Dearomatising Claisen Rearrangements

Toby Mullins

Department of Chemistry, Imperial College London

Supervisor: Professor Donald Craig

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Abstract

This thesis is divided into four chapters.

Chapter one is a review of dearomatising [3,3]-sigmatropic rearrangements and is split by sub-classification of Claisen rearrangements.

Chapter two introduces the decarboxylative Claisen rearrangement (dCr) and details investigations of the application of this reaction to compounds containing furan rings.

Chapter three focuses on the natural product hinckdentine A. It begins with a brief review of previous studies towards the natural product, before discussing attempts to synthesise this compound by a decarboxylative Claisen rearrangement. However, this route does not prove feasible and attention is then turned to the synthesis of hinckdentine A via alternative dearomatising Claisen rearrangements.

Chapter four provides experimental procedures and characterisation data.

Declaration of originality

I confirm that this thesis contains work which is solely my own, except where explicitly stated and referenced. No part of this thesis has been submitted previously for a degree at this, or any other, university.

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Lastly, I want to thank my family, and especially Vicky, for their love and support over the past few years.

List of abbreviations

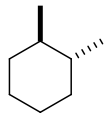
Å	Ångström(s)
a	antarafacial
$A_{AL}1$	unimolecular acid-catalysed alkyl bond breaking hydrolysis
Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2'-bipyridyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
BOX	bis(oxazoline)
$^{n\text{-}}$Bu	*normal*-butyl
$^{t\text{-}}$Bu	*tertiary*-butyl
°C	degree centigrade
cod	1,5-cyclooctadiene
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichoromethane
dCr	decarboxylative Claisen rearrangement
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIC	*N*,*N*'-diisopropylcarbodiimide
DMA.DMA	dimethylacetamide dimethylacetal
DMAP	4-dimethylaminopyridine
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
h	hours
HFIP	hexafluoro-2-propanol

HMPA	hexamethylphosphoramide
IPA	propan-2-ol (*iso*-propyl alcohol)
IR	infa red
LDA	lithium diisopropylamide
m	meta
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
mmol	millimole(s)
MS	mass spectrometry
µw	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
PHOX	phosphinooxazoline
PMB	*para*-methoxy benzyl
PPTS	pyridinium *para*-toluenesulfonate
$^{i-}$Pr	*iso*-propyl
$^{n-}$Pr	*normal*-propyl
R	generic alkyl group
rt	room temperature
s	suprafacial
SM	starting material
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
T_3P®	propylphosphonic anhydride
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS or TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifuloroacetic acid
TFAA	trifluoroacetic anhydride

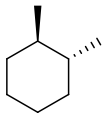
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)
TSA	*para*-toluenesulfonic acid

Stereochemical notation

The Maehr convention for indicating relative and absolute stereochemistry has been used throughout this report.[1] Therefore, solid and broken lines are used to denote racemates, and solid and broken wedges denote absolute configuration.



racemate



single enantiomer

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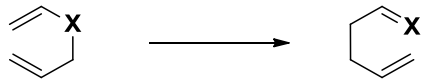
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1 – Dearomatising Claisen Rearrangements

1.1 [3,3]-sigmatropic rearrangements

The [3,3]-sigmatropic rearrangement is a pericyclic reaction that proceeds via a six membered transition state, involving concerted σ-bond formation and σ-bond breaking (Scheme 1).



Scheme 1: The [3,3]-sigmatropic rearrangement. X = CH_2 = Cope. X = O = Claisen

The process may be described as $[\sigma^2s+\pi^2s+\pi^2s]^2$ and may proceed *via* either a chair or boat like transition state giving a different stereochemical outcome depending on which pathway is followed (Figure 1). The boat transition state is often disfavoured due to non-bonding interactions (Figure 2).

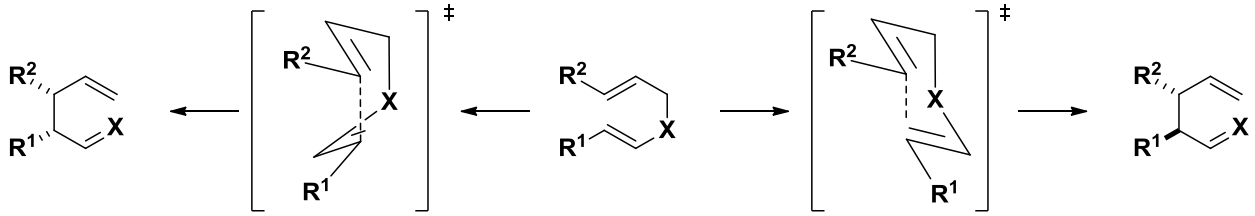


Figure 1: Sigmatropic rearrangement via boat and chair transistion states

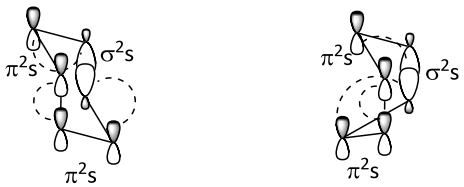
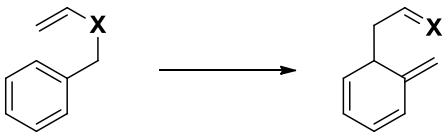


Figure 2: Woodward-Hoffman analysis of a [3,3]-sigmatropic rearrangement

When one of the terminal olefin functionalities of the starting material is incorporated into an aromatic ring, the rearrangement process leads to disruption of this aromatic system (Scheme 2).

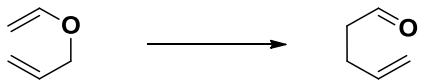


Scheme 2: A dearomatising [3,3]-sigmatropic rearrangement

In some cases the de-aromatised product may be isolated, but more commonly the compound re-aromatises by tautomerisation *in situ*. Reactions of both types will be discussed in Chapter One. Further precedent developed within the Craig group for dearomatising Claisen rearrangements leading to isolable, non-aromatic products will be presented at the start of Chapter Two.

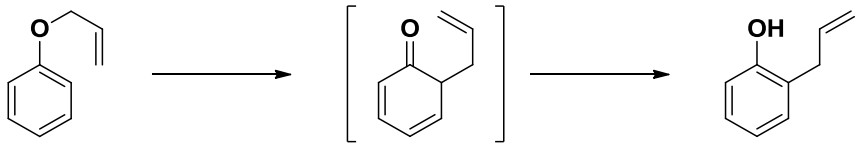
1.2 Dearomatising Claisen rearrangements

The Claisen rearrangement is the [3,3]-sigmatropic rearrangement of an allyl vinyl ether to give a γ,δ-unsaturated ketone (Scheme 3).



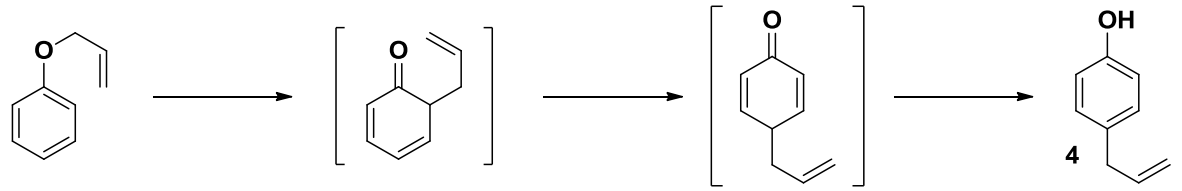
Scheme 3: The Claisen rearrangement

The first example of the Claisen rearrangement was that of allyl phenol ether **1**.[3] In this case, the aromatic system is disrupted during the sigmatropic rearrangement to give a de-aromatised intermediate **2**, which then tautomerises to give the *ortho*-substituted phenol **3** (Scheme 4). This type of rearrangement has since come to be known as the aromatic-Claisen or *ortho*-Claisen rearrangement. Due to the ubiquity of the aromatic Claisen rearrangement, only a few key examples will be given rather than an exhaustive review.

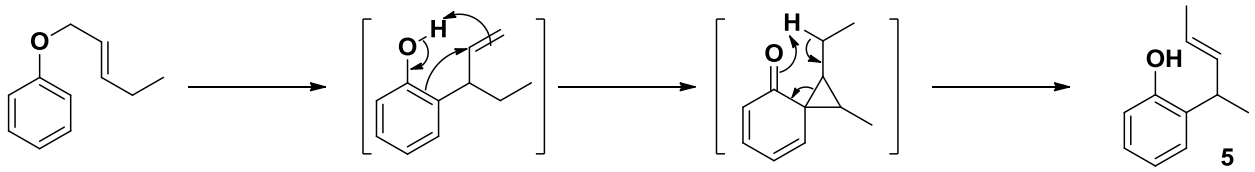


Scheme 4: The aromatic Claisen rearrangement

The high temperatures required for this reaction mean that the formation of by-products is often observed. The most common of these are the *para*-substituted phenol **4**, formed by the Cope rearrangement of the dearomatised intermediate (Scheme 5) and the abnormal-Claisen rearrangement product **5** formed by an ene-like rearrangement and sigmatropic hydrogen shift (Scheme 6).[4]

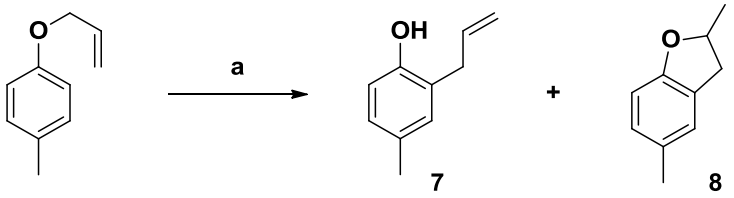


Scheme 5: The *para*-Claisen rearrangement



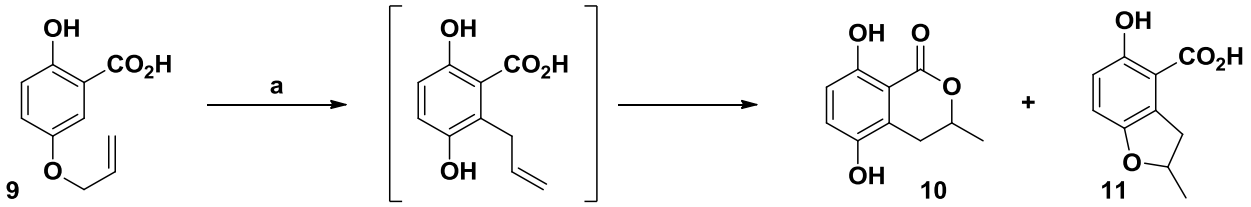
Scheme 6: The abnormal Claisen rearrangement

The necessity for high reaction temperatures has led to a number of studies into catalysis of the aromatic-Claisen rearrangement. The possibility of Brønsted acid catalysis was first noted in 1939, when Tarbell *et al.* observed that for the rearrangement of allyl phenyl ether (Scheme 4), the rate of reaction increased as the reaction progressed, presumably due to the acidic phenol product having a catalytic effect.[5] Schmid *et al.* have since shown that rearrangement can occur at room temperature in TFA as a solvent (Scheme 7).[6] The major product of this reaction was coumaran **8**, which was formed by acid-catalysed cyclisation of the Claisen rearrangement product **7**.



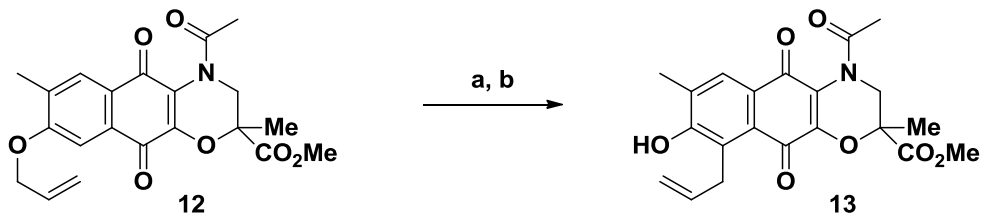
Scheme 7: Synthesis of coumaran **8** by cyclisation of Claisen rearrangement product **7** (a) CF_3CO_2H, rt, 23 h, 8 % **7**; 69 % **8**

Harwood has shown a similar reaction of benzoic acid **9**, which forms a mixture of the cyclised products **10** and **11** from addition of the carboxylic acid and phenolic groups respectively (Scheme 8).[7]



Scheme 8: Claisen rearrangement of ether **9** (a) CF_3CO_2H, rt, 21 h, 63 % **10;** 25 % **11**

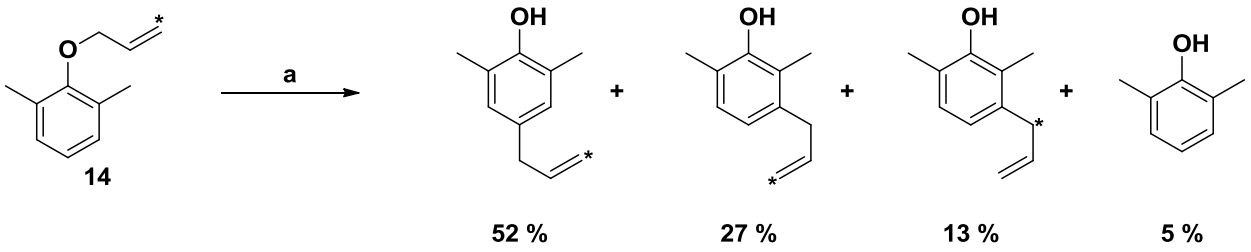
The use of Lewis-acids has likewise been investigated, with initial studies concentrating on the use of boron trihalides. During their studies towards the rubradirin antibiotics, Kozikowski *et al.* observed extensive decomposition during the attempted thermal Claisen rearrangement of **12**, with only trace amounts of the deallylated quinone recovered. However, the use of BCl_3 allowed the rearrangement to take place at ambient temperature in excellent yield (Scheme 9).[8]



Scheme 9: Lewis-Acid catalysed Claisen rearrangement of ether **12** (a) $Na_2S_2O_4$; (b) BCl_3, DCM, –23 °C to rt, 95 % over two steps

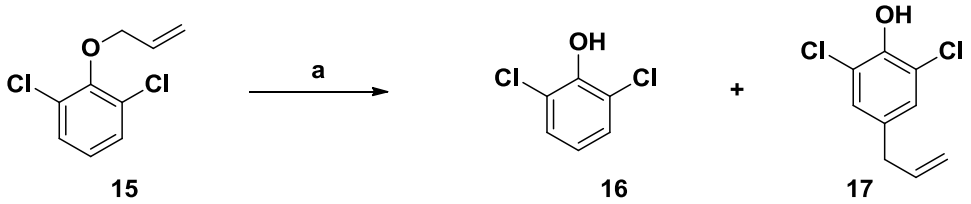
Reduction of the quinone functionality with sodium hydrosulfite, and then treatment with 6 equivalents of BCl_3 gave the C10 allylated product **13** in 95 % yield, with re-oxidation of the hydroquinone occurring on work up.

The use of BCl_3 however does introduce the possibility of alternative, non-concerted, mechanisms operating. During the rearrangement of the 2,6-dimethyl phenol ether **14** a number of side products were observed, with labelling studies indicating that either a dissociative or intermolecular mechanism may be competing (Scheme 10).[9]



Scheme 10: Formation of side products during the Claisen rearrangement of **14** indicating a dissociative mechanism (a) BCl_3, PhCl, 0 °C

Aluminium-based Lewis- acids have also been shown to be effective catalysts in this reaction. For example, in the reaction of allyl 2,6-dichlorophenyl ether (**15**) BCl_3 gave only the cleavage product **16**, whereas Et_2AlCl gave a mixture of the cleavage product and the desired *para*-allylated phenol **17** (Scheme 11).[10] In both cases the propensity for the cleavage reaction is promoted due to the electron-poor aromatic system.

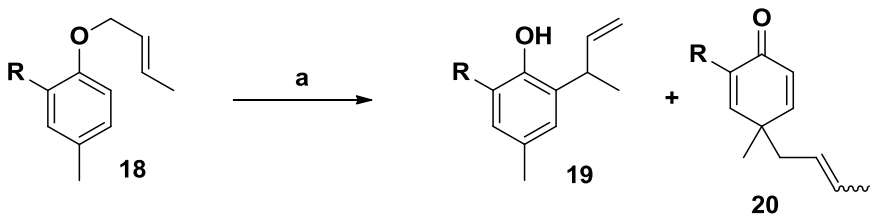


Scheme 11: Lewis-Acid catalysed Claisen rearrangement of ether **15** (a) See Table 1

Entry	Lewis Acid	Solvent	Temperature	Time (min)	Yield (%)	
					16	**17**
1	BCl_3	benzene	–40 °C	120	80 %	-
2	Et_2AlCl	hexane	rt	30	50 %	43 %

Table 1: Claisen rearrangement of allyl ether **15**

Yamamoto *et al*. noted an interesting result when using bulky aluminium catalysts **21** and **22**. Under thermal conditions crotyl 2,4-dimethylphenyl ether (**18**) was reported to rearrange to the *ortho*-allylated product **19** exclusively in high yield, although precise yields and reaction conditions are not given in the paper. However when catalysts **21** and **22** (Figure 3) were used, cyclohexadienenone **20** was formed as a competing product (Scheme 12 and Table 2)



Scheme 12: Lewis-Acid catalysed Claisen rearrangement of ether **18** (a) See Table 2

Entry	R	Lewis Acid	Yield (%)	
			19	**20**
1	Me (*E*/*Z* = 5:1)	**21**	40	40
2	Me (*E*/*Z* = 5:1)	**22**	21	76 (*E*/*Z* = 2:1)
3	^{t}Bu (*E*/*Z* = 4:1)	**22**	-	67 (*E*/*Z* = 5:2)

Table 2: Rearrangement of crotyl 2,4-dimethylphenyl ether. All reaction carried out in DCM for 4 h at –78 °C

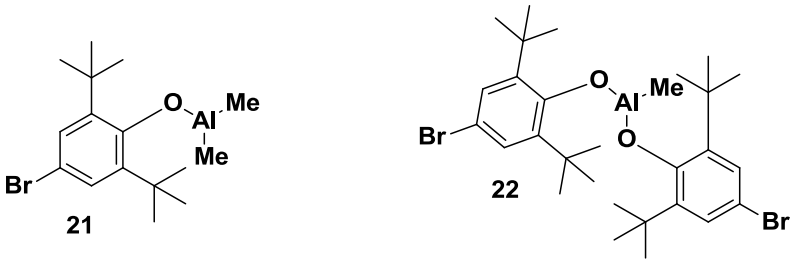
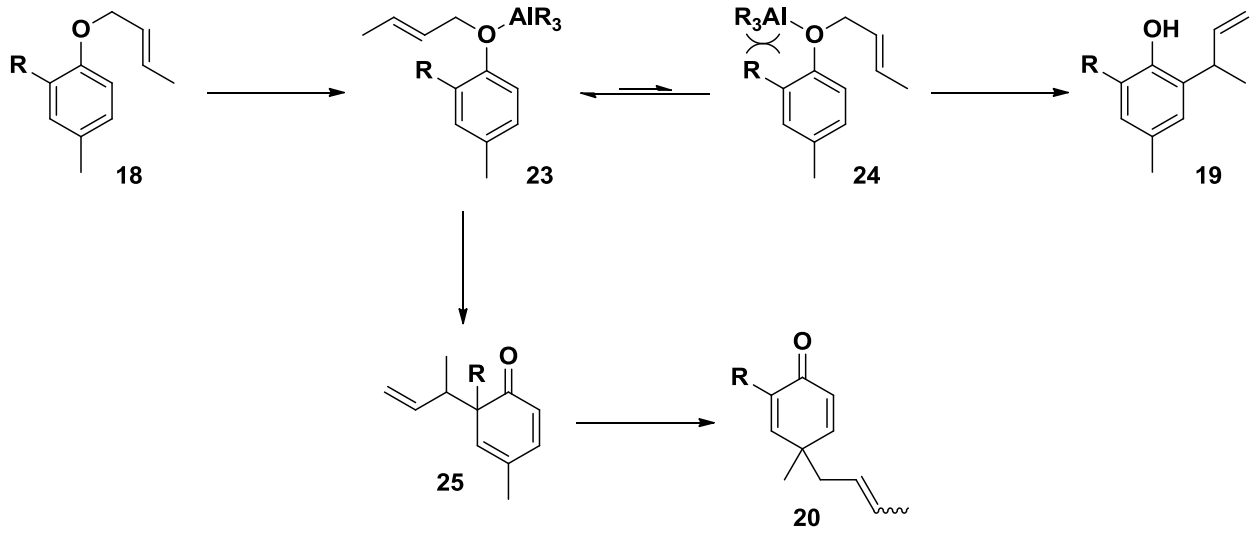


Figure 3: Catalysts **21** and **22**

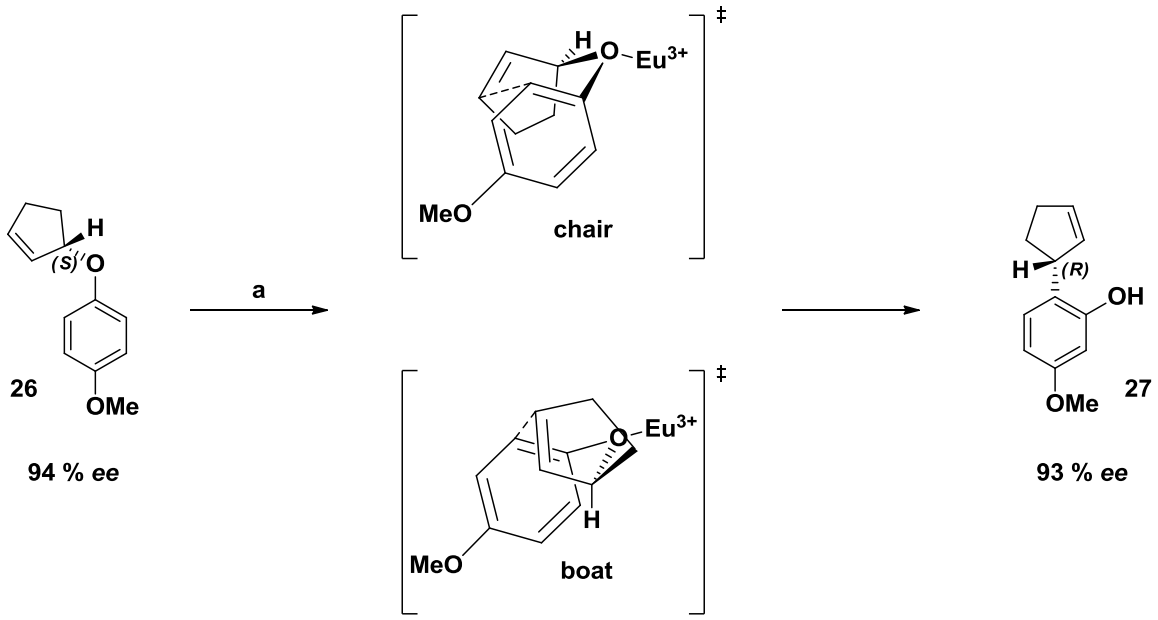
These observations imply that initial coordination of the aluminium reagent causes conformation **23** to be preferred over conformation **24** (Scheme 13). This means that the Claisen rearrangement gives the geminal 2,2-substituted intermediate **25** preferentially over the 2,5-disubstituted phenol **19**. **25** then undergoes a Cope rearrangement to give the more stable cyclohexadienone **20**. Increasing both the size of the aluminium reagent (Table 2, Entry 2) and the size of the *ortho*- substituent (Table 2, Entry 3) favour this pathway further.



Scheme 13: Mechanism for formation of **19** and **20**

As well as main group elements, lanthanide-based reagents have been used in the catalysis of the aromatic Claisen rearrangement, with Trost and Toste reporting the use of europium(III) reagents (Scheme 14).[11]

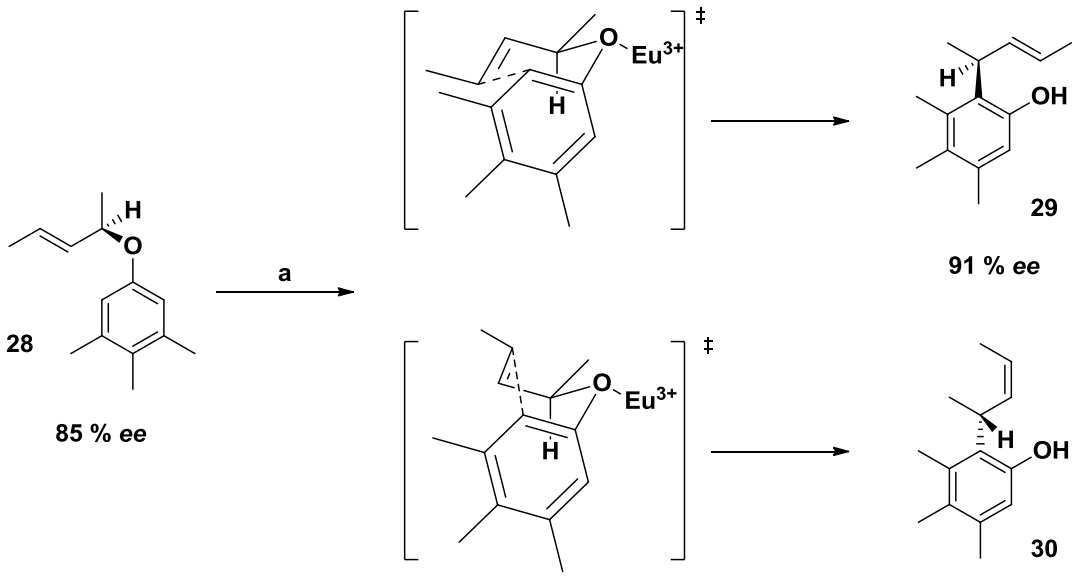
Due to the stereospecific nature of the Claisen rearrangement it is possible to control the stereochemistry of C-C bond formation by using enantiomerically enriched chiral ethers. Ether **26** was synthesised in 94 % *ee via* a Tsjui-Trost reaction with a chiral phosphine ligand, and attention was then turned to carrying out the Claisen rearrangement.



Scheme 14: Claisen rearrangement of enantiomerically enriched ether **26** (a) $Eu(fod)_3$, DCM, 50 °C, 8 h

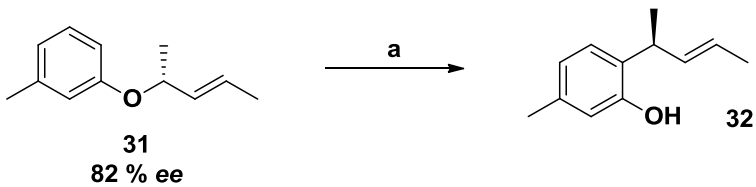
The use of BCl_3 and Et_2AlCl did give the rearranged product, but with significant racemisation. However, the use of $Eu(fod)_3$ in chloroform gave good chirality transfer, with the *ortho*-allylated phenol **27** being formed in 93 % ee.

With acyclic alkenes such as **28** it is possible to adopt transition states leading to a pair of diastereomeric products (Scheme 15) and the rearrangement produced a 6:1 mixture of *E* and *Z* alkenes. However, the fact that the *E* isomer **29** was formed in 91 % ee showed excellent chirality transfer again.



Scheme 15: Claisen rearrangement of enantiomerically enriched ether **28** (a) $Eu(fod)_3$, DCM, 50 °C, 8 h

In some cases however, the uncatalysed thermal Claisen rearrangement can give better results than the catalysed variant. As part of their synthesis of members of the helianane family of natural products, Papeo *et al.* showed the thermal rearrangement of ether **31** gave over twice the yield and a greater *ee* than the $Eu(fod)_3$-catalysed version (Scheme 16, Table 3).[12]

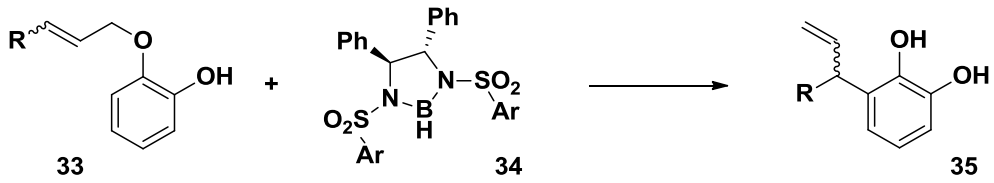


Scheme 16: Claisen rearrangement of enantiomerically enriched ether **31** (a) See Table 16

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	*ee* (%)
1	$Eu(fod)_3$	dichloroethane	80	48	14	76
2	-	*N*,*N*-diethylaniline	190	4	32	80

Table 3: Conditions for Papeo's Claisen rearrangement. [a]After seperation from undesired *Z* isomer

To date, only one example of an enantioselective aromatic Claisen rearrangement with achiral starting materials has been reported. Taguchi *et al.* used stoichiometric amounts of a chiral boron reagent for the rearrangement of catechol mono allylic ethers (Scheme 17).[13]



Scheme 17: Enantioselective aromatic Claisen rearrangement. See Table 4

A variety of catechol monoethers gave enantiomeric excesses of over 90 % (Table 4) with complete regioselectivity for the *ortho*- rearranged product. *Z* and *E* Isomers of the starting material gave opposiite configurations at the new stereocentre (Table 4, entries 1 and 4), although the *Z* isomer required a higher reaction temperature.

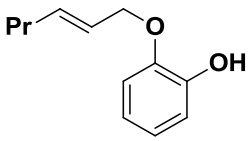
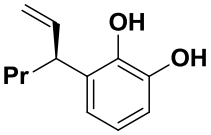
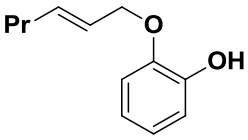
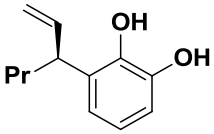
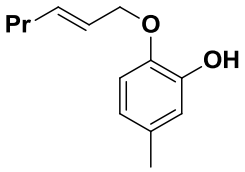
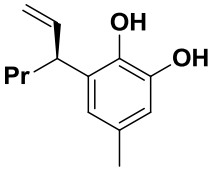
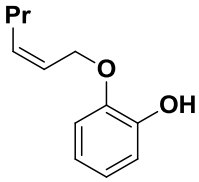
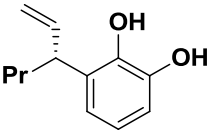
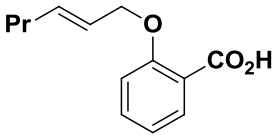
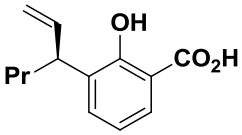
Entry	Starting Material	Ligand[a]	Temp (°C)	Time	Product	Yield (%)	*ee* (%)
1		**34a**	–45	4 d		89	94
2		**34b**	–45	24 h		88	88
3		**34a**	–45	3 d		97	93
4		**34a**	–23	2 d		92	95
5		**34a**	–45	24 h		51	57

Table 4: Enantioselective aromatic Claisen rearrangement. [a]Ar = 4-methyphenyl = a. Ar = 3,5-bis(trifluoromethyl)phenyl = b

Based on these observations, the authors proposed a transition state by which a σ-bond is formed between the phenolic oxygen and the boron, followed by coordination of the allylic oxygen to form a rigid five-membered cyclic intermediate. The *re*-site of the starting material's benzene ring is shielded by one of the sulfonamide aromatic systems, leading to the approach of the allylic group on the *si*-face (Figure 4)

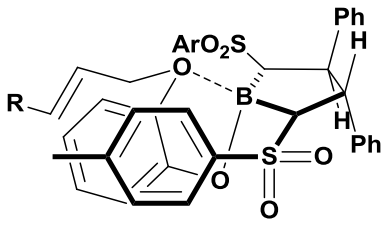
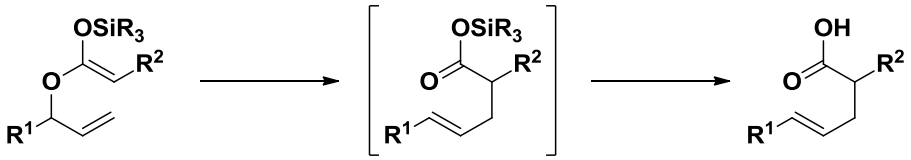


Figure 4: Taguchi's model for an enantioselective aromatic-Claisen rearrangement

This mechanism is supported by the observations that a substrate that would form a six-membered cyclic intermediate (Table 4, Entry 5) reacts with a reduced yield and ee, and the fact that 2-hexenyl phenyl ether, which does not possess a hydroxyl group at the *ortho*-position, does not rearrange under the reaction conditions. However, this model does not explain why the boat transition state, which would lead to the opposite enantiomer, is not observed; or the observation that increasing the size of the sulfonamide group (Table 4, entry 2) leads to a decrease in *ee*.

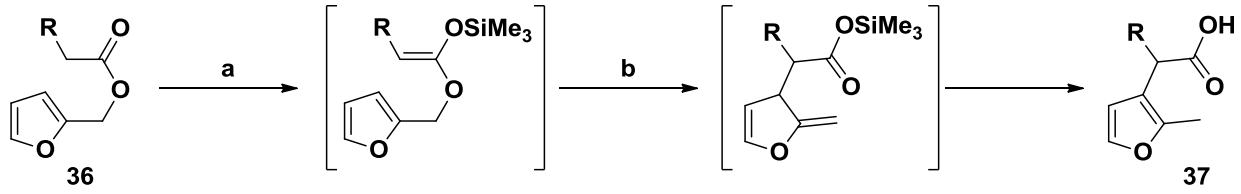
1.3 Dearomatising Ireland-Claisen Rearrangements

The Ireland-Claisen rearrangement is the reaction of a silyl ketene acetal to give a γ,δ-unsaturated carboxylic acid (Scheme 18).[14]



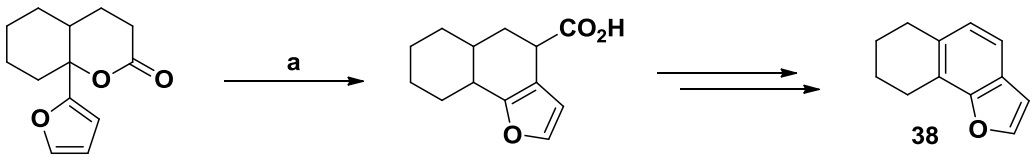
Scheme 18: The Ireland-Claisen rearrangement

To date, the only reported example of a dearomatising Ireland-Claisen rearrangement is that of Fukumoto *et al*. who utilised the methodology in the synthesis of 2,3-disubstituted furans **37** (Scheme 19).[15]



Scheme 19: Dearomatising Ireland-Claisen rearrangement of furan **36** (a) LDA, TMS-Cl, THF, –78 °C; (b) reflux, 5 h - 22 h; then $HCl_{(aq)}$. R = H = 32 %. R = Me = 20 %. R = SPh = 22 %

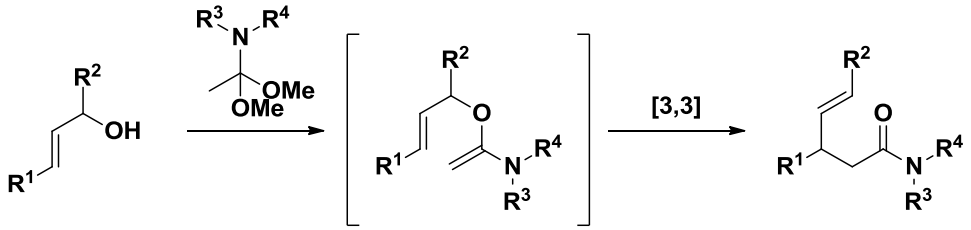
By using a silyl ketene acetal derived from a δ-lactone it is possible to produce annulated furans and gain access to the furanosesquiterpene framework **38** (Scheme 20).[16]



Scheme 20: Access to the furanosesquiterpene framework *via* a dearomatising Ireland-Claisen rearrangement (a) TBSCl, LDA, HMPA-THF, –78 °C; then toluene, reflux, 12 h, 55 %

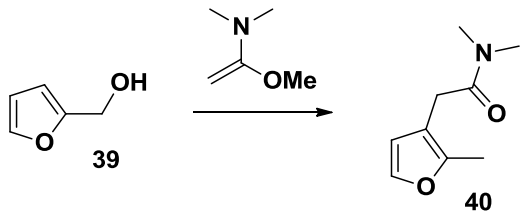
1.4 Dearomatising Eschenmoser-Claisen rearrangements

The Eschenmoser-Claisen rearrangement is the reaction of an allylic alcohol with the acetal of an acetamide to give a γ,δ-unsaturated amide (Scheme 21).[17]

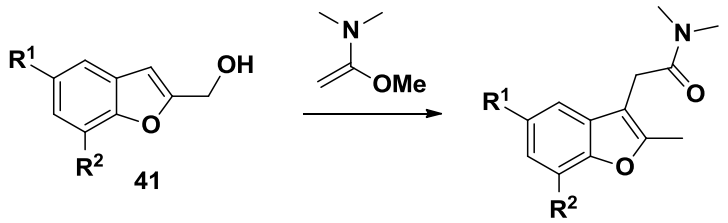


Scheme 21: The Eschenmoser-Claisen rearrangement

The dearomatising Eschenmoser-Claisen rearrangement of heterocycles has not been widely studied. In 1969 Eschenmoser *et al*. reported the rearrangement of furfuryl alcohol **39** to give amide **40** (Scheme 22),[18] and in 2007 Granik *et al*. reported the similar reaction of 2-(hydroxymethyl)-benzofurans **41** (Scheme 23).[19]

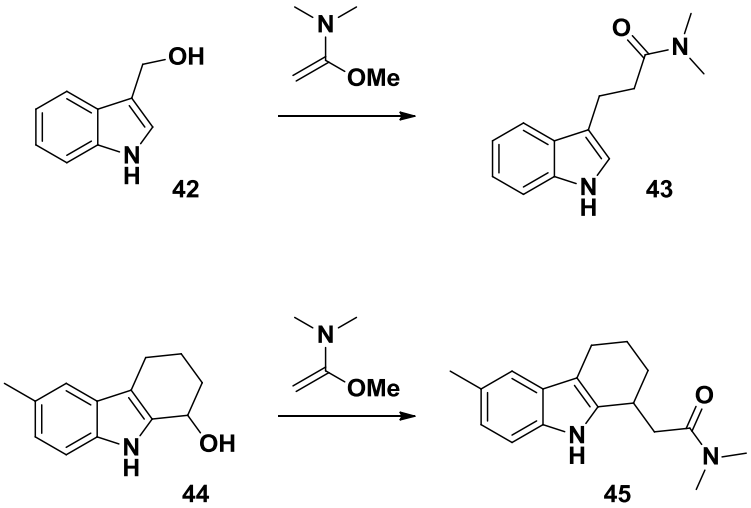


Scheme 22: The Eschenmoser-Claisen rearrangement of furfuryl alcohol **39**



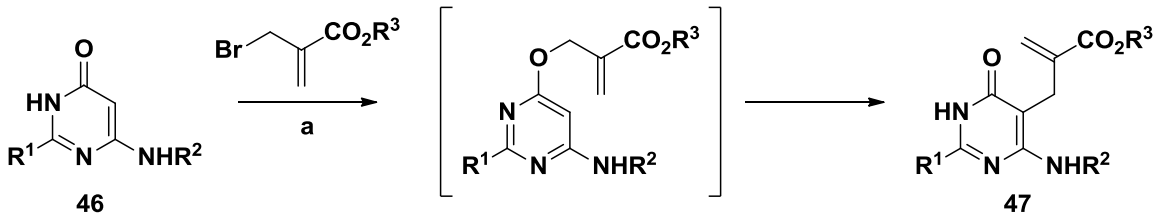
Scheme 23: The Eschenmoser-Claisen rearrangement of benzofurans. 5 examples; R^1 = H, OMe, Br, Cl; R^2 = H, OMe, Cl

Granik also attempted the reaction of 3- and 2-hydroxylmethylindoles **42** and **44** under the same conditions (Scheme 24). In this case, instead of the predicted [3,3]-rearrangement, the only products isolated were amides **43** and **45**, the products of a formal [1,3]-rearrangement. In contrast to the rearrangement of the benzofurans, which required heating at reflux in DMF, these reactions occurred at room temperature.



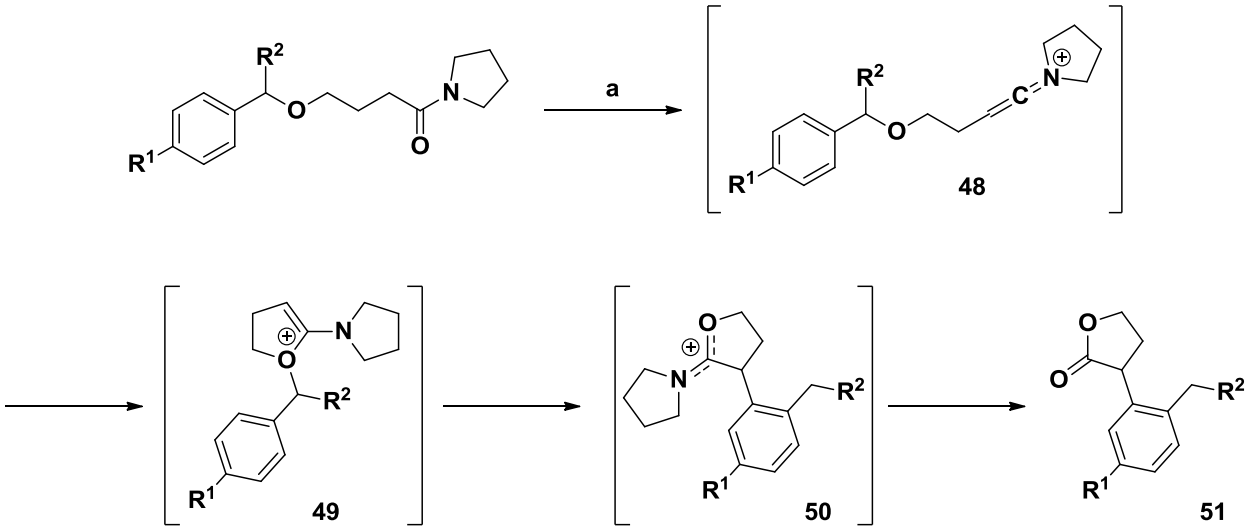
Scheme 24: Attempted Eschenmoser-Claisen rearrangements of indoles

Although there are only a few examples of the classical dearomatising Eschenmoser-Claisen rearrangement, variations utilising alternative methods of synthesising the *O*-allyl ketene hemiaminal intermediate have been studied more extensively. One example of this is the *O*-allylation of 4-pyrimidones **46** and subsequent [3,3]-rearrangement to give C5 functionalised pyrimidines **47** published in 2011 by Suckling *et al.* (Scheme 25).[20]



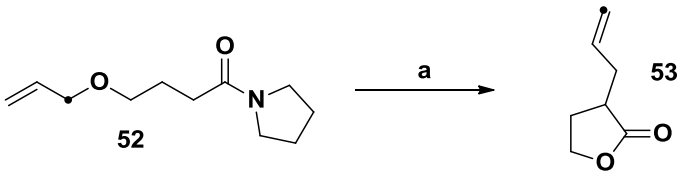
Scheme 25: Dearomatising Eschenmoser-Claisen rearrangement (a) DMF, rt, 7 days, 30 - 83 %. R^1 = SBn, NH_2; R^2 = H, Me, CH_2Ph, CH_2CHCH_2; R^3 = H, Et

Maulide *et al.* formed the hemiaminal by intramolecular trapping of a ketiminium **48** with an allylic alcohol (Scheme 26) in a similar manner to the Ficini-Claisen rearrangement.[21] The oxonium intermediate **49** then underwent a [3,3]-rearrangement to give carbenium **50**, which was then hydrolysed to form **51**.



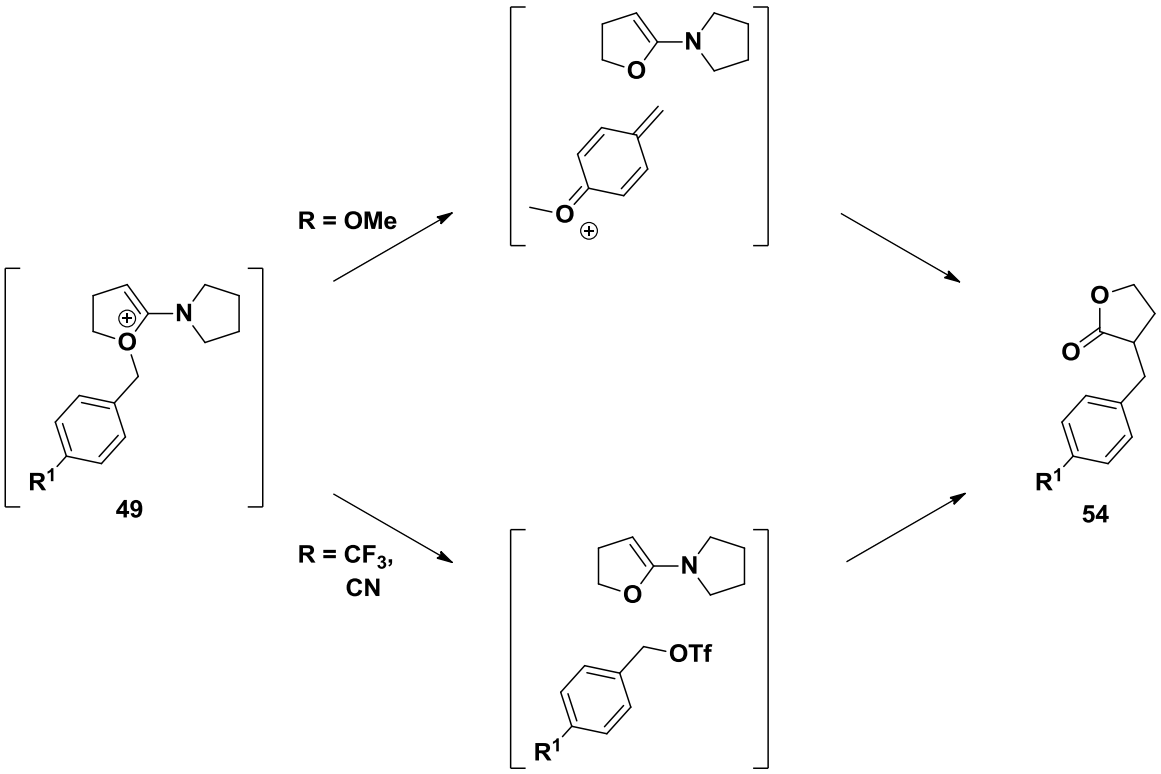
Scheme 26: Dearomatising Eschenmoser-Claisen rearrangement of oxonium **49** (a) Tf_2O, collidine, DCM, µw, 120 °C, 31 – 90 %. R^1 = H, F, I, Cl, Me, Br; R^2 = H, CO_2Me

Evidence for the reaction proceeding via a sigmatropic rearrangement mechanism comes from the studies shown in Scheme 27. When ^{13}C-labelled allyl ether **52** was subjected to the reaction conditions, the only product isolated was **53**, bearing the labelled carbon at the terminal allyl position.



Scheme 27: ^{13}C labelling studies (a) Tf_2O, collidine, DCM, µw, 120 °C

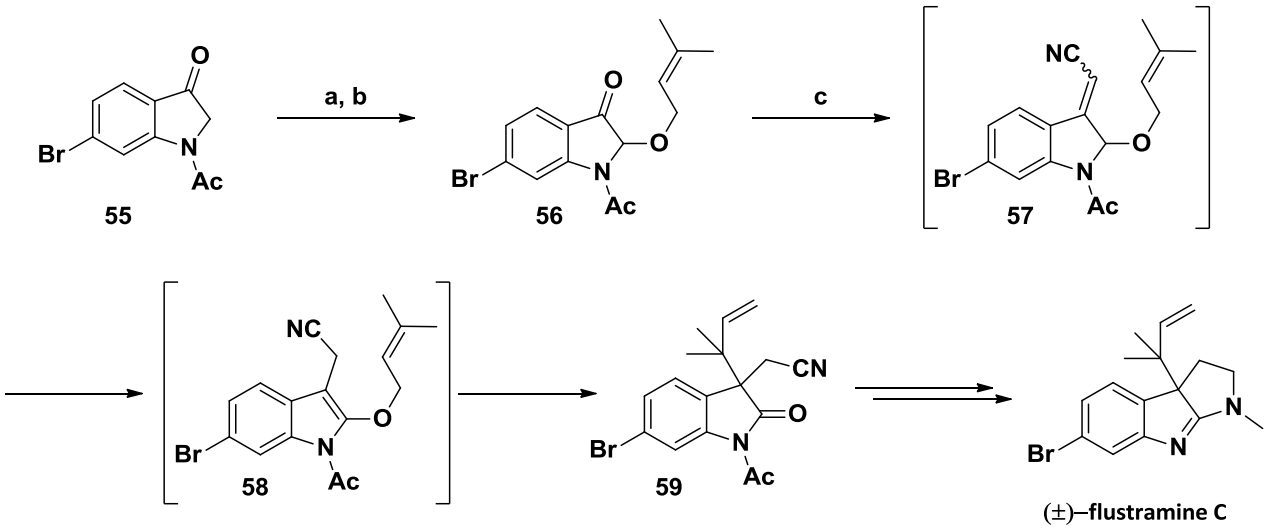
As well as the desired [3,3] rearrangement product, the formal [1,3] rearrangement product **54** was also detected in certain examples. When R was a strongly electron-withdrawing or -donating group (R = CN, CF_3, OMe), **54** was the only product isolated. This observation was explained by the mechanisms given in Scheme 28.



Scheme 28: Formation of the [1,3] rearrangement product **54**

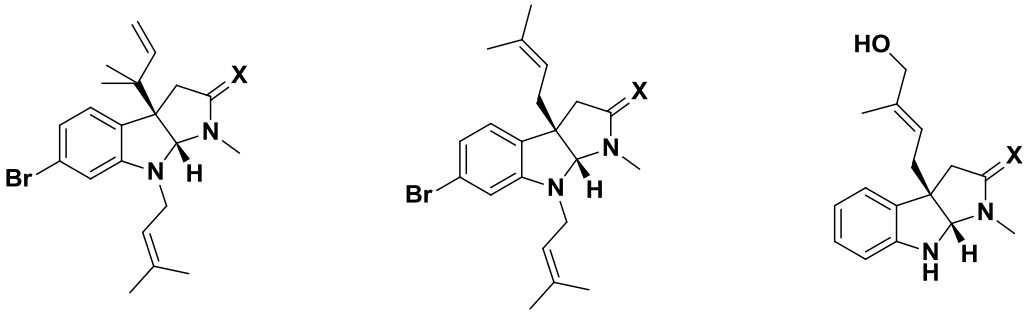
The most common use of the dearomatising Eschenmoser-Claisen rearrangement is in the synthesis of 3-allyl-2-oxindoles, where the vinylic double bond is the C2-C3 bond of the indole nucleus. In 1996, Sakamoto and Kawasaki published the synthesis of the marine alkaloid flustramine C.[22] 2-Allyloxyindolin-3-one **56** was generated by bromination of indolin-3-one **55** and substitution with prenyl alcohol. In a one-pot procedure this was then treated with diethylcyanomethylphosphonate to give alkene **57**, which isomerised under the reaction conditions to give indole **58**, possessing the necessary *O*-allyl

ketene hemiaminal functionality required for an Eschenmoser-Claisen rearrangement. The sigmatropic rearrangement proceeded smoothly at room temperature to give the indolin-2-one **59** in good yield.



Scheme 29: Kawasaki's synthesis of flustramine C (a) Br_2; (b) prenyl alcohol, 4 ÅMS, 89 % over two steps; (c) $(EtO)_2P(O)CH_2CN$, $^{t-}$BuOK, 73 %

Kawasaki has subsequently extended this tandem olefination, isomerisation and Claisen rearrangement methodology to the synthesis of a number of alkaloids containing the pyrrolo[2,3-b]indole ring system (Figure 5).[23,24,25]



flustramine A (X = H_2)
flustramide A (X= O)

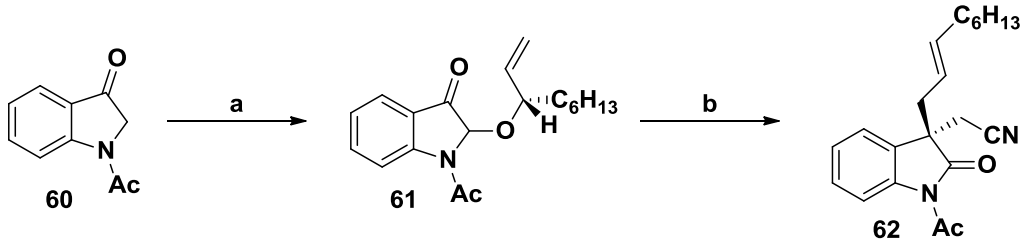
flustramine B (X = H_2)
flustramide B (X= O)

pseudophrynaminol

Figure 5: Natural products synthesised via Kawasaki's tandem olefination, isomerization, Claisen methodology

It has since been shown that it is possible to utilise this methodology to carry out an asymmetric Eschenmoser-Claisen rearrangement using an enantiomerically pure alcohol (Scheme 30). Bromination of indolin-3-one **60** and subsequent substitution with (*S*)-1-nonen-3-ol gave **61** as a mixture of diastereomers.

A Horner-Wadsworth-Emmons reaction initiated the olefination, isomerization and Claisen rearrangement cascade, forming indolin-2-one **62** in excellent yield and enantiomeric excess.



Scheme 30: Asymmetric Eschenmoser-Claisen rearrangement (a) Br_2, DCM, 0 °C then (*S*)-1-nonen-3-ol, MeCN/DMF, 4 Å MS, rt, 4 days, 73 %; (b) $(EtO)_2P(O)CH_2CN$, KO^{t}Bu, DMF, –78 °C to rt, 88 %, 97 % *ee*

The initial assignment of the (*S*) configuration of the *C3* stereocentre was based upon the molecular orbital calculation of transition states of model system **63** (Figure 6), showing that transition state A was preferred by 4.88 kcal/mol. This was then confirmed by elaboration of the product to (−)-pseudophrynaminol and comparison with the natural product.

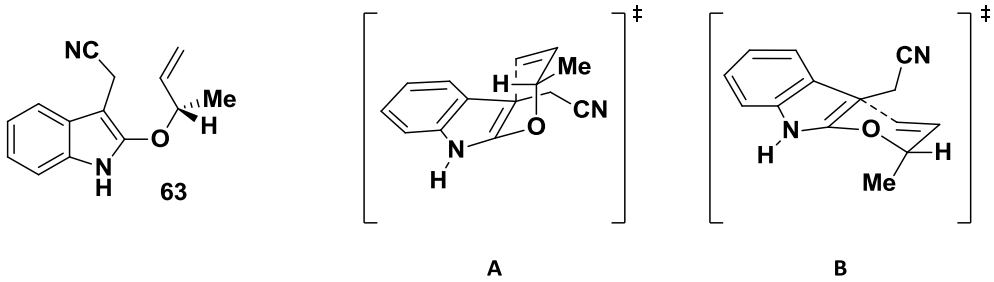
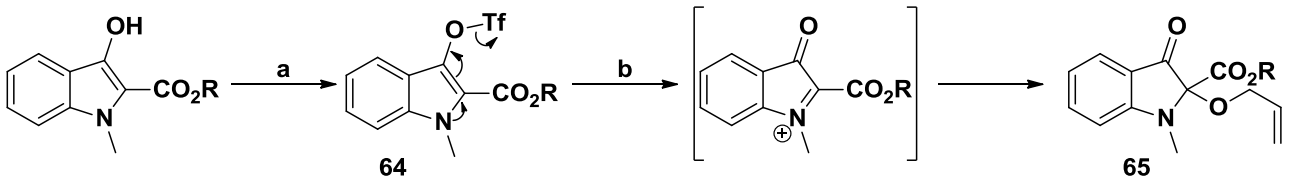


Figure 6: Transition states for the Eschenmoser-Claisen rearrangement of chiral ethers

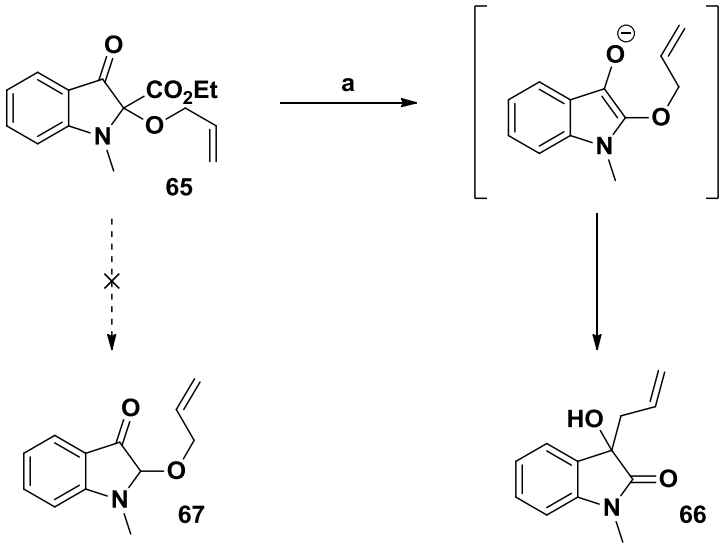
Mérour *et al* attempted to synthesise the 2-allyloxyindolin-3-one required for Kawasaki's cascade approach from 2-allyloxydihydroindole derivatives **65** which were formed as unexpected products while attempting a Heck reaction of triflate **64** (Scheme 31). The reaction also occurs in the absence of $Pd(OAc)_2$ but with a longer reaction time and lower yield.



64 65

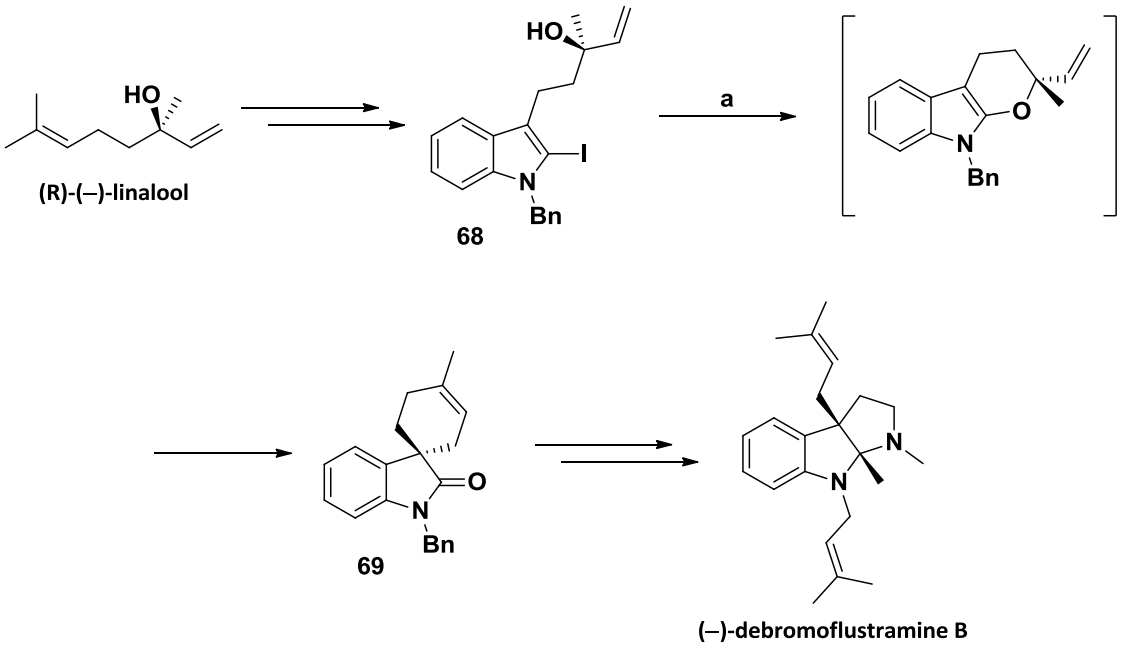
Scheme 31: Formation of 2-allyloxydihydroindoles under palladium-catalysed conditions (a) $PhN(Tf)_2$, NaH, THF; (b) allyl alcohol, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 100 °C

Attempts to decarboxylate **65** *via* standard saponification methods gave the rearranged product **66** rather than the expected 2-allyloxyindolin-3-one **67** (Scheme 32).[26] The authors reasoned that this was due to the anionic enolate formed under the saponification conditions accelerating the rate of rearrangement and allowing it to proceed at room temperature.



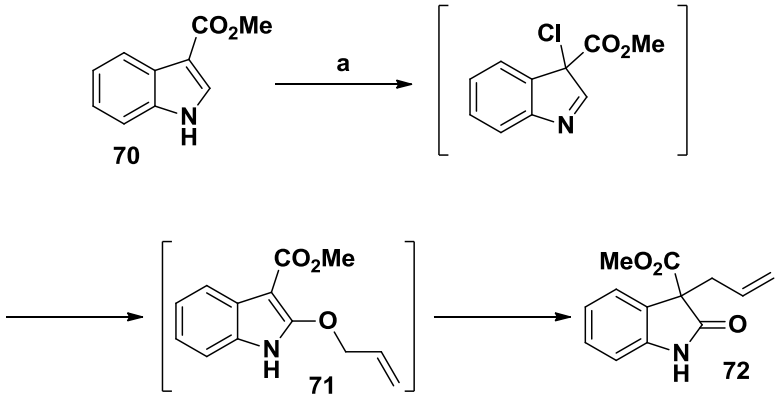
Scheme 32: Unexpected [3,3]-rearrangement during an attempted decarboxylation reaction a) KOH, $EtOH/H_2O$, rt, 3 h

Kobayashi and Nagazaki have also utilised the dearomatising Eschenmoser-Claisen rearrangement in the synthesis of the pyrrolo[2,3-*b*]indole ring system.[27,28] In this case the authors used a tandem Ulmann coupling, Claisen rearrangement reaction sequence to transform iodide **68** into spirocycle **69**, which was then further functionalised to give (–)-desbromoflustramine B (Scheme 33).



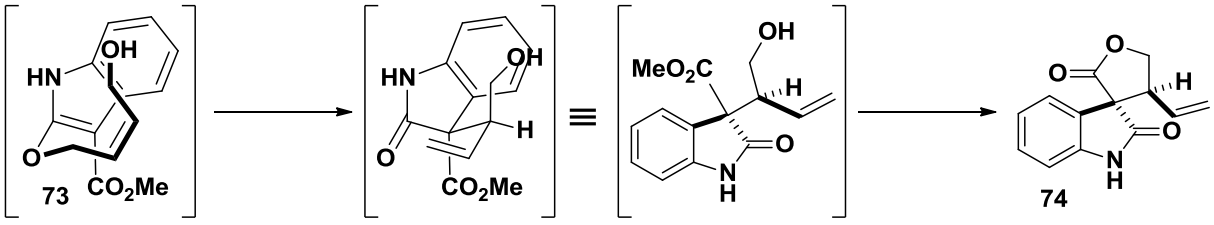
Scheme 33: Tandem Ulmann-Claisen sequence in the synthesis of debromoflustramine B (a) CuCl, 2-aminopyridine, NaOMe/MeOH, diglyme, 130 °C, 82 %

In 2000, Booker-Milburn and Fedouloff were attempting to synthesise 2-propenyloxyindole-3-carboxylic acid derivative **71** from ester **70**, following an established method for the synthesis of 2-alkoxyindoles. However, the only product isolated was the 2-oxindole derivative **72**, formed by a [3,3]-rearrangement (Scheme 34).[29] This procedure proved successful for a number of different allylic alcohols at room temperature, whereas propargylic alcohols required heating to reflux in dichloromethane.



Scheme 34: Booker-Milburn's synthesis of 2-oxindoles *via* a dearomatising Eschenmoser-Claisen rearrangement (a) NCS, dimethylpiperazine, DCM, 0 °C, 2 h; then allyl alcohol, trichloroacetic acid, rt, 2 h, 91 %

An interesting result was noted with *Z*-buten-1,4-diol **73**, which spontaneously cyclised after the rearrangement step to give the *anti*-substituted γ-lactone **74**. This observation can be rationalised on the basis that the sigmatropic rearrangement takes place via a chair transition state (Scheme 35).



Scheme 35: Transition state for Booker-Milburn's Eschenmoser-Claisen rearrangement

Kozlowski *et al.* have since developed this methodology to give the first example of a catalytic enantioselective Eschenmoser-Claisen rearrangement using copper BOX and palladium BINAP or PHOX catalysts (Figure 7).[30,31] Care was needed with the isolation of 2-propenyloxyindole-3-carboxylate ester **71** as it rearranges at room temperature, however the authors showed that it could be stored at –20 °C for one year.

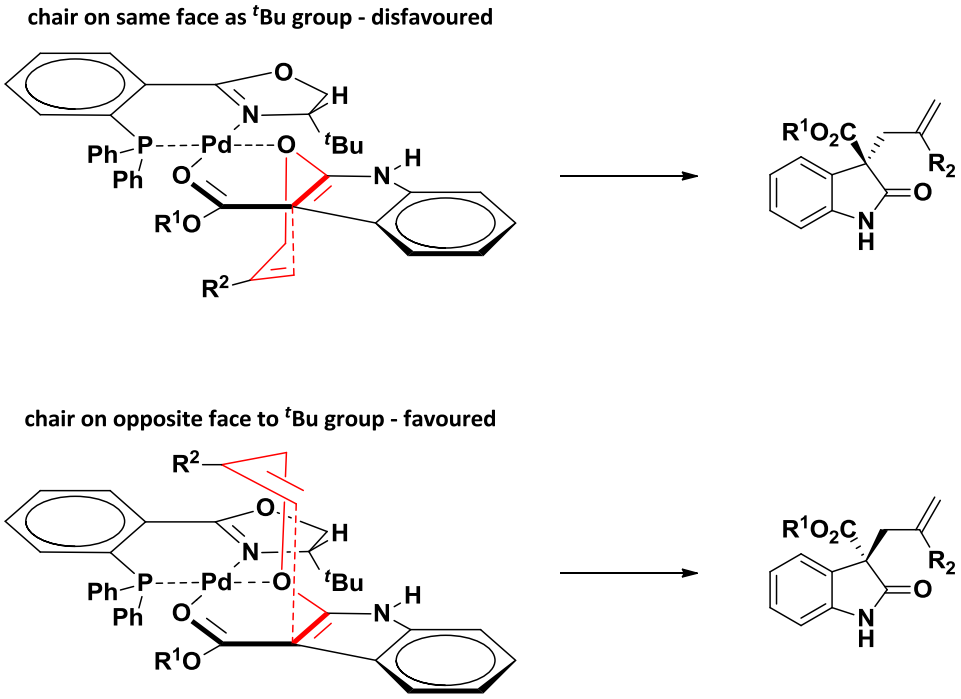
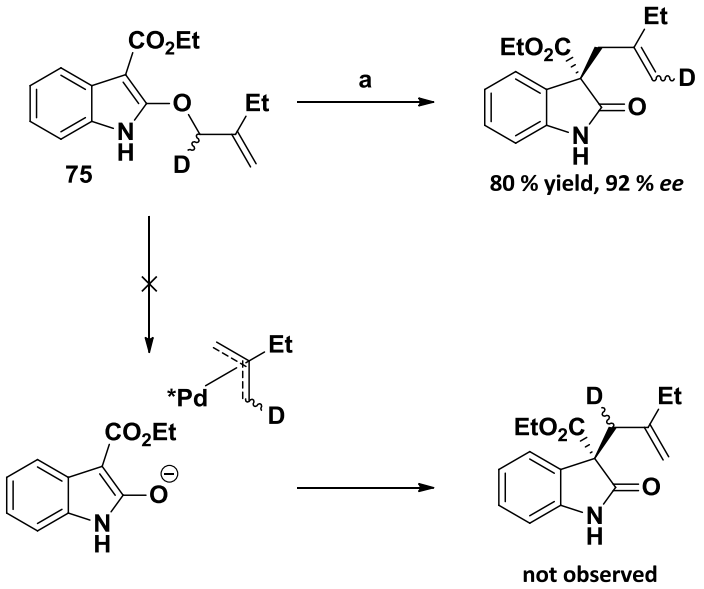


Figure 7: Catalytic enantioselective Eschenmoser-Claisen rearrangement

The reaction requires a bidentate indole possessing an ester at the C3 position. When this was replaced with a nitrile group no reaction was observed. Increasing the size of the C3 ester group (R^1 in Figure 7) resulted in an increase in enantioselectivity, but increasing the size of the vinylic substituent (R^2 in Figure 7) had a detrimental effect on the enantiomeric excess.

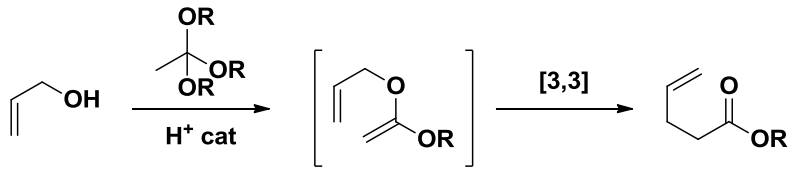
To eliminate the possibility of a π-allyl cation pathway with palladium (II) catalysts, deuterium labelling studies were carried out on indole **75** (Scheme 36). The lack of scrambling of the deuterium label confirmed that the reaction proceeds *via* a concerted sigmatropic mechanism.



Scheme 36: Kozlowski's deuterium labelling experiments (a) ^{t}BuPHOX, $Pd(SbF_6)_2$, DCM, 0 °C

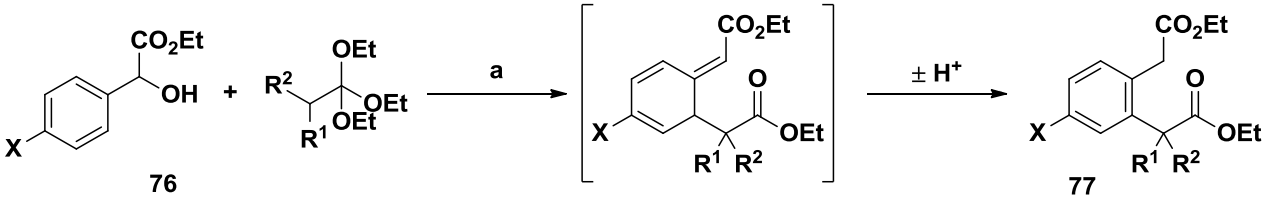
1.5 Dearomatising Johnson-Claisen rearrangements

The Johnson-Claisen rearrangement is the reaction of allylic alcohols with an orthoester to give γ,δ-unsaturated esters (Scheme 37).[32] In contrast to the Eschenmoser-Claisen rearrangement acidic catalysis is often required.



