

A Thesis Submitted for the Degree of PhD at the University of Warwick

Permanent WRAP URL:

<http://wrap.warwick.ac.uk/149905>

Copyright and reuse:

This thesis is made available online and is protected by original copyright.

Please scroll down to view the document itself.

Please refer to the repository record for this item for information to help you to cite it.

Our policy information is available from the repository home page.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk

**Indanones:
Resolutions and Reactions**

By

Matthew W. M. Earl

A thesis submitted in partial fulfilment of the requirements for the
degree of Doctor of Philosophy in Chemistry

University of Warwick, Department of Chemistry

December 2019

CONTENTS

LIST OF FIGURES	iv
LIST OF SCHEMES	v
LIST OF TABLES	viii
ACKNOWLEDGEMENTS	ix
DECLARATION	x
ABSTRACT	xi
ABBREVIATIONS	xii
1.0 Enantiomerically Enriched 3-Aryl-indan-1-ones	1
1.1 Biological Importance of Indan-1-ones	1
1.2 Towards Enantioenriched Indan-1-ones	7
1.2.1 Direct Pathways – Asymmetric Synthesis.....	8
1.2.2 Indirect Pathways – Racemic Synthesis & Chiral Resolution.....	9
1.3 Oxidative Kinetic Resolution of Secondary Alcohols	16
1.4 Previous work in the Fox Group.....	24
1.5 Aims of Research.....	29
1.6 References.....	31
2.0 A “2 + 2.5-step” Asymmetric Synthesis	39
2.1 Synthesis of Racemic 3-Aryl-indan-1-ones	39
2.1.1 Overview	39
2.1.2 Claisen–Schmidt Condensation.....	39
2.1.3 Nazarov Cyclisation of Substituted Chalcones	40
2.2 Chiral Resolution of Racemic 3-Aryl-indan-1-ones	45
2.2.1 Overview	45
2.2.2 Diastereoselective Reduction of Racemic Indan-1-ones.....	46
2.2.3 Oxidative Kinetic Resolution of <i>cis</i> -Indan-1-ols.....	49
2.2.4 Oxidation of Residual Enantioenriched <i>cis</i> -Indan-1-ols	57
2.3 Summary	58
2.4 Experimental for Chapter 2.....	59
2.4.1 General	59
2.4.2 Substituted Chalcone Formation by Claisen–Schmidt Condensation – General Procedure A	61
2.4.3 Formation of 3-Aryl-indan-1-ones by Nazarov Cyclisation – General Procedure B.....	66

2.4.4	Diastereoselective Reduction of 3-Aryl-indan-1-ones with NaBH ₄ – General Procedure C.....	71
2.4.5	Diastereoselective Reduction of 3-Aryl-indan-1-ones with L-Selectride – General Procedure D	76
2.4.6	Preparation of Ruthenium Catalyst for Oxidative Kinetic Resolutions: (1 <i>S</i> ,2 <i>S</i>)-Ru(<i>p</i> -cymene)(TsDPEN), (<i>S,S</i>)- 63	78
2.4.7	Oxidative Kinetic Resolutions – General Procedure E	78
2.4.8	MnO ₂ Oxidation of Enantiopure Indan-1-ols – General Procedure F	87
2.4.9	Plots for Selectivity Factor Determination	90
2.5	References	94
3.0	A Building Block to Medicinal Scaffolds.....	97
3.1	Medicinal Scaffolds; Structures and Their Biological Importance.....	97
3.1.1	Dihydroquinolinones and Dihydroisoquinolinones.....	97
3.1.2	Tetrahydroisoquinolines	102
3.2	Synthesis of Dihydroquinolinones and Dihydroisoquinolinones	105
3.2.1	Beckmann Rearrangement.....	106
3.2.2	Schmidt Reaction.....	111
3.2.3	Anti-inflammatory Compound 6-B345TTQ – A Synthetic Target	129
3.3	Synthesis of Tetrahydroisoquinolines.....	136
3.3.1	Reduction of Dihydroisoquinolinones.....	136
3.3.2	Acetylation of Tetrahydroisoquinolines for HPLC Analysis	141
3.3.3	Antidepressant Compound Diclofensine – A Synthetic Target	143
3.4	Synthesis of Benzylidene Indan-1-ones.....	147
3.5	Summary	150
3.6	Experimental for Chapter 3.....	151
3.6.1	General	151
3.6.2	Formation of Indan-1-one Oximes – General Procedure G	153
3.6.3	Formation of Indan-1-one Oxime Mesylates – General Procedure H	158
3.6.4	Beckmann Rearrangement of Indan-1-one Oxime Mesylates – General Procedure I.....	164
3.6.5	Schmidt Reaction of Indan-1-ones – General Procedure J.....	171
3.6.6	Heck Coupling Reaction of 2-Bromobenzonitrile and Styrene – Confirmation of (<i>E</i>)-2-Styrylbenzotrile, 291	207

3.6.7	LiBH ₄ –TMSCl Reduction of 4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2 <i>H</i>)-one, 241	208
3.6.8	NaBH ₄ –Tf ₂ O Reduction of 4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2 <i>H</i>)-one, 241	209
3.6.9	LiAlH ₄ Reduction of Dihydroquinolinones – General Procedure K.....	210
3.6.10	Acetylation of Tetrahydroquinolines – General Procedure L	221
3.6.11	<i>N</i> -Methylation of Tetrahydroquinolines – General Procedure M	234
3.6.12	Benzylidene Indan-1-one Formation – General Procedure N	245
3.7	Experimental Continued – Synthesis of (<i>S</i>)- and (<i>R</i>)-6-B345TTQ, (<i>S</i>)- and (<i>R</i>)- 99	270
3.7.1	Knoevenagel Condensation of 3,4,5-Trimethoxybenzaldehyde and Meldrum’s Acid.....	270
3.7.2	Formation of (±)-6-B345TTQ by Conjugate Addition	270
3.7.3	Friedel–Crafts Acylation of 1-Bromonaphthalene	271
3.7.4	Synthesis of Substituted Chalcone 318	272
3.7.5	Synthesis of 6-B345TTQ Precursor Indan-1-one, 319	273
3.7.6	Schmidt Reaction of Racemic Indan-1-one Precursor, 319	273
3.7.7	Diastereoselective Reduction of Indan-1-one Precursor, 319	275
3.7.8	Successive Oxidative Kinetic Resolutions Towards Individual Enantiomers of Indan-1-one Precursor, (<i>S</i>)- and (<i>R</i>)- 319	276
3.7.9	Schmidt Reaction of Precursor Indan-1-one Individual Enantiomers; Formation of (<i>S</i>)- and (<i>R</i>)-6-B345TTQ, (<i>S</i>)- and (<i>R</i>)- 99	278
3.8	References.....	281
4.0	Conclusions and Future Work	296
4.1	Conclusions.....	296
4.2	Future Work.....	301
4.3	References.....	302

LIST OF FIGURES

Figure 1 Indanes found in biologically active natural products and drugs.	1
Figure 2 Structures of indan-1-one (4) and indan-2-one (5), and indan-1-ones found in biologically active natural products and drugs.....	1
Figure 3 Indanocine and inhibitors of enzyme aromatase.....	2
Figure 4 Colchicine and colchicine-domain binders that have gained intense interest as potential anti-cancer agents.....	3
Figure 5 Newly designed indanone-indole hybrids 20-24	3
Figure 6 Biologically active <i>s-trans</i> chalcone 25 and potent 3-aryl-indan-1-ones related to combretastatin A-4.....	4
Figure 7 Potent anti-cancer gallic acid-based indanones.	5
Figure 8 Indan-1-ones possessing anti-inflammatory activity.	7
Figure 9 Kinetic resolution of a racemic starting material (SM) to give product (P). ...	13
Figure 10 Representational energy diagram for kinetic resolution.	13
Figure 11 Reported ruthenium catalysts for the oxidative kinetic resolution of alcohols.	20
Figure 12 Mn(salen) catalysts used in oxidative kinetic resolutions of alcohols.....	20
Figure 13 Anti-inflammatory compound 6-B345TTQ (99) and inactive analogue 6-B234TTQ (100).	24
Figure 14 Tethered (<i>R,R</i>)-TsDPEN-ruthenium catalyst, (<i>R,R</i>)- 108 , and three stereoisomers of indan-1-ol 109 from ATH reactions.	26
Figure 15 Targeted enantiomerically enriched 3-aryl-indan-1-ones 118-125	29
Figure 16 Transformations of 3-aryl-indan-1-ones (126) into medicinal scaffolds.....	30
Figure 17 Reaction profile for the oxidative kinetic resolution of indan-1-ol 153	53
Figure 18 Plots of e.e. vs. conversion as a function of <i>s</i> for starting material (<i>left</i>) and product (<i>right</i>). [Obtained from a paper by Greenhalgh et al.].....	54
Figure 19 Plot of ' $\ln[1 - c(1 + e.e._p)]$ ' against ' $\ln[1 - c(1 - e.e._p)]$ ' for the oxidative kinetic resolution of <i>cis</i> -indan-1-ol 153 ; selectivity factor, $s = 80 (\pm 3.52)$	56
Figure 20 Selectivity factors, <i>s</i> , acquired from linear regression analysis for the oxidative kinetic resolution of 3-aryl-indan-1-ols 149-156 catalysed by Ru catalyst (<i>S,S</i>)- 63 ; errors were calculated using Equation 16 in accordance with best practice guidelines published by Greenhalgh <i>et al.</i>	57
Figure 21 Structures of dihydroquinolinone (163) and dihydroisoquinolinone (164)...	97
Figure 22 Naturally occurring and synthetic biologically active dihydroquinolinones.	98

Figure 23 Dihydroquinolinones as medicinal scaffolds.....	98
Figure 24 Natural products containing the dihydroisoquinolinone skeleton.	100
Figure 25 Biologically interesting dihydroisoquinolinones.....	101
Figure 26 Structures of tetrahydroisoquinoline (186) and tetrahydroquinoline (187).	102
Figure 27 Tetrahydroisoquinoline framework in bioactive natural products.....	103
Figure 28 Diclofensine (198), nomifensine (199) and other biologically interesting synthetic tetrahydroisoquinolines.	104
Figure 29 Steric interactions between –OH group and C _{Ar} -H in (<i>Z</i>)- (<i>left</i>) and (<i>E</i>)- (<i>right</i>) indan-1-one oximes.	109
Figure 30 ¹ H NMR data reported for tetrazole 274 , dihydroquinolinone 163 , and dihydroisoquinolinone 164	117
Figure 31 Tetrazole isomers 268 and 269 isolated from the Schmidt reaction of 125	118
Figure 32 Observed side-products 288 and 289 in Schmidt reactions of 4 and 276 , respectively.	122
Figure 33 Confirmation of 4-bromo-1-acetonaphthone (315) by ¹ H NMR spectroscopy.....	132
Figure 34 Example NOE experiment, confirming (<i>E</i>)-alkene configuration. Top ¹ H NMR spectrum: benzylidene indan-1-one 378 . Bottom ¹ H NMR spectrum: benzylidene indan-1-one 378 irradiated at δ = 6.995 ppm.....	149
Figure 35 3D structures of benzylidene indan-1-one 378 , as generated by Chem3D 17.0. Left image: (<i>E</i>)- 378 , with atom distance calculated at 1.9 Å. Right image: (<i>Z</i>)- 378 , with atom distance calculated at 4.9 Å.	149
Figure 36 Successful synthesis of (<i>R</i>)- and (<i>S</i>)-6-B345TTQ (99) and diclofensine (198).	299

LIST OF SCHEMES

Scheme 1 Synthesis and anti-cancer profile of 2-benzylidene indanone 35	5
Scheme 2 Enantioselective reductive Heck cyclisation towards enantioenriched indan-1-ones.	8
Scheme 3 Use of chiral imidazolidinone auxiliary 43 in the synthesis of enantioenriched 3-aryl-indan-1-ones (46).	9
Scheme 4 The Nazarov cyclisation of divinyl ketones.....	10
Scheme 5 Classical resolution using a chiral resolving agent (X).....	11
Scheme 6 First kinetic resolution by synthetic means; racemic mandelic acid (54).	12

Scheme 7 Schematic principle of an ideal oxidative kinetic resolution.	16
Scheme 8 Oxidative kinetic resolution of 1-phenylethanol (59); comparison of methods reported by Rychnovsky, Ohkubo, and Noyori.	17
Scheme 9 Noyori's Ru-catalysed oxidative kinetic resolution of secondary alcohols. ...	18
Scheme 10 Ruthenium-catalysed oxidation catalytic cycle.	19
Scheme 11 Comparison of (-)-sparteine and its (+)-surrogate for the Pd-catalysed oxidative kinetic resolution of indan-1-ol (92); includes structures of (-)-sparteine (89), (-)-cytisine (91) and its (+)-sparteine surrogate (90).	21
Scheme 12 Aerobic Ir-catalysed oxidative kinetic resolution of indan-1-ol (68) and α -tetralol (69) reported by Ikariya <i>et al.</i>	22
Scheme 13 Asymmetric oxidation of α -hydroxy ester 94 using a chiral salicylaldimine-vanadium catalyst.	22
Scheme 14 Work by Sekar <i>et al.</i> on the oxidative kinetic resolution of (\pm)-benzoin (96) using cobalt, copper and iron catalysts.	23
Scheme 15 Cyclisation steps in acylation and alkylation approaches towards enantioenriched 3-substituted naphthyl-indan-1-ones (102).	25
Scheme 16 Synthetic route to racemic naphthyl-indan-1-ones (107).	26
Scheme 17 Conceived kinetic resolution pathway of racemic 3-aryl-indan-1-ones.	27
Scheme 18 Kinetic resolution of 3-aryl-indan-1-ols using Novozym [®] 435.	27
Scheme 19 Ruthenium-catalysed oxidative kinetic resolution of substituted racemic <i>cis</i> -indan-1-ols 113-117	28
Scheme 20 Disconnection approach from 3-aryl-indan-1-one derivatives.	39
Scheme 21 Side product formation in the Nazarov cyclisation of chalcones.	41
Scheme 22 Substituent effects in the Nazarov cyclisation.	43
Scheme 23 "2.5-step" sequence towards enantiopure indan-1-one derivatives.	45
Scheme 24 <i>Cis</i> -reduction of racemic 121 and 125 using L-Selectride.	48
Scheme 25 Ideal oxidative kinetic resolution of <i>cis</i> -3-aryl-indan-1-ols 157	49
Scheme 26 Synthesis of Noyori's catalyst, (1 <i>S</i> ,2 <i>S</i>)-Ru(<i>p</i> -cymene)(TsDPEN)((<i>S,S</i>)- 63).	50
Scheme 27 Oxime formation and Beckmann rearrangement to <i>N</i> -substituted amides.	106
Scheme 28 Beckmann rearrangement mechanism.	106
Scheme 29 Two directional Beckmann rearrangement of indan-1-one oxime mesylates.	108

Scheme 30 Optimised conditions for the conversion of indan-1-one oxime mesylates into dihydroquinolinones.....	108
Scheme 31 Schmidt reaction mechanism.	112
Scheme 32 Effect of acid on Schmidt reaction of indan-1-one 4	112
Scheme 33 Effect of <i>ortho</i> - and <i>para</i> - methoxy groups on the regiochemistry of the Schmidt reaction with indan-1-ones.....	113
Scheme 34 Postulated mechanism of tetrazole formation.	117
Scheme 35 Possible mechanism towards nitrile product 288	122
Scheme 36 Postulated mechanism for the formation of 2'-cyanostilbene (291).	123
Scheme 37 Commonly accepted mechanism for the Heck reaction.....	124
Scheme 38 Regioselectivity in the Heck reaction of styrene and 2-bromobenzonitrile.	126
Scheme 39 Possible pathways for the formation of alkene 302	126
Scheme 40 Modified mechanism to account for tetrazole racemisation.	128
Scheme 41 Unsuccessful Beckmann approach towards 6-B345TTQ (99) and related dihydroquinolinones.....	130
Scheme 42 Overall synthetic route towards 6-B345TTQ precursor indan-1-one 319	131
Scheme 43 Schmidt reaction of 6-B345TTQ precursor indan-1-one 319	133
Scheme 44 <i>Cis</i> -reduction of 319 by NaBH ₄ to give exclusive formation of 322	133
Scheme 45 Formation of both enantiomers of 6-B345TTQ precursor 319 via successive oxidative kinetic resolutions of <i>cis</i> - 322	134
Scheme 46 Schmidt reaction giving both enantiomers of target 6-B345TTQ (99).	135
Scheme 47 Formation of imine intermediate 324	138
Scheme 48 Mechanism of the Eschweiler–Clarke reaction.	144
Scheme 49 Base-promoted Aldol condensation of a ketone (357) with an aldehyde (354).	147
Scheme 50 Overall synthetic route towards chiral 3-aryl-indan-1-ones: (a) NaOCH ₃ , CH ₃ OH or KOH, CH ₃ OH; (b) TFA or TFA, P ₂ O ₅ ; (c) NaBH ₄ , CH ₂ Cl ₂ : CH ₃ OH or L-Selectride, THF; (d) (<i>S,S</i>)-Ru complex ((<i>S,S</i>)- 63), acetone; (e) MnO ₂ , CH ₂ Cl ₂	296
Scheme 51 Comparison of Schmidt and Beckmann approaches for the synthesis of δ -lactams from 3-aryl-indan-1-ones.....	298
Scheme 52 Effect of substrate structure on Nazarov and Schmidt reactions.	300
Scheme 53 Pathway to benzylidene indan-1-one 35 and disconnection of piperonal (403).	301
Scheme 54 Potential base-catalysed racemisation of 3-aryl-indan-1-ones... ..	302

LIST OF TABLES

Table 1 Claisen–Schmidt reactions towards substituted chalcones 135-142	40
Table 2 Nazarov cyclisations of substituted chalcones 135-142 , with P ₂ O ₅	41
Table 3 Nazarov cyclisations of 3-methoxy-chalcones 135-138 under milder conditions.....	42
Table 4 Nazarov cyclisations of substituted chalcones 135-142 , without P ₂ O ₅	43
Table 5 Hammett values derived from the dissociation constants of benzoic acids.	44
Table 6 <i>Cis</i> -reduction of racemic 3-aryl-indan-1-ones 118-125	46
Table 7 Preliminary oxidative kinetic resolutions of racemic <i>cis</i> -indan-1-ols 149-156 .	50
Table 8 Oxidative kinetic resolutions of racemic <i>cis</i> -indan-1-ols 149-156	52
Table 9 MnO ₂ oxidation of residual enantiomerically enriched indan-1-ols 149-156 ..	58
Table 10 Effect of benzene ring substitution on the regiochemistry of Beckmann rearrangement of indan-1-one oximes.	107
Table 11 Formation of indan-1-one oximes 218-225 and oxime mesylates 226-233 ..	109
Table 12 Beckmann rearrangement reactions of racemic 3-aryl-indan-1-one oxime mesylates 226-233	110
Table 13 Optimisation of the Schmidt reaction of 3-aryl-indan-1-one 118	114
Table 14 Schmidt reactions of racemic 3-aryl-indan-1-ones 118-125	115
Table 15 Effect of NaN ₃ on the Schmidt reactions of racemic indan-1-ones 118-125 .	119
Table 16 Additional Schmidt reactions of racemic indan-1-ones and 1-tetralones.....	120
Table 17 Results of Heck coupling of styrene and 2-bromobenzonitrile.....	125
Table 18 Schmidt reactions of enantioenriched 3-aryl-indan-1-ones 118-125	127
Table 19 Optimisation of reduction conditions for dihydroisoquinolinone 241	137
Table 20 LiAlH ₄ reductions of racemic dihydroisoquinolinones 234-241	139
Table 21 LiAlH ₄ reductions of enantioenriched dihydroisoquinolinones 234-241	140
Table 22 Acetylation of racemic tetrahydroisoquinolines 323 and 325-331	141
Table 23 Acetylation of enantioenriched tetrahydroisoquinolines 323 and 325-331 ..	142
Table 24 <i>N</i> -methylation of racemic tetrahydroisoquinolines 323 and 325-331	145
Table 25 <i>N</i> -methylation of enantioenriched tetrahydroisoquinolines 323 and 325-331	146
Table 26 Aldol condensations of 3-aryl-indan-1-ones 118-125 with benzaldehydes..	148
Table 27 Overall yields for (<i>R</i>)- and (<i>S</i>)-3-aryl-indan-1-ones, via racemates 118-125	297

ACKNOWLEDGEMENTS

To would like to begin by acknowledging my supervisor, Dr David Fox, primarily for giving me this research opportunity, in which I have learnt a great deal and developed both practical and theoretical skills. The continued support and guidance that he has given me throughout my time within his research group has been instrumental to meeting the aims of this project; for this I am extremely grateful. Additionally I would like to thank the University of Warwick for the funding of this project.

I would also like to extend my gratitude to all past and present members of the Fox Group whom I've had the privilege of working alongside. In particular, I'd like to thank Matt Blackmore, Dr Paul Kerby, Dr Anish Mistry and Dr Jamie Tomlinson for their ideas and advice throughout the project as well as providing a friendly and entertaining working environment. Again, I would like to recognise Dr Paul Kerby's previous work in this field, which proved useful to the work herein. Furthermore, additional thanks goes to Dr Jamie Tomlinson for teaching me how to use the chiral HPLC instrument.

Support provided by the technical staff within the department is also greatly appreciated; Dr Lijiang Song, Philip Aston and James Morrey, in addition to Dr Ivan Prokes and Robert Perry, are all gratefully acknowledged for their assistance with Mass Spectrometry and NMR Spectroscopy, respectively.

Finally, I would like to thank my family and friends for their continuous support and encouragement over the past 4 years, throughout which they have made my PhD far more manageable and enjoyable.

DECLARATION

All work described herein was carried out in the Chemistry Department of the University of Warwick, between October 2015 and September 2019. Unless otherwise stated, it is the work of the author and has not been submitted in whole or part of any other degree at this or any other university. Any material described that is not original has been identified and appropriately referenced.

ABSTRACT

Chiral 3-aryl-indan-1-ones are incredibly useful compounds; they not only occur as the primary pharmacophore of a wide array of drugs and natural products, but also serve as building blocks towards medicinal scaffolds and other attractive compounds. There are countless examples of indan-1-ones exhibiting considerable medicinal properties, however often only the racemate is reported in such cases. This thesis describes the development of a general route for the synthesis of enantiomerically enriched 3-aryl-indan-1-ones and their subsequent transformations into a range of interesting compounds.

Chapter 1 provides an introduction to indan-1-ones – in particular those bearing a pendant 3-aryl group – and an insight into their biological importance. Asymmetric approaches towards these species are briefly examined, with a focus on the different resolution techniques that are available. This is followed by a more thorough discussion on oxidative kinetic resolutions of secondary alcohols, which serves as an avenue towards enantioenriched 3-aryl-indan-1-ones.

A convenient synthetic route that allows access to the individual enantiomers of 3-aryl-indan-1-ones in high enantiomeric excesses is discussed in **Chapter 2**. To begin, the straightforward synthesis of a series of racemic 3-aryl-indan-1-ones from commercially available starting materials is communicated. Following this is a “2.5-step” resolution of these racemic species into their individual enantiomers, the principal step being a highly stereospecific ruthenium-catalysed oxidative kinetic resolution.

Chapter 3 demonstrates the usefulness of 3-aryl-indan-1-ones as building blocks towards a variety of interesting medicinal scaffolds. The chapter opens with a survey of the biological properties of these compounds, after which two ring expansion transformations of 3-aryl-indan-1-ones – the Beckmann rearrangement and Schmidt reaction – are investigated. Further manipulations towards additional compounds of medicinal interest are then described, followed by the facile transformation of 3-aryl-indan-1-ones into their biologically active benzylidene counterparts. The syntheses of both enantiomers of two highly bioactive synthetic targets are also presented herein.

ABBREVIATIONS

Ac	Acetyl
AChE	Acetylcholinesterase
AIDS	Acquired immune deficiency syndrome
aq.	Aqueous
AR	Adrenoceptor
Ar	Aryl
<i>as</i>	Asymmetric (in IR assignments)
ATH	Asymmetric Transfer Hydrogenation
BINAM	2,2'-Bis(diphenylphosphinoamino)-1,1'-binaphthyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Br	Broad
Bu-	Butyl
c	Concentration
<i>ca.</i>	Circa
CA-4	Combretastatin A-4
Conv.	Conversion
COSY	Correlation spectroscopy
CTCL	Cutaneous T-cell lymphoma
d	Doublet
DA	Dopamine (receptor)
d.e.	Diastereomeric excess
Decomp.	Decomposition (melting point)
DEPT	Distortionless enhancement by polarisation transfer
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
EBV	Epstein–Barr virus
<i>E. coli</i>	<i>Escherichia coli</i>
e.e.	Enantiomeric excess
EDC	Ethylene dichloride
eq. / equiv.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl

EZH2	Enhancer of zeste homolog 2
FDA	Food and drug administration
FOXAP	Ferrocenyloxazolinylphosphine
GTP	Guanosine-5'-triphosphate
h	Hour(s)
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Heteronuclear multiple-quantum correlation spectroscopy
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSV	Herpes simplex virus
<i>i-</i>	<i>Iso</i>
IC ₅₀	Half maximal inhibitory concentration
IR	Infrared
LA	Lewis acid
lit.	Literature
Ltd.	Limited
M	Molar
<i>m / m-</i>	Multiplet (in ¹ H NMR assignments), medium (in IR assignments) <i>/ Meta</i>
MAO	Monoamine oxidase
MDL-27048	(<i>E</i>)-3-(4-(dimethylamino)phenyl)-1-(2,5-dimethoxyphenyl)-2-methylprop-2-en-1-one
Me	Methyl
MIC	Minimum inhibitory concentration
min.	Minute
m.p.	Melting point
Ms	Mesyl
N.B.	Nota bene
nbd	Norbornadiene
Nf	Nonafate (nonafluorobutanesulfonate)
NMDA	<i>N</i> -methyl-D-aspartate
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect

NPC	Nasopharyngeal carcinoma
<i>o</i> -	<i>Ortho</i>
<i>p</i> / <i>p</i> -	Pentet / <i>Para</i>
PARP	Poly(ADP-ribose) polymerase
pet	Petroleum
Ph	Phenyl
PhD	Doctor of Philosophy
PPA	Polyphosphoric acid
Pr-	Propyl
q	Quartet
<i>rac</i>	Racemic
R&D	Research and development
rt	Room Temperature
<i>s</i> / <i>s</i>	Singlet (in ¹ H NMR assignments), strong (in IR assignments) / Selectivity factor, Symmetric (in IR assignments)
SAHA	Suberoylanilide hydroxamic acid
SM	Starting material
SMA	Spinal muscular atrophy
<i>t</i> / <i>t</i> -	Triplet / <i>Tertiary</i>
TBAB	Tetrabutylammonium bromide
Temp.	Temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TET	Tetracycline
THF	Tetrahydrofuran
Tf	Triflate (trifluoromethanesulfonate)
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TOF	Time of flight
TPSA	Topological polar surface area
TS	Transition state
TsDPEN	<i>N-p</i> -tosyl-1,2-diphenylethylenediamine
UV	Ultraviolet
w	Weak
WT	Wild type

1.0 Enantiomerically Enriched 3-Aryl-indan-1-ones

1.1 Biological Importance of Indan-1-ones

The indane framework – that of a 5-membered aliphatic ring fused to an aromatic ring – is an important cyclic component found in a large number of biologically active molecules (Figure 1);¹⁻³ many natural products and drug candidates contain this motif, such as natural products mutisianthol (**1**) and jungianol (**2**),⁴⁻⁶ and the drug indinavir® (**3**) which is marketed as a protease inhibitor for the treatment of HIV and AIDS.^{1,7}

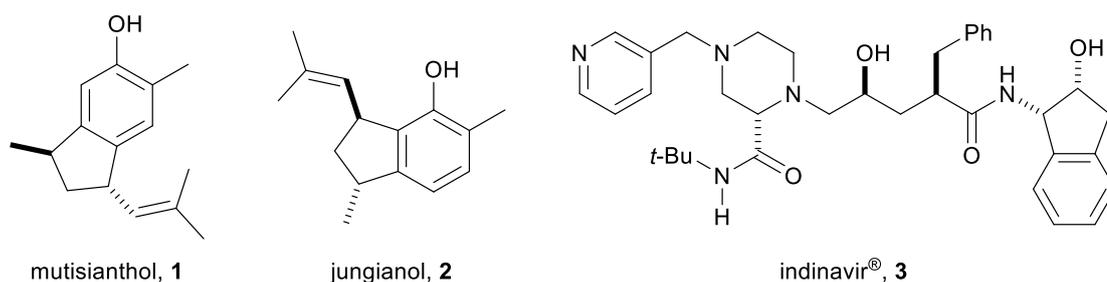


Figure 1 Indanes found in biologically active natural products and drugs.

Indanones are derivatives of indanes, of which there are two isomers possible: indan-1-one and indan-2-one (**4** and **5**, Figure 2). Indan-1-ones are an important class of bioactive compounds,^{8, 9} including tripartin (**6**), a natural product shown to inhibit histone demethylase,¹⁰ and the family of pterosin sesquiterpenes (e.g. **7** and **8**), which can exhibit antimicrobial,¹¹ antispasmodic,¹² and cytotoxic activities.¹³

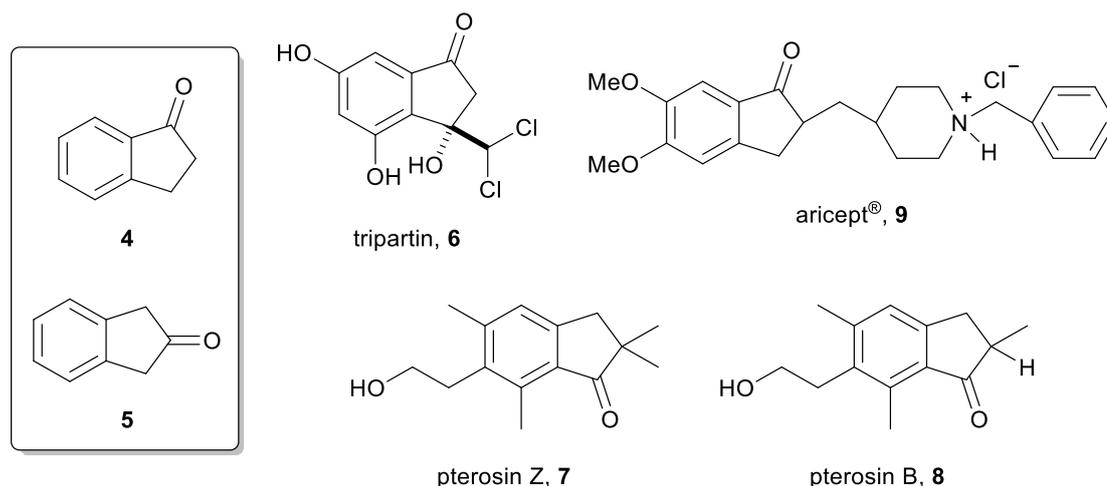


Figure 2 Structures of indan-1-one (**4**) and indan-2-one (**5**), and indan-1-ones found in biologically active natural products and drugs.

In addition to natural products, the indan-1-one skeleton is frequently observed within drugs. Also shown in Figure 2, and perhaps the most renowned indan-1-one derivative, is donepezil (aricept® **9**). Discovered in 1995,¹⁴ donepezil is a very potent acetylcholinesterase (AChE) inhibitor with an IC₅₀ of only 5.7 nM and, as such, has been used as a first-line therapy for Alzheimer's disease. It works by increasing the levels of cortical acetylcholine, a neurotransmitter crucial to cognitive function. The most significant characteristics of donepezil that make it ideal are its strong anti-AChE activity, a very high selectivity for AChE, and a half-life within humans (and animals) long enough to allow for convenient once-daily dosage.^{15, 16}

In addition to fighting Alzheimer's disease, indan-1-ones have been found to possess anti-cancer activity.¹⁷⁻²⁴ Examples include indanocine (**10**), a microtubule-binding indanone that has been identified as a selective inducer of apoptosis in multidrug-resistant cancer cells,²² and compounds **11-15**, inhibitors of enzyme aromatase for the potential treatment of cancer (Figure 3).²⁴

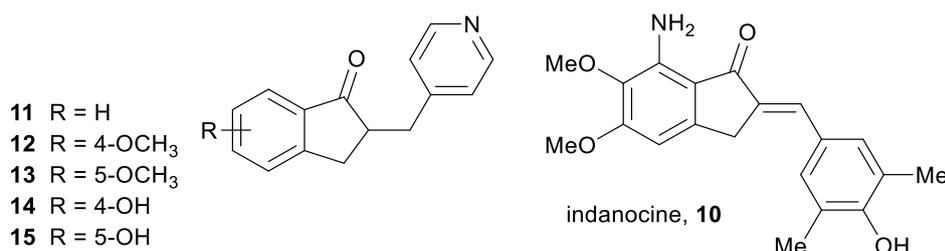


Figure 3 Indanocine and inhibitors of enzyme aromatase.

Microtubules are a major target for anti-cancer chemotherapy due to their significance in the mitosis and cell division processes.²⁵ The structure of microtubules mainly consists of tubulin, a dimeric protein molecule containing two non-identical α and β subunits.²⁶ Colchicine (**16**, Figure 4), a tropolone derivative, binds to tubulin at the interface of the α/β -tubulin subunits and near the GTP-binding site of α -tubulin. Binding slows down the polymerisation and consequent elongation of the tubulin, therefore slowing subsequent depolymerisation and thus inhibiting cell mitosis.²⁷

Major colchicine-domain binders include chalcones such as MDL-27048 (**17**),²⁸ as well as combretastatin A-4 (CA-4, **18**).²⁹ These and other diverse chalcones have gained intense interest as potential anti-cancer agents, binding both rapidly and reversibly to the colchicine-binding site, causing them to be strong antimitotic agents and, as such, have been found to be potent anti-cancer agents against various human cancer cell lines.³⁰⁻³² The latest advances of cytotoxic chalconoids targeting tubulin polymerisation has been recently reviewed.³³

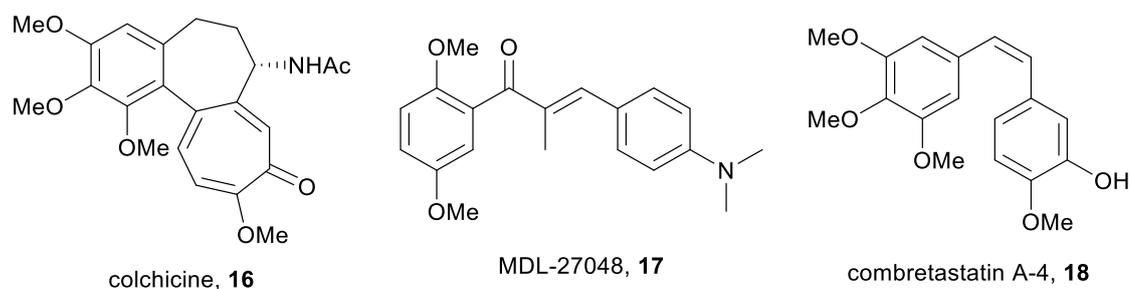


Figure 4 Colchicine and colchicine-domain binders that have gained intense interest as potential anti-cancer agents.

With the knowledge that indanones possess anti-cancer properties, Dulla *et al.* synthesised a number of indanone-indole hybrids (**20-24**) from indanones (e.g. **10**) and indoles (e.g. **19**, Figure 5), the latter of which are also known to exhibit similar medicinal benefits.²¹

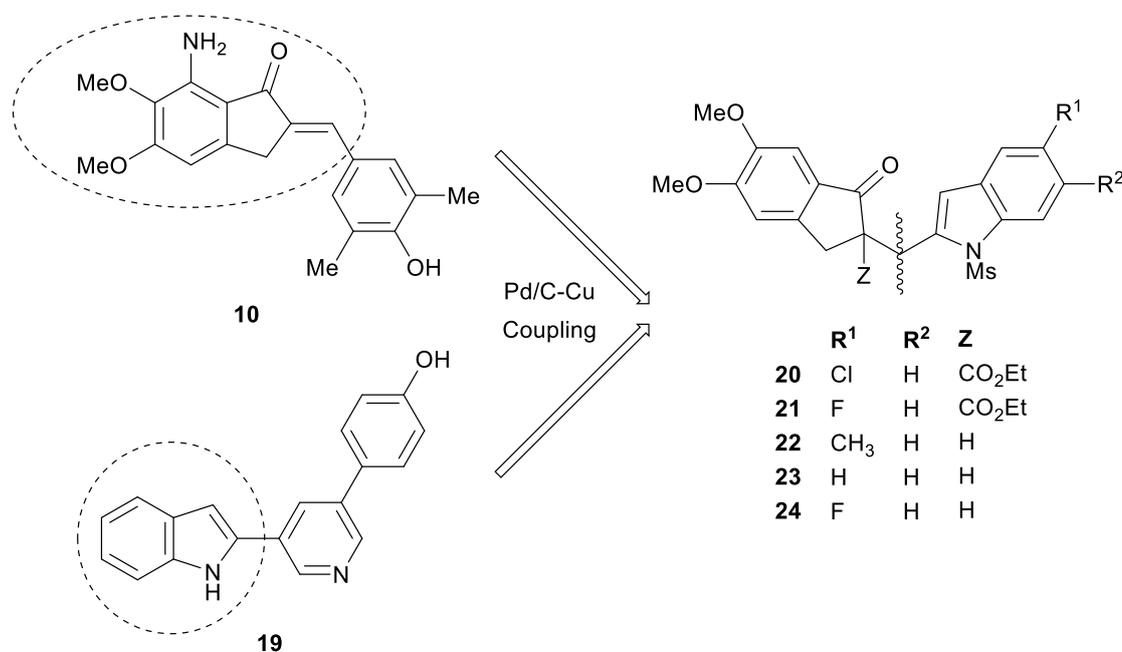


Figure 5 Newly designed indanone-indole hybrids **20-24**.

This new framework, made via a Pd/C–Cu mediated coupling–cyclisation strategy as a key step, was anticipated to also show promising anti-cancer properties – *in vitro* pharmacological properties of this class of molecule had not previously been explored. All synthesised compounds were evaluated for their anti-proliferative properties *in vitro* against six cancer cell lines, including human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205) and breast cancer cells (MDA-MB-231 and MCF7). Despite all compounds showing selective growth inhibition of cancer cells,

20-24 were found to be most promising with IC₅₀ values in the range of 0.1–1.2 μM, indicating their potential as novel anti-cancer agents.²¹

Although there are a large number of biologically important 2-substituted indan-1-one compounds, the following discussions will focus on indan-1-ones substituted at the 3-position.

As part of an investigation into the tubulin binding properties of combretastatin A-4 (**18**) and related chalcone analogs, Lawrence *et al.* found that the *s-trans* configuration of chalcone **25** proved to be important to its biological activity (Figure 6).^{18, 31} As a result of this discovery, the same group initiated a study of conformationally constrained analogs that mimic this *s-trans* arrangement, leading to the synthesis of a series of racemic “CA-4-like” indanones (**26-30**, Figure 6). The cell growth inhibitory properties in the K562 human chronic myelogenous leukaemia cell line of a number of these indanones were determined. Most of the indanones examined showed promising anti-cancer properties, though unsurprisingly it was the 3,4,5-trimethoxy-substituted variants that generally possessed greater cell growth inhibitory properties, with indanone **28** (IC₅₀ = 0.13 μM) bearing the greatest resemblance to CA-4 displaying high activity – the presence of three methoxy groups is known to be highly beneficial for good tubulin-binding properties.¹⁸

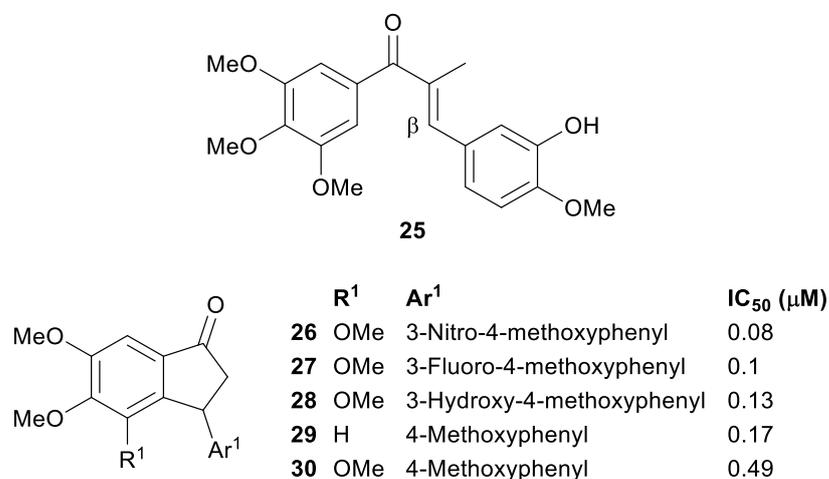


Figure 6 Biologically active *s-trans* chalcone **25** and potent 3-aryl-indan-1-ones related to combretastatin A-4.

Saxena *et al.* reported 3-substituted gallic acid-based indanone derivatives with powerful anti-cancer activity against various human cancer cell lines (Figure 7), including oral, liver and hormone-dependent breast cancer.¹⁷ Notably, the most potent compound (**31**, IC₅₀ = 2.2 μM), showed no toxicity to human red blood cells even at higher concentrations, despite being reported only as a racemic mixture. All of the compounds

studied possessed a 3,4,5-trimethoxy- phenyl fragment, which is known to bind with microtubules to induce tubulin polymerisation inhibition, inducing cytotoxicity through the antitubulin effect.³⁴

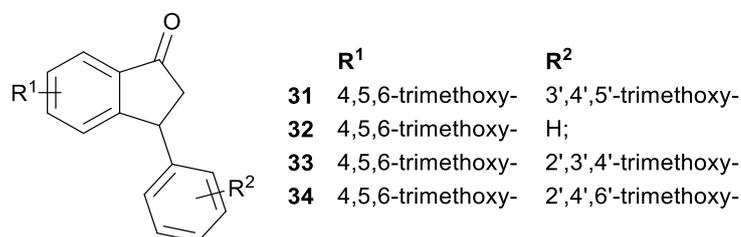
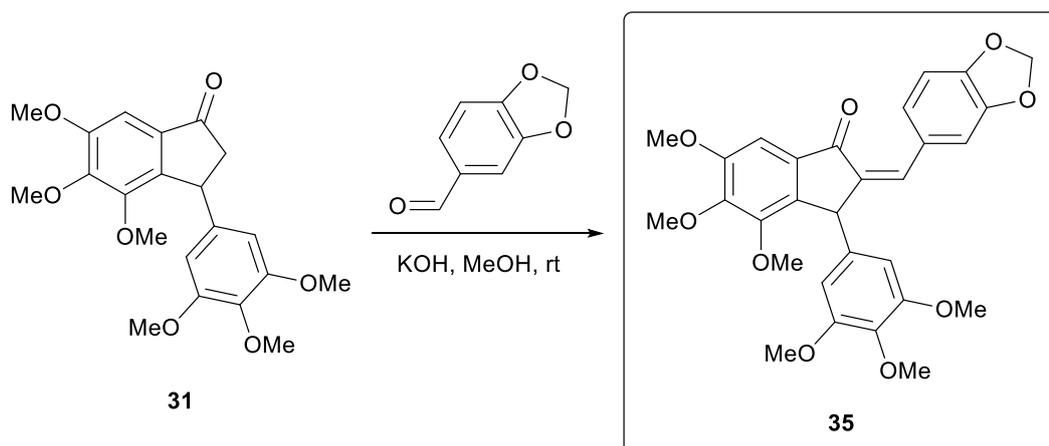


Figure 7 Potent anti-cancer gallic acid-based indanones.

Later work by the same team (Negi *et al.*) involved the synthesis of a series of 2-benzylidene indan-1-ones, via Claisen–Schmidt condensation of intermediate indanone **31** with various benzaldehydes (Scheme 1), and the subsequent evaluation of their biological activities.¹⁹



Anti-cancer Profile of 35:

- Cytotoxicity: MCF-7, IC₅₀ = 10 nM
- *In vivo* sub-acute toxicity: Non-toxic up to 1000 mg/kg dose for 28 days
- *In vivo* anticancer activity: Ehrlich ascites carcinoma 45.48 % tumour reduction at 20 mg/kg dose
- Induces apoptosis caspase pathway
- Cell cycle arrest at G2/M phase

Scheme 1 Synthesis and anti-cancer profile of 2-benzylidene indanone **35**.

These compounds exhibited strong cytotoxicity against human cancer cell lines (IC₅₀ = 0.01–0.88 μM) and also tubulin polymerisation inhibition (IC₅₀ = 0.62–2.04 μM). The 3,4-methylenedioxybenzylidene analogue **35** was the best compound of the series; the IC₅₀'s of this compound against MCF-7 (breast) and HCT (colon) cell lines were 0.01 and 0.10 μM, respectively, and it was shown to effectively inhibit tubulin polymerisation. Moreover, *in vivo* acute oral toxicity tests in Swiss-albino mice showed compound **35** to be non-toxic up to 1000 mg/kg dose, despite being reported as a racemate. Further *in vitro*

and *in vivo* studies demonstrated potent cytotoxicities ($IC_{50} = 0.01\text{--}14.8\ \mu\text{M}$) of **35** against various human carcinoma cells, as well as 45.5 % inhibition of tumour growth at 20 mg/kg dose in Ehrlich ascites carcinoma within Swiss albino mice. This led to the conclusion that benzylidene indanone **35** is an antimetabolic, apoptosis inducing, safe and moderate anti-tumour lead molecule.^{20, 23}

Benzylidene indan-1-ones have also been shown as promising candidates for the treatment of Alzheimer's disease. Li *et al.* designed, synthesised, and tested a number of these indanone derivatives to assess their potential as anti-Alzheimer's disease agents.³⁵ Most compounds demonstrated good inhibitory activity against AChE, with IC_{50} values in the nanomolar range, and some displayed activities similar to donepezil. Benzylidene indan-1-ones were made by the direct condensation of indan-1-ones and appropriate substituted benzaldehydes in a methanolic NaOH solution.

Gallic acid-based indan-1-ones have also been shown to combat *E. coli*, in particular reducing the minimum inhibitory concentration (MIC) of tetracycline (TET) against multidrug resistance clinical isolate of *E. coli*.³⁶ TET antibiotics are well-known mainly because of their broad spectrum of antimicrobial properties, cost-efficiency, and relatively low toxicity.³⁷ Tetracyclines are effective not only against prokaryotic organisms but also against some eukaryotic parasites,³⁸ however their clinical usefulness has been declining because of the appearance of an increasing number of TET-resistant isolates of clinically important bacteria; one of the predominant resistance mechanisms in prokaryotic systems, TET efflux, was first discovered in a study on *E. coli*.³⁹ Efflux pumps continuously emerge as a major problem of multidrug resistance in the last three decades, rendering existing antibiotics ineffective and thus new therapeutic options needed.⁴⁰ Within this study by Dwivedi *et al.*, a series of indan-1-ones were synthesised and evaluated for their antibacterial potential both alone and in combination with TET. Compound **31** – highlighted above for having anti-cancer activity – was found to be the best derivative with respect to drug resistance reversal in combination with TET against all strains of *E. coli*, acting through efflux pump inhibition. In addition, **31** extended the post-antibiotic effect – the phenomenon of continued suppression of growth after short exposure of bacteria to the antimicrobial agents – and was non-toxic and well tolerated up to 300 mg/kg dose in subacute oral toxicity study in mice.³⁶

The indan-1-one framework was further highlighted as an important pharmacophore with the synthesis of two indanone acetic acids (**36** and **37**) and their pyrazolone derivatives (**38** and **39**) in 2010 (Figure 8).⁴¹ These compounds demonstrated anti-inflammatory

activity in rats (20 mg/kg dose), with both acetic acid derivatives displaying 70 % inhibition of edema, persisting for 3 hours, and 60-70 % inhibition persisting for 5 hours in the case of the pyrazolone adducts.

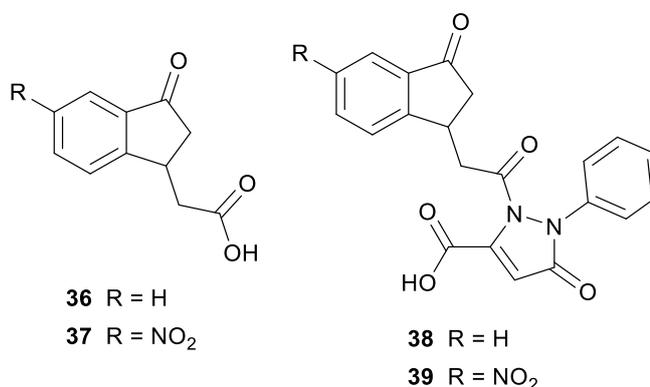


Figure 8 Indan-1-ones possessing anti-inflammatory activity.

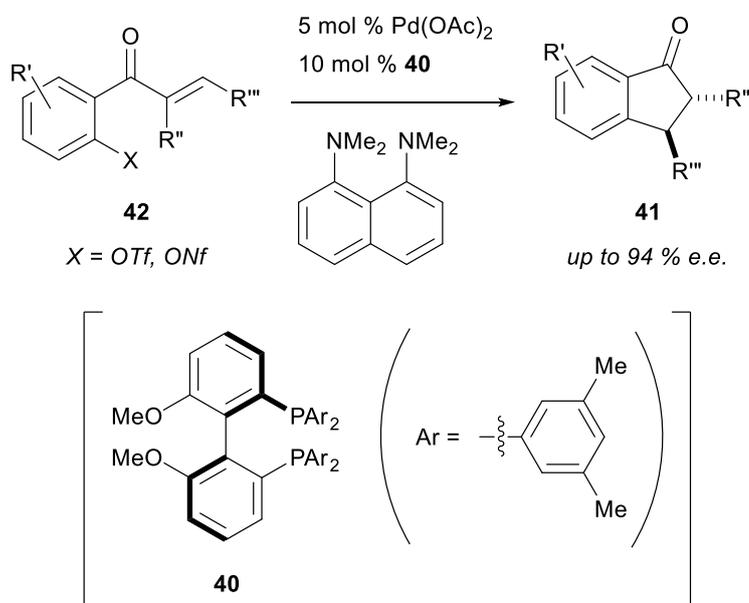
Overall, it has been seen that the indan-1-one moiety with functionality at the 2- and/or 3- positions has been the core structural unit of a variety of drugs and natural products; from anti-cancer and anti-inflammatory activities, to treating Alzheimer's disease and *E. coli*, it is clear that synthetic and natural chiral indan-1-ones are of great importance to the pharmaceutical industry. As such, a convenient and effective method towards these substrates is highly sought-after, especially given that often only one of a drug's enantiomers is responsible for the desired physiological effects, while the other enantiomer is less active, inactive, or can sometimes cause adverse effects.⁴² Arguably the most (in)famous example of a drug with undesirable side effects is thalidomide.⁴³

1.2 Towards Enantioenriched Indan-1-ones

In recent years the discovery and development of drugs and active ingredients has moved away from chemical processes that give racemic compounds towards those that produce stereochemically defined products. To this end, several 'tools' are becoming increasingly available such as the chiral pool, asymmetric catalysis, chiral reagents, chiral auxiliaries, preparative chiral HPLC, resolution and biotransformation.⁴⁴ Asymmetric synthesis should ideally yield stereochemically enriched molecules both practically and efficiently, however developing an enantioselective route is rarely simple, often proving to be time-consuming and resource-intensive, among other defining factors.⁴⁵ A number of synthetic pathways towards enantioenriched indan-1-ones have already been developed.

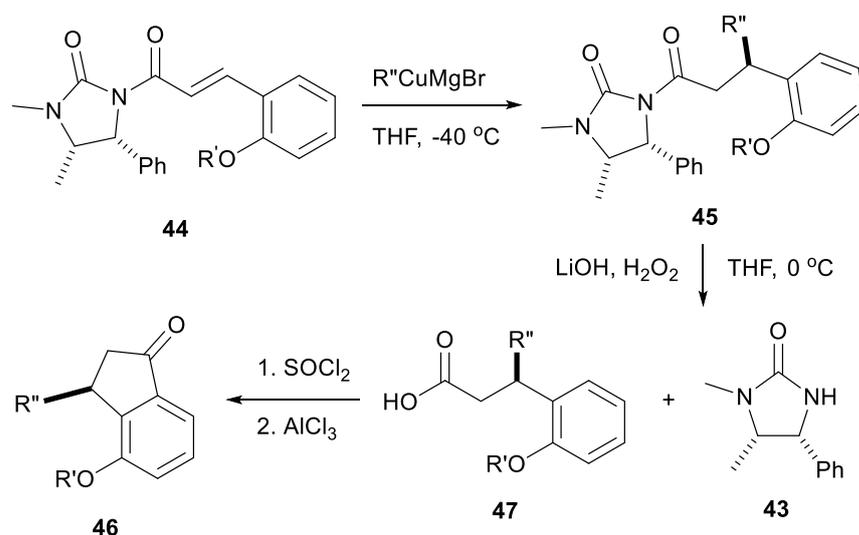
1.2.1 Direct Pathways – Asymmetric Synthesis

One major approach towards enantioenriched indan-1-ones is asymmetric synthesis, the primary technique of which is perhaps asymmetric catalysis, in which chiral coordination complexes are utilised as catalysts. Examples include rhodium-catalysed hydroacylations,^{46, 47} rhodium-catalysed asymmetric intramolecular 1,4-addition,⁴⁸ and asymmetric Heck cyclisations.⁴⁹ The latter was first reported by Püschl and co-workers as a racemic synthesis of 3-aryl-indan-1-ones.⁵⁰ However, Buchwald *et al.* improved the methodology by introducing the ancillary phosphine ligand (*R*)-3,5-XylMeOBIPHEP (**40**) to efficiently deliver enantiomerically enriched 3-substituted indan-1-ones (**41**) via an intramolecular palladium-catalysed asymmetric Heck reaction from the corresponding (*E*)-chalcones (**42**, Scheme 2).⁴⁹ Enantioenriched 3-aryl-indanones were typically formed in good yields and high enantioselectivities.



Scheme 2 Enantioselective reductive Heck cyclisation towards enantioenriched 3-aryl-indan-1-ones.⁴⁹

The use of chiral auxiliaries to give enantioenriched 3-aryl-indan-1-ones is also known, for instance the work by Rocher and coworkers in 1994 (Scheme 3).⁵¹ The authors utilised imidazolidinone auxiliary **43** to introduce chirality during the addition of a Grignard reagent to α,β -unsaturated ketone **44**, allowing a substituent (R²) to be incorporated in the desired configuration in **45**. The auxiliary was removed with lithium hydroxide and hydrogen peroxide, and the enantioenriched indan-1-one **46** was then formed from **47** via an intramolecular Friedel–Crafts acylation.



Scheme 3 Use of chiral imidazolidinone auxiliary **43** in the synthesis of enantioenriched 3-aryl-indan-1-ones (**46**).⁵¹

Organocatalysis,⁵² or indeed enantioselective organocatalysis,⁵³ on the other hand, has not been well-documented within the literature as an approach towards enantioenriched indan-1-ones. The same is true for chiral pool synthesis, which involves making use of the chiral pool provided by nature, i.e. using enantiopure starting materials. In instances where the requisite starting material is produced by nature in great abundance, or where the target is itself a complex natural product which would be very expensive to synthesise in a laboratory, the chiral pool approach is unbeatable. However, the range of compounds provided by nature is limited with respect to structure and stereochemistry, which severely limits the versatility of the chiral pool.⁴⁵ This appears to be the case with respect to the target indanones.

1.2.2 Indirect Pathways – Racemic Synthesis & Chiral Resolution

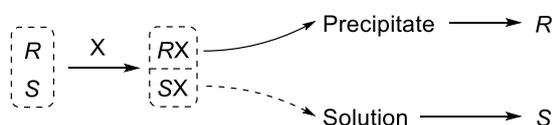
Whilst multiple enantioselective methods are available for the direct (asymmetric) synthesis of enantioenriched 3-aryl-indan-1-ones, one of the most common and effective approaches towards indan-1-ones is a Nazarov cyclisation reaction of the corresponding chalcones,⁵⁴⁻⁵⁶ which yields a racemic mixture, thus opening up an avenue for chiral resolution into the two enantiomers.⁴⁵ Named after Russian chemist I. N. Nazarov (1906–1957), the Nazarov cyclisation is broadly defined as the acid-catalysed cationic pericyclic closure of divinyl ketones to 2-cyclopentenones.^{57, 58} The transformation was initially discovered in 1903 by Vorländer and coworkers,⁵⁹ but it was not until Nazarov *et al.* comprehensively investigated the cyclisation in the 1940s and 1950s that the reaction became more fully understood.^{60, 61} The Nazarov reaction involves the cyclisation of

process is still favoured. Recent advances of the Nazarov cyclisation have been reviewed, including examinations of both asymmetric,⁷⁰ and catalytic Nazarov processes.⁵⁴

Asymmetric synthesis, the preparation from achiral precursors using chiral auxiliaries, reagents or catalysts, is an attractive way to produce enantioenriched materials, however it is not always the best approach.⁷⁴ The major alternative approach is chiral resolution, in which enantiomers are separated by chemical or physical means. An unattractive consequence of performing a resolution, as opposed to asymmetric synthesis, is that only 50 % (of the total yield) of one enantiomer can be formed. Therefore, except in those rare cases where both enantiomers can be employed productively, this approach is less favourable and often avoided. The first reported resolution was Louis Pasteur's investigation of tartaric acid in 1857, which was the first observation of enantioselectivity in a biological (biochemical) process.^{75, 76} There are three types of resolution available:⁴⁵

1) Classical Resolution

'Classical' resolutions comprise the use of a chiral resolving agent that binds (covalently or non-covalently) to each enantiomer to generate a pair of diastereomers, which can be separated based on differing physical properties, followed by removal of the resolving agent from the substrate via a chemical reaction (Scheme 5).⁷⁷



Scheme 5 Classical resolution using a chiral resolving agent (X).

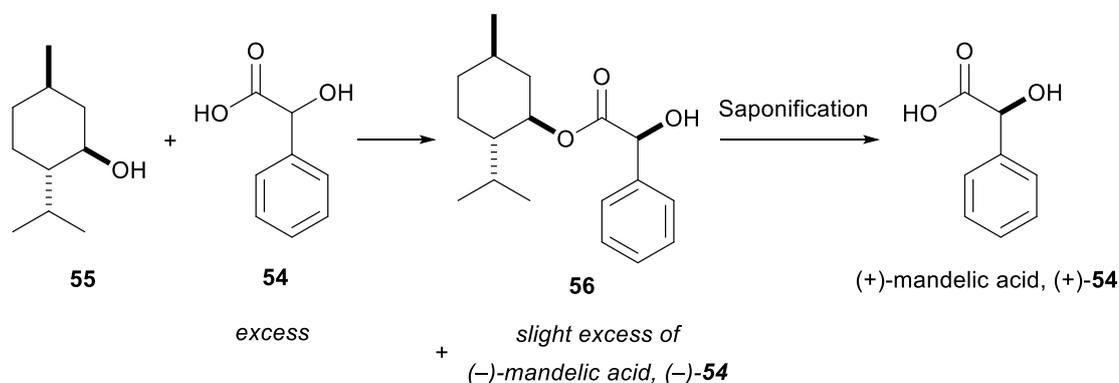
A racemate can only be resolved with ease if the enantiomers form separate crystals, i.e. salt formation is straightforward. The process is subtle and complex, yet classical resolution techniques are overwhelmingly used over other more complex methods. This was highlighted by an article published by Carey *et al.* in 2006,⁷⁸ in which they surveyed the chemical syntheses within the Process Chemistry R&D departments of GlaxoSmithKline, AstraZeneca and Pfizer. For the 128 drug candidate molecules assessed resolution was the predominant method of chirality generation, of which two thirds were performed by classical salt formation and the remainder evenly distributed between dynamic kinetic, chromatographic and enzymatic methods. The availability of screening methods to develop classical resolutions, the increased understanding of crystallisations and the ease of scale-up continue to make this the preferred methodology for many chiral molecules.⁷⁹

2) Chiral Chromatography

Chiral chromatography employs a chiral stationary phase to resolve enantiomers contained in a mobile phase, and can be carried out on analytical or preparative scale. Preparative chiral HPLC is a technique that can result in significant savings of both time and labour, which is exemplified through its use within the synthesis of preclinical drugs.⁸⁰ Preparative chiral HPLC has also found its way into the formation of enantioenriched indan-1-ones.⁸¹ However, this technique still faces many challenges, including issues of loading capacity, chemical and/or mechanical stability, availability in large quantities at reasonable cost, and solvent limitations. All of these issues can have a great impact on both solubility and retention of the chiral compound, and thus on the productivity.⁸²

3) Kinetic Resolution

Kinetic resolutions are a means of differentiating two enantiomers in a racemic mixture by different rates of reaction with a chiral catalyst or reagent. Kinetic resolution by synthetic means was first reported by Marckwald and McKenzie in 1899 through their work on the esterification of racemic mandelic acid (**54**) with optically active (–)-menthol (**55**, Scheme 6).⁸³



Scheme 6 First kinetic resolution by synthetic means; racemic mandelic acid (**54**).^{83, 84}

They discovered that heating **55** with an excess of racemic mandelic acid (**54**) formed ester **56** more rapidly than its diastereomer, allowing the isolation of a small amount of pure (–)-mandelic acid. McKenzie later showed that the saponification rates of the esters also differed and that pure (+)-mandelic acid could be obtained by partial saponification of **56**.⁸⁴ This result initiated the use of kinetic resolutions in organic chemistry.^{45, 85}

The theory behind a kinetic resolution is that the reaction of one enantiomer is promoted over the other giving a mixture of enantioenriched starting material and product, which

can then be separated.^{45, 86} At the outset of a reaction, the system displays its best synthetic selectivity between the enantiomers because an equal amount of each enantiomer is present, however as the reaction proceeds, statistics begin to interfere as the fast-reacting enantiomer is depleted and its concentration reduces, causing the rate of the slow-reacting enantiomer to become significant. This means that although the maximum yield for the process is necessarily 50 %, unfortunately high enantiomeric excesses are found at the extremes of conversion – the enantioenrichment of the product is largest at the start of the reaction while that of the remaining starting material is largest just before the end of the reaction.⁷⁷ The ideal scenario is depicted in Figure 9, whereby only one of the starting material enantiomers reacts, i.e. SM_R , to give enantiopure product P_R and leaving enantioenriched unreacted starting material SM_S . In this case, $k_R \gg k_S$, where k_R and k_S are the rates of reaction for substrate enantiomers SM_R and SM_S respectively.

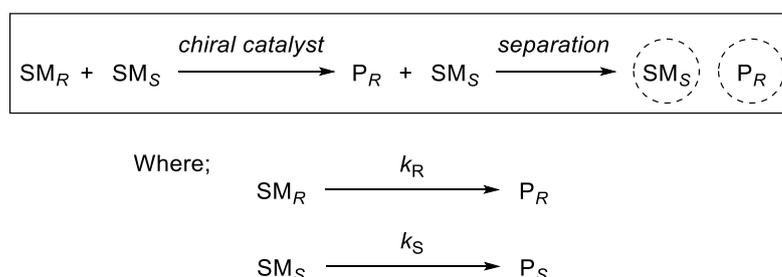


Figure 9 Ideal kinetic resolution of a racemic starting material (SM) to give product (P).

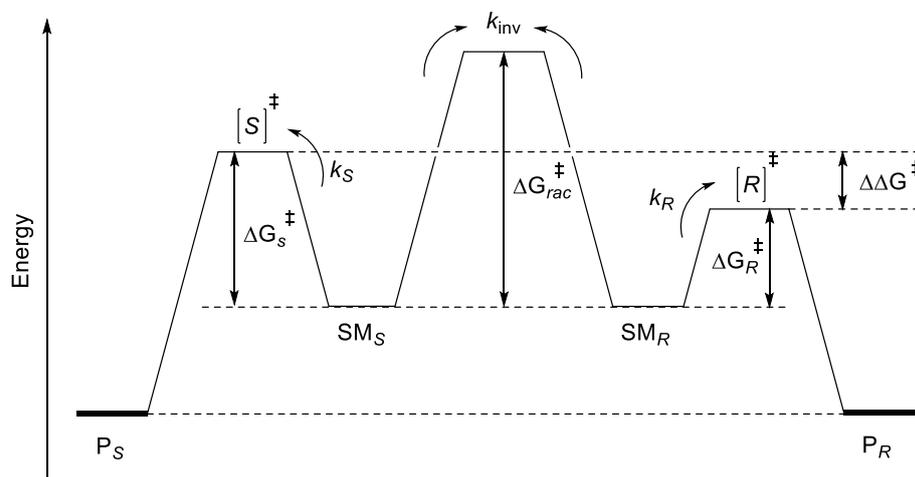


Figure 10 Representational energy diagram for a kinetic resolution.⁸⁷

By definition, both enantiomeric products exist at the same Gibbs free energy level, as do those of the starting material enantiomers.⁴⁵ However, the transition state energy, ΔG^\ddagger , of each transformation can differ due to diastereomeric interactions with the chiral catalyst; for instance in Figure 10, ΔG^\ddagger is smaller for the (*R*)- enantiomer, thus requires less

activation energy and so reacts faster than the (*S*)-enantiomer. The difference between these activation energies is denoted $\Delta\Delta G^\ddagger$.⁴⁵ In a catalytic kinetic resolution the relative rates of reaction for the substrate enantiomers, typically expressed as the selectivity factor, s , or $k_{rel} = k_{fast} / k_{slow}$, are dictated by the magnitude of $\Delta\Delta G^\ddagger$, as follows:⁸⁶

$$s = k_{rel} = \frac{k_{fast}}{k_{slow}} = e^{\Delta\Delta G^\ddagger/RT} \quad (1)$$

This selectivity value has been utilised for assessing the efficiency of the resolution, whereby s will be high for an efficient kinetic resolution.⁸⁸⁻⁹¹ In fact, since e.e. changes as a function of conversion in standard kinetic resolution reactions, s values are generally considered to be more useful for the evaluation (and comparison) of kinetic resolution catalysts. For simple first-order kinetics in substrate concentration, the selectivity can also be expressed in terms of e.e. of the recovered starting material and conversion (c), which will be derived below.^{45, 86, 88, 92} If it is assumed that the (*S*)-enantiomer of the starting material racemate will be recovered in excess (i.e. $k_R > k_S$), and that conversion is equal to c ($0 < c < 1$) at time t , then the amount of recovered starting material, $[S_{SM}]$, and its enantiomeric excess at time t is given by Equations 2 and 3 respectively. [N.B. c = conversion (%) / 100; $e.e._{SM}$ = e.e. of remaining starting material (%) / 100.]

$$[S_{SM}] + [R_{SM}] = 1 - c \quad (2) \quad e.e._{SM} = \frac{[S_{SM}] - [R_{SM}]}{[S_{SM}] + [R_{SM}]} \quad (3)$$

By combining these two relations, the concentrations of the (*R*)- or (*S*)-enantiomers (of starting material) can be calculated at any time:

$$[S_{SM}] = \frac{(1 - c)(1 + e.e._{SM})}{2} \quad (4) \quad [R_{SM}] = \frac{(1 - c)(1 - e.e._{SM})}{2} \quad (5)$$

For an irreversible first-order reaction with respect to substrate, the basic set of kinetic equations are:

$$\frac{d[R_{SM}]}{dt} = -k_R[R_{SM}] \quad \text{and} \quad \frac{d[S_{SM}]}{dt} = -k_S[S_{SM}]$$

Therefore, the relative rate is expressed as Equation 6, which can be simplified to Equation 7 by elimination of time t and taking $k_R/k_S = k_{rel} = s$:

$$\frac{d[R_{SM}]/dt}{d[S_{SM}]/dt} = \left(\frac{k_R}{k_S}\right) \left(\frac{[R_{SM}]}{[S_{SM}]}\right) \quad (6) \quad \longrightarrow \quad \frac{d[R_{SM}]}{[R_{SM}]} = s \frac{d[S_{SM}]}{[S_{SM}]} \quad (7)$$

Subsequent integration of Equation 7 and further manipulation leads to Equation 8, where $[R_0]$ and $[S_0]$ are defined as the initial concentrations of the two enantiomers ($t = 0$):

$$s = \frac{\ln([R_{SM}]/[R_0])}{\ln([S_{SM}]/[S_0])} = \frac{\ln([R_{SM}]) - \ln([R_0])}{\ln([S_{SM}]) - \ln([S_0])} \quad (8)$$

Substitution of Equations 4 and 5 into Equation 8, and rearrangement gives Equation 9.

$$s = \frac{\ln[(1-c)(1-e.e_{SM})] - \ln 2 - \ln([R_0])}{\ln[(1-c)(1+e.e_{SM})] - \ln 2 - \ln([S_0])} \quad (9)$$

Finally, knowing that $[R_0] = [S_0] = 1/2$ for a racemic starting material allows the selectivity factor to be given as a function of conversion and the enantiomeric excess of the starting material (Equation 10):

$$s = \frac{\ln[(1-c)(1-e.e_{SM})]}{\ln[(1-c)(1+e.e_{SM})]} \quad (10)$$

The selectivity can also be expressed in terms of the enantiomeric excess of the product. If it is assumed that the (*R*)-enantiomer of the product will be predominant (i.e. $k_R > k_S$), and that conversion is equal to c ($0 < c < 1$) at time t , then the amount of product, $[R_P]$, and its enantiomeric excess at time t is given by Equations 11 and 12 respectively.

$$[S_P] + [R_P] = c \quad (11) \quad e.e._P = \frac{[R_P] - [S_P]}{[R_P] + [S_P]} \quad (12)$$

By taking into account that at any time any amount of the (*R*)-enantiomer of the initial racemic mixture is distributed between the chiral product and the recovered starting material, Equation 13 may be derived, which is independent of s . [N.B. $e.e._P = \text{e.e. of product (\%)} / 100$.]

$$\frac{e.e._{SM}}{e.e._P} = \frac{([S_{SM}] - [R_{SM}])/(1-c)}{([R_P] - [S_P])/c} = \frac{c}{1-c} \quad (13)$$

From Equation 13, it can be seen that:

$$1 - e.e._{SM} = \frac{1-c - (c)(e.e._P)}{1-c} \longrightarrow (1-c)(1 - e.e._{SM}) = 1 - c(1 + e.e._P)$$

$$1 + e.e._{SM} = \frac{1-c + (c)(e.e._P)}{1-c} \longrightarrow (1-c)(1 + e.e._{SM}) = 1 - c(1 - e.e._P)$$

This allows to modify the fundamental equation (Equation 10) to give the selectivity factor as a function of conversion and the enantiomeric excess of the product (Equation 14):

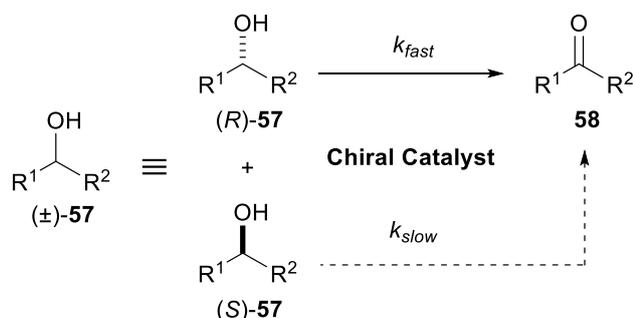
$$s = \frac{\ln[1 - c(1 + e.e._P)]}{\ln[1 - c(1 - e.e._P)]} \quad (14)$$

Equations 10 and 14 have been established for well-defined conditions: pseudo first-order in substrate (but any order in stoichiometric or catalytic chiral auxiliary) and no change of mechanism during the course of the reaction.⁹² For reactions in which the *s* value is not identical or similar at different conversions, a change in the structure of the reagent during the reaction is possible, or it might be the case that the reaction is not first-order with respect to the substrate.

Further practical and theoretical considerations behind kinetic resolutions is well explained in a review by Jacobsen *et al.* from 2001,⁴⁵ therefore they will not be covered in further detail here. A more thorough discussion on the rate laws associated with kinetic resolutions can be found elsewhere,^{85, 86, 88, 90} including those based on stoichiometric,⁹² biochemical,^{86, 93, 94} and dynamic kinetic resolutions,⁹⁴ which are outside the scope of this report. A comprehensive review of catalytic non-enzymatic kinetic resolutions was published recently by Hélène Pellissier, in which the different types of compounds that have been resolved through this process are examined.⁹⁶ This report, however, will focus solely on the oxidative kinetic resolution of secondary alcohols.

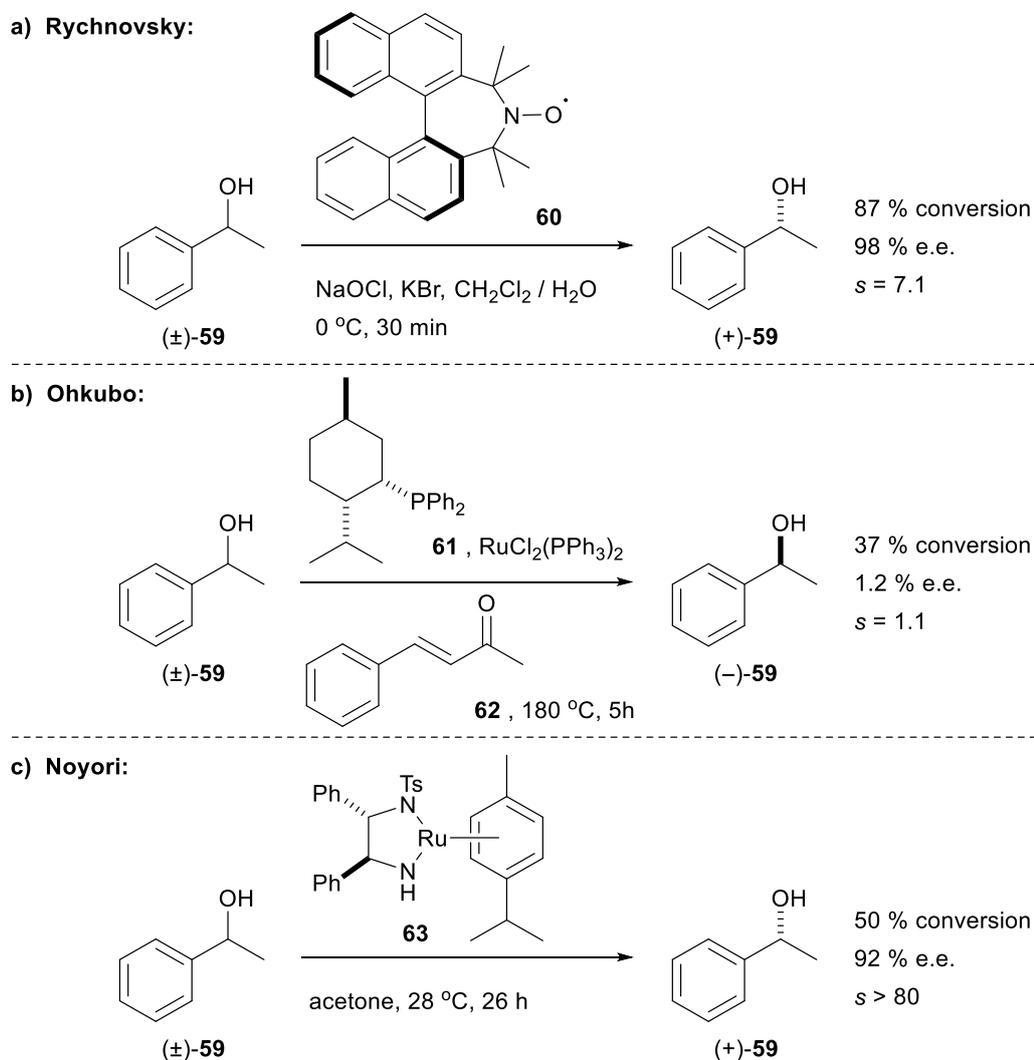
1.3 Oxidative Kinetic Resolution of Secondary Alcohols

Within an ideal oxidative kinetic resolution, one alcohol enantiomer (e.g. (*R*)-**57**) reacts faster with the catalyst to provide oxidised product **58**, while the other enantiomer ((*S*)-**57**) reacts far more slowly – ultimately the remaining enantiopure alcohol (*S*)-**57** and ketone **58** can be separated by standard techniques (Scheme 7). The enantiomeric excess of the starting material **57** will always increase with increasing conversion for any oxidative kinetic resolution with a selectivity factor greater than 1, therefore kinetic resolutions have the capacity to provide alcohols with high enantioenrichment for even modestly selective processes at higher levels of conversion. For this reason oxidative kinetic resolutions are typically used to access enantioenriched alcohols.⁹⁶



Scheme 7 Schematic principle of an ideal oxidative kinetic resolution.

The first example of a non-enzymatic catalytic enantioselective oxidation of alcohols was reported by Rychnovsky through his work on the oxidation of benzylic secondary alcohols, such as 1-phenylethanol (**59**), using chiral nitroxyl radical **60** and sodium hypochlorite as the oxidising agent (*a*, Scheme 8).⁹⁷

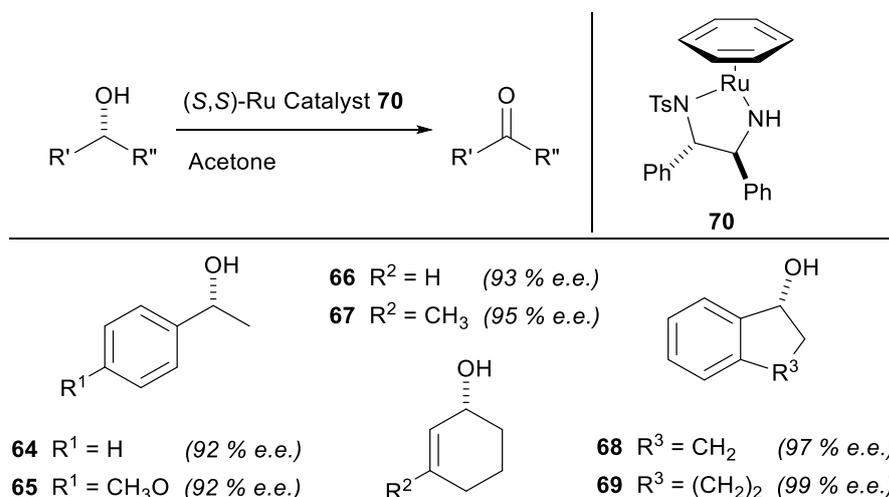


Scheme 8 Oxidative kinetic resolution of 1-phenylethanol (**59**); comparison of methods reported by Rychnovsky,⁹⁷ Ohkubo,⁹⁹ and Noyori.¹⁰⁰

Despite improvements to this method,⁹⁸ attention with respect to oxidative kinetic resolution of secondary alcohols has generally turned towards transition metal-catalysed procedures; the first such approach was demonstrated by Ohkubo *et al.*,⁹⁹ whereby a transfer hydrogenation process using $\text{RuCl}_2(\text{PPh}_3)_2$ as the catalyst, a menthol-derived phosphine ligand (**61**) and enone **62** as the sacrificial hydrogen acceptor was employed to provide (*S*)-1-phenylethanol ((*S*)-**59**) in only 1.2 % e.e. (*b*, Scheme 8). In 1997, Noyori *et al.* developed a highly enantioselective variant of a ruthenium-catalysed kinetic resolution of secondary alcohols,¹⁰⁰ adopting conditions similar to those employed for the

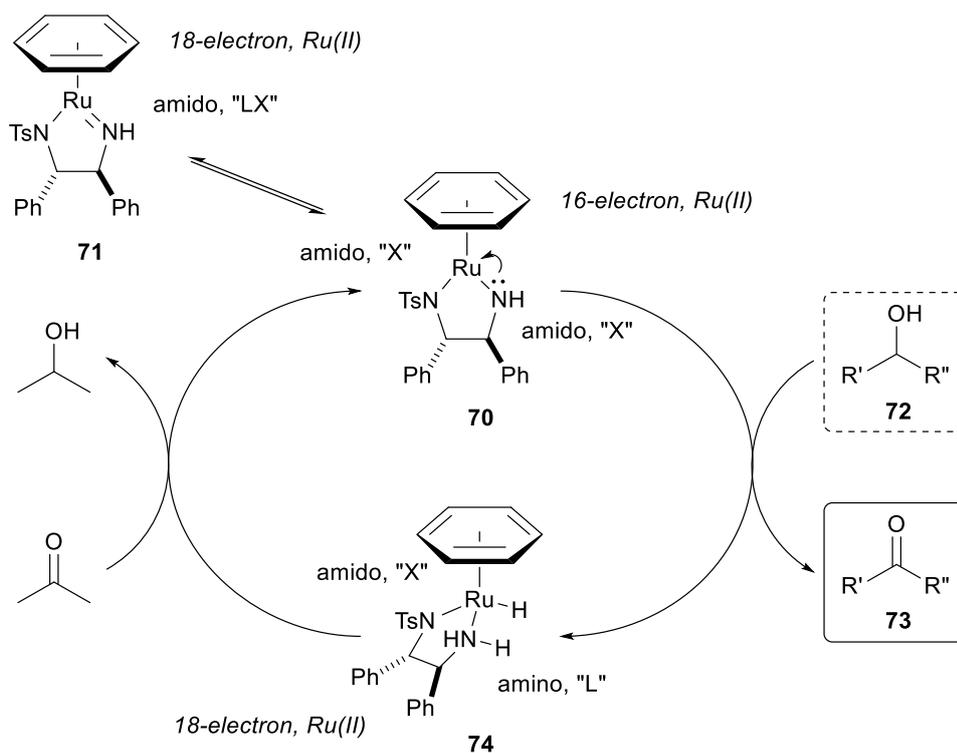
asymmetric hydrogenation of ketones and therefore demonstrating the reversible characteristic nature of this transformation.¹⁰¹ The asymmetric catalytic oxidation of 1-phenylethanol (**59**) using this method – (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (**63**) in acetone at 28 °C – proved far more effective than that of Ohkubo, giving the (*R*)-enantiomer ((*R*)-**59**) in 92 % e.e. (c, Scheme 8).

Noyori further highlighted the versatility of his ruthenium-diamine catalysts by resolving a range of secondary alcohols **64-69** with acetone as both the hydrogen acceptor and reaction solvent (Scheme 9); this work involved the use of ruthenium complex **70**, which comprises an unsubstituted arene ligand instead of cymene as seen previously. Of particular note were the oxidative kinetic resolutions of racemic indan-1-ol and α -tetralol, which gave the corresponding (*R*)-enantiomers ((*R*)-**68** and (*R*)-**69**) in 97-99 % e.e. at almost 50 % conversion in only 6 hours. Most of these alcohols were difficult to obtain in high enantiomeric purity by reduction of the corresponding ketones with 2-propanol,¹⁰² which emphasises the advantage of Noyori's oxidative kinetic resolution method. Arguably the most attractive feature of this ruthenium-catalysed reaction is the use of acetone as the inexpensive and well-behaving hydrogen acceptor.



Scheme 9 Noyori's Ru-catalysed oxidative kinetic resolution of secondary alcohols.¹⁰⁰

The active catalyst within the oxidation catalytic cycle (Scheme 10) is widely recognised by organic chemists as a 16-electron square planar complex (**70**) with both nitrogen atoms of the *bis*-diamine acting as an amido X-type ligand to the ruthenium atom.¹⁰¹ However, **70** can be viewed as an 18-electron species (**71**) whereby the non-tosylated nitrogen donates its lone pair of electrons to the metal, thus behaving as an amido LX-type ligand to generate a Ru=N double bond – for simplicity, formal atom charges on the ligand and metal atom are invariably not shown in chemical structures featuring such interactions.¹⁰³



Scheme 10 Ruthenium-catalysed oxidation catalytic cycle.

The catalytic cycle begins with the active species **70** acquiring two hydrogen atoms from one of the starting material enantiomers (**72**) via transfer hydrogenation, which gives the product ketone (**73**) and unreacted enantioenriched alcohol. The 18-electron ruthenium species that forms (**74**) – one amido nitrogen ligand and one amino-type ligand – is then converted back to its oxidising form via the transfer of the two hydrogens to acetone.

Since Noyori's report in 1997 on the kinetic resolution of secondary alcohols by hydrogen transfer,¹⁰⁰ the employment of chiral diamine Ru(II) complexes – with acetone as the hydrogen acceptor – as an oxidative method of resolving alcohols has not been prevalent within the literature.^{104, 105} One rare example, published in 2003, reported the oxidative kinetic resolution of a range of 3-hydroxymethyl-1-tetralols as well as 3-hydroxymethyl-1-indanol using Noyori's Ru(II)-(S,S)-TsDPEN catalyst **63**; the corresponding (S)-ketones and remaining (R,R)-alcohols were obtained in moderate to high e.e., albeit after increasing catalyst loading and employing methanol alongside acetone as the solvent.¹⁰⁶ Higher enantioselectivities have been reported for the oxidative kinetic resolution of similar secondary alcohols with a range of different chiral ruthenium catalysts, including [RuCl₂(PPh₃)(FOXAP)], utilising optically active FOXAP ligands **75** and **76**,¹⁰⁷ and Ru(salen) complexes (**77-79**), employing ligands derived from the highly popular salen (N,N'-bis(salicylidene)ethylenediamine) ligand (Figure 11).¹⁰⁸

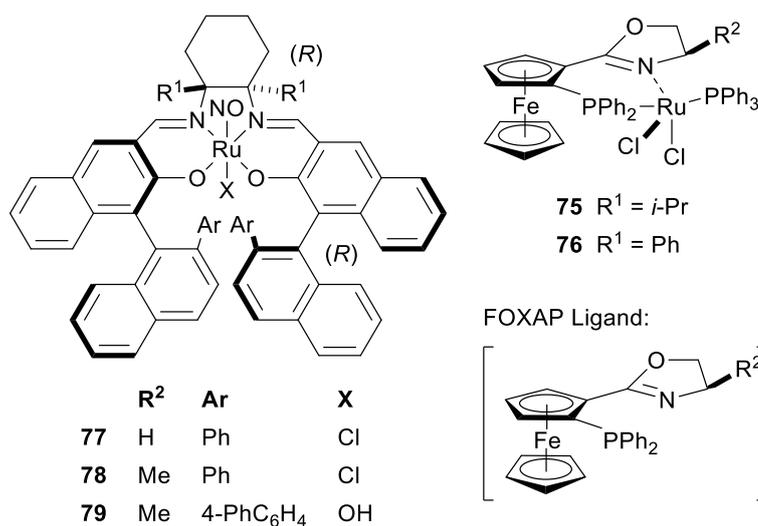


Figure 11 Reported ruthenium catalysts for the oxidative kinetic resolution of alcohols.

In addition to ruthenium catalysts, a diversity of other transition metal catalysts, such as rhodium,¹⁰⁹⁻¹¹¹ have been used to good effect in the oxidative kinetic resolution of secondary alcohols.^{96, 112} In 2003, Xia reported the oxidative kinetic resolution of secondary alcohols using manganese-salen catalysts **80-84** with iodobenzene diacetate as the stoichiometric oxidant (Figure 12).¹¹³

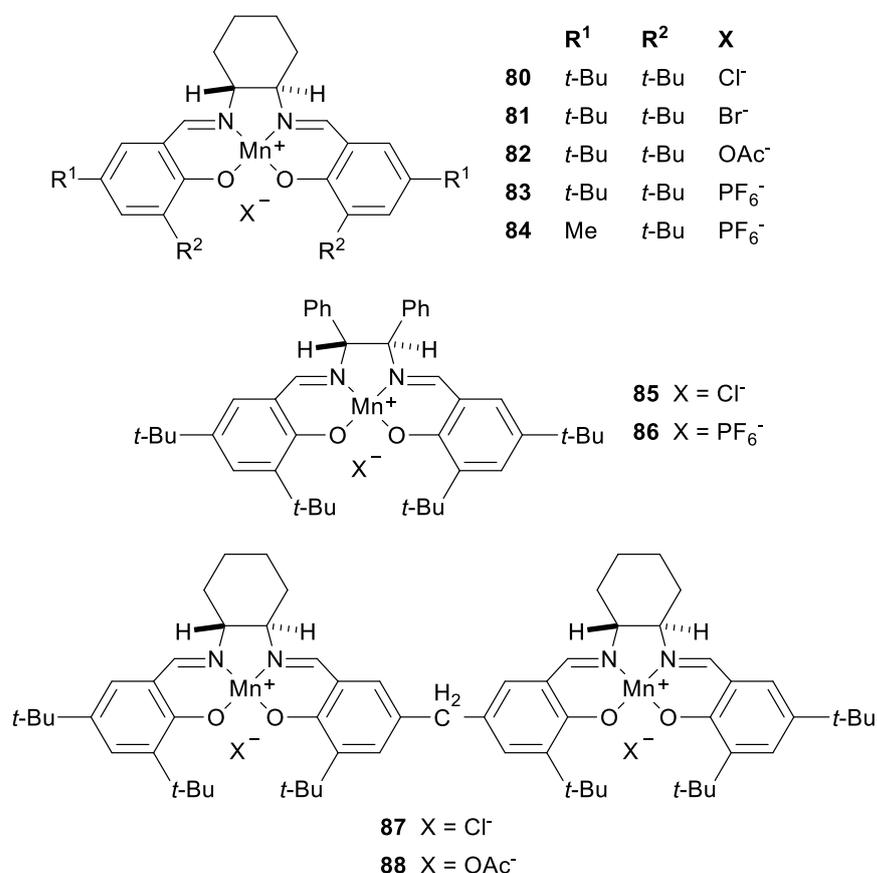
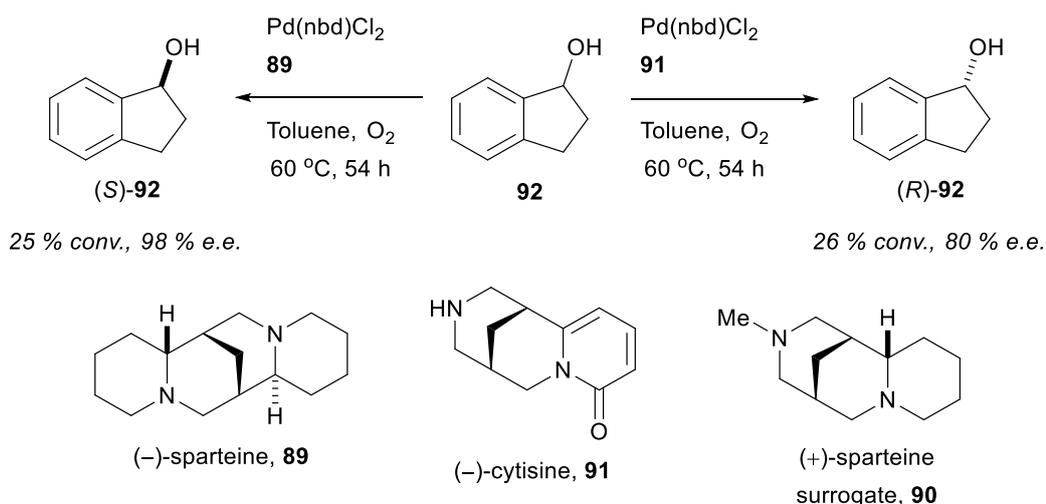


Figure 12 Mn(salen) catalysts used in oxidative kinetic resolutions of alcohols.

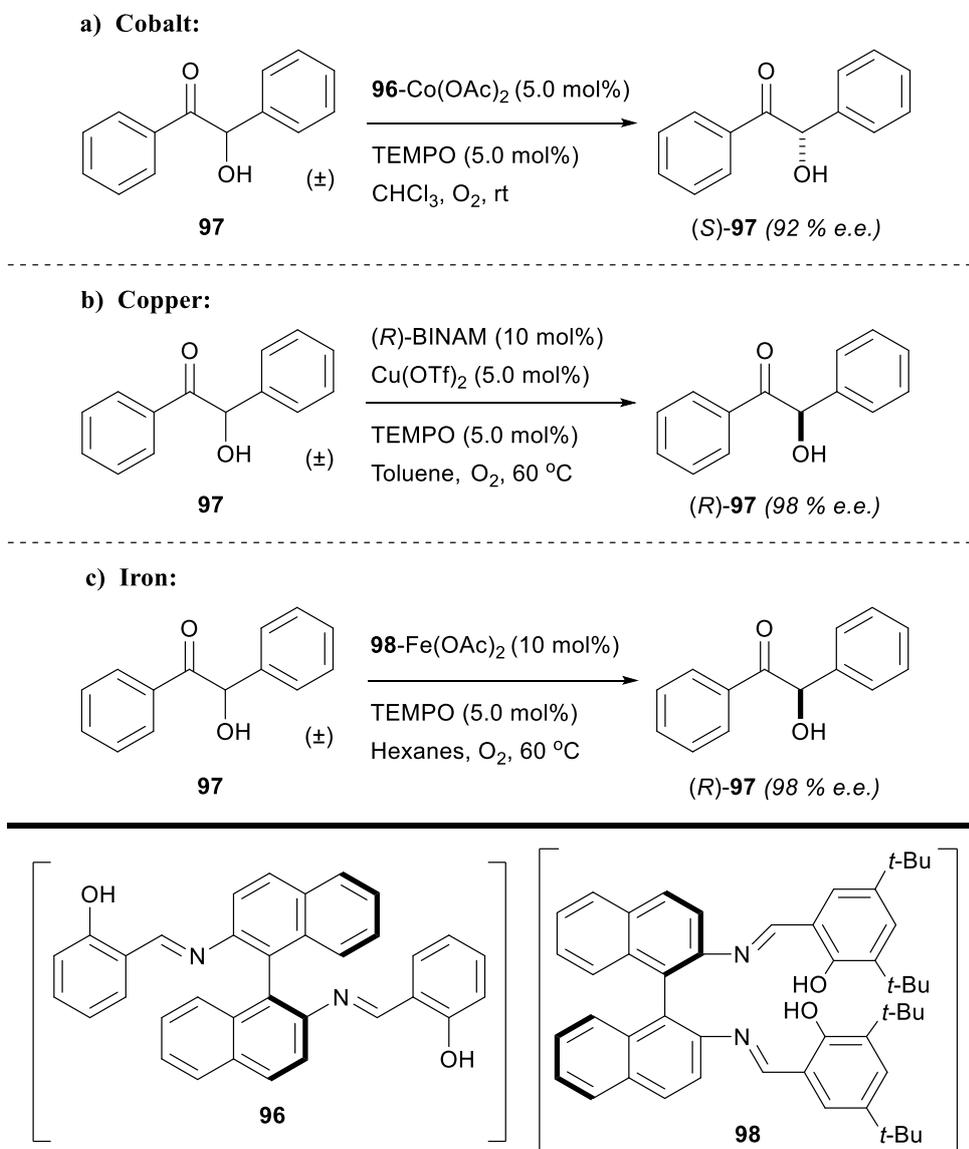
Xia demonstrated that water could be successfully used as a benign solvent in this reaction system, which is an attractive feature from a green chemistry standpoint.¹¹⁴ Several improvements to this method included changes to the water-based solvent system, modification of the catalyst and counteranion (**85-88**, Figure 12), and the introduction of additives such as KBr, for which enantioselectivities of up to >99 % e.e. for range of aliphatic and unsaturated alcohols were demonstrated.^{115, 116}

Palladium is another transition metal that has received interest in this area. The groups of Stoltz and Sigman independently developed an aerobic oxidative kinetic resolution that uses (–)-sparteine (**89**) as the chiral ligand, catalytic Pd(OAc)₂ and O₂ as the stoichiometric oxidant (Scheme 11).¹¹⁷⁻¹¹⁹ This is an attractive approach due to the practicality of being able to harvest atmospheric oxygen, in addition to sub-stoichiometric amounts of both Pd(II) and **89** being tolerable. This methodology has permitted the successful resolution of a number of allylic, benzylic and cyclopropyl secondary alcohols in good to high selectivity.^{120, 121} Whilst this is an attractive approach, it only gives the (–)-enantiomer in large quantities – sparteine is only commercially available as its (–)-antipode. One attempt to combat these issues involved the use of an alternative chiral diamine (**90**) derived from (–)-cytisine (**91**) as a (+)-sparteine surrogate for oxidative kinetic resolution. This was exemplified by the kinetic resolution of indan-1-ol (**92**), whereby (*R*)-**92** was obtained in 80 % e.e. when the (+)-surrogate **90** was employed. In spite of this, the reaction progressed with inferior stereocontrol compared to that observed for (–)-sparteine (**89**), which gave the (*S*)-product in 98 % e.e. (Scheme 11).¹²²



Scheme 11 Comparison of (–)-sparteine and its (+)-surrogate for the Pd-catalysed oxidative kinetic resolution of indan-1-ol (**92**); includes structures of (–)-sparteine (**89**), (–)-cytisine (**91**) and its (+)-sparteine surrogate (**90**).

Furthermore, α -hydroxy esters and similar benzoin s have recently been resolved using complexes based on cobalt by Sekar and coworkers, with the reactions also performed in the presence of molecular oxygen; $\text{Co}(\text{OAc})_2$ in conjunction with an (*S*)-BINAM based salen ligand (**96**) was found to be the best system, selectively resolving (\pm)-benzoin (**97**) in 92 % e.e. (a, Scheme 14).^{127, 128}



Scheme 14 Work by Sekar *et al.* on the oxidative kinetic resolution of (\pm)-benzoin (**96**) using cobalt, copper and iron catalysts.

In the same year, Yamada *et al.* reported moderate to high enantioselectivities, with only one instance of >90 e.e. (96 % e.e.), for the oxidative kinetic resolution of a series of benzylic alcohols using a chiral ketoiminatocobalt(II) complex as the catalyst.¹²⁹ One major downside with metals such as ruthenium, palladium, manganese, cobalt and iridium is that they are expensive, with chiral ligands that are often not readily available and must

therefore be arduously synthesised. In this context, the use of copper to catalyse the oxidative kinetic resolution of alcohols represents an economic, mild and biomimetic functional model of the mononuclear copper enzyme galactose oxidase.¹³⁰ As such, Sekar *et al.*, alongside their work highlighted above, developed the first Cu-catalysed oxidative kinetic resolution of benzoin, providing high enantioselectivities of up to 98 % e.e., albeit at low yields, using (*R*)-BINAM and copper(II) triflate in air (*b*, Scheme 14).¹³¹

The same authors reported the asymmetric oxidation of benzoin using another environmentally benign and relatively inexpensive metal, iron. The Fe complex, comprising ligand **98** also derived from (*R*)-BINAM, generally provided very high enantioselectivities although at only moderate yields; application of the iron-catalysed method to (\pm)-benzoin (**97**) afforded the (*R*)-enantiomer in 98 % e.e. (*c*, Scheme 14) – this was the first reported iron-catalysed oxidative kinetic resolution of alcohols.¹³² In 2013, the first example of using a nanoparticle surface for oxidative kinetic resolution of alcohols was reported; within the oxidations of a number of benzylic alcohols using the precatalyst *trans*-(*R,R*)-[Fe(NCMe)CO(PPh₂C₆H₄CH=NCHPh⁻)₂][BF₄]₂ it was believed that the active species was in fact small (4-5 nm) zero-valent Fe nanoparticles.¹³³

1.4 Previous work in the Fox Group

Prior efforts in the Fox group involved the attempted synthesis of both enantiomers of a non-cytotoxic anti-inflammatory compound, 6-B345TTQ (**99**), which was previously only published and patented as a racemate, with no other mention of activity on structurally similar compounds except for its 2,3,4-trimethoxy- counterpart (**100**), which showed no pharmacological effects (Figure 13) – see **Section 3.2.1** for further discussion of **99**.^{134, 135} The prior research also extended to structurally similar 4-aryl-3,4-dihydroquinolin-2-ones.⁸⁷

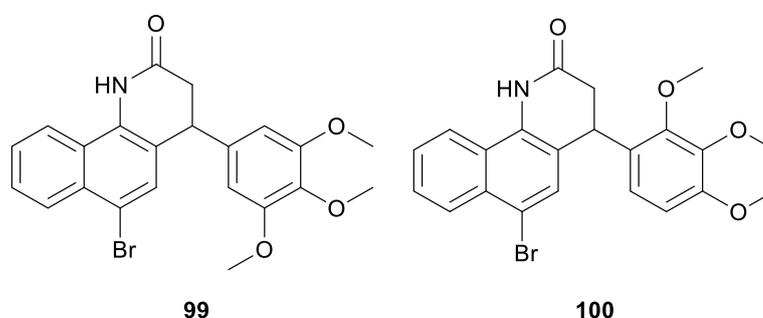
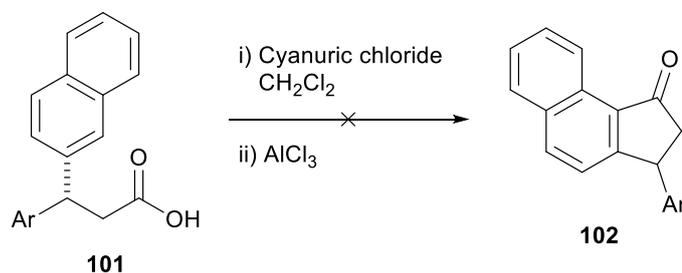


Figure 13 Anti-inflammatory compound 6-B345TTQ (**99**) and inactive analogue 6-B234TTQ (**100**).

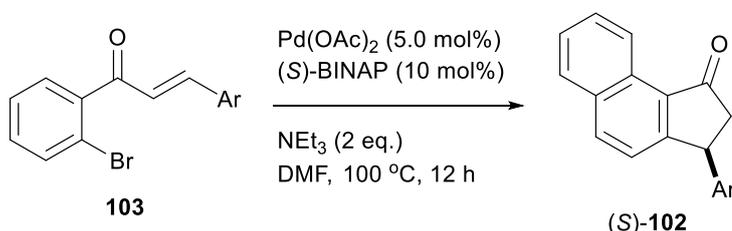
Towards this aim, a range of avenues towards synthesising enantiomerically enriched 3-aryl-indan-1-ones were scoped.⁸⁷ Initially, two asymmetric approaches to give these enantiopure materials were attempted. The first method was an acylation approach, involving a stereoselective Michael addition of an aryl cuprate, as described by Rocher and coworkers,⁵¹ making use of an Evans (chiral) auxiliary.¹³⁶ Chirality was effectively introduced into the system in the form of enantiomerically enriched 3,3-diaryl propanoic acids, however subsequent cyclisation of these substrates (**101**) to give the desired chiral indan-1-ones (**102**) proved unsuccessful, despite several attempts (*a*, Scheme 15).⁸⁷

Following this, asymmetric catalysis was explored, with an intramolecular Heck reaction the method of choice. A number of 2'-bromo-chalcones (**103**) were synthesised and then cyclised according to a method reported by Buchwald *et al.*⁴⁹ Very poor yields and enantioselectivities were obtained with BINAP employed (*b*, Scheme 15) and, although the optimised (*R*)-3,5-XylMeOBIPHEP ligand (**40**) used in conjunction with an aromatic triflate gave improved results, they were still considered low particularly for the naphthyl derivatives. In addition, no product was observed for some substrates, particularly those with a *para*- electron withdrawing group attached to the pendant 3-aryl ring.⁸⁷

a) Acylation Approach:



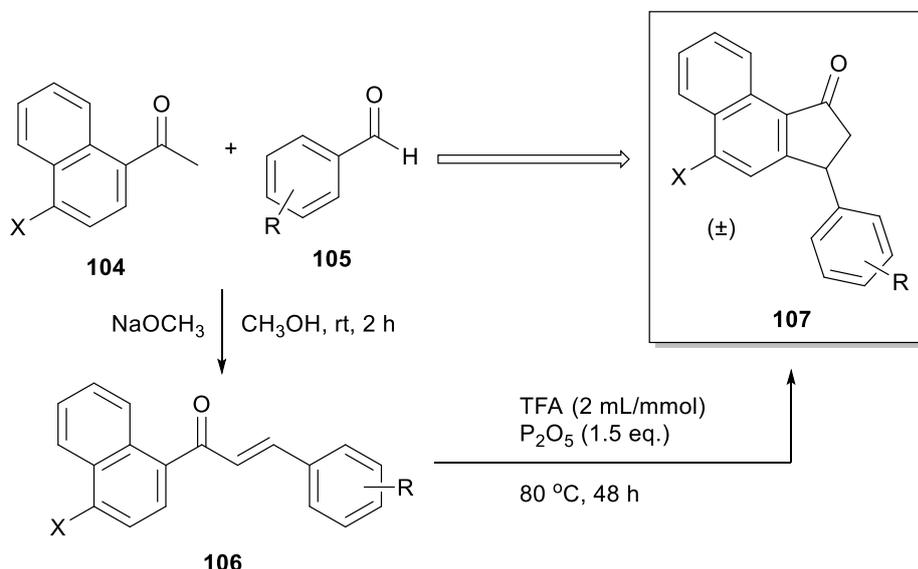
b) Alkylation Approach:



Scheme 15 Cyclisation steps in acylation and alkylation approaches towards enantioenriched 3-substituted naphthyl-indan-1-ones (**102**).⁸⁷

Consequently, attention was turned towards kinetic resolution, whereby a small library of racemic indan-1-ones was assembled and subsequently resolved. The racemic synthesis was achieved via a Claisen–Schmidt condensation of acetophenones (**104**) and

benzaldehydes (**105**) to yield appropriate chalcone derivatives (**106**), according to common literature procedures,^{137, 138} followed by a Nazarov cyclisation to give indan-1-ones of type **107** using TFA as the acid-mediator (Scheme 16);⁶⁹ in an attempt to improve the transformation for the substrates at hand, it was found a combination of TFA with P₂O₅ offered the best yields, and consequently this method was used thereafter.⁸⁷



Scheme 16 Synthetic route to racemic naphthyl-indan-1-ones (**107**).⁸⁷

The racemic indan-1-ones were then subjected to asymmetric transfer hydrogenation (ATH) using tethered (*R,R*)-TsDPEN-ruthenium catalyst, (*R,R*)-**108**;¹³⁹ the catalyst was provided by the Wills group from the University of Warwick and a formic acid : triethylamine (5 : 2) solution was prepared using the method by Sterk *et al.*¹⁴⁰ Unfortunately, this transformation showed poor selectivity, with both ketone enantiomers reacting and a total of three alcohol stereoisomers forming (Figure 14). As a result, attention was turned to a different resolution approach.

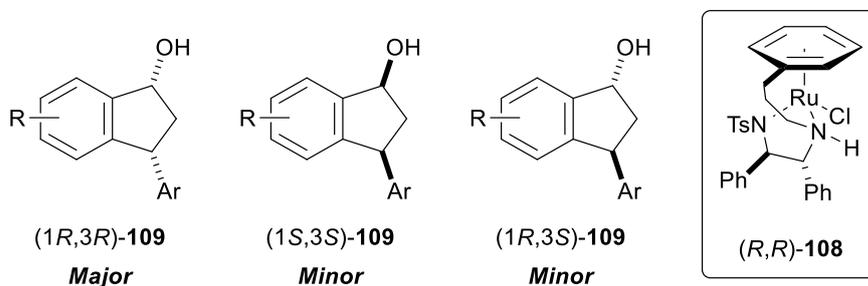
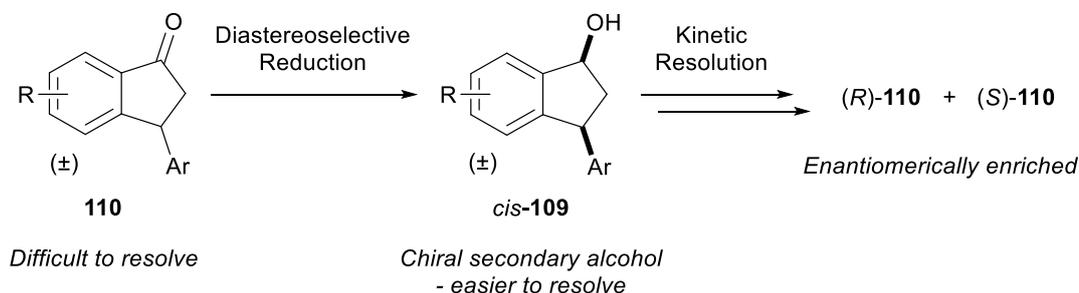


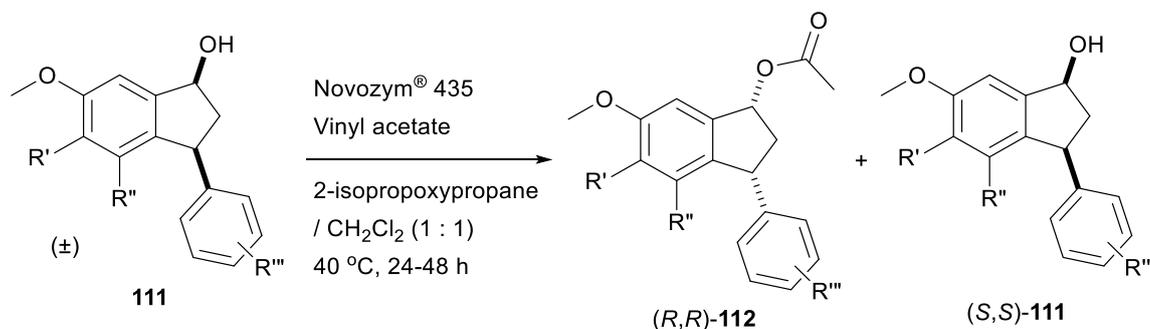
Figure 14 Tethered (*R,R*)-TsDPEN-ruthenium catalyst, (*R,R*)-**108**, and three stereoisomers of indan-1-ol **109** from ATH reactions.⁸⁷

It was believed that resolving the corresponding indan-1-ols would be more fruitful; the route chosen involved selectively reducing the racemic indan-1-ones (**110**) to give a pair of *cis*-diastereomers (**109**), which could then be more easily resolved (Scheme 17).



