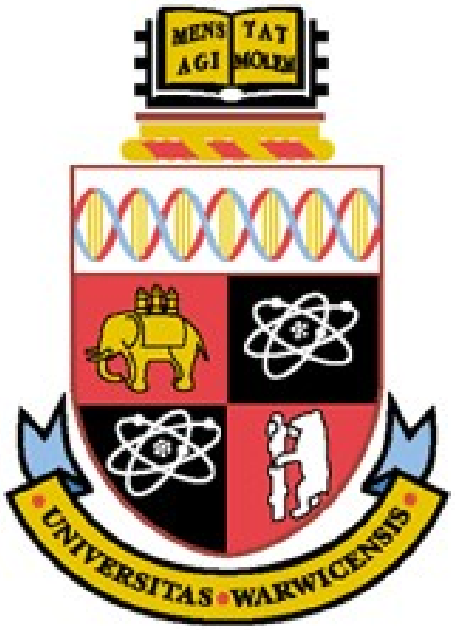

Chiral Indanones and their Derivatives

By

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A thesis submitted in partial fulfilment of the requirements for the degree

of Doctor of Philosophy in Chemistry

UNIVERSITY OF WARWICK, DEPARTMENT OF CHEMISTRY

September 2015

CONTENTS

ACKNOWLEDGEMENTS

My sincere gratitude goes to my supervisor, Dr David Fox, for giving me the opportunity to work in his research group. Without his guidance, inspiration and seemingly limitless knowledge and passion for chemistry, this project would not have been anywhere near as enjoyable. Additionally, I would like to thank the University of Warwick and Funxtional Therapeutics for funding this research.

I would like to thank all members of the Fox Group, both past and present, for providing me with support and ideas. It has been a real pleasure to both work and socialise in such a vibrant research group.

Many thanks must go to the technical staff in the department. Dr Lijiang Song, Philip Aston and Dr Rebecca Wills are gratefully acknowledged for their support with Mass Spectrometry. Additionally I would like to thank Dr Ivan Prokes, Edward Tunnah and Robert Perry from the NMR department.

I would like to especially thank Caroline Bray for her love and support throughout the completion of this thesis. Her devotion, especially through the stressful period of thesis writing, will always be cherished.

Finally, I would like to thank my family for their continuous support throughout my PhD. I am extremely grateful for their advice, encouragement and love throughout this endeavour.

Paul Kerby, **September 2015**

DECLARATION

I hereby declare that all of the work described in this thesis is the original work carried out at the University of Warwick between October 2011 and September 2015. I declare that the material described that is not original has been identified and appropriately referenced. I certify that the material within this thesis has not been submitted for a degree at any other university.

ABSTRACT

This thesis begins with an introduction to inflammation and the role of cell signalling and adhesion molecules within the body, drawing particular attention to the function of integrins and their ligands. **Chapter 1** discusses the importance of the α4-integrin / paxillin interaction for α4β1-dependent cell migration and the recruitment of leukocytes. Herein, literature research into the identification of a racemic, non-cytotoxic molecule that inhibits this interaction is discussed, concluding with synthetic approaches towards the enantiomerically pure synthesis of this compound and its analogues.

Chapter 2 opens with the discussion of some literature approaches to the synthesis of the indanone framework, followed by describing some initial synthetic work that was performed and the particular problems encountered with these methods. The attention of this chapter focuses on the kinetic resolution of indanones, applying both an enzymatic acylation and an oxidative kinetic resolution. The chapter demonstrates substrate viability in the aforementioned resolution techniques.

Chapter 3 begins with discussing previous work in the synthesis of the target racemic compound. Following this, a detailed review of appropriate synthetic transformations is discussed, proceeding onto work towards the transformation of the enantiomerically enriched indanones into their corresponding quinolinones. The approach herein discusses some unanticipated results during this transformation.

ABBREVIATIONS

3,5-Xyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis[bis(3,5-dimethylphenyl)phosphine
APH	Asymmetric Pressure Hydrogenation
ATH	Asymmetric Transfer Hydrogenation
br.	IR: broad (peak) NMR: broad (peak)
CAL-B	*Candida Antarctica Lipase B*
CBS	Corey-Bakshi-Shibata (reduction)
Conv.	Conversion
COSY	Correlation Spectroscopy
COX	Cyclooxygenase
DABCO	1,4-Diazabicyclo[2.2.2]octane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
decomp.	Decomposed (*Melting Points*).
DEPT	Distortionless Enhancement by Polarization
DFT	Density Functional Theory
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
Dusp6	Dual Specificity Phosphatase 6
E	Enzyme Selectivity Factor
e.e.	Enantiomeric Excess

ECM	Extracellular Matrix
EDG	Electron Donating Group
ESI	Electrospray Ionization
EWG	Electron Withdrawing Group
FAK	Focal Adhesion Kinase
FAT	Focal Adhesion Targeting
GC	Gas Chromatography
GPCR	G Protein-Coupled Receptor
h	Hour / hours
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HMQC	Heteronuclear Multiple-Quantum Correlation Spectroscopy
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IC_{50}	Half Maximal Inhibitory Concentration
IL-1	Interleukin-1
ImSAID	Immune Selective Anti-Inflammatory Derivatives
kDa	kilodalton
LFA-1	Lymphocyte Function Associated Antigen-1
LRMS	Low Resolution Mass Spectrometry
L-Selectride	Lithium tri-*sec*-butylborohydride solution
m	NMR: multiplet IR: medium (absorption)
m.p.	Melting Point
mcpba	*Meta*-Chloroperoxybenzoic acid

MS	Molecular Sieves
NDA	Non-Disclosure Agreement
NHC	N-heterocyclic Carbine
NMR	Nuclear Magnetic Resonance
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PC	Planar Chromatography
PECAM	Platelet Endothelial Cell Adhesion Molecule
PMP	1,2,2,6,6-Pentamethylpiperidine
PPA	Polyphosphoric acid
PSGL	P-Selectin Glycoprotein Ligand
BINAP	2,2′-Bis(diphenylphospino)-1,1′-binapthyl
rt	Room Temperature
S	General: seconds IR: strong (absorption) NMR: singlet Selectivity Factor (catalyst)
SAR	Structural Activity Relationship
TEBA	Benzyltriethylammonium chloride
Temp.	Temperature
tert	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TNF	Tumor Necrosis Factor

TOF	Time of Flight (mass spectrometry)
TsDPEN	*N*-*p*-Tosyl-1,2-diphenylethylenediamine
VCAM-1	Vascular Cell Adhesion Molecule-1
VLA-4	Very Late Antigen-4
w	IR: weak (absorption)

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CHAPTER 1- INTRODUCTION

1.1 Inflammation

Inflammation is a defence mechanism to the presence of injurious stimuli in the body. This complex biological response of vascular tissues is essential for the remedy of harmful stimuli, including pathogens, irritants or damaged cells.[1] In its zeal to protect the body, the immune response will destroy as much tissue as necessary to achieve this goal.[2] If left unregulated, a hyperactive inflammatory response can respond to the traumatic effects of an accident, for instance, from burns or surgery on the body, by attacking and destroying healthy tissue.[3]

Inflammation can be categorised as either acute or chronic inflammation, often governed by the type of cells involved in the inflammatory response.[4] The initial response, acute inflammation, is the inaugural reaction to harmful stimuli, and is achieved by an increased movement of leukocytes (especially granulocytes) and plasma into the injured tissues.[5] A cascade of biochemical events propagate and advance the inflammatory response, notably the local vascular system, immune system and various cells within the damaged tissue.[6] The latter type, chronic inflammation, leads to a progressive change in the type of cells at the inflammatory site, characterised by a simultaneous healing and destruction of tissue from the inflammatory response.[7]

Inflammation is a necessary response to tissue injury, imperative for responding to microbial, autoimmune, metabolic or physical insults,[4] but when uncontrolled, the prolonged inflammation can lead to a wide array of diseases, including arthritis,[8] diabetes,[9] Alzeheimers disease,[10] or Parkinson's disease, [11] and many others.[12,13]

1.1.1 The Process of Inflammation

The main symptoms of such responses in the inflammatory response are often associated with swelling, intensified heat and redness, as a consequence of the vascular response at the site of injury.

The swelling is the result of vicissitudes in vascular permeability, ensuing the exudation of fluid, white blood cells and plasma proteins. The vessels dilate and become 'leaky' resulting in the cells of the endothelium to contract,[14,15] forming gaps between the cells through which fluid and plasma proteins can move. The increased vascular permeability lets plasma proteins and fluid to leave the blood vessels, known as exudation, with the degree of exudation being variable depending on the amount of proteins that leave the vessels.[16]

The heat and redness symptoms are an effect of an increased blood flow, which in turn is the result of vasodilation.[17] This involves the widening of the arterioles (decreasing vascular resistance) followed by the capillaries and venules.[18] Vasodilation results from a relaxation of the smooth muscle layer of arterioles and the sphincter of pre-capillaries, which opens up previously inactive capillaries resulting in a significant increase in blood flow in the injured area. This process of increasing the delivery of supplies is known as *active hyperaemia*.[19]

The cellular response is predominantly involved in the activation and recruitment of white blood cells, (leukocytes), to the site of injury. Here, leukocytes commence to stick to the endothelium of the venules, known as *leukocyte extravasation*.[11]

The traditional three-step process of leukocyte extravasation involves; rolling, adhesion and transmigration, and were all identified by pathologists in the nineteenth century.[20,21] However, with the discovery of selectins, integrins, chemokines and their respective ligands / receptors, the emergence of a more detailed leukocyte cascade was developed (**Stages 1-7**),[22] explaining more specifically the recruitment of leukocyte subsets to particularly sites. An overview of this process is shown below in **Figure 1**, where particular attention for this research (**Section 1.1.2**) will focus on **Stages 4-6**.

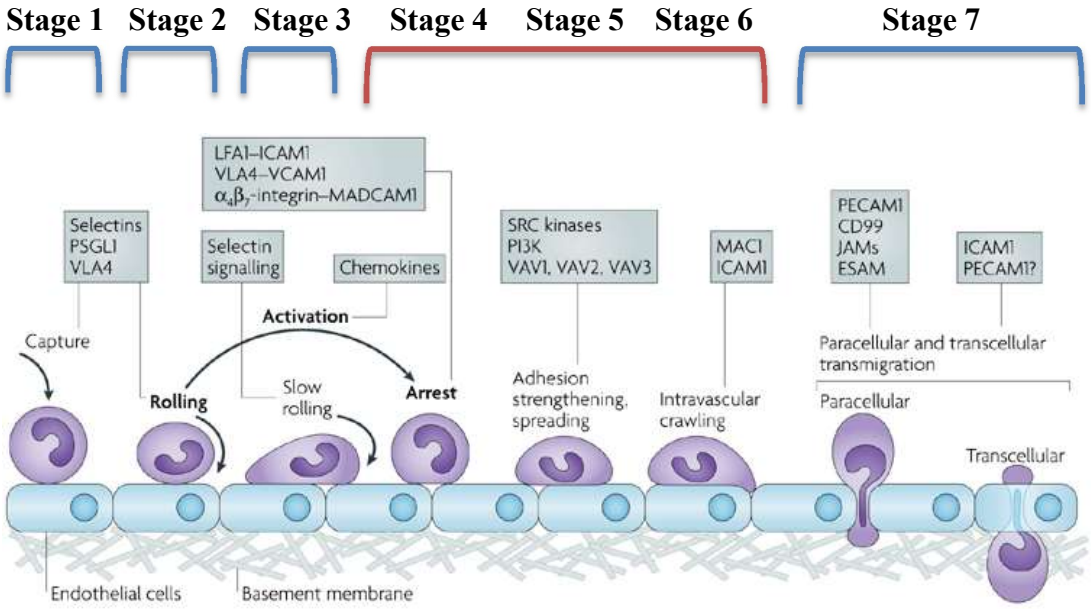


Figure 1 – The Leukocyte Adhesion Cascade, (reproduced from K. Ley, *Nature Reviews Immunology*, 2007)[22]

In the initial capture stage **(Stage 1)**, upon recognition of pathogens in tissue, (and subsequent activation), macrophages in the affected tissue release cytokines (IL-1, TNFα and chemokines), causing the endothelial cells of local blood cells to express cellular adhesion molecules. Circulating leukocytes are attracted to this site of injury due to presence of chemokines, through a process called chemotaxis,[13] and are paramount for beginning the rolling adhesion phase of leukocyte extravasation.

Once captured, the rolling of the leukocyte **(Stage 2)** is mediated by P-selectin, E-selectin (both expressed by inflamed endothelium cells) and L-selectin (expressed by most leukocytes). The interaction of these selectins with the P-selectin glycoprotein ligand 1 (PSGL-1),[23] enables leukocytes to adhere to the inflamed endothelium, even under conditions of blood flow due to their exceptional high on and off-rates.[24]

Cell surface adhesion molecules, known as integrins, have also been shown to participate in mediating leukocyte rolling **(Stage 2 / Stage 3)**. In particular, lymphocytes have been shown to roll on immobilised vascular cell-adhesion molecule 1 (VCAM1) by engaging their cell-surface ligand very late antigen 4 (VLA4; also called $\alpha_4\beta1$). The VLA4 dependent rolling is observed mostly for monocyte-like cell lines,[25,26] including T-cell lines[27] and T-cells.[28]

Integrins however play a much more fundamental role in the leukocyte extravasation, **(Stages 4-6)**, and remain an area of particular interest for this research. With the leukocyte in a process of slow rolling, chemokines and chemoattractants rapidly trigger the activation of integrins,[29] starting the leukocyte arrest phase. (**Stage 4**) Integrins primarily expressed on most circulating leukocytes, are the anchors in this cellular adhesion process and serve in adhesion strengthening (**Stage 5**) and intracellular crawling (**Stage 6**).[30]

In the final transmigration step **(Stage 7)**, the leukocyte, immobilised on the endothelium, transmigrates through gaps in the endothelial cells despite the on-going blood flow. Transmigration of the leukocytes occurs as PECAM proteins effectively pull the cell through the endothelium,[31] where they then undergo a migration along a chemotactic gradient moving towards the target area, once in the interstitial fluid.[17]

1.1.2 Role of Cell Signalling and Adhesion Molecules

An area of particular interest for this project involves the region of adhesion molecules and co-stimulation molecules, involved in **Stages 4-6** from **Figure 1**. The role of co-stimulation molecules are to deliver vital signals to leukocytes, especially T-Cells (or T-lymphocytes), where T-cells, being most circulating lymphocytes, play a primary role in nearly all chronic inflammatory reactions.[26] Cell adhesion molecules are important in mediating this leukocyte migration from the vasculature blood stream to sites of inflammation.[32] The role of these cellular adhesion proteins, more specifically integrins, are explained below.

Integrins – Structure and Role in Cell Signalling

Cellular plasma membranes effectively create a barrier between the inside (intracellular) and outside (extracellular) of the cell it defines. For the cell to sense and respond to its environment,[33] including other cells and the supportive structures that make up the extracellular matrix (ECM), bidirectional signalling across the plasma membrane has to be mediated by receptors and other structures.[34] These cell surface receptors that mediate cell-ECM interactions are integrins.[30,35,36]

Integrins are heterodimers, with non-covalently associated α and β subunits; comprising of 18 α- and 8 β- known subunits that can assemble into 24 distinct integrin receptors, all with different binding properties and tissue distribution.[30,34] Each of these heterodimers consist of a large extracellular domain, allowing protein binding in the extracellular environment, a transmembrane domain (single membrane), and a short intracellular cytoplasmic tail domain.[37]

Although integrins are involved in other biological activities, including cell migration, patrolling[38] and binding to cells of certain viruses,[39] they have two main functions:

- Attachment of the cell to the extracellular matrix
- Signal transduction to the cell from the extracellular matrix

Integrins function by linking the actin cytoskeleton of a cell to various external structures. The cytoplasmic part of each integrin binds to specific adaptor proteins, connecting to the actin filaments inside a cell (**Figure 2**).[40]

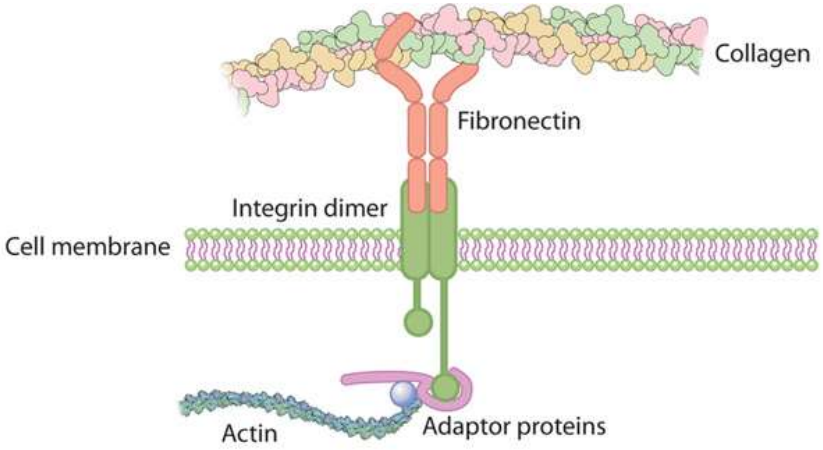


Figure 2 – Integrin binding from the cytoskeleton to the ECM (reproduced from C. Connor, *Essentials of Cell Biology*, 2010)[40]

It is important to note that integrin attachments to neighbouring cells can break and reform as the cell migrates laterally (**Figure 1**, **Stage 6 -** *slow crawling*), thus it is vital for integrins to be able to mediate these cell adhesions.[41,42] Integrins usually have to be activated before they can mediate adhesion,[36] a process is known as *integrin activation*, which controls cell adhesion, migration, and extracellular assembly.[43] Circulating leukocytes however do express abundant integrins on their surface, but they have low ligand binding capability; and therefore to mediate stable adhesion, they must undergo changes in conformation through integrin activation.[44]

Integrins exist in an equilibrium between a bent low-affinity state and an upright high-affinity state,[45] shown in **Figure 3** below,[46] where integrin adhesion receptors can rapidly increase their affinity (*activation*) in response to intracellular signalling, known as *inside-out signalling*.[47] Integrins can additionally be activated from outside the cell (*outside-in signalling)*,[48] but in either case, binding of talin to β-integrin subunit cytoplasmic domains is a key convergence point for signals regulating integrin activation.[49] There are a complex array of other cellular receptors that can activate integrins, such as chemokines,[50] or α-actinin,[51] but remain out the focus of this study.

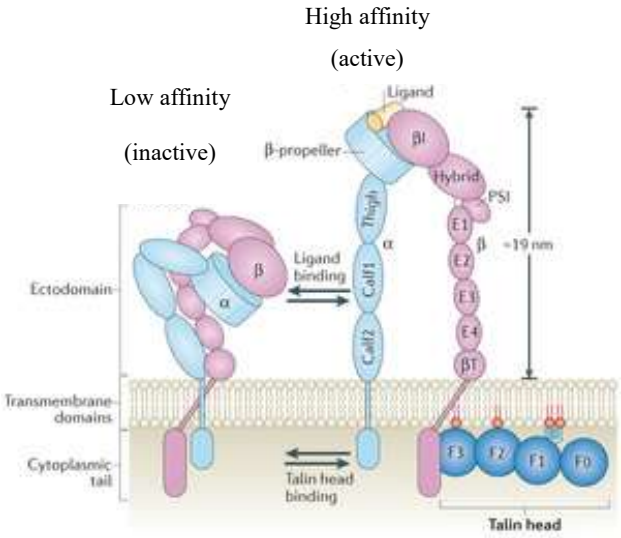


Figure 3 – Integrin structure and activation. (reproduced from A. Calderwood, *Nature Reviews Molecular Cell Biology*, 2013)[45]

Upon activation by their ligands, a change in conformation is observed (**Figure 3**), allowing the opening of the ligand-binding pocket,[37,52] which increases the intrinsic affinity for ligand and results in stable or persistent bonds. Clustering of integrins on the leukocyte surface, particularly at focal sites (focal adhesion) results in strong ligand affinity and avidity.[53] Chemokines initiate further inside-out signalling through G protein-coupled receptors (GPCRs),[44,54] which up-regulate α4β1 and $\alpha_L\beta_2$ integrin binding of leukocyte integrins to immunoglobulin superfamily members; ICAM1 and VCAM1, expressed by endothelial cells, [55-57] resulting in leukocyte arrest, (**Stage 4**).

The signalling cascade initiated by GPCRs that lead to activation of integrin affinity however is not fully understood.[44] The ligand-induced clustering of integrins and allosteric conformation changes contribute to the initiation of outside-in signalling (**Figure 4**).[58] This outside-in signalling results in a variety of leukocyte functions, including spreading, motility and adhesion strengthening and stabilisation (**Stage 5**), and is required for successful leukocyte migration (**Stage 6**).[22]

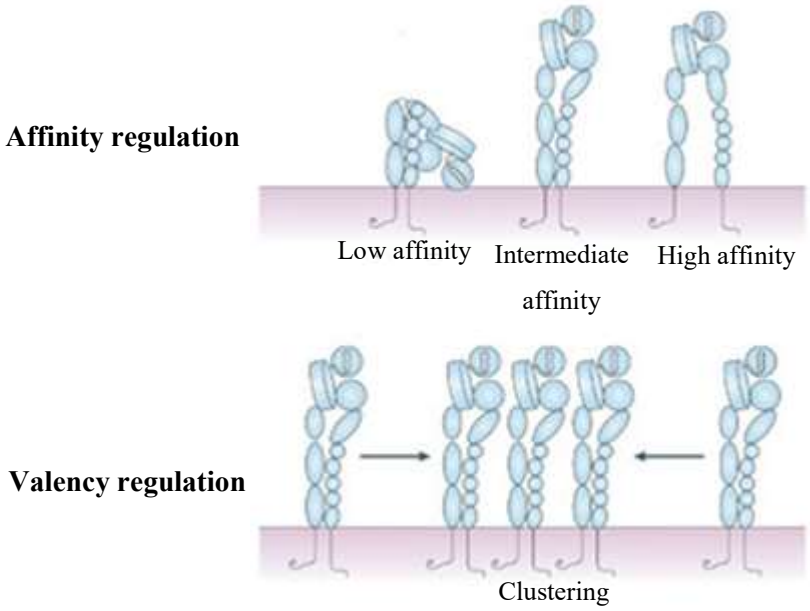


Figure 4 - Structural changes of lymphocyte function associated antigen 1 (LFA1) (reproduced from T. Kinashi, *Nature Reviews Immunology*, 2005)[58]

Since the cytoplasmic domains of the integrin contains no enzymatic functions, activation of signalling cascades require interactions with cytoplasmic signalling adaptors, for example, talin, α-actinin or filamin, usually via the β-integrin chain.[44]

The α4-integrin cytoplasmic domain is unique however, because it specifically binds paxillin, a signalling adaptor molecule, which further supports other protein-protein interactions.[59,60] The role of α4-integrin-paxillin in outside signalling is relevant to leukocyte migration, and is discussed in more detail below.

1.1.3 The α4-Integrin / Paxillin Interaction

Paxillin is a 68kDa focal adhesion-associated, phosphotyrosine-containing protein that has a role in several signalling pathways.[61] This signal-transduction adaptor protein is used to regulate cell spreading and motility in the body. It contains a LIM domain that are zinc-binding structures resembling a double zinc-finger domain, which mediate protein-protein interactions.[62] Paxillin specifically binds to the cytoplasmic tail of the α4-integrin chain, *via* its amino terminus,[59] but research has shown this only happens when the serine-988 is dephosphorylated.[63]

This dephosphorylation happens only when VLA4 (α4β1-integrins), expressed by leukocytes, are in a high-affinity conformation, either constitutively, where the integrin is constantly active through lymphoid development, or transiently, through recruitment to the site of inflammation by inside-out signalling from G-protein coupled receptors.[44,64] The implications of these observations are that outside-in signalling is initiated through adaptor proteins associated with the β1-integrin chain in addition to the association with paxillin and the α4-integrin chain.[44] More importantly for this research, the interaction between the α4-integrin and paxillin in outside-in signalling was found relevant to leukocyte migration.[65]

The α4-integrin-paxillin interaction is involved in two main processes:

1) **α4β1 integrin dependent cell adhesion under shear flow** – (cell tethering and cell adhesion), providing a needed connection to the actin cytoskeleton.[66]
2) **α4β1 dependent leukocyte migration** – (leukocyte crawling), through temporal and spatial regulation of GTPase Rac.[67]

1) α4-Integrin / Paxillin Interaction – Cell Adhesion

The α4β1 integrin can support tethering and rolling of leukocytes under shear flow conditions, a role largely associated with selectins previously mentioned.[68-70] The interaction of paxillin with the cytoplasmic domain of the α4 integrin subunit is critical for supporting tethering cell adhesion under shear flow conditions as it provides an essential connection to the actin cytoskeleton.[66] More specifically, paxillin binding to the skeletal tail of talin was found to be vital in linking the α4-integrin with the actin cytoskeleton.[68] Jurkat cells (an immortalised line of human T-lymphocyte cells), expressing an α4Y991A mutation, disrupted the α4-integrin / paxillin binding, reduced tethering bond strength with talin in the α4-integrin adhesion complex.[68]

Talin has already been recognised as a fundamental molecule in regulating integrin affinity for ligands (*inside-out signalling*),[71] however, it was found that talin had no effect on α4 integrin affinity modulation. Cells expressing α4-integrin with disrupted paxillin binding had no defect on the α4β1 integrin affinity for its ligand VCAM1,[72] moreover, ligand induced conformational changes in α4β1 were not altered by knocking down talin levels.[68] Thus the role of the α4-interaction is to mediate leukocyte tethering, through association with the cytoskeleton, strengthening adhesions under flow conditions.[66]

The α4-paxillin interaction is also an important factor in establishing firm cell adhesion under shear stress conditions.[66,68] It should be noted that this is in contrast to static cell adhesion, which remains unaltered by disrupting the α4-paxillin interaction.[72] The mechanism of this cell adhesion strengthening is known to regulate adhesion dynamics through focal adhesion kinases (FAK), although the exact process of this interaction remains relatively unknown.[73,74]

2) α4-Integrin / Paxillin Interaction – Cell Migration

Once a leukocyte has firmly arrested on the vascular endothelium, it will then migrate laterally to the junction of two or more cells where it can migrate through them, proceeding to the site of concern in the underlying tissue.[66] α4-integrins have been shown to function in both of these migratory steps,[75] where the α4-paxillin interaction has been shown as essential for α4β1 dependent leukocyte migration.[76]

A dynamic regulation of cell adhesion allows cell migration, where new adhesions are formed at the leading edge of cell, and subsequently adhesions at the lateral and trailing edge are released, propelling the body of the cell forward (**Figure 5**).[77,78] Temporal and spatial regulation of the small GTPase Rac is fundamental for effective cell migration,[67] where Rac is activated at the leading edge, promoting lamellipodia formation.[66]

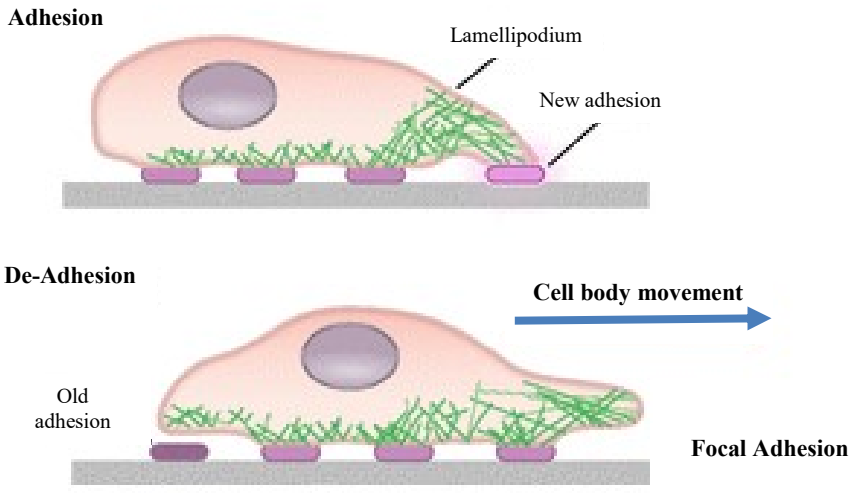


Figure 5 – Cell movement from new adhesions on the leading edge (reproduced from D. J. Tschumperlin, *Physiology*, 2013)[77]

Rac activation on the other hand is inhibited at the lateral and trailing edge, thus preventing lamellipodia formation.[79]

The α4-integrin subunit is dephosphorylated at ser988 at the lateral and trailing edge of a migrating cell, which is associated with paxillin binding, inhibiting Rac activation.[80,81] Paxillin does this through recruiting GTPase activating protein GIT1,[81] which inhibits Arf6, another member of the GTPase family. Inhibition of Arf6 subsequently inhibits the activation of Rac, albeit by an unknown mechanism.[66] This causes de-adhesion, which is required for the cell to move forward. Conversely, at the leading edge of the migrating cell, the α4-subunit is phosphorylated, resulting in a disruption of the α4-paxillin interaction, and thus Rac activation will promote lamellipodia formation, allowing the cell to migrate directionally.[79]

The α4-integrins can additionally function as a signalling molecule augmenting cell migration by other integrins.[63] α4β1 integrins have been shown to stimulate αLβ2 dependent cell migration, which requires the α4-paxillin interaction.[64] Although paxillin does not regulate the affinity of α4β1, its association with high affinity α4β1 contributes to the communication with the β2-integrin, driving cell migration.[63,64]

In summary, the leukocyte movement from the blood into the peripheral tissue is a central feature of the immune surveillance; however, they also contribute to the pathogenesis of inflammatory and autoimmune diseases. The roles of the α4β1-integrin / paxillin interaction in leukocyte trafficking can be summarised as:

- Leukocyte cell adhesion, both tethered and firm cell adhesion
- Leukocyte movement through GTPase Rac regulation

These discoveries make the α4-paxillin interaction a potentially attractive therapeutic target in regulating leukocyte trafficking for the treatment of numerous chronic inflammatory and autoimmune diseases, and thus remain the focus of this research.

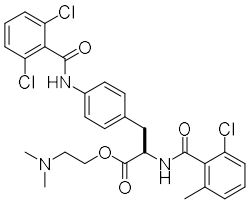
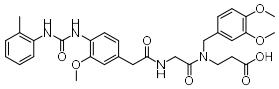
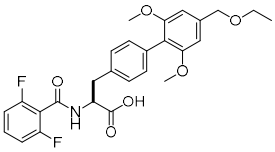
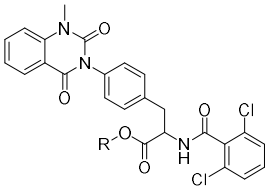
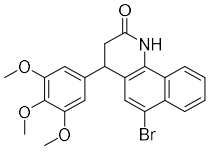
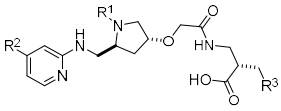
1.1.4 Current Anti-Inflammatory Drugs

Although inflammation is the body's first line of defence against injury and infection, it can also be regarded as a 'double-edged sword.' An ungoverned inflammatory response can result in the destruction of healthy tissue and ultimately cause further damage than the original problem would have produced. Anti-inflammatory medications can be categorized as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Steroidal-Based Anti-Inflammatory Drugs, Immune Selective Anti-Inflammatory Derivatives (ImSAIDs) with many herbs also exhibiting anti-inflammatory properties.[18] Many of these drugs target the cyclooxygenase (COX) enzymes, where amongst other functions; these are responsible for the production of gastro-protectional prostaglandins.[82] Consequently, inhibition of COX, specifically COX-1 by drugs such as NSAIDs, can be detrimental to the body, leading to gastric ulcers and renal toxicity.[83]

Given the role of the α4-integrins in the trafficking of leukocytes,[84] they have proven attractive for a number of chronic inflammatory autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, atherosclerosis and inflammatory bowel disease.[85] Inhibition of α4-integrins have been shown as effective in alleviating a wide variety of chronic inflammatory diseases in animal models,[86-89] inhibiting the recruitment of leukocytes to areas of inflammation.[90]

Some examples of humanized α4-integrin targeting molecules are shown below in **Table 1**.

Table 1 – Selected structures of small, non-peptide inhibitors for integrins that have been clinically targeted[91]

Name	Structure	Stage	Indication	Target
Valategrast		Terminated at Phase II	Asthma	α4β1
IVL745		Terminated at Phase II	Asthma	α4β1
Firategrast (SB-683699)		Phase II	Multiple Sclerosis	α4β1
AJM300 [a]			Ulcerative Colitis	α4β1
6-B345TTQ			Unknown	α4-paxillin interaction
JSM6427 [a]		Phase I	Age-Related Macular Degeneration	α5β1

[a] The nature of the R-group functionality has not been disclosed.

Nazilzumab, a humanized antibody against the α4-integrin cell adhesion has proven its therapeutic effectiveness for the treatment of autoimmune diseases such as multiple sclerosis,[92] or inflammatory bowel disease.[93,94] The mechanism of this α4-integrin antagonist is through inhibiting the interaction of α4-integrin with ligands such as VCAM1.[95]

However, given the role of α4-integrins in normal physiological functions, such as immune surveillance and haematopoiesis, the risk of side effects of α4-integrin blockage is a concern.[66] At full receptor blockade, these antagonists lead to a complete loss of α4-integrin function, carrying the risk of serious side effects including defects in placentation, hematopoieses and heart development.[96] Moreover, T-cell blockage into the central nervous system is likely accountable for the occurrence of progressive multifocal leukoencephalopathy, in humans treated with anti-α4-integrin antibodies.[97]

Consequently, a more selective approach of targeting the α4-integrins to suppress leukocyte trafficking, whilst still enabling normal physiological trafficking may be therapeutically beneficial. To this aim, targeting α-integrin / paxillin interaction may resolve this problem.[66]

Research has shown that mice developed bearing a Tyr991Ala mutation, specifically in the cytoplasmic tail of the α4-integrin chain, blocked Paxillin binding. These mice were viable, but showed an impaired recruitment of mononuclear leukocytes to inflammation in the peritoneal cavity.[76] Furthermore, they showed no defect in haematopoiesis or immune system development.

Instead of blocking the α-integrin, blocking the α4-integrin / paxillin interaction leaves α4-integrin mediated static adhesion intact,[59,72] which suggests that interfering with the α4-integrin signalling is a more favourable therapeutic approach. This has been demonstrated with a few synthetic targets,[98] one of which, being the focus of this research.[90]

1.2 Discovery of a Small Molecule that Inhibits the Paxillin - α4-Integrin Interaction

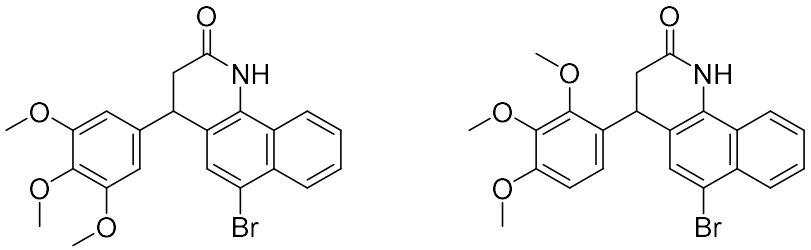
Ginsberg et al, published research identifying; **A Small Molecule That Inhibits the Interaction of Paxillin and α4 Integrin Inhibits Accumulation of Mononuclear Leukocytes at a Site of Inflammation**.[90] The paper investigates the use of small drug molecules to mitigate a wide range of chronic inflammatory diseases in animal models by inhibition of the recruitment of leukocytes to sites of inflammation.

1.2.1 Literature Results

In this paper[90] the authours screened a large chemical library (~40,000 compounds) to identify small molecules that could hinder this α4-paxillin interaction, whereby a non-cytotoxic inhibitor that impaired integrin α4-mediated (but not αLβ2-mediated) Jurkat T-cell migration was discovered. Jurkat T-cells are an immortalised line of T-lymphocyte cells that can be used to study T-cell signalling. These can be regarded as 'naïve T-cells' whereby they can be mutated or genetically engineered for specific screening properties, commonly used in immunological testing.[99]

The findings demonstrated that pharmacological blockade of the α4-integrin / paxillin interaction impaired α4β1-dependent migration and the recruitment of leukocytes. This is proof of principal for a novel anti-inflammatory strategy.

The compound, **6-B345TTQ**, **1** shown below in **Figure 6**, displayed a disruption in the α4-integrin and paxillin interaction and therefore interfered with the α4-integrin signalling. It was reported to inhibit the α4-paxillin interaction in cells *in vitro* by acting as a competitive inhibitor. An isomer of this compound however, **6-B234TTQ**, **2**, (**Figure 6**), shifting a methoxy group from position 5 to 2, showed no inhibitory effects on α4-mediated cell migration, cell spreading, or recruitment of leukocytes to an inflammatory site. Compound 6-B345TTQ, **1**, inhibited α4-mediated monocyte and T-cell migration by 52.6 % and 56.4 % respectively, but did not specifically reduce T-cell migration mediated by other α integrin subunits, highlighting its specificity on α4-mediated cell migration.



1 **2**

Figure 6 – Compound 6-B345TTQ (**1**) and its analogue, 6-B234TTQ (**2**)

Additionally, it had no effect to block the residual migration of cells bearing the α4(Y991A) mutation,[76] supporting that the compound specifically blocks migration by the α4-interaction. However, further work examining the effect of this compound on firm adhesion under fluid shear stress remains untested, or at least unpublished. Compound **1** additionally showed notable specificity with respect to inhibition of paxillin paralogues *in vitro*, blocking the binding of both leupaxin and paxillin to the α4-integrin. By compound **1** blocking this binding, its supports its anti-migratory effects to be independent of which paxillin paralogues are expressed.

No effects were observed upon the interactions of leupaxin with focal adhesion kinase (FAK). FAK, or PTK2 protein tyrosine kinase 2, is a focal adhesion protein kinase involved in cellular adhesion and spreading processes. FAK is phosphorylated in response to integrin engagement, leading to the recruitment to focal adhesions.[100,101]

Additionally, compound **1** had no effects on interactions of leupaxin with FAK or with Git-1, where these interactions are important in the signalling downstream of integrins.[102] Git-1 contains an ARFGAP domain, which enables it to act as a GTPase activating protein.[103] Compound **1** however did inhibit the interaction of paxillin with FAT (focal adhesion targeting) and Git-1.

In thioglycollate-induced peritonitis in mice, administration of compound **1** resulted in significantly reduced infiltration of monocytes / macrophages after 48 hours since the induction of inflammation. Furthermore, neutrophils in both transgenic α4(Y991A) mice treated with compound **1** were unaffected. Compound **2**, the control, had no discernable impact on the recruitment of leukocytes *in vivo*.

The overall findings demonstrated by this paper showed that pharmacological blockade of the α4 integrin-paxillin interaction impairs the α4β1-dependent migration and the recruitment of leukocytes, presenting a novel anti-inflammatory strategy.

Compound **1** was both patented and published as a racemate,[90,104] with no other mention of activity on structurally similar compounds, other than the related 2,3,4-trimethoxy-counterpart, **2**.

This provided an opportunity to asymmetrically synthesise both enantiomers of compound **1**, for biological testing, with the intention to identify an active enantiomer. Approximately 50 % of marketed drugs are chiral, with the remainder of these being a mixtures of enantiomers.[105] The potential advantages of using single enantiomers of chiral drugs can reflect their dosage, efficacies, side effect profiles or even indicated use.[106] Additionally, for progression and success in clinical trials, the single enantiomer or indeed racemic mixture needs to be shown as superior for the chosen form.[107]

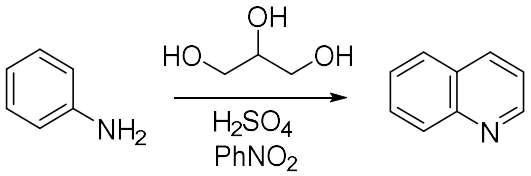
The intention of this thesis was to synthesise both enantiomers of compound **1**, whilst also synthesising similarly related compounds for structural activity relationships in biological testing. A literature review was performed, assessing previous methods to the quinolone and quinolin-2-one structure, more specifically directing towards 4-aryl-3,4-dihydroquinolin-2-(1*H*)-ones, and is shown in **Section 1.1.2**.

1.2.2 Synthesis of Quinolinones and Related Compounds

The quinolone scaffold is present in many classes of biologically-active compounds.[108] Since their discovery in the early 1960s as therapeutic agents, with the introduction of nalidixic acid in 1962 for the treatment of urinary tract infections,[109] quinolones have drawn a more profound attention due to their broad range of pharmacological properties. Quinolones are a class of bicyclic molecules, related to the hetereoaromatic coal tar isolate quinoline (**Figure 7)**.

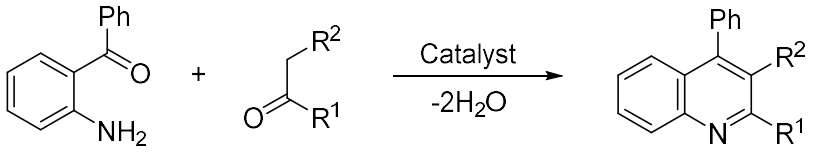
Figure 7 – The structure of quinoline (*left*) and quinolin-2-one (*right*)

The most common approach to the quinoline structure is the Skraup synthesis. Subsequent to the elucidation of its structure,[110] the synthesis of quinoline by Skraup was arguably the greatest single impetus to its further study.[111] Here, a mixture of aniline, sulphuric acid, glycerol, nitrobenzene and iron (II) sulfate are heated together (the last reagent used as a moderator to prevent a 'runaway reaction').[112] Nitrobenzene can be replaced with an alternate oxidant such as iodine or chloranil, and is required to convert the 1,2-dihydroquinoline into the final product, quinoline (**Scheme 1**).



Scheme 1 – Skraup synthesis in the formation of quinoline

An alternate approach is the Friedländer synthesis,[113] whereby a 2-aminophenyl ketone is condensed with an aldehyde (or ketone) containing a methylene unit, in the presence of an acid or base catalyst.

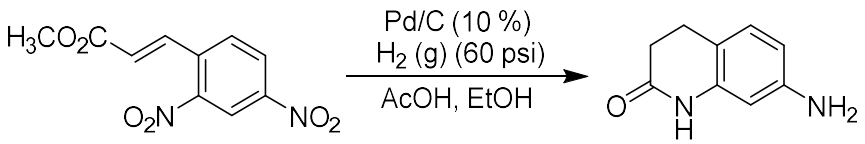


Scheme 2 – Friedländer Synthesis towards quinoline derivatives

The reaction has been catalysed by toluenesulfonic acid,[114] trifluoroacetic acid,[115] iodine,[116] various Lewis acids,[117] with several reviews being published.[111,118,119]

The synthesis of quinolin-2-ones are remarkably similar to those of quinolines, with one of the very first synthesises of the quinoline class being that of quinolin-2-one, reported in 1852.[120] This was prepared by the reductive cyclisation of 2-nitrocinnamic acid using ammonium sulfide.[120]

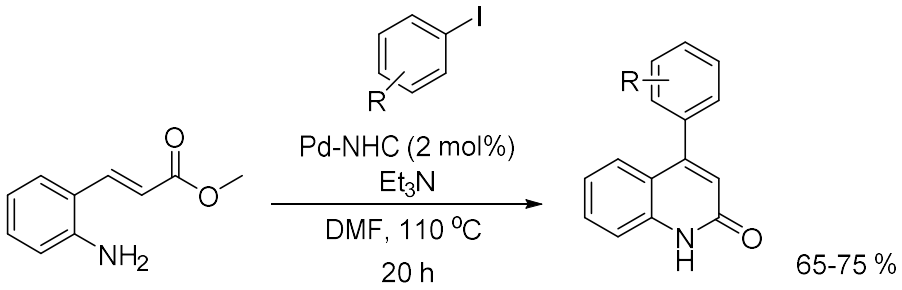
Similar reductive cyclisations have used palladium on carbon and hydrogen gas to yield quinolin-2-ones (**Scheme 3**).[121]



Scheme 3 – Reductive cyclisation towards quinolin-2-one derivatives[121]

Other reagents have involved trifluoroacetic acid,[122] iron with acetic acid, [123] hydrogen sulfide[124] or zinc in near-critical water,[125] typically from Bayliss-Hillman adducts.

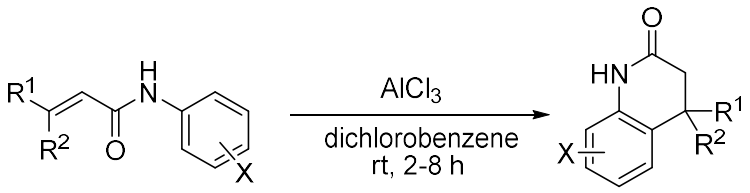
A similar transformation from the corresponding amine had been reported, using a benzimidazole-based palladium N-heterocyclic carbene (Pd-NHC) to effectively catalyse the C-C cross-coupling reaction via a Heck reaction,[126] (**Scheme 4**).



Scheme 4 – Synthesis of 4-aryl substituted 2-quinolones via a Heck reaction[126]

A small variety of 4-aryl-2-quinolones were synthesised with methoxy- and methyl substituents for the R functionality with reasonable yields (65-75 %). This approach offered a one-pot protocol towards the synthesis of the 4-aryl-2-quinolone structure involving a Heck coupling and cyclisation reaction.

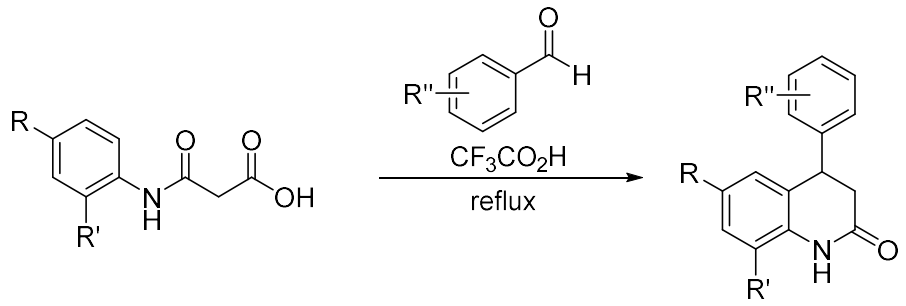
The synthesis of 4-substituted-3,4-dihydroquinolin-2-one structures are commonly synthesised from the corresponding *N*-cinnamoyl derivatives (**Scheme 5**).



Scheme 5 – $AlCl_3$-catalysed Friedel-Crafts alkylation[127]

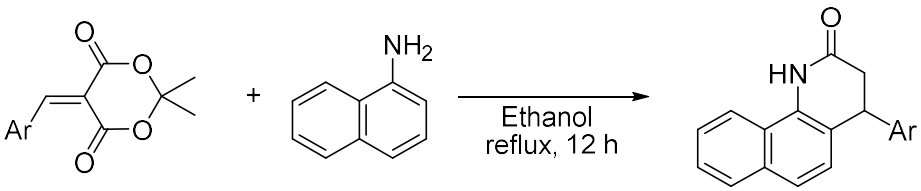
A variety of functional groups were tolerated in this transformation, however, poor yields were obtained when R^2 = Ph, R^1 = H (11 %). Similar improved transformations of *N*-cinnamoyl derivatives have been catalysed with zeolites,[128] hydrobromic acid,[129] polyphosphoric acid,[130] and trifluoromethanesulfonic acid.[131]

Jure et al.[132] demonstrated a one-pot synthesis of 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones (**Scheme 6**) via the condensation of monoanilides with aromatic aldehydes, followed by decarboxylation and subsequent hydroarylation, catalysed by trifluoroacetic acid.



Scheme 6 – Synthesis of 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones via monoanilides with aromatic aldehydes, catalysed by trifluoroacetic acid[132]

Alternatively, arylidene derivatives have been transformed into the corresponding 4-aryl-3,4-dihydroquinolin-2-(1*H*)-ones via reflux in ethanol (**Scheme 7**).

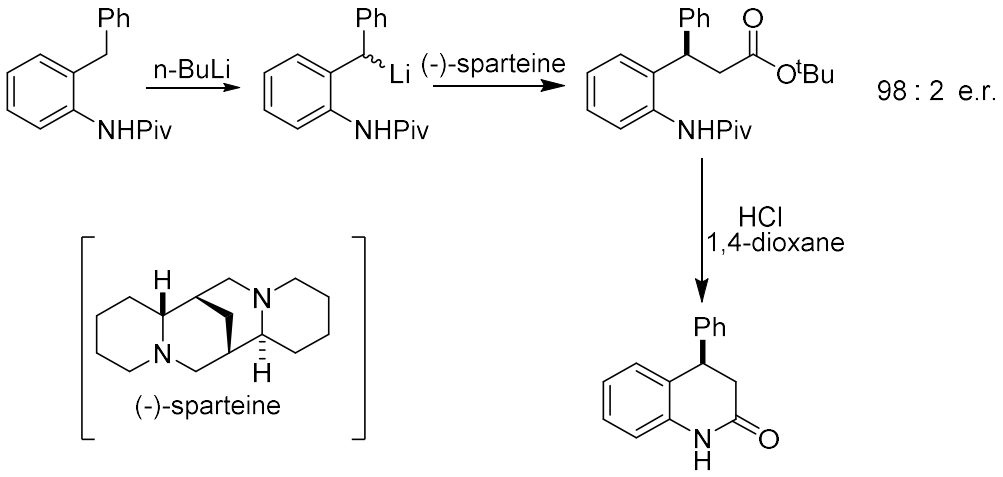


Scheme 7 – Reaction of 2-arylidenes with 1-aminonaphthylamines[133]

Similar results were obtained by refluxing in an aqueous medium, catalysed by TEBA (benzyltriethylammonium chloride).[134] Additionally this reaction was performed in refluxing acetic acid, yielding similar results with aromatic amines.[135]

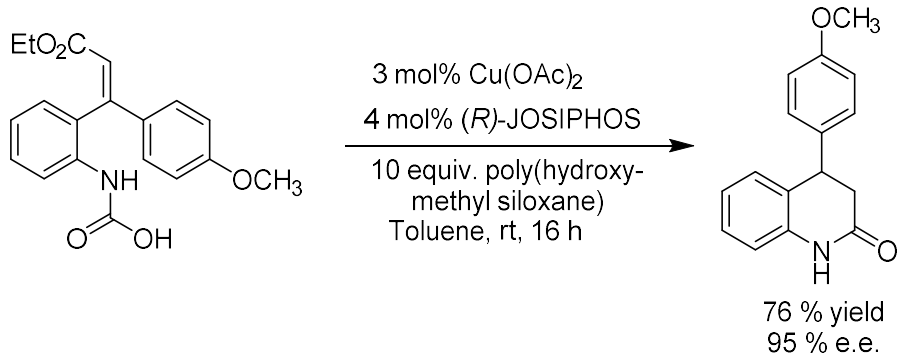
Stereoselective preparations of 4-aryl-3,4-dihydroquinolin-2-ones however remain quite limited,[136] although some highly enantioselective processes towards the corresponding diarylmethine-precursors exist,[137-139] and are discussed below.

Kim et al.,[140] showed a (-)-sparteine-mediated dynamic thermodynamic resolution of 2-(α-lithiobenzyl)-*N*-pivaloylaniline, using a temperature and concentration controlled epimerisation sequence. Increasing the concentration of substrate in methyl tert-butyl ester solvent (0.05 to 0.20) was found to offer an improved enantiomeric ratio (37 : 63 to 98 : 2 respectively); however the reaction example was limited to the substrate shown below in **Scheme 8**.



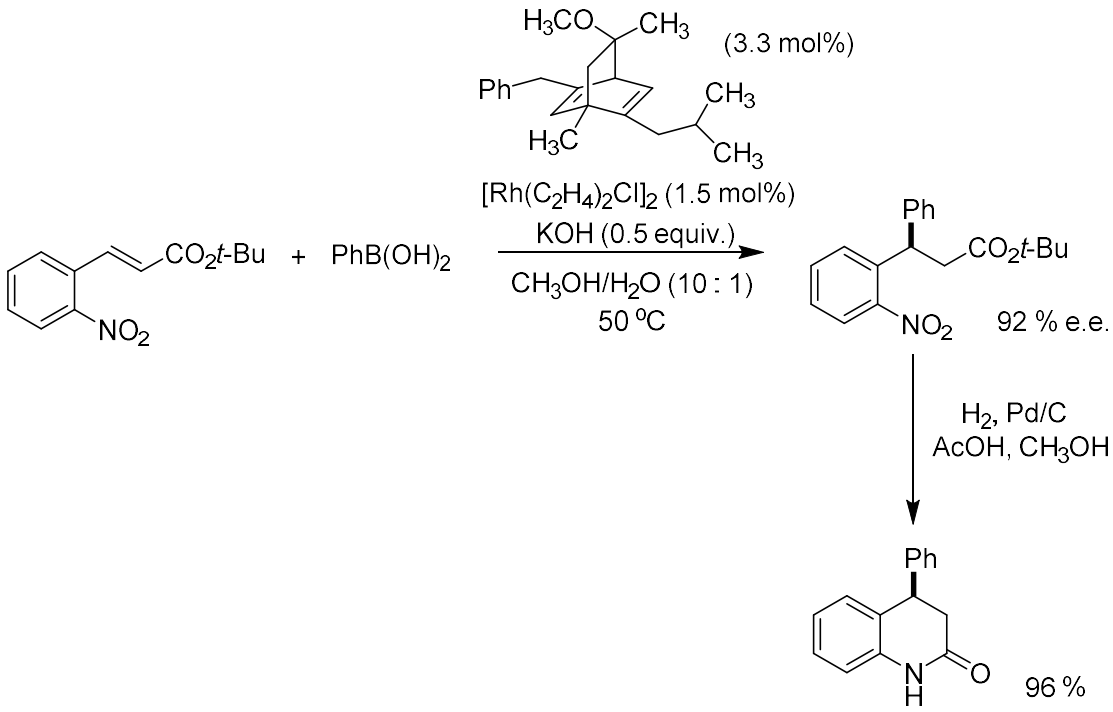
Scheme 8 – (-)-Sparteine-mediated dynamic thermodynamic resolution[140]

Taylor and co-workers[141] targeted similar precursors towards the synthesis of enantiomerically enriched 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones by performing an asymmetric reduction and intramolecular cyclisation (**Scheme 9**).



Scheme 9 – Synthesis of 4-aryl-3,4-dihydroquinolin-2-ones via Heck adducts[141]

Carreira et al.[136] published an enantioselective approach towards the synthesis of *tert*-butyl 3,3-diarylpropanoates as useful building blocks in the preparation of 4-aryl-3,4-dihydroquinolones (**Scheme 10**).



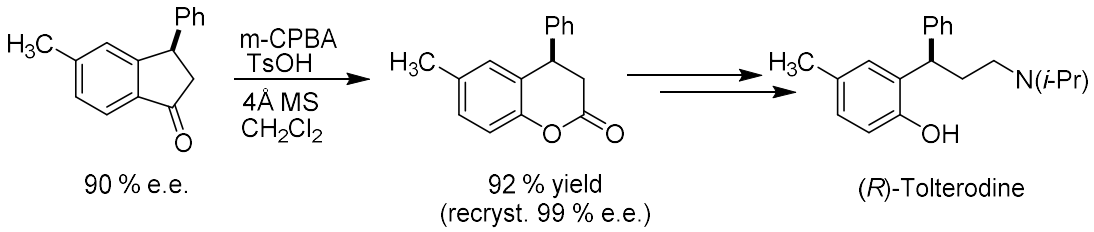
Scheme 10 – Rhodium (I) catalysed conjugate addition towards 4-aryl-3,4-dihydroquinolin-2-ones[136]

The Rh(I)-catalysed conjugate addition of aryl boronic acids gave good enantioselectivities (89-93 % e.e.) and good yields (69-95 %) towards the diaryl derivatives. These were subsequently converted to the dihydroquinolin-2-ones by Pd/C and H_2.

These chiral diaryl-structural precursors shown above (**Scheme 8** to **Scheme 10**) are present in a number of notable pharmaceuticals (for example, tolterodine[142] and sertraline[143]), including some natural products.[144,145]

A number of these enantiomerically enriched targets were also synthesised from chiral 3-arylindan-1-ones precursors. An example of this is the catalytic asymmetric synthesis of the muscarinic receptor (*R*)-tolterodine.[146]

A chiral 3-arylindan-1-one was firstly synthesised, and upon Baeyer-Villiger reaction gave the corresponding coumarin (**Scheme 11**). Subsequent ring opening and additional manipulations yielded the desired (*R*)-tolterodine.



Scheme 11 – Synthesis of muscarinic receptor, (*R*)-tolterodine[146]

With chiral indan-1-ones being demonstrated as suitable precursors to structurally analogous 4-arylcoumarins (**Scheme 11**), this prompted the idea that chiral 3-arylindan-1-ones could be useful precursors to the synthesis of enantiomerically enriched 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones. Literature methods for Beckmann reactions from the corresponding indanone oxime were additionally available.[147] As a result, our attention turned towards the synthesis of enantiomerically enriched indan-1-ones and subsequent Beckmann rearrangements, and remained the focus of this research.

1.3 Research Aims

The focal research paper[90] has identified a small non-cytotoxic inhibitor of the α4-integrin / paxillin interaction, promoting inhibition of leukocyte recruitment and migration. This compound was published as a racemate, and consequently synthesis and identification of the active enantiomer remained an interest (**Figure 8**).

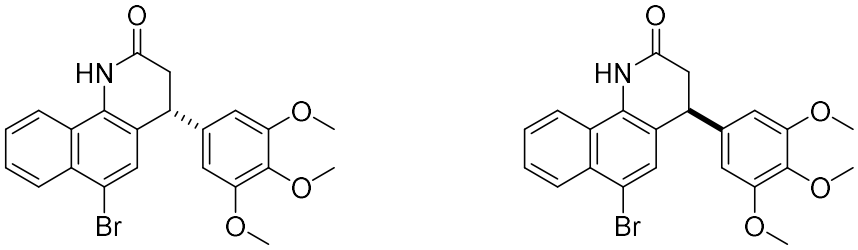


Figure 8 – Identification of active enantiomer, (*R*)-**1** or (*S*)-**1**

Additionally, compound **2**, showed a loss in activity upon changing the 3,4,5-methoxy- positions to 2,3,4-. Consequently, investigation into the activity of the following structural modifications became of interest (**Figure 9**).

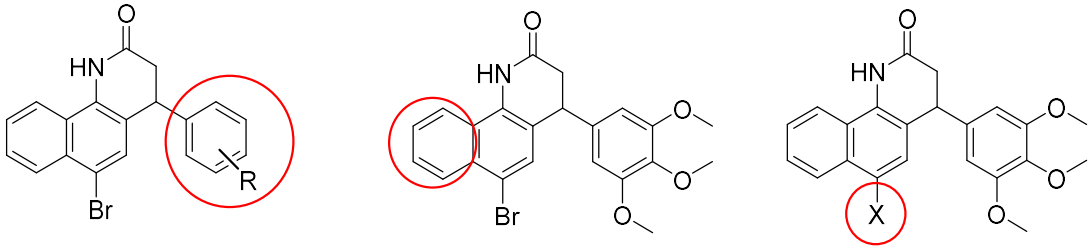
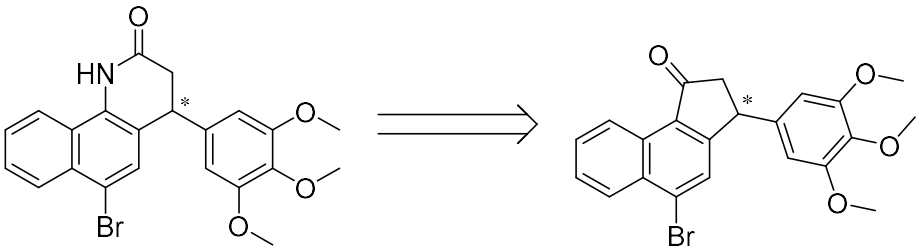


Figure 9 – Structural activity – initial areas of interest

Literature methods towards the synthesis of enantiomerically enriched derivatives of compound **1** remained limited, although enantioselective methods to structurally similar 3-aryl indan-1-ones were relatively abundant, and consequently our attention focused on this synthetic approach.

The following disconnection was applied for the synthesis of compound **1**, shown below in **Scheme 12**.



1 **3**

Scheme 12 – Disconnection for compound 6-B345TTQ, **1**, to the corresponding 3-aryl-indan-1-one, **3**

Towards the synthesis of compound **1**, the following objectives were established:

1) **Synthesis of enantiomerically enriched 3-aryl-indan-1-ones:** To synthesise both enantiomers of the 3-aryl indan-1-one precursor, **3** towards the synthesis of compound **1**. Additionally, similarly related substrates, given consideration to **Figure 9**, will also be synthesised.

   (Chapter 2)

2) **Beckmann rearrangement of enantiomerically enriched 3-aryl-indan-1-ones:** From the corresponding enantiomerically enriched 3-aryl indan-1-ones, Beckmann cyclisations will be investigated, in efforts towards the corresponding enantiomerically enriched 4-aryl-3,4-dihydroquinolin-2-one compounds, notably compound **1**.

   (Chapter 3)

Biological testing of individual enantiomers and corresponding analogues, where applicable, will be outsourced in collaboration with industrial sponsors, and thus remains out of the focus of this research.

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CHAPTER 2- SYNTHESIS OF SUBSTITUTED INDANONES

2.1 Introduction

The indane framework is found in a large number of important molecules.[148] Chiral 3-substituted indan-1-ones are important intermediates in the synthesis of interesting compounds with biological activity.[149] In addition the multitude of diverse indanone natural products[150,151] requires both selective and efficient synthetic routes.[152] Many of these methods will be discussed in this chapter.

2.1.1 Structure and Nomenclature of Indanones & Indenones

The indanone framework, in its simplicity, consists of a benzene ring fused to a cyclopentanone. The nomenclature of the indanone structure is fundamentally contingent on the position of the cyclopentanone ring; producing indan-1-one and indan-2-one structures, shown below in **Figure 10**.

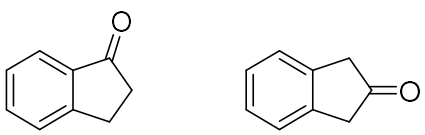


Figure 10 – Indan-1-one (left) and indan-2-one (right)

2.1.2 Indanones in Use

While a variety of indan-1-one related compounds are important bioactive molecules, perhaps the most renowned indan-1-one derivative is donepezil (Aricept®). Donepezil was discovered in 1995 as reversible acetylcholinesterase inhibitor, used as a first-line therapy for mitigation of Alzheimer's disease by increasing the levels of cortical acetylcholine, a neurotransmitter crucial to cognitive function.[153]

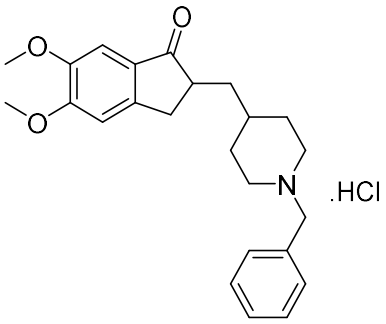


Figure 11 – Donepezil hydrochloride

Not only is Donepezil a very potent compound with acetylcholinesterase IC_{50} in units of nM, quite interestingly, it was also patented for its ability to reduce locally expressed effects caused by topically applied ophthalmic pharmaceuticals. Subsequently, a variety of donepezil analogues, comparable in activity, have been produced, keeping this area of research very active in the illnesses it addresses (**Figure 12** below).

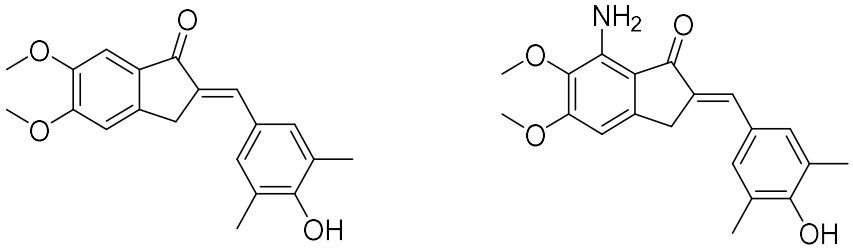


Figure 12 – The structure of indanorine[154] and indanocine[155] respectively

Camps et al.[156] synthesised a variety of *cis*-fused spiro(cyclopenta[*a*]indene-2,2′-inden)diones, in connection with the synthesis of novel donepezil-based anti-Alzheimer agents. These were derived from a one-pot synthesis, by treatment of 5- and 6- substituted indan-1-ones with various aldehydes and sodium ethoxide. Although no activity information was presented in the paper, it highlighted a novel synthesis to some interesting indan-1-one derived compounds with potential pharmaceutical properties.

Another indan-1-one related compound, indacrinone, with a very similar structure to those in **Figure 13**, displayed antihypertensive properties and is used for patients with gout, as it readily decreases reabsorption of uric acid.[157,158]

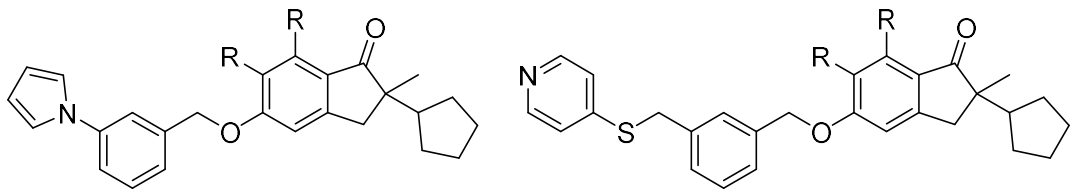


Figure 13 - Potentiators of mGluR2 receptors patented by Merck

Isolated from the bracken *Pteridium aquilinium*, the indan-1-one moiety also constitutes the core of natural Pterosine compounds (**Figure 14**). Pterosines have been shown to exhibit cytotoxic and antibacterial activity at micromolar concentrations,[159,160] with several synthesises being demonstrated.[161] The importance of the indan-1-one pharmacophore was confirmed, as the alcohol counterparts displayed much lower activity.[162]

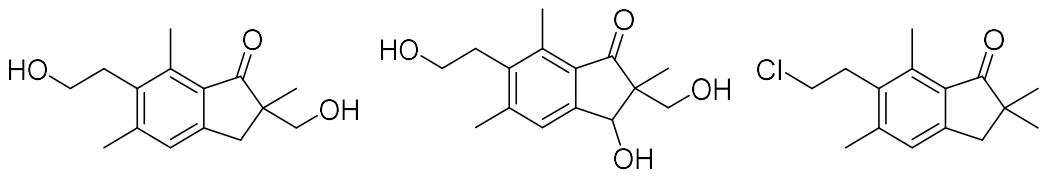


Figure 14 – Several biologically interesting Pterosines; Pterosin A, L & H

The indanone moiety was further highlighted as an important pharmacaphore, with the development of indenone compounds used to stimulate fibroflast growth factor by inhibition of Dusp6 (dual specificity phosphatase 6) in micromolar concentrations (*in vitro* study). Reduction of the carbonyl group or lack of the benzylidene group resulted in the dramatic loss of activity.[163]

Quite interestingly, potent and selective COX-2 inhibitors, Flusolide (and its thioether analogue), **Figure 15**, were discovered, with the potential to exert powerful anti-inflammatory effects, while also minimising the deleterious side effects from the inhibition of COX-1.[164-167]

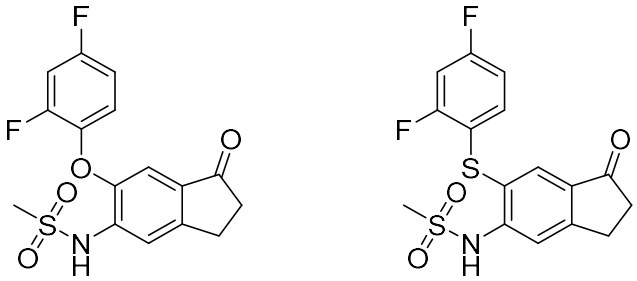


Figure 15 – Flusolide and its thioether analogue

Although there are a large number of biologically important 2-substituted indan-1-one compounds, this discussion will focus on 3-substituted indan-1-one compounds. Such derivatives (**Figure 16**) have demonstrated anti-inflammatory activity, with *in vivo* doses of ~20 mg/kg exhibiting 70 % inhibition of edema, with the effect persisting for 3-5 hours.[168]

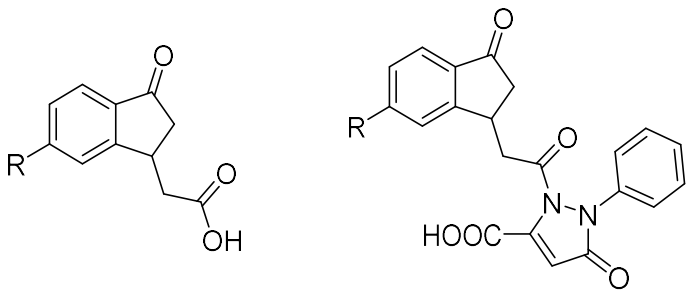


Figure 16 – Indanone acetic acid and its derivative – with anti-inflammatory activity

Saxena et al.[169] reported 3-substituted Gallic acid-based indanone derivatives with very effective anticancer activity in a variety of human cancer cells lines. Furthermore, some of the more potent compounds displayed no toxicity to human erythrocytes even at high concentrations, nonetheless only being reported as a racemic mixture.

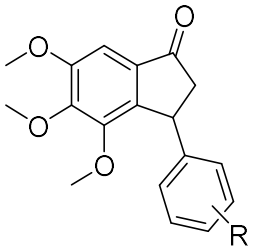


Figure 17 – The structure of a gallic acid-based indanone

The indanone moiety with chiral centres at the 2- and 3- position has been the core structural unit of a variety of other drugs and natural products, namely Pauciflora F,[170] Taiwaniaquinone B & D,[171] and a Tolterodine precursor.[146] One of the more prominent chiral indanones for this project is Indatraline; a non-selective monoamino transporter inhibitor, shown to block the reuptake of dopamine, norepinephrine and serotonin. Numerous synthetic routes have been established for this compound.[172-174]

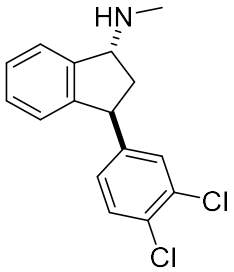


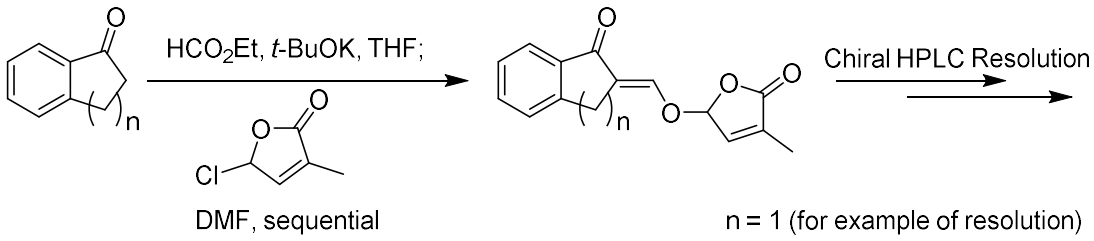
Figure 18 – Structure of indatraline

Ultimately, indanones have found a profound use in the pharmaceutical industry; fortuitously for the synthesis of indanone substructures related to compound 6-B345TTQ, a plethora of useful synthetic techniques have already been developed.

2.1.3 Synthesis of Indanones

Developing an enantioselective synthetic route for a new drug candidate or key intermediate can be a resource-intensive and time-consuming process of pharmaceutical development.[175] Consequently, preparative chiral HPLC has found a very useful position in some challenging synthetic situations, already demonstrating an effective use in the synthesis of a preclinical drug candidate.[176]

Zwanenburg et al.[177] utilised preparative chiral HPLC during the synthesis of pharmaceutically important indan-1-one derivatives, when the coupling of chiral reagents resulted in decomposition during purification. In view of synthetic problems, the decision to use semi-preparative chiral HPLC was supported by the rationale that only a small amount of sample was required at this stage for biological testing.

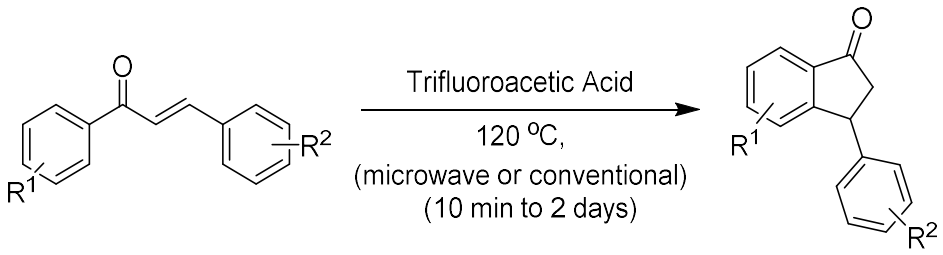


Scheme 13 – Chiral resolution of indanone derivative; Strigolactone analogues

Similar reasoning was applied for the use of preparative chiral HPLC for more complex spirocyclic indanone derivatives.[178] Moreover, planar chromatography (PC) has played an important role for the real-time monitoring of chiral synthetic progress, owing to its simplicity, low cost and flexibility, has allowed results that can be usefully related to the ones achieved in columns.[179] Stationary phases employed for planar chromatography are mainly based on cellulose derivatives.[180-184]

While the paradigm for developing and carrying out an enantioselective synthesis is well established, strategies for the efficient use of preparative chiral HPLC are still evolving. Nonetheless, it remains relatively fruitless with the separation of immensely varying enantiomers, where even small variations on the structure of solutes can have adverse effects on separation. For instance, the change of a protecting group can sometimes dramatically influence chromatographic resolution and productivity.[185,186]

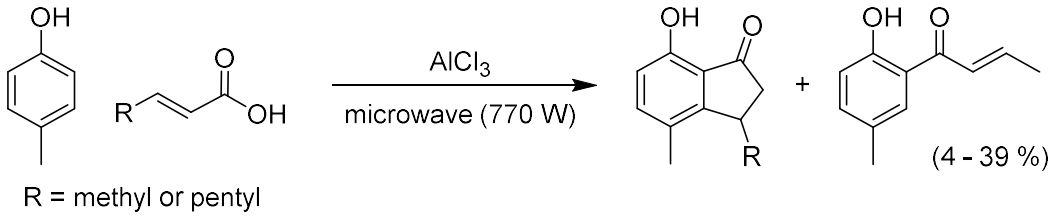
Whilst enantioselective methods are available for the direct synthesis of chiral indanones, one of the more common methods for indan-1-one synthesis encompasses Nazarov cyclisations. Although many examples exist, they generally focus around the same conditions, including the use of methanesulfonic acid,[187] polyphosphoric acid (PPA),[188] or more commonly, trifluoroacetic acid (TFA) under either thermal or microwave conditions.[169,189-192]



Scheme 14 – Trifluoroacetic acid-catalysed Nazarov reaction

Substituents R^1 and R^2, (**Scheme 14**) in this transformation were generally quite varied, although R^1 being electron donating, with R^2 conversely electron withdrawing offer the best yields. Interestingly, a more suitable HUSY zeolite catalyst allowed a similar transformation,[193] with further examples provided in **Section 2.3.2.3**. Often, Nazarov conditions require 'forcing conditions' for the cyclisation,[194] whilst other methods have proceeded via a chalcone epoxide derivative, cyclising with a Lewis Acid catalyst such as $InCl_3$.[195,196]

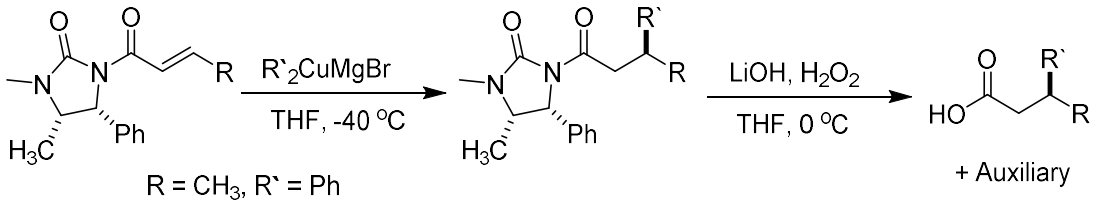
Similar results were obtained with an analogous compound performing a Scholl reaction,[197] (sometimes called Friedel-Crafts Arylation). More commonly used Friedel-Crafts acylations employed unsaturated carboxylic acids (crotonic / cinnamic acid) derivatives with the addition of a Lewis Acid catalyst and a substituted aromatic reagent.[198-200]



Scheme 15 – Friedel-Crafts acylation of substituted crotonic acids

Modest yields were obtained, although improved yields were obtained with the use of trifluoromethanesulfonic acid,[158,201] albeit favourable substrates were again used as examples for this transformation. Similar transformations have been developed using (2-cyano-phenyl)phenylacetonitriles via spontaneous Dieckmann-type cyclisations.[202]

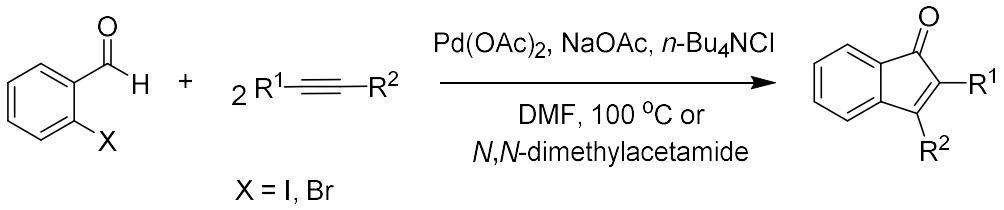
The introduction of chirality in the 3-position of the indanone framework has been accomplished via a variety of different approaches. In 1994, Rocher and coworkers[203] used chiral auxiliaries to incorporate a substituent shown in the desired configuration (**Scheme 16**), followed by a previously encountered Friedel-Crafts acylation method to yield the corresponding chiral indanone. Incorporation of chiral auxiliaries has also been applied to muscarinic receptor antagonist Tolterodine.[204]



Scheme 16 – Asymmetric cuprate addition to unsaturated carboxylate derivatives

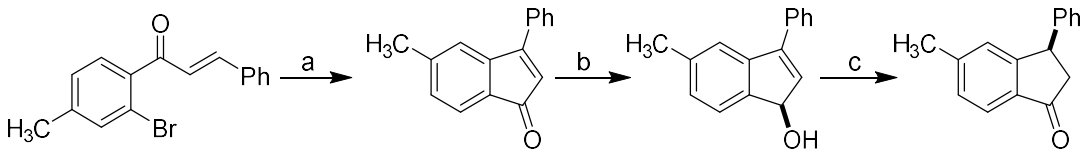
Similar transformations were employed towards the synthesis of (+)-Sertraline and (+)-Indatraline, performing a lithiation / borylation and protodeboronation method, starting from a chiral homoallylic alcohol.[143] The chiral alcohol was prepared from enzymatic resolution prior to the aforementioned method, offering excellent enantioselectivities (>95 % e.e.).

Inden-1-one precursors were additionally synthesised from the reaction of internal alkynes with *o*-iodo- or *o*-bromobenzaldehyde using a palladium catalyst under mild conditions and in moderate yields (**Scheme 17**).[205]



Scheme 17 – Larock annulation to form substituted indan-1-ones[205]

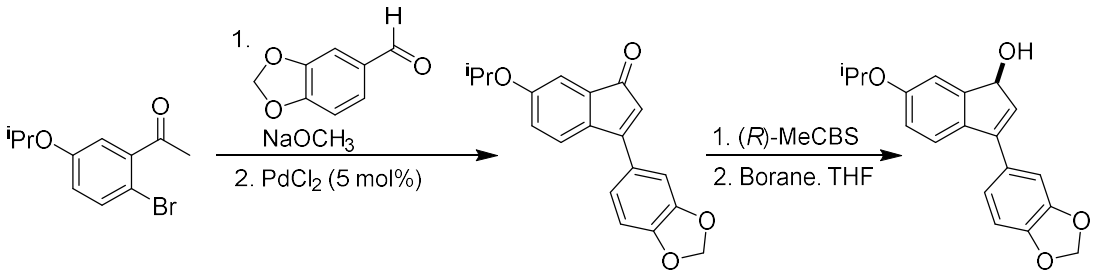
Closely related inden-1-one structures, used as intermediates for the synthesis of natural products such as C-nor-D-homosteroids,[206] or Tolterodine,[146] offered excellent templates for asymmetric transformations to the corresponding indan-1-ones (**Scheme 18**).



Scheme 18 – Synthesis of chiral 3-arylindan-1-one via the appropriate inden-1-one; (a) $PdCl_2$, PPh_3, K_2CO_3, DMF, 130 °C, 1 h. (b) (*S*)-Me-CBS, BH_3.THF, -20 °C, 2 h. (c) Et_3N, DABCO, THF, 60 °C, 4 h

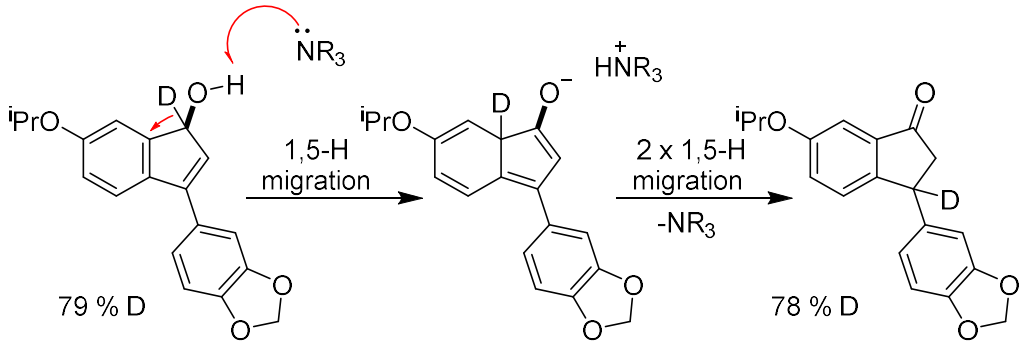
It was found that a more sterically demanding group such as a trimethylsilyl or tertiary alkyl group, favoured the 2-position of the inden-1-one. Less hindered alkynes unfortunately gave a mixture of regioisomers, although Larock et al. further developed the method, permitting different solvent/base conditions.[207]

Further developments utilised a non-reductive Heck cyclisation, followed by an asymmetric hydrogenation.[208] The use of (*R*)-MeCBS to reduce the inden-1-one, following work from Itsuno[209] and Corey,[210] afforded the inden-1-ol in excellent enantioselectivities (90-92 % e.e.), depending on the base employed.



Scheme 19 – Enantioselective synthesis of inden-1-ol intermediate towards endothelin receptor antagonist SB-209670

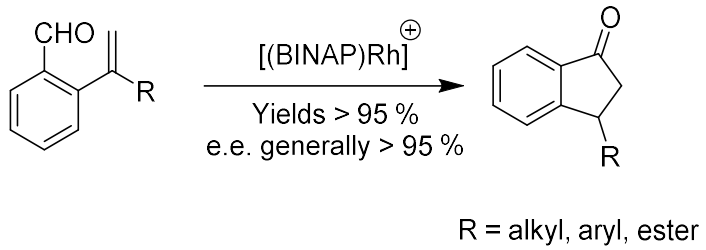
Interestingly from a mechanistic point of view, it is believed that the treatment of the inden-1-ol (**Scheme 19**) with DABCO yielded the corresponding indan-1-one via a 1,5-H migration, shown below in **Scheme 20**.



Scheme 20 – 1,5-H migration of inden-1-ol substituent with tertiary amine

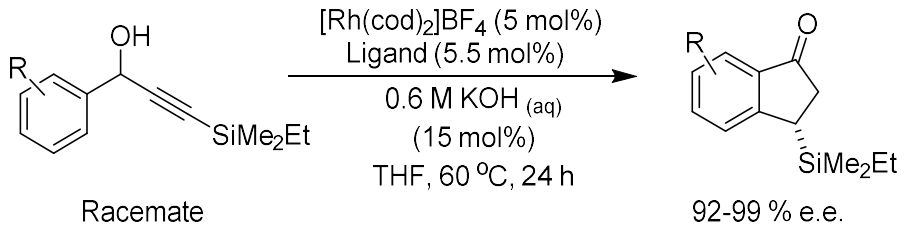
The selective hydrogen rearrangement was initially attempted with a $Pd(PPh_3)_2Cl_2$ / Et_3N system, prompting a mechanistic assumption of a palladium hydride catalysed olefin isomerisation, however, when DABCO was used as the amine base, a slight increase in stereospecificity (92.2 % e.e.) was obtained, owing to a *syn*-facial 1,5-shift. This transformation is believed to happen due to geometric constraints, where it is believe DABCO should be incapable of undergoing palladium oxidation, thus negating the formation of the palladium hydride catalytic species.[211]

Alternative methods shown by Morehead and co-workers demonstrated a rhodium-catalysed hydroacylation towards the synthesis of 3-substituted indanones.[212] This process offered high yields and enantiomeric excess (generally > 95 % in most cases).



Scheme 21 – Hydroacylation of 2-vinyl benzaldehyde systems

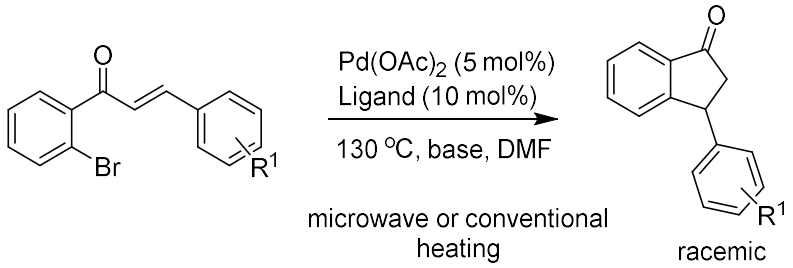
Similarly, Hayashi and co-workers[213,214] also made use of rhodium in the synthesis of chiral indanones, starting from the corresponding alkynes, (**Scheme 22**).



