UNIVERSITY OF SOUTHAMPTON

Faculty of Natural and Environmental Sciences

School of Chemistry

A New Route to the API Ropinirole Hydrochloride
and
Towards New Synthetic Applications of Squaramides

by

Zeshan Yousuf

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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A NEW ROUTE TO THE API ROPINIROLE HYDROCHLORIDE AND TOWARDS NEW SYNTHETIC APPLICATIONS OF SQUARAMIDES

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This thesis describes our efforts in developing a new synthesis of the active pharmaceutical ingredient (API) ropinirole hydrochloride, used in the symptomatic treatment of Parkinson's disease and Restless Leg Syndrome. The API in Requip™ (marketed by GlaxoSmithKline) is currently prepared in 12% overall yield using a nine-step sequence, however, several generic routes have since been established in the pharmaceutical market. Herein we describe a shorter and more efficient route to ropinirole hydrochloride that could prove attractive from an industrial perspective.

The strategies employed in developing the new synthesis of the API are presented - adopting Plieninger's approach to 4-substituted indoles with a contemporary twist. Key transformations include the use of a dissolving metal reduction followed by an ozonolysis under flow to construct the API's heterocyclic core. In our first approach the target is attained in six-steps from 1-aminonaphthalene. However, by increasing the oxidation level of the starting material we were able to achieve a synthesis of ropinirole hydrochloride in four steps from a commercial starting material.

Also described in this thesis are our efforts towards probing the synthetic versatility of squaramides. Preliminary results indicate that the stabilisation exhibited by their derivatives may lead to alternative thermal rearrangement pathways, complimentary to squarates.

Contents

Declaration of Authorship

I, Zeshan Yousuf declare that the thesis entitled “A New Route to the API Ropinirole Hydrochloride and Towards New Synthetic Applications of Squaramides” and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- none of this work has been published before submission.

Signed: ..…………………………………………………………………….

Date: ………...………………………………………………………….…….

To my dear mum

Acknowledgements

Alhamdulillah I have made it this far! I'd like to thank my parents without whom I wouldn't be in this position. This is for you, mum. You probably thought I was wasting my time and spending far too many years in uni but I was doing it for you. It's been tough, tougher than I'd imagined it would be but it's over now. And to all those who made dua for my success, may we all be granted the best of successes.

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I'm gonna miss soton. What an experience!

Abbreviations

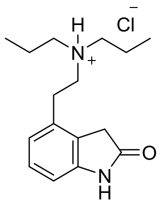
app.	apparent
aq.	aqueous
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
Boc	tertiary-butoxy carbonyl
br	broad
cat.	catalytic
CNS	central nervous system
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density function theory
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylamine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNPH	2,4-dinitrophenylhydrazine
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
EI	electron ionisation
ESI	electrospray ionisation
g	gram
Glu-O	glucuronate
h	hour(s)
HMTA	hexamethylenetetramine
HMPT	hexamethyphosphorous triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration
IMS	industrial methylated spirit
IPA	isopropyl alcohol
J	coupling constant
K	kilo
L	litre(s)
LRMS	low resolution mass Spectrometry
µw	microwave
M	molar
m	medium/multiplet/milli
m	meta
min	minute(s)

MEM	2-methoxyethoxymethyl ether
mol	mole(s)
m/z	mass/charge ratio
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-oxide
NMR	nuclear magnetic resonance
NPhth	phthalimide
o	*ortho*
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PG	protecting group
py	pyridine
q	quartet
RT	room temperature
s	singlet/strong
sat.	saturated
sh	sharp
SOMO	singly occupied molecular orbital
t	triplet
t	tertiary
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
tert	tertiary
TES	triethylsilyl
Tf	triflate
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet
v_{max}	absorption maxima
w	weak

Chapter 1: Introduction to Ropinirole Hydrochloride

1.1 Background

The active pharmaceutical ingredient (API) ropinirole hydrochloride **1.1** (Figure 1.1) is of great pharmaceutical significance as a symptomatic treatment for Parkinson's disease (PD) and Restless Leg Syndrome (RLS). As the API in Requip™, a trademarked drug marketed by GlaxoSmithKline, it is a selective dopamine agonist, relative to D_1, with a high affinity for G protein-coupled trans-membrane D_2 and D_3 receptors and weak interactions with D_4, D_5 and 5-HT (serotonin). The agonistic activity at D_2 – which is known to affect locomotor activity – triggers the release of the neurotransmitter, dopamine, across the synaptic cleft.[1-4] An approximate ratio of 20:1 for binding to D_3 and D_2 receptors was found in cloned receptor binding studies with respective inhibitory constants (K_i) of 69 nM and 1380 nM for the displacement of radioisotopically labelled iodosulpride, similar to that for the endogenous neurotransmitter dopamine.[4,5] In the perfused rabbit ear artery test (REA), the API was found to have an EC_{50} of 72 nM,[6] comparing reasonably well with dopamine (37 nM).[7]



1.1

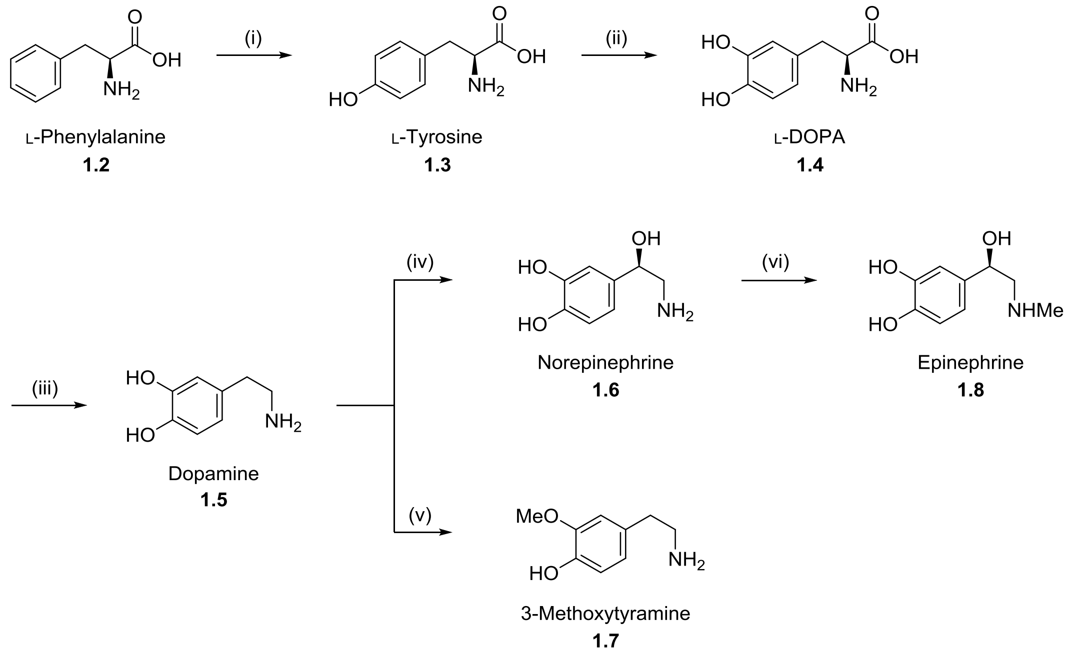
Figure 1.1 Ropinirole hydrochloride **1.1**.

After the expiration of their patents in May 2008, GSK reported a drop in sales of around 40% of Requip™ in the second quarter of that year, as generic drugs were launched into the market. Since then, several of these generic drugs with ropinirole hydrochloride as the API have been approved by the FDA, contributing to a reduction of 60% in the marketing price of Requip™ XL (extended release) in the UK.

Parkinson's disease is a degenerative neurological condition which affects the central nervous system leading to the deterioration of motor and sensory functions. It results from reduced dopamine secretion or weakened dopaminergic neurons in the substantia nigra and is reported to affect 0.2% of the UK population.[8] Dopamine agonists are used to mimic the action of dopamine neurotransmitters, to compensate for the low levels of this catecholamine in the brain. These are vital for signal pathways in the subtantia nigra, allowing smooth motor functions. The effect explains the drug's efficacy in the treatment of RLS (also known as Willis-Ekbom disease) which is characterised by involuntary urges to move one's limbs and affects up to 10% of the European population.[9]

Reports on the effective treatment of RLS with iron supplements in a small group study found that sufferers were often iron deficient. However, these results were not substantiated in further epidemiological studies. The link between iron and RLS was found to be due to the effect of the former on the function of tyrosine hydroxylase[2] – an enzyme which, in a rate-limiting step, catalyses the production of L-DOPA **1.4**, a precursor in the biosynthesis of dopamine **1.5** (Scheme 1.1).[10] Thus, a low concentration of iron may result in low levels of dopamine in the brain. The unknown pathogenesis of the idiopathic disease demonstrates the complexity of its development.

Ropinirole appears to exhibit neuroprotective behaviour, slowing the degeneration of neurons without being prone to the down-regulation, associated with L-DOPA, or dyskinesia. Indeed, clinical data suggests that this can occur in up to 90% of patients on long term treatment of L-DOPA.[11] Nonetheless, common side-effects such as nausea and hallucinations have been linked with ropinirole HCl along with hypersexuality and compulsive gambling, which may be a result of enhanced D_3 activity.[12]



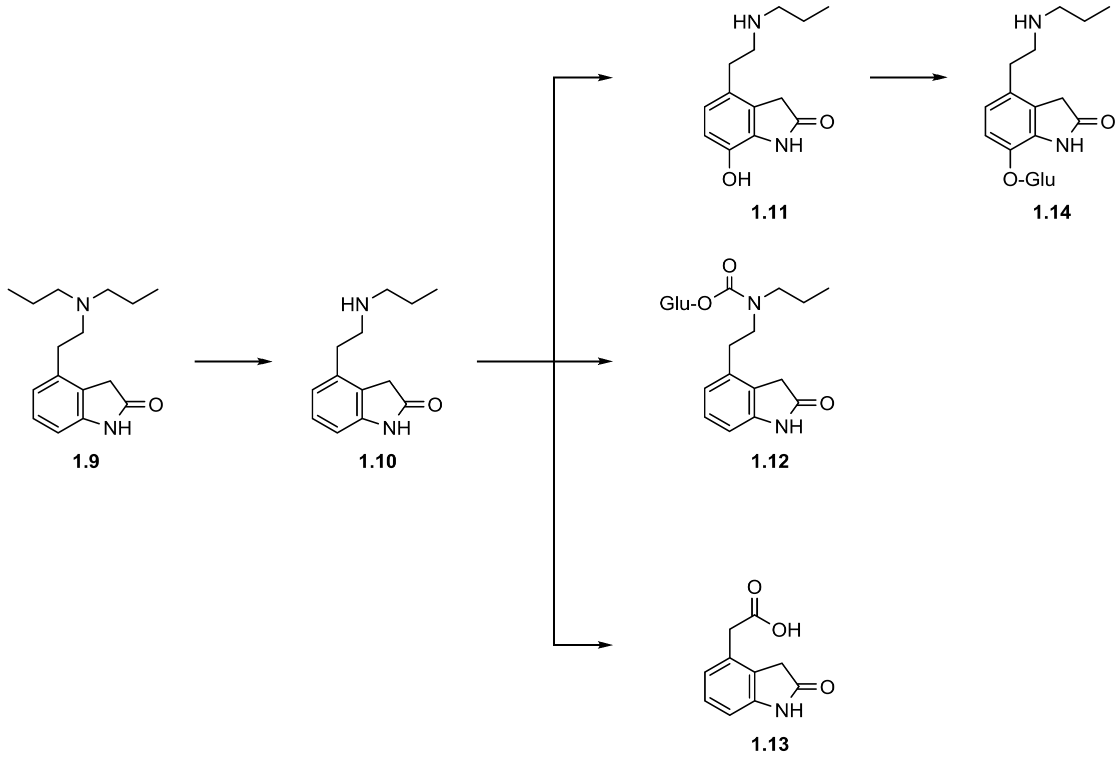
Reagents and conditions: (i) Phenylalanine hydroxylase; (ii) tyrosine hydroxylase; (iii) DOPA decarboxylase; (iv) dopamine β-hydroxylase; (vi) catechol-*O*-methyl transferase; (vi) phenylethanolamine *N*-methyltransferase.

Scheme 1.1 Dopamine **1.5** biosynthesis.[10]

Unlike dopamine, ropinirole can cross the brain-blood barrier, negating the need for a supplement such as levodopa **1.4** (L-DOPA), which itself is a common treatment for PD.[13,14] In reality, the latter is often used in combination with the drug for early-stage treatment. As a non-ergoline dopamine agonist, the API does not induce severe adverse effects such as fibrosis and aneurysm,[15] however long-term studies are still in their infancy with a recent report of aneurysm in a patient following long-term treatment with ropinirole.[3] The 5-HT$_{2b}$ receptor has been implicated in valvular heart diseases for which the ergot-derived dopamine agonists have an affinity. It is however important to note the aforementioned weak interaction of ropinirole with the 5-HT$_{2b}$ receptor.

1.2 Xenobiotic Metabolism of Ropinirole

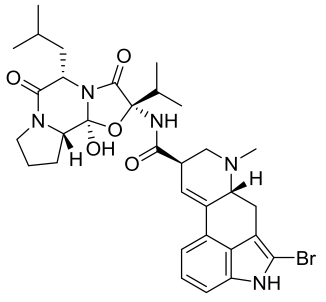
The bioavailability of the drug, when taken orally, is 50% with rapid and near-complete absorption (94% in man) from the gastrointestinal tract. Peak concentrations are achieved between 1-2 h. First-pass metabolism of ropinirole is largely mediated by the CYP1A2 enzyme where the major metabolic pathway is via *N*-depropylation to **1.10** (accounting for up to 40% of dose in urine compared to less than 10% of ropinirole) with β-glucoronidation to **1.14** accounting for phase II metabolism (Scheme 1.2).[16] Low plasma protein binding (11%) of the API was also found in man, with a high steady state volume of distribution (7 L/kg) for *per os* (P.O., oral) administration which is consistent with the lipophilicity of the drug, its ability to cross the brain-blood barrier and to dispense itself into tissue and organs. Amongst the metabolites in the metabolic pathway in man, none are believed to have any dopamine agonist activity (*in vivo*), where the major route of excretion is renal (> 90% following intravenous and P.O. administration).



Scheme 1.2 Major metabolic pathways of ropinirole **1.9** in man.[16]

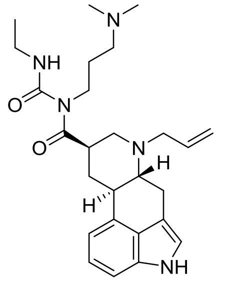
1.3 Common Anti-Parkinson's and RLS Drugs

Numerous symptomatic treatments for PD exist, amongst which, the most common dopamine agonists (ergoline **1.15→1.18** and non-ergoline **1.19→1.22**) are shown in Figure 1.2.[17] The focus of non-ergoline drugs developed in this area is often geared towards achieving dopamine receptor selectivity (such as D_2 versus D_1) with minimal side-effects. Other classes of drug, including glutamate agonists, anticholinergics and monoamine oxidase (MOA-B) inhibitors, have also been used to treat motor symptoms, albeit to a lesser extent.



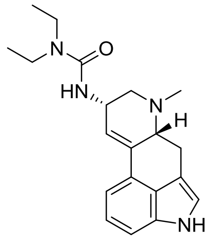
Bromocriptine

1.15



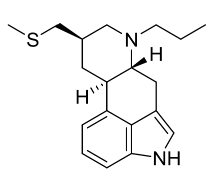
Cabergoline

1.16



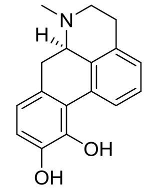
Lisuride

1.17



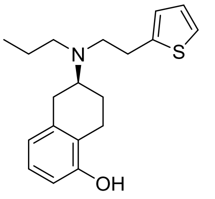
Pergolide

1.18



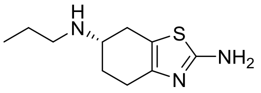
Apomorphine

1.19



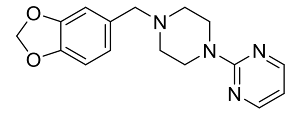
Rotigotine

1.20



Pramipexole

1.21

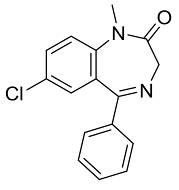


Piribedil

1.22

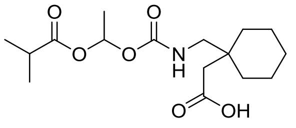
Figure 1.2 Anti-Parkinson's dopaminergic drugs.

Similarly, dopamine agonists such as cabergoline, pramipexole and rotigotine are reported to reduce RLS symptoms, along with benzodiazepines and gabapentin encabil[18] (Figure 1.3).



Diazepam

1.23



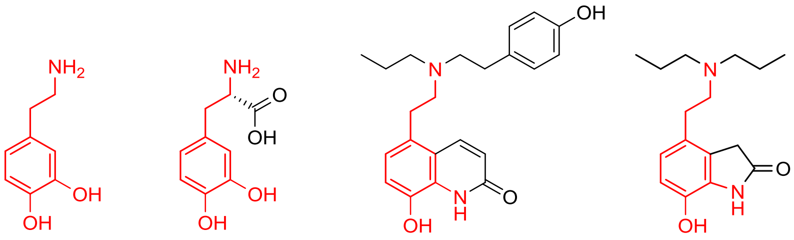
Gabapentin Encarbil

1.24

Figure 1.3 Anti-RLS drugs.

1.4 Bioisoteric Nature of Dopaminergic Agonists

Catecholamine mimics such as carbosyril **1.25** (Figure 1.4) have been noted for their marked potency compared to dopamine **1.5**.[19,20] In the case of **1.25**, which is more than three times more active at D_2 receptor sites (than dopamine), the NH group mimics the *meta*-OH group. It was long believed that analogous *para*-OH groups on such moieties were required for activation of dopamine receptors.[21] Indeed, **1.26** had been successfully employed by Smith, Kline & French (SK&F) for activating D_2 receptors in the peripheral nervous system (PNS), improving cardiovascular conditions (such as congestive heart failure and angina pectoris) and exhibiting vasodilation, decreasing renal vascular resistance, amongst other benefits.[22]

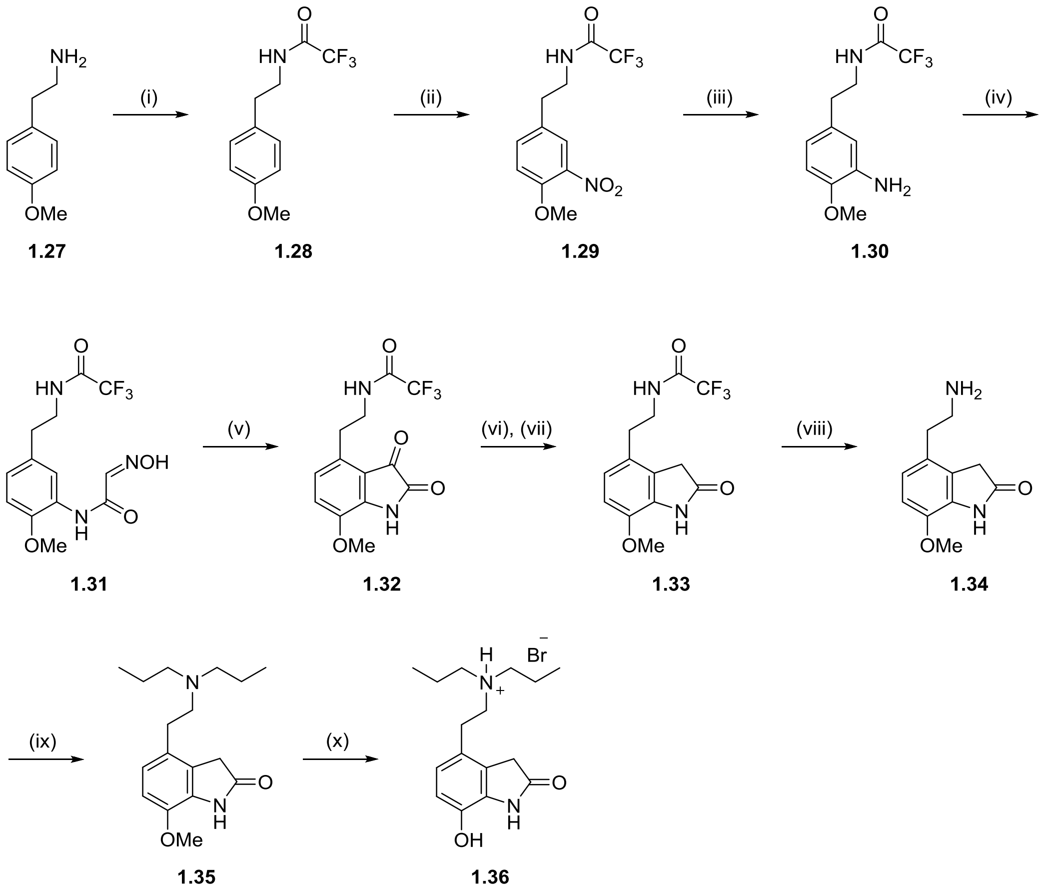


1.5 **1.4** **1.25** **1.26**

Figure 1.4 Similarity of 7-hydroxyropinirole **1.26** to catecholamines.

1.4.1 Synthesis of 7-Hydroxyropinirole Hydrobromide 1.36

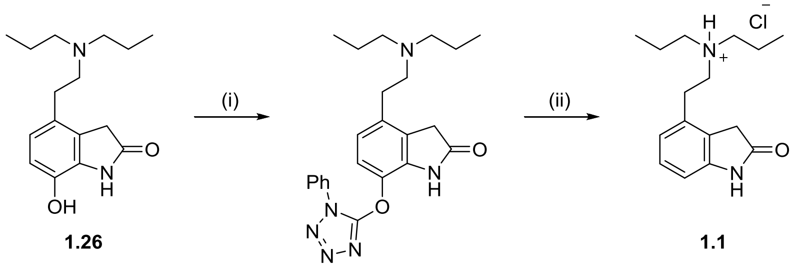
The SK&F synthesis of the hydrobromide salt of 7-hydroxyropinirole **1.26** began with amine **1.27** (Scheme 1.3) which was protected as its trifluoroacetamide **1.28** prior to nitration of the aromatic with HNO_3 and TFA (to light-sensitive **1.29**) and hydrogenation to aniline **1.30**.[21,23,24] A Sandmeyer isonitrosoacetanilide isatin synthesis with chloral hydrate and hydroxylamine next gave oxime **1.31** which cyclised to isatin **1.32** in the presence of concentrated H_2SO_4. Isatin **1.32** was then reduced via a thioketal, or directly,[25] with catalytic Raney™ nickel or Pd/C to yield oxindole **1.33**. Hydrolysis then gave amine **1.34** which underwent reductive alkylation with propanal to the desired tertiary amine **1.35**. Finally, deprotection of the aryl methyl ether with BBr_3 or concentrated HBr relinquished the desired hydroxyl group to give their target **1.36** in 2% yield overall.



Reagents and conditions: (i) TFAA, CH_2Cl_2, 88%; (ii) conc. HNO_3, TFA, 84%; (iii) Raney™ Ni (cat.), $H_2NNH_2.H_2O$, EtOH, 76%; (iv) 2,2,2-trichloroethane-1,1-diol, conc. H_2SO_4, $(NH_3OH)_2SO_4$, 68%; (v) conc. H_2SO_4, 64%; (vi) $(CH_2SH)_2$, $BF_3.OEt_2$, CH_2Cl_2; (vii) Raney™ Ni, EtOH, 70% over 2 steps; (viii) 6 M HCl, EtOH, 87%; (ix) H_2, EtCHO, 10% Pd/C, AcOH, 21%; (x) conc. HBr, 75%.

Scheme 1.3 SK&F's route to 7-hydroxyropinirole HBr **1.36**.[21,23]

Remarkably, removal of the OH group from the free base **1.26** (Scheme 1.4),[6,26] through coupling with chlorophenyltetrazole and hydrogenolysis, led to ropinirole **1.9** which retained the dopaminergic activity (albeit with a lowering of D_2 activity by a factor of forty), and was no longer subject to tachypylaxis and it was more readily absorbed from the gastrointestinal tract than the 7-hydroxy congener.[27]


1.26

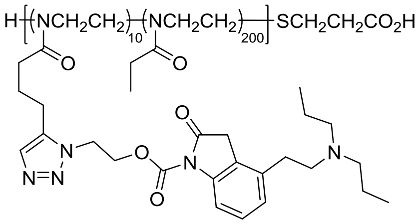
1.37

1.1

Reagents and conditions: (i) 5-Chloro-1-phenyl-1*H*-tetrazole, K_2CO_2, DMF, 68%; (ii) H_2, 10% Pd/C, AcOH, then HCl, 74%.

Scheme 1.4 Reduction of **1.37** to ropinirole HCl **1.1**.[6]

Functionalisation of API's onto a poly(oxazoline) polymer via a hydrolysable linker (**1.38**, Figure 1.5) dramatically increases their half-lives through gradual and near zero-order hydrolysis, in some instances, to release the drug into the bloodstream.[28] Subcutaneous administration was the most effective means of administrating the drug in pharmacokinetic testing, increasing the half-life of rotigotine **1.20** from less than 3 h to 60 h (depending on the nature of the polymer chain). This method of sustained release of the API overcomes problems associated with the initial high concentration of the API followed by rapid clearance associated with oral or parenteral administration. Indeed, such discontinuous stimulation may exacerbate neuron misfiring and degeneration.



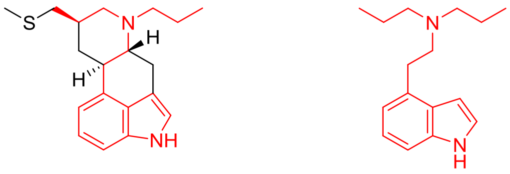
1.38

Figure 1.5 Polymer-functionalised ropinirole **1.38**.[28]

Such polymers are particularly useful for APIs of low oral bioavailability and low aqueous solubility as well as those which may undergo peripheral metabolism. By tuning the nature of the linking groups between the polymer and drug, the size of the polymer and route of administration (intravenous versus subcutaneous), the drug release profile kinetics can be tightly controlled.

1.4.2 Biological Relevance of Indole 1.39

Regarding the bioactivity of ropinirole **1.9**, findings from Lilly almost a decade beforehand inferring the potential CNS effect of 4-substituted oxindoles along with the dopaminergic action of indole **1.39** (a suggested pharmacophore of many ergot alkaloids such as **1.18**, Figure 1.6) perhaps alluded to the unexpected efficacy of the API in question.[29,30] Almost five years later, SK&F filed a patent uncovering ropinirole's use as an anti-Parkinson's drug.[22]

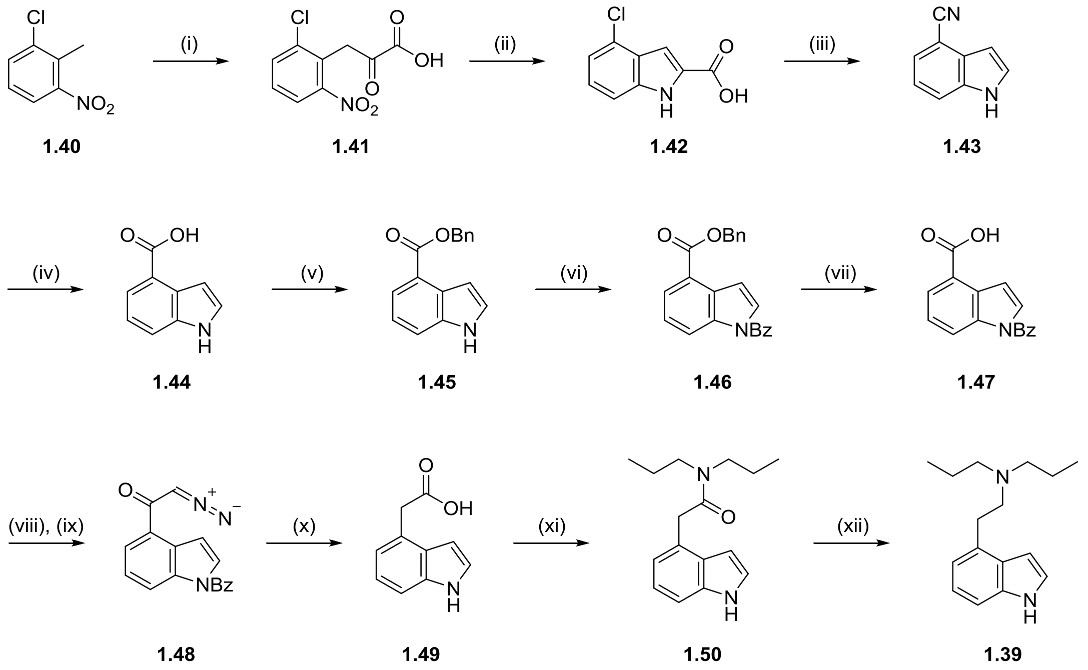


1.18 **1.39**

Figure 1.6 Common indole scaffold in bioactive compounds.

1.4.3 Synthesis of Indole 1.39

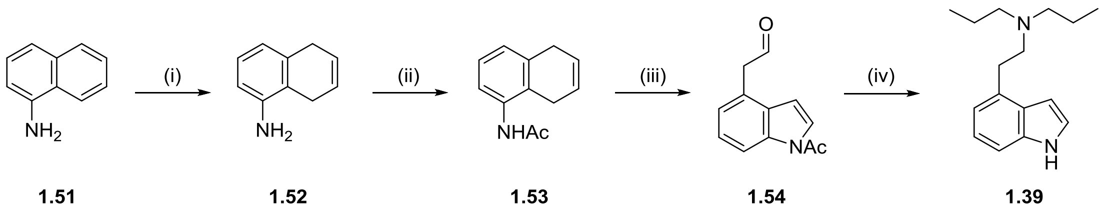
Indole **1.39** has been synthesised by Cannon *et al.*[30,31] from **1.40** using Uhle's Reissert indole synthesis[32] wherein the 4-chloro substituent of **1.42** is coupled with Cu_2CN_2 and decarboxylated to give key intermediate **1.43** in 20% yield over three steps, after which hydrolysis and double protection to **1.46** and deprotection of the benzyl ester gives 93% of **1.47** (Scheme 1.5). Acid **1.47** was then subjected to an Arndt-Eistert homologation with concurrent debenzoylation to indole-4-acetic acid **1.49**. Amide formation, with activated phosphine, and reduction completed the laborious twelve-step sequence.



Reagents and conditions: (i) $(CO_2Et)_2$, Na, EtOH, 42% (71% brsm); (ii) $FeSO_4.5H_2O$, sat. NH_4OH, H_2O, 92%; (iii) Cu_2CN_2, quinolone, 51%; (iv) aq. 30% KOH, Δ, 90%; (v) *N*,*N*'-dicyclohexyl-*O*-benzylisourea, DMF, 89%; (vi) BzCl, NaOH, $(^n Bu_4N)HSO_4$, CH_2Cl_2, 97%; (vii) H_2, 10% Pd/C, AcOEt, 93%; (viii) $SOCl_2$, CH_2Cl_2; (ix) CH_2N_2, Et_3N, Et_2O, 78% over 2 steps; (x) aq. AgOBz, Et_3N, EtOH; (xi) $^n Pr_2NH$, HMPT, CCl_4, THF, 85%; (xii) $LiAlH_4$, THF, 61%.

Scheme 1.5 Cannon's route to indole **1.39**.[30-32]

An attempt to prepare indole **1.39** by Eli Lilly using Pleininger's methodology proved problematic with an Lemieux-Johnson alkene cleavage of 5,7-dihydro-1-naphthylamide **1.53**, employing toxic OsO_4, and indolisation to **1.54** proceeding in just 24% yield.[33] No yields were given for the remaining steps and interestingly, the opportunity for improvement was never examined (Scheme 1.6).

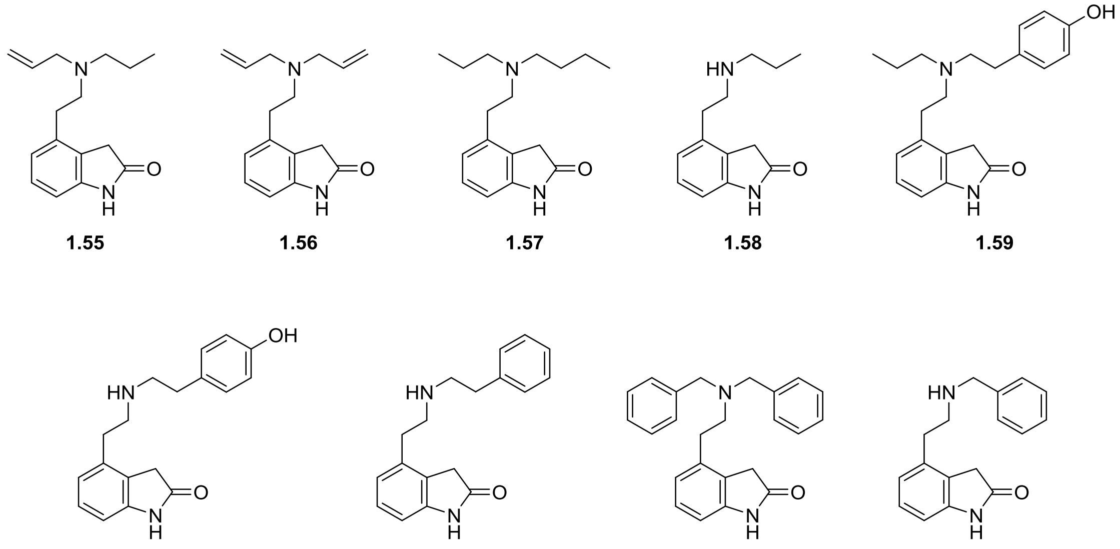


Reagents and conditions: (i) Na, EtOH, xylene; (ii) Ac_2O; (iii) OsO_4 (cat.), $NaIO_4$, then oxalic acid, H_2O, 24%; (iv) $^n Pr_2NH$, $NaBH_3CN$, EtOH, then Na.

Scheme 1.6 Eli Lilly's route to indole **1.39**.[33]

1.5 Related Compounds and their Bioactivity

Several analogues of ropinirole and 7-hydroxyropinirole were synthesised (**1.55→1.63**, Figure 1.7) and tested for their biological activity.[27,34] In particular, variance of the amine substituents was found to deliver significant D_2 agonists; the same pattern was found for the isatin analogues.[35] Considerable effort has been paid to hydroxyphenyl **1.59**, although little has been published regarding the biological assays and relative potency of each of the analogue compounds.

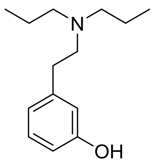


1.55 **1.56** **1.57** **1.58** **1.59**

1.60 **1.61** **1.62** **1.63**

Figure 1.7 Dopaminergic analogues of ropinirole **1.9**.[27]

It was reasoned that for effective dopamine agonism, catechol mimics required two hydroxyl groups – or vinylogous moieties - since the dehydroxylated equivalent of dipropyldopamine, dipropyl-*m*-tyramine **1.64** (Figure 1.8),[23] showed no *in vitro* activity on peripheral dopamine receptors. Methylation of 7-hydroxyropinirole also depleted its biological activity. However, as we have seen with ropinirole, the inclusion of the '*para*'-hydroxyl group is not a prerequisite.

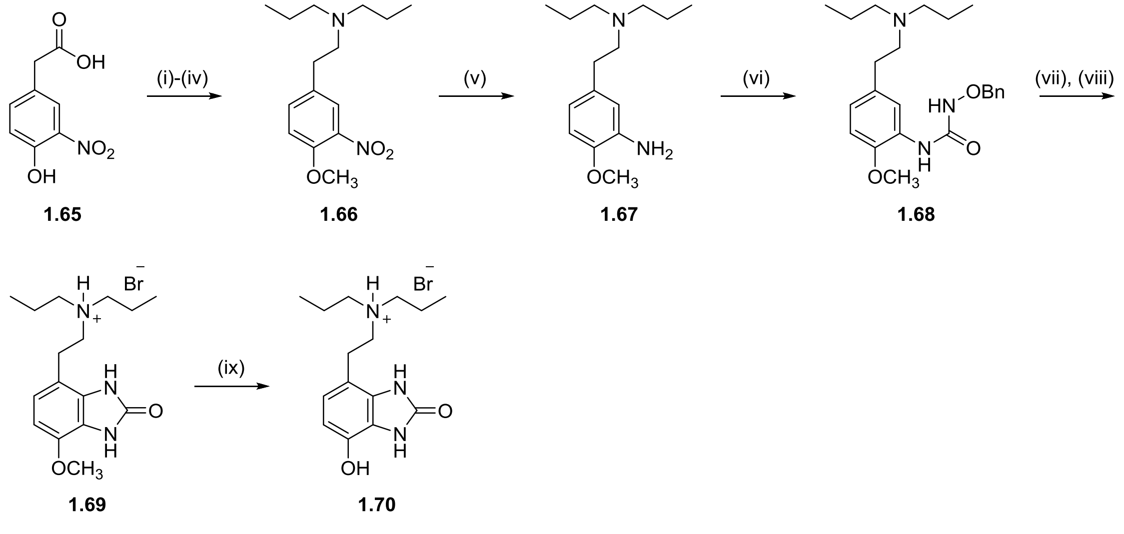


1.64

Figure 1.8 *N*,*N*-dipropyl-*m*-tyramine **1.64**.

As discussed previously, the hydroxyl congener of ropinirole hydrohalide, **1.36**, is forty times more potent at the D_2 presynaptic peripheral receptor than the API. These preliminary results insinuated that the '*meta*'-hydroxyl group and, as with the case with our oxindoles, the methylene group of the lactam unit were paramount for interaction with receptor proteins. Indeed, methylation of the oxindole nitrogen rendered this 7-hydroxyropinirole analogue inactive as a drug at the D_2 site. Monomethylation at the C-3 carbon showed little perturbation of binding affinity whereas dimethylation led to a complete loss of potency. This could be due to either a steric factor or the loss of an acidic proton.[34]

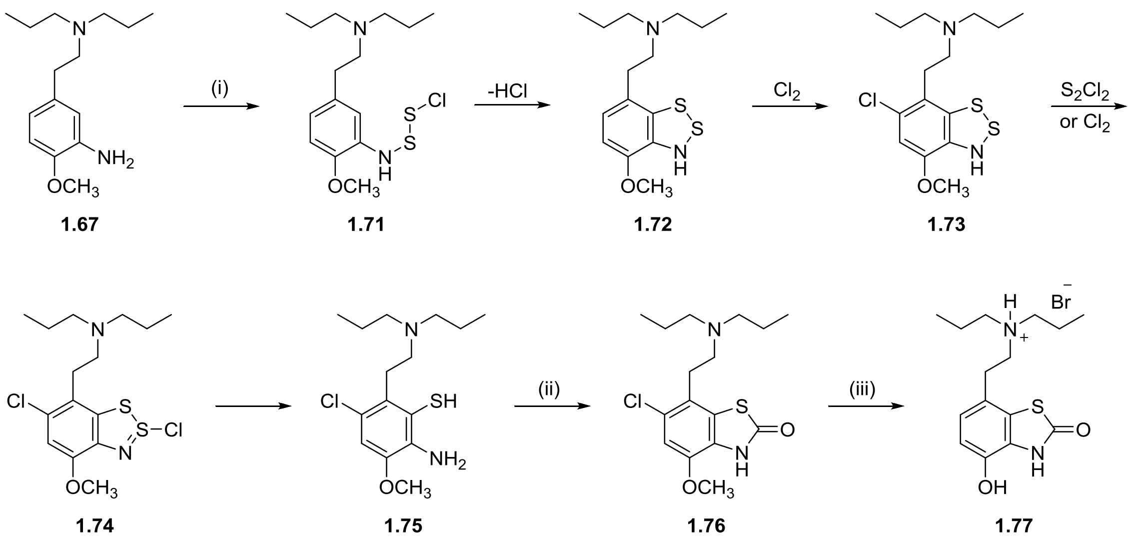
The diminished activity due to the loss of an acidic proton seemed unlikely as the isatin analogues showed anti-hypertensive activity. Furthermore, replacing the methylene unit with a secondary amine (to give **1.70**) led to a consequential lowering of p*K*a of the 3-position, yet it failed to display any improvements in biological assays. Acid **1.65** was converted to tertiary amine **1.67** (42% yield over five steps) in a few routine transformations after which coupling to urea **1.68** was followed by $Pb(OAc)_4$ assisted cyclisation to benzimidazolone **1.69** (Scheme 1.7). BBr_3 deprotection delivered the analogue salt **1.70** in 86% yield. Replacement of the methylene unit with oxygen presented no change in D_2 affinity.



Reagents and conditions: (i) $SOCl_2$; (ii) $^{n}Pr_2NH$, $CHCl_3$, 60% over 2 steps; (iii) K_2CO_3, $(CH_3)_2SO_4$, H_2O, DMF, 97%; (iv) B_2H_6, THF, 100%; (v) H_2, 2% PtO_2, 73%; (vi) $COCl_2$, $CHCl_3$, then $BnONH_2$; (vii) $Pb(OAc)_4$, $CHCl_3$; (viii) H_2, Raney™ Ni (cat.), EtOH, 22% over 3 steps; (ix) BBr_3, $CHCl_3$, 86%.

Scheme 1.7 SK&F's route to benzimidazolone HBr **1.70**.[34]

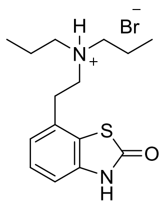
Remarkably, switching for sulfur analogue **1.77** led to a sixty four-fold increase in binding to REA, with no adenylase cylase activity (no D_1 agonism) and was competitively antagonized by (*S*)-sulpiride. Thus, it was clear that alkylation of the C-3 methylene chain was inducing a steric factor, forcing the geometry of the aminoethylene chain away from the optimal conformation for positive agonist-receptor interaction. The synthesis of the oxo-benzothiazole **1.77** was achieved using a Herz reaction,[36] where the amino group of **1.67** attacks S_2Cl_2 and electrophilic aromatic substitution resulting in **1.72** (Scheme 1.8). The subsequest steps to **1.74** have been the subject of debate,[37,38] where one proposed sequence descrbed the *in-situ* formation of Cl_2, via an Orton rearrangement, to subject the phenyl ring to electrophilic aromatic chlorination to give **1.73**. Oxidation with either another molecule of S_2Cl_2 or Cl_2 results in **1.74** which is hydrolysed to *o*-aminothiophenol **1.75**. Alternatively, chlorination of the aromatic could also occur after the formation of the oxo-benzothiazole ring and plausibly may occur via nucleophilic substitution. Benzothiazolone formation with $COCl_2$ to **1.76**, reductive dechlorination and phenol deprotection then furnished **1.77** in 25% yield from **1.67**.



Reagents and conditions: (i) S_2Cl_2, AcOH, then $Na_2S_2O_4$, aq. NaOH, 72%; (ii) $COCl_2$, $PhCH_3$, Δ, 94%; (iii) (a) Na, xylene, pentan-1-ol, 59%, (b) conc. HBr, 63%.

Scheme 1.8 SK&F's route to benzothiazolone HBr **1.77**.[34,39]

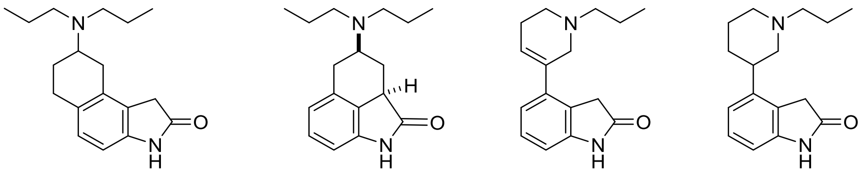
As inferred earlier, removal of the 7-hydroxy functional group from ropinirole lowered effective dose values, albeit within the range of potency. The des-OH benzothiazolone **1.78** (Figure 1.9) demonstrated a lowering of three orders of magnitude in inhibitory concentration values compared to **1.77**. Free amines, however, tended to have D_1 agonistic activity as seen from their adenylate cyclase stimulation.



1.78

Figure 1.9 Des-OH benzothiazolone HBr **1.78**.

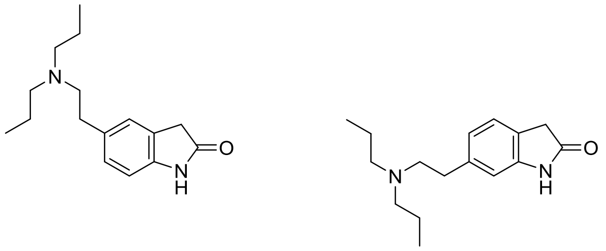
Tethering the ethylamine side chains of ropinirole, as in the racemate of **1.79** (Figure 1.10),[40,41] not only exhibited D_2 activity but showed potency towards both the D_3 and 5-HT$_1$ receptors, thereby acting as effective re-uptake inhibitors for norepinephrine and 5-HT with therapeutic effects for various CNS disorders such as depression, schizophrenia and PD amongst others.



1.79 **1.80** **1.81** **1.82**

Figure 1.10 Conformationally restricted ropinirole **1.9** analogues.

Similarly, tethered amine **1.80**,[42,43] the related tetrahydropiridinyl **1.81** and piperidinyl **1.82** compounds[44] were also dopaminergic stimulators, the latter two particularly displaying anti-anoxic properties. Isomers of ropinirole **1.83** and **1.84** were synthesised to further verify the hypothesis that a *meta*-hydroxy group (or appropriate mimic) was needed for dopaminergic activity (Figure 1.11)[23]. As anticipated, neither exhibited peripheral D_2 activity for vasoconstriction response.

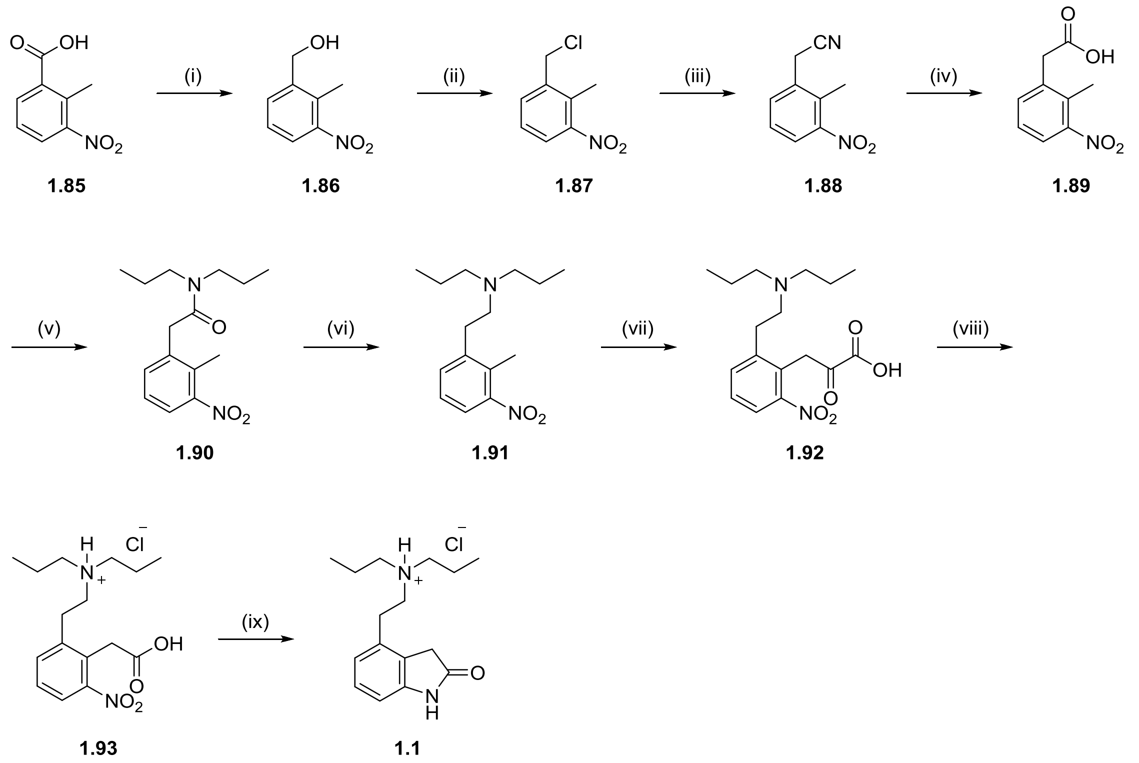


1.83 **1.84**

Figure 1.11 Regioisomers of ropinirole **1.9**.

1.6 SK&F's Initial Route to the API

A suitable bench-scale route to ropinirole had been developed by SK&F from the relatively cheap benzoic acid **1.85**. This was reduced to alcohol **1.86** with borane and then converted to nitrile **1.88** by refluxing in concentrated HCl followed by displacement of the resulting chloride with KCN (Scheme 1.9).[45] Acid hydrolysis then liberated homologue **1.89** in high yield. Conversion to amide **1.90** via the acid chloride next gave access to amine **1.91** by another borane reduction. Homologation of the toluenic carbon was then effected by deprotonation and condenstation with diethyl oxalate. Cleavage of the resulting pyruvic acid **1.92** with H_2O_2 and NaOH next formed **1.93**, which was converted to its HCl salt before being subjected to a reductive cyclisation to the API **1.1**.[46] An overall yield of 23% was reported for this sequence. The length of the route in conjunction with the nature and cost of materials made this an unattractive and prohibitive route for large scale synthesis.

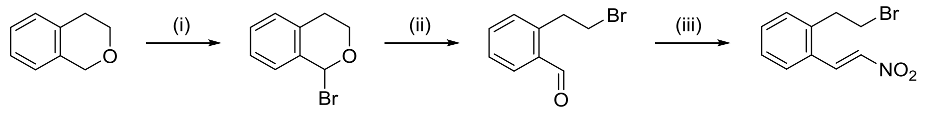


Reagents and conditions: (i) BH_3.THF, THF, 100%; (ii) conc. HCl, 100%; (iii) KCN, EtOH, H_2O, 99%; (iv) H_2SO_4, AcOH, H_2O, 97%; (v) $SOCl_2$ then ${}^{n}Pr_2NH$, 90%; (vi) BH_3.THF, THF, 83%; (vii) $(CO_2Et)_2$, KOEt, then H_2O, 52%; (viii) H_2O_2, aq. NaOH, then HCl, 80%; (ix) H_2, 5% Pd/C, EtOH, 78%.

Scheme 1.9 SK&F's first route to ropinirole HCl **1.1**.[45]

1.7 GSK's 2nd Generation Route to the API

Commercially available isochroman **1.94**, which can be synthesised from 2-phenylethanol in a Pictet-Spengler-type reaction, was used as the starting point for a 2nd generation synthesis (Scheme 1.10). A radical bromination of the reactive methylenic carbon gave **1.95**. By contrast, photochemical bromination followed by treatment with 48% HBr solution successfully delivered benzaldehyde **1.96** in 85% yield on a laboratory scale. Moving this process to the pilot-plant proved troublesome as the procedure failed to produce comparable yields, with the reaction delivering just 46% of desired product **1.96** which, even with specialised photochemical reactors, could not be improved upon. Nitro-styrene formation in basic methanolic medium then furnished **1.97** in 80% yield.[47,48]



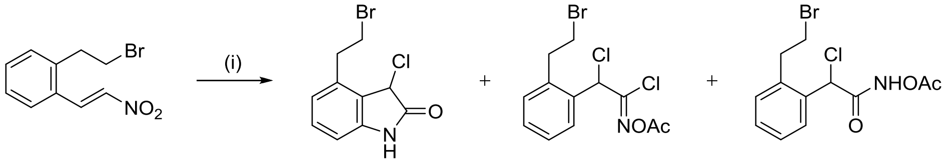
1.94 **1.95** **1.96** **1.97**

Reagents and conditions: (i) Br_2, hv; (ii) 48% HBr, 46% over 2 steps; (iii) CH_3NO_2, NaOMe, MeOH, then aq. HCl, 80%.

Scheme 1.10 SK&F's initial isochroman **1.94** ring opening.[47,48]

1.7.1 Royer Ring Closure

An unusual Lewis acid-assisted ring closure employing AcCl in CH_2Cl_2, developed by René Royer in the late 1970s, next delivered 3-chlorooxindole **1.98** in 53% yield along with two major by-products, **1.99** and **1.100**, both of which could conveniently be separated from the desired product via crystallisation of the desired product from CH_2Cl_2/petroleum ether (Scheme 1.11).[47,48]

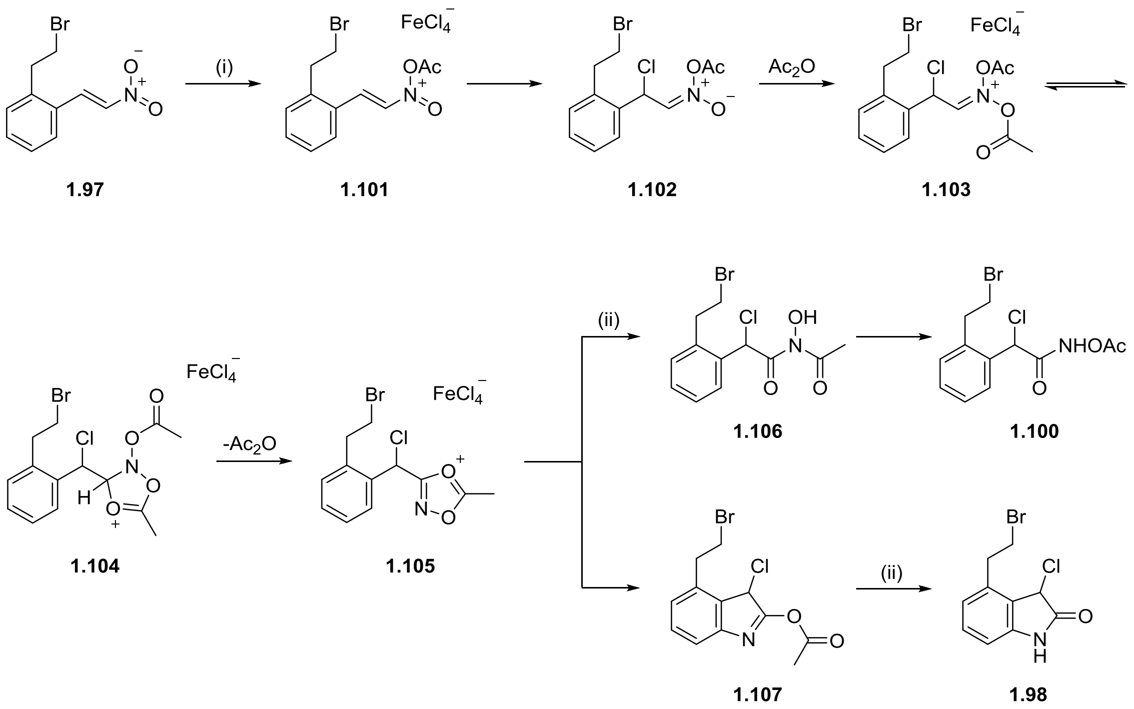


1.97 **1.98** **1.99** **1.100**

Reagents and conditions: (i) AcCl, $FeCl_3$, CH_2Cl_2.

Scheme 1.11 Royer cyclisation to oxindole **1.98**.[47-50]

The mechanism of the Royer ring closure (Scheme 1.12)[51-53] is believed to involve coordination of the nitro group to $FeCl_3$ which induces a Michael-type addition of chloride, leading to nitronate **1.102** after acylation. Alternatively, acylation of **1.97** precedes chlorination of **1.101** to **1.102**. Acylation again then furnishes **1.103** to trigger cyclisation to **1.104** with ensuing elimination of AcOH giving intermediate **1.105**. Premature quenching of **1.105** with H_2O results in **1.106** which rearranges to by-product **1.100**. The desired pathway, however, results from a ring closure to intermediate **1.107** which, upon quenching, is hydrolysed to the target indolone **1.98**. The major by-product **1.99** is likely to result from the quenching of the imminium **1.103** with chloride and elimination of AcOH, although routes from several of the intermediates could also deliver the same dichlorooxime.

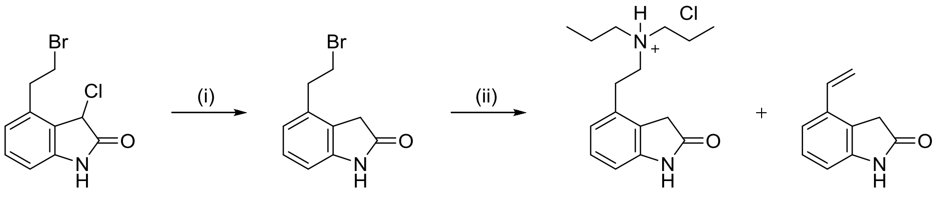


Reagents and conditions: (i) AcCl, $FeCl_3$, CH_2Cl_2; (ii) H_2O.

Scheme 1.12 Proposed mechanism for the Royer cyclisation.[51-53]

Several conventional Lewis acids for the cyclisation were tested by Royer *et al.*, such as $AlCl_3$, $ZnCl_2$ and $TiCl_4$, of which the former provided the best yields for **1.98** and the latter two furnished **1.99** exclusively, although none were as effective as $FeCl_3$.[53] A pilot-plant yield of 54% for oxindole **1.98** had been achieved by GSK with $FeCl_3$, despite a bench-scale yield of 98% having been reported prior to that.[50]

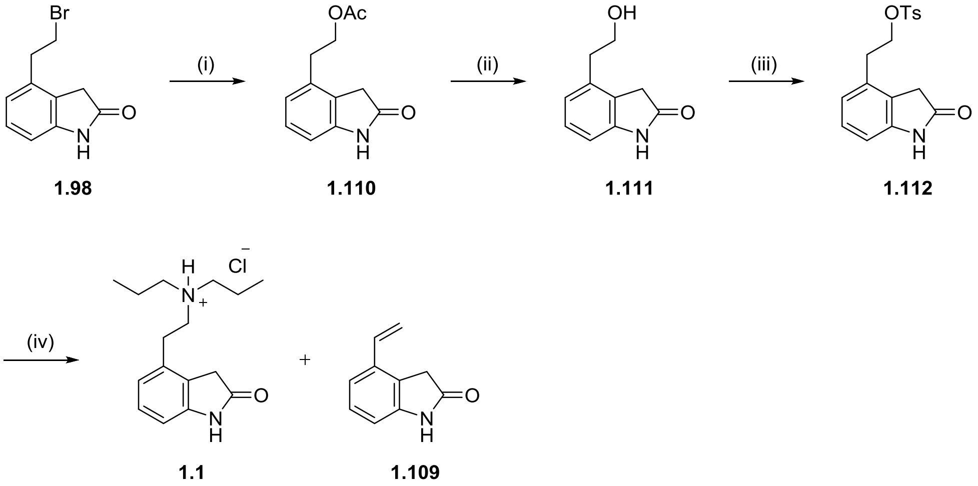
Catalytic Transfer Hydrogenolysis (CTH) of **1.98** with NaH_2PO_2 and catalytic Pd/C was next used to reduce the C-Cl bond prior to S_N2 substitution with ^{n}Pr$_2$NH (Scheme 1.13). E2 elimination leading to styrene **1.109** proved highly problematic as only 57% of the API salt was isolated along with 38% of the by-product.



Reagents and conditions: (i) $NaH_2PO_2.xH_2O$, 10% Pd/C, EtOAc, H_2O, 95%; (ii) ^{n}Pr$_2$NH, H_2O, then HCl, 57% of **1.1** and 38% of **1.109**.

Scheme 1.13 S_N2 substitution of bromide **1.108** to ropinirole HCl **1.1**.

No improvement was seen in a screening of the corresponding chloride and iodide. However, with sulfonate ester **1.112**, high selectivity (40:1 ratio) for substitution was observed with ropinirole HCl formed in 85% (Scheme 1.14). The improvement was attributed to its large size which raises the energy barrier for adoption of reactive conformers with the appropriate anti-periplanar relationship required for E2 elimination to take place. Indeed, the better leaving group ability of iodine further promoted the undesired reaction. Thus, alkyl bromide **1.98** was refluxed with NaOAc in aqueous EtOH to afford ester **1.110**, after which hydrolysis provided alcohol **1.111** in a moderate yield of 70%. Tosylation in CH_2Cl_2 with pyridine delivered the API precursor **1.112** in 87% yield, with the final substitution affording the target salt.

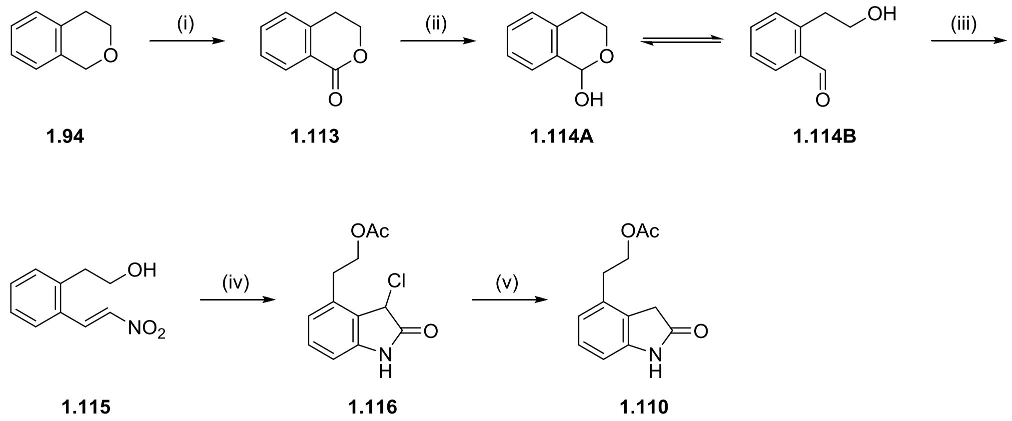


Reagents and conditions: (i) NaOAc, aq. EtOH, 89%; (ii) conc. HCl, H_2O, 70%; (iii) TsCl, py, CH_2Cl_2, 87%; (iv) ^{n}Pr$_2$NH, H_2O, then HCl, 85% of **1.1**.

Scheme 1.14 Improved substitution to ropinirole HCl **1.1**.[47]

1.7.2 Improved Route for Ring Opening

The desire to proceed via tosylate **1.112** prompted research into an alternative route that could deliver this more easily. Thus, a new isochroman ring opening route was sought to provide alcohol **1.114B** (Scheme 1.15). Benzylic oxidation of isochroman to lactone **1.113** was accomplished using PCC[54] and this was immediately followed by reduction to lactol **1.114A**, in equilibrium with **1.114B**, in 73% yield over two steps.[55,56] Nitrostyrene formation and Royer ring closure, as before, afforded the acylated product **1.116** in 42%. Catalytic transfer hydrogenolysis reduction of the C-Cl bond then gave the key oxindole intermediate **1.110** to intersect the previous synthesis of the API.