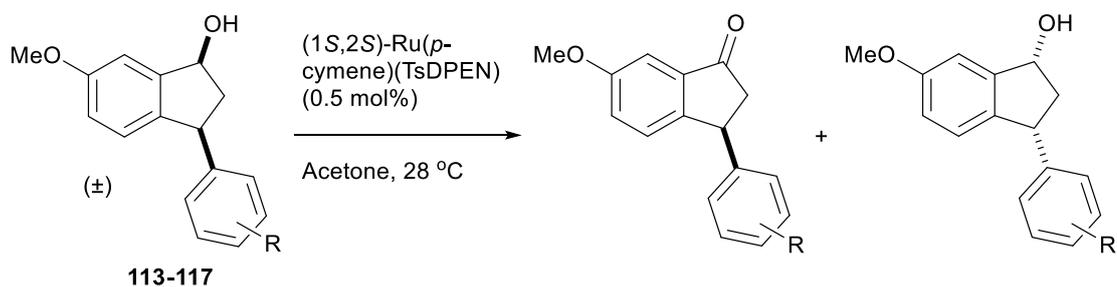
Scheme 17 Conceived kinetic resolution pathway of racemic 3-aryl-indan-1-ones.

Given the high *cis*-selectivity reported for the reduction of indan-1-ones using sodium borohydride,¹⁴¹ this method was applied with excellent selectivity for the indan-1-one structures.⁸⁷ An enzymatic acylation process, obtained from the literature, was then employed to facilitate the kinetic resolution of the recently formed racemic *cis*-indan-1-ols (**111**); treatment of the alcohol with vinyl acetate (irreversible acyl donor), catalysed by the acrylic resin-immobilised lipase enzyme Novozym[®] 435,¹⁴² gave excellent enantioselectivities (>99 % e.e.) and near quantitative yields for most substrates (Scheme 18).⁸⁷ Unfortunately however, the method failed to produce the desired acylated naphthyl- derivatives, despite modifications to the solvent, reaction time and temperature – likely a consequence of the reported deep narrow active site,¹⁴³ in addition to unfavourable interactions.¹⁴⁴ The resulting enantiomerically enriched (*R,R*)-indan-1-yl acetates ((*R,R*)-**112**) were subsequently transformed into the corresponding (*R,R*)-indan-1-ols by cleavage of the carbonyl bond using potassium carbonate and methanol.¹⁴⁵ Finally, a manganese dioxide oxidation was employed to convert both enantiomers of each indan-1-ol to the desired enantiomerically enriched 3-aryl-indan-1-ones.¹⁴⁶



Scheme 18 Kinetic resolution of 3-aryl-indan-1-ols using Novozym[®] 435.⁸⁷

The inability to resolve the naphthyl-indan-1-ol derivatives using the enzymatic acylation approach led to the employment of an oxidative kinetic resolution utilising Noyori's (*S,S*)-TsDPEN-ruthenium catalyst **63** and method.¹⁰⁰ Initially, the reaction was performed on some *cis*-6-methoxy-3-aryl-indan-1-ol substituents (**113-117**, Scheme 19). All reactions were only allowed to reach <50 % conversion, which meant that only ketone enantioselectivities were analysed. As shown in Scheme 19, the asymmetric oxidation of these substrates generally gave moderate ketone enantioselectivities and, with conversions as low as those reported, alcohol enantioselectivities would have been equally as modest.⁸⁷



R	Conversion / %	Ketone (S) e.e. / %
113 H	33 %	78 %
114 4-OCH ₃	26 %	86 %
115 3,4-OCH ₃	34 %	70 %
116 4-F	38 %	99 %
117 4-Cl	45 %	78 %

Scheme 19 Ruthenium-catalysed oxidative kinetic resolution of substituted racemic *cis*-indan-1-ols **113-117**.⁸⁷

Despite these results, a range of substituted naphthyl- derived indan-1-ols were subjected to the oxidative kinetic resolution method, using identical conditions to those employed previously. These substrates appeared far more suited towards this reaction, with generally very high enantioselectivities achieved with respect to both ketones and alcohols.⁸⁷ Finally, as in the case of the enzymatic acylation resolution, the residual alcohol products were oxidised using manganese dioxide to give the corresponding enantiomerically enriched indan-1-ones.¹⁴⁶ Overall, the oxidative kinetic resolution method shown in this study provided a novel method for the access of enantiomerically enriched 3-aryl-indan-1-ols and indan-1-ones.⁸⁷

1.5 Aims of Research

It is unequivocally evident that chiral indan-1-ones with functionality at the 2- and/or 3- positions are of huge biological importance,^{9, 18-25, 37, 41} frequently occurring as the primary pharmacophore of a wide array of drugs and natural products.¹⁰⁻¹⁷ In fact, the majority of compounds that have been shown to exhibit beneficial medicinal properties were only reported as racemic compounds. As such, a convenient and effective method to resolving these racemic molecules would be highly beneficial.

The primary aim of this research is to synthesise a series of enantiomerically enriched 3-aryl-indan-1-ones, varying with respect to the substituents on both aromatic rings (Figure 15), and efforts towards achieving this aim will be covered in Chapter 2. Based on previous work in the Fox group,⁸⁷ and the relatively straightforward construction of racemic indan-1-ones,^{18, 19} chiral resolution is the preferred method over a more direct approach such as asymmetric catalysis, especially since both ketone enantiomers are desired. Specifically, the focus will be on oxidative kinetic resolution, whereby a range of racemic *cis*-3-aryl-indan-1-ols will be subjected to Noyori's (*S,S*)-TsDPEN-Ru catalyst and method;¹⁰⁰ in view of the novelty of this transformation for the access of enantiomerically enriched 3-aryl-indan-1-ols and 3-aryl-indan-1-ones, a more detailed investigation into the transformation is greatly desired.

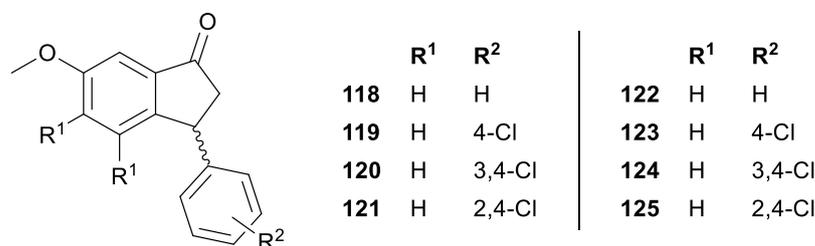


Figure 15 Targeted enantiomerically enriched 3-aryl-indan-1-ones **118-125**.

6-Methoxy and 4,5,6-trimethoxy- derivatives were chosen based on former work within the Fox group,⁸⁷ in addition to anti-cancer properties attributed to the three methoxy groups attached to the indanone ring.¹⁸⁻²⁰ Indan-1-ones comprising chlorine-based 3-aryl derivatives were also of interest – in addition to the unsubstituted (phenyl) ring – since these substrates have been shown to possess notable activity against some human cancer cell lines, despite only being reported as racemic compounds;^{18, 19} synthesising these species asymmetrically may result in enhanced medicinal properties,⁴² which is an attractive prospect.

Chapter 3 will focus on various transformations of 3-aryl-indan-1-ones (**125**), emphasising their use as building blocks towards medicinal scaffolds (Figure 16). A significant portion of this chapter will be devoted to two ring expansion reactions, the Beckmann rearrangement and the Schmidt reaction, with a focus on comparing the two transformations with respect to substrate structure and reaction conditions. It is the desire for these ring expansion reactions to facilitate the synthesis of enantiomerically enriched 4-aryl-dihydroquinolinones (**127**) and 4-aryl-dihydroisoquinolinones (**128**), two ring systems that are associated with a wide range of biological properties and exist as the structural motif in several natural products and bioactive synthetic compounds. The attempted synthesis of both enantiomers of the non-cytotoxic anti-inflammatory compound 6-B345TTQ (**99**) – a long term aim of the Fox group (see **Section 1.4**) – will also be illustrated within this chapter.

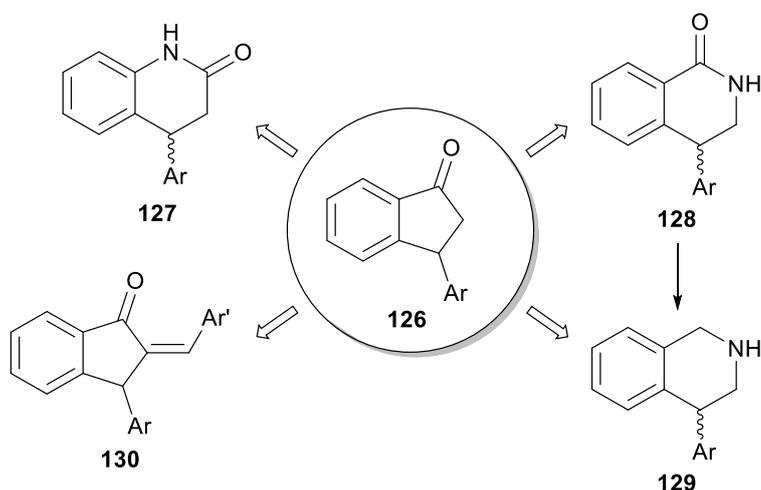


Figure 16 Transformations of 3-aryl-indan-1-ones (**126**) into medicinal scaffolds.

4-Aryl-tetrahydroisoquinolines (**129**) have also received significant attention due to their presence in an array of naturally occurring biologically active molecules, and a large number of papers and patents detailing their vast bioactivities have been published. As such, Chapter 3 will also cover the synthesis of various enantiomerically enriched 4-aryl-tetrahydroisoquinolines through reduction of the corresponding δ -lactams and further manipulations. The diverse biological properties exhibited by these compounds will be highlighted in **Section 3.1**. The chapter will conclude with the formation of a series of racemic benzylidene indan-1-ones (**130**), associated with anti-cancer activity,^{20, 21, 24} via Claisen-Schmidt condensation of 3-aryl-indan-1-ones and a range of benzaldehydes.

1.6 References

1. H. M. C. Ferraz, A. M. Aguilar, L. F. Silva, Jr. and M. V. Craveiro, *Quim. Nova*, 2005, **28**, 703.
2. H. Sheridan, S. Lemon, N. Frankish, P. McArdle, T. Higgins, J. P. James and P. Bhandari, *Eur. J. Med. Chem.*, 1990, **25**, 603-608.
3. M. Pass, R. E. Bolton, S. J. Coote, H. Finch, S. Hindley, A. Lowdon, E. McDonald, J. McLaren, M. Owen, N. A. Pegg, C. J. Mooney, C.-M. Tang, S. Parry and C. Patel, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 431-436.
4. D. H. Dethe, R. Boda and G. M. Murhade, *Org. Chem. Front.*, 2015, **2**, 645-648.
5. G. G. Bianco, H. M. C. Ferraz, A. M. Costa, L. V. Costa-Lotufo, C. Pessoa, M. O. de Moraes, M. G. Schrems, A. Pfaltz and L. F. Silva, *J. Org. Chem.*, 2009, **74**, 2561-2566.
6. T.-L. Ho and C.-K. Chen, *Nat. Prod. Lett.*, 1994, **4**, 313-320.
7. B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, P. L. Darke, J. A. Zugay, E. A. Emini and W. A. Schleif, *J. Med. Chem.*, 1994, **37**, 3443-3451.
8. A. I. Syrchina and A. A. Semenov, *Chem. Nat. Compd.*, 1982, **18**, 1-11.
9. S. A. Patil, R. Patil and S. A. Patil, *Eur. J. Med. Chem.*, 2017, **138**, 182-198.
10. S.-H. Kim, S. H. Kwon, S.-H. Park, J. K. Lee, H.-S. Bang, S.-J. Nam, H. C. Kwon, J. Shin and D.-C. Oh, *Org. Lett.*, 2013, **15**, 1834-1837.
11. A. Kobayashi, H. Egawa, K. Koshimizu and T. Mitsui, *Agric. Biol. Chem.*, 1975, **39**, 1851-1856.
12. H. Sheridan, N. Frankish and R. Farrell, *Eur. J. Med. Chem.*, 1999, **34**, 953-966.
13. J. Shu, J. Liu, Y. Zhong, J. Pan, L. Liu and R. Zhang, *Phytochem. Lett.*, 2012, **5**, 276-279.
14. H. Sugimoto, Y. Iimura, Y. Yamanishi and K. Yamatsu, *J. Med. Chem.*, 1995, **38**, 4821-4829.
15. H. Sugimoto, *Pure Appl. Chem.*, 1999, **71**.
16. H. Sugimoto, *Chem. Rec.*, 2001, **1**, 63-73.
17. H. O. Saxena, U. Faridi, S. Srivastava, J. K. Kumar, M. P. Darokar, S. Luqman, C. S. Chanotiya, V. Krishna, A. S. Negi and S. P. S. Khanuja, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3914-3918.
18. N. J. Lawrence, E. S. M. Armitage, B. Greedy, D. Cook, S. Ducki and A. T. McGown, *Tetrahedron Lett.*, 2006, **47**, 1637-1640.

19. A. P. Prakasham, A. K. Saxena, S. Luqman, D. Chanda, T. Kaur, A. Gupta, D. K. Yadav, C. S. Chanotiya, K. Shanker, F. Khan and A. S. Negi, *Biorg. Med. Chem.*, 2012, **20**, 3049-3057.
20. A. Singh, K. Fatima, A. Singh, A. Behl, M. J. Minto, M. Hasanain, R. Ashraf, S. Luqman, K. Shanker, D. M. Mondhe, J. Sarkar, D. Chanda and A. S. Negi, *Eur. J. Pharm. Sci.*, 2015, **76**, 57-67.
21. B. Dulla, E. Sailaja, U. Reddy Ch, M. Aeluri, A. M. Kalle, S. Bhavani, D. Rambabu, M. V. B. Rao and M. Pal, *Tetrahedron Lett.*, 2014, **55**, 921-926.
22. L. M. Leoni, E. Hamel, D. Genini, H. Shih, C. J. Carrera, H. B. Cottam and D. A. Carson, *J. Natl. Cancer Inst.*, 2000, **92**, 217-224.
23. D. Chanda, S. Bhushan, S. K. Guru, K. Shanker, Z. A. Wani, B. A. Rah, S. Luqman, D. M. Mondhe, A. Pal and A. S. Negi, *Eur. J. Pharm. Sci.*, 2012, **47**, 988-995.
24. R. W. Hartmann, H. Bayer and G. Gruen, *J. Med. Chem.*, 1994, **37**, 1275-1281.
25. M. A. Jordan and L. Wilson, *Nat. Rev. Cancer*, 2004, **4**, 253-265.
26. B. B. Biswas, K. Sen, G. Ghosh Choudhury and B. Bhattacharyya, *J. Bioscience*, 1984, **6**, 431-457.
27. B. Bhattacharyya, D. Panda, S. Gupta and M. Banerjee, *Med. Res. Rev.*, 2008, **28**, 155-183.
28. V. Peyrot, D. Leynadier, M. Sarrazin, C. Briand, M. Menendez, J. Laynez and J. M. Andreu, *Biochemistry*, 1992, **31**, 11125-11132.
29. G. R. Pettit, S. B. Singh, E. Hamel, C. M. Lin, D. S. Alberts and D. Garcia-Kendal, *Experientia*, 1989, **45**, 209-211.
30. M. L. Edwards, D. M. Stemerick and P. S. Sunkara, *J. Med. Chem.*, 1990, **33**, 1948-1954.
31. S. Ducki, D. Rennison, M. Woo, A. Kendall, J. F. D. Chabert, A. T. McGown and N. J. Lawrence, *Biorg. Med. Chem.*, 2009, **17**, 7698-7710.
32. L. B. Salum, W. F. Altei, L. D. Chiaradia, M. N. S. Cordeiro, R. R. Canevarolo, C. P. S. Melo, E. Winter, B. Mattei, H. N. Daghestani, M. C. Santos-Silva, T. B. Creczynski-Pasa, R. A. Yunes, J. A. Yunes, A. D. Andricopulo, B. W. Day, R. J. Nunes and A. Vogt, *Eur. J. Med. Chem.*, 2013, **63**, 501-510.
33. H. Mirzaei and S. Emami, *Eur. J. Med. Chem.*, 2016, **121**, 610-639.
34. A. S. Negi, Y. Gautam, S. Alam, D. Chanda, S. Luqman, J. Sarkar, F. Khan and R. Konwar, *Biorg. Med. Chem.*, 2015, **23**, 373-389.

35. L. Huang, H. Miao, Y. Sun, F. Meng and X. Li, *Eur. J. Med. Chem.*, 2014, **87**, 429-439.
36. G. R. Dwivedi, N. Tiwari, A. Singh, A. Kumar, S. Roy, A. S. Negi, A. Pal, D. Chanda, A. Sharma and M. P. Darokar, *Appl. Microbiol. Biotechnol.*, 2016, **100**, 2311-2325.
37. B. S. Speer, N. B. Shoemaker and A. A. Salyers, *Clin. Microbiol. Rev.*, 1992, **5**, 387-399.
38. G. M. Eliopoulos and M. C. Roberts, *Clin. Infect. Dis.*, 2003, **36**, 462-467.
39. L. McMurry, R. E. Petrucci and S. B. Levy, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 3974-3977.
40. L. Roberts and S. Simpson, *Science*, 2008, **321**, 355-355.
41. A. N. Passi, K. M. Prajapati, D. J. D. Sen and S. I. Anand, *Int. J. Drug Dev. Res.*, 2010, **2**, 182-189.
42. J. McConathy and M. J. Owens, *Prim. Care Companion J. Clin. Psychiatry*, 2003, **5**, 70-73.
43. J. H. Kim and A. R. Scialli, *Toxicol. Sci.*, 2011, **122**, 1-6.
44. M. K. O'Brien and B. Vanasse, *Curr. Opin. Drug Discov. Devel.*, 2000, **3**, 793-806.
45. J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5-26.
46. K. Kundu, J. V. McCullagh and A. T. Morehead, *J. Am. Chem. Soc.*, 2005, **127**, 16042-16043.
47. R. Shintani, K. Yashio, T. Nakamura, K. Okamoto, T. Shimada and T. Hayashi, *J. Am. Chem. Soc.*, 2006, **128**, 2772-2773.
48. Y.-N. Yu and M.-H. Xu, *J. Org. Chem.*, 2013, **78**, 2736-2741.
49. A. Minatti, X. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 9253-9258.
50. A. Püschl, H. C. Rudbeck, A. Faldt, A. Confante and J. Kehler, *Synthesis*, 2005, **2005**, 291-295.
51. E. Stephan, R. Rocher, J. Aubouet, G. Pourcelot and P. Cresson, *Tetrahedron: Asymmetry*, 1994, **5**, 41-44.
52. P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138-5175.
53. M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discov. Today*, 2007, **12**, 8-27.
54. T. Vaidya, R. Eisenberg and A. J. Frontier, *ChemCatChem*, 2011, **3**, 1531-1548.
55. A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577-7606.
56. M. A. Tius, *Eur. J. Org. Chem.*, 2005, **2005**, 2193-2206.

57. K. L. Habermas, S. E. Denmark and T. K. Jones, in *Organic Reactions*, John Wiley & Sons, Inc., 2004.
58. Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc., 2010.
59. D. Vorländer and M. Schroedter, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 1490-1497.
60. I. N. Nazarov and I. I. Zaretskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1942, 200.
61. I. N. Nazarov and I. I. Zaretskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1941, 211-224.
62. A. P. Marcus, A. S. Lee, R. L. Davis, D. J. Tantillo and R. Sarpong, *Angew. Chem. Int. Ed.*, 2008, **47**, 6379-6383.
63. F. Gavina, A. M. Costero and A. M. Gonzalez, *J. Org. Chem.*, 1990, **55**, 2060-2063.
64. J. Zhu, C. Zhong, H.-F. Lu, G.-Y. Li and X. Sun, *Synlett*, 2008, **2008**, 458-462.
65. N. Ghavtadze, R. Fröhlich and E.-U. Würthwein, *Eur. J. Org. Chem.*, 2009, **2009**, 1228-1240.
66. D. J. Kerr, E. Hamel, M. K. Jung and B. L. Flynn, *Biorg. Med. Chem.*, 2007, **15**, 3290-3298.
67. J. M. Allen, K. M. Johnston, J. F. Jones and R. G. Shotter, *Tetrahedron*, 1977, **33**, 2083-2087.
68. N. Ghavtadze, R. Fröhlich and E.-U. Würthwein, *Eur. J. Org. Chem.*, 2008, **2008**, 3656-3667.
69. M. K. Seery, S. M. Draper, J. M. Kelly, T. McCabe and T. B. H. McMurry, *Synthesis*, 2005, **2005**, 470-474.
70. N. Shimada, C. Stewart and M. A. Tius, *Tetrahedron*, 2011, **67**, 5851-5870.
71. N. Shimada, B. O. Ashburn, A. K. Basak, W. F. Bow, D. A. Vicic and M. A. Tius, *Chem. Commun.*, 2010, **46**, 3774-3775.
72. W. He, X. Sun and A. J. Frontier, *J. Am. Chem. Soc.*, 2003, **125**, 14278-14279.
73. V. K. Aggarwal and A. J. Belfield, *Org. Lett.*, 2003, **5**, 5075-5078.
74. H.-J. Federsel, *Nat. Rev. Drug Discov.*, 2005, **4**, 685-697.
75. L. Pasteur, *Mol. Med.*, 1995, **1**, 599-601.
76. J. Gal, *Chirality*, 2008, **20**, 5-19.
77. M. Todd, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, pp. 1-12.
78. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337-2347.

79. A. Borghese, V. Libert, T. Zhang and C. A. Alt, *Org. Process Res. Dev.*, 2004, **8**, 532-534.
80. T. D. Nelson, C. J. Welch, J. D. Rosen, J. H. Smitrovich, M. A. Huffman, J. M. McNamara and D. J. Mathre, *Chirality*, 2004, **16**, 609-613.
81. A. S. Mwakaboko and B. Zwanenburg, *Plant Cell Physiol.*, 2011, **52**, 699-715.
82. S. Andersson and S. G. Allenmark, *J. Biochem. Bioph. Methods*, 2002, **54**, 11-23.
83. W. Marckwald and A. M. Kenzie, *Ber. Dtsch. Chem. Ges.*, 1899, **32**, 2130-2136.
84. A. McKenzie, *J. Chem. Soc., Trans.*, 1904, **85**, 378-386.
85. D. G. Blackmond, *J. Am. Chem. Soc.*, 2001, **123**, 545-553.
86. H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, John Wiley & Sons, Inc., 1988, pp. 249-330.
87. P. Kerby, PhD thesis, University of Warwick, 2016.
88. M. Kitamura, M. Tokunaga and R. Noyori, *J. Am. Chem. Soc.*, 1993, **115**, 144-152.
89. V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237-6240.
90. G. Balavoine, A. Moradpour and H. B. Kagan, *J. Am. Chem. Soc.*, 1974, **96**, 5152-5158.
91. P. R. Carlier, W. S. Mungall, G. Schroder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 2978-2979.
92. M. R. Maddani, J.-C. Fiaud and H. B. Kagan, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, ch. 2, pp. 13-74.
93. C. S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294-7299.
94. C. E. Humphrey, M. Ahmed, A. Ghanem and N. J. Turner, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, ch. 4, pp. 123-160.
95. K. Nakano and M. Kitamura, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, ch. 5, pp. 161-216.
96. H. Pellissier, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, ch. 3, pp. 75-122.
97. S. D. Rychnovsky, T. L. McLernon and H. Rajapakse, *J. Org. Chem.*, 1996, **61**, 1194-1195.
98. Y. Kashiwagi, F. Kurashima, C. Kikuchi, J.-i. Anzai, T. Osa and J. M. Bobbitt, *Tetrahedron Lett.*, 1999, **40**, 6469-6472.

99. K. Ohkubo, K. Hirata, K. Yoshinaga and M. Okada, *Chem. Lett.*, 1976, **5**, 183-184.
100. S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 288-290.
101. K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 285-288.
102. S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562-7563.
103. R. J. Lundgren and M. Stradiotto, "Key Concepts in Ligand Design" in *Ligand Design in Metal Chemistry: Reactivity and Catalysis*, Wiley-VCH, Weinheim, 2016, **1**, pp. 1-14.
104. Y. Iura, T. Sugahara and K. Ogasawara, *Tetrahedron Lett.*, 1999, **40**, 5735-5738.
105. J. Zhang, X. Yang, H. Zhou, Y. Li, Z. Dong and J. Gao, *Green Chem.*, 2012, **14**, 1289-1292.
106. Y. Caro, M. a. Torrado, C. F. Masaguer and E. Raviña, *Tetrahedron: Asymmetry*, 2003, **14**, 3689-3696.
107. Y. Nishibayashi, A. Yamauchi, G. Onodera and S. Uemura, *J. Org. Chem.*, 2003, **68**, 5875-5880.
108. Y. Nakamura, H. Egami, K. Matsumoto, T. Uchida and T. Katsuki, *Tetrahedron*, 2007, **63**, 6383-6387.
109. Y. Ishii, K. Suzuki, T. Ikariya, M. Saburi and S. Yoshikawa, *J. Org. Chem.*, 1986, **51**, 2822-2824.
110. M. Kitamura, K. Manabe, R. Noyori and H. Takaya, *Tetrahedron Lett.*, 1987, **28**, 4719-4720.
111. S. Arita, T. Koike, Y. Kayaki and T. Ikariya, *Angew. Chem. Int. Ed.*, 2008, **47**, 2447-2449.
112. Z. S. M. G. Z. J. Zhang Yuecheng, *Prog. Chem.*, 2012, **24**, 212-224.
113. W. Sun, H. Wang, C. Xia, J. Li and P. Zhao, *Angew. Chem. Int. Ed.*, 2003, **42**, 1042-1044.
114. M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807-810.
115. Z. Li, Z. H. Tang, X. X. Hu and C. G. Xia, *Chem. Eur. J.*, 2005, **11**, 1210-1216.
116. K. Pathak, I. Ahmad, S. H. R. Abdi, R. I. Kureshy, N.-u. H. Khan and R. V. Jasra, *J. Mol. Catal. A: Chem.*, 2007, **274**, 120-126.

117. S. K. Mandal, D. R. Jensen, J. S. Pugsley and M. S. Sigman, *J. Org. Chem.*, 2003, **68**, 4600-4603.
118. D. R. Jensen and M. S. Sigman, *Org. Lett.*, 2003, **5**, 63-65.
119. E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, 2001, **123**, 7725-7726.
120. M. S. Sigman and D. R. Jensen, *Acc. Chem. Res.*, 2006, **39**, 221-229.
121. D. C. Ebner, J. T. Bagdanoff, E. M. Ferreira, R. M. McFadden, D. D. Caspi, R. M. Trend and B. M. Stoltz, *Chem. Eur. J.*, 2009, **15**, 12978-12992.
122. M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870-11871.
123. S. Sahoo, P. Kumar, F. Lefebvre and S. B. Halligudi, *J. Catal.*, 2009, **262**, 111-118.
124. L. Yin, X. Jia, X. S. Li and A. S. C. Chan, *Chin. Chem. Lett.*, 2010, **21**, 774-777.
125. V. D. Pawar, S. Bettigeri, S.-S. Weng, J.-Q. Kao and C.-T. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 6308-6309.
126. A. T. Radosevich, C. Musich and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 1090-1091.
127. S. K. Alamsetti and G. Sekar, *Chem. Commun.*, 2010, **46**, 7235-7237.
128. S. Kumar Alamsetti, P. Muthupandi and G. Sekar, *Chem. Eur. J.*, 2009, **15**, 5424-5427.
129. T. Yamada, S. Higano, T. Yano and Y. Yamashita, *Chem. Lett.*, 2009, **38**, 40-41.
130. N. Ito, S. E. V. Phillips, C. Stevens, Z. B. Ogel, M. J. McPherson, J. N. Keen, K. D. S. Yadav and P. F. Knowles, *Nature*, 1991, **350**, 87-90.
131. S. K. Alamsetti, S. Mannam, P. Mutupandi and G. Sekar, *Chem. Eur. J.*, 2009, **15**, 1086-1090.
132. P. Muthupandi, S. K. Alamsetti and G. Sekar, *Chem. Commun.*, 2009, 3288-3290.
133. J. F. Sonnenberg, D. Pichugin, N. Coombs and R. H. Morris, *Top. Catal.*, 2013, **56**, 1199-1207.
134. C. Kummer, B. G. Petrich, D. M. Rose and M. H. Ginsberg, *J. Biol. Chem.*, 2010, **285**, 9462-9469.
135. M. H. Ginsberg and C. Kummer, *Small Molecule Inhibitors of the α 4-Paxillin Interaction*, WO Pat., 034 896 A2, 2011.
136. D. A. Evans, L. D. Wu, J. J. M. Wiener, J. S. Johnson, D. H. B. Ripin and J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411-6417.
137. C. Hedberg and P. G. Andersson, *Adv. Synth. Catal.*, 2005, **347**, 662-666.

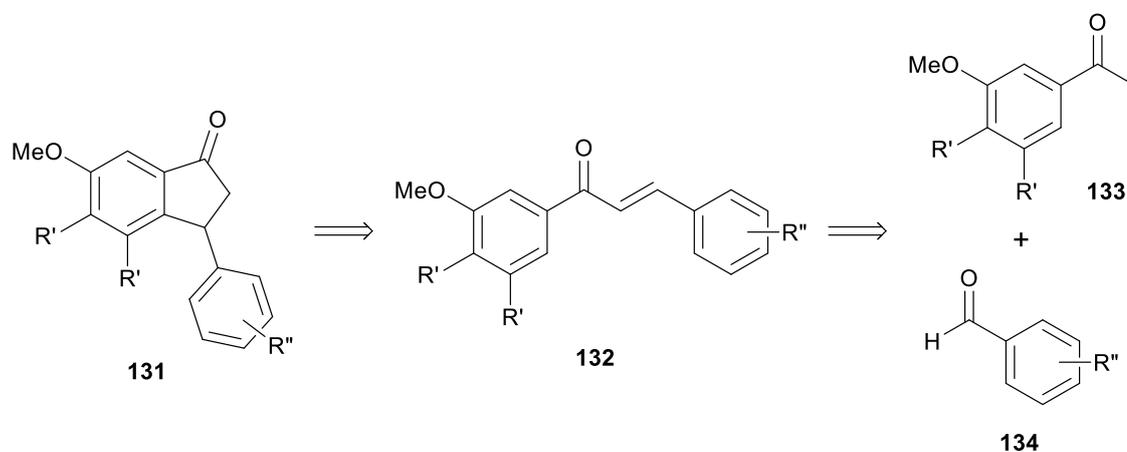
138. G. Dannhardt, W. Kiefer, G. Krämer, S. Maehrlein, U. Nowe and B. Fiebich, *Eur. J. Med. Chem.*, 2000, **35**, 499-510.
139. K. E. Jolley, A. Zanotti-Gerosa, F. Hancock, A. Dyke, D. M. Grainger, J. A. Medlock, H. G. Nedden, J. J. M. Le Paih, S. J. Roseblade, A. Seger, V. Sivakumar, I. Prokes, D. J. Morris and M. Wills, *Adv. Synth. Catal.*, 2012, **354**, 2545-2555.
140. D. Šterk, M. Stephan and B. Mohar, *Org. Lett.*, 2006, **8**, 5935-5938.
141. X.-H. Gu, H. Yu, A. E. Jacobson, R. B. Rothman, C. M. Dersch, C. George, J. L. Flippen-Anderson and K. C. Rice, *J. Med. Chem.*, 2000, **43**, 4868-4876.
142. M. Jorgensen, P. H. Andersen, K. G. Jensen, M. G. Hvenegaard, L. Badolo and M. F. Jacobsen, *Deuterated 1-Piperazino-3-phenyl-indanes for Treatment of Schizophrenia*, US Pat., 0 322 811 A1, 2012.
143. J. Uppenberg, N. Oehrner, M. Norin, K. Hult, G. J. Kleywegt, S. Patkar, V. Waagen, T. Anthonsen and T. A. Jones, *Biochemistry*, 1995, **34**, 16838-16851.
144. F. Haeffner, T. Norin and K. Hult, *Biophys. J.*, 1998, **74**, 1251-1262.
145. B. Das, J. Banerjee, A. Majhi, N. Chowdhury, K. Venkateswarlu and H. Holla, *Indian J. Chem., Sect. B*, 2006, **45**, 1729-1733.
146. R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, 1959, **24**, 1051-1056.

2.0 A “2 + 2.5-step” Asymmetric Synthesis

2.1 Synthesis of Racemic 3-Aryl-indan-1-ones

2.1.1 Overview

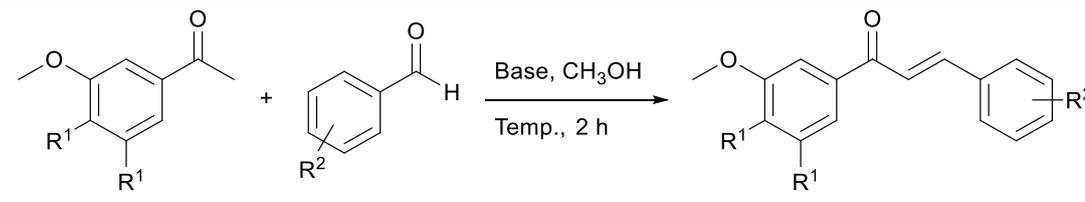
A small library of racemic 3-aryl-indan-1-ones (**131**) was required prior to kinetic resolution into their corresponding enantiomers. As discussed in **Section 1.2.2**, the most common route towards these materials involves a Nazarov cyclisation of chalcones (**132**), which can themselves be synthesised by Claisen–Schmidt condensation of an acetophenone (**133**) and an aromatic aldehyde (**134**) (Scheme 20). This process tolerates a number of functional groups relevant to this project.



Scheme 20 Disconnection approach from 3-aryl-indan-1-one derivatives.

2.1.2 Claisen–Schmidt Condensation

Chalcone formation via Claisen–Schmidt condensation of acetophenones and benzaldehydes has been well-documented,¹⁻⁴ and was first reported independently by Claisen and Schmidt in 1881.^{5, 6} The reaction is a type of aldol condensation, in which the reacting aldehyde/ketone reacts with an aromatic carbonyl compound lacking an alpha-hydrogen – typically base promoted – to give an α,β -unsaturated ketone with high chemoselectivity.⁷ Chalcones have found important use in the pharmaceutical industry as a result of the interesting biological activities they possess (see **Section 1.1.2**).^{4, 8} Within this study, chalcones **135-142** were synthesised via Claisen–Schmidt condensation, utilising conditions adapted from common literature procedures,^{2, 3} and the results are displayed in Table 1. All chalcones were formed at short reaction times in generally very high yields with product typically precipitating out within 1 hour and, as a result, most substrates were easily isolated through filtration of the reaction mixture.

Table 1 Claisen–Schmidt condensations towards substituted chalcones **135-142**.

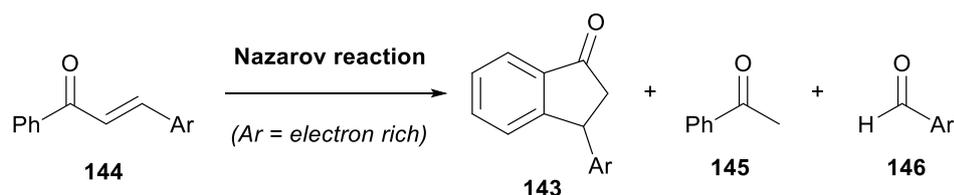
R ¹	R ²	Base ^s	Temp. / °C	Yield / % ^b	Chalcone
H	H	NaOCH ₃ (1.5 eq.)	20	94	135
H	4-Cl	KOH (3.75 M)	50	81	136
H	3,4-Cl	KOH (3.75 M)	50	93	137
H	2,4-Cl	KOH (3.75 M)	50	88	138
OCH ₃	H	NaOCH ₃ (1.5 eq.)	20	94	139
OCH ₃	4-Cl	KOH (3.75 M)	50	73	140
OCH ₃	3,4-Cl	KOH (3.75 M)	50	94	141
OCH ₃	2,4-Cl	KOH (3.75 M)	50	99	142

^a Reaction performed with aqueous KOH (3.75 M) instead of NaOCH₃ to avoid nucleophilic aromatic substitution; ^b Isolated yield.

The condensations gave exclusively *E*- (*trans*-) chalcones, confirmation of which was achieved by ¹H NMR through inspection of the coupling constants for the vinylic protons. This geometry is generally more thermodynamically stable as a result of strong steric effects between the carbonyl and 3-aryl groups within the *Z*-isomer.⁹

2.1.3 Nazarov Cyclisation of Substituted Chalcones

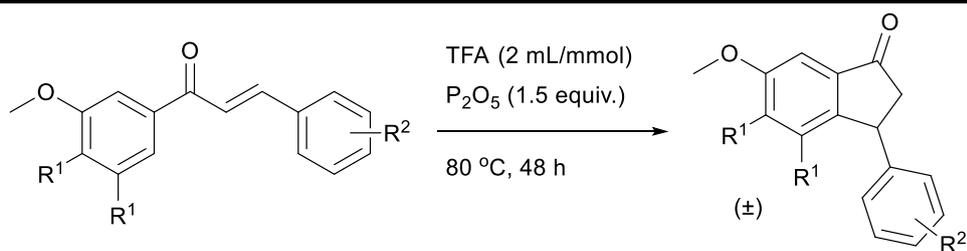
The Nazarov cyclisation of substituted chalcones into corresponding indan-1-ones is well-known,^{1, 10-12} and a more thorough discussion can be found in **Section 1.2.2**. Within this study, chalcones **135-142** were all cyclised using TFA as the acid.¹³ Phosphorous pentoxide was also employed in the Nazarov reaction in accordance with previous work in the Fox group,¹⁴ whereby the use of P₂O₅ resulted in greater yields of 3-aryl-indan-1-ones (**143**) from chalcones (**144**), as well as minimised the formation of known side products – acetophenones (**145**) and aldehydes (**146**) – that result from a water promoted *retro*-Claisen–Schmidt reaction; this process typically occurs for ‘unfavourable’ substrates with respect to cyclisation, i.e. Ar = electron rich (Scheme 21).¹¹ P₂O₅ is commonly used for the removal of water from solvents.¹⁵



Scheme 21 Side product formation in the Nazarov cyclisation of chalcones.

The Nazarov cyclisations were successful for the 3,4,5-trimethoxy-chalcones, giving desired 3-aryl-indan-1-ones **122-125** in good to excellent yields (Table 2). Unfortunately, the reaction of 3-methoxy-chalcones **135-138** yielded an unknown by-product, with all starting material being consumed within 3 hours and only a relatively small amount of the desired indan-1-one forming. The formation and identity of this unknown by-product was deemed unimportant and thus not further explored. Instead, attention was turned towards improving the Nazarov cyclisation of 3-methoxy-chalcones **135-138**.

Table 2 Nazarov cyclisations of substituted chalcones **135-142**, with P₂O₅.



Chalcone	R ¹	R ²	Yield / % ^a	Indan-1-one
135	H	H	- ^b	118
136	H	4-Cl	11	119
137	H	3,4-Cl	18	120
138	H	2,4-Cl	9	121
139	OCH ₃	H	51	122
140	OCH ₃	4-Cl	79	123
141	OCH ₃	3,4-Cl	91	124
142	OCH ₃	2,4-Cl	82	125

^a Isolated yield; ^b Unable to isolate after silica column chromatography.

Both the reaction temperature and age of the TFA had a small positive effect on conversion to the desired indan-1-ones. In addition, upon sampling the reactions performed at lower temperature, it was discovered that all starting material had been consumed within 3 hours, and the ¹H NMR spectrum of the sample obtained at this time showed fewer side products than that typically seen after 24 hours.

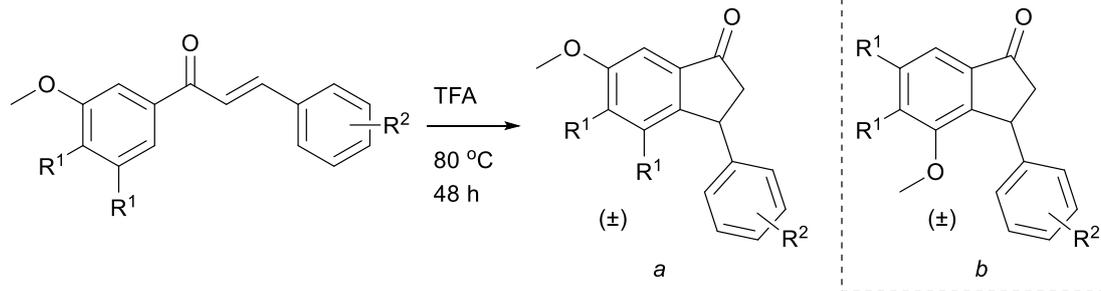
As a result, the Nazarov cyclisations of chalcones **135-138** were repeated for 3 hours at 40 °C (Table 3). These milder conditions gave indan-1-ones **118-121** in greater yields than previously accessed, however the overall yields were still low in comparison to their trimethoxy- counterparts, and still gave significant amounts of the unknown by-product.

Table 3 Nazarov cyclisations of 3-methoxy-chalcones **135-138** under milder conditions.

Chalcone	R	Yield / % ^a	Indan-1-one
135	H	15	118
136	4-Cl	29	119
137	3,4-Cl	23	120
138	2,4-Cl	43	121

^a Isolated yield.

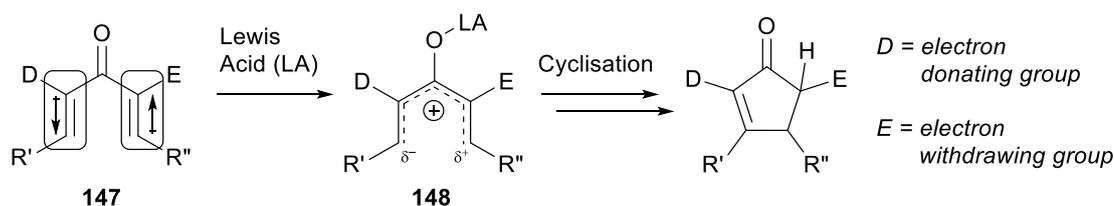
The formation of the unknown material was thought to be a result of the P₂O₅ present in the reaction. This was confirmed when the reactions were repeated without the phosphorus reagent; the Nazarov cyclisation gave desired 3-aryl-indan-1-ones in excellent yields without any of the unknown species forming (Table 4). Consistent with literature reports,^{16, 17} the cyclisation of the 3-methoxy-chalcones formed both the 6-methoxy- and 4-methoxy-3-aryl-indan-1-one derivatives, the ratio of which was determined by ¹H NMR spectroscopy, in comparison with the literature.¹⁷ Unfortunately, the desired 6-methoxy-3-aryl-indan-1-ones could not be completely separated from the undesired isomer by silica column chromatography, however since the ratio of desired : undesired isomers was large for each substrate, the mixtures were characterised as formed and then used for the subsequent *cis*-reduction (see **Section 2.2.2**) – it was discovered that the alcohols resulting from the undesired isomers could be removed far more easily by column chromatography.

Table 4 Nazarov cyclisations of substituted chalcones **135-142**, without P₂O₅.


Chalcone	R ¹	R ²	Yield / % ^a	Ratio <i>a</i> : <i>b</i> ^b	Indan-1-one
135	H	H	84	0.94 : 0.06	118
136	H	4-Cl	82	0.95 : 0.05	119
137	H	3,4-Cl	89	0.94 : 0.06	120
138	H	2,4-Cl	96	0.94 : 0.06	121
139	OCH ₃	H	97	N/A	122
140	OCH ₃	4-Cl	98	N/A	123
141	OCH ₃	3,4-Cl	97	N/A	124
142	OCH ₃	2,4-Cl	97	N/A	125

^a Isolated yield; ^b Ratio determined by ¹H NMR spectroscopy prior to purification.

As expected, reactions of chalcones **139-142** with three methoxy groups on the 1-aryl ring gave higher yields than the single methoxy analogues; the Nazarov cyclisation is accelerated by electron donating substituents in the aromatic ring at the 1-position of the chalcone, since they are a resonance contributor to the enone system.^{12, 18} In fact, the presence of both electron donating and electron withdrawing groups in the starting chalcone (**147**) can facilitate cyclisation and regioselectivity, although they must be positioned so they are able to polarise the conjugated system (**148**), as demonstrated by Scheme 22.¹⁸ By analogy to the substituted chalcones studied in this work, the 1-aryl ring is the electron donating group (*D*); the carbocation that forms after ring closure is stabilised by the methoxy groups *ortho*- and *para*- to the δ⁻ carbon atom through delocalisation of the oxygen lone pairs – the mesomeric effect.¹⁹

**Scheme 22** Substituent effects in the Nazarov cyclisation.¹⁸

The 3-aryl ring, however, is not in the correct position (*E*) to influence the cyclisation, instead it is in place of R". Nonetheless, the effect this ring has on the reaction can be predicted based on the same principles; for greater reactivity the vinyl electrophile needs to be electron deficient, specifically the β -carbon. As a result, the reaction should theoretically be more favoured for substrates in which there are electron withdrawing substituents attached to the 3-aryl ring. This was generally observed in the Nazarov cyclisations performed, albeit not through reaction yields, but instead their rates. The rates of cyclisation were as follows: **139** > **142** > **138** > **135** > **140** > **136** > **141** > **137**. For deeper analysis, one must consider the chemistry of halogen atoms such as chlorine. Due to the electronegativity of halogens they exhibit a negative inductive effect (-I), however they also have a positive mesomeric effect (+M) that arises from the presence of 'free' electrons in their outer shell. These effects are opposite and so are able to partially cancel each other out.²⁰ Based on the Hammett values (Table 5), the *meta*- positions experience more of this substituent effect,²¹ which is a result of a lower mesomeric effect at this site. Therefore, halogens such as chlorine are *ortho*- and *para*- directing, but deactivate the ring (I > M).

Table 5 Hammett values derived from the dissociation constants of benzoic acids.^{20, 21}

Substituent	σ_{para}	σ_{meta}
Bromo-	0.232	0.391
Chloro-	0.227	0.373
Fluoro-	0.062	0.337

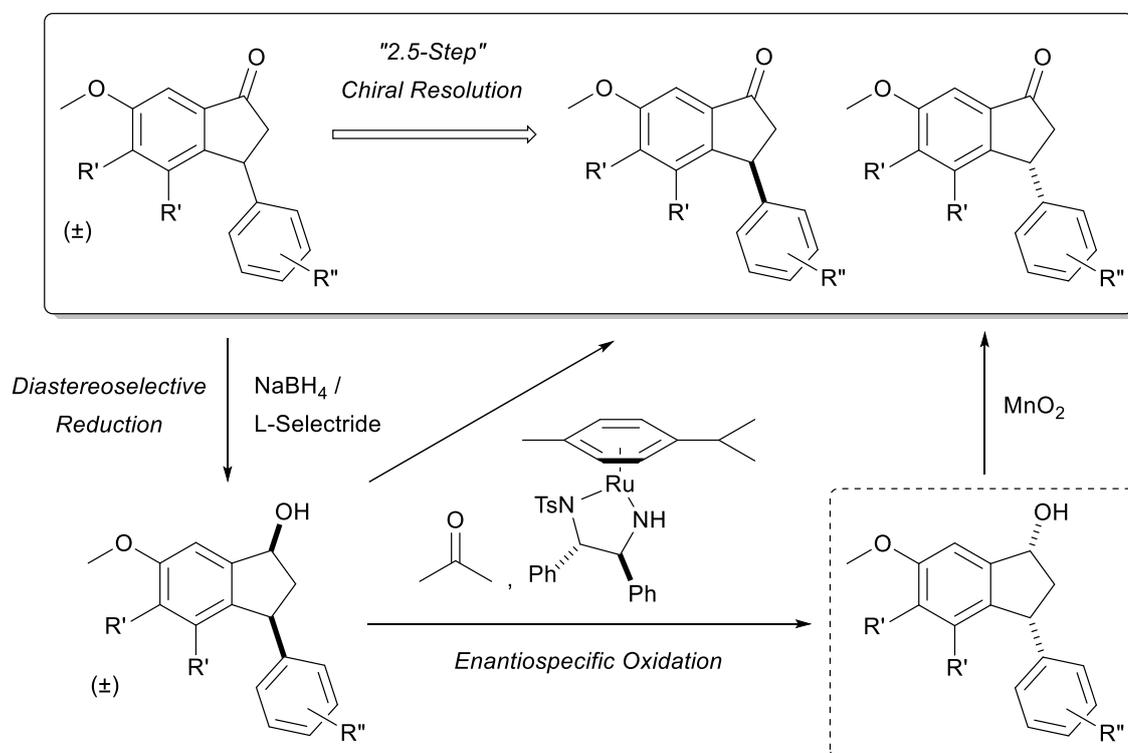
This explains why **136** and **140** (4-Cl) react slower than the chalcones bearing a phenyl group (**135** and **139**), since the positive mesomeric effect of the chlorine atom outweighs its inductive effect because it is so far away from the vinyl electrophile – the phenyl group in **135** and **139** is electron withdrawing by induction. Furthermore, chalcones with an *ortho*- and *para*- chlorine atom (**138** and **142**) react faster than **136** and **140**, with similar rates to the unsubstituted analogues; this likely arises due to the *ortho*- chlorine atom possessing a larger inductive effect than mesomeric effect because of its proximity to the target alkene, hence the electron withdrawing and donating effects of the two chlorine atoms balance out. The rates observed for the Nazarov cyclisation of chalcones **137** and **141** (2,4-Cl) is surprising; one would expect these substrates to react faster than they do, given the low mesomeric and high inductive nature of the *meta*- chlorine atom they

possess. This result suggests some other factor might be in operation here, possibly a steric effect caused by the positioning of the chlorine in the ring, which may hinder the molecule's ability to achieve the correct conformation to react and hence result in higher transition state energy. Finally, as anticipated, within each 'chalcone pair', i.e. identical 3-aryl functional group (e.g. **138** and **142**), the trimethoxy- derivative reacted faster.

Overall, 3-aryl-indan-1-ones **118-125** were obtained in very high yields from the TFA-mediated Nazarov cyclisation of their corresponding substituted chalcones, without the addition of P_2O_5 .

2.2 Chiral Resolution of Racemic 3-Aryl-indan-1-ones

2.2.1 Overview



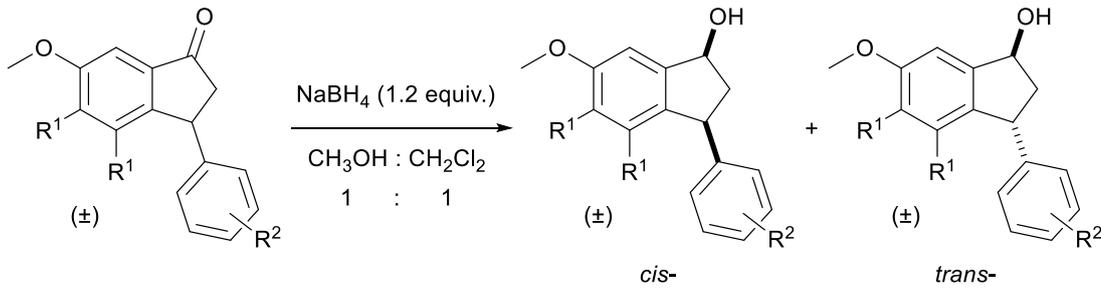
Scheme 23 "2.5-step" sequence towards enantiopure indan-1-one derivatives.

With the racemic 3-aryl-indan-1-ones in hand, attention was turned towards the chiral resolution process to afford individual ketone enantiomers, via the corresponding indan-1-ols. The employed route, obtained from previous work by the Fox group,¹⁴ comprised a "2.5-step" sequence comprising a diastereoselective *cis*-reduction into a pair of indan-1-ol diastereomers, followed by the key enantiospecific oxidation, and finally oxidation of the unreacted enantioenriched alcohols into the corresponding ketones (Scheme 23).

2.2.2 Diastereoselective Reduction of Racemic Indan-1-ones

Racemic indan-1-ones **118-125** were reduced into their corresponding *cis*-indan-1-ols,²² whereby a range of 3-aryl-indan-1-one derivatives were reduced with sodium borohydride to give the corresponding *cis*-alcohols in high purity and generally good yields. The results of the *cis*-reductions are shown in Table 6.

Table 6 *Cis*-reduction of racemic 3-aryl-indan-1-ones **118-125**.



<i>rac</i> -Indan-1-one			<i>rac</i> -Indan-1-ol	
	R ¹	R ²	Ratio <i>cis</i> - : <i>trans</i> - ^b	Yield <i>cis</i> - / % ^a
118	H	H	149 0.96 : 0.04 (0.98 : 0.02) ^d	94
119	H	4-Cl	150 0.94 : 0.06 (0.96 : 0.04) ^d	91
120	H	3,4-Cl	151 0.84 : 0.16 (0.93 : 0.07) ^d	90
121	H	2,4-Cl	152 0.89 : 0.11 (0.92 : 0.08) ^d	- ^c
122	OCH ₃	H	153 0.88 : 0.12 (0.88 : 0.12) ^d	86
123	OCH ₃	4-Cl	154 0.81 : 0.19 (0.88 : 0.12) ^d	80
124	OCH ₃	3,4-Cl	155 0.78 : 0.22 (0.85 : 0.15) ^d	79
125	OCH ₃	2,4-Cl	156 0.78 : 0.22 (0.82 : 0.18) ^d	- ^c

^a Isolated yield of *cis*- diastereomer; ^b *Cis*- / *trans*- ratio determined by ¹H NMR spectroscopy prior to purification; ^c Formed as an inseparable *cis*- / *trans*- mixture; ^d Reductions performed with 1.0 equiv. of NaBH₄.

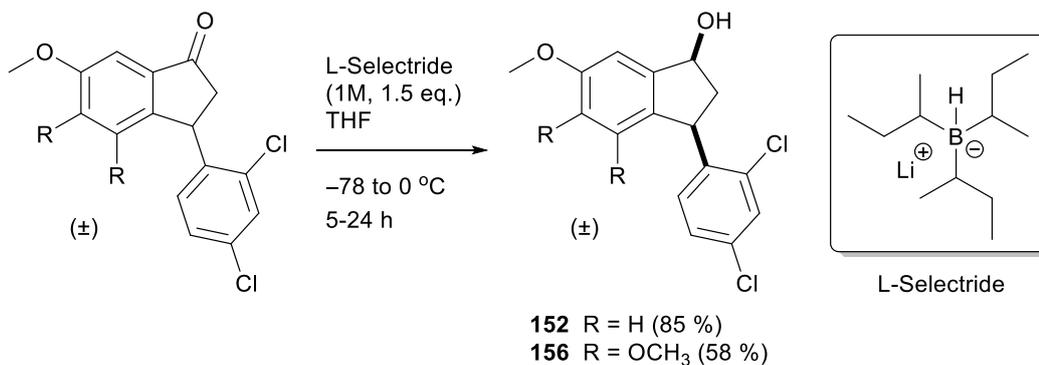
Cis- and *trans*- diastereomers were distinguished by comparison with literature.^{22, 23} The reduction proceeded with very high selectivity and excellent yields for the single methoxy indan-1-ones derivatives **118-121**. However, the reactions did not give the *cis*-isomer exclusively as was seen in literature,²² and previous work in the Fox group, even for those compounds (**118** and **119**) previously reduced by this method in the group.¹⁴ Attempts at trying to increase the diastereoselectivity through changes to both solvent and equivalents of NaBH₄ were found to generally improve the *cis*- : *trans*- ratio slightly, but failed to afford a single diastereomer. It is not clear why the reductions were not completely selective, especially given the identical procedure; one can therefore only assume that changes to the reaction setup is responsible, for instance how slowly the sodium borohydride was added, or how long the reaction was stirred at 0 °C after NaBH₄ addition prior to allowing it warm to room temperature – these conditions were not previously explicitly stated.

Indan-1-ones with three methoxy groups attached to the 1-aryl ring were also reduced in high yields, however the *cis*- : *trans*- ratios obtained were all markedly lower than for the single methoxy analogues, which is consistent with previous work in the group;¹⁴ this suggests that the presence of more substituents on this ring is detrimental to the selectivity of the *cis*-reduction by NaBH₄. As with the single methoxy analogues, efforts were made to improve the diastereoselectivity of the reaction by reducing the equivalents of sodium borohydride employed; these actions proved more fruitful with these substrates, in general resulting in a greater *cis*- : *trans*- ratio, although still did not give selectivity similar to that obtained for the single methoxy analogues.

The 3-aryl substituent also appeared to have an impact on outcome of the sodium borohydride reduction. Yields obtained from the reductions clearly decreased as the number of chlorine atoms incorporated into the ring increased, but there was also a noticeable trend between the *cis*- : *trans*- ratio and the number of chlorine atoms. There was greater formation of the *trans*- diastereomer with more chlorine atoms present, with the percentage of *trans*- isomer increasing by about 7 % on the introduction of two chlorine atoms in the case of the single methoxy indan-1-ones, and by *ca.* 10 % for the trimethoxy- derivatives.

Unfortunately, the *cis*- and *trans*- diastereomers of two of the indan-1-ol derivatives could not be separated by silica column chromatography; those possessing chlorine atoms in the 2- and 4-positions of the 3-aryl ring (**152** and **156**). As a result, attention was turned to a more selective method that utilises the more sterically demanding reducing agent

L-Selectride in an attempt to obtain the *cis*- diastereomers exclusively.^{24, 25} Its application to substrates **121** and **125** is shown in Scheme 24. The reactions gave lower yields than those with sodium borohydride, forming some unknown side-products in addition to unreacted starting material – ¹H NMR spectra of the crude products were indiscernible apart from key peaks corresponding to the product alcohols and starting ketones. Crucially, however, the desired *cis*-diastereomers were formed exclusively.



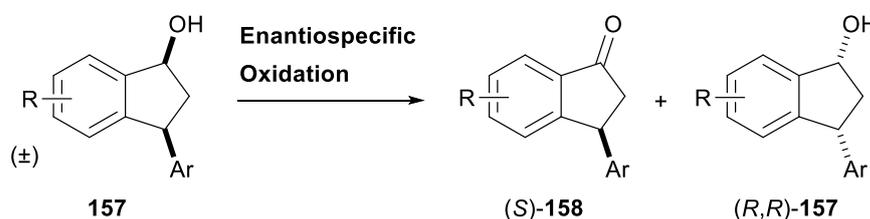
Scheme 24 *Cis*-reduction of racemic **121** and **125** using L-Selectride.

Due to the success of these two reactions, the L-Selectride method was applied to the other trimethoxy- indan-1-one derivatives in an attempt to obtain the corresponding *cis*-indan-1-ols with greater selectivity than those showed by the sodium borohydride reduction. Unfortunately, it was clear the reactions yielded a considerable amount of the undesired *trans*-isomer, similar to that obtained from the NaBH₄ reactions, although the exact *cis*- / *trans*- ratios could not be established from the ¹H NMR spectra of the crude mixtures. This heavily suggests the positioning of the substituents on the 3-aryl ring is important to the diastereoselectivity of the L-Selectride reduction. From this work it appears as though there is a requirement for an *ortho*- substituent to direct the selectivity towards the *cis*-indan-1-ol, however previous work from the group saw the completely selective reduction of trimethoxy- indan-1-ones bearing a 3-fluoro- or 4-methoxy- substituted ring in the 3-position using L-Selectride. Overall, these results elude to the possibility of electronic effects influencing the L-Selectride reduction, in addition to the clear steric factors in play.

In summary, two different methods of reduction were successfully applied across the series of 3-aryl-indan-1-ones, possessing a variety of substituents on the two aromatic rings; the desired corresponding *cis*-indan-1-ols were either obtained after isolation by column chromatography from a *cis*- : *trans*- diastereomeric mixture formed on reduction by sodium borohydride,²² or exclusively from the more reductive L-Selectride process.^{24, 25}

2.2.3 Oxidative Kinetic Resolution of *cis*-Indan-1-ols

As discussed in **Section 1.3**, oxidative kinetic resolutions are commonly employed with a focus on obtaining enantioenriched alcohols,^{26, 27} however they can be equally as valuable with respect to the access of enantiopure ketones when an additional stereogenic centre is present. As such, the principal step in the resolution of racemic 3-aryl-indan-1-ones **118-125** into their enantiomers was the kinetic oxidative resolution, which involves the selective oxidation of a single *cis*-indan-1-ol enantiomer (**157**) into the corresponding enantiopure 3-aryl-indan-1-one (e.g. (*S*)-**158**) and leaving behind the other indan-1-ol enantiomer (e.g. (*R,R*)-**157**) in high enantiomeric purity – this is the ideal scenario, occurring at ~50 % conversion (Scheme 25).

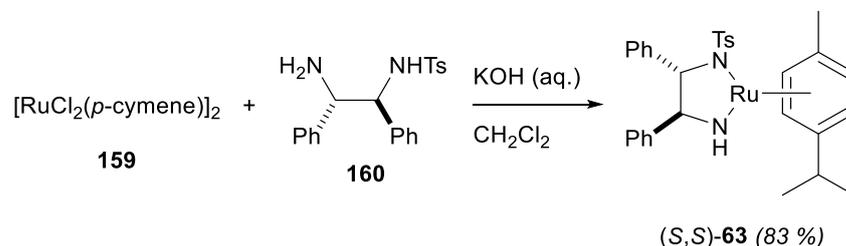


Scheme 25 Ideal oxidative kinetic resolution of *cis*-3-aryl-indan-1-ols (**157**).

The conditions of choice for asymmetric oxidation was that of Noyori, utilising his (*S,S*)-TsDPEN-Ru catalyst ((*S,S*)-**63**) and method, which was reported as highly enantioselective for a range of secondary alcohols, including indan-1-ol.²⁸

Noyori's asymmetric oxidation is an enantiospecific process, one that is typically highly enantioselective; the stereochemistry of the product is defined by the stereochemistry of the (chiral) enantioenriched substrate (*stereospecificity*), but one stereoisomer is reacting preferentially over the other due to more favourable interactions with the chiral catalyst (*stereoselectivity*) – a stereospecific process is necessarily stereoselective but not all stereoselective processes are stereospecific.²⁹ An example of a solely stereoselective process is the asymmetric transfer hydrogenation of a (prochiral) ketone,³⁰ whilst an S_N2 reaction at a sp^3 centre of an enantiomerically pure compound, which proceeds with inversion of configuration, is an example of a totally stereospecific process. For the case of the asymmetric oxidation studied within this work, a racemic mixture of *cis*-indan-1-ol **157** is present instead of a single enantiomer. The (*S,S*)-stereoisomer of **157** can only be oxidised to give the (*S*)- enantiomer of the product while the same is true of (*R,R*)-**157** to give (*R*)-**158**, therefore the process is enantiospecific. The reaction is also enantioselective since one indan-1-ol enantiomer oxidises preferentially; it is the extent of reaction of one enantiomer over the other that is measured – enantiomeric excess.

Prior to the oxidation of *cis*-indan-1-ols, the active catalyst (*S,S*)-**63** was prepared from ruthenium dimer **159** and (*S,S*)-TsDPEN (**160**) according to Noyori's procedure (Scheme 26), confirmed through comparison of spectroscopic and observational data to those within the literature.²⁸



Scheme 26 Synthesis of Noyori's catalyst (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) ((*S,S*)-**63**).

Small-scale oxidations of 3-aryl-indan-1-ols **149-156** were then performed as a preliminary test of conditions, to ascertain the point at which the reaction has reached 50 % conversion for each substrate, and to devise a simple and effective sampling procedure for reaction profiling (Table 7).

Table 7 Preliminary oxidative kinetic resolutions of racemic *cis*-indan-1-ols **149-156**.

	Racemic <i>cis</i> -Indan-1-ol		Catalyst Loading / mol%	(S)-Indan-1-one		(1 <i>R</i> ,3 <i>R</i>)-Indan-1-ol	
	R ¹	R ²		e.e. / % ^a		e.e. / % ^a	
149	H	H	0.5	118	92	149	93
150	H	4-Cl	0.5	119	95	150	80
151	H	3,4-Cl	0.5	120	96	151	78
152	H	2,4-Cl	1	121	91 ^{b, d}	152	76 ^{c, d}
153	OCH ₃	H	0.5	122	91	153	76
154	OCH ₃	4-Cl	0.5	123	89	154	93
155	OCH ₃	3,4-Cl	1	124	83	155	98
156	OCH ₃	2,4-Cl	2	125	87 ^{b, d}	156	85 ^{c, d}

^a e.e. % determined by chiral HPLC analysis; ^b (*R*)-configuration; ^c (1*R*,3*S*)-configuration;

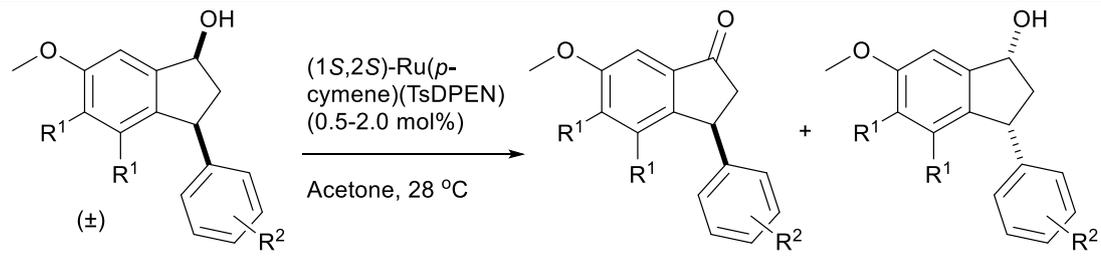
^d configuration deduced through literature comparison.

The majority of *cis*-indan-1-ols were successfully oxidised using Noyori's method and a 0.5 mol% catalyst loading of (*S,S*)-**63**, with 50 % conversion being achieved within 7 hours – this was the desired maximum duration for the asymmetric oxidations for reaction profiling purposes. Compounds **152**, **155** and **156** required higher catalyst loadings to achieve the desired conversion within this timeframe; 1 mol% gave 50 % conversion of **152** and **155**, although a loading of 2 mol% was needed to drive the oxidation of **156** to the same extent within 7 hours – the reaction of **156** was attempted with 1 mol% at higher temperature (50 °C) but 25.5 hours was required to reach 50 % conversion.

A notable observation during this initial study was the partial deactivation of the ruthenium catalyst, as evidenced from a non-linear relationship exhibited between catalyst loading and conversion, which was believed to be a result of the sensitivity of the active 16-electron ruthenium catalyst with respect to acid – neutral conditions are required.²⁸ This was confirmed when diminished conversion was observed for oxidations whereby the acetone was stored over molecular sieves prior to their use, which are known to be acidic;³¹ a fresh batch of dried acetone was required for each reaction. K₂CO₃ (1.00 eq.) was added to the reactions to combat the catalyst deactivation, which was sufficient to neutralise any acid present without hindering sampling.

The stereochemistry of each product was confirmed by analogy, where both enantiomers of 6-methoxy-3-phenyl-indan-1-one (**118**) and 6-methoxy-3-(3,4-dichlorophenyl)-indan-1-one (**120**) were consistent with literature reports.³² All reactions showed high selectivity towards a single *cis*-indan-1-ol enantiomer, giving generally high enantioselectivity for both ketone and alcohols at 50 % conversion. In fact, many of the substrates demonstrated greater overall enantioselectivity – slightly less product e.e. but far larger alcohol e.e. – just after the 50 % point had been reached.

With optimum conditions and a sampling procedure for the asymmetric oxidation in hand, larger scale oxidative kinetic resolutions of 3-aryl-indan-1-ols **149-156** were carried out; as before all reactions were performed with 0.50 mol% of catalyst (*S,S*)-**63** apart from those of **152** and **155** (1.00 mol%) and **156** (2.00 mol%). The oxidative kinetic resolutions yielded enantioenriched indan-1-ones **118-125** and enantioenriched indan-1-ols **149-156** in good to excellent enantioselectivities (Table 8). Observed yields were also very good; since the reaction was only permitted to reach about 50 % conversion, the total yield for each reaction is the combined ketone and alcohol yields.

Table 8 Oxidative kinetic resolutions of racemic *cis*-indan-1-ols **149-156**.


Racemic <i>cis</i> -Indan-1-ol		Conv. / %	<i>(S)</i> -Indan-1-one		<i>(1R,3R)</i> -Indan-1-ol				
R ¹	R ²		Yield / % ^a	e.e. / % ^b	Yield / % ^a	e.e. / % ^b			
149	H	H	48	118	43	87	149	45	89
150	H	4-Cl	49	119	41	95	150	47	94
151	H	3,4-Cl	50	120	42	96	151	43	90
152	H	2,4-Cl	51	121	46	91 ^{c, e}	152	44	93 ^{d, e}
153	OCH ₃	H	51	122	47	89	153	51	89
154	OCH ₃	4-Cl	51	123	44	93	154	47	89
155	OCH ₃	3,4-Cl	52	124	44	85	155	42	90
156	OCH ₃	2,4-Cl	51	125	46	85 ^{c, e}	156	50	90 ^{d, e}

^a Isolated yield, as a % of racemic starting material; ^b e.e. % determined by chiral HPLC analysis; ^c (*R*)-configuration; ^d (*1R,3S*)-configuration; ^e configuration deduced through literature comparison.

To further analyse the oxidative kinetic resolution of 3-aryl-indan-1-ols **149-156** multiple reaction profiles of ‘% enantiomeric excess’ against ‘% conversion’ were constructed, with the example displayed in Figure 17 being that of the oxidation of indan-1-ol **153**. These profiles give more accurate illustrations of the efficiency and selectivity of the reactions, thus allowing easier and more thorough comparisons to be made between substrate structure and the oxidation process. Before the reaction begins, at time = 0 mins, the e.e. of the starting material alcohol is zero since a racemic mixture is present and as no conversion has taken place, the enantiomeric excess of the product ketone can’t be established. The selectivity of the oxidation is at its highest once the reaction starts – assumed when one molecule of starting material is transformed into product (time is just greater than 0 mins) – hence the e.e. of the ketone is effectively 100 %. As the reaction progresses, the enantiomeric excess of the indan-1-ol increases quickly as one enantiomer is consumed preferentially over the other, however as less of this enantiomer becomes

‘available’ for oxidation the reaction slows and the catalyst starts to convert the opposite enantiomer, lowering the product e.e. as a result. Consequently, greater ketone enantiomeric excess is obtained at shorter reaction times whilst the same is true for the alcohol the further the oxidation progresses. At ~50 % conversion the reaction should theoretically attain the ‘best’ enantiomeric excess for both product indan-1-one and starting material indan-1-ol.

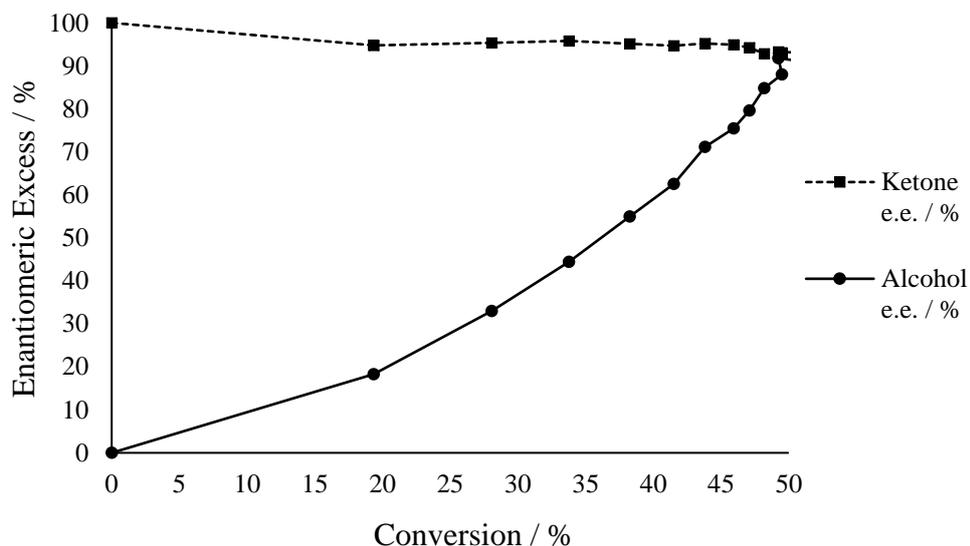


Figure 17 Reaction profile for the oxidative kinetic resolution of indan-1-ol **153**.

Every constructed reaction profile possessed a similar shape to the example shown in Figure 17. Comparison of these reaction profiles to generic plots of e.e. vs conversion for both starting material and product in kinetic resolutions (Figure 18), which are generated from Equations 10 and 14,³³ provides a qualitative insight into the selectivity factor, s , for the oxidative kinetic resolution studied within this work.

$$s = \frac{\ln[(1 - c)(1 - e.e._{SM})]}{\ln[(1 - c)(1 + e.e._{SM})]} \quad (10) \quad s = \frac{\ln[1 - c(1 + e.e._{P})]}{\ln[1 - c(1 - e.e._{P})]} \quad (14)$$

The higher the selectivity factor the more efficient the kinetic resolution. This can be seen in the plots in Figure 18, in which at 50 % conversion the e.e. of starting material and product tends towards 100 % as s increases. From these plots it is evident that a selectivity factor of greater than 50 is required to obtain ~90 % e.e. for both starting material and product at 50 % conversion. Similar levels of enantiomeric excess were observed for the oxidative kinetic resolutions performed in this work at this extent of conversion, suggesting $s \geq 50$ for each substrate studied; for instance alcohol e.e. is 91 % and ketone e.e. is 93 % at ~50 % conversion for the asymmetric oxidation of **153**.

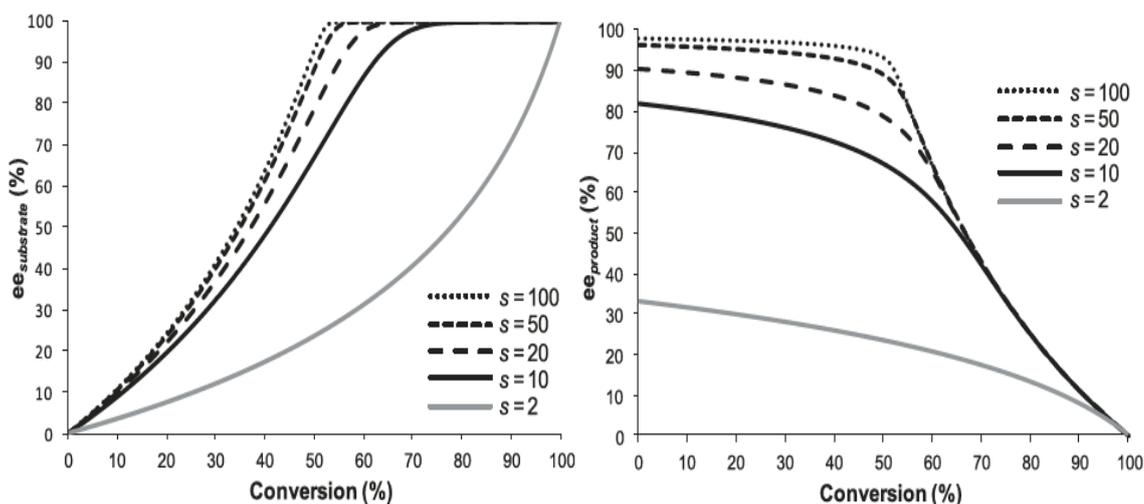


Figure 18 Plots of e.e. vs. conversion as a function of s for starting material (*left*) and product (*right*). [Obtained from a paper by Greenhalgh *et al.*³³]

While it is relatively straightforward to calculate s values from conversion and e.e. data using these equations, it is unlikely that they will be accurate. The evaluation of s depends in no small part on the accuracy of the measurements of enantiomeric excess and conversion and, as a consequence, any analytical error should be considered in its calculation. This is not a serious problem with e.e. measurements due to the employment of methods such as HPLC, however determination of the conversion requires care and precision, especially since this is commonly achieved through less accurate techniques such as ^1H NMR spectroscopy.³⁴ Fortunately, in a kinetic resolution in which both the starting material and product are chiral, such as the one studied in this work, the reaction conversion can be calculated from the associated e.e. values using Equation 15.

$$c = \frac{e.e._{\text{SM}}}{e.e._{\text{SM}} + e.e._{\text{P}}} \quad (15)$$

The use of Equation 15 not only reduces the error in the calculation of the selectivity factor, but also renders the overall error in s dependent on the accuracy of the e.e. measurements. The absolute error in s has been closely estimated in recent work by Greenhalgh *et al.* (Equation 16), which serves as a reasonable guide for kinetic resolutions whereby both e.e. and conversion have been determined by HPLC analysis using a chiral support and standard processing software.³³ The authors note that Equation 16 most likely gives an overestimation as it effectively compounds the errors in measuring both starting material and product e.e. values.

$$\text{absolute error} \approx 0.0003s^2 + 0.02s \quad (16)$$

It can be seen from Equation 16 that errors associated with low s values are relatively small, whereas errors in higher s values are much more significant. It is for this reason that Greenhalgh *et al.* recommend the selectivity factor is reported to the nearest integer for s values below 50 and to the nearest 10 for kinetic resolutions with $s = 50-200$.³³

As discussed in **Section 1.2.2**, Equations 10 and 14 hold true for kinetic resolutions in which the selectivity-determining step is first-order in substrate. Although this is generally assumed to be the case, in reality it is not unlikely that this dependence changes during the course of the resolution. Rate laws for synthetically useful kinetic resolutions are almost never determined, for it is often too challenging to do so, and different e.e. vs conversion curves are obtained in kinetic resolutions displaying other kinetic dependencies on substrate.³⁵

The intrinsic error within its calculation, coupled with the assumed first-order kinetics with respect to substrate, render accurate determination of the selectivity factor very difficult, and it is often found that s values vary significantly with conversion.³⁶ Indeed, similar results were discovered within this work. For example, in the case of the oxidative kinetic resolution of indan-1-ol **153** – the profile of which is shown in Figure 17 – the s value can be calculated from Equation 10 or 14 as 90 (± 4.23) at 49.5 % conversion, however at 36.6 % conversion this value is calculated to be 70 (± 2.87). Discrepancies such as these highlight the difficulty associated with calculating accurate values of s for the oxidative kinetic resolutions of 3-aryl-indan-1-ols **149-156** from solitary conversion and e.e. data. Nonetheless, another method for the calculation of selectivity factors has been realised,³³ one that gives arguably a more accurate s value that is representative of the entire resolution and independent of reaction conversion. This alternative route is to perform a linear regression analysis, which involves rearrangement of Equation 14 to Equation 17.

$$\ln[1 - c(1 + e.e.p)] = s \ln[1 - c(1 - e.e.p)] \quad (17)$$

Equation 17 resembles a typical straight line equation, therefore plotting ‘ $\ln[1 - c(1 + e.e.p)]$ ’ against ‘ $\ln[1 - c(1 - e.e.p)]$ ’ for all time points should theoretically yield a straight line that passes through the origin with gradient equal to s . This is evidenced by Figure 19, which is a plot for the oxidative kinetic resolution of 3-aryl-indan-1-ol **153**. The selectivity factor of 80 (± 3.52) for this reaction can be extracted from the equation for the fitted regression line, which is displayed on the plot.

[N.B. A similar approach for the determination of the selectivity factors using starting material e.e. values, by plotting ‘ $\ln[(1 - c)(1 - e.e._{SM})]$ ’ against ‘ $\ln[(1 - c)(1 + e.e._{SM})]$ ’ for all time points – acquired from rearrangement of Equation 10 – gave identical results, as one would expect.]

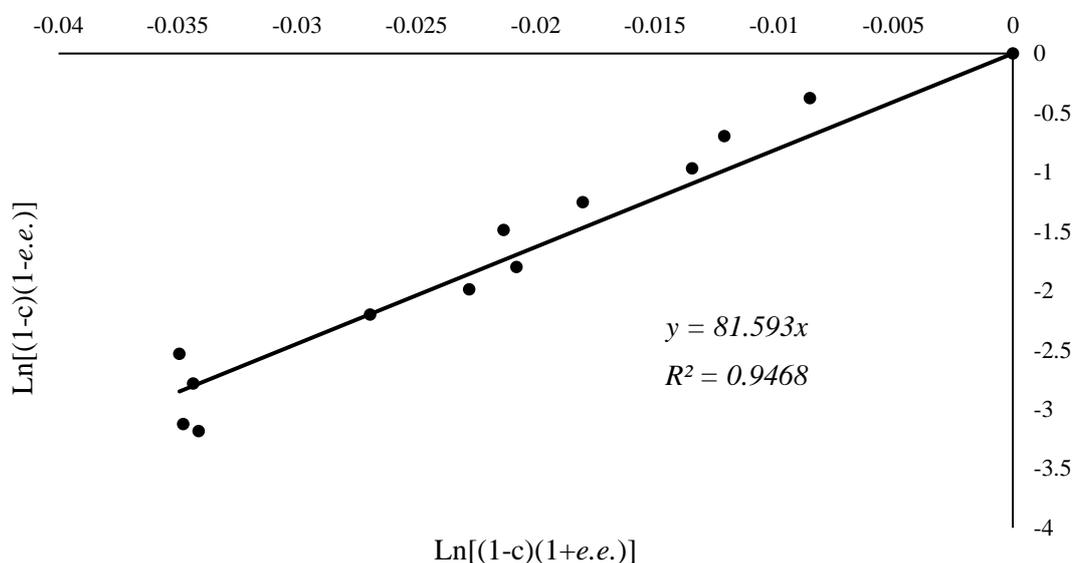


Figure 19 Plot of ‘ $\ln[1 - c(1 + e.e._p)]$ ’ against ‘ $\ln[1 - c(1 - e.e._p)]$ ’ for the oxidative kinetic resolution of *cis*-indan-1-ol **153**; selectivity factor, $s = 80 (\pm 3.52)$.

Also shown in Figure 19 is the coefficient of determination, R^2 , for the fitted regression line. The value is very high (95 %) – as was the case for each reaction – indicating uniformity over the course of the kinetic resolution, which suggests that this is a reasonable approach towards determination of the selectivity factors for the ruthenium-catalysed oxidative kinetic resolution. As such, these s values were determined for each substrate (Figure 20).

As previously stated, the higher the selectivity factor the more efficient the resolution, this is because lower conversions are required to achieve higher product enantiomeric excesses. There are no clear trends in the s values calculated for the oxidative kinetic resolution of 3-aryl-indan-1-ols **149-156**, however they are all greater than 50, with the exception of **156**. These values are very good, especially considering the desire to obtain both indan-1-ols and indan-1-ones in high enantioenrichment, the latter of which typically requires higher selectivity factors; as reflected by the e.e. vs conversion plots in Figure 18, s values in excess of 50 are generally required if product of high enantiomeric purity is to be obtained in useful yield, whereas even a selectivity factor as low as 10 can theoretically allow isolation of starting material in 98 % e.e. with a quite reasonable 30 % recovery.

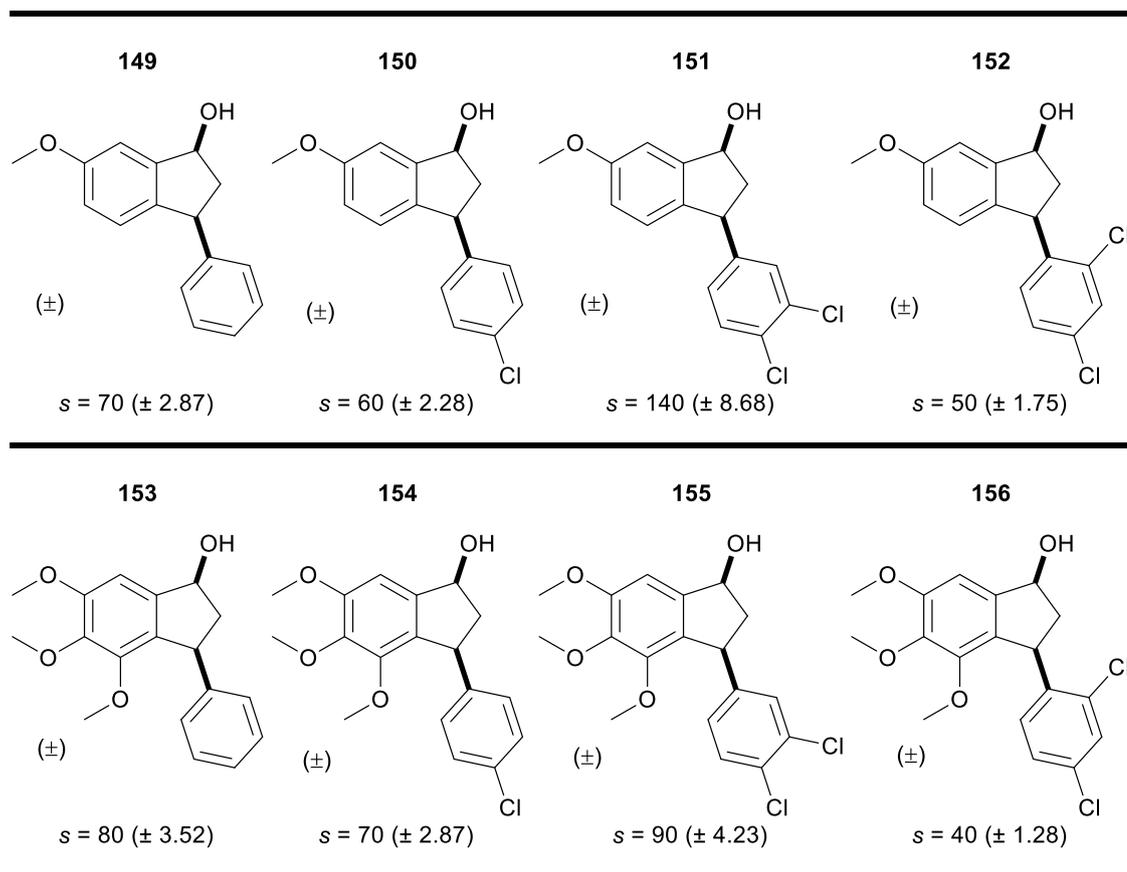
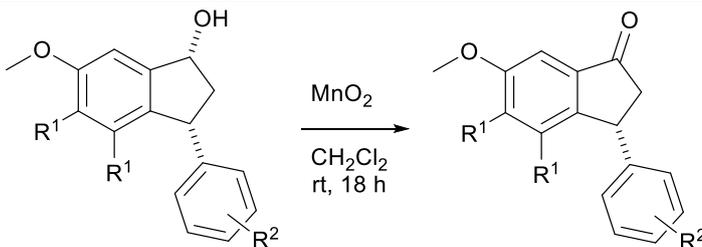


Figure 20 Selectivity factors, s , acquired from linear regression analysis for the oxidative kinetic resolution of 3-aryl-indan-1-ols **149-156** catalysed by Ru catalyst (*S,S*)-**63**; errors were calculated using Equation 16 in accordance with best practice guidelines published by Greenhalgh *et al.*³³

2.2.4 Oxidation of Residual Enantioenriched *cis*-Indan-1-ols

The final step involved the simple and effective oxidation of the residual enantiopure *cis*-indan-1-ols by manganese dioxide;^{37, 38} MnO_2 is a widely used oxidant for the transformation of allylic and benzylic alcohols into aldehydes and ketones, offering mild conditions and extremely high selectivity for these substrates, as well as involving straightforward work-up that comprises filtration of the suspended solid and solvent removal.³⁹ Oxidation of enantioenriched alcohols **149-156** – recovered after the oxidative kinetic resolutions – with MnO_2 yielded the desired enantiomerically enriched 3-aryl-indan-1-ones **118-125** in good to excellent yields and enantioselectivities (Table 9); there are no clear trends between the nature of the indan-1-ol and the yield of the reaction.

Table 9 MnO₂ oxidation of residual enantiomerically enriched indan-1-ols **149-156**.

Indan-1-ol (1 <i>R</i> ,3 <i>R</i>)			Indan-1-one (<i>R</i>)		
	R ¹	R ²		Yield / % ^a	e.e. / % ^b
149	H	H	118	85	85
150	H	4-Cl	119	83	91
151	H	3,4-Cl	120	80	88
152^{c, e}	H	2,4-Cl	121^{d, e}	86	89
153	OCH ₃	H	122	82	94
154	OCH ₃	4-Cl	123	81	91
155	OCH ₃	3,4-Cl	124	99	93
156^{c, e}	OCH ₃	2,4-Cl	125^{d, e}	75	88

^a Isolated yield; ^b e.e. % determined by chiral HPLC analysis; ^c (1*R*,3*S*)-configuration; ^d (*S*)-configuration; ^e configuration deduced through analogy with previous results.

2.3 Summary

Within this chapter a convenient and attractive synthetic route has been discussed that allows access to the individual enantiomers of 3-aryl-indan-1-ones, compounds which are known to possess an array of interesting biological properties. Racemic 3-aryl-indan-1-ones were synthesised in overall very good yields via the Nazarov cyclisation of substituted chalcones, which were prepared using a Claisen–Schmidt condensation of commercially available acetophenones and aromatic aldehydes.

The “2.5-step” chiral resolution involved initial reduction of the racemic ketones to give corresponding *cis*-indan-1-ols in high diastereoselectivity. Subsequent ruthenium-catalysed oxidative kinetic resolution, utilising Noyori’s (*S,S*)-TsDPEN-Ru catalyst ((*S,S*)-**63**) and method,²⁸ proceeded with high enantioselectivity, affording enantioenriched 3-aryl-indan-1-ones and 3-aryl-indan-1-ols in generally excellent enantiomeric excesses at ~50 % conversion. Finally, oxidation of the unreacted enantiopure alcohols provided the opposite 3-aryl-indan-1-one enantiomers in good to excellent yields.

2.4 Experimental for Chapter 2

2.4.1 General

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. Heat transfer for reactions was achieved using drysyn[®] apparatus and were performed using commercially available reagents and solvents which, unless otherwise stated, were used as received. Reactions involving moisture sensitive compounds were performed under a dry, oxygen-free atmosphere and in dry solvents. Such solvents were dried prior to use using the methods described in “Purification of Laboratory Chemicals, 6th Ed.”, and used accordingly.¹⁵ 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 H₂SO₄ and 0.75 M Na₂SO₄).

Reactions were followed by thin layer chromatography (TLC), performed on aluminium plates coated with 0.2 mm silica gel (DC Kieselgel 60 F₂₅₄, Merck), developed either from UV fluorescence (254 nm) or potassium permanganate followed by heating. Column chromatography was carried out using SiO₂ (40-63 microns).

Melting points were determined on a Stuart Scientific SMP10 melting point apparatus (uncorrected), with 3 runs of each compound, and the average value given in °C rounded to the nearest degree.

Infrared (IR) spectra were recorded as thin films on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer and results are quoted in wavenumbers (cm⁻¹). Peak intensities are specified as strong (s), medium (m), weak (w) and broad (br). Sulfoxide S=O stretches are denoted as asymmetric (*as*) and symmetric (*s*).

NMR spectra were recorded on Bruker Advance DRX 250, 300, 400 and 600 MHz spectrometers at room temperature (298 K). Chemical shifts are reported in parts per million (ppm), downfield relative to tetramethylsilane (TMS) (0.00 ppm), and referenced from CDCl₃ in most instances (δ_{H} : 7.26 ppm and δ_{C} : 77.2 ppm). Coupling constants (*J*) are reported in Hertz (Hz) and rounded to the nearest 0.5 Hz. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m) and broad (br.), whilst more complex multiplicities are in line with these denotations, e.g. doublet of doublets (dd). Spectra were analysed using MestReNova[®], with ¹H and ¹³C assignments established on the basis of COSY, DEPT, HMQC and HMBC correlations, in addition to NOE experiments. [Carbon spectra were determined with broadband decoupling].

Mass spectra were obtained using the University of Warwick Mass Spectrometry Service, where low resolution electrospray ionisation (ESI) mass spectra were recorded on an Agilent 6130B single Quad instrument, and high resolution ESI mass spectra (HRMS) were recorded using a Bruker micro-TOF ESI spectrometer by either Dr Lijiang Song, Mr Philip Aston or Mr James Morrey.

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 cm² g⁻¹. Concentrations (c) are given in grams / Litre (g/L). The samples were prepared using spectroscopic grade CHCl₃.

Naming of compounds has been performed in accordance with IUPAC guidelines.⁴⁰ (*R*)- and (*S*)- configurations were assigned according to the Cahn–Ingold–Prelog priority rules.⁴¹

NMR assignments for each compound are using the following notations:

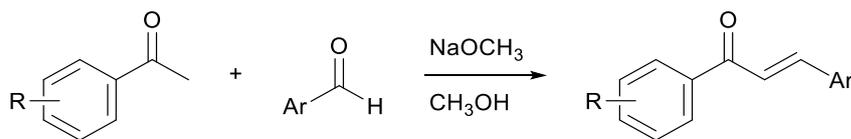
¹H NMR Assignments:

ArH (aromatic hydrogen), CHX (non-aromatic hydrogens).

¹³C NMR Assignments:

ArC (aromatic carbon bearing no hydrogens), ArCH (aromatic carbon bearing a hydrogen), CH (non-aromatic carbon, bearing a hydrogen), C (non-aromatic carbon, bearing no hydrogens).

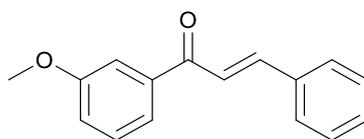
2.4.2 Substituted Chalcone Formation by Claisen–Schmidt Condensation – General Procedure A



The following procedure was performed in accordance with previous literature.²

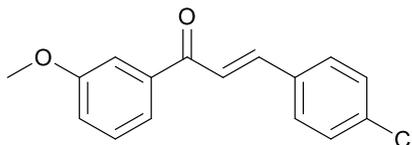
To a solution of substituted acetophenone (1.00 equiv.) and substituted benzaldehyde (1.00 equiv.) in MeOH (0.75 mL/mmol), was added NaOMe (1.48 equiv.). The resulting mixture was stirred at room temperature for 3 hours unless otherwise stated. If a precipitate formed, this was filtered, washed with MeOH and dried under vacuum. If no precipitate formed, HCl (2.00 M) was added slowly and the mixture was evaporated to near dryness under reduced pressure. The residue was suspended in saturated NaHCO₃ (aq.) and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

(*E*)-1-(3'-Methoxyphenyl)-3-phenylprop-2-en-1-one, 135



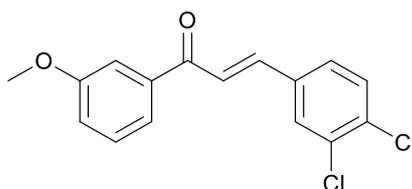
General procedure A was applied using 3-methoxyacetophenone (9.20 mL, 67.0 mmol), benzaldehyde (6.84 mL, 67.0 mmol), MeOH (50.0 mL) and NaOMe (5.35 g, 99.0 mmol) and was used without further purification. The title compound was formed as a viscous yellow oil (15.0 g, 94 %); ν_{\max} /cm⁻¹ (neat) 3001 (m, ArC-H), 2834 (m, C-H), 1662 (s, C=C), 1588 (s, C=O) 1254 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.82 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.65 (1H, dd, $J = 3.5, 1.0$ Hz, ArH), 7.64 (1H, d, $J = 2.0$ Hz, ArH), 7.61 (1H, dt, $J = 7.5, 1.0$ Hz, ArH), 7.55 (1H, dd, $J = 2.5, 1.5$ Hz, ArH), 7.51 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.44-7.39 (4H, m, 4 x ArH), 7.14 (ddd, $J = 8.0, 2.5, 1.0$ Hz, ArH), 3.89 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 190.3 (C=O), 159.9 (ArC), 144.9 (C(O)CH=CH), 139.6 (ArC), 134.9 (ArC), 130.6 (ArCH), 129.6 (ArCH), 129.0 (2 x ArCH), 128.5 (2 x ArCH), 122.1 (C(O)CH=CH), 121.1 (ArCH), 119.3 (ArCH), 112.9 (ArCH), 55.5 (OCH₃); m/z (ESI) 261 [M+Na]⁺; HRMS (ESI) C₁₆H₁₄O₂Na⁺ requires 261.0886, found 261.0886 [M+Na]⁺. These data are consistent with those previously reported.^{14, 42, 43}

(E)-3-(4-Chlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one, 136



General procedure A was applied using 3-methoxyacetophenone (9.20 mL, 67.0 mmol), 4-chlorobenzaldehyde (9.42 g, 67.0 mmol), MeOH (50.0 mL) and KOH solution (3.75 M, 3.00 mL) instead of NaOMe. The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a pale yellow solid (14.8 g, 81 %); m.p. 85-86 °C (lit.⁴⁴ 83 °C); ν_{\max} /cm⁻¹ (neat) 2998 (m, ArC-H), 2837 (m, C-H), 1655 (s, C=C), 1565 (s, C=O) 1255 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.76 (1H, d, J = 16.0 Hz, C(O)CH=CH), 7.62-7.58 (2H, m, 2 x ArH), 7.58-7.56 (1H, m, ArH), 7.55-7.53 (1H, m, ArH), 7.48 (1H, d, J = 16.0 Hz, C(O)CH=CH), 7.43 (1H, d, J = 8.0 Hz, ArH), 7.41-7.40 (1H, m, ArH), 7.40-7.38 (1H, m, ArH), 7.14 (1H, dd, J = 8.0, 2.5 Hz, ArH), 3.89 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 190.0 (C=O), 160.0 (ArC), 143.4 (C(O)CH=CH), 139.5 (ArC), 136.5 (ArC), 133.4 (ArC), 129.6 (ArCH), 129.6 (2 x ArCH), 129.3 (2 x ArCH), 122.5 (C(O)CH=CH), 121.1 (ArCH), 119.5 (ArCH), 112.9 (ArCH), 55.5 (OCH₃); m/z (ESI) 295 [M+Na]⁺; HRMS (ESI) C₁₆H₁₃³⁵ClO₂Na⁺ requires 295.0496, found 295.0498 [M+Na]⁺. These data are consistent with those previously reported.^{14, 44}

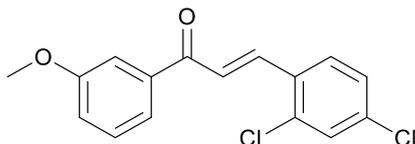
(E)-3-(3,4-Dichlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one, 137



General procedure A was applied using 3-methoxyacetophenone (9.20 mL, 67.0 mmol), 3,4-dichlorobenzaldehyde (11.7 g, 67.0 mmol), MeOH (50.0 mL) and KOH solution (3.75 M, 3.00 mL) instead of NaOMe. The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a pale yellow solid (19.1 g, 93 %); m.p. 113-114 °C (lit.⁴⁵ 116 °C); ν_{\max} /cm⁻¹ (neat) 3020 (m, ArC-H), 2832 (m, C-H), 1663 (s, C=C), 1597 (s, C=O) 1250 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.73 (1H, d, J = 2.0 Hz, ArH), 7.70 (1H, d, J = 16.0 Hz, C(O)CH=CH), 7.60 (1H, dt, J = 7.7, 1.0 Hz, ArH), 7.54 (1H, dd, J = 2.5, 1.5 Hz, ArH), 7.50 (1H, d, J = 8.5 Hz, ArH), 7.49 (1H, d, J = 16.0 Hz, C(O)CH=CH), 7.46 (1H, dd, J = 8.5, 2.0 Hz, ArH), 7.43 (1H, t, J = 8.0 Hz, ArH), 7.15 (1H, ddd, J = 8.0, 2.5, 0.5

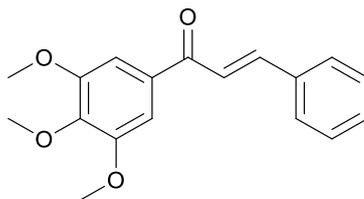
Hz, ArH), 3.89 (3H, s, OCH₃); δ_C (126 MHz, CDCl₃) 190.0 (C=O), 160.0 (ArC), 141.9 (C(O)CH=CH), 139.2 (ArC), 135.0 (ArC), 134.4 (ArC), 133.4 (ArC), 131.0 (C(O)CH=CH), 129.8 (ArCH), 129.7 (ArCH), 127.5 (ArCH), 123.6 (ArCH), 121.1 (ArCH), 119.7 (ArCH), 112.9 (ArCH), 55.5 (OCH₃); m/z (ESI) 329 [M+Na]⁺; HRMS (ESI) C₁₆H₁₂³⁵Cl₂O₂Na⁺ requires 329.0107, found 329.0106 [M+Na]⁺. These data are consistent with those previously reported.^{21, 45, 46}

(E)-3-(2,4-Dichlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one, 138



General procedure A was applied using 3-methoxyacetophenone (9.20 mL, 67.0 mmol), 2,4-dichlorobenzaldehyde (11.7 g, 67.0 mmol), MeOH (50.0 mL) and KOH solution (3.75 M, 3.00 mL) instead of NaOMe. The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a pale yellow solid (18.1 g, 88 %); m.p. 100-101 °C; ν_{\max} /cm⁻¹ (neat) 3072 (m, ArC-H), 2834 (m, C-H), 1657 (s, C=C), 1585 (s, C=O) 1260 (s, C-O); δ_H (500 MHz, CDCl₃) 8.10 (1H, d, *J* = 16.0 Hz, C(O)CH=CH), 7.68 (1H, d, *J* = 8.5 Hz, ArH), 7.58 (1H, dt, *J* = 8.0, 1.5 Hz, ArH), 7.53 (1H, dd, *J* = 2.5, 1.5 Hz, ArH), 7.46 (1H, d, *J* = 2.0 Hz, ArH), 7.45 (1H, d, *J* = 16.0 Hz, C(O)CH=CH), 7.41 (1H, t, *J* = 8.0 Hz, ArH), 7.30 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 7.15 (1H, ddd, *J* = 8.0, 2.5, 0.5 Hz, ArH), 3.88 (3H, s, OCH₃); δ_C (126 MHz, CDCl₃) 189.8 (C=O), 160.0 (ArC), 139.3 (C(O)CH=CH), 139.2 (ArC), 136.5 (ArC), 136.1 (ArC), 131.9 (ArC), 130.2 (ArCH), 129.7 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 125.1 (C(O)CH=CH), 121.2 (ArCH), 119.6 (ArCH), 113.0 (ArCH), 55.6 (OCH₃); m/z (ESI) 329 [M+Na]⁺; HRMS (ESI) C₁₆H₁₂³⁵Cl₂O₂Na⁺ requires 329.0107, found 329.0110 [M+Na]⁺. This compound is known but was previously reported without characterisation data.⁴⁷

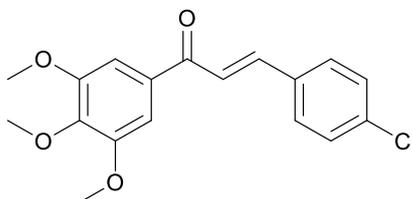
(E)-3-Phenyl-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one, 139



General procedure A was applied using 3,4,5-trimethoxyacetophenone (14.0 g, 67.0 mmol), benzaldehyde (6.84 mL, 67.0 mmol), MeOH (50.0 mL) and NaOMe (5.35 g, 99.0 mmol) and was used without further purification. The title compound was formed as a

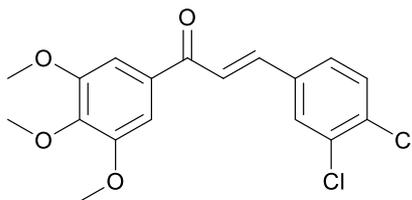
pale yellow solid (18.8 g, 94 %); m.p. 80-81 °C (lit.⁴⁸ 87-88 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2988 (m, ArC-H), 2831 (m, C-H), 1656 (s, C=C), 1601 (s, C=O) 1121 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.82 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.66 (1H, dd, $J = 3.5, 1.0$ Hz, ArH), 7.65 (1H, d, $J = 2.0$ Hz, ArH), 7.48 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.46-7.42 (3H, m, 4 x ArH), 7.28 (2H, s, 2 x ArH), 3.96 (6H, s, 2 x OCH₃), 3.94 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 189.3 (C=O), 153.2 (2 x ArC), 144.8 (C(O)CH=CH), 142.5 (ArC), 134.9 (ArC), 133.5 (ArC), 130.6 (ArCH), 129.0 (2 x ArCH), 128.5 (2 x ArCH), 122.8 (C(O)CH=CH), 106.1 (2 x ArCH), 61.0 (OCH₃), 56.4 (2 x OCH₃); m/z (ESI) 321 [M+Na]⁺; HRMS (ESI) C₁₈H₁₈O₄Na⁺ requires 321.1097, found 321.1097 [M+Na]⁺. These data are consistent with those previously reported.⁴³

(E)-3-(4-Chlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one, 140



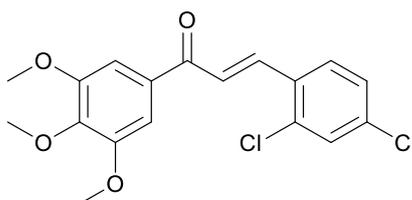
General procedure A was applied using 3,4,5-trimethoxyacetophenone (14.1 mL, 67.0 mmol), 4-chlorobenzaldehyde (9.42 g, 67.0 mmol), MeOH (50.0 mL) and KOH solution (3.75 M, 3.00 mL) instead of NaOMe. The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a pale yellow solid (16.2 g, 73 %); m.p. 112-114 °C (lit.⁴⁹ 115-116 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2987 (m, ArC-H), 2834 (m, C-H), 1655 (s, C=C), 1601 (s, C=O) 1124 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.77 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.61-7.59 (1H, m, ArH), 7.59-7.56 (1H, m, ArH), 7.45 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.42-7.41 (1H, m, ArH), 7.41-7.39 (1H, m, ArH), 7.27 (2H, s, 2 x ArH), 3.96 (6H, s, 2 x OCH₃), 3.95 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 188.9 (C=O), 153.2 (2 x ArC), 143.3 (C(O)CH=CH), 142.7 (ArC), 136.5 (ArC), 133.4 (ArC), 133.3 (ArC), 129.6 (2 x ArCH), 129.3 (2 x ArCH), 122.1 (C(O)CH=CH), 106.1 (2 x ArCH), 61.0 (OCH₃), 56.5 (2 x OCH₃); m/z (ESI) 355 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵ClO₄Na⁺ requires 355.0708, found 355.0704 [M+Na]⁺. These data are consistent with those previously reported.^{49, 50}

(E)-3-(3,4-Dichlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one, 141



General procedure A was applied using 3,4,5-trimethoxyacetophenone (14.1 mL, 67.0 mmol), 3,4-dichlorobenzaldehyde (11.7 g, 67.0 mmol), MeOH (50.0 mL) and KOH solution (3.75 M, 3.00 mL) instead of NaOMe. The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a pale yellow solid (23.0 g, 94 %); m.p. 138-139 °C (lit.⁴⁶ 139-140 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3083 (m, ArC-H), 2833 (m, C-H), 1663 (s, C=C), 1606 (s, C=O) 1125 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.74 (1H, d, $J = 2.0$ Hz, ArH), 7.70 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.51 (1H, d, $J = 8.5$ Hz, ArH), 7.45 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.45 (1H, d, $J = 2.0$ Hz, ArH), 7.27 (2H, s, 2 x ArH), 3.96 (6H, s, 2 x OCH₃), 3.95 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 188.5 (C=O), 153.3 (2 x ArC), 142.9 (ArC), 141.9 (C(O)CH=CH), 135.0 (ArC), 134.4 (ArC), 133.3 (ArC), 133.1 (ArC), 131.0 (ArCH), 129.7 (ArCH), 127.6 (C(O)CH=CH), 123.2 (ArCH), 106.2 (2 x ArCH), 61.0 (OCH₃), 56.5 (2 x OCH₃); m/z (ESI) 389 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆³⁵Cl₂O₄Na⁺ requires 389.0318, found 389.0313 [M+Na]⁺. These data are consistent with those previously reported.^{46, 50}

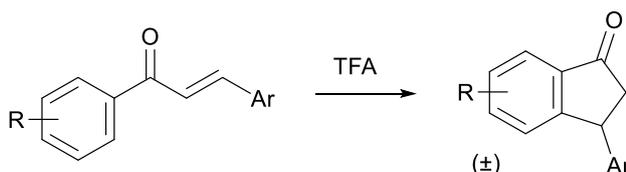
(E)-3-(2,4-Dichlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one, 142



General procedure A was applied using 3,4,5-trimethoxyacetophenone (14.1 mL, 67.0 mmol), 2,4-dichlorobenzaldehyde (11.7 g, 67.0 mmol), MeOH (50.0 mL) and KOH solution (3.75 M, 3.00 mL) instead of NaOMe. The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. The title compound was formed as a pale yellow solid (24.5 g, 99 %); m.p. 149-150 °C (lit.⁴⁹ 151-153 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3089 (m, ArC-H), 2838 (m, C-H), 1656 (s, C=C), 1596 (s, C=O) 1121 (s, C-O); δ_{H} (500 MHz, CDCl₃) 8.07 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.68 (1H, d, $J = 8.5$ Hz, ArH), 7.48 (1H, d, $J = 2.0$ Hz, ArH), 7.38 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.31 (1H, ddd, $J = 8.5, 2.0, 0.5$ Hz, ArH), 7.26 (2H, s, 2 x ArH), 3.95 (9H,

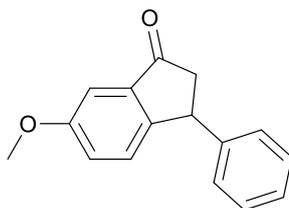
s, 3 x OCH₃); δ_C (126 MHz, CDCl₃) 189.2 (C=O), 153.2 (2 x ArC), 142.8 (ArC), 139.3 (C(O)CH=CH), 136.5 (ArC), 136.0 (ArC), 133.0 (ArC), 131.9 (ArC), 130.2 (ArCH), 128.6 (ArCH), 127.6 (ArCH), 125.1 (C(O)CH=CH), 106.3 (2 x ArCH), 61.0 (OCH₃), 56.4 (2 x OCH₃); m/z (ESI) 389 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆³⁵Cl₂O₄Na⁺ requires 389.0318, found 389.0317 [M+Na]⁺. These data are consistent with those previously reported.^{49, 50}

2.4.3 Formation of 3-Aryl-indan-1-ones by Nazarov Cyclisation – General Procedure B



The following procedure was performed in accordance with previous literature.¹³ Substituted chalcone (1.00 equiv.) in trifluoroacetic acid (1.20 mL/mmol) was refluxed at 80 °C for 24 hours under N₂, unless otherwise stated. The resulting mixture was carefully washed (Et₂O) into cold NaOH (2.00 M). Organics were then extracted with additional Et₂O, followed by successive washing of the organic layer with NaOH (2.00 M) until pH > 7 had been achieved. Finally, the organics were washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

6-Methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, **118** (0.99:0.01 mixture of isomers)

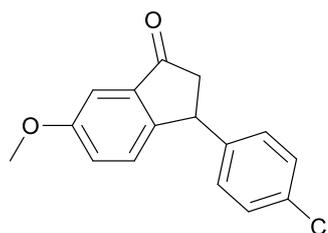


General procedure B was applied using (*E*)-1-(3-methoxyphenyl)-3-phenylprop-2-en-1-one **135** (15.0 g, 62.9 mmol) and trifluoroacetic acid (75.5 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave an inseparable 0.99:0.01 mixture of **118** to 4-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one as an off-white solid (12.6 g, 84 %); m.p. 69-71 °C (lit.¹³ 69-71 °C); ν_{\max} /cm⁻¹ (neat) 3026 (m, ArC-H), 2834 (m, C-H), 1699 (s, C=O), 1271 (s, C-O); δ_H (500 MHz, CDCl₃) 7.33-7.28 (2H, m, 2 x ArH), 7.26-7.21 (2H, m, 2 x ArH), 7.17-7.15 (2H, m, 2 x ArH), 7.13-7.12 (1H, m, ArH), 7.11-7.10 (1H, m, ArH), 4.52 (1H, dd, *J* = 8.0, 3.5 Hz, C(Ar)H), 3.86 (3H, s,

OCH₃), 3.25 (1H, dd, $J = 19.0, 8.0$ Hz, C(H)H), 2.69 (1H, dd, $J = 19.0, 3.5$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 206.0 (C=O), 159.8 (ArC), 150.9 (ArC), 143.9 (ArC), 138.0 (ArC), 128.9 (2 x ArCH), 127.6 (ArCH), 127.5 (2 x ArCH), 126.9 (ArCH), 124.5 (ArCH), 104.4 (ArCH), 55.7 (OCH₃), 47.6 (CH₂), 43.8 (C(Ar)H); m/z (ESI) 261 [M+Na]⁺; HRMS (ESI) C₁₆H₁₄O₂Na⁺ requires 261.0886, found 261.0884 [M+Na]⁺. These data are consistent with those previously reported.^{13, 14, 32}

3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, **119**

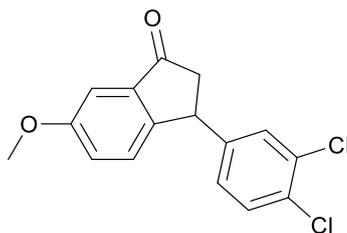
(0.99:0.01 mixture of isomers)



General procedure B was applied using (*E*)-3-(4-chlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one **136** (14.7 g, 53.9 mmol) and trifluoroacetic acid (64.7 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave an inseparable 0.99:0.01 mixture of **119** to 3-(4-chlorophenyl)-4-methoxy-2,3-dihydro-1H-inden-1-one as a white solid (12.1 g, 82 %); m.p. 120-123 °C; ν_{\max} /cm⁻¹ (neat) 3063 (m, ArC-H), 2829 (m, C-H), 1707 (s, C=O), 1279 (s, C-O); δ_H (500 MHz, CDCl₃) 7.29-7.26 (2H, m, 2 x ArH), 7.23 (1H, d, $J = 2.5$ Hz, ArH), 7.17 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.15-7.11 (1H, m, ArH), 7.07-7.05 (1H, m, ArH), 7.05-7.03 (1H, m, ArH), 4.50 (1H, dd, $J = 8.0, 3.5$ Hz, C(Ar)H), 3.86 (3H, s, OCH₃), 3.25 (1H, dd, $J = 19.0, 8.0$ Hz, C(H)H), 2.63 (1H, dd, $J = 19.0, 3.5$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 205.5 (C=O), 159.9 (ArC), 150.2 (ArC), 142.5 (ArC), 138.0 (ArC), 132.7 (ArC), 129.0 (2 x ArCH), 128.9 (2 x ArCH), 127.5 (ArCH), 124.6 (ArCH), 104.5 (ArCH), 55.7 (OCH₃), 47.5 (CH₂), 43.2 (C(Ar)H); m/z (ESI) 295 [M+Na]⁺; HRMS (ESI) C₁₆H₁₃³⁵ClO₂Na⁺ requires 295.0496, found 295.0493 [M+Na]⁺. These data are consistent with those previously reported.¹⁴

3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, **120**

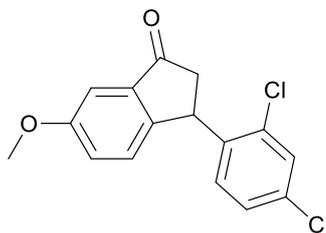
(0.94:0.06 mixture of isomers)



General procedure B was applied using (*E*)-3-(3,4-dichlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one **137** (9.00 g, 29.3 mmol) and trifluoroacetic acid (35.2 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (3:1), gave an inseparable 0.94:0.06 mixture of **120** to 3-(3,4-dichlorophenyl)-4-methoxy-2,3-dihydro-1H-inden-1-one as a yellow oil (8.00 g, 89 %); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3057 (m, ArC-H), 2835 (m, C-H), 1704 (s, C=O), 1279 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.37 (1H, d, $J = 8.5$ Hz, ArH), 7.24 (1H, d, $J = 2.5$ Hz, ArH), 7.21 (1H, d, $J = 2.0$ Hz, ArH), 7.19 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.14 (1H, d, $J = 8.5$ Hz, ArH), 6.94 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 4.49 (1H, dd, $J = 8.0, 3.5$ Hz, C(Ar)H), 3.87 (3H, s, OCH_3), 3.25 (1H, dd, $J = 19.0, 8.0$ Hz, C(H)H), 2.61 (1H, dd, $J = 19.0, 3.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 203.9 (C=O), 159.1 (ArC), 148.3 (ArC), 143.2 (ArC), 137.1 (ArC), 131.9 (ArC), 130.0 (ArC), 129.8 (ArCH), 128.5 (ArCH), 126.4 (ArCH), 125.9 (ArCH), 123.7 (ArCH), 103.7 (ArCH), 54.7 (OCH_3), 46.2 (CH_2), 41.9 (C(Ar)H); m/z (ESI) 329 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{16}\text{H}_{12}^{35}\text{Cl}_2\text{O}_2\text{Na}^+$ requires 329.0107, found 329.0104 $[\text{M}+\text{Na}]^+$. These data are consistent with those previously reported.^{22, 32, 45}

3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, **121**

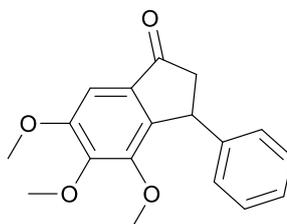
(0.98:0.02 mixture of isomers)



General procedure B was applied using (*E*)-3-(2,4-dichlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one **138** (7.71 g, 25.1 mmol) and trifluoroacetic acid (30.1 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (5:1), gave an inseparable 0.98:0.02 mixture of **121** to 3-(2,4-dichlorophenyl)-4-methoxy-2,3-dihydro-1H-inden-1-one as an off-white solid (7.41 g, 96 %); m.p. 80-83 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3060 (m, ArC-H), 2836 (m, C-H), 1707 (s, C=O), 1279 (s, C-O); δ_{H} (500 MHz,

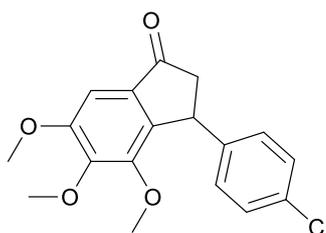
CDCl₃) 7.36 (1H, d, *J* = 2.0 Hz, ArH), 7.18-7.16 (1H, m, ArH), 7.13 (2H, s, 2 x ArH), 7.05 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 6.72 (1H, d, *J* = 7.0 Hz, ArH), 4.92 (1H, d, *J* = 8.0 Hz, C(Ar)H), 3.79 (3H, s, OCH₃), 3.24 (1H, dd, *J* = 19.0, 8.0 Hz, C(H)H), 2.48 (1H, d, *J* = 19.0 Hz, C(H)H); δ_C (126 MHz, CDCl₃) 203.9 (C=O), 159.0 (ArC), 147.7 (ArC), 139.1 (ArC), 137.5 (ArC), 133.6 (ArC), 132.2 (ArC), 128.5 (ArCH), 128.2 (ArCH), 126.6 (ArCH), 126.5 (ArCH), 123.6 (ArCH), 103.8 (ArCH), 54.7 (OCH₃), 44.9 (CH₂), 38.9 (C(Ar)H); *m/z* (ESI) 329 [M+Na]⁺; HRMS (ESI) C₁₆H₁₂³⁵Cl₂O₂Na⁺ requires 329.0107, found 329.0101 [M+Na]⁺.