Scheme 22 – Rhodium-catalyzed asymmetric synthesis of indanones via axially chiral bisphosphine ligand

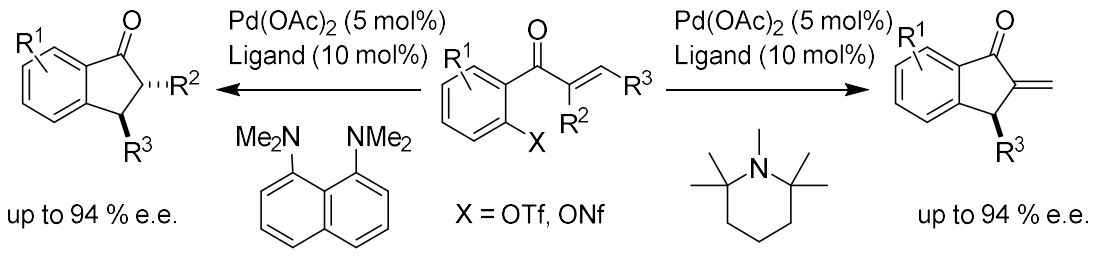
Although the aforementioned substrates employed in the 3-position were exclusively silicon derivatives offering high enantioselectivities (92-99 % e.e.), other methods below presented more pertinent substrate-cyclisations with aromatic functionality.

Initial attempts at an intramolecular asymmetric cyclisation by Püschl and co-workers[215] were unsuccessful, but demonstrated an attractive method of forming substituted indanones from (*E)*-2′-bromochalcones, using high reaction temperatures (155 °C) or microwave conditions. Additionally, they illustrated that no reaction was achieved with conventional heating with –CN and –Cl in the 4-position (R^1).



Scheme 23 – Transformation of 2′-bromochalcones to corresponding indan-1-ones

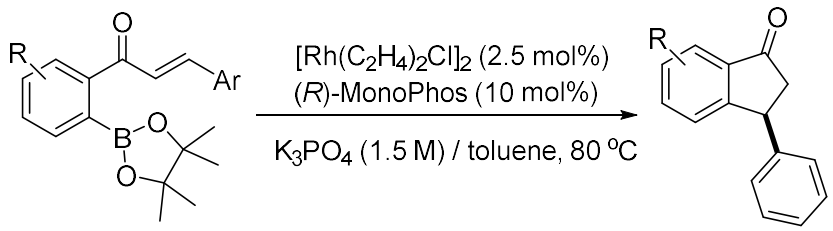
Buchwald and co-workers[216] enhanced this method, demonstrating an effective method of transforming (*E*)-2′-bromochalcones into their corresponding chiral indanones with good yield and high enantioselectivity for some substituents.



Scheme 24 –Enantioselective reductive Heck cyclisation

Optimisation of the reductive Heck reaction with $PdCl_2$, using an (*R*)-3,5-Xyl-MeOBIPHEP ligand afforded chiral indanones with good enantioselectivities (50-94 % e.e.) and yields (42-90 %).

A similar approach was performed using a rhodium-(*R*/*S*)-Monophos catalyst,[217] offering more attractive yields, (up to 95 % e.e.).



Scheme 25 – Rhodium-catalysed asymmetric intramolecular 1,4-addition of pinacol-borane chalcone derivatives

This approach reported a broader range of aromatic functionality, permitting both electron donating and withdrawing aromatic substituents (Ar), with good enantioselectivities (81 – 95 % e.e.).

In conclusion, the indan-1-one moiety, and indeed the inden-1-one precursor have further demonstrated a huge application in a variety of natural products and pharmaceuticals, including Fredericamycin A,[218] Tolterodine,[146] Sertraline,[219] Indatraline,[174] and a variety of Pterosins.[220] Subsequently, a plethora of synthetic techniques exist. By assessing particular methods more applicable to this project, it was important to evaluate and 'scope' particular reactions to their success for appropriate substrates. These were cemented within the aims of the project, and indeed, initial 'scoping' reactions (**Section 2.2**) were performed in accordance with this objective.

2.2 Initial Synthetic Reactions

The objective of this chapter was the synthesis of enantiomerically enriched indan-1-one precursors to compound 6-B345TTQ, **1**, shown below in **Figure 19**. Additionally, the intention was to synthesise similarly related compounds, changing the R- and X-groups shown below.

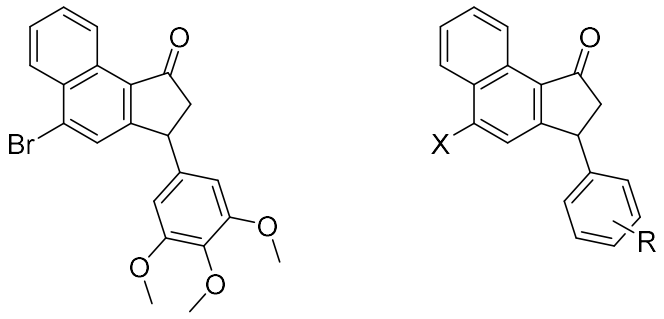


Figure 19 – Synthetic precursors for the compound 6-B345TTQ, **1** (left), and related compounds

The following section of work describes some initial synthetic routes that were attempted based on literature methods.

2.2.1 Conjugate Addition Reactions

The following method included a stereoselective Michael addition of an aryl cuprate, applied by Rocher and coworkers.[203] The method makes use of an Evans auxiliary,[221] with the appropriate disconnection described below (**Figure 20**). It should be noted, that the initial approach focused on a related compound without the bromine (X = H, **Figure 19** shown previously).

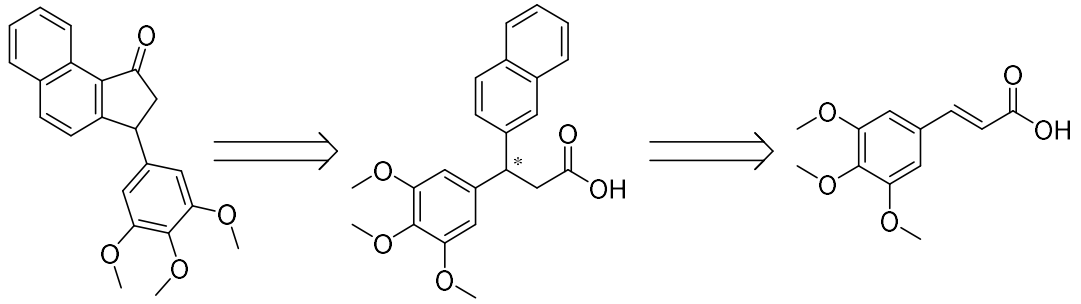
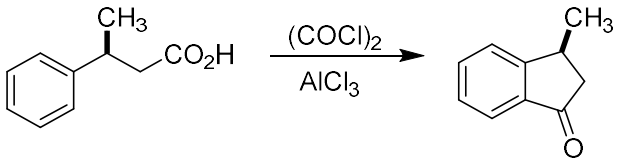


Figure 20 – Disconnection approach to an enantiomerically enriched propanoic acid

Discussion of the Approach:

The approach by Rocher and coworkers,[203] is shown previously in **Scheme 16**, and upon forming the enantiomerically enriched 3,3-substituted propanoic acid, via chiral auxiliary induced enantioselective Michael addition of an aryl cuprate; the acid then being cyclised after conversion to the acid chloride.

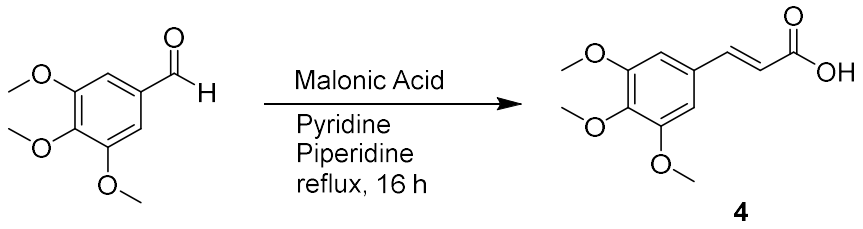


Scheme 26 – Cyclization of enantiomerically enriched acid

The acid chloride was cyclised using $AlCl_3$ from the corresponding acid chloride, where similarly related methods have also been employed for this transformation.

Results & Discussion

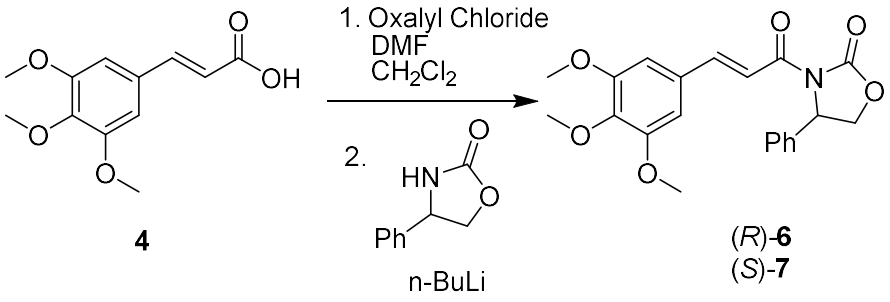
The 3-aryl subsituted acrylic acid was synthesised via a Knoevenagel-type condensation reaction with malonic acid and a suitable base at reflux.[222]



Scheme 27 – Knoevenagel condensation reaction on aromatic aldehyde

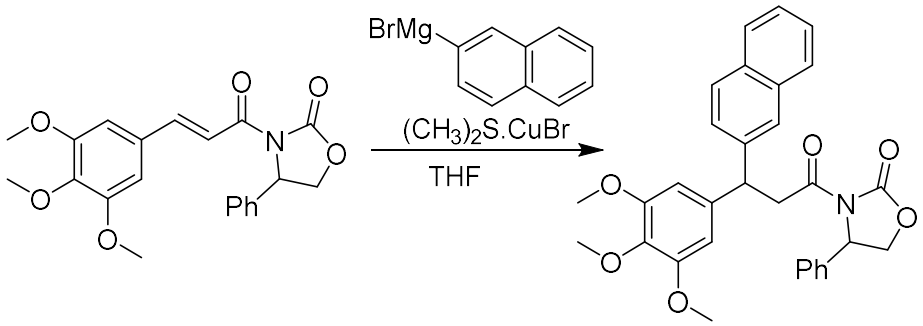
The method produced compound **4** in a good yield (86 %), where the (*E*)-stereochemistry was confirmed by ^{1}H NMR, by inspection of the coupling constants for the vinylic protons.

The chiral auxiliary was attached using a familiar n-BuLi/THF/RCOCl method,[223] producing the enantiomerically enriched product in good yield (**Scheme 28**). The method involved formation of the appropriate acid chloride, using oxalyl chloride and a catalytic amount of *N*,*N*,-dimethylformamide, and subsequent reaction with (*R*)- or (*S*)-lithiated 4-phenyl oxazolidinone.



Scheme 28 – Attachment of Chiral Auxiliary

The aryl Grignard reagent was first produced successfully by standard synthetic conditions,[224] starting from 2-bromonaphthalene, reacting with magnesium turnings and catalytic iodine in diethyl ether. The Grignard reagent was then introduced to a pre-cooled solution of copper(I)bromide dimethylsulfide complex, followed by slow addition to the enantiomerically enriched oxazolidinone-products mentioned previously, shown below in **Scheme 29**.

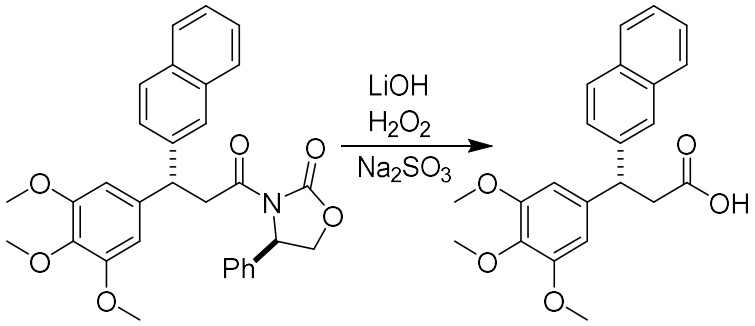


(*R*)-**6**
(*S*)-**7**

(4*R*,3`*S*)-**9**
(4*S*,3`*R*)-**10**

Scheme 29 – Conjugate addition of 2-naphthalene

The diastereoselectivity shown above was a 10 : 1 ratio for both (4*R*,3′*S*)-**9** and (4*S*,3′*R*)-**10** enantiomers, shown by inspection of the ^{1}H NMR spectrum. The ^{1}H NMR spectra were compared to that of the (4*R*,3′*R*), formed after cleavage of the original auxiliary (**Scheme 30**), followed by attachment of the opposite auxiliary enantiomer to that attached before, allowing the formation of (4*R*,3′*R*) and (4*S*,3′*S*) isomers.

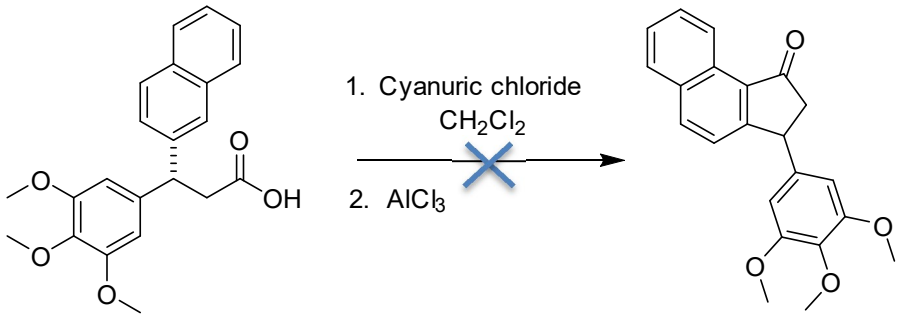


(4*R*,3`*S*)-**9**
(4*S*,3`*R*)-**10**

(*R*)-**12**
(*S*)-**11**

Scheme 30 – Cleavage of Chiral Auxiliary

Once the auxiliary had been removed by a combination of lithium hydroxide and hydrogen peroxide, an attempted cyclisation using the original conditions by Rocher and coworkers[203] was performed. Attempting the cyclisation by first producing the acid chloride using cyanuric chloride, followed by an *in-situ* cyclisation with $AlCl_3$ was unsuccessful, yielding only the starting material after work-up, (**Scheme 31**).



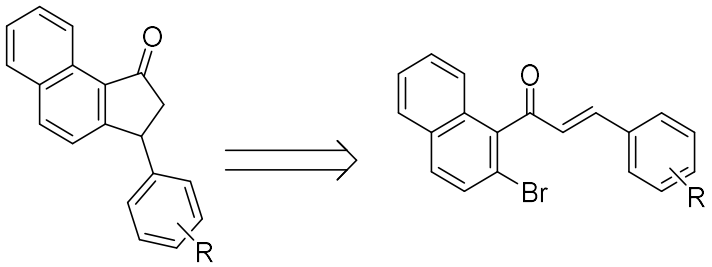
(*R*)-**12**
(*S*)-**11**

Scheme 31 – Cyclisation to enantiomerically enriched indan-1-one

Attempts at heating the reaction, isolating the acid chloride prior to the cyclisation (rather than *in-situ*) and changes in solvent also gave the starting material after work-up. Consequently, this method was not developed further.

2.2.2 Intramolecular Heck Cyclisation

Buchwald et al.[216] reported a method of forming enantiomerically enriched indan-1-one derivatives from some attractively simple 2′-bromochalcones. Consequently, the following disconnection approach was applied (**Scheme 32**).

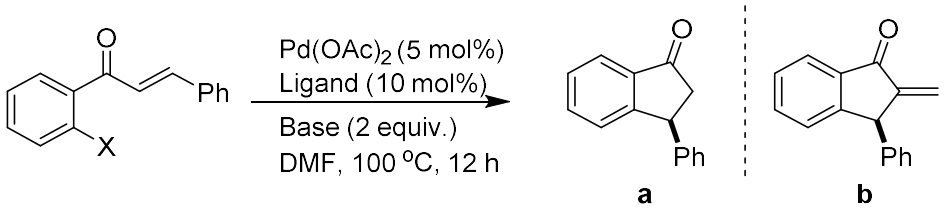


Scheme 32 – Disconnection approach to some 2′-bromochalcones derivatives

Discussion of the Approach:

Results from the Buchwald et al. research are shown in **Table 2**.[216]

Table 2 –Enantioselective Reductive-Heck Reaction of Substituted Chalcones reported by Buchwald et al.[216]

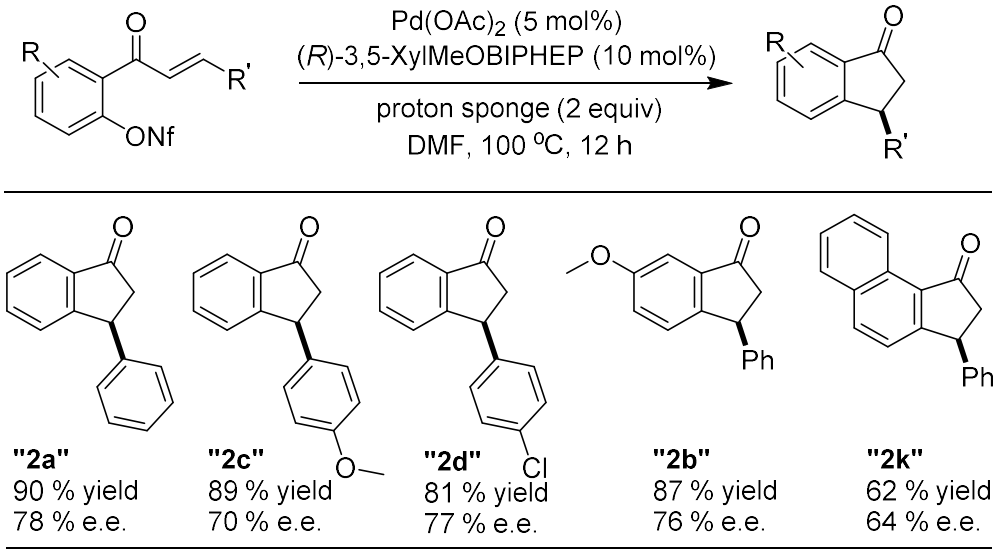


Entry	X	Ligand	Amine	Ratio a:b	Yield [%] [a]	e.e. [%] [b]
1	OTf	(*R*)-BINAP	$MeNCy_2$	100:0	32	54
2	OTf	(*R*)-BINAP	NEt_3	100:0	40	53
3	OTf	(*R*)-BINAP	ps [c]	100:0	65	55
4	OTf	(*R*)-3,5-XylMeOBIPHEP	ps	100:0	88	79
5	ONf	(*R*)-3,5-XylMeOBIPHEP	PMP [d]	0:100	74	80
6	I	(*R*)-3,5-XylMeOBIPHEP	ps	100:0	25	76
7	Br	(*R*)-3,5-XylMeOBIPHEP	ps	100:0	30	77

[a] Determined by GC; [b] Determined by HPLC on a Chiracel OJ column; [c] ps = proton sponge; [d] PMP = 1,2,2,6,6-pentamethylpiperidine.

The ratio of **a** and **b** from transformation of the 2′-substituted chalcone can be governed exclusively by the amine base used, with PMP conversely yielding exclusively **b**, upon comparison to more common amines such as triethylamine or 1,8-bis(dimethylamino)naphthalene (proton sponge), **Table 2**. The proton sponge (ps) offered a minor improvement in yield compared with triethylamine (**Table 2**, **Entry 2** & **3**). Evaluating different phosphine ligands demonstrated a modest enantioselectivity using (*R*/*S*)-BINAP, with further enhancements using a (*R*)-3,5-XylMeOBIPHEP ligand for the $Pd(OAc)_2$ catalyst.

Buchwald also showed that the effect of the aromatic halide of triflate seemed to have negligible effect on the enantioselectivity (**Table 2**, **Entry 4**, **6 & 7**), although it did offer a noticeable effect on the yield.[216] Given the simplicity of synthesising a 2′-bromo-substituted chalcone from commercially available 2′-bromoacetophenone, this approach seemed an attractive option. Some additional examples are shown in **Scheme 33**, where for this project it was initially decided to proceed with BINAP as the ligand, owing to its more affordable assessment of the success of the reaction.

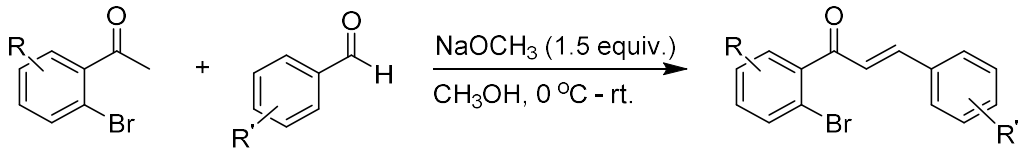


Scheme 33 – Selected results from the Pd-catalysed reductive Heck cyclisation [216]

Results & Discussion

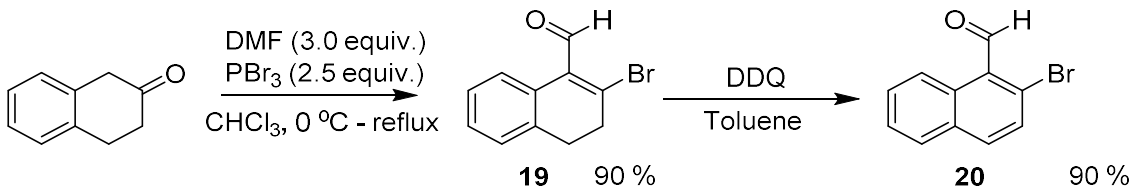
Synthesis of 2′-bromochalcones

Commonly, chalcone synthesis involves a Claisen-Schmidt condensation, with many methods being discussed further in **Section 2.3.2.2**. The general procedure involved the condensation of commercially available 2′-bromoacetophenone and aromatic aldehyde under basic conditions, generally offering excellent yields.[225]



Scheme 34 – Synthesis of substituted 2′-bromochalcones

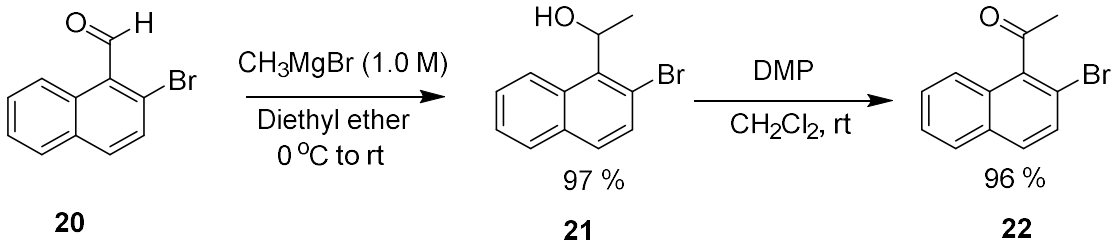
Although 2′-bromoacetophenone is commercially available, its naphthyl-counterpart is not. Synthesis of the 2′-bromonaphthalen-1-one, **22** proceeded from the commercially available β-tetralone. This was converted into 2′-bromo-1-naphthaldehyde, **20**,[226,227] followed by transformation to the corresponding 2′-bromo-1-naphthal-1-one, **22**. The initial stage consisted of a Vilsmeier-Haack-Arnold formylation of β-tetralone, using phosphorus tribromide and *N*,*N*-dimethylformamide affording the β-bromovinyl aldehyde, **19**, (**Scheme 35**).[227-231]



Scheme 35 – Synthesis of 2′-bromoacetonaphthalen-1-one precursor

The vinylic aldehyde was then aromatised into 2′-bromonaphthaldehyde, **20**, via dehydrogenation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in excellent yields for both steps (81 %).

The next step involves addition of Grignard reagent to the aldehyde to form the secondary alcohol, which is readily oxidised using Dess-Martin periodinane to afford the desired 2′-bromonaphthale-1-one (**Scheme 36**).



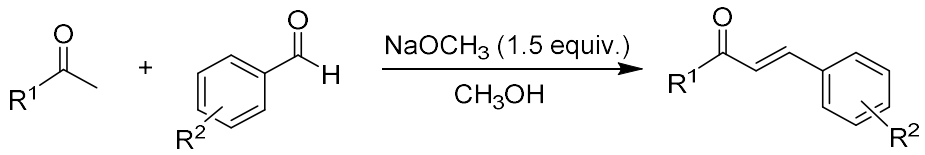
20 **21** **22**

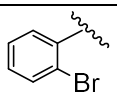
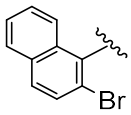
Scheme 36 – Synthesis of 2′-bromoacetonaphthone from its aldehyde counter-part

The general formation of substituted 2′-bromochalcones proceeded with good yields and exclusive *trans*- geometry, confirmed by the coupling constants for the vinylic hydrogens.[232] In the case of 2′-bromochalcone, **Table 3**, **Entry 1**, a small trace (~1 % by ^{1}H NMR) of the *cis*-isomer was detected. This was subsequently converted into the more thermodynamically stable *trans*-isomer,[233] by refluxing with DABCO in methanol.[234] Additionally, elevated temperatures (45 °C) were required for the naphthyl-counterpart, **Table 3**, **Entry 7** & **8**. The condensation reaction showed no preference between an electron donating or withdrawing benzaldehyde, and the reaction generally boasted easy purification, through decantation/recrystallization.

The results for the synthesis of the 2′-bromochalcones are shown below in **Table 3**.

Table 3 – Synthesis of substituted 2′-bromochalcones



Entry	R^1 Groups	R^2 Groups	Temperature. (°C)	Yield (%) [a]	Chalcone
1		H	25	91	**13**
2		4-OCH_3	25	76	**14**
3		3,4-OCH_3	25	80	**15**
4		3,4,5-OCH_3	25	78	**16**
5		4-CN	25	67	**17**
6		4-Cl	25	59	**18**
7		H	45	68	**23**
8		3,4,5-OCH_3	45	72	**24**

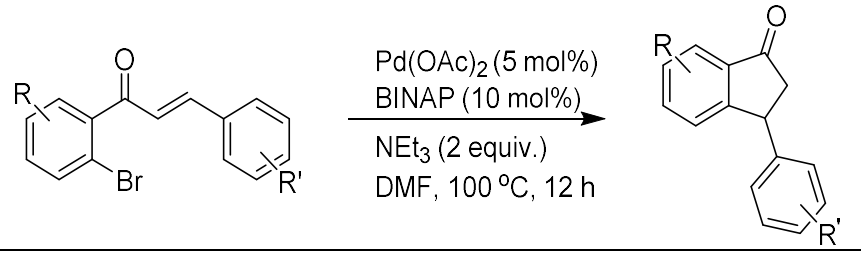
[a] Isolated yield.

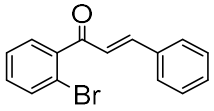
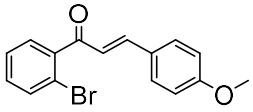
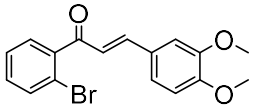
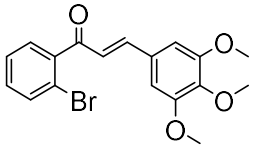
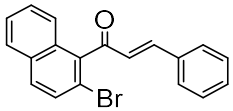
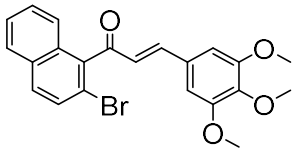
Intramolecular Heck cyclization of 2′-bromochalcones

Buchwald et al.[216] optimised the intramolecular heck-type cyclisation conditions utilising an (*R*)-3,5-XylMeOBIPHEP ligand with proton sponge as a base and an aromatic triflate. The literature found that a variation in temperature, solvent or palladium source did not improve the yield nor e.e.% of the product. Using a more hindered ligand, (*R*)-3,5-*tert*-butylMeOBIPHEP was found to have a deleterious effect on both yield and enantiomeric excess, supporting the hypothesis that the extent of the "3,5-dialkyl-*meta*-effect" on enantioselectivity is substrate dependent.[235,236]

The results obtained in this study for the reductive Heck cyclisation are presented below in **Table 4**.

Table 4 - Intramolecular Heck-type cyclisation of substituted-2′-bromochalcones



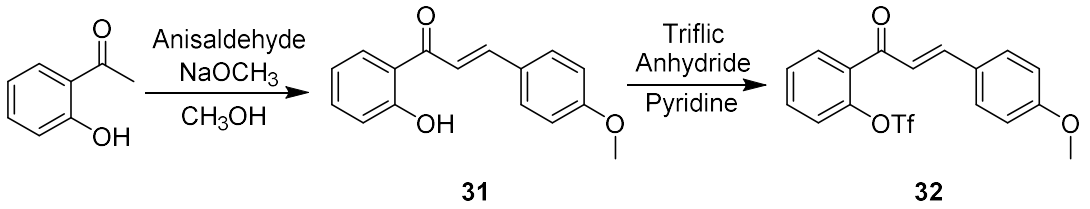
Chalcone		BINAP (*R*/*S*)	Yield % [a]	e.e. % (enantiomer) [b]	Indanone
	**13**	*R*	40	50 (*S*)	(*S*)-**25**
	**14**	*S*	36	43 (*R*)	(*R*)-**26**
	**15**	*S*	33	40 (*R*)	(*R*)-**27**
	**16**	*S*	28	19 (*R*)	(*R*)-**28**
	**23**	*S*	41	10 (*R*)	(*R*)-**29**
	**24**	*S*	42	(*rac*)	**30**

[a]Isolate yield; [b] Enantiomeric excess determined by HPLC.

The aforementioned results were less than satisfactory for an initial screening of enantioselectivity. The results showed a general decline in e.e. for both the naphthyl-chalcone species and indeed for more electron donating substituents. Looking at the enantioselectivities obtained in the literature (**Scheme 33**),[216] the naphthyl-component and electron donating substituents on the 3-position of the chalcone resulted in a lower enantioselectivity and lower yield, consistent with the results obtained above.

It should be noted that although cyclisation of a 4″-chloro and 4″-cyano group was attempted, no product was observed. These results were consistent with existing literature, where they only observed product using an alternative base; *N*,*N*-dimethylcyclohexylamine.[215]

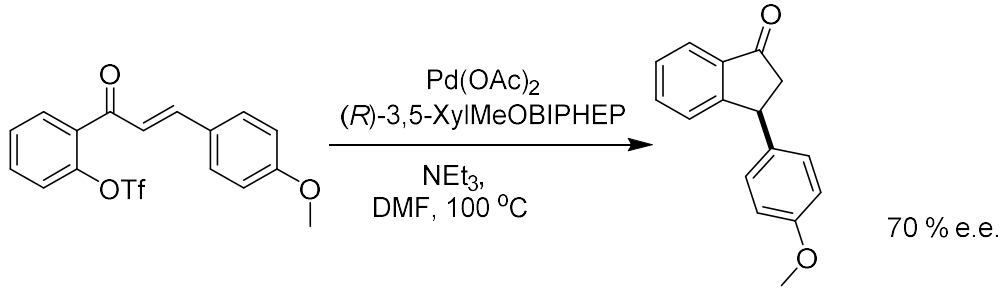
Improved results were obtained using the optimised (*R*)-3,5-XylMeOBIPHEP ligand, consistent with the literature.[216] Firstly, the triflate was synthesised via the method shown below in **Scheme 37**.



31 **32**

Scheme 37 – Synthesis of Triflyl-chalcone, **32**

The (*S*)-**26** product was formed in 36 % yield and 70 % e.e. from the Heck cyclisation, using the optimised ligand, (**Scheme 38**).



32 **(*S*)-26**

Scheme 38 – Reductive Heck-cyclisation using the (*R*)-3,5-XylMeOBIPHEP ligand

The results however, both obtained and in literature, demonstrated a lower enantiomeric excess for the naphthyl-chalcone species and electron donating species on the '*aldehyde*' aromatic ring. Consequently, given the desired indan-1-one derivatives, the general encouragement to continue this work was quite low, and thus was not continued further.

2.2.3 Conclusive Remarks – Initial Synthetic Reactions

In summary, the aforementioned results were relatively unattractive, based on the following drawbacks:

Chiral Auxiliary Method:

- Formation of a diastereomeric mixture (10 : 1), with difficult separation by silica column chromatography.
- Unable to cyclise the enantiomerically enriched 3,3-substituted propanoic acid by current literature methods

Reductive Heck Cyclisation

- Poor substrate applicability, given naphthyl substituents adjacent to the carbonyl, and electron donating substituents on the aromatic ring in the 3-position were generally unfavourable – resulting in poor enantiomeric excess
- Limitations for the introduction of the desired bromine moiety present in Compound 6-B345TTQ. Given the catalyst is palladium, this functionality will unlikely be tolerated in the transformation.[237]

Consequently, our attention turned towards kinetic resolution. The attractiveness of kinetic resolution for this project is discussed below in **Section 2.3**.

2.3 Kinetic Resolution

The goal of asymmetric synthesis – whether performed industrially or in an academic setting – is to prepare stereochemically enriched molecules in the most practical and efficient method possible. Nonetheless, the strategy is rarely simple, as the ways in which practicality and efficiency are defined are a consequence of a vast number of factors; reagent costs, time permitted/required, number of manipulations, specifications for product purity, availability of equipment and potential hazards, to name a few. Fundamentally, there are considered to be three different approaches,[238] defined as the following:

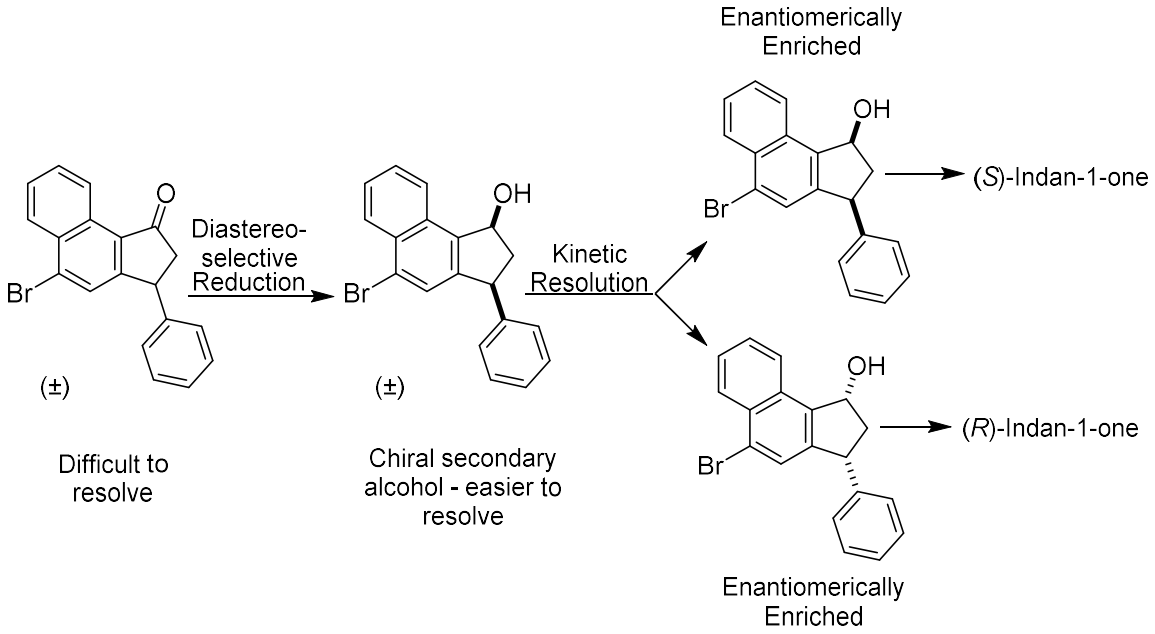
- Stereoselective synthesis (*chiral reagents or catalysts)*
- Making use of the chiral pool *(provided by nature)*
- Separation of enantiomers by physical or chemical means *(resolution)*

The chiral pool is unfortunately limited with respect to the target indanones, and attempted asymmetric manipulations have proven difficult given the preferred functional groups. For this reason, resolution was chosen as a vitally important strategy for accessing both single enantiomers.

Although in many instances, great effort has been directed towards avoiding such approaches as a result of perceived inelegance and inefficiency from poor atom economy, fortuitously for this project, both enantiomers can be achieved from one manipulation. In this project, both enantiomers are required, so chiral resolution is valuable and remains the focus of this chapter.

Proposal:

The strategy, once in possession of a small library of racemic indan-1-ones, was to kinetically resolve the racemic mixture, either directly from the indan-1-one, or from the corresponding indan-1-ol, into the respective enantiomers. A brief over of this resolution is shown below in **Scheme 39**.

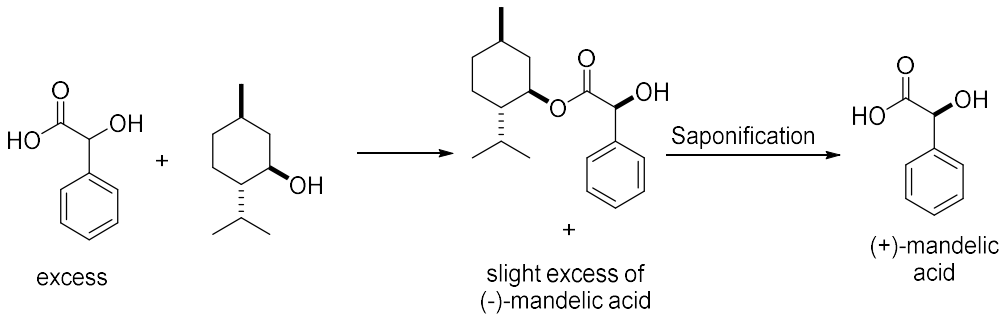


Scheme 39 – Kinetic resolution of racemic indan-1-ols

Current methods for related kinetic resolutions of indan-1-ol derivatives are discussed below. Furthermore, methods to synthesise the racemic indan-1-one or indan-1-ol structures required for the kinetic resolution are discussed further in **Section 2.3.2**.

2.3.1 Introduction to Kinetic Resolution

The first reported resolution was achieved as far back as 1858 by Louis Pasteur,[239] after reacting aqueous racemic ammonium tartrate with mould from *Penilicilium glaucum*. Chiral microorganisms contained in the mould were responsible for the selective metabolism of (*R*,*R*)-tartrate, leaving an excess of (*S*,*S*)-tartrate. Marckwald and McKenzie[240] provided the first kinetic resolution by synthetic means, with the esterification of racemic mandelic acid with optically active (-)-menthol.



Scheme 40 – First kinetic resolution by synthetic means; racemic mandelic acid

The importance of this observation paved the way for other successful resolutions of other chiral acids; dawning the emergence of kinetic resolution for a useful method in organic chemistry.[241-243]

Kinetic resolution is a means of differentiating two enantiomers in a racemic mixture, by means of a chiral catalyst or reagent (**Figure 21**).[244]

$$SM_R + SM_S \xrightarrow{chiral\ catalyst} P_R + SM_S \xrightarrow{separation} SM_S \quad P_R$$

Where;

$$SM_R \xrightarrow{k_R} P_R$$

$$SM_S \xrightarrow{k_S} P_S$$

Figure 21 - Kinetic resolution of a racemic mixture, SM

Under certain chiral circumstances, substrate enantiomers SM_R and SM_S react at different rates, k_R and k_S, affording enantiomeric products, P_R and P_S (or indeed, one unreacted enantiomer of the starting material, for example SM_S, depending on the resolution), respectively. This principle facilitates biological or chemical kinetic resolutions of racemic compounds.

While both enantiomers of the starting material, by definition, exist at the same Gibbs free energy level, as do to the enantiomeric products, P,[245] the transition state energy can differ. **Figure 22** shows an energy profile, where the reaction of the R enantiomer has a lower activation energy and thus would react faster than the S enantiomer.

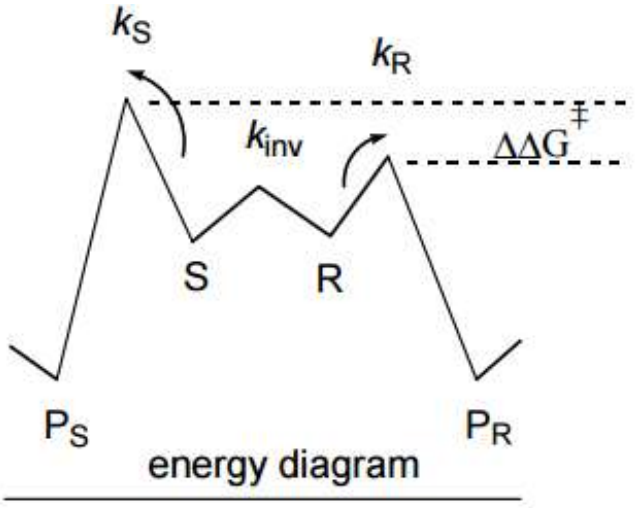


Figure 22 – Representative energy diagram for kinetic resolution

The energy difference between the high- and low-energy transition states, is defined as $\Delta\Delta G^{\ddagger}$.[238] The free energy difference, $\Delta\Delta G^{\ddagger}$, can be written in terms of the relative rates of reaction for each enantiomer, k_R / k_S, which can also be expressed as the selectivity factor, (**S**).[246] The selectivity of a kinetic resolution has been utilized for assessing this efficiency.[247-250]

The ideal kinetic resolution is that in which only one enantiomer reacts, for example, where $k_R \gg k_S$, then the selectivity of the kinetic resolution, being related to the rate constants of the reaction of the R and S enantiomers, can be expressed as the following:[251,252]

$$s = \frac{k_R}{k_S} = e^{\Delta\Delta G^{\ddagger} / RT} \qquad \textbf{Equation 1}$$

For simple first-order kinetics in substrate concentration, analytical solutions have been derived. The k_R / k_S ratio of **Equation 1** is correlated to the extent of substrate conversion, and the enantiomeric excess of the recovered substrate and product, ee_{SM} and ee_P respectively.[253]

$$\frac{k_R}{k_S} = \frac{\ln[(1-conv)(1-ee_{SM})]}{\ln[(1-conv)(1+ee_{SM})]} = \frac{\ln[1-conv(1+ee_P)]}{\ln[1-conv(1-ee_P)]} \qquad \textbf{Equation 2}$$

In enzyme catalysed kinetic resolution the enantioselectivity is normally expressed as the Enantiomeric Ratio, (**E**) value,[254,255] which corresponds to the ratio of specificity constants, demonstrated in **Equation 2**. The E value for irreversible enzymatic transformations is generally calculated using **Equation 3** and **Equation 4**.[253,256-259]

When the conversion is lower than 50 %, **Equation 3** applies:

$$E = \frac{\ln[1-conv(1+ee_P)]}{\ln[1-conv(1-ee_P)]} \qquad \textbf{Equation 3}$$

When the conversion is greater than 50 %, **Equation 4** applies:

$$E = \frac{\ln[(1-conv)(1-ee_{SM})]}{\ln[(1-conv)(1+ee_{SM})]} \qquad \textbf{Equation 4}$$

Where conv = conversion (%)/100; ee_p = e.e. of product / 100; ee_{sm} = e.e. of remaining starting material/100.

Equation 3 and **Equation 4** give reliable results for very low and very high extents of conversion, restricted by accuracies derived from sample manipulation. Consequently, the following equation is recommended as an alternative, because the only values that need to be measured are the optical purities (HPLC) of the substrate and product. The latter are deemed as relative quantities in contrast to conversion, which is an absolute quantity.[260]

$$E = \frac{ln\frac{(ee_P\,(1 - ee_{Sm})}{(ee_P + ee_{Sm})}}{ln\frac{[ee_P(1 + ee_{Sm})]}{(ee_P + \ ee_{Sm})}} \qquad \textbf{Equation 5}$$

Although the selectivity factor (s) is mathematically identical and thus synonymous to the E-value,[249,261] in chemo-catalysis, the selectivity factor is more widely used.[243,262,263] Product enantiomeric ratios can be regarded as moderate to good for selectivity factors of 15-30, while below this value they are not useful practical purposes, and above this range are considered excellent.[238]

It must be noted however, that values of E > 200 cannot accurately be determined, for reasons due to inaccuracies emerging from the determination of the enantiomeric excess.[264] Small variations or imprecisions by NMR, HPLC or GC, can cause a significant change in the numerical value of E.

Dynamic Kinetic Resolution:

Dynamic kinetic resolution can occur when a starting material has the ability to racemise easily during a reaction. The enantiomer with the lower barrier to activation has the potential to form, theoretically, up to 100 % yield of enantiomerically enriched product, in contrast to standard kinetic resolution, which has a maximum yield of 50 %. While a number of excellent methods are available,[265] including a variety of suitable racemisation agents,[266,267] it does depend on starting materials that can be racemised in the relevant reaction conditions.[268]

Practicality of Kinetic Resolution:

The following criteria present a recommendation for practical kinetic resolution:[238]

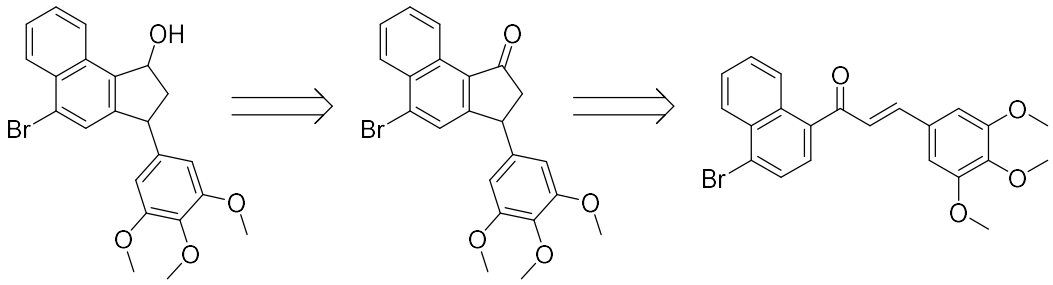
- Inexpensive racemate and/or catalyst
- Simple separation of racemic starting material
- Selective catalyst and low catalyst loading
- No appropriate direct enantioselective methods

The enantiomeric purity of products, P_R and P_S are limited by the degree of enantiomer discrimination in the reaction, however, when these are excellent, the kinetic resolution can be a worthy method to obtain P_R and P_S.[269] A range of catalysts and methodologies are present that satisfy the above criteria for indan-1-ols, and resolution techniques performed on these substrates are illustrated below.

2.3.2 Synthesis of 3-Aryl Indan-1-ones and Indan-1-ols

The strategy, once in possession of a small library of racemic indan-1-ones, was to kinetically resolve the racemic mixture, either directly, or from the corresponding indan-1-ol, into the corresponding enantiomers.

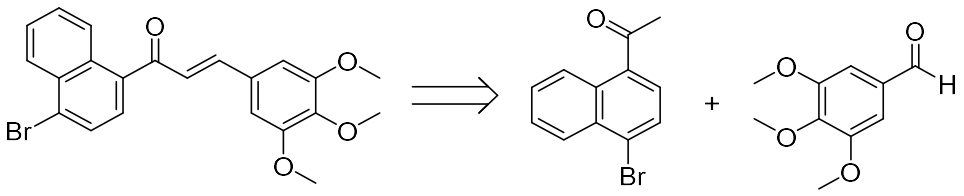
The indan-1-ols can be synthesised by the reduction of indanones, which in turn, can be made by a Nazarov cyclisation of chalcones. This transformation tolerates a number of functional groups relevant to this project, (**Scheme 41**).



Scheme 41 – Disconnection approach from indan-1-ol derivatives

(See **Section 2.3.2.4** and **2.3.2.3** respectively)

The chalcone compounds can be synthesised by a Claisen-Schmidt condensation reaction of an acetophenone and an aromatic aldehyde (**Scheme 42**).



Scheme 42 – Synthesis of racemic indan-1-ones from the corresponding

(See **Section 2.3.2.2**)

The Nazarov cyclisation reaction is accelerated by electron-donating groups in the aromatic ring at the 1-position of the chalcone structure.[270] Consequently, for testing the Nazarov reaction on similarly related structures, the commercially available 3′-methoxyacetophenone was used (**Figure 24**). Indan-1-ones with electron donating substituents have been synthesised in the literature, including two trimethoxy-indan-1-one derivatives with potential anti-cancer activity (**Figure 23**).[169] As these have only been reported as racemic compounds, it would be interesting to test whether this can be made asymmetrically by the methods presented below.

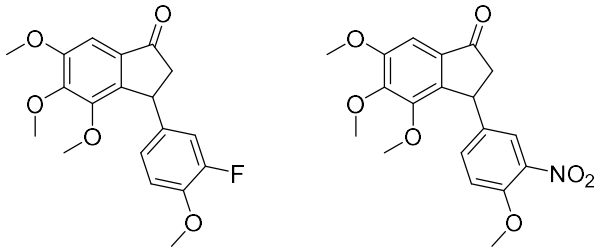


Figure 23 – Examples of electron donating indanone substituents with biological activity

Consequently, these commercially available acetophenones were used to test the following reactions, but would additionally provide a small catalogue of similarly related compounds to the desired 6-B345TTQ indan-1-one precursor. Moreover, we were interested in testing these analogues for biological activity.

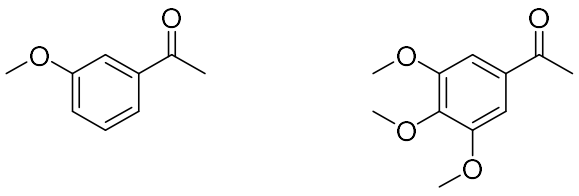
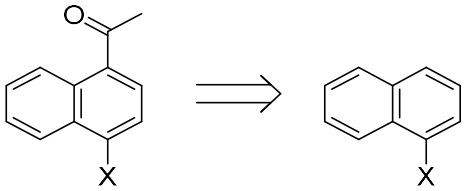


Figure 24 – Commercially available electron donating acetophenone substituents used in this project (3-methoxyacetophenone and 3,4,5-trimethoxyacetophenone)

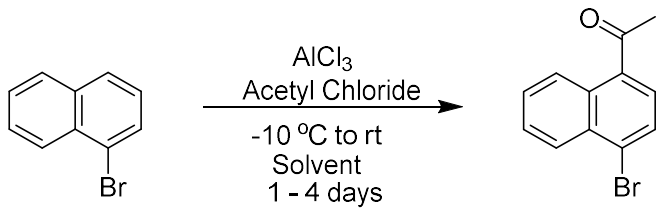
1-Acetyl-4-halonaphthalene substituents are not commercially available. This disconnection for their synthesis would involve a Friedel-Crafts acylation of the corresponding 1-halonaphthalene (**Scheme 43**)



Scheme 43 – Disconnection approach for the 1-acetyl-4-halonaphthalen-1-one

2.3.2.1 Friedel-Crafts Acylation of Halo-naphthalenes

Although 4′-haloacetophenones have been synthesised via Sandmeyer-type reactions on 4′-amino-1′-acetophenones,[271-273] from the corresponding aryl triflates[274] or boronic acids[275]; a more common and practical approach involved a Friedel-Crafts acylation from readily available 1-halonaphthalenes.[276-281]



Scheme 44 – Friedel-Crafts acylation: synthesis of 1′-acetyl-4′-bromonaphthalene

This method was further considered advantageous over bromination of the appropriate aryl ketone,[282] where the 4′-isomer is a minor product amongst a variety of others.[283]

Conditions for this Friedel-Crafts transformation remained fairly consistent over various literature reports, albeit the use of dichloromethane as the solvent in contrast to carbon disulfide[281] offered a minor improvement in yield (*62-91 % yield, >95 % selectivity*). Under certain conditions, notably with $AlCl_3$ and CCl_4 as the solvent, it was found that 1-chloronaphthalene isomerised to the 2-isomer upon standing.[284] Although Schweitzer[285] first prepared a bromoacetonaphthone by the reaction shown in **Scheme 44** in carbon disulfide, the structure was not proven. It was not until Dziewonski and Sternbach[286] carried out the same reaction and demonstrated that 4′-bromo-1′-acetonaphthone was the principal product by oxidation to the corresponding known 4′-bromo-1′-naphthoic acid.

This regioselectivity is unexpected when one appreciates the inherent substituent effects. When the substituent at the 1-position is an electron-donating group, it will subsequently activate the ring to which it is attached, stabilising any substitution in an *ortho* or *para* position. Similarly an electron-withdrawing group will have the opposite effects.

Based on experimental data, halogens exhibit a negative inductive effect (-*I*), with a positive mesomeric effect (+*M*), offering a substituent effect of modest positivity.[287] The opposite effects exhibited for halogens for -*I* and +*M* causes partial cancellation, but overall causes deactivation of the aromatic system. The *meta* positions experience more of this substituent effect (compared to *para*, **Table 5**), due to the fact that the mesomeric effect is greatly reduced in a meta substituent. Therefore, halogen substituents are *ortho / para* directing, but deactivate the ring.

Table 5 – Hammett values derived from the dissociation constants of benzoic acids[287-289]

Substituent	σ_{para}	σ_{meta}
Bromo-	0.232	0.352
Chloro-	0.227	0.373
Fluoro-	0.062	0.337

Normally, for a benzene system, a chloro-substituent is thus expected to deactivate the aromatic ring by a combination of –*I* and +*M* mechanism, where I > M, and thus overall deactivation ensues.[290]

For a 1-halo-naphthalene, one would therefore expect electrophilic aromatic substitution to occur in the non-substituted ring. **Table 6** below shows some literature Friedel-Crafts acylations on 1-chloronaphthalene, demonstrating an effect of solvent and temperature on the ratio of isomers formed.[291]

Table 6 – Friedel-Crafts acetylations of 1-chloronaphthalene by the Perrier procedure[a]: effect of solvents on isomeric composition[291]

Solvent	Temp. (°C) [b]	Isomers (%)						
		2-	3-	4-	5-	6-	7-	8-
$CHCl_3$	20	3.6	2.4	79.8	4.4	4.8	4.4	0.56
CH_2Cl_2	20	2.8	2.5	83.3	3.8	3.7	3.5	0.40
$C_2H_4Cl_2$	20	2.4	2.9	81.1	3.7	8.1	1.3	0.63
CS_2	20	3.8	4.5	83.6	3.8	2.0	1.5	0.73
$MeNO_2$	20	22.0	0.04	62.3	2.7	5.4	5.3	2.3
$PhNO_2$	4	20.3	0.76	32.5	9.5	21.3	15.5	0.053
$PhNO_2$	20	12.9	1.0	36.9	6.0	25.0	18.2	0.042

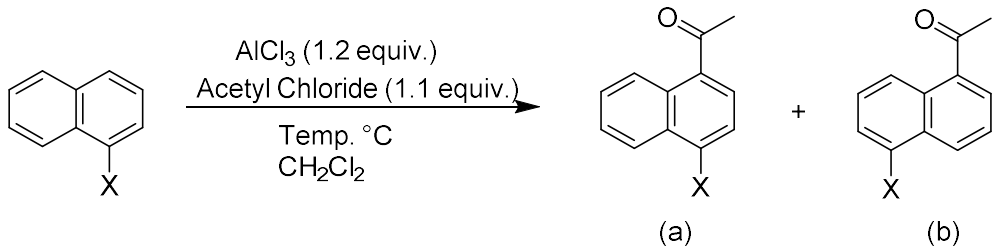
[a] The Perrier procedure involves final addition of substrate to the pre-formed complex of acyl chloride and aluminium chloride in the solvent; [b] Duration 6h.

Furthermore, the nitration of 1-chloronaphthalene was observed to give isomers; 1,4- (31-63 %), 1,8- (30-65 %) and 1,5- (0-20 %),[292] with sulfonation which gave a mixture of 1,4- and 1,5-compounds.[293] Similarly, sulfonation of 1-fluoronaphthalene appeared to give exclusively 4-substitution,[294] and 1-bromonaphthalene nitrates in the 4-position,[293] highlighting the unpredictability. In contrast with reports from nitrations, where substantial (*ca*. 40 %) of 1′-chloro-8′-nitronaphthalene was reported,[295] *peri*-acetylation is subject to serious hindrance (C1-8 *peri* interaction),[296] analogous to 1-methylnaphthalene acetylations, where it was not formed at all.[297]

Results & Discussion

The desired 4′-halo-1′-acetonaphthones were synthesised using aluminium chloride as a Lewis acid, acetyl chloride and the appropriate 1-halonaphthalene in dichloromethane. **Table 7** shows the effect of temperature on the ratio of obtained isomers for this transformation; (1,4- vs 1,5-isomers).

Table 7 - Friedel-Crafts acetylation of 1-*halo*-naphthalenes with aluminium chloride catalyst



Substituent X	Temperature (°C) [a]	Ratio (a : b) [b]	Yield (a) [c]	
Br	20	80 : 20	- [d]	
Br	0	88 : 12	- [d]	
Br	-10	>95 : 5	62	**35**
Cl	-10	>95 : 5	96	**34**
F	-10	>95 : 5	84	**33**

[a] Temperature controlled by a thermostat water bath containting antifreeze; [b] Ratio determined by ^{1}H NMR; [c] Isolated yield after column chromatography; [d] Yield was not isolated for this isomeric mixture.

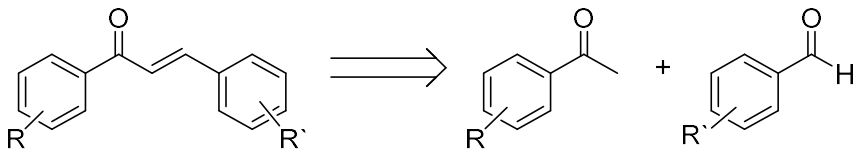
Although other isomers were likely produced in small quantities, seemingly from the very small peaks present on the baseline (crude ^{1}H NMR spectrum), they were not easily distinguishable nor isolatable from the crude mixture. Reducing the temperature showed an increased preference for substitution at the 4-position.

The ratio (a : b) was determined by ^{1}H NMR spectrometry, using the integration of the CH_3 peak at 2.73 and 2.75 ppm respectively.[279] In contrast to previous literature reporting this isomeric mixture to be the 4-(*major*) and 2-(*minor*) products,[281] comparison of the chemical shifts to that of the 2-acylated isomer,[298] found the CH_3 peak for this latter isomer to be further up-field at 2.58 ppm, suggesting it was not a product. The reactivity of the *peri*- (8-) position of 1-halonaphthalene was not observed at all in the Friedel-Crafts acetylation reaction conducted at -10 °C (**Table 7**), and reassuringly was reported in the literature showing only small amounts in a variety of solvents performed at 20 °C (**Table 6**) on 1-chloronaphthalene.[291]

Pure 4′-bromo-1′-acetylnaphthone was isolated as a beige solid, rather than a brown oil as reported.[281,299] Nonetheless, the reaction gave the appropriate 4′-halo-1′-acetonaphthones for the Claisen-Schmidt Condensation in good yields and excellent selectivity (>95 % acetylation in the 4-position).

2.3.2.2 Claisen-Schmidt Condensation towards Substituted Chalcones

For the synthesis of substituted chalcones as a precursor to the desired indan -1-ones moiety, the following disconnection was applied, shown below in **Scheme 45**.



Scheme 45 – Disconnection approach of substituted-chalcones

Discussion on the Chalcone Moiety, the Synthesis and Application

Chalcone derivatives were synthesised according to common literature procedures.[146] The chalcone moiety is a common substructure in a number of different natural products belonging to the flavonoid family.[300-302] Chalcone derivatives are very versatile as pharmaceutically active compounds and substrates for the evaluation of various organic syntheses.[303] With the chalcone moiety having such varied pharmacological activity, the attraction for medicinal chemists has therefore presented several strategies in the development of chalcones.

First reported by Claisen[304] and Schmidt[305] concurrently in 1881, this reaction is essentially the condensation of an aromatic aldehyde with a ketone (or indeed, another aldehyde[306]), in the presence of both an acid or a base, to form an α,β-unsaturated ketone with high chemoselectivity.[307] The reaction, identical to the Aldol condensation[306,308], is generally known as the Claisen-Schmidt condensation,[309-311] or Claisen-Schmidt reaction.[312-314]

This method has found a vast use in pharmaceuticals,[315] and has subsequently been utilised in the synthesis of a 644-member library of chalcones, by a parallel synthesis from substituted acetophenones and benzaldehydes.[308,316,317]

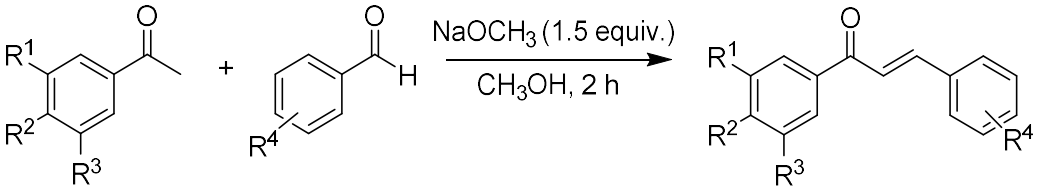
The principal synthetic route to these chalcone are classically catalysed by strong acids,[318,319] and more likely by base, both with or without solvents.[313,320-323] Various reagents have been introduced, using a variety of catalysts, including: solid NaOH,[320] BF_3OEt_2,[324] $InCl_3$,[325] TMSCl/NaI,[326] $Cu(OTf)_2$,[327] $RuCl_3$,[328] $FeCl_3$,[329] SmI_3,[330] molecular iodine[331] or $SOCl_2$.[332] Additionally, microwave irradiation methods have also been reported, offering significant reductions in reaction time.[333] Catalysts include: KF-Al_2O_3,[334] NaOH-Al_2O_3,[335] acidic alumina[335] or bis(*p*-methoxyphenyl)telluroxide.[336]

Many of these methods involve expensive, toxic or hazardous catalysts, or with long reaction times. Aside from these examples, some facile yet versatile methods exist for the preparation of substituted chalcone derivatives.[146]

Results & Discussion:

Within the current study, chalcone derivatives were synthesised according to common literature procedures,[146] (**Table 8**). The reaction tolerated both electron-donating and withdrawing substituents, although for electron withdrawing aldehyde-substituents (4-F and 4-Cl), an alternate method was employed, using a potassium hydroxide solution in methanol, to avoid nucleophilic aromatic substitution.[337]

Table 8 – Claisen-Schmidt Reactions towards substituted methoxychalcones

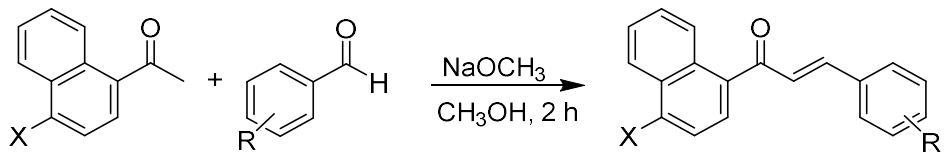


R^1	R^2	R^3	R^4	Temp. (°C)	Yield (%) [a]	Chalcone
OCH_3	H	H	H	20	91	**36**
OCH_3	H	H	4-OCH_3	20	87	**37**
OCH_3	H	H	3,4-OCH_3	20	63	**38**
OCH_3	H	H	3,4,5-OCH_3	20	95	**39**
OCH_3	H	H	2,3,4-OCH_3	20	97	**40**
OCH_3	H	H	4-F	50 [b]	96	**41**
OCH_3	H	H	4-Cl	50 [b]	56	**42**
OCH_3	OCH_3	OCH_3	3-F, 4-OCH_3	20 [b]	94	**57**
OCH_3	OCH_3	OCH_3	3-NO_2, 4-OCH_3	20	99	**58**
H	Br	H	3,4,5-OCH_3	20	86	**43**

[a] Isolated yield; [b] Reaction performed with aqueous KOH (15 % m/v) instead of $NaOCH_3$ to avoid nucleophilic aromatic substitution.

Similarly, chalcone derivatives were synthesised from the corresponding 1′-acetyl-4′-halonaphthylenes derivatives formed in **Section 2.3.2.1**, shown below in **Table 9**.

Table 9 – Claisen-Schmidt Condensation of Substituted 1-Acetylnaphthalenones



Entry	Ketone	X Group	R Groups	Temperature (°C)	Yield (%) [a]	Chalcone
1	**35**	Br	H	20	98	**48**
2	**35**	Br	4-OCH_3	20	97	**49**
3	**35**	Br	2,3-OCH_3	20	81	**50**
4	**35**	Br	3,4-OCH_3	20	85	**51**
5	**35**	Br	3,5-OCH_3	20	75	**52**
6	**35**	Br	2,3,4-OCH_3	20	99	**54**
7	**35**	Br	3,4,5-OCH_3	20	99	**53**
8	**35**	Br	4-F	20 [b]	55	**55**
9	**35**	Br	4-Cl	20 [b]	82	**56**
10		H	H	20	92	**44**
11		H	3,4,5-OCH_3	20	95	**45**
12	**33**	F	3,4,5-OCH_3	20 [b]	81	**46**
13	**34**	Cl	3,4,5-OCH_3	20 [b]	84	**47**

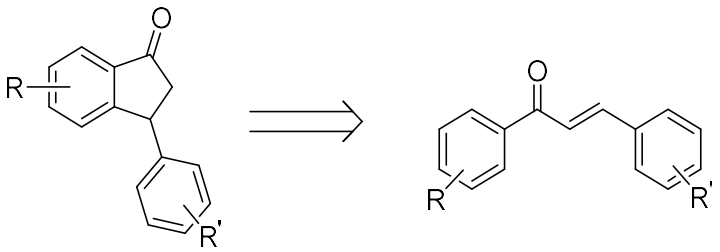
[a] Isolated yield; [b] Reaction performed with aqueous KOH (15 % m/v) instead of $NaOCH_3$ to avoid nucleophilic aromatic substitution.

The more thermodynamically stable *trans*-geometry was confirmed by ^{1}H NMR spectrometry, by inspection of the coupling constants for the vinylic CHs (CH-2 and CH-3). Chalcones predominantly exist as the *E*-isomer, with the configuration of the *Z*-isomer generally being less stable, due to strong steric effects between the carbonyl and 3-aryl-group.[233]

In summary, a variety of substituted chalcones have been synthesised in a simple manner, yielding exclusively *trans*-isomers. Moreover, the substrates were easily isolated, in most cases, by simple filtration from the reaction mixture.

2.3.2.3 Nazarov Reaction of Substituted Chalcones

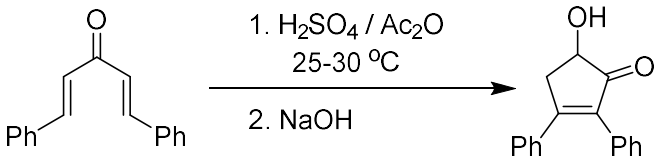
The synthesis of substituted indan-1-ones involves a Nazarov cyclisation, and a disconnection for this approach is shown below in **Scheme 46**.



Scheme 46 – Disconnection approach of substituted indan-1-ones

Discussion on the Nazarov Reaction

In 1903, Vorländer and co-workers found that treatment of dibenzylideneacetone with concentrated sulfuric acid and acetic anhydride and subsequent hydrolysis by sodium hydroxide yielded a cyclic ketol, the structure of which being unknown at the time (**Scheme 47**).[338]

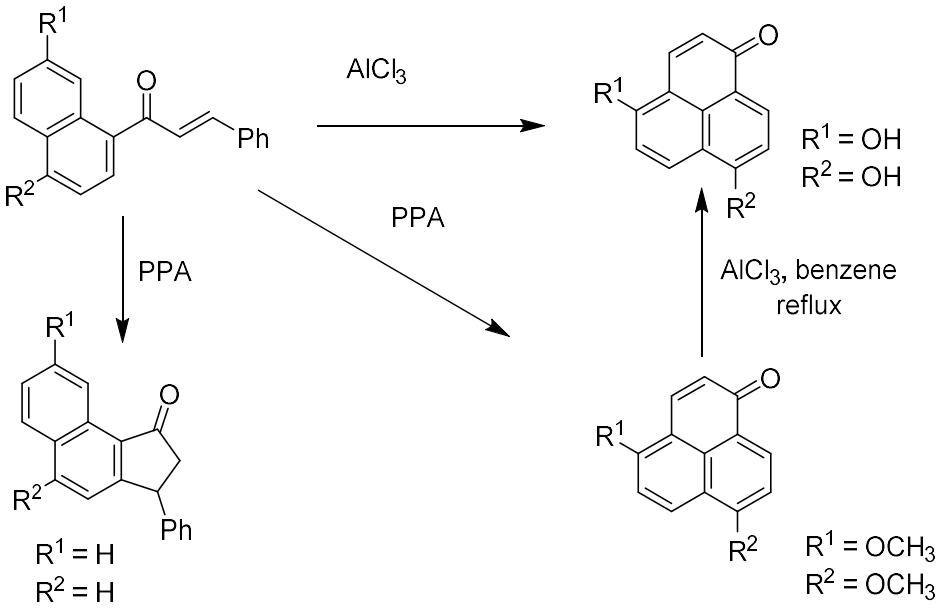


Scheme 47 – Cyclisation observed by Vorländer and co-workers

Later in the 1940s and 1950s, Nazarov et al. revisited the topic and extensively studied the cyclization, particularly cyclization of the intermediate allyl vinyl ketones to the corresponding 2-cyclopentenones.[339, 340, 341] Braude and Coles proposed a carbocation intermediate as a consequence of acid protonation on the sites of unsaturation,[342] however it was not until 1967 when Woodward, through deuterium labelling, confirmed the pericyclic cyclization occurred in a conrotatory fashion.[343]

Indan-1-ones have also been synthesised via a Nazarov reaction, catalysed by strong acids. Catalysts have included; polyphosphoric acid (PPA),[344-347] $AlCl_3$,[270,348] trifluoroacetic acid (TFA),[169,189-191,349] trifluoromethanesulfonic acid (TFMSA),[350] cupric triflate,[187] methanesulfonic acid (MSA),[187] $BF_3.OEt_2$,[351] sulfuric acid,[352] and a HUSY-zeolite catalyst.[193] It is believed that P_2O_5 is the active cyclisation agent in PPA.[188]

The acid-catalysed cyclisations of naphthyl-chalcone derivatives is reported to proceed at either the 2- or 8-position of the naphthyl-ring, according to either substituent or catalyst changes.[353]

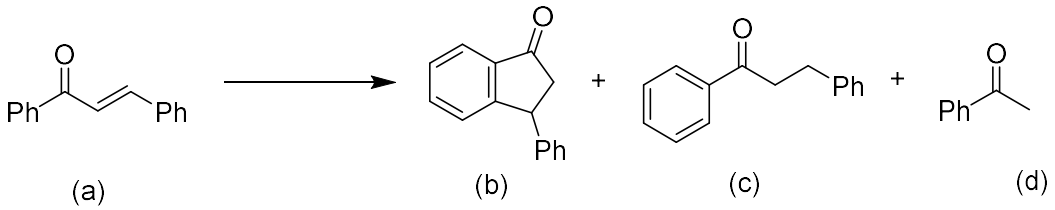


Scheme 48 – Catalyst and substrate effect on 2- and 8-position selectivity[353]

Substituents with electron donating groups in the 4- and 7-positions were found to cyclise chiefly at the 8-position. It is not known if $AlCl_3$ was responsible for the selectivity in this cyclisation as only ring substituted methoxy- groups were tested.[346]

Results & Discussion

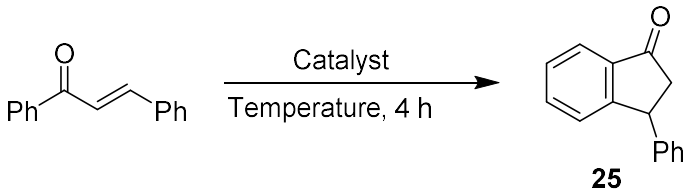
Within this study, the Nazarov reaction was performed using trifluoroacetic acid as the catalyst.[354] An attempted improvement of the transformation was attempted (**Table 10**), to minimise some observed side-products (**Scheme 49**), such as the intermolecular 2,3-dihydrochalcone product (c),[201] or the *retro*-Claisen Schmidt product (d).[189] The observation of these side products were in the ^{1}H NMR spectrum of the crude reaction product, comparable to literature values.



Scheme 49 – Observable side-products (c) and (d)

The synthesis of 3-phenyl indan-1-one, **25** using trifluoroacetic acid was problematic, and ^{1}H NMR analysis of the crude reaction mixture showed approximately 20 % acetophenone product, possibly formed by a water promoted retro-Claisen-Schmidt reaction. Adding phosphorus pentoxide to the reaction reduced the formation of this by-product.[355] A combination of trifluoroacetic acid with phosphorus pentoxide offered the best yield of the desired 3-phenyl indan-1-one, **25** (**Table 10**, **Entry 4**), and consequently this method was used thereafter.

Table 10 – Optimisation of the Nazarov Cyclisation of *trans*-chalcone



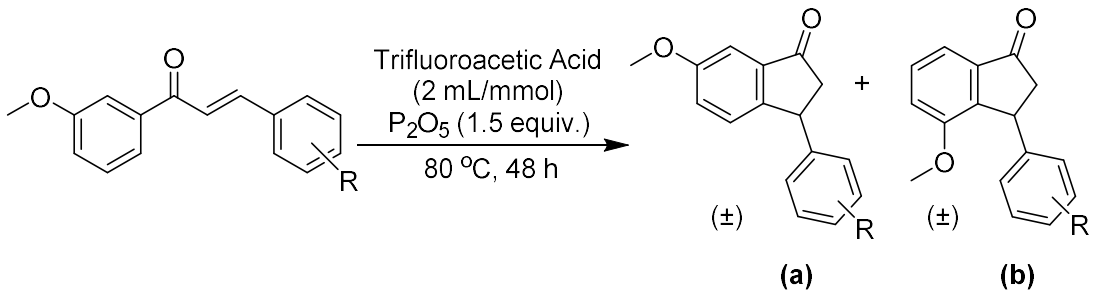
25

Entry [a]	Catalyst / Conditions	Temperature (°C) [b]	Yield %[c]
1	PPA (2 equiv.)[e]	136	31
2	P_2O_5 (2 equiv.), in toluene	110	14
3	TFA (2 mL/mmol)	73	32
4	TFA : P_2O_5 (2 mL/mmol, 2 equiv.)	73	54
5	TFA : $AlCl_3$ (2 mL/mmol, 2 equiv.)	73	35
6	Eatons Reagent (2 equiv.)[f]	73	-

[a] Reaction based on chalcone (1.00 g, 4.8 mmol); [b] Temperature monitored via an internal thermometer; [c] Isolated yield; [e] PPA containing 2 equivalents of P_2O_5, based on 100 % PPA (72.4 % P_2O_5 content); [f] Eaton's reagent, P_2O_5 : methanesulfonic acid (1 : 10), with P_2O_5 content at 2 equivalents.

The Nazarov reaction of 3′-methoxy substituted chalcones, shown below in **Table 11**, formed both the 6-methoxy- and 4-methoxy-3-aryl-indan-1-one derivatives, consistent with literature reports.[348,356] The ratio was determined by ^{1}H NMR spectrometry, in comparison with literature examples. The desired 6-methoxy-3-aryl-indan-1-ones were separated from the mixture by column chromatography.

Table 11 – Nazarov Reactions of 3′-methoxy-substituted chalcones

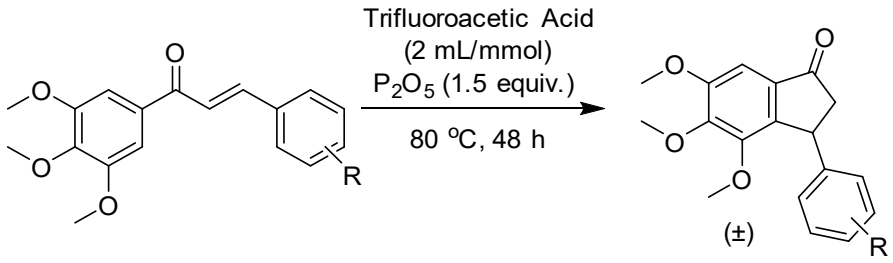


Chalcone	R Groups	Ratio a : b [b]	3′-Methoxy Indan-1-one	
			Yield % [a]	
36	H	17 : 1	84	**59**
37	4-OCH_3	17 : 1	41	**60**
38	3,4-OCH_3	17 : 1	38	**61**
39	3,4,5-OCH_3	- [c]	35	**62**
40	2,3,4-OCH_3	10 : 1	24	**63**
41	4-F	11 : 1	87	**64**
42	4-Cl	12 : 1	84	**65**

[a] Isolated yield; [b] Isomer % determined by ^{1}H NMR prior to purification; [c] Not deducible from crude ^{1}H NMR.

Electron donating substituents on the 3-aryl ring impeded the cyclisation, resulting in much lower yields. Conversely, increased electron density on the 1-aryl ring were found to greatly improve the reaction yield (**Table 12**), possibly by stabilising the positive-charge character in the intermediate.[357]

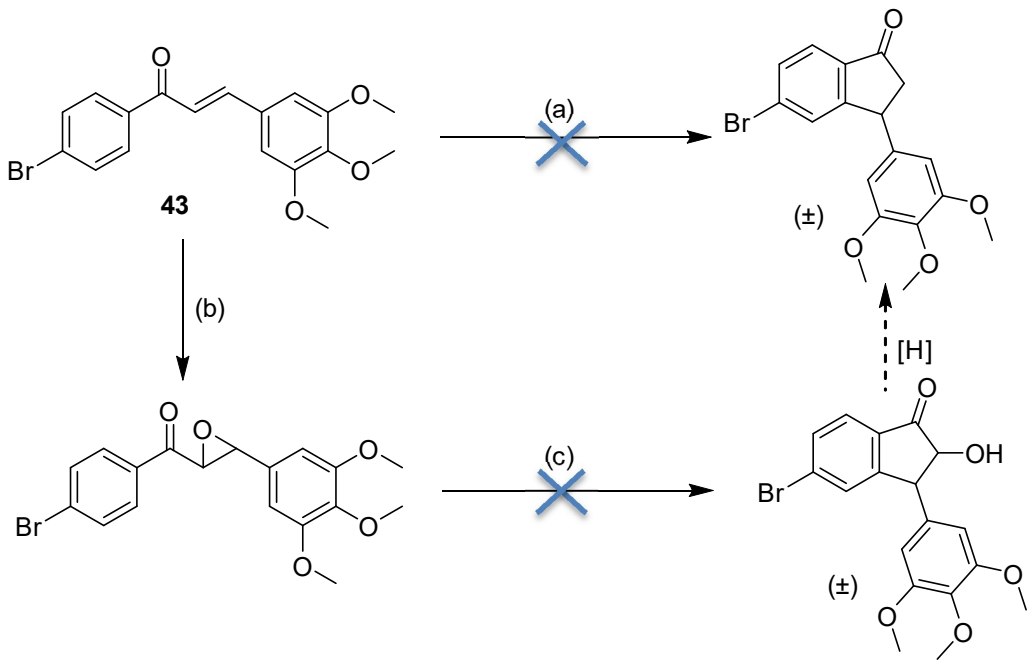
Table 12 – Nazarov Reactions on 3′,4′,5′-trimethoxy-substituted chalcones



Chalcone	R Groups	Yield % [a]	Indan-1-one
57	3-F, 4-OCH_3	72	**66**
58	3-NO_2, 4-OCH_3	85	**67**

[a] Isolated yield.

Attempts at the Nazarov cyclisation using the optimised reaction conditions for substrate **43** were unsuccessful. An alternate route[195] via the chalcone-epoxide, also proved ineffective, (**Scheme 50**).

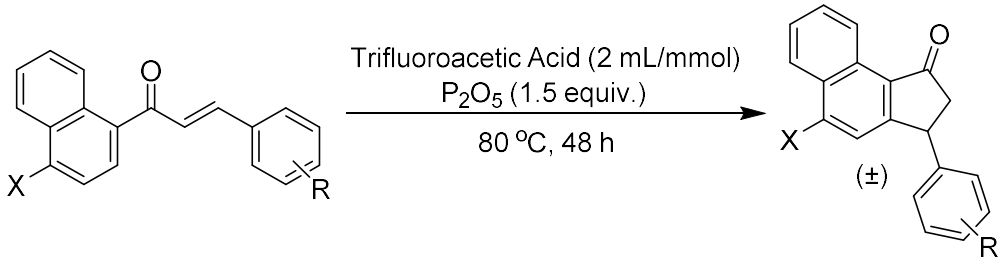


Scheme 50 – Attempted synthesis of indan-1-one compound

(a) TFA (2 mL/mmol, P_2O_5 (1.5 equiv.); (b) H_2O_2 (30 wt%), NaOH (5M sol.); (c) $InCl_3$, CH_2Cl_2.

Similar results were found for the Nazarov cyclisation of naphthyl- chalcone derivatives regarding the electron donating and withdrawing character of substituents. The cyclisation only occurred in the 2-position, consistent with the literature, rather than the 8-position, found with other catalytic systems.[353] However, even after multiple attempts, the transformation of the 3,5-dimethoxy derivative, **52**, to the corresponding naphthalen-1-one was unsuccessful. These results for the naphthyl-derivatives are shown below in **Table 13**.

Table 13 – Nazarov Reactions on substituted naphthyl- chalcones

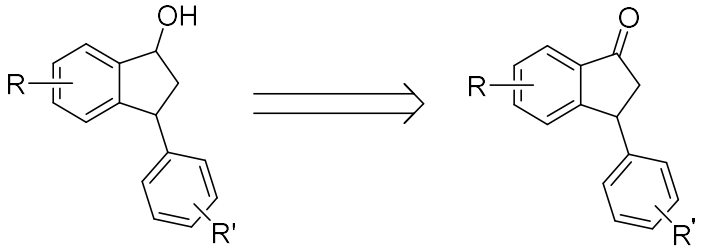


Chalcone	X Group	R Groups	Yield % [a]	Indan-1-one
48	Br	H	70	**72**
49	Br	4-OCH_3	30	**73**
50	Br	2,3-OCH_3	28	**74**
51	Br	3,4-OCH_3	28	**75**
52	Br	3,5-OCH_3	- [b]	
54	Br	2,3,4-OCH_3	24	**77**
53	Br	3,4,5-OCH_3	30	**76**
55	Br	4-F	72	**78**
56	Br	4-Cl	76	**79**
44	H	H	62	**68**
45	H	3,4,5-OCH_3	41	**69**
46	F	3,4,5-OCH_3	31	**70**
47	Cl	3,4,5-OCH_3	33	**71**

[a] Isolated yield, [b] No product isolated.

2.3.2.4 Selective *cis*-Reduction of Racemic Indan-1-ones

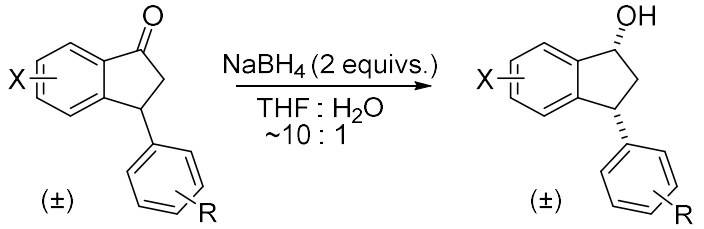
The planned synthesis of substituted indan-1-ols would occur via reduction of the indanone carbonyl group, with a disconnection shown below in **Scheme 51**.



Scheme 51 – Disconnection approach of substituted-indan-1-ols

Discussion on the Reductive Methods for the Indan-1-one Moiety

Reduction of the racemic 3-aryl indan-1-ones (**Scheme 52**), with sodium borohydride was shown to yield only the *cis*-diastereoisomers.[344,358] In contrast, the corresponding 4-phenyl-1-tetralone analogues are reported to be reduced as a mixture of *cis*- and *trans*-diastereoisomers.[358]

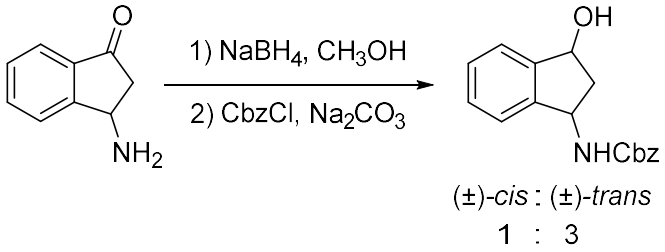


Scheme 52 – Sodium borohydride *cis*-reduction of some dopamine-uptake inhibitor precursors

Compounds with X = H, 3-Cl, 4-Cl, 4-F or 4-OCH_3 were all reported to react to give *cis*-isomers exclusively. A variety of R-groups also had little effect on the high stereoselectivity.[358]

A recent patent additionally demonstrated the use of sodium borohydride towards the synthesis of some deuterated 1-piperazino-3-phenyl-indanes for the treatment of schizophrenia.[359] This selectivity has also been observed with some other pharmaceutically important compounds.[360]

While this selectivity is well known, 3-acylamino indan-1-ones react with the *trans*-diastereoisomer as the major product, **Scheme 53**.[361]



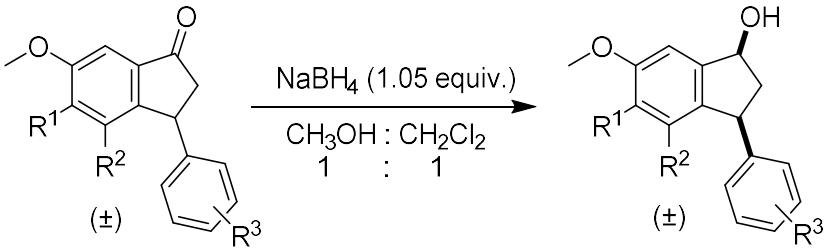
Scheme 53 – Borohydride reduction of 3-aminoindan-1-ols

The moderate diastereoselectivity observed can be explained by the initial reaction between borohydride and the free amino group to form the corresponding boramide. In good agreement with previously published results,[362] this would favour an intramolecular reduction, leading to a *trans*- configuration. Furthermore, both *cis*- and *trans*- stereochemistry was confirmed by X-ray crystallography.[361]

Results & Discussion

Given the high selectivity reported[344] for a *cis*-reduction of indan-1-ones using sodium borohydride, this method was applied with excellent selectivity for the substituted indan-1-one structures. The results bearing methoxy-substituents on the indan-ring are shown below in **Table 14**.

Table 14 – Selective *cis*-reduction of racemic 6-methoxy-3-arylindan-1-ones

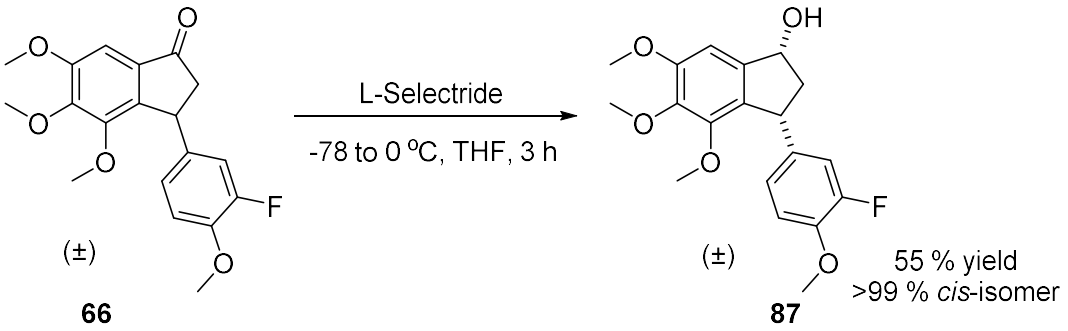


rac-Indan-1-one			*rac*-Indan-1-ol	
	R^1/R^2	**R^3**	**Yield %** [a]	
59	H	H	98	**80**
60	H	4-OCH_3	77	**81**
61	H	3,4-OCH_3	71	**82**
62	H	3,4,5-OCH_3	70	**83**
63	H	2,3,4-OCH_3	66	**84**
64	H	4-F	80	**85**
65	H	4-Cl	91	**86**
66	OCH_3	3-F, 4-OCH_3	65 [b]	**87**
66	OCH_3	3-F, 4-OCH_3	55 [c]	**87**
67	OCH_3	3-NO_2, 4-OCH_3	51 [d,e]	**88**

[a] Isolated yield. [b] Formed in an inseparable *cis*- / *trans*- ratio of 4 : 1; [c] L-Selectride method used,[363] giving exclusively the *cis*-isomer; [d] Formed in a separable *cis*- / *trans*- ratio of (4 : 1); [e] Isolated yield of *cis*-isomer.

