution in *t*-butanol (5ml), adding the base dropwise over several hours. The reaction was stirred overnight, and the butanol removed by ether/water extraction. The combined organic extracts (3 x 20ml) were concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product (0.14g, 23%). The product was obtained as yellow crystals: M.p. 125-127°C; IR (film) υmax/cm$^{-1}$ 2929, 1684, 1550, 1220cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.13-2.26 and 2.35-2.40 (2H, 2 x m, $ArCH_2C\underline{H}_2$), 2.69-2.86 and 3.02-3.11 (2 x m, $ArC\underline{H}_2CH_2$), 3.18-3.28 (2H, m, $C_6H_5C\underline{H}_2$), 3.49-3.62 (2H, m, $C\underline{H}_2C$=CH), 6.53 (1H, s, C=C<u>H</u>), 7.11-7.45, (12H, m, 12 x Ar-C<u>H</u>), 8.20 (1H, d, J=8Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 25.4, 30.9, 38.9, 44.0 (4 x <u>C</u>$H_2$), 52.9 (CO<u>C</u>$CH_2$), 120.3, 123.0, 124.1, 125.9 x 2, 126.1, 127.4, 127.7, 128.1, 129.5, 130.5 (C=<u>C</u>H and 12 x Ar-<u>C</u>H), 131.9 (quat. <u>C</u>), 132.8 (Ar-<u>C</u>H), 137.2, 142.6, 143.0, 143.9, 146.5 (5 x quat. <u>C</u>), 198.0 (<u>C</u>=O); MS, m/z, (RI) 351 ($M^+$, 22), 350 (76), 259 (100), 231 (37).

**2-benzyl-2-(1*H*-2-indenyl)1,2,3,4-tetrahydro-1-naphthalenol (5.9)**

To a stirred solution of the alkylated dimer (**5.8**) (100mg, 0.29mmol) in methanol (5ml) at 0°C was added sodium borohydride (0.02g, 0.58mmol). The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the white crystalline alcohol as a diastereomeric mixture (87mg, 87%): M.p. 60-62°C; IR (film) υmax/cm$^{-1}$ 2931, 2361, 2343, 1551, 1496, 1456, 1252cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.97-2.13 (1H, m, 1H of

$ArCH_2C\underline{H}_2$), 2.34 (1H, m, 1H of $ArCH_2C\underline{H}_2$), 2.80-3.40 (4H, m, 2 x $ArC\underline{H}_2$), 3.58 (2H, m, $PhC\underline{H}_2$), 4.73 and 4.80 (1H, 2 x s, C<u>H</u>OH), 6.33 and 6.69 (1H, 2 x s, C=C<u>H</u>), 7.03-7.54 (13H, 4 x m, 13 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 24.8 and 27.6 ($ArCH_2\underline{C}H_2$), 25.2 and 25.6 ($Ar\underline{C}H_2$), 38.5 and 38.7 ($Ph\underline{C}H_2$), 41.5 and 44.3 ($Ar\underline{C}H_2$), 45.1 ($CH_2\underline{C}CHOH$), 119.9 and 120.3, 122.9 and 123.1, 123.5 and 123.9 (3 x Ar-<u>C</u>H), 125.6, 125.7, 125.9, 126.0 (3 x Ar-<u>C</u>H), 127.4, 127.5 (3 x Ar-<u>C</u>H), 128.6 and 128.8 (Ar-<u>C</u>H), 128.8 and 129.0 (C=<u>C</u>H), 129.3 and 129.5 (Ar-<u>C</u>H), 129.6, 130.0 (2 x Ar-<u>C</u>H), 135.2, 136.7, 137.2, 142.6, 144.2, 152.2 (5 x Ar-<u>C</u> and <u>C</u>=CH); MS, m/z, (RI) 334 ($M-H_2O$), 261 (100), 243 (34), 215 (13), 145 (28), 117 (74), 91 (68), 65 (19); HRMS ($+Na^+$) 375.1713, $C_{26}$ $H_{24}$ O Na requires 375.1725; error -3.1ppm.

**2-(1-methoxy-2-phenylethyl)-1,2,3,4-tetrahydro-1-naphthalenone (5.10)**

To a solution of (3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane (**5.3**) (1.69g, 7.75mmol) in anhydrous DCM at –78°C was added phenylacetaldehyde dimethyl acetal (1.29g, 7.75mmol) and tin tetrachloride (2.02g, 7.75mmol). The reaction was stirred at –70°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol product, a diastereomeric mixture, as an off-white solid (1.0g, 46%): M.p. 61-63°C; IR (film) υmax/$cm^{-1}$ 2931, 1684, 1601, 1456, 1222, 1098$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.02-2.24 and 2.32-2.43 (2H, 2 x m, $C\underline{H}_2$), 2.67-3.17 (5H, m, 2 x Ar-$C\underline{H}_2$ and C<u>H</u>), 3.27 and 3.36 (3H, 2 x s, $OC\underline{H}_3$), 4.27 and 4.50 (1H, 2 x m, C<u>H</u>$OCH_3$), 7.24-7.41 (7H, m, 7 x Ar-C<u>H</u>), 7.49 (1H, m, Ar-C<u>H</u>), 8.07 and 8.11 (1H, 2 x d, J~7.5Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 21.7 and 23.0 ($\underline{C}H_2$), 28.5 and 28.8 ($\underline{C}H_2$), 37.5 x 2 ($\underline{C}H_2$), 49.4 and 49.9 (<u>C</u>H), 57.5 and 58.2 ($\underline{C}HOCH_3$), 125.6 and 126.0, 126.1 and 126.2, 126.8 and 127.0 (3 x Ar-<u>C</u>H), 127.8, 128.1, 128.2, 128.4, 128.9 x 2 (5 x Ar-<u>C</u>H), 132.4 and 132.6 (Ar-<u>C</u>), 132.8 and 133.0 (Ar-<u>C</u>H), 138.1 and 139.6, 143.7 and 143.8 (2 x Ar-<u>C</u>), 198.0 and 198.4 (C=O); MS, m/z, (RI) 249 (77), 248 (100), 118 (18), 115 (10), 89 (14); HRMS ($+Na^+$), 303.1346, $C_{19}$ $H_{20}$ $O_2$ Na requires 303.1361; error -5.0ppm.

**2-benzyl-2-[2-phenyl-1-ethenyl]-1,2,3,4-tetrahydro-1-naphthalenone (5.11)**

To a solution of the aldol product (**5.10**) (0.5g, 1.79mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (1.2ml, 8.95mmol). To this solution was added potassium *tert*-butoxide (0.23g, 1.79mmol) as a solution in *t*-butanol (5ml), adding the base drop-wise over several hours. The reaction was stirred overnight, and the butanol removed by ether/water extraction. The combined organic extracts (3 x 20ml) were concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product as a pale oil (0.24g, 40%). IR (film) υmax/cm$^{-1}$ 3030, 2927, 1682, 1601, 1455, 1228cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.13-2.16 (2H, m, $CH_2\underline{CH_2}CH$), 2.84-2.87 and 2.89-2.91, 2.97-3.09 (2H, 2 x m, $C\underline{H_2}$), 3.15-3.30 (2H, m, $C\underline{H_2}$), 6.28 (2H, 2 x s, $C\underline{H}$=$C\underline{H}$), 7.17-7.34 (12H, m, 12 x Ar-$C\underline{H}$), 7.43-7.47 (1H, m, Ar-$C\underline{H}$), 8.18 (1H, dd, $J_1$=7.5Hz, $J_2$=1Hz, COAr-$C\underline{H}$); $^{13}$CNMR $\delta_C$ 25.5 (Ar$\underline{C}H_2CH_2$), 31.6 ($ArCH_2\underline{C}H_2$), 43.5 ($COC\underline{C}H_2Ar$), 51.9 ($\underline{C}H$), 125.8, 125.9, 126.2, 127.1, 127.4, 127.6, 128.1 x 2, 130.4, 130.6, 130.9, 132.8 (14 x Ar-$\underline{C}H$ and $\underline{C}H$=$\underline{C}H$), 198.4 ($\underline{C}$=O); MS, m/z, (RI) 338 ($M^+$, 15), 247 (100), 91 (37); HRMS (+$Na^+$) 361.1586, $C_{25}$ $H_{22}$ O Na requires 361.1568; error 5.0ppm.