4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one, **122**



General procedure B was applied using (*E*)-3-phenyl-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **139** (12.0 g, 40.2 mmol) and trifluoroacetic acid (48.3 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave **122** as a yellow oil (11.6 g, 97 %); ν_{max}/cm⁻¹ (neat) 3060 (m, ArC-H), 2853 (m, C-H), 1702 (s, C=O), 1095 (s, C-O); δ_H (500 MHz, CDCl₃) 7.30-7.25 (2H, m, 2 x ArH), 7.22-7.17 (1H, m, ArH), 7.13-7.11 (1H, m, ArH), 7.11-7.10 (1H, m, ArH), 7.09 (1H, s, ArH), 4.58 (1H, dd, *J* = 8.0, 2.5 Hz, C(Ar)H), 3.92 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.32 (3H, s, OCH₃), 3.19 (1H, dd, *J* = 19.5, 8.0 Hz, C(H)H), 2.62 (1H, dd, *J* = 19.5, 2.5 Hz, C(H)H); δ_C (126 MHz, CDCl₃) 205.4 (C=O), 154.9 (ArC), 150.4 (ArC), 148.8 (ArC), 144.7 (ArC), 144.4 (ArC), 132.2 (ArC), 128.6 (2 x ArCH), 127.3 (2 x ArCH), 126.7 (ArCH), 100.3 (ArCH), 60.9 (OCH₃), 60.0 (OCH₃), 56.2 (OCH₃), 47.2 (CH₂), 41.6 (C(Ar)H); *m/z* (ESI) 321 [M+Na]⁺; HRMS (ESI) C₁₈H₁₈O₄Na⁺ requires 321.1097, found 321.1102 [M+Na]⁺. This compound is known but was previously reported without characterisation data.^{10, 11}

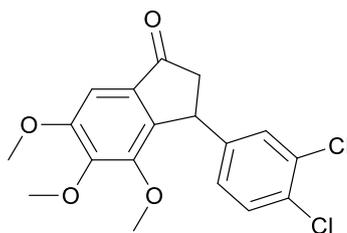
3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one, **123**



General procedure B was applied using (*E*)-3-(4-chlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **140** (12.0 g, 36.1 mmol) and trifluoroacetic acid (43.3

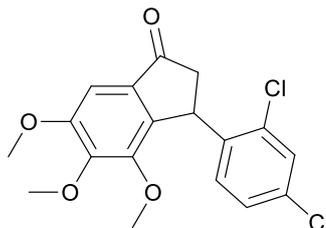
mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave **123** as an off-white solid (11.8 g, 98 %); m.p. 72-74 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3080 (m, ArC-H), 2833 (m, C-H), 1702 (s, C=O), 1091 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.28-7.25 (1H, m, ArH), 7.25-7.23 (1H, m, ArH), 7.08 (1H, s, ArH), 7.07-7.02 (2H, m, 2 x ArH), 4.55 (1H, dd, $J = 8.0, 2.5$ Hz, C(Ar)H), 3.92 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.41 (3H, s, OCH₃), 3.18 (1H, dd, $J = 19.0, 8.0$ Hz, C(H)H), 2.55 (1H, dd, $J = 19.0, 2.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 204.8 (C=O), 155.1 (ArC), 150.3 (ArC), 148.7 (ArC), 144.0 (ArC), 143.0 (ArC), 132.3 (ArC), 132.2 (ArC), 128.8 (2 x ArCH), 128.6 (2 x ArCH), 100.3 (ArCH), 60.9 (OCH₃), 60.1 (OCH₃), 56.3 (OCH₃), 47.0 (CH₂), 41.0 (C(Ar)H); m/z (ESI) 355 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵ClO₄Na⁺ requires 355.0708, found 355.0706 [M+Na]⁺. This compound is known but was previously reported without characterisation data.¹¹

3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, **124**



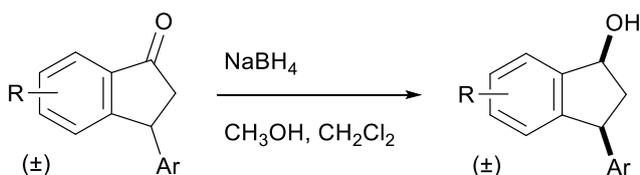
General procedure B was applied using (*E*)-3-(3,4-dichlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **141** (8.00 g, 21.8 mmol) and trifluoroacetic acid (32.7 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave **124** as an off-white solid (7.75 g, 97 %); m.p. 133-136 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2939 (m, ArC-H), 2833 (m, C-H), 1709 (s, C=O), 1121 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.35 (1H, d, $J = 8.5$ Hz, ArH), 7.21 (1H, d, $J = 2.0$ Hz, ArH), 7.09 (1H, s, ArH), 6.95 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 4.53 (1H, dd, $J = 8.0, 2.5$ Hz, C(Ar)H), 3.93 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 3.49 (3H, s, OCH₃), 3.18 (1H, dd, $J = 19.0, 8.0$ Hz, C(H)H), 2.54 (1H, dd, $J = 19.0, 2.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 203.2 (C=O), 154.3 (ArC), 149.2 (ArC), 147.6 (ArC), 143.7 (2 x ArC), 142.0 (ArC), 131.5 (ArC), 131.1 (ArC), 129.5 (ArCH), 128.2 (ArCH), 125.6 (ArCH), 99.4 (ArCH), 59.9 (OCH₃), 59.1 (OCH₃), 55.3 (OCH₃), 45.7 (CH₂), 39.7 (C(Ar)H); m/z (ESI) 389 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆³⁵Cl₂O₄Na⁺ requires 389.0318, found 389.0320 [M+Na]⁺. This compound is known but was previously reported without characterisation data.¹¹

3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, **125**



General procedure B was applied using (*E*)-3-(2,4-dichlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **142** (10.0 g, 27.2 mmol) and trifluoroacetic acid (32.7 mL). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave **125** as an off-white solid (9.65 g, 97 %); m.p. 105-108 °C; ν_{\max} /cm⁻¹ (neat) 3003 (m, ArC-H), 2836 (m, C-H), 1707 (s, C=O), 1099 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.43 (1H, s, ArH), 7.21-7.08 (2H, m, 2 x ArH), 6.67 (1H, s, ArH), 5.04 (1H, d, *J* = 8.0 Hz, ArH), 3.93 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 3.57 (3H, s, OCH₃), 3.24 (1H, dd, *J* = 19.0, 8.0 Hz, C(H)H), 2.46 (1H, d, *J* = 19.0 Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 204.3 (C=O), 155.3 (ArC), 150.1 (ArC), 148.5 (ArC), 142.4 (2 x ArC), 134.2 (ArC), 132.9 (ArC), 132.8 (ArC), 129.3 (ArCH), 128.4 (ArCH), 127.4 (ArCH), 100.4 (ArCH), 61.0 (OCH₃), 60.2 (OCH₃), 56.3 (OCH₃), 45.9 (CH₂), 37.3 (C(Ar)H); m/z (ESI) 389 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆³⁵Cl₂O₄Na⁺ requires 389.0318, found 389.0318 [M+Na]⁺. This compound is known but was previously reported without characterisation data.¹¹

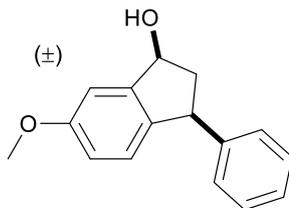
2.4.4 Diastereoselective Reduction of 3-Aryl-indan-1-ones with NaBH₄ – General Procedure C



The following procedure was performed in accordance with previous literature.²²

To the substituted indan-1-one (1.00 equiv.) in MeOH:CH₂Cl₂ (1:1, 10.0 mL/g) was added NaBH₄ (1.20 equiv.) portionwise at 0 °C under constant stirring, unless otherwise stated. The resulting reaction mixture was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The reaction mixture was then dissolved in Et₂O and washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

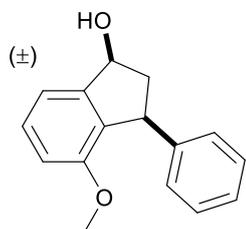
Cis-6-Methoxy-3-phenyl-2,3-dihydro-1H-inden-1-ol, 149



General procedure C was applied using 6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **118** (6.00 g, 25.2 mmol), MeOH:CH₂Cl₂ (60.0:60.0 mL) and NaBH₄ (1.14 g, 30.2 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2.5:1), gave **149** as an off-white solid (5.70 g, 94 %)*; m.p. 84-86 °C; ν_{\max} /cm⁻¹ (neat) 3249 (br, O-H), 3026 (m, ArC-H), 2831 (m, C-H), 1277 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.34-7.29 (2H, m, 2 x ArH), 7.24 (1H, d, $J = 7.5$ Hz, ArH), 7.23 (1H, d, $J = 1.5$ Hz, ArH), 7.22-7.20 (1H, m, ArH), 7.01 (1H, d, $J = 2.0$ Hz, ArH), 6.84 (1H, d, $J = 8.5$ Hz, ArH), 6.79 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 5.23 (1H, t, $J = 7.5$ Hz, CH(OH)), 4.13 (1H, t, $J = 8.5$ Hz, C(Ar)H), 3.82 (3H, s, OCH₃), 3.02 (1H, dt, $J = 13.0, 7.0$ Hz, C(H)H), 1.93 (1H, ddd, $J = 13.0, 9.0, 8.0$ Hz, C(H)H), 1.90 (1H, br. s, CH(OH)); δ_{C} (126 MHz, CDCl₃) 159.4 (ArC), 146.7 (ArC), 144.6 (ArC), 137.6 (ArC), 128.6 (2 x ArCH), 128.2 (2 x ArCH), 126.6 (ArCH), 125.9 (ArCH), 115.2 (ArCH), 108.1 (ArCH), 75.1 (CH(OH)), 55.5 (OCH₃), 47.7 (CH₂), 47.6 (C(Ar)H); m/z (ESI) 263 [M+Na]⁺; HRMS (ESI) C₁₆H₁₆O₂Na⁺ requires 263.1043, found 263.1045 [M+Na]⁺. These data are consistent with those previously reported.¹⁴

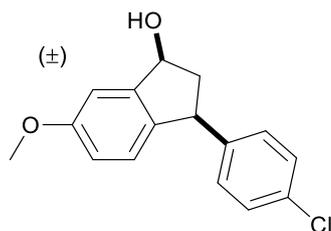
**(Also isolated was cis-4-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-ol 161 (114 mg, 2 %), resulting from the reaction of the 4-methoxy isomer of 118):*

Cis-4-Methoxy-3-phenyl-2,3-dihydro-1H-inden-1-ol, 161



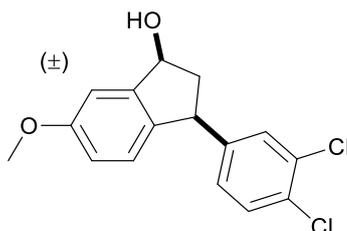
Off-white solid; m.p. 101-104 °C; ν_{\max} /cm⁻¹ (neat) 3255 (br, O-H), 3027 (m, ArC-H), 2835 (m, C-H), 1261 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.33 (1H, t, $J = 8.0$ Hz, ArH), 7.28-7.23 (2H, m, 2 x ArH), 7.20-7.15 (3H, m, 3 x ArH), 7.12 (1H, d, $J = 7.5$ Hz, ArH), 6.80 (1H, d, $J = 8.0$ Hz, ArH), 5.22 (1H, dd, $J = 7.0, 4.5$ Hz, CH(OH)), 4.39 (1H, dd, $J = 8.5, 4.5$ Hz, C(Ar)H), 3.61 (3H, s, OCH₃), 2.97 (1H, ddd, $J = 14.0, 8.5, 7.0$ Hz, C(H)H), 2.00 (1H, dt, $J = 14.0, 4.5$ Hz, C(H)H), 1.77 (1H, br. s, CH(OH)); δ_{C} (126 MHz, CDCl₃) 156.7 (ArC), 147.1 (ArC), 145.8 (ArC), 132.8 (ArC), 129.5 (ArCH), 128.2 (2 x ArCH), 127.5 (2 x ArCH), 125.9 (ArCH), 116.7 (ArCH), 110.8 (ArCH), 75.9 (CH(OH)), 55.3 (OCH₃), 46.6 (C(Ar)H), 45.9 (CH₂); m/z (ESI) 263 [M+Na]⁺; HRMS (ESI) C₁₆H₁₆O₂Na⁺ requires 263.1043, found 263.1043 [M+Na]⁺.

Cis*-3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, **150*



General procedure C was applied using 3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one **119** (6.00 g, 22.0 mmol), MeOH:CH₂Cl₂ (60.0:60.0 mL) and NaBH₄ (1.00 g, 26.4 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2.5:1), gave **150** as an off-white solid (5.52 g, 91 %); m.p. 114-115 °C; ν_{\max} /cm⁻¹ (neat) 3234 (br, O-H), 3006 (m, ArC-H), 2833 (m, C-H), 1273 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.30-7.26 (2H, m, 2 x ArH), 7.17-7.13 (2H, m, 2 x ArH), 7.00 (1H, d, J = 1.0 Hz, ArH), 6.84-6.78 (2H, m, 2 x ArH), 5.24 (1H, t, J = 7.0 Hz, CH(OH)), 4.11 (1H, t, J = 8.0 Hz, C(Ar)H), 3.82 (3H, s, OCH₃), 3.01 (1H, dt, J = 13.0, 7.0 Hz, C(H)H), 1.88 (1H, br. s, CH(OH)), 1.88 (1H, ddd, J = 13.0, 9.0, 8.0 Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 159.6 (ArC), 146.6 (ArC), 143.2 (ArC), 137.1 (ArC), 132.3 (ArC), 129.5 (2 x ArCH), 128.7 (2 x ArCH), 125.8 (ArCH), 115.3 (ArCH), 108.2 (ArCH), 75.0 (CH(OH)), 55.5 (OCH₃), 47.6 (CH₂), 47.0 (C(Ar)H); m/z (ESI) 297 [M+Na]⁺; HRMS (ESI) C₁₆H₁₅ClO₂Na⁺ requires 297.0653, found 297.0660 [M+Na]⁺. These data are consistent with those previously reported.^{14, 51}

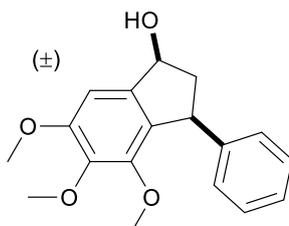
Cis*-3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, **151*



General procedure C was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one **120** (6.00 g, 19.5 mmol), MeOH:CH₂Cl₂ (60.0:60.0 mL) and NaBH₄ (0.89 g, 23.4 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2.5:1), gave **151** as an off-white solid (5.46 g, 90 %); m.p. 103-104 °C (lit.⁵² 104-106 °C); ν_{\max} /cm⁻¹ (neat) 3345 (br, O-H), 3005 (m, ArC-H), 2855 (m, C-H), 1279 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.37 (1H, d, J = 8.0 Hz, ArH), 7.32 (1H, d, J = 2.0 Hz, ArH), 7.06 (1H, dd, J = 8.5, 2.0 Hz, ArH), 7.01-7.00 (1H, m, ArH), 6.85-6.80 (2H, m, 2 x ArH), 5.24 (1H, t, J = 7.0 Hz, CH(OH)), 4.10 (1H, t, J = 8.0 Hz, C(Ar)H), 3.83 (3H, s, OCH₃), 3.01 (1H, dt, J = 13.0, 7.0 Hz, C(H)H), 2.01 (1H, br. s, CH(OH)), 1.87

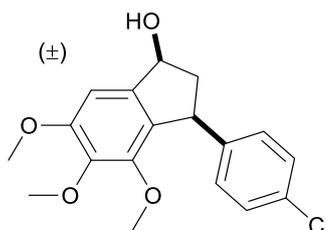
(1H, ddd, $J = 13.0, 8.5, 7.5$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 159.7 (ArC), 146.6 (ArC), 145.1 (ArC), 136.4 (ArC), 132.5 (ArC), 130.5 (ArCH), 130.5 (ArC), 130.1 (ArCH), 127.6 (ArCH), 125.7 (ArCH), 115.5 (ArCH), 108.3 (ArCH), 74.9 (CH(OH)), 55.5 (OCH₃), 47.3 (CH₂), 46.9 (C(Ar)H); m/z (ESI) 331 [M+Na]⁺; HRMS (ESI) C₁₆H₁₄Cl₂O₂Na⁺ requires 331.0263, found 331.0268 [M+Na]⁺. These data are consistent with those previously reported.^{22, 45, 51}

***Cis*-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, 153**



General procedure C was applied using 4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one **122** (4.00 g, 13.4 mmol), MeOH:CH₂Cl₂ (40.0:40.0 mL) and NaBH₄ (0.61 g, 16.1 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave **153** as an off-white solid (3.47 g, 86 %); m.p. 75-77 °C; ν_{\max} /cm⁻¹ (neat) 3271 (br, O-H), 3004 (m, ArC-H), 2832 (m, C-H), 1121 (s, C-O); δ_H (500 MHz, CDCl₃) 7.33-7.29 (2H, m, 2 x ArH), 7.27-7.24 (2H, m, 2 x ArH), 7.23-7.19 (1H, m, ArH), 6.84 (1H, s, ArH), 5.24-5.18 (1H, m, CH(OH)), 4.33 (1H, dd, $J = 8.5, 6.0$ Hz, C(Ar)H), 3.92 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.36 (3H, s, OCH₃), 3.03 (1H, ddd, $J = 14.0, 8.5, 7.5$ Hz, C(H)H), 1.98 (1H, ddd, $J = 14.0, 6.0, 5.0$ Hz, C(H)H), 1.93 (1H, d, $J = 7.0$ Hz, CH(OH)); δ_C (126 MHz, CDCl₃) 154.3 (ArC), 150.1 (ArC), 146.1 (ArC), 142.7 (ArC), 140.6 (ArC), 130.4 (ArC), 128.3 (2 x ArCH), 127.7 (2 x ArCH), 126.2 (ArCH), 102.6 (ArCH), 75.9 (CH(OH)), 60.8 (OCH₃), 59.9 (OCH₃), 56.2 (OCH₃), 46.8 (C(Ar)H), 46.5 (CH₂); m/z (ESI) 323 [M+Na]⁺; HRMS (ESI) C₁₈H₂₀O₄Na⁺ requires 323.1254, found 323.1269 [M+Na]⁺.

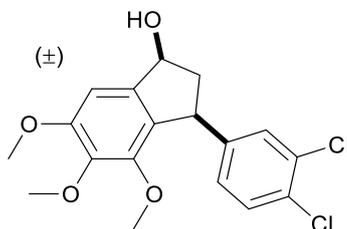
***Cis*-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, 154**



General procedure C was applied using 3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one **123** (4.00 g, 12.0 mmol), MeOH:CH₂Cl₂ (40.0:40.0 mL) and NaBH₄ (0.55 g, 14.4 mmol). Purification by flash column chromatography, eluting with

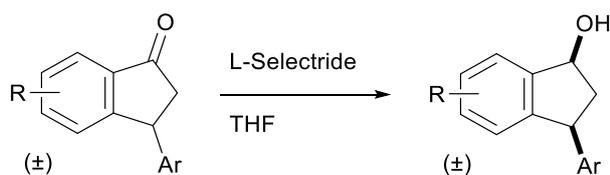
pet ether:EtOAc (2:1), gave **154** as a yellow oil (3.20 g, 80 %); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3450 (br, O-H), 2936 (m, ArC-H), 2837 (m, C-H), 1114 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.30-7.25 (2H, m, 2 x ArH), 7.22-7.18 (2H, m, 2 x ArH), 6.83 (1H, s, ArH), 5.24-5.19 (1H, m, CH(OH)), 4.30 (1H, dd, $J = 8.5, 5.5$ Hz, C(Ar)H), 3.92 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.42 (3H, s, OCH₃), 3.00 (1H, ddd, $J = 14.0, 8.5, 7.5$ Hz, C(H)H), 1.95 (1H, br. d, $J = 7.0$ Hz, CH(OH)), 1.92 (1H, dt, $J = 14.0, 5.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 154.5 (ArC), 150.0 (ArC), 144.6 (ArC), 142.7 (ArC), 140.5 (ArC), 131.8 (ArC), 130.0 (ArC), 129.1 (2 x ArCH), 128.4 (2 x ArCH), 102.6 (ArCH), 75.8 (CH(OH)), 60.8 (OCH₃), 60.0 (OCH₃), 56.2 (OCH₃), 46.3 (C(Ar)H), 46.2 (CH₂); m/z (ESI) 357 [M+Na]⁺; HRMS (ESI) $\text{C}_{18}\text{H}_{19}\text{ClO}_4\text{Na}^+$ requires 357.0864, found 357.0881 [M+Na]⁺.

***Cis*-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, 155**



General procedure C was applied using 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one **124** (4.00 g, 10.9 mmol), MeOH:CH₂Cl₂ (40.0:40.0 mL) and NaBH₄ (0.49 g, 13.1 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave **155** as an off-white solid (3.18 g, 79 %); m.p. 110-111 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3501 (br, O-H), 2961 (m, ArC-H), 2843 (m, C-H), 1337 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.38 (1H, d, $J = 2.0$ Hz, ArH), 7.36 (1H, d, $J = 8.5$ Hz, ArH), 7.28 (1H, s, ArH), 7.11 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 5.22 (1H, m, CH(OH)), 4.27 (1H, dd, $J = 8.5, 5.5$ Hz, C(Ar)H), 3.92 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.48 (3H, s, OCH₃), 2.99 (1H, ddd, $J = 14.0, 8.5, 7.5$ Hz, C(H)H), 1.98 (1H, br. d, $J = 5.5$ Hz, CH(OH)), 1.91 (1H, ddd, $J = 14.0, 5.5, 5.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 154.7 (ArC), 150.0 (ArC), 146.4 (ArC), 142.6 (ArC), 140.4 (ArC), 132.1 (ArC), 130.2 (ArCH), 129.9 (ArC), 129.8 (ArCH), 129.4 (ArC), 127.2 (ArCH), 102.6 (ArCH), 75.7 (CH(OH)), 60.8 (OCH₃), 60.1 (OCH₃), 56.2 (OCH₃), 46.1 (C(Ar)H), 45.9 (CH₂); m/z (ESI) 391 [M+Na]⁺; HRMS (ESI) $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{O}_4\text{Na}^+$ requires 391.0474, found 391.0475 [M+Na]⁺.

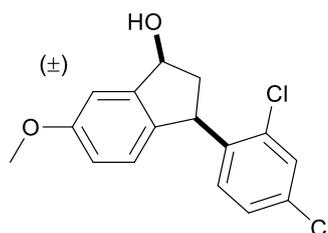
2.4.5 Diastereoselective Reduction of 3-Aryl-indan-1-ones with L-Selectride – General Procedure D



The following procedure was performed in accordance with previous literature.²⁴

To a solution of lithium tri-*sec*-butylborane (L-Selectride®) in THF (1.00 M, 1.50 equiv.) at -78 °C was added substituted indan-1-one in THF (1.00 M, 1.00 equiv.) slowly and the mixture was stirred for 5 hours. The reaction mixture was then warmed up gradually to room temperature and saturated NH₄Cl (aq.) was cautiously added, in addition to a small amount of HCl (2.00 M). After extraction with CH₂Cl₂, the combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography as specifically mentioned.

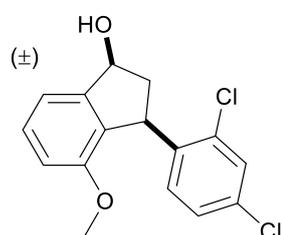
Cis*-3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, **152*



General procedure D was applied using 3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one **121** (4.00 g, 13.0 mmol) and L-Selectride (1.00 M, 19.5 mL, 19.5 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2.5:1), gave **152** as an off-white solid (3.41 g, 85 %)*; m.p. 121-122 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3315 (br, O-H), 2995 (m, ArC-H), 2833 (m, C-H), 1284 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.42 (1H, d, $J = 2.0$ Hz, ArH), 7.15 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 7.05 (1H, d, $J = 8.5$ Hz, ArH), 7.02 (1H, d, $J = 2.0$ Hz, ArH), 6.90 (1H, d, $J = 8.5$ Hz, ArH), 6.84 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 5.26 (1H, t, $J = 7.0$ Hz, CH(OH)), 4.65 (1H, t, $J = 8.0$ Hz, C(Ar)H), 3.83 (3H, s, OCH₃), 3.08 (1H, dt, $J = 13.0, 7.5$ Hz, C(H)H), 1.81 (1H, br. s, CH(OH)), 1.81 (1H, ddd, $J = 13.0, 8.0, 7.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 159.7 (ArC), 146.8 (ArC), 141.2 (ArC), 135.8 (ArC), 134.6 (ArC), 132.6 (ArC), 130.0 (ArCH), 129.1 (ArCH), 127.5 (ArCH), 125.9 (ArCH), 115.6 (ArCH), 108.5 (ArCH), 75.0 (CH(OH)), 55.5 (OCH₃), 45.6 (CH₂), 43.4 (C(Ar)H); m/z (ESI) 331 [M+Na]⁺; HRMS (ESI) C₁₆H₁₄Cl₂O₂Na⁺ requires 331.0263, found 331.0261 [M+Na]⁺.

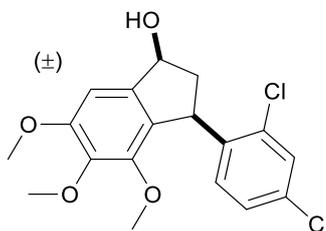
**(Also isolated was cis-3-(2,4-dichlorophenyl)-4-methoxy-2,3-dihydro-1H-inden-1-ol 162 (127 mg, 3 %), resulting from the reaction of the 4-methoxy isomer of 121):*

Cis-3-(2,4-Dichlorophenyl)-4-methoxy-2,3-dihydro-1H-inden-1-ol, 162



Off-white solid; m.p. 139-142 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3383 (br, O-H), 2964 (m, ArC-H), 2834 (m, C-H), 1265 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.39 (1H, d, $J = 2.0$ Hz, ArH), 7.36 (1H, t, $J = 8.8$ Hz, ArH), 7.12 (1H, d, $J = 7.5$ Hz, ArH), 7.05 (1H, dd, $J = 8.5$, 2.0 Hz, ArH), 6.82 (1H, d, $J = 8.0$ Hz, ArH), 6.79 (1H, d, $J = 8.5$ Hz, ArH), 5.23 (1H, dd, $J = 7.0$, 4.0 Hz, CH(OH)), 4.73 (1H, dd, $J = 9.0$, 4.0 Hz, C(Ar)H), 3.65 (3H, s, OCH₃), 3.01 (1H, ddd, $J = 14.0$, 9.0, 7.0 Hz, C(H)H), 1.88 (1H, dt, $J = 14.0$, 4.0 Hz, C(H)H), 1.72 (1H, br. s, CH(OH)); δ_{C} (126 MHz, CDCl_3) 156.4 (ArC), 147.4 (ArC), 141.8 (ArC), 133.9 (ArC), 132.0 (ArC), 131.2 (ArC), 129.9 (ArCH), 129.3 (ArCH), 128.9 (ArCH), 127.0 (ArCH), 116.8 (ArCH), 110.6 (ArCH), 75.7 (CH(OH)), 55.3 (OCH₃), 44.0 (CH₂), 42.8 (C(Ar)H); m/z (ESI) 331 [M+Na]⁺; HRMS (ESI) C₁₆H₁₄Cl₂O₂Na⁺ requires 331.0263, found 331.0261 [M+Na]⁺.

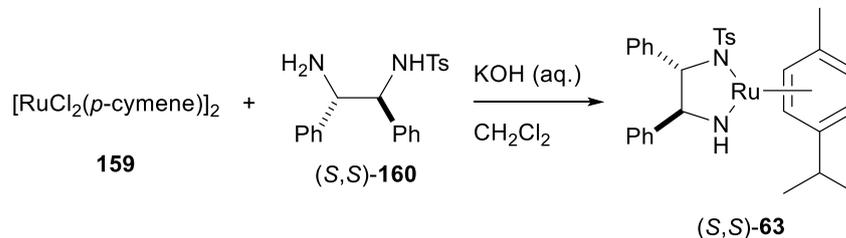
Cis-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-ol, 156



General procedure D was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (8.20 g, 10.9 mmol) and L-Selectride (1.00 M, 16.3 mL, 16.3 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2.5:1), gave **156** as a light brown oil (4.74 g, 58 %); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3440 (br, O-H), 2936 (m, ArC-H), 2837 (m, C-H), 1335 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.42 (1H, d, $J = 2.0$ Hz, ArH), 7.13 (1H, dd, $J = 8.5$, 2.0 Hz, ArH), 6.97 (1H, d, $J = 8.5$ Hz, ArH), 6.84 (1H, s, ArH), 5.24-5.19 (1H, m, CH(OH)), 4.77 (1H, dd, $J = 8.0$, 5.5 Hz, C(Ar)H), 3.93 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.57 (3H, s, OCH₃), 3.05 (1H, ddd, $J = 14.0$, 8.5, 7.0 Hz, C(H)H), 1.90-1.82 (1H, m, CH(OH)), 1.90-1.82 (1H, m, C(H)H); δ_{C} (126 MHz, CDCl_3) 154.6 (ArC), 149.8 (ArC), 142.5 (ArC), 142.0 (ArC), 140.8 (ArC), 133.8 (ArC), 132.3 (ArC), 129.7 (ArCH), 128.9 (ArCH), 128.6 (ArC), 127.2 (ArCH), 102.7 (ArCH), 75.8 (CH(OH)), 60.9 (OCH₃), 60.1 (OCH₃), 56.2 (OCH₃), 44.8 (CH₂), 42.6 (C(Ar)H);

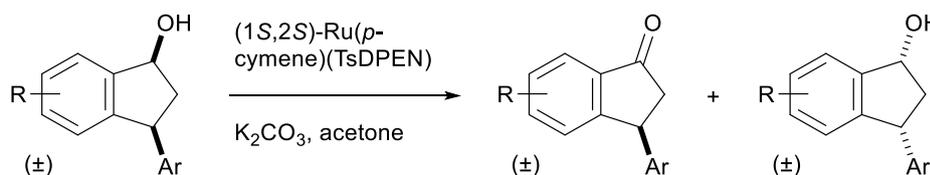
m/z (ESI) 391 [M+Na]⁺; HRMS (ESI) C₁₈H₁₈Cl₂O₄Na⁺ requires 391.0474, found 391.0475 [M+Na]⁺.

2.4.6 Preparation of Ruthenium Catalyst for Oxidative Kinetic Resolutions: (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN), (S,S)-63



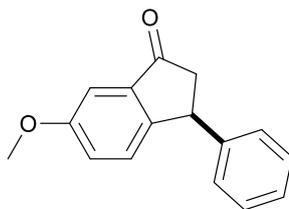
The following procedure was performed in accordance with previous literature.⁵³ To a mixture of [RuCl₂(η⁶-*p*-cymene)]₂ **159** (100 mg, 0.16 mmol), (1*S*,2*S*)-(+)-TsDPEN **160** (120 mg, 0.33 mmol) in dry CH₂Cl₂ (10.0 mL) was added KOH (130 mg, 2.32 mmol). The reaction mixture was stirred at room temperature for 25 minutes, then water (10.0 mL) was added to the reaction mixture changing the solution from orange to a deep purple. The purple organic layer was washed with 25 mL of water, dried with calcium hydride and concentrated *in vacuo*, yielding a deep purple complex (162 mg, 83 %); m.p. 79-80 °C (decomp.), (lit.⁵³ 80 °C (decomp.)); spectroscopic and observational data are consistent with those previously reported.^{14, 53}

2.4.7 Oxidative Kinetic Resolutions – General Procedure E



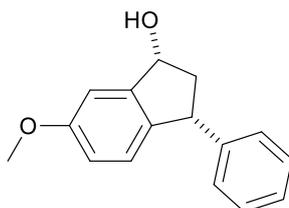
The following procedure was performed in accordance with previous literature.²⁸ To a mixture of substituted racemic *cis*-indan-1-ol (1.00 equiv.) in dry acetone (10.0 mL/mmol) was added K₂CO₃ (1.00 equiv.) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (0.50 mol%), and the resulting solution stirred at 28 °C for up to 7 hours under N₂, monitored by ¹H NMR and HPLC, unless otherwise stated. The reaction was concentrated *in vacuo* at the desired conversion (~50 %), and the products were separated by flash column chromatography as specifically mentioned.

(S)-6-Methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, (S)-118



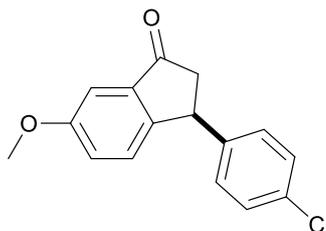
General procedure E was applied using *cis*-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol **149** (240 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**118** and (1*R*,3*R*)-**149** in a ratio of 49:51. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (103 mg, 43 %), as a % of racemic starting material, in 87 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (*c* = 0.20, CHCl₃) +64.6, $[\alpha]_D^{28}$ (lit.²⁹ (*c* = 0.6, CHCl₃) +43.3); enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 5:95, 1.00 mL/min., 223 nm, (*S*)-isomer 9.53 min., (*R*)-isomer 10.59 min.).

(1*R*,3*R*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-149



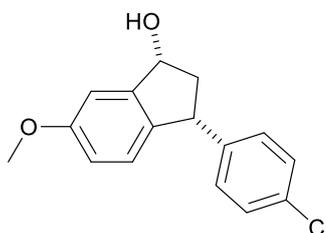
General procedure E was applied using *cis*-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol **149** (240 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**118** and (1*R*,3*R*)-**149** in a ratio of 49:51. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (108 mg, 45 %), as a % of racemic starting material, in 89 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (*c* = 0.20, CHCl₃) -17.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 6:94, 1.00 mL/min., 220 nm, (*S,S*)-isomer 13.97 min., (*R,R*)-isomer 22.20 min.).

(S)-3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, (S)-119



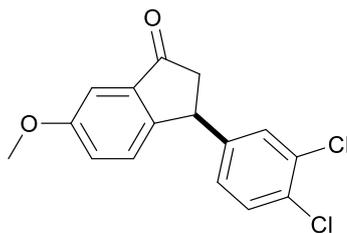
General procedure E was applied using *cis*-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol **150** (275 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**119** and (1*R*,3*R*)-**150** in a ratio of 47:53. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as a white solid (113 mg, 41 %), as a % of racemic starting material, in 95 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (*c* = 0.20, CHCl₃) +65.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 224 nm, (*S*)-isomer 13.65 min., (*R*)-isomer 15.12 min.).

(1R,3R)-3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol, (1R,3R)-150



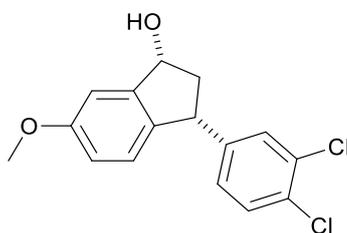
General procedure E was applied using *cis*-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol **150** (275 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**119** and (1*R*,3*R*)-**150** in a ratio of 47:53. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (129 mg, 47 %), as a % of racemic starting material, in 94 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (*c* = 0.20, CHCl₃) -15.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 210 nm, (*S,S*)-isomer 28.44 min., (*R,R*)-isomer 34.54 min.).

(S)-3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, (S)-120



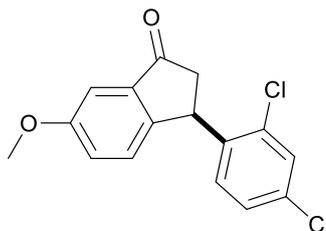
General procedure E was applied using *cis*-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **151** (309 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**120** and (1*R*,3*R*)-**151** in a ratio of 49:51. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as a yellow oil (131 mg, 42 %), as a % of racemic starting material, in 96 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.20, CHCl₃) +60.9, $[\alpha]_D^{28}$ (lit.²⁹ (c = 1.23, CHCl₃) +44.1); enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 234 nm, (*S*)-isomer 16.59 min., (*R*)-isomer 17.87 min.).

(1R,3R)-3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol, (1R,3R)-151



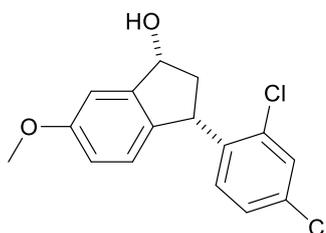
General procedure E was applied using *cis*-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **151** (309 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**120** and (1*R*,3*R*)-**151** in a ratio of 49:51. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (134 mg, 43 %), as a % of racemic starting material, in 90 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.20, CHCl₃) -10.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 6:94, 1.00 mL/min., 218 nm, (*S,S*)-isomer 14.33 min., (*R,R*)-isomer 25.50 min.).

(R)-3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, (R)-121



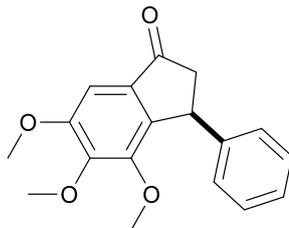
General procedure E was applied using *cis*-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **152** (309 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (6 mg, 10.0 μmol, 1.00 mol%) to give compounds (*R*)-**121** and (1*R*,3*S*)-**152** in a ratio of 51:49. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (142 mg, 46 %), as a % of racemic starting material, in 91 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ (c = 0.20, CHCl₃) +39.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 223 nm, (*R*)-isomer 10.15 min., (*S*)-isomer 11.11 min.).

(1R,3S)-3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol, (1R,3S)-152



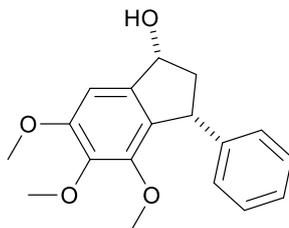
General procedure E was applied using *cis*-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **152** (309 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (6 mg, 10.0 μmol, 1.00 mol%) to give compounds (*R*)-**121** and (1*R*,3*S*)-**152** in a ratio of 51:49. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (135 mg, 44 %), as a % of racemic starting material, in 93 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +35.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 212 nm, (*S,R*)-isomer 25.21 min., (*R,S*)-isomer 32.01 min.).

(S)-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, (S)-122



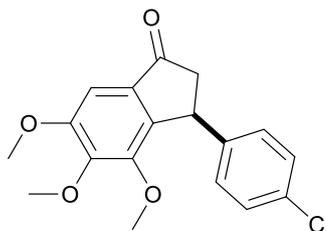
General procedure E was applied using *cis*-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol **153** (300 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**122** and (1*R*,3*R*)-**153** in a ratio of 48:52. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as a yellow oil (141 mg, 47 %), as a % of racemic starting material, in 89 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{26}$ (*c* = 0.33, CHCl₃) +76.2; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 5:95, 1.00 mL/min., 272 nm, (*S*)-isomer 9.01 min., (*R*)-isomer 10.59 min.).

(1R,3R)-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-ol, (1R,3R)-153



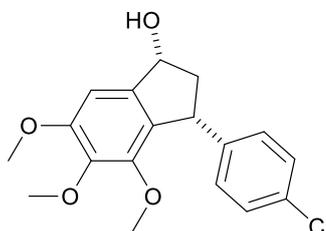
General procedure E was applied using *cis*-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol **153** (300 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**122** and (1*R*,3*R*)-**153** in a ratio of 48:52. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (152 mg, 51 %), as a % of racemic starting material, in 89 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (*c* = 0.20, CHCl₃) -39.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 220 nm, (*S,S*)-isomer 14.17 min., (*R,R*)-isomer 17.08 min.).

(S)-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, (S)-123



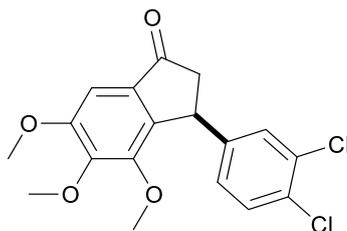
General procedure E was applied using *cis*-3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **154** (335 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**123** and (1*R*,3*R*)-**154** in a ratio of 48:52. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (146 mg, 44 %), as a % of racemic starting material, in 93 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (*c* = 0.26, CHCl₃) –50.9; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 3:97, 1.00 mL/min., 225 nm, (*R*)-isomer 13.23 min., (*S*)-isomer 15.40 min.).

(1*R*,3*R*)-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-154



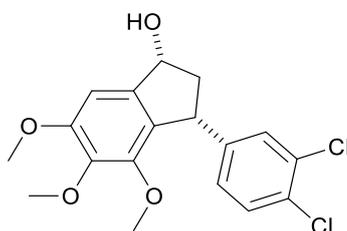
General procedure E was applied using *cis*-3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **154** (335 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (3 mg, 5.00 μmol) to give compounds (*S*)-**123** and (1*R*,3*R*)-**154** in a ratio of 48:52. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as a yellow oil (159 mg, 47 %), as a % of racemic starting material, in 89 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (*c* = 0.20, CHCl₃) –39.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 3:97, 1.00 mL/min., 223 nm, (*R,R*)-isomer 31.16 min., (*S,S*)-isomer 39.86 min.).

(S)-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, (S)-124



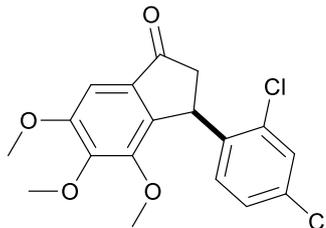
General procedure E was applied using *cis*-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **155** (369 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (6 mg, 10.0 μmol, 1.00 mol%) to give compounds (*S*)-**124** and (1*R*,3*R*)-**155** in a ratio of 51:49. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (161 mg, 44 %), as a % of racemic starting material, in 85 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ (c = 0.20, CHCl₃) -48.6; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 3:97, 1.00 mL/min., 225 nm, (*R*)-isomer 13.17 min., (*S*)-isomer 14.77 min.).

(1*R*,3*R*)-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, (1*R*,3*R*)-155



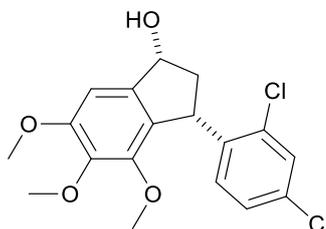
General procedure E was applied using *cis*-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **155** (369 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (6 mg, 10.0 μmol, 1.00 mol%) to give compounds (*S*)-**124** and (1*R*,3*R*)-**155** in a ratio of 51:49. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (157 mg, 42 %), as a % of racemic starting material, in 90 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -19.6; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 3:97, 1.00 mL/min., 219 nm, (*R,R*)-isomer 32.21 min., (*S,S*)-isomer 37.12 min.).

(R)-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, (R)-125



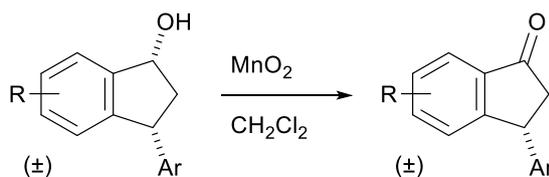
General procedure E was applied using *cis*-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **156** (369 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (12 mg, 20.0 μmol, 2.00 mol%) to give compounds (*R*)-**125** and (1*R*,3*S*)-**156** in a ratio of 48:52. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as an off-white solid (170 mg, 46 %), as a % of racemic starting material, in 85 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ (c = 0.20, CHCl₃) -49.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 224 nm, (*R*)-isomer 11.35 min., (*S*)-isomer 12.53 min.).

(1R,3S)-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-ol, (1R,3S)-156



General procedure E was applied using *cis*-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **156** (369 mg, 1.00 mmol), K₂CO₃ (138 mg, 1.00 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (12 mg, 20.0 μmol, 2.00 mol%) to give compounds (*R*)-**125** and (1*R*,3*S*)-**156** in a ratio of 48:52. The title compound was isolated by flash column chromatography, eluting with pet ether:EtOAc (2:1), as a light brown oil (184 mg, 50 %), as a % of racemic starting material, in 90 % e.e.; spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.20, CHCl₃) +41.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 224 nm, (*S,R*)-isomer 32.72 min., (*R,S*)-isomer 41.68 min.).

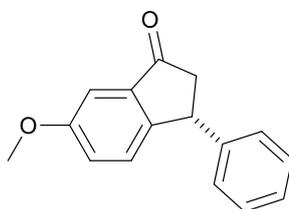
2.4.8 MnO₂ Oxidation of Enantiopure Indan-1-ols – General Procedure F



The following procedure was performed in accordance with previous literature.³⁸

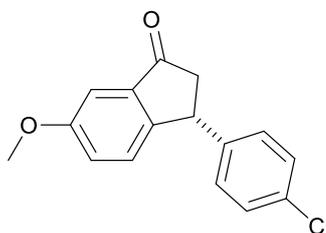
To a solution of enantiomerically enriched indan-1-ol (1.00 equiv.) in CH₂Cl₂ was added manganese (IV) oxide (1.50 equiv.) at room temperature. The mixture was stirred for 18 hours, filtered through Celite[®] and concentrated *in vacuo*. The product was then used without further purification, unless specifically mentioned.

(*R*)-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*R*)-118



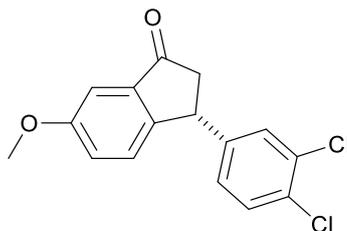
General procedure F was applied using (1*R*,3*R*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol **149** (108 mg, 0.50 mmol) and manganese (IV) oxide (586 mg, 6.74 mmol), yielding (*R*)-**118** as an off-white solid (92 mg, 85 %, 75 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (*c* = 0.20, CHCl₃) –66.6; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 5:95, 1.00 mL/min., 223 nm, (*S*)-isomer 9.76 min., (*R*)-isomer 10.68 min.).

(*R*)-3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one, (*R*)-119



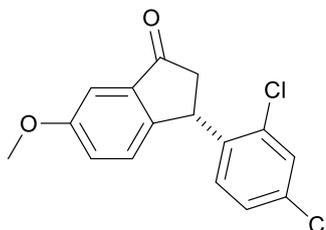
General procedure F was applied using (1*R*,3*R*)-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **150** (129 mg, 0.47 mmol) and manganese (IV) oxide (612 mg, 7.04 mmol), yielding (*R*)-**119** as a white solid (106 mg, 83 %, 91 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (*c* = 0.20, CHCl₃) –68.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 224 nm, (*S*)-isomer 14.20 min., (*R*)-isomer 15.33 min.).

(R)-3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, (R)-120



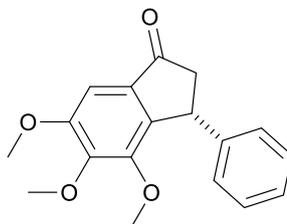
General procedure F was applied using (1*R*,3*R*)-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **151** (140 mg, 0.45 mmol) and manganese (IV) oxide (590 mg, 6.79 mmol), yielding (*R*)-**120** as a yellow oil (112 mg, 80 %, 86 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ ($c = 0.20$, CHCl_3) -67.4 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 237 nm, (*S*)-isomer 16.92 min., (*R*)-isomer 17.92 min.).

(S)-3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, (S)-121



General procedure F was applied using (1*R*,3*S*)-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol **152** (130 mg, 0.42 mmol) and manganese (IV) oxide (548 mg, 6.31 mmol), yielding (*S*)-**121** as an off-white solid (112 mg, 86 %, 85 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.20$, CHCl_3) -48.4 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 223 nm, (*R*)-isomer 10.56 min., (*S*)-isomer 10.53 min.).

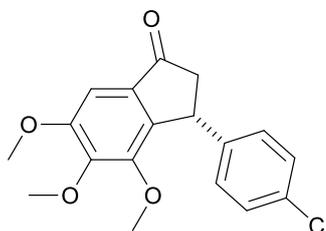
(R)-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, (R)-122



General procedure F was applied using (1*R*,3*R*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol **153** (152 mg, 0.51 mmol) and manganese (IV) oxide (660 mg, 7.59 mmol), yielding (*R*)-**122** as a yellow oil (124 mg, 82 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.24$, CHCl_3) -76.5 ; enantiomeric

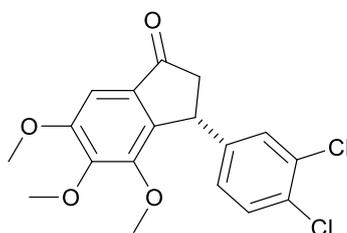
excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 5:95, 1.00 mL/min., 272 nm, (*S*)-isomer 9.21 min., (*R*)-isomer 10.48 min.).

(*R*)-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one, (*R*)-123



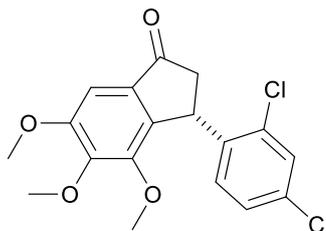
General procedure F was applied using (1*R*,3*R*)-3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **154** (159 mg, 0.48 mmol) and manganese (IV) oxide (619 mg, 7.12 mmol), yielding (*R*)-**123** as an off-white solid (128 mg, 81 %, 91 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.26$, CHCl_3) -50.9 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 3:97, 1.00 mL/min., 225 nm, (*R*)-isomer 12.35 min., (*S*)-isomer 14.56 min.).

(*R*)-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one, (*R*)-124



General procedure F was applied using (1*R*,3*R*)-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **155** (156 mg, 0.42 mmol) and manganese (IV) oxide (551 mg, 6.34 mmol), yielding (*R*)-**124** as an off-white solid (158 mg, >99 %, 90 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ ($c = 0.20$, CHCl_3) -48.6 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 3:97, 1.00 mL/min., 223 nm, (*R*)-isomer 13.05 min., (*S*)-isomer 14.87 min.).

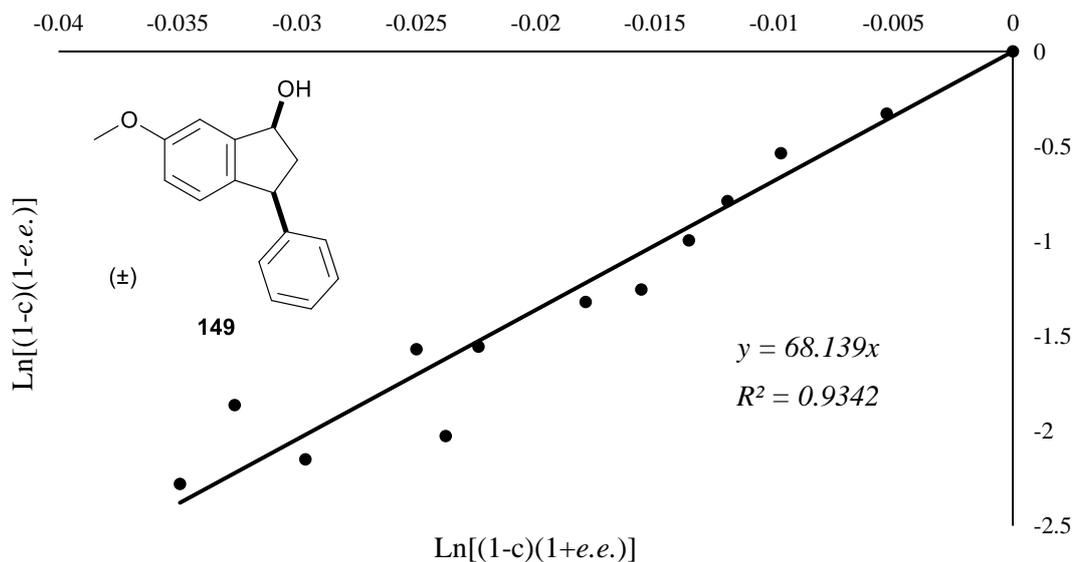
(S)-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, (S)-125



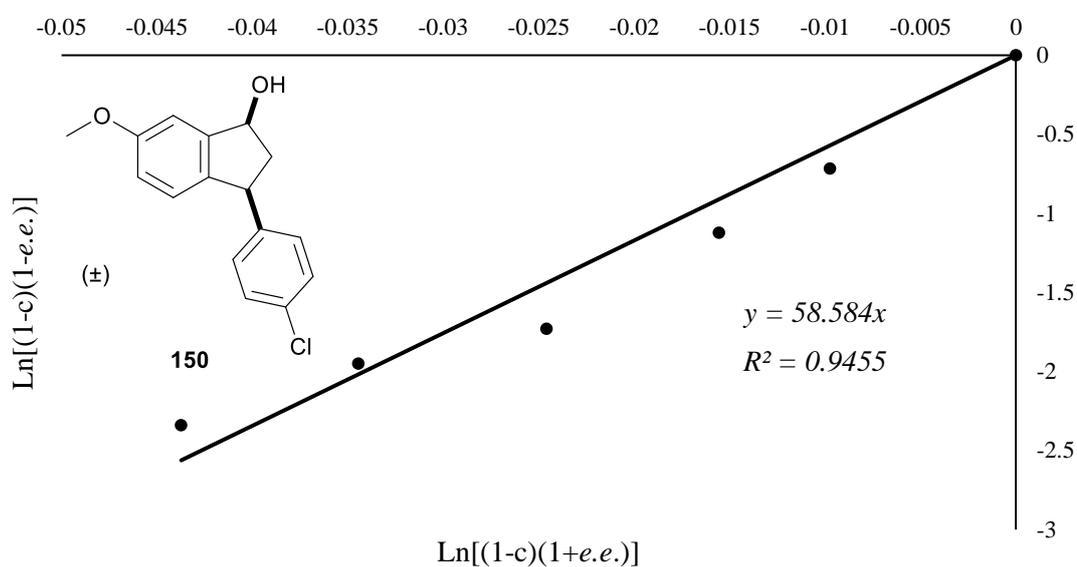
General procedure F was applied using (1*R*,3*S*)-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol **156** (184 mg, 0.50 mmol) and manganese (IV) oxide (650 mg, 7.47 mmol), yielding (*S*)-**125** as an off-white solid (138 mg, 75 %, 88 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.20$, CHCl_3) +33.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 3:97, 1.00 mL/min., 224 nm, (*R*)-isomer 10.73 min., (*S*)-isomer 11.72 min.).

2.4.9 Plots for Selectivity Factor Determination

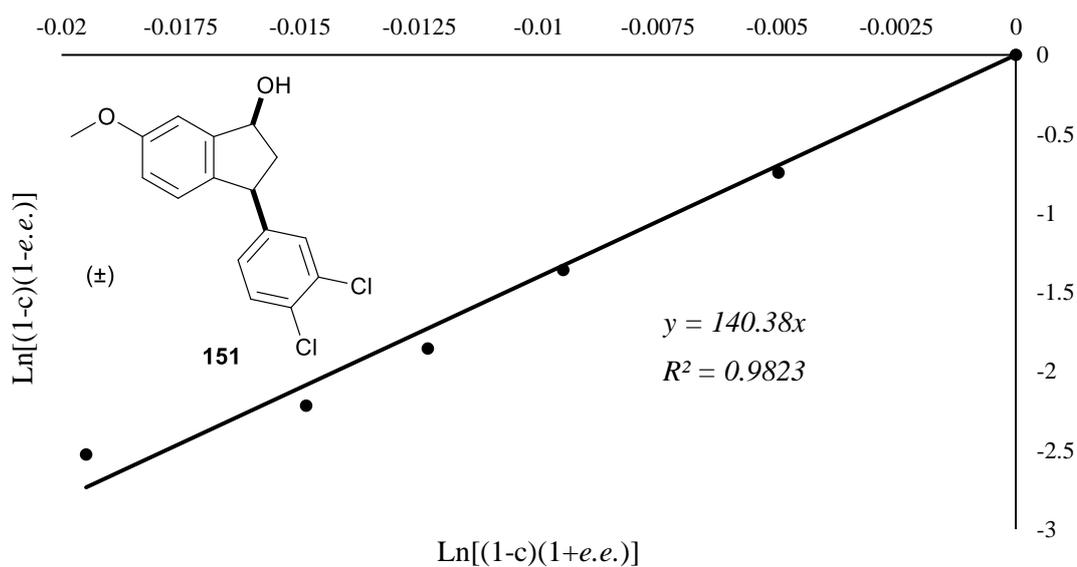
Oxidative Kinetic Resolution of *cis*-6-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, *cis*-149:



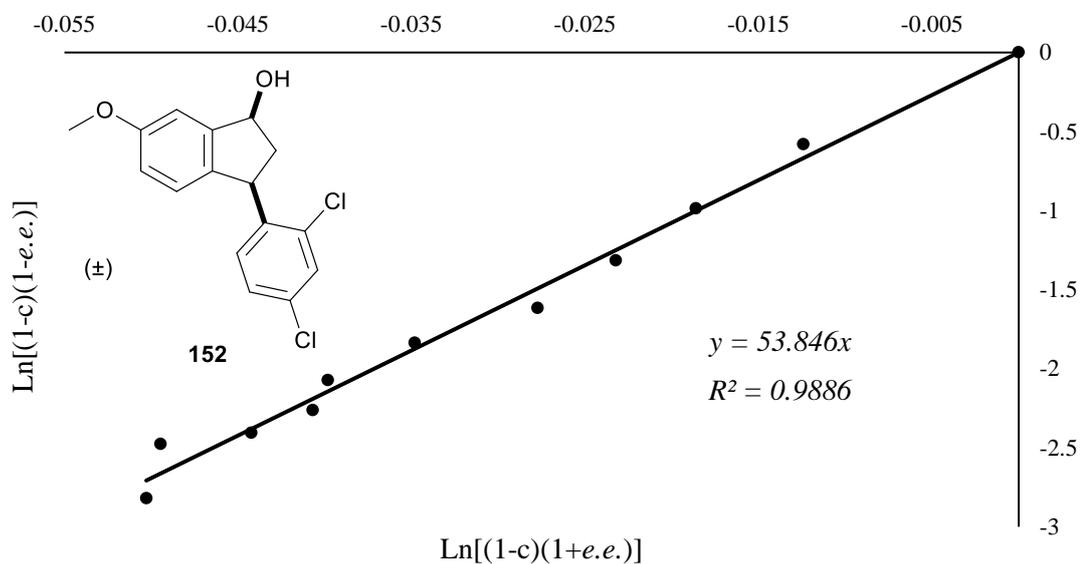
Oxidative Kinetic Resolution of *cis*-3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, *cis*-150:



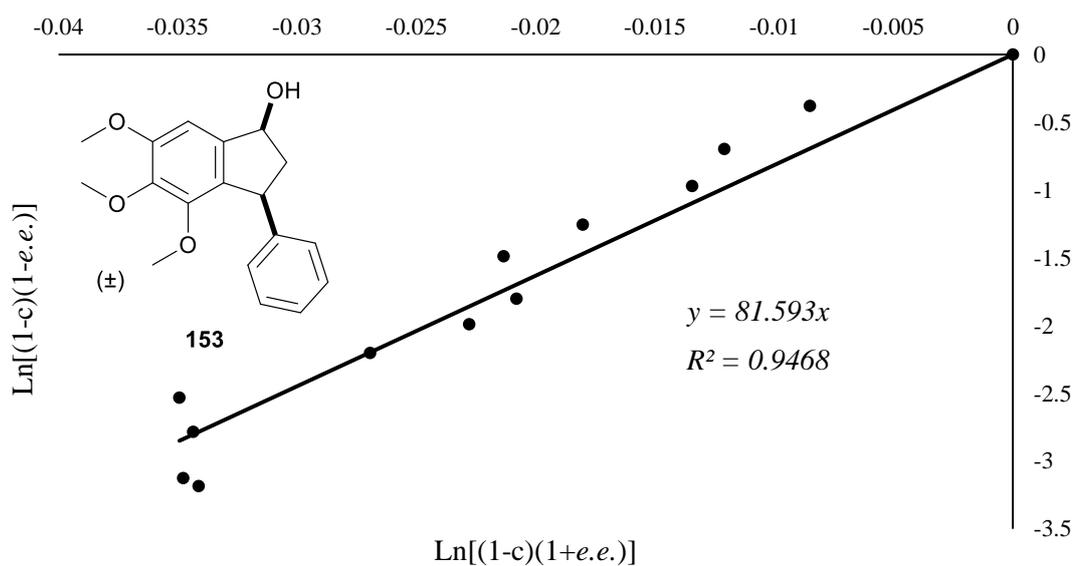
Oxidative Kinetic Resolution of *cis*-3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, *cis*-151:



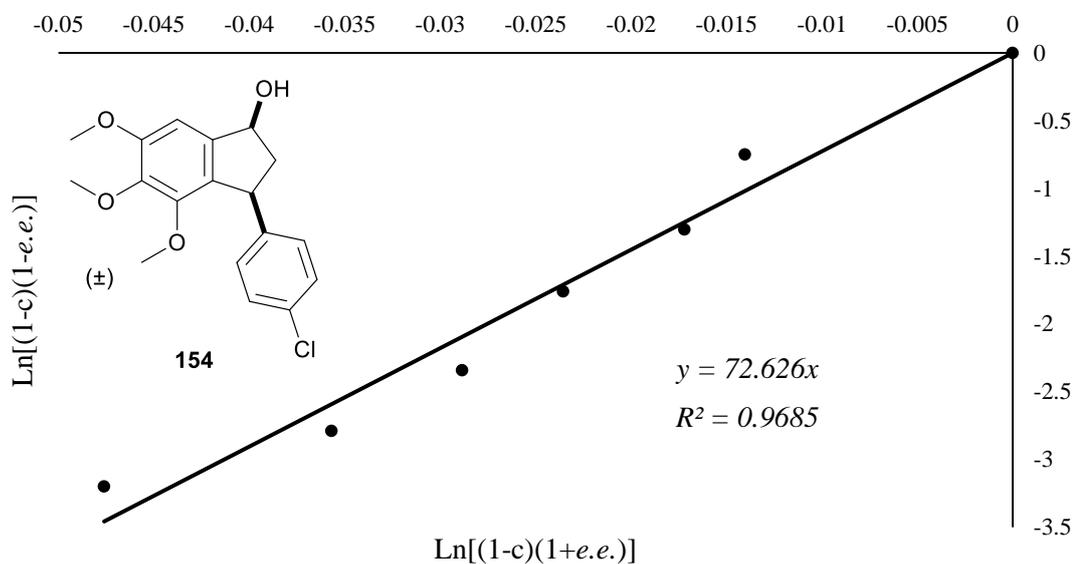
Oxidative Kinetic Resolution of *cis*-3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol, *cis*-152:



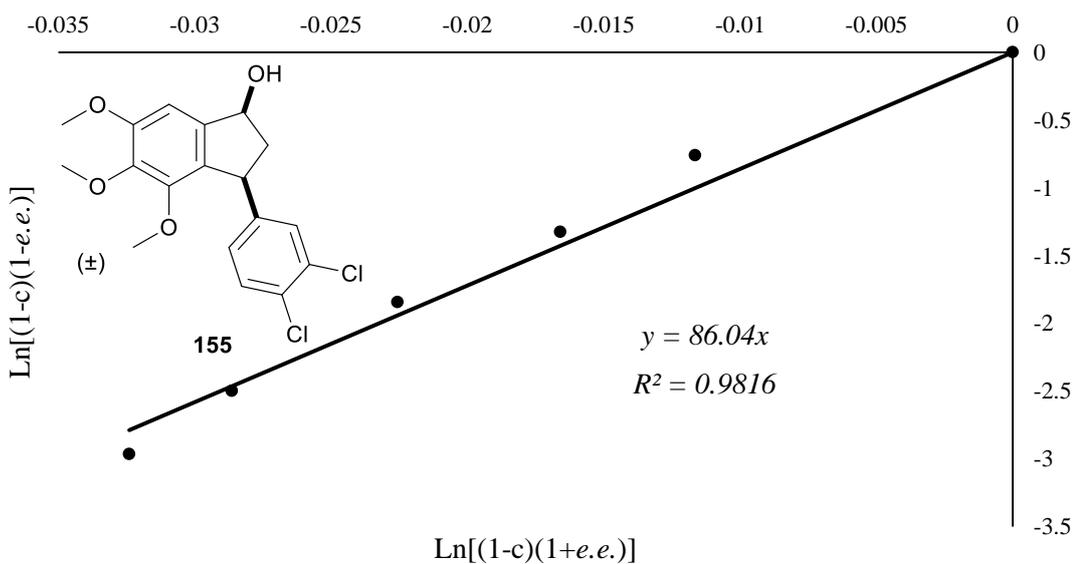
Oxidative Kinetic Resolution of *cis*-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, *cis*-153:



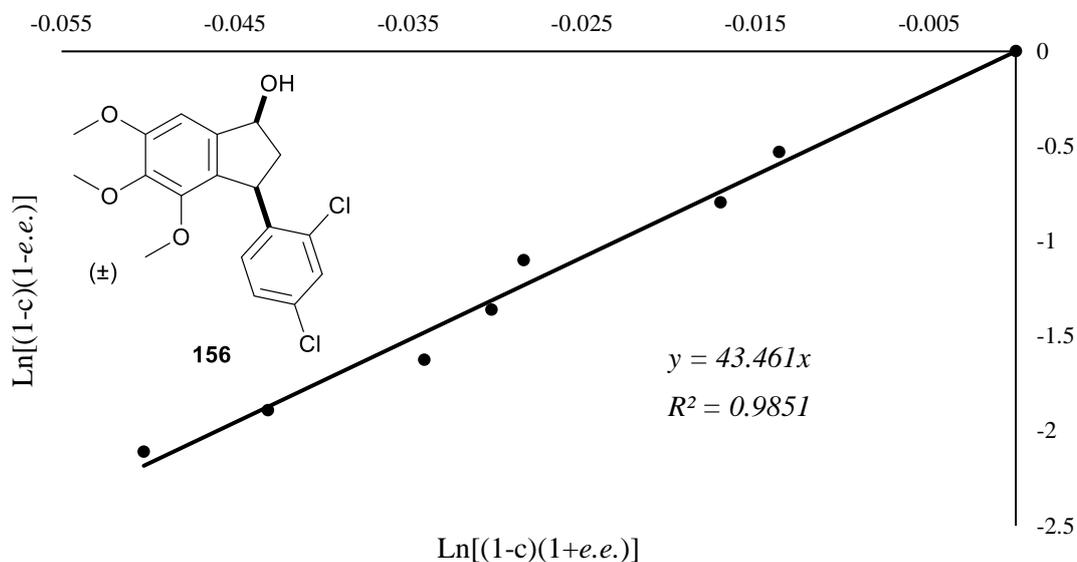
Oxidative Kinetic Resolution of *cis*-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, *cis*-154:



Oxidative Kinetic Resolution of *cis*-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, *cis*-155:



Oxidative Kinetic Resolution of *cis*-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol, *cis*-156:



2.5 References

1. D. J. Kerr, E. Hamel, M. K. Jung and B. L. Flynn, *Biorg. Med. Chem.*, 2007, **15**, 3290-3298.
2. C. Hedberg and P. G. Andersson, *Adv. Synth. Catal.*, 2005, **347**, 662-666.
3. G. Dannhardt, W. Kiefer, G. Krämer, S. Maehrlein, U. Nowe and B. Fiebich, *Eur. J. Med. Chem.*, 2000, **35**, 499-510.
4. B. P. Chetana, S. K. Mahajan and A. K. Suvarna, *J. Pharm. Sci. Res.*, 2009, **1**, 11-22.
5. L. Claisen and A. Claparède, *Ber. Dtsch. Chem. Ges.*, 1881, **14**, 2460-2468.
6. J. G. Schmidt, *Ber. Dtsch. Chem. Ges.*, 1881, **14**, 1459-1461.
7. A. T. Nielsen and W. J. Houlihan, in *Organic Reactions*, John Wiley & Sons, Inc., 2004.
8. H. Mirzaei and S. Emami, *Eur. J. Med. Chem.*, 2016, **121**, 610-639.
9. S. Padhye, A. Ahmad, N. Oswal and F. H. Sarkar, *J. Hematol. Oncol.*, 2009, **2**, 38-38.
10. H. O. Saxena, U. Faridi, S. Srivastava, J. K. Kumar, M. P. Darokar, S. Luqman, C. S. Chanotiya, V. Krishna, A. S. Negi and S. P. S. Khanuja, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3914-3918.
11. N. J. Lawrence, E. S. M. Armitage, B. Greedy, D. Cook, S. Ducki and A. T. McGown, *Tetrahedron Lett.*, 2006, **47**, 1637-1640.

12. J. Zhu, C. Zhong, H.-F. Lu, G.-Y. Li and X. Sun, *Synlett*, 2008, **2008**, 458-462.
13. M. K. Seery, S. M. Draper, J. M. Kelly, T. McCabe and T. B. H. McMurry, *Synthesis*, 2005, **2005**, 470-474.
14. P. Kerby, PhD thesis, University of Warwick, 2016.
15. W. L. F. Armarego and C. L. L. Chai, in *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann, Oxford, 2009, pp. 1-60.
16. F. Gavina, A. M. Costero and A. M. Gonzalez, *J. Org. Chem.*, 1990, **55**, 2060-2063.
17. W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1980, pp. 1555-1566.
18. W. He, X. Sun and A. J. Frontier, *J. Am. Chem. Soc.*, 2003, **125**, 14278-14279.
19. G. S. D. Sharma and S. V. Eswaran, *Resonance*, 1997, **2**, 73-75.
20. C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165-195.
21. L. P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 96-103.
22. X.-H. Gu, H. Yu, A. E. Jacobson, R. B. Rothman, C. M. Dersch, C. George, J. L. Flippen-Anderson and K. C. Rice, *J. Med. Chem.*, 2000, **43**, 4868-4876.
23. M. López-García, I. Alfonso and V. Gotor, *Chem. Eur. J.*, 2004, **10**, 3006-3014.
24. B. Yin, D.-N. Ye, K.-H. Yu and L.-X. Liu, *Molecules*, 2010, **15**.
25. H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, 1972, **94**, 7159-7161.
26. Z. Yuecheng, Z. Shanshan, M. Guorui, Z. Jiquan, *Prog. Chem.*, 2012, **24**, 212-224.
27. H. Pellissier, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, ch. 3, pp. 75-122.
28. S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 288-290.
29. P. Muller, *Pure Appl. Chem.*, 1994, **66**, 1077-1184.
30. S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562-7563.
31. N. Asakura, T. Hirokane, H. Hoshida and H. Yamada, *Tetrahedron Lett.*, 2011, **52**, 534-537.
32. A. Minatti, X. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 9253-9258.
33. M. D. Greenhalgh, J. E. Taylor and A. D. Smith, *Tetrahedron*, 2018, **74**, 5554-5560.
34. M. R. Maddani, J.-C. Fiaud and H. B. Kagan, in *Separation of Enantiomers*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014, ch. 2, pp. 13-74.

35. D. W. Johnson and D. A. Singleton, *J. Am. Chem. Soc.*, 1999, **121**, 9307-9312.
36. J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5-26.
37. R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, 1959, **24**, 1051-1056.
38. C. Pinedo-Rivilla, J. Aleu and I. G. Collado, *Tetrahedron: Asymmetry*, 2011, **22**, 1653-1657.
39. M. Fernández and G. Tojo, *Oxidation of Alcohols to Aldehydes and Ketones*, Springer Science+ Business Media, Incorporated, 2006.
40. G. P. Moss, *Pure Appl. Chem.*, 1998, **70**, 143-216.
41. R. S. Cahn, C. Ingold and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, **5**, 385-415.
42. S. Tripathi, R. Kapoor and L. D. S. Yadav, *Adv. Synth. Catal.*, 2018, **360**, 1407-1413.
43. P. Hermange, T. M. Gøgsig, A. T. Lindhardt, R. H. Taaning and T. Skrydstrup, *Org. Lett.*, 2011, **13**, 2444-2447.
44. U. Shadakshari and S. K. Nayak, *Tetrahedron*, 2001, **57**, 8185-8188.
45. H. Yu, I. J. Kim, J. E. Folk, X. Tian, R. B. Rothman, M. H. Baumann, C. M. Dersch, J. L. Flippen-Anderson, D. Parrish, A. E. Jacobson and K. C. Rice, *J. Med. Chem.*, 2004, **47**, 2624-2634.
46. R. Kumar, P. Sharma, A. Shard, D. K. Tewary, G. Nadda and A. K. Sinha, *Med. Chem. Res.*, 2012, **21**, 922-931.
47. Z. Li, G. Wen, L. He, J. Li, X. Jia and J. Yang, *RSC Adv.*, 2015, **5**, 52121-52125.
48. M. L. Edwards, D. M. Stemerick and P. S. Sunkara, *J. Med. Chem.*, 1990, **33**, 1948-1954.
49. S. Ducki, D. Rennison, M. Woo, A. Kendall, J. F. D. Chabert, A. T. McGown and N. J. Lawrence, *Biorg. Med. Chem.*, 2009, **17**, 7698-7710.
50. L. B. Salum, W. F. Altei, L. D. Chiaradia, M. N. S. Cordeiro, R. R. Canevarolo, C. P. S. Melo, E. Winter, B. Mattei, H. N. Daghestani, M. C. Santos-Silva, T. B. Creczynski-Pasa, R. A. Yunes, J. A. Yunes, A. D. Andricopulo, B. W. Day, R. J. Nunes and A. Vogt, *Eur. J. Med. Chem.*, 2013, **63**, 501-510.
51. J. G. A. Walton, D. C. Jones, P. Kiuru, A. J. Durie, N. J. Westwood and A. H. Fairlamb, *ChemMedChem*, 2011, **6**, 321-328.
52. K. P. Bogeso, A. V. Christensen, J. Hyttel and T. Liljefors, *J. Med. Chem.*, 1985, **28**, 1817-1828.
53. K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 285-288.

3.0 A Building Block to Medicinal Scaffolds

3.1 Medicinal Scaffolds; Structures and Their Biological Importance

3.1.1 Dihydroquinolinones and Dihydroisoquinolinones

Dihydroquinolinone (**163**) and its isomer dihydroisoquinolinone (**164**) are 2-ring condensed heterocyclic compounds composed of a benzene ring and a six-membered lactam (Figure 21).

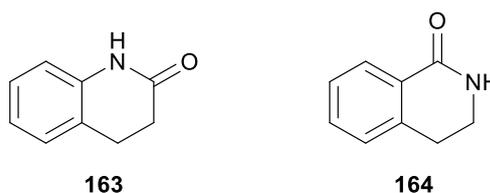


Figure 21 Structures of dihydroquinolinone (**163**) and dihydroisoquinolinone (**164**).

Both compounds are often used as a structural component of drugs, whereby the benzene ring adds rigidity and can interact with the aromatic rings of peptides or nucleic acids through π - π stacking to form noncovalent interactions.¹ Their various physicochemical properties (e.g. cLogP, TPSA and aqueous solubility), which are important when it comes to drug design, can be tuned by introducing a range of functional groups in different positions of the fused lactam. Furthermore, it is known that these species are relatively tolerant of metabolic hydrolysis in living organisms, possibly because of the inability of larger molecules, including proteins such as proteases, to attack the carbonyl group due to steric hindrance caused by the fixed *cis*-form coupled with the presence of the neighbouring methylene group(s) – a nucleophile must attack at the carbonyl carbon atom at a 107 degree angle to the C=O bond.²

Dihydroquinolinone is a skeleton found in many natural products, such as yaequinolone J1 (**165**),³ pinolinone (**166**),⁴ and veprisine (**167**),⁵ as well as a number of biologically active synthetic structures (Figure 22); these and related species have been shown to be effective NMDA antagonists (e.g. **168**),⁶ 5-HT₃ receptor antagonists (e.g. **169**),⁷ and HIV-1 reverse transcriptase inhibitors (e.g. **170**).⁸ Further demonstrating their medicinal importance, structures comprising this structural motif have been the subject of many patents, for example those specifying the utilisation of these compounds in the treatment of cancer,⁹ as antiviral agents against herpes (HSV-1),¹⁰ and in the treatment of the spinal muscular atrophy (SMA) neurodegenerative disease.¹¹

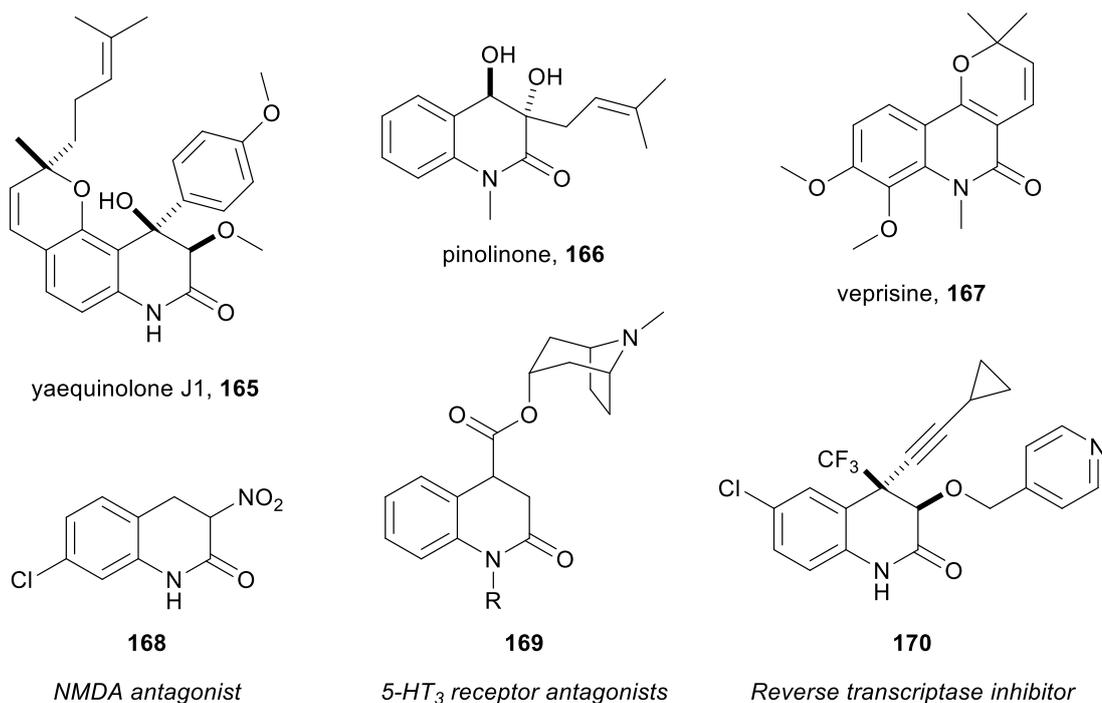


Figure 22 Naturally occurring and synthetic biologically active dihydroquinolinones.

Further activity against neurodegenerative diseases has been recently demonstrated in the case of dihydroquinolinone **171** (Figure 23), where it exhibited highly selective inhibitory activity against both human monoamine oxidase (MAO) isozymes A and B *in vitro* – an IC₅₀ value of 2.9 nM was observed against the latter.¹² MAO-B oxidises dopamine in the central nervous system, hence MAO-B inhibitors can be used for the treatment of Parkinson's disease.

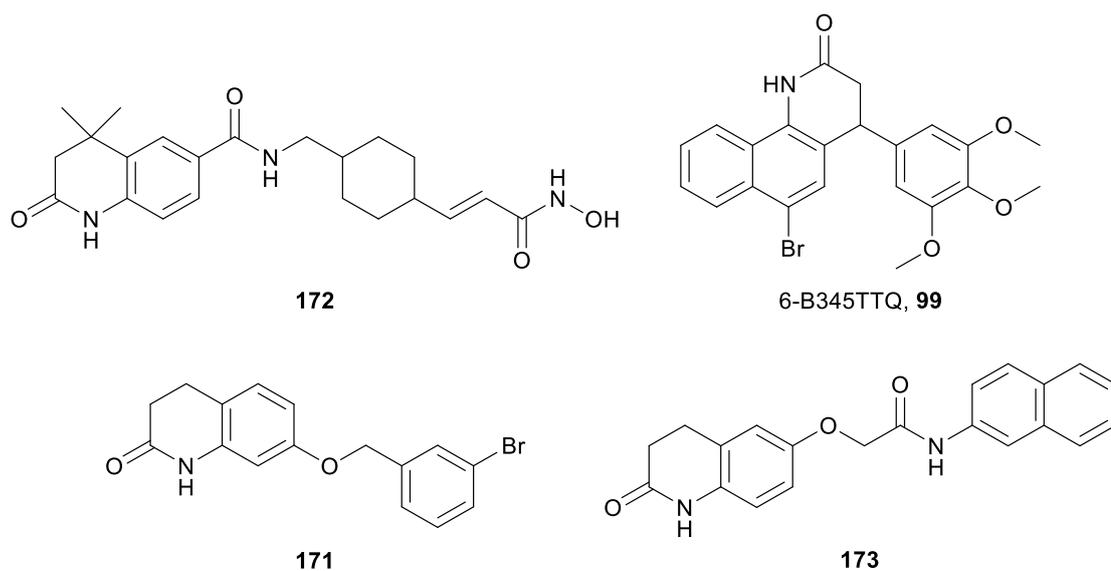


Figure 23 Dihydroquinolinones as medicinal scaffolds.

Synthetic dihydroquinolinones have also been shown to possess anti-cancer activity. Compound **172** displayed histone deacetylase (HDAC) inhibitory behaviour; HDAC catalyses the deacetylation of lysine residues on histone and non-histone proteins to epigenetically control transcriptional regulations, thereby playing an important role in proliferation, differentiation, cell cycle arrest, and/or apoptosis of tumour cells. **172** displayed more than 10 times stronger inhibitory activity against each human HDAC isozyme *in vitro* than that of suberoylanilide hydroxamic acid (SAHA) – approved for the treatment of cutaneous T-cell lymphoma (CTCL) by the US Food and Drug Administration (FDA) – with IC₅₀ values measured at 3.8–58.0 nM.¹³ A rare type of head and neck cancer, nasopharyngeal carcinoma (NPC), is thought to be caused by the Epstein–Barr virus (EBV) and a targeted therapy against this type of cancer is greatly desired. To this end, compound **173** showed anti-proliferative activity against NPC TW01 cells *in vitro* (IC₅₀ value = 0.6 μM).¹⁴

Another synthetic dihydroquinolinone possessing notable biological activity is the aforementioned anti-inflammatory compound 6-B345TTQ (**99** – see **Section 1.4**). Compound **99** was reported and patented as a mitigator of a wide range of chronic inflammatory diseases, demonstrating high activity and selectivity without any cytotoxicity, and thus presenting a novel anti-inflammatory strategy.^{15, 16} The authors screened a total of ~40,000 compounds with respect to inhibition of the α4-integrin–paxillin interaction; inhibition of α4-integrins have previously been shown to be effective towards alleviating a wide variety of chronic inflammatory diseases in animal models,^{17, 18} inhibiting the recruitment of leukocytes (white blood cells) to areas of inflammation.¹⁵ 6-B345TTQ was identified as a non-cytotoxic inhibitor of this interaction, one that impaired integrin α4-mediated but not αLβ2-mediated Jurkat T cell migration. The specificity of its action was verified by its lack of effect on the residual α4-mediated cell functions in cells bearing the α4 (Y991A) mutation.

Similar to their lactam isomers, the dihydroisoquinolinone core also represents an important structural motif found among a wide variety of alkaloids (Figure 24),¹⁹ including thalflavine (**174**),²⁰ sallisonine D (**175**),²¹ narciclasine (**176**),²² (+)-pancratistatin (**177**),²³ and hyalachelin B (**178**).²⁴ Dihydroisoquinolinones have also been identified as key scaffolds for fragment-based drug discovery,²⁵ with the ring system displaying a range of biological activities,²⁶ including anti-inflammatory,²² anti-cancer,^{27–30} antiviral,³¹ and antimalarial characteristics.³²

Likewise, there are a number of patents that detail the use of dihydroisoquinolinones for application against a variety of conditions, including: treatment of dopamine-related dysfunction of the central or peripheral nervous system (e.g. Parkinson's disease);³³ treating asthma;³⁴ treating or preventing hyperproliferative disease, which is associated with cancer;³⁵ and treatment against abiotic stress, for boosting plant growth and/or for increasing plant yield.³⁶

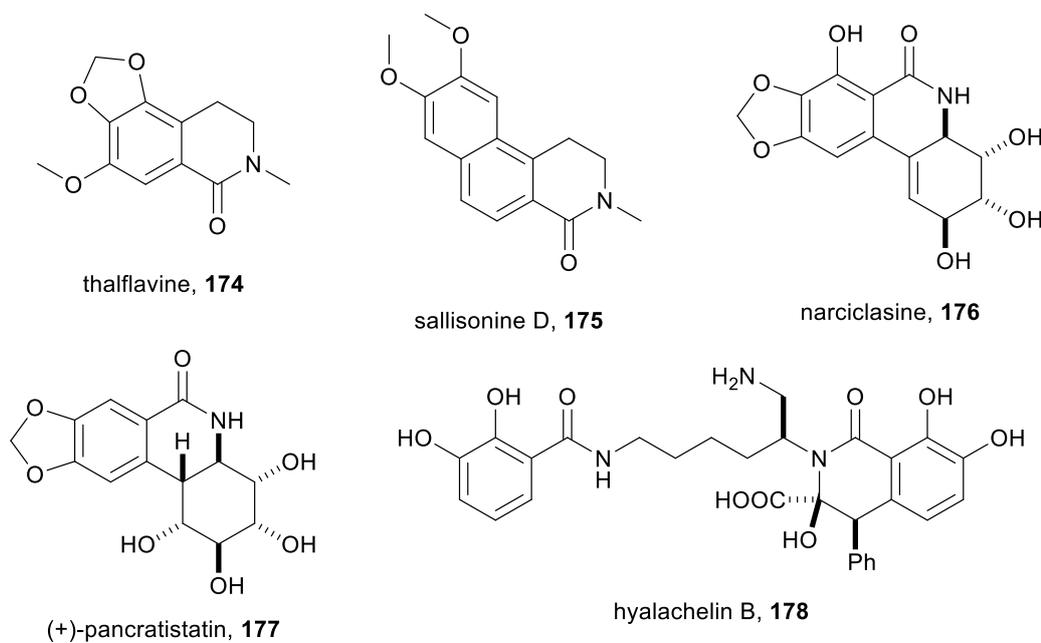


Figure 24 Natural products containing the dihydroisoquinolinone skeleton.

Dihydroisoquinolinones have recently been demonstrated as potent inhibitors of enhancer of zeste homolog 2 (EZH2), the mutation or over-expression of which has been linked to many forms of cancer.³⁷ EZH2 inhibits genes responsible for suppressing tumour development, therefore blocking EZH2 activity has been identified as a potential avenue to slow tumour growth. To this end, Kung *et al.* designed a novel series of dihydroisoquinolinones as potential EZH2 inhibitors, with compound **179** identified as the lead candidate (Figure 25).²⁹ **179** possessed good efficacy in a diffuse large B-cell lymphoma Karpas-422 tumour model, displaying robust *in vivo* anti-tumour growth activity and dose-dependent de-repression of EZH2 target genes, as well as exhibiting on-target pharmacodynamic effects *in vivo*. This was built upon with the synthesis of compound **180** in 2018, which exhibited greater potency and stronger *in vivo* anti-tumour efficacy observed in preclinical models.³⁰ These improvements, coupled with more favourable thermodynamic solubility properties, suggested a good potential for compound **180** to effectively modulate EZH2 activity in human clinical settings.

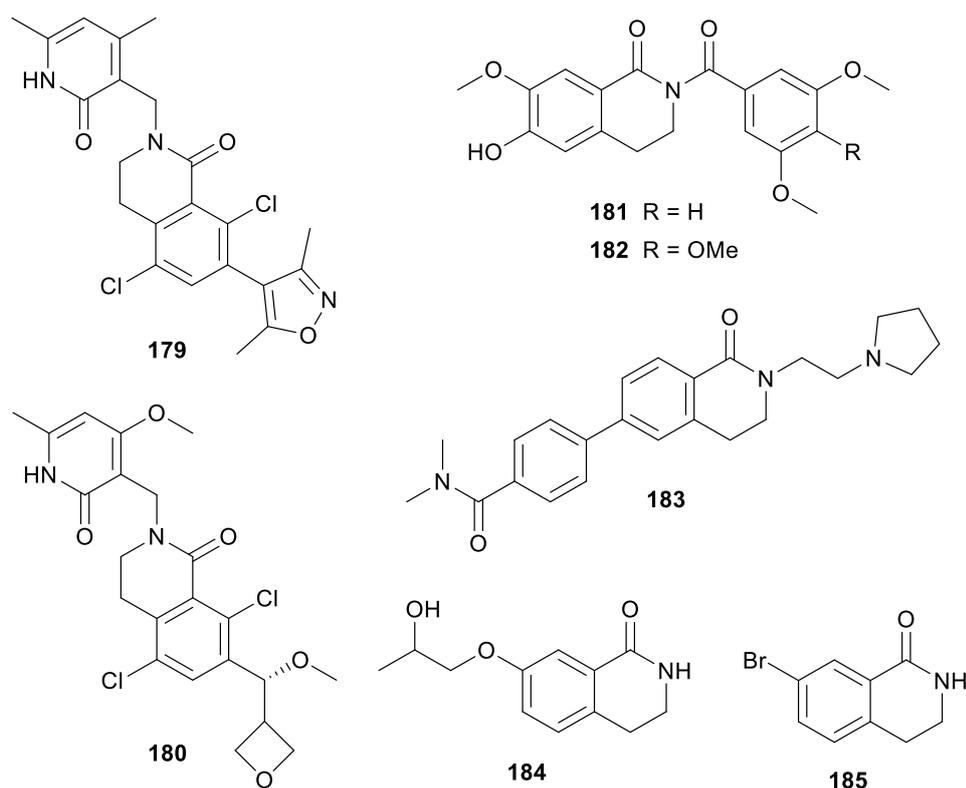


Figure 25 Biologically interesting dihydroisoquinolinones.

Further anti-cancer activity of the dihydroisoquinolinone skeleton was demonstrated by Leese *et al.* whereby compounds **181** and **182** were found to be nearly equipotent to combretastatin A-4 (**18**, CA-4 – see **Section 1.1.2**) as inhibitors of tubulin assembly and colchicine binding.²⁸ **181** and **182** also possessed activities in the low micromolar and nanomolar range against the proliferation of prostate and breast cancer cells.

In 2010, a new class of α_1 -adrenoceptor (α_1 -AR) antagonists were successfully synthesised with compound **183** displaying the greatest activity towards α_1 -AR within *in vivo* assays, comparable to that of known α_1 -AR antagonists.²⁷ It is well known that α_1 -ARs, as the members of the G-protein-coupled receptor ‘superfamily’, play a crucial role in regulating the functions of several physiological processes, in particular in the cardiovascular and central nervous systems.³⁸ Poly(ADP-ribose) polymerases (PARPs), found throughout the cell, also play a role in cardiovascular processes. The activation of PARP can lead to the development of various cardiovascular and inflammatory issues, though can also influence the ability of cells to repair injured deoxyribonucleic acid (DNA). Therefore, depending on the circumstances, pharmacological inhibitors of PARP may be able to lessen inflammatory cell and organ injury, or may be able to enhance the cytotoxicity of anti-tumour agents.³⁹ The lack of selective inhibitors for individual PARP family members has limited our understanding of their roles in cells, however

dihydroisoquinolinone **184** was recently shown to selectively inhibit a mutant of PARP10 (LG-PARP10) that contains a unique pocket in its active site; **184** demonstrated a 10-fold selectivity for LG-PARP10 compared to its wild type (WT) counterpart ($IC_{50} = 8.6 \mu\text{M}$).²⁶ Further biological activity of these species was demonstrated by Zhou *et al.*, in which they reported the action of a number of dihydroisoquinolinone-based compounds against the H3 receptor.⁴⁰ H3 receptors are primarily found in the brain and modulate the release of histamine, which triggers secondary release of excitatory neurotransmitters. Consequently, antagonists to the H3 receptor have stimulant and nootropic effects, hence are being researched as potential drugs for the treatment of neurodegenerative conditions such as Alzheimer's disease. The best compound, dihydroisoquinolinone **185**, exhibited potent *in vitro* binding and functional activities at the H3 receptor, good selectivities against other neurotransmitter receptors and ion channels, acceptable pharmacokinetic properties, and a favourable *in vivo* profile.⁴⁰

3.1.2 Tetrahydroisoquinolines

Tetrahydroisoquinolines (**186**) and tetrahydroquinolines (**187**) are the reduced forms of dihydroisoquinolinones and dihydroquinolinones, comprising a benzene ring fused to a six-membered aliphatic cyclic amine (Figure 26); similar to their lactam counterparts they are also associated with a range of biological properties.^{41, 42}

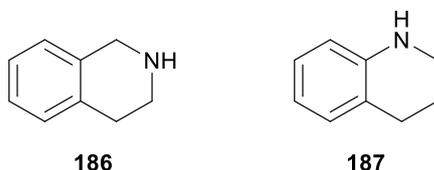


Figure 26 Structures of tetrahydroisoquinoline (**186**) and tetrahydroquinoline (**187**).

Tetrahydroisoquinolines have received significant attention due to their presence in a variety of naturally occurring biologically active molecules (Figure 27).^{41, 43, 44} For instance, Ecteinascidin 743 (**188**) is an extremely potent anti-tumour agent isolated from a marine tunicate, *Ecteinascidia turbinata*.⁴⁵ (*S*)-Norcoclaurine (**189**) has been proven to be an effective β -1 and β -2 adrenergic agonist,⁴⁶ whilst its analogue (*S*)-coclaurine (**190**) is a nicotinic acetylcholine receptor antagonist isolated from a variety of plant sources such as *Nelumbo nucifera*.⁴⁷ Jantine (**191**), isolated from the climbing shrub *Cocculus hirsutus*, is one of the medicinal alkaloids possessing significant anti-hyperglycemic activity.⁴⁸ Another naturally occurring tetrahydroisoquinoline is canadine (**192**), which can act as a calcium

channel blocker.⁴⁹ *Amaryllidaceae* alkaloids such as cherylline (**193**) and latifine (**194**) have been isolated from *Crinum latifolium* and other *Crinum* species.⁵⁰

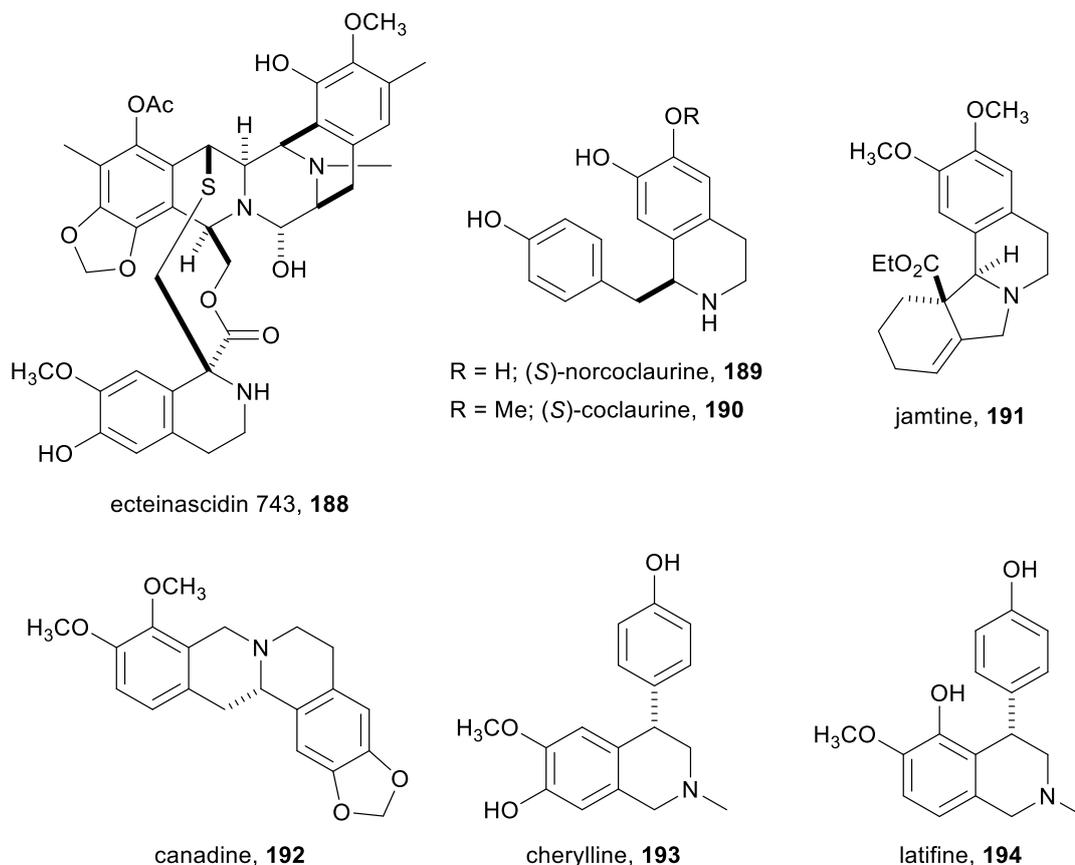


Figure 27 Tetrahydroisoquinoline framework in bioactive natural products.