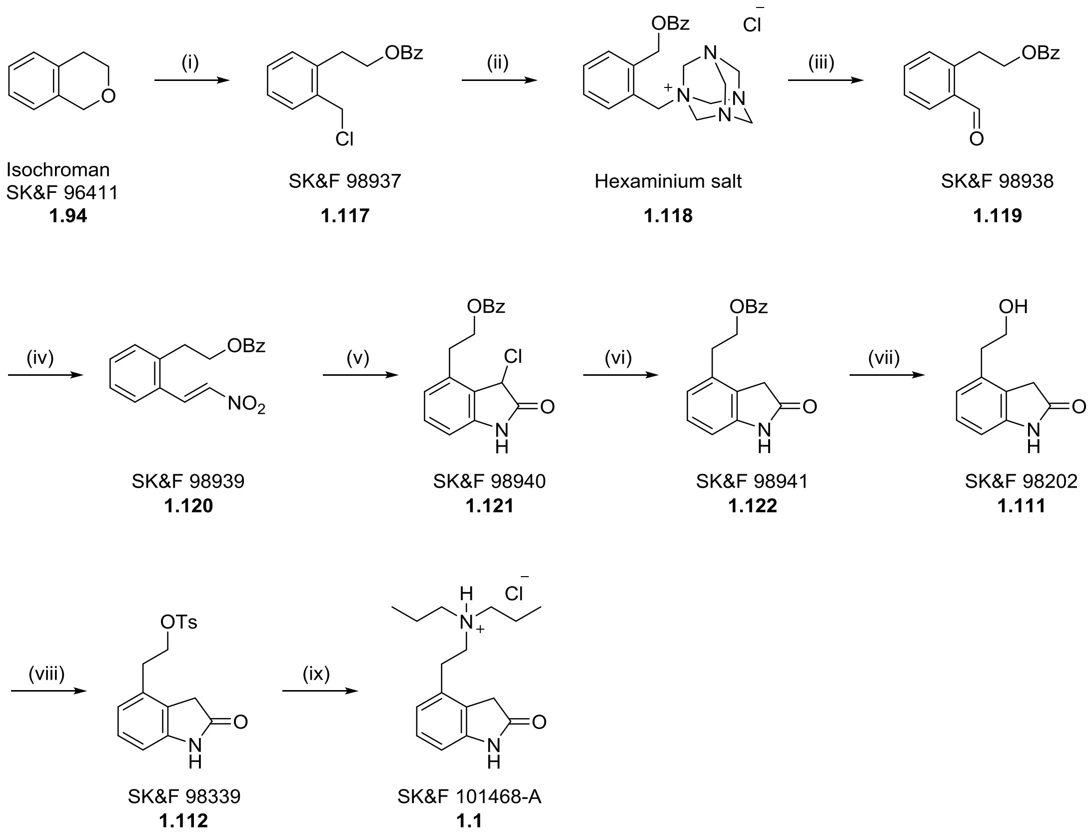
Reagents and conditions: (i) PCC, CH_2Cl_2; (ii) DIBAL-H, 73% over 2 steps; (iii) CH_3NO_2, NaOMe, MeOH, 81%; (iv) AcCl, $FeCl_3$, CH_2Cl_2, 42%; (v) $NaH_2PO_2.x.H_2O$, 10% Pd/C, EtOAc, H_2O, 85%.

Scheme 1.15 Modified ring opening of isochroman **1.94**.[47,55]

It was found that acylation of alcohol **1.115** prior to Royer cyclisation improved the yield of chlorooxindole formation, thus a better approach to an *O*-acylated precursor was desired.

1.7.3 Industrial Process Route

The stage was now set to establish the manufacturing route to ropinirole. Treating isochroman **1.94** with AcCl and stoichiometric $AlCl_3$ effected its ring opening to **1.117** in a modest 45% yield (Scheme 1.16). Significant polymerisation was observed which was attributed to the reactivity of the acetyl residue with the Lewis acid. Improvements in yield, up to 95%, were made when $ZnCl_2$ was used as the Lewis acid and the acetyl group was switched to a benzoyl group (this also prevented hydrolysis of the ester in the later Henry reaction).[47] Sommelet oxidation of chloride **1.117** with HMTA occurred with modest conversion, typically giving yields in the 52–60% range for **1.119** on plant scale (Scheme 1.16). Preparing the nitrosytrene in neutral conditions, using McDonald's variation of the Henry reaction allowed crystallisation of the product from the reaction mixture in 87% yield – a feat that was not achieved with the classical method using a nitromethane anion. It was noted that imine formation with $BuNH_2$ followed by condensation with CH_3NO_2 prevented the isolation of a nitro alcohol side product which resulted in a loss of yield. Royer cyclisation of **1.120** to **1.121** then proceeded in 54–69% yield, and catalytic transfer hydrogenolysis in 95% yield at best using hydrazine hydrate as the hydrogen source. Basic hydrolysis of ester **1.122** then liberated alcohol **1.111** (85% yield over two steps). Tosylation, employing pyridine, next provided precursor **1.112** in up to 89% yield with substitution and acid treatment affording ropinirole hydrochloride **1.1** in 85% yield.



Reagents and conditions: (i) PhCOCl, $ZnCl_2$ (cat.), CH_2Cl_2; (ii) HMTA, IMS; (iii) AcOH, H_2O; (iv) CH_3NO_2, $^{n}BuNH_2$, AcOH, IPA, MeOH, 54–69% over 4 steps; (v) AcCl, $FeCl_3$, CH_2Cl_2, 39–55%; (vi) $N_2H_4.H_2O$, 10% Pd/C or $NaH_2PO_2.xH_2O$, 10% Pd/C or H_2, 10% Pd/C ; (vii) NaOH, H_2O, 78–90% over 2 steps; (viii) TsCl, py, CH_2Cl_2, 79–89%; (ix) $^{n}Pr_2NH/H_2O$, then HCl, 71–85%, 12–25% overall.

Scheme 1.16 GSK's industrial process for the synthesis of ropinirole HCl **1.1**.[48]

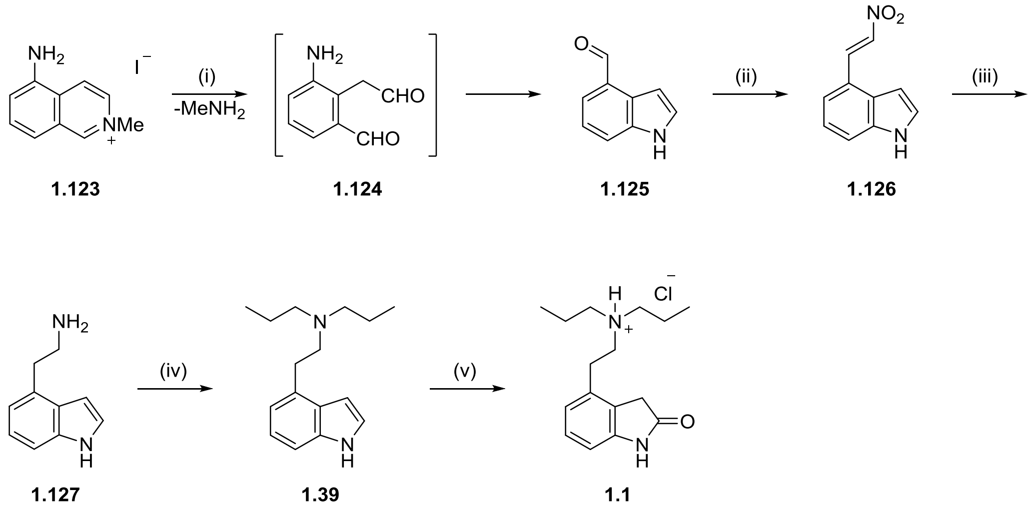
These improvements led to a 75% saving in cost and this route was adopted for the manufacturing of the API. Several of the synthetic transformations were adapted into single stages. Accordingly, an overall yield of *ca*. 12% of ropinirole hydrochloride could be realised for the industrial process.[48]

However, the current synthetic route employed by GSK is no longer cost effective as various other pharmaceutical companies are now manufacturing the generic drug. As such, significantly shorter and more cost-effective routes to the API have subsequently been established.

1.8 Alternative Syntheses of Ropinirole HCl

1.8.1 Urquima's Route to the API

One notable example is a synthesis developed by Urquima S.A. which began with the alkylated 5-amino-isoquinolinium **1.123** (Scheme 1.17).[57,58] This underwent hydrolysis and cyclisation to 4-formylindole **1.125** on treatment with a biphasic system consisting of an alkyl acetate as the organic solvent with an excess of an aqueous 2:1 mixture of $NaHSO_3/Na_2SO_3$. After several days at reflux, the crude was recrystallised from toluene to obtain pure crystals of indole **1.125**. The aldehyde functional group was then reacted with CH_3NO_2 to form nitrostyrene **1.126** which was reduced and alkylated to indole **1.39**. Oxidation with a halogenating agent such as NBS in aqueous acid then provided the API **1.1** in 39% yield from **1.123**. The best yield (81%) for indolone formation was obtained using $PyHBr_3$ in 1:1 $AcOH/H_2O$.

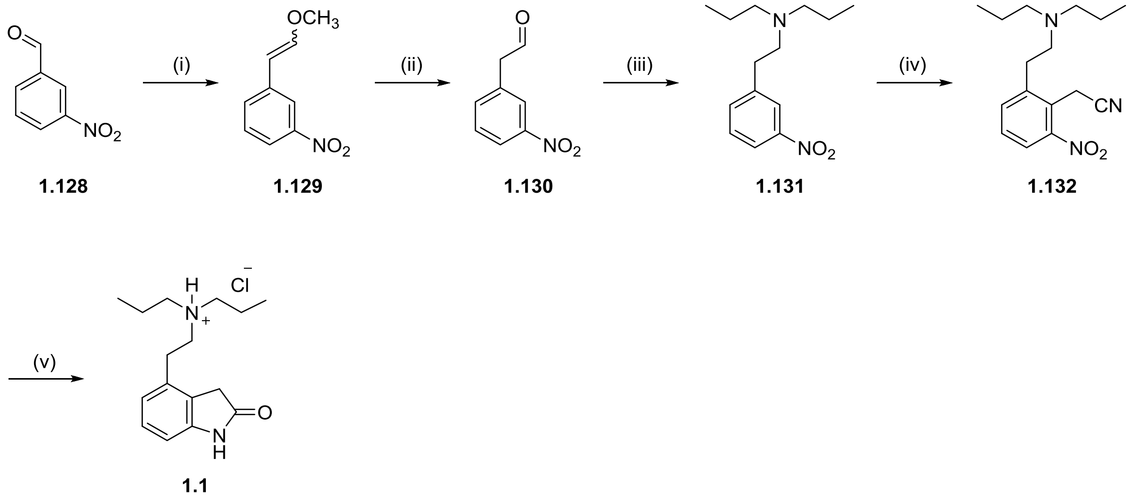


Reagents and conditions: (i) Aq. $NaHSO_3/Na_2SO_3$, ^{n}BuOAc, 86%; (ii) NH_4OAc, CH_3NO_2, Δ, 82%; (iii) $LiAlH_4$, THF, 81%; (iv) $EtCO_2H$, $NaBH_4$, 85%; (v) $PyHBr_3$, 1:1 $AcOH/H_2O$, then HCl, 81%.

Scheme 1.17 Patented route to ropinirole HCl **1.1** by Urquima S.A.[57]

1.8.2 Liu's Route to the API

Liu *et al*. found that under specific conditions, selective nucleophilic substitution of cyanoalkyls to 3-substituted nitrobenzenes could occur without the formation of regioisomers and used this as a basis for a new route to ropinirole.[59,60] As such, 3-nitrobenzaldehyde **1.128** was homologated (Scheme 1.18) upon treatment with a Wittig reagent to give enol ether **1.129**, which on hydrolysis provided aldehyde **1.130**. Reductive amination to tertiary amine **1.131** then set up Makosza's nucleophilic substitution as the key step.[60] Using the anion derived from 4-chlorophenoxyacetonitrile, addition was followed by elimination of *p*-chlorophenol and then protonation to give **1.132** in 67% yield. Nitro reduction and hydrolysis then induced cyclisation to ropinirole and salt formation completed the synthesis of the API **1.1** in an overall yield of 36% for the five steps.



Reagents and conditions: (i) $CH_3OCH_2PPh_3Cl$, KO^{t}Bu, THF, 88%; (ii), 2 M HCl, THF, 95%; (iii) ^{n}Pr$_2$NH, $NaBH_3CN$, THF, MeOH, 80%; (iv) 4-ClPhOCH$_2$CN, KO^{t}Bu, DMF, 67%; (v) (a) H_2, 5% Pd/C, (b) aq. NaOH, dioxane, Δ, then HCl, 80%.

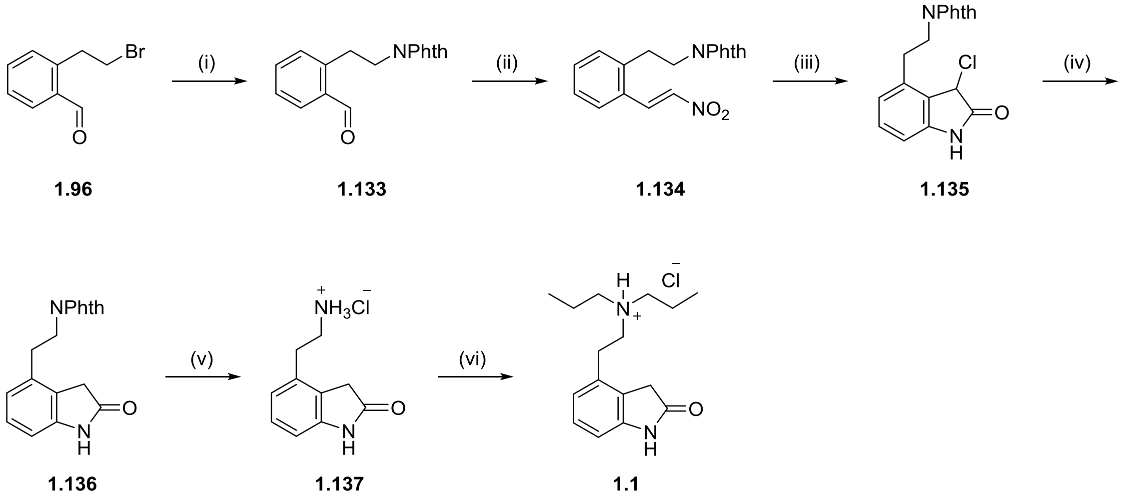
Scheme 1.18 Patented route to ropinirole HCl **1.1** by Liu *et al*.[59]

1.8.3 Alternative Routes to the API Employing GSK's Strategies

Several routes to ropinirole branching from GSK and SK&F's early syntheses have emerged since the expiration of their patents. By and large, these sequences employed subtle changes to SK&F's work to strictly establish new routes to the API.

Tarur's Synthesis

Tarur *et al*. took SK&F's early stage intermediate **1.96** (*vide supra,* Scheme 1.10) and converted it into phthalimide **1.133** (Scheme 1.19), after which nitro styrene formation to **1.134** set up the Royer ring closure to oxindole **1.135** in 53% yield.[61] Catalytic transfer hydrogenolysis followed by deprotection delivered amine **1.137** in a favourable 64% yield over two steps, with a modest-yielding reductive alkylation finishing off the synthesis.

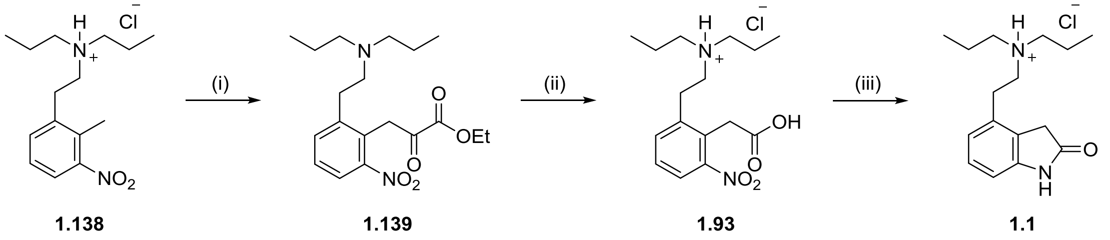


Reagents and conditions: (i) KNPhth, DMSO, 82%; (ii) CH_3NO_2, MeOH, AcOH, ${}^nBuNH_2$, $CH(OMe)_3$, 62%; (iii) $FeCl_3$, CH_2Cl_2, 53%; (iv) $NaH_2PO_2.xH_2O$, 10% Pd, 85%; (v) N_2H_4, MeOH, AcOH, then HCl, 75%; (vi) EtCHO, 10% Pd/C, 41%.

Scheme 1.19 Patented route to ropinirole HCl **1.1** by Tarur *et al*.[61]

Pharmathen's Synthesis

The HCl salt of amine **1.91**, a precursor to ropinirole in SK&F's original laboratory scale route (*vide supra,* Scheme 1.9), was converted it to the desired oxindole in three similar steps with 40% yield (Scheme 1.20) by Pharmathen S.A..[62] Pyruvate **1.139** formation with preformed NaOEt and diethyloxalate, followed by peroxide cleavage led to acid **1.93** in 68% yield over two steps. Reductive cyclisation and acidification afforded the API in 77% yield. Purification by recrystallisation using MeOH and acetone afforded the target salt in ≥ 99.9% purity.

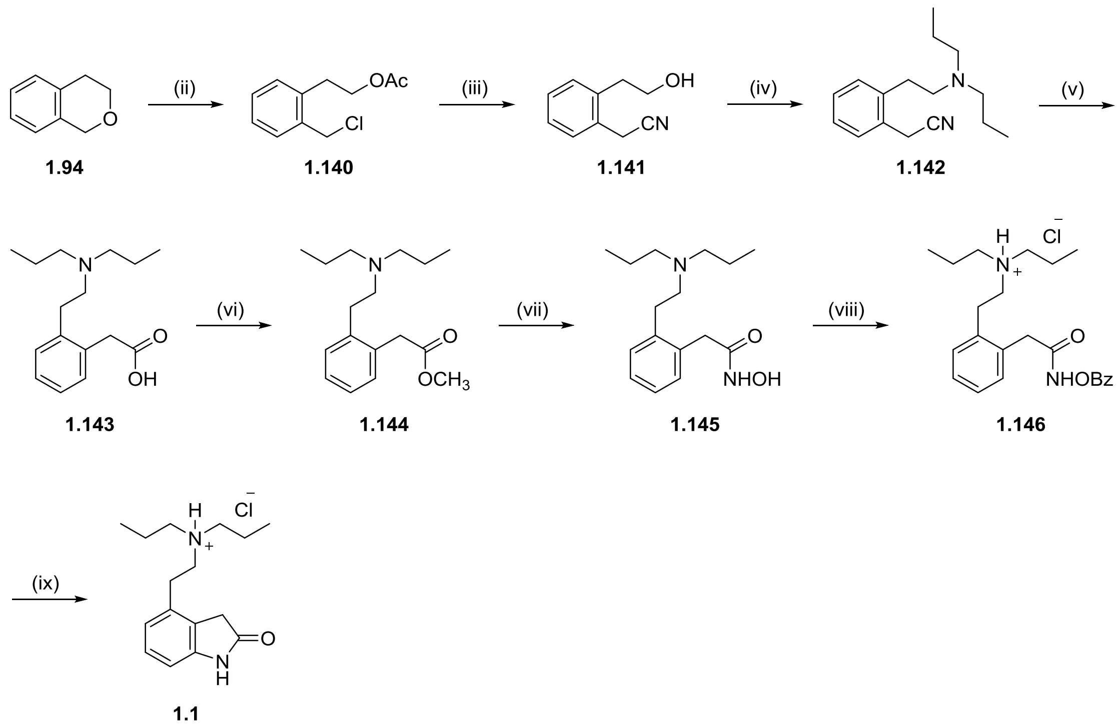


Reagents and conditions: (i) Na, EtOH, $(CO_2Et)_2$; (ii) H_2O_2, NaOH, $Na_2S_2O_5$, then HCl, 68% over 2 steps; (iii) H_2, 10% Pd/C, MeOH, 77%.

Scheme 1.20 Patented route to ropinirole HCl **1.1** by Pharmathen S.A.[62]

Bertolino's Synthesis

Isochroman ring opening with AcCl and $ZnCl_2$ followed by treatment of the resulting chloride with aqueous NaCN in CH_2Cl_2 was the starting point for a similar route to the dopamine agonist, ropinirole hydrochloride **1.1** (Scheme 1.21).[63] Displacement of the sulfonate ester derived from alcohol **1.141** gave tertiary amine **1.142** and acid hydrolysis of the cyano group produced a carboxylic acid **1.143**. Conversion to ester **1.144** followed, using $SOCl_2$ in MeOH to realise this transformation. Amidation with hydroxylamine and benzoylation to **1.146** then facilitated its cyclisation to ropinirole hydrochloride **1.1** through the action of $FeCl_3$. Though astute, the cyclisation proceeded in poor yield (42%), limiting the efficacy and economic advantage of the process, which had an overall yield of 14%.

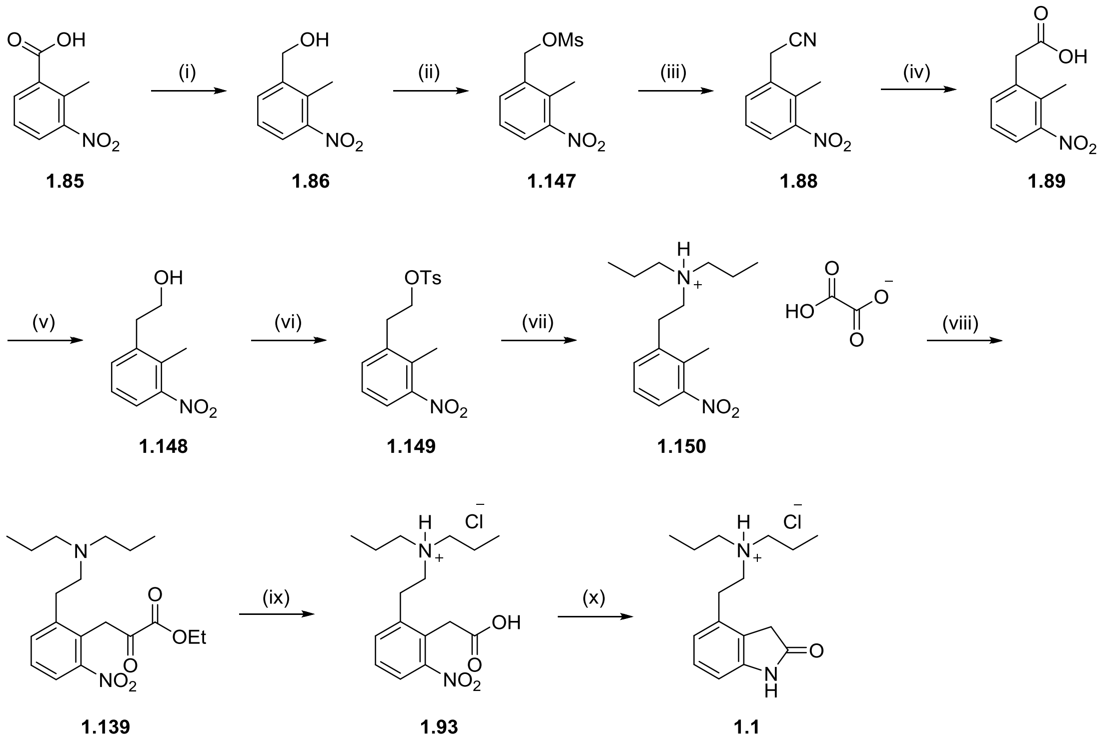


Reagents and conditions: (i) $(CH_2O)_n$; (ii) $ZnCl_2$ (cat.), AcCl, CH_2Cl_2; (iii) (a) NaCN, H_2O, ^{n}Bu$_4$NBr, CH_2Cl_2, (b) NaOH, 89%; (iv) (a) MsCl, Et_3N, (b) ^{n}Pr$_2$NH, 80%; (v) H_2SO_4, H_2O, 99%; (vi) MeOH, $SOCl_2$, 68%; (vii) $HONH_2$.HCl, NaOH, 84%; (viii) BzCl, CH_2Cl_2, 84%; (ix) $FeCl_3$, CH_2Cl_2, then HCl, 42%.

Scheme 1.21 Patented route to ropinirole HCl **1.1** by Bertolino *et al*.[63]

Alembic's Synthesis

Alembic Limited also patented a route to the API, starting with acid **1.85** (Scheme 1.22).[64,65] This was first reduced down to alcohol **1.86** with $NaBH_4$ in THF in the presence of MsOH (84% yield). Homologation was next accomplished by cyanide displacement of mesylate **1.147** to nitrile **1.88**. Acid hydrolysis to **1.89** followed by reduction with $NaBH_4$/MsOH then furnished alcohol **1.148** which was converted to the oxalate salt **1.150** after sequential treatment with TsCl, ^{n}Pr$_2$NH and oxalic acid. The subsequent steps to ropinirole hydrochloride were as reported by SK&F (*vide supra,* Scheme 1.9).

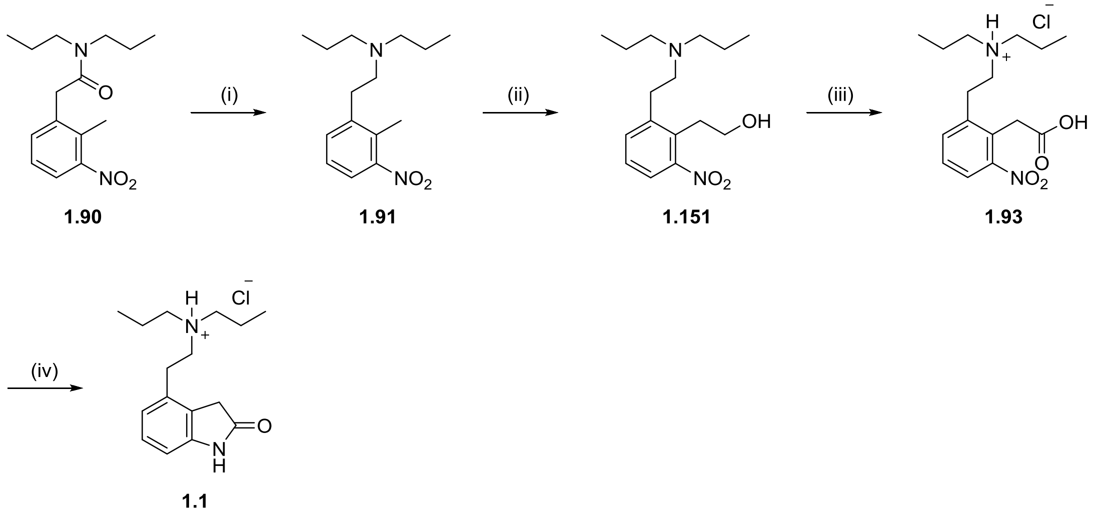


Reagents and conditions: (i) $NaBH_4$, MsOH, THF, 84%; (ii) MsCl, Et_3N, DCM; (iii) aq. NaCN, CH_3CN; (iv) conc. H_2SO_4, H_2O, 51% over 3 steps; (v) $NaBH_4$, MsOH, THF; (vi) TsCl, Et_3N, CH_2Cl_2; (vii) ^{n}Pr_2NH, H_2O, then oxalic acid; (viii) Na, EtOH, $(CO_2Et)_2$, THF; (ix) H_2O_2, aq. NaOH, then HCl, 36–43%; (x) H_2, 10% Pd/C, MeOH, 73–83%.

Scheme 1.22 Patented route to ropinirole HCl **1.1** by Alembic Ltd.[64]

Ildong Pharmaceutical's Synthesis

Ildong Pharmaceutical has also described a route to the API which again mirrored SK&F's early synthesis (*vide supra,* Scheme 1.9), with the slightest of modifications (Scheme 1.23).[66] In particular, a condensation of **1.91** with paraformaldehyde was used to obtain **1.151** and its oxidation to the API precursor **1.93** was accomplished with $NaNO_2$ in TFA. The familiar reductive cyclisation finished the synthesis to **1.1** in 84% yield for the final step.

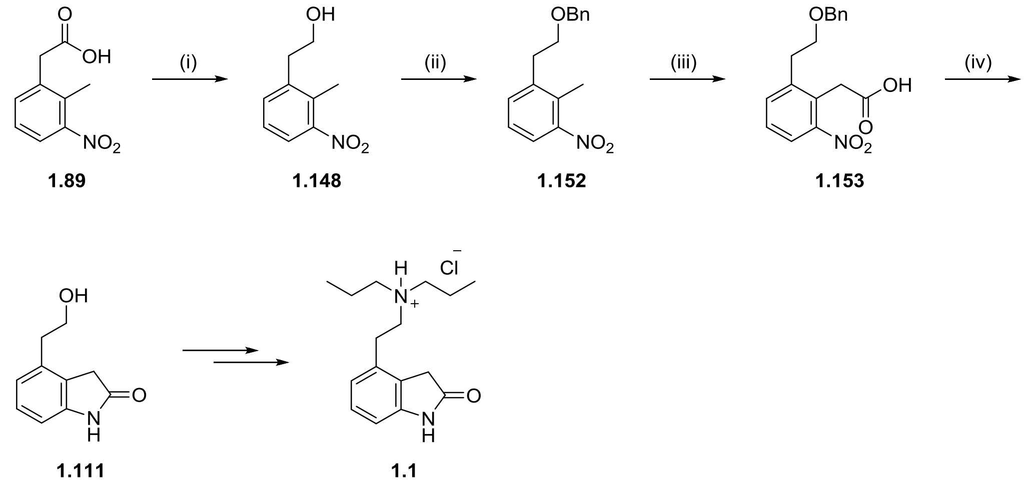


Reagents and conditions: (i) $NaBH_4$, I_2, THF, 82%; (ii) $(CH_2O)_n$, NaOMe, DMSO, 86%; (iii) $NaNO_2$, TFA, then HCl, 81%; (iv) Fe, conc. HCl, EtOH, 84%.

Scheme 1.23 Patented route to ropinirole HCl **1.1** by Ildong Pharmaceuticals.[66]

Shanghai AoBo's Synthesis

Shanghai AoBo Bio-Pharmaceutical Technology improved SK&F's route to key intermediate **1.111** when starting from acid **1.89** (Scheme 1.24).[67] Its reduction to the alcohol was followed by benzylation to intermediate **1.152**. Pyruvate formation and hydrolysis next delivered **1.153** which, following the familiar hydrogenative cyclisation protocol, gave common precursor **1.111** in 71% yield. In this way, a formal and scalable route to ropinirole hydrochloride was realised in 40% overall yield (applying GSK's characteristic yields for **1.111→1.1**). Attempting to form the pyruvate of the free alcohol of **1.148** resulted in styrene formation, due to oxalate formation and E2 elimination. Thus, benzylation was essential and added just one step to the sequence as the reductive cyclisation facilitated concomitant deprotection.



Reagents and conditions: (i) $NaBH_4$, MsOH, THF; (ii) BnBr, KOH, acetone; (iii) (a) $(CO_2Et)_2$, NaOEt, THF, (b) H_2O_2, aq. NaOH; (iv) H_2, 10% Pd/C, AcOH, EtOAc, 71% from **1.89**.

Scheme 1.24 Patented route to ropinirole HCl **1.1** by Shanghai AoBo.[67]

Since the development of SK&F's protracted process route to ropinirole, many syntheses have been reported, most of which involve modifications in either the early or late stages of the original process. However, the length of several of these sequences, along with the use of toxic, pyrophoric or excess reagents (such as $NaBH_3CN$, BH_3, $LiAlH_4$ and $FeCl_3$), render most impractical or uneconomical on a large scale. Amongst the aforementioned routes, Urquima and Liu's are the shortest syntheses. As the former requires formation of the isoquinolinium salt precursor, it has a step count of six and an overall yield of 34%. Liu's synthesis employed an incisive nucleophilic substitution stage and delivered the API in five steps and 39% overall yield. Thus, it represented the benchmark against which our work would be judged.

Chapter 2: Results and Discussion

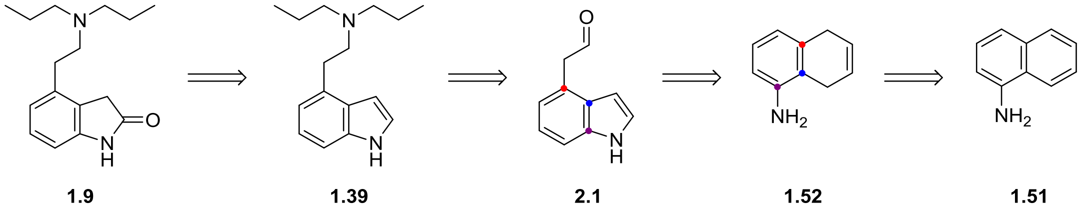
A New Route to the API Ropinirole Hydrochloride

2.1 Aims

The aim of the project was to develop an original route or a bespoke method that would realise the synthesis of the target ropinirole hydrochloride and cut costs by half (to under £1000/kg of API). Indeed, we realised that to accomplish our goal, we would need to halve the number of steps involved and/or double the overall efficiency of the process. We also demanded a move towards greener chemistry that would be financially, practically and environmentally astute.

2.2 Our Approach

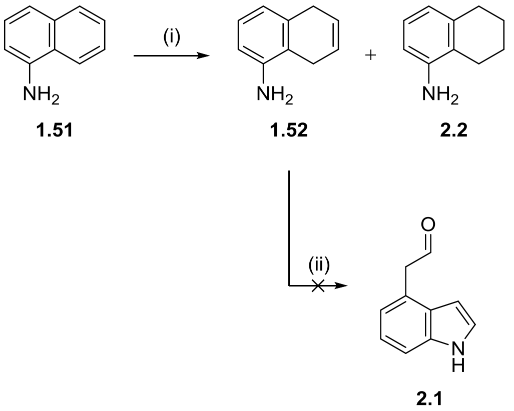
Our retrosynthetic analysis adopted Eli Lilly's stategy (*vide supra*, Scheme 1.6) and envisioned the synthesis of ropinirole from indole **1.39** which, in turn, could be prepared from aldehyde **2.1** by reductive amination. Our key step was to be an oxidative cleavage of dihydronaphthalene **1.52**, which we sought to accomplish in a single step. As the precursor **1.52** is known to be accessible from naphthylamine **1.51** through a Birch reduction, this approach appeared highly attractive.



Scheme 2.1 Retrosynthesis of ropinirole **1.9**.

2.3 Synthesis of the Key Aldehyde Intermediate

Our first task was to convert the commercially available aminonaphthalene **1.51** into the alkene precursor **1.52** via a dissolving metal reduction with Et_2O and ^{t}BuOH in NH_3 at reflux (Scheme 2.2). Better efficacy was achieved with Na, than with Li, however, a notable inseparable by-product – namely the over-reduced tetrahydronaphthalene **2.2** – was observed, constituting *ca*. 15% of the mass balance by NMR. The disparity in findings to that of the literature[68] was no doubt due to the rate of addition of Na, as a high local concentration of electrons can reduce the alkene further to saturation. More frequent additions of smaller portions of Na resulted in an improved conversion with 95% yield of the desired alkene formed, contaminated with *ca*. 5% of over-reduction product **2.2**. The reaction could easily be performed on a multi-gram scale without detriment. The crude was taken forward without further purification, with multiple recrystallisations from petroleum ether required to attain analytically pure product **1.52**.

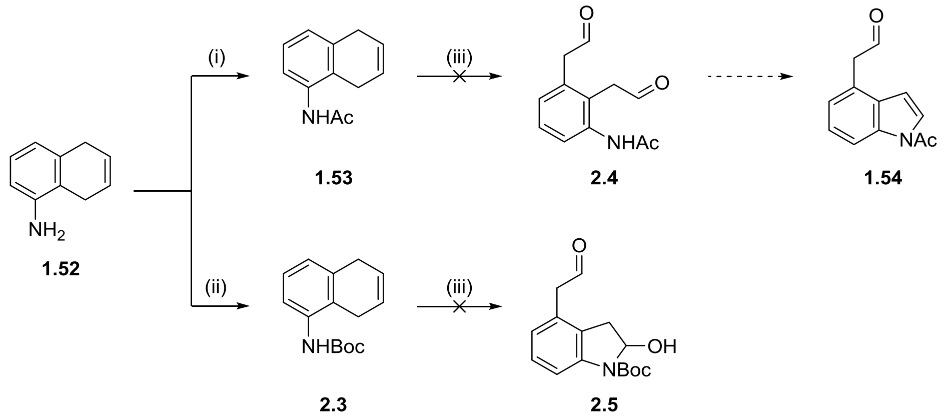


Reagents and conditions: (i) Na, NH_3, ^{t}BuOH, Et_2O, -33 °C, 95% and 5% of **1.52** and **2.2** (determined by NMR); (ii) O_3, MeOH, -78 °C, then PPh_3.

Scheme 2.2 Birch reduction of 1-aminonaphthalene **1.51**.

Initial attempts to oxidatively cleave alkene **1.52** with ozone proved fruitless. Upon several attempts using CH_2Cl_2 as the solvent, a yellow insoluble solid was obtained following PPh_3 work-up. We postulated that the ozonide intermediates were unstable and thus led to oligomerisation or, more likely, that the free amine was being oxidised leading to alternative reaction pathways and degradation. If the former of these were true, the use of a 'participating' solvent might help to stabilise such intermediates. Alas, after obtaining similar results with MeOH as the solvent, it was clear that protection of the nitrogen was necessary for us to progress.

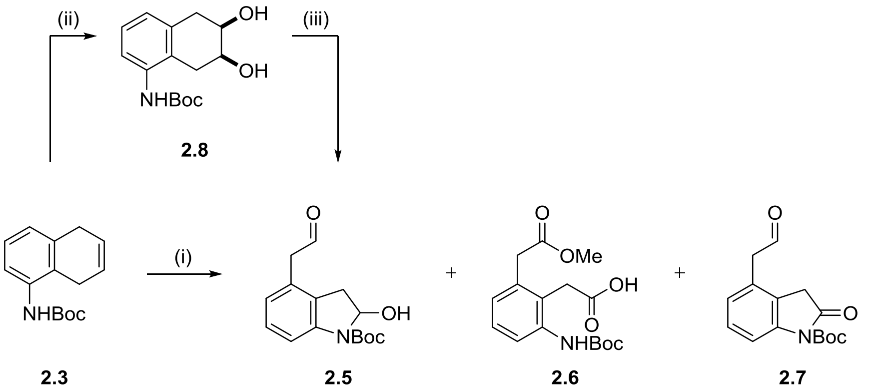
We opted for acetamide protection in **1.53** as Plieninger had had success in forming indole **1.54**.[69] However the low solubility of **1.53** in MeOH (5 g/L at RT) necessitated high dilutions for the ozonolysis, with significant precipitation of the amide at the reaction temperature (-78 °C) rendering the procedure impractical. To address this issue, we elected for a carbamate protecting group to provide a readily soluble alkene and thus a good handle to carry out our key step. Facile conversion to Boc amine **2.3** with Boc anhydride and sulfamic acid in H_2O provided the desired precursor in 97% yield (94% yield on gram scale, Scheme 2.3). On larger scale, Et_2O was employed as the solvent, to aid diffusion of the reagent and catalyst. As before, ozonolysis in CH_2Cl_2 was ineffective in providing the key intermediate **2.5**. The problematic ozonolysis seemed to confirm previous fruitless attempts such as that of Kerr *et al.* in employing this approach to indole synthesis.[70]



Reagents and conditions: (i) Ac_2O, NH_2SO_3H, (cat.), H_2O, 98%; (ii) $(Boc)_2O$, NH_2SO_3H, H_2O, 97%; (iii) O_3, MeOH, -78 °C, then PPh_3.

Scheme 2.3 Preliminary ozonolysis results.

Undeterred by this result, we decided to run the ozonolysis in MeOH, which proved reactive enough to give an unexpected carboxylic acid side product **2.6** in 20% yield (Run 1, Scheme 2.4). Oxindole **2.7** was also detected (Run 2, *ca.* 20 % by NMR) in a separate run, although attempts to optimise for this product failed as we were unable to reproduce these results. At this juncture, we iteratively performed multiple ozonolyses, including varying percentages of co-solvents (CH_2Cl_2 and MeOH); however neither of these yields could be reproduced and therefore optimised.



	2.5	2.6	2.7
Run 1	**-**	**20%**	**-**
Run 2	**-**	**-**	***ca.* 20% by NMR**
Run 3	**60%**	**-**	**-**

Reagents and conditions: (i) O_3, MeOH (Run 1 and 2), EtOAc (Run 3), -78 °C; (ii) OsO_4 (cat.), NMO, citric acid, 1:1:1 $H_2O/{}^tBuOH/MeOH$, 78%; (iii) $NaIO_4$, 1:1 H_2O/THF, 62%.

Scheme 2.4 Ozonolysis products.

Thus EtOAc was tested as an unreactive participating solvent and did not disappoint when subjecting alkene **2.3** to ozone as much cleaner conversions were obtained and aldehyde **2.5** was isolated in 66% yield following PPh_3 work-up (Run 3), whereas a catalytic OsO_4 and $NaIO_4$ oxidative scission protocol delivered **2.5** in 48% yield over two steps via **2.8** (Scheme 2.4). Given the toxic and industrially unfriendly nature of the Upjohn dihydroxylation, this latter protocol was not optimised any further.

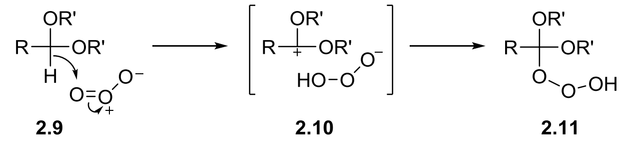
2.4 Investigating Hemi-Aminal Oxidation to Oxindoles

The formation of indolone **2.7** and carboxylic acid **2.6** was presumed to arise from oxidation of hemi-aminal **2.5** by ozone. Similar oxidations of acetals with ozone are well known and have been extensively researched, in particular by Deslongchamps *et al*.[71,72] If this was indeed the case, it opened up a short route to ropinirole. In essence, oxidation of hemi-aminal **2.5** to the corresponding oxindole would allow us to conduct two oxidations in one pot, making it a very attractive route.

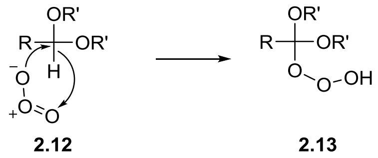
2.4.1 Ozone Oxidation of Acetals

Acetals react with ozone via insertion of O_3 into the C-H bond of the mutually adjacent methylene group. Several mechanisms have been postulated for the oxidation (**2.9→2.20**, Scheme 2.5).[73]

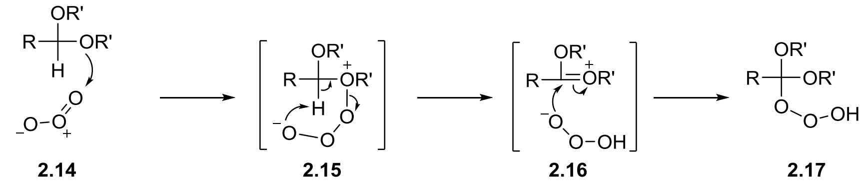
(a) Hydride transfer



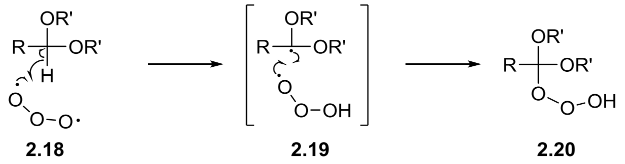
(b) 1,3-Dipolar insertion



(c) Attack of ether oxygen



(d) Radical abstraction



Scheme 2.5 Postulated mechanisms of the oxidation of acetals with ozone.[73]

Experimental data suggests that oxidation occurs by either hydride transfer to ozone or via 1,3-dipolar insertion. The radical abstraction pathway has largely been ruled out as such mesomerically stabilised radical intermediates have been shown to be inert to ozone. Moreover, DFT calculations have shown that the lowest energy pathway is hydride transfer from the acetal to ozone, leading to an ion pair.[74] Despite this, experimentally it was found that solvent effects had little influence on reaction rate.

Of greater significance is the stereoelectronics of the system which induces a stereospecific oxidation of acetals.[72,75] Deslongchamps *et al*. found that only certain conformations of acetals were reactive towards ozone and that amongst the nine gauche conformations an acetal can occupy, only three, **2.21→2.23**, are reactive (Figure 2.1).

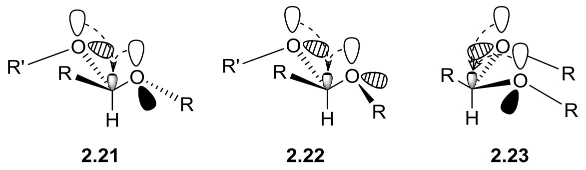
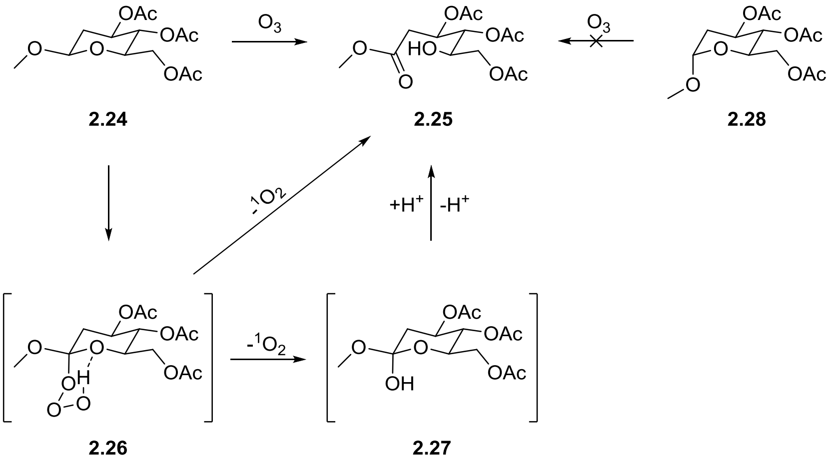


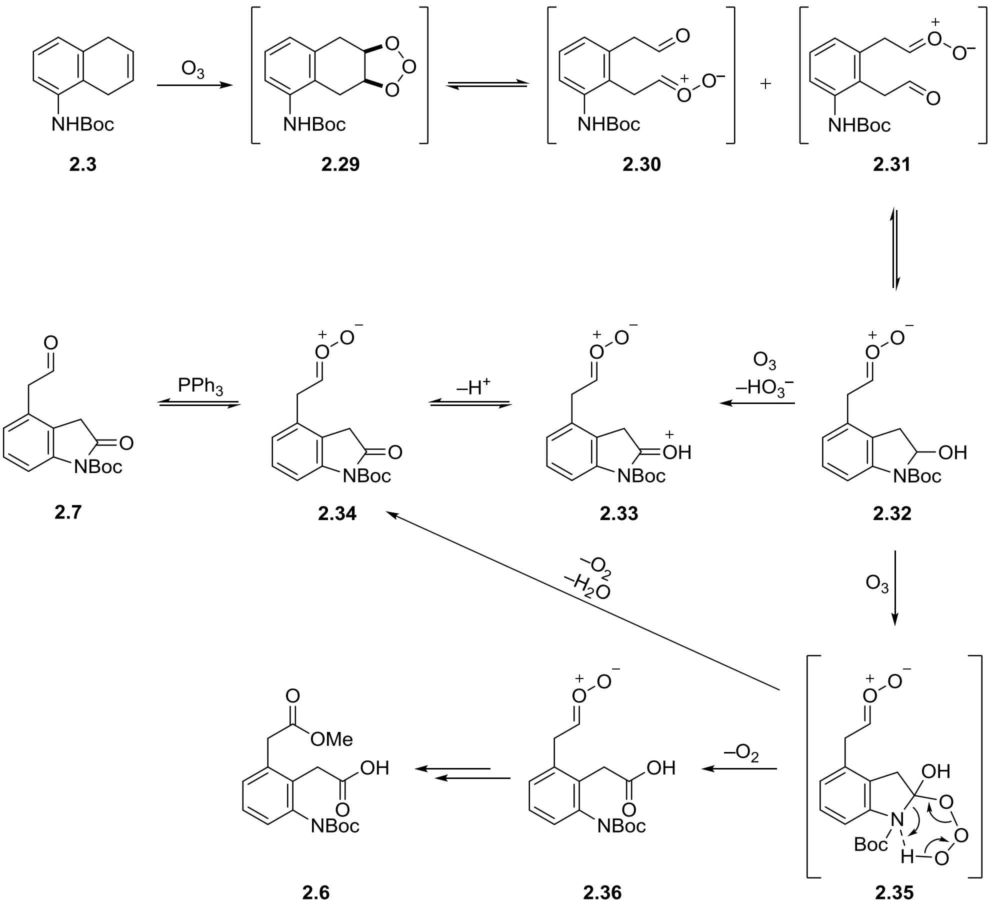
Figure 2.1 Active conformations for the oxidation of acetals with ozone.[72]

Experimental results also indicated that certain conditions must be met for oxidation to take place: namely each of the acetal oxygens must have one of its lone pairs anti-periplanar to the C-H bond into which ozone insertion takes place. This was shown with the reaction of various α- and β-methyl glucopyranosides (Scheme 2.6)[72] where only the latter, *viz*. **2.24**, has the correct orientation of orbitals in their (rigid) lowest energy conformer. Since α-glucosides have only one of the oxygen atoms donating electron density into the σ* orbital of the C-H bond (with the other oxygen atom having an electron pair in a gauche orientation) it will remain unreacted, or do so with a low rate, provided the system does not have enough energy to overcome the anomeric effect. After insertion, the intermediate **2.26** may lose $^1O_2$ to give **2.25** directly or via hemi-orthoester **2.27**. It is noteworthy that systems with fixed reverse-anomeric synperiplanar orientations also undergo rapid ozone insertions.[75]



Scheme 2.6 Selective oxidation of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **2.24** with ozone.[72]

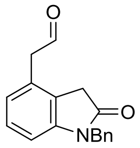
The lowest energy conformation of acyclic acetals is one which should disqualify it from reacting with ozone as it is analogous to the rigid chair conformation of α-glucosides. However, in this case a low energy bond rotation ensures that a reactive conformer co-exists, albeit at low concentration. Taking into account the abovementioned findings, we can propose that oxidation of hemi-aminal **2.5** (and therefore its precursor **2.32**) could occur by a similar mechanism (**2.3**→**2.6**/**2.7**, Scheme 2.7). By analogy, the anomeric CH bond can oxidise to **2.35**, giving zwitterion **2.36** with the loss of molecular oxygen. Reductive work-up would then give the side product **2.6**, which could also result from oxidation of the hydroperoxyaminal formed upon intramolecular trapping of **2.30**).



Scheme 2.7 Theoretical pathways for oxidation of hemi-aminal **2.32** with ozone.

In the case of our hemi-aminal **2.5**, oxidation could also proceed via **2.33** where ejection of a hydride would lead to oxindole **2.7** upon work-up. This mechanism is consistent with that proposed by Marshall and Garofalo in relation to the oxidation of hemi-acetals to esters.[76]

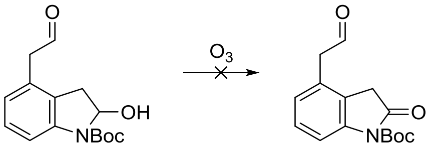
Clearly, conformation is not an issue for our desired reaction to proceed, due to the flexible nature of the five-membered ring. The early finding of Deslongchamps is that two n→σ* interactions are needed to facilitate the reaction, thus for our hydroxyindoline **2.5**, the nitrogen lone pair will have its participation attenuated by conjugation to both the proximal carbonyl group and the arene. Consequently it is less available to eject a hydride. It is therefore plausible that ozonising *N*-benzyl-1-amino-5,8-dihydronaphthalene in EtOAc could give **2.37** as the sole product (Figure 2.2).



2.37

Figure 2.2 Desired oxindole with benzyl protecting group.

Unfortunately, exposure of **2.5** to ozone with varying reaction times led to degradation through destruction of the aromatic ring. Similarly, ozonisation of the isolated hydroxyindoline (Scheme 2.8) failed to produce the projected compound **2.7**, and no oxindole compounds were isolated in our experiments. As such, alternative methods were investigated in an effort to attain the indolone.

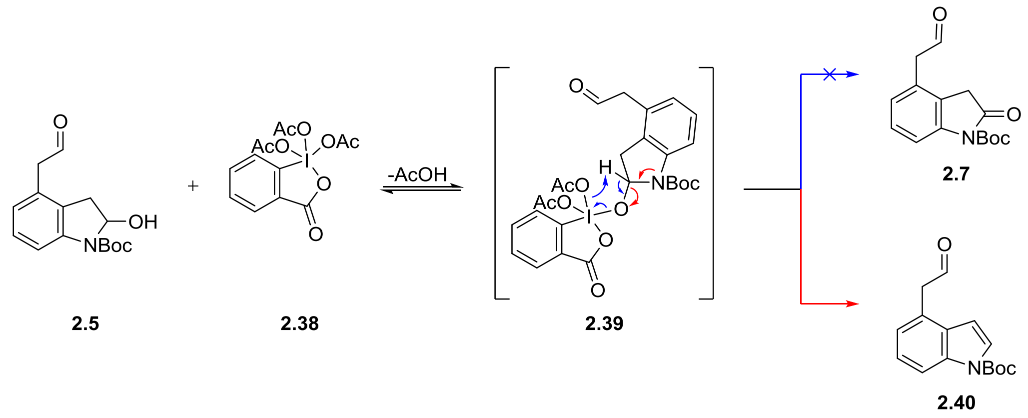


2.5 **2.7**

Scheme 2.8 Theoretical oxidation of hemi-aminal **2.5** to oxindole **2.7**.

2.4.2 Alternative Procedures for the Attempted Hemi-Aminal Oxidation of 2.5

Several reagents were investigated in an attempt to oxidise the hydroxyindoline **2.5** to the corresponding oxindole without affecting the aldehyde functionality. In most cases, dehydration was observed, such as with DMP **2.38**, as the primary pathway, resulting in aromatisation to indole **2.40** (Scheme 2.9). Unreacted starting material was also present in many of the product mixtures (Table 2.1).



Scheme 2.9 Desired oxidation of hemi-aminal **2.5** with DMP.

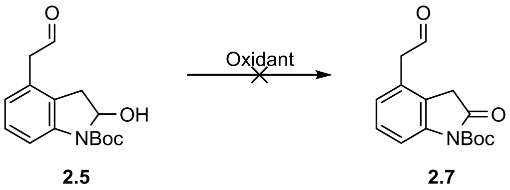
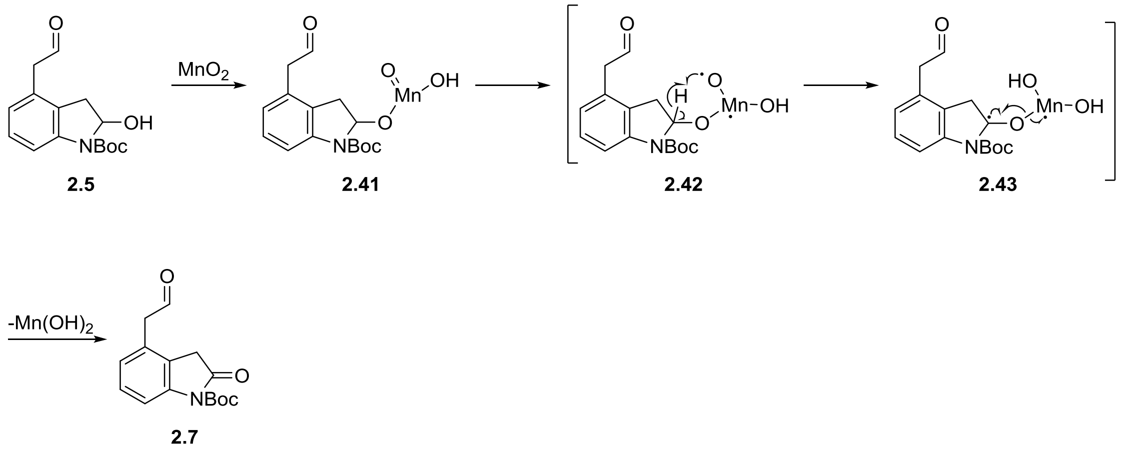


Table 2.1 Attempted oxidation of hemi-aminal **2.5** to oxindole **2.7**.

Entry	Oxidant	Reaction outcome[1]
1	DMP	Dehydration to indole
2	PDC	Dehydration to indole
3	$PyHBr_3$	Dehydration to indole
4	TEMPO (cat.)/I_2	SM
5	KI (cat.)/I_2	SM
6	MnO_2	No reaction

[1] Determined by TLC and/or NMR.

At this juncture, we shifted our attention to a radical pathway as it was envisaged that a SOMO formed on H-atom abstraction from the hemi-aminal would be highly stabilised by the two adjacent heteroatoms. Unfortunately, no such reaction had occured with MnO_2 **2.5→2.7** (Scheme 2.10, Table 2.1). Consequently, hemi-aminal **2.5** was taken forward as, in spite of much effort, no efficient oxidation protocol could be established.



Scheme 2.10 Desired oxidation of hemi-aminal **2.5** with MnO_2.

2.5 Flow Ozonolysis

Ozone has a familiar place in industry.[77,78] Though commonly used in waste water treatment, major safety issues arising from its use as a reagent have limited its application in large-scale synthesis.[79,80] This is a great pity as it an economical and atom-efficient oxidant, with water and oxygen as its primary by-products. As such, the opportunity arose to perform ozonolysis in a continuous flow in a set-up (Figure 2.3) akin to that developed by Motherwell *et al*,[81] which emerged as an attractive proposition as it would allow us to overcome the aforementioned safety concerns and could more readily be developed into an industrial process.

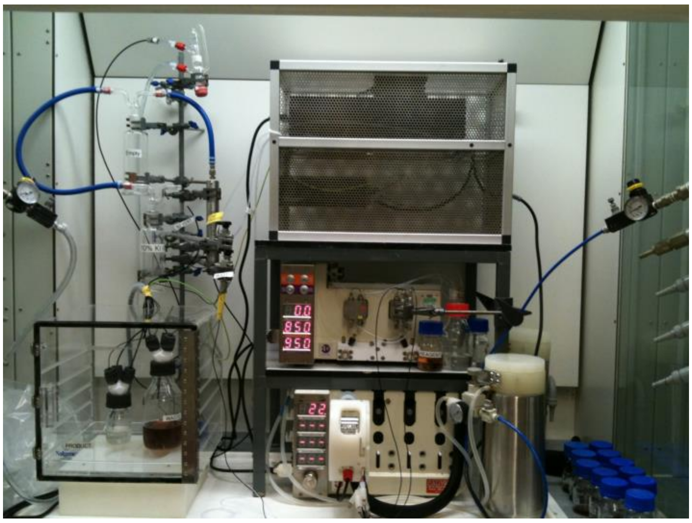


Figure 2.3 Vapourtec flow ozonolysis set-up at GSK.

Greater control of reaction conditions and improved reaction profile through efficient and uniform mixing of reagents (coupled with high surface area to volume ratios) is pivotal in making the decision to adopt continuous flow processes.[82-84] Relative to batch reactors, smaller quantities of reagents are present in a given volume, allowing for intrinsically hazardous reactants, intermediates or conditions to be employed. Tighter control of temperature and pressure alleviates safety risks and allows for processes previously ruled as too impractical to be implemented beyond bench-scale. Thus, the introduction of flow ozonolysis has allowed this to be considered for several processes, and its potential novel application in the synthesis of an API would further validate its applicability, especially if it offered advantages over existing alternatives (such as Lemieux-Johnson oxidation and $KMnO_4$).

2.5.1 Flow Set-up

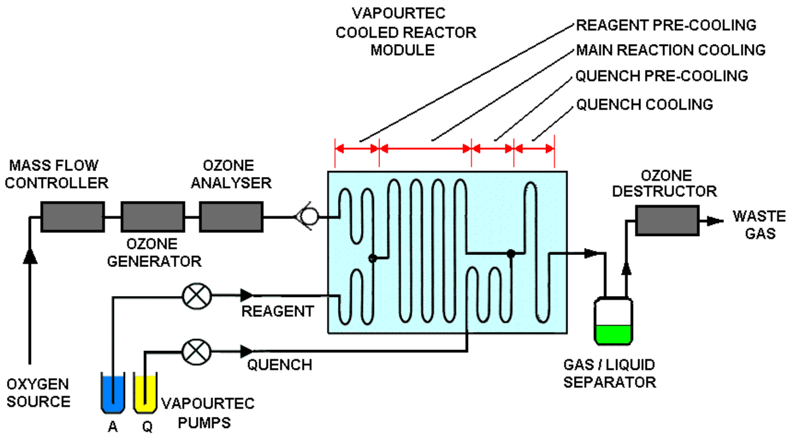


Figure 2.4 Diagram of flow ozonolysis set-up.[85]

In the flow ozonolysis set-up (Figures 2.4[85] and 2.5), O_3 is generated by feeding oxygen through a mass flow controller to the ozone generator (and a UV analyser). It is then cooled in the Vapourtec R2 reactor, along with the reactant, and progresses into a T-piece to facilitate mixing. The two phases travel through the reactor in (wavy) annular flow after which another T-junction allows the pre-cooled quench to be added to mix after which the gas and liquid phases are separated gravitationally. The waste gas is passed through a catalytic degrader to quench any unreacted ozone. Dry ice is used to cool a stream of nitrogen gas which in turn cools the reagents, allowing control of the reactor temperature. Several check-valves and three-way valves complete the circuit and prevent back-flow. Additionally, nitrogen gas was connected to the reactor inlet to allow the system to be purged at the end of a run.

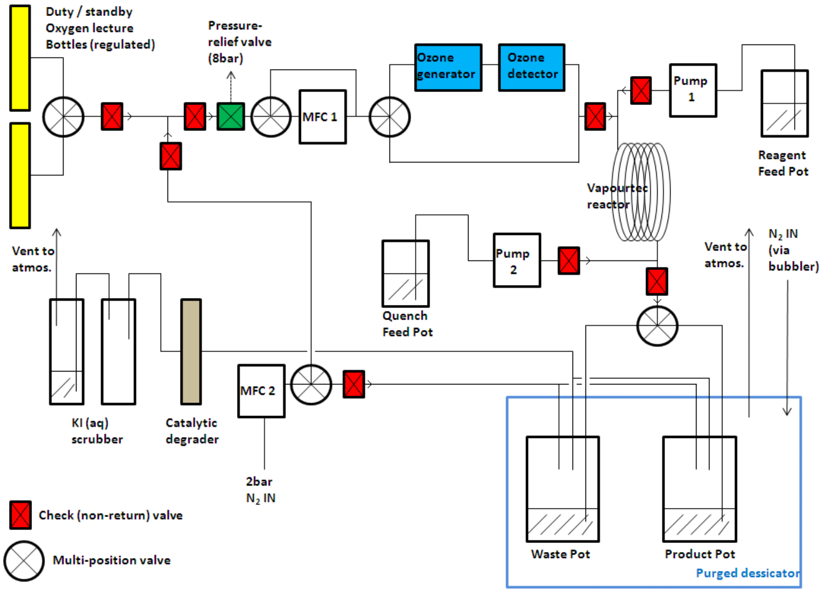
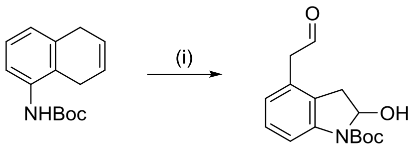


Figure 2.5 Schematic of flow ozonolysis set-up.

