Novel Approaches to the Synthesis of Wieland-Miescher Ketone Analogues

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Declaration

I, Rhian Louise Turner, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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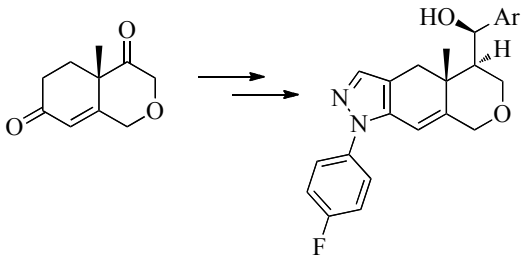
Contents

Abstract

Important for the regulation of bodily glucose levels and within the fight-or-flight response, the glucocorticoid receptor has become an interesting pharmaceutical target, with the discovery that both natural and synthetic glucocorticoids induce a significant anti-inflammatory effect. Current research focuses on the synthesis and identification of novel selective glucocorticoid receptor modulators, which lack the debilitating side effects associated with these drugs. Building upon the work of previously successful glucocorticoid modulators, pyrazole **2** is the target for this work. The first part of this thesis describes investigations into the synthesis of the Wieland-Miescher ketone (WMK) analogue **1**; an important intermediate in the prospective synthesis of pyrazole **2**. The traditional route towards WMK analogues *via* a Robinson annulation proved to be unsuccessful, with a range of catalysts trialed for the key Robinson annulation step and with difficulties arising from the synthesis of the key pyran-3,5-dione precursor. The second route proved to be more successful with the methoxy-protected WMK being afforded, *via* a 6-step route with a key Birch reduction step.



1 **2**

Scheme 1

α-Aminosulfonamides are a relatively unknown functionality, which possess the ability to mimic natural amino acids and behave as peptidomimetics. Previous literature has described this advantageous functional group as both synthetically challenging and an unstable moiety. Employing novel radical reaction conditions developed within the Wilden group, a selection of both the unusual α-aminosulfonamide and the more readily available β-aminosulfonamide have been synthesised in significant yields.

Acknowledgements

Firstly, I immensely grateful to my supervisor, Jon Wilden for giving me the opportunity to complete this work and for his continued support, patience and motivational pep-talks throughout my time at UCL, as well as proof-reading this thesis over the last few weeks.

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Finally, my eternal gratitude goes to my husband, Stuart, for all his love and support during my PhD and without whom, this work would not have been possible.

Abbreviations

AIBN	Azobisisobutyronitrile
AP-1	Activator Protein 1
Ar	Aryl
Boc	*tert*-Butyloxycarbonyl
BHT	Butylated Hydroxytoluene
Bn	Benzyl
Bt	Benzotriazole
Bu	Butyl
Cp	Cyclopentadienyl
cw-EPR	Continuous wave electron paramagnetic resonance
DAC	Deacylcortivazol
DBD	DNA-binding domain
DCE	Dichloroethane
DCM	Dichloromethane
DMA	Dimethylamine
DMEDA	*N,N'*-dimethylethylenediamine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
E	Electrophile
EDG	Electron Donating Group
ee	Enantiomeric excess
Et	Ethyl
eq.	Equivalent
EWG	Electron Withdrawing Group
FBW	Fritsch-Buttenberg-Wiechell
FF	Fluticasone Furoate
FP	Fluticasone Propionate
GR	Glucocorticoid Receptor
GRE	Glucocorticoid Receptor Elements

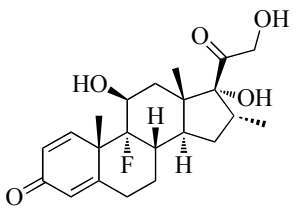
GSK	GlaxoSmithKline
HMBC	Heteronuclear multiple-bond correlation
HPK	Hajos-Parrish Ketone
h	Hour
HR	Hinge Region
HSP	Heat shock protein
Hz	Hertz
i	iso
IL-6	Interleukin 6
KDA	Potassium diisopropylamide
KHMDS	Potassium hexamethyldisilazide
LBD	Ligand binding domain
LDA	Lithium diisopropylamide
LiDBB	Lithium di-*tert*-butylbiphenyl
LiHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital
m	meta
Me	Methyl
mmol	millimole
mol	Mole
mp	Melting point
MR	Mineralcorticoid receptor
Ms	Mesyl
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
NTD	N – terminal domain
o	ortho
p	para

Ph	Phenyl
PNBSA	*p*-Nitrobenzenesulfonic acid
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
PR	Progesterone receptor
Pr	Propyl
PTAD	4-Phenyl-1,2,4-triazole-3,5-dione
rt	Room temperature
t* or *tert	tertiary
TA	Transactivation
TEBACl	Triethylbenzylammonium chloride
TEMPO	(2,2,6,6-Tetramethylpiperidine-1-yl)oxy
Tf	Triflic
THN	Tetrahydronaphthalene
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TNFα	Tumor necrosis factor
TR	Transrepression
Triton B	Benzyltrimethylammonium hydroxide
Ts	Tosyl
TsOH	*p*-Toluenesulfonic acid/tosylic acid
WMK	Wieland-Miescher ketone

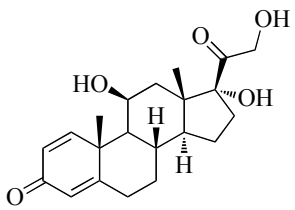
1. The Glucocorticoid Receptor & Glucocorticoids

1.1 The Glucocorticoid Receptor

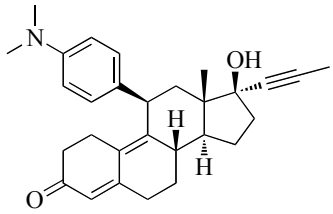
As a member of the nuclear hormone receptor family, the glucocorticoid receptor, along with its siblings, the mineralcorticoid, progesterone, androgen and estrogen receptors, make interesting pharmacological targets due to their ligand dependent activity.[1] The endogenous steroid hormones of each of these receptors all share an almost identical core steroid skeleton, with the receptors themselves sharing over 50% of their amino acid sequences.[2] These similarities allow the interaction of agonists with alternative members of the family causing significant problems in the development of drug candidates. Glucocorticoids (GC) in particular display high levels of interaction with the mineralcorticoid receptor (MR) and the GC drugs dexamethasone **3** and prednisolone **4** can also be used as MR agonists.[3-5] However, cross reactivity is one of the causes of a number of the debilitating side effects that are associated with the prolonged use of GCs. Unsurprisingly this is not a problem unique to Glucocorticoid Receptor (GR) and its ligands but occurs with all nuclear hormone receptors. A notable example is the progesterone antagonist, mifepristone **5**, which displays promise as a clinically useful contraceptive but its overt GR antagonism compromises its utility.[6]



Dexamethasone
3



Prednisolone
4



Mifepristone
5

Figure 1

Unlike other members of the family, the GR is located within almost every cell in the body[5] and in the absence of a ligand, resides in the cell's cytoplasm surrounded by chaperone proteins.[2,7] Consisting of 777 amino acids,[8] the GR is a modular protein with 3 domains, a C-terminal ligand binding domain, a DNA binding domain and an N-terminal domain.[9]

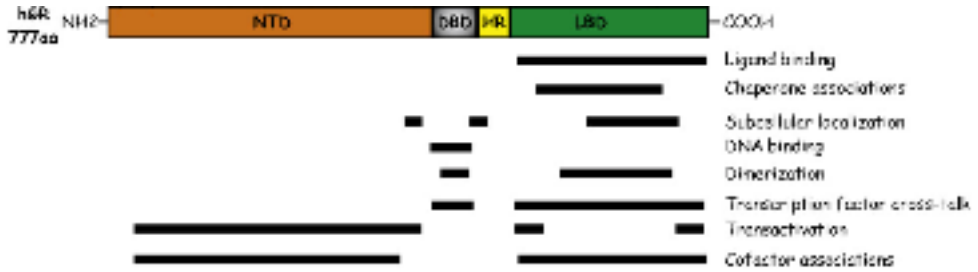


Figure 2: Glucocorticoid Receptor Modular Structure showing the associated functions with each domain.[8]

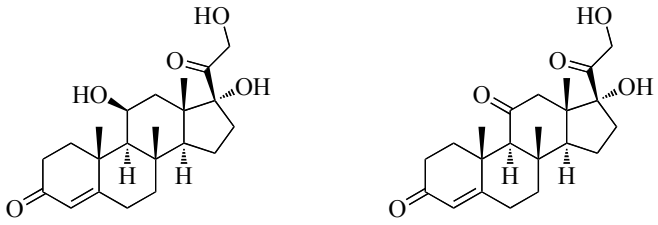
As expected, the ligand-binding domain is the region where acceptable ligands bind to the receptor, consisting of 12 helices with 4 β strands, which fold into a three-layered helical structure, creating a hydrophobic pocket for ligand bindings.[2,9] The central DNA binding domain is responsible for recognising the target sequences within DNA. Thereby causing the dimerisation of the GR-GC complex and subsequent binding to specific sequences within the promoter region of the target genes.[10] Structurally, this domain contains two distinct zinc fingers, which are critical for receptor dimerisation and unique for the nuclear hormone receptors, setting them apart from other DNA binding proteins.[9,11] The role of the N-terminal domain is less significant than the other two but is important for activation and both co-factor and basal transcription factor interactions.[8]

1.2 Cortisol & Synthetic Glucocorticoid Drugs

The endogenous glucocorticoid, cortisol **6** (fig. 3), enables an organism to respond to stress, be it physical or emotional.[5,8] Synthesised in the adrenal gland, cortisol is involved in glucose regulation in the blood, as well as fat and protein metabolism and involvement in the body's growth and reproductive processes.[5]

The "spectacular" anti-inflammatory effect of glucocorticoids was first observed in the 1940s when the cortisol derivative, cortisone **7** (fig. 3), was first isolated and administered to a rheumatoid arthritis sufferer by chemist Edward Kendall and physician Philip Hench.[12] Cortisone was hailed as a "wonder drug" in the treatment of inflammatory conditions and this work saw both Kendall and Hench awarded the 1950 Nobel Prize for Medicine.[12] However, recent research has shown that cortisone is inactive for GR and is in fact a pro-drug, which is metabolised to give cortisol as the

active molecule.[12] It was not long after its launch that the long-term detrimental side effects of cortisone were revealed.

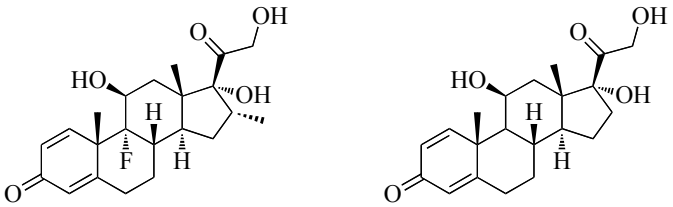


Cortisol
6

Cortisone
7

Figure 3

Synthetic glucocorticoids, dexamethasone **3** and prednisolone **4** (fig. 4) were identified as having a similar beneficial anti-inflammatory profile to cortisone but with slightly reduced side effects. They have become the glucocorticoids of choice to treat a range of inflammatory diseases, including asthma, allergic rhinitis and rheumatoid arthritis. In 2010, it was estimated that over 50 % of patients suffering from rheumatoid arthritis were being treated with glucocorticoids more or less continuously[13] and these first synthetic glucocorticoids are still the main treatment of conditions involving inflammatory processes.[9]



Dexamethasone
3

Prednisolone
4

Figure 4

However a series of wide-ranging and debilitating side effects, osteoporosis, muscle and skin atrophy, hypertension and glaucoma, hamper extensive prolonged use of these drugs.[4,14-16] A number of these side effects are due to cross reactivity with other receptors in the nuclear hormone family, notably the mineralcorticoid receptor, which dexamethasone **3** and prednisolone **4** both display agonism for and may contribute to the hypertensive side effects.[9] Another cause of these side effects is also due to the

upregulation and transcription of metabolic and endocrine genes.[17] This upregulation is controlled by the mechanism of action by the GC upon binding to the receptor and it is known as transactivation.

1.3 Transactivation & Transrepression

In the absence of a ligand, the GR is located in the cell's cytoplasm and is surrounded by a large complex of heat-shock proteins (HSP), which bind to the receptor and prevent interaction with DNA.[18] The introduction and binding of a ligand causes a conformational change in the HSP complex and the GR dissociates from its chaperones, exposing the nuclear localisation signals, which encourage translocation to the cell's nucleus.[17,18] Within the nucleus, the GR-ligand complex will bind to the palindromic sequence of glucocorticoid response elements (GRE), which initiate the transcription of genes and consequently the synthesis of proteins.[5,18] This mechanism is known as transactivation and results in the transcription of the metabolic and endocrine genes.

An alternative mechanism of the GR-GC complex involves a conformational change, which does not allow binding to DNA in the nucleus but instead exists as a monomer.[17] This change in conformation creates an affinity for the complex to bind to the transcription factors, NF-κB and AP-1, causing the inhibition of pro-inflammatory cytokines TNFα and IL-6.[14] It is this inhibition that causes the advantageous anti-inflammatory effects of glucocorticoid therapy, while the DNA interacting transactivation mechanism is responsible for the side-effects associated with glucocorticoids.

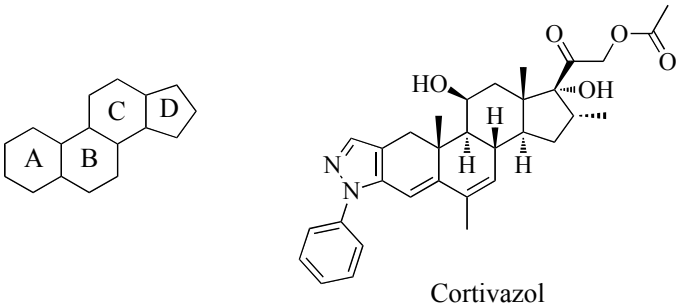
In light of this clear separation between the mechanisms of the beneficial anti-inflammatory effects and the side effects, the possibility of designing suitable compounds, which are selective for transrepression over transactivation, has been suggested. Studies have shown that the GR is essential for life with GR deficient mice dying shortly after birth. Mice possessing modified GRs, which prevent dimerisation and DNA binding, have displayed reduced levels of transactivation. However a significant level of transrepression activity has been maintained, thereby supporting the theory that these two mechanisms can potentially be separated in the human GR by an appropriate ligand.[4,19]

1.4 Selective Glucocorticoid Modulators

Over the decades, there has been much research into the identification of potential alternatives to the established glucocorticoid drugs. However since observations have been made regarding the mechanism of action, which separates the beneficial and adverse effects of these drugs, attention has been drawn to identification of selective ligands for the GR. Thereby enabling the prolonged use of these drugs and the potential to increase the patient's quality of life.

1.4.1 Steroidal Selective Glucocorticoid Modulators

Historically, the body's glucocorticoid, cortisol **6** (fig. 3) has been used as a starting point for exploring potential beneficial modifications. Interestingly, the two blockbuster glucocorticoid drugs, dexamethasone and prednisolone, have only minor differences to cortisol, which include an additional alkene bond in the A ring and the introduction of a fluorine atom and methyl group in dexamethasone. As such, it has been a natural progression for researchers to focus on modifications to the steroidal skeleton and much of the focus has been on appendages to skeleton's D ring.[15,20,21] Interestingly and significantly for this work, the introduction of a pyrazole motif adjacent to the steroid's A ring to afford cortivazol **8** (fig. 5), as a potent glucocorticoid which rivals dexamethasone.[22,23]

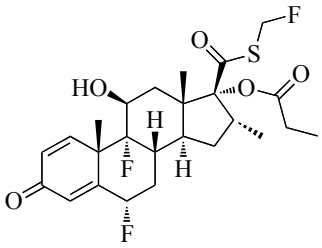


Cortivazol
8

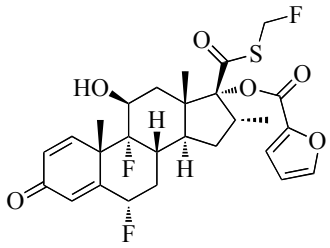
Figure 5

One success story which has seen a compound make it to market, is that of fluticasone Furoate (FF) **10** and its sister compound fluticasone propionate (FP) **9** (fig. 6), topical intranasal glucocorticoids used for treatment against seasonal and perennial allergic rhinitis, displaying the coveted once-daily efficacy.[24] With the propionate ester **9**

released first in 2012 and the furoate ester **10** in 2014, both compounds incorporate a 17β - fluoromethylthioester moiety instead of the hydroxyl seen in cortisol and dexamethasone **3**, as well as the introduction of two fluorine atoms in the B-ring. The important structural change in these compounds was the introduction of the ester functionality instead of the hydroxyl in the parent steroid. As it will be seen in this example and subsequent studies, the GR ligand-binging domain displays a high level of flexibility due to its accommodation of a number of different structures and functionality. These fluticasone esters have highlighted a previously undocumented pocket within the ligand-binding domain, the 17α pocket. The ability of the esters to access this pocket resulted in compounds, displaying a high GR binding affinity with the furoate ester (FF) **10** showing the highest binding affinity reported to date.[24]



Fluticasone Propionate
9



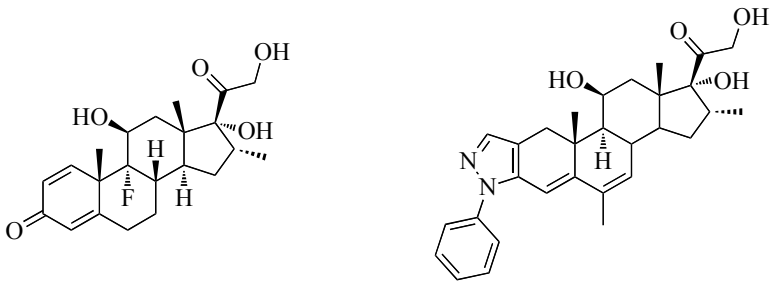
Fluticasone Furoate
10

Figure 6

X-ray crystal structures of these ligands bonded to the glucocorticoid receptor binding pocket confirm the propionate & furoate esters are encompassed by the lipophilic 17α pocket.[24] While the propionate ester only shows a partial fulfillment of the pocket, the furoate ester shows a complete fulfillment. Being esters rather than a hydroxyl, these compounds do not allow for the hydrogen bond between the 17α hydroxyl group and Gln642 observed in dexamethasone but instead are compensated by favourable van der Waals interactions.[24] It is thought that alongside the favourable van der Waals interactions, the complete fulfillment of the 17α pocket by the furoate ester moiety, is the reason for the high binding affinity for this compound for the GR.

Alongside this work, researchers also explored the X-ray crystal structures of other steroidal ligands bound to the glucocorticoid receptor. In a screen of dexamethasone **3**, FF **10** and deacylcortivazol (DAC) **11** (fig. 7) showed that dexamethasone **3** occupied

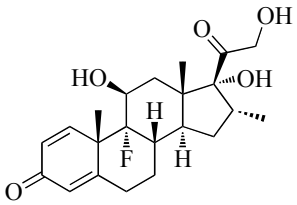
the smallest binding pocket within the ligand-binding domain of the GR, while FF and DAC extended it in two directions.[25] The extension of FF into the aforementioned 17α pocket and the pyrazole unit appended to the A ring in DAC did not affect the position of helix 12, which is associated with the functionality of nuclear receptors. The flexibility of the binding pocket in the glucocorticoid receptor suggests the potential for further extensions to the steroid skeleton and also the accommodation of non-steroidal structures.



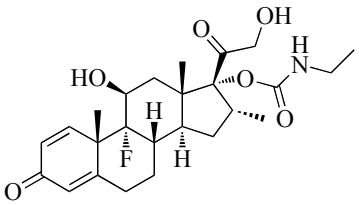
3 Deacylcortivazol **11**

Figure 7

Building on from the success of the fluticasone esters as GR agonists, researchers at Merck investigated the tolerance of the 17α pocket with the use of the carbamate functionality. Derived from betamethasone **12** (fig. 8), the resulting carbamate analogues showed a good binding affinity for GR, with some examples displaying the same or better affinity than prednisolone. The ethyl analogue **13** (fig. 8) showed exceptional affinity for the GR with an IC_{50} = 5.1 nM when compared to prednisolone (IC_{50} = 13.8 nM) and also displayed a desirable dissociated profile against the progesterone receptor. Increasing the alkyl chain length leads to compounds being only partial agonists with non-dissociated profiles, while branched alkyls and the introduction of further polarity led to a decrease in affinity for GR.[21]



Betamethasone
12



13

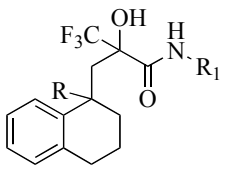
Figure 8

1.4.2 Non-Steroidal Selective Glucocorticoid Modulators

With steroidal structures being large and to a degree possessing a difficult synthesis, the evident flexibility seen with the GR and the 'structural diversity' offered by non-steroidal ligands have drawn attention to the potential of non-steroidal ligands to afford selective glucocorticoids.[26]

Recent literature has highlighted a number of non-steroidal compounds, which have been identified as GR ligands with a varying degree of both potency and selectivity.[27,28] A large variety of structures have been reported, with the development of improvements to notable ligands being chronicled.

Alongside the success GSK experienced with their fluticasone esters **9** and **10** (fig. 6), research continued into the search for the holy grail of GR ligands, a selective and potent oral drug and their direction turned towards non-steroidal compounds based around tetrahydronaphthalene (THN) structures **14** (fig. 9).



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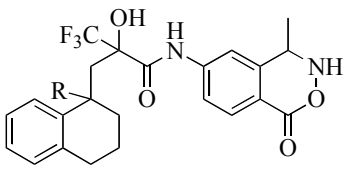


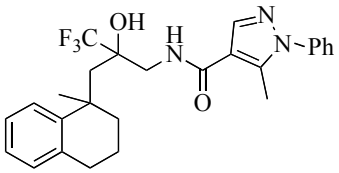
15

Figure 9

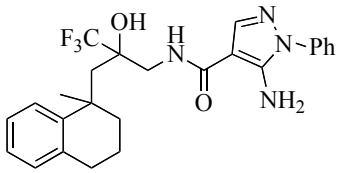
When R_1 is set as a 5-aminobenzoxainone moiety **15** (fig. 9), the resulting series of compounds showed that GR agonism is "balanced on a knife edge" with the nature of R acting as an agonist trigger, modifying the behaviour of the ligand to switch between

agonism and antagonism. When R = H the ligand displays an antagonist profile but by making the small change to an ethyl group dramatically changes the ligand into a full agonist.[29]

In addition to the controllable agonist/antagonist profile, a number of these compounds showed selectivity for transrepression over transactivation assays and a 100-fold increase in potency for the GR over other members of the receptor family, displaying the desired selective profile.[29] However the 5-aminobenzoxainone moiety severely limits the chemistry of the molecule and alongside indications from *in vitro* studies on liver samples that this group could be readily metabolised, the compounds described so far were not considered compatible as an oral therapy.[30]



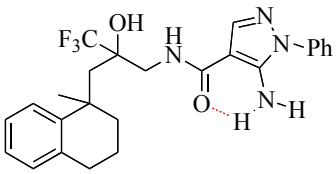
16



17

Figure 10

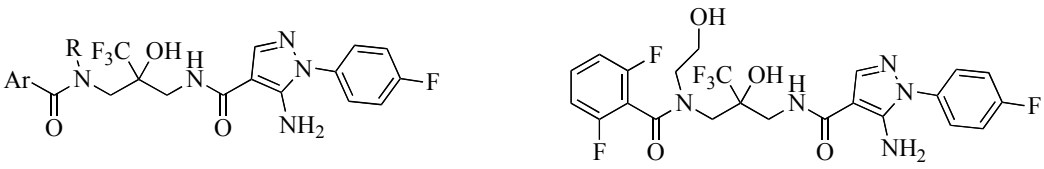
As an alternative to the benzoxainone moiety, a variety of normal and reverse amides and sulfonamides were surveyed with the reverse amide pyrazole moiety displaying a promising profile. The 5-methylpyrazole analogue **16** (fig. 10) is a potent binder for the GR displaying partial TR agonism and no TA agonism. Replacement of the 5-methyl for a 5-amino group in **17**, which, through a hydrogen bonding network, forms a 6–membered ring (fig. 11), transforms this compound into to a full agonist for TR with a 10-fold increase in potency. However this compound is also a full agonist for the TA assays. Although this series of compounds displayed an outstanding selectivity for GR over other receptors in the family and are potent agonists, they lack TR/TA selectivity resulting in a disappointing series.[30]



17

Figure 11

With research concentrating on the search for oral drugs, it was thought necessary to replace the THN moiety with an aryl group, which gives a more appropriate pharmokinetic profile for an oral therapy. This aryl group is designed to occupy the same hydrophobic pocket as the ester groups in FP and FF (fig. 6), the 17α pocket. By linking the aryl group to the right hand side of the molecule seen in **17** (fig. 11) with an N-substituted amide, which would provide an agonist trigger in the form of N-alkylation, giving rise to pyrazole **18**. A variety of substitution patterns were trialed on the aryl ring with polar substituents resulting in a reduced potency, while a di-*ortho* substitution pattern proved to enhance potency. All compounds showed excellent selectivity for the GR over other receptors in the family. Variations in the trigger group lead to an increase in potency with an ethyl group being the most potent and able to turn the powerful 2,6-substitution pattern from a partial agonist to a full agonist in compound **19** (fig. 12). This series of molecules has not produced a number of potent agonists with oral drug-like properties; however none of these ligands displayed a dissociated TR/TA profile.[31]

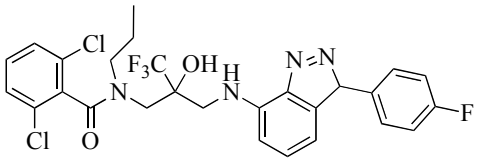


18 **19**

Figure 12

As previously stated the 5-aminopyrazole and the neighbouring amide seen in these compounds forms a 6-membered ring through hydrogen bonding, which dramatically increased its potency when compared to the analogous methyl. An increased activity is observed with the replacement of this hydrogen bond with a bicyclic indazole system **20** (fig. 13). Alongside the optimisation of the *N*-alkyl agonist trigger for the most potent ethyl, resulted in the discovery of compound **20**, which had a similar level of TR

potency as dexamethasone. As one of the most potent non-steroidal glucocorticoids reported up to this point this compound showed great potential, however disappointingly it has a profile that resembles an inhaled steroidal glucocorticoid drugs, with extreme potency high lipophilicity and molecular weight. A physicochemical profile makes it unsuitable for the development of an oral drugs.[32]

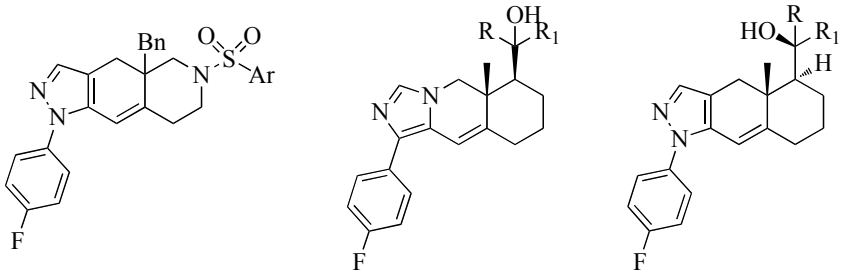


20

Figure 13

1.5 Cortivazol and Non-Steroidal Analogues

As previously highlighted, cortivazol **8** (fig. 5) is a steroidal glucocorticoid, which possesses a heterocyclic surrogate for the 3-keto group on steroidal glucocorticoids to give rise to a potent glucocorticoid that rivals dexamethasone.[22,23] Since its discovery in 1963, the pyrazole modification has been utilised in a number of studies.



21 **22** **23**

Figure 14

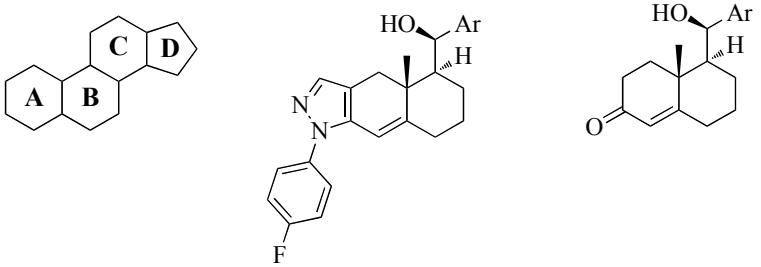
Introduction of the pyrazole into the arylsulfonamide **21** (fig. 14) led to around a 40-fold increase in GR functional activity with a antagonist profile, which was enhanced by the bridgehead benzyl moiety.[33] However this compound has no selectivity over PR.

When the neutral pyrazole **23** is replaced by the isosteric and isoelectronic basic imidazole **22** (fig. 14) the resulting compound is tolerated by the GR. However these

compounds lack functional activity in transrepression assays, while the analogous pyrazole compounds **23** are reported to be partial agonists when secondary alcohols are employed. Tertiary alcohols lead to a significant increase in activity for both the pyrazole and imidazole.[34-36] Disappointingly, this enhancement leads to an increase in transactivation efficacy in the pyrazole examples, while the imidazole examples display a dissociated profile with partial agonism in the TR assays and inactivation in TA assays.[34-36] However direct comparisons cannot be made between the pyrazole and imidazole compounds due to differences in the assays used by the three independent groups.

1.6 Design of Ligand

Two complementary papers emerged in 2004, which both highlighted the cortivazol derivative **24** (fig. 15) as selective and potent non-steroidal GR modulator.[35,36] *Via* a survey of the reported glucocorticoids, both groups observed a number of points, which contributed to the design of derivative **24**. Firstly, the majority of structural modifications occur in the C and D rings of the steroid, with the A and B rings only experiencing minor modifications such as the addition of fluorine or unsaturation. Thus suggesting that the binding area of the C-D rings is more flexible than that for the A-B ring and raising the question whether the C-D rings are required. Secondly, the 11α hydroxyl group on steroidal glucocorticoids has been shown to be important for selective binding to the GR over other members of the receptor family.[35-37] Lastly, the incorporation of heterocyclic A ring appendages, in particular pyrazole, have been shown to greatly enhance the anti-inflammatory activity of glucocorticoids. These conclusions led to the investigation of the cortivazol derivative **24**, with an aromatic moiety acting as a surrogate for the C and D rings.

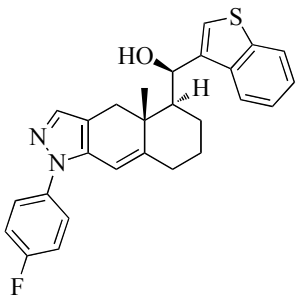


24 **25**

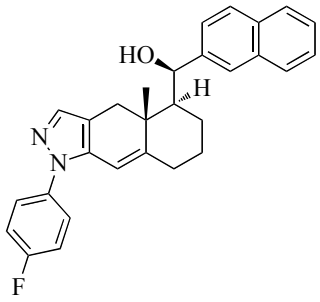
Figure 15

Initially, Shah and Scanlan began their investigations with the arylpyrazole-free derivatives **25** (fig. 15), which showed that the ligand binding pocket of GR is tolerant for the substitution of C and D rings and by varying the substitution patterns on Ar, dissociation between transrepression and transactivation can be achieved. However potencies for these compounds could not be calculated and the fusion of the arylpyrazole was considered due to the precedent set by the work by Hirschmann.[22]

With this adaptation achieved, Scanlan showed that this array of compounds had a GR binding in a range of 10-200% of dexamethasone depending on the substitution pattern on the aryl ring. Although, they have comparable potencies to the natural glucocorticoid, cortisol, they were between 20 to 100-fold less potent than the synthetic glucocorticoid, dexamethasone.[36] All compounds are selective for the GR over other members of the receptor family, while the majority of the compounds tested showed a slight dissociated profiles, compounds **26** and **27** (fig. 16) are 10-fold more selective for transrepression.[36]



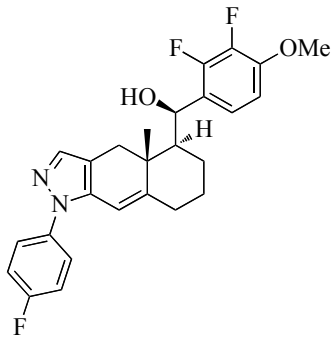
26



27

Figure 16

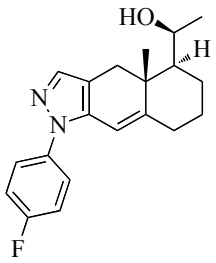
Ali *et al* at Merck showed that the small hydrophobic substituents in the *ortho* and *para* position on the C-D ring surrogate resulted in the best GR ligands, with the difluoromethoxy example **28** (fig. 17) producing the optimal dissociation pattern. It was also highlighted that tertiary alcohol derivatives at the 11α displayed a greater efficacy and potency than the corresponding secondary alcohols. However this improvement was seen in both the transrepression and transactivation assays and did not lead to improved dissociated ligands.[35]



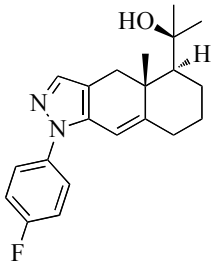
28

Figure 17

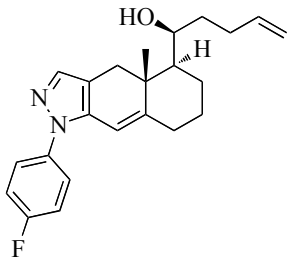
In addition to the aryl series, the Merck group also investigated replacing the aromatic groups with alkyl, alkenyl and benzyl moieties. Surprisingly the simple alkyl examples **29** and **30** (fig. 18) displayed significant affinity and functional assay towards GR. The alkenyl series also showed an increase in potency towards GR, with the 4-butenyl analogue **31** being the most potent, however this did not result in a dissociated profile. Dissociation was achieved with the benzyl series, with the *para*-methoxy example **32** being the optimal example observed in this series. However, these three series did not possess the pharmokinetics to allow them to perform well in the *in vivo* studies.[35]



29



30



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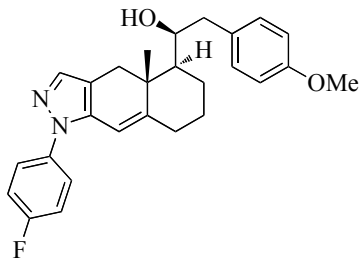
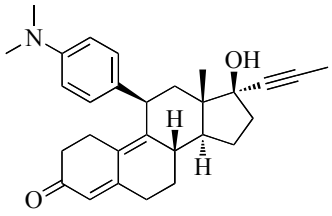


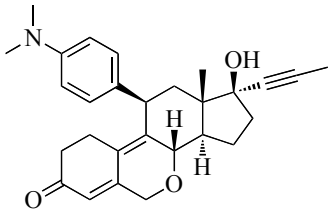
32

Figure 18

Another interesting paper relating to this area of research concerning the search for selective steroids was by researchers at Johnson and Johnson, who investigated adaptations to the progesterone receptor antagonist, mifepristone **5**.[6] As a member of the nuclear steroid hormone family, ligands of the progesterone receptor (PR) suffer from the same issues as GR ligands, in particular cross reactivity between the receptors in the family and as previously stated mifepristone displays potent GR antagonism. To combat this, substitution of the 7-methylene group for an oxygen gave rise to compound **33** (fig. 19), which proved to be 10-fold more selective for PR over GR.[6]



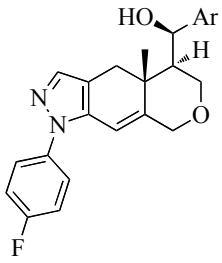
Mifepristone
5



33

Figure 19

These three papers[6,35,36] have all highlighted advancements in the search for selective steroid receptor ligands. In the search for selective GR modulators, it would be an interesting prospect to combine the two findings from these papers to investigate whether the substitution of a methylene unit for either an oxygen or heteroatom could provide an enhanced selective profile.. In light of this, compound **2** (fig. 20) is the target compound for this work.