R^3 substituents mostly appear to have little effect on the outcome of the *cis* : *trans*- ratio. The *cis*-isomer (**80** and **86**) was deduced by comparison with results obtained in the literature,[361] with others by analogy.

The presence of multiple methoxy-substituents on the indanone-ring (4,5,6-methoxy) had a noticeable, yet minor effect on the selectivity of the *cis* : *trans* relationship, producing the diastereoisomers in a 4 : 1 ratio for **87** and **88**. Attempts at lowering the temperature and performing the reduction at -78 °C had a slight improvement on this ratio, producing the indan-1-ol **87** in a *cis*-/*trans*- ratio of 5 : 1. Although the stereoisomers could be separated by standard silica column chromatography for the 3-nitro-4-methoxy-3-aryl indanol, **88**, a more difficult situation arose trying to separate the similarly related 3-F, 4-OCH_3 substituent, **87**. Consequently, an alternative, more selective reductive method was applied, using the more sterically demanding L-Selectride reducing agent.[363,364] Application to substrate **87**, is shown below in **Scheme 54**.

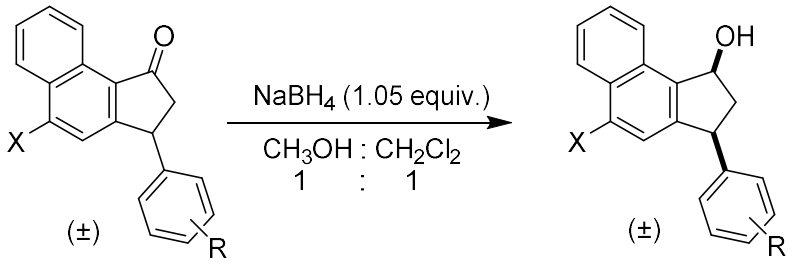


Scheme 54 – Reduction of 3-(3′-fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one, using L-Selectride at -78 °C

Although the reaction was deemed less 'clean' from inspection of the ^{1}H NMR spectrum of the crude reaction mixture with a comparably lower yield to that of sodium borohydride, the *cis*-isomer was formed exclusively.

The sodium borohydride method however was successfully applied to all the naphthalen-1-one derivatives, (**Table 15**), with outstanding selectivity, yielding exclusive *cis*-isomers in all cases.

Table 15 – Selective *cis*-Reduction of Substituted Indan- and Naphthalen-1-ones



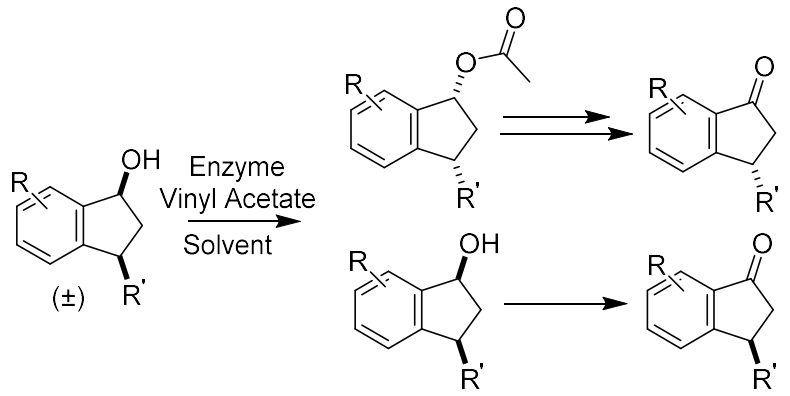
rac-Indan-1-one			*rac*-Indan-1-ol	
	X Groups	**R Groups**	**Yield %** [a]	
72	Br	H	81	**93**
73	Br	4-OCH_3	91	**94**
74	Br	2,3-OCH_3	73	**95**
75	Br	3,4-OCH_3	89	**96**
77	Br	2,3,4-OCH_3	82	**98**
76	Br	3,4,5-OCH_3	88	**97**
78	Br	4-F	64	**99**
79	Br	4-Cl	92	**100**
68	H	H	87	**89**
69	H	3,4,5-OCH_3	61	**90**
70	F	3,4,5-OCH_3	57	**91**
71	Cl	3,4,5-OCH_3	60	**92**

[a] Isolated yield.

In summary, the sodium borohydride reduction method[344] produced all the corresponding indan-1-ol derivatives with good yields and excellent *cis*-selectivity. For more demanding substituents, **87**, the L-Selectride reagent proved effective.

2.4 Kinetic Resolution – Enzymatic Acylation

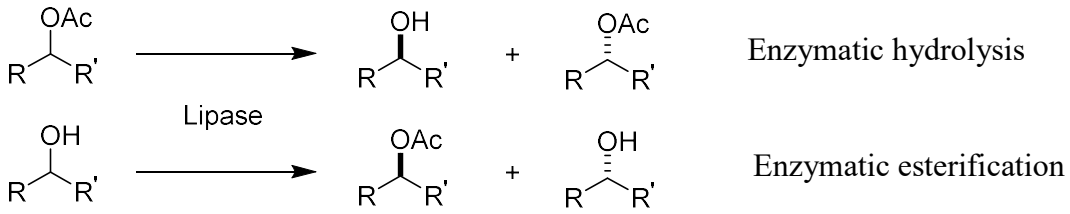
For the kinetic resolution of racemic *cis*-3-aryl indan-1-ols, the following resolution was proposed, using an enzymatic acylation process (**Scheme 55**).



Scheme 55 – Proposed enzymatic kinetic resolution for substituted indan-1-ols

Enzymatic routes are often more attractive than the conventional counterparts from an environmental and economic standpoint.[365] From academic curiosity to standard practice, biocatalysts have proven their effectiveness, even on an industrial scale.[366,367]

Lipases are a particularly well-established assembly of enzymes for the kinetic resolution of racemic alcohols, both in aqueous and non-aqueous media. Lipases can catalyse both hydrolysis and esterification reactions towards chiral alcohols.[368-372]

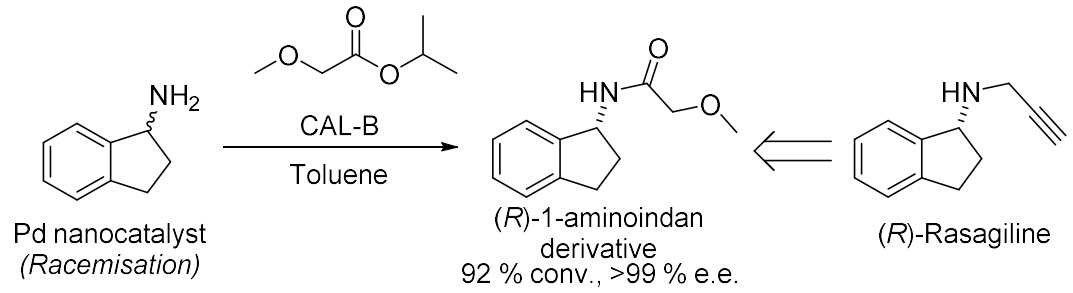


Scheme 56 – Lipase-catalysed hydrolysis & esterification

As with chemo-catalysed kinetic resolution procedures,[373,374] enzymatic acylation kinetic resolution has seen the broadest application in a synthetic context.

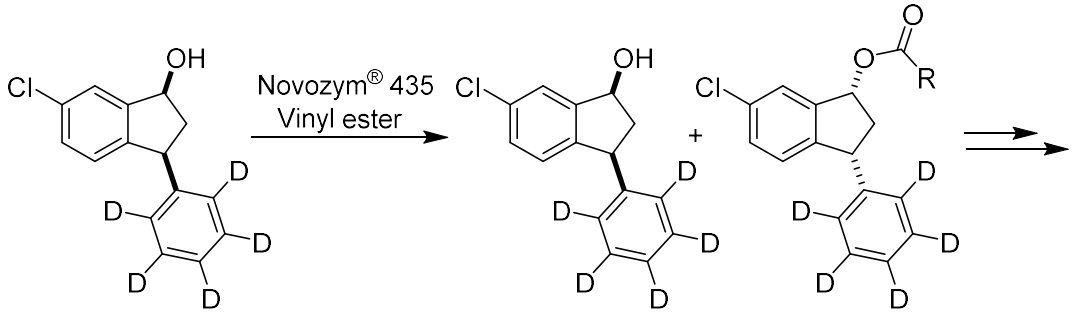
On small scale, enol esters such as vinyl acetate, isopropenyl acetate and ethoxyvinyl esters are considered by far the best activated and most used acyl donors.[375-377] The leaving group is an enol that immediately tautomerizes to the ketoform,[378] thus the reaction essentially becomes irreversible as no nucleophile remains in the reaction.

Candida Antarctica B (CAL-B) has been used as a highly enantioselective enzyme for a kinetic resolution to give (*R*)-1-aminoindan, an intermediate in the synthesis of (*R*)-Rasagiline, a treatment for Parkinson's disease, **Scheme 57**.[379]



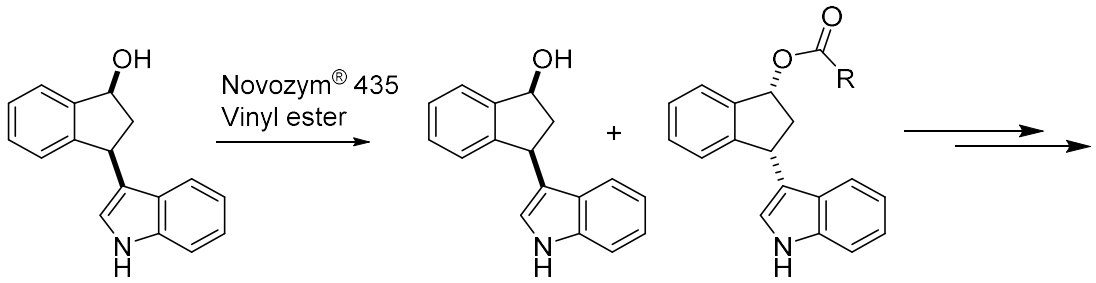
Scheme 57 – Kinetic resolution of racemic 1-aminoindan moiety

CAL-B has also been used in the kinetic resolution of other 3-aminoindan-1-ol and indane-1,3-diamine derivatives.[361] Novozym® 435, an acrylic resin immobilised enzyme; *Candida Antarctica B* (CAL-B), has shown a profound use in classical kinetic resolution of a variety of alcohols and their corresponding esters.[265] A relevant patent has shown the enzymatic resolution by acylation on similarly related *cis*-arylindan-1-ols, for the treatment of schizophrenia is shown below in **Scheme 58**.[359]



Scheme 58 – Novozym® 435 used for the resolution of deuterated indan-1-ols[359]

This method has also been used for the enzymatic chiral resolution of *cis*-3-(1*H*-indol-3-yl)-indan-1-ols (**Scheme 59**) into their corresponding enantiomers, as intermediates towards compounds effective for the treatment of central nervous system disorders.[360] The racemic *cis*-indan-1-ols were treated with irreversible acyl donors such as vinyl butyrate, catalysed by the immobilised lipase, Novozym® 435.



Scheme 59 – Example of enzymatic kinetic resolution using Novozym® 435 [360]

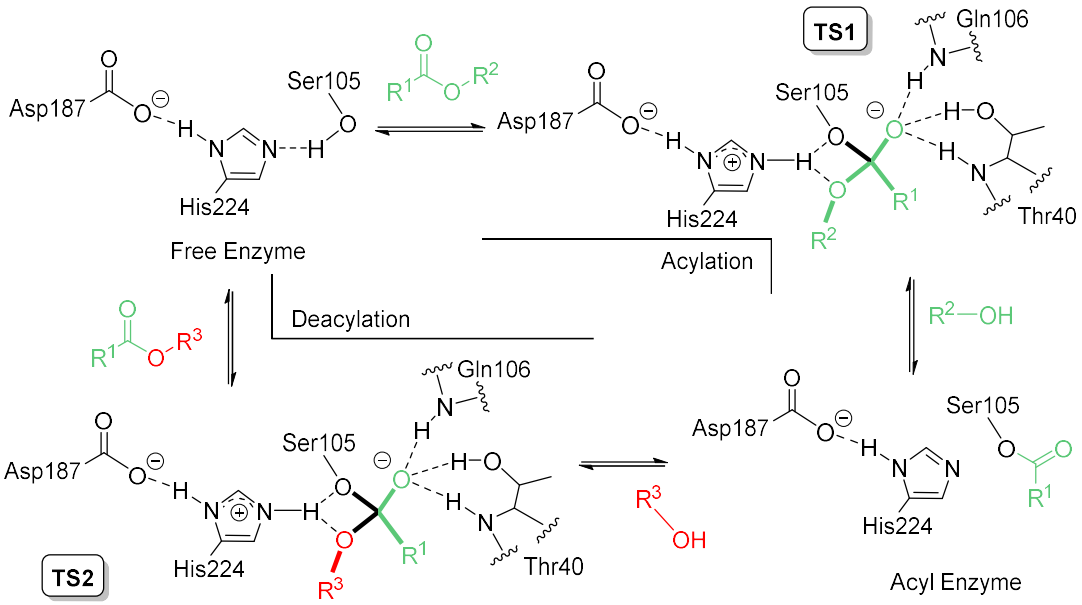
The immobilisation of lipase enzymes on a solid carrier leads to a number of benefits for biocatalysts,[380] such as:

- Convenient and safer handling
- Efficient catalyst separation and recycling, providing cost-savings
- Increased stability in organic solvents and heat

The work in this project uses the immobilised CAL-B enzyme; Novozym® 435.

In CAL-B, the catalytic triad is made up of a Ser105, Asp187 and His224 residue, existing as a globular α/β type protein, with these residues located at the carboxy-terminal edge of the parallel β-sheet. The three dimensional structure of CAL-B was determined by X-ray crystallography,[381] and CAL-B, compared to other lipases, has a very limited available space in the active site pocket, resulting in its high selectivity.

The mode of action was suggested to adopt a similar mechanism of action to other lipases,[381] with the reaction mechanism illustrated below in **Scheme 60**.



Scheme 60 – Reaction mechanism of *Candida Antarctica B* (CAL-B) [381]

A carboxylic ester ($R^1CO_2R^3$) binds in the active site, where the carbonyl carbon is attacked by the Ser105 nucleophile, resulting in transition state (TS1). The attack is promoted by His224, which accepts a proton from Ser105, acting as a general base.

The carbonyl oxygen, now a single bond, forms 3 hydrogen bonds within the oxyanion hole (two with Thr40 and one to Gln106),[381,382] followed by the alcohol leaving, forming the acyl enzyme. In the example shown in **Scheme 58** and **Scheme 59**, the leaving group is an enol that immediately tautomerizes to the ketoform, removing this nucleophilic presence from the reaction.

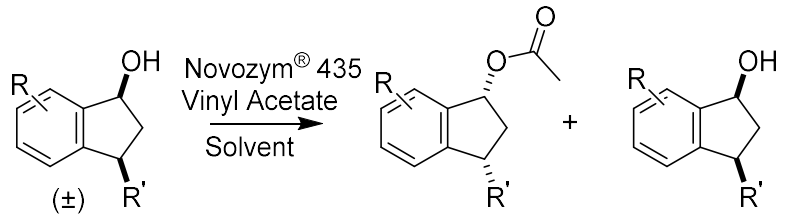
Finally, the second alcohol (R^3OH) attacks the carbonyl carbon of the acyl enzyme, going through a second transition state (TS2), forming the transacylated product, which is subsequently released from the reaction. The free enzyme is then regenerated.

Literature has reported that in order to reach the catalytic serine, the substrate needs to travel inside a 10 x 4 Å wide and 12 Å long hydrophobic channel.[381,383] Additionally, it was reported that interactions from more negative electrostatic potential functional groups,[383] such as substituents with a halogen atom, created an unfavourable interaction, reducing the enantioselectivity.

This binding site of CAL-B, having a deep narrow active site into which the substrate can bind in a hairpin manner,[384] can result in very high enantioselectivities, or conversely result in the complete opposite effect, where no product is acylated. The following section describes the work performed in this study.

Results & Discussion

Within the current study, the enzymatic resolution of racemic *cis*-indan-1-ols was performed by a literature procedure.[359,360] The process for this resolution involved Novozym® 435 as the catalyst, an acyl donor and the racemic *cis*-alcohols formed from **Section 2.3.2.4**. This process is shown below in **Scheme 61**.



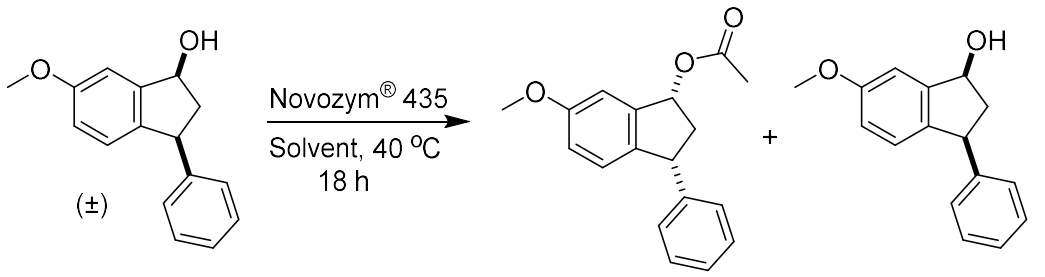
Scheme 61 – General scheme for kinetic resolution to chiral indan-1-ones

Although the acyl donor was initially performed with vinyl butyrate in accordance with the literature procedure, and indeed was successful with high enantioselectivity (> 99 % for the acetate, (1*R*,3*R*)-**102**), vinyl acetate was chosen from its increased ease in purification on a small scale.[378] Additionally, conducting the reaction at 40 °C offered shorter reaction times without hampering enantioselectivity, nor denaturing the enzyme, as seen for other reactions using Novozym® 435.[385]

For the enzymatic kinetic acylation of various different substituted indan-1-ols, some of the substrates encountered difficulties with solubility. Some of the substrates, notably the more sterically encumbered indan-1-ols, were completely insoluble in the 2-isopropoxypropane, the solvent employed in the literature.[360] Although some research has reported a negligible effect of solvent on the chemoselectivity of Novozym® 435,[386] other research has shown the solvent choice to be crucial, in some cases, showing a strong preference for hydrophilic solvents.[387]

Consequently a range of solvents were tested to see the effect on enantioselectivity and conversion of the transformation (**Table 16**).

Table 16 – Optimisation and viability of solvent conditions for Novozym® 435 catalysed acylation after 18 hours



80 (1*R*,3*R*)-**101** (1*S*,3*S*)-**80**

Entry	Solvent	Ratio [a] OAc : OH	e.e. % [b] OAc	e.e. % [b] OH
1	Acetone	11 : 89	>99	11
2	2-Isopropoxypropane	48 : 52	>99	90
3	Chloroform	10 : 90	>99	12
4	Dichloromethane	38 : 62	>99	60
5	Toluene	26 : 74	>99	34
6	*N*,*N*-Dimethylformamide	4 : 96	>99	>2
7	Ethyl Acetate	27 : 73	>99	36
8	2-Propanol	13 : 87	>99	11
9	Acetonitrile	21 : 79	>99	28
10	Methanol	2 : 98	>99	>1
11	Ethanol	8 : 92	>99	8
12	Tetrahydrofuran	5 : 95	>99	4

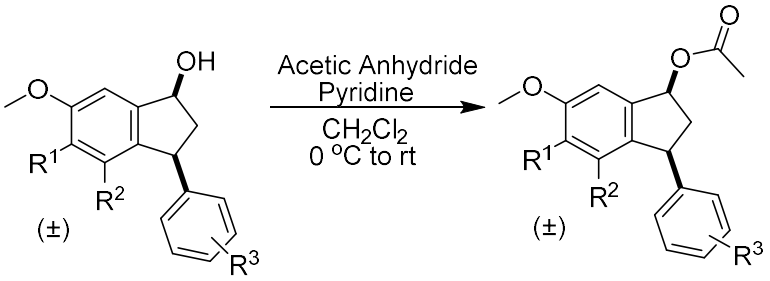
[a] Ratio determined by ^{1}H NMR Analysis; [b] Enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : n-hexane = 5 : 95, 1 mL/min.; Acetate: 211 nm, (1*R*,3*R*)-isomer 6.37 min., (1*S*,3*S*)-isomer 6.96 min.; Alcohol: 208 nm, (1*S*,3*S*)-isomer 24.61 min., (1*R*,3*R*)-isomer 40.77 min.

The resolution was performed on racemic *cis*-6-methoxy-3-phenylindan-1-ol substrate, **80**, where the solubility of the alcohol was generally good in all the aforementioned solvents.

Whilst the conversion varied dramatically in different solvents (and thus affecting the enantiomeric excess of recovered alcohol), the acetate was formed with high enantioselectivity (>99 %) in all solvents. Using the above data, it was found that a combination of dichloromethane and 2-isopropoxypropane (1 : 1) dissolved all desired substrates in addition to providing good conversions and enantioselectivities.

In order to effectively measure the enantioselectivity of the enzymatic acylation by HPLC, racemic acylated indan-1-yl acetates were synthesised directly from the racemic indan-1-ols using acetic anhydride and pyridine (**Table 17**).

Table 17 – Acetylation of racemic indan-1-ols using acetic anhydride



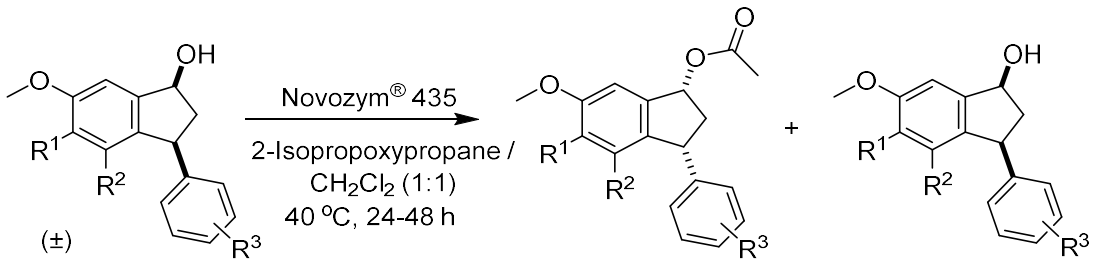
Indan-1-ol			Indan-1-yl Acetate	
Rac-	**R^1/R^2**	**R^3**	**Yield (%)** [a]	***Rac-***
80	H	H	88	**101**
81	H	4-OCH_3	91	**103**
82	H	3,4-OCH_3	82	**104**
83	H	3,4,5-OCH_3	85	**105**
84	H	2,3,4-OCH_3	80	**106**
85	H	4-F	90	**107**
86	H	4-Cl	89	**108**
87	OCH_3	3-F, 4-OCH_3	93	**109**
88	OCH_3	3-NO_2, 4-OCH_3	91	**110**

[a] Isolated yield.

Excellent yields were obtained for the acylation of racemic indan-1-ols and retention times for the racemic indan-1-yl acetates (HPLC) were obtained.

The enzymatic kinetic resolution was first performed on the substrates analogous to literature examples,[359] as shown below in **Table 18**.

Table 18 - Kinetic Resolution of Substituted Indan-1-ols using Novozym® 435



Racemic *cis*-Indan-1-ol		Conv. % [a]	Acetate (1*R*,3*R*)			Alcohol (1*S*,3*S*)		
R^1/R^2	R^3			Yield % [b]	e.e. % [c]		Yield % [b]	e.e. % [c]
H	H	50	**101**	47	>99	**80**	48	>99
H	4-OCH_3	50	**103**	46	>99	**81**	46	>99
H	3,4-OCH_3	47	**104**	42	>99	**82**	44	77
H	3,4,5-OCH_3	50	**105**	48	>99	**83**	47	99
H	2,3,4-OCH_3	45	**106**	40	>99	**84**	50	81
H	4-F	49	**107**	47	>99	**85**	48	94
H	4-Cl	50	**108**	47	>99	**86**	48	>99
OCH_3	3-F, 4-OCH_3	49	**109**	45	>99	**87**	47	96
OCH_3	3-NO_2, 4-OCH_3	50	**110**	46	>99	**88**	48	98

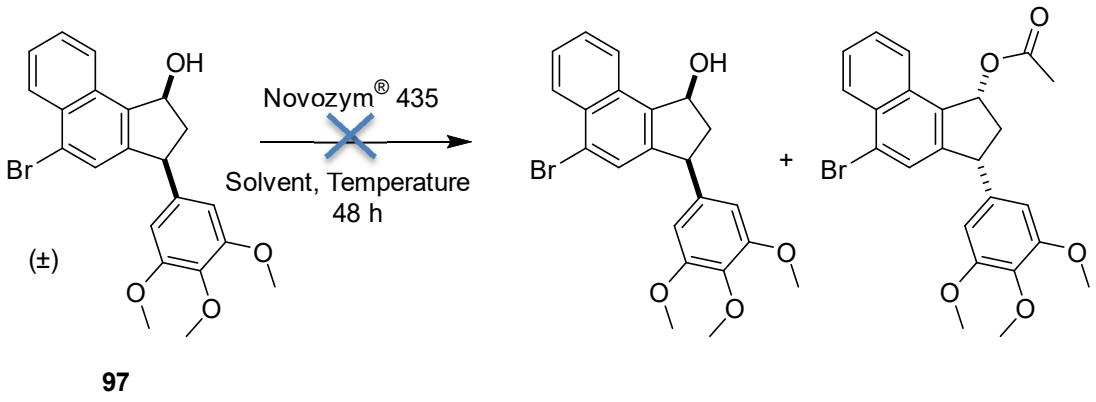
[a] Conversion determined by ^{1}H NMR; [b] Isolated yield, as a % of racemic starting material; [c] e.e. % determined by chiral HPLC analysis (see **Chapter 5** for conditions).

The above method produced all of the (*R*)-indan-1-yl acetates in excellent enantioselectivities (>99 %). In most cases where conversion was roughly 50 %, the (*S*)-alcohol was also produced with high enantioselectivity (up to 99 %).

A clear observation is seen for alcohol substrates with a lower enantiomeric excess, where as expected, it is a consequence of a lower conversion. Extension of the reaction time afforded the desired alcohols in higher enantiomeric excess, while not proceeding over the 50 % conversion threshold under the conditions presented.

The enzyme substrate selectivity, acylating the (*R*)-alcohol only, is in good agreement with literature observations,[359,385,386] and additionally, upon oxidising the (1*R,3R*)-6-methoxy-3-phenlindan-1-ol, (1*R*,3*R*)-**80**, to the corresponding (*R*)-ketone, (*R*)-**59**, provided consistent HPLC and optical rotation data to that of literature examples.[216,388] The same observations were found upon oxidation of the (*S,S*)-enantiomer, (1*S*,3*S*)-**80**, confirming the observed stereochemistry.[389] The (*R*)- and (*S*)-configurations of the remaining substrates were deduced by analogy.

After successful attempts of performing kinetic resolution with 6-methoxy-3-arylindan-1-ols, and the similarly related 4,5,6-trimethoxy-3-arylindan-1-ol substituents, both with varying functional groups on the aromatic ring (R^3), attempts to perform the reaction with the naphthylen-1-ol substituent, **97** were carried out in 2-isopropoxypropane / CH_2Cl_2, but remained unsuccessful (**Scheme 62**).



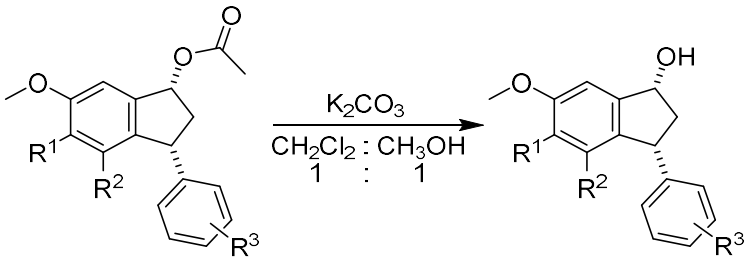
97

Scheme 62 – Attempted enzymatic acylation kinetic resolution of **97**

Numerous attempts, including variations in solvent, reaction time and temperature failed to produce the desired acylated naphthalen-1-ol derivative with Novozym® 435. The reaction yielded only the starting alcohol, upon comparison of the ^{1}H NMR to that of the racemic acylated naphthalen-1-ol, **111**.

The resulting enantiomerically enriched (*R,R*)-indan-1-yl acetates were subsequently transformed into the corresponding (*R,R*)-indan-1-ols by cleavage of the carbonyl bond using potassium carbonate and methanol,[390] as shown below in **Table 19**.

Table 19 – Deacetylation of Enantiomerically Enriched (*R,R*)-Indan-1-yl Acetates

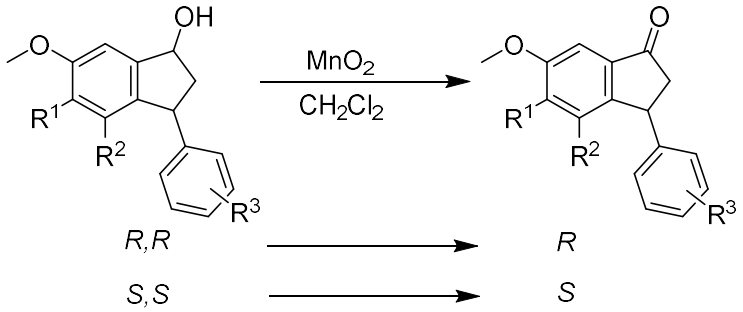


Indan-1-yl Acetate			Indan-1-ol	
(1*R*,3*R*)-	**R^1 / R^2**	**R^3**	**Yield (%)** [a]	**(1*R*,3*R*)-**
101	H	H	91	**80**
103	H	4-OCH_3	87	**81**
104	H	3,4-OCH_3	85	**82**
105	H	3,4,5-OCH_3	91	**83**
106	H	2,3,4-OCH_3	89	**84**
107	H	4-F	78	**85**
108	H	4-Cl	81	**86**
109	OCH_3	3-F, 4-OCH_3	74	**87**
110	OCH_3	3-NO_2, 4-OCH_3	81	**88**

[a] Isolated yield.

Finally, both enantiomers of each indan-1-ol were oxidised to the desired enantiomerically enriched indan-1-ones. A manganese dioxide oxidation was used,[391] which allowed a comparatively easy purification process,[392] (**Table 20**).

Table 20 – MnO_2 oxidation of enantiomerically enriched *cis*-indan-1-ols



Entry	Indan-1-ol			Indan-1-one	
		R^1 / R^2	R^3	Yield (%) [a]	
1	(1*R*,3*R*)-**80**	H	H	82	(*R*)-**59**
	(1*S*,3*S*)-**80**			84	(*S*)-**59**
2	(1*R*,3*R*)-**81**	H	4-OCH_3	81	(*R*)-**60**
	(1*S*,3*S*)-**81**			76	(*S*)-**60**
3	(1*R*,3*R*)-**82**	H	3,4-OCH_3	74	(*R*)-**61**
	(1*S*,*1S*)-**82**			80	(*S*)-**61**
4	(1*R*,3*R*)-**83**	H	3,4,5-OCH_3	75	(*R*)-**62**
	(1*S*,3*S*)-**83**			70	(*S*)-**62**
5	(1*R*,3*R*)-**84**	H	2,3,4-OCH_3	71	(*R*)-**63**
	(1*S*,3*S*)-**84**			72	(*S*)-**63**
6	(1*R*,3*R*)-**85**	H	4-F	81	(*R*)-**64**
	(1*S*,3*S*)-**85**			84	(*S*)-**64**
7	(1*R*,3*R*)-**86**	H	4-Cl	84	(*R*)-**65**
	(1*S*,3*S*)-**86**			86	(*S*)-**65**
8	(1*R*,3*R*)-**87**	OCH_3	3-F, 4-OCH_3	89	(*R*)-**66**
	(1*S*,3*S*)-**87**			86	(*S*)-**66**
9	(1*R*,3*R*)-**88**	OCH_3	3-NO_2, 4-OCH_3	90	(*R*)-**67**
	(1*S*,3*S*)-**88**			89	(*S*)-**67**

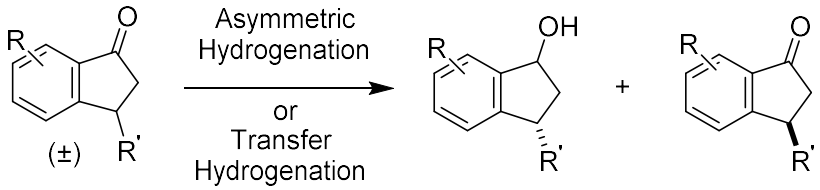
[a] Isolated yield.

In summary, the enzymatic resolution of 6-methoxy- and 4,5,6-trimethoxy-3-aryl-indan-1-ones provided a very effective and highly enantioselectivity (>99 % in most cases) method of achieving both enantiomers.

The reported deep narrow active site,[384] in addition to unfavourable interactions are likely resulting in the inability for Novozym® 435 to acylate the naphthylen-1-ol substrate.[393] Nonetheless, this method did present an excellent procedure for the isolation of both enantiomerically enriched (*R*)- and (*S*)-indan-1-ols by enzymatic resolution, and subsequent indan-1-ones (see **Table 19** and **Table 20**), through deacetylation/oxidation, regarding the appropriate enantiomer.

2.5 Kinetic Resolution – Asymmetric Transfer Hydrogenation

For the kinetic resolution of racemic 3-aryl substituted indan-1-ones, the following resolution was proposed, using an asymmetric transfer hydrogenation process shown below in **Scheme 63**.



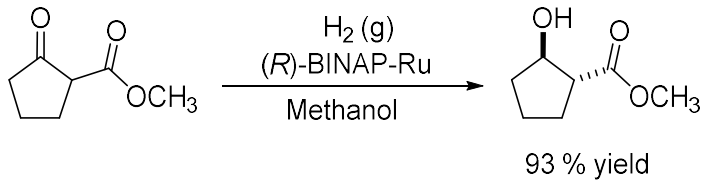
Scheme 63 – Proposed asymmetric hydrogen transfer kinetic resolution

By using a chiral catalyst, it is hoped that one enantiomer would react faster than the other with full catalyst control. This transformation could either be stopped before 50 % conversion, where it is desired that high asymmetric control would yield only one reduced isomer (alcohol). Additionally, if the catalyst exhibited high catalytic control, the reaction could be driven to 100 % conversion, allowing the two reduced diastereoisomers to be separated by standard silica column chromatography.

Asymmetric Ketone Reduction

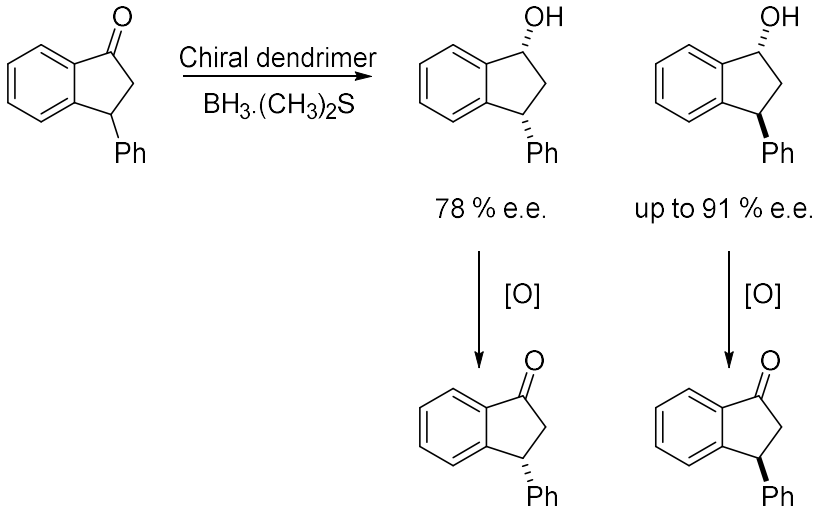
An example of asymmetric hydrogenation is Noyori's asymmetric hydrogenation,[394] using a ruthenium-BINAP catalyst and hydrogen gas, (**Scheme 64**). In this case, an acidic hydrogen between the two carbonyl groups is allowed to epimerise at the chiral centre, where in the presence of the chiral catalyst, one of the β-ketoesters preferentially reacts faster.[395] This dynamic kinetic resolution approach with the (*R*)-BINAP catalyst gave the (*S*)-alcohol *anti*-product in 93 % e.e.

This reaction is shown below in **Scheme 64**, where methanol appeared to have a major influence on the diastereoselectivity of the reaction.



Scheme 64 – Noyori's classic dynamic kinetic resolution of dicarbonyl systems[395]

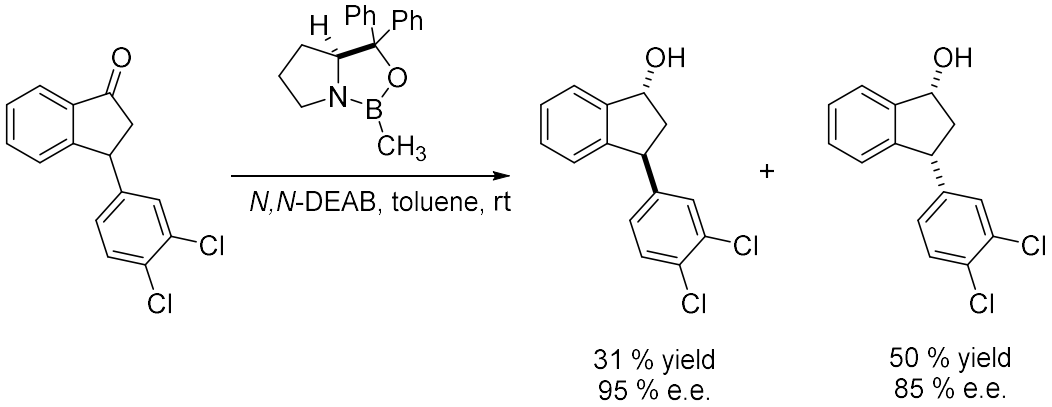
Zhao et al.[219] reported a chiral dendrimer to resolve indan-1-ones, with application towards the synthesis of (+)-sertraline, (**Scheme 65**).



Scheme 65 – Asymmetric reduction of indan-1-ones using a chiral dendrimer and $BH_3.(CH_3)_2S$, towards the synthesis of (+)-sertraline[219]

The chiral dendrimer contained a prolinol core, and the research reported a mixture of *cis*- and *trans*-isomers obtained in a ratio of (1 : 1), separable by column chromatography. The *cis*-isomer had an e.e. of about 80 %, whereas the *trans* isomer had an e.e. of about 95 %. This approach is particularly useful as both indan-1-one enantiomers can be obtained from the racemic mixture in good enantiomeric excess.

Although Corey first demonstrated the use of oxazaborolidine catalysts in the reduction of ketones by borane, notably in the reduction of tetralone,[396] Lee et al. further utilised this method to enantiomerically resolve indan-1-one derivatives, specifically towards the synthesis of (+)-indatraline, (**Scheme 66**).[397]

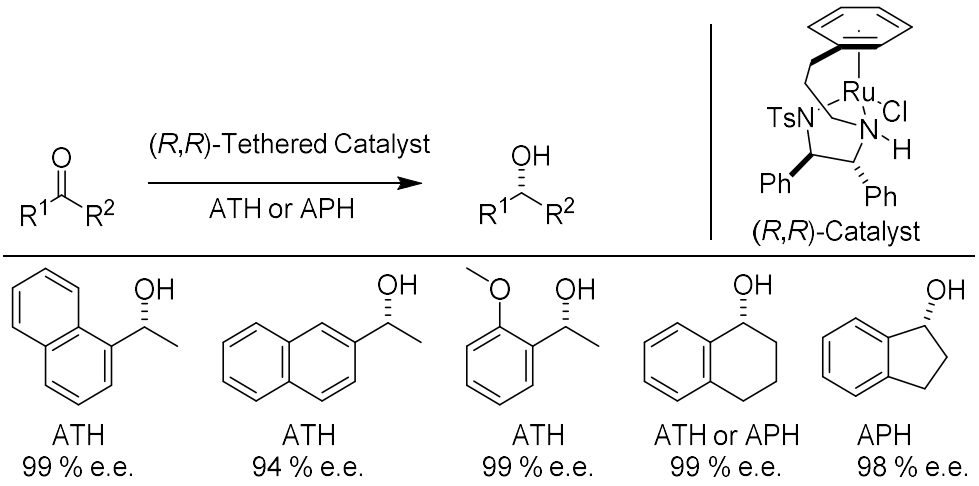


Scheme 66 – Oxazaborolidine-catalysed asymmetric carbonyl reduction of an indan-1-one derivative, (+)-indatraline[397]

Treatment of the ketone with an (*S*)-(-)-2-methyl-CBS-oxazaborolidine catalyst and catecholborane yielded a separable mixture of (1*R*,3*S*)-*trans*-indanol and its diastereoisomer, (1*R*,3*R*), with high enantioselectivities (31 % yield, 95 % e.e. and 50 % yield, 85 % e.e. respectively).[397]

With extensive research available on the asymmetric reductions of prochiral ketones, our attention turn towards the work of Noyori[398] and Wills.[399] A variety of examples of asymmetric hydrogenation / asymmetric transfer hydrogenation on a variety of ketone substituents were available in the literature, offering high enantioselectivities (~99 % e.e.) in most examples.[400]

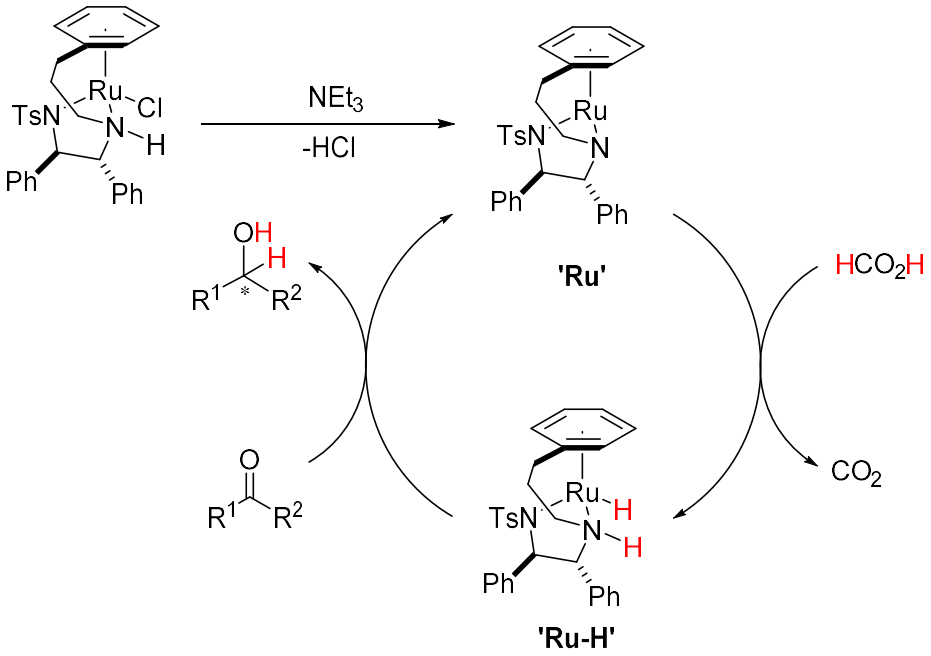
Some examples applicable to this research are shown below in **Scheme 67**.[401]



Scheme 67 – Asymmetric transfer hydrogenation (ATH) and asymmetric pressure hydrogenations (APH) of particular ketone substrates[401]

Based on previous work from Noyori and Wills,[401] one would expect catalyst-selectivity to afford the (*R*)-enantiomer (alcohol) when subjected to the (*R,R*)-catalyst (**Scheme 67**).

The catalytic cycle in which the transformation is believed to happen is shown below in **Scheme 68**.[402,403]



Scheme 68 – Proposed mechanism for the asymmetric transfer hydrogenation[402]

The strong base leads to the facile elimination of HCl to yield the 16-electron catalytic species '**Ru**'. The triethylammonium formate is thought to bond to the metal oxygen, with subsequent loss of CO_2 leading to the formation of the 18-electron reactive intermediate '**Ru-H**'. The prochiral ketone is then reduced by the 18-electron reactive intermediate '**Ru-H'** to give the corresponding enantiomerically enriched alcohol. The hydridic Ru-H and protic N-H in this 18-electron reactive intermediate are transferred to the carbonyl oxygen and carbonyl carbon respectively.

The stereo-determining step in the catalytic cycle shown in **Scheme 68** is generally imposed by a directing functional group interacting with the complex. Aryl groups, such as a phenyl group,[398] are some of the more common direction groups for this process. Noyori et al.[404] performed some DFT calculations on a non-tethered catalyst, suggesting that the CH/π attractive interactions shown below in **Figure 25** stabilises the transition state, leading to the high enantioselectivities of the products.

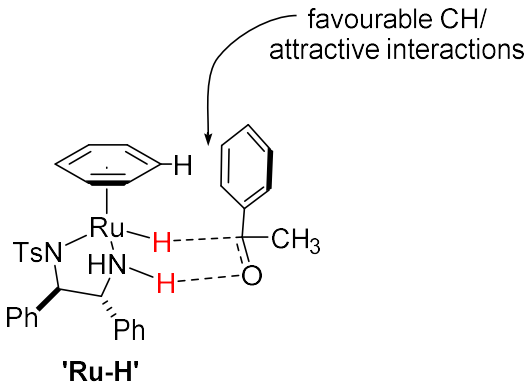
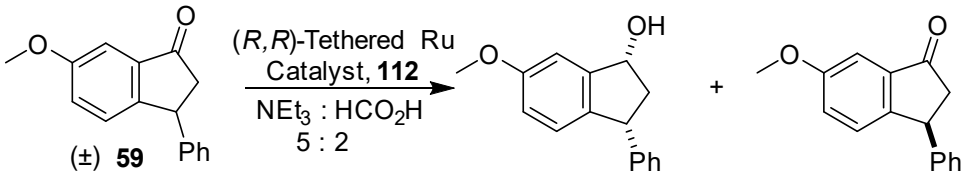


Figure 25 – Favourable CH/π attractive interactions

The work suggested that the CH/π attractive interaction was between the η^6-arene ring and the aryl substituent in the prochiral ketone. The following research utilises a tethered-Ru catalyst based on the high enantioselectivities in the literature, to perform an asymmetric transfer hydrogenation kinetic resolution on a selected indan-1-one.

Results & Observations

In this current study, with the aim was to isolate single enantiomers; 3-arylindan-1-ol and 3-arylindan-1-one via kinetic resolution, the racemic ketone starting material, **59**, was subject to the asymmetric transfer hydrogenation (ATH) method using the tethered (*R,R*)-TSDPEN-ruthenium catalyst.[401]



Scheme 69 – Asymmetric transfer hydrogenation of compound **59**

The catalyst was provided by the Wills group at Warwick University and the formic acid : triethylamine (5 : 1) solution was prepared from the method by Sterk et al.[405]

After 12 hours, the reaction was observed to proceed to 85 % conversion with respect to ketone consumption. Inspection of the HPLC chromatogram showed three distinct product peaks were observed in addition to the residual ketone (see **Figure 26** below).

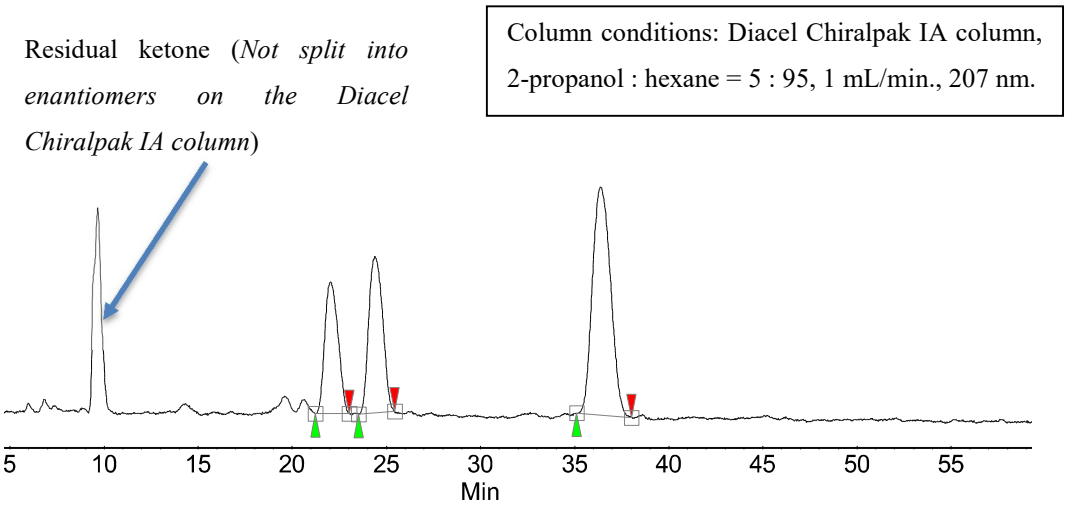


Figure 26 – Initial HPLC for the Ru-catalysed ATH of **59** after 12 hours

The racemic *cis*-6-methoxy-3-phenylindan-1-ol compound, **80**, was formed via the selective reduction using sodium borohydride (see **Section 2.3.2.4**), yielding exclusively the *cis*-alcohol. This provided both reference ^{1}H NMR peaks and HPLC retention times for this isomer. Indeed, the individual *cis*-isomers were also synthesised by an enzymatic resolution method (see **Section 2.3.2.4**) providing reference HPLC retention times for each enantiomer.

Overlay of the racemic *cis*-6-methoxy-3-phenylindan-1-ol quickly identified two of the HPLC peaks (**Figure 27**).

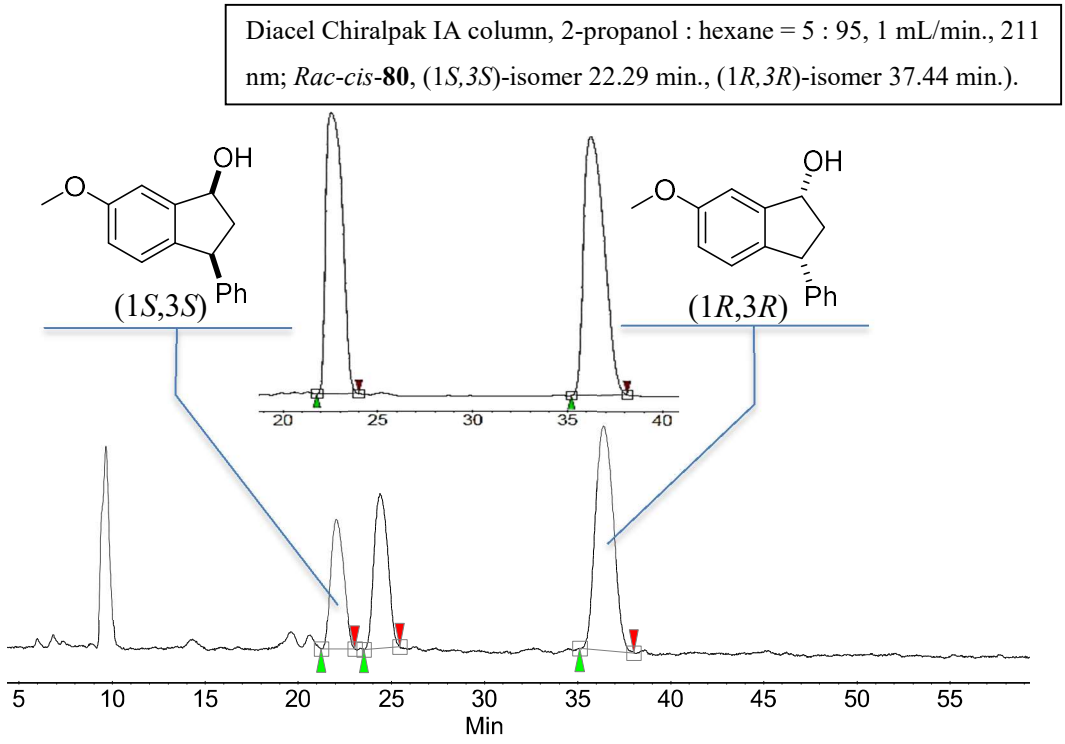
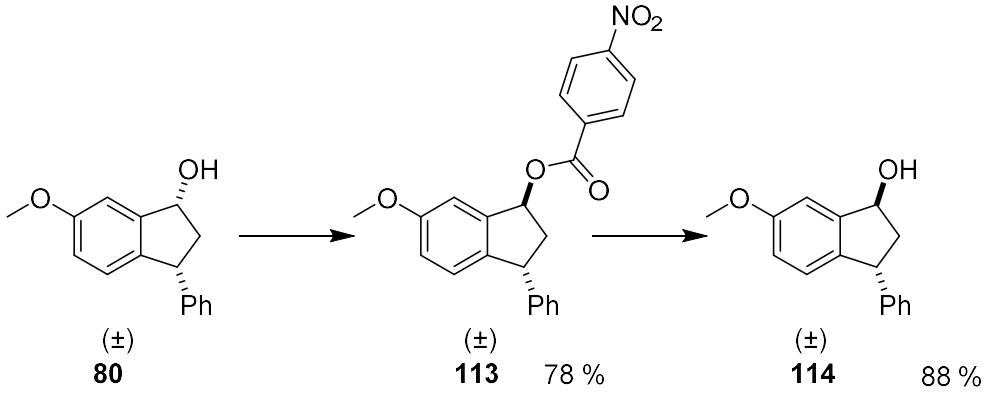


Figure 27 - Overlay of the racemic *cis*-6-methoxy-3-phenylindan-1-one, **80**, on the HPLC of the Ru-catalysed ATH of **59**, (12 hours)

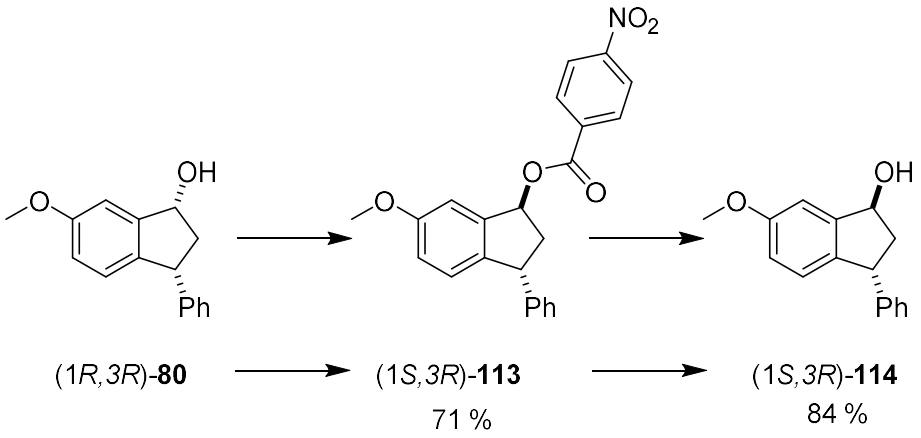
The sample was additionally 'spiked' with racemic *cis*-alcohol, showing an increased intensity for the aforementioned peaks, further supporting the assignment of the observed peaks.

With one unaccountable peak remaining, it was hypothesised that this would be attributed to either racemic or enantiopure *trans*-6-methoxy-3-phenylindan-1-ol. Firstly, for identification of the racemic-*trans*-isomer on the HPLC trace, it was synthesised using a Mitsunobu transformation,[406] from the corresponding racemic *cis*-isomer, **80**, shown in **Scheme 70** below.

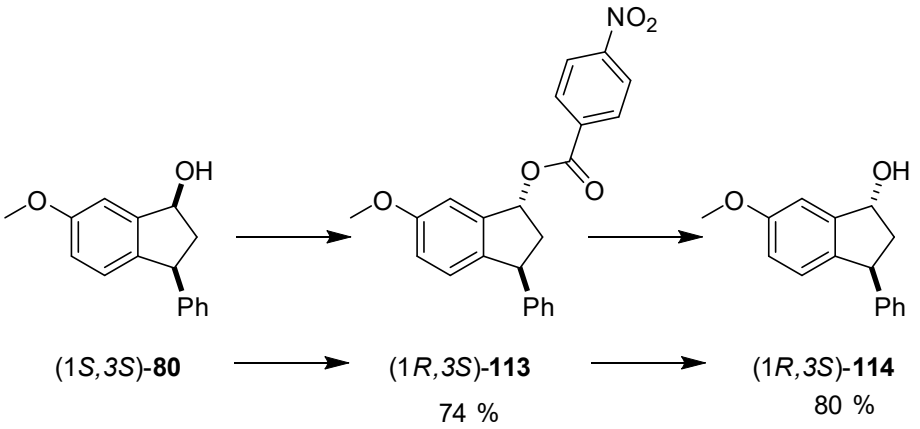


Scheme 70 – Mitsunobu reaction to afford the racemic *trans*-**114**

Similarly, the individual *trans*-alcohol enantiomers were synthesised from the enantiomerically enriched indan-1-ols, by the same approach shown in **Scheme 70**.



Scheme 71 – Mitsunobu reaction to give the enantiomerically enriched (1*S*,3*R*)-**114**



Scheme 72 – Mitsunobu reaction to give the enantiomerically enriched (1*R*,3*S*)-**114**

Overlay of the racemic *trans*-indan-1-ol HPLC trace concluded that the unidentified peak was that of the (1*R*,3*S*)-*trans*-isomer.

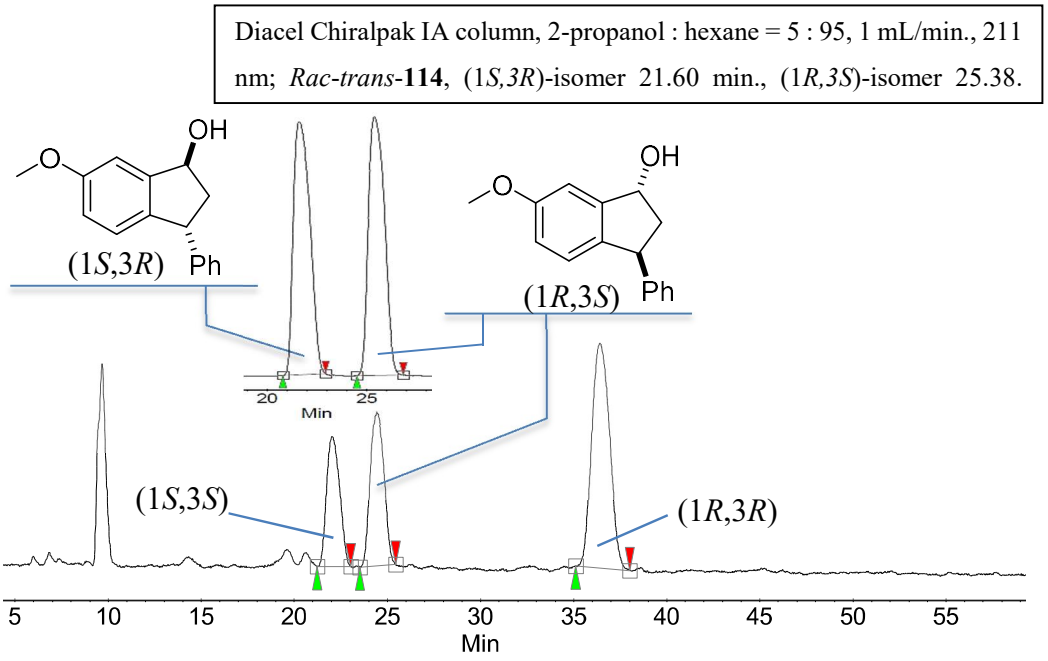


Figure 28 – Overlay of the racemic *trans*-6-methoxy-3-phenylindan-1-one HPLC on the Ru-catalysed ATH of **59**, (12 hours)

The sample was again 'spiked,' this time with racemic *trans*-alcohol, **114**, confirming the assignments of the peaks. The racemic *trans*-'spiked' sample resulted in an additional peak, shown below in **Figure 29**.

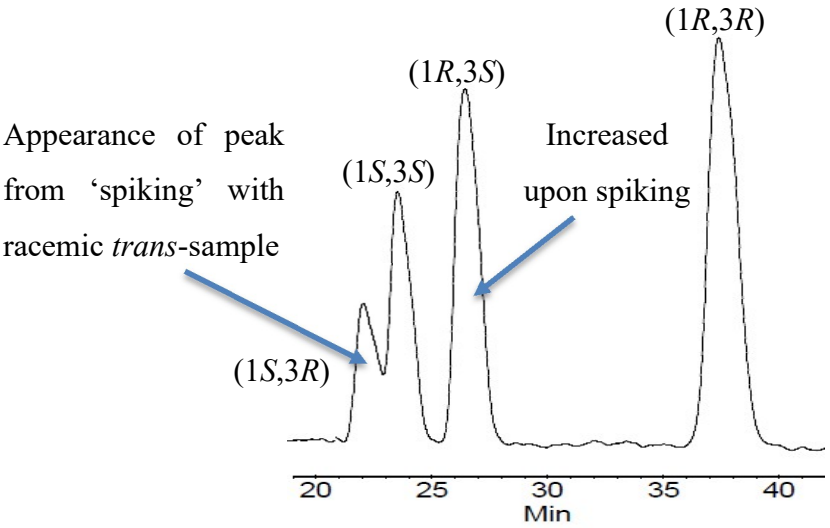


Figure 29 – 'Spiking' of racemic *trans*-**114** alcohol to the HPLC sample obtained after 12 hours

The identified peaks for this reaction are summarised below in **Figure 30**:

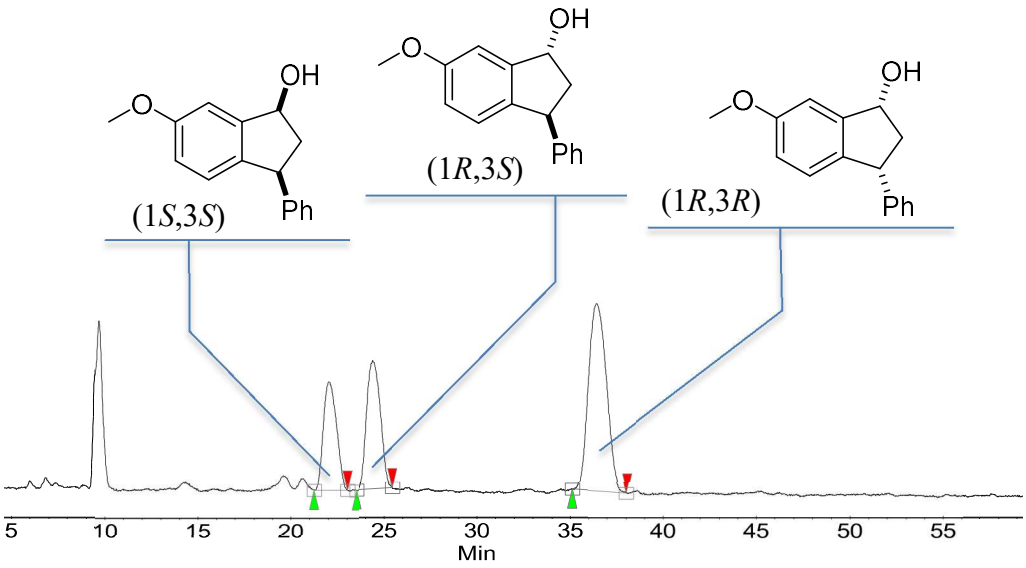


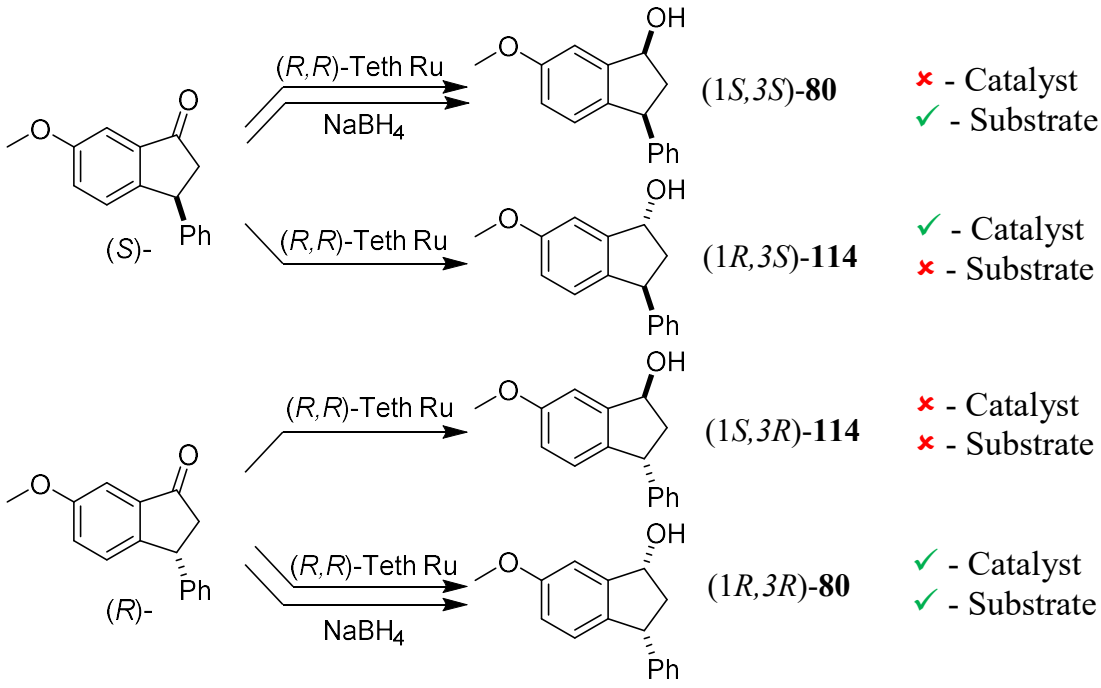
Figure 30 – Summary of identified peaks from HPLC chromatogram

This transformation gave the alcohol in a poorly selective process, and additionally the residual ketone was found to have a 30 % e.e. after the 85 % conversion shown in **Figure 26**, (12 hours).

After 1 hour, the reaction had proceeded to 46 % conversion with a 50 % e.e. for the ketone, with the residual alcohols formed in a 5 : 4 : 91 ratio for the (1*S*,3S), (1*R*,3*S*), (1*R*,3*R*) isomers respectively.

Taking the reaction to 65 % conversion after 2 hours gave the residual (*S*)-ketone in 46 % e.e. (Diacel Chiralpak AS column, 2-propanol : hexane = 5 : 95, 1 mL/min., 219 nm; (*S*)-isomer 16.23 min., (*R*)-isomer 25.74 min.). As both enantiomers of ketone are consumed in this process, albeit at different rates, the reaction is not favourable for the ketone component either, and thus our attention turned to a different resolution approach.

The rationale behind the results obtained can be explained when the transition states of each component are considered in the reaction, **Scheme 73**.



Scheme 73 – Possible outcomes for the asymmetric transfer hydrogenation of racemic 6-methoxy-3-phenyl indan-1-one, **59**

These preferences can be explained given the following transition states, **Figure 31**. The unfavourable steric clash can be seen for the formation of the (1*S*,3*R*)-alcohol between the 3-phenyl ring of the indan-1-one and the aromatic ring on the ruthenium catalyst. Additionally, favourable CH/π interactions[404] can be seen between the indanone aromatic ring and the C-H from the ruthenium aromatic ring, providing a possible explanation for the ratio of isomers observed in this transformation. Further computational studies would be required to support these transition states however.

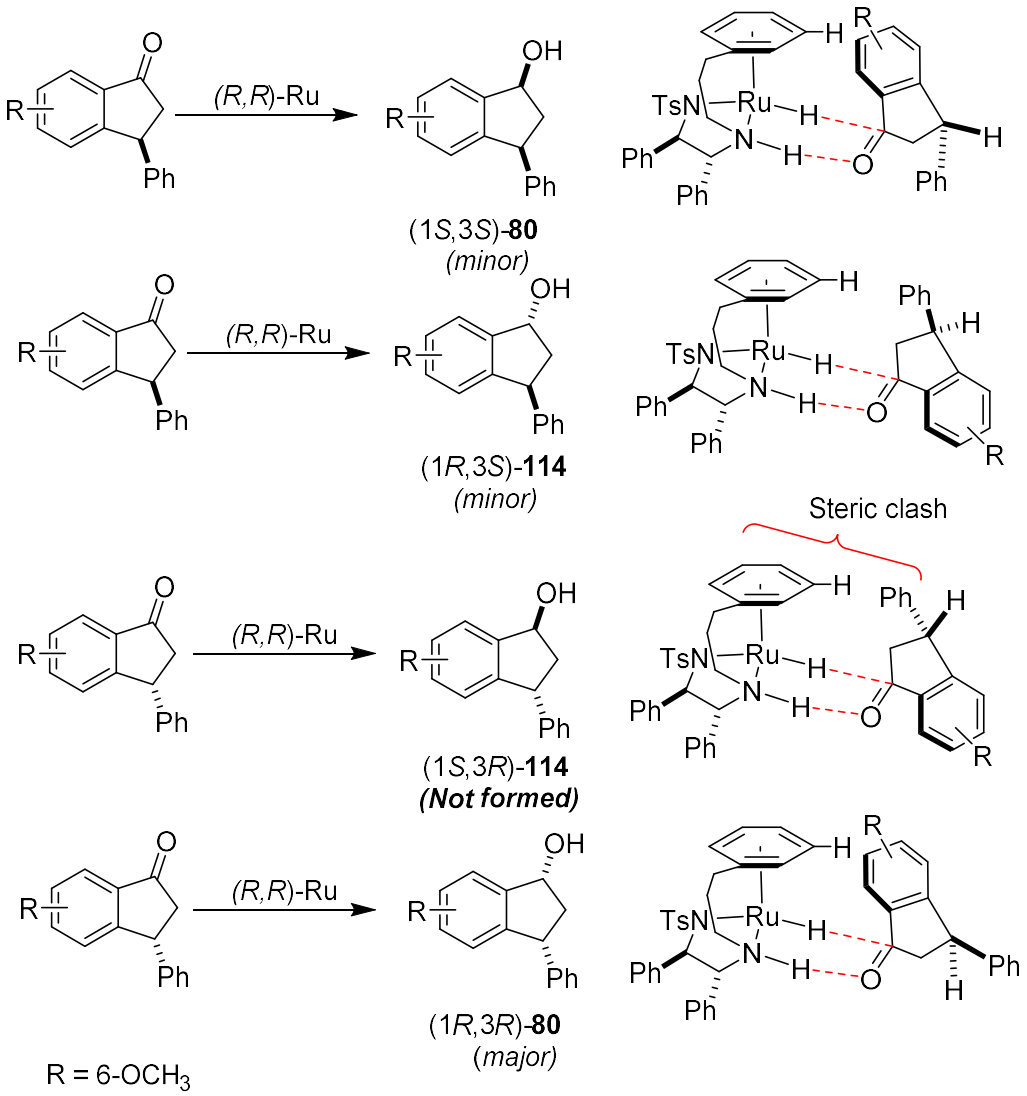


Figure 31 – Proposed transition states - asymmetric transfer hydrogenation of **59**

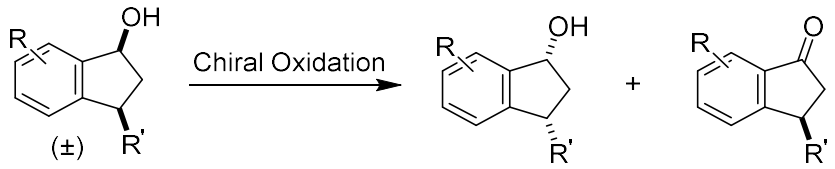
2.6 Kinetic Resolution – Oxidative Kinetic Resolution

Given that the asymmetric transfer hydrogenation reaction shown in **Section 1.5** has an outcome of four possible stereoisomers, (**Scheme 73**), our attention turned towards the reverse of this process, to perform an oxidative kinetic resolution on racemic *cis*-indan-1-ols formed in **Section 2.3.2.4**.

As the *cis*-geometry of the racemic indan-1-ol is controlled in the sodium borohydride reduction of the appropriate ketone, the approach can be advantageous upon comparison to the asymmetric transfer hydrogenation performed previously, such that:

- Reduction – Conversion of 2 enantiomers into a possible 4 stereoisomers
- Oxidation – Conversion of 2 enantiomers into a possible 2 stereoisomers

Consequently, the following approach was applied, shown below in **Scheme 74**.

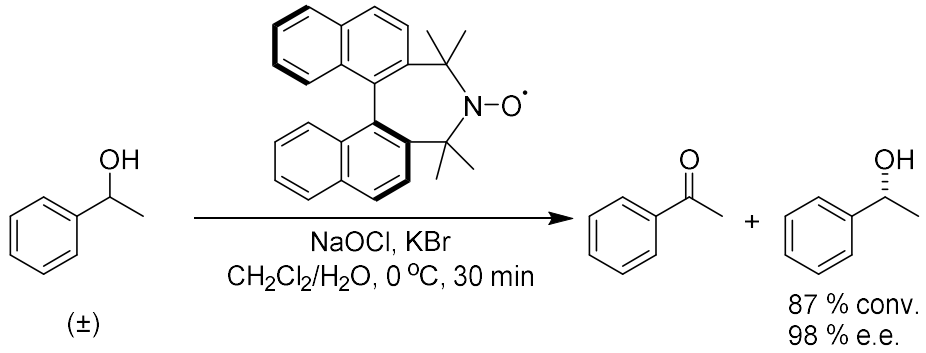


Scheme 74 – Proposed chiral oxidation of racemic *cis*-indan-1-ols

For an ideal outcome, the conversion is desired to be 50 %, with high enantiomeric excess of both the residual alcohol and the oxidised ketone. This approach is discussed in more detail below.

Discussion on Oxidative Kinetic Resolution

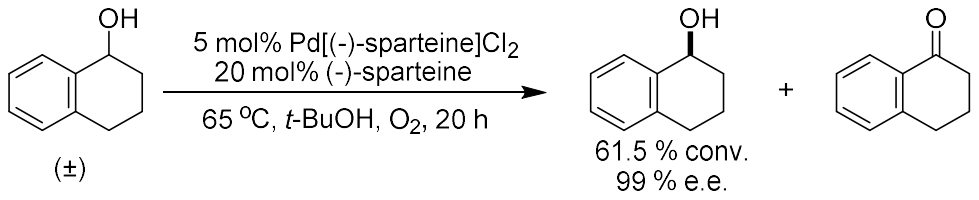
One of the first approaches to kinetic resolution via alcohol oxidation was from the work by Ruchnovsky et al,[407] reporting the oxidation of 1-phenylethanol using a chiral nitroxyl radical catalyst and sodium hypochlorite as the oxidising agent, (**Scheme 75**).



Scheme 75 – Chiral nitroxy radical-catalysed oxidative kinetic resolution[407]

Additional improvements to this method have since been realised,[408] however, other approaches to the oxidative kinetic resolution of secondary alcohols generally employ transition metal catalysts.[409]

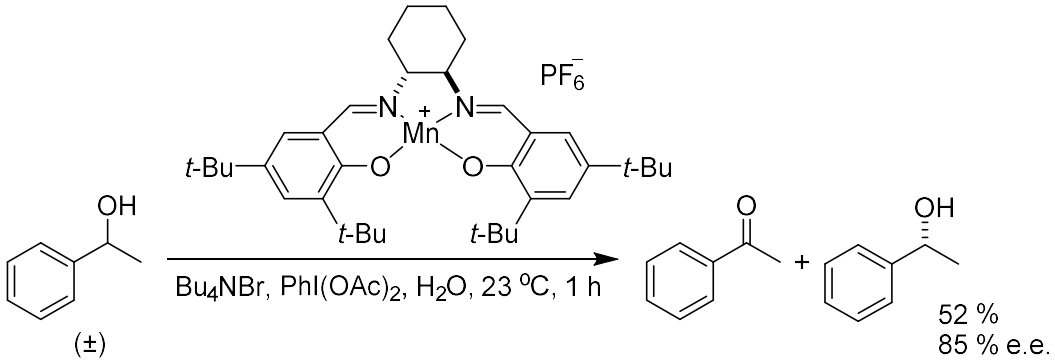
Sigman et al.[410] reported a system using (-)-sparteine as the chiral ligand, with a $Pd(OAc)_2$ catalyst and O_2 as the stoichiometric oxidant, shown below in **Scheme 76**.



Scheme 76 – (-)-Sparteine used as a chiral ligand with $Pd(OAc)_2$ and O_2 as the stoichiometric oxidant[410]

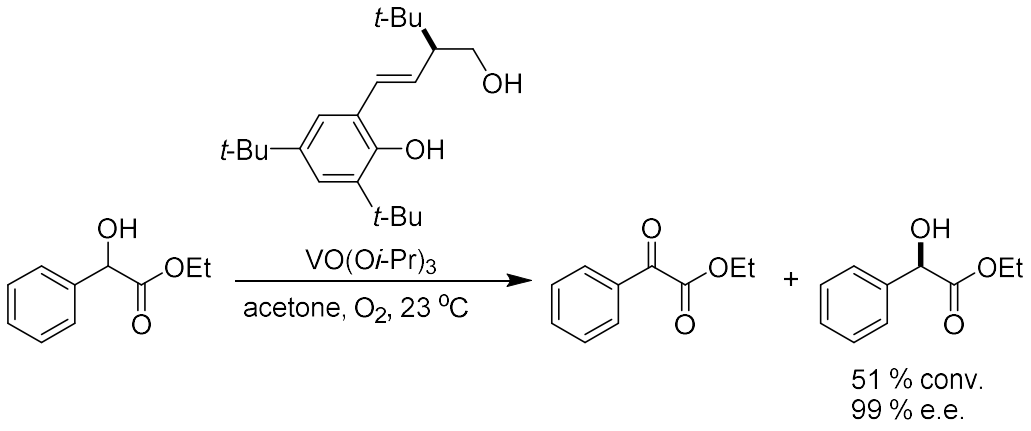
The system was optimised using *t*-BuOH as a solvent to obtain modest selectivity for a wide range of secondary alcohols.

Xia has similarly reported an oxidative kinetic resolution of benzylic alcohols using a manganese-salen catalyst, with iodobenzene diacetate as the stoichiometric oxidant,[411] shown below in **Scheme 77**.



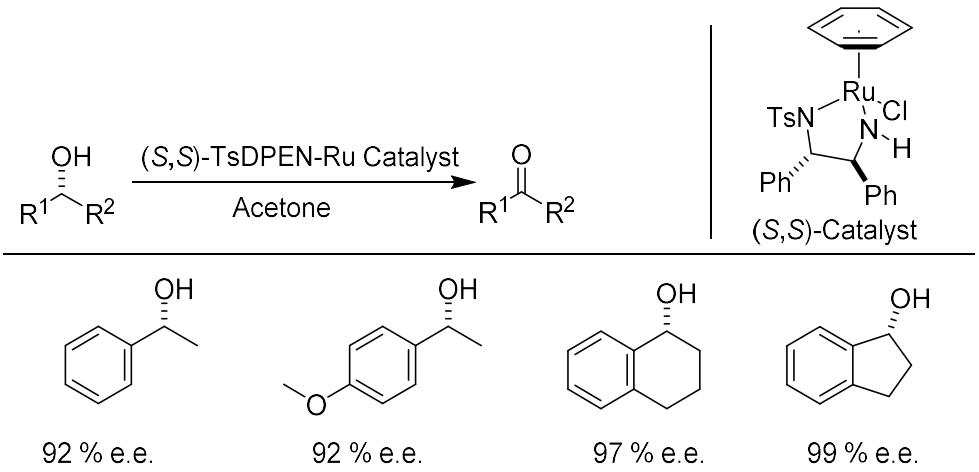
Scheme 77 – Oxidative of benzylic alcohols using a manganese-salen catalyst[411]

It was later reported by Xia that solvent changes allowed for better selectivity in some substrates.[412] Additionally, Toste et al. reported a vanadium catalyst using a chiral salicylaldimine ligand for the asymmetric oxidation of α-hydroxy esters,[413,414] (**Scheme 78**).



Scheme 78 – Chiral salicylaldimine-vanadium catalyst used for asymmetric oxidation of α-hydroxy esters[413,414]

Noyori has developed highly enantioselective variants of a ruthenium catalysed kinetic resolution of secondary alcohols, using a ruthenium diamine catalyst, with acetone as the hydrogen acceptor.[415] The process is essentially the reverse of that shown in **Scheme 68**, where acetone is reduced to propan-2-ol, with the appropriate alcohol enantiomer being oxidised into the corresponding enantiomerically-enriched ketone. Selected results of this transformation are shown below in **Scheme 79**, showing the enantioselectivity of the residual alcohol.



Scheme 79 – Kinetic resolution of secondary alcohols by Ruthenium catalysed oxidation[415]

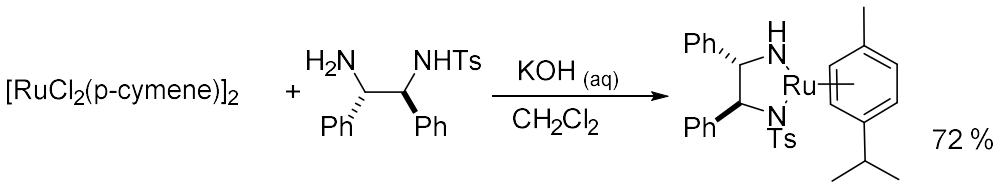
The resolution of racemic indan-1-ol and α-tetralol gave the (*R*)-enantiomers in 97-99 % e.e. at 50-55 % conversion upon being subjected to the (*S*,*S*)-catalyst. Many of the given examples were also difficult to obtain in high enantiomeric purity by reduction of the corresponding ketone with 2-propanol.[416-418]

Encouraged by these results, the following research was performed in accordance with the aforementioned method,[415] and is discussed below.

Results and Discussion

In this current study, the following oxidative kinetic resolution was performed in accordance with the method provided by Noyori et al.[415]

Synthesis of the active catalyst for this reaction was performed using Noyori's procedure, yielding dark purple crystals for the 16 electron species. Unfortunately, attempts at obtaining a crystal structure were unsuccessful, however the spectroscopic and observational data was consistent with the literature.[415] Formation of the catalyst is shown below in **Scheme 80**.

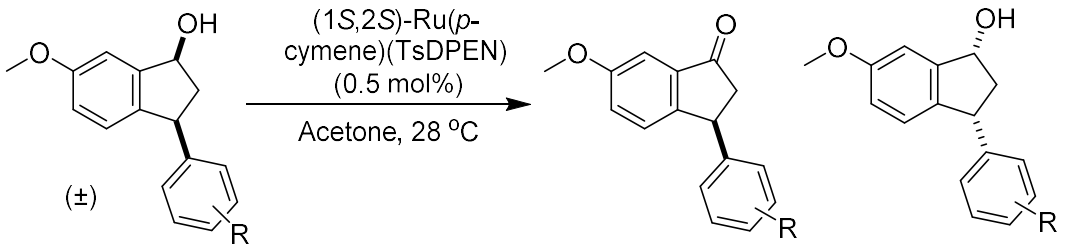


Scheme 80 – Synthesis of Ru Complex (1*S*,2*S)*-Ru(*p*-cymene)(TsDPEN), **115**

Although both the (*R*,*R*)- and (*S,S*)- ruthenium catalysts were synthesised, only the (*S*,*S*)-**115** ruthenium catalyst was employed for the following oxidative kinetic resolutions.

Firstly, the reaction was performed on the 6-methoxy-3-aryl indan-1-ol substituents, as shown below in **Table 21**. As the reactions were allowed to proceed to less than 50 % conversion, only the ketone enantioselectivity was analysed.

Table 21 – Oxidative Kinetic Resolution of Substituted Racemic *cis*-6-methoxy-3-arylindan-1-ols



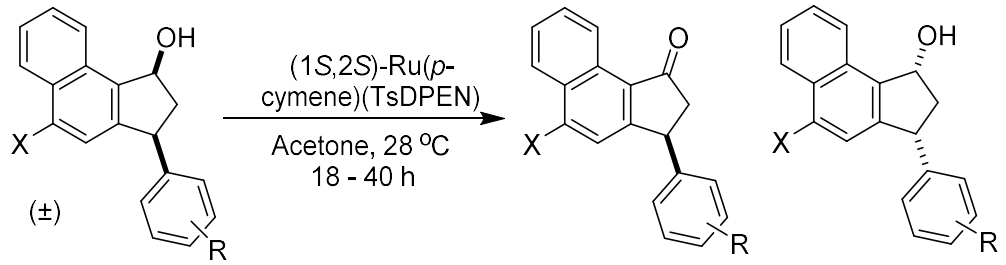
Racemic *cis*-Indan-1-ol		Ratio	Conversion	Ketone (*S*)
R-		Alcohol : Ketone	(%)	e.e.% [c]
80	H	1.9 : 1	33	78
81	4-OCH_3	2.8 : 1	26	86
82	3,4-OCH_3	2.0 : 1	34	70
85	4-F	2.6 : 1	38	99
86	4-Cl	1.2 : 1	45	78

[a] Conversion determined by ^{1}H NMR Analysis; [b] Isolated yield, as a % of racemic starting material; [c] e.e. % determined by chiral HPLC analysis (see **Chapter 5**).

The stereochemistry of each product was confirmed by analogy, where both enantiomers of the 6-methoxy-3-phenylindan-1-one, (*R*)-**59** and (*S*)-**59**, were consistent with literature reports.[216] Additionally, these results were consistent with those obtained from the enzymatic acylation kinetic resolution. The enzymatic approach for these substrates was generally considered more suitable for the above substrates, however, the ruthenium oxidation did provide opportunity for the kinetic resolution of the naphthyl- derivatives, where they were unsuccessful in the enzymatic acylation.