2.5.2 Design of Experiment for the Ozonolysis of Alkene 2.3

An initial Design of Experiment (DoE) was performed to establish approximate conditions to attain an optimum yield of the reaction (Scheme 2.11) and to gain an understanding of the influence of each parameter on the course of the reaction.



2.3 **2.5**

Reagents and conditions: (i) O_3, EtOAc, PPh_3, flow.

Scheme 2.11 Flow ozonolysis of alkene **2.3**.

DoEs involve the screening of conditions (over a defined set of values), using many possible combinations of factors. Statistical analysis software allows the projected number of experiments to be truncated without significant loss of information. It achieves this by considering the combinatorial effect of these factors on the reaction.

For example, a 2-level 3-factor design has three variables measured for their influence on the reaction, which could either be positive or negative (hence ‘2-level’). Such a factorial design requires 2^3 experiments to be run for suitable analysis, demonstrated by the eight corners of a cube (Figure 2.6). Where two and three factors are involved, the maximum number of experiments is required to be performed, as a simplification would result in an unreliable analysis. A 4-factor design, however, would necessitate at least 2^{4-1} experimental runs for a reasonable analysis, thereby halving the experimental efforts.

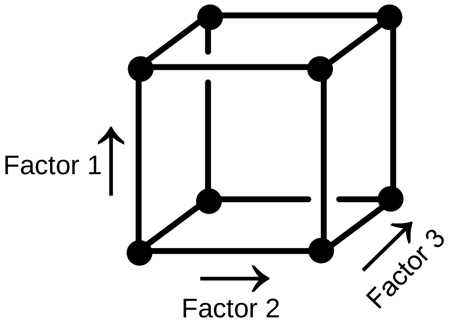


Figure 2.6 Representation of a 2-level 3-factor DoE.

The parameters selected for our design were: gas/ozone flow rate (25–100 mL/min); reagent flow rate (0.2–1.5 mL/min); PPh_3 quench equivalents (1–3) and reactor temperature (-25–10 °C). With one exception, all of these parameters delivered significant positive product responses; indeed, only gas flow rate exhibited a slight negative influence on product response (yield). This can be seen from the half-normal plot where the squares to the right of the straight line equate to significant (co-)factors (Figure 2.7). The unitless x-axis is made up of standardised response values (relative to the mean) and is plotted against the calculated response of half the normal distribution.

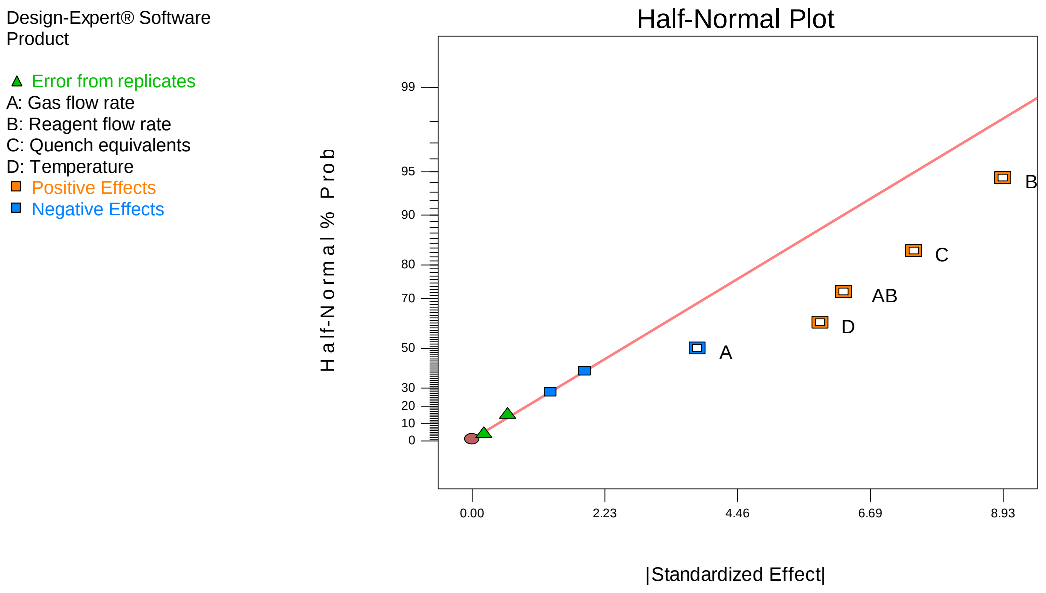


Figure 2.7 Half-normal plot depicting significant (co-)factors.

It transpired that the centre point (corresponding to 62.5 mL/min for gas flow rate, 0.85 mL/min for reagent flow rate, 2.25 for quench equivalents and -7 °C for reaction temperature) gave isolated and NMR yields of 75 and 77% respectively (with $PhCH_3$ as the internal standard), which were higher than predicted (Figure 2.8). The significant model curvature from the estimated linear model meant another DoE with narrower limits needed to be undertaken, keeping gas flow rate constant. The z- or ‘product’-axis refers to a relative response, measured from integration values of the product aldehyde peak obtained from crude ^{1}H NMRs of each run.

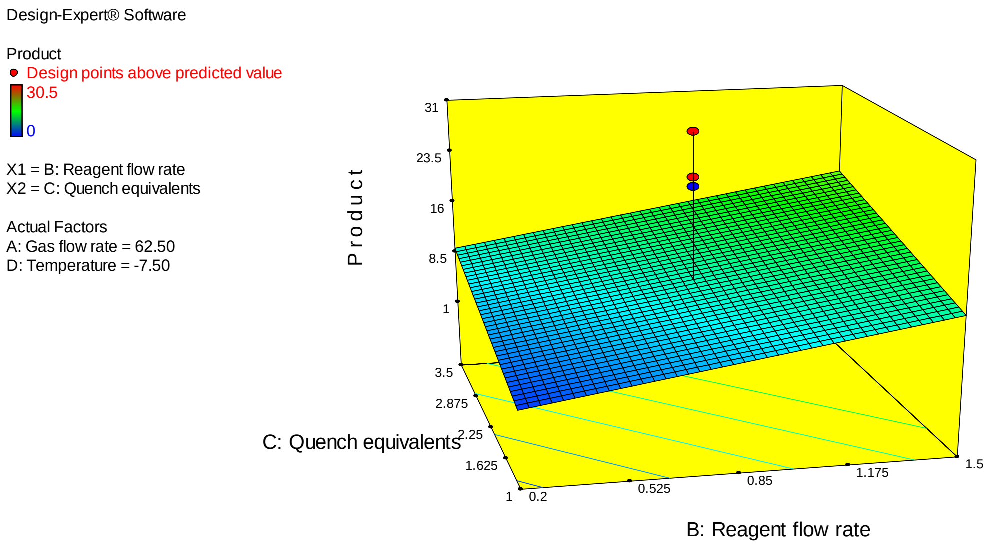


Figure 2.8 3-D response model showing outlying centre points.

Our second (3-factor) DoE appeared to show a levelling of product response within the tested ranges of 0.7–1.5 mL/min for reagent flow rate, 2–3.5 equivalents of the quench reagent PPh_3 and -10–10 °C for the reaction temperature. This time, only reagent flow rate was implicated as a significant factor with the centre point again lying outside of the predicted model (Figure 2.9).

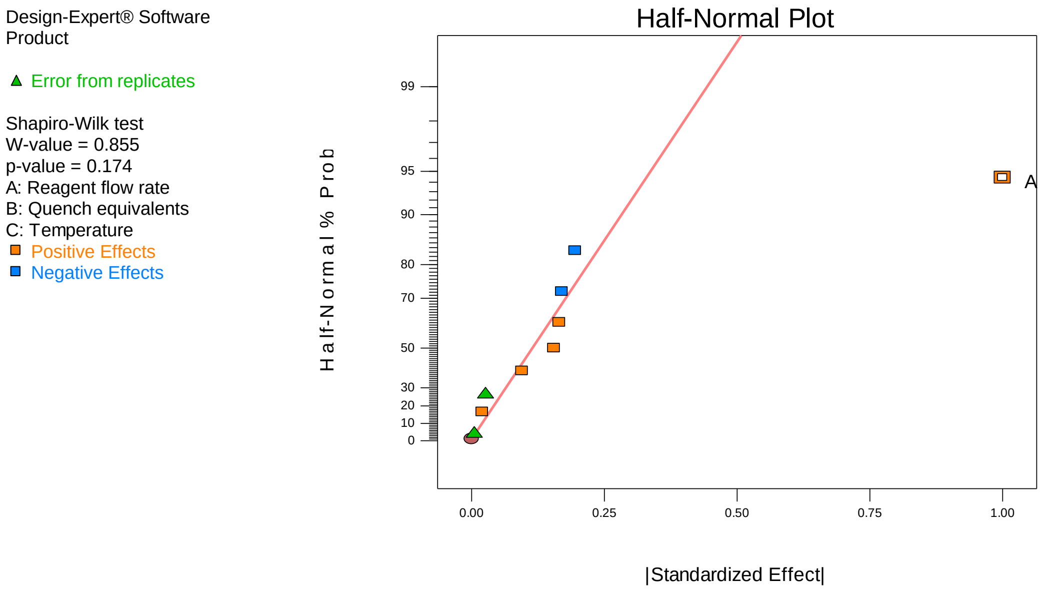
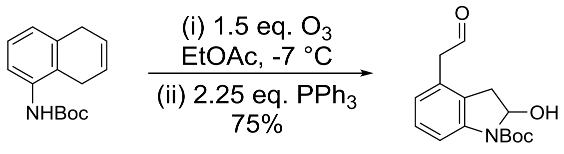


Figure 2.9 Half normal plot of second DoE.

Unfortunately, due to the development of a mechanical fault with the flow ozonolysis system, we were unable to validate the latter DoE results. As a consequence we were unable to perform further optimisation studies within the limited time-frame available whilst on placement at GSK. Applying our centre point conditions from our first DoE, nonetheless, delivered an improvement in the ozonolysis yield with the following parameters (Scheme 2.12).



2.3 **2.5**

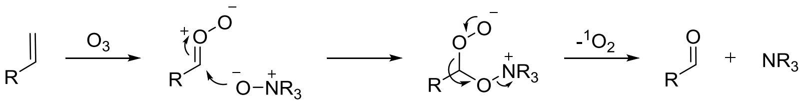
Alkene **2.3**:	0.2 M in EtOAc, 0.85 mL/min
PPh_3:	0.3 M in EtOAc, 1.28 mL/min
Ozone:	202 g/Nm^3, 62.5 mL/min
Ozonolysis reactor:	2 mL
Quench reactor:	0.393 mL
Temperature:	-7 °C

Scheme 2.12 Flow parameters for the ozonolysis of alkene **2.3**.

2.6 Assessing Ozonolysis Work-Up Reagents

2.6.1 Carbonyl Oxide Fragmentation with Amine *N*-Oxides

Having established a working procedure for hemi-aminal **2.5** formation using PPh_3 as a quenching agent, a cleaner and more efficient work-up was now sought. A judicious work-up involving *N*-oxides appeared to fulfil our criteria as it paved the way for us to avoid using atom-inefficient PPh_3, making an altogether cleaner and resourceful route to ropinirole (Scheme 2.13). It is reported that *N*-oxides **2.46** add to carbonyl oxides to give a highly unstable intermediate such as **2.47** which then collapse via a Grob-type pathway to form an aldehyde **2.48**, molecular oxygen and the free tertiary amine **2.49**.[86]

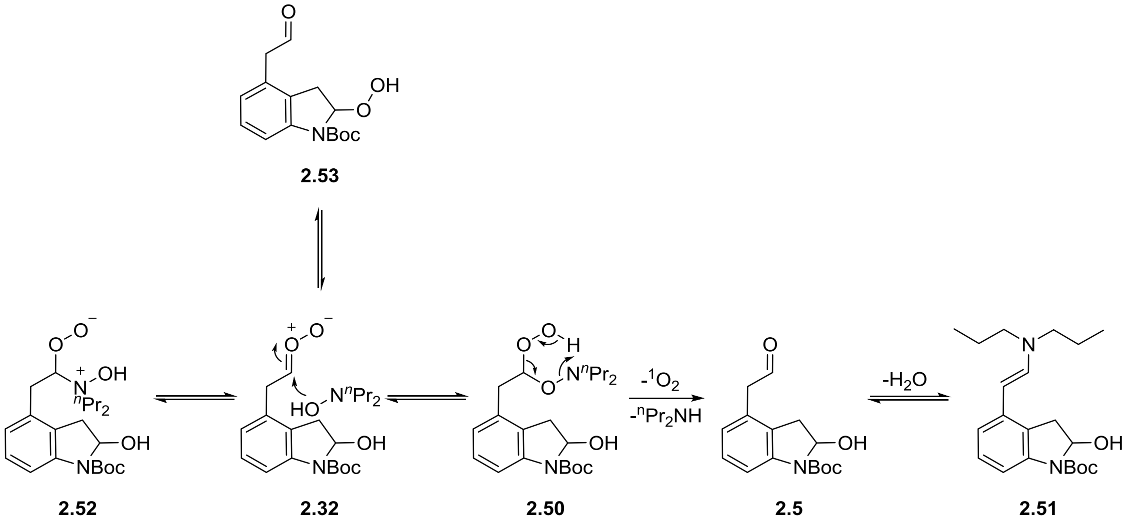


2.44 **2.45** **2.46** **2.47** **2.48** **2.49**

Scheme 2.13 Reductive *N*-oxide work-up of a carbonyl oxide.

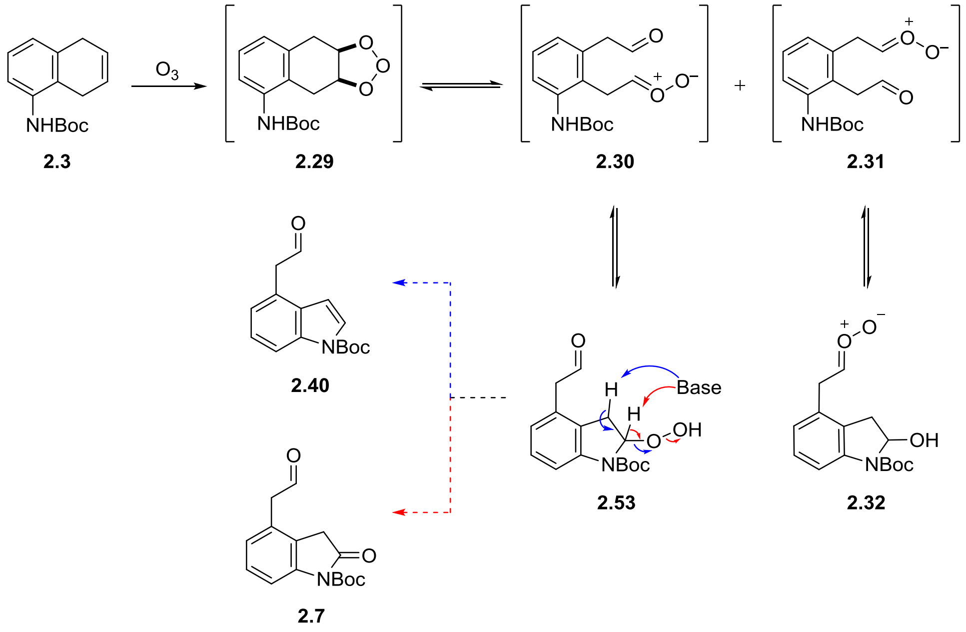
2.6.2 Carbonyl Oxide Fragmentation with Hydroxylamines

We reasoned that the oxide of a secondary amine, a hydroxylamine, might give the same result. Trapping with the hydroxyl would lead to intermediate **2.50** to induce collapse via a six-membered pericyclic decomposition pathway. This was of particular interest as the next step in our synthetic pathway involves the union of our aldehyde **2.5** with $^{n}Pr_2NH$. Therefore, if $^{n}Pr_2NOH$ could be used as a quenching agent for the ozonolysis then the amine by-product, $^{n}Pr_2NH$, could condense with the aldehyde to deliver imine **2.51** (Scheme 2.14). Its subsequent reduction would then give an advanced ropinirole precursor.



Scheme 2.14 Proposed hydroxylamine work-up of a carbonyl oxide.

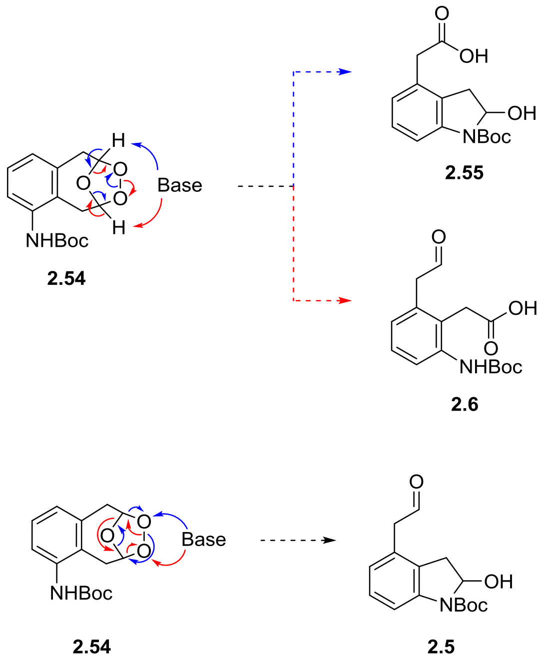
The authors had reported the use of 'oxides of secondary amines' in the reductive work-up of carbonyl oxides (*vide supra*, Scheme 2.13) but had not elaborated on this further. However, in our particular case, in the ozonolysis of **2.3**, the 1,2,3-trioxolane **2.29** is intramolecularly trapped and thus gives carbonyl oxide **2.32** and hydroperoxyaminal **2.53** (Scheme 2.15). Were these two intermediates to be in equilibrium, we could envisage a highly successful outcome. Plausibly, a base-induced elimination[87,88] of **2.53** could lead to either indole **2.10** or desired indolone **2.7**. A number of different *N*-oxides and hydroxylamines work-up procedures were examined but neither of these delivered the desired aldehyde **2.7** (*vide infra,* Table 2.2).



Scheme 2.15 Possible base-induced elimination of hydroperoxy aminal **2.53**.

2.6.3 Reaction of Ozonides with Amines

As common as phosphines are in their use as work-up reagents, we wondered if amines might also be used as a surrogate.[89] Indeed the use of Et_3N has been reported with apparent efficacy,[90,91] however, to date this protocol has largely been over-looked. This may be due to that fact that PPh_3 and DMS reductive work-ups generally suffice. The purported mechanism of the reaction between Et_3N and a 1,2,4-trioxolane **2.54** is via deprotonation with electrocyclic ring opening to both **2.55** and **2.6** (Scheme 2.16). However, several other mechanisms are plausible (**2.54**→**2.5**).[92] Alas, in our hands, quenching of the ozonolysis reaction with Et_3N and $^nPr_2NH$ produced a black tar upon removal of solvent (Table 2.2). Similary, work-up with $NaBH(OAc)_3$ and $^nPr_2NH$, implementing Dussault's procedure,[93] yielded no meaningful results, fairing similarly upon attempting Schreiber's method (used in the literature to form terminally differentiated products).[94]



Scheme 2.16 Possible base-induced decomposition of trioxolane **2.54**.

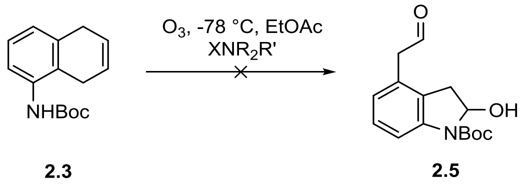


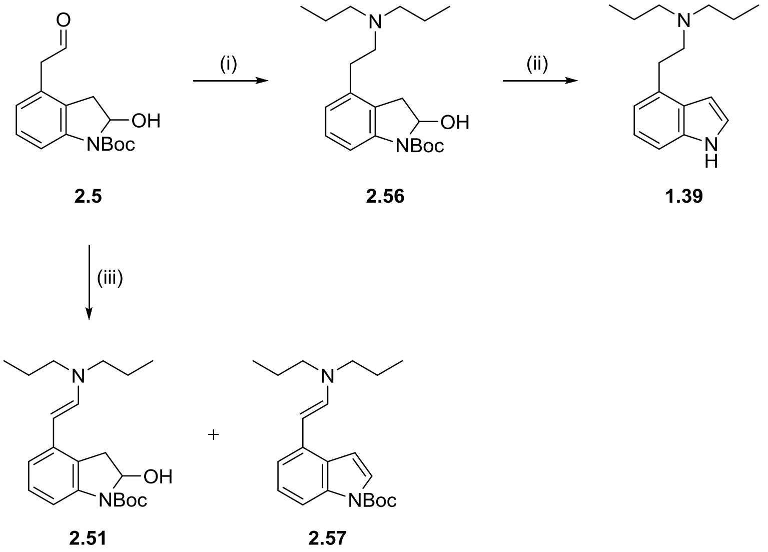
Table 2.2 Amine and *N*-oxide work-up of ozonolyis reactions.

Entry	X	R	R’	Reaction outcome[1]
1	H	Et	Et	Degradation
2	H	^{n}Pr	-	Degradation
3[2]	O	Et	Et	Degradation
4[2]	HO	^{n}Pr	-	Degradation
5	O	Me	$-(C_2H_4)O(C_2H_4)-$	Degradation

[1]Determined by TLC and/or NMR; [2]Formed from oxidation with ozone as per literature.[86]

2.7 End Route to Ropinirole HCl

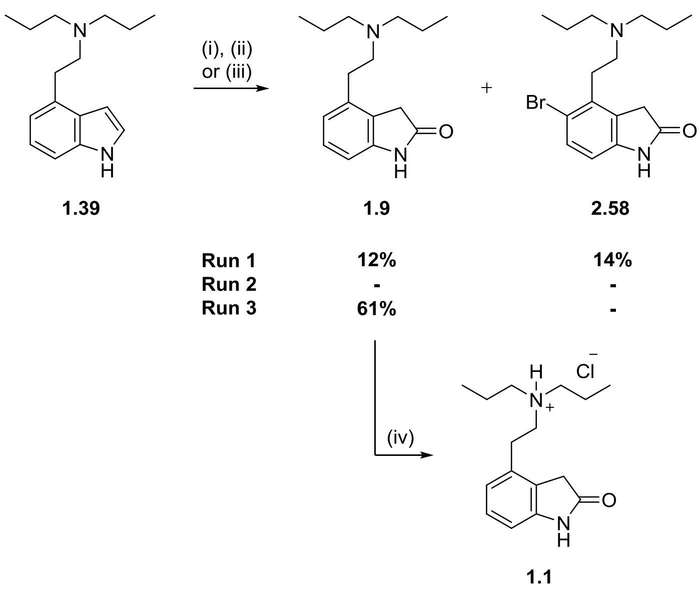
Having achieved a continuous flow ozonolysis in good yield (after modest optimisation), we subjected aldehyde **2.5** to a reductive amination with ^{n}Pr$_2$NH and NaBH$_4$ in MeOH (Scheme 2.17). Alas these conditions appeared to degrade the starting material. Thus a milder reducing agent was investigated in the form of NaBH(OAc)$_3$. In this case no reduction of the intermediate imine was observed and enamine **2.51** was formed as the major product, with partial dehydration to indole **2.57**. Opting for $NaBH_3CN$ as an intermediary hydride donor provided **2.56** in 47% yield when conducted in MeOH. However, by switching to CH_2Cl_2 as the solvent, this yield was increased to 60%. Pleasingly, simplifying the isolation process by omitting the work-up and loading the crude mixture directly onto a chromatography column with rapid elution led to quantitative isolation of the desired amine **2.56**.



Reagents and conditions: (i) $^{n}Pr_2NH$, $NaBH_3CN$, AcOH, CH_2Cl_2, 100%; (ii) 1:1 TFA/CH_2Cl_2, 96% or conc. HCl, acetone, 71%; (iii) $^{n}Pr_2NH$, $NaBH(OAc)_3$, AcOH, MeOH.

Scheme 2.17 Synthesis of indole **1.39**.

Deprotection of the Boc group with TFA was next examined and pleasingly this proceeded in excellent yield and occurred with concomitant dehydration of the hemi-aminal to give indole **1.39** in 96% yield. In practice, it proved beneficial to employ concentrated HCl in acetone[95] for this reaction which was shown to be less capricious, albeit resulting in a lower yield of 71% for **1.39**. Upon scale-up of the reaction with TFA, degradation of the reaction mixture was observed, with the formation of a dark precipitate. The final transformation, oxidation of indole **1.39** to ropinirole **1.9**, was reported in a patent to give the desired product in 87% yield upon heating **1.39** with $PyHBr_3$.[57] However, in our hands, several attempts to reproduce this result gave low conversions to ropinirole **1.9**, in part due to concurrent formation of the 5-brominated species **2.58** (Run 1, Scheme 2.18). Use of NCS, for the oxidation was also reported in the aforementioned patent, but in our hands it returned starting material (Run 2). Gratifyingly, using NBS as the oxidant gave clean conversion of indole **1.39** to ropinirole **1.39** in 61% isolated yield (Run 3). HCl salt formation to the API proceeded quantitatively to complete the synthesis in an overall 40% yield. This is a marked improvement on the current nine-step process which has an overall yield of *ca.* 12%.



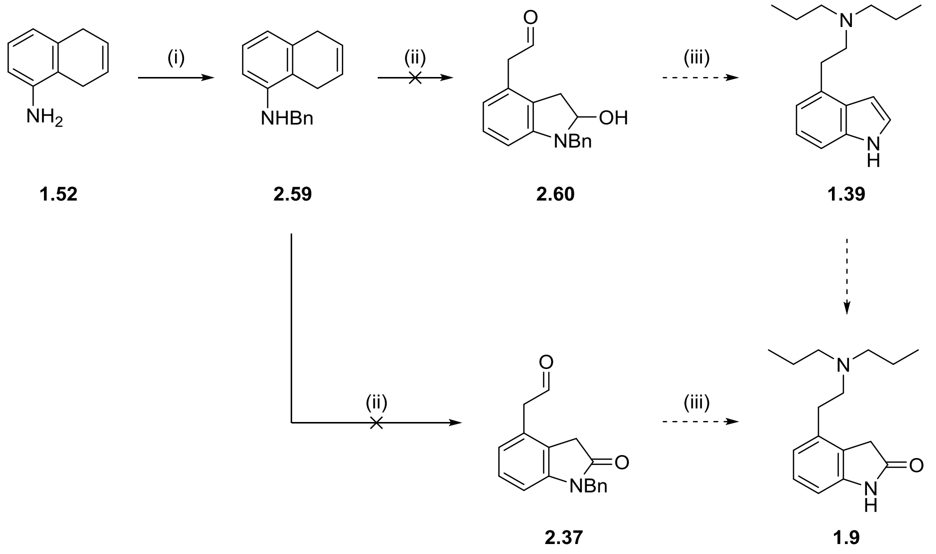
	1.9	2.58
Run 1	**12%**	**14%**
Run 2	**-**	**-**
Run 3	**61%**	**-**

Reagents and conditions: (i) $PyHBr_3$, 1:1 $AcOH/H_2O$ (Run 1); (ii) NCS, ^{t}BuOH, THF, conc. HCl (Run 2); (iii) NBS, ^{t}BuOH, THF, conc. HCl (Run 3); (iv) 2 M HCl in Et_2O, 100%.

Scheme 2.18 Synthesis of ropinirole HCl **1.1**.

2.8 Alternative Protecting Group Strategies

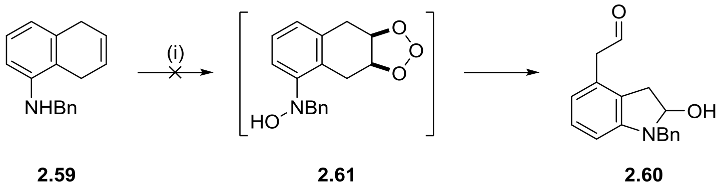
Several strategies were penned in an attempt to circumvent the complications experienced in the initial oxidative cleavage reaction and to improve the route further still. For example, use of a benzyl protecting group would allow us to unite the reductive amination and deprotection steps (Scheme 2.19, **2.60→1.39**). Moreover, it also opens up the prospect of oxidising the ozonolysis intermediates directly to indolone **2.37** (*vide supra*, Chapter 2.4). Unfortunately, ozonolysis of **2.59** gave only degradation products, which was presumably due to facile amine oxidation.



Reagents and conditions: (i) BnBr, K_2CO_3, THF, Δ, 45%; (ii) O_3, EtOAc, -78°C, then PPh_3; (iii) $^{n}Pr_2NH$, H_2, Pd/C (cat.), AcOH, MeOH.

Scheme 2.19 *N*-benzyl route to ropinirole **1.9**.

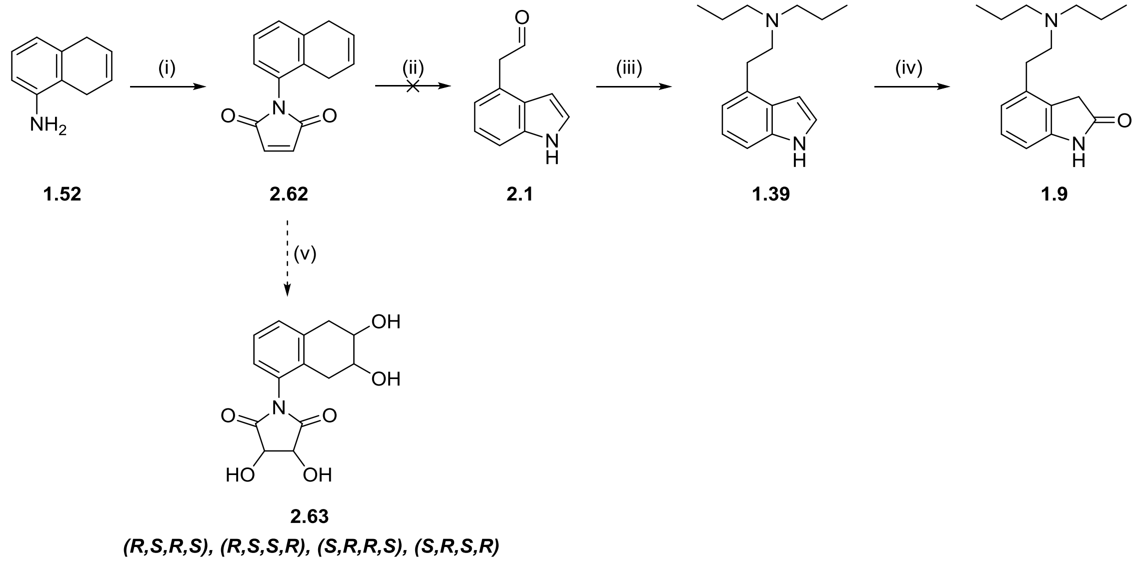
It was tentatively suggested that such *N*-oxidation might be favourable as oxidation to hydroxylamine **2.61** could act as the reducing agent towards ozonide **2.61** (Scheme 2.20). Unfortunately, this could not be realised, given the observed degradation during the reaction.



Reagents and conditions: (i) O_3, EtOAc, -78°C.

Scheme 2.20 Potential *N*-oxidation of **2.59** via ozone.

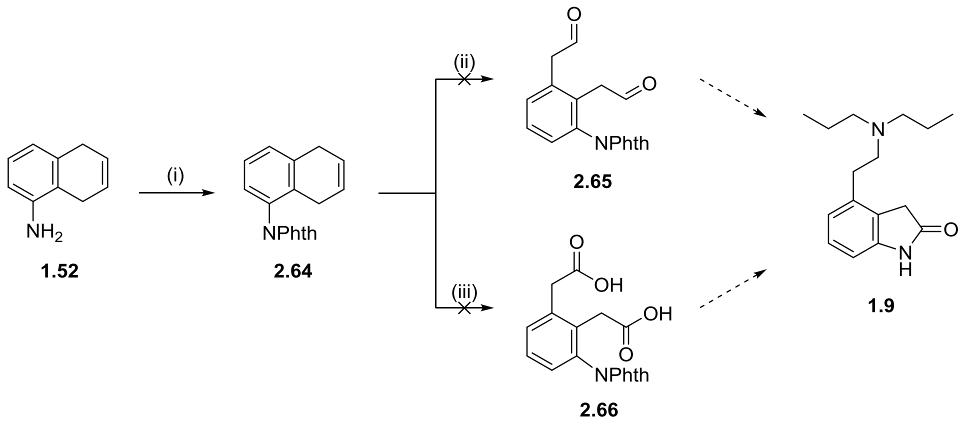
We also investigated the use of maleimide protection of naphthylamine **1.52** to **2.62** (attained in 76% yield) in the hope that this would liberate **2.1** upon ozonolysis with a reductive work-up (Scheme 2.21). However, the substrate proved to be inadequate, leading to decomposition on exposure to ozone. Attempted bisdihydroxylation of **2.62** to **2.63** using Upjohn conditions seemingly failed, returning a water-soluble species of which the identity was not established, though this may have been the desired tetrahydroxy species **2.63**.



Reagents and conditions: (i) Maleic acid, $PhCH_3$, Δ, 76%; (ii) O_3, EtOAc, -78 °C, then PPh_3; (iii) $^{n}Pr_2NH$, $NaBH_3CN$, AcOH, CH_2Cl_2; (iv) NBS, $^{t}BuOH$, THF, conc. HCl; (v) OsO_4 (cat.), NMO, citric acid, 1:1 $H_2O/^{t}BuOH$.

Scheme 2.21 Maleimide route to ropinirole **1.9**.

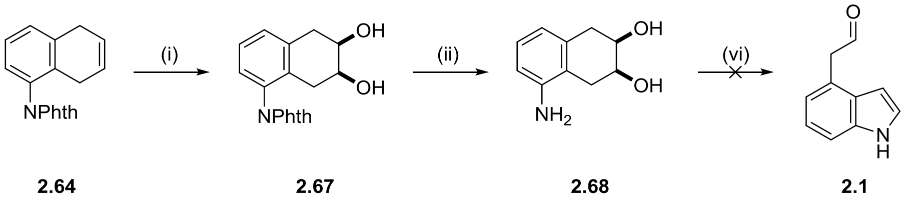
We also set about exploring the ozonolysis of naphthylimide **2.64** (formed in 90% yield by refluxing **1.52** in $PhCH_3$ with preformed phthalic anhydride) anticipating that it would allow formation of both dialdehyde **2.65** and diacid **2.66**, offering two end routes to the target oxindole **1.9** (Scheme 2.22). Again, ozonisation led to degradation, thereby thwarting our ambitions.



Reagents and conditions: (i) Ac_2O, CH_2Cl_2, then phthalic acid, PPTS, $PhCH_3$, Δ, 90%; (ii) O_3, EtOAc, -78 °C, then PPh_3; (iii) O_3, EtOAc, -78 °C, then aq. H_2O_2.

Scheme 2.22 Naphthylimide route to ropinirole **1.9**.

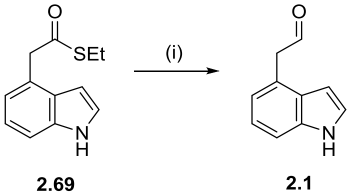
At this point, naphthylimide **2.64** was subjected to catalytic dihydroxylation (Scheme 2.23), which proceeded efficiently to give diol **2.67** in 79% yield. Its deprotection to amine **2.68** also progressed smoothly in 97% yield. Periodate cleavage of **2.68** returned **2.1**, which appeared to be unstable and oligomerised on standing at RT, even when stored under inert atmosphere.



Reagents and conditions: (i) OsO_4 (cat.), NMO, citric acid, 1:1 $H_2O/{}^tBuOH$, 79%; (ii) $N_2H_4.H_2O$, EtOH, 97%; (iii) $NaIO_4$, 1:1 THF/H_2O.

Scheme 2.23 Dihydroxylation route to indole **2.1**.

The instability of **2.1** was unexpected as this aldehyde has been reported as an intermediate by Hobley *et al.*, who prepared it by Pd-catalysed Et_3SiH reduction of the corresponding thioester **2.69** (Scheme 2.24).[96]



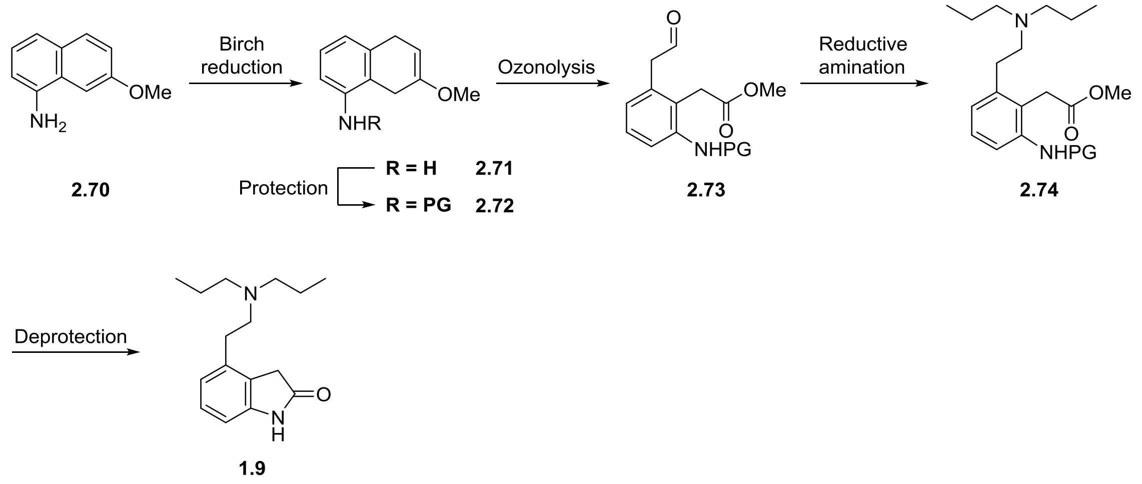
Reagents and conditions: (i) Et_3SiH, 10% Pd/C, acetone, 94%.

Scheme 2.24 Hobley's silane reduction of thioester **2.69** to indole **2.1**.[96]

2.9 Improved Route to Ropinirole HCl

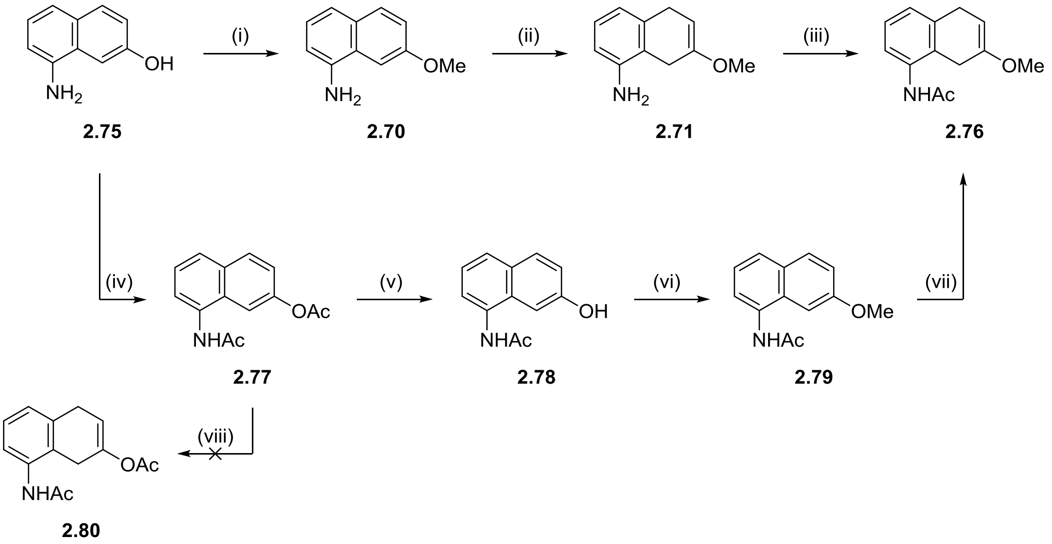
In an effort to further improve our route, and to cut the number of steps involved, we next sought to overcome the need to proceed via an indole by increasing the oxidation level of the C-7 carbon in the starting naphthylamine. Oxidative cleavage of the resulting vinyl ether **2.72** (Scheme 2.25), as before, would be expected to yield an ester moiety, which would cyclise to ropinirole **1.9** on deprotection of the amine functionality. If this could be realised, it would eliminate the modest yielding indole oxidation procedure and result in a shorter overall route.

Accordingly, our synthesis would begin with commercially available methoxynaphthalene **2.70** which upon Birch reduction and *N*-protection would give enol ether **2.71**. Ozonolysis, as before, would then produce aldehyde **2.73** with reductive amination and *N*-deprotection completing the five-step synthetic sequence.



Scheme 2.25 Proposed new route to ropinirole **1.9**.

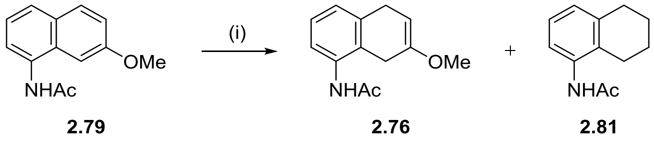
Starting for convenience from the free naphthol **2.75**, its protection with NaH and MeI in DMF provided precursor **2.70** in 90% yield following recrystallisation from hexane (Scheme 2.26). Birch reduction with Li in liquid NH_3 at -78 °C next delivered alkene **2.71** in quantitative yield. At this point we opted for an acetyl protection of the NH_2 group as it is significantly cheaper than Boc protection. Moreover, it would acidify the amine group significantly to allow selective reduction of the less electron-rich *O*-substituted aromatic ring in **2.79** for an alternative sequence. Nonetheless, acylation of **2.71** proceeded smoothly in acetone, in the presence of K_2CO_3, providing **2.76** quantitatively.



Reagents and conditions: (i) NaH, MeI, DMF, 90%; (ii) Li, NH_3, ^{t}BuOH, THF, -78°C, 100%; (iii) Ac_2O, K_2CO_3, acetone, 100%; (iv) Ac_2O, Et_3N, CH_2Cl_2, 100%; (v) sat. $NaHCO_3$, MeOH, 96%; (vi) MeI, K_2CO_3, acetone, 90%; (vii) Na, NH_3, ^{t}BuOH, THF, -33°C, 50%; (viii) Na, NH_3, ^{t}BuOH, THF, -33°C.

Scheme 2.26 Forward synthesis to intermediate vinyl ether **2.76**.

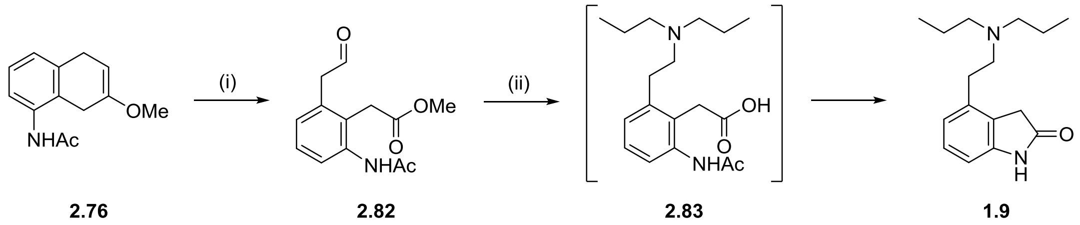
The more laborious route to **2.76** consisted of diacylation of aminonaphthol **2.75** to **2.77** (Scheme 2.26). Dissolving metal reduction of the latter failed to produce **2.80**, with complete degradation of the reaction mixture having occurred. The ester **2.77** was then hydrolysed with saturated $NaHCO_3$ in MeOH, to give naphthol **2.78** in good yield. Methylation to **2.79** followed by dissolving metal reduction using the previous conditions (with Na at -33 °C) then delivered alkene **2.76**. In this case, however, Birch reduction gave at best 50% of the desired product, with much of the remaining mass balance being recovered starting material. Suspecting that the poor efficiency might be due to aerial oxidation of the product back to **2.79**, the work-up was performed under an inert atmosphere with degassed solvents. Alas, this gave a similar outcome and the nature of the two compounds rendered their separation difficult. Increasing the stoichiometry of Na led to partial over-reduction to tetralin **2.81**, identified as a significant by-product (Scheme 2.27), with unreacted starting material detected by TLC.



Reagents and conditions: (i) Na, NH_3, ^{t}BuOH, THF, -33 °C, 33% of **2.76** and 10% of **2.81**.

Scheme 2.27 Problematic Birch reduction of naphthalene **2.79**.

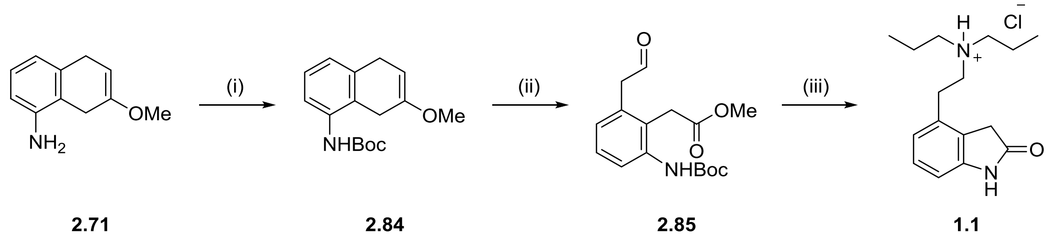
Ozonolysis of alkene **2.76** yielded aldehyde **2.82** in 58% yield (typically lower) using polymer-bound PPh_3 as the quench reagent (Scheme 2.28). The product from this procedure often required repurification by flash column chromatography. The stubborn deprotection/cylisation of the subsequent aminated intermediate **2.83** now steered us back towards the use of a carbamate protection of dihydromethoxynaphthylamine **2.71**.



Reagents and conditions: (i) O_3, EtOAc, -78°C, then polymer-PPh_3, 58%; (ii), ${}^{n}Pr_2NH$, $NaBH_3CN$, AcOH, CH_2Cl_2, then conc. HCl, *ca*. 20%.

Scheme 2.28 Cyclisation to ropinirole **1.9**.

Using amine **2.71**, Boc protection proceeded with reasonable efficiency to give **2.84** in 86% with the rest of the mass balance consisting of partially recovered starting material (Scheme 2.29). Oxidative cleavage of **2.84** with ozone, as before, afforded aldehyde **2.85** in 71% yield, along with a small amount of an unidentified by-product. Interestingly, prolonged exposure of **2.84** to air led to isomerisation to **2.86** (Figure 2.10). *N*-oxide work-up of the ozonolysis reaction was also attempted as intramolecular trapping of the molozonide was no longer a possibility. However, this resulted in decomposition of the oxidised intermediate. Harries, one of the pioneers of ozonolysis, was purported to have used H_2O during his research,[97] with Dussault having exemplified its use even further.[98] As attractive as this appeared to be, the use of H_2O as a work-up reagent/solvent ceded no success.



Reagents and conditions: (i) $(Boc)_2O$, H_2NSO_3H (cat.), Et_2O, 86%; (ii) O_3, EtOAc, -78 °C, then PPh_3, 71%; (iii) ${}^{n}Pr_2NH$, $NaBH_3CN$, AcOH, CH_2Cl_2, then 2 M HCl in Et_2O, 73%.

Scheme 2.29 Carbamate route to ropinirole HCl **1.1**.

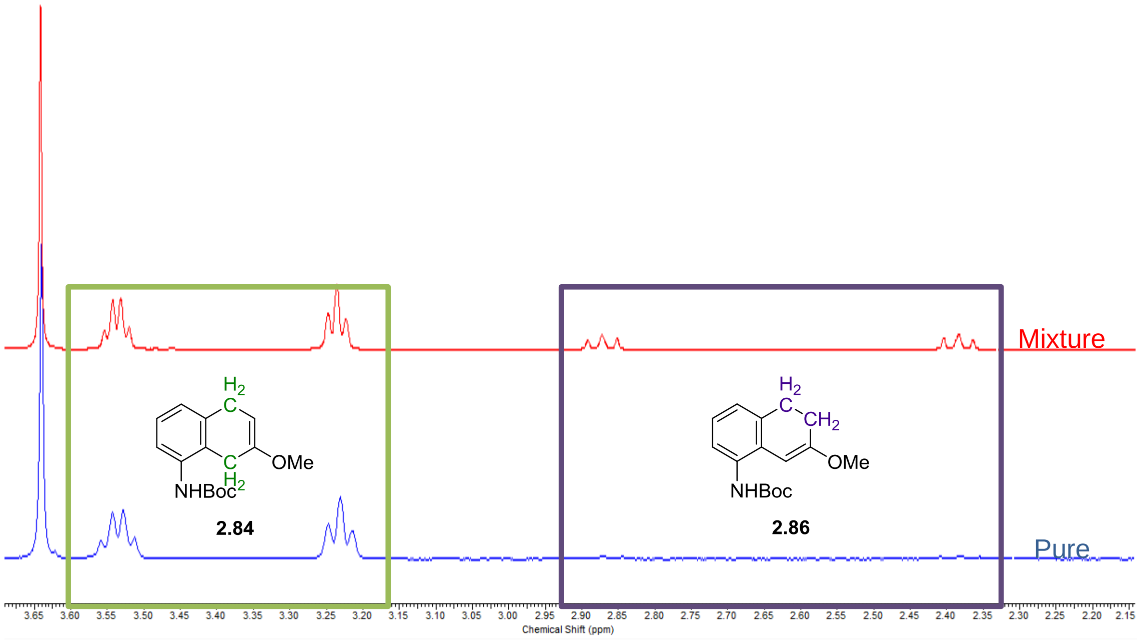


Figure 2.10 Isomerisation of alkene **2.84** to **2.86** on standing.

Reductive amination of **2.85** with $NaBH_3CN$ in CH_2Cl_2 provided an uncyclised intermediate which, after aqueous work-up and treatment with concentrated HCl, formed ropinirole **1.9** in 73% isolated yield. Quantitative formation of its HCl salt **1.1** was then achieved with ethereal HCl solution and the API could also be obtained in 60% yield upon recrystallistion of the crude salt.

2.10 Conclusions

An improved route to ropinirole, relative to GSK's current process, has been established from 1-aminonaphthalene using a dissolving metal reduction and ozonolysis under flow as key steps. The route delivers the API in six steps with an overall yield of 40% and paves the way for a novel flow API synthesis as an industrial process. In addition, our route could reduce GSK's process costs significantly to around £870/kg of ropinirole, excluding labour and overheads (Figure 2.11, applying HCl for the deprotection step). Whereas when using TFA in step five, the cost per kg of ropinirole rises to £1650, due mainly to the use of the reagent as a co-solvent. Despite the considerably lower cost with HCl, the modest dilution and moderate yield contribute to the substantial fractional pricing. Indeed, with further optimisation of the flow ozonolysis, where a comprehensive 5-level centre composite design (CCD) DoE analysis could help us realise our attempted hemi-aminal oxidation of **2.5** to **2.7** (*vide supra*, Chapter 2.4), further cost savings can be envisioned.

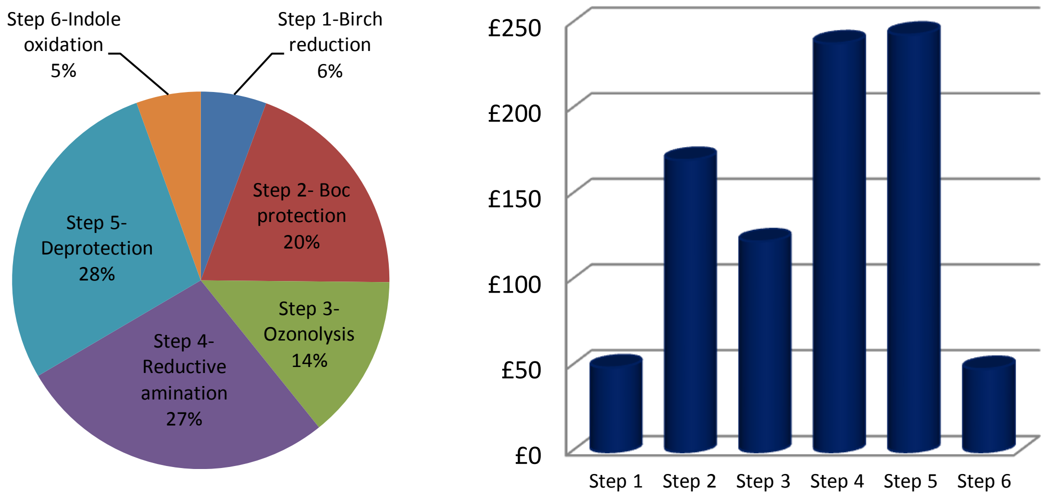


Figure 2.11 Estimated pricing of our first route to ropinirole.

Furthemore, by beginning with 7-methoxynaphthyl-1-amine **2.70**, we were able to realise the transformation to the API ropinirole HCl **1.1** in four steps, which to the best of our knowledge is the shortest and most efficient to be described to date. Modifyng Plieninger's indole synthesis, Birch reduction delivered enol ether **2.71** which, after Boc protection, was ozonolytically cleaved to ester **2.85** which cyclised upon *N*-deprotection to the desired oxindole in 45% yield overall (*vide supra*, Scheme 2.29). In this case, the high cost of the starting material gives rise to a process cost of £1400/kg of ropinirole, excluding labour and overheads (Figure 2.12), where this one step accounts for 70% of the cost of production. Given that process costs are largely governed by labour and overheads, which in turn are generally dependant on the number of 'stages' involved in a given route, our shorter route would conceivably be cheaper and thus more economical than GSK's synthesis (the cost of which, due to its sensitive nature, cannot be disclosed in this work).

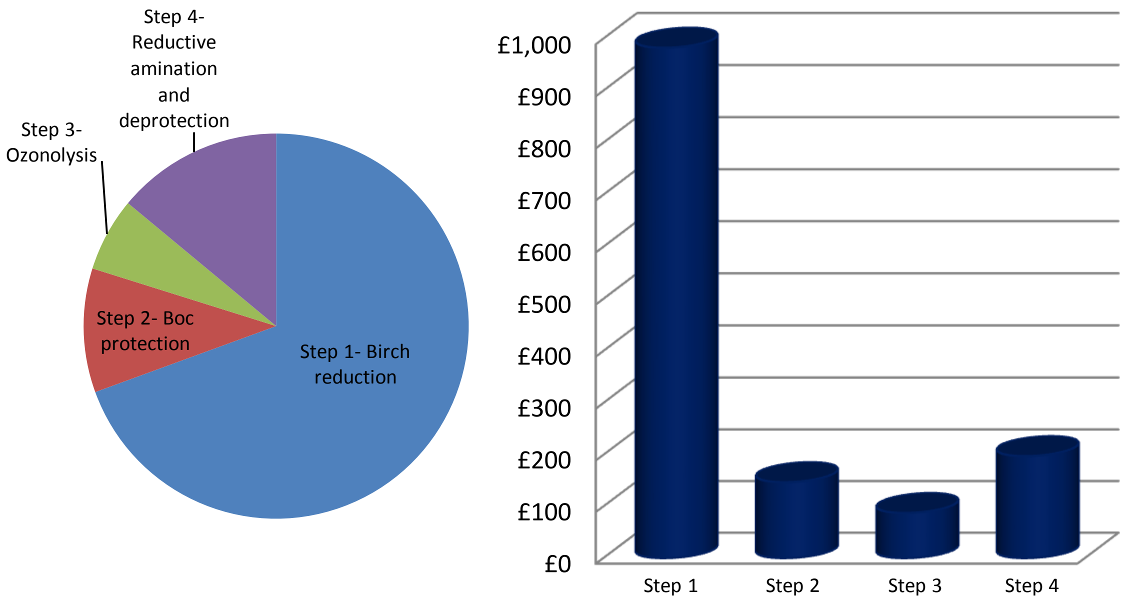


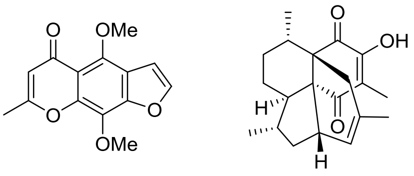
Figure 2.12 Estimated pricing of our second route to ropinirole.

Use of cheap and readily available reagents, such as NH_3, Li and O_3, makes this route attractive and robust from a financial perspective. The emergence of flow ozonolysis also allays many of the safety concerns associated with the use of ozone in large-scale syntheses. With further effort, benign replacements could doubtless be found for the $NaBH_3CN$ and CH_2Cl_2 (both toxic) employed in our synthesis. Moreover, by conducting the critical oxidative cleavage step under continuous flow, the sequence becomes viable for transfer to the pilot plant in due course.

Chapter 3: Introduction to Squaramides

3.1 Background

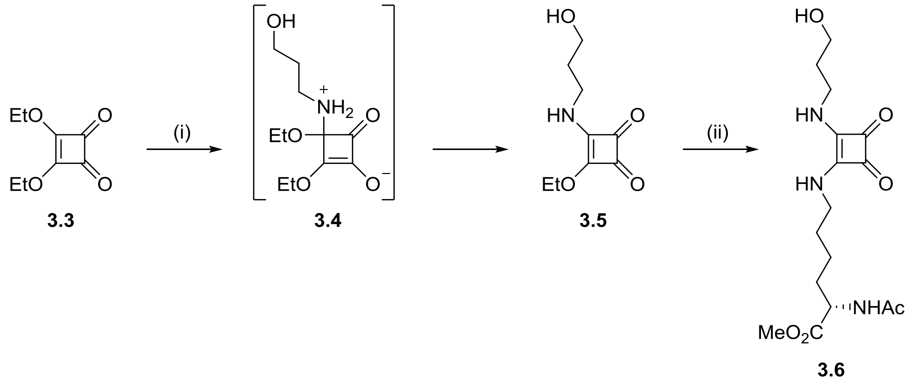
Over the past few decades there has been a surge in the application of squarates in organic synthesis due, in part, to the availability of the starting materials and precursors from squaric acid (3,4-dihydroxycyclobut-3-ene-1,2-dione). An improvement in such method development has paved the way for many astute total syntheses such as, *inter alia*, Khellin **3.1** by Moore and Reed[99] and (–)-colombiasin A **3.2** by Harrowven *et al*.[100] (Figure 3.1).



3.1 **3.2**

Figure 3.1 Squaric acid-synthesised natural products.

Squaramides, however, have received relatively little attention. Their notable applications in medicinal chemistry are largely a result of their H-bonding abilities which are superior compared to the vinylogous urea functional group.[101] As such, there has been an increase in squaramide moieties appearing in clinical candidates. Numerous medicinal applications have been explored including the development of anti-malarial and anti-HIV scaffolds. Synthetic manipulation of squarates, via a purported 1,4-Michael addition-elimination process,[102] is the easiest route to squaramides, where the nature and equivalents of amine nucleophiles provide routes to mixed squaramide systems (Scheme 3.1, **3.3→3.6**).



Reagents and conditions: (i) $HOC_3H_6NH_2$, EtOH, 84%; (ii) N_α-Acetyl-L-lysine methyl ester, Et_3N, EtOH, 78%.

Scheme 3.1 Synthesis of mixed squaramide **3.6.**[101]

While squaric acid is only aromatic upon di-deprotonation to conjugate base **3.8**, the nitrogen analogues **3.10** exhibit aromaticity when ‘activated’ through H-bonding. Indeed, they show Nucleus-Independent Calculated Shifts (NICS values at 0.6 Å above the ring plane) in the region of -8.7 ppm (Figure 3.2), which are comparable with benzene (-10.1 ppm). As such, squaramides display π-stacking, further adding to their stability.

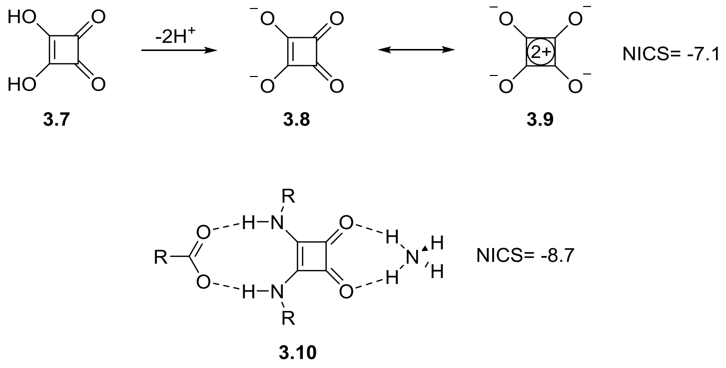
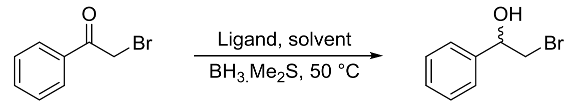
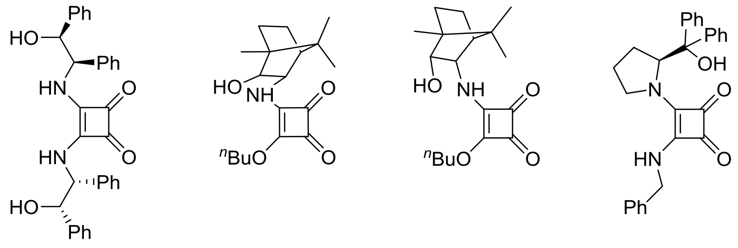


Figure 3.2 NICS values of squarate **3.9** and squaramide complex **3.10**.

An illustration of the stability and versatility of aminated squarates can be seen with the work of Xie *et al.*, who have shown that enantioselective reductions of carbonyls such as **3.11** can be achieved with high enantioselectivity, up to 99% ee (Entry 3, Table 3.1),[103] using prolinol and camphor-derived squaramide catalysts. A similar oxazaborolidine mechanism to that of Corey’s related protocol is likely, where a six-membered diastereomeric transition state sets up hydride delivery to α-bromobenzophenone **3.11**.