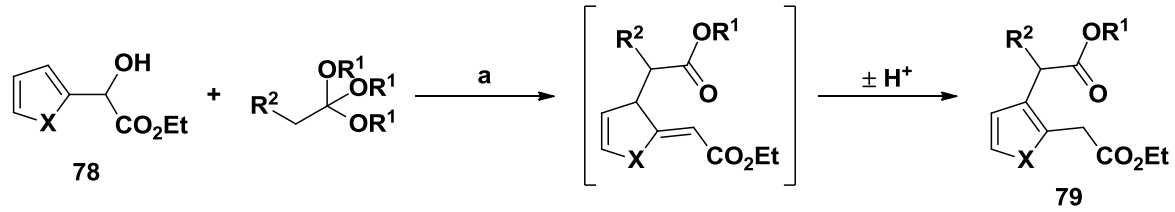
Scheme 37: The Johnson-Claisen rearrangement

Raucher has studied the dearomatising Johnson-Claisen rearrangement for benzylic alcohols that also bear an electron-withdrawing group at the benzylic position. This reaction has been shown to be successful for phenyl rings **76** to give *ortho*-diester **77** (Scheme 38) as well as 5-membered heterocycles **78** to give 2,3-disubstituted **79** (Scheme 39).[33,34]



76 **77**

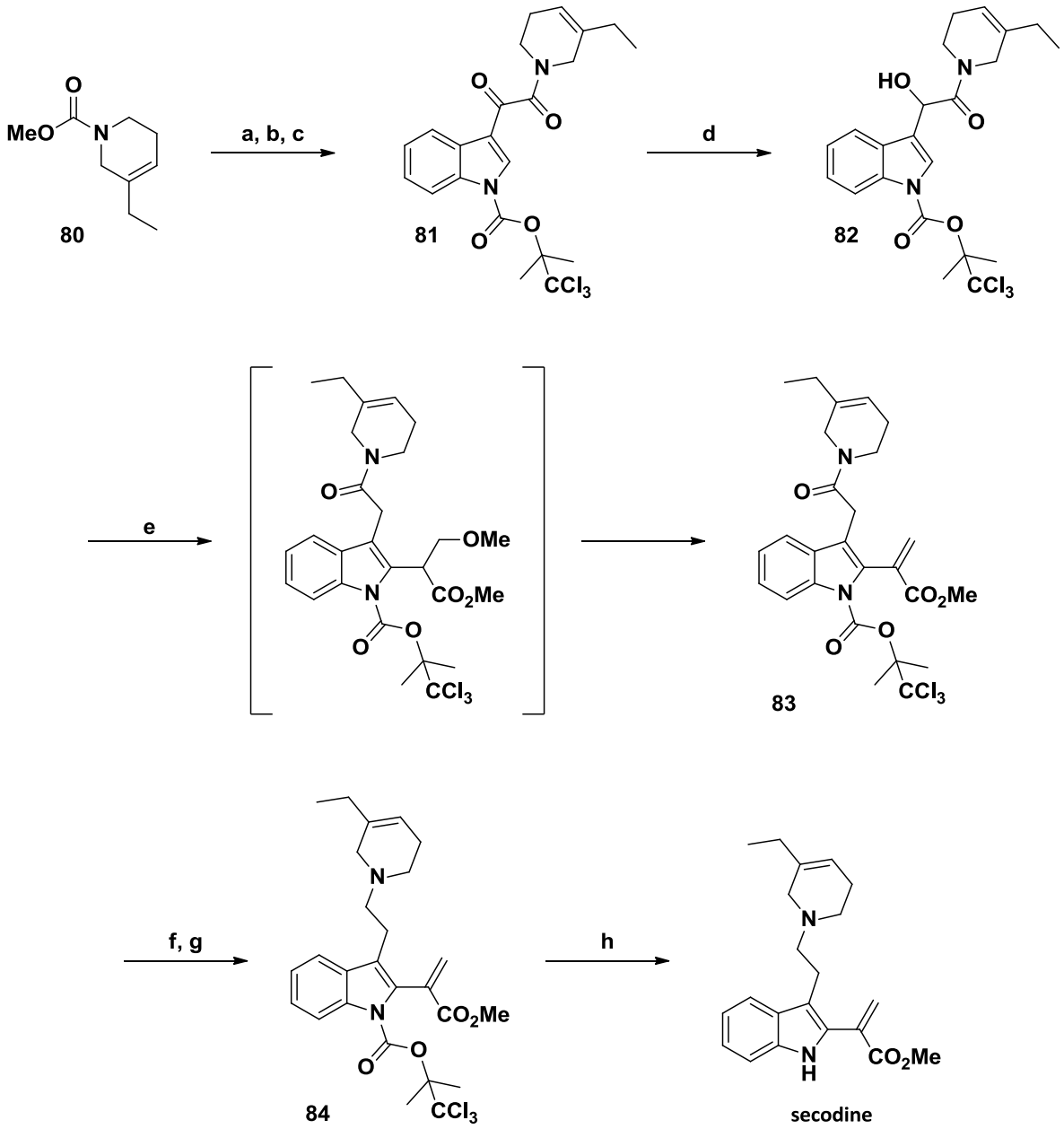
Scheme 38: The Johnson-Claisen rearrangement of benzylic alcohols (a) hexanoic acid (cat), 220 °C, 18 - 75 %. X = H, Me, OMe; R^1 = H, Me; R^2 = H, Me



78 **79**

Scheme 39: The Johnson-Claisen rearrangement of furans, thiophenes and pyrroles (a) hexanoic acid (cat.), 220 °C, 18 - 84 %. X = O, S, NTs; R^1 = Et, Me; R^2 = H, Me, ^{n}Pr

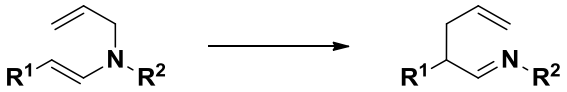
This methodology has also been extended to include indoles and applied to the synthesis of the alkaloid secodine (Scheme 40). [35] Keto-amide **81** was synthesised by addition of an amine generated from amide **80** to indole-3-glyoxyl chloride. **81** was then reduced with sodium borohydride and the resulting alcohol **82** underwent a dearomatising Johnson-Claisen rearrangement and elimination to give ester **83**, possessing the required functionality at the 2-position of the indole. Reduction *via* the thio-amide gave amine **84** and protecting group removal yielded the natural product in 18 % overall yield.



Scheme 40: Synthesis of secodine *via* a dearomatising Johnson-Claisen rearrangement (a) MeLi (3 equiv), Et_2O, 0 °C, 20 min; then HCl; (b) indole-3-glyoxyl chloride, Et_2O, 0 °C, 4 h, 90 % over two steps; (c) $ClCO_2C(CH_3)_2CCl_3$, Et_3N, DCM, rt, 30 min, 80 %; (d) $NaBH_4$, MeOH, 0 °C, 20 min, 63 %; (e) $CH_3OCH_2CH_2C(OMe)_3$, 2,4,6-trimethylbenzoic acid, 225 °C, 100 min, 65 %; (f) Lawesson's reagent, C_6H_6, reflux, 2 h; (g) $Et_3O^+BF_4^-$, DCM then $NaBH_3CN$, MeOH/HOAc, 0 °C, 81 % over two steps; (h) Zn, HOAc, 0 °C, 20 min, 76 %

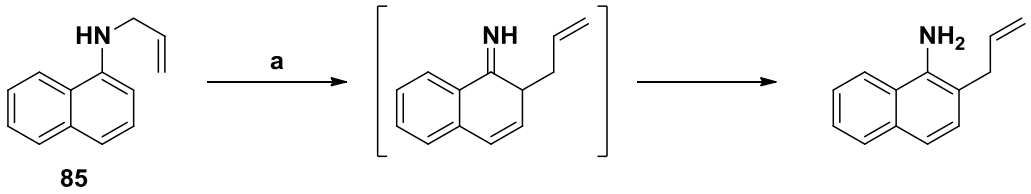
1.6 Dearomatising aza-Claisen rearrangements

The aza-Claisen (or amino-Claisen rearrangement) is a variant of the Claisen rearrangement where the oxygen heteroatom is replaced with a nitrogen atom (Scheme 41).



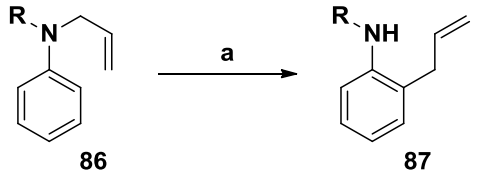
Scheme 41: The aza-Claisen rearrangement

Studies have shown that the energy of activation for the aromatic aza-Claisen is approximately 6 kcal/mol higher than that of the aromatic Claisen rearrangement.[36] Although there are examples of uncatalysed aromatic aza-Claisen rearrangements of fused aromatic systems such as **85** (Scheme 42),[36] the majority of examples proceed with either Lewis or Brønsted acid catalysis.



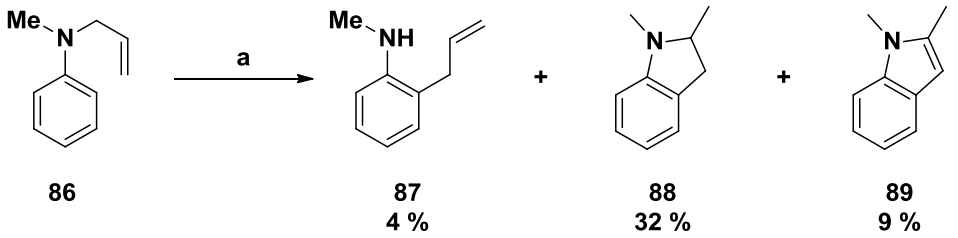
Scheme 42: Thermal aza-Claisen rearrangement (a) 280 °C, 3 h, sealed tube, 90 %

Stille *et al.* carried out a study into the Lewis-acid catalysis of the rearrangement of *N*-allyl aniline **86** (Scheme 43).[37] They found that the most successful catalysts were $AlCl_3$, $ZnCl_2$ and $BF_3{\cdot}OEt_2$. The reaction with $BF_3{\cdot}OEt_2$ was carried out by heating to reflux in toluene (110 °C), whereas $AlCl_3$ and $ZnCl_2$ required the use of xylene (140 °C) as a solvent. Interestingly, no reaction was observed when electron-withdrawing nitrogen protecting groups (acetamide and sulfonamides) were used.



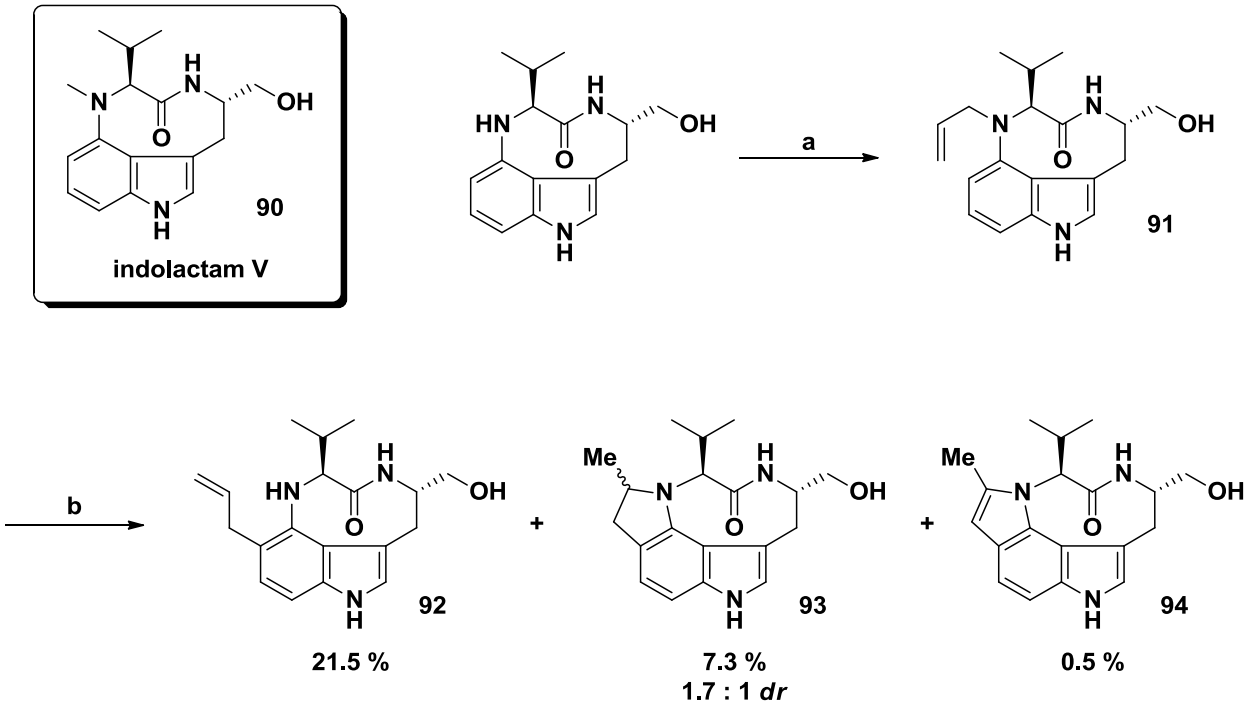
Scheme 43: Lewis-acid catalysed aza-Claisen rearrangement (a) $AlCl_3$ (1.2 equiv), xylenes, 140 °C, 8 h, R = Me = 68 %. R = Bn = 15 %

The stoichiometry of the Lewis- acid also played a part in the isolated products. When 1.5 equivalents were used the reaction gave rapid consumption of staring material, but poor isolated yields. Use of 1.2 equivalents gave the optimal results, and the use of a substoichiometric amount (0.75 equivalents) led to longer reaction times and the formation of small amounts of the cyclised products **88** and **89** (Scheme 44)



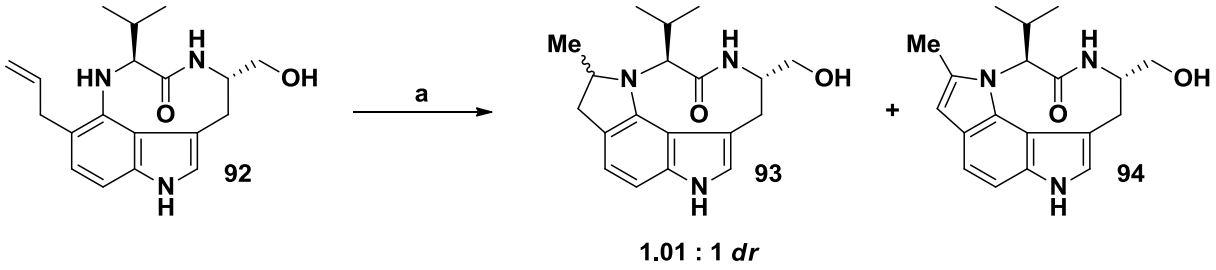
Scheme 44: Substoichiometric Lewis-acid catalysed aza-Claisen rearrangement (a) $AlCl_3$ (0.75 equiv), xylenes, 140 °C, 48 h

Since Stille's paper the dearomatising aza-Claisen rearrangement has been used extensively in the synthesis of indoles and 2,3-dihydroindoles. In 1996 Wender used Stille's methodology in the synthesis of conformationally restricted analogues of (–)-indolactam V (**90**).[38] When treated with 0.45 equivalents of $AlCl_3$, allyl aniline **91** rearranged to give a mixture of open chain allyl and cyclised products (Scheme 45).



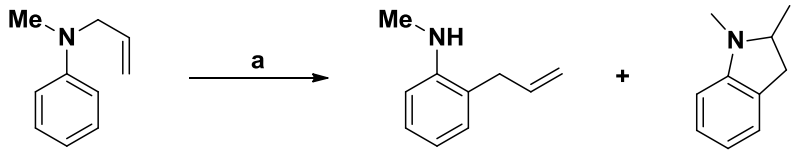
Scheme 45: Aza-Claisen rearrangement during the synthesis of (–)-indolactam V analogues (a) allyl bromide, $NaHCO_3$, MeOH, 38 %; (b) $AlCl_3$, xylenes, 140 °C, sealed tube, 20 min

To show that the cyclised products **93** and **94** were formed from **92** by addition of nitrogen to the double bond, **92** was subjected to the same reaction conditions and the cyclised products **93** and **94** were formed in 10.9 % and 1.0 % yields respectively (Scheme 46).



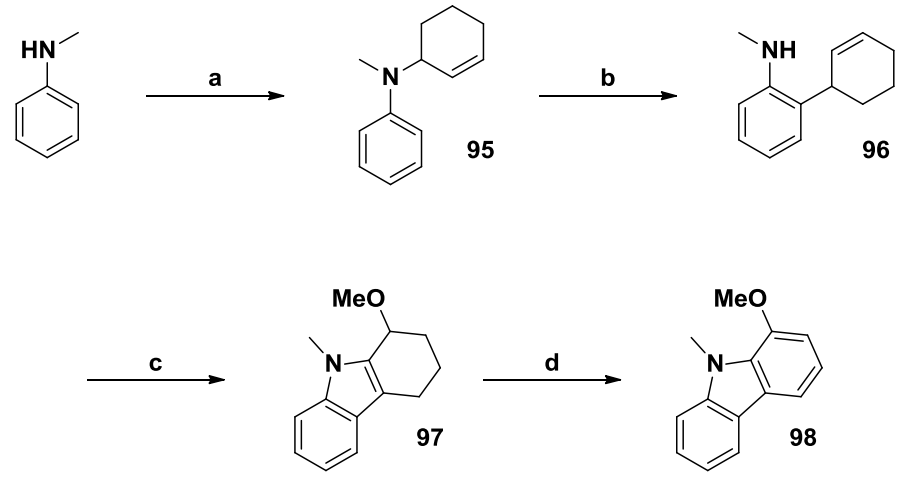
Scheme 46: Formation of cyclised products **93** and **94** from aza-Claisen product **92** (a) $AlCl_3$, xylenes, 140 °C, sealed tube, 20 min

Sreekumar and Padmakumar have shown that when using an excess of zeolite reagents, the indoline derivatives **88** can be synthesised preferentially with the open chain allyl derivatives **87** only isolated in low yield (Scheme 47).[39]



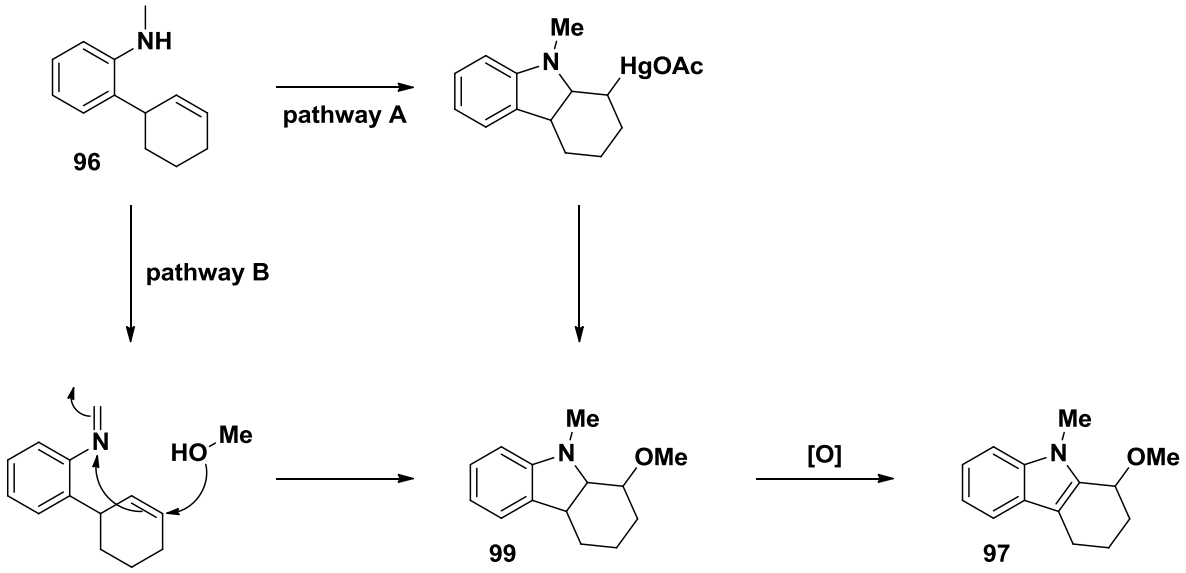
Scheme 47: Formation of indolines under aza-Claisen conditions (a) HY-Zeolite (10 equiv w/w), hexane, 80 °C, 2 h

Majumdar has also carried out a similar rearrangement under Brønsted-acid catalysis.[40] Refluxing *N*-allyl aniline **95** in ethanolic hydrochloric acid gave 2-(2'-cyclohexenyl)-*N*-alkyl aniline **96** via a [3,3] rearrangement. Oxidative ring closure, using a mercury (II) acetate catalyst gave fused cyclohexyl indole **97**, which could then be oxidised to carbazole **98** by treatment with DDQ (Scheme 48).



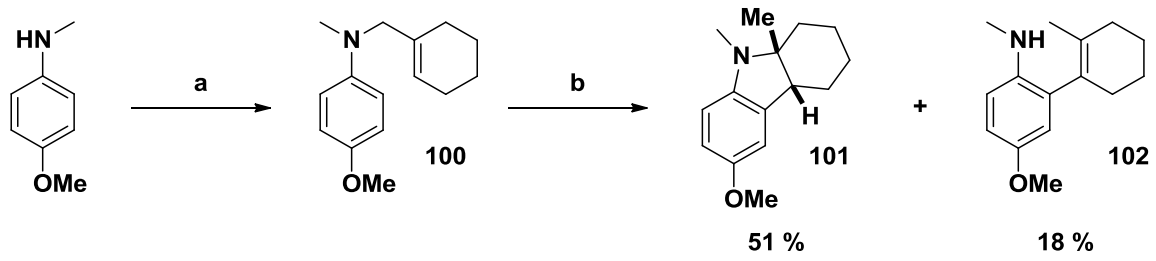
Scheme 48: Synthesis of indoles *via* an aza-Claisen – oxidative ring closure sequence (a) 3-bromocyclohexene, acetone, K_2CO_3, reflux, 5 h, 90 %; (b) HCl, EtOH, reflux, 15 h, 88 %; (c) $Hg(OAc)_2$, AcOH, MeOH, rt, 24 h, 80 %; (d) DDQ, xylene, reflux, 12 h, 83 %

Two potential mechanisms for the ring closing reaction were proposed by the authors (Scheme 49). In pathway A, an aminomercuration reaction followed by displacement with alcohol gives intermediate **99**, which is then oxidised to the indole **97**. Pathway B involves oxidation of the aniline functionality to an imine followed by cyclisation to give the same intermediate **99**. These suggested mechanisms however would require two equivalents of mercury (II) acetate, whereas only one was used. This suggests that air may be oxidising the intermediate organomercurial species, regenerating mercury (II).



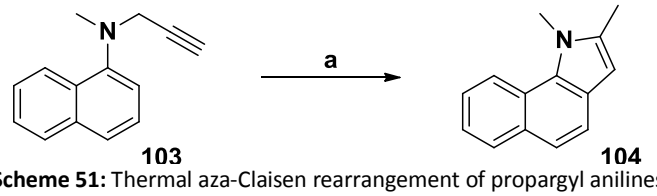
Scheme 49: Majumdar's proposed mechanism for formation of **97**

In 2008, Novak *et al*. reported the aza-Claisen rearrangement of *N*-allylaniline derivatives **100** catalysed by $BF_3{\cdot}OEt_2$ (Scheme 50) as part of a study into a potential acetylcholinersterase inhibitor.[41] Under the reaction conditions the product aniline underwent a 5-*exo*-*trig* cyclisation to give the *syn*- fused cyclohexane **101**. A small amount of **102**, formed from the rearrangement product by double bond migration, was also isolated.



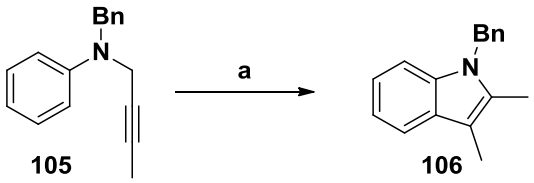
Scheme 50: Formation of indolines under aza-Claisen conditions (a) 1-(chloromethyl)cyclohex-1-ene, Et_3N, H_2O, rt, 3 h, 78 %; (b) $BF_3{\cdot}OEt_2$, sulfolane, 190 °C, 30 min

Another use of the aza-Claisen rearrangement in indole synthesis is the reaction of propargyl anilines **103**. Zsindley and Schmid used this methodology to synthesise 2-methyl indoles **104** in 1973 (Scheme 51),[42] although the high temperatures required (240 – 260 °C) led to low isolated yields.



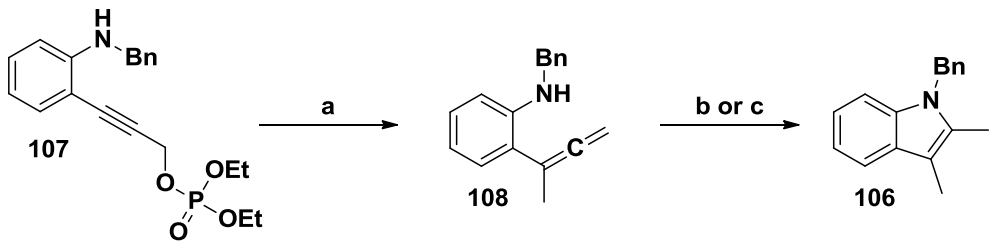
Scheme 51: Thermal aza-Claisen rearrangement of propargyl anilines

Saito and Hanzawa have since reported a rhodium catalysed variant (Scheme 52).[43] A phosphine ligand was crucial for the formation of **106** as in its absence only 13 % of the product was isolated. The authors ruled out the possibility of the reaction being catalysed by adventitious amounts of Brønsted- acid by showing that when the rhodium catalyst was replaced by triflic acid the starting material **105** was recovered in a quantitative yield.



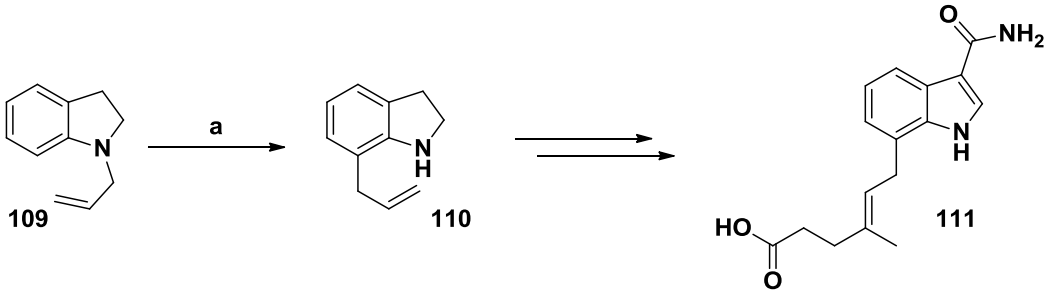
Scheme 52: Formation of indoles under rhodium catalysed aza-Claisen conditions (a) 10 mol % $[Rh(cod)_2]OTf$, 10 mol % dppp, HFIP, reflux, 5 h, 93 %

To better understand the mechanism of reaction under these conditions, allene **108** was generated by addition of methyl magnesium bromide to propargylic phosphate ester **107** (Scheme 53). When **108** was subjected to the same reaction conditions as above, indole **106** was isolated in 74 % yield. Interestingly, when **108** was heated in the absence of the catalyst, indole **106** was also formed albeit in a slightly reduced yield (51 %). The authors surmised that the overall reaction therefore took place *via* a Rh-catalysed [3,3]-sigmatropic rearrangement followed by a cyclisation induced by both the catalyst and heating.



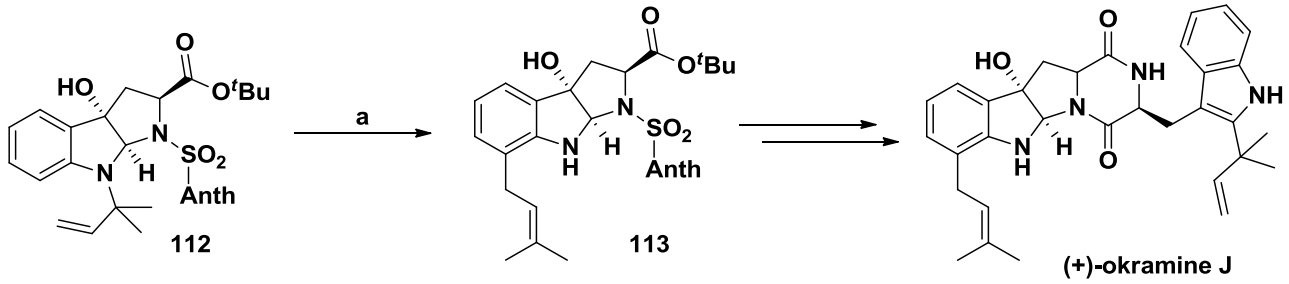
Scheme 53: Evidence for **108** as an intermediate during the formation of **106** (a) CuCN.2LiCl, MeMgBr, THF 0 °C; (b) 10 mol % $[Rh(cod)_2]OTf$, 10 mol % dppp, HFIP, reflux, 3 h, 74 %; (c) No catalyst, HFIP, reflux, 3 h, 51 %

The aza-Claisen rearrangement has also been used in the introduction of allylic groups to the C7 position of an indole. Lai used a $BF_3{\cdot}OEt_2$ catalysed rearrangement to convert *N*-allyl indoline **109** to C7-allyl indoline **110** (Scheme 54).[44] The allylic side chain was then further functionalised to give an indole analogue **111** of mycophenolic acid, which was then tested for its ability to inhibit inosine monophosphate dehydrogenase,



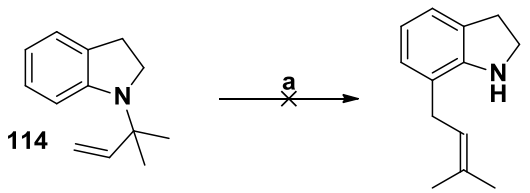
Scheme 54: Aza-Claisen rearrangement during the synthesis of mycophenolic acid analogues (a) $BF_3{\cdot}OEt_2$, sulfolane, 210 °C, 47 %

The introduction of an prenyl group via a Brønsted acid-catalysed aza-Claisen was reported by Ganesan *et al*. in their 2003 synthesis of (+)-okaramine J (Scheme 55).[45]



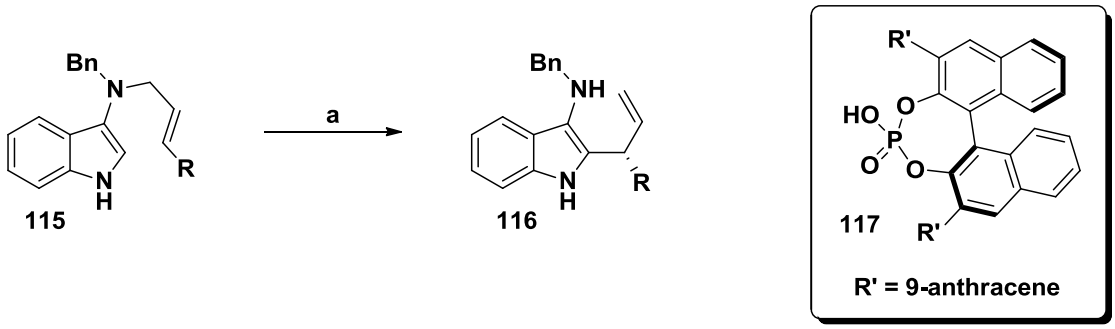
Scheme 55: Aza-Claisen rearrangement during the synthesis of (+)-okramine J (a) TFA (5 equiv), DCM, rt, 16 h, 84 %

Interestingly this reaction was carried out at room temperature, whereas previous examples of the dearomatising aza-Claisen rearrangement have all required heating. The authors believed that the rearrangement of **112** to give **113** was facilitated by a Thorpe-Ingold effect, which causes the vinyl group to adopt the desired conformation away from the bulky sulfonamide. This observation was supported by the observation that the model system **114** did not rearrange under the same conditions (Scheme 56).



Scheme 56: Failed rearrangement of model system **114** (a) TFA (5 equiv), DCM, rt, 16 h

Tantillo and Tambar have recently reported the enantioselective aza-Claisen rearrangement of indoles using chiral phosphoric acids (Scheme 57).[46] This methodology proved compatible with a number of R = Ar groups, including heterocycles, naphthalenes, and phenyl rings bearing both electron-withdrawing and electron-donating substituents. However, replacing R with an aliphatic group dramatically decreased the ee. Substituting the indole with both electron-withdrawing and electron-donating substituents also gave good levels of enantioselectivity.



Scheme 57: Enantioselective aza-Claisen rearrangement (a) 5 mol % **117**, PhMe, 60 °C, 36 h, R = Ar = 83 - 91 % yield, 85 - 96 % ee

As well as being the first example of an enantioselective aromatic aza-Claisen rearrangement, this methodology also constitutes the first example of an aza-Claisen rearrangement using a catalytic amount of Brønsted acid. Indeed, when **115** was treated with 10 mol % TFA under the same conditions, the desired product was isolated **116** in only 40 % yield, along with 20 % starting material and considerable amounts of decomposition products. This showed that phosphoric acids have a unique mode of activity in catalysing the aza-Claisen rearrangement of indoles. Modelling studies of the transition state showed that the indole interacted with the chiral phosphate counter ion via both the *NH* of the ammonium functionality and the C2-proton of the indole (Figure 8). The authors believed that this interaction both accelerated the rate of rearrangement and organised the transition state for high enantioselectivity, with the 9-anthracene group of the phosphate blocking the *si*-face of the substrate.

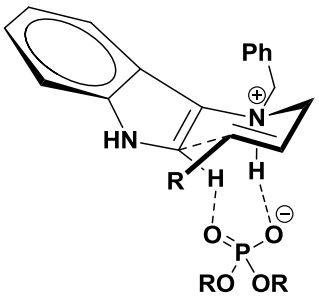
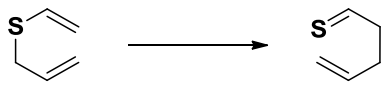


Figure 8: Transition state for enantioselective aza-Claisen

The modelling studies also showed an edge to face CH-π interaction between the R = Ar group and the other 9-anthracene group of the counter ion, which is consistent with the explanation that replacing this substituent with an alkyl group leads to a decreased selectivity.

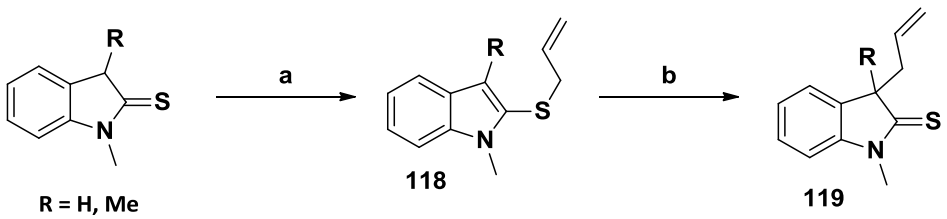
1.7 De-aromatising thio-Claisen rearrangements

The thio-Claisen rearrangement is a variant of the Claisen rearrangement where the oxygen heteroatom is replaced with a sulfur atom (Scheme 58).



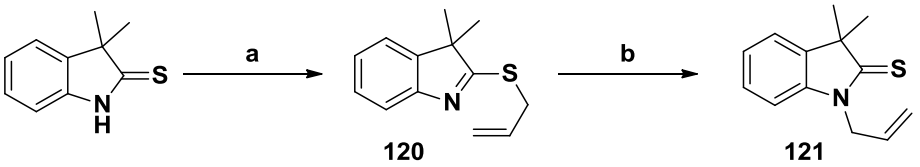
Scheme 58: The thio-Claisen rearrangement

The first studies into the dearomatising thio-Claisen rearrangement were carried out by Bycroft *et al*. in 1970.[47] They showed that it was possible for ally-2-indolylsulfides **118** to rearrange in boiling toluene to the thiones **119** (Scheme 59).



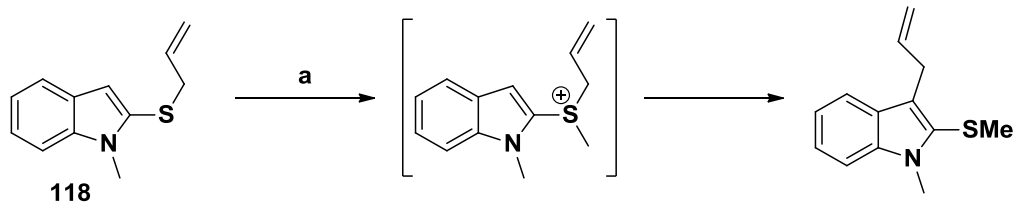
Scheme 59: Thio-Claisen rearrangement of ally-2-indolylsulfides (a) allyl bromide, K_2CO_3, acetone; (b) PhMe, reflux

When the 3-position of the indole was blocked by substitution, allyl-2-indolylsulfide **120** would rearrange to the N-allyl derivative **121** (Scheme 60). The higher activation energy of this rearrangement, compared to that shown in Scheme 59, meant that heating to reflux in tetralin was required.



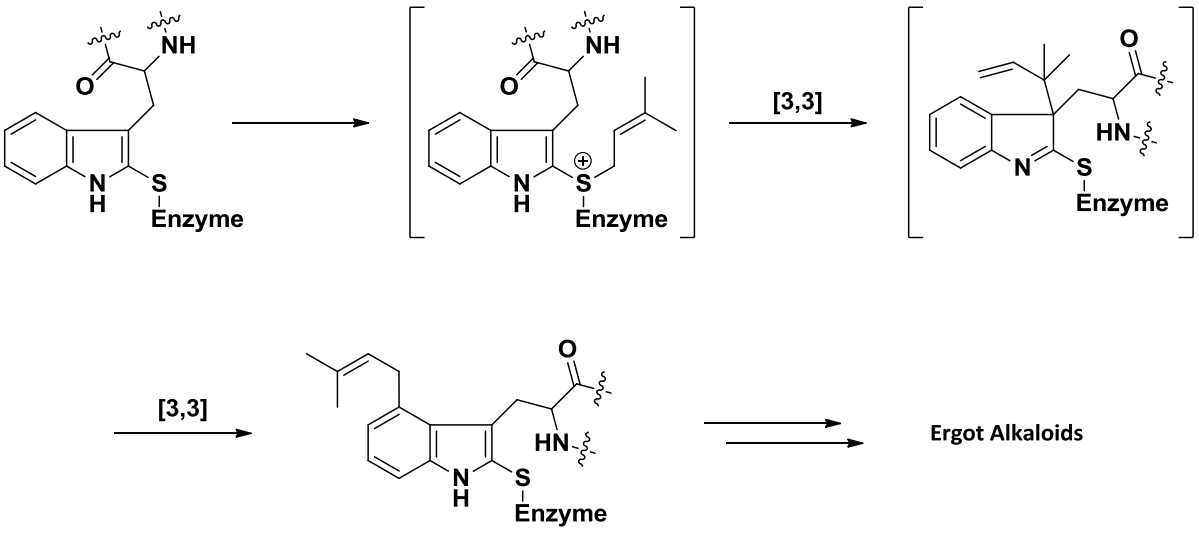
Scheme 60: Thio-Claisen rearrangement of 3,3-disubstituted ally-2-indolylsulfides (a) allyl bromide, K_2CO_3, acetone; (b) tetralin, reflux

However, when ally-2-indolylsulfide **118** was treated with an alkylating agent, the resulting methyl sulfonium cation rearranged spontaneously at room temperature (Scheme 61).[48]



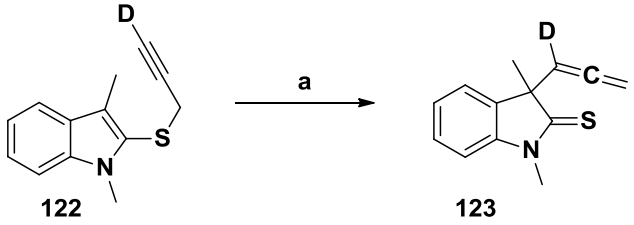
Scheme 61: Room temperature Thio-Claisen rearrangement of methyl sulfonium cation (a) methyl flurosulfonate, rt

Bycroft postulated that this may have a biosynthetic implication in the synthesis of the ergot alkaloids (Scheme 63) *via* sequential thio-Claisen and Cope rearrangements. This hypothesis has however since been disproven, and it has been shown that the prenyl group is introduced via a direct alkylation at the C4 indole position with dimethylallyl diphosphate.[49]



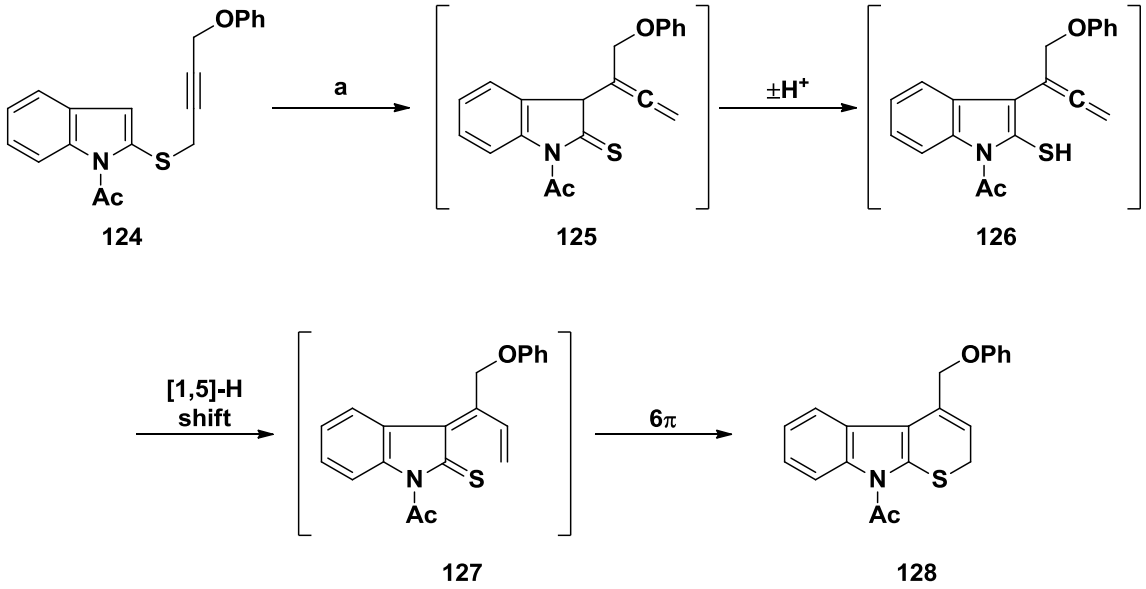
Scheme 62: Bycroft's proposed biosynthetic route to the Ergot alkaloids

Bycroft also demonstrated a sulfur analogue of the Saucy-Marbet reaction using propargyl thioethers **122** (Scheme 63). Deuterium labelling experiments confirmed that the reaction proceeded via a [3,3]-sigmatropic mechanism to give only **123**.



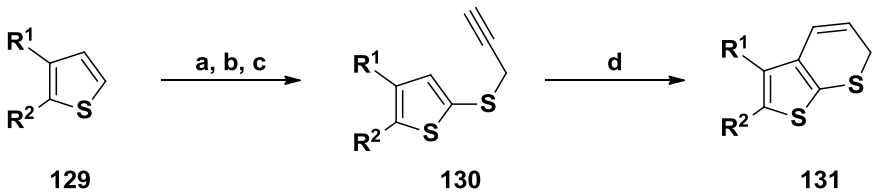
Scheme 63: Thio-Claisen rearrangement of propargyl thioethers (a) PhMe, reflux

Majumdar[50] (Scheme 64) and Mashelkar[51] (Scheme 65) have since used this variant of the Saucy-Marbet reaction to generate annulated thiopyrans.



Scheme 64: Synthesis of an annulated thiopyran via a thio-Claisen rearrangement of a propargyl thioether (a) chlorobenzene, reflux, 1 h, 80 %

Upon heating, indole **124** undergoes a dearomatising-Claisen rearrangement to give allene **125**. **125** then spontaneously undergoes tautomerisation to give **126**, which in turn undergoes a [1,5]-hydride shift to give **127**. A final electrocyclisation gives thiopyran **128**.

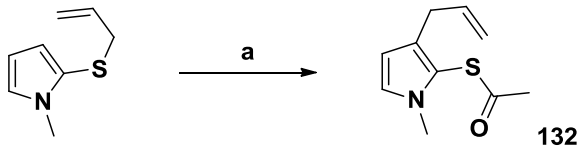


129 130 131

Scheme 65: Synthesis of an annulated thiopyran via a thio-Claisen rearrangement of a propargyl thioether (a) nBuLi, THF, –70 °C, 30 min; (b) S, –70 °C, 30 min; (c) propargyl bromide, –30 °C, 1 h, 49 – 83 %; (d) DMF, 150 °C, 30 min, 70 – 75 %. 5 examples.

Propargyl thioether **130** was synthesised *via* a lithiation at the 2-position of thiophene **129** and then underwent rearrangement *via* the mechanism given above to form thiopyran **131**.

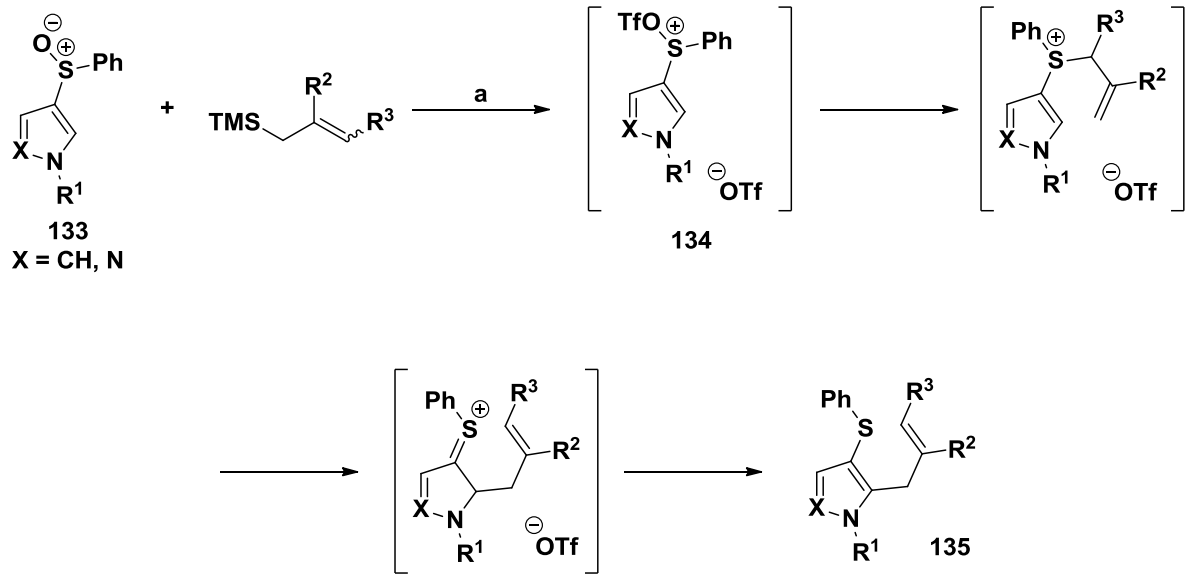
In 1978, Loader investigated the thio-Claisen rearrangement of 2-allylthio pyrroles as a potential route to 2,3-disubstituted pyrroles.[52] Attempts to isolate the unsubstituted thiol product proved unsuccessful, but the use of acetic anhydride as a co-solvent during the reaction allowed synthesis of the thioester **132** (Scheme 66). It is not clear whether the sulfur-acetyl bond was formed before or after the rearrangement step.



132

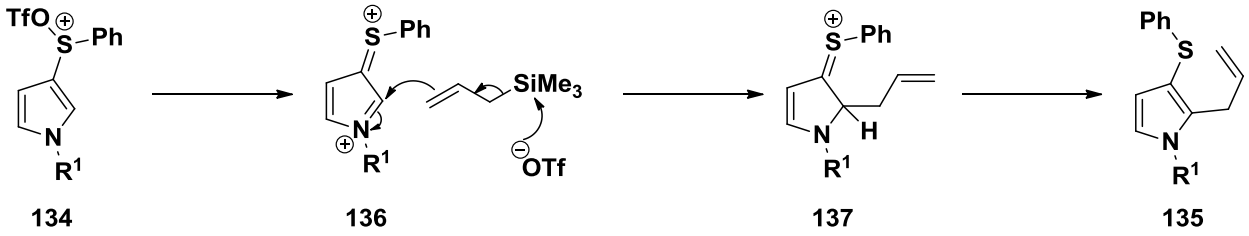
Scheme 66: Thio-Claisen rearrangement of 2-allylthio pyrroles (a) Ac_2O, quinoline, 170 °C, 15 min

Procter *et al.* have reported the rearrangement of the 3-arylsulfonium salts of pyrroles and pyrazoles **133**.[53] This interrupted Pummerer, thio-Claisen cascade allows easy access to *ortho*-allylated heterocycles **135**, without the use of metal catalysts.



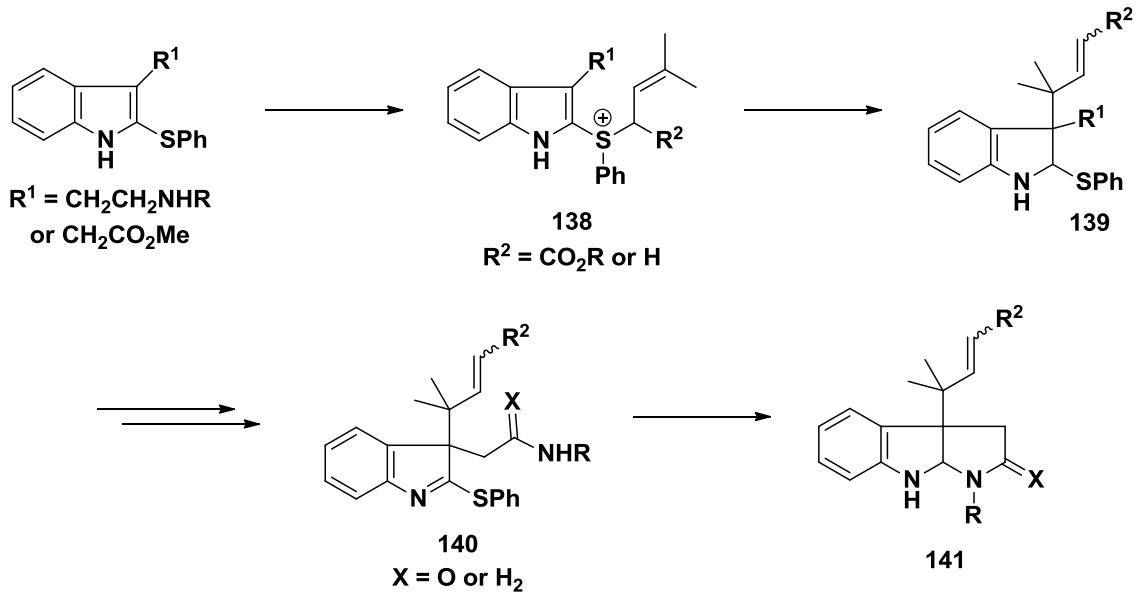
Scheme 67: Pummer, thio-Claisen cascade reaction. (a) Tf_2O, MeCN

A possible alternative mechanism, by which nitrogen lone pair donation and loss of triflate from intermediate **134** would give an extended thionium ion **136**, which could then undergo direct nucleophilic attack from the allyl silane to give **137** (Scheme 68) was ruled out due to the fact that the use of allyl silanes where R^2 = H and $R^3 \neq$ H gave only the linear alkene formed from double allylic inversion.



Scheme 68: Discounted alternative reaction mechanism

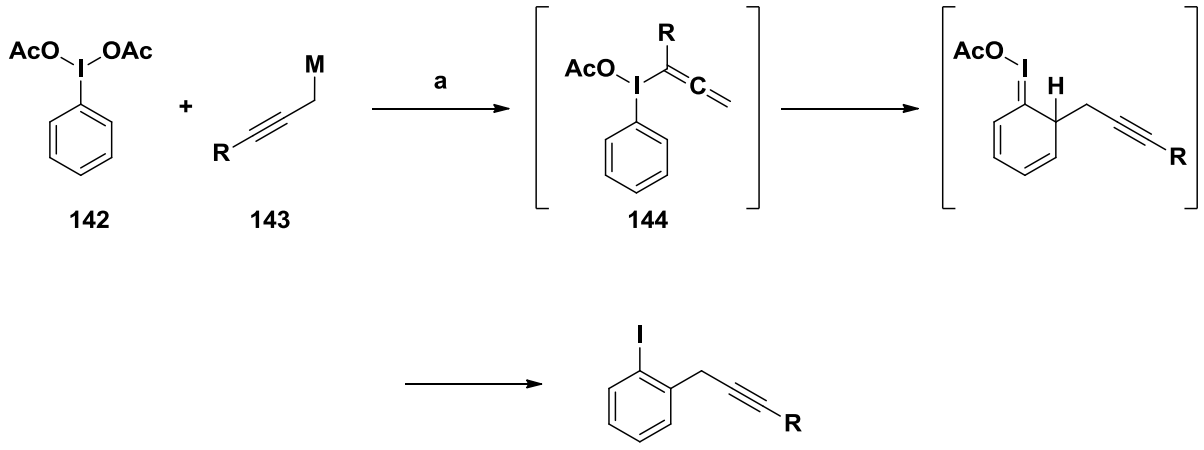
Similarly to the Eschenmoser-Claisen rearrangement described earlier, the thio-Claisen rearrangement has been utilised in the synthesis of different members of the Flustramine family.[54–56] In these syntheses the indole C3-quaternary centre of **139** is formed by the thio-Claisen rearrangement of **138** and the formation of the final pyrollidine ring in **141** is caused by cyclisation onto the thioimidate functionality of **140** with thiol elimination (Scheme 69).



Scheme 69: Synthesis of Flustramine alkaloids via a thio-Claisen strategy

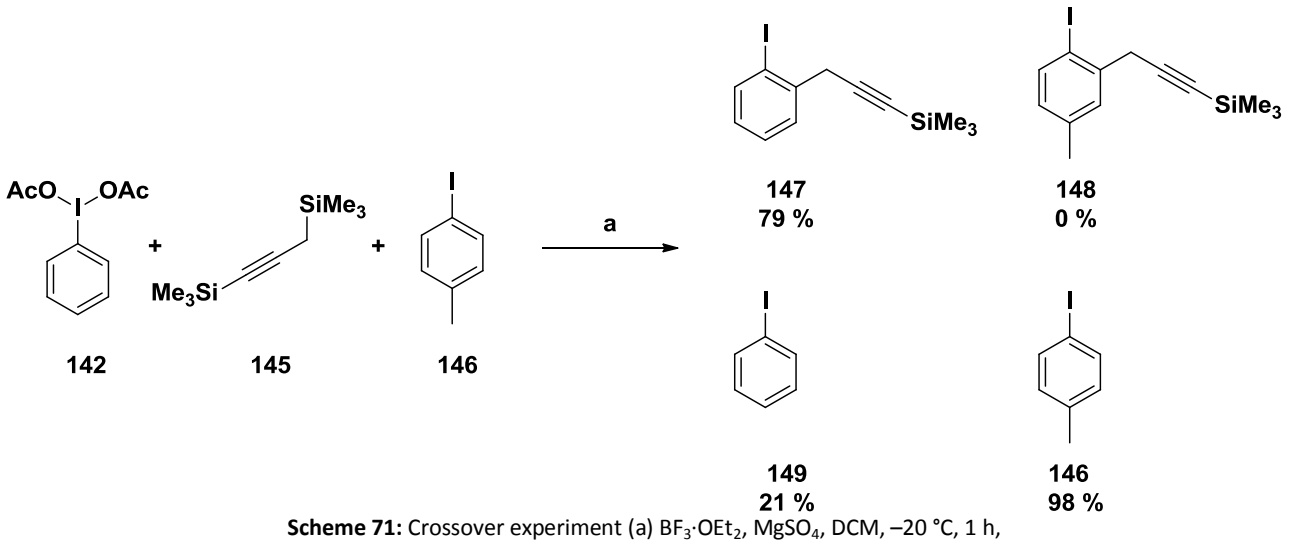
1.8 Dearomatising iodonio-Claisen rearrangements

In 1991 Ochiai *et al.* reported the iodonio-Claisen rearrangement of allenyliodinanes **144**; formed from an S_E2' reaction between aryliodinanes **142** and propargyl silanes, germanes and stannanes **143** (Scheme 70).[57]



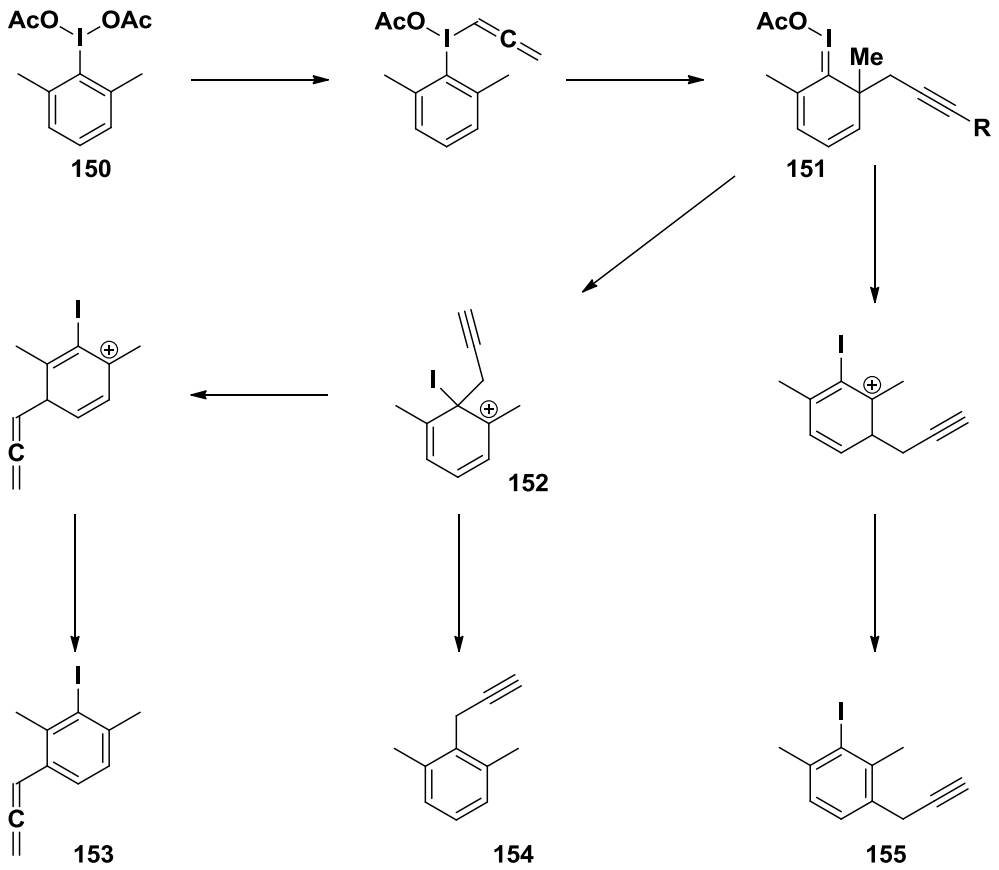
Scheme 70: Iodonio-Claisen rearrangement (a) $BF_3{\cdot}OEt_2$, $MgSO_4$, DCM, –20 °C, 1 h, 82 %

Competition studies provided evidence for the intramolecularity of the rearrangement process. When iodosyl benzene **142** was reacted with alkyne **145** in the presence of 4-methyliodobenzene **146**, rearrangement product **147** was formed in a 79 % yield along with a small amount of the reduction product **149**. The crossover product **148** was not detected and **146** was recovered in an almost quantitative yield (Scheme 71). The equivalent result was observed when 4-methyliodosyl benzene was reacted with **145** in the presence of iodobenzene. The lack of cross over products indicates that either an ionic or radical dissociation-reassociation mechanism is unlikely.



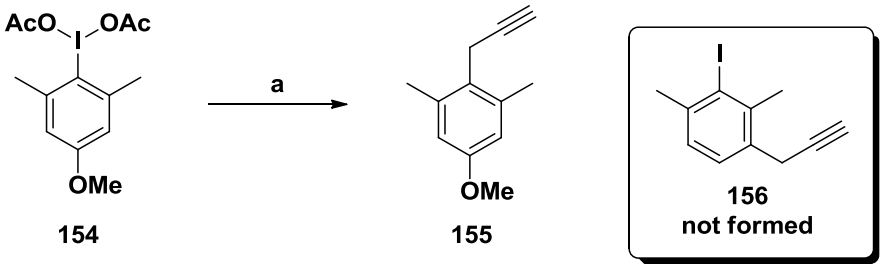
Scheme 71: Crossover experiment (a) $BF_3{\cdot}OEt_2$, $MgSO_4$, DCM, –20 °C, 1 h,

When both of the *ortho*- positions of the aryliodinane **150** were blocked, a mixture of *meta*- (**153** and **155**) and *ipso*- (**154**) substituted products were isolated (Scheme 72), formed by [1,2]-sigmatropic rearrangements of the initial iodonio-Claisen product **151**.



Scheme 72: Formation of *meta*- and *ipso*- substituted products by [1,2]-rearrangements. **(a)** propargyl silane, $BF_3{\cdot}OEt_2$, $MgSO_4$, DCM, –20 °C, 2 h

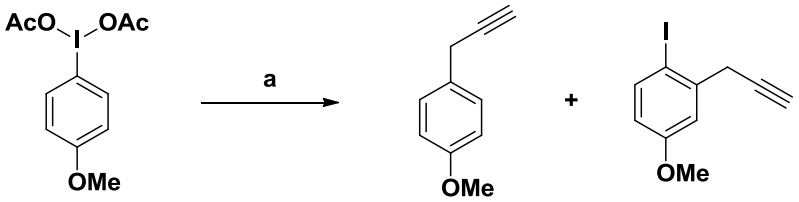
The *ipso*-subsituted product **155** could be formed exclusively over the *meta*-substituted product **156** by the introduction of a methyoxy group at the *para* position on to the phenyl ring **154** (Scheme 73).[58]



Scheme 73: Exclusive formation of *ipso*-substituted product (a) **145**, $BF_3{\cdot}OEt_2$, $MgSO_4$, DCM, –20 °C, 1 h, 67 %

With a *para*-methoxy group present in **158**, the *ipso*-substituted product **159** was formed as the major product even with the *ortho*-positions unsubstituted (Scheme 74, Table 5, Entry 1) as the π-donor methoxy group stabilises the transition state leading to cation **152**. The *ipso*- substituted product is also favoured by solvents with low basicities (according to Taft's β scale of hydrogen-bond acceptor basicities[59]). In the

formation of the *ortho*- product **160**, the rate-determining step is the deprotonation involved in the reductive elimination of acetic acid; while in the formation of the *ipso*- product **159**, the rate-determining step is the [1,2]-rearrangement. Increasing the basicity of the solvent would have an accelerating effect on the former but would show little effect on the latter.[60]



158 **159** **160**

Scheme 74: Solvent effects on *ipso* versus *ortho* selectivity (a) propargyl silane, $BF_3{\cdot}OEt_2$, $MgSO_4$, , –20 °C, 1 h, see Table 5

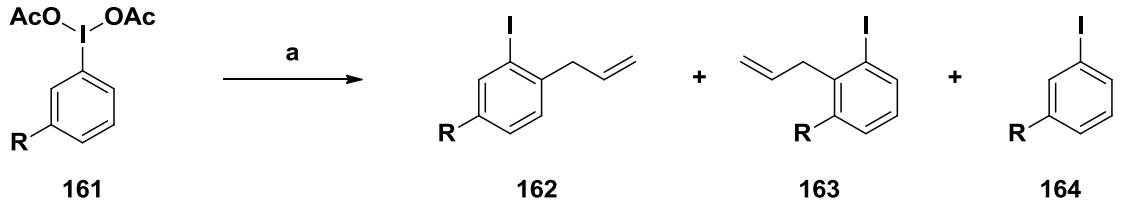
Entry	Solvent	Total Yield	*Ipso*:*ortho* ratio[a]
1	DCM	75	55:45
2	$CHCl_3$	59	53:47
3	hexane	18	47:53
4	benzene	71	46:54
5	CCl_4	54	44:56
6	MeCN	88	42:58
7	Et_2O	80	30:70
8	MeOH	59	20:80

Table 5: Solvent effects on ipso versus ortho selectivity. [(a)]Determined by GC.

Similar studies have since been reported by Norton *et al.*,[61] and the products of the dearomatising iodonio-Claisen rearrangement have been observed as unwanted by-products in a number of cases.[62–64]

In 2012, Zhu *et al*. reported the formation of *ortho*-allyiodoarenes from the reaction of iodosyl benzenes **161** and allyltrimethyl silane (Scheme 75).[65] The authors noted that the formation of iodobenzene **164**, formed by reductive elimination of allyl acetate, competed with the desired reaction. Production of the desired product **162** was favoured when the aromatic ring possessed an electron-donating group at the 3-position of the ring (Table 6, Entry 4), whereas the presence of an electron-withdrawing group meant only

trace amounts of products were isolated (Table 6, Entry 3). The use of lower temperatures (Table 6, Entry 6) and the use of acetonitrile as a co-solvent (Table 6, Entry 5) which presumably stabilises the iodonium(III) species by coordination to the iodine atom thereby suppressing the reductive elimination reaction, also improved the outcome.



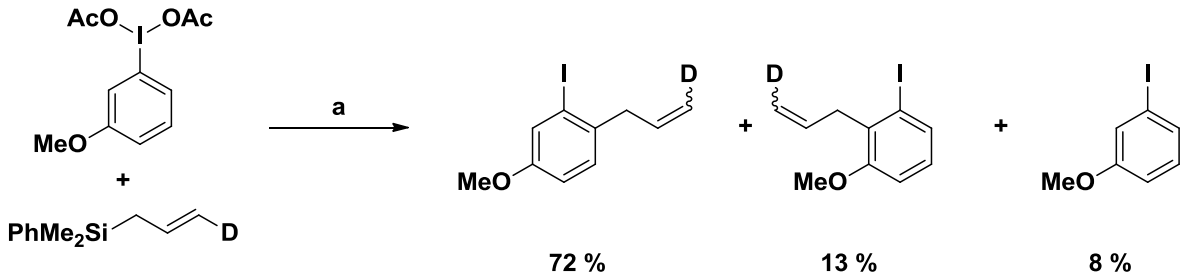
161 **162** **163** **164**

Scheme 75: Formation of allyiodoarenes by an iodonio-Claisen rearrangement (a) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 2 h, see Table 6

Entry	R	Solvent	Temperature	162 : 163 : 164	Overall yield (%)
1	H	DCM	–20 °C	0.1 : 1.0[a]	36
2	Me	DCM	–20 °C	0.3 : 0.2 : 1.0	80
3	CF_3	DCM	–20 °C	-	68
4	OMe	DCM	–20 °C	3.8 : 0.9 : 1.0	trace
5	OMe	MeCN	–20 °C	9.1 : 2.2 : 1.0	84
6	OMe	DCM/MeCN (1:1)	–50 °C	10 : 1.6 : 1.0	86
7	O^iPr	DCM/MeCN (1:1)	–50 °C	8.3 : 1.6 : 1.0	93

Table 6: Optimisation of ortho-allylation conditions. [a]Ratio of **162** : **164**

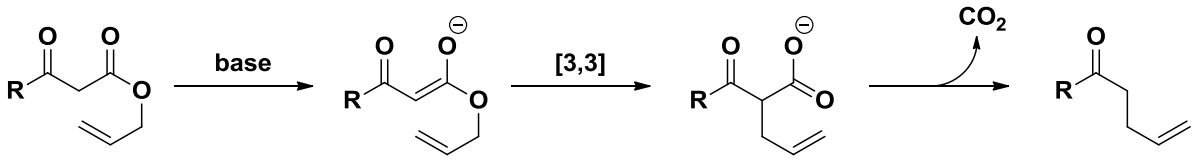
The use of deuterated allyl silanes confirmed the mechanism as a [3,3]-sigmatropic rearrangement, with complete incorporation of the deuterium atom at the terminal position of the alkene (Scheme 76).



Scheme 76: Labelling studies (a) $BF_3{\cdot}OEt_2$, DCM/MeCN (1:1), – 50 °C, 2 h

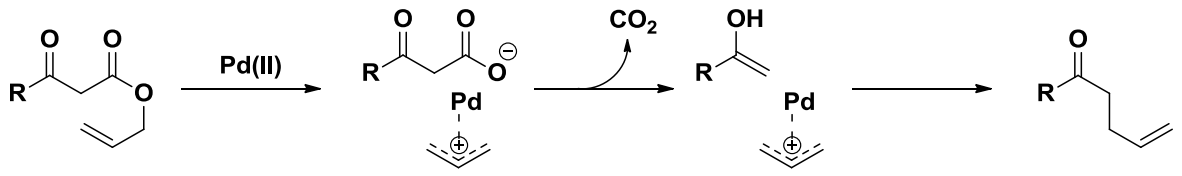
1.9 Dearomatising Carroll rearrangements

The Carroll rearrangement is the reaction of a β-keto allyl ester derived enolate to give a γ,δ-unsaturated ketone (Scheme 77), via a [3,3]-sigmatropic rearrangement and decarboxylation.[66]



Scheme 77: The Carroll rearrangement

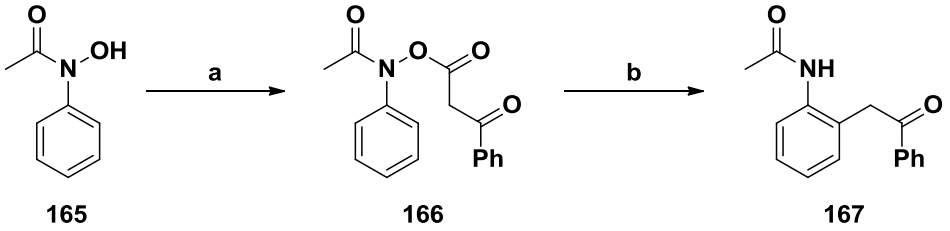
Tsuji has since published a palladium-catalysed variant of the Carroll rearrangement that proceeds via an allyl cation organometallic complex (Scheme 78).[67]



Scheme 78: Palladium catalysed Carroll rearrangement

Only one example of a dearomatising Carroll rearrangement has been published to date.[68] *N*-Hydroxyamide **165** was converted to its *O*-acetoacetyl derivative **166** under standard coupling conditions.

Heating to 110 °C in toluene then caused rearrangement and decarboxylation to give the *ortho*-substituted anilide **167** (Scheme 79).



165 **166** **167**

Scheme 79: Dearomatising Carroll rearrangement (a) benzoylacetic acid, DCC; (b) toluene, 110 °C, 51 % over two steps

2 The decarboxylative Claisen rearrangement (dCr)

2.1 Background

The decarboxylative Claisen rearrangement is a variant on the classical Ireland-Claisen rearrangement developed in 2005 by the Craig group.[69] In this reaction an allylic sulfonyl acetate is treated with a mixture of *N,O*-bis(trimethylsilyl) acetamide and potassium acetate to form a silyl ketene acetal, which undergoes a [3,3]-rearrangement and subsequent desilylation-decarboxylation to give a homoallylic sulfone (Figure 9). The reaction can be carried out with sub-stoichiometric amounts of BSA and KOAc, and microwave irradiation has been shown to accelerate the rate of reaction.

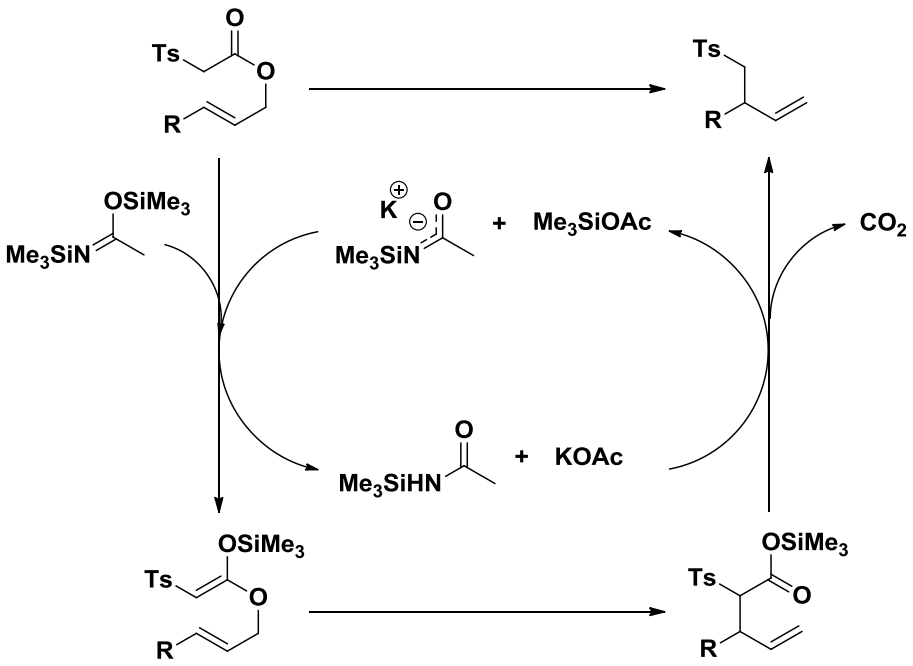
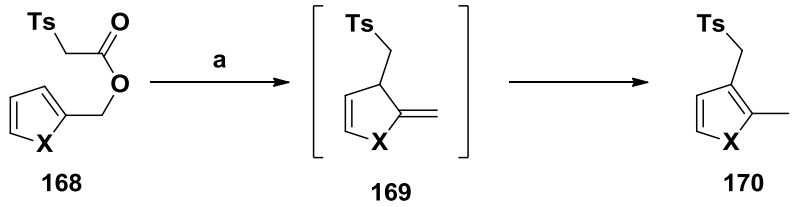


Figure 9: The decarboxylative Claisen rearrangement

When the allylic double bond is incorporated into a heteroaromatic ring, the rearrangement is accompanied by a loss of aromaticity (Scheme 80).[70]

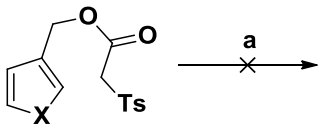


Scheme 80: Dearomatising dCr of five-membered heterocycles (a) BSA, KOAc, PhMe, see Table 7

Entry	X	Yield (%)	
		100 °C, 15 h	μw, 150 °C, 3 min
1	O	63	75
2	S	75	22
3	NTs	67	77

Table 7: Dearomatising dCr reactions of five membered heterocycles

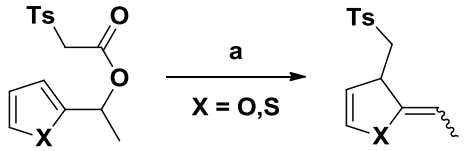
This reaction has been shown to be successful for 2-substituted furans, thiophenes and pyrroles **168** (Table 7), whereas the 3-substituted analogues **171** are inert under the reaction conditions (Scheme 81). This observation can be rationalised in terms of the greater electron density at the 2-position of the heteroaromatic ring, which has a weakening effect on the benzylic C-O bond.