Encouraged by these results, the following substituted naphthylen-1-ols were subjected to the oxidative kinetic resolution method. The (*S,S*)-catalyst, **115** was used with acetone as the proton acceptor; the results being shown below in **Table 22**.

Table 22 – Oxidative Kinetic Resolution of Substituted Racemic *cis*-Indan-1-ols

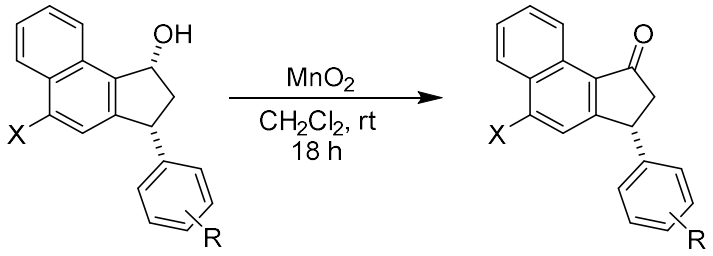


Racemic *cis*-Indan-1-ol			Conv. % [a]	Ketone (*S*)			Alcohol (1*R*,3*R*)		
	R-	X-			Yield % [b]	e.e.% [c]		Yield % [b]	e.e.% [c]
93	H	Br	35	**72**	32	>99		-	33
			57[d]		-	-	**93**	40	87
94	4-OCH_3	Br	50	**73**	48	96	**94**	48	95
95	2,3-OCH_3	Br	50	**74**	47	96	**95**	48	>99
97	3,4,5-OCH_3	Br	52	**76**	49	96	**97**	46	>99
98	2,3,4-OCH_3	Br	55	**77**	51	93	**98**	39	>99
99	4-F	Br	43	**78**	41	95		-	60
			56[d]		-	-	**99**	41	>99
100	4-Cl	Br	48	**79**	40	91	**100**	42	>99
89	H	H	49	**68**	46	76	**89**	46	80
90	3,4,5-OCH_3	H	51	**69**	46	91	**90**	45	97
91	3,4,5-OCH_3	F	52	**70**	47	98	**91**	46	>99
92	3,4,5-OCH_3	Cl	48	**71**	44	96	**92**	48	95

[a] Reaction conversion determined by ^{1}H NMR Analysis; [b] Isolated yield, as a % of racemic starting material; [c] e.e. % determined by chiral HPLC analysis (see **Chapter 5** for conditions); [d] Conversion after second oxidative kinetic resolution, after separation of both materials from the first resolution.

The residual alcohol products where then oxidised using MnO_2 to give the corresponding enantiomerically enriched indan-1-ones (**Table 23** below).

Table 23 – Manganese Oxidation of *cis*-Enantiomerically Enriched Indan-1-ols



Entry	Alcohol (1*R*,3*R*)-	R Group	X Group	Indanone	Yield % [a]
1	**93**	H	Br	(*R*)-**72**	77
2	**94**	4-OCH_3	Br	(*R*)-**73**	81
3	**95**	2,3-OCH_3	Br	(*R*)-**74**	81
4	**97**	3,4,5-OCH_3	Br	(*R*)-**76**	87
5	**98**	2,3,4-OCH_3	Br	(*R*)-**77**	69
6	**99**	F	Br	(*R*)-**78**	80
7	**100**	Cl	Br	(*R*)-**79**	79
8	**89**	H	H	(*R*)-**68**	72
9	**90**	3,4,5-OCH_3	H	(*R*)-**69**	89
10	**91**	3,4,5-OCH_3	F	(*R*)-**70**	91
11	**92**	3,4,5-OCH_3	Cl	(*R*)-**71**	86

[a] Isolated yield.

In summary, the oxidative kinetic resolution method shown in this study provides a novel method for the access of enantiomerically enriched indan-1-ols and indan-1-ones, not previously accessible by other methods tried previously in this project.

2.7 Conclusions

In this chapter, we have illustrated the difficulty in synthesising specific enantiomerically enriched 3-arylindan-1-ones by some existing methodologies. A reductive Heck cyclisation method[216] gave poor yields and enantioselectivity for the desired substrates. Additionally, a cyclisation of enantiomerically enriched 3,3-diaryl propanoic acids was attempted, but remained unsuccessful.

We have shown an enzymatic acylation kinetic resolution for 3-aryl indan-1-ols, which were synthesised from the corresponding indan-1-ones. This resolution provided both the (*R*)-acylated and recovered (*S*)-indan-1-ols in excellent enantioselectivities and in near quantitative yields. Furthermore, due to the relatively low environmental implications associated with enzymatic catalysts, this method provided an ideal prospect for the scale-up of certain substrates.[419]

Unfortunately, naphthyl-indan-1-ol derivatives were not acylated in the enzymatic resolution, and consequently an oxidataive kinetic resolution was performed, using an (*S,S*)-Ru catalyst, **115**. This method generally gave good enantioselectivities, yielding the desired (*R*)- and (*S*)-**76** indan-1-one precursor in 99 % e.e.

A summary of the enzymatic selectivity, (**E**), for the enzymatic acylation kinetic resolution and chemo-catalyst selectivity, (**S**), for the ruthenium oxidative kinetic resolution is shown in **Figure 32** below for each appropriate substrate. These have been calculated using **Equation 3** & **Equation 4** from **Section 2.3.1** The (1*R,*3*R*) is drawn and is the faster reacting enantiomer in the enzyme acylation reaction, and the recovered starting material in the (*S*,*S*)-catalysed oxidation. We had wished to obtain S-values from the ruthenium oxidation for all substrates, but this remains future work.

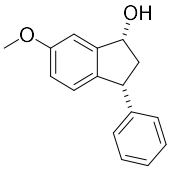
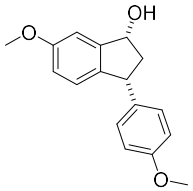
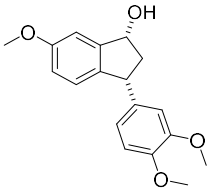
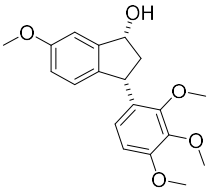
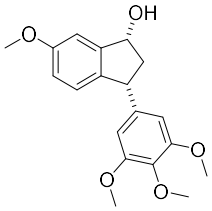
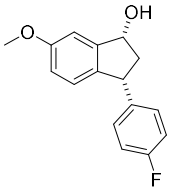
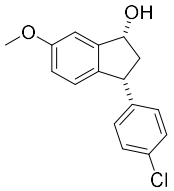
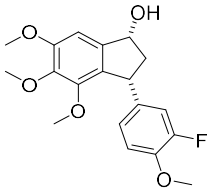
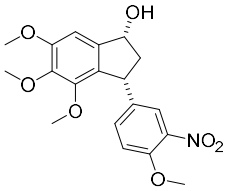
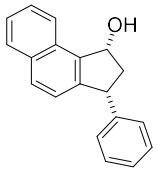
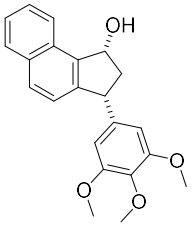
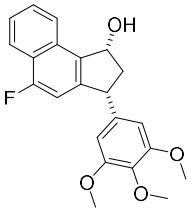
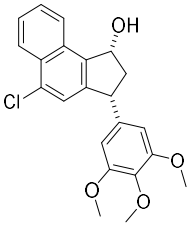
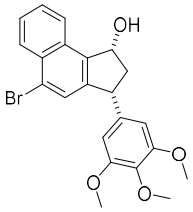
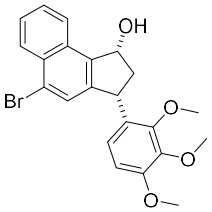
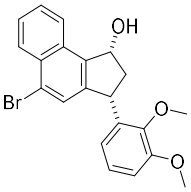
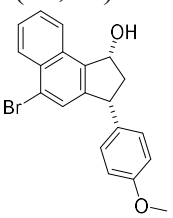
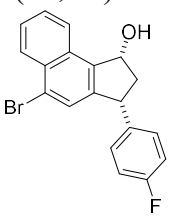
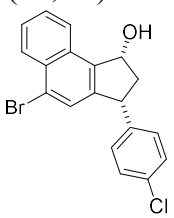
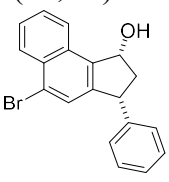
(1*R*,3*R*)-**80**  **E** = >100 [a] **S** = 13 [b]	(1*R*,3*R*)-**81**  **E** = >100 [a] **S** = 14 [b]	(1*R*,3*R*)-**82**  **E** = >33 [a] **S** = 8 [b]	(1*R*,3*R*)-**84**  **E** = >100 [a]
(1*R*,3*R*)-**83**  **E** = >100 [a]	(1*R*,3*R*)-**85**  **E** = >100 [a] **S** = >100 [b]	(1*R*,3*R*)-**86**  **E** = >100 [a] **S** = 16 [b]	(1*R*,3*R*)-**87**  **E** = >100 [a]
(1*R*,3*R*)-**88**  **E** = >100 [a]	(1*R*,3*R*)-**89**  **E** = No reaction **S** = 16 [b]	(1*R*,3*R*)-**90**  **E** = No reaction **S** = 78 [b]	(1*R*,3*R*)-**91**  **E** = No reaction **S** = >100 [a]
(1*R*,3*R*)-**92**  **E** = No reaction **S** = >100 [b]	(1*R*,3*R*)-**97**  **E** = No reaction **S** = >100 [a]	(1*R*,3*R*)-**98**  **E** = No reaction **S** = 49 [a]	(1*R*,3*R*)-**95**  **E** = No reaction **S** = >100 [b]
(1*R*,3*R*)-**94**  **E** = No reaction **S** = >100 [b]	(1*R*,3*R*)-**99**  **E** = No reaction **S** = 16 [a]	(1*R*,3*R*)-**100**  **E** = No reaction **S** = 56 [b]	(1*R*,3*R*)-**93**  **E** = No reaction **S** = >100 [b]

Figure 32 – Summary of catalyst selectivity factors, where E represents enzyme selectivity and S represents the ruthenium oxidation selectivity; [a] Based on recovered starting material (*alcohol*). [c] Based on products.

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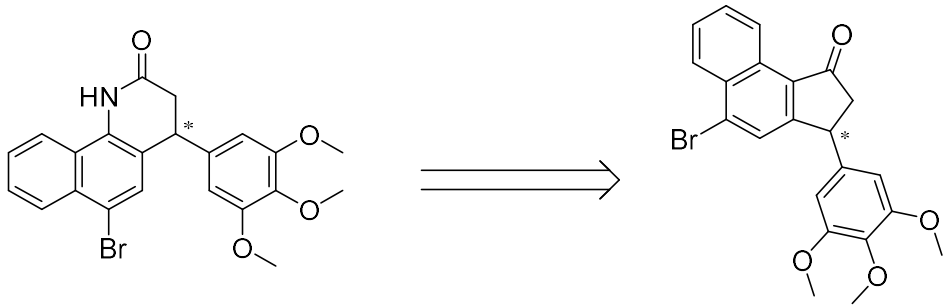
CHAPTER 3- ASYMMETRIC SYNTHESIS OF SUBSTITUTED 4-ARYLQUINOLIN-2-ONES

3.1 Introduction

This chapter discusses research towards the synthesis of enantiomerically enriched 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones from the corresponding 3-arylindan-1-ones synthesised in the previous chapter. The intention is to asymmetrically synthesise both enantiomers of compound 6-B345TTQ, **1**, for biological testing, and to identify the active enantiomer. A disconnection for this approach is shown below in **Scheme 81**.

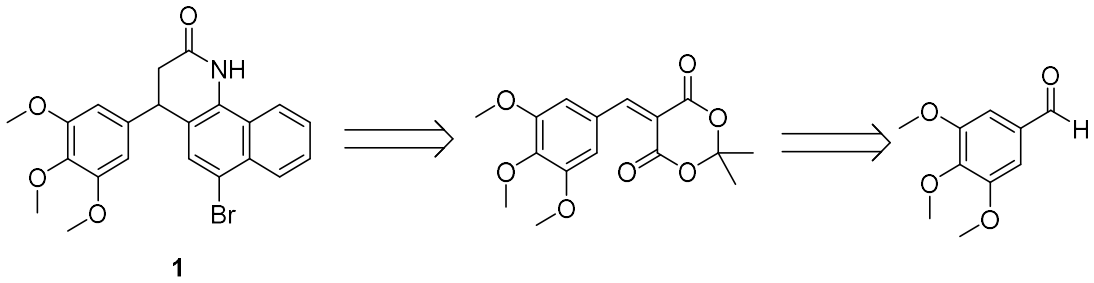


Scheme 81 – Disconnection approach for the synthesis of compound 6-B345TTQ, **1**

Consequently, this chapter will focus on the Beckmann rearrangement of indan-1-one derivatives. This synthetic approach was chosen from literature in this field showing examples for similarly related structures, and is discussed below. The precursors for this transformation will be the naphthyl-indan-1-one compounds synthesised from the oxidative kinetic resolution, **Table 22**, **Chapter 2**.

3.1.1 Previous Synthesis of Racemic 4-Arylquinolin-2-ones

Previous work[420] in our research group has focused on the synthesis of compounds 6-B345TTQ, **1**, as a racemate, and structurally similar analogues. The synthetic approach involved a two-step process, encompassing the formation and subsequent reaction of substituted arylidene derivatives (**Scheme 82**).



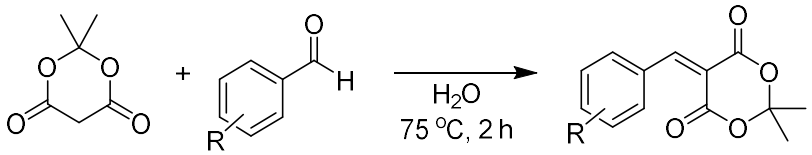
Scheme 82 – Disconnection of compound of racemic compound, 6-B345TTQ, **1**.

This process was important for comparison of spectroscopic data to results obtained within this chapter, and for comparative biological testing of racemates with their corresponding enantiomers. This two-step synthetic process is discussed below.

Knoevenagel Condensation

The first step involved a Knoevenagel condensation using substituted aromatic aldehydes with 2,2-dimethyl-1,3-dioxane-4,6-dione, Meldrum's acid. Although this reaction is generally catalysed by bases such as pyridines,[421,422] or by pyridine / glacial acetic acid in benzene with water removal,[423] the applied method was based on previous work by Bigi et al.,[424] performing a Knoevenagel condensation by heating at 75 °C in water. Excellent yields were obtained for this transformation particularly for electron donating substituents.[420] These results obtained in this previous work are discussed below (**Table 24**).

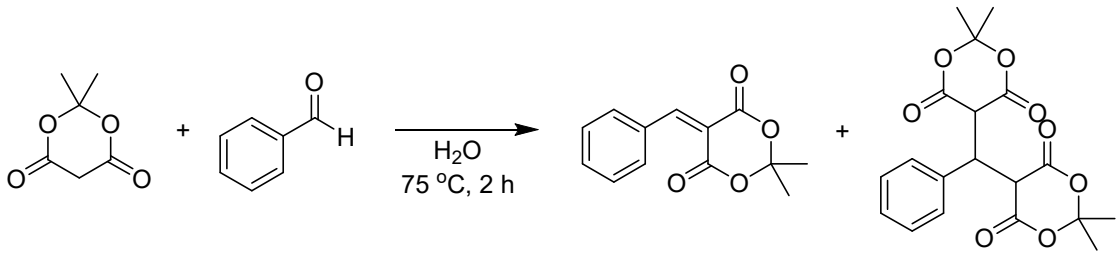
Table 24 – Knoevenagel condensation of aromatic aldehydes with Meldrum's acid[420]



Entry	R Groups	Yield (%) [a]
1	3,4,5-OCH_3	90
2	2,3,4-OCH_3	91
3	2,4,5-OCH_3	88
4	2,3-OCH_3	85
5	3,4-OCH_3	87
6	4-OCH_3	83
7	4-F	64 [b]
8	4-Cl	59 [b]
9	H	(*bis*-adduct formation)

[a] Isolated yield; [b] *Bis*-adducts were additionally observed, although products were more easily separated from the *bis*-product, albeit with a reduced yield.

The presence of the *bis*-adduct formation (**Scheme 83**) from the reaction with benzaldehyde (and aldehydes with electron withdrawing substituents) was observed. Solvent effects appeared crucial, as performing the ^{1}H NMR in d_6-DMSO resulted in the *bis*-adduct forming an equimolar mixture of arylidene and Meldrum's acid.

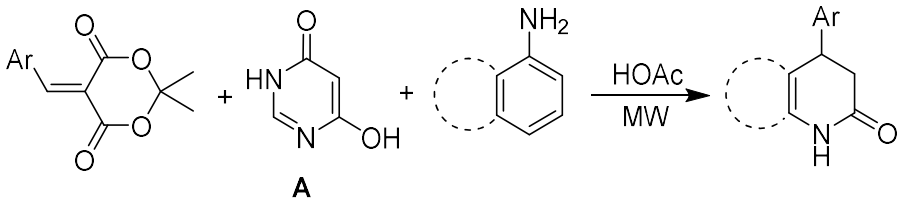


Scheme 83 – Formation of a *bis*-adduct in the Knoevenagel condensation[420]

Consequently a more judicious choice of solvent was required to minimise the formation of the *bis*-adduct (DMSO for example), or an excess of aldehyde. As it was found that generally the product precipitates out of solution, excess aldehyde was used.

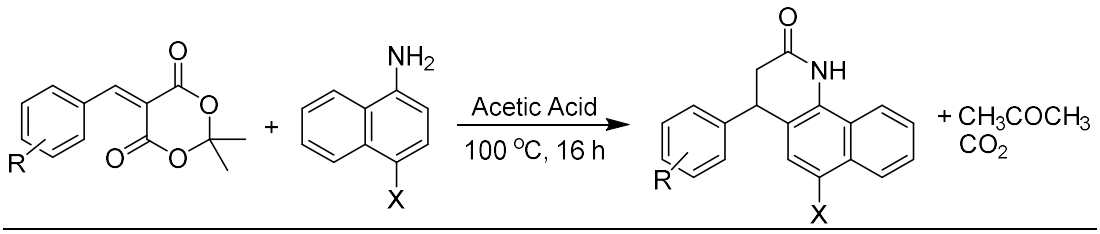
Conjugate Addition Reaction

The reaction of the arylidene products formed previously into the corresponding 4-arylquinolin-2-ones was by a method developed by Hao et al.,[425] (**Scheme 84**), with the results being shown below in **Table 25**. The reaction was reported as a microwave-assisted process towards the synthesis of some spirocyclic compounds,[425] but fortunately gave quinolin-2-ones. **Scheme 84-A** was found to not participate in the reaction.



Scheme 84 – Synthesis of quinolin-2(1*H*)-one Derivative

Table 25 – Conjugate addition of aromatic amines to arylidene-derivatives[420]

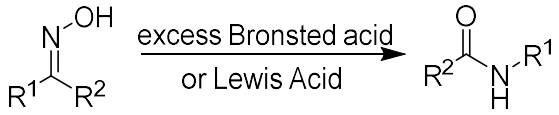


Entry	R-Groups	X Groups	Yield %
1	3,4,5-OCH_3	H	55
2	3,4,5-OCH_3	Cl	58
3	3,4,5-OCH_3	Br	60
4	2,3,4-OCH_3	Br	51
5	3,4-OCH_3	Br	66
6	2,3-OCH_3	Br	62
7	4-OCH_3	Br	69
8	4-F	Br	54
9	4-Cl	Br	53

This previously reported work[420] provided spectroscopic data for compound 6-B345TTQ, **1**, and similarly related compounds.

3.1.2 Beckmann Rearrangements toward Quinolin-2-ones

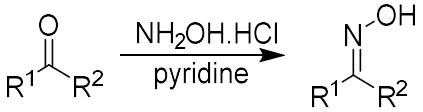
The conversion of aldoximes and ketoximes to the corresponding amides under acidic conditions is known as the Beckmann rearrangement.[426] It is especially useful in the industrial synthesis of ε-caprolactam, an important monomer for the production of synthetic fibres.[427,428] More commonly, the Beckmann rearrangement is performed in strongly acidic and dehydrating media, including phosphorus pentachloride, concentrated sulfuric acid, or the so-called 'Beckmann's mixture', containing acetic acid, acetic anhydride and hydrogen chloride.[429]



Scheme 85 – General Beckmann rearrangement to *N*-substituted amides

The R group *anti* to the leaving group on the nitrogen will migrate, (R^1 in the example shown in **Scheme 85**), however if the oxime isomerises under the reaction conditions, a mixture of two amide products are obtained.[430]

Formation of the oxime is generally prepared using hydroxylamine as the reactant with a suitable acid or base catalyst, with many examples present in the literature.[431-436] A traditional procedure involves refluxing the ketone and hydroxylamine hydrochloride in pyridine,[437] shown below in **Scheme 86**.



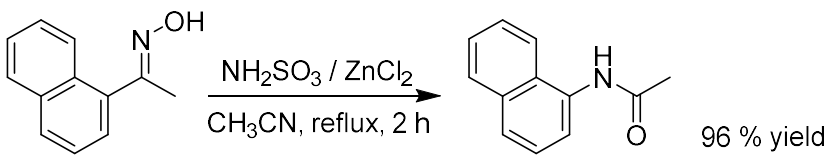
Scheme 86 – Transformation of a ketone to its corresponding oxime derivative[437]

Additionally, oximes may be converted to *O*-substituted oximes, typically *O*-tosyl oximes, allowing milder transformations than in traditional Beckmann conditions.[438]

Classical media for Beckmann rearrangements of unsubstituted oximes are strongly acidic conditions, using concentrated sulfuric acid,[439] anhydrous hydrogen fluoride,[440] aluminium chloride[441] or polyphosphoric acid,[442] usually with good yields. Many of these reagents are not suitable for large-scale synthesis or sensitive substrates, [443,444] and thus, enormous efforts[445] have been dedicated to the development of milder and more effective versions of this reaction.

Along this line, a wealth of useful reagents have been used, including; silica gel,[446] thionyl chloride,[447] montmorillonite KSF,[448] P_2O_5,[449] bismuth (III) chloride,[450] PCl_5,[451] dichlorophosphate,[452] cyanuric chloride,[453,454] molydenum trioxide on silica gel,[455] HSO_3Cl,[456] and gallium (III) triflate.[457] A variety of metallic Lewis acid catalysts have also been utilised, including; $[RhCl(cod)]_2$,[458] $Yb(OTf)_3$,[459] $RuCl_3$,[460] and $HgCl_2$.[461] Several liquid-phase catalysis have also be employed such as ethyl chloroformate / boron trifluoride etherate,[462] sulfamic acid,[454] anhydrous oxalic acid,[463] chlorosulfonic acid,[453] bis(2-oxo-3-oxazolidinyl) phosphoric chloride,[464] and diethyl chlorophosphate.[465]

Conveniently, naphthyl groups have been shown to migrate with high selectivity offering excellent yields using a NH_2SO_3 / $ZnCl_2$ catalyst system, (**Scheme 87**).[466]

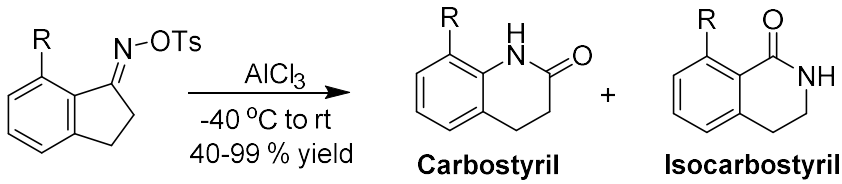


Scheme 87 – Beckmann rearrangement catalysed by NH_2SO_3H / $ZnCl_2$ [466]

Similar results have been found for this transformation using cyanuric chloride,[453,454] or using triphosphazene catalyst system.[467]

Beckmann rearrangements of indan-1-one oxime derivatives have been performed using a number of reagents with varying success. Substituents on the indanone ring have a profound effect on the ratio of isomers formed (**Table 26**).[468]

Table 26 – Aluminium chloride-catalysed Beckmann rearrangement[468]

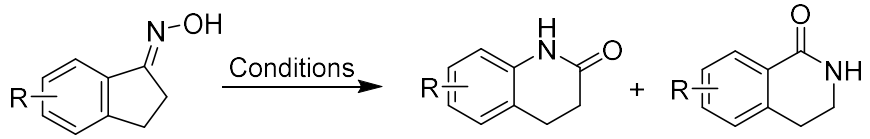


R Groups	(*E*) / (*Z*) Oxime Ratio	Yield (%)	
		Carbostyril	Isocarbostyril
H	97 / 3	92	8
CH_3	100 / 0	85	15
OCH_3	100 / 0	74	26
NO_2	80 / 20	27	73

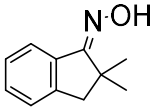
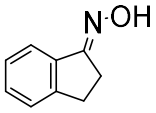
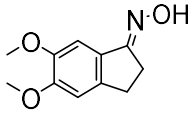
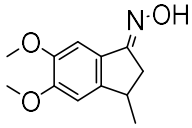
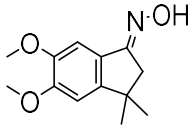
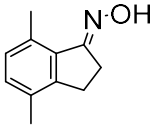
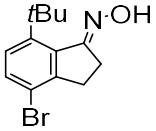
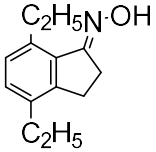
Lee and colleagues[468] showed that in the absence of Lewis acids the rotational barrier of the oxime C=N bond is quite high, but in the presence of Lewis acid catalysts the rotational barrier is lower.[438] The complex formation of $AlCl_3$ and tosylate allows double bond rotation with the product distribution being determined by the relative stability of the oxime (*E*) / (*Z*) isomers. Torisawa et al.[469] found a similar result, although they proposed a 1,2-pinacol rearrangement around a single C-N bond.

Similar reports across a variety of publications have shown different isomer ratios depending on the substituents on the indan-1-one structure. Beckmann rearrangements of these substrates are shown with their respective ratio of isomers in **Table 27**.[443]

Table 27 – Beckmann rearrangements of different Indan-1-one substrates[443]



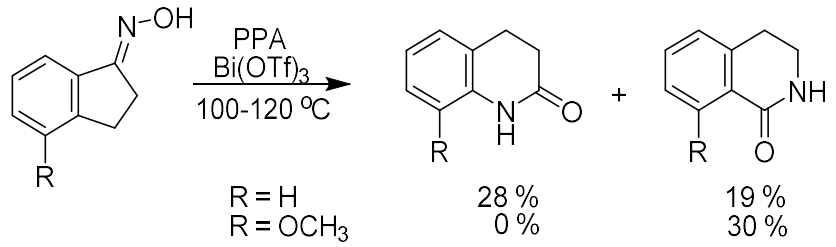
Indan-1-one Oxime Derivatives | **Carbostyril** (*Aryl migration*) | **Isocarbostyril** (*Alkyl migration*)

Entry	Substrate	Conditions	Ratio (% migration) [a]		Ref.
			Carbostyril	Isocarbostyril	
1		PPA, 125-130 °C	100	- [b]	470
2		PPA, 110-130 °C, 5-10 min	90	10	471
3		PPA, 100 °C, 75 min	100	- [b]	472
4		P_2O_5 / CH_3SO_3H	- [b]	100	473
5		P_2O_5 / CH_3SO_3H	- [b]	100	473
6		PPA, 110-130 °C, 5-10 min	34	66	471
7		PPA, 110-130 °C, 5-10 min	19	81	471,474-476
8		PPA, 110-130 °C, 5-10 min	27	73	471

[a] Based on lactams only; [b] Limited discussion on isomeric ratio.

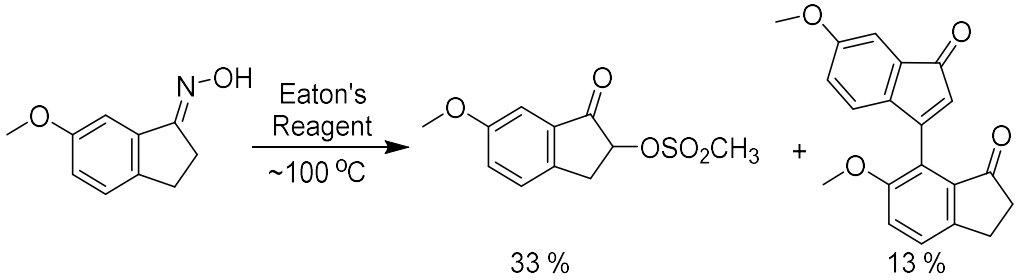
The example in **Table 27**, **Entry 1**, additionally reported some fragmentation in the reaction, from the presence of a nitrile band in infrared spectroscopy. The structure however was not elucidated. Some of these publications are seemingly old too, and thus there is concern to the reported ratio, but nonetheless, these results provide an insight into influence of the substrate in the Beckmann rearrangement.[147]

Similar substrate changes were observed upon the acidic rearrangement of indanone oximes using PPA and $Bi(OTf)_3$ (**Scheme 88**). The carbostyril core was found to be highly dependent of the substituent of the aromatic ring, regardless of the stereochemistry of the oximes.[438]



Scheme 88 – Beckmann rearrangement of different substituted indan-1-ones

Torisawa et al.[147] found that performing the rearrangement with Eaton's reagent (P_2O_5-CH_3SO_3H), failed to give normal Beckmann products (carbostyril or isocarbostyril) with methoxyindan-1-one oximes, (**Scheme 89**).

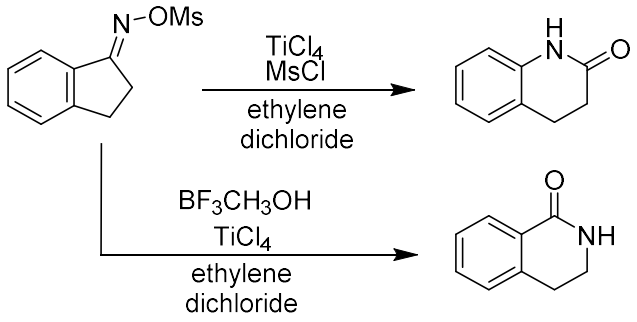


Scheme 89 – Formation of α-sulfonyloxy- and dimeric- products with Eaton's reagent

Further experimentation with the tosylate derivative yielded the same products albeit in a slightly higher yield, with the remainder of the products being oxime or ketone.

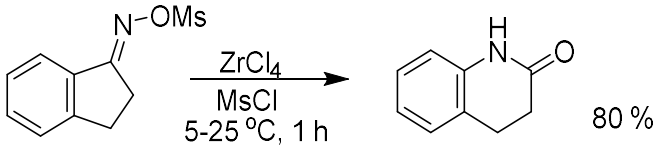
Beckmann reagents have been reported to effect selective (thus two directional) transformations from a single oxime isomer using polyphosphoric acid, as reported by Paquette et al.[477] Accordingly, Torisawa et al.[478], reported selective conversion into the corresponding isocarbostyril using $TiCl_4$.

Remarkably, $TiCl_4$ in the presence of mesyl chloride and ethylene dichloride yielded the carbostyril product, but replacement of MsCl with BF_3CH_3OH as a key additive,[469] effective conversion into the isocarbostyril was found in near quantitative yields,[478] (**Scheme 90**). Oxime mesylates were also found to be superior to tosylates.[479]



Scheme 90 – Two directional Beckmann rearrangements

$ZrCl_4$ was found to be sluggish in the same conditions presented towards the isocarbostyril compounds, (with BF_3CH_3OH, **Scheme 90**), although it was presented as a suitable promoter for carbostyril synthesis.[469] The reaction was successful using $ZrCl_4$ with BF_3OEt_2 as the solvent,[479] however, upon discovering that residual MsCl in samples from oxime mesylation offered improved conversion, it was later realised that mesyl chloride as the solvent offered more optimised conditions, (**Scheme 91**).



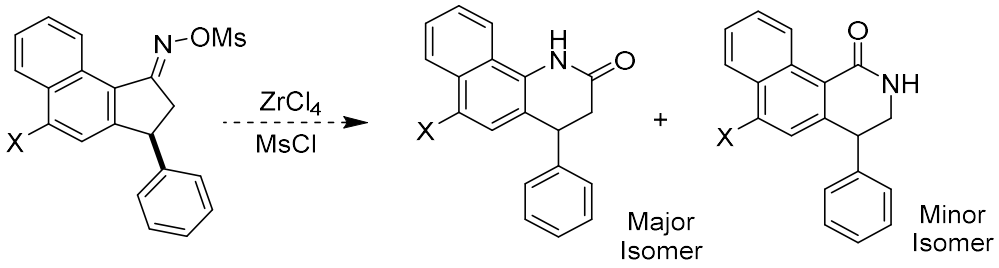
Scheme 91 – Beckmann rearrangement of indan-1-one oxime mesylates in the presence of $ZrCl_4$ and MsCl as a solvent[469]

It was hypothesised that $ZrCl_4$ offered stronger coordination, and thus less scrambling of the oxime mesylate in the transition state, relative to weaker acids like Eaton's reagent of $FeCl_3$, where mixtures of isomers were obtained.[469]

3.2 Results & Discussion

In this study, the appropriate naphthyl-indan-1-ones formed from the previous chapter were subjected to Beckmann conditions presented in the literature by Torisawa.[469] The method involved employing a $ZrCl_4$ catalyst in mesyl chloride as the solvent, with the appropriate indan-1-one oxime mesylates.

The intention was to transform the indan-1-one oxime mesylate into the corresponding 4-aryl-3,4-dihydroquinolin-2(1*H*)-one shown below in **Scheme 92**.



Scheme 92 – Beckmann rearrangement of 3-aryl indan-1-ones

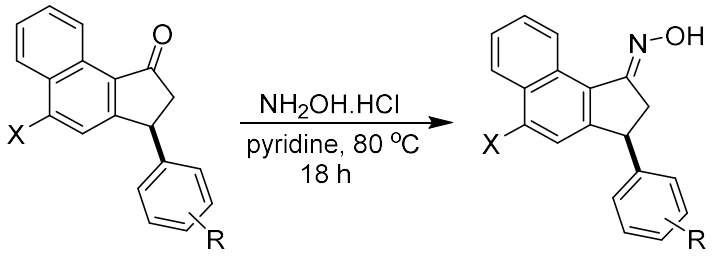
Given the advancements in indan-1-one Beckmann rearrangements presented by Torisawa,[469] the aim was to synthesise 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones as the major isomers, rather than the 4-aryl-3,4-dihydroquinolin-1(2*H*)-one. More specifically, the aim was to synthesise the target enantiomers of compound 6-B345TTQ, **1** and structurally similar analogues.

3.2.1 Indan-1-one Oxime Formation

Formation of the indan-1-one oxime derivatives was prepared by the common procedure, heating the appropriate ketone and hydroxylamine hydrochloride in pyridine for 18 hours, (**Scheme 86**).[437]

The reaction was carried out on the (*S*)-indan-1-one compounds formed from oxidative kinetic resolution, **Table 22**, in the previous chapter, giving the corresponding oximes in good yields. The results are shown below in **Table 28**.

Table 28 – 3-Arylindan-1-one oxime formation using NH_2-OH.HCl in pyridine



Entry	(*S*)-Ketone	R Groups	X Groups	Oxime	Yield % [a]
1	**68**	H	H	(*S*)-**123**	90
2	**70**	3,4,5-OCH_3	F	(*S*)-**122**	83
3	**72**	H	Br	(*S*)-**116**	88
4	**73**	4-OCH_3	Br	(*S*)-**117**	83
5	**76**	3,4,5-OCH_3	Br	(*S*)-**119**	84
6	**77**	2,3,4-OCH_3	Br	(*S*)-**118**	79
7	**78**	4-F	Br	(*S*)-**120**	90
8	**79**	4-Cl	Br	(*S*)-**121**	89

[a] Isolated yield.

Although a crystal structure was not obtained for the oxime products, the stereochemistry was deduced as *trans*- given previous literature reports.[468,469,480]

Lee et al.[468] found that *cis*-indan-1-one oximes were isomerised to *trans* even on mildly acidic silica, and although they could not isolate pure *cis*-oxime, they were able to isolate the more stable *trans*-oxime by subsequent recrystallization. The oxime substrates (**Table 28**) were recrystallized and isolated, where the ^{13}C NMR spectrum indicated the presence of only a single isomer.

Previously reported oximes, especially indan-1-one oximes, throughout this chapter were found to be predominately *trans*-, so it was reasonable at this point to assume the single oxime isomer isolated for each of the compounds in **Table 28** was indeed *trans*.

One can imagine that the relative stability of the *trans*-oxime isomer mesylate is greater than that of the *cis*-isomer, given the steric repulsion between the mesyl group and the naphthyl-ring (C_{Ar}-H), (**Figure 33**).

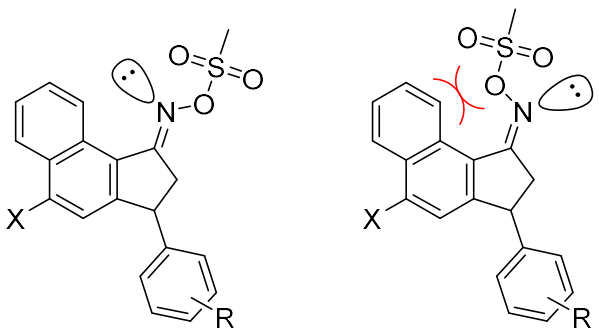
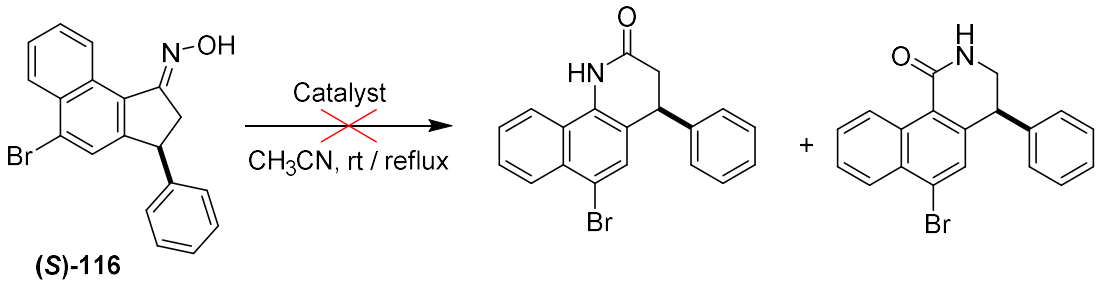


Figure 33 – Diagram showing the *trans*-oxime mesylate (*left*) compared with the *cis*-oxime mesylate isomer (*right*)

Consequently, by analogy, these compounds were deduced as the more stable *trans*-isomer, given the overwhelming reported data mentioned previously in **Section 3.1.2**.

3.2.2 Beckmann Rearrangement

Initial experiments involved the Beckmann rearrangement of the indanone oxime, (*S*)-116, with $AlCl_3$ (3 equiv.),[468] both at room temperature and at reflux in acetonitrile. Additionally, changing the catalyst to phenyl dichlorophosphate (1.5 equiv.),[481] at both ambient or reflux temperature in acetonitrile yielded the same results (**Scheme 93**).

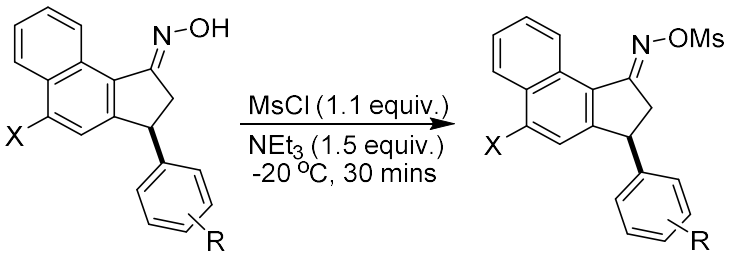


Scheme 93 – Attempted Beckmann rearrangement of substrate (*S*)-116

In both cases, only the starting oxime, (*S*)-116, was observed, with some hydrolysed ketone product, (*S*)-**72**, also identified in small amounts.

Consequently, in this study, our attention for the Beckmann reactions were performed in accordance with the procedure from Torisawa et al.,[469] (**Scheme 91**), using a zirconium (IV) chloride catalyst and mesyl chloride as the solvent. At least 3 equivalents of $ZrCl_4$ were required for optimisation in accordance with the literature.[468]

The oxime mesylates were formed from the corresponding indan-1-one oxime derivatives shown in **Table 28**. These were synthesised using mesyl chloride and triethylamine in dichloromethane at -20 °C, (**Scheme 94**).



Scheme 94 – Formation of indan-1-one oxime mesylates

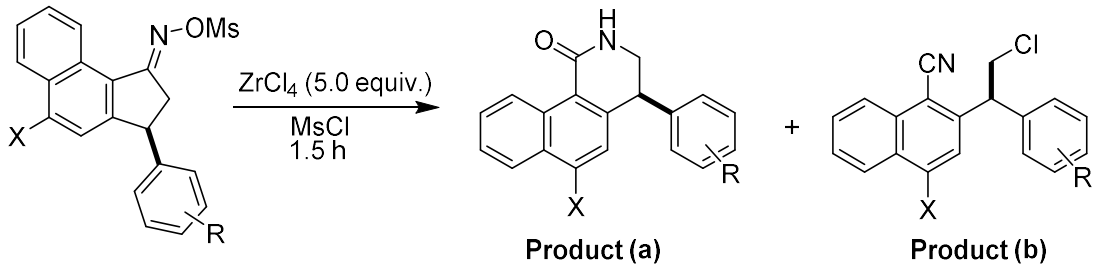
The mesylates were not fully characterised, but were identified using ^{1}H NMR spectroscopy, formed in near quantitative yields. They were then immediately reacted in the Beckmann conditions presented by Torisawa.[469]

Initial inspection of the ^{1}H NMR spectrum of the crude reaction mixture indicated there were indeed two products as anticipated, however, to our surprise, upon comparison of the ^{1}H NMR spectrum to those of the racemic products formed in previous work (**Section 3.1.1**) the desired products, 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones, were not formed at all.

Separation of the two products and subsequent analysis confirmed that the 4-aryl-3,4-dihydroquinolin-1(2*H*)-one product was formed, (**Table 29**). This was deduced upon comparison of the ^{1}H NMR spectrum with the racemic compounds formed from **Section 3.1.1**, where a relatively downfield signal was observed for the CH_2 cyclic protons, with additional ^{3}J coupling to NH, consistent with literature.[468]

The other product was seemingly more challenging to identify, however, analysis of the mass spectrum and IR, (showing the presence of a nitrile group (2217 cm^{-1})), it was found that the product was rather unexpectedly formed as a 2-(chloro-1-arylethyl)-1-naphthonitrile derivative. These results are shown below in **Table 29**.

Table 29 – Beckmann rearrangement of 3-arylindan-1-one mesylated oximes using $ZrCl_4$ in mesyl chloride



Oxime	R Groups	X Groups	Ratio [a] (a:b)	Product (a)		Product (b)	
				Product	Yield % [b]	Product	Yield % [b]
(*S*)-123	H	H	37 : 63	**(*S*)-137**	30	**(*S*)-138**	55
(*S*)-122	3,4,5-OCH_3	F	60 : 40	**(*S*)-135**	49	**(*S*)-136**	31
(*S*)-116	H	Br	48 : 52	**(*S*)-124**	45	**(*S*)-125**	45
(*S*)-117	4-OCH_3	Br	5 : 95	**(*S*)-126**	5	**(*S*)-127**	70
(*S*)-119	3,4,5-OCH_3	Br	53 : 47	**(*S*)-129**	50	**(*S*)-130**	35
(*S*)-118	2,3,4-OCH_3	Br	8 : 92	**-**	- [c]	**(*S*)-128**	66
(*S*)-120	4-F	Br	32 : 68	**(*S*)-131**	28	**(*S*)-132**	52
(*S*)-121	4-Cl	Br	39 : 61	**(*S*)-133**	33	**(*S*)-134**	56

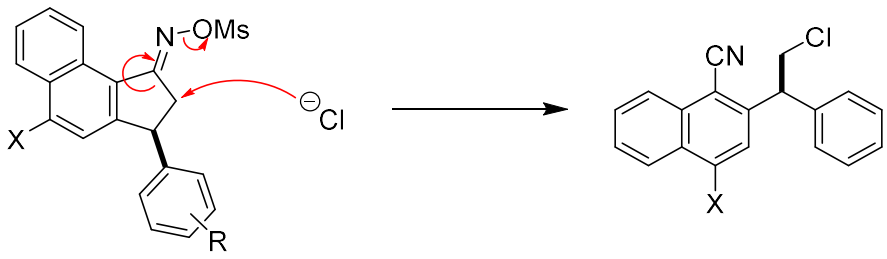
[a] Ratio determined by NMR; [b] Isolated yield; [c] Product not isolated from crude reaction mixture.

To our surprise, the reaction yielded the unusual quinolin-1(2*H*)-one isomer and the Beckmann fragmentation product. The ratio of these products varied greatly on substituents on the aromatic ring in addition to the X-group on the naphthyl ring, with no seemingly obvious trends to the obtained ratio.

Werner and Piguet first reported Beckmann fragmentation[482] in 1904,[483] where certain oximes, particularly oximes having a quaternary centre *anti* to the hydroxyl leaving group, are likely to undergo the rearrangement to form nitriles instead of amides.[484] This process is sometimes called a secondary Beckmann rearrangement,[485] Beckmann fission[486] or abnormal Beckmann rearrangement,[487] where other oximes such as bridged bicyclic ketoximes,[488,489] or oximes with an electron donating substituent at the α-carbon can also undergo fragmentation.[484]

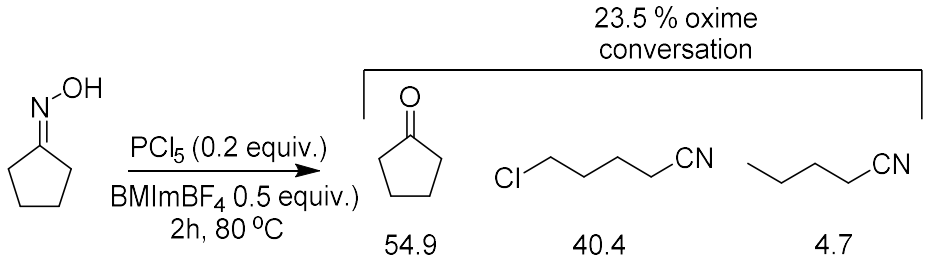
In some cases, the fragmentation product is largely predominant, or sometimes even the only product observed.[438] Fragmentation occurs when the α-carbon-carbon bond breaks rather than migrates, and becomes increasingly important when assisted by neighbouring groups, either through hyperconjugation or by electron donation, when the ability of the α-carbon atom to support a positive charge increases. Such examples are quaternary carbons, benzylic carbons or α-amino / hydroxy oximes.[438]

Examples involving indanone or tetralone derivatives have previously been reported with polyphosphoric acid.[490] Examples of α-hydroxy oximes under Beckmann conditions have also been shown to give fragmented products,[483,491] however, chlorinated substituted fragmentation products remain limited.[139,492] For the results obtained in **Table 29**, a plausible mechanism is shown below in **Scheme 95**.



Scheme 95 – Possible mechanism towards unexpected fragmentation product

Literature examples appear limited for this type of reaction involving a ring opening from chloride, although it has been observed before as shown in **Scheme 96**,[451] where the corresponding Beckmann fragmentation products were observed unexpectedly.



Scheme 96 – Beckmann rearrangement of cyclopentanone oxime in $BMImBF_4/PCl_5$

The cyclopentanone oxime was formed at a much lower conversion than the cyclohexanone oxime, where the corresponding lactam was observed.[451] It has been reported that the ring strain was the driving force for fragmentation.[493,494]

Previous literature results indicated that the selection of catalyst and solvent was crucial for the conversion of indan-1-ones into carbostyrils,[478,479,495] and thus it appears for the results obtained in **Table 29**, it is likely to be subjective to the catalyst / solvent conditions. Future work for the synthesis of the desired 4-aryl-3,4-dihydroquinolin-2(*H*)-ones are discussed in **Chapter 4**.

3.3 Conclusion

In this chapter, we have shown an unexpected outcome to the Beckmann rearrangement of naphthyl-indan-1-one oxime mesylates, formed from the corresponding ketones from **Chapter 2**. The work herein has demonstrated a Beckmann fragmentation reaction under the conditions presented, with a possible mechanism accounting for these observations, as well as a potential enantioselective route to aryl-isocarbostyril derivatives. Measurement of product enantioselectivities will require the synthesis of racemic compounds for chiral HPLC comparison.

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CHAPTER 4- CONCLUSIONS

Ginsberg et al.[90] published research identifying a small molecule that inhibits the interaction of paxillin and α4-integrin, inhibiting accumulation of leukocytes to the site of inflammation. The identified compounds were published and patented[104] as a racemate, shown below in **Figure 34**.

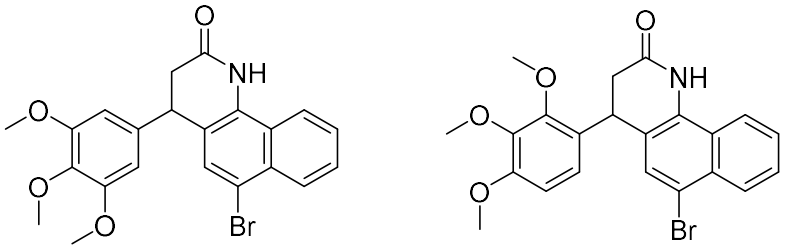


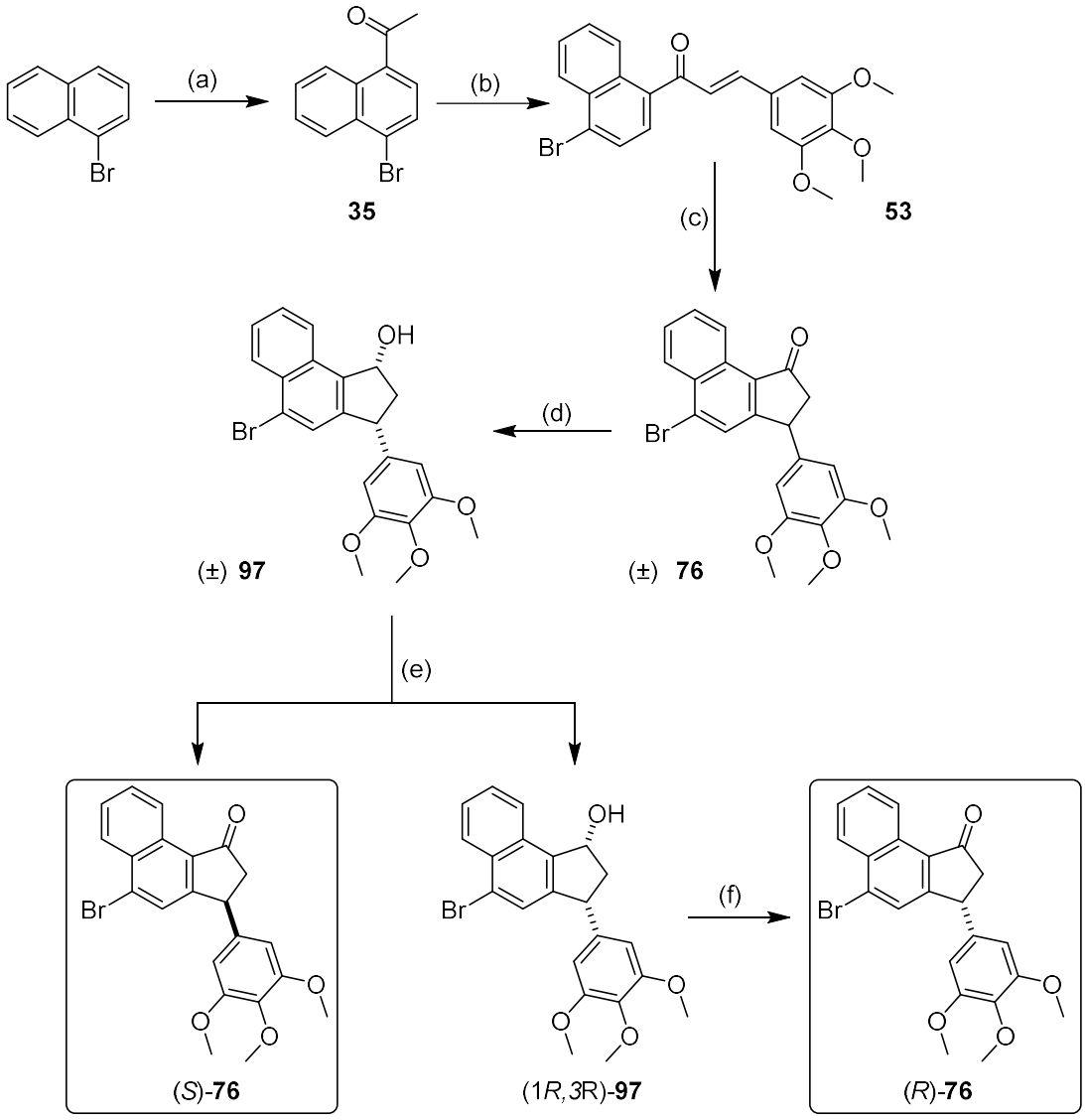
Figure 34 - Compound 6-B345TTQ (**1**) and its analogue, 6-B234TTQ (**2**)

The synthesis of indan-1-one precursors to this compound and its analogues were synthesised in Chapter 2. Initial methods were attempted, including a reductive heck cyclisation, using the procedure from Buchwald et al,[216] and a conjugate addition reaction,[203] using an Evans auxiliary and an aryl cuprate. These methods were deemed unsuccessful, either from poor enantioselectivity or from being unable to cyclise the appropriate 3,3-diarylpropionic acid, respectively.

Consequently, our attention turned to kinetic resolution, where Novozym® 435 was used to selectively acylate various substituted (1*R*,3*R*)-3-aryl indan-1-ols with excellent enantioselectivities for both the acetate and the recovered alcohol starting material. This provided a small catalogue of indan-1-ones which were utilised further.

Unfortunately the enzyme was unable to acylate the desired naphthyl-indan-1-ol derivatives, and thus other kinetic resolutions methods were tried.

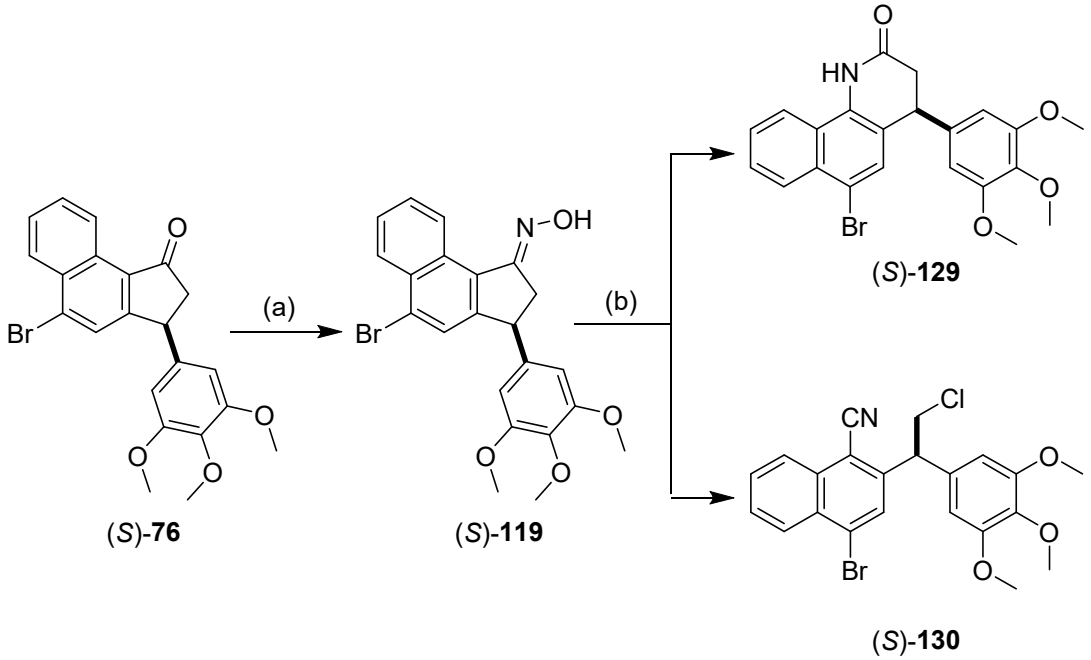
Although a ruthenium asymmetric transfer hydrogenation was attempted, resulting in a mixture of *cis*- and *trans*- indan-1-ol isomers with poor enantiomeric excess, the ruthenium catalysed oxidative kinetic resolution of racemic *cis*-indan-1-ols selectively oxidised the (1*S*,3*S*)-alcohol with excellent enantioselecitivites for both the ketone and the recovered alcohol starting material. The process for the synthesis of this precursor, (and thus similarly related analogues), is illustrated below, **Scheme 97**.



Scheme 97 – Synthetic route towards the indan-1-one precursors; (*S*)-**76** and (*R*)-**76**

(a) $AlCl_3$, acetyl chloride; (b) $NaOCH_3$, CH_3OH; (c) TFA, P_2O_5; (d) $NaBH_4$, CH_2Cl_2 / CH_3OH; (e) Oxidative Kinetic resolution, (*S*,*S*)-Ru complex, **115**; (f) MnO_2, CH_2Cl_2.

Transformation of the ketone to the corresponding 4-aryl-3,4-dihydroquinolin-2(1*H*)-one was attempted by first synthesising the corresponding oxime mesylates, followed by a Beckmann reaction using $ZrCl_4$ with MsCl as the solvent. The reaction gave a mixture of products shown below, (**Scheme 98**), and unfortunately the desired quinolin-2-one was not formed.



Scheme 98 – Beckmann results obtained from using $ZrCl_4$ in $MsCl_4$

(a) MsCl, NEt_3; (b) $ZrCl_4$, MsCl

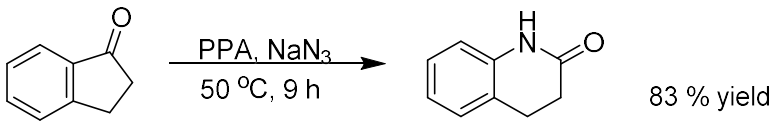
The ratio of nitrile-product and isoquinolin-1-one product varied greatly on the substituents. Other catalyst sytems were tried, but only the starting material oxime and the corresponding ketone were isolated upon workup.

Possible improvements on this transformation to yield the desired quinolin-2(1*H*)-one are discussed in the following section.

4.1 Future Work

In order to transform the enantiomerically enriched indan-1-one precursors from Chapter 2 into the corresponding quinolin-2(1*H*)-ones, either alternate Beckmann conditions could be tested, or other methods could be attempted.

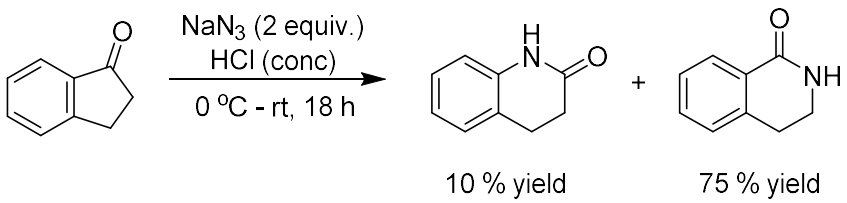
An alternate synthetic approach could be to perform a Schmidt reaction. Conley[496] reported a polyphosphoric acid-catalysed Schmidt rearrangement, **Scheme 99**.



Scheme 99 – Schmidt reaction on indan-1-one using PPA[496]

This method reported the exclusive formation of the 3,4-dihydroquinolin-2(1*H*)-one (dihydrocarbostyril) under the conditions presented. The temperature appears to be crucial to this Schmidt reaction, where the rearrangement was found to proceed extremely slowly below 50 °C.

However, it appears that this transformation remains very catalyst specific, as it was reported that using concentrated HCl instead of polyphosphoric acid gave a ratio of products, with the desired 3,4-dihydroquinolin-2-(1*H*)-one being the minor product.[497,498]



Scheme 100 – Schmidt reaction of indan-1-one using conc. HCl[497]

Fortunately, it has been reported that performing the reaction in polyphosphoric acid (**Scheme 99**),[496] trichloroacetic acid[499] or sulphuric acid,[500] instead of concentrated HCl, yields the desired 3,4-dihydroquinolin-2-(1*H*)-one as the major isomer.

Synthesis of a variety of racemic 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones via the two-step process shown in **Section 3.1.1**, provide an attractive opportunity to obtain both enantiomers by preparative chiral HPLC, albeit, analytical chiral HPLC testing would be required, where substrate separation could vary dramatically.

4.2 Bibliography

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CHAPTER 5- EXPERIMENTAL

5.1.1 General Experimental Information

NMR spectra were recorded on Bruker Advance DRX 250, 300, 400, 500 and 600 and 700 MHz spectrometers at room temperature (298 K). Chemical shifts are reported in parts per million (ppm), related to $(CH_3)_4Si$ (TMS), for ^{1}H and ^{13}C spectra. ^{19}F NMR spectra are referenced to an internal reference, trifluoroacetic acid, with ^{31}P NMR being internally referenced to phosphoric acid. Coupling constants (*J*) are reported in Hertz (Hz) and are reported to the nearest 0.5 Hz. Multiplicities are given as multiplet (m), singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), sextet (sext.) and broad singlet (br. s). ^{1}H and ^{13}C assignments were established on the basis of COSY, DEPT, HMQC and HMBC correlations.

All mass spectra are High Resolution Mass Spectra (HRMS) unless specified otherwise, and were obtained from either Dr Lijiang Song and Mr Philip Aston using a Bruker micro-TOF ESI spectrometer at the University of Warwick. Low Resolution Mass spectra (LRMS) were obtained via an Agilent 6130b ESI Quad mass spectrometer. Elemental analysis was peformed by Warwick Analytical Services.

Melting points were determined on a Stuart Scientific melting point apparatus and are uncorrected. Infra-red spectra were recorded using either a Perkin Elmer Spectrum 100 FT-IR spectrometer or an Alpha Bruker Platinum ATR single reflection diamond ATR module.

Chiral HPLC was performed on a HPLC instrument consisting of a Varian Prostar 335 Photodiode Array Detector, a Varian Prostar Solvent Delivery Module and a Varian Prostar 420 Autosampler. Optical rotations were recorded on an Optical Activity Ltd. AA-1000 millidegree auto-ranging polarimeter (589 nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations (c) are given in grams / Litre (g/L).

Microwave reactions were performed on a Personal Chemistry (now Biotage®) Emrys Optimizer with Pyrex reaction vessels equipped with Teflon stir bars and Teflon coated reaction vessel caps. These were secured with aluminium crimp seals.

Room temperature (rt) refers to ambient temperature (20-22 °C), 5 °C refers to a cold water bath and 0 °C refers to an ice-slush bath. Heated experiments were conducted using thermostatically controlled oil baths or heating blocks. Reactions involving moisture sensitive compounds were performed under an atmosphere of dry, oxygen-free-nitrogen and in dry solvents. Solvent was dried prior to use using the methods described in *Purification of Laboratory Chemicals, 6th Ed.*, and used accordingly.[355] The use of 'petroleum ether' refers to 'petroleum ether (40-60 °C)' unless otherwise stated. pH 2 buffer is an aqueous solution (0.25 M H_2SO_4 and 0.75 M Na_2SO_4). Thin layer chromatography (TLC) analysis was performed on aluminium sheets coated with 0.2 mm silica gel (DC Kieselgel 60 F_{254}, Merck). Visualisation was effected by UV light (254 nm) or by potassium permanganate solution followed by heating. Silica column chromatography was performed on 40-60 Å silica gel.

Single X-ray crystal structures were performed by Dr Guy J. Clarkson on an Oxford Diffraction Gemini XRD which was obtained with support from Advantage West Midlands and part funded by the European Regional Development Fund.

Novozym® 435 (*immobilised Candida Antartica B*) was supplied by Novo Nordisk and has an activity of 7550 PLU/G.

Naming of compounds has been performed in accordance with IUPAC guidelines.[501] (*R*) and (*S*) configurations were assigned according to the Cahn-Ingold-Prelog priority rules.[502] The following is an example of this applied numbering system (**Figure 35**):

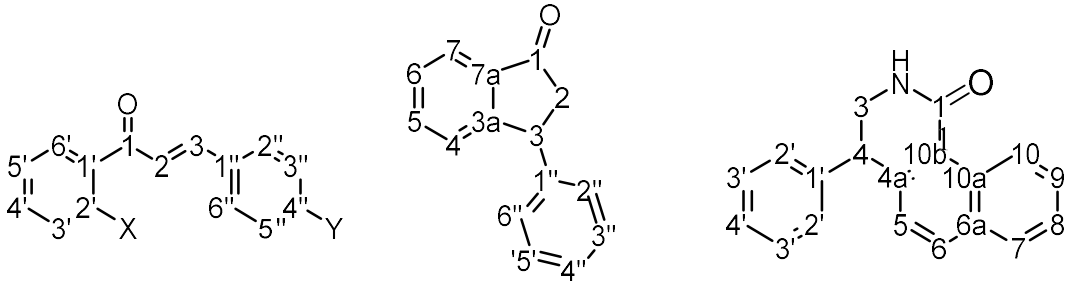


Figure 35 – Examples of the applied compound characterisation numbering system[503,504]

(In some cases, equivalent hydrogen / carbon atoms are labelled with the lowest assignment.)

NMR assignments for each compound are using the following notations:

^{1}H NMR Assignments:

ArH-# (aromatic hydrogen), CH_X-# (non-aromatic hydrogens), where # denotes the position of the carbon attached, according to the IUPAC guidelines.

^{13}C NMR Assignments:

C_{Ar}-# (aromatic carbon bearing no hydrogens), C_{Ar}H-# (aromatic carbon bearing a hydrogen), CH-# (non-aromatic carbon, bearing a hydrogen), C-# (non-aromatic carbon, bearing no hydrogens).

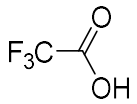
5.1.1.1 Purification of Purchased Chemicals

Palladium (II) Acetate

The following procedure was performed in accordance with previous literature.[505] $Pd(OAc)_2$ was dissolved in minimal refluxing benzene (0.5 g $Pd(OAc)_2$ / 8.0 mL benzene). A black precipitate was removed from the refluxing solution by vacuum filtration. The resulting solution was cooled to room temperature and amber crystals began to form immediately. After 1 hour the solution was filtered to give the recrystallised $Pd(OAc)_2$ as gold plates. The recrystallised $Pd(OAc)_2$ was then stored under a nitrogen atmosphere.

NMR ^1H spectrometric data consistent in change with literature values.[505]

Trifluoroacetic Acid

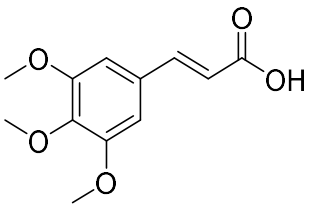


The following procedure was performed in accordance with previous literature.[355] To a stirred flask of trifluoroacetic acid (100 mL) under nitrogen was added P_2O_5 (~10.00 g), and the reaction mixture was stirred overnight. Trifluoroacetic acid was then distilled off and stored under nitrogen.

5.2 Experimental for Chapter 2

5.2.1 Conjugate Addition Reaction

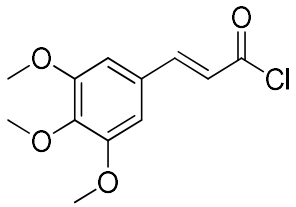
(*E*)-3-(3′,4′,5′-Trimethoxyphenyl)acrylic acid



4

The following procedure was performed in accordance with previous literature.[222] To a solution of 3,4,5-trimethoxybenzaldehyde (3.14 g, 16 mmol) in pyridine (20 mL) was added malonic acid (2.08 g, 20 mmol) in pyridine (20 mL) and two drops of piperidine. The reaction mixture was refluxed for 16 hours and evaporated to remove pyridine. The residue was suspended in H_2O (30 mL) and extracted with EtOAc (2 x 50 mL). The solution was further washed with $NaHCO_3$, brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude solid was washed with diethyl ether and dried, yielding a beige solid (3.28 g, 86 %); m.p. 127-128 °C, (lit.[506] 127-128 °C); ν_{max}/cm^{-1} 3003 (m, COO-H, stretch), 1652 (s, C=O, stretch), 1115 (s, C-O, stretch) ; δ_H (400 MHz, d_6-DMSO) 12.7-12.0 (1H, br. s, COOH), 7.52 (1H, d, *J* 16, CH-3), 7.02 (2H, s, 2 x ArH-2′), 6.54 (1H, d, *J* 16, CH-2); δ_C (100 MHz, d_6-DMSO) 167.8 (C-1), 153.1 (2 x C_{Ar}-3′), 144.0 (C-3), 139.2 (C_{Ar}-4′), 129.9 (C_{Ar}-1′), 118.8 (C-2), 105.8 (2 x C_{Ar}-2′), 60.1 (C_{Ar}-4′ O*C*H_3), 56.0 (2 x C_{Ar}-3′ O*C*H_3); m/z (MH^+ $C_{12}H_{14}O_5H^+$ requires 239.0914) found 239.0916.

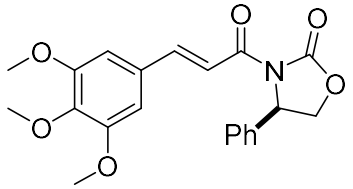
(*E*)-3-(3′,4′,5′-Trimethoxyphenyl)acryloyl chloride



5

To a solution of (*E*)-3-(3′,4′,5′-trimethoxyphenyl)acrylic acid, **4** (2.00 g, 8.4 mmol) in dry dichloromethane (30 mL), was added oxalyl chloride (0.79 g, 9.2 mmol) and 1 drop of DMF. The solution was stirred at room temperature for 1 h and then evaporated to afford (*E*)-3-(3′,4′,5′-trimethoxyphenyl)acryloyl chloride, **5** as a dark yellow solid (2.13 g, 99 %); m.p. 97-98 °C; (lit.[507] 97-98 °C); ν_{max}/cm^{-1} 1744 (s, C=O, stretch), 1128 (s, C-O, stretch), 813 (s, C-Cl, stretch); δ_H (400 MHz, $CHCl_3$) 7.76 (1H, d, *J* 15.5, CH-3), 6.80 (2H, s, 2 x ArH-2′), 6.55 (1H, s, CH-2), 3.92 (3H, s, C_{Ar}-4′ O*C*H$_3$), 3.91 (6H, s, 2 x C_{Ar}-3′ O*C*H$_3$); δ_C (100 MHz, $CDCl_3$) 165.9 (C-1), 153.5 (2 x C_{Ar}-3′), 150.7 (CH-3), 141.7 (C_{Ar}-4′), 128.3 (C_{Ar}-1′), 121.3 (CH-2), 106.3 (2 x C_{Ar}H-2′), 61.0 (C_{Ar}-4′ O*C*H$_3$), 56.2 (2 x C_{Ar}-3′ O*C*H$_3$).

(*R*,*E*)-4-phenyl-3′-(3′-(3″,4″,5″-trimethoxyphenyl)acryloyl)oxazolidin-2-one

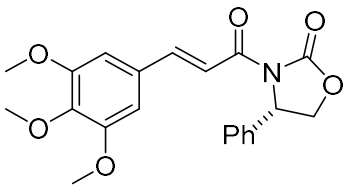


6

n-Butyllithium (2.5 M in hexane, 10.7 mmol) was added to a solution of (*R*)-(-)-4-phenyl-2-oxazolidinone (1.57 g, 9.6 mmol) in dry THF (30 mL) at -78 °C under nitrogen. The resulting mixture was stirred for 45 minutes and a solution of the

corresponding acyl chloride, **5**, (2.50 g, 9.7 mmol) in THF (15 mL) was added at -78 °C. The reaction mixture was stirred for an additional 30 minutes and warmed to ambient temperature overnight. Saturated aqueous ammonium chloride (20 mL) was added to the mixture and diluted with water (30 mL). After extraction with ether (3 x 30 mL), the combined organics were dried over $MgSO_4$, filtered and concentration *in vacuo*. The crude product was subsequently purified by column crystallography on silica gel (ethyl acetate : hexane 1 : 2) yielding a white solid (2.90 g, 78 %); m.p. 138-139 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +8.1; ν_{max}/cm^{-1} 3100 (m, C_{Ar}-H, stretch), 1776 (s, C=O, stretch), 1246 (s, C-O, stretch); δ_H (400 MHz, d_6-DMSO) 7.74 (1H, d, *J* 15.5, CH-3′), 7.63 (1H, d, *J* 15.5, CH-2′), 7.44-7.39 (2H, m, 2 x ArH-2″′), 7.38-7.31 (3H, m, 2 x ArH-3″′ & ArH-4″′), 7.00 (2H, s, 2 x ArH-2″), 5.61 (1H, dd, *J* 8.5, 4, CH-4), 4.82 (1H, t, *J* 8.5, C*H*H-5), 4.23 (1H, dd, *J* 8.5, 4, CH*H*-5), 3.83 (6H, s, 2 x C_{Ar}-3″ O*C*H_3), 3.72 (3H, s, C_{Ar}-4″ O*C*H_3); δ_C (100 MHz, d_6-DMSO) 164.1 (C_{Ar}-1), 153.9 (C_{Ar}-1′), 153.1 (2 x C_{Ar}-3′), 144.9 (CH-3′), 139.8 (C_{Ar}-4″), 139.7 (C_{Ar}), 129.8 (C_{Ar}), 128.8 (C_{Ar}H), 128.0 (C_{Ar}H), 125.8 (C_{Ar}H), 117.0 (CH-2′), 105.8 (2 x C_{Ar}H-2″), 70.2 (CH_2-5), 60.1 (C_{Ar}-4″ O*C*H_3), 57.2 (CH-4), 56.0 (2 x C_{Ar}-3 O*C*H_3); m/z (MNa^+ $C_{21}H_{21}NO_6Na^+$ requires 406.1261) found 406.1259.

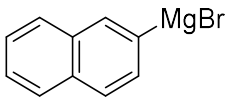
(*S*,*E*)-4-phenyl-3′-(3′-(3″,4″,5″-trimethoxyphenyl)acryloyl)oxazolidin-2-one



7

The reaction procedure was performed in accordance with the previous compound, using the (*S*)-(+)-4-phenyl-2-oxazolidinone (1.57 g, 9.6 mmol) enantiomer instead, yielding a white crystalline solid (2.76 g, 74 %); Spectroscopic data similar to that of other enantiomer; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) -9.0.

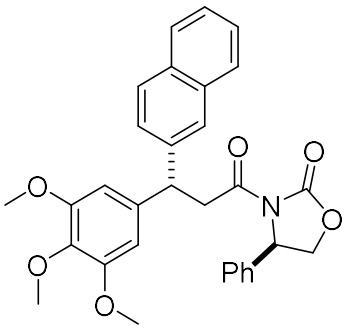
2-Naphthylmagnesium Bromide Solution



8

The following procedure was performed in accordance with previous literature. Under nitrogen atmosphere, a three-necked, round bottom flask was fitting with a reflux condenser, pressure-equalized addition funnel, stirring bar and a thermometer, was charged with magnesium turnings, (0.43 g, 18 mmol) and two iodine crystals. Then 30 mL of a solution of 2-bromonaphthalene (3.55 g, 17.0 mmol) in THF (20 mL) was added. As soon as the reaction has started, the remainder of the THF solution was added at such a rate that a gentle reflux was maintained. After complete addition, reflux was continued for 1 hour by heating with an oil bath. Finally, the reaction mixture was allowed to cool to room temperature prior to further use. Note: Although titration methods were available to determine the concentration,[508,509] upon testing this with the aforementioned Grignard reagent, the colour change was very insignificant and thus difficult to observe. Consequently, a large excess of Grignard reagent was used in further synthesis steps.

(*R*)-3-((*S*)-3′-(naphthalen-2″-yl)-3′-(3‴,4‴,5‴-trimethoxyphenyl)propanoyl)-4-phenyloxazolidin-2-one

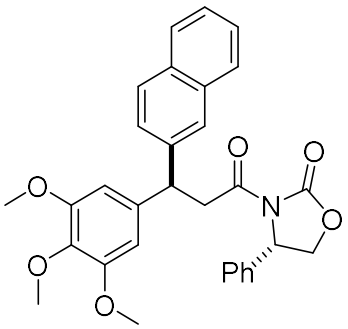


9

The following procedure was performed using the method from previous literature.[510] To a pre-cooled (-40 °C) solution of copper(I)bromide methylsulfide complex (1.21 g, 5.9 mmol), in THF (20 mL) was added dimethylsulfide (6 mL), followed by the slow addition of 2-naphthylmagnesium bromide solution, **8**, (~12 mmol). The mixture was then allowed to warm to -20 °C and a solution of (*R*,*E*)-4-phenyl-3′-(3′-(3″,4″,5″-trimethoxyphenyl)acryloyl)oxazolidin-2-one, **6**, (1.45 g, 3.9 mmol), was added drop-wise over 1 hour. The reaction mixture was then stirred at -20 °C for 1 hour, and stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous ammonium chloride (100 mL), the mixture being extracted with ethyl acetate (3 x 30 mL). The combined organic fractions were washed with ammonium hydroxide (2 x 15 % aq. 40 mL), water (50 mL), brine (50 mL) and dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica column chromatography, eluting with ethyl acetate : hexane (1 : 1), giving a white solid (1.84 g, 61 %); m.p. 146-147 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.21, $CHCl_3$) -51.9; ν_{max}/cm^{-1} 3050 (w, C_{Ar}-H, stretch), 1771 (s, C=O, stretch), 1709 (s, C=O, stretch), 1124 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.80-7.71 (3H, m, 3 x ArH), 7.66 (1H, s, ArH-1′), 7.48-7.41 (2H, m, 2 x ArH), 7.37 (1H, dd, *J* 8.5, 2, ArH), 7.16 (1H, ddd, *J* 7.5, 4,

1, ArH), 7.09-7.04 (2H, m, 2 x ArH), 7.00-6.96 (2H, m, 2 x ArH), 6.54 (2H, s, 2 x ArH-2‴), 5.34 (1H, dd, *J* 8.5, 4, CH-4), 4.72 (1H, t, *J* 8, CH-3′), 4.60 (1H, t, *J* 9, C*H*H-5), 4.17 (1H, dd, *J* 9, 4, C*H*H-5), 3.86 (2H, dd, *J* 9, 8, CHH-2′), 3.80 (3H, s, C_{Ar}-4‴ O*C*H$_3$), 3.79 (6H, s, 2 x C_{Ar}-3‴ O*C*H$_3$); δ_C (100 MHz, $CDCl_3$) 171.0 (C_{Ar}-1), 153.8 (2 x C_{Ar}-3‴), 153.2 (C_{Ar}-1′), 140.5 (C_{Ar}), 138.7 (C_{Ar}), 138.4 (C_{Ar}), 132.5 (C_{Ar}), 132.3 (C_{Ar}), 129.1 (C_{Ar}H), 129.0 (C_{Ar}H), 128.5 (C_{Ar}H), 128.3 (C_{Ar}H), 127.9 (C_{Ar}H), 127.6 (C_{Ar}H), 126.4 (C_{Ar}H), 126.1 (C_{Ar}H), 125.8 (C_{Ar}H), 125.7 (C_{Ar}H), 125.5 (C_{Ar}H), 105.1 (2 x C_{Ar}H-2‴), 69.9 (CH-5), 60.8 (C_{Ar}-4‴ O*C*H$_3$), 57.7 (CH-4), 56.2 (2 x C_{Ar}-3‴ O*C*H$_3$), 47.2 (CH-3′), 40.7 (CH_2-2); m/z (MNa^+ $C_{31}H_{29}NO_6Na^+$ Requires 534.1887) found 534.1888.

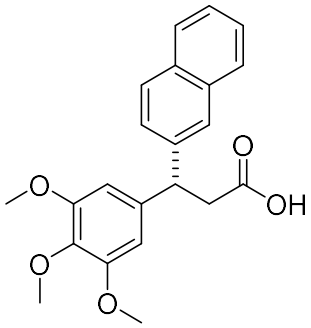
(*S*)-3-((*R*)-3′-(naphthalen-2″-yl)-3′-(3‴,4‴,5‴-trimethoxyphenyl)propanoyl)-4-phenyloxazolidin-2-one



10

The reaction procedure was performed in accordance with the previous compound, using the (*S*,*E*)-4-phenyl-3′-(3′-(3″,4″,5″-trimethoxyphenyl)acryloyl)oxazolidin-2-one, **7** (1.45 g, 3.9 mmol) enantiomer instead, yielding a white crystalline solid (2.96 g, 63 %); Spectroscopic data similar to that of other enantiomer; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.20, $CHCl_3$) +52.5.

(*S*)-3-(naphthalen-2′-yl)-3-(3″,4″,5″-trimethoxyphenyl)propanoic acid

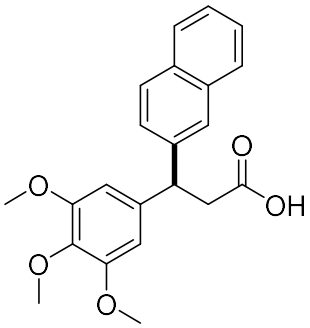


11

To a solution of (*R*)-3-((*S*)-3′-(naphthalen-2″-yl)-3′-(3‴,4‴,5‴-trimethoxyphenyl)propanoyl)-4-phenyloxazolidin-2-one, **9** (400 mg, 0.8 mmol) in a THF : H_2O, (4 : 1, 40 mL), at 0 °C, was added hydrogen peroxide solution (30 % w/w in water, 0.4 mL), followed by lithium hydroxide (28 mg, 1.2 mmol), and the reaction was stirred at room temperature for 2 hours. Saturated aqueous sodium sulfite was added and the organic solvents were removed *in vacuo*. The aqueous phase was washed with dichloromethane (2 x 30 mL), then cooled to 0 °C, acidified to pH 2 with sulfate buffer and the product extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*, to give the title compound as a white solid (244 mg, 85 %); m.p. 183-184 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +1.5; ν_{max}/cm^{-1} 3674 (m, COO-H, stretch), 1693 (s, C=O, stretch), 1120 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.86-7.76 (3H, m, 3 x ArH), 7.71 (1H, s, ArH-1′), 7.53-7.42 (2H, m, 2 x ArH), 7.35 (1H, d, *J* 8.5, ArH), 6.49 (2H, s, 2 x ArH-2″), 4.65 (1H, t, *J* 8, CH-3), 3.82 (3H, s, C_{Ar}-4″ O*C*H_3), 3.80 (6H, s, 2 x C_{Ar}-3″ O*C*H_3), 3.26-3.10 (2H, m, 2 x CHH-2); δ_C (100 MHz, $CDCl_3$) 177.0 (C_{Ar}-1), 153.3 (2 x C_{Ar}-3″), 140.4 (C_{Ar}), 138.8 (C_{Ar}), 136.7 (C_{Ar}), 133.4 (C_{Ar}), 132.3 (C_{Ar}), 128.4 (C_{Ar}H), 127.9 (C_{Ar}H), 127.6 (C_{Ar}H), 126.3 (C_{Ar}H), 126.2 (C_{Ar}H), 125.8 (C_{Ar}H), 125.5 (C_{Ar}H),

104.8 (2 x C_{Ar}H-2″), 60.8 (C_{Ar}-4″ O*C*H$_3$), 56.1 (2 x C_{Ar}-3″ O*C*H$_3$), 46.9 (CH-3), 40.4 (CH_2-2); m/z (MNa^+ $C_{22}H_{22}O_5Na^+$ Requires 389.1359) found 389.1358.

(*R*)-3-(naphthalen-2′-yl)-3-(3″,4″,5″-trimethoxyphenyl)propanoic acid



12

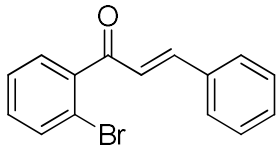
The reaction procedure was performed in accordance with the previous compound, using (*S*)-3-((*R*)-3′-(naphthalen-2″-yl)-3′-(3‴,4‴,5‴-trimethoxyphenyl)propanoyl)-4-phenyloxazolidin-2-one, **10** (400 mg, 0.8 mmol), yielding a white crystalline solid (249 mg, 87 %); Spectroscopic data similar to that of other enantiomer; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) -2.5.

5.2.2 Asymmetric Reductive Heck Cyclisation

5.2.2.1 Claisen-Schmidt Condensation Reaction for the General Formation of Substituted-Bromochalcones

The following procedure was performed in accordance with previous literature.[146] To a solution of 2′-bromoacetophenone (2.5 mmol) and substituted benzaldehyde (2.5 mmol) in dry methanol (20 mL), was added sodium methoxide (3.8 mmol) in dry methanol (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 hours and warmed to room temperature overnight. If a precipitate formed, this was filtered, washed with methanol and dried under vacuum. If no precipitate formed, aqueous HCl (2 M, 20 mL) was added slowly and the mixture was evaporated to near dryness under reduced pressure. The residue was suspended in saturated $NaHCO_3$ (50 mL) and extracted with diethyl ether (3 x 100 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. If cis/trans isomers were present, the crude mixture was dissolved in methanol and DABCO (5 mol%) was added. The reaction was stirred at reflux for 2 hours, cooled and concentrated *in vacuo*. The product was re-dissolved in diethyl ether ether (50 mL), washed with $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Further purification for all compounds was either performed with silica column chromatography or recrystallised as mentioned specifically.

