

Ring-Opening Strategies towards the Total Synthesis of the Isodomoic Acids

A thesis submitted to the University of Manchester
for the degree of Doctor of Philosophy
in the Faculty of Engineering and Physical Sciences

2006

Benjamin T. Read
School of Chemistry

ProQuest Number: 11004799

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 11004799

Published by ProQuest LLC (2018). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

(ENQF9)



TH27162

Contents

<i>Abstract</i>	5
<i>Declaration</i>	6
<i>Notes on Copyright and Ownership of Intellectual Property Rights</i>	6
<i>The Author</i>	7
<i>Acknowledgements</i>	7
<i>Abbreviations</i>	8
<i>Atom Numbering Conventions for Selected Structures</i>	11

Chapter 1: Introduction

1.1 The Isodomoic Acids	
1.1.1 Discovery and Isolation.....	12
1.1.2 Biological and Environmental Activity.....	13
1.1.3 Previous Syntheses of the Domoic Acid Family	
1.1.3.1 Domoic Acid.....	15
1.1.3.2 Isodomoic Acid G	17
1.1.3.3 Semisynthesis: Photolysis of Domoic Acid	18
1.1.3.4 Semisynthesis: Isopropenyl Modification of Kainic Acid.....	19
1.1.3.5 Domoic Acid Analogues via Cobalt-Mediated Cyclisation...	20
1.2 Previous Work in the Clayden Research Group	
1.2.1 Discovery of the Anionic Dearomatising Cyclisation.....	23
1.2.2 Development of the Cyclisation Reaction: Synthesis of	
(±)-Kainic Acid	24
1.2.3 Asymmetric Cyclisation and the Synthesis of (–)-Kainic Acid	28
1.2.4 Synthesis of (–)-Isodomoic Acid C.....	28
1.2.5 Studies towards other Isodomoic Acids: Approaches to the	
Trisubstituted Alkene	30
1.2.6 Cyclisation of <i>N</i> -Benzoyloxazolidines.....	33
1.2.6.1 Mechanistic Studies	35
1.2.7 Other Benzamide Cyclisations	38
1.3 Aim of the Project.....	41

Chapter 2: Cyclisation of *N*-Benzoyloxazolidines

2.1 Preliminary Cyclisation	
2.1.1 Preparation of the Cyclisation Precursor.....	43
2.1.2 Dearomatising Cyclisation	46
2.1.3 Controlled Hydrolysis and Epimerisation of the Cyclisation Product	50
2.2 Enone Stabilisation	
2.2.1 Conjugate Addition Reactions	55
2.2.2 Alternative Cyclisation Reactions	61
2.2.3 Opening the Oxazolidine Ring.....	70

Chapter 3: Fragmentation Methodology

3.1 Trial Reaction.....	73
3.2 Model System	
3.2.1 Synthesis of Fragmentation Precursors	74
3.2.2 Model Fragmentation Reactions	85
3.2.3 Deuterium Labelling Study	89
3.2.4 Proposed Mechanistic and Stereochemical Rationale.....	91
3.2.5 Effect of Irradiation.....	98
3.2.6 Conclusion.....	99
3.3 Future Work: Silicon-Directed Beckmann Fragmentation	101

Chapter 4: Novel Benzamide Cyclisations

4.1 Background.....	103
4.2 Benzamide Synthesis	106
4.2.1 Synthesis of Acid Chlorides.....	107
4.2.2 Synthesis of Amines.....	110
4.2.3 Approaches to the Benzamides	114
4.2.3.1 Linear Synthesis.....	114
4.2.3.2 Convergent Synthesis.....	117
4.3 Cyclisation Reactions.....	123
4.4 Conclusions and Future Work.....	135

Chapter 5: Experimental Procedures

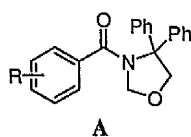
5.1 General Procedures	137
5.2 Experimental Details for Chapter 2	139
5.3 Experimental Details for Chapter 3	168
5.4 Experimental Details for Chapter 4	200
5.5 Detailed X-Ray Crystallographic Data	
5.5.1 Data for Compound 225a	238
5.5.2 Data for Compound 226a	245
5.5.3 Data for Compound 228a	254
5.5.4 Data for Compound 343	263
<i>References</i>	269

Word Count: 53,919

Abstract

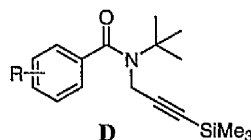
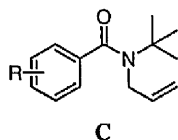
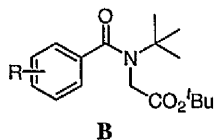
This thesis describes advances in the development of a synthetic route towards the isodomoic acids, incorporating a dearomatising cyclisation reaction as a key step.

The cyclisations of *N*-benzoyloxazolidines, **A**, are considered in Chapter 2, and extensive work on the stabilisation of the dearomatised products is outlined. A synthetic route involving these compounds would necessitate subsequent opening of the oxazolidine ring, and this is considered as one means of stabilisation.



The synthesis of the isodomoic acids by this route also requires the dearomatised ring to be opened, providing a further possible method of stabilising cyclised oxazolidines. After a trial reaction on an oxazolidine, the application of silicon-directed fragmentation to a model system is described in Chapter 3.

Chapter 4 narrates further investigation into the scope of the dearomatising cyclisation reaction. Compounds with ester, allyl and propargyl groups on nitrogen (**B–D**) are all shown to be capable of cyclising onto a benzenoid acceptor ring. This work complements the previous Chapters, representing alternatives to the oxazolidine cyclisation, whilst still potentially being able to incorporate 'metal'-directed ring-opening methodology.



Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Notes on Copyright and Ownership of Intellectual Property Rights

Copyright in text of this thesis rests with the Author. Copies (by any process) either in full, or of extracts, may be made only in accordance with instructions given by the Author and lodged in the John Rylands University Library of Manchester. Details may be obtained from the Librarian. This page must form part of any such copies made. Further copies (by any process) of copies made in accordance with such instructions may not be made without the permission (in writing) of the Author.

The ownership of any intellectual property rights which may be described in this thesis is vested in the University of Manchester, subject to any prior agreement to the contrary, and may not be made available for use by third parties without the written permission of the University, which will prescribe the terms and conditions of any such agreement.

Further information on the conditions under which disclosures and exploitation may take place is available from the Head of School of Chemistry.

The Author

The Author graduated from the University of Cambridge with First Class Honours in the degrees of *Bachelor of Arts* and *Master of Natural Sciences* in 2003, and was awarded the *Queens' College Davies Prize for Chemistry* in the same year.

From October 2003 until September 2006 the Author undertook a period of original research in the School of Chemistry at the University of Manchester, under the supervision of Professor Jonathan Clayden. The results of these investigations are outlined in this thesis.

Acknowledgements

To my family – especially Fran, Mum, Dad, Anna, Daisy, Ellen, Jim, Stella and Katherine – I would like to thank you all for your love, support and encouragement through everything in recent years. It has meant so much to me, and without you I would not be where I am now.

Sincere thanks go to Merck Sharp and Dohme for such generous funding of my project. I am especially grateful to Frank and Mary for looking after me at Terlings Park: your help and advice was invaluable and made my time spent working with you a pleasure.

I am also indebted to all those at the University of Manchester who supported me during my research, offering assistance, guidance and advice. Special mention should go to Tim and Gareth for proofreading, and to those 'unsung heroes' providing Technical and Administrative Services in the School of Chemistry, particularly Val, Rehana, Gareth and Gen.

This thesis is dedicated to Fran and Grandad.

Abbreviations

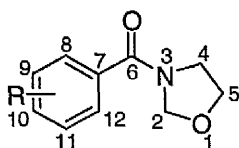
Ac	acetyl
anal.	analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
calc.	calculated
cat.	catalytic
CI ⁺	chemical ionisation (positive ionisation)
COD	1,5-cyclooctadiene
COSY	correlated spectroscopy
Cp	cyclopentadienyl
crotyl	<i>trans</i> -2-butenyl
δ	chemical shift (parts per million); partial charge
d	density
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dec.	with decomposition
DEPT	distortionless enhancement through polarisation transfer
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethyl- <i>N,N'</i> -propylene urea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
E	electrophile
e.e.	enantiomeric excess
EI ⁺	electron impact (positive ionisation)
eq.	equivalent(s)

ES ⁺	electrospray (positive ionisation)
Et	ethyl
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond connectivity
HMDS	1,1,1,3,3,3-hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
<i>i</i>	iso
imid	imidazole
IR	infrared
<i>k</i>	rate constant
λ	wavelength
LC	liquid chromatography
LDA	lithium diisopropylamide
lit.	literature value
<i>m</i>	meta
M	molar; unspecified metal; molecular mass (mass spectrometry)
MCPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mol%	molar percentage
m.p.	melting point
MS	mass spectrometry
<i>n</i>	normal
NBS	<i>N</i> -bromosuccinimide
ν_{\max}	absorption maximum
n.O.e.	nuclear Overhauser effect
NMR	nuclear magnetic resonance
<i>o</i>	ortho
[O]	oxidation

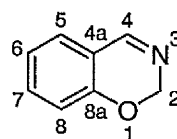
o/n	overnight
<i>p</i>	para
P	unspecified protecting group
Ph	phenyl
ppm	parts per million
Pr	propyl
prenyl	3,3-dimethylallyl
py	pyridine
pyr	pyrrolidinone ring
R, R'	unspecified substituents
R _f	retention factor
R _L , R _S	large/small substituents
R _t	retention time
R.T.	room temperature
<i>s</i>	secondary
sat.	saturated
soln.	solution
<i>t</i>	tertiary
TBAF	tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
<i>tert</i>	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	tetramethylsilane; trimethylsilyl
triflate	trifluoromethanesulfonate
UV	ultraviolet
wt%	weight percentage

Atom Numbering Conventions for Selected Structures

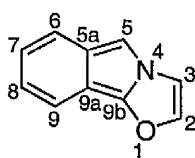
(Oxazolidin-3-yl)-(aryl)methanones



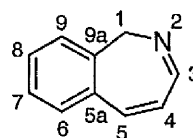
2*H*-Benzo[*e*][1,3]oxazine



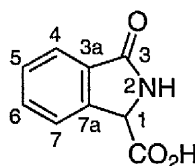
Oxazolo[2,3-*a*]isoindole



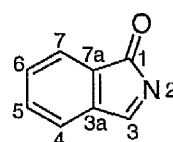
1*H*-Benzo[*c*]azepine



3-Oxoisoindoline-1-carboxylic acid



Isoindol-1-one



All compounds synthesised by the Author were racemic, unless otherwise indicated, and the stereochemistry shown in Schemes and Figures is relative. Asterisks in compound names (*R** and *S**) indicate relative stereochemistry in a racemic mixture.

Chapter 1: Introduction

1.1 The Isodomoic Acids^{1,2}

1.1.1 Discovery and Isolation

Since the isolation of (–)-kainic acid, **1**, from marine alga *Digenea simplex* in 1953,³ a number of structurally related compounds have been discovered (Figure 1).

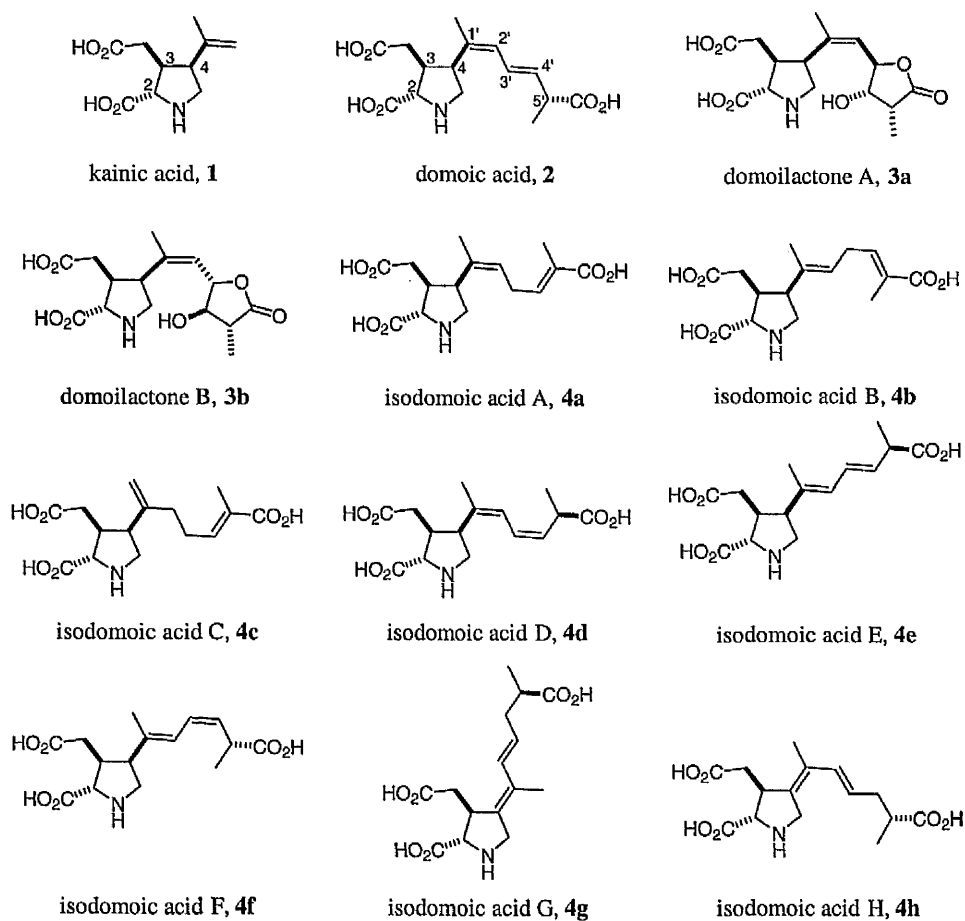


Figure 1: Selected Kainoid Natural Products

(–)-Domoic acid, **2**, with an octadienoic side-chain modification at C4, was also initially found in a marine alga, *Chondria armata*, in 1958.⁴ Over the following 30 years this alga proved to be a source of other kainoids related to domoic acid,

including domoic acid A and B, nordomoic acid (lacking the C5' methyl group) and isodomoic acids A to D, a group of diene geometrical and regioisomers.^{5,6}

In 1989 a reversed-phase HPLC method was developed to allow rapid, sensitive and unequivocal identification of domoic acid and its known isomers in various shellfish and phytoplankton.⁷ By this technique other related compounds have been detected in new areas of the world's waters. Examination of samples of the edible mussel *Mytilus edulis* from Canada in 1990 yielded two new isodomoic acid isomers, E and F, along with domoic acid and isodomoic acid D.⁸ Re-examination of *Chondria armata* from Kyushu Island, Japan, gave two further isomers, acids G and H,⁹ and the C5' epimer of domoic acid.¹⁰

Much work in identifying other primary producers of domoic acid and its isomers has been carried out since 1989.¹¹ *Pseudo-nitzschia multiseriata* (originally named *Nitzschia pungens* f. *multiseriata*) was suggested as the diatom (single-celled alga) responsible for contamination of shellfish with domoic acid in 1987, which led to human poisoning in Canada;¹² a cultured sample did indeed produce domoic acid.¹³ Other species of *Pseudo-nitzschia* have also been shown to produce domoic acid, including *P. calliantha*^{11b} (not *P. pseudodelicatissima* as initially reported),¹⁴ *P. australis*,¹⁵ *P. fraudulenta*,¹⁶ *P. multistriata*,¹⁷ *P. pungens*,¹⁸ *P. seriata*¹⁹ and *P. turgidula*.¹⁸

Diatoms have also recently been found to be responsible for production of isodomoic acids A and B (*N. navis-varingica*)²⁰ and isodomoic acid C (*P. australis*).²¹

1.1.2 Biological and Environmental Activity²²

Interest in the study of the kainoids has been aroused by their potent biological effects. Insecticidal^{5,23} and anthelmintic^{4,24} (anti-intestinal worm) properties have long been reported and applied therapeutically, but it is their neuroexcitatory properties that have provoked investigation into the kainoid amino acids in recent years.²⁵ Neuronal degeneration is a factor common to a number of brain diseases,

and the injection of kainoids in animals has been shown to give rise to symptoms that mimic those observed in epilepsy,²⁶ Huntington's disease^{25a,27} and dementia.²⁸

The mode of kainoid biological action is thought to arise from their structural similarity to glutamic acid (Figure 2), a mammalian central nervous system neurotransmitter.²⁹ Potency of neuroexcitation depends on strength of binding at the kainate receptor, one of the three types of ionotropic (ion channel) glutamate receptor.³⁰ Binding is influenced strongly by the stereochemistry at C4,^{29b} the nature of the C4 substituent^{23,25c,31} and molecular conformation.^{29c} Alkene configuration in the C4 side-chain in domoic acid derivatives seems to be particularly critical, with the *Z*-configuration of a C1' mono-alkene 400 times more active than the *E*-configuration, and the potency of domoic acid more than 5,000 times that of tetrahydrodomoic acid, with a fully reduced side-chain.³²

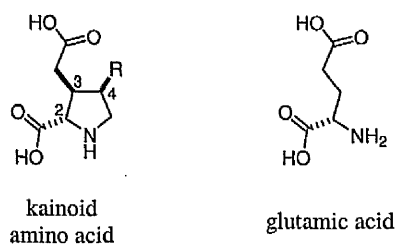


Figure 2: Structural Comparison of Kainoids with Glutamic Acid

Following the 1987 case of 'amnesic shellfish poisoning' on Prince Edward Island, Canada, in which three people died and more than 150 were taken ill as a result of eating contaminated blue mussels (*Mytilus edulis*), domoic acid was identified as the causative substance.^{12,33} Contamination resulted from ingestion of toxic domoic acid-producing algae by the shellfish. Manifestation of this poisoning has been observed in sea mammals³⁴ and birds³⁵ as well as humans.

The biological mode of action of domoic acid results in neuronal depolarisation: the resultant short-term memory loss is symptomatic of domoic acid poisoning (reported by 25% of those affected by the Canadian outbreak). Other symptoms include dizziness, nausea and vomiting, ultimately leading to coma, brain damage or death in the most severe cases.³³

Pharmacological studies with the kainoid amino acids may be of use in furthering knowledge of the debilitating brain diseases their action mimics, and in developing antidotes to reduce human brain damage in future cases of domoic acid poisoning.

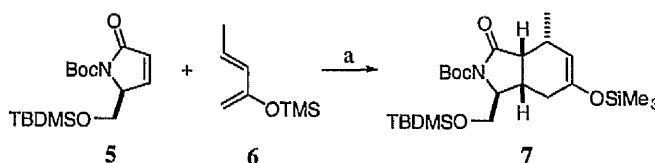
Outbreaks of domoic acid poisoning occur when populations of domoic acid-producing organisms 'bloom' to a sufficiently high concentration for levels of the poison to become dangerous to health. This can be a perennial problem in areas of the world's oceans where essential nutrients are brought up from deep water to levels penetrated by light, such as the western coast of North America.²²

It is hoped that the future threat to human health by shellfish poisoning resulting from domoic acid ingestion will be minimised by the extensive monitoring programmes now in place. These, for example, have led to the early detection of domoic acid production by *P. seriata* in Scottish waters³⁶ and by *P. australis* in Irish waters.³⁷ Other novel methods of protection employed by the shellfish industry include delaying mussel harvest until after ice-cover in Canada, processing shellfish with constant water changes, and the ongoing research into isolation of bacteria that can break down domoic acid.^{38,39}

1.1.3 Previous Syntheses of the Domoic Acid Family

1.1.3.1 Domoic Acid

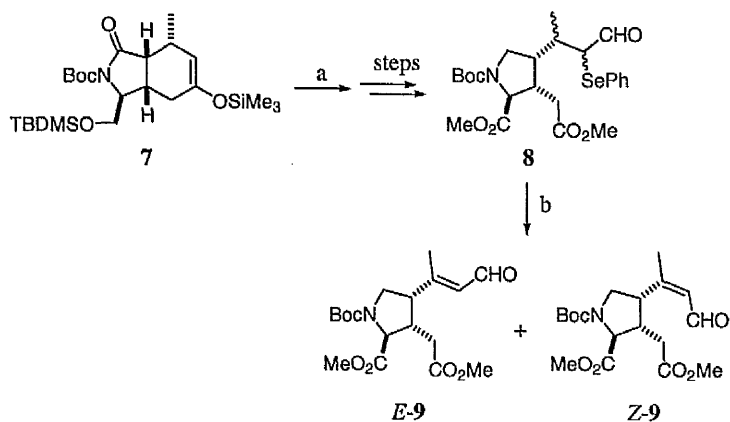
Although many syntheses of kainic acid have been reported,² just one total synthesis of domoic acid has been published, by Ohfuné and Tomita in 1982, aiming to prove its absolute stereochemistry.⁴⁰ From advanced intermediate **5**, a Diels-Alder reaction with **6** gave bicyclic compound **7** (Scheme 1).



Reagents and conditions: (a) 135 °C, sealed tube, 3 days

Scheme 1

Control of stereochemistry was remarkable, with just one stereoisomer of **7** detected; this was consistent with the Woodward-Hoffmann rules, along with second-order effects.⁴¹ The diene approached from the lower face of **5** as drawn, to avoid the bulky *tert*-butyldimethylsilyl group; regiochemistry was controlled by asynchronous diene-dienophile orbital overlap and bond formation, with *para* trimethylsilanyloxy and amide carbonyl groups favoured over *meta*; secondary diene-dienophile interactions promoted *endo* product formation. With the *cis*-fused ring junction controlling the crucial stereochemistry around the pyrrolidinone ring, ozonolysis of **7** opened the six-membered ring, and subsequent steps led to selenide **8** (Scheme 2).



Reagents and conditions: (a) O₃, DCM, -78 °C; DMS, R.T., 6 h; (b) see Table 1 below

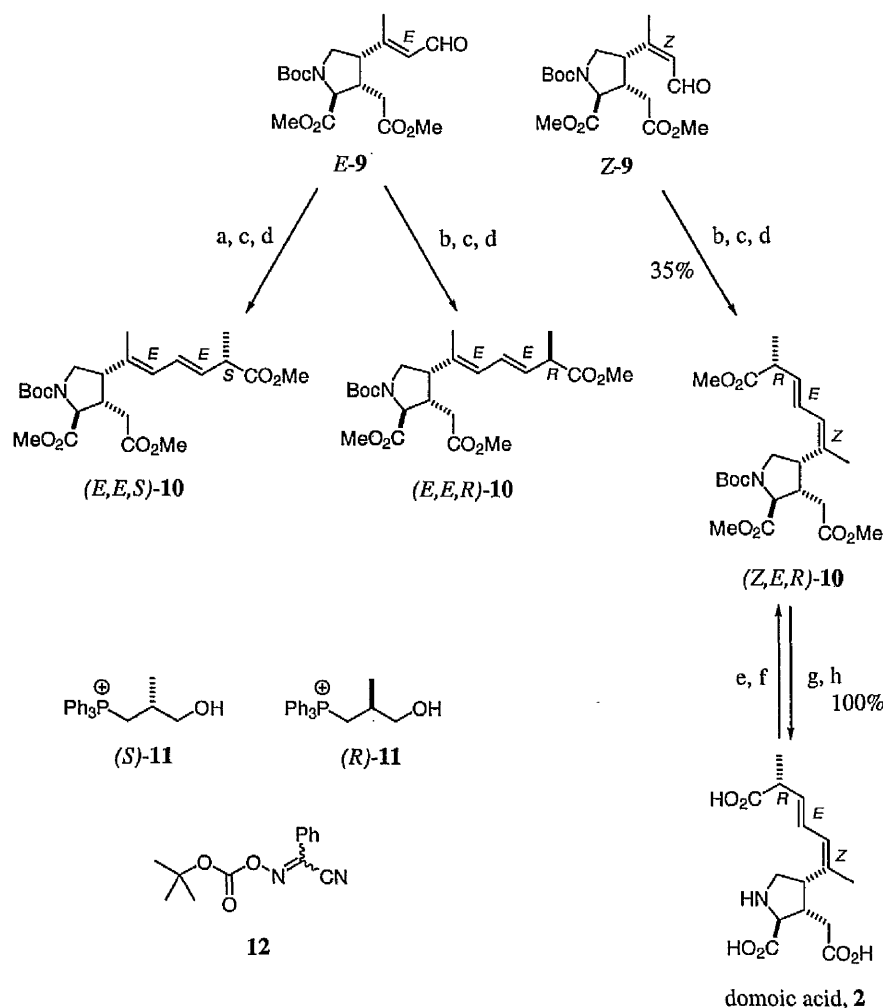
Scheme 2

Two methods were developed for the deselenation of **8** (Table 1), giving moderate control of the alkene geometry of **9**.

Conditions	Total Yield of 9	Ratio <i>E-9</i> : <i>Z-9</i>
O ₃ , DCM, -78 °C; Et ₃ N	33%	10 : 1
NBS, THF, R.T., 2 min; NaOAc (aq.), 15 min	67%	1 : 2

Table 1: Deselenation Conditions giving Control of Alkene Geometry

Wittig chemistry was then used to form three derivatives of **9** (Scheme 3). Derivatisation of an authentic sample of (–)-domoic acid gave (Z,E,R)-**10**, thus proving its absolute stereochemistry.



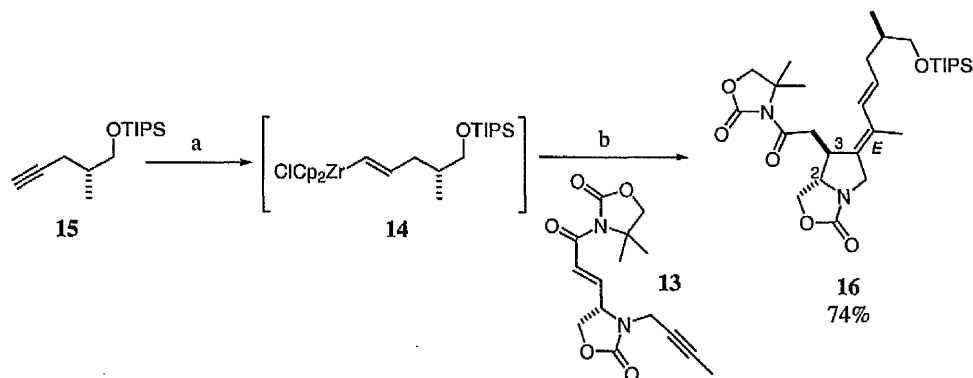
Reagents and conditions: (a) (S)-**11**, *n*-BuLi (2 eq.), THF, –78 °C, 2 min; 0 °C, 10 min; (b) (R)-**11**, *n*-BuLi (2 eq.), THF, –78 °C, 2 min; 0 °C, 10 min; (c) Jones reagent, 0 °C, 1 h; (d) CH₂N₂; (e) Boc-ON (**12**), Et₃N; (f) CH₂N₂; (g) 2.5% KOH (aq.), R.T., 24 h; (h) TFA, R.T., 15 min; NaOH (1 eq.)

Scheme 3

1.1.3.2 Isodomoic Acid G

A recent total synthesis of isodomoic acid G has been published by Montgomery *et al.*, using a strategy previously applied to the synthesis of kainic acid.⁴² Isodomoic acids G and H differ from isomers A to F and domoic acid, the parent of the family, in that they possess exocyclic alkenes. Therefore this work was

able to utilise a key nickel-catalysed alkyne-alkenylzirconium coupling of **13** with **14** (Scheme 4). This step gave complete control of C2-C3 relative stereochemistry and simultaneously yielded the correct diene geometry.



Reagents and conditions: (a) Cp_2ZrHCl , THF, R.T.; (b) **13**, $\text{Ni}(\text{COD})_2$ (10 mol%), ZnCl_2 (20 mol%), THF, 0 °C

Scheme 4

Although the stereocontrol demonstrated in this synthesis is remarkable, there is no scope for its extension to other isodomoic acids, except isomer H.

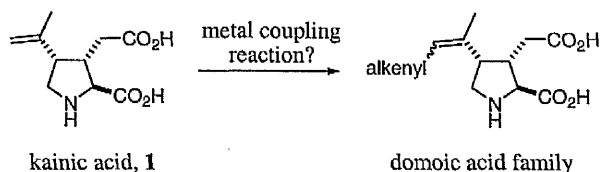
1.1.3.3 Semisynthesis: Photolysis of Domoic Acid

Although scarce in its natural sources, domoic acid is far more abundant than the isodomoic acids. It has been reported to exist at levels of greater than 1% dry weight in the Canadian phytoplankton *Pseudo-nitzschia multiseries*.³³

Work by Wright *et al.* has demonstrated that, of the mixture of domoic acid isomers obtained by purification of the concentrated extraction mixture of the mussel *Mytilus edulis*, more than 90% is domoic acid, with isodomoic acids D, E and F at just 5%, 2% and 1% respectively.⁸ Isodomoic acids D–F were prepared by photochemical isomerisation of domoic acid, with exposure to 254 nm light for nine to twelve minutes giving domoic acid, isodomoic acid D, isodomoic acid E and isodomoic acid F in a ratio of 0.28 : 0.12 : 0.27 : 0.13 respectively per unit starting material.

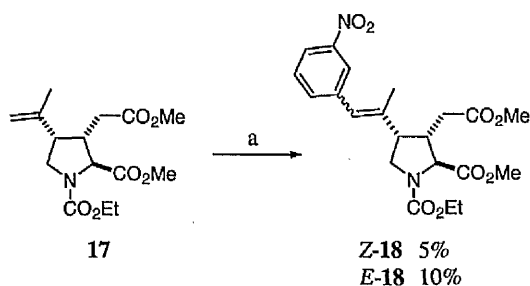
1.1.3.4 Semisynthesis: Isopropenyl Modification of Kainic Acid

Modification of the isopropenyl side-chain of kainic acid with a metal coupling reaction seems an obvious route to the domoic acid family of kainoids (Scheme 5), as a semi-synthesis from the natural product, or utilising one of the many published syntheses of kainic acid.²



Scheme 5: Isopropenyl Modification of Kainic Acid

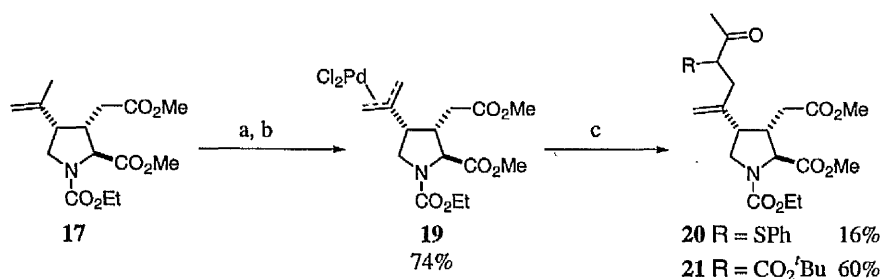
Mertes *et al.* applied this chemistry to investigate how substitution on the kainic acid isopropenyl group affected receptor binding.⁴³ Only an aryl coupling was attempted, giving a mixture of isomers in low yield (Scheme 6).



Reagents and conditions: (a) Pd(OAc)₂, 3-nitroaniline, MeCN, 60 °C; *t*-butylnitrite, 60 °C, portionwise over 3 h; 60 °C, 4 h; 25 °C, o/n; Pd(OAc)₂, 3-nitroaniline, *t*-butylnitrite, 60 °C, 2 h; 25 °C, 2 days

Scheme 6

Methyl rather than methylene substitution was also reported in this paper, with π -allyl palladium complex **19** proving susceptible to nucleophilic attack (Scheme 7).



Reagents and conditions: (a) Pd(OCOCF₃)₂, EtOAc, R.T., overnight; (b) *n*-Bu₄NCl, R.T., 24 h; (c) *t*-butylacetoacetate or phenylthioacetone, NaH, THF; **19**, Ph₃P, THF, 25 °C, o/n (**20**) or 38 h (**21**)

Scheme 7

No attempts to extend this work to the synthesis of domoic acid or isodomoic acids D, E or F (methylene coupling), or isodomoic acid C (methyl substitution), have since been reported in the literature. The poor yields, lack of stereocontrol, sensitivity to the choice of aryl substrate and scarce availability of kainic acid probably mean this would be an inefficient route to the isodomoic acids.

1.1.3.5 Domoic Acid Analogues via Cobalt-Mediated Cyclisation⁴⁴

Modification of a procedure previously applied to the synthesis of kainic acid⁴⁵ has allowed Baldwin *et al.* to synthesise **22**, a side-chain analogue of domoic acid that is structurally similar to isodomoic acid C (Figure 3).

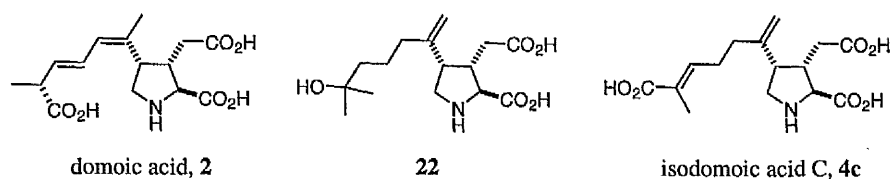
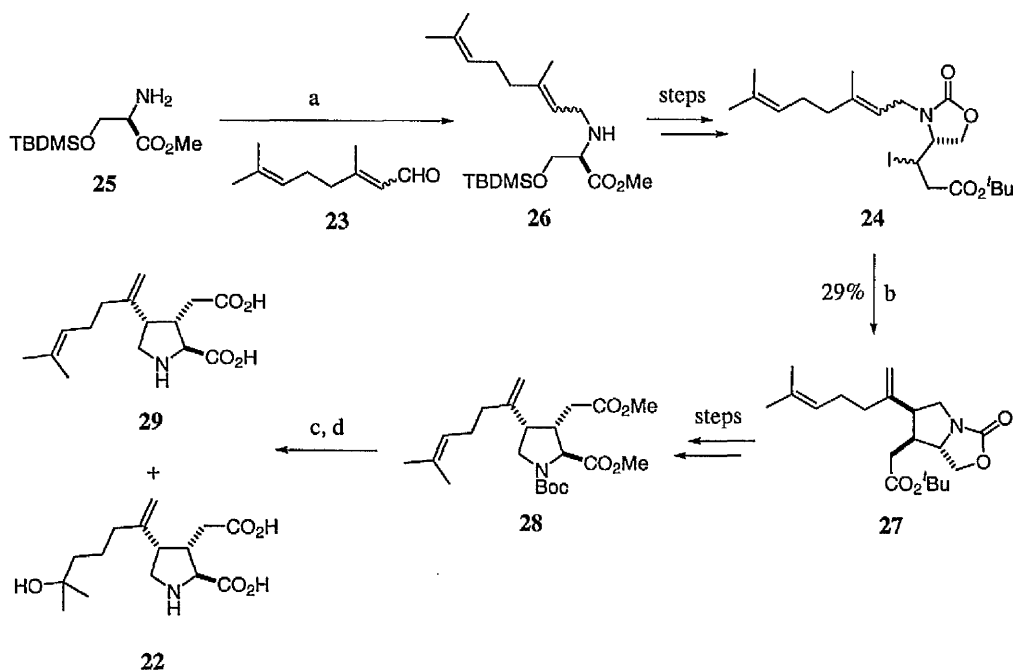


Figure 3: Comparison of Baldwin's Domoic Acid Analogue with Natural Products

The side-chain was introduced early in the synthesis, by a reductive amination reaction with citral (Scheme 8). Although the commercially available citral **23** was a 95 : 5 mixture of geometrical isomers, this turned out to be unimportant, as they gave a common product on cobalt(I)-mediated cyclisation of **24**, the key step in this synthesis.



Reagents: (a) NaBH_4 , citral (**23**); (b) Co(I) ; (c) KOH (aq.) ; (d) TFA

Scheme 8

Compound **28** could be isolated as a stable compound, but deprotection with aqueous potassium hydroxide then trifluoroacetic acid gave only a trace of **29**, with **22** as the major product, obtained in 72% yield from **28** as the trifluoroacetate salt **30** (Figure 4).

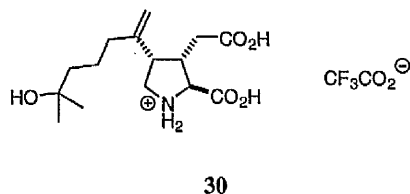


Figure 4: The Isolated Form of Baldwin's Domoic Acid Analogue

When this work was published in 1991, Baldwin's intention was to develop the strategy and apply it to the synthesis of other kainoids and kainoid analogues.⁴⁴ However, to date, no approaches to the isodomoic acids have been published, with work instead focusing on 4-arylsulfanyl analogues **31**,⁴⁶ and 4-aryl, alkenyl and alkynyl analogues⁴⁷ of the acromelic acids (Figure 5).

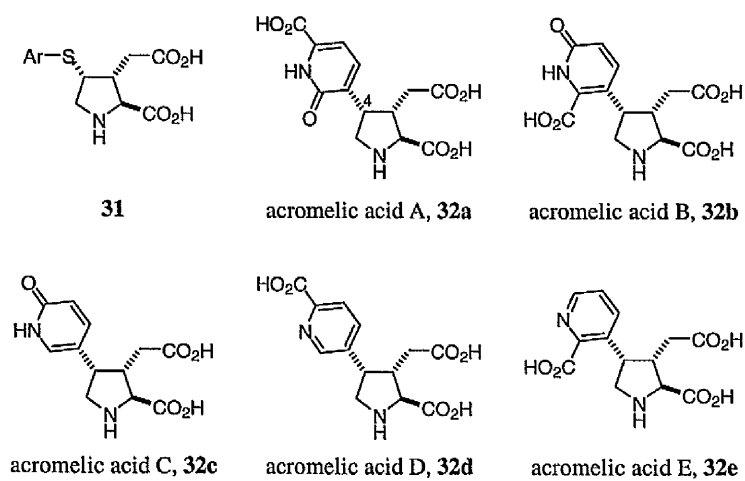
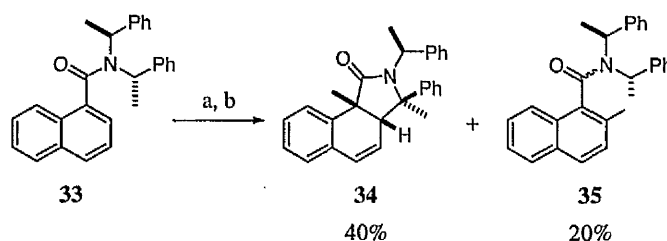


Figure 5: Baldwin's Domoic Acid Analogue Targets

1.2 Previous Work in the Clayden Research Group

1.2.1 Discovery of the Anionic Dearomatising Cyclisation

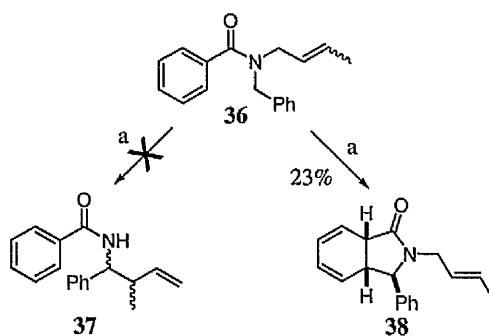
Two independent, coincidental observations at the University of Manchester in the mid-1990s prompted research into the previously unreported anionic dearomatising cyclisation of naphthamides and benzamides.⁴⁸ Lithiation of **33** gave **34** as the major product, in 40% yield, with half as much of the expected *ortho*-methylated compound **35** (as a 1 : 1 mixture of atropisomers) (Scheme 9).⁴⁹



Reagents and conditions: (a) *s*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$; (b) MeI

Scheme 9

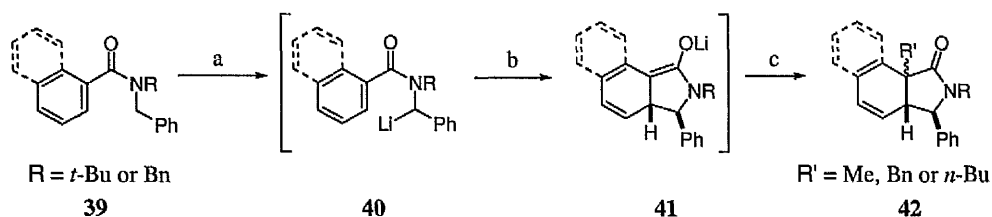
Secondly, the attempted [2,3]-aza-Wittig rearrangement of **36** to **37** actually resulted in another cyclised product, **38**, with lost aromaticity (Scheme 10).⁵⁰



Reagents and conditions: (a) *t*-BuLi, HMPA, THF, $-78\text{ }^{\circ}\text{C}$

Scheme 10

These two manifestations of the same reaction were subsequently investigated within the Clayden group and found to be a general reaction of *N*-benzyl naphthamides⁵¹ and *N*-benzyl benzamides⁵² (Scheme 11).



Reagents: (a) *t*-BuLi; (b) HMPA; (c) MeI, BnBr or *n*-BuBr

Scheme 11

While these reactions are interesting, their true value is tested by applicability to synthesis. The observation that the dearomatised products possess the kainoid relative stereochemistry around the pyrrolidinone ring (Figure 6) led to investigation of this application within the Clayden research group.

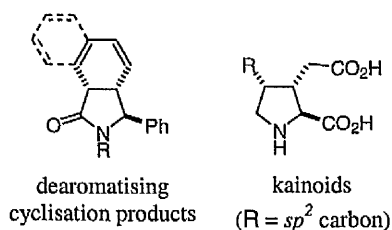


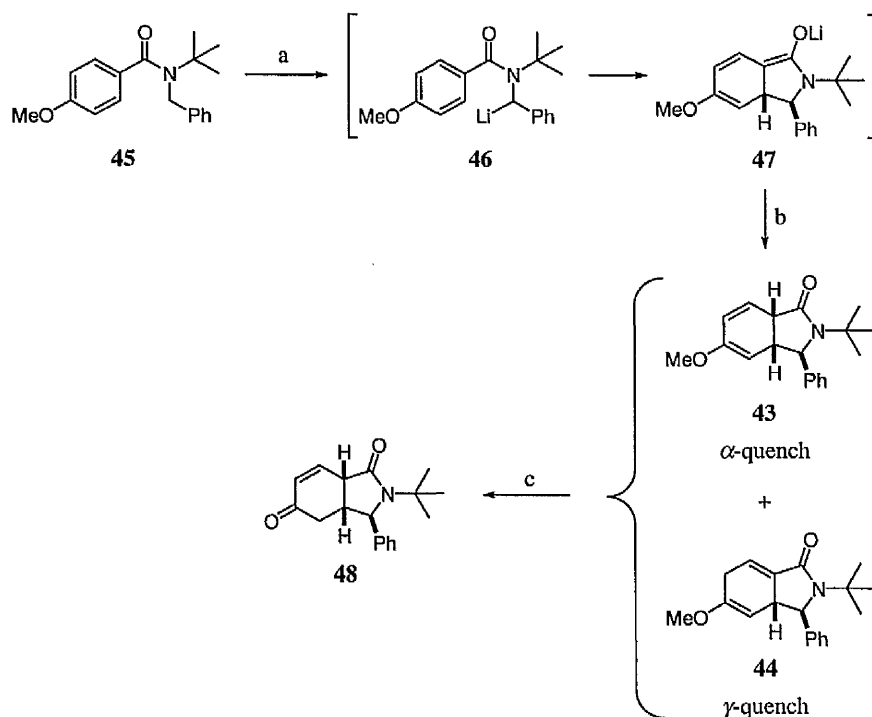
Figure 6: Stereochemical Comparison of Dearomatised Cyclisation Products with Kainoid Natural Products

1.2.2 Development of the Cyclisation Reaction: Synthesis of (±)-Kainic Acid

Key modifications to cyclisation conditions and substrates made the reaction more amenable to use in synthesis:

- a. *tert*-Butylbenzylbenzamide cyclised satisfactorily, but E1 elimination of the *tert*-butyl group proved almost impossible.⁵³ Replacement of the *tert*-butyl group with the acid labile cumyl (2-phenylisopropyl) group⁵⁴ avoided the removal difficulties, although the cumylamine starting material was somewhat expensive commercially.

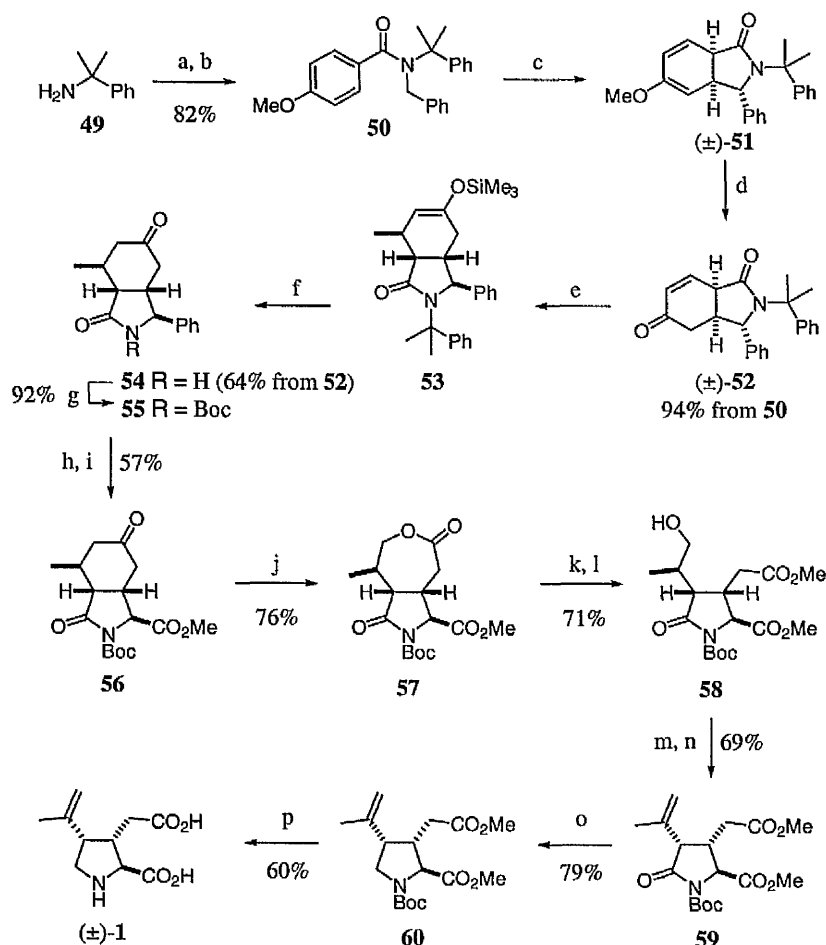
- b. Methoxy functionalisation of the benzamide ring led to methyl enol ethers such as **43** and **44** as the dearomatised products. These could be hydrolysed to the thermodynamically preferred enone without isolation of the intermediate enol ethers (Scheme 12).⁵⁵



Reagents: (a) *t*-BuLi, HMPA; (b) H⁺; (c) HCl, H₂O-MeOH

Scheme 12

With this groundwork completed, a racemic synthesis of kainic acid was published in 2000.⁵³ The full route is outlined in Scheme 13 below.



Reagents and conditions: (a) *p*-anisoyl chloride, Et₃N, DCM; (b) NaH, BnBr, DMF, R.T., 18 h; (c) *t*-BuLi (2 eq.), HMPA (12 eq.), THF, -40 °C, 60 h; sat. aq. NH₄Cl soln.; (d) 1 M aq. HCl soln., THF; (e) Me₂CuLi, TMSCl, THF, -78 °C, 1 h; (f) TFA, reflux, 6 h; (g) Boc₂O, Et₃N, DMAP, DCM; (h) NaIO₄, cat. RuCl₃, 1 : 1 acetone : H₂O; (i) Me₃SiCHN₂, PhH, MeOH; (j) MCPBA, DCM; (k) NaOH (2.2 eq.), MeOH, reflux, 2 h; (l) Me₃SiCHN₂, PhH, MeOH; (m) *o*-NO₂C₆H₄SeCN, Bu₃P, THF, R.T.; (n) H₂O₂, py, THF, -40 °C; (o) NaBH(OMe)₃ (2 eq.), THF, reflux; (p) 10 : 1 TFA : H₂O, reflux, 4 h

Scheme 13: Clayden Group Synthesis of (±)-Kainic Acid

Cumylamine, **49**, was acylated with *para*-anisoyl chloride, then alkylated with benzyl bromide. Benzylic lithiation was effected with *tert*-butyllithium and hexamethylphosphoramide (HMPA), but the cyclisation required 60 hours to go to completion because of the bulky cumyl group. *In situ* enol ether hydrolysis gave bicyclic enone **52** with the required pyrrolidinone stereochemistry. Conjugate methyl addition on the *exo* face followed by acid hydrolysis of the trimethylsilyl-trapped enolate also cleaved the *N*-cumyl group, which was subsequently reprotected with *tert*-butoxycarbonyl. The phenyl ring was oxidised with catalytic

ruthenium tetroxide, formed *in situ* from ruthenium trichloride and sodium periodate, the resulting carboxylic acid being esterified with trimethylsilyldiazomethane. Baeyer-Villiger oxidation was surprisingly regioselective, perhaps explained by *exo*-face peracid attack together with steric interactions, with the axial methyl group favouring the intermediate conformation shown in Figure 7. The more favourable migration was then that where the carbon–carbon bond broken was the one lying antiperiplanar to the breaking oxygen–oxygen bond, shown as bold bonds in the Figure.

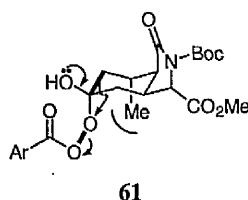


Figure 7: Proposed Mechanistic Explanation
for Regioselectivity in the Baeyer-Villiger Reaction

The resultant lactone was cleaved with sodium hydroxide. Subsequent elimination of water was achieved via oxidation and elimination of a selenide. Borohydride reduction and global deprotection under acidic conditions gave (\pm)-kainic acid, which was purified by recrystallisation from methanol.

Subsequent practical developments came with the discoveries that lithium diisopropylamide was sufficiently basic to perform the benzylic lithiation (at temperatures above $-30\text{ }^{\circ}\text{C}$), and that raising the temperature to around $0\text{ }^{\circ}\text{C}$ promoted cyclisation without the need for carcinogenic HMPA.⁵⁶ The milder conditions were also compatible with a wider range of substrates, such as those reactive towards *tert*-butyllithium (e.g. bromides or nitriles), or those containing electron-withdrawing groups.

1.2.3 Asymmetric Cyclisation and the Synthesis of (–)-Kainic Acid

Replacement of lithium diisopropylamide with chiral base **62** (Figure 8) immediately gave stereoselective cyclisation, which was optimised to give 75% e.e. at lower reaction temperatures (facilitated by the higher basicity of **62** than lithium diisopropylamide).⁵⁷ Overall yields were moderate (64%) using **62**, with removal of the protonated amine problematic. Fortunately, the hydrochloride salt of base **63** was less soluble in organic solvents than that of **62**, allowing easier separation and further optimisation of the reaction to give a yield of 72%, with 81% e.e.⁵⁷

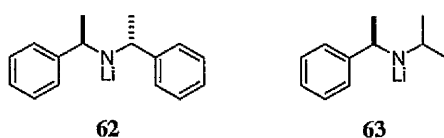


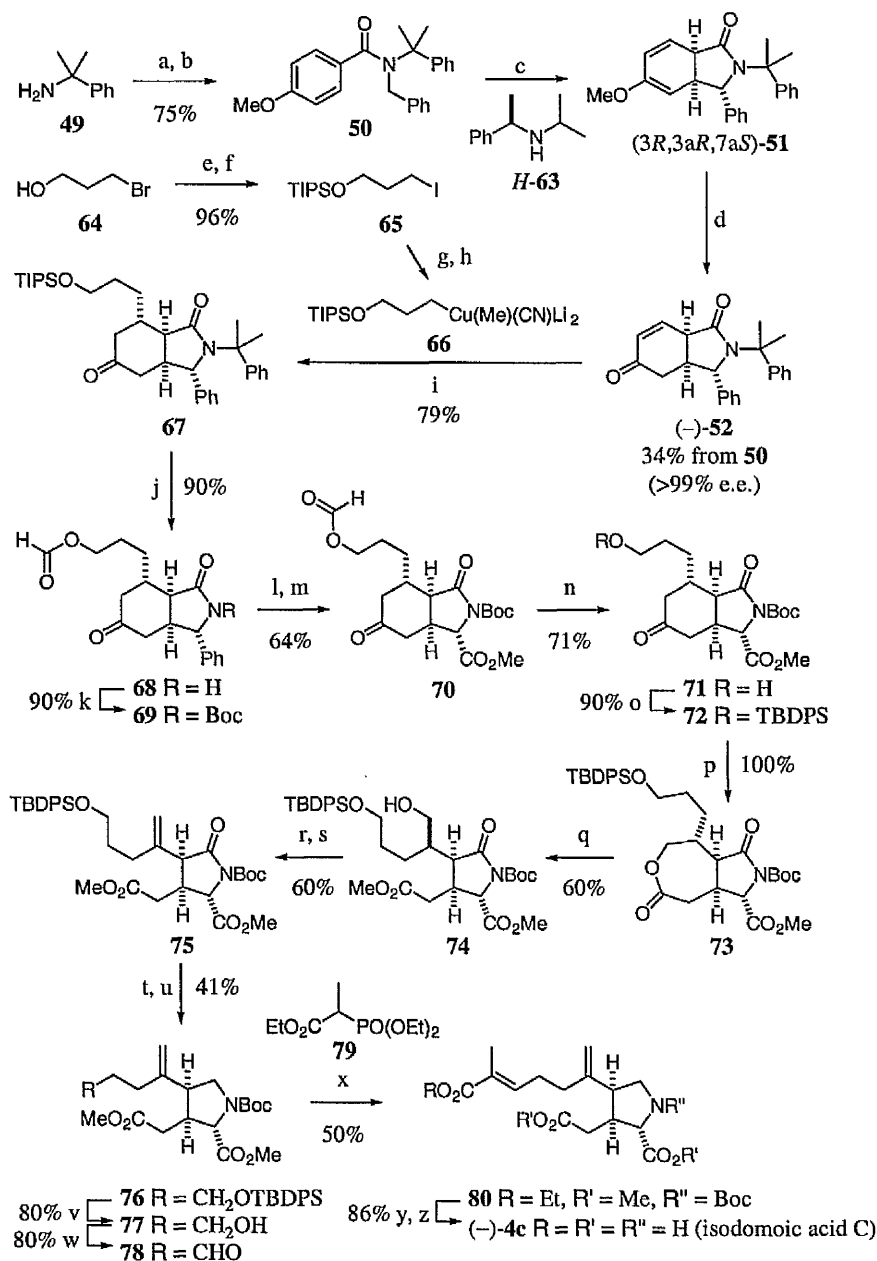
Figure 8: Chiral Bases used to give Asymmetric Cyclisation

In the full published synthesis of (–)-kainic acid,⁵⁸ a yield of 52% using base **63** for this key step was obtained after recrystallisation, with an enantiomeric excess of 99%.

1.2.4 Synthesis of (–)-Isodomoic Acid C

The synthesis of (–)-isodomoic acid C has recently been completed in the Clayden research group by Knowles,⁵⁹ using a modification of the (–)-kainic acid synthesis (see Sections 1.2.2 and 1.2.3). The side-chain was incorporated by conjugate cuprate addition of a three-carbon precursor onto enone (–)-**52**. The full route is outlined in Scheme 14 below.

Of particular note is the early oxidation of the phenyl ring to yield the C2 carboxylate substituent (step 1): this must precede formation of the side-chain alkenes, to avoid their unwanted oxidation under the reaction conditions. Prior to this oxidation it was also necessary to convert the triisopropyl-protected alcohol to



Reagents and conditions: (a) *p*-anisoyl chloride, Et₃N, DCM, 0 °C, 12 h; (b) BnBr, NaH, DMF; (c) *H*-63, *n*-BuLi, THF, -78 °C to R.T., 5 h; sat. aq. NH₄Cl soln.; (d) 3 M aq. HCl soln.; recrystallisation from EtOAc; (e) TIPSCl, imid, DCM, R.T., 18 h; (f) NaI, acetone, reflux, 18 h; (g) *t*-BuLi, Et₂O, -78 °C; (h) MeLi, CuCN, Et₂O, -78 °C to R.T.; (i) 66, Et₂O, -78 °C, 2 h; (j) HCO₂H, reflux, 30 min; (k) Boc₂O, DMAP, Et₃N, DCM, R.T., 18 h; (l) NaIO₄, RuCl₃, MeCN, H₂O, EtOAc, R.T., 18 h; (m) TMS-CHN₂, PhMe, MeOH, R.T., 5 min; (n) 1 M aq. NaOH, MeOH, -78 °C, 1 h; (o) TBDPSCl, imid, DCM, R.T., 18 h; (p) MCPBA, DCM, R.T., 72 h; (q) NaOMe, MeOH, -78 °C; (r) *o*-NO₂C₆H₄SeCN, *n*-Bu₃P, THF, R.T., 2 h; (s) H₂O₂, py, THF, -40 °C to R.T., 12 h; (t) DIBAL, THF, -78 °C, 1 h; MeOH; (u) Et₃SiH, BF₃·Et₂O, DCM, -78 °C, 2.5 h; (v) TBAF, THF, R.T., 2 h; (w) Dess-Martin periodinane, DCM, R.T., 30 min; (x) 79, DBU, LiCl, MeCN, R.T., 1 h; (y) LiOH, MeOH, 12 h, R.T.; (z) TFA, reflux, 2 h

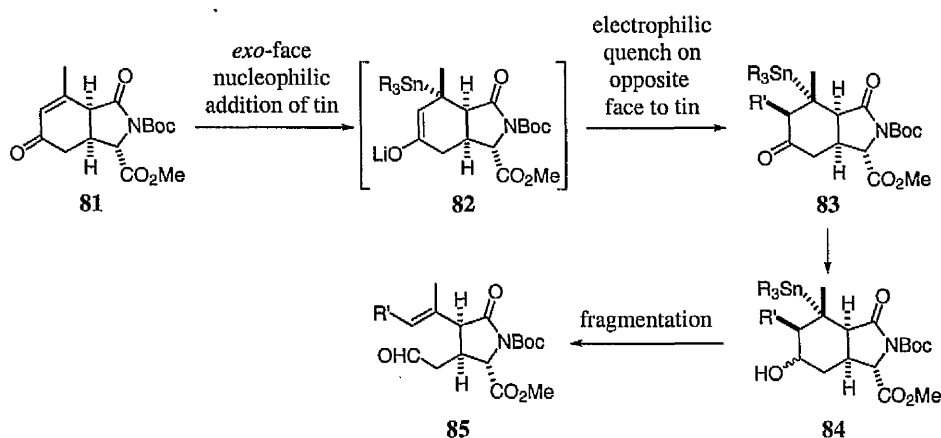
Scheme 14: Clayden Group Enantioselective Synthesis of Isodomoic Acid C

the formate ester, as the silyl protecting group was not stable to the oxidation conditions.

It is unfortunate that this elegant synthesis is limited by the formation of a 1,1-disubstituted alkene in the side-chain, and does not address the additional challenge of forming the trisubstituted alkene present in the other members of the isodomoic acid family (isomers A, B and D to F).

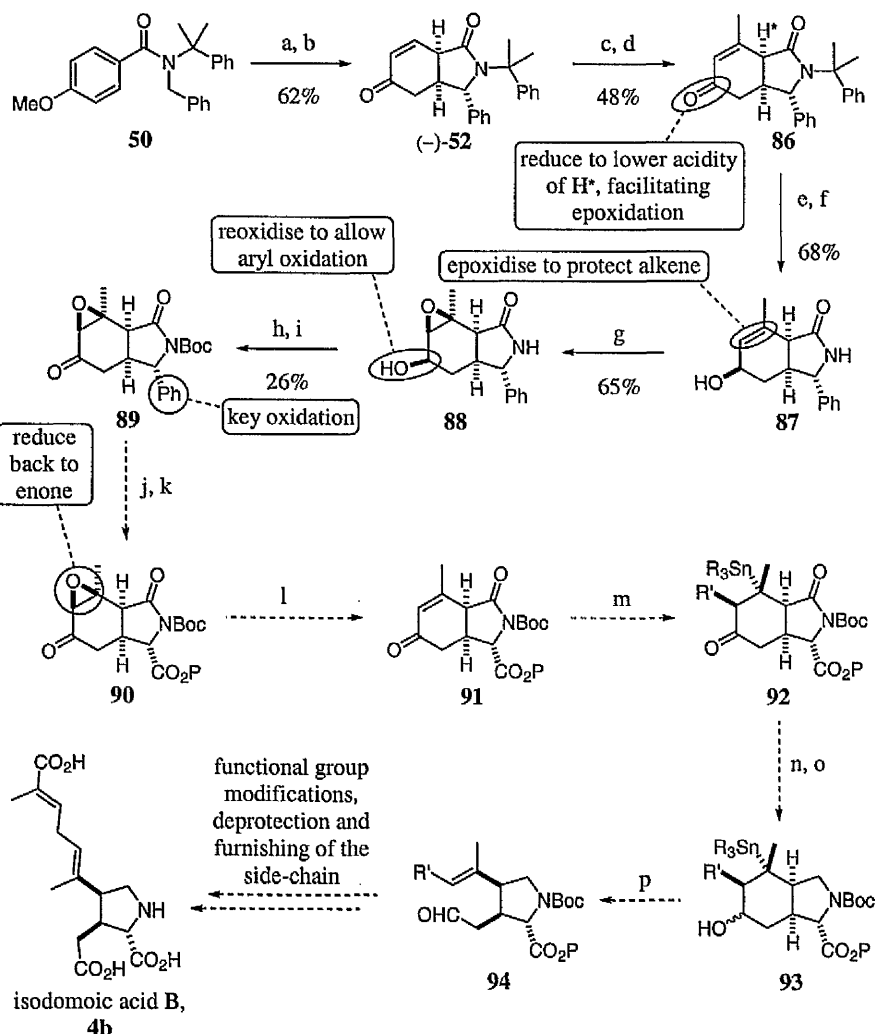
1.2.5 Studies towards other Isodomoic Acids: Approaches to the Trisubstituted Alkene

Extension of Tchabanenko's kainic acid synthesis⁵³ to domoic acid and the rest of the isodomoic acids has been attempted by Hebditch,⁶⁰ based on a strategy of sequential nucleophilic and electrophilic functionalisation of methyl enone **81**, with subsequent fragmentation (Scheme 15). The side-chain precursor R' would be chosen to correspond to the desired isodomoic acid.



Scheme 15: Formation of Trisubstituted Alkenes using a Tin-Mediated Fragmentation Reaction

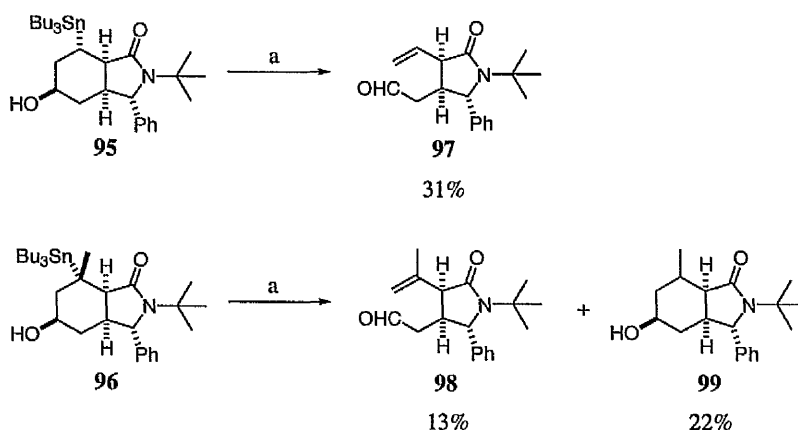
Unfortunately this strategy was beset by chemoselectivity problems, with oxidation of a phenyl ring to give the carboxylic acid at C3 of **81** (in the manner of **55** to **56** in Scheme 13 on page 26) impossible in the presence of the enone alkene (and potentially also the unsaturated isodomoic acid side-chain). In order to solve this problem, a lengthy and undesirable series of protection steps was required (illustrated as an approach to isodomoic acid B in Scheme 16).



Reagents and conditions: (a) LDA, THF, 0 °C, R.T.; sat. aq. NH₄Cl soln.; (b) HCl; (c) MeLi, CuBr, TMSCl, THF, -78 °C; sat. aq. NH₄Cl soln.; (d) Pd(OAc)₂, MeCN; (e) HCO₂H, reflux; (f) CeCl₃, EtOH; NaBH₄; (g) MCPBA, Na₂HPO₄, DCM; (h) (COCl)₂, DMSO, Et₃N, DCM; (i) Boc₂O, DMAP, Et₃N, DCM; (j) NaIO₄, RuCl₃, MeCN, H₂O, EtOAc, buffer; (k) protection of acid; (l) I₂, PPh₃, MeCN; (m) Bu₃SnLi, THF; R'Br; (n) DIBAL; (o) Et₃SiH, BF₃·Et₂O; (p) Pb(OAc)₄, CaCO₃, PhH, reflux

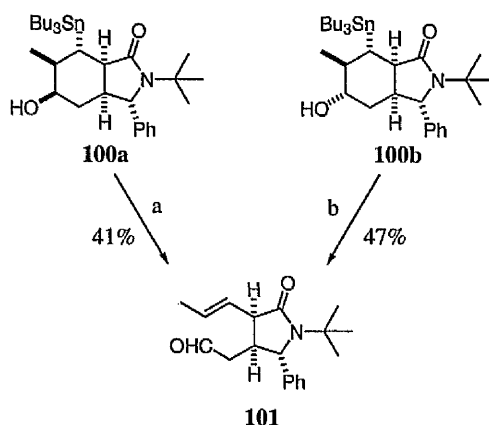
Scheme 16: Hebditch's Protection Strategy towards Isodomoic Acid B

Furthermore, the tin-mediated fragmentation⁶¹ only proceeded in low yield on model systems, with a yield of 31% observed with **95**, and just 13% of the desired product from **96**, a more accurate model for the planned synthetic route (Scheme 17).



Scheme 17

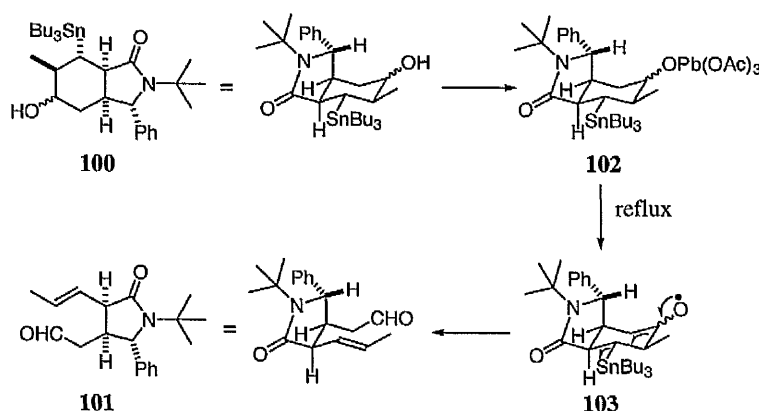
The stereochemistry of fragmentation demonstrated by Isoe *et al.*^{61b} was tested with model compounds **100a** and **100b** (Scheme 18). As expected, both gave *E*-alkene **101** on treatment with portions of lead tetraacetate, although the reaction proceeded more quickly with **100a**, and only required one equivalent of the oxidant (compared with 1.25 equivalents for **100b**). Yields were higher for these reactions, up to 47%, perhaps due to the addition of calcium carbonate to remove acetic acid, which may previously have been responsible for product decomposition and protodestannylation of the starting stannane.



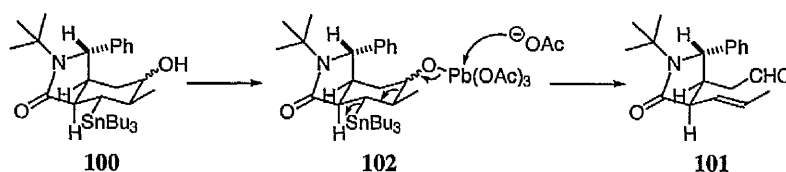
Scheme 18

The stereochemistry of the resultant double bond was unambiguously assigned as *trans*, from the magnitude of the three-bond coupling observed across the alkene

by proton NMR. This was consistent with *anti* elimination of tin by a radical mechanism (Scheme 19),⁶² or the equivalent ionic mechanism involving acetate (Scheme 20).^{61a}



Scheme 19: Tin-Mediated Fragmentation via Homolytic Bond Cleavage

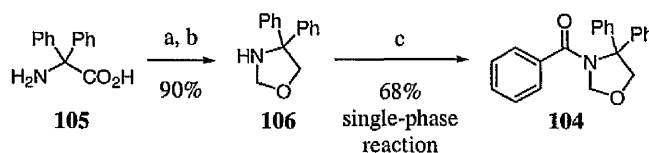


Scheme 20: Ionic Mechanism of Tin-Mediated Fragmentation

1.2.6 Cyclisation of *N*-Benzoyloxazolidines

Purewal has carried out some introductory work on the cyclisation of *N*-benzoyloxazolidines, though it was not developed and applied to the synthesis of the isodomoic acids.⁶³ The early steps in a new proposed synthetic route to these compounds (see Section 1.3) have much precedence in this work.

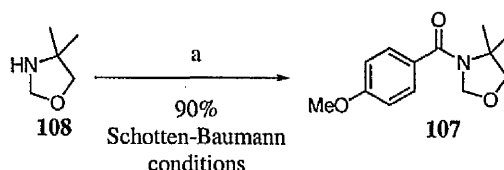
Purewal was able to synthesise a cyclisation precursor, benzoyloxazolidine **104**, in a yield of 61% over three steps, using diphenylglycine **105** as the commercially available starting material (Scheme 21). The amide coupling was performed in a single-phase reaction by stirring the reactants at room temperature with triethylamine in dichloromethane for 3 days.



Reagents and conditions: (a) LiAlH_4 , THF, reflux, 16 h; (b) $(\text{CH}_2\text{O})_n$, MgSO_4 , DCM, R.T., 18 h; (c) PhCOCl , Et_3N , DCM, R.T., 3 days

Scheme 21

His alternative cyclisation precursor, acyloxazolidine **107**, was formed in one step from the commercially available oxazolidine **108**, using the dual-phase Schotten-Baumann conditions,⁶⁴ in 90% yield (Scheme 22).

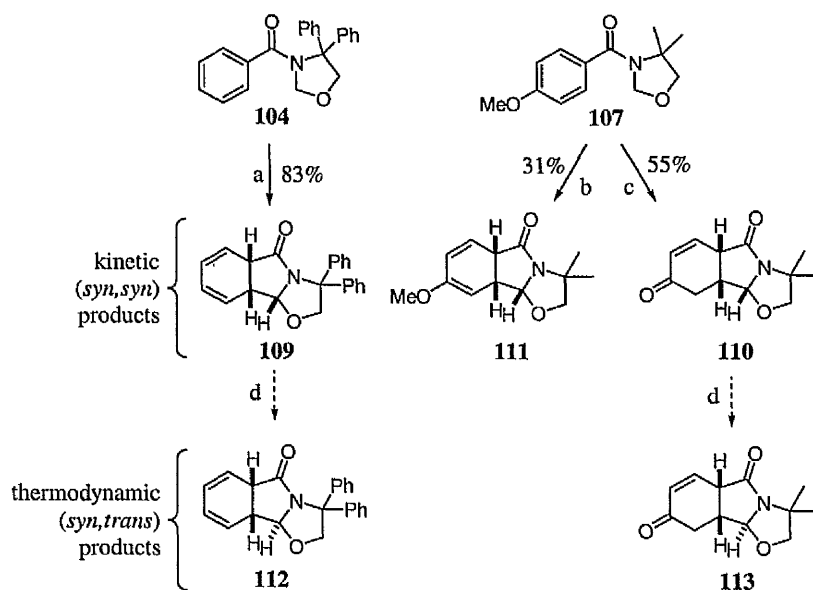


Reagents and conditions: (a) *p*-anisoyl chloride, 3 M aq. NaOH soln., DCM, R.T., 16 h

Scheme 22

Dearomatising cyclisation of **104** gave diene **109** as the kinetic product (Scheme 23); the cyclisation of *para*-methoxy benzamide **107** could be made to give kinetic enone **110** directly, or alternatively enol ether **111** could be isolated by avoiding acidic conditions in the work-up. A method was developed to convert kinetic (*syn, syn*) epimers of the cyclised products to the corresponding thermodynamic (*syn, trans*) tricyclic products, by stirring with hydrochloric acid in diethyl ether, although Purewal did not apply this methodology to compounds **109** or **110** in Scheme 23.

Other experiments showed that lithium diisopropylamide was not sufficiently basic to lithiate these oxazolidines, and use of *tert*- rather than *sec*-butyllithium avoided the problem of nucleophilic addition of the alkyllithium to the aromatic ring. Oxazolidine substitution adjacent to nitrogen was necessary to prevent butyllithium attacking the amide carbonyl.