3.11 **3.12**

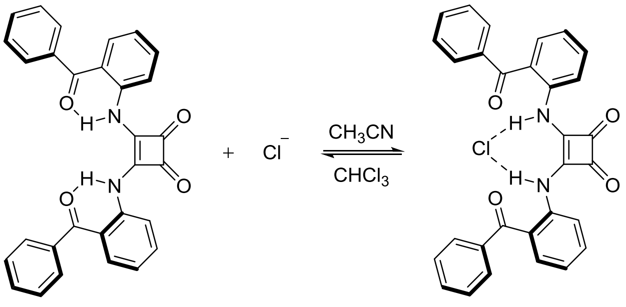


3.13 **3.14** **3.15** **3.16**

Table 3.1 Asymmetric reduction of carbonyl **3.11**.[101,103]

Entry	Ligand	Solvent	ee (%)	Configuration
1	**3.13**	$PhCH_3$	96	(*R*)
2	**3.14**	THF	94	(*S*)
3	**3.15**	THF	99	(*R*)
4	**3.16**	$PhCH_3$	92	(*S*)

Another use of squaramides worthy of mention lies in chemical biology, where, in one case, the environment-sensitive chloride receptor **3.17** has the potential to surmount defective ion transport in diseases such as cystic fibrosis. The robust H-bonding ability of squaramides allows for tight binding of chloride ions in polar solvents such as CH_3CN, in what the authors describe as a ‘valve open’ mode (Scheme 3.2, **3.18**). Conversely, apolar solvents (*e.g.* $CHCl_3$) release the chloride ions as the squaramides adopt their ‘valve closed’ form. The ability to easily switch between the two modes allows this to be an excellent candidate for an environment-sensitive receptor in analytical and medicinal applications.[101]

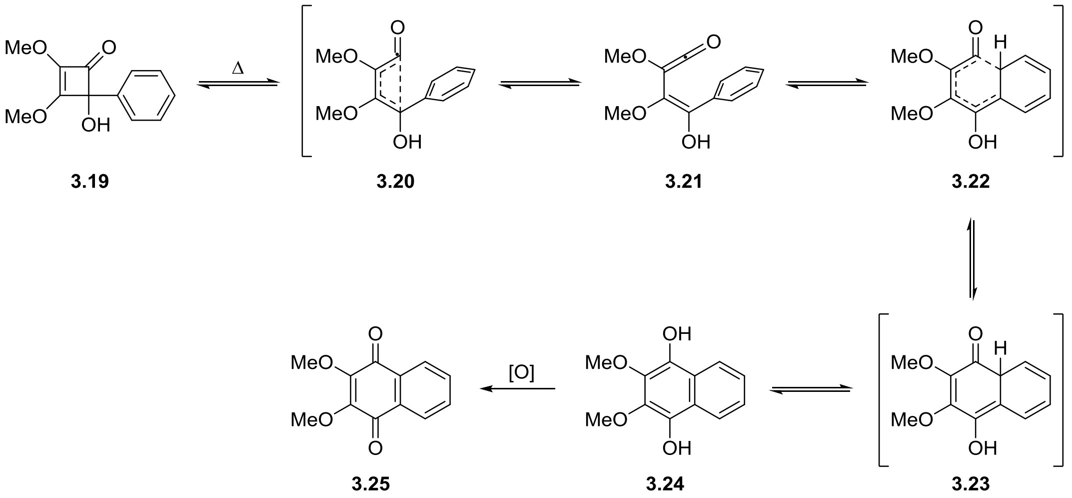


3.17 **3.18**

Scheme 3.2 Environment-sensitive Cl^- ion receptor.

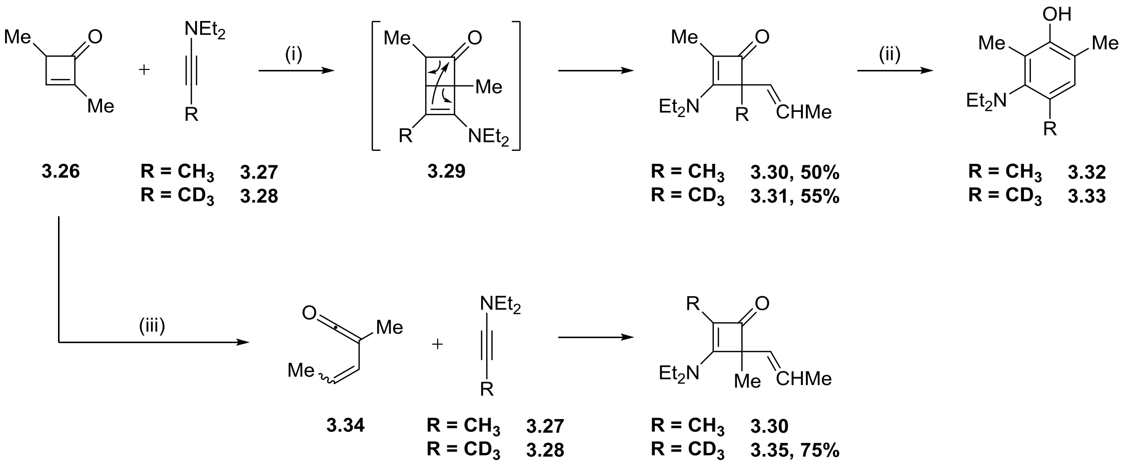
3.2 Rearrangement of Non-Fused Squaramides

Only a handful of examples of thermal rearrangements of squaramides have been reported. This is in stark contrast to the chemistry of squarates where the much studied Moore rearrangement has long been used to convert adducts into highly substituted quinones and aromatics via electrocyclic rearrangement (Scheme 3.3, **3.19→3.25**).[104,105]



Scheme 3.3 Torquoselective thermal rearrangement of squarate **3.19**.

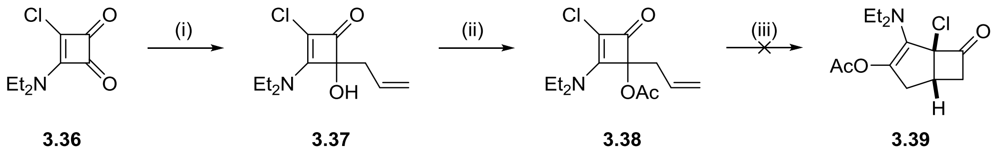
One of the earliest examples of squaramide ring opening was reported by Ficini *et al*.[106] Their attempt to prepare bicyclic adduct **3.29** through a [2+2] cycloaddition of cycobutenone **3.26** and ynamide **3.27** unexpectedly delivered vinylcyclobutenone **3.30** (Scheme 3.4), given the reaction temperature of -50 °C was too low for the Danheiser annulation to proceed. When this was subsequently thermolysed above 140 °C, rearrangement proceeded to phenol **3.32**. In order to verify the proposed structure of intermediate **3.30**, ketene **3.34** (formed by thermolysis of **3.26** in refluxing cyclohexanone) was reacted with ynamide **3.27** to afford the identical intermediate **3.30**. However, when the ynamide R = CD_3 **3.28**, the isomeric products (**3.31** and **3.35**) obtained from reaction with ketene **3.34** and cyclobutenone **3.26** demonstrated that the two pathways were distinct in their mechanisms.



Reagents and conditions: (i) CH_3CN, -50 °C, 55%; (ii) 140 °C; (iii) cyclohexane, Δ.

Scheme 3.4 Thermal rearrangement of squaramides **3.30** and **3.31**.[106]

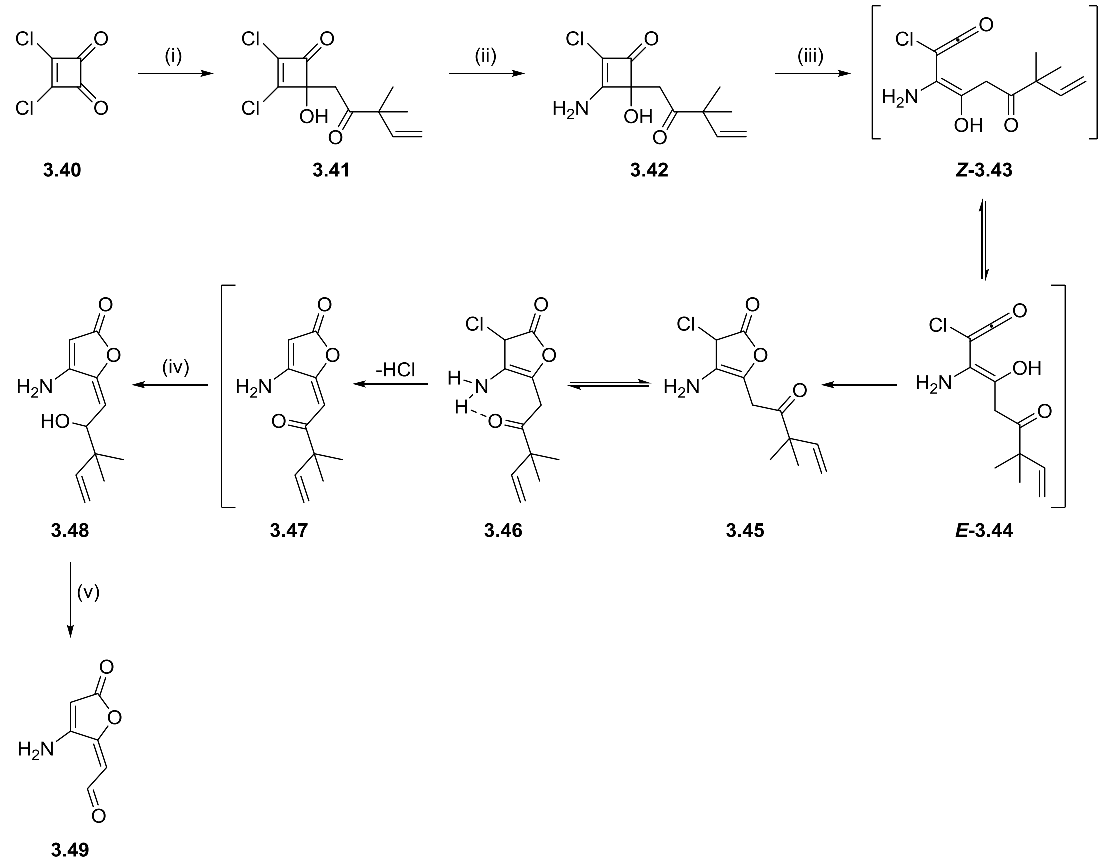
Later, Eguchi *et al*. attempted to prepare bicyclo[3.2.0]heptenone **3.39** by thermolysis of mono-squaramide **3.38** (Scheme 3.5).[107] Their failure to realise this transformation was attributed to a stabilisation of cyclobutenones when conjugated to nitrogen atoms. It is useful to note how exposure of **3.36** to the strong Lewis acid $TiCl_4$ does not change the regiochemical course of addition of $AllylSiMe_3$, as might have been expected through its coordination to the most electron rich carbonyl of the vinylogous amide.



Reagents and conditions: (i) $AllylSiMe_3$, $TiCl_4$, 0 °C, 83%; (ii) AcCl, Et_3N, 67%; (iii) mesitylene, Δ.

Scheme 3.5 Attempted thermolysis of squaramide **3.38**.[107]

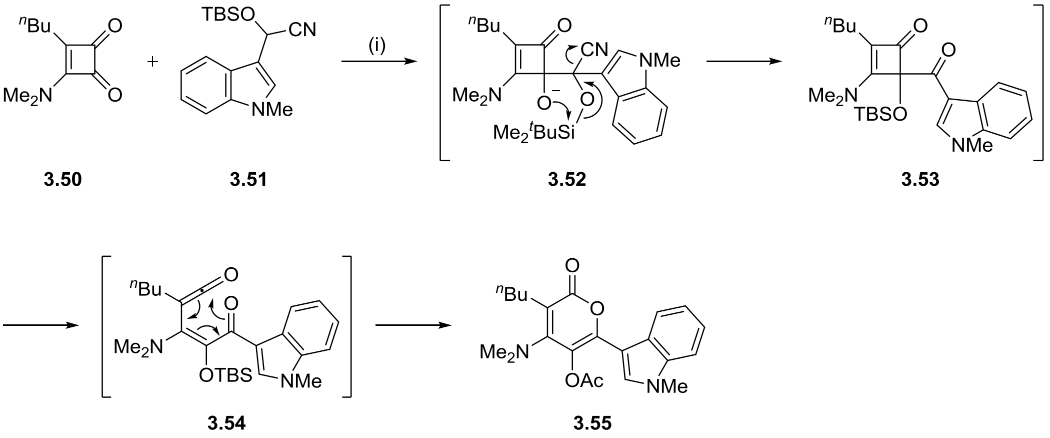
Interestingly, thermolysis of chloroaminocyclobutenone **3.42** in xylene led to γ-lactone **3.48**, indicating the influence that the amine has on the course of the Moore rearrangement (Scheme 3.6). The *Z*-vinylketene equilibrates to the *E*-intermediate since the former does not have a proximal reactive functional group to trap the ketene, *viz.* ***Z*-3.43**→ ***E*-3.44**. H-bonding between the NH and pendant ketone in **3.46** favours the *E*-geometry (**3.47**) with respect to the *exo*-alkene. In this example, pyridine was added to neutralise the liberated HCl. Reduction of the carboxybutenolide and oxidative C-C bond cleavage furnished the natural product, basidalin **3.49** in 14% yield from 3,4-dichlorocyclobut-3-ene-1,2-dione **3.40**.



Reagents and conditions: (i) Trimethyl((2-methylpent-4-en-2-yl)oxy)silane, $TiCl_4$, 0 °C, 69%; (ii) 7 M NH_3 in EtOH, 45%; (iii) xylene, py, Δ, 85%; (iv) $NaBH_4$, $CeCl_3.7H_2O$, 1:1 $MeOH/CH_2Cl_2$, 80%; (v) $Pb(OAc)_4$, CH_2Cl_2, -78 °C, 65%.

Scheme 3.6 Total synthesis of (*E*)-basidalin **3.49**.[107]

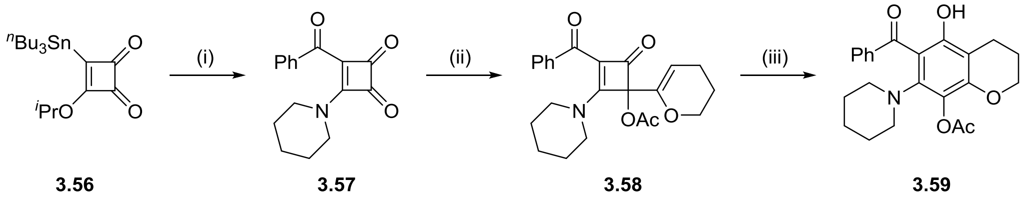
Liebskind *et al*. have developed an efficient route to α-pyrones, useful synthetic precursors found in natural products, through squaramide thermolysis.[108] The addition of *O*-silyl cyanohydrin **3.51** to cyclobutenedione **3.50** led to acylcyclobutenone **3.53** via adduct **3.52** (Scheme 3.7). The instability of **3.53** was apparent as, at the reaction temperature of -78 °C, this species underwent facile rearrangement to α-pyrone **3.55**.



Reagents and conditions: (i) LiHMDS, $CeCl_3$, -78 °C, then TBAF, Ac_2O, 57%.

Scheme 3.7 *In situ* rearrangement of mono-squaramide **3.53** to α-pyrone **3.55**.[108]

Acylcyclobutendiones have generally been found to be too unstable to allow synthetic manipulation. An exception to this rule is provided by aminated analogues such as **3.57** (Scheme 3.8).[109,110] When exposed to alkyllithium reagents, these readily give acetates akin to **3.58** after trapping with Ac_2O. Thermolysis can then be achieved in mesitylene at reflux, to generate a hydroquinone like **3.59**.[110] Rearrangement of cyclobutenones with electron rich alkenes, such as enol ethers, proceeded faster than those having no activating group, suggesting that ring closure was the rate determining step.

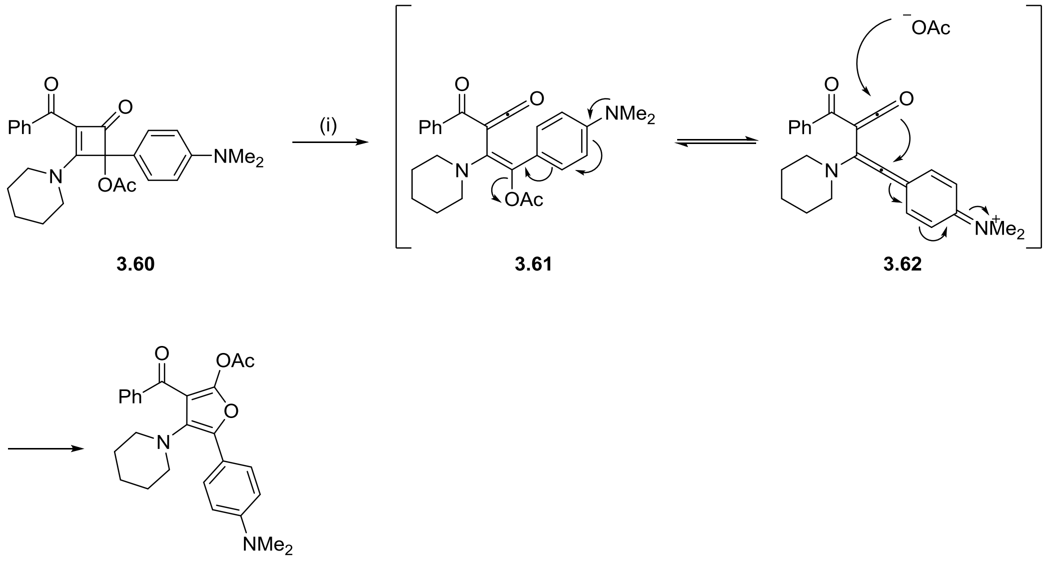


Reagents and conditions: (i) BzCl, benzylchlorobis(triphenylphosphine)palladium (cat.), CuI (cat.), THF, Δ, then piperidine, 79%; (ii) 6-(tri-^{n}butylstannyl)-3,4-dihydro-2*H*-pyran, ^{n}BuLi, THF, -78 °C, then Ac_2O, 55%; (iii) mesitylene, Δ, 100%.

Scheme 3.8 Thermal rearrangement of mono-squaramide **3.58**.[110]

Phenyl and *ortho*/*para*-methoxyphenyl appendages failed to trap the vinylketene intermediate. Substituting the squaramides for secondary amines led to shorter reaction times (10 min vs 5 min), which again may have been due to H-bonding assisting the ring opening step.

Surprisingly, the dimethylaminophenyl adduct **3.60** led to furan **3.63** upon thermolysis in refluxing mesitylene (Scheme 3.9). In this case, the authors suggest that the reaction proceeds via the transient allenylketene intermediate **3.62**. Trapping of the ketene intermediate **3.62**with acetate could then trigger furan formation, leading to the observed product **3.63**.



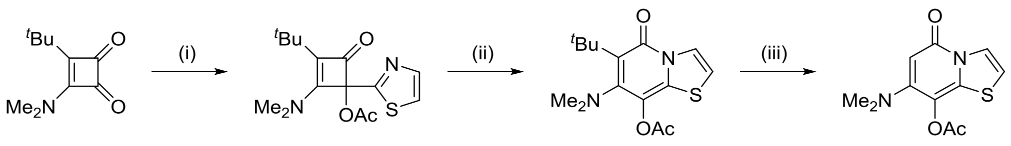
3.60 **3.61** **3.62**

3.63

Reagents and conditions: (i) Mesitylene, Δ, 83%.

Scheme 3.9 Unusual thermal rearrangement of mono-squaramide **3.60**.[110]

In another example of aminocyclobuteneone rearrangement, crude squaramide **3.65** was thermolysed neat at 140 °C to give fused pyridone **3.66** in 97% yield (Scheme 3.10).[111] Addition of lithiated thiazole to **3.64** took place at -78 °C which was followed by warming to 0°C and an Ac$_2$O quench to yield **3.65**. Treatment of the pyridone with Zn(OAc)$_2$/AcOH induced cleavage of the ^{t}Bu group to afford **3.67** in excellent yield. The ring opening of oxygen analogues proceeded on similar timescale at the lower temperature of 120 °C.

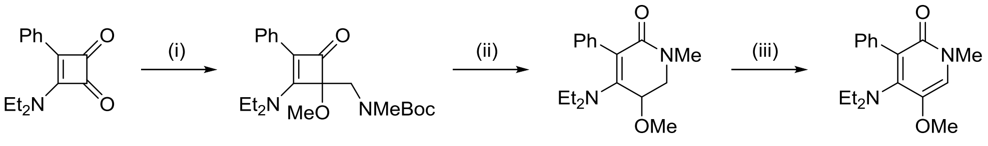


3.64 **3.65** **3.66** **3.67**

Reagents and conditions: (i) 2-Tri-^{n}butylstannylthiazole, ^{n}BuLi, THF, -78 °C, then Ac$_2$O; (ii) 140 °C, 97% over 2 steps; (iii) Zn(OAc)$_2$, AcOH, 100%.

Scheme 3.10 Thermal rearrangement of mono-squaramide **3.65**to fused pyridone **3.66**.[111]

Similarly, mono-squaramide **3.68** was treated with lithiated Boc-dimethylamine at -78 °C, and on quenching with MeOTf provided cyclobutenone **3.69** in 85% yield (Scheme 3.11).[112] Its thermolysis neat at 155–160 °C then triggered rearrangement to **3.70**, after which NBS oxidation afforded the desired 2-pyridinone **3.71** in good yield.

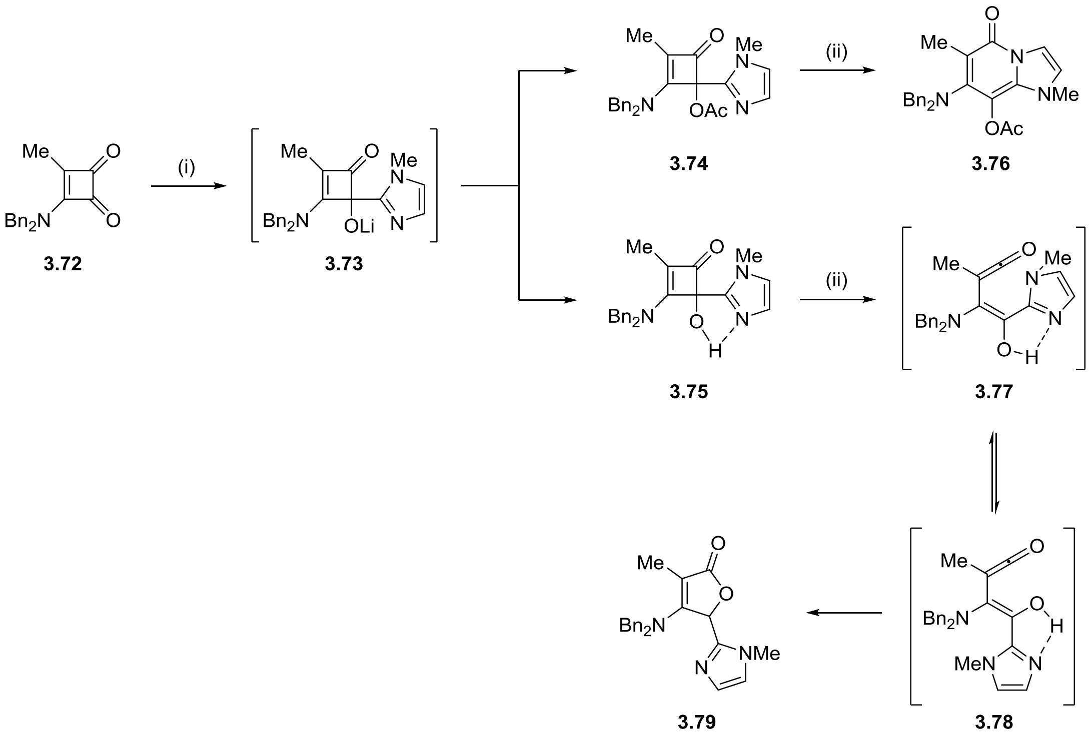


3.68 **3.69** **3.70** **3.71**

Reagents and conditions: (i) *N*-Boc-(tri^{n}butylstannyl)dimethylamine, ^{n}BuLi, THF, -78 °C, then MeOTf, 85%; (ii) TFA, then 155–160 °C, 89%; (iii) NBS, py, THF, 99%.

Scheme 3.11 Thermal rearrangement of mono-squaramide **3.69** to pyridinone **3.70**.[112]

2-Lithioazaheteroaromatics have also been added to mono-squaramides to form pyridones upon thermolysis.[113] Upon addition of lithiated 1-methylimidazole to **3.72**, Ac_2O was added to quench the alkoxide **3.73**. This, however, resulted in incomplete acylation, giving a mixture of protected and unprotected intermediates **3.74** and **3.75**. Thermolysis of the crude in dioxane led to pyridinone **3.76** in a lowly 33% yield (Scheme 3.12). A remarkable by-product stemming from **3.75** was observed, namely lactone **3.79** in 37%. It has long been known that thermal rearrangements of squarates proceeded in a torquoselective fashion and favour formation of (*E*)-vinylketenes.[104] This is somewhat of an anomaly as the formation of γ-lactone **3.79** suggests that it proceeds via (*Z*)-vinylketene **3.78**. It was reasoned that H-bonding between the imidazole and OH group in **3.75** may be responsible for the switch, allowing the transient intermediate **3.77** sufficient lifetime to equilibrate to **3.78** and undergo facile ring closure. Alternatively, a reversal in the torquoselectivity of ring opening with squaramides must be involved. If true, it would represent a significant discovery in cyclobutenone chemistry.



Reagents and conditions: (i) 1-Methylimidazole, ^{n}BuLi, THF, -78 °C, then Ac_2O; (ii) dioxane, Δ, 33% of **3.76** and 37% of **3.79**.

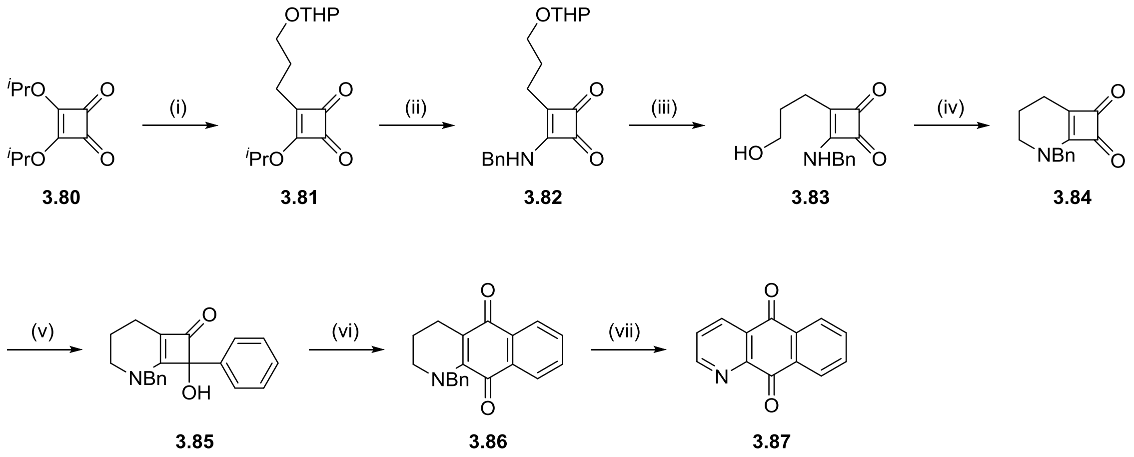
Scheme 3.12 Thermal rearrangement of mono-squaramide **3.75** to furanone **3.79**.[113]

More efficient conversion of **3.73** to the acylated intermediate **3.74** was achieved when the crude reaction mixture was warmed to RT prior to quenching. This itself is astonishing as with squarates, such conditions would have led to complete decomposition of the alkoxide adduct via an anion-accelerated ring opening. The fact that this did not occur provided further evidence of the enhanced stability of squaramides.

Thus far, Liebskind and others have demonstrated that the thermal rearrangement of squaramides is possible, albeit with lower reactivity compared to the analogous squarates. However, as examples are scarce they reveal very little about the thermochemistry of these cyclobutenones.

3.3 Rearrangement of Fused Squaramides

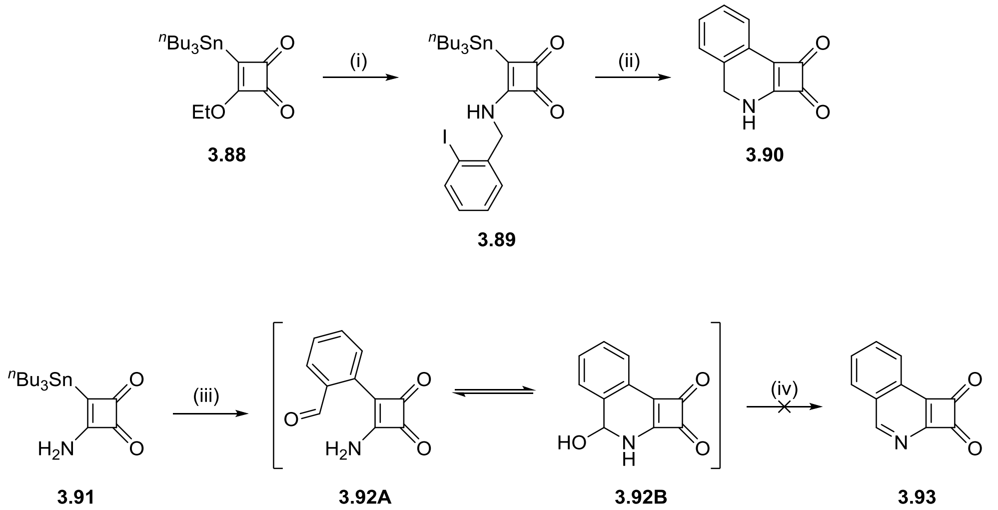
Fused squaramides such as **3.85** were shown by Liebskind *et al*. to ring open at reflux in xylene, to yield tetrahydroquinoline quinones such as **3.86** (Scheme 3.13).[114] The synthesis of **3.86** began with diisopropoxy squarate **3.80**, which was subjected to a Grignard addition and amination to give the masked alcohol **3.82**. Deprotection to **3.83** and an intramolecular Mistonobu reaction then furnished cyclobutendione **3.84**, which was stable enough to allow chemical transformation. PhLi addition, for example, proceeded to adduct **3.85** in 70% yield, with its thermal rearrangement delivering benzoquinone **3.86**. Thus, to form benzo[*g*]quinolone **3.87**, DDQ oxidation of **3.86** was performed with concomitant debenzylation (in modest yield).



Reagents and conditions: (i) THPO(CH$_2$)$_3$MgBr, THF, -78 °C, then TFAA, 57%; (ii) BnNH$_2$, MeOH, 95%; (iii) conc. HCl, H$_2$O, Δ, 95%; (iv) DEAD, PPh$_3$, THF, 65%; (v) PhLi, THF, -78 °C, 70%; (vi) xylene, Δ, 89%; (vii) DDQ, PhH, 42%.

Scheme 3.13 Thermal rearrangement of fused mono-squaramide **3.85**.[114]

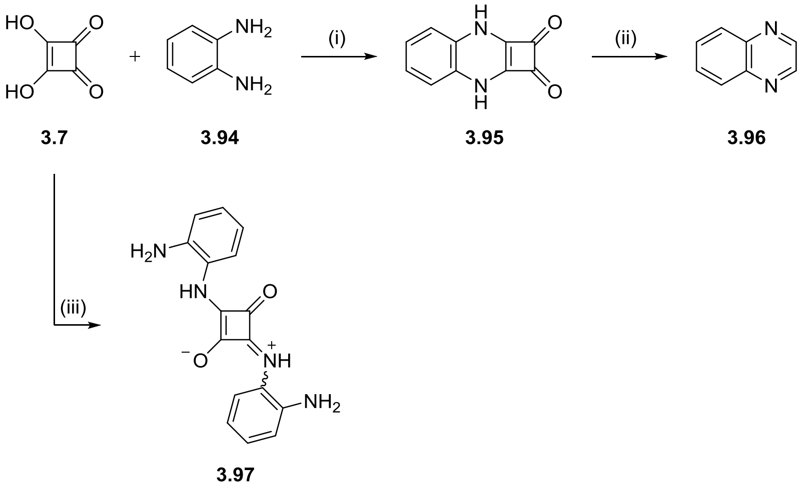
Similarly, **3.90** was synthesised from **3.89** in 61% yield via an intramolecular Stille coupling (Scheme 3.14). Notably, when a similar tactic was used to form isoquinoline **3.93**, the product proved to be highly unstable. It therefore seems that an increase in saturation induces strain in the bicycle, thereby explaining the ease of ring opening of adducts of dihydropyridinecyclobutendiones compared to non-fused squaramides.



Reagents and conditions: (i) 2-Iodobenzylamine, MeOH, 86%; (ii) Pd(PPh_3)$_4$ (cat.), THF, Δ, 61%; (iii) 2-iodobenzaldehyde, 1:1 Pd(benzyl)Cl(PPh_3)$_2$/CuI (cat.), PhH, 92%; (iv) CH_2Cl_2.

Scheme 3.14 Synthesis of fused mono-squaramides.[114]

Fused squaramides such as **3.95** were reported by Skujins and Webb in the late 1960s (Scheme 3.15)..[115] Thus, when squaric acid **3.7** was heated in dilute H_2SO_4 with *o*-phenylenediamine **3.94**, it gave the condensation product cyclobuta[*b*]quinoxalines **3.95** as a brightly coloured solid that decomposed at high temperatures to quinoxaline **3.96**. Side products, tentatively assigned as squaraines such as **3.97**, were obtained with excess diamines.

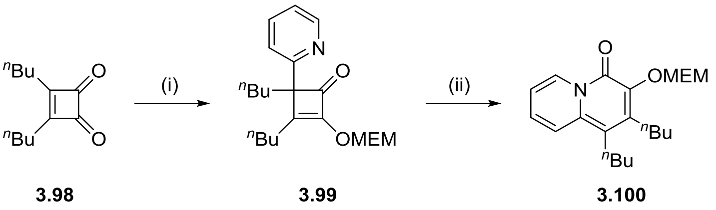


Reagents and conditions: (i) Aq. H_2SO_4, H_2O, Δ; (ii) 330 °C; (iii) excess *o*-phenylenediamine.

Scheme 3.15 Synthesis of cyclobuta[*b*]quinoxaline **3.95**.[115]

3.4 Rearrangement of Aminocyclobutenones

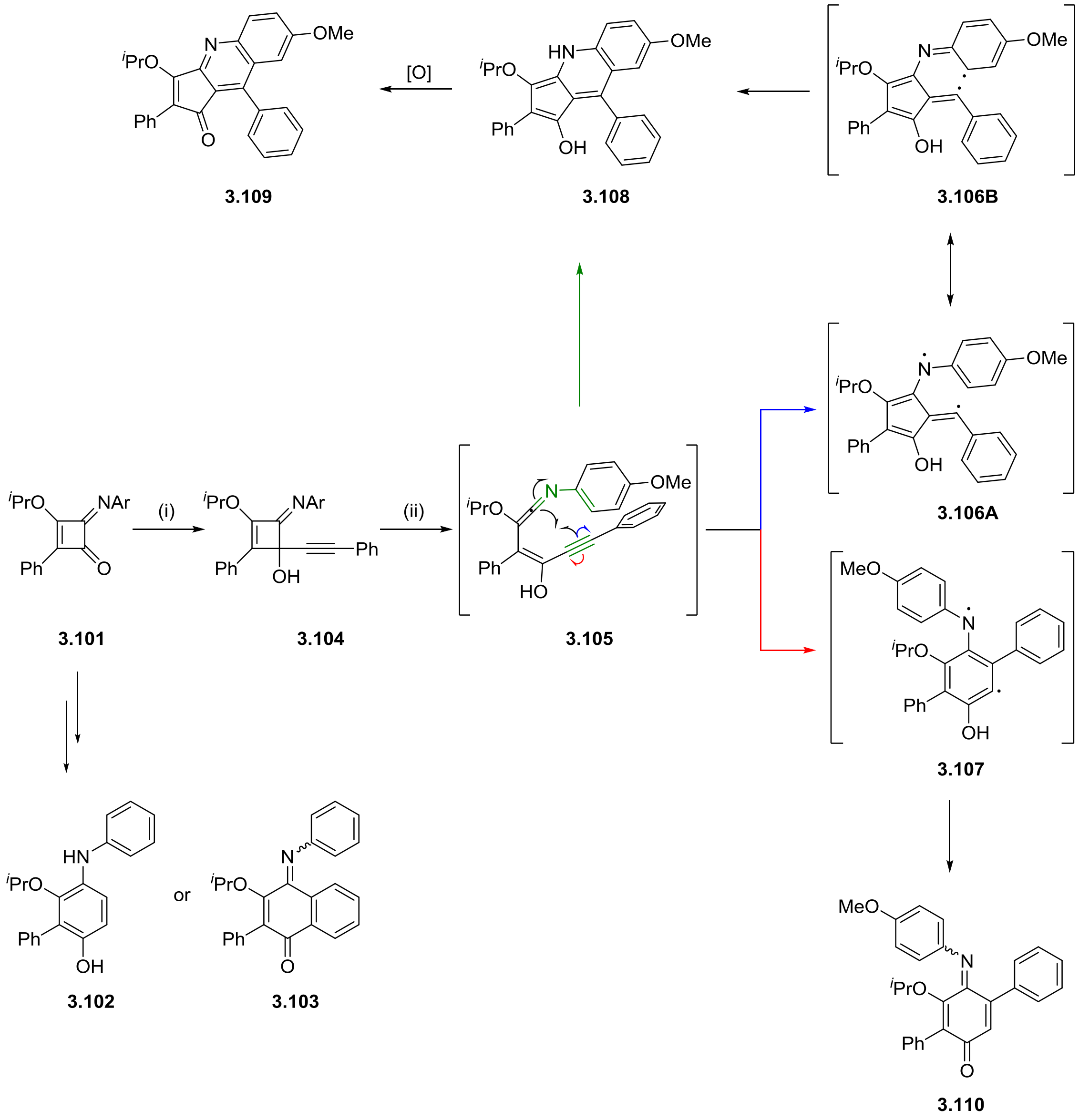
An alternative pyridinone synthesis by Liebskind[116] employed a 1,4-cuprate addition of a pyridyl nucleophile to di^{n}butylsquarate **3.98** and *in situ* trapping with MEMCl (Scheme 3.16). Thermolysis of **3.99** at 140 °C for 20 h proceeded in 79% yield to give **3.100**. Such 1,4-additions opened up a new route to highly functionalised catechols.



Reagents and conditions: (i) 2-Bromopyridine, ^{t}BuLi, CuCN, LiCl, THF, -78 °C, then MEMCl, 31%; (ii) xylene, Δ, 79%.

Scheme 3.16 Thermal rearrangement of cyclobutenone **3.99** to pyridinone **3.100**.[116]

Iminocyclobutenones have also been fashioned by Moore *et al*. These were thermolysed in xylene or PhCl to give aminohydroquinones and aminonaphthaquinones,[117] such as **3.102** and **3.103** respectively, where the synthesis of the latter presents an expedient route to aminonaphthols. A notable result arising from the introduction of an imino group was observed with acetylene **3.104** (Scheme 3.17). Upon thermolysis, the familiar diradical pathways[118] were believed to be triggered, leading to intermediates **3.106A** and **3.107**, where the former had sufficient lifetime to cyclise to the cyclopenta-annulated quinoline **3.109**. Typically, iminoquinone **3.110** was also formed, from **3.107**, albeit in lesser quantity. Interestingly, the radical transformation should have yielded the *E*-analogue of **3.106A**, had it followed the same course as the corresponding cyclobutenone, although this intriguing reversal in regioselectivity received little comment from the authors. Conceivably, ring-opening of **3.104** to ketenimine **3.105** could set up a 6-π electrocyclisation between the alkyne and the arylimine moeity to give **3.108** after tautomerisation.



Reagents and conditions: (i) PhC≡CH, ^{n}BuLi, THF, -78 °C, 67%; (ii) Δ, 49% of **3.109** and 16% of **3.110**.

Scheme 3.17 Thermal rearrangement of of aminosquarate **3.104**.[117]

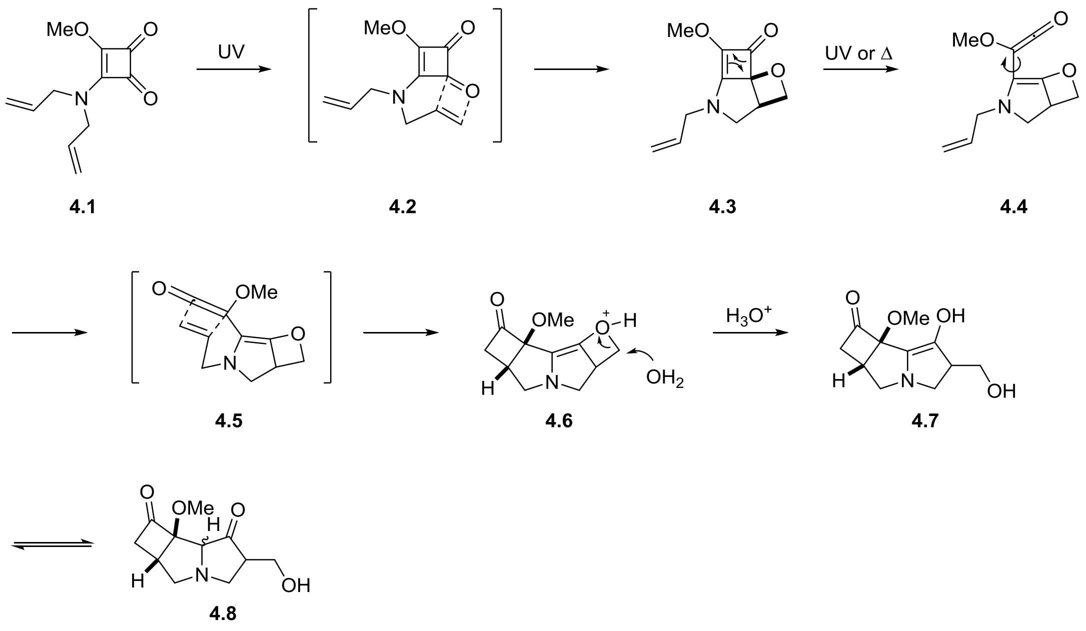
We have seen several sporadic examples of mixed squaramide thermal rearrangements, with some unusual or reticent reactivity relative to their squarate analogues. Despite the unsuccessful [2+2] cyclisation attempted by Eguchi *et al.*, we envisaged a study of a more complex system in the Moore rearrangement of aminocyclobutenones. Moreover, the relative few examples of such reactions present an opportunity for us to study their rearrangement pathways further in order to gain an understanding of these systems.

Chapter 4: Results and Discussion
Towards New Synthetic Applications of Squaramides

4.1 Aims

The rearrangement of cyclobutenones has been of longstanding interest within our group.[105] After the notable contribution of Harrowven *et al.* in investigating the reaction course of cyclobutenones (squarates), we recognised that their amine counterparts, squaramides, had received relatively little attention in the open literature. As such, the opportunity to explore and understand the chemistry of squaramides surfaced. From this, we sought to exemplify further thermal rearrangements of squaramides to lead us to a thorough investigation of the reaction influences to complement the findings on squarates. Also of interest would be the influence (if any) of the presence of nitrogen(s) in the alkynylcyclobutenone system on reaction outcome, regarding the ratio of quinone and 5*H*-furanone formation.

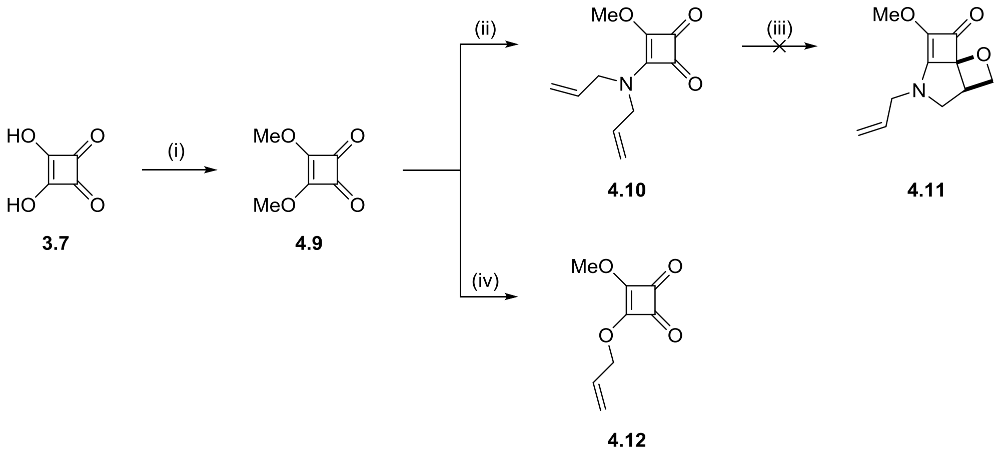
Our initial focus, however, began with **4.1** as we wondered if it might be possible to make complex scaffolds, such as **4.8** (Scheme 4.1), by exploiting the higher valency of nitrogen in squaramides and using this to introduce further reactive centres. Amination of dimethyl squarate with diallylamine, for example, would afford an opportunity for a [2+2] cycloaddition between the alkene and the proximal carbonyl of squaramide **4.1** to give a spirocyclic intermediate **4.3**. In principle, this could either open spontaneously to **4.4** or do so under heat or UV irradiation,[104] ideally using the same lamp used to induce the cycloaddition. Rotation around the σ-bond may then give reactive conformer **4.5** to set up another [2+2] cycloaddition leading to the tricyclic heterocycle **4.8**.



Scheme 4.1 Paternò-Büchi reaction and rearrangement to tricycle **4.8**.

4.2 Preliminary Efforts to 4.8

This idea was easy to examine as amination of dimethyl squarate **4.9** with diallylamine proceeded very smoothly in MeOH at 0 °C to RT, to give **4.10** in 100% yield after 2 h (Scheme 4.2). This was in stark contrast to the analogous reaction with allyl alcohol where 12% conversion to **4.12** was realised after one week. Alas, upon irradiation of **4.10** in CH_3CN or PhH using UVA, B and C lamps in an attempt to form **4.11**, only starting material and degradation products were observed.

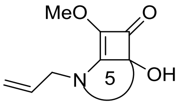


Reagents and conditions: (i) $CH(OCH_3)_3$, MeOH, Δ, 72%; (ii) diallylamine, MeOH, 100%; (iii) UVA/B/C; (iv) allyl alcohol, THF, 12%.

Scheme 4.2 Attempted Paternò-Büchi reaction of **4.10**.

4.3 Intramolecular Tether Approach to Heterocyclic Precursors

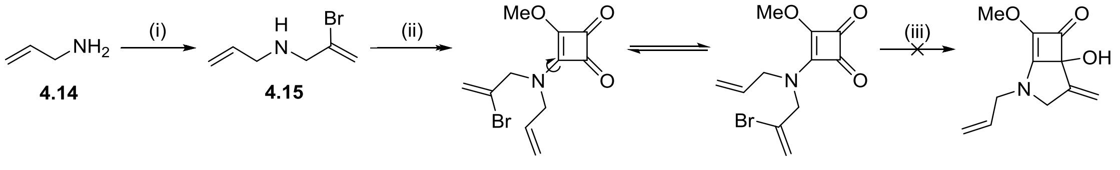
4.3.1 Five-Membered Tether



4.13

Figure 2.1 Five-membered squaramide tether.

The failure of **4.10** to undergo cycloaddition was unexpected and it was unclear whether the desired reaction had taken place, only for the spirocyclic product to revert back to starting material. Thus we envisaged forming a bicyclic intermediate such as **4.13** (Figure 2.1) in the hope that it might confer more stability to the ketene intermediate formed on ring opening of the cyclobutenone. To form the five-membered tether, we attempted an intramolecular anionic cyclisation, thus amine **4.15** was produced by alkylation of allylamine **4.14** with allyl bromoallylamine (Scheme 4.3). Formation of mono-squaramide (squaramate) **4.16** proceeded smoothly in 99% yield. Treatment of this with ^{t}BuLi failed to produce anything meaningful other than partial proto-debromination. This may have been due to the adoption of a rigid conformation of the amine, **4.16A** and **4.16B**, rendering 50% of the material unreactive.

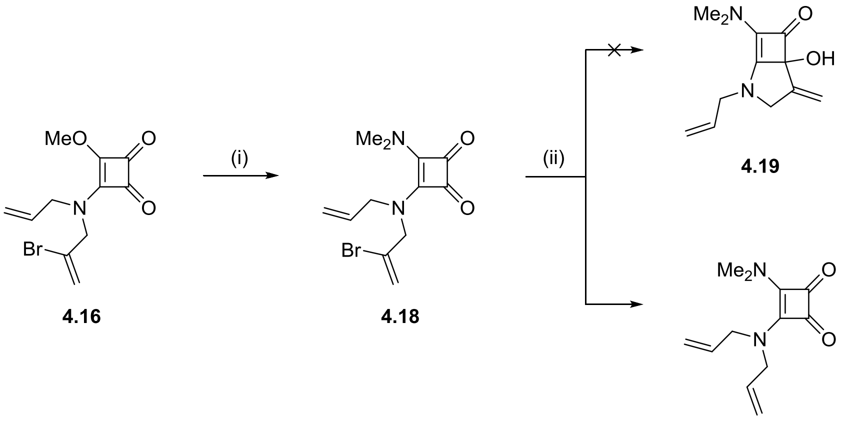


4.14 **4.15** **4.16A** **4.16B** **4.17**

Reagents and conditions: (i) 2,3-Dibromopropene, Na_2CO_3, THF, 33%; (ii) **4.9**, MeOH, 99%; (iii) ^{t}BuLi, THF, -78 °C.

Scheme 4.3 Attempted synthesis of tethered squaramate **4.17**.

We postulated that by introducing another amine, as in diamine **4.18** (Scheme 4.4), the tendency for conformational locking[101] would be greatly reduced. To that end we prepared squaramide **4.18** in 88% yield by the addition of one equivalent of neutralised $Me_2NH.HCl$ in MeOH. When this was then treated with ^{t}BuLi (Scheme 4.4), proto-debromination to **4.20** was the only observed pathway.

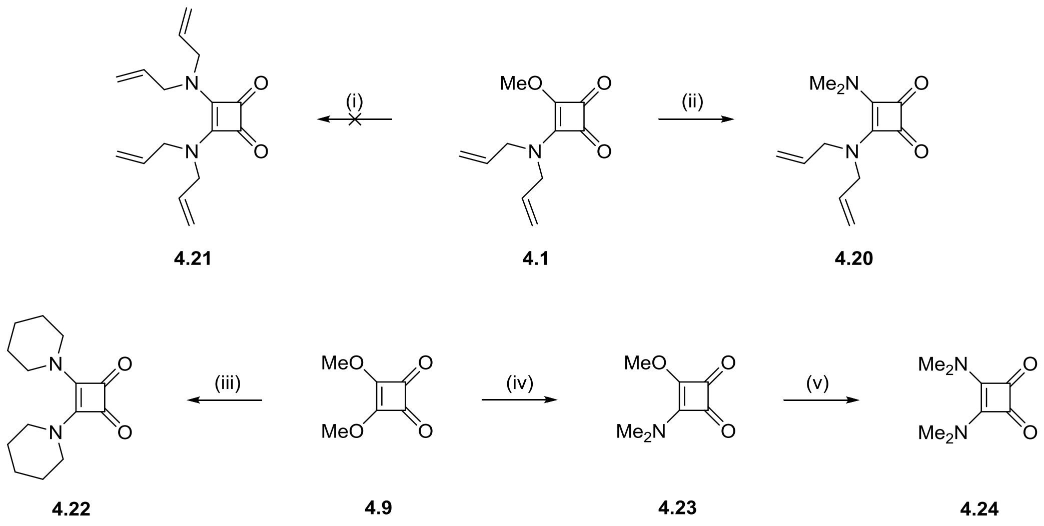


4.16 **4.18** **4.19** **4.20**

Reagents and conditions: (i) $Me_2NH.HCl$, Et_3N, MeOH, 88%; (ii) ^{t}BuLi/^{n}BuLi, THF, -78 °C.

Scheme 4.4 Attempted synthesis of tethered squaramide **4.19**.

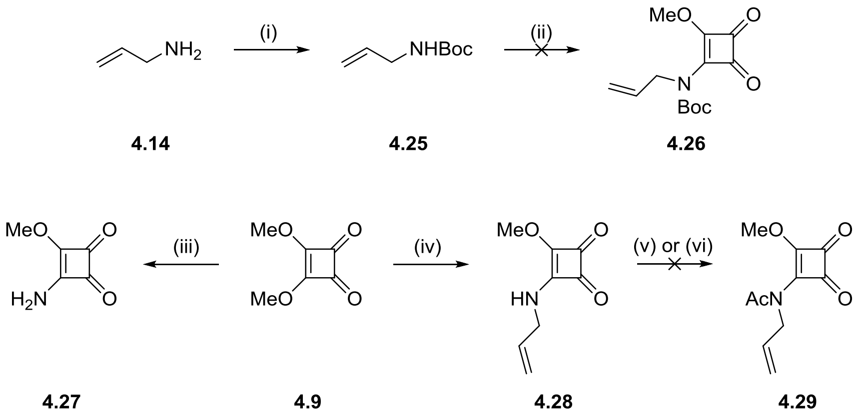
Interestingly, it was not possible to introduce a second diallylamine *viz.* **4.24** by displacement of both methoxy substituents in dimethyl squarate **4.9** (Scheme 4.5). We proposed that this was due to the conformational locking of the first amine and the build-up of steric clash between the extremities. Smaller groups such as dimethylamine in **4.20** or tethered chains as with piperidine exhibited no such steric interactions, allowing access to squaramides such as **4.22**→**4.24**.



Reagents and conditions: (i) Diallylamine, MeOH; (ii) $Me_2NH.HCl$, Et_3N, MeOH, 84% (iii) piperidine, MeOH, 99%; (iv) $Me_2NH.HCl$, Et_3N, MeOH, 43%; (v) $Me_2NH.HCl$, Et_3N, MeOH, 100%.

Scheme 4.5 Squaramide synthesis.

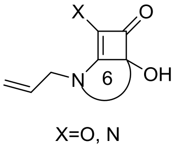
By withdrawing electron density through resonance, as in **4.26** and **4.29** (Scheme 4.6), we would no longer be hindered by the rigid conformation of mixed squaramates and the possible lack of reactivity of squaramides. Nonetheless the lack of nucleophilicity of carbamate **4.25** and stability of amide **4.29** prevented their formation and isolation. This was also assumed to be the reason for the failure to acylate **4.27**.



Reagents and conditions: (i) $(Boc)_2O$, NH_2SO_3H (cat.), Et_2O, 99%; (ii) **4.9**, MeOH; (iii) 7 M NH_3 in MeOH, 2:1 hexane:MeOH, 97%; (iv) **4.14**, MeOH, 83%; (v) Ac_2O, NH_2SO_3H (cat.), CH_2Cl_2; (vi) AcOH, DCC, CH_2Cl_2.

Scheme 4.6 Attempted synthesis of conformationally free squaramates.

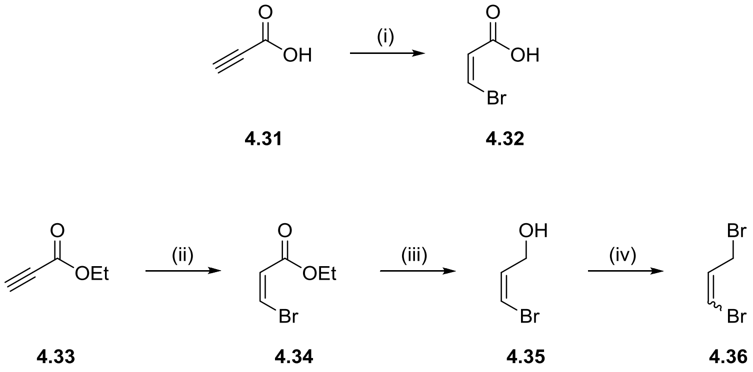
4.3.2 Six-Membered Tether



4.30

Figure 4.2 Six-membered squaramide tether.

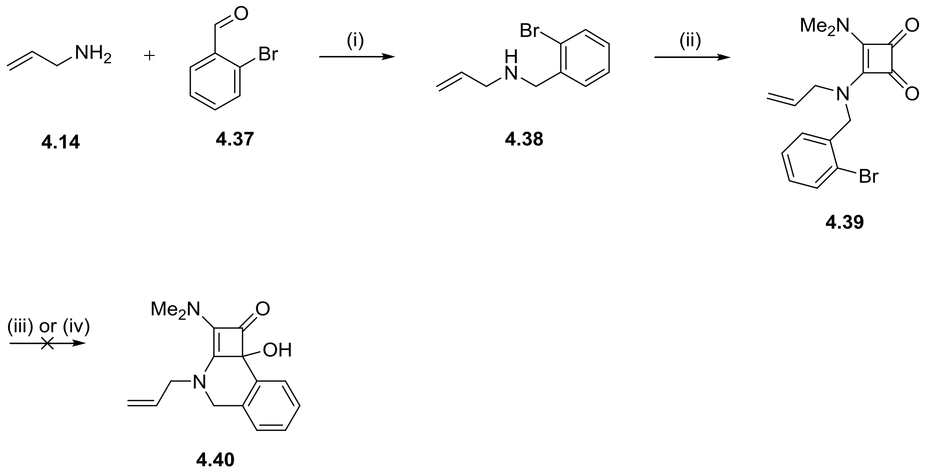
Electing to examine a six-membered tether to confer stability (Figure 4.2), we attempted to form **4.32**. Alas, it proved difficult to reproduce the route to **4.32**, with catalytic CuBr in concentrated HBr, as described in the literature (Scheme 4.7).[119] Thus opting for ester **4.33**, we selectively formed *cis*-alkene **4.34** with LiBr and AcOH[120] in 74% yield, then reduced the ester group to the corresponding alcohol **4.35**, the volatility of which caused some loss in yield. Attempted bromination to **4.36** returned mostly starting material with little of the desired product. Moreover, it was evident that the latter was a mixture of *cis* and *trans*-stereoisomers.



Reagents and conditions: (i) CuBr (cat.), conc. HBr, 32%; (ii) LiBr, AcOH, CH_3CN, 74%; (iii) $LiAlH_4$, Et_2O, 57%; (iv) PBr_3, CH_2Cl_2, -25 °C.

Scheme 4.7 Attempted synthesis of dibromide **4.36**.

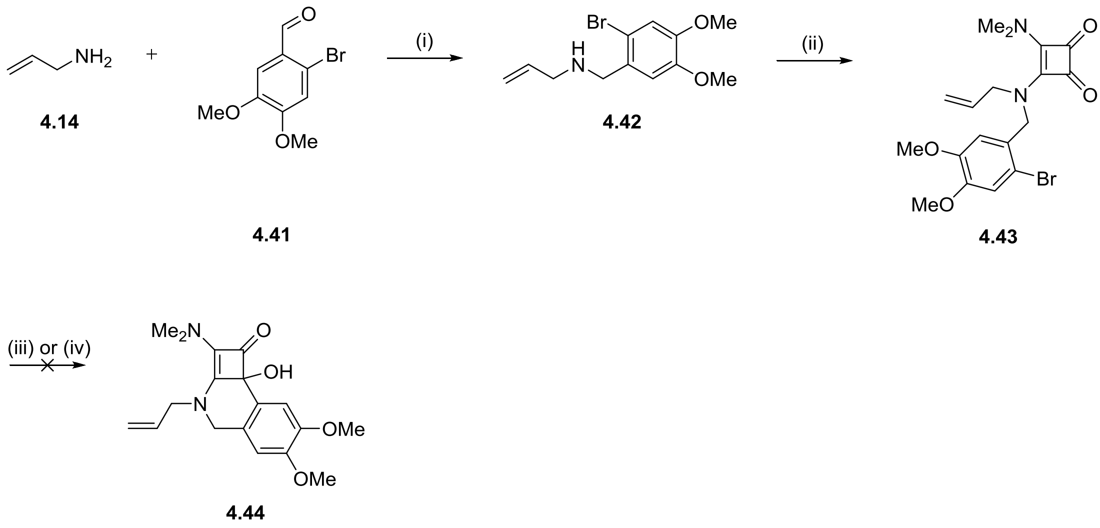
To overcome this problem, and to make Li-halogen exchange more facile, we next targeted arene **4.39** (Scheme 4.8). To that end, amine **4.38** was formed by reductive amination with allylamine **4.14** and 2-bromobenzaldehyde **4.37**. Addition to squarate **4.9** was followed by a second amination with Me_2NH in a one-pot sequence, resulting in the formation of squaramide **4.39** in 84%.



Reagents and conditions: (i) NaBH$_4$, MeOH, 97%; (ii) **4.9**, MeOH, then Me$_2$NH.HCl, Et$_3$N, MeOH, 84%; (iii) ^{t}BuLi/^{n}BuLi, THF, -78 °C; (iv) Mg/Li, THF/Et$_2$O.

Scheme 4.8 Attempted synthesis of tethered squaramide **4.40**.

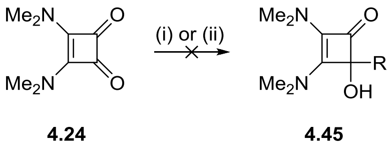
Attempted Li-halogen exchange and cyclisation with ^{n}BuLi and ^{t}BuLi again proved unsuccessful, as did an attempted Barbier reaction. In each case, no reaction to **4.40** had taken place and clean starting material was observed in the crude NMR, except with ^{n}BuLi where 1,2-nucleophilic addition had taken place, leading to a complex mixture. In a similar manner, amine **4.42** was formed by reductive amination and used to access squaramide **4.43** in 84% yield through diamination (Scheme 4.9). Treatment of these squaramides with Mg or Li to effect the Barbier-type reactions yielded only recovered starting material on work-up, indicating that no insertion of the metals into the C-Br bond had taken place. Subjecting **4.43** to ^{t}BuLi displayed no reactivity as before, with partial addition onto the carbonyl amides with ^{n}BuLi.



Reagents and conditions: (i) NaBH$_4$, MeOH, 74%; (ii) **4.9**, MeOH, then Me$_2$NH.HCl, Et$_3$N, MeOH, 84%; (iii) ^{t}BuLi/^{n}BuLi, THF, -78 °C; (iv) Mg, THF.

Scheme 4.9 Attempted synthesis of tethered squaramide **4.44**.

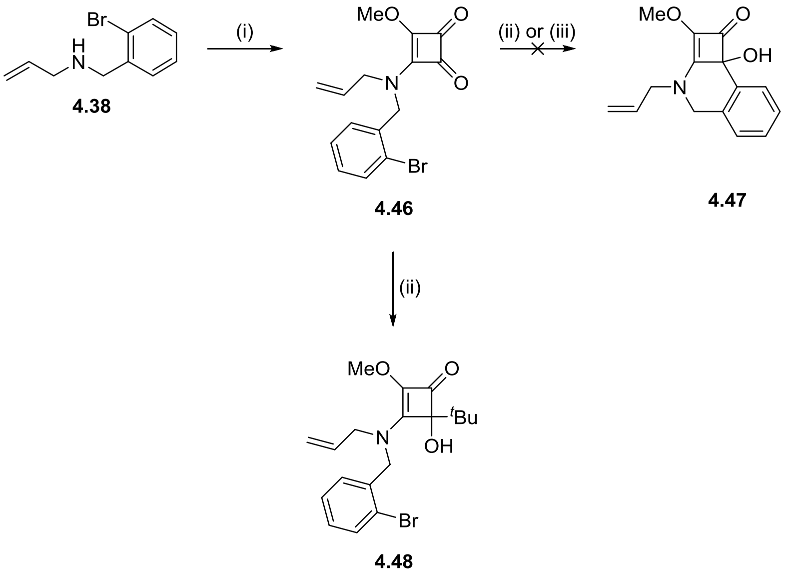
To illustrate the lack of reactivity of a squaramide towards nucleophilic addition, we subjected bis(dimethyamino)squaramide **4.24** to vinylmagnesium chloride, vinyllithium and 2-lithiopyridine (Scheme 4.10). On each occasion, near complete recovery of starting material was realised upon prolonged reaction times at -78 °C. Performing these reactions at elevated temperatures had yet to be tried and could potentially reveal an optimum temperature (range) for additions to squaramides with/without the occurrence of anion accelerated ring opening.