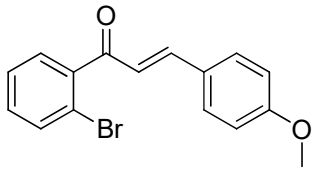
(*E*)-1-(2′-Bromophenyl)-3-phenylprop-2-en-1-one



13

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 2′-bromoacetophenone (1.69 mL, 12.5 mmol), benzaldehyde (1.28 mL, 12.5 mmol) and sodium methoxide (0.75 g, 18.8 mmol). The crude product was subjected to DABCO/methanol isomerism as mentioned in the general procedure. The *trans*-crude product then purified by silica column chromatography, eluting with diethyl ether : petroleum ether (1 : 4), yielding the title compound as a yellow oil (0.98 g, 91 %); ν_{max}/cm^{-1} 3059 (w, C_{Ar}-H, stretch), 1645 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J* 7.5, 1, ArH-3′), 7.60 (2H, dd, *J* 7, 3, 2 x ArH-2″), 7.47-7.30 (7H, m, 2 x ArH-3″, ArH-4′, ArH-5′, ArH-6′, ArH-4″, CH-3), 7.10 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 194.6 (C-1), 146.5 (CH-3), 141.0 (C_{Ar}-1′), 134.3 (C_{Ar}-1″), 133.3 (C_{Ar}H-3′), 131.3, 130.8, 129.1, 128.9, 128.5, 127.3 (C_{Ar}H-4′, C_{Ar}H-5′, C_{Ar}H-6′, 2 x C_{Ar}H-2″, 2 x C_{Ar}H-3″ & C_{Ar}H-4″), 126.0 (CH-2), 119.4 (C_{Ar}-2′); m/z (MNa^+ $C_{15}H_{11}{}^{79}BrONa^+$ Requires 308.9885) found 308.9883, MNa^+ $C_{15}H_{11}{}^{81}BrONa^+$ Requires 3310.9866) found 310.9864. Data consistent with those previously reported.[216]

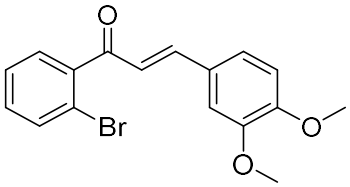
(*E*)-1-(2′-Bromophenyl)-3-(4″-methoxyphenyl)prop-2-en-1-one



14

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 2′-bromoacetophenone (0.34 mL, 2.5 mmol), 4-methoxybenzaldehyde (0.31 mL, 2.5 mmol) and sodium methoxide (0.20 g, 3.8 mmol). The crude product was purified by silica column chromatography, eluting with diethyl ether : petroleum ether (1 : 4), yielding the title compound as a yellow solid (0.61 g, 76 %); m.p. 89-90 °C, (lit.[511] 88-90 °C); ν_{max}/cm^{-1} 3062 (w, C_{Ar}-H, stretch), 1591 (s, C=O, stretch), 1253 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.63 (1H, d, *J* 8, ArH-3′), 7.50 (2H, d, *J* 9, 2 x ArH-2″), 7.41-7.35 (3H, m, ArH-5′, ArH-6′, CH-3), 7.31 (1H, ddd, *J* 8, 6, 3, ArH-4′), 6.96 (1H, d, *J* 16, CH-2), 6.91 (2H, d, *J* 9, 2 x ArH-3″), 3.83 (3H, s, C_{Ar}-4″ OCH_3); δ_C (100 MHz, $CDCl_3$) 194.7 (C-1), 161.9 (C_{Ar}-4″), 146.6 (CH-3), 141.3 (C_{Ar}-1′), 133.3 ($C_{Ar}H$-3′), 131.1 ($C_{Ar}H$-4′), 130.4 (2 x $C_{Ar}H$-2″), 129.0, 127.2 ($C_{Ar}H$-5′ & $C_{Ar}H$-6′), 127.0 (C_{Ar}-1″), 123.9 (CH-2), 119.4 (C_{Ar}-2′), 114.4 (2 x $C_{Ar}H$-3″), 55.4 (C_{Ar}-4″ O*C*H_3); m/z (MNa^+ $C_{16}H_{13}{}^{79}BrO_2Na^+$ requires 338.9991) found 338.9991, (MNa^+ $C_{16}H_{13}{}^{81}BrO_2Na^+$ requires 340.0004) found 340.0006. Data consistent with those previously reported.[216]

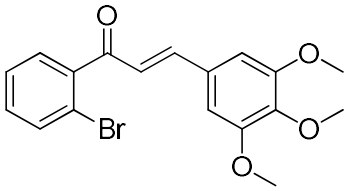
(*E*)-1-(2′-Bromophenyl)-3-(3″,4″-dimethoxyphenyl)prop-2-en-1-one



15

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 2′-bromoacetophenone (0.34 mL, 2.5 mmol), 3,4-dimethoxybenzaldehyde (0.42 g, 2.5 mmol) and sodium methoxide (0.20 g, 3.8 mmol) and was used without further purification. The title compound was formed as a yellow powder (0.70 g, 80 %); m.p. 112-113 °C; ν_{max}/cm^{-1} 2971 (w, C_{Ar}-H, stretch), 1633 (s, C=O, stretch), 1125 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.64 (1H, d, *J* 8, ArH-3′), 7.41-7.40 (2H, m, ArH-5′, ArH-6′), 7.36-7.30 (2H, m, CH-3, ArH-4′), 7.13 (1H, dd, *J* 8.5, 1.5, ArH-6″), 7.08 (1H, d, *J* 1.5, ArH-2″), 6.95 (1H, d, *J* 16, CH-2), 6.87 (1H, d, *J* 1.5, ArH-5″), 3.92 (3H, s, C_{Ar}-4″ OCH_3), 3.91 (3H, s, C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 194.8 (C-1), 151.7 (C_{Ar}-4″), 149.3 (C_{Ar}-3″), 147.0 (CH-3), 141.4 (C_{Ar}-1′), 133.3 (C_{Ar}H-3′), 131.1 (C_{Ar}H-4′), 129.0, 127.3, 127.3 (C_{Ar}H-5′, C_{Ar}H-6′ & C_{Ar}-1″), 124.2 (CH-2), 123.5 (C_{Ar}H-6″), 119.4 (C_{Ar}-2′), 111.1 (C_{Ar}H-5″), 110.0 (C_{Ar}H-2″), 56.0 (C_{Ar}-4″ O*C*H_3), 56.0 (C_{Ar}-3″ O*C*H_3); m/z (MNa^+ $C_{17}H_{15}{}^{79}BrO_3Na^+$ requires 369.0097) found 369.0097, (MNa^+ $C_{17}H_{15}{}^{81}BrO_3Na^+$ requires 371.0076) found 371.0077.

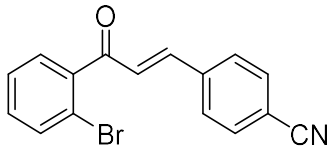
(*E*)-1-(2′-Bromophenyl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



16

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 2′-bromoacetophenone (3.39 mL, 25.1 mmol), 3,4,5-trimethoxybenzaldehyde (4.93 g, 25.1 mmol) and sodium methoxide (2.04 g, 37.7 mmol) and was used without further purification. The title compound was formed as a white solid (7.39 g, 78 %); m.p. 124-127 °C; ν_{max}/cm^{-1} 2840 (w, C_{Ar}-H, stretch), 1638 (s, C=O, stretch), 1122 (m, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* 8, ArH-3′), 7.43-7.41 (2H, m, ArH-5′, ArH-6′), 7.36-7.29 (2H, m, ArH-4′, CH-3), 6.98 (1H, d, *J* 16, CH-2), 6.78 (2H, s, 2 x ArH-2″), 3.88 (3H, s, C_{Ar}-4″ OCH_3), 3.88 (6H, s, 2 x C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 194.7 (C-1), 153.5 (2 x C_{Ar}-3″), 146.8 (CH-3), 141.2 (C_{Ar}-1′), 140.7 (C_{Ar}-4″), 133.4 (C_{Ar}H-3′), 131.3 (C_{Ar}H-4′), 129.8 (C_{Ar}-1″), 129.1, 127.3 (C_{Ar}H-5′ & C_{Ar}H-6′), 125.5 (CH-2), 119.4 (C_{Ar}-2′), 105.7 (2 x C_{Ar}H-2″), 61.0 (2 x C_{Ar}-3″ O*C*H_3), 56.2 (C_{Ar}-4″ O*C*H_3); m/z (MNa^+ $C_{18}H_{17}{}^{79}BrO_4Na^+$ requires 399.0202) found 399.0206, (MNa^+ $C_{18}H_{17}{}^{81}BrO_4Na^+$ requires 401.0183) found 401.0187.

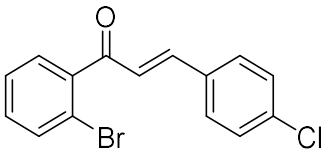
(*E*)-1-(2′-Bromophenyl)-3-(4″-cyanophenyl)prop-2-en-1-one



17

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 2′-bromoacetophenone (0.34 mL, 2.5 mmol), 4-cyanobenzaldehyde (0.33 g, 2.5 mmol) and sodium methoxide (0.20 g, 3.8 mmol) and was used without further purification. The title compound was formed as a yellow solid (0.53 g, 67 %); m.p. 130-131 °C, (lit.[512] 130-131 °C); ν_{max}/cm^{-1} 2987 (w, C_{Ar}-H, stretch), 2226 (m, C≡N, stretch), 1702 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.70-7.64 (5H, m, 2 x ArH-2″, 2 x ArH-3″, ArH-3′), 7.47-7.41 (3H, m, ArH-5′, ArH-6′, CH-3), 7.36 (1H, ddd, *J* 8.5, 6.5, 2.5, ArH-4′), 7.20 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 193.7 (C-1), 143.0 (CH-2). 140.6 (C_{Ar}-1′), 138.7 (C_{Ar}-1″), 133.5 (C_{Ar}H-3′), 132.7 (2 x C_{Ar}H-3″), 131.9 (C_{Ar}H-4′), 128.8 (2 x C_{Ar}H-2″), 129.4, 128.8, 127.5, (C_{Ar}H-5′, C_{Ar}H-6′ & CH-2), 119.5 (C_{Ar}-2′), 118.3 (C_{Ar}-4″ *C*N), 113.9 (C_{Ar}-4″); m/z (MH^+ $C_{16}H_{10}{}^{79}BrNOH^+$ requires 312.0019) found 312.0017, (MH^+ $C_{16}H_{10}{}^{81}BrNOH^+$ requires 313.9999) found 313.9996. Data consistent with those previously reported.[216]

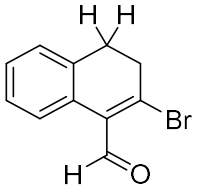
(*E*)-1-(2′-Bromophenyl)-3-(4″-chlorophenyl)prop-2-en-1-one



18

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 2′-bromoacetophenone (0.34 mL, 2.5 mmol), 4-chlorobenzaldehyde (0.35 g, 2.5 mmol) and sodium methoxide (0.20 g, 3.8 mmol) and was used without further purification. The title compound was formed as a white solid (0.48 g, 59 %); m.p. 102-103 °C, (lit.[511] 101-103 °C); ν_{max}/cm^{-1} 3052 (w, C_{Ar}-H, stretch), 1640 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* 8.5, ArH-3′), 7.49 (2H, d, *J* 8, 2 x ArH-2″), 7.43-7.32 (6H, m, 2 x ArH-3″, CH-3, ArH-5′, ArH-6′ & ArH-4′), 7.07 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 194.3 (C-1), 144.5 (CH-3), 141.0 (C_{Ar}-1′), 136.8 (C_{Ar}-4″), 133.5 (C_{Ar}H-3′), 132.9 (C_{Ar}-1″), 131.5 (C_{Ar}H-4′), 129.7, 129.3, 129.2, 127.4 (2 x C_{Ar}H-3″, 2 x C_{Ar}H-2″, C_{Ar}H-5′ & C_{Ar}H-6′), 126.5 (CH-2), 119.5 (C_{Ar}-2′); m/z (MH^+ $C_{15}H_{11}{}^{79}Br^{35}ClOH^+$ requires 320.9676) found 320.9679, (MH^+ $C_{15}H_{11}{}^{81}Br^{35}ClOH^+$ requires 322.9655) found 322.9657.

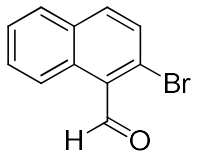
2-Bromo-3,4-dihydronaphthalene-1-carbaldehyde



19

The aforementioned product was synthesised in accordance with previous literature.[226] Dry DMF (0.79 mL, 10.3 mmol) was cooled to 0 °C in dry chloroform (30 mL) and phosphorous tribromide (0.81 mL, 8.6 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 hour to give a pale yellow suspension. A solution of *β*-tetralone (0.45 mL, 3.4 mmol) in dry chloroform (20 mL) was added to the yellow suspension, and the mixture was heated at reflux for 1 hour. The reaction mixture was then cooled to 0 °C and made basic with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with dichloromethane, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was then purified using flash column chromatography, eluting with diethyl ether : petroleum ether (1 : 4) yielded the product as a yellow oil which solidified upon standing (0.73 g, 90 %); m.p. 25-26 °C, (lit.[226] 26-27 °C); ν_{max}/cm^{-1} 2946 (w, C_{Ar}-H, stretch), 1681 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 10.33 (1H, s, CH-1), 7.99-7.97 (1H, m, ArH), 7.29-7.25 (2H, m, 2 x ArH), 7.23-7.17 (1H, m, ArH), 3.08-3.04 (2H, m, CH_2-4), 2.97-2.92 (2H, m, CH_2-3); δ_C (100 MHz, $CDCl_3$) 192.6 (C-1 *C*OH), 145.0 (C-1), 134.6, 132.7, 129.9 (C-2, 2 x C_{Ar}), 128.3 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 37.8 (CH_2-3), 28.7 (CH_2-4); m/z (MNa^+ $C_{11}H_9{}^{79}BrONa^+$ requires 258.9723) found 258.9729, (MNa^+ $C_{11}H_9{}^{81}BrONa^+$ requires 260.9709) found 260.9703. Data consistent with those previously reported.[226]

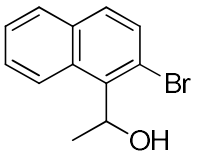
2-Bromo-1-naphthaldehyde



20

The aforementioned product was synthesised in accordance with previous literature.[226] 2-Bromo-3,4-dihydro-1-naphthaldehyde, **19** (5.43 g, 22.9 mmol) and DDQ (5.20 g, 22.9 mmol) was heated at reflux in toluene (50 mL) for 12 hours. After being cooled to room temperature, the mixture was filtered through a Celite® bed and the filtrate was evaporated to dryness. The residue obtained was purified by silica column chromatography eluting with EtOAc:hexanes (1:5) yielding a beige solid (4.83 g, 90 %); m.p. 81-82 °C, (lit.[226] 80-82 °C); ν_{max}/cm^{-1} 3067 (w, C_{Ar}-H, stretch), 1673 (s, C=O, stretch); δ_H (400 MHz, $CHCl_3$) 10.75 (1H, s, C-1 COH), 9.09 (1H, d, *J* 8.5, ArH-5), 7.89 (1H, d, *J* 8.5, CH-3), 7.86 (1H, d, *J* 8.5, ArH-8), 7.71 (1H, d, *J* 8.5, ArH-4), 7.69 (1H, ddd, *J* 8.5, 7, 1.5, ArH-6), 7.60 (1H, ddd, *J* 8, 7, 1.5, ArH-7); δ_C (100 MHz, $CHCl_3$) 194.8 (C-1 COH), 135.4 (C_{Ar}H-3), 132.9 (C_{Ar}H), 131.7 (C_{Ar}H & C_{Ar}-1), 130.7 (C_{Ar}H-4), 130.5 (C_{Ar}-2), 129.7 (C_{Ar}H-6), 128.4 (C_{Ar}H-8), 127.2 (C_{Ar}H-7), 124.7 (C_{Ar}H-5); m/z (MH^+ $C_{11}H_7{}^{79}BrOH^+$ requires 234.9753) found 234.9763, (MH^+ $C_{11}H_7{}^{81}BrOH^+$ requires 236.9733) found 236.9742. Data consistent with those previously reported.[226]

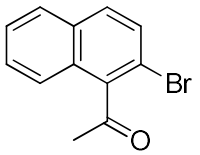
1-(2′-Bromonaphthalen-1-yl)ethanol



21

The aforementioned product was synthesised in accordance with previous literature.[513] To a solution of methylmagnesium bromide in diethyl ether (1.0 M, 8.6 mmol) was added 2′-bromo-1-naphthaldehyde, **20** (2.00 g, 8.6 mmol) in THF (20 mL) dropwise at 0 °C. The reaction mixture was gradually warmed to room temperature and the reaction mixture was stirred for 2 hours. The mixture was then quenched with aqueous NH_4Cl (50 mL), washed with brine (50 mL) and dried over $MgSO_4$. The solution was then concentrated *in vacuo*, with further purification being performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 3), affording the product as a white solid (2.09 g, 97 %); m.p. 99-100 °C; ν_{max}/cm^{-1} 3284 (s, OH, stretch), 2978 (w, C_{Ar}-H, stretch); δ_H (400 MHz, $CHCl_3$) 8.83 (1H, dd, *J* 7.5, 2.5, ArH-8′), 7.83-7.80 (1H, m, ArH-5′), 7.58-7.56 (2H, m, ArH-3′ & ArH-4′), 7.55-7.48 (2H, m, ArH-6′ & ArH-7′), 5.96 (1H, q, *J* 6.5, CH-1), 2.46 (1H, br. s, CH-1 O*H*), 1.74 (3H, d, *J* 6.5, CH_3-2) ; δ_C (100 MHz, $CDCl_3$) 138.2 (C_{Ar}-1′), 133.7 (C_{Ar}), 130.2 (C_{Ar}), 129.4 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 125.9 ($C_{Ar}H$), 125.8 ($C_{Ar}H$), 120.4 (C_{Ar}-2′), 71.8 (CH-1), 22.3 (CH_3-2); m/z (MNa^+ $C_{12}H_{11}{}^{79}BrONa^+$ requires 272.9885) found 272.9889, (MNa^+ $C_{12}H_{11}{}^{81}BrONa^+$ requires 274.9865) found 274.9878. Data consistent with those previously reported.[513]

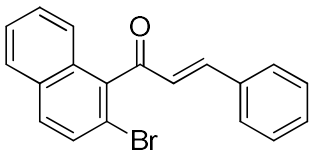
1-(2′-Bromonaphthalen-1-yl)ethanone



22

To a solution of 1-(2′-bromonaphthalen-1-yl)ethanol, **21** (1.50 g, 6.0 mmol) in CH_2Cl_2 (30 mL) was added Dess-Martin periodinane (3.80 g, 9.0 mmol) at room temperature under constant stirring for 12 hours. The resulting suspension was filtered, washed once with H_2O and concentrated *in vacuo*. The crude product was then purified using silica column chromatography eluting with petroleum ether : $CHCl_3$ (4 : 1) affording the product as a colourless oil (1.43 g, 96 %); ν_{max}/cm^{-1} 3059 (w, C_{Ar}-H, stretch), 1702 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.84-7.82 (1H, m, ArH-8′), 7.71 (1H, d, *J* 9, ArH-4′), 7.63-7.60 (1H, m, ArH-5′), 7.56 (1H, d, *J* 9, ArH-3′), 7.54-7.51 (2H, m, ArH-6′ & ArH-7′), 2.70 (3H, s, CH_3-2); δ_C (100 MHz, $CDCl_3$) 204.4 (C-1), 140.1 (C_{Ar}-1′), 132.0 (C_{Ar}), 130.2 ($C_{Ar}H$), 130.0 (C_{Ar}), 129.4 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 123.9 ($C_{Ar}H$), 114.7 (C_{Ar}-2′), 31.9 (CH_3-2); m/z (MNa^+ $C_{12}H_9{}^{79}BrONa^+$ requires 270.9729) found 270.9733, (MNa^+ $C_{12}H_9{}^{81}BrONa^+$ requires 272.9709) found 272.9712.

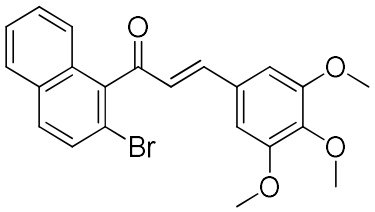
(*E*)-1-(2′-Bromonaphthalen-1-yl)-3-phenylprop-2-en-1-one



23

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 1-(2′-bromonaphthalen-1-yl)ethanone, **22** (0.5 g, 2.0 mmol), benzaldehyde (0.20 mL, 2.0 mmol) and sodium methoxide (0.16 g, 3.0 mmol) at 45 °C for 5 hours, and was used without further purification. The title compound was formed as a beige solid (0.46 g, 68 %); m.p. 157-158 °C; ν_{max}/cm^{-1} 1635 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.90-7.87 (1H, m, ArH-8′), 7.80 (1H, d, *J* 9, ArH-4′), 7.70-7.65 (2H, m, ArH-3′ & ArH-5′), 7.56-7.47 (4H, m, ArH-6′, ArH-7′, 2 x ArH-2″), 7.41 – 7.34 (3H, m, 2 x ArH-3″, ArH-4″), 7.28 (1H, d, *J* 16, CH-3), 7.12 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 196.9 (C-1), 147.9 (C-3), 138.0 (C_{Ar}-1′), 134.2 (C_{Ar}-1″), 132.0 (C_{Ar}), 131.6 (C_{Ar}), 131.1 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 124.9 $C_{Ar}H$), 116.8 (C_{Ar}-2′); m/z (MH^+ $C_{19}H_{13}{}^{79}BrOH^+$ requires 337.0223) found 337.0225, (MH^+ $C_{19}H_{13}{}^{81}BrOH^+$ requires 339.0203) found 339.0205.

(*E*)-1-(2′-Bromonaphthalen-1-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



24

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.1**, using 1-(2′-bromonaphthalen-1-yl)ethanone, **22** (0.4 g, 1.6 mmol), 3′,4′,5′-trimethoxybenzaldehyde (0.32 g, 1.6 mmol) and sodium methoxide (0.13 g, 2.4 mmol) at 45 °C for 5 hours, and was further purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 9). The title compound was formed as a white solid (0.49 g, 72 %); m.p. 140-141 °C; ν_{max}/cm^{-1} 1633 (s, C=O, stretch), 1136, (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* 7.5, ArH-8′), 7.79 (1H, d, *J* 9, ArH-4′), 7.69-7.64 (2H, m, ArH-5′, ArH-3′), 7.56-7.47 (2H, m, ArH-6′ & ArH-7′), 7.16 (1H, d, *J* 16, CH-3), 7.04 (1H, d, *J* 16, CH-2), 6.73 (2H, s, 2 x ArH-2″), 3.87 (3H, s, C_{Ar}-4″ OCH_3), 3.84 (6H, s, 2 x C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 196.7 (C-1), 153.4 (2 x C_{Ar}-3″), 147.9 (CH-3), 140.8 (C_{Ar}-4″), 138.0 (C_{Ar}-1′), 132.0, 131.5 (C_{Ar} & C_{Ar}), 130.3 (C_{Ar}H-4′), 129.6 (C_{Ar}H-3′), 129.5 (C_{Ar}-1″), 128.2 (C_{Ar}H-8′), 127.7 (C_{Ar}H-7′), 126.6 (C_{Ar}H-6′), 126.6 (CH-2), 124.9 (C_{Ar}H-5′), 116.8 (C_{Ar}-2′), 105.77 (2 x C_{Ar}H-2″), 60.9 (C_{Ar}-4″ O*C*H_3), 56.1 (2 x C_{Ar}-3″ O*C*H_3); m/z (MH^+ $C_{22}H_{19}{}^{79}BrO_4H^+$ requires 427.0539) found 427.0542, (MH^+ $C_{22}H_{19}{}^{81}BrO_4H^+$ requires 429.0520) found 429.0520.

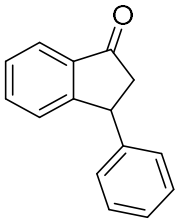
5.2.2.2 Reductive Heck Cyclisations of Substituted-bromochalcones – Method 1 (Microwave)

The following procedure was performed in accordance with previous literature.[216] To a Biotage® 5 mL microwave vial charged with a magnetic stirrer was added the appropriate 2′-bromochalcone (1.75 mmol), palladium (II) acetate (0.1 mmol), (*R*/S)-BINAP (0.2 mmol) and triethylamine (3.5 mmol). The remaining solids were dissolved in DMF (2 mL/mmol bromochalcone), and the solution was purged with nitrogen for 10 minutes. The vial was sealed with an aluminium crimp seal, and pre-stirred for 2 minutes. The reaction mixture was then irradiated for 40 minutes at 100 °C under microwave irradiation (300 W). The reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL / mmol of bromochalcone) and filtered through Celite®. The reaction mixture was then washed with aqueous HCl (1.0 M, 20 mL/mmol of bromochalcone). The organic phase was separated, washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Further purification was either performed with silica column chromatography or recrystallized as mentioned specifically.

5.2.2.3 Reductive Heck Cyclisations of Substituted-bromochalcones Method 2-(Conventional Heating)

The following procedure was performed in accordance with previous literature.[216] Using the same quantities as **Section 5.2.2.2**, the mixture was purged with nitrogen for 10 minutes, followed by conventional heating to 100 °C for 12 hours. The subsequent work-up procedure was performed as mentioned above, with the crude material purified by column chromatography on silica gel, as mentioned specifically.

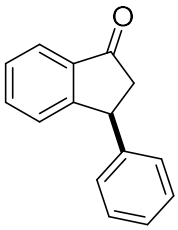
3-Phenyl-2,3-dihydro-1*H*-inden-1-one



25

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-phenylprop-2-en-1-one, **13** (0.50 g, 1.8 mmol), palladium (II) acetate (0.02 g, 0.1 mmol), *rac*-BINAP (0.11 g, 0.2 mmol) and triethylamine (0.49 mL, 3.5 mmol). Further purification of the crude material was performed using silica chromatography eluting with hexane : ethyl acetate (5 : 1), yielding the title compound as a white solid (163 mg, 45 %); m.p. 35-36 °C, (lit.[216] 35 °C); ν_{max}/cm^{-1} 2940 (w, C_{Ar}-H, stretch), 1640 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* 7.5, ArH-8), 7.56 (1H, t, *J* 7.5, ArH-7), 7.41 (1H, t, *J* 7.5, ArH-7), 7.33-7.22 (4H, m, ArH-5, ArH-4′ & 2 x ArH-3′), 7.13 (2H, d, *J* 7, 2 x ArH-2″), 4.57 (1H, dd, *J* 8, 4, CH-3), 3.22 (1H, dd, *J* 19, 8, C*H*H-2), 2.55 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.0 (C-1), 157.9 (C_{Ar}), 143.7 (C_{Ar}-1′), 136.7 (C_{Ar}), 135.1 (C_{Ar}H-6), 128.9 (C_{Ar}H), 127.9 (C_{Ar}H), 127.6 (C_{Ar}H), 127.0 (C_{Ar}H), 126.9 (C_{Ar}H), 123.4 (C_{Ar}H-8), 46.8 (CH_2-2), 44.4 (CH-3); m/z (MNa^+ $C_{15}H_{12}ONa^+$ requires 231.0780) found 231.0779. Data consistent with those previously reported.[216]

(*S*)-3-Phenyl-2,3-dihydro-1*H*-inden-1-one

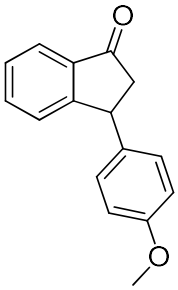


(*S*)-25

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-phenylprop-2-en-1-one, **13** (0.50 g, 1.8 mmol), palladium (II) acetate (0.02 g, 0.1 mmol), (*R*)-BINAP (0.11 g, 0.2 mmol) and triethylamine (0.49 mL, 3.5 mmol). Further purification of the crude material was performed using silica chromatography eluting with hexane : ethyl acetate (5 : 1), yielding the title compound as a white solid (145 mg, 40 %, 50 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : n-hexane = 5 : 95, 1 mL/min., 208 nm, (*R*) isomer 8.97 min., (*S*) isomer 10.45 min.). Data consistent with those previously reported.[216]

3-(4′-Methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one

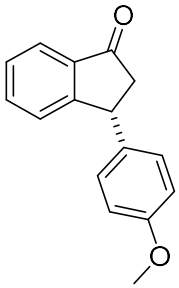


26

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-(4″-methoxyphenyl)prop-2-en-1-one, **14** (0.20 g, 0.6 mmol), palladium (II) acetate (7.1 mg, 0.03 mmol), *rac*-BINAP

(40 mg, 0.06 mmol) and triethylamine (0.18 mL, 1.3 mmol). Further purification of the crude material was performed using silica chromatography eluting with hexane : ethyl acetate (5 : 1), yielding the title compound as a yellow solid (55.6 mg, 37 %); m.p. 70-71 °C, (lit.[216] 75-77 °C); ν_{max}/cm^{-1} 2956 (w, C_{Ar}-H, stretch), 1702 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 7.5, ArH-8), 7.57 (1H, t, *J* 7.5, ArH-6), 7.41 (1H, t, *J* 7.5, ArH-7), 7.27 (1H, d, *J* 7, ArH-5), 7.04 (2H, *J* 8.5, 2 x ArH-2′), 6.85 (2H, d, *J* 8.5, 2 x ArH-3′), 4.54 (1H, dd, *J* 8, 4, CH-3), 3.80 (3H, s, C_{Ar}-4′ OCH_3), 3.22 (1H, dd, *J* 19, 8, C*H*H-2), 2.65 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.1 (C-1), 158.5 (C_{Ar}-4′), 158.2 (C_{Ar}), 136.6 (C_{Ar}), 135.7 (C_{Ar}), 135.0 (C_{Ar}H-6), 128.5 (2 x C_{Ar}H-3′), 127.1 (C_{Ar}H-7), 126.8 (C_{Ar}H-5), 123.3 (C_{Ar}H-8), 114.2 (2 x C_{Ar}H-2′), 55.2 (C_{Ar}-4′ O*C*H_3), 46.9 (CH_2-2), 43.6 (CH-3); m/z (MNa^+ $C_{16}H_{14}O_2Na^+$ requires 261.0886) found 261.0893. Data consistent with those previously reported.[216]

(*R*)-3-(4′-Methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



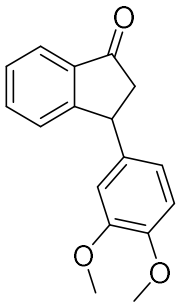
(*R*)-26

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-(4″-methoxyphenyl)prop-2-en-1-one, **14** (0.20 g, 0.6 mmol), palladium (II) acetate (7.1 mg, 0.03 mmol), *(S)*-BINAP (40 mg, 0.06 mmol) and triethylamine (0.18 mL, 1.3 mmol). Further purification of

the crude material was performed using silica chromatography eluting with hexane : ethyl acetate (5 : 1), yielding the title compound as a yellow solid (54.1 mg, 36 %, 43 % e.e.);

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OJ column, 2-propanol : n-hexane = 5 : 95, 1 mL/min., 206 nm, (*S*) isomer 20.80 min., (*R*) isomer 35.02 min.). Data consistent with those previously reported.[216]

3-(3′,4′-Dimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one

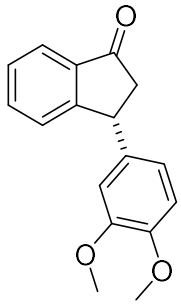


27

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-(3″,4″-methoxyphenyl)prop-2-en-1-one, **15** (0.30 g, 0.9 mmol), palladium (II) acetate (9.7 mg, 0.04 mmol), (*rac*)-BINAP (54 mg, 0.09 mmol) and triethylamine (0.24 mL, 1.7 mmol). Further purification of the crude material was performed using silica chromatography eluting with dichloromethane, yielding the title compound as a yellow oil (76.5 mg, 33 %); ν_{max}/cm^{-1} 3051 (w, C_{Ar}-H, stretch), 1707 (s, C=O, stretch), 1221 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d *J* 7.5, ArH-8), 7.58 (1H, t, *J* 7.5, ArH-6), 7.42 (1H, t, *J* 7.5, ArH-7), 7.29 (1H, d, *J* 7.5, ArH-5), 6.81 (1H, d, *J* 8, ArH-5′), 6.70 (1H, dd, *J* 8, 2, ArH-6′), 6.60 (1H, d, *J* 2, ArH-2′), 4.53 (1H, dd, *J* 8, 4, CH-3), 3.86 (3H, s, C_{Ar}-

4′ OCH_3), 3.80 (3H, s, C_{Ar}-3′), 3.22 (1H, dd, *J* 19, 8, C*H*H-2), 2.68 (1H, dd, *J* 19, 4, C*H*H-2); δ_C (100 MHz, $CDCl_3$) 206.1 (C-1), 158.0 (C_{Ar}), 149.3 (C_{Ar}-3′), 148.0 (C_{Ar}-4′), 136.7 (C_{Ar}), 136.2 (C_{Ar}), 135.1 (C_{Ar}H-6), 127.8 (C_{Ar}H-7), 126.8 (C_{Ar}H-5), 123.3 (C_{Ar}H-8), 119.8 (C_{Ar}H-6′), 111.4 (C_{Ar}H-5′), 110.6 (C_{Ar}H-2′), 55.9 (C_{Ar}-4′ O*C*H_3), 55.9 (C_{Ar}-3′ O*C*H_3) 46.9 (CH_2-2), 44.1 (CH-3); m/z (MNa^+ $C_{17}H_{16}O_3Na^+$ requires 291.0992) found 291.0991. Data consistent with those previously reported.[216]

(*R*)-3-(3′,4′-Dimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one

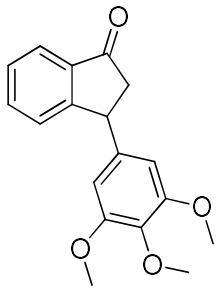


(*R*)-27

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-(3″,4″-methoxyphenyl)prop-2-en-1-one, **15** (0.30 g, 0.9 mmol), palladium (II) acetate (9.7 mg, 0.04 mmol), (*S*)-BINAP (54 mg, 0.09 mmol) and triethylamine (0.24 mL, 1.7 mmol). Further purification of the crude material was performed using silica chromatography eluting with dichloromethane, yielding the title compound as a yellow solid (76.0 mg, 33 %, 40 % e.e.).

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : n-hexane = 5 : 95, 1 mL/min., 206 nm, (*S*) isomer 11.91 min., (*R*) isomer 13.89 min.). Data consistent with those previously reported.[216]

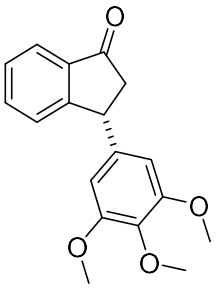
3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



28

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-(3″,4″,5″-methoxyphenyl)prop-2-en-1-one, **16** (0.30 g, 0.8 mmol), palladium (II) acetate (8.9 mg, 0.04 mmol), (*rac*)-BINAP (49 mg, 0.08 mmol) and triethylamine (0.22 mL, 1.6 mmol). Further purification of the crude material was performed using silica chromatography eluting with ethyl acetate : hexane (1 : 3), yielding the title compound as a yellow solid (66.4 mg, 28 %); m.p. 110-111 °C; ν_{max}/cm^{-1} 2962 (w, C_{Ar}-H, stretch), 1710 (s, C=O, stretch), 1232 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 7.5, ArH-8), 7.60 (1H, t, *J* 7.5, ArH-6), 7.44 (1H, t, *J* 7.5, ArH-7), 7.33 (1H, d, *J* 7.5, ArH-5), 6.31 (2H, s, 2 x ArH-2″), 4.51 (1H, dd, *J* 19, 8, CH-3), 3.79 (3H, s, C_{Ar}-4′ OCH_3), 3.22 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.22 (1H, dd, *J* 19, 8, C*H*H-2), 2.70 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 205.7 (C-1), 157.5 (C_{Ar}), 153.4 (2 x C_{Ar}-3′), 139.2 (C_{Ar}-4′), 136.8 (C_{Ar}), 136.5 (C_{Ar}), 135.0 (C_{Ar}H-6), 127.8 (C_{Ar}H-7), 126.7 (C_{Ar}H-5), 123.2 (C_{Ar}H-8), 104.5 (2 x C_{Ar}H-2′), 60.7 (C_{Ar}-4′ O*C*H_3), 56.0 (2 x C_{Ar}-3′ O*C*H_3), 46.6 (CH_2-2), 44.6 (CH-3); m/z (MH^+ $C_{18}H_{18}O_4H^+$ requires 299.1278) found 299.1277.

(*R*)-3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one

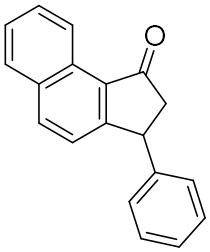


(*R*)-28

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromophenyl)-3-(3″,4″,5″-methoxyphenyl)prop-2-en-1-one, **16** (0.30 g, 0.8 mmol), palladium (II) acetate (8.9 mg, 0.04 mmol), (*S*)-BINAP (49 mg, 0.08 mmol) and triethylamine (0.22 mL, 1.6 mmol). Further purification of the crude material was performed using silica chromatography eluting with ethyl acetate : hexane (1 : 3), yielding the title compound as a yellow solid (66.4 mg, 28 %, 19 % e.e.)

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : n-hexane = 5 : 95, 1 mL/min., 207 nm, (*R*) isomer 34.30 min., (*S*) isomer 41.97 min.).

3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one

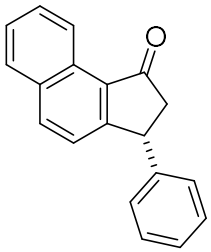


29

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromonaphthalen-1-yl)-3-phenylprop-2-en-1-one,

23 (0.20 g, 0.5 mmol), palladium (II) acetate (6.0 mg, 0.03 mmol), (*rac*)-BINAP (33 mg, 0.05 mmol) and triethylamine (0.15 mL, 1.1 mmol). Further purification of the crude material was performed using silica chromatography eluting with ethyl acetate : hexane (1 : 3), yielding the title compound as a beige solid (63 mg, 46 %); m.p. 119-120 °C, (lit.[216] 115 °C); ν_{max}/cm^{-1} 3022 (m, C_{Ar}-H, stretch), 1695 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 9.24 (1H, d, *J* 8.5, ArH-9), 8.00 (1H, d, *J* 8.5, ArH-5), 7.89 (1H, d, *J* 8, ArH-6), 7.72 (1H, t, *J* 7.5, ArH-8), 7.59 (1H, t, *J* 7.6, ArH-7), 7.31 (4H, m, ArH-4′, ArH-4 & 2 x ArH-3′), 7.15 (2H, d, *J* 7, 2 x ArH-2′), 4.63 (1H, dd, *J* 8, 3, CH-3), 3.35 (1H, dd, *J* 19, 8, C*H*H-2), 2.81 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.5 (C-1), 160.7 (C_{Ar}), 143.3 (C_{Ar}-1′), 136.1 (C_{Ar}H-5), 132.7 (C_{Ar}), 130.6 (C_{Ar}), 129.1 (C_{Ar}H), 128.9 (C_{Ar}H), 128.0 (C_{Ar}H), 127.7 (C_{Ar}H), 127.0 (C_{Ar}H), 126.9 (C_{Ar}H-6′), 124.2 (C_{Ar}H-9), 123.8 (C_{Ar}H), 47.4 (CH_2-2), 44.4 (CH-3), Missing one C_{Ar}; m/z (MH^+ $C_{19}H_{14}OH^+$ requires 259.1117) found 259.1117. Data consistent with those previously reported.[216]

(*R*)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[a]naphthalen-1-one



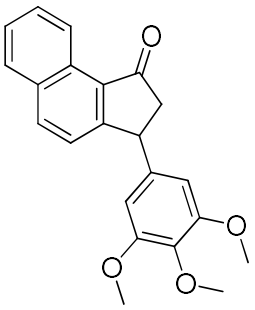
(*R*)-**29**

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromonaphthalen-1-yl)-3-phenylprop-2-en-1-one, **23** (0.20 g, 0.5 mmol), palladium (II) acetate (6.0 mg, 0.03 mmol), (*S*)-BINAP (33 mg, 0.05 mmol) and triethylamine (0.15 mL, 1.1 mmol). Further purification of the

crude material was performed using silica chromatography eluting with ethyl acetate : hexane (1 : 3), yielding the title compound as a beige solid (56.2 mg, 41 %, 10 % e.e.);

Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : n-hexane = 5 : 95, 1 mL/min., 213 nm, (*S*) isomer 10.12 min., (*R*) isomer 14.41 min.). Data consistent with those previously reported.[216]

3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[a]naphthalen-1-one



30

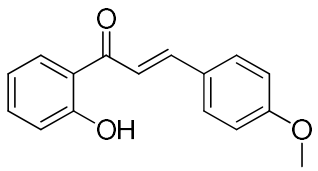
The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-1-(2′-bromonaphthalen-1-yl)-3-phenylprop-2-en-1-one, **24** (0.10 g, 0.23 mmol), palladium (II) acetate (2.6 mg, 0.01 mmol), (*rac*)-BINAP (15 mg, 0.02 mmol) and triethylamine (0.07 mL, 0.5 mmol). Further purification of the crude material was performed using silica chromatography eluting with ethyl acetate : hexane (1 : 3), yielding the title compound as a yellow solid (33.4 mg, 42 %); m.p. 148-149 °C; ν_{max}/cm^{-1} 2929 (w, C_{Ar}-H, stretch), 1690 (s, C=O, stretch), 1220 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 9.23 (1H, d, *J* 8.5, ArH-9), 8.03 (1H, d, *J* 8.5, ArH-

5), 7.91 (1H, d, *J* 8, ArH-6), 7.72 (1H, ddd, *J* 8.5, 7, 1, ArH-8), 7.60 (1H, ddd, *J* 8, 7, 1, ArH-7), 7.35 (1H, d, *J* 8.5, ArH-4), 6.35 (2H, s, 2 x ArH-2′), 4.57 (1H, dd, *J* 8, 3.5, CH-3), 3.84 (3H, s, C_{Ar}-4′ OCH_3), 3.77 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.33 (1H, dd, *J* 19, 8, C*H*H-2), 2.81 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.3 (C-1), 160.4 (C_{Ar}), 153.6 (2 x C_{Ar}-3′), 139.0 (C_{Ar}-1′), 137.0 (C_{Ar}-4′), 136.2 (C_{Ar}H-5), 132.8 (C_{Ar}), 130.7 (C_{Ar}), 129.1 (C_{Ar}H-8), 129.0 (C_{Ar}), 128.1 (C_{Ar}H-6), 127.0 (C_{Ar}H-6), 124.2 (C_{Ar}H-9), 123.8 (C_{Ar}H-4), 104.7 (2 x C_{Ar}H-2′), 60.8 (C_{Ar}-4′ O*C*H_3), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 47.4 (CH_2-2), 44.8 (CH-3); m/z (MH^+ $C_{22}H_{20}O_4H^+$ requires 349.1434) found 349.1426.

5.2.2.4 Claisen-Schmidt Condensation Reaction for the General Formation of Substituted-Hydroxychalcones

The following procedure was performed in accordance with previous literature.[514] To a solution of 2′-hydroxyacetophenone (15 mmol) and substituted aldehyde (15 mmol) in ethanol (40 mL) at 50 °C was added aqueous NaOH solution (50 %, 20 mL) dropwise to the reaction over a period of 30 minutes. The reaction mixture was further stirred at 50 °C for 5 hours, and then kept at room temperature overnight. The reaction mixture was then diluted with ice-cold H_2O (50 mL) and acidified with aqueous HCl (2M, 20 mL), maintaining the temperature at 0 °C. The precipitates that formed were filtered off, dried over $MgSO_4$ and recrystallised as mentioned specifically if required. If precipitates did not form, the product was extracted in dichloromethane, washed twice with brine and concentration *in vacuo*. The residue was then purified using flash column chromatography eluting with CH_2Cl_2 : petroleum ether or recrystallised as mentioned specifically.

(*E*)-1-(2′-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one

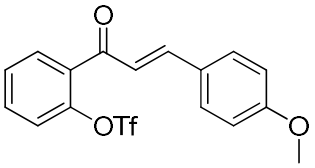


31

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.4**, using 2′-hydroxyacetophenone (2.00 g, 15 mmol), 4-methoxybenzaldehyde (1.82 mL, 15 mmol) and aquous NaOH solution (50 %, 20 mL), with the crude product being purified by recrystallisation in ethanol yielding a

yellow solid (3.32 g, 89 %); m.p. 92-93 °C, (lit.[216] 88-90 °C); ν_{max}/cm^{-1} 2970 (w, C_{Ar}-H, stretch), 1634 (s, C=O, stretch), 1272 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 12.94 (1H, s, COH), 7.93 – 7.89 (2H, m, CH-3, ArH-6′), 7.63 (2H, d, *J* 9, 2 x ArH-2″), 7.54 (1H, d, *J* 15.5, CH-2), 7.49 (1H, ddd, *J* 8.5, 7.5, 1.5, ArH-4′), 7.02 (1H, dd, *J* 8.5, 1, ArH-3′), 6.98-6.91 (3H, m, ArH-5′, 2 x ArH-3″), 3.87 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 193.7 (C-1), 163.5 (C_{Ar}-2′), 162.0 (C_{Ar}-4″), 145.3 (CH-3), 136.1 (C_{Ar}H-4′), 130.5 (2 x ArH-2″), 129.5 (C_{Ar}H-6′), 127.3 (C_{Ar}-1″), 120.1 (C_{Ar}-1′), 118.7 (C_{Ar}H-5′), 118.6 (C_{Ar}H-3′), 117.6 (CH-2), 114.5 (2 x C_{Ar}H-3″), 55.4 (C_{Ar}-4″ O*C*H_3); m/z (MNa^+ $C_{16}H_{14}O_3Na^+$ requires 277.0835) found 277.0837. Data consistent with those previously reported.[216]

(*E*)-2′-(3-(4″-methoxyphenyl)acryloyl)phenyl trifluoromethanesulfonate



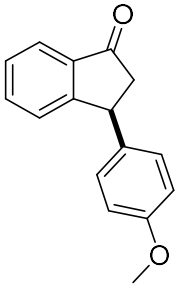
32

The following method was performed in accordance with the literature.[216] To a solution of (*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one, **31** (0.50 g, 2.0 mmol) in pyridine (5 mL) at 0 °C, was added trifluoromethanesulfonic anhydride (0.43 mL, 2.6 mmol), and the reaction was stirred for 12 hours at room temperature. The solution was then diluted with diethyl ether (50 mL), washed with a saturated solution of $CuSO_4$ (50 mL) and water (50 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude material was purified by column chromatography, eluting with ethyl acetate : hexane

(1 : 4) to yield the title compound as a viscous yellow oil (0.64 g, 84 %); ν_{max}/cm^{-1} 2937 (w, C_{Ar}-H, stretch), 1587 (s, C=O, stretch), 1202 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* 7.5, 2, ArH-6′), 7.65 (1H, d, *J* 16, CH-3), 7.65-7.59 (1H, m, ArH-4′), 7.58 (2H, d, *J* 9, 2 x ArH-2″), 7.52 (td, *J* 7.5, 1, ArH-5′), 7.41 (1H, d, *J* 8, ArH-3′), 7.10 (1H, d, *J* 16, CH-2), 6.95 (2H, d, *J* 9, 2 x ArH-2″), 3.88 (3H, s, C_{Ar}-4″ OCH_3); δ_C (100 MHz, $CDCl_3$) 189.7 (C-1), 162.2 (C_{Ar}-4″), 146.8 (CH-3), 133.5 (C_{Ar}), 132.7 ($C_{Ar}H$), 130.7 ($C_{Ar}H$), 130.6 (2 x $C_{Ar}H$-3″), 128.4 ($C_{Ar}H$), 127.0 (C_{Ar}), 122.5 ($C_{Ar}H$), 120.1 (C_{Ar}), 116.9 (C_{Ar}-2′ $OSO_2\mathit{C}F_3$), 114.5 (2 x $C_{Ar}H$-2″), 55.5 (C_{Ar}-4″ $O\mathit{C}H_3$); m/z (MNa^+ $C_{17}H_{13}O_5SF_3Na^+$ requires 409.0328) found 409.0322. Data consistent with those previously reported.[216]

5.2.2.5 Asymmetric Reductive Heck Cyclisations of Substituted-Triflylchalcones

(*S*)-3-(4′-Methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*S*)-**26**

The aforementioned product was synthesised using the general method outlined in **Section 5.2.2.3**, using (*E*)-2′-(3-(4″-methoxyphenyl)acryloyl)phenyl trifluoromethanesulfonate, **32**, (0.20 g, 0.5 mmol), palladium (II) acetate (5.8 mg, 0.05 mmol), *(R)*-3,5-XylMeOBIPHEP (52.1 mg, 0.08 mmol) and triethylamine (0.2 mL, 1 mmol). Further purification of the crude material was performed using silica chromatography eluting with hexane : ethyl acetate (5 : 1), yielding the title compound as a yellow solid (44 mg, 36 %, 70 % e.e.);

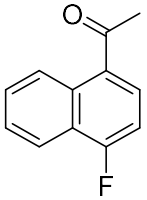
Spectroscopic data similar to that of racemate; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OJ column, 2-propanol : n-hexane = 5 : 95, 1 mL/min., 206 nm, (*R*) isomer 20.80 min., (*S*) isomer 35.02 min.). Data consistent with those previously reported.[216]

5.2.3 Synthesis of Racemic Indan-1-ones

5.2.3.1 Friedel-Crafts Acylation of 1-Halo-Naphthalenes

The following procedure was performed using the method from previous literature.[278] To a solution of acetyl chloride (53.1 mmol) and $AlCl_3$ (62.7 mmol) in dry CH_2Cl_2 (100 mL) at -10 °C was added 1-halonaphthalene (48.3 mmol) in CH_2Cl_2 (1 mL/ 1 mmol) slowly over a period of 2 hours. The reaction mixture was then stirred for 18 hours at -10 °C and at room temperature for 2 h. The reaction mixture was then cooled to 0 °C and H_2O was added slowly until gas evolution ceased. The organics were then collected, washed with saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compounds were used without further purification.

1-(4′-Fluoronaphthalen-1-yl)ethanone

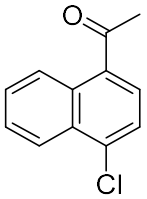


33

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.1**, using 1-fluoronaphthalene (8.85 mL, 68.4 mmol), $AlCl_3$ (10.95 g, 82.0 mmol) and acetyl chloride (5.37 mL, 75.3 mmol) yielding a yellow oil (10.77 g, 84 %); ν_{max}/cm^{-1} 1673 (s, C=O, stretch), 1229 (s, C-F, stretch); δ_H (400 MHz, $CDCl_3$) 8.81 (1H, d, *J* 8.5, ArH-8′), 8.08 (1H, d, *J* 8, ArH-5′), 7.89 (1H, dd, *J* 8, 5.5, ArH-2′), 7.59 (1H, ddd, *J* 8.5, 7, 1.5, ArH-7′), 7.52 (1H, ddd, *J* 8, 7, 1, ArH-6′), 7.07 (1H, dd, *J* 10, 8, ArH-3′), 2.65 (3H, s, CH_3-2); δ_C (100 MHz, $CDCl_3$) 200.2 (C-1), 161.3 (d, $^1J_{CF}$ 260, C_{Ar}-4′), 132.3 (d, $^3J_{CF}$ 6, C_{Ar}-8a), 131.4 (d, $^4J_{CF}$ 4, C_{Ar}-1′), 130.1 (d, $^3J_{CF}$ 10,

C_{Ar}H-2′), 129.1 (C_{Ar}H-7′), 126.8 (d, $^{4}J_{CF}$ 2, C_{Ar}H-6′), 126.3 (d, $^{4}J_{CF}$ 2, C_{Ar}H-8′), 124.1 (d, $^{2}J_{CF}$ 16, C_{Ar}-4a′), 120.7 (d, $^{3}J_{CF}$ 7, C_{Ar}H-5′), 108.1 (d, $^{2}J_{CF}$ 21, C_{Ar}H-3′), 29.7 (CH_3-2); δ_F (282 MHz, $CDCl_3$) -144.6 (ddd, *J* 8, 5.5, 2, C_{Ar}F-4′); m/z (MNa^+ $C_{12}H_9FONa^+$ requires 211.0530) found 211.0531. Characterisation data consistent with that previously recorded.[278]

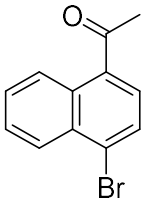
1-(4′-Chloronaphthalen-1-yl)ethanone



34

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.1**, using 1-chloronaphthalene (8.39 mL, 61.5 mmol), yielding a red oil (12.07 g, 96 %); ν_{max}/cm^{-1} 1673 (s, C=O, stretch), (1180 (s, C-Cl, stretch); δ_H (400 MHz, $CDCl_3$) 8.79-8.72 (1H, m, ArH-8′), 8.38-8.30 (1H, m, ArH-5′), 7.83 (1H, d, *J* 8, ArH-2′), 7.65 (2H, m, ArH-6′ & ArH-7′), 7.60 (1H, d, *J* 8, ArH-3′), 2.73 (3H, s, CH_3-2); δ_C (100 MHz, $CDCl_3$) 201.0 (C-1), 136.9 (C_{Ar}-4′), 134.6 (C_{Ar}-1′), 131.3 (C_{Ar}), 131.1 (C_{Ar}), 128.7 (C_{Ar}H-7′), 128.2 (C_{Ar}H-2′), 127.5 (C_{Ar}H-6′), 126.4 (C_{Ar}H-8′), 124.8, 124.7 (C_{Ar}H-3′ & C_{Ar}H-5′), 30.0 (CH_3-2); m/z (MNa^+ $C_{12}H_9{}^{35}ClONa^+$ requires 227.0234) found 227.0227. Characterisation data consistent with that previously recorded.[278]

1-(4′-Bromonaphthalen-1-yl)ethanone



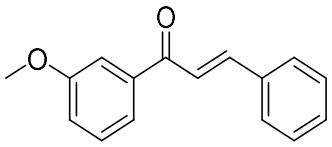
35

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.1**, using 1-bromonaphthalene (6.76 mL, 48.3 mmol), yielding a red oil. The crude product was then subject to Soxhlet extraction in refluxing methanol for 12 hours and the filtrate was concentrated *in vacuo*. The residual slurry was then re-dissolved in cold methanol and filtered repeatedly until no residual black oil persisted. The solution was then concentrated *in vacuo* yielding a beige solid (7.58 g, 62 %); m.p. >300 °C (decomp.); ν_{max}/cm^{-1} 3001 (m, C_{Ar}-H, stretch), 1673 (s, C=O, stretch); δ_H (500 MHz, $CDCl_3$) 8.73-8.70 (1H, m, ArH-8′), 8.34-8.32 (1H, m, ArH-5′), 7.84 (1H, d, *J* 8, ArH-2′), 7.74 (1H, d, *J* 8, ArH-3′), 7.67-7.64 (2H, m ArH-6′ & ArH-7′), 2.74 (3H, s, CH_3-2); δ_C (125 MHz, $CDCl_3$) 201.2 (C-1), 135.4 (C_{Ar}-4′), 132.4 (C_{Ar}), 131.2 (C_{Ar}), 128.7 (C_{Ar}H-6′), 128.7 (C_{Ar}H-2′), 128.3 (C_{Ar}H-3′), 127.8 (C_{Ar}H-5′), 127.6 (C_{Ar}H-7′), 126.4 (C_{Ar}H-8′), 30.1 (CH_3-2); m/z (MNa^+ $C_{12}H_9{}^{79}BrONa^+$ requires 270.9729) found 270.9734, (MNa^+ $C_{12}H_9{}^{81}BrONa^+$ requires 272.9709) found 272.9715. Characterisation data consistent with that previously recorded.[278]

5.2.3.2 Claisen-Schmidt Condensation Reaction for the General Formation of Substituted-Chalcones

The following procedure was performed in accordance with previous literature.[146] To a solution of substituted acetophenone (67 mmol) and substituted benzaldehyde (67 mmol) in dry methanol (30 mL), was added sodium methoxide (99 mmol) in dry methanol (20 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2.5 hours unless otherwise stated. If a precipitate formed, this was filtered, washed with methanol and dried under vacuum. If no precipitate formed, aqueous HCl (2 M, 20 mL) was added slowly and the mixture was evaporated to near dryness under reduced pressure. The residue was suspended in saturated $NaHCO_3$ (50 mL) and extracted with diethyl ether (3 x 100 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Further purification was either performed with silica column chromatography or recrystallised as mentioned specifically.

(*E*)-1-(3′-Methoxyphenyl)-3-phenylprop-2-en-1-one

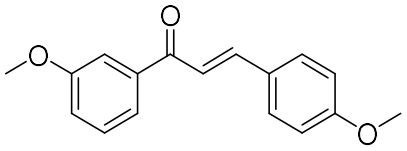


36

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (9.14 mL, 67 mmol), benzaldehyde (6.76 mL, 67 mmol) and sodium methoxide (5.40 g, 99 mmol) and was used without further purification. The title compound was formed as a viscous yellow oil (14.4 g, 91 %); ν_{max}/cm^{-1} 3001 (m, C_{Ar}-H, stretch), 1661 (s, C=O, stretch), 1252 (s, C-O,

stretch); δ_H (400 MHz, $CDCl_3$) 7.71 (1H, d, *J* 16, CH-3), 7.50-7.47 (3H, m, 3 x ArH), 7.44 (1H, dd, *J* 2.5, 1.5, ArH), 7.39 (1H, d, *J* 16, CH-2), 7.28-7.24 (4H, m, 4 x ArH), 6.99 (1H, ddd, *J* 8, 2.5, 1, ArH), 3.71 (3H, s, C_{Ar}-3′ OCH_3); δ_C (100 MHz, $CDCl_3$) 190.2 (C-1), 159.8 (C_{Ar}-6), 144.8 (C-3), 139.5 (C_{Ar}), 134.8 (C_{Ar}), 130.5 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 122.0 (CH-2), 121.0 ($C_{Ar}H$), 119.3 ($C_{Ar}H$), 112.8 ($C_{Ar}H$), 55.4 (C_{Ar}-3′ O*C*H_3); m/z (MNa^+ $C_{16}H_{14}O_2Na^+$ requires 261.0879) found 261.0886.

(*E*)-1-(3′-Methoxyphenyl)-3-(4″-methoxyphenyl)prop-2-en-1-one

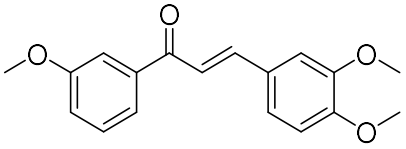


37

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (9.14 mL, 67 mmol), 4-methoxybenzaldehyde (8.15 mL, 67 mmol) and sodium methoxide (5.39 g, 99 mmol) and was used without further purification. The title compound was formed as a yellow solid (15.5 g, 87 %); m.p. 50-51 °C, (lit.[515] 45-47 °C); ν_{max}/cm^{-1} 2833 (m, C_{Ar}-H, stretch), 1653 (s, C=O, stretch), 1247 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* 15.5, CH-3), 7.59-7.51 (4H, m, 2 x ArH & 2 x ArH-2″), 7.40-7.34 (2H, m, CH-2 & ArH), 7.09 (1H, dd, *J* 8, 2.5, ArH-4′), 6.90 (2H, d, *J* 9, 2 x ArH-3″), 3.84 (3H, s, C_{Ar}-3′ OCH_3), 3.81 (3H, s, C_{Ar}-4″ OCH_3); δ_C (100 MHz, $CDCl_3$) 190.0 (C-1), 161.5 (C_{Ar}-4″), 159.7 (C_{Ar}-3′), 144.5 (CH-3), 139.7 (C_{Ar}-1′), 130.1 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 127.4 (C_{Ar}-1″), 120.8 ($C_{Ar}H$), 119.6 (CH-2), 118.8 ($C_{Ar}H$-4″), 114.3 (2 x

C_{Ar}H-3″), 112.7 (C_{Ar}H), 55.3 (C_{Ar}-3′ O*C*H$_3$), 55.2 (C_{Ar}-4″ O*C*H$_3$); m/z (MH^+ $C_{17}H_{16}O_3H^+$ requires 269.1172) found 269.1173.

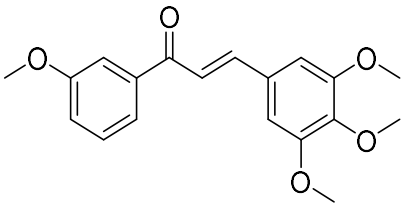
(*E*)-1-(3′-Methoxyphenyl)-3-(3″,4″-dimethoxyphenyl)prop-2-en-1-one



38

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (9.14 mL, 67 mmol), 3,4-dimethoxybenzaldehyde (11.07 g, 67 mmol) and sodium methoxide (5.39 g, 99 mmol) and was used without further purification. The title compound was formed as a yellow solid (12.57 g, 63 %); m.p. 63-64 °C, (lit.[516] 66-68 °C, (ethanol)); ν_{max}/cm^{-1} 2831 (m, C_{Ar}-H, stretch), 1649 (s, C=O, stretch), 1255 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.72 (1H, d, *J* 15.5, CH-3), 7.55 (1H, d, *J* 7.5, ArH-6′), 7.51-7.48 (1H, m, ArH-2′), 7.35 (1H, t, *J* 8, ArH-5′), 7.33 (1H, d, *J* 15.5, CH-2), 7.17 (1H, dd, *J* 8.5, 2, ArH-6″), 7.12 (1H, d, *J* 8.5, ArH-2″), 7.06 (1H, dd, *J* 8, 2.5, ArH-4′), 6.84 (1H, d, *J* 8.5, ArH-5″), 3.89 (3H, s, C_{Ar}-3″ OCH$_3$), 3.87 (3H, s, C_{Ar}-4″ OCH$_3$), 3.82 (3H, s, C_{Ar}-3′ OCH$_3$); δ_C (100 MHz, $CDCl_3$) 189.9 (C-1), 159.6 (C_{Ar}-3′), 151.3 (C_{Ar}-4″), 149.0 (C_{Ar}-3″), 144.8 (CH-3), 139.7 (C_{Ar}-1′), 129.3 (C_{Ar}H-5′), 127.6 (C_{Ar}-1″), 123.0 (C_{Ar}H-6″), 120.7 (C_{Ar}H-6′), 119.8 (CH-2), 118.7 (C_{Ar}H-4′), 112.8 (C_{Ar}H-2′), 110.9 (C_{Ar}H-5′), 109.9 (C_{Ar}H-2″), 55.8 (C_{Ar}-3″ O*C*H$_3$ & C_{Ar}-4″ O*C*H$_3$), 55.2 (C_{Ar}-3′ O*C*H$_3$); m/z (MH^+ $C_{18}H_{18}O_4H^+$ requires 299.1278) found 299.1283.

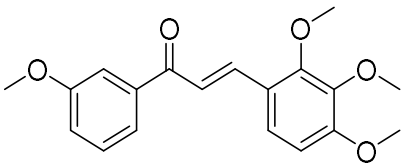
(*E*)-1-(3′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



39

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (4.57 mL, 33 mmol), 3,4,5-trimethoxybenzaldehyde (6.53 g, 33 mmol) and sodium methoxide (2.70 g, 50 mmol) and was used without further purification. The title compound was formed as a viscous yellow oil (3.01 g, 95 %); ν_{max}/cm^{-1} 2938 (m, C_{Ar}-H, stretch), 1648 (s, C=O, stretch), 1121 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.72 (1H, d, *J* 15.5, CH-3), 7.59 (1H, d, *J* 7.5, ArH-6′), 7.53 (1H, m, ArH-2′), 7.41 (1H, t, *J* 8, ArH-5′), 7.38 (1H, d, *J* 15.5, CH-2), 7.13 (1H, dd, *J* 8, 2.5, ArH-4′), 6.86 (2H, s, 2 x ArH-2″), 3.92 (6H, s, 2 x C_{Ar}-3″ OCH_3), 3.90 (3H, s, C_{Ar}-4″ OCH_3), 3.88 (3H, s, C_{Ar}-3′ OCH_3); δ_C (100 MHz, $CDCl_3$) 190.1 (C-1), 159.8 (C_{Ar}-3′), 153.4 (C_{Ar}-4″), 144.9 (CH-3), 140.4 (2 x C_{Ar}-3″), 139.6 (C_{Ar}-1″), 130.3 (C_{Ar}-1′), 129.5 (C_{Ar}-5′), 121.4 (CH-2), 120.9 (C_{Ar}H-6′), 118.9 (C_{Ar}H-4′), 113.0 (C_{Ar}H-2′), 105.6 (2 x C_{Ar}H-2″), 60.9, 56.2, 55.4 (C_{Ar}-3′ O*C*H_3, C_{Ar}-4″ O*C*H_3 & 2 x C_{Ar}-3″ O*C*H_3); m/z (MH^+ $C_{19}H_{20}O_5H^+$ requires 329.1384) found 329.1376.

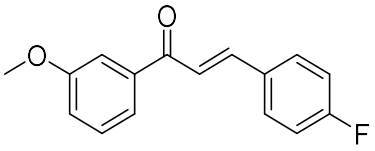
(*E*)-1-(3′-Methoxyphenyl)-3-(2″,3″,4″-trimethoxyphenyl)prop-2-en-1-one



40

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (9.14 mL, 67 mmol), 2,3,4-trimethoxybenzaldehyde (12.79 g, 67 mmol) and sodium methoxide (5.39 g, 99 mmol) and was used without further purification. The title compound was formed as a viscous yellow oil (21.16 g, 97 %); ν_{max}/cm^{-1} 2939 (m, C_{Ar}-H, stretch), 1648 (s, C=O, stretch), 1256 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.00 (1H, d, *J* 16, CH-3), 7.58 (1H, d, *J* 7.5, ArH-6′), 7.52 (1H, d, *J* 16, CH-2), 7.54-7.52 (1H, m, ArH-2′), 7.41-7.35 (2H, m, ArH-5′ & ArH-6″), 7.10 (1H, ddd, *J* 8, 2.5, 0.5, ArH-4′), 6.70 (1H, d, *J* 9, ArH-5″), 3.89 (3H, s, C_{Ar}-2″ OCH_3), 3.88 (3H, s, C_{Ar}-3″ OCH_3), 3.86 (3H, s, C_{Ar}-4″ OCH_3), 3.86 (3H, s, C_{Ar}-3′ OCH_3); δ_C (100 MHz, $CDCl_3$) 190.5 (C-1), 159.8 (C_{Ar}-3′), 155.7 (C_{Ar}-3″), 153.7 (C_{Ar}-2″), 142.4 (C_{Ar}-4″), 140.0 (CH-3), 139.9 (C_{Ar}), 129.4 (C_{Ar}H-5′), 123.8 (C_{Ar}H-6″), 121.9 (C_{Ar}-1″), 121.3 (CH-2), 120.9 (C_{Ar}H-6′), 118.9 (C_{Ar}H-4′), 112.8 (C_{Ar}H-2′), 107.6 (C_{Ar}H-5″), 61.3 (C_{Ar}-2″ O*C*H_3), 60.8 (C_{Ar}-4″ O*C*H_3), 56.0 (C_{Ar}-3″ O*C*H_3), 55.3 (C_{Ar}-3′ O*C*H_3); m/z (MNa^+ $C_{19}H_{20}O_5Na^+$ requires 351.1203) found 351.1210.

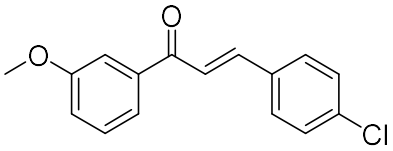
(*E*)-1-(3′-Methoxyphenyl)-3-(4″-fluorophenyl)prop-2-en-1-one



41

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (9.14 mL, 67 mmol), 4-fluorobenzaldehyde (7.14 mL, 67 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a white solid (16.31 g, 96 %); m.p. 67-68 °C; ν_{max}/cm^{-1} 2839 (m, C_{Ar}-H, stretch), 1649 (s, C=O, stretch), 1229 (s, C-F, stretch); δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* 15.5, CH-3), 7.65-7.60 (2H, m, 2 x ArH-2″), 7.60-7.57 (1H, m, ArH-6′), 7.53 (1H, dd, *J* 2.5, 1.5, ArH-2′), 7.43 (1H, d, *J* 15.5, CH-2), 7.42-7.38 (1H, m, ArH-5′), 7.14-7.07 (3H, m, ArH-4′ & 2 x ArH-3″), 3.87 (3H, s, C_{Ar}-3′ OCH_3; δ_C (100 MHz, $CDCl_3$) 190.0 (C-1), 164.0 (d, $^1J_{CF}$ 252, C_{Ar}-4″), 159.9 (C_{Ar}-3′), 143.5 (CH-3), 139.4 (C_{Ar}-1′), 131.1 (d, $^4J_{CF}$ 3.5, C_{Ar}-1″), 131.1 (d, $^3J_{CF}$ 8.5, 2 x C_{Ar}H-2″), 129.5 (C_{Ar}H-5′), 121.7 (CH-2), 121.0 (C_{Ar}H-6′), 119.3 (C_{Ar}H-4′), 116.1 (d, $^2J_{CF}$ 22, 2 x C_{Ar}H-3″), 112.8 (C_{Ar}H-2′), 55.4 (C_{Ar}-3′ O*C*H_3); δ_F (282 MHz, $CDCl_3$) -109.5 - -106.7 (m, CF-4″) m/z (MNa^+ $C_{16}H_{13}FO_2Na^+$ requires 279.0792) found 279.0791.

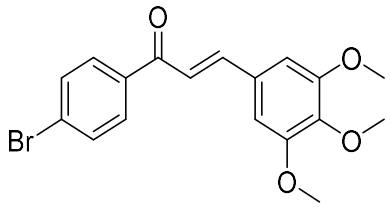
(*E*)-1-(3′-Methoxyphenyl)-3-(4″-chlorophenyl)prop-2-en-1-one



42

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3′-methoxyacetophenone (6.50 mL, 47 mmol), 4-chlorobenzaldehyde (6.65 g, 47 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a white solid (7.20 g, 56 %); m.p. 85-86 °C, (lit.[517] 83 °C); ν_{max}/cm^{-1} 2836 (m, C_{Ar}-H, stretch), 1655 (s, C=O, stretch), 1253 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* 16, CH-3), 7.63-7.52 (4H, m, ArH-6′, ArH-2′ & 2 x ArH-2″), 7.48 (1H, d, *J* 16, CH-2), 7.44-7.36 (3H, m, ArH-5′ & 2 x ArH-3″), 7.19-7.12 (1H, m, ArH-4′), 3.89 (3H, s, C_{Ar}-3′ O*C*H$_3$); δ_C (100 MHz, $CDCl_3$) 189.9 (C-1), 159.9 (C_{Ar}-3′), 143.3 (CH-3), 139.4 (C_{Ar}-1′), 136.4 (C_{Ar}-4″), 133.4 (C_{Ar}-1″), 129.6 (2 x C_{Ar}H-2″), 129.2 (2 x C_{Ar}H-3″), 122.5 (CH-2), 121.0 (C_{Ar}H), 119.4 (C_{Ar}H-4′), 112.9 (C_{Ar}H-2′), 55.5 (C_{Ar}-3′ O*C*H$_3$); m/z (MNa^+ $C_{16}H_{13}{}^{35}ClO_2Na^+$ requires 295.0496) found 295.0489.

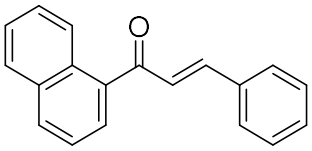
(*E*)-1-(4′-Bromophenyl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



43

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 4′-bromoacetophenone (10.00 g, 50 mmol), 3,4,5-trimethoxybenzaldehyde (9.86 g, 50 mmol) and sodium methoxide (4.07 g, 75 mmol) and was used without further purification. The title compound was formed as a pale yellow solid (16.29 g, 86 %); m.p. 132-133 °C, (lit.[518] 102 °C); ν_{max}/cm^{-1} 2942 (m, C_{Ar}-H, stretch), 1605 (s, C=O, stretch), 1177 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.5, 2 x ArH-2′), 7.70 (1H, d, *J* 15.5, CH-3), 7.63 (2H, d, *J* 8.5, 2 x ArH-3′), 7.33 (1H, d, *J* 15.5, CH-2), 6.85 (2H, s, 2 x ArH-2″), 3.91 (6H, s, 2 x C_{Ar}-3″ OCH_3), 3.89 (3H, s, C_{Ar}-4″ OCH_3); δ_C (100 MHz, $CDCl_3$) 189.4 (C-1), 153.4 (2 x C_{Ar}-3″), 145.6 (CH-3), 140.6 (C_{Ar}-4″), 136.9 (C_{Ar}-1′), 131.9 (2 x C_{Ar}H-3′), 130.1 (C_{Ar}-1″), 130.0 (2 x C_{Ar}H-2′), 127.8 (C_{Ar}-4′), 120.8 (CH-2), 105.7 (2 x C_{Ar}H-2″), 61.0 (C_{Ar}-4″ O*C*H_3), 56.2 (2 x C_{Ar}-3″ O*C*H_3); m/z (MH^+ $C_{18}H_{17}{}^{79}BrO_4H^+$ requires 377.0383) found 377.0385, (MH^+ $C_{18}H_{17}{}^{81}BrO_4H^+$ requires 379.0365) found 379.0366.

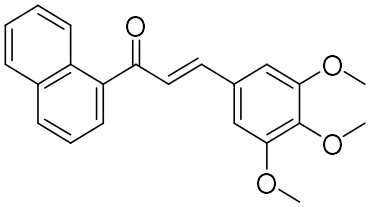
(*E*)-1-(Naphthalen-1′-yl)-3-phenylprop-2-en-1-one



44

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetylnaphthalene (4.46 mL, 30 mmol), benzaldehyde (3.12 mL, 30 mmol) and sodium methoxide (2.38 g, 44 mmol) and was used without further purification. The title compound was formed as a yellow oil (7.16 g, 94 %); ν_{max}/cm^{-1} 3009 (m, C_{Ar}-H, stretch), 1641 (s, C=O, stretch), 1279 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.45 (1H, d, *J* 8, ArH-8′) 7.99 (1H, d, *J* 8, ArH), 7.92 (1H, d, *J* 7.5, ArH), 7.80 (1H, d, *J* 7, ArH), 7.67 (1H, d, *J* 16, CH-3), 7.65-7.51 (6H, m, 6 x ArH), 7.39 (2H, dd, *J* 5, 1.5, 2 x ArH), 7.35 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 195.2 (C-1), 145.6 (CH-3), 136.7 (C_{Ar}), 134.3 (C_{Ar}), 133.6 (C_{Ar}), 131.4 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 130.2 (C_{Ar}), 128.7 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 125.4 ($C_{Ar}H$), 124.3 ($C_{Ar}H$), (missing 1 x $C_{Ar}H$); m/z (MNa^+ $C_{19}H_{14}ONa^+$ requires 281.0937) found 281.0932.

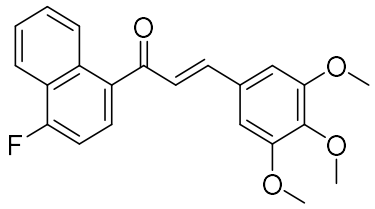
(*E*)-1-(Naphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



45

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetylnaphthalene (4.46 mL, 30 mmol), 3,4,5-trimethoxybenzaldehyde (5.77 g, 30 mmol) and sodium methoxide (2.38 g, 44 mmol) and was used without further purification. The title compound was formed as a yellow oil (4.40 g, 95 %); ν_{max}/cm^{-1} 3010 (m, C_{Ar}-H, stretch), 1659 (s, C=O, stretch), 1251 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.29 (1H, d, *J* 9, ArH), 7.98 (1H, d, *J* 8, ArH), 7.90 (1H, m, ArH), 7.75 (1H, d, *J* 7, ArH), 7.59-7.52 (3H, m, 3 x ArH), 7.49 (1H, d, *J* 16, CH-3), 7.20 (1H, d, *J* 16, CH-2), 6.79 (2H, s, ArH-2″), 3.89 (3H, s, C_{Ar}-4″ OCH_3), 3.86 (6H, s, 2 x C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 195.7 (C-1), 153.3 (2 x C_{Ar}-3″), 146.1 (C-3), 140.3 (C_{Ar}-4″), 137.0 (C_{Ar}), 133.7 (C_{Ar}), 131.3 ($C_{Ar}H$), 130.3 (C_{Ar}), 129.9 (C_{Ar}), 128.3 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 125.5 ($C_{Ar}H$), 124.4 ($C_{Ar}H$), 105.5 (2 x C_{Ar}-2″), 60.9 (C_{Ar}-4″ O*C*H_3), 56.0 (2 x C_{Ar}-3″ O*C*H_3); m/z (MNa^+ $C_{22}H_{20}O_4Na^+$ requires 371.1254) found 371.1248.

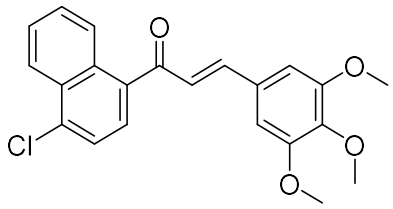
(*E*)-1-(4′-Fluoronaphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



46

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-fluoronapthalene, **33** (10.00 g, 53 mmol), 3,4,5-trimethoxybenzaldehyde (10.43 g, 53 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a yellow solid (15.78 g, 81 %); m.p. 96-97 °C; ν_{max}/cm^{-1} 2941 (s, C_{Ar}-H, stretch), 1650 (s, C=O, stretch), 1121 (s, C-F, stretch); δ_H (400 MHz, $CDCl_3$) 8.41-8.38 (1H, m, ArH-8′), 8.21-8.18 (1H, m, ArH-5′), 7.77 (1H, dd, *J* 8, 5.5, ArH-2′), 7.67-7.59 (2H, m, ArH-6′ & ArH-7′), 7.51 (1H, d, *J* 16, CH-3), 7.20 (1H, dd, *J* 10.5, 7.5, ArH-3′), 7.19 (1H, d, *J* 16, CH-2), 6.80 (2H, s, 2 x ArH-2″), 3.90 (3H, s, C_{Ar}-4″ OCH_3), 3.89 (6H, s, 2 x C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 194.4 (C-1), 160.4 (d, $^1J_{CF}$ 258, C_{Ar}-4′), 153.5 (2 x C_{Ar}-3″), 146.1 (CH-2), 140.5 (C_{Ar}-4″), 133.1 (d, $^4J_{CF}$ 4, C_{Ar}), 132.3 (d, $^4J_{CF}$ 5, C_{Ar}), 129.9 (C_{Ar}-1″), 128.5 (C_{Ar}H-2′), 127.9 (d, $^4J_{CF}$ 9.5, C_{Ar}H-6′), 126.8 (C_{Ar}H-7′), 126.0 (CH-2), 125.6 (C_{Ar}H-8′), 123.9 (d, $^2J_{CF}$ 16, C_{Ar}-4a′), 120.7 (d, $^3J_{CF}$ 6, C_{Ar}H-5′), 108.2 (d, $^2J_{CF}$ 21, C_{Ar}H-3′), 105.6 (2 x C_{Ar}H-2″), 60.9 (C_{Ar}-4″ O*C*H_3), 56.1 (2 x C_{Ar}-3″ O*C*H_3); δ_F (282 MHz, $CDCl_3$) -117.1 (ddd, *J* 7, 5.5, 2, C_{Ar}F-4′); m/z (MH^+ $C_{22}H_{19}FONa^+$ requires 389.1160) found 389.1157.

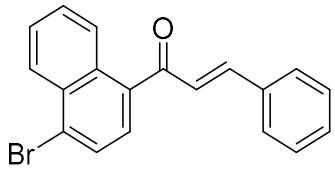
(*E*)-1-(4′-Chloronaphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one



47

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-chloronaphthalene, **34** (9.00 g, 44 mmol), 3,4,5-trimethoxybenzaldehyde (8.62 g, 44 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a yellow solid (14.06 g, 84 %); m.p. 125-126 °C; ν_{max}/cm^{-1} 2937 (m, C_{Ar}-H, stretch), 1650 (s, C=O, stretch), 1123, (s, C-O, stretch), 1095 (s, C-Cl, stretch); δ_H (400 MHz, $CDCl_3$) 8.33 (1H, d, *J* 8.5, ArH-8′), 8.28 (1H, d, *J* 8.5, ArH-5′), 7.70-7.58 (4H, m, ArH-2′, ArH-3′, ArH-6′ & ArH-7′), 7.45 (1H, d, *J* 16, CH-3), 7.14 (1H, d, *J* 16, CH-2), 6.78 (2H, s, 2 x ArH-2″), 3.89 (3H, s, C_{Ar}-4″ OCH_3), 3.87 (6H, s, 2 x C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 195.1 (C-1), 153.5 (2 x C_{Ar}-3″), 146.7 (CH-3), 140.7 (C_{Ar}-4″), 136.3 (C_{Ar}), 135.2 (C_{Ar}), 131.6 (C_{Ar}), 131.0 (C_{Ar}), 129.8 (C_{Ar}), 128.1 (C_{Ar}H), 127.6 (C_{Ar}H), 126.5 (C_{Ar}H), 126.4 (C_{Ar}H), 126.0 (C_{Ar}H), 125.0 (C_{Ar}H), 124.8 (C_{Ar}H), 105.7 (2 x C_{Ar}H-2″), 61.0 (C_{Ar}-4″ O*C*H_3), 56.1 (2 x C_{Ar}-3″ O*C*H_3); m/z (MNa^+ $C_{22}H_{19}ClO_4Na^+$ requires 405.0864) found 405.0865.

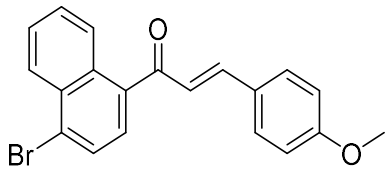
(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-phenylprop-2-en-1-one



48

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromo-naphthalene, **35** (10.00 g, 40 mmol), benzaldehyde (4.08 mL, 40 mmol) and sodium methoxide (3.25 g, 60 mmol) and was used without further purification. The title compound was formed as an orange oil (13.21 g, 98 %); ν_{max}/cm^{-1} 1650 (s, C=O, stretch), 1069 (s, C-Br, stretch); δ_H (400 MHz, $CDCl_3$) 8.38-8.32 (2H, m, 2 x ArH), 7.88-7.85 (1H, d, *J* 7.5, ArH), 7.69-7.56 (6H, m, CH-3 & 5 x ArH), 7.44-7.40 (3H, m, 3 x ArH), 7.29 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 194.9 (C-1), 146.3 (CH-3), 136.9 (C_{Ar}), 134.2 (C_{Ar}), 132.1 (C_{Ar}), 131.4 (C_{Ar}), 130.8 ($C_{Ar}H$), 128.9 (2 x $C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.4 (2 x $C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), (missing 1 x C_{Ar}); m/z (MH^+ $C_{19}H_{13}{}^{79}BrOH^+$ requires 337.0223) found 337.0223, (MH^+ $C_{19}H_{13}{}^{81}BrOH^+$ requires 339.0203) found 339.0203.

(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(4″-methoxyphenyl)prop-2-en-1-one

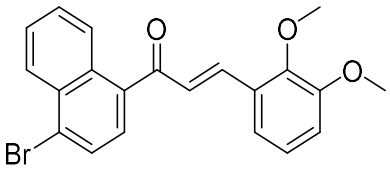


49

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromo-naphthalene, **35** (10.00 g, 40 mmol), 4-methoxybenzaldehyde (4.88 mL, 40 mmol) and sodium methoxide (3.25 g, 60 mmol)

and was used without further purification. The title compound was formed as a yellow solid (14.23 g, 97 %); m.p. 105-106 °C, (lit.[519] 123-124 °C); ν_{max}/cm^{-1} 2938 (w, C_{Ar}-H, stretch), 1649 (s, C=O, stretch), 1172 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.34 (1H, d, *J* 8.5, ArH-8′), 8.26 (1H, d, *J* 8.5, ArH-5′), 7.85 (1H, d, *J* 7.5, ArH-3′), 7.78-7.82 (2H, m, ArH-6′ & ArH-7′), 7.56-7.48 (4H, m, CH-3, ArH-2′ & 2 x ArH-2″), 7.12 (1H, d, *J* 16, CH-2), 6.91 (2H, d, *J* 8.5, 2 x ArH-3″), 3.83 (3H, s, C_{Ar}-4″ OCH_3); δ_C (100 MHz, $CDCl_3$) 195.3 (C-1), 161.9 (C_{Ar}-4″), 146.6 (CH-3), 137.4 (C_{Ar}-1′), 132.2 (C_{Ar}-4′), 131.6 (C_{Ar}-1″), 130.3 (2 x C_{Ar}H-2″), 128.8 (C_{Ar}H-3′), 128.0 (C_{Ar}H), 127.8 (C_{Ar}H), 127.5 (C_{Ar}H-8′), 127.0 (C_{Ar}-1″) 126.6 (C_{Ar}H-2′), 126.1 (C_{Ar}H-5′), 124.8 (CH-2), 114.5 (2 x C_{Ar}H-3″), 55.4 (C_{Ar}-4″ O*C*H_3), (missing 1 x C_{Ar}); m/z (MH^+ $C_{20}H_{15}{}^{79}BrO_2H^+$ requires 367.0328) found 367.0331, (MH^+ $C_{20}H_{15}{}^{81}BrO_2H^+$ requires 369.0309) found 369.0310.

(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(2″,3″-dimethoxyphenyl)prop-2-en-1-one

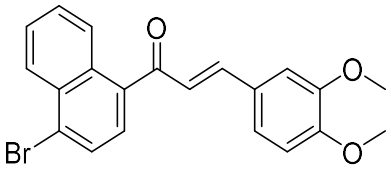


50

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromo-naphthalene, **35** (10.00 g, 40 mmol), 2,3-dimethoxybenzaldehyde (6.67 g, 40 mmol) and sodium methoxide (3.25 g, 60 mmol) and was used without further purification. The title compound was formed as an off-white solid (12.91 g, 81 %); m.p. 106-107 °C; ν_{max}/cm^{-1} 2942 (w, C_{Ar}-H, stretch),

1655 (s, C=O, stretch), 1270 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 8.38-8.30 (2H, m, ArH-8′ & ArH-5′), 7.92 (1H, d, *J* 16, CH-3), 7.86 (1H, d, *J* 7.5, ArH-3′), 7.68-7.58 (3H, m, ArH-6′, ArH-7′ & ArH-2′), 7.31 (1H, d, *J* 16, CH-2), 7.23 (1H, dd, *J* 8, 1, ArH-6″), 7.08 (1H, t, *J* 8, ArH-5″), 6.97 (1H, dd, *J* 8, 1, ArH-4″), 3.88 (3H, s, C_{Ar} OCH_3), 3.79 (3H, s, C_{Ar} OCH_3); δ_C (125 MHz, $CDCl_3$) 195.2 (C-1), 153.1 (C_{Ar}), 148.9 (C_{Ar}), 141.2 (C-3), 137.1 (C_{Ar}), 132.3 (C_{Ar}), 131.7 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.6 (C_{Ar}), 128.1 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.7 (C_{Ar}), 126.2 ($C_{Ar}H$), 124.3 ($C_{Ar}H$-3″), 119.4 ($C_{Ar}H$-6″), 114.5 ($C_{Ar}H$-4″), 61.3 (C_{Ar} O*C*H_3), 55.9 (C_{Ar} O*C*H_3); m/z (MNa^+ $C_{21}H_{17}{}^{79}BrO_3Na^+$ requires 419.0253) found 419.0254, (MNa^+ $C_{21}H_{17}{}^{81}BrO_3Na^+$ requires 421.0233) found 421.0237.