171
X = O or S

Scheme 81: Attempted dCr of furans and thiophenes substituted at the 3-position (a) BSA, KOAc, PhMe, 100 °C, 30 h

When the exocylic double bond was unsubstituted, the dearomatised intermediates **169** tautomerised under the reaction conditions to regenerate the aromatic heterocycle **170** (Scheme 80). However, with esters generated from a secondary alcohol **172**, the dCr reaction gave non-aromatic products **173** that were relatively stable towards re-aromatisation (Scheme 82).[71]



172 **173**

Scheme 82: Isolation of dearomatised product **173** (a) BSA, KOAc, μw, 150 °C, 3 x 1 min

The enhanced stability of **173** relative to **169** can be rationalised by the greater stabilisation of the more highly substituted exocyclic alkene and increased steric buttressing between the 3-tosylmethyl group and the 2-substituent. The resulting bis(enol) ether **173** (X=O) was then reacted with a variety of different electrophiles (Table 8). Ethyl glyoxylate (Table 8, entry 1) and Eschenmoser's salt (Table 8, Entry 2) reacted with **173** cleanly, whereas less reactive aldehydes required activation with $ZnCl_2$ (Table 8, entries 3-8). The use of other Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ resulted in either decomposition, or direct rearomatisation of **173**.

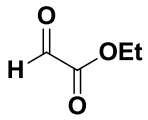
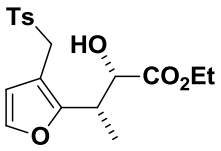
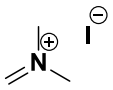
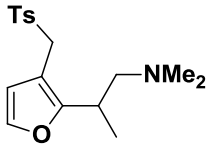
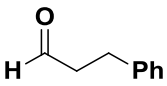
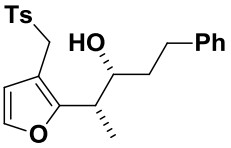
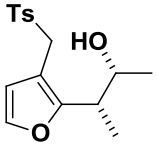
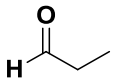
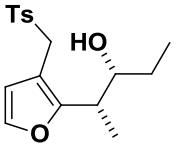
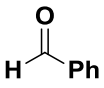
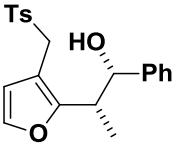
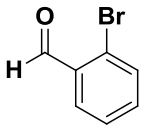
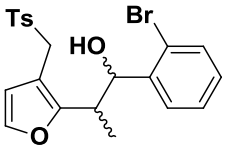
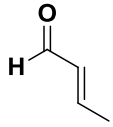
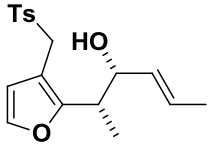
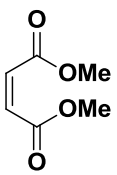
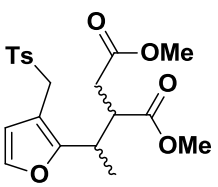
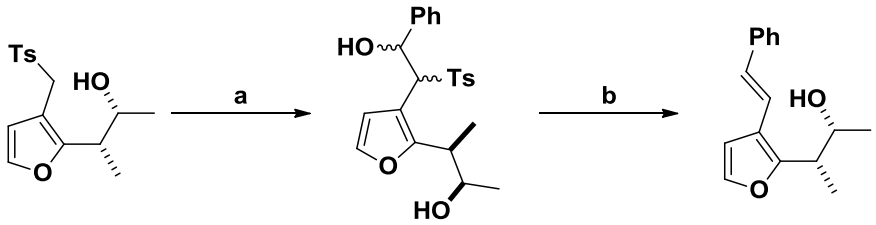
Entry	Electrophile	temp, solvent, additive, time	Product	Yield (%) (*syn*:*anti*)
1		rt, DCM, none, 2 h		91 (10:1)[a]
2		rt, DCM, none, 3 h		66
3		0 °C, DCM, $ZnCl_2$, 1 h		59 (10:1)
4		0 °C, DCM, $ZnCl_2$, 1 h		60 (10:1)
5		0 °C, DCM, $ZnCl_2$, 1 h		62 (10:1)
6		0 °C, DCM, $ZnCl_2$, 1 h		75 (10:1)
7		0 °C, DCM, $ZnCl_2$, 1 h		82 (5:3)
8		0 °C, DCM, $ZnCl_2$, 1 h		58 (5:1)
9		150 °C, *m*-xylene, KOAc, 16 h		73 (5:3)

Table 8: Reaction of bis(enol) ether **173** with electrophiles. [a]Lower selectivity was observed at increased temperatures

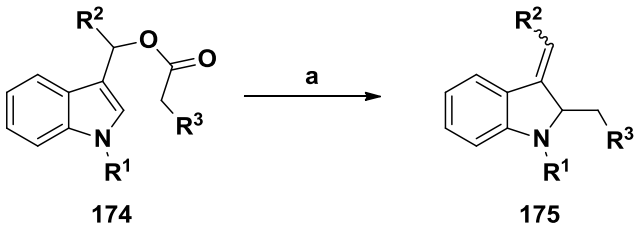
It has been found that carrying out the reaction using pulsed microwave irradiation as opposed to longer, continuous heating gives a higher yield of isolated product.[72] This pattern has also been observed in other examples of the Claisen rearrangement.[73]

It also proved possible to use the tosyl methylene group as a functional handle at the 3-position of the furan, an example of which is shown in Scheme 83. Functionalising the 3-position of a furan can often be difficult by standard methods, as in many cases the ring preferentially undergoes lithiation reactions and reacts with nucleophiles at the 2- and 5- positions.



Scheme 83: Further functionalisation reactions (a) n-BuLi, THF, –78 °C, 10 min then PhCHO, –78 °C, 1 h, 81 %; (b) Na(Hg), Na_2HPO_4, MeOH, rt, 1.5 h, 21 %

Compounds containing an indole also react under dCr conditions (Scheme 84 and Table 9).[74] In comparison to the furan and thiophene examples the dearomatised product **175** was isolated even for esters derived from primary alcohols (Table 9, entries 1-3).



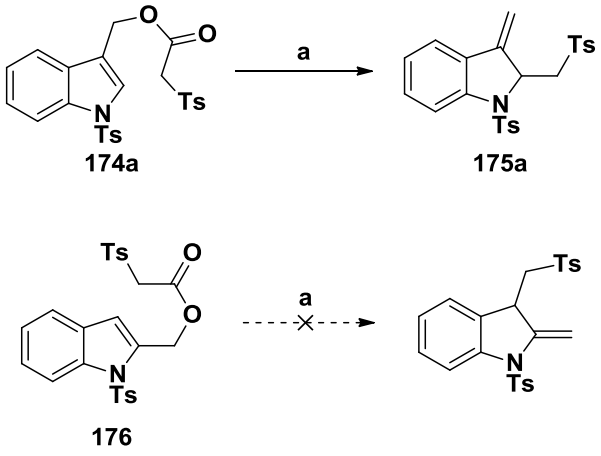
174 **175**

Scheme 84: dCr reaction of indoles **174** (a) BSA, KOAcm PhMe, µw, 150 °C, see Table 9

Entry	R^1	R^2	R^3	time[a]	yield (%)
1	Ts	H	Ts	5 x 1 min	32
2	Boc	H	Ts	4 x 1 min	68
3	Boc	H	CN	4 x 1 min	70
4	Boc	H	CO_2Et	4 x 1 min	22[b]
5	Boc	Me	Ts	4 x 1 min	87[c]
6	Boc	Me	CN	5 x 1 min	82[c]
7	Boc	Me	CO_2Et	4 x 1 min	53[c]

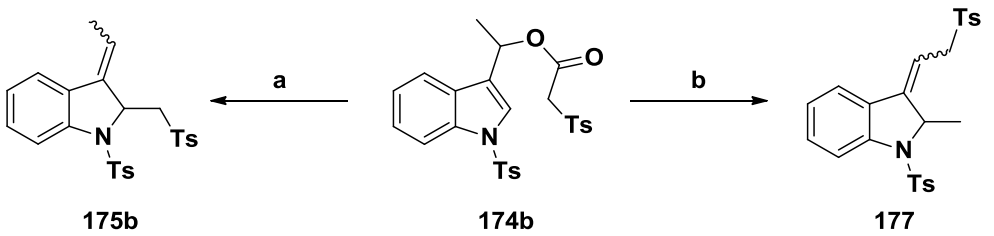
Table 9: dCr reaction of indoles. [a]1 min air assisted cooling between heating cycle. [b]Exposure to silica gel resulted in re-aroamtisation to the tautomeric indole. [c]Product obtained as a mixture of geometric isomers

In an analogous manner to furans and thiophenes, only the 3-substituted indoles **174** react under these conditions (Scheme 85) due to the increased electron density at the C3 position relative to the C2 position of the indole.



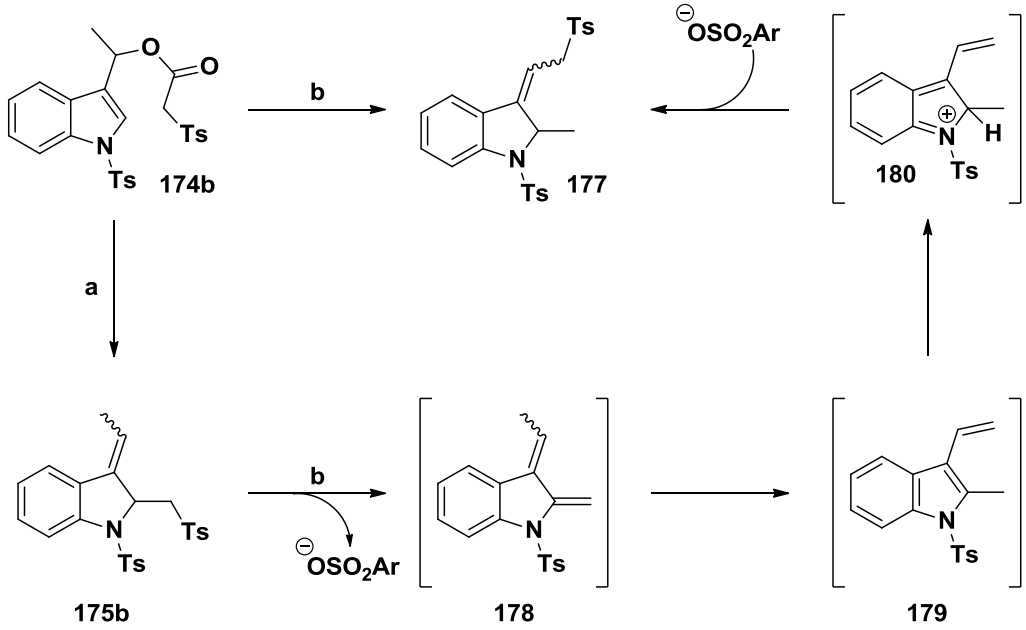
Scheme 85: Attempted dCr of indoles substituted at the 3-position (a) BSA, KOAc, PhMe, 110 °C, 18 h

An interesting example was observed for the reaction of **174b** under dCr conditions (Scheme 86). Using conventional heating the expected product **175b** was observed, however under microwave irradiation at a higher temperature, the isomeric product **177** was observed.



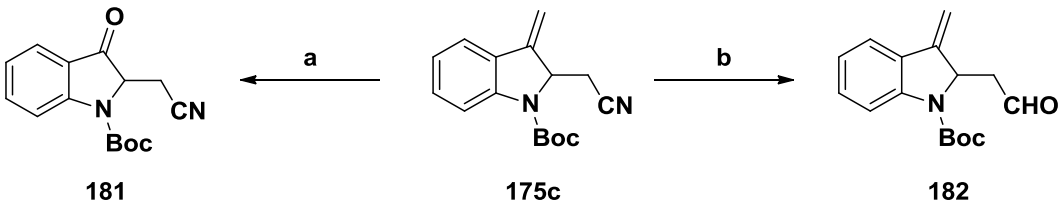
Scheme 86: Formation of isomeric products (a) BSA, KOAc, PhMe, 110 °C, 18 h, 60 %; (b) BSA, KOAc, PhMe, µw, 150 °C, 4 x 1 min, 60 %

It was reasoned that **177** was formed from **175b** by elimination of tosylsulfinic acid to give **178**; re-aromatisation to give **179**; followed by protonation at the C2 position and interception of the resulting cation **180** by a tosylsulfinate anion (Scheme 87). Support for this mechanism came from the observation that subjection of **175b** to the microwave reaction conditions also led to the formation of **177**.



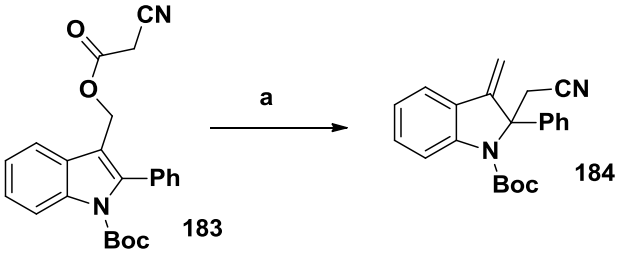
Scheme 87: Proposed mechanism for the formation of isomeric products (a) BSA, KOAc, PhMe, 110 °C, 18 h; (b) BSA, KOAc, PhMe, µw, 150 °C, 4 x 1 min,

Again, the exocyclic double bond and the cyano methyl group can be used as handles for further functionalisation (Scheme 88).



Scheme 88: Further functionalisation reactions (a) O_3/O_2, DCM, –78 °C, 15 min, then Me_2S, rt, 16 h, 40 %; (b) DIBAL-H, PhMe, –78 °C to rt, 2 days, 59 %

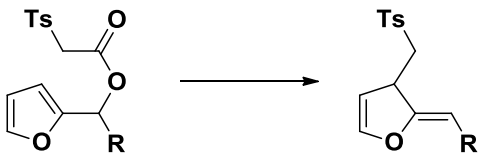
It was also shown to be possible for more sterically congested indoles to undergo dCr reaction (Scheme 89). Indole **183** gave indoline **184**, containing a C2 quaternary centre under the reaction conditions.



Scheme 89: Formation of a quaternary centre (a) BSA, KOAc, PhMe, µw, 150 °C, 4 x 1 min, 56 %

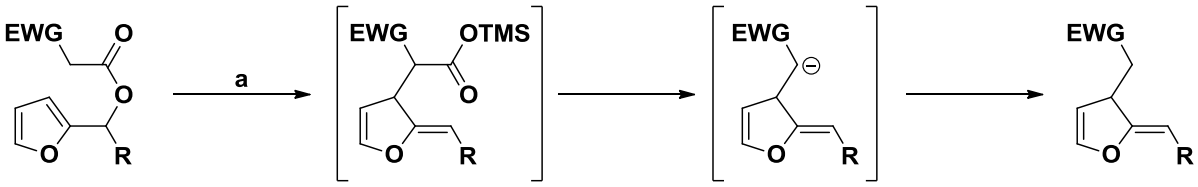
2.2 Project aims and objectives

The aim of the first part of this project was be to investigate the dCr reaction of furans, starting by looking at the effect that changing the substituent at the benzylic position (R in Scheme 90) has on the rearrangement. To date, the only examples have been those derived from 2-acetyl furan (R = Me).



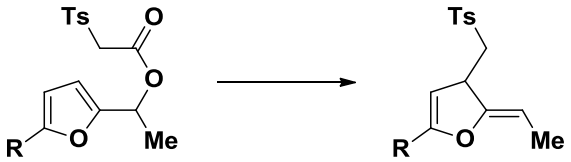
Scheme 90: Varying the alkyl group at the benzylic position

For the reaction to be successful, the ester must contain an electron-withdrawing group in order to stabilise the intermediate anion formed by the desilylation-decarboxylation step (Scheme 91). Using furans as a heteroaromatic core, only the use of esters derived from tosylacetic acid have previously been investigated, so it was decided to study the use of other activating groups.



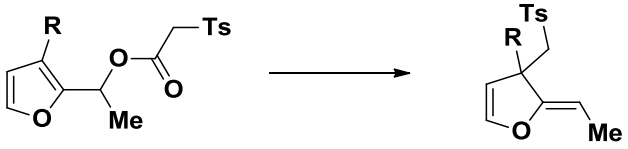
Scheme 91: Varying the electron-withdrawing group

It was considered worthwhile to study also the effect of further substitution of the furan ring at the 5-position, where it would not have a direct effect on the rearrangement, but would alter the electron density of the furan.



Scheme 92: Furans substituted at the 5-position

Finally, the possibility of introducing an alkyl group at the 3-position was considered worthy of study: dCr reaction would give a product containing a quaternary carbon centre with no possibility of re-aromatisation due to the additional C3 substituent.

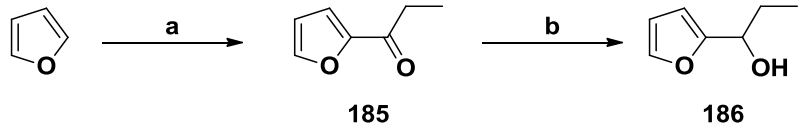


Scheme 93: Furans possessing an alkyl group at the 3-position

2.3 The decarboxylative Claisen rearrangement of furans

2.3.1 – Varying the alkyl group at the benzylic position

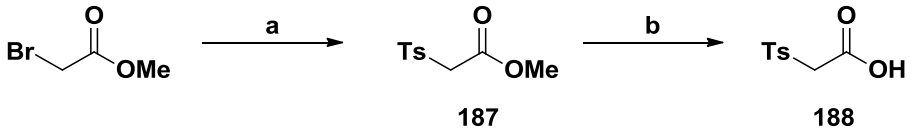
Ketone **185** was synthesised via the method of O'Doherty *et al.*,[75] whereby an excess of 2-lithio furan was added to a solution of propionic acid in THF. This was then reduced to alcohol **186** with sodium borohydride (Scheme 94).



185 186

Scheme 94: Synthesis of alcohol **186** (a) ^{n}BuLi, rt, 3 h then propionic acid, THF, rt, 2.5 h, 70 %; (b) $NaBH_4$, MeOH, rt, 1 h, 76 %

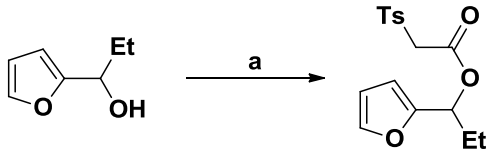
Tosylacetic acid (**188**) was generated by S_N2 reaction of a sulfinate anion with methyl bromoacetate and subsequent ester hydrolysis (Scheme 95).



187 188

Scheme 95: Synthesis of tosylacetic acid (a) sodium p-toluene sulfinate, DMF, rt, 24 h, 91 %; (b) LiOH, THF/H_2O, rt, 48 h, 86 %

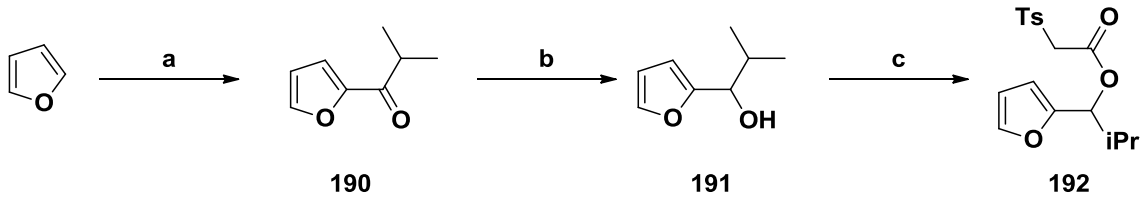
Formation of the ester bond using diisopropyl carbodiimide as a coupling agent gave the desired compound **189** for a dCr reaction (Scheme 96).



186 189

Scheme 96: Synthesis of ester **189** (a) tosylacetic acid, DIC, DMAP, DCM, rt, 43 h, 70 %

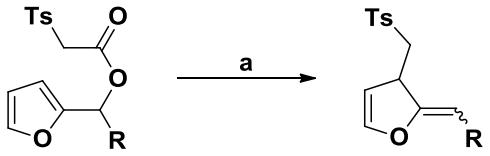
The isopropyl analogue **192** was synthesised in the same manner starting from isobutyric acid (Scheme 97).



190 **191** **192**

Scheme 97: Synthesis of ester **192** (a) ^{n}BuLi, rt, 3 h then isobutyric acid, THF, rt, 18 h, 59 %; (b) $NaBH_4$, MeOH, rt, 3 h, 92 %; (c) tosylacetic acid, DIC, DMAP, DCM, rt, 48 h, 84 %

Esters **189** and **192** were then subjected to the standard dCr condition previously optimised within the group. The reaction proceeded smoothly in each case to give the dearomatised furan products **193** and **194** respectively (Scheme 98, Table 10) which are relatively stable as long as they are not placed in an acidic environment. Partial re-aromatisation was observed when $MgSO_4$ was used as a drying agent during work-up, although this can be avoided by the use of Na_2SO_4 instead. It was found necessary also to add at least 1 % Et_3N to the eluent used for silica gel chromatography. In order to record a ^{13}C NMR spectrum in $CDCl_3$, it was found to be necessary to filter the deuterated solvent through a plug of basic alumina to minimise re-aromatisation, which typically occurred if samples were left overnight in untreated chloroform.



R = Et 193
R = ^{i}Pr 194

Scheme 98: dCr of esters **189** and **192** (a) BSA, KOAc, 150 °C, µw, 3 x 1 min, see Table 10

Entry	R	Yield (%)	dr
1	Et	67	10:1
2	^{i}Pr	80	13:1

Table 10: dCr of esters **189** and **192**

The major isomer was assigned as the *Z*-isomer by comparison with previous work.[71] Although the ethyl-substituted ester **189** (Table 1, entry 1) gave the same diastereomeric ratio as the methyl version previously reported, the reaction of the *iso*-propyl variant **192** showed increased selectivity. This can be explained by examining the proposed transition states given in Figure 10. Thus, the transition state leading to the *Z*- isomer places the alkyl substituent at an equatorial position of the chair, whereas the transition

state leading to the *E*- isomer places the alkyl group axial. This means that the larger the substituent, the greater the preference for the Z-isomer.

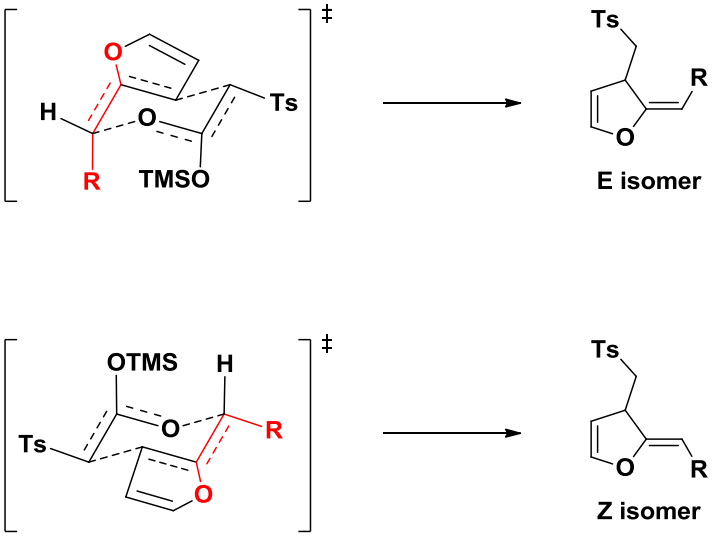
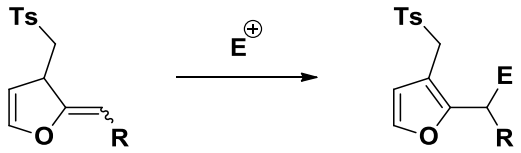


Figure 10: Transition states leading to E- and Z- isomers

The bis(enol)ethers were then reacted with a range of electrophiles (Table 11). As shown previously for the methyl variant, activated electrophiles such as Eschenmoser's salt (Table 11, entry 1) reacted readily without the need for a Lewis acid. Methyl vinyl ketone would not react with bis(enol) ether **193** at room temperature without the presence of two equivalents of zinc (II) chloride (Table 11, entry 2). Although the yield for this reaction was low, there was no evidence for formation of the 1,2-addition product. Combination of **193** with acetyl chloride gave only the re-aromatised product **197** (Table 11 entry 3), even though the acid chloride had been distilled from quinoline immediately prior to use. Oxidation of the double bond with *meta*-chloroperbenzoic acid (Table 11, entry 4) gave alcohol **198**. Reaction with I_2 again gave just the rearomatised product **125** (Table 11, entry 5) presumably due to the presence of small amounts of HI.



Scheme 99: Reaction of bis(enol)ethers **193** (R = Et) and **194** (R = ^{i}Pr)with electrophiles.

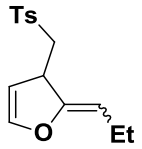
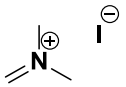
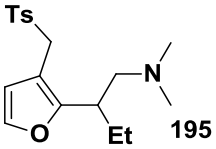
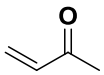
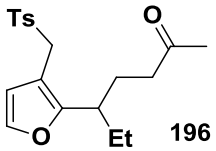
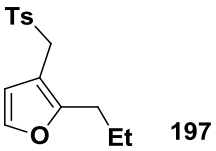
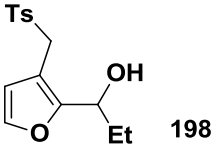
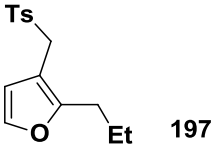
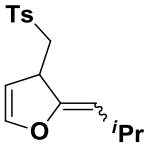
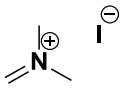
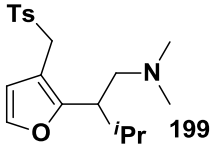
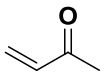
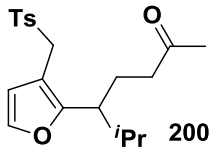
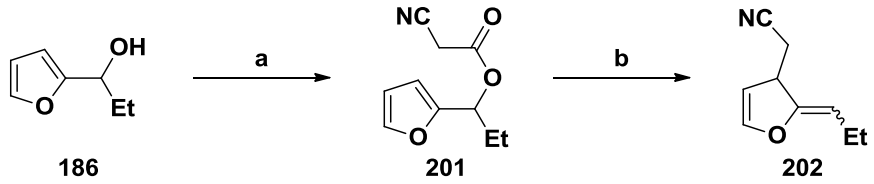
Entry	Nucleophile	Electrophile	Additive	Product	Yield (%)
1			-	 **195**	68
2			$ZnCl_2$	 **196**	35
3			-	 **197**	90
4		mCPBA	-	 **198**	43
5		I_2	-	 **197**	64
6			-	 **199**	91
7			$ZnCl_2$	 **200**	41

Table 11: Reaction of bis(enol)ethers **193** and **194** with electrophiles. All reactions carried out in DCM at rt.

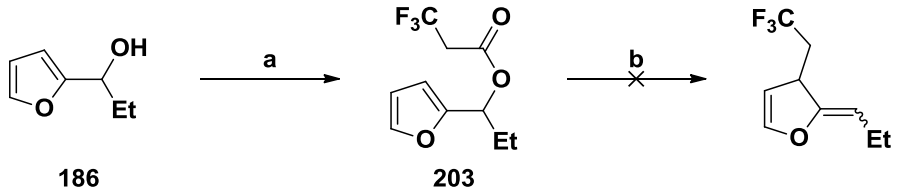
2.3.2 – Varying the electron-withdrawing group

Next, the dCr reaction was attempted using other activating groups. The reaction of alcohol **186** with cyanoacetic acid proceeded smoothly, and the dCr reaction of the resulting ester **201** gave bis(enol)ether **202**, again in a 10:1 dr (Scheme 100).



Scheme 100: Synthesis of bis(enol)ether **202** (a) cyanoacetic acid, DIC, DMAP, DCM, rt, 26 h, 80 %; (b) BSA, KOAc, 150 °C, µw, 3 x 1 min, 41 %

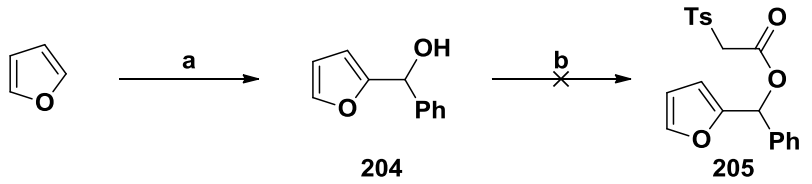
Synthesis of the trifluoromethyl containing analogue **203** was carried out by the same method, however the dCr reaction did not give the expected product (Scheme 101). Although analysis by ^{1}H and ^{13}C NMR, using both 1D and 2D techniques, showed that the 2-substituted furan ring and benzylic ethyl group were still intact, it was clear that the trifluoromethyl group had been lost, as there were no signals in the ^{19}F NMR or distinctive coupling patterns in the ^{13}C NMR. It also appeared that acetamide functionality from the BSA had been incorporated in some fashion, as evidenced by the ^{1}H NMR showing two broad singlet 1H peaks at δ_H = 11.82 and 11.61 ppm and two singlet 3H peaks at δ_H = 2.21 and 2.17 ppm.



Scheme 101: Attempted dCr of trifluoromethyl containing analogue **203** (a) trifluoropropionic acid, T_3P®, Et_3N, DCM, rt, 5 h, 85 %; (b) BSA, KOAc, 150 °C, µw, 3 x 1 min

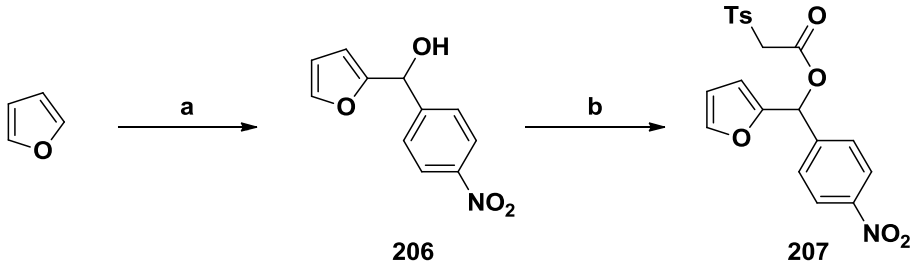
2.3.3 – Furans with an aryl substituent at the benzylic position

It was then decided to investigate furans possessing aryl substitution at the benzylic position. Reaction of 2-lithio furan with benzaldehyde gave alcohol **204** (Scheme 102). Attempts to esterify with tosylacetic acid under both DIC and T_3P® coupling conditions did not prove successful however. It is assumed that the instability of the doubly benzylic ester with respect to hydrolysis is responsible for the decomposition observed.



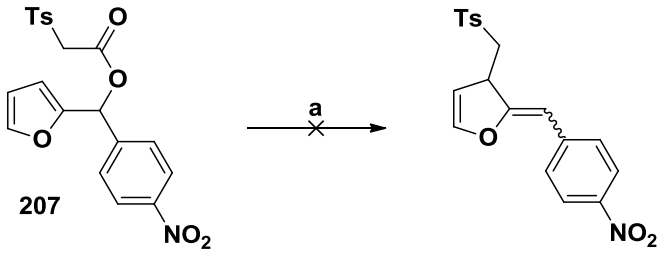
Scheme 102: Attempted synthesis of ester **205** (a) $^{n-}$BuLi, THF, 0 °C, 30 min, then benzaldehyde, rt, 16 h, 58 %; (b)tosylacetic acid, DIC, DMAP, DCM, rt

It was hoped that this problem could be circumvented by introducing an electron-withdrawing group onto the aromatic ring, thereby decreasing the likelihood of an $A_{AL}1$ mechanism. Accordingly ester **207** was synthesised in good yield via the same method as before (Scheme 103).



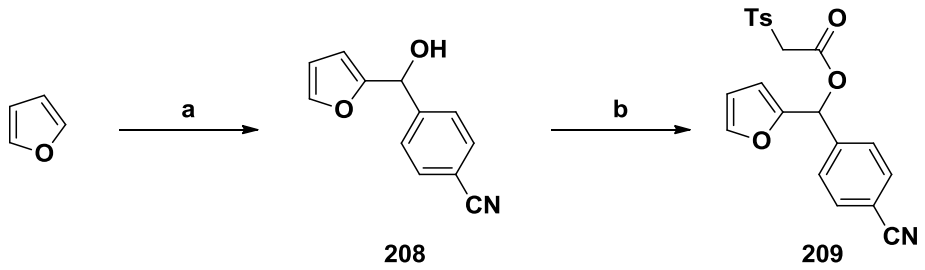
Scheme 103: Synthesis of ester **207** containing an electron deficient aromatic ring (a) $^{n-}$BuLi, THF, 0 °C, 30 min, then *p*-nitrobenzaldehyde, rt, 1.5 h, 69 %; (b), tosylacetic acid DIC, DMAP, DCM, rt, 48 h, 88 %

Unfortunately, when **207** was subjected to dCr conditions, only decomposition was observed (Scheme 104).



Scheme 104: Attempted dCr of ester **207** (a) BSA, KOAc, 150 °C, µw

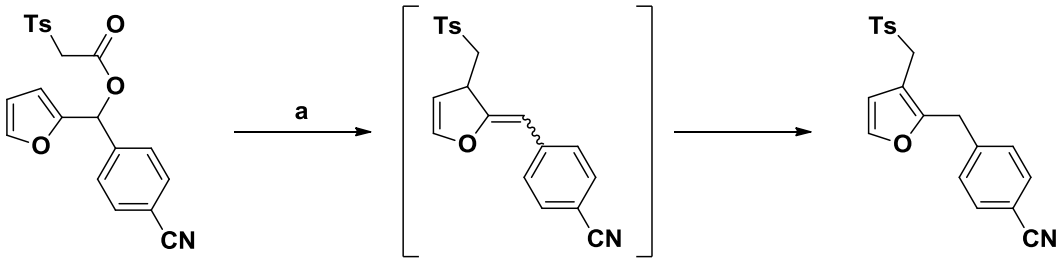
Ester **209**, possessing a nitrile group in place of the nitro was then synthesised in the same manner (Scheme 105).



208 209

Scheme 105: Synthesis of ester **209** (a) $^{n-}$BuLi, THF, 0 °C, 30 min, then *p*-cyanobenzaldehyde, rt, 16 h, 68 %; (b) tosylacetic acid, T_3P, Et_3N, rt, 18 h, 58 %

When **209** was subjected to standard dCr conditions, rearrangement occurred, but only the re-aromatised product **211** was isolated (Scheme 106). ^{1}H NMR analysis of the crude product showed no indication of **210**, indicating that this re-aromatisation happened during the reaction and work-up process, and not during silica gel chromatography. It is assumed that this occurs as a result of the increased acidity of the proton at the 3-position of the furan ring, due to the presence of the electron poor aromatic system.

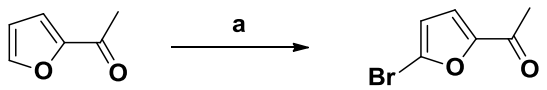


209 210 211

Scheme 106: dCr of ester **209** (a) BSA, KOAc, 150 °C, µw, 3 x 1 min, 60 %

2.3.4 – Furans substituted at the 5-position

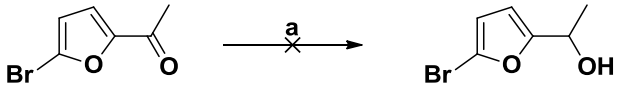
It was then decided to examine the effect of changing the electron density of the furan ring system in the dCr reaction. To achieve this, 2-acetyl furan was brominated at the 5- position (Scheme 107) with a view to later introducing aromatic rings of differing electron densities *via* cross coupling reactions.



212

Scheme 107: Bromination of 2-acetyl furan (a) NBS, DMF, rt 108 h, 40 %

It was hoped to be able to reduce the ketone before the introduction of the aromatic ring as this would allow a later stage diversification. Unfortunately however, reduction conditions lead to decomposition of the starting material (Scheme 108, Table 12).



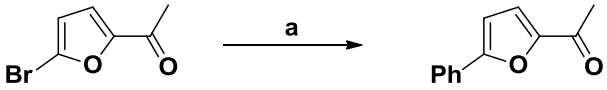
212

Scheme 108: Attempted reduction of ketone **212** (a) see Table 12

Entry	Reductant	Solvent	Temperature	Time	Result
1	$NaBH_4$	MeOH	rt	4 h	decomposition
2	DIBAL	THF	0 °C	3 h	decomposition

Table 12: Attempted reduction of ketone **212**

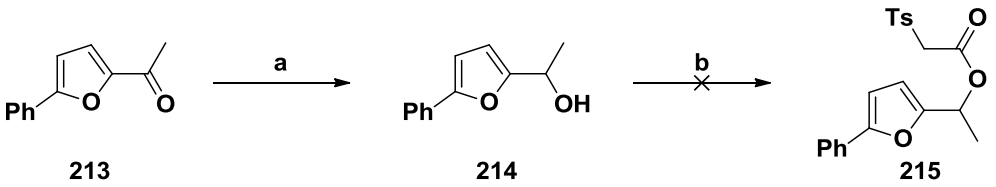
As a result of this a phenyl group was introduced at the 5-position under Suzuki conditions using tetrakis(triphenylphosphine)palladium(0) as a catalyst (Scheme 109).



212 **213**

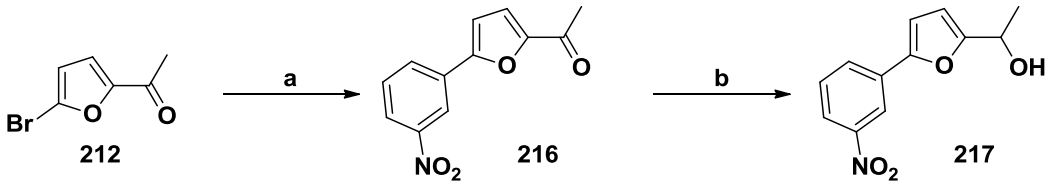
Scheme 109: Suzuki coupling (a) $PhB(OH)_2$, $Pd(PPh_3)_2$, Na_2CO_3, $PhMe/H_2O$, 80 °C, 20 h, 92 %

Although the ketone functionality could be reduced with sodium borohydride, attempts to esterify the resulting alcohol **214** again resulted only in decomposition (Scheme 110). It is assumed that the extended π-system increased the susceptibility of ester **215** to hydrolysis via an $A_{AL}1$ pathway.



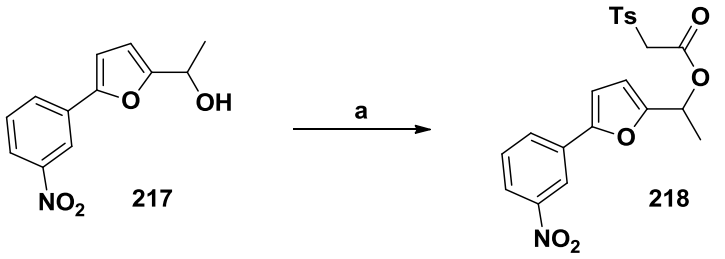
Scheme 110: Attempted synthesis of ester **215** (a) $NaBH_4$, MeOH, rt, 15 min, 78 %; (b) tosylacetic acid DIC, DMAP, DCM, rt, 48 h

Suzuki reaction of 3-nitrophenylboronic acid with bromofuran **212** under the same conditions gave no reaction even after heating at 80 °C for 76 h. However, changing the catalyst system to $Pd(OAc)_2$ and PPh_3, allowed synthesis of ketone **216** in a good yield, which was then reduced with sodium borohydride to give alcohol **217** (Scheme 111).



Scheme 111: Synthesis of alcohol **217** (a) 3-nitrophenylboronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, $PhMe/H_2O$, 80 °C, 18 h, 87 %; (b) $NaBH_4$, MeOH, rt, 3 h, 64 %

Esterification of **217** proved to be a very sluggish reaction (Scheme 112, Table 13). Under Mitsunobu conditions (Table 13 entry 1) the reaction was incomplete even after five days at room temperature. Use of DIC as a coupling agent enabled the synthesis of ester **218** in good yield after prolonged reaction times (Table 13, entry 2).

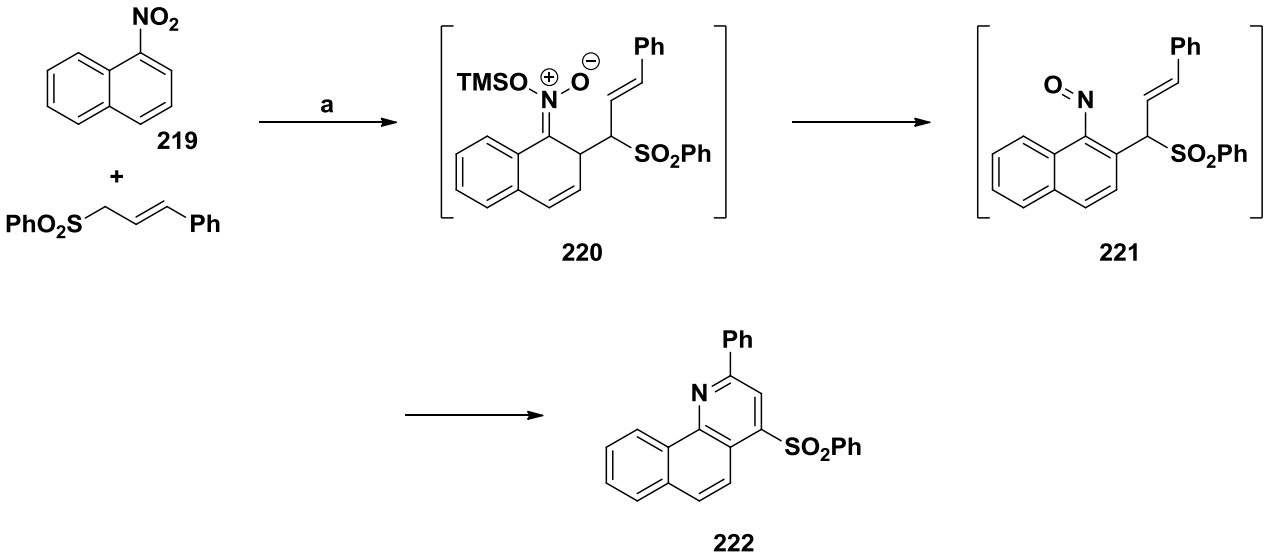


Scheme 112: Esterification of alcohol **217** (a) See Table 13

Entry	Reagents	Solvent	Time	Conversion[a]	Isolated yield
1	DIAD, PPh_3	DCM	5 days	18 %	-
2	DIC, DMAP	DCM	4 days	100 %	89 %

Table 13: Esterification of alcohol **217** with tosylacetic acid. All reactions at rt. [a]Ratio of product:SM by ^{1}H NMR analysis of the crude reaction mixture

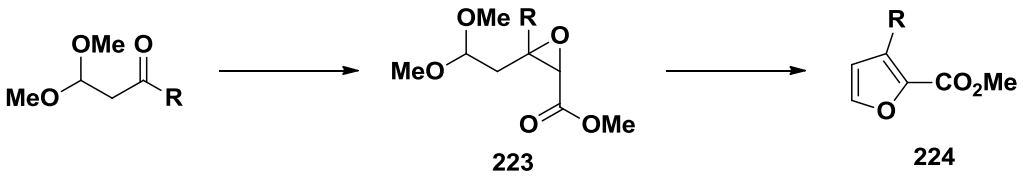
Subjection of ester **218** to dCr conditions again lead to decomposition. Combined with the fact that ester **207** had also decomposed under the reaction conditions, it was hypothesised that aryl nitro groups are not compatible with the dCr. This is presumably due to the fact that BSA is sufficiently electrophilic to silylate the nitro group. Various examples of this reactivity have been reported, with the most relevant by Wróbel in 1998, whereby BSA activates nitroarene **219** to nucleophilic attack by a sulfone anion (Scheme 113).[76] This intermediate **220** then loses trimethylsilanol to give nitroso intermediate **221** which undergoes intramolecular condensation to yield quinoline **222**.



Scheme 113: Silylation of an aromatic nitro group by BSA (a) BSA, DBU, MeCN, 24 h, 82 %

2.3.5 Furans posessing an alkyl group at the 3-position

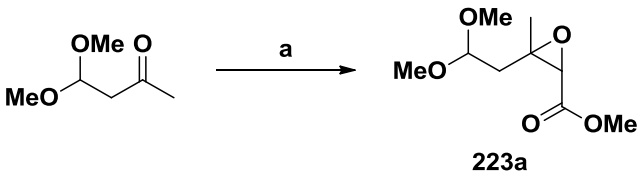
Initial attempts to synthesise a furan ring possessing a substituent at the 3-position focused on a 1956 paper from Burness.[77] This method involved the synthesis of epoxide **223** via a Darzens reaction and subsequent thermal rearrangement to furan **224**.



Scheme 114: Synthesis of 3-alkyl furans reported by Burness

Attempts at the Darzen's reaction gave a mixture of products. Neither purification by distillation nor silica gel chromatography were attempted as it was envisioned that both of these processes could cause

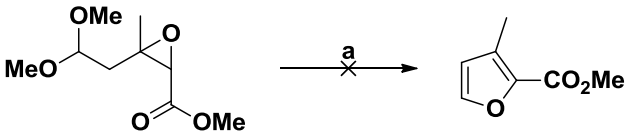
rearrangement of the epoxide. Evidence for the formation of the desired compound **223a** as part of the mixture came from the presence of a peak at δ_H = 3.59 ppm in the ^{1}H NMR corresponding to the epoxide proton. This peak integrated correctly for 1H relative to the 6H peak at δ_H = 3.15 ppm corresponding to the two methoxy groups. Unfortunately no NMR data for this compound has been published to make a comparison.



223a

Scheme 115: Synthesis of epoxide **223a** *via* a Darzen's reaction (a) methylchloroacetate, NaOMe, Et_2O, rt, 16 h

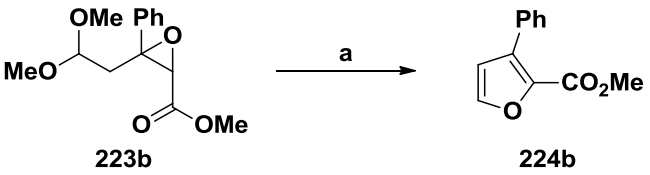
Epoxide **223a** was then heated at 160 °C according to the procedure described in the original paper. No formation of methanol was observed, although as the reaction was only carried out at a 4.1 mmol scale, the volume evolved would have been very low. ^{1}H NMR analysis of the crude reaction mixture showed no evidence of aromatic protons.



223a **224a**

Scheme 116: Attempted synthesis of furan **224a** under thermal conditions (a) 160 °C, 8 h

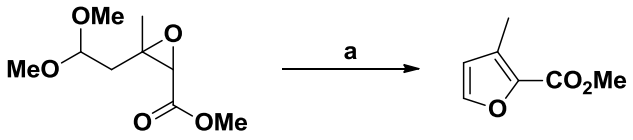
When Burness attempted to synthesise the 3-phenyl analogue **224b** via the same route, it was discovered that the presence of an acid catalyst (*p*-TSA) and an increased reaction temperature of 250 °C were required (Scheme 117). As a result of this experimental observation, Burness reasoned that the rearrangement of the methyl variant was actually catalysed by free hydrogen chloride arising from the presence of a chlorine-containing compound as an impurity. This hypothesis was supported by the fact that a Belstein test of epoxide **223a** was positive.



223b 224b

Scheme 117: Burness' synthesis of 3-phenyl analogue **224b** (a) p-TSA (5 mol %), 250 °C, 42 %

As a consequence of these results, it was decided to attempt the rearrangement of the epoxide with a variety of acid catalysts (Scheme 118, Table 14).



223a 224a

Scheme 118: Attempted synthesis of furan **224a** with acid catalysts (a) see Table 14

Entry	Acid	Equivalents	Temperature	Time	Yield
1	*p*-TSA	0.15	100 °C	1.5 h	trace[a]
2	*p*-TSA	0.15	rt	1.5 h	0 %[a]
3	*p*-TSA	0.15	rt	78 h	trace[a]
4	CSA	0.15	80 °C	8 h	trace[a]
5	*p*-TSA	0.15	100 °C (μw)	45 min	trace[a]
6	$BF_3{\cdot}OEt_2$	0.15	rt	72 h	0 %[a]
7	$Cu(OTf)_2$	0.15	rt	24 h	0 %[a]
8	NH_4Cl	0.10	rt	78 h	0 %

Table 14: Rearrangement of epoxide **223a** with acid catalysts. All reactions carried out in toluene. [a]Extensive decomposition observed

In most cases this lead to decomposition of the starting material with a black-tarry substance being formed. The only exception was that of NH_4Cl (Table 14, entry 8) where no reaction was observed. In certain cases

a trace amount (> 1 %) of the desired furan was isolated (Figure 11). However the extremely low yield and difficulty separating it from the crude meant this route was abandoned.

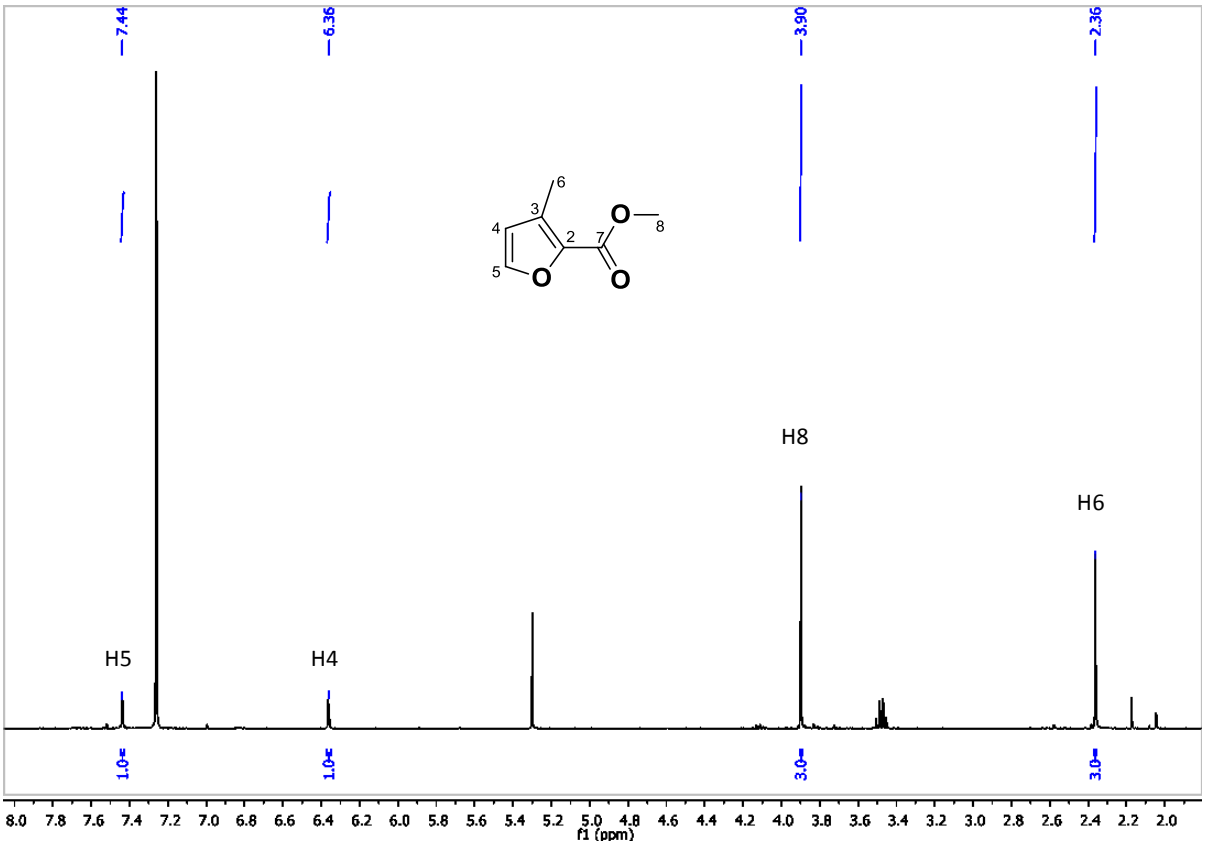
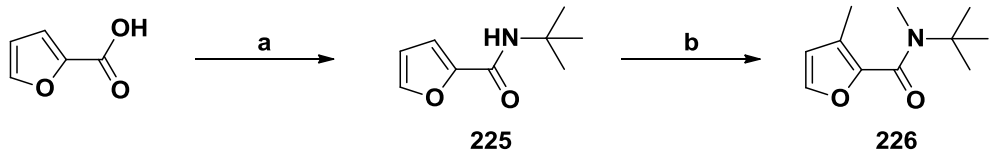


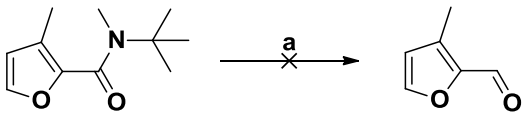
Figure 11: ^{1}H NMR of product isolated from rearrangement reaction

An alternative route for the synthesis of 3-methyl furans is the introduction of the methyl group *via* a directed lithiation. Therefore amide **226** was synthesised from 2-furoic acid according to the method of Chadwick *et al.*[78]



Scheme 119: Synthesis of 3-substituted furan **226** (a) ^{t}butylamine, DIC, DMAP, DCM, rt, 2 h, 40 %; (b) ^{s}BuLi, DME, –78 °C, 1 h then MeI, rt, 16 h, 79 %

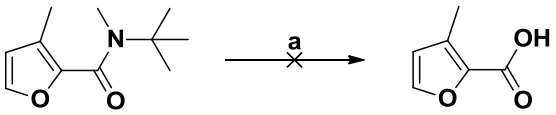
It was hoped that amide **226** could be selectively reduced to aldehyde **227**, which in a separate step could be further reduced to the alcohol required for the synthetic sequence. Unfortunately, the reaction of amide **226** with the ATE complex formed by addition of ^{n}butyl lithium to DIBAL proved unsuccessful and returned only starting material (Scheme 120).



226 **227**

Scheme 120: Attempted reduction of amide **226** to aldehyde **227** (a) DIBAL, ^{n}BuLi, THF, 0 °C, 30 min; then **226**, rt for 22h, 50 °C for 28 h

Due to the failure of this reaction, hydrolysis of amide **226** was examined (Scheme 121). This would give acid **228** which could again be reduced to the required alcohol. Unfortunately, under acidic conditions (Table 15, entries 1 and 2) decomposition was observed and under basic conditions there was no reaction (Table 15, entries 3 and 4).



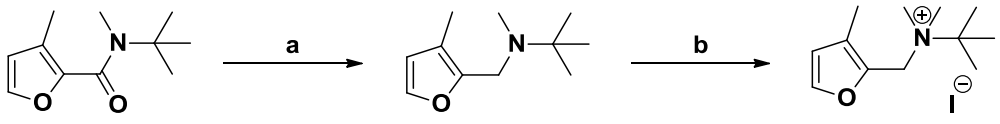
226 **228**

Scheme 121: Attempted hydrolysis of amide **226** (a) See Table 15

Entry	Reagent and solvent	Temperature	Time	Result
1	10 % $H_2SO_{4\,(aq)}$	reflux	21 h	decomposition
2	2M $HCl_{(aq)}$	rt	45 min	decomposition
3	2M $LiOH_{(aq)}$ / THF	rt	120 h	SM
4	2M $LiOH_{(aq)}$ / THF	50 °C	120 h	SM

Table 15: Conditions for attempted hydrolysis of amide **226**

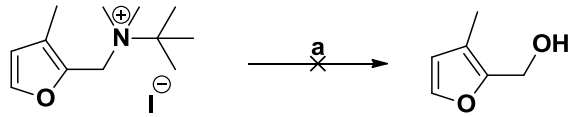
It was then decided to reduce the amide directly to the amine **229**, which was then alkylated with methyl iodide to give quaternary ammonium salt **230** (Scheme 122).



226 **229** **230**

Scheme 122: Reduction of amide **226** to amine **229** (a) DIBAL, THF, reflux, 3 h, 96 %; (b) MeI, rt, 24 h, 88%

Unfortunately attempts to displace the ammonium functionality with hydroxide failed (Scheme 123, Table 16). In each case ^{1}H NMR analysis of the crude product showed that the starting material had been completely consumed and the presence of compounds containing a 2,3-disubstituted furan ring. However the yields of crude material were always very low (less than 15 % by mass) and no products corresponding to the desired alcohol could be isolated.



230

Scheme 123: Attempted hydrolysis of quaternary ammonium salt **230** (a) see Table 16

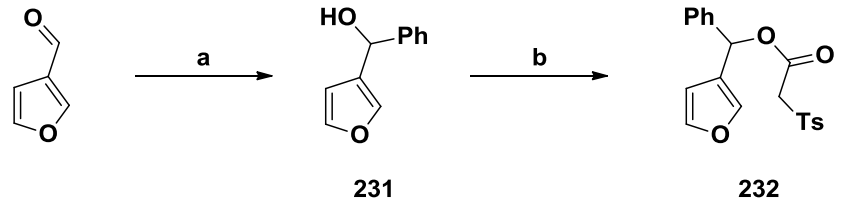
Entry	Reagents/solvent	Time
1	H_2O/MeCN	16 h
2	H_2O/DMF	69 h
3	KOH/ H_2O	24 h

Table 16: Attempted hydrolysis of quaternary ammonium salt **230**

2.3.6 – Furans with an ester functionality at the 3-position

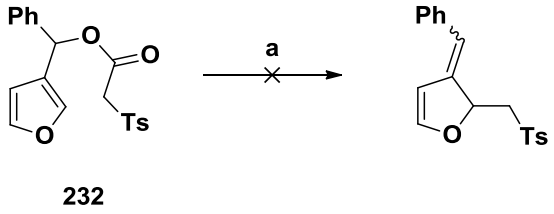
Previous work within the group had shown the 3-substituted furans of the form **171** would not undergo rearrangement in the same manner as 2-substituted furans. This is due to the intrinsic electronic properties of the furan ring, whereby the lower electron density at the 3- position is insufficient to weaken the benzylic C-O bond enough for rearrangement to occur.

In section 2.2.3, the instability of esters derived from furan-2-yl(phenyl)methanol was discussed; it was postulated that this was due to the weakness of the doubly benzylic C-O bond. It was hoped that this reactivity could be used to increase the chance of successful dCr reactions of 3-substituted furans. Ester **232** was synthesised from 3-furancarboxaldehyde in two steps (Scheme 124), and proved to be stable enough to isolate and characterise.



Scheme 124: Synthesis of ester **232** (a) PhMgBr, THF, rt, 2.5 h, 95 %; (b) toslyacetic acid, DIC, DMAP, DCM, rt, 48 h, 94 %

Although thermal stability studies in chloroform showed that ester **232** was stable at 150 °C, when exposed to dCr conditions only decomposition was observed (Scheme 125, Table 17).



Scheme 125: Attempted dCr of ester **232** (a) BSA, KOAc, PhMe, see Table 17

Entry	Temperature (°C)	Time
1	150	3 x 1 min
2	100	2 x 1 min

Table 17: Conditions for attempted dCr of ester **232**

2.4 Conclusions

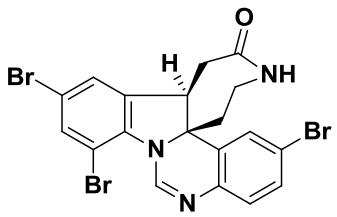
The reactivity of 2-substituted furan esters under dCr conditions has been developed, with both alkyl and electron-poor aryl groups at the benzylic position tolerated. The reaction of the bis (enol) ethers produced from this the dcearboxylative Claisen rearrangement with a number of electrophiles has been studied. It has been shown that aromatic nitro groups are incompatible with dCr conditions and that increasing the electron density of the furan ring leads to decomposition of the starting esters. The dCr reaction works well with esters derived from tosylacetic and cyanoacetic acids; however the use of trifluoromethyl as an activating group means that the desired reaction does not take place. Attempts to use the dCr reaction to form a quaternary centre at the 3- position of the furan failed due to issues with synthesising the required starting materials.

3 Hinckdentine A

3.1 Background

3.1.1 Structure and Isolation

Hinckdentine A (**233,** Figure 12) is an indole-based alkaloid isolated from the bryozoan *Hincksinoflustra deniticulata*, found in shallow water off the coast of Australia. It was first isolated in 1987 by Blackman *et. al.* by HPLC in a 0.005 % yield, with the structure and absolute configuration confirmed by single crystal X-ray diffraction.[79]



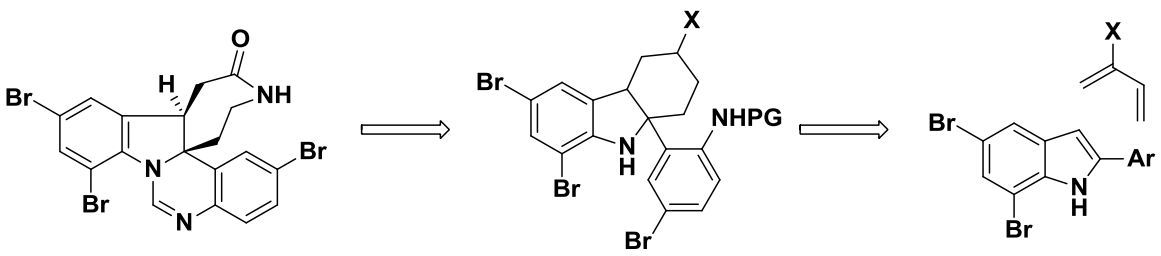
233

Figure 12: Hinckdentine A

There has been no published biological activity, but the unique structure, consisting of a seven-membered lactam fused to a indolo [1,2-*c*]quinazoline core has led to four groups publishing synthetic approaches.

3.1.2 Joule's Approach[80]

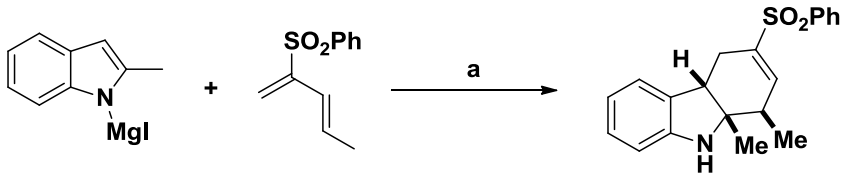
Joule *et al.* envisioned that hinckdentine A could be approached from intermediate **234** (Figure 13), in which substituent X could be utilised for a ring expansion to give the seven-membered lactam. In turn, they hoped that intermediate **234** could be formed by the [4+2] cycloaddition of a butadiene with indole **235**.



233 **234** **235**

Figure 13: Joule's retrosynthesis of hinckdentine A

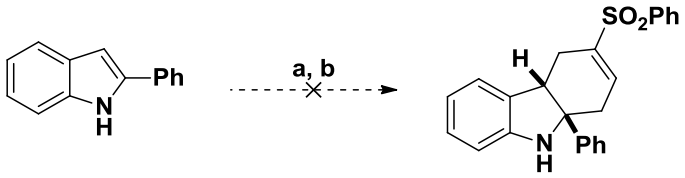
The cycloaddition of 2-methylindoylmagnesium iodide (**236**) with 2-phenylsulfonyl-1,3-butadiene (**237**) to give **238** had previously been reported by Bäckvall *et al* (Scheme 126)[81], and Joule hoped to develop this methodology to provide a route to **234**.



236 **237** **238**

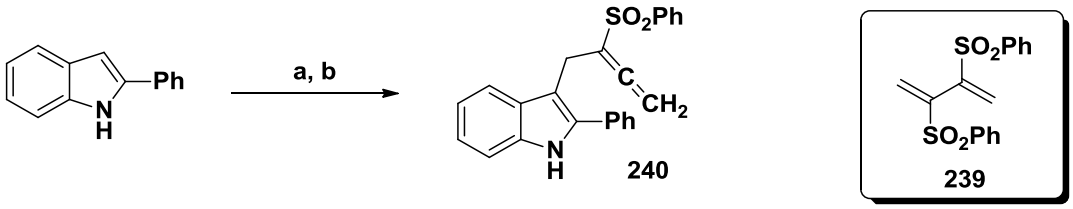
Scheme 126: Cycloaddition of 2-methylindoylmagnesium iodide and 2-phenylsulfonyl-1,3-butadiene as reported by Bäckvall (a) PhH, Et_2O; 1 h; 0 °C; 23 %

Unfortunately, neither the Grignard derivative of 2-phenyl indole, nor the lithio- or potassio- derivatives, successfully underwent this reaction (Scheme 127).



Scheme 127: Attempted cycloaddition of 2-phenyllindoylmagnesium iodide and 2-phenylsulfonyl-1,3-butadiene (a) MeMgI; THF, Et_2O; –78 °C; (b) 2-phenylsulfonylbuta-1,3-diene (**237**); DCM

Attempts to use the more reactive diene **239** gave only allene **240** under the reaction conditions (Scheme 128).



Scheme 128: Formation of unexpected product during attempted cycloaddition (a) MeMgI; THF, Et_2O; –78 °C; (b) **239**; DCM; 30 min; –78 °C

Joule then showed that 2-methylindole gave an analogous product under the same reaction conditions. Their proposed mechanism for the formation of this allene is given in Figure 14.

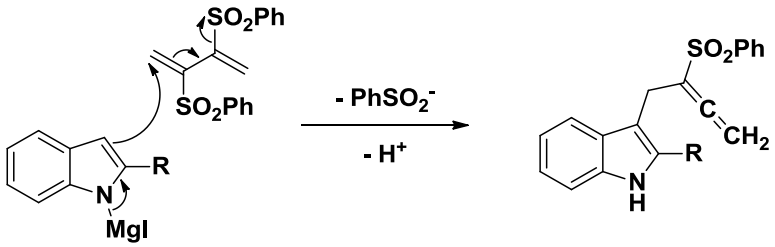
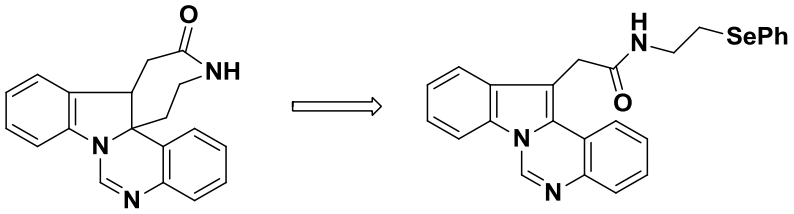


Figure 14: Proposed mechanism for formation of allene **240**

3.1.3 Cava's Approach[82]

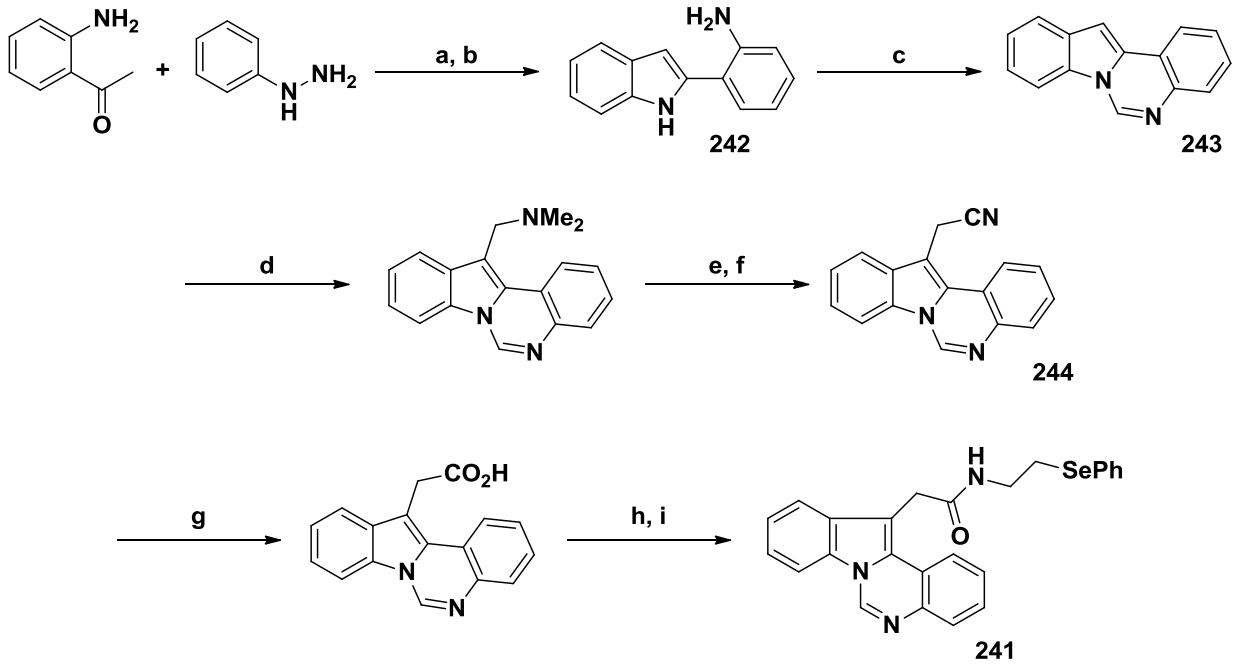
Cava's proposed approach to hinckdentine A involved the formation of the lactam ring by the cyclisation of a radical formed from the homolytic cleavage of a carbon-selenium bond (Figure 15).



des-bromo 233 **241**

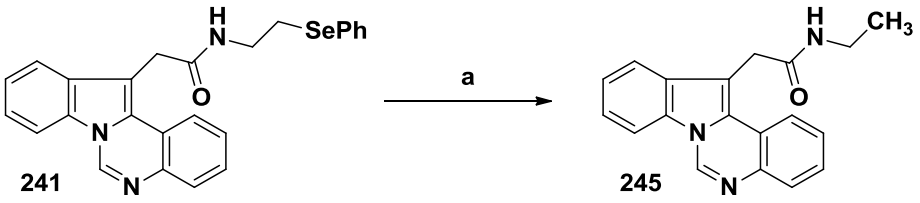
Figure 15: Cava's approach to the hinckdentine A core

The indolo[1,2-*c*]quinazoline core **243** was produced *via* a Fischer indole synthesis and treatment of the resulting aniline **242** with hot formic acid. This was then subjected to Mannich reaction, alkylation and S_N2 displacement with a cyanide anion. Hydrolysis of the resulting nitrile **244** and amide formation *via* the acyl chloride gave the required phenyl seleno compound **241** (Scheme 129).



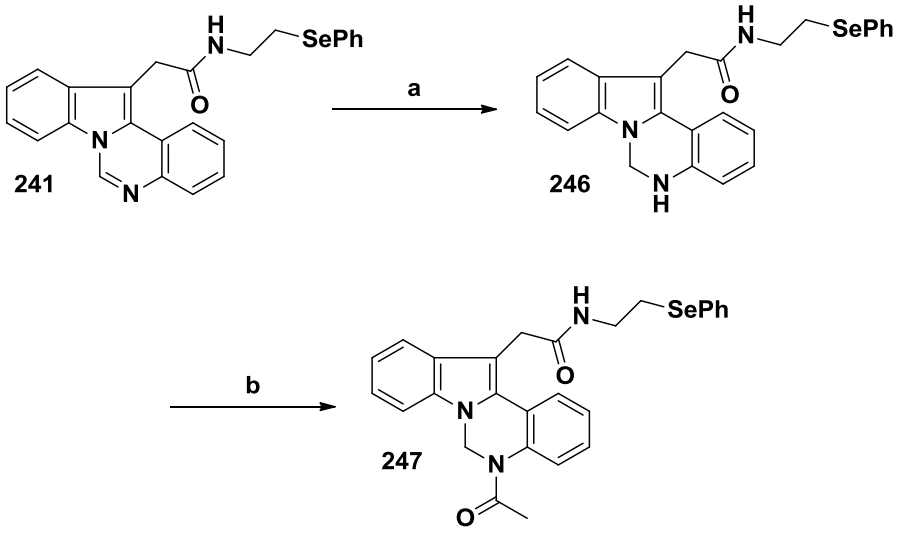
Scheme 129: Synthesis of **241** (a) HOAc, EtOH, 80 °C, 6 h, 88 %; (b) $MeSO_3H$, P_2O_5, 85 °C, 30 min, 90 %; (c) HCO_2H, 90 °C, 1 h, 73 %; (d) Me_2NH, HCOH, HOAc, rt, 3 h, 82 %; (e) MeI, PhH, rt, 12 h, 97 %; (f) NaCN, MeCN, H_2O, reflux, 5 h, 70 %; (g) HCl, dioxane, reflux, 90 h, 80 %; (h) $(COCl)_2$, MeCN, DMF, rt, 5 h; 96 %; (i) $PhSeCH_2CH_2NH_2$, pyridine, MeCN, rt, 3 h, 30 %

Unfortunately, when **241** was treated with a variety of radical initiators, including AIBN and tris(trimethylsilyl)silane the only product observed was the ethyl amide **245** (Scheme 130).