2

Figure 20

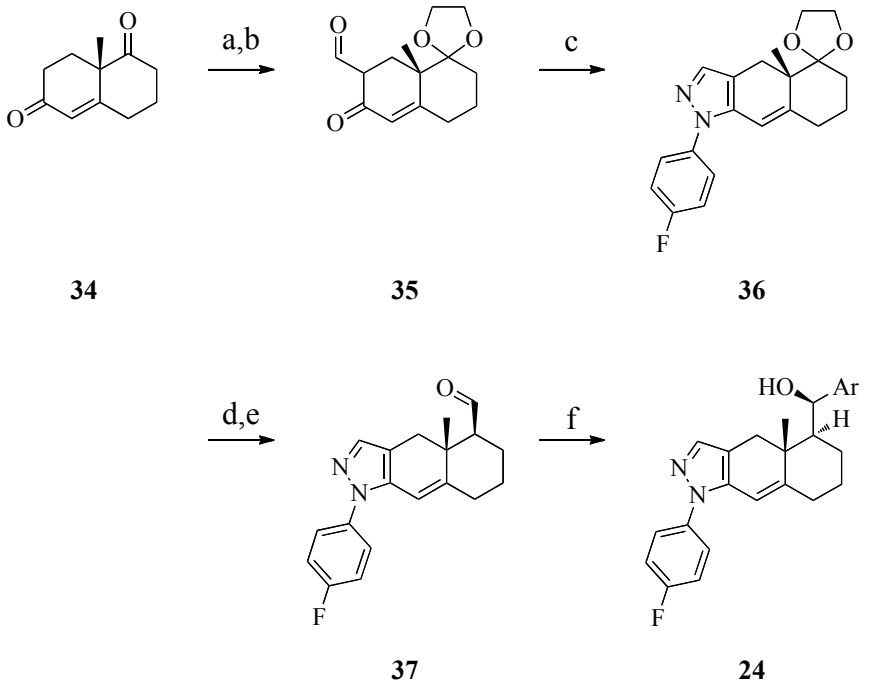
While this work has been primarily focused on the synthesis and application of the oxygen analogue **2**, hypothetically, it does not need to be restricted to the use of oxygen

as the only heteroatom in this position. The employment of other heteroatoms at this position, or any of the alternative positions on this ring, would provide their own unique chemical and medicinal profiles. Nitrogen for example would open up the possibility of further variation on its additional bonding position, which may have the potential to open up, as yet, undiscovered binding pockets within the GR-LBD. The possibility of installing either sulfur or phosphorus in the same position would bring the similar bonding profiles as the oxygen and nitrogen analogues but with ability to increase the oxidation levels of the heteroatoms and a significant increase in steric bulk providing an added advantage in this instance.

2. Synthesis of Wieland-Miescher Ketone Analogue

2.1 First Synthetic Plan

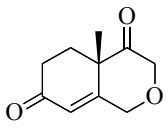
The route to the carbon analogue **24** has been well documented by both Scanlan[36] and the Merck group[35] from the Wieland-Miescher Ketone (WMK) **34** (scheme 2), which after protection of the ketone, involves formylation and reaction with 4-fluorophenylhydrazine to afford the pyrazole **36**. Deprotection and subsequent treatment with potassium hexamethyldisilazide (KHMDS) and (methoxymethyl)triphenylphosphonium chloride will afford aldehyde **37**, which will yield the target molecule **24** when treated with the appropriate aryl lithium reagent, with isomer **24** being reported as the significantly major isomer in most cases or as a single diastereomer.[35,36]



Scheme 2: (a) $HOCH_2CH_2OH$, *p*TsOH, 93%; (b) HCO_2Et, NaH, C_6H_6, MeOH, 93%; (c) 4-fluorophenylhydrazine, NaOAc, HOAc, 41%; (d) 6N HCl, THF, 100%; (e) $Ph_3PCHOMeCl$, KHMDS, THF, 75%; (f) PhLi, Et_2O, 52-87%

With this precedent, this procedure was viewed as a suitable route for the target molecule **2**. Although the synthesis of the Wieland-Miescher Ketone has been widely reported in the literature,[38-40] the oxygen analogue **1** (fig. 21), required as the starting

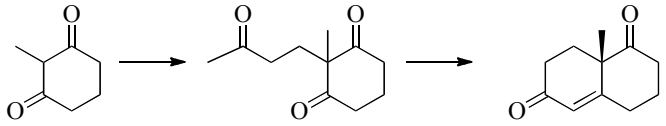
material for target compound **2**, is novel and subsequently, its synthesis would represent an important intermediate in this route.



1

Figure 21

A convenient approach would be to follow the pathways that that been previously reported and described further in due course for the carbon analogue **34**. 2-methylcyclohexa-1,3-dione **38** (scheme 3) is utilised exclusively as the starting material in these syntheses followed by elaboration to the triketone **39**, which can undergo a Robinson Annulation.



38 **39** **34**

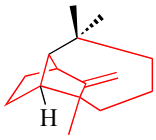
Scheme 3

With this synthesis in mind, it would be necessary to synthesise pyran-3,5-dione, which has been previously reported.[41-44]

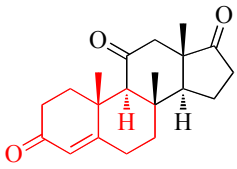
2.2 The Wieland-Miescher Ketone

The Wieland-Miescher Ketone **34** possesses a simple bicyclic diketone structure, which can be accessed *via* a Robinson Annulation, an aldol derived reaction, which enables the formation of three new carbon-carbon bonds to form a 6-membered ring.[45,46] Since its discovery in 1950, WMK has been widely utilised in the synthesis of a vast number of natural products and pharmaceuticals, with the one of the earliest examples being the work by Corey *et al* into the synthesis of longifolene **40** in 1961 and 1964.[47,48] Alongside its elaboration into steroidal structures with adrenosterone **41**[49] and digitoxigenin **42**[49] below being examples of this, it has also enjoyed an integral role the

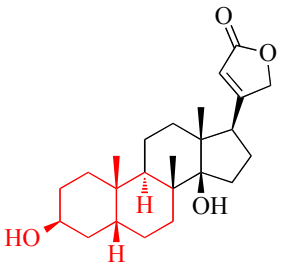
synthesis of more complex natural products such as Danishefsky's synthesis of taxol **43** in 1996.[50]



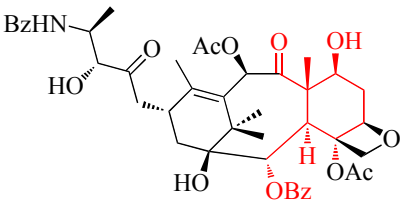
Longifolene
40



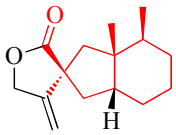
Adrenosterone
41



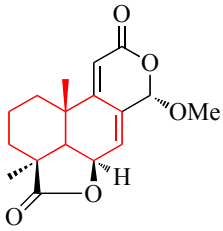
Digitoxigenin
42



Taxol
43



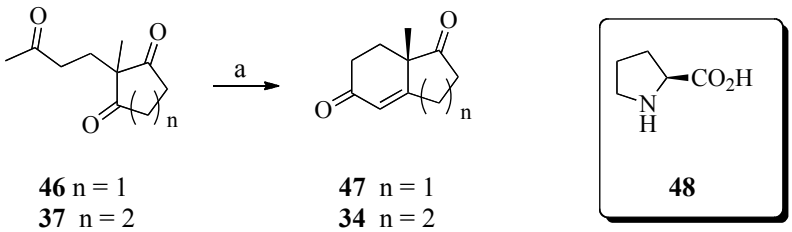
(+)-bakkenolide A
44



Oidolactone B
45

Figure 22

The original synthesis of WMK used triketone **39** as the starting material and was subjected to sodium hydroxide basic conditions.[45] However, in the early 1970s, two simultaneous works emerged by Hajos & Parrish[51] and Eder *et al,*[39] which utilised the simple, commercially available chiral amino acid, L-proline **48**, as an asymmetric organocatalyst to afford both WMK **34** and its 6,5 bicyclic sister compound, the Hajos-Parrish Ketone (HPK) **47**, from the corresponding triketone in high yields and moderate enantiomeric excess. Surprisingly, although this research highlighted the beneficial effect of the employment of proline, it was not until the turn of the century that further research was conducted into the application of proline and other simple, chiral secondary amines as catalysts in organic reactions. Since then a vast number of organocatalysts have emerged to catalyse an ever-increasing number of organic reactions.[52,53]



46 n = 1
37 n = 2

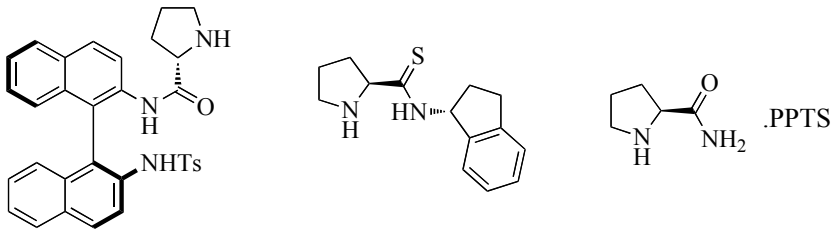
47 n = 1
34 n = 2

48

Scheme 4: When n = 1 (a) L-proline, DMF, 1M HCl, 7 h, 100 °C, 76%; when n = 2 (a) L-proline, CH_3CN, 1M $HClO_4$, 25 h, 80 °C, 83%.[39]

However groundbreaking this initial investigation has been, there are still potential issues with this procedure and room for improvements to be made. Bradshaw and Bonjoch report that the Hajos-Parrish proline synthesis affords superior enantioselectivity for the HPK **47** over the WMK (93% *ee* vs. 71% *ee*).[40,54] Alongside the use of high boiling point solvents, column chromatography, toxic reagents, which all make scaling up the reaction problematic, and the need to undergo numerous recrystallisations to afford the pure product, this difference in enantioselectivities has meant that further work has been conducted into the synthesis of WMK **34**.[54]

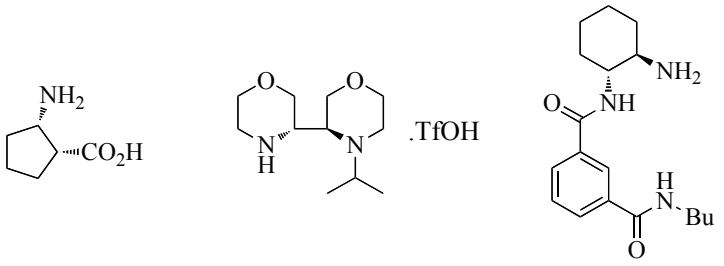
A vast array of catalysts have been reported to promote this reaction to form both HPK and WMK, each reporting a variety of yields, enantioselectivities, reaction times and catalyst loading. Some of these new catalysts have built upon the precedent set by Hajos and Eder and used proline as the starting point for the design of a new catalyst. A selection of this type of catalyst can be seen in figure 23, with the binamprolinamide **49** being the most successful, affording a 90% *ee* and 95% yield with a catalyst loading of 5 mol% after 27 h.[55] The prolinethioamide catalyst **50** also afforded a high enantioselectivity with 86% *ee* and 99% yield, again with only a 5 mol% catalyst loading over 24 h,[56] while the simple prolinamide **51**, with the use of pyridinium *p*-toluenesulfonate (PPTS) additive resulted in a high enantioselectivity but a moderate yield, 87% *ee* and 68% respectively but required a much higher catalyst loading and reaction time at 30 mol% and 144 h.[57]



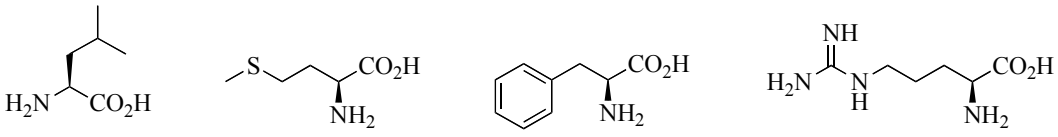
49 **50** **51**

Figure 23

Other catalysts that have been utilised in the asymmetric organocatalytic formation of WMK have structures, which are not derived from the traditional proline. Although interestingly, Davies *et al* have based their catalyst on an amino acid structure but use a β amino acid design rather than the traditional α arrangement to afford the cispentacin catalyst **52** (fig. 24).[58] This catalyst gave a moderate success yielding 75% of WMK with an 86% *ee* when a catalyst loading of 30 mol% was employed over 108 h but was the most successful of a range of β amino acids trialed. The bimorpholine catalyst **53** was more successful, resulting in a 91% *ee* and 84% yield with a catalyst loading of 5 mol% over 70 h.[59] A urea based catalyst **54** has also emerged, which affords the desired ketone **34** in a high yield, 85% and high enantioselectivity, 95% *ee*, with a low catalyst loading, 10 mol%, and a relatively short reaction time, 16 h.[60] This catalyst was concurrently employed in the synthesis of the HPK, however this attempt was not as successful as for the WMK synthesis, with only a 20% conversion after 94 h but an 81% *ee* was achieved.[60]



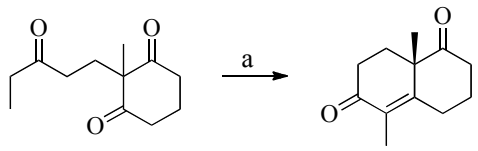
52 **53** **54**



55 **56** **57** **58**

Figure 24

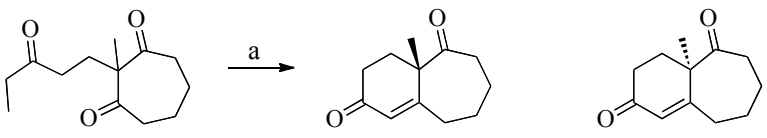
In addition, a screen of amino acids by Nagamine *et al* suggested that proline might not always be the best amino acid for this type of catalysis. When investigating the synthesis of WMK analogue **60** (scheme 5) from the corresponding triketone **59**, the use of proline saw a considerable increase in reaction time (132 h) and resulted in a low yield and enantioselectivity, 13% and 11% *ee* respectively, with both the lowest yield and % *ee*s in this study. However the use of both L-leucine **55** and L-methionine **56** (fig. 24) increased both the yield and enantioselectivity resulting in the highest yield of 74% and 84% *ee*. The highest enantioselectivity in this screen was recorded for the use of L-phenylalanine **57** as the catalyst at 91% *ee* and 56% yield. Notably all the reaction times were dramatically reduced from that of proline to 22 h.[61]



59 **60**

Scheme 5: (a) L-amino acid (1 eq), 1M $HClO_4$, DMSO, 90 °C

The researchers also investigated the synthesis of 6,7-bicyclic WMK analogue **62** (scheme 6) with the same screen of amino acid and again found that L-proline was not the best amino acid for this transformation, with only a 7% yield and 6% *ee* after 114 h. The best amino acid in this example was L-methionine **56** which resulted in a 99% yield with moderate enantioselectivity, but best for this series, at 53% *ee*. However a long reaction time was still required at 96 h. Interestingly, when L-arginine **58** was employed, the enantioselectivity was reversed to afford the opposite enantiomer **63** in an 80% yield with 13% *ee*.[61]

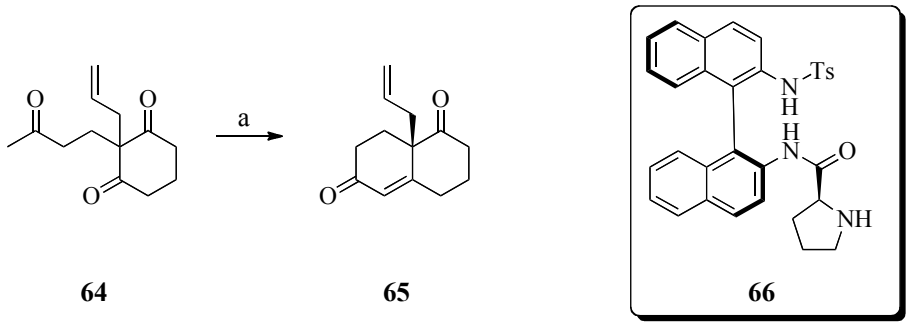


61 **62** **63**

Scheme 6: (a) L-amino acid (1 eq), $HClO_4$ (0.5 eq), DMSO, 90 °C

This work suggests that L-proline is not the best catalyst to use in the synthesis of analogues of WMK, however this is not always the case and a catalyst's ability to

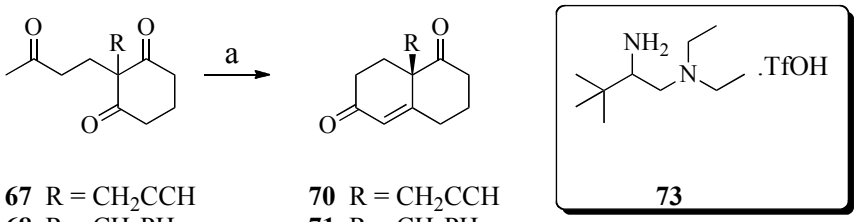
catalyse a Robinson Annulation type reaction depends upon the nature of the analogue in question. Bradshaw *et al* investigated the synthesis of analogue **65** from its triketone precursor **64**. Here 100 mol% of L-proline in DMSO resulted in a 72% yield of the desired ketone **65** with 84% *ee*, after 24 h. Reduction of the catalyst loading to 25 mol% increased the reaction time to 48 h and increased the yield to 80 %, however a reduction in the enantioselectivity was observed at 74% *ee*. The optimised conditions for this reaction utilised Binam-L-prolinamide catalyst **66** in a solvent free manner, with 2.5 mol% catalyst loading resulting in a 93% yield and 97% *ee*.[40]



64 **65** **66**

Scheme 7: (a) catalyst 66 (2.5 mol%), benzoic acid (1 mol%), solvent free, 5 days, rt

Alongside the synthesis of WMK **34**, Zhou et al also investigated the synthesis of analogues **70**-**72** with the amine catalyst **73** and WMK was afforded in a 95% yield with 92% *ee*. When the methyl group was substituted for a variety of other functionalities, the high yields were still maintained ranging from 80-95% but the enantioselectivities afforded varied much more greatly, with the benzyl derivative resulting in a 57% *ee* and the alkynyl derivative afforded an enantioselectivity of 92% *ee*.[62]



67 R = CH_2CCH
68 R = CH_2PH
69 R = Ph

70 R = CH_2CCH
71 R = CH_2PH
72 R = Ph

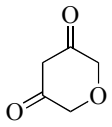
73

Scheme 8: (a) catalyst **73** (10 mol%), *m*$NO_2C_6H_4CO_2H$ (5 mol%), neat, rt

2.3 Investigations into the Robinson Annulation

2.3.1 Amino Acid Investigations

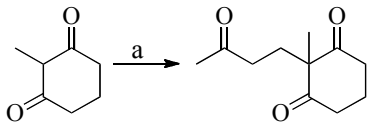
Initial investigations into the key Robinson annulation step focused on employing the readily available carbon analogue over the more precious and synthetically time consuming pyran-3,5-dione **74** (see section 2.4). Before the key reaction could be attempted, synthesis of its precursor was conducted.



74

Figure 25

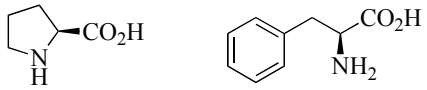
As with the key Robinson annulation step, there has been much research into the synthesis of its precursor **39** and the procedure reported by Gutzwiller *et al* is one that is still being used and built upon today.[63] The original procedure involves the Michael addition of 2 equivalents of methyl vinyl ketone to 2-methylcyclohexa-1,3-dione **38** in the presence of 10 mol% hydroquinone, water and acetic acid[63] and has proven to be an efficient procedure when used on a large scale.[40] However this procedure is less successful when it is employed on a small scale and there have been modifications to this procedure in recent years. Alterations have been made to the use of base with potassium hydroxide[64] and catalytic benzyltrimethylammonium hydroxide (Triton B),[61] both in the presence of methanol, providing high yields (93% and 83% respectively) of the triketone **39**. However it had been triethylamine, which has seen the most prolific use as a base in this reaction.[58,65-67] One procedure which employs this amine that has been widely utilised[62,68] since its first report is the one conceived by Bradshaw *et al*.[40] This solvent free procedure gave the advantage of reducing the traditional large excess of the highly toxic methyl vinyl ketone to only 1.1 equivalents and employing a catalytic 10 mol% amount of triethylamine to afford the triketone in a 97% yield at room temperature.[40]



38 **39**

Scheme 9: (a) Methylvinylketone, NEt_3 (1 mol%), 58%

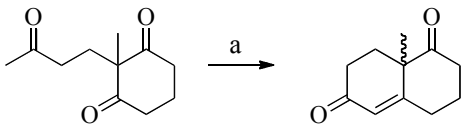
With the evident advantages of this solvent free procedure over the others reported (room temperature, short reaction times, low excess of reagents and high yields), it was this procedure, which was employed in this work and in the presence of 1 mol%, the triketone **39** was furnished in a pleasing 58% yield after 18 h.



48 **57**

Figure 26

The preliminary investigation into the cyclisation of the triketone to form WMK involved the use of L-proline **48** (fig. 26) as the catalyst. Performed in dimethyl sulfoxide (DMSO) with 10 mol% of catalyst at room temperature, the reaction provided the WMK in a disappointing yield of 9% after a reaction time of 3 days. However as the literature has shown, organocatalytic ability within amino acids is not limited to proline.[61] Therefore in addition to the use of proline, investigations were expanded to include L-phenylalanine **57** (fig. 26). However, disappointingly, no product was afforded when this amino acid was employed as a catalyst with our system.



39 **34**

Scheme 10: (a) 10 mol% L-proline, dimethyl sulfoxide, rt, 3 days, 9%

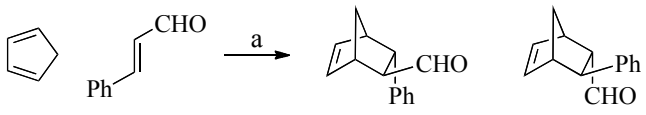
Although the enantioselectivity of the proline reaction was not investigated, there were a number of points where this reaction could be altered to enhance the yield. However

it was felt that this reaction provided an excellent opportunity to investigate an alternative organocatalytic system.

2.3.2 Previous Hydrazine-based Catalysts

An interesting organocatalytic system to emerge recently is that of hydrazines. First described by Tomkinson *et al*, they conceived a catalyst in order to build upon the suggestion that efficient and effective catalytic turnover of amine catalysts requires the catalyst to possess a highly nucleophilic nitrogen atom, which would accelerate the rate determining step; the formation of the iminium ion.[69]

In order to increase the nucleophilicity displayed by the nitrogen in amine catalysts, Tomkinson *et al* utilised the α effect associated with the introduction of a heteroatom bearing a lone pair of electrons, which has the ability to influence the reactivity at the adjacent atom, to form the hydrazine moiety in either an acyclic or cyclic fashion.[69,70] Using the Diels-Alder reaction between dienes and electron deficient dienophiles as a handle on which to investigate these catalysts, they highlighted the powerful ability of the α effect to promote iminium ion catalysis. In particular, the researchers found that in addition to an α heteroatom, the introduction of an electron-withdrawing group attached to this heteroatom greatly enhances a catalyst's activity.

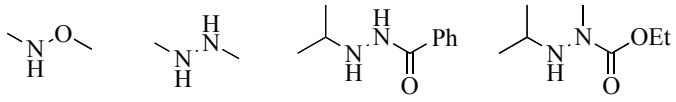


75 **76** **77** **78**

Scheme 11: (a) 10 mol% catalyst, methanol, rt

Research into this effect initially found that the use of *N,O*-dimethylhydroxylamine hydrochloride **79** (fig. 27) both increased the yield of the reaction between cinnamaldehyde **76** and cyclopentadiene **75** (scheme 11) from 7% in the absence of a catalyst to 80% and also reversed its selectivity from *endo* in the absence of a catalyst to *exo* selectivity. This reversal in selectivity was also noted in the simple secondary amine example. However, the catalyst-free selectivity was observed with dimethylhydrazine hydrochloride **80** and a reduced yield at 48% compared to the use of

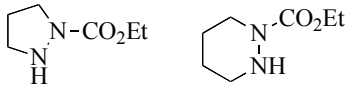
hydroxylamine. Although, this proved to be the exception as upon the introduction of electron-withdrawing groups attached to the α heteroatom, the *exo*-favoured selectivity was observed again when the hydrazine amide catalyst **81** (fig. 27) was utilised. This catalyst proved to be the most successful in this study in terms of reaction yield (82%) and ease of catalyst synthesis,[69] although further work identified the use of the ethyl carbamate catalyst **82** (fig. 27) as affording the greatest yield recorded at 98% after a 6 h reaction time.[70] All ratios of *exo: endo* products proved to be of a similar value for all the catalysts in a roughly 2:1 ratio, although the preference for *exo* or *endo* isomers depended upon the catalyst employed.[69]



79 **80** **81** **82**

Figure 27

Considering the evidence that cyclic secondary amine catalysts possess enhanced activity when compared to their acyclic counterparts, the investigations of Tomkinson *et al* evolved to incorporate this evidence into their catalyst design.[71] In contrast with the findings with secondary amines, 5-membered hydrazines **83** (fig. 28) produced disappointing results even when an electron-withdrawing group was incorporated. However, expansion of the ring to six atoms **84** (fig. 28) resulted in an increase in yield (99%) when compared to the acyclic examples. A reduction in the catalyst loading from 10 mol% did not lead to an increase in the yield, however halving the reaction time from 6 to 3 h did not disastrously affect the yield, affording 90% of the reaction product mixture. Again these catalysts yielded a 2:1 ratio of *exo: endo* products.[71]

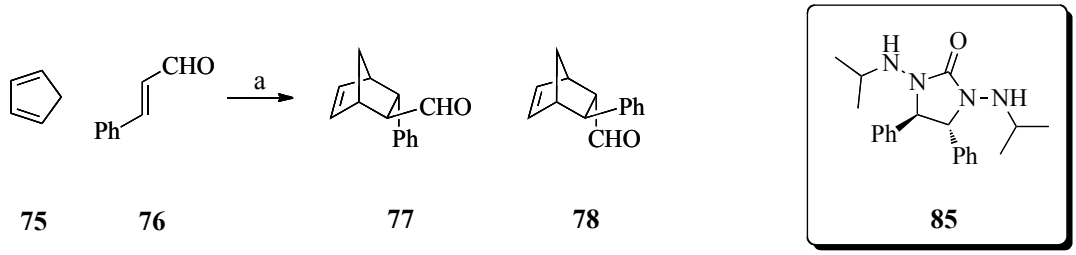


83 **84**

Figure 28

In addition to the work conducted by Tomkinson *et al*, other researchers have used hydrazine catalysts to catalyse the Diels-Alder reaction between cinnamaldehyde **76** and

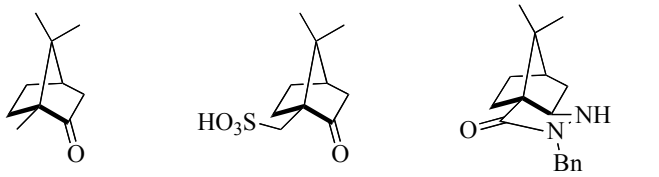
cyclopentadiene **75** (scheme 12). Suzuki *et al* employed 5 mol% of the urea-based hydrazine catalyst **85** (scheme 12), in the presence of 30 mol% *p*-toluenesulfonic acid and DMF, to afford the product in a yield of 91% with a *exo: endo* ratio of 55:45 and an enantioselectivity for the *endo* isomer of 79 %*ee*.[72]



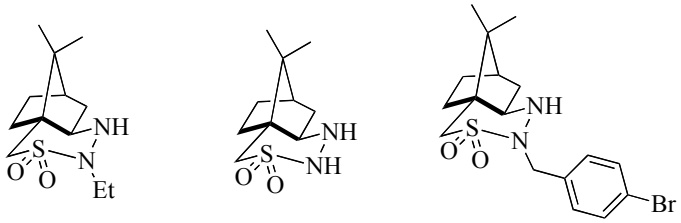
75 **76** **77** **78** **85**

Scheme 12: (a) 85 (5 mol%), *p*-TsOH (30 mol%), DMF

Camphor **86** (fig. 29) and its derivatives, in particular camphor sulfonic acid **87** (fig. 29), are readily available optically pure compounds and possess great potential as chiral catalysts for a range of organic reactions. The incorporation of hydrazine functionality into this naturally occurring terpenoid has led to a number of catalysts, which have been employed in the catalysis of the Diels-Alder reaction. Catalysts **88**, **89** and **90** (fig. 29) all catalyse the Diels-Alder reaction previously described with a range of medium to high yields.[73-75] 20 mol% of Ogilvie *et al*'s benzyl derivative catalyst **88** gave the highest yield at 96 %, with an *exo: endo* ratio of 2:1 and providing the *endo* isomer in an 88 %*ee*.[73] Modifying the carbonyl functionality for a sulfonamide in Lee *et al*s' catalyst **89** (fig. 29) did not result in a reduction of the yield (95%), however the *exo: endo* ratio was reduced to 1:1, with the *endo* isomer being afforded in a 90 %*ee*.[74] Removal of the alkylation on the hydrazine in Langlois *et al*s' catalyst **90** (fig. 29) resulted in the slight reduction of yield (87%), with the *exo: endo* ratio affording a preference for the *exo* isomer (1.5:1) but with only a 62%*ee*.[75] However introduction of a bromobenzyl moiety **91** (fig. 29) in this position led to an increase in the enantioselectivity to 88%*ee* for both the *endo* and *exo* isomers but both the yield and *endo-exo* selectivity were sacrificed at 52% and 1:1 respectively.[75]



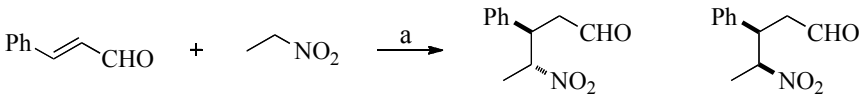
86 **87** **88**



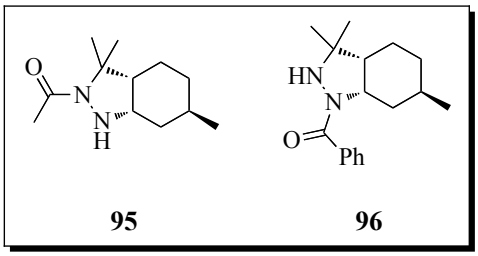
89 **90** **91**

Figure 29

In addition to the work that has been described into the use of hydrazine based catalysts in the Diels-Alder reaction, researchers have also investigated its use in other organic transformation and Jakob *et al* have employed them in the Michael addition of nitroethane **92** to cinnamaldehyde **76**.[76] Here the hydrazine catalyst **95** produced high enantioselectivities of the both the *syn* and *anti* products with 82 and 78 %*ee*s respectively. However the catalyst's effectiveness was significantly reduced with a low conversion rate at 4% after a reaction time of 3 days and a 1.1:1 *anti: syn* ratio. Alterations to the catalyst design to afford **96** resulted in an increase in conversion to 51% over the same reaction time and a selectivity for the *anti* isomer (1.7:1 *anti: syn*). Although, use of this catalyst did result in the opposite enantiomer being afforded, the enantioselectivities were also greatly reduced, with the *anti* isomer only recording a 5 %*ee*.[76]



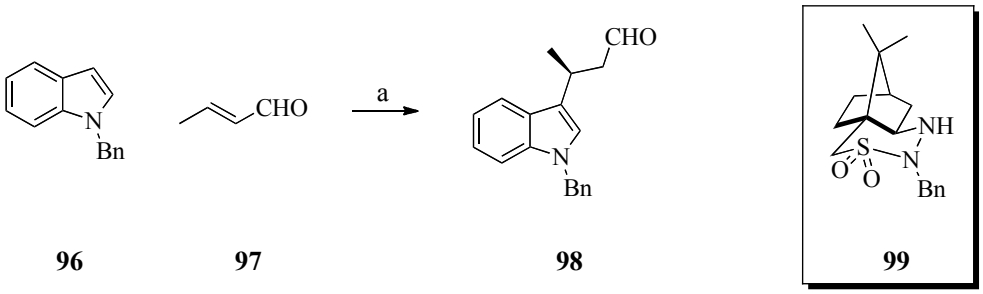
76 **92** *anti* **93** *syn* **94**



95 **96**

Scheme 13: (a) 20 mol% catalyst, neat, 50 ºC, 3 days

Building on from Lee *et al*s' work on the catalysis of the Diels-Alder reaction by camphor sulfonyl hydrazine catalyst **89** (fig. 29),[74] the same group investigated the scope of this catalyst design and have reported its success with the Micheal addition reaction between *N*-benzylindole **96** and crotonaldehyde **97**.[77] Here 30 mol% of the *N*-benzyl analogue **99** produced the product **98** in a 71% yield with an 81 %*ee*.[77]



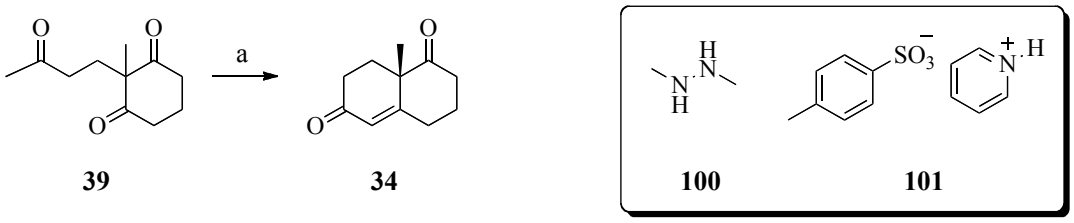
96 **97** **98** **99**

Scheme 14: (a) 30 mol% catalyst, 30 mol% trifluoroacetic acid, toluene, - 40 ºC, 20 h

2.3.3 Hydrazine Catalyst Studies into the Robinson Annulation

This work sought to utilise the cheap commercially available hydrazine, dimethyl hydrazine dihydrochloride, as the catalyst of choice and investigations began with the use of 10 mol% in methanol at room temperature. After a long reaction time of 3 days, pleasingly, a trace amount of WMK was observed.