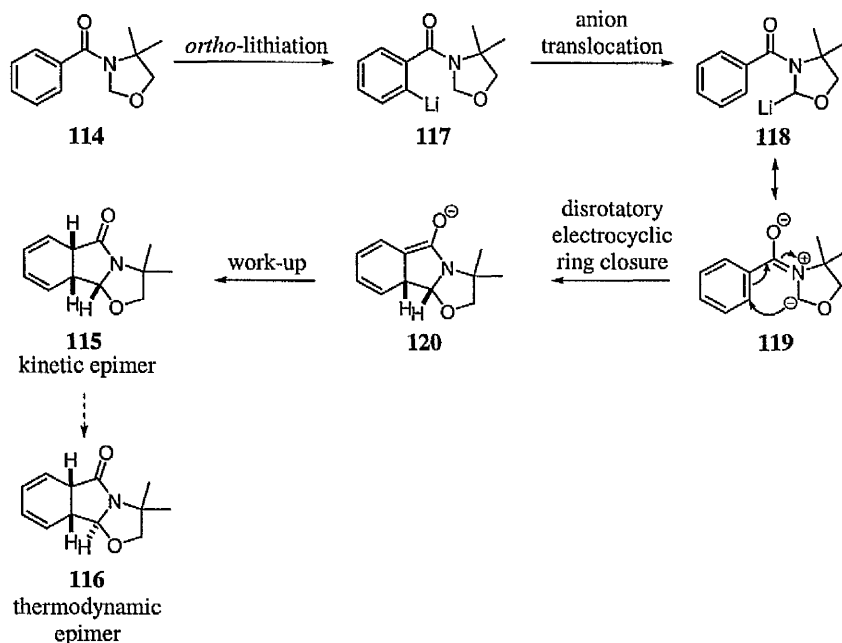
Reagents and conditions: (a) *t*-BuLi, DMPU, THF, -78°C , 16 h; sat. aq. NH_4Cl soln., -78°C , 1 h; (b) *s*-BuLi, DMPU, THF, -78°C , 16 h; sat. aq. NH_4Cl soln., -78°C , 1 h; (c) *t*-BuLi, DMPU, THF, -78°C , 30 min; 0°C , 2 h; sat. aq. NH_4Cl soln., 0°C , 1 h; 1 M aq. HCl soln. (d) 2 M HCl in Et_2O , Et_2O , R.T., 2 h

Scheme 23: Purewal's Cyclisation Reactions

1.2.6.1 Mechanistic Studies

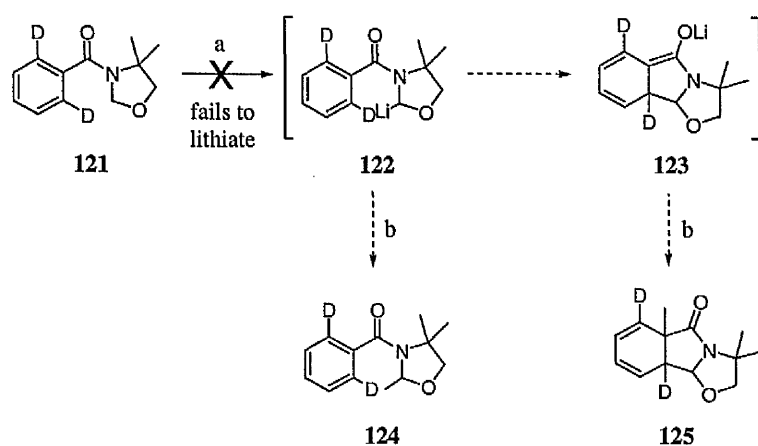
Purewal also carried out studies with *N*-benzoyloxazolidinones to elucidate mechanistic details of their anionic dearomatising cyclisation, for formation of the lithiated cyclisation precursor and its subsequent rearrangement to the dearomatised product.⁶³ Deuterium substitution for protons in the starting material allowed the reaction pathway to be blocked at various stages, exploiting the large primary kinetic isotope effect $k_{\text{H}}/k_{\text{D}}$ observed at low temperatures.

Cyclisation of cyclic precursor **114** supported a proposed pericyclic mechanism (Scheme 24), with the Woodward-Hoffmann rules⁴¹ predicting the formation of epimer **115** as the initial (kinetic) product, later epimerised to **116**. An ionic mechanism would have been expected to give the latter (thermodynamic) product directly.



Scheme 24: Suggested Mechanism for the Anionic Dearomatising Cyclisation

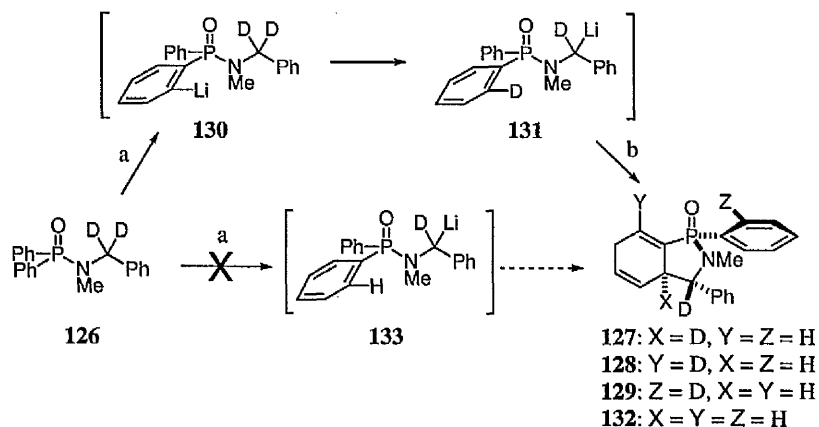
When *ortho*-lithiation was 'blocked' by 2,6-deuteration, no direct α -lithiation was observed (Scheme 25), an indication that anion translocation in the *ortho*-lithiated species is a key feature of the mechanism for oxazolidine cyclisations. This appears to be due to the relatively low kinetic acidity of the α -position of the oxazolidine, because direct α -lithiation has been demonstrated in the cyclisation of *N*-benzyl α -naphthamides.⁶⁵



Reagents and conditions: (a) *s*-BuLi, DMPU, THF, -78°C , 16 h; (b) MeI

Scheme 25

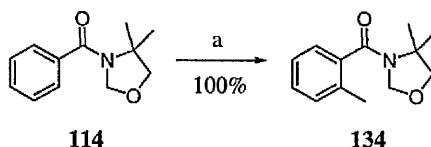
The proposed translocation is consistent with deuterium-labelling studies in *N*-(benzyl)diphenylphosphinamides.⁶⁶ Dideuterated compound **126** in Scheme 26 gave a 1 : 1 : 2 mixture of **127** : **128** : **129** on cyclisation, the statistical ratio expected after an anion translocation (**130** to **131**). Compound **132** was not observed, the product that would have arisen from direct benzylic lithiation and cyclisation.



Reagents and conditions: (a) *s*-BuLi (2.5 eq.), DMPU (6 eq.), THF, -90°C , 30 min; (b) 2,6-di-*tert*-butyl-4-methylphenol, THF, -90°C , 30 min; H_2O

Scheme 26

Associated theoretical work has demonstrated that the barrier to anion translocation in phosphinamides is inhibitive large without a lithium-chelating catalyst (for example DMPU or HMPA).⁶⁷ This also explains the sole formation of *ortho*-quenched products, with no cyclisation, observed by Purewal in the absence of such an additive (Scheme 27).⁶³



Reagents and conditions: (a) *t*-BuLi, THF, -78°C , 16 h; MeI

Scheme 27

It should, however, be noted that another theoretical study by the same group has cast some doubt on the pericyclic mechanism.⁶⁸ Transition state modelling for the cyclisation of *N,N*-dimethylbenzamide anion **135** (Figure 9) exhibited the

geometrical characteristics of a Michael-type ionic reaction, similar to compounds that cannot react in a pericyclic manner (**136** and **137**).

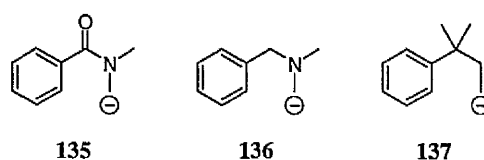
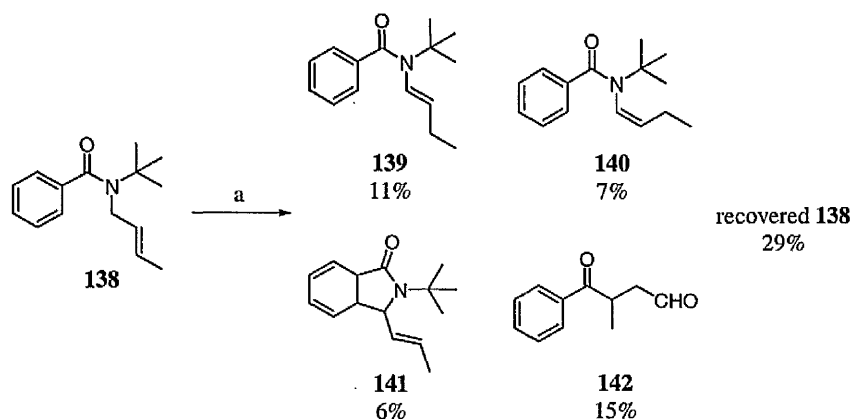


Figure 9: Structures of Anions used for Transition State Modelling

1.2.7 Other Benzamide Cyclisations

Aside from the *N*-benzoyloxazolidine cyclisations performed by Purewal (Section 1.2.6),⁶³ only a very limited number of successful non-benzyl cyclisations onto benzenoid acceptor rings have been reported.

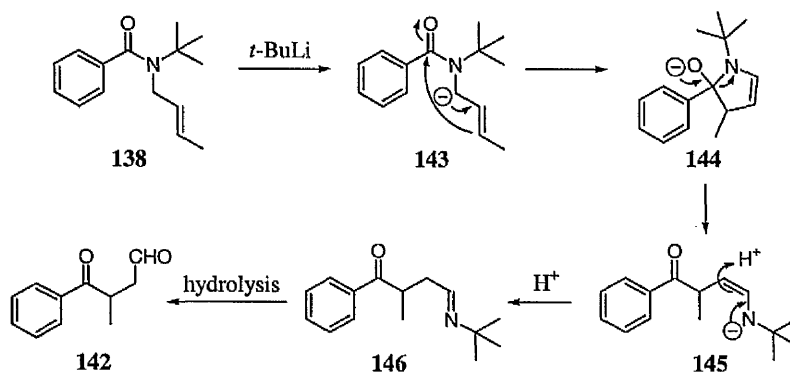
In 2000, Ahmed observed the dearomatising cyclisation of *N*-crotyl-*N*-(*tert*-butyl)benzamide, **138**, in very low yield, amongst a number of other by-products (Scheme 28).⁶⁹ The predominant products arose from rearrangement to enamines, by γ -quenching the lithiated species, or acyl transfer from nitrogen to carbon.



Reagents and conditions: (a) *t*-BuLi, THF, -78°C , 2 h; HMPA, 16 h; sat. aq. NH_4Cl soln.

Scheme 28

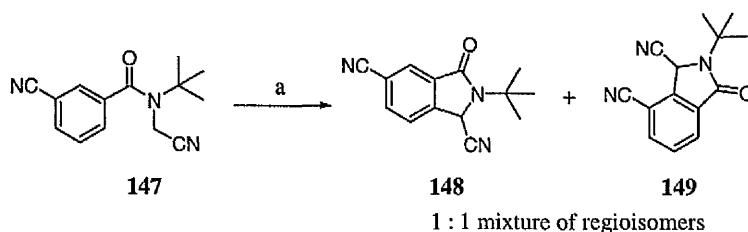
The suggested mechanism of formation of **142** is shown in Scheme 29 below.



Scheme 29: Aldehyde Formation via Acyl Transfer

N-Prenyl- and *N*-allyl-substituted *N*-(*tert*-butyl)benzamides rearranged to the analogous enamines and aldehydes under similar conditions, although in these cases no cyclised products were detected.

More recently, Hamilton successfully cyclised an *N*-(cyanomethyl)benzamide, though spontaneous rearomatisation of the products could not be prevented (Scheme 30).⁷⁰



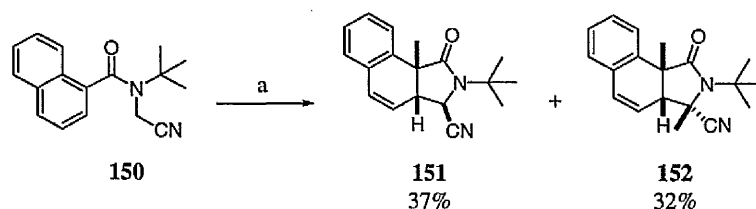
Reagents and conditions: (a) LDA, THF, $-40\text{ }^{\circ}\text{C}$, 4 h; sat. aq. NH_4Cl soln.

Scheme 30

The cyclisation required an electron-withdrawing *meta*-cyano group on the aromatic ring, in addition to the amide. No cyclisation products were observed without this substitution, despite trials using a range of reaction durations and temperatures, differing quantities of base, DMPU as an additive, and with both protic and iodomethane quenches. The lower reactivity of *N*-cyanomethyl benzamides was explained by conjugation of the anion with the cyano group; there was also a possible tendency for the nitrile to react with lithium diisopropylamide.

With an electron-donating *para*-methoxy group instead of the *meta*-cyano group no cyclised products could be obtained.

The delicately balanced factors that control dearomatising cyclisation reactions are further illustrated by Hamilton's work with naphthamides,⁷⁰ which was continued by Luján.⁷¹ Cyanomethyl cyclisation onto an unsubstituted naphthamide gave a combined 69% yield of dearomatised compounds (Scheme 31).



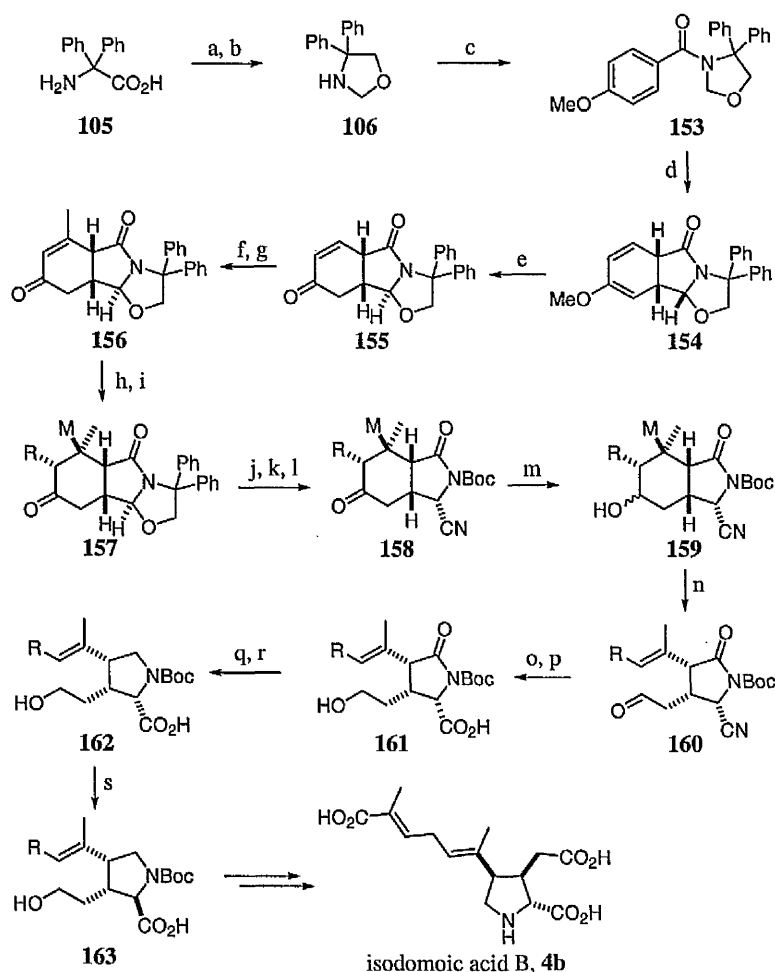
Reagents and conditions: (a) KHMDS (1.5 eq.), THF, R.T., 5 min; MeI

Scheme 31

The improved cyclisation, and higher stability of the products against rearomatisation, were assumed to be due to the lower aromaticity of naphthamides compared with benzamides: naphthamides can cyclise whilst still retaining a six- π -electron aromatic system.

1.3 Aim of the Project

The initial aim of this project was to use Purewal's oxazolidine chemistry to extend the groundwork into the synthesis of the isodomoic acids, most recently carried out by Hebdtich. A proposed route to isodomoic acid B is shown in Scheme 32 below.



Reagents: (a) LiAlH_4 ; (b) $(\text{CH}_2\text{O})_n$; (c) *p*-anisoyl chloride; (d) *t*-BuLi, DMPU; sat. aq. NH_4Cl soln. (e) HCl ; (f) Me_2CuLi ; (g) $\text{Pd}(\text{OAc})_2$; (h) $\text{R}'_3\text{SnLi}$ or $\text{R}'_3\text{SiLi}$; (i) RBr ; (j) TMSCN ; (k) Ca , NH_3 ; (l) Boc_2O ; (m) NaBH_4 ; (n) $\text{Pb}(\text{OAc})_4$ ($\text{M} = \text{Sn}$) or $\text{PhI}(\text{OAc})_2/\text{I}_2$ ($\text{M} = \text{Si}$); (o) NaBH_4 ; (p) base, H_2O ; (q) DIBAL; (r) Et_3SiH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (s) LiHMDS

Scheme 32: Proposed Route to Isodomoic Acid B

A key feature of the proposed synthesis is the opening of the oxazolidine ring of **157** with cyanide.⁶³ This would avoid the need for harsh ruthenium-catalysed oxidation of the phenyl ring, as used in the syntheses of kainic acid and isodomoic

acid C (Sections 1.2.2 and 1.2.4). This is advantageous because the oxidation conditions are not compatible with enone or side-chain unsaturation, exemplified by the complicated protection strategy required by Hebditch (outlined in Section 1.2.5). The 2-hydroxy-1,1-diphenylethyl group on nitrogen that results from the oxazolidine ring-opening is effectively a protecting group, which can be removed under Birch-type conditions.⁶³ Acid **162** resulting from nitrile hydrolysis might be epimerised to give the desired kainoid stereochemistry (method of Taylor *et. al.*).⁷²

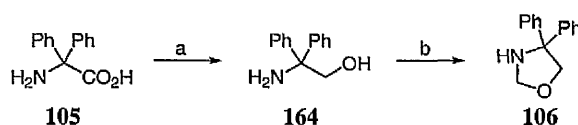
Another point of investigation is the 'metal' used to promote fragmentation, as Hebditch had only limited success with tin. There is precedence for the use of silicon in the chemistry of Posner *et al.*⁷³

Chapter 2: Cyclisation of *N*-Benzoyloxazolidines

2.1 Preliminary Cyclisation

2.1.1 Preparation of the Cyclisation Precursor

Preparatory work required the formation 4,4-diphenyloxazolidine from diphenylglycine using Purewal's method (Scheme 33).⁶³



Reagents and conditions: (a) LiAlH₄, THF, reflux, 16 h; (b) (CH₂O)_n, MgSO₄, DCM, R.T., 18 h

Scheme 33

Lithium aluminium hydride reduction of diphenylglycine to 2,2-diphenylglycinol, at reflux in tetrahydrofuran, with at least 2.3 equivalents of reducing agent, initially gave poor results. Yields were improved by adding the lithium aluminium hydride as a powder, rather than as a tetrahydrofuran slurry, and yet further by utilising a commercially sourced solution in tetrahydrofuran (Table 2). An optimal yield of 97% was obtained by heating at reflux for 22 hours, using 2.3 equivalents of lithium aluminium hydride.

Lithium Aluminium Hydride		Reflux	Yield of 164
Slurry in THF	2.3 eq.	22 h	20%
Solid	2.3 eq.	16 h	45%
Solution in THF	2.3 eq.	22 h	97%
	2.3 eq.	3 days	80%
	3.4 eq.	3 days	88%

Table 2: Optimisation of the Reduction of Diphenylglycine

These conditions were very similar to those with which Purewal obtained 90% yield of the required product, but the isolated yield was maximised by applying the stringent work-up procedure of Leonard *et al.* to avoid emulsions: successively adding water (one millilitre per gram of lithium aluminium hydride used), 15% aqueous sodium hydroxide (one millilitre per gram), then additional water (three millilitres per gram).⁷⁴

2,2-Diphenylglycinol was cyclised to the oxazolidine by condensation with paraformaldehyde, reproducing Purewal's quantitative yield. Thus 4,4-diphenyloxazolidine was formed from diphenylglycine in 97% yield.

As discussed in Section 1.2.6, Purewal used two methods for coupling oxazolidines with aroyl chlorides. He applied dual-phase Schotten-Baumann conditions⁶⁴ to the reactions of 4,4-dimethyloxazolidine **108** with *para*-anisoyl chloride and benzoyl chloride, with isolated yields of 90% and 100% respectively. Also, a single-phase reaction in dichloromethane was used to benzoylate 4,4-diphenyloxazolidine **106**, though the yield was significantly lower (see Table 3 below).



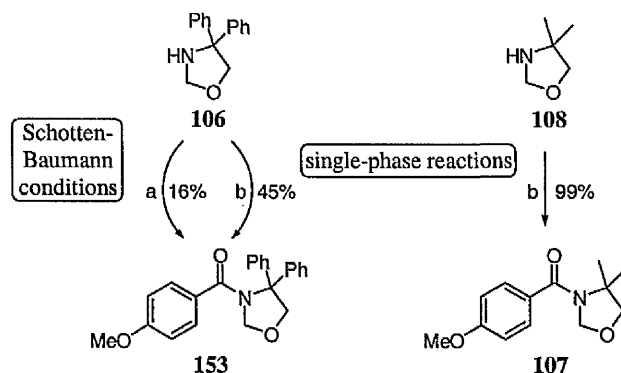
Oxazolidine	Aroyl Chloride	Conditions	Yield
 108	benzoyl	Schotten-Baumann	100%
	<i>para</i> -anisoyl	Schotten-Baumann	90%
 106	benzoyl	single-phase	68%

Table 3: Conditions and Yields for Purewal's Amide Coupling Reactions

Applying Schotten-Baumann conditions to the coupling of **106** with *para*-anisoyl chloride gave a discouraging 16% yield, after reacting for twenty hours (Scheme 34). Changing to the single-phase reaction conditions led to an

improvement in yield, to 45%, but a reaction duration of three days was required. For comparison, these single-phase conditions were tested with **108** and *para*-anisoyl chloride, giving the amide in a yield of 99%! (These results are summarised in Scheme 34.) Thus it appeared that the two bulky phenyl groups on the oxazolidine, rather than the *para*-methoxy group on the acid chloride, were responsible for the low observed yields of **153**.



Reagents and conditions: (a) *p*-anisoyl chloride, 3 M aq. NaOH, DCM, R.T., 20 h; (b) *p*-anisoyl chloride, Et₃N, DCM, R.T., 3 days

Scheme 34: Initial Trials of Amide Coupling Reactions

Given that the single-phase reaction showed more promise, optimisation of the reagents and conditions was attempted (see Table 4; entry 1 shows the initial conditions). 4-(Dimethylamino)pyridine appeared to over-activate the acid chloride, as only a trace of the desired product was obtained amongst a mixture of products also containing the starting oxazolidine and other unidentified compounds (entry 2). Attempting to fully deprotonate the oxazolidine with sodium hydride before adding the anisoyl chloride gave an isolated yield of 11% in another messy reaction (entry 3).

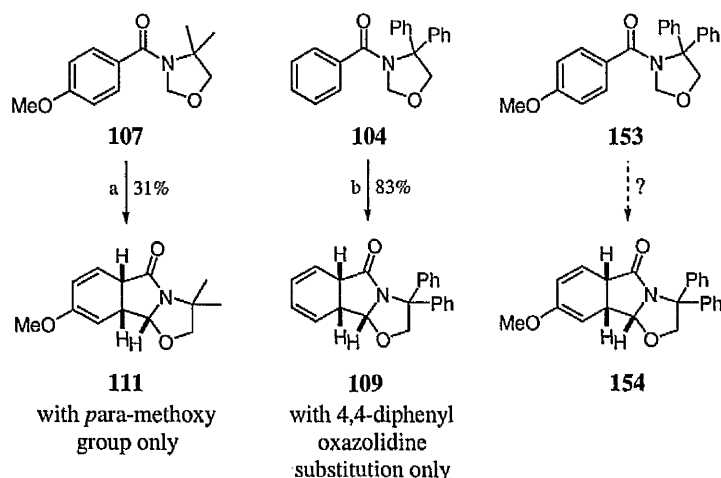
Approach of the hindered oxazolidine to the acid chloride could involve a high-energy transition state, but the strong amide bond in the product would be expected to make the reaction energetically favourable overall. The solvent was changed to 1,2-dichloroethane (a solvent of similar polarity to dichloromethane, but with a boiling point of 83 °C) to give a 95% yield of **153** (over two steps from **164**) after heating at reflux for 18 hours (entry 4).

	Reagents	Conditions	Yield
1	ArCOCl (1.2 eq.), Et ₃ N, DCM	R.T., 3 days	45%
2	ArCOCl (1.5 eq.), DMAP (1.1 eq.), Et ₃ N, DCM	R.T., 3 days + reflux, 22 h	trace trace
3	ArCOCl (1.5 eq.), NaH (1.2 eq.), THF	R.T., 18 h	11%
4	ArCOCl (1.5 eq.), Et ₃ N, 1,2-DCE	reflux, 18 h	95%

Table 4: Optimisation of the Amide Coupling Reaction

2.1.2 Dearomatising Cyclisation

Previous work by Purewal has involved cyclising benzamides with either a *para*-methoxy aryl substituent (**107**), or 4,4-diphenyl substitution on the oxazolidine ring (**104**), but never both (Scheme 35).



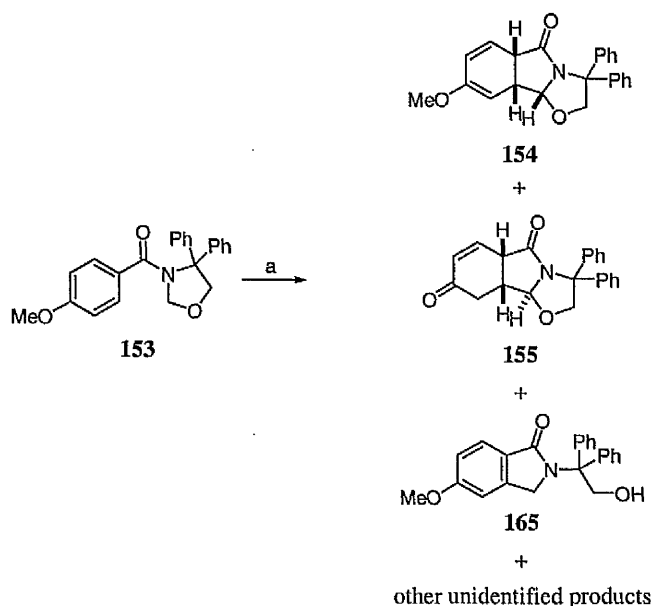
Reagents and conditions: (a) *s*-BuLi (1.5 eq.), DMPU (30 eq.), THF, -78°C , 16 h; sat. aq. NH_4Cl soln., -78°C , 1 h; (b) *t*-BuLi (1.5 eq.), DMPU (30 eq.), THF, -78°C , 16 h; sat. aq. NH_4Cl soln., -78°C , 1 h

Scheme 35: Related Cyclisations Performed by Purewal

The better yield was obtained for the cyclisation of **104**, using *tert*-butyllithium and very dilute reaction conditions (around 10 mM starting material concentration). Application of this method to **153** gave no conversion from the starting amide, probably a result of failed lithiation (deep red colouration of the

reaction mixture, usually indicative of substrate deprotonation by butyllithium in these cyclisation reactions, was not observed). It did not seem sensible to spend time optimising these inefficiently dilute and extremely moisture sensitive conditions prior to scale-up. Instead, reactions involving less solvent were pursued, for which there was precedence in Purewal's work, though they were lower yielding on his substrates.

These more concentrated reaction conditions (30 mM in tetrahydrofuran) gave good conversion from the starting benzamide, although the crude product mixtures were initially rather messy, with enol ether **154** amongst a number of other products (Scheme 36). It should be noted that there was evidence of the enol ether in the crude product mixtures occasionally being hydrolysed to enone **155** between sampling and NMR analysis. This was avoided by storing the deuterated chloroform over anhydrous potassium carbonate prior to use.

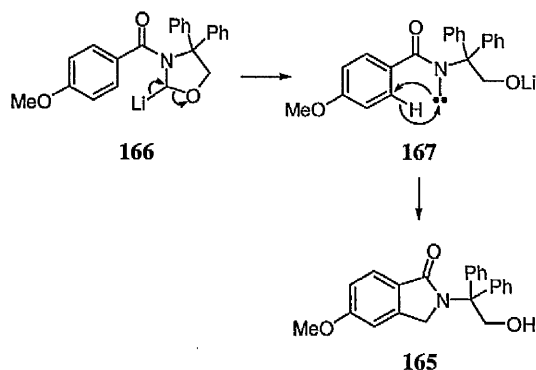


Reagents and conditions: (a) *t*-BuLi (1.5 eq.), DMPU (6 eq.), THF, -78°C , 40 min; 0°C , 2 h; sat. aq. NH_4Cl soln., 0°C , 1 h; 1 M aq. HCl soln.

Scheme 36: Products Obtained on Cyclisation of **153***

* See Table 5 on page 49 for yields for this reaction under various conditions

One by-product was **165**, which may have arisen from anion rearrangement to a carbene, followed by insertion of this carbene into an *ortho* aryl carbon–hydrogen bond, as suggested by Purewal and outlined in Scheme 37.⁶³



Scheme 37: By-Product Formation via a Carbene-Insertion Reaction

The work-up procedure incorporated acid washes of the organic extracts, intended to hydrolyse enol ether **154** to the corresponding enone (exclusively the *syn,syn* epimer by precedent).⁶³ As this hydrolysis seemed to be so inconsistent (sometimes occurring in NMR samples, but not going to completion with acid washes), isolation of the enol ether was attempted, by washing with water instead of aqueous acid.

A number of cyclisation reactions were performed, each using 30 mM starting material concentration in tetrahydrofuran and the quantities of reagents given in Scheme 36; the results are summarised in Table 5 below. In all cases almost total recovery of mass was achieved. The product ratio **153** : **165** : **154** was estimated from proton NMR spectra of the crude product mixtures.

It can be seen that it was necessary to warm the reaction to $-20\text{ }^{\circ}\text{C}$ or above to initiate cyclisation (entries 4 and 5). Entry 5 seems to indicate that at lower reaction temperatures carbene-insertion product **165** is a more significant by-product. A good, reproducible yield of enol ether was obtained using the temperature regime shown in entries 1 and 7. This was scaled up successfully, with complete consumption of starting material, though slightly more by-product was formed (entry 8).

Purification of the crude product mixtures was not straightforward. Using basified petroleum ether–ethyl acetate solvent systems (typically 8 : 1 to 4 : 1 with 1% triethylamine), it was possible to obtain a pure sample of **165** by flash column chromatography, but not to separate the enol ether from any residual starting material. Recrystallisation of the enol ether was impossible, as it always resulted in partial hydrolysis.

Characterisation of **154** was on a sample obtained from a reaction where a negligible amount of starting material remained in the crude product mixture. Its relative stereochemistry was assigned from nuclear Overhauser effect experiments.

Temperature Regime Before Quenching	Product Ratio			Additional Notes
	Amide 153	By-Product 165	Enol Ether 154	
1 -78 °C, 40 min; 0 °C, 2.5 h	7	20	73	200 mg scale
2 -78 °C, 1 h; -40 °C, 18 h; 0 °C, 2.5 h	45	9	46	messy
3 -78 °C, 1 h; -50 °C, 1.5 h; -40 °C, 16 h; 0 °C, 2.5 h	42	18	40	3.1 eq. of <i>t</i> -BuLi used; messy reaction
4 -78 °C, 1 h; -40 °C, 18 h	100	0	0	
5 -78 °C, 1 h; -20 °C, 18 h	0	60	40	
6 -78 °C, 1 h; 0 °C, 16 h	22	26	52	
7 -78 °C, 40 min; 0 °C, 2.5 h	12	16	72	repeat of entry 1 (reproducibility check)
8 -78 °C, 40 min; 0 °C, 2.5 h	0	33	67	repeat of entry 1 (scale-up to one gram)

Table 5: Cyclisation Optimisation

The highest isolated yields of **154** were 29% and 35%, for entries 5 and 8 respectively. The apparent loss of **154** during purification was possibly due to its hydrolysis on the column, although hydrolysis products were not detected by thin layer chromatography.

It should also be noted that the enol ether appeared to rearomatise readily, and great care had to be taken when removing solvents, especially if heating was required. No rearomatised product was isolated, but its presence could be identified by a number of characteristic aromatic proton NMR signals around δ 8.2, and a broad singlet at δ 4.65 (indicated by arrows in Figure 10). This was a major by-product when recrystallisation from hot solvents was attempted.

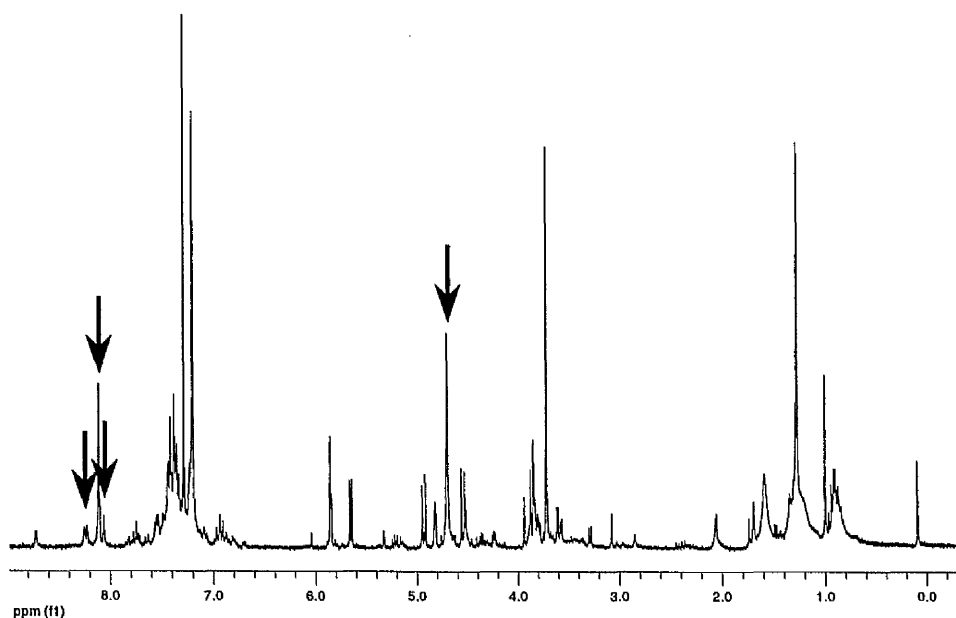
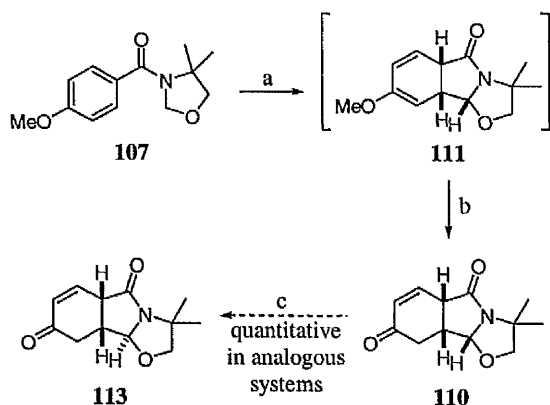


Figure 10: NMR Signals due to Rearomatisation in the Cyclisation Reaction

2.1.3 Controlled Hydrolysis and Epimerisation of the Cyclisation Product

Purewal's work with dimethyl oxazoloisindolones demonstrated the relative instability of enol ether **111**, with an acid wash giving complete conversion to *syn,syn* enone **110** (Scheme 38). This enone was stable enough to be isolated, and was usually the initial cyclisation product. Quantitative conversion to the *syn,anti*

epimer was effected in analogous systems by stirring at room temperature for two hours with a solution of hydrochloric acid in diethyl ether.

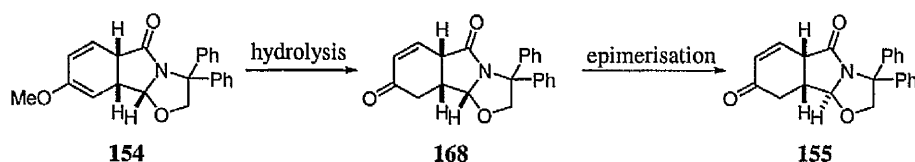


Reagents and conditions: (a) *t*-BuLi, DMPU, THF, -78°C , 16 h; sat. aq. NH_4Cl soln., -78°C , 1 h; (b) 1 M aq. HCl; (c) 2 M HCl in Et_2O , Et_2O , R.T., 2 h

Scheme 38: Purewal's Hydrolysis and Epimerisation of Cyclisation Products

A similar treatment of enol ether **154** with hydrochloric acid in diethyl ether did not initially give clean conversion to either potential enone epimer: the resulting product mixture typically appeared to contain various enone- and enol ether-related regio- and stereoisomers, along with evidence of rearomatisation.

Stirring a dichloromethane solution of **154** with silica, to provide a far milder source of acid, showed a general trend of slow conversion to the thermodynamic enone epimer **155**, via *syn,syn* epimer **168**, as shown in Scheme 39 and Table 6. The three data entries came from three separate reaction vessels. Coupled with variable but significant overnight loss of solvent, this may account for the observed inconsistencies.



Reagents and conditions: silica, DCM or 1,2-DCE, R.T., 1–5 days (see Table 6)

Scheme 39

Duration	Reaction Profile (Product Ratios) by Proton NMR		
	Enol Ether	<i>Syn,syn</i> Enone	Thermodynamic
	154	Epimer 168	Enone Epimer 155
1 day	82	< 1	18
2 days	7	37	56
5 days	48	11	41

Table 6: Mild Hydrolysis and Epimerisation on Stirring with Silica

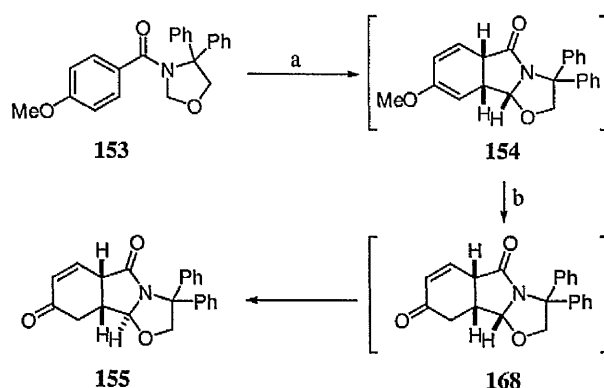
Stirring at room temperature with silica in 1,2-dichloroethane (a less volatile solvent) gave the thermodynamic enone epimer in the same way, with 21% conversion to **155** after a day, 40% after 2 days, and 72% after 5 days. However, in these cases, proton NMR analysis showed no evidence of the *syn,syn* enone epimer being present, and also indicated that some rearomatisation was taking place. It was impossible to tell whether this was indicative of the situation in the reaction mixture, or a result of the heat needed to remove the solvent.

A more encouraging hydrolysis was carried out in an NMR tube, by adding a trace of concentrated hydrochloric acid, as an emulsion in chloroform, to a pre-prepared sample of **154** in deuterated chloroform. An NMR sample acid concentration of 0.9 mM gave no reaction after 5 days, but increasing the concentration to 5.7 mM gave clean conversion to the thermodynamic enone within 1.5 hours.

The identity of the thermodynamic enone was confirmed by treating an NMR sample of a mixture of **168** and **155** with hydrochloric acid in the same way. Again, this rapidly gave conversion to a single enone, the *syn,anti* epimer, confirming that this epimer was indeed the thermodynamic reaction product.

The problems experienced in attempting to isolate the unstable enol ether **154**, along with success in cleanly converting it to the thermodynamic enone with acid, led to the development of a two-step tandem reaction. The crude cyclisation product mixture was treated with acid to give **155** directly, without isolation of the

intermediate enol ether. (Once isolated, redissolving **154** in diethyl ether was often troublesome, contributing to the observed decomposition.) Initially the quenched cyclisation mixture was extracted into dichloromethane prior to acidic hydrolysis and epimerisation, closely mimicking the successful NMR sample test reaction conditions. Problems with subsequent removal of DMPU were avoided by instead extracting the crude cyclisation mixture into diethyl ether, from which the DMPU was easily washed out. In this case, treatment of the solution with hydrochloric acid in diethyl ether effected complete conversion of **154** to **155** (Scheme 40).



Reagents and conditions: (a) *t*-BuLi, DMPU, THF, $-78\text{ }^{\circ}\text{C}$, 40 min; $0\text{ }^{\circ}\text{C}$, 2.5 h; sat. aq. NH_4Cl soln., $0\text{ }^{\circ}\text{C}$, 1 h; extraction into Et_2O ; (b) 2 M HCl in Et_2O , Et_2O , R.T., 17 h

Scheme 40

It is interesting that the procedure of treating the unisolated solution of **154** with hydrochloric acid in diethyl ether was successful, even though an aqueous acid wash or use of the same acid solution after isolation of **154** did not have the desired effect. This probably resulted in part from the poor solubility of **154** in diethyl ether.

Thus the conditions given in Scheme 40 gave satisfactory formation of enone **155** from **153**, with complete mass recovery in the crude reaction product mixture. A typical composition of this mixture was 15:20:65 of compounds **153**:**165**:**155**, estimated by proton NMR, where **165** is the unwanted by-product shown in Scheme 37 on page 48.

Despite this level of conversion, isolation of the enone also proved to be difficult, with isolated yields of **155** never exceeding 35%, and various compounds supposed to be oxidation products regularly seen with the enone. This highest isolated yield was achieved with flash column chromatography of the crude product mixture of a 400 milligram scale reaction, using a degassed petroleum ether–ethyl acetate solvent system basified with 1% triethylamine. Scaling up to 1.1 gram gave a lower isolated yield of 24%, reflecting a lower conversion of **153** to **155** observed by NMR analysis of the crude reaction mixture. (This probably resulted from difficulty in maintaining the larger solvent volume at low temperature during the cyclisation, giving deviation from the carefully optimised conditions developed on the smaller scale.)

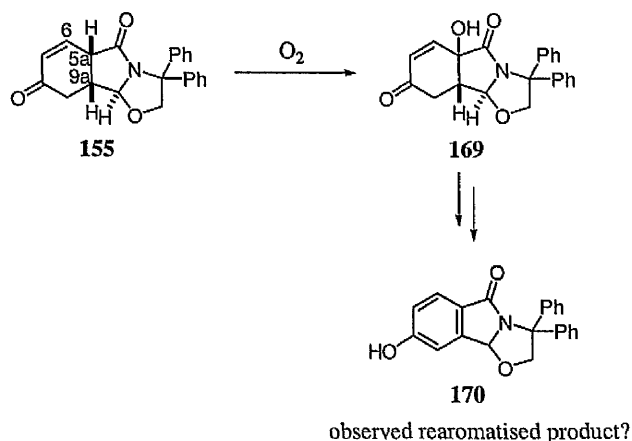
In conclusion, the sequence of cyclisation of **153**, followed by hydrolysis and epimerisation of the kinetic cyclisation product, avoiding isolation of the unstable intermediate enol ether, was moderately successful. From NMR analysis and mass recovery, conversion appeared to be good, albeit with sensitivity to the precise reaction conditions. The resulting thermodynamic enone **155** was also unstable and difficult to isolate, leaving its stabilisation as the next area for investigation, discussed in Section 2.2.

2.2 Enone Stabilisation

2.2.1 Conjugate Addition Reactions

On cyclising compound **153**, unsuccessful attempts were made to isolate the initial enol ether product **154** (Section 2.1.2), then thermodynamic enone **155** directly from **153** (Section 2.1.3).

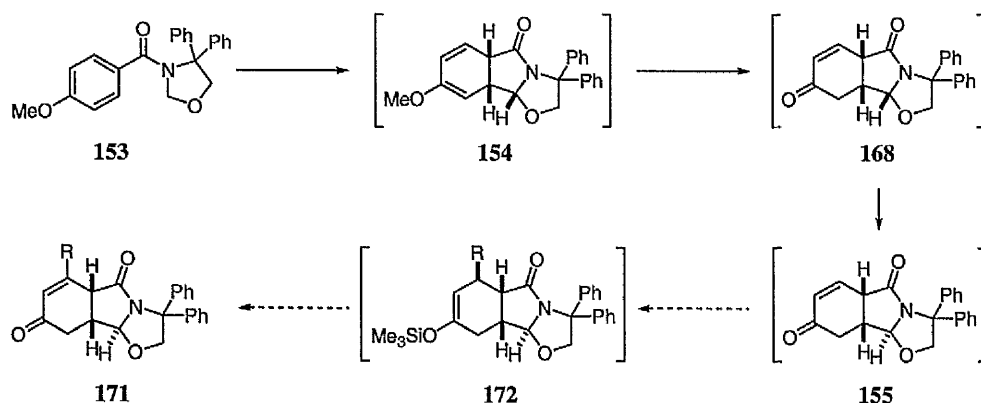
The sequence of oxidative degradation of the cyclised products, cited in Section 2.1.3 as the probable reason for the difficulty in isolating enone **155** in high yield, was thought to begin with oxidation at C5a, as shown in Scheme 41. On one occasion a compound with a spectrum similar to that of enone **155** (also known to be in the mixture) was observed by proton NMR spectroscopy. However, no signal due to C5aH was present, and loss of coupling to this position in the signals for C9aH and C6H was also observed, supporting its assignment as **169**, resulting from hydroxylation at C5a. Compound **170** might be expected to be the final rearomatised product.



Scheme 41: Possible Mechanism for the Oxidative Decomposition of **155**

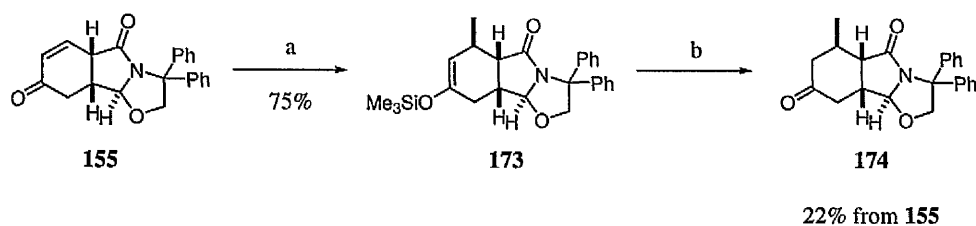
In an attempt to make the C5a position of **155** more resistant to oxidation, conjugate addition reactions were carried out on the crude cyclised product. It was hoped that, on reoxidation to the enone (**171** in Scheme 42), the newly introduced substituent at C6 might sterically shield C5a, inhibiting oxidation at

this position. As substitution at C6 was required in the proposed synthetic route (see Section 1.3), this method of enone stabilisation would have been ideal.



Scheme 42: Enone Stabilisation using Conjugate Addition Reactions

A small-scale (90 milligram) test reaction of the *exo*-face conjugate addition of dimethylcuprate to a pure sample of enone **155** was performed, trapping the addition product as trimethylsilyl enol ether **173** (Scheme 43). Although **173** could not be isolated, the conversion from **155** was estimated to be 75% based on proton NMR data. Compound **174** was deemed to be a likely by-product in a subsequent palladium(II) reoxidation of **173**, effected by any impurity acetic acid present. In this test reaction **174** was deliberately formed by stirring **173** with 80% aqueous acetic acid,⁷⁵ to facilitate its identification if formed in later reactions.

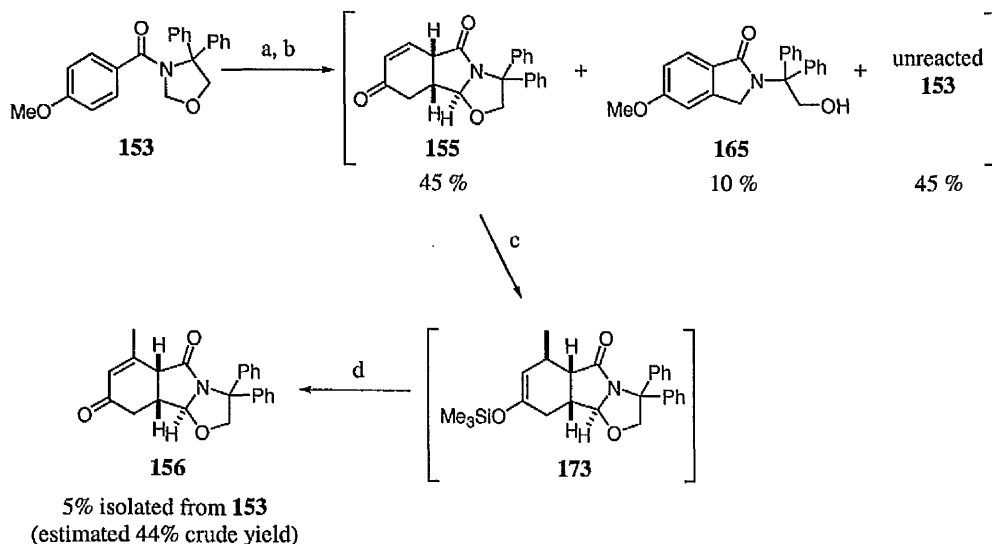


Reagents and conditions: (a) MeLi, CuBr, THF, -78°C , 20 min; **155**, TMSCl, THF, -78°C , 1.5 h; sat. aq. NH_4Cl soln.; (b) 80% AcOH/ H_2O , R.T., 1 h

Scheme 43

The same reaction was attempted on the crude product mixture resulting from the cyclisation of **153** on a gram scale. In addition to 45 mol% **155**, this mixture

contained approximately 45 mol% unreacted **153** and 10 mol% carbene-insertion by-product **165** (Scheme 44). (Lower conversion from **153** to **155** in this reaction may have been due to slower addition of the butyllithium. This was necessary to keep the reaction mixture at low temperature (below $-76\text{ }^{\circ}\text{C}$) during the addition, but seemed to result in a larger proportion of the newly-formed organolithium being reprotonated during the longer period allowed for lithiation.)



Reagents and conditions: (a) *t*-BuLi, DMPU, THF, $-76\text{ }^{\circ}\text{C}$, 40 min; $0\text{ }^{\circ}\text{C}$, 2.5 h; sat. aq. NH_4Cl soln., $0\text{ }^{\circ}\text{C}$, 1 h; (b) 2 M HCl in Et_2O , Et_2O , R.T., 17 h; (c) MeLi, CuBr, THF, $-78\text{ }^{\circ}\text{C}$, 20 min; **155** (45 mol% in mixture with **165** and **153**), TMSCl, THF, $-78\text{ }^{\circ}\text{C}$, 1.5 h; sat. aq. NH_4Cl soln.; (d) $\text{Pd}(\text{OAc})_2$, MeCN, R.T., 17 h

Scheme 44

The conjugate addition step appeared to proceed well, with the crude product mixture containing similar quantities of **153** and **173**, as estimated by proton NMR, i.e. approximately quantitative conversion of **155** to **173**. Reaction of this crude mixture with palladium(II) acetate (following Hebditch's successful procedure in forming **86** in Scheme 16 on page 31)⁶⁰ gave encouraging conversion of **173** to **156**, with an unisolated yield of 44% from **155** (estimated from proton NMR data by comparison with the amount of **153** remaining in the crude mixture). However, problems with decomposition and loss of mass on column chromatography, reminiscent of those encountered with **155**, gave an overall isolated yield of just 5% for the formation of **156** from **153**.

The application of conjugate addition reactions to enone stabilisation was extended by introducing the more bulky phenyldimethylsilyl group at C6, using a nucleophile derived from phenyldimethylsilyllithium, **174a** (synthesised as a solution in tetrahydrofuran).⁷⁶ Figure 11 summarises the formation of phenyldimethylsilyllithium, by reaction of phenyldimethylsilyl chloride with lithium metal. The silyllithium initially formed rapidly reacts with more phenyldimethylsilyl chloride to form disilane **174b**, but, with excess lithium, the desired silyllithium becomes the predominant species in solution. Concentrations of up to 0.67 M were achieved for fresh solutions, and this increased further on standing at $-18\text{ }^{\circ}\text{C}$ for several days, to approximately 0.8 M.

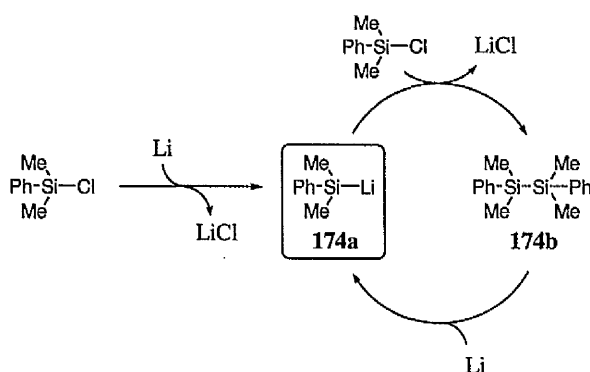
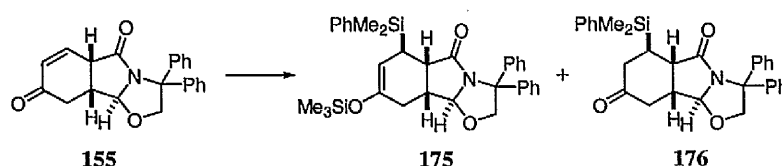


Figure 11: Formation of Phenyldimethylsilyllithium

Phenyldimethylsilyllithium itself did not react with enone **155**, either conjugatively (as reported by Fleming *et al.* for a β -amino enone)⁷⁷ or directly at the enone carbonyl. Transmetalation to zinc⁷⁸ did lead to reaction of the resultant silyl zincate, exclusively in a conjugate fashion. Two variants of the method were tried (Scheme 45). In the first, chlorotrimethylsilane was included at the start of the reaction to enhance enone electrophilicity. A drawback of this was the potential for reaction of the silyl chloride with phenyldimethylsilyllithium. In the second, chlorotrimethylsilane was added as a quench after the reaction's duration.



Reagents and conditions: **Method 1:** Et_2Zn , PhMe_2SiLi , THF, 0°C , 10 min; **155**, TMSCl , THF, -78°C , 1 h; R.T., 1.5 h; sat. aq. NH_4Cl soln.; **Method 2:** Et_2Zn , PhMe_2SiLi , THF, 0°C , 5 min; **155**, THF, -78°C , 40 min; TMSCl , -78°C , 30 min; R.T., 1.5 h; sat. aq. NH_4Cl soln.

Scheme 45

In both cases proton NMR showed that the crude product mixture contained ketone **176** (formed by hydrolysis of **175**) along with the required silyl enol ether, but no evidence of unreacted **155** or oxidation products. The crude starting material also contained amide **153** and carbene-insertion product **165** from the cyclisation reaction: both were left unchanged after the conjugate addition.

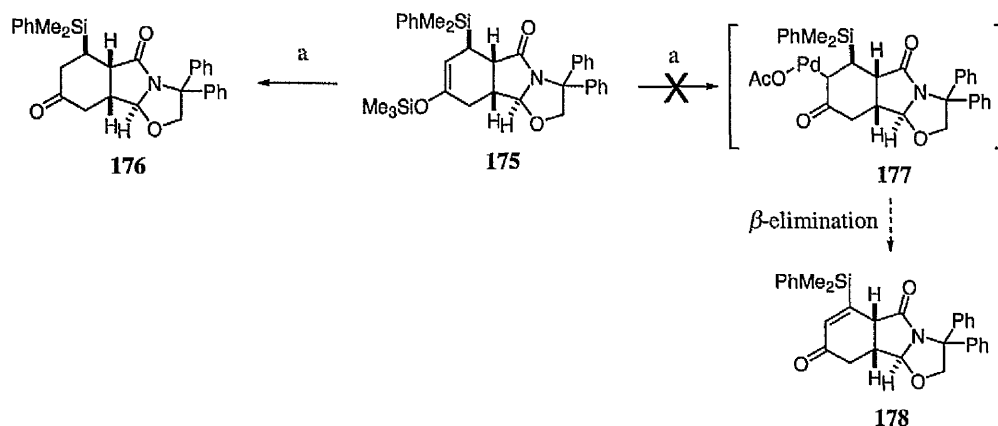
As **175** could not be isolated, comparison of the reactions was by integration of proton NMR spectra. Amide **153**, assumed to be unaffected by the reaction conditions and completely extracted along with **175** and **176**, was used as a control. As a second point of comparison, a two-step procedure consisting of method 2 followed by complete hydrolysis of **175** was carried out. (The hydrolysis was again effected by stirring the crude product mixture from the first reaction with 80% aqueous acetic acid.)⁷⁵ This one-pot, two-step protocol gave an isolated yield of 61% of **176** based on the estimated amount of **155** in the original crude starting material.

Table 7 summarises the results. Firstly the ratio **175** : **176** was scaled to equalise the amount of control (**153**) in each. Secondly, these were converted to projected yields based on the isolated amount of **176** from the two-step reaction. The tabulated data indicate that Method 2 was superior, both in terms of the total amount of conjugate addition and minimisation of undesired hydrolysis of **175**.

	Relative amount in the crude product mixture*			Estimated potential yields†		
	175	176	175 + 176	175	176	175 + 176
Method 1	0.53	0.62	1.15	31	36	67
Method 2	0.84	0.45	1.29	49	26	75
Two-step	0.00	1.05	1.05	0	61‡	61

Table 7: Comparison of Conjugate Addition Methods

To allow further substitution β to the carbonyl (i.e. introducing the required methyl group as well as the fragmentation-directing silyl group), reoxidation of the silyl enol ether would be necessary. The conditions previously used for the reoxidation of **173** to **156** (Scheme 44) were applied to the product mixtures resulting from both Method 1 and Method 2. However, in both cases, only hydrolysis of the enol ether was observed. Incorporation of palladium may have been prevented by the steric bulk of the phenyldimethylsilyl group; an acetate anion from the palladium acetate reagent then effected the silyl enol ether cleavage (Scheme 46).



Reagents and conditions: (a) $\text{Pd}(\text{OAc})_2$, MeCN, R.T., 17.5 h

Scheme 46

* Compared with **153** (1.00) in each case, as observed by proton NMR

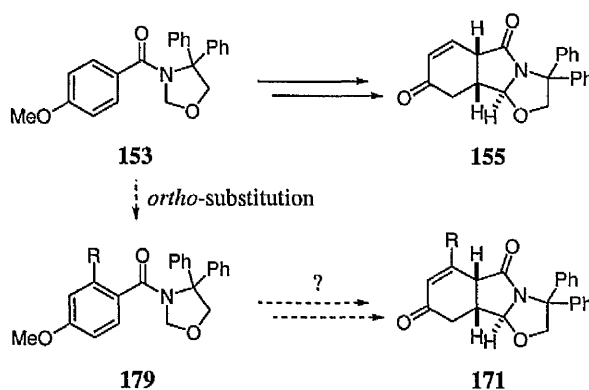
† Based on the 61% isolated yield for the two-step reaction to **176**

‡ Isolated yield

At this stage the use of other oxidants to achieve reoxidation to the β -silyl enone was a possible area for future investigation. Before time was invested in this research, the subsequent fragmentation was studied on an analogous series of compounds (see Section 3.2.2).

2.2.2 Alternative Cyclisation Reactions

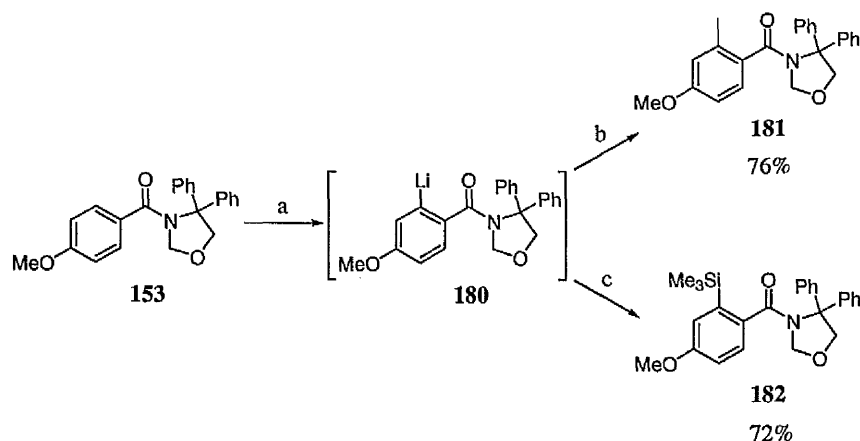
Purewal reported a 'failure' of the cyclisation reaction when carried out in the absence of DMPU, with *ortho*-lithiated amide **117** not undergoing anion translocation (see Scheme 24 on page 36), and hence the organolithium being quenched by electrophiles in the *ortho* position.⁶³ This was applied to advantage in his mechanistic studies: for example, quenching with deuterated methanol formed the desired 2,6-dideuterated cyclisation precursors (e.g. **121** in Scheme 25 on page 36). It was hoped that the same principle could be used to *ortho*-substitute cyclisation precursors, potentially leading to C6-substitution in the cyclised products (Scheme 47).



Scheme 47: Cyclisation of *ortho*-Substituted Benzamides

As with the conjugate addition reactions described in Section 2.2.1, the potential benefit of substituting in this position was twofold. Firstly, steric bulk in this position was expected to stabilise the enone against oxidative degradation. Secondly, substitution at C6 was actually required in the proposed synthetic route (see Section 1.3): incorporation of a methyl or trialkylsilyl group at C6 before the cyclisation would remove the need for a conjugate addition step at a later stage.

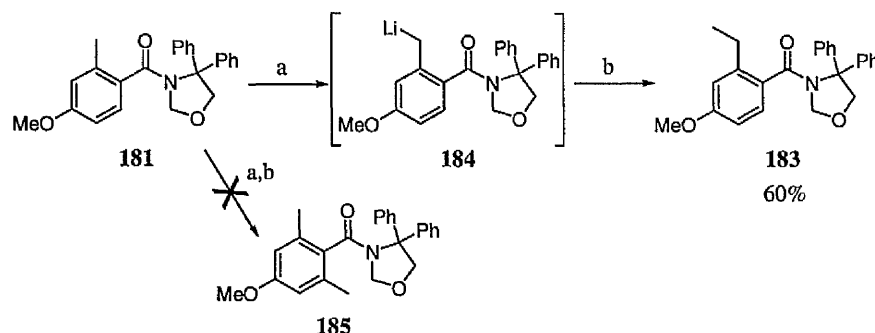
Amide **153** was lithiated in the absence of DMPU, then quenched with iodomethane or chlorotrimethylsilane (Scheme 48). The *ortho*-methyl and *ortho*-trimethylsilyl benzamides were successfully isolated in yields of 76% and 72% respectively.



Reagents and conditions: (a) *t*-BuLi, THF, -78 °C, 40 min; (b) MeI, -78 °C, 2 h; (c) TMSCl, -78 °C, 2 h

Scheme 48

Cyclisation of *ortho*-methyl benzamide **181** was attempted by the established procedure outlined previously, but gave only starting material. In order to find out whether the amide was lithiated by *tert*-butyllithium under these reaction conditions, the reaction was quenched with iodomethane after 45 minutes, when the solution would normally be allowed to warm to 0 °C to promote cyclisation. The *ortho*-ethyl analogue **183** was formed in approximately 60% yield (the remainder being unreacted starting material), showing that benzylic lithiation was favoured over *ortho*-lithiation (Scheme 49). *Ortho*-ethyl compound **183** could not be separated from **181**.



Reagents and conditions: (a) *t*-BuLi, DMPU, THF, -78°C , 45 min; (b) MeI, -78°C , 30 min

Scheme 49

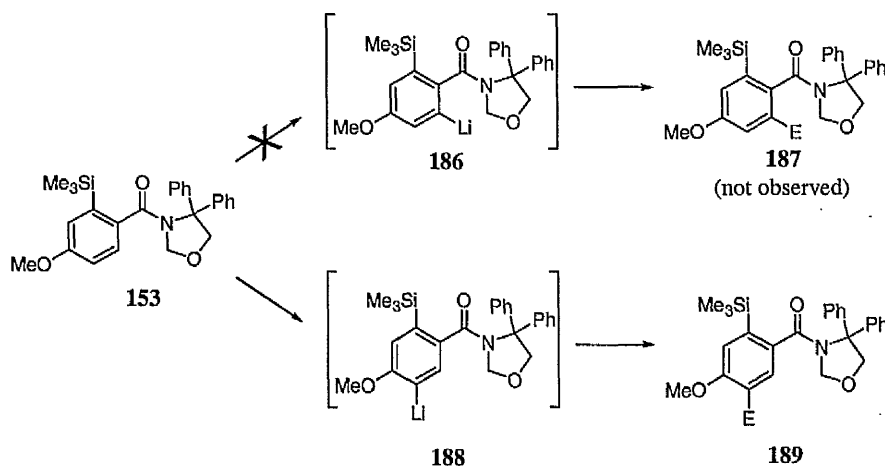
The cyclisation of *ortho*-trimethylsilyl compound **182** was attempted by the same method. In this case, benzylic lithiation was not a possibility, although lithiation of methyl groups α to silicon is precededented.⁷⁹ Again, the standard cyclisation conditions gave only starting material, so an iodomethane quench was used to attempt to identify the site of lithiation; in this case, methylation was not observed.

At this stage a series of experiments was carried out in order to determine whether *ortho*-lithiation of this benzamide was possible, the results of which are summarised in Table 8 below. Initially the cyclisation conditions were repeated with quenching before warming from -78°C . An iodomethane quench after 40 minutes gave no methyl incorporation (entry 2), but after 20 minutes both iodomethane and deuteromethanol quenches led to incorporation of the electrophile (entries 3 and 4 respectively).

Substitution did not occur in the expected position. Instead, lithiation always appeared to be *ortho* to the methoxy group and *para* to the trimethylsilyl group (Scheme 50).

	Butyllithium	Additives	Quench*	Reaction Notes	% E†
1	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	MeI	0 °C quench	0
2	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	MeI	40 min	0
3	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	MeI	20 min	30
4	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	CD ₃ OD	20 min	20
5	<i>sec</i> (1.5 eq.)	TMEDA (1 eq.)	CD ₃ OD	reverse addition, 70 min	20
6	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	CD ₃ OD	5 min	10
7	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	CD ₃ OD	25 min	15
8	<i>tert</i> (1.5 eq.)	DMPU (6 eq.)	CD ₃ OD	45 min	25
9	<i>tert</i> (1.5 eq.)	DMPU (10%)	CD ₃ OD	reverse addition, 45 min	0
10	<i>tert</i> (5.1 eq.)	DMPU (10%)	CD ₃ OD	reverse addition, 45 min	40
11	<i>sec</i> (1.5 eq.)	—	CD ₃ OD	reverse addition, 45 min	30
12	<i>sec</i> (4.9 eq.)	—	CD ₃ OD	reverse addition, 45 min	> 95
13	<i>sec</i> (1.5 eq.)	DMPU (10%)	CD ₃ OD	reverse addition, 45 min	0
14	<i>sec</i> (4.9 eq.)	DMPU (10%)	CD ₃ OD	reverse addition, 45 min	0

Table 8: Incorporation of Electrophiles (E) under Various Reaction Conditions



Reagents and conditions: see Table 8

Scheme 50

* All quenched at -78 °C unless indicated otherwise

† Percentage incorporation of the electrophile, with the remainder quenched by a proton

This conclusion was supported by analysis of the aromatic signals in the proton NMR spectra after quenching, compared with those of **182**. Figure 12 indicates the three clear signals from protons on the ring being lithiated.

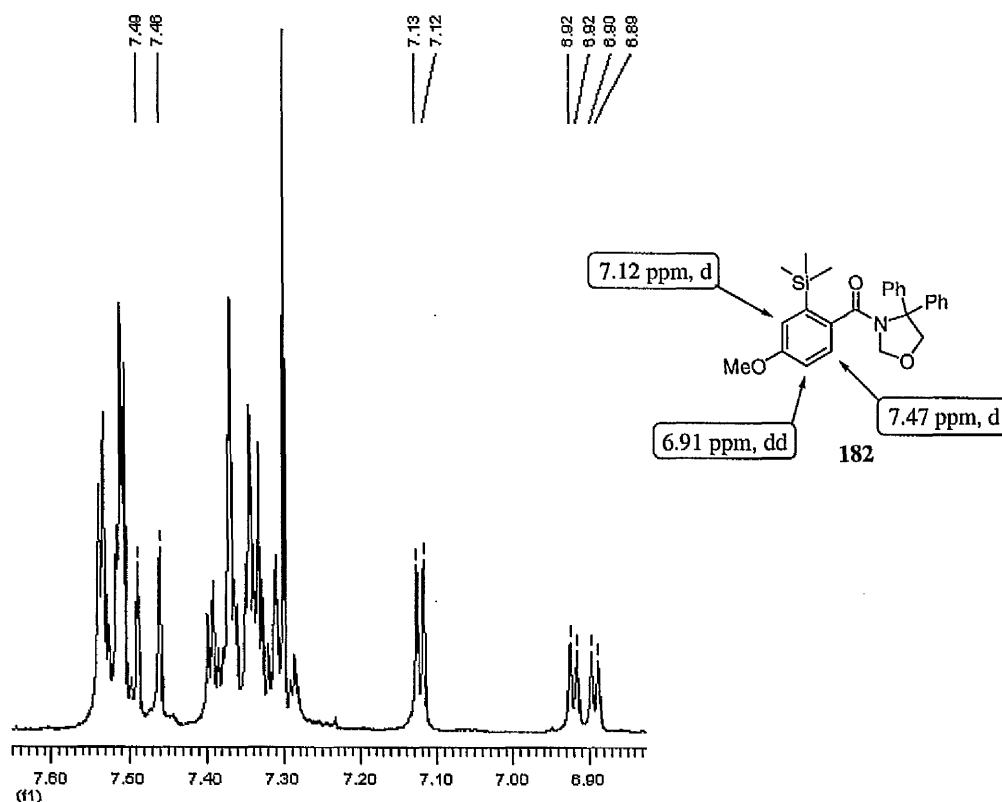


Figure 12: Aromatic Proton NMR Signals for *ortho*-Trimethylsilyl Amide **182**

Figure 13 is an example of the result of partial lithiation, the spectrum of a mixture of **182** and a compound of structure **189**. The appearance of two new singlets corresponding to the two remaining protons (*para* to one another) is clear, particularly at 7.48 ppm. (Indeed, this was the signal used to estimate the degree of electrophilic substitution in Table 8.)

This position of lithiation was also observed when Beak's *sec*-butyllithium–tetramethylethylenediamine system^{80a} (entry 5, cited in Snieckus's review on directed *ortho*-metalation)^{80b} and a range of other conditions were used. Entry 12 in Table 8 shows that a large excess of base and absence of an additive (DMPU slowly reacts with butyllithium) gave maximal lithiation.

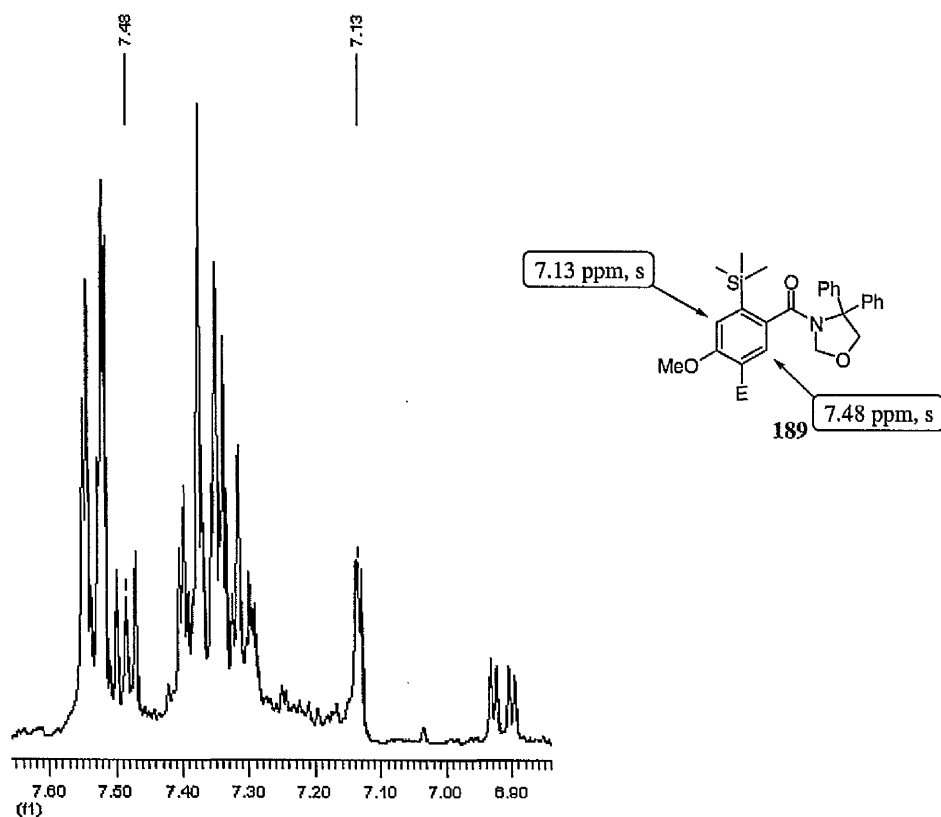


Figure 13: Aromatic Proton NMR Signals of **189**, from Partial *meta*-Substitution of **182**

A possible explanation for the failure of **182** to *ortho*-lithiate could lie in the molecular conformation adopted on lithiation. It is reported that steric effects prevent the amide carbonyl and aromatic ring lying coplanar in *N*-substituted benzamides, with the dihedral angles in the lowest energy conformations calculated as 58° for simple tertiary benzamide **190** and 110° with *ortho*-trimethylsilyl substitution (Figure 14).⁸¹

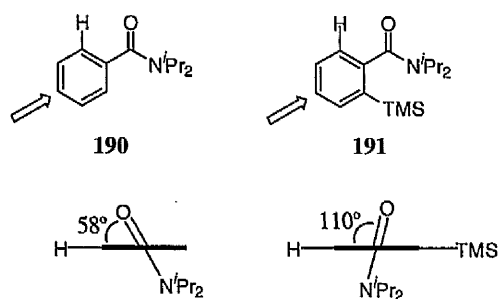
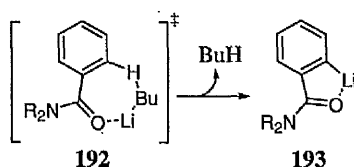


Figure 14: Molecular Conformations in *ortho*-Substituted Tertiary Benzamides

A relative efficiency of lithiation of 1800 : 1 for compounds **190** : **191** was quoted, explained by a correlation between dihedral angle and the ability to form planar transition state **192**, and hence chelated organolithium **193** (Scheme 51).