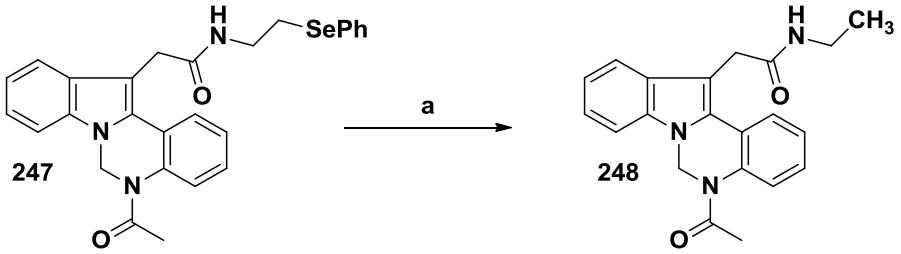
Scheme 130: Formation of undesired product **245** during attempted radical cyclisation (a) AIBN, Bu_3SnH, PhMe, reflux, 4 h, 75 %

Cava then decided to remove the aromaticity of the pyrimidine ring in the hope that this would facilitate the desired cyclisation. This was achieved by reducing the imine functionality of **241** with sodium borohydride in methanol before protecting aniline **246** as the acetamide **247** (Scheme 131).



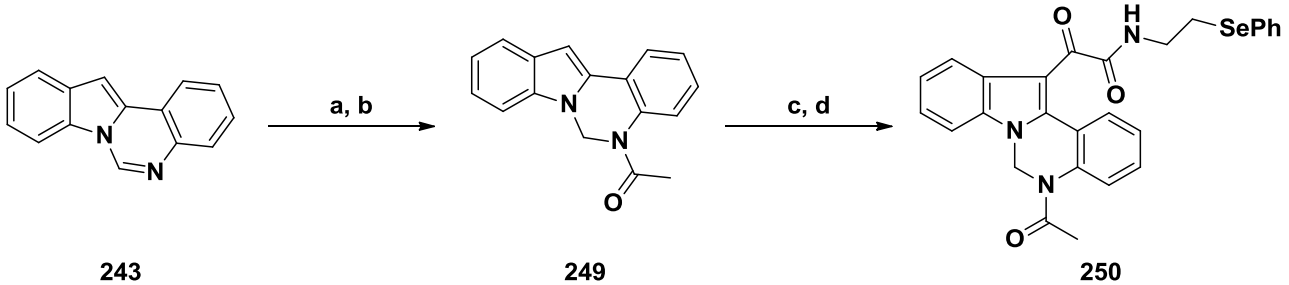
Scheme 131: Removal of the aromaticity of the pyrimidine ring (a) $NaBH_4$, MeOH, reflux, 10 h, 80 %; (b) Ac_2O, pyridine, 80 °C, 30 min, 90 %

Once again, the radical cyclisation failed and only the ethyl amide **248** was isolated (Scheme 132).



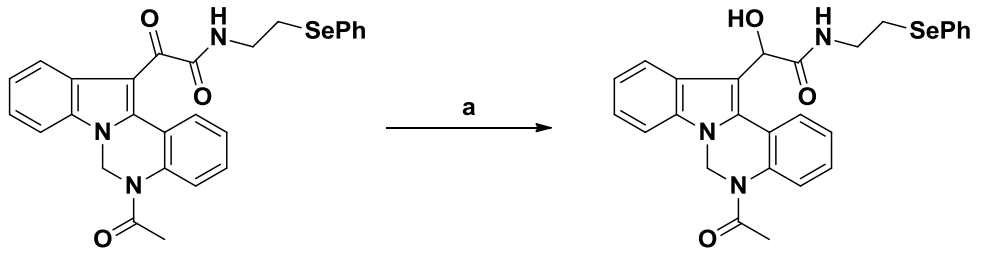
Scheme 132: Formation of undesired product **248** during attempted radical cyclisation (a) AIBN, Bu_3SnH, PhMe, reflux, 1 h, 79 %

The next approach was to introduce a carbonyl group α to the indole, in the hope that this would activate the indole C2-C3 double bond to radical addition. To test this hypothesis indolo[1,2-c]quinazoline **243** was reduced with sodium borohydride and protected as acetamide **249**. This was then acylated with oxalyl chloride, and the intermediate acyl chloride trapped by a primary amine to give α-keto amide **250**.



Scheme 133: Introduction of a carbonyl group α to the indole (a) $NaBH_4$, MeOH, reflux, 5 h, 80 %; (b) Ac_2O, pyridine, reflux, 5 h, 91 %; (c) $(COCl)_2$, Et_2O, 0 °C to rt, 2 h; (d) $PhSeCH_2CH_2NH_2$, Et_2O, rt, 12 h, 75 % over two steps

When **250** was treated with tributyl tin hydride and AIBN only alcohol **251** was isolated and neither the cyclisation product nor the open chain ethyl derivative was observed (Scheme 134). A possible explanation is that reduction of the ketone gives the bulky *O*-tributyl-stannyl derivative that for steric reasons may prevent radical attack even when a large excess of tributyltin hydride is used.

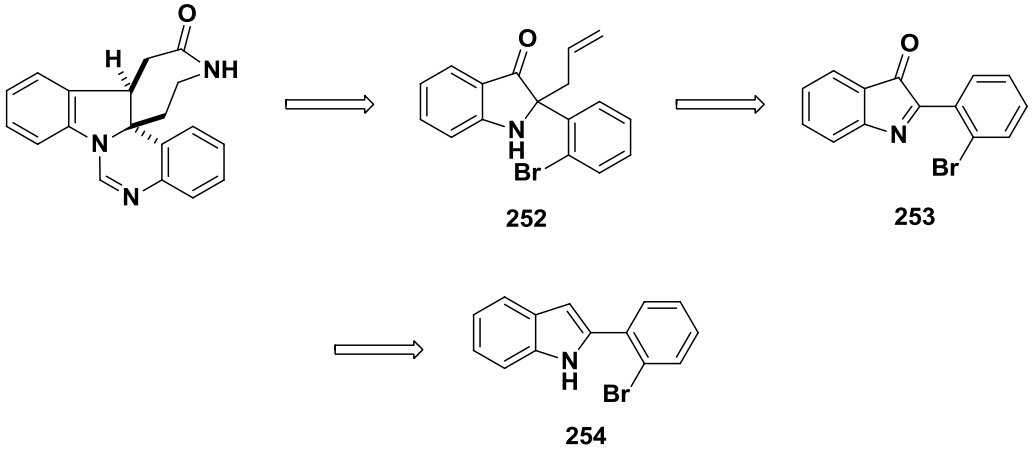


250 **251**

Scheme 134: Formation of undesired product **251** during attempted radical cyclisation (a) AIBN, Bu_3SnH, PhMe, reflux, 4 h, 81 %

3.1.4 McWhorters's Synthesis of 8-Desbromohinckdentine A[83]

In 2003, McWhorter and Liu published a synthesis of 8-desbromohinckdentine A. Their retrosynthetic analysis involved the early stage formation of the C2 quaternary centre *via* nucleophilic addition to indolenine **253** (Figure 16).



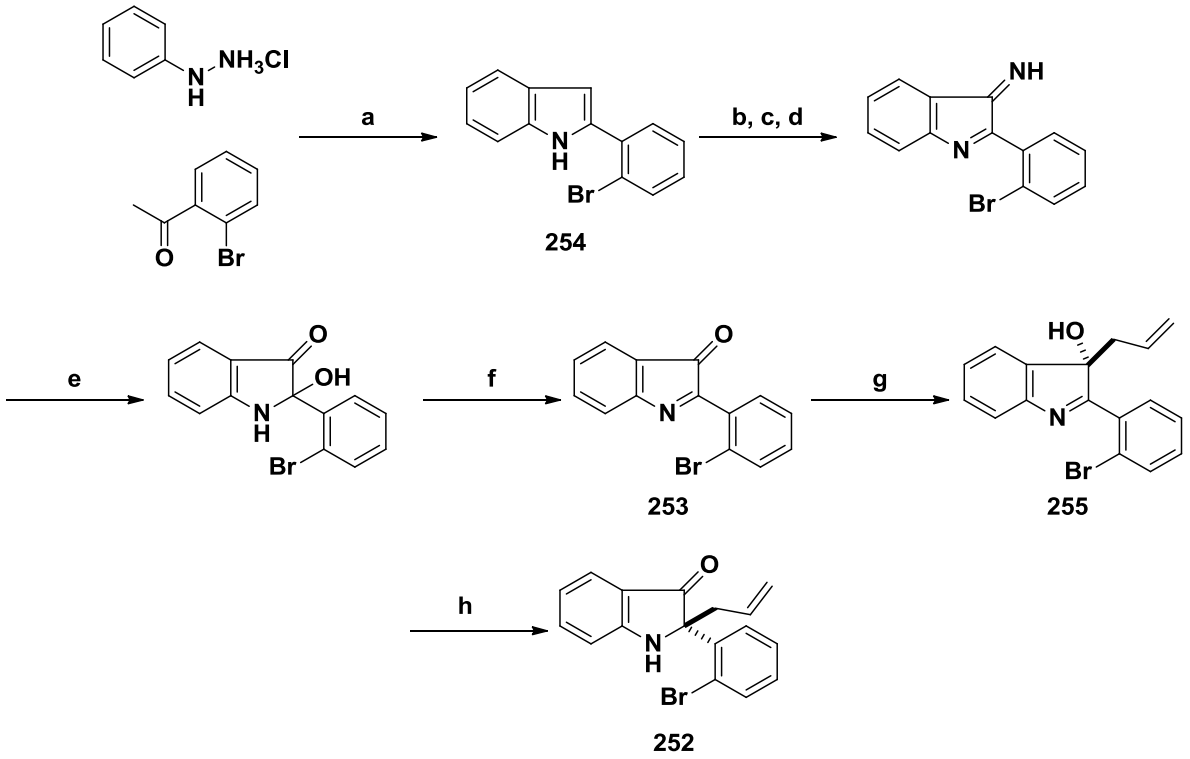
252 **253**

254

Figure 16: McWhorter's retrosynthesis of desbromohinckdentine A

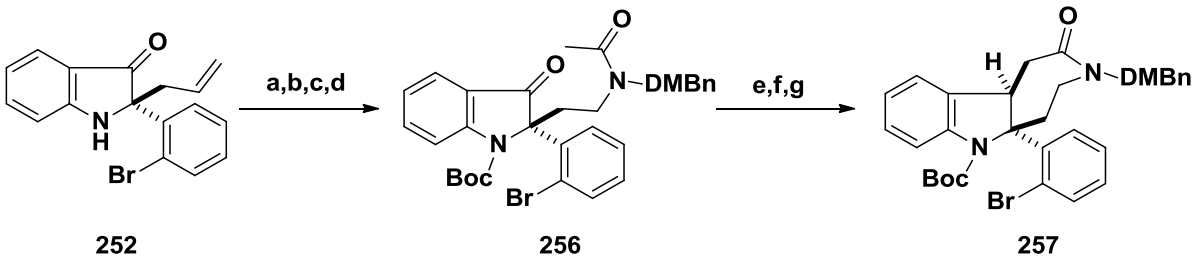
The indole core **254** was prepared via a Fischer indole synthesis, and was then oxidised to indolenine **253** following the procedure described by Hassner.[84] Although it is possible to achieve this oxidation in one step with singlet oxygen, this method did not prove amenable to scale-up. Based on previous work reported by Marchetti *et al*,[85] the authors had hoped that they would be able to add an allyl anion to indolenine **253** to give the quaternary centre directly. However, when treated with allylmagnesium bromide, only the

carbonyl addition product **255** was isolated. This was then converted into the desired indolone **252** via a pinacol like rearrangement with formic acid (Scheme 135).



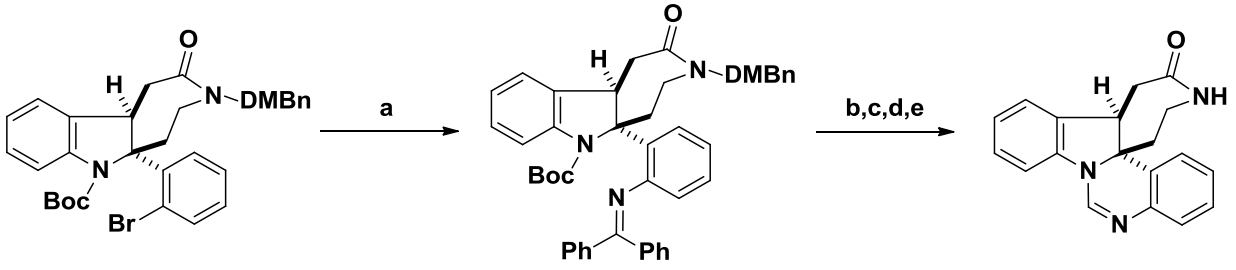
Scheme 135: Synthesis of indolenine **252**, containing a C2 quaternary centre (a) polyphosphoric acid, 120 °C, 4 h, 78 %; (b) $NaNO_2$, HOAc, rt, 3 h, 97 %; (c) $Na_2S_2O_4$, NaOH, H_2O, EtOH, reflux, 24 h, 94 %; (d) PbO_2, PhH, reflux, 24 h, 98 %; (e) 1 M HCl(aq), PhMe, rt, 12 h, 98 %; (f) reduced pressure, 105 °C, 4 h, 99 %; (g) allylmagnesium bromide, rt, 2 h, 89 %; (h) 88 % HCO_2H, PhMe, reflux, 30 min, 96 %

Indolone **252** was then protected as its *N*-*tert*-butyl carbamate; followed by ozonolysis, reductive amination and acylation to give **256.** Ring-closure *via* an aldol reaction; and subsequent dehydration and reduction gave lactam **257** as a single isomer (Scheme 136).



Scheme 136: Formation of seven membered lactam (a) Boc_2O, DMAP CH_3CN, rt, 17 h, 96 %; (b) O_3, MeOH, - 78 °C, then Me_2S, –78 °C to rt; (c) 2,4-dimethoxybenzylamine, HOAc, $NaBH_3CN$, MeOH/THF, rt, 16 h, 60 % over two steps; (d) Ac_2O, pyridine, 0 ° to rt, 20 h, 91 %; (e) LDA, THF, –78 °C, 5 min, then HOAc, THF –78 °C to rt, 92 %; (f) MsCl, pyridine, 0°C to rt, 20 h, 96 %; (g) Mg turnings, MeOH, rt, 24 h, 79 %

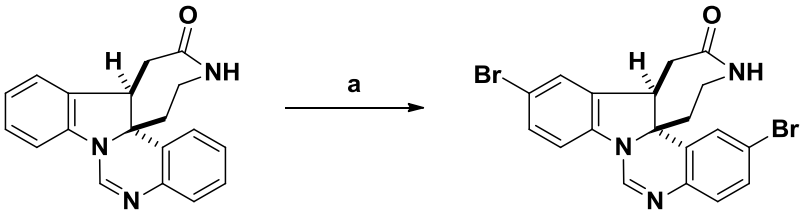
With the lactam ring in place, attention was turned to the synthesis of the quinazoline. A Buchwald-Hartwig coupling afforded protected aniline **258** and removal of the Boc and diphenylmethylene protecting groups followed by condensation with hot formic acid gave the dihydropyrimidine ring. A final deprotection gave the carbon framework of hinckdentine A **259** (Scheme 137).



257 258 259

Scheme 137: Formation of quinazoline system (a)Ph_2C=NH, $^{t-}$BuONa, $Pd(DPPF)_2Cl_2$, DPPF, PhMe, 140 °C, 48 h, 62 %; (b) 2 M $HCl_{(aq)}$, THF, rt, 5 h, 97 % (c) 20 % TFA in CH_2Cl_2, 0 °C to rt, 8 h, 95 % (d) 1:1 HCO_2H/IPA, 75 °C, 4 h, 72 %, (e) HCO_2H, 100 °C, 2 h, 93 %

The authors had planned initially to modify the synthesis to incorporate the three bromine atoms at an earlier stage, however with the hinckdentine framework in hand they decided to investigate the direct bromination of **259**. Bromination in ethanol or chloroform with bromine at 60 °C gave a mixture of monobrominated and tribrominated substrates, whereas bromination in formic acid, methanesulfonic acid or trifluoromethanesulfonic acid gave cleanly the dibrominated **260** (Scheme 138). Using a 1:1 mixture of 98 % sulfuric acid and fuming sulfuric acid as the solvent did give some evidence of tribrominated products, but also resulted in the formation of other by products.



259 260

Scheme 138: Bromination to give 8-desbromohinckdentine A (a) Br_2, HCO_2H, rt, 48 h, 92 %

3.1.5 Kawasaki's synthesis of Hinckdentine A[86]

In 2009, Kawasaki *et al.* published the first, and to date only, total synthesis of hinckdentine A. The synthesis involved a late-stage bromination of tetrahydroquinazoline **261**, containing a bulky *N*- substituent, followed by oxidation to the dihydroquinazoline. The lactam ring was formed from amino

nitrile **262**, and the indole C3 carbon-carbon bond by olefination of ketone **263**. The quaternary indole C2 centre was established by a Mannich-type addition of a carbon nucleophile to the α-keto iminium created by dehydration of **264**. 2-Hydroxyindolin-3-one **264** was prepared by the oxidation of 2-aryl indole **265** (Figure 17). The route is discussed in further detail below.

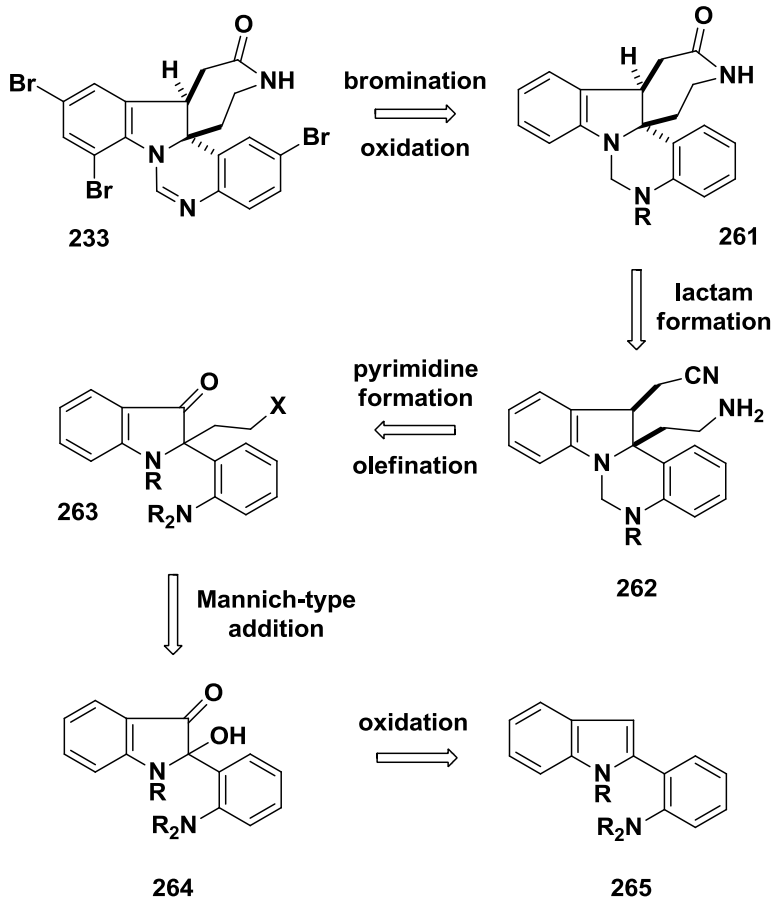
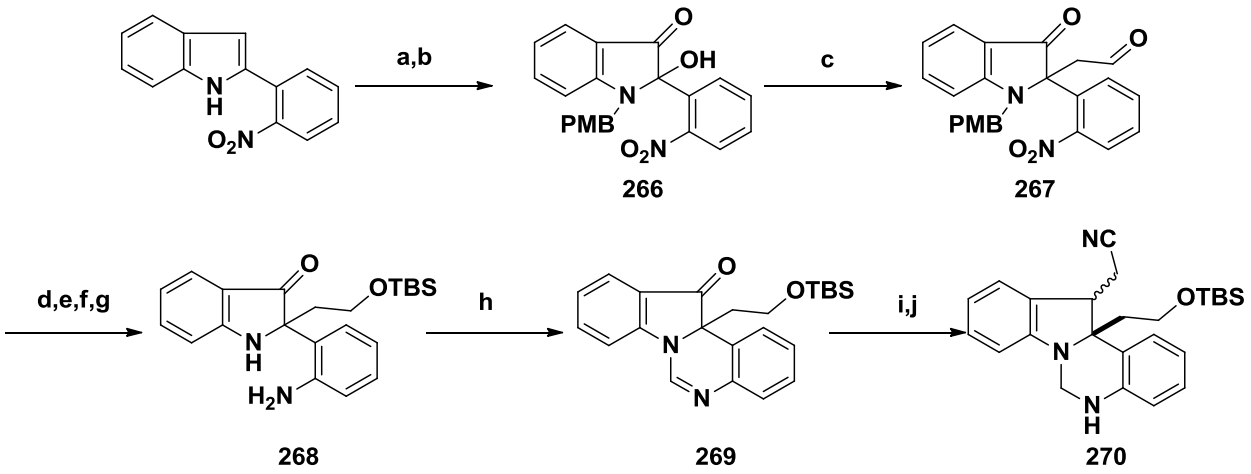


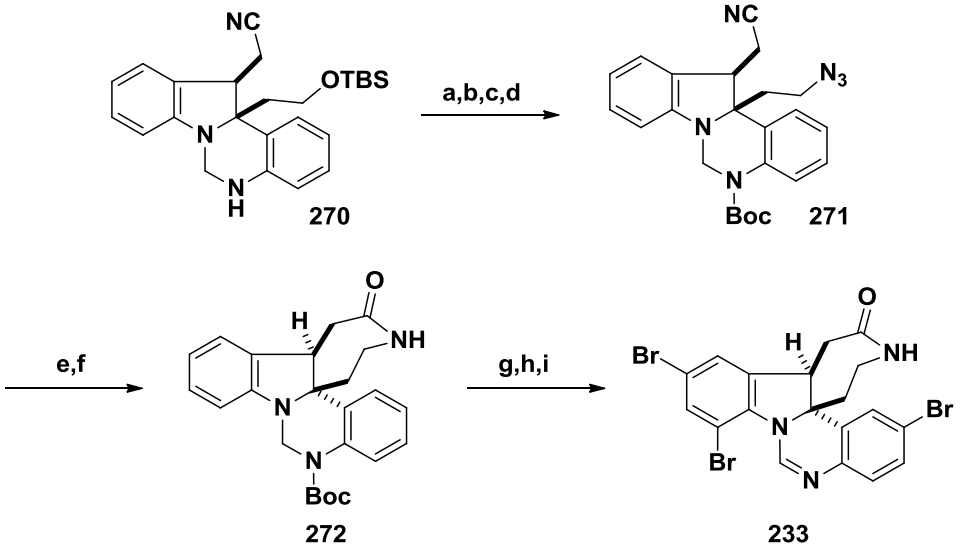
Figure 17: Kawasaki's retrosynthetic analysis of Hinckdentine A

Protection of 2-(2-nitrophenyl) indole and *m*-CPBA oxidation gave indolinone **266** in 85 % yield over two steps. The reactivity of **266** with respect to nucleophilic attack under acidic conditions was investigated, and the best results were observed with a silyl ketene acetal and CSA. Reduction of the resulting aldehyde **267**, protecting group changes and reduction of the nitro functionality gave aniline **268**. This was converted into dihydropyrimidine **269** by reaction with trimethylorthoformate, and the C3 carbon-carbon bond was formed *via* a Horner-Wadsworth-Emmons olefination. Reduction of the alkene and imine groups furnished nitrile **270** as a 5:1 *syn*:*anti* mixture(Scheme 139).



Scheme 139: Synthesis of indoline **270**, containing a C2 quaternary centre (a) NaH, PMBCl, TBAI, DMF, rt, 2.5 h, 90 %; (b) *m*-CPBA, THF, rt, 2 h, 94 %; (c) trimethyl(vinyloxy)silane, CSA, CH_2Cl_2, 0 °C, 10 min, 56 %; (d) $NaBH_4$, MeOH, 0 °C, 3.5 h, 93 %; (e) TBSCl, NEt_3, DMAP, CH_2Cl_2, rt, 1.5 h, 96 %; (f) DDQ, DCE, rt, 3 days, 83 %; (g) Zn, AcOH, CH_2Cl_2, rt, 10 min, 81 %; (h) $HC(OMe)_3$, PPTS, rt, 3.5 h, 86 %; (i) $(EtO)_2P(O)CH_2CN$, NaH, DMF, rt, 55 min, 98 %, (*E*:*Z* = 4:1); (j) Mg, MeOH, rt, rt, 2 h, 77 % (*syn*:*anti* = 5:1)

Tert-butyl carbamate protection of the aniline, followed by silyl ether cleavage, mesylation and nucleophilic displacement by NaN_3 gave azide **271**. This was then reduced under Staudinger conditions and a subsequent ruthenium-catalysed ring closure gave lactam **272**. Treatment of **272** with NBS gave the tribrominated product. The authors reasoned that the bulky Boc group on the quinazoline nitrogen atom prevented a fourth bromination taking place. Removal of the carbamate protecting group and oxidation with TPAP gave hinckdetine A (**233**) in 4 % yield over 19 steps



Scheme 140: Completion of hinckdentine A synthesis (a) Boc_2O, NEt_3, DMAP, MeCN, rt, 1 day, 81 %; (b) HF.py, THF, rt 2.5 h, 96 %; (c) MsCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, 30 min, 95 %; (d) NaN_3, DMF, 80 °C, 1 h, 91 %; (e) PPh_3, H_2O, THF, reflux, 1 h; (f) $RuH_2(PPh_3)_4$, H_2O, $(CH_3OCH_2)_2$, 150 °, sealed tube, 24 h, 66 % over two steps; (g) NBS, THF, 0 °C, 5 h, 64 %; (h) TFA, CH_2Cl_2, rt, 1 h, 84 %; (i) TPAP, NMO, MeCN, 0 °C, 87 %

3.2 Retrosynthetic approach

Our retrosynthetic approach to hinckdentine A is highlighted in Figure 18.

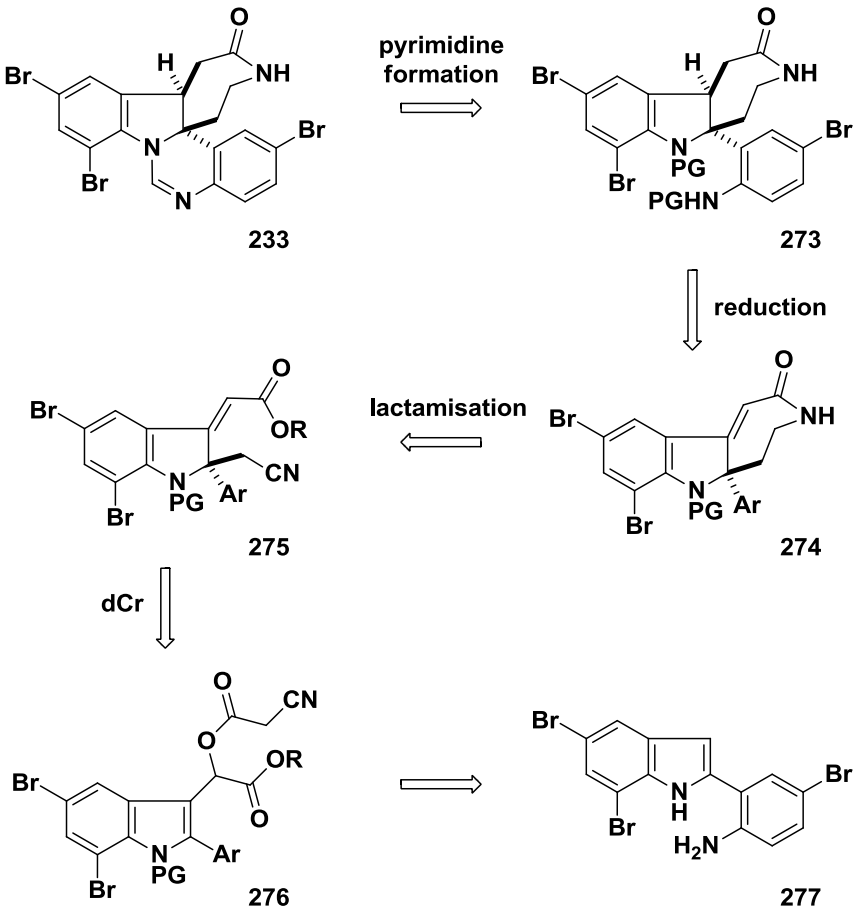
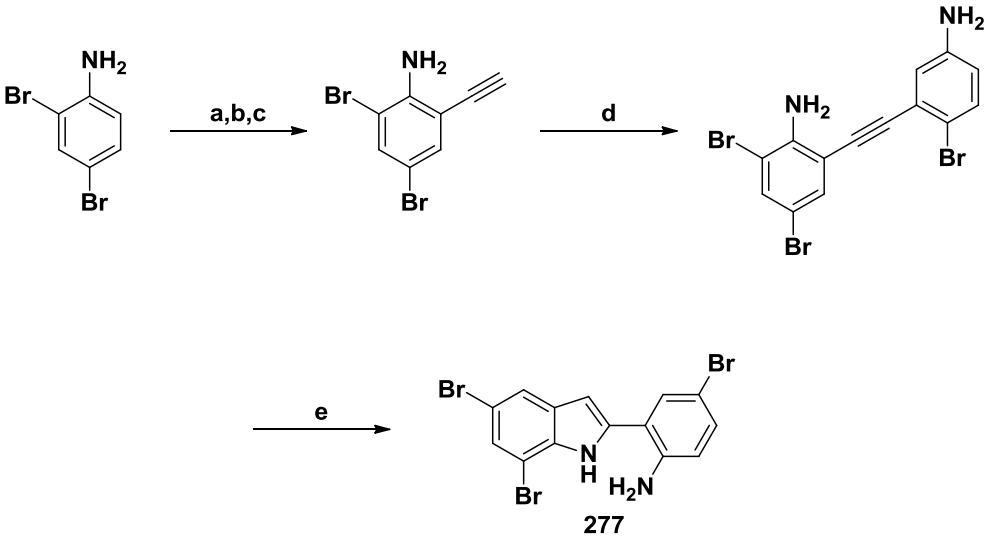


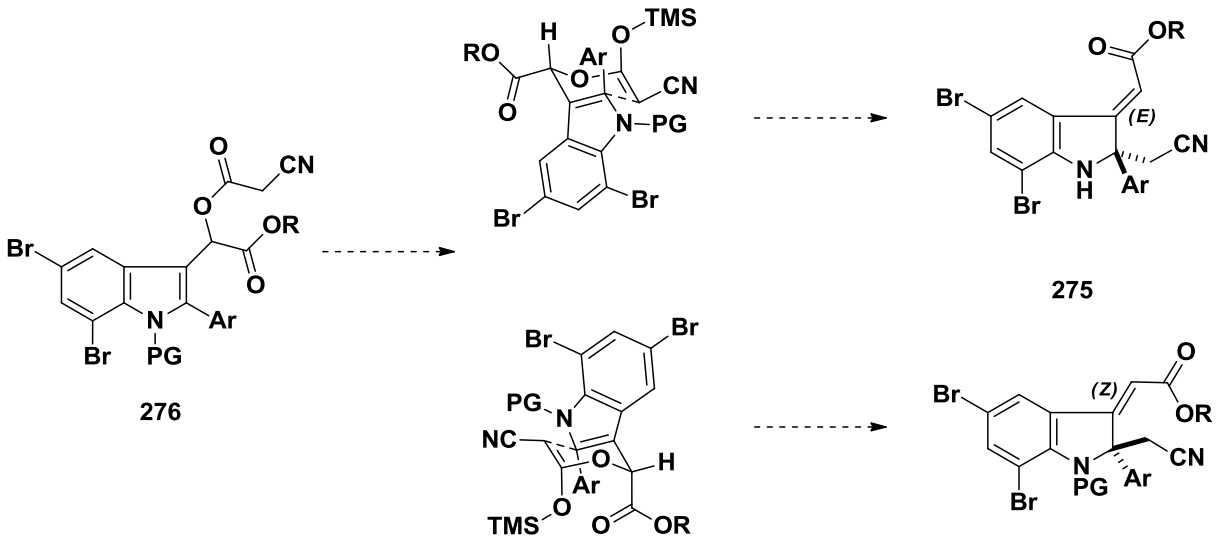
Figure 18: Retrosynthetic approach to Hinckdentine A

The required starting material **277** may be prepared via a published route from 2,3-dibromoaniline over 5 steps in a 28 % overall yield (Scheme 141).[87] This would then be functionalised at the C3-position by a Friedel-Crafts acylation with oxalyl chloride, and quenching of the intermediate acyl chloride with an alcohol. N-protection, carbonyl reduction and subsequent esterification with cyanoacetic acid would give **276**, which will on subjection to dCr conditions would give **275**, containing the necessary quaternary centre for hinckdentine A.



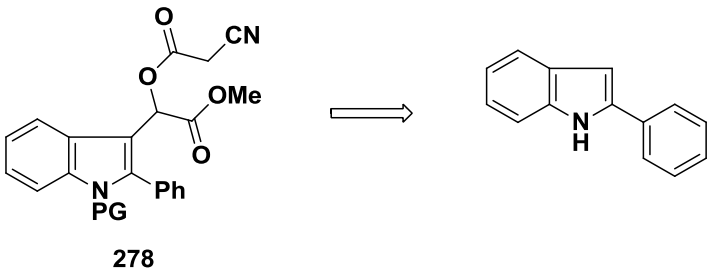
Scheme 141: Synthesis of requried starting material **277** as reported by Knochel (a) I_2, $AgSO_4$, EtOH, 88 %; (b) trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 3 h, 67 %; (c) TBAF, THF, rt, 1 h, 85 %; (d) 4-bromo-2-iodoaniline, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 3 h, 90 %; (e) KH, NMP, rt, 1 h, 62 %

It was anticipated that **275** would be formed as a mixture of two diastereomers (Figure 142), and that reduction of the nitrile of the *Z*-isomer followed by lactamisation would give α,β-unsaturated amide **274**. Stereoselective addition of H_2 to the convex face of the double bond would give the unsaturated *syn*-lactam **273**, following which the dihydropyrimidine ring would be introduced by condensation of the deprotected analogue of dianiline **273** with trimethylorthoformate or formic acid.



Scheme 142: Predicted formation of diastereomers of **275** via a dCr reaction

In order to test the feasibility of this dCr reaction, it was decided to first carry out studies on the model system **278**, which can be generated from the commercially available 2-phenyl indole.



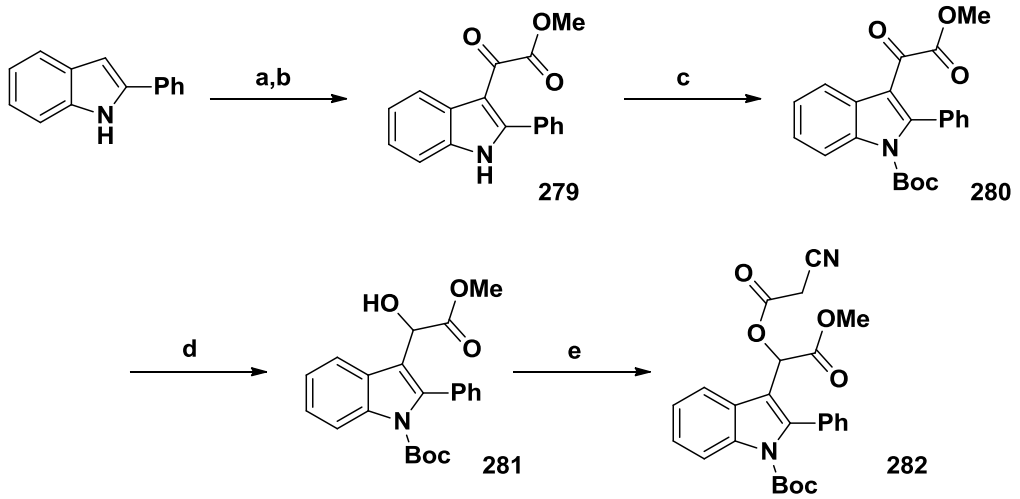
278

Figure 19: Model system for dCr reaction

3.3 Results and discussion

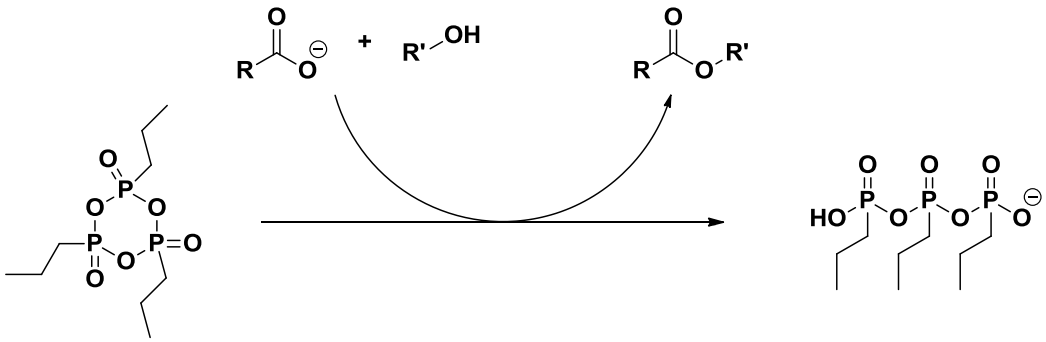
3.3.1 Synthesis of model system by Friedel Crafts Acylation

Ester **282** was synthesised in five steps from 2-phenyl indole (Scheme 143). Friedel-Crafts acylation with oxalyl chloride, followed by quenching of the intermediate acyl chloride with methanol, afforded **279**, which was then protected as its *N*-*tert*-butyl carbamate **280** and reduced with sodium borohydride to yield **281**. Subsequent esterification with cyanoacetic acid, using propylphosphonic anhydride as a coupling agent, gave cyanoacetate **282**.



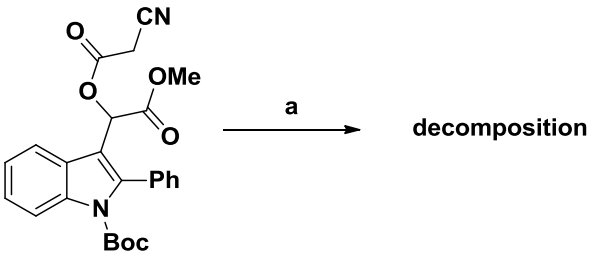
Scheme 143: Synthesis of ester **282** (a) oxalyl chloride, Et_2O, rt, 1 h; (b) MeOH, rt 15 min; 73 % over two steps; (c) NaH, Boc_2O, rt 2 h, 77 %; (d) $NaBH_4$, MeOH, rt, 50 min, 65 %; (e) cyanoacetic acid, T_3P®, Et_3N, DCM, rt, 1 h, 90 %

Using T_3P® as a coupling agent meant that in this case no column chromatography was needed to purify the final product as the by-products of the reaction are water soluble (Scheme 144).



Scheme 144: Esterification with T_3P®

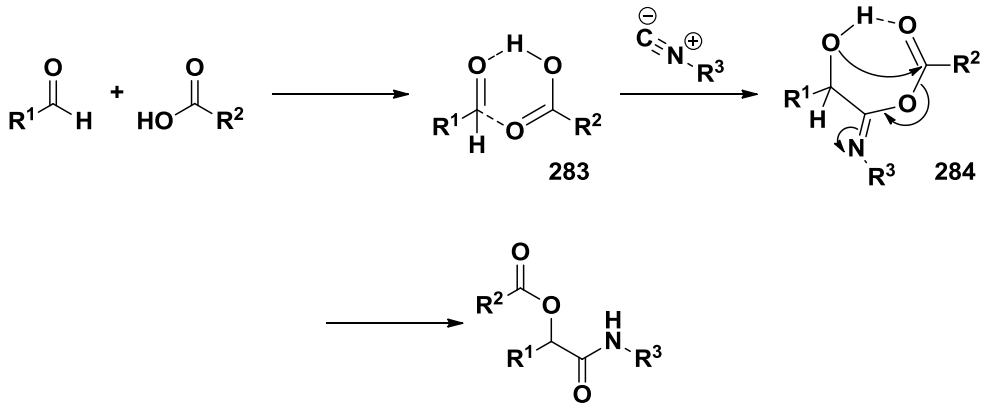
Unfortunately, when ester **282** was subjected to standard dCr conditions (Scheme 145) extensive decomposition occurred, with no identifiable products isolated. Analysis by ^{1}H NMR of the crude product showed no evidence for the methoxy signal, so it was decided to attempt a synthesis incorporating a more robust carboxylic acid-derived functional group at this position. Due to the low overall yield of this process, particularly in the protection and reduction reactions, an alternative route was also sought.



Scheme 145: Attempted dCr of of ester **282** (a) BSA, KOAC, PhMe, 150 °C, µw, 5 min

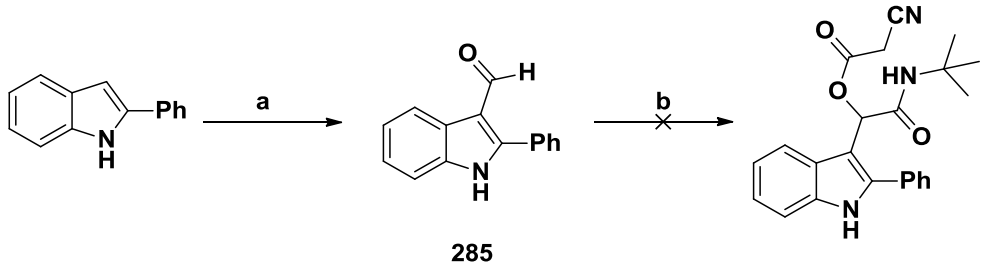
3.3.2 Synthesis of model system by a Passerini reaction

The Passerini reaction, first developed in 1921, is a 3 component coupling reaction between an isonitrile, a carboxylic acid and an aldehyde (Scheme 146).[88] The mechanism is thought to involve the formation of a loosely hydrogen-bonded adduct **283** which then undergoes α-addition across the isocyanide carbon atom. The resulting non-isolable intermediate **284** then undergoes an intramolecular transacylation to give an α-acyloxycarboxamide.[89]



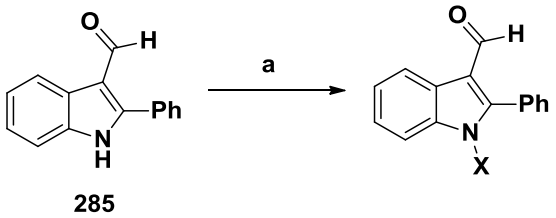
Scheme 146: Passerini reaction mechanism

Aldehyde **285** was generated in good yield by a Vilsmeier-Haack formylation of 2-phenyl indole. However, this proved inert to Passerini conditions, even in the presence of a Lewis acid as an activating agent (Scheme 147).



Scheme 147: Attempted Passerini reaction of aldehyde **285** (a) $POCl_3$, DMF, 1 h, 50 °C then $NaHCO_{3\,(aq)}$, 15 min, 60 °C, 90 % (b) ^{t}-BuNC, cyanoacetic acid, $Cu(OTf)_2$, DCM, –78 °C to 50 °C

It was hoped that increasing the electrophilicity of the aldehyde would increase the reactivity under Passerini conditions, so attempts were made to protect the indole nitrogen with an electron-withdrawing group (Scheme 148, Table 18). Tosylation proved difficult under both phase-transfer conditions and with sodium hydride (Table 18, Entries 1-11) with the isolated yield consistently under 10 %. Protection with Boc anhydride under phase transfer conditions proved much more successful (Table 18, entries 12 and 13) and the best results were obtained with Boc_2O in pyridine (Table 18, entry 14).

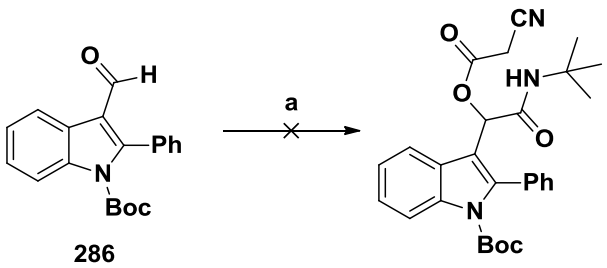


Scheme 148: Synthesis of *N*-protected indole. (a) See Table 18

Entry	Reagents	Solvent	Time	Temp	Yield (%)
1	TsCl, KOH, NBu_4I	PhMe/H_2O	12 h	rt	4
2	TsCl, NaOH, NBu_4Br	PhMe/H_2O	12 h	rt	7
3	TsCl, NaOH, NBu_4Br	PhH/H_2O	5 h	rt	8
4	TsF, NaOH, NBu_4Br	PhMe/H_2O	24 h	rt	5
5	TsF, NaOH, NBu_4Br	PhH/H_2O	24 h	rt	0
6	TsF, NaOH, NBu_4Br	DCM/H_2O	24 h	rt	0
7	TsF, NaOH, NBu_4Br	THF/H_2O	24 h	rt	0
8	TsCl, NaH	THF	12 h	rt	4
9	TsCl, NaH	THF	1 h	85 °C	5
10	TsCl, NaH	DMF	1 h	120 °C	0
11	TsF, NaH	DMF	72 h	100 °C	10
12	Boc_2O, NaOH, NBu_4Br	PhMe/H_2O	30 min	rt	54
13	Boc_2O, NaOH, NBu_4Br	PhH/H_2O	30 min	rt	45
14	Boc_2O	pyridine	5 h	rt	93

Table 18: Conditions for the protection of indole **285**

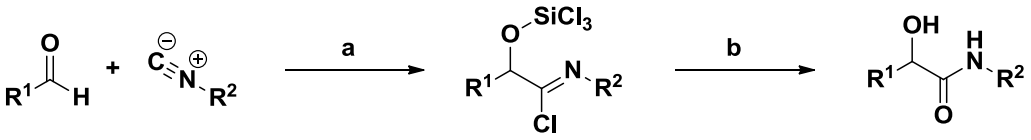
Unfortunately however, the Boc-protected indole still gave none of the desired product when subjected to the Passerini conditions (Scheme 149).



286

Scheme 149: Attempted Passerini reaction of aldehyde **286** (a) ^{t}BuNC, cyanoacetic acid, $Cu(OTf)_2$, DCM, –78 °C to 50 °C

In 2005, Denmark *et al.* reported the Passerini-type reaction of isonitriles with aldehydes to give α-hydroxyamides (Scheme 150).[90] This 'interrupted Passerini' reaction employed a catalytic system of a stoichiometric amount of silicon tetrachloride activated by a catalytic amount of a Lewis-base. Although it was shown that the reaction would proceed without the presence of the Lewis base (Table 19, entry 1), the yield was higher when one was used. The use of a chiral Lewis-base also promoted the formation of an enantiomerically enriched alcohol (Table 19, entry 3).

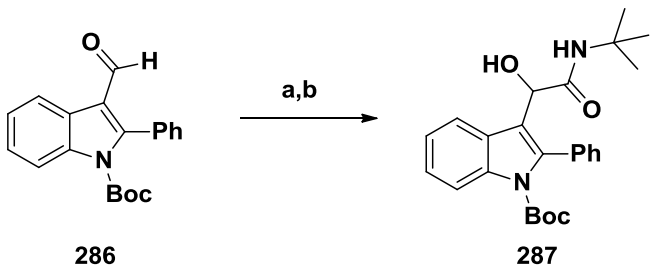


Scheme 150: Denmark's "interrupted-Passerini" reaction. (a) $SiCl_4$ (1 equiv), catalyst, DCM, –78 °C; (b) $NaHCO_{3\,(aq)}$, rt

Entry	Catalyst	Loading (mol %)	Conversion (%)	Yield (%)	er
1	none	-	83	79	-
2	HMPA	10	100	90	-
3	pyridine-*N*-oxide	10	100	94	-
4	chiral bisphosphoramide	5	100	83	90.2/9.8

Table 19: Denmark's screening of Lewis Bases. R^1 = Ph. R^2 = ^{t}Bu

Aldehyde **286** underwent reaction with *tert*-butyl isonitrile and silicon tetrachloride in the presence of HMPA to give the desired alcohol **287** (Scheme 151). Surprisingly increasing the reaction time actually led to a decreased isolated yield, indicating that the product was decomposing under the reaction conditions. The use of pyridine-*N*-oxide also gave a comparable yield (Table 20)



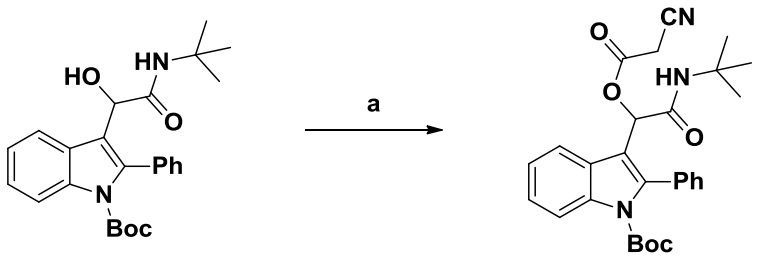
286 **287**

Scheme 151: Reaction of aldehyde **286** under Denmark's "interrupted-Passerini" conditions (a) ^{t}BuNC, Lewis base (see Table 20), $SiCl_4$, –78 °C; (b) $NaHCO_{3\,(aq)}$, 2 h , rt

Entry	Lewis Base	Time (h)	Isolated Yield (%)	Yield brsm (%)
1	HMPA	4	52	80
2	HMPA	5.5	29	52
3	pyridine-*N*-oxide	4	53	83

Table 20: Conditions for the "Interrupted Passerini" reaction of aldehyde **286**

The esterification conditions used in the previous route gave the desired ester **288** in only 27 % yield, so alternative procedures were screened (Scheme 152 and Table 21). Yamaguchi esterification (Table 21, entry 2) gave an increased yield and in situ formation of cyanoacetic anhydride with trifluoroacetic anhydride (Table 21, entry 3) also proved successful. The best yields were achieved under Mitsunobu conditions (Table 21, entries 4 and 5). The hydrazine by-product formed in the reaction with DIAD proved impossible to separate from the product by column chromatography; so the more expensive di-2-methoxyethyl azodicarboxylate (DMEAD), which forms a hydrazine that is water-soluble, was used instead.



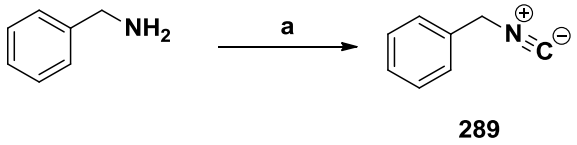
287 **288**

Scheme 152: Esterification of alcohol **287** (a) cycanoacetic acid, see Table 21

Entry	Reagents	Solvent	Time (h)	Yield (%)
1	T_3P®, Et_3N	DCM	24	27[a]
2	Et_3N, DMAP, 2,4,6-trichlorobenzoyl chloride	DCM	48	43[a]
3	TFAA	DCM	20	40[a]
4	PPh_3, DIAD	THF	24	55[b]
5	PPh_3, DMEAD	THF	36	57[a]

Table 21: Esterification of **287** with cyanoacetic acid. [a]Isolated yield. [b]From analysis of ^{1}H NMR

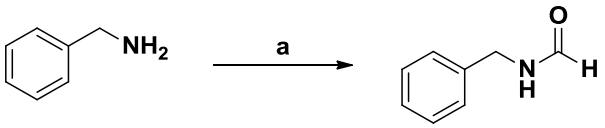
In the hope of improving the slightly disappointing yield from the 'interrupted Passerini' reaction it was decided to investigate the use of other isonitriles. In 1976, Gokel *et al.* reported the synthesis of isonitriles under phase-transfer Hoffmann carbylamine conditions (Scheme 153).[91] When this reaction was attempted isonitrile **289** was produced in a 39 % crude yield, but the requirement for two equivalents of amine and the thermal instability of the product made it impossible to cleanly separate the product by distillation.



289

Scheme 153: Attempted synthesis of benzylisonitrile under phase-transfer Hoffmann carbylamine conditions (a) NaOH, $CHCl_3$, Et_3NBnCl, H_2O/DCM, rt, 4 h, 39 %

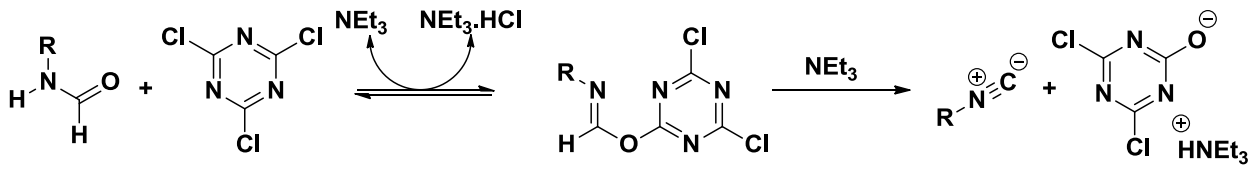
Another method for the synthesis of isonitriles involves the dehydration of the *N*-formyl amine derivative. Benzylamine was formylated in quantitative yield by stirring with ethyl formate over 24 hours (Scheme 154).



290

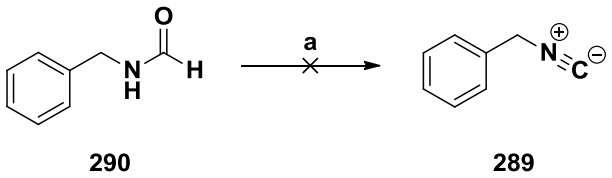
Scheme 154: Formylation of benzylamine (a) EtOCHO, 45 °C, 24 h, quant.

The first attempt at the dehydration reaction of **290** involved the method developed by Porcheddu *et al.* using cyanuric chloride and a base under microwave conditions (Scheme 155).[92]



Scheme 155: Dehydration of formamides with cyanuric chloride

Inconsistencies in the paper meant there was some confusion over the exact conditions required, and therefore a range was screened (Table 22). Although analysis by TLC and ^{1}H NMR showed complete consumption of the starting material, there was no evidence for the formation of the isonitrile.



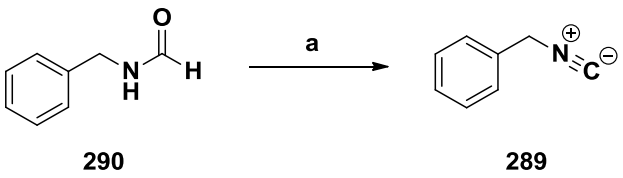
290 **289**

Scheme 156: Attempted dehydration of formamide **290** with cyanuric chloride (a) cyanuric chloride, pyridine, µw, see Table 22

Entry	Temperature (°C)	Time (min)	Result
1	50	3	SM consumed – no isonitrile isolated
2	50	10	SM consumed – no isonitrile isolated
3	70	10	SM consumed – no isonitrile isolated
4	90	10	SM consumed – no isonitrile isolated
5	100	10	SM consumed – no isonitrile isolated

Table 22: Conditions for the dehydration of N-benzyl formamide with cyanuric chloride

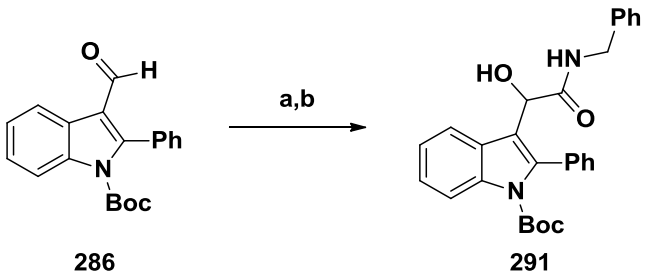
However, the use of $POCl_3$ and pyridine as dehydrating reagents successfully gave benzyl isonitrile **289** in 21 % yield (Scheme 157).



290 **289**

Scheme 157: Dehydration of formamide **289** with phosphorus oxychloride (a) $POCl_3$, pyridine, petroleum ether, 70 °C, 15 min, 21 %

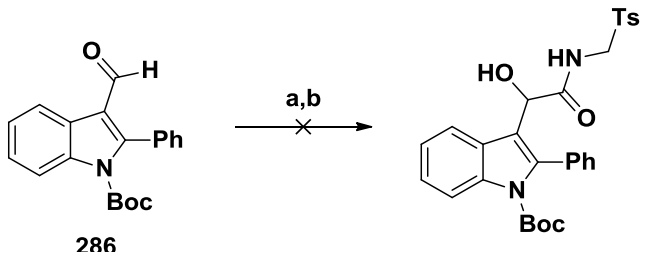
Under Denmark's conditions, α-hydroxy amide **291** was formed in a slightly higher yield than the $^{t-}$butyl variant (Scheme 158).



286 **291**

Scheme 158: Reaction of aldehyde **286** under Denmark's "interrupted-Passerini" conditions (a) BnNC, pyridine-*N*-oxide, $SiCl_4$, -78 °C, 4 h; (b) $NaHCO_3$ (aq), rt, 2 h, 61 %

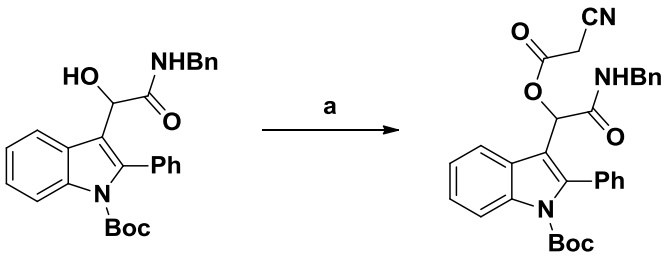
However, the reaction of aldehyde **286** with commercially available tosylmethylisocyanide under the same conditions gave no product and recovery of the starting aldehyde (Scheme 159).



286

Scheme 159: Attempted reaction of aldehyde **286** with tosylmethylisocyanide (a) $TsCH_2NC$, pyridine-*N*-oxide, $SiCl_4$, –78 °C, 4 h; (b) $NaHCO_3$ (aq), rt, 2 h

Most standard esterification conditions with **291** gave only return of starting material, although the use of DIC under prolonged microwave heating did give the desired ester **292** in a low yield (Table 23, Entry 2).



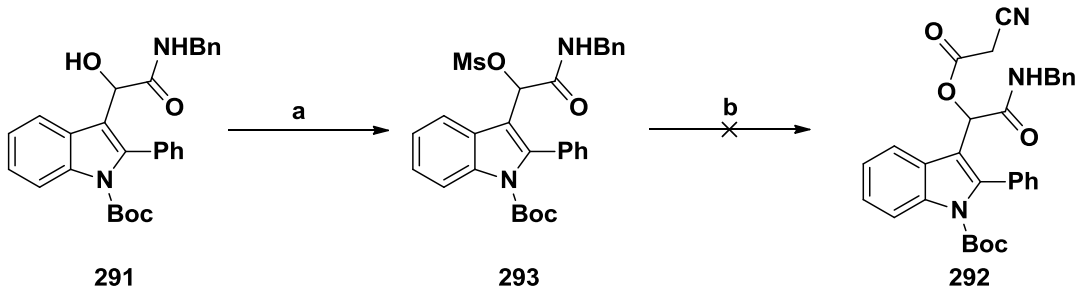
291 **292**

Scheme 160: Esterification of alcohol **291** (a) cyanoacetic acid, see Table 23

Entry	Reagents	Solvent	Time (h)	Temperature	Yield (%)
1	DIC, DMAP	DCM	72	rt	no reaction
2	DIC, DMAP	DCM	5	90 °C (μw)	18
3	TFAA	MeCN	67	rt	no reaction
4	DIAD, PPh_3	THF	51	rt	no reaction
5	DIAD, PPh_3	THF	51	rt	no reaction

Table 23: Esterification of alcohol **211**

Attempts to trap the mesylate derivative of alcohol **291** with the potassium salt of cyanoacetic acid also proved fruitless (Scheme 161), although ^{1}H NMR analysis of the crude reaction mixture before addition of the carboxylate indicated that the mesylate had been formed.



291 **293** **292**

Scheme 161: Attempted synthesis of ester **292** *via* mesylate **293** (a) MsCl, pyridine, rt, 48 h; (b) KO_2CCH_2CN, THF, rt, 72 h

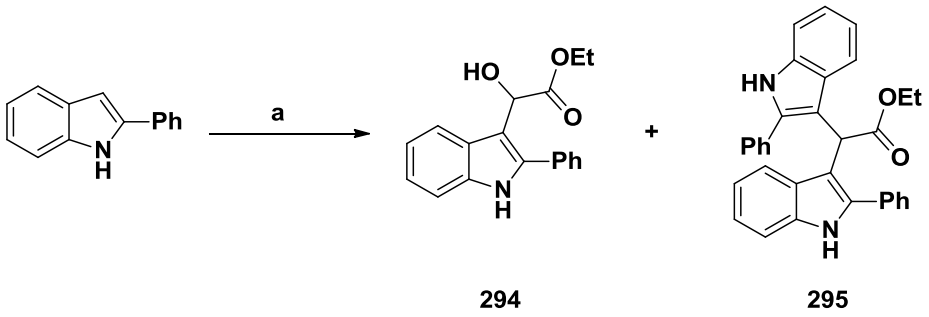
It was reasoned that the low yield of the esterification of secondary amides **287** and **291** compared to that of ester **281** may be due to the free NH. However, attempts to *N*-silylate the amide led to a complex mixture of products.

3.3.3 Synthesis of a model system by Friedel Crafts hydroxy-alkylation

Due to the problems encountered with the esterification of compounds **287** and **291**, both of which contained a secondary amide moiety, it was decided to redesign a route that would contain an α-hydroxy ester. In Section 3.3.1 it was shown that a methyl ester at this position was incompatible with the reaction

conditions, so a larger alkyl group would be required. The commercially available ethyl glyoxalate was chosen as a starting point for Friedel-Crafts hydroxy-alkylation, with the view that it could be replaced with a more highly substituted glyoxalate later if the synthetic route proved successful.

Addition of ethyl glyoxalate to 2-phenylindole gave either the desired alcohol **294**, or bisindole **295** depending on the conditions used (Scheme 162, Table 24).



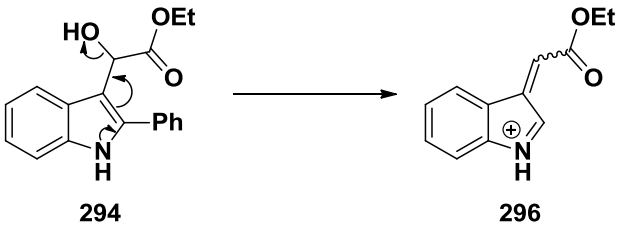
294 **295**

Scheme 162: Friedel-Crafts hydroxyalkylation. (a) ethyl glyoxalate, see Table 24

Entry	Solvent	Lewis Acid	Equivalents gyloxylate	Temperature	Time (h)	Yield (%)	
						294	295
1	THF	$BF_3{\cdot}OEt_2$	1.5	rt	19	-	24
2	DCM	$Cu(OTf)_2$	4	–78 °C	4	55	-
3	DCM	-	4	rt	3	73	-
4	DCM	-	1.5	rt	24	89	-
5	benzene	-	4	rt	3.5	92	-
6	benzene	-	1.5	rt	7.5	82	-

Table 24: Friedel-Craft hydroxylakylation conditions

Bisindole **295** is likely formed by dehydration of the product alcohol **294** and interception of the extended iminium ion **296** by another molecule of starting material (Scheme 163).

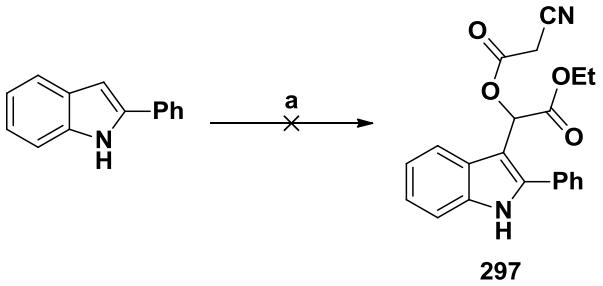


294 296

Scheme 163: Formation of extended iminium ion **296**

The use of the highly oxophilic Lewis Acid $BF_3{\cdot}OEt_2$ (Table 24, entry 1) gave exclusively the bisindole **295** product as it promotes this dehydration reaction. Decreasing the polarity of the solvent led to an increase in yield of the desired alcohol (Table 24, entries 3 and 5), presumably because intermediate **296** would have greater stabilisation in more polar solvents.

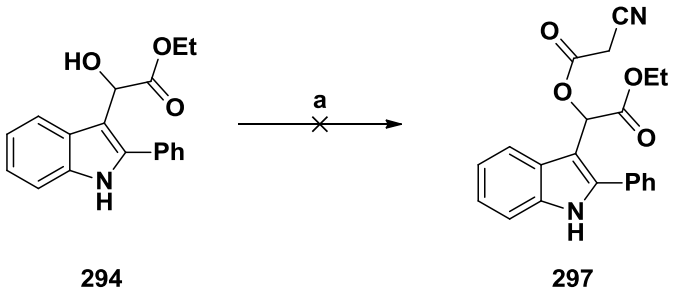
It was hoped that the formation of iminium **296** could be useful synthetically if trapping with a carboxylate salt led to the desired diester (Scheme 164). Unfortunately however, attempts to intercept the intermediate with the potassium salt of cyanoacetic acid did not give the desired product.



297

Scheme 164: Attempted synthesis of ester **297** by trapping of extended iminium ion **296** (a) ethyl glyoxylate, KO_2CCH_2CN, $BF_3{\cdot}OEt_2$, THF, rt, 24 h

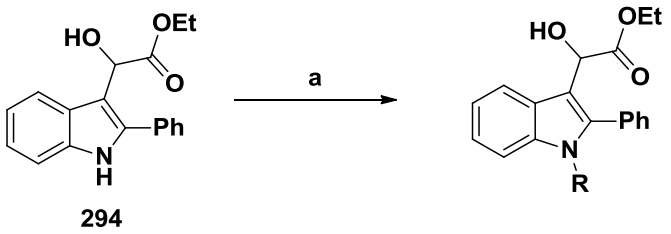
Attempts to esterify **294** proved unsuccessful (Scheme 165), with only decomposition observed, presumably through the same pathway discussed above.



294 297

Scheme 165: Attempted esterification of alcohol **294** (a) cyanoacetic acid, DMAP, DIC, CH_2Cl_2, rt

Attempts to protect the nitrogen with an electron-withdrawing group, which would hopefully suppress the dehydration pathway, did not prove successful. The same conditions used previously for indole **285** (Table 25, entry 1) gave a complex mixture of products, whereas more standard methods with sodium hydride returned only starting material (Table 25, entries 2 and 3).



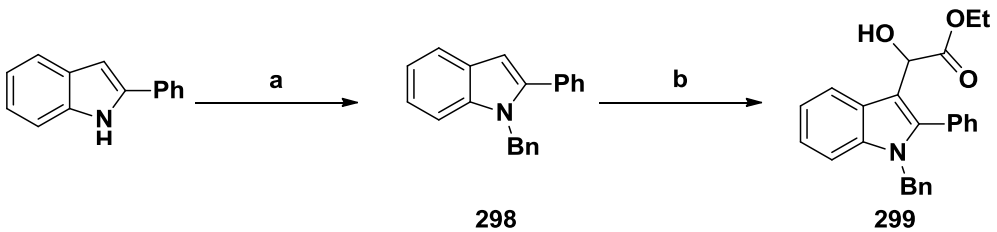
294

Scheme 166: Attempted protection of indole **294**. (a) See Table 25

Entry	Reagents	Solvent	Temp	Time (h)	Result
1	Boc_2O	pyridine	rt	8	intractable mixture
2	TsCl, NaH, DMAP	DMF	rt	15	SM
3	Boc_2O, NaH	DMF	rt	94	SM

Table 25: Attempted protection of indole **294**

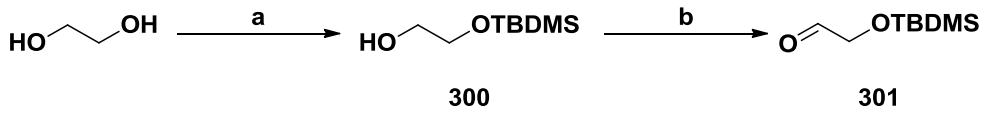
To circumvent this liability, 2-phenylindole was first *N*-protected with a benzyl group and then subjected to Friedel-Crafts conditions which yielded alcohol **299** in good yield (Scheme 167).



298 299

Scheme 167: Synthesis of α-hydroxy ester **299** (a) NaH, BnCl, DMF, rt, 48 h, 92 %; (b) ethyl glyoxylate, CH_2Cl_2, rt, 64 h, 84 %

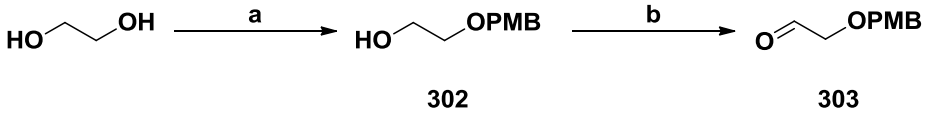
To expand the library of potential dCr substrates it was decided to synthesise other aldehydes that could also undergo this Friedel-Crafts reaction. Aldehyde **301** was prepared in two steps from ethylene glycol (Scheme 168) although both steps proceeded in poor yield, presumably due to the high volatility of the products.



300 301

Scheme 168: Synthesis of aldehyde **301** (a) TBDMS-Cl, NEt_3, DMAP, CH_2Cl_2, rt 20 h, 36 %; (b) DMSO, $(ClCO)_2$, pyridine, NEt_3, CH_2Cl_2, -78 °C to rt, 20 %

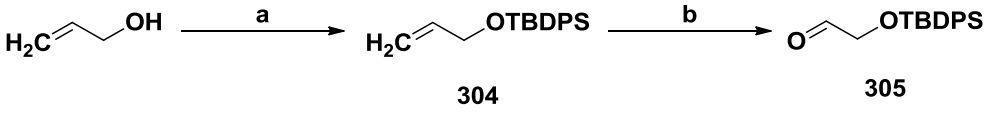
Changing the protecting group to *para*-methoxy benzyl allowed the synthesis of aldehyde **303** in 49 % yield over the two steps from ethylene glycol (Scheme 169).



302 303

Scheme 169 : Synthesis of aldehyde **303** (a) NaH, PMB-Cl, TBAI, THF, 80 °C, 4.5 h, 81 %; (b) DMSO, $(ClCO)_2$, pyridine, NEt_3, CH_2Cl_2, -78 °C to rt, 13 h, 60 %

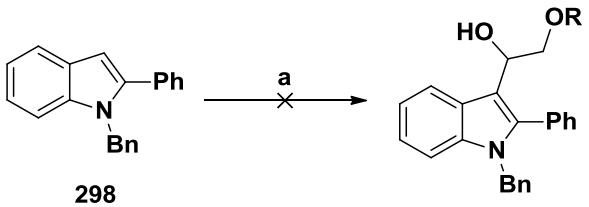
Aldehyde **305** was also synthesised by a slightly different route involving ozonolytic cleavage of a C=C double bond (Scheme 170).



304 305

Scheme 170: Synthesis of aldehyde **305** (a) imidazole, TBDPS-Cl, DMF, rt, 3.5 h, 99 %; (b) O_3, DCM, –78 °C, 1h, then PPh_3, rt, 4 h, 79 %

Unfortunately, attempts to effect reaction of aldehydes **303** and **305** with indole **298** did not prove successful (Table 26). Without a catalyst only starting material was observed, and in the presence of a Lewis acid a complex mixture of products was formed. This result was not wholly unsurprising due to the decreased electrophilicity of the aldehyde carbon atom in **303** and **305** compared to ethyl glyoxylate.