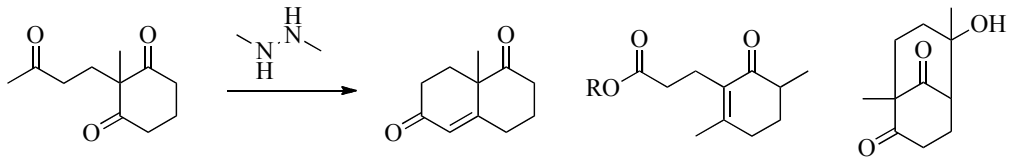
Hydrazines have the potential to behave as both an acidic and a nucleophilic catalyst and to enable the advancement of our catalytic system, it was felt necessary to confirm the catalyst was acting in a nucleophilic manner. To rule out the possibility of acid catalysis, pyridinium *p*-toluenesulfonate (PPTS) **101** (scheme 15), which has the same pK_a as dimethyl hydrazine dihydrochloride **100** of around 5, was employed under the same conditions. Thorough analysis of the reaction material showed no evidence of the reaction product confirming that the hydrazine catalyst was acting in a nucleophilic manner.



Scheme 15: (a) catalyst (10 mol%), methanol, 3 days

With this tentative conformation in hand, attention moved to the effect of the solvent on the reaction. A selection of non-polar and polar solvents were trialed with 10 mol% of the catalyst at room temperature for 1 week (table 1). In addition to methanol, both dichloromethane (DCM) and dimethylformamide (DMF) showed a trace amount of solvent and prompted a further study of chlorinated solvents, alcohols and DMF at elevated temperatures. This resulted in an increase in the yield of WMK when DMF was employed to 6%, however the chlorinated solvents DCM and chloroform did not result in an increase in yield.

In this study so far, it was methanol that had provided the most optimistic results and it was felt further investigation into methanol and other alcohol solvents was necessary.



39 **34** **102** R = Me, **103** R = Et, **104** R = ^{i}Pr **105**

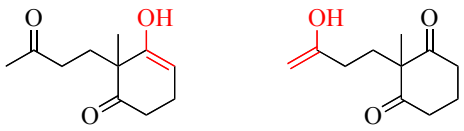
Entry	*Solvent*	*Temp (ºC)*	*Time (h)*	*Compound*	*Yield (%)*
1	Methanol	20	168	**34**	6
2	Dichloromethane	20	168	**34**	Trace
3	Toluene	20	168	**34**	Trace
4	Dimethyl sulfoxide	20	168	**34**	Trace
5	Dimethylformamide	20	168	**34**	Trace
6	Tetrahydrofuran	20	168	-	0
7	Diethyl ether	20	168	-	0
8	Acetonitrile	20	168	**34**	Trace
9	Dichloromethane	40	24	**34**	Trace
10	Chloroform	70	24	**34**	Trace
11	Dimethylformamide	75	24	**34**	6
12	**Methanol**	**65**	**6**	**102**	**80**
13	*tert*-Butanol	65	3	**105**	22
14	Ethanol	65	6	**103**	42
15	Isopropanol	65	18	**104**	96
16	None	20	168	**105**	52

Table 1: Trace compounds determined from crude ^{1}H NMR with characteristic peak at 5.8 ppm

Upon the utilisation of these solvents at 65 ºC, unexpected products were afforded in moderate to high yields. The less hindered alcohols, methanol, ethanol and iso-propanol yielded the corresponding esters **102**-**104**, while the bridged diketone compound **105** was the product when *tert*-butanol was employed. Interestingly, the

employment of solvent free conditions also resulted in the diketone **105** observed when *tert*-butanol was used.

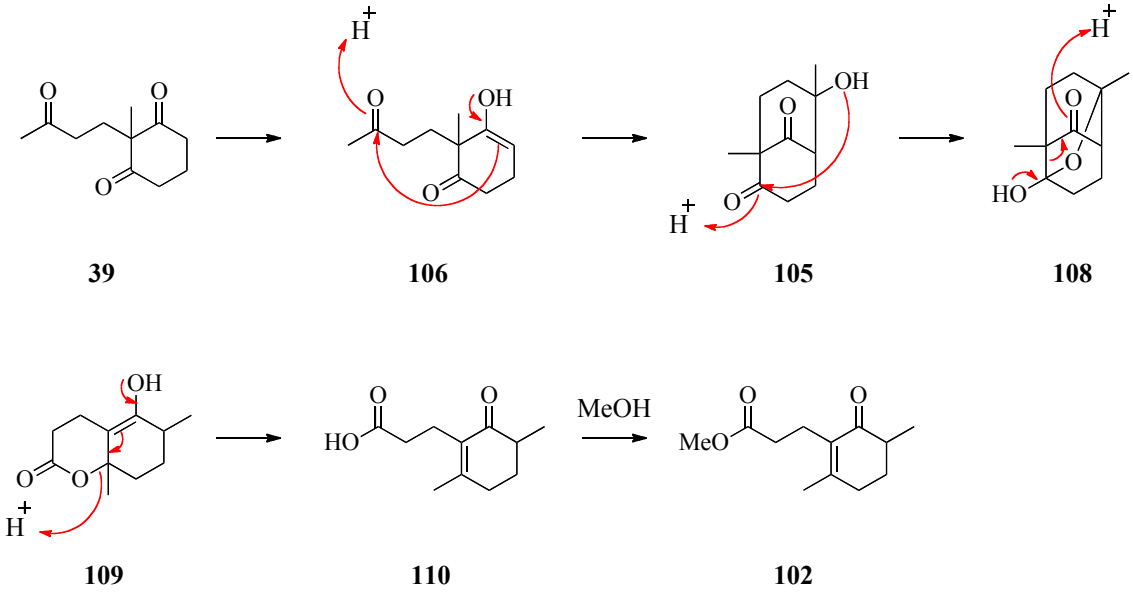
Interestingly, these compounds have been previously reported as alternative products for a traditional Robinson Annulation by Muskopf and Coates.[64] When investigating the Robinson Annulation, it was found that treatment of triketone **39** with sodium methoxide in excess methanol resulted in ester **102** as the major product. It was proposed that these compounds were formed from the cyclic enol **106** (fig. 30) rather than the acyclic enol **107**, which precedes the Robinson Annulation.



106 **107**

Figure 30

Attack of this enol to the acyclic ketone would afford the bridged diketone **105**, which in favourable conditions could undergo cyclisation by hydroxyl attack of the non-bridging ketone to yield oxa-twistanol **108** (scheme 16). Ring cleavage would afford bicyclic lactone **109**, which could undergo an elimination to yield the carboxylic acid **110**. With an excess of alcohol present, esterficiation proceeds rapidly to afford the corresponding ester.



39 **106** **105** **108**

109 **110** **102**

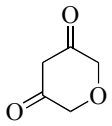
Scheme 16

With these undesired products being formed in moderate to high yields in this work, it suggests that the nucleophilic hydrazine catalyst is predominately interacting with the cyclic ketones rather than the acyclic ketone. Thus suggesting that the cyclic carbonyls are potentially more electrophilic than the acyclic ketone.

At this stage in this work, due to the predominance of these undesired compounds with the hydrazine catalyst and the disappointing yields of WMK reported for the other solvents and catalysts, investigations into the Robinson annulation on the carbon analogue were halted at this point.

2.4 Synthesis of Pyran-3,5-dione

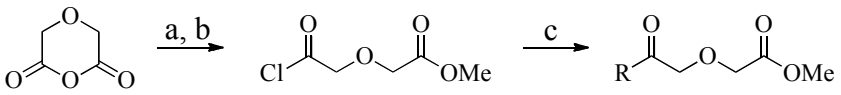
With the carbon analogue of WMK **34**, the starting material, cyclohexa-1,3-dione is commercially available, which makes its elaboration to the WMK precursor, triketone **39**, a simple, quick and easy synthesis. However for this work, the oxygen analogue is not available commercially and requires synthesis prior to its elaboration to form the WMK analogue precursor.



74

Figure 31

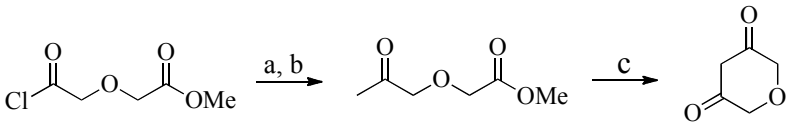
One synthetic route towards pyran-3,5-dione **74** was reported in 1977 by Terasawa and Okada.[43] Their synthesis began with the readily available diglycolic anhydride **111**, which was subjected to methanolysis and resulted the diester in a near quantitative yield. Treatment with thionyl chloride gave the corresponding acyl chloride **112** (scheme 17).[43]



111 **112** **113** R = Me
114 R = Et
115 R = Pr
116 R = Bn

Scheme 17: (a) MeOH, HCl (b) $SOCl_2$, 93% (c) R_2Cd

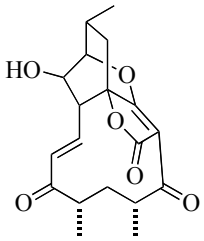
The synthetic key alkylation step sought to utilise dialkylcadmium reagents and for analogues where the alkyl group being installed was ethyl, propyl and benzyl, the reaction was successful in affording the analogues in yields of 50-60%. However the use of both dimethylcadmium and methylmagnesium bromide, which should install the methyl (ketone **113** (scheme 17)) needed to yield pyran-3,5-dione **74**, did not provide the desired compound. However the employment of methylmagnesium iodide did provide ketone **113** in a low yield. To overcome these disappointing results, Terasawa & Okado synthesised ketone **113** *via* the addition of diazomethane, followed by reduction with hydroiodic acid in a 58% yield (scheme 18). Cyclisation is induced by the addition of sodium hydride to afford pyran-3,5-dione in a 47% yield.[43]



112 **113** **74**

Scheme 18: (a) diazomethane, NEt_3 (b) HI, 58% (c) NaH, THF, 47%

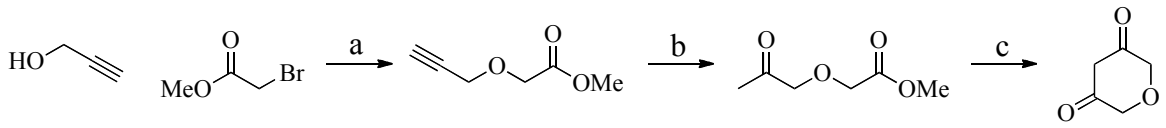
Despite the use of toxic and explosive materials, this synthesis has been employed by Rath *et al* as the starting material in their model study into the total synthesis of the antibiotic Abyssomicin C **117** (fig. 32).[78] However, despite its recent use, this procedure was not attempted in this work for the above reasons and alternative synthesises were sought.



Abyssomicin C
117

Figure 32

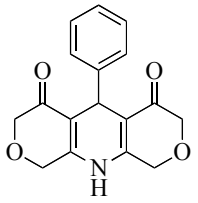
An alternative route, which has been reported by a number of groups with variations occurring in their choice of reagents, begins with the deprotonation of propargyl alcohol **118** by sodium hydride followed by the addition of methyl bromoacetate **119** to afford the alkyne **120** in a 57% yield (scheme 19).[44] Hydration of the alkyne with the traditional reagents of mercury acetate and sulfuric acid resulted in a moderate yield of the ketoester **113**, which was cyclised in a 31% yield with a mixture of potassium *tert*-butoxide in *tert*-butanol.[44]



118 **119** **120** **113** **74**

Scheme 19: (a) NaH, THF, 57% (b) $Hg(OAc)_2$, H_2SO_4, 55% (c) KO^tBu, ^tBuOH, Et_2O, 31%

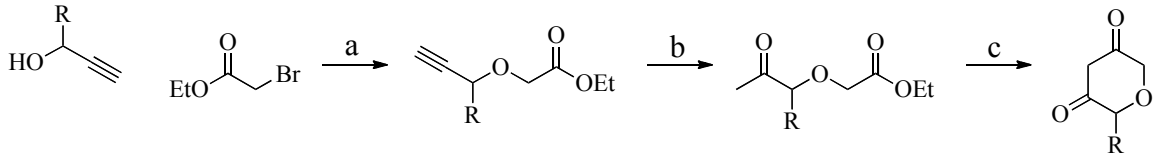
This synthesis has proved to be a successful one, which has been elaborated by Altenback *et al* in the synthesis of pyran containing dihydropyridines **121** (fig. 33), a series of K_{ATP} channel openers.[42,44]



121

Figure 33

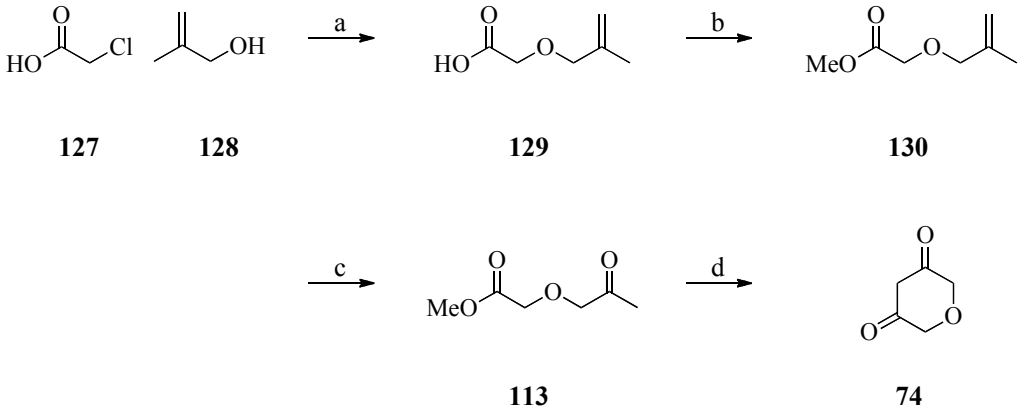
The use of propargyl alcohol, followed by hydration of the alkyne bond to form a pyran-3,5-dione based species was not a novel idea for Altenback *et al*. It was first reported by Morgan and van Heyningen in 1957 and the synthesises both follow an identical path, with the choice of ethyl bromoacetate and reagents differing.[79] However Morgan and van Heyningen did not report the synthesis of the pure pyran-3,5-dione **74** instead they reported the synthesis of analogues **126** (scheme 20), with variation arising from the alkyl groups on the propargyl alcohol.



122 **123** **124** **125** **126**

Scheme 20: R = Me, Et, Pr, ^{i}Pr, $C_6H_{13;}$ (a) $NaNH_2$ (b) Hg^{2+}, H^+ (c) $NaOEt_2$, EtOH

Lastly, Li *et al* have designed an alternative route to ketoester **113**, which involves the use of chloroacetic acid **127** and methallyl alcohol **128** as the starting material (scheme 21).[41] Following esterification, the compound is subjected to a Lemieux-Johnson oxidation to afford the ketoester **113**, which can undergo a cyclisation in the present of sodium *tert*-butoxide to yield pyran **74** in a yield of 78%. This synthesis has the advantage of being devised for and conducted on a multikilogram scale.



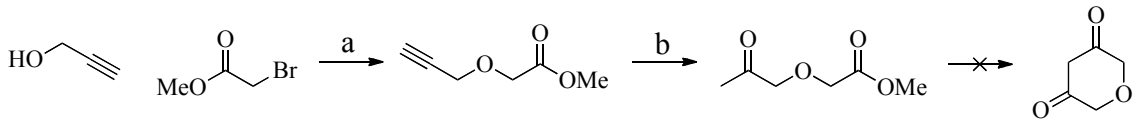
127 **128** **129** **130**

113 **74**

Scheme 21: (a) KO^{t}Bu, THF, 88% (b) MeOH, Amberlyst, 79% (c) OsO_4 polymer bound, $NaIO_4$, THF, H_2O, 89% (d) NaO^{t}Bu, THF, 78%

In this work, both the propargyl alcohol and the chloroacetic acid literature procedures were attempted in the synthesis of pyran-3,5-dione **74**. Attempts at the propargyl

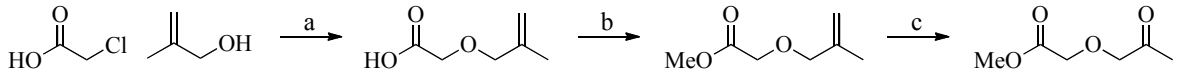
alcohol synthesis resulted in disappointing yields of 37% of the addition product **118** and 18% of the ketoester hydration product **111**.



118 **119** **120** **113** **74**

Scheme 22: (a) NaH, THF, 37%; (b) $Hg(OAc)_2$, H_2SO_4, 18%

Prior to attempts at the cyclisation, synthesis of the ketoester **113** *via* the chloroacetic acid was trialled. The use of the literature procedure conditions resulted in a high yield of 70 %, but by altering the conditions to utilise sodium hydride as the base and DMF as the solvent, the product **129** was afforded in an increased yield of 94%. Methylation proceeded uneventfully with a yield of 55%, followed by oxidative cleavage to give the ketoester in a yield of 42%.



127 **128** **129** **130** **113**

Scheme 23: (a) NaH, DMF, 94%; (b) MeOH, Amberlyst, 55%; (c) OsO_4-polymer bound, $NaIO_4$, THF, 42%

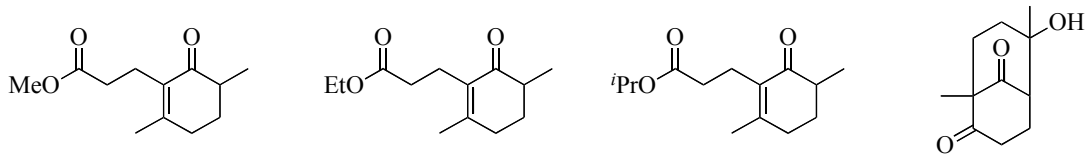
With the ketoester **113** in hand, cyclisation was attempted by both the procedures described in the literature. Crude NMRs suggested that both procedures were successful at the cyclisation to afford pyran-3,5-dione. However issues were encountered with the purification of the compound.

Initial purification investigations began with the use of column chromatography, which employed 25% methanol and ethyl acetate as the eluent. This proved to be unsuccessful at eluting the product from the column. Further investigations turned towards the literature procedures, which have not employed chromatography as a route towards purification and instead have utilised recrystallisation techniques exclusively. However, there is not a concenus on the perfect solvent mixture to achieve a successful recrystallisation amongst researchers, with Alternbach *et al* [44] employing a 1:1 combination of hexanes and ethyl acetate, while Li *et al*[41] utlised solely ethyl acetate.

Within this work, both of these combinations were trialled but to no avail on both counts.

2.5 Summary of Robinson Annulation Approach

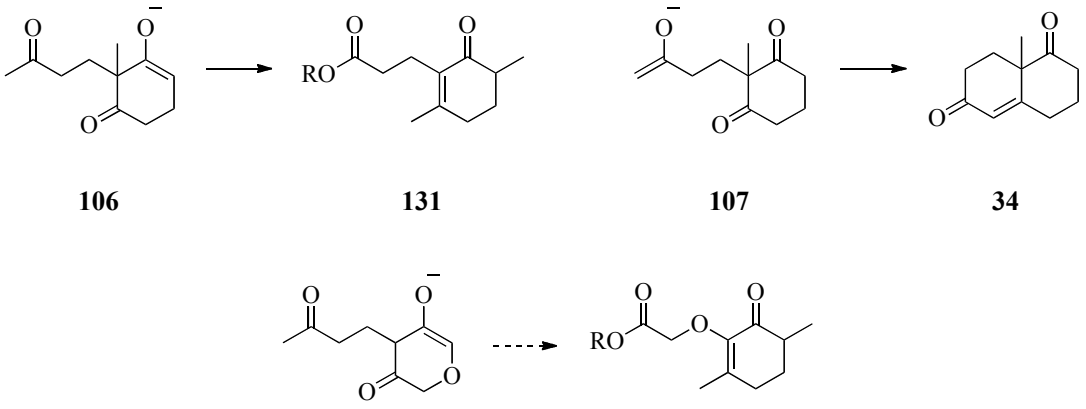
With the difficulties encountered with the isolation of pyran-3,5-dione and also the disappointing results of the Robinson annulation investigations, concerns were raised regarding the viability of this approach. The investigations into the Robinson annulation resulted in a low yield of the desired WMK and the prevalence of the esters **102-104** (fig.34) as the reaction product when a hydrazine catalyst was used.



102 **103** **104** **105**

Figure 34

With the latter's formation being due to deprotonation of the cyclic ketone, giving rise to **106** (scheme 24) rather than the expected deprotonation of the alkyl ketone, **107**, being the greatest cause of concen. Thereby suggesting that the electronegativity of the cyclic ketones is slightly greater than the acyclic ketone. It was felt that the introduction of the oxygen into the cyclohexane in the β position would increase this electronegativity, thereby giving rising to the enolate **132** and potentially yielding the unwanted ester **133**. However the inability to synthesis and isolate the pyran **74** did not allow for the testing of this hypothesis.



106 **131** **107** **34**

132 **133**

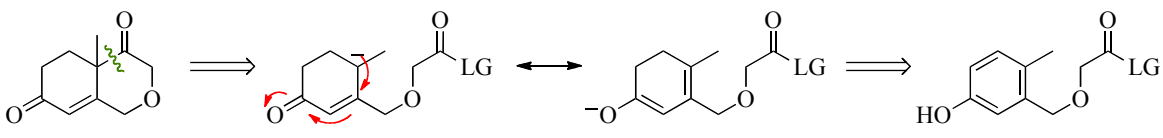
Scheme 24

2.6 New Approach to Wieland – Miescher Ketone Analogue

2.6.1 Retrosynthetic Analysis

At this point it was thought necessary to reconsider the approach to the synthesis of the WMK analogue **1**. With the literature only describing Robinson Annulation synthesises towards WMK **34**, this new thought process represents a novel approach.

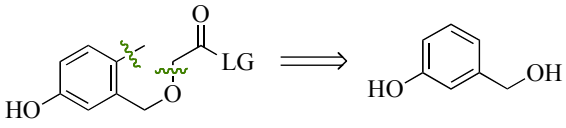
As the Robinson Annulation approach utilises the use of the pyran as a template for further elaboration, it was thought beneficial to avoid this and use the carbocycle as the core, with the pyran built around it. The obvious first disconnection, with this in mind, is to disconnect along the carbonyl and carbocycle bond, leaving a negatively charged carbon on the carbocycle. Tautomerisation can afford the enolate **135** (scheme 25), which, with the conjugated diene in the carbocycle, looks close to aromaticity, thereby suggesting a key step of a Birch reduction.



1 **134** **135** **136**

Scheme 25

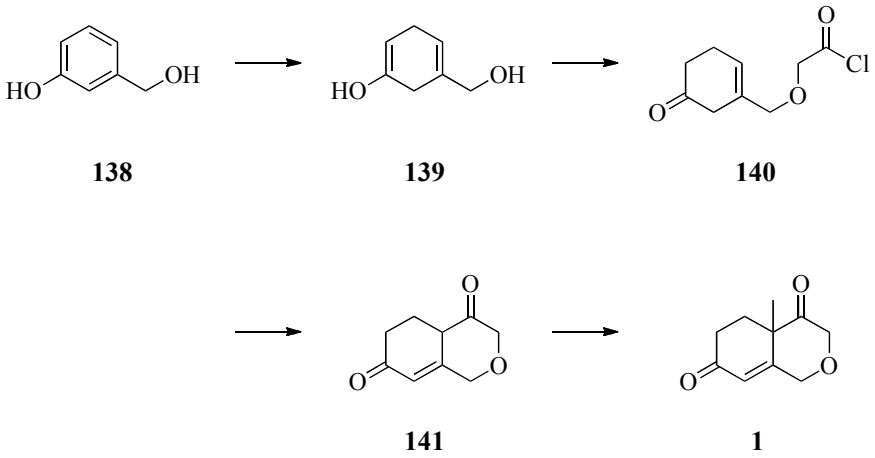
Further disconnections involved the removal of the methyl and the acetic moiety to afford inexpensive and commercially available 3-hydroxybenzyl alcohol **138** (scheme 26).



137 **138**

Scheme 26

Two potential synthesises were foreseen from this starting material encompassing a key Birch reduction step. The first sees the Birch reduction as the first step, with the hydroxyl controlling the regioselectivity of the reduction. Addition of chloroacetyl chloride to the benzyl alcohol would afford acyl chloride **140** (scheme 27), which could be cyclised and the methyl added at the end of the synthesis.



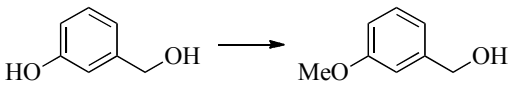
138 **139** **140**

141 **1**

Scheme 27

In our projected synthesis, the free phenol hydroxy in **139** has the potential to interfere with the forward synthesis. Particularly, during the addition of chloroactyl chloride to afford **140**, where it is envisioned would employ the reagent mixture of sodium hydride and DMF. In this step, selectivity of the addition would be questionable, with potentially a mixture of addition on to the primary alcohol or the enol being afforded. In view of this, it would be pertinent to protect the hydroxyl as a methoxy, which would maintain the desired regioselectivity of the Birch reduction and be stable enough to survive the basic nature of the majority of steps. Conveniently, the 3-

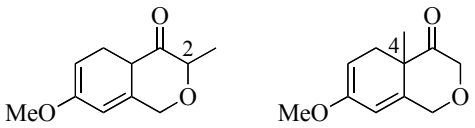
methoxybenzylalcohol **142** (scheme 28) is commercially available, thereby removing the need to conduct the protection and the danger of double methylation.



138 **142**

Scheme 28

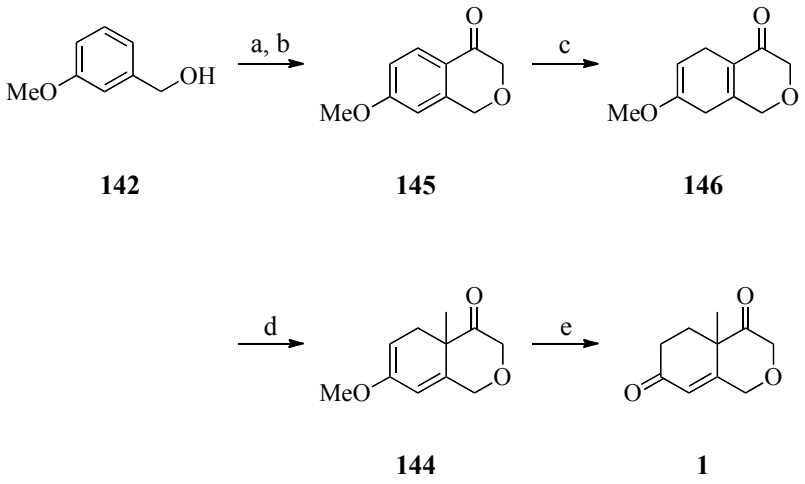
Additionally, this starting material and synthesis, advantageously has the potential to give increased control of the Birch Reduction's regioselectivity. However, there could be disadvantages with this route as a base induced methylation could see methylation in the 2 position adjacent to the pyran oxygen seen in **143** (fig. 35), rather than the desired methylation at the more hindered 4 position as in **144**.



143 **144**

Figure 35

The second projected synthesis (scheme 29) would also utilise 3-methoxybenzyl alcohol **142** as the starting material and the pyran would be formed prior to the Birch reduction. There would be issues around the reduction, however, as the methoxy and keto moieties would be in competition over control of the reactions regioselectivity (see section 2.6.2 for more details). This step could be followed by methylation, which would also install the alkene in the correct position for WMK, to afford compound **144** and deprotection of the methoxy would afford the WMK analogue.

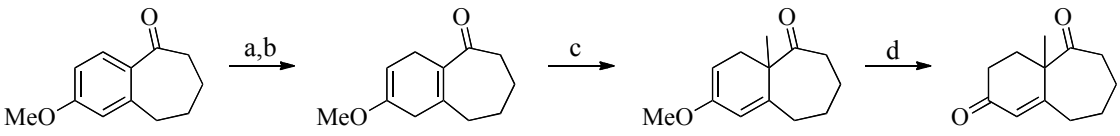


142 **145** **146**

144 **1**

Scheme 29: (a) chloroacetic acid, NaH, DMF (b) thionyl chloride, Lewis Acid (c) Na, $NH_{3(l)}$ (d) LDA, MeI (e) HCl

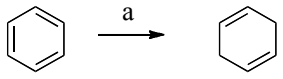
It has come to our attention that a similar route has previously been undertaken to synthesis another WMK analogue **150**.[80] However, while the product is different in this work and the researcher begin their synthetic route further along the synthesis than suggested here, this work provides confidence in the potential success of this new approach.



147 **148** **149** **150**

Scheme 30: (a) $Na_{(s)}$, EtOH, $NH_{3(l)}$, Et_2O (b) $Al(O^iPr)_3$, Acetone, toluene, 100% (c) KNH_2, $NH_{3(l)}$, Et_2O, MeI, 100% (d) Oxalic acid dihydrate, acetone, 90%.

2.6.2 The Birch Reduction

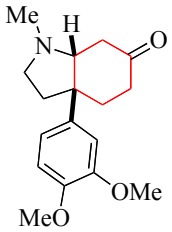


151 **152**

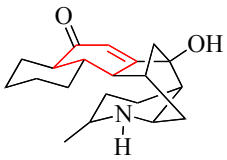
Scheme 31: (a) Group 1 metal, $NH_{3(l)}$

The Birch reduction, otherwise known as a dissolving metal reduction, is a powerful synthetic tool, which enables the reduction of an aromatic ring to an unconjugated cyclohexadiene **149** (scheme 31), in the presence of a group 1 metal and liquid

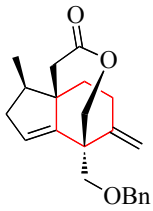
ammonia.[81,82] Its utility has been demonstrated in a number of total synthesises as shown in figure 32.[83-87]



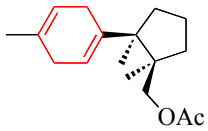
(+)-mesembrine



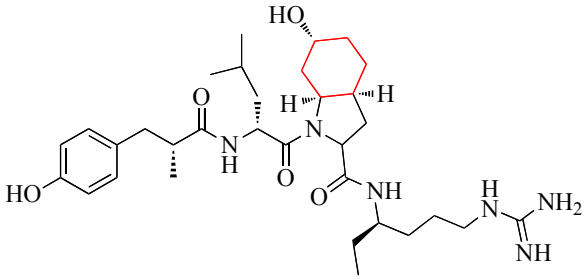
Galbulimima alkaloid (±)-GB 13



(±)-8-deoxyanisation



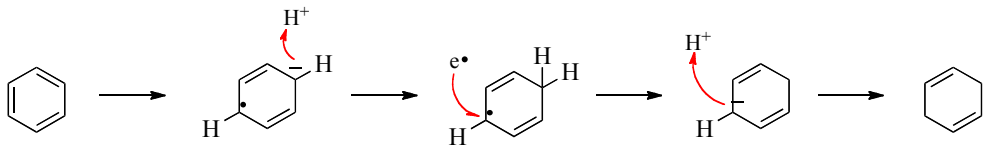
(±)-dihydrotochuinyl acetate



Aeruginosin 298-A

Figure 36

First reported in 1937 by Wooster and Godfrey,[88] the scope of the reaction was fully investigated by Birch in the 1950s[89,90] and it employs the electron that is released when group 1 metals, sodium, lithium or potassium, dissolve in liquid ammonia. This solvated electron gives the characteristic blue colour associated with the Birch Reduction reaction mixture and will reduce ammonia to amide and hydrogen gas. As this transformation is slow, an aryl ring **151**, which is a better electron acceptor than ammonia, will preferentially be reduced, with the electron filling the antibonding LUMO, forming a radical anion **153**.[82,91] The anion will readily accept a proton from a proton source, usually ethanol or *tert*-butanol, leaving a radical species **154**, which will form an anion upon reaction with another solvated electron. Again exposure to a proton source will quench the anionic charge yielding the 1,4-diene product **152**.[82,91]



151 **153** **154** **155** **152**

Scheme 31

During the process of the reduction the anions and radicals are delocalised within the ring, thereby allowing the option of a conjugated diene or an unconjugated diene. The Birch reduction exclusively yields the unconjugated isomer.

The regioselectivity of this reaction is not only limited to the nature of conjugation of the dienes but their position, in relation to substituents on the ring, is influenced too by the nature of these substituents. The key mechanistic step in the Birch reduction is the protonation of the radical anion intermediate **153** (scheme 31), which is formed after the initial electron transfer and this determines the regioselectivity of the product. An electron donating substituent **158** (scheme 32) will result in a decrease in reaction rate with protonation favoured at the *ortho* position, resulting in the substituent in a non-reduced position in the product **159**.[82,91,92] On the other hand, an electron withdrawing substituent **156** will see an increase in the rate of the reaction and favour protonation at the *para* position, resulting in the substituent in a reduced position on the ring **157**.[82,91,92]

156 **157** **158** **159**

Scheme 32

2.6.3 Investigations into Birch Reduction followed by Cyclisation Synthesis

Surprisingly, the Birch reduction of 3-methoxybenzylalcohol **142** has not been documented in the literature. However its analogue, 4-methoxybenzylalcohol **160,** has[93-95] and all these procedures utilise sodium metal and *tert*-butanol alongside liquid ammonia. With this combination of reagents being successful for its analogue, they

were employed in the attempted reduction of the *meta* analogue **142**. However the initial investigation was unsuccessful, yielding only starting material. As the characteristic blue colour of solvated electrons seen in Birch reductions was not observed in this first reaction, the sequence of additions for reagents was reversed with the metal being added prior to the benzylalcohol to ensure that the electrons responsible for the reduction were present. Again this failed to produce the desired product, yielding only the starting material **142**.