In addition, several synthetic tetrahydroisoquinolines have been described which are of importance in the treatment of a number of neurological and physiological disorders (Figure 28).^{51, 52} Tetrahydroisoquinolines bearing a pendant 4-aryl group are of particular biological significance.⁵³⁻⁵⁹ Tetrahydroisoquinoline **195**, specifically the (*S*)-(-)-enantiomer, was found to be a potent renal vasodilator through selective stimulation of the dopamine receptor DA₁;⁵⁵ the DA₁ agonist activity of **195** was about 10 times stronger than dopamine for increasing renal blood flow in anaesthetised dogs. Anan *et al.* later synthesised a series of tetrahydroisoquinoline derivatives demonstrating DA₁ agonist activities, with compound **196** identified as the most potent renal vasodilator.⁵⁶

Various pharmacological applications of tetrahydroisoquinolines have been patented:⁶⁰ they have been used to treat histamine H₃ receptor-mediated disorders;^{61, 62} used to combat respiratory complaints like snoring and sleep apnoea;⁶³ and used in the treatment and prevention of chronic and neuropathic pain.⁶⁴ 4-Aryl-tetrahydroisoquinolines have also been patented as hypotensive agents,⁶⁵ anti-ulcer agents,⁶⁶ local anaesthetics,⁶⁷ as

well as neurological and physiological agents,^{68, 69} in particular to treat depression.^{53, 60, 65, 70, 71} The use of tetrahydroisoquinolines in the treatment of neurological disorders such as depression is perhaps most frequent in the literature.^{53, 57, 58}

Compound **197** was discovered to be a very potent inhibitor of the serotonin transporter ($IC_{50} = 3.0$ nM), norepinephrine transporter ($IC_{50} = 8.3$ nM), and dopamine transporter ($IC_{50} = 3.1$ nM). It also showed efficacy in the rat forced swim and mouse tail suspension models, exhibiting substantial occupancy levels at the three transporters in both rat and mouse brain.⁵⁷ Diclofensine (**198** – further discussed in **Section 3.3.3**),⁵⁸ and the more (in)famous nomifensine (**199**),⁵³ are also highly effective inhibitors of reuptake of these central neurotransmitters such as serotonin, norepinephrine, and dopamine. Nomifensine was marketed for use as an antidepressant in the 1970s, but was ultimately withdrawn mainly due to its association with immune haemolytic anaemia.⁷²

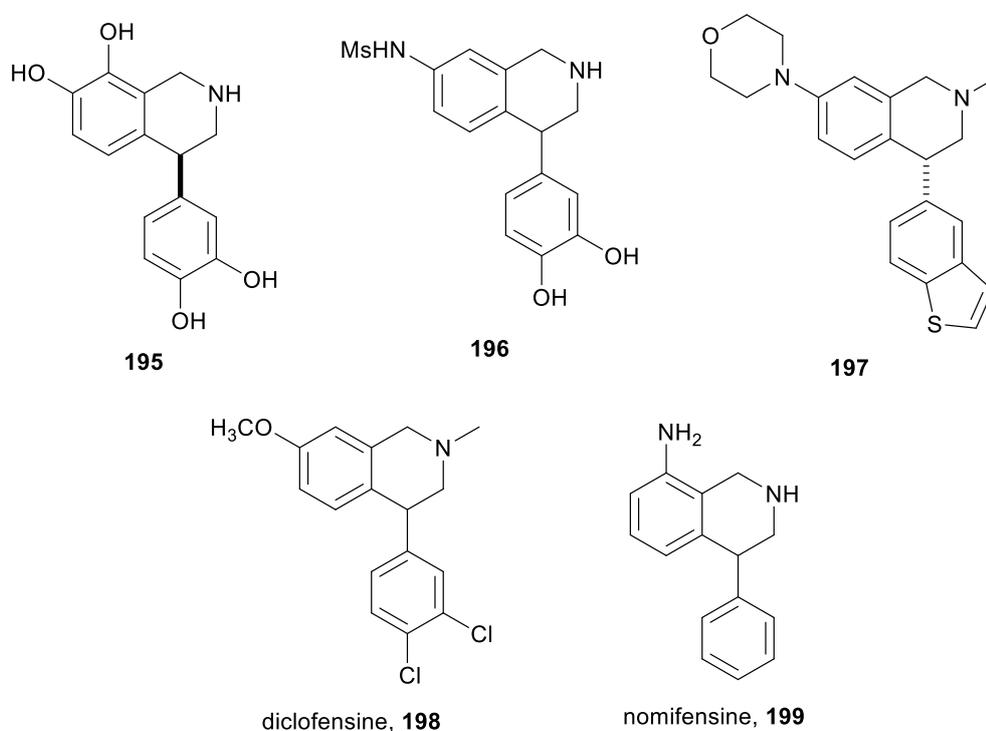


Figure 28 Diclofensine (**198**), nomifensine (**199**) and other biologically interesting synthetic tetrahydroisoquinolines.

Tetrahydroquinolines, the reduced form of dihydroquinolinones, are outside the scope of this report, however they also exist within a number of alkaloids.^{42, 44, 73} Furthermore, similar to their isoquinoline analogues, they are associated with a wide range of interesting biological properties, such as anti-cancer activity,⁷⁴⁻⁷⁶ anti-fungal activity,^{77, 78} anti-bacterial activity,^{79, 80} anti-malarial activity,⁸¹ anti-hypertensive activity,⁸² antidepressant activity,⁸³ antileishmanial activity,⁷⁶ and have been identified in the potential treatment against Alzheimer's disease.⁸⁴⁻⁸⁶ Various biological applications and

numerous syntheses of these compounds has been comprehensively reviewed by Menéndez *et al.*⁴²

A number of patents detailing the medicinal applications of these types of compounds are available,^{87, 88} for example the treatment of liver,⁸⁹ and inflammatory diseases,⁹⁰ as well as analgesics to combat pain,^{91, 92} and as antidepressant agents.⁹³

3.2 Synthesis of Dihydroquinolinones and Dihydroisoquinolinones

The importance of dihydroquinolinones and their lactam isomers in medicinal chemistry has stimulated considerable attention from organic chemists and encouraged the development of new synthetic pathways to prepare these compounds. Various synthetic strategies towards dihydroquinolinones include Friedel–Crafts cyclisations,⁹⁴⁻⁹⁶ radical reactions,⁹⁷ solid-phase synthesis,⁹⁸ transition metal-catalysed reactions by palladium,⁹⁹⁻¹⁰⁴ or rhodium catalysts,¹⁰⁵⁻¹⁰⁷ and even tandem catalytic processes employing a combination of palladium and rhodium with copper.¹⁰⁸⁻¹¹⁰ Synthetic approaches to the dihydroisoquinolinone ring system are similar to those for its isomer,¹¹¹⁻¹¹⁴ with cobalt catalysis,¹¹⁵ and a tandem Re-Mg process also reported,¹¹⁶ although reactions in which an aromatic amine precursor is cyclised with addition of one or two carbon atoms are the most common approaches.¹¹⁷ Despite several methods existing for the preparation of both benzofused six-membered ring lactams, a highly efficient method towards these compounds continues to be an attractive area of research in organic chemistry.

Dihydroisoquinolinones and dihydroquinolinones can be conveniently made from indan-1-ones via ring expansion transformations, as evidenced by newly published reports detailing the formation of both of these species from indan-1-ones via the Schmidt reaction,¹¹⁸ and from their corresponding indan-1-one oximes under Beckmann conditions.¹¹⁹ A Curtius rearrangement has also been utilised as a method of dihydroisoquinolinone formation,¹²⁰ however the similar Schmidt reaction is far more common. Indeed, a number of literature reports involve the use of Schmidt conditions to fashion dihydroisoquinolinones possessing interesting biological activities.^{27, 28, 40, 121}

The previously synthesised 3-aryl-indan-1-ones **118-125** were utilised to test two different ring expansion reactions as a way to construct the aforementioned δ -lactams. The first method is a Beckmann rearrangement (**Section 3.2.1**), proceeding via oxime intermediates, and the second approach is the widely utilised Schmidt reaction (**Section 3.2.2**).

While the Beckmann rearrangement has been widely utilised in the formation of lactams and other amides,^{123, 127-129} not many literature reports have described the transformation of indan-1-one oximes to dihydroisoquinolinones and dihydroquinolinones. The Beckmann rearrangement of the unsubstituted indan-1-one oxime **207** has been shown to give δ -lactam products in low yields and, despite the reaction proving more successful for substituted starting materials, yields vary greatly depending on the nature of the substituents.^{125, 129, 130} Substituents on both the benzene and aliphatic rings are influential, having a profound effect on the ratio of isomers formed.^{131, 132} Lansbury *et al.* found that the regioselectivity of the rearrangement reaction shifted more towards alkyl migration as the size of the substituents at the 4- and 7-position increased (Table 10).¹²⁵

Table 10 Effect of benzene ring substitution on the regiochemistry of Beckmann rearrangements of indan-1-one oximes.¹²⁵

assumed configuration
aryl migration
alkyl migration

	Indan-1-one Oxime		Ratio / % migration			
	R ¹	R ²		Aryl		Alkyl
207	H	H	163	90	164	10
208	Me	Me	211	34	214	66
209	C ₂ H ₅	C ₂ H ₅	212	27	215	73
210	<i>t</i> -Bu	Br	213	19	216	81

The Beckmann rearrangement of indan-1-one oximes is also heavily dependent on the reagents employed. This was evidenced through work by Torisawa *et al.*,¹³⁰ in which various indan-1-one oximes were subjected to different Beckmann conditions. All reactions were sluggish towards conventional conditions and some oximes were presumed to isomerise prior to migration, leading to unexpected dihydroisoquinolinone formation. The rearrangement with Eaton's reagent (P₂O₅-CH₃SO₃H) failed to give typical Beckmann products whilst more success was achieved with PPA, with further improvements observed when a mixture of PPA with Bi(OTf)₃ was employed.

218-225 on stirring with hydroxylamine hydrochloride in pyridine at 80 °C, and then reacted with mesyl chloride and trimethylamine, in CH₂Cl₂ at -20 °C, to give oxime mesylates **226-233** (Table 11).

Table 11 Formation of indan-1-one oximes **218-225** and oxime mesylates **226-233**.

Indan-1-one		Oxime		Oxime Mesylate	
R ¹	R ²	Yield % ^a		Yield % ^{a, b}	
118	H	218	99	226	99
119	H	219	99	227	99
120	H	220	95	228	99
121	H	221	99	229	99
122	OCH ₃	222	99	230	99
123	OCH ₃	223	95	231	99
124	OCH ₃	224	98	232	99
125	OCH ₃	225	92	233	99

^a Isolated yield, used without further purification; ^b Residual MsCl present.

The two-step process was very high yielding, with oximes **218-225** and subsequent oxime mesylates **226-233** forming in excellent yields. Only single isomers were observed, believed to be (*E*)- through comparison to the literature,^{131, 135} and previous work from the Fox group;¹³⁶ the (*E*)-isomer is known to be more stable, which is believed to be a consequence of unfavourable steric interactions between the hydroxyl group and C_{Ar}-H (Figure 29) – this idea can be extended to the mesylate group in oxime mesylates.¹³¹

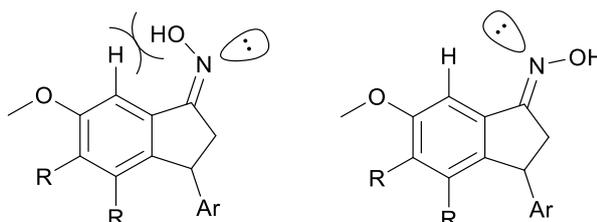
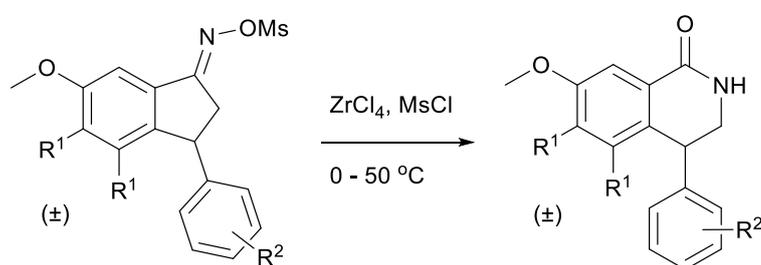


Figure 29 Steric interactions between –OH group and C_{Ar}-H in (*Z*)- (*left*) and (*E*)- (*right*) indan-1-one oximes.

The mesylation process appeared to be quantitative although mesyl chloride was still present in the ^1H NMR spectra of the crude reaction products and thus the recorded yields likely inflated – the presence of this residual reagent was shown to increase the success of the subsequent Beckmann rearrangement,¹³⁵ hence no attempts were made to remove it from the crude oxime mesylates. Oxime mesylates **226-233** were then subjected to the Beckmann conditions discussed above – stirring with zirconium chloride and mesyl chloride – although the reaction had to be performed at 50 °C to afford complete conversion (Table 12).

Table 12 Beckmann rearrangement reactions of racemic 3-aryl-indan-1-one oxime mesylates **226-233**.



	Oxime Mesylate		Dihydroisoquinolinone	
	R ¹	R ²		Yield % ^a
226	H	H	234	62
227	H	4-Cl	235	77
228	H	3,4-Cl	236	74
229	H	2,4-Cl	237	73
230	OCH ₃	H	238	55
231	OCH ₃	4-Cl	239	86
232	OCH ₃	3,4-Cl	240	68
233	OCH ₃	2,4-Cl	241	78

^a Isolated yield.

The rearrangement gave only a single lactam product in generally high yields, in accordance with reports by Torisawa *et al.*,¹³⁵ however these products were identified as dihydroisoquinolinones **234-241** instead of the expected isomers – no additional product(s) were established from the ^1H NMR spectra of the crude reaction products. This result is more in line with the work by Smisman *et al.*,¹³² whereby similar indan-1-one oximes – methoxy groups in the 5- and 6-positions – were transformed into dihydroisoquinolinones exclusively using P₂O₅ and methanesulfonic acid. Evidently, the

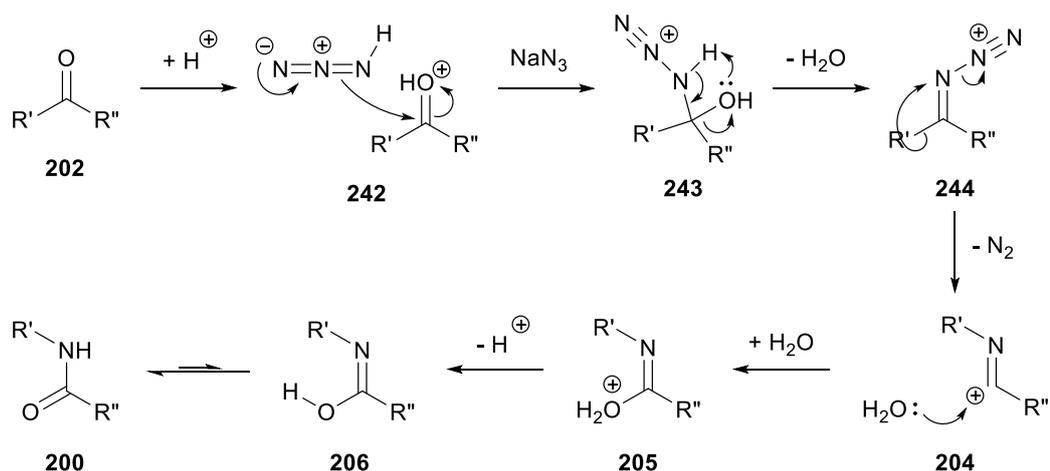
presence of the methoxy group in the 6-position is influential on the regioselectivity of the Beckmann rearrangement irrespective of other reagents employed, causing alkyl migration to be the predominant pathway. Since migration of the group *anti*- to the leaving group attached to nitrogen is known to migrate during the reaction,¹²³ yet it is strongly believed that the indan-1-one oxime mesylates exist in the more stable (*E*)- form, isomerisation to the less favoured (*Z*)-configuration is likely taking place prior to migration, in line with literature reports.¹²⁵

Little can be ascertained from the results in Table 12 about the effect of substrate structure on the yield of dihydroisoquinolinones obtained from the Beckmann rearrangement of 3-aryl-indan-1-one oxime mesylates. There are no clear trends between the single methoxy and trimethoxy- derivatives, nor can any strong conclusions be drawn on the effect of the pendant 3-aryl ring on the rearrangement. Nonetheless, notably lower yields were observed for the reactions of **234** (62 %) and **238** (55 %) – with an unsubstituted (phenyl) ring. This may suggest the transformation is more successful for indan-1-ones bearing an electron-deficient 3-aryl ring, which would further strengthen the idea that the Beckmann rearrangement is governed by electronics in addition to steric factors.¹²⁶

Overall, the 3-step synthetic route towards dihydroisoquinolinones **234-241**, though reasonably high yielding, was not completely ideal; removal of pyridine and MsCl in steps 1 and 3 respectively proved to be problematic and time-consuming due to their utilisation as the solvent in these reactions. As a result, an alternative pathway towards dihydroisoquinolinones and dihydroquinolinones was sought.

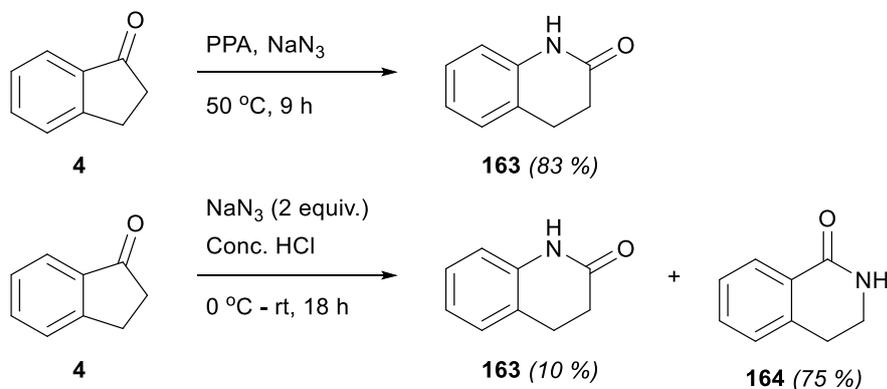
3.2.2 *Schmidt Reaction*

Another transformation known for forming amides from ketones is the Schmidt reaction, which follows a similar mechanism to the Beckmann rearrangement, but involves the use of an azide as a nucleophile.¹³⁷ The process is acid-catalysed, in which the carbonyl group in **202** is first activated by protonation for nucleophilic attack by hydrazoic acid (**242**) – formed in situ from an azide. Subsequent loss of water from **243** yields a short-lived ketimino-diazonium ion (**244**), which gives rise to an iminocarbenium ion intermediate (**204**) after one of the α -carbons, R' or R'', migrates to the nitrogen atom, with loss of nitrogen. This intermediate is then trapped by water, and the product amide **199** is ultimately formed after proton loss (**205**) and subsequent tautomerisation of **206** (Scheme 31).¹³⁸⁻¹⁴⁰



Scheme 31 Schmidt reaction mechanism.

In fact, for the synthesis of bicyclic lactams, the Schmidt reaction has generally been found to be more convenient than the Beckmann rearrangement approach.¹⁴¹ In 1958 Conley reported the polyphosphoric acid-catalysed Schmidt rearrangement of a number of ketones, including that of indan-1-one **4** which gave exclusive formation of 3,4-dihydroquinolin-2-(1*H*)-one (**163**) as a result of aryl migration (Scheme 32).¹⁴² The rearrangement was found to proceed extremely slowly below 50 °C.

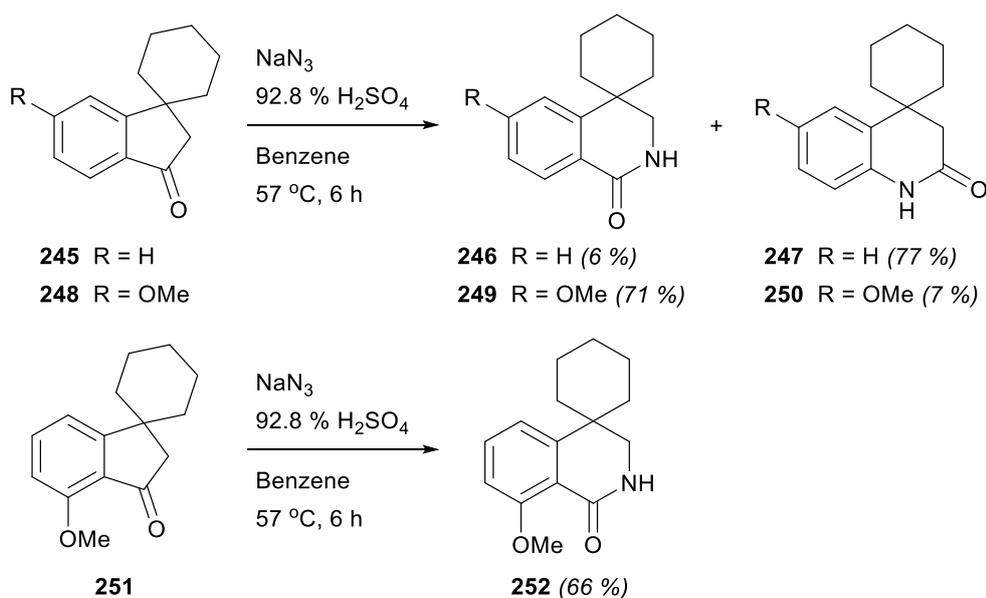


Scheme 32 Effect of acid on the Schmidt reaction of indan-1-one **4**.

Similarly, it has been reported that performing the reaction in trichloroacetic acid or H₂SO₄ usually yields 3,4-dihydroquinolin-2-(1*H*)-one (**163**) as the major isomer.^{143, 144} However, it appears that this transformation remains very catalyst specific, as it was reported that the Schmidt reaction of **4** using concentrated HCl gave a ratio of lactams, with dihydroisoquinolinone **164** being the major product.^{145, 146}

It is well-known that the Schmidt reaction of aryl-alkyl ketones, for instance acetophenone, proceeds via aryl group migration preferentially, with steric effects playing a major role – the larger group is believed to migrate.¹³⁹ However, it has become clear

that this is not always the case, in fact the outcome of the Schmidt reaction can vary considerably depending on the nature of the substituents on the aromatic ring;^{144, 147} the general conclusion is that electronic and steric effects can compete with one another.^{138, 148, 149} Particular attention has been paid towards methoxy substituents, a group that in resonance terms is electron-donating and in inductive terms is electron-withdrawing.^{137, 143, 144, 150, 151} The direction of the rearrangement in the Schmidt reaction with indan-1-ones is strongly affected by the substituents in the aromatic ring in positions *para*- and *ortho*- to the carbonyl group – this effect appears to be far more pronounced for the 5-membered indanones than the larger 6-membered tetralone derivatives.¹⁴³ Specifically, alkyl migration is the predominant pathway when methoxy substituents are present in the *ortho*- and *para*- positions, whereby they are able to stabilise the iminocarbenium ion intermediate **204** that forms in the reaction. This is exemplified by a paper by Minami *et al.*, in which the outcome of a number of Schmidt reactions with indan-1-one substrates were reported (Scheme 33).¹⁵⁰



Scheme 33 Effect of *ortho*- and *para*- methoxy groups on the regiochemistry of the Schmidt reaction with indan-1-ones.

As expected, indan-1-one **245**, containing no methoxy group in the benzene ring, afforded predominantly dihydroquinolinone **247** (77 %) and only a trace of the dihydroisoquinolinone **246** (6 %). However, the same reaction of indan-1-one **248**, with the MeO group in the *para*- position, remarkably afforded dihydroisoquinolinone **249** in 71 % yield and its isomer **250** in only 7 % yield, whilst indan-1-one **251** (*ortho*-MeO) furnished the dihydroisoquinolinone **252** exclusively in 66 % yield. It is therefore clear

that the presence of a methoxy group in the aromatic ring plays an important role in determining the regiochemistry of the Schmidt reaction.¹⁵⁰

Since the Schmidt reaction is known to be heavily dependent on the conditions employed, such as the acid employed and the temperature at which the reaction is performed,^{142-146, 152, 153} a number of conditions were initially tested on the racemic 3-aryl-indan-1-one **118** in order to achieve optimum conditions for these substrates (Table 13). Three sets of conditions were chosen from the literature, each making use of a different acid catalyst: polyphosphoric acid,¹⁴² concentrated HCl,¹⁴¹ and methanesulfonic acid.¹⁵⁴ Reaction of indanone **118** with PPA (entry 1) afforded the desired dihydroquinolinone **253**, alongside its isomer **234** and an unknown material – later discovered to be a tetrazole – but only reached ~30 % completion after 48 hours. This is in contrast to the reaction of indan-1-one **4**, which Conley showed gave exclusive formation of the dihydroquinolinone **163** on reaction with sodium azide with PPA at 50 °C (Scheme 32);¹⁴² this is most likely a result of the presence of the methoxy group attached to the aromatic ring.¹⁵⁰

Table 13 Optimisation of the Schmidt reaction of 3-aryl-indan-1-one **118**.

The reaction scheme shows the conversion of 3-aryl-indan-1-one (**118**) to two dihydroquinolinone isomers, **234** and **253**. The starting material **118** has a methoxy group at the 6-position and a phenyl group at the 3-position of the indanone ring. The products **234** and **253** are dihydroquinolinone derivatives with the same substituents, differing in the position of the nitrogen atom in the six-membered ring.

Entry ^a	Conditions	Product Ratio / % ^b			
		118 ^c	234	253	Unkn.
1	NaN ₃ , PPA, 50 °C, 48 h	71	7	16	6
2	NaN ₃ , HCl, 1,4-dioxane, 50 °C, 3-4 days	100	- ^d	- ^d	- ^d
3	NaN ₃ , HCl, 1,4-dioxane, 80 °C, 3-4 days	100	- ^d	- ^d	- ^d
4	NaN ₃ , MsOH, CHCl ₃ , 70 °C, 3.5 h	0	48	29	23

^a Reaction based on indan-1-one **118** (100 mg, 0.42 mmol); ^b Ratio determined by ¹H NMR of the crude reaction product; ^c Unreacted starting material; ^d No conversion observed.

Concentrated HCl is known to cause opposite Schmidt regioselectivity to other acids, such as polyphosphoric acid, trichloroacetic acid or H₂SO₄,^{145, 146} however the reaction with indanone **118** resulted in no conversion (100 % recovered starting material) at both 50 °C (entry 2) and 80 °C (entry 3). Finally, the use of methanesulfonic acid proved far

more successful, giving complete conversion in only 3.5 hours and yielding the same three products as the reaction with PPA. Methanesulfonic acid has historically been more commonly employed in the Schmidt transformation of dialkyl ketones,^{155, 156} such as the synthesis of amino acids from β -keto esters,^{154, 157} but its use in the reaction of aryl-alkyl ketones – like 3-aryl-indan-1-ones **118-125** – is becoming increasingly popular; a number of aryl-alkyl ketones were subjected to the Schmidt reaction in a continuous-flow microreactor to exclusively yield the amide resulting from aryl migration.¹⁴⁰

Based on the results in Table 13, methanesulfonic acid was chosen as the acid mediator for all Schmidt reactions going forward; not only did it yield the desired lactam product, it also gave full conversion in only 3.5 hours and there were no solubility or mechanical issues – the use of PPA as both the catalyst and solvent, coupled with its high viscosity, led to difficulties in terms of reaction set up, stirring and solubility. With optimum conditions in hand, the series of eight 3-aryl-indan-1-ones **118-125** were subjected to the Schmidt reaction. The results of these Schmidt reactions are presented in Table 14.

Table 14 Schmidt reactions of racemic 3-aryl-indan-1-ones **118-125**.

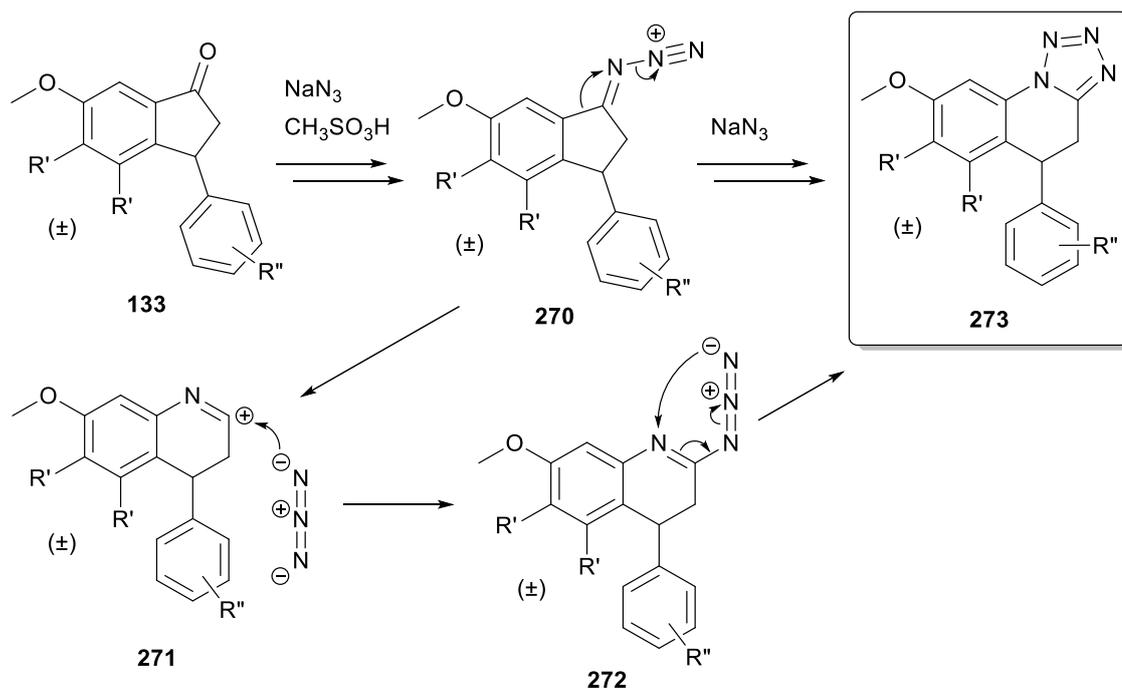
Racemic Indan-1-one			Product Ratio / % ^a						
	R ¹	R ²	<i>a</i>		<i>b</i>		<i>c</i>		<i>Other</i>
118	H	H	234	47	253	30	261	23	-
119	H	4-Cl	235	50	254	32	262	18	-
120	H	3,4-Cl	236	56	255	33	263	11	-
121	H	2,4-Cl	237	61	256	29	264	10	-
122	OCH ₃	H	238	83	257	3	265	13	-
123	OCH ₃	4-Cl	239	87	258	4	266	9	-
124	OCH ₃	3,4-Cl	240	88	259	5	267	6	-
125	OCH ₃	2,4-Cl	241	91	260	2	268	5	2 ^b

^a Ratio determined by ¹H NMR of the crude reaction product; ^b Material determined to be the tetrazole isomer (**269**). [N.B. Also isolated was the dihydroisoquinolinone resulting from the reaction of the 4-methoxy isomers of **118-121**.]

The reaction of each 3-aryl-indan-1-one gave a mixture of products; in all cases both lactams formed, with the lactam arising from alkyl group migration predominating (*a*), and the minor lactam being 4-aryl-3,4-dihydroquinolin-2-ones, which result from aryl group migration (*b*). As expected, the ratio of alkyl : aryl group migration was significantly higher for indan-1-ones **122-125** as a result of increased methoxy group substitution on the aromatic ring, which is consistent with literature reports – in particular the presence of the methoxy group *para*- to the carbonyl group.^{143, 150}

The effect of the pendant 3-aryl ring on the Schmidt reaction of 3-aryl-indan-1-ones can also be seen in the results displayed in Table 14. As more chlorine atoms are introduced into the 3-aryl ring and thus the aromatic ring becomes more electron withdrawing, there is greater dihydroisoquinolinone formation. Furthermore, as ring substitution changes from 3,4-Cl to 2,4-Cl the extent of which this δ -lactam forms increases even more, which can be rationalised by the greater inductive electron withdrawing effect of chlorine in the *ortho*- position relative to *meta*-.¹⁵⁸ A conceivable explanation is that the electron withdrawing nature of the pendant 3-aryl ring causes aryl migration to be disfavoured due to its proximity to the positively charged iminocarboxonium ion that forms during this pathway, despite being attached to a carbon two atoms away. It is possible the electron donating mesomeric effect of the chlorine atoms, in particular those in the directing *ortho*- and *para*- positions,¹⁵⁹ is negligible here due to their inability to directly contribute electrons to the intermediate carbocation.

In addition to both lactam isomers, tetrazole species were also observed in the Schmidt reactions of 3-aryl-indan-1-ones **118-125** (*c*, Table 14). The formation of tetrazoles from ketones and hydrazoic acid in the presence of an acid catalyst was first observed by Karl Schmidt in 1924,¹³⁷ and their formation from cyclic ketones has since been well-documented.^{155, 160, 161} For instance, the Schmidt reaction has been used extensively in the steroid field to prepare tetrazole-fused steroid derivatives.¹⁶²⁻¹⁶⁵ The mechanism of tetrazole formation within this transformation has been heavily scrutinised, but now it is widely understood that they form through reaction of hydrazoic acid with an intermediate iminocarboxonium ion, followed by an electrocyclic ring closure – this process is assumed to be in direct competition with amide formation whereby it is water that attacks the carbocation.^{166, 167} Based on these beliefs, a conceivable mechanism behind tetrazole formation in the Schmidt reaction of 3-aryl-indan-1-ones (**133**) is shown in Scheme 34; aryl migration in **270** leads to iminocarboxonium ion intermediate **271**, which reacts with additional NaN₃ followed by electrocyclisation of the 6 π -system in **272** to give **273**.



Scheme 34 Postulated mechanism of tetrazole formation.

Interestingly, only a single tetrazole isomer was observed in the reactions of all 3-arylindan-1-ones with the exception of indanone **125**, which might be connected to the presence of the *ortho*-chlorine atom in the 3-aryl ring, in addition to the three methoxy groups on the primary aromatic ring. A literature search for tetrazoles with a structure similar to those synthesised in this work showed that tetrazole **274** has been previously made, with ^1H NMR spectroscopic data available (Figure 30),¹⁶⁸ however neither its isomer nor other related tetrazoles have been reported. Nonetheless, the syntheses of lactam isomers **163** and **164** that are analogous to tetrazole **274** have been reported,^{169, 170} and their ^1H NMR spectroscopic data are shown in Figure 30. The most notable difference between these two lactams is the chemical shift of the CH_2 protons next to the amide functional group; the protons adjacent to the electronegative nitrogen atom are shifted downfield in **164** ($\delta_{\text{H}} = 3.56$ ppm) compared to its isomer **163** ($\delta_{\text{H}} = 2.65$ ppm). This deshielding effect by the nitrogen can be extended to the tetrazoles studied in this work.

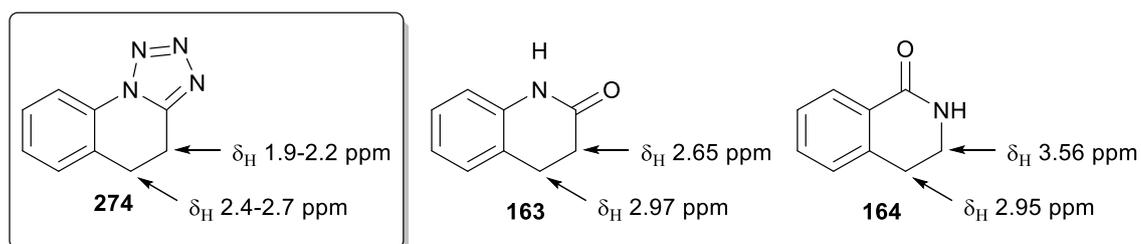


Figure 30 ^1H NMR data reported for tetrazole **274**,¹⁶⁸ dihydroquinolinone **163**,¹⁶⁹ and dihydroisoquinolinone **164**.¹⁷⁰

Since both tetrazole isomers **268** and **269** were isolated after the Schmidt reaction of **126**, the deduction of the absolute configuration of tetrazoles **261-268** was made possible through comparison of their NMR spectra; the CH₂ proton and carbon environments were located at significantly higher chemical shifts for one tetrazole over the other, which was assigned as **269** due to their proximity to the electronegative nitrogen atom (Figure 31). Tetrazoles **261-267** possessed relatively lower chemical shifts for these proton and carbon environments, similar to those observed for **268**, hence they were also assigned as the quinoline tetrazole isomer by analogy.

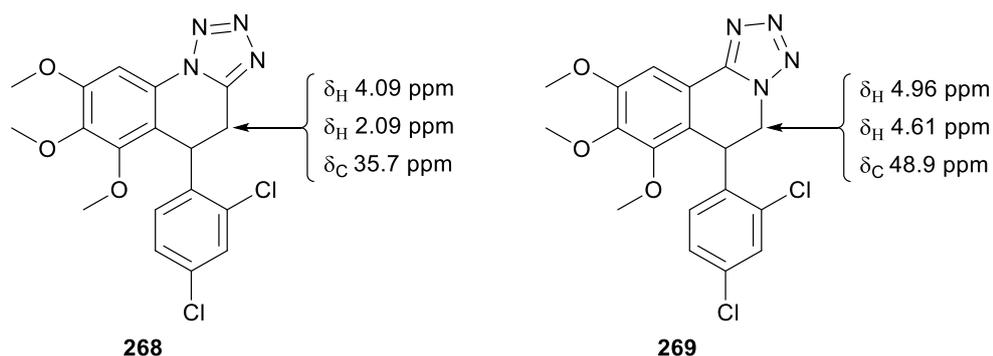
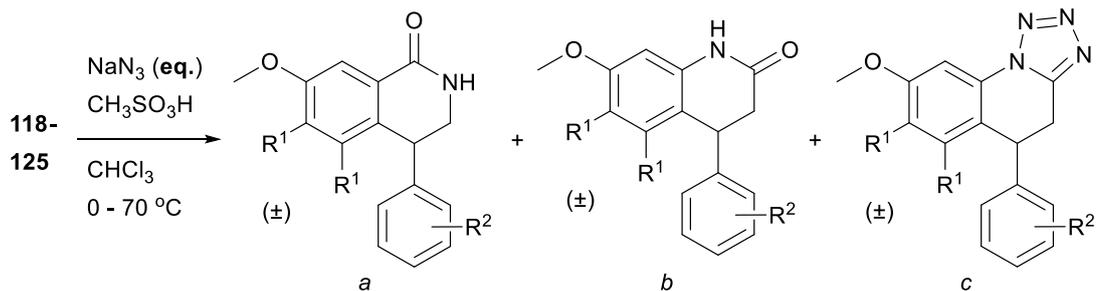


Figure 31 Tetrazole isomers **268** and **269** isolated from the Schmidt reaction of **125**.

At first, the formation of the observed tetrazole isomer in the Schmidt reactions of 3-aryl-indan-1-ones **118-125** came as a surprise; tetrazoles **261-268** arise from aryl migration yet alkyl migration is the major pathway, hence one would expect the other tetrazole isomer to predominantly form in the reactions. However, on further analysis of the mechanism for tetrazole formation, the presence of the observed isomer could possibly be explained by the stability of the iminocarbenium ion that forms after aryl/alkyl migration. As previously mentioned, the cation that results from alkyl migration is stabilised by the *para*-methoxy group on the aromatic ring through resonance and, as such, may be less reactive towards attack by azide. On the other hand, the cation that forms from aryl migration is less stable and thus more reactive with respect to any nucleophile present in the reaction, including hydrazoic acid, therefore forms the tetrazole alongside the dihydroquinolinone.

To further validate this notion, the Schmidt reaction was repeated for all 3-aryl-indan-1-ones in which different equivalents of sodium azide were employed (Table 15) – greater quantities of NaN₃ should theoretically result in greater tetrazole formation. The reaction of 3-aryl-indan-1-ones **118-125** with 1.1 equivalents of sodium azide failed to reach completion, with starting material remaining in all cases.

Table 15 Effect of NaN₃ on the Schmidt reactions of racemic indan-1-ones **118-125**.



Racemic Indan-1-one			NaN ₃ (eq.)	Product Ratio / % ^a					
R ¹	R ²			<i>a</i>		<i>b</i>		<i>c</i>	
118	H	H	1.1	36	34	17			
			2	234	47	253	30	261	23
			3	44	33	23			
119	H	4-Cl	1.1	46	35	13			
			2	235	50	254	32	262	18
			3	50	31	19			
120	H	3,4-Cl	1.1	60	31	10			
			2	236	60	255	29	263	10
			3	60	30	11			
121	H	2,4-Cl	1.1	54	30	8			
			2	237	61	256	29	264	10
			3	64	25	11			
122	OCH ₃	H	1.1	79	3	11			
			2	238	83	257	3	265	13
			3	83	3	13			
123	OCH ₃	4-Cl	1.1	78	4	6			
			2	239	87	258	4	266	9
			3	88	4	8			
124	OCH ₃	3,4-Cl	1.1	84	5	6			
			2	240	88	259	5	267	6
			3	89	4	6			
125	OCH ₃	2,4-Cl	1.1	85	2	3			
			2	241	93	260	2	268^b	6
			3	93	2	6			

^a Ratio determined by ¹H NMR; ^b Formed alongside tetrazole isomer (**269**).

As expected, increasing the amount of sodium azide to 2.0 equivalents led to 100 % reaction completion. There was greater dihydroisoquinolinone and tetrazole formation, yet the amount of dihydroquinolinone that formed generally decreased, especially for single methoxy derivatives **118-121**, for which the formation of dihydroquinolinones is more prominent. Since dihydroquinolinone and tetrazole creation is in direct competition, this result suggests that the iminocarbenium ion intermediate that forms in this reaction pathway is indeed highly reactive and prefers to react with sodium azide over water due to its greater presence in the reaction. Increasing the equivalents of sodium azide further (3.0 eq.) resulted in little-to-no change in the regioselectivity of the Schmidt reactions.

Table 16 Additional Schmidt reactions of racemic indan-1-ones and 1-tetralones.

$\text{Substrate} \xrightarrow[\text{CHCl}_3, 0-70^\circ\text{C}]{\text{NaN}_3, \text{CH}_3\text{SO}_3\text{H}}$
 $\text{a} + \text{b} + \text{c}$

	Substrate	Product Ratio / % ^a					
		<i>a</i>		<i>b</i>		<i>c</i>	
4		164	45	163	51	-	- ^{b, c}
275		279	56	283	44	-	- ^b
276		280	29	284	40	-	- ^{b, c}
277		281	4	285	96	-	- ^b
278		282	62	286	34	287	4

^a Ratio determined by ¹H NMR of crude reaction product; ^b No tetrazole formation observed; ^c Formation of additional products observed – see discussion below.

To further study the cause of tetrazole formation, in terms of substrate structure, in addition to further confirm the likely cause of promoted alkyl migration observed for 3-aryl-indan-1-ones **118-125**, the Schmidt reaction of five additional compounds was performed, three indan-1-ones as well as two 1-tetralones for completeness – to compare with the literature.^{141, 143, 144} Table 16 shows the results. The Schmidt reaction of 1-tetralone **277** yielded primarily lactam **285** over its isomer **281**, which is similar to literature reports for the Schmidt reaction with PPA and H₂SO₄ as the acid mediators,^{141, 143, 144} and the reverse of the HCl-promoted reaction.¹⁴¹

The Schmidt reaction of 6-methoxy-1-tetralone **278**, on the other hand, resulted in a reverse of regiochemistry with alkyl migration to **282** (62 %) favoured over aryl migration to **286** (34 %). This is also consistent with literature reports for PPA, H₂SO₄ and HCl,^{141, 143, 144} and is anticipated since the presence of an electron donating methoxy group in the aromatic ring helps stabilise the iminocarbonium ion intermediate that forms after alkyl migration. Very little tetrazole formation was observed in the Schmidt reactions of both 1-tetralones, with only tetrazole **287** forming from the reaction of **278** in a 4 % product ratio.

Notably, no tetrazole formation was observed in the reactions of the three additional indan-1-ones, suggesting the presence of methoxy group(s) attached to the aromatic ring and a pendant 3-aryl ring are requirements for their formation. The Schmidt reaction of indan-1-one **4**, with no methoxy groups attached to the aromatic ring nor a phenyl ring in the 3-position, gave an almost 50 : 50 ratio between lactam products **163** and **164**. This result highlights the importance of the acid mediator on the reaction, with it previously being reported that the Schmidt reaction of **4** in PPA gives the dihydroquinolinone predominantly whilst conc. HCl reverses the regiochemistry.^{142, 145} As expected, introduction of an electron donating methoxy group to the aromatic ring – as is the case for indan-1-one **275** – results in greater alkyl migration to the dihydroisoquinolinone **279** over its isomer **283**. The opposite outcome occurs in the Schmidt reaction of 3-phenyl-indan-1-one **276**, whereby dihydroquinolinone **284** (40 %) forms in preference over dihydroisoquinolinone **280** (29 %), although it is unclear here if the presence of the phenyl ring has an influence on aryl/alkyl migration since two by-products were observed.

The Schmidt reaction of **4** and **276** also gave rise to additional products, besides the expected δ -lactams. These were identified as nitriles **288** and **289**, isolated in 2 % and 1 % yield in the reactions of indan-1-one **4** and 3-phenyl-indan-1-one **276**, respectively (Figure 32).

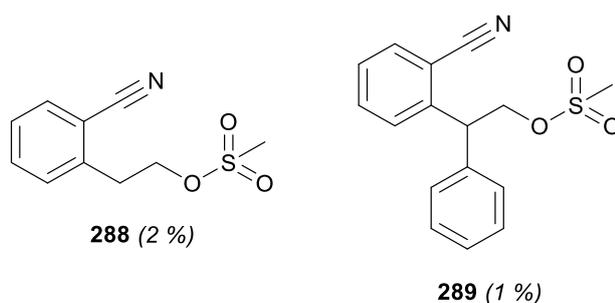
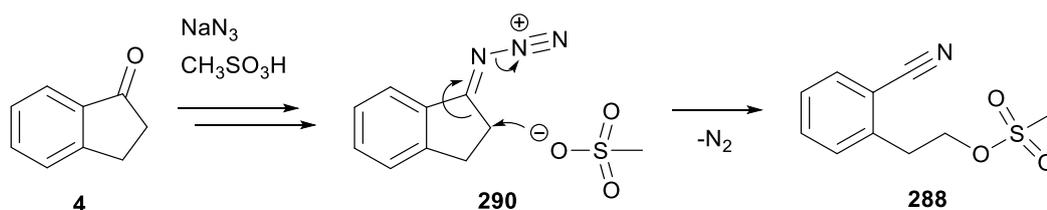


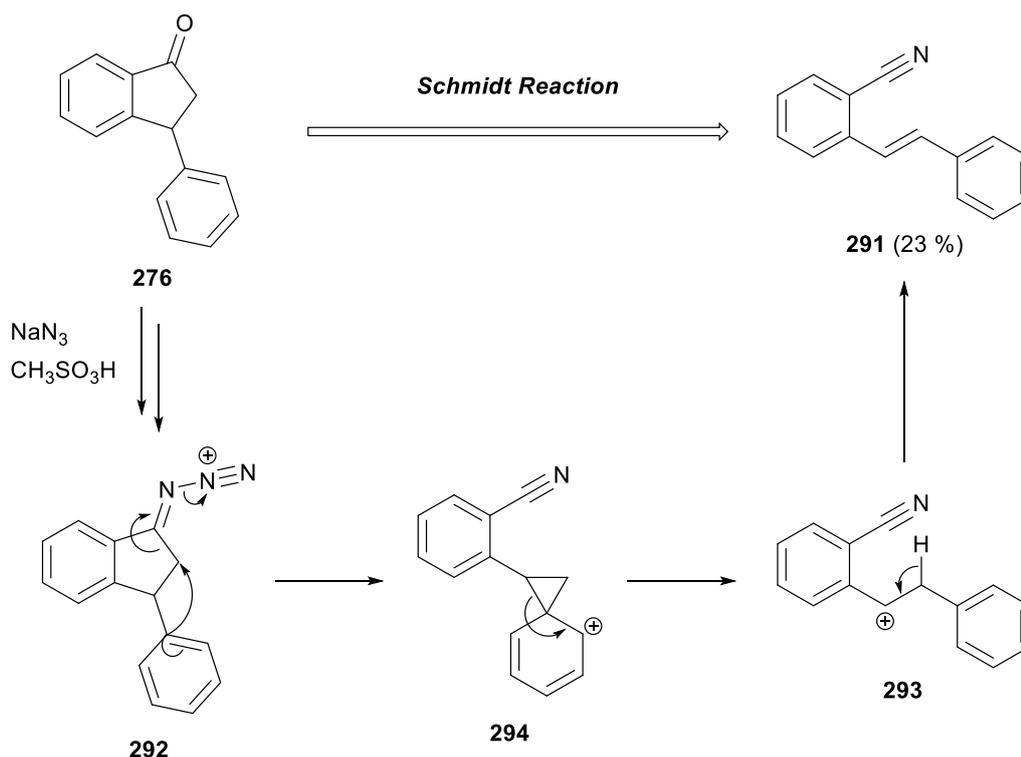
Figure 32 Observed side-products **288** and **289** in Schmidt reactions of **4** and **276**, respectively.

The formation of a nitrile species akin to **288** and **289** is typically observed within the Beckmann rearrangement, and is attributed to fragmentation, a competing pathway whereby the α -carbon-carbon bond breaks rather than migrates.^{127, 171} Indeed, the formation of a similar product was observed in previous work within the Fox group (see **Section 3.2.3**),¹³⁶ and as such a plausible mechanism for the formation of **288** is shown in Scheme 35; it is believed that a mesylate anion attacks the α -carbon in **290**, causing ring opening and concurrent formation of a nitrile group with the loss of nitrogen gas. The absence of this nitrile species in the reactions of all indan-1-ones bearing methoxy groups on the aromatic ring suggests that the presence of these electron donating groups negates this fragmentation pathway, most likely because the typical Schmidt pathway towards dihydroisoquinolinones is promoted through stabilisation of the iminocarbenium ion intermediate.



Scheme 35 Possible mechanism towards nitrile product **288**.

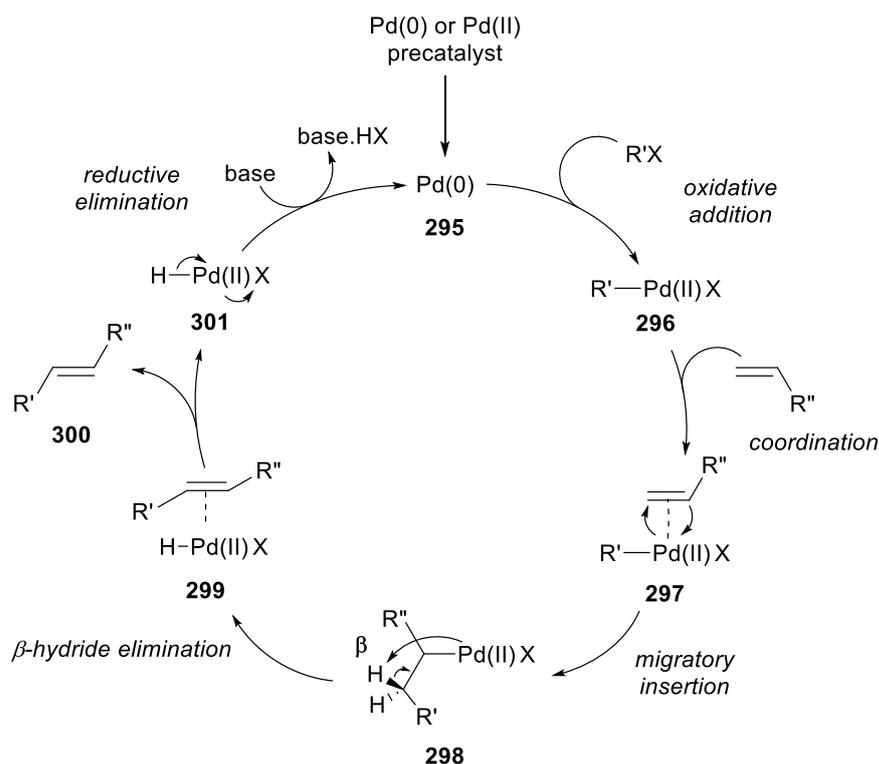
A second by-product, 2'-cyanostilbene (**291**), was isolated in the Schmidt reaction of indan-1-one **276** and its formation likely involves a 1,2-shift of the phenyl group, which is a well-documented process.¹⁷²⁻¹⁷⁴ A 1,2-phenyl shift is a type of Wagner–Meerwein rearrangement, a carbocation 1,2-rearrangement reaction in which a hydrogen atom, alkyl group or aryl group migrates from one carbon to a neighbouring carbon.^{175, 176} A possible mechanism for the formation of **291** (23 %) is shown in Scheme 36.



Scheme 36 Postulated mechanism for the formation of 2'-cyanostilbene (**291**).

It is thought that the fragmentation pathway is assisted by a 1,2-shift of the phenyl ring (**292**) via neighbouring group participation, with eventual elimination in **293** to yield the *trans*-alkene product **291**. Contrary to the migration of a hydrogen atom or alkyl group, a 1,2-phenyl shift is known to pass through a bicyclic intermediate (**294**) where the cation is delocalised throughout the rest of the ring.¹⁷⁷ Notably, none of this species formed for 3-aryl-indan-1-ones containing methoxy group(s) on the aromatic ring, further signifying the promotive effect of this electron donating group on the typical Schmidt reaction – through stabilisation of the carbocation intermediate that forms after alkyl migration.

It was hoped the structure of 2'-cyanostilbene (**291**) could be confirmed through the Heck coupling reaction of styrene and 2-bromobenzonitrile. The Mizoroki–Heck reaction is the Pd(0)-mediated coupling of an aryl or vinyl halide/triflate with an alkene to form a new carbon-carbon bond. It was first reported in the early 1970s through independent studies by Mizoroki and Heck as the Pd(0)-catalysed vinylation of aryl halides.^{178, 179} The Heck reaction is a very attractive synthetic tool for chemists and has been vastly used in the construction of complex structures.¹⁸⁰⁻¹⁸² Three major factors contribute to its broad utility: high functional group tolerance; a remarkable capacity to forge C-C bonds in situations of considerable steric congestion; and an ability to orchestrate the reaction in cascade processes that form multiple rings.¹⁸³



Scheme 37 Commonly accepted mechanism for the Heck reaction.¹⁸⁴

The general mechanism for the Heck reaction is widely accepted (Scheme 37).^{185, 186} The initial, and usually key, catalytic step is oxidative addition of the aryl/vinyl halide or triflate to the 14-electron Pd(0) catalyst **295** to afford a σ -complex (**296**);¹⁸⁴ the order of reactivity for this step is $X = I > OTf > Br > Cl$.¹⁸³ After alkene coordination (**297**) is migratory insertion to give another σ -complex (**298**). This step governs the regiochemistry of the reaction, and is dependent on the nature of the leaving group 'X'; if 'X' is a halide then steric considerations cause the new C-C bond to predominantly form at the least hindered end, whereas electronic factors cause the aryl/vinyl group to be transferred to the end of the alkene with the lowest electron density if 'X' is a triflate – the Cabri–Hayashi model.¹⁸⁷⁻¹⁸⁹ Subsequent β -hydride elimination and eventual release from **299** gives the product alkene **300**. Finally, the hydridopalladium(II) complex **301** is converted back to **295** through base-mediated reductive elimination, completing the catalytic cycle.

The reaction was first attempted as a batch process, with Pd(OAc)₂ and PPh₃ as the catalyst (1.00 mol%) and ancillary ligand (2.00 mol%), and triethylamine (1.5 eq.) and THF as the base and solvent, respectively. Despite refluxing the mixture under N₂ for 26.5 hours, the reaction only reached about 8 % conversion, with a large quantity of both starting materials still present and, although it did appear as though the desired alkene **291** had formed, one could not be completely certain as the 2-bromobenzonitrile could

not be removed by column chromatography – it was clear that (almost) full conversion was required. To this end a microwave reactor was employed, enabling greater reaction temperatures (and pressures), and both the temperature and loadings of catalyst and ligand were screened (Table 17).

Table 17 Results of the Heck coupling of styrene and 2-bromobenzonitrile.

Pd(OAc)_2
 $\text{PPh}_3, \text{NEt}_3$
 THF, N_2
 Temp., 1 h

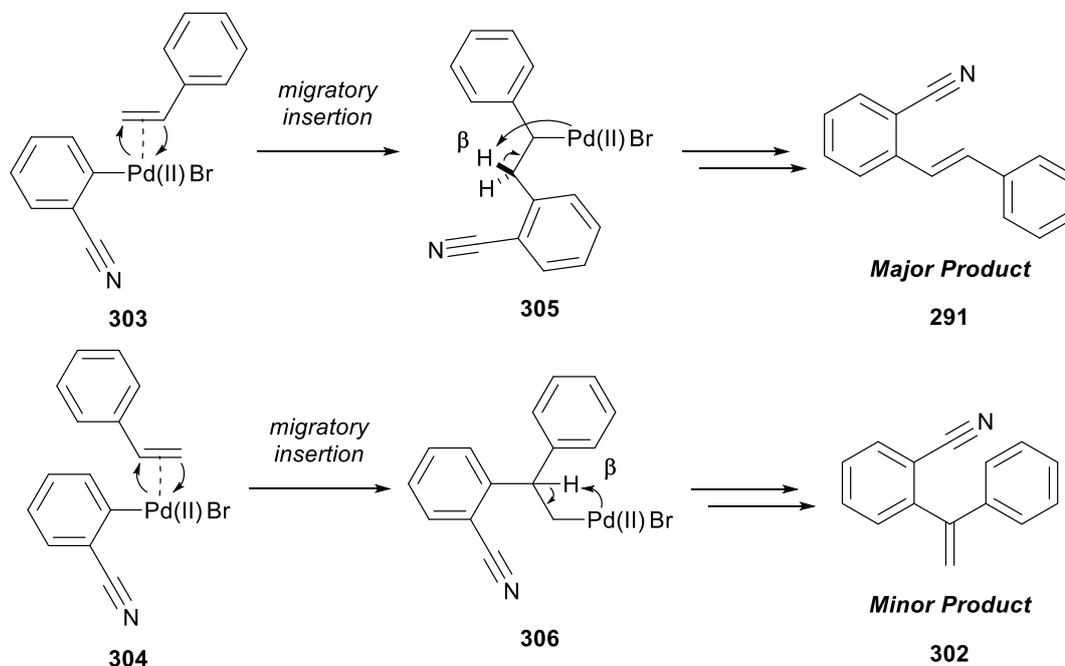
Major Product **Minor Product**
291 **302**

Entry	Temp. / °C	Loading / mol%		Conversion / % ^a	Product Ratio / % ^a	
		Pd(OAc) ₂	PPh ₃		291	302
1	100	2	4	19	0.94	0.06
2	140	2	4	50	0.93	0.07
3	140	4	8	56	0.93	0.07
4	140	5	10	61	0.93	0.07
5	160	4	8	75	0.92	0.08
6	160	5	10	92	0.92	0.08

^a Determined by ¹H NMR of the crude reaction product.

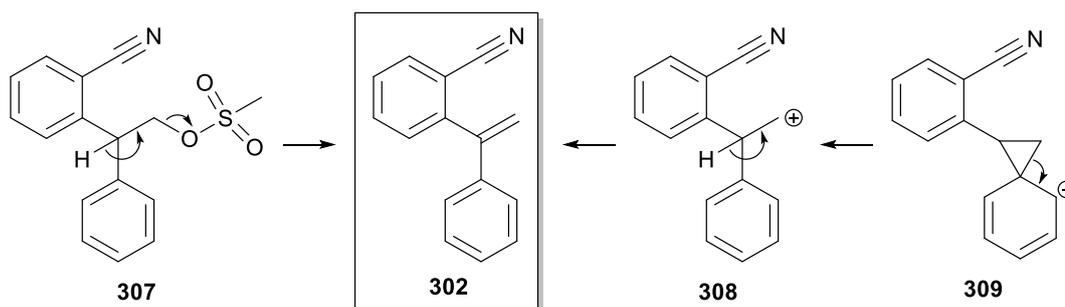
From Table 17 it is clear that conversion to the desired product **291** increases with both temperature and catalyst loading. Initially, increasing the temperature from 100 °C to 140 °C resulted in an increase in conversion from 19 % (entry 1) to 50 % (entry 2) respectively. It was then found that increasing the catalyst loading from 2 mol% to 4 mol% and finally 5 mol% caused an increase in conversion from 50 % (entry 2) to 56 % (entry 3) and 61 % (entry 4), whilst increasing the temperature by another 20 °C (160 °C) gave 75 % conversion to **291** (entry 5). The best results were found at 160 °C and 5 mol% catalyst loading (entry 6), with 92 % conversion being achieved – higher temperatures were not tested due to pressure concerns. Despite the reaction not reaching completion, the high level of conversion allowed the removal of 2-bromobenzonitrile from the desired product. However, it became clear that another product (**302**) was present in a small quantity; its identity was confirmed to be the regioisomer of **291** through a combination of various NMR analyses – distinguishable by two singlets at about $\delta_{\text{H}} = 5.90$ ppm and $\delta_{\text{H}} = 5.50$ ppm in ¹H NMR spectroscopy. The formation of this

regioisomer can be explained by the migratory insertion step in the Heck catalytic cycle (Scheme 38); the C-C bond can form at the less or more hindered end of the coordinated alkene (**303** or **304**), yielding σ -complexes **305** or **306**, respectively. Since the latter route is less preferred, **302** forms in only very small quantities. Furthermore, it is evident that the amount of this minor alkene product increases as temperature increases, albeit only slightly.



Scheme 38 Regioselectivity in the Heck reaction of styrene and 2-bromobenzonitrile.

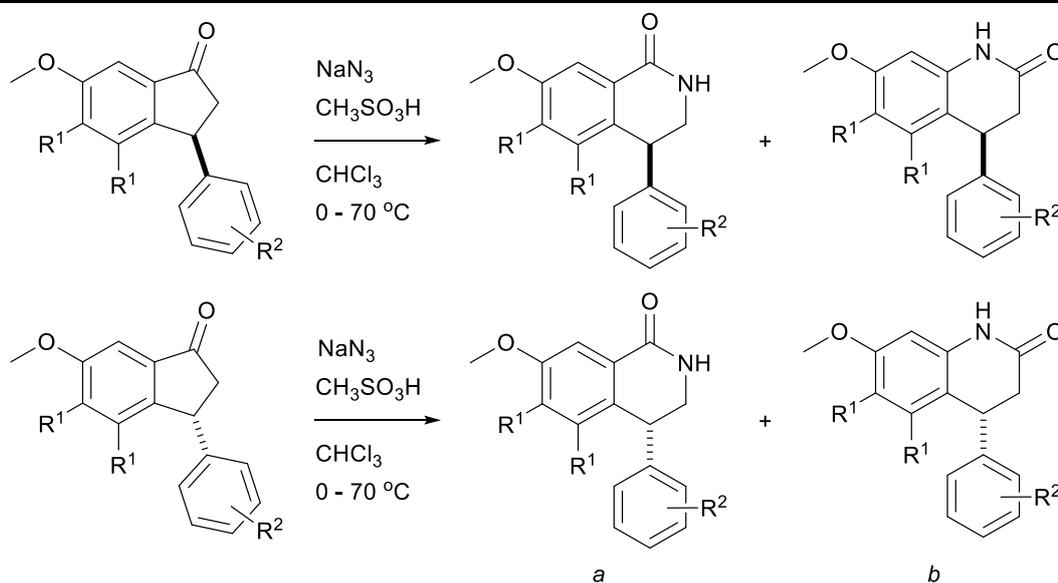
In light of the discovery of this alkene regioisomer, the ^1H NMR spectrum of the crude material acquired after the Schmidt reaction of 3-phenyl-indan-1-one **276** was re-examined to see if any of **302** had formed. Indeed, it was found that a very small amount of this alkene (3 %) had been produced, however the mechanism behind its formation is unclear. Two possible pathways have been identified (Scheme 39): direct elimination of the mesylate nitrile species **307**, or elimination of primary cation **308** that may form on opening of bicyclic intermediate **309**.



Scheme 39 Possible pathways for the formation of alkene **302**.

The enantiomerically enriched 3-aryl-indan-1-ones were then subjected to the Schmidt conditions previously employed, and the results are displayed in Table 18.

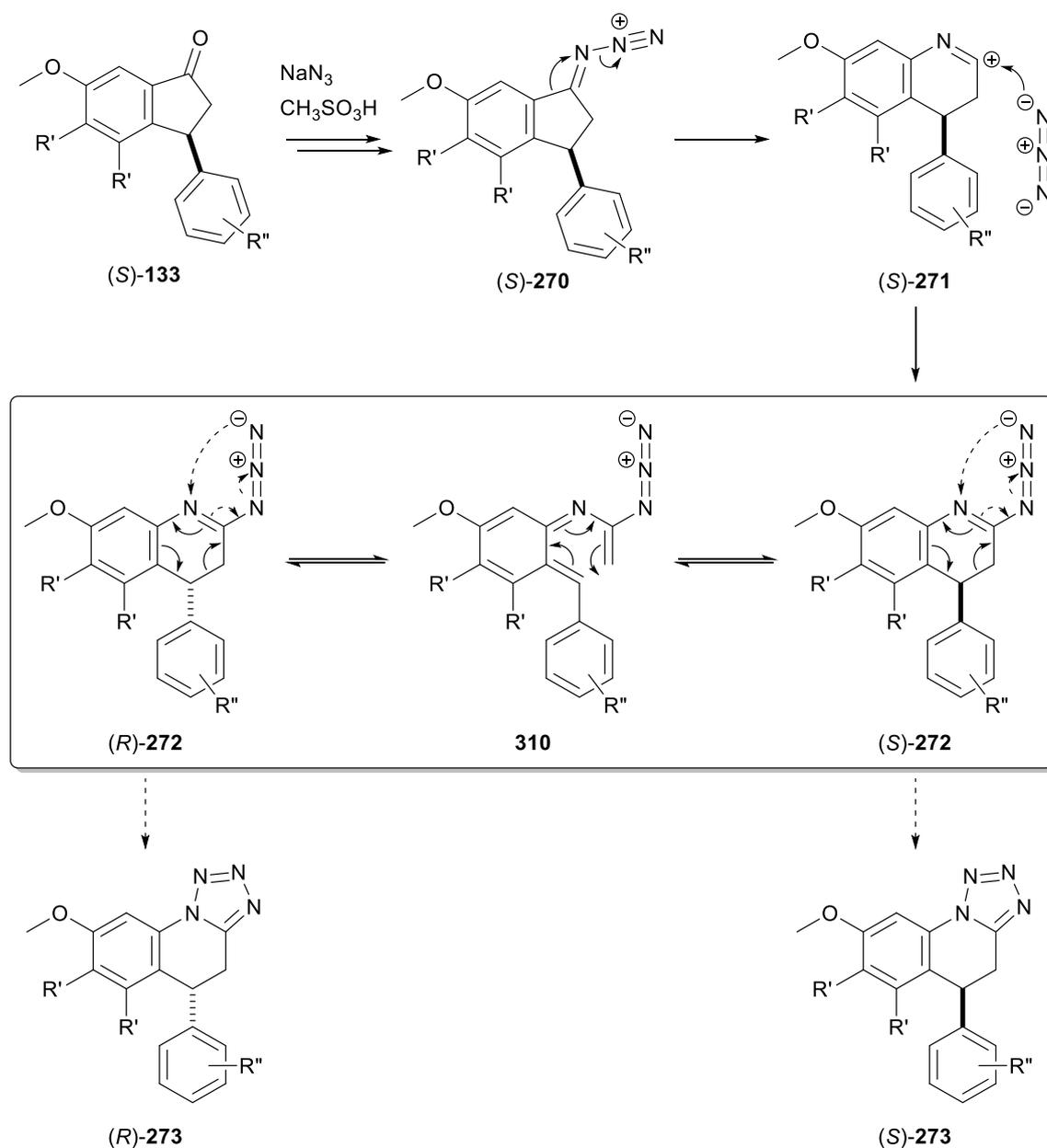
Table 18 Schmidt reactions of enantioenriched 3-aryl-indan-1-ones **118-125**.



Indan-1-one			Reaction Products					
R ¹	R ²		<i>a</i>	Yield / % ^a	e.e. / % ^b	<i>b</i>	Yield / % ^a	e.e. / % ^b
(<i>S</i>)-118			(<i>S</i>)-234	43	98	(<i>S</i>)-253	33	97
(<i>R</i>)-118	H	H	(<i>R</i>)-234	30	> 99	(<i>R</i>)-253	37	> 99
(<i>S</i>)-119			(<i>S</i>)-235	48	> 99	(<i>S</i>)-254	34	> 99
(<i>R</i>)-119	H	4-Cl	(<i>R</i>)-235	50	> 99	(<i>R</i>)-254	34	98
(<i>S</i>)-120			(<i>S</i>)-236	53	99	(<i>S</i>)-255	24	96
(<i>R</i>)-120	H	3,4-Cl	(<i>R</i>)-236	52	> 99	(<i>R</i>)-255	32	> 99
(<i>S</i>)-121			(<i>S</i>)-237	61	96	(<i>S</i>)-256	26	92
(<i>R</i>)-121	H	2,4-Cl	(<i>R</i>)-237	58	96	(<i>R</i>)-256	21	94
(<i>S</i>)-122			(<i>S</i>)-238	79	> 99	(<i>S</i>)-257	5	> 99
(<i>R</i>)-122	OCH ₃	H	(<i>R</i>)-238	81	> 99	(<i>R</i>)-257	5	> 99
(<i>S</i>)-123			(<i>S</i>)-239	78	91	(<i>S</i>)-258	4	> 99
(<i>R</i>)-123	OCH ₃	4-Cl	(<i>R</i>)-239	67	99	(<i>R</i>)-258	5	> 99
(<i>S</i>)-124			(<i>S</i>)-240	82	99	(<i>S</i>)-259	4	> 99
(<i>R</i>)-124	OCH ₃	3,4-Cl	(<i>R</i>)-240	78	> 99	(<i>R</i>)-259	3	97
(<i>S</i>)-125			(<i>S</i>)-241	89	96	(<i>S</i>)-260	3	93
(<i>R</i>)-125	OCH ₃	2,4-Cl	(<i>R</i>)-241	84	96	(<i>R</i>)-260	2	96

^a Ratio determined by ¹H NMR; ^b enantiomeric excess calculated using chiral HPLC.

Excellent enantioselectivities were observed for all dihydroisoquinolinones and dihydroquinolinones, however all tetrazoles were formed as racemic mixtures, hence their omission from Table 18. This observation was unexpected and sheds new light on the mechanism behind tetrazole formation; where it was previously believed that addition of hydrazoic acid was directly followed by electrocyclisation to give the product (Scheme 34), it is now clear that an additional step must be present, one that breaks a C-C bond next to the chiral carbon atom that results in a loss of stereochemical information. A new mechanism that accounts for the racemisation observed in this work is presented in Scheme 40.



Scheme 40 Modified mechanism to account for tetrazole racemisation.

It is now thought that an additional 6π electrocyclisation process (solid arrows) takes place alongside the one that yields the product tetrazole (dashed arrows); electrocyclic ring-opening in **272** gives the conjugated species **310**, which then ring-closes again to give the opposite enantiomer of **272** – hydrazoic acid must add to cation **271** prior to any electrocyclisations otherwise the lactam products would also racemise. For complete racemisation to occur these electrocyclic ring-opening and ring-closing steps must be both reversible and faster than the electrocyclisation that affords tetrazole.

3.2.3 Anti-inflammatory Compound 6-B345TTQ – A Synthetic Target

As discussed in **Section 1.4**, former work within our group involved the attempted synthesis of both enantiomers of a non-cytotoxic anti-inflammatory compound, 6-B345TTQ (**99**), with the intention of identifying an active enantiomer. The potential advantages of using single drug enantiomers are many, for instance greater efficacy and thus reduced dosage and cost.¹⁹⁰ Compound **99** was previously only patented and published as a racemate, alongside its non-active 2,3,4-trimethoxy- counterpart (**100**) (Figure 13).^{15, 16}

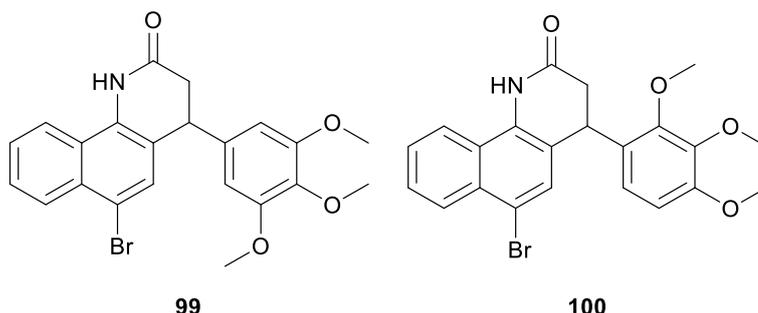
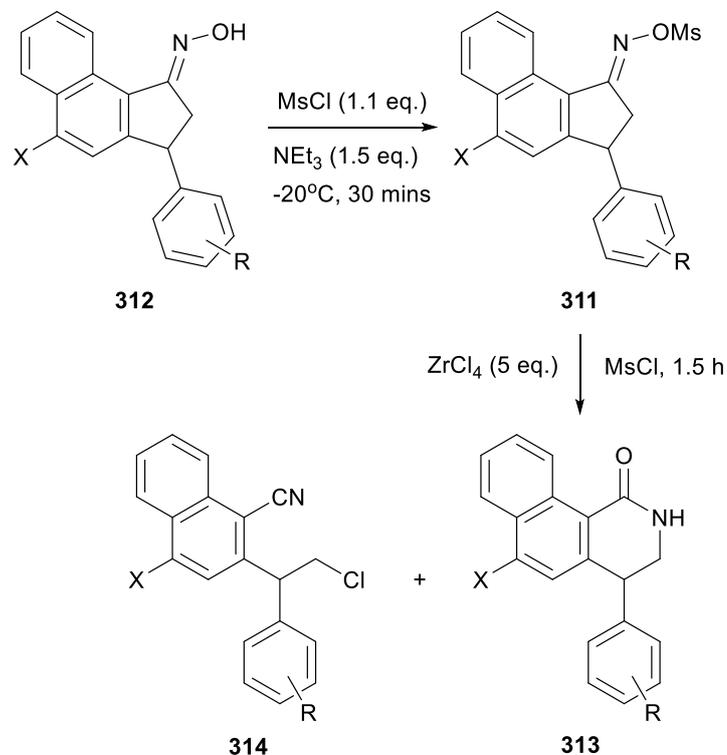


Figure 13 Anti-inflammatory compound 6-B345TTQ (**99**) and its inactive analogue 6-B234TTQ (**100**).

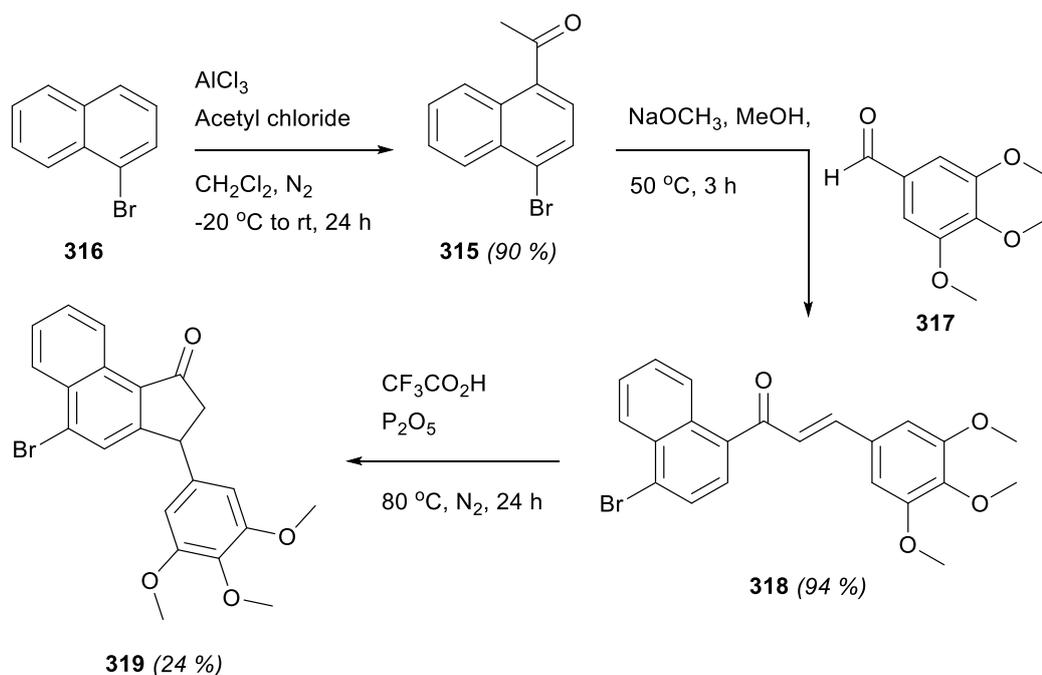
This prior work employed a Beckmann rearrangement in an attempt to synthesise anti-inflammatory target **99** in addition to structurally similar 4-aryl-3,4-dihydroquinolin-2-ones;¹³⁶ a series of naphthyl-indan-1-ones **107** were initially made and then converted into their corresponding oxime mesylates (**311**) – via oxime intermediates **312** – before being exposed to Beckmann conditions presented by Torisawa *et al.*^{130, 135} The reactions gave a mixture of products (Scheme 41), neither of which were the desired dihydroquinolinone substrates – substituents on the indanone ring have been shown to have a profound effect on the ratio of isomers formed.¹³¹ The ratio of dihydroisoquinolinone products (**313**) and nitrile products (**314**) varied greatly on the nature of substituents on the aromatic rings, with seemingly no obvious trends in the

obtained ratio. This nitrile species was believed to form via the fragmentation mechanism shown in Scheme 35 (see **Section 3.2.2**), with chloride acting as the nucleophile instead of a mesylate anion. Other catalyst systems were also tried, but only the starting material oxime and the corresponding ketone were isolated upon workup.¹³⁶



Scheme 41 Unsuccessful Beckmann approach towards 6-B345TTQ (**99**) and related dihydroquinolinones.¹³⁶

In light of the previous success of the Schmidt reaction of 3-aryl-indan-1-ones **118-125** with respect to dihydroquinolinone formation, it was believed that this transformation could be utilised as an alternative pathway towards the synthesis of the individual enantiomers of anti-inflammatory target 6-B345TTQ (**99**). To this end, the indan-1-one precursor of this target molecule was synthesised in the same way as 3-aryl-indan-1-ones **118-125**, as described in **Section 2.1** – the overall synthetic route is shown in Scheme 42. Since one of the starting materials of the process, 4-bromo-1-acetonaphthone (**315**), was not commercially available, it was first synthesised via Friedel–Crafts acylation of 1-bromonaphthalene (**316**) using acetyl chloride and aluminium chloride as a Lewis acid. This was followed by a Claisen–Schmidt condensation reaction of **315** with 3,4,5-trimethoxybenzaldehyde (**317**), then subsequent Nazarov cyclisation of chalcone **318** yielded the 6-B345TTQ precursor indan-1-one (**319**). P₂O₅ was found to be necessary in this cyclisation step to prevent formation of by-products as discussed in **Section 2.1.3**, in line with previous work by the Fox group.¹³⁶



Scheme 42 Overall synthetic route towards 6-B345TTQ precursor indan-1-one **319**.

The regioselectivity of the Friedel–Crafts acylation is rather unexpected when one considers the inherent substituent effects of bromine. As discussed in **Section 2.1.3**, halogens exhibit a negative inductive effect (-I) but a positive mesomeric effect (+M), therefore they will deactivate the aromatic ring to which they are attached but will direct any electrophilic attack to the *ortho*- and *para*- positions ($I > M$);^{158, 159} indeed, this deactivation causes the Friedel–Crafts acylation of chlorobenzene to be particularly slow relative to benzene.¹⁹¹ One would therefore expect electrophilic aromatic substitution of 1-bromonaphthalene to occur on the non-substituted ring, primarily at C5 or C8, although substitution at this latter position is subject to *peri* interactions with the group attached to C1 and thus may be unfavourable on steric and/or electronic grounds.¹⁹² In reality, however, for the Friedel–Crafts acylation of 1-bromo and 1-chloronaphthalene it is the 1,4-regioisomer that predominates.^{136, 191, 193} The reasons behind this regiochemical outcome are currently unclear, although for this π -system it appears as though the Cl/Br atom is of the $I < M$ type, whereby it is able to donate electrons much more effectively to the α -naphthyl *para*- position.

Previous work within the Fox group showed that reducing the temperature at which the Friedel–Crafts acylation was performed resulted in an increased preference for substitution at the 4-position.¹³⁶ The reaction was further optimised in this work, with the best result obtained through the very slow addition (*ca.* 5.5 hours) of 1-bromonaphthalene to a stirred suspension of AlCl_3 and acetyl chloride in dry CH_2Cl_2 at -20°C . These

conditions gave 4-bromo-1-acetonaphthone (**315**) in excellent yield (90 %) and regioselectivity (>97 % acylation in the 4-position). The 1,4-configuration was confirmed by comparison to literature reports,¹⁹⁴ distinguishable by the presence of two doublets in the aromatic region of the ¹H NMR spectrum ($\delta_{\text{H}} = 7.82$ ppm and $\delta_{\text{H}} = 7.73$ ppm), which would only be expected for this regioisomer (Figure 33). The regioselectivity of the reaction was determined through integration of the CH₃ peaks at $\delta_{\text{H}} = 2.75$ ppm (1,5-isomer) and $\delta_{\text{H}} = 2.73$ ppm (1,4-isomer) in the ¹H NMR spectrum of the crude material.

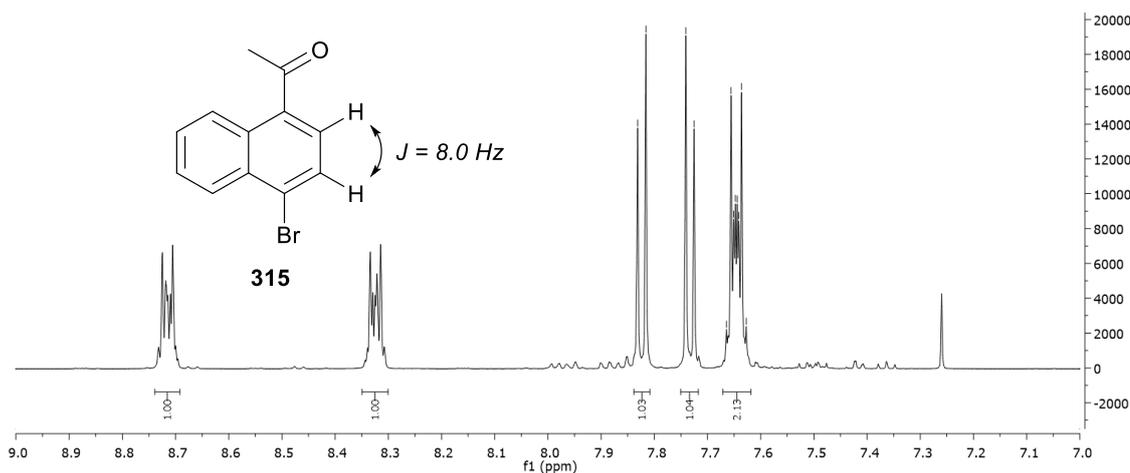
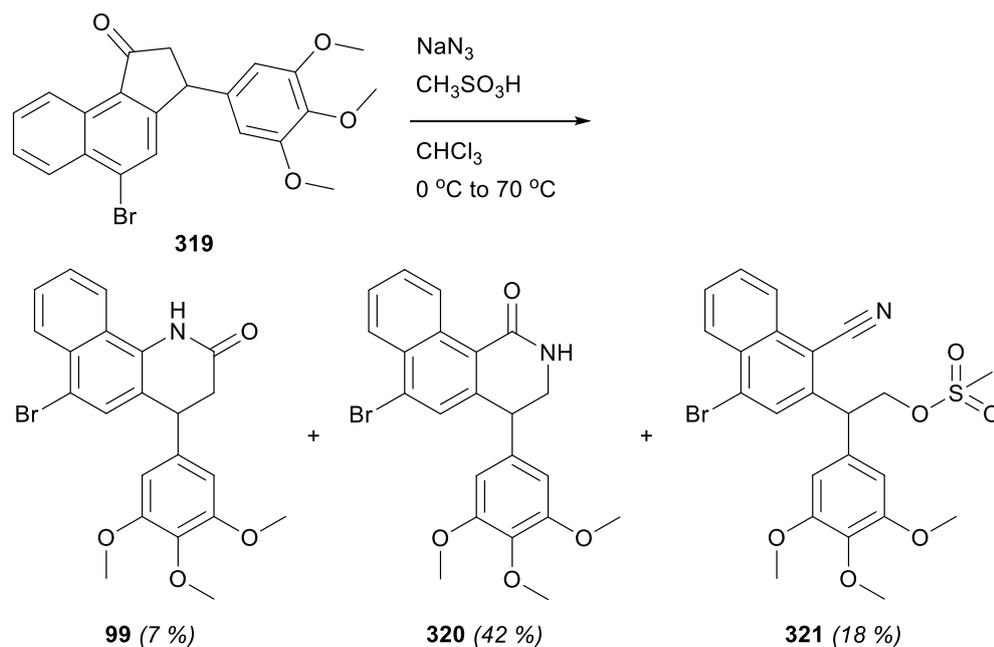


Figure 33 Confirmation of 4-bromo-1-acetonaphthone (**315**) by ¹H NMR spectroscopy.

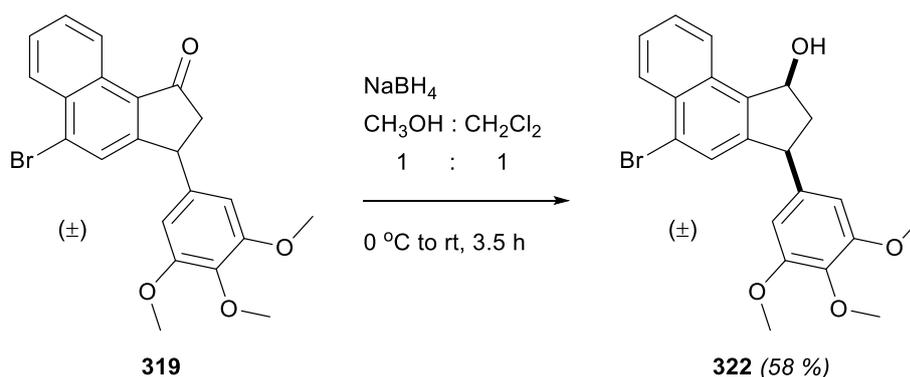
Similarly excellent yields were obtained for the subsequent Claisen–Schmidt condensation, however the final Nazarov cyclisation step was low yielding, which was expected due to the unsuitability of the substrate towards the reaction – the electron-rich nature of the 3-aryl ring significantly slows desired cyclisation (see **Section 2.1.3**).¹⁹⁵

The Schmidt conditions previously utilised (see **Section 3.2.2**) – methanesulfonic acid and sodium azide in chloroform at 70 °C – were applied to indan-1-one **319** in an effort to synthesise the anti-inflammatory target 6-B345TTQ (**99**) as a racemate (Scheme 43); this would serve as a proof of concept before the synthesis of the individual enantiomers is pursued. The reaction afforded racemic **99**, as desired, albeit in a low yield (7 %) – the identity of **99** was confirmed through its separate synthesis via a 2-step method devised by a previous member of the Fox group.¹³⁶ Its isomer **320** formed as the major isomer (42 %), alongside a small amount of unreacted starting material (5 %) and an unknown material that appeared to decompose back to indan-1-one **319** during purification by column chromatography. In addition, a nitrile product **321** was generated (18 %), with a structure similar to **288** and **289** that were previously seen in the Schmidt reactions of indan-1-one **4** and 3-phenyl-indan-1-one **276**, respectively. The formation of this species is believed to be caused by the aforementioned Beckmann fragmentation process.^{127, 171}



Scheme 43 Schmidt reaction of 6-B345TTQ precursor indan-1-one **319**.

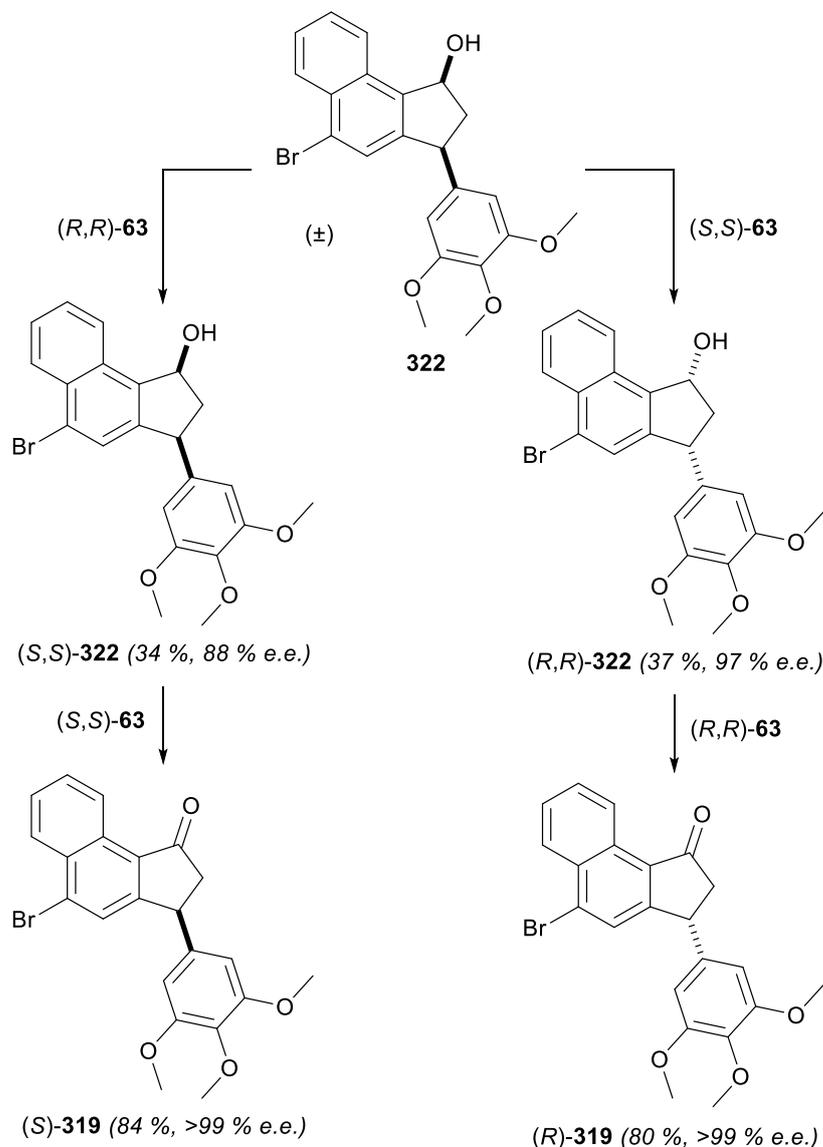
With the knowledge that the target drug (\pm)-6-B345TTQ can be successfully synthesised via the Schmidt reaction of its precursor indan-1-one **319**, albeit in very low yield (1.4 % overall yield), attention turned towards the synthesis of the individual enantiomers. This was accomplished utilising the transformations previously reported within this project – a diastereoselective reduction followed by an enantiospecific oxidation (see **Section 2.2**). Indan-1-one **319** was first exclusively reduced into the *cis*-diastereomer of indan-1-ol **322** using sodium borohydride (Scheme 44).



Scheme 44 *Cis*-reduction of **319** by NaBH_4 to give exclusive formation of **322**.

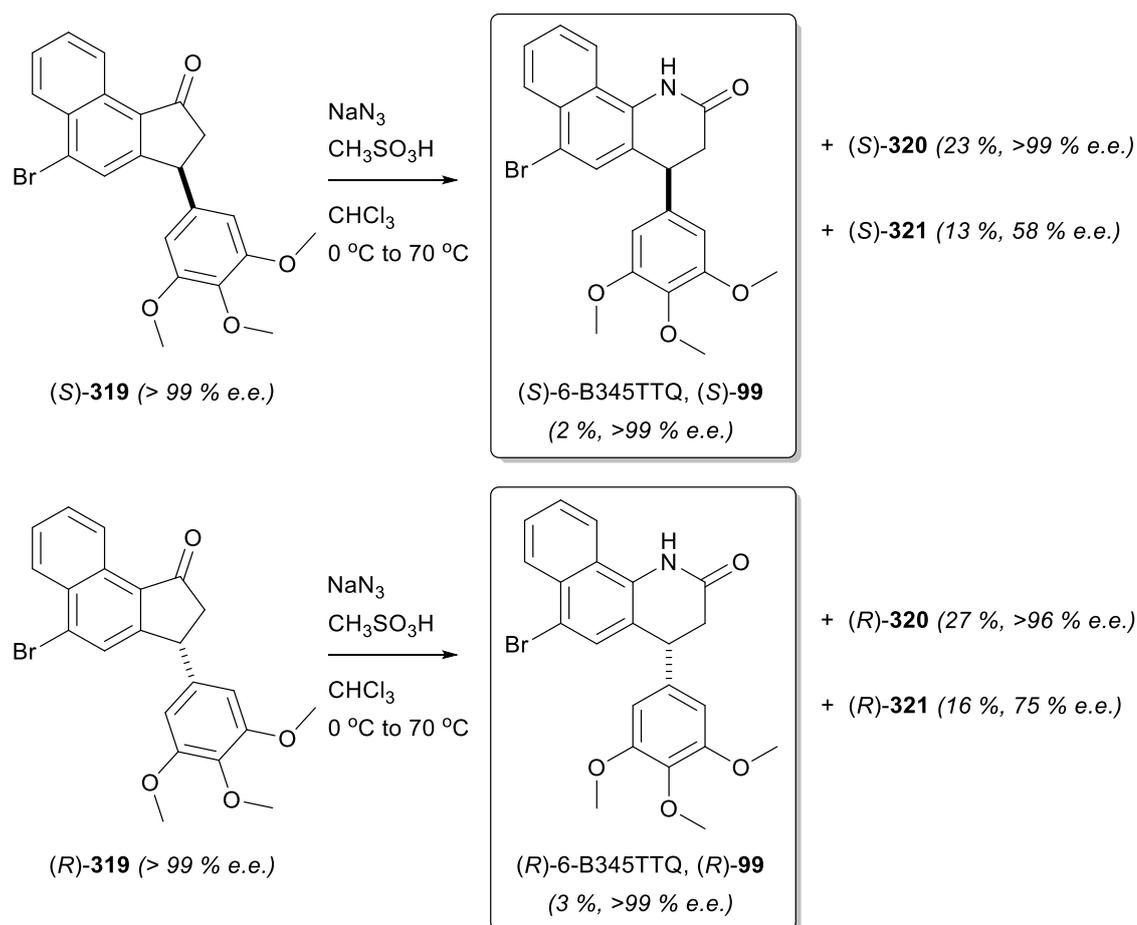
To ensure both enantiomers of drug target **99** were ultimately obtained in as high enantiomeric excess as possible, successive oxidative kinetic resolutions were performed utilising Noyori's ruthenium catalyst **63** and method;¹⁹⁶ first *cis*-indan-1-ol **322** was separated into two batches, with each batch oxidised with opposite enantiomers of **63** –

one using (*S,S*)-**63** and the other (*R,R*)-**63** – and then the recovered enantioenriched alcohols were individually subjected to another oxidation using the ruthenium catalyst derived from the opposite enantiomer of the TsDPEN ligand (Scheme 45).



Scheme 45 Formation of both enantiomers of 6-B345TTQ precursor **319** via successive oxidative kinetic resolutions of *cis*-**322**.

With both enantiomers of the 6-B345TTQ precursor **319** in hand, the final step towards the anti-inflammatory target **99** involved the Schmidt reaction, using the same conditions as those employed previously within the racemic synthesis (Scheme 46). As expected, the reaction of both enantiomers gave the same products in similar ratios as the racemic transformation, affording (*R*)- and (*S*)-dihydroquinolinone **99** and (*R*)- and (*S*)-dihydroisoquinolinone **320** as the minor and major isomer, respectively, in 96-99 % e.e. In addition, both enantiomers of the nitrile product **321** also formed, however the e.e. of each enantiomer of this product was considerably lower than that of the starting ketones.



Scheme 46 Schmidt reaction giving both enantiomers of target 6-B345TTQ (**99**).

Overall, the long term aim of the Fox group – to synthesise the individual enantiomers of non-cytotoxic anti-inflammatory compound 6-B345TTQ (**99**) – has now been achieved, with both enantiomers obtained in >99 % e.e. The overall yields for both enantiomers, starting from 1-bromonaphthalene (**316**), however, was unfortunately extremely low. The complete synthetic route can be broken down into three parts: the synthesis of the racemate of precursor indan-1-one **319**, the resolution of **319** into its individual enantiomers, and finally ring expansion to give both enantiomers of **99**. The yield for the synthesis of the racemic indan-1-one intermediate was 20 %, low due to a difficult Nazarov cyclisation step. The subsequent resolution afforded both the (*R*)- and (*S*)- enantiomer in >99 % e.e. and 17 % overall yield (for each enantiomer). The final part, the Schmidt reaction of the individual enantiomers of indan-1-one **319**, gave (*R*)- and (*S*)-6-B345TTQ in 2 % and 3 % yields respectively – the formation of this particular lactam is highly disfavoured. Combining the yields for each part gives the total overall yield for both (*R*)- and (*S*)-**99** as <1.0 % (0.07 % and 0.10 %, respectively).

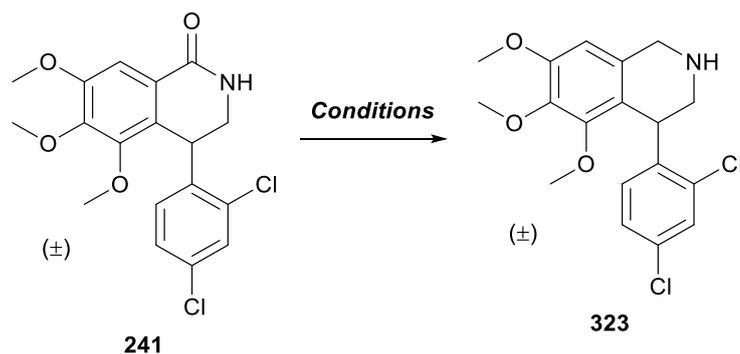
3.3 Synthesis of Tetrahydroisoquinolines

Due to the important applications of tetrahydroisoquinolines, their synthesis has been extensively studied. Classical approaches towards this class of compound involves intramolecular cyclisation using the ring closure of iminium intermediates via the Pictet–Spengler,¹⁹⁷ or Bischler–Napieralski reactions.¹⁹⁸ In recent years substantial efforts have been made into the development of tetrahydroisoquinolines, such as C–H activation strategies,¹⁹⁹ acid-catalysed cyclisations,²⁰⁰ and intramolecular Friedel–Crafts reactions.²⁰¹ The synthesis of important 4-aryl-tetrahydroisoquinolines is not as prevalent, although the most common routes include the intramolecular cyclisation of *N*-benzyl- β -hydroxyphenethylamines,²⁰² or α -hydroxy- β -amino esters,²⁰³ and direct arylation of tetrahydroisoquinolines at the C-4 position.²⁰⁴

Another approach towards 4-aryl-tetrahydroisoquinolines is the reduction of the corresponding lactam. The reduction of amides to amines is an important transformation in the pharmaceutical industry,²⁰⁵ although strong reducing agents are typically required due to the high stability of secondary amides, for instance LiAlH₄,²⁰⁶⁻²⁰⁸ diborane,²⁰⁹ borane-SMe₂,²¹⁰ or DIBAL-H.²¹¹ A number of attempts at achieving secondary amide reduction under milder conditions (reagents and/or temperature) have been reported, typically involving activation of the carbonyl group prior to reduction; methods include activation using trimethylsilyl chloride and subsequent reduction with a borohydride reagent (e.g. NaBH₄ or LiBH₄),²¹² or LiAlH₄,²¹³ or activation with triflic anhydride and NaBH₄ reduction.^{214, 215}

3.3.1 Reduction of Dihydroisoquinolinones

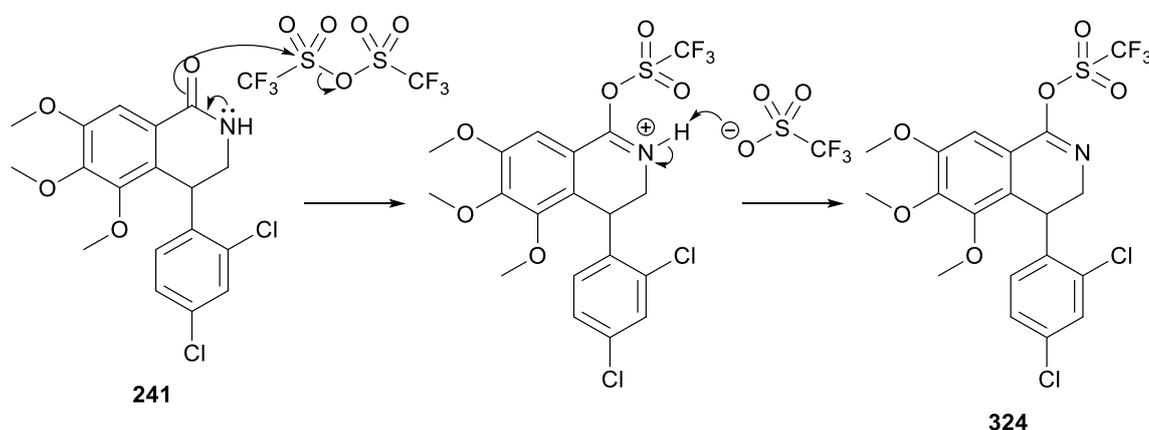
In order to achieve the desired reduction of dihydroisoquinolinones **234-241**, a number of methods were examined using racemic **241** (Table 19), beginning with milder conditions. Initial tests involved a borane-based reduction, using either NaBH₄ (entries 1-3) or LiBH₄ (entry 4) as per reports by Giannis *et al.*,²¹² but these were generally unsuccessful with either no or very little conversion to the desired tetrahydroisoquinoline **323**. A procedure from Huang *et al.* was then attempted comprising a two-step process, the first being activation of the carbonyl group with triflic anhydride and the second step utilising NaBH₄ as a reductant.²¹⁴

Table 19 Optimisation of reduction conditions of dihydroisoquinolinone **241**.

Entry ^a	Conditions	Yield / % ^b
1	NaBH ₄ (2.0 eq.), TMSCl (4.0 eq.), THF, 80 °C, 18 h.	- ^c
2	NaBH ₄ (4.0 eq.), TMSCl (4.0 eq.), THF, 80 °C, 18 h.	- ^c
3	NaBH ₄ (4.0 eq.), H ₂ SO ₄ (4.0 eq.), THF, 80 °C, 18 h.	- ^c
4	LiBH ₄ (4.0 eq.), TMSCl (4.0 eq.), THF, 80 °C, 18 h.	12 ^c
5	(i) Tf ₂ O (1.1 eq.), CH ₂ Cl ₂ , 0 °C, 0.5 h. (ii) NaBH ₄ (1.3 eq.), THF, rt, 18 h.	11 ^c (23) ^d
6	(i) Tf ₂ O (3.0 eq.), CH ₂ Cl ₂ , 0 °C, 0.5 h. (ii) NaBH ₄ (4.0 eq.), THF, rt, 18 h.	42 ^c (16) ^d
7	(i) Tf ₂ O (3.0 eq.), CH ₂ Cl ₂ , 0 °C, 0.5 h. (ii) NaBH ₄ (4.0 eq.), THF, 80 °C, 18 h.	- ^c
8	(i) (COCl) ₂ (3.0 eq.), CH ₂ Cl ₂ , 0 °C, 1 h. (ii) NaBH ₄ (3.0 eq.), THF, 80 °C, 1 h.	- ^c
9	LiAlH ₄ (s) (1.7 eq.), THF, 80 °C, 2 h.	1 ^c
10	LiAlH ₄ (s) (3.0 eq.), THF, 80 °C, 18 h.	9 ^c
11	LiAlH ₄ (2.0 M) (3.0 eq.), THF, 80 °C, 18 h.	92 ^e

^a Reaction based on dihydroisoquinolinone **241** (38 mg, 0.10 mmol); ^b Isolated yield; ^c Reaction incomplete; ^d Isolated by-product **324**; ^e Crude yield.

Increasing the amount of both Tf_2O and NaBH_4 led to a greater formation of the desired amine **323** from 11 % (entry 5) to 42 % (entry 6), although full conversion was still not achieved. A by-product was isolated in these reactions, which was determined to be imine **324**, believed to be an intermediate that forms on reaction of amide **241** with Tf_2O via the mechanism shown in Scheme 47. It was thought that by increasing the reaction temperature of the second step this intermediate could be further pushed towards the product amine, however this resulted in no conversion (entry 7). Changing the activating agent to oxalyl chloride also gave no conversion to **323** (entry 8); the ^1H NMR spectrum of the reaction mixture after initial removal of the $(\text{COCl})_2$ showed no starting material present and instead a mixture of indiscernible compounds, however after workup only starting material was present – possibly an imine intermediate similar to **324** formed, but this reformed the starting amide on workup with base.



Scheme 47 Formation of imine intermediate **324**.

The final reduction method attempted involved the use of LiAlH_4 , a strong reducing agent, commonly used to reduce secondary amides such as dihydroisoquinolinones.^{207, 208} To begin, solid LiAlH_4 was tried, yielding very little of the amine **323** when 1.7 equivalents of the reductant employed at $80\text{ }^\circ\text{C}$ for 2 hours (1 %, entry 9). Increasing the amount of LiAlH_4 to 3.0 equivalents and reacting at $80\text{ }^\circ\text{C}$ for 18 hours led to greater formation of **323** (9 %, entry 10), although the reaction still failed to progress very far. It was thought that the reason for low conversion was the very low solubility of commercial solid LiAlH_4 in THF, despite the reasonable published solubility ($0.13\text{ g/mL @ }25\text{ }^\circ\text{C}$).²¹⁶ To circumvent this, a commercial 2.0 M solution of LiAlH_4 in THF was employed (entry 11), giving full conversion and high crude yield (92 %) of the desired amine **323** under the conditions previously used. The product was formed in high purity so was not purified further.

Due to the success seen in the reduction of amide **241** using the 2.0 M solution of LiAlH₄ at 80 °C for 18 hours, dihydroisoquinolinones **234-241** were reduced to their corresponding amines using these conditions on a larger scale (Table 20).

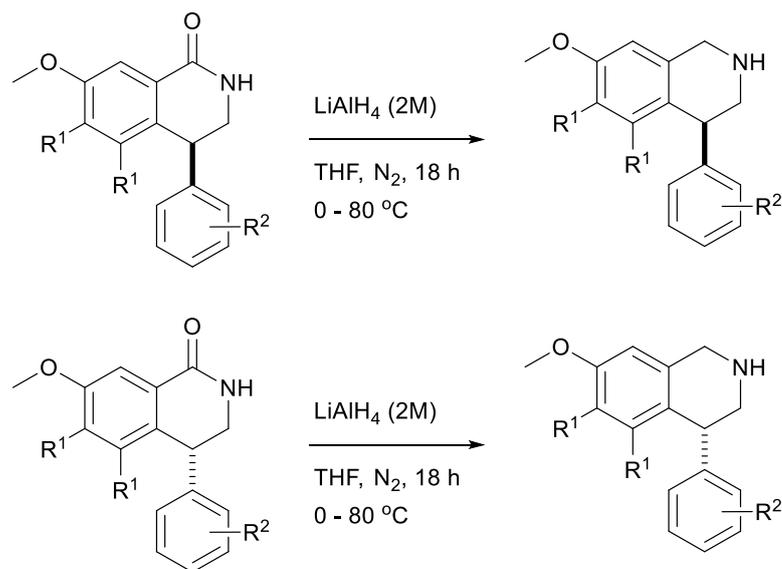
Table 20 LiAlH₄ reductions of racemic dihydroisoquinolinones **234-241**.

Dihydroisoquinolinone			Tetrahydroisoquinoline	
	R ¹	R ²		Yield / % ^a
234	H	H	325	91
235	H	4-Cl	326	84
236	H	3,4-Cl	327	77
237	H	2,4-Cl	328	73
238	OCH ₃	H	329	75
239	OCH ₃	4-Cl	330	82
240	OCH ₃	3,4-Cl	331	65
241	OCH ₃	2,4-Cl	323	65

^a Isolated yield.