(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(3″,4″-dimethoxyphenyl)prop-2-en-1-one

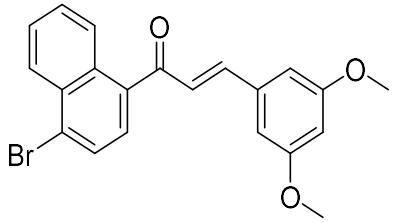


51

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromo-naphthalene, **35** (10.00 g, 40 mmol), 3,4-dimethoxybenzaldehyde (6.67 g, 40 mmol) and sodium methoxide (3.25 g, 60 mmol) and was used without further purification. The title compound was formed as a pale yellow solid (13.56 g, 85 %); m.p. 134-135 °C; ν_{max}/cm^{-1} 2995 (w, C_{Ar}-H, stretch), 1619 (s, C=O, stretch), 1135 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.33 (1H, d, *J* 8, ArH-8′), 8.24 (1H, d, *J* 8.5, ArH-5′), 7.84 (1H, d, *J* 7.5, CH-3′), 7.68-7.56 (3H, m,

ArH-6′, ArH-7′ & ArH-2′), 7.48 (1H, d, *J* 16, CH-3), 7.14-7.05 (3H, CH-2, ArH-2″ & ArH-6″), 6.85 (1H, d, *J* 8.5, ArH-5″), 3.90 (3H, s, C_{Ar} O*C*H$_3$), 3.90 (3H, s, C_{Ar} O*C*H$_3$; δ_C (100 MHz, $CDCl_3$) 195.4 (C-1), 151.8 (C_{Ar}), 149.3 (C_{Ar}), 146.9 (CH-3), 137.4 (C_{Ar}), 132.3 (C_{Ar}), 131.7 (C_{Ar}), 128.8 (C_{Ar}H), 128.1 (C_{Ar}H), 127.9 (C_{Ar}H), 127.6 (C_{Ar}H), 127.3 (C_{Ar}), 126.7 (C_{Ar}H), 126.2 (C_{Ar}H), 125.1 (C_{Ar}H), 123.5 (CH-2), 111.1 (C_{Ar}H-5″), 110.0 (C_{Ar}H-5″), 56.0 (C_{Ar} O*C*H$_3$), 55.9 (C_{Ar} O*C*H$_3$), (missing 1 x C_{Ar}); m/z (MNa^+ $C_{21}H_{17}{}^{79}BrO_3Na^+$ requires 419.0253) found 419.0255, (MNa^+ $C_{21}H_{17}{}^{81}BrO_3Na^+$ requires 421.0235) found 421.0237.

(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(3″,5″-dimethoxyphenyl)prop-2-en-1-one

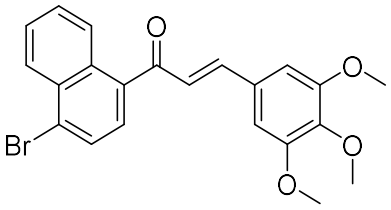


52

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromo-naphthalene, **35** (10.00 g, 40 mmol), 3,5-dimethoxybenzaldehyde (6.67 g, 40 mmol) and sodium methoxide (3.25 g, 60 mmol) and was used without further purification. The title compound was formed as a viscous yellow oil (11.96 g, 75 %); ν_{max}/cm^{-1} 2935 (w, C_{Ar}-H, stretch), 1649 (s, C=O, stretch), 1153 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.73 (1H, d, *J* 8.5, ArH-8′), 8.30 (1H, d, *J* 8.5, ArH-5′), 7.89 (1H, d, *J* 7.5, ArH-3′), 7.72-7.55 (3H, m, ArH-6′, ArH-7′ & ArH-2′), 7.50 (1H, d, *J* 16, CH-3), 7.30 (1H, d, *J* 16, CH-2), 6.72 (2H, s, 2

x ArH-2″), 6.55 (1H, s, ArH-4″), 3.83 (6H, s, 2 x C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 195.2 (C-1), 161.1 (2 x C_{Ar}-3″), 146.6 (CH-3), 136.9 (C_{Ar}), 136.2 (C_{Ar}), 132.3 (C_{AR}), 131.6 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.7 (C_{Ar}), 126.1 ($C_{Ar}H$), 106.4 (2 x $C_{Ar}H$-2″), 103.3 ($C_{Ar}H$-4″), 55.5 (C_{Ar}-3″ O*C*H_3); m/z (MNa^+ $C_{21}H_{17}{}^{79}BrO_3Na^+$ requires 419.0253) found 419.0254, (MNa^+ $C_{21}H_{17}{}^{81}BrO_3$ requires 421.0234) found 421.0233.

(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one

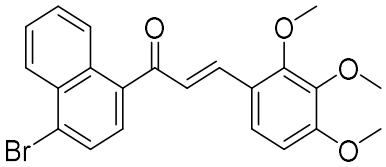


53

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromonaphthalene, **35** (10.00 g, 40 mmol), 3,4,5-trimethoxybenzaldehyde (7.88 g, 40 mmol) and sodium methoxide (3.25 g, 60 mmol), stirred at 50 °C for 2 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a yellow solid (17.04 g, 99 %); m.p. 121-122 °C; ν_{max}/cm^{-1} 2937 (m, C_{Ar}-H, stretch), 1648 (s, C=O, stretch), 1126 (s, C-O, stretch), 1003 (s, C_{Ar}-Br, stretch); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, d, *J* 8.5, ArH-8′), 8.25 (1H, d, *J* 8.5, ArH-5′), 7.85 (1H, d, *J* 8.5, ArH-3′), 7.67-7.58 (2H, m, ArH-6′ & ArH-7′), 7.54 (1H, d, *J* 7.5, ArH-2′), 7.44 (1H, d, *J* 16, CH-3), 7.14 (1H, d, *J* 16, CH-2), 6.78 (2H, s, 2 x ArH-2″), 3.89 (3H, s, C_{Ar}-4″ OCH_3), 3.87 (6H, s, 2 x

C_{Ar}-3″ OCH_3); δ_C (100 MHz, $CDCl_3$) 195.2 (C-1), 153.4, 153.4 (C_{Ar}-4″ & 2 x C_{Ar}-3″), 146.8 (CH-3), 140.7 (C_{Ar}-1″), 137.1 (C_{Ar}-4′), 132.2 (C_{Ar}), 131.6 (C_{Ar}), 129.7 (C_{Ar}-1′), 128.7 (C_{Ar}-2′), 128.1, 127.9 (C_{Ar}-6′ & C_{Ar}-7′), 127.6 (C_{Ar}-8′), 126.7 (C_{Ar}H), 126.3 (C_{Ar}H), 126.0 (C_{Ar}H), 105.7 (2 x C_{Ar} 2″), 60.9 (C_{Ar}-4″ O*C*H_3), 56.1 (2 x C_{Ar} 3″ O*C*H_3); m/z (MH^+ $C_{22}H_{19}{}^{79}BrO_4H^+$ requires 427.0539) found 427.0548, (MH^+ $C_{22}H_{19}{}^{81}BrO_4H^+$ requires 429.0520) found 429.0534.

(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(2″,3″,4″-trimethoxyphenyl)prop-2-en-1-one

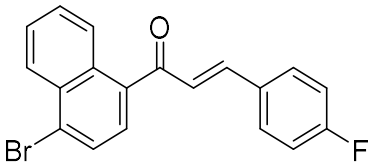


54

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromonaphthalene, **35** (10.00 g, 40 mmol), 2,3,4-dimethoxybenzaldehyde (7.87 g, 40 mmol) and sodium methoxide (3.25 g, 60 mmol) and was used without further purification. The title compound was formed as a yellow solid (16.94 g, 99 %); m.p. 103-104 °C; ν_{max}/cm^{-1} 2950 (s, C_{Ar}-H, stretch), 1649 (s, C=O, stretch), 1091 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.33 (1H, d, *J* 8, ArH-8′), 8.29 (1H, d, *J* 8.5, ArH-5′), 7.85 (1H, d, *J* 7.5, ArH-3′), 7.79 (1H, d, *J* 16, CH-3), 7.67-7.58 (2H, m, ArH-6′ & ArH-7′), 7.54 (1H, d, *J* 7.5, ArH-2′), 7.32 (1H, d, *J* 9, ArH-6″), 7.22 (1H, d, *J* 16, CH-2), 6.69 (1H, d, *J* 9, ArH-5″), 3.88 (3H, s, C_{Ar}-3″ OCH_3), 3.84 (3H, C_{Ar}-4″ OCH_3), 3.83 (3H, s, C_{Ar}-2″ OCH_3); δ_C (100 MHz, $CDCl_3$) 195.6 (C-1), 156.1 (C_{Ar}-3″), 153.6 (C_{Ar}-2″), 142.2 (C_{Ar}-4″), 141.9 (CH-3), 137.4 (C_{Ar}-1′), 132.1 (C_{Ar}), 131.6 (C_{Ar}), 128.7 (C_{Ar}H-3′), 127.8 (C_{Ar}H), 127.7 (C_{Ar}H), 127.5

($C_{Ar}H$), 126.7 ($C_{Ar}H$-2′), 126.2 (C_{Ar}), 126.1, 125.9 ($C_{Ar}H$-5′ & CH-2), 123.7 $C_{Ar}H$-2″), 121.3 (C_{Ar}-1″), 107.6 ($C_{Ar}H$-5″), 61.4 (C_{Ar}-2″ O*C*H$_3$), 60.8 (C_{Ar}-4″ O*C*H$_3$), 56.0 (C_{Ar}-3″ O*C*H$_3$); m/z (MNa^+ $C_{22}H_{19}{}^{79}BrO_4Na^+$ requires 449.0359) found 449.0361, (MNa^+ $C_{22}H_{19}{}^{81}BrO_4Na^+$ requires 451.0340) found 451.0343.

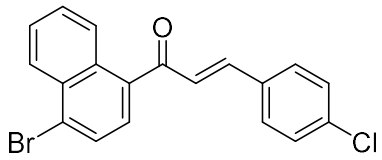
(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(4″-fluorophenyl)prop-2-en-1-one



55

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromonaphthalene, **35** (10.00 g, 40 mmol), 4-fluorobenzaldehyde (4.31 mL, 40 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a off-white solid (7.95 g, 55 %); m.p. 76-77 °C; ν_{max}/cm^{-1} 2974 (w, C_{Ar}-H, stretch), 1660 (s, C=O, stretch), 1223 (s, C-F, stretch); δ_H (400 MHz, $CDCl_3$) 8.39-8.27 (2H, m, ArH-8′ & ArH-5′), 7.84 (1H, d, *J* 8, ArH-3′), 7.75 (1H, d, *J* 8, ArH-2′), 7.71-7.52 (6H, m, 2 x ArH-2″, CH-3, ArH-6′ & ArH-7′), 7.20 (1H, d, *J* 16, CH-2), 7.14-7.11 (2H, m, ArH-3″); δ_C (100 MHz, $CDCl_3$) 194.9 (C-1), 164.3 (d, $^1J_{CF}$ 252, C_{Ar}-4″), 145.1 (CH-3), 136.9 (C_{Ar}), 135.4 (C_{Ar}), 132.3 (C_{Ar}), 131.6 (C_{Ar}), 131.2 (C_{Ar}), 130.5 (d, $^3J_{CF}$ 8.5, 2 x $C_{Ar}H$-2″), 128.3 ($C_{Ar}H$), 182.2 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 126.1 (CH-2), 116.3 (d, $^2J_{CF}$ 22, 2 x $C_{Ar}H$-3″) m/z (MNa^+ $C_{19}H_{12}{}^{79}BrFONa^+$ requires 376.9948) found 376.9950, (MNa^+ $C_{19}H_{12}{}^{81}BrFONa^+$ requires 378.9929) found 378.9931.

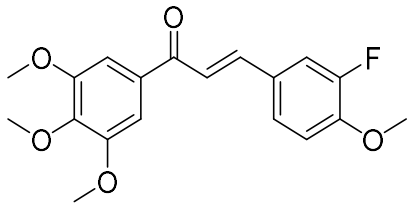
(*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(4″-chlorophenyl)prop-2-en-1-one



56

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 1-acetyl-4-bromonaphthalene, **35** (10.00 g, 40 mmol), 4-chlorobenzaldehyde (5.64 g, 40 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a yellow solid (12.25 g, 82 %); m.p. 125-126 °C, (lit.[519] 100-101 °C); ν_{max}/cm^{-1} 1657 (s, C=O, stretch), 1087 (s, C-Br, stretch), 987 (s, C-Cl, stretch); δ_H (400 MHz, $CDCl_3$) 8.36 (1H, d, *J* 8.5, ArH-8′), 8.32 (1H, d, *J* 8.5, ArH-5′), 7.87 (1H, d, *J* 7.5, ArH-3′), 7.69 (2H, m, ArH-6′ & ArH-7′), 7.59 (1H, d, *J* 7.5, ArH-2′), 7.55 (1H, d, *J* 16, CH-3), 7.50 (2H, d, *J* 8.5, 2 x ArH-2″), 7.38 (2H, d, *J* 8.5, 2 x ArH-3″), 7.24 (1H, d, *J* 16, CH-2); δ_C (100 MHz, $CDCl_3$) 194.7 (C-1), 144.9 (CH-3), 136.9 (C_{Ar}), 136.8 (C_{Ar}), 132.9 (C_{Ar}), 132.3 (C_{Ar}), 131.6 (C_{Ar}), 129 (2 x $C_{Ar}H$), 129.3 (2 x $C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.9 (C_{Ar}), 126.1 ($C_{Ar}H$); m/z (MH^+ $C_{19}H_{12}{}^{79}BrClOH^+$ requires 370.9833) found 370.9835, (MH^+ $C_{19}H_{12}{}^{81}BrClOH^+$ requires 372.9812) found 372.9808.

(*E*)-1-(3″-Fluoro-4″-methoxyphenyl-1-(3′,4′,5′-trimethoxyphenyl)prop-2-en-1-one

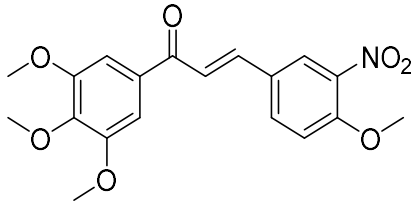


57

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3,4,5-trimethoxyacetophenone (6.81 g, 32 mmol), 3-fluoro-4-methoxybenzaldehyde (5.00 g, 32 mmol) and potassium hydroxide solution (3 M, 3 mL) instead of sodium methoxide. The reaction was performed in methanol (40 mL) and was used without further purification. The title compound was formed as a yellow solid (10.58 g, 94 %); m.p. 108-109 °C, (lit.[520] 103-105 °C); ν_{max}/cm^{-1} 1650 (s, C=O, stretch), 1127 (s, C-F, stretch); δ_H (400 MHz, $CDCl_3$); 7.71 (1H, d, *J* 15.5, CH-3), 7.41 (1H, dd, *J* 12, 2, ArH-2″), 7.33 (1H, d, *J* 15.5, CH-2), 7.33 (1H, m, ArH-6″), 7.25 (2H, s, 2 x ArH-2′), 6.97 (1H, t, *J* 8.5, ArH-5″), 3.93 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.92 (3H, s, C_{Ar} OCH_3), 3.92 (3H, s, C_{Ar} OCH_3); δ_C (100 MHz, $CDCl_3$) 188.8 (C-1), 153.1 (2 x C_{Ar}-3′), 152.4 (d, $^1J_{CF}$ 247, C_{Ar}-3″), 149.7 (d, $^2J_{CF}$ 11, C_{Ar}-4″), 143.3 (d, $^4J_{CF}$ 2, CH-3), 142.4 (C_{Ar}-4′), 133.4 (C_{Ar}-1′), 128.1 (d, $^3J_{CF}$ 6.5, C_{Ar}-1″), 126.2 (C_{Ar}H-6″), 120.5 (CH-2), 114.6 (d, $^2J_{CF}$ 18.5, C_{Ar}H-2″), 113.1 (C_{Ar}H-5″), 106.0 (2 x C_{Ar}H-2′), 60.9 (C_{Ar}-4″ O*C*H_3), 56.3 (2 x C_{Ar}-3′ O*C*H_3), 56.2 (C_{Ar}-4′ O*C*H_3); δ_F (282 MHz,

$CDCl_3$) -134.8 (dd, *J* 12, 8.5, CF-3″); m/z (MNa^+ $C_{19}H_{19}FO_5Na^+$ requires 369.1109) found 369.1104.

(*E*)-1-(4″-Methoxy-3″-nitrophenyl)-1-(3′,4′,5′-trimethoxyphenyl)prop-2-en-1-one



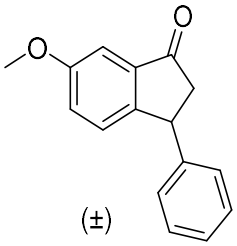
58

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.2**, using 3,4,5-trimethoxyacetophenone (6.24 g, 30 mmol), 4-methoxy-3-nitrobenzaldehyde (5.38 g, 30 mmol) and sodium methoxide (2.24 g, 45 mmol) and was used without further purification. The title compound was formed as a yellow solid (10.99 g, 99 %); m.p. 142-143 °C, (lit.[521] 143-145 °C); ν_{max}/cm^{-1} 1650 (s, C=O, stretch), 1126 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.24 (1H, d, *J* 2, ArH-2″), 7.86 (1H, dd, *J* 9, 2.5, ArH-5″), 7.82 (1H, d, *J* 16, CH-3), 7.52 (1H, d, *J* 16, CH-2), 7.35 (2H, s, 2 x ArH-2′), 7.22 (1H, d, *J* 9, ArH-5″), 4.09 (3H, s, C_{Ar}-4″ OCH_3), 4.03 (6H, s, 2 x C_{Ar}-3′ OCH_3), 4.02 (3H, s, C_{Ar}-4′ OCH_3); δ_C (100 MHz, $CDCl_3$) 188.4 (C-1), 154.1 (C_{Ar}-4″), 153.2 (2 x C_{Ar}-3′), 142.7 (C_{Ar}-4′), 141.6 (CH-3), 139.9 (C_{Ar}-3″), 134.5 (C_{Ar}H-6″), 133.1 (C_{Ar}-1′), 127.6 (C_{Ar}-1″), 124.7 (C_{Ar}H-2″), 121.9 (CH-2), 113.8 (C_{Ar}H-5″), 106.1 (2 x C_{Ar}H-2′), 60.9 (C_{Ar}-4′ OCH_3), 56.7 (C_{Ar}-4″ OCH_3), 56.3 (2 x C_{Ar}-3′ OCH_3); m/z (MH^+ $C_{19}H_{19}NO_7H^+$ requires 374.1234) found 374.1234.

5.2.3.3 Nazarov-type Reactions for the General Formation of Substituted Indanones

The following procedure was performed in accordance with previous literature.[354] Substituted chalcone (8.4 mmol) and phosphorus pentoxide (12.6 mmol) in trifluoroacetic acid (20 mL, ~2 mL/mmol) was refluxed for 48 hours under N_2. To the resulting viscous brown mixture was added H_2O (50 mL) slowly under constant stirring, and the product was extracted into CH_2Cl_2 (40 mL). The organic layer was washed with 2M NaOH (40 mL) twice, saturated $NaHCO_3$ (40 mL) twice, dried over $MgSO_4$ and concentrated *in vacuo*. The brown residue was then purified by silica column chromatography as mentioned specifically.

6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one

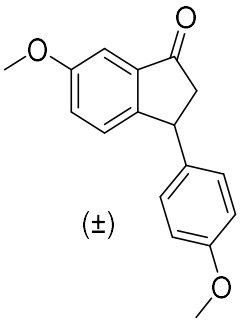


59

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-phenylprop-2-en-1-one, **36**, (1.50 g, 6.3 mmol), trifluoroacetic acid (15 mL ~2 mL/mmol) and phosphorus pentoxide (2.68 g, 9.5 mmol). The crude product by purified by silica column chromatography, eluting with dichloromethane : petroleum ether (1 : 2), yielding orange needles (1.26 g, 84 %); m.p. 69-70 °C, (lit.[354] 69-70 °C); ν_{max}/cm^{-1} 2954 (m, C_{Ar}-H, stretch), 1698 (s, C=O, stretch), 1279 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.33-7.29 (2H, m, 2 x ArH), 7.26-7.23 (2H, m, 2 x ArH), 7.17-7.16 (2H, m, 2 x ArH), 7.13-7.11 (2H, m, 2 x ArH), 4.52 (1H, dd, *J* 8, 5.5, CH-3), 3.86 (3H, s, C_{Ar}-6 OCH_3), 3.26 (1H, dd, *J*

19.5, 8, C*H*H-2), 2.70 (1H, dd, *J* 19.5, 3.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.0 (C-1), 159.7 (C_{Ar}-6), 150.8 (C_{Ar}), 143.9 (C_{Ar}), 137.9 (C_{Ar}), 128.8 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 124.5 ($C_{Ar}H$), 104.3 ($C_{Ar}H$), 55.6 (C_{Ar}-6 O*C*H_3), 47.5 (C-2), 43.7 (C-3); m/z (MNa^+ $C_{16}H_{14}O_2Na^+$ requires 261.0886) found 261.0892.

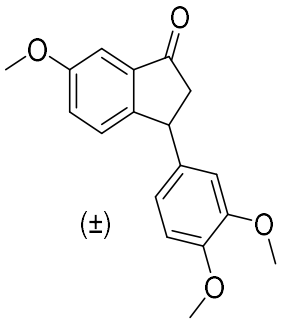
6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



60

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-(4″-methoxyphenyl)prop-2-en-1-one**, 37**, (10.00 g, 37.3 mmol), trifluoroacetic acid (75 mL, ~2 mL/mmol) and phosphorus pentoxide (15.9 g, 56.0 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding an orange oil (4.07 g, 41 %); ν_{max}/cm^{-1} 2835 (w, C_{Ar}-H, stretch), 1734 (s, C=O, stretch), 1239 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 7.23-7.21 (1H, m, ArH-7), 7.16-7.15 (2H, m, ArH-4 & ArH-5), 7.03 (2H, d, *J* 8.5, 2 x ArH-2′), 6.84 (2H, d, *J* 8.5, 2 x ArH-3′), 4.47 (1H, dd, *J* 7.5, 3.5, CH-3), 3.86 (3H, s, C_{Ar} OCH_3), 3.79 (3H, s, C_{Ar} OCH_3)m 3.23 (1H, dd, *J* 19, 8, C*H*H-2), 2.65 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 206.1 (C-1), 159.7 (C_{Ar}), 158.5 (C_{Ar}), 151.1 (C_{Ar}), 137.9 (C_{Ar}), 136.0 (C_{Ar}), 128.5 (2 x $C_{Ar}H$-2′), 127.6 ($C_{Ar}H$), 124.5 ($C_{Ar}H$), 114.2 (2 x $C_{Ar}H$-3′), 104.3 ($C_{Ar}H$-7), 55.6 (C_{Ar} O*C*H_3), 55.3 (C_{Ar} O*C*H_3), 47.7 (CH_2-2), 43.0 (CH-3); m/z (MNa^+ $C_{17}H_{16}O_3Na^+$ requires 291.0992) found 291.0991.

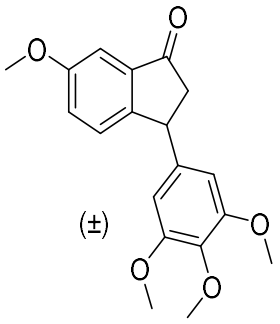
3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



61

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-(3″,4″-dimethoxyphenyl)prop-2-en-1-one**, 38**, (10.00 g, 33.5 mmol), trifluoroacetic acid (70 mL, ~2 mL/mmol) and phosphorus pentoxide (14.30 g, 50.3 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a yellow solid (3.75 g, 38 %); m.p. 84-85 °C, (lit. 84-85 °C); ν_{max}/cm^{-1} 2936 (w, C_{Ar}-H, stretch), 1705 (s, C=O, stretch), 1250 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.30-7.23 (2H, m, 2 x ArH), 7.21-7.18 (2H, m, 2 x ArH), 6.82 (1H, d, *J* 8, ArH), 6.71 (1H, d, *J* 8, ArH), 6.60 (1H, d, *J* 9, ArH), 4.53-4.45 (1H, m, CH-3), 3.88 (6H, s, C_{Ar}-4′ OCH_3 & C_{Ar}-6 OCH_3), 3.82 (3H, s, C_{Ar}-3′ OCH_3), 3.26 (1H, dd, *J* 19.5, 8, C*H*H-2), 2.70 (1H, dd, *J* 19.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 199.4 (C-1), 159.7 (C_{Ar}), 151.0 (C_{Ar}), 137.9 (C_{Ar}), 136.4 (C_{Ar}), 129.8 (C_{Ar}), 127.6 ($C_{Ar}H$), 124.6 ($C_{Ar}H$), 119.7 ($C_{Ar}H$), 111.3 ($C_{Ar}H$), 110.4 ($C_{Ar}H$), 104.3 ($C_{Ar}H$), 55.9 (C_{Ar} O*C*H_3), 55.9 C_{Ar} O*C*H_3), 55.9 C_{Ar} O*C*H_3), 55.7 C_{Ar} O*C*H_3), 47.7 (CH_2-2), 43.5 (CH-3), (missing 1 x C_{Ar}); m/z MNa^+ $C_{18}H_{18}O_4Na^+$ requires 321.1097) found 321.1090.

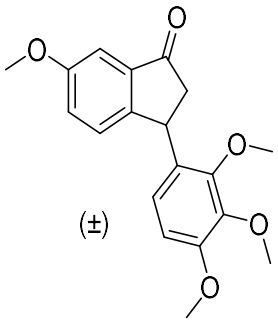
6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



62

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one, **39**, (10.00 g, 30.4 mmol), trifluoroacetic acid (60 mL, ~2 mL/mmol) and phosphorus pentoxide (12.95 g, 45.7 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane : petroleum ether (80 : 20), yielding a yellow oil (3.48 g, 35 %); ν_{max}/cm^{-1} 2965 (w, C_{Ar}-H, stretch), 1680 (s, C=O, stretch), 1202 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.30-7.24 (4H, m, 4 x ArH), 6.32 (2H, s, 2 x ArH-2′), 4.49-4.45 (1H, m, CH-3), 3.89 (3H, s, C_{Ar}-6 OCH_3), 3.85 (3H, s, C_{Ar}-4′ OCH_3), 3.81 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.26 (1H, dd, *J* 19.5, 8, C*H*H-2), 2.71 (1H, dd, *J* 19.5, 2, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 193.3 (C-1), 159.8 (C_{Ar}), 153.5 (C_{Ar}), 150.5 (C_{Ar}), 139.6 (C_{Ar}), 138.0 (C_{Ar}), 127.7 ($C_{Ar}H$), 124.6 ($C_{Ar}H$), 104.4 (2 x $C_{Ar}H$-2′), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 55.7 (C_{Ar}-4′ O*C*H_3), 47.5 (CH_2-2), 44.2 (CH-3), (missing 1 x C_{Ar}); m/z (MH^+ $C_{19}H_{20}O_5H^+$ requires 329.1384) found 329.1374.

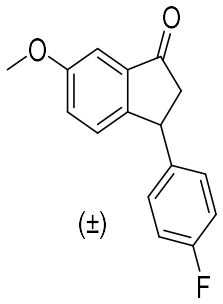
6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



63

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-(2″,3″,4″-trimethoxyphenyl)prop-2-en-1-one, **40**, (10.00 g, 30.4 mmol), trifluoroacetic acid (60 mL, ~2 mL/mmol) and phosphorus pentoxide (12.95 g, 45.7 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a yellow oil (2.37 g, 24 %); ν_{max}/cm^{-1} 2937 (w, C_{Ar}-H, stretch), 1705 (s, C=O, stretch), 1270 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.27-7.15 (3H, m, 3 x ArH), 6.70 (1H, d, *J* 8.5, ArH-6′), 6.59 (1H, d, *J* 8.5, ArH-5′), 4.72-4.67 (1H, m, CH-3), 3.86 (6H, m, 2 x C_{Ar} OCH_3), 3.86 (3H, s, C_{Ar} OCH_3), 3.65 (3H, s, C_{Ar} OCH_3), 3.21 (1H, dd, *J* 19, 8, C*H*H-2), 2.73 (1H, dd, *J* 19, 3, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.6 (C-1), 154.6 (C_{Ar}), 151.1 (C_{Ar}), 142.4 (C_{Ar}), 138.1 (C_{Ar}), 129.5 (C_{Ar}), 127.3 ($C_{Ar}H$), 124.1 ($C_{Ar}H$), 122.7 ($C_{Ar}H$), 107.0 (C_{Ar}), 104.4 ($C_{Ar}H$), 60.7 (C_{Ar} O*C*H_3), 56.0 (C_{Ar} O*C*H_3), 55.7 (C_{Ar} O*C*H_3), 46.6 CH_2-2), 38.8 (CH-3), (missing 1 x C_{Ar}); m/z (MNa^+ $C_{19}H_{20}O_5Na^+$ requires 351.1203) found 351.1199.

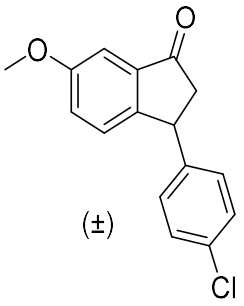
3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



64

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-(4″-fluorophenyl)prop-2-en-1-one, **41**, (10.00 g, 58.5 mmol), trifluoroacetic acid (120 mL, ~2 mL/mmol) and phosphorus pentoxide (24.9 g, 87.8 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a white solid (8.67 g, 87 %); m.p. 92-93 °C, (lit.[522] 88-91 °C); ν_{max}/cm^{-1} 2098 (w, C_{Ar}-H, stretch), 1702 (s, C=O, stretch), 1218 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 7.23 (1H, d, *J* 2.5, ArH-7), 7.17 (1H, dd, *J* 8.5, 2.5, ArH-5), 7.14 (1H, d, *J* 8.5, ArH-4), 7.07 (2H, dd, *J* 8.5, 5.5, 2 x ArH-2′), 6.99 (2H, t, *J* 8.5, 2 x ArH-3′), 4.51 (1H, dd, *J* 8, 3.5, CH-3), 3.86 (3H, s, C_{Ar}-4″ OCH_3), 3.25 (1H, dd, *J* 19, 8, C*H*H-2), 2.63 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.6 (C-1), 161.7 (d, $^1J_{CF}$ 245, C_{Ar}-4″), 159.8 (C_{Ar}-6), 150.5 (C_{Ar}), 139.6 (d, $^4J_{CF}$ 3, C_{Ar}-1′), 138.0 (C_{Ar}), 129.0 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-2′), 127.5 (C_{Ar}H-4), 124.6 (C_{Ar}H-5), 115.7 (d, $^2J_{CF}$ 21.5, 2 x C_{Ar}-3′), 104.4 (C_{Ar}H-7), 55.6 (C_{Ar}-6 O*C*H_3), 47.6 (CH_2-2), 43.0 (CH_3); δ_F (282 MHz, $CDCl_3$) -115.9 (m, C_{Ar}F-4′); m/z (MNa^+ $C_{16}H_{13}FO_2Na^+$ requires 279.0792) found 279.0793.

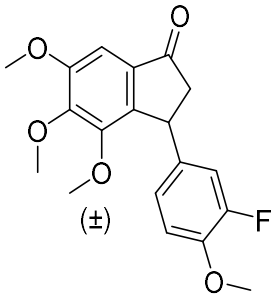
3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



65

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3′-methoxyphenyl)-3-(4″-chlorophenyl)prop-2-en-1-one, **42**, (7.00 g, 25.7 mmol), trifluoroacetic acid (50 mL, ~2 mL/mmol) and phosphorus pentoxide (10.92 g, 38.5 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a white solid (5.91 g, 84 %); m.p. 125-126 °C, (lit.[217] 118 °C); ν_{max}/cm^{-1} 2953 (w, C_{Ar}-H, stretch), 1705 (s, C=O, stretch), 1279 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.5, 2 x ArH-3″), 7.22 (1H, d, *J* 2.5, ArH-7), 7.17 (1H, dd, *J* 8.5, 2.5, ArH-5), 1H (1H, d, *J* 8.5, ArH-4), 7.05 (2H, d, *J* 8.5, 2 x ArH-2″), 4.49 (1H, dd, *J* 8, 3.5, CH-3), 3.85 (3H, s, C_{Ar}-6 O*C*H_3), 3.24 (1H, dd, *J* 19, 8, C*H*H-2), 2.62 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.3 (C-1), 159.8 (C_{Ar}-6), 150.1 (C_{Ar}), 142.4 (C_{Ar}), 137.9 (C_{Ar}), 132.6 (C_{Ar}), 128.9 (2 x C_{Ar}H-2″), 128.8 (2 x C_{Ar}H-3″), 127.4 (C_{Ar}H-4), 124.5 (C_{Ar}H-5), 104.4 (C_{Ar}H-7), 55.5 (C_{Ar}-6 O*C*H_3), 47.3 (CH_2-2), 43.0 CH-3); m/z (MNa^+ $C_{16}H_{13}{}^{35}ClO_2Na^+$ requires 295.0496) found 295.0502.

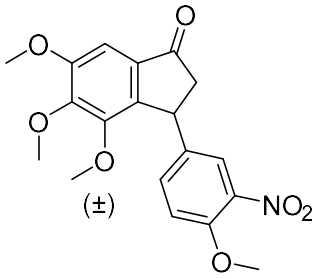
3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one



66

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(3″-fluoro-4″-methoxyphenyl-1-(3′,4′,5′-trimethoxyphenyl)prop-2-en-1-one, **57**, (10.00 g, 28.9 mmol), trifluoroacetic acid (60 mL, ~2 mL/mmol) and phosphorus pentoxide (12.27 g, 43.3 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a off-white solid (7.23 g, 72 %); m.p. 116-117 °C; ν_{max}/cm^{-1} 2937 (w, C_{Ar}-H, stretch), 1705 (s, C=O, stretch), 1242 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 7.07 (1H, s, ArH-7), 6.87 (1H, t, *J* 8.5, ArH-6′), 6.83-6.79 (2H, m, ArH-5′ & ArH-2′), 4.51 (1H, dd, *J* 8, 2.5, CH-3), 3.91 (3H, s, C_{Ar} OCH_3), 3.90 (3H, s, C_{Ar} OCH_3), 3.85 (3H, s, C_{Ar}-4′ OCH_3), 3.43 (3H, s, C_{Ar} OCH_3), 3.16 (C*H*H-2), 2.54 (CH*H*-2); δ_C (125 MHz, $CDCl_3$) 204.9 (C-1), 155.0 (C_{Ar}), 152.3 (d, $^1J_{CF}$ 246, C_{Ar}-3′), 150.3 (C_{Ar}), 148.7 (C_{Ar}), 146.2 (d, $^2J_{CF}$ 11, C_{Ar}-4′), 143.9 (C_{Ar}), 137.4 (d, $^3J_{CF}$ 5.5, C_{Ar}-1′), 132.1 (C_{Ar}), 122.7 (d, $^3J_{CF}$ 3.5, C_{Ar}H-5′), 114.9 (d, $^2J_{CF}$ 18.5, C_{Ar}H-2′), 113.4 (d, $^4J_{CF}$ 1.5, C_{Ar}H-6′), 100.3 (C_{Ar}H-7), 60.9 (C_{Ar} O*C*H_3), 60.1 (C_{Ar} O*C*H_3), 56.3 (C_{Ar} O*C*H_3), 56.2 (C_{Ar} O*C*H_3), 47.0 (CH_2-2), 40.7 (CH-3); δ_F (282 MHz, $CDCl_3$) -134.8 (dd, *J* 12, 8, C_{Ar}F-3′) m/z (MNa^+ $C_{19}H_{19}FO_5Na^+$ requires 369.1109) found 369.1112.

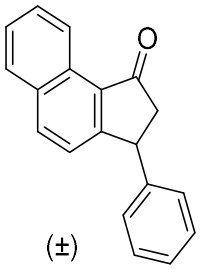
3-(3′-Nitro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one



67

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4″-Methoxy-3″-nitrophenyl)-1-(3′,4′,5′-trimethoxyphenyl)prop-2-en-1-one, **58** (12.00 g, 32.1 mmol), trifluoroacetic acid (64 mL, ~2 mL/mmol) and phosphorus pentoxide (13.69 g, 48.2 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a white solid (10.20 g, 85 %); m.p. 140-141 °C; ν_{max}/cm^{-1} 2988 (w, C_{Ar}-H, stretch), 1697 (s, C=O, stretch), 1128 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 2, ArH-2′), 7.24 (1H, dd, *J* 8.5, 2, ArH-6′), 7.04 (1H, s, ArH-7), 7.00 (1H, d, *J* 8.5, ArH-5′), 4.56 (1H, dd, *J* 8, 2.5, CH-3), 3.90 (3H, s, C_{Ar}-4′ OCH_3), 3.89 (3H, s, C_{Ar}-7 OCH_3), 3.87 (3H, s, C_{Ar}-6 OCH_3), 3.48 (3H, s, C_{Ar}-7 OCH_3), 3.17 (1H, dd, *J* 19, 8, C*H*H-2), 2.51 (1H, dd, *J* 19, 2.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 204.1 (C-1), 155.3 (C_{Ar}), 155.3 (C_{Ar}), 151.6 (C_{Ar}), 150.1 (C_{Ar}), 148.6 (C_{Ar}), 142.9 (C_{Ar}), 139.4 (C_{Ar}), 136.7 (C_{Ar}), 132.7 (C_{Ar}H-2′), 124.3 (C_{Ar}H-6′), 113.8 (C_{Ar}H-5′), 100.4 (C_{Ar}H-7), 60.9 (C_{Ar}-6 O*C*H_3), 60.2 (C_{Ar}-5 O*C*H_3), 56.6 (C_{Ar}-7 O*C*H_3), 56.2 (C_{Ar}-4′ O*C*H_3), 46.6 (CH_2-2), 40.3 (CH-3); m/z (MNa^+ $C_{19}H_{19}NO_7Na^+$ requires 396.1054) found 396.1055.

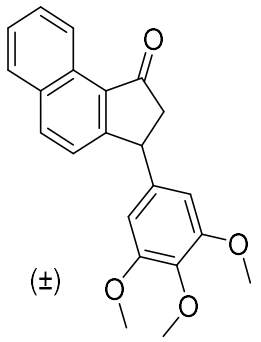
3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



68

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(naphthalen-1′-yl)-3-phenylprop-2-en-1-one, **44**, (7.00 g, 27.1 mmol), trifluoroacetic acid (55 mL, ~2mL/mmol) and phosphorus pentoxide (11.54 g, 40.7 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 9), yielding a white solid (4.34 g, 62 %); m.p. 119-120 °C, (lit.[216] 115 °C); ν_{max}/cm^{-1} 3022 (m, C_{Ar}-H, stretch), 1695 (s, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 9.24 (1H, d, *J* 8.5, ArH-9), 8.00 (1H, d, *J* 8.5, ArH-5), 7.89 (1H, d, *J* 8, ArH-6), 7.72 (1H, t, *J* 7.5, ArH-8), 7.59 (1H, t, *J* 7.6, ArH-7), 7.31 (4H, m, ArH-4′, ArH-4 & 2 x ArH-3′), 7.15 (2H, d, *J* 7, 2 x ArH-2′), 4.63 (1H, dd, *J* 8, 3, CH-3), 3.35 (1H, dd, *J* 19, 8, C*H*H-2), 2.81 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.5 (C-1), 160.7 (C_{Ar}), 143.3 (C_{Ar}-1′), 136.1 (C_{Ar}H-5), 132.7 (C_{Ar}), 130.6 (C_{Ar}), 129.1 (C_{Ar}H), 128.9 (C_{Ar}H), 128.0 (C_{Ar}H), 127.7 (C_{Ar}H), 127.0 (C_{Ar}H), 126.9 (C_{Ar}H-6′), 124.2 (C_{Ar}H-9), 123.8 (C_{Ar}H), 47.4 (C-2), 44.4 (C-3), Missing one C_{Ar}; m/z (MH^+ $C_{19}H_{14}OH^+$ requires 259.1117) found 259.1117.

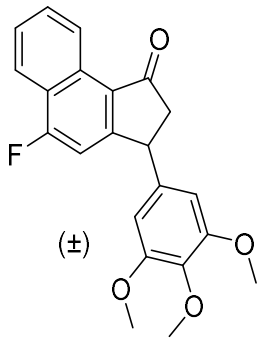
3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



69

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(naphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one, **45**, (9.50 g, 27.3 mmol), trifluoroacetic acid (55 mL, ~2mL/mmol) and phosphorus pentoxide (11.61 g, 40.9 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 9), yielding a yellow solid (4.18 g, 44 %); m.p. 148-149 °C; ν_{max}/cm^{-1} 2939 (w, C_{Ar}-H, stretch), 1690 (s, C=O, stretch), 1240 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 9.23 (1H, d, *J* 8.5, ArH-9), 8.03 (1H, d, *J* 8.5, ArH-5), 7.91 (1H, d, *J* 8, ArH-6), 7.72 (1H, ddd, *J* 8.5, 7, 1, ArH-8), 7.60 (1H, ddd, *J* 8, 7, 1, ArH-7), 7.35 (1H, d, *J* 8.5, ArH-4), 6.35 (2H, s, 2 x ArH-2′), 4.57 (1H, dd, *J* 8, 3.5, CH-3), 3.84 (3H, s, C_{Ar}-4′ OCH_3), 3.77 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.33 (1H, dd, *J* 19, 8, C*H*H-2), 2.81 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.3 (C-1), 160.4 (C_{Ar}), 153.6 (2 x C_{Ar}-3′), 139.0 (C_{Ar}-1′), 137.0 (C_{Ar}-4′), 136.2 (C_{Ar}H-5), 132.8 (C_{Ar}), 130.7 (C_{Ar}), 129.1 (C_{Ar}H-8), 129.0 (C_{Ar}), 128.1 (C_{Ar}H-6), 127.0 (C_{Ar}H-6), 124.2 (C_{Ar}H-9), 123.8 (C_{Ar}H-4), 104.7 (2 x C_{Ar}H-2′), 60.8 (C_{Ar}-4′ O*C*H_3), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 47.4 (CH-2), 44.8 (CH-3); m/z (MH^+ $C_{22}H_{20}O_4H^+$ requires 349.1434) found 349.1426.

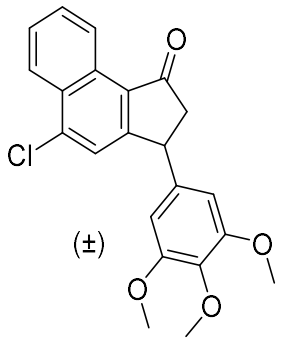
5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



70

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-fluoronaphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one, **46**, (12.00 g, 32.8 mmol), trifluoroacetic acid (70 mL, ~2 mL/mmol) and phosphorus pentoxide (13.95 g, 49.1 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 4), yielding a yellow solid (3.72 g, 31 %); m.p. 190-191 °C; ν_{max}/cm^{-1} 2959 (w, C_{Ar}-H, stretch), 1687 (s, C=O, stretch), 1244 (s, C-O, stretch), 1116 (s, C-F, stretch); δ_H (400 MHz, $CDCl_3$) 9.22 (1H, d, *J* 8.5, ArH-9), 8.13 (1H, d, *J* 8.5, ArH-6), 7.70 (1H, t, *J* 7.5, ArH-8), 7.65 (1H, t, *J* 7.5, ArH-7), 6.98 (1H, d, *J* 10, ArH-4), 6.34 (2H, s, 2 x ArH-2′), 4.53 (1H, dd, *J* 7.5, 3, CH-3), 3.84 (3H, s, C_{Ar}-4′ OCH_3), 3.78 (6H, s, C_{Ar}-3′ OCH_3), 3.32 (1H, dd, *J* 19, 7.5, C*H*H-2), 2.81 (1H, dd, *J* 19, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 204.8 (C-1), 163.6 (d, $^2J_{CF}$ 264.5, C_{Ar}-5), 161.9 (d, $^3J_{CF}$ 10.5, C_{Ar}-3a), 153.6 (2 x C_{Ar}-3′), 138.3 (C_{Ar}-1′), 137.1 (C_{Ar}-4′), 130.4 (d, $^3J_{CF}$ 7, C_{Ar}-9a), 130.2 (C_{Ar}H-8), 127.3 (d, $^5J_{CF}$ 1, C_{Ar}H-7), 127.2 (d, $^4J_{CF}$ 3, C_{Ar}-9b), 124.3 (d, $^4J_{CF}$ 2.5, C_{Ar}H-9), 123.3 (d, $^2J_{CF}$ 17, C_{Ar}-5a), 121.2 (d, $^3J_{CF}$ 6, C_{Ar}H-6), 107.5 (d, $^2J_{CF}$ 21, C_{Ar}H-4), 104.6 (2 x C_{Ar}H-2′), 60.8 (C_{Ar}-4′ O*C*H_3), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 47.2 (CH-2), 45.0 (CH-3); δ_F (282 MHz, $CDCl_3$) -109.1 (d, *J* 10, C_{Ar}F-5); m/z (MNa^+ $C_{22}H_{19}FO_4Na^+$ requires 389.1160) found 389.1161.

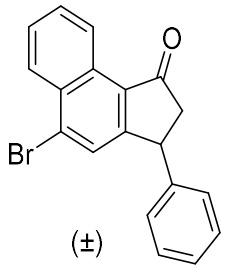
5-Chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



71

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-chloronaphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one, **47**, (13.00 g, 34.0 mmol), trifluoroacetic acid (70 mL, ~2 mL/mmol) and phosphorus pentoxide (14.46 g, 50.9 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 4), yielding a yellow solid (4.29 g, 33 %); m.p. 185-186 °C; ν_{max}/cm^{-1} 2937 (w, C_{Ar}-H, stretch), 1690 (s, C=O, stretch), 1229 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.27 (1H, d, *J* 8, ArH-9), 8.34 (1H, d, *J* 8.5, ArH6), 7.78 (1H, ddd, *J* 8.5, 7, 1, ArH-7), 7.71 (1H, ddd, *J* 8.5, 7, 1, ArH-8), 7.45 (1H, s, ArH-4), 6.34 (2H, s, 2 x ArH-2′), 4.53 (1H, dd, 7.5, 3.5, CH-3), 3.85 (3H, s, C_{Ar}-4′ OCH_3), 3.79 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.33 (1H, dd, 19, 7.5, C*H*H-2), 2.82 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.4 (C-1), 160.0 (C_{Ar}), 153.7 (2 x C_{Ar}-3′), 140.5 (C_{Ar}), 138.2 (C_{Ar}-4′), 130.2 (C_{Ar}), 130.0 (C_{Ar}H-7), 129.8 (C_{Ar}), 129.5 (C_{Ar}), 127.9 (C_{Ar}H-8), 124.9 (C_{Ar}H), 124.6 (C_{Ar}H), 124.2 (C_{Ar}H-4), 104.7 (2 x C_{Ar}H-2″), 60.8 (C_{Ar}-4′ O*C*H_3), 56.2 (2 x C_{Ar}-3′ O*C*H_3), 47.3 (CH_2-2), 44.7 (CH-3); m/z (MNa^+ $C_{22}H_{19}{}^{35}ClO_4Na^+$ requires 405.0864) found 405.0869.

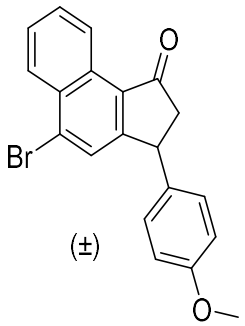
5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



72

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-bromonaphthalen-1′-yl)-3-phenylprop-2-en-1-one, **48**, (11.00 g, 32.6 mmol), trifluoroacetic acid (65 mL, ~2 mL/mmol) and phosphorus pentoxide (13.89 g, 48.9 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 4), yielding a yellow solid (7.71 g, 70 %); m.p. 140-145 °C; ν_{max}/cm^{-1} 3022 (w, C_{Ar}-H, stretch), 1694 (s, C=O, stretch), 1181 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.26 (1H, d, *J* 8.5, ArH-9), 8.31 (1H, d, *J* 8.5, ArH-6), 7.76 (1H, ddd, *J* 8.5, 7, 1, ArH-8), 7.69 (1H, ddd, *J* 8.5, 7,1, ArH-7), 7.63 (1H, s, ArH-4), 7.34 (2H, t, *J* 7.5, 2 x ArH-3′), 7.30-7.27 (1H, m, ArH-4′), 7.15 (2H, d, *J* 7, 2 x ArH-2′), 4.61 (1H, dd, *J* 7.5, 3.5, CH-3), 3.33 (1H, dd, *J* 19, 8, C*H*H-2), 2.81 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.6 (C-1), 160.3 (C_{Ar}), 142.6 (C_{Ar}), 132.1 (C_{Ar}), 131.2 (C_{Ar}), 130.2 (C_{Ar}), 129.9 (C_{Ar}H-8), 129.7 (C_{Ar}), 129.1 (C_{Ar}H), 128.2 (C_{Ar}H), 128.1 (C_{Ar}H), 127.7 (C_{Ar}H), 127.5 (C_{Ar}H), 127.3 (C_{Ar}H), 124.6 (C_{Ar}H-9), 47.4 (CH_2-2), 44.2 (CH-3); m/z (MNa^+ $C_{19}H_{13}{}^{79}BrONa^+$ requires 359.0042) found 359.0044, (MNa^+ $C_{19}H_{13}{}^{81}BrONa^+$ requires 361.0023) found 361.0027.

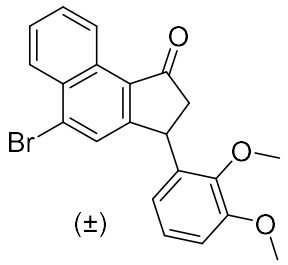
5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one



73

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-bromonaphthalen-1′-yl)-3-(4″-methoxyphenyl)prop-2-en-1-one, **49** (8.00 g, 21.8 mmol), trifluoroacetic acid (45 mL, ~2 mL/mmol) and phosphorus pentoxide (9.28 g, 32.6 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 3), yielding a yellow solid (2.36 g, 30 %); m.p. 143-144 °C; ν_{max}/cm^{-1} 2934 (w, C_{Ar}-H, stretch), 1687 (s, C=O, stretch), 1277 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.25 (1H, d, *J* 8, ArH-9), 8.29 (1H, d, *J* 8.5, ArH-6), 7.75 (1H, ddd, *J* 8.5, 7, 1, ArH-8), 7.67 (1H, ddd, *J* 8.5, 7, 1, ArH-7), 7.62 (1H, s, ArH-4), 7.06 (2H, d, *J* 8.5, 2 x ArH-2′), 6.87 (2H, d, *J* 8.5, 2 x ArH-3′), 4.55 (1H, dd, *J* 7.5, 3.4, CH-3), 3.80 (3H, s, C_{Ar}-4′ OCH_3), 3.30 (1H, dd, *J* 19, 8, C*H*H-2), 2.76 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.8 (C-1), 160.6 (C_{Ar}-4′), 158.8 (C_{Ar}), 134.6 (C_{Ar}), 132.0 (C_{Ar}), 131.2 (C_{Ar}), 130.1 (C_{Ar}), 129.9 ($C_{Ar}H$), 129.7 (C_{Ar}), 128.8 (2 x $C_{Ar}H$-2′), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 124.6 ($C_{Ar}H$), 114.5 (2 x $C_{Ar}H$-3′), 55.3 (C_{Ar}-4′ O*C*H_3), 47.6 (CH_2-2), 43.5 (CH-3); m/z (MH^+ $C_{20}H_{15}{}^{79}BrO_2H^+$ requires 367.0328) found 367.0332, (MH^+ $C_{20}H_{15}{}^{81}BrO_2H^+$ requires 369.0310) found 369.0313.

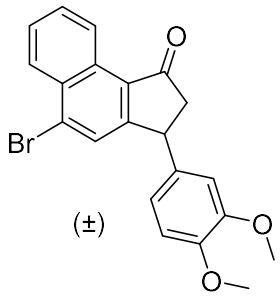
5-Bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



74

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(2″,3″-dimethoxyphenyl)prop-2-en-1-one, **50** (16.00 g, 40.3 mmol), trifluoroacetic acid (81 mL, ~2 mL/mmol) and phosphorus pentoxide (17.15 g, 60.4 mmol). The crude product by purified by silica column chromatography, eluting with dichloromethane : petroleum ether (2 : 1), yielding a beige solid (4.48 g, 28 %); m.p. 174-175 °C; ν_{max}/cm^{-1} 2929 (w, C_{Ar}-H, stretch), 1697 (s, C=O, stretch), 1279 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 9.28 (1H, d, *J* 8.5, ArH-9), 8.32 (1H, d, *J* 8.5, ArH-6), 7.77 (1H, t, *J* 7.5, ArH-8), 7.72-7.66 (2H, m, ArH-7 & ArH-4), 7.00 (1H, t, *J* 8, ArH-5′), 6.87 (1H, d, *J* 8, ArH-4′), 6.56 (1H, d, *J* 7.5, ArH-6′), 4.98 (1H, d, *J* 6, CH-3), 3.90 (3H, s, C_{Ar}-3′ OCH_3), 3.72 (3H, s, C_{Ar}-2′ OCH_3), 3.31 (1H, dd, *J* 19, 8, C*H*H-2), 2.84 (1H, d, *J* 19, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.0 (C-1), 160.6 (C_{Ar}), 153.0 (C_{Ar}-3′), 147.2 (C_{Ar}-2′), 136.0 (C_{Ar}), 131.8 (C_{Ar}), 131.2 (C_{Ar}), 130.3 (C_{Ar}), 129.8 (C_{Ar}), 129.8 (C_{Ar}H), 128.1 (C_{Ar}H), 128.0 (C_{Ar}H), 127.5 (C_{Ar}H), 124.5 (C_{Ar}H-9), 124.5 (C_{Ar}H-5′), 120.3 (C_{Ar}H-6′), 111.4 (C_{Ar}H-4′), 60.8 (C_{Ar}-2′ O*C*H_3), 55.8 (C_{Ar}-3′ O*C*H_3), 46.5 (CH_2-2), 38.5 (CH-3); m/z (MNa^+ $C_{21}H_{17}{}^{79}BrO_3Na^+$ requires 419.0253) found 419.0248, (MNa^+ $C_{21}H_{17}{}^{81}BrO_3Na^+$ requires 421.0235) found 421.0232.

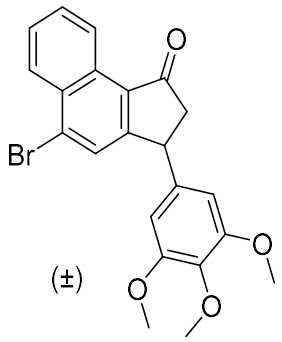
5-Bromo-3-(3′,4′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



75

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(3″,4″-dimethoxyphenyl)prop-2-en-1-one, **51** (12.70 g, 32.0 mmol), trifluoroacetic acid (64 mL, ~2 mL/mmol) and phosphorus pentoxide (13.61 g, 48 mmol). The crude product by purified by silica column chromatography, eluting with dichloromethane : petroleum ether (2 : 1), yielding a beige solid (3.56 g, 28 %); m.p. 185-186 °C; ν_{max}/cm^{-1} 2934 (w, C_{Ar}-H, stretch), 1692 (s, C=O, stretch), 1236 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.25 (1H, d, *J* 8, ArH-9), 8.31 (1H, d, *J* 8.5, ArH-6), 7.75 (1H, ddd, *J* 8, 7, 1, ArH-8), 7.68 (1H, ddd, *J* 8.5, 7, 1, ArH-7), 7.64 (1H, s, ArH-4), 6.83 (1H, d, *J* 8, ArH-4′), 6.72 (1H, dd, *J* 8, 2, ArH-6′), 6.60 (1H, d, *J* 2, ArH-2′), 4.55 (1H, dd, *J* 7.5, 3.5, CH-3), 3.87 (3H, s, C_{Ar}-4′ OCH_3), 3.80 (3H, s, C_{Ar}-3′ OCH_3), 3.32 (1H, dd, *J* 19, 8, C*H*H-2), 2.79 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.7 (C-1), 160.5 (C_{Ar}), 149.5 (C_{Ar}), 148.3 (C_{Ar}), 135.0 (C_{Ar}), 132.1 (C_{Ar}), 131.3 (C_{Ar}), 130.1 (C_{Ar}), 130.0 (C_{Ar}H), 129.7 (C_{Ar}), 128.2 (C_{Ar}H), 128.1 (C_{Ar}H), 127.6 (C_{Ar}H), 124.6 (C_{Ar}H-9), 120.0 (C_{Ar}H-6′), 111.5 (C_{Ar}H-4′), 110.6 (C_{Ar}H-2′), 56.0 (C_{Ar}-3′ O*C*H_3 & C_{Ar}-4′ O*C*H_3), 47.5 (CH_2-2), 43.9 (CH-3); m/z (MNa^+ $C_{21}H_{17}{}^{79}BrO_3Na^+$ requires 419.0253) found 419.0256, (MNa^+ $C_{21}H_{17}{}^{81}BrO_3Na^+$ requires 421.0235) found 421.0251.

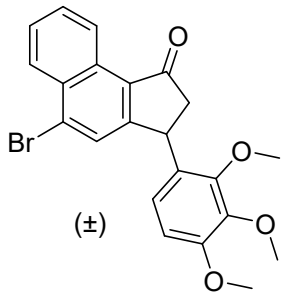
5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]napthalen-1-one



76

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-bromonaphthalen-1′-yl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-one, **53** (10.00 g, 23.4 mmol), trifluoroacetic acid (47 mL, ~2 mL/mmol) and phosphorus pentoxide (9.97 g, 35.1 mmol). The crude product by purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 4), yielding a yellow solid (3.00 g, 30 %); m.p. 207-208 °C; ν_{max}/cm^{-1} 2936 (m, C_{Ar}-H, stretch), 1686 (s, C=O, stretch), 1108 (s, C-O, stretch), 1001 (s, C_{Ar}-Br, stretch); δ_H (400 MHz, $CDCl_3$) 9.26 (1H, d, *J* 8, ArH-9), 8.32 (1H, d, *J* 8.5, ArH-6), 7.77 (1H, m, ArH-8), 7.70 (1H, m, ArH-7), 6.34 (2H, s, 2 x ArH-2″), 4.53 (1H, dd, *J* 7.5, 3.5, CH-3), 3.85 (3H, s, C_{Ar}-4′ OCH_3), 3.79 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.31 (1H, dd, *J* 19, 7.5, C*H*H), 2.81 (1H, dd, *J* 19, 3.5, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.5 (C_{Ar}-1), 160.0 (C_{Ar}), 153.7 (2 x C_{Ar}-3′), 138.2 (C_{Ar}), 138.2 (C_{Ar}), 132.1 (C_{Ar}), 131.3 (C_{Ar}), 130.2 (C_{Ar}), 129.9 (C_{Ar}H), 129.7 (C_{Ar}), 128.2 (C_{Ar}H), 128.0 (C_{Ar}H), 127.6 (C_{Ar}H-6′), 124.6 (C_{Ar}H-9), 104.7 (2 x C_{Ar}H-2′), 60.8 (C_{Ar}-4′ O*C*H_3), 56.2 (2 x C_{Ar}-3′ O*C*H_3), 47.3 (CH_2-2), 44.6 (CH-3); (MH^+ $C_{22}H_{19}{}^{79}BrO_4H^+$ requires 427.0539) found 427.0534, (MH^+ $C_{22}H_{19}{}^{81}BrO_4H^+$ requires 429.0520) found 429.0519.

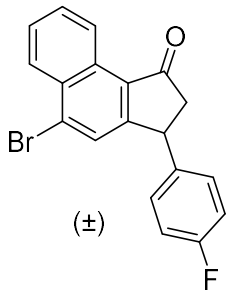
5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



77

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(2″,3″,4″-trimethoxyphenyl)prop-2-en-1-one, **54** (11.50 g, 26.9 mmol), trifluoroacetic acid (54 mL, ~2 mL/mmol) and phosphorus pentoxide (11.46, 40.4 mmol). The crude product by purified by silica column chromatography, eluting with ethyl acetate : petroleum ether (1 : 4), yielding an orange oil (2.76 g, 24 %); ν_{max}/cm^{-1} 2934 (w, C_{Ar}-H, stretch), 1696 (s, C=O, stretch), 1233 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 9.25 (1H, d, *J* 8.5, ArH-9), 8.30 (1H, d, *J* 8.5, ArH-6), 7.74 (1H, ddd, *J* 8.5, 7, 1.5, ArH-8), 7.69-7.64 (2H, m, ArH-7 & ArH-4), 6.65 (1H, d, *J* 8.5, ArH-6′), 6.59 (1H, d, *J* 8.5, ArH-5′), 4.81 (1H, dd, *J* 7.5, 3, CH-3), 3.88 (3H, s, C_{Ar}-4′ O*C*H$_3$), 3.84 (3H, s, C_{Ar}-3′ OCH$_3$), 3.68 (3H, s, C_{Ar}-2′ OCH$_3$), 3.26 (1H, dd, *J* 19, 8, C*H*H-2), 2.79 (1H, dd, *J* 19, 3, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 206.1 (C-1), 160.6 (C_{Ar}), 153.2 (C_{Ar}-3′), 152.0 (C_{Ar}-2′), 142.5 (C_{Ar}-4′), 131.7 (C_{Ar}), 131.1 (C_{Ar}), 130.3 (C_{Ar}), 129.8 (C_{Ar}), 129.8 (C_{Ar}H), 128.2 (C_{Ar}), 128.1 (C_{Ar}H), 130.0 (C_{Ar}H), 127.5 (C_{Ar}H), 124.5 (C_{Ar}H-9′), 122.9 (C_{Ar}H-6′), 107.4 (C_{Ar}H-5′), 60.9 (C_{Ar} O*C*H$_3$), 60.8 C_{Ar} O*C*H$_3$), 56.0 (C_{Ar}-3′ O*C*H$_3$), 46.7 (CH_2-2), 38.9 (CH-3); m/z (MH^+ $C_{22}H_{19}{}^{79}BrO_4H^+$ requires 427.0539) found 427.0539, (MH^+ $C_{22}H_{19}{}^{81}BrO_4H^+$ requires 429.0522) found 429.0520.

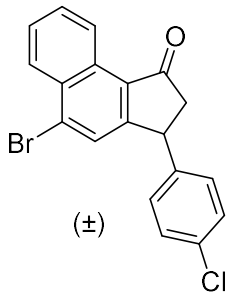
5-Bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



78

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(4″-fluorophenyl)prop-2-en-1-one, **55** (7.00 g, 19.7 mmol), trifluoroacetic acid (39 mL, ~2 mL/mmol) and phosphorus pentoxide (8.39 g, 29.6 mmol.). The crude product by purified by silica column chromatography, eluting with dichloromethane : petroleum ether (1 : 2), yielding a yellow solid (5.04 g, 72 %); m.p. 145-146 °C; ν_{max}/cm^{-1} 3059 (w, C_{Ar}-H, stretch), 1689 (s, C=O, stretch); δ_H (500 MHz, $CDCl_3$) 9.24 (1H, d, *J* 8.5, ArH-9), 8.30 (1H, d, *J* 8.5, ArH-5), 7.78-7.73 (1H, m, ArH-8), 7.71-7.67 (1H, m, ArH-7), 7.60 (1H, s, ArH-4), 7.14-7.08 (2H, m, 2 x ArH-2′), 7.02 (2H, t, *J* 8.5, 2 x ArH-3′), 4.60 (1H, dd, *J* 8, 3.5, CH-3), 3.32 (1H, dd, *J* 19, 8, C*H*H-2), 2.75 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 205.3 (C-1), 162.0 (d, $^1J_{CF}$ 246, C_{Ar}F-4′), 160.0 (C_{Ar}), 138.4 (d, $^4J_{CF}$ 3 C_{Ar}-1′), 132.2 (C_{Ar}), 131.3 (C_{Ar}), 130.2 (C_{Ar}), 130.1 (C_{Ar}H), 129.7 (C_{Ar}), 129.3 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-2′), 128.3 (C_{Ar}H), 130.0 (C_{Ar}H), 127.6 (C_{Ar}H), 124.6 (C_{Ar}H), 116.0 (d, $^2J_{CF}$ 21.5, 2 x C_{Ar}H-3′), 47.5 (CH_2-2), 43.5 (CH-3); δ_F (282 MHz, $CDCl_3$) -115.1 (m, C_{Ar}F-4′); m/z (MH^+ $C_{19}H_{12}{}^{79}BrFOH^+$ requires 355.0128) found 355.0133, (MH^+ $C_{19}H_{12}{}^{81}BrFOH^+$ requires 357.0110) found 357.0018.

5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



79

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.3**, using (*E*)-1-(4′-Bromonaphthalen-1′-yl)-3-(4″-chlorophenyl)prop-2-en-1-one, **56** (12.00 g, 32.3 mmol), trifluoroacetic acid (65 mL, ~2 mL/mmol) and phosphorus pentoxide (13.75, 48.4 mmol). The crude product by purified by silica column chromatography, eluting with dichloromethane : petroleum ether (1 : 2), yielding a yellow solid (9.12 g, 76 %); m.p. 148-149 °C; ν_{max}/cm^{-1} 3026 (w, C_{Ar}-H, stretch), 1687 (s, C=O, stretch), 1158 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 9.21 (1H, d, *J* 8, ArH-9), 8.29 (1H, d, *J* 8.5, ArH-6), 7.74 (1H, t, *J* 7.5, ArH-8), 7.67 (1H, t, *J* 7.5, ArH-7), 7.58 (1H, s, ArH-4), 7.29 (2H, d, *J* 8.5, 2 x ArH-3′), 7.06 (2H, d, *J* 8.5, 2 x ArH-2′), 4.57 (1H, dd, *J* 8, 3.5, CH-3), 3.31 (1H, dd, *J* 19, 8, C*H*H-2), 2.72 (1H, dd, *J* 19, 3.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 205.2 (C-1), 159.7 (C_{Ar}), 141.2 (C_{Ar}-1′), 133.2 (C_{Ar}), 132.4 (C_{Ar}), 131.4 (C_{Ar}), 130.2 (C_{Ar}), 130.1 (C_{Ar}H), 129.6 (C_{Ar}), 129.3 (2 x C_{Ar}H-2″), 129.1 (2 x C_{Ar}H-3″), 128.3 (C_{Ar}H), 127.9 (C_{Ar}H), 127.6 (C_{Ar}H), 124.6 (C_{Ar}H-9), 47.3 (CH_2-2), 43.6 (CH-3); m/z (MNa^+ $C_{19}H_{12}{}^{79}Br^{35}ClONa^+$ requires 392.9652) found 392.9653, (MNa^+ $C_{19}H_{12}{}^{81}Br^{35}ClONa^+$ requires 394.9631) found 394.9634.

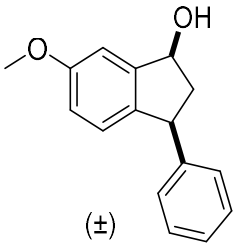
5.2.3.4 Selective *cis*-reduction using Sodium Borohydride

The following procedure was performed in accordance with previous literature.[344] To the substituted indan-1-one (8.4 mmol) in methanol : dichloromethane (1 : 1, 20 mL), was added $NaBH_4$ (8.8 mmol) portionwise at 0 °C under constant stirring. The resulting reaction mixture was stirred at room temperature for 2 hours, and the solvent was removed *in vacuo*. The reaction mixture was then dissolved in diethyl ether (50 mL) and washed with water (40 mL), brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography or as mentioned specifically.

5.2.3.5 Selective c*is*-reduction using L-Selectride

The following procedure was performed in accordance with previous literature.[364] To a solution of lithium tri-*sec*-butylborane solution (L-Selectride®) in THF (1.0 M, 15.0 mL, 15.0 mmol) at -78 °C was added 3-substituted inden-1*H*-one in THF (2.0 M, 4.00 g, 11.5 mmol) slowly and the mixture was stirred for 3 hours. The reaction mixture was then warmed up gradually to room temperature, and saturated aqueous NH_4Cl was added. After extraction with CH_2Cl_2, the combined organic layers were washed with brine (20 mL), water (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography as mentioned specifically.

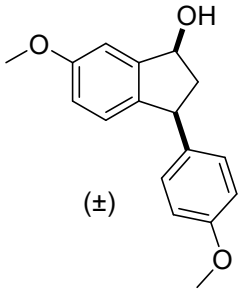
(1*RS*,3*RS*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol



80

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one, **59** (5.60 g, 23.5 mmol) and sodium borohydride (0.93 g, 24.7 mmol). The product was used without further purification, yielding an off-white solid (5.53 g, 98 %); m.p. 103-104 °C; ν_{max}/cm^{-1} 3434 (br., O-H, stretch), 3025 (m, C_{Ar}-H, stretch), 1278 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.36-7.33 (2H, m, 2 x ArH-3′), 7.28-7.24 (3H, m, ArH-4′ & 2 x ArH-2′), 7.04 (1H, d, *J* 2.5, ArH-7), 6.87 (1H, d, *J* 8.5, ArH-4), 6.82 (1H, dd, *J* 2.5, 8.5, ArH-5), 5.27 (1H, t, *J* 7.5, CH-1), 4.14 (1H, t, *J* 8.5, CH-3), 3.85 (3H, s, C_{Ar}-6 OCH_3), 3.04 (1H, dt, *J* 13, 7, CH*H*-2), 2.01 (1H, br. s, C-1 OH), 1.93 (1H, ddd, *J* 13, 9, 7.5, C*H*H-2); δ_C (100 MHz, $CDCl_3$) 159.4 (C_{Ar}-6), 146.6 (C_{Ar}), 144.5 (C_{Ar}-1′), 137.6 (C_{Ar}), 128.5, 128.1, 126.5 (C_{Ar}H-4′, 2 x C_{Ar}H-2′ & 2 x C_{Ar}H-3′), 125.8 (C_{Ar}H-4), 115.2 (C_{Ar}H-5), 108.0 (C_{Ar}H-7), 75.1 (CH-1), 55.5 (C_{Ar}-6 O*C*H_3), 47.7 (CH_2-2), 47.5 (CH-3); m/z (MNa^+ $C_{16}H_{16}O_2Na^+$ requires 263.1043) found 263.1038.

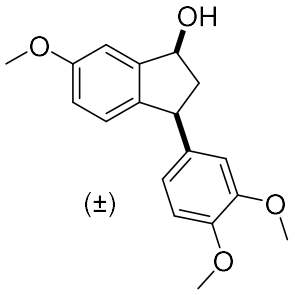
(1*RS*,3*RS*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



81

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 6-methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one, **60** (3.00 g, 11.2 mmol), and sodium borohydide (0.44 g, 11.7 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a off-white solid (2.33 g, 77 %); m.p. 119-120 °C; ν_{max}/cm^{-1} 3428 (br., O-H, stretch), 2951 (w, C_{Ar}-H, stretch), 1239 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.14 (2H, d, *J* 8.5, 2 x ArH-2′), 7.01 (1H, m, ArH-7), 6.86 (2H, d, *J* 8, 2 x ArH-3′), 6.84-6.77 (2H, m, ArH-4 & ArH-5), 5.23 (1H, t, *J* 7.5, CH-1), 4.09 (1H, t, *J* 8.5, CH-3), 3.83 (3H, s, C_{Ar}-6 OCH_3), 3.80 (3H, s, C_{Ar}-4′ OCH_3), 3.06-2.95 (1H, m, C*H*H-2), 1.96 (1H, br. s, C-1 OH) 1.89 (1H, dt, *J* 12.5, 8.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 159.3 (C_{Ar}-6), 158.2 (C_{Ar}-4′), 146.5 (C_{Ar}), 137.9 (C_{Ar}), 136.6 (C_{Ar}), 129.1 (2 x C_{Ar}H-2′), 125.8 (C_{Ar}H-4), 115.1 (C_{Ar}H-5), 113.9 (2 x C_{Ar}H-3′), 107.9 (C_{Ar}H-7), 75.0 (CH-1), 55.5, 55.3 (C_{Ar}-5 O*C*H$_3$ & C_{Ar}-4′ O*C*H$_3$), 47.9 (CH_2-2), 46.7 (CH-3); m/z (MNa^+ $C_{17}H_{18}O_3Na^+$ requires 293.1448) found 293.1157.

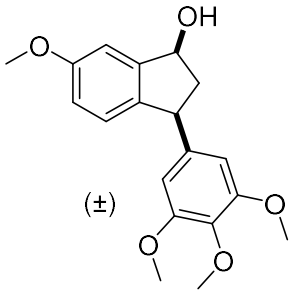
(1*RS*,3*RS*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



82

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 3-(3′,4′-dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one**, 61** (3.25 g, 10.9 mmol) and sodium borohydride (0.43 g, 11.4 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a off-white solid (2.32 g, 71 %); m.p. 95-96 °C; ν_{max}/cm^{-1} 3250 (br., O-H, stretch), 2998 (C_{Ar}-H, stretch), 1233 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.02-6.98 (1H, m, ArH-7), 6.88-6.81 (1H, m, ArH), 6.81-6.72 (3H, m, ArH), 5.22 (1H, t, *J* 7.5, CH-1), 4.07 (1H, t, *J* 8, CH-3), 3.86 (3H, s, C_{Ar} OCH_3), 3.80 (3H, s, C_{Ar}-6 OCH_3), 3.80 (3H, s, C_{Ar} OCH_3), 2.98 (1H, dt, *J* 13, 7, C*H*H-2), 2.25 (1H, br. s, C-1 OH) 1.91 (1H, dd, *J* 12.5, 8.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 159.2 (C_{Ar}-6), 148.9 (C_{Ar}), 147.5 (C_{Ar}), 146.5 (C_{Ar}), 137.6 (C_{Ar}), 137.0 (C_{Ar}), 125.9 ($C_{Ar}H$), 120.1 ($C_{Ar}H$), 115.0 ($C_{Ar}H$), 111.0 ($C_{Ar}H$), 107.9 ($C_{Ar}H$-7), 74.7 (CH-1), 55.8 (C_{Ar} O*C*H_3), 55.7 (C_{Ar} O*C*H_3), 55.4 (C_{Ar} O*C*H_3), 47.6 (CH_2-2), 47.1 (CH-3), (missing 1 x C_{Ar}); m/z MNa^+ $C_{18}H_{20}O_4Na^+$ requires 323.1254) found 323.1253.

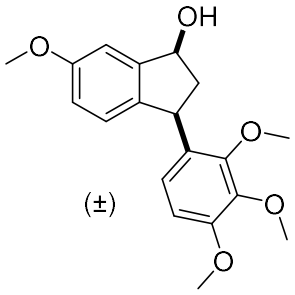
(1*RS*,3*RS*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



83

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 6-methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one, **62** (4.00 g, 12.2 mmol) and sodium borohydride (0.48 g, 12.8 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a yellow oil (2.82 g, 70 %); ν_{max}/cm^{-1} 3473 (br., O-H, stretch), 2936 (w, C_{Ar}-H, stretch), 1118 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 7.01 (1H, d, *J* 2, ArH-7), 6.91 (1H, d, *J* 8.5, ArH-4), 6.81 (1H, dd, *J* 8.5, 2.5, ArH-5), 6.44 (2H, s, ArH-2′), 5.23 (1H, t, *J* 7.5, CH-1), 4.09-4.03 (1H, m, CH-3), 3.84 (3H, s, C_{Ar}-4′ OCH_3), 3.83 (3H, s, C_{Ar}-6 OCH_3), 3.81 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.01 (1H, dt, *J* 13, 7, C*H*H-2), 1.93 (1H, ddd, *J* 13, 9, 8, CH*H*-2), missing C_{Ar}-1 O*H*); δ_C (125 MHz, $CDCl_3$) 159.5 (C_{Ar}-6), 153.3 (2 x C_{Ar}-3′), 146.5 (C_{Ar}), 140.2 (C_{Ar}), 137.3 (C_{Ar}-4′), 125.8 (C_{Ar}H-4), 122.6 (C_{Ar}), 115.2 (C_{Ar}H-5), 108.0 (C_{Ar}H-7), 105.0 (2 x C_{Ar}H-2′), 74.8 (CH-1), 60.8 (C_{Ar} O*C*H_3), 56.1 (C_{Ar} O*C*H_3), 55.5 (C_{Ar} O*C*H_3), 47.9 (CH-3), 47.6 (CH_2-2); m/z (MNa^+ $C_{19}H_{22}O_5Na^+$ requires 353.1359) found 353.1369.

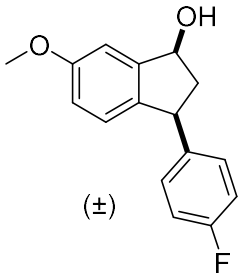
(1*RS*,3*RS*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



84

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 6-methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one**, 63** (2.37 g, 7.2 mmol) and sodium borohydride (0.29 g, 7.6 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a yellow oil (1.57 g, 66 %); ν_{max}/cm^{-1} 3399 (br., O-H, stretch), 2935 (w, C_{Ar}-H, stretch), 1191 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.06-7.02 (1H, m, ArH-7), 6.94-6.87 (1H, m, ArH-4), 6.83-6.77 (2H, m, ArH-5 and ArH-6′), 6.62 (1H, d, *J* 8.5, ArH-5′), 5.21 (1H, t, *J* 6, CH-1), 4.37 (1H, t, *J* 7.5, CH-3), 3.87 (3H, s, C_{Ar} OCH_3), 3.84 (3H, s, C_{Ar} OCH_3), 3.83 (3H, C_{Ar} OCH_3), 3.58 (3H, s, C_{Ar} OCH_3), 3.10-3.00 (1H, m, C*H*H-2), 2.62 (1H, br. s, C-1 OH), 1.97-1.85 (1H, m, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 159.3 (C_{Ar}), 152.4 (C_{Ar}), 146.6 (C_{Ar}), 138.0 (C_{Ar}), 131.2 (C_{Ar}), 125.5 (C_{Ar}H-4), 125.5 (C_{Ar}), 123.3 (C_{Ar}H), 115.4 (C_{Ar}H), 108.4 (C_{Ar}H-7), 107.4 (C_{Ar}H-5′), 75.4 (CH-1), 60.8 (C_{Ar} O*C*H_3), 60.7 (C_{Ar} O*C*H_3), 55.9 (C_{Ar} O*C*H_3), 55.4 (C_{Ar} O*C*H_3), 46.0 (CH_2-2), 42.3 (CH-3), (missing 1 x C_{Ar}); m/z (MNa^+ $C_{19}H_{22}O_5Na^+$ requires 353.1359) found 353.1356.

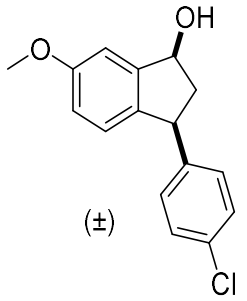
(1*RS*,3*RS*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



85

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 3-(4′-fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one, **64** (8.67 g, 33.8 mmol) and sodium borohydride (1.34 g, 35.5 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a white solid (6.99 g, 80 %); m.p. 89-90 °C; ν_{max}/cm^{-1} 3232 (br., O-H, stretch), 3038 (w, C_{Ar}-H, stretch), 1220 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.21-7.15 (2H, m, 2 x ArH-2′), 7.03-6.96 (3H, m, 2 x ArH-3′ & ArH-7), 6.84-6.78 (2H, m, ArH-4 & ArH-5), 5.28-5.17 (1H, m, CH-1), 4.18-4.06 (1H, m, CH-3), 3.83 (3H, s, C_{Ar}-6 OCH_3), 3.01 (1H, dt, *J* 13, 7, C*H*H-2), 1.99 (1H, br. s, C-1 OH) 1.88 (1H, ddd, *J* 13, 9, 7.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 161.6 (d, $^1J_{CF}$ 245, C_{Ar}-4′), 159.5 (C_{Ar}-6), 146.6 (C_{Ar}), 140 (d, $^4J_{CF}$ 3, C_{Ar}-1′), 137.4 (C_{Ar}), 129.5 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-2′), 125.7 (C_{Ar}H-4), 115.3 (d, $^2J_{CF}$ 21, 2 x C_{Ar}H-3′), 115.2 (C_{Ar}H-5), 108.1 (C_{Ar}H-7), 75.0 (CH-1), 55.5 (C_{Ar}-6 O*C*H_3), 47.7 (CH_2-2), 46.8 (CH-3); δ_F (376 MHz, $CDCl_3$) -116.7 (m, C_{Ar}F-4′); m/z (MNa^+ $C_{16}H_{15}FO_2Na^+$ requires 281.0948) found 281.0946.

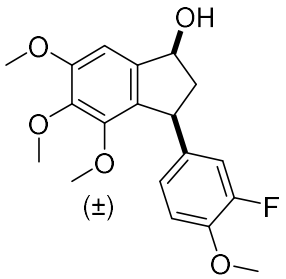
(1*RS*,3*RS*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



86

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 3-(4′-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (3.69, 13.5 mmol), **65** and sodium borohydride (0.54 g, 14.2 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a off white-solid (3.38 g, 91 %); m.p. 101-102 °C; ν_{max}/cm^{-1} 3248 (br., O-H, stretch), 2934 (w, C_{Ar}-H, stretch), 1201 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.29-7.22 (2H, m, 2 x ArH-3′), 7.17-7.11 (2H, m, 2 x ArH-2′), 7.01-6.98 (1H, m, ArH-7), 6.81-6.77 (2H, m, ArH-4, ArH-5), 5.22 (CH-1), 4.14-4.06 (1H, m, CH-3), 3.81 (3H, s, C_{Ar}-6 OCH_3), 2.99 (1H, dt, *J* 13, 7, C*H*H-2), 2.14 (1H, br. s, C-1 OH), 1.87 (1H, ddd, *J* 13, 9, 7.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 159.5 (C_{Ar}-6), 146.6 (C_{Ar}), 143.1 (C_{Ar}), 137.1 (C_{Ar}), 132.2 (C_{Ar}), 129.5 (2 x C_{Ar}H-2′), 128.6 (2 x C_{Ar}H-3′), 125.7 (C_{Ar}H-4), 115.2 (C_{Ar}H-5), 108.2 (C_{Ar}H-7), 74.9 (CH-1), 55.5 (C_{Ar}-6 O*C*H_3), 47.5 (CH_2-2), 46.9 (CH-3); m/z (MNa^+ $C_{16}H_{15}ClO_2Na^+$ requires 297.0653) found 297.0651.

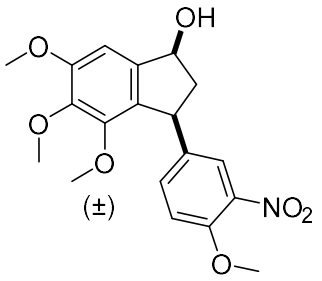
(1*RS*,3*RS*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol



87

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.5**, using 3-(3′-fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one, **66** (4.00 g, 11.5 mmol) and L-Selectride (1.0 M, 15 mL, 15.0 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (1 : 9), yielding a viscous yellow oil (2.21 g, 55 %); ν_{max}/cm^{-1} 3419 (br., O-H, stretch), 2936 (w, C_{Ar}-H, stretch), 1112 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 6.99 (1H, dd, *J* 12.5, 2, ArH-2′), 6.94 (1H, dd, *J* 8.5, 1.5, ArH-6′), 6.89 (1H, t, *J* 8.5, ArH-5′), 6.80 (1H, s, ArH-7), 5.17 (1H, dd, *J* 11, 6, CH-1), 4.25 (1H, dd, *J* 8.5, 5.5, CH-3), 3.90 (3H, s, C_{Ar}-6 OCH_3), 3.86 (3H, C_{Ar}-4′ OCH_3), 3.81 (3H, s, C_{Ar}-5 OCH_3), 3.44 (3H, s, C_{Ar}-4 OCH_3), 3.00-2.92 (1H, m, C*H*H-2), 1.84 (1H, ddd, *J* 14, 5.5, 4.5, CH*H*-2), 1.84 (1H, d, *J* 4.5, C-1 OH); δ_C (100 MHz, $CDCl_3$) 154.4 (C_{Ar}-6), 152.3 (d, $^1J_{CF}$ 245 C_{Ar}-3′), 150.1 (C_{Ar}-4), 145.8 (d, $^2J_{CF}$ 11, C_{Ar}-4′), 142.7 (C_{Ar}-5), 140.4 (C_{Ar}), 139.3 (d, $^2J_{CF}$ 6, C_{Ar}-1′), 130.1 (C_{Ar}), 123.0 (d, $^3J_{CF}$ 3, C_{Ar}H-5′), 115.4 (d, $^2J_{CF}$ 18, C_{Ar}H-2′), 113.2 (d, $^4J_{CF}$ 2, C_{Ar}H-6′), 102.6 (C_{Ar}H-7), 75.8 (CH-1), 60.8 (C_{Ar}-5′ O*C*H_3), 60.0 (C_{Ar}-4 O*C*H_3), 56.3, 56.1 (C_{Ar}-4′ O*C*H_3 & C_{Ar}-6 O*C*H_3), 46.1 (CH-3), 46.0 (CH_2-2); δ_F (376 MHz, $CDCl_3$) -135.4 (m, C_{Ar}F-3′); m/z (MNa^+ $C_{19}H_{21}FO_5Na^+$ requires 371.1265) found 371.1266.