Reagents and conditions: (i) 2-Bromopyridine, ^{n}BuLi, THF, -78 °C; (ii) vinylMgCl/vinylLi, THF, -78 °C.

Scheme 4.10 Attempted addition onto squaramide **4.24**.

Thus, we switched our attention back to mixed squaramates and envisaged that at -78 °C, at least 50% of **4.46** would be in the correct conformation to react with the vinylogous ester carbonyl for which reactivity towards organolithiums is well established (Scheme 4.11). Unfortunately, no Br-Li exchange was observed on exposure of **4.46** to ^{t}BuLi, with preferential addition to the vinylogous ester carbonyl occurring to yield 17% of **4.48**.

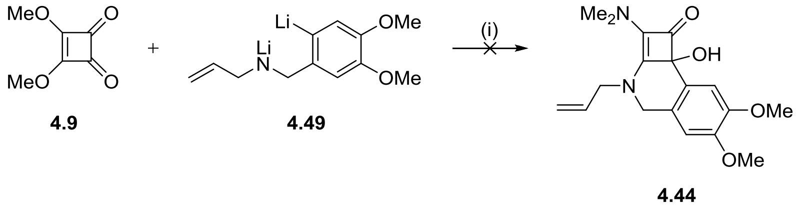


Reagents and conditions: (i) **4.9**, MeOH, 92%; (ii) ^{t}BuLi, THF, -78 °C, 17% of **4.48**; (iii) ^{n}BuLi, THF, -78 °C.

Scheme 4.11 Attempted synthesis of tethered squaramide **4.47**.

4.4 Intermolecular Tether Approach to Heterocyclic Precursors

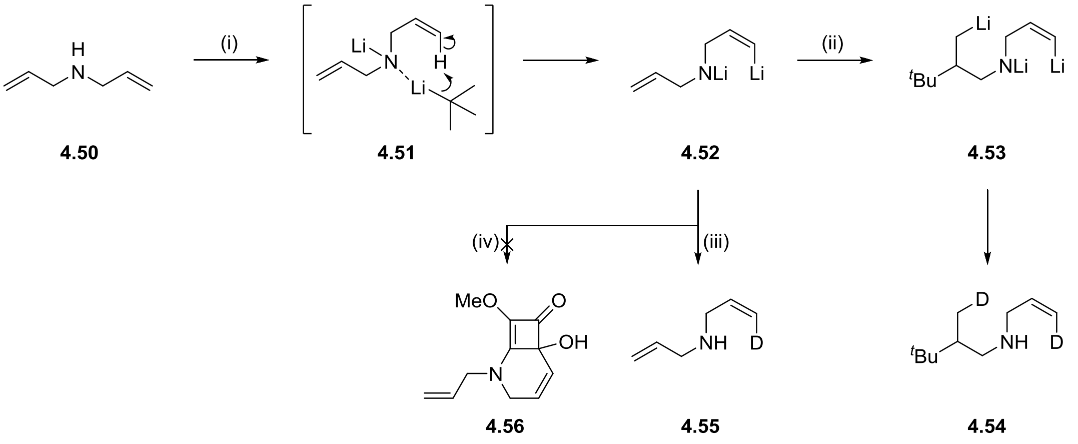
We then attempted to treat dimethyl squarate with the dianion of **4.42**, in the form of **4.49** (Scheme 4.12) in the hope that this might give access to **4.44**, which eluded us previously. Kobayashi had fromed a similar electron rich aryl anion with ^{n}BuLi at -78 °C,[121] thus it was anticipated that formation of dianion **4.49** under similar conditions could be achieved. Alas, only decomposition was observed upon cannulation of the dianion into the dimethyl squarate reaction vessel.



Reagents and conditions: (i) **4.49**, ^{n}BuLi, THF, -78 °C, then **4.9**.

Scheme 4.12 Attempted synthesis of tethered squaramide **4.44**.

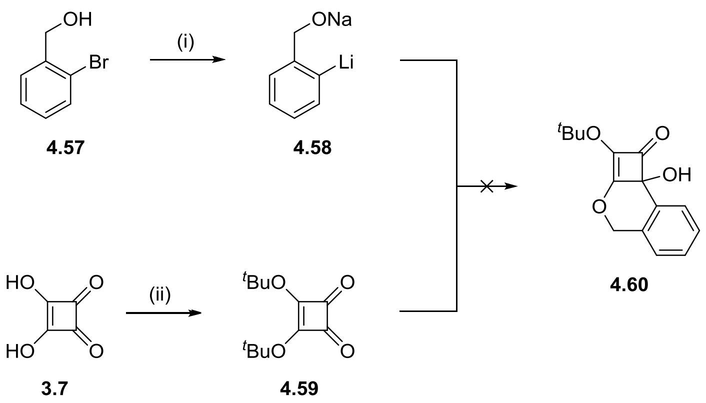
Our attention next turned to the formation of dianion **4.52** from diallylamine. Inspired by a report by Barluenga *et al.*[122] on trianion formation when diallylamine **4.50** is exposed to ^{t}BuLi (via double deprotonation and nucleophilic addition) (Scheme 4.13, **4.50**→**4.54**), we initially repeated their work to verify that the *cis*-lithiated product could be formed discriminately. To our delight, isolation of **4.55** following a D_2O of **4.52** quench suggested that this was indeed the case. Thereafter dianion **4.52** was cannulated into a solution of dimethyl squarate **4.9** at -78 °C, but without success. Inverting the order of addition produced a similar result.



Reagents and conditions: (i) ^{n}BuLi, THF, Et_2O, -50–-30 °C, then ^{t}BuLi, -30 °C–RT; (ii) ^{t}BuLi, -20 °C–RT, then D_2O, 93%; (iii) D_2O, 55% crude; (iv) **4.9**.

Scheme 4.13 Barluenga's trianion **4.53**[122] and our attempted bicycle **4.56** formation.

Dianion **4.58**, derived from bromobenzyl alcohol **4.57**, was also investigated with the expectation that the softer nature of the alkoxide relative to the amide may prevent decomposition of any unstable intermediate and thus yield tethered compound **4.60** (Scheme 4.14). As such, dimethyl squarate **4.9** and ^{t}butoxymethylcyclobutendione **4.59** were used to quench these dianions. However, while the former led to unstable intermediates giving myriad products, the latter showed no apparent reactivity and returned recovered starting material (along with *ca*. 10% of an unidentified side product). An elevation in temperature could have potentially been employed to overcome any steric barrier to this reaction.



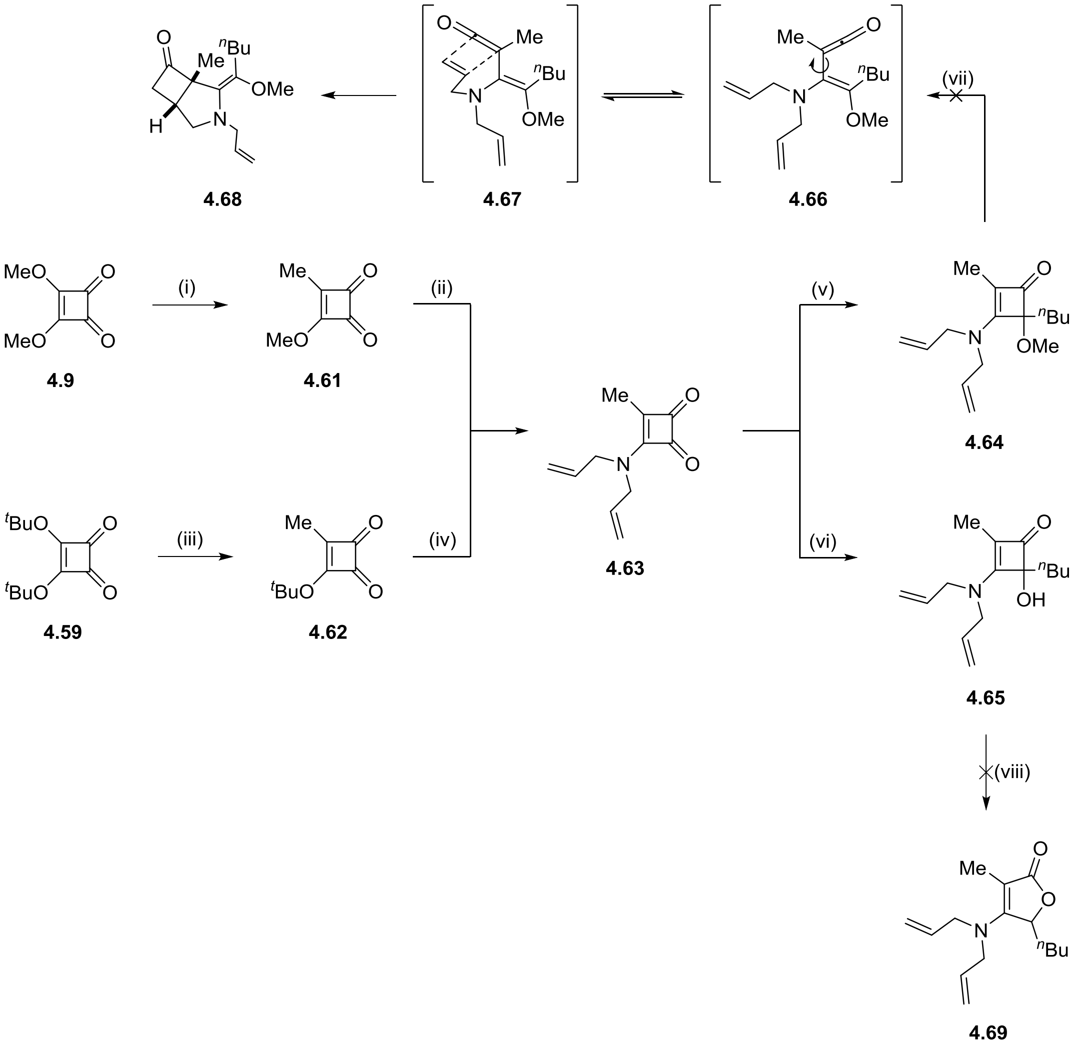
Reagents and conditions: (i) NaH, THF, RT, then ^{n}BuLi, -78 °C; (ii) $CH(OCH_3)_3$, ^{t}BuOH, Δ, 60%.

Scheme 4.14 Attempted synthesis of tethered squarate **4.60**.

4.5 Non-Tethered Approach to Heterocyclic Precursors

4.5.1 Attempting the [2+2] Cyclisation

These disappointing results directed us to simplify our model substrate further and discard the tether approach which had proven intractable at this point. Starting from either dimethyl or di^{t}butyl squarate, methylation to **4.61** and **4.62** respectively provided appropriate precursors for amination to deliver mono-squaramide **4.63** (Scheme 4.15). These could be alkylated selectively by addition to the ketonic carbonyl to give **4.65**, or **4.64** if quenched with Meerwein's salt. Prolonged thermolysis of the latter in refluxing xylene furnished only starting material, as did heating at 200 °C under flow (**4.64**→**4.68**). The unprotected squaramate **4.65** also ceded no reaction on heating to 150 °C under flow, or on irradiation with UVB/C light.



Reagents and conditions: (i) MeLi, THF, -78 °C, then TFAA, 75%; (ii) diallylamine, MeOH, 86%; (iii) MeLi, THF, -78 °C, then TFAA, 82%; (iv) diallylamine, MeOH, 82%; (v) ^{n}BuLi, THF, -78 °C, then Me_4OBF_4, 64%; (vi) ^{n}BuLi, THF, -78 °C, 69%; (vii) 200 °C, flow; (viii) 150 °C, flow or UVB/C, CH_3CN.

Scheme 4.15 Attempted synthesis of bicycle **4.68**.

In-house calculations by Theo P. Gonçalves (B3LYP) have shown that the ring opening of squaramides requires higher energy than the analogous squarates, as implied by our findings. In particular, electron rich substituents at C-2 and C-3 (X or Y) increase the energy barrier for (thermal) ring opening (**4.71**→**4.77**, Figure 4.3). For example, substituting methoxy groups in both aforementioned positions for dimethylamine increases the activation energy by almost 2 kcal/mol.

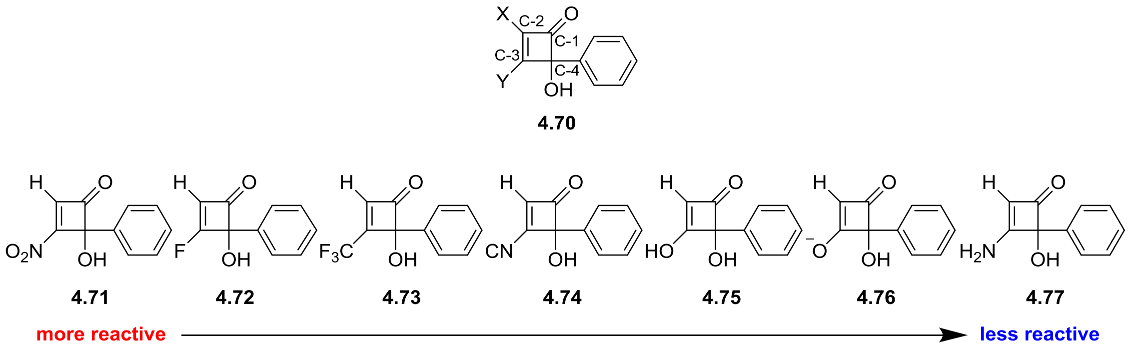
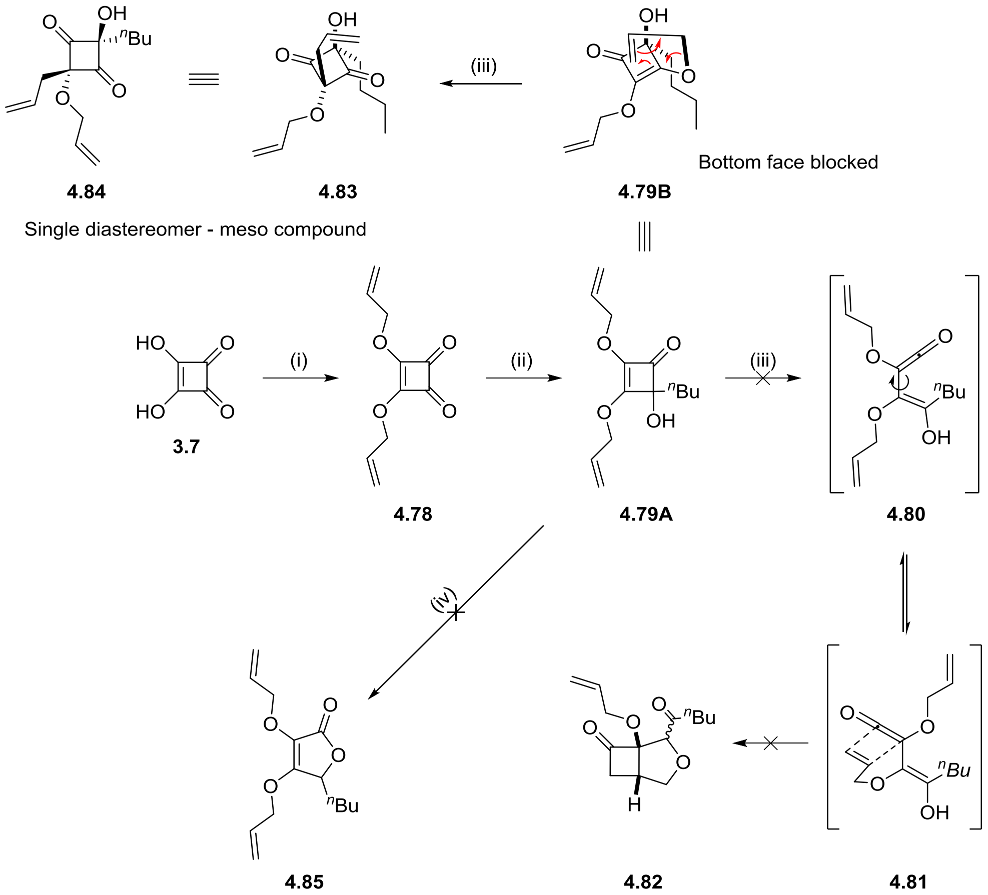


Figure 4.3 Relative reactivities of cyclobutenones.

Calculations with squarates have shown that, with a phenyl appendage at C-4, the ring closing step is rate determining in a Moore rearrangement. Hence, it is conceivable that a higher activation energy for the ensuing cyclisation was preventing the forward reaction.

Consequently, it seems likely that ring opening was taking place, albeit at a slower rate than with squarates, but that the intermediate has insufficient energy/lifetime to undergo the [2+2] cycloaddition and so collapses back to return starting material. As a comparison to squaramides, squarate **4.79A** was formed in 75% yield upon addition of ^{n}BuLi to diallyl squarate **4.78** (made by refluxing squaric acid in allylbromide in 59% yield, Scheme 4.16). However, heating squarate **4.79A** at 150 °C under flow did not deliver **4.82**; rather it led exclusively to **4.84** as a result of a facile Claisen rearrangement (**4.79B**). Full characterisation of this dione, unfortunately, was hampered by its decomposition on silica. The stereochemistry proposed is reasoned from the blocking of one face by the relatively large butyl group. Subjecting **4.79A** to UVB irradiation, disappointingly, failed to deliver furanone **4.85** and returned the starting material with partial degradation.



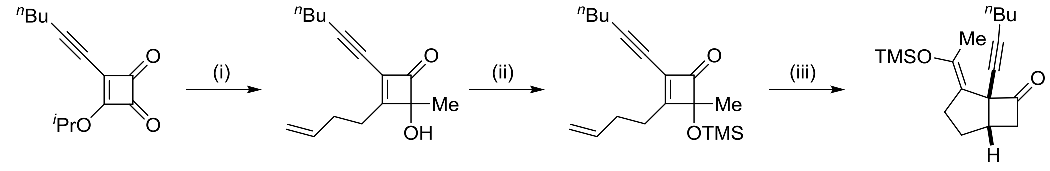
Bottom face blocked

Single diastereomer - meso compound

Reagents and conditions: (i) Allylbromide, DIPEA, Δ, 59%; (ii) ^{n}BuLi, THF, -78 °C, 75%; (iii) 150 °C, dioxane, flow; (iv) UVB/C, CH_3CN.

Scheme 4.16 Unexpected Claisen rearrangement of squarate **4.79** to dione **4.84**.

Support for our hypothesis that the [2+2] cyclisation is the rate determining step can be seen in the work of Moore *et al.*[123] They demonstrated the analogous reaction with squarate **4.88**, involving ring-opening to the vinylketene, rotation of a σ-bond and [2+2] cyclisation with the ketene which proceeded to give **4.89** in 1 h at reflux in xylene (Scheme 4.17). Notably, precursor **4.87** was formed from **4.86** in a one-pot procedure through sequential addition of MeLi, TMSCl, 4-lithio-1-butene and HCl in an overall yield of 60%.

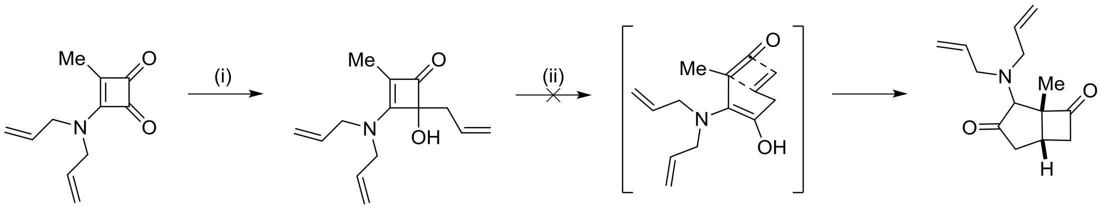


4.86 **4.87** **4.88** **4.89**

Reagents and conditions: (i) MeLi, THF, -78 °C, then TMSCl, then 4-lithio-1-butene, then aq. HCl, 60%; (ii) TMSCl, Et_3N, THF, 78%; (iii) xylene, Δ, 95%.

Scheme 4.17 Moore's [2+2] clyclisation to bicyclo[3.2.0]heptanone **4.89**.[123]

To alleviate the requirement for the open-ring intermediate **4.91** to undergo a σ-bond rotation, we next prepared allylcyclobutenone **4.90** by addition of allylmagnesium bromide to 2-methyl-3-diallylaminocyclobutenone **4.63** in a reasonable 62% yield (Scheme 4.18). Alas, heating adduct **4.90** at temperatures up to 200 °C, as before, produced none of the desired product **4.92**. Indeed, only upon microwave irradiation at 200 °C was anything other than starting material observed, although no stable compounds were isolated from that experiment.

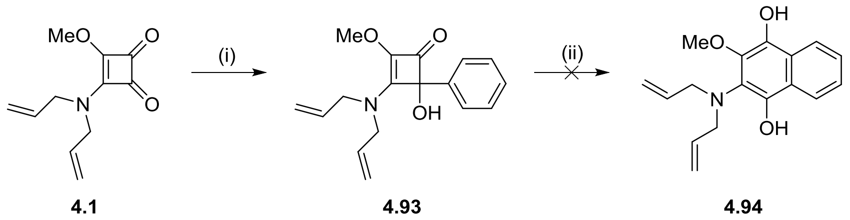


4.63 **4.90** **4.91** **4.92**

Reagents and conditions: (i) AllylMgBr, THF, -78 °C, 62%; (ii) 200 °C, dioxane, flow or 200 °C, DMF, µw.

Scheme 4.18 Attempted synthesis of bicyclo[3.2.0]heptandione **4.92**.

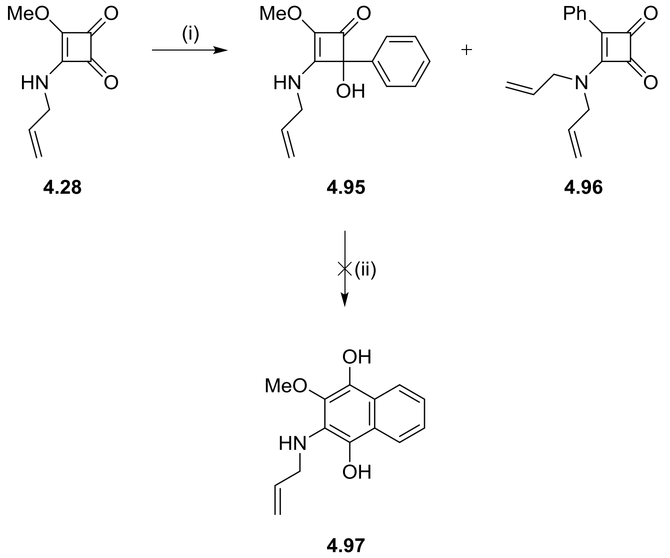
Several experiments were carried out to test the selectivity of addition of Grignard and alkyllithium reagents to mono-squaramides with the aim of investigating these in Moore rearrangements. PhLi was added to mono-squaramide **4.1** in good yield with <10% addition at the vinylogous amide carbonyl (as evidenced by NMR analysis of the crude reaction mixture). No rearrangement of this substrate **4.93** to **4.94** was observed upon thermolysis in refluxing xylene (Scheme 4.19).



Reagents and conditions: (i) PhLi, THF, -78 °C, 74%; (ii) xylene, Δ.

Scheme 4.19 Attempted synthesis of dihydronaphthoquinone **4.94**.

It was envisaged that with secondary squaramide **4.28** (Scheme 4.20), exclusive addition of PhLi to the vinylogous ester carbonyl would occur as deprotonation of the amide would render the conjugated carbonyl inert towards nucleophilic addition. This experiment gave 61% yield of the desired product **4.95** with the rest of the mass balance being mainly due to the elimination product **4.96**. Thermolysis of **4.95** in xylene at reflux led to degradation, with none of the anticipated naphthalene **4.97** observed. The result tentatively suggests that the free amine may be stabilising the ketene intermediate and lowering its reactivity and/or resulting in a relative lowering of activation energy for alternative reaction pathways.



Reagents and conditions: (i) PhLi, THF, -78 °C, 61% of **4.95** and 36% of **4.96**; (ii) xylene, Δ.

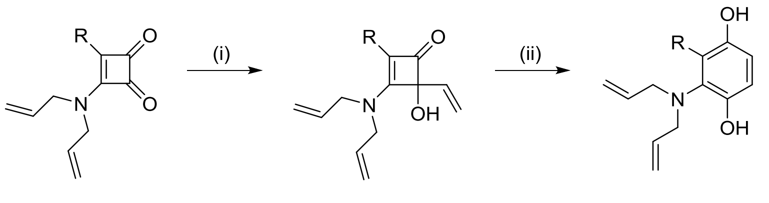
Scheme 4.20 Attempted synthesis of dihydroxynaphthalene **4.97**.

4.5.2 Exemplification of the Thermal Rearrangement of Squaramides

Synthesis of Dihydroquinones

Vinyl groups are one of the best traps for the vinylketene intermediate formed on thermolysis of cyclobutenones, which is attributed to the availability of a low energy 6π electrocyclisation pathway. Thus, if ring opening of **4.98** led to the ketene intermediate, it would be expected to form dihydroquinone **4.100** - rather than collapsing back to starting material (Scheme 4.21).

Vinylmagnesium chloride addition to methyl and methoxy aminocyclobutenones furnished **4.98** and **4.99** in yields of 51% and 78% respectively. Pleasingly, thermolysis of **4.98** in xylene at reflux proceeded to dihydroquinone **4.100** in 54% with complete conversion after 4 h. Similarly, methoxy squaramide **4.99** yielded 45% of dihydroquinone **4.101** after 10 h, with significant degradation having occurred during both thermolyses. This breakthrough confirmed that our mixed squaramides were indeed opening to the vinyl ketene intermediate and that perhaps the amino substituent was slowing down the subsequent electrocyclic reaction. However, it is also noteworthy that as the vinyl groups are able to hyperconjugate with the σ*-bond of the cyclobutenone, these substrates can be driven forward effectively.



R = Me 4.63
R = OMe 4.1

R = Me 4.98, 51%
R = OMe 4.99, 78%

R = Me 4.100, 54%
R = OMe 4.101, 45%

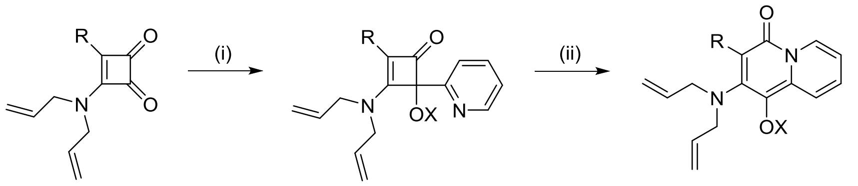
Reagents and conditions: (i) VinylMgCl, THF, -78 °C; (ii) xylene, Δ.

Scheme 4.21 Moore rearrangement of squaramides to dihydroquinones.

Exploring an Alternate Trap of the Vinylketene Intermediate

As the vinylketene intermediate is also prone to trapping with nucleophiles, we next prepared a series of mixed-squaramides with a 2-pyridyl residue at C-4. These were prepared by the addition of 2-lithiopyridine to squaramides in yields ranging from 66%

to 71% (Scheme 4.22). Thermolysis at 100 °C in xylene led to complete conversion in 15 min with the methyl analogue **4.102**. On the other hand, the methoxy analogue **4.103** required further heating, with complete consumption of starting material requiring 35 min in refluxing xylene, with **4.106** isolated in 65% yield. Hydrogen bonding between the pyridyl nitrogen and the OH group may assist the ring opening in this case as it increases electron density on the C-4 oxygen substituent. In turn, this feeds into the anti-bonding orbital of the C-C σ-bond thereby lowering the energy required for ring opening, leading to pseudo-anion acceleration. Thus, in comparison, the *O*-protected analogue **4.104**, took 5 h for clean conversion to **4.107**, which was isolated in 88% yield.



R = Me 4.63
R = OMe 4.1

R = Me, X = H 4.102, 67%
R = OMe, X = H 4.103, 66%
R = OMe, X = Me 4.104, 71%

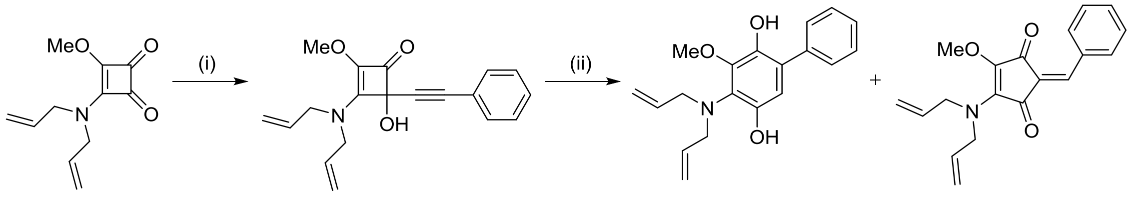
R = Me, X = H 4.105, *ca.* 89%
R = OMe, X = H 4.106, 65%
R = OMe, X = Me 4.107, 88%

Reagents and conditions: (i) 2-Bromopyridine, ^{n}BuLi, THF, -78 °C, (then MeOTf for **4.104**); (ii) xylene Δ.

Scheme 4.22 Rearrangement of squaramides to quinolizinones.

Preliminary Investigation of Alkynylsquaramides

As we had yet to investigate the rearrangement of amino alkynylcylcobutenones, this was identified as our concluding experiment. Consequently, addition of lithiated phenylacetylene to methoxydiallylaminocyclobutenedione **4.1** gave squaramate **4.108** in 60% yield. These were thermolysed as before, in refluxing xylene, with complete consumption of starting material after 16 h (Scheme 4.23). The crude NMR indicated that the reaction had given hydroquinone **4.109** along with cyclopentenedione **4.110** as the only distinguishable products, amongst a plethora of other compounds, as evidenced by the presence of numerous unassigned proton resonances.

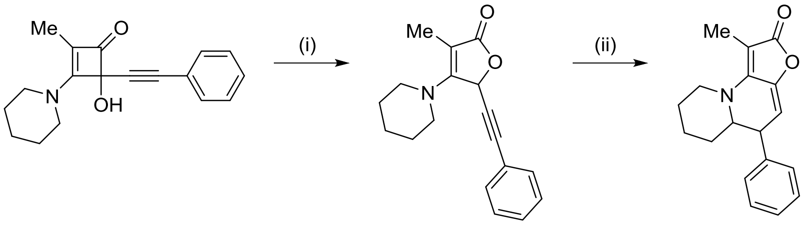


4.1 **4.108** **4.109** **4.110**

Reagents and conditions: (i) PhC≡CH, ^{n}BuLi, THF, -78 °C, 60%; (ii) xylene, Δ.

Scheme 4.23 Thermal rearrangement of 4-alkynylcyclobutenone **4.108**.

A subsequent study of this system by another member of our research group has revealed some unusual behaviour in related thermolyses. For example, thermolysis of **4.111** gave furanone **4.112** as the major product (under flow at 150 °C), with no observed quinone (Scheme 4.24). It was further found that **4.112** underwent further transformation to tricyclic lactone **4.113** on heating to 200 °C, through a hitherto undescribed rearrangement pathway.



4.111 **4.112** **4.113**

Reagents and conditions: (i) 150 °C, dioxane, flow; (ii) 200 °C, dioxane, flow.

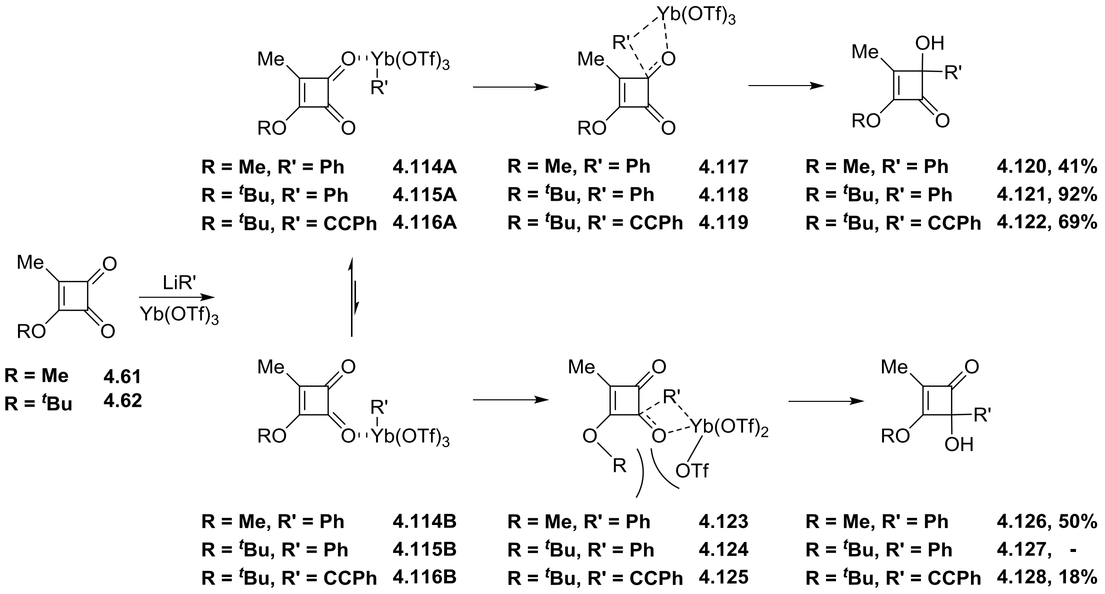
Scheme 4.24 Thermal rearrangement of 4-alkynylcyclobutenone **4.111**.

4.6 Conclusions and Future Work

The approach to tricyclic heterocycle **4.8** via cyclobutenone rearrangement led us to undertake an investigation into the nature and reactivity of analogous mixed squaramides. Seminal calculations showed a marginal increase in the activation energy required for electrocyclic ring opening of mono-squaramides relative to squarates, with further calculations needed to support our inference that ring closure of the ketene intermediate is of significantly higher energy in such systems. Accordingly, we have demonstrated that the electrocyclic ring opening of these substrates does occur in refluxing xylene but that subsequent [2+2] cycloaddition reactions do not lead to useful outcomes. This may be due to the need to overcome significant enthalpy and entropy penalties. For this reason, as we approached the end of our study, we shifted our focus towards gaining an understanding of the thermal rearrangements of squaramides, particularly pertaining to those with alkynyl adducts.

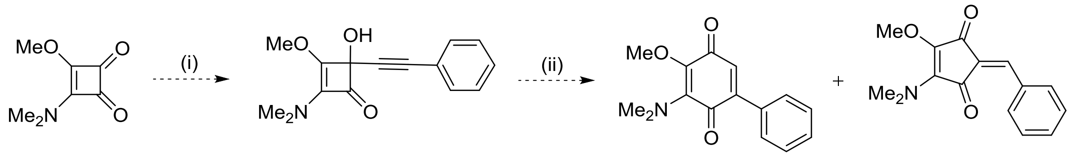
Thermolysis of alkynylcyclobutenones have been well described in literature to give quinones and cyclopentenones as the rearrangement products[118] (*vide supra* Scheme 4.23), however, given the unusual behaviour regarding aminoalkynylcycobutenones obtained by a colleague, we have opened up a wider investigation of the thermochemistry of mixed squaramides within our group. The unanticipated butenolide **4.112** product along with an even more astonishing cyclisation side product **4.113** at elevated temperatures offers a glimpse into the potential versatility of squaramides for the rapid construction of some unusual fused ring systems.

Further investigations will be sought to exploit the stabilising effect of the nitrogen substituent to our advantage. Selectivity in the additions of organolanthanides to aminocyclobutenones will also be examined along with the impact of such substituents on the course of various thermal and photochemical rearrangements. The electronic influence of the amine may allow us to exclusively target the vinylogous ester carbonyl over the vinylogous amide carbonyl in nucleophilic addition reactions. Of particular interest here would be the steric factors that would need to be in place to influence the course of such reactions. In the case of squarates (Scheme 4.25),[124] the reversal of the regiochemical course with $Yb(OTf)_3$ is believed to be governed by steric clash between the ytterbium 'ate' species and the alkoxy substituent in **4.123→4.125**, which results in a lower lower reaction barrier, thus driving the reaction towards addition of the nucleophile to the vinylogous ester carbonyl, in **4.117→4.119**, rather than the ketonic carbonyl.



Scheme 4.25 Regiochemical course of organoytterbium addition to squarates.[124]

Critically, in systems such as **4.123**, insufficient steric clash between the alkoxy group and the 'ate' species results in indiscriminant addition to both carbonyls, with PhYb(OTf)$_3$Li adding to methylmethoxycyclobutendione **4.61** to give a 1:1 ratio of addition products **4.120** and **4.126**. By contrast, with the ^{t}butoxy analogue **4.62** as the electrophile, complete reversal in the 'normal' mode of addition is observed, leading exclusively to adduct **4.121**. Addition of PhC≡CYb(OTf)$_3$Li to **4.62**, however, gives approximately 18% of the undesired ketonic addition product **4.128** with 69% of desired **4.122**. Substituting the ^{t}butoxy group for a bulky amine would be expected to deliver the analogous regioselectivity whereas, conceivably, replacement with a non-bulky amine could also provide a similar outcome even in the presence of a vinylogous ester carbonyl (Scheme 4.26), provided the electronic influence of the nitrogen can overcome any steric factor.



4.23 **4.129** **4.130** **4.131**

Scheme 4.26 Organoytterbium addition to squaramate **4.23**.

Chapter 5: Experimental

5.1 General Experimental

Solvents and Reagents: Commercially available reagents were purchased from Acros Organics, Sigma-Aldrich, Alfa Aesar, Fluorochem and Apollo Chemicals and were used as received unless otherwise stated. Solvents were purchased from Fischer Scientific and Rathburn and used as received unless stated as dry. In which case, diethyl ether, tetrahydrofuran, 1,4-dioxane and toluene were distilled over sodium/benzophenone and dichloromethane was distilled over calcium hydride immediately prior to use.

Chromatography: Thin layer chromatography was performed on Merck DC-Alufolien 60 F254 0.2 mm precoated plates. Product spots were visualised by ultraviolet light (254 and 365 nm) and stained with one of the following solutions as appropriate: potassium permanganate in aqueous NaOH, DNPH in H_2SO_4/EtOH, vanillin in H_2SO_4/EtOH or *p*-anisaldehyde in H_2SO_4/EtOH. Flash column chromatography was carried out on silica gel (200–400 mesh) with the stated solvent system.

Melting Points: Melting points were recorded on a Reichert Austria apparatus and are uncorrected.

Infrared Spectra: Infrared spectra were recorded neat as an oil film or solid compression on a Nicolet 380 FT-IR. Absorption maxima (v_{max}) are described as s (strong), sh (sharp), m (medium), w (weak) and br (broad) and are quoted in wavenumbers (cm^{-1}).

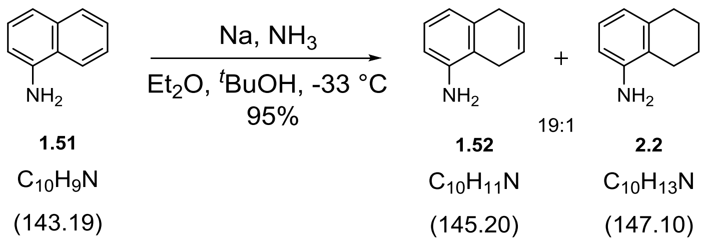
NMR spectroscopy: Proton (^1H) and carbon (^{13}C) spectra were recorded on a Bruker AV300 (at 300 and 75 MHz, respectively) or Bruker DPX400 (at 400 and 101 MHz, respectively) spectrometer at 298 K unless otherwise stated. Chemical shifts are quoted in parts per million downfield of tetramethylsilane with residual solvent as the internal standard. Assignments were made on the basis of chemical shifts, coupling constants, DEPT-135 and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), app.

(apparent) and br. (broad). Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz.

Mass Spectrometry: ESI mass spectra were recorded using a Waters ZMD single quadrupole mass spectrometer with a 2700 autosampler and a 600 pump with MeCN as the eluent. EI were measured on a thermoquest trace single quadrupole GC-MS at 70 eV. High resolution mass spectra were recorded on either a Bruker Apex III FT-ICR mass spectrometer equipped with a 4.7 T actively shielded superconducting magnet and Apollo ESI ion source or a Bruker maXis ESI-ToF coupled to a Dionex Ultimate 3000 HPLC and Apollo ESI ion source. High resolution mass spectra were recorded by Dr. John Langley, Ms. Julie Herniman and Ms. Sarah Clark at the University of Southampton.

5.2 Experimental Procedures for Chapter 2

5,8-Dihydronaphthalen-1-amine (1.52) and 5,6,7,8-tetrahydronaphthalen-1-amine (2.2)



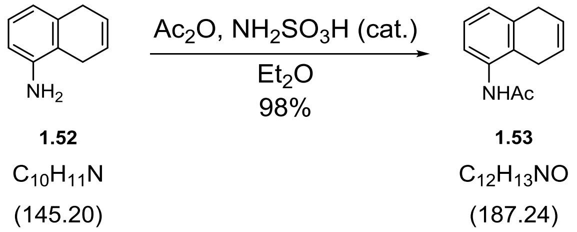
Following the procedure of Rogers *et al*.[68] To a solution of aminonaphthalene **1.52** (50 g, 0.35 mol) in Et_2O (250 mL) were added ^{t}BuOH (35 mL) and NH_3 (*ca.* 200 mL). Na (22 g, 0.94 g-atom) was added portion wise to the refluxing solution over a period of 3 h, followed by additional ^{t}BuOH (35 mL) and EtOH (70 mL) in two equal portions over 1 h. The NH_3 was allowed to evaporate over 20 h after which the mixture was quenched with NH_4Cl (aq) (30 mL) and H_2O (200 mL). The aqueous phase was extracted with Et_2O (3 x 1 L) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as purple crystals (50.8 g, 0.35 mol, 100%) contaminated with 5% of the over-reduced product **2.2**. An analytically pure sample was obtained by recrystallisation with petroleum ether.

MP	35–37 °C (petroleum ether) [Lit. 35–37 °C (petroleum ether)].[68]
FTIR (υ_{max} (cm^{-1}))	3396 (s), 3309 (m), 3214 (m), 3029 (m), 2930 (w), 2858 (m), 2807 (m), 1671 (m), 1622 (m), 1584 (s), 1278 (s), 770 (s), 654 (s).
δ_H (300 MHz, $CDCl_3$)	7.11 (1H, app t, *J* = 7.7 Hz, Ar$\underline{H}$), 6.69 (1H, d, *J* = 7.5 Hz, Ar$\underline{H}$), 6.63 (1H, d, *J* = 7.9 Hz, Ar$\underline{H}$), 6.11–5.90 (2H, m, C$\underline{H}$=C$\underline{H}$), 3.64 (2H, br s, N$\underline{H}_2$), 3.51 (2H, br t, *J* = 5.3 Hz, C$\underline{H}_2$), 3.16 (2H, br t, *J* = 5.3 Hz, C$\underline{H}_2$). Contaminated with resonances for **2.2**: 2.77 (2H, t, *J* = 6.4 Hz, C$\underline{H}_2$), 2.49 (2H, t, *J* = 6.4 Hz, C$\underline{H}_2$), 1.94–1.75 (4H, m, C$\underline{H}_2$C$\underline{H}_2$).

δ_C (75 MHz, CDCl$_3$)	143.7 (C), 134.6 (C), 126.5 (CH), 124.8 (CH), 123.1 (CH), 119.3 (C), 119.0 (CH), 112.4 (CH), 29.6 (CH$_2$), 25.1 (CH$_2$).
LRMS (ESI$^+$), m/z	187 ([M+CH$_3$CN+H]$^+$, 100%).
HRMS, m/z	$C_{10}H_{12}N$ [M+H]$^+$ requires 146.0964; found 146.0962.

Physical and spectroscopic data are in accordance with that reported in the literature.[68]

N-(5,8-Dihydronaphthalen-1-yl)acetamide (1.53)



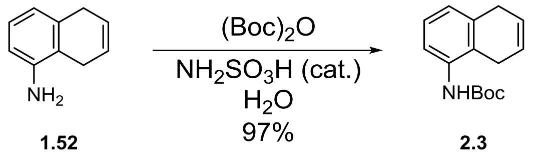
Adapting the procedure of Upadhyaya *et al.*[125] To a mixture of amine **1.52** (5.48 g, 37.7 mmol) and NH$_2$SO$_3$H (183 mg, 2.0 mmol) was added Ac$_2$O (4.50 g, 42 mmol). After 24 h, Et$_2$O (10 mL) was added. After a further 3 h, the crude mixture was filtered, washed with Et$_2$O (50 mL) and H$_2$O (100 mL) and dried *in vacuo* to afford the title compound as a pink solid (6.90 g, 36.9 mmol, 98%).

MP	150–155 °C (EtOH/H$_2$O) [Lit. 164 °C (EtOH)].[126]
FTIR (υ_{max} (cm^{-1}))	3279 (m), 3023 (w), 2889 (w), 2862 (w), 2814 (w), 2048 (w), 1651 (s), 1535 (s), 1468 (m), 1270 (w), 780 (w), 710 (m), 605 (m).
δ_H (300 MHz, CDCl$_3$)	7.58 (1H, d, *J* = 8.1 Hz, ArH), 7.19 (1H, app t, *J* = 7.7 Hz, ArH), 6.98 (1H, d, *J* = 8.0 Hz, ArH), 6.00–5.80 (2H, m, CH=CH), 3.44 (2H, br s, CH$_2$), 3.25 (2H, br s, CH$_2$), 2.21 (3H, s, CH$_3$).
δ_C (75 MHz, CDCl$_3$)	168.5 (C=O), 134.8 (C), 134.8 (C), 126.8 (C), 126.3 (CH), 125.9 (CH), 124.5 (CH), 123.0 (CH), 121.8 (CH), 29.7 (CH$_2$), 25.5 (CH$_2$), 24.1 (CH$_3$).

LRMS (ESI$^+$), m/z	251 ([M+CH_3CN+Na]$^+$, 58%).
HRMS, m/z	$C_{12}H_{14}NO$ [M+H]$^+$ requires 188.1070; found 188.1070.

Physical and spectroscopic data are in accordance with that reported in the literature.[69,126]

*t*ert-Butyl 5,8-dihydronaphthalene-1-yl carbamate (2.3)



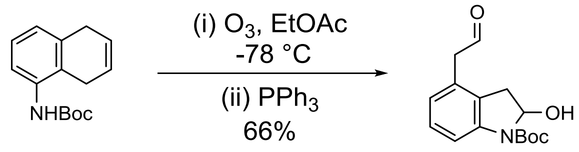
1.52 $C_{10}H_{11}N$ (145.20) → **2.3** $C_{15}H_{19}NO_2$ (245.32)

Adapting the method of Upadhyaya *et al.*[125] To a mixture of amine **1.52** (55 mg, 0.38 mmol) and NH_2SO_3H (18 mg, 0.19 mmol) was added $(Boc)_2O$ (99 mg, 0.45 mmol). The mixture was sonicated for 30 min then H_2O (1 mL) was added. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petroleum ether/Et_2O) afforded the title compound as a pink solid (90 mg, 0.37 mmol, 97%). On a 2.46 g (16.9 mmol) scale, employing 17 mL of H_2O, 96 mg (0.99 mmol) of NH_2SO_3H and 5.16 g, (23.6 mmol) of $(Boc)_2O$, the yield was 94% (3.91 g, 15.9 mmol).

MP	96–98 °C (EtOH/H_2O).
FTIR (υ_{max} (cm^{-1}))	3256 (br), 3032 (w), 2975 (w), 1692 (s), 1524 (s), 1469 (w), 1244 (m), 115 (s), 752 (m).
δ_H (300 MHz, $CDCl_3$)	7.66 (1H, d, *J* = 7.7 Hz, Ar$\underline{H}$), 7.16 (1H, app t, *J* = 7.9 Hz, Ar$\underline{H}$), 6.89 (1H, d, *J* = 7.7 Hz , Ar$\underline{H}$), 6.21 (1H, br s, N$\underline{H}$), 5.86–5.95 (2H, m, C$\underline{H}$=C$\underline{H}$), 3.44–3.41 (2H, m, C$\underline{H}_2$), 3.23–3.20 (2H, m, C$\underline{H}_2$), 1.53 (9H, s, (C$\underline{H}_3$)$_3$).

δ_C (101 MHz, CDCl$_3$)	153.0 ($\underline{C}$=O), 135.4 ($\underline{C}$), 134.4 ($\underline{C}$), 126.3 ($\underline{C}$H), 124.6 ($\underline{C}$H), 124.1 ($\underline{C}$), 124.2 ($\underline{C}$H), 122.8 ($\underline{C}$H), 118.9 ($\underline{C}$H), 80.3 ($\underline{C}$), 29.7 ($\underline{C}H_2$), 28.3, (($\underline{C}H_3)_3$), 25.2 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	309 ([M+CH$_3$CN+Na]$^+$, 100%).
HRMS, m/z	$C_{15}H_{19}NNaO_2$ [M+Na]$^+$ requires 268.1308; found 268.1313.

***tert*-Butyl 2-hydroxy-4-(2-oxoethyl)-2,3-dihydro-1*H*-indole-1-carboxylate (2.5)**



2.3
$C_{15}H_{19}NO_2$
(245.32)

2.5
$C_{15}H_{19}NO_4$
(277.32)

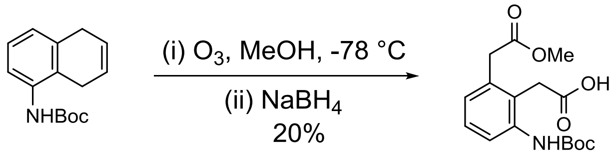
To a solution of carbamate **2.3** (1.00 g, 4.08 mmol) in EtOAc (15 mL) at -78 °C was bubbled through O_3 (1–5% in O_2). Once the solution had turned colourless (approximately 2 h), pure O_2 was bubbled through for 10 min then PPh$_3$ (3.00 g, 11.4 mmol) was added. After 16 h at RT, the solution was concentrated *in vacuo*. Purification by flash column chromatography (1:1–2:1 Et$_2$O/petroleum ether) afforded the title compound as a gummy yellow oil (756 mg, 2.73 mmol, 66%).

Alternatively, adapting the procedure of Motherwell *et al.*[81] A stock solution of carbamate **2.3** (reagent, 0.2 M in EtOAc, 0.85 mL/min) was ozonised (1.5 eq., 202 g/Nm^3, 62.5 mL/min) under flow at -7 °C with PPh$_3$ (quench, 2.25 eq., 0.3 M in EtOAc, 1.28 mL/min) using a Vapourtec R2+ device. An aliquot (4.6 mL) was collected then concentrated *in vacuo* and purified by flash column chromatography (30% EtOAc/cyclohexane) to afford the title compound as a gummy yellow oil (77 mg, 0.28 mmol, 75%).

FTIR (υ_{max} (cm^{-1}))	3434 (br), 2970 (m), 2926 (m), 2852 (w), 1677 (s), 1598 (m), 1461 (s), 1367 (s), 1159 (m), 934 (m), 770 (m).

δ_H (400 MHz, CDCl$_3$)	9.69 (1H, t, J = 2.0 Hz, C$\underline{H}$O), 7.38 (1H, br s, Ar$\underline{H}$), 7.21 (1H, app t, J = 7.8 Hz, Ar$\underline{H}$), 6.84 (1H, d, J = 7.6 Hz, Ar$\underline{H}$), 6.01 (1H, br s, C$\underline{H}$), 3.65 (2H, d, J = 1.5 Hz, C$\underline{H}_2$CHO), 3.23 (1H, dd, J = 17.2, 7.6 Hz, C$\underline{H}_a$H$_b$), 2.88 (1H, d, J = 17.2, Hz, CH$_a\underline{H}_b$), 1.62 (9 H, s, (C$\underline{H}_3$)$_3$). Broadening of resonances observed due to rotamers.
δ_C (101 MHz, CDCl$_3$)	198.1 ($\underline{C}$HO), 153.2 ($\underline{C}$=O), 140.8 ($\underline{C}$), 128.4 ($\underline{C}$H), 128.0 ($\underline{C}$), 124.0 ($\underline{C}$H), 113.7 ($\underline{C}$H), 83.1 ($\underline{C}$H), 82.7 ($\underline{C}$), 48.0 ($\underline{C}$H$_2$), 34.4 ($\underline{C}$H$_2$), 28.4 (($\underline{C}$H$_3$)$_3$). One ($\underline{C}$) not observed. Attenuation of resonances observed due to coupling of proximal ^{13}C nuclei to ^{15}N nucleus.
LRMS (ESI$^+$), m/z	577 ([2M+Na]$^+$, 100%).
HRMS, m/z	$C_{15}H_{18}NNaO_4$ [M+Na]$^+$ requires 300.1206; found 300.1206.

2-(2-((*tert*-Butoxycarbonyl)amino)-6-(2-methoxy-2-oxoethyl)phenyl)acetic acid (2.6)



2.3
$C_{15}H_{19}NO_2$
(245.32)

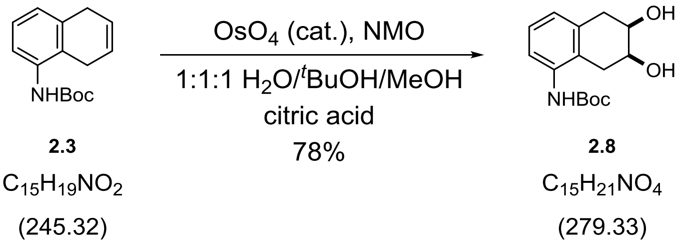
2.6
$C_{16}H_{21}NO_6$
(323.34)

To a solution of carbamate **2.3** (368 mg, 1.50 mmol) in MeOH (15 mL) at -78 °C was bubbled through O$_3$ (1–5% in O$_2$). Once the solution had turned blue, pure O$_2$ (g) was bubbled through for 10 min then NaBH$_4$ (153 mg, 4.04 mmol) was added. After 16 h at RT, the solution was concentrated *in vacuo*. Purification by flash column chromatography (1:1 EtOAc/Et$_2$O) afforded the title compound as a yellow solid (98 mg, 0.30 mmol, 20%).

MP	130 °C (EtOH/H$_2$O).

FTIR (υ$_{max}$ (cm^{-1}))	3343 (m), 2933 (w), 1731 (s), 1692 (s), 1587 (w), 1517 (m), 1439 (w), 1241 (m), 1157 (m).
δ$_H$ (400 MHz, CD_3OD)	7.38 (1H, d, *J* = 7.9 Hz, Ar$\underline{H}$), 7.21 (1H, app t, *J* = 7.8 Hz, Ar$\underline{H}$), 7.07 (1H, d, *J* = 7.6 Hz, Ar$\underline{H}$), 3.77 (2H, s, $C\underline{H}_2$), 3.70 (2H, s, $C\underline{H}_2$), 3.64 (3H, s, $OC\underline{H}_3$), 1.51 (9H, s, $(C\underline{H}_3)_3$).
δ$_C$ (101 MHz, CD_3OD)	175.1 ($\underline{C}$=O), 173.6 ($\underline{C}$=O), 156.2 ($\underline{C}$=O), 138.8 ($\underline{C}$), 135.8 ($\underline{C}$), 129.8 ($\underline{C}$), 129.0 ($\underline{C}$H), 128.6 ($\underline{C}$H), 125.8 ($\underline{C}$H), 81.3 ($\underline{C}$), 52.7 ($\underline{C}H_3$), 40.1 ($C\underline{H}_2$), 35.0 ($\underline{C}H_2$), 28.8 ($(\underline{C}H_3)_3$).
LRMS (ESI$^+$), m/z	346 ([M+Na], 100%).
HRMS, m/z	$C_{16}H_{21}NNaO_6$ $[M+Na]^+$ requires 346.1261; found 346.1271.

tert-Butyl ((6RS,7SR)-6,7-dihydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate (**2.8**)

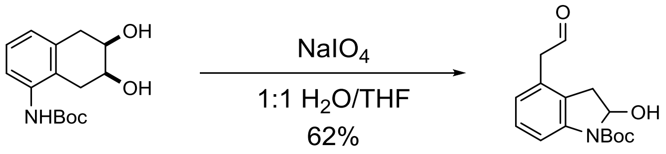


Following the procedure of Sharpless *et al.*[127] To a solution of carbamate **2.3** (907 mg, 3.70 mmol) in $H_2O/^tBuOH/MeOH$ (1:1:1, 100 mL) were added citric acid monohydrate (590 mg, 2.81 mmol), OsO_4 (2.5% w/w in ^tBuOH, 50 µl, 5 µmol) and NMO (658 mg, 5.62 mmol). After 16 h, the reaction mixture was extracted with EtOAc (4 x 100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1:1 $EtOAc/Et_2O$) afforded the title compound as a white solid (801 mg, 2.87 mmol, 78%).

MP	174–175 °C ($EtOH/H_2O$).

FTIR (υ_{max} (cm^{-1}))	3344 (br), 2971 (w), 2920 (w), 1392 (s), 1246 (m), 1161 (m), 1008 (m), 777 (w), 623 (m).
δ_H (300 MHz, CD_3OD)	7.18 (1H, d, *J* = 7.7 Hz, ArH), 7.09 (1H, t, *J* = 7.7 Hz, ArH), 6.93 (1H, d, *J* = 7.7 Hz, ArH) 4.08–3.98 (2H, m, CH(OH)CH(OH)), 3.07–2.92 (2H, m, CH_2), 2.92–2.76 (2H, m, CH_2), 1.51 (9H, s, $(CH_3)_3$).
δ_C (75 MHz, CD_3OD)	156.6 (C=O), 137.4 (C), 136.1 (C), 129.9 (C), 127.5 (CH), 127.2 (CH), 124.2 (CH), 81.0 (C), 70.2 (CH), 70.1 (CH), 35.7 (CH_2), 31.4 (CH_2), 28.9 ($(CH_3)_3$).
LRMS (ESI$^+$), m/z	343 ([M+CH_3CN+Na]$^+$, 51%), 302 ([M+Na]$^+$, 100%),
HRMS, m/z	$C_{16}H_{17}N_5Na$ [M+Na]$^+$ requires 302.1376; found 302.1370.

tert-Butyl 2-hydroxy-4-(2-oxoethyl)-2,3-dihydro-1*H*-indole-1-carboxylate (2.5)

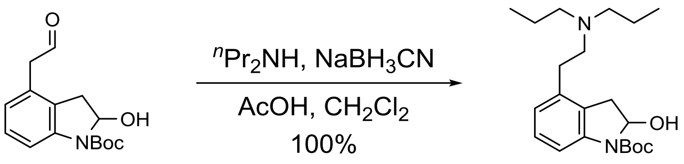


2.8
$C_{15}H_{21}NO_4$
(279.33)

2.5
$C_{15}H_{19}NO_4$
(277.32)

Following the procedure of Binder *et al.*[128] To a solution of diol **2.8** (38 mg, 0.14 mmol) in H_2O/THF (1:1, 2 mL) was added a solution of $NaIO_4$ (51 mg, 0.24 mmol) in H_2O (2 mL). After 18 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (2:1 Et_2O/petroleum ether) afforded the title compound as a gummy yellow oil (24 mg, 0.09 mmol, 62%). Data as reported above.

***tert*-Butyl 4-(2-(dipropylamino)ethyl)-2-hydroxyindoline-1-carboxylate (2.56)**



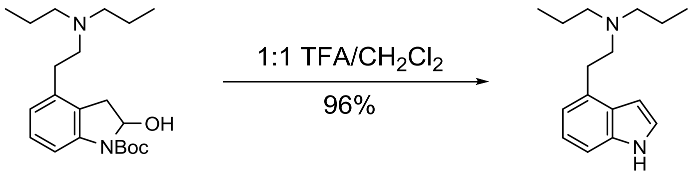
2.5 $C_{16}H_{19}NO_4$ (277.32)

2.56 $C_{21}H_{34}N_2O_3$ (362.51)

To a solution of aldehyde **2.5** (5.13 g, 18.5 mmol) in CH_2Cl_2 (250 mL) were added $^nPr_2NH_2$ (5.8 mL, 42.3 mmol) and AcOH (1.1 mL, 19.2 mmol). After 45 min, $NaBH_3CN$ (2.67 g, 42.4 mmol) was added and after a further 2 h, the reaction mixture was concentrated *in vacuo.* Purification by flash column chromatography (1:0–30:1 CH_2Cl_2/MeOH) afforded the title compound as a gummy pale yellow oil (6.70 g, 18.5 mmol, 100%).

FTIR (υ_{max} (cm^{-1}))	3367 (br), 2970 (w), 2936 (w), 1694 (m), 1597 (w), 1462 (w), 1369 (w), 1136 (w), 907 (m), 725 (s), 645(w).
δ_H (300 MHz, $CDCl_3$)	7.57 (1H, br s, Ar$\underline{H}$), 7.08 (1H, app t, *J* = 7.9 Hz, Ar$\underline{H}$), 6.76 (1H, d, *J* = 7.8 Hz, Ar$\underline{H}$), 5.93 (1H, br s, C$\underline{H}$), 5.74 (1H, br s, O$\underline{H}$), 3.24 (1H, dd, *J* = 17.1, 7.6 Hz, $C\underline{H_a}H_b$), 2.91 (1H, d, *J* = 17.4 Hz, $CH_a\underline{H_b}$), 2.82 (4H, s, $C\underline{H_2}C\underline{H_2}$), 2.72–2.58 (4H, m, 2xN$C\underline{H_2}$), 1.67–1.56 (4H, m, 2x$C\underline{H_2}$), 1.55 (9H, s, $(C\underline{H_3})_3$), 0.89 (6H, t, *J* = 7.4 Hz, 2x$C\underline{H_3}$). Broadening of resonances observed due to rotamers.
δ_C (75 MHz, $CDCl_3$)	140.4 ($\underline{C}$), 134.8 ($\underline{C}$), 127.9 ($\underline{C}H$), 127.0 ($\underline{C}$), 122.8 ($\underline{C}H$), 112.7 ($\underline{C}H$), 82.9 ($\underline{C}H$), 82.2 ($\underline{C}$), 54.7 (2x$\underline{C}H_2$), 53.1 ($\underline{C}H_2$), 34.3 ($\underline{C}H_2$), 28.6 ($\underline{C}H_2$), 28.2 ($(\underline{C}H_3)_3$), 18.3 (2x$\underline{C}H_2$), 11.4 (2x$\underline{C}H_3$). One ($\underline{C}$) not observed. Attenuation of resonances observed due to coupling of proximal ^{13}C nuclei to ^{15}N nucleus.
LRMS (ESI^+), m/z	363 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{21}H_{35}N_2O_3$ $[M+H]^+$ requires 363.2642; found 363.2642.