Scheme 51: Formation of a Chelated Organolithium Monomer

In fact, with a dihedral angle close to or greater than the perpendicular, the distance between the carbon and oxygen atoms would be too large to be bridged by a single lithium atom as shown in structure **193**. In such cases a bridged dimer such as **194** would be required (Figure 15), shown to exist in the solid state even for *ortho*-lithiated **190**, a compound with no *ortho* substituent.⁸²

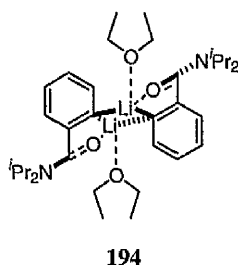
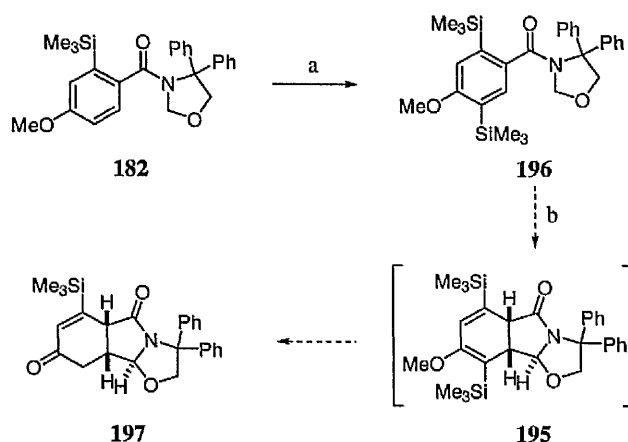


Figure 15: A Bridged Organolithium Dimer

The specific failure with the *ortho*-trimethylsilyl cyclisation precursor **182** could therefore be explained by an inability to form the required bridged dimer, perhaps because of the additional steric demands posed by the bulky diphenyloxazolidine substituent on the amide nitrogen atom.

Although the regioselective lithiation for the required translocation–cyclisation sequence was not observed, this did not represent an insurmountable problem. It was speculated that a trimethylsilyl quench in this position might force any subsequent lithiation *ortho* to the amide (Scheme 52). The cyclised intermediate **195** should then give the required β -trimethylsilyl substituted enone, with the other trimethylsilyl group spontaneously being hydrolysed.



Reagents: (a) *s*-BuLi; TMSCl; (b) *t*-BuLi, DMPU; sat. aq. NH₄Cl soln.

Scheme 52

Formation of 2,5-bis(trimethylsilyl) amide **196** was attempted utilising the lithiation conditions given in entry 12 of Table 8, followed by quenching with ten equivalents of chlorotrimethylsilane. The reaction did not proceed cleanly, with the crude product mixture showing 12 spots by thin layer chromatography. After two cycles of column chromatography the required product was obtained, still with significant amounts of impurities, in less than 5% yield. Its identity was supported by the aromatic signals in its proton NMR spectrum (Figure 16), with two singlets corresponding to the *para* unsubstituted positions.

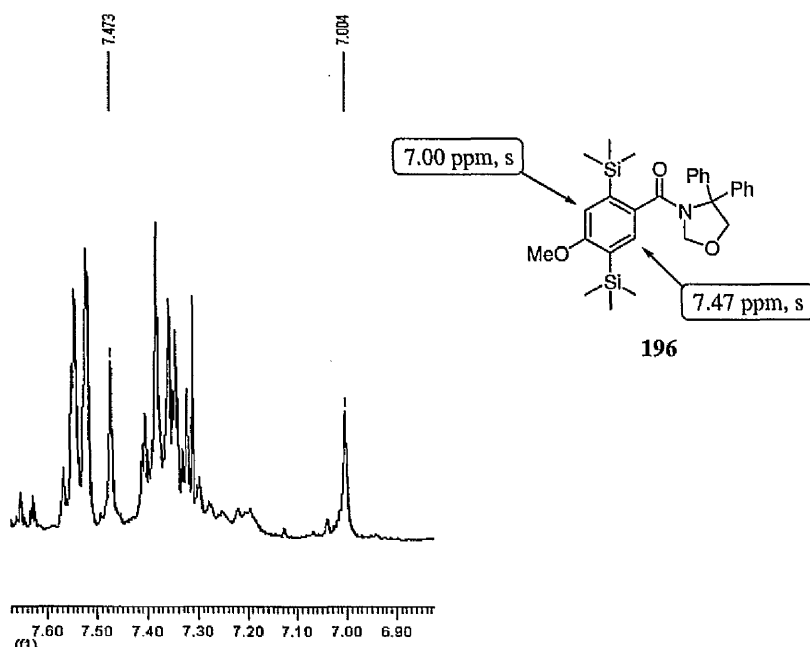
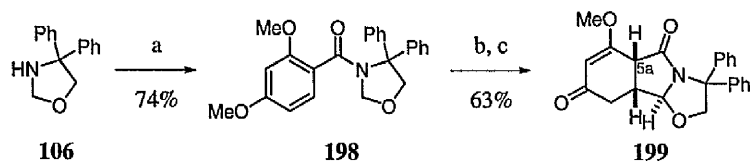


Figure 16: Characteristic Aromatic Proton NMR Signals of *para*-Unsubstituted Benzamide **196**

The poor yield and messy reaction probably resulted from the combination of a large excess of butyllithium and the presence of Lewis acidic chlorotrimethylsilane: by-products showed evidence of oxazolidine ring-opening and intermolecular reactions. Given the difficulty in controlling the reaction and little scope for finding milder lithiation conditions (only one of the range of conditions summarised in Table 8 gave a large extent of lithiation), this route was abandoned.

A third cyclisation substrate with 2,4-dimethoxy substitution was also synthesised, using 2,4-dimethoxyanisoyl chloride in the amide formation (Scheme 53). The cyclisation was attempted by the usual protocol, giving a stable cyclised product in reasonable yield (Scheme 53).*



Reagents and conditions: (a) 2,4-dimethoxybenzoyl chloride, Et₃N, 1,2-DCE, reflux, 18 h; (b) *t*-BuLi, DMPU, THF, -78 °C, 40 min; 0 °C, 2.5 h; sat. aq. NH₄Cl soln.; (c) 2 M HCl in Et₂O, Et₂O, R.T., 18 h

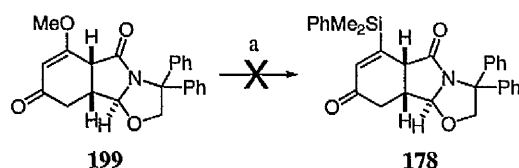
Scheme 53

The remarkable stability of the methoxy-substituted enone (compared with, for example, the methyl substitution in **156**, shown in Scheme 44 on page 57) was thought to be because of the lower acidity of C5aH when situated between lactam and vinylogous ester, rather than lactam and enone. Thus enone stabilisation by starting material substitution was achieved, although the stabilisation was thought to be predominantly due to electronic rather than steric factors.

In order to be synthetically useful, it is necessary to functionalise the 4-methoxy enone with silicon or tin, to allow fragmentation, and with a methyl group, to yield the desired kainoid side-chain after this fragmentation. Reaction with the phenyldimethylsilyl zincate discussed in Section 2.2.1 was unsuccessful

* A single regioisomer of the enone was formed, assumed to be that shown in Scheme 53 based on benzyl cyclisation precedent⁵⁶

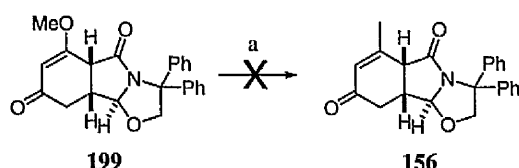
(Scheme 54), with the reaction giving mostly unreacted starting material, as well as some evidence of oxazolidine ring opening. Application of simpler trimethylsilyl nucleophiles, experimentally harder to utilise due to their volatility and the need for toxic HMPA,⁷³ were not attempted.



Reagents and conditions: (a) Et₂Zn, PhMe₂SiLi, THF, 0 °C, 10 min; **199**, TMSCl, THF, -78 °C, 1 h; R.T., 1.5 h; sat. aq. NH₄Cl

Scheme 54

Attempted dimethylcuprate addition gave no conversion from starting material (Scheme 55). (Conjugate methyl addition–elimination onto an analogous bicyclic β -methoxy enone had also previously been shown to be a poor reaction, with around 6% isolated yield of the desired β -methyl enone.)⁸³



Reagents and conditions: (a) MeLi, CuBr, THF, -78 °C, 20 min; warm to 0 °C; recool to -78 °C; **199**, TMSCl, THF, -78 °C, 1.5 h; R.T., 30 min; sat. aq. NH₄Cl

Scheme 55

With the two examples of *ortho*-substituted compounds failing to cyclise, and the cyclised *ortho*-methoxy benzamide failing to undergo conjugate addition–elimination reactions, the strategy of enone stabilisation by modification of the cyclisation precursor was pursued no further.

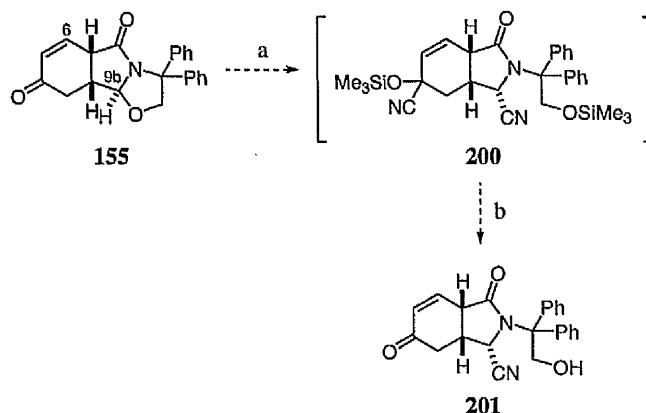
2.2.3 Opening the Oxazolidine Ring

The enone on the tricyclic oxazolo[2,3-*a*]isoindolone skeleton is far more unstable than that of the bicyclic isoindolone skeleton featured in the chemistry carried out by Hebditch (for example **52** in Scheme 16 on page 31).⁶⁰

The previous unsuccessful attempts to stabilise enone **155** outlined in Sections 2.2.1 and 2.2.2 have cast some doubt on the likelihood of oxazolidines being a useful development in the synthesis of the isodomoic acids. The stabilisation of these compounds by opening the oxazolidine ring with cyanide, building on work by Purewal,⁶³ would make the route to isodomoic acid shown in Scheme 32 on page 41 a more realistic proposition.

As with the investigation into enone stabilisation methodology utilising conjugate addition reactions (Section 2.2.1), the samples of **155** used in this technique were contained in crude product mixtures from the previous dearomatising cyclisation step. Typically **155** was present in 45 mol%, with a similar quantity of benzamide **153** and around 10 mol% of by-product **165** (see Scheme 44 on page 57).

The first of Purewal's reagent systems to be tried was trimethylsilyl cyanide with trimethylsilyl triflate.⁶³ Using two equivalents of cyanide, Purewal observed reaction at both aminal and enol ether carbon centres. Thus the cyanide addition reaction was followed by treatment with tetrabutylammonium fluoride to 'unmask' the desired enone (Scheme 56).

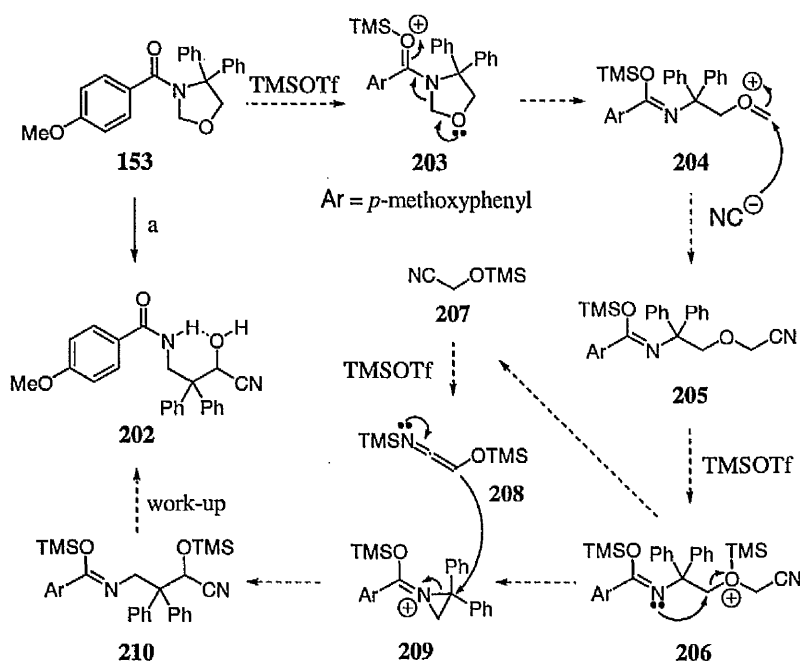


Reagents and conditions: (a) TMSCN (2 eq.), TMSOTf, DCM, -78 °C, 30 min; R.T., 2 h; (b) wet TBAF, R.T., 1 h

Scheme 56

This reaction was very messy, with numerous compounds contained in the crude product mixture as demonstrated by thin layer chromatography. Purification by flash column chromatography yielded a mixed fraction containing a compound of

the required product's molecular weight (identified by LC-MS). However, the C6H and C9bH signals were still apparent in the proton NMR spectrum, demonstrating that the oxazolidine ring and enone were still intact. After a longer reaction time (20 hours at room temperature) there was no evidence at all of the desired product mass by LC-MS. Purification and examination of the product mixture suggested that benzamide **153** had incorporated cyanide and rearranged. The product, **202**, tentatively assigned from mass spectrometry and NMR data, and a possible mechanism for its formation, are shown in Scheme 57. The protons of the methylene group of **202** appeared diastereotopic by NMR, suggesting a stable cyclic conformation, perhaps arising from the intramolecular hydrogen bond indicated in the Scheme.



Reagents and conditions: (a) TMSCN, TMSOTf, DCM, -78°C , 30 min; R.T., 20 h; wet TBAF, R.T., 1 h

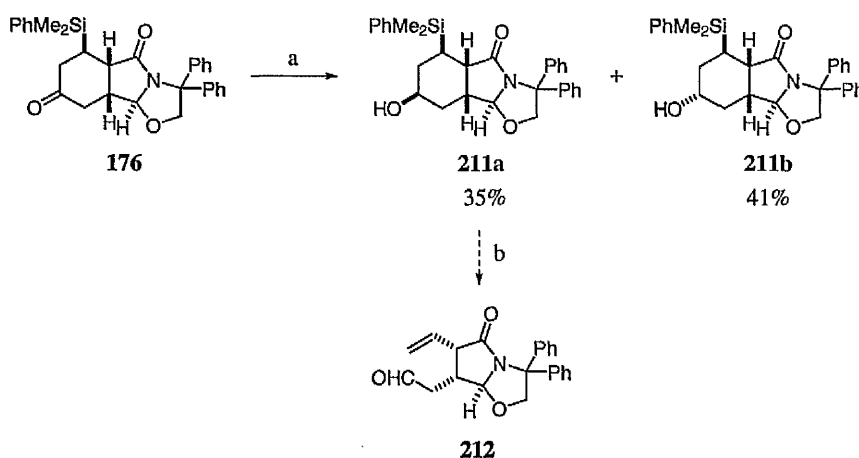
Scheme 57: Possible Mechanism for the Formation of Rearranged Cyanohydrin 202

Changing the Lewis acid to titanium tetrachloride (Purewal's alternative catalyst) gave selective and complete reaction of the enone, leaving the benzamide untouched. By proton NMR no new products were observed after reaction, from which it was concluded that the enone had been destroyed under the reaction conditions. No further investigations were carried out into the ring-opening of the oxazolidine with cyanide.

Chapter 3: Fragmentation Methodology

3.1 Trial Reaction

In Section 2.2.1, β -silyl ketone **176** was described as an undesired product resulting from silyl enol ether hydrolysis in an attempted reoxidation reaction (Scheme 46 on page 60). However, on reduction of the ketone, it became an ideal substrate for a trial fragmentation reaction. The oxidative fragmentation of compound **211a**, obtained by facile borohydride reduction of **176**, was attempted using the method of Posner *et al.*, as shown in Scheme 58.⁷³



Reagents and conditions: (a) NaBH_4 , MeOH, R.T., 18 h; (b) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, 0 °C, 23 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.

Scheme 58

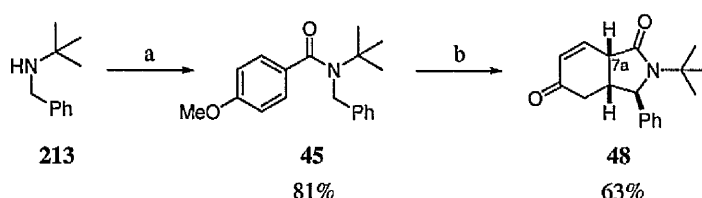
The crude reaction product mixture showed trace amounts of two aldehydes by proton NMR, but these were unstable to column chromatography and could not be isolated. All starting material had been consumed, and the reaction showed promise, but no clear major product was observed.

It was hoped that the fragmentation might ultimately prove to be a means by which the tricyclic compounds could be stabilised (as an alternative to the work discussed in Section 2.2). In the meantime the methodology was investigated and developed on an analogous series of bicyclic compounds from the work of Yasin⁸⁴ and Hebditch,⁶⁰ as these could be synthesised more straightforwardly.

3.2 Model System

3.2.1 Synthesis of Fragmentation Precursors

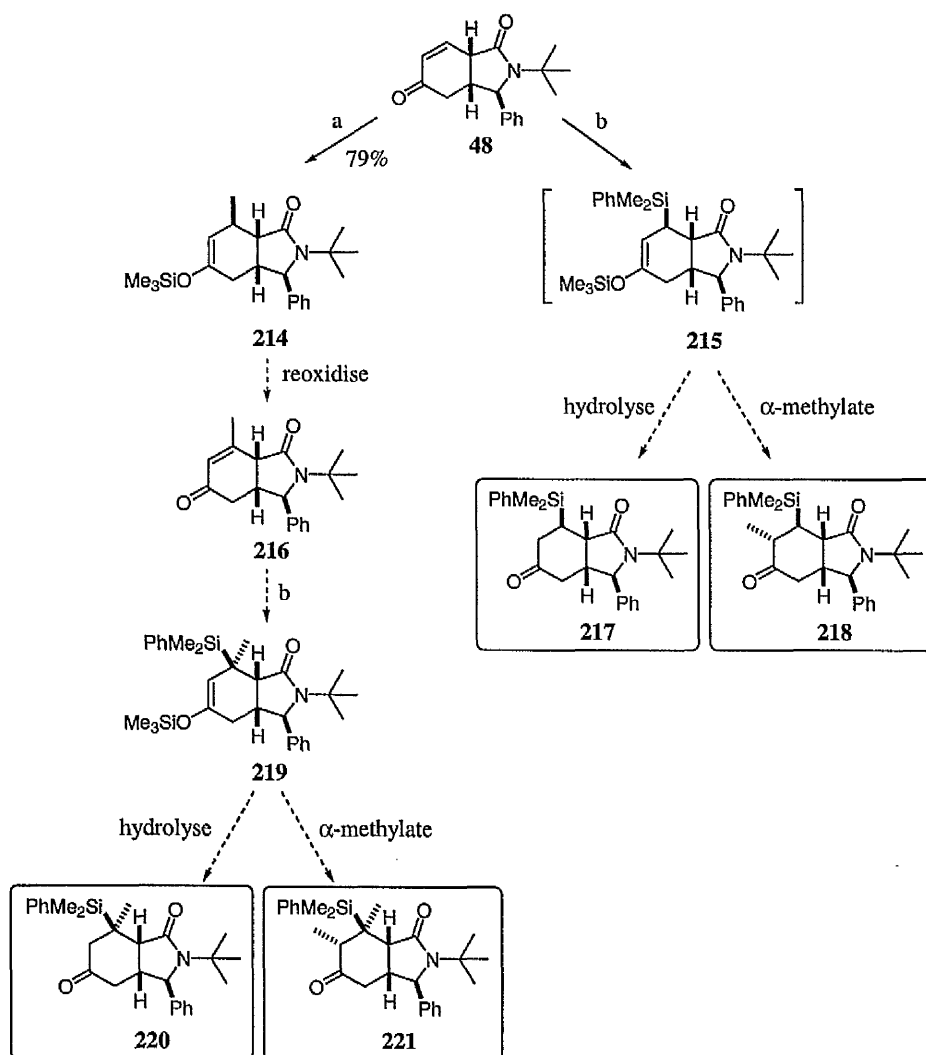
Using previously published methodology, racemic enone **48** was formed by the dearomatising cyclisation of *N*-benzylbenzamide **45** (Scheme 59).⁸⁴ Empirically this bicyclic enone was observed to be far more stable than the corresponding tricyclic oxazolidine. It is assumed that C7aH in **48** is less acidic than the equivalent hydrogen in the oxazolidine system, removing oxidation at this position as a possible decomposition route.



Reagents and conditions: (a) *p*-anisoyl chloride, 2 M aq. NaOH soln., DCM, R.T., 4.5 h; (b) LDA, THF, R.T., 1.5 h; sat. aq. NH₄Cl soln.; 2 M aq. HCl soln.

Scheme 59

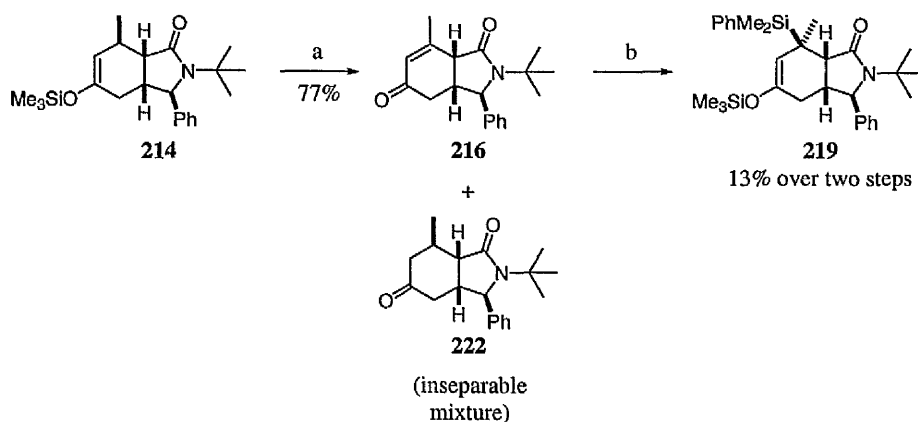
Enone **48** was amenable to β -functionalisation by attack of both methyl and phenyldimethylsilyl nucleophiles (Scheme 60). It was hoped that a combination of hydrolysis, α -methylation and reoxidation of the resulting silyl enol ethers would make the full range of functionalised ketones accessible (shown in the same Scheme), ready for development of the model fragmentation methodology.



Reagents and conditions: (a) MeLi, CuBr, THF, $-78\text{ }^{\circ}\text{C}$, 20 min; **48**, TMSCl, THF, $-78\text{ }^{\circ}\text{C}$, 1.5 h; sat. aq. NH_4Cl soln.; (b) Et_2Zn , PhMe_2SiLi , THF, $0\text{ }^{\circ}\text{C}$, 5 min; **48**, THF, $-78\text{ }^{\circ}\text{C}$, 40 min; TMSCl, $-78\text{ }^{\circ}\text{C}$, 30 min; R.T., 1.5 h; sat. aq. NH_4Cl soln.

Scheme 60: Proposed Formation of a Range of β -Silyl Ketones

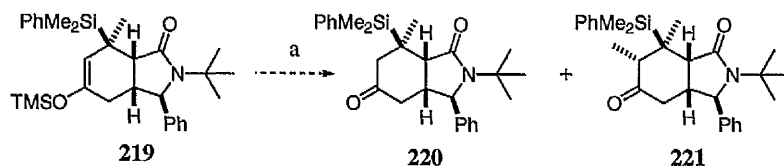
Silyl enol ether **214** resulting from conjugate attack by dimethylcuprate was isolated in 79% yield. Reoxidation with palladium(II) acetate was attempted, giving approximately 3 : 2 reoxidation : hydrolysis (Scheme 61). The two products were inseparable, and yields of 46% and 31% respectively were estimated based on recovered mass and integration of the mixed proton NMR spectrum. The mixture was reacted with a phenyldimethylsilyl zincate nucleophile, in the hope that reaction would occur exclusively with the enone and allow separation of the unreacted ketone (Scheme 61).



Reagents and conditions: (a) $\text{Pd}(\text{OAc})_2$, MeCN, R.T., 17 h; (b) Et_2Zn , PhMe_2SiLi , THF, 0°C , 5 min; (**216** + **222**), THF, -78°C , 40 min; TMSCl , -78°C , 30 min; R.T., 1.5 h; sat. aq. NH_4Cl soln.

Scheme 61

This reaction did indeed yield the uncontaminated silyl enol ether **219**, but in a disappointing 13% yield over the two steps; no unreacted ketone was isolated. α -Methylation of **219** was then attempted, with the crude product mixture treated with aqueous acetic acid to hydrolyse any unreacted silyl enol ether (Scheme 62).⁷⁵ Subsequent flash column chromatography yielded three major products (no unreacted starting material), none of which had a mass spectrum consistent with either of the required products. After this result work towards **220** and **221** was adjourned, to allow investigation of the simpler syntheses of ketones **217** and **218**.

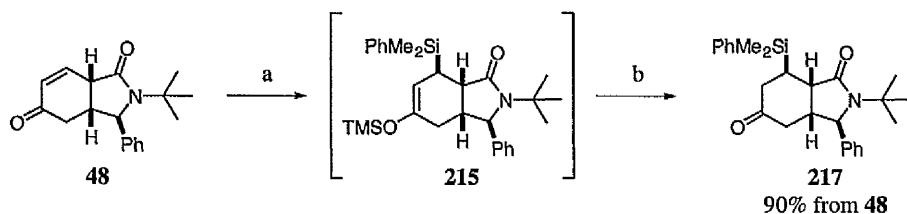


Reagents and conditions: (a) MeLi, THF, 0°C , 30 min; MeI, 0°C , 3 h; 90% $\text{AcOH}/\text{H}_2\text{O}$, R.T., 40 min

Scheme 62

Enol ether **215** resulting from phenyldimethylsilyl attack on **48** (Scheme 63) was thought not to be stable to column chromatography, because a streak was observed by thin layer chromatography. (It was subsequently isolated by column chromatography as unreacted starting material in another reaction.) However, the conjugate addition reaction was shown to be high-yielding, when simple

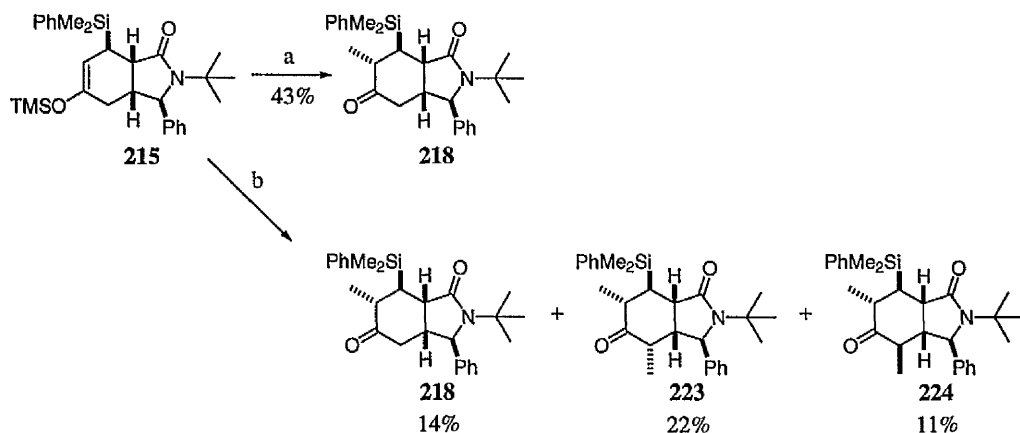
hydrolysis of the crude reaction mixture gave ketone **217** in 90% yield over the two steps.



Reagents and conditions: (a) Et_2Zn , PhMe_2SiLi , THF, 0°C , 5 min; **48**, THF, -78°C , 40 min; TMSCl , -78°C , 30 min; R.T., 1.5 h; sat. aq. NH_4Cl soln.; (b) 80% $\text{AcOH}/\text{H}_2\text{O}$, R.T., 1 h

Scheme 63

The attempted α -methylation of **215** to ketone **218** (on the right-hand side of Scheme 60 on page 75) was less reliable, with the lithium enolate initially giving only 43% of the desired product (yield over two steps from **48**), along with other polymethylated products (Scheme 64, Route 'a'). An attempt was made to improve selectivity for the monomethylated product by including dimethyl zinc as an additive,^{85,*} but this only resulted in more polymethylation, with the by-products shown in Scheme 64 tentatively assigned from proton NMR spectra of impure column chromatography fractions.



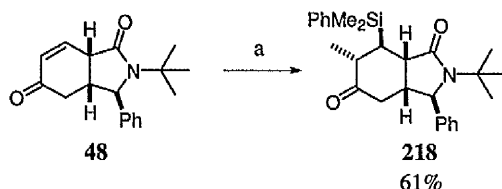
Reagents and conditions: (a) MeLi , THF, 0°C , 10 min; MeI , 0°C , 3 h; (b) MeLi , THF, 0°C , 10 min; Me_2Zn , 0°C , 10 min; MeI , 0°C , 3 h

Scheme 64

* HMPA, also included in the literature method, was omitted due to its high toxicity.

In both cases unreacted starting material **215** was obtained after chromatography. It was thought that allowing longer reaction times with methyl lithium for conversion to the lithium enolate, before addition of iodomethane, would increase the yield, but increasing the reaction time from 10 to 30 minutes gave no real improvement (44% over the two steps). This time a negligible amount of starting material was observed in the proton NMR spectrum of the crude reaction product, and none was isolated after chromatography.

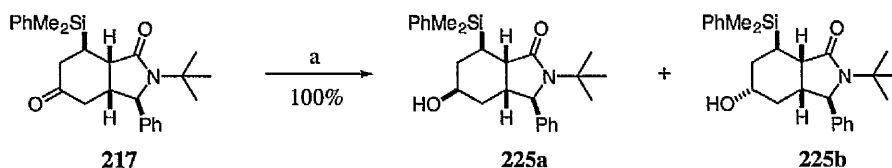
A one-pot reaction of **48** to **218** without isolation of an intermediate silyl enol ether was attempted (Scheme 65), initially giving some practical experimental problems due to the poor solubility of the concentrated crude product in a range of solvents (diethyl ether, dichloromethane, ethyl acetate, petroleum ether and water). Nevertheless, after dissolving the crude product mixture in dimethyl sulfoxide and utilising acidic and basic washes to break up any zinc complexes present, the required product was obtained in 61% yield, a significant improvement on the previously discussed method. On scaling up to a 2 gram reaction the yield decreased to 43%.



Reagents and conditions: (a) Et_2Zn , PhMe_2SiLi , THF, 0°C , 5 min; -78°C , 25 min; 0°C , 30 min; MeI, 0°C , 30 min; R.T., 1 h

Scheme 65

Before oxidative fragmentation could be attempted, the ketones needed to be reduced. This was readily effected with sodium borohydride in methanol, initially carried out on the most simple ketone **217** (Scheme 66), giving quantitative reduction to a 2 : 1 mixture of the two alcohol isomers **225a** and **225b** shown, on both 400 milligram and 1.3 gram scales.



Reagents and conditions: (a) NaBH₄, MeOH, R.T., 18 h.

Scheme 66

The alcohols' relative stereochemistries were assigned from the magnitudes of the proton coupling constants around the cyclohexanol ring, by assuming that the preferred conformation was chair-like. The proposed three-dimensional structures are shown in Figure 17 below, with the multiplicities of key protons listed in Table 9.

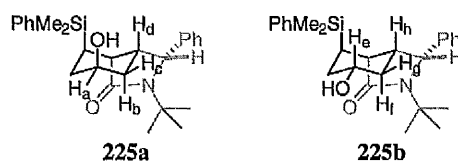


Figure 17: Proposed Chair-Like Conformations of Cyclohexanols **225a** and **225b**

Compound	Proton	Multiplicity	Coupling Constants (Hz)
225a	H _a	m	none > 6
	H _b	td	11 (H _{b,c} & H _{b,d}) and 4 (H _{b,a})
	H _c	dd	11 (H _{c,b}) and 6 (H _{c,d})
	H _d	dt	11 (H _{d,b}) and 6
225b	H _e	tt	12 (H _{e,f}) and 4 (H _{e,g})
	H _f	q	12 (H _{f,e} , H _{f,g} & H _{f,h})

Table 9: Selected Observed Coupling Constants in **225a** and **225b**

In both cases the five-membered ring substituent bearing the large phenyl group was assumed to be equatorial, with the silyl (long carbon–silicon bond)⁸⁶ and carbonyl (*sp*² small in space) groups adopting axial positions. In structure **225a**, H_b had two 11 Hz couplings, to H_c (geminal) and H_d (axial–axial vicinal). The remaining coupling to H_a was much smaller (4 Hz), perhaps indicating that H_a is situated equatorially. In **225b**, H_f coupled with three other protons, all with large

J -values, indicating that both H_e and H_h are also axial. It should be noted that the coupling constants of 11–12 Hz were not large enough to demonstrate axial–axial relationships conclusively: such values would also have been consistent with couplings between pseudo-axial protons if a boat conformation had been adopted.

To shed further light on the preferred molecular conformation, the structure of **225a** was investigated by X-ray crystallography, on the microcrystalline needles obtained by recrystallisation from ethyl acetate–hexane. This demonstrated that, at least in the solid state, the preferred conformation was indeed a slightly distorted chair, with the distortion most apparent in the axial substituents (Figure 18). The relative stereochemistry, that until this point had been assumed, was confirmed. Furthermore, the crystal structure also showed that the requirement of the phenyl-substituted five-membered ring to lie equatorially was sufficiently powerful to force the hydroxyl and phenyldimethylsilyl groups, and the carbonyl-substituted five-ring, into axial positions. It was assumed that *epi*-hydroxy compound **225b** would adopt a similar chair conformation, with the hydroxyl group equatorial on the six-membered ring.

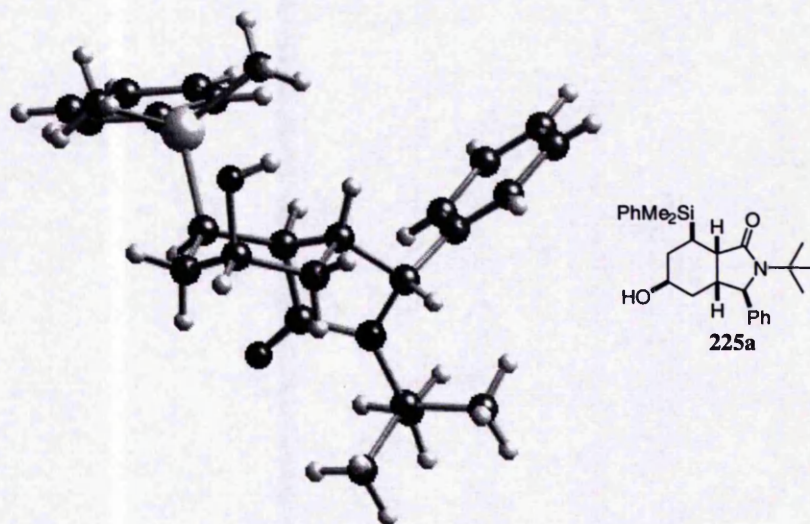
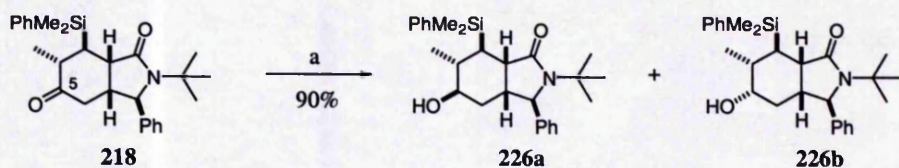


Figure 18: X-Ray Crystal Structure of **225a**

The borohydride reduction (complete by thin layer chromatography after 2.5 hours) was applied to α -methyl ketone **218** (Scheme 67), again giving a 2 : 1 mixture of the $5R^*$ and $5S^*$ epimers **226a** and **226b**, though in slightly lower yield (58% and 32% respectively, 90% total conversion to isolated products).



Reagents and conditions: (a) NaBH₄, MeOH, R.T., 2.5 h

Scheme 67

Needle-like microcrystals of **226a** were obtained by recrystallisation from ethyl acetate–hexane. X-ray crystallography was expected to show a solid-state molecular conformation similar to that of **225a**, and was carried out in the most part to confirm the relative methyl stereochemistry. However, the structure obtained, pictured in Figure 19, is clearly built around a twist boat- rather than chair-like cyclohexanol ring. It seems that it is too unfavourable for four of the five substituted positions on the six-membered ring to support bulky axial substituents. Instead of flipping to the alternative chair, a twist-boat conformation provides some relief of steric clashes, whilst still allowing the phenyl-substituted five-membered ring to adopt a pseudo-equatorial position.

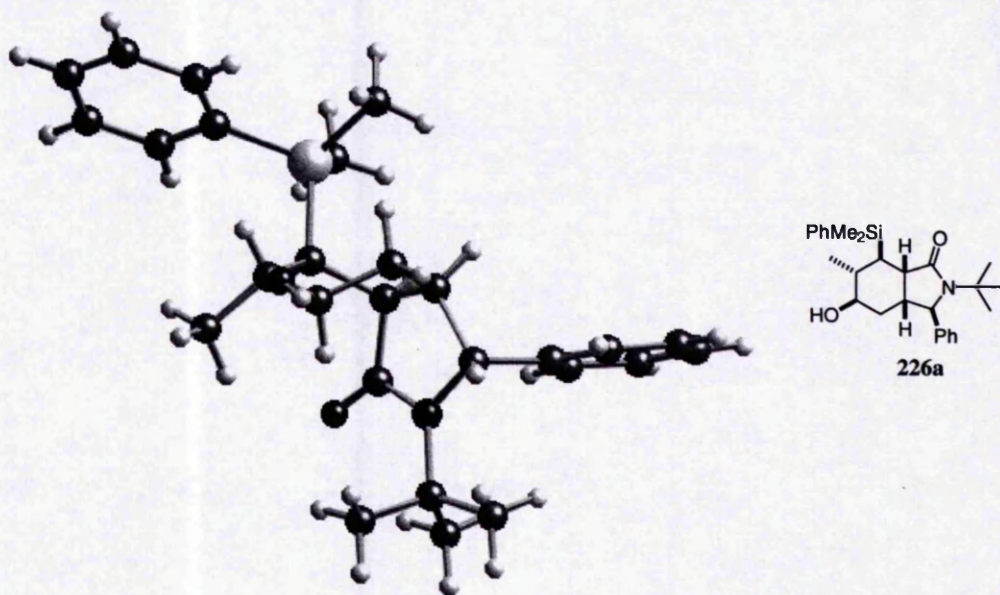


Figure 19: X-Ray Crystal Structure of **226a**

Rotating the diagram (Figure 20) allows the relative stereochemistry to be observed more clearly. As expected, methyl iodide added *anti* to silicon, even though this was on the *endo* face of the bicyclic structure.⁸⁷

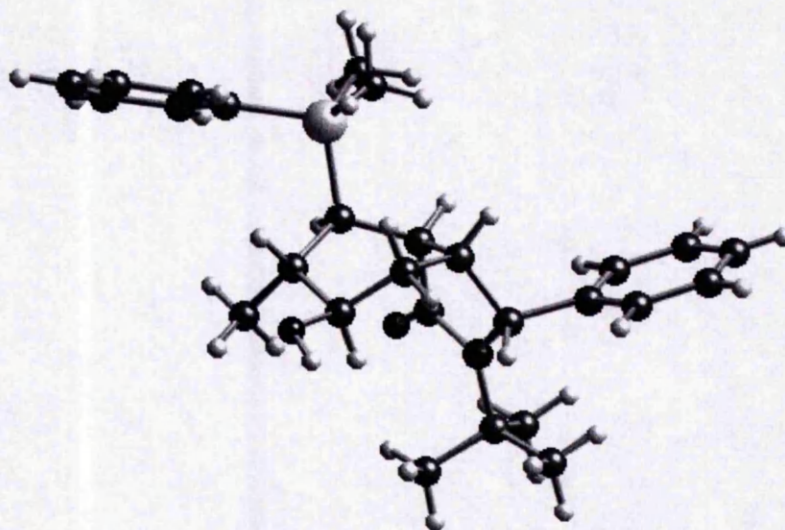
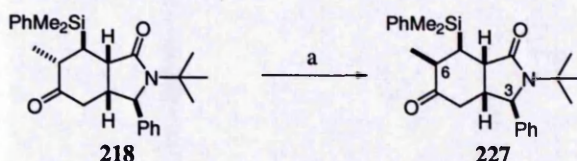


Figure 20: Relative Stereochemistry in the X-Ray Crystal Structure of 226a

Although an X-ray crystal structure could not be obtained for *epi*-hydroxy compound **226b**, with potentially one less axial group it was expected to adopt a chair conformation, the hydroxyl group now in an equatorial environment.

Epimerisation of the methyl group would be useful to allow study of the mechanism and stereochemistry of the subsequent fragmentation. It was hoped that this could be effected in α -methyl ketone **218** by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a strong and hindered amine base, as had previously been used to this effect with great success.⁸⁸ The reaction (Scheme 68) could not be monitored by thin layer chromatography (product **227** co-ran with **218**), so at various times the reaction was worked up and the product mixture examined by proton NMR. Formation of the new epimer was particularly apparent from shifts in the C3H(Ph) and C6H(Me) peaks, and could be monitored by integration of these signals.



Reagents and conditions: (a) DBU, see Table 10 below for reaction solvent, temperature and duration; aq. acid wash to remove DBU

Scheme 68

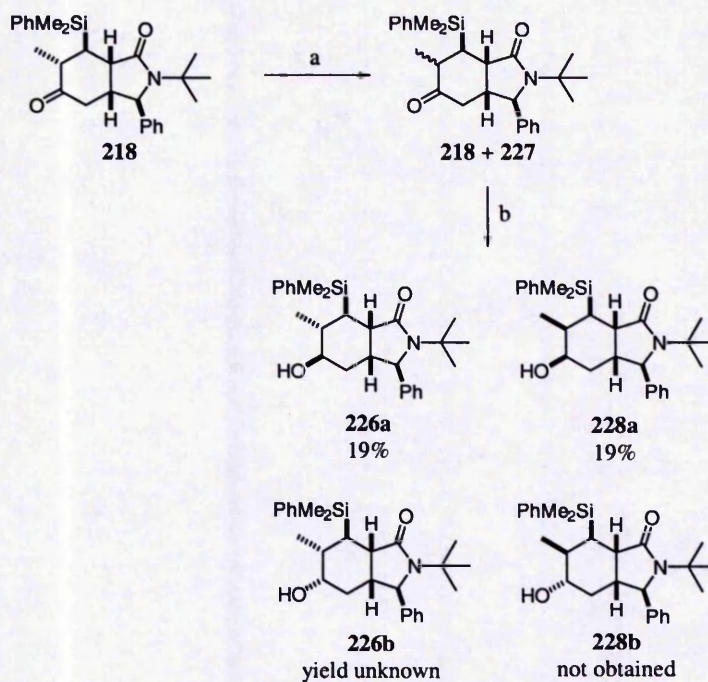
					218 : 227
Conditions	Solvent	Temperature	Duration		Ratio
1 —	DCM	R.T.	47 h		81 : 19
2 As entry 1, plus	DCM	Reflux	21.5 h		76 : 24
3 As entry 2, plus	1,2-DCE	Reflux	22.5 h		68 : 32

Table 10: DBU-Catalysed Epimerisation Conditions and Conversions

The results in Table 10 indicate that partial epimerisation under these conditions was effected, but that there was still a remarkable preference for the *endo* epimer (**218**). This may have been due to significant steric clash between the methyl and phenyldimethylsilyl groups in the *exo* epimer, despite the relatively long carbon–silicon bond. It not clear whether the ratios in Table 10 result from a gradual conversion to the *exo*-methyl epimer with more forcing conditions, or just reflect the Boltzmann populations of the two epimers at elevated temperatures, where the rate of cooling is too fast to allow re-equilibration.

The epimerisation of ketone **218** was repeated on a larger scale, with *in situ* borohydride reduction to the alcohols (Scheme 69). A two-stage purification process was used to obtain clean samples of three of the four possible alcohol isomers. Firstly, column chromatography using Horizon Biotage apparatus separated **226a** and **228a** from **226b**. Then a preparative HPLC method was used to separate **226a** from **228a**, and to purify the sample of **226b**. **228b** was not observed.

The identities of **226a** and **228a** were confirmed by X-ray crystallography (both readily crystallised as white needles from the HPLC mobile phase, 85 : 15 acetonitrile : 0.1% aqueous trifluoroacetic acid). Interestingly, the six-membered ring of **228a** preferred to adopt a chair-like conformation in the solid state (Figure 21), in stark contrast to the twist-boat observed for **226a** (see Figure 19 above).



Reagents and conditions: (a) DBU, 1,2-DCE, reflux, 23 h; (b) NaBH₄, MeOH, R.T., 2.5 h

Scheme 69: Products Isolated from the Epimerisation-Reduction of 218

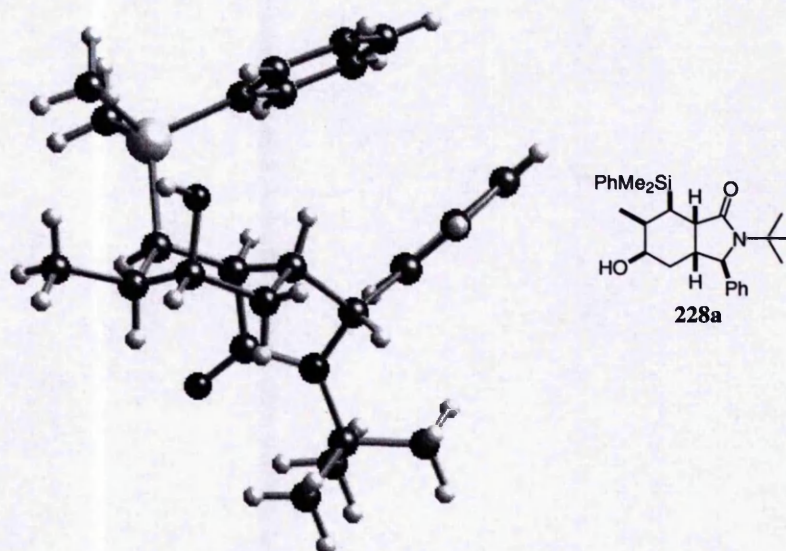


Figure 21: X-Ray Crystal Structure of 228a

By way of conclusion, the conformational preferences of cyclohexanols **225a/b**, **226a/b** and **228a**, empirically observed or predicted, are summarised in Table 11 below.

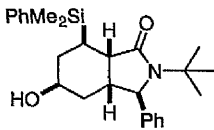
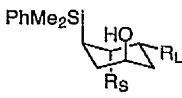
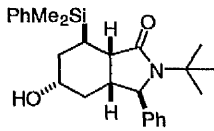
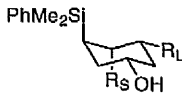
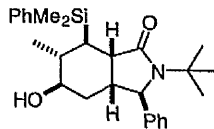
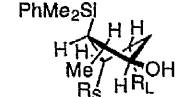
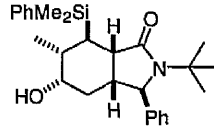
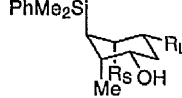
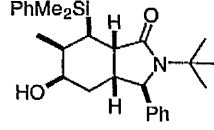
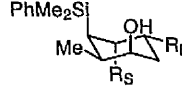
Cyclohexanol	Conformation ^{*,†}	Explanatory Notes
 <p>225a</p>	 <p>(X-ray structure)</p>	R_L adopts equatorial environment in chair, forcing other groups axial
 <p>225b</p>	 <p>(predicted)</p>	Predicted structure based on 225a
 <p>226a</p>	 <p>(X-ray structure)</p>	Chair conformation with R_L equatorial would have four contiguous axial substituents; twist-boat with R_L pseudo-equatorial is preferable to ring-flipped chair
 <p>226b</p>	 <p>(predicted)</p>	Predicted structure based on 225b ; chair now satisfactory with only three axial substituents (see 228a below)
 <p>228a</p>	 <p>(X-ray structure)</p>	Chair conformation with R_L equatorial and three axial substituents

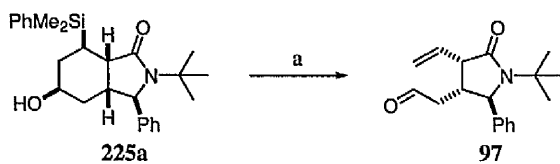
Table 11: Observed and Predicted Cyclohexanol Conformations

3.2.2 Model Fragmentation Reactions

In order to simplify product identification and analysis of the reaction's efficiency, the fragmentation was initially carried out on a single isomer of the simplest alcohol, using the same conditions as for the oxazolidine trial fragmentation (Scheme 70).

* Hydrogen atoms omitted for clarity

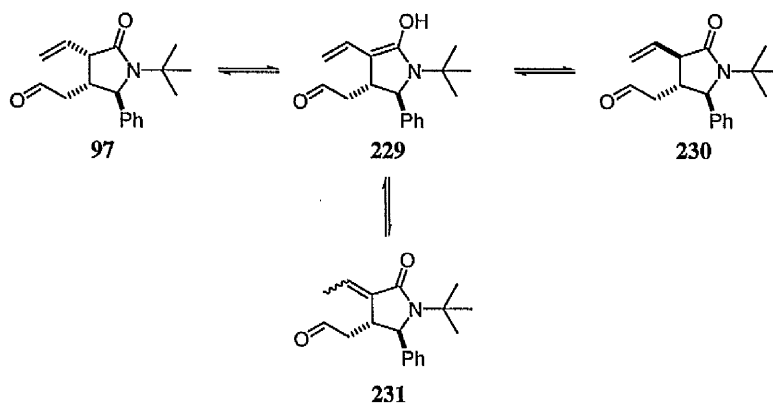
† R_L = CH(Ph) substituent; R_S = carbonyl substituent



Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$ (1.1 eq.), I_2 (1.0 eq.), DCM, 0 °C, 3 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.

Scheme 70

After an hour a number of new compounds were observed by thin layer chromatography, as well as unreacted starting material. The profile did not change significantly after a further two hours, so the reaction was worked up. Proton NMR analysis of the crude product mixture showed the presence of a small amount of two aldehydes, as had also been observed in the trial oxazolidine fragmentation (see Section 3.1), but these could not be isolated (although approximately 70% of the starting alcohol was recovered). Isomerisation of the initial product aldehyde **97** is made possible by the enolisable lactam: via conjugated enol tautomer **229** three further aldehydes are potentially accessible (Scheme 71).

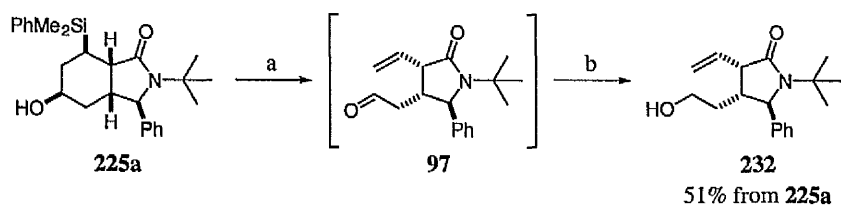


Scheme 71: Isomerisation of Aldehyde 97 via Enol Tautomer 229

The failure of the reaction to proceed to completion was thought not to be because of reagent decomposition; Posner *et al.* used the same reagent system over a longer period to obtain good yields (84–91%) of fragmented products.⁷³ The reaction was repeated at reflux instead of 0 °C, and after 2.5 h no starting material was observed in the proton NMR spectrum of the crude product mixture. Again, a mixture of two aldehydes was observed, but these could not be obtained cleanly

by column chromatography. Analysis of product fractions by proton NMR gave signals not previously observed in the crude product mixture, suggesting the aldehydes were not stable to chromatography on silica. Furthermore, by electrospray mass spectrometry, the expected aldehydes were not detected.

Another reaction, this time reducing the crude aldehyde without isolation (Scheme 72), gave a more promising result. The resulting alcohol was stable to chromatography on silica, and was obtained in 51% yield over the two steps.



Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, 0°C ; reflux, 2 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.; (b) NaBH_4 , MeOH, 21.5 h.

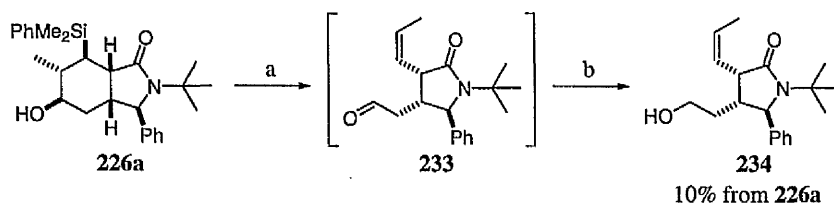
Scheme 72

Attempted further optimisation of the procedure, fragmenting at reflux in 1,2-dichloroethane (boiling point 83°C), gave a decrease in yield to 33%, perhaps due to decomposition of the intermediate aldehyde at elevated temperature.

Fragmentation was attempted on the other alcohol epimer, **225b**, using the same conditions. The two isomers were expected to lead to the same aldehyde intermediate, and therefore to give identical products after reduction. Monitoring this reaction was not as straightforward, because of the similarity of the starting material and product retention factors (0.17 and 0.19 respectively, 2 : 1 petroleum ether : ethyl acetate). Working up the fragmentation step after two hours, followed by borohydride reduction (18 hours) and column chromatography, gave a combined fraction of starting material, fragmented product (approximate relative composition 70 : 30, estimated by proton NMR) and other by-products. Thus β -silyl alcohol **225b** was far less susceptible to clean fragmentation than its hydroxyl epimer. Increasing the fragmentation reaction time to 22.5 hours still failed to consume all starting material. In this instance the mass recovery was less

than 25%, again suggesting decomposition of the intermediate aldehyde under the reaction conditions.

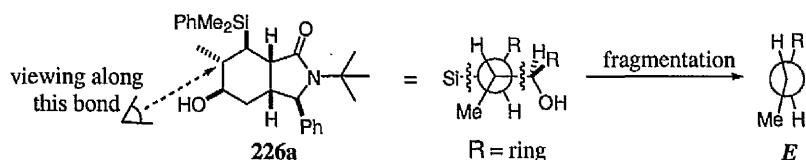
The fragmentation–reduction of *endo*-methyl alcohol **226a** was attempted using the methodology that had previously given 51% yield with **225a**. In this case the isolated yield over two steps was just 10%, along with 54% recovered starting material. An 11 Hz vicinal coupling was observed across the alkene, typical of *cis* geometry (Scheme 73).



Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, $0\text{ }^\circ\text{C}$; reflux, 2 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.; (b) NaBH_4 , MeOH, 18 h

Scheme 73

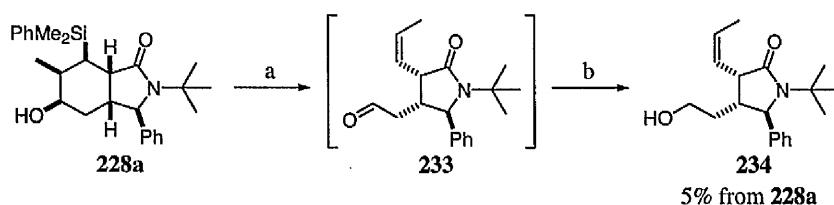
Initially this looked to be a promising result: the fragmentation methodology would have its greatest synthetic impact if it could be shown to be highly stereoselective. However, the stereochemistry of the starting material (confirmed by X-ray crystallography) appeared to be inconsistent with the product geometry. Taking the starting material and manipulating the conformation to make the two fragmenting bonds antiperiplanar (see the Newman projection in Scheme 74 below), the reaction would have been expected to favour formation of the *E*-alkene! This argument is further supported by Hebditch's results summarised in Scheme 18 on page 32.⁶⁰ It appeared that this fragmentation was proceeding by a different mechanism (see discussion in Section 3.2.4).



Scheme 74: Expected Alkene Stereochemistry via Antiperiplanar Fragmentation

Endo-hydroxy compound **226b** fragmented far more slowly than the corresponding *exo*-hydroxy compound, as also observed with those β -silyl alcohols lacking an α -methyl group (**225a** and **225b**). The fragmentation was attempted with an extended period of heating at reflux (18 hours), until the characteristic wine-red solution had become black in colour, but still a negligible amount of conversion from the starting material was observed. It was concluded that the reagent system decomposed before fragmentation could be effected.

Fragmentation of *epi*-methyl isomer **228a** over 3.5 hours gave an isolated yield of just 5% of the alkene over two steps (the rest being recovered starting material), though sufficient fragmented product was obtained to demonstrate that the *same* *cis*-alkene product **234** was formed as had resulted from **226a** (Scheme 75).



Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, 0°C ; reflux, 3.5 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.; (b) NaBH_4 , MeOH, 16.5 h

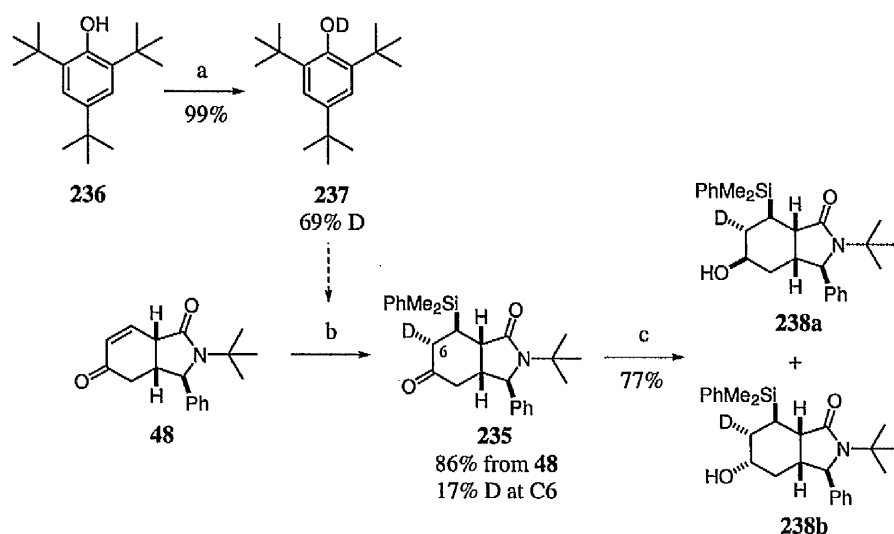
Scheme 75

It appeared that the reaction's mechanism was more complex than originally expected. A proposed rationale for the observed results, supported by mechanistic studies, is given in Section 3.2.4 below.

3.2.3 Deuterium Labelling Study

α -Deutero- β -silyl alcohols were also fragmented, in order to provide additional insight into the fragmentation mechanism in the absence of the methyl group as a stereochemical marker. The substitution of hydrogen with deuterium had the added advantage of not affecting the mechanistic pathway, because there was no change in the sterics within the molecule.

Enone **48** was functionalised in a similar manner to that previously shown in Scheme 63 on page 77, omitting the chlorotrimethylsilane and substituting a deuterating quench for the aqueous acetic acid hydrolysis step. Initially methanol- d_4 was used, but this gave uncontrolled polydeuteration in all four α -positions of the ketone. Using 2,4,6-tri-*tert*-butylphen(ol- d) as a bulky deuterating agent (deuterium content estimated to be 69%, based on proton NMR spectrum integrals) led to approximately 17% *endo*-incorporation of deuterium at the C6 position of the enone (see Scheme 76), along with about 10% undesired *exo*-substitution at C4.



Reagents and conditions: (a) NaH, DMSO- d_6 , R.T., 1 h; D₂O (b) Et₂Zn, PhMe₂SiLi, THF, 0 °C, 5 min; **48**, THF, -78 °C, 30 min; 0 °C, 80 min; **237**, THF, -78 °C, 10 min; R.T., 75 min; sat. aq. NH₄Cl soln.; (c) NaBH₄, MeOH, R.T., 2 h

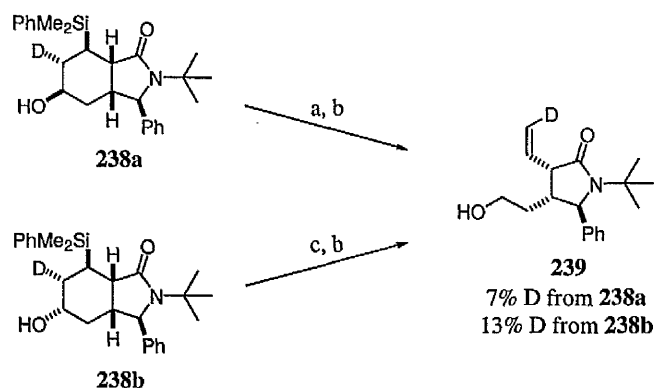
Scheme 76

Reduction of ketone **235** to two separable alcohol epimers was effected with sodium borohydride. The level of deuteration at C6 in **238a** appeared to have been maintained, estimated at 14% by proton NMR integration; the other levels of deuteration carried into the alcohols at C4 and C6 could not be confidently determined because of overlapping signals in the NMR spectra.

The low level of deuteration in ketone **235** may have been due to the excess of quench used in the method (2.5 equivalents), coupled with preferential reaction of the 31% of non-deuterated material because of a large kinetic isotope effect at low

temperature. However, a modified reaction with one equivalent each of diethylzinc, phenyldimethylsilyllithium and the quench **237** gave lower levels of conversion from enone **48**, and of deuterium incorporation in the isolated ketone.

The α -deutero- β -silyl alcohols **238a** and **238b** were fragmented using the methods discussed in Section 3.2.2 to give common deuterioalkene **239** (Scheme 77). Deuteration levels in the alkene were estimated to be 7% and 13% from alcohols **238a** and **238b** respectively, based on proton NMR integration. As previously highlighted with the non-deuterated compounds, **239** could not be separated from **238b** by column chromatography.



Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, reflux, 2 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.; (b) NaBH_4 , MeOH, 2 h; (c) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, reflux, 3 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.

Scheme 77

The ramifications of this result, giving implied mechanistic insight into the fragmentation of compounds **225a** and **225b** (see page 87), are discussed in Section 3.2.4 below.

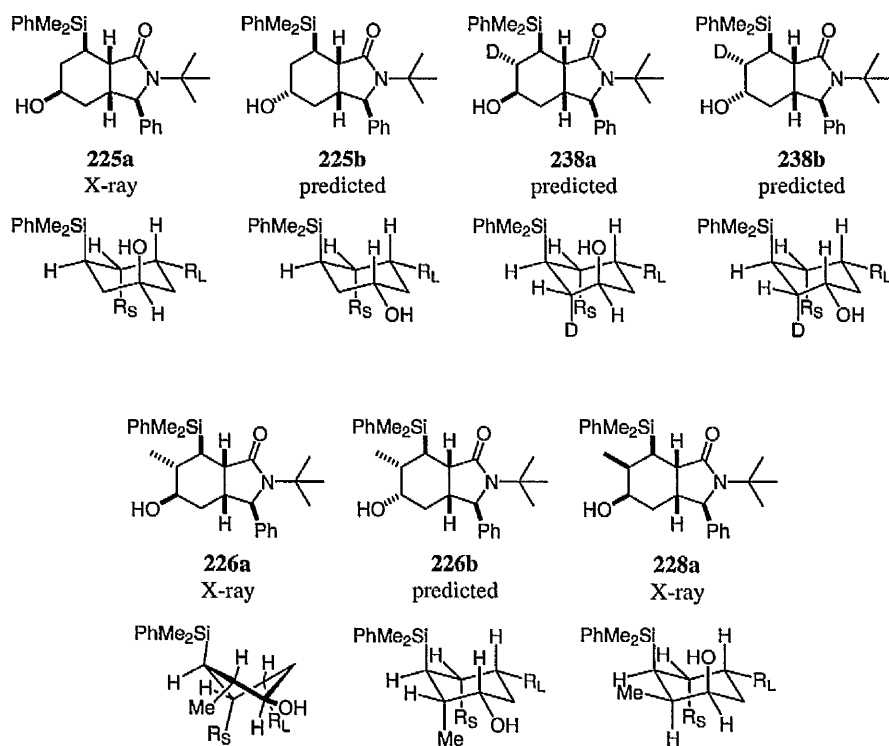
3.2.4 Proposed Mechanistic and Stereochemical Rationale

The fragmentation reactions reported in Section 3.2.2 suffered low yields, poor mass recovery and an apparent sensitivity of the intermediate aldehydes to the reaction conditions. Therefore it is possible that each substrate was reacting through two or more competing pathways, with preferential decomposition of some intermediates leading to just one product alkene being isolated from each

reaction. However, with just one product isolated from each reaction, and to simplify the explanation of the observed selectivities, it was assumed that the reactions were highly stereoselective, in each case reacting almost exclusively through a single pathway.

We initially supposed that the fragmentations would all be concerted, with the two fragmenting bonds antiperiplanar. However, this all-encompassing pathway did not explain the formation of a common alkene from methyl epimers **226a** and **228a**, and from α -deuterated epimers **238a** and **238b**, nor the higher reactivity of *exo*-hydroxy compounds compared with the *endo*-hydroxy epimers. Rather, competing pathways are suggested, with the most favourable followed if possible, thus giving the appearance of good stereoselectivity in each reaction.

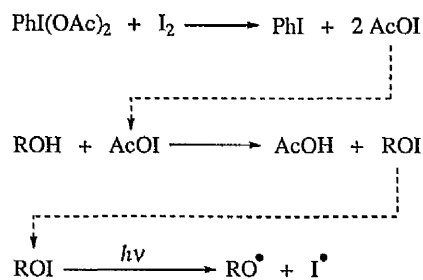
In the ground state molecular conformations (as observed in the solid state by X-ray crystallography) the phenyldimethylsilyl substituent is expected to adopt an axial environment, reducing the diaxial clashes that would result if instead the 5-ring benzyl substituent was axial. (X-ray data suggests that the carbon-carbon bond is about 25% shorter than the 1.9 Å carbon-silicon bond.) It is then suggested that the 6-membered ring containing these substituents adopts a chair conformation, unless this would be spatially unreasonable, apparently the case with more than three axial substituents larger than hydrogen/deuterium. This accounts for the observed and predicted ground state molecular conformations summarised in Figure 22 below (some of which are explained in more detail in Table 11 on page 85).



R_S = amide C=O substituent; R_L = CH(Ph) substituent

Figure 22: Observed and Predicted Ground State Molecular Conformations

It is reported in the literature that the combination of molecular iodine and iodobenzene diacetate would have generated an oxygen radical from the hydroxyl group, via the corresponding alkyl hypoiodite (Scheme 78).⁸⁹ The hypoiodite formation was taken to be a common first step in all the reactions.

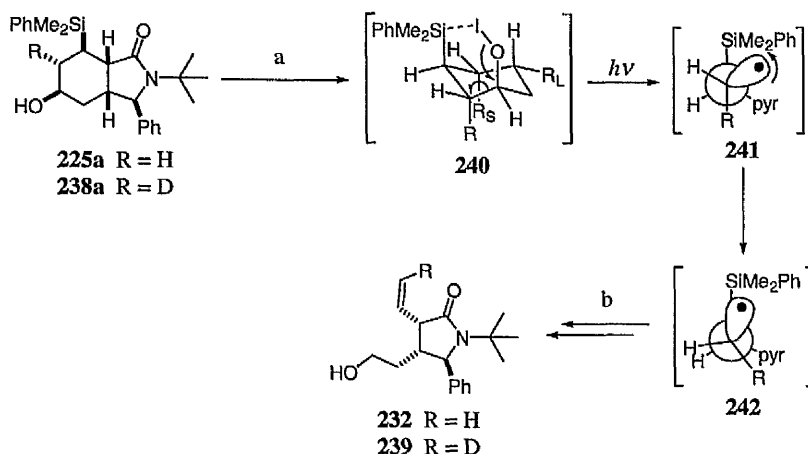


Scheme 78: Hypoiodite and Radical Generation

An intramolecular interaction between iodine and silicon (of the form $\text{O}-\text{I}^{\delta+} \cdots \text{Si}^{\delta-}$) might be envisaged to promote cleavage of the oxygen-iodine bond in the hypoiodite. Therefore, after hypoiodite formation, the ground state

conformations may have undergone a ring flip to a reacting conformation with silicon closer in space to iodine. If such an interaction was possible for a given reaction, this would have been the conformation reacting in the dominant mechanistic pathway. Then, if the reacting conformation was not set up for antiperiplanar fragmentation, the reaction would have proceeded in two steps, with an intermediate, configurationally stable, sp^3 radical rotating towards silicon prior to alkene formation.⁹⁰ If an iodine–silicon interaction was not possible, the reaction proceeded more slowly, without activated cleavage. The reacting conformation in this case was dictated by minimisation of diaxial interactions, taking into account the large hypiodite substituent formed in the reaction, and may have led to a two-step synperiplanar, or concerted antiperiplanar fragmentation.

For non-methylated, *exo*-hydroxy compounds **225a** and deuterium-labelled **238a**, these factors manifested themselves as outlined in Scheme 79. The ground state conformation was already set up with silicon and oxygen close in space, allowing iodine to bridge between them, as shown in **240**. Cleavage of the oxygen–iodine bond, followed by homolytic carbon–carbon cleavage without conformational change, gave intermediate sp^3 radical conformation **241**. Maintaining continuous orbital overlap between the radical and carbon–silicon bond, maximising hyperconjugation, promoted preferential radical rotation towards silicon, avoiding the loss of stabilisation that would have resulted if the radical became perpendicular to the carbon–silicon bond. (It is suggested that this factor dominated a potential conflicting preference for rotation to the thermodynamically more stable *E*-alkene.) Intermediate radical **242** then fragmented to give **232** or **239** after aldehyde reduction.

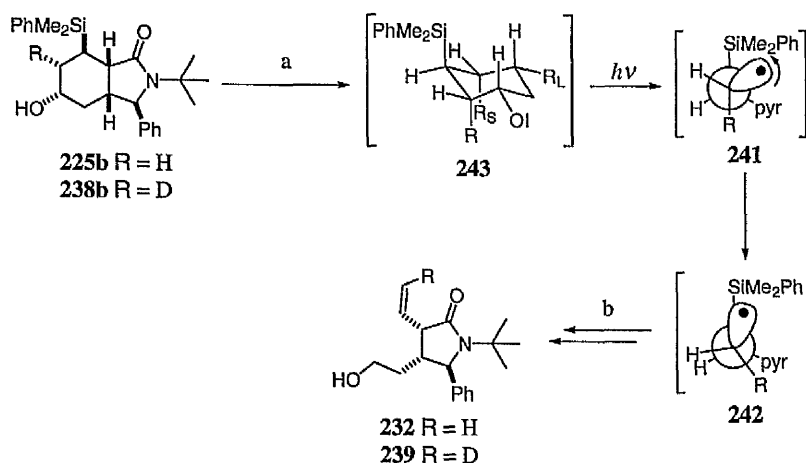


R_S = amide C=O substituent; R_L = CH(Ph) substituent; pyr = pyrrolidinone ring

Reagents: (a) $\text{PhI}(\text{OAc})_2$, I_2 ; (b) NaBH_4

Scheme 79: Z-Alkene Formation via a Bridged Intermediate

Endo-hydroxy compounds **225b** and **238b**, with the hydroxyl group *anti* to silicon, could not adopt a bridged hypiodite conformation analogous to **240** in Scheme 79, explaining the reduced reactivity of this isomer. The reacting conformation **243** was that in which the hypiodite was equatorial, to avoid a diaxial clash with R_L . In **243** the fragmenting bonds were not antiperiplanar, so fragmentation could have proceeded in two steps through an intermediate sp^3 radical, as with **225a** and **238a** (Scheme 80).