Moderate to high yields were achieved for the reduction of each amide. The reduction was lower yielding for trimethoxy- substrates **238-241**, and generally the greater the degree of substitution of the 4-aryl group the lower the yield; this suggests the reduction has some steric control, and works better for smaller, less bulky amides.

The enantiomerically enriched dihydroisoquinolinones were then subjected to the reduction conditions previously employed, and the results are displayed in Table 21. As in the case of their racemic counterparts, the enantiomerically enriched amides **234-241** were successfully reduced, in typically high (crude) yields. However, it was not possible to determine the e.e. of these compounds via chiral HPLC due to their high polarity, with the HPLC trace typically containing broad elongated peaks with little-to-no separation.

Table 21 LiAlH₄ reductions of enantioenriched dihydroisoquinolinones **234-241**.

Dihydroisoquinolinone			Tetrahydroisoquinoline	
	R ¹	R ²		Yield / % ^a
(<i>S</i>)-234			(<i>S</i>)-325	94
(<i>R</i>)-234	H	H	(<i>R</i>)-325	94
(<i>S</i>)-235			(<i>S</i>)-326	92
(<i>R</i>)-235	H	4-Cl	(<i>R</i>)-326	97
(<i>S</i>)-236			(<i>S</i>)-327	96
(<i>R</i>)-236	H	3,4-Cl	(<i>R</i>)-327	94
(<i>S</i>)-237			(<i>S</i>)-328	88
(<i>R</i>)-237	H	2,4-Cl	(<i>R</i>)-328	92
(<i>S</i>)-238			(<i>S</i>)-329	90
(<i>R</i>)-238	OCH ₃	H	(<i>R</i>)-329	86
(<i>S</i>)-239			(<i>S</i>)-330	89
(<i>R</i>)-239	OCH ₃	4-Cl	(<i>R</i>)-330	81
(<i>S</i>)-240			(<i>S</i>)-331	93
(<i>R</i>)-240	OCH ₃	3,4-Cl	(<i>R</i>)-331	85
(<i>S</i>)-241			(<i>S</i>)-323	90
(<i>R</i>)-241	OCH ₃	2,4-Cl	(<i>R</i>)-323	93

^a Isolated crude yield.

3.3.2 Acetylation of Tetrahydroisoquinolines for HPLC Analysis

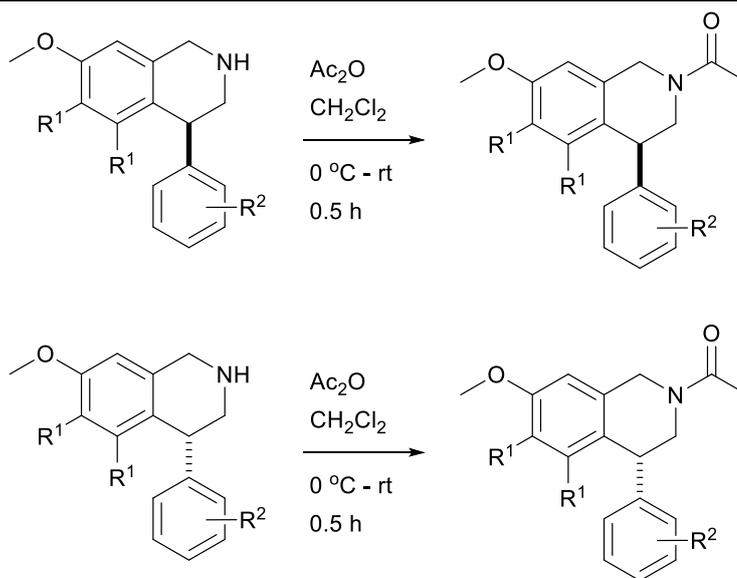
In order to effectively measure the enantiomeric excess of amines **323** and **325-331** by HPLC their conversion to a class of compound with less polarity and ideally a different functionality was necessary. To this end, racemic amines **323** and **325-331** were acetylated using acetic anhydride in CH₂Cl₂ at room temperature for 30 minutes.²¹⁷ Acetamides **332-339** were formed as a mixture of rotamers albeit in excellent yields and high (structural) purity and, as such, were not purified further (Table 22) – no attempts were made to identify the major conformation as this was unnecessary for their purpose.

Table 22 Acetylation of racemic tetrahydroisoquinolines **323** and **325-331**.

Tetrahydroisoquinoline		Acetamide	
	R ¹	R ²	Yield / % ^a
325	H	H	332 85
326	H	4-Cl	333 87
327	H	3,4-Cl	334 88
328	H	2,4-Cl	335 88
329	OCH ₃	H	336 88
330	OCH ₃	4-Cl	337 89
331	OCH ₃	3,4-Cl	338 90
323	OCH ₃	2,4-Cl	339 90

^a Isolated crude yield.

Retention times for both enantiomers of the racemic acetamides were then acquired by chiral HPLC. With these in hand, the enantiomerically enriched tetrahydroisoquinolines were acetylated akin to their corresponding racemates to give enantiomerically enriched acetamides **332-339** in excellent (crude) yields and enantiomeric excesses – the results are displayed in Table 23. The retention of stereochemical information between lactams **234-241** and acetamides **332-339** heavily suggests that amines **323** and **325-331** were also formed in very high e.e.

Table 23 Acetylation of enantioenriched tetrahydroisoquinolines **323** and **325-331**.

Tetrahydroisoquinoline		Acetamide		
R ¹	R ²	Yield / % ^a	e.e. / % ^b	
(<i>S</i>)- 325	H	(<i>S</i>)- 332	98	96
(<i>R</i>)- 325	H	(<i>R</i>)- 332	98	96
(<i>S</i>)- 326	H	(<i>S</i>)- 333	95	> 99
(<i>R</i>)- 326	4-Cl	(<i>R</i>)- 333	99	98
(<i>S</i>)- 327	H	(<i>S</i>)- 334	86	91
(<i>R</i>)- 327	3,4-Cl	(<i>R</i>)- 334	97	99
(<i>S</i>)- 328	H	(<i>S</i>)- 335	97	97
(<i>R</i>)- 328	2,4-Cl	(<i>R</i>)- 335	97	95
(<i>S</i>)- 329	OCH ₃	(<i>S</i>)- 336	91	94
(<i>R</i>)- 329	H	(<i>R</i>)- 336	91	> 99
(<i>S</i>)- 330	OCH ₃	(<i>S</i>)- 337	89	95
(<i>R</i>)- 330	4-Cl	(<i>R</i>)- 337	96	> 99
(<i>S</i>)- 331	OCH ₃	(<i>S</i>)- 338	95	97
(<i>R</i>)- 331	3,4-Cl	(<i>R</i>)- 338	85	> 99
(<i>S</i>)- 323	OCH ₃	(<i>S</i>)- 339	92	95
(<i>R</i>)- 323	2,4-Cl	(<i>R</i>)- 339	92	99

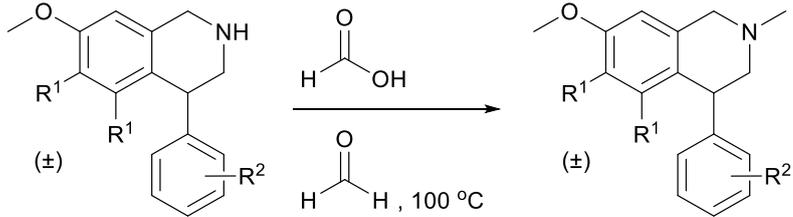
^a Isolated crude yield; ^b Enantiomeric excess calculated using chiral HPLC.

3.3.3 Antidepressant Compound Diclofensine – A Synthetic Target

To give further application to this work, it was our desire to make the individual enantiomers of a known bioactive tetrahydroisoquinoline, as well as related compounds. Diclofensine (**198**) is one such derivative – introduced in **Section 3.1.2** – and is very similar in structure to those previously synthesised (see **Section 3.3.1**). It was developed by Hoffmann-La Roche Inc. in the mid-1970s in the search for a ‘new generation’ of antidepressants.⁵⁸ Early clinical trials suggested the usefulness of this new drug as an antidepressant,^{218,219} whereby patients suffering from moderate to severe depression were treated with diclofensine and improvements were observed in their moods, with relatively few side effects.²²⁰ These trials also provided the first estimates of the range of clinical dosage. Subsequent studies on the drug found that it acts as a reuptake inhibitor of dopamine,^{221, 222} norepinephrine,²²³ and serotonin, with affinities (K_i) of 16.8 nM, 15.7 nM, and 51.0 nM for their respective transporters.²²⁴ The (+)-enantiomer, corresponding to (*S*)-diclofensine, was also discovered to be 50-80 fold more active than its (–)-antipode.²¹⁸ Despite these findings, the drug was ultimately dropped from clinical development due to concerns about its abuse potential – results from some investigations indicated similar behavioural response (i.e. addiction) towards diclofensine as other psychomotor stimulants such as cocaine and amphetamine.^{225, 226}

Pharmacological profiling of novel psychoactive substances like diclofensine is still ongoing,²²⁷ as a way of obtaining better understanding of their psychotropic effects and toxicity. In 2018, Luethi *et al.* investigated the potential of diclofensine to inhibit the norepinephrine, dopamine, and serotonin transporters in human embryonic kidney cells stably transfected with the respective transporters.²²² It was found to potently bind to the monoamine transporters in the submicromolar range and had similar inhibition potential for all three transporters in the range of 2.5–4.8 μM. The pharmacological profile was also suggestive of stimulant properties and a potential for abuse.

The synthesis of diclofensine and analogues from tetrahydroisoquinolines **323** and **325-331** requires methylation of the amine nitrogen. One of the most common methods for the *N*-methylation of tetrahydroisoquinolines is the Eschweiler–Clarke reaction,^{228, 229} which has been used in the synthesis of a number of biologically interesting *N*-methylated tetrahydroisoquinolines,²³⁰⁻²³² and was even utilised in the synthesis of the antidepressant drug venlafaxine.²³³ The reaction allows the formation of tertiary methylamines from secondary amines via treatment with formaldehyde in the presence of formic acid. Attractively, the reaction does not produce quaternary ammonium salts, but instead will

Table 24 *N*-methylation of racemic tetrahydroisoquinolines **323** and **325-331**.

Tetrahydroisoquinoline		Methylated Amine	
R ¹	R ²		Yield / % ^a
325	H	346	40
326	H	347	75
327	H	198	77
328	H	348	96
329	OCH ₃	349	22
330	OCH ₃	350	45
331	OCH ₃	351	62
323	OCH ₃	352	79

^a Isolated yield.

With the knowledge that tetrahydroisoquinolines **323** and **325-331** can be successfully methylated at the nitrogen atom under Eschweiler–Clarke conditions, attention turned towards the *N*-methylation of the enantiomerically enriched species previously synthesised. The results of these reactions are displayed in Table 25.

As in the case of their racemic counterparts, the enantiomerically enriched amines **323** and **325-331** were successfully methylated, in varying (crude) yields. Similar to their parent tetrahydroisoquinolines it was unfortunately not possible to determine the enantiomeric excesses of these compounds via chiral HPLC due to their high polarity, with the HPLC trace typically containing broad elongated peaks with little-to-no separation. However, since acetylated amines **332-339** were formed in very high enantiomeric excesses with retention of stereochemical information (see **Section 3.3.2**), and that the Eschweiler–Clarke reaction has been shown to proceed without racemisation,²³⁴ it can be assumed that methylated amines **198** and **346-352** were also formed in very high e.e.

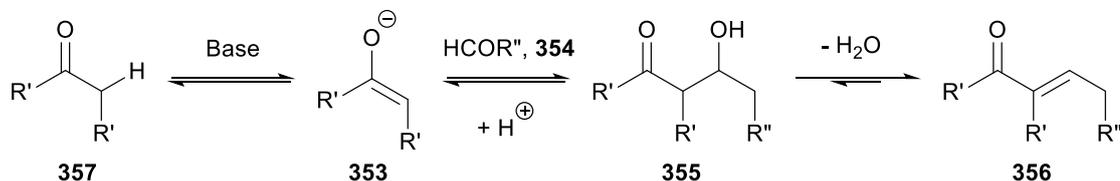
Table 25 *N*-methylation of enantioenriched tetrahydroisoquinolines **323** and **325-331**.

Tetrahydroisoquinoline		Methylated Amine	
R ¹	R ²		Yield / % ^a
(<i>S</i>)- 325	H	(<i>S</i>)- 346	24
(<i>R</i>)- 325	H	(<i>R</i>)- 346	40
(<i>S</i>)- 326	H	(<i>S</i>)- 347	71
(<i>R</i>)- 326	4-Cl	(<i>R</i>)- 347	73
(<i>S</i>)- 327	H	(<i>S</i>)- 198	90
(<i>R</i>)- 327	3,4-Cl	(<i>R</i>)- 198	90
(<i>S</i>)- 328	H	(<i>S</i>)- 348	96
(<i>R</i>)- 328	2,4-Cl	(<i>R</i>)- 348	96
(<i>S</i>)- 329	OCH ₃	(<i>S</i>)- 349	19
(<i>R</i>)- 329	H	(<i>R</i>)- 349	24
(<i>S</i>)- 330	OCH ₃	(<i>S</i>)- 350	65
(<i>R</i>)- 330	4-Cl	(<i>R</i>)- 350	58
(<i>S</i>)- 331	OCH ₃	(<i>S</i>)- 351	92
(<i>R</i>)- 331	3,4-Cl	(<i>R</i>)- 351	87
(<i>S</i>)- 323	OCH ₃	(<i>S</i>)- 352	95
(<i>R</i>)- 323	2,4-Cl	(<i>R</i>)- 352	98

^a Isolated yield.

3.4 Synthesis of Benzylidene Indan-1-ones

The primary reactive site within indan-1-ones is the carbonyl group and, as such, the majority of transformations of these substrates progress through this functional group. In addition to ring expansion reactions indan-1-ones are able to react via the carbon atom alpha to the carbonyl group, the hydrogen atoms attached to which are more acidic due to resonance stabilisation. One such reaction involving these α -protons is an aldol reaction, which is a highly popular C–C bond forming process in organic synthesis,²³⁵ exemplified by its employment in the large-scale production of a number of commercial drugs.²³⁶ It was discovered independently by Russian chemist Alexander Borodin in 1869,²³⁷ and French chemist Charles-Adolphe Wurtz in 1872.²³⁸ Under basic conditions, the reaction commonly involves the nucleophilic addition of a ketone enolate (**353**) to another carbonyl compound (**354**) to form a β -hydroxy ketone (**355**), or “aldol” (aldehyde + alcohol), which is sometimes followed by dehydration to an α,β -unsaturated ketone (**356**) under harsh conditions (Scheme 49). Alternatively, when an acid is used, the ketone (**357**) tautomerises to the enol, which then attacks the acid-activated carbonyl group of another molecule via the α -carbon. This usually dehydrates to give the unsaturated carbonyl compound (**356**).



Scheme 49 Base-promoted Aldol condensation of a ketone (**357**) with an aldehyde (**354**).

As discussed in **Section 1.1**, Negi *et al.* synthesised a series of 2-benzylidene indan-1-ones via the Claisen–Schmidt condensation – a type of Aldol condensation (see **Section 2.1.2**) – of 3-aryl-indan-1-ones with benzaldehydes.²³⁹⁻²⁴¹ These compounds were reported to exhibit strong cytotoxicity against human cancer cell lines and inhibit tubulin polymerisation, with some demonstrating little-to-no toxicity in Swiss-albino mice.

In order to test the scope and simplicity of this transformation, a number of benzaldehydes were employed, those that were both already available to us and that were reported to give rise to benzylidene indan-1-ones displaying more potent anti-cancer activity,²³⁹ 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde and 4-fluorobenzaldehyde were selected, in addition to benzaldehyde as a reference. These benzaldehydes were reacted with 3-aryl-indan-1-ones **118-125** with solid NaOH in a 1 : 1 mixture of methanol : CH₂Cl₂ at room temperature for 2 hours.²⁴²

Yields of benzylidene indan-1-ones **358-389** were generally good to excellent, with some exceptions, and no obvious trends can be seen in the aldol condensations of 3-aryl-indan-1-ones **118-125** (Table 26).

Table 26 Aldol condensations of 3-aryl-indan-1-ones **118-125** with benzaldehydes.

Indan-1-one	Product Yield / % ^a									
	R ¹	R ²	Ar = C ₆ H ₅		Ar = 3-OMe		Ar = 3,4-OMe		Ar = 4-F	
118	H	H	358	82	366	72	374	69	382	87
119	H	4-Cl	359	76	367	44	375	72	383	73
120	H	3,4-Cl	360	51	368	65	376	53	384	65
121	H	2,4-Cl	361	88	369	82	377	91	385	85
122	OCH ₃	H	362	77	370	64	378	55	386	80
123	OCH ₃	4-Cl	363	94	371	90	379	81	387	90
124	OCH ₃	3,4-Cl	364	78	372	79	380	78	388	75
125	OCH ₃	2,4-Cl	365	82	373	95	381	57	389	83

^a Isolated yield.

No other products were observed in these reactions and the (*E*)-alkene formed exclusively, the configuration of which was confirmed by extensive NOE analysis. NOE experiments were performed for a selection of benzylidene products, accounting for all changes to structure: the number of methoxy groups on the indan-1-one aryl ring, the substitution pattern of the pendant 3-aryl ring, and the substitution of the benzylidene aromatic ring. For all compounds analysed, there was a strong NOE present between the two *ortho*-hydrogens on the benzylidene ring and the alkyl proton, as demonstrated by the example shown in Figure 34, which is the NOE experiment for benzylidene indan-1-one **378**. This indicates a close spatial proximity between these two hydrogen atoms which, after looking at 3D models, is only present in the (*E*)-alkene – for example the atom distance was calculated in Chem3D 17.0 as 1.9 Å for (*E*)-**378** and 4.9 Å for (*Z*)-**378** (Figure 35).

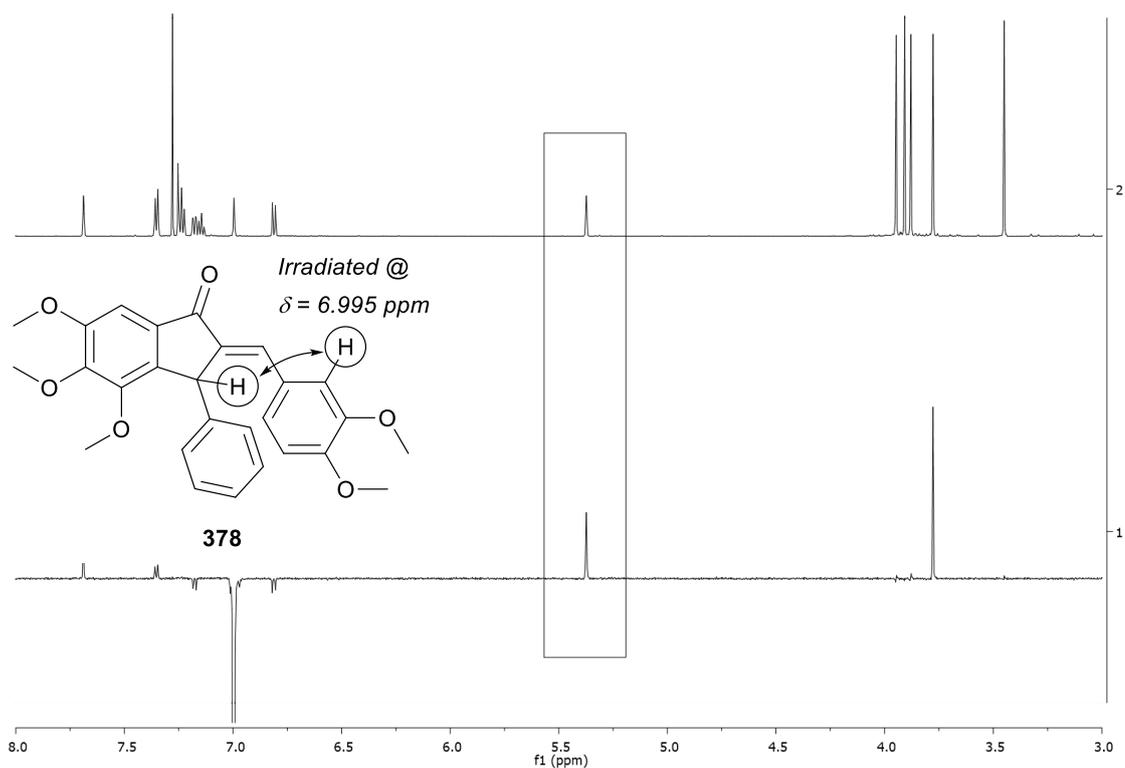


Figure 34 Example NOE experiment, confirming (*E*)-alkene configuration. Top ^1H NMR spectrum: benzylidene indan-1-one **378**. Bottom ^1H NMR spectrum: benzylidene indan-1-one **378** irradiated at $\delta = 6.995$ ppm.

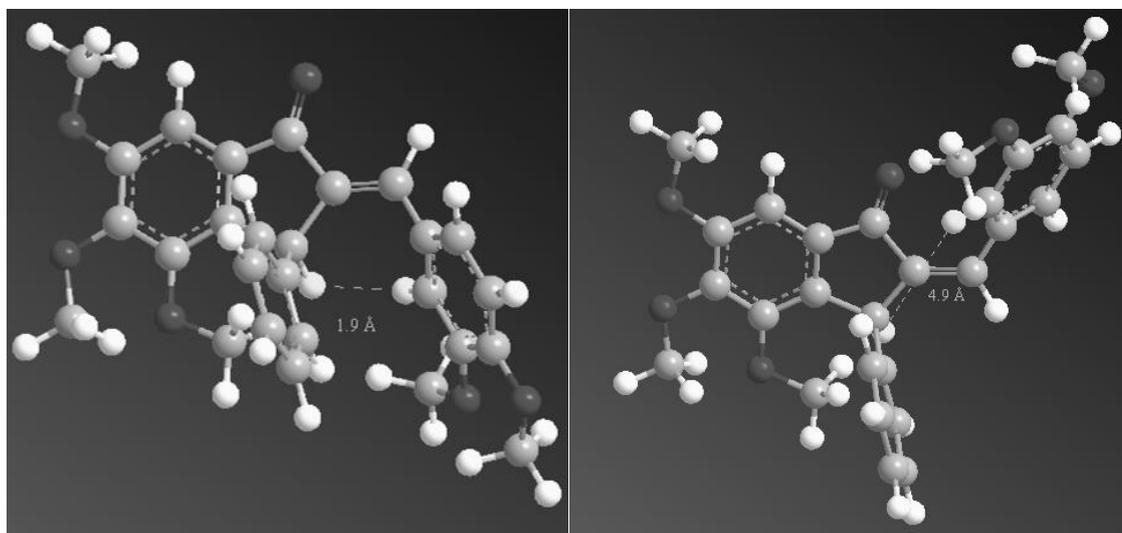


Figure 35 3D structures of benzylidene indan-1-one **378**, as generated by Chem3D 17.0. Left image: (*E*)-**378**, with atom distance calculated at 1.9 Å. Right image: (*Z*)-**378**, with atom distance calculated at 4.9 Å.

3.5 Summary

This chapter comprised the synthesis of biologically interesting medicinal scaffolds through ring expansion transformations of enantioenriched 3-aryl-indan-1-ones and further manipulations.

The Beckmann route, comprising a total of three steps from corresponding indan-1-ones, yielded 4-aryl-dihydroisoquinolinones exclusively and involved tedious and time-consuming quenches and work-ups. It was believed that isomerisation to the less favoured (*Z*)-configuration was taking place prior to migration to account for the regioselectivity observed for the Beckmann rearrangement, in line with literature reports.¹²⁵

Mixtures of products were obtained from the Schmidt reaction of indan-1-ones with sodium azide and methanesulfonic acid. Tetrazoles typically formed alongside the usual δ -lactams – dihydroisoquinolinones and dihydroquinolinones – increasing as more NaN₃ was used. The regiochemistry of the reaction was influenced by substrate structure; the most notable observation was that of increased methoxy group substitution on the 1-aryl ring promoting the Schmidt reaction and causing greater alkyl group migration, in agreement with literature reports.^{143, 150}

Reaction of individual 3-aryl-indan-1-one enantiomers under the Schmidt conditions previously employed afforded the desired enantiomerically enriched δ -lactams in excellent enantiomeric excesses, however single tetrazole enantiomers could not be obtained due to apparent racemisation during their formation. A number of highly enantioenriched 4-aryl-tetrahydroisoquinolines, including both enantiomers of antidepressant drug diclofensine (**198**), were then successfully prepared through reduction of corresponding lactam enantiomers and subsequent *N*-methylation.

The successful synthesis of the individual enantiomers of non-cytotoxic anti-inflammatory compound 6-B345TTQ (**99**) was also discussed in this chapter, which was a long term aim of the Fox group. Both enantiomers were obtained in >99 % e.e., albeit a total synthetic yield of <1.00 % for (*R*)- and (*S*)-**99** (0.07 % and 0.10 %, respectively).

Finally, the Claisen–Schmidt condensation of 3-aryl-indan-1-ones with various benzaldehydes afforded benzylidene indan-1-ones in good to excellent yields; these types of compounds are associated with interesting biological activities.²³⁹⁻²⁴³ No other products were observed alongside the desired benzylidene indan-1-ones, and extensive NOE analysis confirmed their configuration as the (*E*)-alkene.

3.6 Experimental for Chapter 3

3.6.1 General

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. Heat transfer for reactions was achieved using drysyn[®] apparatus and were performed using commercially available reagents and solvents which, unless otherwise stated, were used as received. Reactions involving moisture sensitive compounds were performed under a dry, oxygen-free atmosphere and in dry solvents. Such solvents were dried prior to use using the methods described in “Purification of Laboratory Chemicals, 6th Ed.”, and used accordingly.²⁴⁴ 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 H₂SO₄ and 0.75 M Na₂SO₄).

Reactions were followed by thin layer chromatography (TLC), performed on aluminium plates coated with 0.2 mm silica gel (DC Kieselgel 60 F₂₅₄, Merck), developed either from UV fluorescence (254 nm) or potassium permanganate followed by heating. Column chromatography was carried out using SiO₂ (40-63 microns).

Melting points were determined on a Stuart Scientific SMP10 melting point apparatus (uncorrected), with 3 runs of each compound, and the average value given in °C rounded to the nearest degree.

Infrared (IR) spectra were recorded as thin films on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer and results are quoted in wavenumbers (cm⁻¹). Peak intensities are specified as strong (s), medium (m), weak (w) and broad (br). Sulfoxide S=O stretches are denoted as asymmetric (*as*) and symmetric (*s*).

NMR spectra were recorded on Bruker Advance DRX 250, 300, 400 and 600 MHz spectrometers at room temperature (298 K). Chemical shifts are reported in parts per million (ppm), downfield relative to tetramethylsilane (TMS) (0.00 ppm), and referenced from CDCl₃ in most instances (δ_{H} : 7.26 ppm and δ_{C} : 77.2 ppm). Coupling constants (*J*) are reported in Hertz (Hz) and rounded to the nearest 0.5 Hz. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m) and broad (br.), whilst more complex multiplicities are in line with these denotations, e.g. doublet of doublets (dd). Spectra were analysed using MestReNova[®], with ¹H and ¹³C assignments established on the basis of COSY, DEPT, HMQC and HMBC correlations, in addition to NOE experiments. [Carbon spectra were determined with broadband decoupling].

Mass spectra were obtained using the University of Warwick Mass Spectrometry Service, where low resolution electrospray ionisation (ESI) mass spectra were recorded on an Agilent 6130B single Quad instrument, and high resolution ESI mass spectra (HRMS) were recorded using a Bruker micro-TOF ESI spectrometer by either Dr Lijiang Song, Mr Philip Aston or Mr James Morrey.

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 cm² g⁻¹. Concentrations (c) are given in grams / Litre (g/L). The samples were prepared using spectroscopic grade CHCl₃.

Naming of compounds has been performed in accordance with IUPAC guidelines.²⁴⁵ (*R*)- and (*S*)- configurations were assigned according to the Cahn–Ingold–Prelog priority rules.²⁴⁶

NMR assignments for each compound are using the following notations:

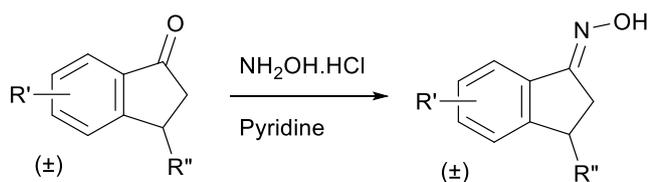
¹H NMR Assignments:

ArH (aromatic hydrogen), CHX (non-aromatic hydrogens).

¹³C NMR Assignments:

ArC (aromatic carbon bearing no hydrogens), ArCH (aromatic carbon bearing a hydrogen), CH (non-aromatic carbon, bearing a hydrogen), C (non-aromatic carbon, bearing no hydrogens).

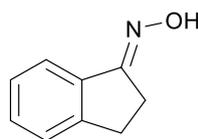
3.6.2 Formation of Indan-1-one Oximes – General Procedure G



The following procedure was performed in accordance with previous literature.²⁴⁷

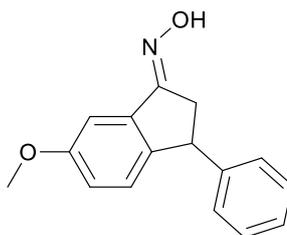
To a solution of substituted indan-1-one (1.00 equiv.), in pyridine (5.00 mL/mmol), was added hydroxylamine hydrochloride (2.00 equiv.), and the reaction stirred at 80 °C for 22 hours. The reaction was cooled to room temperature and HCl (1.00 M) added and the product extracted with CH₂Cl₂. The combined organic layers were then washed with further HCl (1.00 M), water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The product was then used without further purification.

(E)-2,3-Dihydro-1H-inden-1-one Oxime, 207



General procedure G was applied using 2,3-dihydro-1H-inden-1-one **4** (500 mg, 3.78 mmol), pyridine (18.9 mL) and hydroxylamine hydrochloride (526 mg, 2.72 mmol). The title compound was formed as a white solid (521 mg, 93 %); m.p. 146-148 °C (lit.²⁵⁵ 146-148 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3034 (br, O-H), 2840 (m, C-H), 1654 (s, C=N), 1264 (s, C-O), 955 (s, N-O); δ_{H} (500 MHz, CDCl₃) 9.00 (1H, s, OH), 7.70 (1H, d, $J = 7.5$ Hz, ArH), 7.39-7.31 (2H, m, 2 x ArH), 7.30-7.23 (1H, m, ArH), 3.12-3.05 (2H, m, 2 x C(H)H), 3.05-2.96 (2H, m, 2 x C(H)H); δ_{C} (126 MHz, CDCl₃) 164.1 (C=N), 148.5 (ArC), 136.0 (ArC), 130.4 (ArCH), 127.0 (ArCH), 125.6 (ArCH), 121.6 (ArCH), 28.5 (CH₂), 26.0 (CH₂); m/z (ESI) 170 [M+Na]⁺; HRMS (ESI) C₉H₉NONa⁺ requires 170.0576, found 170.0575 [M+Na]⁺. These data are consistent with those previously reported.²⁴⁸

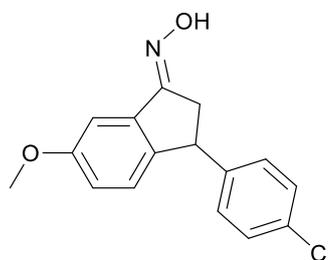
(E)-6-Methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one Oxime, 218



General procedure G was applied using 6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **118** (500 mg, 2.10 mmol), pyridine (10.5 mL) and hydroxylamine hydrochloride (292

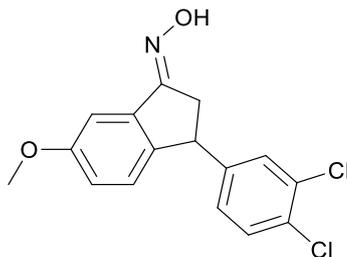
mg, 4.20 mmol). The title compound was formed as an off-white solid (525 mg, 99 %); m.p. 145-146 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3168 (br, O-H), 2834 (m, C-H), 1655 (s, C=N), 1229 (s, C-O), 961 (s, N-O); δ_{H} (500 MHz, CDCl_3) 7.73 (1H, s, OH), 7.33-7.27 (2H, m, 2 x ArH), 7.25-7.21 (1H, m, ArH), 7.19 (1H, d, $J = 2.5$ Hz, ArH), 7.14-7.10 (2H, m, 2 x ArH), 6.99 (1H, d, $J = 8.5$ Hz, ArH), 6.92 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 4.44 (1H, dd, $J = 8.5, 4.0$ Hz, C(Ar)H), 3.84 (3H, s, OCH₃), 3.55 (1H, dd, $J = 19.0, 8.5$ Hz, C(H)H), 2.92 (1H, dd, $J = 19.0, 4.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 163.0 (C=N), 159.5 (ArC), 145.1 (ArC), 143.8 (ArC), 137.0 (ArC), 128.7 (2 x ArCH), 127.6 (2 x ArCH), 126.9 (ArCH), 126.7 (ArCH), 119.5 (ArCH), 103.8 (ArCH), 55.6 (OCH₃), 46.5 (C(Ar)H), 37.3 (CH₂); m/z (ESI) 254 [M+H]⁺; HRMS (ESI) C₁₆H₁₆NO₂⁺ requires 254.1176, found 254.1180 [M+H]⁺.

(E)-3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one Oxime, 219



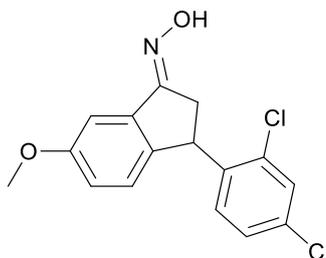
General procedure G was applied using 3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **119** (500 mg, 1.83 mmol), pyridine (9.2 mL) and hydroxylamine hydrochloride (255 mg, 3.67 mmol). The title compound was formed as an off-white solid (521 mg, 99 %); m.p. 174-175 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3408 (br, O-H), 2832 (m, C-H), 1605 (s, C=N), 1217 (s, C-O), 950 (s, N-O); δ_{H} (500 MHz, CDCl_3) 8.14 (1H, s, OH), 7.28-7.24 (2H, m, 2 x ArH), 7.20 (1H, d, $J = 2.0$ Hz, ArH), 7.07-7.03 (2H, m, 2 x ArH), 6.98-6.95 (1H, m, ArH), 6.93 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 4.41 (1H, dd, $J = 8.5, 4.0$ Hz, C(Ar)H), 3.83 (3H, s, OCH₃), 3.54 (1H, dd, $J = 19.0, 8.5$ Hz, C(H)H), 2.87 (1H, dd, $J = 19.0, 4.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 162.6 (C=N), 159.7 (ArC), 143.6 (ArC), 143.3 (ArC), 137.0 (ArC), 132.4 (ArC), 128.9 (2 x ArCH), 128.9 (2 x ArCH), 126.7 (ArCH), 119.5 (ArCH), 103.9 (ArCH), 55.6 (OCH₃), 46.9 (C(Ar)H), 37.3 (CH₂); m/z (ESI) 288 [M+H]⁺; HRMS (ESI) C₁₆H₁₅³⁵ClNO₂⁺ requires 288.0786, found 288.0777 [M+H]⁺.

(E)-3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one Oxime, 220



General procedure G was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **120** (500 mg, 1.63 mmol), pyridine (8.1 mL) and hydroxylamine hydrochloride (226 mg, 3.26 mmol). The title compound was formed as an off-white solid (499 mg, 95 %); m.p. 133-134 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3199 (br, O-H), 2834 (m, C-H), 1607 (s, C=N), 1294 (s, C-O), 959 (s, N-O); δ_{H} (500 MHz, CDCl_3) 8.34 (1H, s, OH), 7.36 (1H, d, $J = 8.5$ Hz, ArH), 7.22-7.19 (2H, m, 2 x ArH), 6.97 (H, d, $J = 8.5$ Hz, ArH), 6.96-6.92 (2H, m, 2 x ArH), 4.44 (1H, dd, $J = 8.5, 4.0$ Hz, C(Ar)H), 3.84 (3H, s, OCH₃), 3.54 (1H, dd, $J = 19.0, 8.5$ Hz, C(H)H), 2.86 (1H, dd, $J = 19.0, 4.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 169.9 (C=N), 160.0 (ArC), 144.3 (ArC), 143.9 (ArC), 134.4 (ArC), 133.0 (ArC), 131.3 (ArC), 130.9 (ArCH), 129.5 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 122.5 (ArCH), 104.9 (ArCH), 55.8 (OCH₃), 45.5 (C(Ar)H), 38.8 (CH₂); m/z (ESI) 322 [M+H]⁺; HRMS (ESI) $\text{C}_{16}\text{H}_{14}^{35}\text{Cl}_2\text{NO}_2^+$ requires 322.0396, found 322.0395 [M+H]⁺.

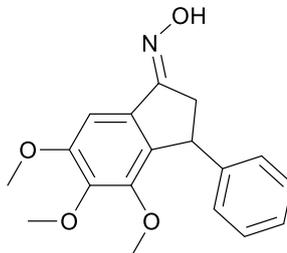
(E)-3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one Oxime, 221



General procedure G was applied 3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **121** (500 mg, 1.63 mmol), pyridine (8.10 mL) and hydroxylamine hydrochloride (226 mg, 3.26 mmol). The title compound was formed as an off-white solid (522 mg, >99 %); m.p. 159-161 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3117 (br, O-H), 2835 (m, C-H), 1610 (s, C=N), 1224 (s, C-O), 952 (s, N-O); δ_{H} (500 MHz, CDCl_3) 8.37 (1H, s, OH), 7.43 (1H, d, $J = 2.0$ Hz, ArH), 7.22 (1H, d, $J = 2.5$ Hz, ArH), 7.11 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 7.04 (1H, d, $J = 8.0$ Hz, ArH), 6.97 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.80 (1H, d, $J = 8.0$ Hz, ArH), 4.95-4.87 (1H, m, C(Ar)H), 3.84 (3H, s, OCH₃), 3.61 (1H, dd, $J = 19.0, 9.0$ Hz, C(H)H), 2.79 (1H, dd, $J = 19.0, 2.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 162.2 (C=N), 159.8 (ArC), 141.6 (ArC), 141.2 (ArC), 137.6 (ArC), 134.5 (ArC), 132.9 (ArC), 129.3

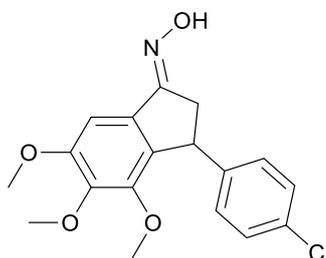
(ArCH), 127.5 (2 x ArCH), 126.8 (ArCH), 119.6 (ArCH), 104.2 (ArCH), 55.6 (OCH₃), 42.5 (C(Ar)H), 36.1 (CH₂); m/z (ESI) 344 [M+Na]⁺; HRMS (ESI) C₁₆H₁₃³⁵Cl₂NO₂Na⁺ requires 344.0216, found 344.0218 [M+Na]⁺.

(E)-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one Oxime, 222



General procedure G was applied using 4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **122** (500 mg, 1.68 mmol), pyridine (8.40 mL) and hydroxylamine hydrochloride (233 mg, 3.35 mmol). The title compound was formed as a beige solid (525 mg, >99 %); m.p. 140-142 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3129 (br, O-H), 2834 (m, C-H), 1601 (s, C=N), 1353 (s, C-O), 1109 (s, N-O); δ_{H} (500 MHz, CDCl₃) 7.29-7.23 (2H, m, 2 x ArH), 7.26 (1H, s, OH), 7.18 (1H, t, $J = 7.0$ Hz, ArH), 7.11 (2H, d, $J = 7.5$ Hz, 2 x ArH), 7.05 (1H, s, ArH), 4.52 (1H, dd, $J = 8.5, 2.5$ Hz, C(Ar)H), 3.88 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.43 (1H, dd, $J = 19.0, 8.5$ Hz, C(H)H), 3.31 (3H, s, OCH₃), 2.94 (1H, dd, $J = 19.0, 2.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 163.2 (C=N), 154.7 (ArC), 150.3 (ArC), 145.4 (ArC), 144.8 (ArC), 137.6 (ArC), 131.1 (ArC), 128.5 (2 x ArCH), 127.3 (2 x ArCH), 126.5 (ArCH), 99.0 (ArCH), 60.8 (OCH₃), 59.9 (OCH₃), 56.2 (OCH₃), 44.7 (C(Ar)H), 37.3 (CH₂); m/z (ESI) 336 [M+Na]⁺; HRMS (ESI) C₁₈H₁₉NO₄Na⁺ requires 336.1206, found 336.1208 [M+Na]⁺.

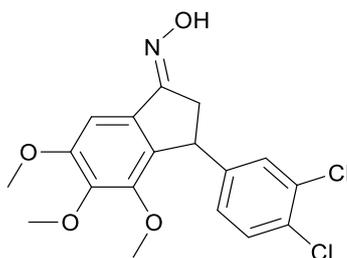
(E)-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one Oxime, 223



General procedure G was applied using 3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **123** (500 mg, 1.50 mmol), pyridine (7.50 mL) and hydroxylamine hydrochloride (209 mg, 3.00 mmol). The title compound was formed as an off-white solid (498 mg, 95 %); m.p. 140-141 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3109 (br, O-H), 2837 (m, C-H), 1597 (s, C=N), 1350 (s, C-O), 948 (s, N-O); δ_{H} (500 MHz, CDCl₃) 7.27

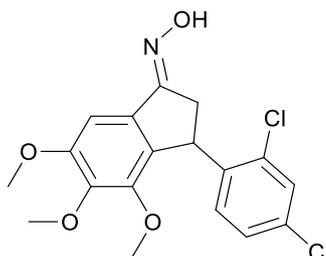
(1H, s, OH), 7.26-7.23 (2H, m, 2 x ArH), 7.07 (1H, s, ArH), 7.06-7.04 (2H, m, 2 x ArH), 4.51 (1H, dd, $J = 8.5, 2.5$ Hz, C(Ar)H), 3.90 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.48-3.40 (1H, m, C(H)H), 3.40 (3H, s, OCH₃), 2.88 (1H, dd, $J = 19.0, 2.5$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 170.6 (C=N), 155.2 (ArC), 150.1 (ArC), 146.6 (ArC), 142.6 (ArC), 139.1 (ArC), 132.6 (ArC), 128.8 (ArCH), 128.5 (2 x ArCH), 128.2 (ArC), 99.9 (ArCH), 61.0 (OCH₃), 60.2 (OCH₃), 56.4 (OCH₃), 44.0 (C(Ar)H), 38.9 (CH₂); m/z (ESI) 370 [M+Na]⁺; HRMS (ESI) C₁₈H₁₈³⁵ClNO₄Na⁺ requires 370.0817, found 370.0808 [M+Na]⁺.

(E)-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one Oxime, 224



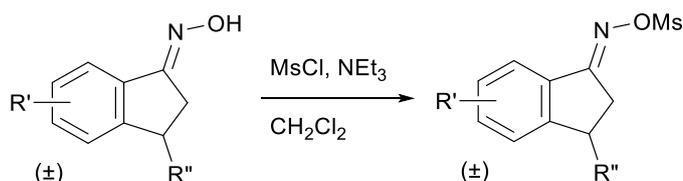
General procedure G was applied using 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **124** (500 mg, 1.36 mmol), pyridine (6.80 mL) and hydroxylamine hydrochloride (190 mg, 2.72 mmol). The title compound was formed as a pale brown solid (510 mg, 98 %); m.p. 81-83 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3089 (br, O-H), 2835 (m, C-H), 1596 (s, C=N), 1107 (s, C-O), 918 (s, N-O); δ_H (500 MHz, CDCl₃) 7.33 (1H, d, $J = 8.5$ Hz, ArH), 7.26 (1H, s, OH), 7.20 (1H, d, $J = 1.5$ Hz, ArH), 7.01 (1H, s, ArH), 6.94 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 4.47 (1H, dd, $J = 8.5, 3.0$ Hz, C(Ar)H), 3.89 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.46 (3H, s, OCH₃), 3.41 (1H, dd, $J = 19.0, 8.5$ Hz, C(H)H), 2.85 (1H, dd, $J = 19.0, 3.0$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 162.3 (C=N), 155.1 (ArC), 150.1 (ArC), 145.7 (ArC), 144.7 (ArC), 136.0 (ArC), 132.4 (ArC), 131.1 (ArCH), 130.4 (ArCH), 130.3 (ArC), 129.2 (ArCH), 126.7 (ArCH), 99.0 (ArCH), 60.9 (OCH₃), 60.1 (OCH₃), 56.2 (OCH₃), 43.8 (C(Ar)H), 36.9 (CH₂); m/z (ESI) 404 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵Cl₂NO₄Na⁺ requires 404.0427, found 404.0426 [M+Na]⁺.

(E)-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one Oxime, 225



General procedure G was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (500 mg, 1.36 mmol), pyridine (6.80 mL) and hydroxylamine hydrochloride (190 mg, 2.72 mmol). The title compound was formed as a beige solid (479 mg, 92 %); m.p. 183-185 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3186 (br, O-H), 2839 (m, C-H), 1659 (s, C=N), 1349 (s, C-O), 1104 (s, N-O); δ_{H} (500 MHz, CDCl_3) 7.44-7.39 (1H, m, ArH), 7.26 (1H, s, ArH), 7.08 (1H, d, $J = 8.0$ Hz, ArH), 7.03 (1H, s, ArH), 6.69 (1H, s, OH), 5.04-4.90 (1H, m, C(Ar)H), 3.90 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.56 (3H, s, OCH₃), 3.49 (1H, dd, $J = 19.0, 9.0$ Hz, C(H)H), 2.81-2.69 (1H, m, C(H)H); δ_{C} (126 MHz, CDCl_3) 162.4 (C=N), 155.1 (ArC), 150.1 (ArC), 144.6 (ArC), 141.3 (ArC), 135.0 (ArC), 134.0 (ArC), 132.6 (ArC), 131.7 (ArC), 129.2 (2 x ArCH), 127.3 (ArCH), 99.0 (ArCH), 61.0 (OCH₃), 60.2 (OCH₃), 56.2 (OCH₃), 40.4 (C(Ar)H), 36.2 (CH₂); m/z (ESI) 404 [M+Na]⁺; HRMS (ESI) $\text{C}_{18}\text{H}_{17}^{35}\text{Cl}_2\text{NO}_4\text{Na}^+$ requires 404.0427, found 404.0428 [M+Na]⁺.

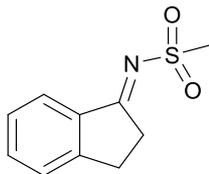
3.6.3 Formation of Indan-1-one Oxime Mesylates – General Procedure H



The following procedure was performed in accordance with previous literature.¹³⁵

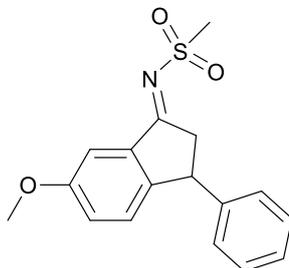
To a solution of substituted indan-1-one oxime (1.00 equiv.) and trimethylamine (1.50 equiv.) in CH_2Cl_2 (15.0 mL/mmol), at -20 °C, was added mesyl chloride (1.10 equiv.) over 5 minutes, and the reaction stirred at -20 °C for a further 20 minutes. The reaction mixture was allowed to warm to room temperature and then HCl (1.00 M) added. The organics were separated and washed with NaHCO_3 and brine, then dried over MgSO_4 , filtered and concentrated *in vacuo*. The product was used without further purification.

(E)-N-(2,3-Dihydro-1H-inden-1-ylidene)methanesulfonamide, 217



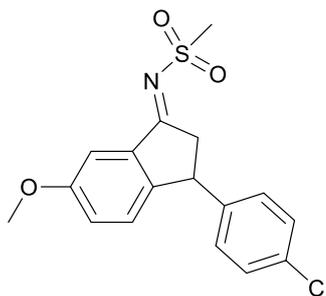
General procedure H was applied using (*E*)-2,3-dihydro-1*H*-inden-1-one oxime **207** (475 mg, 3.23 mmol), trimethylamine (675 μ L, 4.84 mmol), CH_2Cl_2 (48.4 mL) and mesyl chloride (275 μ L, 3.55 mmol). The title compound was formed as a pale brown solid (617 mg, 85 %); m.p. 118-120 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1466 (s, C=N), 1333 (s, S=O (*as*)), 1173 (s, S=O (*s*)), 1152 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.79 (1H, d, $J = 7.5$ Hz, ArH), 7.48 (1H, t, $J = 7.5$ Hz, ArH), 7.38 (1H, d, $J = 7.5$ Hz, ArH), 7.32 (1H, d, $J = 7.5$ Hz, ArH), 3.24 (3H, s, SCH₃), 3.15-3.06 (4H, m, 2 x CH₂); δ_{C} (126 MHz, CDCl_3) 172.1 (C=N), 150.3 (ArC), 133.3 (ArC), 132.7 (ArCH), 127.4 (ArCH), 125.9 (ArCH), 123.1 (ArCH), 36.5 (CH₂), 28.5 (CH₂), 28.0 (SCH₃); m/z (ESI) 248 [M+Na]⁺; HRMS (ESI) C₁₀H₁₁NO₃SNa⁺ requires 248.0352, found 248.0351 [M+Na]⁺.

(E)-N-(6-Methoxy-3-phenyl-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 226



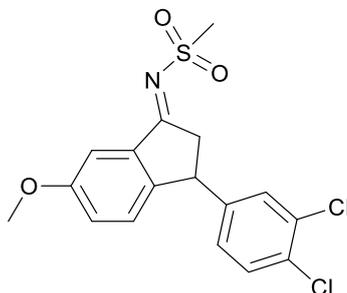
General procedure H was applied using (*E*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one oxime **218** (475 mg, 1.88 mmol), trimethylamine (392 μ L, 2.81 mmol), CH_2Cl_2 (28.0 mL) and mesyl chloride (160 μ L, 2.06 mmol). The title compound was formed as a brown solid (590 mg, >99 %); m.p. 132-134 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1485 (s, C=N), 1324 (s, S=O (*as*)), 1175 (s, S=O (*s*)), 1141 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.33-7.28 (2H, m, 2 x ArH), 7.27-7.22 (2H, m, 2 x ArH), 7.11-7.06 (2H, m, 2 x ArH), 7.06-7.03 (2H, m, 2 x ArH), 4.47 (1H, dd, $J = 8.0, 4.0$ Hz, C(Ar)H), 3.86 (3H, s, OCH₃), 3.66 (1H, dd, $J = 19.5, 8.0$ Hz, C(H)H), 3.26 (3H, s, SCH₃), 3.02 (1H, dd, $J = 19.5, 4.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 170.8 (C=N), 159.7 (ArC), 145.8 (ArC), 143.6 (ArC), 134.3 (ArC), 128.9 (2 x ArCH), 127.5 (2 x ArCH), 127.1 (ArCH), 127.1 (ArCH), 122.3 (ArCH), 104.6 (ArCH), 55.7 (OCH₃), 46.4 (C(Ar)H), 39.1 (CH₂), 36.5 (SCH₃); m/z (ESI) 332 [M+H]⁺; HRMS (ESI) C₁₇H₁₈NO₄S⁺ requires 332.0951, found 332.0948 [M+H]⁺.

(E)-N-(3-(4-Chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 227



General procedure H was applied using (*E*)-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one oxime **219** (475 mg, 1.65 mmol), trimethylamine (345 μ L, 2.48 mmol), CH_2Cl_2 (24.8 mL) and mesyl chloride (141 μ L, 1.82 mmol) – Et_2O (12.4 mL, 7.50 mL/mmol) was also added to aid starting material solubilisation. The title compound was formed as a pale brown solid (603 mg, >99 %); m.p. 155-157 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1488 (s, C=N), 1360 (s, S=O (*as*)), 1173 (s, S=O (*s*)), 1113 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.29-7.25 (3H, m, 3 x ArH), 7.06 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.04-6.99 (3H, m, 3 x ArH), 4.45 (1H, dd, $J = 8.0, 3.5$ Hz, C(Ar)H), 3.86 (3H, s, OCH₃), 3.65 (1H, dd, $J = 19.5, 8.0$ Hz, C(H)H), 3.25 (3H, s, SCH₃), 2.96 (1H, dd, $J = 19.5, 3.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 170.4 (C=N), 159.9 (ArC), 145.2 (ArC), 142.1 (ArC), 134.3 (ArC), 133.0 (ArC), 129.1 (2 x ArCH), 128.8 (2 x ArCH), 127.0 (ArCH), 122.4 (ArCH), 104.7 (ArCH), 55.8 (OCH₃), 45.8 (C(Ar)H), 39.0 (CH₂), 36.6 (SCH₃); m/z (ESI) 388 [M+Na]⁺; HRMS (ESI) $\text{C}_{17}\text{H}_{16}^{35}\text{ClNO}_4\text{SNa}^+$ requires 388.0381, found 388.0382 [M+Na]⁺.

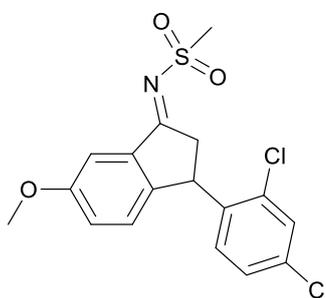
(E)-N-(3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 228



General procedure H was applied using (*E*)-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one oxime **220** (450 mg, 1.40 mmol), trimethylamine (292 μ L, 2.10 mmol), CH_2Cl_2 (21.0 mL) and mesyl chloride (119 μ L, 1.54 mmol). The title compound was formed as a brown solid (559 mg, >99 %); m.p. 75-77 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1605 (s, C=N), 1360 (s, S=O (*as*)), 1176 (s, S=O (*s*)), 1131 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.38 (1H, d, $J = 8.0$ Hz, ArH), 7.27 (1H, d, $J = 2.5$ Hz, ArH), 7.17 (1H, d, $J = 2.0$ Hz, ArH),

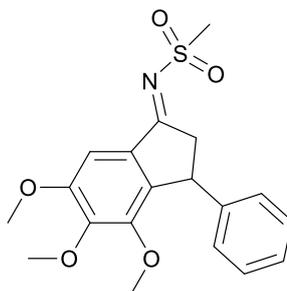
7.07 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.02 (1H, d, $J = 8.5$ Hz, ArH), 6.93 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 4.44 (1H, dd, $J = 8.5, 3.5$ Hz, C(Ar)H), 3.87 (3H, s, OCH₃), 3.66 (1H, dd, $J = 19.5, 8.5$ Hz, C(H)H), 3.26 (3H, s, SCH₃), 2.95 (1H, dd, $J = 19.5, 3.5$ Hz, C(H)H); δ_c (126 MHz, CDCl₃) 162.1 (C=N), 159.8 (ArC), 145.4 (ArC), 145.2 (ArC), 142.5 (ArC), 137.1 (ArC), 132.7 (ArC), 130.7 (ArCH), 129.6 (ArCH), 127.0 (ArCH), 126.7 (ArCH), 119.7 (ArCH), 104.1 (ArCH), 55.6 (OCH₃), 45.6 (C(Ar)H), 43.8 (SCH₃), 37.2 (CH₂); m/z (ESI) 422 [M+Na]⁺; HRMS (ESI) C₁₇H₁₅³⁵Cl₂NO₄SNa⁺ requires 421.9991, found 421.9980 [M+Na]⁺.

(E)-N-(3-(2,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 229



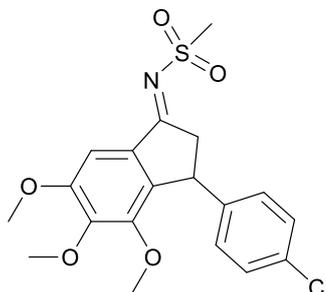
General procedure H was applied using (*E*)-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one oxime **221** (475 mg, 1.47 mmol), trimethylamine (308 μ L, 2.21 mmol), CH₂Cl₂ (22.0 mL) and mesyl chloride (126 μ L, 1.62 mmol) – Et₂O (11.0 mL, 7.50 mL/mmol) was also added to aid starting material solubilisation. The title compound was formed as a pale brown solid (590 mg, >99 %); m.p. 153-155 °C; ν_{max}/cm^{-1} (neat) 1584 (s, C=N), 1361 (s, S=O (*as*)), 1176 (s, S=O (*s*)), 1100 (s, N-S); δ_H (500 MHz, CDCl₃) 7.44 (1H, d, $J = 1.5$ Hz, ArH), 7.28 (1H, s, ArH), 7.13 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 7.10 (2H, s, 2 x ArH), 6.77 (1H, d, $J = 6.0$ Hz, ArH), 4.96-4.91 (1H, m, C(Ar)H), 3.88 (3H, s, OCH₃), 3.72 (1H, dd, $J = 19.5, 8.5$ Hz, C(H)H), 3.25 (3H, s, SCH₃), 2.89 (1H, m, C(H)H); δ_c (126 MHz, CDCl₃) 170.1 (C=N), 160.1 (ArC), 143.6 (ArC), 139.9 (ArC), 135.1 (ArC), 134.7 (ArC), 133.6 (ArC), 129.7 (ArCH), 127.7 (2 x ArCH), 127.2 (ArCH), 122.5 (ArCH), 105.1 (ArCH), 55.9 (OCH₃), 42.8 (C(Ar)H), 37.8 (CH₂), 36.7 (SCH₃); m/z (ESI) 422 [M+Na]⁺; HRMS (ESI) C₁₇H₁₅³⁵Cl₂NO₄SNa⁺ requires 421.9991, found 421.9990 [M+Na]⁺.

(E)-N-(4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 230



General procedure H was applied using (*E*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one oxime **222** (450 mg, 1.44 mmol), trimethylamine (300 μ L, 2.15 mmol), CH_2Cl_2 (21.5 mL) and mesyl chloride (122 μ L, 1.58 mmol). The title compound was formed as a pale brown solid (558 mg, 99 %); m.p. 125-127 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1590 (s, C=N), 1351 (s, S=O (*as*)), 1176 (s, S=O (*s*)), 1108 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.31-7.25 (2H, m, 2 x ArH), 7.20 (1H, t, $J = 7.5$ Hz, ArH), 7.08 (2H, s, 2 x ArH), 7.07 (1H, s, ArH), 4.54 (1H, dd, $J = 8.5, 2.5$ Hz, C(Ar)H), 3.93 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.54 (1H, dd, $J = 19.5, 8.5$ Hz, C(H)H), 3.32 (3H, s, OCH₃), 3.24 (3H, s, SCH₃), 3.01 (1H, dd, $J = 19.5, 2.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 171.1 (C=N), 155.1 (ArC), 150.3 (ArC), 146.8 (ArC), 144.2 (ArC), 140.0 (ArC), 128.8 (2 x ArCH), 128.4 (ArC), 127.3 (2 x ArCH), 127.0 (ArCH), 100.1 (ArCH), 61.0 (OCH₃), 60.2 (OCH₃), 56.5 (OCH₃), 44.8 (C(Ar)H), 39.2 (CH₂), 36.6 (SCH₃); m/z (ESI) 414 [M+Na]⁺; HRMS (ESI) $\text{C}_{19}\text{H}_{21}\text{NO}_6\text{SNa}^+$ requires 414.0982, found 414.0980 [M+Na]⁺.

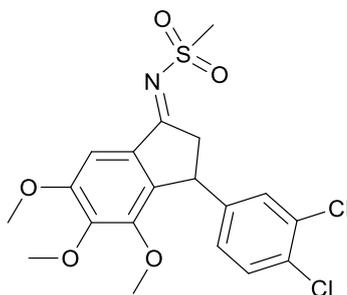
(E)-N-(3-(4-Chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 231



General procedure H was applied using (*E*)-3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one oxime **223** (450 mg, 1.29 mmol), trimethylamine (271 μ L, 1.94 mmol), CH_2Cl_2 (19.4 mL) and mesyl chloride (110 μ L, 1.42 mmol). The title compound was formed as a beige solid (544 mg, 99 %); m.p. 133-135 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1591 (s, C=N), 1357 (s, S=O (*as*)), 1181 (s, S=O (*s*)), 1117 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.27-7.24 (2H, m, 2 x ArH), 7.07 (1H, s, ArH), 7.03-6.99 (2H, m, 2 x ArH), 4.52 (1H, dd, $J =$

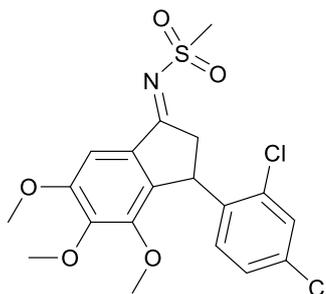
8.5, 2.5 Hz, C(Ar)H), 3.93 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.53 (1H, dd, $J = 19.5, 8.5$ Hz, C(H)H), 3.40 (3H, s, OCH₃), 3.24 (3H, s, SCH₃), 2.95 (1H, dd, $J = 19.5, 2.5$ Hz, C(H)H); δ_c (126 MHz, CDCl₃) 163.0 (C=N), 155.0 (ArC), 150.3 (ArC), 145.0 (ArC), 144.0 (ArC), 137.2 (ArC), 132.3 (ArC), 130.9 (ArC), 128.8 (2 x ArCH), 128.7 (2 x ArCH), 99.2 (ArCH), 61.0 (OCH₃), 60.2 (OCH₃), 56.3 (OCH₃), 44.2 (C(Ar)H), 43.9 (SCH₃), 37.3 (CH₂); m/z (ESI) 448 [M+Na]⁺; HRMS (ESI) C₁₉H₂₀³⁵ClNO₆SNa⁺ requires 448.0592, found 448.0588 [M+Na]⁺.

(*E*)-*N*-(3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide, 232



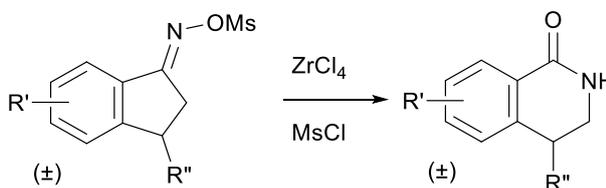
General procedure H was applied using (*E*)-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one oxime **224** (450 mg, 1.18 mmol), trimethylamine (246 μ L, 1.77 mmol), CH₂Cl₂ (17.7 mL) and mesyl chloride (100 μ L, 1.29 mmol). The title compound was formed as a pale brown solid (536 mg, 99 %); m.p. 64-66 °C; ν_{\max} /cm⁻¹ (neat) 1594 (s, C=N), 1352 (s, S=O (*as*)), 1179 (s, S=O (*s*)), 1109 (s, N-S); δ_H (500 MHz, CDCl₃) 7.36 (1H, d, $J = 8.5$ Hz, ArH), 7.17 (1H, d, $J = 2.0$ Hz, ArH), 7.08 (1H, s, ArH), 6.92 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 4.50 (1H, dd, $J = 8.5, 2.5$ Hz, C(Ar)H), 3.93 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.54 (1H, dd, $J = 19.5, 8.5$ Hz, C(H)H), 3.48 (3H, s, OCH₃), 3.24 (3H, s, SCH₃), 2.94 (1H, dd, $J = 19.5, 2.5$ Hz, C(H)H); δ_c (126 MHz, CDCl₃) 170.2 (C=N), 155.5 (ArC), 150.2 (ArC), 146.7 (ArC), 144.4 (ArC), 138.3 (ArC), 132.8 (ArC), 131.0 (ArC), 130.8 (ArCH), 129.3 (ArCH), 128.4 (ArC), 126.7 (ArCH), 100.1 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 43.9 (C(Ar)H), 38.7 (CH₂), 36.7 (SCH₃); m/z (ESI) 482 [M+Na]⁺; HRMS (ESI) C₁₉H₁₉³⁵Cl₂NO₆SNa⁺ requires 482.0202, found 482.0199 [M+Na]⁺.

(E)-N-(3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-ylidene)methanesulfonamide, 233



General procedure H was applied using (*E*)-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one oxime **225** (450 mg, 1.18 mmol), trimethylamine (246 μ L, 1.77 mmol), CH_2Cl_2 (17.7 mL) and mesyl chloride (100 μ L, 1.29 mmol). The title compound was formed as a pale brown solid (535 mg, 99 %); m.p. 145-146 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1589 (s, C=N), 1353 (s, S=O (*as*)), 1179 (s, S=O (*s*)), 1146 (s, N-S); δ_{H} (500 MHz, CDCl_3) 7.42 (1H, s, ArH), 7.11 (1H, d, $J = 8.0$ Hz, ArH), 7.08 (1H, s, ArH), 6.66 (1H, s, ArH), 5.09-4.86 (1H, m, C(Ar)H), 3.94 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 3.57 (3H, s, OCH₃), 3.22 (3H, s, SCH₃), 2.92-2.77 (1H, m, C(H)H), 1.94-1.74 (1H, m, C(H)H); δ_{C} (126 MHz, CDCl_3) 170.2 (C=N), 155.5 (ArC), 150.1 (ArC), 146.5 (ArC), 137.4 (2 x ArC), 134.2 (ArC), 133.3 (ArC), 129.5 (ArCH), 129.1 (ArC), 127.6 (ArCH), 127.5 (ArCH), 100.2 (ArCH), 61.2 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 56.4 (C(Ar)H), 38.0 (CH₂), 36.7 (SCH₃); m/z (ESI) 482 [M+Na]⁺; HRMS (ESI) $\text{C}_{19}\text{H}_{19}^{35}\text{Cl}_2\text{NO}_6\text{SNa}^+$ requires 482.0202, found 482.0203 [M+Na]⁺.

3.6.4 Beckmann Rearrangement of Indan-1-one Oxime Mesylates
– **General Procedure I**

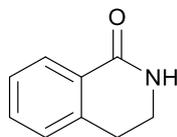


The following procedure was performed in accordance with previous literature.¹³⁵

To a solution of oxime mesylate (1.00 equiv.), in mesyl chloride (25.0 mL/mmol), was added ZrCl_4 (5.00 equiv.) at 0 $^\circ\text{C}$ and stirred for 18 hours. The reaction mixture was then heated up to 50 $^\circ\text{C}$ and stirred for a further 2 hours. The reaction was allowed to cool to room temperature and the mixture poured into an ice-cold solution of NaOH (1.00 M) and stirred for a further hour. The product was extracted with EtOAc, washed with

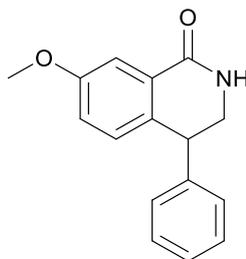
Na₂CO₃, then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

3,4-Dihydroquinolin-2(1H)-one, **164**



General procedure I was applied using (*E*)-*N*-(2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **217** (550 mg, 2.44 mmol), mesyl chloride (61.0 mL) and ZrCl₄ (2.84 g, 12.2 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 3,4-dihydroquinolin-2(1*H*)-one **163** as a yellow solid (139 mg, 39 %); m.p. 56-58 °C (lit.¹⁷⁰ 58-59 °C); ν_{\max} /cm⁻¹ (neat) 3239 (m, N-H), 2864 (m, C-H), 1657 (s, C=O), 1334 (s, C-O); δ_{H} (500 MHz, CDCl₃) 8.09 (1H, d, $J = 7.5$ Hz, ArH), 7.51-7.43 (1H, m, ArH), 7.38 (1H, t, $J = 7.5$ Hz, ArH), 7.24 (1H, d, $J = 7.5$ Hz, ArH), 6.55 (1H, s, CONH), 3.60 (2H, td, $J = 6.5, 3.0$ Hz, CH₂), 3.03 (2H, t, $J = 6.5$ Hz, CH₂); δ_{C} (126 MHz, CDCl₃) 166.4 (C=O), 138.9 (ArC), 132.2 (ArCH), 128.9 (ArC), 128.0 (ArCH), 127.3 (ArCH), 127.1 (ArCH), 40.3 (CH₂), 28.4 (CH₂); m/z (ESI) 170 [M+Na]⁺; HRMS (ESI) C₉H₉NONa⁺ requires 170.0576, found 170.0578 [M+Na]⁺. These data are consistent with those previously reported.^{170, 249}

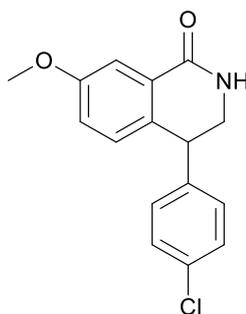
7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one, **234**



General procedure I was applied using (*E*)-*N*-(6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **226** (550 mg, 1.74 mmol), mesyl chloride (43.6 mL) and ZrCl₄ (2.03 g, 8.72 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 7-methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one **234** as an off-white solid (275 mg, 62 %); m.p. 150-151 °C; ν_{\max} /cm⁻¹ (neat) 3180 (m, N-H), 2861 (m, C-H), 1662 (s, C=O), 1269 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.68 (1H, d, $J = 2.5$ Hz, ArH), 7.36-7.31 (2H, m, 2 x ArH), 7.29 (1H, t, $J = 7.0$ Hz, ArH), 7.21-7.15 (2H, m, 2 x ArH), 7.10 (1H, s, CONH), 6.99 (1H, dd, $J = 8.5, 3.0$ Hz, ArH), 6.90 (1H, d, $J = 8.5$ Hz, ArH), 4.27 (1H, dd, $J = 7.5, 5.5$ Hz, C(Ar)H), 3.87 (3H, s, OCH₃), 3.80 (1H, ddd, $J = 12.0, 5.5, 3.0$ Hz, C(H)H), 3.70 (1H, ddd, $J =$

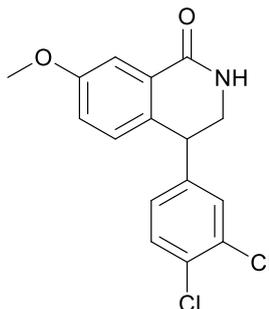
12.0, 7.5, 3.0 Hz, C(H)H); δ_c (126 MHz, CDCl₃) 166.4 (C=O), 158.9 (ArC), 141.0 (ArC), 133.6 (ArC), 130.0 (ArC), 129.0 (2 x ArCH), 128.7 (2 x ArCH), 128.5 (2 x ArCH), 127.3 (ArCH), 120.0 (ArCH), 111.1 (ArCH), 55.6 (OCH₃), 47.3 (CH₂), 43.5 (C(Ar)H); m/z (ESI) 276 [M+Na]⁺; HRMS (ESI) C₁₆H₁₅NO₂Na⁺ requires 276.0995, found 276.0999 [M+Na]⁺.

4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, **235**



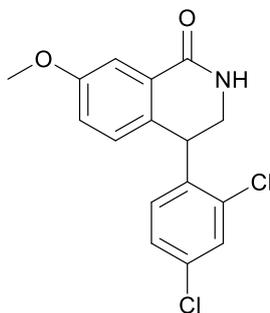
General procedure I was applied using (*E*)-*N*-(3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **227** (550 mg, 1.50 mmol), mesyl chloride (37.6 mL) and ZrCl₄ (1.75 g, 7.52 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 4-(4-chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **235** as an off-white solid (335 mg, 77 %); m.p. 152-153 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3180 (m, N-H), 2834 (m, C-H), 1671 (s, C=O), 1483 (s, C-O); δ_H (500 MHz, CDCl₃) 7.70 (1H, d, *J* = 3.0 Hz, ArH), 7.33-7.30 (2H, m, 2 x ArH), 7.14-7.10 (2H, m, 2 x ArH), 7.02 (1H, dd, *J* = 8.5, 3.0 Hz, ArH), 6.90 (1H, d, *J* = 8.5 Hz, ArH), 6.29 (1H, s, CONH), 4.26 (1H, dd, *J* = 7.0, 5.5 Hz, C(Ar)H), 3.89 (3H, s, OCH₃), 3.64 (1H, ddd, *J* = 12.0, 5.5, 3.0 Hz, C(H)H), 3.64 (1H, ddd, *J* = 12.0, 7.0, 3.0 Hz, C(H)H); δ_c (126 MHz, CDCl₃) 165.9 (C=O), 159.1 (ArC), 139.5 (ArC), 133.2 (ArC), 132.9 (ArC), 129.9 (ArC), 129.8 (2 x ArCH), 128.9 (ArCH), 128.9 (2 x ArCH), 120.2 (ArCH), 111.3 (ArCH), 55.6 (OCH₃), 47.4 (CH₂), 42.9 (C(Ar)H); m/z (ESI) 288 [M+H]⁺; HRMS (ESI) C₁₆H₁₅³⁵ClNO₂⁺ requires 288.0786, found 288.0785 [M+H]⁺.

4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, **236**



General procedure I was applied using (*E*)-*N*-(3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **228** (500 mg, 1.25 mmol), mesyl chloride (31.0 mL) and ZrCl₄ (1.46 g, 6.25 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **236** as an off-white solid (300 mg, 74 %); m.p. 203-204 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3177 (m, N-H), 2837 (m, C-H), 1666 (s, C=O), 1238 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.70 (1H, d, $J = 2.5$ Hz, ArH), 7.40 (1H, d, $J = 8.5$ Hz, ArH), 7.29-7.27 (1H, m, ArH), 7.04 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.00 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.92 (1H, d, $J = 8.5$ Hz, ArH), 6.26 (1H, s, CONH), 4.24 (1H, t, $J = 6.0$ Hz, C(Ar)H), 3.90 (3H, s, OCH₃), 3.85 (1H, ddd, $J = 12.0, 6.0, 3.0$ Hz, C(H)H), 3.63 (1H, ddd, $J = 12.0, 6.0, 3.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 165.8 (C=O), 159.3 (ArC), 141.4 (ArC), 132.8 (ArC), 132.1 (ArC), 131.5 (ArC), 130.7 (ArCH), 130.3 (ArCH), 129.9 (ArC), 128.9 (ArCH), 127.8 (ArCH), 120.3 (ArCH), 111.5 (ArCH), 55.6 (OCH₃), 47.2 (CH₂), 42.6 (C(Ar)H); m/z (ESI) 322 [M+H]⁺; HRMS (ESI) C₁₆H₁₄³⁵Cl₂NO₂⁺ requires 322.0396, found 322.0396 [M+H]⁺.

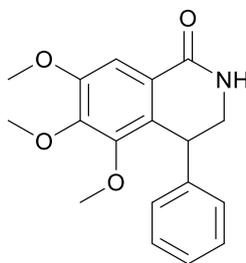
4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, **237**



General procedure I was applied using (*E*)-*N*-(3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **229** (550 mg, 1.37 mmol), mesyl chloride (34.4 mL) and ZrCl₄ (1.60 g, 6.87 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 4-(2,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **237** as an off-white solid

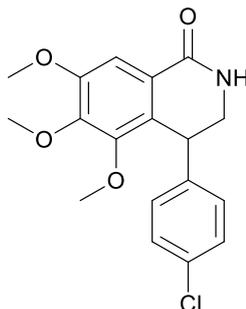
(325 mg, 73 %); m.p. 193-194 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3187 (m, N-H), 2837 (m, C-H), 1673 (s, C=O), 1252 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.72 (1H, d, $J = 2.7$ Hz, ArH), 7.47 (1H, d, $J = 2.0$ Hz, ArH), 7.12 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 7.06 (1H, dd, $J = 8.5, 3.0$ Hz, ArH), 6.98 (1H, d, $J = 8.5$ Hz, ArH), 6.74 (1H, d, $J = 8.5$ Hz, ArH), 6.05 (1H, s, CONH), 4.72 (1H, t, $J = 4.5$ Hz, C(Ar)H), 3.91 (3H, s, OCH₃), 3.94-3.88 (1H, m, C(H)H), 3.65 (1H, dt, $J = 12.5, 4.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 170.0 (C=O), 159.9 (ArC), 138.5 (ArC), 138.0 (ArC), 134.3 (ArC), 133.5 (ArC), 129.8 (ArCH), 129.8 (ArCH), 129.4 (ArCH), 127.6 (ArCH), 116.7 (ArC), 109.0 (ArCH), 101.8 (ArCH), 55.5 (OCH₃), 37.6 (CH₂), 37.1 (C(Ar)H); m/z (ESI) 344 [M+Na]⁺; HRMS (ESI) C₁₆H₁₃³⁵Cl₂NO₂Na⁺ requires 344.0216, found 344.0217 [M+Na]⁺.

5,6,7-Trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one, **238**



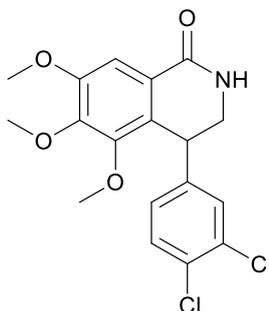
General procedure I was applied using (*E*)-*N*-(4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **230** (500 mg, 1.28 mmol), mesyl chloride (31.9 mL) and ZrCl₄ (1.49 g, 6.39 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 5,6,7-trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one **238** as an off-white solid (220 mg, 55 %); m.p. 193-194 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3183 (m, N-H), 2839 (m, C-H), 1666 (s, C=O), 1343 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.54 (1H, s, ArH), 7.28-7.23 (2H, m, 2 x ArH), 7.23-7.18 (1H, m, ArH), 7.13-7.08 (2H, m, 2 x ArH), 6.30 (1H, d, $J = 4.5$ Hz, CONH), 4.47 (1H, d, $J = 5.0$ Hz, C(Ar)H), 4.01 (1H, dd, $J = 12.5, 5.0$ Hz, C(H)H), 3.95 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 3.53 (1H, ddd, $J = 12.5, 5.0, 1.0$ Hz, C(H)H), 3.51 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 165.9 (C=O), 152.9 (ArC), 150.0 (ArC), 146.0 (ArC), 142.0 (ArC), 128.5 (2 x ArCH), 127.9 (2 x ArCH), 127.6 (ArC), 126.9 (ArCH), 124.3 (ArC), 106.5 (ArCH), 60.8 (OCH₃), 60.8 (OCH₃), 56.2 (OCH₃), 47.4 (CH₂), 37.3 (C(Ar)H); m/z (ESI) 336 [M+Na]⁺; HRMS (ESI) C₁₈H₁₉NO₄Na⁺ requires 336.1206, found 336.1197 [M+Na]⁺.

4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, **239**



General procedure I was applied using (*E*)-*N*-(3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **231** (500 mg, 1.17 mmol), mesyl chloride (29.4 mL) and $ZrCl_4$ (1.37 g, 5.87 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 4-(4-chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **239** as an off-white solid (350 mg, 86 %); m.p. 166-167 °C; ν_{max}/cm^{-1} (neat) 3185 (m, N-H), 2833 (m, C-H), 1680 (s, C=O), 1339 (s, C-O); δ_H (500 MHz, $CDCl_3$) 7.56 (1H, s, ArH), 7.27-7.22 (2H, m, 2 x ArH), 7.09-7.03 (2H, m, 2 x ArH), 5.86 (1H, d, $J = 4.5$ Hz, CONH), 4.45 (1H, d, $J = 5.0$ Hz, C(Ar)H), 4.03 (1H, dd, $J = 12.5, 5.0$ Hz, C(H)H), 3.97 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.49 (1H, ddd, $J = 12.5, 5.0, 1.0$ Hz, C(H)H); δ_C (126 MHz, $CDCl_3$) 165.6 (C=O), 153.2 (ArC), 149.9 (ArC), 146.0 (ArC), 140.5 (ArC), 132.8 (ArC), 129.2 (2 x ArCH), 128.6 (2 x ArCH), 127.0 (ArC), 124.1 (ArC), 106.6 (ArCH), 60.9 (OCH_3), 60.8 (OCH_3), 56.2 (OCH_3), 47.4 (CH_2), 36.9 (C(Ar)H); m/z (ESI) 370 [$M+Na$] $^+$; HRMS (ESI) $C_{18}H_{18}^{35}ClNO_4Na^+$ requires 370.0817, found 370.0816 [$M+Na$] $^+$.

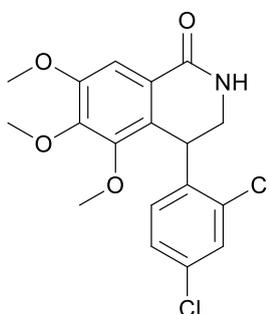
4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, **240**



General procedure I was applied using (*E*)-*N*-(3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **232** (500 mg, 1.09 mmol), mesyl chloride (27.2 mL) and $ZrCl_4$ (1.27 g, 5.43 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **240** as an

off-white solid (284 mg, 68 %); m.p. 203-204 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3174 (m, N-H), 2937 (m, C-H), 1672 (s, C=O), 1343 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.55 (1H, s, ArH), 7.34 (1H, d, $J = 8.5$ Hz, ArH), 7.25 (1H, d, $J = 2.0$ Hz, ArH), 6.94 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 5.95 (1H, d, $J = 4.5$ Hz, CONH), 4.42 (1H, d, $J = 5.0$ Hz, C(Ar)H), 4.03 (1H, dd, $J = 12.5, 5.0$ Hz, C(H)H), 3.97 (3H, s, OCH₃), 3.93 (3H, s, OCH₃), 3.62 (3H, s, OCH₃), 3.50 (1H, ddd, $J = 12.5, 5.0, 1.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 165.5 (C=O), 153.4 (ArC), 149.9 (ArC), 146.0 (ArC), 142.3 (ArC), 132.6 (ArC), 131.1 (ArC), 130.4 (ArCH), 129.8 (ArCH), 127.3 (ArCH), 126.1 (ArC), 124.0 (ArC), 106.7 (ArCH), 61.0 (OCH₃), 60.8 (OCH₃), 56.2 (OCH₃), 47.2 (CH₂), 36.7 (C(Ar)H); m/z (ESI) 404 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵Cl₂NO₄Na⁺ requires 404.0427, found 404.0424 [M+Na]⁺.

4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, **241**



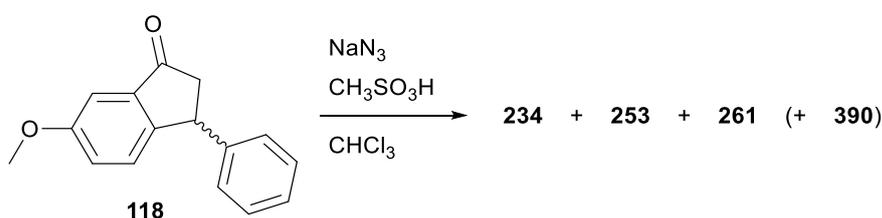
General procedure I was applied using (*E*)-*N*-(3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)methanesulfonamide **233** (500 mg, 1.09 mmol), mesyl chloride (27.2 mL) and ZrCl₄ (1.27 g, 5.43 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, yielded 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **241** as an off-white solid (322 mg, 78 %); m.p. 230-231 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3170 (m, N-H), 2926 (m, C-H), 1667 (s, C=O), 1344 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.57 (1H, s, ArH), 7.47 (1H, d, $J = 2.0$ Hz, ArH), 7.06 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.65 (1H, d, $J = 8.5$ Hz, ArH), 5.93 (1H, d, $J = 4.5$ Hz, CONH), 4.90 (1H, d, $J = 5.0$ Hz, C(Ar)H), 3.98 (3H, s, OCH₃), 4.01-3.95 (1H, m, C(H)H), 3.92 (3H, s, OCH₃), 3.58 (3H, s, OCH₃), 3.57-3.51 (1H, m, C(H)H); δ_{C} (126 MHz, CDCl_3) 165.8 (C=O), 153.4 (ArC), 149.8 (ArC), 146.2 (ArC), 137.3 (ArC), 133.8 (ArC), 133.4 (ArC), 130.6 (ArCH), 129.5 (ArCH), 127.0 (ArCH), 126.3 (ArC), 124.7 (ArC), 106.5 (ArCH), 60.9 (OCH₃), 60.8 (OCH₃), 56.2 (OCH₃), 45.1 (CH₂), 33.6 (C(Ar)H); m/z (ESI) 404 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵Cl₂NO₄Na⁺ requires 404.0427, found 404.0426 [M+Na]⁺.

3.6.5 Schmidt Reaction of Indan-1-ones – General Procedure J

The following procedure was performed in accordance with previous literature.¹⁵⁴

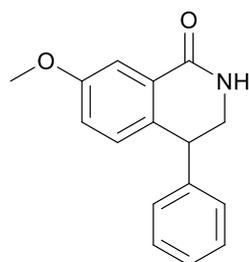
To a solution of substituted indan-1-one (1.00 equiv.) in CHCl₃ (4.70 mL/mmol), at 0 °C, was initially added methanesulfonic acid (9.43 equiv.) and then sodium azide (2.00 equiv.) in small portions. The resulting mixture was refluxed for 6 hours, then quenched into ice water and neutralised with NH₄OH solution. The organics were extracted with Et₂O, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

Schmidt Reaction of 6-Methoxy-3-phenyl-2,3-dihydro-1*H*-indan-1-one, **118**



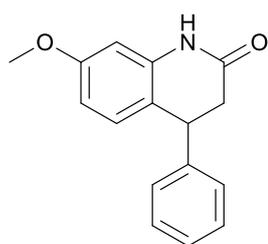
General procedure J was applied using 6-methoxy-3-phenyl-2,3-dihydro-1*H*-indan-1-one **118** (100 mg, 0.42 mmol), CHCl₃ (1.97 mL), methanesulfonic acid (257 μL, 3.96 mmol) and sodium azide (55 mg, 0.84 mmol). Work-up yielded a brown oil, comprising a 0.47:0.30:0.23 mixture of 7-methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one **234**, 7-methoxy-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one **253** and 9-methoxy-6-phenyl-5,6-dihydrotetrazolo[5,1-*a*]isoquinoline **261**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **234** as an off-white solid (26 mg, 24 %), **253** as an off-white solid (26 mg, 24 %), and **261** as an off-white solid (9 mg, 8 %). Also isolated was 5-methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one **390**, resulting from the reaction of the 4-methoxy isomer of **118**, as an off-white solid (5 mg, 5 %). Spectroscopic data for each compound are as follows:

7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one, **234**



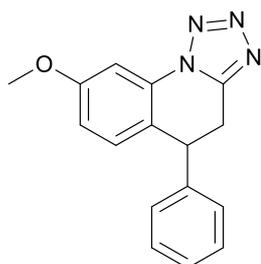
Spectroscopic data are in agreement with those previously acquired.

7-Methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one, 253



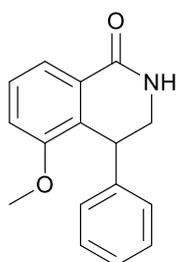
m.p. 158-160 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3210 (m, N-H), 2837 (m, C-H), 1677 (s, C=O), 1373 (s, C-O); δ_{H} (500 MHz, CDCl_3) 8.78 (1H, s, CONH), 7.38-7.32 (2H, m, 2 x ArH), 7.31-7.26 (1H, m, ArH), 7.23-7.19 (2H, m, 2 x ArH), 6.83 (1H, d, $J = 8.5$ Hz, ArH), 6.53 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.45 (1H, d, $J = 2.5$ Hz, ArH), 4.26 (1H, dd, $J = 8.0, 7.0$ Hz, C(Ar)H), 3.80 (3H, s, OCH₃), 2.96 (1H, dd, $J = 16.0, 7.0$ Hz, C(H)H), 2.91 (1H, dd, $J = 16.0, 8.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 171.0 (C=O), 159.5 (ArC), 142.0 (ArC), 138.1 (ArC), 129.3 (ArCH), 128.9 (2 x ArCH), 127.8 (2 x ArCH), 127.2 (ArCH), 118.9 (ArC), 108.6 (ArCH), 101.7 (ArCH), 55.5 (OCH₃), 41.4 (C(Ar)H), 38.8 (CH₂); m/z (ESI) 276 [M+Na]⁺; HRMS (ESI) C₁₆H₁₅NO₂Na⁺ requires 276.0995, found 276.0986 [M+Na]⁺. These data are consistent with those previously reported.²⁵⁰

8-Methoxy-5-phenyl-4,5-dihydro-1,2,4-triazolo[1,5-a]quinoline, 261



m.p. 135-137 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2838 (m, C-H), 1630 (m, C=N), 1494 (s, N=N), 1259 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.42 (1H, d, $J = 2.5$ Hz, ArH), 7.23-7.17 (3H, m, 3 x ArH), 7.09 (1H, d, $J = 8.5$ Hz, ArH), 7.01 (1H, d, $J = 2.5$ Hz, ArH), 7.01-6.97 (2H, m, 2 x ArH), 5.63 (1H, dd, $J = 7.0, 5.0$ Hz, C(Ar)H), 3.86 (3H, s, OCH₃), 3.67 (1H, dd, $J = 14.0, 5.0$ Hz, C(H)H), 3.32 (1H, dd, $J = 14.0, 7.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 160.6 (C=N), 160.4 (ArC), 138.5 (ArC), 133.5 (ArC), 129.6 (2 x ArCH), 128.6 (2 x ArCH), 127.6 (ArCH), 125.6 (2 x ArCH), 124.2 (ArC), 117.7 (ArCH), 107.4 (ArCH), 61.9 (OCH₃), 55.8 (C(Ar)H), 39.2 (CH₂); m/z (ESI) 301 [M+Na]⁺; HRMS (ESI) C₁₆H₁₄N₄ONa⁺ requires 301.1060, found 301.1058 [M+Na]⁺.

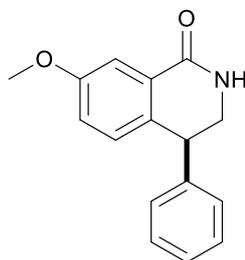
5-Methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one, 390



m.p. 215-217 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3201 (m, N-H), 2856 (m, C-H), 1663 (s, C=O), 1267 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.81 (1H, d, $J = 8.0$ Hz, ArH), 7.41 (1H, t, $J = 8.0$ Hz, ArH), 7.25-7.20 (3H, m, 3 x ArH), 7.12-7.08 (2H, m, 2 x ArH), 7.04 (1H, d, $J = 8.0$ Hz, ArH), 5.70 (1H, d, $J = 3.0$ Hz, CONH), 4.53 (1H, d, $J = 4.5$ Hz, C(Ar)H), 4.02 (1H, dd, $J = 12.5, 4.5$ Hz, C(H)H), 3.74 (3H, s, OCH₃), 3.54 (1H, ddd, $J = 12.5, 5.5, 1.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 164.9 (C=O), 154.8 (ArC), 140.2 (ArC), 129.1 (ArC), 127.9 (ArC), 127.4 (2 x ArCH), 127.2 (ArCH), 126.8 (2 x ArCH), 125.8 (ArCH), 119.0 (ArCH), 113.3

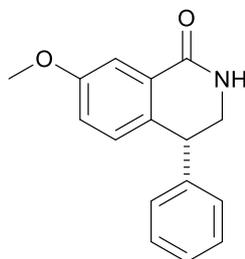
(ArCH), 54.8 (OCH₃), 46.3 (CH₂), 35.9 (C(Ar)H); m/z (ESI) 276 [M+Na]⁺; HRMS (ESI) C₁₆H₁₅NO₂Na⁺ requires 276.0995, found 276.0998 [M+Na]⁺.

(S)-7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one, (S)-234



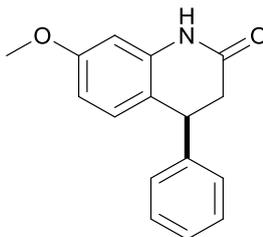
General procedure J was applied using (*S*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*S*)-**118** (143 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (66 mg, 43 %, 98 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁸ (c = 0.12, CHCl₃) -14.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 15:85, 1.00 mL/min., 218 nm, (*R*)-isomer 10.77 min., (*S*)-isomer 11.69 min.).

(R)-7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one, (R)-234



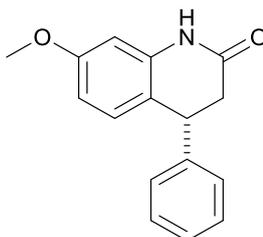
General procedure J was applied using (*R*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*R*)-**118** (143 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (46 mg, 30 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁷ (c = 0.12, CHCl₃) +14.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 15:85, 1.00 mL/min., 218 nm, (*R*)-isomer 10.80 min., (*S*)-isomer 11.79 min.).

(S)-7-Methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one, (S)-253



General procedure J was applied using (*S*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*S*)-**118** (143 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (50 mg, 33 %, 97 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +28.9; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 221 nm, (*R*)-isomer 18.56 min., (*S*)-isomer 20.01 min.).

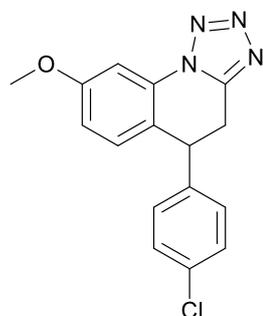
(R)-7-Methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one, (R)-253



General procedure J was applied using (*R*)-6-methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*R*)-**118** (143 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (57 mg, 37 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -34.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 221 nm, (*R*)-isomer 17.11 min., (*S*)-isomer 19.81 min.).

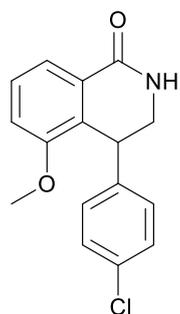
140.5 (ArC), 138.0 (ArC), 133.0 (ArC), 129.3 (ArCH), 129.1 (2 x ArCH), 129.0 (2 x ArCH), 118.3 (ArC), 108.6 (ArCH), 101.8 (ArCH), 55.5 (OCH₃), 40.8 (C(Ar)H), 38.7 (CH₂); m/z (ESI) 288 [M+H]⁺; HRMS (ESI) C₁₆H₁₅³⁵ClNO₂⁺ requires 288.0786, found 288.0788 [M+H]⁺.

5-(4-Chlorophenyl)-8-methoxy-4,5-dihydro-1,5-diazepino[1,5-a]quinoline, 262



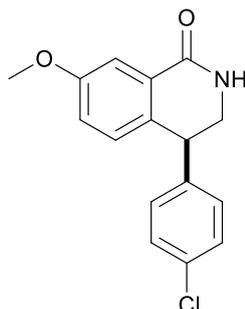
m.p. 162-164 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2843 (m, C-H), 1673 (m, C=N), 1492 (s, N=N), 1246 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.42 (1H, d, $J = 2.5$ Hz, ArH), 7.23 (1H, d, $J = 8.5$ Hz, ArH), 7.13 (2H, d, $J = 8.5$ Hz, 2 x ArH), 7.06 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.87 (2H, d, $J = 8.5$ Hz, 2 x ArH), 5.66-5.62 (1H, m, C(Ar)H), 3.87 (3H, s, OCH₃), 3.58 (1H, dd, $J = 14.0, 4.5$ Hz, C(H)H), 3.44 (1H, dd, $J = 14.0, 6.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 160.7 (C=N), 160.5 (ArC), 138.1 (ArC), 133.5 (ArC), 131.7 (ArC), 130.9 (2 x ArCH), 128.7 (2 x ArCH), 125.4 (ArCH), 124.3 (ArC), 117.9 (ArCH), 107.6 (ArCH), 61.6 (OCH₃), 55.8 (C(Ar)H), 38.3 (CH₂); m/z (ESI) 335 [M+Na]⁺; HRMS (ESI) C₁₆H₁₃³⁵ClN₄ONa⁺ requires 335.0670, found 335.0670 [M+Na]⁺.

4-(4-Chlorophenyl)-5-methoxy-3,4-dihydroisoquinolin-1(2H)-one, 391



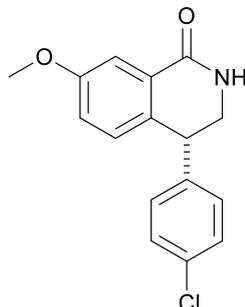
m.p. 175-177 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3188 (m, N-H), 2851 (m, C-H), 1668 (s, C=O), 1264 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.82 (1H, d, $J = 8.0$ Hz, ArH), 7.43 (1H, t, $J = 8.0$ Hz, ArH), 7.24-7.21 (2H, m, 2 x ArH), 7.08-7.04 (3H, m, 3 x ArH), 5.83 (1H, d, $J = 4.0$ Hz, CONH), 4.51 (1H, d, $J = 4.5$ Hz, C(Ar)H), 4.04 (1H, dd, $J = 12.5, 4.5$ Hz, C(H)H), 3.77 (3H, s, OCH₃), 3.54-3.49 (1H, ddd, $J = 12.5, 5.5, 1.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 165.9 (C=O), 155.7 (ArC), 139.8 (2 x ArC), 132.7 (ArC), 129.9 (ArC), 129.2 (2 x ArCH), 128.5 (2 x ArCH), 128.5 (ArCH), 120.1 (ArCH), 114.4 (ArCH), 55.8 (OCH₃), 47.1 (CH₂), 36.4 (C(Ar)H); m/z (ESI) 288 [M+H]⁺; HRMS (ESI) C₁₆H₁₅³⁵ClNO₂⁺ requires 288.0786, found 288.0785 [M+H]⁺.

(S)-4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, (S)-235



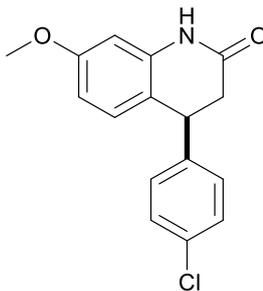
General procedure J was applied using (*S*)-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**119** (164 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (82 mg, 48 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -7.30; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 7:93, 1.00 mL/min., 219 nm, (*S*)-isomer 26.13 min., (*R*)-isomer 29.53 min.).

(R)-4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, (R)-235



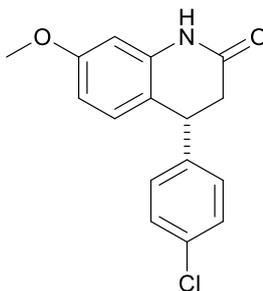
General procedure J was applied using (*R*)-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**119** (164 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (86 mg, 50 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.20, CHCl₃) +7.10; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 7:93, 1.00 mL/min., 219 nm, (*S*)-isomer 26.52 min., (*R*)-isomer 27.86 min.).

(S)-4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1H)-one, (S)-254



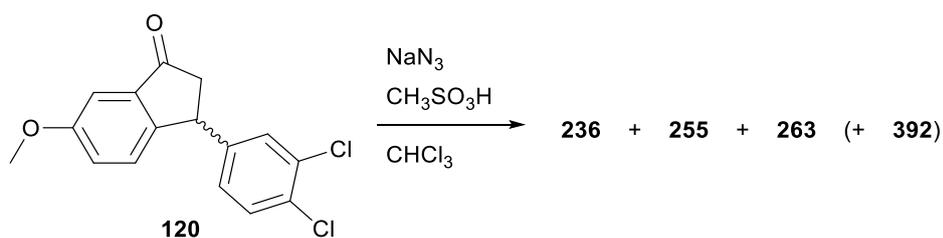
General procedure J was applied using (*S*)-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**119** (164 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (58 mg, 34 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +27.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 15:85, 1.00 mL/min., 223 nm, (*R*)-isomer 12.83 min., (*S*)-isomer 18.31 min.).

(R)-4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1H)-one, (R)-254



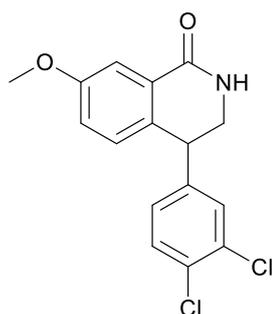
General procedure J was applied using (*R*)-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**119** (164 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (59 mg, 34 %, 98 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -37.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 15:85, 1.00 mL/min., 223 nm, (*R*)-isomer 12.65 min., (*S*)-isomer 19.52 min.).

Schmidt Reaction of 3-(3,4-Dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one, **120**



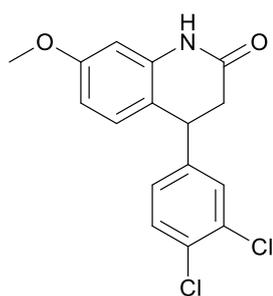
General procedure J was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one **120** (100 mg, 0.33 mmol), CHCl₃ (1.53 mL), methanesulfonic acid (199 μ L, 3.07 mmol) and sodium azide (42 mg, 0.65 mmol). Work-up yielded an off-white solid, comprising a 0.60:0.27:0.13 mixture of 4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **236**, 4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1*H*)-one **255**, and 6-(3,4-dichlorophenyl)-9-methoxy-5,6-dihydrotetrazolo[5,1-*a*]isoquinoline **263**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **236** as an off-white solid (55 mg, 53 %), **255** as an off-white solid (26 mg, 24 %), and **263** as an off-white solid (10 mg, 9 %). Also isolated was 4-(3,4-dichlorophenyl)-5-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **392**, resulting from the reaction of the 4-methoxy isomer of **120**, as an off-white solid (3 mg, 3 %). Spectroscopic data for each compound are as follows:

4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one, **236**



Spectroscopic data are in agreement with those previously acquired.

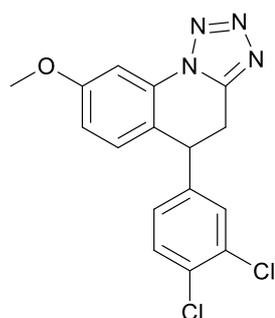
4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1*H*)-one, **255**



m.p. 216-217 °C; ν_{\max} /cm⁻¹ (neat) 3179 (m, N-H), 2842 (m, C-H), 1674 (s, C=O), 1381 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.87 (1H, s, CONH), 7.41 (1H, d, *J* = 8.5 Hz, ArH), 7.26 (1H, d, *J* = 2.0 Hz, ArH), 7.03 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 6.86 (1H, d, *J* = 8.5 Hz, ArH), 6.57 (1H, dd, *J* = 8.5, 2.5 Hz, ArH), 6.40 (1H, d, *J* = 2.5 Hz, ArH), 4.23 (1H, t, *J* = 7.0 Hz, C(Ar)H), 3.82 (3H, s,

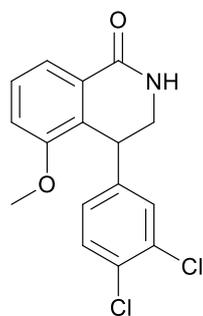
OCH₃), 2.96 (1H, dd, $J = 16.0, 7.0$ Hz, C(H)H), 2.84 (1H, dd, $J = 16.0, 7.0$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 169.5 (C=O), 159.9 (ArC), 142.3 (ArC), 137.9 (ArC), 132.9 (ArC), 131.3 (ArC), 130.9 (ArCH), 129.7 (ArCH), 129.3 (ArCH), 127.1 (ArCH), 117.5 (ArC), 108.7 (ArCH), 101.9 (ArCH), 55.5 (OCH₃), 40.7 (C(Ar)H), 38.6 (CH₂); m/z (ESI) 322 [M+H]⁺; HRMS (ESI) C₁₆H₁₄³⁵Cl₂NO₂⁺ requires 332.0396, found 332.0394 [M+H]⁺.

5-(3,4-Dichlorophenyl)-8-methoxy-4,5-dihydro-1H-tetrazolo[1,5-a]quinoline, 263



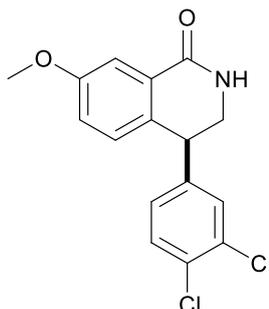
m.p. 169-171 °C; ν_{\max} /cm⁻¹ (neat) 2851 (m, C-H), 1632 (m, C=N), 1468 (s, N=N), 1249 (s, C-O); δ_H (500 MHz, CDCl₃) 7.47 (1H, d, $J = 2.0$ Hz, ArH), 7.27 (1H, d, $J = 6.5$ Hz, ArH), 7.26 (1H, d, $J = 6.5$ Hz, ArH), 7.10 (2H, dd, $J = 8.5, 2.0$ Hz, 2 x ArH), 6.79 (1H, s, ArH), 5.64 (1H, t, $J = 5.5$ Hz, C(Ar)H), 3.90 (3H, s, OCH₃), 3.55 (1H, dd, $J = 14.5, 5.0$ Hz, C(H)H), 3.45 (1H, dd, $J = 14.5, 6.5$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 160.9 (C=N), 160.5 (ArC), 137.8 (ArC), 133.5 (ArC), 132.7 (ArC), 132.0 (ArC), 131.5 (ArCH), 130.6 (ArCH), 128.8 (ArCH), 125.3 (ArCH), 124.3 (ArC), 118.0 (ArCH), 107.7 (ArCH), 61.2 (OCH₃), 55.9 (C(Ar)H), 38.2 (CH₂); m/z (ESI) 369 [M+Na]⁺; HRMS (ESI) C₁₆H₁₂³⁵Cl₂N₄ONa⁺ requires 369.0280, found 369.0282 [M+Na]⁺.

4-(3,4-Dichlorophenyl)-5-methoxy-3,4-dihydroisoquinolin-1(2H)-one, 392



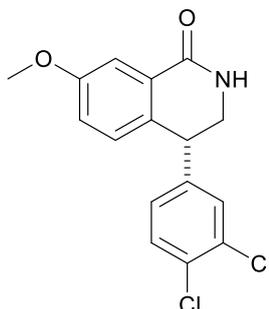
m.p. 198-200 °C; ν_{\max} /cm⁻¹ (neat) 3194 (m, N-H), 2837 (m, C-H), 1661 (s, C=O), 1269 (s, C-O); δ_H (500 MHz, CDCl₃) 7.82 (1H, d, $J = 8.0$ Hz, ArH), 7.45 (1H, t, $J = 8.0$ Hz, ArH), 7.31 (1H, d, $J = 8.5$ Hz, ArH), 7.24 (1H, d, $J = 2.0$ Hz, ArH), 7.08 (1H, d, $J = 8.0$ Hz, ArH), 6.94 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 5.98 (1H, d, $J = 4.0$ Hz, CONH), 4.48 (1H, d, $J = 4.5$ Hz, C(Ar)H), 4.04 (1H, dd, $J = 12.5, 4.5$ Hz, C(H)H), 3.79 (3H, s, OCH₃), 3.54 (1H, ddd, $J = 12.5, 5.5, 1.0$ Hz, C(H)H); δ_C (126 MHz, CDCl₃) 165.8 (C=O), 155.7 (ArC), 141.7 (ArC), 132.4 (ArC), 131.0 (ArC), 130.3 (ArCH), 129.9 (ArCH), 129.8 (ArC), 128.8 (ArCH), 127.8 (ArC), 127.3 (ArCH), 120.2 (ArCH), 114.4 (ArCH), 55.8 (OCH₃), 46.9 (CH₂), 36.2 (C(Ar)H); m/z (ESI) 344 [M+Na]⁺; HRMS (ESI) C₁₆H₁₃³⁵Cl₂NO₂Na⁺ requires 344.0216, found 344.0214 [M+Na]⁺.

(S)-4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, (S)-236



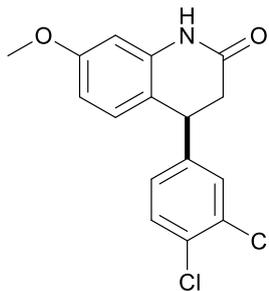
General procedure J was applied using (*S*)-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**120** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (102 mg, 53 %, 99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -3.30; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 217 nm, (*S*)-isomer 39.84 min., (*R*)-isomer 42.65 min.).

(R)-4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, (R)-236



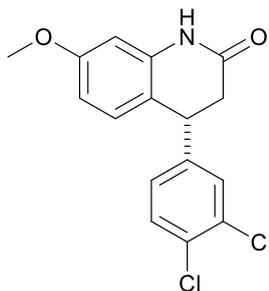
General procedure J was applied using (*R*)-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**120** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (100 mg, 52 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.20, CHCl₃) +4.10; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 217 nm, (*S*)-isomer 41.12 min., (*R*)-isomer 43.38 min.).

(S)-4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1H)-one, (S)-255



General procedure J was applied using (*S*)-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**120** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (47 mg, 24 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +21.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 221 nm, (*R*)-isomer 19.99 min., (*S*)-isomer 21.36 min.).

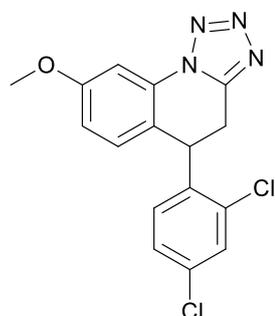
(R)-4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1H)-one, (R)-255



General procedure J was applied using (*R*)-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**120** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (62 mg, 32 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -34.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 221 nm, (*R*)-isomer 20.00 min., (*S*)-isomer 22.01 min.).