4-[2-(*N*,*N*-Dipropylamino)ethyl]indole (1.39)



2.56 $C_{21}H_{34}N_2O_3$ (362.51)

1.39 $C_{16}H_{24}N_2$ (244.38)

To a solution of amine **2.56** (62 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added TFA (12 mL). After 3 h, aq. NaOH (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phased were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (25:1 CH_2Cl_2/MeOH) afforded the title compund as a gummy yellow oil (40 mg, 0.16 mmol, 96%).

Alternatively, adapting the procedure of Coffey *et al*.[95] To a solution of amine **2.56** (27 mg, 0.07 mmol) in acetone (1 mL) was added 12 M HCl (1 mL). The reaction mixture was heated at 50 °C for 1 h, basified with 2 M NaOH (10 mL) then concentrated *in vacuo*. Following extraction with EtOAc (3 x 50 mL), the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1:0–9:1 CH_2Cl_2/MeOH) afforded the title compound as a yellow oil (13 mg, 0.05 mmol, 71%). On a 6.70 g (18.5 mmol) scale, employing 20 mL of 12 M HCl, 100 mL of acetone and 20 mL of sat. K_2CO_3 as the base, the yield was 64% (2.90 g, 11.9 mmol) using.

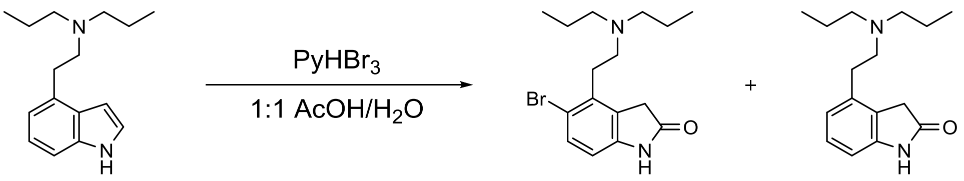
FTIR (υ_{max} (cm^{-1})) 3241 (br), 2971 (m), 2939 (w), 2882 (w), 1673 (s), 1462 (m), 1344 (m), 1177 (s), 1130 (s), 758 (m).

δ_H (300 MHz, $CDCl_3$) 8.94 (1H, br s, N$\underline{H}$), 7.34 (1H, d, *J* = 8.4 Hz, Ar$\underline{H}$), 7.21 (1H, app t, *J* = 2.9 Hz, Ar$\underline{H}$), 7.09 (1H, dd, *J* = 8.1, 7.3 Hz, Ar$\underline{H}$), 6.89 (1H, d, *J* = 7.3 Hz, Ar$\underline{H}$), 6.57 (1H, m, Ar$\underline{H}$), 3.31 (4H, s, C$\underline{H}_2$C$\underline{H}_2$), 3.10–2.96 (4H, m, 2xNC$\underline{H}_2$), 1.89–1.67 (4H, m, 2xC$\underline{H}_2$), 0.96 (6H, t, *J* = 7.3 Hz, 2xC$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$)	136.0 ($\underline{C}$), 127.7 ($\underline{C}$), 127.0 ($\underline{C}$), 124.9 ($\underline{C}H$), 122.0 ($\underline{C}H$), 119.6 ($\underline{C}H$), 110.6 ($\underline{C}H$), 99.8 ($\underline{C}H$), 53.9 (2x$\underline{C}H_2$), 52.7 ($\underline{C}H_2$), 27.9 ($\underline{C}H_2$), 16.8 (2x$\underline{C}H_2$), 11.1 (2x$\underline{C}H_3$).
LRMS (ESI^+), m/z	245 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{16}H_{25}N_2$ $[M+H]^+$ requires 245.2012; found 254.2014.

Physical and spectroscopic data are in accordance with that reported in the literature.[57]

5-Bromo-4-[2-(dipropylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one (2.58) and 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one (1.9)



1.39 $C_{16}H_{24}N_2$ (244.38)

2.58 $C_{16}H_{23}BrN_2O$ (339.27)

1.9 $C_{16}H_{24}N_2O$ (260.19)

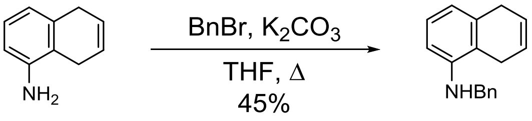
Following the procedure of Urquima S.A.[57] To a solution of indole **1.39** (40 mg, 0.16 mmol) in AcOH and H_2O (1:1, 1 mL) was added a solution of $PyHBr_3$ (65 mg, 0.20 mmol) in AcOH and H_2O (1:1, 1 mL). The reaction mixture was heated at 50 °C for 2 h then cooled to RT, concentrated *in vacuo* and 2 M NaOH (2 mL) added. Following extraction with EtOAc (3 x 30 mL), the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1:0–10:1 CH_2Cl_2/MeOH) afforded the title compound as a yellow oil (8 mg, 0.02 mmol, 14%) along with a 2:1 mixture of **2.58** and **1.9** (11 mg).

FTIR (υ_{max} (cm^{-1}))	3183 (br), 2957 (m), 2804 (w), 1698 (s), 1617 (m), 1458 (m), 776 (m).
δ_H (300 MHz, $CDCl_3$)	8.64 (1H, br s, N$\underline{H}$), 7.39 (1H, d, J = 8.4 Hz, Ar$\underline{H}$), 6.7 (1H, d, J = 8.4 Hz, Ar$\underline{H}$), 3.61 (2H, s, $C\underline{H}_2$), 3.10–2.87 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.85–2.72 (4H, m, 2xN$C\underline{H}_2$),

	1.78–1.61 (4H, m, 2xC<u>H</u>$_2$), 0.97 (6H, t, *J* = 7.3 Hz, 2xC<u>H</u>$_3$).
δ$_C$ (75 MHz, CDCl$_3$)	176.4 (<u>C</u>=O), 142.0 (<u>C</u>), 132.13 (<u>C</u>H), 132.06 (<u>C</u>), 126.6 (<u>C</u>), 116.9 (<u>C</u>), 109.8 (<u>C</u>H), 54.8 (2x<u>C</u>H$_2$), 51.3 (<u>C</u>H$_2$), 35.7 (<u>C</u>H$_2$), 29.5 (<u>C</u>H$_2$), 18.5 (2x<u>C</u>H$_2$), 11.6 (2x<u>C</u>H$_3$).
LRMS (ESI$^+$), m/z	341 ([M{^{81}Br}+H]$^+$, 100%), 339 ([M{^{79}Br}+H]$^+$, 98%).
HRMS, m/z:	$C_{16}H_{24}{}^{79}BrN_2O$ [M{^{79}Br}+H]$^+$ requires 339.1067; found 339.1070.

Data for **1.9** are reported on pages 124 and 125.

N-Benzyl-5,8-dihydronaphthalen-1-amine (2.59)



1.52
$C_{10}H_{11}N$
(145.20)

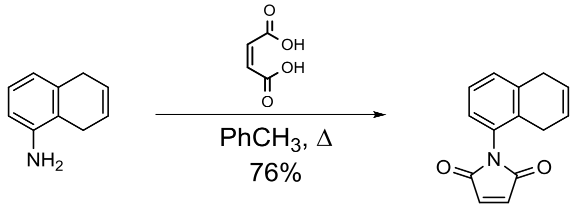
2.59
$C_{17}H_{17}N$
(235.32)

To a solution of amine **1.52** (1.00 g, 6.89 mmol) in THF (30 mL) was added K_2CO_3 (1.40 g, 10.1 mmol) followed by BnBr (1.0 mL, 12.1 mmol). The resulting suspension was heated at reflux for 2 days then cooled to RT. Purification by flash column chromatography (0–30% petroleum ether/Et_2O) afforded the title compound as white crystals (733 mg, 3.12 mmol, 45%).

MP	109–110 °C (petroleum ether).
FTIR (υ$_{max}$ (cm^{-1}))	3437 (s), 3029 (sh), 2844 (m), 2816 (m), 1588 (s), 1506 (s), 1469 (s), 1319 (m), 764 (m).
δ$_H$ (400 MHz, CDCl$_3$)	7.42–7.35 (4H, m, 4xAr<u>H</u>), 7.30 (1H, m, Ar<u>H</u>), 7.08 (1H, app t, *J* = 7.8 Hz , Ar<u>H</u>), 6.58 (1H, d, *J* = 7.6, Ar<u>H</u>), 6.52 (1H, d, *J* = 8.1, Ar<u>H</u>), 5.96–5.88 (2H, m, C<u>H</u>=C<u>H</u>), 4.39

	(2H, s, NC<u>H</u>$_2$), 3.91 (1H, br s, N<u>H</u>), 3.46–3.44 (2H, m, C<u>H</u>$_2$), 3.10–3.09 (2H, m, C<u>H</u>$_2$).
δ_C (101 MHz, CDCl$_3$)	145.1 (<u>C</u>), 139.3 (<u>C</u>), 134.2 (<u>C</u>), 128.6 (2x<u>C</u>H), 127.6 (<u>C</u>H), 126.7 (<u>C</u>H), 127.3 (<u>C</u>H), 124.7 (<u>C</u>H), 122.9 (2x<u>C</u>H), 118.7 (<u>C</u>), 117.9 (<u>C</u>H), 107.7 (<u>C</u>H), 48.5 (<u>C</u>H$_2$), 29.8, (<u>C</u>H$_2$), 25.0 (<u>C</u>H$_2$).
LRMS (ESI$^+$), m/z	236 ([M+H]$^+$, 100%).
HRMS, m/z	$C_{17}H_{18}N$ [M+H]$^+$ requires 236.1434; found 236.1434.

1-(5,8-Dihydronaphthalen-1-yl)-1*H*-pyrrole-2,5-dione (2.62)



1.52 $C_{10}H_{11}N$ (145.20)

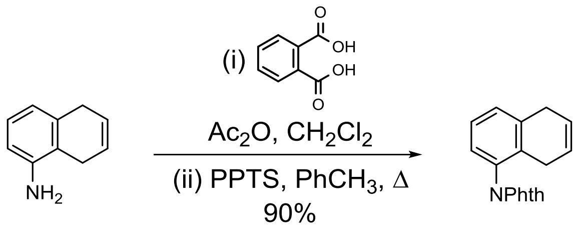
2.62 $C_{14}H_{11}NO_2$ (225.24)

To a solution of amine **1.52** (5.00 g, 34.4 mmol) in PhCH$_3$ (150 mL) was added maleic acid (6.00 g, 51.7 mmol). The resulting suspension was heated at reflux for 20 h after which the reaction mixture was cooled to RT, filtered, washed with EtOH (100 mL) and dried *in vacuo.* Purification by flash column chromatography (30% EtOAc/heptane) afforded the title compound as a yellow powder (5.90 g, 26.0 mmol, 76%).

MP	102–104 °C (EtOAc/heptane).
FTIR (υ_{max} (cm^{-1}))	3035 (w), 2879 (w), 2824 (w), 1703 (s), 1469 (sh), 1387 (s), 1148 (sh).
δ_H (400 MHz, CDCl$_3$)	7.24 (1H, d, J = 7.6 Hz, Ar<u>H</u>), 7.21 (1H, app t, J = 7.5 Hz, Ar<u>H</u>), 6.98 (1H, d, J = 7.5 Hz, Ar<u>H</u>), 6.82 (2H, s, 2xC<u>H</u>), 5.88 (1H, m, C<u>H</u>=), 5.78 (1H, m, C<u>H</u>=), 3.44–3.43 (2H, m, C<u>H</u>$_2$), 3.09–3.08 (2H, m, C<u>H</u>$_2$).

δ_C (101 MHz, $CDCl_3$)	169.7 (2x<u>C</u>=O), 136.1 (<u>C</u>), 134.3 (2x<u>C</u>H), 132.8 (<u>C</u>), 129.8 (<u>C</u>H), 129.4 (<u>C</u>), 126.6 (<u>C</u>H), 126.4 (<u>C</u>H), 124.2 (<u>C</u>H), 123.2 (<u>C</u>H), 29.6 (<u>C</u>H_2), 25.6 (<u>C</u>H_2).
LRMS (ESI^+), m/z	473 ($[2M+Na]^+$, 76%), 289 ($[M+CH_3CN+Na]^+$, 100%).
HRMS, m/z	$C_{14}H_{12}NO_2$ $[M+H]^+$ requires 226.0863; found 226.0861.

2-(5,8-Dihydronaphthalen-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (2.64)



1.52
$C_{10}H_{11}N$
(145.20)

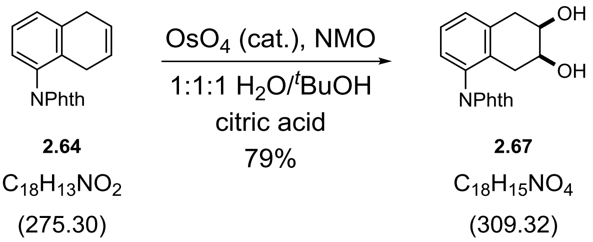
2.64
$C_{18}H_{13}NO_2$
(275.30)

Adapting the procedure of Eglinton *et al.*[129] To phthalic acid (1.00 g, 6.0 mmol) in CH_2Cl_2 (15 mL) was added Ac_2O (3.5 ml, 34.3 mmol). The mixture was heated at reflux for 4 h then cooled to RT. After 12 h, the mixture was concentrated *in vacuo*. The resulting white powder was suspended in $PhCH_3$ (30 mL), amine **1.52** (800 mg, 5.51 mmol) and PPTS (3 mg, 0.01 mmol) were added and the resulting mixture was heated at reflux under under Dean and Stark apparatus for 15 h then cooled to RT. Concentration *in vacuo* afforded the title compound as a white solid (1.49 g, 5.41 mmol, 98%).

MP	219–220 °C (Et_2O/petroleum ether).
FTIR (υ_{max} (cm^{-1}))	2055 (w), 1775 (w), 1708 (s), 1469 (m), 1378 (m), 1109 (m), 796 (w), 769 (m), 664 (m).
δ_H (400 MHz, $CDCl_3$)	7.97 (2H, dd, *J* = 8.5, 2.3 Hz, 2xAr<u>H</u>), 7.80 (2H, dd, *J* = 8.6, 2.5 Hz, 2xAr<u>H</u>), 7.32 (1H, t, 7.6 Hz, Ar<u>H</u>), 7.26 (1H, d, *J* = 7.6, Hz, Ar<u>H</u>), 7.10 (1H, dd, *J* = 7.6, 1.5 Hz, Ar<u>H</u>), 5.90 (1H, m, C<u>H</u>=), 5.79 (1H, m, C<u>H</u>=), 3.53–3.42 (2H, m, C<u>H</u>$_2$), 3.24–3.14 (2H, m, C<u>H</u>$_2$).

δ_C (101 MHz, $CDCl_3$)	167.4 (2x<u>C</u>=O), 136.1 (<u>C</u>), 134.3 (2x<u>C</u>H), 132.9 (<u>C</u>), 132.0 (2x<u>C</u>), 130.0 (<u>C</u>), 129.9 (<u>C</u>H), 126.6 (<u>C</u>H), 126.5 (<u>C</u>H), 124.2 (<u>C</u>H), 123.7 (2x<u>C</u>H), 123.4 (<u>C</u>H), 29.8 (<u>C</u>H_2), 25.7 (<u>C</u>H_2).
LRMS (ESI^+), m/z	339 ($[M+CH_3CN+Na]^+$, 100%).
HRMS, m/z	$C_{18}H_{14}NO_2$ $[M+H]^+$ requires 276.1019; found 276.1019.

2-((6RS,7SR)-6,7-Dihydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)isoindoline-1,3-dione (2.67)

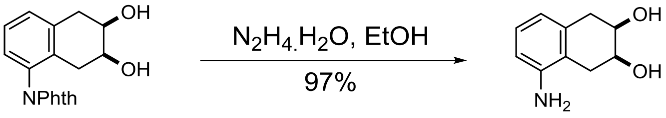


Adapting the procedure of Sharpless *et al.*[127] To a suspension of phthalamide **2.64** (400mg, 1.45 mmol) in H_2O/^{t}BuOH (12 mL, 1:1) were added citric acid (611 mg, 2.91 mmol) and OsO_4 (2.5% w/w in IPA, 50 µL, 5 µmol,) followed by NMO (185 mg, 1.58 mmol). Acetone (6 mL) was added to solubilise the suspension and the solution was heated at 50 °C for 15 min then cooled to RT where it was maintained for 2 days. The reaction mixture was concentrated *in vacuo* and filtered to give an off-white solid which was washed with 2 N HCl (10 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* and combined with the previously obtained precipitate to afford the title compound as a white solid (355 mg, 1.15 mmol, 79%).

MP	321–325 °C (EtOH/H_2O).
FTIR (υ_{max} (cm^{-1}))	3481 (br s), 3452 (m), 2932 (w), 1761 (w), 1701 (s), 1605 (w), 1470 (m), 1383 (m), 1071 (m), 719 (m).
δ_H (400 MHz, d6-DMSO)	8.00–7.92 (4H, m, 4xAr<u>H</u>), 7.27–7.16 (3H, m, 3xAr<u>H</u>), 4.68 (1H, br s, C<u>H</u>OH), 4.63 (1H, br s, C<u>H</u>OH), 3.89 (1H,

	br s, O<u>H</u>), 3.80 (1H, br s, O<u>H</u>), 2.97–2.89 (2H, m, C<u>H</u>$_2$), 2.59–2.53 (2H, m, C<u>H</u>$_2$).
δ$_C$ (101 MHz, d6-DMSO)	167.1 & 167.0 (2x<u>C</u>=O), 136.2 (<u>C</u>), 134.80 & 134.77 (2x<u>C</u>H), 133.4 (<u>C</u>), 131.56 & 131.55 (2x<u>C</u>), 130.7 (<u>C</u>), 129.9 (<u>C</u>H), 126.6 (<u>C</u>H), 126.1 (<u>C</u>H), 123.49 & 123.48 (2x<u>C</u>H), 67.6 (<u>C</u>H), 67.6 (<u>C</u>H), 34.8 (<u>C</u>H$_2$), 30.1 (<u>C</u>H$_2$). Rotamers observed in NMR.
LRMS (ESI$^+$), m/z	641 ([2M+Na]$^+$, 42%), 363 (100%).
HRMS, m/z	$C_{18}H_{15}NNaO_4$ [M+Na]$^+$ requires 332.0893; found 332.0894.

(2*RS*,3*SR*)-5-Amino-1,2,3,4-tetrahydronaphthalene-2,3-diol (2.68)



2.67
$C_{18}H_{15}NO_4$
(309.32)

2.68
$C_{10}H_{13}NO_2$
(179.22)

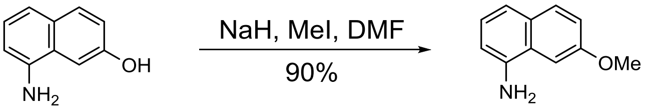
To a suspension of diol **2.67** (140 mg, 0.45 mmol) in EtOH (15 mL) was added $N_2H_4.xH_2O$ (50 µL, 1.03 mmol). The reaction mixture heated at reflux for 4 h then cooled to RT, filtered and washed with EtOH (5 mL). The resulting wet solid was re-dissolved in EtOAc (20 mL), washed with 2 M NaOH (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a white solid (78 mg, 0.44 mmol, 97%)

MP	167 °C (EtOAc/petroleum ether).
FTIR (υ$_{max}$ (cm^{-1}))	3306 (br), 2919 (m), 1623 (s), 1591 (m), 1467 (m), 775 (m).
δ$_H$ (400 MHz, d6-Acetone)	6.82 (1H, t, *J* = 7.6 Hz, Ar<u>H</u>), 6.49 (1H, d, *J* = 7.6 Hz, Ar<u>H</u>), 6.37 (1H, d, *J* = 7.6 Hz, Ar<u>H</u>), 4.28 (2H, br s, N<u>H</u>$_2$), 4.06 (1H, br s, C<u>H</u>OH), 3.98 (1H, br s, C<u>H</u>OH), 3.64 (1H,

	br s, O$\underline{H}$), 3.62 (1H, br s, O$\underline{H}$), 2.91 (1H, dd, *J* = 16.7, 7.1 Hz, ArC$\underline{H}_a$H$_a$'), 2.80 (1H, m, ArCH$_a$$\underline{H}_a$'), 2.67 (1H, dd, *J* = 16.7, 6.1 Hz, ArC$\underline{H}_b$H$_b$'), 2.60 (1H, dd, *J* = 16.7, 6.1 Hz, ArCH$_b$$\underline{H}_b$').
δ_C (101 MHz, d6-Acetone)	146.6 ($\underline{C}$), 135.4 ($\underline{C}$), 127.0 ($\underline{C}$H), 119.5 ($\underline{C}$), 118.8 ($\underline{C}$H), 112.8 ($\underline{C}$H), 69.84 ($\underline{C}$H), 69.81 ($\underline{C}$H), 35.5 ($\underline{C}$H$_2$), 31.0 ($\underline{C}$H$_2$).
LRMS (ESI$^+$), m/z	180 ([M+H]$^+$, 62%)
HRMS, m/z	$C_{10}H_{13}NNaO_2$ [M+Na]$^+$ requires 202.0838; found 202.0837.

Physical and spectroscopic data are in accordance with that reported in the literature.[130]

7-Methoxynaphthalen-1-amine (2.70)



2.75 $C_{10}H_{09}NO$ (159.18)

2.70 $C_{11}H_{11}NO$ (173.21)

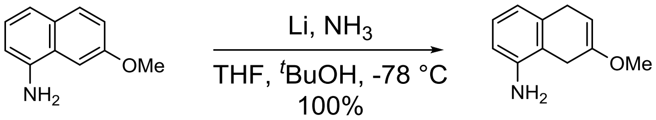
Adapting the procedure of Jin *et al.*[131] A suspension of NaH (310 mg, 7.75 mmol) in DMF (15 mL) was cooled to 0 °C and naphthol **2.75** (1.00 g, 6.28 mmol) was added portionwise. Upon complete addition, the reaction mixture was warmed to RT then after 15 min was cooled to 0 °C and MeI (400 µL, 6.43 mmol) added. The mixture was warmed to RT for 1 h then concentrated *in vacuo* and recrystallised from hexane to afford the title compound as brown flakes (978 mg, 5.64 mmol, 90%).

MP	78–80 °C (hexane) [Lit. 78–79 °C].[132]
FTIR (υ_{max} (cm^{-1}))	3428 (sh), 3354 (sh), 2996 (w), 1625 (m), 1579 (m), 1434 (m), 1229 (s), 822 (s).

δ_H (300 MHz, $CDCl_3$)	7.73 (1H, d, *J* = 9.1 Hz, Ar<u>H</u>), 7.30 (1H, d, *J* = 8.0 Hz, Ar<u>H</u>), 7.21–7.14 (2H, m, 2xAr<u>H</u>), 7.08 (1H, d, *J* = 2.2 Hz, Ar<u>H</u>), 6.81 (1H, dd, *J* = 7.3, 0.7 Hz, Ar<u>H</u>), 4.02 (2H, br s, N<u>H</u>$_2$), 3.95 (3H, s, OC<u>H</u>$_3$).
δ_C (75 MHz, $CDCl_3$)	157.2 (<u>C</u>), 140.9 (<u>C</u>), 130.2 (<u>C</u>H), 129.8 (<u>C</u>), 124.7 (<u>C</u>), 123.9 (<u>C</u>H), 119.2 (<u>C</u>H), 118.2 (<u>C</u>H), 110.7 (<u>C</u>H), 99.8 (<u>C</u>H), 55.3 (<u>C</u>H$_3$).
LRMS (ESI$^+$), m/z	215 ([M+CH_3CN+H]$^+$, 100%).

Physical and spectroscopic data are in accordance with that reported in the literature.[131,133]

7-Methoxy-5,8-dihydronaphthalen-1-amine (2.71)



2.70 $C_{11}H_{11}NO$ (173.21)

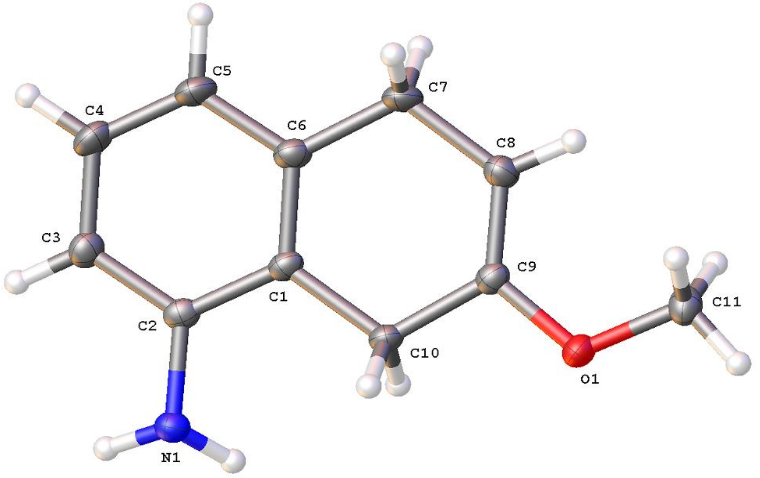
2.71 $C_{11}H_{13}NO$ (175.23)

Adapting the procedure of Bayer Aktiengesellschaft.[134] A suspension of amine **2.70** (3.00 g, 17.3 mmol) in THF (35 mL) and added ^{t}BuOH (4.8 mL) and cooled to -78 °C. NH_3 (350 mL) was condensed into the reaction mixture then addition of Li (370 mg, 53.6 g-atom) was added portionwise over a period of 1.5 h. Degassed MeOH (1 mL) and degassed H_2O (10 mL) were then added and the mixture was warmed to RT to allow the NH_3 to evaporate. Further degassed H_2O (100 mL) was then added. The aqueous phase was extracted with degassed EtOAc (3 x 150 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a brown solid (3.04 g, 17.3 mmol, 100%).

MP	88-90 °C [Lit. 84-85 °C].[135]
FTIR (υ_{max} (cm^{-1}))	3389 (sh), 3327 (m), 3242 (m), 3028 (w), 2881 (m), 2825 (sh), 1693 (sh), 1647 (m), 1467 (m), 1227 (m), 789 (s).

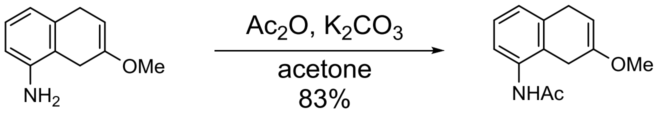
δ_H (300 MHz, $CDCl_3$)	7.01 (1H, app t, J = 7.7 Hz, Ar<u>H</u>), 6.63 (1H, d, J = 7.5 Hz, Ar<u>H</u>), 6.55 (1H, d, J = 7.5 Hz, Ar<u>H</u>), 4.83 (1H, m, C<u>H</u>=), 3.65 (3H, s, OC$\underline{H}_3$), 3.60 (2H, br s, N$\underline{H}_2$), 3.56–3.50 (2H, m, C$\underline{H}_2$), 3.16–3.10 (2H, m, C$\underline{H}_2$).
δ_C (101 MHz, $CDCl_3$)	152.0 (<u>C</u>), 143.8 (<u>C</u>), 134.7 (<u>C</u>), 126.5 (<u>C</u>H), 118.8 (<u>C</u>), 118.4 (<u>C</u>H), 112.1 (<u>C</u>H), 90.9 (<u>C</u>H), 54.1 ($\underline{C}H_3$), 29.6 ($\underline{C}H_2$), 27.8 ($\underline{C}H_2$).
LRMS (ESI^+), m/z	457 ($[2M+Na]^+$, 48%), 217 ($[M+CH_3CN+H]^+$, 100%),
HRMS, m/z	$C_{11}H_{14}NO$ $[M+H]^+$ requires 176.1070; found 176.1070.

X-ray



Physical and spectroscopic data are in accordance with that reported in the literature.[135]

N-(7-Methoxy-5,8-dihydronaphthalen-1-yl)acetamide (2.76)



2.71
$C_{11}H_{13}NO$
(175.23)

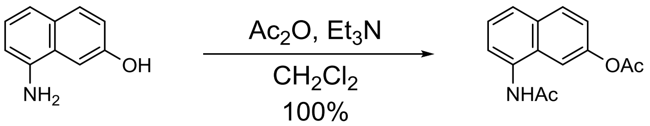
2.76
$C_{13}H_{15}NO_2$
(217.26)

To a solution of amine **2.71** (40 mg, 0.23 mmol) in acetone (2 mL) was added K_2CO_3 (35 mg, 0.25 mmol) followed by Ac_2O (30 µL, 0.32 mmol). After 1 h the reaction mixture was heated at reflux for 1 h after which it was cooled to RT and concentrated *in* *vacuo*. Purification by flash column chromatography (100% EtOAc) afforded the title compound as a pale brown solid (41 mg, 0.19 mmol, 83%).

MP	205 °C (EtOAc/hexane) [Lit. 191-192 °C].[135]
FTIR (υ_{max} (cm^{-1}))	3263 (sh), 3037 (w), 2826 (w), 1687 (w), 1655 (s), 1538 (m), 1219 (m), 793 (m).
δ_H (400 MHz, d6-DMSO)	9.25 (1H, br s, N$\underline{H}$), 7.22 (1H, d, *J* = 7.7 Hz, Ar$\underline{H}$), 7.12 (1H, t, *J* = 7.7 Hz, Ar$\underline{H}$), 7.10 (1H, d, *J* = 7.7 Hz, Ar$\underline{H}$), 4.84 (1H, m, C$\underline{H}$=), 3.55 (3H, s, OC$\underline{H}_3$), 3.51–3.43 (2H, m, C$\underline{H}_2$), 3.26–3.19 (2H, m, C$\underline{H}_2$), 2.05 (3H, s, C$\underline{H}_3$).
δ_C (101 MHz, d6-DMSO)	168.2 ($\underline{C}$=O), 152.4 ($\underline{C}$), 135.7 ($\underline{C}$), 134.5 ($\underline{C}$), 127.8 ($\underline{C}$), 125.7 ($\underline{C}$H), 124.8 ($\underline{C}$H), 122.7 ($\underline{C}$H), 90.1 ($\underline{C}$H), 53.9 ($\underline{C}H_3$), 29.1 ($\underline{C}H_2$), 28.1 ($\underline{C}H_2$), 23.2 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	281 ([M+CH_3CN+Na]$^+$, 100%).
HRMS, m/z	$C_{13}H_{15}NNaO_2$ [M+Na]$^+$ requires 240.0995; found 240.0995.

Physical and spectroscopic data are in accordance with that reported in the literature.[135]

8-Acetamidonaphthalen-2-yl acetate (2.77)



2.75 $C_{12}H_{11}NO_2$ (159.18)

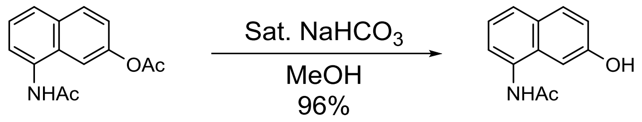
2.77 $C_{14}H_{13}NO_3$ (243.26)

Adapting the procedure of Vermeulen *et al*.[136] To a suspension of amine **2.75** (4.38 g, 27.5 mmol) in CH_2Cl_2 (80 mL) were added Ac_2O (5.7 mL, 60.3 mmol) and Et_3N (8.4 mL, 60.2 mmol). After 4 h, the reaction mixture was washed with H_2O (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% EtOAc) afforded with title compound as a pink solid (6.59 g, 27.1 mol, 99%).

MP	192-195 (MeOH) [Lit. 184 (MeOH)].[137]
FTIR (υ_{max} (cm^{-1}))	3256 (br), 3025 (w), 2160 (w), 1758 (sh), 1663 (sh), 1539 (m), 1503 (m), 1209 (s), 1186 (s).
δ_H (400 MHz, d6-DMSO)	9.90 (1H, br s, N$\underline{H}$), 7.99 (1H, d, J = 8.8 Hz, Ar$\underline{H}$), 7.82–7.77 (3H, m, 3xAr$\underline{H}$), 7.49 (1H, app t, J = 7.8 Hz, Ar$\underline{H}$), 7.36 (1H, d, J = 8.7 Hz, Ar$\underline{H}$), 2.35 (3H, s, C$\underline{H}_3$CO$_2$), 2.20 (3H, s, C$\underline{H}_3$CON).
δ_C (101 MHz, d6-DMSO)	169.5 ($\underline{C}$=O), 169.0 ($\underline{C}$=O), 148.3 ($\underline{C}$), 133.6 ($\underline{C}$), 131.7 ($\underline{C}$), 129.7 ($\underline{C}$H), 128.0 ($\underline{C}$), 125.4 ($\underline{C}$H), 124.8 ($\underline{C}$H), 122.0 ($\underline{C}$H), 121.8 ($\underline{C}$H), 114.0 ($\underline{C}$H), 23.5 ($\underline{C}$H$_3$), 20.9 ($\underline{C}$H$_3$).
LRMS (ESI$^+$), m/z	266 ([M+Na]$^+$), 100%).
HRMS, m/z	$C_{14}H_{14}NO_3$ [M+H]$^+$ requires 244.0968; found 244.0966.

Physical and spectroscopic data are in accordance with that reported in the literature.[137]

N-(7-Hydroxynaphthalen-1-yl)acetamide (2.78)



2.77 $C_{10}H_9NO$ (243.26)

2.78 $C_{12}H_{11}NO_2$ (201.22)

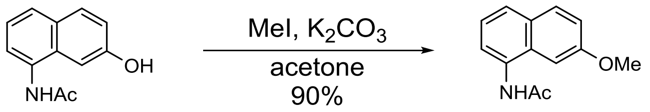
Adapting the procedure of Vermeulen *et al.*[136] To a suspension of **2.77** (4.00 g, 16.4 mmol) in MeOH (40 mL) was added sat. NaHCO$_3$ (20 mL). The mixture was heated at reflux for 1 h and then cooled to RT, acidified with 1 M HCl (10 mL) and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded the title compound as a pink solid (3.18 g, 15.8 mmol, 96%).

MP	200 °C dec. (H$_2$O) [Lit. 198 °C dec. (H$_2$O)].[138]

FTIR (υ$_{max}$ (cm^{-1}))	3150 (br), 3051 (s), 1618 (s), 1546 (s), 1505 (s), 1442 (s), 1379 (s), 1272 (s), 741 (s).
δ$_H$ (300 MHz, d6-DMSO)	9.80 (1H, s, N<u>H</u>), 9.77 (1H, s, O<u>H</u>), 7.78 (1H, d, *J* = 9.0 Hz, Ar<u>H</u>), 7.62 (1H, d, *J* = 7.9 Hz, Ar<u>H</u>), 7.50 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 7.28 (1H, d, *J* = 2.3 Hz, Ar<u>H</u>), 7.23 (1H, app t, *J* = 7.7 Hz, Ar<u>H</u>), 7.11 (1H, dd, *J* = 8.8, 2.4 Hz, Ar<u>H</u>), 2.16 (3H, s, C<u>H</u>$_3$).
δ$_C$ (101 MHz, d6-DMSO)	168.7 (<u>C</u>=O), 155.4 (<u>C</u>), 132.1 (<u>C</u>), 129.9 (<u>C</u>), 129.7 (<u>C</u>H), 128.4 (<u>C</u>), 125.2 (<u>C</u>H), 122.5 (<u>C</u>H), 122.0 (<u>C</u>H), 118.5 (<u>C</u>H), 104.4 (<u>C</u>H), 23.3 (<u>C</u>H$_3$).
LRMS (ESI$^+$), m/z	265 ([M+CH$_3$CN+Na]$^+$, 100%).

Physical and spectroscopic data are in accordance with that reported in the literature.[133]

N-(7-Methoxynaphthalen-1-yl)acetamide (2.79)



2.78
$C_{12}H_{11}NO_2$
(201.22)

2.79
$C_{13}H_{13}NO_2$
(215.25)

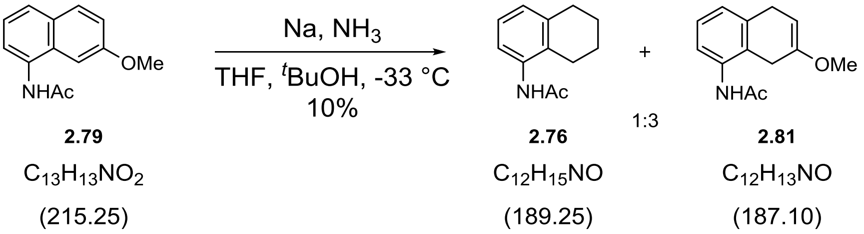
Adapting the procedure of Mewshaw *et al.*[133] To a suspension of phenol **2.78** (1.00 g, 4.97 mmol) in acetone (20 mL) was added K$_2$CO$_3$ (1.72 g, 12.4 mmol) followed by MeI (620 µL, 9.96 mmol). The mixture was then heated at reflux for 1 h then cooled to RT. Purification by flash column chromatography (100% EtOAc) afforded the title compound as a pale brown powder (962 mg, 4.47 mmol, 90%).

MP	178–180 °C (EtOH) [Lit. 175–176 °C (EtOH)].[139]
FTIR (υ$_{max}$ (cm^{-1}))	3270 (m), 2928 (w), 2830 (w), 1536 (m), 1643 (m), 1251 (s), 822 (m).

δ_H (300 MHz, d6-DMSO)	9.82 (1H, s, NH), 7.84 (1H, d, J = 8.7 Hz, ArH), 7.67 (1H, d, J = 7.9 Hz, ArH), 7.66 (1H, d, J = 7.5 Hz, ArH), 7.38 (1H, d, J = 1.9 Hz, ArH), 7.31 (1H, app t, J = 7.9 Hz, ArH), 7.19 (1H, dd, J = 9.0, 2.3 Hz, ArH), 3.90 (3H, s, OCH_3), 2.19 (3H, s, CH_3).
δ_C (75 MHz, d6-DMSO)	168.8 (C=O), 157.3 (C), 132.6 (C), 129.8 (CH), 129.2 (C), 128.8 (C), 124.8 (CH), 123.0 (CH), 122.1 (CH), 118.2 (CH), 101.6 (CH), 55.2 (CH_3), 23.6 (CH_3).
LRMS (ESI$^+$), m/z	279 ($[M+CH_3CN+Na]^+$, 100%).

Physical and spectroscopic data are in accordance with that reported in the literature.[133]

***N*-(5,6,7,8-Tetrahydronaphthalen-1-yl)acetamide (2.76) and *N*-(7-methoxy-5,8-dihydronaphthalen-1-yl)acetamide (2.81)**



Following the procedure of Rogers *et al.*[68] To a suspension of naphthylamide **2.79** (555 mg, 2.58 mmol) in THF (8 mL) were added ^{t}BuOH (0.5 mL) and NH_3 (*ca.* 20 mL). Na (120 mg, 5.22 mg-atom) was added portionwise to the refluxing solution over a period of 15 min, followed by additional ^{t}BuOH (0.5 mL) and EtOH (1 mL). The reaction was then quenched with sat. NH_4Cl (7 mL) and the NH_3 was allowed to evaporate after which H_2O (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatograpy (5–50% EtOAc/CH_2Cl_2) afforded the title compound as a white solid (50 mg, 0.26 mmol, 10%) along with product **2.76** as a pale brown solid (158 mg, 0.84 mmol, 33%).

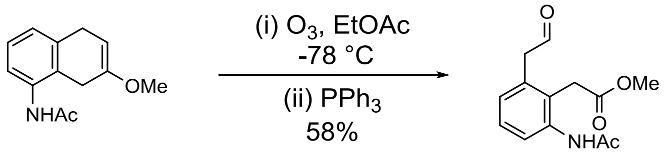
Data for **2.81**:

MP	154–159 °C (CH_2Cl_2/petroleum ether) [Lit. 151–152 °C].[140]
FTIR (υ_{max} (cm^{-1}))	3272 (m), 2930 (m), 1654 (s), 1534 (s).
δ_H (300 MHz, $CDCl_3$)	7.61 (1H, d, *J* = 7.7 Hz, ArH), 7.13 (1H, t, *J* = 7.7 Hz, ArH), 6.3 (1H, d, *J* = 7.7 Hz, ArH), 2.79 (2H, t, *J* = 5.9 Hz, CH_2), 2.60 (2H, t, *J* = 5.9, CH_2), 2.21 (3H, s, CH_3), 1.90–1.71 (4H, m, CH_2CH_2).
δ_C (101 MHz, $CDCl_3$)	168.2 (C=O), 138.1 (C), 135.3 (C), 126.4 (CH), 128.5 (C), 125.8 (CH), 120.9 (CH), 29.8 (CH_2), 24.5 (CH_2), 24.3 (CH_3), 22.8 (CH_2), 22.5 (CH_2).
LRMS (ESI$^+$), m/z	253 ([M+CH_3CN+Na]$^+$, 100%).

Physical and spectroscopic data are in accordance with that reported in the literature.[140]

Data for **2.76** are reported on pages 116 and 117.

Methyl 2-(2-acetamido-6-(2-oxoethyl)phenyl)acetate (2.82)



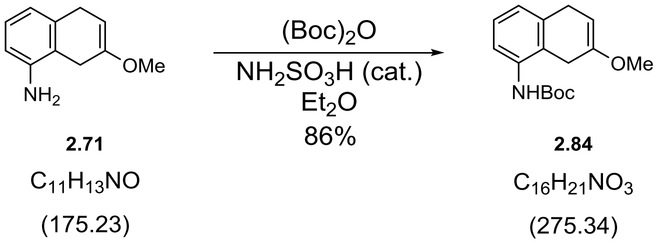
2.76
$C_{13}H_{15}NO_2$
(217.26)

2.82
$C_{13}H_{15}NO_4$
(249.26)

To a solution of alkene **2.76** (100 mg, 0.46 mmol) in EtOAc (100 mL) at -78 °C was bubbled through a stream of O_3 (1–5% in O_2). After the disappearance of the pale yellow colour, the solution was purged with O_2 then polymer-bound PPh_3 (3 mmol/g, 385 mg, 1.15 mmol) was added. After 16 h at RT, the crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (60–100% EtOAc/petrol) afforded the title compound as a yellow oil (67 mg, 0.27 mmol, 58%).

FTIR (υ_{max} (cm^{-1}))	3259 (br), 3017 (w), 2954 (sh), 2843 (w), 1720m (s), 1664 (s), 1526 (m), 1283 (m), 1161 (m).
δ_H (400 MHz, CDCl$_3$)	9.71 (1H, t, *J* = 1.8 Hz, C$\underline{\text{H}}$O), 8.57 (1H, br s, N$\underline{\text{H}}$), 7.77 (1H, d, *J* = 8.1 Hz, Ar$\underline{\text{H}}$), 7.32 (1H, app t, *J* = 7.9 Hz, Ar$\underline{\text{H}}$), 7.05 (1H, d, *J* = 7.6 Hz, Ar$\underline{\text{H}}$), 3.84 (2H, d, *J* = 1.8 Hz, C$\underline{\text{H}}_2$CHO), 3.72 (3H, s, OC$\underline{\text{H}}_3$), 3.63 (2H, s, C$\underline{\text{H}}_2$), 2.23 (3H, s, C$\underline{\text{H}}_3$).
δ_C (101 MHz, CDCl$_3$)	198.5 ($\underline{\text{C}}$HO), 172.5 ($\underline{\text{C}}$=O), 168.8 ($\underline{\text{C}}$=O), 137.6 ($\underline{\text{C}}$), 131.7 ($\underline{\text{C}}$), 128.4 ($\underline{\text{C}}$H), 128.0 ($\underline{\text{C}}$H), 125.8 ($\underline{\text{C}}$), 124.9 ($\underline{\text{C}}$H), 52.7 ($\underline{\text{C}}$H$_3$), 48.8 ($\underline{\text{C}}$H$_2$), 34.2 ($\underline{\text{C}}$H$_2$), 24.3 (($\underline{\text{C}}$H$_3$)$_3$).
LRMS (ESI$^+$), m/z	272 ([M+Na$^+$], 100%).
HRMS, m/z	$C_{13}H_{15}NNaO_4$ [M+Na]$^+$ requires 272.0893; found 272.0896.

tert-Butyl (7-methoxy-5,8-dihydronaphthalen-1-yl)carbamate (2.84)

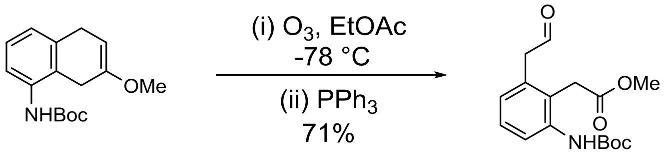


Adapting the procedure of Upadhyaya.[125] To a solution of amine **2.71** (100 mg, 0.57 mmol) in Et$_2$O (2 mL) was added (Boc)$_2$O (130 µL, 0.57 mmol) followed by H$_2$NSO$_3$H (5 mg, 0.05 mmol). After 2 h, the crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexane) afforded the title compound as a pink solid (135 mg, 0.49 mmol, 86%).

MP	90 °C (Et$_2$O/hexane).
FTIR (υ_{max} (cm^{-1}))	3339 (br), 2975 (m), 2936 (m), 1693 (s), 1637 (sh), 1515 (m), 1440 (m), 1227 (m), 1153 (sh).

δ_H (400 MHz, CDCl$_3$)	7.66 (1H, d, *J* = 8.3 Hz, Ar$\underline{H}$), 7.17 (1H, app t, *J* = 7.7 Hz, Ar$\underline{H}$), 6.92 (1H, d, *J* = 7.5 Hz, Ar$\underline{H}$), 6.24 (1H, br s, N$\underline{H}$), 4.83 (1H, m, C$\underline{H}$), 3.64 (3H, s, OC$\underline{H}_3$), 3.58–3.49 (2H, m, C$\underline{H}_2$), 3.28–3.19 (2H, m, C$\underline{H}_2$), 1.53 (9H, s, C(C$\underline{H}_3$)$_3$).
δ_C (101 MHz, CDCl$_3$)	161.5 ($\underline{C}$=O), 153.7 ($\underline{C}$), 133.2 ($\underline{C}$), 131.2 ($\underline{C}$), 128.1 ($\underline{C}$), 124.4 ($\underline{C}$H), 123.8 ($\underline{C}$H), 122.2 ($\underline{C}$H), 90.3 ($\underline{C}$H), 80.2 ($\underline{C}$), 54.9 ($\underline{C}$H$_3$), 29.1 ($\underline{C}$H$_2$), 28.3 (($\underline{C}$H$_3$)$_3$), 27.2 ($\underline{C}$H$_2$).
LRMS (ESI$^+$), m/z	339 ([M+CH$_3$CN+Na]$^+$, 100%).
HRMS, m/z	$C_{16}H_{21}NNaO_3$ [M+Na]$^+$ requires 298.1414; found 298.1415.

Methyl 2-(2-((tert-butoxycarbonyl)amino)-6-(2-oxoethyl)phenyl)acetate (2.85)



2.84
$C_{16}H_{21}NO_3$
(275.34)

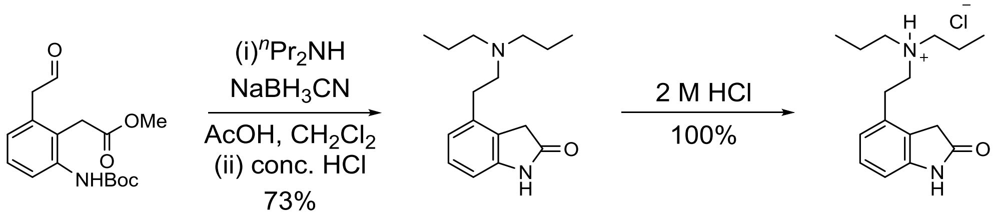
2.85
$C_{16}H_{21}NO_5$
(307.34)

To a solution of alkene **2.84** (200 mg, 0.73 mmol) in EtOAc (100 mL) containing Sudan Red III (2 mg) at -78 °C was bubbled through O_3 (1–5% in O_2). After the disappearance of the pale red colour, the solution was purged with O_2 then PPh$_3$ (478 mg, 1.82 mmol) was added. After 16 h at RT, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (1:1–2:1 Et$_2$O/hexane) afforded the title compound as a yellow oil (160 mg, 0.52 mmol, 71%).

FTIR (υ_{max} (cm^{-1}))	3345 (br), 2978 (sh), 2839 (w), 1718 (s), 1589 (sh), 1514 (m), 1437 (m), 1238 (s), 1156 (s).
δ_H (400 MHz, CDCl$_3$)	9.70 (1H, t, *J* = 2.0 Hz, C$\underline{H}$O), 7.71 (1H, d, *J* = 8.1 Hz, Ar$\underline{H}$), 7.50 (1H, br s, N$\underline{H}$), 7.29 (1H, app t, *J* = 7.8 Hz, Ar$\underline{H}$), 6.99 (1H, d, *J* = 7.6 Hz, Ar$\underline{H}$), 3.82 (2H, d, *J* = 2.0

	Hz, C$\underline{H}_2$CHO), 3.72 (3H, s, OC$\underline{H}_3$), 3.64 (2H, s, C$\underline{H}_2$), 1.53 (9H, s, (C$\underline{H}_3$)$_3$).
δ_C (101 MHz, CDCl$_3$)	198.7 ($\underline{C}$HO), 172.0 ($\underline{C}$=O), 153.5 ($\underline{C}$=O), 138.1 ($\underline{C}$), 131.7 ($\underline{C}$), 128.3 ($\underline{C}$H), 127.0 ($\underline{C}$H), 123.8 ($\underline{C}$H), 125.5 ($\underline{C}$), 80.5 ($\underline{C}$), 52.6 ($\underline{C}$H$_3$), 48.8 ($\underline{C}$H$_2$), 34.1 ($\underline{C}$H$_2$), 28.3 (($\underline{C}$H$_3$)$_3$).
LRMS (ESI$^+$), m/z	330 ([M+Na]$^+$, 100%).
HRMS, m/z	$C_{16}H_{21}NNaO_5$ [M+Na]$^+$ requires 330.1312; found 330.1312.

4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one hydrochloride (1.1)



2.85
$C_{16}H_{21}NO_5$
(307.34)

1.9
$C_{16}H_{24}N_2O$
(260.37)

1.1
$C_{16}H_{25}ClN_2O$
(296.84)

To a solution of aldehyde **2.85** (140 mg, 0.46 mmol) in CH_2Cl_2 (3 mL) was added ^{n}Pr$_2$NH (140 µL, 1.02 mmol) followed after 5 min by AcOH (100 µL). After a furher 10 min, NaBH$_3$CN (70 mg, 1.11 mol) was added and, after 2 h, sat. K_2CO_3 (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were concentrated *in vacuo* (to 10 mL). Concentrated HCl (1 mL) was added and stirred for 16 h after which the reaction was basified with sat. K_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. The crude brown oil was purified by flash column chromatography (0–10% MeOH/CH_2Cl_2) to afford ropinirole **1.9** as a dark orange oil (87 mg, 0.33 mmol, 73%). 2 M HCl in Et$_2$O (1 mL) was added and the precipitate was collected by decantation and dried *in vacuo* to afford the title compound as a yellow solid (99 mg, 0.33 mmol, 100%).

Data for ropinirole **1.9**:

FTIR (υ_{max} (cm^{-1}))	3194 (br), 2957 (m), 2933 (m), 2804 (w), 1702 (s), 1618 (sh), 1606 (sh), 1458 (sh), 1247 (m), 775 (m).
δ_H (400 MHz, $CDCl_3$)	8.32 (1H, br s, $N\underline{H}$), 7.08 (1H, t, *J* = 7.7 Hz, $Ar\underline{H}$), 6.78 (1H, d, *J* = 7.7 Hz, $Ar\underline{H}$), 6.66 (1H, d, *J* = 7.7 Hz, $Ar\underline{H}$), 3.42 (2H, s, $C\underline{H}_2$), 2.65 (4H, br s, $C\underline{H}_2C\underline{H}_2$), 2.53–2.36 (4H, m, $2xNC\underline{H}_2$), 1.44 (4H, app sxt, *J* = 7.5 Hz, $2xC\underline{H}_2$), 0.83 (6H, t, *J* = 7.3 Hz, $2xC\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	177.1 ($\underline{C}$=O), 142.2 ($\underline{C}$), 137.4 ($\underline{C}$), 128.0 ($\underline{C}H$), 124.0 ($\underline{C}$), 122.9 ($\underline{C}H$), 107.3 ($\underline{C}H$), 56.2 ($2x\underline{C}H_2$), 54.3 ($\underline{C}H_2$), 35.0 ($\underline{C}H_2$), 30.9 ($\underline{C}H_2$), 20.4 ($2x\underline{C}H_2$), 11.9 ($2x\underline{C}H_3$).
LRMS (ESI$^+$), m/z	261 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{16}H_{25}N_2O$ $[M+H]^+$ requires 261.1961; found 261.1963.

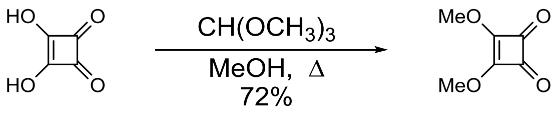
Data for ropinirole HCl **1.1**:

MP	242-245 °C (CH_3CN) [Lit. 241-243 °C (CH_3CN)].[45]
FTIR (υ_{max} (cm^{-1}))	3401 (br), 3194 (br), 2970 (m), 1694 (s), 1619 (sh), 1460 (sh).
δ_H (400 MHz, d6-DMSO)	10.54 (1H, br s, $N\underline{H}$), 10.42 (1H, s, $N\underline{H}$), 7.14 (1H, app t, *J* = 7.8 Hz, $Ar\underline{H}$), 6.85 (1H, d, *J* = 7.7 Hz, $Ar\underline{H}$), 6.72 (1H, d, *J* = 7.7 Hz, $Ar\underline{H}$), 3.55 (2H, s, $C\underline{H}_2$), 3.19 (2H, br s, $NC\underline{H}_2$), 3.11–3.00 (4H, m, $2xNC\underline{H}_2$), 2.99–2.90 (2H, m, $C\underline{H}_2$), 1.70 (4H, app sxt, *J* = 7.5 Hz, $2xC\underline{H}_2$), 0.92 (6H, t, *J* = 7.3 Hz, $2xC\underline{H}_3$).
δ_C (101 MHz, d6-DMSO)	176.1 ($\underline{C}$=O), 143.7 ($\underline{C}$), 133.0 ($\underline{C}$), 127.8 ($\underline{C}H$), 125.0 ($\underline{C}$), 121.7 ($\underline{C}H$), 107.8 ($\underline{C}H$), 53.1 ($2x\underline{C}H_2$), 51.6 ($\underline{C}H_2$), 34.6 ($\underline{C}H_2$), 26.8 ($\underline{C}H_2$), 16.4 ($2x\underline{C}H_2$), 10.9 ($2x\underline{C}H_3$).

Physical and spectroscopic data are in accordance with that reported in the literature.[45,57]

5.3 Experimental Procedures for Chapter 4

3,4-Dimethoxycyclobut-3-ene-1,2-dione (4.9)



3.7
$C_4H_2O_4$
(114.06)

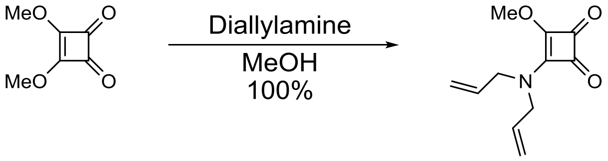
4.9
$C_6H_6O_4$
(142.11)

Following the procedure of Harrowven *et al*.[105] To a suspension of diacid **3.7** (10.0 g, 0.09 mol) in MeOH (100 mL) was added trimethylorthoformate (20 mL, 0.18 mol) which was then heated at reflux for 16 h. The reaction mixture was cooled to RT then concentrated *in vacuo*. Purification by flash column chromatography (20–50% EtOAc/petroleum ether) afforded the title compound as a white solid (9.00 g, 0.063 mol, 72%).

MP	54–55 °C [Lit. 52–54 °C (EtOAc/petroleum ether].[105]
FTIR (υ_{max} (cm^{-1}))	2965 (w), 1811 (sh), 1723 (s), 1589 (s), 1477 (s).
δ_H (400 MHz, $CDCl_3$)	4.34 (6H, s, $2xOC\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	189.0 ($2x\underline{C}$=O), 184.3 ($2x\underline{C}$), 60.9 ($2x\underline{C}H_3$).
LRMS (EI), m/z	142 ($[M]^{\bullet+}$, 100%), 86 ($[M-2x(C=O)]^+$, 41%).

Physical and spectroscopic data are in accordance with that reported in the literature.[105]

3-(Diallylamino)-4-methoxycyclobut-3-ene-1,2-dione (4.1)



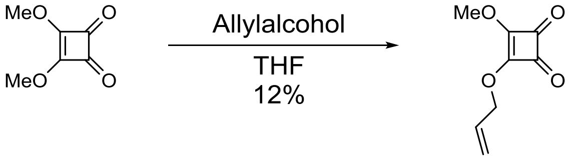
4.9
$C_6H_6O_4$
(142.11)

4.1
$C_{11}H_{13}NO_3$
(207.23)

To a solution of dimethyl squarate **4.9** (1.00 g, 7.03 mmol) in MeOH (20 mL) at 0 °C was added diallylamine (840 µL, 6.80 mmol). The reaction mixture was allowed to warm to RT then concentrated *in vacuo* after 2 h. Purification by flash column chromatography (0–30% EtOAc/hexane) afforded the title compound as a pale yellow oil (1.41 g, 6.81 mmol, 100%).

FTIR (υ_{max} (cm^{-1}))	2946 (w), 1796 (sh), 1707 (m), 1589 (s), 1481 (s).
δ_H (400 MHz, $CDCl_3$)	5.79 (2H, ddt, *J* =16.8, 10.5, 6.1Hz, 2xC<u>H</u>=), 5.34–5.18 (4H, m, 2xC$\underline{H}_2$=), 4.39 (3H, s, OC$\underline{H}_3$), 4.29 (2H, d, *J* = 6.1, NC$\underline{H}_2$), 3.98 (2H, d, *J* = 6.1, NC$\underline{H}_2$).
δ_C (101 MHz, $CDCl_3$)	188.9 (<u>C</u>=O), 182.9 (<u>C</u>=O), 176.8 (<u>C</u>), 171.8 (<u>C</u>), 131.8 (<u>C</u>H), 131.2 (<u>C</u>H), 119.9 ($\underline{C}H_2$), 119.5 ($\underline{C}H_2$), 60.5 ($\underline{C}H_3$), 51.0 ($\underline{C}H_2$), 50.6 ($\underline{C}H_2$).
LRMS (ESI^+), m/z	271 ($[M+CH_3CN+Na]^+$, 100%).
HRMS, m/z	$C_{11}H_{13}NNaO_3$ $[M+Na]^+$ requires 230.0788; found 230.0789.

3-(Allyloxy)-4-methoxycyclobut-3-ene-1,2-dione (4.12)



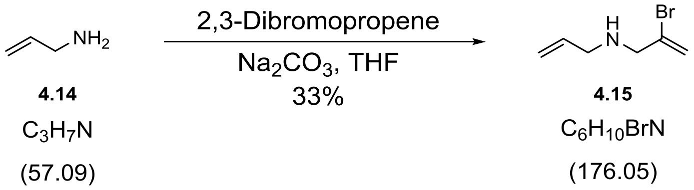
4.9
$C_6H_6O_4$
(142.11)

4.12
$C_8H_8O_4$
(168.15)

To a solution of dimethyl squarate **4.9** (300 mg, 2.11 mmol) in THF (3 mL) at 0 °C was added allyl alcohol (140 µL, 2.06 mmol). The reaction mixture was allowed to warm to RT then concentrated *in vacuo* after 1 week. Purification by flash column chromatography (5–30% EtOAc/petroleum ether) afforded the title compound as a pale yellow oil (42 mg, 0.25 mmol, 12%).

FTIR (υ_{max} (cm^{-1}))	2961 (w), 1811 (sh), 1730 (m), 1591 (s), 1467 (s), 1329 (s).
δ_H (400 MHz, $CDCl_3$)	6.03 (1H, ddt, *J* = 16.9, 10.4, 6.1 Hz, $\mathrm{C\underline{H}}$=), 5.50 (1H, m, $\mathrm{C\underline{H}_aH_b}$=), 5.42 (1H, br dd, *J* = 10.1, 1.0 Hz, $\mathrm{CH_a\underline{H}_b}$=), 5.13 (2H, dt, *J* = 6.1. 1.3 Hz, $\mathrm{OC\underline{H}_2}$), 4.38 (3H, s, $\mathrm{OC\underline{H}_3}$).
δ_C (101 MHz, $CDCl_3$)	189.1 ($\mathrm{\underline{C}}$=O), 189.0 ($\mathrm{\underline{C}}$=O), 184.6 ($\mathrm{\underline{C}}$), 183.9 ($\mathrm{\underline{C}}$), 130.7 ($\mathrm{\underline{C}H}$), 121.4 ($\mathrm{\underline{C}H_2}$), 74.2 ($\mathrm{\underline{C}H_2}$), 60.9 ($\mathrm{\underline{C}H_3}$).
LRMS (ESI$^+$), m/z	191 ([M+Na]$^+$, 29%), 153 (100%).
HRMS, m/z	$C_8H_9O_4$ [M+H]$^+$ requires 169.0495; found 169.0495.

N-Allyl-2-bromoprop-2-en-1-amine (4.15)



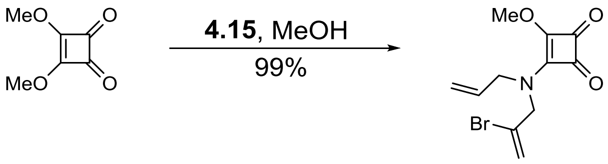
To a solution of 2,3-dibromopropene (1 mL, 9.90 mmol) in THF (10 mL) at 0 °C were added Na_2CO_3 (1.06 g, 10.0 mmol) and allylamine **4.14** (750 µL, 10.0 mmol). The reaction mixture was allowed to warm to RT over 10 min and after a further 16 h was filtered, washed with Et_2O and concentrated *in vacuo*. Purification by distillation (53–55 °C at 10 mbar) afforded the title compound as a colourless oil (581 mg, 3.30 mmol, 33%).