**2-benzyl-2-[2-phenyl-1-ethenyl]-1,2,3,4-tetrahydro-1-naphthalenol (5.12)**

To a stirred solution of the alkylated product (**5.11**) (0.24g, 0.71mmol) in methanol (10ml) at 0°C was added sodium borohydride (0.05g, 1.42mmol). The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the white crystalline alcohol as a 2:1 diastereomeric mixture (0.22g, 90%). M.p. 132-134°C; IR (film) υmax/cm$^{-1}$ 3028, 2925, 1550, 1494, 1005cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.83-1.96 (2H, m, 1H of $ArCH_2C\underline{H_2}$ and O$\underline{H}$), 2.19-2.30 (1H, m, 1H of $ArCH_2C\underline{H_2}$), 2.87-3.25 (4H, m, 2 x $ArC\underline{H_2}$), 4.58 and 4.63 (1H, 2 x s, CHO$\underline{H}$), 6.11 (1H, 2 x d, J=16.6Hz, $C\underline{H}$=CH), 6.49 (1H, 2 x d, J=16.6Hz, CH=$C\underline{H}$), 7.13-7.56 (14H, m, 14 x Ar-$C\underline{H}$); $^{13}$CNMR $\delta_C$ 25.2 and 25.6 ($\underline{C}H_2$), 26.3 and 26.8 ($\underline{C}H_2$), 42.1 and 43.5 ($\underline{C}H_2$), 43.7 and 43.8 (CHOH$\underline{C}$), 72.4 and 72.6 ($\underline{C}$HOH), 125.6, 125.7, 125.8, 125.9 x 2, 126.6, 127.0, 127.2, 127.3, 127.5, 128.0, 128.2, 128.4, 128.6, 128.7, 129.0, 129.2, 130.4, 130.7 x 2 (13 x Ar-$\underline{C}H$), 132.8 and 132.9 (Ar-$\underline{C}H$),

135.2, 136.0, 136.9, 137.1 x 2, 137.5 (4 x Ar-C); MS, m/z, (RI) 323 (89), 249 (100), 117 (46); HRMS ($+Na^+$) 363.1716, $C_{25}$ $H_{24}$ O Na requires 363.1725; error -3.0ppm.

**2-[2-(2-hydroxyethoxy)-2,3-dihydro-1H-2-indenyl]-1-phenyl-1-propanone (5.15)**

To a solution of 1-phenyl-1-propenyl (1,1,1,-trimethylsilyl) ether (1.01g, 4.90mmol) in anhydrous DCM at –70°C was added 1',3'-Dihydro-spiro[[1,3]dioxolane-2,2'-indene] (0.86g, 4.90mmol) and tin tetrachloride (0.57ml, 4.90mmol). The reaction was stirred at –70°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol product as a pale oil (1.05g, 69%). IR (film) υmax/$cm^{-1}$ 3460, 2939, 1737, 1679, 1596, 1448, 1227, 1086, 1057$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.31-1.33 (3H, d, J=7Hz, $CH_3$), 2.35 (1H, broad s, OH), 3.14 (2H, 2 x d, J~4.5Hz, $CH_2$), 3.28 (2H, dd, $J_1$=5.5Hz, $J_2$~4.5Hz, $CH_2$), 3.36-3.46 (4H, m, $OCH_2CH_2O$), 4.15 (1H, q, J=7Hz, CH), 7.15-7.20 (4H, m, 4 x Ar-CH), 7.47 (2H, m, 2 x Ar-CH), 7.56 (1H, m, Ar-CH), 8.01 (2H, m, 2 x COAr-CH); $^{13}$CNMR $\delta_C$ 13.6 ($CH_3$), 39.3, 41.1 (2 x $CH_2Ar$), 45.8 (CH), 61.5, 63.7 ($OCH_2CH_2OH$), 87.9 (quat. C), 123.6, 123.7, 126.2, 127.9, 128.2, 132.5 (9 x Ar-CH), 137.9, 140.6, 140.9 (3 x Ar-C), 203.0 (C=O); MS, m/z, (RI) 249 (M+1, enone, 100), 248 ($M^+$, enone, 25), 176 (13), 105 (9); HRMS ($+Na^+$) 333.1470, $C_{20}$ $H_{22}$ $O_3$ Na requires 333.1467; error 9.5ppm.

**2-(1H-2-indenyl)-2-methyl-1,3-diphenyl-1-propanone (5.16)**

To a solution of the aldol product (**5.15**) (0.53g, 1.71mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (1.02ml, 8.55mmol). To this solution was added potassium *tert*-butoxide (0.19g, 1.71mmol) as a solution in *t*-butanol (5ml), adding the base dropwise over several hours. The reaction was gently heated for two days, adding another 5 equivalents of alkylating agent on the second day. The butanol was removed by ether/water extraction. The combined organic extracts (3 x 20ml) were concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product (0.23g, 40%) as a pale oil: IR (film) υmax/$cm^{-1}$ 3068, 3031, 1681, 1463, 1240, 967, 910 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz)

$\delta_H$ 1.51 (3H, s, C<u>H</u>$_3$), 3.21-3.33 (2H, irr. dd, C<u>H</u>$_2$), 3.46-3.52 (2H, t, J=12.5Hz, C<u>H</u>$_2$), 6.72 (1H, s, C=C<u>H</u>), 6.90-6.93 (2H, m, 2 x Ar-C<u>H</u>), 7.16-7.47 (10H, m, 10 x Ar-C<u>H</u>), 7.77-7.93 (2H, m, 2 x COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 22.8 (<u>C</u>H$_3$), 38.9, 44.4 (2 x <u>C</u>H$_2$), 53.7 (CH$_3$<u>C</u>CH$_2$), 120.5, 123.3, 124.1, 125.9, 126.1, 127.3 x 2, 127.8 x 2, 128.1 x 2, 128.5, 130.2 x 2, 131.4 (14 x Ar-<u>C</u>H and C=<u>C</u>H), 137.0 x 2, 142.6, 144.0, 150.8 (4 x Ar-<u>C</u> and <u>C</u>=CH), 202.6 (<u>C</u>=O); MS, m/z, (RI) 338 ($M^+$, 7), 233 (100), 105 (28).

**2-(1H-2-indenyl)-2-methyl-1,3-diphenyl-1-propanol (5.17)**

To a solution of the benzylated product (**5.16**) (0.23g, 0.68mmol) in methanol (5ml) was added sodium borohydride (34mg, 1.02mmol). The reaction was stirred at room temperature for one hour, and the methanol removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the alcohol as two separable diastereomers, the predominant of which was isolated, a white crystalline solid with the following properties: m.p. 74-76°C; IR (film) υmax/cm$^{-1}$ 3615, 3563, 3066, 3032, 2977, 1604, 1551, 1496, 1455, 1392, 1252, 1206, 1044, 1024 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.05 (3H, s, C<u>H</u>$_3$), 2.08 (1H, broad s, O<u>H</u>), 3.04 (2H, s, C<u>H</u>$_2$), 3.42-3.60 (2H, q, J=22-23Hz, C<u>H</u>$_2$), 4.81 (1H, s, C<u>H</u>OH), 6.66 (C=C<u>H</u>), 7.05 (2H, broad s, 2 x Ar-C<u>H</u>), 7.18-7.21 (5H, m, 5 x Ar-C<u>H</u>), 7.28-7.35 (6H, m, 6 x Ar-C<u>H</u>), 7.44-7.46 (1H, d, J=7.04Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 18.8 (<u>C</u>H$_3$), 39.9 (<u>C</u>H$_2$), 44.6 (<u>C</u>H$_2$), 46.2 (<u>C</u>CH$_3$), 79.8 (<u>C</u>HOH), 120.1, 123.0, 123.7, 125.7, 125.8, 127.2 x 2, 127.3, 127.7, 129.6, 130.0 (C=<u>C</u>H and 14 x Ar-<u>C</u>H), 137.5, 140.4, 142.9, 144.2, 152.4 (5 x quat. <u>C</u>); MS, m/z, (RI) 145 (11), 144 (100), 115 (44); HRMS (+$Na^+$) 363.1731, $C_{25}$ $H_{24}$ O Na requires 363.1725; error 1.8ppm.