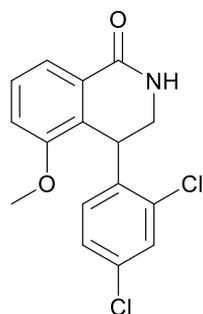
165.9 ($\underline{\text{C}}=\text{O}$), 159.4 ($\text{Ar}\underline{\text{C}}$), 137.1 ($\text{Ar}\underline{\text{C}}$), 134.1 ($\text{Ar}\underline{\text{C}}$), 133.6 ($\text{Ar}\underline{\text{C}}$), 131.5 ($\text{Ar}\underline{\text{C}}$), 131.1 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 130.5 ($\text{Ar}\underline{\text{C}}$), 129.6 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 129.2 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 127.3 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 120.6 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 111.3 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 55.6 ($\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 45.4 ($\underline{\text{C}}(\text{Ar})\underline{\text{H}}$), 39.2 ($\underline{\text{C}}\underline{\text{H}}_2$); m/z (ESI) 344 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{16}\text{H}_{13}^{35}\text{Cl}_2\text{NO}_2\text{Na}^+$ requires 344.0216, found 344.0219 $[\text{M}+\text{Na}]^+$.

5-(2,4-Dichlorophenyl)-8-methoxy-4,5-dihydro-1H-tetrazolo[1,5-a]quinoline, 264



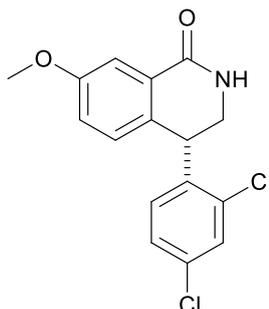
m.p. 181-183 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2851 (m, C-H), 1542 (m, C=N), 1432 (s, N=N), 1227 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.54 (1H, d, $J = 2.5$ Hz, $\text{Ar}\underline{\text{H}}$), 7.48 (1H, d, $J = 2.0$ Hz, $\text{Ar}\underline{\text{H}}$), 7.24 (1H, dd, $J = 8.0, 2.0$ Hz, $\text{Ar}\underline{\text{H}}$), 7.20 (1H, d, $J = 8.5$ Hz, $\text{Ar}\underline{\text{H}}$), 7.08-7.05 (1H, m, $\text{Ar}\underline{\text{H}}$), 7.05 (1H, d, $J = 8.0$, $\text{Ar}\underline{\text{H}}$), 5.70 (1H, t, $J = 7.0$ Hz, $\text{C}(\text{Ar})\underline{\text{H}}$), 3.92 (3H, s, $\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 3.55 (1H, dd, $J = 14.0, 7.0$ Hz, $\text{C}(\underline{\text{H}})\underline{\text{H}}$), 3.43 (1H, dd, $J = 14.0, 6.5$ Hz, $\text{C}(\underline{\text{H}})\underline{\text{H}}$); δ_{C} (126 MHz, CDCl_3) 160.9 ($\underline{\text{C}}=\text{N}$), 160.4 ($\text{Ar}\underline{\text{C}}$), 138.3 ($\text{Ar}\underline{\text{C}}$), 135.1 ($\text{Ar}\underline{\text{C}}$), 134.7 ($\text{Ar}\underline{\text{C}}$), 132.9 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 131.0 ($\text{Ar}\underline{\text{C}}$), 129.8 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 127.6 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 125.7 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 124.0 ($\text{Ar}\underline{\text{C}}$), 117.9 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 107.6 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 60.4 ($\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 55.9 ($\underline{\text{C}}(\text{Ar})\underline{\text{H}}$), 37.2 ($\underline{\text{C}}\underline{\text{H}}_2$); m/z (ESI) 369 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{16}\text{H}_{12}^{35}\text{Cl}_2\text{N}_4\text{ONa}^+$ requires 369.0280, found 369.0276 $[\text{M}+\text{Na}]^+$.

4-(2,4-Dichlorophenyl)-5-methoxy-3,4-dihydroisoquinolin-1(2H)-one, 393



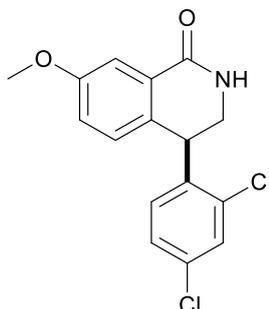
m.p. 195-197 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3200 (m, N-H), 2853 (m, C-H), 1685 (s, C=O), 1265 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.84 (1H, d, $J = 8.0$ Hz, $\text{Ar}\underline{\text{H}}$), 7.47 (1H, d, $J = 8.0$ Hz, $\text{Ar}\underline{\text{H}}$), 7.46-7.44 (1H, m, $\text{Ar}\underline{\text{H}}$), 7.07 (1H, d, $J = 8.0$ Hz, $\text{Ar}\underline{\text{H}}$), 7.02 (1H, dd, $J = 8.5, 2.0$ Hz, $\text{Ar}\underline{\text{H}}$), 6.60 (1H, d, $J = 8.5$ Hz, $\text{Ar}\underline{\text{H}}$), 5.90 (1H, d, $J = 4.0$ Hz, $\text{CONH}\underline{\text{H}}$), 4.93 (1H, d, $J = 5.0$ Hz, $\text{C}(\text{Ar})\underline{\text{H}}$), 3.97 (1H, dd, $J = 13.0, 5.0$ Hz, $\text{C}(\underline{\text{H}})\underline{\text{H}}$), 3.75 (3H, s, $\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 3.57 (1H, dd, $J = 13.0, 5.5$ Hz, $\text{C}(\underline{\text{H}})\underline{\text{H}}$); δ_{C} (126 MHz, CDCl_3) 166.0 ($\underline{\text{C}}=\text{O}$), 155.6 ($\text{Ar}\underline{\text{C}}$), 136.7 ($\text{Ar}\underline{\text{C}}$), 134.1 ($\text{Ar}\underline{\text{C}}$), 133.3 ($\text{Ar}\underline{\text{C}}$), 130.7 ($\text{Ar}\underline{\text{C}}$), 130.4 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 129.5 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 128.8 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 127.6 ($\text{Ar}\underline{\text{C}}$), 126.9 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 120.0 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 114.4 ($\text{Ar}\underline{\text{C}}\underline{\text{H}}$), 55.9 ($\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 44.9 ($\underline{\text{C}}\underline{\text{H}}_2$), 33.5 ($\underline{\text{C}}(\text{Ar})\underline{\text{H}}$); m/z (ESI) 344 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{16}\text{H}_{13}^{35}\text{Cl}_2\text{NO}_2\text{Na}^+$ requires 344.0216, found 344.0217 $[\text{M}+\text{Na}]^+$.

(S)-4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, (S)-237



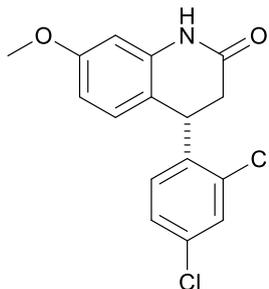
General procedure J was applied using (*S*)-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**121** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (118 mg, 61 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +25.9; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 218 nm, (*S*)-isomer 15.29 min., (*R*)-isomer 17.35 min.).

(R)-4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one, (R)-237



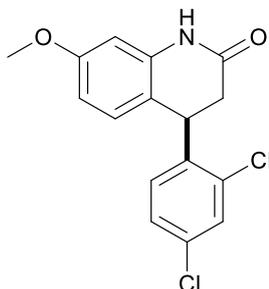
General procedure J was applied using (*R*)-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**121** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (113 mg, 58 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -19.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 218 nm, (*S*)-isomer 15.44 min., (*R*)-isomer 17.07 min.).

(S)-4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1H)-one, (S)-256



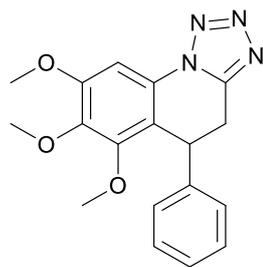
General procedure J was applied using (*S*)-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**121** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (51 mg, 26 %, 92 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +27.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 222 nm, (*R*)-isomer 12.83 min., (*S*)-isomer 15.85 min.).

(R)-4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroquinolin-2(1H)-one, (R)-256



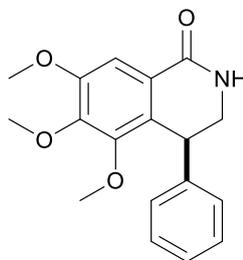
General procedure J was applied using (*R*)-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**121** (184 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (40 mg, 21 %, 94 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -41.9; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 222 nm, (*R*)-isomer 12.65 min., (*S*)-isomer 16.16 min.).

6,7,8-Trimethoxy-5-phenyl-4,5-dihydro-1H-tetrazolo[1,5-a]quinoline, 265



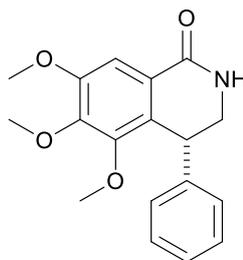
m.p. 100-102 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2851 (m, C-H), 1581 (w, C=N), 1482 (s, N=N), 1105 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.25-7.18 (3H, m, 3 x ArH), 6.96-6.92 (2H, m, 2 x ArH), 5.92 (1H, t, $J = 4.5$ Hz, C(Ar)H), 4.37 (3H, s, OCH₃), 4.14 (3H, s, OCH₃), 4.08 (3H, s, OCH₃), 4.00 (1H, dd, $J = 14.0, 4.0$ Hz, C(H)H), 3.75 (1H, dd, $J = 14.0, 4.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 160.7 (C=N), 155.7 (ArC), 149.5 (ArC), 143.7 (ArC), 133.2 (ArC), 130.6 (ArC), 129.2 (2 x ArCH), 128.2 (2 x ArCH), 127.2 (ArCH), 118.5 (ArC), 101.3 (ArCH), 61.3 (OCH₃), 61.2 (OCH₃), 61.1 (OCH₃), 56.4 (C(Ar)H), 36.8 (CH₂); m/z (ESI) 361 [M+Na]⁺; HRMS (ESI) C₁₈H₁₈N₄O₃Na⁺ requires 361.1271, found 361.1272 [M+Na]⁺.

(S)-5,6,7-Trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one, (S)-238



General procedure J was applied using (*S*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-indolen-1-one (*S*)-122 (179 mg, 0.60 mmol), CHCl_3 (2.82 mL), methanesulfonic acid (368 μL , 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (148 mg, 79 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{28}$ ($c = 0.20$, CHCl_3) +55.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 221 nm, (*R*)-isomer 12.68 min., (*S*)-isomer 18.79 min.).

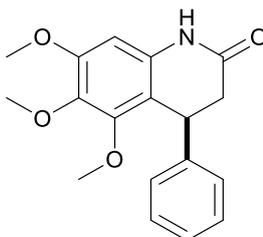
(R)-5,6,7-Trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one, (R)-238



General procedure J was applied using (*R*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-indolen-1-one (*R*)-122 (179 mg, 0.60 mmol), CHCl_3 (2.82 mL), methanesulfonic acid (368

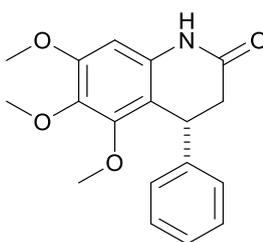
μL , 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (153 mg, 81 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.20$, CHCl_3) -54.5 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 221 nm, (*R*)-isomer 12.63 min., (*S*)-isomer 19.59 min.).

(*S*)-5,6,7-Trimethoxy-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one, (*S*)-257



General procedure J was applied using (*S*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*S*)-**122** (179 mg, 0.60 mmol), CHCl_3 (2.82 mL), methanesulfonic acid (368 μL , 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (9 mg, 5 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.10$, CHCl_3) $+7.50$; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 222 nm, (*S*)-isomer 11.41 min., (*R*)-isomer 17.92 min.).

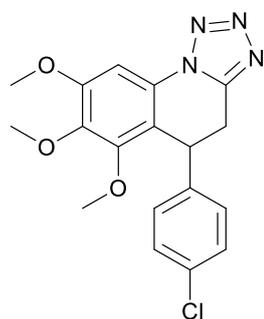
(*R*)-5,6,7-Trimethoxy-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one, (*R*)-257



General procedure J was applied using (*R*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*R*)-**122** (179 mg, 0.60 mmol), CHCl_3 (2.82 mL), methanesulfonic acid (368 μL , 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (10 mg, 5 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.06$, CHCl_3) -16.7 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 222 nm, (*S*)-isomer 11.52 min., (*R*)-isomer 17.60 min.).

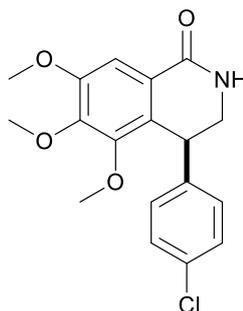
(ArCH), 61.0 (2 x OCH₃), 56.2 (OCH₃), 38.2 (CH₂), 35.2 (C(Ar)H); m/z (ESI) 370 [M+Na]⁺; HRMS (ESI) C₁₈H₁₈³⁵ClNO₄Na⁺ requires 370.0817, found 370.0818 [M+Na]⁺.

5-(4-Chlorophenyl)-6,7,8-trimethoxy-4,5-dihydro-1H-tetrazolo[1,5-a]quinoline, 266



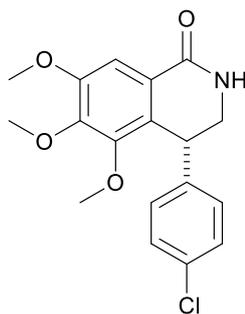
m.p. 141-143 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2849 (m, C-H), 1535 (w, C=N), 1467 (s, N=N), 1115 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.12 (1H, s, ArH), 6.99 (2H, d, $J = 8.5$ Hz, 2 x ArH), 6.67 (2H, d, $J = 8.5$ Hz, 2 x ArH), 5.72 (1H, t, $J = 4.0$ Hz, C(Ar)H), 4.18 (3H, s, OCH₃), 3.95 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 3.79 (1H, dd, $J = 14.5, 4.0$ Hz, C(H)H), 3.58 (1H, dd, $J = 14.5, 4.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 160.7 (C=N), 155.8 (ArC), 149.5 (ArC), 143.7 (ArC), 133.2 (ArC), 131.6 (ArC), 130.5 (2 x ArCH), 130.1 (ArC), 128.4 (2 x ArCH), 118.5 (ArC), 101.5 (ArCH), 61.3 (OCH₃), 61.1 (OCH₃), 61.0 (OCH₃), 56.4 (C(Ar)H), 36.0 (CH₂); m/z (ESI) 395 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵ClN₄O₃Na⁺ requires 395.0881, found 395.0885 [M+Na]⁺.

(S)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, (S)-239



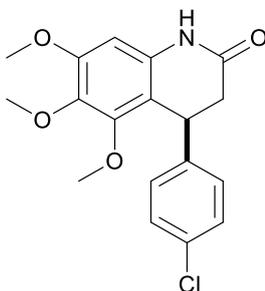
General procedure J was applied using (*S*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*S*)-**123** (200 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μ L, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (162 mg, 78 %, 91 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{28}$ ($c = 0.20$, CHCl₃) +26.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 223 nm, (*S*)-isomer 11.36 min., (*R*)-isomer 12.92 min.).

(R)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, (R)-239



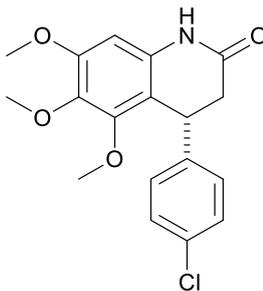
General procedure J was applied using (*R*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*R*)-**123** (200 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (140 mg, 67 %, 99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.20, CHCl₃) -32.6; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 223 nm, (*S*)-isomer 11.72 min., (*R*)-isomer 12.84 min.).

(S)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one, (S)-258



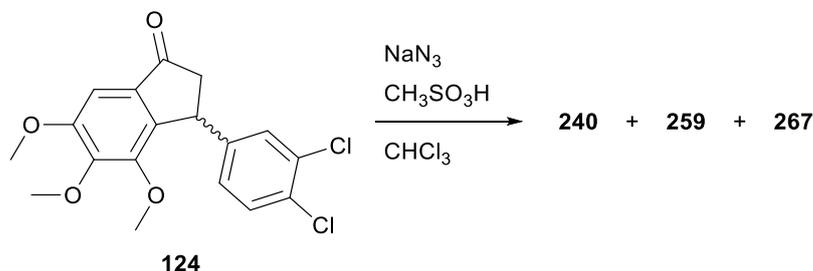
General procedure J was applied using (*S*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*S*)-**123** (200 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (8 mg, 4 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.10, CHCl₃) +5.80; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 224 nm, (*R*)-isomer 27.09 min., (*S*)-isomer 28.61 min.).

(R)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one, (R)-258



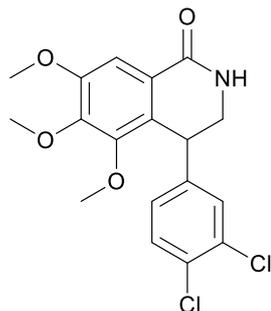
General procedure J was applied using (*R*)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one (*R*)-**123** (200 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (11 mg, 5 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.11, CHCl₃) -9.10; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 224 nm, (*R*)-isomer 26.86 min., (*S*)-isomer 29.53 min.).

Schmidt Reaction of 3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one, 124



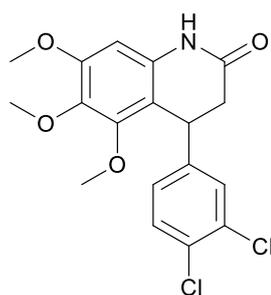
General procedure J was applied 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one **124** (100 mg, 0.27 mmol), CHCl₃ (1.28 mL), methanesulfonic acid (167 μL, 2.57 mmol) and sodium azide (35 mg, 0.54 mmol). Work-up yielded a yellow-brown solid, comprising a 0.89:0.05:0.06 mixture of 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **240**, 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1*H*)-one **259**, and 6-(3,4-dichlorophenyl)-7,8,9-trimethoxy-5,6-dihydro-tetrahydro[5,1-*a*]isoquinoline **267**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **240** as an off-white solid (70 mg, 67 %), **259** as an off-white solid (3 mg, 3 %) and **267** as an off-white solid (3 mg, 3 %). Spectroscopic data for each compound are as follows:

4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, 240



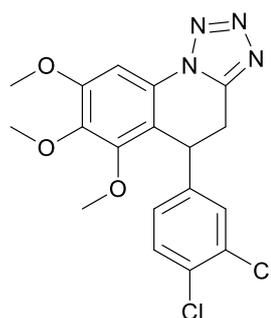
Spectroscopic data are in agreement with those previously acquired.

4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one, 259



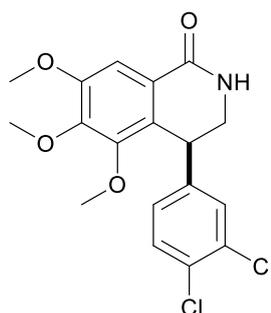
m.p. 218-220 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3184 (m, N-H), 2851 (m, C-H), 1678 (s, C=O), 1105 (s, C-O); δ_{H} (500 MHz, CDCl_3) 8.48 (1H, s, CONH), 7.33 (1H, d, $J = 8.5$ Hz, ArH), 7.21 (1H, d, $J = 2.0$ Hz, ArH), 6.97 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.22 (1H, s, ArH), 4.54 (1H, d, $J = 7.5$ Hz, C(Ar)H), 3.88 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 2.99 (1H, dd, $J = 16.5, 7.5$ Hz, C(H)H), 2.78 (1H, d, $J = 16.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 169.7 (C=O), 153.9 (ArC), 151.2 (ArC), 143.2 (ArC), 138.1 (ArC), 133.0 (ArC), 132.7 (ArC), 130.9 (ArC), 130.7 (ArCH), 129.1 (ArCH), 126.4 (ArCH), 110.2 (ArC), 95.7 (ArCH), 61.0 (2 x OCH₃), 56.2 (OCH₃), 38.0 (CH₂), 35.0 (C(Ar)H); m/z (ESI) 404 [M+Na]⁺; HRMS (ESI) $\text{C}_{18}\text{H}_{17}^{35}\text{Cl}_2\text{NO}_4\text{Na}^+$ requires 404.0427, found 404.0426 [M+Na]⁺. This compound is known but was previously reported without characterisation data.²⁵¹

5-(3,4-Dichlorophenyl)-6,7,8-trimethoxy-4,5-dihydro-1H-tetrazolo[1,5-a]quinolone, 267



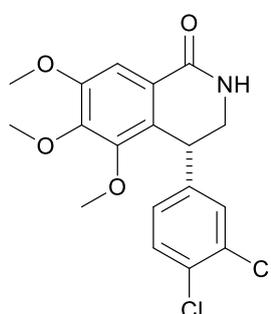
m.p. 144-146 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2850 (m, C-H), 1542 (w, C=N), 1467 (s, N=N), 1112 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.15 (1H, s, ArH), 7.09 (1H, d, $J = 8.0$ Hz, ArH), 6.94 (1H, d, $J = 2.0$ Hz, ArH), 6.52 (1H, dd, $J = 8.0, 2.0$ Hz, ArH), 5.72 (1H, t, $J = 4.0$ Hz, C(Ar)H), 4.19 (3H, s, OCH₃), 3.96 (3H, s, OCH₃), 3.93 (3H, s, OCH₃), 3.78 (1H, dd, $J = 14.5, 4.0$ Hz, C(H)H), 3.58 (1H, dd, $J = 14.5, 4.7$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 160.7 (C=N), 156.0 (ArC), 149.5 (ArC), 143.8 (ArC), 133.5 (ArC), 132.1 (ArC), 131.5 (ArC), 131.2 (ArCH), 130.2 (ArCH), 129.8 (ArC), 128.4 (ArCH), 118.4 (ArC), 101.7 (ArCH), 61.4 (OCH₃), 61.2 (OCH₃), 60.7 (OCH₃), 56.5 (C(Ar)H), 35.7 (CH₂); m/z (ESI) 429 [M+Na]⁺; HRMS (ESI) $\text{C}_{18}\text{H}_{16}^{35}\text{Cl}_2\text{N}_4\text{O}_3\text{Na}^+$ requires 429.0492, found 429.0490 [M+Na]⁺.

(S)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one,
(S)-240



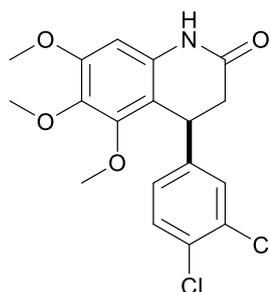
General procedure J was applied using (*S*)-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**124** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (188 mg, 82 %, 99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +20.9; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 224 nm, (*S*)-isomer 10.93 min., (*R*)-isomer 12.75 min.).

(R)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one,
(R)-240



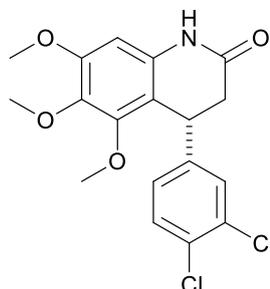
General procedure J was applied using (*R*)-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**124** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (180 mg, 78 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -17.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 224 nm, (*S*)-isomer 11.00 min., (*R*)-isomer 12.71 min.).

(S)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one,
(S)-259



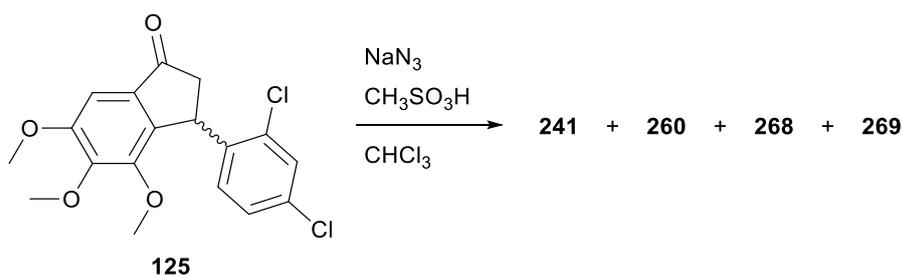
General procedure J was applied using (*S*)-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**124** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (9 mg, 4 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.08, CHCl₃) +2.20; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 222 nm, (*R*)-isomer 27.77 min., (*S*)-isomer 29.09 min.).

(R)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one,
(R)-259



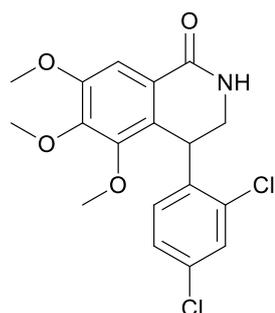
General procedure J was applied using (*R*)-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**124** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (8 mg, 3 %, 97 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.07, CHCl₃) -13.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 222 nm, (*R*)-isomer 28.01 min., (*S*)-isomer 30.78 min.).

Schmidt Reaction of 3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, **125**



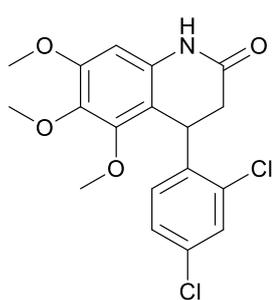
General procedure J was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (100 mg, 0.27 mmol), CHCl₃ (1.28 mL), methanesulfonic acid (167 μ L, 2.57 mmol) and sodium azide (35 mg, 0.54 mmol). Work-up yielded an off-white solid, comprising a 0.91:0.02:0.05:0.02 mixture of 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one **241**, 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one **260**, 5-(2,4-dichlorophenyl)-6,7,8-trimethoxy-4,5-dihydrotetrazolo[1,5-*a*]quinolone **268**, and 6-(2,4-dichlorophenyl)-7,8,9-trimethoxy-5,6-dihydrotetrazolo[5,1-*a*]isoquinoline **269**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **241** as an off-white solid (76 mg, 73 %), **260** as an off-white solid (1 mg, 1 %), **268** as an off-white solid (4 mg, 4 %), and **269** as an off-white solid (1 mg, 1 %). Spectroscopic data for each compound are as follows:

4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, **241**



Spectroscopic data are in agreement with those previously acquired.

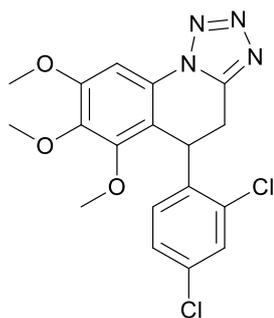
4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one, **260**



m.p. 241-242 °C; ν_{\max} /cm⁻¹ (neat) 3185 (m, N-H), 2851 (m, C-H), 1681 (s, C=O), 1106 (s, C-O); δ_{H} (500 MHz, CDCl₃) 8.23 (1H, s, CONH), 7.44 (1H, d, *J* = 1.5 Hz, ArH), 7.06 (1H, dd, *J* = 8.5, 1.5 Hz, ArH), 6.69 (1H, d, *J* = 8.5 Hz, ArH), 6.23 (1H, s, ArH), 4.97 (1H, d, *J* = 8.0 Hz, C(Ar)H), 3.90 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.63 (3H, s, OCH₃), 2.95 (1H, dd, *J* = 16.5, 8.0 Hz,

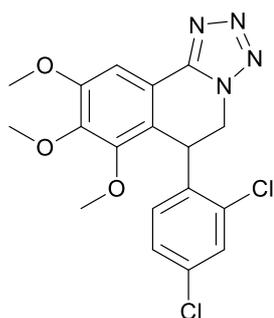
C(H)H), 2.81 (1H, d, $J = 16.5$ Hz, C(H)H); δ_c (126 MHz, CDCl₃) 169.5 (C=O), 154.0 (ArC), 151.3 (ArC), 138.4 (ArC), 138.3 (ArC), 133.8 (ArC), 133.7 (ArC), 133.3 (ArC), 129.8 (ArCH), 129.1 (ArCH), 127.4 (ArCH), 110.2 (ArC), 95.4 (ArCH), 61.0 (OCH₃), 60.9 (OCH₃), 56.2 (OCH₃), 36.4 (CH₂), 32.5 (C(Ar)H); m/z (ESI) 404 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵Cl₂NO₄Na⁺ requires 404.0427, found 404.0428 [M+Na]⁺. This compound is known but was previously reported without characterisation data.²⁵¹

5-(2,4-Dichlorophenyl)-6,7,8-trimethoxy-4,5-dihydro-1H-tetrazolo[1,5-a]quinoline, 268



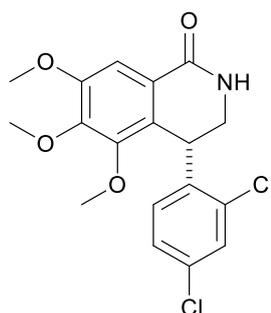
m.p. 178-180 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2847 (m, C-H), 1586 (w, C=N), 1466 (s, N=N), 1118 (s, C-O); δ_H (500 MHz, CDCl₃) 7.43 (1H, d, $J = 2.0$ Hz, ArH), 7.30 (1H, s, ArH), 7.21 (1H, dd, $J = 8.0, 2.0$ Hz, ArH), 7.05 (1H, d, $J = 8.0$ Hz, ArH), 5.75 (1H, dd, $J = 9.0, 3.5$ Hz, C(Ar)H), 4.13 (3H, s, OCH₃), 4.09 (1H, dd, $J = 14.5, 3.5$ Hz, C(H)H), 3.98 (3H, s, OCH₃), 3.96 (3H, s, OCH₃), 2.99 (1H, dd, $J = 14.5, 9.0$ Hz, C(H)H); δ_c (126 MHz, CDCl₃) 160.5 (C=N), 156.1 (ArC), 149.9 (ArC), 144.1 (ArC), 135.1 (ArC), 134.3 (ArC), 133.2 (ArCH), 131.4 (ArC), 131.3 (ArC), 129.6 (ArCH), 127.3 (ArCH), 118.1 (ArC), 101.6 (ArCH), 61.3 (OCH₃), 61.2 (OCH₃), 60.4 (OCH₃), 56.6 (C(Ar)H), 35.7 (CH₂); m/z (ESI) 429 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆³⁵Cl₂N₄O₃Na⁺ requires 429.0492, found 429.0495 [M+Na]⁺.

6-(2,4-Dichlorophenyl)-7,8,9-trimethoxy-5,6-dihydro-1H-tetrazolo[5,1-a]isoquinoline, 269



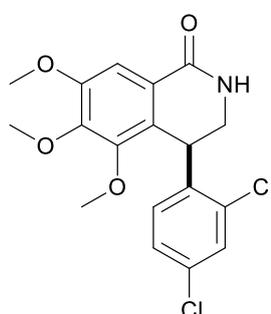
m.p. 138-140 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2850 (m, C-H), 1586 (w, C=N), 1468 (s, N=N), 1107 (s, C-O); δ_H (500 MHz, CDCl₃) 7.62 (1H, s, ArH), 7.49 (1H, d, $J = 2.0$ Hz, ArH), 6.94 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.25 (1H, d, $J = 8.5$ Hz, ArH), 5.36 (1H, d, $J = 6.0$ Hz, C(Ar)H), 4.96 (1H, dd, $J = 14.0, 5.0$ Hz, C(H)H), 4.61 (1H, dd, $J = 14.0, 7.0$ Hz, C(H)H), 4.04 (3H, s, OCH₃), 3.93 (3H, s, OCH₃), 3.65 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 154.7 (C=N), 151.3 (ArC), 150.8 (ArC), 145.6 (ArC), 136.2 (ArC), 134.3 (ArC), 133.7 (ArC), 130.1 (ArCH), 129.4 (ArCH), 127.5 (ArCH), 121.9 (ArC), 117.1 (ArC), 104.4 (ArCH), 61.0 (2 x OCH₃), 56.5 (OCH₃), 48.9 (CH₂), 34.5 (C(Ar)H); m/z (ESI) 429 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆³⁵Cl₂N₄O₃Na⁺ requires 429.0492, found 429.0496 [M+Na]⁺.

(S)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one,
(S)-241



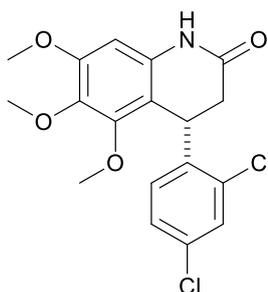
General procedure J was applied using (*S*)-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**125** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (204 mg, 89 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -20.6; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 229 nm, (*R*)-isomer 8.49 min., (*S*)-isomer 10.11 min.).

(R)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one,
(R)-241



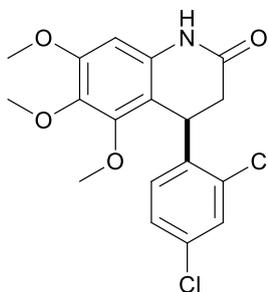
General procedure J was applied using (*R*)-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**125** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (192 mg, 84 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) 26.9; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 229 nm, (*R*)-isomer 8.44 min., (*S*)-isomer 10.49 min.).

**(S)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one,
(S)-260**



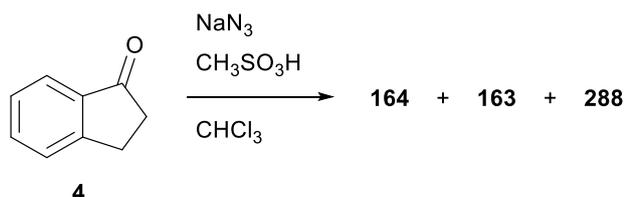
General procedure J was applied using (*R*)-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*S*)-**125** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (6 mg, 3 %, 93 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (*c* = 0.03, CHCl₃) -17.2; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 223 nm, (*S*)-isomer 8.00 min., (*R*)-isomer 10.33 min.).

**(R)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroquinolin-2(1H)-one,
(R)-260**



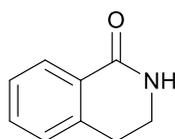
General procedure J was applied using (*R*)-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one (*R*)-**125** (220 mg, 0.60 mmol), CHCl₃ (2.82 mL), methanesulfonic acid (368 μL, 5.66 mmol) and sodium azide (78 mg, 1.20 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded the title compound as an off-white solid (4 mg, 2 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (*c* = 0.02, CHCl₃) +2.50; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 223 nm, (*S*)-isomer 8.39 min., (*R*)-isomer 10.41 min.).

Schmidt Reaction of 2,3-Dihydro-1*H*-inden-1-one, **4**



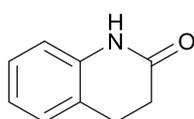
General procedure J was applied using 2,3-dihydro-1*H*-inden-1-one **4** (100 mg, 0.76 mmol), CHCl₃ (3.56 mL), methanesulfonic acid (464 μL, 7.14 mmol) and sodium azide (98 mg, 1.51 mmol). Work-up yielded a white solid, comprising a 0.45:0.51:0.04 mixture of 3,4-dihydroisoquinolin-1(2*H*)-one **164**, 3,4-dihydroquinolin-2(1*H*)-one **163** and 2-cyanophenethyl methanesulfonate **288**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **164** as a yellow solid (38 mg, 34 %), **163** as a white solid (36 mg, 32 %), and **288** as a white solid (3 mg, 2 %). Spectroscopic data for each compound are as follows:

3,4-Dihydroisoquinolin-1(2*H*)-one, **164**



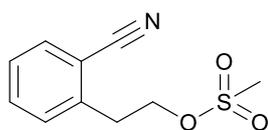
Spectroscopic data are in agreement with those previously acquired.

3,4-Dihydroisoquinolin-2(1*H*)-one, **163**



m.p. 164-165 °C (lit.¹⁶⁹ 165-167 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3131 (m, N-H), 2855 (m, C-H), 1678 (s, C=O), 1432 (s, C-O); δ_{H} (500 MHz, CDCl₃) 8.69 (1H, s, CONH), 7.23-7.15 (2H, m, 2 x ArH), 7.04-6.98 (1H, m, ArH), 6.83 (1H, d, $J = 7.5$ Hz, ArH), 3.06-2.93 (2H, m, CH₂), 2.72-2.62 (2H, m, CH₂); δ_{C} (126 MHz, CDCl₃) 171.9 (C=O), 137.3 (ArC), 128.0 (ArCH), 127.6 (ArCH), 123.7 (ArC), 123.1 (ArCH), 115.4 (ArCH), 30.8 (CH₂), 25.4 (CH₂); m/z (ESI) 170 [M+Na]⁺; HRMS (ESI) C₉H₉NONa⁺ requires 170.0576, found 170.0579 [M+Na]⁺. These data are consistent with those previously reported.¹⁶⁹

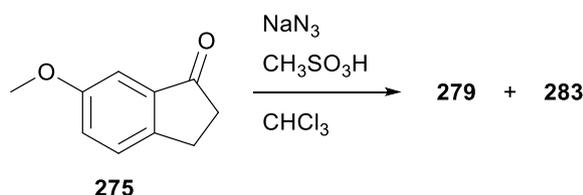
2-Cyanophenethyl methanesulfonate, **288**



m.p. 96-98 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2937 (m, ArC-H), 2852 (m, C-H), 2225 (m, C≡N), 1350 (s, S=O (*as*)), 1170 (s, S=O (*s*)); δ_{H} (500 MHz, CDCl₃) 7.69 (1H, d, $J = 8.0$ Hz, ArH), 7.62-7.58 (1H, m, ArH), 7.44 (1H, d, $J = 8.0$ Hz, ArH), 7.41 (1H, t, $J = 8.0$ Hz, ArH), 4.52 (2H, t, $J = 6.5$ Hz, CH₂), 3.32 (2H, t, $J = 6.5$ Hz, CH₂), 2.98 (3H, s, SCH₃); δ_{C} (126 MHz, CDCl₃) 140.2 (ArC), 133.1 (2 x ArCH), 130.5 (ArCH), 127.9 (ArCH), 117.7 (C≡N), 112.9 (ArC), 68.3

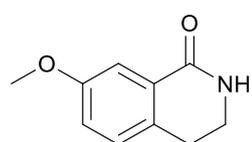
($\underline{\text{C}}\text{H}_2$), 37.6 ($\underline{\text{S}}\text{C}\text{H}_3$), 34.3 ($\underline{\text{C}}\text{H}_2$); m/z (ESI) 248 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{10}\text{H}_{11}\text{NO}_3\text{SNa}^+$ requires 248.0352, found 248.0352 $[\text{M}+\text{Na}]^+$. This compound is known but has previously only been reported with ^1H NMR data, which are consistent with those reported here.²⁵²

Schmidt Reaction of 6-Methoxy-2,3-dihydro-1*H*-inden-1-one, **275**



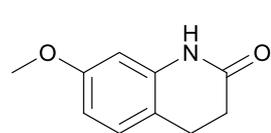
General procedure J was applied using 6-methoxy-2,3-dihydro-1*H*-inden-1-one **275** (81 mg, 0.50 mmol), CHCl_3 (2.35 mL), methanesulfonic acid (306 μL , 4.72 mmol) and sodium azide (65 mg, 1.00 mmol). Work-up yielded an off-white solid, comprising a 0.56:0.44 mixture of 7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **279** and 7-methoxy-3,4-dihydroquinolin-2(1*H*)-one **283**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **279** as an off-white solid (44 mg, 49 %) and **283** as a white solid (32 mg, 36 %). Spectroscopic data for each compound are as follows:

7-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one, **279**



m.p. 108-110 °C (lit.^{143, 249} 112-113 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3194 (m, N-H), 2853 (m, C-H), 1662 (s, C=O), 1328 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.59 (1H, d, $J = 2.5$ Hz, ArH), 7.12 (1H, d, $J = 8.5$ Hz, ArH), 7.00 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.55 (1H, s, CONH), 3.84 (3H, s, OCH_3), 3.54 (2H, td, $J = 6.5, 3.0$ Hz, $\underline{\text{C}}\text{H}_2$), 2.93 (2H, t, $J = 6.5$ Hz, $\underline{\text{C}}\text{H}_2$); δ_{C} (126 MHz, CDCl_3) 166.5 ($\underline{\text{C}}=\text{O}$), 158.9 (ArC), 131.2 (ArC), 130.0 (ArC), 128.6 (ArCH), 119.9 (ArCH), 111.2 (ArCH), 55.7 ($\underline{\text{O}}\underline{\text{C}}\text{H}_3$), 40.6 ($\underline{\text{C}}\text{H}_2$), 27.6 ($\underline{\text{C}}\text{H}_2$); m/z (ESI) 178 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{10}\text{H}_{12}\text{NO}_2^+$ requires 178.0863, found 178.0861 $[\text{M}+\text{H}]^+$. These data are consistent with those previously reported.²⁴⁹

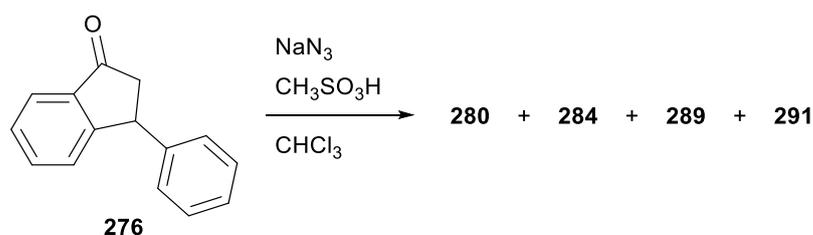
7-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-one, **283**



m.p. 146-147 °C (lit.¹⁴³ 145-146 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3196 (m, N-H), 2834 (m, C-H), 1673 (s, C=O), 1379 (s, C-O); δ_{H} (500 MHz, CDCl_3) 8.58 (1H, s, CONH), 7.05 (1H, d, $J = 8.5$ Hz, ArH), 6.53 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.37 (1H, d, $J = 2.5$ Hz, ArH), 3.78 (3H, s, OCH_3),

2.90 (2H, t, $J = 7.5$ Hz, $\underline{\text{CH}}_2$), 2.62 (2H, dd, $J = 8.0, 7.0$ Hz, $\underline{\text{CH}}_2$); δ_{C} (126 MHz, CDCl_3) 172.2 ($\underline{\text{C}}=\text{O}$), 159.4 ($\text{Ar}\underline{\text{C}}$), 138.3 ($\text{Ar}\underline{\text{C}}$), 128.8 ($\text{Ar}\underline{\text{CH}}$), 115.9 ($\text{Ar}\underline{\text{C}}$), 108.3 ($\text{Ar}\underline{\text{CH}}$), 101.8 ($\text{Ar}\underline{\text{CH}}$), 55.6 ($\text{O}\underline{\text{CH}}_3$), 31.2 ($\underline{\text{CH}}_2$), 24.7 ($\underline{\text{CH}}_2$); m/z (ESI) 178 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{10}\text{H}_{12}\text{NO}_2^+$ requires 178.0863, found 178.0860 $[\text{M}+\text{H}]^+$. These data are consistent with those previously reported.²⁵³

Schmidt Reaction of 3-Phenyl-2,3-dihydro-1H-inden-1-one, **276**

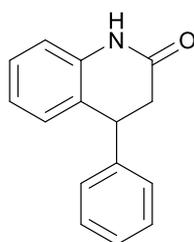


General procedure J was applied using 3-phenyl-2,3-dihydro-1H-inden-1-one **276** (312 mg, 1.5 mmol), CHCl_3 (7.05 mL), methanesulfonic acid (918 μL , 14.2 mmol) and sodium azide (195 mg, 3.00 mmol). Work-up yielded an off-white solid, comprising a 0.29:0.40:0.09:0.22 mixture of 4-phenyl-3,4-dihydroisoquinolin-1(2H)-one **280**, 4-phenyl-3,4-dihydroquinolin-2(1H)-one **284**, 2-(2-cyanophenyl)-2-phenylethyl methanesulfonate **289** and (*E*)-2-styrylbenzocnitrile **291**, respectively. Purification by gradient column chromatography, eluting with pet ether:EtOAc (3:1 to 1:2), afforded **280** as an off-white solid (79 mg, 23 %), **284** as an off-white solid (141 mg, 42 %), **289** as pale yellow solid (7 mg, 1 %), and **291** as a yellow oil (70 mg, 23 %). Spectroscopic data for each compound are as follows:

4-Phenyl-3,4-dihydroisoquinolin-1(2H)-one, **280**

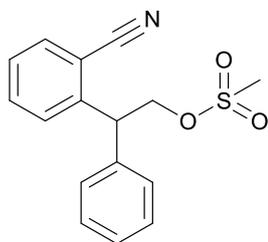
m.p. 170-172 °C (lit.²⁵⁴ 173.5-174 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3197 (m, N-H), 2942 (m, ArC-H), 2891 (m, C-H), 1670 (s, C=O); δ_{H} (500 MHz, CDCl_3) 8.16 (1H, dd, $J = 7.0, 1.0$ Hz, ArH), 7.45-7.37 (2H, m, 2 x ArH), 7.37-7.27 (3H, m, 3 x ArH), 7.21-7.16 (2H, m, 2 x ArH), 6.97 (1H, d, $J = 7.0$ Hz, ArH), 6.35 (1H, s, CONH), 4.33 (1H, dd, $J = 7.0, 6.0$ Hz, C(Ar)H), 3.82 (1H, ddd, $J = 12.0, 5.0, 3.0$ Hz, C(H)H), 3.71 (1H, ddd, $J = 12.0, 11.0, 2.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 166.2 ($\underline{\text{C}}=\text{O}$), 141.5 ($\text{Ar}\underline{\text{C}}$), 140.8 ($\text{Ar}\underline{\text{C}}$), 132.6 ($\text{Ar}\underline{\text{CH}}$), 129.1 ($\text{Ar}\underline{\text{C}}$), 128.9 (2 x $\text{Ar}\underline{\text{CH}}$), 128.7 (2 x $\text{Ar}\underline{\text{CH}}$), 128.3 ($\text{Ar}\underline{\text{CH}}$), 127.8 ($\text{Ar}\underline{\text{CH}}$), 127.6 ($\text{Ar}\underline{\text{CH}}$), 127.5 ($\text{Ar}\underline{\text{CH}}$), 47.3 ($\underline{\text{CH}}_2$), 44.4 ($\underline{\text{C}}(\text{Ar})\text{H}$); m/z (ESI) 246 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{15}\text{H}_{13}\text{NONa}^+$ requires 246.0889, found 246.0885 $[\text{M}+\text{Na}]^+$. These data are consistent with those previously reported.²⁵⁵

4-Phenyl-3,4-dihydroisoquinolin-2(1H)-one, 284



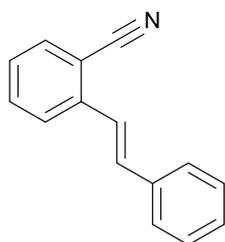
m.p. 176-178 °C (lit.¹⁰⁶ 181-182 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3190 (m, N-H), 2979 (m, ArC-H), 2889 (m, C-H), 1666 (s, C=O); δ_{H} (500 MHz, CDCl_3) 8.73 (1H, s, CONH), 7.34 (2H, t, $J = 7.5$ Hz, 2 x ArH), 7.31-7.25 (1H, m, ArH), 7.23-7.18 (3H, m, 3 x ArH), 6.97 (1H, t, $J = 7.5$ Hz, ArH), 6.92 (1H, d, $J = 7.5$ Hz, ArH), 6.87 (1H, d, $J = 8.0$ Hz, ArH), 4.34-4.28 (1H, m, C(Ar)H), 3.00-2.89 (2H, m, CH_2); δ_{C} (126 MHz, CDCl_3) 170.9 (C=O), 141.6 (ArC), 137.2 (ArC), 129.1 (2 x ArCH), 128.5 (ArCH), 128.2 (ArCH), 128.0 (2 x ArCH), 127.4 (ArCH), 126.8 (ArC), 123.5 (ArCH), 115.8 (ArCH), 42.2 (C(Ar)H), 38.5 (CH_2); m/z (ESI) 246 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{15}\text{H}_{13}\text{NONa}^+$ requires 246.0889, found 246.0885 $[\text{M}+\text{Na}]^+$. These data are consistent with those previously reported.¹⁰⁶

2-(2-Cyanophenyl)-2-phenylethyl methanesulfonate, 289



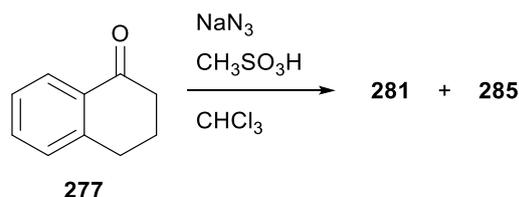
m.p. 112-114 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2934 (m, ArC-H), 2852 (m, C-H), 2226 (m, $\text{C}\equiv\text{N}$), 1358 (s, S=O (*as*)), 1172 (s, S=O (*s*)); δ_{H} (500 MHz, CDCl_3) 7.71-7.64 (3H, m, 3 x ArH), 7.48-7.44 (1H, m, ArH), 7.37-7.26 (5H, m, 5 x ArH), 5.92 (1H, dd, $J = 9.5, 4.0$ Hz, C(Ar)H), 3.28 (1H, dd, $J = 14.0, 4.0$ Hz, C(H)H), 3.16 (1H, dd, $J = 14.0, 9.5$ Hz, C(H)H), 2.45 (3H, s, SCH_3); δ_{C} (126 MHz, CDCl_3) 142.8 (ArC), 135.7 (ArC), 133.6 (ArCH), 133.1 (ArCH), 129.9 (2 x ArCH), 129.2 (ArCH), 129.0 (2 x ArCH), 127.7 (ArCH), 127.0 (ArCH), 116.9 ($\text{C}\equiv\text{N}$), 110.1 (ArC), 82.8 (C(Ar)H), 43.6 (CH_2), 37.7 (SCH_3); m/z (ESI) 324 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{SNa}^+$ requires 324.0665, found 324.0670 $[\text{M}+\text{Na}]^+$.

(E)-2-Styrylbenzonitrile, 291



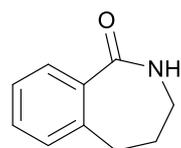
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3027 (m, ArC-H), 2221 (m, $\text{C}\equiv\text{N}$), 1633 (m, C=C), 960 (s, HC=C-H); δ_{H} (500 MHz, CDCl_3) 7.77 (1H, d, $J = 8.0$ Hz, ArH), 7.62 (1H, d, $J = 7.5$ Hz, ArH), 7.58-7.52 (3H, m, 3 x ArH), 7.43 (1H, d, $J = 16.0$ Hz, HC=CH), 7.37 (2H, t, $J = 7.5$ Hz, 2 x ArH), 7.30 (2H, t, $J = 7.5$ Hz, ArH), 7.24 (1H, d, $J = 17.0$ Hz, HC=CH); δ_{C} (126 MHz, CDCl_3) 140.7 (ArC), 136.3 (ArC), 133.5 (HC=CH), 133.3 (ArCH), 132.9 (ArCH), 129.0 (2 x ArCH), 128.9 (ArCH), 127.7 (ArCH), 127.3 (2 x ArCH), 125.4 (ArCH), 124.2 (HC=CH), 118.1 ($\text{C}\equiv\text{N}$), 111.4 (ArC); m/z (ESI) 228 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{15}\text{H}_{11}\text{NNa}^+$ requires 228.0784, found 228.0785 $[\text{M}+\text{Na}]^+$. These data are consistent with those previously reported.²⁵⁶

Schmidt Reaction of 3,4-Dihydronaphthalen-1(2H)-one, **277**



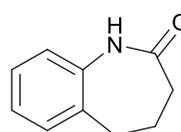
General procedure J was applied using 3,4-dihydronaphthalen-1(2H)-one **277** (67 μ l, 0.50 mmol), CHCl_3 (2.35 mL), methanesulfonic acid (306 μ L, 4.72 mmol) and sodium azide (65 mg, 1.00 mmol). Work-up yielded an off-white solid, comprising a 0.04:0.96 mixture of 2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-1-one **281** and 1,3,4,5-tetrahydro-2H-benzo[*b*]azepin-2-one **285**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **281** as a pale yellow solid (4 mg, 5 %), and **285** as an off-white solid (68 mg, 84 %). Spectroscopic data for each compound are as follows:

2,3,4,5-Tetrahydro-1H-benzo[*c*]azepin-1-one, **281**



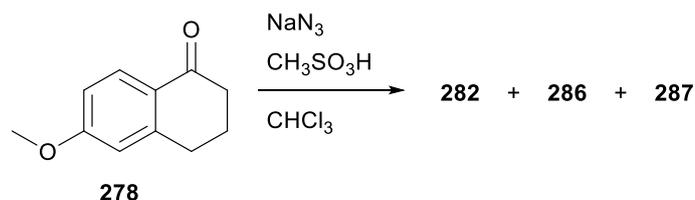
m.p. 84-86 °C (lit.¹⁴⁵ 102-103 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3205 (m, N-H), 2922 (m, ArC-H), 2853 (m, C-H), 1644 (s, C=O); δ_{H} (500 MHz, CDCl_3) 7.71 (1H, d, $J = 7.5$ Hz, ArH), 7.41 (1H, t, $J = 7.5$ Hz, ArH), 7.34 (1H, t, $J = 7.5$ Hz, ArH), 7.19 (1H, d, $J = 7.5$ Hz, ArH), 6.38 (1H, s, CONH), 3.13 (2H, q, $J = 6.5$ Hz, CH_2), 2.87 (2H, t, $J = 7.0$ Hz, CH_2), 2.02 (2H, p, $J = 7.0$ Hz, CH_2); δ_{C} (126 MHz, CDCl_3) 173.9 (C=O), 138.4 (ArC), 135.1 (ArC), 131.4 (ArCH), 129.0 (ArCH), 128.8 (ArCH), 127.2 (ArCH), 39.8 (CH_2), 30.6 (CH_2), 30.5 (CH_2); m/z (ESI) 162 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{10}\text{H}_{12}\text{NO}^+$ requires 162.0913, found 162.0915 $[\text{M}+\text{H}]^+$. These data are consistent with those previously reported.²⁵⁷

1,3,4,5-Tetrahydro-2H-benzo[*b*]azepin-2-one, **285**



m.p. 138-140 °C (lit.¹⁴³ 139-140 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3181 (m, N-H), 2921 (m, ArC-H), 2863 (m, C-H), 1657 (s, C=O); δ_{H} (500 MHz, CDCl_3) 7.95 (1H, s, CONH), 7.26-7.20 (2H, m, 2 x ArH), 7.13 (1H, t, $J = 7.5$ Hz, ArH), 6.99 (1H, d, $J = 7.5$ Hz, ArH), 2.81 (2H, t, $J = 7.0$ Hz, CH_2), 2.36 (2H, t, $J = 7.5$ Hz, CH_2), 2.24 (2H, p, $J = 7.0$ Hz, CH_2); δ_{C} (126 MHz, CDCl_3) 175.3 (C=O), 138.0 (ArC), 134.5 (ArC), 130.0 (ArCH), 127.6 (ArCH), 125.8 (ArCH), 121.9 (ArCH), 32.9 (CH_2), 30.5 (CH_2), 28.6 (CH_2); m/z (ESI) 162 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{10}\text{H}_{12}\text{NO}^+$ requires 162.0913, found 162.0911 $[\text{M}+\text{H}]^+$. These data are consistent with those previously reported.²⁵⁸

Schmidt Reaction of 6-Methoxy-3,4-dihydronaphthalen-1(2H)-one, **278**



General procedure J was applied using 6-methoxy-3,4-dihydronaphthalen-1(2H)-one **278** (88 mg, 0.50 mmol), CHCl₃ (2.35 mL), methanesulfonic acid (306 μL, 4.72 mmol) and sodium azide (65 mg, 1.00 mmol). Work-up yielded an off-white solid, comprising a 0.62:0.34:0.04 mixture of 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-1-one **282**, 7-methoxy-1,3,4,5-tetrahydro-2H-benzo[*b*]azepin-2-one **286** and 8-methoxy-5,6-dihydro-4H-benzo[*f*]tetrazolo[1,5-*a*]azepine **287**, respectively. Purification by flash column chromatography, eluting with pet ether:EtOAc (1:2), afforded **282** as a white solid (50 mg, 52 %), **286** as an off-white solid (34 mg, 35 %), and **287** as pale yellow solid (3 mg, 3 %). Spectroscopic data for each compound are as follows:

7-Methoxy-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-1-one, **282**

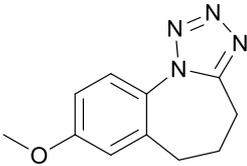
m.p. 160-162 °C (lit.¹⁴³ 160-161 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3274 (m, N-H), 2854 (m, C-H), 1647 (s, C=O), 1362 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.67 (1H, d, $J = 8.5$ Hz, ArH), 6.84 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.71 (1H, d, $J = 2.0$ Hz, ArH), 6.67 (1H, s, CONH), 3.84 (3H, s, OCH₃), 3.13 (2H, q, $J = 6.5$ Hz, CH₂), 2.84 (2H, t, $J = 7.0$ Hz, CH₂), 2.01 (2H, p, $J = 7.0$ Hz, CH₂); δ_{C} (126 MHz, CDCl₃) 174.1 (C=O), 162.0 (ArC), 140.7 (ArC), 131.0 (ArCH), 127.6 (ArC), 114.4 (ArCH), 111.9 (ArCH), 55.4 (OCH₃), 39.9 (CH₂), 30.9 (CH₂), 30.6 (CH₂); m/z (ESI) 192 [M+H]⁺; HRMS (ESI) C₁₁H₁₄NO₂⁺ requires 192.1019, found 192.1017 [M+H]⁺. These data are consistent with those previously reported.²⁵⁹

7-Methoxy-1,3,4,5-tetrahydro-2H-benzo[*b*]azepin-2-one, **286**

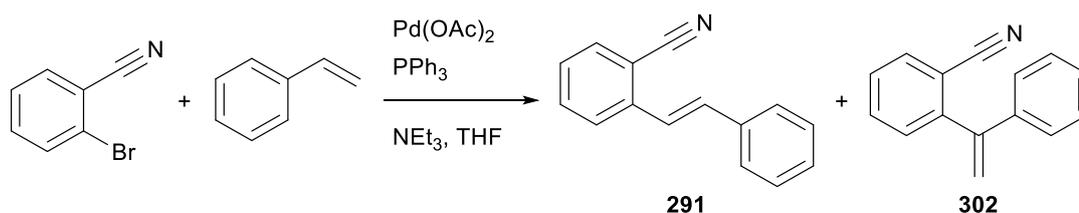
m.p. 140-142 °C (lit.¹⁴³ 141-142 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3170 (m, N-H), 2855 (m, C-H), 1675 (s, C=O), 1378 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.71 (1H, s, CONH), 6.92 (1H, d, $J = 8.0$ Hz, ArH), 6.76 (1H, s, ArH), 6.77-6.73 (1H, m, ArH), 3.80 (3H, s, OCH₃), 2.77 (2H, t, $J = 7.0$ Hz, CH₂), 2.33 (2H, t, $J = 7.0$ Hz, CH₂), 2.21 (2H, p, $J = 7.0$ Hz, CH₂); δ_{C} (126 MHz, CDCl₃) 175.3 (C=O), 157.6 (ArC), 136.1 (ArC), 130.9 (ArC), 123.2 (ArCH), 115.4 (ArCH), 112.3 (ArCH), 55.6 (OCH₃), 32.6 (CH₂), 30.7 (CH₂), 28.3 (CH₂); m/z (ESI) 192 [M+H]⁺;

HRMS (ESI) $C_{11}H_{14}NO_2^+$ requires 192.1019, found 192.1020 $[M+H]^+$. These data are consistent with those previously reported.²⁵⁹

8-Methoxy-5,6-dihydro-4H-benzof[tetrazolo[1,5-a]azepine, 287

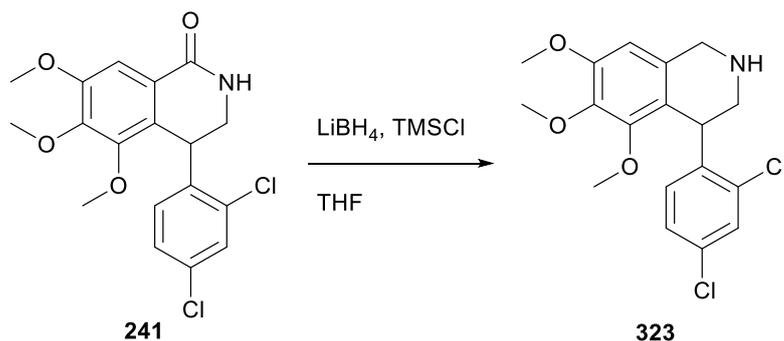
 m.p. 110-112 °C; ν_{max}/cm^{-1} (neat) 2849 (m, C-H), 1612 (m, C=N), 1275 (s, N=N), 1212 (m, C-N); δ_H (500 MHz, $CDCl_3$) 8.25 (1H, d, $J = 8.5$ Hz, ArH), 6.93 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.81 (1H, d, $J = 2.5$ Hz, ArH), 4.61 (2H, t, $J = 6.5$ Hz, CH_2), 3.87 (3H, s, OCH_3), 3.01-2.95 (2H, m, CH_2), 2.43-2.35 (2H, m, CH_2); δ_C (126 MHz, $CDCl_3$) 162.1 ($C=N$), 154.4 (ArC), 141.6 (ArC), 132.3 (ArCH), 115.9 (ArCH), 115.7 (ArC), 112.8 (ArCH), 55.6 (OCH_3), 48.9 (CH_2), 33.4 (CH_3), 26.4 (CH_2); m/z (ESI) 217 $[M+H]^+$; HRMS (ESI) $C_{11}H_{13}N_4O^+$ requires 217.1084, found 217.1082 $[M+H]^+$.

3.6.6 Heck Coupling Reaction of 2-Bromobenzonitrile and Styrene – Confirmation of (E)-2-Styrylbenzonitrile, 291



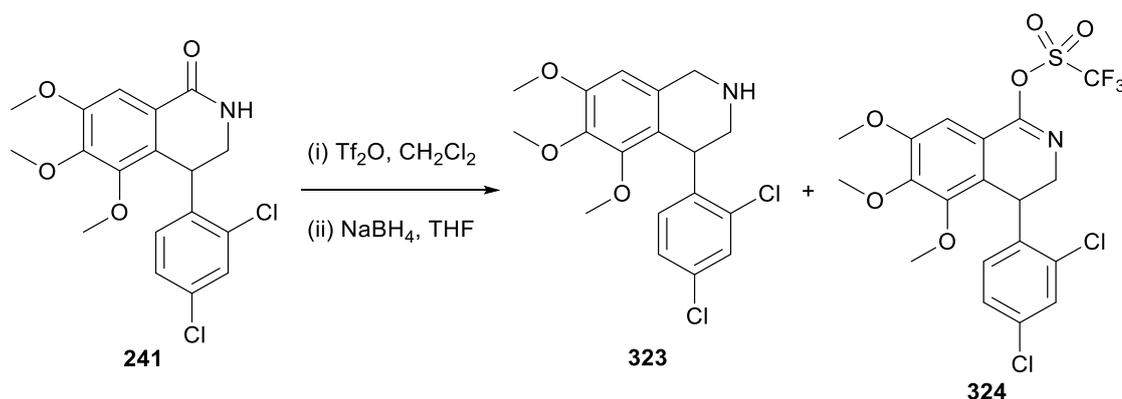
To a microwave reaction vial was added 2-bromobenzonitrile (182 mg, 1.00 mmol, 1.00 equiv.), styrene (115 μ L, 1.00 mmol, 1.00 equiv.), triethylamine (209 μ L, 1.50 mmol, 1.50 equiv.), THF (6.00 mL, 6.00 mL/mmol), palladium acetate (11 mg, 0.05 mmol, 5.00 mol%) and triphenylphosphine (26 mg, 0.10 mmol, 0.10 equiv.). The vial was sealed and heated to 160 °C, with stirring, for 1 hour in a microwave reactor. The volatiles were then removed under vacuum and water added. Organics were re-dissolved in EtOAc, washed with water and extracted with further EtOAc. Extracts were combined, washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave an inseparable 0.92:0.08 mixture of **291** to 2-(1-phenylvinyl)benzonitrile **302** as a yellow oil (72 mg, 35 %). Spectroscopic data of **291** are in agreement with those previously acquired.

3.6.7 LiBH_4 -TMSCl Reduction of 4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, **241**



To a mixture of 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one **241** (38 mg, 0.10 mmol, 1.00 equiv.) and LiBH_4 (9 mg, 0.40 mmol, 4.00 equiv.) in THF (1.00 mL, 10.0 mL/mmol), at 0 °C under N_2 , was added chlorotrimethylsilane (51 μL , 0.40 mmol, 4.00 equiv.) slowly over 5 minutes. The resulting mixture was heated up to 80 °C and stirred for 18 hours. The reaction was allowed to cool to room temperature and water was cautiously added. Solvent were removed under reduced pressure and the organics were extracted with Et_2O , washed with NaOH (2.00 M) and brine, then dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:3) to 100 % EtOAc, yielded 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **323** as a pale yellow oil (5 mg, 12 %), alongside unreacted starting material; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3359 (w, N-H), 2835 (m, C-H), 1584 (m, N-H), 1116 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.43 (1H, d, $J = 2.0$ Hz, ArH), 7.06 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.71 (1H, d, $J = 8.5$ Hz, ArH), 6.41 (1H, s, ArH), 4.59-4.53 (1H, m, C(Ar)H), 4.01 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.22 (1H, dd, $J = 13.0, 5.0$ Hz, C(H)H), 3.11 (1H, dd, $J = 13.0, 2.0$ Hz, C(H)H), 1.70 (1H, s, NH); δ_{C} (126 MHz, CDCl_3) 152.8 (ArC), 151.5 (ArC), 142.0 (ArC), 140.9 (ArC), 134.0 (ArC), 132.4 (ArC), 132.2 (ArC), 130.7 (ArCH), 129.3 (ArCH), 126.6 (ArCH), 122.3 (ArC), 104.2 (ArCH), 60.8 (OCH_3), 60.3 (OCH_3), 56.0 (OCH_3), 49.0 (CH_2), 48.2 (CH_2), 34.9 (C(Ar)H); m/z (ESI) 368 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{18}\text{H}_{20}^{35}\text{Cl}_2\text{NO}_3^+$ requires 368.0815, found 368.0814 $[\text{M}+\text{H}]^+$.

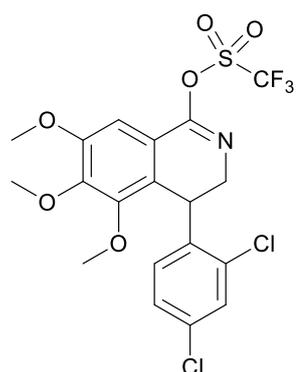
3.6.8 $\text{NaBH}_4\text{-Tf}_2\text{O}$ Reduction of 4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one, **241**



The following procedure was performed in accordance with previous literature.²¹⁴

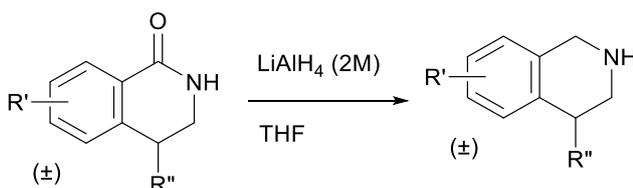
To a solution of 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one **240** (38 mg, 0.10 mmol, 1.00 mmol) in CH_2Cl_2 (0.40 mL, 4.00 mL/mmol), at 0 °C under N_2 , was added triflic anhydride (19 μL , 0.11 mmol, 1.10 equiv.). After stirring for 0.5 hours NaBH_4 (5 mg, 0.13 mmol, 1.30 equiv.) was added in one portion and the mixture was diluted with THF (0.25 mL, 2.50 mL/mmol). The reaction mixture was stirred for a further 1 hour at room temperature, quenched with water, and the pH was adjusted to 10.5–11.0 by the addition of a saturated Na_2CO_3 (aq.) at 0 °C. The organics were extracted with Et_2O , washed with brine, then dried over MgSO_4 , filtered and concentrated *in vacuo*. Work-up yielded a 0.45:0.21:0.34 mixture of unreacted starting material, 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **323** and 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1-yl trifluoromethanesulfonate **324**, respectively. Purification by gradient column chromatography, eluting with pet ether:EtOAc (1:2) to 100 % EtOAc, afforded 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1-yl trifluoromethanesulfonate as a colourless oil (12 mg, 23 %) and 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **323** as a pale yellow oil (4 mg, 11 %). Spectroscopic data of **323** are in agreement with those previously acquired, and those for **324** are as follows:

4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1-yl trifluoromethanesulfonate, 324



ν_{\max} /cm⁻¹ (neat) 2853 (m, C-H), 1717 (m, C=N), 1377 (s, S=O (as)), 1190 (s, S=O (s)), 1122 (s, C-F); δ_{H} (500 MHz, CDCl₃) 7.58 (1H, s, ArH), 7.51 (1H, d, J = 2.0 Hz, ArH), 7.11 (1H, dd, J = 8.5, 2.0 Hz, ArH), 6.58 (1H, d, J = 8.5 Hz, ArH), 5.04-4.98 (1H, m, C(Ar)H), 4.54 (1H, dd, J = 13.0, 1.5 Hz, C(H)H), 4.12 (1H, dd, J = 13.0, 4.0 Hz, C(H)H), 3.95 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 3.58 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 162.6 (C=N), 154.1 (ArC), 149.7 (ArC), 148.5 (ArC), 134.8 (ArC), 134.6 (ArC), 134.2 (ArC), 130.2 (ArCH), 130.1 (ArCH), 127.9 (ArC), 127.5 (ArCH), 122.5 (ArC), 118.3 (ArC), 107.9 (ArCH), 61.2 (OCH₃), 61.1 (OCH₃), 56.4 (OCH₃), 51.4 (CH₂), 34.7 (C(Ar)H); m/z (ESI) 536 [M+Na]⁺; HRMS (ESI) C₁₉H₁₆³⁵Cl₂F₃NO₆SNa⁺ requires 535.9920, found 535.9916 [M+Na]⁺.

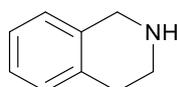
3.6.9 LiAlH₄ Reduction of Dihydroquinolinones – General Procedure K



The following procedure was adapted from previous literature.^{207, 208}

To a solution of dihydroisoquinolinone (1.00 equiv.) in THF (40.0 mL/mmol), at 0 °C under N₂, was added LiAlH₄ (3.00 equiv., 2 M in THF) dropwise. The resulting mixture was heated up to 80 °C and stirred for 18 hours. The reaction was allowed to cool to room temperature and water was cautiously added. Organics were extracted with Et₂O, washed with NaOH (2.00 M) and brine, then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

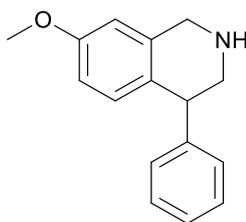
1,2,3,4-Tetrahydroisoquinoline, 186



General procedure K was applied using 3,4-dihydroisoquinolin-1(2H)-one **164** (40 mg, 0.27 mmol), THF (10.9 mL) and LiAlH₄ (408 μ L, 0.82 mmol), and used without further purification. The title compound was formed as a yellow oil (30 mg, 83 %);

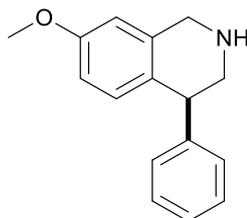
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3284 (w, N-H), 2851 (m, C-H), 1583 (m, N-H), 1259 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.15-7.11 (2H, m, 2 x ArH), 7.11-7.06 (1H, m, ArH), 7.04-6.96 (1H, m, ArH), 4.02 (2H, s, CH_2), 3.14 (2H, t, $J = 6.0$ Hz, CH_2), 2.80 (2H, t, $J = 6.0$ Hz, CH_2), 1.95 (1H, s, NH); δ_{C} (126 MHz, CDCl_3) 136.1 (ArC), 134.9 (ArC), 129.5 (ArCH), 126.4 (ArCH), 126.2 (ArCH), 125.9 (ArCH), 48.4 (CH_2), 44.0 (CH_2), 29.3 (CH_2); m/z (ESI) 134 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_9\text{H}_{12}\text{N}^+$ requires 134.0964, found 134.0967 $[\text{M}+\text{H}]^+$. These data are consistent with those previously reported.²⁶⁰

7-Methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline, **325**



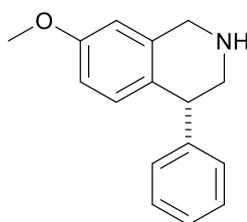
General procedure K was applied using 7-methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one **234** (127 mg, 0.50 mmol), THF (20.0 mL) and LiAlH_4 (750 μL , 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline **325** as a light brown oil (109 mg, 91 %); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3297 (w, N-H), 2834 (m, C-H), 1609 (m, N-H), 1253 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.29 (2H, t, $J = 7.5$ Hz, 2 x ArH), 7.22 (1H, t, $J = 7.5$ Hz, ArH), 7.12-7.06 (2H, m, 2 x ArH), 6.82 (1H, d, $J = 8.5$ Hz, ArH), 6.69 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.62 (1H, d, $J = 2.5$ Hz, ArH), 4.14 (1H, d, $J = 16.5$ Hz, C(H)H), 4.08 (1H, d, $J = 16.5$ Hz, C(H)H), 4.07 (1H, t, $J = 7.0$ Hz, C(Ar)H), 3.79 (3H, s, OCH_3), 3.42 (1H, s, NH), 3.40 (1H, dd, $J = 13.0, 5.0$ Hz, C(H)H), 3.09 (1H, dd, $J = 13.0, 6.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 158.1 (ArC), 144.9 (ArC), 136.9 (ArC), 131.4 (ArCH), 129.4 (ArC), 128.9 (2 x ArCH), 128.6 (2 x ArCH), 126.6 (ArCH), 113.1 (ArCH), 110.3 (ArCH), 55.4 (OCH_3), 52.1 (CH_2), 48.4 (CH_2), 44.0 (C(Ar)H); m/z (ESI) 240 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{16}\text{H}_{18}\text{NO}^+$ requires 240.1383, found 240.1385 $[\text{M}+\text{H}]^+$. These data are consistent with those previously reported.²⁶¹

(S)-7-Methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (S)-325



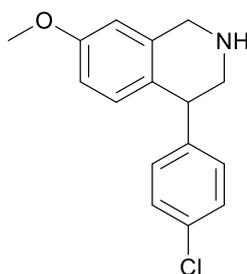
General procedure K was applied using (S)-7-methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one (**S**)-**234** (50 mg, 0.20 mmol), THF (8.00 mL) and LiAlH₄ (300 μL, 0.60 mmol), and used without further purification. The title compound was formed as an off-white solid (45 mg, 94 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.19, CHCl₃) -0.90.

(R)-7-Methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (R)-325



General procedure K was applied using (R)-7-methoxy-4-phenyl-3,4-dihydroisoquinolin-1(2H)-one (**R**)-**233** (38 mg, 0.15 mmol), THF (6.00 mL) and LiAlH₄ (225 μL, 0.45 mmol), and used without further purification. The title compound was formed as an off-white solid (37 mg, 94 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.05, CHCl₃) +1.00.

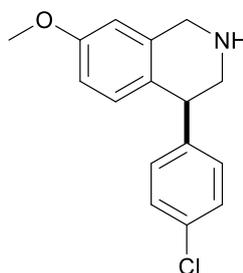
4-(4-Chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 326



General procedure K was applied using 4-(4-chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one **235** (144 mg, 0.50 mmol), THF (20.0 mL) and LiAlH₄ (750 μL, 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **326** as a pale yellow oil (115 mg, 84 %); ν_{\max} /cm⁻¹ (neat) 3297 (w, N-H), 2834 (m, C-H), 1609 (m, N-H), 1253 (m, C-N); δ_{H} (500 MHz, CDCl₃) 7.27-7.24 (2H, m, 2 x ArH), 7.05-6.99

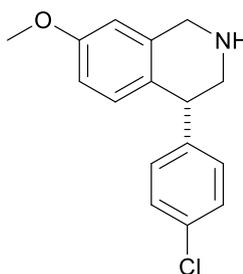
(2H, m, 2 x ArH), 6.79 (1H, d, $J = 8.5$ Hz, ArH), 6.68 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.61 (1H, d, $J = 2.0$ Hz, ArH), 4.12 (1H, d, $J = 16.5$ Hz, C(H)H), 4.06 (1H, d, $J = 16.5$ Hz, C(H)H), 4.02 (1H, t, $J = 6.0$ Hz, C(Ar)H), 3.79 (3H, s, OCH₃), 3.38 (1H, dd, $J = 13.0, 5.0$ Hz, C(H)H), 3.03 (1H, dd, $J = 13.0, 6.5$ Hz, C(H)H), 2.13 (1H, s, NH); δ_C (126 MHz, CDCl₃) 158.2 (ArC), 143.7 (ArC), 137.3 (ArC), 132.3 (ArC), 131.3 (ArCH), 130.2 (2 x ArCH), 129.0 (ArC), 128.7 (2 x ArCH), 113.1 (ArCH), 110.4 (ArCH), 55.4 (OCH₃), 52.4 (CH₂), 48.7 (CH₂), 43.7 (C(Ar)H); m/z (ESI) 274 [M+H]⁺; HRMS (ESI) C₁₆H₁₇³⁵ClNO⁺ requires 274.0993, found 274.0997 [M+H]⁺. This compound is known but was previously reported without characterisation data.⁷⁰

(S)-4-(4-Chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, (S)-326



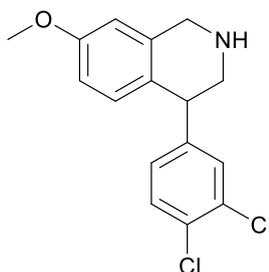
General procedure K was applied using (S)-4-(4-chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one (S)-**235** (58 mg, 0.20 mmol), THF (8.00 mL) and LiAlH₄ (300 μ L, 0.60 mmol), and used without further purification. The title compound was formed as a pale yellow oil (51 mg, 92 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ ($c = 0.15$, CHCl₃) -31.3 .

(R)-4-(4-Chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, (R)-326



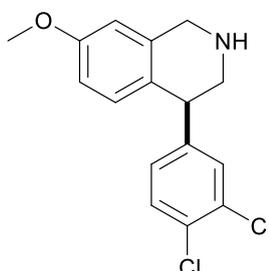
General procedure K was applied using (R)-4-(4-chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one (R)-**235** (58 mg, 0.20 mmol), THF (8.00 mL) and LiAlH₄ (300 μ L, 0.60 mmol), and used without further purification. The title compound was formed as a pale yellow oil (53 mg, 97 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.21$, CHCl₃) $+6.30$.

4-(3,4-Dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, **327**



General procedure K was applied using 4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **236** (97 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **327** as an orange-yellow oil (71 mg, 77 %); ν_{\max} /cm⁻¹ (neat) 3297 (w, N-H), 2834 (m, C-H), 1609 (m, N-H), 1252 (m, C-N); δ_{H} (500 MHz, CDCl₃) 7.35 (1H, d, *J* = 8.0 Hz, ArH), 7.19 (1H, d, *J* = 2.0 Hz, ArH), 6.94 (1H, dd, *J* = 8.0, 2.0 Hz, ArH), 6.79 (1H, d, *J* = 8.5 Hz, ArH), 6.69 (1H, dd, *J* = 8.5, 2.5 Hz, ArH), 6.62 (1H, d, *J* = 2.5 Hz, ArH), 4.11 (1H, d, *J* = 16.5 Hz, C(H)H), 4.04 (1H, d, *J* = 16.5 Hz, C(H)H), 4.00 (1H, t, *J* = 5.5 Hz, C(Ar)H), 3.79 (3H, s, OCH₃), 3.37 (1H, dd, *J* = 13.0, 5.0 Hz, C(H)H), 3.02 (1H, dd, *J* = 13.0, 6.0 Hz, C(H)H), 1.81 (1H, s, NH); δ_{C} (126 MHz, CDCl₃) 158.3 (ArC), 145.8 (ArC), 137.6 (ArC), 132.5 (ArC), 131.3 (ArCH), 130.8 (ArCH), 130.5 (ArC), 130.4 (ArCH), 128.4 (ArC), 128.3 (ArCH), 113.2 (ArCH), 110.6 (ArCH), 55.4 (OCH₃), 52.4 (CH₂), 48.8 (CH₂), 43.6 (C(Ar)H); *m/z* (ESI) 308 [M+H]⁺; HRMS (ESI) C₁₆H₁₆³⁵Cl₂NO⁺ requires 308.0603, found 308.0606 [M+H]⁺. These data are consistent with those previously reported.²⁶¹

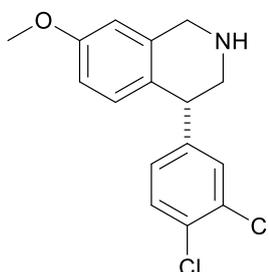
(*S*)-4-(3,4-Dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, (*S*)-**327**



General procedure K was applied using (*S*)-4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (*S*)-**236** (81 mg, 0.25 mmol), THF (10.0 mL) and LiAlH₄ (375 μL, 0.75 mmol), and used without further purification. The title compound was

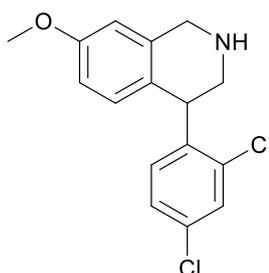
formed as an orange-yellow oil (74 mg, 96 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{26}$ ($c = 0.23$, CHCl_3) -3.20 .

(R)-4-(3,4-Dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, (R)-327



General procedure K was applied using (R)-4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**R**)-**236** (81 mg, 0.25 mmol), THF (10.0 mL) and LiAlH_4 (375 μL , 0.75 mmol), and used without further purification. The title compound was formed as an orange-yellow oil (72 mg, 94 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.30$, CHCl_3) $+4.60$.

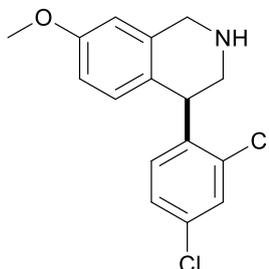
4-(2,4-Dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 328



General procedure K was applied using 4-(2,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one **237** (161 mg, 1.50 mmol), THF (20.0 mL) and LiAlH_4 (750 μL , 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **328** as an off-white solid (112 mg, 73 %); m.p. 75-77 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3313 (w, N-H), 2833 (m, C-H), 1609 (m, N-H), 1251 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.42 (1H, d, $J = 2.0$ Hz, ArH), 7.09 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 6.77 (1H, d, $J = 8.5$ Hz, ArH), 6.74 (1H, d, $J = 8.5$ Hz, ArH), 6.70 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.63 (1H, d, $J = 1.5$ Hz, ArH), 4.50 (1H, t, $J = 5.0$ Hz, C(Ar)H), 4.10 (1H, d, $J = 16.5$ Hz, C(H)H), 4.05 (1H, d, $J = 16.5$ Hz, C(H)H), 3.79 (3H, s, OCH₃), 3.35 (1H, dd, $J = 13.0, 5.0$ Hz, C(H)H), 3.08 (1H, dd, $J = 13.0, 5.0$ Hz, C(H)H), 1.75 (1H, s, NH); δ_{C} (126 MHz, CDCl_3) 158.3 (ArC), 141.4 (ArC), 137.9 (ArC), 134.5 (ArC), 132.7 (ArC), 131.8 (ArCH), 131.3 (ArCH), 129.3 (ArCH), 128.3 (ArC), 127.1 (ArCH), 113.3 (ArCH), 110.5 (ArCH), 55.4 (OCH₃), 49.9 (CH₂), 48.8

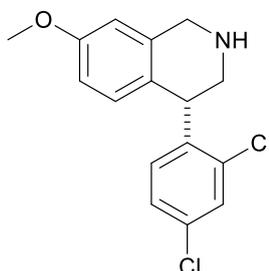
(CH₂), 40.0 (C(Ar)H); m/z (ESI) 308 [M+H]⁺; HRMS (ESI) C₁₆H₁₆³⁵Cl₂NO⁺ requires 308.0603, found 308.0604 [M+H]⁺.

(R)-4-(2,4-Dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, (R)-328



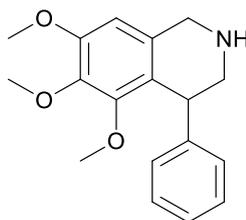
General procedure K was applied using (R)-4-(2,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**R**)-**237** (81 mg, 0.25 mmol), THF (10.0 mL) and LiAlH₄ (375 μL, 0.75 mmol), and used without further purification. The title compound was formed as an off-white solid (71 mg, 92 %); spectroscopic data are similar to those of the racemate; [α]_D²⁸ (c = 0.50, CHCl₃) +7.50.

(S)-4-(2,4-Dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline, (S)-328



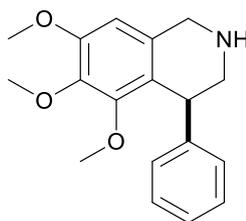
General procedure K was applied using (S)-4-(2,4-dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one (**S**)-**237** (81 mg, 0.25 mmol), THF (10.0 mL) and LiAlH₄ (375 μL, 0.75 mmol), and used without further purification. The title compound was formed as an off-white solid (68 mg, 88 %); spectroscopic data are similar to those of the racemate; [α]_D²⁸ (c = 0.53, CHCl₃) -8.90.

5,6,7-Trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline, 329



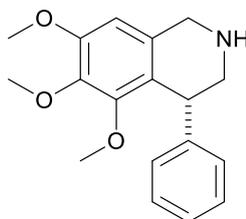
General procedure K was applied using 5,6,7-trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one **238** (157 mg, 0.50 mmol), THF (20.0 mL) and LiAlH₄ (750 μL, 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline **329** as a colourless oil (113 mg, 75 %); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3313 (w, N-H), 2836 (m, C-H), 1601 (m, N-H), 1114 (m, C-N); δ_{H} (500 MHz, CDCl₃) 7.30-7.22 (2H, m, 2 x ArH), 7.18 (1H, t, $J = 7.5$ Hz, ArH), 7.08-7.03 (2H, m, 2 x ArH), 6.41 (1H, s, ArH), 4.20-4.13 (1H, m, C(Ar)H), 4.03 (2H, s, CH₂), 3.86 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.32 (3H, s, OCH₃), 3.27 (1H, dd, $J = 13.0, 4.5$ Hz, C(H)H), 3.12 (1H, dd, $J = 13.0, 2.0$ Hz, C(H)H), 2.86 (1H, s, NH); δ_{C} (126 MHz, CDCl₃) 152.6 (ArC), 151.8 (ArC), 146.1 (ArC), 140.9 (ArC), 131.6 (ArC), 128.4 (2 x ArCH), 128.2 (2 x ArCH), 126.3 (ArCH), 123.0 (ArC), 104.1 (ArCH), 60.8 (OCH₃), 60.2 (OCH₃), 56.0 (OCH₃), 51.3 (CH₂), 47.9 (CH₂), 38.5 (C(Ar)H); m/z (ESI) 300 [M+H]⁺; HRMS (ESI) C₁₈H₂₂NO₃⁺ requires 300.1594, found 300.1597 [M+H]⁺.

(S)-5,6,7-Trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (S)-329



General procedure K was applied using (*S*)-5,6,7-trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (*S*)-**238** (94 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was formed as an off-white solid (81 mg, 90 %); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{28}$ ($c = 0.30$, CHCl₃) +25.3.

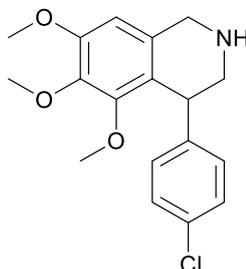
(R)-5,6,7-Trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (R)-329



General procedure K was applied using (*R*)-5,6,7-trimethoxy-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (*R*)-**238** (94 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was

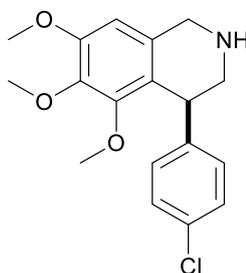
formed as an off-white solid (77 mg, 86 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.24$, CHCl_3) -22.9 .

4-(4-Chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, **330**



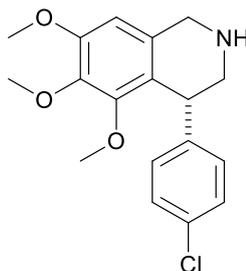
General procedure K was applied using 4-(4-chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **239** (174 mg, 0.50 mmol), THF (20.0 mL) and LiAlH_4 (750 μL , 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **330** as a pale yellow oil (137 mg, 82 %); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3305 (w, N-H), 2836 (m, C-H), 1601 (m, N-H), 1118 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.26-7.20 (2H, m, 2 x ArH), 7.03-6.99 (2H, m, 2 x ArH), 6.41 (1H, s, ArH), 4.15-4.08 (1H, m, C(Ar)H), 4.01 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.25 (1H, dd, $J = 13.0, 4.5$ Hz, C(H)H), 3.07 (1H, dd, $J = 13.0, 2.5$ Hz, C(H)H), 2.23 (1H, s, NH); δ_{C} (126 MHz, CDCl_3) 152.7 (ArC), 151.7 (ArC), 144.9 (ArC), 140.9 (ArC), 131.9 (ArC), 131.8 (ArC), 129.5 (2 x ArCH), 128.5 (2 x ArCH), 122.6 (ArC), 104.2 (ArCH), 60.8 (OCH_3), 60.3 (OCH_3), 56.0 (OCH_3), 51.4 (CH_2), 48.1 (CH_2), 38.1 (C(Ar)H); m/z (ESI) 334 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{18}\text{H}_{21}^{35}\text{ClNO}_3^+$ requires 334.1204, found 334.1208 $[\text{M}+\text{H}]^+$.

(*S*)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, (*S*)-**330**



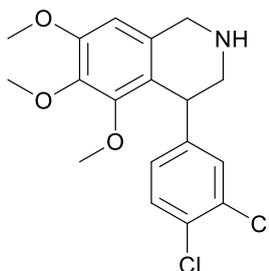
General procedure K was applied using (*S*)-4-(4-chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (*S*)-**239** (104 mg, 0.30 mmol), THF (12.0 mL) and LiAlH_4 (450 μL , 0.90 mmol), and used without further purification. The title compound was formed as a pale yellow oil (90 mg, 89 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ ($c = 0.33$, CHCl_3) $+9.70$.

(R)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, (R)-330



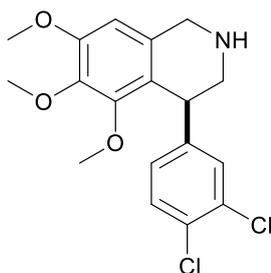
General procedure K was applied using (R)-4-(4-chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (**R**)-**239** (104 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was formed as a pale yellow oil (82 mg, 81 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.28, CHCl₃) -17.4.

4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, 331



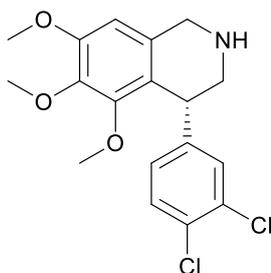
General procedure K was applied using 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one **240** (191 mg, 1.50 mmol), THF (20.0 mL) and LiAlH₄ (750 μL, 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **331** as a yellow solid (120 mg, 65 %); m.p. 60-61 °C; ν_{\max} /cm⁻¹ (neat) 3328 (w, N-H), 2836 (m, C-H), 1601 (m, N-H), 1116 (m, C-N); δ_{H} (500 MHz, CDCl₃) 7.33 (1H, d, J = 8.5 Hz, ArH), 7.17 (1H, d, J = 2.0 Hz, ArH), 6.94 (1H, dd, J = 8.5, 2.0 Hz, ArH), 6.41 (1H, s, ArH), 4.09-4.05 (1H, m, C(Ar)H), 4.01 (2H, s, CH₂), 3.86 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.44 (3H, s, OCH₃), 3.26 (1H, dd, J = 13.0, 4.5 Hz, C(H)H), 3.07 (1H, dd, J = 13.0, 2.5 Hz, C(H)H), 1.74 (1H, s, NH); δ_{C} (126 MHz, CDCl₃) 152.9 (ArC), 151.7 (ArC), 146.9 (ArC), 140.8 (ArC), 132.3 (ArC), 132.0 (ArC), 130.2 (ArCH), 130.1 (ArC), 130.1 (ArCH), 127.6 (ArCH), 121.9 (ArC), 104.3 (ArCH), 60.8 (OCH₃), 60.3 (OCH₃), 56.0 (OCH₃), 51.4 (CH₂), 48.2 (CH₂), 38.2 (C(Ar)H); m/z (ESI) 368 [M+H]⁺; HRMS (ESI) C₁₈H₂₀³⁵Cl₂NO₃⁺ requires 368.0815, found 368.0813 [M+H]⁺.

(S)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, (S)-331



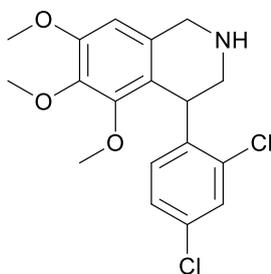
General procedure K was applied using (S)-4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (**S**)-**240** (115 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was formed as a yellow solid (103 mg, 93 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.44, CHCl₃) +16.4.

(R)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, (R)-331



General procedure K was applied using (R)-4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (**R**)-**240** (115 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was formed as a yellow solid (94 mg, 85 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.22, CHCl₃) -5.60.

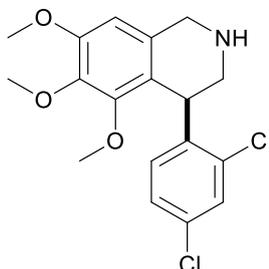
4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, 323



General procedure K was applied using 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one **241** (191 mg, 0.50 mmol), THF (20.0 mL) and LiAlH₄ (750 μL, 1.50 mmol). Purification by flash column chromatography, eluting with 100 % EtOAc, yielded 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline

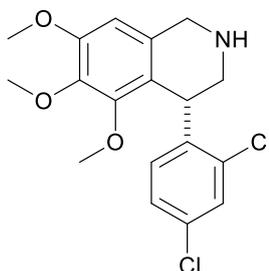
323 as a pale yellow oil (121 mg, 65 %). Spectroscopic data are in agreement with those previously acquired.

(R)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, (R)-323



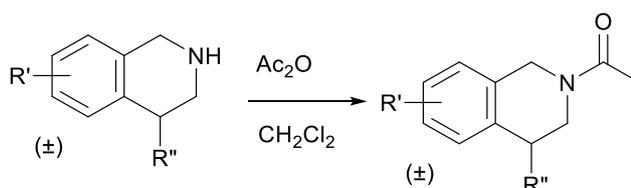
General procedure K was applied using (R)-4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (**R**)-**241** (115 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was formed as a pale yellow oil (103 mg, 93 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.25, CHCl₃) +22.0.

(S)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, (S)-323



General procedure K was applied using (S)-4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (**S**)-**241** (115 mg, 0.30 mmol), THF (12.0 mL) and LiAlH₄ (450 μL, 0.90 mmol), and used without further purification. The title compound was formed as a pale yellow oil (100 mg, 90 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.42, CHCl₃) -36.7.

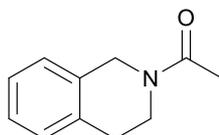
3.6.10 Acetylation of Tetrahydroquinolines – General Procedure L



The following procedure was performed in accordance with previous literature.²¹⁷

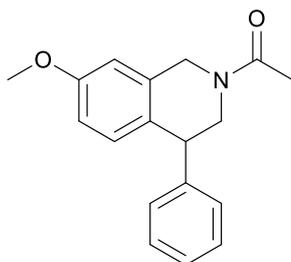
To a solution of tetrahydroisoquinoline (1.00 equiv.) in CH₂Cl₂ (10.0 mL/g), at 0 °C under N₂, was added Ac₂O (1.05 equiv.) dropwise. The resulting mixture was stirred at room temperature for 30 minutes and water added. Organics were extracted with CH₂Cl₂, washed with saturated NaHCO₃ (aq.), then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then used without further purification.

1-(3,4-Dihydroisoquinolin-2(1H)-yl)ethan-1-one, 394 (0.58:0.42 mixture of rotamers)



General procedure L was applied using 1,2,3,4-tetrahydroisoquinoline **186** (10 mg, 75.1 μmol), CH₂Cl₂ (100 μL) and Ac₂O (7.45 μL, 78.8 μmol). The title compound was formed as a yellow oil (10 mg, 76 %); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2850 (m, C-H), 1641 (s, C=O), 1233 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.23-7.08 (4H, m, 4 x ArH), 4.73 (2H, s, CH₂), 3.67 (2H, t, $J = 6.0$ Hz, CH₂), 2.91 (2H, t, $J = 6.0$ Hz, CH₂), 1.43 (3H, s, CH₃); δ_{C} (126 MHz, CDCl₃) 169.7 (C=O), 134.2 (ArC), 133.7 (ArC), 128.4 (ArCH), 126.8 (ArCH), 126.8 (ArCH), 126.7 (ArCH), 44.2 (CH₂), 44.1 (CH₂), 30.4 (CH₃), 29.6 (CH₂); m/z (ESI) 198 [M+Na]⁺; HRMS (ESI) C₁₁H₁₃NONa⁺ requires 198.0889, found 198.0889 [M+Na]⁺. These data are consistent with those previously reported.²⁶²

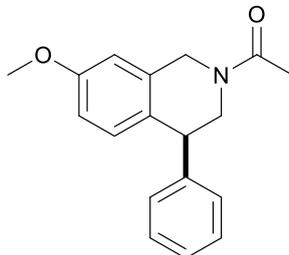
1-(7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, 332 (0.81:0.19 mixture of rotamers)



General procedure L was applied using 7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline **325** (10 mg, 41.8 μmol), CH₂Cl₂ (100 μL) and Ac₂O (4 μL, 43.9 μmol). The title compound was formed as an off-white solid (10 mg, 85 %); m.p. 52-54 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2850 (m, C-H), 1643 (s, C=O), 1253 (s, C-O); δ_{H} (500 MHz, CDCl₃) 7.31-7.26 (2H, m, 2 x ArH), 7.25-7.20 (1H, m, ArH), 7.06-7.01 (2H, m, 2 x ArH), 6.89 (1H, d, $J = 8.0$ Hz, ArH), 6.74-6.71 (2H, m, 2 x ArH), 5.20 (1H, d, $J = 17.5$ Hz, C(H)H), 4.48 (1H, d, $J = 17.5$ Hz, C(H)H), 4.18 (1H, t, $J = 4.0$ Hz, C(Ar)H), 3.80 (2H, m, CH₂), 3.80 (3H, s, OCH₃), 1.66 (3H, s, CH₃); δ_{C} (126 MHz, CDCl₃) 170.0 (C=O), 158.7 (ArC), 143.1 (ArC), 134.9 (ArC), 130.7 (ArCH), 128.8 (2 x ArCH), 128.5 (2 x ArCH), 128.2

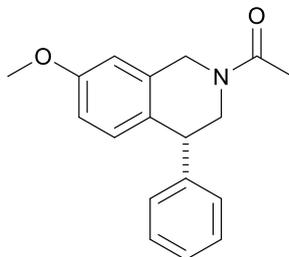
(ArC), 127.1 (ArCH), 113.6 (ArCH), 110.8 (ArCH), 55.4 (OCH₃), 51.5 (CH₂), 44.8 (C(Ar)H), 44.6 (CH₂), 20.9 (CH₃); m/z (ESI) 304 [M+Na]⁺; HRMS (ESI) C₁₈H₁₉NO₂Na⁺ requires 304.1308, found 304.1308 [M+Na]⁺.

(S)-1-(7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (S)-332



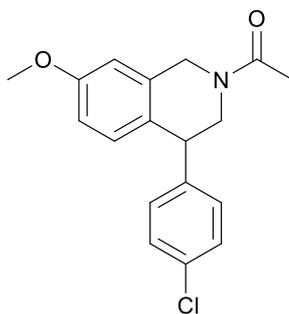
General procedure L was applied using (*S*)-7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*S*)-**325** (10 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (11 mg, 98 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁷ (c = 0.20, CHCl₃) +47.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 216 nm, (*S*)-isomer 17.39 min., (*R*)-isomer 22.36 min.).

(R)-1-(7-Methoxy-4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (R)-332



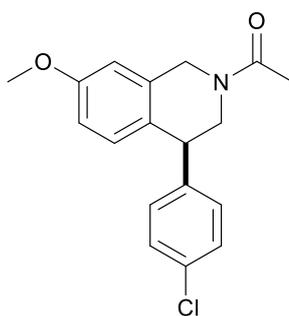
General procedure L was applied using (*R*)-7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*R*)-**325** (10 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (11 mg, 98 %, 96 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁵ (c = 0.19, CHCl₃) -41.2; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 216 nm, (*S*)-isomer 17.68 min., (*R*)-isomer 22.05 min.).

1-(4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, 333 (0.76:0.24 mixture of rotamers)



General procedure L was applied using 4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **326** (10 mg, 36.5 μmol), CH_2Cl_2 (100 μL) and Ac_2O (4 μL , 38.4 μmol). The title compound was formed as an off-white solid (10 mg, 87 %); m.p. 106–109 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2850 (m, C-H), 1645 (s, C=O), 1254 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.28–7.23 (2H, m, 2 x ArH), 6.99–6.96 (2H, m, 2 x ArH), 6.88–6.84 (1H, m, ArH), 6.75–6.71 (1H, m, ArH), 6.72–6.68 (1H, m, ArH), 5.20 (1H, d, $J = 17.5$ Hz, C(H)H), 4.46 (1H, d, $J = 17.5$ Hz, C(H)H), 4.15 (1H, t, $J = 4.0$ Hz, C(Ar)H), 3.80 (3H, s, OCH₃), 3.79–3.77 (2H, m, CH₂), 1.70 (3H, s, CH₃); δ_{C} (126 MHz, CDCl_3) 169.9 (C=O), 158.8 (ArC), 141.7 (ArC), 134.8 (ArC), 133.0 (ArC), 130.7 (ArCH), 129.8 (2 x ArCH), 128.9 (2 x ArCH), 127.7 (ArC), 113.8 (ArCH), 110.9 (ArCH), 55.5 (OCH₃), 51.3 (CH₂), 44.5 (CH₂), 44.2 (C(Ar)H), 21.0 (CH₃); m/z (ESI) 338 [M+Na]⁺; HRMS (ESI) $\text{C}_{18}\text{H}_{18}^{35}\text{ClNO}_2\text{Na}^+$ requires 338.0918, found 338.0919 [M+Na]⁺.

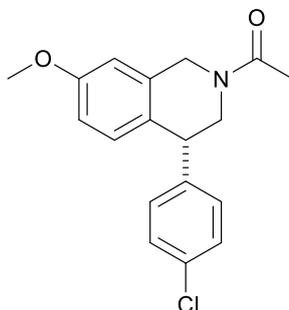
(S)-1-(4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (S)-333



General procedure L was applied using (S)-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (S)-**326** (11 mg, 40.0 μmol), CH_2Cl_2 (100 μL , 2.5 mL/mmol) and Ac_2O (4 μL , 42.0 μmol). The title compound was formed as an off-white solid (12 mg, 95 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{27}$ ($c = 0.22$, CHCl_3) +36.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel

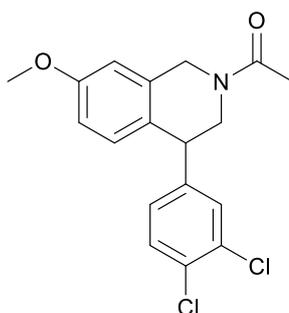
OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 220 nm, (*S*)-isomer 16.79 min., (*R*)-isomer 24.20 min.).

(*R*)-1-(4-(4-Chlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, (*R*)-333



General procedure L was applied using (*R*)-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-**326** (11 mg, 40.0 μmol), CH_2Cl_2 (100 μL , 2.5 mL/mmol) and Ac_2O (4 μL , 42.0 μmol). The title compound was formed as an off-white solid (13 mg, 99 %, 98 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{25}$ ($c = 0.23$, CHCl_3) -41.5 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 220 nm, (*S*)-isomer 17.81 min., (*R*)-isomer 23.38 min.).

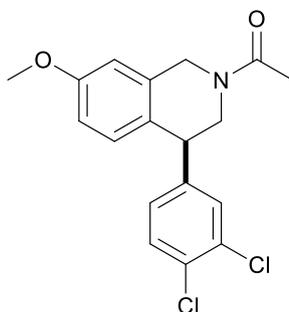
1-(4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, **334 (0.69:0.31 mixture of rotamers)**



General procedure L was applied using 4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **327** (10 mg, 32.4 μmol), CH_2Cl_2 (100 μL) and Ac_2O (3 μL , 34.1 μmol). The title compound was formed as an off-white solid (10 mg, 88 %); m.p. 55-58 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2850 (m, C-H), 1645 (s, C=O), 1253 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.37-7.33 (1H, m, ArH), 7.19 (1H, d, $J = 1.5$ Hz, ArH), 6.86-6.81 (2H, m, 2 x ArH), 6.75-6.71 (2H, m, 2 x ArH), 5.15 (1H, d, $J = 17.5$ Hz, C(H)H), 4.49 (1H, d, $J = 17.5$ Hz, C(H)H), 4.16-4.08 (1H, m, C(Ar)H), 3.80 (3H, s, OCH₃), 3.79-3.77 (2H, m, CH₂), 1.76 (3H, s, CH₃); δ_{C} (126 MHz, CDCl_3) 169.8 (C=O), 159.0 (ArC), 143.5 (ArC), 134.8 (ArC), 132.9 (ArC), 131.3 (ArC), 130.7 (ArCH), 130.6 (ArCH), 130.4 (ArCH), 127.9 (ArCH),

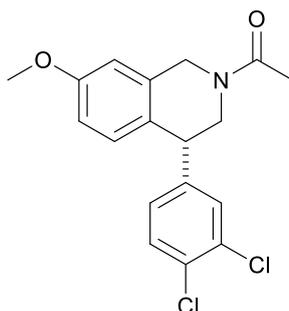
127.0 (ArC), 113.9 (ArCH), 111.0 (ArCH), 55.5 (OCH₃), 51.1 (CH₂), 44.5 (CH₂), 44.1 (C(Ar)H), 21.1 (CH₃); m/z (ESI) 372 [M+Na]⁺; HRMS (ESI) C₁₈H₁₇³⁵Cl₂NO₂Na⁺ requires 372.0529, found 372.0529 [M+Na]⁺.

(S)-1-(4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (S)-334



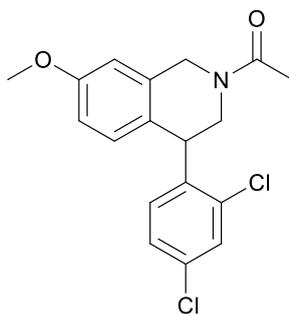
General procedure L was applied using (S)-4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (S)-**327** (12 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (12 mg, 86 %, 91 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁷ (c = 0.25, CHCl₃) +37.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 211 nm, (R)-isomer 26.48 min., (S)-isomer 30.50 min.).

(R)-1-(4-(3,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (R)-334



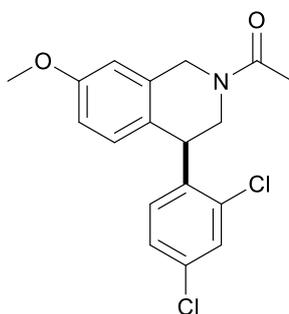
General procedure L was applied using (R)-4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (R)-**327** (12 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (14 mg, 97 %, 99 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁷ (c = 0.21, CHCl₃) -41.8; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 211 nm, (R)-isomer 25.77 min., (S)-isomer 30.76 min.).

1-(4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, 335 (0.88:0.12 mixture of rotamers)



General procedure L was applied using 4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **328** (10 mg, 32.4 μmol), CH_2Cl_2 (100 μL) and Ac_2O (3 μL , 34.1 μmol). The title compound was formed as an off-white solid (10 mg, 88 %); m.p. 47-49 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2849 (m, C-H), 1647 (s, C=O), 1252 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.44 (1H, d, $J = 2.0$ Hz, ArH), 7.06 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.89-6.84 (1H, m, ArH), 6.78-6.72 (2H, m, 2 x ArH), 6.52 (1H, d, $J = 8.5$ Hz, ArH), 5.32 (1H, d, $J = 17.5$ Hz, C(H)H), 4.61 (1H, t, $J = 3.0$ Hz, C(Ar)H), 4.35 (1H, d, $J = 17.5$ Hz, C(H)H), 3.95 (1H, dd, $J = 13.5, 3.0$ Hz, C(H)H), 3.81 (3H, s, OCH_3), 3.72 (1H, dd, $J = 13.5, 4.0$ Hz, C(H)H), 1.62 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 169.9 ($\text{C}=\text{O}$), 159.0 (ArC), 139.0 (ArC), 135.4 (ArC), 133.9 (ArC), 133.6 (ArC), 131.7 (ArCH), 130.8 (ArCH), 129.3 (ArCH), 127.5 (ArCH), 126.7 (ArC), 114.0 (ArCH), 110.9 (ArCH), 55.5 (OCH_3), 48.9 (CH_2), 44.5 (CH_2), 40.9 ($\text{C}(\text{Ar})\text{H}$), 20.7 (CH_3); m/z (ESI) 372 [$\text{M}+\text{Na}$] $^+$; HRMS (ESI) $\text{C}_{18}\text{H}_{17}^{35}\text{Cl}_2\text{NO}_2\text{Na}^+$ requires 372.0529, found 372.0528 [$\text{M}+\text{Na}$] $^+$.