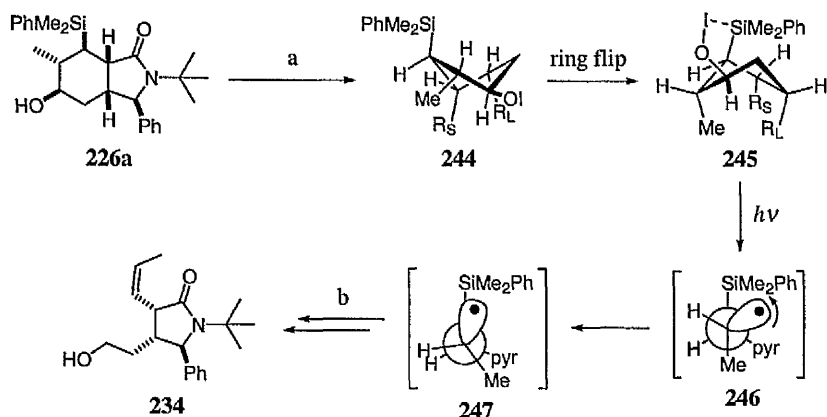


R_S = amide C=O substituent; R_L = CH(Ph) substituent; pyr = pyrrolidinone ring

Reagents: (a) $\text{PhI}(\text{OAc})_2$, I_2 ; (b) NaBH_4

Scheme 80: Z-Alkene Formation via Selective Rotation of an Intermediate sp^3 Radical

Endo-methyl-*exo*-hydroxy compound **226a** has a twist-boat ground state (see Figure 22 on page 93). On hypoiodite formation (**244** to **245** in Scheme 81) the molecule could flip to an alternative iodine-bridged conformation, fragmenting to *Z*-alkene **234** as seen previously.

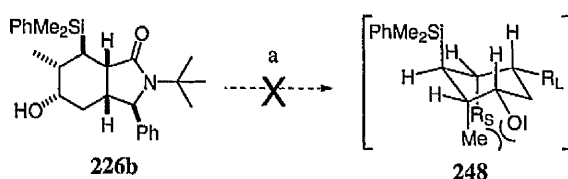


R_S = amide C=O substituent; R_L = CH(Ph) substituent; pyr = pyrrolidinone ring

Reagents: (a) $\text{PhI}(\text{OAc})_2$, I_2 ; (b) NaBH_4

Scheme 81: *Z*-Alkene Formation via a Bridged Twist-Boat Intermediate

Compound **226b** was predicted to adopt a chair ground state conformation, with one less axial substituent than **226a**. No fragmentation of **226b** was observed, perhaps because hypoiodite formation was hindered by nearby methyl and R_L groups on the same face of the molecule (Scheme 82).



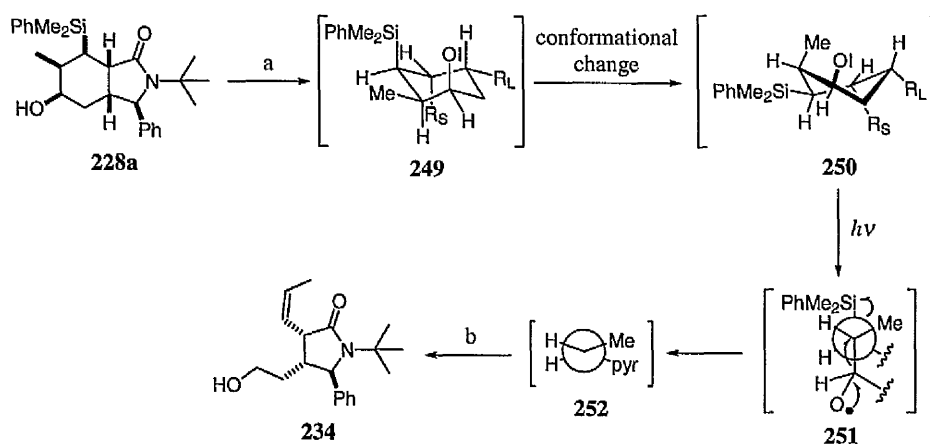
R_S = amide C=O substituent; R_L = CH(Ph) substituent

Reagents: (a) $\text{PhI}(\text{OAc})_2$, I_2

Scheme 82

Compound **228a** has a methyl group situated between the phenyldimethylsilyl and hydroxyl groups, on the same face. It is proposed that this prevented the large iodine atom being accommodated between axial silicon and oxygen in **249**

(Scheme 83). Although molecular modelling* predicted **249** to be the ground-state conformation, it also suggested that there was an accessible twist-boat conformation, with the silicon and uncoordinated hypiodite substituents in equatorial positions (**250**). The calculated 15.3 kJ mol^{-1} energy difference between **249** and **250** gives Boltzmann populations of 99.7% and 0.3% respectively. Hypiodite cleavage in both **249** and **250** is believed to be relatively slow without the proposed promotion by silicon–iodine coordination, but the one-step antiperiplanar fragmentation from **251** to **252**, forming the Z-alkene, might be expected to be the faster of the two. Thus the reaction's outcome can be explained by assuming that the reaction was dominated by the faster rate at which **250** reacted compared with **249**, rather than the equilibrium ratio of these conformers.



Scheme 83: Antiperiplanar Fragmentation yielding a Z-Alkene

Figure 23 summarises the proposed factors which governed the outcome of the fragmentation reactions discussed above. The nature of the fragmentation of each compound (activated or unactivated; one-step or two-step) represents the dominant mechanism, leading to the observed product for that reaction, and provides an insight into the relative rates of the reactions.

* Spartan '04 software (Wavefunction Inc.) single-point ground-state energy global calculation using molecular mechanics force field (MMFF)

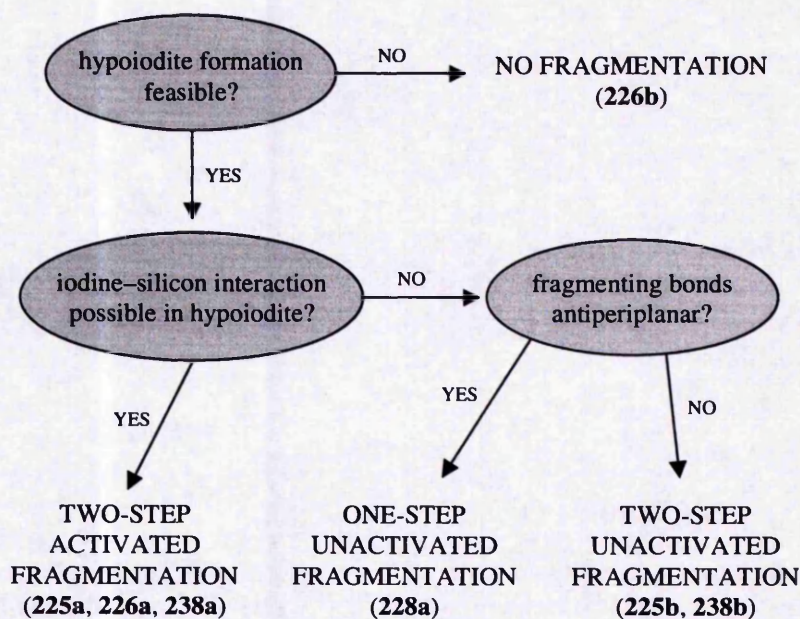


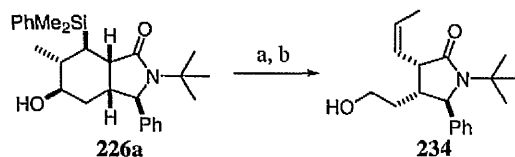
Figure 23: Summary of Factors in Silicon-Directed Fragmentation Reactions

3.2.5 Effect of Irradiation

Although the decision to use thermal fragmentation was based on an experimental procedure previously published in the literature,⁷³ it is of note that the homolytic hypoiodite cleavage was thought to be light dependent (see Scheme 78 on page 93).⁸⁹ This suggested that it might be possible to use irradiation to promote the processes given above, perhaps leading to faster reactions and higher yields.

As a preliminary investigation, the fragmentation of **226a** was performed at 0 °C and at reflux, with irradiation over a wide range of wavelengths (Scheme 84).*

* The reactions were simultaneously irradiated with a 500 W tungsten filament lamp ($\lambda > 500$ nm) and a 400 W iron-halogen lamp ($250 \text{ nm} < \lambda < 600 \text{ nm}$), as previously used by Knowles.^{59b}



Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, I_2 , DCM, 0°C ; 0°C or reflux, $h\nu$, 2 h; sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln.; (b) NaBH_4 , MeOH, 2.5 h

Scheme 84

The product profiles obtained after reduction and column chromatography are summarised in Table 12, along with that previously obtained at an ambient light level (entry 1). In all cases *Z*-alkene **234** was the only isolated fragmented product.

Light Level		Reaction Temperature	Recovered 226a	Yield of 234
1	Ambient	Reflux	54%	10%
2	Irradiated	0°C	77%	7%
3	Irradiated	Reflux	56%	16%

Table 12: Comparison of Thermal and Irradiated Fragmentation Reactions

A comparison of entries 1 and 3 implies that irradiation had no effect on the rate of conversion from **226a**, with a similar quantity of starting β -silyl alcohol recovered from each after two hours' reaction. As previously observed, the reaction proceeded less well at a lower temperature (entries 2 and 3), even with irradiation. Therefore irradiation did not appear to lead to any significant promotion of the reaction, as had been seen with an increase in reaction temperature.

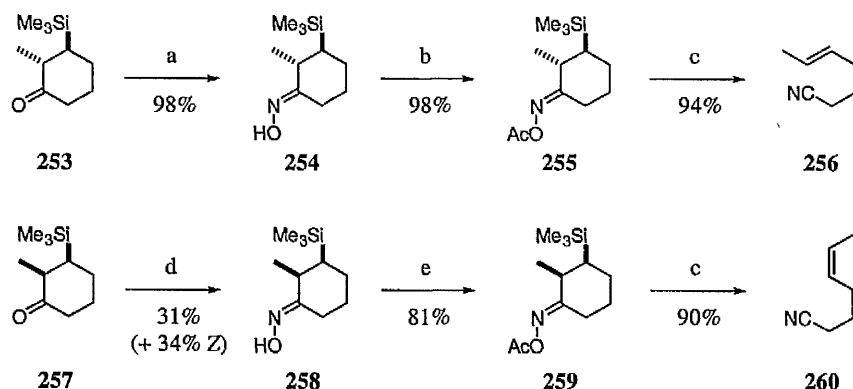
3.2.6 Conclusion

The silicon-directed fragmentation reaction was intended to incorporate a trisubstituted double bond in the isodomoic acid side-chains stereospecifically. The model reactions in Scheme 73 and Scheme 75 (pages 88 and 89) indicate that this is unlikely to be possible, as the reaction was neither high-yielding nor able to

facilitate control of the product alkene's configuration by choice of starting material stereochemistry. This methodology was therefore not applied to the stabilisation of the tricyclic oxazolidines, a possibility raised in Section 3.1.

3.3 Future Work: Silicon-Directed Beckmann Fragmentation

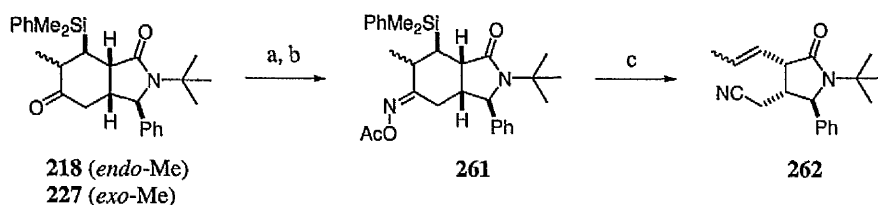
Immediate future work could focus on investigating the potential application of a similar silicon-directed fragmentation reported by Nishiyama *et al.*⁹¹ After conversion of a cyclohexanone to an oxime, then to its oxime acetate, a Beckmann fragmentation was used to form alkenes stereoselectively and in high yields (Scheme 85).



Reagents and conditions: (a) hydroxylamine hydrochloride, NaOAc, EtOH, 0 °C, 1 h; (b) Ac₂O, py, 0 °C, 2 h; (c) TMSOTf, DCM, 0 °C, 3 h; (d) hydroxylamine hydrochloride, NaOAc, EtOH, 0 °C, 1.5 h; (e) Ac₂O, py, DCM, 0 °C, 1 h

Scheme 85: Literature Examples of a Beckmann Fragmentation

This methodology could be initially applied to the model system previously used (Section 3.2), incorporating the phenyldimethylsilyl directing group to avoid using toxic HMPA and volatile trimethylsilyl compounds. Fleming *et al.* have demonstrated the viability of using the phenyldimethylsilyl group to direct a Beckmann fragmentation.⁹² A possible approach is summarised in Scheme 86.



Reagents: (a) hydroxylamine hydrochloride; (b) Ac₂O, py; (c) TMSOTf

Scheme 86: Possible Application of the Beckmann Fragmentation

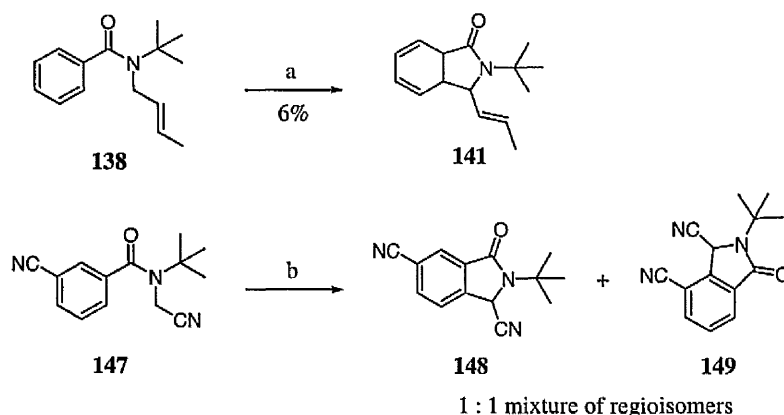
The development of fragmentation methodology was suspended to allow development of the crucial dearomatising cyclisation, work outlined in Chapter 4.

Chapter 4: Novel Benzamide Cyclisations

4.1 Background

Synthetic routes involving the dearomatising cyclisation of *N*-benzylbenzamides required harsh conditions for oxidising a phenyl group to a carboxylic acid, hampering attempts to utilise an enone precursor to the isodomoic acids (Section 1.2.5). Initially, oxazolidine cyclisations were investigated as a possible alternative, but extensive difficulties experienced in stabilising the dearomatised compounds ultimately proved to be too restrictive for that methodology to be generally synthetically useful (Chapter 2).

It was envisaged that other non-benzyl cyclising groups might facilitate a mild synthetic route towards the isodomoic acids, though few successful examples have been reported to date (summarised in Section 1.2.7 and Scheme 87 below). Research into the development of such cyclisations is described in this Chapter.

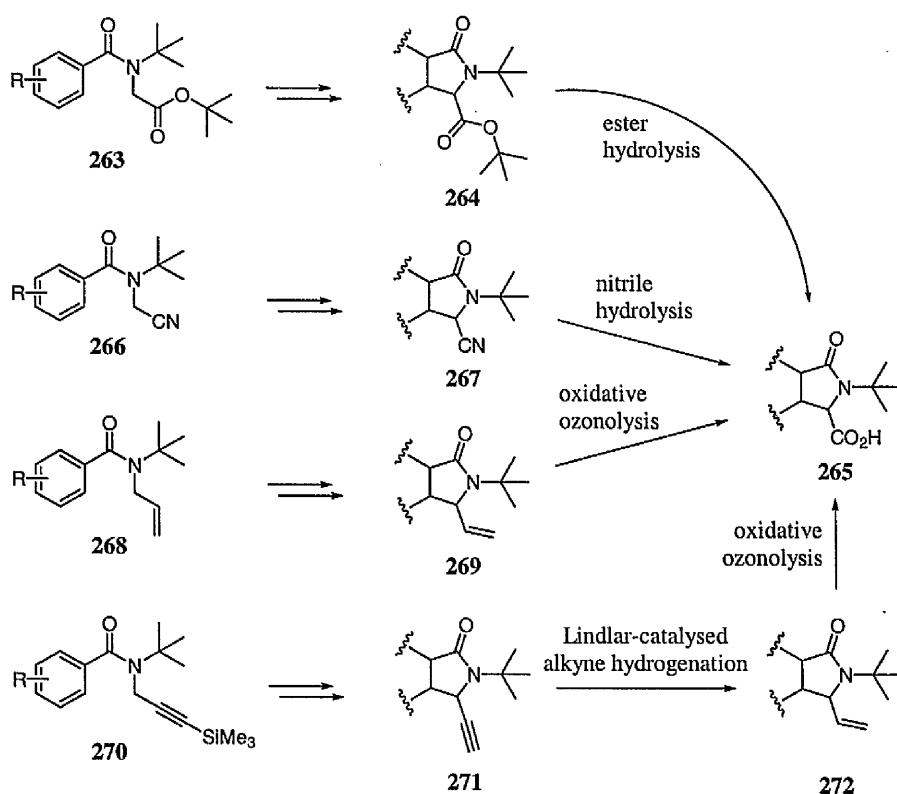


Reagents and conditions: (a) *t*-BuLi, THF, -78°C , 2 h; HMPA, 16 h; sat. aq. NH_4Cl soln.; (b) LDA, THF, -40°C , 4 h; sat. aq. NH_4Cl soln.

Scheme 87: Previous Examples of Non-Benzyl Cyclisations in the Clayden Group

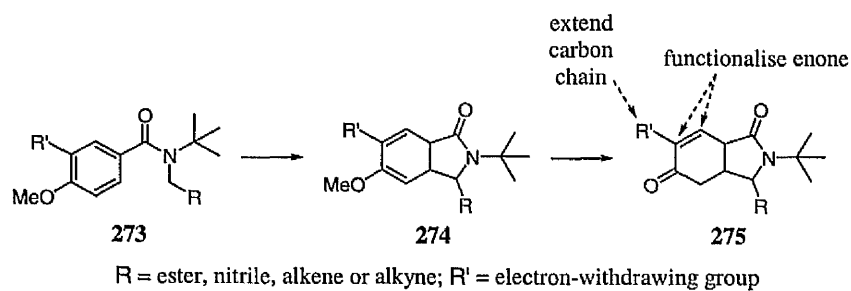
The overall aim of this section of research was to develop the promising results outlined above into a synthetically useful benzamide cyclisation. Introductory studies would attempt to extend the range of cyclising groups, and investigate their compatibility with various substitution patterns on the acceptor ring, whilst still remaining focused on the eventual application to isodomoic acid synthesis.

A variety of cyclising groups were selected to be investigated, namely *tert*-butylacetate, cyanomethyl, allyl (or crotyl or prenyl) and trimethylsilylpropargyl. These were chosen because of their common potential to stabilise an adjacent anion by charge delocalisation (in order to control deprotonation), and the ease with which the cyclised compounds might be converted to the acid functionality required in the target natural products (Scheme 88).



Scheme 88: Transformations of Cyclising Groups to Kainoid Acid Functionality

The substitution patterns on the benzenoid ring were to be chosen based on commercial availability, synthetic considerations, and the apparent need for a *meta* electron-withdrawing group. In particular, for the synthesis of the isodomoic acids, it would be necessary to include both a *para* methoxy group (to allow full functionalisation using an enone), and the facility to build a carbon chain at the *meta* position (Scheme 89).

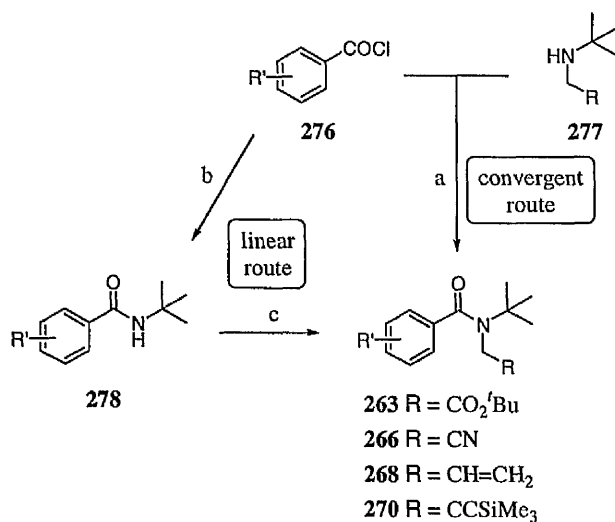


Scheme 89: Structural Requirements in Kainoid Synthesis

For consistency, all compounds used to develop the methodology would be *N*-*tert*-butyl tertiary amides, as used in the reactions of Ahmed⁶⁹ and Hamilton⁷⁰ shown in Scheme 87 above.

4.2 Benzamide Synthesis

A convergent approach to the benzamides, modelled on the work of Hamilton,⁷⁰ was the first choice of route. This would involve coupling aromatic acid chlorides and secondary amines that had been synthesised independently, rather than alkylating a common secondary amide (Scheme 90).



Reagents: (a) Et_3N ; (b) $t\text{-BuNH}_2$; (c) NaH , RCH_2Br

Scheme 90: Linear and Convergent Routes towards Tertiary Benzamides

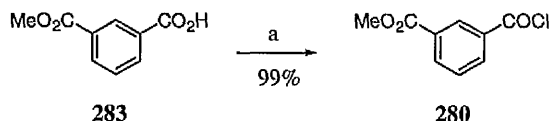
Four acid chlorides with the required substitution pattern on the aromatic ring were initially selected (Figure 24). All targets had a *meta* electron-withdrawing group: either a nitrile, as used in Hamilton's cyanomethyl cyclisation shown in Scheme 87 on page 103, or an ester, which would allow straightforward chain extension at this position. Possible isodomoic acid precursors also included a methoxy group in the *para* position.



Figure 24: Initial Acid Chloride Targets

4.2.1 Synthesis of Acid Chlorides

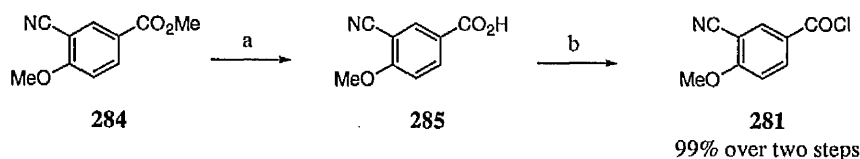
Acid chloride **279** was commercially available; **280** was readily formed in one step from *mono*-methyl isophthalate, **283** (Scheme 91).



Reagents and conditions: (a) SOCl_2 , R.T., 15 min; reflux, 75 min

Scheme 91

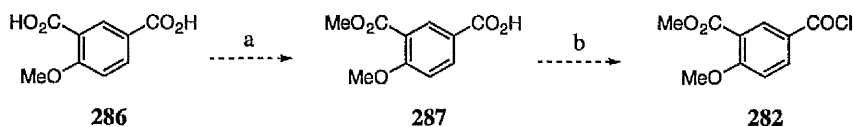
A two-step procedure was required to form acid chloride **281** from the commercially sourced methyl ester precursor **284**. This was also performed with a near-quantitative yield (Scheme 92).



Reagents and conditions: (a) NaOH , $\text{MeOH}/\text{H}_2\text{O}$, R.T., 2 h; HCl ; (b) SOCl_2 , reflux, 2 h

Scheme 92

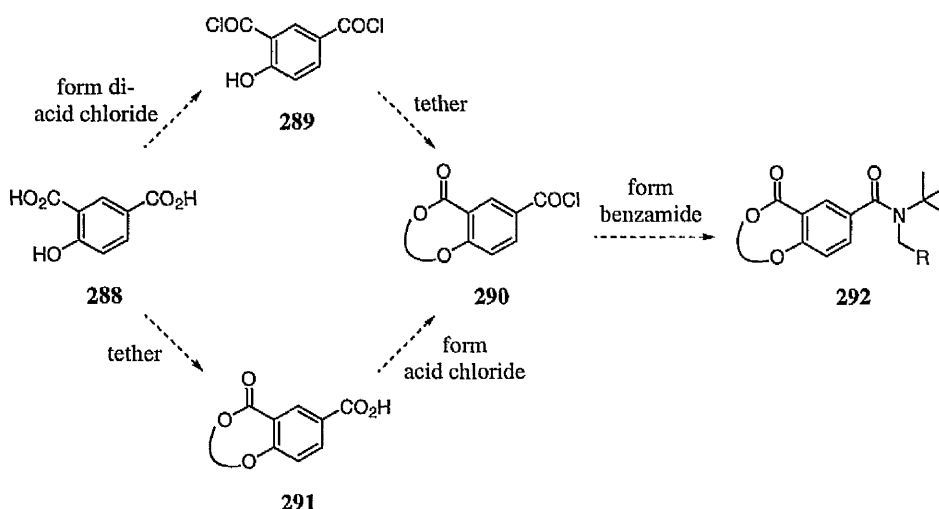
A mono-ester of 4-methoxyisophthalic acid was not commercially available, so an attempt was made to form acid chloride **282** from commercial di-acid **286**, via mono-acid **287** (Scheme 93). Although the reaction had been reported in the literature (albeit in a low yield of 53%),⁹³ esterification *ortho* to the methoxy group could not be achieved. The literature method reported selective precipitation of **287** over unreacted **286** by careful acidification to pH 4.8. At this pH only **286** was obtained, with no evidence of an additional methyl signal by proton NMR. Further acidification to pH 1.8 gave additional precipitation, but this also proved to be unreacted starting material (total recovery of starting material was 73%).



Reagents and conditions: (a) HCl, MeOH, R.T., 1 h; sat. aq. NaHCO₃ soln.; HCl; (b) SOCl₂, reflux

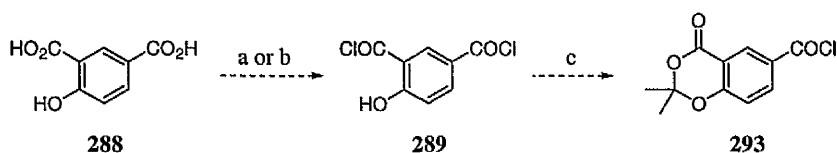
Scheme 93

Two tethering approaches were also examined as a means of ‘desymmetrising’ a di-acid (Scheme 94). These would still yield a benzamide with the properties required for the subsequent dearomatising cyclisation, i.e. an electron-withdrawing group *meta* to the amide and a precursor to a *para* methoxy group.



Scheme 94: Approaches towards a Tethered Benzamide

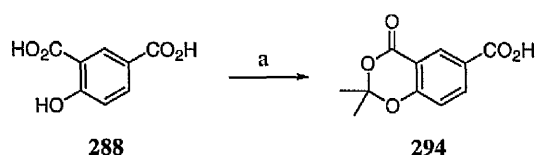
The first method, forming the di-acid chloride before tethering with the *ortho* phenol using acetone (Scheme 95), was based on that reported by Deshpande *et al.*, in which an *ortho*-hydroxy mono-benzoic acid was tethered.⁹⁴ However, with two carboxylic acids in the starting phenol, no product could be obtained. Mass spectrometry indicated that one chlorine atom was present after the acid chloride formation step (product could not be identified), but no methyl groups were apparent in the proton NMR spectrum after attempting to tether with acetone.



Reagents and conditions: (a) SOCl_2 , reflux, 3.5 h; (b) $(\text{COCl})_2$, DMF (1 drop), DCM, R.T., 24 h; (c) acetone, R.T., 24 h

Scheme 95

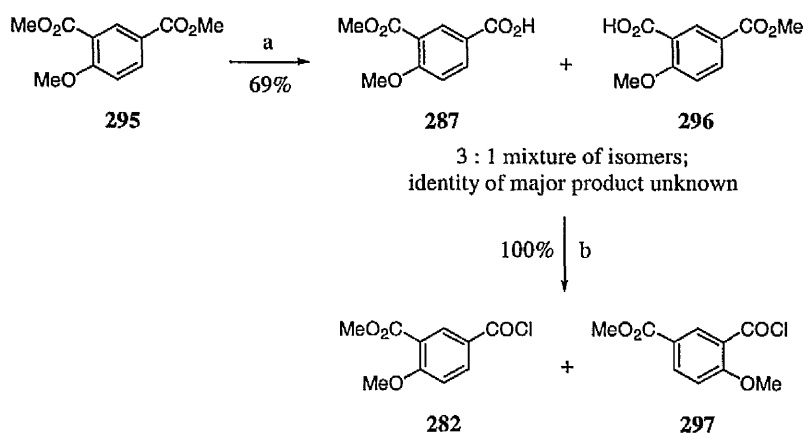
A second tethering method from the work of Danishefsky showed more promise,⁹⁵ with the target mono-acid detected by NMR and mass spectrometry after treatment with acetone and trifluoroacetic anhydride (Scheme 96). Unfortunately the product was unstable, possibly due to an incompatibility of the acid and acetal functionalities, and decomposed to starting material when recrystallisation was attempted.



Reagents and conditions: (a) acetone, TFAA, TFA, 0 °C; R.T., 24 h

Scheme 96

At this stage development of the tethering methodology was suspended, to investigate an alternative route to mono-acid **287** in Scheme 93 above. From dimethyl ester **295**, selective hydrolysis to the mono-acid was attempted using one equivalent of potassium hydroxide (Scheme 97).⁹⁶ The reaction gave exclusive mono-hydrolysis as desired, but unfortunately poor differentiation between the two esters. A 3 : 1 mixture of mono-acids was obtained; at this stage the identity of the major product was unknown. The mixed mono-acids **287** and **296** were converted to the acid chlorides in quantitative yield, giving the target acid chloride **282** as a mixture with undesired regioisomer **297**.



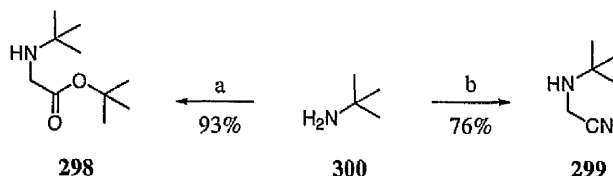
Reagents and conditions: (a) KOH (1 eq.), MeOH, 0 °C, 2 h; R.T., 2 h; reflux, 20 h; (b) SOCl₂, reflux, 2 h

Scheme 97

It proved necessary to react acid chlorides **282** and **297** as a mixture before they could be separated as the benzamides; the identities of the major and minor regioisomers could only be elucidated by examination of their cyclisation products.

4.2.2 Synthesis of Amines

With routes to suitable acid chlorides in place, focus was turned to the secondary *N*-alkyl-*tert*-butylamines required to incorporate the cyclising groups shown in Scheme 90 on page 106. The *N*-*tert*-butyl ester and *N*-cyanomethyl amines **298** and **299** were synthesised from *tert*-butylamine using Hamilton's method (Scheme 98).⁷⁰

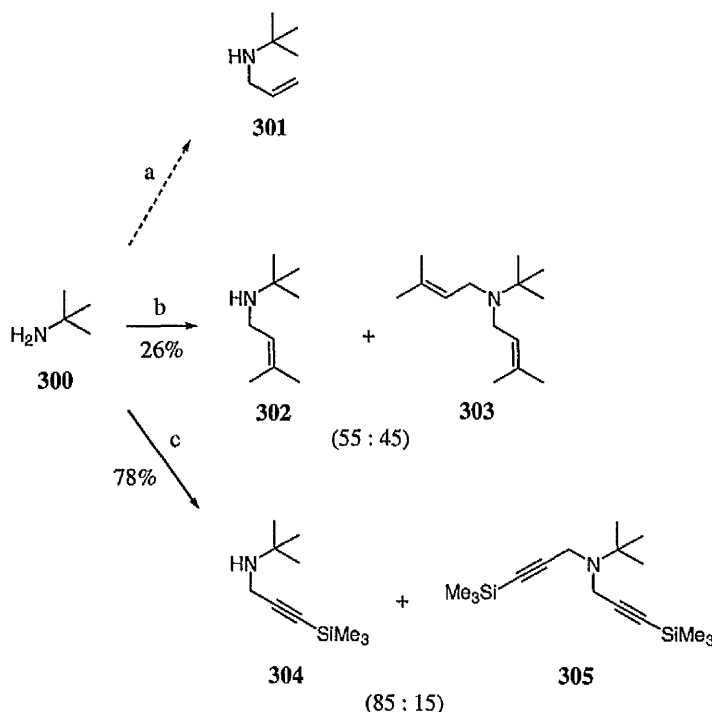


Reagents and conditions: (a) *t*-butyl bromoacetate, MeCN, R.T., 5.5 h; (b) bromoacetonitrile, MeCN, R.T., 5 h

Scheme 98

The same method was used in an attempt to form *N*-allyl-*tert*-butylamine, **301** (Scheme 99), but the product evaporated on removal of the solvent under reduced

pressure. The increased volatility was a predictable result of lower intermolecular interactions in the absence of the polar ester or nitrile groups of amines **298** and **299**. Increasing the molecular weight, by substituting the allyl group with a prenyl group, allowed some product to be isolated, though polyalkylation appeared to be a problem by analysis of mixed proton NMR data (Scheme 99). This type of by-product was also observed, to a lesser degree, when trimethylsilylpropargyl bromide was used.



Reagents and conditions: (a) allyl bromide, MeCN, R.T., 5.5 h; (b) 3,3-dimethylallyl bromide, MeCN, R.T., 5 h; (c) 3-bromo-1-trimethylsilyl-1-propyne, MeCN, R.T., 6 h

Scheme 99: Polyalkylated Amine Products

The amount of polyalkylation observed was the result of a balance of factors. With an extra electron-donating alkyl group, the nitrogen lone pair in the secondary amines is expected to be more nucleophilic than that of *tert*-butylamine. This additional electronic reactivity is offset to some degree by additional steric crowding around the reacting centre.

Polyalkylation was less of a problem with the alkyne than the alkene, even though the *sp* carbon centres held the steric bulk significantly further from nitrogen. The

observed ratio of mono- and di-alkylated products can be explained by the relative electron-withdrawing effects of sp and sp^2 centres (with more 's' character resulting in electrons being held more tightly to the nucleus). Competition for hyperconjugative interactions by the adjacent alkene or alkyne may also have influenced the reactions. With two perpendicular π -orbitals in the alkyne, the methylene C–H bonds always have some component delocalised into the alkyne; with only one π -orbital in the alkene there is less σ – π interaction, and more hyperconjugation overall between the methylene C–H bonds and the nitrogen lone pair (Figure 25).

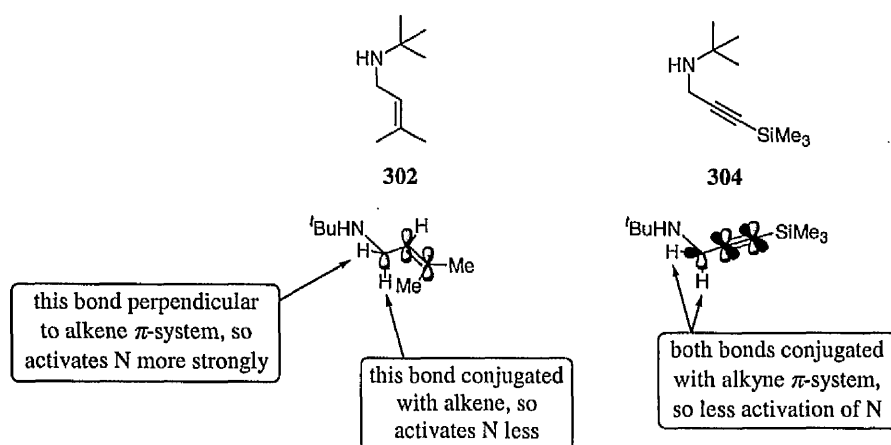
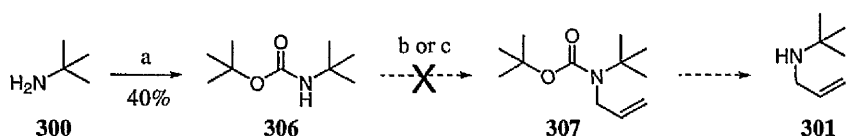


Figure 25: Comparison of Hyperconjugation Effects in Secondary Amines

Using the method of Chen *et al.*,⁹⁷ *tert*-butylamine was Boc-protected to prevent polyalkylation on nitrogen. Unfortunately, the resulting urethane proved to be unreactive towards allyl bromide when deprotonated, and allylamine **301** could not be made in this way (Scheme 100). The low reactivity after protection is presumably a combination of the steric hindrance of two nearby *tert*-butyl groups, and the electron-withdrawing effect of an adjacent carbonyl group with an attached oxygen atom.

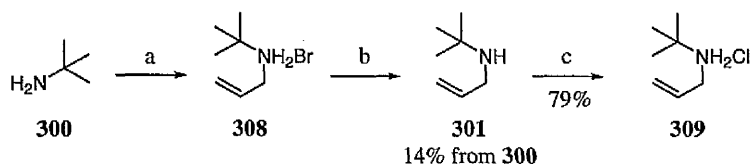


Reagents and conditions: (a) Boc_2O , MoO_2Cl_2 , DCM, R.T., 17 h; (b) NaH, THF, R.T., 30 min; allyl bromide, R.T., 19 h; reflux, 46 h; (c) NaH, DMF, R.T., 2 h; allyl bromide, R.T., 5 days

Scheme 100

Another potential solution to the problem of polyalkylation could be in reversing the order of addition, as used by Tilley and Sayigh.⁹⁸ By adding the alkyl bromide slowly to a heated solution of *tert*-butylamine, any secondary amine formed would compete with the primary amine for the hydrobromic acid generated by the reaction. In this way the more basic secondary amine would be constantly 'trapped' as the hydrobromide salt, rendering it inert to further reaction.

The reaction appeared to proceed well, with good recovery of the crude hydrobromide salt of the allylamine after removal of solvent and unreacted starting materials by distillation. However, only a low yield of the free amine was isolated after extraction and redistillation, thought to be the result of poor partitioning between diethyl ether and aqueous potassium hydroxide. (This yield might be improved in future by saturating the aqueous layer with salt prior during extraction of the product.) The amine was isolated as its hydrochloride salt in 11% overall yield (Scheme 101).



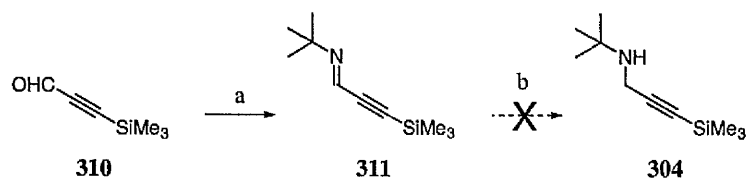
Reagents and conditions: (a) allyl bromide, DMF, 60–85 °C; 130 °C, 3 h; (b) 15% KOH/H₂O; (c) 2 M HCl/Et₂O, Et₂O

Scheme 101

It is of note that Tilley and Sayigh did not report the yield of their reaction to form amine **301**; in a later publication by Walton *et al.*, **301** was formed in just 10% yield by a similar approach.⁹⁹ Unfortunately this method could not be used to

form propargylamine **304**, even in small quantities, because the propargyl bromide decomposed under the reaction conditions.

Suvorova and Stadnichuk have reported the synthesis of the desired propargylamine via reductive amination.¹⁰⁰ The imine formation step proceeded well, with around 90% conversion from the starting aldehyde and complete recovery of mass (Scheme 102). The observed formation of only the *E*-imine isomer was consistent with Suvorova and Stadnichuk's result. However, after reduction using lithium aluminium hydride (cleavage of the silicon–carbon bond was reported to accompany borohydride reduction), no product amine could be isolated by distillation.



Reagents and conditions: (a) *t*-BuNH₂, MgSO₄, DCM, R.T., 18 h; (b) 2 M LiAlH₄ in THF, Et₂O, 0 °C; R.T., 22 h

Scheme 102

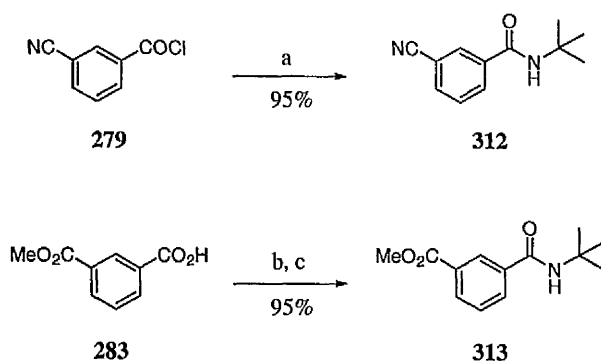
4.2.3 Approaches to the Benzamides

Four classes of benzamide had been identified as targets, differing in the cyclising group on nitrogen (see Scheme 90 on page 106). The most synthetically useful approaches were based on the convergent route shown in Scheme 90, and are discussed for each cyclising group (amine precursor) in turn in Section 4.2.3.2. Limited attempts at the linear synthesis were also performed, as summarised below.

4.2.3.1 Linear Synthesis

Formation of the secondary *tert*-butyl amides was achieved by reaction of acid chlorides with *tert*-butylamine, using an excess of the amine to act as both the nucleophile and the base. The reaction was attempted with the two most

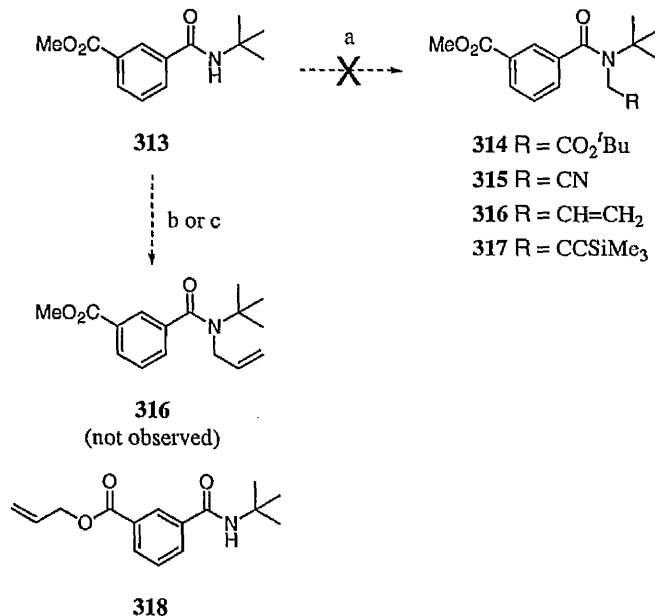
straightforwardly obtained acid chlorides, *meta*-cyano and *meta*-ester, and proceeded in high yield in both cases (Scheme 103).



Reagents and conditions: (a) *t*-BuNH₂ (2.2 eq.), DCM, R.T., 4 h; (b) SOCl₂, reflux, 80 min; (c) *t*-BuNH₂, DCM, R.T., 2.5 h

Scheme 103

The subsequent *N*-alkylation was not expected to be problematic, yet with secondary amide **313** it could not be accomplished using a range of electrophiles and conditions (Scheme 104).



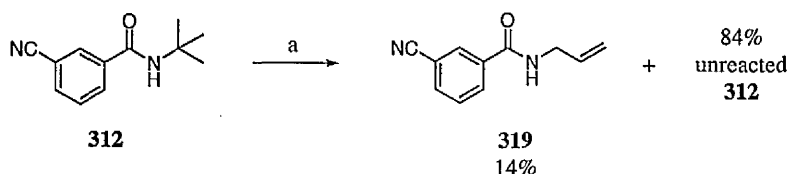
Reagents and conditions: (a) NaH, THF, R.T., 30 min; RBr, R.T., 3 days; (b) NaH, DMF, R.T., 2 h; allyl bromide, R.T., 5 days; H₂O; (c) NaH, redistilled DMF, R.T., 1.5 h; allyl bromide, R.T., 21 h; sat. aq. NH₄Cl soln.

Scheme 104

The reactions in tetrahydrofuran (Method 'a') were monitored by thin layer chromatography over three days. Conversion from starting material was generally very slow; no new products were detected at all for the reaction with allyl bromide. Bromoacetonitrile appeared to be unstable under the reaction conditions, with baseline material generated after a few hours, and deep brown colouration of the reaction mixture. Reaction with the propargyl bromide was messy, giving a number of new product spots by thin layer chromatography. The only quench that gave a promising result was *tert*-butyl bromoacetate, with gradual conversion to one new spot, though still predominantly starting material after three days.

With dimethylformamide as a solvent (Methods 'b' and 'c'), hydrolysis of the methyl ester was a problem, giving allyl ester **318** as the only new product. This was thought to be due to the presence of water, though formation of the by-product could not be avoided even after rigorous redistillation of the reaction solvent.

Reaction of *meta*-cyano benzamide **312** with allyl bromide under the same conditions also failed to yield the desired product. Without the ester of **313**, some *N*-allylation was observed, though it was accompanied by loss of the *tert*-butyl group on nitrogen (Scheme 105).

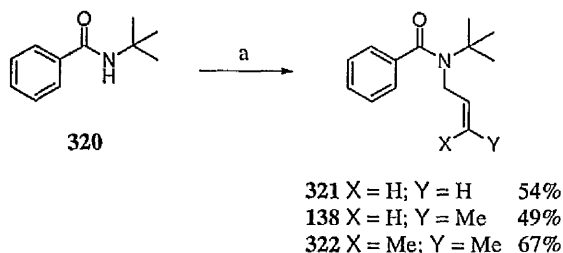


Reagents and conditions: (a) NaH, DMF, R.T., 30 min; allyl bromide, R.T., 15.5 h; allyl bromide, 100 °C, 5.5 h

Scheme 105

The *N*-alkylation had previously been successful, though fairly low-yielding, for reactions of a secondary benzamide with an unsubstituted aromatic ring (Scheme 106).⁶⁹ The failure of the reactions above, and of the attempted alkylation of Boc-protected *tert*-butylamine (Scheme 100 on page 113), indicate that electron-

withdrawing groups adjacent to the amide carbonyl group may have a detrimental deactivating effect on the nucleophilicity of the deprotonated amide. This is further supported by the high yield reported for the alkylation of an electron-rich benzamide in the synthesis of kainic acid (forming tertiary benzamide **50** in Scheme 13 on page 26).

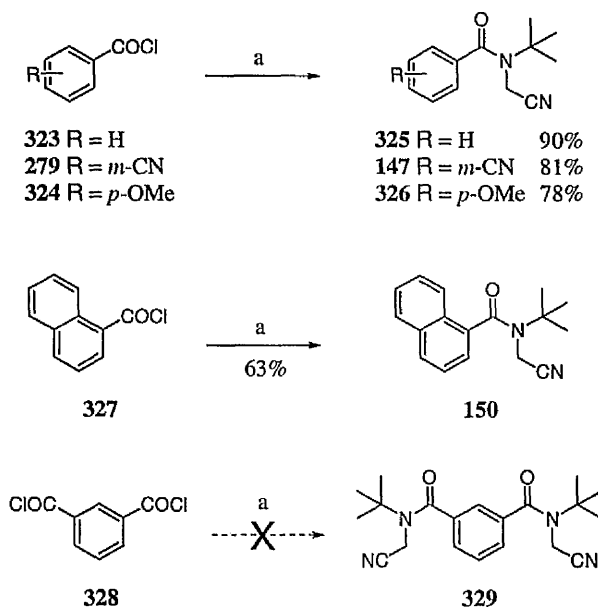


Reagents and conditions: (a) NaH, DMF, R.T., 1.5–6 h; RBr, R.T., 1–3 days

Scheme 106

4.2.3.2 Convergent Synthesis

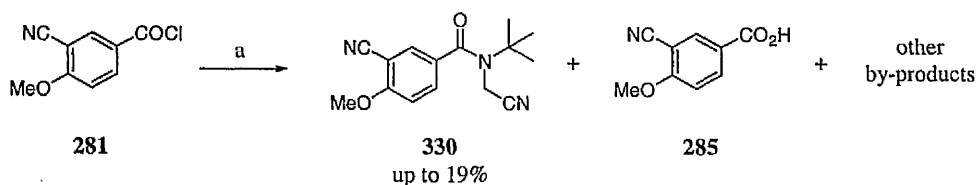
Cyanomethyl amine **299** had been synthesised by Hamilton and was used to form benzamide **147**, one of only a very limited number of non-benzyl benzamides previously demonstrated to be capable of undergoing cyclisation (see Scheme 87 on page 103). The success of benzamide formation with this amine had been shown to vary somewhat, according to the substitution pattern around the aromatic ring, and to fail completely with the di-acid chloride of isophthalic acid (Scheme 107).⁷⁰



Reagents and conditions: (a) *t*-BuNHCH₂CN (**299**), Et₃N, DCM, R.T., o/n

Scheme 107: Hamilton's Benzamide Formation Reactions

An interesting extension to the previously observed cyclisation of **147** would be to investigate benzamides with both the *meta* cyano group and a *para* methoxy group. Attempts were made to form benzamide **330**, from previously synthesised acid chloride **281**, but the desired product was only ever isolated in low yield (Scheme 108). It appeared that the amine was prone to decomposition, as the reactions did not proceed 'spot-to-spot' by thin layer chromatography, and by-products containing no *tert*-butyl group or no cyanomethyl group were also formed. The acid chloride was typically hydrolysed to the acid during the course of the reaction.

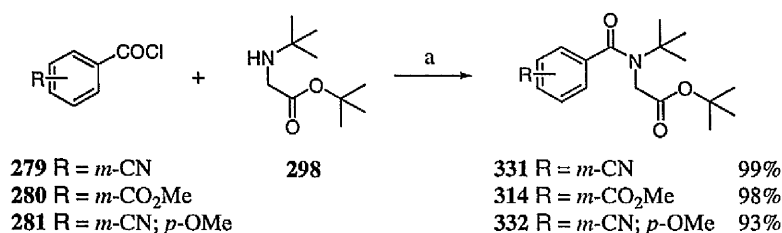


Reagents and conditions: (a) *t*-BuNHCH₂CN (**299**), Et₃N or py, DCM, R.T., 2 h to 3 days

Scheme 108

Turning attention to *tert*-butyl ester amine **298** appeared to confirm the sensitivity of **299**, as by similar methods a range of benzamides were formed in excellent

yields, from some of the range of acid chlorides described in Section 4.2.1 (Scheme 109).



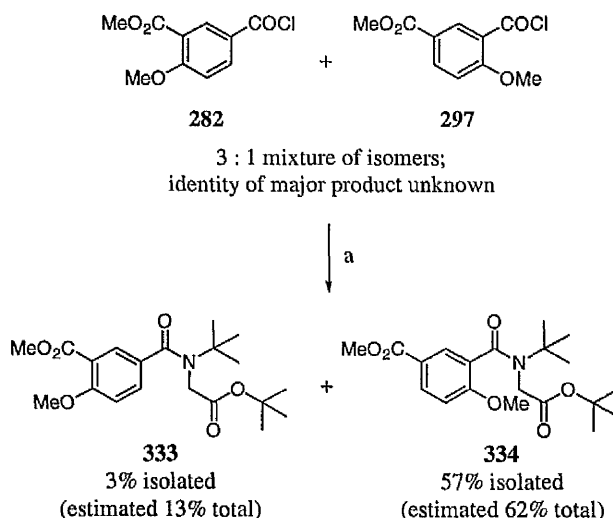
Reagents and conditions: (a) Et₃N, DCM, R.T., 17 h

Scheme 109

The yield for the formation of benzamide **332** was significantly lower, at 65%, when pyridine was used in place of triethylamine.

meta-Ester-*para*-methoxy acid chloride **282** had only been synthesised as a mixture with its regioisomer **297** (Scheme 97 on page 110), and was reacted as a mixture to give benzamides **333** and **334** (Scheme 110). Although they ran very closely by thin layer chromatography, the benzamides could be separated by repeated column chromatography. Benzamide **334**, the faster-running fraction, could be obtained cleanly in a greater quantity; the total yields from the reaction were estimated by analysis of the proton NMR spectrum of the mixed fraction.

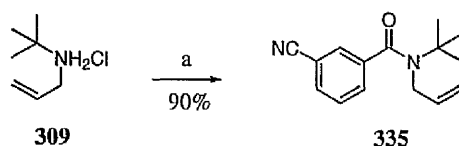
The identities of the benzamides were tentatively assigned based on the characteristics of their proton NMR spectra: one compound possessed a methylene group with diastereotopic protons, while in the other the pair of protons adjacent to nitrogen gave a singlet. Restricted rotation about the aryl-carbonyl bond in benzamide **334**, caused by the *ortho*-methoxy group, could have given rise to the observed diastereotopicity. This assignment was later proved to be correct, from the products obtained on cyclisation (see Section 4.3).



Reagents and conditions: (a) *t*-butyl ester amine 298, Et₃N, DCM, R.T., 17 h; repeated column chromatography

Scheme 110

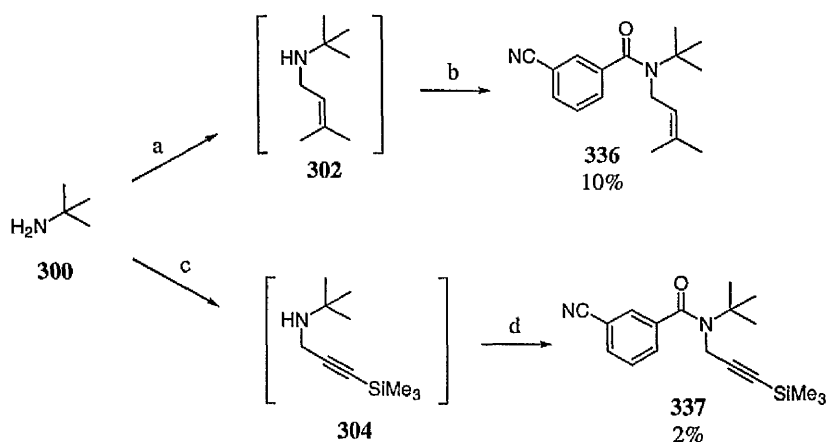
The hydrochloride salt of *N*-allyl-*tert*-butylamine proved to be a convenient reagent in the formation of an *N*-allyl benzamide. After generating the free base with triethylamine, this amine reacted in high yield with *meta*-cyano benzoyl chloride (Scheme 111).



Reagents and conditions: (a) Et₃N, DCM, R.T.; *m*-CNC₆H₄COCl, DCM, R.T., 17.5 h

Scheme 111

In Scheme 99 on page 111 the syntheses of *N*-prenyl and *N*-propargyl amines were outlined, although they were only formed as mixtures with the dialkylated amines. The alkylation reactions were carried out in acetonitrile, and by cannulating a solution of an acid chloride in this solvent into the reactions, the desired benzamides were isolated in low yields (Scheme 112). In both cases the secondary *tert*-butyl benzamide was isolated as the major reaction product.

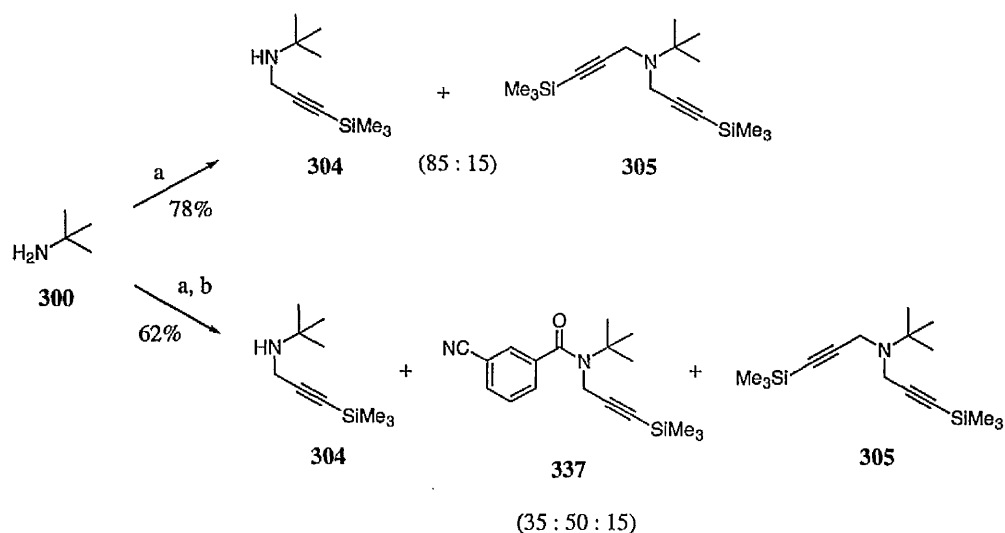


Reagents and conditions: (a) 3,3-dimethylallyl bromide, Et_3N , MeCN, R.T., 8 days; (b) $m\text{-CNC}_6\text{H}_4\text{COCl}$, MeCN, R.T., 5 h; (c) 3-bromo-1-trimethylsilyl-1-propyne, Et_3N , MeCN, R.T., 3 days; (d) $m\text{-CNC}_6\text{H}_4\text{COCl}$, MeCN, R.T., 4 h

Scheme 112

The alkylation reactions in Scheme 112 above had been modified by addition of triethylamine, naïvely included to trap the hydrobromic acid generated and encourage more complete reaction of the alkyl bromides with *tert*-butylamine. It would appear from the low yields of benzamides **336** and **337** that its presence actually lowered the amount of secondary amine formed. This lends further backing to the method of Tilley and Sayigh that was used to form allylamine **301** (see Scheme 101 on page 113), where the secondary amine formed was itself ‘trapped’ by hydrobromic acid, preventing further alkylation.⁹⁸

To allow investigation of propargyl cyclisations, other attempts were made to form benzamide **337**, by reacting 3-cyanobenzoyl chloride with crude reaction mixtures that may have contained amine **304**. Attempts with the dimethylformamide reflux and reductive amination (Scheme 102 on page 114) protocols were fruitless; a breakthrough was made by combining the original alkylation in acetonitrile (without triethylamine) with a benzamide coupling in dichloromethane (Scheme 113).



Reagents and conditions: (a) 3-bromo-1-trimethylsilyl-1-propyne, MeCN, R.T., 6 h; (b) *m*-CNC₆H₄COCl, Et₃N, DCM, R.T., 15 h; column chromatography

Scheme 113

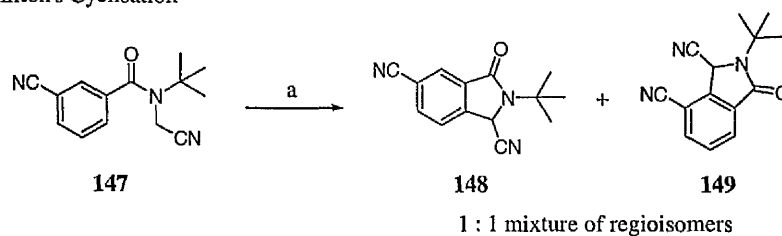
The mixture of products after reaction with the cyanobenzoyl chloride (and subsequent column chromatography) showed the same observed ratio of mono- to dialkylated products (85 : 15), with only partial reaction of amine **304**. The presence of baseline material on chromatography suggested that the acid chloride had partially hydrolysed during the course of the reaction, thus explaining the incomplete reaction of **304**.

4.3 Cyclisation Reactions

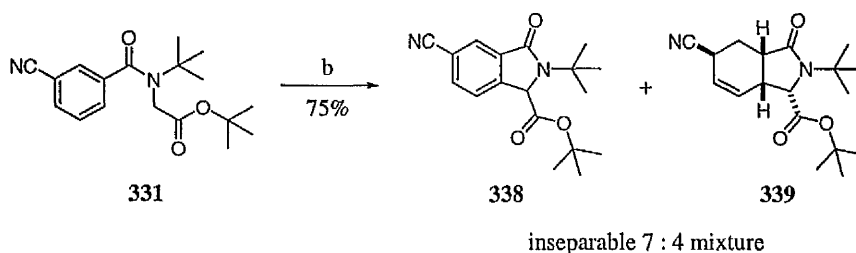
Benzamides with an ester cyclising group on nitrogen were the easiest compounds to synthesise (Section 4.2.3), and most of the cyclisation studies were carried out with this class of compound. Early work indicated that hexamethyldisilazide was a suitable base, and that reaction typically took place on warming to 0 °C, after deprotonating the substrate at -78 °C.

A comparison with Hamilton's cyanomethyl cyclisation gave some obvious differences (Scheme 114).⁷⁰ The ester cyclising group gave a more regioselective reaction, and products arising from reaction *ortho* to the nitrile were not detected. Furthermore, unprecedented formation of a dearomatised product was observed, although it appeared to have undergone further reduction to the hexahydroisoindolone.*

Hamilton's Cyclisation



New Ester Cyclisation

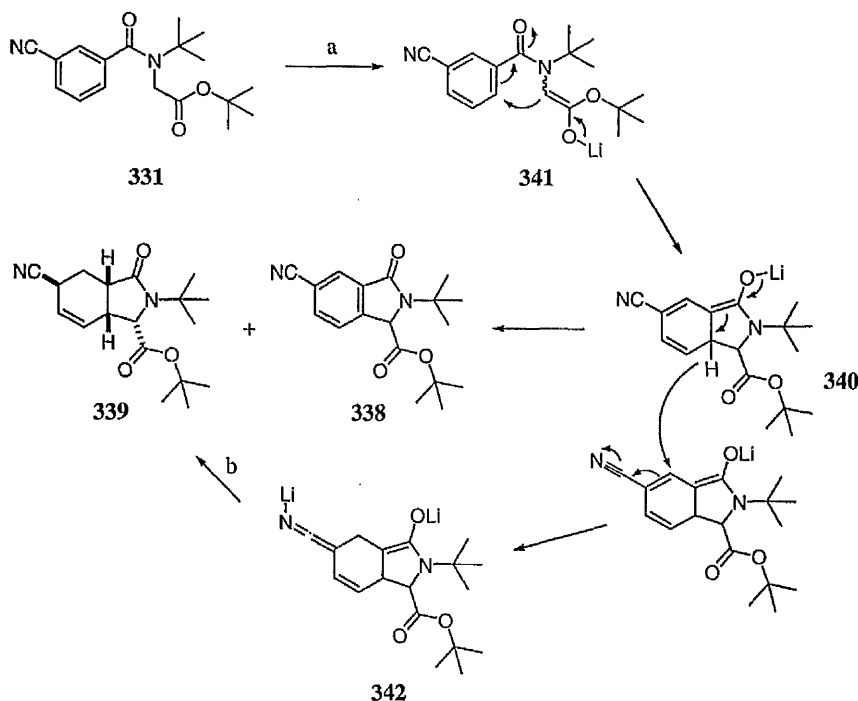


Reagents and conditions: (a) LDA, THF, -40 °C, 4 h; sat. aq. NH₄Cl soln.; (b) LiHMDS, THF, -78 °C, 15 min; 0 °C, 1 h; sat. aq. NH₄Cl soln.

Scheme 114: Regiocontrol and Dearomatisation in the Ester Cyclisation

* The stereochemistry of the ester in **339** was assumed to be *endo* based on the X-ray crystal structure of a related compound, shown in Figure 26 on page 125

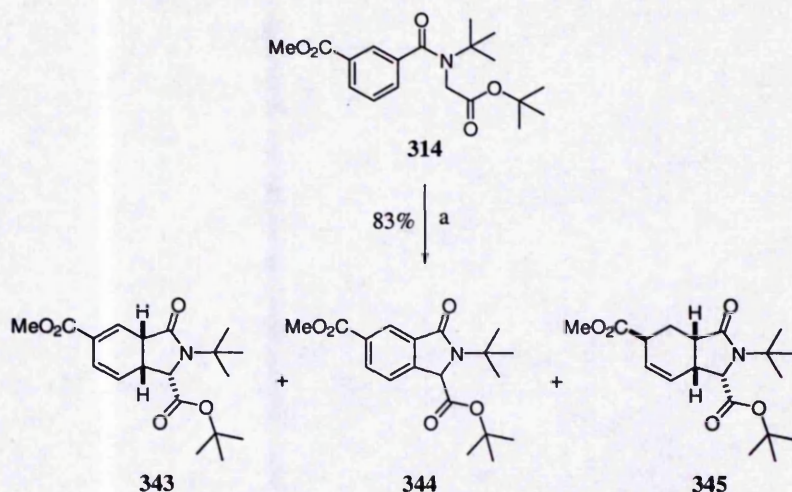
Product **339** may have resulted from the disproportionation of intermediate enolate **340** (Scheme 115). Enolate **340** possibly achieved rearomatisation by conjugate hydride donation to the α,β -unsaturated nitrile of another molecule, forming double enolate **342**. It is also probable that a second rearomatisation mechanism was acting, giving rise to the observed predominance of **338**; exclusive disproportionation would have been expected to give products **338** and **339** in equal quantities.



Reagents: (a) LiHMDS; (b) sat. aq. NH_4Cl soln.

Scheme 115: Possible Disproportionation Mechanism for Rearomatisation and Mono-Alkene Formation

Dearomatised products were also obtained from the cyclisation of *meta*-ester benzamide **314** under similar conditions. In this case the target diene was isolated, along with rearomatised and mono-alkene compounds as the only by-products (Scheme 116). (Re-examination of crude proton NMR data for the *meta*-cyano cyclisation above indicated possible diene formation, though that product was not isolated.)



Reagents and conditions: (a) LiHMDS, THF, -78°C , 15 min; 0°C , 1 h; sat. aq. NH_4Cl soln.

Scheme 116

Diene **343** was slightly contaminated with **345** after column chromatography; recrystallisation from pentane–ethyl acetate yielded a crystal of **343** suitable for X-ray crystallography, accompanied by rearomatisation of a large proportion of the starting diene. Surprisingly, the crystal structure obtained from this analysis showed the *tert*-butyl ester on the *endo* face of the bicyclic skeleton (Figure 26).

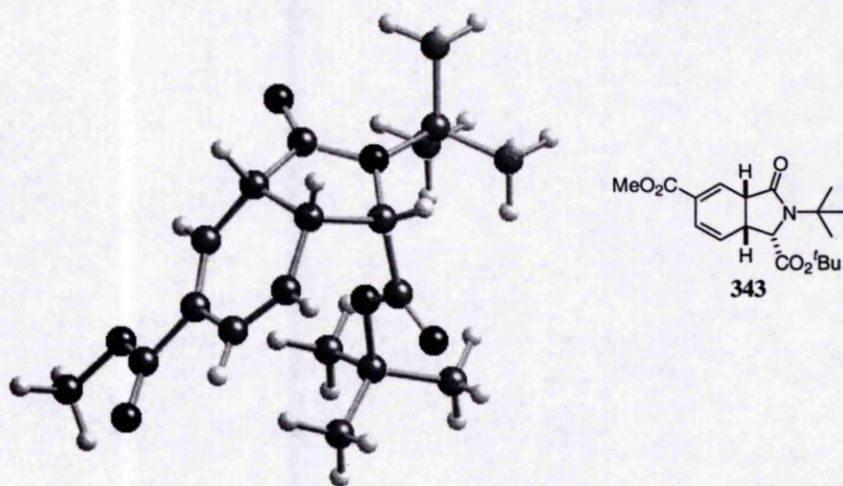
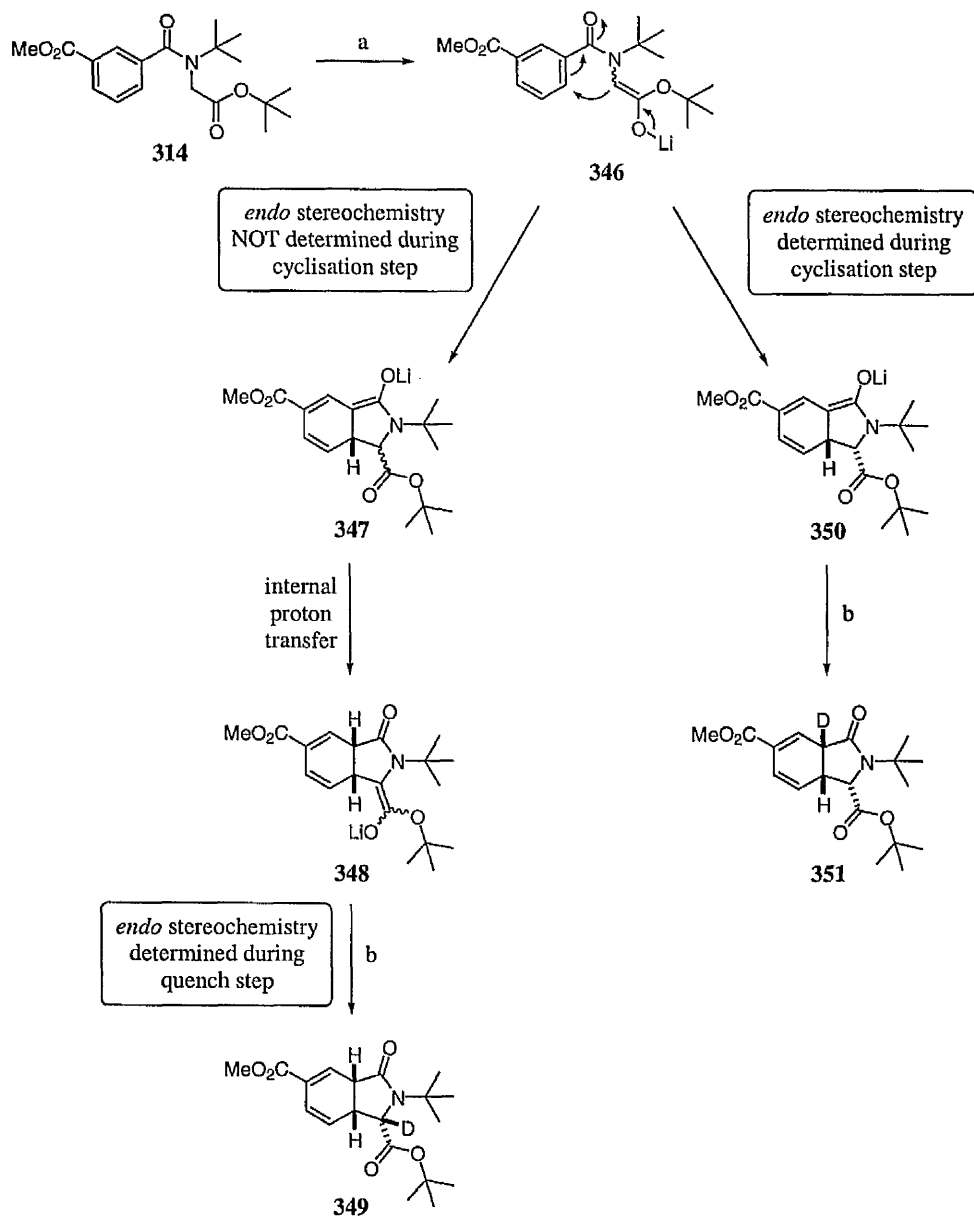


Figure 26: X-Ray Crystal Structure of **343**

This was another unprecedented result for benzamide cyclisations, with *N*-benzylbenzamides previously yielding *exo*-phenyl products (see, for example, Scheme 12 on page 25). On the basis of this result, dearomatised products from

the other ester cyclisation reactions described in this Chapter are assumed to contain *endo* ester groups, though this has not been proven in other cases.

The reaction was repeated with a deuteriomethanol quench in an attempt to explain the formation of the sterically disfavoured product. Deuteration α to the *tert*-butyl ester would suggest that the stereochemistry at this centre was determined at the

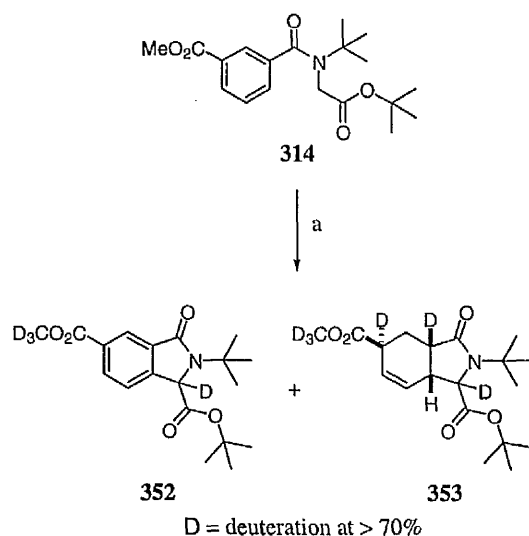


Reagents: (a) LiHMDS; (b) methanol-*d*

Scheme 117: Investigating *endo*-Ester Formation using a Deuterium Quench

quench stage, implying kinetically controlled reaction quenching; deuteration α to the lactam carbonyl would imply that the ester stereochemistry was characteristic of the cyclisation itself (Scheme 117).

Unfortunately, the diene was not isolated from the reaction (perhaps due to a subtle change of the reaction by use of a methanolic rather than aqueous quench), but a mixed fraction of the rearomatised and mono-alkene products was obtained. This showed deuteration α to the *tert*-butyl ester carbonyl in rearomatised product **352**, and α to all three carbonyl groups in mono-alkene **353**; in addition, partial transesterification of the methyl ester with methoxide- d_3 was seen (Scheme 118).



Reagents and conditions: (a) LiHMDS, THF, -78°C , 15 min; 0°C , 1 h; methanol- d_4

Scheme 118

Ignoring the incidental transesterification, it is unlikely that methoxide generated on quenching was sufficiently basic to lead to post-quench deuteration. Incorporation of deuterium α to the *tert*-butyl ester implies that the stereochemistry at this centre is set at the quench stage, with the stereochemistry after cyclisation being lost as a result of re-enolisation. However, the polydeuteration seen in **353** leads to the conclusion that the formation of *endo*-ester products does not fall into one of the two simple models given in Scheme 117, and that a more complex mechanism was acting. In particular,

product or enolate disproportionation, and the possibility of forming polyenolates before quenching, have not been taken into account in the models.

The cyclisation was attempted under oxygen-free conditions, following careful freeze-thaw degassing of all reagents and solvents. The appearance of the proton NMR spectrum of the crude product mixture, and quantities of fractions obtained from column chromatography, were very similar to those seen with the original conditions. It was concluded that, unlike with the oxazolidine cyclisation reactions discussed in Chapter 2, rearomatisation could not be suppressed by degassing, providing further evidence for a disproportionation mechanism.