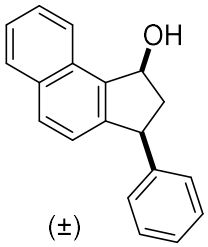
(1*RS*,3*RS*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol



88

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 3-(3′-nitro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one, **67** (3.12 g, 8.4 mmol) and sodium borohydride (0.33 g, 8.8 mmol). The crude product was purified by silica column chromatography, eluting with ethyl acetate : dichloromethane (5 : 95), yielding a yellow oil (1.60 g, 51 %); ν_{max}/cm^{-1} 3420 (br., O-H, stretch), 2970 (w, C_{Ar}-H, stretch), 1112 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 2.5, ArH-2′), (1H, dd, *J* 8.5, 2.5, ArH-6′), 7.00 (1H, d, *J* 8.5, ArH-5′), 6.79 (1H, s, ArH-7), 5.23-5.13 (1H, m, CH-1), 4.29 (1H, dd, *J* 8.5, 5.5, CH-3), 3.92 (3H, s, C_{Ar}-4′ OCH_3), 3.88 (3H, s, C_{Ar}-6 OCH_3), 3.80 (3H, s, C_{Ar}-5 OCH_3), 3.46 (3H, s, C_{Ar}-4 OCH_3), 2.95 (1H, ddd, *J* 14, 8.5, 7, C*H*H-2), 2.20 (1H, br. s, C-1 OH), 1.93-1.85 (1H, m, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 154.6 (C_{Ar}-6), 151.2 (C_{Ar}-4′), 149.8 (C_{Ar}-4), 142.5 (C_{Ar}-5), 140.4 (C_{Ar}), 139.2 (C_{Ar}), 138.4 (C_{Ar}), 133.4 (C_{Ar}H-6′), 129.3 (C_{Ar}), 124.8 (C_{Ar}H-2′), 113.3 (C_{Ar}H-5′), 102.7 (C_{Ar}H-7), 75.4 (CH-1), 60.7 (C_{Ar}-5 O*C*H_3), 60.0 (C_{Ar}-4 O*C*H_3), 56.5 (C_{Ar}-4′ O*C*H_3), 56.1 (C_{Ar}-6 O*C*H_3), 45.7 (CH_2-2), 45.7 (CH-3); m/z (MNa^+ $C_{19}H_{21}NO_7Na^+$ requires 398.1210) found 398.1210.

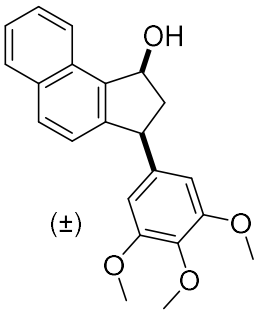
(1*RS*,3*RS*)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



89

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **68** (3.50 g, 13.5 mmol) and sodium borohydride (0.54 g, 14.2 mmol). The crude product was purified by recrystallisation in methanol, yielding a white solid (3.07 g, 87 %); m.p. 137 °C, (lit. 138 °C); ν_{max}/cm^{-1} 3274 (br., O-H, stretch), 3054 (m, C_{Ar}-H, stretch); δ_H (400 MHz, $CDCl_3$) 8.38 (1H, d, *J* 8, ArH-9), 7.91 (1H, d, *J* 8, ArH-6), 7.80 (1H, d, *J* 8.5, ArH-5), 7.64-7.57 (1H, m, ArH-8), 7.52 (1H, dd, *J* 13.5, 6.5, ArH-7), 7.38-7.32 (3H, m, ArH-4′ & 2 x ArH-3′), 7.29 (2H, d, *J* 7.5, 2 x ArH-2′), 7.17 (1H, d, *J* 8.5, ArH-4), 5.88-5.79 (1H, d, *J* 5, CH-1), 4.42 (1H, dd, *J* 8.5, 6, CH-3), 3.24 (1H, ddd, *J* 16, 8.5, 7.5, C*H*H-2), 2.19-2.08 (2H, m, CH*H*-2 & C-1 OH); δ_C (100 MHz, $CDCl_3$) 145.3 (C_{Ar}-1′), 143.4 (C_{Ar}), 139.2 (C_{Ar}), 133.3 (C_{Ar}), 130.1 (C_{Ar}), 129.7 (C_{Ar}H-5), 128.5 (C_{Ar}H), 128.1 (C_{Ar}H), 126.6 (C_{Ar}H), 126.5 (C_{Ar}H), 125.5 (C_{Ar}H-7), 124.2 (C_{Ar}H-9), 123.4 (C_{Ar}H-4), 75.4 (CH-1), 49.4 (CH-3), 45.9 (CH_2-2); m/z (MNa^+ $C_{19}H_{16}ONa^+$ requires 283.1093) found 283.1093.

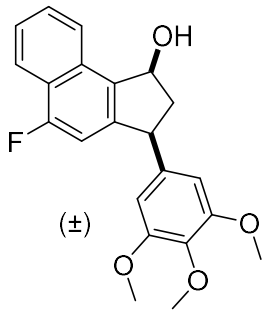
(1*RS*,3*RS*)-3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



90

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **69** (2.00 g, 5.7 mmol) and sodium borohydride (0.22 g, 6.0 mmol). The crude product was purified by silica column chromatography, eluting with diethyl ether : petroleum ether (1 : 4), yielding a orange solid (1.23 g, 61 %); m.p. 125-126 °C; ν_{max}/cm^{-1} 3513 (br. s, OH, stretch), 2923 (w, C_{Ar}-H, stretch), 1294 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, d, *J* 8, ArH-9), 7.87 (1H, d, *J* 8, ArH-6), 7.76 (1H, d, *J* 8.5, ArH-5), 7.56-7.44 (2H, m, ArH-8 & ArH-7), 7.17 (1H, d, *J* 8.5, ArH-4), 6.53 (2H, s, 2 x ArH-2″), 5.77 (1H, t, *J* 6, CH-1), 4.26 (1H, t, *J* 7.5, CH-3), 3.86 (3H, s, C_{Ar}-4′ OCH_3), 3.76 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.16 (1H, dt, *J* 13.5, 8, C*H*H-2), 2.77 (1H, br. s, C-1 OH), 2.13 (1H, dt, *J* 13.5, 6, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 153.1 (2 x C_{Ar}-3′), 143.1 (C_{Ar}), 140.9 (C_{Ar}), 139.0 (C_{Ar}-4′), 136.3 (C_{Ar}), 133.1 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (C_{Ar}H-5), 128.3 (C_{Ar}H-6), 126.3 (C_{Ar}H-8), 125.3 (C_{Ar}H-7), 124.0 (C_{Ar}H-9), 123.1 (C_{Ar}H-4), 105.0 (2 x C_{Ar}H-2′), 74.9 (CH-1), 60.6 (C_{Ar}-4′ O*C*H_3), 55.8 (2 x C_{Ar}-3′ O*C*H_3), 49.6 (CH-3), 45.7 (CH_2-2); m/z (MNa^+ $C_{22}H_{20}O_4Na^+$ requires 373.1410) found 373.1413.

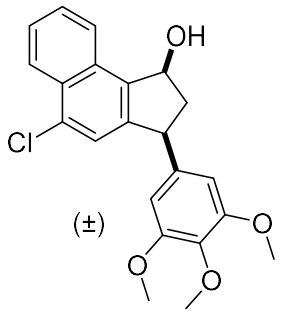
(1*RS*,3*RS*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-ol



91

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one**, 70** (1.73 g, 4.7 mmol) and sodium borohydride (0.19 g, 5.0 mmol). The crude product was purified by recrystallisation in methanol, yielding a yellow solid (1.02 g, 57 %); m.p. 170-171 °C; ν_{max}/cm^{-1} 3438 (br. s, OH, stretch), 1252 (s, C-O, stretch), 1123 (s, C-F, stretch); δ_H (500 MHz, $CDCl_3$) 8.33 (1H, d, *J* 8.5, ArH-9), 8.11 (1H, d, *J* 8.5, ArH-6), 7.62 (1H, t, *J* 7.5, ArH-8), 7.55 (1H, t, *J* 7.5, ArH-7), 6.83 (1H, d, *J* 10.5, ArH-4), 6.49 (2H, s, 2 x ArH-2′), 5.77 (1H, dd, *J* 11, 5.5, CH-1), 4.27 (1H, dd, *J* 8, 7, CH-3), 3.85 (3H, s, C_{Ar}-4′ OCH_3), 3.79 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.19 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.18 (1H, d, *J* 6.5, C-1 OH), 2.16-2.10 (1H, m, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 159.8 (d, $^1J_{CF}$ 253, C_{Ar}-5), 153.4 (2 x C_{Ar}-3′), 143.7 (d, J_{CF} 8, C_{Ar}), 140.3 (C_{Ar}), 136.6 (C_{Ar}-4′), 131.1 (d, $^3J_{CF}$ 5, C_{Ar}), 127.6 (C_{Ar}H-8), 125.8 (C_{Ar}H-7), 124.1 (d, $^4J_{CF}$ 2, C_{Ar}H-9), 123.5 (d, $^2J_{CF}$ 17, C_{Ar}-5a), 121.4 (d, $^3J_{CF}$ 6, C_{Ar}H-6), 106.7 (d, $^2J_{CF}$ 21, C_{Ar}H-4), 105.0 (2 x C_{Ar}H-2′), 74.8 (CH-1), 60.8 (C_{Ar}-4′ O*C*H_3), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 50.1 (d, $^4J_{CF}$ 1, CH-3), 46.0 (CH_2-2), (missing 1 x C_{Ar}); δ_F (376 MHz, $CDCl_3$) -117.3 (m, C_{Ar}F-5); m/z (MNa^+ $C_{22}H_{21}FO_4Na^+$ requires 391.1316) found 391.1322.

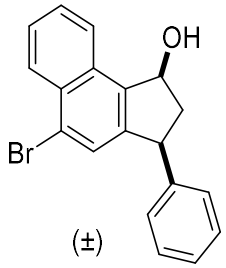
(1*RS*,3*RS*)-5-Chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



92

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **71** (1.17 g, 3.1 mmol) and sodium borohydride (0.12 g, 3.2 mmol). The crude product was purified by recrystallisation in methanol, yielding a white solid (0.71 g, 60 %); m.p. 183-184 °C; ν_{max}/cm^{-1} 3392 (br. s, OH, stretch), 1231 (s, C-O, stretch), 1123 (s, C-Cl, stretch); δ_H (500 MHz, $CDCl_3$) 8.37 (1H, dd, *J* 6.5, 2.5, ArH-9), 8.31 (1H, dd, *J* 7, 2.5, ArH-6), 7.65-7.58 (2H, m, ArH-7 & ArH-8), 7.27 (1H, s, ArH-4), 6.49 (2H, s, ArH-2′), 5.80 (1H, t, 7, CH-1), 4.27 (1H, dd, 8.5, 6.5, CH-3), 3.85 (3H, s, C_{Ar}-4′ OCH_3), 3.80 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.19 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.22-2.10 (2H, m, CH*H*-2 & C-1 OH); δ_C (125 MHz, $CDCl_3$) 153.4 (2 x C_{Ar}-3′), 143.5 (C_{Ar}), 138.3 (C_{Ar}), 136.7 (C_{Ar}-4′), 133.3 (C_{Ar}), 131.0 (C_{Ar}), 130.4 (C_{Ar}), 127.4, 126.6 (C_{Ar}H-7 & C_{Ar}H-8), 125.2 (C_{Ar}H-6), 124.6 (C_{Ar}H-9), 123.6 (C_{Ar}H-4), 105.0 (2 x C_{Ar}H-2′), 74.9 (CH-1), 60.8 (C_{Ar}-4′ O*C*H_3), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 49.8 (CH-3), 45.8 (CH_2-2), (missing 1 x C_{Ar}); m/z (MNa^+ $C_{22}H_{21}ClO_4Na^+$ requires 407.1021) found 407.1021.

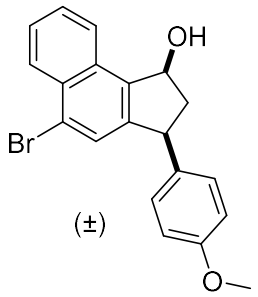
(1*RS*,3*RS*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



93

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **72** (1.20, 3.6 mmol) and sodium borohydride (0.14 g, 3.7 mmol). The crude product was purified by recrystallisation in methanol, yielding a white solid (0.96 g, 81 %); m.p. 202-203 °C; ν_{max}/cm^{-1} 3373 (br. s, OH, stretch), 1033 (s, C-Br, stretch); δ_H (500 MHz, $CDCl_3$) 8.38-8.35 (1H, m, ArH-9), 8.30-8.26 (1H, m, ArH-6), 7.65-7.57 (2H, m, ArH-7 & ArH-8), 7.45 (1H, s, ArH-4), 7.36-7.31 (2H, m, 2 x ArH-3′), 7.26 (3H, m, 2 x ArH-2′ & ArH-4′), 5.79 (1H, dd, *J* 7, 5, CH-1), 4.38 (1H, dd, *J* 8.5, 6, CH-3), 3.23 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.16-2.14 (1H, m, CH*H*-2), 1.97 (1H, br. s, C-1 OH); δ_C (125 MHz, $CDCl_3$) 144.5 (C_{Ar}), 144.0 (C_{Ar}), 139.2 (C_{Ar}), 131.6 (C_{Ar}), 131.1 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 124.7 ($C_{Ar}H$), 124.4 ($C_{Ar}H$-9), 75.2 (CH-1), 49.4 (CH-3), 45.9 (CH_2-2), (missing 1 x C_{Ar}); m/z (MNa^+ $C_{19}H_{15}{}^{79}BrONa^+$ requires 361.0198) found 361.0200, (MNa^+ $C_{19}H_{15}{}^{81}BrONa^+$ requires 363.0180) found 363.0182.

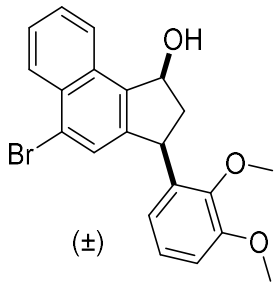
(1*RS*,3RS)-5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



94

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one, **73** (0.65 g, 1.8 mmol) and sodium borohydride (70 mg, 1.9 mmol). The crude product was purified by recrystallisation in methanol, yielding an off-white solid (0.59 g, 91 %); m.p. 169-170 °C; ν_{max}/cm^{-1} 3434 (br. s, OH, stretch), 1292 (s, C-O, stretch), 1036 (s, C-Br, stretch); δ_H (500 MHz, $CDCl_3$) 8.39-8.34 (1H, m, ArH-9), 8.30-8.26 (1H, m, ArH-6), 7.64-7.57 (2H, m, ArH-7 & ArH-8), 7.44 (1H, s, ArH-4), 7.17 (2H, d, *J* 8.5, 2 x ArH-2′), 6.87 (2H, d, *J* 8.5, 2 x ArH-3′), 5.76 (1H, dd, *J* 12, 7, CH-1), 4.33 (1H, dd, *J* 8.5, 6.5, CH-3), 3.81 (3H, s, C_{Ar}-4′ OCH_3), 3.20 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.09 (1H, ddd, *J* 14, 6, 5, CH*H*-2), 1.98 (1H, d, *J* 7, C-1 OH); δ_C (125 MHz, $CDCl_3$) 158.4 (C_{Ar}-4′), 144.4 (C_{Ar}), 139.1 (C_{Ar}), 136.6 (C_{Ar}), 131.5 (C_{Ar}), 131.2 (C_{Ar}), 129.0 (2 x C_{Ar}H-2′), 127.9 (C_{Ar}H-6), 127.5 (C_{Ar}H-4), 127.4, 126.9 (C_{Ar}H-7 & C_{Ar}H-8), 124.7 (C_{Ar}H-9), 124.3 (C_{Ar}), 114.2 (2 x C_{Ar}H-3′), 75.1 (CH-1), 55.3 (C_{Ar}-4′ O*C*H_3), 48.5 (CH-3), 46.1 (CH_2-2); m/z (MNa^+ $C_{20}H_{17}{}^{79}BrO_2Na^+$ requires 391.0304) found 391.0306, (MNa^+ $C_{20}H_{17}{}^{81}BrO_2Na^+$ requires 393.0286) found 393.0287.

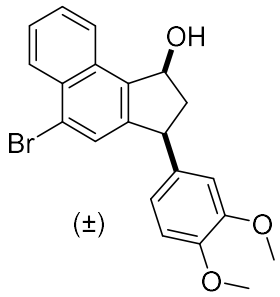
(1*RS*,*3RS*)-5-Bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



95

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **74** (1.97 g, 5.0 mmol) and sodium borohydride (0.20 g, 5.2 mmol). The crude product was purified by recrystallisation with methanol, yielding a off-white solid (1.45 g, 73 %); m.p. 145-146 °C; ν_{max}/cm^{-1} 3384 (br. s, OH, stretch), 2939 (w, C_{Ar}-H, stretch), 1017 (m, C-Br, stretch); δ_H (400 MHz, $CDCl_3$) 8.33 (1H, d, *J* 7.5, ArH-9), 8.26 (1H, d, *J* 8, ArH-6), 7.67-7.55 (2H, m, ArH-7 & ArH-8), 7.50 (1H, s, ArH-4), 7.04 (1H, t, *J* 8, ArH-5′), 6.87 (1H, d, *J* 8, ArH-6′), 6.79 (1H, d, *J* 7.5, ArH-4′), 5.78-5.67 (1H, m, CH-1), 4.58-4.53 (1H, m, CH-3), 3.86 (3H, s, C_{Ar}-2′ OCH_3), 3.31-3.28 (4H, m, C_{Ar}-3′ OCH_3 & C*H*H-2), 3.11-3.09 (1H, m, C-1 OH), 2.13 (1H, d, *J* 14.5, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 153.1 (C_{Ar}-2′), 144.0 (C_{Ar}-3′), 138.5 (C_{Ar}), 131.4 (C_{Ar}), 131.3 (C_{Ar}), 127.8 (C_{Ar}H), 127.5 (C_{Ar}H), 127.3 (C_{Ar}H), 126.8 (C_{Ar}H-9), 125.0 (C_{Ar}H-4′), 124.4 (C_{Ar}H-6′), 124.0 (C_{Ar}), 121.7 (C_{Ar}H-4′), 75.1 (CH-1), 60.3 (C_{Ar}-3′ O*C*H3), 55.7 (C_{Ar}-2′ O*C*H$_3$), 45.6 (CH-3), 44.3 (CH_2-2), (missing 2 x C_{Ar}); m/z (MNa^+ $C_{21}H_{19}{}^{79}BrO_3Na^+$ requires 421.0410) found 421.0413, (MNa^+ $C_{21}H_{19}{}^{81}BrO_3Na^+$ requires 423.0392) found 423.0395.

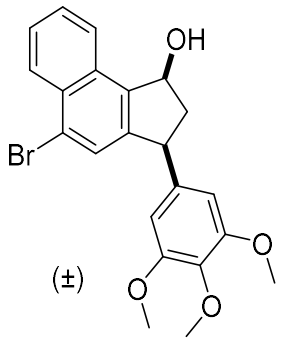
(1*RS*,3*RS*)-5-Bromo-3-(3′,4′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



96

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(3′,4′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **75** (100 mg, 0.3 mmol) and sodium borohydride (10.0 mg, 0.3 mmol). The crude product was purified by recrystallisation with methanol, yielding an off-white solid (89 mg, 89 %); m.p. 169-170 °C; ν_{max}/cm^{-1} 3421 (br. s, OH, stretch), 2955 (w, C_{Ar}-H, stretch), 1233 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.40-8.22 (2H, m, ArH-9 & ArH-6), 7.68-7.52 (2H, m, ArH-8 & ArH-7), 7.46 (1H, s, ArH-4), 6.86-6.72 (3H, m, ArH-2′, ArH-5′ & ArH-6′), 5.78 (1H, m, CH-1), 4.32 (1H, m, CH-3), 3.88 (3H, s, C_{Ar} O*C*H$_3$), 3.82 (3H, s, C_{Ar} O*C*H$_3$), 3.30 (1H, m, C*H*H-2), 2.13 (1H, m, CH*H*-2), 2.04 (1H, d, *J* 7, C-1 OH) ; δ_C (100 MHz, $CDCl_3$) 147.9 (C_{Ar}), 144.3 (C_{Ar}), 139.1 (C_{Ar}), 137.1 (C_{Ar}), 131.6 (C_{Ar}), 131.2 (C_{Ar}), 128.0 (C_{Ar}H-9), 127.5 (C_{Ar}-H), 126.9 (C_{Ar}H), 124.7 (C_{Ar}H), 120.1 (C_{Ar}H), 111.3 (C_{Ar}H), 111.2 (C_{Ar}), 75.1 (CH-1), 55.9 (C_{Ar} O*C*H$_3$), 49.1 (C_{Ar} O*C*H$_3$), 46.0 (CH_2-2), (missing 1 x C_{Ar} & 1 x CH); m/z (MNa^+ $C_{21}H_{19}{}^{79}BrO_3Na^+$ requires 421.0410) found 421.0407, (MNa^+ $C_{21}H_{19}{}^{81}BrO_3Na^+$ requires 423.0392) found 423.0392.

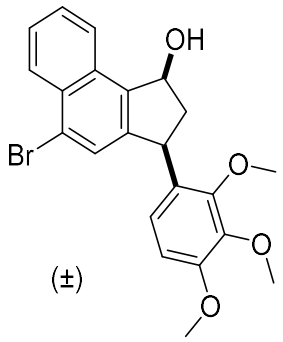
(1*RS*,3*RS*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphtalen-1-ol



97

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]napthalen-1-one, **76** (1.00 g, 2.3 mmol) and sodium borohydride (93 mg, 2.5 mmol). The crude product was purified by recrystallisation in methanol, yielding a yellow solid (0.88 g, 88 %); m.p. 207-208 °C; ν_{max}/cm^{-1} 2936 (m, C_{Ar}-H, stretch), 1686 (s, C=O, stretch), 1108 (s, C-O, stretch), 1001 (s, C_{Ar}-Br, stretch); δ_H (500 MHz, $CDCl_3$) 8.41-8.33 (1H, m, ArH-9), 8.30-8.27 (1H, m, ArH-6), 7.64-7.58 (2H, m, ArH-7 & ArH-8), 7.48 (1H, s, ArH-4), 6.49 (2H, s, 2 x ArH-2′), 5.80-5.75 (1H, m, CH-1), 4.28 (1H, dd, *J* 8.5, 6.5, CH-3), 3.86 (3H, s, C_{Ar}-4′ OCH_3), 3.80 (6H, 2 x C_{Ar}-3′ OCH_3), 3.19 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.14 (1H, ddd, *J* 14, 6.5, 5, CH*H*-2), 2.18 (1H, C-1 OH); δ_C (125 MHz, $CDCl_3$) 153.4 (2 x C_{Ar}-3′), 143.9 (C_{Ar}), 140.1 (C_{Ar}), 139.1 (C_{Ar}), 136.7 (C_{Ar}-4′), 131.5 (C_{Ar}), 131.1 (C_{Ar}), 127.9 (C_{Ar}H-6), 127.5 (C_{Ar}H), 127.4 (C_{Ar}H), 126.9 (C_{Ar}H), 124.6 (C_{Ar}H-9), 124.3 (C_{Ar}), 105.0 (2 x C_{Ar}H-2′), 74.9 (CH-1), 60.8 (C_{Ar}-4′ O*C*H_3), 56.1 (2 x C_{Ar}-3′ O*C*H_3), 49.7 (CH-3), 45.8 (CH_2-2); (MH^+ $C_{22}H_{19}{}^{79}BrO_4H^+$ requires 427.0539) found 427.0534, (MH^+ $C_{22}H_{19}{}^{81}BrO_4H^+$ requires 429.0520) found 429.0519.

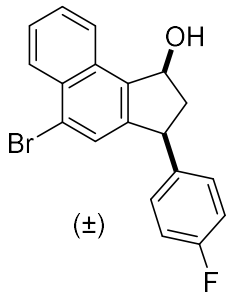
(1*RS*,3*RS*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



98

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **77** (0.92 g, 2.2 mmol) and sodium borohydride (86 mg, 2.3 mmol). The crude product was purified by silica column chromatography, eluting with dichloromethane, yielding a orange oil (0.87 g, 82 %); ν_{max}/cm^{-1} 3404 (br. s, OH, stretch), 2937 (w, C_{Ar}-H, stretch), 1148 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 8.32 (1H, dd, *J* 7.5, 1.5, ArH-9), 8.26 (1H, dd, *J* 7.5, 1, ArH-6), 7.65-7.56 (2H, m, ArH-7 & ArH-8), 7.49 (1H, s, ArH-4), 6.82 (1H, d, *J* 8.5, ArH-6′), 6.63 (1H, d, *J* 8.5, ArH-5′), 5.76-5.67 (1H, m, CH-1), 4.50 (1H, dd, *J* 9.5, 4.5, CH-3), 3.86 (3H, s, C_{Ar}-4′ OCH_3), 3.85 (3H, s, C_{Ar}-3′ OCH_3), 3.40 (3H, s, C_{Ar}-2′ OCH_3), 3.23 (1H, ddd, *J* 14.5, 9.5, 8, C*H*H-2), 2.98 (1H, d, *J* 9, C-1 OH), 2.09 (1H, ddd, *J* 14.5, 4, 3, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 152.9 (C_{Ar}), 151.6 (C_{Ar}-2′), 144.1 (C_{Ar}), 142.6 (C_{Ar}), 139.6 (C_{Ar}), 131.4 (C_{Ar}), 131.3 (C_{Ar}), 130.8 (C_{Ar}), 127.7 (C_{Ar}H-6), 127.4, 127.2 (C_{Ar}H-7 & C_{Ar}H-8), 126.8 (C_{Ar}H-9), 125.0 (C_{Ar}H-6′), 124.0 (C_{Ar}), 123.7 (C_{Ar}), 107.4 (C_{Ar}H-5′), 75.0 (CH-1), 60.7 (C_{Ar} O*C*H_3), 60.6 (C_{Ar}-2′ O*C*H_3), 56.0 (C_{Ar} O*C*H_3), 45.2 (CH-3), 44.4 (CH_2-2); m/z (MNa^+ $C_{22}H_{21}{}^{79}BrO_4Na^+$ requires 451.0515) found 451.0516, (MNa^+ $C_{22}H_{21}{}^{81}BrO_4Na^+$ requires 453.0498) found 453.0528.

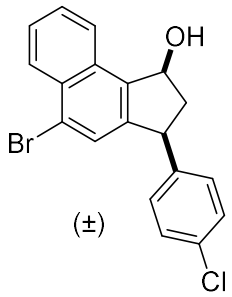
(1*RS*,3*RS*)-5-Bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



99

The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **78** (1.00 g, 2.8 mmol) and sodium borohydride (0.11 g, 3.0 mmol). The crude product was purified by recrystallisation in methanol, yielding an off-white solid (0.95 g, 64 %); m.p. 201-202 °C; ν_{max}/cm^{-1} 3454 (br, s, OH, stretch), 1505 (s, C-O, stretch), 1075 (s, C-Br, stretch); δ_H (500 MHz, $CDCl_3$) 8.37-8.33 (1H, m, ArH-9), 8.31-8.26 (1H, m, ArH-6), 7.65-7.59 (2H, m, ArH-7 & ArH-8), 7.42 (1H, s, ArH-4), 7.22 (2H, dd, *J* 8.5, 5.5, 2 x ArH-2′), 7.02 (2H, t, *J* 8.5, 2 x ArH-3′), 5.79 (1H, dd, *J* 11.5, 7, CH-1), 4.40 (1H, dd, *J* 8.5, 6, CH-3), 3.21 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.09 (1H, ddd, *J* 14, 6, 4.5, CH*H*-2), 2.00 (1H, d, *J* 7, C-1 OH); δ_C (125 MHz, $CDCl_3$) 161.8 (d, $^1J_{CF}$ 245, C_{Ar}-4′), 143.9 (C_{Ar}), 140.3 (d, $^4J_{CF}$ 3, C_{Ar}-1′), 139.1 (C_{Ar}), 131.6 (C_{Ar}), 131.0 (C_{Ar}), 129.5 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-2′), 128.0 (C_{Ar}H), 127.6 (C_{Ar}H), 127.3 (C_{Ar}H), 127.0 (C_{Ar}H), 124.7 (C_{Ar}H-9), 124.5 (C_{Ar}), 115.6 (d, $^2J_{CF}$ 21, 2 x C_{Ar}H-3′); δ_F (376 MHz, $CDCl_3$) -116.2 (m, C_{Ar}F-4′); m/z (MNa^+ $C_{19}H_{14}{}^{79}BrFONa^+$ requires 379.0104) found 379.0104, (MNa^+ $C_{19}H_{14}{}^{81}BrFONa^+$ requires 381.0086) found 381.0086

(1*RS*,3*RS*)-5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



100

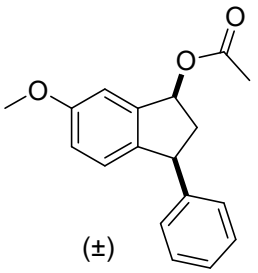
The aforementioned product was synthesised using the general method outlined in **Section 5.2.3.4**, using 5-bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, **79** (1.20 g, 3.2 mmol) and sodium borohydride (0.13 g, 3.39 mmol). The crude product was purified by recrystallisation in methanol, yielding a beige solid (1.11 g, 92 %); m.p. 207-208 °C; ν_{max}/cm^{-1} 3455 (br. s, OH, stretch), 1074 (m, C-Br, stretch); δ_H (500 MHz, $CDCl_3$) 8.39-8.35 (1H, m, ArH-9), 8.30-8.26 (1H, m, ArH-6), 7.66-7.57 (2H, m, ArH-7 & ArH-8), 7.45 (1H, s, ArH-4), 7.37-7.32 (2H, m, 2 x ArH-2′), 7.29-7.24 (2H, m, 2 x ArH-3′), 5.79 (1H, dd, *J* 7, 5, CH-1), 4.39 (1H, dd, *J* 8.5, 6, CH-3), 3.23 (1H, ddd, *J* 14, 8.5, 7.5, C*H*H-2), 2.14 (1H, ddd, *J* 14, 6, 4.5, CH*H*-2), 1.97 (1H, br. s, C-1 OH); δ_C (125 MHz, $CDCl_3$) 144.5 (C_{Ar}), 144.0 (C_{Ar}), 139.3 (C_{Ar}), 131.6 (C_{Ar}), 131.1 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 124.7 ($C_{Ar}H$-9), 124.4 (C_{Ar}), 75.1 (CH-1), 49.4 (CH-3), 45.9 (CH_2-2), (missing 1 x C_{Ar}); m/z (MNa^+ $C_{19}H_{14}{}^{79}BrClONa^+$ requires 394.9809) found 394.9812, (MNa^+ $C_{19}H_{14}{}^{81}BrClONa^+$ requires 396.9788) found 396.9787.

5.2.4 Kinetic Resolution – Enzymatic Acylation

5.2.4.1 Acetylation of Racemic 3-Substituted Inden-1-ols

The following procedure was performed in accordance with previous literature.[523] To a solution of 3-substituted inden-1-ol (2.1 mmol) in dichloromethane (40 mL) at 0 °C was added pyridine (2.7 mmol) followed by the drop-wise addition of acetic anhydride (2.7 mmol) over 10 minutes. The resulting solution was then warmed to room temperature and stirred for 16 hours overnight. The reaction mixture was washed three times with aqueous HCl solution (1M, 40 mL), brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was then purified as mentioned specifically.

(1′*RS*,3′*RS*)-6′-Methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

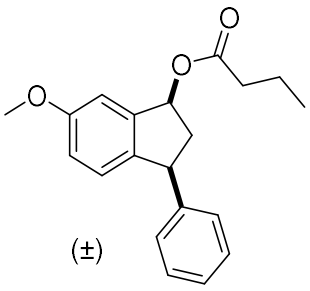


101

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, **80** (0.50 g, 2.1 mmol), acetic anhydride (0.26 mL, 2.7 mmol) and pyridine (0.22 mL, 2.7 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 2), yielding an off-white solid (0.52 g, 88 %); m.p. 81-82 °C; ν_{max}/cm^{-1} 3026 (w, C_{Ar}-H, stretch), 1721 (s, C=O, stretch), 1233 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.34 (2H, t, *J* 7, 2 x ArH-2″), 7.30-7.23 (3H, m, 2 x ArH-3″, ArH-4″), 76.96 (1H, d, *J* 2.5, ArH-7′), 6.93 (1H, d, *J*

8.5, ArH-4′), 6.87 (1H, dd, *J* 8.5, 2.5, ArH-5′), 6.25 (1H, t, *J* 7, CH-1′), 4.26 (1H, t, *J* 8, CH-3′), 3.85 (3H, s, C_{Ar}-6′ OCH_3), 3.14 (1H, dt, *J* 13.5, 7.5, C*H*H-2′), 2.16 (3H, s, CH_3-2), 2.12-2.05 (1H, m, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 171.1 (C-1), 159.4 (C_{Ar}-6′), 144.8 (C_{Ar}), 142.6 (C_{Ar}), 138.5 (C_{Ar}), 128.5 (2 x C_{Ar}H-2″), 128.1, 126.6 (2 x C_{Ar}H-3″ & C_{Ar}H-4″), 126.0 (C_{Ar}H-4′), 116.0 (C_{Ar}H-5′), 108.9 (C_{Ar}H-4′), 76.9 (CH-1′), 55.5 (C_{Ar}-6′ O*C*H_3), 48.0 (CH-3′), 43.3 (CH_2-2′), 21.3 (CH_3-2); m/z (MNa^+ $C_{18}H_{18}O_3$ requires 305.1148) found 305.1151.

(1′*RS*,3′*RS*)-6′-Methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl butyrate

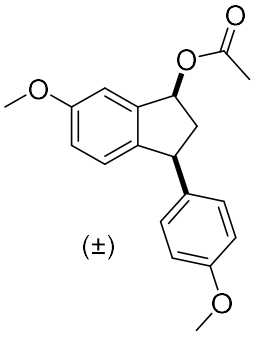


102

The following procedure was performed in accordance with previous literature.[524] To a solution of butyric acid (4.6 mmol), DMAP (0.4 mmol), DCC (9.2 mmol) in CH_2Cl_2 (30 mL), was added (1*SR*,3*SR*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, **80** (4.2 mmol) and the reaction was stirred at room temperature overnight. The reaction mixture was then filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography eluting with ethyl acetate: petroleum ether (1 : 9), yielding a pale yellow oil (1.12 g, 86 %); ν_{max}/cm^{-1} 2962 (m, C-H, stretch), 1728 (s, C=O, stretch), 1171 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.31 (2H, t, *J* 7.5, 2 x ArH-3″), 7.25-7.21 (3H, m, ArH-4″ & 2 x ArH-2″), 6.91-6.88 (2H, m, ArH-4′ & ArH-7′), 6.83 (1H, dd, *J* 8.5, 2.5, ArH-5′), 6.23 (1H, t, *J* 7, CH-1′), 4.23 (1H, t, *J* 8, CH-

3′), 3.81 (3H, s, C_{Ar}-6′ OCH_3), 3.10 (1H, dt, *J* 13.5, 8, C*H*H-2′), 2.36 (2H, m, CH_2-2), 2.04 (1H, ddd, *J* 14, 7.5, 6.5, CH*H*-2′), 1.69 (2H, m, CH_2-3), 0.96 (3H, t, CH_3-4); δ_C (100 MHz, $CDCl_3$) 173.7 (C-1), 159.3 (C_{Ar}-6′), 144.8 (C_{Ar}-1″), 142.7 (C_{Ar}), 138.4 (C_{Ar}), 128.4 (2 x C_{Ar}H-3″), 128.0, 126.5 (C_{Ar}H-4″ & 2 x C_{Ar}H-2″), 125.9 (C_{Ar}H-4′), 115.8 (C_{Ar}H-5′), 108.8 (C_{Ar}H-7′), 76.5 (CH-1′), 55.4 (C_{Ar}-6′ O*C*H_3), 47.9 (CH-3′), 43.3 (CH_2-2′), 36.4 (CH_2-2), 18.5 (CH_2-3), 13.6 (CH_3-4); m/z (MNa^+ $C_{20}H_{22}O_3Na^+$ requires 333.1461) found 333.1467.

(1′*RS*,3′*RS*)-6′-Methoxy-3′-(4″-methoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

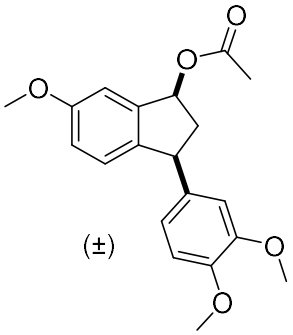


103

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, **81** (100 mg, 0.4 mmol), acetic anhydride (0.05 mL, 0.5 mmol) and pyridine (0.04 mL, 0.5 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 1), yielding a an off-white solid (105 mg, 91 %); m.p. 88-89 °C; ν_{max}/cm^{-1} 2916 (w, C_{Ar}-H, stretch), 1720 (s, C=O, stretch), 1239 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.41 (2H, d, *J* 8.5, 2 x ArH-2″), 6.94-6.81 (5H, m, 2 x ArH-3″, ArH-4′, ArH-5′, ArH-7′),

6.20 (1H, t, *J* 6.5, CH-1′), 4.18 (1H, t, *J* 8, CH-3′), 3.82 (3H, s, C_{Ar}-6′ OCH_3), 3.80 (3H, s, C_{Ar}-4″ OCH_3), 3.08 (1H, dt, *J* 15, 7.5, C*H*H-2′), 2.14 (3H, s, CH_3-2), 2.05-2.00 (1H, m, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 171.1 (C-1), 159.2 (C_{Ar}-6″), 158.2 (C_{Ar}-4″), 142.4 (C_{Ar}), 138.7 (C_{Ar}), 136.8 (C_{Ar}), 129.0 (2 x C_{Ar}H-2′), 125.9 (C_{Ar}H), 115.9 (C_{Ar}H), 113.9 (C_{Ar}H), 108.7 (C_{Ar}H), 76.7 (CH-1′), 55.5 (C_{Ar} O*C*H_3), 55.1 (C_{Ar} O*C*H_3), 47.1 (CH-3′), 43.4 (CH_2-2′), 21.3 (CH-3′); m/z (MNa^+ $C_{19}H_{20}O_4Na^+$ requires 335.1254) found 335.1250.

(1′*RS*,3′*RS*)-3′-(3″,4″-Dimethoxyphenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

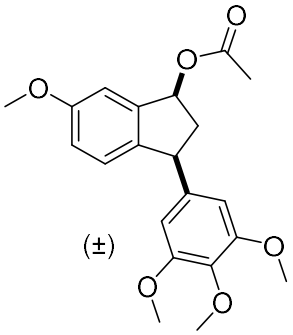


104

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-3-(3′,4′-dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, **82** (100 mg, 0.3 mmol), acetic anhydride (0.04 mL, 0.4 mmol) and pyridine (0.35 mL, 0.4 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 1), yielding a off-white solid (90 mg, 82 %); m.p. 95-96 °C; ν_{max}/cm^{-1} 2960 (w, C_{Ar}-H, stretch), 1719 (s, C=O, stretch), 1246 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 6.95-

6.88 (2H, m, ArH-4′ & ArH-6″), 6.86-6.70 (4H, m, ArH-5″, ArH-5′, ArH-7′, ArH-2″), 6.20 (1H, t, *J* 6.5, CH-1′), 4.12 (1H, t, *J* 7.5, CH-3′), 3.86 (3H, s, C_{Ar} OCH_3), 3.08 (6H, m, C_{Ar} OCH_3 & C_{Ar} OCH_3), 3.15-3.01 (1H, m, C*H*H-2′), 2.13 (3H, s, CH_3-2), 2.06-1.98 (1H, m, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 170.9 (C-1), 159.2 (C_{Ar}), 148.9 (C_{Ar}), 147.5 (C_{Ar}), 142.3 (C_{Ar}), 137.2 (C_{Ar}), 125.8 (C_{Ar}H), 120.0 (C_{Ar}H), 115.8 (C_{Ar}H), 110.9 (C_{Ar}H), 110.8 (C_{Ar}H), 108.7 (C_{Ar}), 76.7 (CH-1′), 55.7 (C_{Ar} O*C*H_3), 55.7 (C_{Ar} O*C*H_3), 55.3 (C_{Ar} O*C*H_3), 47.5 (CH-3′), 43.2 (CH-2′), 21.2 (CH_3-2); m/z MNa^+ $C_{20}H_{22}O_5Na^+$ requires 365.1359) found 365.1362.

(1′*RS*,3′*RS*)-6′-Methoxy-3′-(3″,4″,5″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl aceate

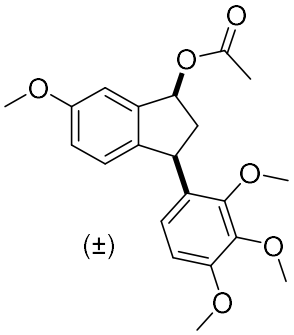


105

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-5-bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphtalen-1-ol**, 83** (100 mg, 0.3 mmol), acetic anhydride (0.04 mL, 0.4 mmol) and pyridine (0.03 mL, 0.4 mmol). Further purification being performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 1), yielding a yellow oil (96 mg, 85 %); ν_{max}/cm^{-1} 2937 (w, C_{Ar}-H, stretch), 1731 (s, C=O, stretch), 1228 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 6.98-

6.91 (2H, m, ArH-4′ & ArH-7′), 6.85 (1H, d, *J* 8.5, ArH-5′), 6.43 (2H, s, 2 x ArH-2″), 6.21 (1H, t, CH-1′), 4.15 (1H, t, *J* 8, CH-3′), 3.84 (3H, s, C_{Ar}-6′ OCH_3), 3.82-3.80 (9H, s, 2 x C_{Ar}-3″ OCH_3 & C_{Ar}-4″ OCH_3), 3.15-3.03 (1H, m, C*H*H-2′), 2.14 (3H, s, CH_3-2), 2.08-1.98 (1H, m, CH*H*-2); δ_C (100 MHz, $CDCl_3$) 171.0 (C-1), 159.4 (C_{Ar}-6′ OCH_3), 153.2 (C_{Ar}), 142.5 (C_{Ar}), 140.4 (C_{Ar}), 138.1 (C_{Ar}), 126.0 (C_{Ar}H-4′), 116.0 (C_{Ar}H-5′), 108.8 (C_{Ar}H-7′), 104.8 (2 x C_{Ar}H-2″), 76.7 (CH-1′), 60.8 (C_{Ar}-6′ O*C*H_3), 56.0 (C_{Ar} O*C*H_3), 55.5 (C_{Ar} O*C*H_3), 48.3 (CH-3′), 43.2 (CH_2-2′), 21.3 (CH_3-2); m/z (MNa^+ $C_{21}H_{24}O_6Na^+$ requires 395.1465) found 395.1465.

(1′*RS*,3′*RS*)-6′-Methoxy-3′-(2″,3″,4″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

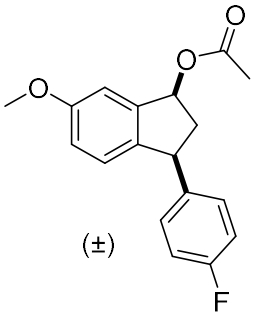


106

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-5-bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **84** (100 mg, 0.3 mmol), acetic anhydride (0.04 mL, 0.4 mmol) and pyridine (0.03 mL, 0.4 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 1), yielding a orange oil (90 mg, 80 %); ν_{max}/cm^{-1} 2938 (w, C_{Ar}-H, stretch), 1728 (s, C=O, stretch), 1231 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 6.94-

6.82 (3H, m, ArH-7′, ArH-4′ & ArH-5′), 6.71 (1H, d, *J* 8.5, ArH-6″), 6.60 (1H, d, *J* 8.5, ArH-5″), 6.20 (1H, t, *J* 6.5, CH-1′), 4.58 (1H, t, *J* 7.5, CH-3′), 3.91 (3H, s, C_{Ar} OCH_3), 3.88 (3H, s, C_{Ar} OCH_3), 3.84 (3H, s, C_{Ar} OCH_3), 3.82 (3H, s, C_{Ar} OCH_3), 3.13-3.03 (1H, m, C*H*H-2′), 2.12 (3H, s, CH_3-2), 2.01-1.92 (1H, m, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 171.1 (C-1), 159.2 (C_{Ar}), 152.2 (C_{Ar}), 142.6 (C_{Ar}), 138.5 (C_{Ar}), 138.3 (C_{Ar}), 130.8 (C_{Ar}), 125.9 (C_{Ar}H-7′), 122.8 (C_{Ar}H-6″), 115.9 (C_{Ar}H), 108.8 (C_{Ar}H), 107.5 (C_{Ar}H-5″), 61.4 (C_{Ar} O*C*H_3), 60.8 (C_{Ar} O*C*H_3), 55.9 (C_{Ar} O*C*H_3), 55.5 (C_{Ar} O*C*H_3), 42.8 (CH_2-2′), 21.4 (CH_3-2); m/z (MNa^+ $C_{21}H_{24}O_6Na^+$ requires 395.1465) found 395.1465.

(1′*RS*,3′*RS*)-3′-(4″-Fluorophenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

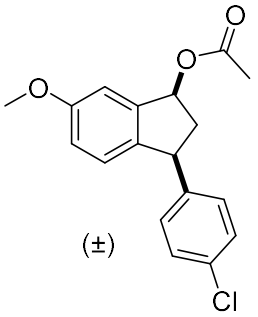


107

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-3-(4′-fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol**, 85** (100 mg, 0.4 mmol), acetic anhydride (0.05 mL, 0.5 mmol) and pyridine (0.04 mL, 0.05 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 1), yielding an off-white solid (0.10 g, 90 %); m.p. 123-124 °C; ν_{max}/cm^{-1} 2835 (w, C_{Ar}-H, stretch), 1724 (s, C=O, stretch), 1234 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.16

(2H, t, *J* 8.5, 2 x ArH-2″), 6.99 (2H, t, 2 x ArH-3″), 6.92 (1H, s, ArH-7′), 6.91-6.81 (2H, m, ArH-4′ & ArH-5′), 6.20 (1H, t, *J* 6.5, CH-1′), 4.22 (1H, t, *J* 7.5, CH-3′), 3.82 (3H, s, C_{Ar}-6′ OCH_3), 3.15-3.05 (1H, m, C*H*H-2′), 2.13 (3H, s, CH_3-2), 2.04-1.94 (1H, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 171.0 (C-1), 162.9 (m, C-4″), 159.4 (C_{Ar}-6′), 142.5 (C_{Ar}), 140.5 (C_{Ar}), 138.2 (C_{Ar}), 129.5 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-3″), 125.9 (C_{Ar}H-7′), 116.1 (C_{Ar}H), 115.3 (d, $^2J_{CF}$ 21, 2 x C_{Ar}H-2″), 108.9 (C_{Ar}H), 55.5 (C_{Ar}-6′ O*C*H_3), 47.3 (CH_2-2′), 43.3 (CH-3′), 21.3 (CH_3-2); δ_F (376 MHz, $CDCl_3$) -116.7 (m, C_{Ar}F-4″) m/z (MNa^+ $C_{18}H_{17}FO_3Na^+$ requires 323.1054) found 323.1060.

(1′*RS*,3′*RS*)-3′-(4″-Chlorophenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

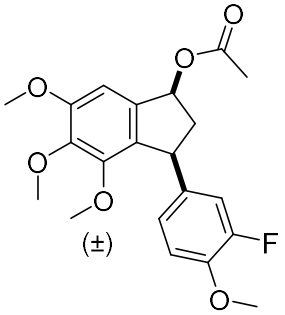


108

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-3-(4′-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, **86** (100 mg, 0.4 mmol), acetic anhydride (0.04 mL, 5 mmol) and pyridine (0.04 mL, 5 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane : petroleum ether (1 : 1), yielding an off-white solid (0.10 g, 89 %); m.p. 122-123 °C; ν_{max}/cm^{-1} 2835 (w, C_{Ar}-H, stretch), 1721 (s, C=O, stretch), 1233 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 7.29 (2H, d, *J*

8.5, 2 x ArH-3″), 7.16 (2H, d, *J* 8.5, 2 x ArH-2″), 6.95 (1H, d, *J* 2, ArH-7′), 6.89 (1H, d, *J* 8.5, ArH-4′), 6.86 (1H, dd, *J* 8.5, 2, ArH-5′), 6.22 (1H, t, *J* 6.5, CH-1′), 4.23 (1H, t, *J* 7.5, CH-3′), 3.84 (3H, C_{Ar}-6′ OCH_3), 3.11 (1H, ddd, *J* 13.5, 8, 7.5, C*H*H-2′), 2.13 (3H, s, CH_3-2), 2.02 (1H, ddd, *J* 13.5, 7.5, 6, CH*H*-2′); δ_C (125 MHz, $CDCl_3$) 171.0 (C-1), 159.5 (C_{Ar}-6′), 143.4 (C_{Ar}), 142.6 (C_{Ar}), 137.9 (C_{Ar}), 132.1 (C_{Ar}), 129.4 (2 x C_{Ar}H-3″), 128.6 (2 x C_{Ar}H-2″), 125.8 (C_{Ar}H-7′), 116.1 (C_{Ar}H-5′), 109.0 (C_{Ar}H-7′), 76.7 (CH-1′), 55.5 (C_{Ar}-6′ O*C*H_3), 47.3 (CH-3′), 43.1 (CH-2′), 21.2 (CH_3-2); m/z (MNa^+ $C_{18}H_{17}{}^{35}Cl$ requires 339.0758) found 339.0748.

(1′*RS*,3′*RS*)-3′-(3″-Fluoro-4″-methoxyphenyl)-4′,5′,6′-trimethoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

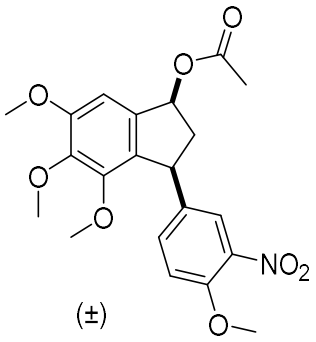


109

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-3-(3′-fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, **87** (100 mg, 0.03 mmol), acetic anhydride (0.04 mL, 0.4 mmol) and pyridine (0.03 mL, 0.04 mmol). Further purification was performed using silica column chromatography eluting with dichloromethane, yielding an orange solid (0.10 g, 93 %); m.p. 78-79 °C; ν_{max}/cm^{-1} 2943 (w, C_{Ar}-H, stretch), 1720 (s, C=O, stretch), 1262 (s, C=O, stretch); δ_H (500 MHz, $CDCl_3$) 6.98-6.94 (2H, m, ArH-5″ & ArH-6″), 6.89-6.83 (1H, m, ArH-2″), 6.78 (1H, s, ArH-7′), 6.13 (1H, dd, *J* 7.5, 2.5, CH-1′), 4.33 (1H, CH-3′), 3.87 (3H, s, C_{Ar}-6′ OCH_3), 3.85 (3H, s, C_{Ar}-4″ OCH_3), 3.81

(3H, s, C_{Ar}-5′ OCH_3), 3.44 (3H, s, C_{Ar}-4′ OCH_3), 3.12-3.08 (1H, m, C*H*H-2′), 2.08 (3H, s, CH_3-2), 2.00 (1H, dt, 14.5, 3, CH*H*-2′); δ_C (125 MHz, $CDCl_3$) 170.9 (C-1), 154.3 (C_{Ar}-6′), 152.2 (d, $^1J_{CF}$ 245, C_{Ar}-3″), 149.8 (C_{Ar}-4′), 145.8 (d, $^2J_{CF}$ 11, C_{Ar}-4″), 143.2 (C_{Ar}-5′), 139.0 (d, $^3J_{CF}$ 5.5, C_{Ar}-1″), 136.3 (C_{Ar}), 132.1 (C_{Ar}), 123.2 (d, $^3J_{CF}$ 3.5 C_{Ar}H-5″), 115.4 (d, $^2J_{CF}$ 18.5, C_{Ar}H-2″), 112.9 (d, $^4J_{CF}$ 1.5, C_{Ar}H-6″), 103.7 (C_{Ar}H-7′), 77.7 (CH-1′), 60.7 (C_{Ar}-4″ O*C*H_3), 60.1 (C_{Ar}-4′ O*C*H_3), 56.2 (C_{Ar} O*C*H_3), 56.1 (C_{Ar} O*C*H_3), 46.3 (CH-3′), 41.9 (CH_2-2′), 21.3 (CH_3-2); δ_F (282 MHz, $CDCl_3$) -135.5 (m, C_{Ar}F-3″); m/z (MNa^+ $C_{21}H_{23}FO_6Na^+$ requires 413.1371) found 413.1367.

(1′*RS*,3′*RS*)-3′-(4″-Methoxy-3″-nitrophenyl)-4′,5′,6′-trimethoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

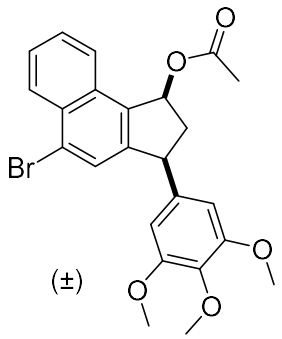


110

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, **88** (100 mg, 0.3 mmol), acetic anhydride (0.04 mL, 0.4 mmol) and pyridine (0.03 mL, 0.04 mmol). Further purification being performed using flash column chromatography eluting with dichloromethane, yielding an orange oil (0.10 g, 91 %); ν_{max}/cm^{-1} 2939 (w, C_{Ar}-H, stretch), 1731 (s, C=O, stretch), 1527 (s, C_{Ar}-NO_2, stretch), 1231 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.82 (1H, s,

ArH-2″), 7.52-7.43 (1H, m, ArH-6″), 7.00 (1H, d, *J* 8, ArH-5″), 6.81 (1H, s, ArH-7′), 6.16 (1H, d, *J* 7, CH-1′), 4.40 (1H, dd, *J* 5.5, 2.5, CH-3′), 3.94 (3H, s, C_{Ar}-5′ OCH_3), 3.88 (3H, s, C_{Ar}-4′ OCH_3), 3.81 (3H, s, C_{Ar}-4″ OCH_3), 3.51 (3H, s, C_{Ar}-6′ OCH_3), 3.05-2.95 (1H, m, C*H*H-2′), 2.11 (3H, s, CH_3-2), 2.04 (1H, dd, *J* 14, 2, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 171.0 (C-1), 154.7 (C_{Ar}), 151.4 (C_{Ar}), 149.7 (C_{Ar}), 143.2 (C_{Ar}), 138.2 (C_{Ar}), 136.3 (C_{Ar}), 133.7 (C_{Ar}H-6″), 131.5 (C_{Ar}), 125.0 (C_{Ar}H-2″), 113.1 (C_{Ar}H-5″), 104.1 (C_{Ar}H-7′), 77.6 (CH-1′), 60.7 (C_{Ar}-4″ O*C*H_3), 60.2 (C_{Ar}-6′ O*C*H_3), 56.5 (C_{Ar}-5′ O*C*H_3), 56.2 (C_{Ar}-4′ O*C*H_3), 46.0 (CH-3′), 41.5 (CH_2-2′), 21.4 (CH_2-2); m/z (MNa^+ $C_{21}H_{23}NO_8Na^+$ requires 440.1316) found 440.1307.

(1′*RS*,3′*RS*)-5′-Bromo-3′-(3″,4″,5″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-cyclopenta[*a*]naphtalen-1′-yl acetate



111

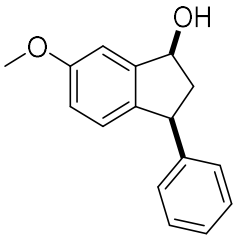
The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.1**, using (1*RS*,3*RS*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphtalen-1-ol, **107** (5.00 g, 14.2 mmol), acetic anhydride (1.5 mL, 20 mmol) and pyridine (3.45 mL, 40 mmol). Further purification being performed using flash column chromatography eluting with dichloromethane : petroleum ether (1 : 2), yielding a beige solid (5.31 g, 79 %); m.p. 109-110 °C; ν_{max}/cm^{-1} 2994 (w, C_{Ar}-H, stretch), 1722 (s, C=O, stretch), 1232 (s, C-O, stretch); δ_H

(400 MHz, $CDCl_3$) 8.33-8.27 (1H, m, ArH-9′), 7.93-7.88 (1H, m, ArH-5′), 7.64-7.59 (2H, m, ArH-4′ & ArH-5′), 7.54 (1H, s, ArH-4′), 6.81-6.73 (1H, m, CH-1′), 6.46 (2H, s, 2 x ArH-2″), 4.38 (1H, dd, *J* 9, 4, CH-3′), 3.85 (3H, s, C_{Ar}-4″ OCH_3), 3.80 (6H, s, 2 x C_{Ar}-3″ O*C*H_3), 3.34-3.23 (1H, m, C*H*H-2′), 2.21-2.09 (4H, m, CH_3-2 & CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 170.5 (C-1), 153.4 (C_{Ar}), 145.7 (C_{Ar}), 140.1 (C_{Ar}), 135.2 (C_{Ar}), 131.5 (C_{Ar}), 130.8 (C_{Ar}), 128.1 (C_{Ar}H-9′), 127.8 (C_{Ar}H), 127.4 (C_{Ar}H), 127.1 (C_{Ar}H), 125.3 (C_{Ar}), 124.3 (C_{Ar}H-5′), 105.0 (2 x C_{Ar}H-2″), 76.3 (CH-1′), 60.8 (C_{Ar}-4″ O*C*H_3), 56.0 (2 x C_{Ar}-3″ O*C*H_3) 50.4 (CH-3′), 42.2 (CH_2-2′), 21.3 (CH_3-2) (missing 1 x C_{Ar}); (MNa^+ $C_{24}H_{23}{}^{79}BrO_5Na^+$ requires 493.0621) found 493.0630, (MNa^+ $C_{24}H_{23}{}^{81}BrO_5Na^+$ requires 495.0604) found 495.0618

5.2.4.2 Kinetic Resolution: Novozym® 435 Acylations

The following procedure was performed in accordance with previous literature.[359] To a solution of (1*RS*,3*RS*)-3-substituted-2,3-dihydro-1*H*-inden-1-ol (10.4 mmol) in 2-isopropoxypropane : dichloromethane (40 mL, 1 : 1) was added vinyl acetate (42 mmol) and Novozym-435 (70 mg/mmol). The reaction mixture was then stirred at an optimised 40 °C for 48 hours. The solids were filtered off and the filtrate was concentrated *in vacuo*. The product counterparts were separated by silica column chromatography eluting with dichloromethane : petroleum ether as mentioned specifically.

(1*S*,3*S*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol

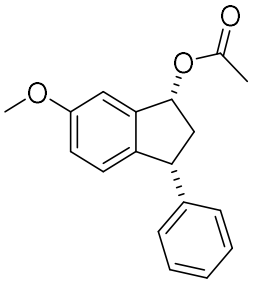


(1*S*,3*S*)-**80**

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (0.50 g, 2.1 mmol) **80**, vinyl acetate (0.77 mL, 8.3 mmol) and Novozym® 435 (145 mg, 70 mg/mmol) to give compound (1*R*,3*R*)-**101** and (1*S*,3*S*)-**80** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (0.24 g, 48 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that

of racemate; $[\alpha]_D^{30}$ (c 0.1, CH_3OH) +25.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 208 nm, (*S*)-isomer 24.61 min., (*R*)-isomer 40.77 min.).

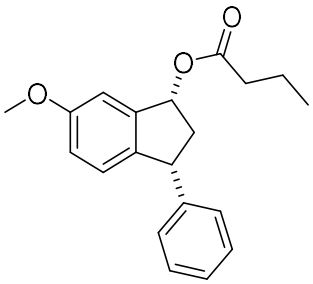
(1′*R*,3′*R*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



(1*R*,3*R*)-101

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (0.50 g, 2.1 mmol) **80**, vinyl acetate (0.77 mL, 8.3 mmol) and Novozym® 435 (145 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**101** and (1*S,*3*S*)-**80** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (0.28 g, 47 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +12.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 211 nm, (*R*)-isomer 6.37 min., (*S*)-isomer 6.96 min.).

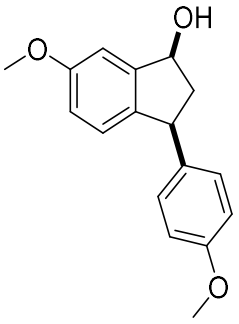
(1′*R*,3′*R*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl butyrate



(1*R*,3*R*)-102

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (0.50 g, 2.1 mmol) **80**, vinyl acetate (0.77 mL, 8.3 mmol) and Novozym® 435 (145 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**102** and (1*S,*3*S*)-**80** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow oil (0.32 g, 49 %), as a % of racemic starting material, in 99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.1, $CHCl_3$) +51.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 208 nm, (*R*)-isomer 5.81 min., (*S*)-isomer 6.88 min.).

(1*S*,3*S*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol

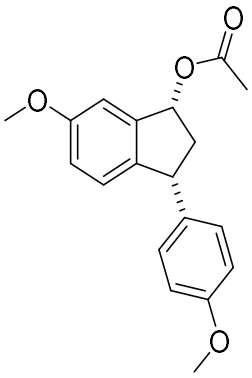


(1*S*,3*S*)-81

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-

inden-1-ol (150 mg, 0.5 mmol) **81**, vinyl acetate (2.0 mL, 2.2 mmol) and Novozym® 435 (39 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**103** and (1*S,*3*S*)-**81** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (69 mg, 46 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.2, $CHCl_3$) +7.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 228 nm, (*S*)-isomer 14.41 min., (*R*)-isomer 28.52 min.).

(1′*R*,3′*R*)-6′-Methoxy-3′-(4″-methoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl acetate

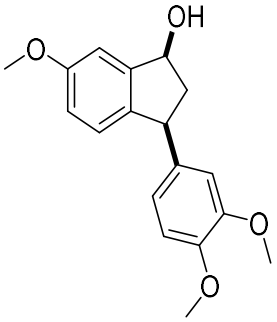


(1*R*,3*R*)-103

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (150 mg, 0.5 mmol) **81**, vinyl acetate (2.0 mL, 2.2 mmol) and Novozym® 435 (39 mg, 70 mg/mmol) to give compound (1′*R,*3′*R*)-**103** and (1*S,*3*S*)-**81** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (80 mg, 46 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to

that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +6.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 5 : 95 , 0.5 mL/min., 229 nm, (*R*)-isomer 20.83 min., (*S*)-isomer 22.49 min.).

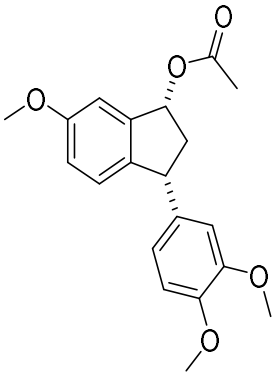
(1*S*,3*S*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-82

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol (0.90 g, 3.0 mmol) **82**, vinyl acetate (1.10 mL, 12 mmol) and Novozym® 435 (210 mg, 70 mg/mmol) to give compound (1*R*,3*R*)-**104** and (1*S*,3*S*)-**82** in a ratio of 47 : 53. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (0.39 g, 44 %), as a % of racemic starting material, in 77 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +12.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 209 nm, (*R*)-isomer 22.40 min., (*S*)-isomer 27.28 min.).

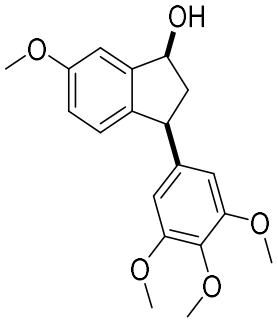
(1′*R*,3′*R*)-3′-(3″,4″-Dimethoxyphenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



(1*R*,3*R*)-104

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol (0.90 g, 3.0 mmol) **82**, vinyl acetate (1.10 mL, 12 mmol) and Novozym® 435 (210 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**104** and (1*S,*3*S*)-**82** in a ratio of 47 : 53. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a off-white solid (0.43 g, 42 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.2, $CHCl_3$) +1.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 0.5 mL/min., 210 nm, (*S*)-isomer 32.85 min., (*R*)-isomer 35.15 min.).

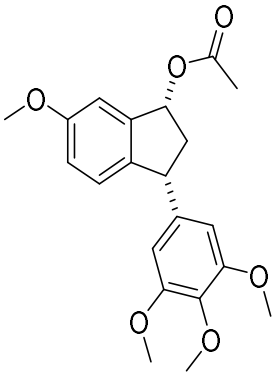
(1*S*,3*S*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-83

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (2.75 g, 8.3 mmol) **83**, vinyl acetate (3.1 mL, 33.3 mmol) and Novozym® 435 (0.58 g, 70 mg/mmol) to give compound (1*R,*3*R*)-**105** and (1*S,*3*S*)-**83** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield a yellow oil (1.30 g, 47 %), as a % of racemic starting material, in 99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.1, $CHCl_3$) +44.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 214 nm, (*R*)-isomer 25.70 min., (*S*)-isomer 33.65 min.).

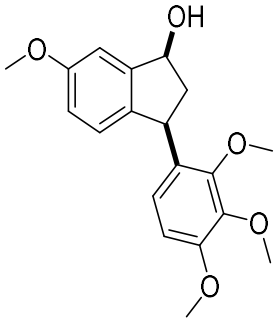
(1′*R*,3′*R*)-6′-Methoxy-3′-(3″,4″,5″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl aceate



(1*R*,3*R*)-105

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (2.75 g, 8.3 mmol) **83**, vinyl acetate (3.1 mL, 33.3 mmol) and Novozym® 435 (0.58 g, 70 mg/mmol) to give compound (1*R,*3*R*)-**105** and (1*S,*3*S*)-**83** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield a yellow oil (1.48 g, 48 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +3.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 214 nm, (*S*)-isomer 12.29 min., (*R*)-isomer 14.77 min.).

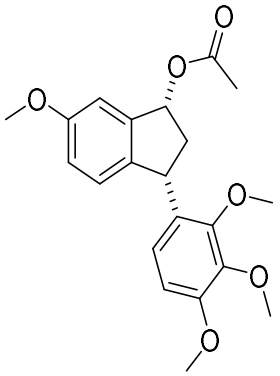
(1*S*,3*S*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-84

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (0.90 g, 2.7 mmol) **84**, vinyl acetate (1.0 mL, 10.9 mmol) and Novozym® 435 (189 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**106** and (1*S,*3*S*)-**84** in a ratio of 45 : 55. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield a yellow oil (0.45 g, 50 %), as a % of racemic starting material, in 81 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.1, $CHCl_3$) +58.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 215 nm, (S)-isomer 16.81 min., (*R*)-isomer 37.62 min.).

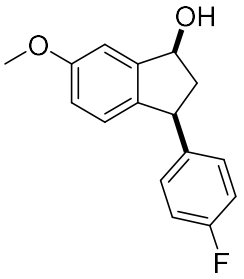
(1′*R*,3′*R*)-6′-Methoxy-3′-(2″,3″,4″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



(1*R*,3*R*)-106

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (0.90 g, 2.7 mmol) **84**, vinyl acetate (1.0 mL, 10.9 mmol) and Novozym® 435 (189 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**106** and (1*S,*3*S*)-**84** in a ratio of 45 : 55. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield an orange oil (0.41 g, 40 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.2, $CHCl_3$) +17.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 214 nm, (*R*)-isomer 6.28 min., (*S*)-isomer 7.13 min.).

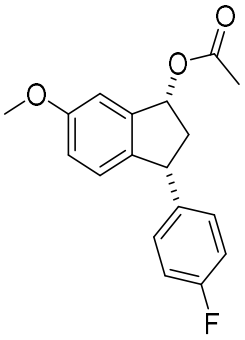
(1*S*,3*S*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-85

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol (3.00 g, 11.6 mmol) **85**, vinyl acetate (4.29 mL, 46.5 mmol) and Novozym® 435 (0.81 g, 70 mg/mmol) to give compound (1*R*,3*R*)-**107** and (1*S*,3*S*)-**85** in a ratio of 49 : 51. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a white solid (1.44 g, 48 %), as a % of racemic starting material, in 94 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +45.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 278 nm, (*S*)-isomer 11.27 min., (*R*)-isomer 18.47 min.).

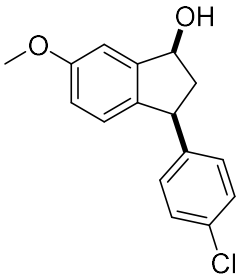
(1′*R*,3′*R*)-3′-(4″-Fluorophenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



(1*R*,3*R*)-107

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol (3.00 g, 11.6 mmol) **85**, vinyl acetate (4.29 mL, 46.5 mmol) and Novozym® 435 (0.81 g, 70 mg/mmol) to give compound (1*R,*3*R*)-**107** and (1*S,*3*S*)-**85** in a ratio of 49 : 51. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (1.64 g, 47 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +11.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 5 : 95 , 0.5 mL/min., 228 nm, (*R*)-isomer 14.99 min., (*S*)-isomer 16.23 min.).

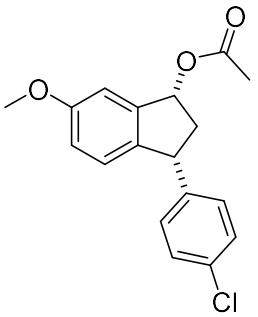
(1*S*,3*S*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-86

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol (1.35 g, 4.9 mmol) **86**, vinyl acetate (1.81 g, 20 mmol) and Novozym® 435 (343 mg, 70 mg/mmol) to give compound (1*R*,3*R*)-**108** and (1*S*,3*S*)-**86** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a white solid (0.65 g, 48 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +34.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 220 nm, (*S*)-isomer 12.35 min., (*R*)-isomer 22.24 min.).

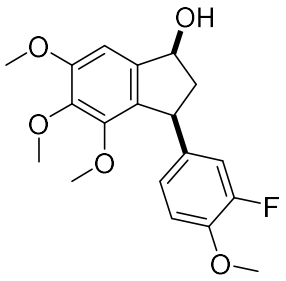
(1′*R*,3′*R*)-3′-(4″-Chlorophenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



(1*R*,3*R*)-108

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol (1.35 g, 4.9 mmol) **86**, vinyl acetate (1.81 g, 20 mmol) and Novozym® 435 (343 mg, 70 mg/mmol) to give compound (1*R*,3*R*)-**108** and (1*S*,3*S*)-**86** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid (0.73 g g, 47 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.1, $CHCl_3$) +11.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 5 : 95 , 0.5 mL/min., 231 nm, (*S*)-isomer 14.36 min., (*R*)-isomer 15.97 min.).

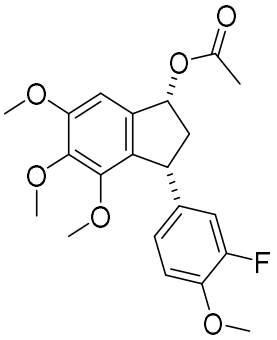
(1*S*,3*S*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-87

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol (1.25 g, 3.6 mmol) **87**, vinyl acetate (1.3 mL, 14.4 mmol) and Novozym® 435 (252 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**109** and (1*S,*3*S*)-**87** in a ratio of 49 : 51. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield a yellow oil (0.59 g, 47 %), as a % of racemic starting material, in 96 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.2, $CHCl_3$) +21.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 224 nm, (*S*)-isomer 14.35 min., (*R*)-isomer 16.72 min.).

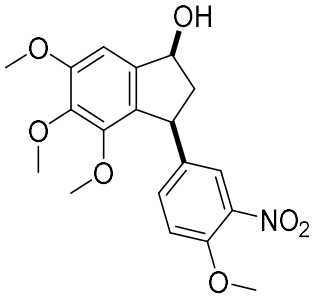
(1′*R*,3′*R*)-3′-(3″-Fluoro-4″-methoxyphenyl)-4′,5′,6′-trimethoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



(1*R*,3*R*)-109

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol (1.25 g, 3.6 mmol) **87**, vinyl acetate (1.3 mL, 14.4 mmol) and Novozym® 435 (252 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**109** and (1*S,*3*S*)-**87** in a ratio of 49 : 51. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield an orange solid (0.63 g, 45 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.2, $CHCl_3$) +7.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 0.5 mL/min., 219 nm, (*S*)-isomer 19.05 min., (*R*)-isomer 21.71 min.).

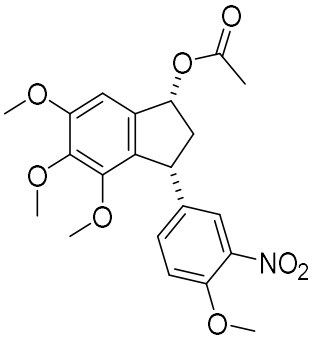
(1*S*,3*S*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy--2,3-dihydro-1*H*-inden-1-ol



(1*S*,3*S*)-88

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol (0.52 g, 1.4 mmol) **88**, vinyl acetate (0.5 mL, 5.5 mmol) and Novozym® 435 (108 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**110** and (1*S,*3*S*)-**88** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield a yellow oil (0.25 g, 48 %), as a % of racemic starting material, in 98 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.1, $CHCl_3$) +61.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 221 nm, (*R*)-isomer 27.02 min., (*S*)-isomer 36.84 min.).

(1′*R*,3′*R*)-3′-(4″-Methoxy-3″-nitrophenyl)-4′,5′,6′-trimethoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate



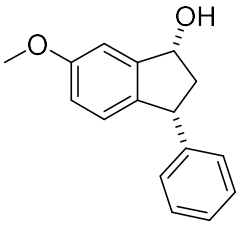
(1*R*,3*R*)-110

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.2**, using (1*RS*,3*RS*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol (0.52 g, 1.4 mmol) **88**, vinyl acetate (0.5 mL, 5.5 mmol) and Novozym® 435 (108 mg, 70 mg/mmol) to give compound (1*R,*3*R*)-**110** and (1*S,*3*S*)-**88** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane to yield a orange oil (0.24 g, 46 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.1, $CHCl_3$) +10.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 221 nm, (*S*)-isomer 30.23 min., (*R*)-isomer 34.04 min.).

5.2.4.3 Deacetylation of Chirally Substituted (*R,R* Inden-1-yl Acetates

The following procedure was performed in accordance with previous literature.[390] To a substituted (1*R*,3*R*)-3′-substituted inden-1-yl acetate (1.5 mmol) in methanol (20 mL) was added K_2CO_3 (4.5 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo*, diluted with H_2O (40 mL), and extracted with EtOAc (2 x 50 mL). The solution was then dried over $MgSO_4$ and concentrated *in vacuo*. The product was generally used without further purification, unless purified further as mentioned specifically.

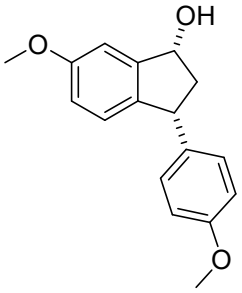
(1*R*,3*R*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-80

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**101** (7.50 g, 26.6 mmol) and potassium carbonate (11.0 g, 79.7 mmol), yielding a white solid (5.80 g, 91 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (**c** 0.10, CH_3OH) -18.5.

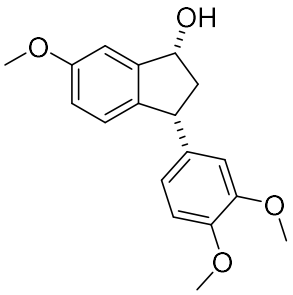
(1*R*,3*R*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-81

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-6′-Methoxy-3′-(4″-methoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**103** (0.20 g, 0.6 mmol) and potassium carbonate (0.24 g, 1.8 mmol), yielding an off-white solid (133 mg, 87 %); spectroscopic data similar to that of racemate**;** $[\alpha]_D^{30}$ (c 0.10, $CHCl_3$) -132.5.

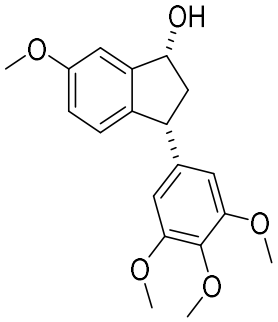
(1*R*,3*R*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-82

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-3′-(3″,4″-Dimethoxyphenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**104** (0.28 g, 0.8 mmol) and potassium carbonate (0.34 g, 2.5 mmol), yielding a off-white solid (208 mg, 85 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.10, $CHCl_3$) -16.0.

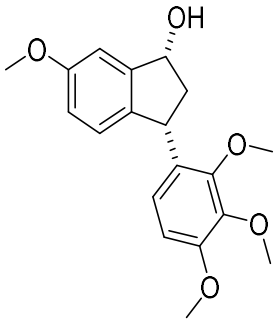
(1*R*,3*R*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-83

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-6′-Methoxy-3′-(3″,4″,5″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl aceate, (1*R*,3*R*)-**105** (0.69 g, 1.9 mmol) and potassium carbonate (0.77 g, 5.6 mmol), yielding a yellow oil (0.56 g, 91 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.10, $CHCl_3$) -50.0.

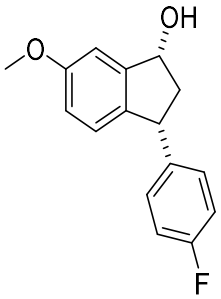
(1*R*,3*R*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-84

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-6′-Methoxy-3′-(2″,3″,4″-trimethoxyphenyl)-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**106** (0.28 g, 0.8 mmol) and potassium carbonate (0.31 g, 2.3 mmol), yielding a yellow oil (0.22 g, 89 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{30}$ (c 0.10, $CHCl_3$) -72.0.

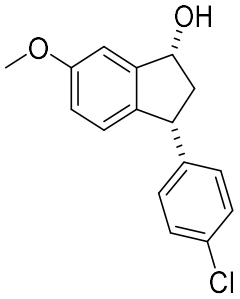
(1*R*,3*R*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-85

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-3′-(4″-Fluorophenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**107** (1.25 g, 4.2 mmol) and potassium carbonate (1.72 g, 12.5 mmol), yielding a white solid (0.84 g, 78 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.10, $CHCl_3$) -51.0.

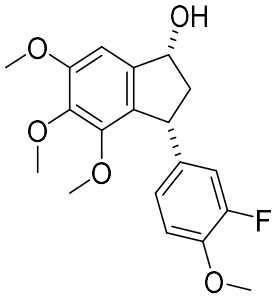
(1*R*,3*R*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-86

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-3′-(4″-Chlorophenyl)-6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**108** (0.59 g, 1.9 mmol) and potassium carbonate (0.77 g, 5.6 mmol), yielding a white solid (0.41 g, 81 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.10, $CHCl_3$) -36.5.

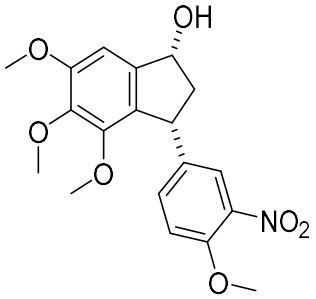
(1*R*,3*R*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*R*)-87

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′*R*,3′*R*)-3′-(3″-Fluoro-4″-methoxyphenyl)-4′,5′,6′-trimethoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**109** (0.33 g, 0.8 mmol) and potassium carbonate (0.35 g, 2.5 mmol), yielding a yellow oil (0.22 g, 74 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.10, $CHCl_3$) -44.5.

(1*R*,3*R*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol



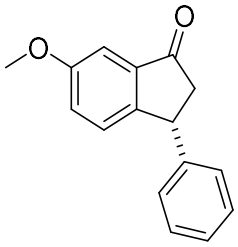
(1*R*,3*R*)-88

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.3**, using (1′R,3′*R*)-3′-(4″-Methoxy-3″-nitrophenyl)-4′,5′,6′-trimethoxy-2′,3′-dihydro-1′*H*-inden-1′-yl acetate, (1*R*,3*R*)-**110** (0.23 g, 0.5 mmol) and potassium carbonate (0.22 g, 1.6 mmol), yielding a yellow oil (0.17 g, 81 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{30}}$ (c 0.10, $CHCl_3$) -63.5.

5.2.4.4 Oxidation of Chiral Aryl Indan-1-ols

The following procedure was performed in accordance with previous literature.[525] To a solution of enantiomerically enriched 3-substituted 2,3-dihydro-1*H*-inden-1-ol (8.3 mmol) in dichloromethane (40 mL) was added manganese (IV) oxide (0.125 mol) at room temperature. The mixture was stirred for 18 hours, filtered through Celite® and concentrated *in vacuo*. The product was then purified as mentioned specifically in each example.

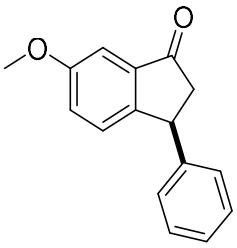
(*R*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one



(*R*)-59

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**80** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding an orange solid (81 mg, 82 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.6, $CHCl_3$) -51.7).

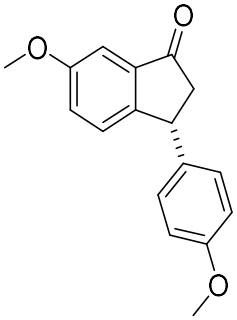
(*S*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one



(*S*)-59

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**80** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding an orange solid (83 mg, 84 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.6, $CHCl_3$) +55.4, (lit.[216] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.6, $CHCl_3$) +43.3)

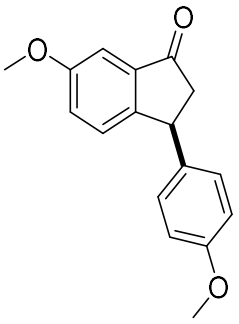
(*R*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*R*)-60

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**81** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding an orange oil (80 mg, 81 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.2, $CHCl_3$) -51.5).

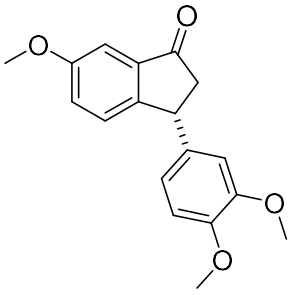
(*S*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*S*)-60

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-6-Methoxy-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**81** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding an orange oil (75 mg, 76 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +102.5).

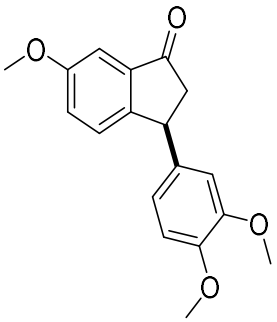
(*R*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



(*R*)-61

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**82** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a yellow solid (73 mg, 74 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c -0.2, $CHCl_3$) -62.5).

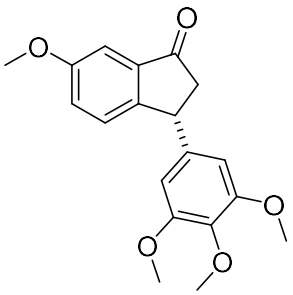
(*S*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



(*S*)-61

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-3-(3′,4′-Dimethoxyphenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**82** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a yellow solid (79 mg, 80 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) +98).

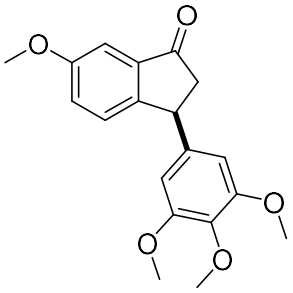
(*R*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*R*)-62

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**83** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a yellow oil (75 mg, 75 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.2, $CHCl_3$) -53.3).

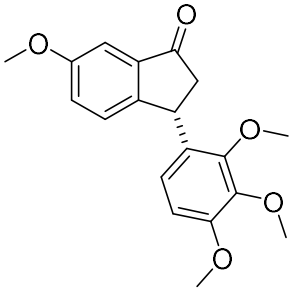
(*S*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*S*)-62

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-6-Methoxy-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**83** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a yellow oil (70 mg, 70 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +106.5).

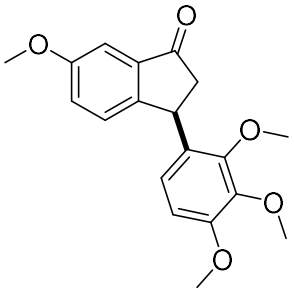
(*R*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*R*)-63

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**84** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a yellow oil (70 mg, 71 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.2, $CHCl_3$) -62.8).

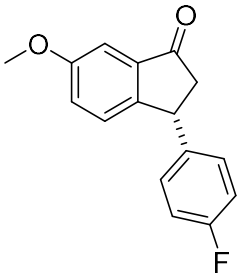
(*S*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-one



(*S*)-63

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-6-Methoxy-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**84** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a yellow oil (71 mg, 72 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.2, $CHCl_3$) +52.5).

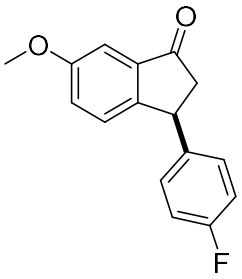
(*R*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



(*R*)-64

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**85** (100 mg, 0.04 mmol) and manganese dioxide (~0.50 g), yielding a white solid (80 mg, 81 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.2, $CHCl_3$) -76.0).

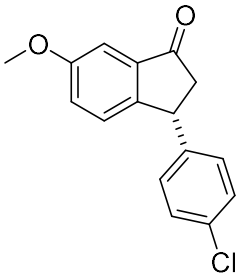
(*S*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



(*S*)-64

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-3-(4′-Fluorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**85** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding a white solid (83 mg, 84 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.2, $CHCl_3$) +72.8).

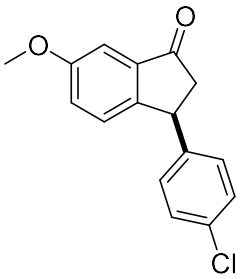
(*R*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



(*R*)-65

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**86** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding a white solid (83 mg, 84 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.2, $CHCl_3$) -61.0).

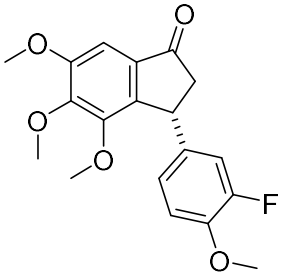
(*S*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one



(*S*)-65

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-3-(4′-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**86** (100 mg, 0.4 mmol) and manganese dioxide (~0.50 g), yielding a white solid (85 mg, 86 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) +121.5), (lit.[217] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ (c 0.5, $CHCl_3$) +52)

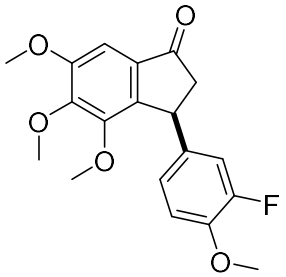
(*R*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one



(*R*)-66

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**87** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a off-white solid (90 mg, 89 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.2, $CHCl_3$) -59.0).

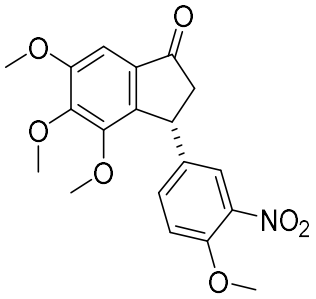
(*S*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one



(*S*)-66

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-3-(3′-Fluoro-4′-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**87** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding an off-white solid (86 mg, 86 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.2, $CHCl_3$) +58.0).