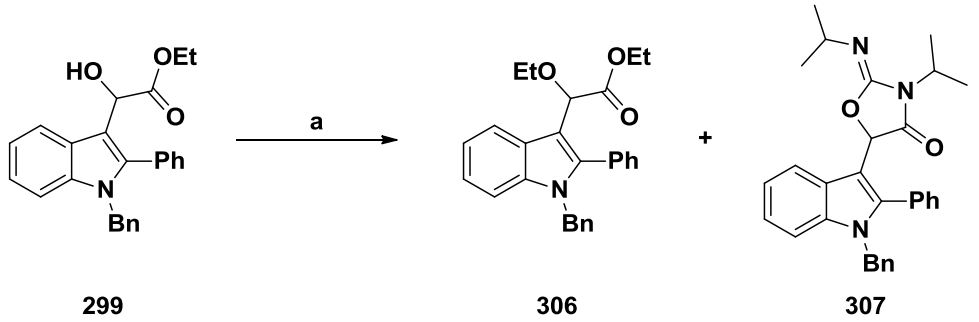
298

Scheme 171: Attempted Friedel-Crafts hydroxyalkylation with aldehydes **303** and **305.** (a) see Table 26

Entry	R	Lewis Acid	Solvent	Temperature	Time	Result
1	PMB	-	DCM	rt	24 h	SM
2	PMB	-	benzene	90 °C	96 h	SM
3	PMB	$Cu(OTf)_2$	benzene	90 °C	2 h	decomposition
4	TBDPS	-	DCM	rt	70 h	SM
5	TBDPS	$BF_3{\cdot}OEt_2$	DCM	rt	5 h	decomposition

Table 26: Reaction of aldehydes **303** and **305** with indole **298**

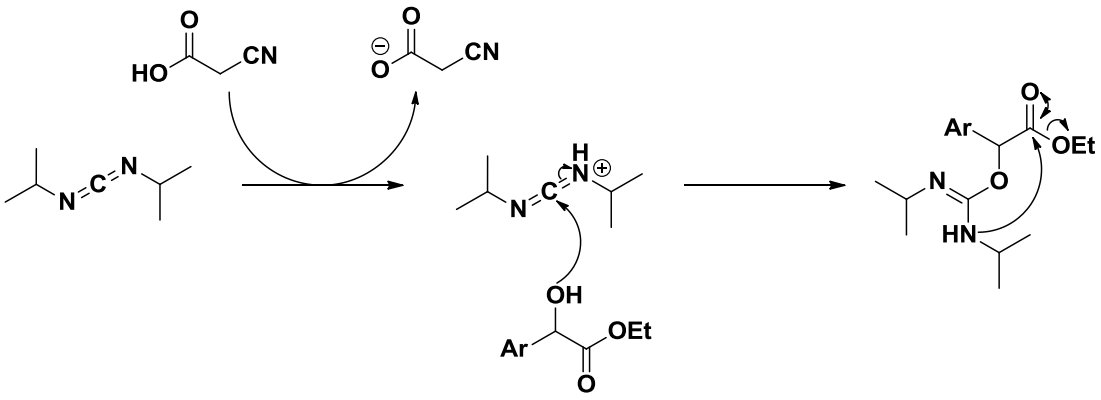
Attempts to esterify alcohol **299** using DIC as a coupling agent lead to the unwanted products **306** and **307** (Scheme 172).



299 **306** **307**

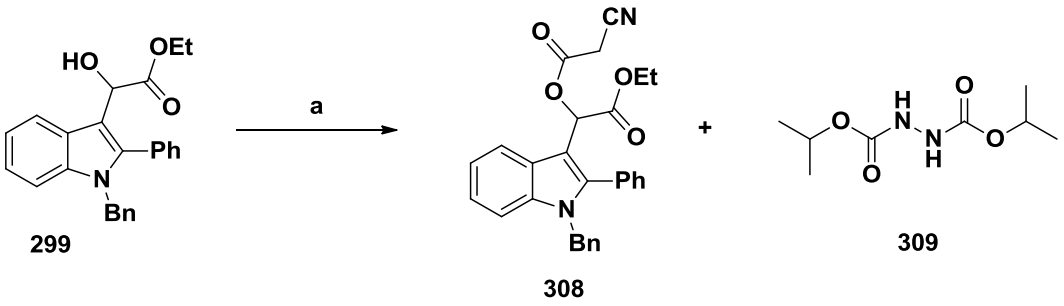
Scheme 172: Undesired products formed during attempted esterification of alcohol **299** (a) cyanoacetic acid, DMAP, DIC, CH_2Cl_2, rt, 42 h

Presumably **307** arises from attack of the diimide by the hydroxyl functionality and cyclisation onto the ester (Scheme 173). This releases an equivalent of ethoxide which can attack another molecule of the starting material via an S_N1 mechanism to form ether **306**.



Scheme 173: Proposed mechanism for formation of **307**

However, under Mitsunobu conditions esterification of **299** proceeded smoothly (Scheme 174). ^{1}H NMR analysis of the crude reaction mixture revealed complete consumption of the starting material and the presence of ester **308**, as evidenced by the AB quartet at δ_H = 3.56 ppm corresponding to the CH_2 α to the nitrile (Figure 20).



Scheme 174: Esterification of alcohol **216** (a) cyanoacetic acid, PPh_3, DIAD, THF, rt, 4 days

When the crude reaction mixture was subjected to silica gel chromatography however, only the starting alcohol **299** was isolated. This led to the conclusion that the ester was undergoing hydrolysis under the purification conditions; a hypothesis that was further supported by the isolation of carbamate **309** which would have been formed had the esterification been successful. Attempts to isolate the ester using basic alumina chromatography also returned only starting material.

It was envisioned that the use of cyanoacetyl chloride would allow the synthesis of ester **308** without the need for purification as the side products could be removed via an aqueous work up. Although the synthesis of the acyl chloride from cyanoacetic acid proceeded smoothly (Scheme 175), the desired ester was not produced cleanly, although once again ^{1}H NMR analysis of the crude product indicated that it was formed as part of a mixture of products.

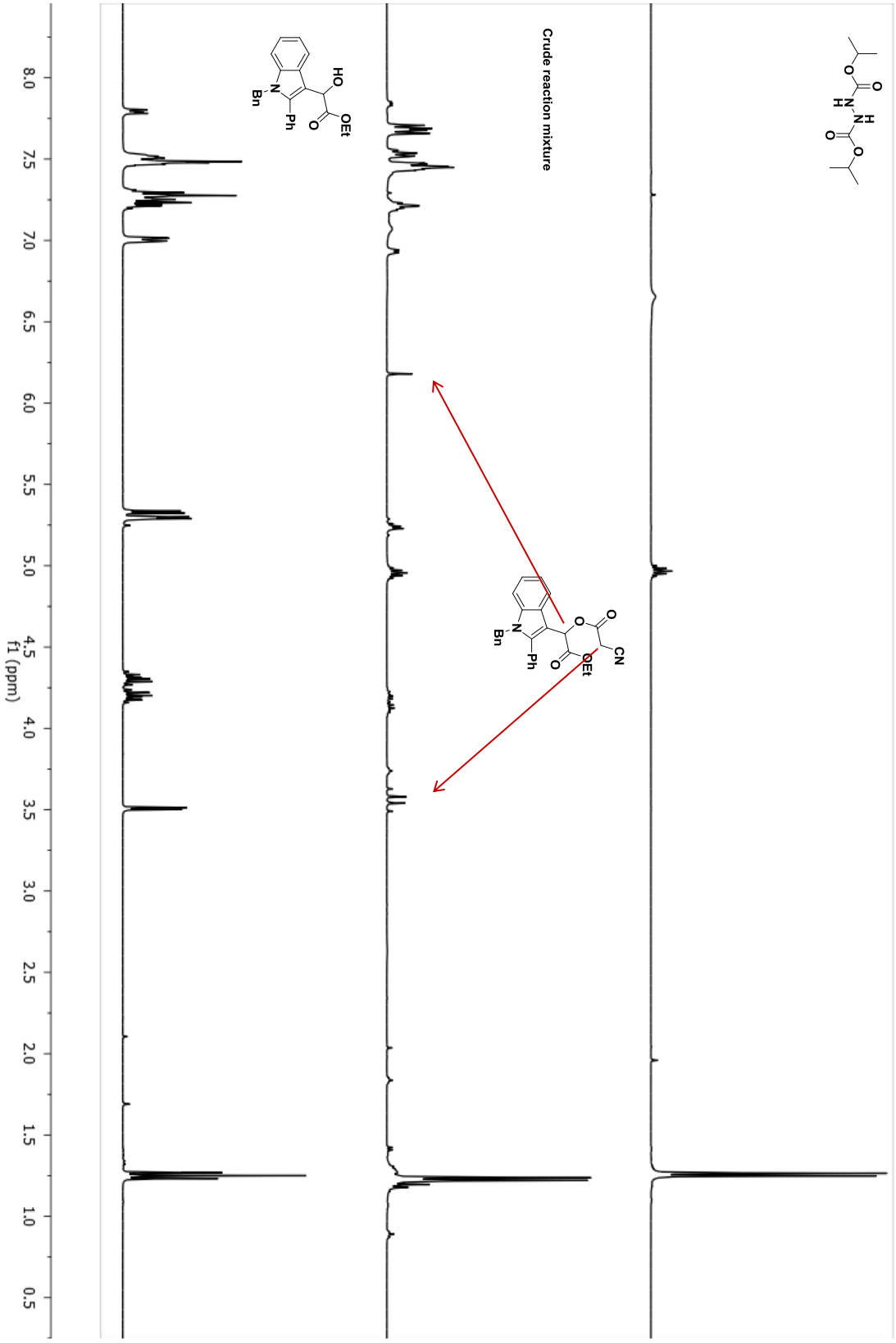
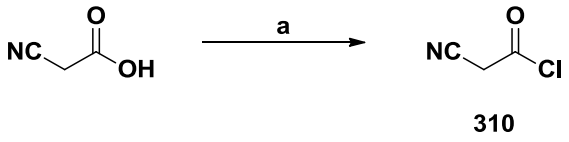


Figure 20: Formation of ester **308** as part of the crude reaction mixture, with indicative signals highlighted in the ^{1}H NMR.

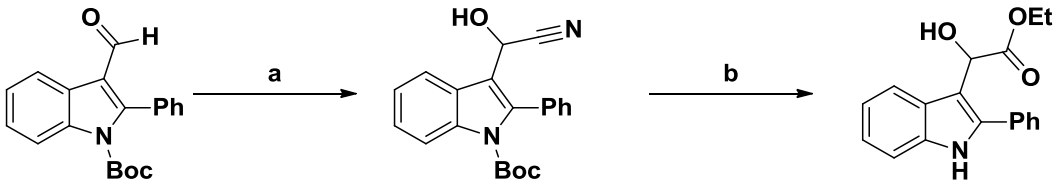


310

Scheme 175: Synthesis of cyanoacetyl chloride (a) PCl_5, Et_2O, rt, 2.5 h, 52 %

3.3.4 Synthesis of a model system *via* a cyanohydrin

These experiments had shown that indoles possessing alkyl protecting groups were not suitable for this synthesis due to the lability of the benzylic C-O bond, and therefore it was decided to synthesise analogues containing electron-withdrawing protecting groups. Reaction of aldehyde **286** with trimethylsilyl cyanide and ZnI_2 gave cyanohydrin **311** (Scheme 176). Although this could not be purified by silica gel chromatography, the crude reaction mixture was subjected to acidic alcoholysis. The only product isolated was the de-protected ester **294** in 60 % yield over two steps, which in Section 3.3.3 had been shown to be ineffective for the synthetic route.

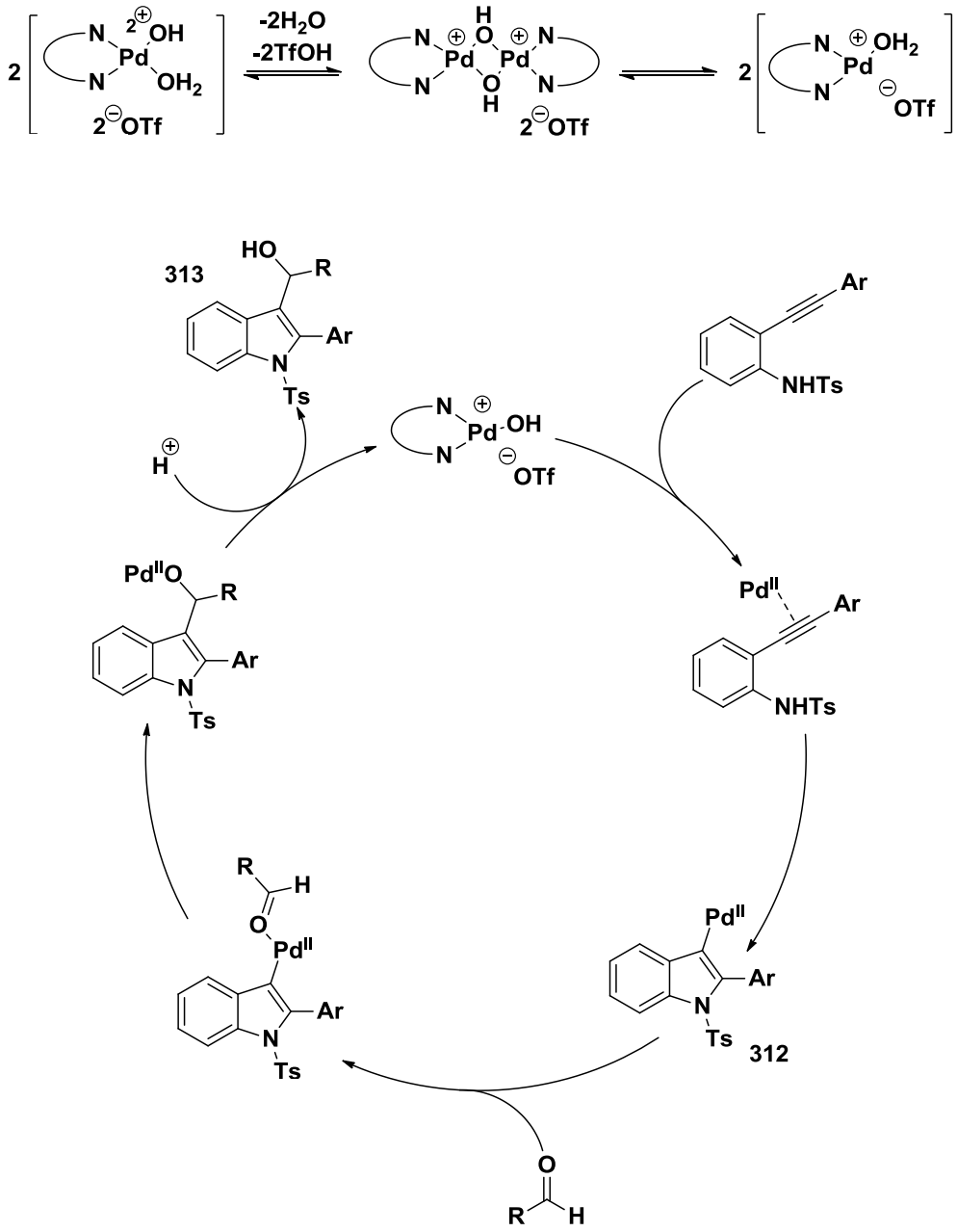


286 311 294

Scheme 176: Synthesis of the undesired ester **294** by alcoholysis of cyanohydrin **311** (a) TMSCN, ZnI_2, CH_2Cl_2, rt, 3.5 h; (b) EtOH, HCl, CH_2Cl_2, rt 15 h

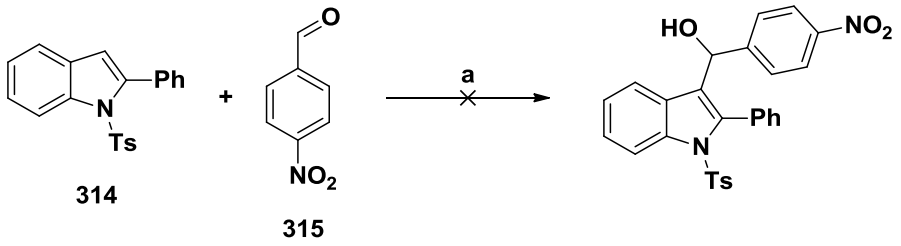
3.3.5 Synthesis of a model system *via* a palladium catalysed cyclisation

In 2010, Lu *et al.* reported the synthesis of 3-hydroxymethyl indoles via a Pd(II)-catalysed reaction.[93] They proposed a mechanism by which the palladium catalyst coordinates to the alkyne and an amino-palladation reaction occurs to give intermediate **312**. The carbon-palladium bond is then intercepted by a highly electrophilic aldehyde, where R is an electron poor aromatic system, to give the desired product **313** (Scheme 177).



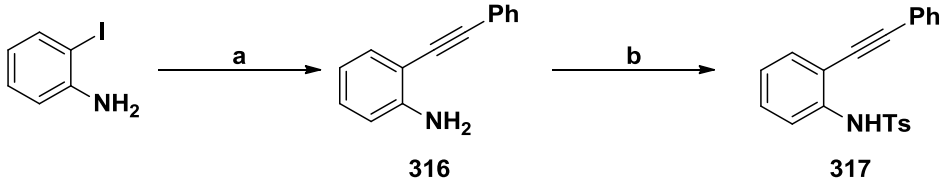
Scheme 177: Cationic Pd(II)-catalysed tandem reaction of 2-arylethynylanilines and aldehydes

Control experiments showed that the mechanism was indeed a tandem reaction, and not a one pot, two-step process (Scheme 178). 2-phenyl-*N*-tosyl indole (**314**), which has previously been shown to form under Pd(II) cyclisation conditions,[94] did not react with 4-nitrobenzaldehyde (**315**) by a palladium catalysed Friedel-Crafts type reaction.



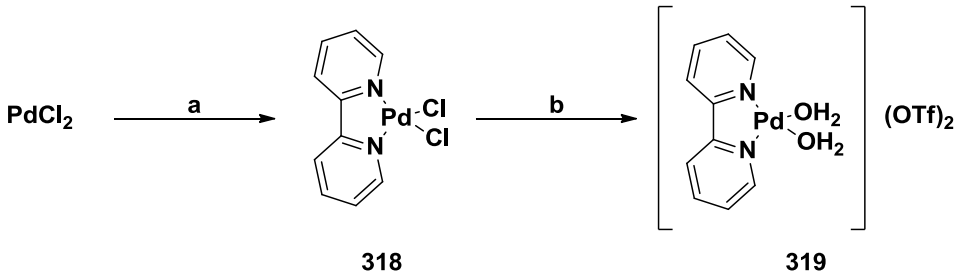
Scheme 178: Mechanistic studies ruling out the presence of **314** in the catalytic cycle (a) $Pd(bpy)(H_2O)_2(OTf)_2$, dioxane, 60 °C, overnight

The required alkyne **317** was synthesised in two steps from *o*-iodoaniline following a literature procedure consisting of a Sonogashira coupling followed by nitrogen protection (Scheme 179).



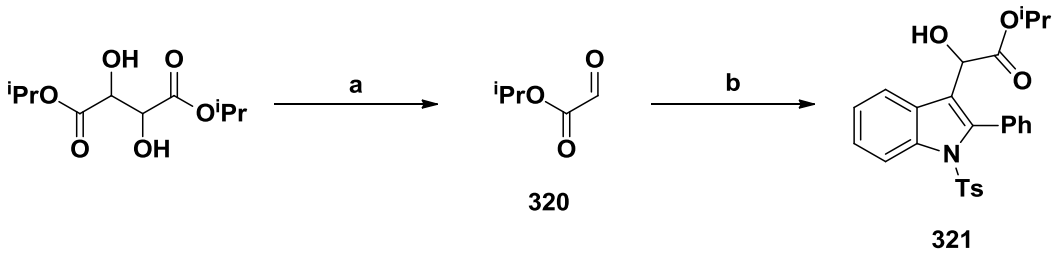
Scheme 179: Synthesis of alkyne **317** (a) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, rt, 48 h, 90 %; (b) TsCl, pyridine, CH_2Cl_2, rt, 48 h, 94 %

The required catalyst **319** was then prepared from palladium (II) chloride (Scheme 180).



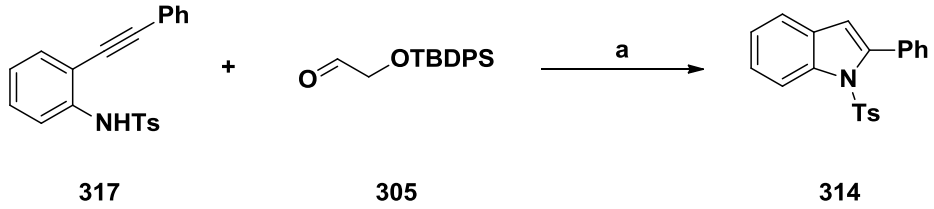
Scheme 180: Synthesis of the required catalyst (a) 2,2'-bipyridine, MeOH, rt, 7 h, 63 %; (b) AgOTf, H_2O, rt, 24 h, 88 %

Gratifyingly, the reaction of aniline **317** with isopropylglyoxylate (**320**) proceeded smoothly, giving the desired alcohol **321** in 96 % yield (Scheme 181). If the dioxane solvent was not efficiently dried prior to the reaction 2-phenyl-*N*-tosyl indole **314** was formed as a competing product and the isolated yield was lower.



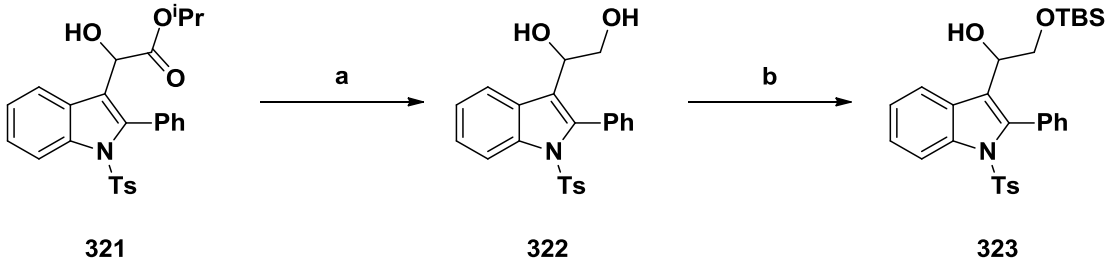
Scheme 181: Synthesis of indole **321** by palladium-catalysed cyclisation (a) $NaIO_4$, H_2O, 0 °C, 2.5 h; (b) aniline **317**, catalyst **319**, dioxane, 60 °C, 16 h, 96 %

Attempts to perform the reaction with the less electrophilic aldehyde **305** returned only the 3-H indole **314** (Scheme 182).



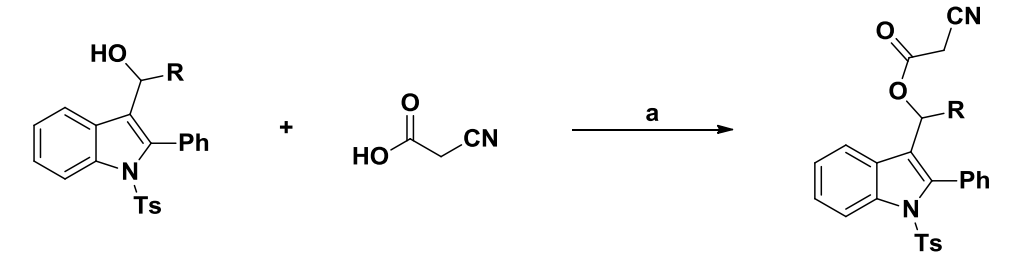
Scheme 182: Formation of the undesired 3-H indole **314** (a) catalyst **319**, dioxane, 60 °C, 41 h, 70 %

It did however prove possible to synthesise an analogue of **321** by reduction of the ester functionality of **321** with lithium aluminium hydride, followed by selective protection of the primary alcohol (Scheme 183).



Scheme 183: Synthesis of protected alcohol**323** (a) $LiAlH_4$, THF, rt, 6 h, 80 %; (b) TBSCl, Et_3N, DMAP, DCM, rt, 21 h, 90 %

Alcohols **321** and **323** were then subjected to standard esterification conditions to give the dCr substrates **324** and **325** (Scheme 184).



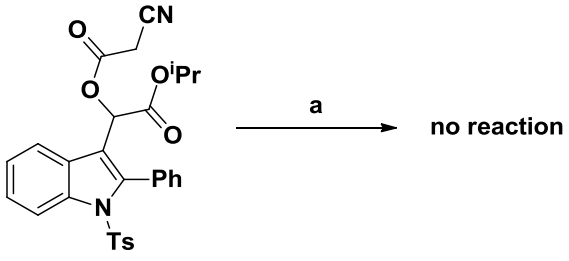
R = $CO_2{}^{i}Pr$ = 321
R = CH_2OTBS = 323

R = $CO_2{}^{i}Pr$ = 324
R = CH_2OTBS = 325

Scheme 184: Esterification of alcohols **321** and **323** (a) $T_3P^{®}$, Et_3N, DCM. R = $CO_2{}^{i}Pr$, 5 h, 78 %. R = CH_2OTBS, 16 h, 68 %

3.3.6 dCr Reaction of model system

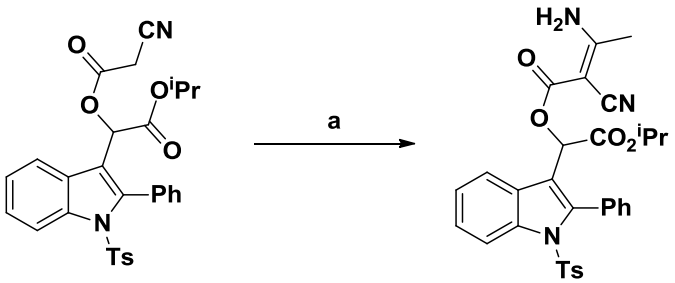
Subjection of ester **324** to standard dCr conditions under microwave heating gave what initially appeared to be a complex mixture of products with a very low isolated yield. Thermal stability studies in toluene returned just starting material at temperatures up to 200 °C with no decomposition observable (Scheme 185).



324

Scheme 185: Thermal stability studies of ester **324** (a) PhMe, µw, 100 °C ,5 min then 120 °C, 5 min, then 150 °C, 5 min, then 200 °C, 5 min

Repetition of the dCr reaction with a more careful analysis of the crude dCr reaction mixture and flushing of the column with methanol revealed the presence of a highly polar compound **326** (Scheme 186). A large difference (3.14 ppm) in chemical shifts for the two protons attached to the newly introduced nitrogen atom was observed, suggesting a hydrogen bond between the ester carbonyl oxygen and the nitrogen and therefore a *Z*-geometry of the enamine.



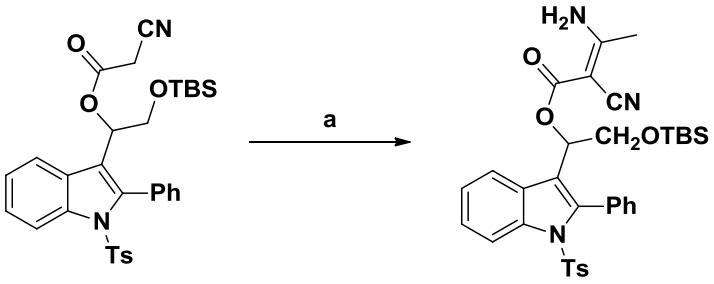
324 **326**

Scheme 186: Formation of enamine **326** under dCr conditions (a) BSA, KOAc, µw, see Table 27

Entry	Temperature	Time	Yield
1	120 °C	15 x 1 min pulses	36 %
2	80 °C	35 min	60 %

Table 27: Attempted dCr reaction of **324**

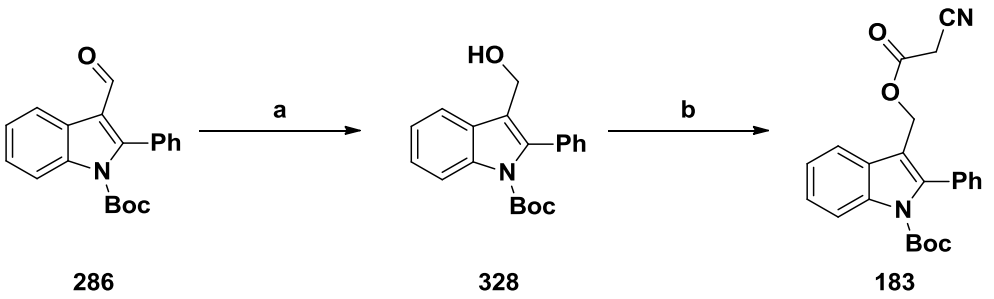
The same result was noted for the protected alcohol **325** (Scheme 187).



325 **327**

Scheme 187: Formation of enamine **327** under dCr conditions (a) BSA, KOAc, µw, 60 min, 56 %

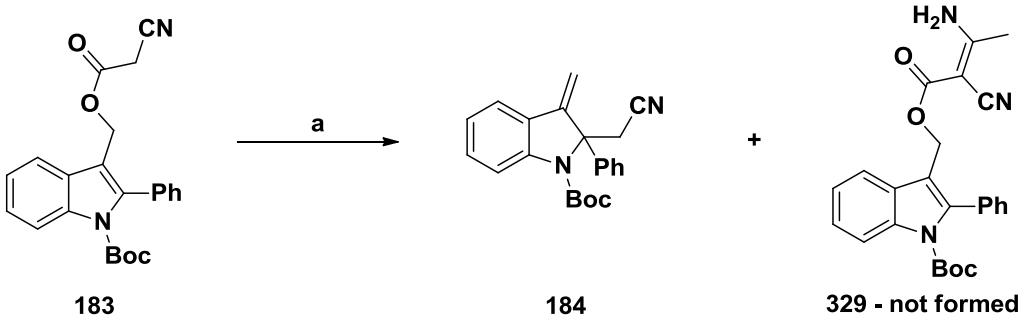
This result contrasted with work previously carried out within the group on indole **183**, which had been shown to rearrange successfully under these conditions, albeit in a relatively low yield of 56 %. This low yield, combined with the fact that the high polarity of **326** makes it difficult to observe under standard TLC conditions, raised the possibility that the analogous compound **329** had indeed been formed during the dCr of **183**, but had not been isolated. To test this indole **183** was synthesised in two steps from aldehyde **286** (Scheme 188), and then subjected to the dCr reaction (Scheme 189).



286 328 183

Scheme 188: Synthesis of ester **183** (a) $NaBH_4$, MeOH, rt, 1 h, 96 %; (b) cyanoacetic acid, $T_3P^®$, Et_3N, DCM, rt, 36 h, 87 %

However the only product isolated was the [3,3]-rearrangement product **184**, with no evidence for the formation of enamine **329** (Scheme 189).



183 184 329 - not formed

Scheme 189: Subjection of ester **183** to dCr conditions showing no evidence for the formation of enamine **329** (a) BSA, KOAc, µw, 150 °C, 4 x 1 min, 37 %

Closer analysis of the ^{13}C NMR of **324** and **325** showed a possible explanation for why the dCr reaction had failed for these examples. As expected, the ^{13}C NMR spectrum of diol **322** contains two signals for the *ortho*- and *meta*- carbons of the phenyl substituent respectively. As the size of the substituent at the homo-benzylic position increases, more signals are observed (Figure 21), indicating that the two *ortho*-positions are no longer equivalent, and neither are the two *meta*- positions.

This chemical inequivalence indicates hindered rotation caused by a sterically crowded environment around the phenyl substituent and, by extension, the C2 position of the indole. This high level of steric shielding at the position where the new carbon-carbon bond would be formed means that the [3,3]-rearrangement cannot take place, and instead the silyl ketene acetal instead reacts with BSA to give the undesired enamine.

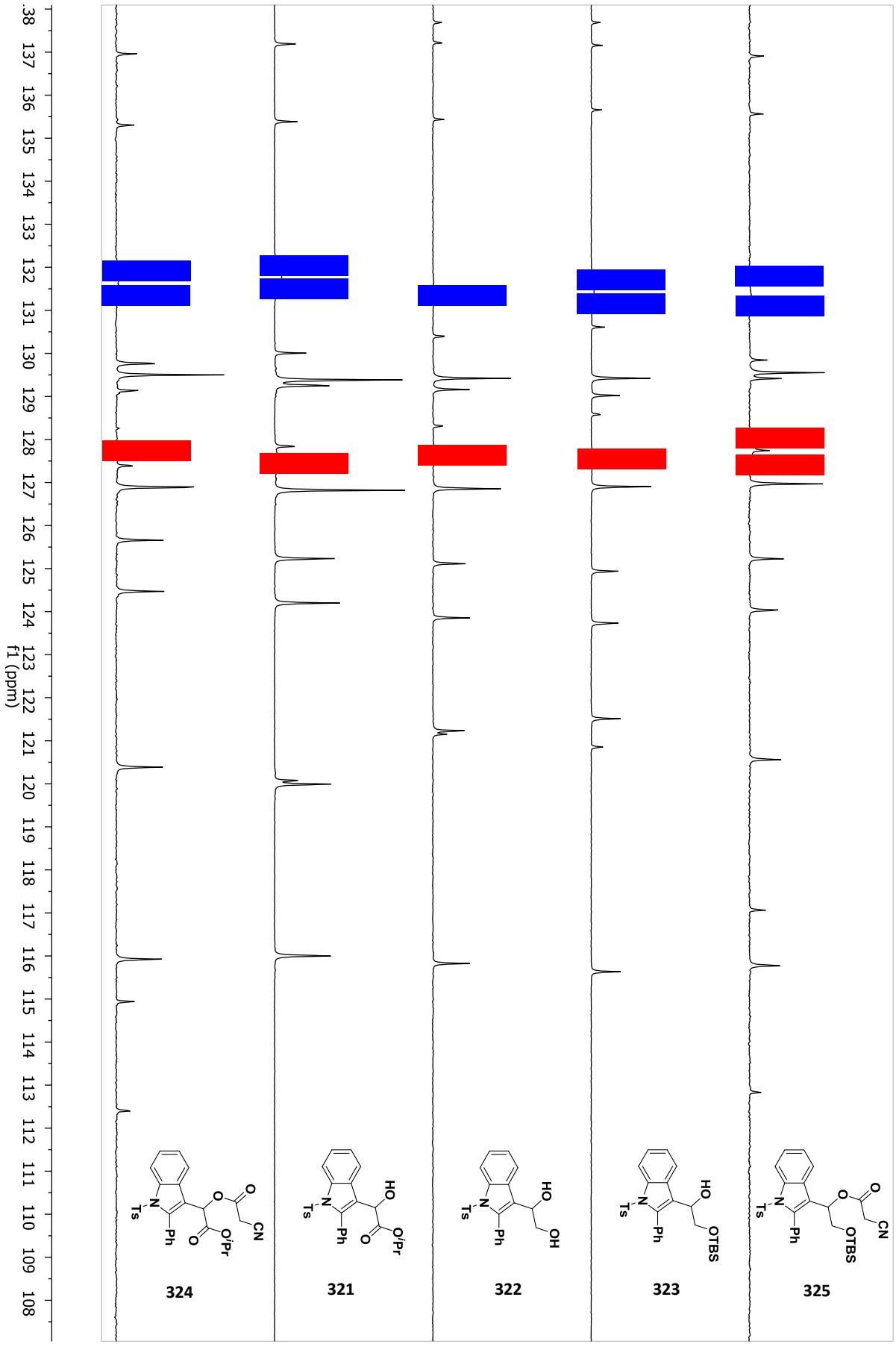


Figure 21: Chemical inequivalence of the carbons of the phenyl substituent in **324** and **325.** Signals corresponding to the *ortho*-carbons are highlighted in blue, and signals corresponding to the *meta*- carbons are highlighted in red.

3.3.7 – Second generation retrosynthesis

With the failure of the dCr reaction it was decided to attempt other routes to hinckdentine A, still using a variant of the Claisen rearrangement to synthesise the required quaternary centre.

In the original retrosynthesis, a nitrile was reduced in order to obtain the amine required for lactamisation. Replacing the nitrile with an amide would still give the amine **331** upon reduction. Amide **332** could be formed from ester **333** by a trimethylaluminium-facilitated reaction, with ester **333** in turn formed from Johnson-Claisen rearrangement of alcohol **334** (Figure 22).

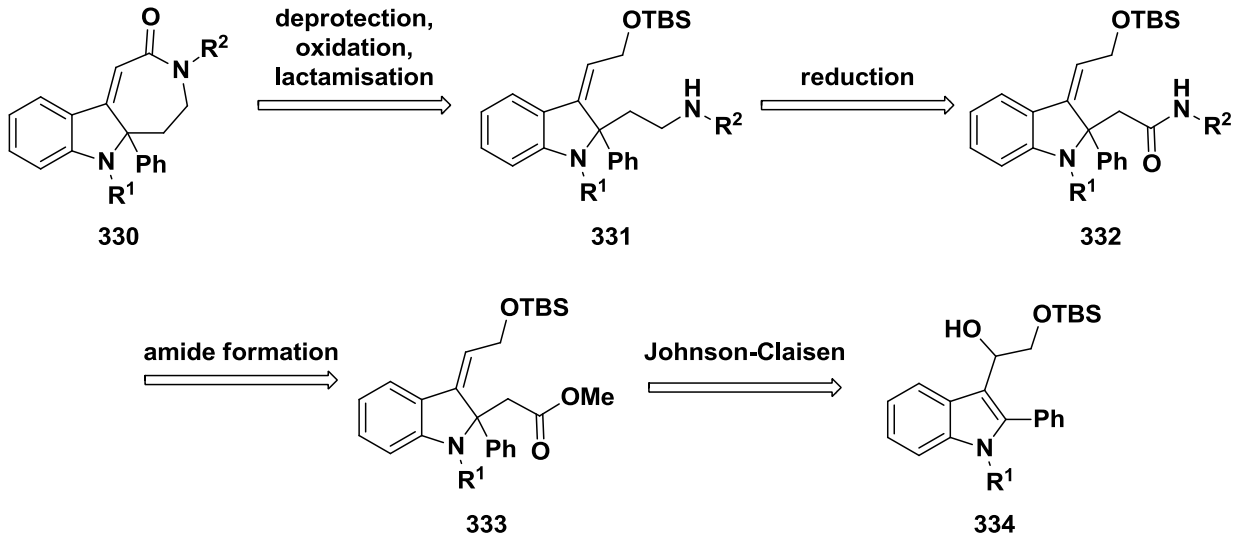


Figure 22: Proposed retrosynthesis of Hinckdentine model system *via* a Johnson-Claisen rearrangement

It should also be possible to synthesise amide **332** directly *via* an Eschenmoser-Claisen rearrangement, which would miss out the need for an amide formation step. However, this would require either the synthesis of a dimethyl acetal derived from a secondary acetamide or a separate deprotection step (Figure 23).

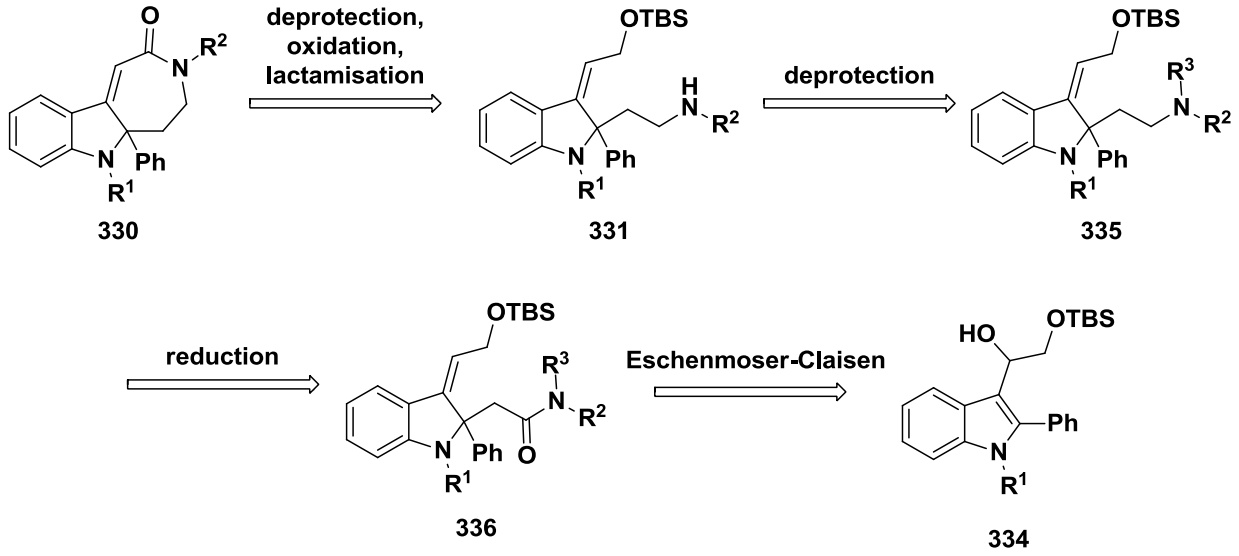


Figure 23: Proposed retrosynthesis of Hinckdentine model system via a Eschenmoser-Claisen rearrangement

An alternative route to amide **332** would be to use a Belluš-Claisen rearrangement with ketene and either thio ether **338** (Figure 24) or amine **339** (Figure 25). If a thiol was used then again an amide forming reaction would be needed.

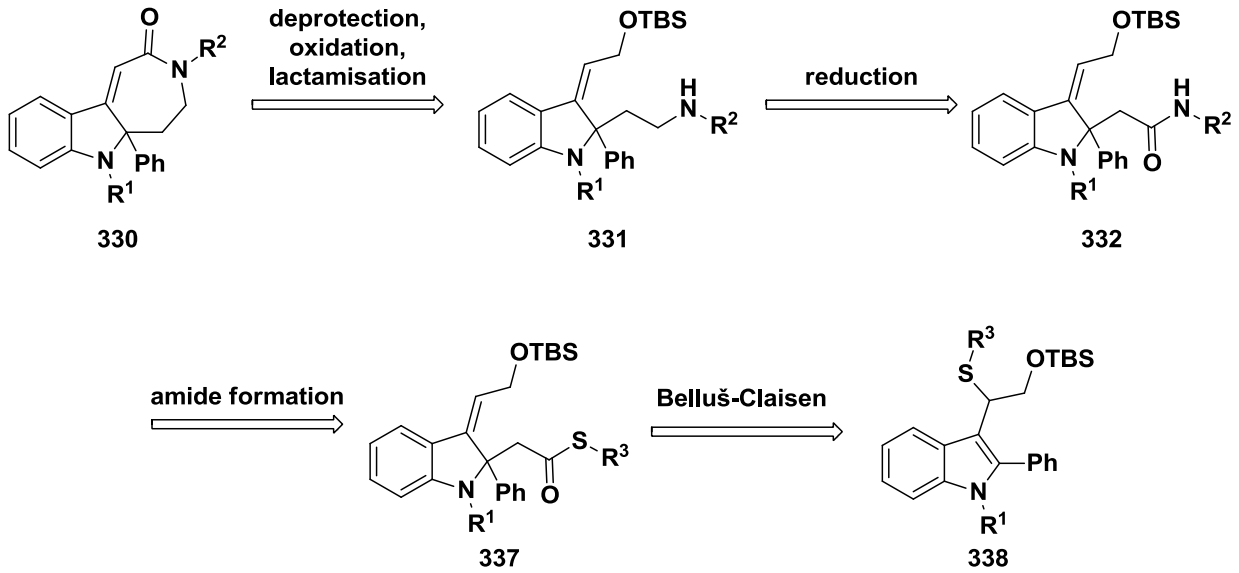


Figure 24: Proposed retrosynthesis of hinckdentine model system via a Belluš-Claisen rearrangement of a thioether

If an amine was used, then similar problems to those encountered in the Eschenmoser-Claisen pathway would have to be overcome.

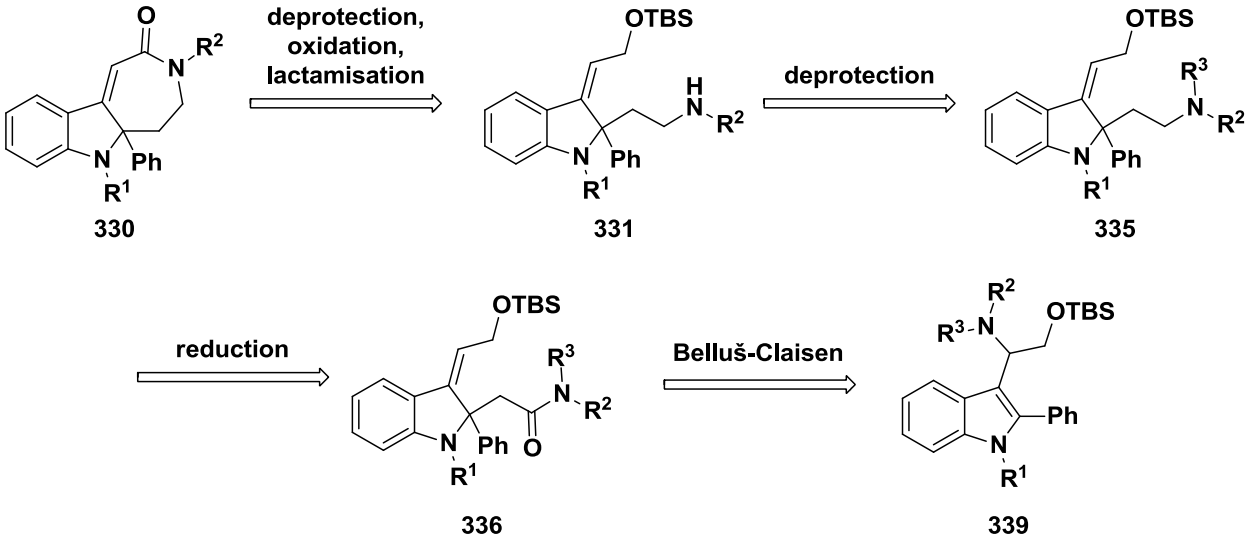


Figure 25: Proposed retrosynthesis of Hinckdentine model system via a Belluš-Claisen rearrangement of an amine

Although ketene itself may be used in the Belluš-Claisen rearrangement, more commonly the highly electrophilic dichloroketene is used.[95] If this was the case then an extra dechlorination step would be required. An alternative approach would be to use cyanoketene, which would require the incorporation of a hydrolysis-decarboxylation step (Figure 26).

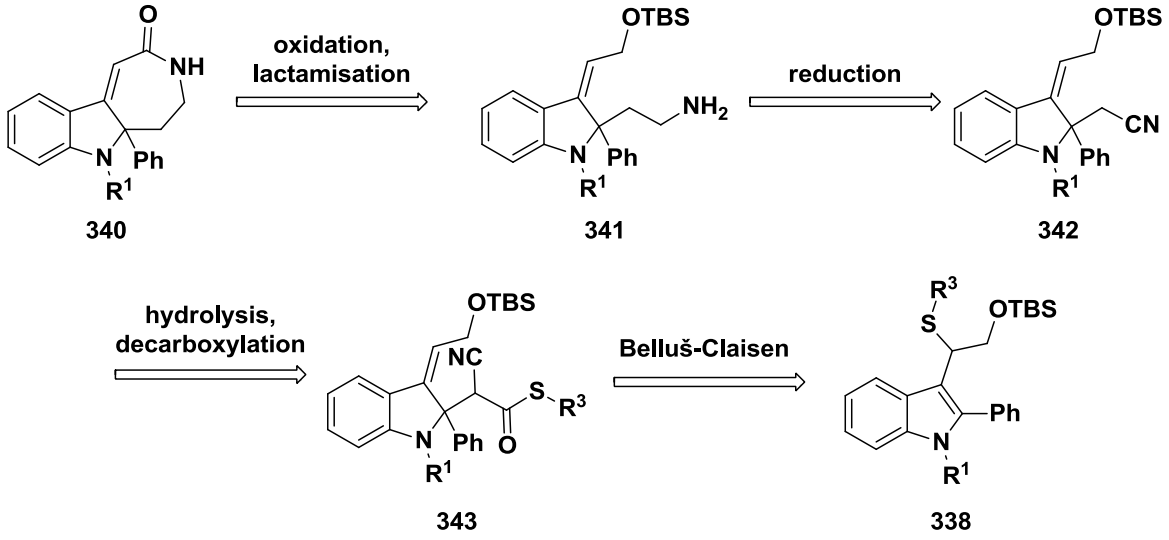
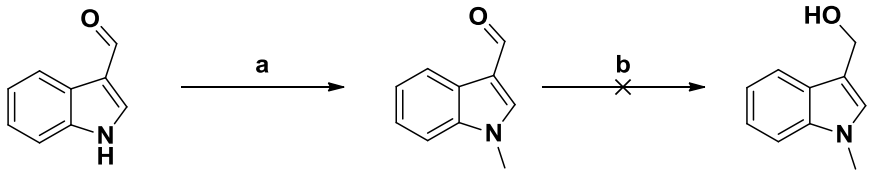


Figure 26: Proposed retrosynthesis of hinckdentine model system via a Belluš-Claisen rearrangement of a thioether and cyanoketene

3.3.8 - Johnson-Claisen reactions of an indole with an alkyl protecting group

As this reaction had not been attempted before, it was decided to first try the transformation on a simple model substrate. An indole possessing an alkyl protecting group was chosen, as it was hoped that the resonant electron-donating effect of the nitrogen atom would weaken the benzylic C-O bond, and that this would allow a lower reaction temperature than an indole possessing an electron-withdrawing group on nitrogen. To generate the alcohol required for the Johnson- and Eschenmoser-Claisen reactions indole-3-carbaldehyde was reacted with sodium hydride and iodomethane and then subjected to reduction conditions (Scheme 190).



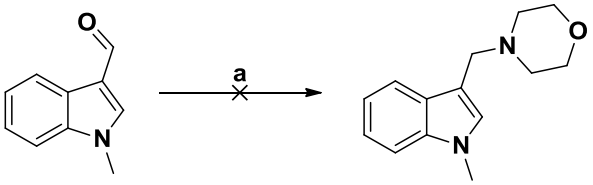
344 **345**

Scheme 190: Attempted synthesis of alcohol **345** (a) NaH, DMF, rt, 1 h; then MeI, rt, 1 h, 78 %; (b) $NaBH_4$, MeOH, rt, 1 h

Unfortunately, alcohol **345** proved highly unstable. A literature search showed that Leete had previously discussed problems with decomposition of this compound in his 1959 paper on 3-hydroxymethyl indoles due to the electron-donating effect of the indole nitrogen weakening the benzylic C-O bond.[96]

3.3.9 - Belluš-Claisen reactions of an indole with an alkyl protecting group

Again a simple model system was chosen to probe the feasibility of this reaction pathway and a morphiline-based amine was chosen due to this being the most developed example in the literarure. Initial attempts to synthesise amine **346** *via* a reductive amination pathway failed (Scheme 191, Table 28) with only the starting aldehyde **344** being returned.



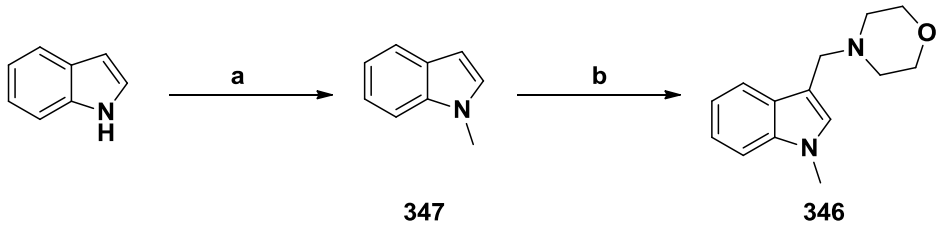
344 **346**

Scheme 191: Attempted synthesis of amine **346** *via* a reductive amination (a) morpholine, $NaBH(OAc)_3$, AcOH, see Table 28

Entry	Solvent	Equiv AcOH	Temp	Time (h)	Outcome
1	DCM	0.1	rt	48	SM recovered
2	THF	0.1	rt	48	SM recovered
3	THF	0.5	rt	48	SM recovered
4	THF	0.5	reflux	24	SM recovered

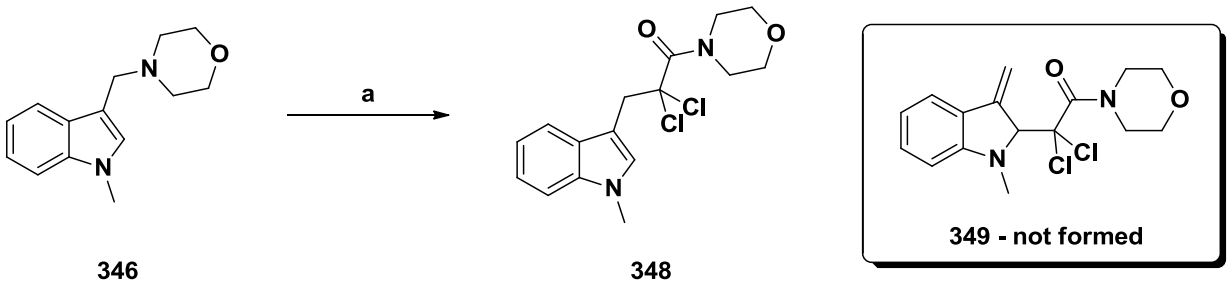
Table 28: Conditions for attempted reductive amination of aldehyde **344**

However, a Mannich reaction with a super stoichiometric amount of $ZnCl_2$ gave the desired amine **346** in 64 % yield (Scheme 192).



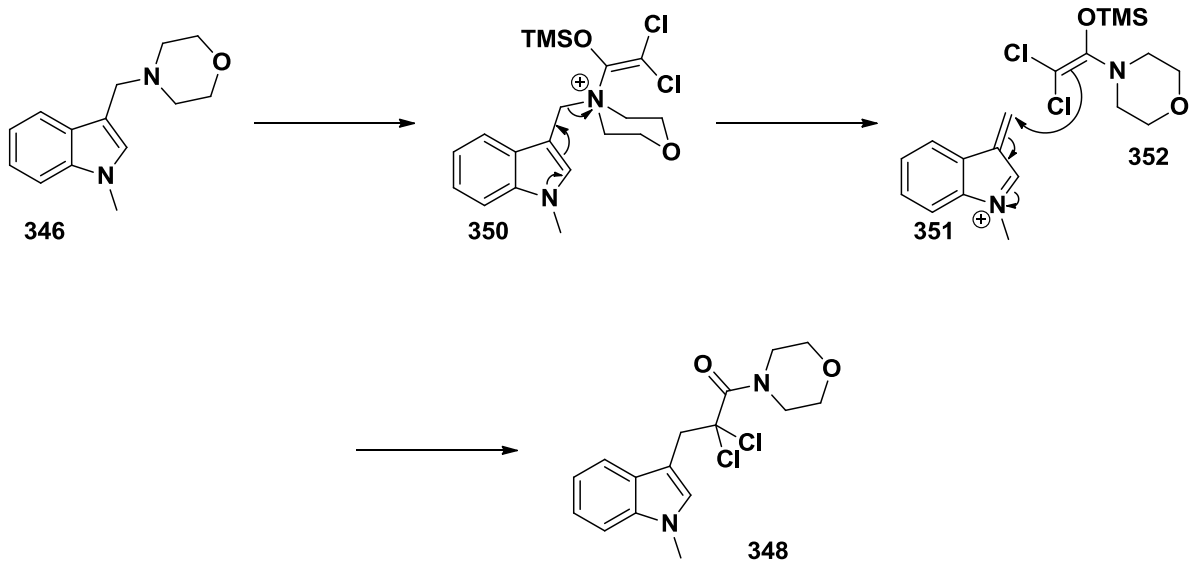
Scheme 192: Synthesis of amine **346** *via* a Mannich reaction (a) NaH, THF, rt 1 h; then MeI, rt, 2 h, 88 % (b) morpholine, $ZnCl_2$, formaldehyde (37 % aq), EtOH, rt, 2.5 h, 64 %

Using conditions developed witin the Craig group,[97] the Belluš-Claisen rearrangement was first tested with dichloroketene, which was produced *in situ* by elimination of HCl from dichloroacetylchloride. Although using this would require an extra dechlorination step, it was envisioned that the the highly electrophilic ketene gave the best chance for success in the Belluš-Claisen reaction. The reaction proceeded rapidly at room temperature giving a mixture of products. Purification by silica gel chromatography isolated a product containing an amide (as evidenced by the peak at 1652 cm^{-1} in the IR spectrum) and the correct mass. However, closer analysis revealed this to be the product of formal [1,3]-rearrangement **348** as opposed to the desired [3,3]-rearrangement product **349** (Scheme 193).



Scheme 193: Formation of the formal [1,3]-rearrangement product **348** (a) dichloroacetyl chloride, TMSOTf, NR_3, see Table 29

Presumably **348** was formed by reaction of the ketene and the amine and subsequent elimination of the charged ammonium ion **350**. The resulting iminium **351** could then be attacked by silyl ketene aminal **352** to generate **348** (Scheme 194).



Scheme 194: Proposed mechanisms for the formation of [1,3]-rearrangement product **263**

Although amide **348** was not the desired product for the synthesis of hinckdentine A, it was still hoped that this methodology could be optimised, as to date the only examples of ketene insertion into carbon-nitrogen bonds have been in organometallic systems.[98]

Due to the speed of the reaction, and the number of products formed, monitoring by TLC proved difficult, so the reaction mixture was stirred for a given amount of time before being quenched by addition of 1M sodium hydroxide. Without the presence of trimethylsilyl triflate none of the desired product was observed (Table 29, entry 2) and decreasing the reaction time increased the isolated yield (Table 29, entry 3). The yield was also increased by lowering the reaction temperature (Table 29, entry 4) and changing the

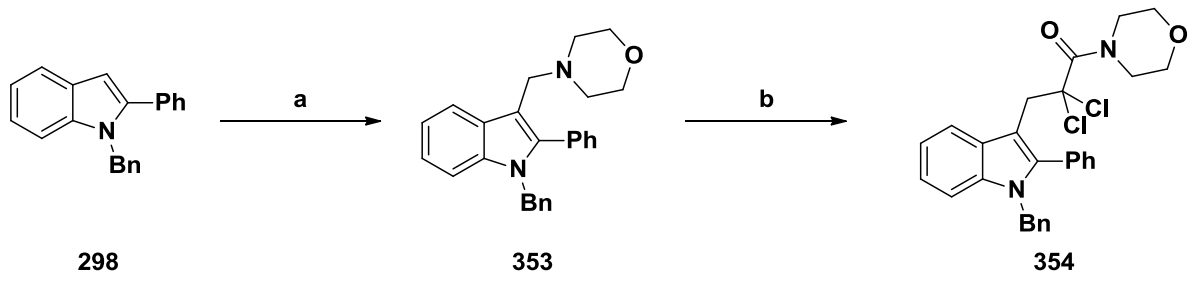
base to triethylamine (Table 29, entry 5). It was hoped that lowering the solvent polarity would increase the yield, as it would hold the two species generated after the elimination step closer together in a solvent cage, allowing a more facile recombination. However, at –78 °C in toluene (Table 29 entry 6) none of amide **348** was isolated and at room temperature (Table 29, entry 7) the yield was only 10 %. Increasing the solvent polarity (Table 29, entry 8) led to no product formation.

Unfortunately, time constraints meant that the optimisation of this reaction was not developed further.

Entry	Additive	Base	Solvent	Temp	Time (min)	Yield (%)
1	TMS-OTf	Et^{i}Pr$_2$N	DCM	rt	30	12
2	-	Et^{i}Pr$_2$N	DCM	rt	30	-
3	TMS-OTf	Et^{i}Pr$_2$N	DCM	rt	5	13
4	TMS-OTf	Et^{i}Pr$_2$N	DCM	–78 °C	5	17
5	TMS-OTf	Et_3N	DCM	–78 °C	5	24
6	TMS-OTf	Et_3N	PhMe	–78 °C	5	-
7	TMS-OTf	Et_3N	PhMe	rt	120	10
8	TMS-OTf	Et_3N	MeCN	–78 °C	5	-

Table 29: Conditions for dichloroketene insertion

The same result was noted for the 2-phenyl analogue **353**, which was produced from **298** in an analagous manner (Scheme 195).



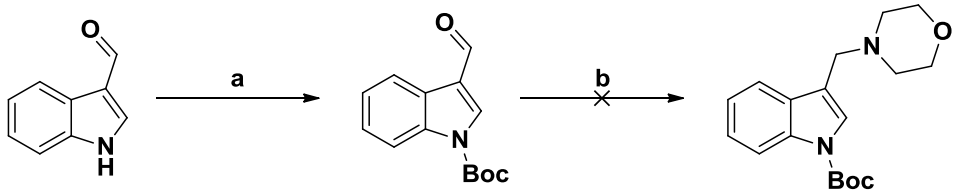
298 **353** **354**

Scheme 195: Formation of the formal [1,3]-rearrangement product **354** (a) morpholine, formaldehyde (37 % $_{aq}$), $ZnCl_2$, EtOH, rt, 28 h, 61 %; (b) dichloroacetyl chloride, Hunig's base, TMS-OTf, DCM rt, 5 min, 24 %

3.3.10 - Belluš-Claisen reactions of an indole with an electron-withdrawing protecting group

It was hoped that the undesired [1,3]-rearrangement pathway could be suppressed by using an electron-withdrawing protecting group on nitrogen. This would hinder the elimination step of the above reaction by making the nitrogen lone pair less accessible. It was anticipated that the synthesis of the desired amine by a Mannich reaction, as described in Section 3.3.9, would be unsuccessful in this case due to the decreased nucleophilicity of the C3 position. However, it was hoped that a reductive amination would be more successful than for **344** due to the increased electrophilicity of the aldehyde carbon.

Protection of indole-3-carbaldehyde with di-*tert*-butyl dicarbonate proceeded smoothly, however once again the reductive amination step failed (Scheme 196 and Table 30).



355 **356**

Scheme 196: Attempted synthesis of amine **356** *via* a reductive amination (a) Boc_2O, Et_3N, DMAP, DCM, rt, 1 h, 89 %; (b) morpholine, see Table 30

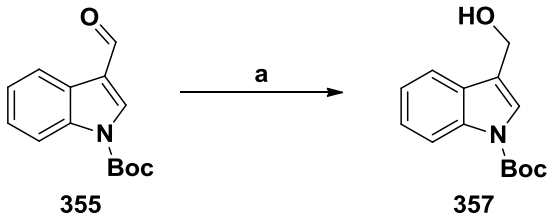
Entry	Catalyst	Reductant	Solvent	Yield (%)
1	AcOH	$Na(OAc)_3BH$	THF	0
2	AcOH	$Na(OAc)_3BH$	DCM	0
3	CF_3CO_2D	-	$CDCl_3$	0
4	4 Å MS	-	$CDCl_3$	0

Table 30: Screening of conditions for reductive amination of **355**

When standard reductive amination conditions (Table 30, entries 1 and 2) failed to give any product, it was decided to investigate whether the iminium intermediate was being formed under the reaction conditions. Therefore, aldehyde **355** and morpholine were reacted in $CDCl_3$ in the presence of either deuterated-TFA

(Table 30, entry 3) or molecular sieves (Table 30, entry 4) and aliquots were taken for ^{1}H NMR analysis. However, in both cases no reaction was observed.

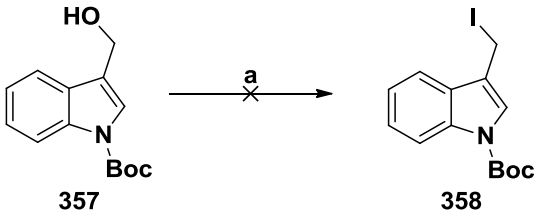
An alternative route to amine **356** was envisaged to be *via* an S_N2 displacement with morpholine. Therefore alcohol **357** was produced from the aldehyde by reduction with sodium borohydride (Scheme 197).



355 357

Scheme 197: Reduction of aldehyde **355** (a) $NaBH_4$, MeOH, rt, 1 h, 98 %

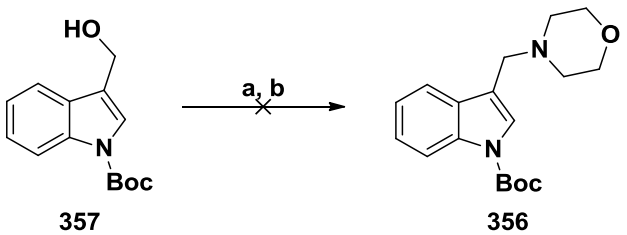
^{1}H NMR analysis of the crude product of an Appel reaction of alcohol **357** with iodine (Scheme 198) gave a promising result, with a slight upfield shift of the benzylic methylene protons. However, attempts to isolate the product resulted only in decomposition.



357 358

Scheme 198: Attempted Appel reaction of alcohol **357** to give iodide **358** (a) I_2, PPh_3, imidazole, DCM, rt, 17 h

Attempts to displace an *in situ* formed tosylate also proved unsuccesful. Despite the starting alcohol being completely consumed (by TLC analysis) before the addition of the amine, the only isolated product was *N*-tosyl morpholine (Scheme 199).

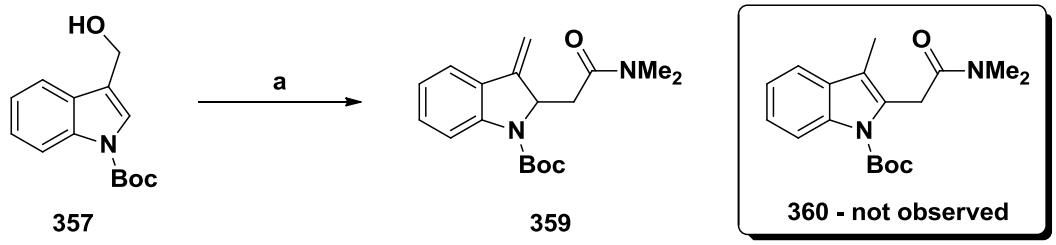


357 356

Scheme 199: Attempted synthesis of amine **356** *via* displacement of a tosylate (a) NaH, THF, rt, 1 h; then TsCl, rt, 1 h; (b) morpholine

3.3.11 - Eschenmoser-Claisen reactions of an indole with an electron-withdrawing protecting group

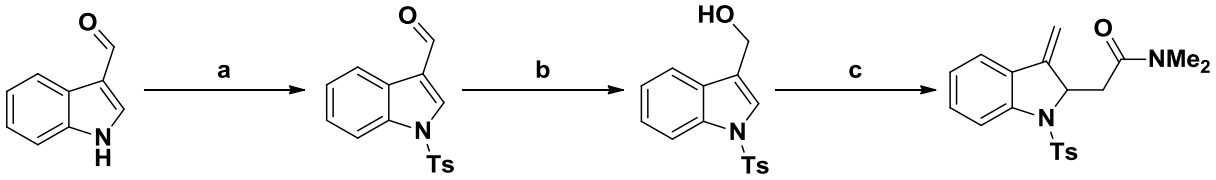
Despite the failure to form amine **356**, it was pleasing to observe that alcohol **357** underwent a dearomatising Eschenmoser-Clasien rearrangement when treated with dimethylacetamide dimethylacetal under microwave conditions (Scheme 200). As with the related dCr reaction of indoles published previously,[74] only the exocyclic alkene was observed, with no evidence for the isomerised indole **360**.



357 359

Scheme 200: Eschenmoser-Claisen rearrangement of alcohol **357** (a) DMA.DMA, toluene, 150 °C, µw, 5 min, 64 %

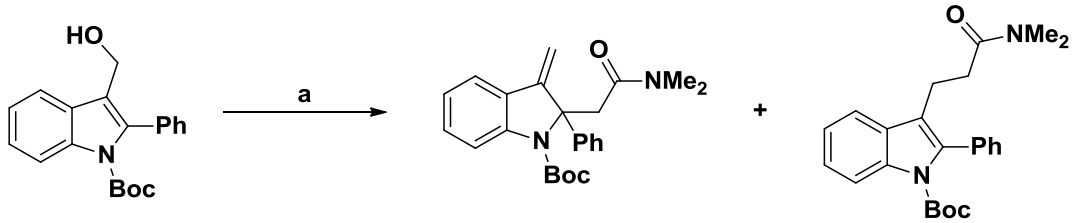
The *N*-tosyl variant **362** also underwent rearrangement under the same conditions to give alkene **363** in 72 % yield over three steps from indole-3-carbaldehyde (Scheme 201).



361 362 363

Scheme 201: Eschenmoser-Claisen rearrangement of alcohol **362** (a) TsCl, Et_3N, DMAP, DCM, rt, 1 h 82 %; (b) $NaBH_4$, MeOH, rt, 1 h, 98 %; (c) DMA.DMA, toluene, 150 °C, µw, 5 min, 89 %

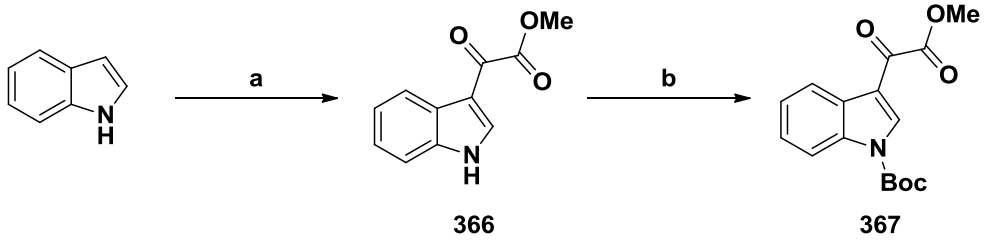
Similarly, it proved possible to form a quaternary centre under the same reaction conditions, although for the 2-phenyl variant the yield was much lower and a longer reaction time, compared to the unsubstituted version, was needed (Scheme 202). A small amount of the formal [1,3]-rearrangement product **365** was also isolated.



328 364 365

Scheme 202: Eschenmoser-Claisen rearrangement of alcohol **328,** and formation of byproduct **274** (a) DMA.DMA, toluene, 150 °C, µw, 45 min, 39 % **273** and 11 % **274**

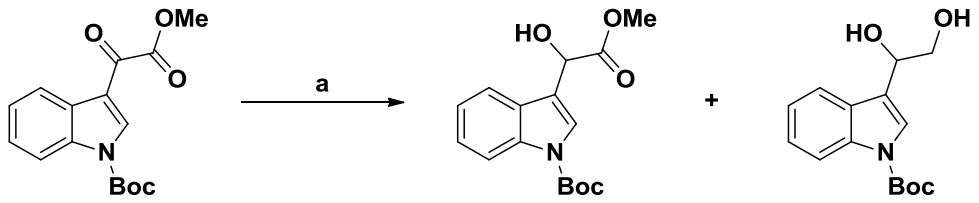
With these promising results in hand attention was turned to the incorporation of the benzylic side chain required for the synthesis of hinckdentine A. Indole underwent Friedel-Crafts acylation with oxalyl chloride followed by quenching with methanol and protection as the *tert*-butyl carbamate (Scheme 203).



366 **367**

Scheme 203: Synthesis of α-keto ester **367** (a) oxalyl chloride, THF, rt, 1 h then MeOH, rt, 15 min, 78 %; (b) NaH, DMF, rt, 1 h then Boc_2O, rt 2 h, 70 %

Reduction of **367** with sodium borohydride gave either α-hydroxy ester **368** or diol **369** depending on the solvent used (Scheme 204, Table 31)



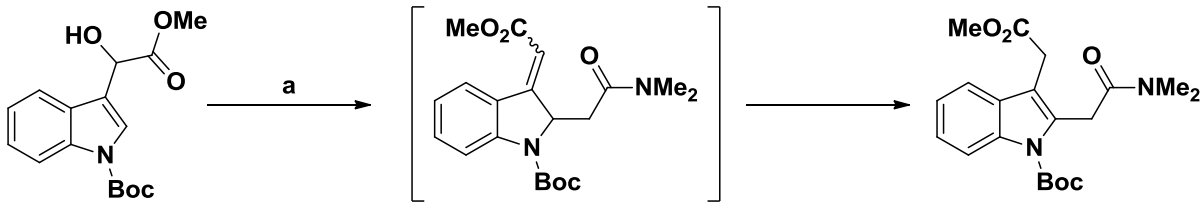
367 **368** **369**

Scheme 204: Reduction of α-keto ester **367** (a) $NaBH_4$, rt, see Table 31

Entry	Equiv $NaBH_4$	Solvent	Time (min)	Yield (%)	
				α-hydroxy ester 368	diol 369
1	1.2	MeOH	45	41	43
2	1.2	THF	30	99	-
3	3	MeOH	90	-	98

Table 31: Reduction of α-keto ester **367**

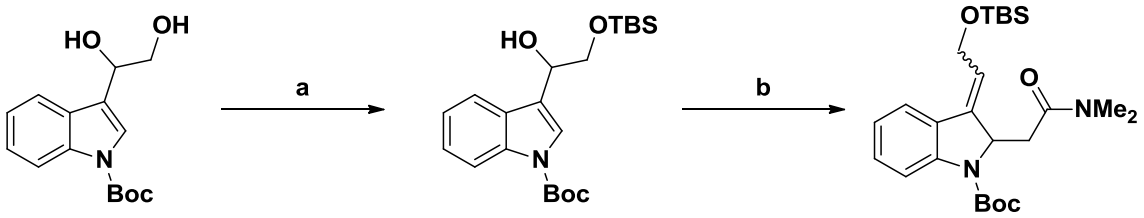
When α-hydroxy ester **368** was subjected to the Eschenmoser-Claisen conditions, only the re-aromatised rearrangement product **371** was isolated (Scheme 205), presumably due to the increased acidity of the C2-proton in the dearomatised intermediate **370** when in conjugation with the electron-withdrawing ester.



368 370 371

Scheme 205: Eschenmoser-Claisen rearrangement of alcohol **368** (a) DMA.DMA, toluene, 150 °C, μw, 7 min, 22 %

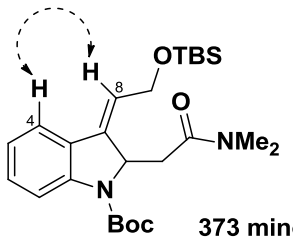
This problem could be avoided by using a protected alcohol in place of the ester, and indeed alcohol **372** underwent the rearrangement successfully (Scheme 206).