Other means of reducing the amount of rearomatisation in the cyclisation of benzamide **314** were investigated. In particular, the effects of the base, solvent and temperature regime were studied.

The reaction gave slightly more diene relative to the amount of rearomatisation, when sodium hexamethyldisilazide was used as the base in place of the lithium salt. With potassium hexamethyldisilazide the reaction was messier, with other by-products and incomplete conversion from starting material (Table 13).

	Base	Product Ratio [*]		
		314	Dienes [†]	Rearomatised Mono-alkene
1	LiHMDS	0	12	57 31
2	NaHMDS	0	22	46 31
3	KHMDS	40	9	39 11

Table 13: Effect of Hexamethyldisilazide Counter-Ion in the Cyclisation of Benzamide **314**

^{*} Relative amounts of listed compounds only (other by-products neglected), based on integration of crude proton NMR spectra; 'rearomatised' = **344**; 'mono-alkene' = **345**

[†] Total of diene isomers: in some cases evidence of another diene isomer was seen, with overlapping doublets of identical coupling constants for C1H (therefore not *exo* and *endo*)

Changing the solvent from tetrahydrofuran to toluene was considered a possible means of suppressing rearomatisation. Less metal chelation by the solvent would be expected to enhance oxygen–lithium coordination in intermediate enolates, making them less liable to undergo further reactions before quenching. Unfortunately, although lithiation seemed to take place on warming to 0 °C (the reaction mixture became deep red in colour), no conversion from the starting benzamide took place.

Cyclising at lower temperatures generally reduced the amount of rearomatisation, but gave less conversion from the benzamide (Table 14). At –40 °C (entry 4) the balance between diene and mono-alkene products favoured the diene, compared with reaction at –30 °C (entry 3), but with a similar amount of rearomatisation. This showed that rearomatisation was only partially dependent on the amount of mono-alkene generated, confirming the complexity of the reaction mechanism.

	Cyclisation Temperature	Conversion from 314	Product Ratio [*]		
			Dienes [†]	Rearomatised	Mono-alkene
1	0 °C	100%	12	57	31
2	–20 °C	80%	7	52	41
3	–30 °C	60%	13	38	49
4	–40 °C	< 50%	40	35	25

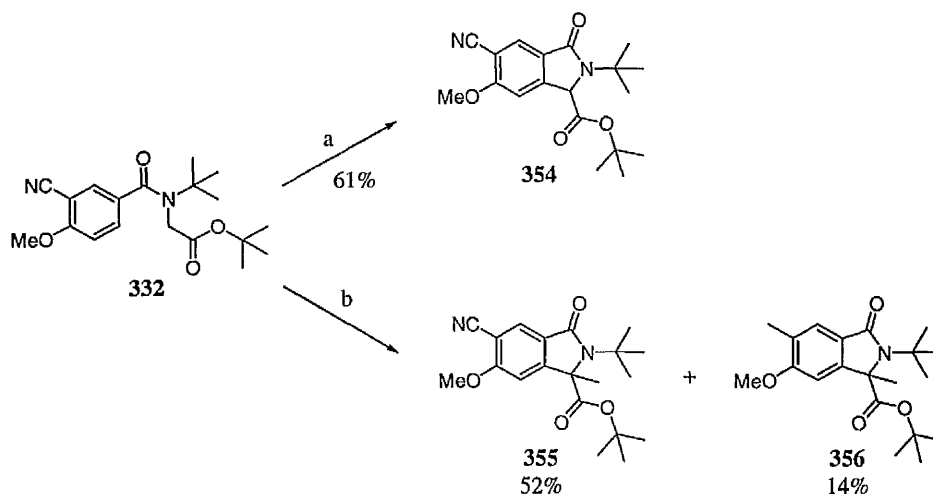
Table 14: Effect of Temperature on the Cyclisation of Benzamide **314**

The complete cyclisation of benzamides **331** and **314** suggested that an electron-withdrawing group in the *meta* position was key to the reaction's success. These results also confirmed the potential synthetic utility of the *tert*-butyl ester cyclising group, with the ester stable under the reaction conditions.

^{*} 'rearomatised' = **344**; 'mono-alkene' = **345**

[†] Total of diene isomers, as in Table 13

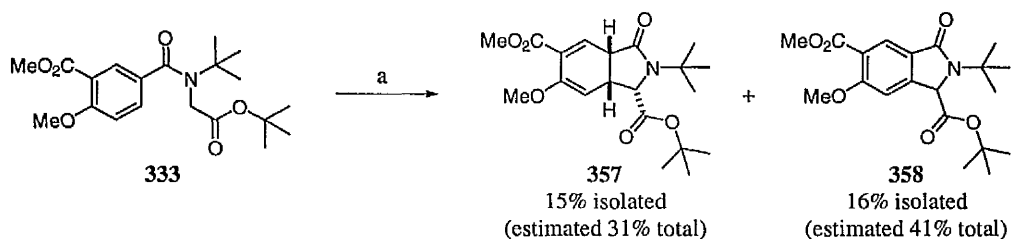
Cyclisation proved possible with an additional *para*-methoxy group, when a *meta* electron-withdrawing group was also present. The cyclisation of *meta*-cyano-*para*-methoxy benzamide **332** was rather messy, and only rearomatised products were obtained after both aqueous and iodomethane quenches (Scheme 119). With an iodomethane quench the *tert*-butyl ester was α -methylated; one by-product had also undergone methyl substitution of the nitrile.



Reagents and conditions: (a) LiHMDS, THF, -78°C, 15 min; 0 °C, 100 min; sat. aq. NH₄Cl soln.; (b) LiHMDS, THF, -78°C, 15 min; 0 °C, 100 min; MeI, 0 °C, 75 min

Scheme 119

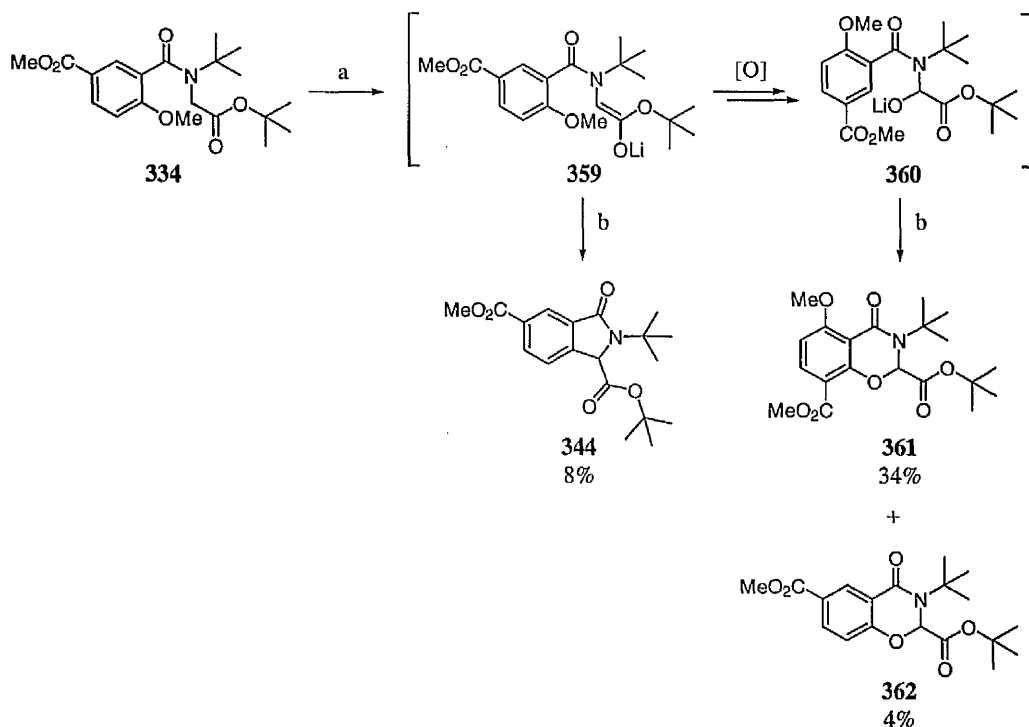
meta-Ester-*para*-methoxy benzamide **333** had only been isolated in low yield (Scheme 110 on page 120). However, the available material allowed a small-scale trial reaction that showed great promise. Although difficult to obtain pure products on chromatography, most of the product mixture was accounted for by just two compounds: diene **357** and the corresponding rearomatised compound **358**. The isolated and estimated total yields (based on integration of the proton NMR spectrum of a mixed fraction) are given in Scheme 120 below.



Reagents and conditions: (a) LiHMDS, THF, -78°C , 15 min; 0°C , 75 min; sat. aq. NH_4Cl soln.

Scheme 120

The products of the cyclisation of **333** had confirmed its identity (as stated in Section 4.2.3.2). For completeness the cyclisation of *ortho*-methoxy benzamide **334** was also examined (Scheme 121). Regioselectivity had previously been very good for ester cyclisations, with the cyclising group preferring to attack the aromatic ring *para* to the electron-withdrawing group. In **334** this position was blocked, and a mixture of regiochemistries was seen in the products.



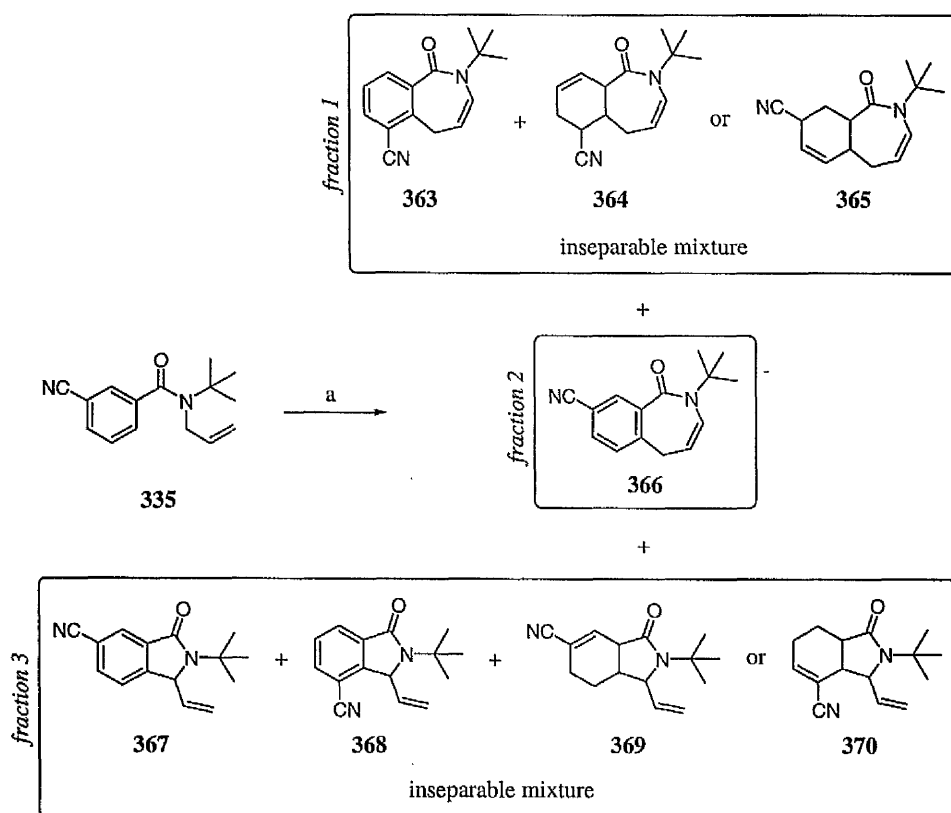
Reagents and conditions: (a) LiHMDS, THF, -78°C , 15 min; 0°C , 90 min; (b) sat. aq. NH_4Cl soln.

Scheme 121

In addition to the expected reaction of enolate **359**, giving **344** after addition-elimination *para* to the methyl ester, products corresponding to reaction of

oxyanion **360** (or the corresponding radical), arising from prior oxidation of the cyclising group, were also isolated. Reaction *ortho* to the methyl ester yielded **361**, whilst attack *ipso* to the methoxy group explains the formation of **362**. No dearomatised products were apparent in the crude proton NMR spectrum.

Higher temperatures were required to react *N*-allyl benzamide **335**. Quenching the mixture of benzamide and base at 0 °C returned starting material with both a protic quench (no cyclisation at this temperature) and benzaldehyde (no lithiation). The successful cyclisation of this compound was carried out by adding the base at 0 °C and warming to room temperature to promote lithiation and cyclisation, giving a range of products (Scheme 122).



Reagents and conditions: (a) LiHMDS, THF, 0 °C, 15 min; R.T., 3.5 h; sat. aq. NH₄Cl soln.

Scheme 122: Possible Products from the Cyclisation of *N*-Allyl Benzamide **335**

On column chromatography three fractions containing useful products were obtained, shown in the three boxes in Scheme 122. The structures were assigned based on proton NMR data alone; no conclusive mass spectrometry data could be

obtained for any fraction. The provisional results showed that the allyl group was apparently capable of two modes of cyclisation: α and γ to nitrogen, giving 6,5- (**367–370**) and 6,7- (**363–366**) fused ring systems respectively.

The structure of **363** could be confidently assigned based on an internal alkene and 1,2,3-trisubstitution on the rearomatised ring. The second component of that fraction was assigned as being that of either **364** or **365**, with four alkenic signals, seven protons on saturated centres, and no terminal vinyl group. Compound **366**, the regioisomer of **363** resulting from cyclisation *para* to the cyano group, was contained in a second fraction, though not isolated cleanly.

The third fraction was more complex by NMR, with a number of compounds containing terminal vinyl groups. The aromatic signals (highlighted in Figure 27 below) indicate the presence of a 1,3,4-trisubstituted rearomatised major product (**367**) in approximately two-thirds molar proportion. Also present were a 1,2,3-trisubstituted rearomatised product (**368**), with a characteristic aromatic triplet (also labelled in Figure 27), and a dearomatised product tentatively assigned as **369** or **370** based on a singlet in the alkenic region (implying a trisubstituted alkene). With structures **363** and **366** already accounted for in previous fractions, **367** and **368** seemed to be the only other likely rearomatised products.

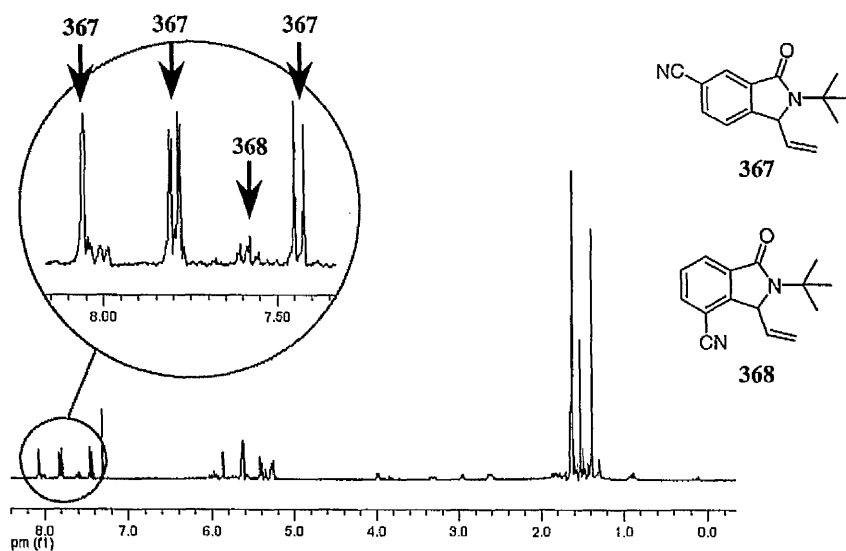
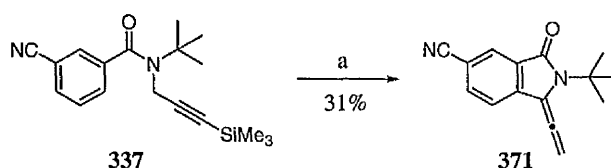


Figure 27: Selected Aromatic Signals of Compounds **367** and **368** in a Mixed Proton NMR Spectrum

Only around one-third of the starting mass was recovered in the crude product mixture. This was perhaps due to decomposition or poor extraction of aldehydes formed by acyl transfer, as previously reported in allyl cyclisations by Ahmed (see Scheme 28 on page 38).⁶⁹ On standing in deuteriochloroform solution the cyclic enamine products **363–365** were susceptible to decomposition to aldehydes.

Anion formation in the *N*-propargyl benzamide **337** occurred more readily than in the allyl benzamide, and complete consumption of the starting material was observed in reactions at both $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$, and $0\text{ }^{\circ}\text{C}$ to room temperature. The crude proton NMR spectra for these reactions were very similar to one another, and a large number of compounds were apparent by thin layer chromatography. There was evidence of a little dearomatisation, and the formation of several rearomatised compounds. Isolation of the compound corresponding to the most intense spot (visualised by ultraviolet light and permanganate dip) gave a rearomatised compound, assigned as allene **371** (Scheme 123), which demonstrated the possibility of cyclisation for this class of compounds too. The isolated product had undergone alkyne isomerisation, bringing an alkene into conjugation with the aromatic ring, and protodesilylation, in addition to cyclisation and rearomatisation.



Reagents and conditions: (a) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 15 min; $0\text{ }^{\circ}\text{C}$, 70 min; sat. aq. NH_4Cl soln.

Scheme 123

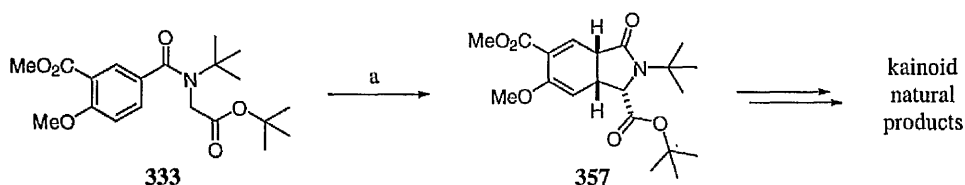
4.4 Conclusions and Future Work

The work outlined in this Chapter allows some useful conclusions to be drawn about the nature of non-benzyl cyclisation reactions. All of the new cyclisation reactions included a *meta* electron-withdrawing group, and this indeed proved necessary and sufficient to facilitate cyclisation, consistent with Hamilton's results for cyanomethyl cyclisations.⁷⁰ Of particular note is the range of cyclised products obtained from the cyclisation of the *meta*-cyano *N*-allyl benzamide **335** (see Scheme 122 on page 132), which previously failed to cyclise when the electron-withdrawing group was absent.⁶⁹

The cyanomethyl group seemed to be an unstable substructure in certain cases. Its decomposition was evident in the formation of *N*-cyanomethyl benzamides, when both bromoacetonitrile and cyanomethyl amine **299** (see Scheme 98 on page 110) were used as reagents. The amine formation, benzamide formation, and cyclisation reactions were inferior when compared with the analogous *tert*-butyl ester reactions (no yield was provided by Hamilton for his successful cyanomethyl cyclisation). Therefore it is recommended that benzamides derived from amino ester **298** (Scheme 98), rather than cyanomethyl benzamides, be used in future studies where stabilisation of an α -anion as an enolate is required.

A key feature of the *tert*-butyl ester cyclisation reactions was the high regiochemical preference for reaction *para* to the electron-withdrawing group, avoiding the formation of 1,2,3-trisubstituted products, even with a small *meta*-cyano group. This was in stark contrast to Hamilton's cyanomethyl reaction, where a 1 : 1 mixture of regioisomers was reported.⁷⁰ The difference was probably accounted for by the relative steric demands of the two cyclising groups, with further evidence provided by the mixture of regiochemistries seen on cyclisation of the small allyl group. Both allyl and propargyl cyclisations proved to be possible, though very complex when compared with the ester cyclisation; unfortunately no synthetically useful products were isolated in either case.

The cyclisations of *tert*-butyl esters were studied with a range of substitution patterns on the aromatic ring. Formation of dearomatised products was evident when a *meta*-methyl ester was used as the electron-withdrawing group, both with and without a *para*-methoxy group. Despite the unexpected preference of the cyclising ester for the *endo* face, formation of diene **357** is very promising for the synthesis of kainoids by this route (Scheme 124).



Reagents and conditions: (a) LiHMDS, THF, -78°C , 15 min; 0°C , 75 min; sat. aq. NH_4Cl soln.

Scheme 124

Particular issues to be resolved in future work are the low yield for the formation of benzamide **333**, and rearomatisation in its cyclisation. Some evidence of disproportionation as a mechanism of rearomatisation, a probable reaction of the intermediate cyclised enolate, has been obtained. Immediate future work to suppress this side-reaction should investigate ways of minimising the opportunity the enolate has to react with other enolate molecules, or with quenched products. Quenches (including reverse-quenches) after shorter reaction times may be one means to this end.

Chapter 5: Experimental Procedures

5.1 General Procedures

Proton and carbon NMR spectra were recorded on Varian Unity 300, Bruker DPX 360, Varian Unity 400 or Bruker AMX 500 Fourier Transform instruments. Proton NMR data are presented as follows: chemical shift δ (in ppm relative to $\delta_{\text{TMS}} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, hept = heptet, m = multiplet, br = broad, obs = obscured), coupling constant J (in Hz, values rounded to nearest 0.5 Hz) and assignment (based on chemical shift, integration, coupling pattern and COSY, DEPT, HMQC and HMBC experiments where necessary).

Infrared spectra were recorded on an ATi Matson Genesis Series Fourier Transform spectrophotometer.

Low resolution electron impact and chemical ionisation mass spectra were recorded on a Waters Trio 2000 quadrupole mass spectrometer. Low resolution electrospray mass spectra were recorded on a Micromass Platform II mass spectrometer. High resolution mass spectra were recorded on a Thermo Finnigan MAT 95XP mass spectrometer.

Melting points were determined using Electrothermal apparatus and are uncorrected.

Analytical thin layer chromatography was carried out on pre-coated UV₂₅₄ plates, with visualisation by ultraviolet light at 254 nm, potassium permanganate, *para*-anisaldehyde or dodecamolybdophosphoric acid (PMA).

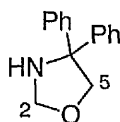
Flash column chromatography¹⁰¹ was carried out using Fluorochem Davisil 40–63 μm 60 Å silica, under a positive pressure by means of compressed air. The use of the term in this report implies removal of the solvent under reduced pressure after purification.

Reagents and solvents were purified by standard means.¹⁰² Dichloromethane was distilled from calcium hydride and subsequently stored under a nitrogen atmosphere; tetrahydrofuran and diethyl ether were distilled from sodium wire and benzophenone and subsequently stored under a nitrogen atmosphere. Triethylamine was distilled from and stored over potassium hydroxide. *N,N'*-Dimethyl-*N,N'*-propylene urea (DMPU) was distilled, under reduced pressure, from calcium hydride, and subsequently stored over molecular sieves. *N,N*-Dimethylformamide (DMF) was distilled from molecular sieves, and subsequently stored under a nitrogen atmosphere. Chlorotrimethylsilane was distilled onto molecular sieves. 'Petrol' refers to the fraction of petroleum ether that boils between 40 °C and 60 °C, and was distilled before use. All other chemicals were used as received, except where otherwise noted in the experimental text.

All experiments were performed in anhydrous conditions under an atmosphere of nitrogen, unless otherwise noted in the experimental text. Apparatus was oven-dried and standard techniques were employed in handling air-sensitive materials.⁷⁴

5.2 Experimental Details for Chapter 2

4,4-Diphenyloxazolidine, 106

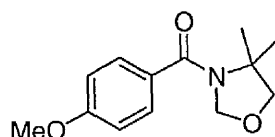


Following the method of Purewal,⁶³ a slurry of 2,2-diphenylglycinol **164*** (8.88 g, 41.6 mmol, 1.0 eq.), paraformaldehyde (1.94 g, 64.5 mmol, 1.5 eq.) and MgSO_4 (20.4 g) in DCM (100 ml) was stirred at room temperature for 19 h. The reaction mixture was filtered and concentrated under reduced pressure to give the crude oxazolidine (9.70 g) as a pale yellow solid, m.p. 78–81 °C (lit.⁶³ 58–62 °C), used in the next step without further purification.

R_f (9 : 1 ethyl acetate : petrol + 1% triethylamine) 0.88; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3308, 3024, 2995, 2856; **¹H NMR** (300 MHz, CDCl_3) δ 7.52–7.47 (4H, m, Ph), 7.39–7.23 (6H, m, Ph), 4.65 (2H, s, C_2H_2), 4.39 (2H, s, C_5H_2).

All data, except melting point, were consistent with those previously reported.⁶³

* See page 149

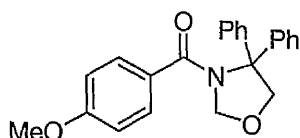
(4,4-Dimethyloxazolidin-3-yl)-(4-methoxyphenyl)methanone, 107

Following the method of Purewal,⁶³ *para*-anisoyl chloride (1.72 ml, * 12.6 mmol, 1.5 eq.) was added dropwise to a solution of 4,4-dimethyloxazolidine (75 wt% in water, 1.20 ml, 8.38 mmol, 1.0 eq.) and triethylamine (3.50 ml, 24.9 mmol, 2.0 eq.) in DCM (10 ml) at 0 °C. The resulting white slurry was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue heated at reflux with 2 M aqueous NaOH solution (10 ml) for 1.5 h. The mixture was extracted with DCM (3 × 20 ml) and the combined organic extracts were washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (2.30 g) as a colourless oil. Flash column chromatography (3 : 1 petrol : ethyl acetate, followed by additional chromatography of mixed fractions, eluting with 7 : 1 to 6 : 1 petrol : ethyl acetate) afforded the title compound (1.95 g, 99%) as a colourless oil.

R_f (1 : 1 petrol : ethyl acetate) 0.47; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2937, 2862, 1632 (C=O), 1608; **¹H NMR** (300 MHz, CDCl₃) δ 7.45 (2H, d, *J* 9.0, C8H and C12H), 6.93 (2H, d, *J* 9.0, C9H and C11H), 4.97 (2H, s, C2H₂), 3.88 (3H, s, OMe), 3.86 (2H, s, C5H₂), 1.62 (6H, s, C4Me₂).

All spectroscopic and chromatographic data were consistent with those previously reported; the title compound was previously obtained as a white wax.⁶³

* d = 1.25 g/ml on melting

(4,4-Diphenyloxazolidin-3-yl)-(4-methoxyphenyl)methanone, 153

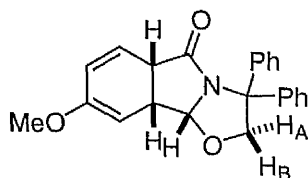
para-Anisoyl chloride (0.93 ml,^{*} 6.79 mmol, 1.5 eq.) was added dropwise to a solution of crude 4,4-diphenyloxazolidine **106**[†] (1.02 g, 4.53 mmol, 1.0 eq.) and triethylamine (1.95 ml, 13.9 mmol, 3.1 eq.) in 1,2-dichloroethane (10 ml) at 0 °C. The stirred solution was allowed to warm to room temperature over 30 min, and heated at reflux for 18 h. The solvent was partially removed under reduced pressure to leave a dark brown slurry. 2 M aqueous NaOH solution (10 ml) was added to the residue and the mixture heated at reflux for 1 h. The aqueous phase was extracted with DCM (3 × 20 ml) and the combined organic extracts washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (1.64 g) as a beige foamy gum. Flash column chromatography (7 : 1 petrol : ethyl acetate) afforded the title compound (1.50 g, 95% over two steps from amino alcohol **164**[‡]) as a white solid, m.p. 131–132 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.70; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1645 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.51–7.29 (12H, m, 2 × Ph (10H), C8H and C12H), 6.90 (2H, d, *J* 8.5, C9H and C11H), 5.36 (2H, s, C2H₂), 4.55 (2H, s, C5H₂), 3.87 (3H, s, OMe); **¹³C NMR** (75.4 MHz, CDCl₃) δ 167.7, 161.5, 141.9, 129.7, 128.8, 128.3, 128.2, 127.6, 113.9, 84.2, 82.8, 71.3, 55.7; **MS** (CI⁺) *m/z* 360 (100%, M + H⁺), 135 (100%, ArCO⁺); **HRMS** calc. for C₂₃H₂₁NO₃ (M⁺) 359.1521, found 359.1515.

^{*} d = 1.25 g/ml on melting

[†] See page 139

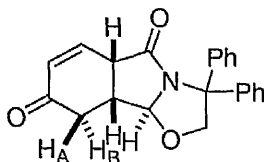
[‡] See page 149

(5a*R**,9a*S**,9b*S**)-8-Methoxy-3,3-diphenyl-2,3,9a,9b-tetrahydro-5a*H*-oxazolo[2,3-*a*]isoindol-5-one, **154**

tert-Butyllithium (1.1 M in pentane, 4.30 ml, 4.73 mmol, 1.5 eq.) was added dropwise to a solution of amide **153** (1.14 g, 3.16 mmol, 1.0 eq.) and DMPU (2.15 ml, 17.8 mmol, 5.6 eq.) in THF (100 ml) at -78°C . The resulting red solution was stirred at -78°C for 40 min, and at 0°C for 2.5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 ml) and stirred at 0°C for 1 h. The solution was allowed to warm to room temperature over 16 h. Water (75 ml) was added, and the aqueous phase extracted with diethyl ether (3×75 ml). The combined organic extracts were washed with water (2×75 ml) and brine (75 ml), dried (MgSO_4), and concentrated under reduced pressure to give the crude product (1.24 g) as an orange gum. Flash column chromatography (5 : 1 petrol : ethyl acetate + 1% triethylamine) afforded the title compound (0.396 g, 35%) as a yellow solid, m.p. 146°C (dec.).

R_f (1 : 1 petrol : ethyl acetate + 1% triethylamine) 0.75; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1663 (C=O); **^1H NMR** (300 MHz, CDCl_3) δ 7.51–7.35 (5H, m, Ph), 7.28–7.18 (5H, m, Ph), 5.89 (1H, dd, J 9.5 and 1.5, C7H), 5.86 (1H, ddt, J 10.0, 4.5 and 1.0, C6H), 5.68 (1H, d, J 6.0, C9bH), 4.96 (1H, d, J 9.0, C2H_A), 4.86 (1H, dt, J 3.0 and 1.5, C9H), 4.58 (1H, d, J 9.0, C2H_B), 3.83 (1H, dddd, J 10.5, 6.0, 3.0 and 1.0, C9aH), 3.75 (1H, s, Me), 3.62 (1H, dd, J 10.5 and 4.0, C5aH); **^{13}C NMR** (75.4 MHz, CDCl_3) δ 172.2, 153.6, 142.6, 142.0, 128.9, 128.3, 127.9, 127.9, 127.5, 125.4, 124.0, 96.0, 87.2, 85.2, 69.1, 54.6, 44.9, 37.8; **MS** (Cl^+) m/z 360 (100%, $\text{M} + \text{H}^+$), 180 (30%), 108 (100%); (EI^+) m/z 180 (30%), 108 (100%); **HRMS** calc. for $\text{C}_{23}\text{H}_{22}\text{NO}_3$ (M^+) 360.1600, found 360.1594.

n.O.e. (400 MHz, CDCl₃) irradiation at δ 5.68 (C9bH) enhanced δ 4.58 (4.6%, C2H_B), 3.83 (14.6%, C9aH) and 3.62 (2.7%, C5aH); irradiation at δ 3.83 (C9aH) enhanced δ 5.68 (13.6%, C9bH), 4.86 (6.2%, C9H) and 3.62 (10.0%, C5aH); irradiation at δ 3.62 (C5aH) enhanced δ 5.89 (5.6%, C6H), 5.86 (5.4%, C7H) and 3.83 (13.3%, C9aH).

(5a*R**,9aS*,9b*R**)-3,3-Diphenyl-2,3,9a,9b-tetrahydro-5a*H*,9*H*-oxazolo[2,3-*a*]isoindole-5,8-dione, **155**

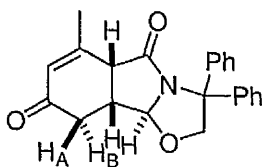
tert-Butyllithium (1.5 M in pentane, 2.90 ml, 4.35 mmol, 1.5 eq.) was added dropwise to a solution of amide **153**[†] (1.05 g, 2.91 mmol, 1.0 eq.) and DMPU (2.00 ml, 16.5 mmol, 5.7 eq.) in THF (95 ml) at -78°C . The deep red solution was stirred at -78°C for 40 min, and 0°C for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 ml), stirred at 0°C for 1 h, and warmed to room temperature. Water (100 ml) was added and the aqueous phase extracted with diethyl ether (3×100 ml). To the combined organic extracts was added HCl (2 M in diethyl ether, 0.97 ml, 1.9 mmol, 0.67 eq.) and the solution stirred at room temperature for 17 h. Saturated aqueous NaHCO_3 solution (250 ml) was added and the aqueous phase extracted with diethyl ether (2×100 ml). The combined organic extracts were washed with water (5×250 ml) and brine (250 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (1.06 g) as an orange solid. Flash column chromatography (degassed 5 : 1 to 3 : 1 petrol : ethyl acetate + 1% triethylamine) afforded the title compound (0.277 g, 24%) as a yellow solid, m.p. 75°C (dec.).

R_f (1 : 1 petrol : ethyl acetate + 1% triethylamine) 0.43; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1707 (enone $\text{C}=\text{O}$), 1687 (amide $\text{C}=\text{O}$); **¹H NMR** (300 MHz, CDCl_3) δ 7.50–7.13 (10H, m, $2 \times \text{Ph}$), 6.82 (1H, dd, J 10.5 and 5.0, C6H), 6.06 (1H, dd, J 10.0 and 2.0, C7H), 5.54 (1H, d, J 5.5, C9bH), 5.14 (1H, d, J 9.0, C2H_A), 4.40 (1H, d, J 9.5, C2H_B), 3.77 (1H, td, J 6.0 and 2.0, C5aH), 3.45–3.33 (1H, m, C9aH), 2.64 (1H, dd, J 16.5 and 7.0, C9H_A), 2.57 (1H, dd, J 16.0 and 11.0, C9H_B); **¹³C NMR** (75.4 MHz, CDCl_3) δ 197.2, 167.9, 143.0, 141.7, 140.8, 130.9, 129.1,

[†] See page 141

129.0, 128.4, 128.2, 128.1, 126.8, 92.2, 85.2, 69.3, 46.5, 36.6, 34.0;
MS (ES^+) m/z 368 (100%, $\text{M} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{22}\text{H}_{19}\text{NO}_3\text{Na}$ ($\text{M} + \text{Na}^+$)
368.1257, found 368.1252.



(5a*R**,9a*S**,9b*S**)-6-Methyl-3,3-diphenyl-2,3,9a,9b-tetrahydro-5a*H*,9*H*-oxazolo[2,3-*a*]isoindole-5,8-dione, **156**

tert-Butyllithium (1.5 M in pentane, 2.90 ml, 4.35 mmol, 1.5 eq.) was added dropwise to a solution of amide **153**[†] (1.05 g, 2.92 mmol, 1.0 eq.) and DMPU (2.00 ml, 16.5 mmol, 5.7 eq.) in THF (95 ml) at $-78\text{ }^{\circ}\text{C}$, at a rate so as to maintain the temperature below $-72\text{ }^{\circ}\text{C}$. The deep red solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 40 min, allowed to warm to $0\text{ }^{\circ}\text{C}$ over 30 min, and stirred at this temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 ml), maintaining the temperature below $5\text{ }^{\circ}\text{C}$, stirred at $0\text{ }^{\circ}\text{C}$ for 1 h, and allowed to warm to room temperature. Water (100 ml) and diethyl ether (25 ml) were added and the aqueous phase extracted with diethyl ether ($3 \times 100\text{ ml}$). The combined organic extracts were stirred with HCl (2 M in diethyl ether, 0.97 ml, 1.94 mmol, 0.66 eq.) for 17 h. Saturated aqueous NaHCO_3 solution (250 ml) was added, and the aqueous phase extracted with diethyl ether ($2 \times 100\text{ ml}$). The combined organic extracts were washed with water ($5 \times 250\text{ ml}$) and brine (250 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (1.02 g) as a yellow solid, used in the next step without purification. (At this stage the composition was approximately 45 : 10 : 45 **153** : by-product **165**[‡] : enone **155**, estimated from proton NMR data, hence containing approximately 1.3 mmol of enone **155**.)

Methylolithium (1.0 M in diethyl ether, 1.60 ml, 1.60 mmol, 3.7 eq.) was added dropwise to a slurry of copper(I) bromide (0.119 g, 0.826 mmol, 1.9 eq.) in THF (7 ml) at $-78\text{ }^{\circ}\text{C}$, and stirred at this temperature for 20 min. The mixture was

[†] See page 141


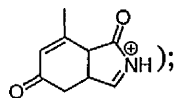
[‡] See page 150

allowed to warm until a clear blue-grey solution of dimethylcuprate was obtained, and recooled to $-78\text{ }^{\circ}\text{C}$. Meanwhile, a portion of the crude product mixture from the previous step (0.150 g) was dissolved in THF (10 ml) and cooled to $-78\text{ }^{\circ}\text{C}$. To this pale yellow solution was added chlorotrimethylsilane (0.07 ml, 0.55 mmol, 1.3 eq.), followed by the dimethylcuprate solution over 15 min. The resulting orange-red solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1.5 h, quenched with saturated aqueous NH_4Cl solution (3 ml) and allowed to warm to room temperature. Water (15 ml) was added and the aqueous phase extracted with diethyl ether ($3 \times 15\text{ ml}$). The combined organic extracts were washed with water (15 ml) and saturated aqueous NaHCO_3 solution (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.184 g) as an orange oil, used in the next step without purification.

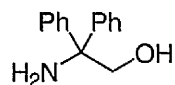
The crude product mixture from the previous step (approximately 50 mol% silyl enol ether **173**[†] by proton NMR, 0.184 g) and palladium(II) acetate (0.0975 g, 0.434 mmol, 1.0 eq.) were stirred in acetonitrile (15 ml) at room temperature for 17 h. The solution was filtered through a pad of celite with ethyl acetate washings, and concentrated under reduced pressure to give the crude product (0.253 g) as a dark orange-brown gum. Flash column chromatography (degassed 5 : 1 petrol : ethyl acetate + 1% triethylamine) afforded the title compound (0.0083 g, 5% from amide **153**) as a white solid, m.p. $51\text{ }^{\circ}\text{C}$ (dec.).

R_f (1 : 1 petrol : ethyl acetate + 1% triethylamine) 0.61; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1710 (enone C=O), 1674 (amide C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.51–7.20 (10H, m, $2 \times \text{Ph}$), 5.90 (1H, m, C7H), 5.58 (1H, d, J 5.0, C9bH), 5.19 (1H, d, J 9.5, C2H_A), 4.42 (1H, d, J 9.5, C2H_B), 3.62 (1H, d, J 6.5, C5aH), 3.50–3.29 (1H, m, C9aH), 2.59 (1H, dd, J 16.5 and 6.0, C9H_A), 2.46 (1H, dd, J 16.5 and 13.0, C9H_B), 2.16 (3H, d, J 1.0, C6Me); **¹³C NMR** (75.4 MHz, CDCl_3) δ 197.1, 167.1, 155.6, 141.9, 140.7, 129.1, 129.1, 128.5, 128.3, 128.1, 127.8, 126.8, 92.3, 85.3, 69.0, 50.9, 38.7, 33.2, 24.2; **MS** (Cl^+) m/z 360 (100%, $\text{M} + \text{H}^+$), 214 (40%,

[†] See page 152

2,2-diphenylglycinol + H⁺), 181 (50%, ) , 164 (50%, );

HRMS calc. for C₂₃H₂₂NO₃ (M + H⁺) 360.1594, found 360.1597.

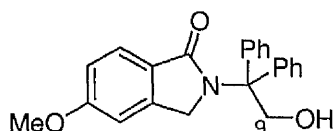
2,2-Diphenylglycinol, 164⁶³

Lithium aluminium hydride (1 M in THF, * 10.0 ml, 10.0 mmol, 2.3 eq.) was added dropwise to a slurry of 2,2-diphenylglycine (0.972 g, 4.28 mmol, 1.0 eq.) in THF (10 ml) at 0 °C, and the mixture heated at reflux for 22 h. The reaction was cooled to 0 °C and quenched by successive addition of water (0.38 ml), 3.75 M aqueous NaOH solution (0.38 ml) and water (1.14 ml).⁷⁴ The mixture was filtered and water (10 ml) was added. The layers were separated and the aqueous phase extracted with DCM (3 × 10 ml). The combined organic extracts were washed with 5 M aqueous NaOH solution (10 ml), water (3 × 10 ml) and brine (10 ml), dried (MgSO₄) and concentrated under reduced pressure to give the title compound (0.886 g, 97%) as a pale yellow solid, m.p. 125–127 °C (lit.⁶³ 114–115 °C).

R_f (9 : 1 ethyl acetate : petrol + 1% triethylamine) 0.24; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3341, 3289, 3088, 3058, 3026, 1599; **¹H NMR** (300 MHz, CDCl₃) δ 7.42–7.26 (10H, m, 2 × Ph), 4.18 (2H, s, CH₂), 2.43 (3H, br, NH₂ and OH).

All data, except melting point, were consistent with those previously reported.⁶³

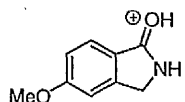
* Commercially sourced solution

2-(2-Hydroxy-1,1-diphenylethyl)-5-methoxy-2,3-dihydroisoindol-1-one, 165

This compound was observed in variable amounts as a by-product in the dearomatising cyclisation of amide **153**.^{*} Flash column chromatography (petrol : ethyl acetate) of crude cyclisation product mixtures gave the title compound as a white solid, m.p. 230–232 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.54; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3402 (O–H), 1656 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.85 (1H, d, *J* 8.5, C7H), 7.45–7.33 (6H, m, Ph), 7.25–7.17 (4H, m, Ph), 7.07 (1H, dd, *J* 8.5 and 2.5, C6H), 6.81 (1H, d, *J* 2.0, C4H), 6.00 (1H, t, *J* 7.5, OH), 4.71 (2H, d, *J* 7.5, C9H₂), 3.96 (2H, s, C3H₂), 3.87 (3H, s, Me); **¹³C NMR** (75.4 MHz, CDCl₃) δ 170.9, 163.5, 143.9, 141.2, 128.9, 128.2, 128.1, 125.8, 125.4, 115.6, 107.3, 73.2, 70.8, 55.9, 53.0;

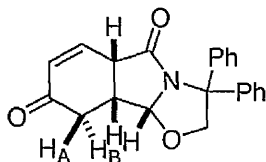
MS (CI⁺) *m/z* 360 (40%, M + H⁺), 164 (100%,



C₂₃H₂₁NO₃ (M⁺) 359.1521, found 359.1515.

^{*} See page 141

(5a*R**,9a*S**,9b*S**)-3,3-Diphenyl-2,3,9a,9b-tetrahydro-5a*H*,9*H*-oxazolo[2,3-*a*]isoindole-5,8-dione, **168**



HCl (0.1 M in CHCl_3 ,[†] 1.0 ml, 0.10 mmol) was added to a solution of enol ether **154**[‡] (0.049 g, 0.14 mmol) in DCM (20 ml). The mixture was stirred vigorously under N_2 at room temperature for 3 h, and the solvent removed under reduced pressure to give a 2 : 3 mixture of the title compound and its C9b epimer **155**[§] (0.050 g) as a white solid, not stable to purification techniques.

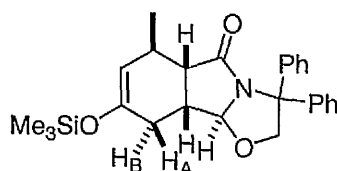
¹H NMR (300 MHz, CDCl_3 , mixture with C9b-epimer **155** [assignments labelled *]) δ 7.52–7.17 (10H* and 8H, m, Ph* and Ph), 7.10 (1H, d, *J* 7.5, Ph), 7.09 (1H, d, *J* 6.0, Ph), 6.86 (1H*, dd, *J* 10.0 and 5.0, C6H*), 6.72 (1H, dd, *J* 6.0 and 3.0, C6H), 6.09 (1H*, dd, *J* 10.0 and 2.0, C7H*), 5.57 (1H*, d, *J* 5.5, C9bH*), 5.25 (1H, d, *J* 7.5, C9bH), 5.25–5.20 (1H, obs m, C7H), 5.17 (1H*, d, *J* 9.5, C2H_A*), 4.96 (1H, d, *J* 9.0, C2H_A), 4.43 (1H*, d, *J* 9.5, C2H_B*), 4.38 (1H, d, *J* 8.5, C2H_B), 3.83 (1H, d, *J* 18.0, C9H_A), 3.79 (1H*, td, *J* 5.5 and 2.0, C5aH*), 3.55–3.35 (1H* and 1H, m, C9aH* and C5aH), 3.04 (1H, t, *J* 17.5, C9H_B), 2.67 (1H*, dd, *J* 16.0 and 7.0, C9H_A*), 2.60 (1H*, dd, *J* 16.0 and 11.0, C9H_B*), 2.42 (1H, ddd, *J* 16.5, 8.0 and 2.0, C9aH).

[†] Prepared as an emulsion of concentrated aqueous HCl solution in chloroform

[‡] See page 142

[§] See page 144

(5a*R**,6*S**,9a*S**,9b*R**)-6-Methyl-3,3-diphenyl-8-trimethylsilanyloxy-2,3,6,9,9a,9b-hexahydro-5a*H*-oxazolo[2,3-*a*]isoindol-5-one, **173**



Methylolithium (1.0 M in diethyl ether, 1.05 ml, 1.05 mmol, 4.2 eq.) was added dropwise to a slurry of copper(I) bromide (0.0761 g, 0.530 mmol, 2.1 eq.) in THF (4 ml) at -78°C , and stirred at this temperature for 20 min. The mixture was allowed to warm until a clear blue-grey solution of dimethylcuprate was obtained, and recooled to -78°C .

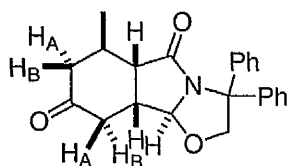
Enone **155**[†] (0.0875 g, 0.253 mmol, 1.0 eq.) was dissolved in THF (6 ml) and cooled to -78°C . To this pale yellow solution was added chlorotrimethylsilane (0.07 ml, 0.55 mmol, 2.2 eq.), followed by the dimethylcuprate solution over 20 min. The resulting orange solution was stirred at -78°C for 1.5 h. The reaction was quenched at -78°C with saturated aqueous NH_4Cl solution (2 ml) to give a bright orange-red solution, and allowed to warm to room temperature. Water (10 ml) was added and the aqueous phase extracted with diethyl ether (2×10 ml). The combined organic extracts were washed with water (10 ml) and saturated aqueous NaHCO_3 solution (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give a 3 : 1 mixture of the title compound and unreacted **155** (0.974 g) as a yellow gum, not stable to purification techniques, used as a crude mixture in the following step.

¹H NMR (300 MHz, CDCl_3 , mixture with **155** [assignments labelled *]) δ 7.53–7.13 (10H* and 10H, m, $2 \times \text{Ph}^*$ and $2 \times \text{Ph}$), 6.85 (1H*, dd, J 10.5 and 5.0, C6H*), 6.09 (1H*, dd, J 10.0 and 1.5, C7H*), 5.57 (1H*, d, J 5.5, C9bH*), 5.53 (1H, d, J 5.0, C9bH), 5.15 (1H, d, J 9.0, C2H_A), 5.14 (1H*, d, J 10.0,

[†] See page 144

C2H_A*), 4.73 (1H, dd, *J* 4.5 and 2.0, C7H), 4.43 (1H*, d, *J* 9.5, C2H_B*), 4.42 (1H, d, *J* 9.5, C2H_B), 3.79 (1H*, obs t, *J* 6.5, C5aH*), 3.47–3.33 (1H*, m, C9aH*), 3.00–2.90 (1H, m, C9aH), 2.82–2.69 (2H, obs m, *J* 6.5 (d), C6H and C5aH), 2.63 (1H*, dd, *J* 15.0 and 7.5, C9H_A*), 2.53 (1H*, dd, *J* 15.0 and 11.0, C9H_B*), 2.19 (1H, ddt, *J* 17.5, 9.5 and 2.0, C9H_B), 2.02 (1H, dd, *J* 17.5 and 7.5, C9H_A), 1.09 (3H, d, *J* 7.0, C6Me), 0.11 (9H, s, SiMe₃); **MS** (EI⁺, mixture with **155**) *m/z* 434 (< 5%, M + H⁺).

(5aR*,9aS*,9bS*)-3,3-Diphenyl-2,3,9a,9b-tetrahydro-5aH,9H-oxazolo[2,3-a]isoindole-5,8-dione, 174



Following the method of Grayson *et al.*,⁷⁵ the crude 3 : 1 mixture of silyl enol ether **173** and enone **155**[†] from the previous step (0.970 g) was dissolved in 80% aqueous acetic acid (6 ml) and stirred at room temperature for 1 h. The reaction mixture was partitioned between water (15 ml) and DCM (15 ml), and the aqueous phase extracted with DCM (2 × 10 ml). The combined organic extracts were washed carefully with saturated aqueous NaHCO₃ solution (2 × 20 ml), water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product mixture (0.0776 g) as a yellow oil. Flash column chromatography (2 : 1 petrol : ethyl acetate) afforded the title compound (0.0198 g, 22% from **155**) as a white solid, m.p. 48 °C (dec.).

R_f (1 : 1 petrol : ethyl acetate) 0.62; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 1707 (ketone C=O), 1604 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.48–7.27 (10H, m, Ph), 5.56 (1H, d, *J* 5.5, C9bH), 5.17 (1H, d, *J* 9.5, C2H_A), 4.41 (1H, d, *J* 9.5, C2H_B), 3.17 (1H, m, C9aH), 2.92 (1H, dd, *J* 7.0 and 6.0, C5aH), 2.52 (1H, dd, *J* 16.0 and 6.0, C9H_A), 2.49–2.38 (1H, obs m, C6H), 2.41 (1H, dd, *J* 16.0 and 12.0, C9H_B), 2.23 (1H, dd, *J* 15.5 and 4.5, C7H_A), 1.97 (1H, dd, *J* 15.5 and 8.0, C7H_B), 1.12 (3H, d, *J* 7.0, Me); **¹H NMR** (300 MHz, C₆D₆) δ 7.41–7.35 (2H, m, Ph), 7.22–7.06 (6H, m, Ph), 7.06–6.92 (2H, m, Ph), 4.78 (1H, d, *J* 5.5, C9bH), 4.71 (1H, d, *J* 9.0, C2H_A), 3.96 (1H, d, *J* 9.0, C2H_B), 2.44 (1H, dd, *J* 15.0 and 5.5, C9H_A), 2.33 (1H, dd, *J* 15.0 and 12.0, C9H_B), 2.20 (1H, dddd, *J* 12.0, 6.5, 5.5 and 5.5, C9aH), 2.13–1.99 (2H, m, C6H and C5aH), 1.93 (1H, dd, *J* 15.5 and 4.0, C7H_A), 1.52 (1H, dd, *J* 16.0 and 8.0, C7H_B), 0.74 (3H, d, *J* 6.5, Me); **¹³C NMR** (75.4 MHz,

[†] See page 144

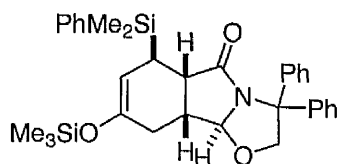
CDCl_3) δ 210.9, 171.3, 141.9, 141.2, 129.0, 129.0, 128.3, 128.1, 128.0, 127.0, 92.9, 85.1, 68.7, 51.2, 45.3, 36.7, 36.5, 29.2, 20.9; **MS** (EI^+) m/z 331 (35%), 193 (100%), 165 (90%); (CI^+) m/z 379 (20%, $\text{M} + \text{NH}_4^+$), 362 (100%, $\text{M} + \text{H}^+$), 250 (55%), 193 (35%), 165 (25%); **HRMS** calc. for $\text{C}_{23}\text{H}_{24}\text{NO}_3$ ($\text{M} + \text{H}^+$) 362.1751, found 362.1749.

n.O.e. (400 MHz, C_6D_6) irradiation at δ 2.43 (C7H_A) enhanced δ 1.52 (18.4%, C7H_B) and 0.74 (<0.6%, Me); irradiation at δ 2.34 (C9H_B) enhanced δ 4.78 (1.9%, C9bH), 2.44 (15.8%, C9H_A) and 2.20 (obs, C9aH); irradiation at δ 2.20 (C9aH) enhanced δ 4.78 (10.9%, C9bH), 2.44 (6.5%, C9H_A), 2.13–1.99 (C5aH and/or C6H) and 0.74 (<0.5%, Me); irradiation at δ 1.92 (C7H_A) enhanced δ 1.52 (18.4%, C7H_B) and 0.74 (<0.6%, Me); irradiation at δ 1.53 (C7H_B) enhanced δ 1.93 (19.1%, C7H_A) and 0.74 (<0.6%, Me); irradiation at δ 0.75 (Me) enhanced δ 2.13–1.99 (C5aH and/or C6H), 1.93 (2.0%, C7H_A) and 1.52 (2.7%, C7H_B).

Phenyldimethylsilyllithium, 174a

Following the method of Fleming *et al.*,^{76b} lithium wire (0.451 g, 65.0 mmol, 3.0 eq.) was washed with hexane and dried under a stream of N₂. THF (18 ml) was added and cooled to 0 °C, followed by addition of chlorodimethylphenylsilane (4.25 ml, 21.7 mmol, 1.0 eq.). The mixture was stirred at 0 °C for 5 h and the resulting deep red solution subsequently stored at -18 °C. Titration of the solution with diphenylacetic acid¹⁰³ gave an estimated phenyldimethylsilyllithium concentration of 0.67 M.

(5a*S**,6*R**,9a*R**,9b*S**)-6-phenyldimethylsilyl-8-trimethylsilyloxy-2,3,6,9,9a,9b-hexahydro-5a*H*-3,3-diphenyloxazolo[2,3-*a*]isoindol-5-one, 175



The enone starting material **155**[†] for this reaction was contained in the crude product mixture obtained from the cyclisation of **153**[‡] (approximately 45 : 10 : 45 **153** : by-product **165**[§] : enone **155** molar proportions, estimated from proton NMR data).

Diethylzinc (1.0 M in hexanes, 0.30 ml, 0.30 mmol, 1.7 eq.) was added to THF (2.5 ml) at 0 °C to give a pale blue solution. Phenyldimethylsilyllithium (0.67 M in THF, 1.45 ml, 0.30 mmol, 1.7 eq.) was added over 2 min to give a wine-red solution, stirred at 0 °C for 5 min, and cooled to –78 °C. A solution of enone **155** (44 wt% as described above, 0.14 g, 0.18 mmol, 1.0 eq.) in THF (0.6 ml) at –78 °C was added over 5 min, washed in with further THF (0.4 ml). The resulting orange-brown solution was stirred at –78 °C for 40 min, quenched with chlorotrimethylsilane (0.05 ml, 0.39 mmol, 2.2 eq.), and stirred at –78 °C for 30 min. The solution was allowed to warm to room temperature, stirred for 1.5 h, and quenched with saturated aqueous NH₄Cl solution (2.5 ml). Water (15 ml) was added and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were washed with water (15 ml) and saturated aqueous NaHCO₃ solution (15 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.231 g) as a yellow oil, containing approximately 41 : 6 : 34 : 18 **153** : by-product **165** : enol ether **175** : hydrolysed

[†] See page 144

[‡] See page 141

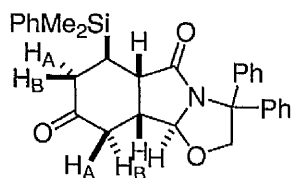
[§] See page 150

enol ether **176**[†] (estimated from proton NMR data). The title compound was not stable to purification techniques.

¹H NMR (300 MHz, CDCl₃, distinct peaks only) δ 5.54 (1H, d, *J* 5.0, C9bH), 5.10 (1H, d, *J* 9.0, C2H_A), 4.75 (1H, dd, *J* 4.5 and 1.5, C7H), 4.40 (1H, d, *J* 9.5, C2H_B); **MS** (ES⁺) *m/z* 742 (20%, [2 × **153**] + Na⁺), 576 (25%, **175** + Na⁺), 419 (40%, [**175** – PhMe₂Si]⁺), 403 (40%, [**175** – PhH]⁺), 382 (100%, **153** + Na⁺), 360 (**153** + H⁺); **HRMS** calc. for C₃₃H₃₉NO₃SiNa (M + Na⁺) 576.2361, found 576.2366.

[†] See page 159

(5a*S**,6*R**,9a*R**,9b*S**)-hexahydro-6-dimethylphenylsilyl-5a*H*,9b*H*-3,3-diphenyloxazolof[2,3-*a*]isoindole-5,8-dione, **176**



The enone starting material for this reaction was contained in the crude product mixture obtained from the cyclisation of **153**[†] (approximately 45 : 10 : 45 **153** : by-product **165**[‡] : enone **155**[§] molar proportions, estimated from proton NMR data).

Diethylzinc (1.0 M in hexanes, 0.85 ml, 0.85 mmol, 1.7 eq.) was added to THF (7 ml) at 0 °C. Phenyltrimethylsilyllithium (0.64 M in THF, 1.34 ml, 0.86 mmol, 1.7 eq.) was added over 2 min to give a wine-red solution, stirred at 0 °C for 5 min, and cooled to –78 °C. A solution of enone **155** (44 wt% as described above, 0.40 g, 0.51 mmol, 1.0 eq.) in THF (2 ml) at –78 °C was added over 5 min, washed in with further THF (1 ml). The resulting yellow-brown solution was stirred at –78 °C for 40 min, and quenched with chlorotrimethylsilane (0.14 ml, 1.10 mmol, 2.2 eq.). After stirring for 30 min the solution was allowed to warm to room temperature, stirred for 1 h and quenched with saturated aqueous NH₄Cl solution (7 ml). Water (15 ml) was added and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were washed with water (15 ml) and saturated aqueous NaHCO₃ solution (15 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.884 g) as a yellow oil.

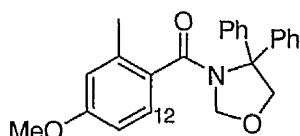
[†] See page 141

[‡] See page 150

[§] See page 144

Without purification, following the method of Grayson *et al.*,⁷⁵ the oil was dissolved in 80% aqueous acetic acid (30 ml) and stirred at room temperature for 1 h. Water (25 ml) was added and the mixture extracted with DCM (3×20 ml). The combined organic extracts were carefully washed with saturated aqueous NaHCO_3 solution (3×20 ml), water (2×20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (0.860 g) as a yellow oil. Flash column chromatography (4 : 1 petrol : ethyl acetate) afforded the title compound (0.150 g, 61% from **155**) as a white solid, m.p. 42 °C (dec.).

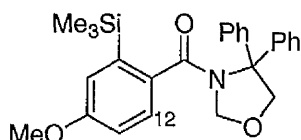
R_f (5 : 1 petrol : ethyl acetate + 1% triethylamine) 0.44; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1710 (ketone C=O and obscured amide C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.56–7.48 (2H, m, Ph), 7.48–7.21 (13H, m, Ph), 5.52 (1H, d, J 5.0, C9bH), 5.15 (1H, d, J 9.5, C2H_A), 4.37 (1H, d, J 9.5, C2H_B), 3.15 (1H, t, J 6.0, C5aH), 2.91 (1H, dq, J 12.0 and 6.0, C9aH), 2.43 (1H, dd, J 16.0 and 5.5, C9H_A), 2.30 (1H, dd, J 16.0 and 12.0, C9H_B), 2.16 (1H, dd, J 16.0 and 6.5, C7H_A), 2.05 (1H, dd, J 16.0 and 8.5, C7H_B), 1.88 (1H, dt, J 8.0 and 6.0, C6H), 0.39 (3H, s, SiMe_A), 0.37 (3H, s, SiMe_B); **¹³C NMR** (75.4 MHz, CDCl_3) δ 211.5, 171.6, 142.0, 140.9, 136.4, 134.3, 129.8, 129.1, 129.0, 128.3, 128.3, 128.1, 128.0, 126.9, 92.9, 85.0, 68.6, 45.7, 38.7, 38.3, 36.2, 19.6, –3.5, –4.1; **MS** (ES^+) m/z 985 (30%, $2\text{M} + \text{Na}^+$), 504 (65%, $\text{M} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{30}\text{H}_{31}\text{NO}_3\text{SiNa}$ ($\text{M} + \text{Na}^+$) 504.1965, found 504.1970.

(4,4-Diphenyloxazolidin-3-yl)-(4-methoxy-2-methylphenyl)methanone, 181

tert-Butyllithium (1.5 M in pentane, 1.40 ml, 2.10 mmol, 1.5 eq.) was added dropwise to a solution of amide **153**^{*} (0.507 g, 1.41 mmol, 1.0 eq.) in THF (45 ml) at -78°C . The red reaction mixture was stirred at -78°C for 40 min, and quenched with iodomethane (0.18 ml, 2.89 mmol). The solution was stirred at -78°C for 2 h and warmed to room temperature. Water (50 ml) was added and the aqueous phase extracted with diethyl ether (2×50 ml). The combined organic extracts were washed with water (2×50 ml) and brine (50 ml), dried (MgSO_4) and concentrated under reduced pressure to give the crude product (0.593 g) as a pale brown foamy gum. Flash column chromatography (5 : 1 to 4 : 1 petrol : ethyl acetate) afforded the title compound (0.400 g, 76%) as a white solid, m.p. $109\text{--}112^{\circ}\text{C}$.

R_f (1 : 1 petrol : ethyl acetate) 0.81; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1652 (C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.54–7.15 (11H, m, $2 \times \text{Ph}$ (10H) and C12H (1H)), 6.81–6.62 (2H, br m, C9H and C11H), 5.06 (2H, br s, C2H₂), 4.55 (2H, s, C5H₂), 3.82 (3H, s, OMe), 2.16 (3H, br s, ArMe); **¹³C NMR** (75.4 MHz, CDCl_3) δ 167.5, 160.4, 141.7, 136.8, 130.1, 128.3, 128.2, 127.7, 127.0, 116.4, 111.4, 84.1, 77.1, 71.0, 55.5, 19.5; **MS** (CI^+) m/z 374 (30%, $\text{M} + \text{H}^+$), 149 (100%, ArCO^+); (EI^+) m/z 149 (100%, ArCO^+), 77 (60%, Ph^+); **HRMS** calc. for $\text{C}_{24}\text{H}_{24}\text{NO}_3$ ($\text{M} + \text{H}^+$) 374.1751, found 374.1750.

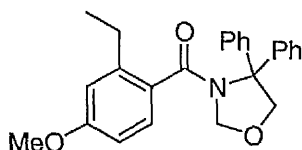
^{*} See page 141

(4,4-Diphenyloxazolidin-3-yl)-(4-methoxy-2-trimethylsilylphenyl)methanone, 182

tert-Butyllithium (1.5 M in pentane, 1.40 ml, 2.10 mmol, 1.5 eq.) was added dropwise to a solution of amide **153**^{*} (0.500 g, 1.39 mmol, 1.0 eq.) in THF (45 ml) at -78°C . The red reaction mixture was stirred at -78°C for 40 min, and quenched with chlorotrimethylsilane (0.45 ml, 3.52 mmol, 2.5 eq.). The solution was stirred at -78°C for 2 h and warmed to room temperature. Saturated aqueous NH_4Cl solution (5 ml) and water (50 ml) were added to the yellow solution, and the aqueous phase was extracted with diethyl ether (2×50 ml). The combined organic extracts were washed with water (2×50 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (0.636 g) as a yellow gum. Flash column chromatography (15 : 1 petrol : ethyl acetate) afforded the title compound (0.430 g, 72%) as a white solid, m.p. $103\text{--}106^{\circ}\text{C}$.

R_f (4 : 1 petrol : ethyl acetate) 0.64; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1652 (C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.56–7.49 (4H, m, Ph), 7.47 (1H, d, J 8.5, C12H), 7.41–7.27 (6H, m, Ph), 7.12 (1H, d, J 2.5, C9H), 6.91 (1H, dd, J 8.5 and 2.5, C11H), 5.12 (2H, s, C2H₂), 4.51 (2H, s, C5H₂), 3.87 (3H, s, OMe), -0.06 (9H, s, SiMe_3); **¹³C NMR** (75.4 MHz, CDCl_3) δ 168.5, 159.9, 141.8, 141.3, 135.7, 128.8, 128.2, 127.5, 121.9, 112.7, 83.5, 82.8, 77.5, 70.6, 55.5, -0.3 ; **MS** (EI^+) m/z 412 (55%, $\text{M} + \text{H}^+$), 207 (35%, ArCO^+), 181 (100%, $\text{ArH} + \text{H}^+$); (CI^+) m/z 207 (100%, ArCO^+); **HRMS** calc. for $\text{C}_{26}\text{H}_{30}\text{NO}_3\text{Si}$ ($\text{M} + \text{H}^+$) 432.1989, found 432.1989; **ANAL. CALC.** for $\text{C}_{26}\text{H}_{29}\text{NO}_3\text{Si}$: C, 72.35; H, 6.77; N, 3.25, found C, 72.19; H, 6.92; N, 3.13.

^{*} See page 141

(4,4-Diphenyloxazolidin-3-yl)-(4-methoxy-2-ethylphenyl)methanone, 183

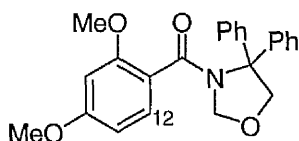
tert-Butyllithium (1.5 M in pentane, 0.31 ml, 0.47 mmol, 1.5 eq.) was added dropwise to a solution of *ortho*-methyl benzamide **181**[†] (0.116 g, 0.312 mmol, 1.0 eq.) and DMPU (0.21 ml, 1.7 mmol, 5.4 eq.) in THF (10 ml) at -78°C . The cherry-red solution was stirred at -78°C for 45 min, and quenched with iodomethane (0.05 ml, 0.80 mmol) to give an orange solution. This was stirred at -78°C for 30 min and allowed to warm to room temperature. Water (15 ml) was added and the aqueous phase extracted with diethyl ether (3×10 ml). The combined organic extracts were washed with water (5×15 ml) and brine (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give a 3 : 2 mixture of the title compound and unreacted **181** (0.118 g) as a pale yellow solid, inseparable by flash column chromatography.

R_f (1 : 1 petrol : ethyl acetate) 0.86; **¹H NMR** (300 MHz, CDCl_3 , mixture with *ortho*-methyl analogue **181** [assignments labelled *]) δ 7.54–7.15 (11H* and 11H, m, $2 \times \text{Ph}^*$ (10H*), $2 \times \text{Ph}$ (10H), ArH* (1H) and ArH (1H)), 6.83–6.60 (2H* and 2H, br m, ArH* and ArH), 5.04 (2H* and 2H, br s, C_2H_2^* and C_2H_2), 4.55 (2H* and 2H, s, C_5H_2^* and C_5H_2), 3.84 (3H, s, OMe), 3.83 (3H*, s, OMe*), 2.15 (3H* and 3H, br s, ArMe* and ArMe); **MS** (EI^+) m/z 388 (30%, $\text{M} + \text{H}^+$), 224 (15%,



), 180 (50%, ArCONH_3^+), 163 (90%, ArCO^+); (CI^+) m/z 163 (90%, ArCO^+); **HRMS** calc. for $\text{C}_{25}\text{H}_{26}\text{NO}_3$ ($\text{M} + \text{H}^+$) 388.1907, found 388.1907.

[†] See page 161

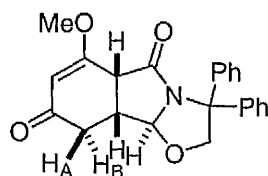
(4,4-Diphenyloxazolidin-3-yl)-(2,4-dimethoxyphenyl)methanone, 198

A solution of 2,4-dimethoxybenzoyl chloride (1.35 g, 6.72 mmol, 1.5 eq.) in 1,2-dichloroethane (3 ml) was added carefully to a solution of diphenyloxazolidine **106**^{*} (1.00 g, 4.45 mmol, 1.0 eq.) and triethylamine (1.85 ml, 13.3 mmol, 3.0 eq.) in 1,2-dichloroethane (7 ml) at 0 °C. The stirred solution was allowed to warm to room temperature, and heated at reflux for 18 h. The solvent was partially removed under reduced pressure to leave a brown slurry. 2 M aqueous NaOH solution (10 ml) was added to the residue and the mixture heated at reflux for 1 h; DCM (10 ml) was added to the cooled mixture. The aqueous phase was extracted with DCM (3 × 20 ml) and the combined organic extracts washed with water (2 × 20 ml) and brine (20 ml), dried (MgSO₄) and concentrated under reduced pressure to give the crude product (1.79 g) as a pale brown solid. Flash column chromatography (5 : 1 to 3 : 1 petrol : ethyl acetate) afforded the title compound (1.29 g, 74%) as a white solid, m.p. 185–187 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.63; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1650 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.59–7.47 (4H, d, *J* 7.0, Ph), 7.46–7.32 (6H, m, Ph), 7.15 (1H, d, *J* 7.5, C12H), 6.56–6.45 (2H, br m, C9H and C11H), 5.09 (2H, s, C2H₂), 4.52 (2H, s, C5H₂), 3.91 (3H, s, OMe), 3.85 (3H, s, OMe); **¹³C NMR** (75.4 MHz, CDCl₃) δ 165.1, 162.2, 157.0, 141.7, 129.1, 128.3, 128.2, 127.5, 105.2, 105.2, 98.8, 84.3, 82.0, 71.2, 55.9, 55.7; **MS** (CI⁺) *m/z* 390 (100%, M + H⁺), 165 (60%, ArCO⁺); (EI⁺) *m/z* 389 (75%, M⁺), 165 (100%, ArCO⁺) **HRMS** calc. for C₂₄H₂₄NO₄ (M + H⁺) 390.1700, found 390.1703; **ANAL. CALC.** for C₂₄H₂₃NO₄: C, 74.02; H, 5.95; N, 3.60, found C, 73.93; H, 6.10; N, 3.53.

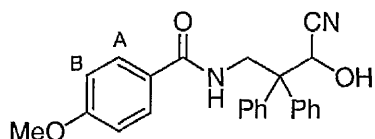
^{*} See page 139

(5aR*,9aS*,9bS*)-6-Methoxy-3,3-diphenyl-2,3,9a,9b-tetrahydro-5aH,9H-oxazolo[2,3-a]isoindole-5,8-dione, 199



tert-Butyllithium (1.5 M in pentane, 2.25 ml, 3.38 mmol, 1.5 eq.) was added dropwise to a solution of amide **198** (0.863 g, 2.22 mmol, 1.0 eq.) and DMPU (1.58 ml, 13.1 mmol, 5.9 eq.) in THF (75 ml) at -78°C . The deep orange solution was stirred at -78°C for 40 min and 0°C for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (7.5 ml), stirred at 0°C for 30 min and warmed to room temperature. Water (75 ml) was added and the aqueous phase extracted with diethyl ether (3×75 ml). HCl (2 M in diethyl ether, 0.64 ml, 1.28 mmol, 0.58 eq.) was added to the combined organic extracts, and the solution stirred at room temperature for 18 h. Water (75 ml) was added, and the aqueous phase extracted with diethyl ether (3×75 ml). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution (75 ml), water (5×75 ml) and brine (75 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (0.880 g) as a pale orange gum. Flash column chromatography (1 : 1 petrol : ethyl acetate + 1% triethylamine) afforded the title compound (0.523 g, 63%) as a white solid, m.p. 73°C (dec.).

R_f (1 : 1 petrol : ethyl acetate + 1% triethylamine) 0.18; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1714 (enone $\text{C}=\text{O}$), 1656 (amide $\text{C}=\text{O}$); **^1H NMR** (300 MHz, CDCl_3) δ 7.46–7.24 (10H, m, $2 \times \text{Ph}$), 5.60 (1H, d, J 5.0, C9bH), 5.37 (1H, s, C7H), 5.22 (1H, d, J 9.5, C2H_A), 4.43 (1H, d, J 9.5, C2H_B), 3.78 (1H, d, J 6.5, C5aH), 3.74 (3H, s, OMe), 3.37 (1H, dtd, J 12.5, 6.5 and 5.5, C9aH), 2.59 (1H, dd, J 16.5 and 6.0, C9H_A), 2.47 (1H, dd, J 16.5 and 13.0, C9H_B); **^{13}C NMR** (75.4 MHz, CDCl_3) δ 198.6, 170.9, 165.6, 141.8, 140.4, 129.2, 129.0, 128.5, 128.3, 128.1, 126.8, 103.6, 92.4, 85.3, 68.8, 56.7, 49.8, 37.9, 32.9; **MS** (ES^+) m/z 398 (100%, $\text{M} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{23}\text{H}_{21}\text{NO}_4\text{Na}$ ($\text{M} + \text{Na}^+$) 398.1363, found 398.1357.

N-(3-Cyano-3-hydroxy-2,2-diphenylpropyl)-4-methoxybenzamide, 202

The starting material for this reaction was the crude product from an attempted dearomatising cyclisation of benzamide **153*** containing approximately 80 mol% **153** (estimated from proton NMR data).