160 **161** **142** **162**

Scheme 33: (a) $Na_{(s)}$ (4 eq), EtOH (35 eq), $NH_{3(l)}$

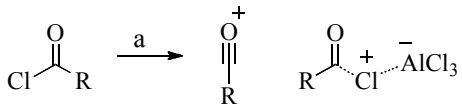
In light of the inability to afford the complete reduction of 3-methoxybenzyl alcohol **142**, investigations into this synthetic route was not furthered in this work.

2.6.4 Investigations into Cyclisation followed by Birch Reduction Synthesis

With the first key intermediate in this synthetic route being the cyclised aromatic ketone **145**, it was important to identify the most efficient synthesis towards it. Acylation of an aromatic ring can be achieved through a number of routes, Friedel – Crafts Acylation, Vilsmeier – Haack reaction and the Houben-Hoesch Reaction.

2.6.4.1 Friedel-Crafts Acylation Investigations

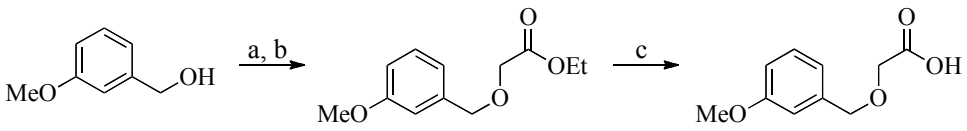
This classic reaction, which has been widely utilised in both an inter- and intramolecular fashion,[92] employs either an acyl chloride or an acid anhydride in the presence of a Lewis acid to produce either a fully dissociated acylium ion **164** or a complex of both the Lewis acid and acyl chloride **165**, depending upon the electronic makeup of the aryl ring.[91,92] In light of the mechanistic work conducted by Sato *et al*,[92,96] which showed that the acylium ion **164** is kinetically dominant when the aryl ring is either electronically evenly balanced (benzene) or contains EWG, the Friedel-Crafts acylation needed in this work would mechanistically depend upon the complex **165**.



163 **164** **165**

Scheme 34: (a) $AlCl_3$

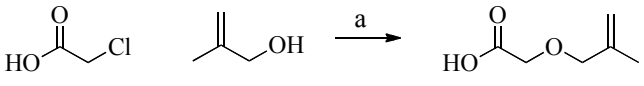
In the literature, ketone **146** has been previously synthesised *via* a Friedel-Crafts acylation of the acid **167**.[97,98] Both groups employed tin(IV) chloride as the Lewis acid in the transformation and with a yield of 52% reported, this procedure provided a logical starting point for these investigations. Synthesis of the acid was reported by Ramadas *et al* and utilised a 2-step route *via* the addition of ethyl bromoacetate to 3-methoxybenzyl alcohol to afford ester **166**, followed by hydrolysis to yield the acid **167**.



142 **166** **167**

Scheme 35: (a) $Na_{(s)}$, benzene; (b) ethyl bromoacetate, benzene, 40% (over two steps); (c) 10% KOH in methanol, 68%

A number of disadvantages were highlighted with the employment of this procedure into our synthesis. Firstly, an additional two-steps were added to the synthesis and utilise a number of hazardous reagents. In addition to its useable but underwhelming yields, it was felt that investigations should be conducted into the viability of conducting this transformation in a single step, in line with our previous work into the addition of chloroacetic acid **127** and methallyl alcohol **128** (scheme 36).

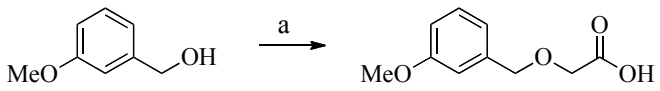


127 **128** **129**

Scheme 36: (a) NaH, DMF, 94%

With this previous work in mind, sodium hydride and DMF were successfully utilised to perform this one step transformation providing the acid **167** in a 96% yield. This

fully optimised reaction protocol employs 4 equivalents of the base in a concentrated solution of 3.4 M. The concentration of the reaction mixture did prove to be an important feature of this reaction with the reaction proceeding more successfully in the more concentrated examples (table 2).



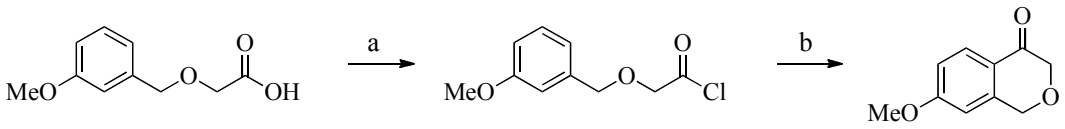
142 **167**

Concentration (M)	*NaH (Eq)*	*Yield (%)*
0.2	3	61
0.1	6	46
0.7	6	67
0.7	5	54
1.1	5	60
2.5	4	80
3.4	**4**	**96**

Table 2: (a) chloroacetic acid (1 eq.), 3-methoxybenzyl alcohol (1.2 eq), NaH, DMF, 80 ºC, 20 h. All reactions employed an acid-base extraction as the method of purification.

As a point of interest, THF was trialed producing a complex mixture of products, which proved onerous to purify and yielded only 17% of the desired acid **167**. In addition, changes in the purification method provided notable increases to the product yield, with an acid-base extraction proving an improved method over column chromatography.

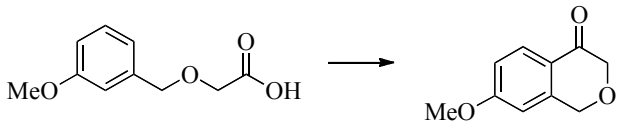
As previously noted both Ramadas *et al* and Runyon *et al* afforded the cyclised ketone **145** from the corresponding acyl chloride **168** with the Lewis acid reagent being tin(IV) chloride.[97,98] However, differences arise from their use of chlorinating agent with Runyon *et al* employing oxalyl chloride and Ramadas *et al* utilising thionyl chloride but this difference does not affect the yield of cyclised product **145** as both groups report yields of around 50%.



167 **168** **145**

Scheme 37: (a) $(COCl)_2$ or $SOCl_2$ (b) $SnCl_4$, 50% from two steps

In this work, oxalyl chloride was chosen in the first instance to act as the chlorinating agent alongside a catalytic amount of DMF, while the cyclisation step was investigated. With both papers using tin(IV) chloride in either excess or equimolar amounts, initial investigations employed one equivalent of tin(IV) chloride to successfully afford 42% of the cyclised ketone **145**. Increasing the reaction time from the reported 1 h to 3 h, increased the yield by a fraction to 47%. However given the toxicity of tin compounds, it would be advantageous for the potential scale up of the reaction to reduce the amount of $SnCl_4$ employed in this step and the initial reduction to 50 mol% of $SnCl_4$ yielded a positive 50% of cyclised ketone **145**. However, further reduction to 25 mol% resulted in an increased reaction time to 5 h and a reduction in the yield to 22%. The ideal amount of $SnCl_4$ needed for the cyclisation was found to be 40 mol% resulting in a maximum of 66% of cyclised ketone **145**. The less successful use of thionyl chloride as the chlorinating agent is highlighted in entry 6 of table 3, with a reduction in the yield to 39%.

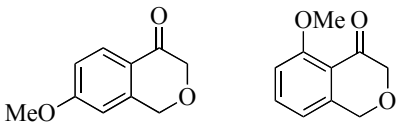


167 **145**

Entry	$SnCl_4$ (mol%)	Time (h)	Yield (%)
1	100	1	42
2	100	3	47
3	50	3	50
4	25	5	22
5	**40**	**3**	**66**
6[a]	40	3	39

Table 3: All reaction take place using acid chloride made *in situ* with an excess of $(COCl)_2$ and are conducted at 0 ºC. (a) Acyl chloride made with an excess of $SOCl_2$.

Although the major product from these reactions is the cyclised ketone isomer **159**, the alternative isomer **169** is also recovered as a minor product in a 5% yield.



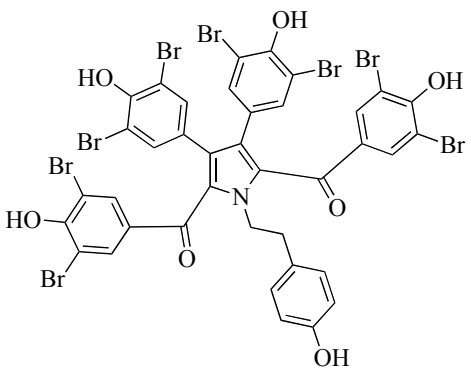
145 **169**

Figure 37

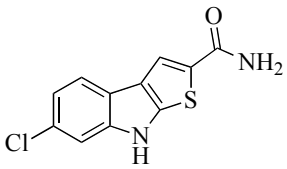
Although $SnCl_4$ displayed significant competence at the successful cyclisation of acid chloride **168** (scheme 37), concerns were still raised regarding the hazardous nature of this compound and the search for an alternative Lewis acid was conducted. This trial employed aluminium trichloride, boron trifluoride diethyl etherate, zinc(II) triflate and samarium(III) triflate. Disappointingly, none of these Lewis acids resulted in the desired product, yielding only starting material. This raised the idea that the cyclisation could be Brønsted acid catalysed rather than Lewis acid catalysed and that $SnCl_4$, which is used as a commercially available 1M solution in DCM, is providing an anhydrous source of hydrochloric acid. However the use of strong acids, methanesulfonic acid and triflic acid, did not yield the desired product, leading to the continued use of the previously optimised $SnCl_4$ conditions.

2.6.4.2 Vilsmeier-Haack Reaction Investigations

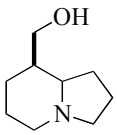
The Vilsmeier-Haack reaction is an aromatic acylation reaction, which employs a substituted amide in the presence of phosphoryl chloride ($POCl_3$) to form a chloroiminium ion, also known as the Vilsmeier reagent, which can act as an electrophile despite the absence of a Lewis acid.[92] First reported in 1927, this reaction has enjoyed wide spread use in the synthesis of heterocycles[99-106] and within natural product synthesis.[107-110]



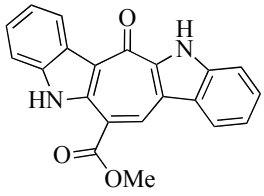
Polycitone A



Thienodolin



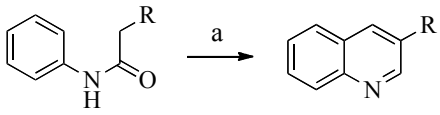
(±) – Tashiromine



Caulersin

Figure 38

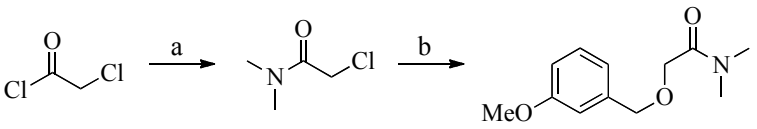
In this work, it was decided to employ this technique in a relatively underused intramolecular manner. In comparison to the intermolecular sister reactions, the intramolecular Vilsmeier-Haack reaction features sparsely in the literature. Meth-Cohn and colleagues have described the use of an intramolecular Vilsmeier-Haack reaction to furnish a quinoline **171** from the acylanilide **170**. Here, the Vilsmeier conditions are utilised to perform, firstly, the formylation of the amide to yield the α-chloroenamine followed by the acylation to give quinoline **171**.[111]



170 **171**

Scheme 38: (a) $POCl_3$, DMF, 120 ˚C

To attempt this type of reaction in this work, installation of the amide functionality was required. With amidations between an amine and a carboxylic acid requiring high temperatures to facilitate the necessary elimination of water to yield the product, it was felt that direct amidation of the acid **167** might prove to be detrimental.[112,113] As such synthesis of the amide prior to reaction with alcohol **142** was approach taken. In order to afford a higher yield of amide **173**, the available acid chloride **172** was employed in place of the corresponding chloroacetic acid **127**, which would allow for the correct functionality to allow for appendage to the benzylalcohol **142**, as well as enabling a higher yielding and speedier reaction time.[113]

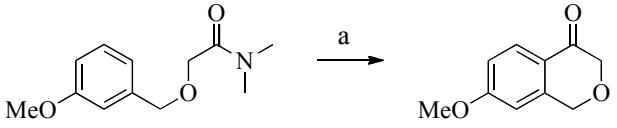


172 **173** **174**

Scheme 39: (a) $HNMe_2$, THF, 50%; (b) 3-methoxybenzyl alcohol **139**, NaH, DMF, 79%.

Upon production of amide **173**, the reaction with benzylalcohol **142** was performed in the same manner as previous reactions with sodium hydride and DMF, yielding the amide **174** in a 79% yield.

Attempts at the intramolecular Vilsmeier began with the use of an excess of $POCl_3$, initially at room temperature followed by heating to 50 °C and then 80 °C. Unfortunately, these conditions did not result in the desired product. Both thionyl chloride and oxalyl chloride were trialed as alternative chlorinating agents. Although both have been utilised as Vilsmeier reagents,[92,114,115] they were again unsuccessful at furnishing ketone **145** from amide **174**.



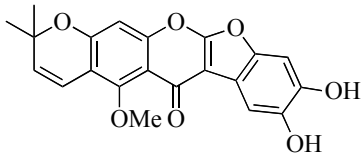
174 **145**

Scheme 40: (a) Tf_2O, 17%

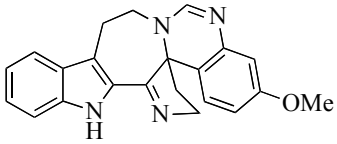
Although traditional Vilsmeier reagents have not produced the desired products in this work, there is scope within the literature for Vilsmeier-type reaction to occur with unorthodox reagents. The one that proved to be successful in this work was first reported by Black in the 1990s,[116,117] employing triflic anhydride, which has been shown to be versatile in other Vilsmeier-Haack type reactions.[118-120] When our amide **174** was subjected to this reagent, it did prove successful in affording the acyl ketone **145**. However the long-term employment of this synthetic method was put into doubt due to the low yield obtained at 17%.

2.6.4.3 Houben-Hoesch Reaction Investigations

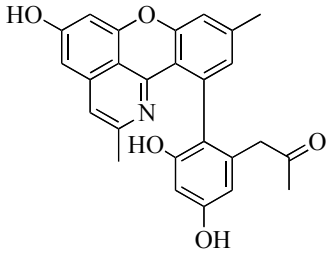
The Houben-Hoesch reaction is a method of affording aromatic ketones from the aromatic electronic substitution of nitriles.[121] First described by Hoesch in 1915[122] and Houben in 1926,[123] this reaction has not enjoyed the recognition that the Friedel-Crafts and Vilsmeier-Haack reactions have. However despite its low key presence within the literature, it has been employed in the synthesis of a number of natural products[124-126] and examples of intramolecular transformations are also present.[127,128]



Hirtellanine A



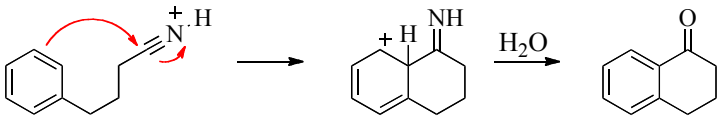
Trigonolimine A



Cassiarin F

Figure 39

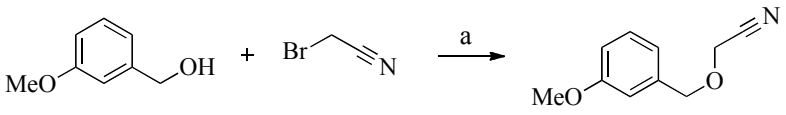
Installation of a ketone functionality through an imine intermediate is initiated by the protonation of the nitrile, traditionally by the use of a Lewis acid-Brønsted acid mixture.[96] However, the use of strong organic acids have proved to be more reliable reagents for the transformation, with triflic acid and trifluoroacetic acid being readily employed.[96,127,128]



175 **176** **177**

Scheme 41

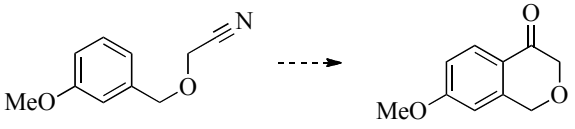
In this work, the nitrile functionality was installed by utilising 3-methoxybenzyl alcohol **142** and bromoacetonitrile **178** under the same sodium hydride/DMF conditions used previously to give nitrile **179** in a disappointing 17% yield.



142 **178** **179**

Scheme 42: (a) NaH, DMF, 17%

Exposure of this nitrile **179** to Houben-Hoesch superacid conditions began with the use of excess methanesulfonic acid, which, disappointingly, resulted in a reaction product, which was unable to be isolated and identified. Reduction of the amount of acid to a catalytic 50 mol% amount again resulted in the same black, unidentifiable reaction mixture. Increasing the acidity of the reaction mixture with the use of triflic acid again gave no identifiable product, while reducing the acidity by employing concentrated sulfuric acid resulted in yielding the starting material.



179 **145**

Entry	Acid	Equivalents	Solvent
1	CH_3SO_3H	excess	None
2	CH_3SO_3H	0.5	DCE
3	CF_3SO_3H	1.2	DCE
4	H_2SO_4	1.2	DCE
5	$(CF_3SO_2)_2O$	1.5	DCE

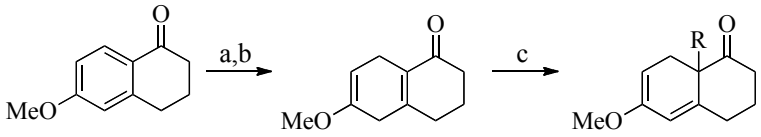
Table 4

With no desired reaction product or alternative products being formed from this route, further elaboration and investigation were not undertaken.

2.6.5 Birch Reduction of 7-Methoxyisochroman-4-one

With the most synthetically viable route to 7-methoxyisochroman-4-one **145** being *via* a Friedel-Crafts acylation, the Birch reduction could be attempted. Although, the reduction of aryl ketone **145** has not been reported within the literature, the carbon

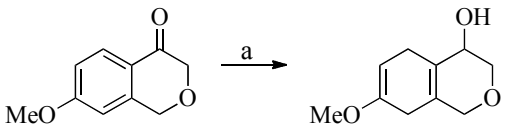
analogue **180** (scheme 43)[129] has, alongside the work by Ireland *et al* into the seven membered analogue.[80] As it can seen from the Paquette *et al* synthesis in scheme 43 and the Ireland *et al* synthesis in scheme 28 (section 2.6.1), both groups of researchers successfully employed sodium and liquid ammonia to afford the Birch reduction, which incidentally also reduced the ketone in both cases. Oxidation has been achieved with both examples by the use of an unusual oxidising agent, aluminium isopropoxide, and the subsequent alkylation is achieved with the employment of potassium amide as the base and an appropriate alkyl halide.



180 **181** **182**

Scheme 43: (a) $Na_{(s)}$, $NH_{3(l)}$, 67% (b) $Al(O^iPr)_3$, acetone, toluene, 88% (c) KNH_2, RCl, $NH_{3(l)}$, (not isolated)

The precedence of this work in the literature gives confidence that the Birch reduction of our aromatic ketone **145** will proceed with the desired regioselectivity for the forward synthesis. Alongside the methoxy-directed reduction, these examples also suggest that the reduction of the ketone should also be expected, with diene **183** being the predicted outcome for our reaction. When treated with 7.5 equivalents of sodium metal in liquid ammonia and excess ethanol, the reduction proceeds as predicted yielding diene **183** in a 58% yield.



145 **183**

Scheme 44: (a) 7.5 $Na_{(s)}$, $NH_{3(l)}$, EtOH, Et_2O, 58%

Although this reaction did prove to be successful in the synthesis of diene **183**, it was also a rather unreliable and capricious reaction. Several changes to the reaction conditions were made to try to overcome this. Changing the metal from sodium to

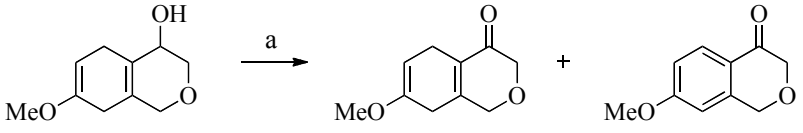
lithium did not provide the product, while changing the co-solvent from anhydrous ether to anhydrous THF also resulted in a slight drop in yield to 45%.

Despite, the unpredictability of this reaction, enough material was afforded to take through to the next step. The oxidation has previously been achieved with the analogous 6-membered **184**[129] and 7-membered **185**[80] carbocycles with the use of the Oppenauer Oxidation, which employs a metal alkoxide acting as a Lewis acid, alongside a simple ketone, usually acetone or butanone.[82,130] Usually performed in toluene or benzene, this simple, easily accessible reagent mixture has the advantage of being highly selective for the oxidation of secondary alcohols to ketones with no over oxidation observed or interference with other functionality within the molecule.[82,130-132]

184 **185**

Figure 40

Both Paquette[129] and Ireland[80] used catalytic aluminium isopropoxide and acetone mixture in toluene. With this being successful in their examples, it was applied to the alcohol analogue **184** in this work. This was equally successful yielding ketone **146** in a 58% yield with no rearomatisation of the reduced ring observed. This observation is noteworthy as, in addition to the employment of the Oppenauer oxidation, an alternative oxidant was trialed. Use of the widely utilised Dess-Martin Periodinane (DMP) was successful at the oxidation of the alcohol to ketone, but it also resulted in providing a significant amount of rearomatised product **145**.

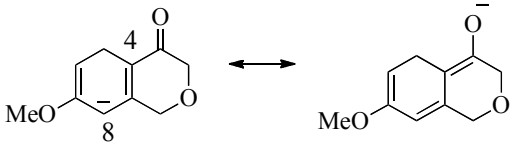


184 **146** **145**

Scheme 45: (a) $Al(O^iPr)_3$, acetone, toluene, reflux, 58%

At room temperature, the use of 150 mol% of DMP in the presence of lutidine resulted in 1:1.6 mixture of ketone **146** and aromatic product **145**. Cooling of the reaction mixture to –10 °C leads to a reduction in the amount of aromatic product recovered with the ratio between **146**:**145** being 1:0.5. Unfortunately, further reaction cooling did not result in further reduction of amount of aromatic product afforded.

The next step in the synthesis was the methylation of the hindered 4 position adjacent to the newly formed ketone. To provide the required regiochemistry necessary for the product, deprotonation at the 8 position as shown in structure **185** and subsequent tautomerisation **186**, was required to facilitate this.



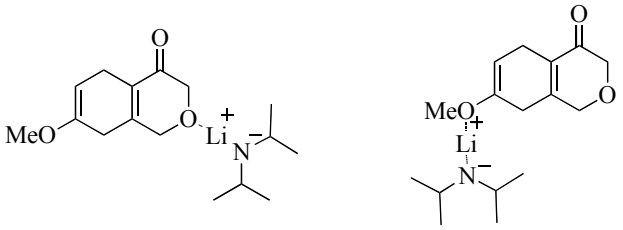
185 **186**

Scheme 46

Previous literature synthesises[80,129] have utilised amide bases to achieve this enolate formation, with methyl iodide acting as the methylating agent. The base of choice has been potassium amide, which is made in *situ* from potassium metal and liquid ammonia. Wishing to avoid the use of both these hazardous materials in this work, an alternative base was sought and initial investigations continued to concentrate on amide bases but began with lithium diisopropylamine (LDA). Being a base that is routinely used in enolate formation,[82,91,133,134] we were confident that the methylated product **144** would be rapidly yielded. At a range of temperatures from –78 °C to room temperature, the methylated product was not observed and instead an inseparable product mixture was isolated.

Although amide bases have been the base of choice by previous researchers, they have limited themselves to the use of those where potassium is the counterion with Paquette *et al*[129] and Ireland *et al*[80] using potassium amide, while Ireland & Thompson[135] and Smith & Richmond[136] employed potassium hexamethyldisilazide (KHMDS). Both the two latter research groups did trial and report the use of lithium amide equivalent bases but to no avail with recovered starting material being afforded. Although in the case of

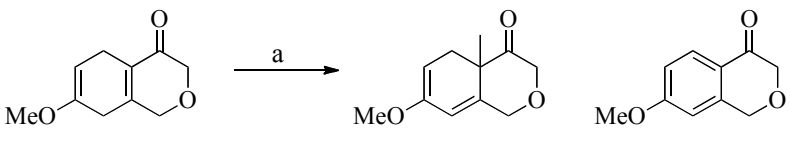
Smith & Richmond, LDA had proved effective at producing the desired deprotonation and rearrangement in an earlier model study. The major difference between the model and their actual system was the level of oxygenation within the molecule, with the model system bearing significantly less oxygen atoms than the actual one. This observation ties in with the hypothesis made by Ireland[135] that the hard nature of the lithium counterion interacts strongly with the oxygen atoms within the molecule thereby preventing the base's further approach to the desired site of deprotonation. With thought given to the observations made thus far to our system, it could be argued that the lithium counterion of LDA is strongly coordinating to the cyclic oxygen of the B ring (structure **187** (Fig. 41)) rather than the methoxy oxygen (**188**) and also potentially to the ketone, thereby removing the base from the site of deprotonation on carbon 8.



187 **188**

Figure 41

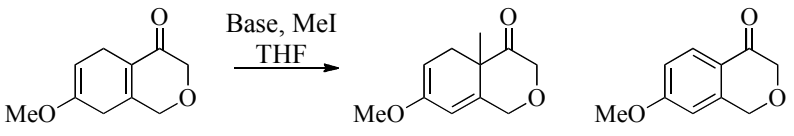
As potassium bases have proved successful for this transformation in the literature, further investigations on our system concentrated on the use of KHMDS and following the initial investigation with 2 equivalents of base, a trace of the methylated compound **144** (scheme 47) was yielded. However repetition of the reaction conditions and alterations to these conditions did not lead to the completion of the reaction and instead yielded a mixture of starting material **146**, methylated **144** and rearomatised product **145**.



146 **144** **145**

Scheme 47: (a) KHMDS (1 eq.), MeI, THF, 23%

With as much as 60% starting material being recovered, patterns emerged from the trialing of a number of conditions, firstly, an increase in the equivalents of base to 5, led to a decrease in the yield of methylated product **144** to zero, while the reduction of the amount of base to equimolar gave the greatest yield of methylation at 23%. In addition, this reduction of base also reduced the ratio between methylation and rearomatisation with only a trace of ketone **145** afforded in this example.



146 **144** **145**

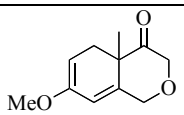
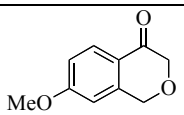
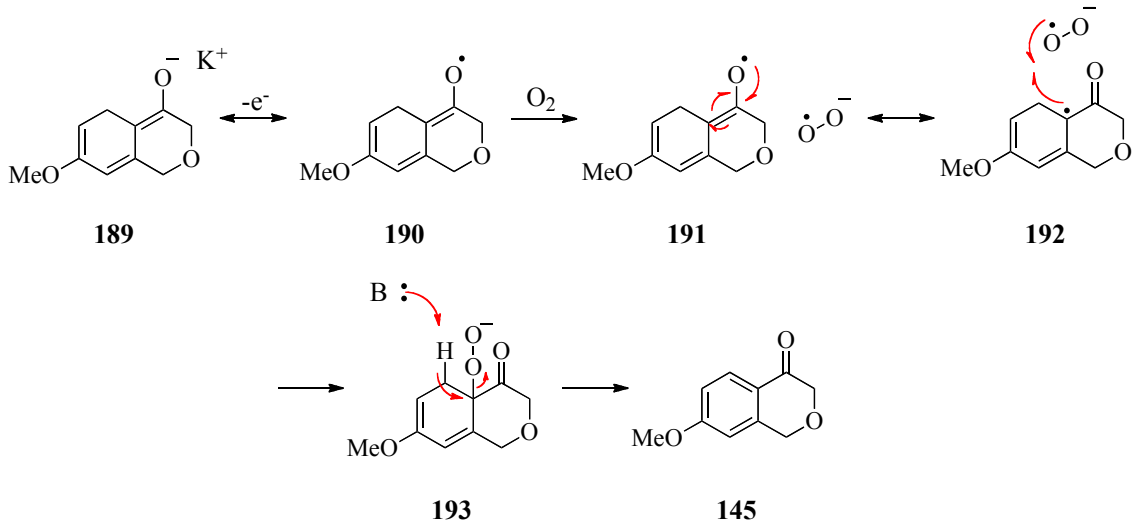
Entry	***Base***	***Equivalents***	 ***Yield (%)***	 ***Yield (%)***
1	KHMDS	2	Trace	0
2	KHMDS	5	0	6
3	**KHMDS**	**1**	**23**	**Trace**
4[a]	KHMDS	1	6	5
5[b]	KHMDS	1	12	5
6[c]	KHMDS	1	6	3
7	LiHMDS	1	0	0
8	LiHMDS	5	0	0

Table 5: (a) Solvent degassed prior to addition of reactants and reagents; (b) TEMPO used as an additive; (c) addition of MeI prior to addition of base

Secondly, with the thinking that the rearomatisation was due to the presence of oxygen within the solvent (THF), a number of examples underwent degassing to investigate this hypothesis. However as it can be seen from entry 4 in table 5, this did not prove to be successful in increasing the yield of the methylated product **144**. Secondly, the addition of the radical inhibitor, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl did increase the ratio of methylation **144** over rearomatisation **145**, thereby suggesting that the rearomatisation occurs *via* a radical mechanism (entry 5 (table 5)).

The suggested radical mechanism for the rearomatisation is shown below in scheme 48, which shows the radical addition of oxygen at the hindered 4 position **193**. This presents the compound with a perfectly situated leaving group, which given the presence of KHMDS as a base, readily undergoes an E_{1CB} mechanism to afford the product. As detailed further in section 3.1, recent and ongoing work within the Wilden group has focused upon the fast radical reaction of potassium alkoxide salts.[137] Building on from these initial studies, the group also has evidence that potassium enolates behave in a similar radical manner,[138] which supports and gives confidence in our suggested mechanism (scheme 48) for this side product. Although direct mechanistic studies have not been undertaken on this example.



189 **190** **191** **192** **193** **145**

Scheme 48

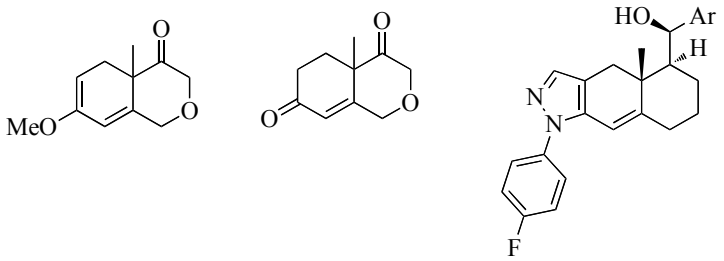
Thirdly, the majority of the reaction conditions saw the addition of base to the diene **146** prior to the addition of the methylating agent, with the view to ensure complete to protonation. However, TLC evidence of this initial reaction mixture showed the presence of the aromatic ketone **145**. In order to attempt to prevent the formation of this ketone **145**, methyl iodide was added to the reaction mixture prior to the base, with the view that once the enolate was formed it could be trapped by the methylating agent hopefully before rearomatisation could occur. However entry 6 shows that this again was not successful.

All the examples described above utilise the base KHMDS and in order to confirm the inability of the lithium counterion to afford the required product, LiHMDS was also

trialed under the equimolar and excess conditions. Again, both these examples did not yield either the methylated product **144** or the aromatic ketone **145**.

2.7 Conclusion and Further Work

This work has documented two attempted synthesises in the development of the Wieland-Miescher Ketone analogue **1**, as a key intermediate in the synthesis of potential glucocorticoid receptor modulators **2**. Although the synthesis of modulators **2** was not able to be attempted, this work has been successful at producing the methoxy-protected Wieland-Miescher Ketone analogue **144**; however more research is required to provide **144** in a reliable and high yielding manner.



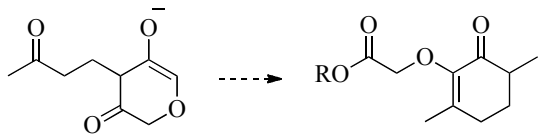
144 **1** **2**

Figure 42

During the course of the initial unsuccessful route towards **1**, our investigations into the development of a novel organocatalysts for the Robinson Annulation of carbocycle **34** resulted in some relatively obscure products. The use of the traditional proline catalyst for the formation of WMK produced a low yield of WMK, while employment of catalytic commercially available hydrazine in the presence of an alcoholic solvent resulted in the unexpected formation of esters **102-104** in high yields.

It was from the high yields of these esters that we drew the conclusion that, with regards to the carbon analogue **34**, the nucleophilic and acidic nature of the cyclic keto α protons were greater than that of the acyclic equivalents. Therefore, the introduction of an electronegative oxygen within the carbocycle would result in an increase in the nucleophilic and acidic nature of the neighbouring protons. Thereby, increasing the difference between the cyclic and acyclic keto α protons and resulting in enolate

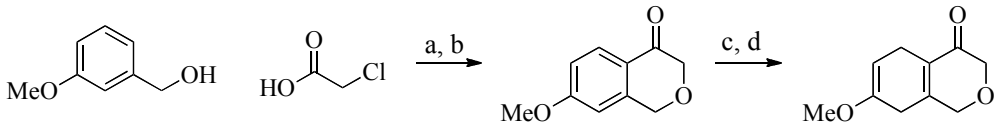
formation exclusively within the pyran and formation of the β ethyl esters **139**. Thus making this an unviable route towards the desired WMK analogue **1**.



132 **133**

Scheme 49

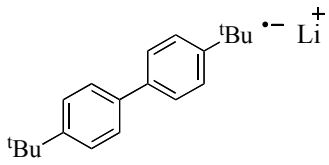
Our second route has proved to be a more successful and in comparison displays a more synthetically interesting synthesis. With use of the Birch reduction as a key step, this route involves five steps to yield the penultimate methoxy analogue **144** in a mixture of moderate to high yields. To complete the synthesis, a further deprotection step is required to yield the desired WMK analogue **1**.