**3-methoxy-2-methyl-1,4-diphenyl-1-butanone (5.18)**

To a solution of 1-phenyl-1-propenyl (1,1,1,-trimethylsilyl) ether (2.2g, 10.68mmol) [prepared in quantitative yield from propiophenone analogously to the formation of (3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane] in anhydrous DCM at –70°C was added phenylacetaldehyde dimethylacetal (1.77g, 10.68mmol) and tin tetrachloride (2.78g, 10.68mmol). The reaction was stirred at –70°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were

dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol product, a diasteromeric mixture, as a pale oil (2.0g, 70%): IR (film) υmax/$cm^{-1}$ 2936, 1686, 1598, 1496, 1449, 1369, 1223, 1100$cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.24 and 1.35 (3H, 2 x d, J=7.04Hz, $C\underline{H}_3$), 2.72-3.11 (2H, m, $C\underline{H}_2$), 3.17 and 3.30 (3H, 2 x s, $OC\underline{H}_3$), 3.54 and 3.74 (1H, 2 x m, C<u>H</u>), 3.86 (1H, m, C<u>H</u>), 7.22-7.35 (5H, m, 5 x Ar-C<u>H</u>), 7.43 (2H, m, 2 x *m*COAr-C<u>H</u>), 7.54 (1H, m, *p*COAr-C<u>H</u>), 7.78 and 7.95 (2H, 2 x m, 2 x COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 12.5 and 13.1 ($\underline{C}H_3$), 36.8 and 38.0 ($\underline{C}H_2$), 44.1 x 2 ($CH_3\underline{C}H$), 58.0 and 58.2 ($O\underline{C}H_3$), 83.3 and 83.9 ($CH_3O\underline{C}H$), 125.8 and 125.9 (Ar-<u>C</u>H), 127.8 x 2 (2 x Ar-<u>C</u>H), 127.9 x 2 (2 x Ar-<u>C</u>H), 128.1 and 128.2 (2 x Ar-<u>C</u>H), 129.2 and 129.3 (2 x Ar-<u>C</u>H), 132.3 and 132.4 (Ar-<u>C</u>H), 136.3 and 137.2 (Ar-<u>C</u>), 138.1 and 138.2 (Ar-<u>C</u>), 202.5 and 203.0 (<u>C</u>=O); MS, m/z, (RI) 269 (M+1, 98), 268 ($M^+$, 44), 237 (86), 134 (40), 105 (100); HRMS (+$Na^+$) 291.1333, $C_{18}$ $H_{20}$ O Na requires 291.1361; error -9.7ppm.

**2-benzyl-2-methyl-1,4-diphenyl-3-buten-1-one (5.19)**

To a solution of the aldol product (**5.18**) (0.2g, 0.75mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (0.44ml, 3.75mmol). To this solution was added potassium *tert*-butoxide (0.08g, 0.75mmol) as a solution in *t*-butanol (5ml), adding the base drop-wise over several hours. The reaction was stirred overnight, and the butanol removed by ether/water extraction. The combined organic extracts (3 x 20ml) were concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product as a pale oil (80mg, 33%): IR (film) υmax/$cm^{-1}$ 3030, 2933, 1724, 1681, 1598, 1497, 1452, 1271, 1237$cm^{-1}$: $^{1}H$ NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.49 (3H, s, $C\underline{H}_3$), 3.30 (2H, s, $C\underline{H}_2$), 6.50 (2H, 2 x d, J~16.5Hz, C<u>H</u>=C<u>H</u>), 7.13 (2H, m, 2 x Ar-C<u>H</u>), 7.22-7.41 (9H, m, 9 x Ar-C<u>H</u>), 7.48 (2H, m, 2 x Ar-C<u>H</u>), 7.87 (2H, m, 2 x COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 22.8 ($\underline{C}H_3$), 45.0 ($\underline{C}H_2$), 53.4 (<u>C</u>H), 125.9 x 2, 127.2, 127.4, 127.6, 128.2, 128.7, 129.9, 130.5, 131.1, 133.7 (15 x Ar-<u>C</u>H and <u>C</u>H=<u>C</u>H), 136.6, 137.0, 137.3 (3 x Ar-<u>C</u>), 203.9 (<u>C</u>=O); MS, m/z, (RI) 326 ($M^+$, 5), 221 (80), 143 (30), 105 (100), 91 (48).

**2-benzyl-2-methyl-1,4-diphenyl-3-buten-1-ol (5.20)**

To a stirred solution of the alkylated product (**5.19**) (80mg, 0.25mmol) in methanol (10ml) at 0°C was added sodium borohydride (0.06g, 0.25mmol). The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the alcohol, a viscuous oil, as a diastereomeric mixture (60mg, 75%): IR (film) υmax/$cm^{-1}$ 3029, 1548, 1496$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 0.96 and 1.17 (3H, 2 x s, C$\underline{H}_3$), 2.17 (1H, broad s, O$\underline{H}$), 2.76-3.06 (2H, m, C$\underline{H}_2$), 4.61 and 4.69 (1H, 2 x s, C$\underline{H}$OH), 6.12 and 6.35 (1H, dd, J=16.5Hz, C$\underline{H}$=CH), 6.20 and 6.54 (1H, dd, J=16Hz, CH=C$\underline{H}$), 7.18-7.42 (15H, m, 15 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 18.5 and 18.7 (C$\underline{H}_3$), 43.8 and 44.1 (C$\underline{H}_2$), 45.6 and 45.7 ($CH_3\underline{C}CH_2$), 79.8 and 79.9 (C$\underline{H}$OH), 125.6 x 2, 125.7, 125.8, 126.6, 126.7, 127.1, 127.2 x 3, 127.3 x 2, 127.7, 128.1 x 2, 129.2, 129.8, 130.4 x 2, 134.2, 134.4 (15 x Ar-C$\underline{H}$ and C$\underline{H}$=C$\underline{H}$), 137.3 x 2, 137.7 and 137.8, 140.7 and 141.1 (3 x Ar-C); MS, m/z, (RI) 310 (1), 221 (12), 131 (100), 91 (53), 77 (22); HRMS (+$Na^+$) 351.1709, $C_{24}$ $H_{24}$ O Na requires 351.1725; error -4.4ppm.

**3'4'-Dihydro-1'*H*-spiro[[1,3]dioxolane-2,2'naphthalene] (5.24)**

To a solution of β-tetralone (2g, 13.7mmol) in ethylene glycol (10ml) was added triethylorthoformate (5ml) and a crystal of *p*ToSH. The reaction was stirred at room temperature for 3 hours, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the dioxane, (2.2g, 85%), a colourless oil with the following physical properties: IR (film) υmax/$cm^{-1}$ 2936, 2882, 1496, 1365, 1260, 1123, 1099, 1063 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.06 (2H, t, J=6.75Hz, $CH_2C\underline{H}_2C$), 3.06-3.09 (4H, m, 2 x Ar-C$\underline{H}_2$), 4.09 (2H, m, $OC\underline{H}_2C\underline{H}_2O$), 7.12-7.21 (4H, m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 28.7 (C$\underline{H}_2$), 32.5 (C$\underline{H}_2$), 39.8 (C$\underline{H}_2$), 65.1 ($O\underline{C}H_2\underline{C}H_2O$), 108.9 (O$\underline{C}$O), 126.5, 126.7, 129.1, 129.9 (4 x Ar-C), 135.1, 136.0 (2 x Ar-C); MS, m/z, (RI) 191 (M+1, 44), 190 ($M^+$, 100), 117 (11).

**2-(1,2,3,4-tetrahydro-2-naphthalenyliden)-1-indanone (5.27)**

To a solution of 1*H*-3-indenyl(1,1,1-trimethylsilyl) ether (**5.25**) (1.13g, 4.86mmol) in anhydrous DCM at –70°C was added (**5.24**) (1.06g, 4.86mmol) and titanium tetrachloride (1.05g, 4.86mmol). The reaction was stirred at –78°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol condensation product as a yellow solid (0.45g, 31%): M.p. 109-110°C; IR (KBr disc) υmax/$cm^{-1}$ 1683, 1597, 1462, 1304, 1222 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.45 (2H, m, C$\underline{H}_2$), 3.10 (2H, m, C$\underline{H}_2$), 3.57 (2H, broad s, C$\underline{H}_2$CO), 3.79 (1H, t, J=7Hz, C$\underline{H}$), 6.70 (1H, s, C=C$\underline{H}$), 7.21 (1H, dd, $J_1$=8.4Hz, $J_2$=7Hz, Ar-C$\underline{H}$), 7.28-7.31 (2H, m, 2 x Ar-CH), 7.35-7.41 (2H, m, 2 x Ar-C$\underline{H}$), 7.47 (1H, d, J=7Hz, Ar-C$\underline{H}$), 7.54 (1H, dd, $J_1$=8.4Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 8.17 (1H, d, J=8Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 27.7, 28.9 (2 x $\underline{C}H_2$Ar), 40.0 ($\underline{C}H_2$C=C), 49.6 ($\underline{C}$H), 120.1, 123.1, 123.9, 125.9, 126.3, 127.3, 128.3, 128.4, (C=$\underline{C}$H and 7 x Ar-$\underline{C}$H), 132.1 (quat. $\underline{C}$), 133.1 (Ar-$\underline{C}$H), 143.0, 143.5, 144.3, 146.1 (4 x quat. $\underline{C}$), 197.1 ($\underline{C}$=O); MS, m/z, (RI) 261 (M+1, 25), 260 ($M^+$, 100), 141 (39), 115 (61), 89 (44), 63 (19); HRMS (+$H^+$), 261.1301, $C_{19}$ $H_{17}$ O requires 261.1279; (+$Na^+$), 283.1081, $C_{19}$ $H_{16}$ O Na requires 283.1099; errors 8.1ppm, -6.2ppm.