Trimethylsilyl triflate (0.20 ml, 1.1 mmol, 1.8 eq.) was added to a solution of benzamide **153** (80 mol%, 0.268 g, 0.60 mmol, 1.0 eq.) in DCM (10 ml) at -78°C . Trimethylsilyl cyanide (1.0 M in DCM, 1.12 ml, 1.12 mmol, 1.9 eq.) was added to the orange solution. The mixture was stirred at -78°C for 30 min and room temperature for 20 h. The reaction was quenched with tetrabutylammonium fluoride (1 M in THF containing 5% water, 2.8 ml, 2.8 mmol, 4.7 eq.) and stirred for 1 h. Water (20 ml) was added and the aqueous phase extracted with DCM (2×20 ml). The combined organic extracts were washed with 2 M aqueous HCl solution (2×20 ml), water (2×20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated to give the crude product mixture (0.631 g) as an orange oil. Flash column chromatography (4 : 1 hexane : ethyl acetate) gave a mixed fraction containing the title compound (0.0466 g) as a brown gum.

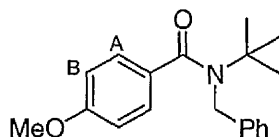
R_f (1 : 1 hexane : ethyl acetate) 0.50; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3367 (O–H), 1633 and 1607 (amide C=O); **¹H NMR** (500 MHz, CDCl_3) δ 7.54 (2H, d, J 9.0, ArH_A), 7.46–7.20 (10H, m, $2 \times \text{Ph}$), 6.88 (2H, d, J 9.0, ArH_B), 5.98 (1H, t, J 6.5, NH), 5.74 (1H, br s, OH), 5.21 (1H, s, $\text{CH}(\text{OH})(\text{CN})$), 4.84 (1H, dd, J 14.5 and 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.85 (1H, m_{obs} , $\text{CH}_\text{A}\text{H}_\text{B}$), 3.83 (3H, s, OMe); **¹³C NMR** (90.6 MHz, CDCl_3) δ 169.8, 163.3, 142.0, 140.2, 129.4, 129.4, 129.3, 128.8, 128.6, 128.4, 128.1, 126.1, 118.7, 114.5, 65.4, 55.9, 46.2, 30.1; **MS** (ES^+) m/z 409 (20%, $\text{M} + \text{Na}^+$), 387 (55%, $\text{M} + \text{H}^+$), 382 (20%, $\text{M} - \text{HCN} + \text{Na}^+$), 360 (100%,

* See page 141

$M - \text{HCN} + \text{H}^+$); **HRMS** calc. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($M + \text{Na}^+$) 409.1523, found 409.1514.

5.3 Experimental Details for Chapter 3

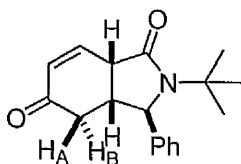
N-Benzyl-*N*-(*tert*-butyl)-4-methoxybenzamide, 45



Following the method of Yasin,⁸⁴ *para*-anisoyl chloride (7.40 ml, 54.0 mmol, 1.0 eq.) was added dropwise to a solution of *N*-*tert*-butylbenzylamine (10.0 ml, 8.81 g, 54.0 mmol, 1.0 eq.) in a mixture of DCM (100 ml) and 2 M aqueous NaOH solution (35 ml) at 0 °C, and stirred at room temperature for 4.5 h. The aqueous phase was extracted with DCM (2 × 100 ml) and the combined organic extracts were washed with brine (100 ml), dried (MgSO₄) and concentrated under reduced pressure to give the crude product (16.0 g) as a pale yellow solid. Recrystallisation from ethyl acetate gave the title compound (13.1 g, 81%) as white prisms, m.p. 124–126 °C (lit.⁸⁴ 98–99 °C).

R_f (2 : 1 petrol : ethyl acetate) 0.63; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1625 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.43 (2H, d, *J* 9.0, ArH_A), 7.39–7.23 (5H, m, Ph), 6.83 (1H, d, *J* 9.0, ArH_B), 4.67 (2H, s, CH₂), 3.80 (3H, s, OMe), 1.51 (9H, s, *t*-Bu).

Data shown is a correction to that previously quoted for this compound.⁸⁴

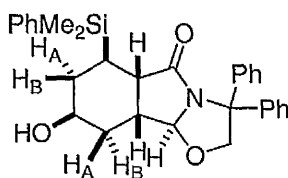
2-tert-butyl-3-phenyl-2,3,3a,7a-tetrahydro-4H-isoindole-1,5-dione, 48

Following the method of Yasin,⁸⁴ LDA (1.08 M in THF, prepared *in situ*, 20.1 ml, 21.7 mmol, 1.3 eq.) was added to a solution of amide **45** (5.03 g, 16.9 mmol, 1.0 eq.) in THF (300 ml) at 0 °C. The resulting orange solution was stirred at room temperature for 1.5 h, quenched with saturated aqueous NH₄Cl solution (10 ml), and 2 M aqueous HCl solution (200 ml) was added. The layers were separated and the aqueous phase extracted with diethyl ether (2 × 200 ml). The combined organic extracts were washed with water (2 × 100 ml) and brine (100 ml), dried (MgSO₄) and concentrated under reduced pressure to give the crude product (4.53 g) as a beige solid. Flash column chromatography (4 : 1 to 3 : 1 petrol : ethyl acetate) afforded the title compound (3.18 g, 63%) as a white solid, m.p. 141–142 °C (lit.⁸⁴ 151–154 °C).

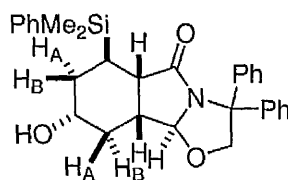
R_f (1 : 1 petrol : ethyl acetate) 0.61; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2975, 2880, 1681 (2 × C=O), 1393; **¹H NMR** (300 MHz, CDCl₃) δ 7.46–7.22 (5H, m, Ph), 7.01 (1H, dd, *J* 10.0 and 5.5, C7H), 6.14 (1H, d, *J* 10.0, C6H), 4.45 (1H, s, C3H), 3.64 (1H, t, *J* 5.5, C7aH), 2.80–2.66 (2H, m, C4H_A and C3aH), 2.57 (1H, dd, *J* 16.5 and 14.0, C4H_B), 1.39 (9H, s, *t*-Bu).

All data, except melting point, were consistent with those previously reported.⁸⁴

(5a*S**,6*R**,8*R**,9a*R**,9b*S**)-octahydro-8-hydroxy-6-dimethylphenylsilyl-3,3-diphenyloxazolo[2,3-*a*]isoindol-5(9b*H*)-one, **211a**



(5a*S**,6*R**,8*S**,9a*R**,9b*S**)-octahydro-8-hydroxy-6-dimethylphenylsilyl-3,3-diphenyloxazolo[2,3-*a*]isoindol-5(9b*H*)-one, **211b**



Sodium borohydride (0.022 g, 0.85 mmol, 2.9 eq.) was added to a solution of ketone **176**[†] (0.138 g, 0.29 mmol, 1.0 eq.) in methanol (12 ml) at room temperature, and the mixture stirred for 18 h. The reaction was quenched with water (3 ml) and most of the solvent removed under reduced pressure. Diethyl ether (20 ml) was added and the mixture washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.140 g) as a white gum. Flash column chromatography (3 : 1 petrol : ethyl acetate) afforded compound **211a** (0.0479 g, 35%) as a white solid, m.p. 186–190 °C, and compound **211b** (0.0566 g, 41%) as a white solid, m.p. 79–82 °C.

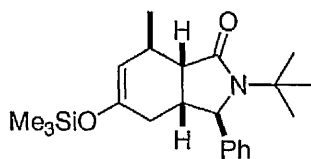
Data for compound **211a**: **R_f** (2 : 1 petrol : ethyl acetate) 0.54; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3461 (O–H), 1699 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.61–7.53 (2H, m, Ph), 7.48–7.36 (8H, m, Ph), 7.36–7.22 (5H, m, Ph), 5.50 (1H, d, *J* 5.0, C9bH), 5.13 (1H, d, *J* 9.5, C2H_A), 4.35 (1H, d, *J* 9.5, C2H_B), 3.96 (1H, qn, *J* 4.0,

[†] See page 159

C8H), 3.01 (1H, dd, J 6.0 and 3.5, C5aH), 2.83 (1H, dq, J 11.5 and 5.5, C9aH), 1.78 (1H, dt, J 17.5 and 5.5, C7H_A), 1.63 (1H, td, J 6.0 and 4.0, C6H), 1.52–1.35 (3H, m, C7H_B and C9H₂), 0.40 (3H, s, SiMe_A), 0.40 (3H, s, SiMe_B); ¹³C NMR (75.4 MHz, CDCl₃) δ 172.4, 142.5, 141.0, 138.8, 134.4, 129.5, 129.2, 129.0, 128.1, 128.0, 127.8, 127.8, 126.9, 94.0, 84.9, 68.5, 65.3, 46.2, 33.6, 30.3, 28.3, 15.4, -2.7, -3.2; MS (ES⁺) m/z 990 (30%, 2M + Na⁺), 506 (100%, M + Na⁺); HRMS calc. for C₃₀H₃₃NO₃SiNa (M + Na⁺) 506.2122, found 506.2115.

Data for compound **211b**: R_f (2 : 1 petrol : ethyl acetate) 0.28; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3445 (O–H), 1699 (C=O); ¹H NMR (300 MHz, CDCl₃) δ 7.58–7.52 (2H, m, Ph), 7.46–7.22 (13H, m, Ph), 5.44 (1H, d, J 5.0, C9bH), 5.15 (1H, d, J 9.5, C2H_A), 4.35 (1H, d, J 9.5, C2H_B), 3.51 (1H, tt, J 11.5 and 3.5, C8H), 2.86 (1H, d, J 6.0, C5aH), 2.59 (1H, dq, J 11.5 and 6.0, C9aH), 2.05–1.90 (2H, m, C6H and C9H_A), 1.80 (1H, ddt, J 13.0, 3.0 and 1.5, C7H_B), 1.09 (1H, q, J 12.0, C9H_B), 1.06–0.86 (1H, m, C7H_A), 0.41 (3H, s, SiMe_A), 0.37 (3H, s, SiMe_B); ¹³C NMR (75.4 MHz, CDCl₃) δ 171.5, 142.4, 140.4, 137.8, 134.1, 129.7, 129.6, 128.9, 128.4, 128.2, 127.8, 127.8, 126.9, 93.3, 84.8, 68.5, 67.0, 45.5, 38.5, 33.7, 31.8, 19.3, -2.4, -2.7; MS (ES⁺) m/z 989 (70%, 2M + Na⁺), 506 (100%, M + Na⁺); HRMS calc. for C₃₀H₃₃NO₃SiNa (M + Na⁺) 506.2122, found 506.2111.

(3*R**,3*aR**,7*R**,7*aS**)-2-*tert*-Butyl-7-methyl-3-phenyl-5-trimethylsilyloxy-2,3,3*a*,4,7,7*a*-hexahydroisoindol-1-one, 214⁶⁰



Methylolithium (1.6 M in diethyl ether, 6.3 ml, 10.1 mmol, 4.0 eq.) was added to a slurry of copper(I) bromide (0.722 g, 5.04 mmol, 2.0 eq.) in THF (40 ml) at -78°C to give a pale green-grey solution, which rapidly turned bright green then pale blue-grey. This solution was stirred at -78°C for 20 min, and allowed to warm for 5 min to dissolve most of the remaining solids. The solution was recooled to -78°C , and added over 20 min to a solution of enone **48**[†] (0.714 g, 2.52 mmol, 1.0 eq.) and chlorotrimethylsilane (0.64 ml, 5.0 mmol, 2.0 eq.) in THF (60 ml) at -78°C . The resulting lime-green solution was stirred at -78°C for 1.5 h, and allowed to warm to room temperature. After 30 min the solution was quenched with saturated aqueous NH_4Cl solution (20 min) and stirred for 30 min. Water (100 ml) was added and the aqueous phase extracted with diethyl ether (3×100 ml). The combined organic extracts were washed with water (2×100 ml) and saturated aqueous NaHCO_3 solution (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (0.922 g) as a white solid. A small portion (0.0863 g) was purified by flash column chromatography (10 : 1 petrol : ethyl acetate) to afford the title compound (0.0690 g, 79%) as a white solid, m.p. $147\text{--}148^{\circ}\text{C}$.

R_f (4 : 1 petrol : ethyl acetate) 0.65; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1675 (C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.44–7.27 (5H, m, Ph), 4.88 (1H, dd, J 4.5 and 2.0, C6H), 4.47 (1H, s, C3H), 2.86 (1H, m, C7H), 2.56 (1H, dd, J 6.0 and 1.5, C7aH), 2.41–2.29 (2H, m, C4H_AH_B and C3aH), 1.99 (1H, ddt, J 19.5, 11.5 and 2.0, C4H_AH_B), 1.39 (9H, s, *t*-Bu), 1.00 (3H, d, J 7.0, C7Me), 0.21 (9H, s, SiMe₃);

[†] See page 169

^{13}C NMR (75.4 MHz, CDCl_3) δ 176.2, 146.9, 142.1, 129.0, 127.7, 126.0, 109.5, 68.1, 54.8, 44.4, 39.3, 32.8, 28.2, 27.3, 23.7, 0.5; **MS** (ES^+) m/z 709 (25%, $2\text{M} - t\text{-Bu} + \text{Na}^+$), 394 (60%, $\text{M} + \text{Na}^+$), 337 (100%, $\text{M} - t\text{-Bu} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{22}\text{H}_{33}\text{NO}_2\text{SiNa}$ ($\text{M} + \text{Na}^+$) 394.2173, found 394.2173.

All data were consistent with those previously reported. This compound was not previously isolated.⁶⁰

(3*R**,3*aR**,7*R**,7*aS**)-2-*tert*-butyl-7-dimethylphenylsilyl-3-phenyl-5-trimethylsilyloxy-2,3,3*a*,4,7,7*a*-hexahydroisindol-1-one, 215



Diethylzinc (1.0 M in hexanes, 4.9 ml, 4.9 mmol, 1.4 eq.) was added to THF (30 ml) at 0 °C to give a pale blue solution. Phenyltrimethylsilyllithium (0.67 M in THF, 7.1 ml, 4.9 mmol, 1.4 eq.) was added at 0 °C over 2 min to give a wine-red solution, stirred at 0 °C for 5 min, and cooled to –78 °C. A solution of enone **48**[†] (0.998 g, 3.52 mmol, 1.0 eq.) in THF (7 ml) at –78 °C was added, with THF washings (5 ml), to give a pale red solution, and stirred at –78 °C for 40 min. The reaction was quenched with chlorotrimethylsilane (0.99 ml, 7.8 mmol, 2.2 eq.), stirred at –78 °C for 30 min, and warmed to room temperature. The reaction was stirred at this temperature for 1.5 h, cooled to 0 °C and carefully quenched with saturated aqueous NH₄Cl solution (10 ml). Water (30 ml) was added at room temperature, and the aqueous phase was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were washed with water (2 × 30 ml) and saturated aqueous NaHCO₃ solution (30 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (2.55 g) as a yellow oil, not thought to be stable to purification by flash column chromatography (streak observed by thin layer chromatography).

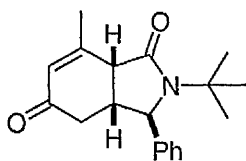
The title compound was later isolated from the crude product mixture of a subsequent reaction by flash column chromatography (6 : 1 petrol : ethyl acetate) as a pale yellow oil.

R_f (4 : 1 petrol : ethyl acetate) 0.67; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1691 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.46–7.26 (6H, m, Ph), 7.23–7.15 (4H, m, Ph),

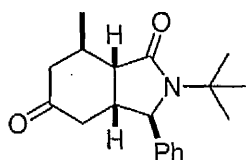
[†] See page 169

4.88 (1H, ddd, J 5.0, 2.5 and 1.0, C6H), 4.36 (1H, s, C3H), 2.72 (1H, d, J 6.0, C7aH), 2.42 (1H, m, C7H), 2.21 (1H, dd, J 17.0 and 7.5, C4H_AH_B), 1.95 (1H, ddt, J 17.0, 8.5 and 2.5, C4H_AH_B), 1.83 (1H, td, J 8.0 and 6.5, C3aH), 1.36 (9H, s, *t*-Bu), 0.26 (3H, s, PhMe_AMe_BSi), 0.22 (3H, s, PhMe_AMe_BSi), 0.19 (9H, s, SiMe₃); ¹³C NMR (75.4 MHz, CDCl₃) δ 176.9, 145.9, 141.9, 137.2, 134.0, 129.2, 128.9, 127.9, 127.5, 125.8, 103.9, 68.0, 54.7, 40.7, 38.0, 32.6, 28.2, 21.6, 0.6, -4.2, -4.3; MS (ES⁺) m/z 514 (100%, M + Na⁺), 492 (10%, M + H⁺); HRMS calc. for C₃₀H₄₁NO₂Si₂ (M + H⁺) 492.2749, found 492.2751.

(3*R**,3*aR**,7*aR**)-2-*tert*-butyl-2,3,3*a*,4-tetrahydro-7-methyl-3-phenyl-7*aH*-isoindole-1,5-dione, **216**⁶⁰



(3*R**,3*aR**,7*R**,7*aS**)-2-*tert*-butyl-2,3,3*a*,4,7,7*a*-hexahydro-7-methyl-3-phenyl-6*H*-isoindole-1,5-dione, **222**⁶⁰



A solution of silyl enol ether **214**[†] (0.814 g, 2.19 mmol, 1.0 eq.) in acetonitrile (70 ml) was cannulated into a solution of palladium(II) acetate (0.522 g, 2.32 mmol, 1.1 eq.) at room temperature over 15 min, washed in with additional acetonitrile (5 ml). The resulting deep orange-brown solution was stirred at room temperature for 17 h. The solution was filtered through a pad of celite with ethyl acetate washings, and concentrated under reduced pressure to give the crude product (1.10 g) as a dark brown gum. Flash column chromatography (4 : 1 petrol : ethyl acetate) afforded an inseparable mixture of enone **216** and ketone **222** (approximately 60 : 40 enone : ketone by proton NMR, 0.493 g) as a pale yellow solid.

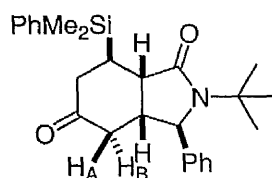
R_f (2 : 1 petrol : ethyl acetate) 0.38; ¹H NMR (300 MHz, CDCl₃, signals of ketone **222** labelled *) δ 7.49–7.26 (5H and 5H*, m, Ph and Ph*), 5.98 (1H, s, C6H), 4.51 (1H, s, C3H), 4.47 (1H*, s, C3H*), 3.43 (1H, d, *J* 6.0, C7aH), 2.77–2.62 and 2.58–2.46 (3H and 5H*, m, C3aH, C4H₂, C3aH*, C4H_AH_B*, C6H*, C7H* and C7aH*), 2.38 (1H*, dd, *J* 14.0 and 11.5, C4H_AH_B*), 2.28 (3H,

[†] See page 172

d, J 1.0, C7Me), 2.06 (1H*, dd, J 15.0 and 7.0, C6H*), 1.43 (9H and 9H*, s, t -Bu and t -Bu*), 1.11 (3H*, d, J 7.0, C7Me*).

All data were consistent with those previously reported.⁶⁰

(3*R**,3*aR**,7*R**,7*aS**)-2-*tert*-Butyl-hexahydro-7-dimethylphenylsilyl-3-phenyl-6*H*-isoindol-1,5-dione, **217**



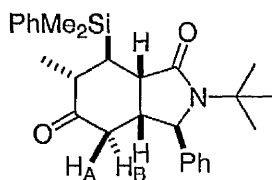
Following the method of Grayson *et al.*,⁷⁵ crude silyl enol ether **215**[†] (1.09 g, ≤ 1.5 mmol) was dissolved in 90% aqueous acetic acid (80 ml) and the solution stirred vigorously at room temperature for 1.5 h. Water (30 ml) was added and the aqueous phase extracted with DCM (3 \times 50 ml). The combined organic extracts were washed carefully with saturated aqueous NaHCO₃ solution (5 \times 40 ml) and brine (50 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.927 g) as a yellow oil. Flash column chromatography (6 : 1 petrol : ethyl acetate) afforded the title compound (0.549 g, 90% over two steps from enone **48**)[‡] as a white solid, m.p. 124–126 °C.

R_f (4 : 1 petrol : ethyl acetate) 0.30; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1714 (ketone C=O), 1686 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.45–7.10 (10H, m, 2 \times Ph), 4.37 (1H, s, C3H), 2.94 (1H, t, *J* 4.5, C7aH), 2.55 (1H, dd, *J* 14.5 and 4.5, C4H_AH_B), 2.43 (1H, dd, *J* 15.0 and 6.5, C6H_AH_B), 2.33 (1H, dd, *J* 14.5 and 12.0, C4H_AH_B), 2.27–2.19 (1H, m, C3aH), 2.14 (1H, dd, *J* 15.5 and 7.0, C6H_AH_B), 2.02 (1H, td, *J* 6.0 and 4.5, C7H), 1.39 (9H, s, *t*-Bu), 0.34 (3H, s, PhMe_AMe_BSi), 0.32 (3H, s, PhMe_AMe_BSi); **¹³C NMR** (75.4 MHz, CDCl₃) δ 211.2, 175.8, 141.8, 136.6, 134.1, 129.6, 129.2, 128.2, 128.0, 125.6, 66.8, 55.2, 43.6, 43.3, 39.8, 38.9, 28.2, 20.4, –3.4, –4.2; **MS** (ES⁺) *m/z* 861 (30%, 2M + Na⁺), 479 (100%), 442 (70%, M + Na⁺), 420 (15%, M + H⁺); **HRMS** calc. for C₂₆H₃₃NO₂SiNa (M + Na⁺) 442.2173, found 442.2175; **ANAL. CALC.** for C₂₆H₃₃NO₂Si: C, 74.42; H, 7.93; N, 3.34, found C, 74.31; H, 8.30; N, 3.27.

[†] A portion of the crude product from the previous step: see page 174

[‡] See page 169

(3*R**,3*aR**,6*S**,7*R**,7*aS**)-2-*tert*-Butyl-hexahydro-6-methyl-7-dimethylphenylsilyl-3-phenyl-6*H*-isoindol-1,5-dione, **218**



Procedure 1: Methyllithium (1.6 M in diethyl ether, 1.70 ml, 2.72 mmol, 2.3 eq.) was added to a solution of crude silyl enol ether **215**[†] (0.837 g, ≤ 1.2 mmol, 1.0 eq.) in THF (40 ml) at 0 °C, and the resulting deep orange solution stirred at 0 °C for 30 min. Iodomethane (0.84 ml, 13.5 mmol, 11 eq.) was added to give a pale yellow solution, and stirred at 0 °C for 3 h. The solution was concentrated under reduced pressure. Diethyl ether (40 ml) was added and the mixture was washed with water (2 \times 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.648 g) as an orange oil. Flash column chromatography (10 : 1 petrol : ethyl acetate) afforded the title compound (0.261 g, 44% over two steps from **48**[‡]) as a white solid, m.p. 128 °C (dec.).

Procedure 2: Diethylzinc (1.1 M in toluene, 1.8 ml, 2.0 mmol, 1.4 eq.) was added to THF (5 ml) at 0 °C to give a pale blue solution. Phenyltrimethylsilyllithium (0.81 M in THF, 2.4 ml, 2.0 mmol, 1.4 eq.) was added at 0 °C over 2 min to give a red-brown solution, stirred at 0 °C for 5 min, and cooled to -78 °C. A solution of enone **48** (0.395 g, 1.39 mmol, 1.0 eq.) in THF (12 ml) at -78 °C was added, giving an orange-brown solution, stirred at -78 °C for 25 min, and 0 °C for 30 min. The reaction was quenched with iodomethane (0.43 ml, 6.9 mmol, 5.0 eq.) to give a bright orange solution, stirred at 0 °C for 30 min, and room temperature for 1 h. The solvent was removed under reduced pressure to give an orange gum, found to be insoluble in diethyl ether, DCM, ethyl acetate, petrol and

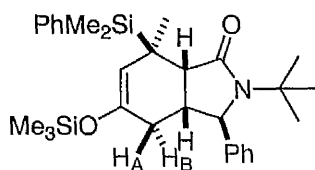
[†] A portion of the crude product from the previous step: see page 174

[‡] See page 169

water. This gum was dissolved in dimethyl sulfoxide, and most of the solvent removed under reduced pressure. The residue was partitioned between DCM (50 ml) and water (50 ml). The aqueous phase was extracted with DCM (50 ml) and the combined organic extracts sequentially washed with 1 M aqueous NaOH solution (50 ml), 1 M aqueous HCl solution (50 ml), saturated aqueous NaHCO₃ solution (50 ml), water (2 × 50 ml) and brine (50 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.701 g) as an orange solid. Purification using Horizon Biotage apparatus (25-S cartridge, hexane to 15% ethyl acetate/petrol) afforded the title compound (0.367 g, 61%) as a white solid.

R_f (4 : 1 petrol : ethyl acetate) 0.40; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 1711 (ketone C=O), 1682 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.44–7.23 (8H, m, Ph), 7.19–7.13 (2H, m, Ph), 4.39 (1H, s, C3H), 2.91 (1H, dd, *J* 7.0 and 3.0, C7aH), 2.50 (1H, dd, *J* 15.0 and 10.5, C4H_AH_B), 2.42 (1H, dd, *J* 14.5 and 7.0, C4H_AH_B), 2.42 (1H, dd, *J* 7.5 and 4.0, C6H), 2.28 (1H, dt, *J* 10.5 and 6.5, C3aH), 2.02 (1H, dd, *J* 4.5 and 3.0, C7H), 1.38 (9H, s, *t*-Bu), 1.16 (3H, d, *J* 7.0, C6Me), 0.32 (3H, s, PhMe_AMe_BSi), 0.29 (3H, s, PhMe_AMe_BSi); **¹³C NMR** (75.4 MHz, CDCl₃) δ 214.2, 176.4, 142.0, 137.1, 134.1, 129.5, 129.2, 128.2, 128.0, 125.6, 67.2, 55.1, 44.3, 43.8, 41.0, 39.0, 28.1, 27.4, 19.6, –3.2, –4.0; **MS** (ES⁺) *m/z* 889 (60%, 2M + Na⁺), 456 (100%, M + Na⁺); **HRMS** calc. for C₂₇H₃₅NO₂SiNa (M + Na⁺) 456.2329, found 456.2335; **ANAL. CALC.** for C₂₇H₃₅NO₂Si: C, 74.78; H, 8.13; N, 3.23, found C, 74.82; H, 8.27; N, 2.93.

(3*R**,3*aR**,7*R**,7*aS**)-2-*tert*-butyl-2,3,3*a*,4,7,7*a*-hexahydro-5-trimethylsilanyloxy-7-methyl-7-dimethyl(phenyl)silanyl-3-phenyl-isoindol-1-one, **219**



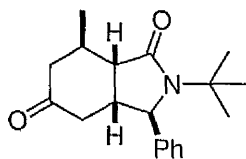
Diethylzinc (1.0 M in hexanes, 1.40 ml, 1.40 mmol, 1.1 eq.) was added to THF (10 ml) at 0 °C to give a pale blue solution. Phenyltrimethylsilyllithium (0.79 M in THF, 1.78 ml, 1.41 mmol, 1.1 eq.) was added at 0 °C over 3 min to give a wine-red solution, stirred at 0 °C for 5 min, and cooled to –78 °C. This solution was cannulated into a solution of crude enone **216**[†] (0.483 g, 1.29 mmol, 1.0 eq.) in THF (10 ml) at –78 °C over 4 min to give a red solution, and stirred at –78 °C for 40 min. The reaction was quenched with chlorotrimethylsilane (0.289 ml, 2.2 mmol, 1.7 eq.), stirred at –78 °C for 30 min, and room temperature for 1.5 h. Saturated aqueous NH₄Cl solution (2.5 ml) and water (15 ml) were carefully added, and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were washed with water (2 × 15 ml) and saturated aqueous NaHCO₃ solution (15 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.817 g) as a yellow oil. Flash column chromatography (4 : 1 petrol : ethyl acetate) afforded the title compound (0.139 g, 13% over two steps) as a pale yellow gum.

R_f (4 : 1 petrol : ethyl acetate) 0.75; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1689 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.55–7.48 (2H, m, Ph), 7.45–7.23 (6H, m, Ph), 7.19–7.10 (2H, m, Ph), 5.64 (1H, m, C6H), 4.26 (1H, s, C3H), 2.79 (1H, d, *J* 6.5, C7aH), 2.14 (1H, ddt, *J* 11.5, 3.5 and 1.5, C4H_AH_B), 2.07 (3H, d, *J* 1.0, C7Me), 1.84 (1H, ddd, *J* 13.5, 6.5 and 3.5, C3aH), 1.72 (1H, dd, *J* 13.5 and 11.5, C4H_AH_B), 1.36 (9H, s, *t*-Bu), 0.32 (3H, s, PhMe_AMe_BSi), 0.25 (3H, s, PhMe_AMe_BSi), 0.11 (9H, s, SiMe₃); **¹³C NMR** (75.4 MHz, CDCl₃) δ 174.8, 143.1,

[†] A portion of the crude product from the previous step: see page 176

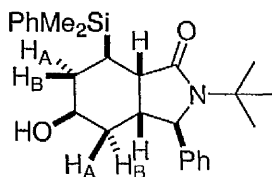
137.4, 134.7, 131.3, 129.3, 129.3, 129.0, 127.7, 127.5, 125.3, 71.3, 66.4, 54.9, 44.5, 42.1, 38.4, 28.1, 23.4, 3.0, -4.6, -4.9; **MS** (ES^+) m/z 528 (55%, $\text{M} + \text{Na}^+$), 506 (70%, $\text{M} + \text{H}^+$), 416 (40%, $[\text{M} - \text{OSiMe}_3]^+$); **HRMS** calc. for $\text{C}_{30}\text{H}_{44}\text{NO}_2\text{Si}_2$ ($\text{M} + \text{H}^+$) 506.2905, found 506.2906.

(3*R**,3*aR**,7*R**,7*aS**)-2-*tert*-butyl-2,3,3*a*,4,7,7*a*-hexahydro-7-methyl-3-phenyl-6*H*-isoindole-1,5-dione, **222**⁶⁰

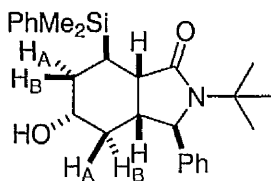


The title compound was obtained as a by-product in the formation of enone **216**. See page 176 for experimental details and proton NMR data.

(3*R**,3*aR**,5*R**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **225a**



(3*R**,3*aR**,5*S**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **225b**



Sodium borohydride (0.0656 g, 1.73 mmol, 2.0 eq.) was added to a solution of ketone **217**[†] (0.359 g, 0.854 mmol, 1.0 eq.) in methanol (35 ml) at room temperature, and the mixture stirred for 18 h. The reaction was quenched with water (2 ml) and the solvent removed under reduced pressure. Diethyl ether (50 ml) was added and the mixture washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.367 g) as a white solid. Flash column chromatography (2 : 1 petrol : ethyl acetate) afforded compound **225a** (0.239 g, 66%) as a white solid, m.p. 137–139 °C, and compound **225b** (0.120 g, 33%) as a white solid, m.p. 138–140 °C.

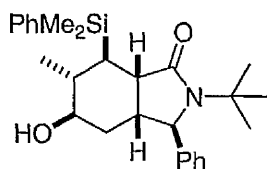
Data for compound **225a**: **R_f** (2 : 1 petrol : ethyl acetate) 0.44; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3431 (O–H), 1668 (C=O); **¹H NMR** (500 MHz, CDCl₃) δ 7.35–7.31 (2H, m, Ph), 7.30–7.25 (2H, m, Ph), 7.24–7.17 (2H, m, Ph), 7.16–7.09 (4H, m, Ph), 4.21 (1H, s, C3H), 3.87 (1H, m, C5H), 2.67 (1H, dd, *J* 6.5 and 3.5, C7aH),

[†] See page 178

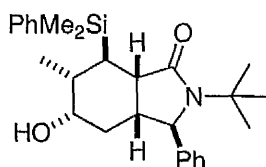
1.96 (1H, dt, J 11.0 and 5.5, C3aH), 1.71 (1H, dt, J 13.5 and 5.0, C6H_AH_B), 1.59 (1H, ddd, J 13.0, 6.5 and 3.0, C6H_AH_B), 1.55 (1H, dt, J 6.0 and 4.0, C7H), 1.42 (1H, td, J 11.0 and 3.5, C4H_AH_B), 1.39 (1H, dd, J 11.5 and 6.0, C4H_AH_B), 1.26 (9H, s, *t*-Bu), 0.22 (3H, s, PhMe_AMe_BSi), 0.19 (3H, s, PhMe_AMe_BSi); ¹³C NMR (125.8 MHz, CDCl₃) δ 177.1, 142.9, 138.9, 134.5, 129.2, 129.1, 128.1, 127.7, 125.9, 67.6, 66.6, 55.1, 40.7, 39.1, 35.3, 31.1, 28.4, 17.0, -2.5, -2.9; MS (ES⁺) m/z 861 (60%), 482 (100%), 444 (10%, M + Na⁺), 422 (90%, M + H⁺); HRMS calc. for C₂₆H₃₆NO₂Si (M + H⁺) 422.2510, found 422.2507; ANAL. CALC. for C₂₆H₃₅NO₂Si: C, 74.06; H, 8.37; N, 3.32, found C, 74.04; H, 8.65; N, 3.22.

Data for compound **225b**: R_f (2 : 1 petrol : ethyl acetate) 0.17; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3401 (O-H), 1682 (C=O); ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.25 (6H, m, Ph), 7.21–7.13 (4H, m, Ph), 4.30 (1H, s, C3H), 3.47 (1H, tt, J 11.5 and 3.5, C5H), 2.68 (1H, d, J 6.0, C7aH), 2.14–2.07 (1H, m, C4H_AH_B), 2.03 (1H, d, J 6.0, C7H), 1.89 (1H, dd, J 12.5 and 1.5, C6H_AH_B), 1.79 (1H, dt, J 12.0 and 6.0, C3aH), 1.40 (1H, td_{obs}, J 12.5 and 6.5, C6H_AH_B), 1.37 (9H, s, *t*-Bu), 1.14 (1H, q, J 12.0, C4H_AH_B), 0.28 (3H, s, PhMe_AMe_BSi), 0.26 (3H, s, PhMe_AMe_BSi); ¹³C NMR (125.8 MHz, CDCl₃) δ 178.7, 144.9, 140.6, 136.6, 131.9, 131.6, 130.7, 130.2, 128.2, 69.6, 69.1, 57.6, 45.4, 42.0, 41.7, 36.4, 30.8, 22.5, 0.0, -0.3; MS (ES⁺) m/z 481 (100%), 445 (15%, M + Na⁺), 422 (70%, M + H⁺); HRMS calc. for C₂₆H₃₆NO₂Si (M + H⁺) 422.2510, found 422.2502; ANAL. CALC. for C₂₆H₃₅NO₂Si: C, 74.06; H, 8.37; N, 3.32, found C, 74.06; H, 8.62; N, 3.22.

(3*R**,3*aR**,5*R**,6*S**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-6-methyl-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **226a**



(3*R**,3*aR**,5*S**,6*S**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-6-methyl-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **226b**



Sodium borohydride (0.0560 g, 1.48 mmol, 2.0 eq.) was added to a solution of ketone **218**[†] (0.3219 g, 0.740 mmol) in methanol (30 ml) at room temperature, and the mixture stirred for 2.5 h. The reaction was quenched with water (2 ml) and the solvent removed under reduced pressure. Diethyl ether (40 ml) was added and the mixture washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.323 g) as a white foam. Flash column chromatography (3 : 1 petrol : ethyl acetate) afforded compound **226a** (0.187 g, 58%) as a white solid, m.p. 179–182 °C, and compound **226b** (0.103 g, 32%) as a white gum.

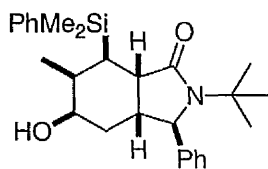
Data for compound **226a**: **R_f** (2 : 1 petrol : ethyl acetate) 0.52; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3429 (O–H), 1668 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.45–7.14 (10H, m, Ph), 4.38 (1H, s, C3H), 3.64 (1H, q, *J* 4.5, C5H), 2.76 (1H, dd, *J* 7.0 and 1.0, C7aH), 2.09–1.99 (1H, m, C3aH), 1.84–1.76 (2H, m, C6H and C7H), 1.75–1.68 (2H, m, C4H₂), 1.39 (9H, s, *t*-Bu), 1.00 (3H, d, *J* 7.0, C6Me), 0.31 (3H, s, PhMe_AMe_BSi), 0.28 (3H, s, PhMe_AMe_BSi); **¹³C NMR** (75.4 MHz, CDCl₃)

[†] See page 179

δ 177.5, 143.0, 138.7, 134.3, 129.2, 129.0, 128.0, 127.6, 125.5, 71.6, 67.7, 54.8, 38.7, 38.4, 35.4, 32.8, 28.1, 23.2, 21.5, -2.8, -3.0; **MS** (ES^+) m/z 536 (25%, $\text{M} - t\text{-Bu} + \text{PhMe}_2\text{Si} + \text{Na}^+$), 474 (15%, $\text{M} + \text{K}^+$), 458 (100%, $\text{M} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{27}\text{H}_{37}\text{NO}_2\text{SiNa}$ ($\text{M} + \text{Na}^+$) 458.2486, found 458.2480.

Data for compound **226b**: **R_f** (2 : 1 petrol : ethyl acetate) 0.32; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3400 (O-H), 1668 (C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.40–7.26 (6H, m, Ph), 7.23–7.11 (4H, m, Ph), 4.34 (1H, s, C3H), 3.62 (1H, dt, J 12.0 and 4.0, C5H), 2.63 (1H, d, J 6.5, C7aH), 2.14 (1H, qd, J 7.0 and 5.0, C6H), 2.01 (1H, s, C7H), 1.86–1.73 (2H, m, C3aH and C4H_AH_B), 1.61–1.53 (1H, m, C4H_AH_B), 1.38 (9H, s, $t\text{-Bu}$), 0.99 (3H, d, J 7.0, C6Me), 0.29 (3H, s, PhMe_AMe_BSi), 0.28 (3H, s, PhMe_AMe_BSi); **¹³C NMR** (75.4 MHz, CDCl_3) δ 177.2, 142.6, 138.1, 134.0, 129.3, 129.0, 128.1, 127.6, 125.5, 68.9, 66.8, 54.8, 43.1, 37.9, 34.4, 32.0, 28.1, 26.8, 14.4, -2.6, -2.9; **MS** (ES^+) m/z 536 (50%, $\text{M} - t\text{-Bu} + \text{PhMe}_2\text{Si} + \text{Na}^+$), 475 (15%, $\text{M} + \text{K}^+$), 458 (85%, $\text{M} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{27}\text{H}_{37}\text{NO}_2\text{SiNa}$ ($\text{M} + \text{Na}^+$) 458.2486, found 458.2488.

(3*R**,3*aR**,5*R**,6*R**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-6-methyl-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **228a**



A solution of ketone **218**[†] (1.33 g, 3.06 mmol, 1.0 eq.) and DBU (0.91 ml, 6.1 mmol, 2.0 eq.) in 1,2-dichloroethane (37 ml) was heated at reflux for 23 h. The solvent was removed under reduced pressure and the residue redissolved in DCM (50 ml). The solution was washed with 1 M aqueous HCl solution (2 × 50 ml), water (50 ml) and saturated aqueous NaHCO₃ solution (50 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give a crude mixture of α -methyl ketone epimers **218** and **227**[‡] (1.41 g) as a pale brown solid.

A solution of the crude mixture from the previous step and sodium borohydride (0.232 g, 6.14 mmol, 2.0 eq.) in methanol (120 ml) was stirred at room temperature for 2.5 h, quenched with water (8 ml) and the solvent removed under reduced pressure. The residue was redissolved in diethyl ether (150 ml) and the solution washed with water (2 × 80 ml) and brine (80 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give a crude mixture of α -methyl alcohols **226a**,[§] **226b**[§] and **228a** (1.30 g) as a white solid.

Purification using Horizon Biotage apparatus (25-S cartridge, hexane to 30% ethyl acetate/petrol) afforded (at 10–25% ethyl acetate/petrol) a mixture of **226a** and **228a** (0.892 g) as a white solid and (at 25–30% ethyl acetate/petrol) impure **226b** (0.341 g) as a white gum.

[†] See page 179

[‡] See Scheme 68 on page 82

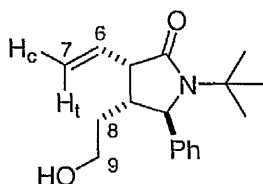
[§] See page 186

The mixture of **226a** and **228a** was separated by preparative HPLC,* using a Waters Sunfire OBD 5 μ m 30 \times 300 mm column, eluting with 60% B/A (0–2 min) then 60–90% B/A (2–8 min) (A = 0.1% aqueous trifluoroacetic acid solution; B = acetonitrile), to give **226a** (0.251 g, 19% from **218**) as a white solid, R_t 6.49 min, and **228a** (0.254 g, 19% from **218**) as a white gum, R_t 6.99 min, m.p. 179–181 °C.

A portion of impure **226b** was purified by preparative HPLC,* using a Waters Sunfire OBD 5 μ m 30 \times 300 mm column, eluting with 55% B/A (0–2 min) then 55–85% B/A (2–8 min) (A = 0.1% aqueous trifluoroacetic acid solution; B = acetonitrile), to give clean **226b** as a white solid, R_t 7.00 min.

Data for compound **228a**: R_f (2 : 1 petrol : ethyl acetate) 0.68; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3441 (O–H), 1665 (C=O); $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.38–7.10 (10H, m, Ph), 4.24 (1H, s, C3H), 3.72 (1H, m, C5H), 2.80 (1H, dd, J 5.5 and 2.0, C7aH), 1.95–1.78 (3H, m, C3aH, C4H_AH_B and C6H), 1.74 (1H, dd, J 5.5 and 3.0, C7H), 1.50–1.38 (1H, m, C4H_AH_B), 1.31 (9H, s, *t*-Bu), 1.08 (1H, d, J 5.0, OH), 0.92 (3H, d, J 7.0, C6Me), 0.33 (3H, s, PhMe_AMe_BSi), 0.29 (3H, s, PhMe_AMe_BSi); $^{13}\text{C NMR}$ (90.6 MHz, CDCl_3) δ 177.4, 143.3, 140.5, 135.0, 129.6, 129.5, 128.5, 128.2, 126.4, 71.5, 66.9, 55.7, 41.9, 39.3, 37.0, 36.1, 29.0, 25.5, 18.6, 0.2, 0.0; **MS** (ES^+) m/z 894 (50%, $2\text{M} + \text{Na}^+$), 495 (30%, $\text{M} + \text{NHMe}_3^+$), 474 (10%, $\text{M} + \text{K}^+$), 458 (100%, $\text{M} + \text{Na}^+$), 436 (5%, $\text{M} + \text{H}^+$); **HRMS** calc. for $\text{C}_{27}\text{H}_{37}\text{NO}_2\text{SiNa}$ ($\text{M} + \text{Na}^+$) 458.2486, found 458.2491; **ANAL. CALC.** for $\text{C}_{27}\text{H}_{35}\text{NO}_2\text{Si}$: C, 74.43; H, 8.56; N, 3.21, found C, 74.65; H, 8.86; N, 3.25.

* The HPLC purification was carried out by staff at Merck Sharp and Dohme, Terlings Park

(3*S**,4*R**,5*R**)-1-*tert*-butyl-4-(2-hydroxyethyl)-5-phenyl-3-vinylpyrrolidin-2-one, 232

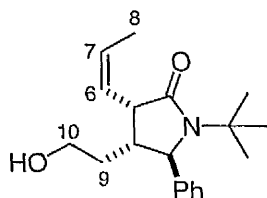
Iodobenzene diacetate (0.104 g, 0.321 mmol, 1.1 eq.) and iodine (0.0792 g, 0.312 mmol, 1.1 eq.) were added to a solution of alcohol **225a**[†] (0.125 g, 0.297 mmol, 1.0 eq.) in DCM (10 ml) at 0 °C. The resulting wine-red solution was heated at reflux for 2 h, cooled to room temperature, and quenched with saturated aqueous Na₂S₂O₃ solution (2 ml). The mixture was diluted with water (10 ml) and the aqueous phase extracted with DCM (3 × 10 ml). The combined organic extracts were washed with water (2 × 10 ml) and brine (10 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude intermediate aldehyde (0.148 g) as a yellow oil.

Sodium borohydride (0.0559 g, 1.48 mmol, 5.0 eq.) was added to a solution of the crude fragmented product in methanol (25 ml), and the mixture stirred at room temperature for 21.5 h. The reaction was carefully quenched with water (2 ml) and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (40 ml), and the solution washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.119 g) as a colourless oil. Flash column chromatography (2 : 1 petrol : ethyl acetate) afforded the title compound (0.0435 g, 51% over two steps) as a white gum.

R_f (2 : 1 petrol : ethyl acetate) 0.15; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3426 (O–H), 1668 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.44–7.27 (5H, m, Ph), 5.84 (1H, ddd, *J* 17.0, 10.5 and 8.5, C6H), 5.31 (1H, ddd, *J* 10.5, 2.0 and 0.5, C7H_c), 5.19 (1H,

[†] See page 184

ddd, J 17.0, 1.5 and 1.0, C7H₄), 4.81 (1H, s, C5H), 3.97–3.82 (2H, m, C9H₂), 3.52 (1H, t, J 8.0, C3H), 2.28 (1H, dddd, J 10.0, 7.5, 4.0 and 1.0, C4H), 1.90 (1H, dtd, J 14.0, 7.0 and 4.0, C8H_A), 1.62 (1H, ddt, J 14.0, 10.0 and 6.0, C8H_B), 1.39 (9H, s, *t*-Bu); ¹³C NMR (75.4 MHz, CDCl₃) δ 175.7, 143.2, 132.8, 129.1, 127.6, 125.8, 120.6, 65.3, 61.4, 55.2, 48.8, 45.5, 32.1, 28.3; MS (ES⁺) m/z 342 (15%, M + MeOH + Na⁺), 326 (75%, M + K⁺), 310 (100%, M + Na⁺), 288 (5%, M + H⁺); HRMS calc. for C₁₈H₂₅NO₂Na (M + Na⁺) 310.1778, found 310.1781.

(3*S**,4*R**,5*R**)-1-*tert*-butyl-4-(2-hydroxyethyl)-5-phenyl-3-((*Z*)-prop-1-enyl)pyrrolidin-2-one, 234

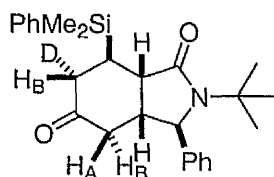
Iodobenzene diacetate (0.101 g, 0.314 mmol, 1.1 eq.) and iodine (0.0714 g, 0.281 mmol, 1.0 eq.) were added to a solution of alcohol **226a**[†] (0.125 g, 0.288 mmol, 1.0 eq.) in DCM (10 ml), and the resulting wine-red solution was heated at reflux for 2 h, allowed to cool to room temperature, and quenched with saturated aqueous Na₂S₂O₃ solution (2 ml). The mixture was diluted with water (10 ml) and the aqueous phase extracted with DCM (3 × 10 ml). The combined organic extracts were concentrated under reduced pressure and the residue dissolved in methanol (25 ml). Sodium borohydride (0.0545 g, 1.44 mmol, 5.0 eq.) was added and the mixture stirred at room temperature for 18 h. The reaction was carefully quenched with water (2 ml) and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (40 ml), and the solution washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.108 g) as a pale orange-brown gum. Flash column chromatography (2 : 1 petrol : ethyl acetate) afforded the title compound (0.0090 g, 10% over two steps) as a white gum.

R_f (2 : 1 petrol : ethyl acetate) 0.18; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3412 (O–H), 1668 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.45–7.37 (2H, m, Ph), 7.36–7.29 (3H, m, Ph), 5.79 (1H, dqd, *J* 11.0, 7.0 and 1.5, C7H), 5.53 (1H, ddq, *J* 10.5, 9.0 and 2.0, C6H), 4.79 (1H, s, C5H), 3.95–3.85 (2H, m, C10H₂), 3.80 (1H, td, *J* 8.0 and 0.5, C3H), 2.28 (1H, dddd, *J* 10.5, 7.5, 4.0 and 1.0, C4H), 1.85 (1H, dtd, *J* 14.0, 7.0 and 4.0, C9H_AH_B), 1.78–1.64 (1H, m, C9H_AH_B), 1.55 (3H, dd, *J* 7.0 and 1.5, C8H₃), 1.39 (9H, s, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 176.4, 143.5, 129.2,

[†] See page 186

129.2, 127.6, 125.8, 124.7, 65.3, 61.6, 55.1, 44.7, 42.4, 32.4, 28.3, 13.7; **MS** (ES^+) m/z 324 (100%, $\text{M} + \text{Na}^+$), 302 (40%, $\text{M} + \text{H}^+$); **HRMS** calc. for $\text{C}_{19}\text{H}_{27}\text{NO}_2\text{Na}$ ($\text{M} + \text{Na}^+$) 324.1934, found 324.1934.

(3*R**,3*aR**,6*S**,7*R**,7*aS**)-2-*tert*-Butyl-hexahydro-6-deutero-3-phenyl-7-dimethyl(phenyl)silyl-6*H*-isoindole-1,5-dione, 235



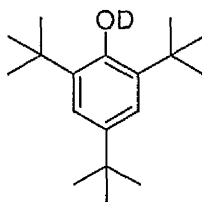
Diethylzinc (1.0 M in hexanes, 2.5 ml, 2.5 mmol, 1.4 eq.) was added to THF (10 ml) at 0 °C to give a pale blue solution. Phenyltrimethylsilyllithium (0.75 M in THF, 3.3 ml, 2.5 mmol, 1.4 eq.) was added at 0 °C over 2 min to give a wine-red solution, stirred at 0 °C for 5 min, and cooled to -78 °C. A solution of enone **48**[†] (0.505 g, 1.78 mmol, 1.0 eq.) in THF (20 ml) was added to give an orange-red solution, stirred at -78 °C for 30 min, and 0 °C for 80 min. The reaction was cooled to -78 °C and quenched by addition of a solution of 2,4,6-tri-*tert*-butylphen(ol-*d*) **237**[‡] (1.17 g, 4.42 mmol) in THF (10 ml) at -78 °C. The yellow reaction mixture was stirred at -78 °C for 10 min, and room temperature for 75 min. The reaction was quenched with saturated aqueous NH₄Cl solution (2.5 ml), diluted with water (20 ml), and the aqueous phase extracted with diethyl ether (2 × 20 ml). The combined organic extracts were washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude α-deutero ketone (2.39 g) as a yellow gum. Flash column chromatography (8 : 1 to 7 : 1 petrol : ethyl acetate) afforded the partially deuterated title compound (0.645 g, 86% total yield) as a yellow gum.

R_f (2 : 1 petrol : ethyl acetate) 0.53; ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.13 (10H, m, 2 × Ph), 4.33 (1H, s, C3H), 2.90 (1H, t, *J* 5.0, C7aH), 2.51 (0.90H, dd, *J* 14.5 and 5.0, C4H_AH_B), 2.40 (0.83H, dd, *J* 15.0 and 6.5, C6H_AH_B), 2.29 (1H, dd, *J* 14.5 and 11.5, C4H_AH_B), 2.24–2.15 (1H, m, C3aH), 2.10 (1H, dd, *J* 15.0 and

[†] See page 169

[‡] See page 196

7.0, C6H_AH_B), 2.04–1.93 (1H, m, C7H), 1.36 (9H, s, *t*-Bu), 0.31 (3H, s, PhMe_AMe_BSi), 0.28 (3H, s, PhMe_AMe_BSi).

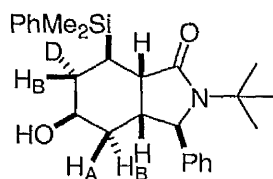
2,4,6-tri-*tert*-butylphen(ol-*d*), 237

Following the method of Stack *et al.*,¹⁰⁴ sodium hydride (60 wt% in mineral oil, 0.200 g, 8.34 mmol, 1.1 eq.) was added to a solution of 2,4,6-tri-*tert*-butylphenol (2.02 g, 7.69 mmol, 1.0 eq.) in DMSO-*d*₆ (20 ml) at room temperature, and the mixture stirred for 1 h. The resulting deep orange solution was quenched and saturated with D₂O (35 ml) to precipitate the product. The slurry was filtered, with D₂O washings, and dried under vacuum to yield the partially deuterated title compound (2.00 g, 99%) as a yellow solid, estimated to be 69% deuterated from proton NMR data.*

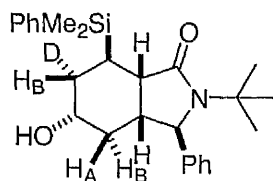
IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3644 (O–H), 2688 (O–D); **¹H NMR** (300 MHz, CDCl₃) δ 7.21 (2H, s, ArH), 5.05 (0.31H, s, OH), 1.46 (18H, s, 2- and 6-*t*-Bu), 1.31 (9H, s, 4-*t*-Bu).

* Deuterium content could not be determined by GC–MS, as previously used in the literature.¹⁰⁴

(3*R**,3*aR**,5*R**,6*S**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-6-deutero-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **238a**



(3*R**,3*aR**,5*S**,6*S**,7*R**,7*aS**)-2-*tert*-Butyl-octahydro-5-hydroxy-6-deutero-3-phenyl-7-(dimethylphenylsilyl)isoindol-1-one, **238b**



Sodium borohydride (0.117 g, 3.10 mmol, 2.0 eq.) was added to a solution of ketone **235**[†] (0.637 g, 1.52 mmol, 1.0 eq.) in methanol (60 ml) at room temperature, and the mixture stirred for 2 h. The reaction was quenched with water (3 ml) and the solvent removed under reduced pressure to leave a grey gum. The residue was dissolved in diethyl ether (50 ml), washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.650 g) as a white solid. Flash column chromatography afforded partially deuterated compounds **238a** (6 : 1 to 4 : 1 petrol : ethyl acetate, 0.327 g, 51% total yield) as a white solid, and **238b** (2 : 1 petrol : ethyl acetate, 0.168 g, 26% total yield) as a white solid.

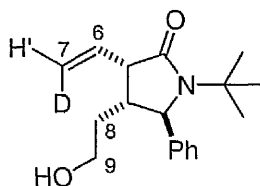
Data for compound **238a**: *R*_f (1 : 1 petrol : ethyl acetate) 0.57; ¹H NMR (500 MHz, CDCl₃) δ 7.41–7.38 (2H, m, Ph), 7.38–7.33 (2H, m, Ph), 7.31–7.26 (2H, m, Ph), 7.23–7.18 (4H, m, Ph), 4.28 (1H, s, C3H), 3.95 (1H, m, C5H), 2.75 (1H, dd, *J* 6.5 and 3.0, C7aH), 2.02 (1H, dt, *J* 11.0 and 5.5, C3aH),

[†] See page 194

1.78 (0.86H, dt, J 14.0 and 4.5, C6H_AH_B), 1.69–1.60 (2H, m, C6H_AH_B and C7H), 1.52–1.42 (~2H, m_{obs}, C4H_AH_B and C4H_AH_B), 1.33 (9H, s, *t*-Bu), 0.30 (3H, s, PhMe_AMe_BSi), 0.26 (3H, s, PhMe_AMe_BSi).

Data for compound **238b**: R_f (1 : 1 petrol : ethyl acetate) 0.36; ^1H NMR (500 MHz, CDCl₃) δ 7.36–7.24 (6H, m, Ph), 7.18–7.12 (4H, m, Ph), 4.27 (1H, s, C3H), 3.44 (1H, tt, J 11.5 and 4.0, C5H), 2.65 (1H, d, J 6.5, C7aH), 2.11–2.04 (~1H, m_{obs}, C4H_AH_B), 2.01 (1H, d, J 6.5, C7H), 1.89–1.82 (1H, m, C6H_AH_B), 1.77 (1H, dt, J 12.0 and 6.0, C3aH), 1.38 (~1H, td_{obs}, J 12.0 and 6.5, C6H_AH_B), 1.34 (9H, s, *t*-Bu), 1.11 (1H, q, J 12.0, C4H_AH_B), 0.25 (3H, s, PhMe_AMe_BSi), 0.24 (3H, s, PhMe_AMe_BSi).

(3*S**,4*R**,5*R**)-1-*tert*-butyl-4-(2-hydroxyethyl)-5-phenyl-3-((*Z*)-2-deuterovinyl)pyrrolidin-2-one, **239**



Iodobenzene diacetate (0.117 g, 0.362 mmol, 1.1 eq.) and iodine (0.0857 g, 0.336 mmol, 1.0 eq.) were added to a solution of alcohol **238a** (0.142 g, 0.336 mmol, 1.0 eq.) in DCM (12 ml) at room temperature, and the resulting wine-red solution heated at reflux for 2 h. The reaction was quenched with saturated aqueous Na₂S₂O₃ solution (2.5 ml) and allowed to cool to room temperature. The mixture was diluted with water (10 ml) and the aqueous phase extracted with DCM (10 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to give the crude intermediate aldehyde (0.210 g) as a yellow oil.

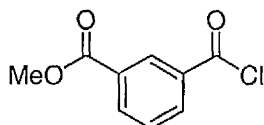
Sodium borohydride (0.0633 g, 1.67 mmol, 5.0 eq.) was added to a solution of the crude aldehyde in methanol (25 ml) at room temperature, and the mixture stirred at room temperature for 2 h. The reaction was carefully quenched with water (3 ml) and the solvent removed under reduced pressure. The residue was dissolved in DCM (40 ml), and the solution washed with water (2 × 20 ml) and brine (10 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.140 g) as a colourless gum. Flash column chromatography (2 : 1 petrol : ethyl acetate) afforded the partially purified title compound (0.0200 g) as a yellow gum.

R_f (1 : 1 petrol : ethyl acetate) 0.36; ¹H NMR (300 MHz, CDCl₃, alkenic region only) δ 5.85 (1H, ddd, *J* 17.0, 10.5 and 8.5, C6H), 5.32 (1H, ddd, *J* 10.5, 1.5 and 0.5, C7H'), 5.19 (0.93H, ddd, *J* 17.0, 1.5 and 1.0, C7H[†]), 4.80 (1H, s, C5H).

[†] partially deuterated

5.4 Experimental Details for Chapter 4

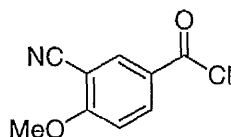
Methyl 3-(chlorocarbonyl)benzoate, 280¹⁰⁵



A suspension of *mono*-methyl isophthalate (0.906 g, 5.03 mmol) in thionyl chloride (6.0 ml, 83 mmol) was stirred at room temperature for 15 min, and heated at reflux for 75 min, until all solids had dissolved. The thionyl chloride was removed under reduced pressure to give the title compound (0.988 g, 99%) as a hygroscopic white wax.

R_f (1 : 1 petrol : ethyl acetate) 0.78; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1764 (acid chloride C=O), 1729 (ester C=O); **¹H NMR** (300 MHz, CDCl₃) δ 8.78–8.76 (1H, m, C2H), 8.38–8.27 (2H, m, C4H and C6H), 7.66–7.59 (1H, m, C5H), 3.97 (3H, s, OMe); **¹³C NMR** (75.4 MHz, CDCl₃) δ 168.1, 165.8, 136.3, 135.4, 134.0, 132.7, 131.6, 129.6, 52.9.

All data were consistent with those previously reported.¹⁰⁵

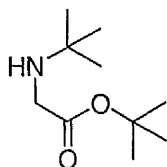
3-Cyano-4-methoxybenzoyl chloride, 281¹⁰⁶

Water (24 ml) and methanol (50 ml) were added to a mixture of methyl 3-cyano-4-methoxybenzoate (0.300 g, 1.57 mmol) and NaOH (6.43 g, 161 mmol), and the mixture was stirred at room temperature for 2 h, by which time one baseline spot was observed by thin layer chromatography (2 : 1 petrol : ethyl acetate). The methanol was removed under reduced pressure, and the resulting slurry was acidified to pH 1 by addition of concentrated HCl solution, precipitating the crude acid. The mixture was diluted with water (150 ml) to dissolve NaCl, and extracted with diethyl ether (3 × 75 ml). The combined organic extracts were washed with brine (50 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give crude 3-cyano-4-methoxybenzoic acid (0.288 g) as a pale yellow solid.

Thionyl chloride (0.37 ml, 5.10 mmol, 3.2 eq.) was added to a suspension of the acid in DCM (50 ml), and heated at reflux for 2 h until all solid had dissolved. The DCM and excess thionyl chloride were removed under reduced pressure to give the title compound (0.303 g, 99%) as a pale yellow solid.

R_f (2 : 1 petrol : ethyl acetate) 0.35; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2238 (C≡N); **¹H NMR** (300 MHz, CDCl₃) δ 8.41 (1H, dd, *J* 2.5 and 0.5, C2H), 8.35 (1H, dd, *J* 9.0 and 2.5, C6H), 7.14 (1H, d, *J* 9.0, C5H), 4.11 (3H, s, OMe); **¹³C NMR** (75.4 MHz, CDCl₃, COCl absent) δ 166.1, 137.9, 137.9, 126.4, 114.9, 111.9, 103.4, 57.2.

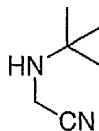
The title compound had not previously been characterised.¹⁰⁶

tert-Butyl 2-(*tert*-butylamino)acetate, 298¹⁰⁷

tert-Butylamine (2.7 ml, 26 mmol, 2.2 eq.) was added dropwise to a solution of *tert*-butyl bromoacetate (1.71 ml, 11.6 mmol, 1.0 eq.) in acetonitrile (30 ml) at room temperature. The solution was stirred at this temperature for 5.5 h, with precipitation. The solvent was removed under reduced pressure to leave a white solid, partitioned between saturated aqueous NaHCO₃ (60 ml), brine (60 ml) and DCM (50 ml); the aqueous phase was extracted with DCM (2 × 40 ml). The combined organic extracts were washed with water (2 × 30 ml) and brine (30 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound (2.02 g, 93%) as a yellow oil.

IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3331 (N–H), 2971 (C–H), 1737 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 3.23 (2H, s, CH₂), 1.55 (1H, br s, NH), 1.40 (9H, s, O–*t*-Bu), 1.03 (9H, s, N–*t*-Bu).

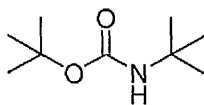
All data were consistent with those previously reported.¹⁰⁷

2-(*tert*-Butylamino)acetonitrile, 299¹⁰⁸

Following the method of Hamilton,⁷⁰ *tert*-butylamine (1.80 ml, 17.1 mmol, 2.2 eq.) was added dropwise to a solution of bromoacetonitrile (0.54 ml, 7.8 mmol, 1.0 eq.) in acetonitrile (20 ml) at room temperature. The solution was stirred at this temperature for 5 h, with precipitation. The solvent was removed under reduced pressure to leave a white solid, partitioned between saturated aqueous NaHCO₃ solution (40 ml), brine (40 ml) and DCM (40 ml); the aqueous phase was extracted with DCM (2 × 30 ml). The combined organic extracts were washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound (0.661 g, 76%) as a yellow oil.

IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3325 (N–H), 2245 (C≡N); **¹H NMR** (300 MHz, CDCl₃) δ 3.53 (2H, s, CH₂), 1.14 (9H, s, *t*-Bu).

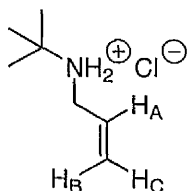
All data were consistent with those previously reported.¹⁰⁹

N,O-Di-*tert*-butylcarbamate, 306

Following the method of Chen *et al.*,⁹⁷ a solution of di-*tert*-butyl dicarbonate (4.18 g, 19.2 mmol, 1.5 eq.) in DCM (5 ml) was added to molybdenum(VI) dichloride dioxide (0.0254 g, 0.128 mmol, 0.01 eq.) in DCM (35 ml), to give a pale green solution. A solution of *tert*-butylamine (1.34 ml, 12.8 mmol, 1.0 eq.) in DCM (25 ml) was cannulated into the reaction mixture, with evolution of gas and yielding a pale grey, cloudy solution, stirred at room temperature for 17 h. The reaction mixture was washed with saturated aqueous NaHCO₃ solution (40 ml), water (3 × 40 ml) and brine (40 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (3.23 g) as a pale yellow oil. Flash column chromatography (15 : 1 petrol : ethyl acetate) afforded the title compound (0.890 g, 40%) as white needles, m.p. 45–47 °C (lit.¹¹⁰ 37–39 °C).

R_f (9 : 1 petrol : ethyl acetate) 0.48; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3359 (N–H), 1704 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 4.60–4.30 (1H, br s, NH), 1.40 (9H, s, O–*t*-Bu), 1.26 (9H, s, N–*t*-Bu).

Proton NMR data were consistent with those previously recorded.¹¹⁰

*N-tert-Butylprop-2-en-1-amine hydrochloride, 309*¹¹¹

Following the method of Tilley and Sayigh,⁹⁸ a solution of allyl bromide (6.20 ml, 71.6 mmol, 1.0 eq.) in DMF (15 ml) was added to a solution of *tert*-butylamine (15.0 ml, 143 mmol, 2.0 eq.) in DMF (55 ml) at 60 °C, at a rate so as to maintain the temperature below 85 °C during the addition. The resulting solution was heated at a slow reflux (130 °C) for 3 h. The DMF and unreacted *tert*-butylamine were removed by distillation, leaving a dark brown oil, which solidified on cooling. This residue was partitioned between 15% aqueous KOH solution (60 ml) and diethyl ether (120 ml), and the aqueous phase extracted with diethyl ether (2 × 60 ml). The combined organic extracts were distilled to give the crude free amine **301*** (1.34 g, 14%)[†] as a colourless liquid, b.p. 106–108 °C (lit.⁹⁸ 112 °C). HCl (2 M in diethyl ether, 5.4 ml, 10.8 mmol) was added to a solution of amine **301** in diethyl ether (5 ml), giving an exotherm. The solvent was evaporated to give the title compound (1.21 g, 11% over two steps) as a white solid, m.p. 176–178 °C.

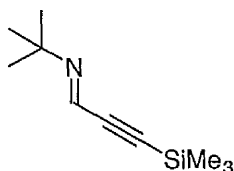
IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2437 (N⁺–H), 1651 (C=C); **¹H NMR** (300 MHz, CDCl₃) δ 9.80–9.20 (2H, br s, NH₂), 6.23 (1H, br dd, *J* 16.5 and 9.5, ArH_A), 5.47 (1H, d, *J* 16.5, ArH_B), 5.34 (1H, d, *J* 9.5, ArH_C), 3.53 (2H, s, CH₂), 1.47 (9H, s, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 129.5, 122.9, 57.6, 45.0, 26.5; **MS** (ES⁺) *m/z* 263 (10%, 2M – Cl[–]), 114 (100%, M – Cl[–]); **HRMS** calc. for C₇H₁₆N (M – Cl[–]) 114.1277, found 114.1280.

The title compound had not previously been characterised.¹¹¹

* See Scheme 101 on page 113

[†] Contaminated with approximately 25 mol% diethyl ether, accounted for in the quoted yield

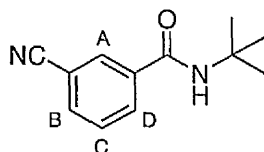
(E)-2-Methyl-N-(3-(trimethylsilyl)prop-2-ynylidene)propan-2-amine, 311^{100a}



tert-Butylamine (0.72 ml, 6.9 mmol, 1.0 eq.) was added to a slurry of 3-(trimethylsilyl)propynal (1.00 ml, 6.81 mmol, 1.0 eq.) and MgSO₄ (8.39 g) in DCM (50 ml) at room temperature, and the reaction mixture was stirred for 18 h. The solution was filtered and most of the solvent carefully removed under slightly reduced pressure, without heating, to give a concentrated DCM solution of the title compound (2.49 g), contaminated with approximately 10 mol% unreacted aldehyde.

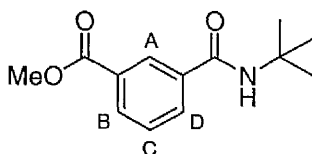
¹H NMR (300 MHz, CDCl₃) δ 7.48 (1H, s, N=CH), 1.19 (9H, s, *t*-Bu), 0.20 (9H, s, SiMe₃); MS (ES⁺) *m/z* 363 (15%, 2M + H⁺), 363 (20%, M + 2MeOH + H⁺), 182 (100%, M + H⁺); HRMS calc. for C₁₀H₂₀NSi (M + H⁺) 182.1360, found 182.1360.

Proton NMR data were consistent with those previously recorded.^{100a}

N-tert-Butyl-3-cyanobenzamide, 312

tert-Butylamine (0.69 ml, 6.6 mmol, 2.2 eq.) was added to a solution of 3-cyanobenzoyl chloride (0.492 g, 2.97 mmol, 1.0 eq.) in DCM (75 ml) at room temperature, and the reaction mixture was stirred for 4 h. The solution was washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound (0.573 g, 95%) as a white solid, m.p. 95–97 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.75; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3316 (br, N–H), 2233 (C≡N), 1645 (C=O), 1538 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 8.00 (1H, td, *J* 1.5 and 0.5, ArH_A), 7.96 (1H, ddd, *J* 8.0, 2.0 and 1.0, ArH_D), 7.75 (1H, dt, *J* 7.5 and 1.5, ArH_B), 7.55 (1H, td, *J* 8.0 and 0.5, ArH_C), 5.95 (1H, br s, NH), 1.48 (9H, s, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 164.9, 137.3, 134.5, 131.3, 130.7, 129.7, 118.3, 113.0, 52.4, 29.0; **MS** (ES⁺) *m/z* 203 (10%, M + H⁺), 147 (100%, M – *t*-Bu + H + H⁺); **HRMS** calc. for C₁₂H₁₅N₂O (M + H⁺) 203.1179, found 203.1183.

Methyl 3-(*tert*-butylcarbamoyl)benzoate, 313

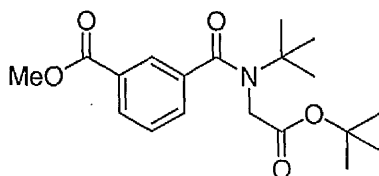
A suspension of *mono*-methyl isophthalate (2.48 g, 13.7 mmol, 1.0 eq.) in thionyl chloride (14.0 ml, 193 mmol, 14 eq.) was heated at reflux for 80 min, until all solids had dissolved. The thionyl chloride was removed under reduced pressure to give the intermediate acid chloride **280**^{*} as a white wax.

tert-Butylamine (3.2 ml, 31 mmol, 2.2 eq.) was added to a solution of the benzoyl chloride in DCM (120 ml) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. The solution was washed with water (2 × 30 ml) and brine (30 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (3.28 g) as a brown gum. Flash column chromatography (7 : 1 to 5 : 1 petrol : ethyl acetate) afforded the title compound (3.09 g, 95% over two steps) as a white solid, m.p. 77–79 °C (lit.¹¹² 77.5 °C).

R_f (2 : 1 petrol : ethyl acetate) 0.58; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3313 (br, N–H), 1732 (ester C=O), 1645 (amide C=O), 1538 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 8.25–8.21 (1H, br m, ArH_A), 8.03–7.96 (1H, br m, ArH_B), 7.91–7.85 (1H, br m, ArH_D), 7.43–7.31 (1H, m, ArH_C), 6.31 (1H, br s, NH), 3.85–3.81 (3H, m, OMe), 1.42 (9H, d, *J* 1.5, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 166.6, 166.2, 136.4, 132.0, 131.8, 130.3, 128.8, 127.7, 52.5, 52.0, 28.9; **MS** (ES⁺) *m/z* 493 (100%, 2M + Na⁺), 471 (25%, 2M + H⁺), 236 (65%, M + H⁺); **HRMS** calc. for C₁₃H₁₈NO₃ (M + H⁺) 236.1281, found 236.1277.

All data were consistent with those previously reported.¹¹²

* See page 200

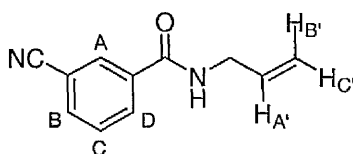
Methyl 3-(*N*-((*tert*-butoxycarbonyl)methyl)-*N*-*tert*-butylcarbamoyl)benzoate, 314

Triethylamine (1.1 ml, 7.9 mmol, 3.2 eq.) and *tert*-butyl 2-(*tert*-butylamino)acetate **298**^{*} (0.766 g, 4.09 mmol, 1.6 eq.) were added to a solution of methyl 3-(chlorocarbonyl)benzoate **280**[†] (0.497 g, 2.50 mmol, 1.0 eq.) in DCM (80 ml) at room temperature, and the reaction mixture was stirred for 17 h. The solution was washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (1.09 g) as a white solid. Flash column chromatography (8 : 1 to 5 : 1 petrol : ethyl acetate) afforded the title compound (0.860 g, 98%) as a white solid, m.p. 69–72 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.70; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 1729 (2 × ester C=O), 1651 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 8.05 (1H, td, *J* 1.5 and 0.5, C2H), 8.01 (1H, ddd, *J* 8.0, 1.5 and 1.5, ArH), 7.57 (1H, ddd, *J* 7.5, 1.5 and 1.5, ArH), 7.41 (1H, td, *J* 7.5 and 0.5, C5H), 3.87 (3H, s, OMe), 3.82 (2H, s, CH₂), 1.51 (9H, s, O-*t*-Bu), 1.41 (9H, s, N-*t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 172.4, 170.1, 166.6, 139.6, 130.9, 130.6, 130.5, 129.0, 127.4, 82.4, 58.2, 52.4, 50.7, 28.4, 28.1; **MS** (ES⁺) *m/z* 537 (100%, M + **298** + H⁺), 372 (5%, M + Na⁺), 350 (30%, M + H⁺); **HRMS** calc. for C₁₉H₂₈NO₅ (M + H⁺) 350.1962, found 350.1957.