142 **127** **145** **146**

Scheme 50: (a) NaH, DMF, 80%; (b) Oxalyl chloride, $SnCl_4$, DCM 50%; (c) $Na_{(s)}$, $NH_{3(l)}$, EtOH 40%; (d) Aluminium Isopropoxide, toluene, acetone 58%

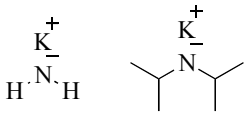
However this route is far from perfect and can be improved upon in a number of ways. Firstly, as noted previously, the key Birch reduction step does suffer from being capricious and attempts to improve its reliability through changes to the metal to lithium, thus far have failed. One interesting development with in the realm of Birch reductions that should be investigated, is that of ammonia-free Birch reductions. Donohoe has pioneered this new approach, which provides synthetic advantages with regards to the practicability of the reaction conditions.[139] The use of lithium di-*tert*-butylbiphenyl (LiDBB) **194** as an electron carrier in place of liquid ammonia, seen in the traditional Birch, has been demonstrated in the total synthesis of the protease inhibitor, *clasto*-lactacystin β-lactone.[140,141]



194

Figure 43

Secondly, the methylation step, currently suffering from both low yields and a capricious nature, requires improvement. Initial improvements could be trialed through the employment of a simpler amide base. To date, the amide base that has been employed is KHMDS, while Paquette *et al*[129] used the simple potassium amide **195** to deprotonate and alkylate at the same position. Although this base requires in *situ* preparation *via* the employment of liquid ammonia and potassium metal, it should be the first point of investigations for improvements. Another potassium base, which at first glance would seem a logical progression given the prolific nature of its lithium counterpart for this type of reaction, is that of potassium diisopropylamide **196** (KDA). However, unlike LDA, the preparation of KDA is not a trivial endeavour with a reliable general method currently proving elusive.[142-144]



195 **196**

Figure 44

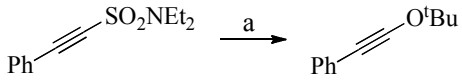
Further efforts could be sought through the use of a less hindered methylating agent. Methyl iodide is a highly successful methylating agent, however it does have the disadvantage of being rather bulky which in terms of this reaction could be highly significant. The use of both chloromethane and bromomethane could be a option, although thought would need to be given to the safe handling of both products given the toxic and gaseous nature of both compounds. However, alternative agents could be sought from the employment of methyl methanesulfonate, which although bulky could be beneficial as a softer electrophile.

3. Investigations into the synthesis of Ynamines and Aminosulfonamides

With the synthesis of the Wieland-Meischer Ketone analogue proving to be caprious, it was felt necessary to expand the work of this thesis beyond this previously described synthesis. Exploration of recently developed methodology developed within the group was undertaken to expand its remit from the synthesis of ynol ethers to ynamines and aminosulfonamides.

3.1 Synthesis of Ynol Ethers

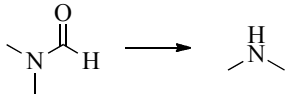
Recent work within the Wilden group has focused on the synthesis of ynol ethers **198** from alkynyl sulfonamides **197** in the presence of potassium *tert*-butoxide (KO^{t}Bu) and anhydrous DMF. [137]



197 **198**

Scheme 51: (a) KO^{t}Bu, DMF, trace

Altering the conditions with regards to the solvent and *tert*-butoxide counterion, did not facilitate the synthesis of ynol ether **198**. The trials made concluded that only this metal counterion and solvent combination (potassium and DMF) resulted in the ynol ether, raising the question; what was special about these conditions. Initial thoughts were based upon the knowledge that over time, DMF slowly decomposes to form carbon monoxide and the secondary amine, dimethylamine (DMA) **200**. With the well documented employment of secondary amines as organocatalysts, it was necessary to investigate whether the decomposition product was behaving in this manner and giving DMF its unique properties in this reaction.

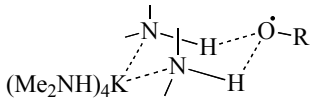


199 **200**

Scheme 52

Employment of an excess of DMA with THF as the solvent did produce the ynol product **198**, with optimised conditions producing a yield of 85%.

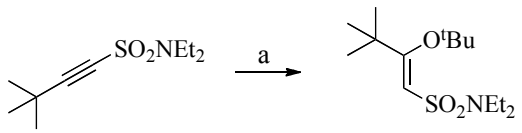
With this reaction displaying attack and substitution of a nucleophilic alkoxy anion at the most electron rich alkynyl carbon, mechanistic investigations were conducted. The use of continuous-wave electron paramagnetic resonance (cw-EPR) demonstrated the existence of an oxygen-centred radical within the reaction mixture. The use of lithium or sodium counterions or the absence of amine resulted in a loss of radical signal. This spectroscopic observation corresponded to the experiemental observations made when these conditions were employed in the reaction. These combined experimental and spectroscopic observations have led to the suggestion of a radical species centred in a potassium-amine-alkoxide complex **201**, which quickly assembles in THF and DMF at a rate that is too fast for the radical inhibitor TEMPO to be effective.[145]



201

Figure 45

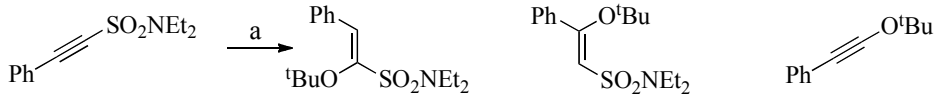
In addition to the interesting mechanistic details associated with this reaction, it has also enjoyed a significant degree of scope at both the α and β ends of the alkyne. A variety of alkoxide salts have been successfully incorporated into this reaction. Methoxide, ethoxide and neopentoxide examples have also been reported *via* the in *situ* formation of the potassium salt from the reaction of the parent alcohol and either potassium metal or potassium hydride.[137,145] A variety of *ortho*, *meta* and *para* electron withdrawing and electron-donating groups and heterocycles are tolerated at the β end of the alkyne; however only aromatic groups result in the formation of an ynol ether. Aliphatic examples yield addition products of the butoxide at the traditional β end of the alkyne **202**.



202 **203**

Scheme 53: (a) KO^{t}Bu, HNMe$_2$, THF

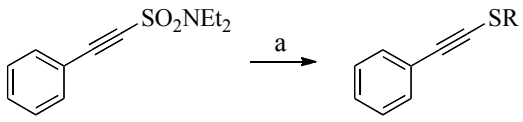
In the development of this synthetic protocol, this β addition product had been observed when standard grade hydrated DMF was employed as the solvent instead of the anhydrous form used in the optimised conditions. Here, the ynol ether was observed alongside both the α and β addition products **204** and **205** in a 1:3 ratio.[137]



197 **204** **205** **198**

Scheme 54: (a) KO^{t}Bu, DMF

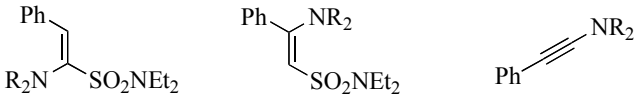
Further elaboration has extended the scope beyond that of oxygen examples. Employment of potassium hydride with thiols has produced a range of potassium thioalkoxide salts, which in the presence of DMA and THF yields the corresponding thiol ynol ethers **206** in 32-73% yields. As seen with the alcohol examples, these thiols display a wide scope of aliphatic examples but are again limited to the use of aromatic alkynyls.[138]



197 **206**

Scheme 55: (a) HSR, KH, HNMe$_2$, THF

With the expansion and success of this area of research into the use of other heteroatoms, it was questioned whether this research could be expanded further with the employment of amine examples, to yield either the ynamine **209**, α-aminosulfonamide **207** or β-aminosulfonamide **208**.

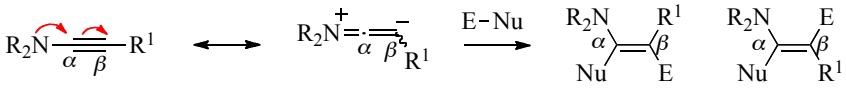


207 **208** **209**

Figure 46

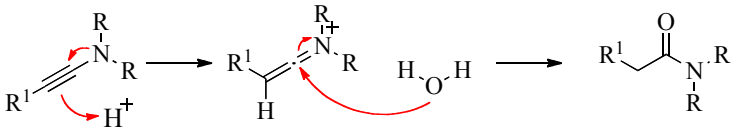
3.2 Synthesis of Ynamines and Ynamides

As a handle for further elaboration and synthetic manipulation, ynamines and ynamides provide a strongly polarised triple bond due to the electron donating ability of the nitrogen, which enables a clear differentiation between the two *sp* carbons allowing for a high degree of regioselectivity.[146-149] Despite being a highly reactive species with all the inherent advantages such a status brings, these compounds have not enjoyed the same widespread utilisation as their related enamine.[148-150]



Scheme 56

In addition and as a consequence of this high reactivity, ynamines have proved to be particularly susceptible to hydrolysis, with protonation of the electron-rich alkyne **218** leading to the highly reactive keteniminium intermediate **211**. Attack of water upon this intermediate leads to the corresponding amide, thereby representing a convoluted and difficult synthesis for amides **212** in general.



210 **211** **212**

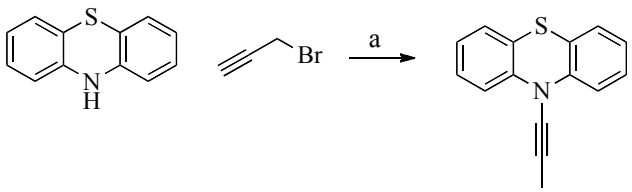
Scheme 57

With the example of an ynamide, addition of a simple carbonyl or sulfonamide appended to the nitrogen has the advantage of tempering the donating ability of the

nitrogen, through resonance delocalization onto the carbonyl or sulfonamide, thereby making the alkyne less reactive, less readily hydrolysed and more stable.[146,148,149]

3.2.1 Synthetic routes to Ynamines

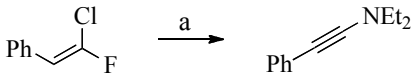
First reported in 1892, it was not until 1958 that an ynamine **215** was isolated and characterized by accident from the reaction mixture of phenothiazine **213** and propargyl bromide **214**.[149,151]



213 **214** **215**

Scheme 58: (a) NaH, xylene, 70%

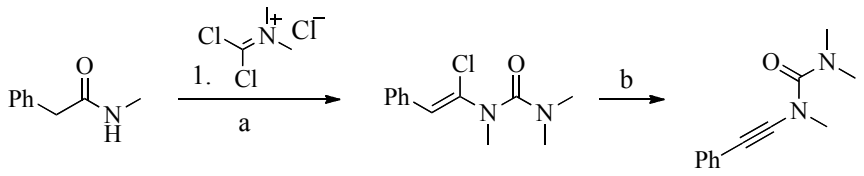
The first general synthesis of ynamines was reported by Viehe in 1963, which involved the exposure of dihalostyrene **216** to the required lithium amide salt at low temperatures to produce high yields of the corresponding ynamines.[149,152]



216 **217**

Scheme 57: (a) $LiNEt_2$, diethyl ether, −80 - −20 °C, 86%

The first ynamide synthesis in 1972, again by Viehe *et al*, employed the chloro-enamide **219** in an elimination reaction to furnish the ynamide **220** in a 64% yield (scheme 58). Although novel in its products, this procedure suffers from a lack of substrate scope, which is dependent upon the availability of the starting chloro-enamide.[146]

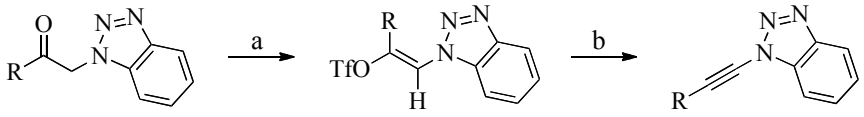


218 **219** **220**

Scheme 58: (a) 2 eq. $NaHCO_3$, H_2O; b) ^tBuOK, THF, rt

3.2.2 *via* Elimination

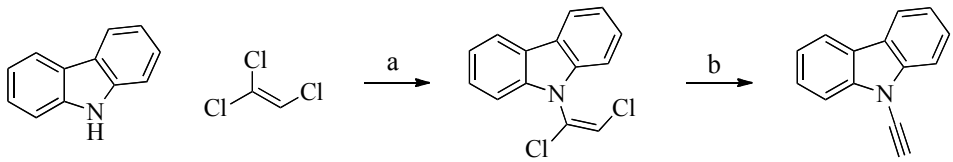
Katritizky *et al* has employed a double elimination in their synthesis of ynamine **223** from the α-aminoketone **221**, which is treated with triflic anhydride to afford enol triflate **222**.[150] Subsequent treatment with sodium methoxide yields the ynamine **223** in a greater than 90% yield.



221 **222** **223**

Scheme 59: (a) Tf_2O, 2,6-lutidine; (b) NaOMe, CH_3CN

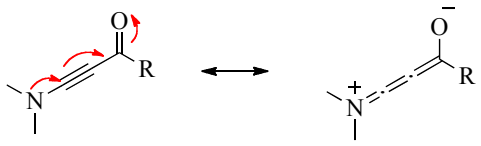
A range of aromatic ynamines **227** have been reported deriving from the addition of trichloroalkene **225** to the free amine **224**. The subsequent elimination is performed in the presence of magnesium to give a yield of 87%.[150]



224 **225** **226** **227**

Scheme 60: (a) cat. TEBACl, NaOH, DMSO; (b)Mg, THF

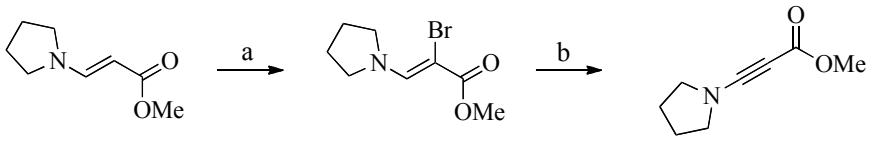
A number of researchers have investigated the synthesis of "push-pull" ynamines, which by possession of an electron-withdrawing group on the β alkynyl carbon, promote the conjugation of electrons throughout the moiety (scheme 61).



228 **229**

Scheme 61

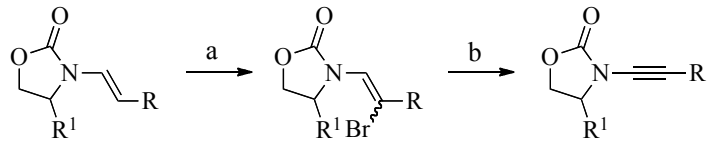
Bloxham & Dell developed a procedure from alkene **230**, which undergoes a bromination to afford the α-bromo ester **231**. Subsequent elimination to the "push-pull" alkyne **232** occurs upon exposure to potassium *tert*-butoxide.[153,154]



230 **231** **232**

Scheme 62: (a) Br_2, NEt_3, DCM; (b) ^{t}BuOK, THF, 52%

Hsung *et al* utilised the brominated enamide **236** (scheme 63), which is derived from the reaction of either bromine or NBS with the starting enamide **233**. Here potassium *tert*-butoxide was employed as the base for the elimination procedure and yielded the ynamide **235** in a range of 72-88% depending upon the nature of R. Initially the yields for this procedure seem positive, however, the preliminary bromination step yields a mixture of *E* and *Z* isomers in a variety of 1:8 to 1.5:1 ratios and under the conditions described here, elimination to afford the ynamide is only successful with the *Z* isomer.[148,155,156]

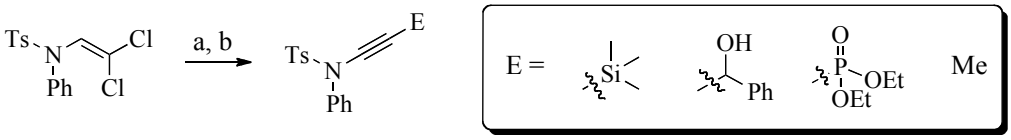


233 **234** **235**

Scheme 63: (a) Br_2 (R=alkyl) or NBS (R = aryl), DCE, reflux; (b) KO^{t}Bu, THF, rt

Sáa *et al* have reported a two-step general route to ynamides **237** from the dichloroalkenylsulfonamide **236**, which allows for quick generalisation of the β position

of the alkyne. Here ^{n}butyl lithium is employed as the base to deprotonate at the α position and cause the moiety to undergo an E_{1cb} mechanism to yield the lithium acetylide, which can be quenched with a variety of electrophiles. A number of electrophiles have been utilised such as TMS, benzaldehyde, phosphate esters and methyl iodide to give a wide substrate scope for the reaction in 73-88% yields.[148,157]

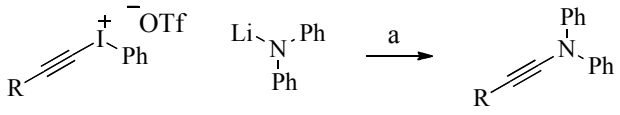


236 **237**

Scheme 64: (a) ^{n}BuLi, THF, –78 °C; (b) E^+, rt

3.2.3 *via* Substitution

As expected the substitution pathway employs the displacement of a leaving group on the *sp* hybridized carbon for the required amine to afford the desired ynamine. One important and widely used route to ynamines has been *via* the use of iodonium salts. In work by Stang *et al*, a range of "push-pull" ynamines were synthesised from the corresponding phenyliodonium triflate **238** in an up to 66% yield.[158] Although on paper this reaction proceeds *via* substitution of the iodonium salt for the amide ion, it is widely believed that instead addition of the amide occurs on the β alkynyl carbon resulting in expulsion of iodobenzene and a vinyl carbene, which undergoes a 1,2-shift to afford the ynamine **240**.[150]

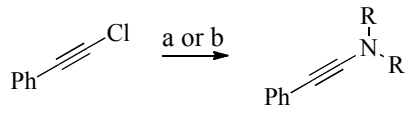


238 **239** **240**

Scheme 65: (a) Et_2O, –78 °C, 43-66%; R= TMS, -C(O)Ph, -C(O)^{t}Bu, *p*-Ts

Generally halogens are employed as the leaving group in these reactions with lithium amides **239** (scheme 65) as the nitrogen source.[159] Tertiary amines have also been utilised by Viehe *et al* in this transformation.[160] The difference between the two procedures hinges around the temperature with the tertiary amine examples requiring

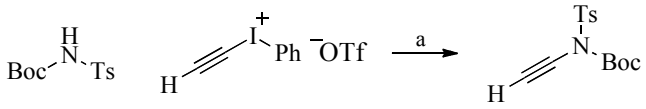
moderate to high temperature (55 °C) and the amide examples low temperatures (−78 °C).



241 **242**

Scheme 66: (a) $LiNR_2$, diethyl ether, −78 °C; (b) NR_3, 55 °C

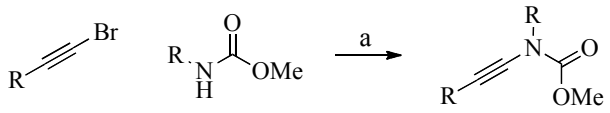
A popular method for the synthesis of ynamides has historically been from the use of alkynyl iodonium salts **244**, which also enjoy employment in the synthesis of ynamines. Here an amide is deprotonated with a suitably strong enough base followed by substitution with an alkynyl iodonium salt **244** and has been reported by a number of researchers.[146,158,161,162] Despite producing ynamides **245** in high yields, the lack of availability of the iodonium salts presents the major disadvantage of this procedure.[146]



243 **244** **245**

Scheme 67: (a) nBuLi, toluene, 0 °C, 84%

The turn of the century saw the resurgence of copper catalysis across the breadth of organic chemistry and its use in the preparation of ynamides has yielded the most efficient procedures.[146] In 2003, Hsung *et al* were the first to employ this catalyst in the synthesis of ynamides, providing the "first direct and atom-economical" route to ynamides.[148] With the use of *N,N'*-dimethylethylenediamine (DMEDA) as a ligand, alkynyl bromides **246** (scheme 68) were coupled with a range of amides **247** with yields of up to 85%, however substrate scope and the use of high temperature are the major drawbacks with this initial procedure.[146,148,163] With the greatest yields being produced for oxazolidinones substrates, amides resulted in poor yields, while sulfonamides did not result in the desired ynamide under these conditions.

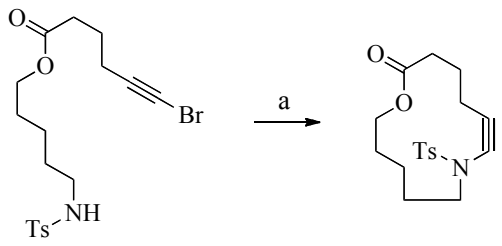


246 **247** **248**

Scheme 68: (a) CuCN (5 mol%), DMEDA (10 mol%), K_3PO_4, toluene, 110 °C

Hsung *et al* presented an improvement on their original procedure which proved to a be a general procedure. The combination of copper sulfate pentahydrate and 1,10-phenanthroline alongside potassium phosphate acting as the base proved to be successful, although a relatively high temperature of 60-95 °C was required.[146,164]

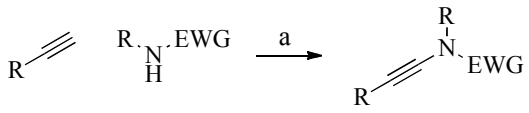
Hsung's second generation catalyst system has been employed in the intramolecular ynamide synthesis resulting in macrocycles **250** (scheme 69).[148,165] Here the same copper sulfate and 1,10-phenathroline catalyst/ligand system were utilised but potassium carbonate was employed as the base in these examples resulting in high yields up to 96% of the macrocycles **250**.



249 **250**

Scheme 69: (a) 10 mol% $CuSO_4.5H_2O$, 20 mol% 1,10-phenanthroline, 2 eq. K_2CO_3, toluene, reflux, 96%

An alkynyl bromide **246** is required for all the copper-catalysed procedures described so far, which can prove to be difficult to synthesise. With this in mind, terminal alkynes would be the ideal starting material and Stahl *et al* reported the first copper catalysed aerobic oxidative coupling of terminal alkynes **251** with an electron deficient amine. By employing a copper chloride catalyst alongside pyridine and sodium carbonate, the reaction benefits from a vast reaction scope including sulfonamides, amides, ureas and oxazolidinones. Although to ensure the reduction of side products, the use of five equivalents of the nucleophile is required.[146,148,149,166,167]

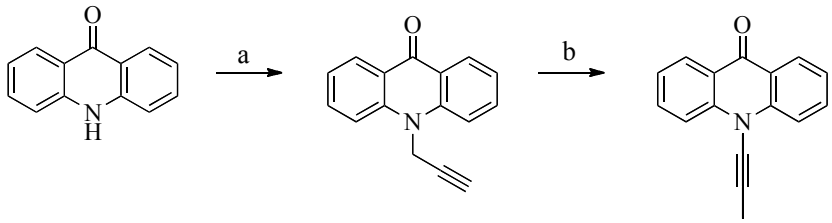


251 **252** **253**

Scheme 70: (a) $CuCl_2$ (20 mol%), O_2, pyridine, Na_2CO_3, toluene, 70 °C

3.2.4 *via* Isomerisation

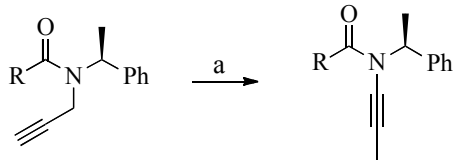
Katritzky *et al* highlight the usability of isomerisation as a synthetic route to ynamines with their synthesis beginning from amine **254**. Here amine **254** is exposed to a basic mixture of sodium hydride in DMF followed by the addition of propargyl bromide to yield **255**. Isomerisation is induced by the mixture of potassium hydroxide and DMSO to give the ynamine **256** in a 55-80% yield.[148,168]



254 **255** **256**

Scheme 71: (a) Propargyl bromide, NaH, DMF; (b) KOH, DMSO

Hsung *et al* has demonstrated the ability of catalytic potassium *tert*-butoxide to cause the isomerisation of propargyl amides **257** to afford the corresponding ynamides **258**.[156]



257 **258**

Scheme 72: (a) KO^{t}Bu (20 mol%), THF, rt

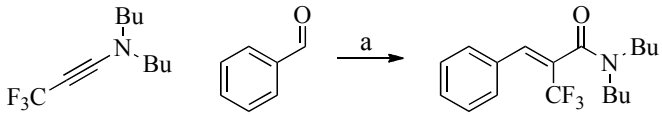
3.3 Reactions of Ynamines and Ynamides

Despite the difficulties in the synthesis of ynamines, the synthetic utility of this functionality is demonstrated in the range of reactions that can be undertaken.

3.3.1 Addition Reactions

Given the electron-donating ability of the nitrogen within ynamines, addition reactions of electrophiles and nucleophiles occur with a high level of regioselectivity.

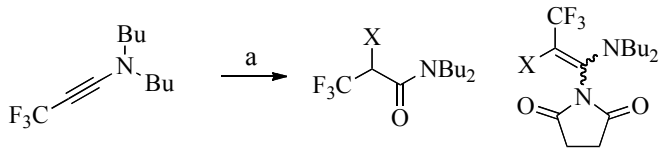
Ishihara *et al* have investigated the manipulation of fluorinated ynamine **259**. Exposure of the fluorinated ynamine **259** and benzaldehyde **260** to a Lewis Acid leads to the formation of amide **261**. The majority of Lewis acids yielded the amide in a high yield, with $BF_3.OEt_2$ performing the best at 92% and providing a range of aromatic, heteroaromatic and alkyl derivatives in high yields.[154]



259 **260** **261**

Scheme 73: (a) $BF_3.OEt_2$, MS 4 Å, DCM, 1 h, 92%

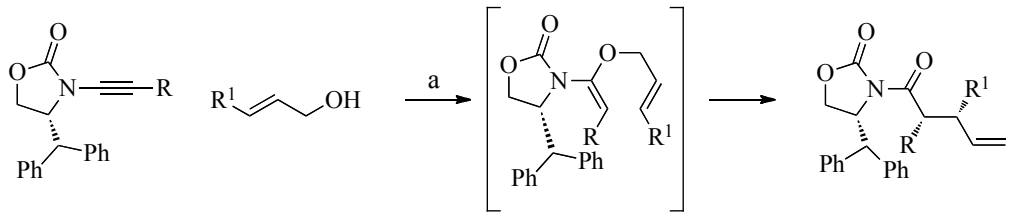
A route to α-bromoamide **262** from ynamine **259** is through the use of the renowned brominating agent, *N*-bromosuccinimide (NBS), which can yield the bromoamide **262** in a 57% yield from an aqueous, room temperature reaction medium. In addition to bromoamide **262**, the addition product **263** is also afforded in a 27% yield. Use of a mixture of acetonitrile and water as the solvent resulted in a preference for amide **263** with an 85% yield and a 12% yield of the addition product 288. The use of *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) under the same conditions result in the corresponding α-haloamide in an 85% and 80% yields respectively. Use of anhydrous acetonitrile will afford the addition product as the only product with a good yield (99-66% depending upon halogen), but as a mixture of geometrical isomers.[154]



259 **262** **263**

Scheme 74: (a) either NXS, MeCN-H_2O, rt, 1 h or NXS, anhy. MeCN, MS 4 Å

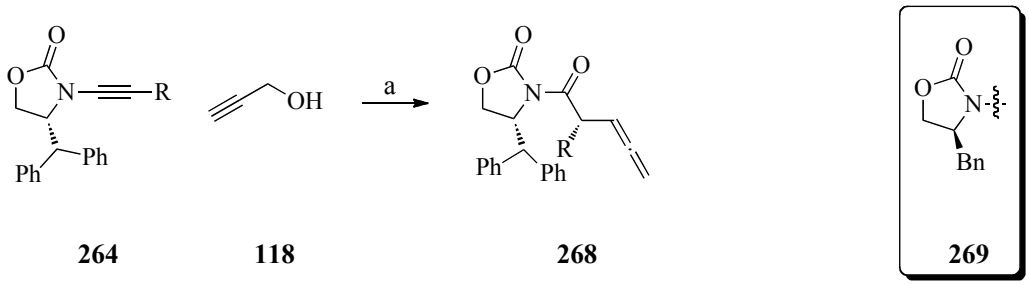
In this example Hsung and coworkers demonstrate the first stereoselective Ficini-Claisen rearrangement through the employment of chiral ynamide **264** and allyl alcohol **264**. In the presence of *p*-nitrobenzenesulfonic acid (PNBSA), the initial oxygen addition of the alcohol onto the α-ynamide carbon, set up the necessary conformation for a Claisen [3,3]-sigmatropic rearrangement to yield the amide **267**, with high diastereoselectivity of the *syn* conformation in a good 60-86% yield.[168] Ynamide **267** exhibits the use of Sibi's chiral auxillary,[168,169] which had proved to be the best auxiliary for this work over others trialed including the Evans auxiliary **270**, with 93:7 ratio of diastereoisomers reported for Sibi's and 68:32 ratio for Evans.[170]



264 **265** **266** **267**

Scheme 75: (a) PNBSA (0.2 eq.), 80 °C, toluene, 15 h

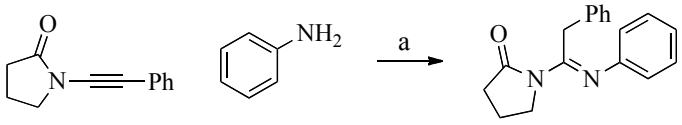
Building on this work, Hsung extended the application for this protocol by applying it to the use of propargyl alcohols **118** instead of allylic ones **265** employed thus far.[171] Here again, a [3,3] sigmatropic rearrangement occurs but with a propargyl alcohol it occurs between an alkyne and an alkene, known generally as a Saucy-Marbet rearrangement,[172] to yield the terminal allene **268**, instead of the terminal alkene **267** seen for the Ficini-Claisen rearrangement. Again, the use of an ynamide based on Sibi's Auxiliary **264** provided amide **268** in a higher diastereoselectivity when compared to the ynamide-Evan's Auxiliary **269** examples, with the greatest being when R was *n*-butyl yielding the corresponding amide in a 85:15 ratio and a 70% yield.



264 **118** **268** **269**

Scheme 76: (a) PNBSA (0.1 eq.), toluene, 80 °C

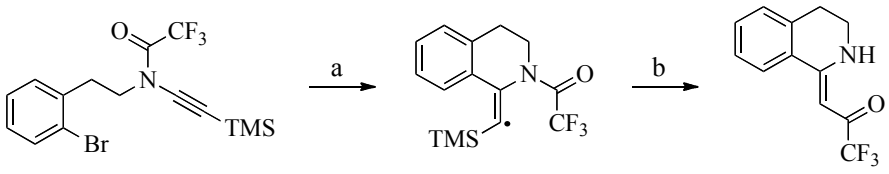
Alongside the work by Hsung, a number of other groups have investigated the effect of metal-catalysed addition reactions of ynamides. Skrydstrup and coworkers employed the use of a gold catalyst to form a mild protocol for the highly regioselective hydroamination of ynamides **270** and anilines **271**.[173] A wide range of both anilines, cyclic and acyclic ynamides have displayed excellent yields of between 89-98% and excellent regioselectivity for the α position on the ynamide.



270 **271** **272**

Scheme 77: (a) $(PPh_3)AuNTf_2$ (1 mol%), CH_2Cl_2, rt, 4 h

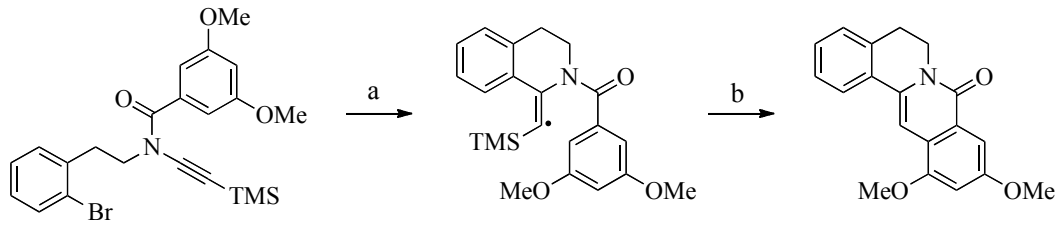
Interestingly, Balieu *et al* have employed an intramolecular radical addition to an ynamide **273** to yield the tetrahydroisoquinoline **275**.[174] Upon subjecting the specifically designed ynamide **273** to both a radical initiator, AIBN, and carrier, tributyltin hydride, a 6-exo-dig radical cyclisation occurs onto the α alkynyl carbon followed by migration of the trifluoroacetyl group to yield **275** in a 49% yield.



273 **274** **275**

Scheme 79: (a) AIBN, Bu_3SnH, benzene, 80 °C; (b) 1M NaOH

Disappointingly, this procedure did not show great substrate scope; however, it has displayed the ability to form two fused rings from ynamide **276**. Under the same reaction conditions as above, this substrate undergoes the same 6-exo-dig cyclisation followed by a 6-endo-trig cyclisation to yield **278**, although with a reduced yield of 30%.[174]

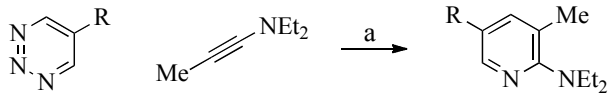


276 **277** **278**

Scheme 80: (a) AIBN, Bu_3SnH, benzene, 80 °C; (b) 1M NaOH

3.3.2 Cycloaddition Reaction

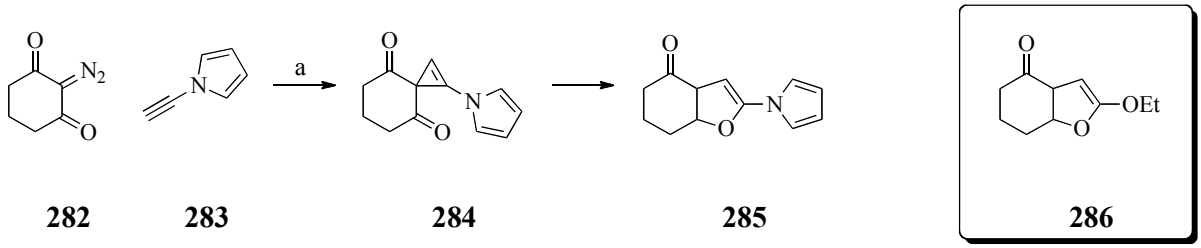
Cycloadditions are a key group of reactions for this functional group and have been used to synthesise nitrogen containing heterocycles.[175] The synthesis of pyridine is a good example of this. Here the unsubstituted triazine **279** is coupled with ynamine **280** in a Diels-Alder reaction to yield the pyridine **281** with loss of nitrogen and a clean regioselectivity with the cycloaddition occurring across the N1/C4 atoms of the 1,2,3-triazine **279**.[175]



279 **280** **281**

Scheme 81: (a) 60 °C, $CHCl_3$, 64-93%

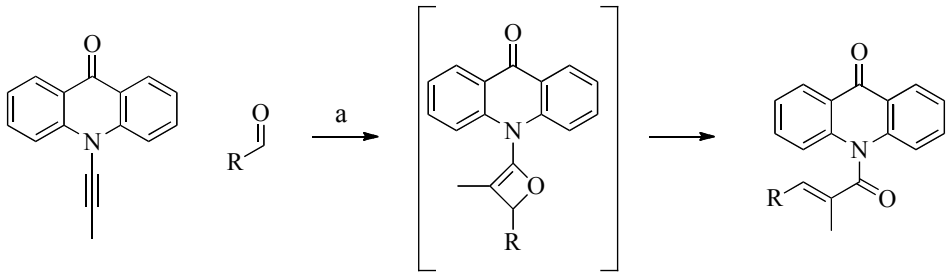
Pirrung *et al* have demonstrated the ability of an alkynyl pyrrole, along with other non-functionalised alkynes and ynol ethers, to undergo [2 + 1] cycloadditions with rhodium carbenoids to form the cyclopropene **284**. Rearrangement of the intermediate will form the fused furan **285** with the pyrrole functionality in the 2 position. A modest 40% yield was reported for this process, which was among the lowest compared to the other reported analogues with the highest being the ethoxy analogue **286** at 79%.[176]



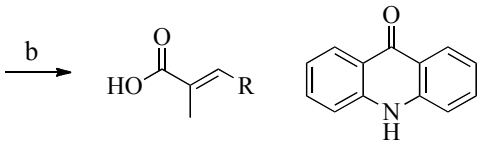
282 **283** **284** **285** **286**

Scheme 82: (a) $Rh(OAc)_2$

Hsung *et al* have employed a [2+2] cycloaddition of an ynamine **256** and an aldehyde **287** to achieve a two-carbon oxidative homologation of the aldehyde. Here the use of catalytic boron trifluoride diethyl etherate sees the cycloaddition and subsequent rearrangement occur to afford the unsaturated amide **288** in a 58-91% yield and a 20:1 preference for the *E* isomer over *Z*.[177] Subsequent treatment with lithium hydroxide gives the acid hydrolysis product **290** in a 90% yield alongside the amine **254**.