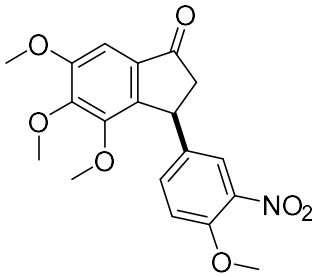
(*R*)-3-(3′-Nitro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one



(*R*)-67

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*R*,3*R*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**88** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a white solid (90 mg, 90 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.2, $CHCl_3$) -66.5).

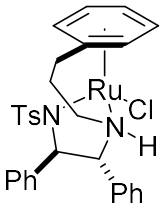
(*S*)-3-(3′-Nitro-4′-methoxyphenyl)-4,5,6-trimethoxy-3,4-dihydro-1*H*-inden-1-one



(*S*)-67

The aforementioned product was synthesised using the general method outlined in **Section 5.2.4.4**, using (1*S*,3*S*)-3-(4′-Methoxy-3′-nitrophenyl)-4,5,6-trimethoxy--2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**88** (100 mg, 0.3 mmol) and manganese dioxide (~0.50 g), yielding a white solid (89 mg, 89 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +133.5).

5.2.5 Kinetic Resolution – Asymmetric Transfer Hydrogenation



112

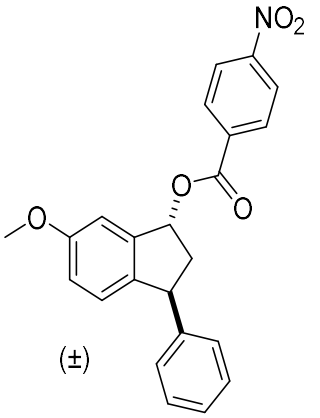
The (*R,R*)-TsDPEN-tethered Ru-Cl catalyst, **112**, was supplied by Martin Wills at the University of Warwick.

5.2.5.1 Asymmetric Hydrogen Transfer

The following procedure was performed in accordance with previous literature.[399] (*R*,*R*)-TsDPEN-tethered Ru-Cl catalyst, **112** (15. 6 mg, 0.03 mmol) was stirred in formic acid/triethylamine (5:2) azeotrope (5.0 mL) at 28 °C under nitrogen for 30 minutes. To this solution was added racemic *cis*-6-methoxy-3-phenylindan-1-one, **59**, (1.20 g, 5.0 mmol) and the solution was stirred for 12 hours under nitrogen. The reaction was concentrated *in vacuo* and the crude reaction mixture was analysed by both ^{1}H NMR and HPLC.

5.2.5.2 Epimerisation of *cis*-Inden-1-ol alcohol via a Mitsunobu Reaction and Ester Hydrolysis

(1*RS*,3*SR*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl 4-nitrobenzoate

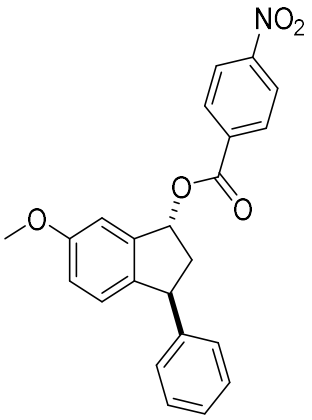


113

The following procedure was performed in accordance with previous literature.[406] To a solution of (1*SR*,3*SR*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, **80** (0.80 g, 3.3 mmol) in THF (30 mL) under nitrogen, was added 4-nitrobenzoic acid (2.20 g, 13.3 mmol) and triphenylphosphine (3.49 g, 13.3 mmol) under constant stirring. The reaction mixture was cooled to 0 °C and diisopropyl azodicarboxylate (2.62 mL, 13.3 mmol) was added dropwise at rate such that the reaction temperature was maintained below 10 °C. Once the reagent had been added the reaction mixture was stirred overnight at room temperature. Excess solvent and volatile components were then removed under reduced pressure. The resulting syrup was dissolved in ethyl acetate, washed twice with NaOH (2M, 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The reaction mixture was then suspended in diethyl ether and any white precipitate was filtered off. The remaining filtrate was then purified by flash column chromatography eluting with diethyl ether : petroleum ether (1:2), yielding a pale

yellow powder (1.00 g, 78 %); m.p. 151-152 °C; ν_{max}/cm^{-1} 2980 (m, C_{Ar}-H, stretch), 1707 (s, C=O, stretch), 1521, 1249 (s, NO_2, stretch), 1102 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.28 (2H, d, *J* 9, 2 x ArH-3), 8.22 (2H, d, *J* 9, 2 x ArH-2), 7.34 (2H, t, *J* 7.5, 2 x ArH-3″), 7.28-7.24 (1H, m, ArH-4″), 7.19-7.17 (2H, m, 2 x ArH-2″), 7.12 (1H, d, *J* 2.5, ArH-7′), 6.96 (1H, d, *J* 8.5, ArH-4′), 6.90 (1H, dd, *J* 8.5, 2.5, ArH-5′), 6.60 (1H, dd, *J* 6.5, 2, CH-1′), 4.65 (1H, t, *J* 7.6, CH-3′), 3.82 (3H, s, C_{Ar}-6′ OCH_3), 2.80 (1H, ddd, *J* 14.5, 7.5, 2, C*H*H-2′), 2.56 (1H, ddd, *J* 14.5, 8, 7, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 164.6 (C-1), 159.3 (C_{Ar}-6′), 150.5 (C_{Ar}-4), 144.2 (C_{Ar}-1″), 141.8 (C_{Ar}), 140.3 (C_{Ar}), 135.8 (C_{Ar}-1), 130.8 (2 x C_{Ar}-2), 128.7 & 127.9 (C_{Ar}-4″ & 2 x C_{Ar}-3″), 126.7 (2 x C_{Ar}-2″), 126.0 (C_{Ar}-4′), 123.5 (2 x C_{Ar}-3), 116.6 (C_{Ar}-5′), 110.5 (C_{Ar}-7′), 79.2 (C-1′), 55.5 (C_{Ar}-6′ OCH_3), 48.5 (C-3′), 43.7 (C-2′); m/z (MNa^+ $C_{23}H_{19}NO_5Na^+$ requires 412.1155) found 412.1159.

(1*R*,3*S*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl 4-nitrobenzoate

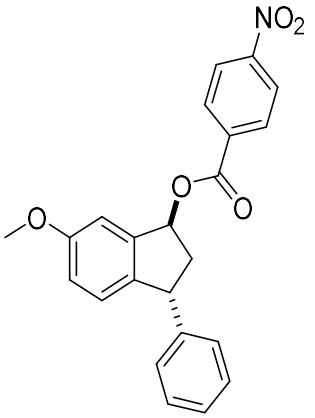


(1*R*,3*S*)-113

The following procedure was performed in accordance with previous literature,[406] using the same method for compound **113**. (1*S*,3*S*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, (1*S*,3*S*)-**80** (2.00 g, 8.3 mmol), 4-nitrobenzoic acid (5.56 g, 30 mmol)

triphenylphosphine (8.73 g, 30 mmol) and diisopropyl azodicarboxylate (6.55 mL, 30 mmol) were used. The title compound was formed as a pale yellow powder (2.39 g, 74 %); spectroscopic data similar to that of racemate. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) +51.5.

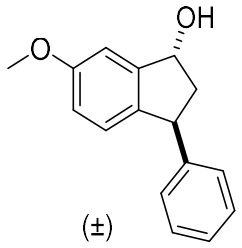
(1*S*,3*R*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl 4-nitrobenzoate



(1*S*,3*S*)-113

The following procedure was performed in accordance with previous literature,[406] using the same method for compound **113**. (1*R*,3*R*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-**80** (350 mg, 1.5 mmol), 4-nitrobenzoic acid (0.97 g, 5.8 mmol), triphenylphosphine (1.53 g, 5.8 mmol) and diisopropyl azodicarboxylate (1.15 mL, 5.6 mmol) were used. The title compound was formed as a pale yellow powder (414 mg, 71 %); spectroscopic data similar to that of racemate. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -40.0.

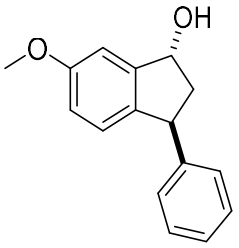
(1*RS*,3*SR*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol



114

To a solution of (1*RS*,3*SR*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl 4-nitrobenzoate, **113** (100 mg, 0.26 mmol) in methanol (20 mL) was added potassium carbonate (0.11 g, 0.77 mmol) portion-wise at room temperature. The reaction mixture was stirred at room temperature for 3 hours. The resulting mixture was then concentrated *in vacuo*. The crude product was dissolved in diethyl ether (40 mL) and washed with water (30 mL), brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by flash column chromatography eluting with ethyl acetate : petroleum ether (1 : 9), yielding a white solid (50 mg, 88 %); m.p. 124-125 °C; ν_{max}/cm^{-1} 3371 (br., O-H, stretch), 2919 (m, C_{Ar}-H, stretch), 1270 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 7.33-7.17 (3H, m, ArH-4′ & 2 x ArH-3′), 7.14-7.10 (2H, m, 2 x ArH-2′), 7.01 (1H, d, *J* 2.5, ArH-7), 6.95 (1H, d, *J* 8.5, ArH-4), 6.84 (1H, dd, *J* 8.5, 2.5, ArH-5), 5.35 (1H, dd, *J* 6.5, 3.5, CH-1), 4.56 (1H, t, *J* 7, CH-3), 3.83 (3H, s, C_{Ar}-6 OCH_3), 2.55 (1H, ddd, *J* 13.5, 8, 3.5, C*H*H-2), 2.41 (1H, dt, *J* 13.5, 6.5, CH*H*-2), 1.73 (1H, br. s, C-1 OH); δ_C (100 MHz, $CDCl_3$) 159.3 (C_{Ar}-6), 146.2 (C_{Ar}), 145.0 (C_{Ar}-1′), 138.6 (C_{Ar}), 128.5, 127.7, 126.3 ($C_{Ar}H$), 126.2 ($C_{Ar}H$-4), 115.6 ($C_{Ar}H$-5), 108.8 ($C_{Ar}H$-7), 75.4 (CH-1), 55.4 (C_{Ar}-6 O*C*H_3), 48.0 (CH-3), 46.8 (CH_2-2); m/z (MNa^+ $C_{16}H_{16}O_2Na^+$ requires 263.1043) found 263.1048

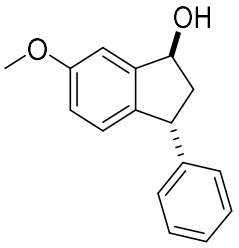
(1*R*,3*S*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol



(1*R*,3*S*)-114

The method was the same used for compound **114**, using (1*S*,3*R*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl 4-nitrobenzoate, (1*R*,3*S*)-**113** (140 mg, 0.4 mmol) and potassium carbonate (0.15 g, 1.1 mmol) The residue was then purified by flash column chromatography eluting with ethyl acetate : petroleum ether (1 : 9), yielding a white solid (72 mg, 84 %); spectroscopic data similar to that of racemate. $[\alpha]_D^{27}$ (c 0.2, $CHCl_3$) -14.0. enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 211 nm, (1*S*,3*R*)-isomer 21.60 min., (1*R*,3*S*)-isomer 25.38 min.).

(1*S*,3*R*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol



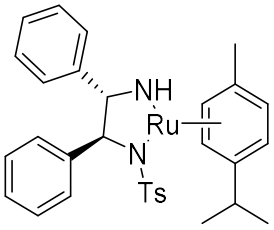
(1*S*,3*R*)-114

The method was the same used for compound **114**, using (1*S*,3*R*)-6′-methoxy-3′-phenyl-2′,3′-dihydro-1′*H*-inden-1′-yl 4-nitrobenzoate, (1*S*,3*R*)-**113** (50 mg, 0.1 mmol) and potassium carbonate (0.05 g, 0.4 mmol) The residue was then purified by flash column chromatography eluting with ethyl acetate:petroleum ether (1:9),

yielding a white solid (24.7 mg, 80 %); spectroscopic data similar to that of racemate. $[\alpha]_D^{27}$ (c 0.2, $CHCl_3$) +13.3. enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 211 nm, (1*S*,3*R*)-isomer 21.60 min., (1*R*,3*S*)-isomer 25.38 min.).

5.2.6 Kinetic Resolution – Oxidative Kinetic Resolution

Preparation of Ruthenium Complex: (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN)



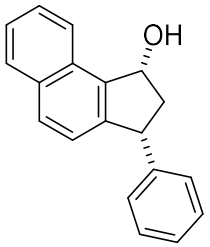
115

The following procedure was performed in accordance with previous literature.[526] To a mixture of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (20 mg, 0.03 mmol), (1*S*,2*S*)-(+)-TsDPEN (24 mg, 0.07 mmol) in dry dichloromethane (2 mL) was added potassium hydroxide (26 mg, 0.46 mmol). The reaction mixture was stirred at room temperature for 5 minutes, and then water (2 mL) was added to the reaction mixture changing the solution from orange to a deep purple. The purple organic layer was washed with 5 mL of water, dried with calcium hydride and concentrated *in vacuo*, yielding a deep purple complex (14.5 mg, 72 %); m.p. 79-80 °C (decomp.), (lit.[527] 80 °C (decomp.)); spectroscopic and observational data consistent with literature.[526,527]

5.2.6.1 Asymmetric Ruthenium Oxidation

To a mixture of substituted racemic *cis*-indan-1-ol (2.0 mmol) in dry acetone (20 mL), was added (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), and the solution was stirred for 24-48 hours under nitrogen, monitored by ^{1}H NMR and HPLC. The reaction was concentrated *in vacuo* at the desired conversion (~50 %), and the products were separated by silica column chromatography as mentioned specifically for each compound.

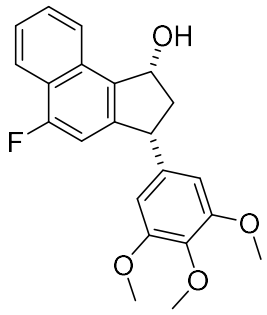
(1R,3R)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-89

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **89** (0.75 g, 2.9 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (9 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**89** and (*S*)-**68** in a ratio of 51 : 49. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a white solid (0.35 g, 46 %), as a % of racemic starting material, in 80 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -178.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 229 nm, (*S*)-isomer 19.96 min., (*R*)-isomer 27.96 min.).

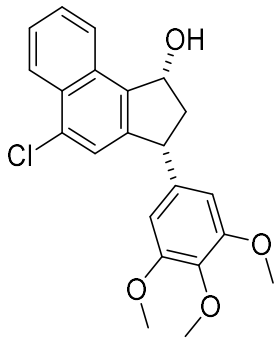
(1*R*,3*R*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-91

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-ol, **91** (0.90 g, 2.4 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (8 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**91** and (*S*)-**70** in a ratio of 48 : 52. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.41 g, 46 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -173.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 230 nm, (*S*)-isomer 26.84 min., (*R*)-isomer 30.32 min.).

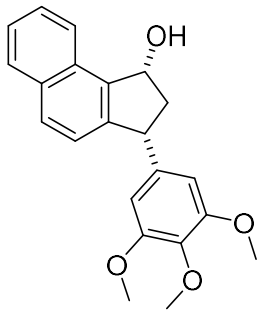
(1*R*,3*R*)-5-Chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-92

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **92** (0.65 g, 1.7 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (5 mg, 8 μmol), to give compound (1*R*,3*R*)-**92** and (*S*)-**71** in a ratio of 52 : 48. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a white solid (0.31 g, 48 %), as a % of racemic starting material, in 95 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -154.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 231 nm, (*R*)-isomer 27.20 min., (*S*)-isomer 28.93 min.).

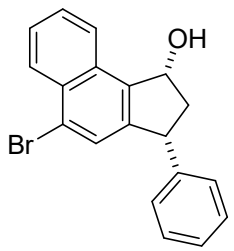
(1*R*,3*R*)-3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-90

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **90** (0.20 g, 0.6 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (2 mg, 3 μmol), to give compound (1*R*,3*R*)-**90** and (*S*)-**69** in a ratio of 49 : 51. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a beige solid (90 mg, 45 %), as a % of racemic starting material, in 97 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -182.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 228 nm, (*R*)-isomer 23.33 min., (*S*)-isomer 28.32 min.).

(1*R*,3*R*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol

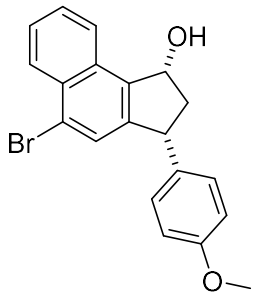


(1*R*,3*R*)-93

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-phenyl-2,3-dihydro-1*H*-

cyclopenta[*a*]naphthalen-1-ol, **93** (0.69 g, 2.0 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (6 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**93** and (*S*)-**72**. The reaction was first taken to 35 % conversion and separated, followed by further resolution to 57 % conversion. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a white solid (0.28 g, 41 %), as a % of racemic starting material, in 87 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -70.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 234 nm, (*R*)-isomer 8.52 min., (*S*)-isomer 9.84 min.).

(1*R*,3*R*)-5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol

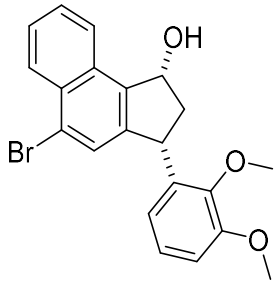


(1*R*,3*R*)-94

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **94** (0.36 g, 0.1 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (3 mg, 5 μmol), to give compound (1*R*,3*R*)-**94** and (*S*)-**73** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off-white solid

(0.17 g, 48 %), as a % of racemic starting material, in 65 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.1, $CHCl_3$) -121.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 231 nm, (*R*)-isomer 12.11 min., (*S*)-isomer 14.85 min.).

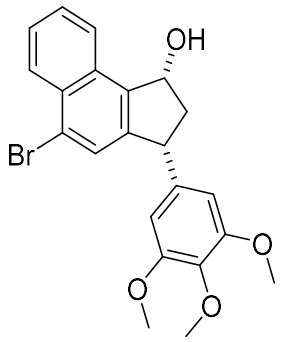
(1*R*,*3R*)-5-Bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-95

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **95** (1.00 g, 2.5 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (8 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**95** and (*S*)-**74** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an off white solid (0.48 g, 48 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$(c 0.1, $CHCl_3$) -124.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 232 nm, (*R*)-isomer 10.16 min., (*S*)-isomer 12.32 min.).

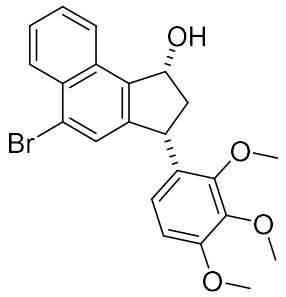
(1*R*,3*R*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-97

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphtalen-1-ol, **97** (0.60 g, 1.4 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (4 mg, 7 μmol), to give compound (1*R*,3*R*)-**97**and (*S*)-**76** in a ratio of 48 : 52. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.28 g, 46 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -104.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 231 nm, (*R*)-isomer 30.80 min., (*S*)-isomer 34.60 min.).

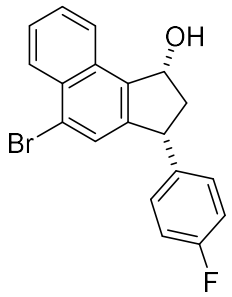
(1*R*,3*R*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-98

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **98** (0.46 g, 1.1 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (3 mg, 5 μmol), to give compound (1*R*,3*R*)-**98** and (*S*)-**77** in a ratio of 45 : 55. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield an orange oil (0.18 g, 39 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) -99.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 231 nm, (*S*)-isomer 9.80 min., (*R*)-isomer 12.07 min.).

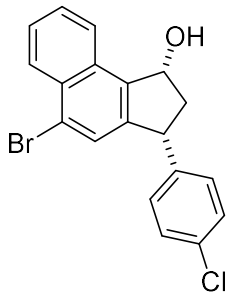
(1*R*,3*R*)-5-Bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



(1*R*,3*R*)-99

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **99** (0.40 g, 1.1 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (3 mg, 6 μmol), to give compound (1*R*,3*R*)-**99** and (*S*)-**78**. The reaction was first taken to 43 % conversion and separated, followed by further resolution to 56 % conversion. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.16 g, 41 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.1, $CHCl_3$) -102.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 234 nm, (*R*)-isomer 9.75 min., (*S*)-isomer 11.23 min.).

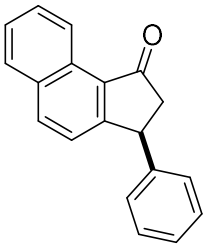
(1*R*,3*R*)-5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol



100

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol**, 100** (0.50 g, 1.3 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (4 mg, 7 μmol), to give compound (1*R*,3*R*)-**100** and (*S*)-**79** in a ratio of 52 : 48. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.21 g, 42 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) -131.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 235 nm, (*R*)-isomer 10.17 min., (*S*)-isomer 11.75 min.).

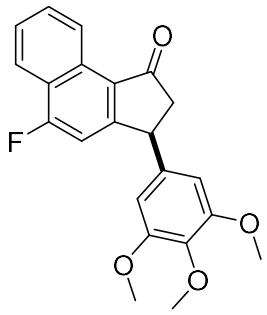
(*S*)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-68

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **89** (0.75 g, 2.9 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (9 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**89** and (*S*)-**68** in a ratio of 51 : 49. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a orange solid (0.36 g, 49 %), as a % of racemic starting material, in 76 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +286.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 218 nm, (*S*)-isomer 10.99 min., (*R*)-isomer 16.97 min.).

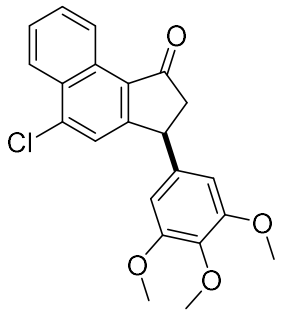
(*S*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one



(*S*)-70

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-ol, **91** (0.90 g, 2.4 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (8 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**91** and (*S*)-**70** in a ratio of 48 : 52. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.42 g, 47 %), as a % of racemic starting material, in 98 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{29}}$ (c 0.1, $CHCl_3$) +232.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 236 nm, (*S*)-isomer 26.77 min., (*R*)-isomer 36.88 min.).

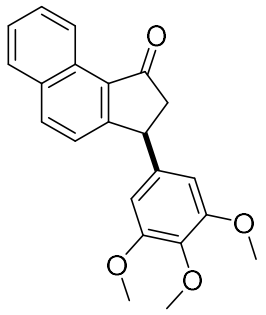
(*S*)-5-Chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-71

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **92** (0.65 g, 1.7 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (5 mg, 8 μmol), to give compound (1*R*,3*R*)-**92** and (*S*)-**71** in a ratio of 52 : 48. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.31 g, 48 %), as a % of racemic starting material, in 96 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) +146.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 243 nm, (*S*)-isomer 26.09 min., (*R*)-isomer 36.09 min.).

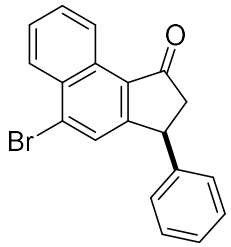
(*S*)-3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-69

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **90** (0.20 g, 0.6 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (2 mg, 3 μmol), to give compound (1*R*,3*R*)-**90** and (*S*)-**69** in a ratio of 49 : 51. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (72 mg, 49 %), as a % of racemic starting material, in 91 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +165.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 214 nm, (*S*)-isomer 17.93 min., (*R*)-isomer 20.55 min.).

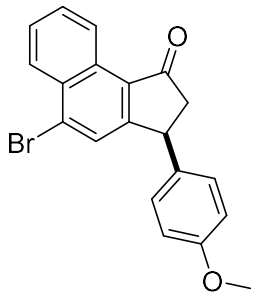
(*S*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-72

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **93** (0.69 g, 2.0 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (6 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**93** and (*S*)-**72**. The reaction was first taken to 35 % conversion and separated, followed by further resolution to 57 % conversion. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.22 g, 32 %), as a % of racemic starting material, in >99 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +114.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 242 nm, (*S*)-isomer 8.48 min., (*R*)-isomer 13.03 min.).

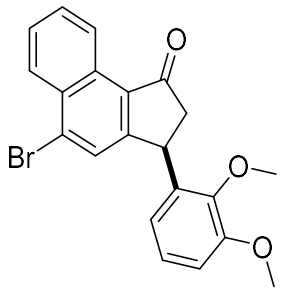
(*S*)-5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one



(*S*)-73

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **94** (0.36 g, 0.1 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (3 mg, 5 μmol), to give compound (1*R*,3*R*)-**94** and (*S*)-**73** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.17 g, 48 %), as a % of racemic starting material, in 96 % e.e.; spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) +91.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 242 nm, (*R*)-isomer 11.24 min., (*S*)-isomer 12.39 min.).

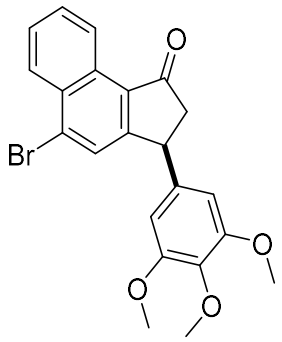
(*S*)-5-Bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-74

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **95** (1.00 g, 2.5 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (8 mg, 0.01 mmol), to give compound (1*R*,3*R*)-**95** and (*S*)-**74** in a ratio of 50 : 50. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a beige solid (0.47 g, 47 %), as a % of racemic starting material, in 96 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +103.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak AD-H column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 240 nm, (*S*)-isomer 11.51 min., (*R*)-isomer 13.37 min.).

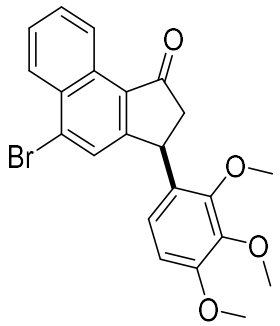
(*S*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]napthalen-1-one



(*S*)-76

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphtalen-1-ol, **97** (0.60 g, 1.4 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (4 mg, 7 μmol), to give compound (1*R*,3*R*)-**97** and (*S*)-**76** in a ratio of 48 : 52. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.29 g, 49 %), as a % of racemic starting material, in 96 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{29}}$ (c 0.1, $CHCl_3$) +109.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 10 : 90 , 1 mL/min., 243 nm, (*S*)-isomer 14.19 min., (*R*)-isomer 17.68 min.).

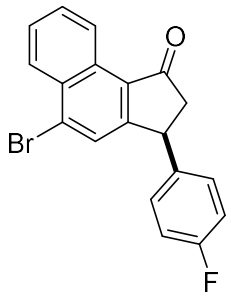
(*S*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-77

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **98** (0.46 g, 1.1 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (3 mg, 5 μmol), to give compound (1*R*,3*R*)-**98** and (*S*)-**77** in a ratio of 45 : 55. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a orange oil (0.23 g, 51 %), as a % of racemic starting material, in 93 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +138.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 241 nm, (*R*)-isomer 10.72 min., (*S*)-isomer 12.51 min.).

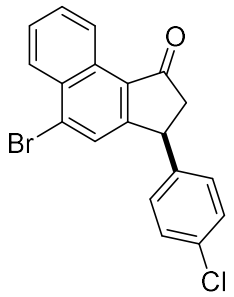
(*S*)-5-Bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*S*)-78

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, **99** (0.40 g, 1.1 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (3 mg, 6 μmol), to give compound (1*R*,3*R*)-**99** and (*S*)-**78**. The reaction was first taken to 43 % conversion and separated, followed by further resolution to 56 % conversion. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.13 g, 35 %), as a % of racemic starting material, in 88 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +97.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 242 nm, (*R*)-isomer 8.44 min., (*S*)-isomer 9.25 min.).

(*S*)-5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



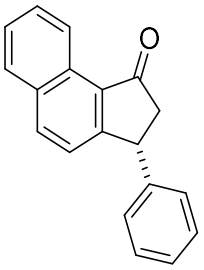
(*S*)-79

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.1**, using (1*RS*,3*RS*)-5-bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol**, 100** (0.50 g, 1.3 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), **115** (4 mg, 7 μmol), to give compound (1*R*,3*R*)-**100** and (*S*)-**79** in a ratio of 52 : 48. The title compound was isolated by silica column chromatography, eluting with dichloromethane : petroleum ether (3 : 1), to yield a yellow solid (0.20 g, 40 %), as a % of racemic starting material, in 91 % e.e.; spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ (c 0.1, $CHCl_3$) +88.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol : hexane = 5 : 95 , 1 mL/min., 242 nm, (*R*)-isomer 8.52 min., (*S*)-isomer 9.17 min.).

5.2.6.2 Oxidation of Chiral Aryl Indan-1-ols

The following procedure was performed in accordance with previous literature.[525] To a solution of enantiomerically enriched 3-substituted 2,3-dihydro-1*H*-inden-1-ol (8.3 mmol) in dichloromethane (40 mL) was added manganese (IV) oxide (0.125 mol) at room temperature. The mixture was stirred for 18 hours, filtered through Celite® and concentrated *in vacuo*. The product was then used without further purification, unless mentioned specifically in each example.

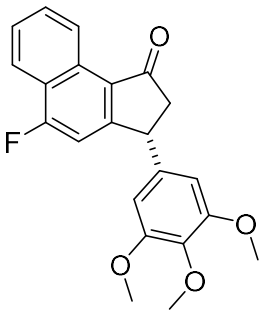
(*R*)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-68

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**89** (200 mg, 0.8 mmol) and manganese dioxide (~1.00 g), yielding a orange solid (144 mg, 72 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -301.5.

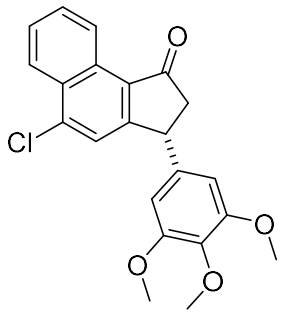
(*R*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one



(*R*)-70

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**91** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (182 mg, 91 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -234.5.

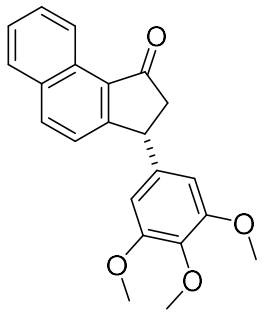
(*R*)-5-Chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one



(*R*)-71

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Chloro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**92** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (172 mg, 86 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{29}}$ (c 0.1, $CHCl_3$) -145.0.

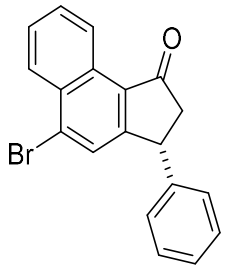
(*R*)-3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-69

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-3-(3′,4′,5′-Trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**90** (200 mg, 0.6 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (178 mg, 89 %); spectroscopic data similar to that of racemate; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{29}}$ (c 0.1, $CHCl_3$) -176.5.

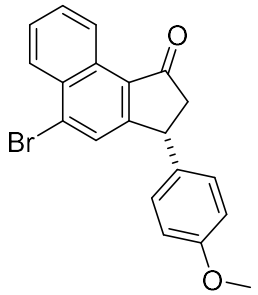
(*R*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-72

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**93** (200 mg, 0.6 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (154 mg, 77 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -100.5.

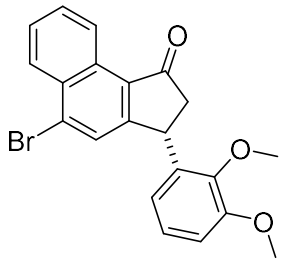
(*R*)-5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one



(*R*)-73

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**94** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (162 mg, 81 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -90.5.

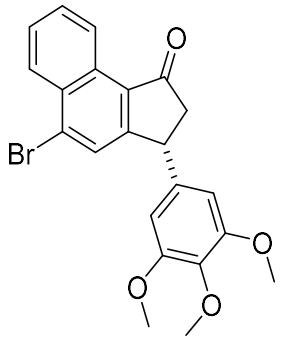
(*R*)-5-Bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-74

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-(2′,3′-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**95** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding a beige solid (162 mg, 81 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -106.0.

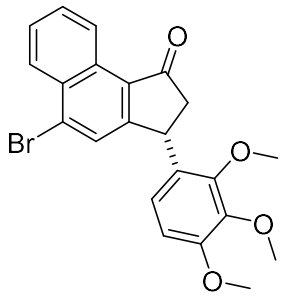
(*R*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]napthalen-1-one



(*R*)-76

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**97** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (174 mg, 87 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -112.5.

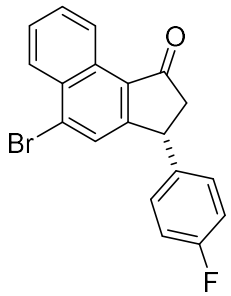
(*R*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-77

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**98** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding an orange oil (138 mg, 69 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -147.0.

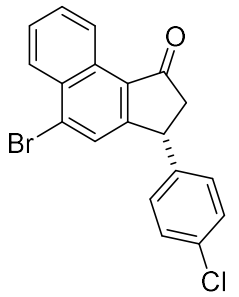
(*R*)-5-Bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-78

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**99** (200 mg, 0.6 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (160 mg, 80 %); spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -109.5.

(*R*)-5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one



(*R*)-79

The aforementioned product was synthesised using the general method outlined in **Section 5.2.6.2**, using (1*R*,3*R*)-5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol, (1*R*,3*R*)-**100** (200 mg, 0.5 mmol) and manganese dioxide (~1.00 g), yielding a yellow solid (158 mg, 79 %); Spectroscopic data similar to that of racemate; $[\alpha]_D^{29}$ (c 0.1, $CHCl_3$) -95.5.

Enzymatic Acylation - See Table 18

R3	R1/R2	Conversion (%) / 100.	Alcohol e.e.% / 100	Acetate e.e.% / 100	>50 % Conv.	<50 % conv	E Value	SM (a) / P (b)
H	H	0.50	0.99	0.99	1057.012101		>100	a
4-OCH3	H	0.50	0.99	0.99	1057.012101		>100	a
3,4-OCH3	H	0.47	0.77	0.99	32.9357779		33	a
3,4,5-OCH3	H	0.50	0.99	0.99	1057.012101		>100	a
2,3,4-OCH3	H	0.45	0.81	0.99	500.7739132		>100	a
4-F OCH3	H	0.49	0.94	0.99	327.1927024		>100	a
4-Cl	H	0.50	0.99	0.99	1057.012101		>100	a
3-F, 4-OCH3	OCH3	0.49	0.96	0.99	9728.604705		>100	a
3-NO2, 4-OCH3	OCH3	0.50	0.98	0.99	458.2105766		>100	a

Ruthenium Oxidation - See Table 22

R Group	X Group	Conversion	Alcohol e.e.% /	Ketone e.e.% / 100	>50 % Conv.	<50 % conv	S Value	SM (a) / P (b)
H	Br	0.35	0.33	0.99		340.0816558	>100	b
4-OCH3	Br	0.5	0.95	0.96		193.6385527	>100	b
2,3-OCH3	Br	0.5	0.99	0.96		193.6385527	>100	b
3,4,5-OCH3	Br	0.52	0.99	0.96	116.4872558		>100	a
2,3,4-OCH3	Br	0.55	0.99	0.93	48.95830564		49	a
4-F	Br	0.43	0.6	0.95	16.04955776		16	a
4-Cl	Br	0.48	0.99	0.91		56.30564976	56	b
H	H	0.49	0.8	0.76		15.85330788	16	b
3,4,5-OCH3	H	0.51	0.97	0.91	119.4888024	77.75615689	78	b
3,4,5-OCH3	F	0.52	0.99	0.98	116.4872558		>100	a
3,4,5-OCH3	Cl	0.48	0.95	0.96		145.81294	>100	b

Ruthenium Oxidation - (6-Methoxy-3-Aryl Indan-1-ols) - See Table 21

R Group		Conversion	Ketone e.e.% / 100			<50 % conv	S Value	SM (a) / P (b)
H		0.37	0.78			12.65775523	13	b
4-OCH3		0.07	0.86			14.16401492	14	b
3,4-OCH3		0.33	0.7			7.896937143	8	b
4-F		0.38	0.99			370.7167597	>100	b
4-Cl		0.46	0.78			16.00972931	16	b

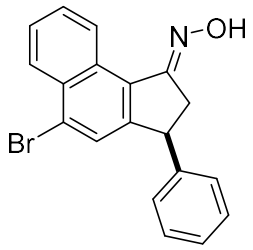
5.3 Experimental for Chapter 3

The general procedure for this section can be found in **Section 5.1.1**.

5.3.1 Formation of Indan-1-one Oximes

The following procedure was performed in accordance with previous literature.[437] To a solution of the appropriate indan-1-one (0.5 mmol), in pyridine (10 mL) was added hydroxylamine hydrochloride (1.0 mmol), and the reaction was stirred at 80 °C for 12 hours. The reaction was cooled to room temperature, and 1M HCl (20 mL) was added. The product was extracted with dichloromethane (2 x 15 mL), and the combined organic layer was washed with 1M HCl (4 x 20 mL), water (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The product, if solid, was then recrystallized in methanol, or used without futher purification if not.

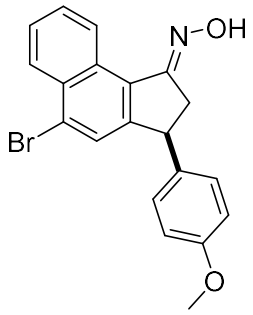
(*S*,*E*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-116

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*S*)-**72**, (0.20 g, 0.6 mmol) and hydroxylamine hydrochloride (82 mg, 1.2 mmol) and the product was used without further purification. The title compound was formed as an off-white solid (184 mg, 88 %); $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +162.5; m.p. 148-149 °C; ν_{max}/cm^{-1} 3412 (s, O-H, stretch), 1506 (m, C=N, stretch); δ_H (500 MHz, $CDCl_3$) 9.07 (1H, dd, *J* 8, 1, ArH-9), 8.30 (1H, dd, *J* 8.5, 1, ArH-6), 7.68 (1H, ddd, *J* 8.5, 7, 1.5, ArH-8), 7.64 (1H, ddd, *J* 8, 7, 1.5, ArH-7), 7.51 (1H, s, ArH-4), 7.32 (2H, t, *J* 7, 2 x ArH-3′), 7.27-7.24 (2H, m, ArH-4′ & C-1 NOH), 7.16-7.13 (1H, m, 2 x ArH-2′), 4.56 (1H, dd, *J* 8.5, 4, CH-3), 3.69 (1H, dd, *J* 19, 9, C*H*H-2), 3.08 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 164.9 (C-1), 151.7 (C_{Ar}), 143.9 (C_{Ar}-1′), 131.5 (C_{Ar}), 130.5 (C_{Ar}), 129.5 (C_{Ar}), 129.0 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 126.7 (C_{Ar}), 47.3 (CH-3), 37.0 (CH_2-2); m/z (MH^+ $C_{19}H_{14}{}^{79}BrNOH^+$ requires 352.0332) found 352.0333, (MH^+ $C_{19}H_{14}{}^{81}BrNOH^+$ requires 354.0313) found 354.0314.

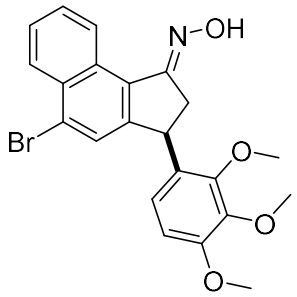
(*S*,*E*)-5-Bromo-3-(4′-methoxyphenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-117

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one, (*S*)-**73**, (0.20 g, 0.5 mmol) and hydroxylamine hydrochloride (76 mg, 1.1 mmol) and the product was used without further purification. The title compound was formed as an off-white solid (173 mg, 83 %); m.p. 171-172 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.1, $CHCl_3$) +183.5; ν_{max}/cm^{-1} 3439 (m, O-H, stretch), 2935 (w, C_{Ar}-H, stretch), 1587 (s, C=N, stretch), 1280 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.09 (1H, d, *J* 8, ArH-9), 8.32 (1H, d, *J* 9, ArH-6), 7.72-7.68 (1H, m, ArH-8), 7.68-7.64 (1H, m, ArH-7), 7.52 (1H, s, ArH-4), 7.26 (1H, s, C-1 NOH), 7.09 (2H, d, *J* 9, 2 x ArH-3′), 6.88 (2H, d, *J* 9, 2 x ArH-2′), 4.54 (1H, dd, *J* 8.5, 4, CH-3), 3.82 (3H, s, C_{Ar}-4′ OCH_3), 3.69 (1H, dd, *J* 19, 8.5, C*H*H-2), 3.05 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 165.0 (C-1), 158.6 (C_{Ar}-4′), 152.0 (C_{Ar}), 136.0 (C_{Ar}), 131.5 (C_{Ar}), 130.3 (C_{Ar}), 129.5 (C_{Ar}), 128.8 (2 x C_{Ar}H-3″), 128.6 (C_{Ar}H), 127.8 (C_{Ar}H), 127.8 (C_{Ar}H), 127.4 (C_{Ar}H), 126.7 (C_{Ar}H), 126.6 (C_{Ar}), 114.3 (2 x C_{Ar}H-2″), 55.3 (C_{Ar}-4′ O*C*H_3), 46.5 (CH-3), 37.2 (CH_2-2); m/z (MH^+ $C_{20}H_{16}{}^{79}BrNO_2$ requires 382.0437) found 382.0438, (MH^+ $C_{20}H_{16}{}^{81}BrNO_2$ requires 384.0419) found 384.0418.

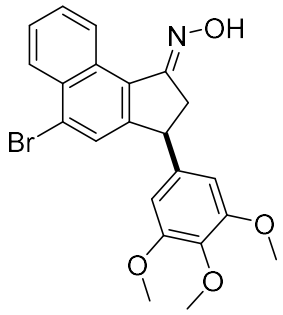
(*S*,*E*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-118

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*S*)-**77**, (0.20 g, 0.5 mmol) and hydroxylamine hydrochloride (65 mg, 0.9 mmol) and the product was used without further purification. The title compound was formed as a pale yellow solid (164 mg, 79 %); $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +117; m.p. 111-112 °C; ν_{max}/cm^{-1} 3422 (m, O-H, stretch), 2935 (m, C_{Ar}-H, stretch), 1494 (s, C=N, stretch), 1290 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.11-9.08 (1H, m, ArH-9), 8.34-8.30 (1H, m, ArH-6), 7.70 (1H, ddd, *J* 8.5, 7, 1.5, ArH-8), 7.65 (1H, ddd, *J* 8, 7, 1.5, ArH-7), 7.57 (1H, s, ArH-4), 7.22 (1H, s, C-1 NOH), 6.63-6.59 (2H, m, ArH-5″ & ArH-6″), 4.84 (1H, dd, *J* 8.5, 3.5, CH-3), 3.92 (1H, s, C_{Ar}-2′ OCH_3), 3.86 (C_{Ar}-3′ OCH_3), 3.79 (C_{Ar}-4′ OCH_3), 3.65 (1H, dd, *J* 18.5, 8.5, C*H*H-2), 3.05 (1H, dd, *J* 18.5, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 165.4 (C-1), 152.8 (C_{Ar}), 152.0 (C_{Ar}), 151.9 (C_{Ar}), 142.3 (C_{Ar}), 131.4 (C_{Ar}), 130.6 (C_{Ar}), 129.7 (C_{Ar}), 128.5 (C_{Ar}H), 127.8 (C_{Ar}H), 127.8 (C_{Ar}H), 127.3 (C_{Ar}H), 126.6 (C_{Ar}H), 126.4 (C_{Ar}), 122.8 (C_{Ar}H), 107 4 (C_{Ar}H), 61.1 (C_{Ar}-4′ O*C*H_3), 60.8 (C_{Ar}-2′ O*C*H_3), 56.0 (C_{Ar}-3′ O*C*H_3), 41.3 (CH-3), 36.5 (CH_2-2); m/z (MNa^+ $C_{22}H_{20}{}^{79}BrNO_4$ requires 464.0468) found 464.0462, (MNa^+ $C_{22}H_{20}{}^{81}BrNO_4$ requires 466.0450) found 466.0444.

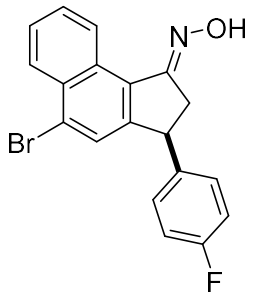
(*S*,*E*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-119

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Bromo-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]napthalen-1-one, (*S*)-**76**, (0.20 g, 0.5 mmol) and hydroxylamine hydrochloride (65 mg, 0.9 mmol) and the product was used without further purification. The title compound was formed as an off-white solid (174 mg, 84 %); $[\alpha]_D^{28}$ (c 0.02, $CHCl_3$) +267.5; m.p. 176-177 °C; ν_{max}/cm^{-1} 3381 (m, O-H, stretch), 1589 (s, C=N, stretch), 1276 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.10 (1H, dd, *J* 8, 1, ArH-9), 8.34 (1H, dd, *J* 8, 1, ArH-6), 7.71 (1H, ddd, *J* 8.5, 6, 1.5, ArH-8), 7.68 (1H, ddd, *J* 8, 7, 1.5, ArH-7), 7.57 (1H, s, ArH-4), 7.32 (1H, s, C-1 NOH), 6.36 (2H, s, 2 x ArH-2′), 4.51 (1H, dd, *J* 8.5, 4, CH-3), 3.87 (3H, s, C_{Ar}-4′ OCH_3), 3.82 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.72 (1H, dd, *J* 19, 8.5, C*H*H-2), 3.08 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 164.8 (C-1), 153.6 (2 x C_{Ar}-3′), 151.4 (C_{Ar}), 139.5 (C_{Ar}-4′), 137.0 (C_{Ar}), 131.6 (C_{Ar}), 130.4 (C_{Ar}), 139.5 (C_{Ar}), 128.7 (C_{Ar}H), 127.9 (C_{Ar}H), 127.8 (C_{Ar}H), 127.6 (C_{Ar}H), 126.7 (C_{Ar}H), 126.7 (C_{Ar}), 104.7 (2 x C_{Ar}-2′), 60.9 (C_{Ar}-4′ O*C*H_3), 56.2 (2 x C_{Ar}-3′ O*C*H_3), 47.7 (CH-3), 37.0 (CH_2-2); m/z (MH^+ $C_{22}H_{20}{}^{79}BrNO_4H^+$ requires 442.0648) found 442.0651, (MH^+ $C_{22}H_{20}{}^{81}BrNO_4H^+$ requires 444.0631) found 444.0634

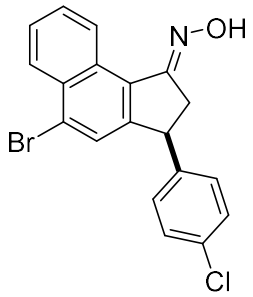
(*S*,*E*)-5-Bromo-3-(4′-fluorophenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-120

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*S*)-**78**, (0.20 g, 0.6 mmol) and hydroxylamine hydrochloride (78 mg, 1.1 mmol) and the product was used without further purification. The title compound was formed as an off-white solid (188 mg, 90 %); $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +148; m.p. 150-151 °C; ν_{max}/cm^{-1} 3413 (s, O-H, stretch), 1506 (s, C=N, stretch); δ_H (500 MHz, $CDCl_3$) 9.09 (1H, dd, *J* 8, 1.5, ArH-9), 8.32 (1H, dd, *J* 8.5, 1, ArH-6), 7.71 (1H, ddd, *J* 8.5, 7, 1.5, ArH-8), 7.67 (1H, ddd, *J* 8, 7, 1.5, ArH-7), 7.50 (1H, s, ArH-4), 7.31 (1H, s, C-1 NOH), 7.13 (2H, dd, *J* 8.5, 5.5, 2 x ArH-2′), 7.03 (2H, t, *J* 8.5, 2 x ArH-3′), 4.58 (1H, dd, *J* 8.5, 4, CH-3), 3.71 (1H, dd, *J* 19, 8.5, C*H*H-2), 3.05 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 164.6 (C-1), 161.9 (d, $^1J_{CF}$ 245, C_{Ar}F-4′), 151.4 (C_{Ar}), 139.7 (C_{Ar}), 131.5 (C_{Ar}), 130.5 (C_{Ar}), 129.5 (C_{Ar}), 129.3 (d, ^3J 8, 2 x C_{Ar}-2′), 128.7 (C_{Ar}H), 127.8 (C_{Ar}H), 127.7 (C_{Ar}H), 127.6 (C_{Ar}H), 126.8 (C_{Ar}), 126.7 (C_{Ar}H), 115.8 (d, $^2J_{CF}$ 21, 2 x C_{Ar}-3′), 46.5 (CH-3), 37.1 (CH_2-2); m/z (MH^+ $C_{19}H_{13}{}^{79}BrFNOH^+$ requires 370.0237) found 370.0236, (MH^+ $C_{19}H_{13}{}^{81}BrFNOH^+$ requires 372.0219) found 372.0217.

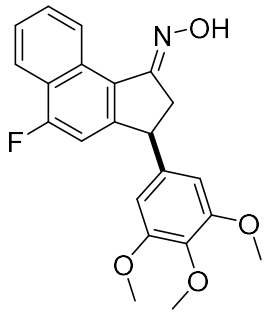
(*S*,*E*)-5-Bromo-3-(4′-chlorophenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-121

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*S*)-**79**, (0.20 g, 0.5 mmol) and hydroxylamine hydrochloride (75 mg, 1.1 mmol) and the product was used without further purification. The title compound was formed as an off-white solid (185 mg, 89 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.1, $CHCl_3$) +212; m.p. 146-147 °C; ν_{max}/cm^{-1} 3406 (m, O-H, stretch), 1561 (m, C=N, stretch); δ_H (500 MHz, $CDCl_3$) 9.08 (1H, dd, *J* 8, 1, ArH-9), 8.32 (1H, dd, *J* 8, 1.5, ArH-6), 7.72-7.67 (2H, m, ArH-7 & ArH-8), 7.52-7.47 (2H, m, C-1 NOH & ArH-4), 7.31 (2H, d, *J* 8.5, 2 x ArH-3′), 7.10 (2H, d, *J* 8.5, 2 x ArH-2′), 4.55 (1H, dd, *J* 8.5, 4, CH-3), 3.70 (1H, dd, *J* 19, 8.5, C*H*H-2), 3.05 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 164.5 (C_{Ar}-1), 151.1 (C_{Ar}), 142.5 (C_{Ar}), 132.9 (C_{Ar}), 131.6 (C_{Ar}), 130.5 (C_{Ar}), 129.5 (C_{Ar}), 129.1 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 12.7 9 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 126.8 (C_{Ar}), 126.7 ($C_{Ar}H$), 46.6 (CH-3), 37.0 (CH_2-2), (Missing one C_{Ar}); m/z (MH^+ $C_{19}H_{13}{}^{79}Br^{35}ClNOH^+$ requires 385.9942) found 385.9946, (MH^+ $C_{19}H_{13}{}^{81}Br^{35}ClNOH^+$ requires 387.9921) found 387.9926.

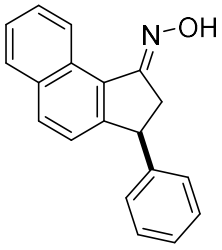
(*S*,*E*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-122

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-5-Fluoro-3-(3′,4′,5′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclophenta[*a*]naphthalen-1-one, (*S*)-**70**, (0.20 g, 0.5 mmol) and hydroxylamine hydrochloride (76 mg, 1.1 mmol) and the product was used without further purification. The title compound was formed as an orange solid (173 mg, 83 %); $[\alpha]_D^{28}$ (c 0.1, $CHCl_3$) +267; m.p. 127-128 °C; ν_{max}/cm^{-1} 3398 (s, O-H, stretch), 1591 (s, C=N, stretch), 1123 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.05 (1H, d, *J* 8.5, ArH-9), 8.16 (1H, d, *J* 8.5, ArH-6), 8.72 (1H, ddd, *J* 8.5, 7, 1, ArH-8), 7.63 (1H, ddd, *J* 8, 7, 1, ArH-7), 7.20 (1H, br. s, C-1 NOH), 6.92 (1H, d, *J* 10, ArH-4), 6.37 (2H, s, 2 x ArH-2′), 4.51 (1H, dd, *J* 8.5, 4, CH-3), 3.87 (1H, s, C_{Ar}-4′ OCH_3), 3.81 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.73 (1H, dd, *J* 19, 8.5, C*H*H-2), 3.08 (1H, dd, *J* 19, 4, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 164.7 (C-1), 160.8 (d, $^1J_{CF}$ 258, C_{Ar}F-5), 153.6 (2 x C_{Ar}-3′), 151.9 (d, $^3J_{CF}$ 9, (C_{Ar}), 139.6 (C_{Ar}-4′), 139.6 (C_{Ar}), 137.0 (C_{Ar}), 129.7 (C_{Ar}), 129.7 (C_{Ar}H), 128.9 (C_{Ar}), 126.6 (C_{Ar}), 126.6 (C_{Ar}H), 126.2 (C_{Ar}H), 126.2 (C_{Ar}H), 123.7 (d, $^3J_{CF}$ 17, C_{Ar}), 121.3 (d, $^3J_{CF}$ 6, C_{Ar}H-6), 107.3 (d, $^2J_{CF}$ 21.5, C_{Ar}H-4), 104.7 (2 x C_{Ar}H-2′), 60.9 (C_{Ar}-4′ O*C*H_3), 56.2 (2 x C_{Ar}-3′ O*C*H_3), 48.1 (CH-3), 37.1 (CH_2-2); m/z (MNa^+ $C_{22}H_{20}FNO_4Na^+$ requires 404.1269) found 404.1271.

(*S*,*E*)-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one Oxime



(*S*)-123

The aforementioned product was synthesised using the general method outlined in **Section 5.3.1**, using (*S*)-3-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*S*)-**68**, (0.20 g, 0.8 mmol) and hydroxylamine hydrochloride (108 mg, 1.6 mmol) and the product was used without further purification. The title compound was formed as an off-white solid (190 mg, 90 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ (c 0.1, $CHCl_3$) +372; m.p. 138-139 °C; ν_{max}/cm^{-1} 3289 (m, O-H, stretch), 2988 (w, C_{Ar}-H, stretch), 1492 (m, C=N, stretch); δ_H (400 MHz, $CDCl_3$) 9.03 (1H, d, *J* 8.5, ArH-9), 7.90 (1H, d, *J* 8, ArH-6), 7.82 (1H, d, *J* 8.5, ArH-5), 7.66 (1H, t, *J* 7.5, ArH-8), 7.56 (1H, t, *J* 7.5, ArH-7), 7.33 (2H, t, *J* 7.5, 2 x ArH-3′), 7.29-7.24 (3H, m, 2 x ArH-2′ & ArH-4′), 7.17 (1H, d, *J* 7.5, ArH-4), 4.62 (1H, dd, *J* 8.5, 3, CH-3), 3.72 (1H, dd, *J* 19, 8.5, C*H*H-2), 3.10 (1H, dd, *J* 19, 3, CH*H*-2); δ_C (125 MHz, $CDCl_3$) 165.6 (C-1), 151.6 (C_{Ar}), 144.7 (C_{Ar}), 133.2 (C_{Ar}), 131.7 (C_{Ar}H-5), 130.5 (C_{Ar}), 128.8 (C_{Ar}H), 128.7 (C_{Ar}), 128.4 (C_{Ar}H), 127.8 (C_{Ar}H), 127.8 (C_{Ar}H), 126.8 (C_{Ar}H), 126.2 (C_{Ar}H), 126.2 (C_{Ar}H), 123.6 (C_{Ar}H), 47.4 (CH-3), 37.0 (CH_2-2); m/z (MNa^+ $C_{19}H_{15}NONa^+$ requires 296.1046) found 296.1043.

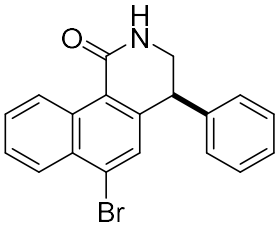
5.3.2 Synthesis of Indan-1-one Oxime Mesylates

The following procedure was performed in accordance with previous literature.[469] To a solution of the appropriate indan-1-one oxime (0.3 mmol) and triethylamine (4 mmol) in dichloromethane (10 mL) at -20 °C, was added mesyl chloride over 5 minutes, and the reaction was stirred at -20 °C for 20 minutes. The reaction mixture was allowed to warm to room temperature, transferred to a separating funnel and 1M HCl (20 mL),was added. The organic layer was separated and further washed with $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was then dried over $MgSO_4$, concentrated *in vacuo* and used without further purificataion. Traces of MsCl were visible in the ^1H NMR spectrum for each compound, but as this was the solvent employed for the Beckmann rearrangement, further purification was not necessary.

5.3.3 Beckmann Rearrangement of Indan-1-one Mesylates

The following procedure was performed in accordance with previous literature.[469] To a solution of the appropriate indan-1-one oxime mesylates (0.4 mmol) in mesyl chloride (10 mL), was added $ZrCl_4$ (2 mmol) at 0 °C and the reaction mixture was stirred for 1.5 hours. The reaction mixture was then poured into an ice-cold solution of NaOH (1.0 M, 20 mL), and stirred for 1 hour. The product was then extracted with ethyl acetate, washed with Na_2CO_3 (5 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was then purified by silica column chromatography as mentioned specifically.

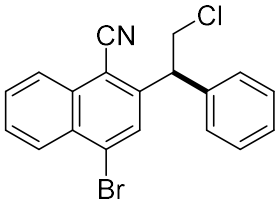
(*S*)-6-Bromo-4-phenyl-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one



(*S*)-124

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**116** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**124** and (*S*)-**125** in a ratio of 48 : 52. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow solid (74 mg, 45 %); $[\alpha]_D^{31}$ (c 0.04, $CHCl_3$) +118.8; m.p. 221-222 °C; ν_{max}/cm^{-1} 3673 (m, N-H, stretch), 2987 (m, C_{Ar}-H, stretch), 1649 (m, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 9.55 (1H, d, *J* 8.5, ArH-10), 8.28 (1H, d, *J* 8.5, ArH-7), 7.76-7.59 (2H, m, ArH-8 & ArH-9), 7.49 (1H, s, ArH-5), 7.37-7.28 (3H, m, 2 x ArH-3′ & ArH-4′), 7.18-7.12 (2H, m, 2 x ArH-2′), 6.29 (1H, br. s, NH-2), 4.40-4.29 (1H, m, CH-4), 3.89 (1H, d, *J* 12.5, C*H*H-3), 3.68-3.60 (1H, m, CH*H*-3); δ_C (100 MHz, $CDCl_3$) 166.0 (C-1), 141.7 (C_{Ar}-1′), 139.6 (C_{Ar}), 132.7 (C_{Ar}), 131.7 (C_{Ar}), 129.6 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.5 (C_{Ar}), 128.4 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 124.2 (C_{Ar}), 46.3 (CH_2-3), 45.4 (CH-4); m/z (MNa^+ $C_{19}H_{14}{}^{79}BrNONa^+$ requires 374.0151) found 374.0153, (MNa^+ $C_{19}H_{14}{}^{81}BrNONa^+$ requires 376.0131) found 376.0133.

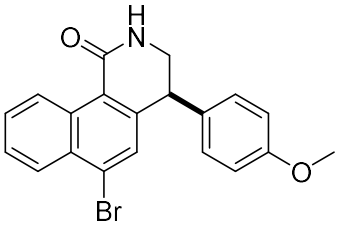
(*S*)-4-Bromo-2-(2′-chloro-1′-phenylethyl)-1-naphthonitrile



(*S*)-125

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, **(*S*)-116** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**124** and (*S*)-**125** in a ratio of 48 : 52. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow solid (77 mg, 45 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{28}}$ (c 0.1, $CHCl_3$) +11.4; m.p. 89-90 °C; ν_{max}/cm^{-1} 3673 (m, N-H, stretch), 2987 (m, C_{Ar}-H, stretch), 1580 (m, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 8.22 (1H, d, *J* 6.5, ArH-8), 8.10 (1H, d, *J* 7, ArH-5), 8.05 (1H, s, ArH-3), 7.69-7.60 (2H, m, ArH-6 & ArH-7), 7.24-7.14 (3H, m, 2 x ArH-3″ & ArH-4″), 7.13-7.05 (2H, m, 2 x ArH-2″), 5.61 (1H, d, *J* 7.5, CH-1′), 3.45-3.25 (2H, m, C*H*H-2′ & CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 144.6 (C_{Ar}-1″), 135.7 (C_{Ar}), 132.6 (C_{Ar}), 131.4 (C_{Ar}), 129.9 ($C_{Ar}H$), 129.5 (2 x $C_{Ar}H$-3″), 129.3 ($C_{Ar}H$), 128.7 (2 x $C_{Ar}H$-2″), 128.4 ($C_{Ar}H$), 128.0 $C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 115.2 (C_{Ar}-1 *C*N), 108.3 (C_{Ar}-1), 60.3 (CH-1′), 46.1 (CH_2-2′); m/z (MNa^+ $C_{19}H_{12}{}^{79}Br^{35}ClFNNa^+$ requires 409.9718) found 409.9722, (MNa^+ $C_{19}H_{12}{}^{81}Br^{35}ClFNNa^+$ requires 411.9695) found 411.9700.

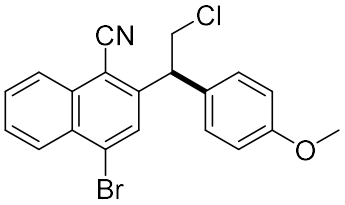
(*S*)-6-Bromo-4-(4′-methoxyphenyl)-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one



(*S*)-126

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**117** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**126** and (*S*)-**127** in a ratio of 5 : 95. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow oil (8 mg, 5 %); $[\alpha]_D^{31}$ (c 0.04, $CHCl_3$) +45; ν_{max}/cm^{-1} 3672 (w, N-H, stretch), 2970 (m, C_{Ar}-H, stretch), 1659 (m, C=O, stretch); δ_H (500 MHz, $CDCl_3$) 9.46 (1H, d, *J* 8.5, ArH-10), 8.28 (1H, dd, *J* 8.5, 1, ArH-7), 7.69 (1H, ddd, *J* 8.5, 7, 1.5, ArH-9), 7.63 (1H, ddd, *J* 8, 7, 1, ArH-8), 7.48 (1H, s, ArH-5), 7.09 (2H, d, *J* 8.5, 2 x ArH-2′), 6.87 (2H, d, *J* 8.5, 2 x ArH-3′), 6.03 (1H, br. s, NH-2), 4.30 (1H, t, *J* 5.5, CH-4), 3.86 (1H, ddd, *J* 12.5, 5, 3, C*H*H-3), 3.80 (3H, s, C_{Ar}-4′ OCH_3), 3.61 (1H, ddd, *J* 12.5, 6, 4.5, CH*H*-3); δ_C (125 MHz, $CDCl_3$) 165.9 (C-1), 159.0 (C_{Ar}-4′), 142.2 (C_{Ar}-1′), 132.8 (C_{Ar}), 131.8 (C_{Ar}), 131.6 (C_{Ar}), 129.6 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.6 (C_{Ar}), 127.5 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 124.1 (C_{Ar}), 114.4 (2 x $C_{Ar}H$-3′), 55.3 (C_{Ar}-4′ O*C*H_3), 46.5 (CH_2-3), 44.7 (CH-4); m/z (MNa^+ $C_{20}H_{16}{}^{79}BrNO_2Na^+$ requires 404.0257) found 404.0247, (MNa^+ $C_{20}H_{16}{}^{81}BrNO_2Na^+$ requires 406.0238) found 406.0228.

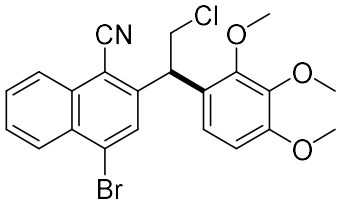
(*S*)-4-Bromo-2-(2′-chloro-1′-(4′′-methoxyphenyl)ethyl)-1-naphthonitrile



(*S*)-127

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(4′-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**117** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**126** and (*S*)-**127** in a ratio of 5 : 95. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow solid (122 mg, 70 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +41.1; m.p. 60-61 °C; ν_{max}/cm^{-1} 2987 (m, C_{Ar}-H, stretch), 2213 (m, C≡N, stretch), 1302 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* 7.5, ArH-8), 8.18 (1H, d, *J* 8.5, ArH-5), 8.11 (1H, s, ArH-3), 7.78-7.68 (2H, m, ArH-6 & ArH-7), 7.08 (2H, d, *J* 8, 2 x ArH-2′′), 6.79 (2H, d, *J* 8, 2 x ArH-3′′), 5.64 (1H, t, *J* 7.5, CH-1′), 3.58 (3H, s, C_{Ar}-4′′ O*C*H_3), 3.42 (1H, dd, *J* 14, 7.5, C*H*H-2′), 3.34 (1H, dd, *J* 14, 7, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 158.8 (C_{Ar}-4′′), 144.7 (C_{Ar}-1′′), 132.6 (C_{Ar}), 131.3 (C_{Ar}), 130.5 (C_{Ar}H), 129.9 (2 x C_{Ar}H-2′′), 129.6 (C_{Ar}), 129.3 (C_{Ar}H), 128.4 (C_{Ar}H), 128.0 C_{Ar}H), 127.7 (C_{Ar}), 126.2 (C_{Ar}H), 115.3 (C_{Ar}-1 *C*N), 114.0 (2 x C_{Ar}H-3′′), 108.4 (C_{Ar}-1), 60.5 (CH-1′), 55.2 (C_{Ar}-4′′ O*C*H_3), 45.3 (CH_2-2′); m/z (MNa^+ $C_{20}H_{15}{}^{79}Br^{35}ClNONa^+$ requires 421.9918) found 421.9912, (MNa^+ $C_{20}H_{15}{}^{81}Br^{35}ClNONa^+$ requires 423.9897) found 423.9891.

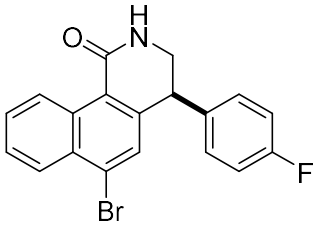
(*S*)-4-Bromo-2-(2′-chloro-1′-(2′′,3′′,4′′-trimethoxyphenyl)ethyl)-1-naphthonitrile



(*S*)-128

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**118** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (S)-6-Bromo-4-(2′,3′,4′-trimethoxyphenyl)-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one and (*S*)-**128** in a ratio of 8 : 92. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow oil (117 mg, 66 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +9.5; ν_{max}/cm^{-1} 2987 (m, C_{Ar}-H, stretch), 2213 (m, C≡N, stretch), 1246 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.29 (1H, d, *J* 6, ArH-8), 8.18 (1H, d, *J* 8.5, ArH-5), 8.15 (1H, s, ArH-3), 7.80-7.62 (2H, m, ArH-6 & ArH-7), 6.71 (1H, d, *J* 8.5, ArH-6″), 6.49 (1H, *J* 8.5, ArH-5″), 5.75 (1H, t, *J* 7.5, CH-1′), 3.93 (3H, s, C_{Ar}-4″ OCH_3), 3.79 (3H, s, C_{Ar}-3″ OCH_3), 3.77 (3H, s, C_{Ar}-2″), 3.43 (1H, dd, *J* 13.5, 7.5, C*H*H-2′), 3.34 (1H, dd, *J* 14, 7.5, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 153.4 (C_{Ar}), 145.0 (C_{Ar}), 132.6 (C_{Ar}), 131.3 (C_{Ar}), 129.8 ($C_{Ar}H$), 129.4 (C_{Ar}), 129.2 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.0 $C_{Ar}H$), 126.2 ($C_{Ar}H$), 125.3 ($C_{Ar}H$-6″), 121.3 (C_{Ar}), 115.2 (C_{Ar}-1 *C*N), 108.5 (C_{Ar}), 106.7 ($C_{Ar}H$-5″), 60.9 (C_{Ar}-3″ O*C*H_3), 60.7 (C_{Ar}-2″ O*C*H_3), 59.3 (CH-1′), 55.9 (C_{Ar}-4″ O*C*H_3), 40.5 (CH_2-2′), (Missing 2 x C_{Ar}).

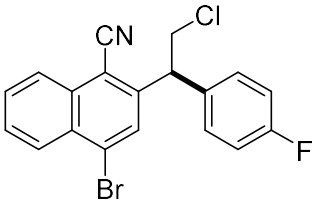
(*S*)-6-Bromo-4-(4′-fluorophenyl)-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one



(*S*)-131

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**120** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**131** and (*S*)-**132** in a ratio of 32 : 68. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow solid (46 mg, 28 %); $[\alpha]_D^{31}$ (c 0.08, $CHCl_3$) +88.1; m.p. 188-189 °C; ν_{max}/cm^{-1} 3673 (m, N-H, stretch), 2987 (m, C_{Ar}-H, stretch), 1650 (m, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 9.45 (1H, d, *J* 8.5, ArH-10), 8.28 (1H, d, *J* 8, ArH-7), 7.75-7.56 (2H, m, ArH-8 & ArH-9), 7.46 (1H, s, ArH-5), 7.20-7.07 (2H, m, 2 x 2′), 7.01 (2H, dd, *J* 11.5, 5, 2 x ArH-3′), 6.52 (1H, br. s, NH-2), 4.38-4.28 (1H, m, CH-4), 3.89 (1H, d, *J* 12.5, C*H*H-3), 3.67-3.53 (1H, m, CH*H*-3) ; δ_C (100 MHz, $CDCl_3$) 166.1 (C-1), 162.2 (d, $^1J_{CF}$ 246, C_{Ar}F-4′), 141.6 (C_{Ar}-1′), 135.4 (C_{Ar}), 132.7 (C_{Ar}), 131.9 (C_{Ar}), 130.0 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-2′), 129.5 (C_{Ar}H), 128.8 (C_{Ar}H), 128.7 (C_{Ar}), 127.6 (C_{Ar}H), 127.4 (C_{Ar}H), 124.2 (C_{Ar}), 115.9 (d, $^2J_{CF}$ 21, 2 x C_{Ar}H-3′), 46.3 (CH_2-3), 44.7 (CH-4); m/z (MNa^+ $C_{19}H_{13}{}^{79}BrFNONa^+$ requires 392.0057) found 392.0057, (MNa^+ $C_{19}H_{13}{}^{81}BrFNONa^+$ requires 394.0036) found 394.0037.

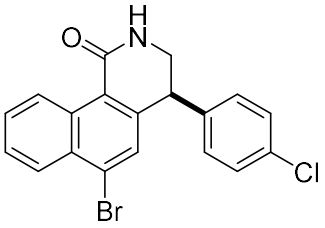
(*S*)-4-Bromo-2-(2′-chloro-1′-(4′′-fluorophenyl)ethyl)-1-naphthonitrile



(*S*)-132

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(4′-fluorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**120** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**131** and (*S*)-**132** in a ratio of 32 : 68. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow solid (90 mg, 52 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.12, $CHCl_3$) +9.5; m.p. 96-97 °C; ν_{max}/cm^{-1} 2987 (m, C_{Ar}-H, stretch), 2219 (m, C≡N, stretch); δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* 8, ArH-8), 8.18 (1H, d, *J* 6.5, ArH-5), 8.11 (1H, s, ArH-3), 7.77-7.71 (2H, m, ArH-6 & ArH-7), 7.17-7.10 (2H, m, 2 x ArH-2″), 7.96 (2H, t, *J* 8.5, 2 x ArH-3″), 5.64 (1H, t, *J* 7.5, CH-1′), 3.44 (1H, dd, *J* 14, 8, C*H*H-2′), 3.36 (1H, dd, *J* 14, 7, CH*H*-2′; δ_C (100 MHz, $CDCl_3$) 162.1 (d, $^1J_{CF}$ 246, C_{Ar}F-4″), 144.4 (C_{Ar}-1″), 132.5 (C_{Ar}), 131.4 (C_{Ar}), 131.4 (C_{Ar}), 131.1 (d, $^3J_{CF}$ 8, 2 x C_{Ar}H-2″), 130.0 (C_{Ar}H), 129.8 (C_{Ar}), 129.4 (C_{Ar}H), 128.3 (C_{Ar}H), 128.0 (C_{Ar}H), 126.2 (C_{Ar}H), 115.6 (d, $^2J_{CF}$ 21.5, 2 x C_{Ar}-3″), 115.3 (C_{Ar}-1 *C*N), 108.3 (C_{Ar}-1), 60.3 (CH-1′), 45.3 (CH_2-2′); m/z (MNa^+ $C_{19}H_{13}{}^{79}Br^{35}ClNNa^+$ requires 391.9812) found 391.9809, (MNa^+ $C_{19}H_{13}{}^{81}Br^{35}ClNNa^+$ requires 393.9789) found 393.9788.

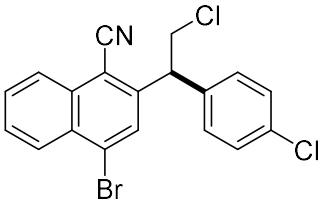
(*S*)-6-Bromo-4-(4′-chlorophenyl)-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one



(*S*)-133

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**121** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**133** and (*S*)-**134** in a ratio of 39 : 61. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give an orange solid (55 mg, 33 %); $[\alpha]_D^{31}$ (c 0.13, $CHCl_3$) +110.7; m.p. 189-190 °C; ν_{max}/cm^{-1} 3673 (m, N-H, stretch), 2987 (m, C_{Ar}-H, stretch), 1650 (m, C=O, stretch); δ_H (400 MHz, $CDCl_3$) 9.44 (1H, d, *J* 8, ArH-10), 8.29 (1H, d, *J* 8, ArH-7), 7.76-7.56 (2H, m, ArH-8 & ArH-9), 7.46 (1H, s, ArH-5), 7.30 (2H, d, *J* 7.5, 2 x ArH-3′), 7.10 (2H, d, *J* 7.5, 2 x ArH-2′), 6.49 (1H, br. s, NH-2), 4.33-4.29 (1H, m, CH-3), 3.89 (1H, d, *J* 12, C*H*H-3), 3.65-3.54 (1H, m, CH*H*-3); δ_C (100 MHz, $CDCl_3$) 166.0 (C-1), 141.2 (C_{Ar}-1′), 138.1 (C_{Ar}), 133.5 (C_{Ar}), 132.7 (C_{Ar}), 131.8 (C_{Ar}), 129.8 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.7 (C_{Ar}), 127.6 ($C_{Ar}H$), 127.4 $C_{Ar}H$), 124.2 (C_{Ar}), 46.2 (CH_2-4), 44.8 (CH-3); m/z (MNa^+ $C_{19}H_{13}{}^{79}Br^{35}ClNONa^+$ requires 407.9761) found 407.9759, (MNa^+ $C_{19}H_{13}{}^{81}Br^{35}ClNONa^+$ requires 409.9739) found 409.9739.

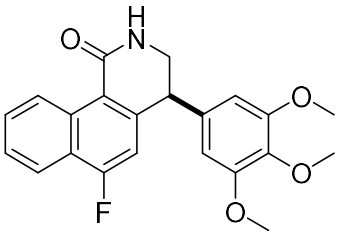
(*S*)-4-Bromo-2-(2′-chloro-1′-(4′′-chlorophenyl)ethyl)-1-naphthonitrile



(*S*)-134

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-bromo-3-(4′-chlorophenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**121** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**133** and (*S*)-**134** in a ratio of 39 : 61. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow solid (98 mg, 56 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.10, $CHCl_3$) +13.5; m.p. 129-130 °C; ν_{max}/cm^{-1} 2987 (m, C_{Ar}-H, stretch), 2218 (m, C≡N, stretch); δ_H (400 MHz, $CDCl_3$) 8.31 (1H, d, *J* 8, ArH-8), 8.20 (1H, d, *J* 7.5, ArH-5), 8.11 (1H, s, ArH-3), 7.81-7.68 (2H, m, ArH-6 & ArH-7), 7.25 (2H, d, *J* 8, 2 x ArH-3′′), 7.12 (2H, d, *J* 8, 2 x ArH-2′′), 5.65 (1H, t, *J* 7.5, CH-1′), 3.43 (1H, dd, *J* 15, 9, C*H*H-2′), 3.37 (1H, dd, *J* 15, 8, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 144.3 (C_{Ar}-1′′), 134.1 (C_{Ar}), 133.4 (C_{Ar}), 132.5 (C_{Ar}), 131.5 (C_{Ar}), 130.8 (2 x C_{Ar}H-2′′), 130.1 (C_{Ar}H), 129.8 (C_{Ar}), 129.4 (C_{Ar}H), 128.9 (2 x C_{Ar}H-3′′), 128.3 (C_{Ar}H), 128.1 (C_{Ar}H), 126.2 (C_{Ar}H), 115.3 (C_{Ar}-1 *C*N), 108.3 (C_{Ar}-1), 60.0 (CH-1′), 45.3 (CH_2-2′); m/z (MNa^+ $C_{19}H_{12}{}^{79}Br^{35}Cl_2NNa^+$ requires 425.9422) found 425.9427, (MNa^+ $C_{19}H_{12}{}^{81}Br^{35}Cl_2NNa^+$ requires 427.9399) found 427.9404.

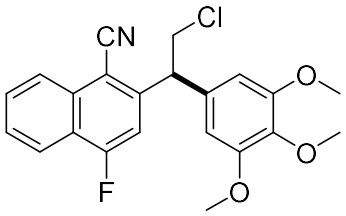
(*S*)-6-Fluoro-4-(3′,4′,5′-trimethoxyphenyl)-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one



(*S*)-135

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-fluoro-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-122 (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**135** and (*S*)-**136** in a ratio of 60 : 40. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give an orange oil (81 mg, 49 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.04, $CHCl_3$) +43.8; ν_{max}/cm^{-1} 3672 (N-H, stretch), 2970 (m, C_{Ar}-H, stretch), 1659 (m, C=O, stretch), 1121 (s, C-O, stretch); δ_H (500 MHz, $CDCl_3$) 9.38 (1H, d, *J* 8.5, ArH-10), 8.05 (1H, d, *J* 8.5, ArH-7), 7.65-7.60 (1H, m, ArH-9), 7.54-7.50 (1H, m, ArH-8), 6.74 (1H, d, *J* 11, ArH-5), 6.32 (2H, s, 2 x ArH-2′), 6.25 (1H, br. s, NH-2), 4.23 (1H, dd, *J* 7, 5.5, CH-4), 3.78 (3H, s, C_{Ar}-4′ OCH_3), 3.77-3.73 (1H, m, C*H*H-3), 3.70 (6H, s, 2 x C_{Ar}-3′ OCH_3), 3.62-3.57 (1H, m, CH*H*-3); δ_C (125 MHz, $CDCl_3$) 165.9 (C-1), 161.0 (d, $^1J_{CF}$ 260, C_{Ar}F-6), 153.6 (2 x C_{Ar}-3′), 143.3 (d, $^3J_{CF}$), 137.5 (C_{Ar}), 136.6 (C_{Ar}), 135.3 (C_{Ar}-4′), 133.7 (d, $^3J_{CF}$ 5), 129.0 (C_{Ar}H), 127.2 (C_{Ar}H), 126.5 (C_{Ar}H), 123.6 (d, $^2J_{CF}$ 15.5, C_{Ar}-6a), 120.5 (d, $^3J_{CF}$ 6.5, C_{Ar}-7), 109.2 (d, $^2J_{CF}$ 21, C_{Ar}H-5), 105.6 (2 x C_{Ar}H-2′), 60.9 (C_{Ar}-4′ O*C*H_3), 56.2 (2 x C_{Ar}-3′ O*C*H_3), 46.4 (CH-4), 46.3 (CH_2-3); m/z (MNa^+ C22H20FO4NNa^+ requires 404.1269) found 404.1272.

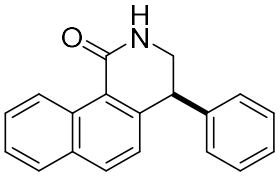
(*S*)-4-Fluoro-2-(2′-chloro-1′-(3″,4″,5″-trimethoxyphenyl)ethyl)-1-naphthonitrile



(*S*)-136

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-5-fluoro-3-(2′,3′,4′-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**122** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**135** and (*S*)-**136** in a ratio of 60 : 40. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a orange oil (54 mg, 31 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +2.8; ν_{max}/cm^{-1} 3067 (m, C_{Ar}-H, stretch), 2219 (m, C≡N, stretch), 1152 (s, C-O, stretch); δ_H (400 MHz, $CDCl_3$) 8.21-8.04 (2H, m, ArH-8 & ArH-5), 7.78-7.63 (2H, m, ArH-6 & ArH-7), 7.49 (1H, d, *J* 11, ArH-3), 6.36 (2H, s, 2 x ArH-2″), 5.79-5.68 (1H, m, CH-1′), 3.77 (3H, s, C_{Ar}-4″ OCH_3), 3.74 (6H, s, 2 x C_{Ar}-3″ OCH_3), 3.43 (1H, dd, *J* 13.5, 8, C*H*H-2′), 3.28 (1H, dd, *J* 14, 7.5, CH*H*-2′); δ_C (100 MHz, $CDCl_3$) 161.7 (d, $^1J_{CF}$ 263, C_{Ar}F-4), 153.2 (2 x C_{Ar}-3″), 146.1 (d, $^3J_{CF}$ 9, C_{Ar}), 137.2 (C_{Ar}-4″), 133.7 (d, $^3J_{CF}$ 6, C_{Ar}), 131.3 (C_{Ar}), 130.3 (C_{Ar}H), 128.4 (C_{Ar}H), 125.6 (C_{Ar}H), 123.1 (d, $^2J_{CF}$ 18, C_{Ar}-4a), 121.3 (d, $^4J_{CF}$ 5, C_{Ar}H-5), 115.4 (C_{Ar}-1 *C*N), 108.6 (d, $^2J_{CF}$ 23.3, C_{Ar}H-3), 106.3 (2 x C_{Ar}H-2″), 104.7 (d, $^4J_{CF}$ 4, C-1), 60.8 (C_{Ar}-4″ O*C*H_3), 60.2 (CH-1′), 56.0 (2 x C_{Ar}-3″ O*C*H_3), 46.5 (CH_2-2′) ; m/z (MNa^+ $C_{22}H_{19}{}^{35}ClFNO_3Na^+$ requires 422.0930) found 422.0944.

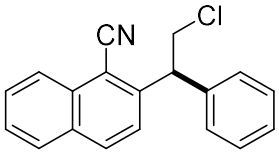
(*S*)-4-phenyl-3,4-dihydrobenz[*h*]isoquinolin-1(2*H*)-one



(*S*)-137

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**123** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**137** and (*S*)-**138** in a ratio of 37 : 63. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow oil (47 mg, 30 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +26.3; ν_{max}/cm^{-1} 3673 (m, N-H, stretch), 2987 (m, C_{Ar}-H, stretch), 1649 (s, C=O, stretch); δ_H (500 MHz, $CDCl_3$) 9.48 (1H, d, *J* 8.5, ArH-10), 7.91 (1H, d, *J* 8.5, ArH-6), 7.85 (1H, d, *J* 8, ArH-7), 7.66 (1H, ddd, *J* 8.5, 7, 1.5, ArH-9), 7.57-7.53 (1H, m, ArH-8), 7.35-7.25 (3H, 2 x ArH-3′ & ArH-4′), 7.21-7.17 (2H, m, 2 x ArH-2′), 7.14 (1H, d, *J* 8.5, ArH-5), 6.94 (1H, br. s, NH-2), 4.39 (1H, t, *J* 5.5, CH-4), 3.91 (1H, ddd, *J* 12.5, 5, 3, C*H*H-3), 3.68 (1H, ddd, *J* 12.5, 6, 4.5, CH*H*-3); δ_C (125 MHz, $CDCl_3$) 166.8 (C-1), 141.7 (C_{Ar}-1′), 140.3 (C_{Ar}), 133.2 (C_{Ar}), 132.9 ($C_{Ar}H$), 131.5 (C_{Ar}), 128.7 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.9 $C_{Ar}H$), 126.0 ($C_{Ar}H$), 125.5 ($C_{Ar}H$), 124.3 (C_{Ar}), 46.2 (CH_2-3), 45.5 (CH-3); m/z (MNa^+ $C_{19}H_{15}NONa^+$ requires 296.1046) found 296.1047.

(*S*)-2-(2′-chloro-1′-phenylethyl)-1-naphthonitrile



(*S*)-138

The aforementioned product was synthesised using the general method outlined in **Section 5.3.3**, using (*S,E*)-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one *O*-methylsulfonyl oxime, (*S*)-**123** (200 mg, 0.4 mmol) and zirconium chloride (50 mg, 2 mmol) to give compound (*S*)-**137** and (*S*)-**138** in a ratio of 37 : 63. The title compound was isolated by silica column chromatography, eluting with dichloromethane : ethyl acetate (2 : 1), to give a yellow oil (95 mg, 55 %); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{31}}$ (c 0.2, $CHCl_3$) +7.5; ν_{max}/cm^{-1} 2987 (m, C_{Ar}-H, stretch), 2217 (m, C≡N, stretch); δ_H (500 MHz, d_6-DMSO) 8.39 (1H, d, *J* 9, ArH-8), 8.14 (1H, d, *J* 8, ArH-4), 8.08-8.03 (2H, m, ArH-5 & ArH-7), 7.84-7.79 (1H, m, ArH-6), 7.76-7.72 (1H, m, ArH-3), 7.26-7.15 (5H, m, 2 x ArH-2″, 2 x ArH-3″ & ArH-4″), 5.77 (1H, t, *J* 8, CH-1′), 3.66 (1H, dd, *J* 13, 6.5, C*H*H-2′), 3.62 (1H, dd, *J* 13, 7, CH*H*-2′); δ_C (125 MHz, d_6-DMSO) 144.6 (C_{Ar}-1″), 137.0 (C_{Ar}), 134.6 (C_{Ar}H), 132.5 (C_{Ar}), 131.6 (C_{Ar}), 130.2 (C_{Ar}H), 129.8 (2 x C_{Ar}H-3″), 129.4 (C_{Ar}H), 128.8 (2 x C_{Ar}H-2″), 128.8 (C_{Ar}H), 127.4 (C_{Ar}H), 125.1 (C_{Ar}H), 124.9 (C_{Ar}H), 115.9 (C_{Ar}-1 *C*N), 108.1 (C_{Ar}-1), 61.5 (CH-1′), 44.0 (CH_2-2′); m/z (MNa^+ $C_{19}H_{14}{}^{35}ClNNa^+$ requires 314.0707) found 314.0708.

5.4 Bibliography

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