^{*} See page 202

[†] See page 200

N-Allyl-3-cyanobenzamide, 319

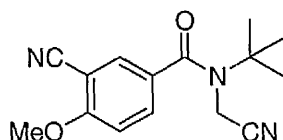
Sodium hydride (60 wt% in mineral oil, 0.119 g, 2.98 mmol, 2.0 eq.) was added to a solution of *N*-*tert*-butyl-3-cyanobenzamide **312**^{*} (0.303 g, 1.50 mmol, 1.0 eq.) in DMF (8 ml) at room temperature, with effervescence. The resulting cream solution was stirred at room temperature for 30 min. Allyl bromide (0.78 ml, 9.0 mmol, 6.0 eq.) was added to give an orange solution, stirred at room temperature for 15.5 h. Additional allyl bromide (0.78 ml, 9.0 mmol, 6.0 eq.) was added, and the mixture heated at 100 °C for 5.5 h. The reaction was quenched with saturated aqueous NH₄Cl solution (1 ml) and partitioned between diethyl ether (20 ml) and water (10 ml). The aqueous phase was extracted with diethyl ether (2 × 30 ml), and the combined organic extracts were washed with water (4 × 15 ml) and brine (15 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product mixture (0.451 g) as a brown oil. Flash column chromatography afforded unreacted starting material (6 : 1 to 5 : 1 petrol : ethyl acetate, 0.253 g, 84% recovery), and the title compound (5 : 1 to 4 : 1 petrol : ethyl acetate, 0.0396 g, 14%) as a pale yellow solid, m.p. 74–76 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.37; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2233 (C≡N), 1644 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 8.09 (1H, td, *J* 1.5 and 0.5, ArH_A), 8.04 (1H, ddd, *J* 8.0, 1.5 and 1.0, ArH_D), 7.76 (1H, dt, *J* 8.0 and 1.5, ArH_B), 7.55 (1H, td, *J* 8.0 and 0.5, ArH_C), 6.76 (1H, br t, *J* 5.5, NH), 5.91 (1H, ddt, *J* 17.0, 10.0 and 5.5, H_{A'}), 5.24 (1H, dq, *J* 17.0 and 1.5, H_{B'}), 5.18 (1H, dq, *J* 10.0 and 1.5, H_{C'}), 4.07 (2H, tt, *J* 5.5 and 1.5, CH₂); **¹³C NMR** (75.4 MHz, CDCl₃) δ 165.6, 135.9, 134.9, 133.8, 131.7, 131.1, 129.9, 118.3, 117.4, 113.1, 42.9; **MS** (ES⁺) *m/z* 241

^{*} See page 207

(55%, $M + \text{MeCN} + \text{Me}_3\text{NH}^+$), 209 (30%, $M + \text{Na}^+$), 187 (20%, $M + \text{H}^+$);

HRMS calc. for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}$ ($M + \text{H}^+$) 187.0866, found 187.0866.

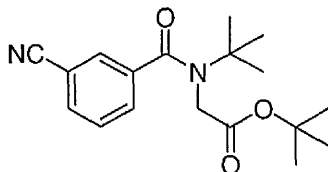
N-tert-Butyl-N-cyanomethyl-3-cyano-4-methoxybenzamide, 330

A solution of 3-cyano-4-methoxybenzoyl chloride **281**^{*} (0.0983 g, 0.503 mmol, 1.0 eq.) in DCM (10 ml) at 0 °C was cannulated into a solution of triethylamine (0.21 ml, 1.5 mmol, 3.0 eq.) and 2-(*tert*-butylamino)acetonitrile **299**[†] (0.0878 g, 0.783 mmol, 1.6 eq.) in DCM (10 ml) at 0 °C, and the reaction mixture stirred at room temperature for 21 h. The solution was sequentially washed with 1 M aqueous HCl solution (2 × 25 ml), water (25 ml) and brine (25 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.0917 g) as a pale yellow solid. Flash column chromatography (3 : 1 petrol : ethyl acetate) afforded the title compound (0.0266 g, 19%) as a white solid, m.p. 153–155 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.40; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2224 (C≡N), 1651 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.82–7.76 (2H, m, C2H and C6H), 7.09 (1H, dd, *J* 8.5 and 0.5, C5H), 4.12 (2H, s, CH₂), 4.02 (3H, s, OMe), 1.62 (9H, s, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 171.2, 162.8, 133.3, 133.3, 130.0, 117.5, 115.5, 111.9, 102.9, 59.1, 56.8, 36.5, 28.3; **MS** (ES⁺) *m/z* 581 (10%, 2M + K⁺), 565 (30%, 2M + Na⁺), 310 (20%, M + K⁺), 294 (100%, M + Na⁺), 272 (5%, M + H⁺); **HRMS** calc. for C₁₅H₁₈N₃O₂ (M + H⁺) 272.1394, found 272.1393.

^{*} See page 201

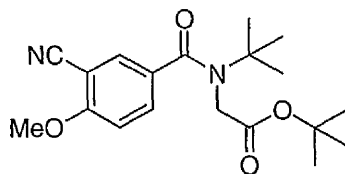
[†] See page 203

tert-Butyl 2-(*N*-*tert*-butyl-3-cyanobenzamido)acetate, 331

Triethylamine (1.2 ml, 8.6 mmol, 2.9 eq.) and *tert*-butyl 2-(*tert*-butylamino)acetate **298*** (0.754 g, 4.03 mmol, 1.4 eq.) were added to a solution of 3-cyanobenzoyl chloride (0.494 g, 2.98 mmol, 1.0 eq.) in DCM (80 ml) at room temperature, and the reaction mixture was stirred for 17 h. The solution was washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (1.16 g) as a yellow-brown oil. Flash column chromatography (8 : 1 to 4 : 1 petrol : ethyl acetate) afforded the title compound (0.936 g, 99%) as a white solid, m.p. 91–92 °C.

R_f (1 : 1 petrol : ethyl acetate) 0.66; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2232 (C≡N), 1739 (ester C=O), 1652 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.73 (1H, td, *J* 1.5 and 0.5, C2H), 7.69–7.62 (2H, m, C4H and C6H), 7.47 (1H, ddd, *J* 8.0, 7.5 and 0.5, C5H), 3.80 (2H, s, CH₂), 1.52 (9H, s, O-*t*-Bu), 1.45 (9H, s, N-*t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 171.0, 170.0, 140.4, 132.9, 130.9, 130.0, 129.7, 118.3, 113.0, 82.8, 58.5, 50.6, 28.3, 28.2; **MS** (ES⁺) *m/z* 504 (55%, M + **298** + H⁺), 317 (20%, M + H⁺), 188 (100%, **298** + H⁺); **HRMS** calc. for C₁₈H₂₅N₂O₃ (M + H⁺) 317.1860, found 317.1865.

* See page 202

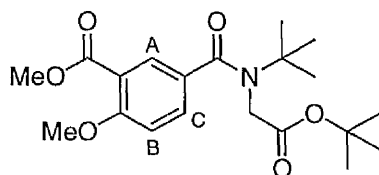
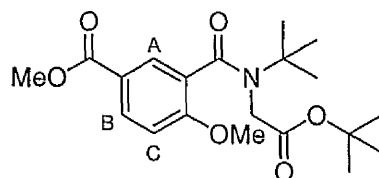
tert-Butyl 2-(*N*-*tert*-butyl-3-cyano-4-methoxybenzamido)acetate, **332**

Triethylamine (1.1 ml, 7.9 mmol, 3.1 eq.) and *tert*-butyl 2-(*tert*-butylamino)acetate **298**^{*} (0.471 g, 2.52 mmol, 1.0 eq.) were added to a solution of 3-cyano-4-methoxybenzoyl chloride **281**[†] (0.504 g, 2.58 mmol, 1.0 eq.) in DCM (80 ml) at room temperature, and the reaction mixture was stirred for 17 h. The solution was washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.898 g) as an orange-brown gum. Flash column chromatography (3 : 1 to 2 : 1 petrol : ethyl acetate) afforded the title compound (0.810 g, 93%) as a white gum.

R_f (2 : 1 petrol : ethyl acetate) 0.28; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2230 (C≡N), 1739 (ester C=O), 1647 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.70 (1H, d, *J* 2.0, C2H), 7.66 (1H, dd, *J* 8.5 and 2.0, C6H), 6.93 (1H, d, *J* 8.5, C5H), 3.93 (3H, s, OMe), 3.83 (2H, s, CH₂), 1.49 (9H, s, O-*t*-Bu), 1.45 (9H, s, N-*t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 171.4, 170.3, 162.0, 133.4, 132.3, 132.0, 115.9, 111.5, 102.0, 82.7, 58.3, 56.6, 50.9, 28.2, 28.2; **MS** (ES⁺) *m/z* 406 (30%, M + NHMe₃⁺), 385 (10%, M + K⁺), 369 (100%, M + Na⁺), 347 (30%, M + H⁺); **HRMS** calc. for C₁₉H₂₆N₂O₄Na (M + Na⁺) 369.1785, found 369.1785.

^{*} See page 202

[†] See page 201

Methyl 5-(*N*-((*tert*-butoxycarbonyl)methyl)-*N*-*tert*-butylcarbamoyl)-2-methoxybenzoate, 333Methyl 3-(*N*-((*tert*-butoxycarbonyl)methyl)-*N*-*tert*-butylcarbamoyl)-4-methoxybenzoate, 334

KOH (0.253 g, 4.50 mmol, 1.0 eq.) was added to a suspension of dimethyl 4-methoxyisophthalate (1.01 g, 4.49 mmol, 1.0 eq.) in methanol (30 ml) at 0 °C. The reaction was stirred at 0 °C for 2 h, room temperature for 2 h, and reflux for 20 h, then cooled to room temperature. The solvent was removed under reduced pressure, and the residue washed ethyl acetate, dissolved in water, and acidified to pH 1 by addition of concentrated HCl solution to precipitate the product acids. The suspension was extracted with DCM (200 ml then 50 ml), and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give a crude mixture of *mono*-methyl 4-methoxyisophthalates **287*** and **296*** (23 : 77 ratio), slightly contaminated with unreacted starting material (~6%), as a white solid (0.689 g), used in the next step without further purification. Concentration of the ethyl acetate wash under reduced pressure yielded unreacted starting material (0.209 g, 21%) as a white solid.

* See Scheme 97 on page 110

^1H NMR (300 MHz, CDCl_3) δ 8.28–8.25 (1H, m, C2H), 8.15–8.09 (1H, m, C6H), 7.31–7.26 (1H, $2 \times \text{d}$, J 9.0, C5H), 3.94 (3H, s, ArOMe), 3.87 ($0.77 \times 3\text{H}$, s, C3CO₂Me), 3.84 ($0.23 \times 3\text{H}$, s, C1CO₂Me); **MS** (ES^-) m/z 419 (10%, $2\text{M} - \text{H}^+$), 209 (100%, $\text{M} - \text{H}^+$).

A portion of the mixture of monohydrolysed esters from the previous step (0.570 g) was heated at reflux with thionyl chloride (6.0 ml) for 17.5 h, then cooled to room temperature. The solvent was removed under reduced pressure to give a crude mixture of acid chlorides **282*** and **297*** (0.608 g) as a white solid, used in the next step without further purification.

A solution of *tert*-butyl 2-(*tert*-butylamino)acetate **298**[†] (0.467 g, 2.49 mmol, 1.5 eq.) in DCM (8 ml) was cannulated into a solution of a portion of the mixture of acid chlorides from the previous step (0.390 g, 1.71 mmol, 1.0 eq.) and triethylamine (0.71 ml, 5.1 mmol, 3.0 eq.) in DCM (20 ml) at room temperature, washed in with additional DCM (2 ml). The reaction mixture was stirred at room temperature for 17 h, washed with water (2×15 ml) and brine (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.853 g) as a pale brown oil. Repeated flash column chromatography afforded compound **334** (7 : 1 to 6 : 1 petrol : ethyl acetate, 0.371 g, 34% over three steps) as a white solid, m.p. 67–69 °C, and compound **333** (5 : 1 petrol : ethyl acetate, 0.0202 g, 2% over three steps) as a pale yellow gum.

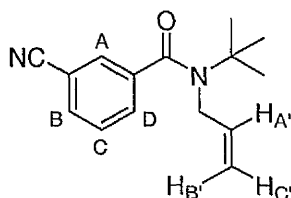
Data for compound **333**: **R_f** (1 : 1 petrol : ethyl acetate) 0.45; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1735 ($2 \times$ ester C=O), 1646 (amide C=O); **^1H NMR** (300 MHz, CDCl_3) δ 7.92 (1H, d, J 2.0, ArH_A), 7.59 (1H, dd, J 8.5 and 2.0, ArH_C), 6.94 (1H, d, J 8.5, ArH_B), 3.92 (3H, s, OMe), 3.87 (2H, s, CH₂), 3.85 (3H, s, OMe), 1.51 (9H, s, O-*t*-Bu), 1.45 (9H, s, N-*t*-Bu); **^{13}C NMR** (75.4 MHz, CDCl_3) δ 172.6, 170.5, 166.1, 160.1, 132.4, 131.1, 130.3, 120.0, 112.1, 82.3, 58.1, 56.4, 52.3, 50.9, 28.3, 28.1; **MS** (ES^+) m/z 443 (100%, $\text{M} + \text{MeCN} + \text{Na}^+$), 434 (60%,

* See Scheme 97 on page 110

† See page 202

M + MeOH + Na⁺), 402 (15%, M + Na⁺); **HRMS** calc. for C₂₀H₃₀NO₆ (M + H⁺) 380.2068, found 380.2072.

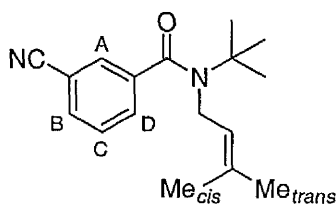
Data for compound **334**: **R_f** (1 : 1 petrol : ethyl acetate) 0.49; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 1741 (*t*-butyl ester C=O), 1726 (methyl ester C=O), 1650 (amide C=O); **¹H NMR** (300 MHz, CDCl₃) δ 8.00 (1H, dd, *J* 8.5 and 2.0, ArH_B), 7.90 (1H, d, *J* 2.0, ArH_A), 6.90 (1H, d, *J* 8.5, ArH_C), 3.89 (1H, d, *J* 19.0, CH_AH_B), 3.87 (3H, s, OMe), 3.84 (3H, s, OMe), 3.71 (1H, d, *J* 19.0, CH_AH_B), 1.54 (9H, s, O-*t*-Bu), 1.40 (9H, s, N-*t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 169.8, 169.5, 166.5, 158.5, 132.3, 129.4, 128.6, 122.9, 110.8, 82.4, 58.1, 56.3, 52.1, 50.1, 28.7, 28.0; **MS** (ES⁺) *m/z* 567 (100%, M + 298 + H⁺), 480 (25%, M + MeCN + Me₃NH⁺), 443 (30%, M + MeCN + Na⁺), 434 (35%, M + MeOH + Na⁺), 402 (30%, M + Na⁺), 266 (60%, M - CH₂CO₂^tBu + H + H⁺); **HRMS** calc. for C₂₀H₂₉NO₆Na (M + Na⁺) 402.1887, found 402.1869.

N-tert-Butyl-*N*-allyl-3-cyanobenzamide, 335

Triethylamine (1.60 ml, 11.5 mmol, 4.1 eq.) was added to a solution of *N*-tert-butylprop-2-en-1-amine hydrochloride **309*** (0.657 g, 4.39 mmol, 1.6 eq.) in DCM (8 ml). The resulting white slurry was cannulated into a solution of 3-cyanobenzoyl chloride (0.469 g, 2.83 mmol, 1.0 eq.) in DCM (50 ml), washed in with additional DCM (2 ml), and stirred at room temperature for 17.5 h. The reaction mixture was washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (0.667 g) as a yellow oil. Flash column chromatography (7 : 1 petrol : ethyl acetate) afforded the title compound (0.615 g, 90%) as a pale yellow oil.

R_f (2 : 1 petrol : ethyl acetate) 0.56; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2232 (C≡N), 1644 (C=O); **¹H NMR** (300 MHz, CDCl₃) δ 7.66–7.61 (2H, m, ArH_A and ArH_D), 7.58 (1H, dt, *J* 8.0 and 1.5, ArH_B), 7.46 (1H, t, *J* 8.0, ArH_C), 5.73 (1H, ddt, *J* 17.0, 10.5 and 5.0, H_{A'}), 5.18 (1H, dtd, *J* 10.5, 2.0 and 1.0, H_{C'}), 5.09 (1H, dtd, *J* 17.0, 2.0 and 1.0, H_{B'}), 3.85 (2H, dt, *J* 5.0 and 2.0, CH₂), 1.54 (9H, s, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 171.3, 140.7, 136.6, 132.6, 130.6, 129.9, 129.5, 118.5, 117.1, 112.8, 58.3, 50.1, 28.8; **MS** (ES⁺) *m/z* 507 (100%, 2M + Na⁺), 306 (25%, M + MeCN + Na⁺), 297 (60%, M + MeOH + Na⁺), 265 (20%, M + Na⁺), 243 (45%, M + H⁺); **HRMS** calc. for C₁₅H₁₉N₂O (M + H⁺) 243.1492, found 243.1484.

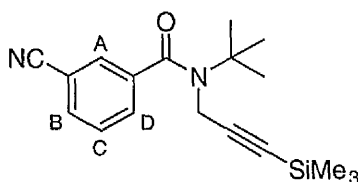
* See page 205

N-tert-Butyl-*N*-(3-methylbut-2-enyl)-3-cyanobenzamide, 336

3,3-Dimethylallyl bromide (0.20 ml, 1.7 mmol, 1.4 eq.) was added to a solution of *tert*-butylamine (0.18 ml, 1.7 mmol, 1.4 eq.) and triethylamine (0.84 ml, 6.0 mmol, 5.0 eq.) in acetonitrile (5 ml) at room temperature, and the reaction mixture stirred at this temperature for 8 days. A solution of 3-cyanobenzoyl chloride (0.200 g, 1.21 mmol) in acetonitrile (3 ml) was cannulated into the reaction mixture, washed in with further acetonitrile (0.5 ml). After 5 h at room temperature the solvent was removed under reduced pressure. The residue was partitioned between DCM (40 ml) and water (20 ml). The organic phase was washed with water (20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (0.231 g) as a brown gum. Flash column chromatography afforded the title compound (7 : 1 petrol : ethyl acetate, 0.0328 g, 10%) as a white solid, m.p. 60–62 °C, and secondary amide **312*** (6 : 1 to 4 : 1 petrol : ethyl acetate, 0.0917 g, 38%) as a white solid.

R_f (4 : 1 petrol : ethyl acetate) 0.38; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2231 ($\text{C}\equiv\text{N}$), 1639 ($\text{C}=\text{O}$); **^1H NMR** (300 MHz, CDCl_3) δ 7.64–7.59 (2H, m, ArH_A and ArH_D), 7.57 (1H, dt, J 8.0 and 1.5, ArH_B), 7.46 (1H, ddd, J 8.0, 7.0 and 1.5, ArH_C), 5.09 (2H, t hept, CH_2), 1.67 (3H, q, J 1.5, Me_{trans}), 1.52 (9H, s, *t*-Bu), 1.25 (3H, q, J 1.0, Me_{cis}); **^{13}C NMR** (75.4 MHz, CDCl_3) δ 171.2, 140.9, 133.8, 132.4, 130.9, 130.3, 129.5, 123.3, 118.5, 112.7, 57.9, 46.3, 28.9, 25.9, 17.8; **MS** (ES^+) m/z 563 (55%, $2\text{M} + \text{Na}^+$), 541 (30%, $2\text{M} + \text{H}^+$), 325 (60%, $\text{M} + \text{MeOH} + \text{Na}^+$), 293 (70%, $\text{M} + \text{Na}^+$), 271 (100%, $\text{M} + \text{H}^+$); **HRMS** calc. for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}$ ($\text{M} + \text{H}^+$) 271.1805, found 271.1803.

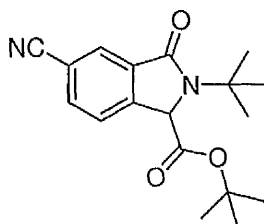
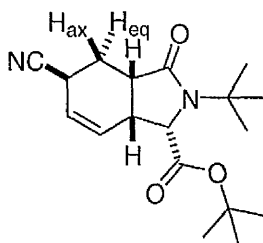
* See page 207

N-tert-Butyl-N-(3-(trimethylsilyl)prop-2-ynyl)-3-cyanobenzamide, 337

3-Bromo-1-trimethylsilyl-1-propyne (0.27 ml, 1.7 mmol, 1.4 eq.) was added to a solution of *tert*-butylamine (0.18 ml, 1.7 mmol, 1.4 eq.) and triethylamine (0.84 ml, 6.0 mmol, 5.0 eq.) in acetonitrile (5 ml) at room temperature, and the reaction mixture stirred at this temperature for 3 days, by which time a white precipitate was observed. A solution of 3-cyanobenzoyl chloride (0.202 g, 1.22 mmol) in acetonitrile (3 ml) was cannulated into the reaction mixture, washed in with further acetonitrile (0.5 ml). After 4 h at room temperature the solvent was removed under reduced pressure. The residue was partitioned between DCM (30 ml) and water (80 ml). The organic phase was washed with water (20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (0.138 g) as a beige solid. Flash column chromatography afforded the title compound (6 : 1 petrol : ethyl acetate, 0.0093 g, 2%) as a white solid, m.p. 76–78 °C, and secondary amide **312**^{*} (6 : 1 to 4 : 1 petrol : ethyl acetate, 0.0983 g, 40%) as a white solid.

R_f (2 : 1 petrol : ethyl acetate) 0.63; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2232 (C≡N), 2178 (C≡C), 1650 (C=O); **¹H NMR** (300 MHz, CDCl_3) δ 7.87 (1H, td, *J* 2.0 and 0.5, ArH_A), 7.75 (1H, dt, *J* 7.5 and 1.5, ArH_D), 7.68 (1H, dt, *J* 8.0 and 1.5, ArH_B), 7.51 (1H, td, *J* 8.0 and 0.5, ArH_C), 3.86 (2H, s, CH₂), 1.60 (9H, s, *t*-Bu), 0.21 (9H, s, SiMe₃); **¹³C NMR** (75.4 MHz, CDCl_3) δ 170.9, 140.0, 133.1, 131.1, 130.3, 129.6, 118.4, 112.9, 103.2, 90.7, 58.7, 38.6, 28.6, −0.1; **MS** (ES⁺) *m/z* 335 (50%, M + Na⁺), 313 (100%, M + H⁺), 239 (50%, M − SiHMe₃ + H⁺); **HRMS** calc. for C₁₈H₂₅N₂OSi (M + H⁺) 313.1731, found 313.1733.

* See page 207

(±)-tert-Butyl 2-tert-butyl-5-cyano-3-oxoisindoline-1-carboxylate, 338(1*S**,3*aS**,5*S**,7*aR**)-tert-Butyl 2-tert-butyl-5-cyano-2,3,3*a*,4,5,7*a*-hexahydro-3-oxo-1*H*-isindole-1-carboxylate, 339

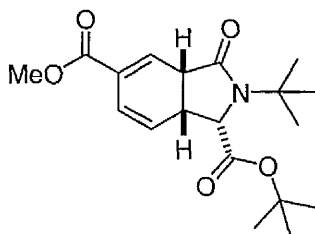
Lithium hexamethyldisilazide (1 M in toluene, 1.87 ml, 1.87 mmol, 3.0 eq.) was added to a solution of benzamide **331**[†] (0.197 g, 0.632 mmol, 1.0 eq.) in THF (20 ml) at -78°C , and the resulting deep orange solution was stirred at -78°C for 15 min, and 0°C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (2.5 ml) at 0°C , and warmed to room temperature. The solvent was removed under reduced pressure, and the residue partitioned between water (20 ml) and diethyl ether (40 ml). The organic phase was washed with water (20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.182 g) as an orange solid. Flash column chromatography (5 : 1 petrol : ethyl acetate) afforded an inseparable 7 : 4 mixture of compounds **338** and **339** (0.148 g) as a white gum.

R_f (2 : 1 petrol : ethyl acetate) 0.49; ¹H NMR (300 MHz, CDCl_3 , signals of rearomatised compound **338** labelled *) δ 8.03 (1H*, dd, *J* 1.5 and 1.0, C4H*),

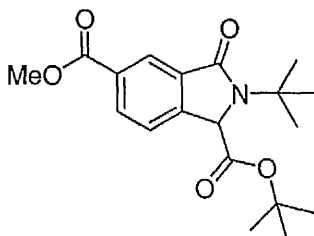
[†] See page 213

7.78 (1H*, dd, J 8.0 and 1.5, C6H*), 7.60 (1H*, dt, J 8.0 and 1.0, C7H*), 5.85 (1H, dt, J 10.0 and 1.0, C7H), 5.80 (1H, dt, J 10.0 and 2.5, C6H), 5.23 (1H*, d, J 0.5, C1H*), 3.82 (1H, br s, C1H), 3.27–3.18 (1H, m, C5H), 2.95 (1H, dt, J 7.5 and 3.5, C3aH), 2.84–2.78 (1H, dm, J 7.5, C7aH), 2.55 (1H, dddd, J 13.0, 4.5, 3.5 and 1.5, C4H_{eq}), 1.77 (1H, ddd, J 13.5, 11.5 and 4.0, C4H_{ax}), 1.55 (9H*, s, O-*t*-Bu*), 1.47 (9H, s, O-*t*-Bu), 1.44 (9H*, s, N-*t*-Bu*), 1.32 (9H, s, N-*t*-Bu); **MS** (ES⁺, fragments containing M = 338 labelled *) m/z 360 (10%, M + MeCN + H⁺), 356 (10%, M* + MeCN + H⁺), 341 (5%, M + Na⁺), 337 (5%, M* + Na⁺), 319 (40%, M + H⁺), 315 (45%, M* + H⁺), 263 (25%, M - *t*-Bu + H + H⁺), 259 (45%, M* - *t*-Bu + H + H⁺), 207 (50%, M - 2*t*-Bu + 2H + H⁺), 203 (100%, M* - 2*t*-Bu + 2H + H⁺).

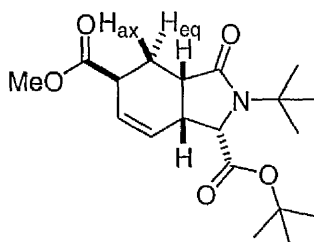
(1*S**,3*aS**,7*aR**)-1-*tert*-Butyl 5-methyl 2-*tert*-butyl-2,3,3*a*,7*a*-tetrahydro-3-oxo-1*H*-isoindole-1,5-dicarboxylate, **343**



(±)-1-*tert*-Butyl 5-methyl 2-*tert*-butyl-3-oxoisindoline-1,5-dicarboxylate, **344**



(1*S**,3*aS**,5*S**,7*aR**)-1-*tert*-Butyl 5-methyl 2-*tert*-butyl-2,3,3*a*,4,5,7*a*-hexahydro-3-oxo-1*H*-isoindole-1,5-dicarboxylate, **345**



Lithium hexamethyldisilazide (1 M in toluene, 1.71 ml, 1.71 mmol, 3.0 eq.) was added to a solution of benzamide **314**[†] (0.199 g, 0.568 mmol, 1.0 eq.) in THF (20 ml) at $-78\text{ }^{\circ}\text{C}$, and the resulting orange solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min, and $0\text{ }^{\circ}\text{C}$ for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (2.5 ml) at $0\text{ }^{\circ}\text{C}$, and warmed to room temperature. The solvent

[†] See page 209

was removed under reduced pressure, and the residue partitioned between water (20 ml) and diethyl ether (40 ml). The organic phase was washed with water (20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.180 g) as a pale yellow solid. Flash column chromatography afforded an inseparable 7 : 2 mixture of compounds **344**[†] and **345** (7 : 1 petrol : ethyl acetate, 0.141 g) as a white solid, and impure **343** (5 : 1 petrol : ethyl acetate, 0.0246 g) as a white solid. Recrystallisation of **343** by slow diffusion of *n*-pentane into an ethyl acetate solution of the impure sample yielded a crystal of **343** suitable for X-ray crystallographic analysis; this procedure was also accompanied by substantial rearomatisation to **344**.

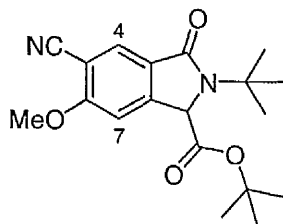
Data for impure compound **343**: R_f (2 : 1 petrol : ethyl acetate) 0.40; ^1H NMR (300 MHz, CDCl_3) δ 6.89 (1H, d, J 3.5, C4H), 6.47 (1H, d, J 10.0, C6H), 5.73 (1H, ddt, J 10.0, 5.5 and 1.0, C7H), 4.36 (1H, d, J 9.0, C1H), 3.74 (3H, s, OMe), 3.51 (1H, dd, J 14.0 and 3.0, C3aH), 3.30 (1H, dddd, J 14.0, 9.0, 5.5 and 1.0, C7aH), 1.57 (9H, s, O-*t*-Bu), 1.48 (9H, s, N-*t*-Bu); MS (ES^+) m/z 409 (50%, $\text{M} + \text{Me}_3\text{NH}^+$), 404 (85%, $\text{M} + \text{MeOH} + \text{Na}^+$), 372 (55%, $\text{M} + \text{Na}^+$), 367 (100%, $\text{M} + \text{NH}_4^+$), 350 (5%, $\text{M} + \text{H}^+$); HRMS calc. for $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_5$ ($\text{M} + \text{NH}_4^+$) 367.2227, found 367.2225.

n.O.e. (400 MHz, CDCl_3) data for compound **343**: irradiation at δ 4.36 (C1H) enhanced δ 5.73 (2.0%, C7H) and 3.30 (5.9%, C7aH); irradiation at δ 3.51 (C3aH) enhanced δ 6.89 (7.7%, C4H) and 3.30 (5.5%, C7aH); irradiation at δ 3.30 (C7aH) enhanced δ 5.73 (8.2%, C7H), 4.36 (7.5%, C1H) and 3.51 (2.8%, C3aH).

Data for mixture of compounds **344**[†] and **345** (rearomatised compound **344** labelled *): R_f (2 : 1 petrol : ethyl acetate) 0.61; ^1H NMR (300 MHz, CDCl_3) δ 8.42 (1H*, d, J 1.0, C4H*), 8.20 (1H*, dd, J 8.0 and 1.5, C6H*), 7.55 (1H*, d, J 8.0, C7H*), 6.00 (1H, dq, J 10.0 and 1.5, C6H), 5.70 (1H, dt, J 10.0 and 3.0, C7H), 5.21 (1H*, s, C1H*), 3.93 (3H*, s, OMe*), 3.82 (1H, s, C1H), 3.69 (3H, s, OMe), 3.12–3.02 (1H, m, C5H), 2.92 (1H, dt, J 7.5 and 4.0, C3aH), 2.77 (1H, dq,

[†] This compound was isolated in a subsequent reaction: see page 231 for full characterisation data

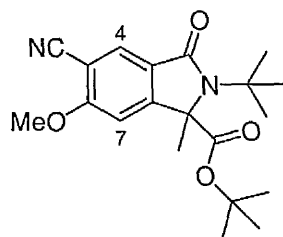
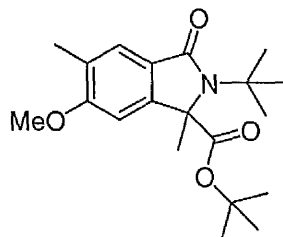
J 7.0 and 2.5, C7aH), 2.46 (1H, dddd, J 13.5, 5.0, 3.5 and 1.0, C4H_{eq}), 1.72–1.61 (1H, m_{obs} including J 13.5, C4H_{ax}), 1.57 (9H*, s, O-*t*-Bu*), 1.48 (9H, s, O-*t*-Bu), 1.43 (9H*, s, N-*t*-Bu*), 1.34 (9H, s, N-*t*-Bu); ^{13}C NMR (75.4 MHz, CDCl₃) δ 175.1, 174.4, 172.0, 168.7, 168.4, 166.5, 144.0, 134.3, 132.9 (C4*), 131.6, 129.1 and 128.1 (C6 and C7), 125.2 (C4*), 122.0 (C7*), 83.5, 82.5, 65.3 (C1), 64.1 (C1*), 55.8, 54.8, 52.7 (OMe*), 52.2 (OMe), 39.2, 37.6, 28.4, 28.2, 28.0, 28.0, 27.8, 23.4 (C4); MS (ES⁺) m/z 717 (20%, 2M* + Na⁺), 695 (15%, 2M* + H⁺), 393 (10%, M + MeCN + H⁺), 389 (35%, M* + MeCN + H⁺), 352 (40%, M + H⁺), 348 (100%, M* + H⁺), 296 (5%, M - *t*-Bu + H + H⁺), 292 (15%, M* - *t*-Bu + H + H⁺).

(±)-tert-Butyl 2-tert-butyl-5-cyano-6-methoxy-3-oxoisindoline-1-carboxylate, 354

Lithium hexamethyldisilazide (1 M in toluene, 1.36 ml, 1.36 mmol, 3.0 eq.) was added to a solution of benzamide **332*** (0.157 g, 0.453 mmol, 1.0 eq.) in THF (15 ml) at -78°C . The resulting orange solution was stirred at -78°C for 15 min, and 0°C for 100 min. The reaction was quenched with saturated aqueous NH_4Cl solution (2 ml), and partitioned between water (20 ml) and diethyl ether (20 ml). The aqueous phase was extracted with diethyl ether (20 ml); the combined organic extracts were washed with 1 M aqueous HCl solution (2×15 ml), water (2×15 ml) and brine (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.173 g) as a pale yellow solid. Flash column chromatography (5 : 1 petrol : ethyl acetate) afforded the title compound (0.0949 g, 61%) as a white solid, m.p. $200\text{--}201^{\circ}\text{C}$.

R_f (1 : 1 petrol : ethyl acetate) 0.54; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2230 ($\text{C}\equiv\text{N}$), 1748 (ester $\text{C}=\text{O}$), 1698 (lactam $\text{C}=\text{O}$); **¹H NMR** (300 MHz, CDCl_3) δ 7.95 (1H, s, C4H), 7.05 (1H, s, C7H), 5.16 (1H, d, J 0.5, C1H), 3.98 (3H, s, OMe), 1.55 (9H, s, O-*t*-Bu), 1.45 (9H, s, N-*t*-Bu); **¹³C NMR** (75.4 MHz, CDCl_3) δ 168.5, 167.3, 164.0, 146.1, 129.6, 126.7, 115.8, 104.7, 103.8, 83.9, 64.1, 56.9, 56.0, 28.0, 28.0; **MS** (ES^+) m/z 711 (45%, $2\text{M} + \text{Na}^+$), 367 (70%, $\text{M} + \text{Na}^+$), 345 (50%, $\text{M} + \text{H}^+$), 289 (60%, $\text{M} - t\text{-Bu} + \text{H} + \text{H}^+$), 233 (100%, $\text{M} - 2t\text{-Bu} + 2\text{H} + \text{H}^+$); **HRMS** calc. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}^+$) 345.1809, found 345.1817.

* See page 214

(±)-tert-Butyl 2-tert-butyl-5-cyano-6-methoxy-1-methyl-3-oxoisindoline-1-carboxylate, 355(±)-tert-Butyl 2-tert-butyl-6-methoxy-1,5-dimethyl-3-oxoisindoline-1-carboxylate, 356

Lithium hexamethyldisilazide (1 M in toluene, 1.35 ml, 1.35 mmol, 3.0 eq.) was added to a solution of benzamide **332**^{*} (0.156 g, 0.451 mmol, 1.0 eq.) in THF (15 ml) at -78°C , and the resulting orange solution was stirred at -78°C for 15 min, and 0°C for 100 min. The reaction was quenched with iodomethane (0.14 ml, 2.3 mmol, 5.1 eq.), stirred at 0°C for 75 min, and warmed to room temperature. The THF and surplus iodomethane were removed under reduced pressure, and the oily brown residue was partitioned between 1 M aqueous HCl solution (15 ml) and diethyl ether (20 ml). The aqueous phase was extracted with diethyl ether (3×20 ml), and the combined organic extracts were washed with water (2×20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.227 g) as a brown oil. Flash column chromatography afforded **356** (10 : 1 petrol : ethyl acetate, 0.0217 g, 14%)

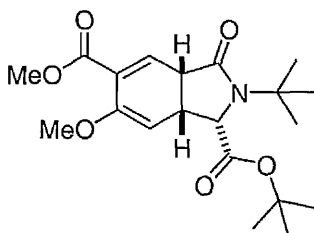
* See page 214

as a yellow gum, and **355** (8 : 1 to 5 : 1 petrol : ethyl acetate, 0.0837 g, 52%) as a pale yellow gum.

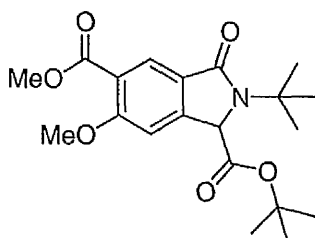
Data for compound **355**: R_f (2 : 1 petrol : ethyl acetate) 0.43; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2232 (C \equiv N), 1733 (ester C=O), 1695 (lactam C=O); **^1H NMR** (300 MHz, CDCl_3) δ 7.92 (1H, s, C4H), 6.83 (1H, s, C7H), 3.94 (3H, s, OMe), 1.85 (3H, s, C1Me), 1.58 (9H, s, N-*t*-Bu), 1.34 (9H, s, O-*t*-Bu); **^{13}C NMR** (75.4 MHz, CDCl_3) δ 170.5, 167.2, 164.3, 153.4, 129.8, 125.0, 115.8, 103.5, 102.8, 83.6, 70.5, 57.2, 57.0, 28.7, 27.8, 25.7; **MS** (ES^+) m/z 739 (75%, $2\text{M} + \text{Na}^+$), 717 (30%, $2\text{M} + \text{H}^+$), 381 (40%, $\text{M} + \text{Na}^+$), 359 (95%, $\text{M} + \text{H}^+$), 303 (75%, $\text{M} - t\text{-Bu} + \text{H} + \text{H}^+$), 247 (100%, $\text{M} - 2t\text{-Bu} + 2\text{H} + \text{H}^+$); **HRMS** calc. for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}^+$) 359.1965, found 359.1963.

Data for compound **356**: R_f (2 : 1 petrol : ethyl acetate) 0.58; **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 1730 (ester C=O), 1691 (lactam C=O); **^1H NMR** (300 MHz, CDCl_3) δ 7.49 (1H, d, J 0.5 C4H), 6.68 (1H, s, C7H), 3.84 (3H, s, OMe), 2.24 (3H, d, J 0.5, C5Me), 1.84 (3H, s, C1Me), 1.61 (9H, s, N-*t*-Bu), 1.35 (9H, s, O-*t*-Bu); **^{13}C NMR** (75.4 MHz, CDCl_3) δ 171.9, 169.7, 161.3, 147.1, 128.3, 125.3, 124.0, 100.9, 82.6, 70.1, 56.6, 56.0, 28.9, 27.8, 26.0, 16.8; **MS** (ES^+) m/z 717 (60%, $2\text{M} + \text{Na}^+$), 370 (40%, $\text{M} + \text{Na}^+$), 348 (75%, $\text{M} + \text{H}^+$), 314 (20%, $\text{M} - t\text{-Bu} + \text{H} + \text{Na}^+$), 292 (80%, $\text{M} - t\text{-Bu} + \text{H} + \text{H}^+$), 236 (100%, $\text{M} - 2t\text{-Bu} + 2\text{H} + \text{H}^+$); **HRMS** calc. for $\text{C}_{20}\text{H}_{30}\text{NO}_4$ ($\text{M} + \text{H}^+$) 348.2169, found 348.2163.

(1*S**,3*aS**,7*aR**)-1-*tert*-Butyl 5-methyl 2-*tert*-butyl-2,3,3*a*,7*a*-tetrahydro-6-methoxy-3-oxo-1*H*-isoindole-1,5-dicarboxylate, **357**



(±)-1-*tert*-Butyl 5-methyl 2-*tert*-butyl-6-methoxy-3-oxoisindoline-1,5-dicarboxylate, **358**

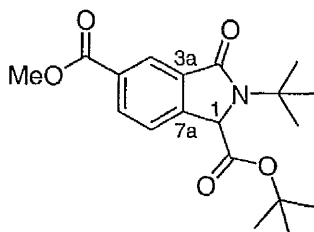
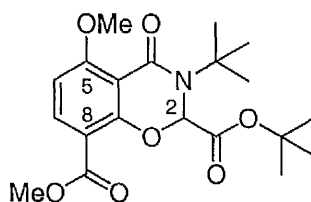
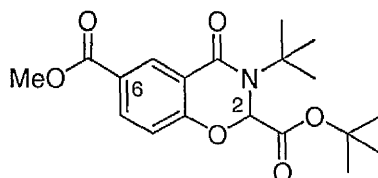


Lithium hexamethyldisilazide (1 M in toluene, 0.18 ml, 0.18 mmol, 3.1 eq.) was added to a solution of benzamide **333**[†] (0.0221 g, 0.0582 mmol, 1.0 eq.) in THF (3 ml) at -78°C , and the resulting orange solution was stirred at -78°C for 15 min, and 0°C for 75 min. The red reaction mixture was quenched with saturated aqueous NH_4Cl solution (0.5 ml) at 0°C , stirred for 30 min, and warmed to room temperature. The solvent was removed under reduced pressure, and the residue partitioned between water (10 ml) and diethyl ether (20 ml). The aqueous phase was extracted with diethyl ether (20 ml), and the combined organic extracts were washed with water (20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.0252 g) as an orange gum. Flash column chromatography afforded impure **357** (5 : 1 petrol : ethyl acetate, 0.0032 g, 15%) as a colourless gum, and impure **358** (3 : 1 petrol : ethyl acetate, 0.0035 g, 16%) as a colourless gum.

[†] See page 215

Data for impure compound **357**: R_f (2 : 1 petrol : ethyl acetate) 0.36; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.45 (1H, ddq, J 6.0, 3.0 and 0.5, C4H), 4.84 (1H, d, J 2.0, C7H), 4.35 (1H, d, J 8.5, C1H), 3.89 (1H, dd, J 6.5 and 5.5, C3aH), 3.78–3.69 (1H, m_{obs} , C7aH), 3.68 (3H, s, CO_2Me), 3.58 (3H, s, $\text{C}=\text{COMe}$), 1.42 (9H, s, O-*t*-Bu), 1.38 (9H, s, N-*t*-Bu); $^{13}\text{C NMR}$ (75.4 MHz, CDCl_3) δ 169.1, 168.6, 162.2, 145.1, 127.4, 126.2, 105.2, 102.2 83.6, 64.1, 56.9, 55.8, 52.7, 30.2, 28.3, 28.2; **MS** (ES^+) m/z 443 (100%, $\text{M} + \text{MeCN} + \text{Na}^+$), 402 (70%, $\text{M} + \text{Na}^+$), 380 (90%, $\text{M} + \text{H}^+$); **HRMS** calc. for $\text{C}_{20}\text{H}_{30}\text{NO}_6$ ($\text{M} + \text{H}^+$) 380.2068, found 380.2067.

Partial data for impure compound **358**: R_f (2 : 1 petrol : ethyl acetate) 0.30; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.14 (1H, s, C4H), 7.04 (1H, s, C7H), 5.13 (1H, s, C1H), 3.92 (3H, s, CO_2Me), 3.88 (3H, s, OMe), 1.54 (9H, s, O-*t*-Bu), 1.42 (9H, s, N-*t*-Bu); **MS** (ES^+) m/z 441 (25%, $\text{M} + \text{MeCN} + \text{Na}^+$), 432 (100%, $\text{M} + \text{MeOH} + \text{Na}^+$), 378 (70%, $\text{M} + \text{H}^+$); **HRMS** calc. for $\text{C}_{20}\text{H}_{28}\text{NO}_6$ ($\text{M} + \text{H}^+$) 378.1911, found 378.1911.

(±)-1-*tert*-Butyl 5-methyl 2-*tert*-butyl-3-oxoisindoline-1,5-dicarboxylate, **344**(±)-2-*tert*-Butyl 8-methyl 3-*tert*-butyl-3,4-dihydro-5-methoxy-4-oxo-2*H*-benzo[*e*][1,3]oxazine-2,8-dicarboxylate, **361**(±)-2-*tert*-Butyl 6-methyl 3-*tert*-butyl-3,4-dihydro-4-oxo-2*H*-benzo[*e*][1,3]oxazine-2,6-dicarboxylate, **362**

Lithium hexamethyldisilazide (1 M in toluene, 1.86 ml, 1.86 mmol, 6.0 eq.) was added to a solution of benzamide **334**^{*} (0.117 g, 0.309 mmol, 1.0 eq.) in THF (12 ml) at -78°C , and the resulting pale yellow solution was stirred at -78°C for 15 min, and 0°C for 90 min. (A colour change to deep orange-red was observed on warming to 0°C , which slowly faded to pale orange.) The reaction was quenched with saturated aqueous NH_4Cl solution (2 ml), warmed to room temperature, and the solvent removed under reduced pressure. The residue was

^{*} See page 215

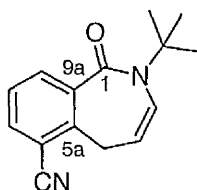
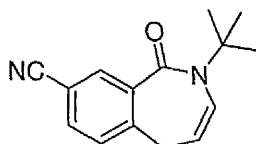
partitioned between diethyl ether (50 ml) and water (20 ml). The aqueous phase was extracted with diethyl ether (20 ml), and the combined organic extracts were washed with water (20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.1073 g) as a pale yellow gum. Flash column chromatography afforded compound **344** (9 : 1 to 8 : 1 petrol : ethyl acetate, 0.0087 g, 8%) as a white solid, m.p. 172–174 °C, compound **362** (8 : 1 petrol : ethyl acetate, 0.0044 g, 4%) as a white solid, m.p. 181–182 °C, and compound **361** (3 : 1 petrol : ethyl acetate, 0.0397 g, 34%) as a white solid, m.p. 162–166 °C.

Data for compound **344**: R_f (1 : 1 petrol : ethyl acetate) 0.76; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1728 ($2 \times$ ester $\text{C}=\text{O}$), 1688 (lactam $\text{C}=\text{O}$); ^1H **NMR** (300 MHz, CDCl_3) δ 8.43 (1H, d, J 1.0, C4H), 8.21 (1H, dd, J 8.0 and 1.5, C6H), 7.55 (1H, dt, J 8.0 and 1.0, C7H), 5.22 (1H, s, C1H), 3.94 (3H, s, OMe), 1.58 (9H, s, O-*t*-Bu), 1.44 (9H, s, N-*t*-Bu); ^{13}C **NMR** (75.4 MHz, CDCl_3) δ 168.7, 168.4, 166.5, 144.1, 134.3, 132.9, 131.6, 125.2, 122.0, 83.5, 64.1, 55.9, 52.7, 28.0, 28.0; **MS** (ES^+) m/z 434 (30%, $\text{M} + 2\text{MeOH} + \text{Na}^+$), 411 (30%, $\text{M} + \text{MeCN} + \text{Na}^+$), 402 (100%, $\text{M} + \text{MeOH} + \text{Na}^+$), 386 (5%, $\text{M} + \text{K}^+$); **HRMS** calc. for $\text{C}_{19}\text{H}_{26}\text{NO}_5$ ($\text{M} + \text{H}^+$) 348.1805, found 348.1806.

Data for compound **361**: R_f (1 : 1 petrol : ethyl acetate) 0.32; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1732 (*tert*-butyl ester $\text{C}=\text{O}$), 1697 (methyl ester and lactam $\text{C}=\text{O}$); ^1H **NMR** (300 MHz, CDCl_3) δ 8.02 (1H, d, J 9.0, C7H), 6.94 (1H, d, J 9.0, C6H), 5.97 (1H, s, C2H), 4.00 (3H, s, CO_2Me), 3.87 (3H, s, ArOMe), 1.59 (9H, s, O-*t*-Bu), 1.29 (9H, s, N-*t*-Bu); ^{13}C **NMR** (75.4 MHz, CDCl_3) δ 169.1, 167.0, 166.5, 160.5, 149.4, 136.4, 120.4, 116.4, 111.9, 89.9, 83.6, 57.5, 56.6, 52.8, 28.7, 27.8; **MS** (ES^+) m/z 457 (40%, $\text{M} + \text{MeCN} + \text{Na}^+$), 448 (100%, $\text{M} + \text{MeOH} + \text{Na}^+$), 416 (55%, $\text{M} + \text{Na}^+$); **HRMS** calc. for $\text{C}_{20}\text{H}_{28}\text{NO}_7$ ($\text{M} + \text{H}^+$) 394.1860, found 394.1861; **ANAL. CALC.** for $\text{C}_{20}\text{H}_{27}\text{NO}_7$: C, 61.06; H, 6.92; N, 3.56, found C, 60.63; H, 6.77; N, 3.47.

Data for compound **362**: R_f (1 : 1 petrol : ethyl acetate) 0.68; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1730 ($2 \times$ ester $\text{C}=\text{O}$), 1680 (lactam $\text{C}=\text{O}$);

¹H NMR (300 MHz, CDCl₃) δ 8.38 (1H, d, *J* 1.5, C5H), 8.20 (1H, dd, *J* 8.0 and 1.5, C7H), 7.34 (1H, d, *J* 8.0, C8H), 4.63 (1H, s, C2H), 3.94 (3H, s, OMe), 1.59 (9H, s, O-*t*-Bu), 1.35 (9H, s, N-*t*-Bu); **¹³C NMR** (75.4 MHz, CDCl₃) δ 171.3, 168.2, 166.3, 148.8, 133.8, 132.6, 132.5, 124.9, 120.4, 89.5, 85.6, 56.9, 52.7, 28.4, 27.7; **MS** (ES⁺) *m/z* 468 (15%, M + 2MeCN + Na⁺), 459 (10%, M + MeCN + MeOH + Na⁺), 450 (20%, M + 2MeOH + Na⁺), 427 (40%, M + MeCN + Na⁺), 418 (100%, M + MeOH + Na⁺); **HRMS** calc. for C₁₉H₂₆NO₆ (M + H⁺) 364.1755, found 364.1755.

(Z)-2-tert-Butyl-2,5-dihydro-1-oxo-1H-benzo[c]azepine-6-carbonitrile, **363**(Z)-2-tert-Butyl-2,5-dihydro-1-oxo-1H-benzo[c]azepine-8-carbonitrile, **366**

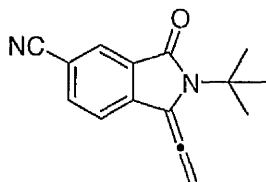
Lithium hexamethyldisilazide (1 M in toluene, 1.46 ml, 1.46 mmol, 3.0 eq.) was added to a solution of benzamide **335**^{*} (0.118 g, 0.488 mmol, 1.0 eq.) in THF (12 ml) at 0 °C, and the resulting orange-red solution was stirred at 0 °C for 15 min, and room temperature for 3.5 h. The reaction was quenched with saturated aqueous NH₄Cl solution (1.2 ml) and the solvent removed under reduced pressure. The residue was partitioned between diethyl ether (40 ml) and water (30 ml). The aqueous phase was extracted with diethyl ether (2 × 20 ml), and the combined organic extracts were washed with water (2 × 20 ml) and brine (20 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product mixture (0.0397 g) as an orange-brown oil. Flash column chromatography afforded a fraction containing approximately 50 mol% compound **363** (15 : 1 petrol : ethyl acetate, 0.0019 g) as an orange gum, and impure **366** (10 : 1 petrol : ethyl acetate, 0.0045 g) as a white solid.

Data for mixed fraction containing compound **363** (signals labelled *):
R_f (2 : 1 petrol : ethyl acetate) 0.69; ¹H NMR (300 MHz, CDCl₃) δ 8.05 (1H*, dd, *J* 8.0 and 1.5, C9H*), 7.64 (1H*, dd, *J* 7.5 and 1.5, C7H*), 7.35 (1H*, t, *J* 7.5,

* See page 218

C8H*), 6.22 (1H*, dd, J 7.5 and 2.0, C3H*), 6.16 (1H, d, J 7.5), 5.84 (1H, q, J 7.5), 5.71 (1H*, q_{obs}, J 7.5, C4H*), 5.74–5.66 (1H, m_{obs}), 5.62 (1H, dt, J 10.0 and 2.0), 4.52–4.42 (1H, m), 3.49 (2H*, d, J 7.5, C5H₂*), 2.99 (1H, ddd, J 7.5, 4.5 and 3.0), 2.92–2.78 (1H, m), 2.42 (1H, ddd, J 13.5, 6.0 and 2.5), 2.13 (1H, ddd, J 13.0, 7.5 and 5.5), 1.88 (1H, dddd, J 14.5, 13.0, 7.5 and 2.0), 1.74 (1H, ddd, J 13.5, 11.0 and 4.5), 1.59 (9H, s), 1.40 (9H*, s, *t*-Bu*).

Data for impure compound **366**: R_f (2 : 1 petrol : ethyl acetate) 0.61; ¹H NMR (300 MHz, CDCl₃) δ 8.15 (1H, d, J 1.5, C9H), 7.58 (1H, dd, J 8.0 and 1.5, C7H), 7.16 (1H, d, J 8.0, C6H), 6.12 (1H, d, J 7.5, C3H), 5.80 (1H, q, J 7.0, C4H), 3.27 (2H, d, J 7.0, C5H₂), 1.58 (9H, s, *t*-Bu).

2-*tert*-Butyl-1-oxo-3-vinylideneisoindoline-6-carbonitrile, **371**

3-Bromo-1-trimethylsilyl-1-propyne (1.69 ml, 10.8 mmol, 1.0 eq.) was added to a solution of *tert*-butylamine (2.5 ml, 24 mmol, 2.2 eq.) in acetonitrile (25 ml) at room temperature, and the reaction mixture stirred at this temperature for 6 h. The solvent was removed under reduced pressure and the residue partitioned between DCM (40 ml), brine (30 ml) and saturated aqueous NaHCO₃ solution (30 ml). The aqueous phase was extracted with DCM (2 × 30 ml) and the combined organic extracts washed with water (2 × 20 ml) and brine (20 ml), and dried (Na₂SO₄). Triethylamine (4.5 ml, 32 mmol, 3.0 eq.) and a solution of 3-cyanobenzoyl chloride (1.74 g, 10.5 mmol, 1.0 eq.) in DCM (3 ml) were added to the organic extracts. After 15 h at room temperature the reaction mixture was washed with water (2 × 30 ml) and brine (30 ml), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product (2.23 g) as a yellow oil. Flash column chromatography (6 : 1 petrol : ethyl acetate) afforded a mixed fraction containing 50 : 35 : 15 benzamide **337** : secondary amine **304** : tertiary amine **305** (1.73 g)* as a pale yellow oil (proportions estimated from proton NMR data).

Lithium hexamethyldisilazide (1 M in toluene, 1.91 ml, 1.91 mmol, 5.0 eq.) was added to a solution of partially purified benzamide **337** from the previous step (50 mol% **337**, 0.202 g, 0.382 mmol, 1.0 eq.) in THF (20 ml) at −78 °C, giving a gradual colour change to cherry-red. The solution was stirred at −78 °C for 15 min, and 0 °C for 70 min. The deep red-brown reaction mixture was quenched with saturated aqueous NH₄Cl solution (2 ml), and warmed to room temperature. The solvent was removed under reduced pressure, and the residue partitioned

* See Scheme 113 on page 122

between water (20 ml) and diethyl ether (40 ml). The aqueous phase was extracted with diethyl ether (20 ml), and the combined organic extracts were washed with water (2×20 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product mixture (0.161 g) as an orange solid. Flash column chromatography (9 : 1 petrol : ethyl acetate) afforded the title compound (0.0278 g, 31% from **337**, 10% over two steps) as a pale yellow solid, m.p. 114 °C (dec.).

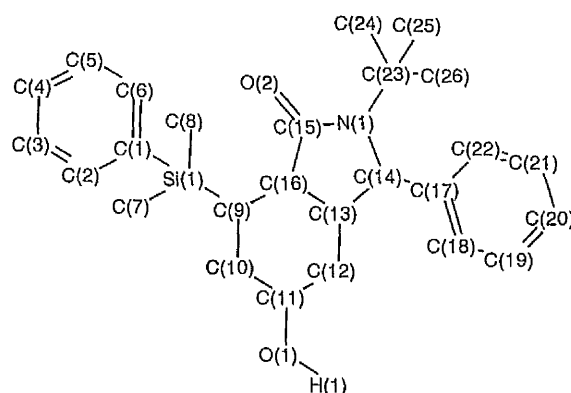
R_f (2 : 1 petrol : ethyl acetate) 0.75; **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2231 ($\text{C}\equiv\text{N}$), 1942 ($\text{C}=\text{C}=\text{C}$), 1710 ($\text{C}=\text{O}$); **¹H NMR** (300 MHz, CDCl_3) δ 8.09 (1H, s, C4H), 7.79 (1H, d, J 8.0, C6H), 7.52 (1H, d, J 8.0, C7H), 5.90 (2H, s, CH_2), 1.74 (9H, s, *t*-Bu); **¹³C NMR** (75.4 MHz, CDCl_3) δ 199.3, 164.8, 141.1, 134.8, 130.1, 127.8, 121.7, 118.8, 112.4, 110.9, 89.5, 59.0, 29.8; **MS** (CI^+) m/z 256 (45%, $\text{M} + \text{NH}_4^+$), 239 (100%, $\text{M} + \text{H}^+$); **HRMS** calc. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ (M^+) 238.1101, found 238.1103.

5.5 Detailed X-Ray Crystallographic Data

5.5.1 Data for Compound 225a

Crystal Data and Structural Refinement

Empirical Formula	$\text{C}_{26}\text{H}_{35}\text{NO}_2\text{Si}$	
Formula weight	421.64	
Crystal size	$1.00 \times 0.05 \times 0.02$ mm	
Temperature	100(2) K	
X-Ray Wavelength	0.71073 Å	
θ Range	2.00–25.03°	
Limiting Indices	$-12 \leq h \leq 13; -15 \leq k \leq 15; -20 \leq l \leq 20$	
Refinement Method	full-matrix least-squares on F^2	
R Factor	0.0628	
Crystal System	monoclinic	
Space Group	$P2_1/n$	
Unit cell dimensions	$a = 11.186(6)$ Å	$\alpha = 90^\circ$
	$b = 12.890(6)$ Å	$\beta = 102.533(8)^\circ$
	$c = 16.982(8)$ Å	$\gamma = 90^\circ$
Unit Cell Volume	$2390(2)$ Å ³	
Z	4	
Calculated Density	1.172 Mg m ⁻³	

Atomic LabelsAtomic Coordinates

	<i>x</i>	<i>y</i>	<i>z</i>
Si(1)	0.5061(1)	0.0784(1)	0.7728(1)
O(1)	0.6850(3)	0.6106(2)	0.8706(2)
O(2)	0.8488(3)	0.9273(3)	0.7111(2)
N(1)	0.8963(3)	0.7692(3)	0.6603(2)
C(1)	0.4258(4)	0.8880(4)	0.7102(3)
C(2)	0.3992(4)	0.8846(4)	0.6255(3)
C(3)	0.3366(5)	0.9648(4)	0.5796(3)
C(4)	0.3002(4)	1.0510(4)	0.6160(3)
C(5)	0.3248(4)	1.0557(4)	0.6992(3)
C(6)	0.3876(4)	0.9742(4)	0.7438(3)
C(7)	0.4578(4)	0.6572(3)	0.7163(3)
C(8)	0.4570(4)	0.7787(4)	0.8709(3)
C(9)	0.6763(4)	0.8108(4)	0.7879(3)
C(10)	0.7618(4)	0.7793(4)	0.8662(3)
C(11)	0.7957(4)	0.6685(3)	0.8702(3)
C(12)	0.8510(4)	0.6364(4)	0.7994(3)
C(13)	0.7705(4)	0.6626(3)	0.7174(3)
C(14)	0.8472(4)	0.6645(4)	0.6520(3)

C(15)	0.8294(4)	0.8351(4)	0.6963(3)
C(16)	0.7231(4)	0.7725(4)	0.7146(3)
C(17)	0.7732(4)	0.6375(4)	0.5695(3)
C(18)	0.7649(5)	0.5351(4)	0.5467(3)
C(19)	0.6908(5)	0.5038(4)	0.4737(4)
C(20)	0.6221(5)	0.5767(5)	0.4244(3)
C(21)	0.6284(5)	0.6785(4)	0.4456(3)
C(22)	0.7046(4)	0.7091(4)	0.5179(3)
C(23)	1.0077(4)	0.8049(4)	0.6318(3)
C(24)	1.0643(4)	0.7114(3)	0.5976(3)
C(25)	0.9750(4)	0.8877(3)	0.5671(3)
C(26)	1.1002(4)	0.8461(4)	0.7047(3)
H(1)	0.6843	0.5576	0.8438
H(2)	0.4240	0.8275	0.5996
H(3)	0.3191	0.9601	0.5237
H(4)	0.2597	1.1052	0.5851
H(5)	0.2997	1.1126	0.7251
H(6)	0.4045	0.9790	0.7997
H(7A)	0.4917	0.5987	0.7484
H(7B)	0.4866	0.6575	0.6670
H(7C)	0.3701	0.6526	0.7041
H(8A)	0.3693	0.7753	0.8611
H(8B)	0.4849	0.8412	0.8998
H(8C)	0.4916	0.7198	0.9022
H(9)	0.6806	0.8866	0.7861
H(10A)	0.8359	0.8206	0.8732
H(10B)	0.7229	0.7952	0.9106
H(11)	0.8553	0.6553	0.9207
H(12A)	0.9295	0.6706	0.8044
H(12B)	0.8657	0.5622	0.8021
H(13)	0.7027	0.6132	0.7032
H(14)	0.9149	0.6150	0.6667
H(16)	0.6551	0.7779	0.6675

H(18)	0.8097	0.4857	0.5807
H(19)	0.6878	0.4344	0.4584
H(20)	0.5709	0.5560	0.3762
H(21)	0.5821	0.7275	0.4120
H(22)	0.7095	0.7790	0.5319
H(24A)	1.1001	0.6655	0.6408
H(24B)	1.1265	0.7349	0.5708
H(24C)	1.0018	0.6753	0.5599
H(25A)	0.9236	0.8580	0.5198
H(25B)	1.0486	0.9140	0.5539
H(25C)	0.9323	0.9433	0.5866
H(26A)	1.0684	0.9078	0.7244
H(26B)	1.1757	0.8620	0.6891
H(26C)	1.1147	0.7945	0.7464

Bond Lengths (Å)

Si(1)–C(7)	1.851(5)	C(11)–H(11)	0.9800
Si(1)–C(8)	1.864(4)	C(12)–C(13)	1.523(6)
Si(1)–C(1)	1.876(5)	C(12)–H(12A)	0.9700
Si(1)–C(9)	1.911(5)	C(12)–H(12B)	0.9700
O(1)–C(11)	1.446(5)	C(13)–C(16)	1.510(6)
O(1)–H(1)	0.8200	C(13)–C(14)	1.544(6)
O(2)–C(15)	1.224(5)	C(13)–H(13)	0.9800
N(1)–C(15)	1.362(5)	C(14)–C(17)	1.505(6)
N(1)–C(14)	1.451(5)	C(14)–H(14)	0.9800
N(1)–C(23)	1.504(5)	C(15)–C(16)	1.523(6)
C(1)–C(6)	1.358(6)	C(16)–H(16)	0.9800
C(1)–C(2)	1.404(6)	C(17)–C(18)	1.372(6)
C(2)–C(3)	1.388(6)	C(17)–C(22)	1.385(6)
C(2)–H(2)	0.9300	C(18)–C(19)	1.394(7)
C(3)–C(4)	1.376(6)	C(18)–H(18)	0.9300
C(3)–H(3)	0.9300	C(19)–C(20)	1.377(7)

C(4)–C(5)	1.380(7)	C(19)–H(19)	0.9300
C(4)–H(4)	0.9300	C(20)–C(21)	1.360(6)
C(5)–C(6)	1.394(6)	C(20)–H(20)	0.9300
C(5)–H(5)	0.9300	C(21)–C(22)	1.391(6)
C(6)–H(6)	0.9300	C(21)–H(21)	0.9300
C(7)–H(7A)	0.9600	C(22)–H(22)	0.9300
C(7)–H(7B)	0.9600	C(23)–C(25)	1.519(6)
C(7)–H(7C)	0.9600	C(23)–C(26)	1.525(6)
C(8)–H(8A)	0.9600	C(23)–C(24)	1.533(6)
C(8)–H(8B)	0.9600	C(24)–H(24A)	0.9600
C(8)–H(8C)	0.9600	C(24)–H(24B)	0.9600
C(9)–C(10)	1.515(6)	C(24)–H(24C)	0.9600
C(9)–C(16)	1.533(6)	C(25)–H(25A)	0.9600
C(9)–H(9)	0.9800	C(25)–H(25B)	0.9600
C(10)–C(11)	1.476(5)	C(25)–H(25C)	0.9600
C(10)–H(10A)	0.9700	C(26)–H(26A)	0.9600
C(10)–H(10B)	0.9700	C(26)–H(26B)	0.9600
C(11)–C(12)	1.525(6)	C(26)–H(26C)	0.9600

Bond Angles (°)

C(7)–Si(1)–C(8)	110.8(2)	C(16)–C(13)–C(12)	111.8(4)
C(7)–Si(1)–C(1)	107.0(2)	C(16)–C(13)–C(14)	102.0(3)
C(8)–Si(1)–C(1)	107.9(2)	C(12)–C(13)–C(14)	110.6(4)
C(7)–Si(1)–C(9)	115.1(2)	C(16)–C(13)–H(13)	110.7
C(8)–Si(1)–C(9)	110.9(2)	C(12)–C(13)–H(13)	110.7
C(1)–Si(1)–C(9)	104.6(2)	C(14)–C(13)–H(13)	110.7
C(11)–O(1)–H(1)	109.5	N(1)–C(14)–C(17)	115.1(4)
C(15)–N(1)–C(14)	113.0(4)	N(1)–C(14)–C(13)	101.7(4)
C(15)–N(1)–C(23)	121.8(4)	C(17)–C(14)–C(13)	112.7(4)
C(14)–N(1)–C(23)	125.2(4)	N(1)–C(14)–H(14)	109.0
C(6)–C(1)–C(2)	116.1(5)	C(17)–C(14)–H(14)	109.0
C(6)–C(1)–Si(1)	122.2(4)	C(13)–C(14)–H(14)	109.0

C(2)–C(1)–Si(1)	121.7(4)	O(2)–C(15)–N(1)	127.4(5)
C(3)–C(2)–C(1)	121.3(5)	O(2)–C(15)–C(16)	125.7(5)
C(3)–C(2)–H(2)	119.3	N(1)–C(15)–C(16)	106.9(4)
C(1)–C(2)–H(2)	119.3	C(13)–C(16)–C(15)	102.7(4)
C(4)–C(3)–C(2)	120.8(5)	C(13)–C(16)–C(9)	117.1(4)
C(4)–C(3)–H(3)	119.6	C(15)–C(16)–C(9)	114.5(4)
C(2)–C(3)–H(3)	119.6	C(13)–C(16)–H(16)	107.3
C(3)–C(4)–C(5)	118.8(5)	C(15)–C(16)–H(16)	107.3
C(3)–C(4)–H(4)	120.6	C(9)–C(16)–H(16)	107.3
C(5)–C(4)–H(4)	120.6	C(18)–C(17)–C(22)	117.9(5)
C(4)–C(5)–C(6)	119.2(5)	C(18)–C(17)–C(14)	118.4(4)
C(4)–C(5)–H(5)	120.4	C(22)–C(17)–C(14)	123.5(4)
C(6)–C(5)–H(5)	120.4	C(17)–C(18)–C(19)	121.4(5)
C(1)–C(6)–C(5)	123.7(5)	C(17)–C(18)–H(18)	119.3
C(1)–C(6)–H(6)	118.1	C(19)–C(18)–H(18)	119.3
C(5)–C(6)–H(6)	118.1	C(20)–C(19)–C(18)	119.3(5)
Si(1)–C(7)–H(7A)	109.5	C(20)–C(19)–H(19)	120.3
Si(1)–C(7)–H(7B)	109.5	C(18)–C(19)–H(19)	120.3
H(7A)–C(7)–H(7B)	109.5	C(21)–C(20)–C(19)	120.5(5)
Si(1)–C(7)–H(7C)	109.5	C(21)–C(20)–H(20)	119.8
H(7A)–C(7)–H(7C)	109.5	C(19)–C(20)–H(20)	119.8
H(7B)–C(7)–H(7C)	109.5	C(20)–C(21)–C(22)	119.6(5)
Si(1)–C(8)–H(8A)	109.5	C(20)–C(21)–H(21)	120.2
Si(1)–C(8)–H(8B)	109.5	C(22)–C(21)–H(21)	120.2
H(8A)–C(8)–H(8B)	109.5	C(17)–C(22)–C(21)	121.3(5)
Si(1)–C(8)–H(8C)	109.5	C(17)–C(22)–H(22)	119.4
H(8A)–C(8)–H(8C)	109.5	C(21)–C(22)–H(22)	119.4
H(8B)–C(8)–H(8C)	109.5	N(1)–C(23)–C(25)	111.2(4)
C(10)–C(9)–C(16)	111.4(4)	N(1)–C(23)–C(26)	108.1(4)
C(10)–C(9)–Si(1)	118.7(3)	C(25)–C(23)–C(26)	110.9(4)
C(16)–C(9)–Si(1)	109.1(3)	N(1)–C(23)–C(24)	108.6(4)
C(10)–C(9)–H(9)	105.6	C(25)–C(23)–C(24)	109.4(4)
C(16)–C(9)–H(9)	105.6	C(26)–C(23)–C(24)	108.5(4)

Si(1)–C(9)–H(9)	105.6	C(23)–C(24)–H(24A)	109.5
C(11)–C(10)–C(9)	114.0(4)	C(23)–C(24)–H(24B)	109.5
C(11)–C(10)–H(10A)	108.8	H(24A)–C(24)–H(24B)	109.5
C(9)–C(10)–H(10A)	108.8	C(23)–C(24)–H(24C)	109.5
C(11)–C(10)–H(10B)	108.8	H(24A)–C(24)–H(24C)	109.5
C(9)–C(10)–H(10B)	108.8	H(24B)–C(24)–H(24C)	109.5
H(10A)–C(10)–H(10B)	107.6	C(23)–C(25)–H(25A)	109.5
O(1)–C(11)–C(10)	106.7(4)	C(23)–C(25)–H(25B)	109.5
O(1)–C(11)–C(12)	111.0(4)	H(25A)–C(25)–H(25B)	109.5
C(10)–C(11)–C(12)	111.7(4)	C(23)–C(25)–H(25C)	109.5
O(1)–C(11)–H(11)	109.1	H(25A)–C(25)–H(25C)	109.5
C(10)–C(11)–H(11)	109.1	H(25B)–C(25)–H(25C)	109.5
C(12)–C(11)–H(11)	109.1	C(23)–C(26)–H(26A)	109.5
C(13)–C(12)–C(11)	113.6(4)	C(23)–C(26)–H(26B)	109.5
C(13)–C(12)–H(12A)	108.8	H(26A)–C(26)–H(26B)	109.5
C(11)–C(12)–H(12A)	108.8	C(23)–C(26)–H(26C)	109.5
C(13)–C(12)–H(12B)	108.8	H(26A)–C(26)–H(26C)	109.5
C(11)–C(12)–H(12B)	108.8	H(26B)–C(26)–H(26C)	109.5
H(12A)–C(12)–H(12B)	107.7		

Intermolecular Hydrogen Bond Lengths (Å)

O(1)–H...O(2)	1.92	O(1)...O(2)	2.725(5)
---------------	------	-------------	----------

Intermolecular Hydrogen Bond Angles (°)

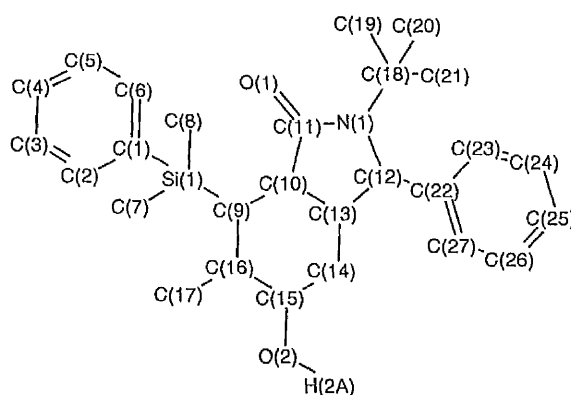
O(1)–H...O(2)	167.8
---------------	-------