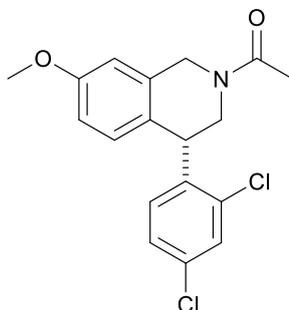
(R)-1-(4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (R)-335



General procedure L was applied using (*R*)-4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-**328** (12 mg, 40.0 μmol), CH_2Cl_2 (100 μL , 2.5 mL/mmol) and Ac_2O (4 μL , 42.0 μmol). The title compound was formed as an off-white solid (14 mg, 97 %, 95 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{26}$ ($c = 0.26$, CHCl_3) -28.9 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA

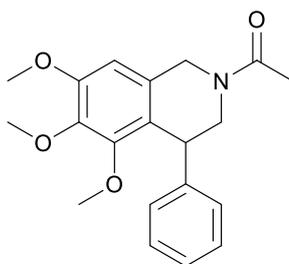
column, 2-propanol:hexane = 5:95, 1.00 mL/min., 213 nm, (*R*)-isomer 15.09 min., (*S*)-isomer 23.64 min.).

(*S*)-1-(4-(2,4-Dichlorophenyl)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, (*S*)-335



General procedure L was applied using (*S*)-4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*S*)-**328** (12 mg, 40.0 μmol), CH_2Cl_2 (100 μL , 2.5 mL/mmol) and Ac_2O (4 μL , 42.0 μmol). The title compound was formed as an off-white solid (14 mg, 97 %, 97 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ ($c = 0.25$, CHCl_3) +30.1; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 213 nm, (*R*)-isomer 15.37 min., (*S*)-isomer 23.28 min.).

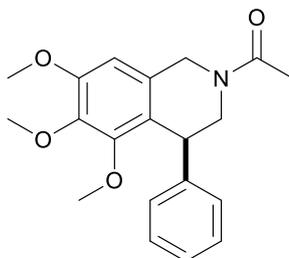
1-(5,6,7-Trimethoxy-4-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, 336 (0.98:0.02 mixture of rotamers)



General procedure L was applied using 5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline **329** (10 mg, 33.4 μmol), CH_2Cl_2 (100 μL) and Ac_2O (3 μL , 35.1 μmol). The title compound was formed as an off-white solid (10 mg, 88 %); m.p. 103-106 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2852 (m, C-H), 1643 (s, C=O), 1243 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.26-7.22 (2H, m, 2 x ArH), 7.20-7.16 (1H, m, ArH), 7.04-6.99 (2H, m, 2 x ArH), 6.51 (1H, s, ArH), 5.48 (1H, d, $J = 17.5$ Hz, C(H)H), 4.40-4.35 (1H, m, C(Ar)H), 4.12 (1H, d, $J = 17.5$ Hz, C(H)H), 3.92-3.87 (1H, m, C(H)H), 3.86 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.63 (1H, dd, $J = 13.5, 4.0$ Hz, C(H)H), 3.38 (3H, s, OCH₃), 1.45 (3H, s CH₃); δ_{C} (126 MHz, CDCl_3) 170.2 (C=O), 153.1 (ArC), 151.4 (ArC), 143.8 (ArC), 141.1 (ArC),

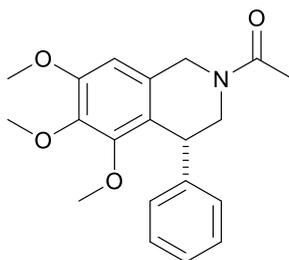
129.1 (ArC), 128.6 (2 x ArCH), 128.0 (2 x ArCH), 126.8 (ArCH), 122.4 (ArC), 104.6 (ArCH), 60.8 (OCH₃), 60.5 (OCH₃), 56.1 (OCH₃), 51.2 (CH₂), 44.1 (CH₂), 40.1 (C(Ar)H), 20.7 (CH₃); m/z (ESI) 364 [M+Na]⁺; HRMS (ESI) C₂₀H₂₃NO₄Na⁺ requires 364.1519, found 364.1518 [M+Na]⁺.

(S)-1-(5,6,7-Trimethoxy-4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one,
(S)-336



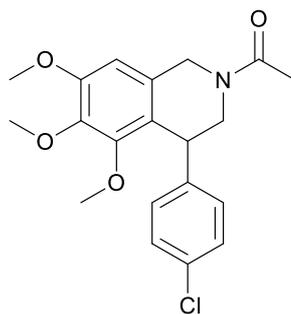
General procedure L was applied using (*S*)-5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*S*)-**329** (12 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (13 mg, 91 %, 94 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁷ (c = 0.25, CHCl₃) +87.3; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 5:95, 1.00 mL/min., 214 nm, (*R*)-isomer 25.09 min., (*S*)-isomer 28.86 min.).

(R)-1-(5,6,7-Trimethoxy-4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one,
(R)-336



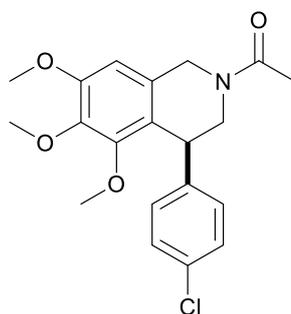
General procedure L was applied using (*R*)-5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*R*)-**329** (12 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (13 mg, 91 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁵ (c = 0.27, CHCl₃) -77.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 5:95, 1.00 mL/min., 214 nm, (*R*)-isomer 25.70 min., (*S*)-isomer 30.37 min.).

1-(4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, 337 (0.93:0.07 mixture of rotamers)



General procedure L was applied using 4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **330** (10 mg, 30.0 μmol), CH_2Cl_2 (100 μL) and Ac_2O (3 μL , 31.5 μmol). The title compound was formed as an off-white solid (10 mg, 89 %); m.p. 108–111 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2849 (m, C-H), 1644 (s, C=O), 1243 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.25–7.21 (2H, m, 2 x ArH), 6.99–6.93 (2H, m, 2 x ArH), 6.50 (1H, s, ArH), 5.47 (1H, d, $J = 17.5$ Hz, C(H)H), 4.36–4.31 (1H, m, C(Ar)H), 4.11 (1H, d, $J = 17.5$ Hz, C(H)H), 3.89–3.84 (1H, m, C(H)H), 3.86 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.62 (1H, dd, $J = 13.5, 4.0$ Hz, C(H)H), 3.42 (3H, s, OCH_3), 1.52 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 170.1 (C=O), 153.3 (ArC), 151.3 (ArC), 142.5 (ArC), 141.0 (ArC), 132.7 (ArC), 129.3 (2 x ArCH), 129.0 (ArC), 128.8 (2 x ArCH), 121.8 (ArC), 104.6 (ArCH), 60.9 (OCH_3), 60.6 (OCH_3), 56.1 (OCH_3), 50.9 (CH_2), 44.0 (CH_2), 39.6 (C(Ar)H), 20.8 (CH_3); m/z (ESI) 398 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{20}\text{H}_{22}^{35}\text{ClNO}_4\text{Na}^+$ requires 398.1130, found 398.1133 $[\text{M}+\text{Na}]^+$.

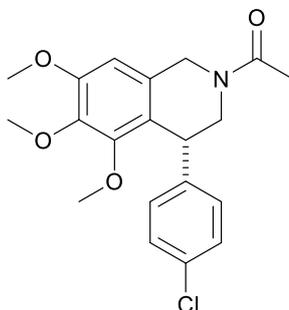
(S)-1-(4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (S)-337



General procedure L was applied using (S)-4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (S)-**330** (13 mg, 40.0 μmol), CH_2Cl_2 (100 μL , 2.5 mL/mmol) and Ac_2O (4 μL , 42.0 μmol). The title compound was formed as an off-white solid (14 mg, 89 %, 95 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{28}$ ($c = 0.28$, CHCl_3) +63.1; enantiomeric excess determined by HPLC

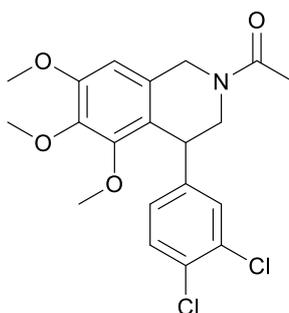
analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 219 nm, (*R*)-isomer 13.88 min., (*S*)-isomer 17.81 min.).

(*R*)-1-(4-(4-Chlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, (*R*)-337



General procedure L was applied using (*R*)-4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-**330** (13 mg, 40.0 μ mol), CH_2Cl_2 (100 μ L, 2.5 mL/mmol) and Ac_2O (4 μ L, 42.0 μ mol). The title compound was formed as an off-white solid (15 mg, 96 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{26}$ ($c = 0.26$, CHCl_3) -64.8 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 10:90, 1.00 mL/min., 219 nm, (*R*)-isomer 13.31 min., (*S*)-isomer 17.99 min.).

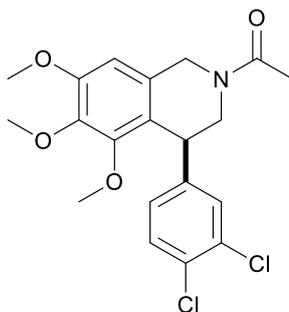
1-(4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, **338 (0.87:0.13 mixture of rotamers)**



General procedure L was applied using 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **331** (10 mg, 27.0 μ mol), CH_2Cl_2 (100 μ L) and Ac_2O (3 μ L, 28.5 μ mol). The title compound was formed as an off-white solid (10 mg, 90 %); m.p. 57-59 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2848 (m, C-H), 1645 (s, C=O), 1242 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.31 (1H, d, $J = 8.5$ Hz, ArH), 7.20 (1H, d, $J = 2.0$ Hz, ArH), 6.81 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.51 (1H, s, ArH), 5.44 (1H, d, $J = 17.5$ Hz, C(H)H), 4.32-4.28 (1H, m, C(Ar)H), 4.12 (1H, d, $J = 17.5$ Hz, C(H)H), 3.90-3.88 (1H, m, C(H)H), 3.87 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.63 (1H, dd, $J = 13.5, 4.0$ Hz, C(H)H), 3.48 (3H, s, OCH₃), 1.59 (3H, s, CH₃); δ_{C} (126 MHz, CDCl_3) 169.9 (C=O), 153.6 (ArC), 151.2 (ArC),

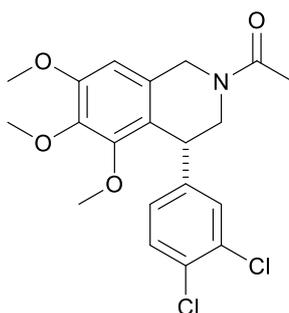
144.3 (ArC), 141.0 (ArC), 132.7 (ArC), 130.9 (ArC), 130.5 (ArCH), 129.9 (ArCH), 129.0 (ArC), 127.3 (ArCH), 121.0 (ArC), 104.7 (ArCH), 60.9 (OCH₃), 60.6 (OCH₃), 56.1 (OCH₃), 50.7 (CH₂), 44.0 (CH₂), 39.4 (C(Ar)H), 21.0 (CH₃); m/z (ESI) 432 [M+Na]⁺; HRMS (ESI) C₂₀H₂₁³⁵Cl₂NO₄Na⁺ requires 432.0740, found 432.0743 [M+Na]⁺.

(S)-1-(4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (S)-338



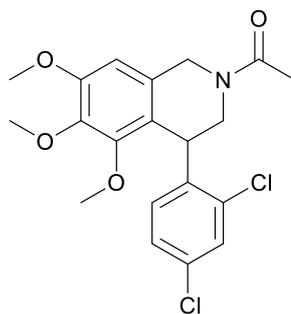
General procedure L was applied using (*S*)-4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (*S*)-**331** (15 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (16 mg, 95 %, 97 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁸ (c = 0.33, CHCl₃) +65.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 8:92, 1.00 mL/min., 215 nm, (*R*)-isomer 19.20 min., (*S*)-isomer 26.84 min.).

(R)-1-(4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (R)-338



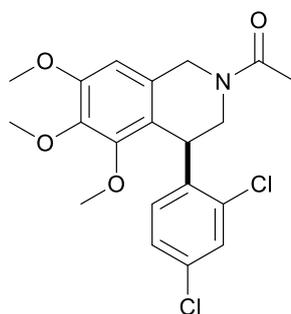
General procedure L was applied using (*R*)-4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-**331** (15 mg, 40.0 μmol), CH₂Cl₂ (100 μL, 2.5 mL/mmol) and Ac₂O (4 μL, 42.0 μmol). The title compound was formed as an off-white solid (14 mg, 85 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; [α]_D²⁶ (c = 0.30, CHCl₃) -62.4; enantiomeric excess determined by HPLC analysis (Diacel Chiralcel OD-H column, 2-propanol:hexane = 8:92, 1.00 mL/min., 215 nm, (*R*)-isomer 18.75 min., (*S*)-isomer 28.12 min.).

1-(4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, 339 (0.95:0.05 mixture of rotamers)



General procedure L was applied using 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **323** (10 mg, 27.0 μmol), CH_2Cl_2 (100 μL) and Ac_2O (3 μL , 28.5 μmol). The title compound was formed as an off-white solid (10 mg, 90 %); m.p. 56-58 $^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2848 (m, C-H), 1647 (s, C=O), 1242 (s, C-O); δ_{H} (500 MHz, CDCl_3) 7.44 (1H, d, $J = 2.0$ Hz, ArH), 7.04 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.52 (1H, d, $J = 8.5$ Hz, ArH), 6.51 (1H, s, ArH), 5.49 (1H, d, $J = 17.5$ Hz, C(H)H), 4.78-4.75 (1H, m, C(Ar)H), 4.09 (1H, d, $J = 17.5$ Hz, C(H)H), 4.01-3.96 (1H, m, C(H)H), 3.87 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.58 (1H, dd, $J = 14.0, 4.0$ Hz, C(H)H), 3.50 (3H, s, OCH_3), 1.51 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 170.0 (C=O), 153.6 (ArC), 151.1 (ArC), 141.0 (ArC), 139.3 (ArC), 133.6 (ArC), 133.3 (ArC), 130.8 (ArCH), 129.5 (ArC), 129.3 (ArCH), 127.2 (ArCH), 121.2 (ArC), 104.6 (ArCH), 60.9 (OCH_3), 60.6 (OCH_3), 56.1 (OCH_3), 48.5 (CH_2), 44.0 (CH_2), 36.2 (C(Ar)H), 20.6 (CH_3); m/z (ESI) 432 [$\text{M}+\text{Na}$] $^+$; HRMS (ESI) $\text{C}_{20}\text{H}_{21}^{35}\text{Cl}_2\text{NO}_4\text{Na}^+$ requires 432.0740, found 432.0739 [$\text{M}+\text{Na}$] $^+$.

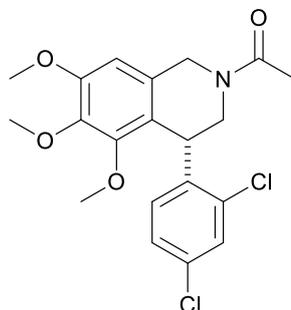
(R)-1-(4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one, (R)-339



General procedure L was applied using (R)-4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (R)-**323** (15 mg, 40.0 μmol), CH_2Cl_2 (100 μL , 2.5 mL/mmol) and Ac_2O (4 μL , 42.0 μmol). The title compound was formed as an off-white solid (15 mg, 92 %, 99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{27}$ ($c = 0.27$, CHCl_3) +49.9; enantiomeric excess determined by HPLC analysis (Diacel

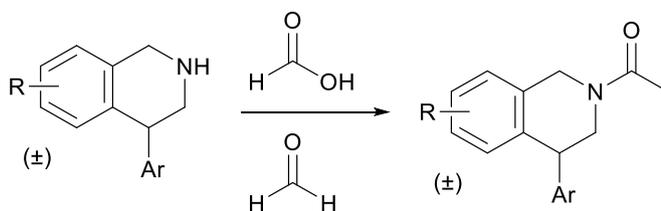
Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 211 nm, (*S*)-isomer 13.80 min., (*R*)-isomer 16.32 min.).

(*S*)-1-(4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one, (*S*)-339



General procedure L was applied using (*S*)-4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (*S*)-**323** (15 mg, 40.0 μ mol), CH_2Cl_2 (100 μ L, 2.5 mL/mmol) and Ac_2O (4 μ L, 42.0 μ mol). The title compound was formed as an off-white solid (15 mg, 92 %, 95 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ ($c = 0.28$, CHCl_3) -55.0 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 5:95, 1.00 mL/min., 211 nm, (*S*)-isomer 13.88 min., (*R*)-isomer 16.84 min.).

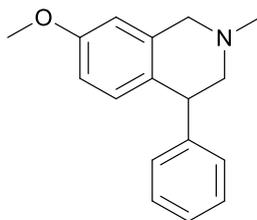
3.6.11 *N*-Methylation of Tetrahydroquinolines – General Procedure M



The following procedure was performed in accordance with previous literature.²³⁰

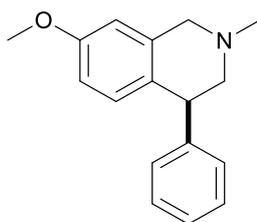
To tetrahydroisoquinoline (1.00 equiv.), at 0 °C, was added formic acid (30.0 equiv.) and then 37 % aqueous formaldehyde (15.0 equiv.) dropwise over 10 minutes. The resulting mixture was heated under reflux for 18 hours, then cooled to 0 °C and HCl (2.00 M) added cautiously. After extraction with EtOAc, the combined extracts were washed with water and brine, then dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography as mentioned specifically.

7-Methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, 346



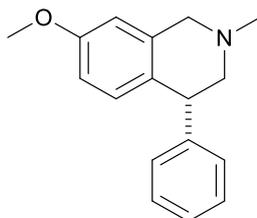
General procedure M was applied using 7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline **325** (24 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as an orange-brown solid (10 mg, 40 %); m.p. 100-103 $^{\circ}\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3028 (m, ArC-H), 2851 (m, C-H), 1650 (s, C=C), 1243 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.38-7.29 (3H, m, 3 x ArH), 7.22-7.15 (2H, m, 2 x ArH), 6.80 (1H, d, $J = 8.5$ Hz, ArH), 6.74 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.63 (1H, d, $J = 2.0$ Hz, ArH), 4.71 (1H, dd, $J = 12.0, 5.5$ Hz, C(Ar)H), 4.43 (1H, d, $J = 15.0$ Hz, C(H)H), 4.30 (1H, d, $J = 15.0$ Hz, C(H)H), 3.77 (3H, s, OCH_3), 3.65 (1H, dd, $J = 12.5, 6.0$ Hz, C(H)H), 3.17 (1H, t, $J = 12.0$ Hz, C(H)H), 2.95 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 158.9 (ArC), 140.4 (ArC), 130.8 (ArCH), 129.2 (2 x ArCH), 129.1 (2 x ArCH), 128.9 (ArC), 128.0 (ArCH), 126.8 (ArC), 115.1 (ArCH), 110.9 (ArCH), 58.4 (CH_2), 55.5 (OCH_3), 55.3 (CH_2), 43.5 (CH_3), 38.5 (C(Ar)H); m/z (ESI) 254 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{17}\text{H}_{20}\text{NO}^+$ requires 254.1539, found 254.1541 $[\text{M}+\text{H}]^+$. This compound is known but has previously only been reported with ^1H NMR data, which are consistent with those reported here.²⁶³

(*S*)-7-Methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-346



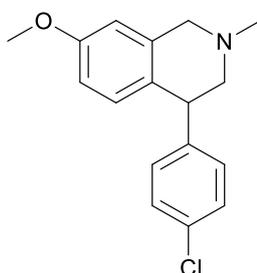
General procedure M was applied using (*S*)-7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*S*)-**325** (24 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as an orange-brown solid (6 mg, 24 %); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{27}$ ($c = 0.10, \text{CHCl}_3$) -2.30 .

(R)-7-Methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (R)-346



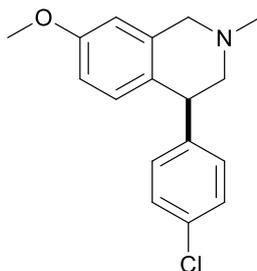
General procedure M was applied using (R)-7-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**R**)-**325** (24 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as an orange-brown solid (10 mg, 40 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{26}$ (c = 0.18, CHCl_3) +3.80.

4-(4-Chlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 347



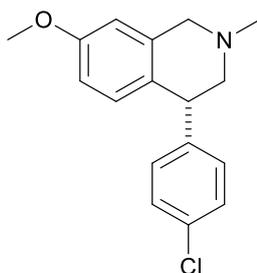
General procedure M was applied using 4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **326** (27 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as an orange-yellow solid (22 mg, 75 %); m.p. 198-202 $^{\circ}\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2929 (m, ArC-H), 2851 (m, C-H), 1649 (s, C=C), 1243 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.34-7.28 (2H, m, 2 x ArH), 7.16-7.10 (2H, m, 2 x ArH), 6.74 (2H, d, $J = 1.5$ Hz, 2 x ArH), 6.65-6.61 (1H, m, ArH), 4.72 (1H, dd, $J = 12.0, 5.5$ Hz, C(Ar)H), 4.46 (1H, d, $J = 15.5$ Hz, C(H)H), 4.31 (1H, d, $J = 15.5$ Hz, C(H)H), 3.75 (3H, s, OCH_3), 3.66 (1H, dd, $J = 12.0, 5.5$ Hz, C(H)H), 3.15 (1H, t, $J = 12.0$ Hz, C(H)H), 2.96 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 159.0 (ArC), 138.9 (ArC), 134.0 (ArC), 130.6 (ArCH), 130.5 (2 x ArCH), 129.5 (2 x ArCH), 128.8 (ArC), 126.2 (ArC), 115.2 (ArCH), 111.0 (ArCH), 58.2 (CH_2), 55.5 (OCH_3), 55.2 (CH_2), 41.0 ($\text{C}(\text{Ar})\text{H}$), 40.1 (CH_3); m/z (ESI) 288 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{17}\text{H}_{19}^{35}\text{ClNO}^+$ requires 288.1150, found 288.1149 $[\text{M}+\text{H}]^+$. This compound is known but was previously reported without characterisation data.^{58, 70}

(S)-4-(4-Chlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (S)-347



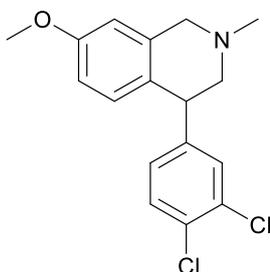
General procedure M was applied using (S)-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (S)-**326** (27 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as an orange-yellow solid (21 mg, 71 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +7.00.

(R)-4-(4-Chlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (R)-347



General procedure M was applied using (R)-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (R)-**326** (27 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as an orange-yellow solid (21 mg, 73 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -10.8.

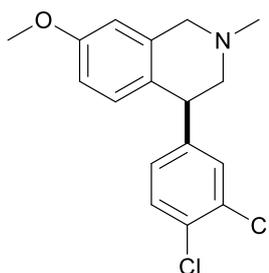
4-(3,4-Dichlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 198



General procedure M was applied using 4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **327** (31 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as a white solid (29 mg, 77 %); m.p. 218-219 $^{\circ}$ C;

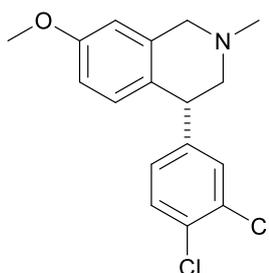
ν_{\max} / cm^{-1} (neat) 2956 (m, ArC-H), 2834 (m, C-H), 1615 (s, C=C), 1264 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.43 (1H, d, $J = 8.0$ Hz, ArH), 7.29 (1H, d, $J = 2.0$ Hz, ArH), 7.08 (1H, dd, $J = 8.0, 2.0$ Hz, ArH), 6.77 (2H, s, 2 x ArH), 6.63 (1H, s, ArH), 4.78 (1H, dd, $J = 11.5, 5.5$ Hz, C(Ar)H), 4.41 (1H, d, $J = 15.5$ Hz, C(H)H), 4.25 (1H, d, $J = 15.0$ Hz, C(H)H), 3.78 (3H, s, OCH_3), 3.62 (1H, dd, $J = 12.0, 5.5$ Hz, C(H)H), 3.08 (1H, t, $J = 12.0$ Hz, C(H)H), 2.93 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 159.2 (ArC), 140.6 (ArC), 133.5 (ArC), 132.4 (ArC), 131.4 (ArC), 131.3 (ArCH), 130.9 (ArCH), 130.6 (ArCH), 128.6 (ArCH), 125.5 (ArC), 115.4 (ArCH), 111.1 (ArCH), 55.6 (OCH_3), 55.2 (CH_2), 55.1 (CH_2), 43.9 (CH_3), 39.7 (C(Ar)H); m/z (ESI) 322 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_2\text{NO}^+$ requires 322.0760, found 322.0762 $[\text{M}+\text{H}]^+$. This compound is known but has previously only been reported with ^1H NMR data, which are consistent with those reported here.^{51, 68}

(S)-4-(3,4-Dichlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (S)-198



General procedure M was applied using (*S*)-4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*S*)-**327** (31 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as a white solid (29 mg, 90 %); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{29}$ ($c = 0.20, \text{CHCl}_3$) +3.10.

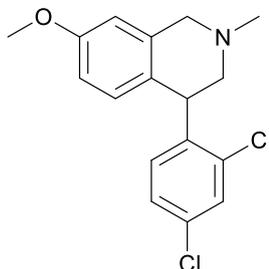
(R)-4-(3,4-Dichlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (R)-198



General procedure M was applied using (*R*)-4-(3,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-**327** (31 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol)

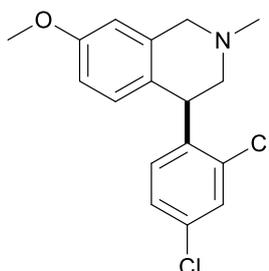
and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as a white solid (29 mg, 90 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ ($c = 0.20$, CHCl_3) -8.90 .

4-(2,4-Dichlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 348



General procedure M was applied using 4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **328** (31 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as a white solid (31 mg, 96 %); m.p. 200-202 $^{\circ}\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2953 (m, ArC-H), 2828 (m, C-H), 1615 (s, C=C), 1262 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.41 (1H, d, $J = 2.0$ Hz, ArH), 7.20 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 7.05 (1H, d, $J = 7.5$ Hz, ArH), 6.80-6.69 (2H, m, 2 x ArH), 6.66 (1H, d, $J = 1.5$ Hz, ArH), 5.10 (1H, dd, $J = 11.0, 6.0$ Hz, C(Ar)H), 4.45 (1H, d, $J = 16.0$ Hz, C(H)H), 4.37 (1H, d, $J = 15.5$ Hz, C(H)H), 3.76 (3H, s, OCH_3), 3.64 (1H, dd, $J = 12.5, 6.0$ Hz, C(H)H), 3.32 (1H, t, $J = 11.5$ Hz, C(H)H), 2.97 (3H, s, CH_3); δ_{C} (126 MHz, CDCl_3) 159.1 (ArC), 136.3 (ArC), 135.1 (ArC), 134.7 (ArC), 130.2 (ArCH), 130.1 (ArCH), 128.6 (ArC), 128.2 (ArCH), 124.9 (ArCH), 124.7 (ArC), 115.6 (ArCH), 111.4 (ArCH), 55.6 (OCH_3), 54.9 (CH_2), 54.8 (CH_2), 42.5 (CH_3), 38.4 ($\text{C}(\text{Ar})\text{H}$); m/z (ESI) 322 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_2\text{NO}^+$ requires 322.0760, found 322.0760 $[\text{M}+\text{H}]^+$.

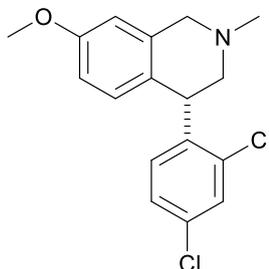
(*R*)-4-(2,4-Dichlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-348



General procedure M was applied using (*R*)-4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-**328** (31 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed

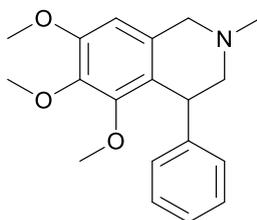
without further purification as a white solid (31 mg, 96 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ ($c = 0.20$, CHCl_3) +12.9.

(S)-4-(2,4-Dichlorophenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (S)-348



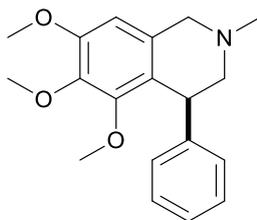
General procedure M was applied using (S)-4-(2,4-dichlorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (S)-**328** (31 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as a white solid (31 mg, 96 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.20$, CHCl_3) -1.50.

5,6,7-Trimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, 349



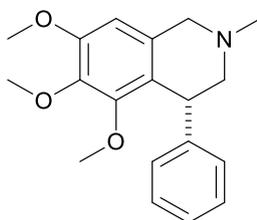
General procedure M was applied using 5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline **329** (15 mg, 0.50 mmol), formic acid (56.5 μL , 1.50 mmol) and 37 % aqueous formaldehyde (56 μL , 0.75 mmol). The title compound was formed without further purification as a yellow-brown solid (4 mg, 22 %); m.p. 53-55 $^{\circ}\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2924 (m, ArC-H), 2852 (m, C-H), 1647 (s, C=C), 1110 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.33-7.27 (2H, m, 2 x ArH), 7.25-7.21 (1H, m, ArH), 7.17-7.11 (2H, m, 2 x ArH), 6.43 (1H, s, ArH), 4.54 (1H, dd, $J = 8.5, 8.0$ Hz, C(Ar)H), 4.27 (1H, d, $J = 15.0$ Hz, C(H)H), 4.06 (1H, d, $J = 16.0$ Hz, C(H)H), 3.86 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.56-3.45 (1H, m, C(H)H), 3.15 (3H, s, OCH₃), 3.14-3.04 (1H, m, C(H)H), 2.78 (3H, s, CH₃); δ_{C} (126 MHz, CDCl_3) 153.7 (ArC), 152.2 (ArC), 143.2 (ArC), 142.5 (ArC), 128.9 (2 x ArCH), 127.9 (2 x ArCH), 127.2 (ArCH), 120.8 (ArC), 114.2 (ArC), 104.9 (ArCH), 60.7 (OCH₃), 59.7 (OCH₃), 58.6 (CH₂), 57.3 (CH₂), 56.2 (OCH₃), 43.5 (CH₃), 39.7 (C(Ar)H); m/z (ESI) 314 $[\text{M}+\text{H}]^+$; HRMS (ESI) $\text{C}_{19}\text{H}_{24}\text{NO}_3^+$ requires 314.1751, found 314.1752 $[\text{M}+\text{H}]^+$.

(S)-5,6,7-Trimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (S)-349



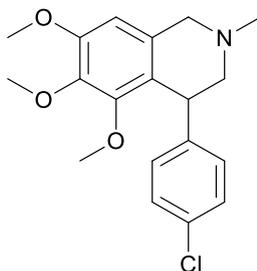
General procedure M was applied using (S)-5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**S**)-**329** (45 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a yellow-brown solid (9 mg, 19 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.17, CHCl₃) +3.80.

(R)-5,6,7-Trimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (R)-349



General procedure M was applied using (R)-5,6,7-trimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**R**)-**329** (45 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a yellow-brown solid (12 mg, 24 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{27}$ (c = 0.17, CHCl₃) -20.7.

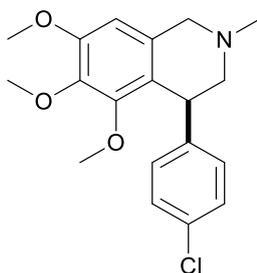
4-(4-Chlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 350



General procedure M was applied using 4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **330** (33 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as pale yellow solid (16 mg, 45 %); m.p. 164-166 $^{\circ}$ C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2928 (m, ArC-H), 2850 (m, C-H), 1653 (s, C=C), 1117 (m, C-N); δ_{H} (500 MHz, CDCl₃) 7.29-7.23 (2H, m, 2 x ArH), 7.10-7.05 (2H, m, 2 x ArH), 6.43 (1H, s, ArH), 4.48 (1H, dd,

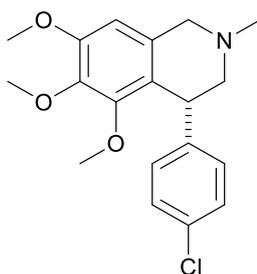
$J = 8.5, 7.0$ Hz, C(Ar)H), 4.22 (1H, d, $J = 15.0$ Hz, C(H)H), 4.03 (1H, d, $J = 14.5$ Hz, C(H)H), 3.85 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.51-3.43 (1H, m, C(H)H), 3.23 (3H, s, OCH₃), 2.99 (1H, dd, $J = 12.5, 9.0$ Hz, C(H)H), 2.74 (3H, s, CH₃); δ_c (126 MHz, CDCl₃) 153.3 (ArC), 151.9 (ArC), 143.6 (ArC), 141.7 (ArC), 132.2 (ArC), 129.5 (2 x ArCH), 128.6 (2 x ArCH), 127.4 (ArC), 121.2 (ArC), 104.7 (ArCH), 60.8 (OCH₃), 59.9 (OCH₃), 59.7 (CH₂), 56.7 (CH₂), 56.1 (OCH₃), 44.1 (CH₃), 39.2 (C(Ar)H); m/z (ESI) 348 [M+H]⁺; HRMS (ESI) C₁₉H₂₃³⁵ClNO₃⁺ requires 348.1361, found 348.1363 [M+H]⁺.

(S)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (S)-350



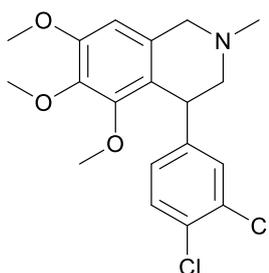
General procedure M was applied using (S)-4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (S)-330 (50 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a pale yellow solid (34 mg, 65 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) +14.1.

(R)-4-(4-Chlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (R)-350



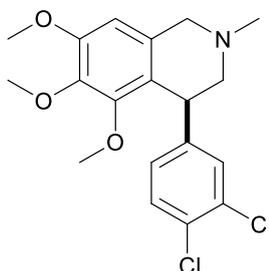
General procedure M was applied using (R)-4-(4-chlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (R)-330 (50 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a pale yellow solid (30 mg, 58 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -17.8.

4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 351



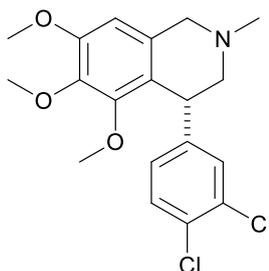
General procedure M was applied using 4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **331** (37 mg, 0.10 mmol), formic acid (113 μL , 3.00 mmol) and 37 % aqueous formaldehyde (112 μL , 1.50 mmol). The title compound was formed without further purification as a pale yellow solid (24 mg, 62 %); m.p. 148-150 $^{\circ}\text{C}$; ν_{max} / cm^{-1} (neat) 2939 (m, ArC-H), 2849 (m, C-H), 1603 (s, C=C), 1121 (m, C-N); δ_{H} (500 MHz, CDCl_3) 7.37 (1H, d, $J = 8.5$ Hz, ArH), 7.22 (1H, d, $J = 2.0$ Hz, ArH), 7.02 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.45 (1H, s, ArH), 4.58 (1H, dd, $J = 8.5, 7.5$ Hz, C(Ar)H), 4.36 (1H, d, $J = 15.0$ Hz, C(H)H), 4.20 (1H, d, $J = 15.0$ Hz, C(H)H), 3.85 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 3.62 (1H, dd, $J = 12.5, 6.5$ Hz, C(H)H), 3.29 (3H, s, OCH₃), 3.11 (1H, dd, $J = 12.5, 10.0$ Hz, C(H)H), 2.87 (3H, s, CH₃); δ_{C} (126 MHz, CDCl_3) 154.1 (ArC), 151.9 (2 x ArC), 143.3 (ArC), 142.3 (ArC), 132.9 (2 x ArC), 131.2 (ArC), 130.9 (ArCH), 129.6 (ArCH), 127.4 (ArCH), 104.9 (ArCH), 60.8 (OCH₃), 59.9 (OCH₃), 57.1 (CH₂), 56.2 (OCH₃), 55.1 (CH₂), 43.8 (CH₃), 38.5 (C(Ar)H); m/z (ESI) 382 [M+H]⁺; HRMS (ESI) C₁₉H₂₂³⁵Cl₂NO₃⁺ requires 382.0971, found 382.0970 [M+H]⁺.

(S)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (S)-351



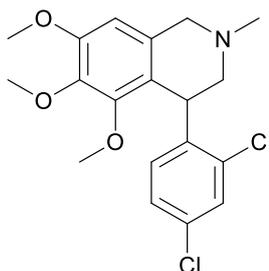
General procedure M was applied using (S)-4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (S)-**331** (55 mg, 0.15 mmol), formic acid (170 μL , 4.50 mmol) and 37 % aqueous formaldehyde (168 μL , 2.25 mmol). The title compound was formed without further purification as a pale yellow solid (53 mg, 92 %); spectroscopic data are similar to those of the racemate; $[\alpha]_{\text{D}}^{28}$ (c = 0.20, CHCl_3) +10.9.

(R)-4-(3,4-Dichlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (R)-351



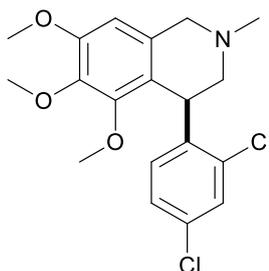
General procedure M was applied using (R)-4-(3,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (R)-**331** (55 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a pale yellow solid (50 mg, 87 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.20, CHCl₃) -24.9.

4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 352



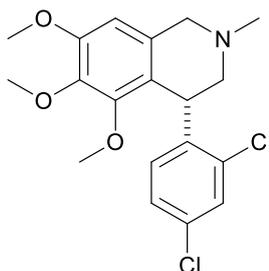
General procedure M was applied using 4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline **323** (37 mg, 0.10 mmol), formic acid (113 μ L, 3.00 mmol) and 37 % aqueous formaldehyde (112 μ L, 1.50 mmol). The title compound was formed without further purification as a pale yellow solid (30 mg, 79 %); m.p. 141-143 $^{\circ}$ C; ν_{\max} /cm⁻¹ (neat) 2938 (m, ArC-H), 2846 (m, C-H), 1604 (s, C=C), 1108 (m, C-N); δ_{H} (500 MHz, CDCl₃) 7.35 (1H, d, J = 2.0 Hz, ArH), 7.10 (1H, dd, J = 8.5, 2.0 Hz, ArH), 6.88 (1H, d, J = 8.5 Hz, ArH), 6.42 (1H, s, ArH), 4.92 (1H, t, J = 7.5 Hz, C(Ar)H), 4.47 (1H, d, J = 15.0 Hz, C(H)H), 4.11 (1H, d, J = 15.0 Hz, C(H)H), 3.80 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 3.57 (1H, dd, J = 13.0, 7.0 Hz, C(H)H), 3.29 (3H, s, OCH₃), 3.23 (1H, dd, J = 13.0, 8.5 Hz, C(H)H), 2.86 (3H, s, CH₃); δ_{C} (126 MHz, CDCl₃) 154.1 (ArC), 151.5 (ArC), 142.4 (ArC), 138.5 (ArC), 133.9 (ArC), 133.7 (ArC), 130.6 (ArCH), 129.6 (ArCH), 127.8 (ArCH), 123.8 (ArC), 118.9 (ArC), 105.0 (ArCH), 60.8 (OCH₃), 60.1 (OCH₃), 57.2 (CH₂), 56.2 (OCH₃), 55.9 (CH₂), 42.3 (CH₃), 38.8 (C(Ar)H); m/z (ESI) 382 [M+H]⁺; HRMS (ESI) C₁₉H₂₂³⁵Cl₂NO₃⁺ requires 382.0971, found 382.0962 [M+H]⁺.

(R)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (R)-352



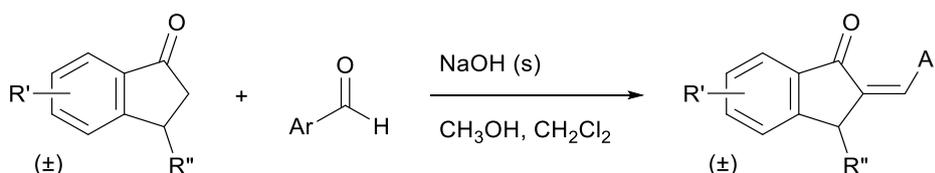
General procedure M was applied using (R)-4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (R)-323 (55 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a pale yellow solid (56 mg, 98 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.20, CHCl_3) +38.6.

(S)-4-(2,4-Dichlorophenyl)-5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (S)-352



General procedure M was applied using (S)-4-(2,4-dichlorophenyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (S)-323 (55 mg, 0.15 mmol), formic acid (170 μ L, 4.50 mmol) and 37 % aqueous formaldehyde (168 μ L, 2.25 mmol). The title compound was formed without further purification as a pale yellow solid (55 mg, 95 %); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.20, CHCl_3) -35.1.

3.6.12 Benzylidene Indan-1-one Formation – General Procedure N

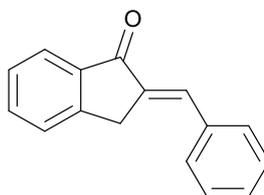


The following procedure was performed in accordance with previous literature.²⁴²

To substituted 3-aryl-indan-1-one (1.00 equiv.) in $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (1:1, 10.0 mL/mmol) was added substituted benzaldehyde (2.00 equiv.) and freshly powdered NaOH (5.00 equiv.). The resulting mixture was stirred for 2 hours at room temperature and then the

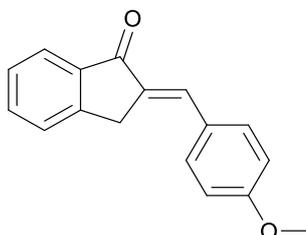
volatiles removed under vacuum. Organics were re-dissolved in EtOAc, washed with water and extracted with further EtOAc. Extracts were combined, washed with brine and then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography as specifically mentioned.

(E)-2-Benzylidene-2,3-dihydro-1H-inden-1-one, 395



General procedure S was applied using indan-1-one (40 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (8:1), gave the title compound as an off-white solid (56 mg, 85 %); m.p. 108-110 °C (lit.²⁶⁴ 109-110 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3021 (m, ArC-H), 2850 (m, C-H), 1691 (s, C=O), 1622 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.92 (1H, d, $J = 7.5$ Hz, ArH), 7.69 (1H, s, C=CH), 7.71-7.66 (2H, m, 2 x ArH), 7.62 (1H, t, $J = 7.5$ Hz, ArH), 7.56 (1H, d, $J = 7.5$ Hz, ArH), 7.50-7.38 (4H, m, 4 x ArH), 4.06 (2H, s, CH₂); δ_{C} (126 MHz, CDCl₃) 194.5 (C=O), 149.8 (ArC), 138.2 (ArC), 135.6 (ArC), 134.9 (ArC), 134.8 (ArCH), 134.1 (C=CH), 130.9 (2 x ArCH), 129.8 (ArCH), 129.1 (2 x ArCH), 127.8 (ArCH), 126.3 (ArCH), 124.6 (ArCH), 32.6 (CH₂); m/z (ESI) 243 [M+Na]⁺; HRMS (ESI) C₁₆H₁₂ONa⁺ requires 243.0780, found 243.0776 [M+Na]⁺. These data are consistent with those previously reported.²⁶⁴

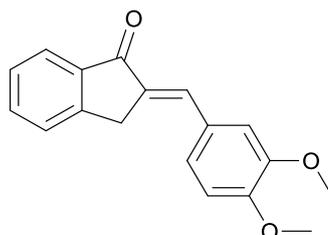
(E)-2-(4-Methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 396



General procedure S was applied using indan-1-one (40 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as an off-white solid (73 mg, 97 %); m.p. 138-140 °C (lit.²⁶⁵ 136-138 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2996 (m, ArC-H), 2841 (m, C-H), 1690 (s, C=O), 1622 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.91 (1H, d, $J = 7.5$ Hz, ArH), 7.65 (1H, s, C=CH), 7.68-7.62 (2H, m, 2 x ArH), 7.60 (1H, t, $J = 7.5$ Hz, ArH), 7.55 (1H, d, $J = 7.5$ Hz, ArH), 7.42

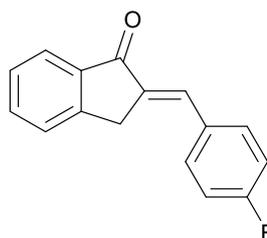
(1H, t, $J = 7.5$ Hz, ArH), 7.01-6.96 (2H, m, 2 x ArH), 4.02 (2H, s, CH₂), 3.87 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 194.5 (C=O), 161.0 (ArC), 149.6 (ArC), 138.4 (ArC), 134.5 (ArCH), 134.0 (C=CH), 132.7 (2 x ArCH), 132.6 (ArC), 128.3 (ArC), 127.7 (ArCH), 126.2 (ArCH), 124.5 (ArCH), 114.6 (2 x ArCH), 55.5 (OCH₃), 32.6 (CH₂); m/z (ESI) 251 [M+H]⁺; HRMS (ESI) C₁₇H₁₅O₂⁺ requires 251.1067, found 251.1062 [M+H]⁺. These data are consistent with those previously reported.²⁶⁵

(E)-2-(3,4-Dimethoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 397



General procedure S was applied using indan-1-one (40 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (5:1), gave the title compound as a yellow solid (66 mg, 78 %); m.p. 169-172 °C (lit.²⁶⁵ 170-173 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2958 (m, ArC-H), 2850 (m, C-H), 1681 (s, C=O), 1597 (s, C=C); δ_H (500 MHz, CDCl₃) 7.91 (1H, d, $J = 7.5$ Hz, ArH), 7.63 (1H, s, C=CH), 7.65-7.59 (1H, m, ArH), 7.56 (1H, d, $J = 7.5$ Hz, ArH), 7.43 (1H, t, $J = 7.5$ Hz, ArH), 7.32 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 7.19 (1H, d, $J = 1.5$ Hz, ArH), 6.96 (1H, d, $J = 8.5$ Hz, ArH), 4.03 (2H, s, CH₂), 3.97 (3H, s, OCH₃), 3.95 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 194.4 (C=O), 150.8 (ArC), 149.5 (ArC), 149.2 (ArC), 138.4 (ArC), 134.5 (ArCH), 134.2 (C=CH), 132.8 (ArC), 128.6 (ArC), 127.8 (ArCH), 126.2 (ArCH), 124.8 (ArCH), 124.5 (ArCH), 113.6 (ArCH), 111.4 (ArCH), 56.1 (OCH₃), 56.1 (OCH₃), 32.5 (CH₂); m/z (ESI) 303 [M+Na]⁺; HRMS (ESI) C₁₈H₁₆O₃Na⁺ requires 303.0992, found 303.0986 [M+Na]⁺. These data are consistent with those previously reported.²⁶⁵

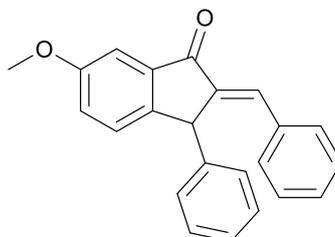
(E)-2-(4-Fluorobenzylidene)-2,3-dihydro-1H-inden-1-one, 398



General procedure S was applied using indan-1-one (40 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μ L, 0.60 mmol) and NaOH (60

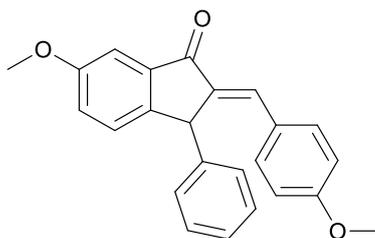
mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (8:1), gave the title compound as a white solid (67 mg, 93 %); m.p. 150-152 °C (lit.²⁶⁵ 164-165 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2921 (m, ArC-H), 2850 (m, C-H), 1687 (s, C=O), 1630 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.91 (1H, d, $J = 7.5$ Hz, ArH), 7.69-7.67 (1H, m, ArH), 7.67-7.65 (1H, m, ArH), 7.64 (1H, s, C=CH), 7.64-7.60 (1H, m, ArH), 7.56 (1H, d, $J = 7.5$ Hz, ArH), 7.43 (1H, t, $J = 7.5$ Hz, ArH), 7.19-7.12 (2H, m, 2 x ArH), 4.02 (2H, s, CH₂); δ_{C} (126 MHz, CDCl_3) 194.3 (C=O), 164.5 (ArC), 149.6 (ArC), 138.1 (ArC), 134.8 (C=CH), 134.4 (ArC), 132.8 (ArCH), 132.8 (ArCH), 132.7 (ArCH), 131.8 (ArC), 127.9 (ArCH), 126.3 (ArCH), 124.6 (ArCH), 116.4 (ArCH), 116.2 (ArCH), 32.5 (CH₂); m/z (ESI) 261 [M+Na]⁺; HRMS (ESI) C₁₆H₁₁FONa⁺ requires 261.0686, found 261.0682 [M+Na]⁺. These data are consistent with those previously reported.²⁶⁶

(E)-2-Benzylidene-6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, 358



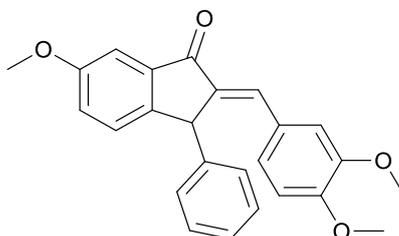
General procedure S was applied using 6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **118** (72 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as an off-white solid (80 mg, 82 %); m.p. 151-153 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3060 (m, ArC-H), 2851 (m, C-H), 1694 (s, C=O), 1624 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.89-7.87 (1H, m, C=CH), 7.54-7.49 (2H, m, 2 x ArH), 7.42 (1H, d, $J = 2.5$ Hz, ArH), 7.33-7.25 (8H, m, 8 x ArH), 7.19-7.15 (2H, m, 2 x ArH), 5.35 (1H, s, C(Ar)H), 3.92 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 194.7 (C=O), 159.9 (ArC), 147.7 (ArC), 141.8 (ArC), 139.4 (ArC), 137.5 (ArC), 135.6 (C=CH), 134.2 (ArC), 131.5 (2 x ArCH), 129.7 (ArCH), 129.0 (2 x ArCH), 128.5 (2 x ArCH), 127.7 (2 x ArCH), 127.0 (ArCH), 126.9 (ArCH), 124.6 (ArCH), 105.5 (ArCH), 55.8 (OCH₃), 48.3 (C(Ar)H); m/z (ESI) 349 [M+Na]⁺; HRMS (ESI) C₂₃H₁₈O₂Na⁺ requires 349.1199, found 349.1199[M+Na]⁺.

(E)-6-Methoxy-2-(4-methoxybenzylidene)-3-phenyl-2,3-dihydro-1H-inden-1-one, 366



General procedure S was applied using 6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **118** (72, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (5:1), gave the title compound as a pale orange solid (77 mg, 72 %); m.p. 213-216 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3027 (m, ArC-H), 2834 (m, C-H), 1682 (s, C=O), 1613 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.83-7.80 (1H, m, C=CH), 7.48-7.43 (2H, m, 2 x ArH), 7.38 (1H, d, *J* = 2.0 Hz, ArH), 7.29-7.24 (5H, m, 5 x ArH), 7.19-7.14 (1H, m, ArH), 7.12 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 6.80-6.75 (2H, m, 2 x ArH), 5.26 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃), 3.78 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 194.7 (C=O), 161.0 (ArC), 159.8 (ArC), 147.5 (ArC), 141.9 (ArC), 137.7 (ArC), 136.7 (ArC), 135.4 (C=CH), 133.6 (2 x ArCH), 129.1 (2 x ArCH), 127.6 (2 x ArCH), 127.0 (ArCH), 126.9 (ArC), 126.8 (ArCH), 124.3 (ArCH), 114.1 (2 x ArCH), 105.4 (ArCH), 55.8 (OCH₃), 55.4 (OCH₃), 48.3 (C(Ar)H); *m/z* (ESI) 379 [M+Na]⁺; HRMS (ESI) C₂₄H₂₀O₃Na⁺ requires 379.1305, found 379.1306 [M+Na]⁺.

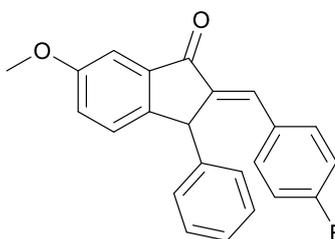
(E)-2-(3,4-Dimethoxybenzylidene)-6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, 374



General procedure S was applied using 6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **118** (72 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as a yellow solid (81 mg, 69 %); m.p. 147-149 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3058 (m, ArC-H), 2835 (m, C-H), 1688 (s, C=O), 1615 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.82-7.80 (1H, m, C=CH), 7.35 (1H, d, *J* = 2.5 Hz, ArH), 7.33-7.28 (3H, m, 3 x ArH),

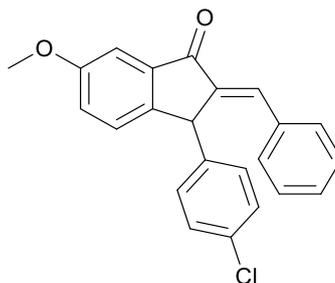
7.28-7.23 (2H, m, 2 x ArH), 7.20-7.16 (1H, m, ArH), 7.15 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 7.10 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.91 (1H, d, $J = 1.5$ Hz, ArH), 6.79 (1H, d, $J = 8.5$ Hz, ArH), 5.27 (1H, s, C(Ar)H), 3.85 (6H, s, 2 x OCH₃), 3.59 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 194.6 (C=O), 159.8 (ArC), 150.8 (ArC), 148.9 (ArC), 147.2 (ArC), 142.0 (ArC), 137.5 (ArC), 136.1 (ArC), 136.0 (C=CH), 129.3 (2 x ArCH), 127.4 (2 x ArCH), 127.3 (ArC), 127.2 (ArCH), 127.1 (ArCH), 126.7 (ArCH), 124.3 (ArCH), 113.3 (ArCH), 110.9 (ArCH), 105.5 (ArCH), 56.0 (OCH₃), 56.0 (OCH₃), 55.8 (OCH₃), 48.3 (C(Ar)H); m/z (ESI) 409 [M+Na]⁺; HRMS (ESI) C₂₅H₂₂O₄Na⁺ requires 409.1410, found 409.1412 [M+Na]⁺.

(E)-2-(4-Fluorobenzylidene)-6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, 382



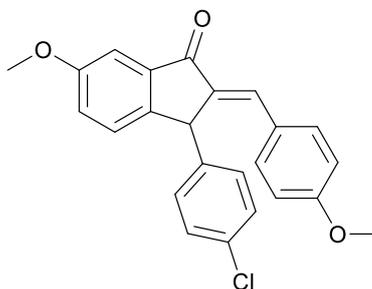
General procedure S was applied using 6-methoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **118** (72 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as an orange solid (90 mg, 87 %); m.p. 190-192 °C; ν_{\max} /cm⁻¹ (neat) 3062 (m, ArC-H), 2849 (m, C-H), 1686 (s, C=O), 1620 (s, C=C); δ_H (500 MHz, CDCl₃) 7.79-7.77 (1H, m, C=CH), 7.46-7.44 (1H, m, ArH), 7.44-7.42 (1H, m, ArH), 7.36 (1H, d, $J = 2.0$ Hz, ArH), 7.26-7.18 (5H, m, 5 x ArH), 7.16-7.14 (1H, m, ArH), 7.12 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.94-6.89 (2H, m, 2 x ArH), 5.25 (1H, s, C(Ar)H), 3.86 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 194.5 (C=O), 164.4 (ArC), 162.4 (ArC), 159.9 (ArC), 147.5 (ArC), 141.5 (ArC), 138.9 (ArC), 137.4 (ArC), 134.3 (C=CH), 133.5 (ArCH), 133.4 (ArCH), 129.1 (2 x ArCH), 127.6 (2 x ArCH), 127.2 (ArCH), 126.9 (ArCH), 124.7 (ArCH), 115.8 (ArCH), 115.6 (ArCH), 105.5 (ArCH), 55.8 (OCH₃), 48.2 (C(Ar)H); m/z (ESI) 367 [M+Na]⁺; HRMS (ESI) C₂₃H₁₇FO₂Na⁺ requires 367.1105, found 367.1106 [M+Na]⁺.

(E)-2-Benzylidene-3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, 359



General procedure S was applied using 3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **119** (100 mg, 0.37 mmol), MeOH:CH₂Cl₂ (1.84:1.84 mL), benzaldehyde (75 μ L, 0.74 mmol) and NaOH (74 mg, 1.84 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as a pale orange solid (100 mg, 76 %); m.p. 164-165 °C; ν_{\max} /cm⁻¹ (neat) 3000 (m, ArC-H), 2831 (m, C-H), 1693 (s, C=O), 1620 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.84-7.82 (1H, m, C=CH), 7.45-7.41 (2H, m, 2 x ArH), 7.37 (1H, d, J = 2.0 Hz, ArH), 7.28-7.24 (3H, m, 3 x ArH), 7.22 (1H, d, J = 8.5 Hz, ArH), 7.19-7.15 (2H, m, 2 x ArH), 7.15-7.11 (3H, m, 3 x ArH), 5.29 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 194.3 (C=O), 160.0 (ArC), 147.0 (ArC), 140.3 (ArC), 139.0 (ArC), 137.6 (ArC), 135.9 (C=CH), 134.0 (ArC), 132.8 (ArC), 131.4 (2 x ArCH), 129.9 (ArCH), 129.2 (2 x ArCH), 129.0 (2 x ArCH), 128.6 (2 x ArCH), 126.8 (ArCH), 124.7 (ArCH), 105.6 (ArCH), 55.8 (OCH₃), 47.6 (C(Ar)H); m/z (ESI) 383 [M+Na]⁺; HRMS (ESI) C₂₃H₁₇³⁵ClO₂Na⁺ requires 383.0809, found 383.0804 [M+Na]⁺.

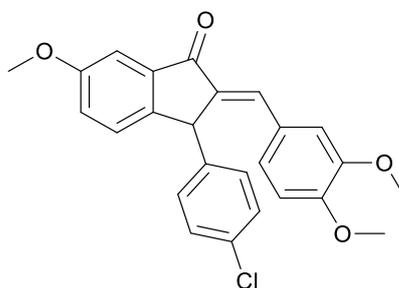
(E)-3-(4-Chlorophenyl)-6-methoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 367



General procedure S was applied using 3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **119** (82 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (5:1), gave the title compound as a pale orange solid (51 mg, 44 %); m.p. 165-168 °C; ν_{\max} /cm⁻¹ (neat) 2958 (m, ArC-H), 2833 (m, C-H), 1697 (s, C=O), 1613 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.84-7.82 (1H, m, C=CH),

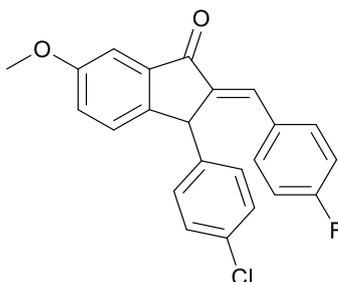
7.46-7.42 (2H, m, 2 x ArH), 7.39 (1H, d, $J = 2.0$ Hz, ArH), 7.29 (1H, s, ArH), 7.27-7.18 (4H, m, 4 x ArH), 7.14 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.83-6.79 (2H, m, 2 x ArH), 5.27 (1H, s, C(Ar)H), 3.89 (3H, s, OCH₃), 3.82 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 194.3 (C=O), 161.1 (ArC), 160.0 (ArC), 146.8 (ArC), 140.4 (ArC), 137.7 (ArC), 136.3 (ArC), 135.7 (C=CH), 133.5 (2 x ArCH), 132.8 (ArC), 129.3 (2 x ArCH), 128.9 (2 x ArCH), 126.7 (ArC), 126.7 (ArCH), 124.3 (ArCH), 114.2 (2 x ArCH), 105.6 (ArCH), 55.8 (OCH₃), 55.5 (OCH₃), 47.6 (C(Ar)H); m/z (ESI) 413 [M+Na]⁺; HRMS (ESI) C₂₄H₁₉³⁵ClO₃Na⁺ requires 413.0915, found 413.0914 [M+Na]⁺.

(E)-3-(4-Chlorophenyl)-2-(3,4-dimethoxybenzylidene)-6-methoxy-2,3-dihydro-1H-inden-1-one, 375



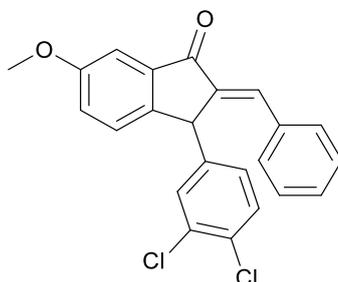
General procedure S was applied using 3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **119** (82 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as a yellow solid (92 mg, 72 %); m.p. 97-98 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2935 (m, ArC-H), 2835 (m, C-H), 1687 (s, C=O), 1615 (s, C=C); δ_H (500 MHz, CDCl₃) 7.82 (1H, d, $J = 1.5$ Hz, C=CH), 7.37 (1H, d, $J = 2.5$ Hz, ArH), 7.28-7.26 (1H, m, ArH), 7.25-7.23 (4H, m, 4 x ArH), 7.14 (1H, d, $J = 2.0$ Hz, ArH), 7.13 (1H, d, $J = 2.0$ Hz, ArH), 6.92 (1H, d, $J = 1.5$ Hz, ArH), 6.81 (1H, d, $J = 8.5$ Hz, ArH), 5.28 (1H, s, C(Ar)H), 3.89 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 3.70 (3H, s, OCH₃); δ_c (126 MHz, CDCl₃) 194.2 (C=O), 160.0 (ArC), 150.9 (ArC), 148.9 (ArC), 146.6 (ArC), 140.5 (ArC), 137.6 (ArC), 136.3 (C=CH), 135.8 (ArC), 133.0 (ArC), 129.4 (2 x ArCH), 128.8 (2 x ArCH), 127.0 (ArC), 126.8 (ArCH), 126.6 (ArCH), 124.3 (ArCH), 113.5 (ArCH), 111.0 (ArCH), 105.6 (ArCH), 56.0 (2 x OCH₃), 55.8 (OCH₃), 47.6 (C(Ar)H); m/z (ESI) 443 [M+Na]⁺; HRMS (ESI) C₂₅H₂₁³⁵ClO₄Na⁺ requires 443.1021, found 443.1012 [M+Na]⁺.

(E)-3-(4-Chlorophenyl)-2-(4-fluorobenzylidene)-6-methoxy-2,3-dihydro-1H-inden-1-one, 383



General procedure S was applied using 3-(4-chlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **119** (82 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as a pale orange solid (83 mg, 73 %); m.p. 177-179 °C; ν_{\max} /cm⁻¹ (neat) 3004 (m, ArC-H), 2832 (m, C-H), 1688 (s, C=O), 1622 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.80-7.77 (1H, m, C=CH), 7.44-7.42 (1H, m, ArH), 7.42-7.40 (1H, m, ArH), 7.36 (1H, d, *J* = 2.0 Hz, ArH), 7.21 (1H, d, *J* = 8.5 Hz, ArH), 7.20-7.17 (2H, m, 2 x ArH), 7.15-7.11 (3H, m, 3 x ArH), 6.98-6.92 (2H, m, 2 x ArH), 5.24 (1H, s, C(Ar)H), 3.86 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 194.1 (C=O), 164.5 (ArC), 162.4 (ArC), 160.1 (ArC), 146.9 (ArC), 140.0 (ArC), 138.5 (ArC), 137.5 (ArC), 134.6 (C=CH), 133.4 (ArCH), 133.3 (ArCH), 133.0 (ArC), 129.3 (2 x ArCH), 129.0 (2 x ArCH), 126.8 (ArCH), 124.8 (ArCH), 115.9 (ArCH), 115.8 (ArCH), 105.6 (ArCH), 55.9 (OCH₃), 47.5 (C(Ar)H); *m/z* (ESI) 401 [M+Na]⁺; HRMS (ESI) C₂₃H₁₆³⁵ClFO₂Na⁺ requires 401.0715, found 401.0709 [M+Na]⁺.

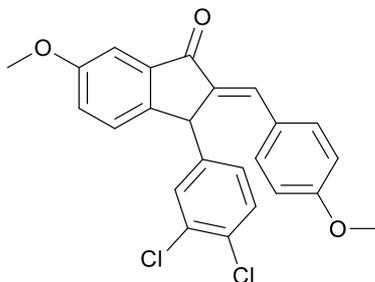
(E)-2-Benzylidene-3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, 360



General procedure S was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **120** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as an orange solid (61 mg, 51 %); m.p. 125-127 °C; ν_{\max} /cm⁻¹ (neat) 3004 (m, ArC-H), 2835

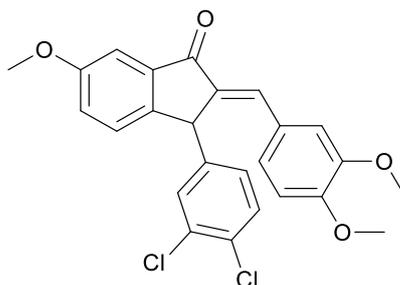
(m, C-H), 1690 (s, C=O), 1619 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.84 (1H, d, $J = 1.0$ Hz, C=CH), 7.45-7.40 (2H, m, 2 x ArH), 7.38 (1H, d, $J = 2.0$ Hz, ArH), 7.30-7.24 (5H, m, 5 x ArH), 7.22 (1H, d, $J = 8.5$ Hz, ArH), 7.15 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.02 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 5.27 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.9 (C=O), 160.2 (ArC), 146.3 (ArC), 142.0 (ArC), 138.5 (ArC), 137.7 (ArC), 136.3 (C=CH), 133.9 (ArC), 133.0 (ArC), 131.2 (2 x ArCH), 131.1 (ArC), 130.9 (ArCH), 130.1 (ArCH), 129.7 (ArCH), 128.7 (2 x ArCH), 127.0 (ArCH), 126.8 (ArCH), 124.8 (ArCH), 105.7 (ArCH), 55.9 (OCH₃), 47.2 (C(Ar)H); m/z (ESI) 417 [M+Na]⁺; HRMS (ESI) $\text{C}_{23}\text{H}_{16}^{35}\text{Cl}_2\text{O}_2\text{Na}^+$ requires 417.0420, found 417.0419 [M+Na]⁺.

(E)-3-(3,4-Dichlorophenyl)-6-methoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 368



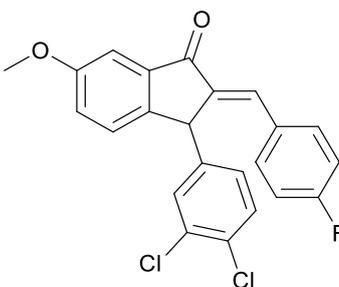
General procedure S was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **120** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (5:1), gave the title compound as an orange solid (83 mg, 65 %); m.p. 141-143 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2937 (m, ArC-H), 2836 (m, C-H), 1682 (s, C=O), 1617 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.82-7.80 (1H, m, C=CH), 7.42-7.39 (2H, m, 2 x ArH), 7.37 (1H, d, $J = 2.5$ Hz, ArH), 7.32 (1H, d, $J = 2.0$ Hz, ArH), 7.29 (1H, d, $J = 8.5$ Hz, ArH), 7.23 (1H, d, $J = 8.5$ Hz, ArH), 7.13 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.07 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 6.83-6.79 (2H, m, 2 x ArH), 5.22 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃), 3.80 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 194.0 (C=O), 161.2 (ArC), 160.1 (ArC), 146.1 (ArC), 142.2 (ArC), 137.9 (ArC), 136.1 (C=CH), 135.8 (ArC), 133.5 (2 x ArCH), 133.1 (ArC), 131.1 (ArC), 131.0 (ArCH), 129.5 (ArCH), 127.0 (ArCH), 126.6 (ArCH), 126.5 (ArC), 124.4 (ArCH), 114.3 (2 x ArCH), 105.7 (ArCH), 55.9 (OCH₃), 55.5 (OCH₃), 47.3 (C(Ar)H); m/z (ESI) 447 [M+Na]⁺; HRMS (ESI) $\text{C}_{24}\text{H}_{18}^{35}\text{Cl}_2\text{O}_3\text{Na}^+$ requires 447.0525, found 447.0526 [M+Na]⁺.

(E)-3-(3,4-Dichlorophenyl)-2-(3,4-dimethoxybenzylidene)-6-methoxy-2,3-dihydro-1H-inden-1-one, 376



General procedure S was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **120** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as an orange-yellow solid (73 mg, 53 %); m.p. 128-131 °C; ν_{\max} /cm⁻¹ (neat) 3003 (m, ArC-H), 2836 (m, C-H), 1688 (s, C=O), 1615 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.81-7.79 (1H, m, C=CH), 7.41 (1H, d, J = 1.5 Hz, ArH), 7.36 (1H, d, J = 2.0 Hz, ArH), 7.30 (1H, d, J = 8.5 Hz, ArH), 7.25-7.23 (1H, m, ArH), 7.13 (1H, dd, J = 9.0, 2.5 Hz, ArH), 7.11 (1H, dd, J = 8.5, 1.5 Hz, ArH), 7.07 (1H, dd, J = 8.5, 2.0 Hz, ArH), 6.89 (1H, d, J = 1.0 Hz, ArH), 6.81 (1H, d, J = 8.5 Hz, ArH), 5.24 (1H, s, C(Ar)H), 3.88 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.73 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.9 (C=O), 160.2 (ArC), 151.1 (ArC), 149.0 (ArC), 145.9 (ArC), 142.4 (ArC), 137.7 (ArC), 136.6 (C=CH), 135.4 (ArC), 133.2 (ArC), 131.3 (ArC), 131.3 (ArCH), 129.5 (ArCH), 126.8 (ArC), 126.8 (ArCH), 126.7 (ArCH), 126.5 (ArCH), 124.4 (ArCH), 113.4 (ArCH), 111.1 (ArCH), 105.8 (ArCH), 56.1 (OCH₃), 56.0 (OCH₃), 55.9 (OCH₃), 47.3 (C(Ar)H); m/z (ESI) 477 [M+Na]⁺; HRMS (ESI) C₂₅H₂₀³⁵Cl₂O₄Na⁺ requires 477.0631, found 477.0634 [M+Na]⁺.

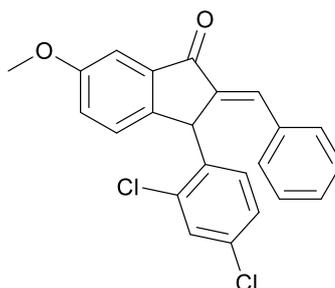
(E)-3-(3,4-Dichlorophenyl)-2-(4-fluorobenzylidene)-6-methoxy-2,3-dihydro-1H-inden-1-one, 384



General procedure S was applied using 3-(3,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **120** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL),

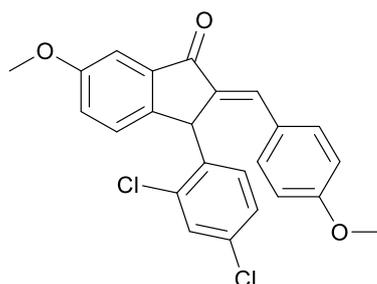
4-fluorobenzaldehyde (64 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as an orange-red solid (81 mg, 65 %); m.p. 155-157 $^{\circ}\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2923 (m, ArC-H), 2851 (m, C-H), 1685 (s, C=O), 1619 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.80 (1H, d, $J = 1.5$ Hz, C=CH), 7.44-7.42 (1H, m, ArH), 7.42-7.40 (1H, m, ArH), 7.37 (1H, d, $J = 2.5$ Hz, ArH), 7.30-7.26 (2H, m, 2 x ArH), 7.22 (1H, d, $J = 8.5$ Hz, ArH), 7.15 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.03 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 7.01-6.95 (2H, m, 2 x ArH), 5.23 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.7 (C=O), 164.5 (ArC), 162.5 (ArC), 160.3 (ArC), 146.2 (ArC), 141.8 (ArC), 138.1 (ArC), 137.6 (ArC), 134.9 (C=CH), 133.3 (ArCH), 133.2 (ArCH), 133.2 (ArC), 131.3 (ArC), 131.0 (ArCH), 129.5 (ArCH), 127.0 (ArCH), 126.7 (ArCH), 124.9 (ArCH), 116.1 (ArCH), 115.9 (ArCH), 105.8 (ArCH), 55.9 (OCH₃), 47.1 (C(Ar)H); m/z (ESI) 435 [M+Na]⁺; HRMS (ESI) $\text{C}_{23}\text{H}_{15}^{35}\text{Cl}_2\text{FO}_2\text{Na}^+$ requires 435.0325, found 435.0327 [M+Na]⁺.

(E)-2-Benzylidene-3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one, 361



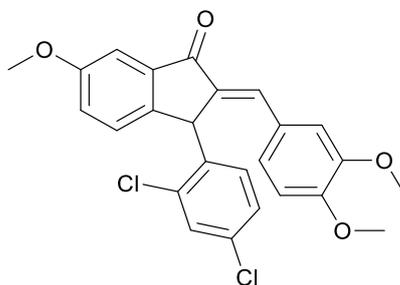
General procedure S was applied using 3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **121** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as a pale orange solid (104 mg, 88 %); m.p. 146-148 $^{\circ}\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3051 (m, ArC-H), 2833 (m, C-H), 1688 (s, C=O), 1621 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.84-7.81 (1H, m, C=CH), 7.43 (1H, s, ArH), 7.42-7.35 (4H, m, 4 x ArH), 7.30-7.26 (3H, m, 3 x ArH), 7.13 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.90 (1H, d, $J = 7.5$ Hz, ArH), 6.72 (1H, s, ArH), 5.91 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 194.0 (C=O), 160.2 (ArC), 146.5 (ArC), 138.6 (ArC), 138.1 (ArC), 137.8 (ArC), 135.7 (C=CH), 134.1 (ArC), 133.9 (ArC), 133.3 (ArC), 131.0 (2 x ArCH), 130.1 (ArCH), 129.4 (ArCH), 128.6 (2 x ArCH), 128.2 (ArCH), 126.8 (ArCH), 126.7 (ArCH), 124.8 (ArCH), 105.7 (ArCH), 55.8 (OCH₃), 43.6 (C(Ar)H); m/z (ESI) 417 [M+Na]⁺; HRMS (ESI) $\text{C}_{23}\text{H}_{16}^{35}\text{Cl}_2\text{O}_2\text{Na}^+$ requires 417.0420, found 417.0422 [M+Na]⁺.

(E)-3-(2,4-Dichlorophenyl)-6-methoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 369



General procedure S was applied using 3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **121** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (5:1), gave the title compound as a pale orange solid (105 mg, 82 %); m.p. 155-157 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3002 (m, ArC-H), 2835 (m, C-H), 1686 (s, C=O), 1621 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.80-7.77 (1H, m, C=CH), 7.46 (1H, s, ArH), 7.40-7.34 (4H, m, 4 x ArH), 7.12 (1H, dd, *J* = 8.5, 2.5 Hz, ArH), 6.91 (1H, d, *J* = 8.0 Hz, ArH), 6.82-6.78 (2H, m, 2 x ArH), 6.75 (1H, s, ArH), 5.85 (1H, s, C(Ar)H), 3.86 (3H, s, OCH₃), 3.79 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 194.1 (C=O), 161.2 (ArC), 160.1 (ArC), 146.3 (ArC), 138.3 (ArC), 138.0 (ArC), 136.0 (ArC), 135.5 (C=CH), 134.1 (ArC), 133.3 (ArC), 133.2 (2 x ArCH), 129.4 (ArCH), 129.3 (ArCH), 128.3 (ArCH), 126.6 (ArCH), 126.5 (ArC), 124.5 (ArCH), 114.3 (2 x ArCH), 105.7 (ArCH), 55.8 (OCH₃), 55.5 (OCH₃), 43.6 (C(Ar)H); *m/z* (ESI) 447 [M+Na]⁺; HRMS (ESI) C₂₄H₁₈³⁵Cl₂O₃Na⁺ requires 447.0525, found 447.0510 [M+Na]⁺.

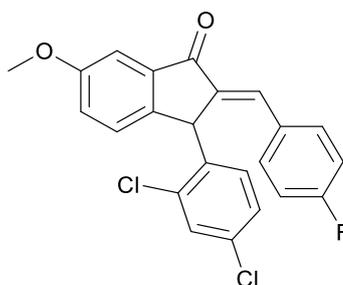
(E)-3-(2,4-Dichlorophenyl)-2-(3,4-dimethoxybenzylidene)-6-methoxy-2,3-dihydro-1H-inden-1-one, 377



General procedure S was applied using 3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **121** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as a yellow solid (124 mg, 91 %); m.p. 126-129 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat)

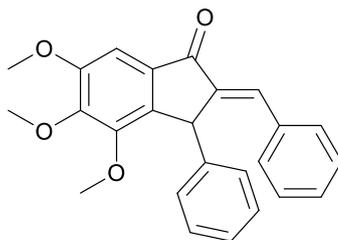
2968 (m, ArC-H), 2837 (m, C-H), 1692 (s, C=O), 1617 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.80 (1H, d, $J = 1.0$ Hz, C=CH), 7.51-7.46 (2H, m, 2 x ArH), 7.36 (1H, d, $J = 2.5$ Hz, ArH), 7.12 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.09 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 6.96 (1H, d, $J = 8.0$ Hz, ArH), 6.84 (1H, s, ArH), 6.80 (1H, d, $J = 8.0$ Hz, ArH), 6.80 (1H, d, $J = 1.0$ Hz, ArH), 5.87 (1H, s, C(Ar)H), 3.88 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.78 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 194.0 (C=O), 160.2 (ArC), 151.1 (ArC), 149.0 (ArC), 146.2 (ArC), 138.5 (ArC), 137.9 (ArC), 136.2 (C=CH), 135.4 (ArC), 133.9 (ArC), 133.5 (ArC), 129.6 (ArCH), 129.2 (ArCH), 128.5 (ArCH), 127.1 (ArCH), 126.8 (ArC), 126.6 (ArCH), 124.5 (ArCH), 112.9 (ArCH), 111.0 (ArCH), 105.7 (ArCH), 56.1 (OCH₃), 55.9 (OCH₃), 55.8 (OCH₃), 43.7 (C(Ar)H); m/z (ESI) 447 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{25}\text{H}_{20}^{35}\text{Cl}_2\text{O}_4\text{Na}^+$ requires 447.0631, found 447.0624 $[\text{M}+\text{Na}]^+$.

(E)-3-(2,4-Dichlorophenyl)-2-(4-fluorobenzylidene)-6-methoxy-2,3-dihydro-1H-inden-1-one, 385



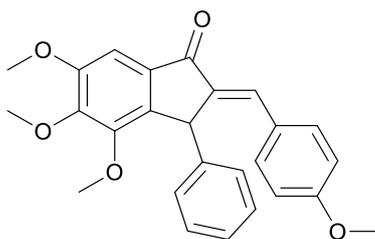
General procedure S was applied using 3-(2,4-dichlorophenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one **121** (92 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (6:1), gave the title compound as a pale orange solid (105 mg, 85 %); m.p. 146-148 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3050 (m, ArC-H), 2834 (m, C-H), 1690 (s, C=O), 1624 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.79-7.76 (1H, m, C=CH), 7.45 (1H, s, ArH), 7.42-7.39 (1H, m, ArH), 7.39-7.37 (1H, m, ArH), 7.37-7.33 (2H, m, 2 x ArH), 7.14 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 7.00-6.94 (2H, m, 2 x ArH), 6.92 (1H, d, $J = 8.0$ Hz, ArH), 6.71 (1H, s, ArH), 5.87 (1H, s, C(Ar)H), 3.87 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.9 (C=O), 164.5 (ArC), 162.5 (ArC), 160.2 (ArC), 138.3 (ArC), 137.9 (ArC), 137.7 (ArC), 134.4 (C=CH), 134.1 (ArC), 133.5 (ArC), 133.1 (ArCH), 133.0 (ArCH), 130.3 (ArCH), 130.2 (ArC), 129.4 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 124.9 (ArCH), 116.0 (ArCH), 115.8 (ArCH), 105.8 (ArCH), 55.9 (OCH₃), 43.4 (C(Ar)H); m/z (ESI) 435 $[\text{M}+\text{Na}]^+$; HRMS (ESI) $\text{C}_{23}\text{H}_{15}^{35}\text{Cl}_2\text{FO}_2\text{Na}^+$ requires 435.0325, found 435.0324 $[\text{M}+\text{Na}]^+$.

(E)-2-Benzylidene-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, 362



General procedure S was applied using 4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **122** (90 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as an off-white solid (89 mg, 77 %); m.p. 165-167 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2965 (m, ArC-H), 2829 (m, C-H), 1687 (s, C=O), 1622 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.71-7.69 (1H, m, C=CH), 7.52-7.48 (2H, m, 2 x ArH), 7.29-7.21 (5H, m, 5 x ArH), 7.25 (1H, s, ArH), 7.17 (2H, t, $J = 7.5$ Hz, 2 x ArH), 7.08 (1H, t, $J = 7.0$ Hz, ArH), 5.40-5.35 (1H, m, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.35 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 194.1 (C=O), 155.0 (ArC), 150.2 (ArC), 148.8 (ArC), 141.6 (ArC), 141.4 (ArC), 140.2 (ArC), 134.5 (C=CH), 134.3 (ArC), 132.2 (ArC), 131.3 (2 x ArCH), 129.6 (ArCH), 128.9 (2 x ArCH), 128.4 (2 x ArCH), 128.3 (2 x ArCH), 127.6 (ArCH), 101.5 (ArCH), 61.0 (OCH₃), 60.3 (OCH₃), 56.4 (OCH₃), 46.2 (C(Ar)H); m/z (ESI) 409 [M+Na]⁺; HRMS (ESI) C₂₅H₂₂O₄Na⁺ requires 409.1410, found 409.1411 [M+Na]⁺.

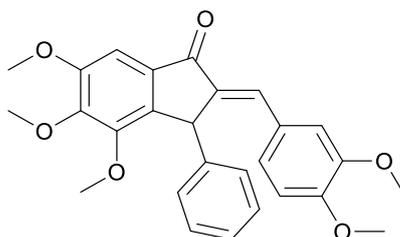
(E)-4,5,6-Trimethoxy-2-(4-methoxybenzylidene)-3-phenyl-2,3-dihydro-1H-inden-1-one, 370



General procedure S was applied using 4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **122** (90 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as a yellow solid (81 mg, 64 %); m.p. 138-140 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2999 (m, ArC-H), 2833 (m, C-H), 1681 (s, C=O), 1619 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.66 (1H, s, C=CH), 7.51-7.47 (2H, m, 2 x ArH), 7.29-7.26 (2H, m, 2 x ArH), 7.24 (1H, s, ArH), 7.22-7.17 (2H, m, 2 x ArH), 7.10 (1H, t, $J = 7.5$ Hz, ArH), 6.81-6.77 (2H, m, 2 x ArH), 5.35-5.32 (1H, m,

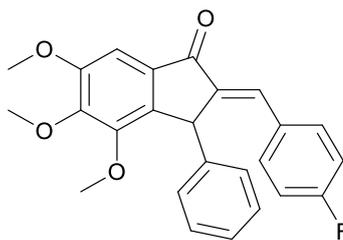
C(ArH), 3.93 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 3.36 (3H, s, OCH₃); δ_C (126 MHz, CDCl₃) 194.1 (C=O), 160.9 (ArC), 155.0 (ArC), 150.1 (ArC), 148.5 (ArC), 141.5 (ArC), 141.3 (ArC), 137.7 (ArC), 134.3 (C=CH), 133.4 (2 x ArCH), 132.4 (ArC), 128.9 (2 x ArCH), 128.4 (2 x ArCH), 127.0 (ArC), 126.7 (ArCH), 114.0 (2 x ArCH), 101.4 (ArCH), 61.0 (OCH₃), 60.3 (OCH₃), 56.4 (OCH₃), 55.4 (OCH₃), 46.3 (C(Ar)H); m/z (ESI) 439 [M+Na]⁺; HRMS (ESI) C₂₆H₂₄O₅Na⁺ requires 439.1516, found 439.1509 [M+Na]⁺.

(E)-2-(3,4-Dimethoxybenzylidene)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, 378



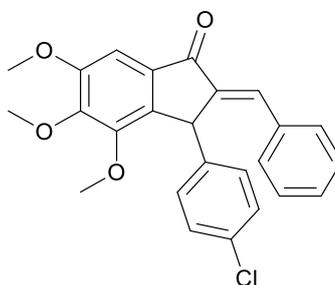
General procedure S was applied using 4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **122** (90 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as a yellow solid (73 mg, 55 %); m.p. 136-138 °C; ν_{max}/cm⁻¹ (neat) 3003 (m, ArC-H), 2833 (m, C-H), 1686 (s, C=O), 1621 (s, C=C); δ_H (500 MHz, CDCl₃) 7.71-7.69 (1H, m, C=CH), 7.38-7.34 (2H, m, 2 x ArH), 7.29 (1H, s, ArH), 7.26-7.22 (2H, m, 2 x ArH), 7.19 (1H, dd, J = 8.5, 1.5 Hz, ArH), 7.15 (1H, t, J = 7.5 Hz, ArH), 7.00 (1H, d, J = 1.0 Hz, ArH), 6.82 (1H, d, J = 8.5 Hz, ArH), 5.41-5.37 (1H, m, C(Ar)H), 3.95 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 3.46 (3H, s, OCH₃); δ_C (126 MHz, CDCl₃) 194.1 (C=O), 155.0 (ArC), 150.7 (ArC), 150.2 (ArC), 148.9 (ArC), 148.5 (ArC), 141.5 (ArC), 141.1 (ArC), 137.3 (ArC), 134.8 (C=CH), 132.2 (ArC), 128.9 (2 x ArCH), 128.5 (2 x ArCH), 127.4 (ArC), 126.9 (ArCH), 126.6 (ArCH), 113.3 (ArCH), 110.9 (ArCH), 101.5 (ArCH), 61.0 (OCH₃), 60.3 (OCH₃), 56.4 (OCH₃), 56.3 (OCH₃), 56.0 (OCH₃), 46.4 (C(Ar)H); m/z (ESI) 469 [M+Na]⁺; HRMS (ESI) C₂₇H₂₆O₆Na⁺ requires 469.1622, found 469.1618 [M+Na]⁺.

(E)-2-(4-Fluorobenzylidene)-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one, 386



General procedure S was applied using 4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1H-inden-1-one **122** (90 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as an off-white solid (97 mg, 80 %); m.p. 163-165 °C; ν_{\max} /cm⁻¹ (neat) 2999 (m, ArC-H), 2837 (m, C-H), 1686 (s, C=O), 1626 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.68-7.66 (1H, m, C=CH), 7.52-7.50 (1H, m, ArH), 7.50-7.48 (1H, m, ArH), 7.28 (1H, s, ArH), 7.25-7.23 (2H, m, 2 x ArH), 7.23-7.18 (2H, m, 2 x ArH), 7.14-7.09 (1H, m, ArH), 7.00-6.94 (2H, m, 2 x ArH), 5.36-5.34 (1H, m, C(Ar)H), 3.95 (3H, s, OCH₃), 3.91 (3H, s, OCH₃) 3.37 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.9 (C=O), 164.3 (ArC), 162.3 (ArC), 155.1 (ArC), 150.2 (ArC), 148.9 (ArC), 141.5 (ArC), 141.2 (ArC), 139.8 (ArC), 133.2 (2 x ArCH), 133.2 (C=CH), 132.1 (ArC), 128.9 (2 x ArCH), 128.4 (2 x ArCH), 126.8 (ArCH), 115.7 (ArCH), 115.5 (ArCH), 101.5 (ArCH), 61.0 (OCH₃), 60.3 (OCH₃), 56.4 (OCH₃), 46.1 (C(Ar)H); m/z (ESI) 427 [M+Na]⁺; HRMS (ESI) C₂₅H₂₁FO₄Na⁺ requires 427.1316, found 427.1314 [M+Na]⁺.

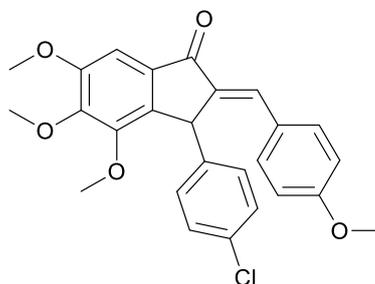
(E)-2-Benzylidene-3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 363



General procedure S was applied using 3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **123** (100 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as a pale yellow solid (119 mg, 94 %); m.p. 146-148 °C; ν_{\max} /cm⁻¹ (neat) 3001 (m, ArC-H),

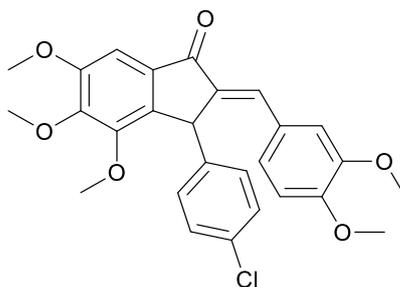
2833 (m, C-H), 1693 (s, C=O), 1623 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.72-7.69 (1H, m, C=CH), 7.48-7.46 (1H, m, ArH), 7.46 (1H, d, $J = 1.5$ Hz, ArH), 7.30-7.28 (1H, m, ArH), 7.28-7.26 (2H, m, 2 x ArH), 7.24 (1H, s, ArCH), 7.18-7.12 (4H, m, 4 x ArH), 5.37 (1H, s, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.44 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.7 (C=O), 155.2 (ArC), 150.1 (ArC), 148.7 (ArC), 140.9 (ArC), 140.0 (ArC), 139.8 (ArC), 134.8 (C=CH), 134.2 (ArC), 132.4 (ArC), 132.2 (ArC), 131.2 (2 x ArCH), 130.1 (2 x ArCH), 129.8 (ArCH), 128.5 (2 x ArCH), 128.5 (2 x ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 45.5 (C(Ar)H); m/z (ESI) 443 [M+Na]⁺; HRMS (ESI) $\text{C}_{25}\text{H}_{21}^{35}\text{ClO}_4\text{Na}^+$ requires 443.1021, found 443.1015 [M+Na]⁺.

(E)-3-(4-Chlorophenyl)-4,5,6-trimethoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 371



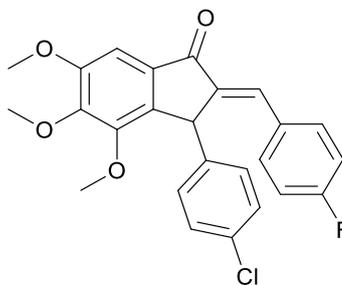
General procedure S was applied using 3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **123** (100 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as a yellow solid (122 mg, 90 %); m.p. 181-182 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3003 (m, ArC-H), 2836 (m, C-H), 1691 (s, C=O), 1625 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.67 (1H, s, C=CH), 7.47-7.43 (2H, m, 2 x ArH), 7.23 (1H, s, ArH), 7.22-7.19 (2H, m, 2 x ArH), 7.18-7.15 (2H, m, 2 x ArH), 6.83-6.78 (2H, m, 2 x ArH), 5.34-5.31 (1H, m, C(Ar)H), 3.93 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.45 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.8 (C=O), 161.0 (ArC), 155.1 (ArC), 150.1 (ArC), 148.5 (ArC), 142.8 (ArC), 140.6 (ArC), 140.0 (ArC), 137.2 (ArC), 134.7 (C=CH), 133.3 (2 x ArCH), 132.4 (ArC), 130.2 (2 x ArCH), 128.5 (2 x ArCH), 126.8 (ArC), 114.1 (2 x ArCH), 101.4 (ArCH), 61.0 (OCH₃), 60.4 (OCH₃), 56.4 (OCH₃), 55.5 (OCH₃), 45.6 (C(Ar)H); m/z (ESI) 473 [M+Na]⁺; HRMS (ESI) $\text{C}_{26}\text{H}_{23}^{35}\text{ClO}_5\text{Na}^+$ requires 473.1126, found 473.1117 [M+Na]⁺.

(E)-3-(4-Chlorophenyl)-2-(3,4-dimethoxybenzylidene)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 379



General procedure S was applied using 3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **123** (100 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as a yellow solid (117 mg, 81 %); m.p. 198-200 °C; ν_{\max} /cm⁻¹ (neat) 2931 (m, ArC-H), 2831 (m, C-H), 1691 (s, C=O), 1618 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.68-7.65 (1H, m, C=CH), 7.28-7.24 (2H, m, 2 x ArH), 7.23 (1H, s, ArH), 7.21-7.17 (2H, m, 2 x ArH), 7.15-7.11 (1H, m, ArH), 6.94 (1H, d, *J* = 1.0 Hz, ArH), 6.80 (1H, d, *J* = 8.5 Hz, ArH), 5.35-5.32 (1H, m, C(Ar)H), 3.93 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.50 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.7 (C=O), 155.2 (ArC), 150.8 (ArC), 150.1 (ArC), 148.9 (ArC), 148.4 (ArC), 140.4 (ArC), 140.0 (ArC), 136.9 (ArC), 135.1 (C=CH), 132.6 (ArC), 132.2 (ArC), 130.1 (2 x ArCH), 128.6 (2 x ArCH), 127.1 (ArC), 126.3 (ArCH), 113.6 (ArCH), 111.0 (ArCH), 101.5 (ArCH), 61.0 (OCH₃), 60.4 (OCH₃), 56.4 (OCH₃), 56.2 (OCH₃), 56.0 (OCH₃), 45.7 (C(Ar)H); m/z (ESI) 503 [M+Na]⁺; HRMS (ESI) C₂₇H₂₅³⁵ClO₆Na⁺ requires 503.1232, found 503.1229 [M+Na]⁺.

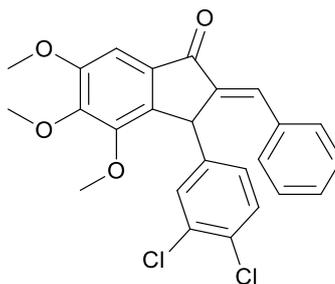
(E)-3-(4-Chlorophenyl)-2-(4-fluorobenzylidene)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 387



General procedure S was applied using 3-(4-chlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **123** (100 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μ L, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification

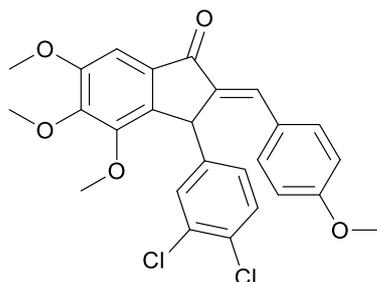
by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as an off-white solid (119 mg, 90 %); m.p. 175-178 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2983 (m, ArC-H), 2841 (m, C-H), 1684 (s, C=O), 1626 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.66 (1H, d, $J = 1.0$ Hz, C=CH), 7.47-7.45 (1H, m, ArH), 7.45-7.42 (1H, m, ArH), 7.23 (1H, s, ArH), 7.16 (4H, s, 4 x ArH), 7.00-6.94 (2H, m, 2 x ArH), 5.32 (1H, d, $J = 1.5$ Hz, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃) 3.44 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.5 (C=O), 164.4 (ArC), 162.4 (ArC), 155.3 (ArC), 150.1 (ArC), 148.8 (ArC), 140.7 (ArC), 139.8 (ArC), 139.4 (ArC), 133.5 (C=CH), 133.2 (ArCH), 133.1 (ArCH), 132.6 (ArC), 132.1 (ArC), 130.1 (2 x ArCH), 128.6 (2 x ArCH), 115.9 (ArCH), 115.7 (ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 45.4 (C(Ar)H); m/z (ESI) 461 [M+Na]⁺; HRMS (ESI) $\text{C}_{25}\text{H}_{20}^{35}\text{ClFO}_4\text{Na}^+$ requires 461.0926, found 461.0929 [M+Na]⁺.

(E)-2-Benzylidene-3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 364



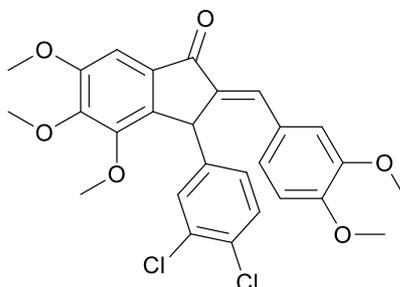
General procedure S was applied using 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **124** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as an orange-brown solid (107 mg, 78 %); m.p. 171-173 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3052 (m, ArC-H), 2838 (m, C-H), 1686 (s, C=O), 1624 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.73 (1H, d, $J = 1.0$ Hz, C=CH), 7.47-7.42 (2H, m, 2 x ArH), 7.32-7.28 (4H, m, 4 x ArH), 7.24 (1H, s, ArH), 7.23 (1H, d, $J = 8.0$ Hz, ArH), 7.06 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 5.37-5.34 (1H, m, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃) 3.52 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.3 (C=O), 155.4 (ArC), 150.0 (ArC), 148.7 (ArC), 141.7 (ArC), 140.1 (ArC), 139.2 (ArC), 135.2 (C=CH), 134.0 (ArC), 132.3 (ArC), 132.2 (ArC), 131.1 (2 x ArCH), 130.8 (ArCH), 130.6 (ArC), 130.2 (ArCH), 129.9 (ArCH), 128.6 (2 x ArCH), 128.1 (ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 45.2 (C(Ar)H); m/z (ESI) 477 [M+Na]⁺; HRMS (ESI) $\text{C}_{25}\text{H}_{20}^{35}\text{Cl}_2\text{O}_4\text{Na}^+$ requires 477.0631, found 477.0635 [M+Na]⁺.

(E)-3-(3,4-Dichlorophenyl)-4,5,6-trimethoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 372



General procedure S was applied using 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **124** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as an orange-brown solid (115 mg, 79 %); m.p. 178-182 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2937 (m, ArC-H), 2838 (m, C-H), 1692 (s, C=O), 1625 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.70-7.68 (1H, m, C=CH), 7.46-7.42 (2H, m, 2 x ArH), 7.37 (1H, d, *J* = 1.5 Hz, ArH), 7.27-7.24 (1H, m, ArH), 7.23 (1H, s, ArH), 7.11 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 6.85-6.81 (2H, m, 2 x ArH), 5.33-5.30 (1H, m, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.54 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.4 (C=O), 161.2 (ArC), 155.4 (ArC), 150.0 (ArC), 148.4 (ArC), 141.8 (ArC), 139.8 (ArC), 136.5 (ArC), 135.1 (C=CH), 133.3 (2 x ArCH), 132.4 (ArC), 132.3 (ArC), 130.8 (ArCH), 130.6 (ArC), 130.3 (ArCH), 128.1 (ArCH), 126.6 (ArC), 114.3 (2 x ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 55.5 (OCH₃), 45.3 (C(Ar)H); *m/z* (ESI) 507 [M+Na]⁺; HRMS (ESI) C₂₆H₂₂³⁵Cl₂O₅Na⁺ requires 507.0736, found 507.0739 [M+Na]⁺.

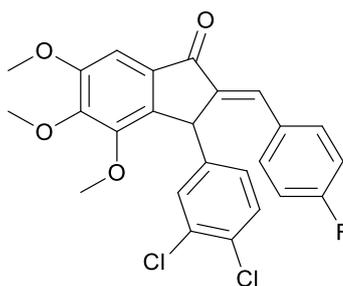
(E)-3-(3,4-Dichlorophenyl)-2-(3,4-dimethoxybenzylidene)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 380



General procedure S was applied using 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **124** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave

the title compound as an orange-brown solid (121 mg, 78 %); m.p. 163-165 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2993 (m, ArC-H), 2835 (m, C-H), 1682 (s, C=O), 1614 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.70-7.67 (1H, m, C=CH), 7.49 (1H, d, $J = 1.5$ Hz, ArH), 7.28-7.26 (1H, m, ArH), 7.23 (1H, s, ArH), 7.13 (1H, dd, $J = 8.5, 1.0$ Hz, ArH), 7.09 (1H, dd, $J = 8.5, 1.5$ Hz, ArH), 6.94-6.92 (1H, m, ArH), 6.82 (1H, d, $J = 8.5$ Hz, ArH), 5.32 (1H, s, C(Ar)H), 3.93 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.57 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.3 (C=O), 155.4 (ArC), 151.0 (ArC), 150.0 (ArC), 149.0 (ArC), 148.3 (ArC), 141.8 (ArC), 139.6 (ArC), 136.2 (ArC), 135.5 (C=CH), 132.4 (ArC), 132.2 (ArC), 131.1 (ArCH), 130.8 (ArC), 130.5 (ArCH), 127.8 (ArCH), 126.9 (ArC), 126.5 (ArCH), 113.3 (ArCH), 111.1 (ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 56.2 (OCH₃), 56.1 (OCH₃), 45.4 (C(Ar)H); m/z (ESI) 537 [M+Na]⁺; HRMS (ESI) $\text{C}_{27}\text{H}_{24}^{35}\text{Cl}_2\text{O}_6\text{Na}^+$ requires 537.0842, found 537.0845 [M+Na]⁺.

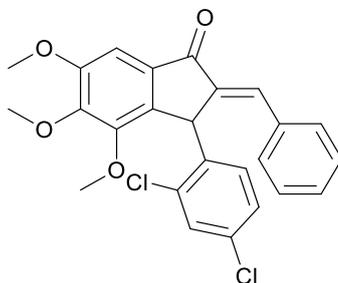
(E)-3-(3,4-Dichlorophenyl)-2-(4-fluorobenzylidene)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 388



General procedure S was applied using 3-(3,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **124** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μL , 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as an orange-brown solid (106 mg, 75 %); m.p. 206-208 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2939 (m, ArC-H), 2839 (m, C-H), 1684 (s, C=O), 1627 (s, C=C); δ_{H} (500 MHz, CDCl_3) 7.69-7.67 (1H, m, C=CH), 7.46-7.44 (1H, m, ArH), 7.44-7.42 (1H, m, ArH), 7.30 (1H, s, ArH), 7.26-7.24 (1H, m, ArH), 7.23 (1H, s, ArH), 7.07 (1H, dd, $J = 8.5, 2.0$ Hz, ArH), 7.02-6.97 (2H, m, 2 x ArH), 5.30 (1H, d, $J = 1.0$ Hz, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.52 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl_3) 193.1 (C=O), 164.5 (ArC), 162.5 (ArC), 155.5 (ArC), 150.0 (ArC), 148.7 (ArC), 141.5 (ArC), 139.9 (ArC), 138.8 (ArC), 133.9 (C=CH), 133.1 (ArCH), 133.0 (ArCH), 132.4 (ArC), 132.1 (ArC), 130.8 (ArC), 130.7 (ArCH), 130.3 (ArCH), 128.1 (ArCH), 116.0 (ArCH), 115.8 (ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 45.1 (C(Ar)H); m/z (ESI) 495

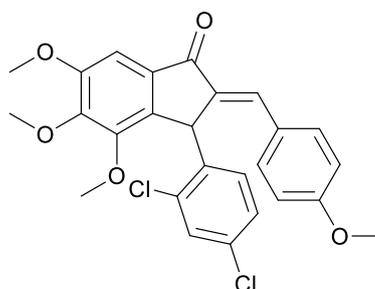
[M+Na]⁺; HRMS (ESI) C₂₅H₁₉³⁵Cl₂FO₄Na⁺ requires 495.0537, found 495.0539 [M+Na]⁺.

(E)-2-Benzylidene-3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 365



General procedure S was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), benzaldehyde (61 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as a pale yellow solid (112 mg, 82 %); m.p. 138-140 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2971 (m, ArC-H), 2835 (m, C-H), 1686 (s, C=O), 1624 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.74 (1H, d, $J = 1.5$ Hz, C=CH), 7.50-7.45 (2H, m, 2 x ArH), 7.34 (1H, s, ArH), 7.32-7.27 (3H, m, 3 x ArH), 7.25 (1H, s, ArH), 6.90 (1H, d, $J = 6.0$ Hz, ArH), 6.63 (1H, s, ArH), 5.84 (1H, s, C(Ar)H), 3.95 (3H, s, OCH₃), 3.90 (3H, s, OCH₃) 3.48 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.4 (C=O), 155.3 (2 x ArC), 150.1 (ArC), 148.8 (ArC), 139.3 (ArC), 137.6 (ArC), 135.4 (C=CH), 133.9 (ArC), 132.9 (ArC), 132.5 (ArC), 132.5 (ArC), 130.8 (2 x ArCH), 129.9 (ArCH), 128.9 (ArCH), 128.5 (2 x ArCH), 128.1 (ArCH), 127.6 (ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 41.3 (C(Ar)H); m/z (ESI) 477 [M+Na]⁺; HRMS (ESI) C₂₅H₂₀³⁵Cl₂O₄Na⁺ requires 477.0631, found 477.0624 [M+Na]⁺.

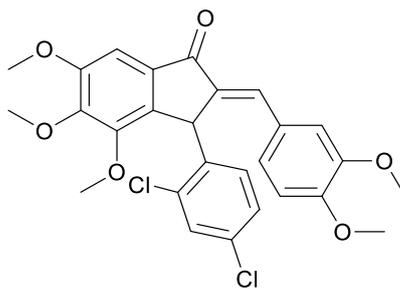
(E)-3-(2,4-Dichlorophenyl)-4,5,6-trimethoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one, 373



General procedure S was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), *p*-anisaldehyde (73 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash

column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as a pale yellow solid (138 mg, 95 %); m.p. 162-164 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2937 (m, ArC-H), 2833 (m, C-H), 1688 (s, C=O), 1621 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.71-7.68 (1H, m, C=CH), 7.49-7.45 (2H, m, 2 x ArH), 7.39 (1H, s, ArH), 7.24 (1H, s, ArH), 6.91 (1H, d, $J = 6.0$ Hz, ArH), 6.85-6.81 (2H, m, 2 x ArH), 6.65 (1H, s, ArH), 5.79 (1H, s, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.49 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.5 (C=O), 161.2 (ArC), 155.3 (2 x ArC), 150.1 (ArC), 148.5 (ArC), 137.7 (ArC), 136.8 (ArC), 135.6 (ArC), 135.2 (C=CH), 133.1 (2 x ArCH), 132.9 (ArC), 132.7 (ArC), 130.1 (ArCH), 128.9 (ArCH), 127.7 (ArCH), 126.5 (ArC), 114.1 (2 x ArCH), 101.4 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 55.5 (OCH₃), 41.3 (C(Ar)H); m/z (ESI) 507 [M+Na]⁺; HRMS (ESI) C₂₆H₂₂³⁵Cl₂O₅Na⁺ requires 507.0736, found 507.0738 [M+Na]⁺.

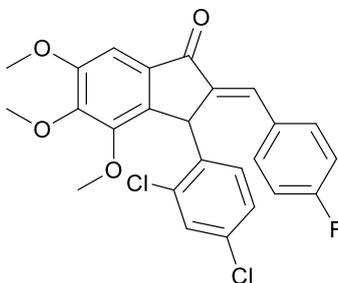
(E)-3-(2,4-Dichlorophenyl)-2-(3,4-dimethoxybenzylidene)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 381



General procedure S was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 3,4-dimethoxybenzaldehyde (100 mg, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (2:1), gave the title compound as a yellow solid (89 mg, 57 %); m.p. 126-128 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2935 (m, ArC-H), 2832 (m, C-H), 1693 (s, C=O), 1620 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.70-7.67 (1H, m, C=CH), 7.39 (1H, s, ArH), 7.25 (1H, s, ArH), 7.18 (1H, d, $J = 8.0$ Hz, ArH), 6.93 (1H, d, $J = 5.0$ Hz, ArH), 6.89 (1H, d, $J = 1.0$ Hz, ArH), 6.81 (1H, d, $J = 8.5$ Hz, ArH), 6.68 (1H, s, ArH), 5.79 (1H, s, C(Ar)H), 3.94 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.50 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.4 (C=O), 155.3 (ArC), 151.0 (ArC), 150.1 (ArC), 148.9 (ArC), 148.6 (ArC), 140.4 (ArC), 137.7 (ArC), 137.0 (ArC), 135.6 (C=CH), 132.9 (ArC), 132.6 (ArC), 130.1 (ArCH), 128.9 (ArCH), 127.8 (ArCH), 126.8 (2 x ArC), 124.6 (ArCH), 114.7 (ArCH), 110.9 (ArCH), 101.4 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.4 (OCH₃), 56.3 (OCH₃),

56.1 (OCH₃), 41.3 (C(Ar)H); m/z (ESI) 515 [M+H]⁺; HRMS (ESI) C₂₇H₂₅³⁵Cl₂O₆Na⁺ requires 515.1023, found 515.1024 [M+H]⁺.