**2-benzyl-2-(3,4-dihydro-2-naphthalenyl)-1-indanone (5.28)**

To a solution of the condensation product (**5.27**) (0.22g, 0.85mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (0.50ml, 4.25mmol). To this solution was added potassium *tert*-butoxide (95mg, 0.85mmol) as a solution in *t*-butanol (5ml), adding the base drop-wise over several hours. The reaction was stirred overnight, and the butanol removed by ether/water extraction. The combined organic extracts (3 x 20ml) were concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product as a white solid (0.16g, 54%). M.p. 130-132°C; IR (film) υmax/$cm^{-1}$ 2929, 1683, 1602, 1455, 1292, 1231$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.23 (1H, m, 1H of C$\underline{H}_2$C$H_2$), 2.36 and 2.40 (1H, 2 x dd, $J_1$=4.5Hz, $J_2$=3.5Hz, 1H of C$\underline{H}_2$C$H_2$), 2.81 and 2.85 (1H, 2 x dd, $J_1$=5Hz, $J_2$~3Hz, 1H of C$\underline{H}_2$C$H_2$), 3.07 (1H, m, 1H of C$\underline{H}_2$C$H_2$), 3.35 (2H, 2 x d, J~13.5Hz, C$\underline{H}_2$), 3.43

(2H, 2 x d, J~23Hz, $C\underline{H}_2$), 6.54 (1H, s, C=C$\underline{H}$), 7.12-7.34 (10H, m, 10 x Ar-C$\underline{H}$), 7.41-7.45 (2H, m, 2 x Ar-C$\underline{H}$), 8.21 (1H, d, J=8Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.4, 30.9, 38.9, 44.0 (4 x $\underline{C}H_2$), 52.9 ($\underline{C}$H), 120.3, 123.0, 124.1, 125.9 x 2, 126.1, 127.4, 127.7, 128.1, 129.5, 130.5 (C=$\underline{C}$H and 12 x Ar-$\underline{C}$H), 131.9 (quat. $\underline{C}$), 132.8 (Ar-$\underline{C}$H), 137.2, 142.6, 143.1, 143.9, 146.5 (5 x quat. $\underline{C}$), 198.0 ($\underline{C}$=O); MS, m/z, (RI) 351 (M+1, 31), 350 ($M^+$, 100), 259 (75), 231 (34), 115 (11); HRMS (+$Na^+$), 373.1547, $C_{26}$ $H_{22}$ O Na requires 373.1568; error -5.7ppm.

**2-benzyl-2-(3,4-dihydro-2-naphthalenyl)-1-indanol (5.29)**

To a stirred solution of the alkylated dimer (**5.28**) (0.16g, 0.29mmol) in methanol (10ml) at 0°C was added sodium borohydride (35mg, 0.58mmol). The reaction mixture was stirred for one hour, allowing the reaction to reach room temperature. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the off-white crystalline alcohol as a diastereomeric mixture (0.15g, 94%). M.p. 74-76°C; IR (film) υmax/$cm^{-1}$ 3408, 3069, 3029, 2930, 1548, 1454, 1379$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.73 and 2.06 (1H, s and d, $J_d$~7Hz, O$\underline{H}$), 2.43-2.66 (3H, m, 3H of C$\underline{H}_2$), 2.78-3.28 (1H, broad m, 5H of C$\underline{H}_2$), 4.96 and 5.30 (1H, s and d, $J_d$~7Hz, C$\underline{H}$OH), 6.16 (1H, s, C=C$\underline{H}$), 6.94-7.07 (3H, m, 3 x Ar-C$\underline{H}$), 7.14-7.25 (6H, m, 6 x Ar-C$\underline{H}$), 7.28-7.55 (m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 24.9 and 25.2 ($\underline{C}H_2$), 27.8 and 27.9 ($\underline{C}H_2$), 35.9 (2), 36.9, 40.2 (2 x $\underline{C}H_2$), 58.1 and 58.5 (alip.quat. $\underline{C}$), 81.0 and 82.2 ($\underline{C}$HOH), 123.2, 123.9, 124.3, 124.9, 125.4, 125.6 (2), 125.7, 125.8, 125.9, 126.0 (2), 126.1, 126.3, 126.4, 126.5, 126.6, 126.7, 127.2 (2), 127.3 (2), 127.8, 128.6, 129.8 (2), 130.0 (2) (13 x Ar-$\underline{C}$H and $\underline{C}$H=$\underline{C}$H), 134.1, 134.3, 134.5, 137.8, 139.7, 142.2 (6 x quat $\underline{C}$); MS, m/z, (RI) 351 ($M^+$, 5), 333 (100), 259 (99), 243 (31), 205 (21), 103 (35); HRMS (+$Na^+$) 375.1737, $C_{26}$ $H_{24}$ O Na requires 375.1725; error 3.3ppm.

**2-(1-methoxy-2-phenylethyl)-1-indanone (5.30)**

To a solution of (1*H*-3-indenyloxy)(trimethyl)silane (**5.25**) (2.11g, 10.3mmol) in anhydrous DCM at –70°C was added phenylacetaldehyde dimethylacetal (1.71ml, 10.3mmol) and tin tetrachloride (1.2ml, 10.3mmol). The reaction was stirred at –70°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced

water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol product as a pale oil, a diasteromeric mixture (2.42g, 88%). M.p. 62-64°C; IR (film) υmax/$cm^{-1}$ 2932, 1714, 1610, 1464, 1293, 1109$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.63-2.69, 2.75-2.81 and 2.86-2.88 (2H, 3 x m, C$\underline{H}_2$), 3.09-3.21 (2H, m, C$\underline{H}_2$), 3,25 and 3.33 (3H, 2 x s, OC$\underline{H}_3$), 3.31-3.36 (1H, m, C$\underline{H}$), 3.97 and 4.27 (1H, 2 x m, C$\underline{H}$), 7.21-7.39 (6H, m, 6 x Ar-C$\underline{H}$), 7.49 (1H, m, Ar-C$\underline{H}$), 7.58 (1H, m, Ar-C$\underline{H}$), 7.77 (1H, m, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 26.4 and 28.8 ($\underline{C}H_2CHCO$), 36.0 and 38.8 ($\underline{C}H_2CHOCH_3$), 48.2 and 50.2 (CO$\underline{C}$H), 57.3 and 57.9 (O$\underline{C}H_3$), 80.8 and 83.1 ($\underline{C}HOCH_3$), 123.2 (Ar-$\underline{C}$H), 125.8, 126.1, 126.2 (2 x Ar-$\underline{C}$H), 126.8 and 126.9 (Ar-$\underline{C}$H), 127.8 and 128.2 (2 x Ar-$\underline{C}$H), 129.0 and 129.1 (2 x Ar-$\underline{C}$H), 134.2 and 134.3 (Ar-$\underline{C}$), 136.7 and 137.2 (Ar-$\underline{C}$), 137.7 and 138.4 (Ar-$\underline{C}$), 153.9 and 154.0 (Ar-$\underline{C}$), 206.3 and 207.1 ($\underline{C}$=O); MS, m/z, (RI) 267 (M+1, 19), 266 ($M^+$, 5), 235 (100), 175 (14), 147 (18); HRMS (+$Na^+$) 289.1182, $C_{18}$ $H_{18}$ $O_2$ Na requires 289.1204; error -7.7ppm.