5.5.2 Data for Compound 226a

Crystal Data and Structural Refinement

Empirical Formula	$\text{C}_{27}\text{H}_{37}\text{NO}_2\text{Si}$	
Formula weight	435.67	
Crystal size	$0.25 \times 0.10 \times 0.05$ mm	
Temperature	100(2) K	
X-Ray Wavelength	0.71073 Å	
θ Range	1.35–26.37°	
Limiting Indices	$-18 \leq h \leq 18; -8 \leq k \leq 8; -29 \leq l \leq 29$	
Refinement Method	full-matrix least-squares on F^2	
R Factor	0.0787	
Crystal System	monoclinic	
Space Group	$P2_1/n$	
Unit cell dimensions	$a = 15.080(2)$ Å	$\alpha = 90^\circ$
	$b = 6.7280(10)$ Å	$\beta = 90.056(3)^\circ$
	$c = 23.965(4)$ Å	$\gamma = 90^\circ$
Unit Cell Volume	$2431.4(6)$ Å ³	
Z	4	
Calculated Density	1.190 Mg m ⁻³	

Atomic Labels



Atomic Coordinates

	x	y	z
Si(1)	0.5973(1)	0.1430(2)	0.9026(1)
O(1)	0.8453(2)	-0.0429(4)	1.0068(1)
O(2)	0.7966(2)	0.6847(4)	0.9289(1)
N(1)	0.8158(2)	0.1997(5)	1.0716(1)
C(1)	0.6147(3)	0.1784(6)	0.8260(2)
C(2)	0.5924(2)	0.3505(7)	0.7981(2)
C(3)	0.6076(3)	0.3739(7)	0.7415(2)
C(4)	0.6465(3)	0.2242(7)	0.7110(2)
C(5)	0.6714(3)	0.0514(7)	0.7379(2)
C(6)	0.6556(3)	0.0299(7)	0.7944(2)
C(7)	0.5108(2)	0.3213(6)	0.9266(2)
C(8)	0.5568(3)	-0.1146(6)	0.9151(2)
C(9)	0.7092(2)	0.1661(6)	0.9374(2)
C(10)	0.7072(2)	0.1481(6)	1.0019(2)
C(11)	0.7969(3)	0.0887(6)	1.0261(2)
C(12)	0.7443(3)	0.3366(6)	1.0861(2)
C(13)	0.6844(2)	0.3411(6)	1.0331(2)
C(14)	0.7001(3)	0.5239(6)	0.9971(2)
C(15)	0.7804(3)	0.5050(6)	0.9600(2)

C(16)	0.7665(3)	0.3421(6)	0.9162(2)
C(17)	0.8553(3)	0.2687(6)	0.8927(2)
C(18)	0.9015(3)	0.1842(6)	1.1031(2)
C(19)	0.9755(3)	0.2421(6)	1.0634(2)
C(20)	0.9018(3)	0.3267(7)	1.1523(2)
C(21)	0.9138(3)	-0.0294(6)	1.1242(2)
C(22)	0.6929(3)	0.2760(6)	1.1381(2)
C(23)	0.6720(3)	0.0803(6)	1.1497(2)
C(24)	0.6209(3)	0.0301(7)	1.1955(2)
C(25)	0.5897(3)	0.1773(8)	1.2302(2)
C(26)	0.6110(3)	0.3734(8)	1.2197(2)
C(27)	0.6618(3)	0.4212(7)	1.1739(2)
H(2)	0.5658	0.4562	0.8183
H(3)	0.5911	0.4943	0.7235
H(4)	0.6561	0.2395	0.6720
H(5)	0.6992	-0.0525	0.7175
H(6)	0.6732	-0.0898	0.8123
H(7A)	0.4535	0.2850	0.9103
H(7B)	0.5268	0.4560	0.9149
H(7C)	0.5066	0.3167	0.9674
H(8A)	0.5447	-0.1327	0.9550
H(8B)	0.6021	-0.2099	0.9032
H(8C)	0.5022	-0.1368	0.8938
H(9)	0.7421	0.0451	0.9249
H(10)	0.6627	0.0444	1.0124
H(12)	0.7699	0.4720	1.0921
H(13)	0.6207	0.3372	1.0447
H(14A)	0.6471	0.5471	0.9735
H(14B)	0.7076	0.6412	1.0216
H(15)	0.8336	0.4726	0.9833
H(16)	0.7335	0.4042	0.8845
H(17A)	0.8902	0.3826	0.8797
H(17B)	0.8443	0.1784	0.8613

H(17C)	0.8882	0.1983	0.9219
H(19A)	0.9766	0.1494	1.0319
H(19B)	1.0324	0.2369	1.0831
H(19C)	0.9652	0.3773	1.0496
H(20A)	0.8961	0.4635	1.1387
H(20B)	0.9576	0.3127	1.1730
H(20C)	0.8519	0.2959	1.1770
H(21A)	0.8642	-0.0648	1.1487
H(21B)	0.9695	-0.0391	1.1451
H(21C)	0.9154	-0.1207	1.0924
H(23)	0.6931	-0.0218	1.1257
H(24)	0.6075	-0.1052	1.2030
H(25)	0.5536	0.1442	1.2613
H(26)	0.5905	0.4751	1.2439
H(27)	0.6758	0.5566	1.1668
H(2A)	0.8140	0.7743	0.9507

Bond Lengths (Å)

C(1)-C(2)	1.379(5)	C(14)-H(14A)	0.9900
C(1)-C(6)	1.398(5)	C(14)-H(14B)	0.9900
C(1)-Si(1)	1.871(4)	C(15)-O(2)	1.441(4)
C(2)-C(3)	1.386(5)	C(15)-C(16)	1.532(5)
C(2)-H(2)	0.9500	C(15)-H(15)	1.0000
C(3)-C(4)	1.375(6)	C(16)-C(17)	1.535(5)
C(3)-H(3)	0.9500	C(16)-H(16)	1.0000
C(4)-C(5)	1.381(6)	C(17)-H(17A)	0.9800
C(4)-H(4)	0.9500	C(17)-H(17B)	0.9800
C(5)-C(6)	1.383(5)	C(17)-H(17C)	0.9800
C(5)-H(5)	0.9500	C(18)-N(1)	1.499(5)
C(6)-H(6)	0.9500	C(18)-C(19)	1.517(5)
C(7)-Si(1)	1.864(4)	C(18)-C(20)	1.520(5)
C(7)-H(7A)	0.9800	C(18)-C(21)	1.535(5)

C(7)–H(7B)	0.9800	C(19)–H(19A)	0.9800
C(7)–H(7C)	0.9800	C(19)–H(19B)	0.9800
C(8)–Si(1)	1.862(4)	C(19)–H(19C)	0.9800
C(8)–H(8A)	0.9800	C(20)–H(20A)	0.9800
C(8)–H(8B)	0.9800	C(20)–H(20B)	0.9800
C(8)–H(8C)	0.9800	C(20)–H(20C)	0.9800
C(9)–C(10)	1.551(5)	C(21)–H(21A)	0.9800
C(9)–C(16)	1.553(5)	C(21)–H(21B)	0.9800
C(9)–Si(1)	1.887(4)	C(21)–H(21C)	0.9800
C(9)–H(9)	1.0000	C(22)–C(23)	1.382(5)
C(10)–C(11)	1.525(5)	C(22)–C(27)	1.383(5)
C(10)–C(13)	1.537(5)	C(23)–C(24)	1.385(5)
C(10)–H(10)	1.0000	C(23)–H(23)	0.9500
C(11)–O(1)	1.238(4)	C(24)–C(25)	1.376(6)
C(11)–N(1)	1.352(5)	C(24)–H(24)	0.9500
C(12)–N(1)	1.461(5)	C(25)–C(26)	1.381(6)
C(12)–C(22)	1.523(5)	C(25)–H(25)	0.9500
C(12)–C(13)	1.559(5)	C(26)–C(27)	1.376(6)
C(12)–H(12)	1.0000	C(26)–H(26)	0.9500
C(13)–C(14)	1.522(5)	C(27)–H(27)	0.9500
C(13)–H(13)	1.0000	O(2)–H(2A)	0.8400
C(14)–C(15)	1.507(5)		

Bond Angles (°)

C(2)–C(1)–C(6)	116.4(4)	C(14)–C(15)–H(15)	109.6
C(2)–C(1)–Si(1)	123.3(3)	C(16)–C(15)–H(15)	109.6
C(6)–C(1)–Si(1)	120.2(3)	C(15)–C(16)–C(17)	111.3(3)
C(1)–C(2)–C(3)	122.0(4)	C(15)–C(16)–C(9)	113.4(3)
C(1)–C(2)–H(2)	119.0	C(17)–C(16)–C(9)	111.2(3)
C(3)–C(2)–H(2)	119.0	C(15)–C(16)–H(16)	106.9
C(4)–C(3)–C(2)	120.5(5)	C(17)–C(16)–H(16)	106.9
C(4)–C(3)–H(3)	119.7	C(9)–C(16)–H(16)	106.9

C(2)–C(3)–H(3)	119.7	C(16)–C(17)–H(17A)	109.5
C(3)–C(4)–C(5)	119.0(4)	C(16)–C(17)–H(17B)	109.5
C(3)–C(4)–H(4)	120.5	H(17A)–C(17)–H(17B)	109.5
C(5)–C(4)–H(4)	120.5	C(16)–C(17)–H(17C)	109.5
C(4)–C(5)–C(6)	119.9(5)	H(17A)–C(17)–H(17C)	109.5
C(4)–C(5)–H(5)	120.1	H(17B)–C(17)–H(17C)	109.5
C(6)–C(5)–H(5)	120.1	N(1)–C(18)–C(19)	107.5(3)
C(5)–C(6)–C(1)	122.2(4)	N(1)–C(18)–C(20)	110.4(3)
C(5)–C(6)–H(6)	118.9	C(19)–C(18)–C(20)	108.8(4)
C(1)–C(6)–H(6)	118.9	N(1)–C(18)–C(21)	109.5(3)
Si(1)–C(7)–H(7A)	109.5	C(19)–C(18)–C(21)	111.0(4)
Si(1)–C(7)–H(7B)	109.5	C(20)–C(18)–C(21)	109.6(4)
H(7A)–C(7)–H(7B)	109.5	C(18)–C(19)–H(19A)	109.5
Si(1)–C(7)–H(7C)	109.5	C(18)–C(19)–H(19B)	109.5
H(7A)–C(7)–H(7C)	109.5	H(19A)–C(19)–H(19B)	109.5
H(7B)–C(7)–H(7C)	109.5	C(18)–C(19)–H(19C)	109.5
Si(1)–C(8)–H(8A)	109.5	H(19A)–C(19)–H(19C)	109.5
Si(1)–C(8)–H(8B)	109.5	H(19B)–C(19)–H(19C)	109.5
H(8A)–C(8)–H(8B)	109.5	C(18)–C(20)–H(20A)	109.5
Si(1)–C(8)–H(8C)	109.5	C(18)–C(20)–H(20B)	109.5
H(8A)–C(8)–H(8C)	109.5	H(20A)–C(20)–H(20B)	109.5
H(8B)–C(8)–H(8C)	109.5	C(18)–C(20)–H(20C)	109.5
C(10)–C(9)–C(16)	113.4(3)	H(20A)–C(20)–H(20C)	109.5
C(10)–C(9)–Si(1)	114.6(3)	H(20B)–C(20)–H(20C)	109.5
C(16)–C(9)–Si(1)	114.6(3)	C(18)–C(21)–H(21A)	109.5
C(10)–C(9)–H(9)	104.2	C(18)–C(21)–H(21B)	109.5
C(16)–C(9)–H(9)	104.2	H(21A)–C(21)–H(21B)	109.5
Si(1)–C(9)–H(9)	104.2	C(18)–C(21)–H(21C)	109.5
C(11)–C(10)–C(13)	103.6(3)	H(21A)–C(21)–H(21C)	109.5
C(11)–C(10)–C(9)	112.5(3)	H(21B)–C(21)–H(21C)	109.5
C(13)–C(10)–C(9)	115.0(3)	C(23)–C(22)–C(27)	118.1(4)
C(11)–C(10)–H(10)	108.5	C(23)–C(22)–C(12)	122.3(4)
C(13)–C(10)–H(10)	108.5	C(27)–C(22)–C(12)	119.5(4)

C(9)–C(10)–H(10)	108.5	C(22)–C(23)–C(24)	121.2(4)
O(1)–C(11)–N(1)	125.0(4)	C(22)–C(23)–H(23)	119.4
O(1)–C(11)–C(10)	124.6(4)	C(24)–C(23)–H(23)	119.4
N(1)–C(11)–C(10)	110.4(3)	C(25)–C(24)–C(23)	119.7(5)
N(1)–C(12)–C(22)	113.7(3)	C(25)–C(24)–H(24)	120.2
N(1)–C(12)–C(13)	104.2(3)	C(23)–C(24)–H(24)	120.2
C(22)–C(12)–C(13)	112.2(3)	C(24)–C(25)–C(26)	119.8(4)
N(1)–C(12)–H(12)	108.8	C(24)–C(25)–H(25)	120.1
C(22)–C(12)–H(12)	108.8	C(26)–C(25)–H(25)	120.1
C(13)–C(12)–H(12)	108.8	C(27)–C(26)–C(25)	119.9(4)
C(14)–C(13)–C(10)	111.9(3)	C(27)–C(26)–H(26)	120.0
C(14)–C(13)–C(12)	112.8(3)	C(25)–C(26)–H(26)	120.0
C(10)–C(13)–C(12)	104.5(3)	C(26)–C(27)–C(22)	121.3(5)
C(14)–C(13)–H(13)	109.2	C(26)–C(27)–H(27)	119.4
C(10)–C(13)–H(13)	109.2	C(22)–C(27)–H(27)	119.4
C(12)–C(13)–H(13)	109.2	C(11)–N(1)–C(12)	112.6(3)
C(15)–C(14)–C(13)	113.0(3)	C(11)–N(1)–C(18)	123.3(3)
C(15)–C(14)–H(14A)	109.0	C(12)–N(1)–C(18)	124.1(3)
C(13)–C(14)–H(14A)	109.0	C(15)–O(2)–H(2A)	109.5
C(15)–C(14)–H(14B)	109.0	C(8)–Si(1)–C(7)	108.64(19)
C(13)–C(14)–H(14B)	109.0	C(8)–Si(1)–C(1)	108.83(19)
H(14A)–C(14)–H(14B)	107.8	C(7)–Si(1)–C(1)	108.64(18)
O(2)–C(15)–C(14)	111.7(3)	C(8)–Si(1)–C(9)	107.41(18)
O(2)–C(15)–C(16)	105.5(3)	C(7)–Si(1)–C(9)	115.88(18)
C(14)–C(15)–C(16)	110.8(3)	C(1)–Si(1)–C(9)	107.26(17)
O(2)–C(15)–H(15)	109.6		

Torsion Angles (°)

C(6)–C(1)–C(2)–C(3)	1.5(6)
Si(1)–C(1)–C(2)–C(3)	178.7(3)
C(1)–C(2)–C(3)–C(4)	–0.3(7)
C(2)–C(3)–C(4)–C(5)	–1.0(7)

C(3)–C(4)–C(5)–C(6)	1.1(7)
C(4)–C(5)–C(6)–C(1)	0.1(7)
C(2)–C(1)–C(6)–C(5)	–1.3(6)
Si(1)–C(1)–C(6)–C(5)	–178.7(3)
C(16)–C(9)–C(10)–C(11)	–67.7(4)
Si(1)–C(9)–C(10)–C(11)	158.1(3)
C(16)–C(9)–C(10)–C(13)	50.6(4)
Si(1)–C(9)–C(10)–C(13)	–83.5(4)
C(13)–C(10)–C(11)–O(1)	–168.9(4)
C(9)–C(10)–C(11)–O(1)	–44.0(6)
C(13)–C(10)–C(11)–N(1)	11.2(4)
C(9)–C(10)–C(11)–N(1)	136.0(4)
C(11)–C(10)–C(13)–C(14)	103.0(4)
C(9)–C(10)–C(13)–C(14)	–20.3(5)
C(11)–C(10)–C(13)–C(12)	–19.4(4)
C(9)–C(10)–C(13)–C(12)	–142.6(3)
N(1)–C(12)–C(13)–C(14)	–100.6(4)
C(22)–C(12)–C(13)–C(14)	135.9(4)
N(1)–C(12)–C(13)–C(10)	21.2(4)
C(22)–C(12)–C(13)–C(10)	–102.3(4)
C(10)–C(13)–C(14)–C(15)	–36.9(5)
C(12)–C(13)–C(14)–C(15)	80.6(4)
C(13)–C(14)–C(15)–O(2)	–176.6(3)
C(13)–C(14)–C(15)–C(16)	66.1(4)
O(2)–C(15)–C(16)–C(17)	79.4(4)
C(14)–C(15)–C(16)–C(17)	–159.5(3)
O(2)–C(15)–C(16)–C(9)	–154.4(3)
C(14)–C(15)–C(16)–C(9)	–33.3(5)
C(10)–C(9)–C(16)–C(15)	–21.8(5)
Si(1)–C(9)–C(16)–C(15)	112.4(3)
C(10)–C(9)–C(16)–C(17)	104.5(4)
Si(1)–C(9)–C(16)–C(17)	–121.3(3)
N(1)–C(12)–C(22)–C(23)	–39.2(6)

C(13)–C(12)–C(22)–C(23)	78.8(5)
N(1)–C(12)–C(22)–C(27)	144.1(4)
C(13)–C(12)–C(22)–C(27)	–97.9(5)
C(27)–C(22)–C(23)–C(24)	0.4(7)
C(12)–C(22)–C(23)–C(24)	–176.3(4)
C(22)–C(23)–C(24)–C(25)	0.4(7)
C(23)–C(24)–C(25)–C(26)	–1.3(7)
C(24)–C(25)–C(26)–C(27)	1.3(7)
C(25)–C(26)–C(27)–C(22)	–0.4(7)
C(23)–C(22)–C(27)–C(26)	–0.4(7)
C(12)–C(22)–C(27)–C(26)	176.4(4)
O(1)–C(11)–N(1)–C(12)	–177.2(4)
C(10)–C(11)–N(1)–C(12)	2.7(5)
O(1)–C(11)–N(1)–C(18)	3.4(7)
C(10)–C(11)–N(1)–C(18)	–176.7(3)
C(22)–C(12)–N(1)–C(11)	107.2(4)
C(13)–C(12)–N(1)–C(11)	–15.3(4)
C(22)–C(12)–N(1)–C(18)	–73.4(5)
C(13)–C(12)–N(1)–C(18)	164.1(4)
C(19)–C(18)–N(1)–C(11)	62.0(5)
C(20)–C(18)–N(1)–C(11)	–179.4(4)
C(21)–C(18)–N(1)–C(11)	–58.7(5)
C(19)–C(18)–N(1)–C(12)	–117.3(4)
C(20)–C(18)–N(1)–C(12)	1.3(6)
C(21)–C(18)–N(1)–C(12)	121.9(4)
C(2)–C(1)–Si(1)–C(8)	139.6(3)
C(6)–C(1)–Si(1)–C(8)	–43.2(4)
C(2)–C(1)–Si(1)–C(7)	21.5(4)
C(6)–C(1)–Si(1)–C(7)	–161.4(3)
C(2)–C(1)–Si(1)–C(9)	–104.5(4)
C(6)–C(1)–Si(1)–C(9)	72.7(4)
C(10)–C(9)–Si(1)–C(8)	–65.2(3)
C(16)–C(9)–Si(1)–C(8)	161.2(3)

C(10)–C(9)–Si(1)–C(7)	56.4(4)
C(16)–C(9)–Si(1)–C(7)	–77.2(3)
C(10)–C(9)–Si(1)–C(1)	177.9(3)
C(16)–C(9)–Si(1)–C(1)	44.3(3)

Intermolecular Hydrogen Bond Lengths (Å)

O(2)–H···O(1)	1.88	O(2)···O(1)	2.716(4)
---------------	------	-------------	----------

Intermolecular Hydrogen Bond Angles (°)

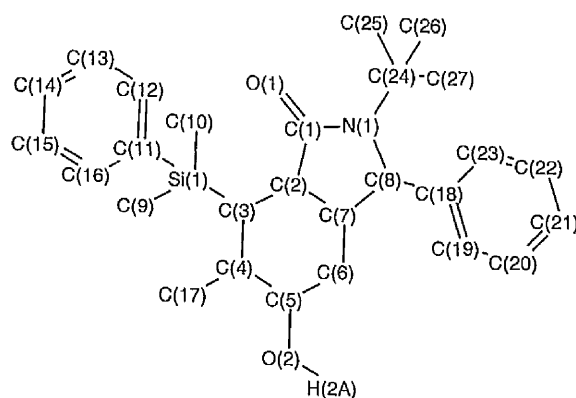
O(2)–H···O(1)	172.6
---------------	-------

5.5.3 Data for Compound 228a

Crystal Data and Structural Refinement

Empirical Formula	C ₂₇ H ₃₇ NO ₂ Si
Formula weight	435.67
Crystal size	0.44 × 0.33 × 0.30 mm
Temperature	100(2) K
X-Ray Wavelength	0.71073 Å
θ Range	1.99–28.31°
Limiting Indices	–14 ≤ h ≤ 14; –16 ≤ k ≤ 16; –24 ≤ l ≤ 24
Refinement Method	full-matrix least-squares on F ²
R Factor	0.0422

Crystal System	monoclinic
Space Group	$P2_1/n$
Unit cell dimensions	$a = 10.6470(14) \text{ \AA}$ $\alpha = 90^\circ$ $b = 12.3220(17) \text{ \AA}$ $\beta = 97.066(2)^\circ$ $c = 18.508(3) \text{ \AA}$ $\gamma = 90^\circ$
Unit Cell Volume	$2409.7(6) \text{ \AA}^3$
Z	4
Calculated Density	1.201 Mg m^{-3}

Atomic LabelsAtomic Coordinates

	<i>x</i>	<i>y</i>	<i>z</i>
H(2)	0.5923	0.3016	0.6617
H(2A)	0.7667	-0.0599	0.6598
H(3)	0.7879	0.2734	0.7413
H(4)	0.7352	0.1295	0.8066
H(5)	0.6962	-0.0471	0.7600
H(6A)	0.5197	0.0617	0.7706
H(6B)	0.4909	-0.0124	0.6995
H(7)	0.5134	0.1345	0.6218
H(8)	0.3282	0.1369	0.7016
H(9A)	0.9582	0.3659	0.6553

H(9B)	0.8257	0.4162	0.6208
H(9C)	0.9219	0.3688	0.5688
H(10A)	0.9613	0.1397	0.5500
H(10B)	0.9028	0.0501	0.5987
H(10C)	1.0107	0.1305	0.6350
H(12)	0.6854	0.0572	0.5190
H(13)	0.5149	0.0540	0.4271
H(14)	0.4067	0.2136	0.3917
H(15)	0.4717	0.3779	0.4471
H(16)	0.6397	0.3811	0.5407
H(17A)	0.9104	0.0207	0.8144
H(17B)	0.9545	0.1396	0.7936
H(17C)	0.9336	0.0474	0.7324
H(19)	0.2586	0.1246	0.5683
H(20)	0.1597	0.2118	0.4652
H(21)	0.1555	0.4014	0.4602
H(22)	0.2560	0.5025	0.5571
H(23)	0.3592	0.4151	0.6599
H(25A)	0.1731	0.2984	0.7336
H(25B)	0.1371	0.2771	0.8138
H(25C)	0.1891	0.1797	0.7686
H(26A)	0.4213	0.4240	0.8528
H(26B)	0.2761	0.4189	0.8669
H(26C)	0.3116	0.4492	0.7878
H(27A)	0.3658	0.1382	0.8627
H(27B)	0.3091	0.2267	0.9131
H(27C)	0.4542	0.2337	0.8989
C(1)	0.5457(1)	0.2847(1)	0.7664(1)
C(2)	0.6040(1)	0.2436(1)	0.6998(1)
C(3)	0.7457(1)	0.2134(1)	0.7110(1)
C(4)	0.7651(1)	0.1107(1)	0.7591(1)
C(5)	0.6816(1)	0.0172(1)	0.7271(1)
C(6)	0.5430(1)	0.0487(1)	0.7212(1)

C(7)	0.5128(1)	0.1505(1)	0.6748(1)
C(8)	0.3843(1)	0.1977(1)	0.6897(1)
C(9)	0.8887(1)	0.3598(1)	0.6155(1)
C(10)	0.9366(1)	0.1240(1)	0.5982(1)
C(11)	0.6809(1)	0.2193(1)	0.5412(1)
C(12)	0.6418(1)	0.1227(1)	0.5054(1)
C(13)	0.5404(1)	0.1207(1)	0.4503(1)
C(14)	0.4764(1)	0.2153(1)	0.4290(1)
C(15)	0.5143(1)	0.3125(1)	0.4622(1)
C(16)	0.6150(1)	0.3141(1)	0.5179(1)
C(17)	0.9033(1)	0.0766(1)	0.7764(1)
C(18)	0.3182(1)	0.2605(1)	0.6250(1)
C(19)	0.2585(1)	0.2016(1)	0.5662(1)
C(20)	0.1991(1)	0.2533(1)	0.5050(1)
C(21)	0.1974(1)	0.3656(1)	0.5018(1)
C(22)	0.2568(1)	0.4255(1)	0.5594(1)
C(23)	0.3178(1)	0.3735(1)	0.6208(1)
C(24)	0.3306(1)	0.2855(1)	0.8108(1)
C(25)	0.1954(1)	0.2577(2)	0.7788(1)
C(26)	0.3353(2)	0.4050(1)	0.8314(1)
C(27)	0.3683(2)	0.2147(1)	0.8773(1)
N(1)	0.4195(1)	0.2632(1)	0.7557(1)
O(1)	0.6025(1)	0.3303(1)	0.8199(1)
O(2)	0.7098(1)	-0.0124(1)	0.6561(1)
Si(1)	0.8129(1)	0.2225(1)	0.6188(1)

Bond Lengths (Å)

C(1)–O(1)	1.2297(15)	C(13)–C(14)	1.383(2)
C(1)–N(1)	1.3596(16)	C(13)–H(13)	0.9500
C(1)–C(2)	1.5343(17)	C(14)–C(15)	1.384(2)
C(2)–C(7)	1.5366(17)	C(14)–H(14)	0.9500
C(2)–C(3)	1.5426(17)	C(15)–C(16)	1.3929(19)

C(2)–H(2)	1.0000	C(15)–H(15)	0.9500
C(3)–C(4)	1.5456(17)	C(16)–H(16)	0.9500
C(3)–Si(1)	1.9338(13)	C(17)–H(17A)	0.9800
C(3)–H(3)	1.0000	C(17)–H(17B)	0.9800
C(4)–C(17)	1.5257(17)	C(17)–H(17C)	0.9800
C(4)–C(5)	1.5291(17)	C(18)–C(19)	1.3934(19)
C(4)–H(4)	1.0000	C(18)–C(23)	1.3944(19)
C(5)–O(2)	1.4311(15)	C(19)–C(20)	1.384(2)
C(5)–C(6)	1.5172(17)	C(19)–H(19)	0.9500
C(5)–H(5)	1.0000	C(20)–C(21)	1.385(2)
C(6)–C(7)	1.5318(17)	C(20)–H(20)	0.9500
C(6)–H(6A)	0.9900	C(21)–C(22)	1.384(2)
C(6)–H(6B)	0.9900	C(21)–H(21)	0.9500
C(7)–C(8)	1.5427(17)	C(22)–C(23)	1.392(2)
C(7)–H(7)	1.0000	C(22)–H(22)	0.9500
C(8)–N(1)	1.4746(16)	C(23)–H(23)	0.9500
C(8)–C(18)	1.5234(18)	C(24)–N(1)	1.4985(15)
C(8)–H(8)	1.0000	C(24)–C(26)	1.5209(19)
C(9)–Si(1)	1.8780(14)	C(24)–C(27)	1.522(2)
C(9)–H(9A)	0.9800	C(24)–C(25)	1.527(2)
C(9)–H(9B)	0.9800	C(25)–H(25A)	0.9800
C(9)–H(9C)	0.9800	C(25)–H(25B)	0.9800
C(10)–Si(1)	1.8653(14)	C(25)–H(25C)	0.9800
C(10)–H(10A)	0.9800	C(26)–H(26A)	0.9800
C(10)–H(10B)	0.9800	C(26)–H(26B)	0.9800
C(10)–H(10C)	0.9800	C(26)–H(26C)	0.9800
C(11)–C(12)	1.4002(18)	C(27)–H(27A)	0.9800
C(11)–C(16)	1.4029(19)	C(27)–H(27B)	0.9800
C(11)–Si(1)	1.8823(14)	C(27)–H(27C)	0.9800
C(12)–C(13)	1.3915(19)	O(2)–H(2A)	0.8400
C(12)–H(12)	0.9500		

Bond Angles (°)

O(1)–C(1)–N(1)	125.80(11)	C(13)–C(14)–H(14)	120.1
O(1)–C(1)–C(2)	126.20(11)	C(15)–C(14)–H(14)	120.1
N(1)–C(1)–C(2)	107.99(10)	C(14)–C(15)–C(16)	119.79(14)
C(1)–C(2)–C(7)	100.69(9)	C(14)–C(15)–H(15)	120.1
C(1)–C(2)–C(3)	117.15(10)	C(16)–C(15)–H(15)	120.1
C(7)–C(2)–C(3)	115.61(10)	C(15)–C(16)–C(11)	121.72(13)
C(1)–C(2)–H(2)	107.6	C(15)–C(16)–H(16)	119.1
C(7)–C(2)–H(2)	107.6	C(11)–C(16)–H(16)	119.1
C(3)–C(2)–H(2)	107.6	C(4)–C(17)–H(17A)	109.5
C(2)–C(3)–C(4)	109.52(10)	C(4)–C(17)–H(17B)	109.5
C(2)–C(3)–Si(1)	109.17(8)	H(17A)–C(17)–H(17B)	109.5
C(4)–C(3)–Si(1)	121.16(9)	C(4)–C(17)–H(17C)	109.5
C(2)–C(3)–H(3)	105.2	H(17A)–C(17)–H(17C)	109.5
C(4)–C(3)–H(3)	105.2	H(17B)–C(17)–H(17C)	109.5
Si(1)–C(3)–H(3)	105.2	C(19)–C(18)–C(23)	118.60(12)
C(17)–C(4)–C(5)	111.90(10)	C(19)–C(18)–C(8)	118.09(12)
C(17)–C(4)–C(3)	113.86(10)	C(23)–C(18)–C(8)	123.29(12)
C(5)–C(4)–C(3)	111.35(10)	C(20)–C(19)–C(18)	121.21(14)
C(17)–C(4)–H(4)	106.4	C(20)–C(19)–H(19)	119.4
C(5)–C(4)–H(4)	106.4	C(18)–C(19)–H(19)	119.4
C(3)–C(4)–H(4)	106.4	C(19)–C(20)–C(21)	119.78(14)
O(2)–C(5)–C(6)	108.12(10)	C(19)–C(20)–H(20)	120.1
O(2)–C(5)–C(4)	111.72(10)	C(21)–C(20)–H(20)	120.1
C(6)–C(5)–C(4)	110.45(10)	C(22)–C(21)–C(20)	119.83(13)
O(2)–C(5)–H(5)	108.8	C(22)–C(21)–H(21)	120.1
C(6)–C(5)–H(5)	108.8	C(20)–C(21)–H(21)	120.1
C(4)–C(5)–H(5)	108.8	C(21)–C(22)–C(23)	120.41(14)
C(5)–C(6)–C(7)	112.61(10)	C(21)–C(22)–H(22)	119.8
C(5)–C(6)–H(6A)	109.1	C(23)–C(22)–H(22)	119.8
C(7)–C(6)–H(6A)	109.1	C(22)–C(23)–C(18)	120.16(13)
C(5)–C(6)–H(6B)	109.1	C(22)–C(23)–H(23)	119.9

C(7)–C(6)–H(6B)	109.1	C(18)–C(23)–H(23)	119.9
H(6A)–C(6)–H(6B)	107.8	N(1)–C(24)–C(26)	110.13(11)
C(6)–C(7)–C(2)	111.18(10)	N(1)–C(24)–C(27)	108.61(11)
C(6)–C(7)–C(8)	109.77(10)	C(26)–C(24)–C(27)	110.75(13)
C(2)–C(7)–C(8)	101.88(10)	N(1)–C(24)–C(25)	109.92(11)
C(6)–C(7)–H(7)	111.2	C(26)–C(24)–C(25)	108.36(13)
C(2)–C(7)–H(7)	111.2	C(27)–C(24)–C(25)	109.06(13)
C(8)–C(7)–H(7)	111.2	C(24)–C(25)–H(25A)	109.5
N(1)–C(8)–C(18)	114.82(10)	C(24)–C(25)–H(25B)	109.5
N(1)–C(8)–C(7)	102.37(9)	H(25A)–C(25)–H(25B)	109.5
C(18)–C(8)–C(7)	112.66(10)	C(24)–C(25)–H(25C)	109.5
N(1)–C(8)–H(8)	108.9	H(25A)–C(25)–H(25C)	109.5
C(18)–C(8)–H(8)	108.9	H(25B)–C(25)–H(25C)	109.5
C(7)–C(8)–H(8)	108.9	C(24)–C(26)–H(26A)	109.5
Si(1)–C(9)–H(9A)	109.5	C(24)–C(26)–H(26B)	109.5
Si(1)–C(9)–H(9B)	109.5	H(26A)–C(26)–H(26B)	109.5
H(9A)–C(9)–H(9B)	109.5	C(24)–C(26)–H(26C)	109.5
Si(1)–C(9)–H(9C)	109.5	H(26A)–C(26)–H(26C)	109.5
H(9A)–C(9)–H(9C)	109.5	H(26B)–C(26)–H(26C)	109.5
H(9B)–C(9)–H(9C)	109.5	C(24)–C(27)–H(27A)	109.5
Si(1)–C(10)–H(10A)	109.5	C(24)–C(27)–H(27B)	109.5
Si(1)–C(10)–H(10B)	109.5	H(27A)–C(27)–H(27B)	109.5
H(10A)–C(10)–H(10B)	109.5	C(24)–C(27)–H(27C)	109.5
Si(1)–C(10)–H(10C)	109.5	H(27A)–C(27)–H(27C)	109.5
H(10A)–C(10)–H(10C)	109.5	H(27B)–C(27)–H(27C)	109.5
H(10B)–C(10)–H(10C)	109.5	C(1)–N(1)–C(8)	111.90(10)
C(12)–C(11)–C(16)	117.01(12)	C(1)–N(1)–C(24)	124.13(10)
C(12)–C(11)–Si(1)	122.00(10)	C(8)–N(1)–C(24)	123.11(10)
C(16)–C(11)–Si(1)	120.97(10)	C(5)–O(2)–H(2A)	109.5
C(13)–C(12)–C(11)	121.39(13)	C(10)–Si(1)–C(9)	105.20(6)
C(13)–C(12)–H(12)	119.3	C(10)–Si(1)–C(11)	108.05(6)
C(11)–C(12)–H(12)	119.3	C(9)–Si(1)–C(11)	106.17(6)
C(14)–C(13)–C(12)	120.27(13)	C(10)–Si(1)–C(3)	119.34(6)

C(14)–C(13)–H(13)	119.9	C(9)–Si(1)–C(3)	106.73(6)
C(12)–C(13)–H(13)	119.9	C(11)–Si(1)–C(3)	110.48(6)
C(13)–C(14)–C(15)	119.79(13)		

Torsion Angles (°)

O(1)–C(1)–C(2)–C(7)	152.46(12)
N(1)–C(1)–C(2)–C(7)	–28.34(12)
O(1)–C(1)–C(2)–C(3)	26.22(18)
N(1)–C(1)–C(2)–C(3)	–154.58(10)
C(1)–C(2)–C(3)–C(4)	68.60(13)
C(7)–C(2)–C(3)–C(4)	–49.88(14)
C(1)–C(2)–C(3)–Si(1)	–156.61(9)
C(7)–C(2)–C(3)–Si(1)	84.90(11)
C(2)–C(3)–C(4)–C(17)	–177.47(10)
Si(1)–C(3)–C(4)–C(17)	54.10(13)
C(2)–C(3)–C(4)–C(5)	54.88(13)
Si(1)–C(3)–C(4)–C(5)	–73.55(12)
C(17)–C(4)–C(5)–O(2)	–68.20(13)
C(3)–C(4)–C(5)–O(2)	60.51(13)
C(17)–C(4)–C(5)–C(6)	171.41(10)
C(3)–C(4)–C(5)–C(6)	–59.88(13)
O(2)–C(5)–C(6)–C(7)	–64.85(13)
C(4)–C(5)–C(6)–C(7)	57.67(13)
C(5)–C(6)–C(7)–C(2)	–50.89(13)
C(5)–C(6)–C(7)–C(8)	–162.84(10)
C(1)–C(2)–C(7)–C(6)	–79.30(11)
C(3)–C(2)–C(7)–C(6)	47.96(14)
C(1)–C(2)–C(7)–C(8)	37.59(11)
C(3)–C(2)–C(7)–C(8)	164.85(10)
C(6)–C(7)–C(8)–N(1)	83.51(11)
C(2)–C(7)–C(8)–N(1)	–34.39(11)
C(6)–C(7)–C(8)–C(18)	–152.62(10)

C(2)–C(7)–C(8)–C(18)	89.48(12)
C(16)–C(11)–C(12)–C(13)	–1.32(19)
Si(1)–C(11)–C(12)–C(13)	177.09(10)
C(11)–C(12)–C(13)–C(14)	0.7(2)
C(12)–C(13)–C(14)–C(15)	0.6(2)
C(13)–C(14)–C(15)–C(16)	–1.3(2)
C(14)–C(15)–C(16)–C(11)	0.7(2)
C(12)–C(11)–C(16)–C(15)	0.64(19)
Si(1)–C(11)–C(16)–C(15)	–177.79(10)
N(1)–C(8)–C(18)–C(19)	–166.66(11)
C(7)–C(8)–C(18)–C(19)	76.67(14)
N(1)–C(8)–C(18)–C(23)	15.25(17)
C(7)–C(8)–C(18)–C(23)	–101.42(14)
C(23)–C(18)–C(19)–C(20)	–0.34(19)
C(8)–C(18)–C(19)–C(20)	–178.52(12)
C(18)–C(19)–C(20)–C(21)	–0.7(2)
C(19)–C(20)–C(21)–C(22)	1.1(2)
C(20)–C(21)–C(22)–C(23)	–0.4(2)
C(21)–C(22)–C(23)–C(18)	–0.7(2)
C(19)–C(18)–C(23)–C(22)	1.04(19)
C(8)–C(18)–C(23)–C(22)	179.12(12)
O(1)–C(1)–N(1)–C(8)	–174.08(12)
C(2)–C(1)–N(1)–C(8)	6.71(13)
O(1)–C(1)–N(1)–C(24)	–4.4(2)
C(2)–C(1)–N(1)–C(24)	176.35(11)
C(18)–C(8)–N(1)–C(1)	–104.57(12)
C(7)–C(8)–N(1)–C(1)	17.84(13)
C(18)–C(8)–N(1)–C(24)	85.68(14)
C(7)–C(8)–N(1)–C(24)	–151.91(11)
C(26)–C(24)–N(1)–C(1)	57.35(17)
C(27)–C(24)–N(1)–C(1)	–64.09(16)
C(25)–C(24)–N(1)–C(1)	176.67(13)
C(26)–C(24)–N(1)–C(8)	–134.14(13)

C(27)–C(24)–N(1)–C(8)	104.42(14)
C(25)–C(24)–N(1)–C(8)	–14.82(17)
C(12)–C(11)–Si(1)–C(10)	37.71(12)
C(16)–C(11)–Si(1)–C(10)	–143.95(11)
C(12)–C(11)–Si(1)–C(9)	150.14(11)
C(16)–C(11)–Si(1)–C(9)	–31.51(12)
C(12)–C(11)–Si(1)–C(3)	–94.51(11)
C(16)–C(11)–Si(1)–C(3)	83.84(11)
C(2)–C(3)–Si(1)–C(10)	–144.66(8)
C(4)–C(3)–Si(1)–C(10)	–16.07(12)
C(2)–C(3)–Si(1)–C(9)	96.46(9)
C(4)–C(3)–Si(1)–C(9)	–134.95(10)
C(2)–C(3)–Si(1)–C(11)	–18.54(10)
C(4)–C(3)–Si(1)–C(11)	110.04(10)

Intermolecular Hydrogen Bond Lengths (Å)

O(2)–H···O(1)	1.94	O(2)···O(1)	2.7811(12)
---------------	------	-------------	------------

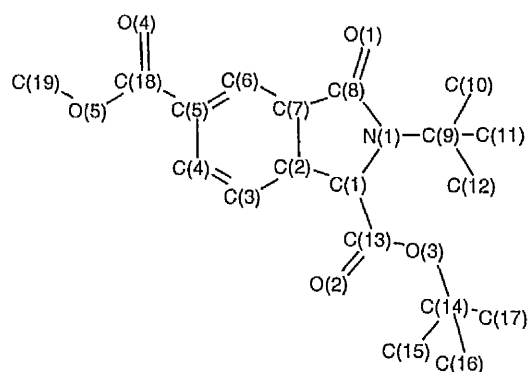
Intermolecular Hydrogen Bond Angles (°)

O(2)–H···O(1)	173.5
---------------	-------

5.5.4 Data for Compound 343Crystal Data and Structural Refinement

Empirical Formula	C ₁₉ H ₂₇ NO ₅
Formula weight	349.42
Crystal size	0.60 × 0.60 × 0.50 mm

Temperature	100(2) K
X-Ray Wavelength	0.71073 Å
θ Range	1.96–26.37°
Limiting Indices	$-19 \leq h \leq 20$; $-8 \leq k \leq 8$; $-16 \leq l \leq 21$
Refinement Method	full-matrix least-squares on F^2
R Factor	0.0380
Crystal System	monoclinic
Space Group	$P2_1/n$
Unit cell dimensions	$a = 16.4127(11)$ Å $\alpha = 90^\circ$ $b = 6.6974(4)$ Å $\beta = 103.662(1)^\circ$ $c = 17.2210(12)$ Å $\gamma = 90^\circ$
Unit Cell Volume	1839.4(2) Å ³
Z	4
Calculated Density	1.262 Mg m ⁻³

Atomic LabelsAtomic Coordinates

	<i>x</i>	<i>y</i>	<i>z</i>
H(1)	0.6760	−0.0770	1.0797
H(2)	0.8132	−0.1386	1.1259
H(3)	0.8051	−0.3264	1.0082

H(4)	0.8811	-0.2147	0.9235
H(6)	0.9063	0.3405	1.0225
H(7)	0.9045	0.1056	1.1390
H(10A)	0.6844	0.5908	1.0921
H(10B)	0.5863	0.5831	1.0894
H(10C)	0.6209	0.4856	1.0186
H(11A)	0.5559	0.1593	1.0376
H(11B)	0.5187	0.2587	1.1064
H(11C)	0.5740	0.0598	1.1245
H(12A)	0.6709	0.2185	1.2388
H(12B)	0.6160	0.4183	1.2239
H(12C)	0.7144	0.4274	1.2281
H(15A)	0.5444	0.1452	0.8353
H(15B)	0.5460	0.3374	0.7805
H(15C)	0.5468	0.3642	0.8730
H(16A)	0.6767	0.5701	0.8900
H(16B)	0.6789	0.5374	0.7984
H(16C)	0.7584	0.4774	0.8681
H(17A)	0.7582	0.1312	0.8204
H(17B)	0.6804	0.1780	0.7470
H(17C)	0.6749	-0.0013	0.8070
H(19A)	1.0447	0.3743	0.8486
H(19B)	0.9831	0.5629	0.8330
H(19C)	0.9572	0.3609	0.7837
O(1)	0.8191(1)	0.4439(1)	1.1486(1)
O(2)	0.6316(1)	-0.0871(1)	0.0288(1)
O(3)	0.6923(1)	0.2190(1)	0.9407(1)
O(4)	0.9504(1)	0.0355(1)	0.0488(1)
O(5)	0.9457(1)	0.3462(1)	0.8967(1)
N(1)	0.7188(1)	0.2045(1)	1.1025(1)
C(1)	0.7110(1)	0.0190(2)	1.0571(1)
C(2)	0.8033(1)	-0.0597(2)	1.0752(1)
C(3)	0.8239(1)	-0.1918(2)	1.0122(1)

C(4)	0.8678(1)	-0.1257(2)	0.9617(1)
C(5)	0.8961(1)	0.0828(2)	0.9639(1)
C(6)	0.8896(1)	0.2050(2)	1.0236(1)
C(7)	0.8561(1)	0.1312(2)	1.0926(1)
C(8)	0.7974(1)	0.2815(2)	1.1182(1)
C(9)	0.6456(1)	0.3125(2)	1.1210(1)
C(10)	0.6332(1)	0.5107(2)	1.0763(1)
C(11)	0.5665(1)	0.1863(2)	1.0950(1)
C(12)	0.6633(1)	0.3473(2)	1.2110(1)
C(13)	0.6731(1)	0.0432(2)	0.9677(1)
C(14)	0.6614(1)	0.2757(2)	0.8551(1)
C(15)	0.5662(1)	0.2811(2)	0.8341(1)
C(16)	0.6970(1)	0.4834(2)	0.8527(1)
C(17)	0.6969(1)	0.1333(2)	0.8027(1)
C(18)	0.9336(1)	0.1485(2)	0.8975(1)
C(19)	0.9859(1)	0.4168(2)	0.8356(1)

Bond Lengths (Å)

O(1)–C(8)	1.2239(14)	C(9)–C(11)	1.5250(18)
O(2)–C(13)	1.2072(14)	C(9)–C(12)	1.5259(17)
O(3)–C(13)	1.3315(14)	C(10)–H(10A)	0.9800
O(3)–C(14)	1.4904(14)	C(10)–H(10B)	0.9800
O(4)–C(18)	1.2090(15)	C(10)–H(10C)	0.9800
O(5)–C(18)	1.3394(16)	C(11)–H(11A)	0.9800
O(5)–C(19)	1.4479(15)	C(11)–H(11B)	0.9800
N(1)–C(8)	1.3553(15)	C(11)–H(11C)	0.9800
N(1)–C(1)	1.4577(14)	C(12)–H(12A)	0.9800
N(1)–C(9)	1.4992(14)	C(12)–H(12B)	0.9800
C(1)–C(13)	1.5273(16)	C(12)–H(12C)	0.9800
C(1)–C(2)	1.5635(16)	C(14)–C(16)	1.5133(18)
C(1)–H(1)	1.0000	C(14)–C(15)	1.5189(17)
C(2)–C(3)	1.4996(16)	C(14)–C(17)	1.5194(17)

C(2)–C(7)	1.5344(16)	C(15)–H(15A)	0.9800
C(2)–H(2)	1.0000	C(15)–H(15B)	0.9800
C(3)–C(4)	1.3298(17)	C(15)–H(15C)	0.9800
C(3)–H(3)	0.9500	C(16)–H(16A)	0.9800
C(4)–C(5)	1.4693(17)	C(16)–H(16B)	0.9800
C(4)–H(4)	0.9500	C(16)–H(16C)	0.9800
C(5)–C(6)	1.3378(17)	C(17)–H(17A)	0.9800
C(5)–C(18)	1.4876(16)	C(17)–H(17B)	0.9800
C(6)–C(7)	1.5046(16)	C(17)–H(17C)	0.9800
C(6)–H(6)	0.9500	C(19)–H(19A)	0.9800
C(7)–C(8)	1.5289(16)	C(19)–H(19B)	0.9800
C(7)–H(7)	1.0000	C(19)–H(19C)	0.9800
C(9)–C(10)	1.5234(17)		

Bond Angles (°)

C(13)–O(3)–C(14)	121.18(9)	H(10B)–C(10)–H(10C)	109.5
C(18)–O(5)–C(19)	115.13(10)	C(9)–C(11)–H(11A)	109.5
C(8)–N(1)–C(1)	112.91(9)	C(9)–C(11)–H(11B)	109.5
C(8)–N(1)–C(9)	123.16(9)	H(11A)–C(11)–H(11B)	109.5
C(1)–N(1)–C(9)	123.50(9)	C(9)–C(11)–H(11C)	109.5
N(1)–C(1)–C(13)	114.42(9)	H(11A)–C(11)–H(11C)	109.5
N(1)–C(1)–C(2)	102.86(9)	H(11B)–C(11)–H(11C)	109.5
C(13)–C(1)–C(2)	112.46(9)	C(9)–C(12)–H(12A)	109.5
N(1)–C(1)–H(1)	109.0	C(9)–C(12)–H(12B)	109.5
C(13)–C(1)–H(1)	109.0	H(12A)–C(12)–H(12B)	109.5
C(2)–C(1)–H(1)	109.0	C(9)–C(12)–H(12C)	109.5
C(3)–C(2)–C(7)	114.77(10)	H(12A)–C(12)–H(12C)	109.5
C(3)–C(2)–C(1)	115.35(10)	H(12B)–C(12)–H(12C)	109.5
C(7)–C(2)–C(1)	103.54(9)	O(2)–C(13)–O(3)	126.48(11)
C(3)–C(2)–H(2)	107.6	O(2)–C(13)–C(1)	121.64(11)
C(7)–C(2)–H(2)	107.6	O(3)–C(13)–C(1)	111.88(9)
C(1)–C(2)–H(2)	107.6	O(3)–C(14)–C(16)	102.57(9)

C(4)–C(3)–C(2)	121.81(11)	O(3)–C(14)–C(15)	109.41(9)
C(4)–C(3)–H(3)	119.1	C(16)–C(14)–C(15)	110.72(11)
C(2)–C(3)–H(3)	119.1	O(3)–C(14)–C(17)	109.74(10)
C(3)–C(4)–C(5)	121.05(11)	C(16)–C(14)–C(17)	110.90(11)
C(3)–C(4)–H(4)	119.5	C(15)–C(14)–C(17)	112.99(10)
C(5)–C(4)–H(4)	119.5	C(14)–C(15)–H(15A)	109.5
C(6)–C(5)–C(4)	121.30(11)	C(14)–C(15)–H(15B)	109.5
C(6)–C(5)–C(18)	122.20(11)	H(15A)–C(15)–H(15B)	109.5
C(4)–C(5)–C(18)	116.49(10)	C(14)–C(15)–H(15C)	109.5
C(5)–C(6)–C(7)	121.07(11)	H(15A)–C(15)–H(15C)	109.5
C(5)–C(6)–H(6)	119.5	H(15B)–C(15)–H(15C)	109.5
C(7)–C(6)–H(6)	119.5	C(14)–C(16)–H(16A)	109.5
C(6)–C(7)–C(8)	112.58(10)	C(14)–C(16)–H(16B)	109.5
C(6)–C(7)–C(2)	114.49(10)	H(16A)–C(16)–H(16B)	109.5
C(8)–C(7)–C(2)	103.81(9)	C(14)–C(16)–H(16C)	109.5
C(6)–C(7)–H(7)	108.6	H(16A)–C(16)–H(16C)	109.5
C(8)–C(7)–H(7)	108.6	H(16B)–C(16)–H(16C)	109.5
C(2)–C(7)–H(7)	108.6	C(14)–C(17)–H(17A)	109.5
O(1)–C(8)–N(1)	126.25(11)	C(14)–C(17)–H(17B)	109.5
O(1)–C(8)–C(7)	124.61(11)	H(17A)–C(17)–H(17B)	109.5
N(1)–C(8)–C(7)	109.14(10)	C(14)–C(17)–H(17C)	109.5
N(1)–C(9)–C(10)	109.35(9)	H(17A)–C(17)–H(17C)	109.5
N(1)–C(9)–C(11)	109.89(10)	H(17B)–C(17)–H(17C)	109.5
C(10)–C(9)–C(11)	109.40(11)	O(4)–C(18)–O(5)	123.54(11)
N(1)–C(9)–C(12)	108.58(10)	O(4)–C(18)–C(5)	123.52(12)
C(10)–C(9)–C(12)	110.53(11)	O(5)–C(18)–C(5)	112.94(10)
C(11)–C(9)–C(12)	109.08(11)	O(5)–C(19)–H(19A)	109.5
C(9)–C(10)–H(10A)	109.5	O(5)–C(19)–H(19B)	109.5
C(9)–C(10)–H(10B)	109.5	H(19A)–C(19)–H(19B)	109.5
H(10A)–C(10)–H(10B)	109.5	O(5)–C(19)–H(19C)	109.5
C(9)–C(10)–H(10C)	109.5	H(19A)–C(19)–H(19C)	109.5
H(10A)–C(10)–H(10C)	109.5	H(19B)–C(19)–H(19C)	109.5

References

1. For a general review of the kainoid amino acids, see A. F. Parsons, *Tetrahedron*, 1996, **52**, 4149.
2. For a review of the chemistry of domoic acid, the isodomoic acids and their analogues, encompassing some of the material in this chapter, see (a) J. Clayden, B. Read and K. R. Hebditch, *Tetrahedron*, 2005, **61**, 5713. An extensive list of syntheses of kainic acid is also provided in this paper. For selected recently published kainic acid syntheses, see (b) D. M. Hodgson, S. Hachisu and M. D. Andrews, *J. Org. Chem.*, 2005, **70**, 8866; (c) B. M. Trost and M. T. Rudd, *J. Am. Chem. Soc.*, 2005, **127**, 4763; (d) M. M. Martínez and D. Hoppe, *Eur. J. Org. Chem.*, 2005, 1427; (e) M. E. Scott and M. Lautens, *Org. Lett.*, 2005, **7**, 3045; (f) Y. Morita, H. Tokuyama and T. Fukuyama, *Org. Lett.*, 2005, **7**, 4337.
3. K. Daigo, S. Murakami, T. Takemoto and Z. Shimizu, *Jap. J. Pharm. Chem.*, 1953, **25**, 571.
4. (a) T. Takemoto and K. Daigo, *Chem. Pharm. Bull.*, 1958, **6**, 578; (b) K. Daigo, *J. Pharm. Soc. Jpn.*, 1959, **79**, 350.
5. (a) M. Maeda, T. Kodama, T. Tanaka, H. Yoshizumi, T. Takemoto, K. Nomoto and T. Fujita, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, 1985, **27**, 616; (b) M. Maeda, T. Kodama, T. Tanaka, H. Yoshizumi, T. Takemoto, K. Nomoto and T. Fujita, *Chem. Pharm. Bull.*, 1986, **34**, 4892.
6. M. Maeda, T. Kodama, T. Tanaka, H. Yoshizumi, T. Takemoto, K. Nomoto and T. Fujita, *Tetrahedron Lett.*, 1987, **28**, 633.
7. M. A. Quilliam, P. G. Sim, A. W. McCulloch and A. G. McInnes, *Intern. J. Environ. Anal. Chem.*, 1989, **36**, 139.
8. J. A. Walter, M. Falk, A. G. McInnes and J. L. C. Wright, *Can. J. Chem.*, 1990, **68**, 22.
9. L. Zaman, O. Arakawa, A. Shimosu, Y. Onoue, S. Nishio, Y. Shida and T. Noguchi, *Toxicon*, 1997, **35**, 205.
10. J. A. Walter, M. Falk and J. L. C. Wright, *Can. J. Chem.*, 1994, **72**, 430.

11. For a detailed account of the process of discovery of domoic acid-producing organisms and an explanation of taxonomy, see (a) S. S. Bates, *J. Phycol.*, 2000, **36**, 978; (b) N. Lundholm, Ø. Moestrup, G. R. Hasle and K. Hoef-Emden, *J. Phycol.*, 2003, **39**, 797.
12. S. S. Bates, C. J. Bird, A. S. W. de Freitas, R. Foxall, M. Gilgan, L. A. Hanic, G. R. Johnson, A. W. McCulloch and P. Odense, *Can. J. Fish. Aquat. Sci.*, 1989, **46**, 1203.
13. D. J. Douglas, S. S. Bates, *Can. J. Fish. Aquat. Sci.*, 1992, **49**, 85.
14. J. L. Martin, K. Haya, L. E. Burridge, D. J. Wildish, *Marine Ecology: Progress Series*, 1990, **67**, 177.
15. D. L. Garrison, S. M. Conrad, P. P. Eilers and E. M. Waldron, *J. Phycol.*, 1992, **28**, 604.
16. L. Rhodes, C. Scholin, I. Garthwaite, A. Haywood and A. Thomas, *Harmful Algae*, B. Reguera, J. Blanco, M. L. Fernández and T. Wyatt, Eds., Intergovernmental Oceanographic Commission, UNESCO, Paris, 1998, 274.
17. D. Sarno and J. Dahlmann, *Harmful Algae News*, 2000, **21**, 5.
18. L. Rhodes, D. White, M. Syhre, M. Atkinson, *Harmful and Toxic Algal Blooms*, Y. Oshima, Y. Fukuyo and T. Yasumoto, Eds., Intergovernmental Oceanographic Commission, UNESCO, Paris, 1996, 155.
19. N. Lundholm, Ø. Moestrup, J. Skov and R. Pocklington, *Phycologia*, 1994, **33**, 475.
20. Y. Kotaki, E. F. Furio, M. Satake, N. Lundholm, T. Katayama, K. Koike, V. P. Fulgueras, F. A. Bajarias, Y. Takata, K. Kobayashi, S. Sato, Y. Fukuyo and M. Kodama, *Toxicon*, 2005, **46**, 946.
21. P. T. Holland, A. I. Selwood, D. O. Mountfort, A. L. Wilkins, P. McNabb, L. L. Rhodes, G. J. Doucette, C. M. Mikulski and K. L. King, *Chem. Res. Toxicol.*, 2005, **18**, 814.
22. For a detailed review of the role of domoic acid as a marine toxin, see L. Mos, *Environ. Toxicol. Pharmacol.*, 2001, **9**, 79, and references therein.

23. M. Maeda, T. Kodama, T. Tanaka, Y. Ohfune, K. Nishimura, K. Nomoto and T. Fujita, *J. Pestic. Sci.*, 1984, **9**, 27.
24. H. Watase, Y. Tomiie and I. Nitta, *Nature (London)*, 1958, **181**, 761.
25. (a) E. G. McGeer, J. W. Olney and P. L. McGeer, Eds., *Kainic Acid as a Tool in Neurobiology*, Raven Press, New York, 1978; (b) J. W. Olney, *Adv. Biochem. Psychopharmacol.*, 1981, **27**, 375; (c) J. C. Watkins, P. Krogsgaard-Larsen and T. Honoré, *Trends Pharmacol. Sci.*, 1990, **11**, 25; (d) H. V. Wheal and A. M. Thomson, Eds., *Excitatory Amino Acids and Synaptic Transmission*, Academic Press, London, 1991; (e) R. P. Simon, Ed., *Excitatory Amino Acids*, Thieme Medical Publishers, New York, 1992; (f) R. H. Waring, G. B. Steventon and S. C. Mitchell, *Molecules of Death*, Imperial College Press, London, 2002.
26. G. Sperk, *Prog. Neurobiol. (Oxford)*, 1994, **42**, 1.
27. (a) J. T. Coyle and R. Schwarcz, *Nature (London)*, 1976, **263**, 244; (b) E. G. McGeer and P. L. McGeer, *Nature (London)*, 1976, **263**, 517.
28. G. R. Stewart, C. F. Zorumski, M. T. Price and J. W. Olney, *Exp. Neurol.*, 1990, **110**, 127.
29. (a) G. A. R. Johnson, D. R. Curtis, J. Davis and R. M. McCulloch, *Nature (London)*, 1974, **248**, 804; (b) J. J. Hansen and P. Krogsgaard-Larsen, *Med. Res. Rev.*, 1990, **10**, 55; (c) K. Hashimoto, Y. Ohfune and H. Shirahama, *Tetrahedron Lett.*, 1995, **36**, 6235.
30. (a) D. T. Monaghan, R. J. Bridges and C. W. Cotman, *Annu. Rev. Pharmacol. Toxicol.*, 1989, **29**, 365; (b) A. B. Young and G. E. Fagg, *Trends Pharmacol. Sci.*, 1990, **11**, 126; (c) B. Sommer and P. H. Seeburg, *Trends Pharmacol. Sci.*, 1992, **13**, 291; (d) P. H. Seeburg, *Trends Neurosci.*, 1993, **16**, 359; (e) M. Hollmann and S. Heinemann, *Annu. Rev. Neurosci.*, 1994, **17**, 31.
31. M. Ishida and H. Shinozaki, *Br. J. Pharmacol.*, 1991, **104**, 873.
32. D. R. Hampson, X. Huang, J. W. Wells, J. A. Walter and J. L. C. Wright, *Eur. J. Pharmacol.*, 1992, **218**, 1.
33. J. L. C. Wright, R. K. Boyd, A. S. W. de Freitas, M. Falk, R. A. Foxall, W. D. Jamieson, M. V. Laycock, A. W. McCulloch, A. G. McInnes,

- P. Odense, V. P. Pathak, M. A. Quilliam, M. A. Ragan, P. G. Sim, P. Thibault, J. A. Walter, M. Gilgan, D. J. A. Richard and D. Dewar, *Can. J. Chem.*, 1989, **67**, 481.
34. C. A. Scholin, F. Gulland, G. J. Doucette, S. Benson, M. Busman, F. P. Chavez, J. Cordar, R. DeLong, A. De Vogelaere, J. Harvey, M. Haulena, K. Lefebvre, T. Lipscomb, S. Loscutoff, L. J. Lowenstine, R. I. Martin, P. E. Miller, W. A. McLellan, P. D. R. Moeller, C. L. Powell, T. Rowles, P. Silvagni, M. Silver, T. Spraker, V. Trainer and F. M. Van Dolah, *Nature*, 2000, **403**, 80.
35. (a) T. M. Work, A. M. Beale, L. Fritz, M. A. Quilliam, M. Silver, K. Buck and J. L. C. Wright, *Toxic Phytoplankton Blooms in the Sea*, T. J. Smayda and Y. Shimizu, Eds., Elsevier Science Publishers B. V., Amsterdam, 1993, 643; (b) A. Sierra-Beltrán, M. Palafox-Urbe, J. Grajales-Montiel, A. Cruz-Villacorta and J. L. Ocha, *Toxicon*, 1997, **35**, 447.
36. J. Fehling, D. H. Green, K. Davidson, C. J. Bolch and S. S. Bates, *J. Phycol.*, 2004, **40**, 622.
37. C. K. Cusack, S. S. Bates, M. A. Quilliam, J. W. Patching and R. Raine, *J. Phycol.*, 2002, **38**, 1106.
38. M. C. Villac, D. L. Roelke, T. A. Villareal and G. A. Fryxell, *Hydrobiologia*, 1993, **269–270**, 213.
39. (a) J. E. Stewart, L. J. Marks, M. W. Gilgan, E. Pfeiffer and B. M. Zwicker, *Can. J. Microbiol.*, 1998, **44**, 456; (b) E. A. Smith, F. Grant, C. M. J. Ferguson and S. Gallacher, *Appl. Environ. Microbiol.*, 2001, **67**, 2345.
40. Y. Ohfuné and M. Tomita, *J. Am. Chem. Soc.*, 1982, **104**, 3511.
41. R. Hoffmann and R. B. Woodward, *The Conservation of Orbital Symmetry*, Academic Press, New York, 1970.
42. (a) N. Yike, K. D. Amarasinghe, B. Ksebati and J. Montgomery, *Org. Lett.*, 2003, **5**, 3771; (b) M. V. Chevliakov and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121**, 11139.
43. G. A. Conway, J. S. Park, L. Maggiora, M. P. Mertes, N. Galton and E. K. Michaelis, *J. Med. Chem.*, 1984, **27**, 52.

44. J. E. Baldwin, M. G. Moloney and A. F. Parsons, *Tetrahedron*, 1991, **47**, 155.
45. J. E. Baldwin, M. G. Moloney and A. F. Parsons, *Tetrahedron*, 1990, **46**, 7263.
46. J. E. Baldwin, G. J. Pritchard and D. S. Williamson, *Tetrahedron*, 2001, **57**, 7991.
47. (a) J. E. Baldwin, G. J. Pritchard and A. M. Fryer, *J. Org. Chem.*, 2001, **66**, 2588; (b) J. E. Baldwin, A. M. Fryer, M. R. Spyvee, R. C. Whitehead and M. E. Wood, *Tetrahedron Lett.*, 1996, **37**, 6923; (c) J. E. Baldwin, S. J. Bamford, M. P. W. Rudolph, M. E. Wood and A. M. Fryer, *Tetrahedron*, 1997, **53**, 5233; (d) J. E. Baldwin, S. J. Bamford, M. P. W. Rudolph, M. E. Wood and A. M. Fryer, *Tetrahedron*, 1997, **53**, 5255; (e) J. E. Baldwin, M. R. Spyvee, R. C. Whitehead, M. E. Wood and A. M. Fryer, *Tetrahedron*, 1997, **53**, 5273.
48. For related observations, see: (a) D. Hoell, J. Lex and K. Müllen, *J. Am. Chem. Soc.*, 1986, **108**, 5983; (b) H.-J. Breternitz, E. Schaumann and G. Adiwidjaja, *Tetrahedron Lett.*, 1991, **32**, 1299; (c) J. K. Crandall and T. A. Ayers, *J. Org. Chem.*, 1992, **57**, 2993; (d) A. Padwa, M. A. Filipkowski, D. N. Kline, S. S. Murphree and P. E. Yeske, *J. Org. Chem.*, 1993, **58**, 2061.
49. (a) C. P. Beech, *Final Year Undergraduate Project Report*, University of Manchester, 1995; (b) J. Clayden, *Strategies and Tactics in Organic Synthesis*, 2004, **4**, 71.
50. S. E. Jaeger, *Ph.D. Thesis*, University of Manchester, 1996.
51. A. Ahmed, J. Clayden and M. Rowley, *Chem. Commun.*, 1998, 297.
52. A. Ahmed, J. Clayden and S. A. Yasin, *Chem. Commun.*, 1999, 231.
53. J. Clayden and K. Tchabanenko, *Chem. Commun.*, 2000, 317.
54. C. Metallinos, S. Nerdinger and V. Snieckus, *Org. Lett.*, 1999, **1**, 1183.
55. J. Clayden, K. Tchabanenko, S. A. Yasin and M. D. Turnbull, *Synlett*, 2001, 302.
56. J. Clayden, C. J. Menet and D. Mansfield, *Org. Lett.* 2000, **26**, 4229.
57. J. Clayden, C. J. Menet and D. J. Mansfield, *Chem. Commun.*, 2002, 38.
58. J. Clayden, C. J. Menet and K. Tchabanenko, *Tetrahedron*, 2002, **58**, 4727.

59. (a) F. E. Knowles, J. Clayden and I. R. Baldwin, *J. Am. Chem. Soc.*, 2005, **127**, 2412; (b) F. E. Knowles, *Ph.D. Thesis*, University of Manchester, 2005.
60. K. R. Hebditch, *Ph.D. Thesis*, University of Manchester, 2004.
61. (a) G. H. Posner, Q. Wang, B. A. Halford, J. S. Elias and J. P. Maxwell, *Tetrahedron Lett.*, 2000, **41**, 9655; (b) K. Nakatani and S. Isoe, *Tetrahedron Lett.*, 1984, **25**, 5335.
62. J. E. Baldwin, R. M. Adlington and J. Robertson, *J. Chem. Soc., Chem. Commun.*, 1988, 1404.
63. S. Purewal, *Ph.D. Thesis*, University of Manchester, 2003.
64. T. C. Boge, Z. S. Cheruvallath, G. I. Georg, G. C. B. Harriman, M. Hepperle, R. H. Himes and H. Park, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 335.
65. A. Ahmed, J. Clayden and M. Rowley, *Tetrahedron Lett.*, 1998, **39**, 6103.
66. I. Fernández, J. González and F. López-Ortiz, *J. Am. Chem. Soc.*, 2004, **126**, 12551.
67. A. M. Ramallal, I. Fernández, F. López-Ortiz and J. González, *Chem. Eur. J.*, 2005, **11**, 3022.
68. A. M. Ramallal, F. López-Ortiz and J. González, *Org. Lett.*, 2004, **6**, 2141.
69. A. Ahmed, *Ph.D. Thesis*, University of Manchester, 2000.
70. S. D. Hamilton, *Ph.D. Thesis*, University of Manchester, 2005.
71. C. Luján, *Erasmus Project Report*, University of Manchester, 2005.
72. (a) A. D. Campbell, T. M. Raynham and R. J. K. Taylor, *Chem. Commun.*, 1999, 245; (b) A. D. Campbell, T. M. Raynham and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3194.
73. M. A. Hatcher, K. Borstnik and G. H. Posner, *Tetrahedron Lett.*, 2003, **44**, 5407.
74. M. Casey, J. Leonard, B. Lygo and G. Procter, *Advanced Practical Organic Chemistry*, 1990, Blackie.
75. P. J. Bradley and D. H. Grayson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1794.

76. (a) M. V. George, D. J. Peterson and H. Gilman, *J. Am. Chem. Soc.*, 1960, **82**, 403; (b) I. Fleming, R. S. Roberts and S. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1209.
77. I. Fleming, E. Marangon, C. Roni, M. G. Russell and S. T. Chamudis, *Chem. Commun.*, 2003, 200.
78. I. Fleming, R. A. N. C. Crump and C. J. Urch, *J. Chem. Soc., Perkin Trans. 1*, 1994, 701.
79. P. A. Brough, S. Fisher, B. Zhao, R. C. Thomas and V. Snieckus, *Tetrahedron Lett.*, 1996, **37**, 2915.
80. (a) P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34; (b) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
81. P. Beak, S. T. Kerrick and D. J. Gallagher, *J. Am. Chem. Soc.*, 1993, **115**, 10628.
82. J. Clayden, R. P. Davies, M. A. Hendy, R. Snaith and A. E. H. Wheatley, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 1238.
83. R. L. Hamilton, *Final Year Undergraduate Project Report*, University of Manchester, 2003.
84. S. A. Yasin, *Ph.D. Thesis*, University of Manchester, 2001.
85. Y. Morita, M. Suzuki and R. Noyori, *J. Org. Chem.*, 1989, **54**, 1785.
86. S. G. Cho, O. K. Rim and Y.-S. Kim, *J. Mol. Struct.*, 1996, **364**, 59.
87. W. Engel, I. Fleming and R. H. Smithers, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1637.
88. Example and methodology: (a) T. G. Back, P. L. Gladstone and M. Parvez, *J. Org. Chem.*, 1996, **61**, 3806; Further examples: (b) D.-S. Hsu, P.-Y. Hsu and C.-C. Liao, *Org. Lett.*, 2001, **3**, 263; (c) L. N. Mander and T. P. O'Sullivan, *Synlett*, 2003, 1367.
89. A. Varvoglis, *Tetrahedron*, 1997, **53**, 1179.
90. (a) A. G. Buckmelter, J. P. Powers and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1998, **120**, 5589; (b) Y. Landais, *C. R. Chimie*, 2005, **8**, 823.
91. H. Nishiyama, K. Sakuta, N. Osaka, H. Arai, M. Matsumoto and K. Itoh, *Tetrahedron*, 1988, **44**, 2413.
92. I. Fleming and C. Ramarao, *Chem. Commun.*, 2000, 2185.
93. C. Cesare, *Eur. Pat. Appl.*, 2003, JP2003026660.

94. M. S. Deshpande, J. Wei, G. Luo, C. Cianci, S. Danetz, A. Torri, L. Tiley, M. Krystal, K.-L. Yu, S. Huang, Q. Gao and N. A. Meanwell, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2393.
95. R. G. Dushin and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1992, **114**, 655.
96. T. R. Kelly, A. Echavarren, N. S. Chandrakumar and Y. Köksal, *Tetrahedron Lett.*, 1984, **25**, 2127.
97. C.-T. Chen, J.-H. Kuo, V. D. Pawar, Y. S. Munot, S.-S. Weng, C.-H. Ku and C.-Y. Liu, *J. Org. Chem.*, 2005, **70**, 1188.
98. J. N. Tilley and A. A. R. Sayigh, *J. Org. Chem.*, 1963, **28**, 2076.
99. D. Griller, D. C. Nonhebel and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1373.
100. (a) I. V. Suvorova, M. D. Stadnichuk and K. S. Mingaleva, *Zhurnal Obshchei Khimii*, 1983, **53**, 817; (b) I. V. Suvorova and M. D. Stadnichuk, *Zhurnal Obshchei Khimii*, 1985, **55**, 1513.
101. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
102. W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, 1988, Pergamon Press.
103. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879.
104. C. R. Goldsmith, R. T. Jonas and T. D. P. Stack, *J. Am. Chem. Soc.*, 2002, **124**, 83.
105. K. Miyajima, M. Takemoto and K. Achiwa, *Chem. Pharm. Bull.*, 1991, **39**, 3175.
106. N. E. Austin, M. S. Hadley, J. D. Harling, F. P. Harrington, G. J. Macdonald, D. J. Mitchell, G. J. Riley, T. O. Stean, G. Stemp, S. C. Stratton, M. Thompson and N. Upton, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1627.
107. G. Arnott, *unpublished result*, University of Manchester, 2005.
108. L. J. Exner, L. S. Luskin and P. L. deBennville, *J. Am. Chem. Soc.*, 1953, **75**, 4841.
109. J. H. Boyer and J. Kooi, *J. Am. Chem. Soc.*, 1976, **98**, 1099.
110. W. H. Pirkle, K. A. Simmons and C. W. Boeder, *J. Org. Chem.*, 1979, **44**, 4891.

111. T. Ueda, K. Kageno, K. Shimizu, S. Hasegawa and S. Harada, *U.S. Pat. Appl.*, 1987, US4644042.
112. J. M. Goldwasser and C. C. Leznoff, *Can. J. Chem.*, 1978, **56**, 1562.