369 372 373

Scheme 206: Eschenmoser-Claisen rearrangement of alcohol **372** (a) TBSCl, Et_3N, DMAP, DCM, rt, 72 h, 63 %; (b) DMA.DMA, toluene, 150 °C, μw, 5 min, 67 %

Alkene **373** was formed as a 2.3: 1 ratio of *E*-:*Z*- isomers, evidence for this provided by nOe studies that showed a correlation between the alkene proton of the minor isomer and the H4 proton of the indole nucleus; a correlation that was not present for the major isomer (Scheme 207 and Figure 27)



Scheme 207: nOe correlation between H4 and H8 in the minor *(Z)*-isomer of **373**

Unfortunately this meant that this route was not suitable for the synthesis of hinckdentine A, as the *Z*-isomer is required for the lactamisation reaction. The possibility of reducing the olefin before the lactamisation reaction was rejected as in order to generate the correct diastereomer, addition of hydrogen to the convex face is required and it was anticipated that this would be more difficult to control in the open-chain form.

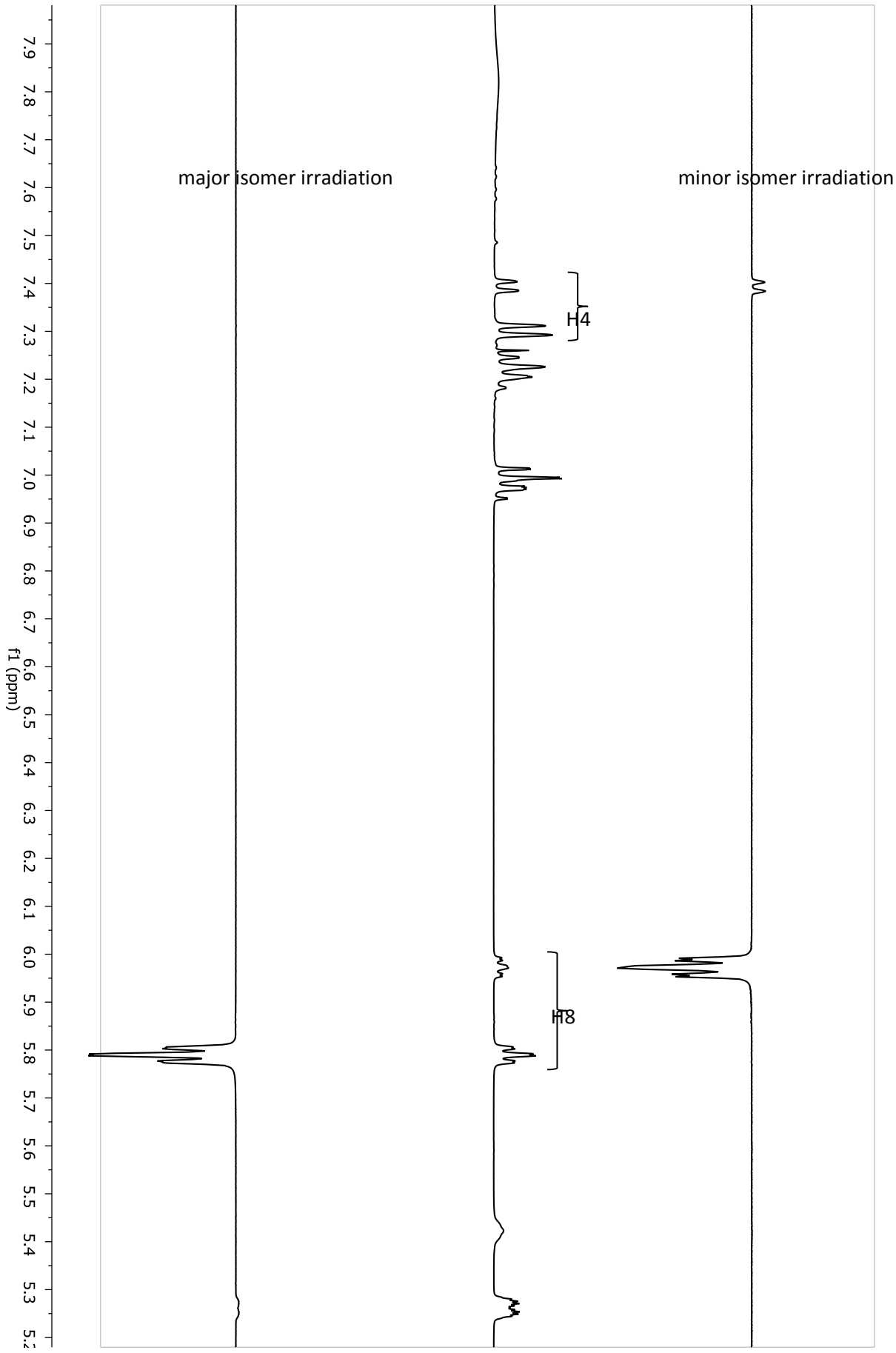
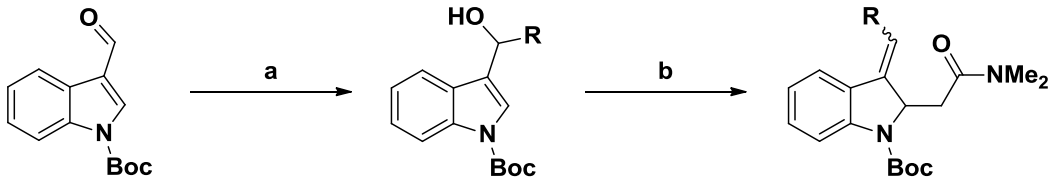


Figure 27: nOe studies for alkene **373.** Irradiation of peaks at δ_H = 6.00 (**H8 minor**) and 5.81 (**H8 major**) ppm

Despite this setback it was decided to investigate this reaction further as there have been no previous reports of the classical Eschenmoser-Claisen reaction of indoles. Aldehyde **355** was therefore combined with a number of Grignard reagents, and the resulting alcohols were subjected to the Eschenmoser-Claisen conditions (Scheme 208 and Table 32).



355

R = Me - 374
R = ^{i}Pr - 376
R = Ph - 378

R = Me - 375
R = ^{i}Pr - 377
R = Ph - 379

Scheme 208: Eschenmoser-Claisen rearrangement of alcohols **374, 376** and **378** (a) RMgX, THF, 0 °C, 1 h; (b) DMA.DMA, toluene, 150 °C, µw, 5 min,

Entry	R	Yield addition (%)	Yield rearrangement (%)	*E*:*Z*
1	Me	96	76	5.2 : 1
2	^{i}Pr	80	76	4.1 : 1
3	Ph	91	46	1.3 : 1

Table 32: Eschenmoser-Claisen rearrangement of substituted 3-hydroxymethyl indoles

The preference for the *E*-isomer can be explained by the fact that the R substituent adopts an equatorial position in the chair-like transition state to minimise 1,3 allylic strain (Figure 28).

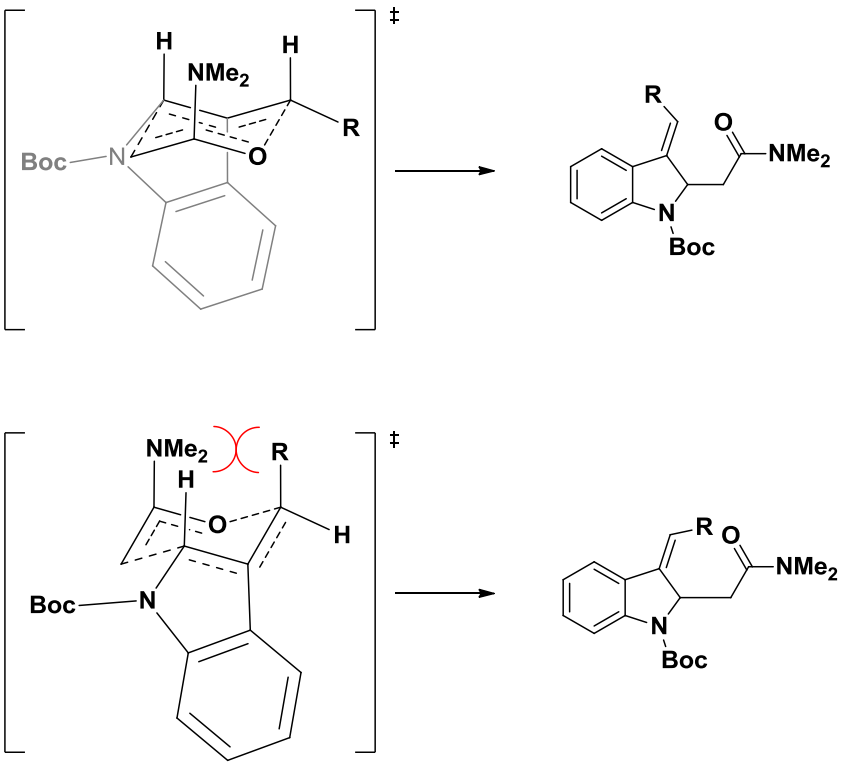


Figure 28: Preferential formation of the *E*-isomer, due to 1,3-allylic strain in the transition state leading to the *Z*-isomer

However, as the R group increases in size an erosion of the *E*-selectivity is observed. This can be explained by the fact that the steric-clash between the R group and the indole 4-H increases to a greater extent than the allylic 1,3 interaction (Figure 29).

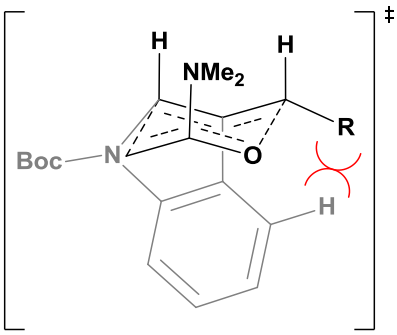


Figure 29: Steric clash between the indole 4-H and the R group in the transition state leading to the *E*-isomer

3.3.12 – Third-generation retrosynthetic approach

Due to the failure of the previous approach it was decided to attempt to form the α,β-unsaturated lactam **330** via a ring closing metathesis (Figure 30). The required diene **380** could be prepared from amine **381** which is in turn produced *via* either an Eschenmoser-Claisen rearrangement and subsequent deprotection from **383** or a Johnson-Claisen rearrangement and subsequent amide formation from **385**. It was envisioned that a tertiary amide would be needed ($R^2 \neq H$) to ensure that the correct conformation was achieved for the ring closure.

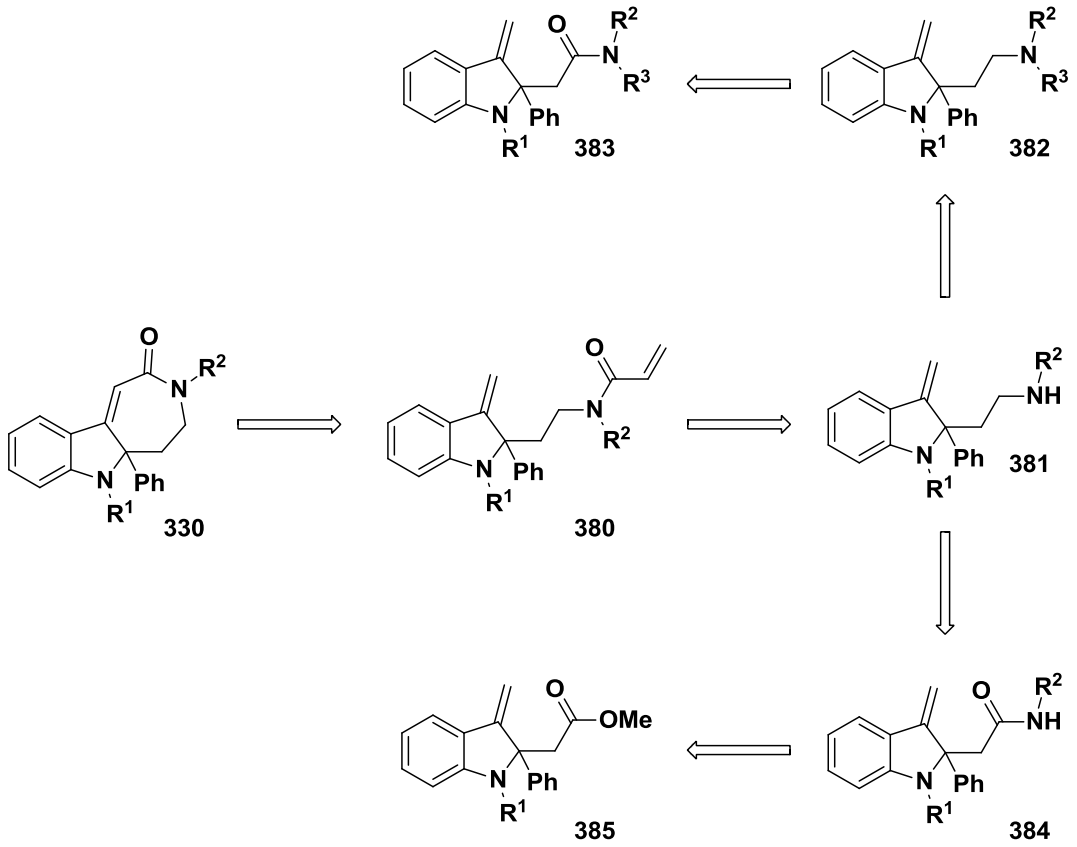
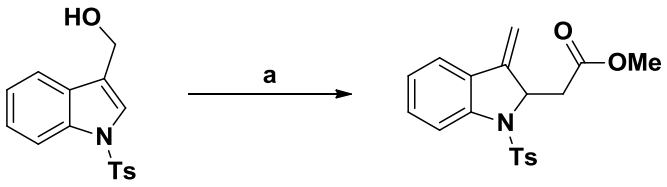


Figure 30: Third generation retrosynthetic approach

3.3.13 - Johnson-Claisen reactions of an indole with an electron-withdrawing protecting group

Initial studies again were carried out using a simpler system that did not possess a phenyl ring at the 2-position of the indole (Scheme 209, Table 33).



362 **386**

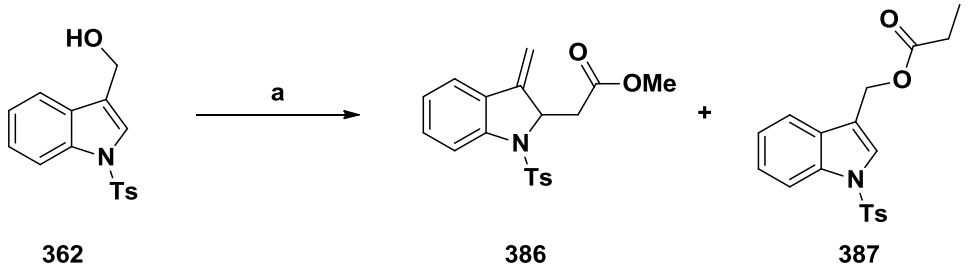
Scheme 209: Johnson-Claisen rearrangement of alcohol **362** (a) trimethylorthoacetate, catalyst, toluene, μw, see Table 33

Entry	Solvent	Equiv. ortho ester	Time (min)	Temp (°C)	Additive	Equiv	Consumption of SM[a]
1	PhMe	6	30	150	-	-	0 %
2	PhMe	6	30	150	$EtCO_2H$	0.1	42 %
3	PhMe	6	3600	rt	$EtCO_2H$	0.1	0 %
4	PhMe	6	30	150	*p*-NO_2-phenol	0.1	42 %
5	PhMe	6	30	150	LiCl	0.1	0 %
6	PhMe	6	30	150	$AlCl_3$	0.1	11 %
7	PhMe	6	30	150	$BF_3{\cdot}OEt_2$	0.1	decomp
8	PhMe	6	30	150	*o*-I-benzoic acid	0.1	0 %
9	-	20	30	150	*p*-NO_2-phenol	0.1	42 %
10	PhMe	6	30	150	*p*-NO_2-phenol	0.5	decomp
11	PhMe	6	60	150	*p*-NO_2-phenol	0.1	46 %
12	PhMe	6	240	170	*p*-NO_2-phenol	0.1	85 %
13	PhMe	6	210	200	*p*-NO_2-phenol	0.1	100 %

Table 33: Johnson-Claisen rearrangement of alcohol **362**. [a]Ratio of product:SM by ^{1}H NMR analysis of the crude reaction mixture

Unlike the Eschenmoser-Claisen rearrangement, the Johnson-Claisen rearrangement did not proceed under heating in the absence of a catalyst (Table 33, entry 1). Using propanoic acid as a catalyst gave the rearranged product **386** in an isolated yield of only 10 %, along with 52% recovered starting material and

12 % of ester **387**, which was presumably formed by addition of the catalyst to the alcohol (Table 33, entry 2 and Scheme 210).

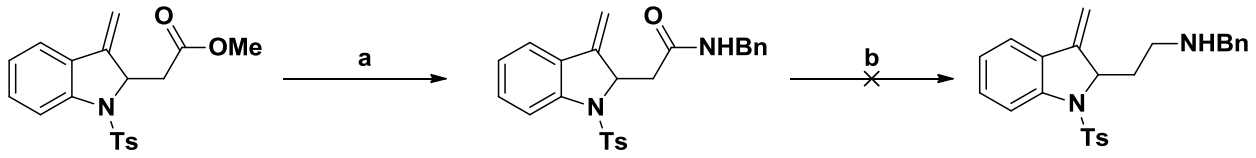


Scheme 210: Johnson-Claisen rearrangement of alcohol **362** and formation of byproduct **387** (a) trimethylorthoacetate, propanoic acid, 150 °C, µw, 30 min, 10 % **386** and 12 % **387**

At room temperature no reaction was observed after 60 hours (Table 33, entry 3). *Para*-nitro-phenol was next chosen as a catalyst (Table 33, entry 4) due to its low pKa (7.1 in H_2O) and the fact that it lacks the ability to undergo addition to the alcohol. The use of Lewis-acids (Table 33, entries 5-7) did not prove successful, with only $AlCl_3$ giving any reaction. Running the reaction in neat ortho ester (Table 33, entry 9) gave no appreciable increase in conversion and increasing the amount of acid catalyst (Table 33, entry 10) resulted only in decomposition. The starting material could be completely consumed by extended heating (Table 33, entry 13).

Despite that fact that the starting material had been completely consumed, the isolated yield of **386** was very low due to the presence of a close-running impurity that was difficult to separate by column chromatography. Although this impurity could not be adequately purified for an accurate analysis, it is possible that this is the re-aromatised product, due to there being no additional signals in the alkene region of the ^{1}H NMR spectrum of the crude product.

Ester **386** then underwent a trimethylaluminium mediated amide formation with benzylamine to give amide **388** (Scheme 211). Reduction of **388** with lithium aluminium hydride was attempted once on a small scale and gave a complex mixture containing a large number of polar compounds. Due to the synthetic bottleneck generated by the low yielding Johnson-Claisen rearrangement, no attempts were made to optimise this reaction and the route was abandoned.



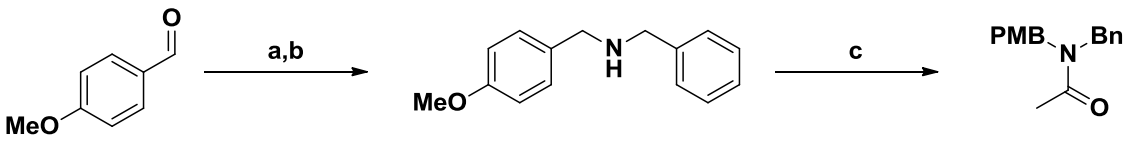
386 388 389

Scheme 211: Attempted synthesis of amine **389** (a) benzylamine, Me_3Al, DCM, rt 15 min, then **386**, rt, 48 h, 55 %; (b) $LiAlH_4$, THF, 80 °C, 1.5 h

3.3.14 - Synthesis of alternative dimethyl acetals

An alternative method of generating amine **381** would be by an Eschenmoser-Claisen rearrangement using the dimethyl acetal of an acetamide possessing two orthogonal protecting groups (Figure 30). The amide produced by this reaction could then be reduced to an amine and one of the protecting groups removed.

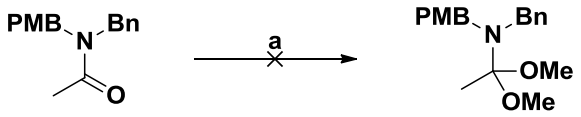
Reductive amination of benzaldehyde and *p*-methoxy aniline gave amine **390** which was then converted to acetamide **391** with acetic anhydride (Scheme 212).



390 391

Scheme 212: Synthesis of acetamide **391** (a) benzaldehyde, 4 Å MS, K_2CO_3, benzene, rt, 16 h; (b) $NaBH_4$, EtOH, rt, 2 h, 95 % over two steps; (c) Ac_2O, Et_3N, DMAP, DCM, rt, 3 h, 95 %

The standard method of forming dimethyl acetals of acetamides involves treatement with an electrophilic methylating agent, followed by treatment with methoxide. The intial approach involved heating acetamide **391** in neat dimethyl sulfate for two hours, before cooling to room temperature, diluting with methanol and adding sodium methoxide (Scheme 213). Unfortunately, this did not prove successful and time constraints meant that other methods were not attempted

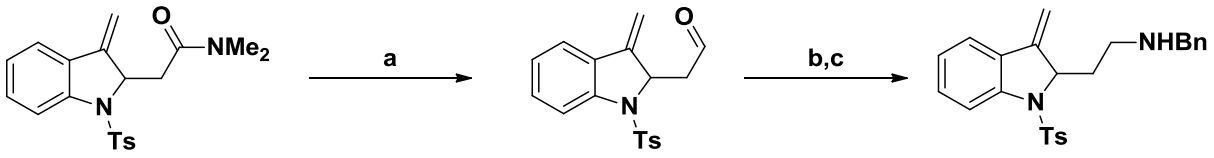


391 392

Scheme 213: Attempted synthesis of dimethyl acetal **392** (a) Me_2SO_4, 80 °C, 2 h then MeOH, rt, 18 h

3.3.15 – Ring-closing metathesis

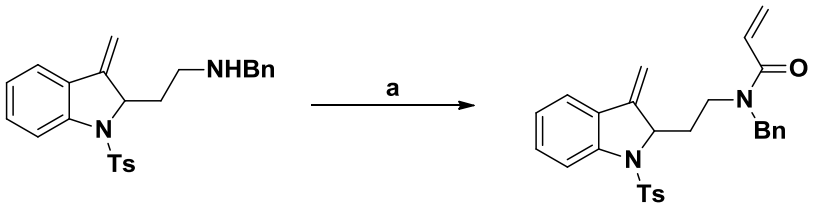
Another route to the desired amine was by reductive amination of aldehyde **393**, which in turn was produced by a selective, low temperature, reduction of amide **363** (Scheme 214).



363 393 394

Scheme 214: Synthesis of amine **394** (a) DIBAL, THF, –42 °C, 6 h, 61 %; (b) benzylamine, K_2CO_3, 4 Å MS, benzene, rt, 16 h; (c) $NaBH_4$, EtOH, rt, 1.5 h, 72 % over two steps

Amide bond formation with acrylic acid and T_3P® as a coupling agent gave diene **395** (Scheme 215), which was observed as a mixture of two rotamers in the room temperature ^1H NMR spectrum(Figure 31).



394 395

Scheme 215: Amide bond formation (a) acrylic acid, T_3P®, Et_3N, DCM, rt, 2 h 98 %

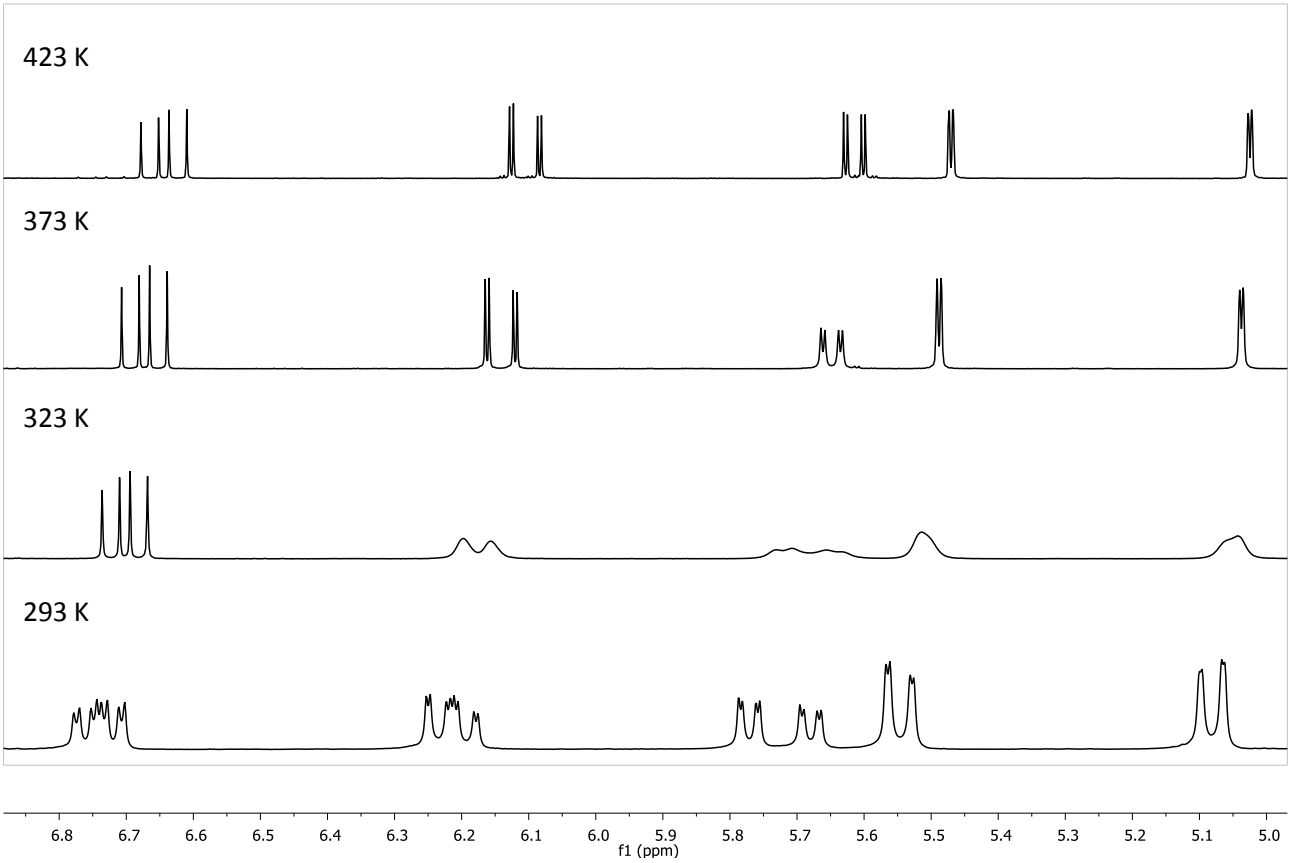
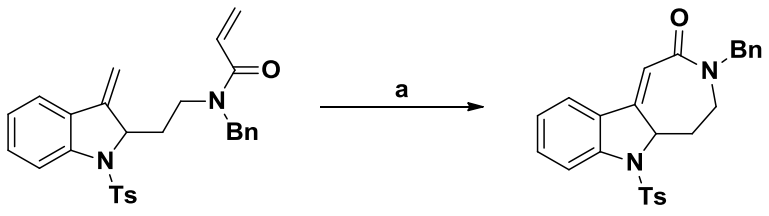


Figure 31: The alkene region of VT ^{1}H NMR studies on amide **395**, in d_6-DMSO, showing the presence of two rotamers

A ring-closing metathesis of **395** was then attempted (Scheme 216, Table 34)



395 **396**

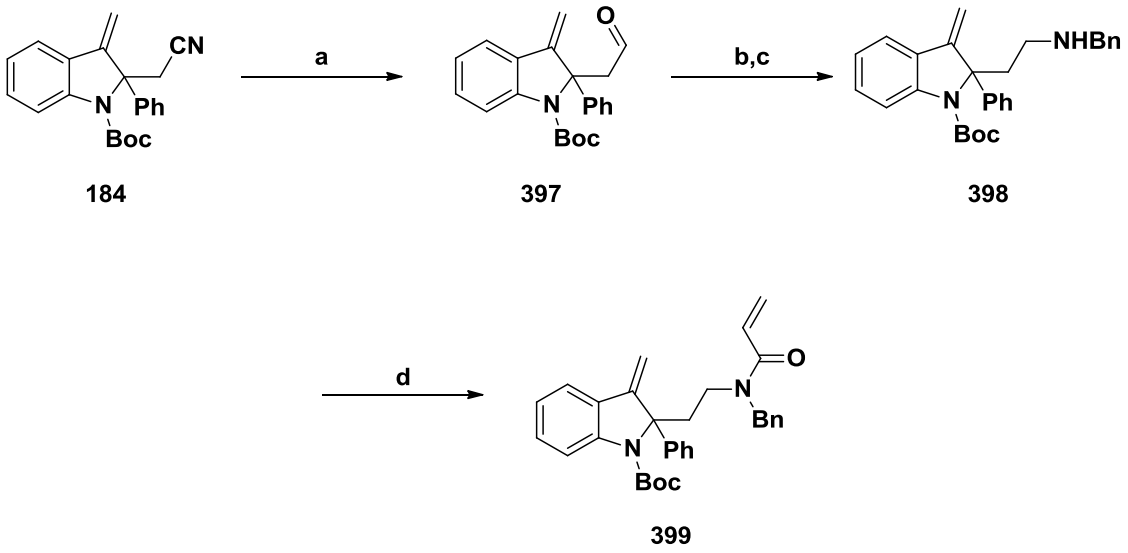
Scheme 216: Attempted ring closing metathesis of diene **395** (a) see Table 34

Entry	Catalyst	Equivalents	Concentration	Temp	Time	Result
1	Grubbs II	0.05	0.02 M	100 °C 120 °C	1 h 2 h	SM
2	Grubbs II	0.05	0.1 M	100 °C 120 °C	1 h 2 h	SM
3	Grubbs II	1	0.1 M	120 °C	90 min	decomp
4	Hoveyda-Grubbs II	0.2	0.1 M	100 °C 120 °C	1 h 2 h	decomp

Table 34: Attempted ring closing metathesis of diene **395**

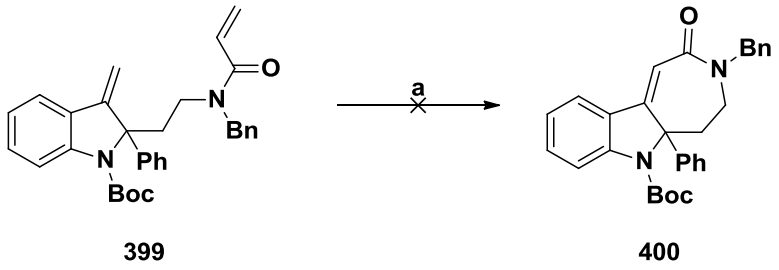
With 0.05 equivalents of the Grubbs II catalyst no reaction was observed when the reaction mixture was heated at 100 °C for 1 hour then 120 °C for 2 hours in the microwave (Table 34, entry 1). The same result was observed when the concentration was increased to 0.1 M (Table 34, entry 2). When one equivalent of Grubbs II was used, the starting material was completely consumed after 90 minutes at 120 °C (Table 34, entry 3), however no identifiable products were isolated and ^{1}H NMR analysis of the crude product showed no signals between δ_H = 5.0 and 6.9 ppm. The use of the Hoveyda-Grubbs II catalyst also led to decomposition (Table 34, entry 4).

It was hoped that the analogous product containing a phenyl substituent at the C2-position of the indole would cyclise more readily due to the Thorpe-Ingold effect. With this in mind, amide **399** was formed using the same method as above (Scheme 217). Although in this case aldehyde **397** was formed by reduction of nitrile **184**, it is theoretically possible to produce the same product from amide **364**.



Scheme 217: Synthesis of diene **399** (a) DIBAL, THF, –78 °C, 1.5 h, 69 %; (b) benzylamine, K_2CO_3, 4 Å MS, benzene, rt, 16 h; (c) $NaBH_4$, EtOH, rt, 2 h, 73 % over two steps; (d) (a) acrylic acid, $T_3P^®$, Et_3N, DCM, rt, 2 h 90 %

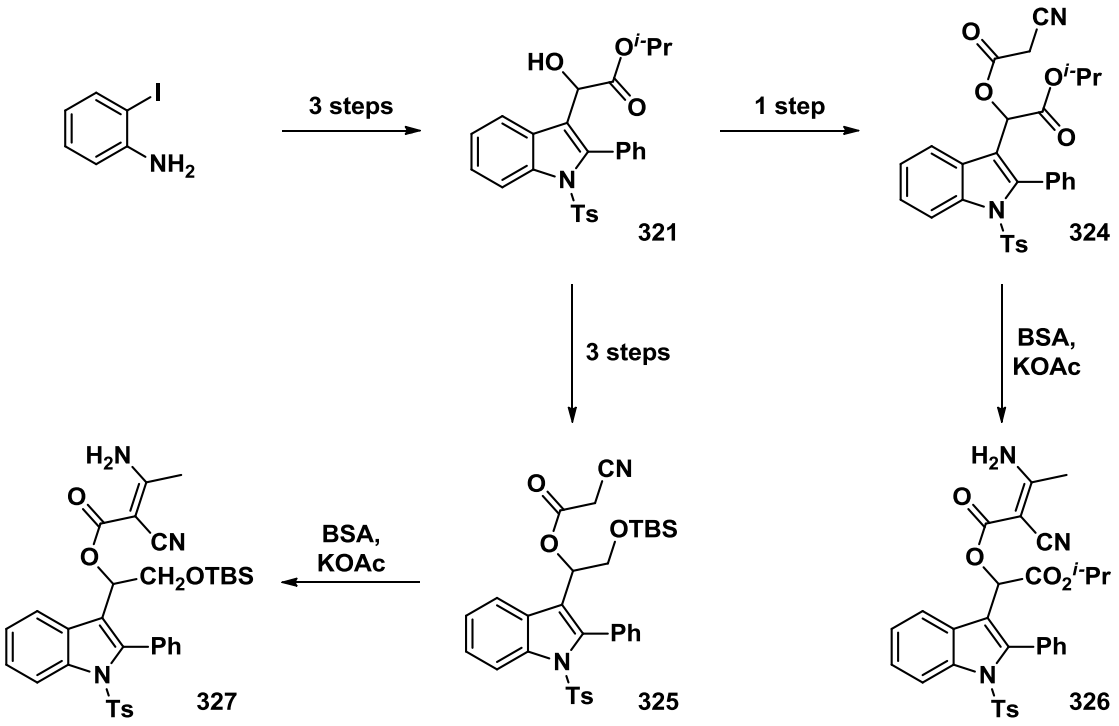
The ring closing-metathesis of **399** was then attempted using Grubbs II and titanium isopropoxide as a cocatalyst, added to inhibit chelate formation between the amide oxygen and the metathesis catalyst.[99] Unfortunately the only isolable product was again starting material (Scheme 218). A trace amount of a less polar compound was observed by TLC, but due to the scale of the reaction it could not be isolated in quantities large enough for NMR analysis, and the mass spectrum did not give any indication of the required peaks for **400**.



Scheme 218: Attempted ring closing metathesis of diene **399** (a) Grubbs II, $Ti(O^iPr)_4$, DCM, 120 °C, µw, 3 h

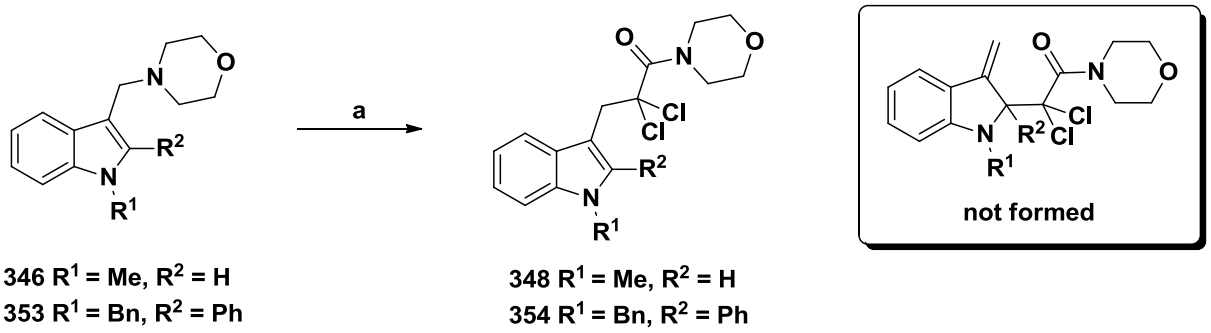
3.4 Conclusions and future work

A route to esters **324** and **325** was developed employing a palladium (II) catalysed reaction in the formation of the indole ring. These esters were then subjected to dCr conditions, but unfortunately the anticipated [3,3]-sigmatropic rearrangement was not observed and instead enamines **326** and **327** were formed (Scheme 219). It was reasoned that this was due to the crowded steric environment around the C2 position of the indole .



Scheme 219: Synthesis of enamines **326** and **327**

The synthetic route was therefore redesigned to use alternate types of dearomatising Claisen rearrangement. The attempted Belluš-Claisen rearrangement of amines **346** and **353** gave the novel ketene insertion products **348** and **354** respectively via a formal [1,3]-rearrangement, presumably due to the electron-donating effect of the indole nitrogen atom (Scheme 220).

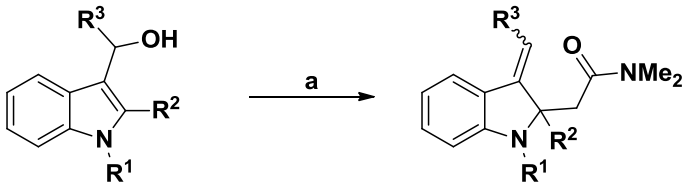


346 R^1 = Me, R^2 = H
353 R^1 = Bn, R^2 = Ph

348 R^1 = Me, R^2 = H
354 R^1 = Bn, R^2 = Ph

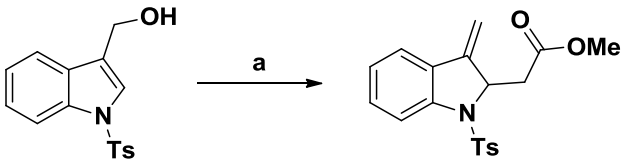
Scheme 220: Formation of ketene insertion products **348** and **354** during the attempted Bellus-Claisen rearrangement of amines **346** and **353** (a) TMSOTf, Et_3N, DCM, –78 °C, 5 min

The dearomatising Eschenmoser-Claisen rearrangement of indoles was then developed, with the rearrangement of **328** giving the required C2 quaternary stereocentre for hinckdentine A. Unfortunately attempts to incorporate a benzylic side chain resulted in the formation of the unwanted *E*- isomer of **373** as the major product.



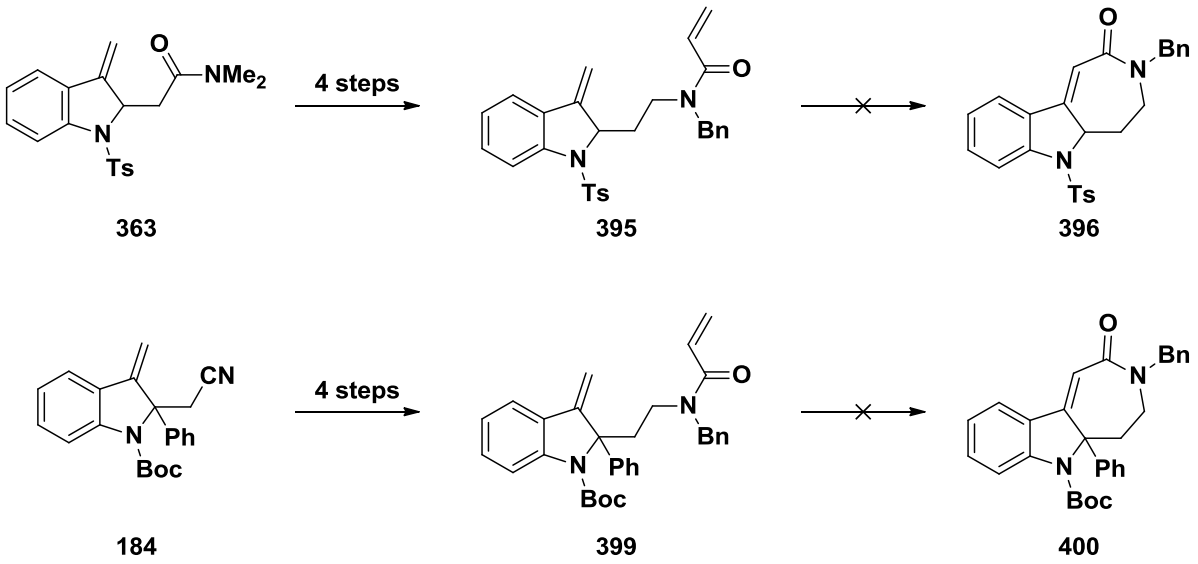
Scheme 221: Dearomatising Eschenmoser-Clasien rearrangements. R^1 = Boc, Ts. R^2 = H, Ph. R^3 = H, Me, ^{i}Pr, Ph, CH_2OTBS. (a) DMA.DMA, PhMe, 150 °C, µw

The third synthetic approach was to form the lactam ring via a ring-closing metathesis. Although the dearomatising Johnson-Claisen rearrangement of **362** gave a very low yield (Scheme 222); dienes **395** and **399** were synthesised via an Eschenmoser-Claisen, reductive amination pathway. Unfortunately however the ring-closing metathesis of these dienes failed to give the desired lactams **396** and **400** (Scheme 223).



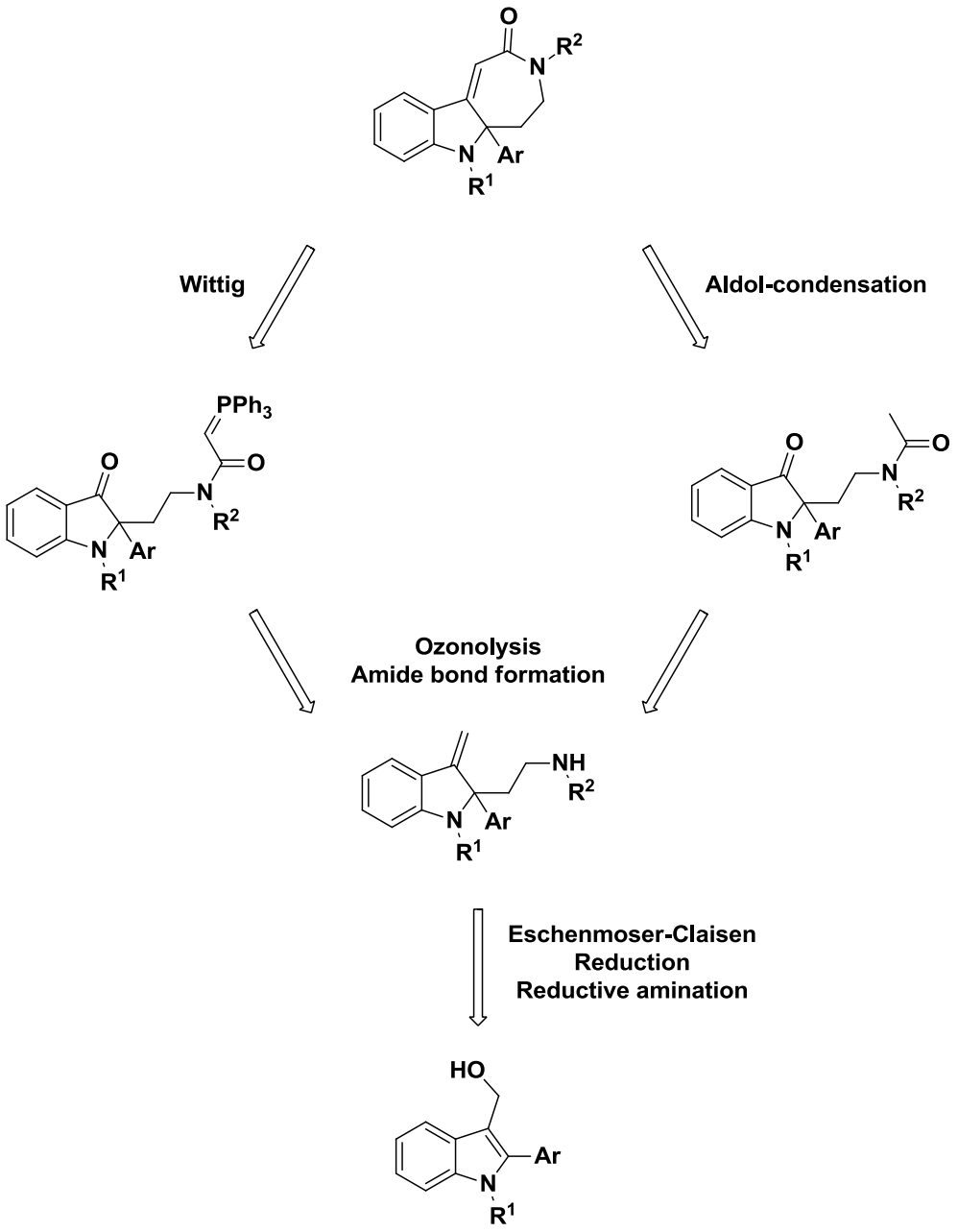
362 **363**

Scheme 222: Dearomatising Johnson-Claisen rearrangement (a) trimethylorthoacetate, 4-nitrophenol, 200 °C, µw, 3.5h, 13%



Scheme 223: Attempted formation of lactam ring *via* a ring-clsoing metathesis

An alternative method to form the carbon-carbon bond at the indole C3 position would be by ozonolytic cleavage of the alkene formed in the dearomatising Eschenmoser-Claisen rearrangement. This would allow the required carbon-carbon bond to be formed by either an aldol-dehydration pathway or a Wittig olefination (Scheme 224). The aldol-dehydration pathway has previously been used in Mchworter's synthesis of 8-desbromo hinckdentine.



Scheme 224: Future work

4 Experimental

4.1 General Experimental

Solvents and reagents

Non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen unless otherwise stated. Dichloromethane, dimethylformamide, tetrahydrofuran, diethyl ether and toluene were purified by filtration through activated alumina columns, employing the method of Grubbs *et al*.[100] Triethylamine and *N*,*N*-diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide pellets. Methanol was distilled from calcium hydride and stored over 3Å molecular sieves. DME was distilled from calcium hydride and used immediately. Petroleum ether refers to the fraction of petroleum ether boiling between 40 °C and 60 °C.

Chromatography

Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} 0.25 mm precoated aluminium plates. Product spots are visualised under UV light (λ_{max} = 254 mm) and/or by staining with potassium permanganate or vanillin. Flash chromatography was performed using silica gel 60 (0.040 – 0.063 mm, Merck) using head pressure by means of head bellows, employing the method of Still *et al*.[101]

Nuclear Magnetic Resonance

^{1}H NMR Spectra were recorded on Bruker AV-400 (400 MHz) or AV-500 (500 MHz) spectrometers and referenced relative to the residual non-deuterated solvent peak. Chemical shifts are reported in parts per million (ppm) with splittings reported as singlet (s), broad singlet (br. s), doublet (d), triplet (t), heptet (hept.) and mulitplet (m). Coupling constants (*J*) are measured to the nearest 0.5 Hz and are presented as observed. ^{13}C NMR Spectra were recorded on Bruker AV-500 (126 MHz) or AV-400 (101 MHz) spectrometers and referenced to the solvent peak.

Infared Spectroscopy

Infared spectra were measured as neat samples on a Perkin-Elmer Spectrum RX FT-IR System spectrometer fitted with a diamond ATR module. Only structurally important absorptions are quoted. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass spectrometry

Mass spectra were recorded using Micromass AutoSpec Premier or Waters LCT Premier instruments under conditions of electrospray ionisation (ES), chemical ionisation (CI) or electron ionisation (EI). Compounds containing bromine are given for the ^{79}Br isotope. Compounds containing chlorine are given for the ^{35}Cl isotope.

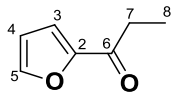
Microwave reactions

Microwave reactions were performed using a Biotage Initiator EXP Microwave System.

Melting Points

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

1-(Furan-2-yl)propan-1-one (185)[75]



To neat furan (10.9 mL, 150 mmol, 10 equiv) at 0 °C was added ^{n}BuLi (2.5 M in hexane, 18.0 mL, 45 mmol, 3 equiv) dropwise. The reaction mixture was stirred at rt for 3 h and the resulting yellow foam was dissolved in THF (15 mL) and transferred dropwise *via* cannular to a solution of propionic acid (1.12 mL, 15 mmol, 1.0 equiv) in THF (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, rt for 2.5 h, then diluted with Et_2O, washed with saturated $NaHCO_{3\ (aq)}$ and saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5 % EtOAc in petroleum ether) gave ketone **185** (1.30 g, 70 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 (1H, s, **H5**), 7.18 (1H, d, *J* = 3.5 Hz, **H3**), 6.53 – 6.52 (1H, m, **H4**), 2.86 (2H, q, *J* = 7.5 Hz, **H7**), 1.21 (3H, t, *J* = 7.5 Hz, **H8**)

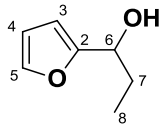
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 190.2 (**C6**), 152.7 (**C2**), 146.1 (**C5**), 116.6 (**C3**), 112.1 (**C4**), 31.7 (**C7**), 8.0 (**C8**)

ν_{max} (thin film)/cm^{-1} 1673 (**C=O**)

EI-MS calcd for $C_7H_8O_2$ $[M]^+$ 124.0524; found 124.0526

These data are in accordance with the literature.[75]

(±)-1-(Furan-2-yl)propan-1-ol (186)[102]



To a solution of ketone **185** (370 mg, 2.98 mmol, 1.0 equiv) in MeOH (9 mL) at 0 °C was added sodium borohydride (147 mg, 3.87 mmol, 1.3 equiv) in one portion. The reaction mixture was stirred at rt for 1 h and quenched with H_2O. The reaction was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alcohol **116** (287 mg, 76 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 (1H, d, *J* = 1.0 Hz, **H5**), 6.34 – 6.33 (1H, m, **H4**), 6.23 (1H, d, *J* = 3.5 Hz, **H3**), 4.59 (1H, t, *J* = 7.0 Hz, **H6**), 2.37 – 2.34 (1H, m, **OH**), 1.93 – 1.81 (2H, m, **H7**), 0.95 (3H, t, *J* = 7.5 Hz, **H8**)

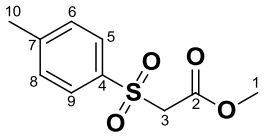
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.7 (**C2**), 141.8 (**C5**), 110.1 (**C4**), 105.9 (**C3**), 69.2 (**C6**), 28.6 (**C7**), 9.9 (**C8**)

ν_{max} (thin film)/cm^{-1} 3364 (**O-H**)

EI-MS Calcd for $C_7H_{10}O_2$ $[M]^+$ 126.0681; found 126.0679

These data are in accordance with the literature.[102]

Methyl tosylacetate (187)[103]



To a solution of sodium *p*-toluene sulfinate (10.7 g, 60.0 mmol, 1.0 equiv) in DMF (80 mL) at 0 °C was added methylbromoacetate (6.82 mL, 72.0 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred at rt for 24 h, diluted with water and extracted three times with EtOAc. The combined organic layers were washed with 5 % $LiCl_{(aq)}$, saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (35 % EtOAc in petroleum ether) gave ester **187** (12.4 g, 91 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.5 Hz, **H5** and **H9**), 7.30 (2H, d, *J* = 8.5 Hz, **H6** and **H8**) 4.06 (2H, s, **H3**), 3.61 (3H, s, **H1**), 2.37 (3H, s, **H10**)

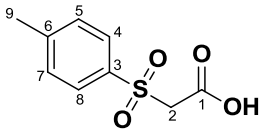
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.9 (**C2**), 145.3 (**C7**), 135.6 (**C4**), 129.7 (**C6** and **C8**), 128.3 (**C5** and **C9**), 60.7 (**C3**), 52.9 (**C1**), 21.5 (**C10**)

ν_{max} (thin film)/cm^{-1} 1740 (**C=O**), 1323, 1147 (**O=S=O**)

ES-MS calcd for $C_{10}H_{12}O_4S$ $[M-H]^-$ 227.0378; found 227.0385

These data are in accordance with the literature.[103]

Tosylacetic acid (188)



To a solution of ester **187** (12.4 g, 54.5 mmol, 1.0 equiv) in THF (100 mL) was added a solution of LiOH (26.1 g, 1090 mmol, 20 equiv) in H_2O (550 mL) at rt. The reaction mixture was stirred at rt for 48 h, diluted with Et_2O and the phases separated. The aqueous layer was acidified to pH 1 by addition of HCl (36 %) and extracted three times with Et_2O. The combined organic layers from the second washing were dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from DCM gave acid **188** (10.0 g, 86 % yield) as a white crystalline solid.

^{1}H NMR (400 MHz, DMSO) δ_H 13.17 (1H, br. s, **OH**), 7.81 (2H, d, *J* = 7.5 Hz, **H4** and **H8**), 7.45 (2H, d, *J* = 7.5 Hz, **H5** and **H7**), 4.44 (2H, s, **H2**), 2.41 (3H, s, **H9**).

^{13}C NMR (101 MHz, DMSO) δ_C 164.5 (**C1**), 145.0 (**C6**), 136.9 (**C3**), 130.1 (**C5** and **C7**), 128.5 (**C4** and **C8**), 60.6 (**C2**), 21.6 (**C9**).

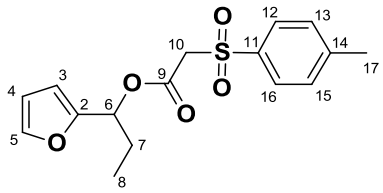
ν_{max} (neat)/cm^{-1} 2954 (**O-H**), 1714 (**C=O**) 1320, 1156 (**O=S=O**)

ES-MS calcd for $C_9H_{10}O_4S$ $[M-H]^-$ 213.0222, found 213.0230

mp = 114 – 116 °C

This data matches that of the commercially available compound.

(±)-1-(Furan-2-yl)propyl 2-tosylacetate (189)



To a solution of alcohol **186** (500 mg, 3.97 mmol, 1.0 equiv) in DCM (7.5 mL) at 0 °C was added tosylacetic acid (1.28 g, 5.95 mmol, 1.5 equiv), DIC (920 µL, 5.95 mmol, 1.5 equiv) and DMAP (75 mg, 0.595 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 43 h, diluted with DCM, washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether with 1 % Et_3N) gave ester **189** (928 mg, 70 % yield) as a pale yellow solid.

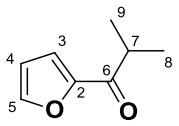
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.0 Hz, **H12** and **H16**), 7.39 (1H, s, **H5**), 7.33 (2H, d, *J* = 8.0 Hz, **H13** and **H15**), 6.36 – 6.33 (2H, m, **H3** and **H4**), 5.74 (1H, t, *J* = 7.5 Hz, **H6**), 4.11 (2H, s, **H10**), 2.46 (3H, s, **H17**), 1.95 (1H, quint., *J* = 7.5 Hz, **H7**), 0.88 (3H, t, *J* = 7.5 Hz, **H8**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.9 (**C9**), 151.2 (**C2**), 145.3 (**C14**), 142.7 (**C5**), 135.7 (**C11**), 129.8 (**C13** and **C15**), 128.6 (**C12** and **C16**), 110.3 (**C4**), 109.5 (**C3**), 72.2 (**C6**), 61.1 (**C10**), 25.4 (**C7**), 21.7 (**C17**), 9.7 (**C9**)

ν_{max} (thin film)/cm^{-1}1736 (**C=O**), 1325, 1147 (**O=S=O**)

ES-MS calcd for $C_{16}H_{18}O_5S$ $[M+MeCN+Na]^+$ 386.1038; found 386.1047

1-(Furan-2-yl)-2-methylpropan-1-one (190)[75]



To neat furan (5.10 mL, 70.0 mmol, 10 equiv) at 0 °C was added ^{n}BuLi (2.5 M in hexane, 8.40 mL, 21.0 mmol, 3 equiv). The reaction mixture was stirred at rt for 3 h and the resulting yellow foam was dissolved in THF (7 mL) and transferred dropwise *via* cannular to a solution of *iso*-butyric acid (650 µL, 7.00 mmol, 1 equiv) in THF (7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at rt for 18 h, diluted with Et_2O, washed with saturated $NaHCO_{3\ (aq)}$ and saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave ketone **190** (581 mg, 59 % yield) as a colourless oil.

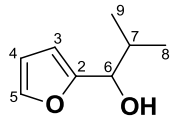
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 (1H, d, *J* = 1.0 Hz, **H5**), 7.18 (1H, d, *J* = 3.5 Hz, **H3**), 6.52 – 6.51 (1H, m, **H4**), 3.32 (1H, sept., *J* = 7.0 Hz, **H7**), 1.19 (6H, d, *J* = 7.0 Hz, **H8** and **H9**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 193.6 (**C6**), 152.1 (**C2**), 146.2 (**C5**), 117.1 (**C3**), 112.1 (**C4**), 36.2 (**C7**), 18.7 (**C8** and **C9**)

ν_{max} (thin film)/cm^{-1} 1668 (**C=O**)

CI-MS calcd for $C_8H_{10}O_2$ $[M+NH_4]^+$ 156.1025; found 156.1029

(±)-1-(Furan-2-yl)-2-methylpropan-1-ol (191)[104]



To a solution of ketone **190** (300 mg, 2.14 mmol, 1.0 equiv) in MeOH (2.5 mL) at 0 °C was added sodium borohydride (97 mg, 2.57 mmol, 1.2 equiv) in three portions. The reaction mixture was stirred at rt for 3 h and quenched with H_2O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Alcohol **191** (276 mg, 92 % yield) was isolated as a colourless oil in analytical purity and no purification was required.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.37 (1H, m, **H5**), 6.35 – 6.33 (1H, m, **H4**), 6.24 (1H, d, *J* = 3.0 Hz, **H3**), 4.37 (1H, d, *J* = 7.0 Hz, **H6**), 2.15 – 2.07 (2H, m, **H7** and **OH**), {1.03 (3H, d, *J* = 7.0 Hz), 0.87 (3H, d, *J* = 7.0 Hz)} (**H8** and **H9**).

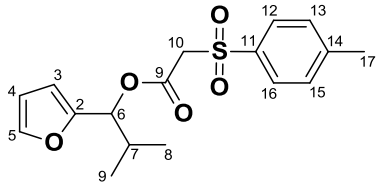
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.2 (**C2**), 141.6 (**C5**), 110.0 (**C4**), 106.5 (**C3**), 73.5 (**C6**), 33.3 (**C7**), {18.7, 18.2} (**C8** and **C9**)

ν_{max} (thin film)/cm^{-1} 3389 (**O-H**)

EI-MS calcd for $C_8H_{12}O_2$ $[M]^+$ 140.0837; found 140.0840

These data are in accordance with the literature.[104]

(±)-1-(Furan-2-yl)-2-methylpropyl 2-tosylacetate (192)



To a solution of alcohol **191** (250 mg, 1.78 mmol, 1.0 equiv) in DCM (2 mL) at 0 °C was added tosylacetic acid (573 mg, 2.68 mmol, 1.5 equiv), DIC (415 µL, 2.68 mmol, 1.5 equiv) and DMAP (33 mg, 0.268 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 48 h, diluted with DCM, washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave ester **192** (504 mg, 84 % yield) as a pale yellow oil.

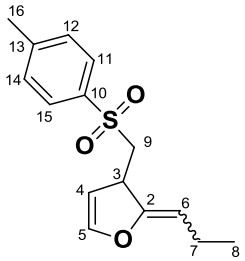
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.0 Hz, **H12** and **H16**), 7.39 (1H, d, *J* = 1.0 Hz, **H5**), 7.33 (2H, d, *J* = 8.0 Hz, **H13** and **H15**), 6.35 – 6.34 (1H, m, **H4**), 6.32 (1H, d, *J* = 3.0 Hz, **H3**), 5.52 (1H, d, *J* = 8.5 Hz, **H6**), 4.12 (2H, s, **H10**), 2.46 (3H, s, **H17**), 2.35 – 2.26 (1H, m, **H7**), {0.97 (3H, d, *J* = 6.5 Hz), 0.83 (3H, d, *J* = 6.5 Hz)} (**H8** and **H9**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.9 (**C9**), 151.0 (**C2**), 145.3 (**C14**), 142.5 (**C5**), 135.6 (**C11**), 129.8 (**C13** and **C15**), 128.5 (**C12** and **C16**), 110.2 (**C4**), 109.7 (**C3**), 76.0 (**C6**), 61.0 (**C10**), 31.0 (**C7**), 21.7 (**C17**), {18.6, 18.4} (**H8** and **H9**)

ν_{max} (thin film)/cm^{-1} 1739 (**C=O**), 1329, 1152 (**O=S=O**)

ES-MS calcd for $C_{17}H_{20}O_5S$ $[M+MeCN+Na]^+$ 400.1195; found 400.1196

(*E*)- and (*Z*)-2-Propylidene-3-(tosylmethyl)-2,3-dihydrofuran (193)



To a microwave vial containing ester **189** (50 mg, 0.150 mmol, 1.0 equiv) and potassium acetate (1.5 mg, 0.015 mmol, 0.1 equiv) was added BSA (200 µL, 0.818 mmol, 5.4 equiv). The resulting mixture was exposed to 3 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether with 1 % Et_3N) gave bis(enol) ether **193** (28 mg, 67 % yield) as a colourless oil in a 10:1 *dr* (determined by comparing the integrals of signals at δ_H = 6.47 and 6.43 ppm)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.0 Hz, **H11** and **H15**), 7.37 (2H, d, *J* = 8.0 Hz, **H12** and **H14**), 6.47 (1H, s, **H5 major**), 6.43 (1H, s, **H5 minor**), 5.31 (1H, t, *J* = 2.5 Hz, **H4 major**), 5.30 (1H, t, *J* = 2.5 Hz, **H4 minor**), 4.48 (1H, td, *J* = 7.5, 2.0 Hz, **H6**), 4.01 – 3.98 (1H, m, **H3 minor**), 3.93 - 3.89 (1H, m, **H3 major**), 3.21 – 3.13 (2H, m, **H9**), 2.46 (3H, s, **H16**), 2.14 – 2.20 (2H, m, **H7**), 0.93 (3H, t, *J* = 7.5 Hz, **H8**)

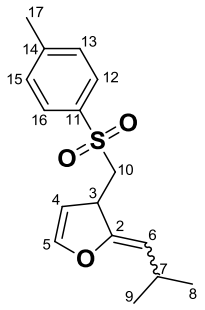
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.4 (**C2**), 145.0, (**C5**), 136.5 (**C10**), 130.1 (**C12** and **C14**), 128.1 (**C11** and **C15**), 105.0 (**C4 minor**), 104.8 (**C4 major**), 104.6 (**C6**), 63.1 (**C9 major**), 61.2 (**C9 minor**), 38.6 (**C3 major**), 37.1 (**C3 minor**), 21.7 (**C16**), 19.8 (**C7 minor**), 18.7 (**C7 major**), 14.8 (**C8 minor**), 14.2 (**C8 major**)

C13 is not observed and is assumed to be overlapping with the peak at 145.0 ppm

ν_{max} (thin film)/cm^{-1} 1319, 1142 (**O=S=O**)

A mass ion could not be generated for this compound by either CI or EI

(*E*)- and (*Z*)-2-(2-Methylpropylidene)-3-(tosylmethyl)-2,3-dihydrofuran (194)



To a microwave vial containing ester **192** (84 mg, 0.248 mmol, 1.0 equiv) and potassium acetate (2.5 mg, 0.025 mmol, 0.1 equiv) was added BSA (200 µL, 0.818 mmol, 3.3 equiv). The resulting mixture was exposed to 3 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether with 1 % Et_3N) gave bis(enol) ether **194** (58 mg, 80 % yield) as a colourless oil in a 13:1 *dr* (determined by comparing the integrals of signals at δ_H = 6.46 and 6.40 ppm).

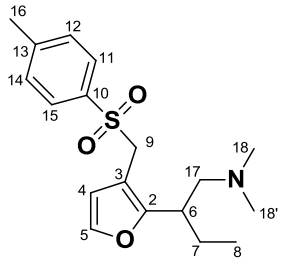
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (2H, d, *J* = 8.0 Hz, **H12** and **H16**), 7.38 (2H, d, *J* = 8.0 Hz, **H13** and **H15**), 6.46 – 6.45 (1H, m, **H5 major**), 6.40 – 6.39 (1H, m, **H5 minor**), 5.32 (1H, t, *J* = 2.5 Hz, **H4 major**), 5.25 (1H, t, *J* = 2.5 Hz, **H4 minor**), 4.34 (1H, dd, *J* = 9.0, 2.0 Hz, **H6**), 4.01 – 3.97 (1H, m, **H3 minor**), 3.90 – 3.88 (1H, m, **H3 major**), 3.22 – 3.11 (2H, m, **H10**), 2.71 – 2.59 (1H, m, **H7**), 2.46 (3H, s, **H17**), {0.95 (3H, d, *J* = 7.0 Hz), 0.92 (3H, d, *J* = 7.0 Hz)} (**H8** and **H9**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.4 (**C2**), 145.1 (**C5**), 145.0 (**C14**), 136.5 (**C11**), 130.1 (**C13**, **C15**), 128.1 (**C12**, **C16**), 111.0 (**C6 minor**), 110.3 (**C6 major**), 105.1 (**C4 minor**), 104.8 (**C4 major**), 63.2 (**C10 major**), 61.8 (**C10 minor**), 38.6 (**C3 major**), 37.1 (**C3 minor**), 25.4 (**C7**), {23.1, 23.0} (**C8** and **C9**), 21.7 (**C17**)

ν_{max} (thin film)/cm^{-1} 1320, 1143 (**O=S=O**)

A mass ion could not be generated for this compound by either CI or ES

(±)-*N,N*-Dimethyl-2-(3-(tosylmethyl)furan-2-yl)butan-1-amine (195)



To a solution of bis(enol) ether **193** (27 mg, 0.097 mmol, 1.0 equiv) in DCM (0.5 mL) at rt was added Eschenmoser's salt (22 mg, 0.116, 1.2 equiv). The reaction mixture was stirred at rt for 18 h, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave amine **195** (22 mg, 68 % yield) as a pale yellow solid.

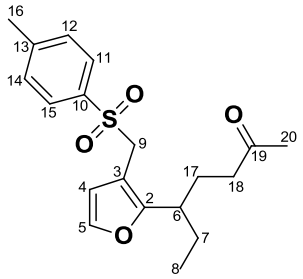
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.5 Hz, **H11** and **H15**), 7.30 (2H, d, *J* = 8.5 Hz, **H12** and **H14**), 7.27 (1H, d, *J* = 1.5 Hz, **H5**), 6.25 (1H, d, *J* = 1.5 Hz, **H4**), {4.21 (1H, d, *J* = 14.5 Hz), 4.15 (1H, d, *J* = 14.5 Hz) (AB system, **H9**)}, 2.68 – 2.60 (1H, m, **H6**), 2.50 – 2.45 (1H, m, **H17A**), 2.44 (3H, s, **H16**), 2.24 – 2.19 (1H, m, **H17B**), 2.16 (6H, s, **H18** and **H18'**), 1.68 – 1.58 (1H, m, **H7A**), 1.48 – 1.36 (1H, m, **H7B**), 0.64 (3H, t, *J* = 7.5 Hz, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.4 (**C2**), 144.7 (**C13**), 141.0 (**C5**), 135.3 (**C10**), 129.7 (**C12** and **C14**), 128.7 (**C11** and **C15**), 111.8 (**C4**), 108.3 (**C3**), 62.4 (**C17**), 53.6 (**C9**), 45.6 (**C18** and **C18'**), 37.0 (**C6**), 24.8 (**C7**), 21.6 (**C16**), 11.6 (**C8**)

ν_{max} (thin film)/cm^{-1} 1316, 1143 (**O=S=O**)

ES-MS calcd for $C_{18}H_{25}NO_3S$ $[M+H]^+$ 336.1633; found 336.1632

(±)-5-(3-(Tosylmethyl)furan-2-yl)heptan-2-one (196)



To a solution of bis(enol) ether **193** (26 mg, 0.093 mmol, 1.0 equiv) in DCM (1 mL) at rt was added $ZnCl_2$ (25 mg, 0.187 mmol, 2.0 equiv) and methyl vinyl ketone (15 µL, 0.187 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 18 h, diluted with DCM, washed with H2O and concentrated under reduced pressure. Purification by silica gel chromatography gave ketone **196** (12 mg, 35 % yield) as a colourless oil.

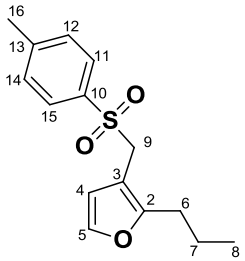
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.0 Hz, **H11** and **H15**), 7.32 (2H, d, *J* = 8.0 Hz, **H12** and **H14**), 7.28 (1H, d, *J* = 1.5 Hz, **H5**), 6.23 (1H, d, *J* = 1.5 Hz, **H4**), 4.10 (2H, s, **H9**), 2.51 – 2.47 (1H, m, **H6**), 2.44 (3H, s, **H16**), 2.25 – 2.18 (2H, m, **H18**), 2.08 (3H, s, **H20**), 1.85 – 1.71 (2H, m, **H17**), 1.53 – 1.40 (2H, m, **H7**), 0.64 (3H, t, *J* = 7.5 Hz, **H8**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 208.8 (**C19**), 156.9 (**C2**), 144.8 (**C13**), 141.1 (**C5**), 135.6 (**C10**), 129.7 (**C12** and **C14**), 128.6 (**C11** and **C15**), 111.6 (**C4**), 108.4 (**C3**), 53.4 (**C9**), 41.1 (**C18**), 37.7 (**C6**), 29.9 (**C20**), 27.4 (**C17**), 27.2 (**C7**), 21.6 (**C16**), 11.8 (**C8**)

ν_{max} (thin film)/cm^{-1} 1713 (**C=O**), 1317, 1145 (**O=S=O**)

ES-MS calcd for $C_{19}H_{24}O_4S$ $[M+MeCN+Na]^+$ 412.1553; found 412.1575

2-Propyl-3-(tosylmethyl)furan (197)



To a solution of bis(enol) ether **193** (25 mg, 0.090 mmol, 1.0 equiv) in DCM (0.5 mL) at rt was added I_2 (46 mg, 0.180 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 20 h, diluted with DCM, washed with 10 % $Na_2S_2O_{3\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave furan **197** (16 mg, 64 % yield) as a colourless oil.

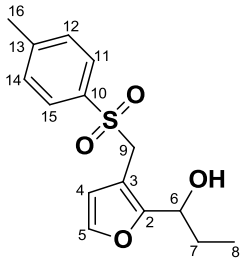
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.5 Hz, **H11** and **H15**), 7.30 (2H, d, *J* = 8.5 Hz, **H12** and **H14**), 7.25 (1H, d, *J* = 2.0 Hz, **H5**), 6.23 (1H, d, *J* = 2.0 Hz, **H4**), 4.11 (2H, s, **H9**), 2.44 (3H, s, **H16**), 2.21 (2H, t, *J* = 7.5 Hz, **H6**), 1.40 (2H, sex., *J* = 7.5 Hz, **H7**), 0.80 (3H, t, *J* = 7.5 Hz, **H8**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.8 (**C2**), 144.7 (**C13**), 140.7 (**C5**), 135.1 (**C10**), 129.6 (**C12** and **C14**), 128.7 (**C11** and **C15**), 111.9 (**C4**), 107.1 (**C3**), 53.7 (**C9**), 27.5 (**C6**), 21.6 (**C16**), 21.2 (**C7**), 13.7 (**C8**)

ν_{max} (thin film)/cm^{-1} 1316, 1139 (**O=S=O**)

EI-MS calcd for $C_{15}H_{18}O_3S$ $[M]^+$ 278.0977; found 278.0981

(±)-1-(3-(Tosylmethyl)furan-2-yl)propan-1-ol (198)



To a solution of bis(enol) ether **193** (31 mg, 0.111 mmol, 1.0 equiv) in DCM (1 mL) at rt was added *m*-CPBA (77 %, 30 mg, 0.133 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 23 h, diluted with DCM, washed with saturated $NaHCO_{3\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (40 % EtOAc in petroleum ether) gave alcohol **198** (14 mg, 43 % yield) as a colourless oil.