FTIR (υ_{max} (cm^{-1}))	3319 (br), 2914 (w), 2821 (w), 1628 (sh), 1456 (m) 1105 (m), 899 (s).
δ_H (400 MHz, $CDCl_3$)	5.90 (1H, ddt, *J* = 17.2, 10.2, 5.9 Hz, $\mathrm{C\underline{H}}$=), 5.79 (1H, dd, *J* = 1.8, 1.0 Hz, $\mathrm{C\underline{H}_aH_b}$=CBr), 5.58 (1H, d, *J* = 1.8 Hz, $\mathrm{CH_a\underline{H}_b}$=CBr), 5.21 (1H, app dq, *J* = 17.2, 1.7 Hz, $\mathrm{C\underline{H}_aH_b}$=), 5.13 (1H, app dq, *J* = 10.2, 1.5 Hz, $\mathrm{CH_a\underline{H}_b}$=), 3.47 (2H, s, $\mathrm{NC\underline{H}_2CBr}$), 3.23 (2H, dt, *J* = 6.1, 1.3 Hz, $\mathrm{NC\underline{H}_2}$), 1.55 (1H, br s, $\mathrm{N\underline{H}}$).

δ_C (101 MHz, $CDCl_3$)	136.2 ($\underline{C}$H), 133.3 ($\underline{C}$Br), 117.7 ($\underline{C}H_2$), 116.4 ($\underline{C}H_2$), 56.6 ($\underline{C}H_2$), 50.2 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	219 ([M{^{81}Br}+CH_3CN+H]$^+$, 99%), 217 ([M{^{79}Br}+CH_3CN+H]$^+$, 100%).
HRMS, m/z	$C_6H_{11}{}^{79}BrN$ [M{^{79}Br}+H]$^+$ requires 176.0069; found 176.0069.

Physical and spectroscopic data are in accordance with that reported in the literature.[141]

3-(Allyl(2-bromoallyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (4.16)



4.9
$C_6H_6O_4$
(142.11)

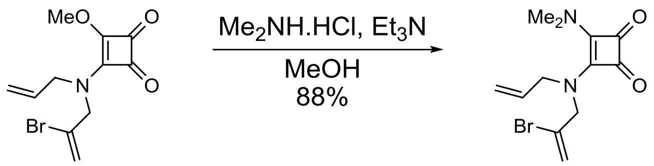
4.16
$C_{11}H_{12}BrNO_3$
(286.12)

To a solution of dimethyl squarate **4.9** (460 mg, 3.24 mmol) in MeOH (4 mL) at 0 °C was added a solution of amine **4.15** (560 mg, 3.18 mmol) in MeOH (2 mL). After 1 h, the reaction mixture was allowed to warm to RT then concentrated *in vacuo* after a further 2 h. Purification by flash column chromatography (5–20% EtOAc/hexane) afforded the title compound as a pale yellow oil (900 mg, 3.16 mmol, 99%).

FTIR (υ_{max} (cm^{-1}))	2945 (w), 1798 (sh), 1709 (s), 1588 (s), 1478 (s), 920 (m).
δ_H (400 MHz, d6-DMSO)	6.09 (1H, br s, $C\underline{H}_aH_b$=CBr), 5.88 (1H, ddt, *J* = 17.2, 10.2, 6.0 Hz, C$\underline{H}$=), 5.77 (1H, d, 2 *J* = 5 Hz, $CH_a\underline{H}_b$=CBr) 5.34–5.22 (2H, m, $C\underline{H}_2$=), 4.50 & 4.23 (2H, 2xs, $NC\underline{H}_2CBr$), 4.31 (3H, s, $OC\underline{H}_3$), 4.20 & 3.95 (2H, 2xd, 2x*J* = 5.6 Hz, $NC\underline{H}_2$).
δ_C (101 MHz, $CDCl_3$)	188.2 & 188.1 ($\underline{C}$=O), 182.4 ($\underline{C}$=O), 177.2 & 177.0 ($\underline{C}$), 171.9 & 171.7 ($\underline{C}$), 132.2 & 131.6 ($\underline{C}$H), 127.4 & 126.7

	($\underline{C}$Br), 122.0 & 121.7 ($\underline{C}H_2$), 119.3 & 119.2 ($\underline{C}H_2$), 60.6 ($\underline{C}H_3$), 55.9 & 55.0 ($\underline{C}H_2$), 50.8 & 50.1 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	329 ([M{^{81}Br}+CH_3CN+H]$^+$, 100%), 327 ([M{^{79}Br}+CH_3CN+H]$^+$, 100%).
HRMS, m/z	$C_{11}H_{12}{}^{79}BrNNaO_3$ [M{^{79}Br}+Na]$^+$ requires 307.9893; found 307.9891.

3-(Allyl(2-bromoallyl)amino)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (4.18)



4.16
$C_{11}H_{12}BrNO_3$
(286.13)

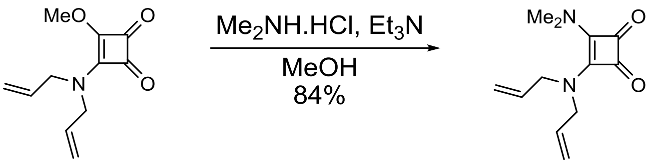
4.18
$C_{12}H_{15}BrN_2O_2$
(299.16)

To a solution of squaramate **4.16** (470 mg, 1.64 mmol) in MeOH (4 mL) at 0 °C was added a suspension of $Me_2NH.HCl$ (275 mg, 3.37 mmol) and Et_3N (480 µL, 3.44 mmol) in MeOH (1 mL). The reaction mixture was allowed to warm to RT then concentrated *in vacuo* after 16 h. Purification by flash column chromatography (50–100% EtOAc/hexane) afforded the title compound as a yellow solid (434 mg, 1.45 mmol, 88%).

MP	49–50 °C (EtOAc/hexane).
FTIR (υ_{max} (cm^{-1}))	2930 (w), 1783 (sh), 1680 (m), 1574 (s), 1500 (s), 1400 (m).
δ_H (400 MHz, $CDCl_3$)	5.87 (1H, br d, *J* = 2.0 Hz, $C\underline{H}_aH_b$=CBr), 5.80 (1H, ddt, *J* = 16.8, 10.5, 5.8 Hz, CH=), 5.69 (1H, d, *J* = 2.0 Hz, $CH_a\underline{H}_b$=CBr), 5.33 (1H, br dd, *J* = 10.5, 1.3 Hz, $C\underline{H}_cH_d$=), 5.28 (1H, dd, *J* = 16.8, 1.3 Hz, $CH_c\underline{H}_d$=), 4.41 (2H, br s, $NC\underline{H}_2$CBr), 4.11 (2H, d, *J* = 5.8 Hz, $NC\underline{H}_2$), 3.25 (6H, s, 2x$NC\underline{H}_3$).

δ_C (101 MHz, $CDCl_3$)	185.0 (C=O), 183.7 (C=O), 169.9 (C), 168.6 (C), 131.6 (CH), 128.2 (CBr), 119.9 (CH_2), 119.9 (CH_2) 56.3 (CH_2), 52.9 (CH_2), 41.0 (2xCH_3).
LRMS (ESI^+), m/z	364 ($[M\{^{81}Br\}+CH_3CN+Na]^+$, 100%), 362 ($[M\{^{79}Br\}+CH_3CN+Na]^+$, 100%).
HRMS, m/z	$C_{12}H_{16}{}^{79}BrN_2O_2$ $[M\{^{79}Br\}+H]^+$ requires 299.0390; found 299.0392.

3-(Diallylamino)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (4.20)



4.1
$C_{11}H_{13}O_3$
(207.23)

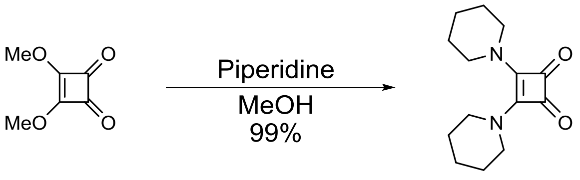
4.20
$C_{12}H_{16}N_2O_2$
(220.27)

To a solution of squaramate **4.1** (174 mg, 0.84 mmol) in MeOH (3 mL) at 0 °C was added a suspension of $Me_2NH.HCl$ (65 mg, 0.79 mmol) and Et_3N (110 µL, 0.79 mmol) in MeOH (1 mL). The reaction mixture was allowed to warm to RT then concentrated *in vacuo* after 16 h. Purification by flash column chromatography (50–100% EtOAc/hexane) afforded the title compound as a white solid (147 mg, 0.67 mmol, 84%).

MP	83–85 °C (EtOAc/hexane).
FTIR (υ_{max} (cm^{-1}))	2931 (w), 1783 (m), 1680 (m), 1584 (s), 1513 (s), 1408 (m).
δ_H (400 MHz, $CDCl_3$)	5.82 (2H, ddt, *J* = 17.0, 10.5, 5.4 Hz, 2xCH=), 5.31 (2H, app dq, *J* = 10.1, 1.3 Hz, 2xCH_aH_b=), 5.26 (2H, app dq, *J* = 17.2, 1.3 Hz, 2xCH_aH_b=), 4.14 (4H, app dt, *J* = 5.6, 1.5 Hz, 2xNCH_2), 3.24 (6H, s, 2xNCH_3).
δ_C (101 MHz, $CDCl_3$)	184.5 (C=O), 183.8 (C=O), 169.5 (C), 169.0 (C), 132.2 (2xCH), 119.1 (2xCH_2), 52.1 (2xCH_2), 41.1 (2xCH_3).

LRMS (ESI$^+$), m/z	284 ([M+CH_3CN+Na]$^+$, 100%).
HRMS, m/z	$C_{12}H_{17}N_2O_2$ [M+H]$^+$ requires 221.1285; found 221.1285.

3,4-Di(piperidin-1-yl)cyclobut-3-ene-1,2-dione (4.22)



4.9 $C_6H_6O_4$ (142.11)

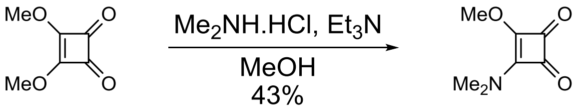
4.22 $C_{14}H_{20}N_2O_2$ (248.32)

To a solution of dimethyl squarate **4.9** (1.00 g, 7.03 mmol) in MeOH (50 mL) at 0 °C was added piperidine (1.7 mL, 17.2 mmol). The solution was allowed to warm to RT then concentrated *in vacuo* after 14 h. Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded the title compound as an off-white solid (1.73 g, 6.97 mmol, 99%).

MP	193–195 °C (EtOAc/hexane) [Lit. 156–157 °C (dioxane)].[142]
FTIR (υ_{max} (cm^{-1}))	2933 (sh), 2861 (sh), 1778 (m), 1658 (sh), 1580 (s), 1534 (s).
δ_H (400 MHz, $CDCl_3$)	3.56 (8H, br s, 4xNC$\underline{H}_2$), 1.68 (12H, br s, 2x(C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$)).
δ_C (101 MHz, $CDCl_3$)	184.5 (2x$\underline{C}$=O), 168.2 (2x$\underline{C}$), 49.6 (4x$\underline{C}H_2$), 26.0 (4x$\underline{C}H_2$), 23.6 (2x$\underline{C}H_2$).
LRMS (ESI$^+$), m/z	249 ([M+H]$^+$, 100%).
HRMS, m/z	$C_{14}H_{21}N_2O_2$ [M+H]$^+$ requires 249.1598; found 249.1602.

Physical and spectroscopic data are in accordance with that reported in the literature.[142]

3-(Dimethylamino)-4-methoxycyclobut-3-ene-1,2-dione (4.23)



4.9 $C_6H_6O_4$ (142.11)

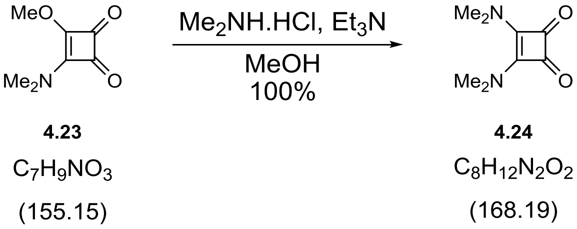
4.23 $C_7H_9NO_3$ (155.15)

To a solution of dimethyl squarate **4.9** (300 mg, 2.11 mmol) in MeOH (10 mL) at 0 °C was added a suspension of $Me_2NH.HCl$ (430 mg, 5.27 mmol) and Et_3N (740 µL, 5.31 mmol) in MeOH (5 mL). The reaction mixture was allowed to warm to RT over 15 min then concentrated *in vacuo* after a further 30 min. Purification by flash column chromatography (50–100% EtOAc/hexane) afforded the title compound as a white solid (140 mg, 0.90 mmol, 43%).

MP	173–175 °C.
FTIR (υ_{max} (cm^{-1}))	2940 (w), 1794 (m), 1670 (sh), 1648 (s), 1617 (s), 1454 (s), 1391(sh).
δ_H (400 MHz, $CDCl_3$)	4.38 (3H, s, $OC\underline{H}_3$), 3.33 (3H, s, $NC\underline{H}_3$), 3.13 (3H, s, $NC\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	188.8 ($\underline{C}$=O), 182.5 ($\underline{C}$=O), 176.4 ($\underline{C}$), 172.0 ($\underline{C}$), 60.4 ($\underline{C}H_3$), 39.2 ($\underline{C}H_3$), 38.7 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	219 ([M+CH_3CN+Na]$^+$, 100%).
HRMS, m/z	$C_7H_{10}NO_3$ [M+H]$^+$ requires 156.0655; found 156.0658.

Physical and spectroscopic data are in accordance with that reported in the literature.[143]

3,4-Bis(dimethylamino)cyclobut-3-ene-1,2-dione (4.24)



4.23 $C_7H_9NO_3$ (155.15)

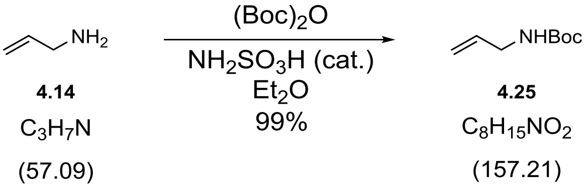
4.24 $C_8H_{12}N_2O_2$ (168.19)

To a solution of squaramate **4.23** (125 mg, 0.81 mmol) in MeOH (8 mL) at 0 °C was added a suspension of $Me_2NH.HCl$ (70 mg, 0.86 mmol) and Et_3N (200 µL, 1.43 mmol) in MeOH (2 mL). The reaction mixture was allowed to warm to RT then concentrated *in vacuo* after 16 h. Purification by flash column chromatography (0.5–3% $MeOH/CH_2Cl_2$) afforded the title compound as a white solid (135 mg, 0.80 mmol, 100%).

MP	227–230 °C.
FTIR (υ_{max} (cm^{-1}))	2881 (w), 1776 (m), 1659 (sh), 1585 (s), 1530 (s).
δ_H (400 MHz, $CDCl_3$)	3.25 (12H, s, 4xNC$\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	184.0 (2x$\underline{C}$=O), 169.1 (2x$\underline{C}$), 41.5 (4x$\underline{C}H_3$).
LRMS (ESI$^+$), m/z	232 ([M+CH_3CN+Na]$^+$, 100%).
HRMS, m/z	$C_8H_{13}N_2O$ [M+H]$^+$ requires 169.0972; found 169.0974.

Physical and spectroscopic data are in accordance with that reported in the literature.[144]

tert-Butyl allylcarbamate (4.25)



4.14 C_3H_7N (57.09)

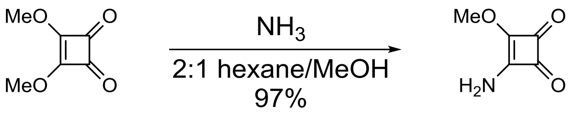
4.25 $C_8H_{15}NO_2$ (157.21)

To a solution of allylamine **4.14** (1 mL, 13.3 mmol) in Et_2O (3 mL) were added $(Boc)_2O$ (2.6 mL, 11.1 mmol) and H_2NSO_3H (65 mg, 0.67 mmol). After 16 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (5–20% Et_2O/hexane) afforded the title compound as white crystals (1.73 g, 11.0 mmol, 99%).

MP	32–33 °C [Lit. 33–35 °C].[145]
FTIR (υ_{max} (cm^{-1}))	3341 (br), 2978 (m), 1690 (s), 1513 (s) 1167 (s).
δ_H (400 MHz, $CDCl_3$)	5.85 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, C$\underline{H}$=), 5.18 (1H, app dq, *J* = 17.2, 1.4 Hz, C$\underline{H}_aH_b$=), 5.11 (1H, app dq, *J* = 10.4, 1.4 Hz, C$H_{\underline{a}}\underline{H}_b$=), 4.59 (1H, br s, N$\underline{H}$), 3.75 (2H, br s, NC$\underline{H_2}$), 1.46 (9H, s, (C$\underline{H}_3$)$_3$).
δ_C (101 MHz, $CDCl_3$)	155.8 ($\underline{C}$=O), 133.9 ($\underline{C}$H), 115.7 ($\underline{C}H_2$), 77.4 ($\underline{C}$), 43.1 ($\underline{C}H_2$), 28.4 (($\underline{C}H_3$)$_3$).
LRMS (EI), m/z	59 ([M-(CH_2=$CHCH_2$)]$^+$, 25%), 57 ([M-(CH_2=$CHCH_2NHCO_2$)]$^+$, 100%), 41 ([M-$NHCO_2C(CH_3)_3$]$^+$, 67%).

Physical and spectroscopic data are in accordance with that reported in the literature.[145]

3-Amino-4-methoxycyclobut-3-ene-1,2-dione (4.27)



4.9 $C_6H_6O_4$ (142.11)

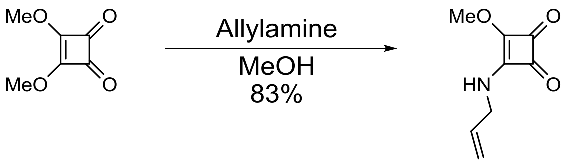
4.27 $C_5H_5NO_3$ (127.03)

Adapting the procedure of Lee *et al.*[146] To a solution of dimethyl squarate **4.9** (450 mg, 3.16 mmol) in 2:1 hexane/MeOH (15 mL) at 0 °C was added NH_3 (450 µL, 7 M in MeOH). After 2 h, the reaction mixture was allowed to warm to RT then concentrated *in vacuo* after a further 16 h. The reaction mixture was filtered and washed with copious amounts of Et_2O to afford the title compound as a yellow solid (390 mg, 3.07 mmol, 97%).

MP	190 °C dec. [Lit. 190 °C dec.].[147]
FTIR (υ_{max} (cm^{-1}))	3324 (m), 3118 (br), 1811 (sh), 1649 (m), 1488 (m). 1396 (m).
δ_H (400 MHz, d6-DMSO)	8.29 (2H, br s, NC$\underline{H}_2$), 4.26 (3H, s, OC$\underline{H}_3$).
δ_C (101 MHz, d6-DMSO)	190.2 ($\underline{C}$=O), 183.2 ($\underline{C}$=O), 178.2 ($\underline{C}$), 174.1 ($\underline{C}$), 59.7 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	189 (100%), 169 ([M+CH_3CN+H]$^+$, 41%).

Physical and spectroscopic data are in accordance with that reported in the literature.[147,148]

3-(Allylamino)-4-methoxycyclobut-3-ene-1,2-dione (4.28)



4.9
$C_6H_6O_4$
(142.11)

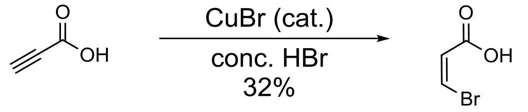
4.28
$C_8H_9NO_3$
(167.16)

To a solution of dimethyl squarate **4.9** (240 mg, 1.69 mmol) in MeOH (5 mL) at 0 °C was added allylamine **4.14** (130 µL, 1.74 mmol). After 1 h, the reaction mixture was allowed to warm to RT then concentrated *in vacuo* after a further 1 h. Purification by flash column chromatography (20–50% EtOAc/hexane) afforded the title compound as a white solid (234 mg, 1.40 mmol, 83%).

MP	110–114 °C.
FTIR (υ_{max} (cm^{-1}))	3279 (br), 2936 (w), 1763 (m), 1572 (s), 1474 (m), 1281 (m).
δ_H (400 MHz, $CDCl_3$)	6.36 (1H, br s, N$\underline{H}$), 5.90 (1H, ddt, *J* = 17.0, 10.3, 5.6 Hz, C$\underline{H}$=), 5.28 (1H, app dq, *J* = 17.1, 1.4 Hz, C$\underline{H}_aH_b$=), 5.26

	(1H, app dq, *J* = 10.2, 1.2 Hz, $CH_{\underline{a}}\underline{H}_{b}$=), 4.40 (3H, s, $OC\underline{H}_3$), 4.33–3.97 (2H, m, $NC\underline{H}_2$).
δ_C (101 MHz, $CDCl_3$)	189.4 ($\underline{C}$=O), 183.1 ($\underline{C}$=O), 177.9 ($\underline{C}$), 172.3 ($\underline{C}$), 132.9 ($\underline{C}H$), 117.8 ($\underline{C}H_2$), 60.5 ($\underline{C}H_3$), 46.9 ($\underline{C}H_2$).
LRMS (ESI^+), m/z	357 ($[2M+Na]^+$, 100%), 231 ($[M+CH_3CN+Na]^+$, 65%).
HRMS, m/z	$C_8H_{10}O_4$ $[M+H]^+$ requires 168.0655; found 168.0655.

(*Z*)-3-Bromoacrylic acid (4.32)



4.31
$C_3H_2O_2$
(70.05)

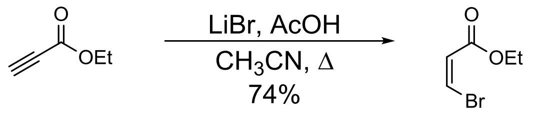
4.32
$C_3H_3BrO_2$
(150.96)

Following the procedure of Heck *et al.*[119] To a solution of CuBr (452 mg, 3.15 mmol) in conc. HBr (9 mL) at 0 °C was added propiolic acid **4.31** (3.40 g, 48.5 mmol). The reaction mixture was allowed to warm to RT and after 26 h was extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a yellow oil (1.50 g, 9.94 mmol, 32%).

FTIR (υ_{max} (cm^{-1}))	3075 (br), 1700 (s), 1611 (s), 1236 (m), 1180 (m), 811 (s).
δ_H (300 MHz, $CDCl_3$)	7.17 (1H, d, *J* = 8.4 Hz, $C\underline{H}Br$=), 6.69 (1H, d, *J* = 8.4 Hz, $C\underline{H}$=).
δ_C (101 MHz, $CDCl_3$)	168.0 ($\underline{C}$=O), 124.2 ($\underline{C}HBr$), 123.7 ($\underline{C}H$).
LRMS (EI), m/z	152 ($[M\{^{81}Br\}]^{\bullet+}$, 100%), 135 ($[M\{^{81}Br\}-OH]^+$, 56%), 71 ($[M-Br]^+$, 62%).

Physical and spectroscopic data are in accordance with that reported in the literature.[119]

Ethyl (*Z*)-3-bromoacrylate (4.34)



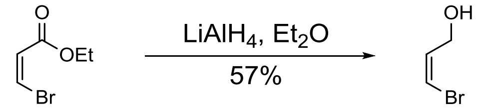
4.33 $C_5H_6O_2$ (98.10) → **4.34** $C_5H_7BrO_2$ (179.01)

Following the procedure of Ma *et al*.[120] To a solution of ester **4.33** (2.5 mL, 24.7 mmol) in CH_3CN (50 mL) were added LiBr (5.55 g, 62.6 mmol) and AcOH (4 mL, 70.0 mmol). The reaction mixture was heated at reflux for 16 h then allowed to cool to RT after which H_2O (10 mL) and sat. K_2CO_3 (5 mL) were added. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a pale yellow oil (3.28 g, 18.3 mmol, 74%).

FTIR (υ_{max} (cm^{-1}))	2983 (w), 1724 (s), 1612 (m), 1205 (s), 1160 (s), 806 (s).
δ_H (400 MHz, $CDCl_3$)	6.99 (1H, d, *J* = 8.6 Hz, C$\underline{H}$Br), 6.62 (1H, d, *J* = 8.6 Hz, C$\underline{H}$), 4.25 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$), 1.33 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	163.9 ($\underline{C}$=O), 124.6 ($\underline{C}$HBr), 121.1 ($\underline{C}$H), 60.8 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$).
LRMS (EI), m/z	152 ([M{^{81}Br}-Et]$^+$, 26%), 135 ([M{^{81}Br}-OEt]$^+$, 100%), 99 ([M-Br]$^+$, 62%).

Physical and spectroscopic data are in accordance with that reported in the literature.[120]

(*Z*)-3-Bromoprop-2-en-1-ol (4.35)



4.34 $C_5H_7BrO_2$ (179.01)

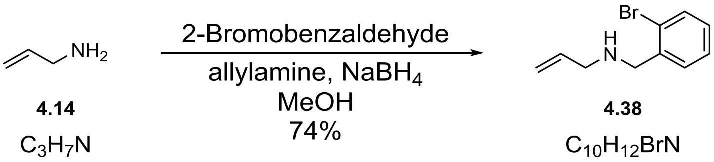
4.35 C_3H_5BrO (136.98)

Following the procedure of Wei and Taylor.[149] To a suspension of $LiAlH_4$ (150 mg, 3.95 mmol) in Et_2O (10 mL) at 0 °C was added a solution of ester **4.34** (1.00 g, 5.59 mmol) in Et_2O (10 mL). After 1 h, H_2O (20 mL) was added and the resultant mixture was filtered and washed with Et_2O (5 mL). The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50% Et_2O/petroleum ether) afforded the title compound as a yellow oil (434 mg, 3.17 mmol, 57%).

FTIR (υ_{max} (cm^{-1}))	3312 (br), 2927 (w), 2872 (w), 1622 (sh), 1453 (w), 1290 (s), 1009 (s), 659 (s).
δ_H (400 MHz, $CDCl_3$)	6.37 (1H, dt, *J* = 7.1, 5.6 Hz, C<u>H</u>=), 6.29 (1H, dt, *J* = 7.1, 1.5 Hz, C<u>H</u>Br), 4.34 (2H, dd, *J* = 5.6, 1.5 Hz, OC<u>H</u>$_2$), 1.68 (1H, br s, O<u>H</u>).
δ_C (101 MHz, $CDCl_3$)	133.9 (<u>C</u>H), 108.9 (<u>C</u>Br), 61.0 (<u>C</u>H$_2$).

Physical and spectroscopic data are in accordance with that reported in the literature.[149]

N-(2-Bromobenzyl)prop-2-en-1-amine (4.38)



4.14 C_3H_7N (57.10)

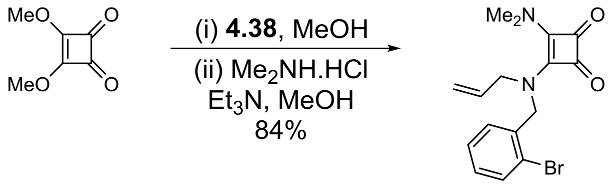
4.38 $C_{10}H_{12}BrN$ (226.11)

To a solution of 2-bromobenzaldehyde **4.37** (600 µL, 5.14 mmol) in MeOH (150 mL) was added allylamine **4.14** (2.2 mL, 29.4 mmol). After 16 h, the solution was cooled to 0 °C and $NaBH_4$ (600 mg, 15.9 mmol) was added, after which it was allowed to warm to RT. After 1 h, H_2O (150 mL) and 2 M HCl (5 mL) were added and the resultant mixture was extracted with CH_2Cl_2 (3 x 30 mL). The aqueous phase was then basified with sat. K_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (860 mg, 3.80 mmol, 74%).

FTIR (υ_{max} (cm^{-1}))	3317 (br), 3067 (w), 2819 (w), 1642 (w), 1567 (w), 1440 (m), 749 (s).
δ_H (400 MHz, $CDCl_3$)	7.55 (1H, dd, *J* = 7.9, 1.0 Hz, Ar$\underline{H}$), 7.40 (1H, dd, *J* = 7.6, 1.5 Hz, Ar$\underline{H}$), 7.30 (1H, m, Ar$\underline{H}$), 7.13 (1H, td, *J* = 7.6, 1.7 Hz, Ar$\underline{H}$), 5.95 (1H, ddt, *J* = 17.2, 10.4, 6.0 Hz, C$\underline{H}$=), 5.23 (1H, app dq, *J* = 17.2, 1.6 Hz, C$\underline{H}_aH_b$=), 5.14 (1H, dq, *J* = 10.3, 1.5 Hz, C$H_a\underline{H}_b$=), 3.88 (2H, s, NC$\underline{H}_2$Ar), 3.29 (2H, dt, *J* = 6.0, 1.3, NC$\underline{H}_2$), 1.58 (1H, br s, N$\underline{H}$).
δ_C (101 MHz, $CDCl_3$)	139.2 ($\underline{C}$), 136.7 ($\underline{C}$H), 132.8 ($\underline{C}$H), 130.3 ($\underline{C}$H), 128.6 ($\underline{C}$H), 127.4 ($\underline{C}$H), 124.0 ($\underline{C}$Br), 116.2 ($\underline{C}H_2$), 53.1 ($\underline{C}H_2$), 51.6 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	228 ([M{^{81}Br}+H]$^+$, 96%), 226 ([M{^{79}Br}+H]$^+$, 100%).
HRMS, m/z	$C_{10}H_{13}{}^{79}BrN$ [M{^{79}Br}+H]$^+$ requires 226.0226; found 226.0231.

Physical and spectroscopic data are in accordance with that reported in the literature.[150]

3-(Allyl(2-bromobenzyl)amino)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (4.39)



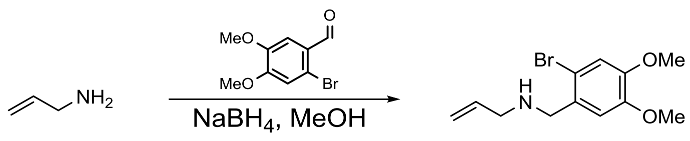
4.9
$C_6H_6O_4$
(142.11)

4.39
$C_{16}H_{17}BrN_2O_2$
(349.22)

To a solution of dimethylsquarate **4.9** (110 mg, 0.77 mmol) in MeOH (5 mL) at 0 °C was added amine **4.38** (193 mg, 0.85 mmol). After 1 h, the reaction mixture was allowed to warm to RT then a suspension of $Me_2NH.HCl$ (120 mg, 1.47 mmol) and Et_3N (200 µL, 1.44 mmol) in MeOH (2 mL) was added. After a further 16 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (10–100% EtOAc/hexane) afforded the title compound as a clear viscous oil (226 mg, 0.65 mmol, 84%).

FTIR (υ_{max} (cm^{-1}))	2930 (w), 1782 (m), 1679 (sh), 1578 (s), 1505 (s).
δ_H (400 MHz, $CDCl_3$)	7.59 (1H, d, *J* = 7.6, Hz, Ar$\underline{H}$), 7.40–7.28 (2H, m, 2xAr$\underline{H}$), 7.20 (1H, app td, *J* = 8.1, 2.0 Hz, Ar$\underline{H}$), 5.86 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, C$\underline{H}$=), 5.31 (1H, dd, *J* = 10.6, 1.0 Hz, C$\underline{H}_aH_b$=), 5.23 (1H, dd, *J* = 17.2, 1.0 Hz, CH$_a\underline{H}_b$=), 4.80 (2H, s, NC$\underline{H}_2$Ar), 4.14 (2H, d, *J* = 5.6 Hz, NC$\underline{H}_2$), 3.17 (6H, s, 2xNC$\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	184.7 ($\underline{C}$=O), 183.8 ($\underline{C}$=O), 169.6 ($\underline{C}$), 169.1 ($\underline{C}$), 134.7 ($\underline{C}$), 133.4 ($\underline{C}$H), 132.0 ($\underline{C}$H), 129.6 ($\underline{C}$H), 129.0 ($\underline{C}$H), 128.0 ($\underline{C}$H), 123.4 ($\underline{C}$Br), 119.4 ($\underline{C}H_2$), 53.7 ($\underline{C}H_2$), 52.7 ($\underline{C}H_2$), 41.0 (2x$\underline{C}H_3$).
LRMS (ESI$^+$), m/z	414 ([M{^{81}Br}+CH_3CN+Na]$^+$, 100%), 412 ([M{^{79}Br}+CH_3CN+Na]$^+$, 96%).
HRMS, m/z	$C_{16}H_{18}{}^{79}BrN_2O_2$ [M{^{79}Br}+H]$^+$ requires 349.0546; found 349.0554.

N-(2-Bromo-4,5-dimethoxybenzyl)prop-2-en-1-amine (4.42)



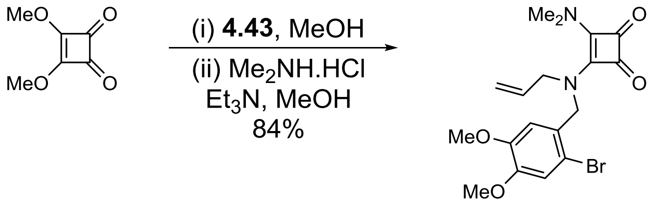
4.14
C_3H_7N
(57.09)

4.42
$C_{12}H_{16}BrNO_2$
(286.16)

To a solution of 2-bromo-4,5-dimethoxybenzaldehyde **4.41** (1.28 g, 5.23 mmol) in MeOH (200 mL) was added allylamine **4.14** (1.1 mL, 14.7 mmol). After 16 h, the solution was cooled to 0 °C and $NaBH_4$ (600 mg, 15.9 mmol) was added. After 1 h, the reaction mixture was allowed to warm to RT then concentrated *in vacuo*. Sat. K_2CO_3 (10 mL) was added and the resultant mixture was extracted with EtOAc (3 x 150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a yellow oil (1.44 g, 5.05 mmol, 97%).

FTIR (υ_{max} (cm^{-1}))	3311 (br), 2933 (w), 1670 (w), 1503 (s), 1208 (s).
δ_H (400 MHz, $CDCl_3$)	7.02 (1H, s, Ar$\underline{H}$), 6.95 (1H, s, Ar$\underline{H}$), 5.95 (1H, ddt, *J* = 17.2, 10.4, 6.1 Hz, C$\underline{H}$=), 5.23 (1H, dd, *J* = 17.2, 1.5 Hz, C$\underline{H}_a$H$_b$=), 5.13 (1H, dd, *J* = 10.4, 1.5 Hz, CH$_a\underline{H}_b$=), 3.88 (3H, s, OC$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$), 3.80 (2H, s, NC$\underline{H}_2$Ar), 3.29 (2H, br d, *J* = 6.1 Hz, NC$\underline{H}_2$), 1.58 (1H, br s, N$\underline{H}$).
δ_C (101 MHz, $CDCl_3$)	148.6 ($\underline{C}$), 148.4 ($\underline{C}$), 136.8 ($\underline{C}$H), 131.3 ($\underline{C}$), 116.1 ($\underline{C}H_2$), 115.5 ($\underline{C}$H), 113.7 ($\underline{C}$Br), 113.1 ($\underline{C}$H), 56.2 ($\underline{C}H_3$), 56.0 ($\underline{C}H_3$), 52.8 ($\underline{C}H_2$), 51.7 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	288 ([M{^{81}Br}+H]$^+$, 100%), 286 ([M{^{81}Br}+H]$^+$, 99%).
HRMS, m/z	$C_{12}H_{17}{}^{79}BrNO_2$ [M{^{81}Br}+H]$^+$ requires 286.0437; found 286.0439.

3-(Allyl(2-bromo-4,5-dimethoxybenzyl)amino)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (4.43)



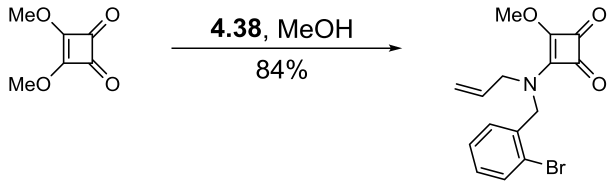
4.9
$C_6H_6O_4$
(142.11)

4.43
$C_{18}H_{21}BrN_2O_4$
(409.27)

To a solution of dimethyl squarate **4.9** (150 mg, 1.05 mmol) in MeOH (5 mL) at 0 °C was added a solution of amine **4.42** (330 mg, 1.16 mmol) in MeOH (2 mL). After 15 min, the reaction mixture was allowed to warm to RT then a suspension of $Me_2NH.HCl$ (115 mg, 1.41 mmol) and Et_3N (250 µL, 1.79 mmol) in MeOH (2 mL) was added. After a further 16 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (50–100% EtOAc/hexane) afforded the title compound as a white solid (363 mg, 0.89 mmol, 84%).

MP	200–202 °C (EtOAc/hexane).
FTIR (υ_{max} (cm^{-1}))	2933 (w), 1782 (sh), 1677 (sh), 1576 (s), 1501 (s).
δ_H (400 MHz, $CDCl_3$)	7.02 (1H, s, Ar$\underline{H}$), 6.90 (1H, s, Ar$\underline{H}$), 5.83 (1H, ddt, *J* = 17.1, 10.5, 5.4 Hz, C$\underline{H}$=), 5.31 (1H, dd, *J* = 10.6, 1.0 Hz, $C\underline{H}_aH_b$=), 5.24 (1H, dd, *J* = 17.2, 1.0 Hz, $CH_a\underline{H}_b$=), 4.77 (2H, s, $NC\underline{H}_2Ar$), 4.06 (2H, br d, *J* = 5.1 Hz, $NC\underline{H}_2$), 3.86 (3H, s, $OC\underline{H}_3$), 3.83 (3H, s, $OC\underline{H}_3$), 3.19 (6H, s, $2xNC\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	184.6 ($\underline{C}$=O), 183.9 ($\underline{C}$=O), 169.8 ($\underline{C}$), 169.0 ($\underline{C}$), 149.3 ($\underline{C}$), 148.8 ($\underline{C}$), 132.1 ($\underline{C}$H), 126.6 ($\underline{C}$), 118.9 ($\underline{C}H_2$), 115.8 ($\underline{C}$H), 113.8 ($\underline{C}$Br), 112.5 ($\underline{C}$H), 56.21 ($\underline{C}H_3$), 56.17 ($\underline{C}H_3$), 53.0 ($\underline{C}H_2$), 52.6 ($\underline{C}H_2$), 41.0 ($2x\underline{C}H_3$).
LRMS (ESI^+), m/z	411 ($[M\{^{81}Br\}+ Na]^+$, 100%), 409 ($[M\{^{79}Br\}+ Na]^+$, 63%).
HRMS, m/z	$C_{18}H_{22}{}^{79}BrN_2O_4$ $[M\{^{79}Br\}+H]^+$ requires 409.0757; found 409.0763.

3-(Allyl(2-bromobenzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (4.46)



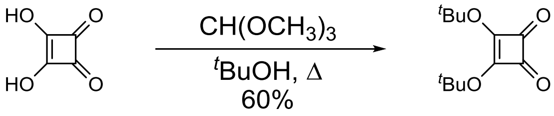
4.9 $C_6H_6O_4$ (142.11)

4.46 $C_{15}H_{14}BrNO_3$ (336.19)

To a solution of dimethyl squarate **4.9** (250 mg, 1.76 mmol) in MeOH (30 mL) at 0 °C was added a solution of amine **4.38** (400 mg, 1.77 mmol) in MeOH (5 mL). After 30 min, the reaction mixture was allowed to warm to RT then concentrated *in vacuo* after a further 8 h. Purification by flash column chromatography (30% EtOAc/hexane) afforded the title compound as viscous clear oil (546 mg, 1.62 mmol, 92%).

FTIR (υ_{max} (cm^{-1}))	2945 (w), 1798 (m), 1708 (sh), 1593 (s), 1482 (sh).
δ_H (400 MHz, $CDCl_3$)	7.58 (1H, m, ArH), 7.39–7.27 (2H, m, 2xArH), 7.20 (1H, m, ArH), 5.75 (1H, m, CH=), 5.27 (1H, d, *J* = 10.1 Hz, CH_aH_b=), 5.21 & 5.19 (1H, 2xd, *J* = 17.1 Hz, CH_aH_b=), 5.03 & 4.70 (2H, 2xbr s, NCH_2Ar), 4.41 & 4.38 (3H, 2xs, OCH_3), 4.18 & 3.86 (2H, 2xd, *J* = 5.4 Hz, NCH_2).
δ_C (101 MHz, $CDCl_3$)	188.6 & 188.3 (C=O), 183.1 & 182.9 (C=O), 177.0 & 176.8 (C), 172.4 & 172.2 (C), 134.2 & 133.7 (C), 133.4 & 133.3 (CH), 131.4 & 130.9 (CH), 130.5 & 129.6 (CH), 129.9 (CH), 127.9 (CH), 124.0 &123.6 (CBr), 120.0 & 119.4 (CH_2), 60.6 (CH_3), 52.2 & 51.4 (CH_2), 51.0 & 50.4 (CH_2).
LRMS (ESI^+), m/z	338 ($[M\{^{81}Br\}+H]^+$, 97%), 336 ($[M\{^{79}Br\}+H]^+$, 100%).
HRMS, m/z	$C_{15}H_{15}{}^{79}BrNO_3$ $[M\{^{79}Br\}+H]^+$ requires 336.0230; found 336.0232.

3,4-Di-*tert*-butoxycyclobut-3-ene-1,2-dione (4.59)



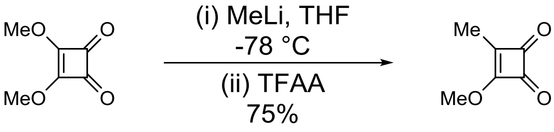
3.7 $C_4H_2O_4$ (114.06) → **4.59** $C_{12}H_{18}O_4$ (226.27)

Following the procedure of Moore *et al*.[151] To a suspension of squaric acid **3.7** (10.0 g, 87.6 mmol) in ^{t}BuOH (240 mL) at reflux was added trimethylorthoformate (90 mL) over a period of 1 h. The distillate was collected over a period of 3 h after which the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexane) afforded the title compound as a white solid (11.8 g, 52.2 mmol, 60%).

MP	105–106 °C [Lit. 103–104 °C].[151]
FTIR (υ_{max} (cm^{-1}))	2981 (w), 1802 (sh), 1722 (s), 1569 (s), 1368 (s), 1137 (s).
δ_H (400 MHz, CDCl$_3$)	1.62 (18H, s, 2x(C$\underline{H}_3$)$_3$).
δ_C (101 MHz, CDCl$_3$)	188.6 (2x$\underline{C}$=O), 186.3 (2x$\underline{C}$), 87.0 (2x$\underline{C}$), 28.7 (2x($\underline{C}H_3$)$_3$).
LRMS (ESI$^+$), m/z	290 ([M+CH$_3$CN+Na]$^+$, 100%).
HRMS, m/z	$C_{12}H_{18}NaO_4$ [M+Na]$^+$ requires 249.1097; found 249.1102.

Physical and spectroscopic data are in accordance with that reported in the literature.[151]

3-Methoxy-4-methylcyclobut-3-ene-1,2-dione (4.61)



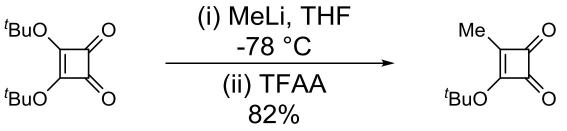
4.9 $C_6H_6O_4$ (142.11) → **4.61** $C_6H_6O_3$ (126.11)

Following the procedure of Moore *et al*.[152] To a solution of dimethyl squarate **4.9** (1.00 g, 7.03 mmol) in THF (30 mL) at -78 °C was added MeLi (1.46 M, 4.8 mL, 7.01 mmol). After 20 min, TFAA was added (1.2 mL, 8.51 mmol) and after a further 15 min, the reaction mixture was removed from the cooling bath. After 5 min, sat. K_2CO_3 (5 mL) and H_2O (20 mL) were added and the resultant mixture was extracted with Et_2O (3 x 150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (20–50% EtOAc/hexane) afforded the title compound as a pale yellow solid (668 mg, 5.30 mmol, 75%).

MP	47–49 °C [Lit. 47–48 °C (Et_2O/hexane)].[152]
FTIR (υ_{max} (cm^{-1}))	2961 (w), 1803 (m), 1752 (s), 1594 (s), 1345 (m).
δ_H (400 MHz, $CDCl_3$)	4.42 (3H, s, $OC\underline{H}_3$), 2.22, (3H, s, $C\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	199.2 ($\underline{C}$=O), 195.4 ($\underline{C}$=O), 193.8 ($\underline{C}$), 180.2 ($\underline{C}$), 60.9 ($\underline{C}H_3$), 9.5 ($\underline{C}H_3$).
LRMS (EI), m/z	126 ($[M]^{\bullet+}$, 13%), 100%), 98 ($[M-(C=O)]^+$, 50%), 83 ($[M-(C=O)-Me]^+$.

Physical and spectroscopic data are in accordance with that reported in the literature.[124,152]

3-(*tert*-Butoxy)-4-methylcyclobut-3-ene-1,2-dione (4.62)



4.59
$C_{12}H_{18}O_4$
(226.27)

4.62
$C_9H_{12}O_3$
(168.19)

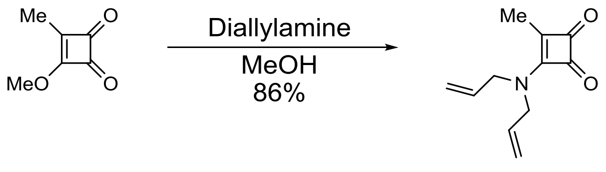
Following the procedure of Moore *et al*.[153] To a solution of squarate **4.59** (5.00 g, 22.1 mmol) in THF (200 mL) at -78 °C was added MeLi (1.5 M, 17 mL, 25.5 mmol). After 1 h, TFAA was added and the resultant solution was allowed to warm to RT. After a further 1 h, sat. NH_4Cl (5 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x

200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (5–15% EtOAc/hexane) afforded the title compound as a white solid (3.04 g, 18.1 mmol, 82%).

MP	69–70 °C (EtOAc/hexane) [Lit. 72–73 °C].[153]
FTIR (υ_{max} (cm^{-1}))	2982 (w), 1794 (s), 1741 (s), 1574 (s), 1373 (m), 1152 (sh).
δ_H (400 MHz, $CDCl_3$)	2.18 (3H, s, C$\underline{H}_3$), 1.61, (9H, s, (C$\underline{H}_3$)$_3$).
δ_C (101 MHz, $CDCl_3$)	200.0 ($\underline{C}$=O), 196.3 ($\underline{C}$=O), 192.5 ($\underline{C}$), 182.6 ($\underline{C}$), 87.7 ($\underline{C}$), 28.7 (($\underline{C}H_3$)$_3$), 9.3 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	232 ([M+CH_3CN+Na]$^+$, 100%).

Physical and spectroscopic data are in accordance with that reported in the literature.[153]

3-(Diallylamino)-4-methylcyclobut-3-ene-1,2-dione (4.63)



4.61
$C_6H_6O_3$
(126.11)

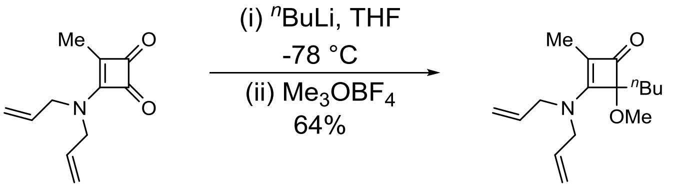
4.63
$C_{11}H_{13}NO_2$
(191.23)

To a solution of cyclobutendione **4.61** (300 mg, 2.38 mmol) in MeOH (5 mL) at 0 °C was added diallylamine **4.14** (210 µL, 1.70 mmol). The reaction mixture was allowed to warm to RT then concentrated *in vacuo* after 2 h. Purification by flash column chromatography (15–35% EtOAc/hexane) afforded the title compound as a yellow oil (298 mg, 1.47 mmol, 86%).

FTIR (υ_{max} (cm^{-1}))	2927 (w), 1780 (sh), 1731 (s), 1582 (s), 1433 (s).

δ_H (400 MHz, $CDCl_3$)	5.90–5.77 (2H, m, 2xC$\underline{H}$=), 5.39–5.20 (4H, m, 2xC$\underline{H}_2$=), 4.37 (2H, d, *J* = 6.1, NC$\underline{H}_2$), 4.00 (2H, d, *J* = 5.1, NC$\underline{H}_2$), 2.26 (3H, s, C$\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	192.6 ($\underline{C}$=O), 191.9 ($\underline{C}$=O), 183.6 ($\underline{C}$), 167.0 ($\underline{C}$), 131.9 ($\underline{C}$H), 131.2 ($\underline{C}$H), 120.0 ($\underline{C}H_2$), 118.7 ($\underline{C}H_2$), 51.9 ($\underline{C}H_2$), 51.5 ($\underline{C}H_2$), 10.5 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	255 ([M+CH_3CN+Na]$^+$, 100%).
HRMS, m/z	$C_{11}H_{14}NO_3$ [M+H]$^+$ requires 192.1019; found 192.1021.

4-Butyl-3-(diallylamino)-4-methoxy-2-methylcyclobut-2-en-1-one (4.64)



4.63
$C_{11}H_{13}NO_2$
(191.23)

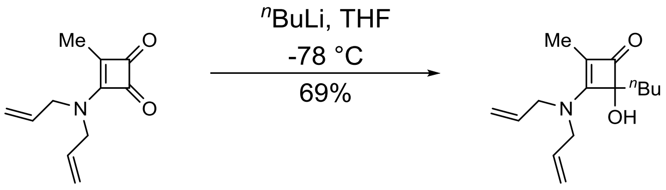
4.64
$C_{16}H_{25}NO_2$
(263.38)

To a solution of mono-squaramide **4.63** (175 mg, 0.86 mmol) in THF (30 mL) at -78 °C was added ^{n}BuLi (2.23 M, 330 µL, 0.76 mmol). After 30 min, the resultant solution was cannulated into a suspension of Me_3OBF_4 (140 mg, 0.95 mmol) in THF (20 mL) at -78 °C. After a further 1 h, sat. K_2CO_3 (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (20–50% EtOAc/hexane) afforded the title compound as a yellow oil (128 mg, 0.49 mmol, 64%).

FTIR (υ_{max} (cm^{-1}))	2931 (m), 1746 (sh), 1588 (s), 1435 (s).
δ_H (400 MHz, $CDCl_3$)	5.90–5.70 (2H, m, 2xC$\underline{H}$=), 5.35–5.23 (4H, m, 2xC$\underline{H}_2$=), 4.10–4.00 (2H, m, NC$\underline{H}_2$), 3.95–3.86 (2H, m, NC$\underline{H}_2$), 3.31 (3H, s, OC$\underline{H}_3$), 1.75 (3H, s, C$\underline{H}_3$), 1.71–1.55 (2H, m, C$\underline{H}_2$), 1.41–1.19 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 0.89 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$).

δ_C (101 MHz, CDCl$_3$)	189.2 (C=O), 170.9 (C), 132.2 (CH), 132.2 (CH), 119.3 (CH$_2$), 118.4 (CH$_2$), 115.1 (C), 96.5 (C), 52.2 (CH$_3$), 51.8 (CH$_2$), 50.7 (CH$_2$), 33.1 (CH$_2$), 27.1 (CH$_2$), 22.9 (CH$_2$), 13.9 (CH$_3$), 6.9 (CH$_3$).
LRMS (ESI$^+$), m/z	327 ([M+CH$_3$CN+Na]$^+$, 100%).
HRMS, m/z	C$_{16}$H$_{26}$NO$_2$ [M+H]$^+$ requires 264.1958; found 264.1959.

4-Butyl-3-(diallylamino)-4-hydroxy-2-methylcyclobut-2-en-1-one (4.65)



4.63 C$_{11}$H$_{13}$NO$_2$ (191.23)

4.65 C$_{15}$H$_{23}$NO$_2$ (249.35)

To a solution of mono-squaramide **4.63** (285 mg, 1.40 mmol) in THF (10 mL) at -78 °C was added ^{n}BuLi (2.3 M, 550 µL, 1.26 mmol). After 30 min, sat. NH$_4$Cl (2 mL) was added and the resultant mixture was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (20–50% EtOAc/hexane) afforded the title compound as an off-white solid (217 mg, 0.87 mmol, 69%).

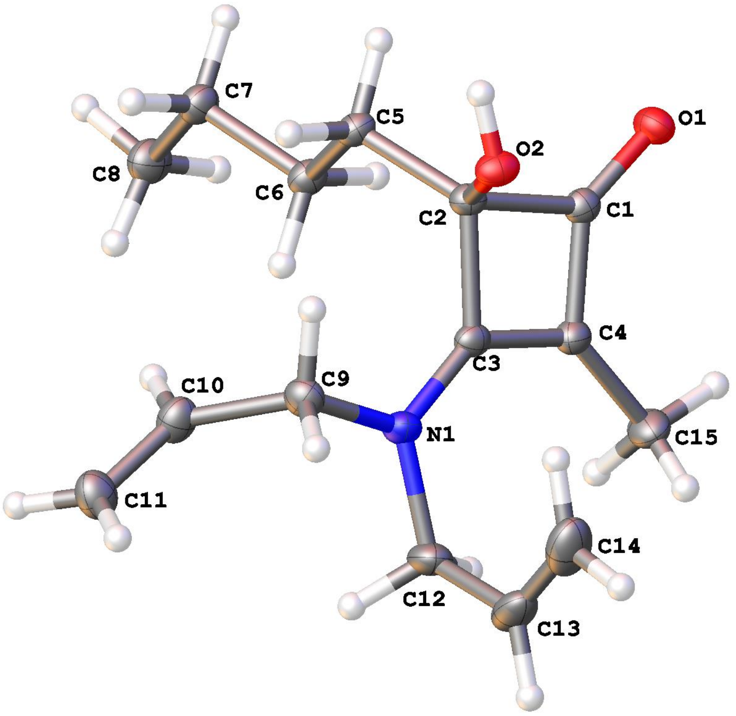
MP	68–72 °C.
FTIR (υ$_{max}$ (cm^{-1}))	3276 (br), 2957 (m), 2929 (m), 1737 (sh), 1562 (s), 1435 (m), 728 (s).
δ_H (400 MHz, CDCl$_3$)	5.92–5.70 (2H, m, 2xCH=), 5.32–5.14 (4H, m, 2xCH$_2$=), 4.95 (1H, br s, OH), 4.17 (1H, dd, *J* = 15.7, 6.1 Hz, NCH$_a$H$_a$'), 3.95 (1H, dd, *J* = 16.7, 4.5 Hz, NCH$_b$H$_b$'), 3.92–3.82 (2H, m, NCH$_a$H$_a$' and NCH$_b$H$_b$'), 1.96 (1H, m, CHH'), 1.68 (1H, m, CHH'), 1.65 (3H, s, CH$_3$), 1.36–1.08 (4H, m, CH$_2$), 0.85 (3H, t, *J* = 7.1 Hz, CH$_3$).

δ_C (101 MHz, CDCl$_3$) 191.0 (C=O), 172.8 (C), 132.6 (CH), 132.0 (CH), 118.8 (CH$_2$), 117.9 (CH$_2$), 113.0 (C), 90.3 (C), 52.4 (CH$_2$), 50.6 (CH$_2$), 33.3 (CH$_2$), 27.4 (CH$_2$), 22.8 (CH$_2$), 13.9 (CH$_3$), 6.8 (CH$_3$).

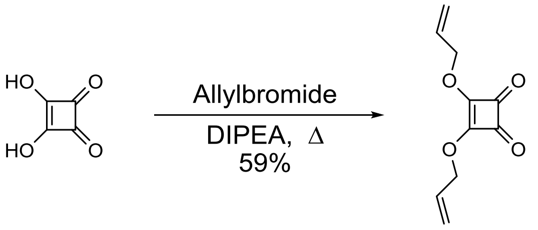
LRMS (ESI$^+$), m/z 521 ([2M+Na]$^+$, 100%), 313 ([M+CH$_3$CN+Na]$^+$, 15%).

HRMS, m/z $C_{15}H_{24}NO_2$ [M+H]$^+$ requires 250.1802; found 250.1807.

X-ray



3,4-Bis(allyloxy)cyclobut-3-ene-1,2-dione (4.78)



3.7 $C_6H_6O_4$ (142.11)

4.78 $C_{10}H_{10}O_4$ (194.18)

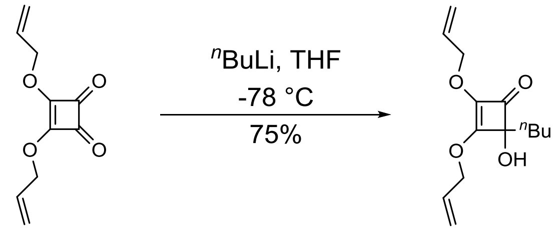
To a solution of dimethyl squaric acid **3.7** (1.60 g, 0.014 mol) in allyl bromide (50 mL) was added DIPEA (2.5 mL, 0.014 mol). The reaction mixture was heated at reflux for

3 h then cooled to RT and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/petroleum ether) afforded the title compound as a yellow oil (1.60 g, 8.24 mmol, 59%).

FTIR (υ_{max} (cm^{-1}))	2958 (w), 1811 (m), 1733 (s), 1590 (s), 1401 (s), 1325 (s).
δ_H (400 MHz, $CDCl_3$)	6.04 (2H, ddt, *J* = 16.9, 10.7, 6.2 Hz, 2xC<u>H</u>=), 5.51 (2H, dd, *J* = 16.8, 1.1 Hz, 2xC$\underline{H}_a H_b$=), 5.42 (1H, d, *J* = 11.0 Hz, 2xC$H_a\underline{H}_b$=), 5.14 (4H, br d, *J* = 6.2 Hz, 2xOC$\underline{H}_2$).
δ_C (101 MHz, $CDCl_3$)	189.0 (2x<u>C</u>=O), 184.0 (2x<u>C</u>), 130.7 (2x<u>C</u>H), 121.5 (2x$\underline{C}H_2$), 74.3 (2x$\underline{C}H_2$).
LRMS (ESI$^+$), m/z	258 ($[M+CH_3Na+Na]^+$, 84%), 203 (100%).
HRMS, m/z	$C_{10}H_{11}O_4$ $[M+Na]^+$ requires 217.0471; found 217.0473.

No Physical and spectroscopic data are reported in the literature other than refractive index (n_D^{20}=1.5275).[154]

2,3-Bis(allyloxy)-4-butyl-4-hydroxycyclobut-2-en-1-one (4.79)



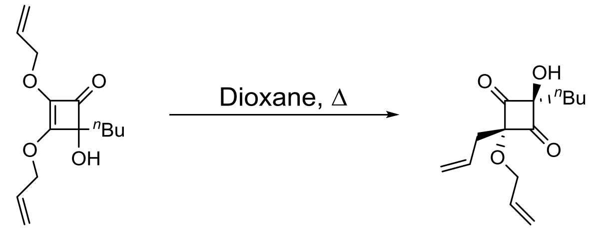
4.78
$C_{10}H_{10}O_4$
(194.18)

4.79
$C_{14}H_{20}O_4$
(252.31)

To a solution of squarate **4.78** (440 mg, 2.27 mmol) in THF (20 mL) at -78 °C was added ^{n}BuLi (2.3 M, 900 µL, 2.07 mmol). After 15 min, sat. NH_4Cl (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexane) afforded the title compound as a yellow oil (390 mg, 1.55 mmol, 75%).

FTIR (υ_{max} (cm^{-1}))	3386 (br), 2957 (m), 2872 (w), 1767 (sh), 1616 (s), 1320 (s).
δ_H (400 MHz, $CDCl_3$)	6.03 (1H, ddt, *J* = 17.2, 10.3, 5.9 Hz, CH=), 5.95 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, CH=), 5.45 (1H, app dq, *J* = 17.2, 1.4 Hz, CH_aH_b=), 5.40–5.34 (2H, m, CH_aH_b= and CH_cH_d=), 5.27 (1H, app dq, *J* = 10.4, 1.3 Hz, CH_cH_d=), 4.91 (1H, app ddt, *J* = 12.7, 5.7, 1.3 Hz, OCH_eH_e’), 4.85 (1H, app ddt, *J* = 12.6, 5.9, 1.4 Hz, OCH_eH_e’), 4.76 (1H, app ddt, *J* = 12.8, 5.8, 1.0 Hz, OCH_fH_f’), 4.71 (1H, app ddt, *J* = 12.8, 5.7, 1.0 Hz, OCH_fH_f’), 2.44 (1H, s, OH), 1.90–1.76 (2H, m, CH_2), 1.38–1.28 (4H, m, CH_2CH_2), 0.90 (3H, t, *J* = 7.1 Hz, CH_3).
δ_C (101 MHz, $CDCl_3$)	186.6 (C=O), 167.3 (C), 132.7 (CH), 132.6 (C), 131.5 (CH), 119.8 (CH_2), 118.8 (CH_2), 86.8 (C), 73.4 (CH_2), 71.2 (CH_2), 32.5 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 13.9 (CH_3).
LRMS (ESI$^+$), m/z	527 ([2M+Na]$^+$, 100%).
HRMS, m/z	$C_{14}H_{20}NaO_4$ [M+Na]$^+$ requires 275.1254; found 275.1258.

2,3-Bis(allyloxy)-4-butyl-4-hydroxycyclobut-2-en-1-one (4.84)



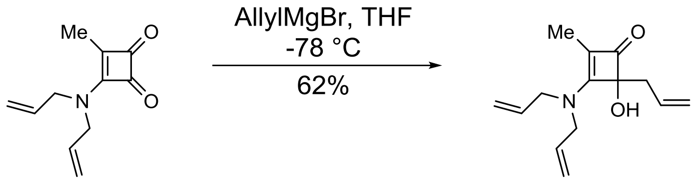
4.79
$C_{14}H_{20}O_4$
(252.31)

4.84
$C_{14}H_{20}O_4$
(252.31)

A solution of squarate **4.79** (50 mg, 0.20 mmol) in dioxane (2 mL) was thermolysed at 150°C for 1 h (0.162 mL/min) under flow using a Vapourtec R4 device. The reaction mixture was then concentrated *in vacuo* and the crude NMR recorded prior to its decomposition on silica.

δ_H (300 MHz, CDCl$_3$)	5.95–5.75 (2H, m, 2xC$\underline{\text{H}}$=), 5.32-5.12 (4H, m, 2xC$\underline{\text{H}}_2$=), 4.12 (2H, d, *J* = 5.5 Hz, OC$\underline{\text{H}}_2$), 2.70 (2H, d, *J* = 7.0 Hz, C$\underline{\text{H}}_2$), 1.86–1.74 (2H, m, C$\underline{\text{H}}_2$), 1.58–1.46 (2H, m, C$\underline{\text{H}}_2$), 1.40–1.29 (2H, m, C$\underline{\text{H}}_2$), 0.92 (3H, t, *J* = 7.1 Hz, C$\underline{\text{H}}_3$). Contaminated with residual dioxane.
δ_C (75 MHz, CDCl$_3$)	207.6 (2x$\underline{\text{C}}$=O), 133.3 ($\underline{\text{C}}$H), 129.1 ($\underline{\text{C}}$H), 121.2 ($\underline{\text{C}}$H$_2$), 118.1 ($\underline{\text{C}}$H$_2$), 97.6 ($\underline{\text{C}}$), 91.5 ($\underline{\text{C}}$), 69.2 ($\underline{\text{C}}$H$_2$), 35.8 ($\underline{\text{C}}$H$_2$), 31.1 ($\underline{\text{C}}$H$_2$), 23.8 ($\underline{\text{C}}$H$_2$), 22.7 ($\underline{\text{C}}$H$_2$), 13.7 ($\underline{\text{C}}$H$_3$). Contaminated with residual dioxane.