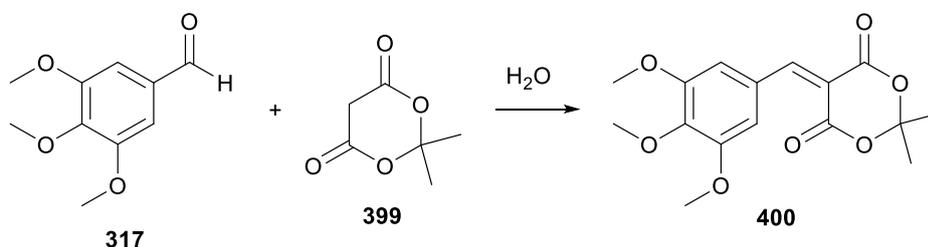
(E)-3-(2,4-Dichlorophenyl)-2-(4-fluorobenzylidene)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one, 389



General procedure S was applied using 3-(2,4-dichlorophenyl)-4,5,6-trimethoxy-2,3-dihydro-1H-inden-1-one **125** (110 mg, 0.30 mmol), MeOH:CH₂Cl₂ (1.50:1.50 mL), 4-fluorobenzaldehyde (64 μL, 0.60 mmol) and NaOH (60 mg, 1.50 mmol). Purification by flash column chromatography, eluting with pet ether:EtOAc (4:1), gave the title compound as a pale yellow solid (119 mg, 83 %); m.p. 124-127 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2979 (m, ArC-H), 2831 (m, C-H), 1693 (s, C=O), 1624 (s, C=C); δ_{H} (500 MHz, CDCl₃) 7.69 (1H, d, $J = 1.0$ Hz, C=CH), 7.49-7.47 (1H, m, ArH), 7.47-7.44 (1H, m, ArH), 7.36 (1H, s, ArH), 7.24 (1H, s, ArH), 7.02-6.96 (2H, m, 2 x ArH), 6.91 (1H, d, $J = 6.0$ Hz, ArH), 6.62 (1H, s, ArH), 5.80 (1H, s, C(Ar)H), 3.94 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.48 (3H, s, OCH₃); δ_{C} (126 MHz, CDCl₃) 193.3 (C=O), 164.5 (ArC), 162.5 (ArC), 155.4 (ArC), 150.1 (ArC), 148.9 (ArC), 139.0 (ArC), 137.4 (ArC), 135.5 (ArC), 134.0 (C=CH), 133.0 (ArC), 132.9 (2 x ArCH), 132.8 (ArCH), 132.4 (ArC), 130.1 (ArC), 128.9 (ArCH), 127.7 (ArCH), 115.8 (ArCH), 115.6 (ArCH), 101.5 (ArCH), 61.1 (OCH₃), 60.4 (OCH₃), 56.5 (OCH₃), 41.1 (C(Ar)H); m/z (ESI) 495 [M+Na]⁺; HRMS (ESI) C₂₅H₁₉³⁵Cl₂FO₄Na⁺ requires 495.0537, found 495.0532 [M+Na]⁺.

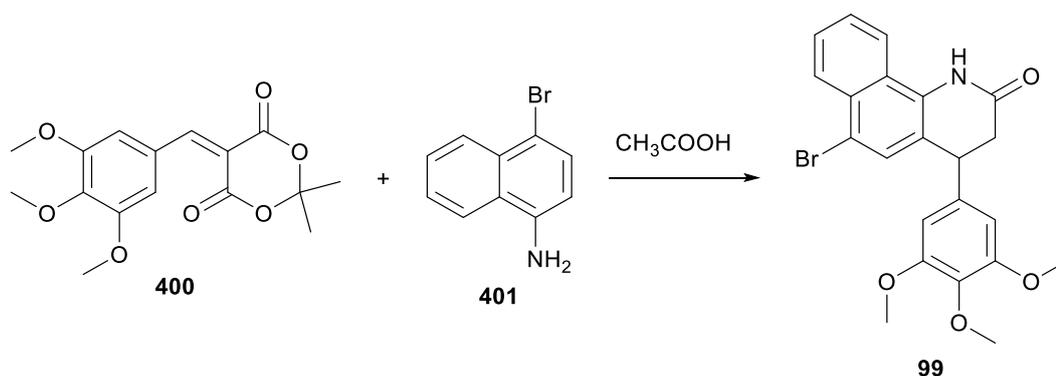
3.7 Experimental Continued – Synthesis of (S)- and (R)-6-B345TTQ, (S)- and (R)-99

3.7.1 Knoevenagel Condensation of 3,4,5-Trimethoxybenzaldehyde and Meldrum's Acid



The following procedure was performed in accordance with previous literature.^{136, 267} 3,4,5-Trimethoxybenzaldehyde **317** (1.00 g, 5.10 mmol, 1.10 equiv.) and Meldrum's acid **399** (735 mg, 5.10 mmol, 1.00 equiv.) were stirred in water (10.0 mL, 2.00 mL/mmol) at 75 °C for 6 hours. The reaction mixture was cooled to room temperature, and the organics extracted using CH₂Cl₂. The organic layer was washed twice with saturated NaHCO₃ (aq.), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by recrystallisation in MeOH gave 2,2-dimethyl-5-(3,4,5-trimethoxybenzylidene)-1,3-dioxane-4,6-dione **400** as a yellow crystalline solid (0.55 g, 34 %); m.p. 156-157 °C (lit.²⁶⁸ 155-156 °C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2979 (m, ArC-H), 1747 (s, C=C), 1714 (s, C=O), 1115 (s, C-O); δ_{H} (500 MHz, CDCl₃) 8.35 (1H, s, HC=C), 7.64 (2H, s, 2 x ArH), 4.01 (3H, s, OCH₃), 3.94 (6H, s, 2 x OCH₃), 1.82 (6H, s, 2 x CH₃); δ_{C} (126 MHz, CDCl₃) 163.9 (C=O), 160.3 (C=O), 158.2 (HC=C), 152.7 (2 x ArC), 143.9 (ArC), 126.6 (ArC), 112.6 (ArCH), 112.5 (HC=C), 104.4 (C(CH₃)₂), 61.2 (OCH₃), 56.3 (2 x OCH₃), 27.6 (2 x CH₃); m/z (ESI) 345 [M+Na]⁺; HRMS (ESI) C₁₆H₁₈O₇Na⁺ requires 345.0945, found 345.0946 [M+Na]⁺. These data are consistent with those previously reported.^{136, 268}

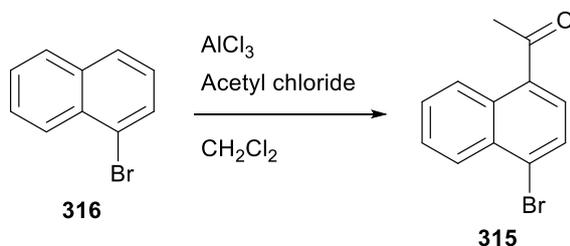
3.7.2 Formation of (±)-6-B345TTQ by Conjugate Addition



The following procedure was performed in accordance with previous literature.²⁶⁹

To 2,2-dimethyl-5-(3,4,5-trimethoxybenzylidene)-1,3-dioxane-4,6-dione **400** (500 mg, 1.55 mmol, 1.00 equiv.), in glacial acetic acid (30.0 mL, 19.5 mL/mmol), was added 1-amino-4-bromonaphthalene **401** (345 mg, 1.55 mmol, 1.00 equiv.). The resulting mixture was heated to 100 °C and stirred under N₂ for 19 hours. The reaction mixture was cooled to room temperature, poured into ice-cold water and then the solids filtered, washing with further cold water. The solids were collected, dissolved in CH₂Cl₂ and washed twice with saturated NaHCO₃ (aq.). The organics were then dried over MgSO₄, filtered and concentrated *in vacuo*. 6-bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]quinolin-2(1*H*)-one **99** was formed as an off-white solid (447 mg, 65 %), which was used without further purification. Spectroscopic data are in agreement with those previously acquired.

3.7.3 Friedel–Crafts Acylation of 1-Bromonaphthalene

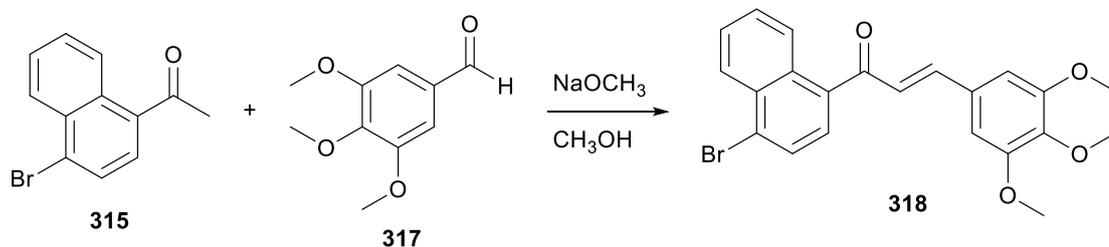


The following procedure was adapted from previous literature.¹⁹³

To a stirred suspension of AlCl₃ (7.60 g, 1.18 mmol, 1.18 equiv.) in dry CH₂Cl₂ (100 mL, 1.75 mL/mmol) was carefully added acetyl chloride (3.78 mL, 53.1 mmol, 1.10 equiv.) under N₂. The resulting mixture was cooled to -20 °C and 1-bromonaphthalene **316** (6.76 mL, 48.3 mmol, 1.00 equiv.) in CH₂Cl₂ (48.3 mL, 1.00 mL/mmol) was added via dropping funnel over 5.5 hours. The reaction mixture was stirred at -20 °C for a further 2 hours then allowed to warm to room temperature, at which it was stirred for 16.5 hours under N₂. The solvent was carefully removed under vacuum, the vessel cooled to 0 °C and water slowly added until gas evolution ceased. The organics were extracted with EtOAc, washed with saturated NaHCO₃ (aq.) and brine, then dried over MgSO₄, filtered and concentrated *in vacuo*. 1-(4-Bromonaphthalen-1-yl)ethan-1-one **315** was formed as a pale yellow oil (10.8 g, 90 %), which was used without further purification; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3000 (m, ArC-H), 1674 (s, C=O), 758 (s, C-Br); δ_{H} (500 MHz, CDCl₃) 8.74-8.69 (1H, m, ArH), 8.35-8.32 (1H, m, ArH), 7.82 (1H, d, *J* = 8.0 Hz, ArH), 7.73 (1H, d, *J* = 8.0 Hz, ArH), 7.67-7.62 (2H, m, 2 x ArH), 2.73 (3H, s, CH₃); δ_{C} (126 MHz, CDCl₃) 201.2 (C=O), 135.4 (ArC), 132.4 (ArC), 131.2 (ArC), 128.8 (ArCH), 128.7 (ArCH), 128.3 (ArCH), 128.3 (ArC), 127.9 (ArCH), 127.6 (ArCH), 126.4 (ArCH), 30.1 (CH₃); *m/z* (ESI)

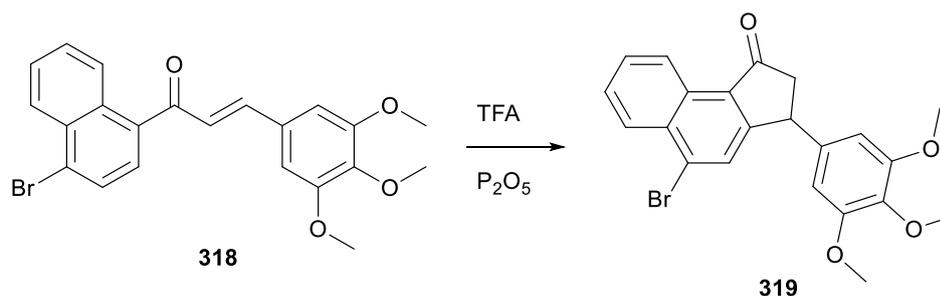
270 + 272 [M+Na]⁺; HRMS (ESI) C₁₂H₉⁷⁹BrONa⁺ requires 270.9729 + C₁₂H₉⁸¹BrONa⁺ requires 272.9709, found 270.9729 + 272.9708 [M+Na]⁺. These data are consistent with those previously reported.^{136, 194}

3.7.4 Synthesis of Substituted Chalcone 318



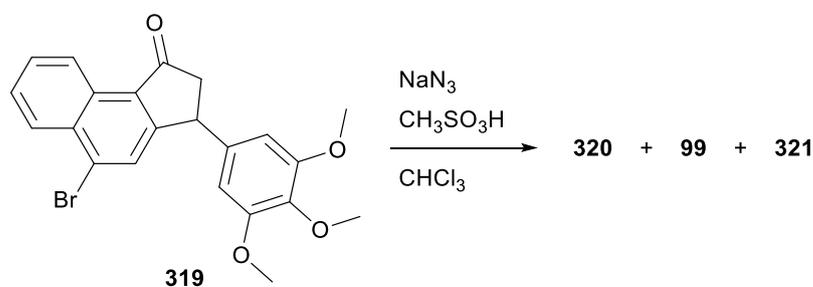
General procedure A was applied using 1-(4-bromophthalen-1-yl)ethan-1-one **315** (10.7 g, 43.0 mmol), 3,4,5-trimethoxybenzaldehyde **317** (8.43 g, 43.0 mmol), MeOH (32.1 mL) and sodium methoxide (3.48 g, 64.4 mmol). The reaction was performed at 50 °C for 3 hours, cooled to room temperature, filtered, and used without further purification. (*E*)-1-(4-bromophthalen-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **318** was formed as a yellow solid (15.6 g, 94 %); m.p. 128-130 °C; ν_{\max} /cm⁻¹ (neat) 2934 (m, ArC-H), 1652 (s, C=C), 1593 (s, C=O), 1118 (s, C-O), 761 (s, C-Br); δ_{H} (500 MHz, CDCl₃) 8.35 (1H, d, $J = 8.5$ Hz, ArH), 8.24 (1H, d, $J = 8.5$ Hz, ArH), 7.87 (1H, d, $J = 7.5$ Hz, ArH), 7.68-7.64 (1H, m, ArH), 7.63-7.58 (1H, m, ArH), 7.55 (1H, d, $J = 7.5$ Hz, ArH), 7.43 (1H, d, $J = 16.0$ Hz, C(O)CH=CH), 7.14 (d, $J = 16.0$ Hz, C(O)CH=CH), 6.78 (2H, s, 2 x ArH), 3.89 (3H, s, OCH₃), 3.88 (6H, s, 2 x OCH₃); δ_{C} (126 MHz, CDCl₃) 195.4 (C=O), 153.5 (2 x ArC), 146.9 (C(O)CH=CH), 140.7 (ArC), 137.2 (ArC), 132.3 (ArC), 131.6 (ArC), 129.8 (ArC), 128.8 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 126.8 (ArCH), 126.5 (C(O)CH=CH), 126.4 (ArC), 126.1 (ArCH), 105.7 (2 x ArCH), 61.0 (OCH₃), 56.2 (2 x OCH₃); m/z (ESI) 449 + 451 [M+Na]⁺; HRMS (ESI) C₂₂H₁₉⁷⁹BrO₄Na⁺ requires 449.0359 + C₂₂H₁₉⁸¹BrO₄Na⁺ requires 451.0351, found 449.0361 + 451.0343 [M+Na]⁺. These data are consistent with those previously reported.¹³⁶

3.7.5 Synthesis of 6-B345TTQ Precursor Indan-1-one, 319



General procedure B was applied using 1-(4-bromonaphthalen-1-yl)ethan-1-one **318** (3.28 g, 7.68 mmol), trifluoroacetic acid (15.4 mL, 2.00 mL/mmol) and phosphorus pentoxide (3.26 g, 11.5 mmol, 1.50 equiv.). Purification by flash column chromatography, eluting with pet ether:EtOAc (3:1), gave 5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1H-cyclopenta[*a*]naphthalen-1-one **319** as a creamy beige solid (775 mg, 24 %); m.p. 193-195 °C; ν_{\max} /cm⁻¹ (neat) 2930 (m, ArC-H), 2834 (m, C-H), 1699 (s, C=O), 1124 (s, C-O), 763 (s, C-Br); δ_{H} (500 MHz, CDCl₃) 9.27 (1H, d, $J = 8.5$ Hz, ArH), 8.33 (1H, d, $J = 8.5$ Hz, ArH), 7.77 (1H, t, $J = 7.5$ Hz, ArH), 7.72-7.68 (1H, m, ArH), 7.69 (1H, s, ArH), 6.34 (2H, s, 2 x ArH), 4.54 (1H, dd, $J = 7.5, 3.5$ Hz, C(Ar)H), 3.85 (3H, s, OCH₃), 3.79 (6H, s, 2 x OCH₃), 3.32 (1H, dd, $J = 19.0, 7.5$ Hz, C(H)H), 2.82 (1H, dd, $J = 19.0, 3.5$ Hz, C(H)H); δ_{C} (126 MHz, CDCl₃) 205.6 (C=O), 160.1 (ArC), 153.7 (2 x ArC), 138.2 (ArC), 137.2 (ArC), 132.2 (ArC), 131.4 (ArC), 130.2 (ArC), 130.0 (ArCH), 129.7 (ArC), 128.3 (ArCH), 128.1 (ArCH), 127.7 (ArCH), 124.6 (ArCH), 104.7 (2 x ArCH), 60.9 (OCH₃), 56.2 (2 x OCH₃), 47.4 (CH₂), 44.6 (C(Ar)H); m/z (ESI) 449 + 451 [M+Na]⁺; HRMS (ESI) C₂₂H₁₉⁷⁹BrO₄Na⁺ requires 449.0359 + C₂₂H₁₉⁸¹BrO₄Na⁺ requires 451.0351, found 449.0360 + 451.0344 [M+Na]⁺. These data are consistent with those previously reported.¹³⁶

3.7.6 Schmidt Reaction of Racemic Indan-1-one Precursor, 319

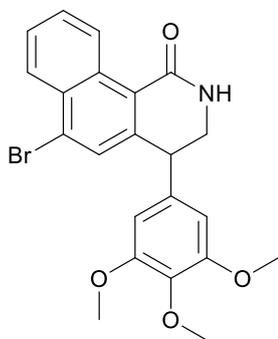


General procedure J was applied using 5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1H-cyclopenta[*a*]naphthalen-1-one **319** (300 mg, 0.70 mmol), CHCl₃ (3.30 mL), methanesulfonic acid (429 μ L, 6.63 mmol) and sodium azide (91 mg, 1.40 mmol). Work-

up yielded a brown oil, comprising a 0.42:0.27:0.18:0.07:0.06 mixture of 6-bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one **320**, an unknown material*, 6-bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]quinolin-2(1*H*)-one **99**, 2-(4-bromo-1-cyanonaphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)ethyl methanesulfonate **321**, and unreacted starting material, respectively. Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to 1:1), afforded **319** as a pale brown solid (68 mg, 22 %), **99** as a brown solid (3 mg, 1 %), and **321** as a pale brown solid (51 mg, 14 %). Spectroscopic data for each compound are as follows:

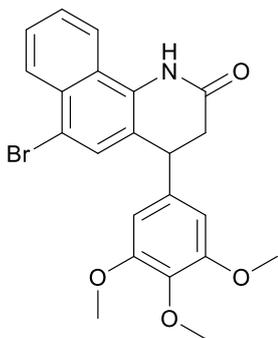
**(Material appeared to decompose back to starting material during purification by column chromatography, thus could not be isolated and identified.)*

6-Bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one, **320**



m.p. 236-238 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3209 (m, N-H), 2935 (m, ArC-H), 2837 (m, C-H), 1660 (s, C=O), 1125 (s, C-O), 729 (s, C-Br); δ_{H} (500 MHz, CDCl_3) 9.42 (1H, d, $J = 8.5$ Hz, ArH), 8.28 (1H, dd, $J = 8.5, 0.5$ Hz, ArH), 7.70-7.60 (2H, m, 2 x ArH), 7.50 (1H, s, ArH), 6.61-6.56 (1H, m, ArH), 6.38 (2H, s, 2 x ArH), 4.28 (1H, t, $J = 5.5$ Hz, C(Ar)H), 3.84 (3H, s, OCH₃), 3.82 (1H, dd, $J = 4.5, 4.0$ Hz, C(H)H), 3.77 (6H, s, 2 x OCH₃), 3.67-3.60 (1H, m, C(H)H); δ_{C} (126 MHz, CDCl_3) 166.1 (C=O), 153.6 (2 x ArC), 141.9 (ArC), 137.4 (ArC), 135.2 (ArC), 132.7 (ArC), 131.8 (ArC), 129.5 (ArCH), 128.7 (ArCH), 128.5 (ArC), 127.6 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 124.3 (ArC), 105.6 (2 x ArCH), 60.9 (OCH₃), 56.2 (2 x OCH₃), 46.3 (CH₂), 45.9 (C(Ar)H); m/z (ESI) 464 + 466 [M+Na]⁺; HRMS (ESI) $\text{C}_{22}\text{H}_{20}^{79}\text{BrNO}_4\text{Na}^+$ requires 464.0468 + $\text{C}_{22}\text{H}_{20}^{81}\text{BrO}_4\text{Na}^+$ requires 466.0450, found 464.0474 + 466.0456 [M+Na]⁺. These data are consistent with those previously reported.¹³⁶

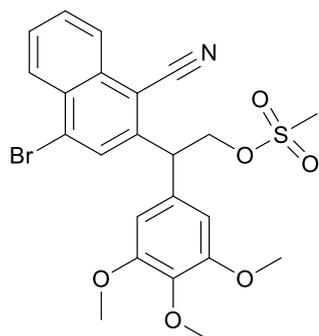
6-bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]quinolin-2(1*H*)-one, **99**



m.p. 230-232 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3230 (m, N-H), 2927 (m, ArC-H), 2853 (m, C-H), 1678 (s, C=O), 1127 (s, C-O), 732 (s, C-Br); δ_{H} (500 MHz, CDCl_3) 8.29-8.22 (2H, m, 2 x ArH), 7.84-7.79 (1H, m, ArH), 7.69-7.62 (2H, m, 2 x ArH), 7.44 (1H, s, ArH), 6.42 (2H, s, 2 x ArH), 4.36 (1H, dd, $J = 8.0, 6.5$ Hz, C(Ar)H), 3.85 (3H, s, OCH₃), 3.80 (6H, s, 2 x OCH₃), 3.06 (1H, dd, $J = 16.0, 6.5$ Hz, C(H)H), 2.99 (1H, dd, $J = 16.0, 8.0$ Hz, C(H)H); δ_{C} (126 MHz, CDCl_3) 169.8 (C=O), 153.7 (2 x ArC), 137.4 (ArC), 136.5 (ArC), 131.5 (ArC),

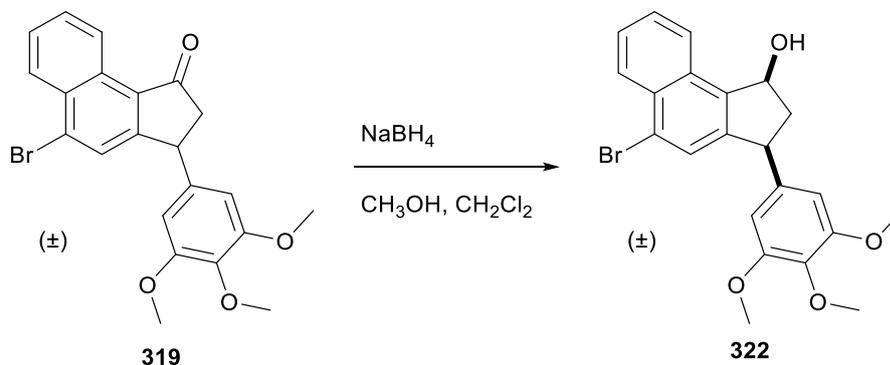
131.5 (ArC), 129.8 (ArCH), 128.3 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 123.2 (ArC), 123.0 (ArC), 119.5 (ArCH), 116.9 (ArC), 104.8 (2 x ArCH), 60.9 (OCH₃), 56.2 (2 x OCH₃), 42.7 (C(Ar)H), 38.8 (CH₂); m/z (ESI) 464 + 466 [M+Na]⁺; HRMS (ESI) C₂₂H₂₀⁷⁹BrNO₄Na⁺ requires 464.0468 + C₂₂H₂₀⁸¹BrO₄Na⁺ requires 466.0450, found 464.0467 + 466.0447 [M+Na]⁺. These data are consistent with those previously reported.^{15, 16, 136}

2-(4-bromo-1-cyanonaphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)ethyl methanesulfonate, 321



m.p. 173-175 °C; ν_{\max} /cm⁻¹ (neat) 2935 (m, ArC-H), 2221 (m, C≡N), 1362 (s, S=O (*as*)), 1126 (s, S=O (*s*)), 732 (s, C-Br); δ_{H} (500 MHz, CDCl₃) 8.34-8.31 (1H, m, ArH), 8.27-8.23 (1H, m, ArH), 8.04 (1H, s, ArH), 7.82-7.73 (2H, m, 2 x ArH), 6.49 (2H, s, 2 x ArH), 6.16 (1H, dd, *J* = 8.5, 5.0 Hz, C(Ar)H), 3.81 (9H, s, 3 x OCH₃), 3.26 (1H, dd, *J* = 14.5, 8.5 Hz, C(H)H), 3.21 (1H, dd, *J* = 14.5, 5.0 Hz, C(H)H), 2.67 (3H, s, S-CH₃); δ_{C} (126 MHz, CDCl₃) 153.5 (2 x ArC), 142.7 (ArC), 137.5 (ArC), 132.8 (ArC), 131.6 (ArC), 130.5 (ArC), 130.2 (ArCH), 130.1 (ArC), 129.6 (ArCH), 128.1 (ArCH), 127.1 (ArCH), 126.0 (ArCH), 115.3 (C≡N), 107.6 (ArC), 106.6 (2 x ArCH), 81.8 (C(Ar)H), 61.0 (OCH₃), 56.2 (2 x OCH₃), 43.6 (CH₂), 38.0 (SCH₃); m/z (ESI) 542 + 544 [M+Na]⁺; HRMS (ESI) C₂₃H₂₂⁷⁹BrNO₆SNa⁺ requires 542.0243 + C₂₃H₂₂⁸¹BrNO₆SNa⁺ requires 544.0225, found 542.0242 + 544.0225 [M+Na]⁺.

3.7.7 Diastereoselective Reduction of Indan-1-one Precursor, 319

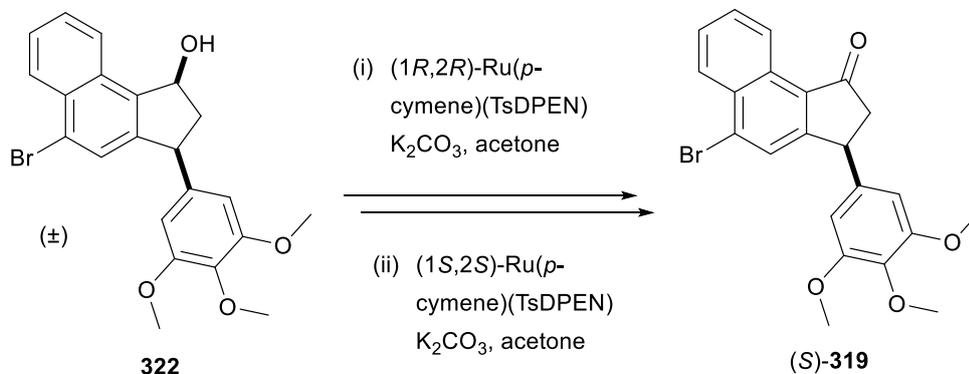


General procedure C was applied using 5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one **319** (2.00 g, 4.68 mmol), MeOH:CH₂Cl₂ (35.0:35.0 mL, 35.0 mL/g) and NaBH₄ (177 mg, 4.68 mmol, 1.0 equiv.). Purification by recrystallisation in MeOH gave (1*RS*,3*RS*)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-

dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol **322** as a white solid (1.92 g, 58 %); m.p. 154-156 °C; ν_{\max} /cm⁻¹ (neat) 3401 (br, O-H), 2963 (m, ArC-H), 2835 (m, C-H), 1124 (s, C-O), 766 (s, C-Br); δ_{H} (500 MHz, CDCl₃) 8.39-8.35 (1H, m, ArH), 8.31-8.27 (1H, m, ArH), 7.66-7.59 (2H, m, 2 x ArH), 7.49 (1H, s, ArH), 6.49 (2H, s, 2 x ArH), 5.80 (1H, m, CH(OH)), 4.29 (1H, dd, *J* = 8.5, 6.5 Hz, C(Ar)H), 3.86 (3H, s, OCH₃), 3.81 (6H, s, 2 x OCH₃), 3.21 (1H, ddd, *J* = 14.0, 8.5, 7.5 Hz, C(H)H), 2.14 (1H, ddd, *J* = 14.0, 6.5, 5.0 Hz, C(H)H), 2.06 (1H, d, *J* = 7.0 Hz, CH(OH)); δ_{C} (126 MHz, CDCl₃) 153.5 (2 x ArC), 144.0 (ArC), 140.2 (ArC), 139.1 (ArC), 136.8 (ArC), 131.6 (ArC), 131.2 (ArC), 128.0 (ArCH), 127.5 (ArCH), 127.5 (ArCH), 127.0 (ArCH), 124.7 (ArCH), 124.4 (ArC), 105.1 (2 x ArCH), 75.0 (CH(OH)), 60.9 (OCH₃), 56.2 (2 x OCH₃), 49.8 (C(Ar)H), 45.9 (CH₂); *m/z* (ESI) 451 + 453 [M+Na]⁺; HRMS (ESI) C₂₂H₂₁⁷⁹BrO₄Na⁺ requires 451.0515 + C₂₂H₂₁⁸¹BrO₄Na⁺ requires 453.0498, found 451.0512 + 453.0495 [M+Na]⁺. These data are consistent with those previously reported.¹³⁶

3.7.8 Successive Oxidative Kinetic Resolutions Towards Individual Enantiomers of Indan-1-one Precursor, (*S*)- and (*R*)-319

5-Bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*S*)-319

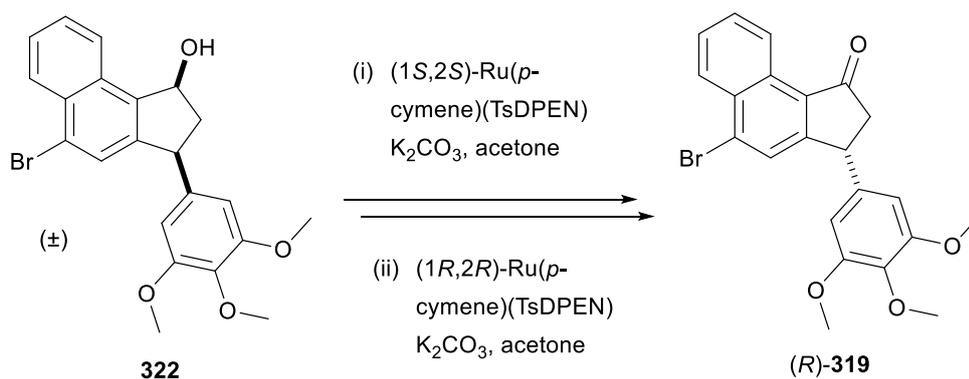


General procedure E was first applied using 5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol **322** (400 mg, 0.93 mmol), K₂CO₃ (128 mg, 0.93 mmol) and (1*R*,2*R*)-Ru(*p*-cymene)(TsDPEN) (6 mg, 9.28 μmol, 1.00 mol%) to give (1*S*,3*S*)-**322** and (*R*)-**319** in a ratio of 52:48. Purification by flash chromatography, eluting with pet ether:EtOAc (3:1), gave ketone (*R*)-**319** as a beige solid (169 mg, 42 %), as a % of racemic starting material, in 85 % e.e., and alcohol (1*S*,3*S*)-**322** as an off-white solid (135 mg, 34 %), as a % of racemic starting material, in 88 % e.e.

General procedure E was then applied using the newly formed alcohol (1*S*,3*S*)-**322** (518 mg, 1.21 mmol, 88 % e.e.), K₂CO₃ (166 mg, 1.21 mmol) and (1*S*,2*S*)-Ru(*p*-

cymene)(TsDPEN) (7 mg, 12.1 μmol , 1.00 mol%) to give (1*R*,3*R*)-**322** and (*S*)-**319** in a ratio of 6:94. The title compound was isolated by flash chromatography, eluting with pet ether:EtOAc (3:1), to yield a white solid (435 mg, 84 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.10$, CHCl_3) +111.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 7:93, 1.00 mL/min., 243 nm, (*S*)-isomer 17.64 min., (*R*)-isomer 23.13 min.).

(*R*)-5-Bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one, (*R*)-319

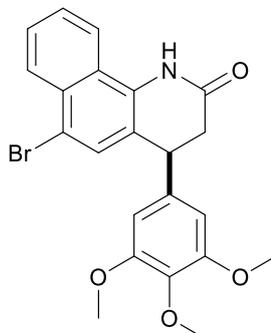


General procedure E was applied using 5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol **322** (400 mg, 0.93 mmol), K_2CO_3 (128 mg, 0.93 mmol) and (1*S*,2*S*)-Ru(*p*-cymene)(TsDPEN) (6 mg, 9.28 μmol , 1.00 mol%) to give (1*R*,3*R*)-**322** and (*S*)-**319** in a ratio of 50:50. Purification by flash chromatography, eluting with pet ether:EtOAc (3:1), gave ketone (*S*)-**319** as a beige solid (138 mg, 35 %), as a % of racemic starting material, in 71 % e.e., and alcohol (1*R*,3*R*)-**322** as an off-white solid (146 mg, 37 %), as a % of racemic starting material, in 97 % e.e.

General procedure E was then applied using the newly formed alcohol (1*R*,3*R*)-**322** (644 mg, 1.50 mmol, 97 % e.e.), K_2CO_3 (206 mg, 1.50 mmol) and (1*R*,2*R*)-Ru(*p*-cymene)(TsDPEN) (9 mg, 15.0 μmol , 1.00 mol%) to give (1*S*,3*S*)-**322** and (*R*)-**319** in a ratio of 2:98. The title compound was isolated by flash chromatography, eluting with pet ether:EtOAc (3:1), to yield a white solid (512 mg, 80 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ ($c = 0.10$, CHCl_3) -91.5; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 7:93, 1.00 mL/min., 243 nm, (*S*)-isomer 17.61 min., (*R*)-isomer 22.73 min.).

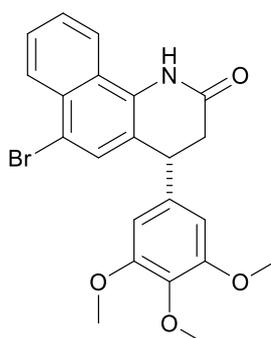
**3.7.9 Schmidt Reaction of Precursor Indan-1-one Individual Enantiomers;
Formation of (S)- and (R)-6-B345TTQ, (R)- and (S)-99**

**(S)-6-bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]quinolin-2(1*H*)-one,
(S)-99**



General procedure J was applied using (S)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (S)-**319** (200 mg, 0.47 mmol), CHCl₃ (2.20 mL), methanesulfonic acid (286 μ L, 4.42 mmol) and sodium azide (61 mg, 0.94 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to 1:1), afforded the title compound as an off-white solid (5 mg, 2 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.05, CHCl₃) +53.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 242 nm, (S)-isomer 20.27 min., (R)-isomer 41.53 min.).

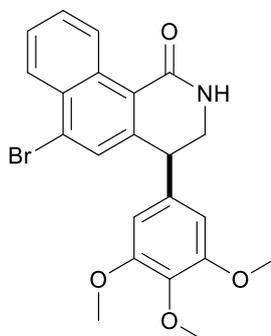
**(R)-6-bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]quinolin-2(1*H*)-one,
(R)-99**



General procedure J was applied using (R)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (R)-**319** (200 mg, 0.47 mmol), CHCl₃ (2.20 mL), methanesulfonic acid (286 μ L, 4.42 mmol) and sodium azide (61 mg, 0.94 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to 1:1), afforded the title compound as an off-white solid (6 mg, 3 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{29}$ (c = 0.05, CHCl₃) -43.0;

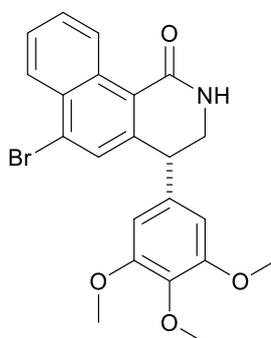
enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 241 nm, (*S*)-isomer 21.24 min., (*R*)-isomer 38.36 min.).

(*S*)-6-Bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one, (*S*)-320



General procedure J was applied using (*S*)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (*S*)-**319** (200 mg, 0.47 mmol), CHCl₃ (2.20 mL), methanesulfonic acid (286 μL, 4.42 mmol) and sodium azide (61 mg, 0.94 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to 1:1), afforded the title compound as a brown solid (47 mg, 23 %, >99 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ (c = 0.05, CHCl₃) +80.0; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 242 nm, (*S*)-isomer 18.84 min., (*R*)-isomer 21.68 min.).

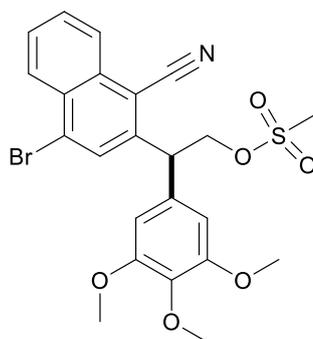
(*R*)-6-Bromo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one, (*R*)-320



General procedure J was applied using (*R*)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (*R*)-**319** (200 mg, 0.47 mmol), CHCl₃ (2.20 mL), methanesulfonic acid (286 μL, 4.42 mmol) and sodium azide (61 mg, 0.94 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to 1:1), afforded the title compound as a brown solid (55 mg, 27 %, >96 % e.e.);

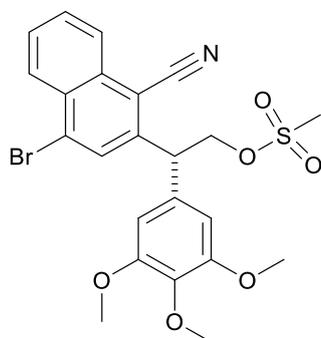
spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ ($c = 0.05$, CHCl_3) -89.0 ; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 241 nm, (*S*)-isomer 19.60 min., (*R*)-isomer 21.03 min.).

(*S*)-2-(4-Bromo-1-cyanonaphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)ethyl methanesulfonate, (*S*)-321



General procedure J was applied using (*S*)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (*S*)-**319** (200 mg, 0.47 mmol), CHCl_3 (2.20 mL), methanesulfonic acid (286 μL , 4.42 mmol) and sodium azide (61 mg, 0.94 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to 1:1), afforded the title compound as a creamy brown solid (32 mg, 13 %, 58 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{28}$ ($c = 0.05$, CHCl_3) $+26.0$; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 237 nm, (*R*)-isomer 18.59 min., (*S*)-isomer 22.59 min.).

(*R*)-2-(4-Bromo-1-cyanonaphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)ethyl methanesulfonate, (*R*)-321



General procedure J was applied using (*R*)-5-bromo-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (*R*)-**319** (200 mg, 0.47 mmol), CHCl_3 (2.20 mL), methanesulfonic acid (286 μL , 4.42 mmol) and sodium azide (61 mg, 0.94 mmol). Purification by gradient column chromatography, eluting with pet ether:EtOAc (2:1 to

1:1), afforded the title compound as a creamy brown solid (38 mg, 16 %, 75 % e.e.); spectroscopic data are similar to those of the racemate; $[\alpha]_D^{30}$ (c = 0.05, CHCl₃) -4.00; enantiomeric excess determined by HPLC analysis (Diacel Chiralpak IA column, 2-propanol:hexane = 10:90, 1.00 mL/min., 237 nm, (R)-isomer 18.89 min., (S)-isomer 22.91 min.).

3.8 References

1. T. Tashima, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3415-3419.
2. H. B. Bürgi, J. D. Dunitz, J. M. Lehn and G. Wipff, *Tetrahedron*, 1974, **30**, 1563-1572.
3. R. Uchida, R. Imasato, K. Shiomi, H. Tomoda and S. Ōmura, *Org. Lett.*, 2005, **7**, 5701-5704.
4. C. Ito, M. Itoigawa, T. Otsuka, H. Tokuda, H. Nishino and H. Furukawa, *J. Nat. Prod.*, 2000, **63**, 1344-1348.
5. E. Christopher, E. Bedir, C. Dunbar, I. A. Khan, C. O. Okunji, B. M. Schuster and M. M. Iwu, *Helv. Chim. Acta*, 2003, **86**, 2914-2918.
6. R. W. Carling, P. D. Leeson, K. W. Moore, J. D. Smith, C. R. Moyes, I. M. Mawer, S. Thomas, T. Chan and R. Baker, *J. Med. Chem.*, 1993, **36**, 3397-3408.
7. H. Hayashi, Y. Miwa, I. Miki, S. Ichikawa, N. Yoda, A. Ishii, M. Kono and F. Suzuki, *J. Med. Chem.*, 1992, **35**, 4893-4902.
8. M. Patel, R. J. McHugh, B. C. Cordova, R. M. Klabe, L. T. Bacheler, S. Erickson-Viitanen and J. D. Rodgers, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1943-1945.
9. U. Hansen, S. Schaus, T. Grant, J. Bishop, J. Kavouris and L. M. Christadore, *Inhibitors of Late SV40 Factor (LSF) as Cancer Chemotherapeutics*, US Pat., 9 597 325 B2, 2017.
10. C. Shao, C. Wang, R. Xu, F. Guan and M. Wei, *Preparation and Anti-hsv-1 Application of Quinolinone Derivatives*, US Pat., 0 028 524 A1, 2018.
11. E. Androphy, G. D. Cuny, J. Cherry and M. A. Glicksman, *Screening Methods for Spinal Muscular Atrophy*, US Pat., 9 212 209 B2, 2015.
12. L. Meiring, J. P. Petzer and A. Petzer, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5498-5502.
13. T. Tashima, H. Murata and H. Kodama, *Biorg. Med. Chem.*, 2014, **22**, 3720-3731.
14. I. L. Chen, J.-J. Chen, Y.-C. Lin, C.-T. Peng, S.-H. Juang and T.-C. Wang, *Eur. J. Med. Chem.*, 2013, **59**, 227-234.

15. C. Kummer, B. G. Petrich, D. M. Rose and M. H. Ginsberg, *J. Biol. Chem.*, 2010, **285**, 9462-9469.
16. M. H. Ginsberg and C. Kummer, *Small Molecule Inhibitors of the α 4-Paxillin Interaction*, WO Pat., 034 896 A2, 2011.
17. R. M. Ransohoff, P. Kivisäkk and G. Kidd, *Nat. Rev. Immunol.*, 2003, **3**, 569.
18. J. S. Smolen and G. Steiner, *Nat. Rev. Drug Discov.*, 2003, **2**, 473.
19. M. Shamma, *The Isoquinoline Alkaloids Chemistry and Pharmacology*, Elsevier, 2012.
20. Y. Aly, A. Galal, L. K. Wong, E. W. Fu, F.-T. Lin, F. K. Duah and P. L. Schiff, *Phytochemistry*, 1989, **28**, 1967-1971.
21. Y.-H. Li, H.-M. Li, Y. Li, J. He, X. Deng, L.-Y. Peng, L.-H. Gao, Q.-S. Zhao, R.-T. Li and X.-D. Wu, *Tetrahedron*, 2014, **70**, 8893-8899.
22. R. Fürst, *Planta Med.*, 2016, **82**, 1389-1394.
23. A. McLachlan, N. Kekre, J. McNulty and S. Pandey, *Apoptosis*, 2005, **10**, 619-630.
24. S. Nadmid, A. Plaza, G. Lauro, R. Garcia, G. Bifulco and R. Müller, *Org. Lett.*, 2014, **16**, 4130-4133.
25. N. Palmer, T. M. Peakman, D. Norton and D. C. Rees, *Org. Biomol. Chem.*, 2016, **14**, 1599-1610.
26. R. K. Morgan, I. Carter-O'Connell and M. S. Cohen, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4770-4773.
27. B.-M. Xi, P.-Z. Ni, Z.-Z. Jiang, D.-Q. Wu, S.-H. Zhang, H.-B. Zhang, T. Wang and W.-H. Chen, *Chem. Biol. Drug Des.*, 2010, **76**, 505-510.
28. M. P. Leese, F. L. Jourdan, M. R. Major, W. Dohle, M. P. Thomas, E. Hamel, E. Ferrandis, M. F. Mahon, S. P. Newman, A. Purohit and B. V. L. Potter, *ChemMedChem*, 2014, **9**, 798-812.
29. P.-P. Kung, E. Rui, S. Bergqvist, P. Bingham, J. Braganza, M. Collins, M. Cui, W. Diehl, D. Dinh, C. Fan, V. R. Fantin, H. J. Gukasyan, W. Hu, B. Huang, S. Kephart, C. Krivacic, R. A. Kumpf, G. Li, K. A. Maegley, I. McAlpine, L. Nguyen, S. Ninkovic, M. Ornelas, M. Ryskin, S. Scales, S. Sutton, J. Tatlock, D. Verhelle, F. Wang, P. Wells, M. Wythes, S. Yamazaki, B. Yip, X. Yu, L. Zehnder, W.-G. Zhang, R. A. Rollins and M. Edwards, *J. Med. Chem.*, 2016, **59**, 8306-8325.
30. P.-P. Kung, P. Bingham, A. Brooun, M. Collins, Y.-L. Deng, D. Dinh, C. Fan, K. S. Gajiwala, R. Grantner, H. J. Gukasyan, W. Hu, B. Huang, R. Kania, S. E.

- Kephart, C. Krivacic, R. A. Kumpf, P. Khamphavong, M. Kraus, W. Liu, K. A. Maegley, L. Nguyen, S. Ren, D. Richter, R. A. Rollins, N. Sach, S. Sharma, J. Sherrill, J. Spangler, A. E. Stewart, S. Sutton, S. Uryu, D. Verhelle, H. Wang, S. Wang, M. Wythes, S. Xin, S. Yamazaki, H. Zhu, J. Zhu, L. Zehnder and M. Edwards, *J. Med. Chem.*, 2018, **61**, 650-665.
31. B. Gabrielsen, T. P. Monath, J. W. Huggins, D. F. Kefauver, G. R. Pettit, G. Groszek, M. Hollingshead, J. J. Kirsi, W. M. Shannon, E. M. Schubert, J. DaRe, B. Ugarkar, M. A. Ussery and M. J. Phelan, *J. Nat. Prod.*, 1992, **55**, 1569-1581.
32. D. M. Floyd, P. Stein, Z. Wang, J. Liu, S. Castro, J. A. Clark, M. Connelly, F. Zhu, G. Holbrook, A. Matheny, M. S. Sigal, J. Min, R. Dhinakaran, S. Krishnan, S. Bashyum, S. Knapp and R. K. Guy, *J. Med. Chem.*, 2016, **59**, 7950-7962.
33. R. B. Mailman, *Dopamine Receptor Ligands with Enhanced Duration of Action*, US Pat., 0 045 486 A1, 2016.
34. H. A. Boulares, C. P. Hans and A. S. Naura, *Regression of Established Atherosclerotic Plaques, and Treating Sudden-Onset Asthma Attacks, using PARP Inhibitors*, US Pat., 0 028 420 A1, 2011.
35. P. Krawczyk, J. A. Aten, R. Kanaar and J. Essers, *Method of Treating Cancer*, US Pat., 0 022 026 A1, 2012.
36. J. Frackenpohl, H.-J. Zeiss, I. Heinemann, L. Willms, T. Müller, M. Busch, P. V. Koskull-Döering, C. H. Rosinger, J. Dittgen and M. J. Hills, *Use of Substituted Isoquinolinones, Isoquinolinediones, Isoquinolinetriones and Dihydroisoquinolinones or in Each Case Salts Thereof as Active Agents Against Abiotic Stress in Plants*, US Pat., 0 302 987 A1, 2014.
37. K. H. Kim and C. W. M. Roberts, *Nat. Med.*, 2016, **22**, 128.
38. J. R. Raymond, M. Hnatowich, R. J. Lefkowitz and M. G. Caron, *Hypertension*, 1990, **15**, 119-131.
39. G. Graziani and C. Szabó, *Pharmacol. Res.*, 2005, **52**, 109-118.
40. D. Zhou, J. L. Gross, A. B. Adedoyin, S. B. Aschmies, J. Brennan, M. Bowlby, L. Di, K. Kubek, B. J. Platt, Z. Wang, G. Zhang, N. Brandon, T. A. Comery and A. J. Robichaud, *J. Med. Chem.*, 2012, **55**, 2452-2468.
41. J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669-1730.
42. V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157-7259.
43. H. He, B. Shen and G. T. Carter, *Tetrahedron Lett.*, 2000, **41**, 2067-2071.

44. W. Wei, P. Sun, S. Yang, L. Kang and Q. Li, *Indole Alkaloid, and Preparation Method and Application Thereof*, CN Pat., 107 098 905 A, 2017.
45. A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan and T. Fukuyama, *J. Am. Chem. Soc.*, 2002, **124**, 6552-6554.
46. H. Minami, E. Dubouzet, K. Iwasa and F. Sato, *J. Biol. Chem.*, 2007, **282**, 6274-6282.
47. Y. Kashiwada, A. Aoshima, Y. Ikeshiro, Y.-P. Chen, H. Furukawa, M. Itoigawa, T. Fujioka, K. Mihashi, L. M. Cosentino, S. L. Morris-Natschke and K.-H. Lee, *Biorg. Med. Chem.*, 2005, **13**, 443-448.
48. A. Padwa and M. D. Danca, *Org. Lett.*, 2002, **4**, 715-717.
49. E. R. Correché, S. A. Andujar, R. R. Kurdelas, M. J. G. Lechón, M. L. Freile and R. D. Enriz, *Biorg. Med. Chem.*, 2008, **16**, 3641-3651.
50. A. Couture, E. Deniau, S. Lebrun and P. Grandclaudeon, *J. Chem. Soc., Perkin Trans. 1*, 1999, 789-794.
51. S. Liu, B. F. Molino and K. Nacro, *Aryl, Heteroaryl, and Heterocycle Substituted Tetrahydroisoquinolines and Use Thereof*, US Pat., 9 034 899 B2, 2010.
52. I. Sato, T. Kamikubo, M. Miura, Y. Matsushima, H. Tanaka, Y. Shiina, S. Yamaki, T. Saito, H. Kiyohara, M. Ohe, K. Mihara, B. P. Morgan, F. Malik, S. E. Collibee, L. Ashcraft, P.-P. Lu, J. M. Warrington and M. Garard, *Tetrahydroisoquinoline Derivatives*, US Pat., 9 914 741 B2, 2018.
53. R. N. Brogden, R. C. Heel, T. M. Speight and G. S. Avery, *Drugs*, 1979, **18**, 1-24.
54. P. A. Dandridge, C. Kaiser, M. Brenner, D. Gaitanopoulos, L. D. Davis, R. L. Webb, J. J. Foley and H. M. Sarau, *J. Med. Chem.*, 1984, **27**, 28-35.
55. H. Anan, A. Tanaka, R. Tsuzuki, M. Yokota, T. Yatsu, K. Honda, M. Asano, S. Fujita, T. Furuya and T. Fujikura, *Chem. Pharm. Bull.*, 1991, **39**, 2910-2914.
56. H. Anan, A. Tanaka, R. Tsuzuki, M. Yokota, T. Yatsu and T. Fujikura, *Chem. Pharm. Bull.*, 1996, **44**, 1865-1870.
57. S. Liu, C. Zha, K. Nacro, M. Hu, W. Cui, Y.-L. Yang, U. Bhatt, A. Sambandam, M. Isherwood and L. Yet, *ACS Med. Chem. Lett.*, 2014, **5**, 760-765.
58. A. Rheiner, *Substituted 4-Phenyl Isoquinolines*, US Pat., 3 947 456 A, 1976.
59. A. D. Pechulis, J. P. Beck, M. A. Curry, M. A. Wolf, A. E. Harms, N. Xi, C. Opalka, M. P. Sweet, Z. Yang, A. S. Vellekoop, A. M. Klos, P. J. Crocker, C. Hassler, M. Laws, D. B. Kitchen, M. A. Smith, R. E. Olson, S. Liu and B. F. Molino, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7219-7222.

60. B. Molino, B. Berkowitz and M. Cohen, *4-Phenyl Substituted Tetrahydroisoquinolines and Use Thereof to Block Reuptake of Norepinephrine, Dopamine and Serotonin*, US Pat., 0 111 393 A1, 2006.
61. C. A. Grice, M. A. Letavic, A. Santillan and K. L. Schwarz, *Tetrahydroisoquinoline Compounds as Modulators of the Histamine H3 Receptor*, US Pat., 0 099 158 A1, 2009.
62. N. I. Carruthers, L. A. Gomez, J. A. Jablonowski, J. M. Keith, M. A. Letavic, K. S. Ly, J. M. B. Miller, E. M. Stocking and R. L. Wolin, *Tetrahydroisoquinoline Compounds for Treatment of CNS Disorders*, WO Pat., 066 197 A1, 2006.
63. U. Heinelt, H.-J. Lang, K. Wirth, T. Licher and A. Hofmeister, *Substituted 4-Phenyltetrahydroisoquinolines, Methods for Producing Them, Their Use as Drug, and Drug Containing Them*, WO Pat., 074 813 A1, 2006.
64. D. E. Frail, S. P. Arneric, D. G. Wishka, E. H. F. Wong and J. P. Beck, *The Use of 4-Phenyl Substituted Tetrahydroisoquinolines in the Treatment of Pain, Migraine and Urinary Incontinence*, WO Pat., 050 629 A2, 2004.
65. G. Grethe and M. R. Uskokovic, *4-Phenyl Isoquinolines and Process for Preparing Same*, US Pat., 3 666 763 A, 1972.
66. C. B. Ivanov, N. S. Ivanova, V. D. Paskov, L. D. Daleva, D. M. Mondeshka, N. D. Berova, R. S. Rakovska, D. N. Tosheva, H. Y. Zaykov, Y. N. Nissimov, V. L. Orachev, R. N. Nacheva, C. N. Tancheva, I. G. Angelova, S. E. Boyadjiev, G. M. Mechkov, B. K. Dimitrov, V. K. Matov and Z. D. Gendjev, *4-Phenyl-1,2,3,4-tetrahydroisoquinolins as Ulcer Agents*, EP Pat., 0 314 828 B1, 1991.
67. Y. Besidski and A. Claesson, *Phenyl-1,2, 3,4-Tetrahydroisoquinolinone Derivatives and Their Use in the Treatment of a Pain Disorder*, WO Pat., 005 459 A1, 2009.
68. C. Wei, V. W. Rosso and Q. Gao, *Crystalline Forms of (S)-7-([1,2,4]Triazolo[1,5-a]pyridin-6-yl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline and Use Thereof*, EP Pat. 2 429 293 B1, 2010.
69. B. F. Molino, S. Liu, B. A. Berkowitz, P. R. Guzzo, J. P. Beck and M. Cohen, *Aryl- and Heteroaryl-Substituted Tetrahydroisoquinolines and Use Thereof to Block Reuptake of Norepinephrine, Dopamine, and Serotonin*, WO Pat., 020 049 A2, 2006.
70. A. Rheiner, *Antidepressant 4-Phenyl-tetrahydroquinolines*, CH Pat., 538 477 A, 1970.

71. F. Gonzalez-Bobes, D. A. Conlon, P. C. Lobben, J. L. Burt, J. Engstrom, J. J. Zhu and Y. Fan, *Processes for Preparing Tetrahydroisoquinolines*, US Pat., 0 022 675 A1, 2016.
72. B. Habibi, J. P. Cartron, M. Bretagne, P. Rouger and C. Salmon, *Vox Sang.*, 1981, **40**, 79-84.
73. I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fourasté and C. Moulis, *Phytochemistry*, 1999, **51**, 1167-1169.
74. O. B. Wallace, K. S. Lauwers, S. A. Jones and J. A. Dodge, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1907-1910.
75. M. M. Ghorab, F. A. Ragab and M. M. Hamed, *Eur. J. Med. Chem.*, 2009, **44**, 4211-4217.
76. J.-C. Castillo, E. Jiménez, J. Portilla, B. Insuasty, J. Quiroga, R. Moreno-Fuquen, A. R. Kennedy and R. Abonia, *Tetrahedron*, 2018, **74**, 932-947.
77. S. Chander, P. Ashok, Y.-T. Zheng, P. Wang, K. S. Raja, A. Taneja and S. Murugesan, *Bioorg. Chem.*, 2016, **64**, 66-73.
78. P. Lei, X. Zhang, Y. Xu, G. Xu, X. Liu, X. Yang, X. Zhang and Y. Ling, *Chem. Cent. J.*, 2016, **10**, 40.
79. E. Ramesh, R. D. R. S. Manian, R. Raghunathan, S. Sainath and M. Raghunathan, *Biorg. Med. Chem.*, 2009, **17**, 660-666.
80. M. R. Barbachyn, G. L. Bundy, P. J. Dobrowolski, A. R. Hurd, G. E. Martin, D. J. McNamara, J. R. Palmer, D. L. Romero, A. G. Romero, J. C. Ruble, D. A. Sherry, L. M. Thomasco and P. L. Toogood, *Tricyclic Tetrahydroquinoline Antibacterial Agents*, US Pat., 7 208 490 B2, 2007.
81. L. Nallan, K. D. Bauer, P. Bendale, K. Rivas, K. Yokoyama, C. P. Hornéy, P. R. Pendyala, D. Floyd, L. J. Lombardo, D. K. Williams, A. Hamilton, S. Sebti, W. T. Windsor, P. C. Weber, F. S. Buckner, D. Chakrabarti, M. H. Gelb and W. C. Van Voorhis, *J. Med. Chem.*, 2005, **48**, 3704-3713.
82. N. A. Powell, F. L. Ciske, C. Cai, D. D. Holsworth, K. Mennen, C. A. Van Huis, M. Jalaie, J. Day, M. Mastronardi, P. McConnell, I. Mochalkin, E. Zhang, M. J. Ryan, J. Bryant, W. Collard, S. Ferreira, C. Gu, R. Collins and J. J. Edmunds, *Biorg. Med. Chem.*, 2007, **15**, 5912-5949.
83. T. A. Smirnova, M. Y. Gavrillov, F. Y. Nazmetdinov, V. É. Kolla and M. E. Kon'shin, *Pharm. Chem. J.*, 1999, **33**, 370-371.
84. G. S. Sidhu, G. Thyagarajan and S. H. Zaheer, *Nature*, 1962, **193**, 692-692.

85. T. Asberom, T. A. Bara, J. W. Clader, W. J. Greenlee, H. S. Guzik, H. B. Josien, W. Li, E. M. Parker, D. A. Pissarnitski, L. Song, L. Zhang and Z. Zhao, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 205-207.
86. Y. A. Rodríguez, M. Gutiérrez, D. Ramírez, J. Alzate-Morales, C. C. Bernal, F. M. Güiza and A. R. Romero Bohórquez, *Chem. Biol. Drug Des.*, 2016, **88**, 498-510.
87. J. Katzenellenbogen, J. Josan, J. Norris and D. P. McDonnell, *Androgen Receptor Ligands*, WO Pat., 059 401 A2, 2017.
88. J. Zhou, L. Robinson, N. Gubernator, E. Saiah, X. Bai and X. Gu, *Tetrahydroquinoline Derivatives as Antithrombotic Agents*, WO Pat., 015 715 A2 2003.
89. H. Koutnikova, C. Marsol, M. Sierra, E. Klotz, A. Braun-Egles and J. Lehmann, *Tetrahydroquinolines as Agonists of Liver- X Receptors*, WO Pat., 072 041 A1, 2004.
90. M. L. Quan, C. Wang, J. Zhou, J. J. Hangeland, D. A. Seiffert and R. M. Knabb *Tetrahydroquinoline Derivatives Useful As Serine Protease Inhibitors*, WO Pat., 080 971 A1, 2004.
91. W. Englberger, M. Przewosny and K. Schiene, *Production of Tetrahydrochinolinbenzofuranen*, DE Pat., 10 304 950, 2004.
92. M. Gerlach, M. Przewosny, W. Englberger, E. Reissmüller, P. Bloms-Funke, C. Maul and U.-P. Jagusch, *Substituted 1,2,3,4-Tetrahydroquinoline-2-carboxylic acid Derivatives*, WO Pat., 058 875 A2, 2001.
93. D. J. Hlasta, *Antidepressant 2-(4,5-Dihydro-1H-imidazolyl)-dihydro-1H-indoles, -1,2,3,4-Tetrahydroquinolines and -1H-Indoles, and Methods of Use Thereas*, US Pat. 5 017 584 A, 1991.
94. J. Tian, L. Li, X. Yan and L. Chen, *J. Heterocycl. Chem.*, 2014, **51**, 1811-1813.
95. K. Y. Koltunov, G. K. S. Prakash, G. Rasul and G. A. Olah, *Heterocycles*, 2004, **62**, 757-772.
96. K. Li, L. N. Foresee and J. A. Tunge, *J. Org. Chem.*, 2005, **70**, 2881-2883.
97. G. Binot and S. Z. Zard, *Tetrahedron Lett.*, 2005, **46**, 7503-7506.
98. K. L. Turner, T. M. Baker, S. Islam, D. J. Procter and M. Stefaniak, *Org. Lett.*, 2006, **8**, 329-332.
99. P. J. Manley and M. T. Bilodeau, *Org. Lett.*, 2004, **6**, 2433-2435.
100. C. Dong and H. Alper, *Tetrahedron: Asymmetry*, 2004, **15**, 35-40.

101. J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2014, **53**, 4945-4949.
102. M. Guan, Y. Pang, J. Zhang and Y. Zhao, *Chem. Commun.*, 2016, **52**, 7043-7046.
103. M. Harmata and X. Hong, *Org. Lett.*, 2007, **9**, 2701-2704.
104. D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2004, **69**, 6772-6780.
105. K.-i. Fujita, Y. Takahashi, M. Owaki, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2004, **6**, 2785-2788.
106. J. Horn, H. Y. Li, S. P. Marsden, A. Nelson, R. J. Shearer, A. J. Campbell, D. House and G. G. Weingarten, *Tetrahedron*, 2009, **65**, 9002-9007.
107. B. Li, Y. Park and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 1125-1131.
108. L. Zhang, L. Sonaglia, J. Stacey and M. Lautens, *Org. Lett.*, 2013, **15**, 2128-2131.
109. H.-Z. Xiao, W.-S. Wang, Y.-S. Sun, H. Luo, B.-W. Li, X.-D. Wang, W.-L. Lin and F.-X. Luo, *Org. Lett.*, 2019, **21**, 1668-1671.
110. Z. Shi, M. Boultadakis-Arapinis and F. Glorius, *Chem. Commun.*, 2013, **49**, 6489-6491.
111. H. Abas, M. M. Amer, O. Olaizola and J. Clayden, *Org. Lett.*, 2019, **21**, 1908-1911.
112. M. M. Amer, A. C. Carrasco, D. J. Leonard, J. W. Ward and J. Clayden, *Org. Lett.*, 2018, **20**, 7977-7981.
113. G. A. Ardizzoia, E. M. Beccalli, E. Borsini, S. Brenna, G. Brogini and M. Rigamonti, *Eur. J. Org. Chem.*, 2008, **2008**, 5590-5596.
114. S. Cui, Y. Zhang and Q. Wu, *Chem. Sci.*, 2013, **4**, 3421-3426.
115. X. Yu, K. Chen, Q. Wang, W. Zhang and J. Zhu, *Org. Chem. Front.*, 2018, **5**, 994-997.
116. Q. Tang, D. Xia, X. Jin, Q. Zhang, X.-Q. Sun and C. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 4628-4631.
117. V. A. Glushkov and Y. V. Shklyayev, *Chem. Heterocycl. Compd.*, 2001, **37**, 663-687.
118. R. Arora, R. Bala, P. Kumari, S. Sood, A. N. Yadav, N. Singh and K. Singh, *Lett. Org. Chem.*, 2018, **15**, 606-613.
119. R. Arora, R. Bala, P. Kumari, S. Sood, V. Kumar, N. Singh and K. Singh, *Curr. Bioact. Compd.*, 2018, **14**, 428-433.
120. B. Mújde, S. Özcan and M. Balci, *Phytochem. Lett.*, 2011, **4**, 407-410.

121. C. Abate, S. V. Selivanova, A. Müller, S. D. Krämer, R. Schibli, R. Marottoli, R. Perrone, F. Berardi, M. Niso and S. M. Ametamey, *Eur. J. Med. Chem.*, 2013, **69**, 920-930.
122. E. Beckmann, *Ber. Dtsch. Chem. Ges.*, 1886, **19**, 988-993.
123. M. B. Smith and J. March, *March's advanced organic chemistry: reactions, mechanisms, and structure*, John Wiley & Sons, 6th edn., 2007.
124. P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Wiley Online Library, 1999.
125. P. T. Lansbury and N. R. Mancuso, *J. Am. Chem. Soc.*, 1966, **88**, 1205-1212.
126. M. Arisawa and M. Yamaguchi, *Org. Lett.*, 2001, **3**, 311-312.
127. Z. Wang, *Comprehensive Organic Name Reactions and Reagents*, Wiley, 2009.
128. T. A. D. Holth, O. E. Hutt and G. I. Georg, *Molecular Rearrangements in Organic Synthesis*, 2015.
129. R. E. Gawley, *Org. React.*, 1988, **35**, 1-420.
130. Y. Torisawa, T. Nishi and J.-i. Minamikawa, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 387-390.
131. B. S. Lee, S. Y. Chu, I. Y. Lee, B. S. Lee, J. U. Song and D. Y. Ji, *Bull. Korean Chem. Soc.*, 2000, **21**, 860-866.
132. E. E. Smissman, J. R. Reid, D. A. Walsh and R. T. Borchardt, *J. Med. Chem.*, 1976, **19**, 127-131.
133. Y. Torisawa, T. Nishi and J.-i. Minamikawa, *Bioorg. Med. Chem.*, 2003, **11**, 2205-2209.
134. Y. Torisawa, S. Aki and J.-i. Minamikawa, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 453-455.
135. Y. Torisawa, T. Nishi and J.-i. Minamikawa, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 448-452.
136. P. Kerby, PhD thesis, University of Warwick, 2016.
137. K. F. Schmidt, *Ber. Dtsch. Chem. Ges.*, 1924, **57**, 704-706.
138. P. A. S. Smith and E. P. Antoniadis, *Tetrahedron*, 1960, **9**, 210-229.
139. H. Wolff, *Org. React.*, 1946, **3**, 307-336.
140. Y. Chen, B. Liu, X. Liu, Y. Yang, Y. Ling and Y. Jia, *Org. Process Res. Dev.*, 2014, **18**, 1589-1592.
141. I. T. Crosby, J. K. Shin and B. Capuano, *Aust. J. Chem.*, 2010, **63**, 211-226.
142. R. T. Conley, *J. Org. Chem.*, 1958, **23**, 1330-1333.
143. M. Tomita, S. Minami and S. Uyeo, *J. Chem. Soc. C.*, 1969, 183-188.

144. D. Evans and I. M. Lockhart, *J. Chem. Soc.*, 1965, 4806-4812.
145. L. López, J. Selent, R. Ortega, C. F. Masaguer, E. Domínguez, F. Areias, J. Brea, M. I. Loza, F. Sanz and M. Pastor, *ChemMedChem*, 2010, **5**, 1300-1317.
146. R. Ortega, E. Raviña, C. F. Masaguer, F. Areias, J. Brea, M. I. Loza, L. López, J. Selent, M. Pastor and F. Sanz, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1773-1778.
147. E. J. Moriconi and M. A. Stemniski, *J. Org. Chem.*, 1972, **37**, 2035-2039.
148. H. J. Schmid, A. Hunger and K. Hoffmann, *Helv. Chim. Acta*, 1956, **39**, 607-618.
149. C. L. Arcus, M. M. Coombs and J. V. Evans, *J. Chem. Soc.*, 1956, 1498-1506.
150. S. Minami, M. Tomita, H. Takamatsu and S. Uyeo, *Chem. Pharm. Bull.*, 1965, **13**, 1084-1091.
151. G. S. D. Sharma and S. V. Eswaran, *Resonance*, 1997, **2**, 73-75.
152. P. A. S. Smith, *J. Am. Chem. Soc.*, 1948, **70**, 320-323.
153. R. D. Westland and W. E. McEwen, *J. Am. Chem. Soc.*, 1952, **74**, 6141-6142.
154. G. I. Georg, X. Guan and J. Kant, *Tetrahedron Lett.*, 1988, **29**, 403-406.
155. T. Sasaki, S. Eguchi and T. Toru, *J. Org. Chem.*, 1971, **36**, 2454-2457.
156. T. Sasaki, S. Eguchi and T. Toru, *J. Org. Chem.*, 1970, **35**, 4109-4114.
157. N. Gálvez, M. Moreno-Mañas, R. M. Sebastián and A. Vallribera, *Tetrahedron*, 1996, **52**, 1609-1616.
158. C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165-195.
159. L. P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 96-103.
160. Y. Sakakida, A. S. Kumanireng, H. Kawamoto and A. Yokoo, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 478-480.
161. H. F. Motiwala, M. Charaschanya, V. W. Day and J. Aubé, *J. Org. Chem.*, 2016, **81**, 1593-1609.
162. A. Siddiqui, K. V. Rao, A. I. Venkatesham and U. M. Rao, *Acta Cienc. Indica*, 1990, **16**, 7-12.
163. M. S. Ahmad and Z. Alam, *ChemInform*, 1989, **20**.
164. A. H. Siddiqui, M. N. Afzal, M. H. Baig, G. V. Lingam and N. S. Rao, *ChemInform*, 1985, **16**.
165. H. Singh, R. K. Malhotra and V. V. Parashar, *Tetrahedron Lett.*, 1973, **14**, 2587-2588.
166. G. I. Koldobskii, V. A. Ostrovskii and B. Z. Gidasov, *Chem. Heterocycl. Compd.*, 1975, **11**, 626-635.
167. S. J. Wittenberger, *Org. Prep. Proced. Int.*, 1994, **26**, 499-531.
168. R. Fusco, L. Garanti and G. Zecchi, *J. Org. Chem.*, 1975, **40**, 1906-1909.

169. P. Gandeepan, P. Rajamalli and C.-H. Cheng, *Synthesis*, 2016, **48**, 1872-1879.
170. S. Wehle, A. Espargaró, R. Sabaté and M. Decker, *Tetrahedron*, 2016, **72**, 2535-2543.
171. O. A. Rakitin, C. W. Rees, D. J. Williams and T. Torroba, *J. Org. Chem.*, 1996, **61**, 9178-9185.
172. D. J. Cram, *J. Am. Chem. Soc.*, 1949, **71**, 3863-3870.
173. W. E. Bachmann and J. W. Ferguson, *J. Am. Chem. Soc.*, 1934, **56**, 2081-2084.
174. K. B. Wiberg, B. A. Hess and A. J. Ashe, *In Carbonium Ions*, Olah, G. A., Schleyer, P. v. R., Eds., Wiley-Interscience: New York, 1972.
175. G. Wagner, *Phys. Chem. Soc.*, 1899, **31**, 690.
176. H. Meerwein, *Justus Liebigs Ann. Chem.*, 1914, **405**, 129-175.
177. C. G. Kim, I. Y. Lee, J. G. Kim and I. C. Lee, *Bull. Korean Chem. Soc.*, 2000, **21**, 477-482.
178. T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581-581.
179. R. F. Heck and J. P. Nolley, *J. Org. Chem.*, 1972, **37**, 2320-2322.
180. L. E. Overman, *Pure Appl. Chem.*, 1994, **66**, 1423-1430.
181. D. L. Comins, M. F. Baevsky and H. Hong, *J. Am. Chem. Soc.*, 1992, **114**, 10971-10972.
182. K. Kagechika and M. Shibasaki, *J. Org. Chem.*, 1991, **56**, 4093-4094.
183. A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945-2964.
184. R. Grüber and P. Fleurat-Lessard, *Organometallics*, 2014, **33**, 1996-2003.
185. C. Amatore and A. Jutand, *J. Organomet. Chem.*, 1999, **576**, 254-278.
186. I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009-3066.
187. W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2-7.
188. F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 1417-1419.
189. W. Cabri, I. Candiani, S. DeBernardinis, F. Francalanci, S. Penco and R. Santo, *J. Org. Chem.*, 1991, **56**, 5796-5800.
190. J. McConathy and M. J. Owens, *Prim. Care Companion J. Clin. Psychiatry*, 2003, **5**, 70-73.
191. P. H. Gore and I. M. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2779-2781.
192. V. Balasubramaniyan, *Chem. Rev.*, 1966, **66**, 567-641.
193. E. A. Dixon, A. Fischer and F. P. Robinson, *Can. J. Chem.*, 1981, **59**, 2629-2641.
194. J. L. Wiley, V. J. Smith, J. Chen, B. R. Martin and J. W. Huffman, *Biorg. Med. Chem.*, 2012, **20**, 2067-2081.
195. W. He, X. Sun and A. J. Frontier, *J. Am. Chem. Soc.*, 2003, **125**, 14278-14279.

196. S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 288-290.
197. B. Herberich, M. Kinugawa, A. Vazquez and R. M. Williams, *Tetrahedron Lett.*, 2001, **42**, 543-546.
198. T. Morimoto, N. Suzuki and K. Achiwa, *Tetrahedron: Asymmetry*, 1998, **9**, 183-187.
199. S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350-2353.
200. L. Pan, R. Chen, D. Ni, L. Xia and X. Chen, *Synlett*, 2013, **24**, 241-245.
201. J.-Y. Min and G. Kim, *J. Org. Chem.*, 2014, **79**, 1444-1448.
202. V. S. Moshkin and V. Y. Sosnovskikh, *Tetrahedron Lett.*, 2013, **54**, 2699-2702.
203. S. G. Davies, A. M. Fletcher, A. B. Frost, M. S. Kennedy, P. M. Roberts and J. E. Thomson, *Tetrahedron*, 2016, **72**, 2139-2163.
204. K. N. Singh, P. Singh, P. Singh and Y. S. Deol, *Org. Lett.*, 2012, **14**, 2202-2205.
205. J. Magano and J. R. Dunetz, *Org. Process Res. Dev.*, 2012, **16**, 1156-1184.
206. P.-Q. Huang, B.-G. Wei and Y.-P. Ruan, *Synlett*, 2003, **2003**, 1663-1667.
207. D. J. Sall and G. L. Grunewald, *J. Med. Chem.*, 1987, **30**, 2208-2216.
208. J. A. Seijas, M. P. Vázquez-Tato, M. M. Martínez and M. G. Pizzolatti, *Tetrahedron Lett.*, 2005, **46**, 5827-5830.
209. H. C. Brown and P. Heim, *J. Org. Chem.*, 1973, **38**, 912-916.
210. S. Krishnamurthy, *Tetrahedron Lett.*, 1982, **23**, 3315-3318.
211. N. Yamazaki, M. Atobe and C. Kibayashi, *Tetrahedron Lett.*, 2001, **42**, 5029-5032.
212. A. Giannis and K. Sandhoff, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 218-220.
213. B. Ravinder, S. Rajeswar Reddy, A. Panasa Reddy and R. Bandichhor, *Tetrahedron Lett.*, 2013, **54**, 4908-4913.
214. P.-Q. Huang and H. Geng, *Org. Chem. Front.*, 2015, **2**, 150-158.
215. S.-H. Xiang, J. Xu, H.-Q. Yuan and P.-Q. Huang, *Synlett*, 2010, **2010**, 1829-1832.
216. A. E. Finholt, A. C. Bond and H. I. Schlesinger, *J. Am. Chem. Soc.*, 1947, **69**, 1199-1203.
217. S. Schunk, M. Reich, M. Engels, T. Germann, R. Jostock and S. Hees, *Spiro Group-Containing Amide Compounds Having Bradykinin 1 Receptor (B1R) Activity*, US Pat., 8 357 717 B2, 2013.
218. C. Cherpillod and L. M. O. Omer, *J. Int. Med. Res.*, 1981, **9**, 324-329.
219. L. M. Omer, *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 1982, **20**, 320-326.

220. J. Culig, R. S. Ehsanullah, C. Hallett, A. Iliopoulou, I. Matheson and P. Turner, *Br. J. Clin. Pharmacol.*, 1983, **15**, 537-543.
221. H. H. Keller, R. Schaffner, M. O. Carruba, W. P. Burkard, M. Pieri, E. P. Bonetti, R. Scherschlicht, M. Da Prada and W. E. Haefely, *Adv. Biochem. Psychopharmacol.*, 1982, **31**, 249-263.
222. G. Di Renzo, S. Amoroso, M. Tagliatela, L. M. T. Canzoniero, P. Maida, G. Lombardi and L. Annunziato, *Life Sci.*, 1988, **42**, 2161-2169.
223. S. Gasić, A. Korn and H. G. Eichler, *Clin. Pharmacol. Ther.*, 1986, **39**, 582-585.
224. P. H. Andersen, *Eur. J. Pharmacol.*, 1989, **166**, 493-504.
225. D. Luethi, M. C. Hoener and M. E. Liechti, *Eur. J. Pharmacol.*, 2018, **819**, 242-247.
226. R. J. Lamb and R. R. Griffiths, *Psychopharmacology*, 1990, **102**, 183-190.
227. A. M. Sahai, C. Davidson, N. Dutta and J. Opacka-Juffry, *Brain Sci.*, 2018, **8**, 63.
228. W. Eschweiler, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 880-882.
229. H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 1933, **55**, 4571-4587.
230. B. Gröll, P. Schaaf and M. Schnürch, *Monatsh. Chem.*, 2017, **148**, 91-104.
231. G. Bobowski, J. M. Gottlieb and B. West, *J. Heterocycl. Chem.*, 1980, **17**, 1563-1568.
232. S. K. Choudhury, P. Rout, B. B. Parida, J.-C. Florent, L. Johannes, G. Phaomei, E. Bertounesque and L. Rout, *Eur. J. Org. Chem.*, 2017, **2017**, 5275-5292.
233. J. P. Yardley, G. E. M. Husbands, G. Stack, J. Butch, J. Bicksler, J. A. Moyer, E. A. Muth, T. Andree and H. Fletcher, *J. Med. Chem.*, 1990, **33**, 2899-2905.
234. E. Farkas and C. J. Sunman, *J. Org. Chem.*, 1985, **50**, 1110-1112.
235. F. A. Carey and R. J. Sundberg, in *Part B: Reactions and Synthesis*, eds. F. A. Carey and R. J. Sundberg, Springer Berlin Heidelberg, Berlin, Heidelberg, 2001, pp. 57-139.
236. J. J. Li, D. S. Johnson, D. R. Sliskovic and B. D. Roth, *Contemporary Drug Synthesis*, John Wiley & Sons, 2004.
237. V. Von Richter, A. Würtz, A. Borodin and R. Kane, *Ber. Dtsch. Chem. Ges.*, 1869, **2**, 552.
238. A. Wurtz, *Bull. Soc. Chim. Fr.*, 1872, **17**, 426-442.
239. A. P. Prakasham, A. K. Saxena, S. Luqman, D. Chanda, T. Kaur, A. Gupta, D. K. Yadav, C. S. Chanotiya, K. Shanker, F. Khan and A. S. Negi, *Biorg. Med. Chem.*, 2012, **20**, 3049-3057.

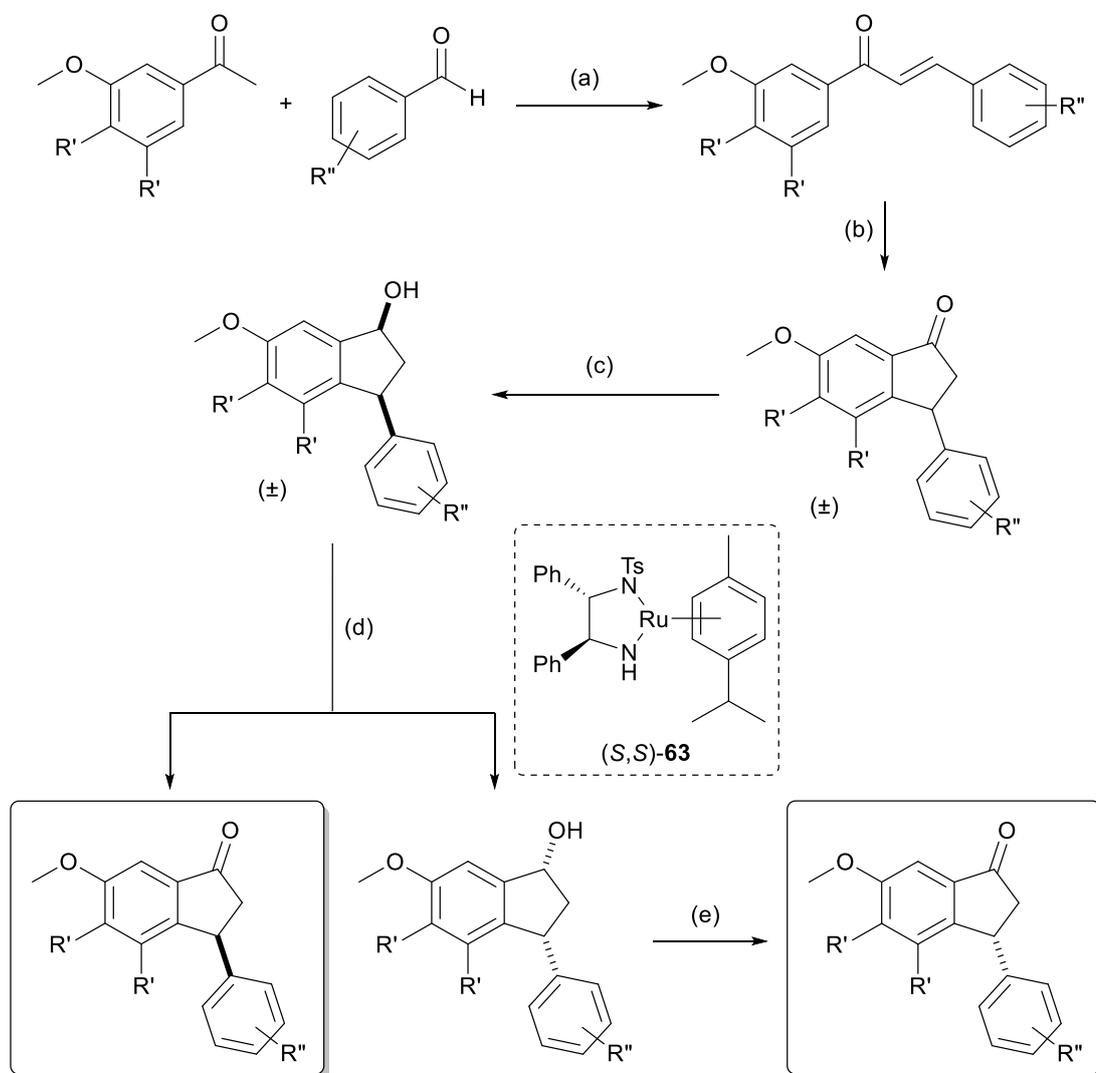
240. A. Singh, K. Fatima, A. Singh, A. Behl, M. J. Minto, M. Hasanain, R. Ashraf, S. Luqman, K. Shanker, D. M. Mondhe, J. Sarkar, D. Chanda and A. S. Negi, *Eur. J. Pharm. Sci.*, 2015, **76**, 57-67.
241. D. Chanda, S. Bhushan, S. K. Guru, K. Shanker, Z. A. Wani, B. A. Rah, S. Luqman, D. M. Mondhe, A. Pal and A. S. Negi, *Eur. J. Pharm. Sci.*, 2012, **47**, 988-995.
242. L. Huang, H. Miao, Y. Sun, F. Meng and X. Li, *Eur. J. Med. Chem.*, 2014, **87**, 429-439.
243. S. A. Patil, R. Patil and S. A. Patil, *Eur. J. Med. Chem.*, 2017, **138**, 182-198.
244. W. L. F. Armarego and C. L. L. Chai, in *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann, Oxford, 2009, pp. 1-60.
245. G. P. Moss, *Pure Appl. Chem.*, 1998, **70**, 143-216.
246. R. S. Cahn, C. Ingold and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, **5**, 385-415.
247. P. G. M. Wuts and T. W. Greene, in *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., 2006, ch. 4, pp. 431-532.
248. H. Zhao, C. P. Vandebossche, S. G. Koenig, S. P. Singh and R. P. Bakale, *Org. Lett.*, 2008, **10**, 505-507.
249. H. Kurouchi, A. Sumita, Y. Otani and T. Ohwada, *Chem. Eur. J.*, 2014, **20**, 8682-8690.
250. J. O. Park and S. W. Youn, *Org. Lett.*, 2010, **12**, 2258-2261.
251. S. Choi, A. N. Calder, E. H. Miller, K. P. Anderson, D. K. Fiejtek, A. Rietz, H. Li, J. J. Cherry, K. M. Quist, X. Xing, M. A. Glicksman, G. D. Cuny, C. L. Lorson, E. A. Androphy and K. J. Hodgetts, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 5144-5148.
252. P. S. Ab, A. S. Mats, K. Annika, L. Öhberg, H. Katharina, H. Andreas, H. Jesper, E. Maria, B. Johan and N. Johan, *Bis(sulfonamide) derivatives and their use as mPGES inhibitors*, US Pat., 0 002 278 A1, 2018.
253. R. J. Faggyas, M. Grace, L. Williams and A. Sutherland, *J. Org. Chem.*, 2018, **83**, 12595-12608.
254. E. F. M. Stephenson, *J. Chem. Soc.*, 1956, 2557-2558.
255. M. D. Wodrich, B. Ye, J. F. Gonthier, C. Corminboeuf and N. Cramer, *Chem. Eur. J.*, 2014, **20**, 15409-15418.
256. X. Yang, X. Jin and C. Wang, *Adv. Synth. Catal.*, 2016, **358**, 2436-2442.

257. K. Hyodo, G. Hasegawa, N. Oishi, K. Kuroda and K. Uchida, *J. Org. Chem.*, 2018, **83**, 13080-13087.
258. W. Mazumdar, N. Jana, B. T. Thurman, D. J. Wink and T. G. Driver, *J. Am. Chem. Soc.*, 2017, **139**, 5031-5034.
259. X.-F. Wang, F. Guan, E. Ohkoshi, W. Guo, L. Wang, D.-Q. Zhu, S.-B. Wang, L.-T. Wang, E. Hamel, D. Yang, L. Li, K. Qian, S. L. Morris-Natschke, S. Yuan, K.-H. Lee and L. Xie, *J. Med. Chem.*, 2014, **57**, 1390-1402.
260. S. O'Sullivan, E. Doni, T. Tuttle and J. A. Murphy, *Angew. Chem. Int. Ed.*, 2014, **53**, 474-478.
261. D. Koszelewski, M. Cwiklak and R. Ostaszewski, *Tetrahedron: Asymmetry*, 2012, **23**, 1256-1261.
262. L. C. Finney, L. J. Mitchell and C. J. Moody, *Green Chem.*, 2018, **20**, 2242-2249.
263. A. P. Venkov and D. M. Vodenicharov, *Synthesis*, 1990, **1990**, 253-255.
264. W. J. Houlihan, M. J. Shapiro and J. A. Chin, *J. Org. Chem.*, 1997, **62**, 1529-1531.
265. R. Bansal, G. Narang, C. Zimmer and R. W. Hartmann, *Med. Chem. Res.*, 2011, **20**, 661-669.
266. T. M. Kadayat, S. Banskota, P. Gurung, G. Bist, T. B. Thapa Magar, A. Shrestha, J.-A. Kim and E.-S. Lee, *Eur. J. Med. Chem.*, 2017, **137**, 575-597.
267. F. Bigi, S. Carloni, L. Ferrari, R. Maggi, A. Mazzacani and G. Sartori, *Tetrahedron Lett.*, 2001, **42**, 5203-5205.
268. E. Fillion, A. M. Dumas and S. A. Hogg, *J. Org. Chem.*, 2006, **71**, 9899-9902.
269. W.-J. Hao, B. Jiang, S.-J. Tu, S.-S. Wu, Z.-G. Han, X.-D. Cao, X.-H. Zhang, S. Yan and F. Shi, *J. Comb. Chem.*, 2009, **11**, 310-314.

4.0 Conclusions and Future Work

4.1 Conclusions

Chiral 3-aryl-indan-1-ones are of huge biological importance, often occurring as the primary pharmacophore of a wide array of drugs and natural products. The majority of compounds that have been shown to exhibit beneficial medicinal properties were only reported as racemates (see **Section 1.1**). As such, a convenient and effective method for the resolution of these racemic molecules is highly beneficial. To this end, Chapter 2 presented a simple and effective five-step process that affords the individual enantiomers of 3-aryl-indan-1-ones in excellent enantiomeric excess from commercially available acetophenones and benzaldehydes (Scheme 50).



Scheme 50 Overall synthetic route towards chiral 3-aryl-indan-1-ones: (a) NaOCH₃, CH₃OH or KOH, CH₃OH; (b) TFA or TFA, P₂O₅; (c) NaBH₄, CH₂Cl₂ : CH₃OH or L-Selectride, THF; (d) (*S,S*)-Ru complex ((*S,S*)-**63**),¹ acetone; (e) MnO₂, CH₂Cl₂.

The overall yields for the complete 5-step synthetic route, via racemates **118-125**, through to enantiomerically enriched 3-aryl-indan-1-ones have been calculated for each substrate and are displayed in Table 27.

Table 27 Overall yields for (*R*)- and (*S*)-3-aryl-indan-1-ones, via racemates **118-125**.

Indan-1-one	Overall Yield / % ^a					Combined Enantiomer Yield / % ^a
	R ¹	R ²	Racemate	(<i>S</i>)-enantiomer	(<i>R</i>)-enantiomer	
118	H	H	79	34	30	64
119	H	4-Cl	66	27	26	53
120	H	3,4-Cl	83	35	28	63
121	H	2,4-Cl	84	39	32	71
122	OCH ₃	H	91	43	38	81
123	OCH ₃	4-Cl	72	31	27	59
124	OCH ₃	3,4-Cl	91	40	38	78
125	OCH ₃	2,4-Cl	96	44	36	80

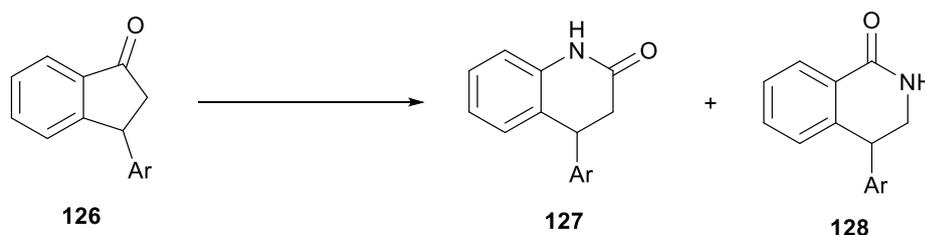
^a Calculated from combined isolated yields.

The two-step synthesis of (±)-3-aryl-indan-1-ones **118-125** was generally high yielding, with good to excellent yields obtained for the Claisen–Schmidt condensation and subsequent Nazarov cyclisation. This route is certainly favourable for access to racemic indan-1-ones containing electron donating groups on the 1-aryl ring and electron withdrawing groups on the pendant 3-aryl ring, which is the ideal situation for effective polarisation of the conjugated chalcone for Nazarov cyclisation (see **Section 2.1.3**).² The tolerance of the Nazarov reaction, however, is known to be lower for substrates possessing an electron rich 3-aryl ring, although this can be counteracted by increasing the electron density of the 1-aryl ring.³ Careful consideration of substrate structure is therefore required when pursuing this route in order to achieve higher yields, which limits the scope of racemic 3-aryl-indan-1-ones that can be made.

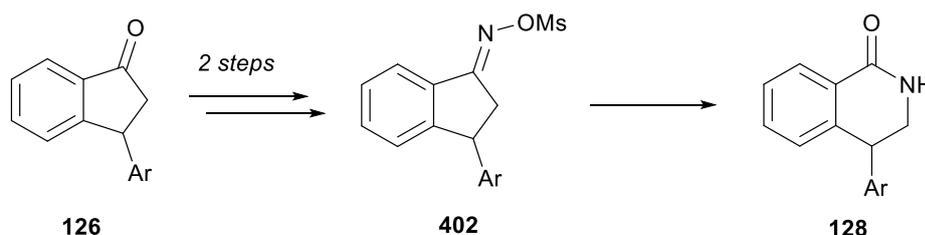
The “2.5-step” resolution of 3-aryl-indan-1-ones is highly efficient, enabling both ketone enantiomers to be synthesised in excellent enantiomeric excess, despite low catalyst loading in the oxidative kinetic resolution (~0.5 mol%). The total yields calculated for the (*S*)-enantiomers are greater than those for the (*R*)-indan-1-ones, which is expected due to the additional step – MnO₂ oxidation – involved in the synthesis of the latter. Nonetheless, the combined enantiomer yields are high. Furthermore, theoretically either 3-aryl-indan-1-one enantiomer can be selectively synthesised through choice of the catalyst; i.e. if the (*R*)-enantiomer has been identified as possessing interesting biological activity, it can be selectively made through employment of the ruthenium catalyst derived from the (*R,R*)-diastereomer of the TsDPEN ligand ((*R,R*)-**63**), instead of (*S,S*)-**63** as used in this work.

Chapter 3 showed that, of two ring expansion reactions tested, the Schmidt reaction – with sodium azide and methanesulfonic acid – is more appropriate over a Beckmann approach for the synthesis of 3-aryl-dihydroquinolinones (**127**) and their isoquinolinone isomers (**128**) from corresponding indan-1-ones (**126**, Scheme 51). The Schmidt reaction gave mixtures of the two lactams in one straightforward step, with the regiochemistry adjustable through manipulation of the substrate structure and reaction conditions, although only low scales were permissible due to safety concerns. Conversely, the Beckmann rearrangement of oxime mesylates yielded 3-aryl-dihydroisoquinolinones exclusively in a total of three steps from corresponding indan-1-ones, via oxime mesylates (**402**), which involved tedious and time-consuming quenches and work-ups.

Schmidt Approach:



Beckmann Approach:



Scheme 51 Comparison of Schmidt and Beckmann approaches for the synthesis of δ -lactams from 3-aryl-indan-1-ones.

Highly enantiomerically enriched dihydroisoquinolinones and dihydroquinolinones were accessible through application of these Schmidt conditions to the individual enantiomers of 3-aryl-indan-1-ones – synthesised via the 5-step route described above. These compounds are heavily associated with a wide range of biological activities, with non-cytotoxic anti-inflammatory compound 6-B345TTQ (**99**) being a key example (see **Section 3.1.1**). Chapter 3 also presented the successful synthesis of the individual enantiomers of **99**, which was a long term aim of the Fox group (Figure 36). The successive oxidative kinetic resolutions were the highlight of this synthesis as they allowed access to both the (*R*)- and (*S*)-enantiomer in >99 % e.e., albeit at the expense of some loss of material. Unfortunately, two limiting steps could be identified within the overall route towards 6-B345TTQ (**99**), which resulted in very low overall yields (<1.0 %) for both enantiomers. Firstly, the Nazarov cyclisation involved the reaction of a chalcone comprising a highly unfavourable structure – an electron deficient 1-aryl ring and electron rich 3-aryl ring – hence the product indan-1-one was formed in only 24 % yield. The second limiting step was the Schmidt reaction, the regioselectivity of which was extremely poor with respect to affording the desired dihydroquinolinone due to alkyl migration being the predominant pathway for this substrate; the Schmidt reaction of the individual enantiomers of the precursor indan-1-one gave (*R*)- and (*S*)-6-B345TTQ in only 2-3 % yields.

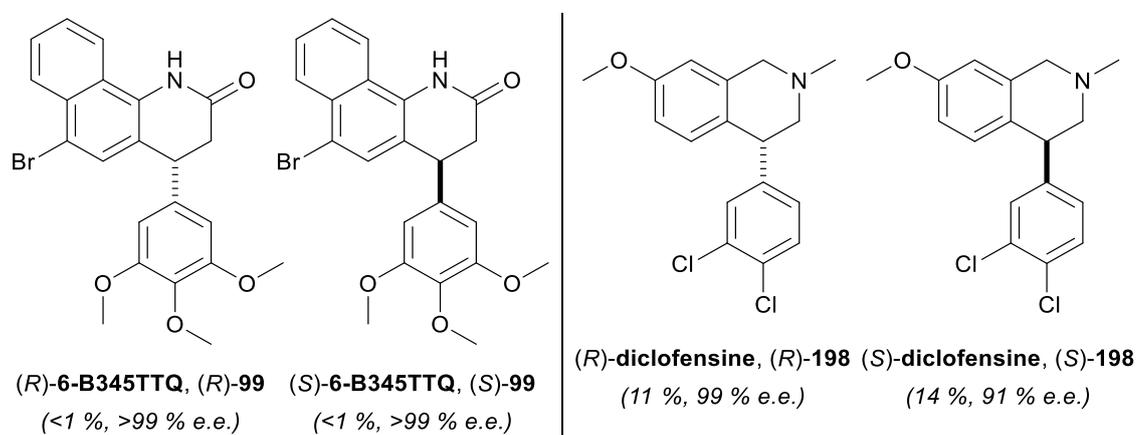
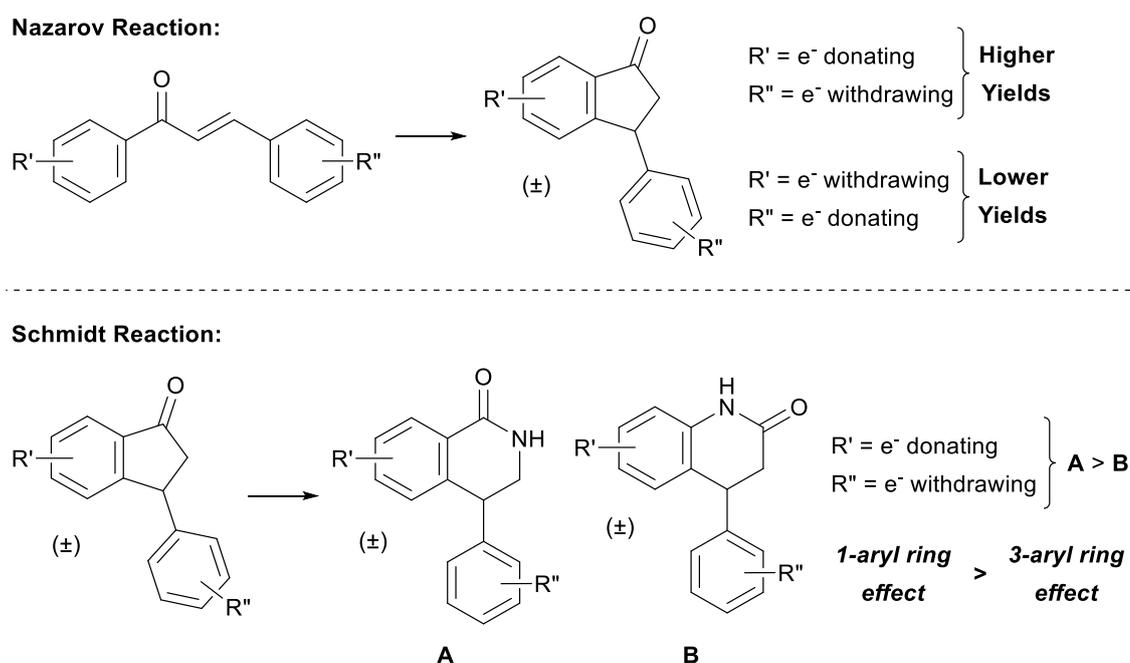


Figure 36 Successful synthesis of (*R*)- and (*S*)-6-B345TTQ (**99**) and diclofenac (**198**).

Through the successful formation of dihydroisoquinolinones in the Schmidt reaction of 3-aryl-indan-1-ones, which was especially favoured for trimethoxy- derivatives, a practical avenue towards 4-aryl-tetrahydroisoquinolines via subsequent reduction was possible. These species have received particular attention for their biological properties, most notably of which is antidepressant activity (see **Section 3.1.2**). As such, a number of highly enantioenriched 4-aryl-tetrahydroisoquinolines, including both enantiomers of

antidepressant drug diclofenine (**198**, Figure 36), were successfully prepared in excellent enantiomeric excesses through reduction of corresponding lactam enantiomers and subsequent *N*-methylation. The usefulness of 3-aryl-indan-1-ones was further demonstrated in Chapter 3 with the facile and high yielding synthesis of racemic benzylidene indan-1-ones, another bioactive class of compound, which were formed via the Claisen–Schmidt condensation of indan-1-ones with various benzaldehydes.

Overall, 3-aryl-indan-1-ones are clearly valuable intermediates in the synthesis of a wide range of medicinal scaffolds, especially given the ease with which both enantiomers can be obtained in excellent enantiomeric excess through a relatively straightforward 5-step procedure. However, as a synthetic strategy towards enantioenriched δ -lactams and corresponding amines it is not without its limitations; these are unquestionably the Nazarov cyclisation and Schmidt reaction, which are heavily influenced by substrate structure (Scheme 52), as exemplified by the synthesis of 6-B345TTQ (**99**).



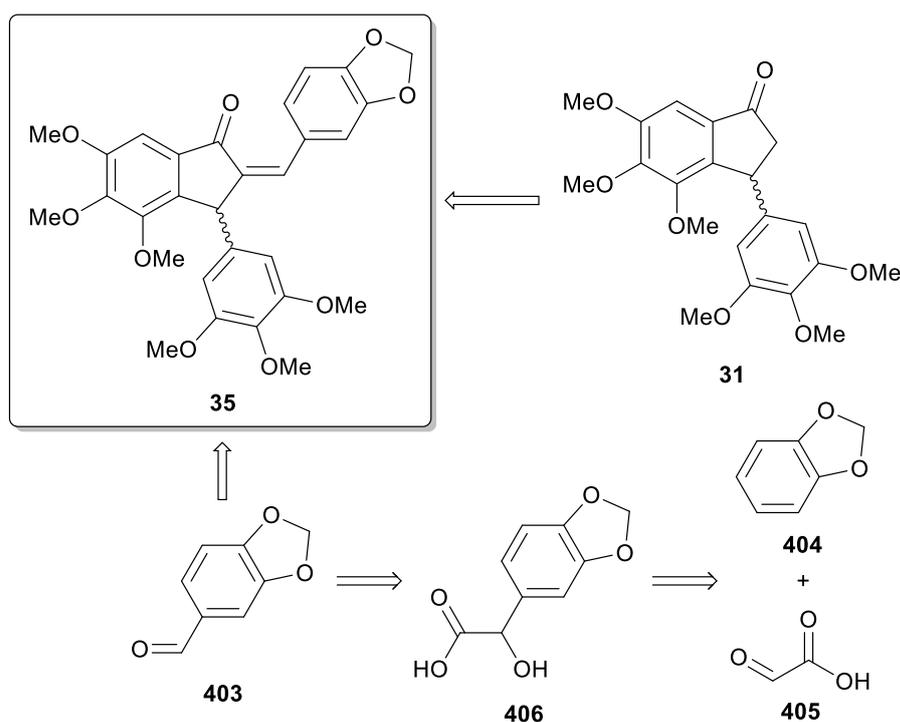
Scheme 52 Effect of substrate structure on Nazarov and Schmidt reactions.

In fact, from a practical viewpoint, the outcome of the Schmidt reaction is far more important given its involvement in the latter stages of the synthetic route towards enantioenriched lactams and corresponding amines, compared to the early Nazarov cyclisation step. The synthetic strategy presented herein is therefore less suitable for the synthesis of certain δ -lactams and corresponding amines, for instance enantioenriched 4-aryl-tetrahydroquinolinones possessing highly electron rich 1-aryl rings, and alternative methods towards their synthesis would likely be more attractive.

4.2 Future Work

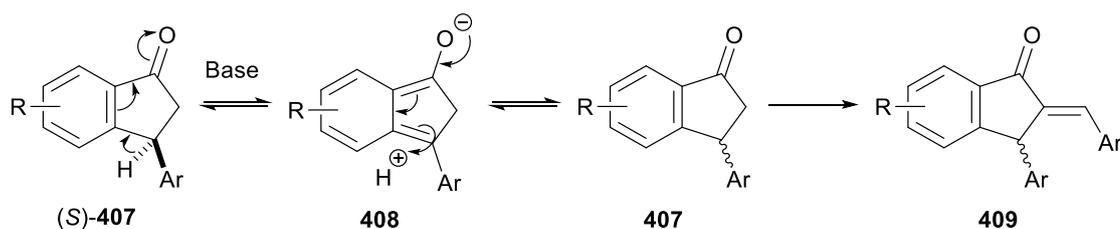
As with any new synthetic methodology, it is necessary to widen the scope of the 5-step route to enantioenriched 3-aryl-indan-1-ones through utilisation of benzaldehydes and acetophenones different to those employed thus far; it would be particularly useful to further investigate the effect of chalcone structure on the Nazarov cyclisation, the optimisation of which proves a key challenge. Furthermore, extensive screening of conditions for the Schmidt reaction of 3-aryl-indan-1-ones would be very beneficial in an attempt to control its regioselectivity, in spite of substrate structure, which would allow access to a larger number of δ -lactams (and corresponding amines) in high yields – the regiochemical outcome of the Schmidt reaction of indan-1-ones is heavily dependent on acid mediator, solvent and temperature (see **Section 3.2.2**).

It was previously discussed that compound **35** has been reported to show strong cytotoxicity against human cancer cell lines and non-toxicity up to 1000 mg/kg dose, despite only being reported as a racemate (see **Section 1.1**). The determination of the active enantiomer is an appealing prospect, which would require the synthesis of both enantiomers of benzylidene indan-1-one **35**. This should be possible using the methodology developed in this work, starting from 3,4,5-trimethoxyacetophenone and 3,4,5-trimethoxybenzaldehyde to afford the individual enantiomers of 3-aryl-indan-1-one **31**. The final step would comprise Claisen–Schmidt condensation of (*R*)- and (*S*)-**31** with piperonal (**403**) to give (*R*)- and (*S*)-**35**, respectively (Scheme 53).



Scheme 53 Pathway to benzylidene indan-1-one **35** and disconnection of piperonal (**403**).

However, one obstacle in this synthesis is the acquisition of piperonal, also known as heliotropin, which is a controlled substance because of its use as a precursor to 3,4-methylenedioxy-*N*-methylamphetamine (MDMA), commonly known as “ecstasy”.⁷ Thankfully, the synthesis of piperonal is relatively straightforward from 1,3-benzodioxole (**404**); one method involves the addition of glyoxylic acid (**405**) to **404** and subsequent oxidation of resulting α -hydroxy acid **406**.⁸ Future work could also involve the formation of the individual enantiomers of the benzylidene indan-1-ones presented in Chapter 3. Base-catalysed racemisation, however, may be a potential issue facing the formation of these species, including (*R*)- and (*S*)-**35**; the acidic hydrogen atom at the stereocentre in (*S*)-**407** may be deprotonated giving rise to the highly conjugated enolate intermediate **408** in which the 3-aryl group is attached to an sp² hybridised carbon atom, therefore there is a loss of stereochemistry (Scheme 54). If racemisation is faster than product formation the benzylidene indan-1-one (**409**) will ultimately be obtained as a racemate; this will be determined in no small part by the competition between deprotonation of the α - and β -protons – a sterically hindered base may prove beneficial towards reducing racemisation.



Scheme 54 Potential base-catalysed racemisation of 3-aryl-indan-1-ones.

4.3 References

1. S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 288-290.
2. W. He, X. Sun and A. J. Frontier, *J. Am. Chem. Soc.*, 2003, **125**, 14278-14279.
3. P. Kerby, PhD thesis, University of Warwick, 2016.
4. L. R. Cafiero and T. S. Snowden, *Org. Lett.*, 2008, **10**, 3853-3856.
5. Z. Li, M. K. Gupta and T. S. Snowden, *Eur. J. Org. Chem.*, 2015, **2015**, 7009-7019.
6. E. J. Corey and J. O. Link, *J. Am. Chem. Soc.*, 1992, **114**, 1906-1908.
7. United Nations Office on Drugs and Crime, *World Drug Report 2014*, United Nations publication, Sales No. E.14.XI.7.
8. K. Harada, M. Shirai, K. Shiba and T. Furuya, *Process for Preparing Piperonal*, US Pat., 6 686 482 B2, 2004.