249 **319** **320** **321**

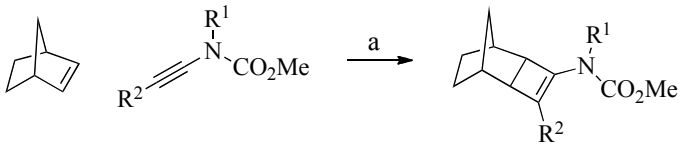


322 **247**

Scheme 83: (a) cat.$BF_3.OEt_2$, DCM or toluene, −78 °C, 5-15 h; (b) 1M LiOH, $THF.H_2O$, rt, 24 h

Tam *et al* reported the first ruthenium catalysed [2+2] cycloaddition by employing norbornene **291** and acyclic ynamides **292** as their model system.[148,178] A range of yields were reported for the ynamide derivatives peaking at 97% when both R^1 and R^2 are phenyl. Under these conditions, an increase in steric bulk on the nitrogen led to a

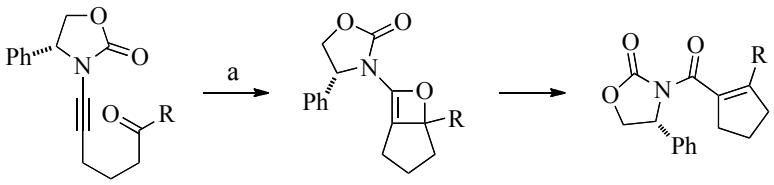
reduction in the yield of the addition product **293**. While this feature was replicated at the other end of the alkyne, the presence of an electron withdrawing aromatic group in the R^2 position also reduced the yield of **293**, although not as significantly as when propargylic alcohols or propargylic silyl ethers were present.



291 **292** **293**

Scheme 84: (a) CpRuCl(COD), THF, 60 °C, 72 h

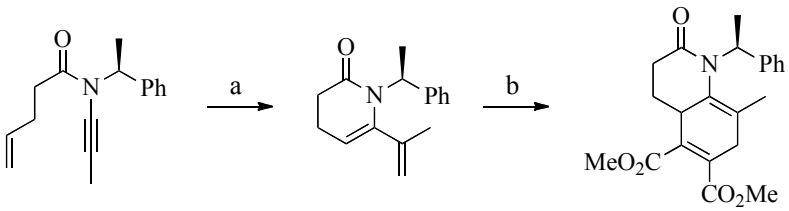
Like synthetic routes and addition reactions previously, Hsung has been active in researching the cycloaddition reactions of ynamides as well. In this example, the use of Lewis acid, boron trifluoride diethyl etherate, catalyses the intramolecular [2+2] cycloaddition between the ynamide and carbonyl functionalities within **294**, thereby quickly yielding the fused 5,4 ring system seen in **295**. However like Hsung's previous work[177] noted in section 3.2.3.2, this compound is not the product of the reaction, as it quickly rearranges to form the unsaturated amide **296** in around 15 mins at room temperature. A range of yields were reported most within 65-88%, while significant reductions were observed when the connecting aliphatic chain was increased, to give a resulting ring size of 7 and when the oxazolidinone was replaced by a benzyl protected sulfonamide with yields of 35 and 33% respectively. Interestingly, this reaction was also successful in the presence of a Brønsted acid with PNBSA affording a similar yield of the aldehyde analogue of ynamide **294** (74%), however, a significant increase in acid and reaction time was required (up to 1.25 eq. and 30 mins). In contrast, triflimide, $HNTf_2$, was employed with the same catalyst loading and reaction time as the Lewis acid, with only a slight drop in yield at 66%.[179]



294 **295** **296**

Scheme 85: (a) $BF_3.OEt_2$ (0.25 eq.), DCM, rt, 15 mins

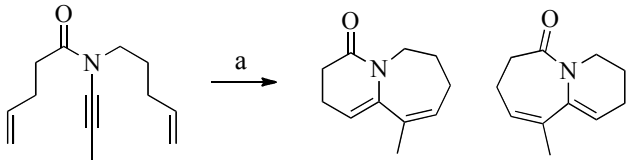
In addition to being a [2+2] cycloaddition, the ynamide **297** example is also an example of a hetero-enyne ring closing metathesis, which was an extension of Hsung previous work on the more traditional Grubbs metathesis of ynamides.[156] Here ynamide **297** is exposed to Grubbs' second generation catalyst forming the amidodiene **298** in high yields of 83-87%. Further work demonstrated that in the presence of dienophiles, these products can undergo a Diels-Alder reaction to form the 6,6 bicycle **299** in an 80% yield, although with disappointing diastereoselectivity.



297 **298** **299**

Scheme 86: (a) Grubbs II, toluene, 75-80 °C; (b) dimethyl acetylenedicarboxylate, toluene, 150 °C

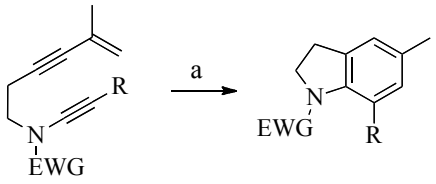
Compared to other heteroalkynes, ynamides possess the unique ability to be tethered to two alkynyl substituents, thereby allowing a tandem ring closing metathesis to occur. Here again, Grubbs's second generation catalyst provided cyclised products **301** and **302** in a combined 77% yield with a 1:1 ratio of products.[156]



300 **301** **302**

Scheme 87: (a) Grubbs II (10 mol%), toluene, 75 °C, 12 h

Direct Diels-Alder or [4+2] cycloaddition reactions have been reported on ynamide species with the first intramolecular example was demonstrated by Witulshi *et al*, yielding diene **304** in a 54% yield.[180]

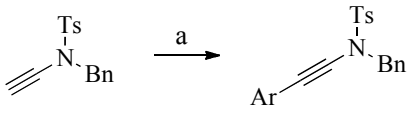


303 **304**

Scheme 88: (a) 80 °C, benzene

3.3.3 Functionalisation Reactions

As expected, by possession of an alkyne in their structure, ynamides are perfectly set up to undergo Sonogashira couplings and again, Hsung has led the way in the extension of this palladium coupling reaction to ynamides.[181] Here exposure of terminal alkyne **305** to an aromatic iodide species in the presence of both palladium and copper catalysts led to the formation of ynamide **306** in yields ranging from 44% to 96%. With both electron-withdrawing and electron-donating groups being tolerated, heteroaromatics also proved to be successful in this coupling reaction with the 4-anisyl analogue producing the highest yield. Alkene derivatives were also afforded, although significantly lower yields were produced in the 31-42% range.

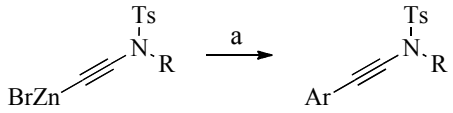


305 **306**

Scheme 89: (a) Ar-I, $Pd(PPh_3)_4$ (3.3 mol%), CuI (1.5 mol%), NEt_3:Toluene (2:1), 65 °C

Saá *et al* employed palladium catalysts in a coupling between an aryl iodide and an ynamide **307**, which possesses a zinc bromide at the β position of the alkyne in a Negishi style coupling.[182] This coupling proceeds best when an electron-withdrawing group or an electron poor heteroaromatic is used as the reagent with used between 92-

42%. Electron-donating group produced a significant reduction with yields of 25% reported with *o*-iodoanisole.

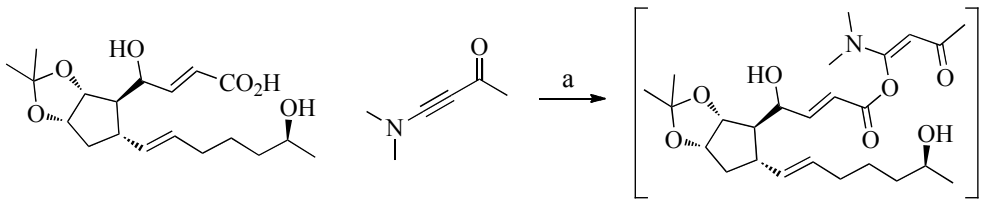


307 **308**

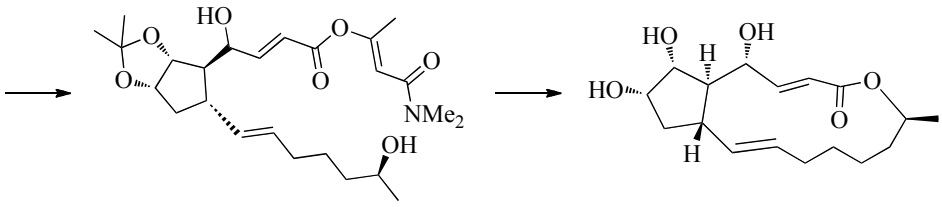
Scheme 90: (a) Ar-H, Pd_2dba_3(5 mol%), PPh_3 (20 mol%), rt, 2 h

3.3.4 Use in Total Synthesis

In addition to the many examples of methodological uses of ynamines, they have also played a role in the total synthesis of the natural product (+)-(6*R*)-hydroxybrefeldin A **313**. Here the carboxylic acid **309** reacts with the α carbon of the keto-ynamine **310** to yield the intermediate **311**, which will rearrange to form the amide **312** in *situ* in a quantitative yield.[87,183,184]



309 **310** **311**

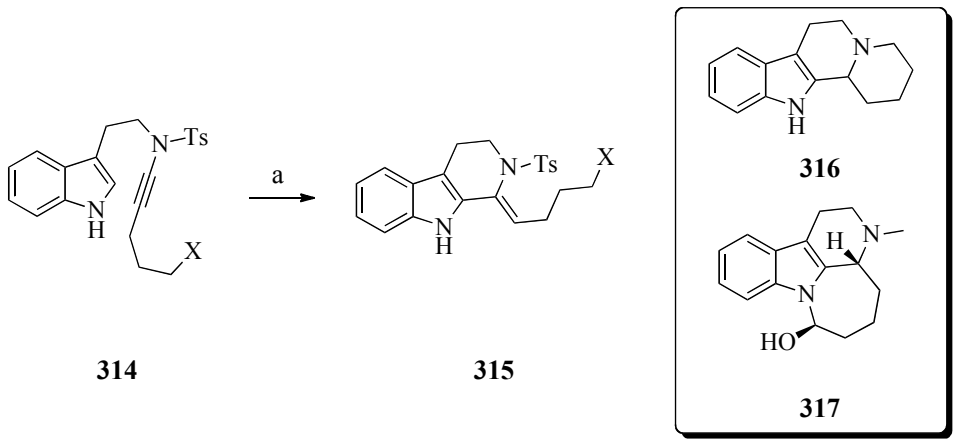


312 **313**

Scheme 91: (a) THF, –50 °C, 1 h

Hsung *et al* have employed ynamides in the synthesis of two related natural products, 10-desbromoarborescidine A **316** and 11-desbromoarborescidine C **317**.[185] Both synthesises use the same key acid catalysed Pictet-Spengler transformation from the ynamide **314** to produce the tosylated piperidine **315** within 5 minutes in a 56% yield

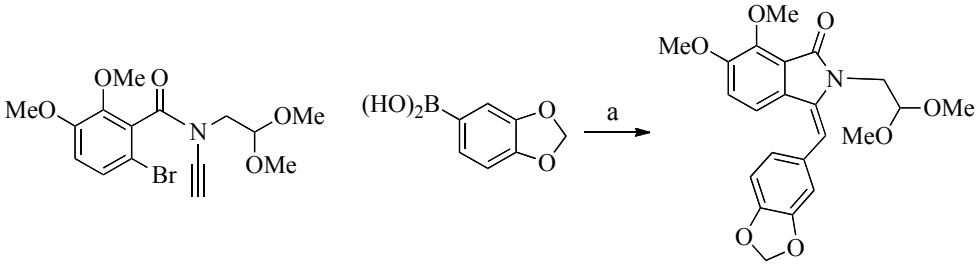
for desbromoarborescidine A and 67% for desbromoarborescidine C synthesises. A further two and five steps were required to produce the target molecules **316** and **317** respectively.



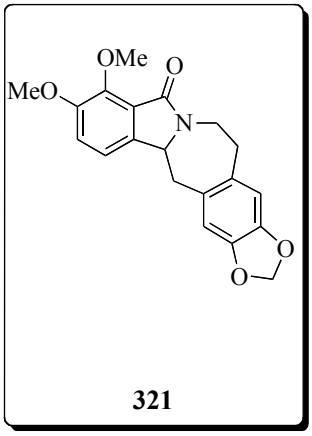
314 **315**

Scheme 92: (a) PNBSA (15 mol%), toluene, 90 °C, 5 mins X = Cl for 10-desbromoarborescidine A; X = OBn for 11-desbromoarborescidine C

Alongside co-workers, Cossey & Meyer employed palladium coupling methodology on ynamides to exert an intramolecular cyclisation in the synthesis of lennoxamine **321**.[186] The key Heck-Suzuki-Miyaura domino reaction resulted in the core isoindolinone of lennoxamine **321** with a 77% yield and an *E*:*Z* ratio of 85:15.



318 **319** **320**



Scheme 93: (a) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), aq. NaOH, THF, reflux

3.4 Aminosulfonamides and Peptidomimetics

Aminosulfonamides have received a significant but not comprehensive level of attention in the literature, particularly within the field of peptidomimetics. Peptidomimetics or pseudopeptides seek to overcome the limitations of the peptide bond by substituting the amide functionality for an isostere, which can mimic the natural peptide in terms of the geometry, polarity and acidity.[187-190] Natural carbon based peptides are highly susceptible to hydrolysis and attack by proteases and one field of thought seeks to replace the bond with a heteroatom equivalent such as phosphonates, sulfonates and sulfonamides.

The advantage of employing a sulfonamide as a peptidomimetic is firstly its possession of a distorted tetrahedral geometry, which is similar to that of the tetrahedral intermediate that is formed during cleavage of the amide bond during attack by proteases and hydrolysis.[191-194] This geometry in sulfonamides means that it is no longer favourable for protease and water attack, thereby making this pseudopeptide bond resistant to this form of attack.[191,194]

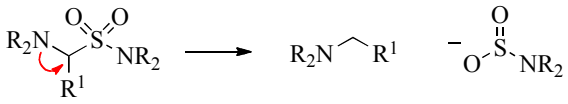
Secondly, the acidity of the proton on the nitrogen is significantly greater in a sulfonamide compared to the native peptide, with pK_a of around 8 and 25 respectively.[192,194] This increase in acidity will also increase the polarity of the sulfonamide and the hydrogen-bond donating abilities of its N-H. Although as hydrogen bond acceptors, sulfonamides do not compare favourably to amides, displaying acceptor levels below that of amides in the same range as esters.[187,192]

Reports within the literature have highlighted a significant difference in the synthesis and stability of the two analoguous aminosulfonamides, the α analogue **322** or in the β analogue **323**.

322 **323**

Figure 46

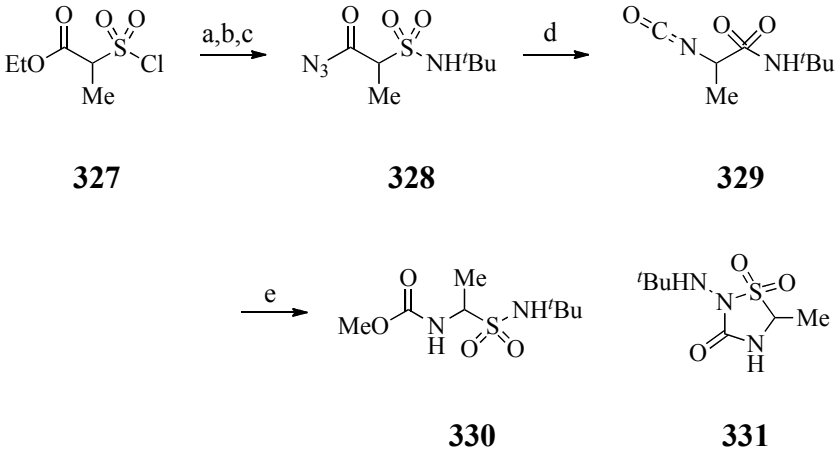
Attention has been focused upon β-aminosulfonamides with minimal advancement being made for the synthesis and employment of the α-analogue. This is somewhat surprising given that the α-configuration most closely resembles that of the natural amino acid that the peptidomimetics seeks to mimic. However, literature reports argue that the α-configuration **324** leads to an unstable moiety that is liable to fragmentation, expelling the sulfonamide unit **326** and the corresponding amine **325**.[192,195-197] This fragmentation is most notably observed when the free α-aminosulfonamide is isolated,[192] but they can be observed when in a non-polar organic solvent.[195]



324 **325** **326**

Scheme 94

Gilmore *et al* first reported the attempted synthesis of α-aminosulfonamides based on glycine and phenylalanine *via* a Curtius rearrangement, raising the question of their stability.[196,197] Paik and White[195] employed the same key Curtius rearrangement step to synthesise the alanine based α-amidosulfonamide **331**. In this instance, despite an inability to isolate sulfonamide **330**, the compound could be identified while in a non-polar organic solvent. Exposure to polar solvents and water lead to fragmentation of the compound.[195]

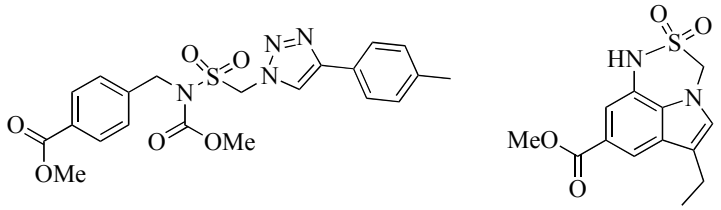


327 **328** **329**

330 **331**

Scheme 95: (a) ^{t}Butylamine; (b) N_2H_4; (c) HNO_2; (d) heat; (e) MeOH

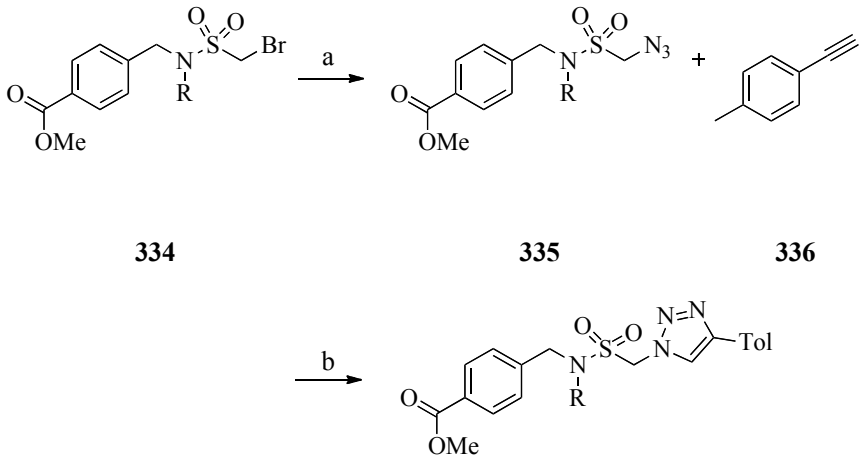
Despite these early negative reports of instability of α-aminosulfonamides, this functionality has been intergrated into larger molecules such as compounds **332**[198]and **333**,[199] which demonstrate that this functionality has the ability to be stable.



332 **333**

Figure 47

However the synthesis of both these compounds do not display novel chemistry. Triazole **332** is synthesised *via* click chemistry from the azide **335**, which is installed by a substitution of the corresponding bromide **334**.[198]

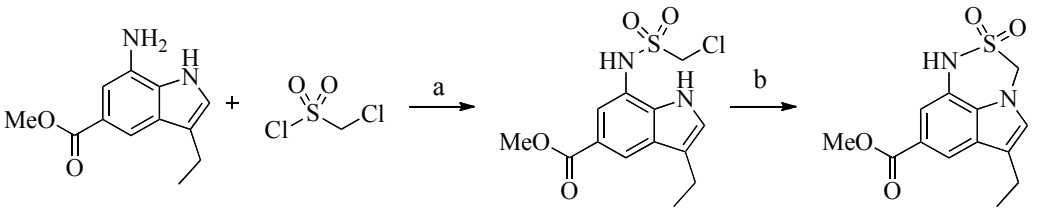


334 **335** **336**

332

Scheme 96: (a) NaN_3, DMF, 79% (b) CuI, DIPEA, sodium L-ascorbate, DMF, 23%

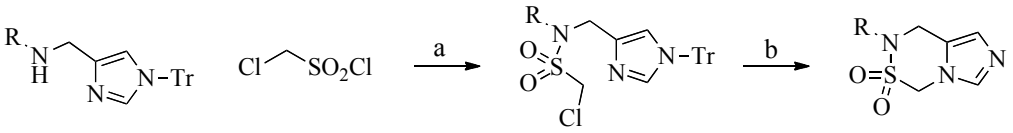
With the indole example **333**, chloromethanesulfonyl chloride is added to indole **338** to afford the sulfonamide **339**. Cyclisation and formation of the α-aminosulfonamide functionality is achieved with the use of sodium hydride and DMF.[199]



337 **338** **339** **333**

Scheme 97: (a) pyridine, DMAP, DCM, 92% (b) NaH, DMF, 41%

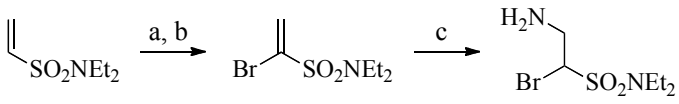
Work by Adams *et al* again shows that the α-aminosulfonamide functionality is stable when tethered in a larger molecule **343**. In this example it is enclosed within a 6 membered ring, with the amino portion occupying the connecting position between the two heterocycles. Again simple chemistry is employed to achieve this.[200]



340 **341** **342** **343**

Scheme 98: DIPEA, DCM, −78 °C (b) DMF, EtOH, DIPEA, microwave

Although routes to β-aminosulfonamides have been more fruitful than those to their α counterparts, they still don't display a succinct and noteworthy synthesis. Instead several multi-step synthesises have been documented. Within our group, a β-aminosulfonamide has been previously synthesised in the synthesis of 2,4-oxazoles.[201] In this example, vinyl sulfonamide **344** undergoes bromination, followed by elimination to afford the bromo vinyl sulfonamide **345**. Ammonia is added *via* a 1,4-addition to yield the β-aminosulfonamide **346**.

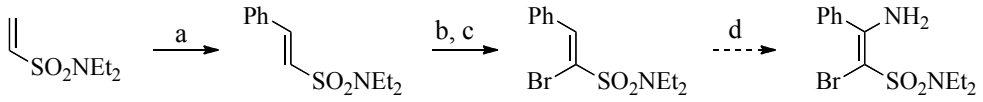


344 **345** **346**

Scheme 99: (a) Br_2 (b) NEt_3 87%; (c) $(NH_4)_2CO_3$, NMP, 60 °C, 80%

However further variation of the aminosulfonamide to include a phenyl group in the β position **349** was unsuccessful. A Heck coupling of vinyl sulfonamide yields the conjugated sulfonamide **347**, which can undergo the same bromination and elimination

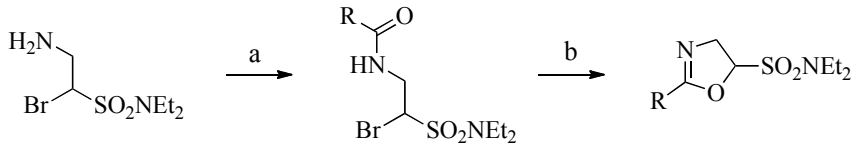
previously used. However the addition of ammonia was unable to be successfully achieved under numerous conditions trialed.[201]



344 **347** **348** **349**

Scheme 100: (a) PhI, $PdCl_2$, NMP, 120 °C, 70% (b) Br_2 (c) NEt_3, 0 °C, DCM, 92% (d) $(NH_4)_2CO_3$, NMP, DMF, TNF, MeOH

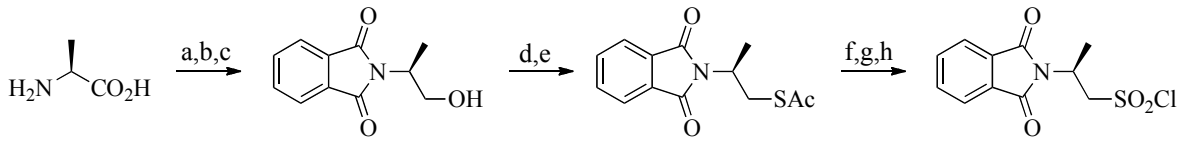
Synthesis of 2,4-oxazole requires a further two steps from this aminosulfonamide involving firstly acylation with a variety of acyl chlorides to yield the amidosulfonamide **350**. Treatment of this amidosulfonamide with sodium *tert*-butoxide affords the oxazoles **351** in a range of yields 50-92%.[201]



346 **350** **351**

Scheme 101: (a) RCOOCl, DCM 55-93% (b) NaO^tBu, DMF 50-92%

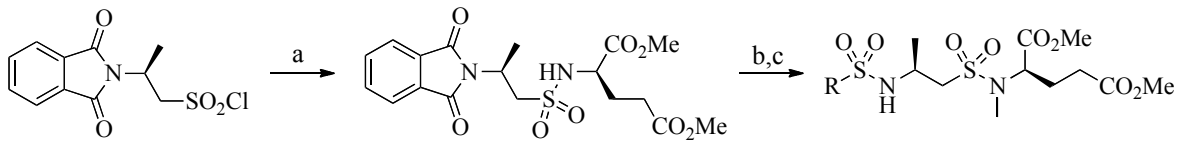
Two routes have employed the *N*-phthalimido protecting group in the synthesis of β-aminosulfonamides, which have displayed medicinal properties. Work by Humljan *et al* employed this group in the protection of L-alanine **352** affording **353**, which undergoes subsitition of the alcohol for a thiol **354** *via* mesylation. Further manipulation yields the sulfonyl chloride **355**.[202]



352 **353** **354** **355**

Scheme 102: (a) $NaBH_4/I_2$, THF, 0 °C-reflux (b) MeOH, 60% (c) phthalic anhydride, 140 °C, 86% (d) MsCl, NEt_3, DCM, 0°C-rt, 96% (e) Cs_2CO_3, HSAc, DMF, 50 °C, 82% (f) H_2O_2, HOAc, rt (g) Pd/C (h) $SOCl_3$, reflux, 85%

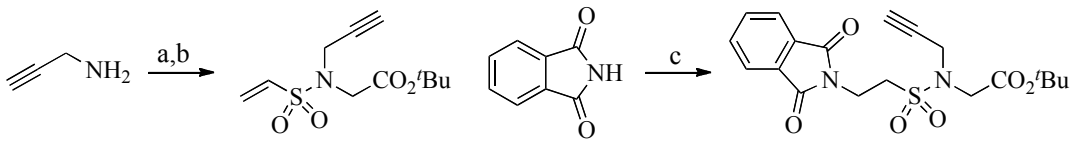
Sulfonyl chloride **355** is coupled with the methoxy protected glutamic acid to yield the *β*-aminosulfonamide **356**. A further two steps enables deprotection of the phthalimide group and then addition of the sulfonamide group gives a *β*-sulfonopeptide inhibitor. However these compounds did not significantly inhibit the enzyme MurD.[202]



355 **356** **357**

Scheme 103: (a) HCl.D-Glu(OMe)$_2$, NEt$_3$, DCM, 0 °C, 75% (b) NH_2NH_2, H_2O, EtOH, rt (c) RSO_2Cl, NEt$_3$, DCM, 0 °C-rt, 30%

The second route by Singhamahapatra *et al* sees the synthesis of functionalised vinyl sulfonamide **360**, which is coupled with the phthalimide protecting group to yield the *β*-aminosulfonamide in a 96% yield.

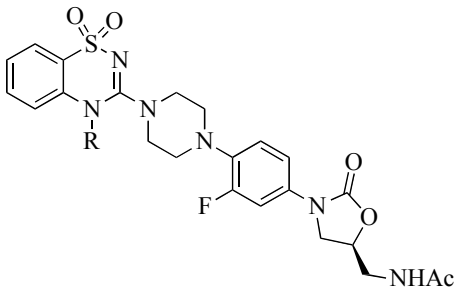


358 **359** **360** **361**

Scheme 104: (a) Bromoacetic acid *tert*-butyl ester, K_2CO_3, MeCN, 0 °C-rt, 24 h (b) 2-chloroethanesulfonyl chloride, DIPEA, DCM, 0 °C-rt, 24 h, 70% (c) MeCN, 60 °C, 24 h, 96%

Although compound **361** hasn't been tested on a medicinal target, its possession of the phthalimide protecting group enables it, like the previous example, to be employed in the synthesis of longer chain peptide mimics.[203]

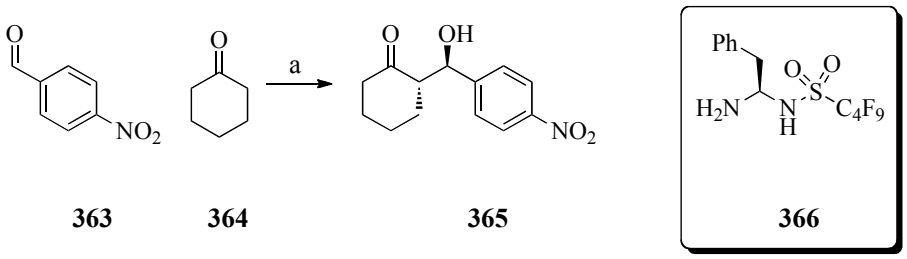
In addition to the synthesis of peptidomimetics, *β*-aminosulfonamides have also been incorporated into compound **362**, which shows promise as a lead scaffold in the development of new anti-*Mycrobacterium* tuberculosis $H_{37}R_v$ agents.[204]



362

Figure 47

Further to the work the conducted on aminosulfonamides in the medicinal chemical setting, there is evidence of a *β*-aminosulfonamide, based on phenylalanine, being used as an organocatalyst for the aldol reaction between cyclohexanone **364** and nitrobenzaldehyde **363**. With a catalyst loading of 10 mol%, the product **365** is afforded in a 82% yield, with 92%*ee* and an *anti*:*syn* ratio of 80:20.[205]



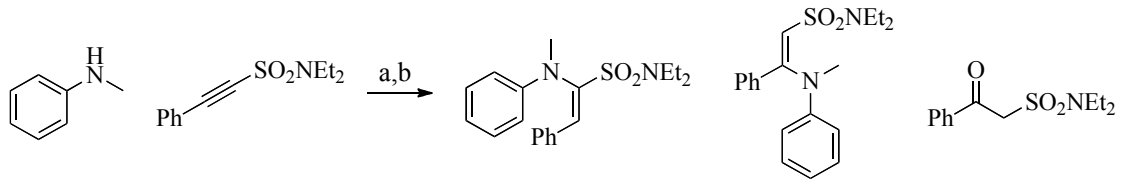
363 **364** **365** **366**

Scheme 105: (a) cat **366** (0.1 eq), brine, rt, 20 h, 82%

3.5 Synthetic Investigations

The immediate drive of this work was to extend the methodology developed within the group into the synthesis of ynol ether to form, ideally, ynamines.[137] With both α and β addition products being reported, it was expected that if an ynamine was not observed, the nitrogen analogues of these alternative products might be. Although not the goal of this work, the presence of either of these addition products would provide an excellent opportunity for their employment in ether the synthesis of heterocycles or as peptidomimetics and represent a novel and hopefully versatile synthetic route towards either of these compounds.

With this in mind, investigations began with the use of *N*-methylaniline **367**, which was exposed to potassium hydride to form the potassium amide salt. Upon complete salt formation, dimethylamine and THF was added to the reaction mixture followed by the swift addition of alkynyl sulfonamide **197** at −78 °C, pleasingly producing the α addition product **368** in a 52% isolated yield after a reaction time of 15 mins.

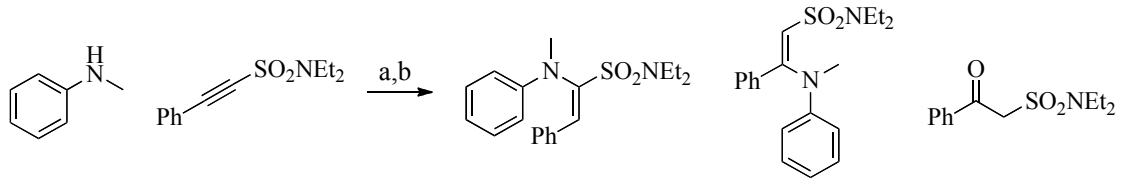


367 **197** **368** **369** **370**

Scheme 106: (a) KH (8 eq.), *N*-methylaniline **367** (4 eq.), THF; (b) $HNMe_2$ (2 M in THF, 4 eq.)

With the α configuration of **368** confirmed by HMBC NMR, the product **368** from this reaction possesses the rare functionality of an α-aminosulfonamide in a significant yield.