**2-benzyl-2-[2-phenyl-1-ethenyl]-1-indanone (5.31)**

To a solution of the aldol product (**5.30**) (0.6g, 2.26mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (1.34ml, 11.3mmol). To this solution was added potassium *tert*-butoxide (0.25g, 2.26mmol) as a solution in *t*-butanol (5ml), adding the base drop-wise over several hours. The reaction was stirred at room temperature overnight. The *t*-butanol was removed by ether/water extraction. The combined organic extracts (3 x 20ml) were concentrated *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the alkylated product (0.31g, 42%) as a white crystalline solid: m.p. 136-138°C; IR (film) υmax/$cm^{-1}$ 3032, 1706, 1496, 1435, 1210$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 3.18-3.40 (4H, m, 2 x C$\underline{H}_2$), 6.49 (2H, s, C$\underline{H}$=C$\underline{H}$), 7.21-7.28 (6H, m, 6 x Ar-C$\underline{H}$), 7.32-7.45 (6H, m, 6 x Ar-C$\underline{H}$), 7.59 (1H, dd, $J_1$~8.3Hz, $J_2$~7.5Hz, Ar-C$\underline{H}$), 7.83 (1H, d, J=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 36.5 ($\underline{C}H_2$), 42.8 ($\underline{C}H_2$), 56.8 (CO$\underline{C}CH_2$), 124.2 (Ar-$\underline{C}$H), 125.9 (3 x Ar-$\underline{C}$H), 126.2 (Ar-$\underline{C}$H), 127.2 (2 x Ar-$\underline{C}$H), 127.7 (2 x Ar-$\underline{C}$H), 128.1 (2 x Ar-$\underline{C}$H), 129.7 (Ar-$\underline{C}$H), 130.0 (2 x Ar-$\underline{C}$H), 131.5 (Ar-$\underline{C}$H), 134.6 (Ar-$\underline{C}$H), 135.2, 136.5, 136.8, 151.9 (4 x Ar-$\underline{C}$), 206.6 ($\underline{C}$=O); MS, m/z, (RI) 325 (M+1, 31), 324 ($M^+$, 81), 233 (58), 215 (100), 205 (36), 89 (12); HRMS (+$Na^+$) 347.1391, $C_{24}$ $H_{20}$ O Na requires 347.1412; error -6.0ppm.

**2-benzyl-2-[2-phenyl-1-ethenyl]-1-indanol (5.32)**

To a solution of the benzylated product (**5.31**) (0.20g, 0.62mmol) in methanol (10ml) was added sodium borohydride (35mg, 0.93mmol). The reaction was stirred at room temperature for one hour, and the methanol removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the alcohol as a diastereomeric mixture of white crystalline solids (0.17g, 84%) with the following properties: M.p. 56-58°C; IR (film) υmax/cm$^{-1}$ 3029, 1496, 1388, 1331cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.76 and 1.95 (1H, 2 x broad s, O<u>H</u>), 2.78-3.16 (2H, m, 2 x C<u>H</u>$_2$), 5.06 and 5.16 (1H, 2 x s, C<u>H</u>OH), 6.23-6.47 (2H, m, C<u>H</u>=C<u>H</u>), 7.17-7.37 (13H, m, 13 x Ar-C<u>H</u>), 7.43 (1H, dd, $J_1$=8.1Hz, $J_2$=7Hz, Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 38.0 and 38.4 (<u>C</u>H$_2$), 38.4 and 43.2 (<u>C</u>H$_2$), 54.7 and 55.3 (HOCH<u>C</u>CH$_2$), 81.0 and 81.8 (<u>C</u>HOH), 123.7 and 124.2 (Ar-<u>C</u>H), 124.4 and 124.5 (Ar-<u>C</u>H), 125.6, 125.7, 125.8, 125.9 (3 x Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 126.7 and 127.0 (Ar-<u>C</u>H), 127.3 and 127.6 (2 x Ar-<u>C</u>H), 127.9 and 128.0 (Ar-<u>C</u>H), 128.0 and 128.1 (2 x Ar-<u>C</u>H), 130.1 and 130.3 (2 x Ar-<u>C</u>H), 131.5 and 131.6 (Ar-<u>C</u>H), 134.3 (Ar-<u>C</u>H), 136.7 (Ar-<u>C</u>), 137.7 (Ar-<u>C</u>), 140.6 (Ar-<u>C</u>), 143.4 (Ar-<u>C</u>); MS, m/z, (RI) 308 (M-$H_2O$, 23), 235 (100), 217 (46), 207 (27), 129 (25), 107 (31), 91 (68); HRMS (+$Na^+$) 349.1581, $C_{24}$ $H_{22}$ O Na requires 349.1568; error 3.7ppm.

**2-[2-(2-hydroxyethoxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-1-phenyl-1-propanone (5.33)**

To a solution of 1-phenyl-1-propenyl (1,1,1-trimethylsilyl) ether (**5.13**) (2.19g, 10.6mmol) in anhydrous DCM at –70°C was added 3'4'-Dihydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalene] (**5.24**) (2.02g, 10.6mmol) and tin tetrachloride (1.24ml, 10.6mmol). The reaction was stirred at –70°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol product as a pale oil, a diasteromeric mixture (0.97g, 28%). IR (film) υmax/cm$^{-1}$ 3438, 2938, 2877, 1676, 1449, 1223, 1095, 1051cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.35 and 1.39 (3H, 2 x d, J=7Hz, C<u>H</u>$_3$), 1.67 and 2.12 (2H, 2 x m, C<u>H</u>$_2$CH$_2$Ar), 2.44 (1H, 2 x broad s, O<u>H</u>), 2.61-2.76 (2H, m, C<u>H</u>$_2$Ar), 2.90-3.14 (2H, m, C<u>H</u>$_2$Ar), 3.36 and 3.54 (4H, 2 x m,

$OC\underline{H}_2C\underline{H}_2OH$), 4.15 (1H, m, C<u>H</u>), 7.02-7.14 (4H, m, 4 x Ar-C<u>H</u>), 7.46-7.51 (2H, m, 2 x Ar-C<u>H</u>), 7.58 (1H, m, Ar-C<u>H</u>), 8.00 and 8.03 (2H, 2 x d, J=7.5 and 7Hz, 2 x COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 12.0 and 12.8 ($\underline{C}H_3$), 25.2 and 25.3 ($\underline{C}H_2$), 29.0 and 29.1 ($\underline{C}H_2$), 34.9 and 35.2 ($\underline{C}H_2$), 44.1 and 45.2 (<u>C</u>H), 61.4 and 61.5 ($O\underline{C}H_2$), 62.3 and 62.8 ($O\underline{C}H_2$), 76.4 and 76.8 ($CH_2\underline{C}CH_2$), 125.2 and 125.4 (Ar-<u>C</u>H), 125.4 and 125.5 (Ar-<u>C</u>H), 127.8 (2 x Ar-<u>C</u>H), 127.9 x 2 (Ar-<u>C</u>H), 128.3 (2 x Ar-<u>C</u>H), 128.7 and 129.0 (Ar-<u>C</u>H), 132.7 x 2 (Ar-<u>C</u>H), 133.7 and 134.1 (Ar-<u>C</u>), 135.3 and 135.9 (Ar-<u>C</u>), 138.0 and 138.1 (Ar-<u>C</u>), 202.8 and 203.0 (<u>C</u>=O); MS, m/z, (RI) 262 ($M^+$ enone, 24), 157 (100), 105 (62); HRMS (+$Na^+$) 347.1591, $C_{21}H_{24}O_3Na$ requires 347.1623; error -9.3ppm.

**2-(3,4-dihydro-2-naphthalenyl)-2-methyl-1,3-diphenyl-1-propanol (5.34)**

To a solution of the aldol product (**5.33**) (0.55g, 1.70mmol) in *t*-butanol/ether (10ml, 1:1) was added benzyl bromide (1ml, 8.41mmol). To this solution was added potassium *tert*-butoxide (0.21g, 1.87mmol) as a solution in *t*-butanol (5ml), adding the base drop-wise over several hours. The reaction was stirred at room temperature overnight. The crude reaction mixture was monitored by GCMS, revealing a mixture of products, including the desired mass: MS, m/z, (RI) 353 ($M^+$, 18), 261 (52), 247 (89), 248 (75), 131 (43), 117 (34), 105 (100). The crude reaction mixture was not purified, but extracted with ether/water (3 x 20ml), and the organic residue concentrated *in vacuo*. To the residue, methanol (10ml) was added, and sodium borohydride (0.20g, 5.29mmol). The reaction was stirred at room temperature for one hour, and the methanol removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the alcohol (0.21g, 35%), a white crystalline solid, primarily as one diasteromer with the following properties: IR (film) υmax/$cm^{-1}$ 3557, 3029, 2929, 1453, 1040$cm^{-1}$; $^1$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 1.05 (3H, s, $C\underline{H}_3$), 2.59 (3H, m, 3H of $C\underline{H}_2$), 2.92 (2H, m, $C\underline{H}_2$), 3.10 (1H, m, 1H of $C\underline{H}_2$), 4.86 (1H, d, J=1.5Hz, C<u>H</u>OH), 6.35 (1H, s, C=C<u>H</u>), 7.02 (1H, m, Ar-C<u>H</u>), 7.08 (2H, m, 2 x Ar-C<u>H</u>), 7.14-7.22 (6H, m, 6 x Ar-C<u>H</u>), 7.33-7.41 (3H, m, 3 x Ar-C<u>H</u>), 7.45 (2H, m, 2 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 16.8 ($\underline{C}H_3$), 24.0 ($\underline{C}H_2$), 27.8 ($\underline{C}H_2$), 41.8 ($C\underline{C}H_2Ph$), 49.0 ($CH_3\underline{C}CH_2$), 77.8 (<u>C</u>HOH), 125.6, 125.9, 126.0, 126.5 x 2, 126.6 (5 x Ar-<u>C</u>H and C=<u>C</u>H), 127.2 x 2 (3 x Ar-<u>C</u>H), 127.3 (2 x Ar-<u>C</u>H), 128.0 (2 x Ar-<u>C</u>H), 129.9 (2 x Ar-<u>C</u>H), 133.8, 134.4, 137.4, 139.9, 142.4 (4 x Ar-<u>C</u> and <u>C</u>=CH); MS, m/z, (RI) 247 (13), 157 (100), 129 (18).