4-Allyl-3-(diallylamino)-4-hydroxy-2-methylcyclobut-2-en-1-one (4.90)



4.63
$C_{11}H_{13}NO_2$
(191.23)

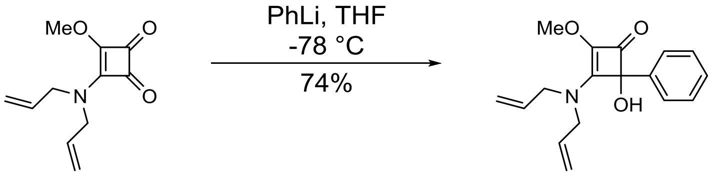
4.90
$C_{14}H_{19}NO_2$
(233.31)

To a solution of squaramide **4.63** (170 mg, 0.84 mmol) in THF (20 mL) at -78 °C was added allylmagnesium bromide (2 M, 440 µL, 0.88 mmol). After 1 h, sat. NH$_4$Cl (500 µL) was added and the resultant mixture was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (30–50% EtOAc/hexane) afforded the title compound as an orange solid (122 mg, 0.52 mmol, 62%).

MP	80–83 °C.
FTIR (υ_{max} (cm^{-1}))	3265 (br), 1739 (sh), 1567 (s), 1436 (m), 1272 (m).
δ_H (400 MHz, CDCl$_3$)	5.91–5.65 (3H, m, 3xC$\underline{\text{H}}$=), 5.32-5.21 (4H, m, 2xC$\underline{\text{H}}_2$=), 5.11 (1H, app dq, *J* = 17.2, 1.5 Hz, C$\underline{\text{H}}_a$H$_b$=), 5.06 (1H, m, CH$_a\underline{\text{H}}_b$=), 4.75 (1H, br s, O$\underline{\text{H}}$), 4.13 (1H, dd, *J* = 15.4, 6.3 Hz, NC$\underline{\text{H}}_c$H$_{c'}$), 3.98 (1H, dd, *J* = 15.7, 6.1 Hz, NCH$_c\underline{\text{H}}_{c'}$), 3.93 (2H, d, *J* = 5.1 Hz, NC$\underline{\text{H}}_2$), 2.80 (1H, app ddt, *J* =

	14.1, 6.6, 1.0 Hz, $C\underline{H}_dH_{d'}$), 2.54 (1H, dd, *J* = 14.4, 7.8 Hz, $CH_d\underline{H}_{d'}$), 1.67 (3H, s, $C\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	190.1 ($\underline{C}$=O), 172.3 ($\underline{C}$), 133.0 ($\underline{C}H$), 132.6 ($\underline{C}H$), 132.0 ($\underline{C}H$), 119.2 ($\underline{C}H_2$), 118.1 ($\underline{C}H_2$), 117.9 ($\underline{C}H_2$), 113.2 ($\underline{C}$), 89.5 ($\underline{C}$), 52.8 ($\underline{C}H_2$), 50.5 ($\underline{C}H_2$), 38.6 ($\underline{C}H_2$), 6.8 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	489 ($[2M+Na]^+$, 100%), 297 ($[M+CH_3CN+Na]^+$, 17%).
HRMS, m/z	$C_{14}H_{20}NO_2$ $[M+H]^+$ requires 234.1489; found 234.1491.

3-(Diallylamino)-4-hydroxy-2-methoxy-4-phenylcyclobut-2-en-1-one (4.93)



4.1
$C_{11}H_{13}NO_3$
(207.23)

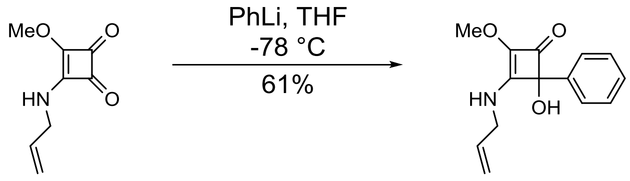
4.93
$C_{17}H_{19}NO_3$
(285.34)

To a solution of squaramate **4.1** (100 mg, 0.48 mmol) in THF (12 mL) at -78 °C was added PhLi (1.28 M, 360 µL, 0.46 mmol). After 1 h, sat. NH_4Cl (500 µL) was added and the resultant mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10–50% EtOAc/hexane) afforded the title compound as an off-white solid (97 mg, 0.34 mmol, 74%).

MP	109–110 °C (EtOAc/hexane).
FTIR (υ_{max} (cm^{-1}))	3293 (br), 2937 (w), 1761 (sh), 1564 (s), 1477 (m). 1278 (m).
δ_H (400 MHz, $CDCl_3$)	7.54–7.48 (2H, m, 2xAr$\underline{H}$), 7.38–7.31 (2H, m, 2xAr$\underline{H}$), 7.29–7.24 (H, m, Ar$\underline{H}$), 5.84 (1H, ddt, *J* = 16.9, 10.6, 5.9 Hz, $C\underline{H}$=), 5.40 (1H, m, $C\underline{H}$=), 5.31–5.19 (2H, m, $C\underline{H}_2$=), 5.06 (1H, d, *J* = 10.0 Hz, $C\underline{H}_aH_b$=), 4.99 (1H, d, *J* = 17.2 Hz, $CH_a\underline{H}_b$=), 4.87 (1H, s, $O\underline{H}$), 4.01 (5H, s, $NC\underline{H}_2$ & $OC\underline{H}_3$), 3.67 (2H, d, *J* = 6.1 Hz, $NC\underline{H}_2$).

δ_C (101 MHz, CDCl$_3$)	178.8 ($\underline{C}$=O), 159.6 ($\underline{C}$), 138.4 ($\underline{C}$), 131.9 (2x$\underline{C}$H), 129.4 ($\underline{C}$), 128.3 (2x$\underline{C}$H), 127.5 ($\underline{C}$H), 125.9 (2x$\underline{C}$H), 119.3 ($\underline{C}H_2$), 118.6 ($\underline{C}H_2$), 87.0 ($\underline{C}$), 58.9 ($\underline{C}H_3$), 51.9 ($\underline{C}H_2$), 50.4 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	593 ([2M+Na]$^+$, 100%), 349 ([M+CH$_3$CN+Na]$^+$, 33%).
HRMS, m/z	$C_{17}H_{20}NO_3$ [M+H]$^+$ requires 286.1438; found 286.1445.

3-(Allylamino)-4-hydroxy-2-methoxy-4-phenylcyclobut-2-en-1-one (4.95)



4.28
$C_8H_9NO_3$
(167.16)

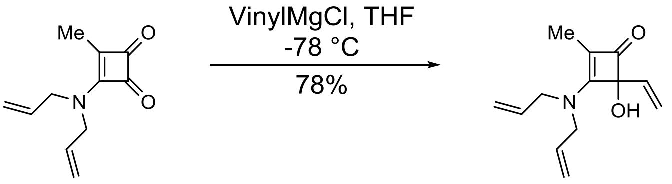
4.95
$C_{14}H_{15}NO_3$
(245.27)

To a solution of squaramate **4.28** (65 mg, 0.39 mmol) in THF (8 mL) at -78 °C was added PhLi (1.28 M, 550 µL, 0.70 mmol). After 1.5 h, sat. NH$_4$Cl (500 µL) was added and the resultant mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10–50% EtOAc/hexane) afforded the title compound as a yellow solid (46 mg, 0.19 mmol, 61%).

MP	140 °C dec.
FTIR (υ$_{max}$ (cm^{-1}))	3262 (br), 2941 (w), 1775 (m), 1708 (m), 1582 (s), 1435 (m).
δ_H (400 MHz, CDCl$_3$)	7.51–7.46 (2H, m, 2xAr$\underline{H}$), 7.37–7.31 (2H, m, 2xAr$\underline{H}$), 7.28 (1H, m, Ar$\underline{H}$), 5.82 (1H, br s, C$\underline{H}$=), 5.28–5.10 (2H, m, C$\underline{H}_2$=), 4.38 (1H, s, O$\underline{H}$), 3.99 (2H, br s, NC$\underline{H}_2$), 3.92 (3H, s, OC$\underline{H}_3$).

δ_C (101 MHz, $CDCl_3$)	179.0 (C=O), 158.6 (C), 137.7 (C), 133.5 (CH), 129.9 (C), 128.3 (2xCH), 127.8 (CH), 125.9 (2xCH), 117.1 (CH_2), 86.8 (C), 58.6 (CH_3), 47.2 (CH_2).
LRMS (ESI^+), m/z	246 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{14}H_{16}NO_3$ $[M+H]^+$ requires 246.1125; found 246.1126.

3-(Diallylamino)-4-hydroxy-2-methyl-4-vinylcyclobut-2-en-1-one (4.98)



4.63
$C_{11}H_{13}NO_2$
(191.23)

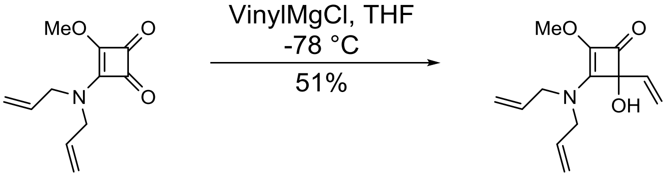
4.98
$C_{13}H_{17}NO_2$
(219.28)

To a solution of mono-squaramide **4.63** (300 mg, 1.57 mmol) in THF (20 mL) at -78 °C was added vinylmagnesium chloride (1.5 M, 1.2 mL, 1.72 mmol). After 1 h, sat. NH_4Cl (500 µL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (30–50% EtOAc/hexane) afforded the title compound as a yellow oil (270 mg, 1.23 mmol, 78%).

FTIR (υ_{max} (cm^{-1}))	3272 (br), 2922 (w), 1741 (sh), 1642 (s), 1557 (s), 1416 (s), 1269 (sh), 921 (sh).
δ_H (400 MHz, $CDCl_3$)	5.97 (1H, dd, *J* = 17.2, 10.6 Hz, CH=), 5.89–5.74 (2H, m, 2xCH=), 5.56 (1H, dd, *J* = 17.3, 1.2 Hz, CH_aH_b=), 5.35–5.16 (5H, m, CH_aH_b= and 2xCH_2=), 3.94 (4H, d, *J* = 5.6 Hz, 2xNCH_2), 1.72 (3H, s, CH_3).
δ_C (101 MHz, $CDCl_3$)	188.3 (C=O), 172.1 (C), 136.0 (CH), 132.7 (CH), 131.9 (CH), 119.4 (CH_2), 117.9 (CH_2), 117.4 (CH_2), 113.4 (C), 90.3 (C), 52.8 (CH_2), 50.3 (CH_2), 7.2 (CH_3).
LRMS (ESI^+), m/z	220 ($[M+H]^+$, 100%).

HRMS, m/z	$C_{13}H_{17}NNaO_2$ $[M+Na]^+$ requires 242.1151; found 242.1154.

3-(Diallylamino)-4-hydroxy-2-methoxy-4-vinylcyclobut-2-en-1-one (4.99)



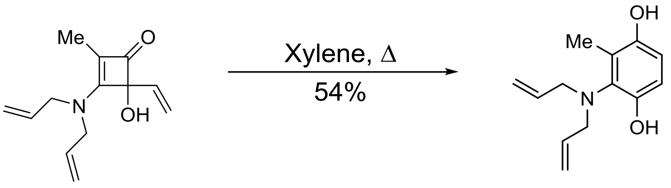
4.1 $C_{11}H_{13}NO_3$ (207.23)

4.99 $C_{13}H_{17}NO_3$ (235.28)

To a solution of squaramate **4.1** (400 mg, 1.93 mmol) in THF (30 mL) at -78 °C was added vinyl magnesium (1.5 M, 1.4 mL, 2.10 mmol). After 1 h, sat. NH_4Cl (1 mL), sat. K_2CO_3 (1 mL) and H_2O (10 mL) were added and the resultant mixture was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (30–50% EtOAc/hexane) afforded the title compound as a yellow oil (233 mg, 0.99 mmol, 51%).

FTIR (υ_{max} (cm^{-1}))	3307 (br), 2981 (w), 1764 (w), 1642 (w), 1575 (s), 1474 (s), 1281 (m), 927 (sh).
δ_H (400 MHz, $CDCl_3$)	5.95 (1H, dd, *J* = 17.2, 10.6 Hz, $C\underline{H}$=), 5.87–5.68 (2H, m, 2x$C\underline{H}$=), 5.56 (1H, dd, *J* = 17.2, 1.1 Hz, $C\underline{H}_aH_b$=), 5.35 (1H, dd, *J* = 10.7, 1.0 Hz, $CH_a\underline{H}_b$=), 5.29–5.15 (4H, m, 2x$C\underline{H}_2$=), 4.02–3.94 (5H, m, $OC\underline{H}_3$ and $NC\underline{H}_2$), 3.86 (2H, br s, $N\underline{C}H_2$).
δ_C (101 MHz, $CDCl_3$)	179.1 ($\underline{C}$=O), 159.8 ($\underline{C}$), 136.2 ($\underline{C}H$), 132.5 ($\underline{C}H$), 131.9 ($\underline{C}H$), 128.2 ($\underline{C}$), 119.2 ($\underline{C}H_2$), 118.6 ($\underline{C}H_2$), 117.9 ($\underline{C}H_2$), 86.2 ($\underline{C}$), 58.6 ($\underline{C}H_3$), 51.7 ($\underline{C}H_2$), 50.6 ($\underline{C}H_2$).
LRMS (ESI^+), m/z	236 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{13}H_{17}NNaO_3$ $[M+Na]^+$ requires 258.1101; found 258.1100.

2-(Diallylamino)-3-methylbenzene-1,4-diol (4.100)



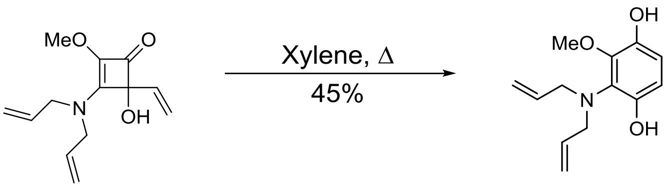
4.98
$C_{13}H_{17}NO_2$
(219.28)

4.100
$C_{13}H_{17}NO_2$
(219.28)

A solution of mono-squaramide **4.98** (50 mg, 0.23 mmol) in xylene (2 mL) was thermolysed for 4 h at reflux then cooled to RT. The reaction mixture was loaded directly onto silica and purified by flash column chromatography (0–20% EtOAc/hexane) to afford the title compound as a purple oil (27 mg, 0.12 mmol, 54%).

FTIR (υ_{max} (cm^{-1}))	3351 (br), 2921 (w), 2845 (w), 1642 (w), 1589 (m), .1470 (s), 1249 (sh), 923 (sh).
δ_H (400 MHz, $CDCl_3$)	6.65 (1H, d, *J* = 8.4 Hz, Ar$\underline{H}$), 6.57 (1H, d, *J* = 8.4 Hz, Ar$\underline{H}$), 5.80 (2H, ddt, *J* = 16.9, 10.2, 6.6 Hz, 2xC$\underline{H}$=), 5.15 (2H, dd, *J* = 17.0, 1.5 Hz, 2xC$\underline{H}_aH_b$=), 5.07 (2H, dd, *J* = 10.0, 1.2 Hz, 2xC$H_a\underline{H}_b$=), 3.74 (2H, dd, *J* = 13.4, 6.7 Hz, NC$\underline{H}_2$), 3.59 (2H, dd, *J* = 13.6, 6.7 Hz, NC$\underline{H}_2$), 2.23 (3H, s, C$\underline{H}_3$). Rotamers observed in NMR.
δ_C (101 MHz, $CDCl_3$)	148.2 ($\underline{C}$), 146.8 ($\underline{C}$), 135.2 (2x$\underline{C}$H), 134.5 ($\underline{C}$), 123.7 ($\underline{C}$), 117.7 (2x$\underline{C}H_2$), 113.9 ($\underline{C}$H), 110.3 ($\underline{C}$H), 56.9 (2x$\underline{C}H_2$), 12.1 ($\underline{C}H_3$).
LRMS (ESI^+), m/z	220 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{13}H_{18}NO_2$ $[M+H]^+$ requires 220.1332; found 220.1331.

2-(Diallylamino)-3-methoxybenzene-1,4-diol (4.101)



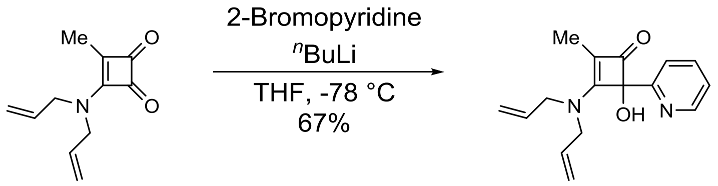
4.99
$C_{13}H_{17}NO_3$
(235.28)

4.101
$C_{13}H_{17}NO_3$
(235.28)

A solution of squaramate **4.99** (50 mg, 0.21 mmol) in xylene (2 mL) was thermolysed for 10 h at reflux then cooled to RT. The reaction mixture was loaded directly onto silica and purified by flash column chromatography (5–20% EtOAc/hexane) to afford the title compound as a purple oil (22 mg, 0.09 mmol, 45%).

FTIR (υ_{max} (cm^{-1}))	3348 (br), 2980 (w), 2844 (m), 1642 (w), 1474 (s), 923 (sh).
δ_H (400 MHz, $CDCl_3$)	6.70 (1H, d, *J* = 8.8 Hz, Ar$\underline{H}$), 6.58 (1H, d, *J* = 8.8 Hz, Ar$\underline{H}$), 5.79 (2H, ddt, *J* = 17.0, 10.2, 6.6 Hz, 2xC$\underline{H}$=), 5.16 (2H, app dq, *J* = 17.1, 1.5 Hz, 2xC$\underline{H}_aH_b$=), 5.07 (2H, app dq, *J* = 10.1, 1.3 Hz, 2xC$H_a\underline{H}_b$=), 3.92 (3H, s, OC$\underline{H}_3$), 3.67 (4H, d, *J* = 6.5 Hz, 2xNC$\underline{H}_2$).
δ_C (101 MHz, $CDCl_3$)	148.4 ($\underline{C}$), 146.7 ($\underline{C}$), 141.8 ($\underline{C}$), 135.3 (2x$\underline{C}$H), 128.8 ($\underline{C}$), 117.8 (2x$\underline{C}H_2$), 114.8 ($\underline{C}$H), 108.3 ($\underline{C}$H), 60.9 ($\underline{C}H_3$), 57.4 (2x$\underline{C}H_2$).
LRMS (ESI$^+$), m/z	236 ([M+H]$^+$, 100%).
HRMS, m/z	$C_{13}H_{18}NO_3$ [M+H]$^+$ requires 236.1281; found 236.1283.

3-(Diallylamino)-4-hydroxy-2-methyl-4-(pyridin-2-yl)cyclobut-2-en-1-one (4.102)



4.63
$C_{11}H_{13}NO_2$
(191.23)

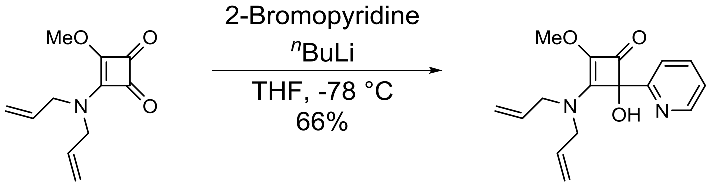
4.102
$C_{16}H_{18}N_2O_2$
(270.33)

To a solution of 2-bromopyridine (220 µL, 2.31 mmol) in THF (5 mL) at -78 °C was added ^{n}BuLi (2.36 M, 980 µL, 2.31 mmol). After 15 min, the resultant solution was cannulated into a solution of mono-squaramide **4.63** (370 mg, 1.94 mmol) in THF (15 mL) at -78 °C. After a further 45 min, sat. NH_4Cl (500 µL), sat. K_2CO_3 (1 mL) and H_2O (50 mL) were added and the resultant mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1% Et_3N/EtOAc) afforded the title compound as a green/yellow foam (360 mg, 1.33 mmol, 67%).

MP	133–135 °C.
FTIR (υ_{max} (cm^{-1}))	3246 (br), 2921 (m), 1744 (sh), 1642 (w), 1557 (s), 1434 (m).
δ_H (400 MHz, $CDCl_3$)	8.85 (1H, ddd, *J* = 4.9, 1.6, 0.9 Hz, Ar$\underline{H}$), 7.72 (1H, app td, *J* = 7.7, 1.7 Hz, Ar$\underline{H}$), 7.44 (1H, app dt, *J* = 7.9, 1.0 Hz, Ar$\underline{H}$), 7.25 (1H, ddd, *J* = 7.5, 4.9, 1.1 Hz, Ar$\underline{H}$), 6.16 (1H, br s, O$\underline{H}$), 5.84 (1H, app ddt, *J* = 17.1, 10.3, 5.1 Hz, C$\underline{H}$=), 5.39–5.21 (3H, m, C$\underline{H}$= and C$\underline{H}_2$=), 4.99 (1H, dd, *J* = 10.1, 1.0 Hz, C$\underline{H}_aH_b$=), 4.92 (1H, dd, *J* = 17.1, 1.3 Hz, C$H_a\underline{H}_b$=), 3.99 (1H, dd, *J* = 17.0, 4.8 Hz, NC$\underline{H}_cH_{c'}$), 3.91 (1H, dd, *J* = 16.8, 5.1 Hz, NC$H_c\underline{H}_{c'}$), 3.68 (1H, dd, *J* = 15.4, 6.5 Hz, NC$\underline{H}_dH_{d'}$), 3.57 (1H, dd, *J* = 15.4, 6.4 Hz, NC$H_d\underline{H}_{d'}$), 1.88 (3H, C$\underline{H}_3$).
δ_C (101 MHz, $CDCl_3$)	185.9 (C=O), 169.8 ($\underline{C}$), 155.6 ($\underline{C}$), 148.0 ($\underline{C}$H), 137.3 ($\underline{C}$H), 131.9 ($\underline{C}$H), 131.9 ($\underline{C}$H), 122.8 ($\underline{C}$H), 120.2 ($\underline{C}$H),

	119.0 ($\underline{C}$), 118.0 ($\underline{C}H_2$), 117.8 ($\underline{C}H_2$), 90.4 ($\underline{C}$), 52.6 ($\underline{C}H_2$), 50.4 ($\underline{C}H_2$), 7.5 ($\underline{C}H_3$).
LRMS (ESI$^+$), m/z	271 ([M+H]$^+$, 100%).
HRMS, m/z	$C_{16}H_{19}N_2O_2$ [M+H]$^+$ requires 271.1141; found 271.1142.

3-(Diallylamino)-4-hydroxy-2-methoxy-4-(pyridin-2-yl)cyclobut-2-en-1-one (4.103)



4.1
$C_{11}H_{13}NO_3$
(207.23)

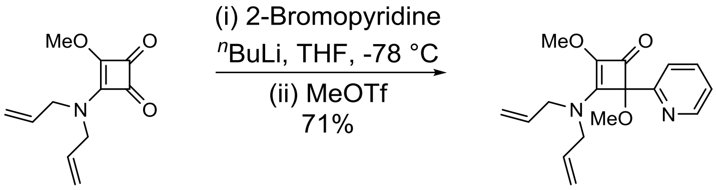
4.103
$C_{16}H_{18}N_2O_3$
(286.33)

To a solution of 2-bromopyridine (150 µL, 1.58 mmol) in THF (5 mL) at -78 °C was added ^{n}BuLi (2.36 M, 670 µL, 1.58 mmol). After 15 min, the resultant solution was cannulated into a solution of squaramate **4.1** (243 mg, 1.17 mmol) in THF (15 mL) at -78 °C. After a further 1 h, sat. NH_4Cl (1 mL), sat. K_2CO_3 (2 mL) and H_2O (50 mL) were added and the resultant mixture was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50–100% EtOAc/hexane, 1% Et_3N) afforded the title compound as an orange oil (221 mg, 0.77 mmol, 66%).

FTIR (υ_{max} (cm^{-1}))	3295 (br), 2931 (m), 1766 (sh), 1642 (w), 1565 (s), 1472 (m), 1280 (m), 929 (m).
δ_H (400 MHz, $CDCl_3$)	8.58 (1H, app dt, *J* = 4.9, 1.3 Hz, Ar$\underline{H}$), 7.74 (1H, app td, *J* = 7.7, 1.7 Hz, Ar$\underline{H}$), 7.51 (1H, app dt, *J* = 8.0, 1.0 Hz, Ar$\underline{H}$), 7.25 (1H, ddd, *J* = 7.3, 5.1, 1.0 Hz, Ar$\underline{H}$), 6.09 (1H, br s, O$\underline{H}$), 5.82 (1H, m, C$\underline{H}$=), 5.39–5.15 (3H, m, C$\underline{H}$= and C$\underline{H}_2$=), 4.96 (1H, d, *J* = 9.8 Hz, C$\underline{H}_aH_b$=), 4.89 (1H, d, *J* = 17.1 Hz, C$H_a\underline{H}_b$=), 4.11–3.85 (5H, m, OC$\underline{H}_3$ & NC$\underline{H}_2$), 3.69–3.45 (2H, m, NC$\underline{H}_2$).

δ_C (101 MHz, $CDCl_3$)	177.3 (C=O), 157.2 (C), 156.0 (C), 148.0 (CH), 137.3 (CH), 131.9 (CH), 131.8 (CH), 131.3 (C), 122.8 (CH), 120.2 (CH), 118.8 (CH_2), 118.5 (CH_2), 87.3 (C), 58.9 (CH_3), 51.4 (CH_2), 50.7 (CH_2).
LRMS (ESI^+), m/z	287 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{16}H_{18}N_2NaO_3$ $[M+Na]^+$ requires 309.1210; found 309.1213.

3-(Diallylamino)-2,4-dimethoxy-4-(pyridin-2-yl)cyclobut-2-en-1-one (4.104)



4.1 $C_{11}H_{13}NO_3$ (207.23)

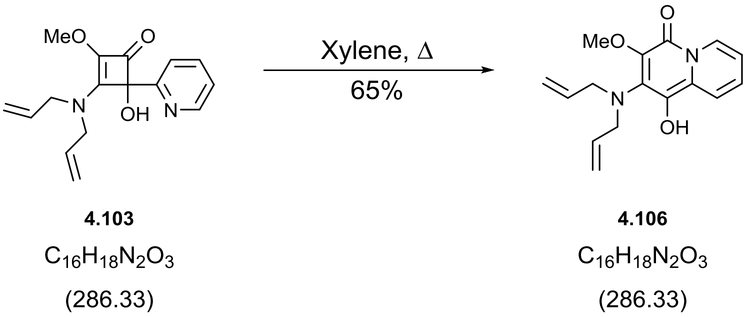
4.104 $C_{17}H_{20}N_2O_3$ (300.35)

To a solution of squaramate **4.1** (95 mg, 0.33 mmol) in THF (5 mL) at -78 °C was added ^{n}BuLi (2.32 M, 150 µL, 0.35 mmol) followed after 5 min by MeOTf (40 µL, 0.37 mmol). The resultant solution was allowed to warm to -50 °C over a period of 2 h, after which sat. K_2CO_3 (1 mL) and H_2O (10 mL) were added and the resultant mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded the title compound as a yellow oil (70 mg, 0.23 mmol, 71%).

FTIR ($υ_{max}$ (cm^{-1}))	2932 (m), 1768 (sh), 1642 (w), 1565 (s), 1602 (s), 1473 (m).
δ_H (400 MHz, $CDCl_3$)	8.57 (1H, app dt, *J* = 4.8, 1.4 Hz, ArH), 7.73–7.66 (2H, m, 2xArH), 7.18 (1H, m, ArH), 5.86 (1H, m, CH=), 5.48 (1H, ddt, *J* = 16.7, 10.3, 6.4 Hz, CH=), 5.37 (1H, d, *J* = 17.0 Hz, CH_aH_b=), 5.30 (1H, d, *J* = 10.0 Hz, CH_aH_b=), 5.09 (1H, d, *J* = 10.1 Hz, CH_cH_d=), 5.05 (1H, d, *J* = 17.4 Hz,

	CH_cH_d=), 4.19 (1H, dd, *J* = 15.0, 5.9 Hz, NCH_eH_e'), 4.05–3.95 (4H, m, OCH_3 and NCH_eH_e'), 3.74 (1H, dd, *J* = 15.3, 6.2 Hz, NCH_fH_f'), 3.65 (1H, dd, *J* = 15.3, 7.0 Hz, NCH_fH_f'), 3.54 (3H, s, OCH_3).
δ_C (101 MHz, $CDCl_3$)	176.4 (C=O), 157.4 (C), 156.4 (C), 148.9 (CH), 136.5 (CH), 132.2 (CH), 132.1 (CH), 131.4 (C), 122.7 (CH), 122.0 (CH), 119.3 (CH_2), 118.6 (CH_2), 95.0 (C), 58.8 (CH_3), 52.1 (CH_3), 52.1 (CH_2), 50.4 (CH_2).
LRMS (ESI^+), m/z	301 ($[M+H]^+$, 62%), 269 ($[M-OCH_3]^+$, 100%).
HRMS, m/z	$C_{17}H_{20}N_2NaO_3$ $[M+Na]^+$ requires 323.1366; found 323.1374.

2-(Diallylamino)-1-hydroxy-3-methoxy-4*H*-quinolizin-4-one (4.106)

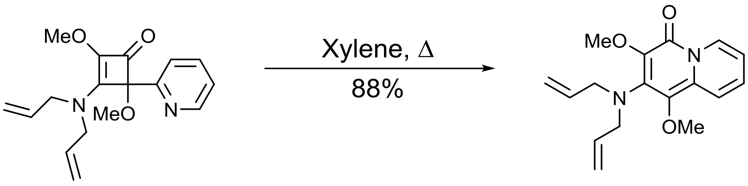


A solution of squaramate **4.103** (65 mg, 0.23 mmol) in xylene (3 mL) was thermolysed for 35 min at reflux then cooled to RT. The reaction mixture was loaded directly onto silica and purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound as a green oil (43 mg, 0.15 mmol, 65%).

FTIR (υ_{max} (cm^{-1}))	3272 (br), 2929 (m), 1743 (m), 1624 (s), 1550 (m), 1285 (m).
δ_H (400 MHz, CD_3OD)	8.82 (1H, d, *J* = 7.5 Hz, ArH), 7.89 (1H, d, *J* = 9.2 Hz, ArH), 7.21 (1H, ddd, *J* = 9.0, 6.5, 0.9 Hz, ArH), 7.02 (1H, ddd, *J* = 7.5, 6.4, 1.3 Hz, ArH), 5.90 (2H, ddt, *J* = 17.0, 10.3, 6.6 Hz, 2xCH=), 5.15 (2H, app dq, *J* = 17.1, 1.4 Hz,

	2xC<u>H</u>$_a$H$_b$=), 5.06 (2H, d, *J* = 10.1 Hz, 2xCH$_a$<u>H</u>$_b$=), 4.00 (3H, s, OC<u>H</u>$_3$), 3.88 (4H, d, *J* = 6.7 Hz, 2xNC<u>H</u>$_2$).
δ_C (101 MHz, CD_3OD)	153.2 (C=O), 141.9 (<u>C</u>), 140.7 (<u>C</u>), 136.6 (2x<u>C</u>H), 134.6 (<u>C</u>), 128.1 (<u>C</u>), 126.3 (<u>C</u>H), 126.0 (<u>C</u>H), 122.0 (<u>C</u>H), 118.5 (2x<u>C</u>H$_2$), 116.9 (<u>C</u>H), 60.1 (<u>C</u>H$_3$), 57.2 (2x<u>C</u>H$_2$).
LRMS (ESI$^+$), m/z	287 ([M+H]$^+$, 100%).
HRMS, m/z	$C_{16}H_{19}N_2O_3$ [M+H]$^+$ requires 287.1390; found 287.1388.

2-(Diallylamino)-1,3-dimethoxy-4*H*-quinolizin-4-one (4.107)



4.104
$C_{17}H_{20}N_2O_3$
(300.35)

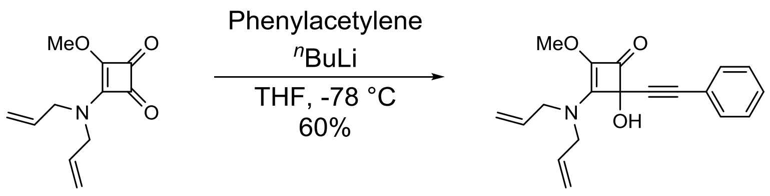
4.107
$C_{17}H_{20}N_2O_3$
(300.35)

A solution of squaramate **4.104** (65 mg, 0.22 mmol) in xylene (3 mL) was thermolysed for 5 h at reflux then cooled to RT. The reaction mixture was loaded directly onto silica and purified by flash column chromatography (30–50% EtOAc/hexane) to afford the title compound as a yellow oil (58 mg, 0.19 mmol, 88%).

FTIR (υ_{max} (cm^{-1}))	2928 (m), 1642 (sh), 1626 (sh), 1552 (s), 1442 (m), 1080 (m).
δ_H (400 MHz, CD_3OD)	8.82 (1H, app dt, *J* = 7.4, 0.9 Hz, Ar<u>H</u>), 7.76 (1H, app dt, *J* = 9.2, 1.0 Hz, Ar<u>H</u>), 7.30 (1H, ddd, *J* = 9.2, 6.5, 1.1 Hz, Ar<u>H</u>), 6.96, (1H, ddd, *J* = 7.5, 6.4, 1.3 Hz, Ar<u>H</u>), 5.91 (2H, ddt, *J* = 17.0, 10.2, 6.6 Hz, 2xC<u>H</u>=), 5.22 (2H, dd, *J* = 17.1, 1.6 Hz, 2xC<u>H</u>$_a$H$_b$=), 5.18–5.11 (2H, m, 2xCH$_a$<u>H</u>$_b$=), 4.07 (4H, d, *J* = 6.5 Hz, 2xNC<u>H</u>$_2$), 3.84 (3H, s, OC<u>H</u>$_3$), 3.76 (3H, s, OC<u>H</u>$_3$).

δ_C (101 MHz, CD_3OD)	155.1 (C=O), 146.9 ($\underline{C}$), 137.0 ($\underline{C}$), 136.6 (2x$\underline{C}$H), 134.5 ($\underline{C}$), 134.0 ($\underline{C}$), 128.9 ($\underline{C}$H), 126.8 ($\underline{C}$H), 120.7 ($\underline{C}$H), 118.5 (2x$\underline{C}H_2$), 115.7 ($\underline{C}$H), 62.0 (O$\underline{C}H_3$), 60.2 (O$\underline{C}H_3$), (2xN$\underline{C}H_2$).
LRMS (ESI^+), m/z	301 ($[M+H]^+$, 100%).
HRMS, m/z	$C_{17}H_{21}N_2O_3$ $[M+H]^+$ requires 301.1547; found 301.1547.

3-(Diallylamino)-4-hydroxy-2-methoxy-4-(phenylethynyl)cyclobut-2-en-1-one (4.108)



4.1
$C_{11}H_{13}NO_3$
(207.23)

4.108
$C_{19}H_{19}NO_3$
(309.36)

To a solution of phenylacetylene (100 µL, 0.91 mmol) in THF (5 mL) at -78 °C was added ^{n}BuLi (2.32 M, 370 µL, 0.86 mmol). After 20 min, the resultant solution was cannulated into a solution of squaramate **4.1** (146 mg, 0.70 mmol) in THF (10 mL) at -78 °C. After a further 30 min, sat. K_2CO_3 (500 µL) and H_2O (20 mL) were added and the resultant mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (20% acetone/hexane) afforded the title compound as a yellow oil (130 mg, 0.42 mmol, 60%).

MP	89–91 °C.
FTIR (υ_{max} (cm^{-1}))	3249 (br), 2938 (w), 1768 (sh), 1643 (w), 1581 (s), 1477 (sh), 1411 (sh).
δ_H (400 MHz, $CDCl_3$)	7.50–7.40 (2H, m, 2xAr$\underline{H}$), 7.36–7.28 (3H, m, 3xAr$\underline{H}$), 5.90 (2H, br s, 2xC$\underline{H}$=), 5.35–5.22 (4H, m, 2xC$\underline{H}_2$=),

	4.26–4.03 (3H, m, NCH_2 and $NC\underline{H}_aH_b$), 3.98 (4H, s, $OC\underline{H}_3$ and $NCH_a\underline{H}_b$), 3.36 (1H, s, $O\underline{H}$).
δ_C (101 MHz, $CDCl_3$)	175.4 (C=O), 157.5 ($\underline{C}$), 132.4 ($\underline{C}H$), 131.8 (3x$\underline{C}H$), 129.5 ($\underline{C}$), 128.7 ($\underline{C}H$), 128.2 (2x$\underline{C}H$), 122.1 ($\underline{C}$), 119.5 ($\underline{C}H_2$), 118.6 ($\underline{C}H_2$), 88.0 ($\underline{C}$), 84.7 ($\underline{C}$), 78.3 ($\underline{C}$), 58.7 ($\underline{C}H_3$), 52.2 ($\underline{C}H_2$), 50.6 ($\underline{C}H_2$).
LRMS (ESI$^+$), m/z	310 ([M+H]$^+$, 62%).
HRMS, m/z	$C_{19}H_{20}NO_3$ [M+H]$^+$ requires 310.1438; found 310.1444.

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Chapter 7: Appendix

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction

X-Ray diffraction - University of Southampton

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Table 1. Crystal data and structure refinement details.

Identification code	**2014sot0011**	
Empirical formula	$C_{11}H_{13}NO$	
Formula weight	175.22	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*121/*c*1	
Unit cell dimensions	a = **13.114(4) Å**	α = **90°**
	b = **5.5691(15) Å**	β = **115.258(4)°**
	c = **13.761(4) Å**	γ = **90°**
Volume	908.9(5) Å^3	
Z	4	
Density (calculated)	1.281 Mg / m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	376	
Crystal	Plate; Colorless	
Crystal size	$0.17 \times 0.05 \times 0.01$ mm^3	
θ range for data collection	2.978 – 27.482°	
Index ranges	$-16 \le h \le 17$, $-7 \le k \le 7$, $-17 \le l \le 15$	
Reflections collected	7844	
Independent reflections	2070 [R_{int} = 0.0685]	
Completeness to θ = 25.242°	99.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	1.000 and 0.858	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2070 / 0 / 127	
Goodness-of-fit on F^2	1.056	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0453, $wR2$ = 0.1212	
R indices (all data)	$R1$ = 0.0478, $wR2$ = 0.1241	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.292 and –0.216 e Å^{-3}	

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination and data collection**: *CrystalClear-SM Expert 3.1 b27* (Rigaku, 2013). **Data reduction, cell refinement and absorption correction**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Structure solution**: *SHELXS-2014* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Structure refinement**: *SHELXL-2014* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Graphics:** *OLEX2* (Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339-341).

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	1332(1)	1421(2)	286(1)	22(1)	1
N1	441(1)	8363(2)	2156(1)	20(1)	1
C1	2146(1)	6263(2)	2335(1)	17(1)	1
C2	1622(1)	8111(2)	2659(1)	18(1)	1
C3	2266(1)	9580(2)	3526(1)	22(1)	1
C4	3421(1)	9208(2)	4082(1)	26(1)	1
C5	3942(1)	7419(2)	3756(1)	26(1)	1
C6	3312(1)	5955(2)	2875(1)	20(1)	1
C7	3924(1)	4067(2)	2538(1)	24(1)	1
C8	3180(1)	2548(2)	1603(1)	21(1)	1
C9	2068(1)	2809(2)	1124(1)	18(1)	1
C10	1416(1)	4634(2)	1425(1)	18(1)	1
C11	1827(1)	–495(2)	–56(1)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C9	1.3813(13)
O1–C11	1.4290(13)
N1–C2	1.4084(14)
C1–C2	1.4111(15)
C1–C6	1.3965(15)
C1–C10	1.5114(14)
C2–C3	1.3955(15)
C3–C4	1.3903(16)
C4–C5	1.3866(17)
C5–C6	1.4004(16)
C6–C7	1.5112(16)
C7–C8	1.5005(15)
C8–C9	1.3269(15)
C9–C10	1.4955(15)
C9–O1–C11	116.01(8)
C2–C1–C10	118.55(9)
C6–C1–C2	119.44(10)
C6–C1–C10	122.00(10)
N1–C2–C1	119.96(9)
C3–C2–N1	119.95(10)
C3–C2–C1	119.93(10)
C4–C3–C2	120.20(10)
C5–C4–C3	120.03(10)
C4–C5–C6	120.54(10)
C1–C6–C5	119.81(10)
C1–C6–C7	121.75(10)
C5–C6–C7	118.45(10)
C8–C7–C6	114.77(9)
C9–C8–C7	122.64(10)
O1–C9–C10	109.45(9)
C8–C9–O1	125.57(10)
C8–C9–C10	124.97(10)
C9–C10–C1	113.75(9)

used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	19(1)	23(1)	20(1)	–6(1)	5(1)	–1(1)
N1	16(1)	20(1)	21(1)	–1(1)	7(1)	1(1)
C1	15(1)	19(1)	16(1)	–1(1)	6(1)	–4(1)
C2	16(1)	18(1)	18(1)	2(1)	7(1)	–3(1)
C3	22(1)	19(1)	24(1)	–4(1)	10(1)	–4(1)
C4	21(1)	27(1)	26(1)	–8(1)	6(1)	–8(1)
C5	15(1)	29(1)	28(1)	–6(1)	4(1)	–5(1)
C6	16(1)	21(1)	22(1)	–1(1)	7(1)	–3(1)
C7	12(1)	28(1)	30(1)	–5(1)	6(1)	–2(1)
C8	18(1)	22(1)	25(1)	–3(1)	10(1)	–1(1)
C9	18(1)	19(1)	17(1)	–2(1)	7(1)	–3(1)
C10	13(1)	21(1)	19(1)	–3(1)	5(1)	–2(1)
C11	27(1)	21(1)	20(1)	–2(1)	9(1)	2(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	210(12)	9800(30)	2327(11)	27(4)	1
H1B	122(13)	8090(30)	1439(13)	29(4)	1
H3	1915	10838	3737	26	1
H4	3853	10180	4686	31	1
H5	4733	7184	4133	31	1
H7A	4489	4874	2351	29	1
H7B	4337	3002	3159	29	1
H8	3518	1352	1344	25	1
H10B	876	3791	1634	22	1
H10A	975	5631	787	22	1
H11A	2311	171	–370	34	1
H11B	1230	–1467	–594	34	1
H11C	2280	–1502	563	34	1

Table 6. Torsion angles [°].

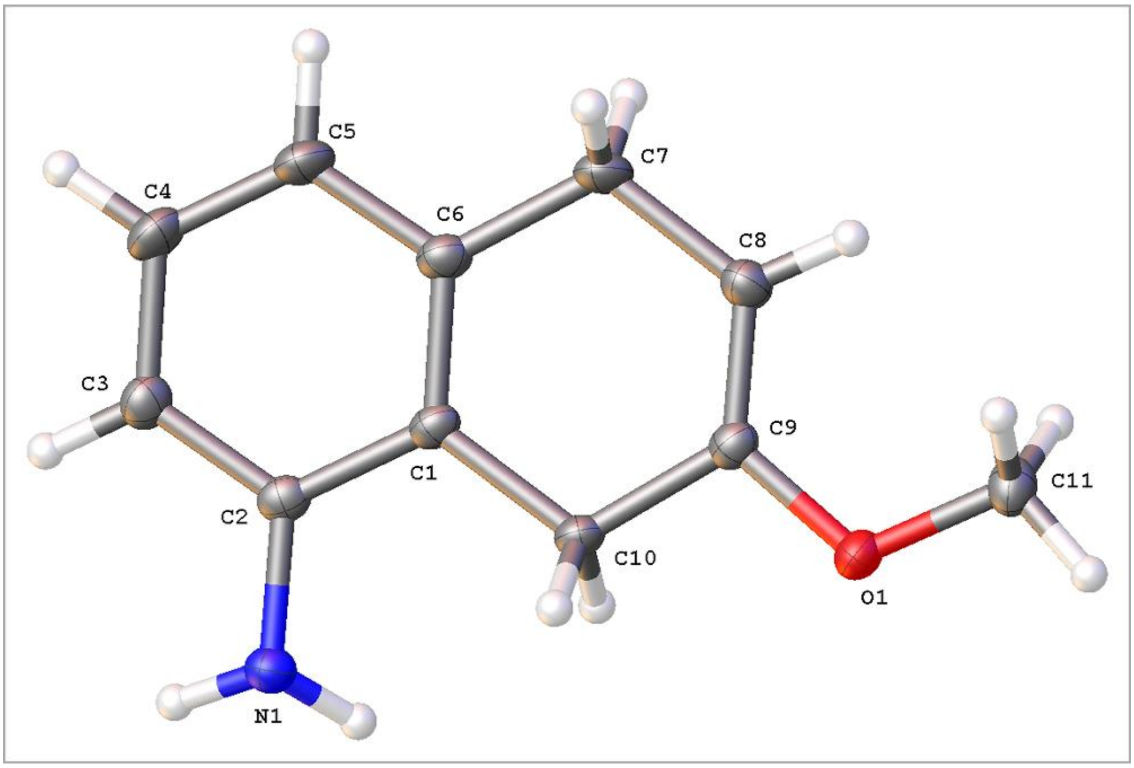
O1–C9–C10–C1	–179.70(8)
N1–C2–C3–C4	174.63(10)
C1–C2–C3–C4	–0.85(16)
C1–C6–C7–C8	–1.15(16)
C2–C1–C6–C5	2.46(16)
C2–C1–C6–C7	–177.70(9)
C2–C1–C10–C9	177.70(8)
C2–C3–C4–C5	1.89(18)
C3–C4–C5–C6	–0.73(18)
C4–C5–C6–C1	–1.45(18)
C4–C5–C6–C7	178.70(11)
C5–C6–C7–C8	178.70(10)
C6–C1–C2–N1	–176.80(9)
C6–C1–C2–C3	–1.32(16)
C6–C1–C10–C9	–3.74(15)
C6–C7–C8–C9	–1.34(17)
C7–C8–C9–O1	–177.67(10)
C7–C8–C9–C10	1.19(18)
C8–C9–C10–C1	1.28(16)
C10–C1–C2–N1	1.79(15)
C10–C1–C2–C3	177.27(9)
C10–C1–C6–C5	–176.09(10)
C10–C1–C6–C7	3.76(16)
C11–O1–C9–C8	2.15(15)
C11–O1–C9–C10	–176.86(8)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1–H1B···O1^{i}	0.905(16)	2.341(16)	3.1693(14)	152.1(13)

Symmetry transformations used to generate equivalent atoms:
(i) –x,–y+1,–z


C5
C4
C6
C7
C8
C3
C9
C1
C11
C2
C10
O1
N1

Single Crystal X-Ray Diffraction

Chemistry - University of Southampton

Contact: Majdouline Roudias, mr2m11@soton.ac.uk, DCH lab 30/3007

Table 1. Crystal data and structure refinement details.

Identification code	**2013mr005_Ka**	
Empirical formula	$C_{15}H_{23}N_1O_2$	
Formula weight	249.35	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	*P*121/*n*1	
Unit cell dimensions	a = **11.3025(8) Å**	α = **90°**
	b = **11.0997(8) Å**	β = **99.408(2)°**
	c = **11.9196(8) Å**	γ = **90°**
Volume	1475.25(18) $Å^3$	
Z	4	
Density (calculated)	1.123 Mg / m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	544	
Crystal	Block; Colourless	
Crystal size	$0.48 \times 0.17 \times 0.14$ mm^3	
θ range for data collection	3.278 – 27.430°	
Index ranges	$-14 \le h \le 11$, $-11 \le k \le 14$, $-14 \le l \le 15$	
Reflections collected	13488	
Independent reflections	3359 [R_{int} = 0.0317]	
Completeness to θ = 25.242°	99.7 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	1.000 and 0.819	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3359 / 0 / 166	
Goodness-of-fit on F^2	1.057	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0374, $wR2$ = 0.0990	
R indices (all data)	$R1$ = 0.0413, $wR2$ = 0.1021	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.361 and –0.154 e $Å^{-3}$	

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination and data collection**: *CrystalClear-SM Expert 3.1 b27* (Rigaku, 2013). **Data reduction, cell refinement and absorption correction**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Structure solution** *SUPERFLIP* (Palatinus, L. & Chapuis, G. (2007). J. Appl. Cryst. 40, 786-790). **Structure refinement**: *SHELXL-2013* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122). **Graphics:** *OLEX2* (Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339-341)

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	5578(1)	1489(1)	6262(1)	21(1)	1
O2	5463(1)	689(1)	3642(1)	20(1)	1
N1	5335(1)	3395(1)	2816(1)	19(1)	1
C1	5462(1)	2020(1)	5334(1)	17(1)	1
C2	4865(1)	1643(1)	4112(1)	16(1)	1
C3	5367(1)	2871(1)	3825(1)	16(1)	1
C4	5844(1)	3151(1)	4947(1)	18(1)	1
C5	3502(1)	1478(1)	3925(1)	18(1)	1
C6	2817(1)	2593(1)	4222(1)	19(1)	1
C7	1460(1)	2417(1)	4080(1)	21(1)	1
C8	818(1)	3580(1)	4320(1)	26(1)	1
C9	4787(1)	2790(1)	1753(1)	21(1)	1
C10	3654(1)	3400(1)	1193(1)	24(1)	1
C11	3501(1)	3825(1)	146(1)	27(1)	1
C12	5996(1)	4509(1)	2692(1)	26(1)	1
C13	7258(1)	4295(1)	2469(1)	32(1)	1
C14	7788(1)	3239(1)	2475(1)	38(1)	1
C15	6534(1)	4168(1)	5565(1)	27(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.2419(11)
O2–H2	0.8400
O2–C2	1.4199(11)
N1–C3	1.3318(12)
N1–C9	1.4770(12)
N1–C12	1.4649(12)
C1–C2	1.5585(12)
C1–C3	2.0180(13)
C1–C4	1.4277(13)
C2–C3	1.5368(12)
C2–C5	1.5308(12)
C3–C4	1.3927(13)
C4–C15	1.4959(13)
C5–H5A	0.9900
C5–H5B	0.9900
C5–C6	1.5312(13)
C6–H6A	0.9900
C6–H6B	0.9900
C6–C7	1.5285(13)
C7–H7A	0.9900
C7–H7B	0.9900
C7–C8	1.5303(14)
C8–H8A	0.9800
C8–H8B	0.9800
C8–H8C	0.9800
C9–H9A	0.9900
C9–H9B	0.9900
C9–C10	1.5048(14)
C10–H10	0.9500
C10–C11	1.3192(15)
C11–H11A	0.9500
C11–H11B	0.9500
C12–H12A	0.9900
C12–H12B	0.9900
C12–C13	1.5109(16)
C13–H13	0.9500
C13–C14	1.3153(19)
C14–H14A	0.9500
C14–H14B	0.9500
C15–H15A	0.9800
C15–H15B	0.9800
C15–H15C	0.9800
C2–O2–H2	109.5
C3–N1–C9	121.47(8)
C3–N1–C12	121.39(8)
C12–N1–C9	116.52(8)
O1–C1–C2	132.15(8)
O1–C1–C3	176.99(8)
O1–C1–C4	135.36(9)
C2–C1–C3	48.85(5)
C4–C1–C2	92.45(7)
C4–C1–C3	43.63(5)
O2–C2–C1	114.06(7)

O2–C2–C3	110.85(7)
O2–C2–C5	112.73(7)
C3–C2–C1	81.37(7)
C5–C2–C1	116.13(7)
C5–C2–C3	118.22(8)
N1–C3–C1	177.47(8)
N1–C3–C2	129.23(8)
N1–C3–C4	135.99(9)
C2–C3–C1	49.78(5)
C4–C3–C1	45.01(5)
C4–C3–C2	94.77(7)
C1–C4–C15	131.71(9)
C3–C4–C1	91.36(8)
C3–C4–C15	136.88(9)
C2–C5–H5A	108.8
C2–C5–H5B	108.8
C2–C5–C6	113.86(7)
H5A–C5–H5B	107.7
C6–C5–H5A	108.8
C6–C5–H5B	108.8
C5–C6–H6A	108.7
C5–C6–H6B	108.7
H6A–C6–H6B	107.6
C7–C6–C5	114.04(8)
C7–C6–H6A	108.7
C7–C6–H6B	108.7
C6–C7–H7A	109.3
C6–C7–H7B	109.3
C6–C7–C8	111.69(8)
H7A–C7–H7B	107.9
C8–C7–H7A	109.3
C8–C7–H7B	109.3
C7–C8–H8A	109.5
C7–C8–H8B	109.5
C7–C8–H8C	109.5
H8A–C8–H8B	109.5
H8A–C8–H8C	109.5
H8B–C8–H8C	109.5
N1–C9–H9A	109.1
N1–C9–H9B	109.1
N1–C9–C10	112.51(8)
H9A–C9–H9B	107.8
C10–C9–H9A	109.1
C10–C9–H9B	109.1
C9–C10–H10	118.3
C11–C10–C9	123.43(9)
C11–C10–H10	118.3
C10–C11–H11A	120.0
C10–C11–H11B	120.0
H11A–C11–H11B	120.0
N1–C12–H12A	108.9
N1–C12–H12B	108.9
N1–C12–C13	113.33(9)
H12A–C12–H12B	107.7
C13–C12–H12A	108.9
C13–C12–H12B	108.9

C12–C13–H13	117.2
C14–C13–C12	125.56(10)
C14–C13–H13	117.2
C13–C14–H14A	120.0
C13–C14–H14B	120.0
H14A–C14–H14B	120.0
C4–C15–H15A	109.5
C4–C15–H15B	109.5
C4–C15–H15C	109.5
H15A–C15–H15B	109.5
H15A–C15–H15C	109.5
H15B–C15–H15C	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å$^2\times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	26(1)	19(1)	18(1)	2(1)	3(1)	–2(1)
O2	21(1)	15(1)	25(1)	–2(1)	7(1)	–1(1)
N1	20(1)	19(1)	19(1)	3(1)	4(1)	–4(1)
C1	15(1)	16(1)	18(1)	–1(1)	4(1)	0(1)
C2	17(1)	14(1)	17(1)	0(1)	4(1)	–1(1)
C3	14(1)	16(1)	21(1)	1(1)	4(1)	0(1)
C4	18(1)	16(1)	21(1)	1(1)	2(1)	–1(1)
C5	17(1)	17(1)	21(1)	–1(1)	4(1)	–3(1)
C6	17(1)	19(1)	21(1)	–1(1)	5(1)	–2(1)
C7	17(1)	24(1)	24(1)	0(1)	4(1)	–2(1)
C8	20(1)	27(1)	33(1)	2(1)	6(1)	2(1)
C9	23(1)	24(1)	18(1)	2(1)	4(1)	–1(1)
C10	18(1)	30(1)	24(1)	–2(1)	5(1)	–1(1)
C11	24(1)	30(1)	27(1)	3(1)	4(1)	6(1)
C12	28(1)	22(1)	27(1)	7(1)	3(1)	–8(1)
C13	27(1)	46(1)	25(1)	8(1)	3(1)	–16(1)
C14	21(1)	61(1)	33(1)	4(1)	6(1)	–4(1)
C15	30(1)	20(1)	28(1)	0(1)	–3(1)	–7(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	5090	42	3691	29	1
H5A	3306	793	4394	22	1
H5B	3223	1269	3118	22	1
H6A	3119	2822	5020	23	1
H6B	2989	3270	3732	23	1
H7A	1277	1779	4607	26	1
H7B	1156	2147	3294	26	1
H8A	923	4186	3747	40	1
H8B	1158	3881	5077	40	1
H8C	–39	3417	4290	40	1
H9A	4605	1944	1924	25	1
H9B	5371	2782	1217	25	1
H10	3016	3484	1617	29	1
H11A	4125	3753	–296	33	1
H11B	2766	4202	–167	33	1
H12A	6033	4993	3394	31	1
H12B	5553	4984	2056	31	1
H13	7706	4980	2312	39	1
H14A	7372	2530	2629	46	1
H14B	8587	3186	2326	46	1
H15A	7280	4291	5260	40	1
H15B	6724	3975	6376	40	1
H15C	6051	4905	5462	40	1

Table 6. Torsion angles [°].

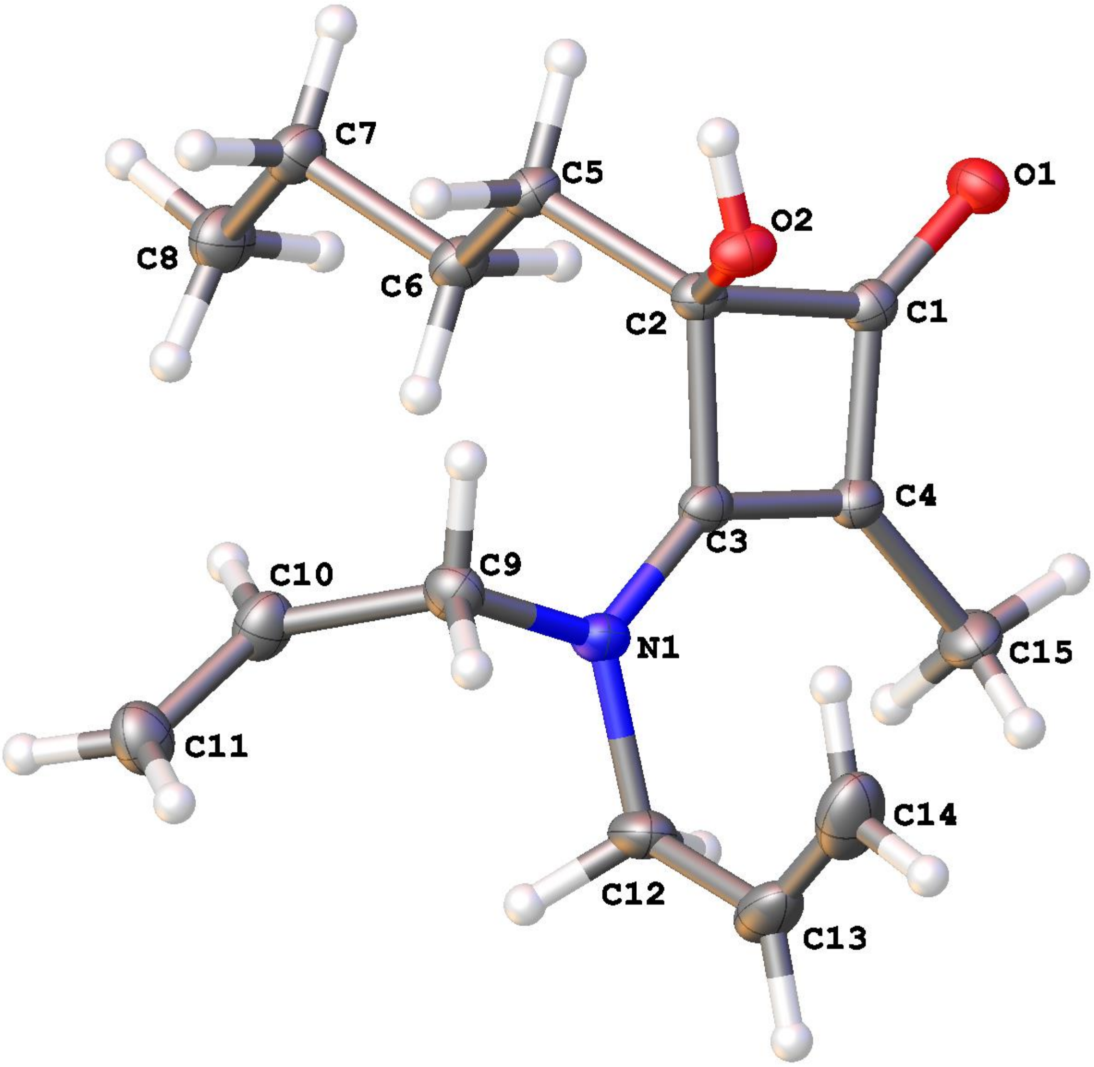
O1–C1–C2–O2	–67.14(12)
O1–C1–C2–C3	–176.20(10)
O1–C1–C2–C5	66.52(13)
O1–C1–C4–C3	175.93(11)
O1–C1–C4–C15	–1.83(19)
O2–C2–C3–N1	64.42(12)
O2–C2–C3–C1	–112.55(8)
O2–C2–C3–C4	–114.18(8)
O2–C2–C5–C6	–169.22(7)
N1–C3–C4–C1	–176.69(11)
N1–C3–C4–C15	0.9(2)
N1–C9–C10–C11	122.16(11)
N1–C12–C13–C14	–5.63(16)
C1–C2–C3–N1	176.98(10)
C1–C2–C3–C4	–1.63(7)
C1–C2–C5–C6	56.52(11)
C1–C3–C4–C15	177.56(16)
C2–C1–C4–C3	–1.73(7)
C2–C1–C4–C15	–179.49(11)
C2–C3–C4–C1	1.76(7)
C2–C3–C4–C15	179.31(12)
C2–C5–C6–C7	–177.77(8)
C3–N1–C9–C10	111.78(10)
C3–N1–C12–C13	89.74(11)
C3–C1–C2–O2	109.05(8)
C3–C1–C2–C5	–117.28(9)
C3–C1–C4–C15	–177.76(14)
C3–C2–C5–C6	–37.71(11)
C4–C1–C2–O2	110.64(8)
C4–C1–C2–C3	1.58(6)
C4–C1–C2–C5	–115.70(8)
C5–C2–C3–N1	–67.92(12)
C5–C2–C3–C1	115.10(9)
C5–C2–C3–C4	113.48(9)
C5–C6–C7–C8	–176.62(8)
C9–N1–C3–C2	–1.54(14)
C9–N1–C3–C4	176.46(10)
C9–N1–C12–C13	–81.36(11)
C12–N1–C3–C2	–172.20(9)
C12–N1–C3–C4	5.79(17)
C12–N1–C9–C10	–77.12(10)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds [Å and °].

D–H⋯*A*	*d*(*D*–H)	*d*(H⋯*A*)	*d*(*D*⋯*A*)	∠(*DHA*)
O2–H2⋯O1^{i}	0.84	1.86	2.7000(10)	172.9

Symmetry transformations used to generate equivalent atoms:
(i) –x+1,–y,–z+1


C7
C5
O2
O1
C8
C6
C2
C1
C4
C3
C10
C9
N1
C15
C11
C14
C12
C13