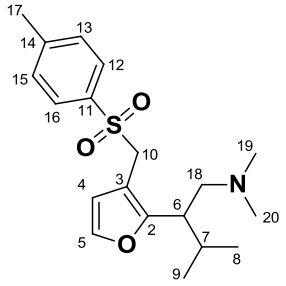
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (2H, d, *J* = 8.0 Hz, **H11** and **H15**), 7.32 (2H, d, *J* = 8.0 Hz, **H12** and **H14**), 7.27 (1H, d, *J* = 1.5 Hz, **H5**), 5.99 (1H, d, *J* = 1.5 Hz, **H4**), 4.60 (1H, t, *J* = 6.5 Hz, **H6**), {4.31 (1H, d, *J* = 14.0 Hz), 4.26 (1H, d, 14.0 Hz)}(AB system, **H9**), 2.45 (3H, s, **H16**), 1.92-1.80 (2H, m, **H7**), 0.89 (3H, t, *J* = 7.5 Hz, **H8**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.3 (**C2**), 145.1 (**C13**), 141.4 (**C5**), 135.0 (**C10**), 129.8 (**C12** and **C14**), 128.6 (**C11** and **C15)**, 112.6 (**C4**), 108.3 (**C3**), 68.1 (**C6**), 53.4 (**C9**), 27.8 (**C7**), 21.7 (**C16**), 9.8 (**C8**)

ν_{max} (thin film)/cm^{-1} 3502 (**O-H**), 1319, 1145 (**O=S=O**)

ES-MS calcd for $C_{15}H_{18}O_4S$ $[M+Na]^+$ 317.0818; found 317.0813

(±)-*N,N*-3-Trimethyl-2-(3-(tosylmethyl)furan-2-yl)butan-1-amine (199)



To a solution of bis(enol) ether **194** (23 mg, 0.079 mmol, 1.0 equiv) in DCM (1 mL) at rt was added Eschenmoser's salt (18 mg, 0.094 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 18 h, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5 % MeOH in DCM) gave amine **199** (25 mg, 91 % yield) as a white solid.

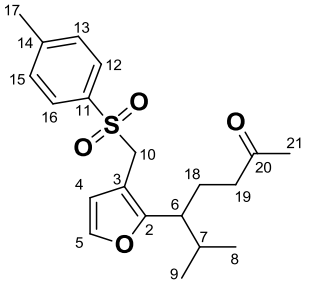
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (2H, d, *J* = 8.0 Hz, **H12** and **H16**), 7.29 (2H, d, *J* = 8.0 Hz, **H13** and **H15**), 7.27 (1H, s, **H5**), 6.26 (1H, d, *J* = 2.0 Hz, **H4**), 4.16 (2H, s, **H10**), 2.66 – 2.57 (2H, m, **H6** and **H18A**), 2.42 (3H, s, **H17**), 2.33 – 2.26 (1H, m, **H18B**), 2.12 (6H, s, **H19** and **H20**), 1.83 (1H, sept.d, *J* = 7.0, 2.0 Hz, **H7**), {0.78 (3H, d, *J* = 7.0 Hz), 0.71 (3H, d, *J* = 7.0 Hz)} (**H8** and **H9**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.9 (**C2**), 144.7 (**C14**), 140.9 (**C5**), 135.4 (**C11**), 129.7 (**C13** and **C15**), 128.7 (**C12** and **C16**), 111.8 (**C4**), 108.9 (**C3**), 59.7 (**C18**), 53.8 (**C10**), 45.4 (**C19** and **C20**), 40.8 (**C6**), 30.3 (**C7**), 21.6 (**C17**), {20.8, 19.0} (**C8** and **C9**)

ν_{max} (thin film)/cm^{-1} 1315, 1139 (**O=S=O**)

ES-MS calcd for $C_{19}H_{27}NO_3S$ $[M+H]^+$ 350.1790; found 350. 1781

(±)-6-Methyl-5-(3-(tosylmethyl)furan-2-yl)heptan-2-one (200)



To a solution of bis(enol) ether **194** (62 mg, 0.212 mmol, 1.0 equiv) in DCM (1 mL) at rt was added zinc (II) chloride (58 mg, 0.424 mmol, 2.0 equiv) and methyl vinyl ketone (34 µL, 0.424 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 16 h, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave ketone **200** (31 mg, 41 % yield) as a colourless oil.

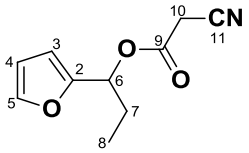
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.5 Hz, **H12** and **H16**), 7.31 (2H, d, *J* = 8.5 Hz, **H13** and **H15**), 7.25 (1H, d, *J* = 2.0 Hz, **H5**), 6.20 (1H, d, *J* = 2.0 Hz, **H4**), 4.07 (2H, d, *J* = 1.5 Hz, **H10**), 2.43 (3H, s, **H17**), 2.40 – 2.35 (1H, m, **H6**), 2.22 – 2.09 (2H, m, **H19**), 2.05 (3H, s, **H21**), 1.91 – 1.78 (2H, m, **H18**), 1.76 – 1.68 (1H, m, **H7**), {0.86 (3H, d, *J* = 7.0 Hz), 0.63 (3H, d, *J* = 7.0 Hz)} (**H8** and **H9**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 208.9 (**C20**), 156.6 (**C2**), 144.9 (**C14**), 141.0 (**C5**), 135.8 (**C11**), 129.8 (**C13** and **C15**), 128.6 (**C12** and **C16**), 111.5 (**C4**), 108.9 (**C3**), 53.5 (**C10**), 42.6 (**C6**), 41.2 (**C19**), 32.2 (**C7**), 29.9 (**C21**), 24.7 (**C18**), 21.6 (**C17**), {20.7, 20.2} (**C8** and **C9**).

ν_{max} (thin film)/cm^{-1} 1710 (**C=O**), 1312, 1139 (**O=S=O**)

ES-MS calcd for $C_{20}H_{26}O_4S$ $[M+H]^+$ 363.1625; found 363.1631

(±)-1-(Furan-2-yl)propyl 2-cyanoacetate (201)



To a solution of alcohol **186** (100 mg, 0.793 mmol, 1.0 equiv) in DCM (1.5 mL) at rt was added cyanoacetic acid (101 mg, 1.19 mmol, 1.5 equiv), DIC (184 µL, 1.19 mmol, 1.5 equiv) and DMAP (15 mg, 0.119 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 36 h, diluted with DCM, washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether with 1 % Et_3N) gave ester **201** (123 mg, 80 % yield) as a pale yellow oil.

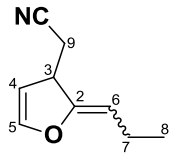
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.41 (1H, m, **H5**), 6.41 – 6.40 (1H, m, **H3**), 6.37 – 6.36 (1H, m, **H4**), 5.82 (1H, t, *J* = 7.5 Hz, **H6**), {3.50 (1H, d, *J* = 19.0 Hz), 3.45 (1H, d, *J* = 19.0 Hz)} (AB system, **H10**) 2.05 (1H, pent., *J* = 7.5 Hz, **H7**), 0.94 (3H, t, *J* = 7.5 Hz, **H8**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.5 (**C9**), 151.0 (**C2**), 143.0 (**C5**), 113.0 (**C11**), 110.4 (**C4**), 109.7 (**C3**), 72.8 (**C6**), 25.4 (**C7**), 24.9 (**C10**), 9.8 (**C8**)

ν_{max} (thin film)/cm^{-1} 1744 (**C=O**)

EI-MS calcd for $C_{10}H_{11}NO_3$ $[M]^+$ 193.0739; found 193.0746

(*E*) and (*Z*)-2-(2-Propylidene-2,3-dihydrofuran-3-yl)acetonitrile (202)



To a microwave vial containg ester **201** (70 mg, 0.362 mmol, 1.0 equiv) and potassium acetate (3.5 mg, 0.036 mmol, 0.1 equiv) was added BSA (270 µL, 1.09 mmol, 3.0 equiv). The resulting mixture was exposed to 3 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (8 % EtOAc in petroleum ether with 1 % Et_3N) gave bis(enol) ether **202** (22 mg, 41 % yield) as a colourless oil in a 10 : 1 *dr* (determined by comparing the integrals of signals at δ_H = 5.26 and 5.20 ppm).

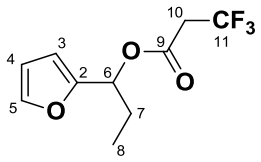
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.59 – 6.57 (1H, m, **H5 major**), 6.56 – 6.55 (1H,m, **H5 minor**), 5.26 (1H, t, *J* = 2.5 Hz, **H4 minor**), 5.20 (1H, t, *J* = 2.5 Hz, **H4 major**), 4.71 (1H, td, *J* = 7.5, 2.0 Hz, **H6**), 3.88 – 3.85 (1H, m, **H3 minor**), 3.74 – 3.70 (1H, m, **H3 major**), 2.54 – 2.42 (2H, m, **H9**), 2.21 – 2.08 (2H, m, **H7 major**), 2.05 – 2.02 (2H, m, **H7 minor**), 1.00 (3H, t, *J* = 7.5 Hz, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.1 (**C2**), 146.2 (**C5 minor**), 146.1 (**C5 major**), 117.5 (**CN**), 106.3 (**C6 minor**), 105.4 (**C6 major**), 103.6 (**C4 major**), 103.4 (**C4 minor**), 40.5 (**C3 major**), 39.0 (**C3 minor**), 24.8 (**C9 major**), 23.3 (**C9 minor**), 20.2 (**C7 minor**), 18.7 (**C7 major**), 15.0 (**C8 minor**), 14.2 (**C8 major**)

ν_{max} (thin film)/cm^{-1} 1744 (**C=O**)

CI-MS calcd for $C_9H_{11}NO$ $[M+H]^+$ 150.0919; found 150.0913

(±)-1-(Furan-2-yl)propyl 3,3,3-trifluoropropanoate (203)



To a solution of alcohol **186** (200 mg, 1.56 mmol, 1.0 equiv) in DCM (15 mL) at rt was added trifluoropropionic acid (275 µL, 3.12 mmol, 2.0 equiv), propylphosphonic anhydride (50 % w/w in EtOAc, 1.49 mL, 2.34 mmol, 1.5 equiv) and triethylamine (326 µL, 2.34 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 5 h and diluted with DCM. The solution was washed with saturated $NaHCO_{3\ (aq)}$, saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (2% EtOAc in petroleum ether with 1 % Et_3N) gave ester **203** (315 mg, 85 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42-7.41 (1H, m, **H5**), 6.38-6.36 (2H, m, **H3**, **H4**), 5.86 (1H, t, *J* = 7.0 Hz, **H6**), 3.24 – 3.16 (2H, m, **H10**), 2.03 (2H, quint. *J* = 7.5 Hz, **H7**), 0.94 (3H, t, *J* = 7.5 Hz, **H8**)

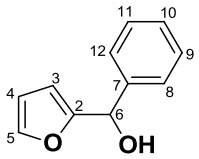
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.5 (**C9**), 151.5 (**C2**), 142.7 (**C5**), 123.4 (q, *J* = 275 Hz, **C11**), 110.3 (**C4**/**C3**), 109.1 (**C4**/**C3**), 71.6 (**C6**), 39.7 (q, *J* = 31 Hz, **C10**), 25.5 (**C7**), 9.6 (**C8**)

^{19}F NMR (377 MHz, $CDCl_3$) δ_F –63.5

ν_{max} (thin film)/cm^{-1} 1750 (**C=O**)

A mass ion could not be generated for this compound by either CI or ES

(±)-Furan-2-yl(phenyl)methanol (204)[104]



To a solution of furan (500 µL, 7.08 mmol, 2.4 equiv) in THF (7 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 1.88 mL, 4.72 mmol, 1.6 equiv) dropwise. The reaction was allowed to warm to 0 °C and stirred at that temperature for 30 mins. The reaction was re-cooled to –78 °C and a solution of benzaldehyde (300 µL, 2.95 mmol, 1.0 equiv) in THF (7 mL) was added dropwise. The resulting solution was stirred at –78 °C for 30 min and then at rt for 16 h. The reaction mixture was poured onto saturated $NH_4Cl_{(aq)}$ and extracted three times with Et_2O. The combined organic layers were washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether) gave alcohol **204** (298 mg, 58 % yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48 – 7.45 (2H, m, **H8** and **H12**), 7.43 – 7.34 (4H, m, **H5**, **H9**, **H10** and **H11**), 6.36 – 6.34 (1H, m, **H4**), 6.15 (1H, d, *J* = 3.0 Hz, **H3**), 5.83 (1H, d, *J* = 4.5 Hz, **H6**), 2.81 (1H, d, *J* = 4.5 Hz, **OH**)

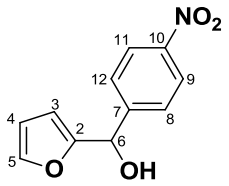
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.0 (**C2**), 142.6 (**C5**), 140.9 (**C7**), 128.5 (**C9** and **C11**), 128.1 (**C10**), 126.7 (**C8** and **C12**), 110.3 (**C4**), 107.5 (**C3**), 70.1 (**C6**)

ν_{max} (thin film)/cm^{-1} 3357 (**OH**)

EI-MS calcd for $C_{11}H_{10}O_2$ $[M]^+$ 174.0681; found 174.0676

These data are in accordance with the literature.[104]

(±)-Furan-2-yl(4-nitrophenyl)methanol (206)[105]



To a solution of furan (875 µL, 12.0 mmol, 2.4 equiv) in THF (10 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 3.20 mL, 8.00 mmol, 1.6 equiv) dropwise. The reaction was allowed to warm to 0 °C and stirred at that temperature for 30 mins. The reaction was re-cooled to –78 °C and a solution of *p*-nitrobenzaldehyde (755 mg, 5.00 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. The resulting solution was stirred at –78 °C for 30 min and then at rt for 1.5 h. The reaction mixture was poured onto saturated $NH_4Cl_{(aq)}$ and extracted three times with Et_2O. The combined organic layers were washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alcohol **206** (751 mg, 69 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.24 (2H, d, *J* = 8.5 Hz, **H9** and **H11**), 7.64 (2H, d, *J* = 8.5 Hz, **H8** and **H12**), 7.42 (1H, d, *J* = 1.0 Hz, **H5**), 6.37 – 6.36 (1H, m, **H4**), 6.19 (1H, d, *J* = 3.0 Hz, **H3**), 5.96 (1H, s, **H6**), 2.73 (1H, br. s, **OH**).

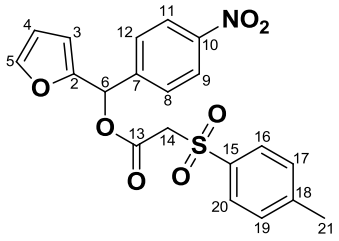
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.5 (**C2**), 147.7 (**C7**), 147.6 (**C10**), 143.2 (**C5**), 127.3 (**C8** and **C12**), 123.7 (**C9** and **C11**), 110.5 (**C4**), 108.1 (**C3**), 69.1 (**C6**)

ν_{max} (thin film)/cm^{-1} 3395 (**OH**), 1516, 1345 (**O=N=O**)

CI-MS calcd for $C_{11}H_9NO_4$ [M-OH]$^+$ 202.0504; found 202.0500

These data are in accordance with the literature.[105]

(±)-Furan-2-yl(4-nitrophenyl)methyl 2-tosylacetate (207)



To a solution of alcohol **206** (500 mg, 2.28 mmol, 1.0 equiv) in DCM (5 mL) at 0 °C was added tosylacetic acid (733 mg, 3.42 mmol, 1.5 equiv), DIC (530 µL, 3.42 mmol, 1.5 equiv) and DMAP (42 mg, 0.342 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 48 h, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (4 % acetone in toluene) gave ester **207** (831 mg, 88 % yield) as a pale yellow solid.

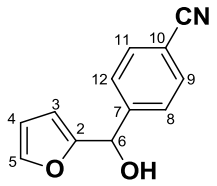
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.25 (2H, d, *J* = 9.0 Hz, **H9** and **H11**), 7.71 (2H, d, *J* = 8.5 Hz, **H16** and **H20**), 7.58 (2H, d, *J* = 8.5 Hz, **H8** and **H12**), 7.44 – 7.43 (1H, m, **H5**), 7.31 (2H, d, *J* = 9.0 Hz, **H17** and **H19**), 6.92 (1H, s, **H6**), 6.39 – 6.38 (1H, m, **H4**), 6.31 (1H, d, *J* = 3.5 Hz, **H3**), {4.24 (1H, d, *J* = 14.0 Hz), 4.19 (1H, d, *J* = 14.0 Hz)} (AB system, **H14**), 2.45 (3H, s, **H21**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C161.4 (**C13**), 149.5 (**C2**), 148.0 (**C10**), 145.6 (**C18**), 144.0 (**C5**), 142.9 (**C7**), 135.5 (**C15**), 129.9 (**C17** and **C19**), 128.4 (**C16** and **C20**), 128.0 (**C8** and **C12**), 123.8 (**C9** and **C11**), 111.3 (**C3**), 110.7 (**C4**), 71.1 (**C6**), 60.9 (**C14**), 21.7 (**C21**)

ν_{max} (thin film)/cm^{-1} 1745 (**C=O**), 1521, 1348 (**O=N=O**), 1328, 1149 (**O=S=O**)

ES-MS calcd for $C_{20}H_{17}NO_7S$ $[M-H]^-$ 414.0647; found 414.0650

(±)-4-(Furan-2-yl(hydroxy)methyl)benzonitrile (208)



To a solution of furan (730 µL, 10.0 mmol, 2.4 equiv) in THF (10 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 2.67 mL, 4.17 mmol, 1.6 equiv) dropwise. The reaction was allowed to warm to 0 °C and stirred at that temperature for 30 mins. The reaction was re-cooled to –78 °C and a solution of *p*-cyanobenzaldehyde (875 mg, 6.67 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. The resulting solution was stirred at –78 °C for 30 min and then at rt for 16 h. The reaction mixture was poured onto saturated $NH_4Cl_{(aq)}$ and extracted three times with Et_2O. The combined organic layers were washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (35 % EtOAc in petroleum ether) gave alcohol **208** (905 mg, 68 % yield) as a white solid.

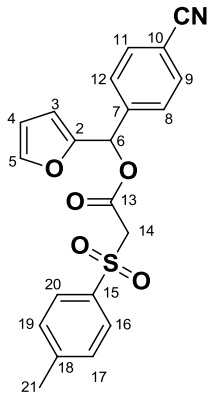
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64 (2H, d, *J* = 8.5 Hz, **H9** and **H11**), 7.56 (2H, d, *J* = 8.5 Hz, **H8** and **H12**), 7.40 – 7.39 (1H, m, **H5**), 6.35 – 6.34 (1H, m, **H4**), 6.16 (1H, d, *J* = 3.0 Hz, **H3**), 5.87 (1H, s, **H6**), 3.10 (1H, br. s, **OH**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.7 (**C2**), 146.1 (**C7**), 143.0 (**C5**), 132.2 (**C9** and **C11**), 127.2 (**C8** and **C12**), 118.8 (**CN**), 111.5 (**C10**), 110.4 (**C4**), 108.0 (**C3**), 69.2 (**C6**)

ν_{max} (thin film)/cm^{-1}3405 (**OH**); 2231 (**C≡N**)

ES-MS calcd for $C_{12}H_9NO_2$ $[M-H]^-$ 198.0555; found 198.0563

(±)- (4-Cyanophenyl)(furan-2-yl)methyl 2-tosylacetate (209)



To a solution of alcohol **208** (100 mg, 0.502 mmol, 1.0 equiv) in DCM (5 mL) at rt was added tosylacetic acid (215 mg, 1.00 mmol, 2.0 equiv), propylphosphonic anhydride (50 % w/w in EtOAc, 480 µL, 0.753 mmol, 1.5 equiv) and triethylamine (105 µL, 0.753 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 18 h, diluted with DCM, washed with saturated $NaHCO_{3\ (aq)}$ and saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (35 % EtOAc in petroleum ether) gave ester **209** (115 mg, 58 % yield) as a yellow solid.

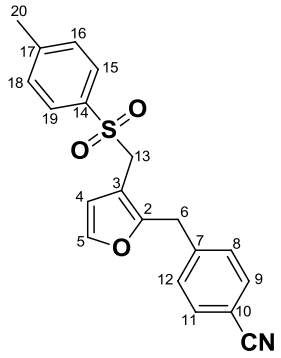
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 – 7.68 (4H, m, **H9**, **H11**, **H16** and **H20**), 7.53 (2H, d, *J* = 8.5 Hz, **H8** and **H12**), 7.43 – 7.42 (1H, m, **H5**), 7.29 (2H, d, *J* = 7.5 Hz, **H17** and **H19**), 6.86 (1H, s, **H6**), 6.38 – 6.37 (1H, m, **H4**), 6.28 (1H, d, *J* = 3.5 Hz, **H3**), {4.22 (1H, d, *J* = 14.0 Hz), 4.17 (1H, d, *J* = 14.0 Hz) (AB system, **H14**)}, 2.46 (3H, s, **H21**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.4 (**C13**), 149.6 (**C2**), 145.6 (**C18**), 144.0 (**C5**), 141.1 (**C7**), 135.5 (**C15**), 132.4 (**C9** and **C11**), 129.9 (**C17** and **C19**), 128.5 (**C16** and **C20**), 127.9 (**C8** and **C12**), 118.4 (**CN**), 112.6 (**C10**), 111.2 (**C3**), 110.6 (**C4**), 71.4 (**C6**), 60.9 (**C14**), 21.8 (**C21**).

ν_{max} (thin film)/cm^{-1} 2230 (**C≡N**), 1744 (**C=O**), 1326, 1148 (**O=S=O**)

ES-MS calcd for $C_{21}H_{17}NO_5S$ $[M-H]^-$ 394.0749; found 394.0744

4-((3-(Tosylmethyl)furan-2-yl)methyl)benzonitrile (211)



To a microwave vial containing ester **209** (77mg, 0.195 mmol, 1.0 equiv) and potassium acetate (2 mg, 0.019 mmol, 0.1 equiv) was added BSA (200 µL, 0.818 mmol, 4.2 equiv). The resulting mixture was exposed to 3 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in petroleum ether with 1 % Et_3N) gave furan **211** (41 mg, 60 % yield) as a white solid.

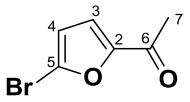
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (2H, d, *J* = 8.0 Hz, **H15** and **H19**), 7.55 (2H, d, *J* = 8.0 Hz, **H9** and **H11**), 7.31 – 7.28 (3H, m, **H5**, **H16** and **H18**), 7.20 (2H, d, *J* = 8.0 Hz, **H8** and **H12**), 6.20 (1H, d, *J* = 2.0 Hz, **H4**), 4.13 (2H, s, **H13**), 3.84 (2H, s, **H6**), 2.46 (3H, s, **H20**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.0 (**C2**), 145.0 (**C17**), 142.6 (**C7**), 141.9 (**C5**), 135.1 (**C14**), 132.3 (**C9** and **C11**), 129.8 (**C16** and **C18**), 129.4 (**C8** and **C12**), 128.6 (**C15** and **C19**), 118.8 (**CN**), 112.4 (**C4**), 110.6 (**C10**), 109.0 (**C3**), 53.5 (**C13**), 32.1 (**C6**), 21.7 (**C20**)

ν_{max} (thin film)/cm^{-1}2257 (**C≡N**), 1315, 1141 (**O=S=O**)

ES-MS calcd for $C_{20}H_{21}NO_3S$ $[M+MeCN+H]^+$ 393.1273; found 393.1282

1-(5-Bromofuran-2-yl)ethanone (212)[106]



To a solution of 2-acetylfuran (1.50 g, 13.6 mmol, 1.0 equiv) in DMF (14 mL) at rt was added *N*-bromosuccinimide (2.67 g, 15.0, 1.1 equiv) in three portions. The reaction mixture was stirred at rt for 108 h, diluted with H_2O and extracted three times with Et_2O. The combined organic layers were washed with 10 % $Na_2S_2O_{3\ (aq)}$, saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether) gave bromofuran **212** (1.04 g, 40 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.13 (1H, d, *J* = 3.5 Hz, **H3**), 6.50 (1H, d, *J* = 3.5 Hz, **H4**), 2.47 (3H, s, **H7**)

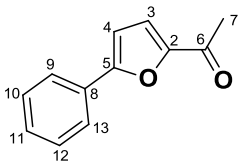
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 185.5 (**C6**), 154.5 (**C2**), 128.2 (**C5**), 119.0 (**C3**), 114.4 (**C4**), 25.8 (**C7**)

ν_{max} (thin film)/cm^{-1} 1656 (**C=O**)

EI-MS calcd for $C_6H_5BrO_2$ $[M]^+$ 187.9473; found 187.9464

These data are in accordance with the literature.[106]

1-(5-Phenylfuran-2-yl)ethanone (213)[107]



To a solution of bromofuran **212** (300 mg, 1.58 mmol, 1 equiv) and tetrakis(triphenylphosphane)palladium(0) (96 mg, 0.079 mmol, 0.05 equiv) in toluene (3 mL) and H_2O (1.5 mL) was added sodium carbonate (336 mg, 3.16 mmol, 2 equiv) and phenylboronic acid (234 mg, 1.90 mmol, 1.2 equiv). The reaction mixture was stirred at 80 °C for 20 h and then cooled to rt and diluted with DCM. The resulting solution was filtered through a Celite® plug and the filter cake was washed with DCM. The combined organic layers were washed with saturated $NaHCO_{3\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether) gave ketone **213** (270 mg, 92 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 – 7.80 (2H, m, **H9**and **H13**), 7.47 – 7.43 (2H, m, **H10** and **H12**), 7.41 – 7.37 (1H, m, **H11**), 7.28 (1H, d *J* = 4.0 Hz, **H3**), 6.80 (1H, d, *J* = 4.0 Hz, **H4**), 2.55 (3H, s, **H7**)

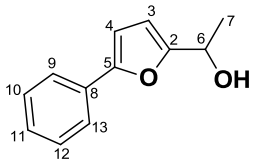
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 186.5 (**C6**), 157.8, (**C5**), 152.0 (**C2**), 129.5 (**C8**), 129.3 (**C11**), 129.0 (**C10** and **C12**), 125.1 (**C9** and **C13**), 119.5 (**C3**), 107.5 (**C4**), 26.1 (**C7**)

ν_{max} (thin film)/cm^{-1} 1667 (**C=O**)

ES-MS calcd for $C_{12}H_{10}O_2$ $[M+H]^+$ 187.0759; found 187.0755

These data are in accordance with the literature.[107]

(±)-1-(5-Phenylfuran-2-yl)ethanol (214)[107]



To a solution of ketone **213** (102 mg, 0.548 mmol, 1.0 equiv) in MeOH (2 mL) at 0 °C was added sodium borohydride (25 mg, 0.658 mmol, 1.2 equiv) in three portions. The reaction mixture was stirred at rt for 15 min and them quenched with H_2O. The resulting solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alcohol **214** (80 mg, 78 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 – 7.69 (2H, m, **H9** and **H13**), 7.43 – 7.39 (2H, m, **H10** and **H12**), 7.31 – 7.26 (1H, m, **H11**), 6.61 (1H, d, *J* = 3.5 Hz, **H4**), 6.34 (1H, d, *J* = 3.5 Hz, **H3**), 4.96 (1H, q, *J* = 6.5 Hz, **H6**), 2.41 (1H, s, **OH**), 1.62 (3H, d, *J* = 6.5 Hz, **H7**)

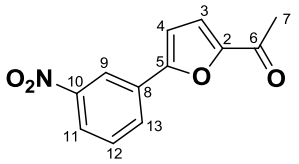
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.3 (**C2**), 153.3 (**C5**), 130.8 (**C8**), 128.7 (**C10** and **C12**), 127.4 (**C11**), 123.7 (**C9** and **C13**), 107.3 (**C3**), 105.6 (**C4**), 63.8 (**C6**), 21.4 (**C7**)

ν_{max} (thin film)/cm^{-1} 3347 (**OH**)

ES-MS calcd for $C_{12}H_{12}O_2$ $[M\text{-}OH]^+$ 171.0810; found 171.0806

These data are in accordance with the literature.[107]

1-(5-(3-Nitrophenyl)furan-2-yl)ethanone (216)



To a solution of bromofuran **212** (300 mg, 1.59 mmol, 1.0 equiv) in toluene (3 mL) and H_2O (1.5 mL) was added palladium (II) acetate (18 mg, 0.080 mmol, 0.05 equiv), triphenylphosphine (42 mg, 0.159 mmol, 0.1 equiv), sodium carbonate (337 mg, 3.18 mmol, 2.0 equiv) and 3-nitrophenylboronic acid (317 mg, 1.90 mmol, 1.2 equiv). The reaction mixture was stirred at 80 °C for 18 h and then cooled to rt and diluted with DCM. The resulting solution was filtered through a Celite® plug and the filter cake was washed with DCM. The combined organic layers were washed with saturated $NaHCO_{3\,(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % petroleum ether in DCM) gave ketone **216** (319 mg, 87 % yield) as a yellow solid.

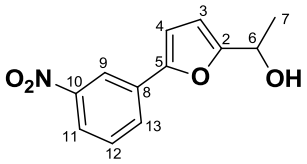
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.59 (1H, t, *J* = 2.0 Hz, **H9**), 8.23 - 8.20 (1H, m, **H11**), 8.14 – 8.11 (1H, m, **H13**), 7.65 (1H, t, *J* = 8.0 Hz, **H12**), 7.31 (1H, d, *J* = 4.0 Hz, **H3** or **H4**), 6.97 (1H, d, *J* = 4.0 Hz, **H3** or **H4**), 2.57 (3H, s, **H7**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 186.4 (**C6**), 154.7 (**C5**), 152.7 (**C2**), 148.8 (**C10**), 131.0 (**C8**), 130.4 (**C13**), 130.1 (**C12**), 123.5 (**C11**), 119.7 (**C9**), 119.2 (**C3** or **C4**), 109.4 (**C3** or **C4**), 26.1 (**C7**)

ν_{max} (thin film)/cm^{-1} 1671 (**C=O**), 1511, 1347 (**O=N=O**)

EI-MS calcd for $C_{12}H_9NO_4$ $[M]^+$ 231.0532; found 231.0525

(±)-1-(5-(3-Nitrophenyl)furan-2-yl)ethanol (217)



To a solution of ketone **216** (105 mg, 0.458 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was added sodium borohydride (35 mg, 0.917 mmol, 2.0 equiv) in two portions. The reaction mixture was stirred at rt for 3 h, quenched with H_2O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (40 % EtOAc in petroleum ether) gave alcohol **217** (68 mg, 64 % yield) as a yellow solid.

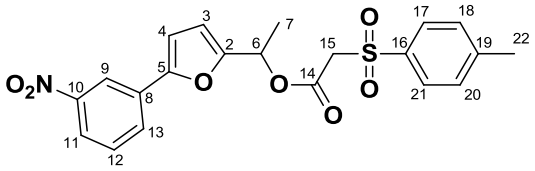
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (1H, t, *J* = 2.0 Hz, **H9**), 8.12 – 8.09 (1H, m, **H11**), 7.91 (1H, dt, *J* = 8.0, 1.0 Hz, **H13**), 7.56 (1H, t, *J* = 8.0 Hz, **H12**), 6.78 (1H, d, *J* = 3.5 Hz, **H3** or **H4**), 6.41 (1H, d, *J* = 3.5 Hz, **H3** or **H4**), 5.00 (1H, q, *J* = 6.0 Hz, **H6**), 2.10 (1H, s, **OH**), 1.65 (3H, d, *J* = 6.0 Hz, **H7**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.7 (**C2**), 150.8 (**C5**), 148.7 (**C10**), 132.3 (**C8**), 129.7 (**C12**), 129.2 (**C13**), 121.7 (**C11**), 118.4 (**C9**), 107.9 (**C3** or **C4**), 107.7 (**C3** or **C4**), 63.8 (**C6**), 21.5 (**C7**)

ν_{max} (thin film)/cm^{-1} 3369 (**OH**), 1524, 1348 (**O=N=O**)

CI-MS calcd for $C_{12}H_{11}NO_4$ $[M\text{-}OH]^+$ 216.0661; found 216.0663

(±)-1-(5-(3-Nitrophenyl)furan-2-yl)ethyl 2-tosylacetate (218)



To a solution of alcohol **217** (57 mg, 0.244 mmol, 1.0 equiv) in DCM (0.5 mL) at rt was added tosylacetic acid (79 mg, 0.366 mmol, 1.5 equiv), DIC (57 µL, 0.366 mmol, 1.5 equiv) and DMAP (5 mg, 0.037 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 96 h, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in petroleum ether with 1 % Et_3N) gave ester **218** (93 mg, 89 % yield) as a yellow oil.

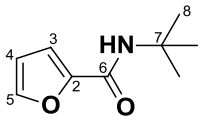
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.45 (1H, t, *J* = 2.0 Hz, **H9**), 8.12 – 8.10 (1H, m, **H11**), 7.96 – 7.94 (1H, m, **H13**), 7.76 (2H, d, *J* = 8.5 Hz, **H17** and **H21**), 7.57 (1H, t, *J* = 8.0 Hz, **H12**), 7.28 (2H, d, *J* = 8.5 Hz, **H18** and **H20**), 6.76 (1H, d, *J* = 3.5 Hz, **H3** or **H4**), 6.47 (1H, d, *J* = 3.5 Hz, **H3** or **H4**), 5.98 (1H, q, *J* = 6.5 Hz, **H6**), 4.13 (2H, s, **H15**), 2.36 (3H, s, **H22**), 1.61 (3H, d, *J* = 6.5 Hz, **H7**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.8 (**C14**), 152.9 (**C2**), 151.6 (**C5**), 148.7 (**C10**), 145.4 (**C19**), 135.7 (**C16**), 131.9 (**C8**), 129.9 (**C12**), 129.8 (**C18** and **C20**), 129.4 (**C13**), 128.6 (**C17** and **C21**), 122.1 (**C11**), 118.6 (**C9**), 111.2 (**C3** or **C4**), 107.9 (**C3** or **C4**), 67.1 (**C6**), 61.1 (**C15**), 21.7 (**C22**), 17.9 (**C7**)

ν_{max} (thin film)/cm^{-1}1738 (**C=O**), 1524, 1349 (**O=N=O**), 1326, 1150 (**O=S=O**)

ES-MS calcd for $C_{21}H_{19}NO_7S$ $[M+Na]^+$ 452.0780; found 452.0776

***N*-Tert-butylfuran-2-carboxamide (225)**[78]



To a solution of 2-furoic acid (2.38 g, 21.2 mmol, 1.0 equiv) in DCM (80 mL) at rt was added DIC (4.94 mL, 31.9 mmol 1.5 equiv) and DMAP (390 mg, 3.19 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 20 min, then t-butylamine (3.35 mL, 31.9 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred for a further 2 h at rt, then was diluted with DCM, washed with saturated $NH_4Cl_{(aq)}$, dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave amide **225** (1.41 g, 40 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 - 7.35 (1H, m, **H5**), 7.01 (1H, d, *J* = 3.5 Hz, **H3**), 6.43 (1H, dd, *J* = 3.5, 4.0 Hz, **H5**), 6.19 (1H, br. s, **NH**), 1.42 (9H, s, **H8**)

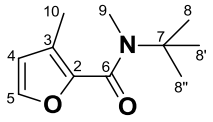
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.8 (**C6**), 148.8 (**C2**), 143.3 (**C5**), 113.4 (**C3**), 112.0 (**C4**), 51.4 (**C7**), 28.9 (**C8**)

ν_{max} (thin film)/cm^{-1} 3298 (**N-H**); 1640 (**C=O**)

CI-MS calcd for $C_9H_{13}NO_2$ $[M+H]^+$ 168.1025; found 168.1020

These data are in accordance with the literature.[78]

***N*-Tert-butyl-*N*,3-dimethylfuran-2-carboxamide (226)**[78]



To a solution of amide **225** (1.23 g, 7.36 mmol, 1.0 equiv) in DME (75 mL) at – 78 °C was added ^{s}BuLi (1.25 M in cyclohexane, 12.9 mL, 16.2 mmol, 2.2 equiv) dropwise, ensuring the temperature was maintained below –70 °C. The reaction mixture was stirred for 1 h at – 78 °C and then methyl iodide (4.58 mL, 73.6 mmol, 10 equiv) was added dropwise. The resulting solution was stirred at – 78 °C for 20 min, then allowed to warm to rt overnight. The reaction was diluted with 1 mL of MeOH, concentrated under redcued pressure and the residue was re-dissolved in EtOAc. This was washed with H_2O and saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether) gave amide **226** (1.14 g, 79 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (1H, d, *J* = 1.5 Hz, **H5**), 6.28 (1H, d, *J* = 1.5 Hz, **H4**), 2.94 (3H, s, **H9**), 2.23 (3H, s, **H10**), 1.48 (9H, s, **H8**, **H8'** and **H8''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.5 (**C6**), 144.8 (**C2**), 141.6 (**C5**), 125.5 (**C3**), 114.2 (**C4**), 56.6 (**C7**), 33.7 (**C9**), 27.6 (**C8**, **C8'** and **C8''**), 11.0 (**C10**)

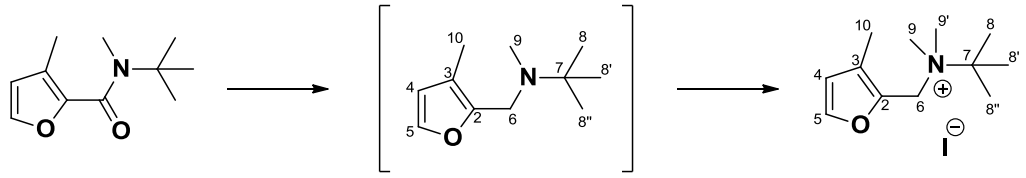
ν_{max} (thin film)/cm^{-1} 1631 (**C=O**)

ES-MS calcd for $C_{11}H_{17}NO_2$ $[M+H]^+$ 196.1338; found 196.1329

These data are in accordance with the literature.[78]

***N*,2-Dimethyl-*N*-((3-methylfuran-2-yl)methyl)propan-2-amine (229)** and

***N,N*,2-Trimethyl-*N*-((3-methylfuran-2-yl)methyl)propan-2-aminium iodide (230)**



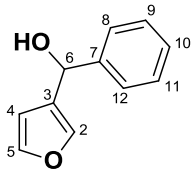
To a solution of amide **226** (500 mg, 2.56 mmol, 1.0 equiv) in THF (10 mL) at rt was added DIBAL (1.0 M in hexane, 6.40 mL, 6.40 mmol, 2.5 equiv). The reaction mixture was heated at reflux for 3 h and then cooled to rt and quenched by addition of EtOAc. Saturated $KNaC_4H_4O_{6\ (aq)}$ was added and the resulting biphasic mixture stirred overnight. The phases were separated and the aqueous phase was re-extracted with EtOAc. The combined organic layers were washed with saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure to give amine **229** (444 mg 96 % yield) as a pale yellow oil that was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (1H, d, *J* = 2.0 Hz, **H5**), 6.19 (1H, d, *J* = 2.0 Hz, **H4**), 3.51 (2H, s, **H6**), 2.19 (3H, s, **H9**), 2.04 (3H, s, **H10**), 1.17 (9H, s, **H8**, **H8'** and **H8''**)

To amine **229** (440 mg, 2.43 mmol, 1.0 equiv) was added methyl iodide (2.40 mL, [1.0 M]) and the reaction mixture was stirred at rt for 24. The resulting solution was concentrated under reduced pressure to give quaternary ammonium salt **230** (694 mg, 88 % yield) as an off-white solid that was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 (1H, d, *J* = 2.0 Hz, **H5**), 6.36 (1H, d, *J* = 2.0 Hz, **H4**), 4.56 (2H, s, **H6**), 3.12 (6H, s, **H9** and **H9'**), 2.27 (3H, s, **H10**), 1.67 (9H, s, **H8**, **H8'** and **H8''**)

(±)-Furan-3-yl(phenyl)methanol (231)[108]



To a solution of 3-furancarboxaldehyde (450 µL, 5.20 mmol, 1.0 equiv) in THF (25 mL) at 0 °C was added phenylmagnesium bromide (3M in Et_2O, 6.76 mmol, 1.3 equiv) dropwise, and then the reaction mixture was stirred at rt for 2.5 h. The reaction was quenched by addition of saturated NH4Cl (aq) and extracted three times with Et_2O. The combined organic layers were washed with saturated NaCl (aq), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether) gave alcohol **231** (815 mg, 95 % yield) as a white solid.

^{1}H NMR (101 MHz, $CDCl_3$) δ_H 7.44 – 7.37 (5H, m, **H5**, **H8**, **H9**, **H11** and **H12**), 7.36 – 7.31 (2H, m, **H2** and **H10**), 6.36 – 6.35 (1H, m, **H4**), 5.76 (1H, s, **H6**), 2.51 (1H, br.s, **OH**)

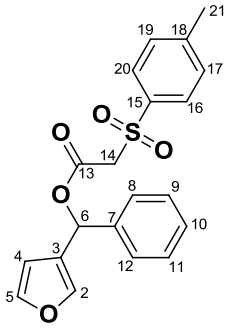
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.5 (**C5**), 143.1 (**C7**), 139.8 (**C2**), 129.0 (**C3**), 128.5 (**C8** and **C12**), 127.9 (**C10**), 126.4 (**C9** and **C11**), 109.3 (**C4**), 69.5 (**C6**)

ν_{max} (thin film)/cm^{-1} 3353 (**OH**)

EI-MS calcd for $C_{11}H_{10}O_2$ $[M]^+$ 174.0681; found 174.0675

These data are in accordance with the literature.[108]

(±)-Furan-3-yl(phenyl)methyl 2-tosylacetate (232)



To a solution of alcohol **231** (380 mg, 2.18 mmol, 1.0 equiv) in DCM (5 mL) at 0 °C was added tosylacetic acid (700 mg, 3.27 mmol, 1.5 equiv), DIC (510 µL, 3.27 mmol, 1.5 equiv) and DMAP (40 mg, 0.327 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 48 h, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave ester **232** (762 mg, 94 % yield) as a thick pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.5 Hz, **H16** and **H20**), 7.40 – 7.32 (6H, m, **H5**, **H8**, **H9**, **H10**, **H11** and **H12**), 7.28 – 7.26 (3H, m, **H2**, **H17** and **H19**), 6.79 (1H, s, **H6**), 6.31 – 6.30 (1H, m, **H4**), {4.18 (1H, d, *J* = 14.0 Hz), 4.15 (1H, d, *J* = 14.0 Hz)} (AB system, **H14**), 2.44 (3H, s, **H21**)

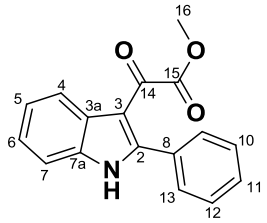
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.7 (**C13**), 145.4 (**C15**), 143.5 (**C5**), 141.3 (**C2**), 138.0 (**C7**), 135.5 (**C18**), 129.8 (**C17** and **C19**), 128.6 ((**C8** and **C12**) or (**C9** and **C11**)), 128.5 (**C16** and **C20**), 127.2 ((**C8** and **C12**) or (**C9** and **C11**)) , 124.4 (**C3**), 109.7 (**C4**), 72.6 (**C6**), 61.2 (**C14**), 21.7 (**C21**)

C10 is not observed and is assumed to be overlapping with another peak in the 130 – 127 ppm region.

ν_{max} (thin film)/cm^{-1} 1738 (**C=O**), 1326, 1148 (**O=S=O**)

ES-MS calcd for $C_{20}H_{18}O_5S$ $[M+MeCN+Na]^+$ 434.1038; found 434.1037

Methyl 2-oxo-2-(2-phenyl-1H-indol-3-yl)acetate (279)



To a solution of 2-phenylindole (5.00 g, 25.9 mmol, 1.0 equiv) in Et_2O (85 mL) at 0 °C was added oxalyl chloride (3.30 mL, 38.8 mmol, 1.5 equiv) dropwise. The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 1 h, at which time a yellow precipitate was observed. MeOH (6.00 mL, 148 mmol, 5.7 equiv) was added and the reaction stirred for a further 15 min at room temperature. The reaction was diluted with DCM and washed with saturated $NaHCO_{3\ (aq)}$. The aqueous layer was re-extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5-30 % EtOAc in petroleum ether) gave ester **279** (5.26 g, 73 % yield) as a pink solid.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ_H 11.49 (1H, s, **NH**), 8.34 – 8.36 (1H, m, **H7**), 7.55 – 7.64 (6H, m, **H4, H9, H10, H11, H12** and **H13**), 7.34 – 7.37 (2H, m, **H5** and **H6**), 3.28 (3H, s, **H16**)

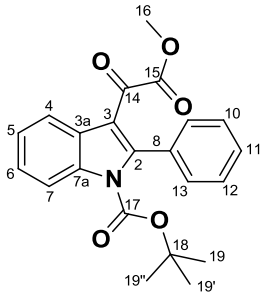
^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ_C 182.7 (**C14**), 165.2 (**C15**), 148.6 (**C2**), 136.1 (**C7a**), 131.1 (**C8**), 129.9 (**C11**), 129.8 ((**C9** and **C13**) or (**C10** and **C12**)), 128.5 ((**C9** and **C13**) or (**C10** and **C12**)), 127.5 (**C3a**), 124.1 (**C5** or **C6**), 123.0 (**C5** or **C6**), 121.6 (**C7**), 111.9 (**C4**), 110.0 (**C3**), 51.1 (**C16**)

ν_{max} (thin film)/cm^{-1} 3237 (**N-H**), 1738 (**C=O ester**), 1610 (**C=O ketone**)

ES-MS calcd for $C_{17}H_{13}NO_3$ $[M+H]^+$ 280.0974; found: 280.0975

mp = 161 – 162 °C

Methyl 2-oxo-2-(*N*-boc-2-phenyl-indol-3-yl)acetate (280)



To a suspension of NaH (260 mg, 10.7 mmol, 2.0 equiv) in THF (20 mL) was added a solution of *N*-H indole **279** (1.50 g, 5.37 mmol, 1.0 equiv) in THF (25 mL) and the reaction mixture was heated to reflux for 1h. After cooling to room temperature, di-*tert*-butyl dicarbonate (2.34 g, 10.7 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 2 h. The reaction was quenched with H_2O and the phases separated. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with NH_4OH (3 % NH_3), dried over $MgSO_4$ and concentrated under reduced pressure. *N*-Boc indole **280** (1.56 g, 77 % yield) was obtained as a pale yellow solid of analytical purity and was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.41 – 8.39 (1H, m, **H7**), 8.25 – 8.22 (1H, m, **H4**), 7.55 – 7.43 (7H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 3.26 (3H, s, **H16**), 1.28 (9H,s, **H19**, **H19'** and **H19''**)

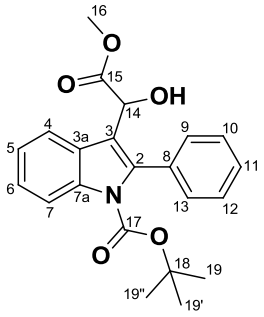
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 184.4 (**C14**), 164.1 (**C15**), 149.1 (**C17**), 147.2 (**C2**), 136.2 (**C7a**), 131.3 (**C8**), 130.7 ((**C9** and **C13**) or (**C10** and **C12**)), 129.5 (**C11**), 127.8 ((**C9** and **C13**) or (**C10** and **C12**)), 126.6 (**C3a**), 126.0 (**C5** or **C6**), 124.9 (**C5** or **C6**), 122.0 (**C7**), 116.0 (**C3**), 114.9 (**C4**), 85.3 (**C18**), 52.0 (**C16**), 27.4 (**C19**, **C19'** and **C19''**)

ν_{max} (thin film)/cm^{-1} 1740 (**C=O ester** and **carbamate**), 1647 (**C=O ketone**)

ES-MS calcd for $C_{22}H_{21}NO_5[M+H]^+$ 380.1498; found 380.1482

mp = 96 – 98 °C

(±)-Tert-butyl 3-(1-hydroxy-2-methoxy-2-oxoethyl)-2-phenyl-1H-indole-1-carboxylate (281)



To a solution of ketone **280** (3.00 g, 7.91 mmol, 1.0 equiv) in THF (35 mL) was added sodium borohydride (300 mg, 7.93 mmol, 1.1 equiv) portionwise over a period of 15 min. The reaction mixture was stirred at room temperature for 50 min, quenched with saturated $NH_4Cl_{(aq)}$ and extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10-15 % EtOAc in hexane) gave alcohol **281** (1.96 g, 65 % yield) as a white foam.

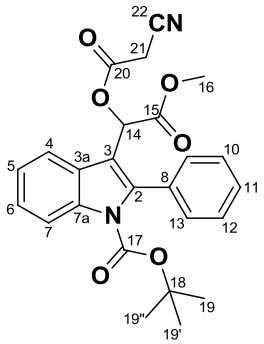
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.30 (1H, d, *J* = 8.5 Hz, **H7**), 7.64 (1H, d, *J* = 8.0 Hz, **H4**), 7.49 – 7.47 (5H, m, **H9, H10, H11, H12** and **H13**), 7.41-7.36 (1H, m, **H6**), 7.31 – 7.27 (1H, m, **H5**), 5.14 (1H, d, *J* = 4.0 Hz, **H14**), 3.74 (3H, s, **H16**), 3.45 (1H, d, *J* = 4.0 Hz, **OH**), 1.27 (9H, s, **H19, H19'** and **H19''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.5 (**C15**), 149.9 (**C17**), 138.8 (**C2**), 136.6 (**C7a**), 132.9 (**C8**), 130.1 ((**C9** and **C13**) or (**C10** and **C12**)), 128.3 (**C11**), 128.0 ((**C9** and **C13**) or (**C10** and **C12**)), 126.8 (**C3a**), 124.9 (**C6**), 123.2 (**C5**), 119.4 (**C4**), 117.0 (**C3**), 115.4 (**C7**), 83.5 (**C18**), 66.2 (**C14**), 53.1 (**C16**), 27.5 (**C19**, **C19'** and **C19''**)

ν_{max} (thin film)/cm^{-1} 3474 (**O-H**), 1729 (**C=O**)

ES-MS calcd for $C_{22}H_{23}NO_5$ $[M+MeCN+Na]^+$ 445.1739, found 445.1753

(±)-*Tert*-butyl 3-(1-(2-cyanoacetoxy)-2-methoxy-2-oxoethyl)-2-phenyl-1H-indole-1-carboxylate (282)



To a solution of alcohol **281** (1.05 g, 2.76 mmol, 1.0 equiv) and cyanoacetic acid (285 mg, 3.35 mmol, 1.2 equiv) in DCM was added triethylamine (0.47 mL, 3.35 mmol, 1.2 equiv). Propylphosphonic anhydride (2.50 mL, 50 % w/w in EtOAc, 5.51 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated $NaHCO_{3\ (aq)}$ and extracted with EtOAc. The organic layers were washed with saturated $NaHCO_{3\ (aq)}$, H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give ester **282** (1.11 g, 90 % yield) as a pale yellow foam of analytical purity.

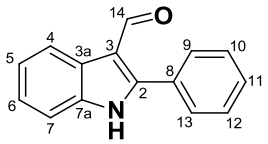
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.32 – 8.29 (1H, m, **H7**), 7.75 (1H, d, *J* = 8.0 Hz, **H4**), 7.50 – 7.41 (6H, m, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 7.36 – 7.33 (1H, m, **H5**), 6.08 (1H, s, **H14**), 3.74 (3H, s, **H16**), {3.62 (1H, d, *J* = 19.0 Hz), 3.53 (1H, d, *J* = 19.0 Hz)} (AB system, **H21**) 1.27 (9H, s, **H19, H19'** and **H19''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 168.1 (**C15**), 162.3 (**C20**), 149.6 (**C17**), 140.1 (**C2**), 136.4 (**C7a**), 132.1 (**C8**), 129.9 (**C11**), 128.8 ((**C9** and **C13)**, or (**C10** and **C11**)), 128.2 ((**C9** and **C13)**, or (**C10** and **C11**)), 126.6 (C**3a**), 125.3 (**C6**), 123.6 (**C5**), 119.7 (**C4**), 115.4 (**C7**), 112.4 (**C22**), 111.9 (**C3**), 84.0 (**C18**), 69.9 (**C4**), 53.1 (**C16**), 27.4 (**C19**, **C19'** and **C19''**), 24.6 (**C21**)

ν_{max} (thin film)/cm^{-1}2264 (**CN**), 1739 (**C=O**)

ES-MS calcd for $C_{25}H_{24}N_2O_6$ $[M+Na]^+$ 471.1532; found 471.1520

2-Phenyl-1H-indole-3-carbaldehyde (285)



To a stirring solution of 2-phenylindole (4.00 g, 20.6 mmol, 1.0 equiv) in DMF (50 mL) at 10 °C was added $POCl_3$ (2.20 mL, 23.6 mmol, 1.15 equiv) dropwise. The solution was then heated at 50 °C for 1 h, cooled and diluted with saturated aqueous $NaHCO_3$ (40 mL). The resulting suspension was heated at 60 °C for 15 min, cooled and the precipitate was collected by filtration to give 3-formyl-2-phenyl indole **285** (4.10 g, 90 % yield) as a pink solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 12.42 (1H, s, **NH**), 9.99 (1H, s, **H14**), 8.24 (1H, d, *J* = 8.0 Hz, **H7**), 7.81 – 7.99 (2H, m, **H9, H13**), 7.65 – 7.59 (3H, m, **H10, H11, H12**), 7.53 (1H, d, J = 7.5 Hz, **H4**), 7.33 – 7.25 (2H, m, **H5** and **H6**)

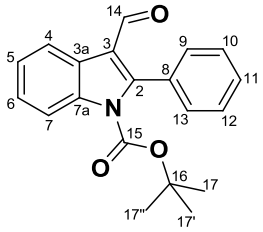
^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C 186.0 (**C14**), 149.6 (**C2**), 136.4 (**C7a**), 130.4 (**C9** and **C13**), 130.34 (**C11**), 130.27 (**C8**), 129.5 (**C10** and **C12**), 126.3 (**C3a**), 124.2 (**C5** or **C6**), 122.9 (**C5** or **C6**), 121.5 (**C7**), 114.0 (**C3**), 112.5 (**C4**)

ν_{max} (thin film)/cm^{-1} 3135 (**NH**), 1626 (**C=O**)

ES-MS calcd for $C_{15}H_{11}NO$ $[M+H]^+$ 222.0919, found 222.0909

mp = 237 – 239 °C

***Tert*-butyl 3-formyl-2-phenyl-1H-indole-1-carboxylate (286)**[109]



To a stirring solution of 3-formyl-2-phenyl indole **285** (2.00g, 9.04 mmol, 1.0 equiv) in pyridine (25 mL) was added di-*tert*-butyl dicarbonate (3.95 g, 18.1 mmol, 2.0 equiv). The solution was stirred for 5 hours at room temperature, and then the solvent was removed under reduced pressure. Purification by silica gel chromatography (1 : 1 : 6 CH_2Cl_2 : EtOAc : hexane) to give *N*-Boc indole **286** (2.74 g, 94 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1H, s, **H14**), 8.44 – 8.42 (1H, m, **H7**), 8.27 – 8.24 (1H, m, **H4**), 7.54 –7.48 (5H, m, **H9, H10, H11, H12** and **H13**), 7.47 - 7.40 (2H, m, **H5** and **H6**), 1.30 (9H, s, **H17, H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 188.2 (**C14**), 149.9 (**C15**), 149.2 (**C2**), 136.3 (**C7a**), 131.0 (**C8**), 130.1 ((**C9** and **C13**) or (**C10** and **C12**)), 129.3 (**C11**), 128.1 ((**C9** and **C13**) or (**C10** and **C12**)), 126.0 (**C6**), 125.5 (**C3a**), 124.8 (**C5**), 122.0 (**C7**), 119.8 (**C3**), 114.9 (**C4**), 85.0 (**C16**), 27.4 (**C17, C17'** and **C17''**)

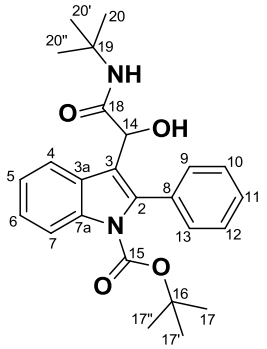
ν_{max} (thin film)/cm^{-1} 1737 (**C=O carbamate**), 1664 (**C=O aldehyde**)

EI-MS calcd for $C_{20}H_{19}NO_3$ $[M]^+$ 321.1365; found 321.1365

mp = 175-176 °C (lit. 178-179 °C)

These data are in accordance with the literature.[109]

(±)-*Tert*-butyl 3-(2-(tert-butylamino)-1-hydroxy-2-oxoethyl)-2-phenyl-1H-indole-1-carboxylate (287)



To a solution of aldehyde **286** (1.00 g, 3.11 mmol, 1.0 equiv) and pyridine-*N*-oxide (60 mg, 0.62 mmol, 0.2 equiv) in DCM (9 mL) was added silicon tetrachloride (400 µL, 3.42 mmol, 1.1 equiv) and the reaction was cooled to -78 °C. A solution of *tert*-butylisonitrile (420 µL, 3.73 mmol, 1.2 equiv) in DCM (3 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at –78 °C for 4 h, before being warmed to room temperature and transferred dropwise to a vigorously stirring solution of saturated $NaHCO_{3\,(aq)}$ (5 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 2 h. The solution was filtered through Celite®, the cake was washed with DCM, and the solution dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10-20 % EtOAc in hexane) gave amide **287** (691 mg, 53 % yield) as a yellow foam.

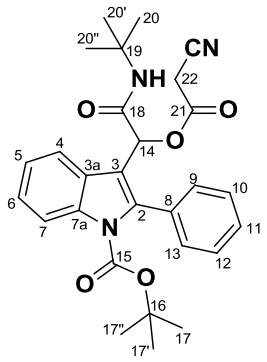
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.26 (1H, d, **H7**), 7.62 (1H, d, **H4**), 7.46 – 7.42 (5H, m, **H9, H10, H11, H12** and **H13**), 7.37 – 7.33 (1H, m, **H5**), 7.28 – 7.32 (1H, m, **H6**), 6.04 (1H, s, **NH**), 4.85 (1H, d, J = 3.0 Hz, **H14**), 3.77 (1H, d, *J* = 3.0 Hz, **OH**), 1.30 (9H, s, **H20, H20', H20''**), 1.23 (9H, s, **H17, H17', H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.1 (**C18**), 149.9 (**C15**), 139.0 (**C2**), 136.8 (**C7a**), 132.9 (**C8**), 130.0 ((**C9** and **C13**) or (**C10** and **C12**)), 128.2 (**C11**), 128.1 ((**C9** and **C13**) or (**C10** and **C12**)), 126.6 (**C3a**), 124.9 (**C6**), 123.0 (**C5**), 119.9 (**C4**), 118.3 (**C3**), 115.3 (**C7**), 83.5 (**C16**), 67.1 (**C14**), 51.5 (**C19**), 28.6 (**C20, C20', C20''**), 27.4 (**C17, C17' C17''**)

ν_{max} (thin film)/cm^{-1} 3340 (**OH**), 1729 (**C=O ester** and **carbamate**), 1657 (**C=O amide**)

EI-MS calcd for $C_{25}H_{30}N_2O_4$ $[M]^+$ 422.2206; found 422.2196

(±)-*Tert*-butyl 3-(2-(tert-butylamino)-1-(2-cyanoacetoxy)-2-oxoethyl)-2-phenyl-1H-indole-1-carboxylate (288)



To a room temperature solution of 2,4,6-trichlorobenzoyl chloride (400 µL, 2.52 mmol, 1.3 equiv) in DCM (8 mL) was added cyanoacetic acid (200 mg, 2.33 mmol, 1.2 equiv) and triethylamine (400 µL, 2.91 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 3 h. The resulting dark yellow solution was concentrated under reduced pressure to give a dark red oil, which was re-dissolved in DCM (4 mL) at room temperature. Alcohol **287** (820 mg, 1.94 mmol, 1.0 equiv), triethylamine (300 µL, 2.13 mmol, 1.1 equiv) and DMAP (24 mg, 0.19 mmol, 0.1 equiv) were added and the solution was stirred at room temperature for 48 h. The reaction was diluted with DCM, washed with saturated $NaHCO_{3\ (aq)}$, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel chromatography (10 – 30 % EtOAc in hexane) gave ester **288** (408 mg, 43 % yield) as a yellow foam.

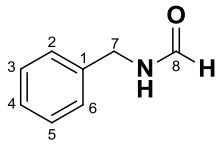
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.30 (1H, d, *J* = 8.0 Hz, **H7**), 7.73 (1H, d, *J* = 8.0 Hz, **H4**), 7.53 – 7.59 (5H, m, **H9**, **H10**, **H11**, **H12** and **H13**), 7.43 – 7.39 (1H, m, **H6**), 7.35 – 7.31 (1H, m, **H5**), 5.95 (1H, s, **H14**), 5.87 (1H, br. s, **NH**), {3.55 (1H, d, *J* = 19.0 Hz) and 3.47 (1H, d, *J* = 19.0 Hz)} (AB quartet, **H22**), 1.34 (9H,s, **H20, H20'** and **H20''**), 1.25 (9H, s, **H17, H17'** and **H17''**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.6 (**C21**), 161.0 (**C18**), 149.6 (**C15**), 140.1 (**C2**), 136.6 (**C7a**), 132.5 (**C8**), 129.9 (**C11**), {128.7, 128.3} (**C9, C10, C12, C13**), 126.3 (**C3a**), 125.2 (**C6**), 123.5 (**C5**), 119.6 (**C4**), 115.5 (**C7**), 113.6 (**C3**), 112.9 (**C23**), 83.9 (**C16**), 71.7 (**C14**), 52.0 (**C19**), 28.6 (**C20, C20'** and **C20''**), 27.4 (**C17, C17'** and **C17''**), 24.7 (**C22**)

ν_{max} (thin film)/cm^{-1} 2250 (**CN**), 1736 (**C=O ester** and **carbamate**), {1679, 1608} (**C=O amide)**

ES-MS calcd for $C_{28}H_{31}N_3O_5$ $[M+Na]^+$ 512.2161; found 512.2166

***N*-Benzylformamide (290)**[110]



Benzylamine (1.00 mL, 9.16 mmol) was dissolved in ethyl formate (9 mL). The reaction mixture was stirred at 45 °C for 24 h and then concentrated under reduced pressure to give formamide **290** (1.23 g, quantitative yield) as a white solid of analytical purity.

This product was observed as a mixture of two rotamers in the NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.20 (1H, s, **H8 major rotamer**), 8.12 (1H, d, *J* = 12.0 Hz, **H8 minor rotamer**), 7.40 – 7.23 (5H, m, **H2, H3, H4, H5, H6**), 6.38 (1H, br. s, **NH major rotamer**), 6.17 (1H, br. s. **NH minor rotamer**), 4.44 (2H, d, *J* = 6.0 Hz, **H7 major rotamer**), 4.37 (2H, d, *J* = 6.5 Hz, **H7 minor rotamer**)

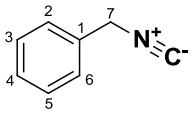
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 164.7 (**C8 minor rotamer**), 161.2 (**C8 major rotamer**), 137.6 (**C1 major rotamer**), 137.5 (**C1 minor rotamer**), {128.9, 128.7, 127.9, 127.8 127.6, 127.0} (**C2-C6 major and minor**), 45.6 (**C7 minor rotamer**) 42.1 **(C7 major rotamer**)

ν_{max} (thin film)/cm^{-1} 1664 (**C=O**)

EI-MS calcd for C_8H_9NO $[M]^+$ 135.0684; found 135.0684

These data are in accordance with the literature.[110]

Benzylisonitrile (289)



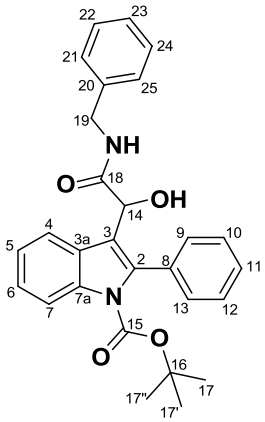
To a three-necked round bottom flask fitted with a reflux condenser and thermometer was added *N*-benzyl formamide **290** (5.00 g, 37.0 mmol, 1.0 equiv), pyridine (18.5 mL, 229 mmol, 6.2 equiv) and petroleum ether (30 mL). The reaction was cooled to 0 °C and $POCl_3$ (2.10 mL, 22.2 mmol, 0.6 equiv) was added dropwise, maintaining an internal temperature of 0 – 5 °C. The reaction was then heated at 70 °C for 15 minutes before being cooled to 0 °C. Ice water (30 mL) was added, and the reaction mixture was stirred at room temperature until all the solid had dissolved. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was distilled, collecting the product that boiled at 80 °C (30 mbar), to give benzyl isonitrile **289** (890 mg, 21 % yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.36 (5H, m, **H2**, **H3**, **H4**, **H5** and **H6**), 4.68 (2H, s, **H7**)

^{13}C NMR (101 MHz, $CDCl_3$) 157.7 (t, *J* = 5.0 Hz, **NC**), 132.4 (**C1**), {129.0, 128.5, 126.6} (**C2-C6**), 45.6 (t, *J* = 7.0 Hz, **C7**)

Due to the obnoxious odour of the isonitrile, no further data was collected. However, the ^{1}H and ^{13} C NMR match the commercially available compound.

(±)-*Tert*-butyl 3-(2-(benzylamino)-1-hydroxy-2-oxoethyl)-2-phenyl-1H-indole-1-carboxylate (291)



To a solution of aldehyde **286** (100 mg, 0.311 mmol, 1.0 equiv) and pyridine-*N*-oxide (6 mg, 0.06 mmol, 0.2 equiv) in DCM (1 mL) was added silicon tetrachloride (40 µL, 0.342 mmol, 1.1 equiv) and the reaction was cooled to –78 °C. A solution of benzylisonitrile **289** (45 µL, 0.373 mmol, 1.2 equiv) in DCM (0.5 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at –78 °C for 4 h, before being warmed to room temperature and transferred dropwise to a vigorously stirring solution of saturated $NaHCO_{3\,(aq)}$ (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 105 min. The solution was filtered through Celite, the cake was washed with DCM, and the solution dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10 % hexane in DCM to 5 % EtOAc in DCM) gave amide **291** (86 mg, 61 % yield) as an off-white foam.

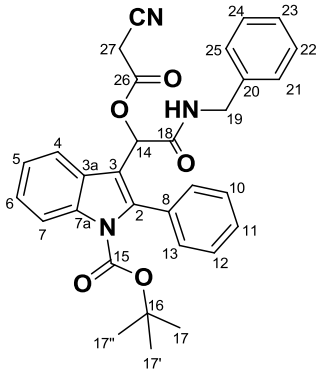
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (1H, d, *J* = 8.5 Hz, **H7**), 7.56 (1H, d, *J* = 8.0 Hz, **H4**), 7.46 – 7.41 (5H, m, **H9, H10, H11, H12** and **H13**), 7.39 – 7.36 (1H, m, **H6**) 7.31 – 7.28 (3H, m, **H22, H23** and **H24**), 7.25 – 7.21 (1H, m, **H5**), 7.18 – 7.16 (2H, m, **H21** and **H25**), 6.70 (1H, t, *J* = 6.0 Hz, **NH**) 5.05 (1H, d, *J* = 3.0 Hz, **H14**), {4.48 (1H, dd, *J* = 6.5, 14.5 Hz) and 4.37 (1H, dd, *J* = 6.0, 14.5 Hz)} (AB system, **H19**), 3.67 (1H, d, *J* = 3.0 Hz, **OH**), 1.25 (9H, s, **H17, H17', H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.1 (**C18**), 149.9 (**C15**), 139.2 (**C2**), 137.7 (**C20**), 136.8 (**C7a**), 132.8 (**C8**), 130.1 ((**C9** and **C13**) or (**C10** and **C12**)), 128.7 (**C22** and **C24**), 128.3 (**C11**), 128.1 ((**C9** and **C13**) or (**C10** and **C12**)), 127.8 (**C21** and **C25**), 127.6 (**C23**), 126.6 (**C3a**), 125.0 (**C6**), 123.1 (**C5**), 120.0 (**C4**), 117.8 (**C3**), 115.4 (**C7**), 83.6 (**C16**), 67.2 (**C14**), 43.6 (**C19**), 27.4 (**C17, C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 3389 (**OH**), 1731 (**C=O ester** and **carbamate**), 1659 (**C=O amide**)

ES-MS calcd for $C_{28}H_{28}N_2O_4$ $[M+Na]^+$ 479.1947; found 479.1946

(±)-*Tert*-butyl 3-(2-(benzylamino)-1-(2-cyanoacetoxy)-2-oxoethyl)-2-phenyl-1H-indole-1-carboxylate (292)



To a solution of alcohol **291** (140 mg, 0.307 mmol, 1.0 equiv) in DCM in a microwave vial was added DMAP (8 mg, 0.061 mmol, 0.2 equiv)), and cyanoacetic acid (52 mg, 0.613 mmol, 2.0 equiv). The reaction mixture was stirred for 5 min at room temperature and then DIC (95 µL, 0.613 mmol, 2.0 equiv) was added dropwise. The vial was capped and the reaction mixture was exposed to 5 cycles of microwave irradiation of 1 hour each at 90 °C. The reaction was diluted with DCM, washed with saturated $NaHCO_{3\ (aq)}$, H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (15 – 30 % EtOAc in hexane) gave ester **292** (29 mg, 18 % yield) as a pale yellow solid.

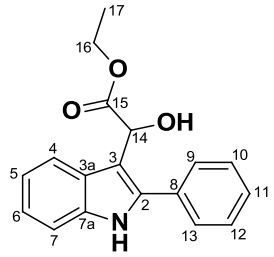
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.29 (1H, d, *J* = 8.5 Hz, **H7**), 7.67 (1H, d, *J* = 8.0 Hz, **H4**), 7.47 – 7.40 (6H, m, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 7.31 – 7.28 (4H, m, **H5**, **H21**, **H23** and **H25**), 7.16 – 7.14 (2H, m, **H22** and **H24**), 6.21 (1H, t, *J* = 6.0 Hz, **NH**), 6.14 (1H, s, **H14**), {4.44 (1H, dd, *J* = 6.0, 6.0 Hz), 4.38 (1H, dd, *J* = 6.0, 6.0 Hz)} (AB system, **H19**), {3.54 (1H, d, *J* = 19.0 Hz), 3.46 (1H, d, *J* = 19.0 Hz)} (AB system, **H27**), 1.24 (9H, s, **H17, H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.7 (**C18**), 161.4 (**C26**), 149.5 (**C15**), 140.2 (**C2**), 137.2 (**C20**), 136.5 (**C7a**), 132.2 (**C8**), 129.8 (**C11**), 128.79 (**C23**), {128.75, 128.3} (**C9**, **C10**, **C12** and **C13**), {127.72, 127.69} (**C21**, **C22**, **C24** and **C25**), 126.3 (**C3a**), 125.4 (**C6**), 123.5 (**C5**), 119.7 (**C4**), 115.6 (**C7**), 113.2 (**C3**), 112.7 (**CN**), 84.1 (**C16**), 71.4 (**C14**), 43.8 (**C19**), 27.4 (**C17, C17'** and **C17''**), 24.7 (**C27**)

ν_{max} (thin film)/cm^{-1} 1737 (**C=O ester** and **carbamate**), 1668 (**C=O amide**)

ES-MS calcd for $C_{31}H_{29}N_3O_5$ $[M+Na]^+$ 546.2005; found 546.1997

(±)-Ethyl 2-hydroxy-2-(2-phenyl-1H-indol-3-yl)acetate (294)



To a solution of 2-phenyl indole (100 mg, 0.517 mmol, 1.0 equiv) in benzene (0.5 mL) was added ethyl glyoxalate (50 % in PhMe, 420 µL, 2.07 mmol, 4.0 equiv) in one portion. The reaction mixture was stirred at room temperature for 3.5 hours and then concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in hexane) gave alcohol **294** (141 mg, 92 % yield) as a pink solid.

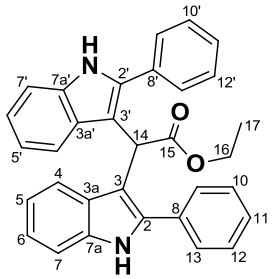
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 11.45 (1H, s, **NH**), 7.76 (2H, d, *J* = 7.0 Hz, **H9** and **H13**), 7.69 (1H, d, *J* = 8.5 Hz, **H7**), 7.56 (2H, t, *J* = 7.5 Hz, **H10** and **H12**), 7.48 – 7.43 (1H, m, **H11**), 7.40 (1H, d, *J* = 8.5 Hz, **H4**), 7.13 (1H, td, *J* = 7.5, 1.5 Hz, **H5**), 7.02 (1H, td, *J* = 7.5, 1.0 Hz, **H6**), 5.79 (1H, d, *J* = 4.5 Hz, **OH**), 5.38 (1H, d, *J* = 4.5 Hz, **H14**), 4.14 – 3.96 (2H, m, **H16**), 1.07 (3H, t, *J* = 7.0 Hz, **H17**)

^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C 173.6 (**C15**), 137.2 (**C2**), 136.4 (**C7a**), 132.5 (**C8**), 129.2 (**C10** and **C12**), 129.1 (**C9** and **C13**), 128.5 (**C11**), 127.2 (**C3a**), 122.1 (**C5**), 120.5 (**C7**), 119.5 (**C6**), 111.7 (**C4**), 110.5 (**C3**), 66.4 (**C14**), 60.8 (**C16**), 14.5 (**C17**)

ν_{max} (thin film)/cm^{-1} 3361 (**N-H**), 1725 (**C=O**)

EI-MS calcd for $C_{18}H_{17}NO_3$ $[M]^+$ 295.1208; found 295.1207

Ethyl 2,2-bis(2-phenyl-1H-indol-3-yl)acetate (295)



To a solution on 2-phenylindole (100 mg, 0.517 mmol, 1.0 equiv) in THF (0.5 mL) was added $BF_3.OEt_2$ (13 µL, 0.103 mmol, 0.2 equiv) and ethyl glyoxylate (50 % in PhMe, 160 µL, 0.776 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 19 hours, diluted with H_2O (5 mL) and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5- 40 % EtOAc in hexane) gave bisindole **295** (58 mg, 24 % yield) as a gummy yellow solid.