**2-(3,4-dihydro-1-naphthalenyl)-1,2,3,4-tetrahydro-1-naphthalenone (5.35)**

To a stirred solution of α-tetralone (5g, 34.2mmol) in toluene (50ml) was added aluminium tri-*tert*-butoxide (8.42g, 34.2mmol). The reaction was heated under reflux, with the flask attached to a Dean-Starck apparatus, to enable azeotropic distillation and removal of water. After 12 hours of reflux, during which time water removal had been performed periodically, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the aldol condensation product (0.75g, 8%), a white crystalline solid, with the following properties: M.p. 132-136°C; IR (KBr disc) υmax/cm$^{-1}$ 2950, 2003, 1679, 1597, 1459, 1307cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.31 (3H, m, 3H of C$\underline{H}_2$), 2.38 (1H, m, 1H of C$\underline{H}_2$), 2.79 (2H, m, C$\underline{H}_2$), 2.97-3.12 (2H, m, C$\underline{H}_2$), 3.89 (1H, dd, $J_1$=9Hz, $J_2$=4.5Hz, C$\underline{H}$), 5.84 (1H, t, J=4.5Hz, C=C$\underline{H}$), 7.13-7.20 (4H, m, 4 x Ar-C$\underline{H}$), 7.31 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.38 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.53 (1H, dd, $J_1$=8Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 8.16 (1H, d, J=8Hz, Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 22.8, 27.7, 27.8, 28.3 (4 x $\underline{C}H_2$), 50.4 ($\underline{C}$H), 122.7, 125.8, 126.3 x 2, 126.7, 127.2, 127.4, 128.3, 132.9 (8 x Ar-$\underline{C}$H and C=$\underline{C}$H), 132.6, 133.4, 134.9, 136.5, 143.6 (5 x quat. $\underline{C}$); MS, m/z, (RI) 275 (M+1, 73), 274 ($M^+$, 100), 256 (24); HRMS (+$Na^+$) 297.1259, $C_{20}$ $H_{18}$ O Na requires 297.1255; error 1.1ppm.

**2-(3,4-dihydro-2-naphthalenyl)-1,2,3,4-tetrahydro-1-naphthalenone (5.37)**

To a solution of (3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane **(5.3)** (1g, 4.59mmol) in anhydrous DCM (10ml) at –70°C was added 3'4'-Dihydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalene] (**5.24**) (0.87g, 4.58mmol) and tin tetrachloride (1.19g, 4.58mmol). The reaction was stirred at –70°C under an atmosphere of nitrogen for one hour, and then quenched by the addition of iced water. The reaction was partitioned between water and DCM and the combined organic extracts (3 x 20ml washings) were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the aldol, rapidly decomposing to the condensation product, a yellow solid (0.5g, 32%): M.p. 94-96°C; IR (KBr disc) υmax/cm$^{-1}$ 2941, 1679, 1599, 1453, 1223, 743cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400Hz) $\delta_H$ 2.25-2.44 (2H, m, C$\underline{H}_2$), 2.93 (2H, m, C$\underline{H}_2$), 3.10 (2H, m, C$\underline{H}_2$), 3.45 (1H, m, C$\underline{H}$), 6.32 (1H, s, C=C$\underline{H}$), 7.01 (1H, m, Ar-C$\underline{H}$), 7.17 (3H, m, 3 x Ar-C$\underline{H}$), 7.29 (1H, d, J=8Hz, Ar-C$\underline{H}$), 7.37 (1H, dd, $J_1$=8.6Hz, $J_2$=7.5Hz, Ar-C$\underline{H}$), 7.52 (1H, ddd, $J_1$=8Hz, $J_2$=7.5Hz,

$J_3$=1Hz, Ar-C<u>H</u>), 8.13 (1H, d, J=8Hz, COAr-C<u>H</u>); $^{13}$CNMR $\delta_C$ 25.7 (<u>C</u>$H_2$), 27.7 (<u>C</u>$H_2$), 27.9 (<u>C</u>$H_2$), 28.2 (<u>C</u>$H_2$), 55.4 (<u>C</u>H), 124.7, 125.4, 125.9, 126.2, 126.3, 126.7, 127.1, 128.3 (C=<u>C</u>H and 7 x Ar-<u>C</u>H), 132.4 (quat. <u>C</u>), 132.9 (Ar-<u>C</u>H), 133.9 (quat. <u>C</u>), 134.5 (quat. <u>C</u>), 139.0 (quat. <u>C</u>), 143.6 (quat. <u>C</u>), 197.7 (<u>C</u>=O); MS, m/z, (RI) 274 ($M^+$, 100), 257 (60), 146 (21), 117 (23); HRMS (+$Na^+$) 297.1262, $C_{20}$ $H_{18}$ O Na requires 297.1255; error 2.1ppm.

**(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropyl methanesulfonate (7.2)**

To a solution of the (*S*)-(-)-2-(*tert*-Butoxycarbonyl-amino)-3-phenyl-1-propanol (5g, 19.9mmol) in dry DCM (20ml) under an atmosphere of nitrogen was added methane sulphonyl chloride (2.63ml, 33.8mmol). To the resultant solution, cooled to 0°C, was added *N*,*N*,-diisopropylethanolamine (3.12ml, 29.8mmol), drop-wise by syringe, over 5 minutes. After 10 minutes stirring at this temperature, 5% aqueous $NaHCO_3$ was added and the reaction allowed to return to room temperature. The reaction mixture was partitioned, and the organic layer removed, washed sequentially with water, 2M HCl and water, then the combined organic layers were dried over anhydrous sodium sulphate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield a white solid (5.17g, 79%), with the following physical properties: $[\alpha]^{22}$ = -19° (c 1, MeOH); IR (KBr disc) υmax/$cm^{-1}$ 3032, 1694, 1530, 1346, 1165$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.43 (9H, s, (C<u>H</u>$_3$)$_3$), 2.90 (2H, m, C<u>H</u>$_2$), 3.02 (3H, s, $SO_2$C<u>H</u>$_3$), 4.13 and 4.26 (3H, m, C<u>H</u>$_2$O and C<u>H</u>), 4.79 (1H, br. s, N<u>H</u>), 7.22-7.3 (5H, m, 5 x Ar-CH); $^{13}$CNMR $\delta_C$ 28.2 (<u>C</u>$H_3$), 37.2 (<u>C</u>H), 126.9 (Ar-<u>C</u>H), 128.7 (2 x Ar-<u>C</u>H), 129.2 (2 x Ar-<u>C</u>H),

***tert*-butyl *N*-[(1*S*)-1-benzyl-2-cyanoethyl]carbamate (7.3)**

To a mixture of potassium cyanide (5g, 76.9mmol) in DMSO (30ml) was added (**7.2**) (3.61g, 11.0mmol). The reaction was heated at reflux for 24 hours, and partitioned between brine and DCM (3 x 50ml). The organic extracts were combined and concentrated *in vacuo*, before purification by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield a white solid (1.94g, 68%), with the following physical properties: M.p. 127-128°C; $[\alpha]^{22}$ = -36° (c 1, MeOH); IR (KBr disc) υmax/$cm^{-1}$ 2978, 2244, 1690, 1531, 1275, 1166$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.45 (9H, s,

$(CH_3)_3$), 2.44 (1H, dd, $J_1$=17Hz, $J_2$~4Hz, 1H of C$\underline{H}_2$), 2.71 (1H, br. dd, 1H of C$\underline{H}_2$), 2.89 (1H, dd, $J_1$~13.5Hz, $J_2$~8.5Hz, 1H of C$\underline{H}_2$), 3.02 (1H, dd, $J_1$~13.5Hz, $J_2$~6.5Hz, 1H of C$\underline{H}_2$), 4.10 and 4.78 (2H, 2 x br. s, C$\underline{H}$ and N$\underline{H}$), 7.23- (5 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 22.5 ($\underline{C}H_2$), 28.2 (($\underline{C}H_3)_3$), 39.4 ($\underline{C}H_2CN$), 48.5 ($\underline{C}H$), 117.2 ($\underline{C}\equiv N$), 127.2 (Ar-$\underline{C}$H), 128.9 (2 x Ar-$\underline{C}$H), 129.1 (2 x Ar-$\underline{C}$H), 136.2 (Ar-$\underline{C}$).