Evaluation of the reaction conditions to ensure the existing ynol ether conditions were optimal and a variety of different bases were trialed, instead of the previously successful potassium hydride. The employment of LDA and sodium hydride did not yield a successful reaction, while butyl lithium resulted in the production of the β-aminosulfonamide **369**, alongside the ketosulfonamide **370** in 20% and 11% yields respectively



367 **197** **368** **369** **370**

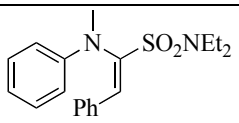
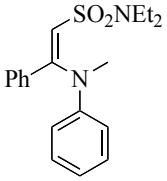
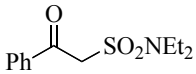
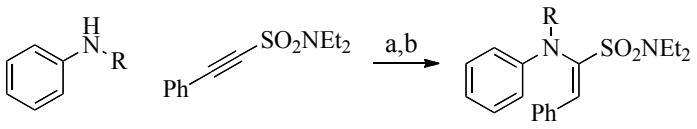
Base	*Product*	*Yield (%)*
KH		**52**
NaH	-	0
LDA	-	0
BuLi		20
		11

Table 6: (a) base, THF; (b) $HNMe_2$

This short survey of bases collaborated the results shown within the ynol ether studies and subsequent mechanistic studies that the potassium counterion is instrumental in this reaction pathway.

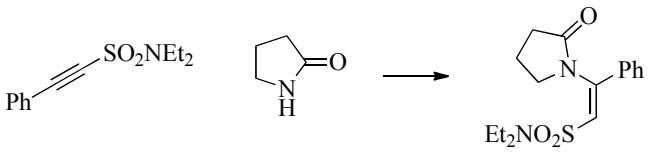
Keeping the reaction conditions the same; the next point of variation that was investigated was the nature of the amine species. With the initial focus on the alkyl nitrogen tether, represented up to now as a methyl, two replacements were employed. These replacements took the form of acyl and benzyl tethers from the commercially available *N*-acetylaniline **371** and *N*-benzylaniline **372**, investigating the effects of an electron-withdrawing group and steric bulk respectively. Positively, the use of increased steric bulk on the amine did not have a detrimental effect on the desired reaction yielding 32% of corresponding α-aminosulfonamide **374**. However, the presence of the acetyl did have a detrimental effect on the reaction with no identifiable products being produced.



371 R = $COCH_3$ **197** **373** R = $COCH_3$
372 R = CH_2Ph **374** R = CH_2Ph

Scheme 107: (a) KH, THF; (b) $HNMe_2$

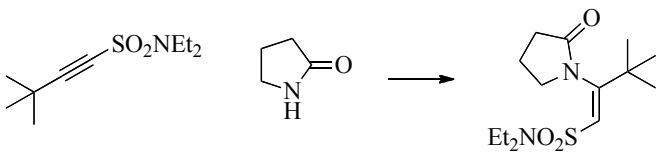
The next question that was raised was regarding whether the phenyl functionality was required or if the reaction could be extended to completely aliphatic amines or amides. Here three different amines were employed and in all examples both potassium and lithium counterions were trialed. The amines utilised here were pyrollidin-2-one **375**, pyrollidine and diisopropylamine. Under the reaction conditions previously detailed, pyrollidin-2-one **375** was the only aliphatic amine to react to yield the β-addition product **376**, when potassium was used as the counterion in a good yield of 71%. When the counterion was lithium as expected no product was formed. However, removal of the electron-withdrawing group on the amine did not afford either α or β products, with both pyrollidine and diisopropylamine yielding no reaction under both conditions.



197 **375** **376**

Scheme 108

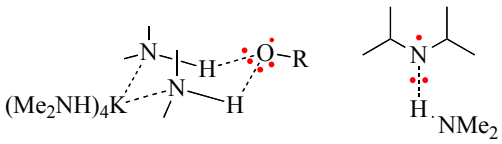
Although pyrollidinone **375** disappointingly yielded the β-aminosulfonamide **376**, it did do so in a high yield and was the only amine, aromatic or aliphatic, to react with the *tert*-butyl alkynyl sulfonamide **202**,[218] despite with a low yield (23%) of **377**.



202 **375** **377**

Scheme 109

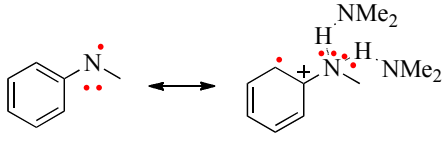
With the mechanistic work conducted on the ynol ether synthesis, there is substantial evidence that both the ynol ether and α addition products are the result of a radical mechanism,[145] while β addition is the product derived from the expected nucleophilic mechanism. The reactive radical species with the oxygen examples, as described previously in section 3.1, sees hydrogen bonding between the two lone pairs of oxygen with protons on dimethylamine, which in turn, bonds to the potassium counterion to form a 6 membered ring **201**, thereby stabilising the radical charge. When an aliphatic amine is introduced to these reaction conditions, this 6 membered ring cannot be formed due to lack of the two lone pairs **378** (fig. 48) meaning that the radical mechanism cannot be supported, allowing for nucleophilic substitution and β addition.



201 **378**

Figure 48

However, when aniline is employed, the phenyl ring allows for resonance and the dispersion of the radical charge into the aromatic ring. In turn this gives the nitrogen an additional electron, creating two lone pairs of electrons and potentially mimicking oxygen **201**. This suggests that the radical mechanism can now proceed and α addition is observed.

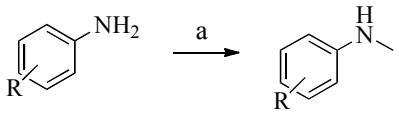


379 **380**

Scheme 110

The last point of variation that was investigated was the substitution on the aniline. Firstly, monomethylation of suitable anilines was required and methyl iodide, alongside potassium carbonate were employed as the reaction conditions for this transformation. Although successful in providing the monomethyated anilines, this procedure did result in the mono-product being the minor product, while the di-methylated anilines were the

major product, which did result in significantly lower yields of monomethylaniline (table 7).



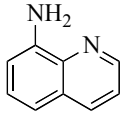
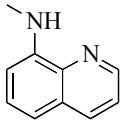
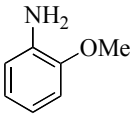
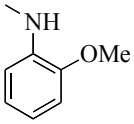
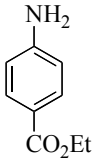
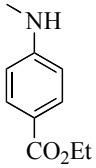
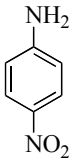
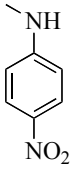
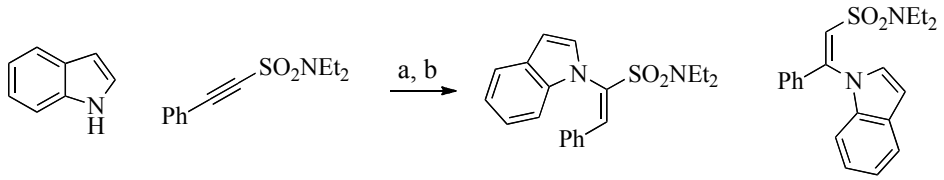
Starting Material	*Product*	*Number*	*Yield (%)*
		**381**	15
		**382**	17
		**383**	31
		**384**	27

Table 7 (a) MeI, K_2CO_3

Upon subjecting anilines **381** - **384** to the reaction conditions, it surprisingly did not result in the corresponding α-aminosulfonamide and produced an inseparable and unidentifiable reaction mixture.

The last aromatic amine to be employed was indole, which gave a high yield of the aminosulfonamide 90%. However proton NMR showed that this was a mixture of α and β aminosulfonamides in a **386**:**387** ratio (2:1).



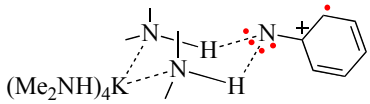
385 **197** **386** **387**

Scheme 111: (a) KH, THF (b) $HNMe_2$ (2M in THF)

With the disappointing results seen when substituents were added to the aromatic ring, this observation suggests that although the phenyl analogue **368** is stable and can be isolated, it is a stability, which is finely balanced, probably between the aniline and the styrene moiety on the α carbon. The slight changes made by the introduction of both electron-withdrawing and electron-donating groups have the ability to disrupt this and the stabilisation of the radical species. Potentially, this causes these products to move towards instability and fragmentation, although no fragmentation products were observed from the reaction mixtures.

3.6 Conclusion and Further Work

Despite the negative attention within the literature towards α-aminosulfonamides, this work has overturned this thought by successfully synthesising and isolating an α-aminosulfonamide; a feat, which has not been as yet reported within the literature. Although the brief investigations so far have failed to extend the radical scope past that of the aniline example, thereby suggesting that minor changes to the electronic make up of the phenyl ring can disrupt the finely balanced nature of the reactive radical species **389**.



389

Figure 49

Further work in this area should firstly investigate the mechanistic detail of this reaction and highlight its similarities and potential differences with regard to the oxygen analogues. From these results, it should be possible to have a clearer idea of what substituents could be add to the phenyl ring to ensure maximum yield and stability of the product.

Of further interest would be the potential to employ these structures in the development of a peptidomimetics, which could more closely mimic the natural amino acid arrangements. The α styrene moiety in particular allows for the potential for further

elaboration and manipulation to provide further functionality, which could be of benefit for peptidomimetic and drug development.

4. Experimental

All reactions were carried out at room temperature, under standard atmospheric pressure with stirring, unless otherwise stated. All reactions involving moisture-sensitive reagents were carried out under an argon atmosphere, using standard vacuum line techniques and glassware that was flame dried and cooled under argon before use. Anhydrous solvents were used following purification from an Anhydrous engineering (USA) system after drying over alumina granules, with the expection of anhydrous DMF, which was purchased from suppliers and used without further purification. Petroleum ether used was from the 40-60 ˚C. All other solvents and reagents were used as supplied without prior purification, unless otherwise stated. Petroleum ether used

Column chromatography was carried out using BDH (40-60 μm) silica gel and analytical thin layer chromatography was carried out using Merck Keiselgel aluminium-backed plates coated with silica gel. Plates were visualised using combinations of ultra-violet light (254 nm) and chemical stains (phosphomolybdic acid and potassium permanganate). All yields are quoted as isolated yields.

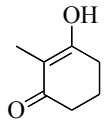
Melting points were determined using a Gallenkamp apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer or a Perkin-Elmer spectrum 100 FT-IR spectrometer as thin films.

^{1}H NMR spectra were recorded at 400, 500 and 600 MHz on a Brüker AMX400, Brüker AMX500 and Brüker AMX600 spectrometers respectively, at ambient temperatures in the stated solvent using residual protic solvent $CHCl_3$ (δ = 7.26 ppm, s) or DMSO (δ = 2.56 ppm, qn) as the internal standard. Chemical shifts are quoted in parts per millon (ppm) using the following abbreviations: **s** (singlet), **d** (doublet), **t** (triplet), **q** (quartet), **qn** (quintet), **m** (multiplet), **br** (broad) or a combination of these. Chemical shifts (δ) are quoted to 2 decimal places and coupling constants (*J*) are quoted to 1 decimal place, with coupling constants being measured in Hertz (Hz). ^{13}C NMR spectra were recorded at 100, 125 and 150 MHz on a Brüker AMX400, Brüker AMX500 and Brüker AMX600 spectrometers respectively, at ambient temperature in the stated solvent using

the central reference of $CHCl_3$ (δ = 77.0 ppm, t) or DMSO (δ = 39.52 ppm, septet) as the internal standard.

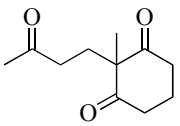
High and low resolution mass spectrometry were recorded by the Mass Spectrometry department at the Department of Chemistry, University College London using a VG70 SE operating in modes, EI or CI depending on the sample.

2-Methylcyclohexan-1,3-dione 390 [206]



To a solution of cyclohexan-1,3-dione (10.0 g, 89.2 mmol) in 5 M sodium hydroxide aqueous solution (20 mL), methyl iodide (11.2 mL, 178.4 mmol) was added and stirred at 65 °C for 18 h. The reaction mixture was cooled to room temperature and the solid was filtered to afford the title compound (8.73 g, 78%) as a colourless solid, mp 195-198 °C (lit[219] value 198-200 °C); ***IR*** ν_{max}/cm^{-1} (film) 3428.6, 2950.6, 2887.9, 2595.1, 2457.1, 1645.7, 1568.6; ***^{1}H NMR*** (DMSO – D_6, 400 MHz, ppm) δ_H 2.29 (4H, t *J* = 6.3 Hz, CH_2), 1.79 (2H, qn, *J* = 6.8 Hz, CH_2), 1.53 (3H, s, CH_3); ***^{13}C NMR*** (DMSO-D_6, 150 MHz, ppm) δ_C 210.4 (s), 198.1 (s), 55.7 (t), 36.4 (t), 24.1 (q), 20.6 (t); ***LCMS*** (EI) *m/z* 126 (100%), 98 (85), 83 (30); ***HRMS*** (EI) $C_7H_{10}O_2$ [M^+] requires 126.06753, found 126.06699. Data consistent with literature values.[206]

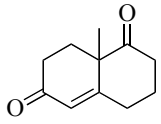
2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione 39 [40]



Freshly distilled methyl vinyl ketone (2.20 mL, 27.03 mmol) was added to a mixture of 2-methyl-1,3-cyclohexadione **390** (3.10 g, 24.6 mmol) and triethylamine (0.034 mL, 0.25 mmol) and stirred at room temperature for 18 h. The crude product was purified by column chromatography (25% ethyl acetate:petroleum ether) to afford the title compound (2.78 g, 58%) as a pale yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 2964.4, 2254.3,

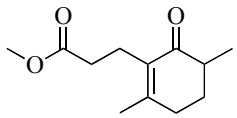
1715.2, 1691.6; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 2.74 (2H, ddd, *J* = 15.7, 8.9 & 5.4 Hz, C*H*$_2$), 2.62 (2H, ddd, *J* = 15.7, 8.9 & 5.4 Hz, C*H*$_2$), 2.33 (2H, t, *J* = 7.9 Hz, C*H*$_2$), 2.09 (3H, s, C*H*$_3$), 2.05-2.02 (3H, m, C*H*$_2$ & CH*H*), 1.93-1.86 (1H, m, C*H*H), 1.23 (3H, s, C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 210.1 (s), 207.6 (s), 64.5 (s), 38.4 (t), 37.8 (t), 30.0 (q), 29.5 (t), 20.2 (q), 17.6 (t); ***LCMS*** (EI) *m/z* 196 (85%), 178 (55), 169 (15), 156 (80), 139 (35), 126 (65), 111 (100), 97 (65), 81 (30), 69 (50); ***HRMS*** (EI) $C_{11}H_{17}O_3$ $[M]^+$ requires 196.10994, found 196.10942. Data consistent with literature values.[65]

8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H, 7H)-dione 34



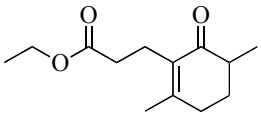
L-Proline (0.015 g, 0.10 mmol) was added to a solution of triketone **39** (0.20 g, 1.02 mmol) in DMSO (1 mL) and stirred at room temperature. After 72 h, the reaction mixture was diluted with water (5 mL) and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$), filtered and concentrated in *vacuo* to afford the crude product, which was purified by column chromatography (40% ethyl acetate:petroleum ether) to afford the title compound (0.018 g, 9%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 2931.8, 2349.5, 1712.4, 1676.8, 1619.4; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 5.85 (1H, s, C=C*H*), 2.75-2.68 (2H, m, C*H*$_2$), 2.53-2.42 (4H, m, 2 x C*H*$_2$), 2.17-2.09 (2H, m, C*H*$_2$), 1.75-1.65 (2H, m, C*H*$_2$), 1.44 (3H, s, C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 211.2 (s), 198.5 (s), 171.4 (d), 125.9 (s), 51.9 (s), 37.8 (t), 33.7 (t), 31.9 (t), 29.7 (t), 23.5 (q), 23.0 (t); ***LCMS*** (CI^+-methane) *m/z* 179 (100%), 161 (90), 149 (15), 137 (50), 122 (15), 112 (5), 97 (5), 85 (10), 79 (5), 71 (15); ***HRMS*** (CI^+-methane) calc'd for $C_{11}H_{15}O_2$ $[M+H]^+$ 179.10720 found 179.10673.

Methyl-3-(2,5-dimethyl-6-oxocyclohex-1-en-1-yl)propanoate 102



Dimethylhydrazine dihydrochloride (0.013 g, 0.010 mmol) was added to a solution of triketone **39** (0.20 g, 1.02 mmol) in methanol (2 mL) and stirred at 70 °C for 6 h. After removal of the solvent in vacuo, the resulting residue was purified by column chromatography (100% dichloromethane) to afford the title compound (0.17 g, 81%), as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 2930.7, 1732.5, 1662.0, 1633.2, 1452.8, 1375.2; ***^{1}H NMR*** ($CDCl_3$, 600 MHz; ppm) δ_H 3.64 (3H, s, OC*H*$_3$), 2.59 (2H, qt, *J* = 15.9 & 7.9 Hz, C*H*$_2$), 2.44-2.38 (1H, m, C*H*), 2.33 (2H, t, *J* = 7.9 Hz, C*H*$_2$), 2.32-2.25 (2H, m, C*H*$_2$), 1.98 (1H, dq, *J* = 13.6 & 4.9 Hz, C*H*), 1.94 (3H, s, C*H*$_3$), 1.68-1.61 (1H, m, C*H*), 1.11 (3H, d, *J* = 6.7 Hz, C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 201.1 (s), 173.9 (s), 155.4 (s), 133.2 (s), 51.6 (q), 40.8 (d), 33.2 (t), 32.2 (t), 30.2 (t), 21.4 (t), 21.9 (q), 15.6 (q); ***LCMS*** (EI) *m/*z 210 (35%), 179 (35), 151 (25), 150 (100), 140 (43), 125 (27), 109 (10), 108 (34), 85 (37), 81 (15); **HRMS** (EI) $C_{12}H_{20}O_3$ [M^+] requires 210.12505, found 210.12422. Data consistent with literature values.[64]

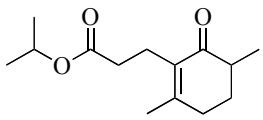
Ethyl-3-(2,5-dimethyl-6-oxocyclohex-1-en-1-yl)propanoate 103



Dimethylhydrazine dihydrochloride (0.013 g, 0.01 mmol) was added to a solution of triketone **39** (0.20 g, 1.02 mmol) in ethanol (2 mL) and stirred at 70 °C for 6 h. After removal of the solvent in *vacuo*, the residue was purified by column chromatography (100 % dichloromethane) to afford the title compound (0.094 g, 42%) as a yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 2927.5, 1737.6, 1662.5, 1631.7, 1455.6, 1379.4; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 4.08 (2H, q, *J* = 7.2 Hz, C*H*$_2$), 2.59 (2H, qt, *J* = 13.7 & 9.2 Hz, C*H*$_2$), 2.44-2.37 (1H, m, C*H*), 2.33-2.26 (4H, m, 2 x C*H*$_2$), 1.98 (1H, dq, *J* = 13.7 & 4.7 Hz, C*H*), 1.94 (3H, s, C*H*$_3$), 1.65 (1H, s, C*H*), 1.23 (3H, t, *J* = 7.2 Hz, C*H*$_3$), 1.11 (3H, d, *J* = 6.8 Hz, C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 150 MHZ, ppm) δ_C 201.1 (s), 173.5 (s), 155.4

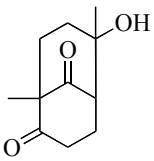
(s), 133.2 (s), 60.3 (t), 40.8 (d), 35.7 (t), 32.3 (t), 30.2 (t), 21.4 (t), 19.8 (t), 15.6 (q), 14.3 (q); ***LCMS*** (EI) *m/z* 225 (15%), 224 (100), 179 (15), 178 (23), 150 (12), 108 (10); ***HRMS*** (EI) $C_{13}H_{20}O_3$ [M^+] requires 224.14070, found 224.13968.

Isopropyl-3-(2,5-dimethyl-6-oxocyclohex-1-en-1yl)propanoate 104



To a solution of triketone **39** (0.20 g, 1.02 mmol) in isopropanol (2 mL), dimethylhydrazine dihydrochloride (0.013 g, 0.01 mmol) was added and stirred at 70 °C for 18 h. After the solvent was removed in *vacuo*, the residue was purified by column chromatography (15 ethyl acetate: petroleum ether) to afford the title compound (0.22 g, 92%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 2979.4, 2932.1, 1726.6, 1660.7, 1632.9; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 4.90 (1H, septet, *J* = 6.3 Hz, C*H*$(CH_3)_2$), 2.55 (2H, qt, *J* = 13.7 & 7.6 Hz, CH_2), 2.41-2.34 (1H, m, C*H*), 2.29-2.24 (4H, m, 2 x CH_2), 1.95 (1H, dq, *J* = 13.7 & 4.6 Hz, C*H*CH_3), 1.91 (3H, s, CH_3), 1.62-1.59 (1H, m, C*H*), 1.17 (6H, d, *J* = 6.3 Hz, CH(C$H_3)_2$), 1.08 (3H, d, *J* = 4.6 Hz, CHCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 210.4 (s), 173.0 (s), 155.3 (s), 133.4 (s), 67.5 (d), 40.9 (d), 33.8 (t), 32.1 (t), 30.2 (t), 21.9 (2 × q), 21.5 (t), 15.3 (q); ***LRMS*** (CI) *m/z* 240 (7%), 239 (48), 197 (14), 179 (100), 150 (5); ***HRMS*** (CI) $C_{14}H_{23}O_3$ [M+H] requires 239.16472, found 239.16461.

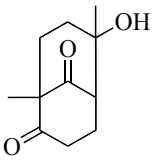
6-hydroxyl-1,6-dimethylbicyclo[3.3.1]nonane-2,9-dione 105



Dimethylhydrazine dihydrochloride (0.013 g, 0.01 mmol) was added to a solution of triketone **39** (0.20 g, 1.02 mmol) in *tert*-butanol (2 mL) and stirred at 70 °C for 3 h. After removal of the solvent in *vacuo*, the resulting residue was purified by column chromatography (10 ethyl acetate:dichloromethane) to afford the title compound (0.039

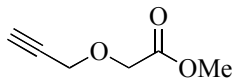
g, 22%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 3426.6, 2934.8, 1727.0, 1695.1; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 2.66 (1H, dt, *J* = 9.0 & 2.1 Hz, C*H*), 2.56 (1H, ddd, *J* = 16.4, 7.2 & 6.1 Hz, C*H*), 2.41 (1H, t, *J* = 8.5 Hz, C*H*), 2.10-2.05 (1H, m, C*H*), 2.04 (1H, dd, *J* = 4.0 & 1.0 Hz, C*H*), 2.02 (1H, dd, *J* = 4.0 & 1.0 Hz, C*H*), 1.93 (1H, bs, O*H*), 1.79 – 1.73 (2H, m, CH_2), 1.64 (1H, dt, *J* = 14.6 & 4.3 Hz), 1.37 (3H, s, CH_3), 1.16 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 211.7 (s), 79.1 (s), 62.6 (s), 57.1 (d), 38.5 (t), 37.2 (t), 32.5 (t), 28.1 (q), 19.4 (t), 16.6 (q); ***LCMS*** (CI) *m/z* 240 (13), 239 (60), 238 (3), 197 (24), 180 (13), 179 (91), 178 (5), 150 (6); ***HRMS*** (CI) $C_{14}H_{23}O_3$ [M+H] requires 239.16472, found 239.16491.

6-hydroxyl-1,6-dimethylbicyclo[3.3.1]nonane-2,9-dione 105



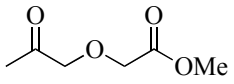
Triketone **39** (0.20 g, 1.02 mmol) was combined with dimethylhydrazine dihydrochloride (0.013 g, 0.01 mmol) and stirred at room temperature for 7 days. The residue was purified by column chromatography (20-40% ethyl acetate:petroleum ether) to afford the title compound (0.10 g, 56%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 3426.6, 2934.8, 1727.0, 1695.1; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 2.66 (1H, dt, *J* = 8.9 & 2.0 Hz, C*H*), 2.55 (1H, ddd, *J* = 16.6, 7.6 & 6.2 Hz, C*H*), 2.42 – 2.35 (1H, m, C*H*), 2.09-2.01 (4H, m), 1.79 – 1.73 (2H, m, CH_2), 1.67-1.62 (1H, m, C*H*), 1.37 (3H, s, CH_3), 1.15 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 210.2 (s), 80.3 (s), 61.8 (s), 57.4 (d), 39.1 (t), 36.0 (t), 32.4 (t), 28.9 (q), 19.9 (t), 15.9 (q); ***LCMS*** (CI) *m/z* 240 (10), 239 (52), 197 (18), 180 (15), 179 (100); ***HRMS*** (CI) $C_{14}H_{23}O_3$ [M+H] requires 239.16472, found 239.16461.

Methyl-2-(prop-2-yn-1-yloxy)acetate 120



To a stirring suspension of potassium *tert*-butoxide (16.01 g, 142.7 mmol) in anhydrous tetrahydrofuran (200 mL) at 0 °C, propargyl alcohol (4.15 mL, 71.4 mL) was added dropwise followed by the dropwise addition of methyl bromoacetate (8.14 mL, 85.6 mmol) and the resulting solution was stirred for 3.5 h at room temperature. After quenching the reaction with distilled water (60 mL), the solution was diluted with dichloromethane (50 mL) and the aqueous layer extracted with dichloromethane (3 x 40 mL). The combined organic layers were washed with brine (50 mL) and dried, filter and concentrated *in vacuo* to afford the crude product, which was purified *via* column chromatography (10% ethyl acetate: petroleum ether) to afford the title compound (3.38 g, 37%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 3291, 2883, 2241, 1745, 1386, 1143; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 4.21 (2H, d, *J* = 3.65 Hz, C*H*$_2$), 4.10 (2H, s, C*H*$_2$), 3.66 (3H, s, C*H*$_3$), 2.44 (1H, t, *J* = 2.4 Hz, C*H*); ***^{13}C NMR*** ($CDCl_3$, 125 MHz, ppm) δ_C 170.3 (s), 78.4 (s), 66.8 (q), 58.5 (d), 52.1 (t), 14.0 (d); ***LCMS*** (CI) *m/z* 129 (100%), 121 (8), 115 (8), 107 (23), 101 (60), 91 (20); ***HRMS*** (CI) $C_6H_9O_3$ [M^+] requires 129.05517, found 129.05538. Data consistent with literature values.[44]

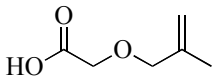
Methyl 2-(2-oxopropoxy)acetate 113 [41]



To a stirring solution of alkyne **120** (3.38 g, 26.4 mmol), and methanol (80 mL), mercury(II) acetate (0.68 g, 2.64 mmol) and concentrated sulfuric acid (0.05 mL) was added and the solution heated to reflux for 20 min. After cooling, the solvent was removed *in vacuo* and dichloromethane (30 mL) was added to the resulting residue. After addition of 1M HCl (30 mL), the aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Purification *via* column chromatography (40% ethyl acetate: petroleum ether) afforded the title compound (0.68

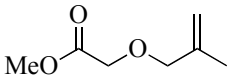
g, 18%) as a yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 3537.3, 2956.9, 2921.8, 1730.7, 1437.8, 1358.5; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 4.21 (2H, s, C*H*$_2$O), 4.20 (2H, s, OC*H*$_2$), 3.76 (3H, s, OC*H*$_3$), 2.18 (3H, s, C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 205.6 (s), 170.4 (s), 74.4 (t), 67.8 (t), 51.8 (q), 25.1 (q); ***LCMS*** (CI) *m/z* 129 (95%), 121 (7), 115 (5), 111 (15), 107 (20), 101 (55), 91 (20): ***HRMS*** (CI) $C_6H_{10}O_4$ $[M+H]^+$ requires 147.06573, found 147.06573. Data consistent with literature values.[41]

2-((2-methylallyl)oxy)acetic acid 129



To a suspension of sodium hydride (2.50 g, 105.8 mmol) in anhydrous dimethylformamide (10 mL) at 0 °C, methallyl alcohol was added dropwise and stirred for 30 mins. A solution of chloroacetic acid (5.00 g, 52.90 mmol) in anhydrous dimethylformamide (10 mL) was added dropwise and warmed to room temperature and stirred until complete by TLC. The reaction was quenched by the dropwise addition of water (10 mL) and 2M $HCl_{(aq)}$ (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with saturated LiCl solution (2 x 30 mL), followed by brine (20 mL) and dried, filtered and concentrated *in vacuo* to afford the title compound (6.50 g, 94%) as a yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 2922.8, 1725.8; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 11.35 (1H, s, O*H*), 5.00 (1H, s, C=C*H*H), 4.98 (1H, s, C=CH*H*), 4.10 (2H, s, C*H*$_2$O), 4.03 (2H, s, OC*H*$_2$), 1.77 (3H, s, C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 100 MHz, ppm) δ_C 182. 9 (s), 140.7 (s), 113.9 (t), 66.3 (t), 40.5(t), 19.3 (q); ***LCMS*** (EI) 130 (7%), 86 (58), 84 (100), 71 (57), 60 (79), 57 (23), 55 (53). Data consistent with literature values.[207]

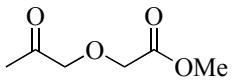
Methyl 2-((2-methylallyl)oxy)acetate 130[41]



Amberlyst-15 ion-exchange resin (0.50 g) was added to a stirring solution of 2-((2-methylallyl)oxy)acetic acid **129** (15.9 g, 112.7 mmol) in methanol (200 mL) and heated

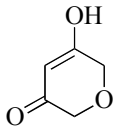
to 60 °C. After 16 h, the reaction mixture was cooled to room temperature and filtered. The resulting solution was concentrated in *vacuo* to afford the title compound (9.66 g, 55 %) as a pale yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 2953.2, 1756.1, 1656.7, 1438.2, 1376.5; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 4.99 (1H, s, C=C*H*H), 4.94 (1H, s, C=H*H*), 4.02 (2H, s, CH_2), 3.82 (2H, s, CH_2), 3.78 (3H, s, OCH_3), 1.77 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 100 MHz, ppm) δ_C 171.0 (s), 141.1 (s), 113.4 (t), 75.9 (t), 67.3 (t), 55.1 (q), 19.3 (q); ***LCMS*** (CI) *m/z* 145 (100%), 131 (19), 113 (8), 109 (14), 103 (46), 91 (22), 85 (40), 74 (9); **HRMS** (CI) $C_7H_{13}O_2$ $[M+H]^+$ requires 145.08647, found 145.08587.