A second product was isolated from the reaction mixture (24%): $[\alpha]^{22} = -62^{\circ}$ (c 1, $CHCl_3$); IR (KBr disc) υmax/cm$^{-1}$ 2925, 1753, 1709, 1405, 1246, 1022cm$^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.81 and 2.93 (2H, 2 x dd, $J_1$~13.5Hz, $J_2$=6.6 and 5.5Hz, Ar-C$\underline{H}_2$), 4.05-4.13 (3H, m, 1H of OC$\underline{H}_2$ and C$\underline{H}$), 4.35 (1H, m, 1H of OC$\underline{H}_2$), 6.73 (1H, br. s, N$\underline{H}$), 7.18 (2H, m, 2 x Ar-C$\underline{H}$), 7.26 (1H, m, *p*Ar-C$\underline{H}$), 7.33 (2H, m, 2 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 40.7 (Ar$\underline{C}H_2$), 53.3 ($\underline{C}$H), 69.0 (O$\underline{C}H_2$), 126.7 (*p*Ar-$\underline{C}$H), 128.4 (2 x Ar-$\underline{C}$H), 128.7 (2 x Ar-$\underline{C}$H), 135.6 (Ar-$\underline{C}$), 159.6 (NH$\underline{C}$=OO); MS, m/z, (RI) 178 (M+1, 100), 177 ($M^+$, 15), 91 (22).

**(3*S*)-3-amino-4-phenylbutanoic acid (7.5)**

A solution of (**7.3**) (2g, 7.69mmol) in dioxane / conc. HCl (10ml, 1:1) was refluxed for 24 hours. The solvent was removed under high vacuum, adding methanol (3 x 20ml during evaporation) to aid in removal of the dioxane. The acid was not further purified; crude NMR analysis was performed to ensure that hydrolysis was complete. The acid, a crude solid, had the following NMR characteristics: $^1$HNMR ($CD_3OD$, 400Hz) $\delta_H$ 2.72 (2H, m, C$\underline{H}_2$), 3.01 (1H, dd, $J_1$~14Hz, $J_2$~9Hz, 1H of C$\underline{H}_2$COOH), 3.22 (1H, dd, $J_1$~14Hz, $J_2$~5.5Hz, 1H of C$\underline{H}_2$COOH), 3.85 (1H, br., C$\underline{H}$), 7.28-7.37 (5H, m, 5 x Ar-C$\underline{H}$), 8.17 (1H, br. s, exchangeable with $D_2O$, COO$\underline{H}$,); $^{13}$CNMR $\delta_C$ 34.4 ($\underline{C}H_2$), 37.5 ($\underline{C}H_2$CO), 49.4 ($\underline{C}$H), 126.9 (Ar-$\underline{C}$H), 128.4 (2 x Ar-$\underline{C}$H), 128.8 (2 x Ar-$\underline{C}$H), 134.9 (Ar-$\underline{C}$), 172.3 ($\underline{C}$=O).

**(3*S*)-3-[(methoxycarbonyl)amino]-4-phenylbutanoic acid (7.7)**

To the crude acid (assumption: 2g, 11.2mmol) in 10ml *t*-Butanol was added sodium hydroxide (0.45g, 11.2mmol) in water (10ml). To this stirred solution, at 0°C, was added methyl chloroformate (1.3ml, 16.8mmol), drop-wise, over 5 minutes. The reaction was stirred overnight, allowing the temperature to rise to ambient, and the solvent was removed

*in vacuo*. TLC analysis revealed the presence of two products, the upper of which, a colourless oil, displayed the following spectral characteristics: IR (KBr disc) υmax/$cm^{-1}$ 3030, 2954, 1732, 1515, 1439, 1255, 1055$cm^{-1}$; $^1$HNMR ($CD_3OD$, 400Hz) $\delta_H$ 2.45-2.55 (2H, m, $C\underline{H}_2$), 2.79-2.91 (2H, m, $C\underline{H}_2CO$), 3.60 and 3.65 (6H, 2 x s, 2 x $COOC\underline{H}_3$), 4.15 (1H, br., C<u>H</u>), 5.50 (1H, br., N<u>H</u>), 7.16-7.32 (5H, m, 5 x Ar-C<u>H</u>); $^{13}$CNMR $\delta_C$ 37.1 ($\underline{C}H_2$), 39.8 ($\underline{C}H_2CO$), 49.0 (<u>C</u>H), 51.5 (2 x $O\underline{C}H_3$), 126.2 (Ar-<u>C</u>H), 128.0 (2 x Ar-<u>C</u>H), 128.8 (2 x Ar-<u>C</u>H), 137.1 (Ar-<u>C</u>), 155.9 (<u>C</u>OO<u>C</u>O), 171.4 (N<u>C</u>OO).

To a mixture of the products (crude) was added 4% methanolic sodium hydroxide (10ml) and the reaction was stirred overnight at room temperature. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the more polar product, the acid, a white crystalline solid (1.32g, 50%), with the following physical properties; M.p. 90-92°C; $[\alpha]^{22} = -20°$ (c 1, MeOH); IR (KBr disc) υmax/$cm^{-1}$ 3033, 1698, 1542, 1266, 1059$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.51-2.63 (2H, m, $C\underline{H}_2$), 2.87-3.02 (2H, m, $C\underline{H}_2CO$), 3.66 (3H, s, $OC\underline{H}_3$), 4.24 (1H, br., C<u>H</u>), 5.41 and 6.31 (1H, 2 x br., N<u>H</u>), 7.21-7.27 (3H, m, 3 x Ar-C<u>H</u>), 7.31-7.34 (2H, m, 2 x Ar-C<u>H</u>), 10.64 (1H, br. s, COO<u>H</u>); $^{13}$CNMR $\delta_C$ 36.8 ($\underline{C}H_2$), 39.7 ($\underline{C}H_2CO$), 48.7 (<u>C</u>H), 51.8 ($O\underline{C}H_3$), 126.3 (Ar-<u>C</u>H), 128.2 (2 x Ar-<u>C</u>H), 128.9 (2 x Ar-<u>C</u>H), 137.0 (Ar-<u>C</u>), 156.1 (N<u>C</u>=O), 176.2 (<u>C</u>OOH).

**methyl *N*-(4-oxo-1,2,3,4-tetrahydro-2-naphthalenyl)carbamate (7.8)**

To a stirred solution of (**7.7**) (0.47g, 1.98mmol) in DCM, containing one drop of DMF (10ml) at 0°C, was added, drop-wise by syringe, oxalyl chloride (0.5ml, 5.26mmol). The reaction was stirred at this temperature for one hour, after which time the solvent and residual oxalyl chloride was removed *in vacuo*. To the residue was added DCM (10ml) and $SnCl_4$ (3ml of a 1M solution in DCM). The reaction was stirred for 24 hours, during which time the flask was allowed to reach room temperature. The reaction was quenched using dilute (1M) HCl, and partitioned between water and DCM (3 x 20ml) to remove contaminating tin salts. The organic layers were combined and concentrated *in vacuo*, before purification by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the cyclised product, a white crystalline solid (0.20g, 45%), with the following physical properties; M.p. 96-97°C; IR (KBr disc) υmax/$cm^{-1}$ 2950, 1687, 1546, 1291$cm^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 2.72 (1H, dd, $J_1$=17Hz, $J_2$=8.5Hz, 1H of $C\underline{H}_2$),

2.96 (1H, dd, $J_1$=17Hz, $J_2$=4Hz, 1H of C$\underline{H}_2$), 3.01 (1H, dd, $J_1$=17Hz, $J_2$=7.5Hz, 1H of C$\underline{H}_2$), 3.34 (1H, br. dd, $J_1$~17Hz, 1H of C$\underline{H}_2$), 3.67 (3H, s, COOC$\underline{H}_3$), 4.38 and 4.96 (2 x br., C$\underline{H}$ and N$\underline{H}$), 7.30 (1H, d, J=7.5Hz, Ar-C$\underline{H}$), 7.37 (1H, dd, $J_1$=8.5Hz, $J_2$=7.5Hz, Ar-CH), 7.55 (1H, dd, $J_1$=8.0Hz, $J_2$=7.5Hz, $J_3$=1.5Hz, Ar-C$\underline{H}$), 8.05 (1H, d, J=7.5Hz, COAr-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 35.6 (C$\underline{H}_2$), 44.5 (C$\underline{H}_2$CO), 46.7 (C$\underline{H}$), 51.7 (C$\underline{H}_3$), 126.7, 126.9, 129.1 (3 x Ar-C$\underline{H}$), 131.6 (Ar-C$\underline{C}$), 133.8 (Ar-C$\underline{H}$), 140.1 (Ar-C$\underline{C}$), 155.7 (C$\underline{C}$OOCH$_3$), 195.4 (C$\underline{C}$=O); MS, m/z, (RI) 220 (M+1, 13), 219 ($M^+$, 9), 144 (100), 118 (44), 89 (24).

**methyl *N*-(1,2,3,4-tetrahydro-2-naphthalenyl)carbamate (7.9)**

To a solution of carbamate (**7.8**) (0.19g, 0.87mmol) in ethanol (2.5ml) was added glacial acetic acid (2.5ml) and a catalytic amount of 10% Pd/C. The reaction was performed under an atmosphere of hydrogen at room temperature for 24 hours. After this time, the reaction was filtered to remove the catalyst, and the solvent evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the deoxygenated product, a white crystalline solid (120mg, 66%), with the following physical properties; M.p. °C; IR (KBr disc) υmax/cm$^{-1}$ 2948, 1686, 1546, 1313, 1275, 1234, 1035cm$^{-1}$; $^1$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.79 (1H, m, 1H of C$\underline{H}_2$), 2.10 (1H, m, 1H of C$\underline{H}_2$), 2.69 (1H, dd, $J_1$=16.5Hz, $J_2$=8.5Hz, 1H of C$\underline{H}_2$), 2.87-2.98 (2H, m, C$\underline{H}_2$), 3.15 (1H, dd, $J_1$=16.5Hz, $J_2$=5Hz, 1H of C$\underline{H}_2$), 3.69 (3H, s, C$\underline{H}_3$), 4.06 and 4.96 (2 x br., C$\underline{H}$ and N$\underline{H}$), 7.07-7.17 (4H, m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 26.8, 28.6, 35.5 (3 x C$\underline{H}_2$), 46.3 (C$\underline{H}$), 51.1 (COOC$\underline{H}_3$), 125.5, 125.7, 128.4, 129.0 (4 x Ar-C$\underline{H}$), 133.7, 135.0 (2 x Ar-C$\underline{C}$), 156.0 (NC$\underline{C}$=O); MS, m/z, (RI) 206 (M+1, 80), 205 ($M^+$, 13), 130 (100), 115 (16), 104 (14).

**(*R*)-1,2,3,4-tetrahydro-[2]naphthylamine; hydrochloride (7.10)**

A stirred solution of (**7.9**) (0.28g, 1.37mmol) in 10% methanol / water (1:1, 10ml) was refluxed for 24 hours. After this time, the solvent was evaporated, and the residue acidified with 2M HCl. The acidified solution was extracted using diethyl ether (3 x 20ml), and the organic layers discarded. The aqueous layer was re-basified using 2M NaOH, and re-extracted with diethyl ether (3 x 20ml), to afford the free amine, a colourless oil (0.17g, 85%). The amine was converted to the hydrochloride salt using gaseous HCl before analysis; M.p. 237-238°C; $[\alpha]^{22}$ = +66° (c 1.25, $H_2O$); IR (KBr disc) υmax/cm$^{-1}$

3061, 1499cm$^{-1}$; $^{1}$HNMR ($D_2O$, 400Hz) $\delta_H$ 1.91 (1H, m, 1H of $ArCH_2C\underline{H}_2$), 2.26 (1H, m, 1H of $ArCH_2C\underline{H}_2$), 2.89-2.99 (3H, m, 3H of 2 x $ArC\underline{H}_2$), 3.23 (1H, dd, $J_1$=16.1Hz, $J_2$=5.5Hz, 1H of Ar-$C\underline{H}_2$), 3.70 (1H, m, C$\underline{H}$), 7.23 (4H, m, 4 x Ar-C$\underline{H}$); $^{13}$CNMR $\delta_C$ 25.9, 26.2, 32.4 (3 x $\underline{C}H_2$), 47.1 ($\underline{C}$H), 126.0, 126.4, 128.4, 128.9 (4 x Ar-$\underline{C}$H), 132.0, 134.7 (2 x Ar-$\underline{C}$).

**3-(1,2,3,4-tetrahydro-2-naphthalenylamino)-1-indanone (*R,S* and *R,R*) (4.60)**

**Diastereomer 1** (less polar)

2D NMR data, cf Figures 7.2 and 7.3

| Label | $\delta^{13}$C (ppm) | $\delta^{1}$H (ppm), mult, J (Hz) | TOCSY (H-H) | HMQC (C-H) |
|---|---|---|---|---|
| 1 | 203.9 | - | - | - |
| 2 | 45.6 | 2.58, dd, 18.5, 3<br>3.09, dd, 18.5, 6.5 | H2 x 1, H3<br>H2 x 1, H3 | H2<br>H2 |
| 3 | 53.0 | 4.69, dd, 7, 3 | H2 | H3 |
| 4 | 125.6 | 7.72, d, 7.5 | H5 | H4 |
| 5 | 134.4 | 7.66, dd, 8.2, 7.5 | H4, H6 | |
| 6 | 125 | 7.47, dd, 8.2, 7.3 | H5, H7 | H6 |
| 7 | 123.0 | 7.78, d, 7.5 | H6 | H7 |
| 8 | - | 2.03, br. s | - | - |
| 1' | 37.0 | 2.72, dd, 16.5, 9<br>2.98-3.08 (part of m) | H1 x 1, H2'<br>H1 x 1, H2' | H1'<br>H1' |
| 2' | 51.7 | 3.24, m | H3' x 1, H1' | H2' |
| 3' | 28.7 | 1.78, m<br>2.22, m | H2', H3' x 1, H4'<br>H3' x 1, H4' | H3'<br>H3' |
| 4' | 27.2 | 2.89, m<br>2.98-3.08 (part of m) | H3'<br>H3' | H4'<br>H4' |
| 5'-8' | 125 x 2, 128, 129 | 7.08-7.15, m | | |

**Diastereomer 2** (more polar)

$^{1}$HNMR ($CDCl_3$, 400Hz) $\delta_H$ 1.61 (1H, br. s, NH), 1.75 (1H, m, 1H of $CH_2CH_2CH$), 2.06 (1H, m, 1H of $CH_2CH_2CH$), 2.58 (1H, dd, $J_{gem}$=18.5Hz, $J_{vic}$=3.0Hz, 1H of $CH_2CO$), 2.76 (1H, dd, $J_{gem}$=15Hz, $J_{vic}$=9.0Hz, 1H of $ArCH_2CH$), 2.87-3.00 (2H, m, 1H each of $ArCH_2CH_2$ and $ArCH_2CH$), 3.07 (1H, dd, $J_1$~18.5Hz, $J_2$=3.0Hz, 1H of $CH_2CO$), 3.16-3.28 (2H, m, 1H of $ArCH_2CH_2$ and $CH_2CHCH_2$), 4.68 (1H, dd, $J_{gem}$=7.0Hz, $J_{vic}$=3.0Hz, $CHCH_2CO$), 7.12-7.17 (4H, m, 4 x Ar-CH (H5′-H8′), 7.47 (1H, dd, $J_1$~8Hz, $J_2$~7Hz, Ar-CH6), 7.64-7.70 (2H, m, Ar-CH5 and Ar-CH4), 7.78 (1H, d, J=7.5Hz, Ar-CH7); $^{13}$CNMR $\delta_C$ 27.5 ($CH_2CH_2CH$), 30.3 ($CH_2CH_2CH$), 36.2 ($ArCH_2CH$), 45.6 ($CH_2CO$), 51.8 ($CH_2CHCH_2$), 53.1 ($CHCH_2CO$), 122.9 (Ar-C7), 125.4, 125.5 x 2 (2 x Ar-C′H and Ar-C4), 128.2, 128.3 (2 x Ar-CH), 128.9 (Ar-C′H), 134.3 (Ar-C), 134.4 (Ar-C5), 135.6, 136.2 (2 x Ar-C), 156.0 (Ar-C), 204.0 (C=O).

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