Methyl 2-(2-oxopropoxy)acetate 113[41]



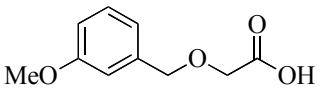
To a stirring solution of methyl 2-((2-methallyloxy)acetate **130** (9.66 g, 67.1 mmol) in tetrahydrofuran (10 mL), osmium tetroxide –polymer bound fibrecat (0.17 g, 0.67 mmol) in distilled water (5 mL) and tetrahydrofuran (50 mL) was added followed by the dropwise addition of a solution of sodium periodate (28.7 g, 134.2 mmol) in distilled water (200 mL). The resulting reaction mixture was stirred at room temperature for 16 h. The colourless heterogenous reaction mixture was filtered and the filter cake washed with water (100 mL). The filtrate was washed with *tert*-butyl methyl ether (150 mL) and the aqueous layers were extracted with dichloromethane (4 x 200 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated in *vacuo* to afford the title compound (3.66 g, 42 %) as a yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 3537.3, 2956.9, 2921.8, 1730.7, 1437.8, 1358.5; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 4.21 (2H, s, CH_2O), 4.20 (2H, s, OCH_2), 3.76 (3H, s, OCH_3), 2.18 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 205.6 (s), 170.4 (s), 74.4 (t), 67.8 (t), 51.8 (q), 25.1 (q); ***LCMS*** (CI) *m/z* 129 (95%), 121 (7), 115 (5), 111 (15), 107 (20), 101 (55), 91 (20): ***HRMS*** (CI) $C_6H_{10}O_4$ $[M+H]^+$ requires 147.06573, found 147.06573. Data consistent with literature values.[41]

Pyran-3,5-dione 74[41]



To a three-necked flask containing refluxing anhydrous tetrahydrofuran (20 mL), a solution of methyl 2-(2-oxopropoxy)acetate **113** (23.19 g, 159 mmol) in anhydrous tetrahydrofuran (250 mL) and a solution of potassium *tert*-butoxide (21.37 g, 190 mmol) in anhydrous tetrahydrofuran (250 mL) were added in a simultaneous dropwise manner. Once the addition was complete, the reaction mixture was stirred at reflux for a further 5 mins before quenching with the dropwise addition of distilled water (10 mL). After cooling to room temperature, the pH of the resulting brown solution was adjusted to 1 using aqueous 2M HCl solution and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in *vacuo* to afford the title compound (16.55 g, 91 %) as a viscous brown oil; ***IR*** ν_{max}/cm^{-1} (film) 2484.81, 1641.99, 1538.51; ***^{1}H NMR*** (DMSO-d_6, 400 MHz, ppm) δ_H 11.8 (1H, s, O*H*), 5.31 (1H, s, C=C*H*), 4.08 (4H, s, 2x CH_2), 3.32 (2H, s, CH_2); ***LCMS*** *m/z* (ES^+) 114.9 (100%). Data consistent with literature values.[41]

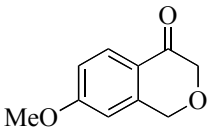
2-((3-methoxybenzyl)oxy)acetic acid 167[97]



To a suspension of sodium hydride (6.09 g, 253 mmol) in anhydrous DMF (20 mL), 3-methoxybenzyl alcohol **142** (9.47 mL, 76.2 mmol) was added dropwise at 0 °C. After stirring for 1 h at 0 °C, a solution of chloroacetic acid (6.00 g, 63.5 mmol) in anhydrous DMF (10 mL) was added dropwise and after stirring at room temperature for 18 h, the reaction mixture was cooled to 0 °C and quenched with the dropwise addition of water (30 mL). The pH of the reaction mixture was adjusted to 10 with concentrated NaOH aqueous solution and washed with diethyl ether (40 mL). The pH of the aqueous layer was adjusted to 2 using concentration HCl aqueous solution and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with saturated LiCl

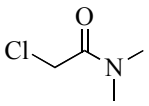
solution (2 x 30 mL), followed by brine (30 mL) and dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound (9.79 g, 96 %) as colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 2939.1, 1730.0, 1587.5, 1266.9; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 7.30 (1H, t, *J* = 8.33 Hz, Ar*H*), 6.97 – 6.93 (2H, m, Ar*H*), 6.89 (1H, dd, *J* = 8.33 & 2.49 Hz, Ar*H*), 4.65 (2H, s, CH_2), 4.16 (2H, s, CH_2), 3.84 (3H, s, OCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 177.4 (s), 159.9 (s), 138.2 (s), 129.8 (d), 120.4 (d), 114.0 (d), 113.4 (d), 73.4 (t), 66.7 (t), 55.3 (q); ***LRMS*** (EI) 262 (25%), 178 (10), 149 (13), 148 (20), 137 (24), 121 (75), 109 (63), 98 (25), 97 (45), 95 (75); ***HRMS*** (EI) $C_{10}H_{12}O_4$ [M^+] requires 196.07301, found 196.07261. Data consistent with literature values.[98]

7-Methoxyisochroman-4-one 145[97]



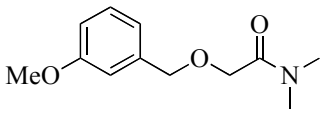
A solution of 2-((3-methoxybenzyl)oxy)acetic acid **167** (4.72 g, 24.1 mmol) in dichloromethane (50 mL) was cooled to 0 °C under argon and oxalyl chloride (4.21 mL, 48.2 mmol) and DMF (0.1 mL) were added dropwise. After stirring at 50 °C for 18 h, the reaction mixture was cooled to 0 °C and following the dropwise addition of tin (VI) chloride (1M in dichloromethane, 10.5 mL) allowed to stir for 1 h. Saturated $NaHCO_3$ solution (30 mL) and water (30 mL) were added to the reaction mixture and the resulting solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), filtered and concentrated in *vacuo*. The resulting crude oil was purified by column chromatography (10-20 % ethyl acetate: petroleum ether) to afford the title compound (2.12 g, 50 %) as a white solid; m.p. 76-79 °C (lit.[98] value 78-80 °C); ***IR*** ν_{max}/cm^{-1} (film) 2969.3, 2845.5, 2809.5, 1672.9 1595.5, 1572.8; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 8.02 (1H, d, *J* = 8.58 Hz, Ar*H*), 6.91 (1H, dd, *J* = 8.58 & 2.50 Hz, Ar*H*), 6.66 (1H, d, *J* = 2.50 Hz, Ar*H*), 4.85 (2H, s, CH_2), 4.33 (2H, s, CH_2), 3.88 (3H, s, OCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 193.0 (s), 169.2 (s), 164.3 (s), 129.2 (s), 123.2 (s), 114.3 (d), 108.9 (d), 73.5 (t), 68.2 (t), 55.3 (q); ***LRMS*** (EI) 149 (8%), 148 (100), 120 (28), 105 (10); ***HRMS*** (EI) $C_{10}H_{10}O_3$ [M^+] requires 178.06245, found 178.06208. Data consistant with literature values.[97]

2-Chloro-N, N-dimethylacetamide 173[208]



A solution of chloroacetyl chloride **172** (3.52 mL, 45.0 mmol) in anhydrous THF (20 mL) was cooled to -20 °C and dimethylamine (2M in THF, 27 mL) was added dropwise. After stirring at room temperature for 18 h, the reaction mixture was cooled to 0 °C and quenched with 2M $HCl_{(aq)}$ (20 mL). The resulting mixture was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were washed with brine (15 mL) before being dried (Na_2SO_4), filtered and concentrated in vacuo to afford a yellow oil. Purification was achieved *via* column chromatography (15% diethyl ether: petroleum ether) to afford the title compound (2.75 g, 50 %) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 2936.8, 1650.4; ***^{1}H NMR*** ($CDCl_3$, 500 MHz, ppm) δ_H 4.12 (2H, s, CH_2), 3.12 (3H, s, NCH_3), 3.01 (3H, s, NCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 168.9 (s), 41.2 (t), 37.8 (q), 36.1 (q). Data consistent with literature values.[208]

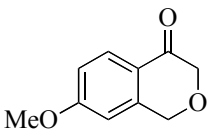
2-(3-methoxybenzyoxy)-N, N-dimethylacetamide 174



To a suspension of sodium hydride (1.32 g, 55.1 mmol) in anhydrous DMF (20 mL), 3-methoxybenzyl alcohol (2.73 mL, 22.02 mmol) was added dropwise at 0 ºC. After stirring at room temperature for 30 mins, the reaction mixture was cooled to 0 ºC and a solution of 2-chloro-*N,N*-dimethylacetamide **173** (2.22 g, 18.4 mmol) in anhydrous DMF (10 mL) was added dropwise. After stirring for 3 h, the reaction was quenched with the dropwise addition of water (5 mL) and partitioned between dichloromethane (20 mL) and water (15 mL). The aqueous layer was extracted with dichloromethane (2 x 15 mL) and the combined organic layers were washed with 2M hydrochloric acid solution (10 mL) and saturated lithium chloride solution (2 x 20 mL). The dichloromethane layers were dried with Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by column chromatography (80% diethyl

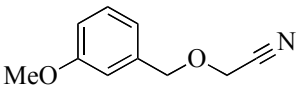
ether: petroleum ether) to afford the title compound (1.97 g, 48%) as a yellow oil; ***IR*** ν_{max}/cm^{-1} (film) 3055.4, 2932.0, 1713.2, 1646.8 1602.4, 1585.8; ***^{1}H NMR*** ($CDCl_3$, 400 MHz, ppm) δ_H 7.27 (1H, t, *J* = 7.88 Hz, Ar*H*), 6.96 – 6.93 (2H, m, Ar*H*), 6.85 (1H, d, *J* = 7.88 Hz, Ar*H*), 4.61 (2H, s, OCH_2C=O), 4.19 (2H, s, ArCH_2O), 3.82 (3H, s, OCH_3), 2.99 (3H, s, NCH_3), 2.97 (3H, s, NCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 169.4 (s), 159.8 (s), 138.1 (s), 129.6 (d), 120.3 (d), 113.1 (d), 113.3 (d), 73.3 (t), 69.1 (t), 55.4 (q), 36.5 (q), 35.7 (q); ***LCMS*** (CI) *m/z* 170 (18%), 169 (9), 163 (3), 157 (15), 147 (10), 146 (51), 144 (80), 131 (14), 121 (3), 116 (18), 104 (20), 86 (71), 84 (68), 77 (25), 51 (50).

7-Methoxyisochroman-4-one 145[97]



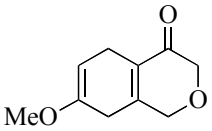
To a stirring solution of amide **179** (0.30 g, 1.35 mmol) in dichloroethane (2 mL), triflic anhydride (0.27 mL, 1.61 mmol) was added in a single portion and heated to 40 °C. After 3 h, the reaction mixture was poured into a 50:50 mixture of diethyl ether and 1M $K_2CO_{3\ (aq)}$ (6 mL) and stirred for 1 h. The phases were separated and the aqueous layer extracted with diethyl ether (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo* to afford the crude product. Purification *via* column chromatography (25 % diethyl ether: petroleum ether) afforded the title compound (0.039 g, 17 %) as a white solid m.p. 80-81 °C (lit.[98] value 78-80 °C); ***IR*** ν_{max}/cm^{-1} (film) 2969.3, 2845.5, 2809.5, 1672.9 1595.5, 1572.8; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 8.02 (1H, d, *J* = 8.58 Hz, Ar*H*), 6.91 (1H, dd, *J* = 8.58 & 2.50 Hz, Ar*H*), 6.66 (1H, d, *J* = 2.50 Hz, Ar*H*), 4.85 (2H, s, CH_2), 4.33 (2H, s, CH_2), 3.88 (3H, s, OCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 193.0 (s), 169.2 (s), 164.3 (s), 129.2 (d), 123.2 (d), 114.3 (d), 108.9 (d), 73.5 (t), 68.2 (t), 55.3 (q); ***LRMS*** (EI) 149 (8%), 148 (100), 120 (28), 105 (10); ***HRMS*** (EI) $C_{10}H_{10}O_3$ [M^+] requires 178.06245, found 178.06208. Data consistent with literature values.[97]

2-((3-methoxybenzyl)oxy)acetonitrile 179



3-Methoxylbenzyl alcohol **142** (0.9 mL, 7.25 mmol) was added dropwise to a suspension of sodium hydride (0.35 g, 14.5 mmol) in anhydrous THF (20 mL) at 0 °C and stirred at room temperature for 1 h. After cooling to 0 °C, bromoacetonitrile (0.59 mL, 8.69 mmol) was added to the solution dropwise and stirred at room temperature for 72 h. After the dropwise addition of water (15 mL), the reaction mixture was washed with 2M $HCl_{(aq)}$ (15 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with saturated LiCl solution (2 x 20 mL), followed by brine (15 mL) and dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford a brown oil. Purification was achieved by column chromatography (80% dichloromethane: petroleum ether) to afford the title compound (0.22 g, 17 %) as a colourless oil; ***^{1}H NMR*** δ_H ($CDCl_3$, 600 MHz, ppm) 7.28 (1H, t, *J* = 7.58 Hz, Ar*H*), 6.95 – 6.93 (2H, m, Ar*H*), 6.84 (1H, dd, *J* = 7.58 & 2.39 Hz, Ar*H*), 4.68 (2H, s, CH_2), 4.25 (2H, s, CH_2), 3.82 (3H, s, OCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 160.0, 137.0, 129.9, 120.7, 114.4, 113.9, 73.1, 55.4, 54.9; ***LRMS*** (EI) *m/z* 167 (8%), 138 (30), 135 (10), 122 (45), 121 (32), 120 (6), 109 (20), 107 (15), 85 (65), 83 (100); ***HRMS*** (EI) $C_{10}H_{11}NO_2$ [M^+] requires 177.07843, found 177.07814.

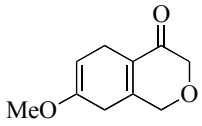
7-Methoxy-3,4,5,8-tetrahydro-1H-isochromen-4-ol 183[97]



To a suspension of **145** (5.00 g, 28.1 mmol) in liquid ammonia (150 mL), anhydrous diethyl ether (24 mL) and ethanol (42.5 mL), sodium metal (4.80 g, 210.7 mmol) was added in portions at a rate to maintain the deep blue colour noted after a third of the sodium had been added. After allowing the ammonia to evaporate, the residue was partitioned between water (100 mL) and diethyl ether (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The

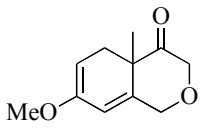
combined organic layers were washed with brine and dried ($MgSO_4$), filtered and concentrated in *vacuo*. The resulting crude solid was purified by column chromatography (25 – 75 % diethyl ether: petroleum ether) to afford the title compound (2.05 g, 40 %) as a colourless solid; m.p 101-103 °C; ***IR*** ν_{max}/cm^{-1} (film) 3423.6, 2952.9, 2938.8, 2832.5, 1668.8; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 4.71 (1H, t, *J* = 3.3 Hz, C=C*H*), 3.96 (2H, d, *J* = 2.2 Hz, CH_2) 3.70 (2H, dt, *J* = 10.8 & 2.2 Hz, CH_2), 3.57 (3H, s, OCH_3) 3.18 (1H, dtt, *J* = 21.2, 7.4 & 3.3 Hz, C*H*H), 2.69 (1H, d, *J* = 21.2 Hz, C=CHCH*H*), 2.55 (2H, t, *J* = 7.44 Hz, CH_2), 2.35 (1H, s, O*H*) 1.82 (1H, d, *J* = 10.8 Hz, C*H*); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 151.6 (s), 128.2 (s), 126.7 (s), 90.7 (d), 71.6 (t), 68.1 (t), 65.9 (d), 54.1 (q), 29.0 (t), 28.5 (t); ***LRMS*** (EI) 180 (5%) 164 (18) 150 (15) 149 (23) 137 (45) 134 (100) 128 (20) 123 (23) 122 (25) 121 (50) 109 (40) 107 (20) 91 (50); ***HRMS*** (EI) $C_{10}H_{14}O_3$ [M^+] requires 182.09375 found 182.09410.

7-Methoxy-5,8-dihydro-1H-isochromen-4(3H)-one 146[97]



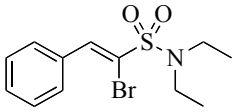
To a solution of alcohol **183** (1.38 g, 7.58 mmol) in dry toluene (14 mL) and acetone (7 mL), aluminium isopropoxide (0.77 g, 3.79 mmol) was added and stirred at reflux for 6 h. After cooling to room temperature, the reaction mixture was poured into brine (15 mL) and filtered through celite. The filter cake was washed with ether (2 x 20 mL) and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were concentrated in *vacuo* and the crude solid was recrystalised from hot methanol to afford the title compound (0.79 g, 58 %) as a white crystalline solid; m.p 114-117 °C; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 4.74 (1H, t, *J* = 3.5 Hz, C*H*=C), 2.27 (2H, s, C(O)CH_2) 4.18 (2H, s, OCH_2) 3.57 (3H, s, OCH_3) 3.03-2.98 (2H, m, C=CHCH_2) 2.84 (2H, t, *J* = 7.3 Hz, MeOCCH_2); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 193.5 (s), 150.9 (s), 149.9 (s), 128.4 (s), 90.69 (d), 73.5 (t), 67.8 (t), 54.3 (q), 30.1 (t), 22.8 (t); ***LRMS*** (CI) *m/z* 181 (20%), 180 (7), 166 (12), 165 (100), 163 (28), 147 (10), 135 (13), 121 (18), 105 (4); ***HRMS*** (CI) $C_{10}H_{13}O_3$ [M^+] requires 181.09647 found 181.08689.

7-Methoxy-4a-methyl,5-dihydro-1H-isochromen-4(3H)-one 144



Potassium hexamethyldisilazane (0.5M in toluene, 1.54 mL, 0.77 mmol) was added dropwise to a solution of enone **146** (0.14 g, 0.77 mmol) in THF (2 mL), cooled to -78 °C and left to stir for 10 min. Methyl iodide (0.096 mL, 1.55 mmol) was added to the reaction mixture. After stirring for 30 min, the reaction mixture was warmed to room temperature and partitioned between water (10 mL) and diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* to afford the crude product. Purification was achieved *via* column chromatography (5% diethyl ether: petroleum ether) to yield the title compound (0.02 g, 13%) as a colourless oil; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 5.63 (1H, d, *J* = 1.9 Hz, C=C*H*), 4.60 (1H, dt, *J* = 6.9 & 2.0 Hz, CH_2C=C*H*), 4.62 (1H, d, *J* = 14.7 Hz, OCH_2), 4.29 (1H, d, *J* = 14.7 Hz, CH_2), 4.25 (1H, d, *J* =17.1 Hz, CH_2), 4.05 (1H, d, *J* = 17.1 Hz, OCH_2), 3.54 (3H, s, OCH_3), 2.54 (1H, d, *J* = 17.0 Hz, CH_2), 2.36 (1H, dd, *J* = 17.0 & 6.9 Hz, CH_2), 1.37 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 125 MHz, ppm) δ_C 211.4 (s), 151.9 (s), 139.5 (s), 118.4 (d), 89. 7 (d), 73. 4 (t), 68.9 (t), 54.7 (q), 46.5 (s), 29.9 (t), 22.4 (q).

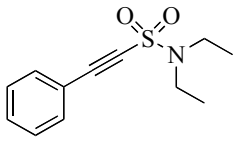
1-Bromo-*N,N*-diethyl-2-phenylethenesulfonamide 391



To a stirring solution of trans-*β*-styrenesulfonyl chloride (3.00 g, 14.8 mmol) in dichloromethane (30 mL), a solution of amine (3.09 mL, 29.6 mmol) in dichloromethane (40 mL) was added dropwise over 15 mins at −78 °C. Upon completion of the addition, the reaction mixture was warmed to room temperature and diluted with dichloromethane (50 mL), followed by washing with 2 M HCl aqueous solution (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and the volume of organic solvent reduced to half the original volume. Bromine (1.89 mL,

37.0 mmol) was added to the stirring crude ethylsulfonamide dichloromethane solution and stirred at room temperature for 1 h, until complete consumption of the starting material was observed by TLC. After cooling to 0 °C, an aqueous solution of 1M sodium thiosulfate (20 mL) added dropwise to the reaction mixture and stirred until the red-brown colour turned yellow. The aqueous phase was separated and extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$), filtered and the volume reduced by half *in vacuo*. The resulting solution was cooled to 0 °C and triethylamine (1.89 mL, 13.6 mmol) was added dropwise. After stirring until complete consumption of the dibromo-intermediate by TLC (1 h), the reaction mixture was diluted with dichloromethane (50 mL) and washed with 2M hydrochloric aqueous solution (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Purification was achieved *via* column chromatography (0-20% diethyl ether:petroleum ether) to afford the title compound (2.19 g, 57%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 3059, 2935, 2870, 1695, 1496, 1435, 1389, 1258; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 8.04 (1H, s, C*H*=C), 7.77-7.75 (2H, m, Ar*H*), 7.45-7.43 (3H, m, Ar*H*), 3.42 (4H, q, *J* = 7.2 Hz, NCH_2CH_3), 1.24 (6H, t, *J* = 7.2 Hz, NCH_2CH_3); ***^{13}C NMR*** ($CDCl_3$, 125 MHz, ppm) δ_C 137.7 (d), 132.5 (d), 130.5 (d), 129.9 (d), 128.7 (s), 119.9 (s), 43.1 (t), 14.5 (q); ***LRMS*** (CI) 240 (100%), 224 (15), 167 (10), 103 (5), 71 (5); ***HRMS*** (CI) calc'd for $C_{12}H_{18}NO_2S$ $[M+H]^+$ requires 240.10582, found 240.10518.

N,N-diethyl-2-phenylethynesulfonamide 197



Vinylbromosulfonamide **391** (2.18 g, 6.85 mmol) in dimethylformamide (5 mL) was added dropwise to a stirring solution of sodium hydride (0.33 g, 13.7 mmol) in dimethylformamide (20 mL) at 0 °C. After complete consumption of the starting material was observed *via* TLC, the reaction mixture was quenched with the dropwise addition of water (5 mL) at 0 °C. After dilution with water (30 mL), the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were washed with saturated lithium chloride aqueous solution (2 x 20 mL) and brine (20

mL). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography (10% diethyl ether: petroleum ether) to give the title compound as colourless oil (0.88 g, 55%); ***IR*** ν_{max}/cm^{-1} 2978, 2181, 1737, 1357, 1152, 1016; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.54 (2H, d, *J* = 7.58 Hz, *o*Ar*H*), 7.47 (1H, t, *J* = 7.6 Hz, *p*Ar*H*), 7.39 (2H, t, *J* = 7.6 Hz, *m*Ar*H*), 3.39 (4H, q, *J* = 7.2 Hz, NCH_2CH_3), 1.29 (6H, t, *J* = 7.2 Hz, NCH_2CH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 132.8 (d), 131.1 (d), 128.8 (d), 118.7 (s), 88.3 (s), 83.9 (s), 43.0 (t), 13.5 (q); ***LRMS*** (CI) *m/z* 238 (29%), 222 (100), 173 (60), 165 (50), 158 (10), 130 (4), 115 (18), 102 (14), 89 (19), 84 (9), 71 (5); ***HRMS*** (CI) calc'd for $C_{12}H_{15}NO_2S$ $[M+H]^+$ requires 238.08963, found 238.08902. Data consistent with literature values.[137]

General procedures for the synthesis of α-aminosulfonamides

Procedure A

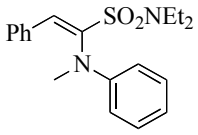
To a flame-dried three-necked flask containing an atmosphere of argon, potassium hydride (0.4 mmol) was added to anhydrous THF (1 mL) in one portion and the stirring suspension was cooled to 0 ºC. Amine (0.4 mmol) was added to the reaction suspension dropwise and stirred at room temperature for 30 mins. After cooling to room temperature, dimethylamine (2.0 M in THF, 0.2 mmol) was added and allowed to stir for 10 mins. Alkynylsulfonamide (0.1 mmol) was added to the reaction mixture in one portion and stirred at 0 ºC for 15 mins. The reaction mixture was quenched with the dropwise addition of *iso*-propanol (0.5 mL), followed by partitioning between water (2 mL) and dichloromethane (2 mL). The aqueous layer was extracted with dichloromethane (2 x 3 mL). The combined organic layers were washed with brine (4 mL) and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography.

Procedure B

To a flame-dried three-necked flask equipped with an argon balloon and a reflux condenser, freshly cut potassium metal (0.4 mmol) was added to the amine (0.4 mmol) and heated until all the potassium had been dispersed. After cooling the salt to 0 ºC, dimethylamine (2.0 M in THF, 0.2 mmol) was added and stirred for 10 mins. Alkynylsulfonamide (0.1 mmol) was added in one portion and stirred at 0ºC for 15

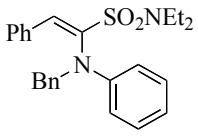
mins. The reaction mixture was quenched with the dropwise addition of *iso*-propanol (0.5 mL), followed by partitioning between water (2 mL) and dichloromethane (2 mL). The aqueous layer was extracted with dichloromethane (2 x 3 mL). The combined organic layers were washed with brine (4 mL) and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography.

(*E*)-*N*,*N*-diethyl-1-(methyl(phenyl)amino)-2-phenylethenesulfonamide 368



Procedure A. *N*-methylaniline. Colourless oil (31 mg, 52%); ***IR*** ν_{max}/cm^{-1} (film) 3054.4, 1448.6, 1318.0,1199.4, 931.2, 749.1 ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.66 (1H, s, C=C*H*), 7.47 (2H, d, *J*= 7.0 Hz, *o*Ar*H*), 7.33-7.27 (3H, m, Ar*H*), 7.22 (2H, t, *J* = 7.5 Hz, NAr*H*), 6.81 (1H, t, *J* = 7.5 Hz, NAr*H*), 6.77 (2H, d, *J* = 7.5 Hz, NAr*H*), 3.25 (3H, s, NCH_3), 2.98-2.91 (4H, m, $N(CH_2CH_3)_2$), 1.91 (6H, t, *J* = 7.2 Hz, $N(CH_2CH_3)_2$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 145.3 (s), 140.6 (s), 136.0 (d), 131.9 (s), 130.5 (d), 130.0 (d), 129.4 (d), 129.1 (d), 119.2 (d), 113.7 (d), 43.5 (t), 38.9 (q), 16.1 (q); ***LRMS*** (CI) 344 (12%) 236 (6), 229 (11), 208 (100), 185 (9), 84 (26); ***HRMS*** (CI) $C_{19}H_{24}N_2O_2S$ [M^+] requires 344.15585, found 344.15549.

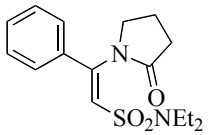
(*E*)-1-(benzyl(phenyl)amino)-*N*,*N*-diethyl-2-phenylethenesulfonamide 374



Procedure A. *N*-benzylaniline. Colourless oil (31 mg, 52%); ***IR*** ν_{max}/cm^{-1} (film) 3359.3, 1596.1, 1494.5 1264.7, 906.5 726.5; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.66 (1H, s, C=C*H*), 7.44 (2H, d, *J* = 7.64 Hz, Ar*H*), 7.32 – 7.29 (2H, m, Ar*H*), 7.25-7.21 (6H, m, Ar*H*), 7.11-7.08 (3H, m, Ar*H*), 6.92 (2H, d, *J* = 7.7 Hz, NAr*H*), 6.84 (1H, t, *J* = 7.3 Hz, *p*-NAr*H*) 4.83 (2H, s, CH_2), 2.88 – 2.82 (4H, m, $N(CH_2CH_3)_2$), 1.07 (6H, t, *J* = 7.1 Hz,

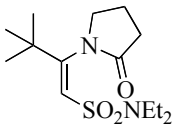
N(CH_2CH_3)$_2$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 145.5 (s), 140.4 (s), 137.6 (d), 136.7 (s), 131.8 (s), 130.5 (d), 130.3 (d), 129.4 (d), 129.1 (d), 128.6 (d), 127.9 (d), 127.2 (d), 119.9 (d), 115.5 (d), 56.4 (t), 42.7 (t), 16.0 (q); ***LRMS*** (CI) 421 (9%), 302 (35), 284 (100), 181 (9), 91 (11); ***HRMS*** (CI) $C_{26}H_{29}N_2O_2S$ [M^+] requires 420.19972, found 420.19811.

(*Z*)-*N*,*N*-diethyl-2-(2-oxopyrrolidin-1-yl)-2-phenylethenesulfonamide 376



Procedure B. 2-Pyrrolidone. Colourless oil (58 mg, 71%); ***IR*** ν_{max}/cm^{-1} (film) 2936.2, 1639.5, 1599.0, 1410.3, 1324.0, 1261.3, 1203.6; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.46-7.39 (5H, m, Ar*H*), 6.54 (1H, s, C=C*H*), 3.62 (2H, t, *J* = 7.3 Hz, C(O)CH_2), 3.36 (4H, q, *J* = 7.2 Hz, N(CH_2CH$_3$)$_2$), 2.59 (2H, t, *J* = 7.4 Hz, NCH_2CH$_2$), 2.21 (2H, quin, *J* = 7.4 Hz, NCH$_2$CH_2CH$_2$), 1.22 (6H, t, *J* = 7.2 Hz, N(CH$_2$CH_3)$_2$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 175.94 (s), 144.56 (s), 134.2 (s), 130.9 (d), 129.2 (d), 126.9 (d), 123.5 (d), 50.1 (t), 42.0 (t), 31.4 (t), 19.5 (t), 14.7 (q); ***LRMS*** (CI) 264 (15%), 250 (100), 219 (35), 214 (27), 197 (14), 186 (58), 169 (22), 149 (15), 137 (33), 131 (40), 119 (15), 109 (13), 97 (21), 83 (22), 57 (33); ***HRMS*** (CI) $C_{16}H_{23}N_2O_3S$ [M^+] requires 323.14239, found 323.14197.

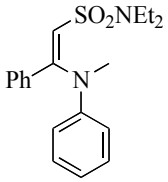
(Z)-N,N-diethyl-3,3-dimethyl-2-(2-oxopyrrolidin-1-yl)but-1-ene-1-sulfonamide 377



Procedure A. 2-pyrrolidone. Colourless oil. (19 mg, 23%); ***^{1}H NMR*** ($CHCl_3$, 600 MHz, ppm) δ_H 6.11 (1H, s, C*H*=C), 3.72 (1H, q, *J* = 8.2 Hz, C(O)CH_2), 3.61-3.56 (1H, m, C(O)CH_2), 3.32 (2H, quin, *J* = 7.1 Hz, N(CH_2CH$_3$)$_2$), 3.25 (2H, quin, *J* = 7.1 Hz, N(CH_2CH$_3$)$_2$), 2.52 – 2.34 (2H, m, NCH_2CH$_2$), 2.23 – 2.02 (2H, m, NCH$_2$CH_2) 1.18 (6H, t, *J* = 7.1 Hz, N(CH$_2$CH_3)$_2$), 1.17 (9H, s, 3 x CH_3); ***^{13}C NMR*** ($CHCl_3$, 150 MHz,

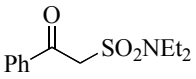
ppm) δ_C 176.4 (s), 157.3 (s), 135.8 (s), 123.2 (d), 52.5 (t), 41.6 (t), 39.8 (s), 31.2 (t), 28.9 (q), 19.6 (t), 14.7 (q); ***LCMS*** (CI) 303 (8%), 301 (4), 230 (99), 166 (58); ***HRMS*** (CI) $C_{14}H_{27}N_2O_3S$ [M^+] requires 303.17369, found 303.17349.

(Z)-*N, N*-diethyl-2-(methyl(phenyl)amino)-2-phenylethenesulfonamide 369



To a stirring solution of *N*-methylaniline (0.03 mL, 0.27 mmol) in anhydrous tetrahydrofuran (5 mL) cooled to −78 °C, ^{n}Butyl Lithium (2.5M in hexanes, 0.12 mL, 0.30 mmol) was added dropwise and stirred for 10 mins. A solution of alkynylsulfonamide **197** (0.07 g, 0.30 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise and the resulting reaction mixture was stirred at −78 °C for 2 h and at room temperature for a further 30 min. The solution was partitioned between water (10 mL) and dichloromethane (10 mL) and the aqueous layer extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified *via* column chromatography (10-30% diethyl ether:petroleum ether) to afford the title compound (0.017 g, 20%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 3043.7, 1442.9, 1324.4,1183.5, 939.4, 751.2 ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.34-7.32 (2H, m, Ar*H*), 7.34-7.27 (3H, m, Ar*H*), 7.21 (2H, t, *J* = 7.7 Hz, Ar*H*), 7.07 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.02 (2H, d, *J* = 8.3 Hz, Ar*H*), 5.28 (1H, s, C*H*=C), 3.14 (3H, s, CH_3), 2.92 (4H, q, *J* = 7.4 Hz, N(CH_2CH$_3$)$_2$), 1.03 (6H, t, *J* = 7.4 Hz, N(CH$_2$CH_3)$_2$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 158.7 (s), 155.0 (s), 133.8 (s), 130.3 (d), 129.4 (d), 129.2 (d), 127.7 (d), 126.2 (d), 100.6 (d), 41.8 (q), 41.4 (t), 14.3 (q); ***LRMS*** (CI) 344 (15%), 236 (11), 228 (5), 210 (50), 184 (11), 84 (22); ***HRMS*** (CI) $C_{19}H_{24}N_2O_2S$ [M^+] requires 344.15585, found 344.15572.

_N,N_-diethyl-2-oxo-phenylethanesulfonamide 370

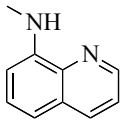


To a stirring solution of *N*-methylaniline (0.03 mL, 0.27 mmol) in anhydrous tetrahydrofuran (5 mL) cooled to −78 °C, ^{n}Butyl Lithium (2.5M in hexanes, 0.12 mL, 0.30 mmol) was added dropwise and stirred for 10 mins. A solution of alkynylsulfonamide **197** (0.07 g, 0.30 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise and the resulting reaction mixture was stirred at −78 °C for 2 h and at room temperature for a further 30 min. The solution was partitioned between water (10 mL) and dichloromethane (10 mL) and the aqueous layer extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified *via* column chromatography (10-30% diethyl ether:petroleum ether) to afford the title compound (0.009 g, 11%) as a colourless oil; ***IR*** ν_{max}/cm^{-1} (film) 2977, 2939, 1675, 1589, 1442, 1335, 1270, 1151, 1021; ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 8.05 (2H, d, *J* = 7.3 Hz, Ar*H*), 7.63 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.51 (2H, t, *J* = 7.1 Hz, Ar*H*), 4.57 (2H, s, CH_2), 3.29 (4H, q, *J* = 7.2 Hz, N(CH_2CH$_3$)$_2$), 1.20 (6H, t, *J* = 7.2 Hz, N(CH$_2$CH_3)$_2$); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 188.2 (s), 136.4 (s), 134.1 (d), 128.9 (d), 58.1 (t), 43.3 (t), 14.1 (q). Data consistent with literature values.[209]

General Method for methylation of anilines

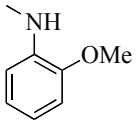
To a stirring suspension of acetonitrile (1 mL) and potassium carbonate (1.2 mmol) at 0 °C, aniline (1 mmol) was added dropwise, followed by the dropwise addition of methyl iodide (3 mmol). The resulting suspension was allowed to stir at room temperature for between 10-30 mins, before the dropwise addition of 2M $HCl_{(aq)}$. The resulting mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with water (2 x 20 mL). After removal of the solvent, column chromatography was used to afford the title compound.

_N_-Methylquinolin-8-amine 381



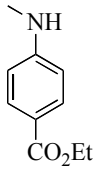
8-Aminoquinone. Colourless oil (0.16 g, 15%); ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 8.71 (1H, dd, *J* = 4.2 & 1.6 Hz, Ar*H*), 8.07 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.42 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.38 (1H, dd, *J* = 8.3 & 4.2 Hz, Ar*H*), 7.05 (1H, d, *J* = 7.8 Hz, Ar*H*), 3.05 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 146.7 (d), 145.8 (s), 136.4 (d), 128.7 (s), 128.1 (d), 121.5 (d), 113.8 (d), 104.4 (d), 30.2 (q). Data consistent with literature values.[210]

2-Methyoxy-*N*-methylaniline 382



o-Anisidine. Colourless oil (0.15 g, 17%); ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.11 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.29 (1H, dd, *J* = 8.3 & 2.2 Hz, Ar*H*), 6.25 (1H, dd, *J* = 8.3 & 2.2 Hz, Ar*H*), 6.18 (1H, t, *J* = 2.2 Hz, Ar*H*), 3.78 (3H, s, OCH_3), 2.83 (3H, s, NCH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 160.9 (s), 150.7 (s), 130.0 (d), 105.9 (d), 102.6 (s), 98.5 (d), 55.3 (q), 33.9 (q). Data consistent with literature values.[211]

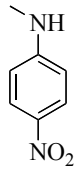
Ethyl 4-(methylamino)benzoate 383



Benzocaine. Yellow solid (0.13 g, 31%) mp. 65-66 °C (literature[222] value 66-67 °C); ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 7.88 (2H, d, *J* = 8.8 Hz, Ar*H*), 6.55 (2H, d, *J* = 8.8 Hz, Ar*H*), 4.31 (2H, q, J = 7.3 Hz, OCH_2CH_3), 2.90 (3H, s, NCH_3), 1.36 (3H, t, J = 7.3

Hz, OCH_2CH_3); **^{13}C NMR** ($CDCl_3$, 150 MHz, ppm) δ_C 167.0 (s), 131.7 (t), 131.3 (s), 118.7 (s), 111.2 (t), 77.3 (t), 60.3 (q), 14.2(q). Data consistent with literature values.[210]

4-Methylaminonitrobenzene 384



4-Nitroaniline. Yellow oil (0.12 g, 27%); ***^{1}H NMR*** ($CDCl_3$, 600 MHz, ppm) δ_H 8.11 (2H, d, *J* = 9.2 Hz, Ar*H*), 6.53 (2H, d, *J* = 9.2 Hz, Ar*H*), 2.94 (3H, s, CH_3); ***^{13}C NMR*** ($CDCl_3$, 150 MHz, ppm) δ_C 138.3 (s), 154.2 (s), 126.5 (d), 110.8 (d), 30.3 (q). Data consistent with literature values.[212]

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