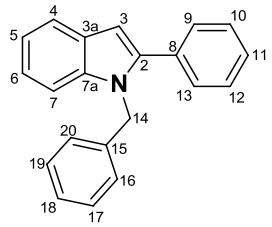
^{1}H NMR (400 MHz, C_6D_6) δ_H 7.77 (2H, d, *J* = 8.5 Hz, **H7** and **H7'**), 7.32 (4H, dd, *J* = 8.0, 1.5 Hz, **H9**, **H13, H9'** and **H13'**), 7.13- 7.11 (2H, m, **H4** and **H4'**), 7.07 – 6.98 (12H, m, **NH**, **H5**, **H6**, **H10**, **H11**, **H12, NH'**, **H5'**, **H6'**, **H10'**, **H11'** and **H12'**), 6.06 (1H, s, **H14**), 3.69 (2H, q, *J* = 7.0 Hz, **H16**), 0.72 (3H, t, *J* = 7.0 Hz, **H17**)

^{13}C NMR (101 MHz, C_6D_6) δ_C 172.8 (**C15**), 135.99, (**C2** or **C8**), 135.96 (**C2** or **C8**), 133.2 (**C7a**), 128.8 (**C9** and **C13**), 128.7 (**C3a**), 128.0 (**C10** and **C12**), 127.4 (**C11**), 121.9 (**C4**), 121.2 (**C7**), 119.9 (**C5** or **C6**), 110.8 (**C5** or **C6**), 110.3 (**C3**), 60.4 (**C16**), 42.1 (**C14**), 13.7 (**C17**)

ν_{max} (thin film)/cm^{-1} 3398 (**N-H**), 1720 (**C=O**)

ES-MS calcd for $C_{32}H_{26}N_2O_2$ $[M+Na]^+$ 493.1892; found 493.1906

1-Benzyl-2-phenyl-1H-indole (298)[111]



To a solution of 2-phenyl indole (4.00 g, 20.6 mmol, 1.0 equiv) in DMF (35 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 1.00 g, 24.8 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min then benzyl chloride (2.88 mL, 24.8 mmol, 1.2 equiv) was added dropwise. The reaction was then removed from the ice bath and stirred at room temperature for 48 hours, diluted with EtOAc (50 mL) and washed with saturated $NaCl_{(aq)}$, 5 % $LiCl_{(aq)}$, saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave N-benzyl indole **298** (5.37 g, 92 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 – 7.71 (1H, m, **H7**), 7.51 – 7.48 (2H, m, **H9** and **H13**), 7.46 – 7.40 (3H, m, **H10**, **H11** and **H12**), 7.35 – 7.18 (6H, m, **H4**, **H5**, **H6**, **H17**, **H18** and **H19**), 7.09 (2H, d, *J* = 7.0 Hz, **H16** and **H20**), 6.71 (1H, s, **H3**), 5.42 (2H, s, **H14**)

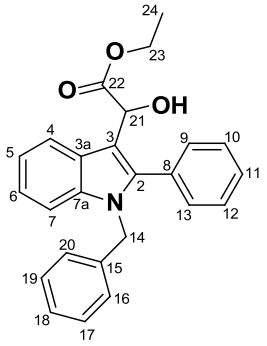
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 141.9 (**C2**), 138.3 (**C15**), 138.0 (**C7a**), 132.7 (**C8**), 129.3 (**C9** and **C13**), 128.8 (**C17** and **C19**), 128.6 (**C10** and **C12**), 128.3 (**C3a**), 128.1 (**C11**), 127.2 (**C18**), 126.0 (**C16** and **C20**), 121.9 (**C4** or **C5** or **C6**), 120.6 (**C7**), 120.2 (**C4** or **C5** or **C6**), 110.6 (**C4** or **C5** or **C6**), 102.4 (**C3**), 47.8 (**C14**)

ν_{max} (thin film)/cm^{-1} 3062, 3029 (**sp^2 C-H**), 2925 (**sp^3 C-H**)

EI-MS calcd for $C_{21}H_{17}N$ $[M]^+$ 283.1361; found 283.1370

These data are in accordance with the literature.[111]

(±)-Ethyl 2-(1-benzyl-2-phenyl-1H-indol-3-yl)-2-hydroxyacetate (299)



To a solution of indole **298** (490 mg, 1.73 mmol, 1.0 equiv) in DCM (5 mL) was added ethyl glyoxalate (50 % in PhMe, 1.06 mL, 5.19 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 64 hours and then concentrated under reduced pressure. Purification by silica gel chromatography (10 – 20 % EtOAc in hexane) gave alcohol **299** (559 mg, 84 % yield) as a pale yellow solid.

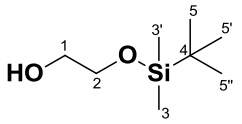
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 – 7.77 (1H, m, **H7**), 7.53 – 7.46 (5H, m, **H9**, **H10**, **H11**, **H12** and **H13**), 7.32 – 7.19 (6H, m, **H4**, **H5**, **H6**, **H17**, **H18** and **H19**), 7.01 (2H, d, *J* = 7.0 Hz, **H16** and **H20**), 5.33 (1H, d, *J* = 4.5 Hz, **H21**), 5.30 (2H, d, *J* = 4.0 Hz, **H14**), {4.31 (1H, dq, *J* = 11.0, 7.0 Hz), 4.20 (1H, dq, *J* = 11.0, 7.0 Hz} (AB system, **H23**), 3.51 (1H, d, *J* = 4.5 Hz, **OH**), 1.25 (3H, t, *J* = 7.0 Hz, **H24**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.7 (**C22**), 140.8 (**C2**), 137.9 (**C15**), 136.9 (**C7a**), 130.9 (**C10** and **C12**), 130.5 (**C8**), 128.9 (**C11**), 128.7 (**C9** and **C13**), 128.5 (**C17** and **C19**), 127.3 (**C18**), 126.1 (**C16** and **C20**), 125.7 (**C3a**), 122.5 (**C6**), 120.6 (**C4** or **C5**), 119.6 (**C7**), 110.8 (**C3**), 110.7 (**C4** or **C5**), 67.0 (**C21**), 62.1 (**C23**), 47.7 (**C14**), 14.2 (**C24**)

ν_{max} (thin film)/cm^{-1} 3513 (**O-H**), 1726 (**C=O**)

ES-MS calcd for $C_{25}H_{23}NO_3$ $[M+H]^+$ 386.1756; found 386.1747

2-(*Tert*-butyldimethylsilyloxy)ethanol (300)



To a solution of ethylene glycol (1.00 g, 16.1 mmol, 1.0 equiv) in DCM (80 mL) was added triethylamine (3.36 mL, 24.1 mmol, 1.5 equiv) and DMAP (200 mg, 1.60 mmol, 0.1 equiv). The solution was cooled to 0 °C and tert-butyldimethylsilyl chloride (2.91 g, 19.3 mmol, 1.2 equiv) was added in five portions over a period of 1 hour. The reaction mixture was then allowed to warm to room temperature and stirred for 20 hours. The reaction was diluted with DCM and washed with saturated $NaHCO_{3\ (aq)}$, saturated $NH_4Cl_{\ (aq)}$ and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave protected alcohol **300** (1.02 g, 36 % yield) as a colourless oil.

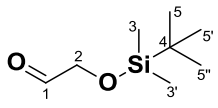
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.69 – 3.67 (2H, m, **H2**), 3.63 – 3.58 (2H, m, **H1**), 2.53 (1H, t, *J* = 6.0 Hz, **OH**), 0.88 (9H, s, **H5, H5'** and **H5''**), 0.06 (6H, s, **H3** and **H3'**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 64.2 (**C2**), 63.6 (**C1**), 25.9 (**C5, C5'** and **C5''**), 18.3 (**C4**), –5.4 (**C3** and **C3'**)

ν_{max} (thin film)/cm^{-1} 3415 (**O-H**), 1116 (**Si-O**)

CI-MS calcd for $C_8H_{20}O_2Si$ $[M+NH_4]^+$ 194.1576; found 194.1564

2-(*Tert*-butyldimethylsilyloxy)acetaldehyde (301)



DMSO (750 µL, 10.6 mmol, 2.4 equiv) was dissolved in DCM (3.5 mL) and cooled in a dry ice/acetone bath. A solution of oxalyl chloride (410 µL, 4.84 mmol, 1.1 equiv) in DCM (15 mL) was added dropwise, maintaining the internal reaction temperature below –65 °C. Once addition was complete the reaction mixture was stirred for 10 minutes, maintaining the reaction temperature. A solution of pyridine (715 µL, 8.80 mmol, 2.0 equiv) and alcohol **300** (775 mg, 4.40 mmol, 1.0 equiv) in DCM (6.5 mL) was added dropwise maintaining the reaction temperature. The reaction mixture was stirred for 15 min maintaining the reaction temperature. Triethylamine (3.07 mL, 22.0 mmol, 5.0 equiv) was added dropwise and the reaction mixture was stirred for a further 15 min before being removed from the dry ice bath and stirred at room temperature for 13 hours. The reaction was quenched with 1M HCl to pH 4 and the phases separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (DCM) gave aldehyde **301** (156 mg, 20 % yield) as a colourless oil.

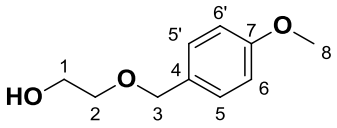
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1H, s, **H1**), 4.21 (2H, s, **H2**), 0.92 (9H, s, **H5, H5'** and **H5''**), 0.10 (6H, s, **H3** and **H3'**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 202.2 (**C1**), 69.6 (**C2**), 25.7 (**C5, C5'** and **C5''**), 18.3 (**C4**), –5.5 (**C3** and **C3'**)

ν_{max} (thin film)/cm^{-1} 1739 (**C=O**)

CI-MS calcd for $C_8H_{18}O_2Si$ $[M+NH_4]^+$ 192.1420; found 192.1426

2-(4-Methoxybenzyloxy)ethanol (302)[112]



To a room temperature solution of ethylene glycol (1.00 g, 16.1 mmol, 3.0 equiv) in THF (10 mL) was added sodium hydride (60 % dispersion in mineral oil, 240 mg, 5.91 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 30 mins and then 4-methoxybenzyl chloride (730 µL, 5.37 mmol, 1.0 equiv) and *tert*-butylammonium iodide (200 mg, 0.540 mmol, 0.1 equiv) were added. The reaction mixture was stirred at 80 °C for 4.5 hours before being cooled to room temperature, quenched with saturated $NH_4Cl_{(aq)}$, and extracted with Et_2O. The combined organic layers were washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 – 60 % EtOAc in hexane) gave protected alcohol **302** (790 mg, 81 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 (2H, d, *J* = 9.0 Hz, **H5** and **H5'**), 6.90 (2H, d, *J* = 9.0 Hz, **H6** and **H6'**), 4.50 (2H, s, **H3**), 3.81 (3H, s, **H8**), 3.74 (2H, t, m, **H1**), 3.56 (2H, t, *J* = 4.5 Hz, **H2**), 2.68 (1H, br. t., **OH**)

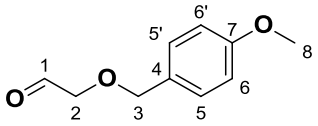
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.3 (**C7**), 130.1 (**C4**), 129.5 (**C5** and **C5'**), 113.8 (**C6** and **C6'**), 72.9 (**C3**), 71.2 (**C2**), 61.8 (**C1**), 55.3 (**C8**)

ν_{max} (thin film)/cm^{-1} 3393 (**O-H**)

EI-MS calcd for $C_{10}H_{14}O_3$ $[M]^+$ 182.0943; found 182.0936

These data are in accordance with the literature.[112]

2-(4-Methoxybenzyloxy)acetaldehyde (303)[113]



DMSO (4.21 mL, 59.3 mmol, 2.4 equiv) was dissolved in DCM (10 mL) and cooled in a dry ice/acetone bath. A solution of oxalyl chloride (2.30 mL, 27.2 mmol, 1.1 equiv) in DCM (20 mL) was added dropwise, maintaining the internal reaction temperature below – 65 °C. Once addition was complete the reaction mixture was stirred for 10 minutes, maintaining the reaction temperature. A solution of pyridine (4.00 mL, 49.4 mmol, 2.0 equiv) and alcohol **302** (4.50 g, 24.7 mmol, 1.0 equiv) in DCM (20 mL) was added dropwise maintaining the reaction temperature. The reaction mixture was stirred for 15 min maintaining the reaction temperature. Triethylamine (17.2 mL, 123.5 mmol, 5.0 equiv) was added dropwise and the reaction mixture was stirred for a further 15 min before being removed from the dry ice bath and stirred at room temperature for 13 hours. The reaction was quenched with 1M HCl to pH 4 and the phases separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in hexane) gave aldehyde **303** (2.69 g, 60 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1H, s, **H1**), 7.31 (2H, d, *J* = 8.5 Hz, **H5** and **H5'**), 6.91 (2H, d, *J* = 8.5 Hz, **H6** and **H6'**), 4.57 (2H, s, **H3**), 4.08 (2H, s, **H2**), 3.82 (3H, s, **H8**)

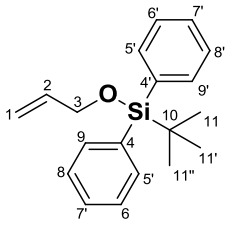
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 200.6 (**C1**), 159.6 (**C7**), 129.8 (**C5** and **C5'**), 128.9 (**C4**), 114.0 (**C6** and **C6'**), 75.0 (**C2**), 73.3 (**C3**), 55.3 (**C8**)

ν_{max} (thin film)/cm^{-1} 1733 (**C=O**)

EI-MS calcd for $C_{10}H_{12}O_3$ $[M]^+$ 180.0786; found 180.0789

These data are in accordance with the literature.[113]

Allyloxy(tert-butyl)diphenylsilane (304)[114]



To a room temperature solution of allyl alcohol (1.00 mL, 14.7 mmol, 1.0 equiv) and imidazole (1.20 g, 17.6 mmol, 1.2 equiv) in DMF (10 mL) was added *tert*-butyl(chloro)diphenylsilane (4.21 mL, 16.2 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at room temperature for 3.5 hours, quenched with H_2O and extracted with Et_2O. The combined organic layers were washed with 5 % LiCl $_{(aq)}$, H_2O, saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (2 % EtOAc in hexane) gave protected alcohol **304** (4.31 g, 99 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 – 7.73 (4H, m, **H5**, **H9**, **H5'** and **H9'**), 7.49 – 7.40 (6H, m, **H6**, **H7**, **H8, H6'**, **H7'** and **H8'**), 5.98 (1H, ddt, *J* = 17.0, 10.5, 4.0 Hz, **H2**), 5.44 (1H, dq, *J* = 17.0, 2.0 Hz, **H1A**), 5.17 (1H, dq, *J* = 10.5, 2.0 Hz, **H1B**), 4.27 (2H, dt, *J* = 4.0, 2.0 Hz, **H3**), 1.13 (9H, s, **H11, H11'** and **H11''**)

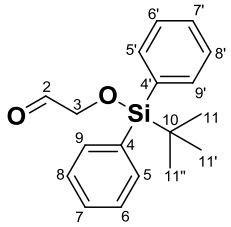
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 137.1 (**C2**), 135.6 (**C5**, **C9**, **C5'** and **C9'**), 133.8 (**C4** and **C4'**), 129.7 (**C7** and **C7'**), 127.7 (**C6**, **C8**, **C6'** and **C8'**), 114.0 (**C1**), 64.7 (**C3**), 26.9 (**C11, C11'** and **C11''**), 19.3 (**C10**)

ν_{max} (thin film)/cm^{-1} 1646 (**C=C**), 1110 (**Si-O**)

CI-MS calcd for $C_{19}H_{24}OSi$ $[M+NH_4]^+$ 314.1940; found 314. 1953

These data are in accordance with the literature.[114]

2-(*Tert*-butyldiphenylsilyloxy)acetaldehyde (305)[115]



To a solution of alkene **304** (8.00 g, 27.0 mmol, 1.0 equiv) in DCM (300 mL) at – 78 °C was passed O_3/O_2 (1.3 mmol O_3/min) for 1 hour at which point a light blue colour was observed. The reaction mixture was warmed to room temperature while de-gassing with N_2 and then quenched with triphenylphosphine (7.08 g, 27.0 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 4 hours and then concentrated under reduced pressure. Purification by silica gel chromatography (5 – 15 % EtOAc in hexane) gave aldehyde **305** (6.38 g, 79 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.80 (1H, s, **H2**), 7.81 – 7.79 (4H, m, **H5**, **H9**, **H5'** and **H9'**), 7.56 – 7.47 (6H, m, **H6, H7, H8**, **H6', H7'** and **H8'**), 4.33 (2H, s, **H3**), 1.24 (9H, s, **H11, H11'** and **H11''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.4 (**C2**), 135.6 (**C5**, **C9**, **C5'** and **C9'**), 132.6 (**C4** and **C4'**), 130.2 (**C7** and **C7'**), 128.1 (**C6**, **C8**, **C6'** and **C8'**), 70.1 (**C3**), 26.9 (**C11, C11'** and **C11''**), 19.4 (**C10**)

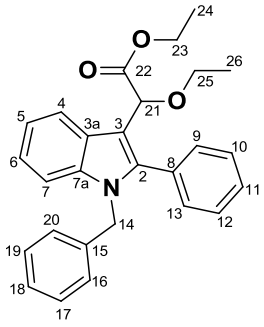
ν_{max} (thin film)/cm^{-1} 1738 (**C=O**), 1105 (**Si-O**)

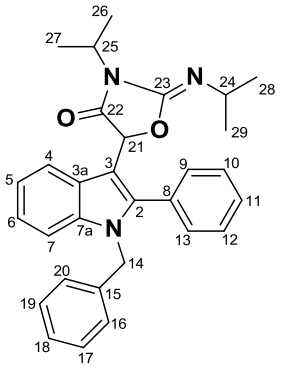
CI-MS calcd for $C_{18}H_{22}O_2Si$ $[M+NH_4]^+$ 316.1733; found 316.1740

These data are in accordance with the literature.[115]

(±)-Ethyl 2-(1-benzyl-2-phenyl-1H-indol-3-yl)-2-ethoxyacetate (306) and

(±)-5-(1-Benzyl-2-phenyl-1H-indol-3-yl)-3-isopropyl-2-(isopropylimino)oxazolidin-4-one (307)





To a room temperature solution of alcohol **299** (122 mg, 0.317 mmol, 1.0 equiv) in DCM (1 mL) was added DMAP (8.0 mg, 0.063 mmol, 0.2 equiv), cyanoacetic acid (54.0 mg, 0.633 mmol, 2.0 equiv) and DIC (100 µL, 0.633, 2.0 equiv mmol). The reaction mixture was stirred at room temperature for 42 hours, diluted with DCM, washed with saturated $NaHCO_{3\ (aq)}$ and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10 – 20 % EtOAc in hexane) gave ether **306** (16 mg, 12 % yield) and oxazolidinone **307** (89 mg, 59 % yield).

Ether 306

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.02 (1H, d, *J* = 5.0 Hz, **H7**), 7.46 (4H, app. s., **H9**, **H10**, **H12** and **H13**), 7.29 – 7.18 (7H, m, **H4**, **H5**, **H6**, **H11**, **H17**, **H18** and **H19**), 6.97 (2H, d, *J* = 7.0 Hz, **H16** and **H20**), {5.28 (1H, d, *J* = 17.0 Hz), 5.21 (1H, d, *J* = 17.0 Hz)} (AB system, **H14**), 5.02 (1H, s, **H21**), {4.25 (1H, dq, *J* = 15.0 , 7.0 Hz), 4.17 (1H, dq, *J* = 15.0, 7.0 Hz)} (AB system, **H23**), 3.46 (2H, q, *J* = 7.0 Hz, **H25**), 1.25 (3H, t, *J* = 7.0 Hz, **H24**), 1.18 (3H, t, *J* = 7.0 Hz, **H26**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.5 (**C22**), 140.8 (**C2**), 137.9 (**C15**), 136.9 (**C7a**), 130.6 (**C8**), 128.8 (**C11**), 128.6 (**C9**, **C10**, **C12** and **C13**), 128.4 (**C17** and **C19**), 127.2 (**C18**), 126.2 (**C3a**), 126.1 (**C16** and **C20**), 122.4 (**C6**), 121.1 (**C7**), 120.4 (**C4** or **C5**), 110.3 (**C4** or **C5**), 109.3 (**C3**), 74.5 (**C21**), 64.1 (**C25**), 61.0 (**C23**), 47.7 (**C14**), 15.1 (**C26**), 14.2 (**C24**).

ν_{max} (thin film)/cm^{-1} 1744 (**C=O**), 1099 (**C-O ether**)

ES-MS calcd for $C_{27}H_{27}NO_3$ $[M+Na]^+$ 436.1889; found 436.1888

Oxazolidinone 307

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 – 7.39 (5H, m, **H7**, **H10**, **H11**, **H12** and **H18**), 7.30 – 7.24 (4H, m, **H9**, **H13**, **H17** and **H19**), 7.20 – 7.16 (2H, m, **H5** and **H6**), 7.12 (1H, td, *J* = 8.0, 1.5 Hz, **H4**), 6.96 (2H, d, *J* = 7.0 Hz, **H16** and **H20**), {5.31 (1H, d, *J* = 17.0 Hz), 5.22 (1H, d, *J* = 17.0 Hz)} (AB system, **H14**), 4.99 (1H, s, **H21**), 4.51 (1H, hept., *J* = 7.0 Hz, **H25**), 4.13 (1H, hept., *J* = 7.0 Hz, **H24**), 1.56 (3H, d, *J* = 7.0 Hz, **H26** or **H27**), 1.53 (3H, d, *J* = 7.0 Hz, **H26** or **H27**), 0.97 (3H, d, *J* = 7.0 Hz, **H28** or **H29**), 0.87 (3H, d, *J* = 7.0 Hz, **H28** or **H29**)

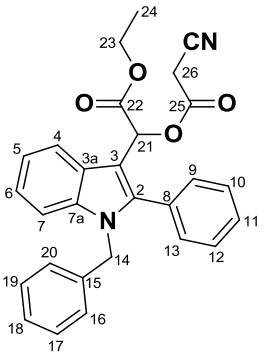
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.6 (**C22**), 155.7 (**C23**), 141.8 (**C2**), 137.7 (**C15**), 137.0 (**C7a**), 132.4 (**C11**), 130.0 (**C18**), 129.2 (**C10** and **C12**), 128.8 ((**C9** and **C13**) or (**C17** and **C19**)), 128.6 (**C18**), 127.3 ((**C9** and **C13**) or (**C17** and **C19**)), 125.9 (**C16** and **C20**), 125.6 (**C3a**), 122.7 (**C5** or **C6**), 120.6 (**C4**), 119.2 (**C7**), 110.9 (**C5** or **C6**), 106.9 (**C3**), 55.6 (**C21**), 47.7 (**C14**), 45.0 (**C24**), 44.1 (**C25**), 21.0 (**C28** or **C29**), 20.0 (**C28** or **C29**), 19.8 (**C26** and **C27**)

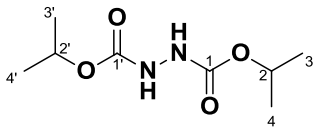
ν_{max} (thin film)/cm^{-1} 1759 (**C=N**), 1698 (**C=O**)

ES-MS calcd for $C_{30}H_{31}N_3O_2$ $[M+H]^+$ 466.2495; found 466.2483

(±)-Ethyl 2-(2-cyanoacetoxy)-2-(2-phenyl-1-benzyl-1H-indol-3-yl)acetate (308) and

Diisopropyl hydrazine-1,2-dicarboxylate (309)





To an ice cooled solution of alcohol **299** (120 mg, 0.311 mmol, 1.0 equiv), triphenyphosphine (90 g, 0.342 mmol, 1.1 equiv) and cyanoacetic acid (29 mg, 0.342 mmol, 1.1 equiv) in THF (0.75 mL) was added DIAD (67 µL, 0.342 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at room temperature for 4 days, diluted with DCM, washed with saturated $NaHCO_{3\ (aq)}$ and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Ester **308** hydrolysed on silica gel to give the starting alcohol **299** and so could not be purified. Key ^1H shifts from NMR analysis of the crude reaction mixture are given below.

Ester 308

^1H NMR (400 MHz, $CDCl_3$) δ_H = 6.18 (1H, s, **H21**), 5.24 (2H, d, *J* = 5.5 Hz, **H14**), 4.24 – 4.08 (2H, m, **H23**), 3.63 – 3.49 (2H, AB quartet, **H26**)

Carbamate 309

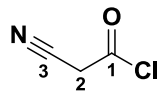
^1H NMR (400 MHz, $CDCl_3$) δ_H = 6.63 (2H, br. s, **NH**), 4.95 (2H, hept, *J* = 6.5 Hz, **H2** and **H2'**), 1.24 (12H, d, *J* = 6.5 Hz, **H3**, **H4, H3'** and **H4'**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.6 (**C1** and **C1'**), 70.1 (**C2** and **C2'**), 22.0 (**C3**, **C4**, **C3'** and **C4'**)

ν_{max} (thin film)/cm^{-1} = 3306 (**N-H**), 1712 (**C=O**)

EI-MS calcd for $C_8H_{16}N_2O_4$ $[M]^+$ 204.1110; found 204.1117

Cyanoacetic acid chloride (310)[116]



To an ice-cooled solution of cyanoacetic acid (5.00 g, 58.8 mmol, 1.0 equiv) in Et_2O (30 mL) in a two-necked round bottom flask fitted with a vigereux condenser was added PCl_5 (12.3 g, 58.8 mmol, 1.0 equiv) in five portions over 15 min. Once addition was complete the reaction mixture was stirred with ice cooling for 30 min, and then at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure to give a yellow residue. Purification by distillation (78 – 80 °C, 8.0 mbar) gave acyl chloride **310** (3.16 g, 52 % yield) as a pale yellow liquid.

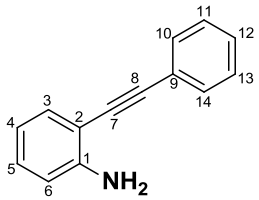
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.03 (2H, s, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.0 (**C1**), 77.1 (**C3**), 35.5 (**C2**).

ν_{max} (thin film)/cm^{-1} = 1790 (**C=O**)

EI-MS calcd for $[C_3H_2NOCl]^+$ 102.9825; found 102.9810.

2-(Phenylethynyl)aniline (316)[117]



To a room temperature solution of 2-iodoaniline (1.50 g, 6.84 mmol, 1.0 equiv) in triethylamine (18 mL) was added $PdCl_2(PPh_3)_2$ (240 mg, 0.342 mmol, 0.05 equiv) and CuI (130 mg, 0.684 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 15 min and then phenylacetylene (900 µL, 8.21 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for a further 48 hours at room temperature, filtered through a pad of Celite®, the filter cake washed with DCM and the combined organics concentrated under reduced pressure. The residue was diluted with H_2O (20 mL), and extracted with Et_2O. The combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (7 % EtOAc in hexane) gave alkyne **316** (1.20 g, 90 % yield) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 – 7.58 (2H, m, **H10** and **H14**), 7.44 – 7.38 (4H, m, **H3**, **H11**, **H12** and **H13**), 7.22 – 7.18 (1H, m, **H5**), 6.80 – 6.76 (2H, m, **H4** and **H6**), 4.32 (2H, br. s, **NH_2**)

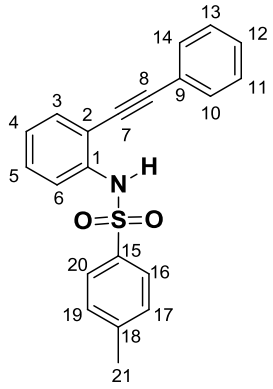
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 147.8 (**C1**), 132.2 (**C3**), 131.5 (**C10** and **C14**), 129.8 (**C5**), 128.5 (**C11** and **C13**), 128.3 (**C12**), 123.4 (**C9**), {118.0, 114.4 (**C4** and **C6**)}, 108.0 (**C2**), 94.8 (**C8**), 86.0 (**C7**)

ν_{max} (thin film)/cm^{-1} 3468, 3370 (**NH_2 assymetric and symmetric stretch**); 2207 (**C≡C stretch**)

CI-MS calcd for for $C_{14}H_{11}N$ $[M+H]^+$ 194.0970; found 194.0966

These data are in accordance with the literature.[117]

4-Methyl-N-(2-(phenylethynyl)phenyl)benzenesulfonamide (317)[117]



To an ice cooled solution of aniline **316** (1.07 g, 5.54 mmol, 1.0 equiv) in DCM (30 mL) was added pyridine (900 µL, 11.1 mmol, 2.0 equiv) and *p*-toluenesulfonyl chloride (1.27 g, 6.64 mmol, 1.2 equiv). The reaction mixture was then stirred at room temperature for 48 hours, diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5 – 20 % EtOAc in hexane) gave sulfonamide **317** (1.82 g, 94 % yield) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.5 Hz, **H16** and **H20**), 7.66 (1H, d, *J* = 7.5 Hz, **H5** or **H6**), 7.52 – 7.47 (2H, m, **H10** and **H14**), 7.42 – 7.38 (4H, m, **H3**, **H11**, **H12** and **H13**), 7.34 – 7.30 (1H, m, **H5** or **H6**), 7.25 (1H, br. s. **NH**), 7.19 (2H, d, 8.0 Hz, **H17** and **H19**) 7.09 (1H, dt, *J* = 7.5, 1.0 Hz, **H4**), 2.36 (3H, s, **H21**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1 (**C18**), 137.5 (**C1**), 136.1 (**C15**), 132.0 (**C3**), 131.6 (**C10** and **C14**), 129.6 (**C17** and **C19**), 129.1 (**C12**), 128.6 (**C11** and **C13**), 127.3 (**C16** and **C20**), 124.6 (**C4**), 122.0 (**C9**), 120.4 (**C5** or **C6**), 114.7 (**C2**), 96.2 (**C8**), 83.7 (**C7**), 21.6 (**C21**)

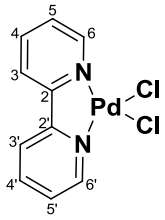
One carbon signal (**C5/6**) is not observed, and is assumed to be overlapping with the peak at 129.6 ppm from the HSQC experiment.

ν_{max} (thin film)/cm^{-1} 1338, 1163 (**O=S=O**)

ES-MS calcd for $C_{21}H_{17}NO_2S$ $[M+H]^+$ 348.1058; found 348.1062

These data are in accordance with the literature.[117]

$PdCl_2$(bipy) (318)[118]

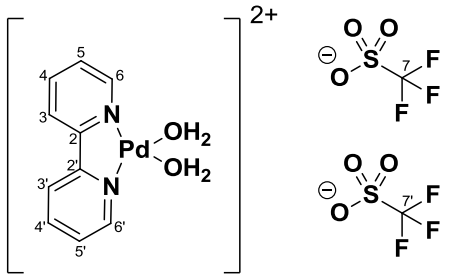


To a solution of 2,2'-bipyridine (175 mg, 1.12 mmol, 1.1 equiv) in MeOH (3 mL) at rt was added palladium (II) chloride (180 mg, 1.02 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 7 h at which point a yellow precipitate was observed. The precipitate was filtered, washed with MeOH and dried under vacuum to give $PdCl_2$(bipy) **318** (213 mg, 63 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 9.14 (2H, d, *J* = 5.5 Hz, **H6** and **H6'**), 8.60 (2H, d, *J* = 8.0 Hz, **H3** and **H3'**), 8.38 (2H, td, *J* = 8.0, 1.5 Hz, **H4** and **H4'**), 7.83 (2H, td, *J* = 5.5, 1.5 Hz, **H5** and **H5'**)

^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C 156.9 (**C2** and **C2'**), 150.2 (**C6** and **C6'**), 141.8 (**C4** and **C4')**, 127.8 (**C5** and **C5'**), 124.4 (**C3** and **C3'**)

[(bpy)Pd^{2+}(H2O)$_2$].($^-$OTf)$_2$ (319)[119]



To a solution of $PdCl_2$(bipy) **318** (134 mg, 0.402 mmol, 1.0 equiv) in H_2O (19 mL) in a round bottomed flask under the protection of tin foil was added silver (II) triflate (207 mg, 0.804 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 36 h and then 100 °C for 30 min. The reaction was filtered and the filtrate was concentrated under reduced pressure. The residue was dried with P_2O_5 under vacuum overnight to give ([(bpy)Pd^{2+}(H_2O)$_2$].($^-$OTf)$_2$ **319** (210 mg, 88 % yield) as a brown solid

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H 8.60 (2H, d, *J* = 8.0 Hz, **H3** and **H3'**), 8.45 (2H, t, *J* = 8.0 Hz, **H4** and **H4'**), 8.31 (2H, d, *J* = 6.0 Hz, **H6** and **H6'**), 7.81 (2H, t, *J* = 6.5 Hz, **H5** and **H5'**)

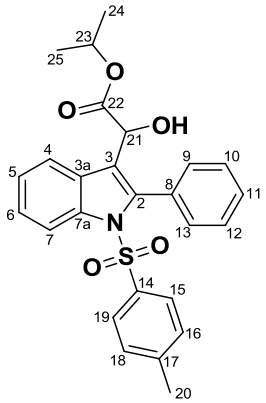
^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C 156.3 (**C2** and **C2'**), 148.8 (**C6** and **C6'**), 142.6 (**C4** and **C4'**), 127.6 (**C5** and **C5'**), 124.3 (**C3** and **C3'**), 120.7 (q, *J* = 323 Hz, **C7** and **C7'**)

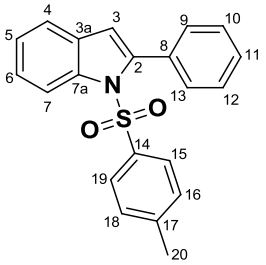
^{19}F NMR (377 MHz, $(CD_3)_2SO$) δ_F –77.8

These data are in accordance with the literature. [119]

(±)-Isopropyl 2-hydroxy-2-(2-phenyl-1-tosyl-1H-indol-3-yl)acetate (321) and

2-Phenyl-1-tosyl-1H-indole (314)





To a solution of di-*iso*propyltartrate (2.23 g, 9.50 mmol, 3.3 equiv) in H_2O (15 mL) at 0 °C was added sodium periodate (2.16 g, 10.1 mmol, 3.5 equiv) in two portions. The reaction mixture was stirred at 0 °C for 2.5 h, extracted four times with EtOAc, dried over $MgSO_4$ and concentrated under reduced pressure. The residue with re-dissolved in dioxane (22 mL) and transferred to a clean, dry flask. Aniline **317** (1.00 g, 2.88 mmol, 1.0 equiv) and $[(bpy)Pd^{2+}(H2O)_2].(^{-}OTf)_2$ **235** (35 mg, 0.058 mmol, 0.02 equiv) were added at rt and then the reaction mixture was stirred at 60 °C for 16 h before being concentrated under reduced pressure. Purification by silica gel chromatography gave 3-hydroxymethyl indole **321** (1.28 g, 96 % yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.38 (1H, d, *J* = 8.5 Hz, **H7**), 7.58 (1H, d, *J* = 8.0 Hz, **H4**), 7.53 – 7.45 (5H, m, **H9**, **H10**, **H11**, **H12** and **H13**), 7.42 – 7.38 (1H, m, **H6**), 7.33 (2H, d, *J* = 8.5 Hz, **H15** and **H19**), 7.30 – 7.26 (1H, m, **H5**), 7.09 (2H, d, *J* = 8.5 Hz, **H16** and **H18**), 5.03 – 4.94 (2H, m, **H21** and **H23**), 3.45 (1H, d, *J* = 3/5 Hz, **OH**), 2.31 (3H, s, **H20**), 1.18 (3H, d, *J* = 6.5 Hz, **H24** or **H25**), 0.80 (3H, d, *J* = 6.5 Hz, **H24** or **H25**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 173.1 (**C22**), 144.8 (**C17**), 139.7 (**C2**), 137.2 (**C7a**), 135.4 (**C14**), 131.9 (**Ph-C**), 131.6 (**Ph-C**), 130.0 (**C8**), 129.4 (**C16** and **C18**), 129.3 (**C11**), 127.8 (**C3a**), 127.5 (br., **Ph-C**), 126.8 (**C15** and **C19**), 125.2 (**C6**), 124.2 (**C5**), 120.1 (**C3**), 120.0 (**C4**), 116.0 (**C7**), 70.3 (**C23**), 66.3 (**C21**), 21.5 (**C20**), 21.3 (**C24** or **C25**).

Hindered rotation has caused chemical in-equivalence of the *o*- and *m*- phenyl carbons (**C9**, **C10**, **C12** and **C13**) giving three signals at 131.9, 131.6 and 127.5 (broad) ppm. One signal (**C24** or **C25**) is not observed, but is assumed to be overlapping with the signal at 21.5 ppm from the HSQC experiment.

ν_{max} (thin film)/cm^{-1}3502 (**O-H**), 1730 (**C=O**), 1374, 1177 (**O=S=O**)

ES-MS calcd for $C_{26}H_{25}NO_5S$ $[M+H]^+$ 464.1532; found 464.1546

If the dioxane is in-efficiently dried prior to use, indole **314** is formed as a competing product.

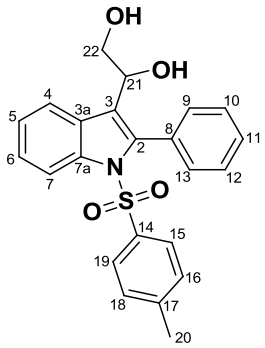
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.37 (1H, d, *J* = 8.5 Hz, **H7**), 7.57 – 7.54 (2H, m, **H9** and **H13**), 7.49 – 7.45 (4H, m, **H4**, **H6**, **H10** and **H12**), 7.40 (1H, t, *J* = 8.0 Hz, **H5**), 7.33 – 7.31 (3H, m, **H11**, **H15** and **H19**), 7.06 (2H, d, *J* = 8.0 Hz, **H16** and **H18**), 6.58 (1H, s, **H3**), 2.31 (3H, s, **H20**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6 (**C17**), 142.2 (**C8**), 138.3 (**C7a**), 134.6 (**C15**), 132.5 (**C2**), 130.6 (**C3a**), 130.4 (**C9** and **C13**), 129.3 (**C16** and **C18**), 128.7 (**C4** or **C6**), 127.6 (**C10** and **C12**), 126.8 (**C15** and **C19**), 124.9 (**C5**), 124.4 (**C11**), 120.8 (**C4** or **C6**), 116.7 (**C7**), 113.7 (**C3**), 21.6 (**C20**)

ν_{max} (thin film)/cm^{-1} 1370, 1171 (**O=S=O**)

ES-MS calcd for $C_{21}H_{17}NO_2S$ $[M+H]^+$ 348.1058; found 348.1061

(±)-1-(2-Phenyl-1-tosyl-1H-indol-3-yl)ethane-1,2-diol (322)



To a solution of alcohol **321** (1.21 g, 2.61 mmol, 1.0 equiv) in THF (12 mL) at 0 °C was added lithium aluminium hydride (208 mg, 5.48 mmol, 2.1 equiv) in three portions. The reaction mixture was stirred at rt for 6 h and then quenched by addition of EtOAc (15 mL). After stirring for 10 min, saturated $KNaC_4H_4O_{6\ (aq)}$ was added and the resulting biphasic mixture stirred overnight. The phases were separated and the aqueous phase was re-extracted with EtOAc. The combined organic layers were washed with saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave diol **322** (848 mg, 80 % yield) as a white solid.

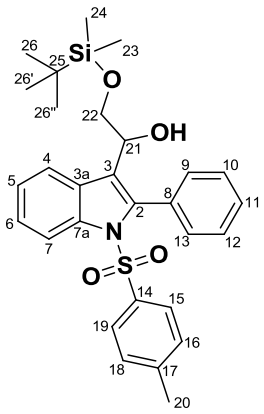
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.36 (1H, d, *J* = 8.5 Hz, **H7**), 7.84 (1H, d, *J* = 8.0 Hz, **H4**), 7.49 – 7.38 (4H, m, **H6**, **H10**, **H11** and **H12**), 7.35 – 7.20 (5H, m, **H5**, **H9**, **H13**, **H15** and **H19**), 7.10 (2H, d, *J* = 8.5 Hz, **H16** and **H18**), 4.66 – 4.44 (1H, m, **H21**), {3.95 – 3.90 (1H, m), 3.56 – 3.50 (1H, m)} (**H22**), 2.47 (1H, br. s, **OH**), 2.34 (3H, s, **H20**), 2.08 (1H. br. s, **OH**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8 (**C17**), 137.7 (**C2**), 137.2 (**C7a**), 135.4 (**C14**), 131.4 (**C9** and **C13**), 130.4 (**C8**), 129.4 (**C16** and **C18**), 129.2 (**C11**), 128.3 (**C3a**), 127.7 (**C10** and **C12**), 126.9 (**C15** and **C19**), 125.1 (**C6**), 123.9 (**C5**), 121.23 (**C4**), 121.15 (**C3**), 115.8 (**C7**), 69.1 (**C21**), 65.9 (**C22**), 21.6 (**C20**)

ν_{max} (thin film)/cm^{-1} 3068 (**O-H**), 1374, 1176 (**O=S=O**)

ES-MS calcd for $C_{23}H_{21}NO_4S$ $[M+Na]^+$ 430.1089; found 430.1111

(±)-2-(*Tert*-butyldimethylsilyloxy)-1-(2-phenyl-1-tosyl-1H-indol-3-yl)ethanol (323)



To a solution of diol **322** (847 mg, 2.08 mmol, 1.0 equiv) in DCM (12 mL) at rt was added triethylamine (350 µL, 2.50 mmol, 1.2 equiv) and DMAP (13 mg, 0.104 mmol, 0.05 equiv). The solution was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (330 mg, 2.18 mmo, 1.05 equiv) was added. The reaction mixture was stirred at rt for 21 h, diluted with DCM, washed with saturated $NH_4Cl_{(aq)}$ and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % Et_2O in petroleum ether) gave protected alcohol **323** (976 mg, 90 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.38 (1H, d, *J* = 8.5 Hz, **H7**), 7.91 (1H, d, *J* = 8.0 Hz, **H4**), 7.52 – 7.37 (6H, m, **H6**, **H10**, **H11**, **H12**, **H15** and **H19**), 7.35 – 7.28 (3H, m, **H5**, **H9** and **H13**), 7.12 (2H, d, *J* = 8.0 Hz, **H16** and **H18**), 4.61 (1H, ddd, *J* = 9.5, 4.0, 1.5 Hz, **H21**), {3.88 (1H, t, *J* = 9.5 Hz), 3.55 (1H, dd, *J* = 9.5, 4.0 Hz)} (**H22**), 2.77 (1H, s, **OH**), 2.35 (3H, s, **H20**), 0.86 (9H, s, **H26**, **H26'** and **H26''**), 0.00 (3H, s, **H23** or **H24**), –0.04 (3H, s, **H23** or **H24**)

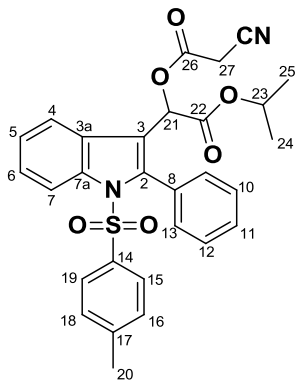
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7 (**C17**), 137.7 (**C2**), 137.2 (**C7a**), 135.7 (**C14**), {131.6, 131.3} (**C9** and **C13**), 130.6 (**C8**), 129.4 (**C16** and **C18**), 129.0 (**C11**), 128.6 (**C3a**), 127.6 (br., **C10** and **C12**), 126.9 (**C15** and **C19**), 124.9 (**C6**), 123.7 (**C5**), 121.5 (**C4**), 120.9 (**C3**), 115.6 (**C7**), 69.2 (**C21**), 66.4 (**C22**), 25.9 (**C26**, **C26'** and **C26''**), 21.6 (**C20**), 18.3 (**C25**),{–5.39, –5.43} (**C23** and **C24**)

Hindered rotation has caused chemical in-equivalence of the *o*- and *m*- phenyl carbons (**C9**, **C10**, **C12** and **C13**) giving three signals at 131.6, 131.3 and 127.6 (broad)

ν_{max} (thin film)/cm^{-1} 3405 (**O-H**), 1375, 1176 (**O=S=O**)

An accurate mass spectrum could not be generated for this compound by either ES or EI.

(±)-Isopropyl 2-(2-cyanoacetoxy)-2-(2-phenyl-1-tosyl-1H-indol-3-yl)acetate (324)



To a solution of alcohol **321** (1.28 g, 2.76 mmol, 1.0 equiv) in DCM at rt was added cyanoacetic acid (470 mg, 5.52 mmol, 2.0 equiv), triethylamine (577 µL, 4.14 mmol, 1.5 equiv) and propylphosphonic anhydride (50 % w/w in EtOAc, 2.28 mL, 3.59 mmol, 1.3 equiv). The reaction mixture was stirred at rt for 5 h and diluted with DCM. The solution was washed with saturated $NaHCO_{3\ (aq)}$, saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (4 % acetone in toluene) gave ester **324** (1.14 g, 78 % yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.39 (1H, d, *J* = 8.5 Hz, **H4**), 7.72 (1H, d, *J* = 8.0 Hz, **H7**), 7.57 – 7.34 (9H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12**, **H13**, **H15** and **H19**), 7.13 (2H, d, *J* = 8.0 Hz, **H16** and **H18**), 5.87 (1H, s, **H21**), 4.96 (1H, hept., *J* = 6.0 Hz, **H23**), {3.55 (1H, d, *J* = 19.0 Hz), 3.48 (1H, d, *J* = 19.0 Hz) (AB system, **H27**)}, 2.35 (3H, s, **H20**), 1.21 (3H, d, *J* = 6.0 Hz, **H24 or H25**), 0.95 (3H, d, *J* = 6.0 Hz, **H24 or H25**)

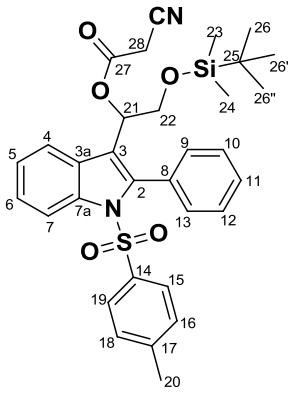
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.6 (**C22**), 162.1 (**C26**), 145.1 (**C17**), 140.7 (**C2**), 137.0 (**C7a**), 135.3 (**C14**), 131.9 (**Ph-C**), 131.4 (**Ph-C**), 129.8 (**C11**), 129.5 (**C16** and **C18**), 129.1 (**C8**), 127.7 (br., **Ph-C**), 127.4 (**C3a**), 126.9 (**C15** and **C19**), 125.5 (**C5** or **C6**), 124.5 (**C5** or **C6**), 120.4 (**C7**), 115.9 (**C4**), 114.9 (**C3**), 112.4 (**CN**), 70.4 (**C23**), 70.0 (**C21**), 24.5 (**C27**), 21.6 (**C24** or **C25**), 21.5 (**C20**), 21.3 (**C24** or **C25**)

Hindered rotation has caused chemical in-equivalence of the *o*- and *m*- phenyl carbons (**C9**, **C10**, **C12** and **C13**) giving three signals at 131.9, 131.4 and 127.7 (broad).

ν_{max} (thin film)/cm^{-1} 2264 (**C≡N**), 1745 (**C=O**)

ES-MS calcd for $C_{29}H_{26}N_2O_6S$ $[M+Na]^+$ 443.1409; found 553.1420

(±)-2-(*Tert*-butyldimethylsilyloxy)-1-(2-phenyl-1-tosyl-1H-indol-3-yl)ethyl 2-cyanoacetate (325)



To a solution of alcohol **323** (976 mg, 1.87 mmol, 1.0 equiv) in DCM (10 mL) at rt was added cyanoacetic acid (318 mg, 3.74 mmol, 2.0 equiv), triethylamine (390 µL, 2.80 mmol, 1.5 equiv) and propylphosphonic anhydride (50 % w/w in EtOAc, 1.55 mL, 2.43 mmol, 1.3 equiv). The reaction mixture was stirred at rt for 16 h and diluted with DCM. The solution was washed with saturated $NaHCO_{3\ (aq)}$, saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (4 % acetone in toluene) gave ester **325** (729 mg, 68 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.39 (1H, d, *J* = 8.5 Hz, **H7**), 7.78 (1H, d, *J* = 8.0 Hz, **H4**), 7.54 – 7.30 (9H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12**, **H13**, **H15** and **H19**), 7.14 (2H, d, *J* = 8.5 Hz, **H16** and **H18**), 5.78 (1H, dd, *J* = 8.5, 4.5 Hz, **H21**), {4.06 (1H, dd, *J* = 11.0, 8.5 Hz), 3.75 (1H, dd, *J* = 11.0, 4.5 Hz)} (**H22**), {3.42 (1H, d, *J* = 19.5 Hz), 3.36 (1H, d, *J* = 19.5 Hz)} (AB system, **H28**), 2.37 (3H, s, **H20**), 0.80 (9H, s, **H26**, **H26'** and **H26''**), {–0.07 (3H, s), –0.10 (3H, s)} (**H23** and **H24**)

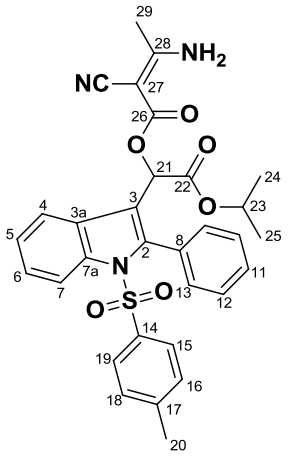
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.9 (**C27**), 145.0 (**C17**), 138.8 (**C2**), 136.9 (**C7a**), 135.6 (**C14**), 131.8 (**Ph-C**), 131.2 (**Ph-C**), 129.8 (**C8**), 129.6 (**C16** and **C18**), 129.4 (**C11**), 127.9 (**Ph-C**), 127.7 (**C3a**), 127.5 (**Ph-C**), 127.0 (**C15** and **C19**), 125.2 (**C5** or **C6**), 124.0 (**C5** or **C6**), 120.6 (**C4**), 117.1 (**C3**), 115.8 (**C7**), 112.8 (**CN**), 74.2 (**C21**), 64.2 (**C22**), 25.8 (**C26**, **C26'** and **C26''**), 24.6 (**C28**), 21.6 (**C20**), 18.3 (**C25**), {–5.52, –5.55} (**C23** and **C24**)

Hindered rotation has caused chemical in-equivalence of the *o*- and *m*- phenyl carbons (**C9**, **C10**, **C12** and **C13**) giving four signals at 131.8, 131.2, 127.9 and 127.5.

ν_{max} (thin film)/cm^{-1} 1753 (**C=O**), 1379, 1175 (**O=S=O**)

ES-MS calcd for $C_{32}H_{36}N_2O_5SSi$ $[M+H]^+$ 589.2192; found 589.2206

(*Z*)-2-(*Tert*-butyldimethylsilyloxy)-1-(2-phenyl-1-tosyl-1H-indol-3-yl)ethyl-3-amino-2-cyanobut-2-enoate (326)



To a microwave vial containing ester **324** (50 mg, 0.094 mmol, 1.0 equiv) and potassium acetate (1 mg, 0.009mmol, 0.1 equiv) was added BSA (230 µL, 0.942 mmol, 10 equiv). The resulting mixture was exposed to microwave irradiation at 80 °C for 35 min. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (50 % EtOAc in petroleum ether) gave β-enamino ester **326** (32 mg, 60 % yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.97 (1H, br. s, **NH**), 8.33 (1H, d, *J* = 8.0 Hz, **H7**), 7.90 (1H, d, *J* = 7.5 Hz, **H4**), 7.52 – 7.34 (9H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12**, **H13**, **H15** and **H19**), 7.11 (2H, d, *J* = 8.0 Hz, **H16** and **H18**), 5.83 – 5.82 (2H, m, **H21** and **NH**), 4.92 (1H, hept., *J* = 6.0 Hz, **H23**), 2.33 (3H, s, **H20**), 2.25 (3H, s, **H29**), {1.17 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.0 Hz)} (**H24** and **H25**)

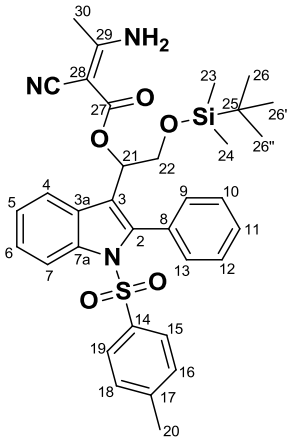
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.2 (**C28**), 167.7 (**C22**), 166.5 (**C26**), 144.8 (**C17**), 139.8 (**C2**), 137.0 (**C7a**), 135.3 (**C14**), 131.8 (**Ph-C**), 131.6 (**Ph-C**), 129.7 (**C8**), 129.5 (**C16** and **C18**), 129.4 (**C11**), 127.9 (**C3a**), 127.5 (**C15** and **C19**), 126.9 (br., **Ph-C**), 125.5 (**C5** or **C6**), 124.5 (**C5** or **C6**), 121.3 (**C4**), 117.5 (**CN**), 116.3 (**C3**), 115.6 (**C7**), 72.6 (**C27**), 69.7 (**C23**), 68.3 (**C21**), 22.1 (**C29**), 21.5 (**C20**), 21.3 (**C24** or **C25**)

Hindered rotation has caused chemical in-equivalence of the *o*- and *m*- phenyl carbons (**C9**, **C10**, **C12** and **C13**) giving three signals at 131.8, 131.6 and 126.9 (broad) ppm. One signal (**C24** or **C25**) is not observed, but is assumed to be overlapping with the signal at 21.5 ppm from the HSQC experiment.

ν_{max} (thin film)/cm^{-1} 3394, 3304 (**N-H**), 2208 (**C≡N**), 1749 (**C=O ester**), 1684, 1630 (**β-enamino ester**), 1375, 1177 (**O=S=O**)

ES-MS calcd for $C_{31}H_{29}N_3O_6S$ $[M+Na]^+$ 594.1675; found 594.1693

(*Z*)-2-Isopropoxy-2-oxo-1-(2-phenyl-1-tosyl-1H-indol-3-yl)ethyl 3-amino-2-cyanobut-2-enoate (327)



To a microwave vial containing ester **325** (50 mg, 0.087 mmol, 1.0 equiv) and potassium acetate (1 mg, 0.009mmol, 0.1 equiv) was added BSA (213 µL, 0.870 mmol, 10 equiv). The resulting mixture was exposed to microwave irradiation at 80 °C for 60 min. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (40 % EtOAc in petroleum ether) gave β-enamino ester **327** (13 mg, 56 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.02 (1H, br. s, **NH**), 8.34 – 8.31 (1H, m, **H7**), 7.98 – 7.96 (1H, m, **H4**), 7.54 – 7.35 (9H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12**, **H13**, **H15** and **H19**), 7.10 (2H, d, *J* = 8.5 Hz, **H16** and **H18**), 5.77 (1H, dd, *J* = 8.0, 5.0 Hz, **H21**), {4.02 (1H, dd, *J* = 11.0, 8.0 Hz), 3.78 (1H, dd, *J* = 11.0, 5.0 Hz)} (**H22**), 2.32 (3H, s, **H20**), 2.17 (3H, s, **H29**), 0.78 (9H, s, **H26**, **H26'** and **H26''**), {–0.07 (3H, s), –0.08 (3H, s)} (**H23** and **H24**)

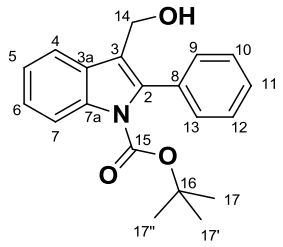
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.5 (**C29**), 166.5 (**C27**), 144.7 (**C17**), 138.3 (**C2**), 136.9 (**C7a**), 135.5 (**C14**), 131.8 (**Ph-C**), 131.5 (**Ph-C**), 130.3 (**C8**), 129.5 (**C16** and **C18**) 129.1 (**C11**), 128.3 (**C3a**), 127.5 (br., **Ph-C**), 126.9 (**C15** and **C19**), 125.0 (**C5** or **C6**), 124.2 (**C5** or **C6**), 121.5 (**C4**), 118.9 (**C3**), 118.2 (**CN**), 115.5 (**C7**), 73.0 (**C28**), 70.9 (**C21**), 64.6 (**C22**), 25.8 (**C26**, **C26'** and **C26''**), 22.0 (**C29**), 21.6 (**C20**), 18.3 (**C25**), {–5.5, –5.6} (**C23** and **C24**)

Hindered rotation has caused chemical in-equivalence of the *o*- and *m*- phenyl carbons (**C9**, **C10**, **C12** and **C13**) giving three signals at 131.8, 131.5 and 127.5 (broad) ppm.

ν_{max} (thin film)/cm^{-1} 3367 (**N-H**), 2209 (**C≡N**), 1681, 1627 (**β-enamino ester**), 1377, 1176 (**O=S=O**)

ES-MS calcd for $C_{34}H_{39}N_3O_5SSi$ $[M+H]^+$ 630.2458; found 630.2466

***Tert*-butyl 3-(hydroxymethyl)-2-phenyl-1H-indole-1-carboxylate (328)**[74]



To a solution of aldehyde **286** (1.50 g, 4.67 mmol, 1.0 equiv) in MeOH (20 mL) at 0 °C was added sodium borohydride (212 mg, 5.60 mmol, 1.2 equiv) in two portions. The reaction mixture was stirred at rt for 1 h, diluted with acetone and concentrated under reduced pressure. The residue was re-dissolved in DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatogrpahy gave alcohol **328** (1.45 g, 96 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.29 (1H, d, *J* = 8.0 Hz, **H7**), 7.77 (1H, d, *J* = 7.5 Hz, **H4**), 7.49 – 7.38 (6H, m, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 7.36 – 7.32 (1H, m, **H5**), 4.65 (2H, s, **H14**), 1.62 (1H, br.s, **OH**), 1.27 (9H, s, **H17**, **H17'** and **H17''**)

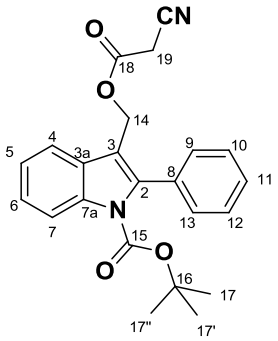
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.1 (**C15**), 137.8 (**C2**), 136.7 (**C7a**), 133.4 (**C8**), 129.7 (**C9** and **C13**), 128.7 (**C3a**), 128.0 (**C11**), 127.9 (**C10** and **C12**), 124.9 (**C6**), 123.1 (**C5**), 119.6 (**C3**), 119.1 (**C4**), 115.3 (**C7**), 83.4 (**C16**), 55.9 (**C14**), 27.5 (**C17**, **C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 3372 (**O-H**), 1728 (**C=O**)

ES-MS calcd for $C_{20}H_{21}NO_3$ $[M+H]^+$ 324.1600; found 324.1588

These data are in accordance with the literature.[74]

***Tert*-butyl 3-((2-cyanoacetoxy)methyl)-2-phenyl-1H-indole-1-carboxylate (183)**[74]



To a solution of alcohol **328** (1.45 g, 4.48 mmol, 1.0 equiv) in DCM (20 mL) at rt was added cyanoacetic acid (762 mg, 8.96 mmol, 2.0 equiv), triethylamine (936 µL, 6.72 mmol, 1.5 equiv) and propylphosphonic anhydride (50 % w/w in EtOAc, 4.28 mL, 6.72 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 36 h and diluted with DCM. The solution was washed with saturated $NaHCO_{3\ (aq)}$, saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave ester **183** (1.52 g, 87 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.30 (1H, d, *J* = 8.5 Hz, **H7**), 7.68 (1H, d, *J* = 7.5 Hz, **H4**), 7.51 – 7.39 (6H, m, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 7.37 – 7.33 (1H, m, **H5**), 5.24 (2H, s, **H14**), 3.43 (2H, s, **H19**), 1.26 (9H, s, **H17**, **H17'** and **H17''**)

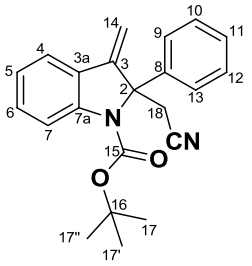
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.9 (**C18**), 149.8 (**C15**), 140.1 (**C2**), 136.5 (**C7a**), 132.7 (**C8**), 129.7 ((**C9** and **C13**) or (**C10** and **C12**)), 128.4 (**C11**), 128.2 (**C13a**), 128.1 ((**C9** and **C13**) or (**C10** and **C12**)), 125.1 (**C6**), 123.4 (**C5**), 118.8 (**C4**), 115.4 (**C7**), 113.7 (**C3**), 112.9 (**CN**), 83.8 (**C16**), 60.1 (**C14**), 27.5 (**C17**, **C17'** and **C17''**), 24.7 (**C19**)

ν_{max} (thin film)/cm^{-1} 1731 (**C=O**)

ES-MS calcd for $C_{23}H_{22}N_2O_4$ $[M+H]^+$ 391.1658; found 391.1667

These data are in accordance with the literature.[74]

(±)-*Tert*-butyl 2-(cyanomethyl)-3-methylene-2-phenylindoline-1-carboxylate (184)[74]



To a microwave vial containing ester **183** (620 mg, 1.59 mmol, 1.0 equiv) and potassium acetate (203 mg, 2.07 mmol, 1.3 equiv) was added BSA (932 µL, 3.81 mmol, 2.4 equiv). The resulting mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, diluted with EtOAc and brine, and the phases separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether with 1 % Et_3N) gave alkene **184** (202 mg, 37 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (1H, br. s, **H7**), 7.51 (1H, d, *J* = 7.5 Hz, **H4**), 7.42 – 7.30 (4H, m, **H6**, **H11** and (**H9** and **H13**) or (**H10** and **H12**)), 7.22 – 7.20 (2H, m, (**H9** and **H13**) or (**H10** and **H12**)), 7.12 (1H, t, *J* = 7.5 Hz, **H5**), {5.63 (1H, s), 4.84 (1H, s)} (**H14**), {3.72 (1H, br. s), 3.42 (1H, d, *J* = 16.0 Hz)} (**H18**), 1.23 (9H, br. s, **H17**, **H17'** and **H17''**)

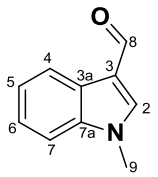
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.7 (**C16**), 149.7 (**C3**), 144.2 (**C3a** or **C7a**), 143.0 (**C3a** or **C7a**), 130.9 (**C6**), 128.8 ((**C9** and **C13**) or (**C10** and **C12**)), 127.8 (**C11**), 126.3 (**C8**), 124.2 ((**C9** and **C13**) or (**C10** and **C12**)), 123.5 (**C5**), 120.9 (**C4**), 116.3 (**CN**), 115.8 (**C7**), 104.5 (**C14**), 82.3 (**C16**), 70.7 (**C2**), 28.6 (**C18**), 27.9 (**C17**, **C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 2254 (**C≡N**), 1704 (**C=O**)

ES-MS calcd for $C_{22}H_{22}N_2O_2$ $[M+H]^+$ 347.1760; found 347.1754

These data are in accordance with the literature.[74]

1-Methyl-1H-indole-3-carbaldehyde (344)[120]



To a solution of indole-3-carboxaldehyde (1.00g, 6.89 mmol, 1.0 equiv) in DMF (10 mL) at 0 °C was added sodium hydride (60 % dispersion in mineral oil, 350 mg, 8.27 mmol, 1.2 equiv) . The reaction mixture was stirred at 0 °C for 10 min and was then warmed to rt. Methyl iodide (515 µL, 8.27 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred for a further 1 h at rt. The reaction was quenched by carful addition of H_2O, and was extracted three times with EtOAc. The combined organic layers were washed with 5 % LiCl $_{(aq)}$, saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (50 % EtOAc in petroleum ether) gave *N*-Me indole **344** (837 mg, 76 % yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.97 (1H, s, **H8**, 8.33 – 8.31 (1H, m, **H7**), 7.64 (1H, s, **H2**), 7.37 – 7.32 (3H, m, **H4**, **H5** and **H6**), 3.85 (3H, s, **H9**)

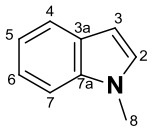
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 184.5 (**C8**), 139.4 (**C2**), 137.9 (**C7a**), 125.3 (**C3a**), 124.0 (**C5**), 122.9 (**C6**), 122.0 (**C7**), 118.0 (**C3**), 109.9 (**C4**), 33.7 (**C9**)

ν_{max} (thin film)/cm^{-1} 1652 (**C=O**)

ES-MS calcd for $C_{10}H_9NO$ $[M+H]^+$ 160.0762; found 160.0751

These data are in accordance with the literature.[120]

1-Methyl-1H-indole (347)[121]



To a solution of indole (1.50 g, 12.8 mmol, 1.0 equiv) in THF (35 mL) at 0 °C was added sodium hydride (60 % dispersion in mineral oil, 770 mg, 19.2 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 15 min and rt for 1 h. The reaction was re-cooled to 0 °C and methyl iodide (1.04 mL, 16.6 mmol, 1.3 equiv) was added dropwise. The reaction mixture was stirred at rt for 2 h and was then quenched by addition of saturated $NH_4Cl_{(aq)}$. The solution was extracted three times with Et_2O, and the combined organic layers were washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave *N*-Me indole **347** (1.47 g, 88 % yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (1H, d, *J* = 8.0 Hz, **H7**), 7.43 (1H, d, *J* = 8.5 Hz, **H4**), 7.37 – 7.33 (1H, m, **H5**), 7.26 – 7.22 (1H, m, **H6**), 7.14 (1H, d, *J* = 3.0 Hz, **H2**), 6.61 (1H, d, *J* = 3.0 Hz, **H3**), 3.86 (3H, s, **H8**)

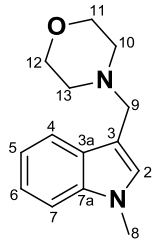
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.8 (**C7a**), 128.9 (**C2**), 128.6 (**C3a**), 121.6 (**C5**), 121.0 (**C7**), 119.4 (**C6**), 109.3 (**C4**), 101.0 (**C3**), 32.9 (**C8**)

ν_{max} (thin film)/cm^{-1} 3053 (**sp^2 C-H**); 2941 (**sp^3 C-H**)

EI-MS calcd for C_9H_9N $[M]^+$ 131.0735; found 131.0733

These data are in accordance with the literature.[121]

4-((1-Methyl-1H-indol-3-yl)methyl)morpholine (346)[122]



To a solution of indole **347** (1.46 g, 11.1 mmol, 1,0 equiv) in EtOH (25 mL) at rt was added morpholine (1.09 mL, 12.2 mmol, 1.1 equiv), formaldehyde (37 % in H_2O, 1.02 mL, 12.2 mmol, 1.1 equiv) and zinc (II) chloride (2.28 g, 16.7 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 2.5 h, diluted with H_2O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5 % MeOH in DCM) gave amine **346** (1.64 g, 64 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (1H, d, *J* = 8.0 Hz, **H7**), 7.37 (1H, d, *J* = 8.0 Hz, **H4**), 7.32 – 7.29 (1H, m, **H5**), 7.23 – 7.19 (1H, m, **H6**), 7.06 (1H, s, **H2**), 3.81 (3H, s, **H8**), 3.80 – 3.77 (6H, m, **H9**, **H11** and **H12**), 2.59 – 2.57 (4H, m, **H10** and **H13**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 137.1 (**C7a**), 128.5 (**C2**), 121.7 (**C5**), 119.7 (**C7**), 119.1 (**C6**), 110.7 (**C3**), 109.2 (**C4**), 67.2 (**C11** and **C12**), 54.0 (**C9**), 53.7 (**C10** and **C13**), 32.7 (**C8**)

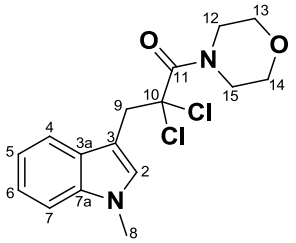
ν_{max} (thin film)/cm^{-1} 3051 (**sp^2 C-H**); 2953 (**sp^3 C-H**), 1113 (**C-O**)

ES-MS calcd for $C_{14}H_{18}N_2O$ $[M+H]^+$ 231.1497; found 231.1503

C3a is not seen and assumed to be overlapping with the C2 signal.

These data are in accordance with the literature.[122]

2,2-Dichloro-3-(1-methyl-1H-indol-3-yl)-1-morpholinopropan-1-one (348)



To a solution of indole **346** (46 mg, 0.200 mmol, 1.0 equiv) in DCM (2 mL) at –78 °C was added trimethylsilyl trifluoromethanesulfonate (36 µL, 0.200 mmol, 1.0 equiv) and triethylamine (42 µL, 0.300 mmol, 1.5 equiv). The reaction mixture was stirred at –78 °C for 5 min, then dichloroacetyl chloride (23 µL, 0.240 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for a further 5 min at –78 °C before being warmed to rt and quenched by addition of 1M NaOH (1 mL). The solution was extracted three times with Et_2O and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in toluene) gave amide **348** (16.6 mg, 24 % yield) as a colourless oil.

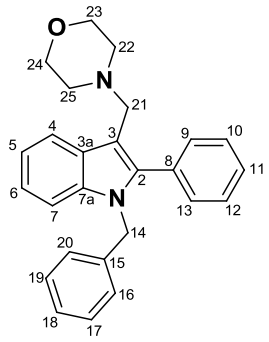
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (1H, d, *J* = 8.0 Hz, **H7**), 7.34 (1H, d, *J* = 8.0 Hz, **H4**), 7.27 – 7.23 (2H, m, **H2**, **H6**), 7.19 – 7.15 (1H, m, **H5**), 4.05 (2H, br. s, **H12/13/14/15**), 3.95 (2H, s, **H9**), 3.83 (3H, s, **H8**), 3.79 – 3.69 (6H, m, **H12/13/14/15**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 164.2 (**C11**), 136.4 (**C7a**), 130.7 (**C2**), 129.4 (**C3a**), 121.5 (**C6**), 119.6 (**C7**), 119.2 (**C5**), 109.2 (**C4**), 107.4 (**C3**), 84.5 (**C10**), 66.8 (**C12/13/14/15**), 66.3 (**C12/13/14/15**). 48.8 (**C12/13/14/15**), 44.3 (**C12/13/14/15**), 41.6 (**C9**), 32.9 (**C8**)

ν_{max} (thin film)/cm^{-1} 1652 (**C=O**)

ES-MS calcd for $C_{16}H_{18}Cl_2N_2O_2$ $[M+H]^+$ 341.0824; found 341.0823

4-((1-Benzyl-2-phenyl-1H-indol-3-yl)methyl)morpholine (353)



To a solution of indole **298** (500 mg, 1.76 mmol, 1.0 equiv) in EtOH (3.5 mL) and toluene (2 mL) was added morpholine (170 µL, 1.94 mmol, 1.1 equiv), formaldehyde (37 % in H_2O, 160 µL, 1.1 equiv) and zinc (II) chloride (360 mg, 2.64 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 28 h, diluted with H_2O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (4 % MeOH in DCM) gave amine **353** (414 mg, 61 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$ δ_H 8.02 – 7.98 (1H, m, **H7**), 7.52 – 7.46 (5H, m, **H9**, **H10**, **H11**, **H12** and **H13**), 7.34 – 7.24 (6H, m, **H4**, **H5**, **H6**, **H17**, **H18** and **H19**), 7.04 – 7.02 (2H, m, **H16** and **H20**), 5.32 (2H, s, **H14**), 3.76 (4H, t, *J* = 4.5 Hz, **H23** and **H24**), 3.72 (2H, s, **H21**), 2.52 (4H, br. s, **H22** and **H25**)

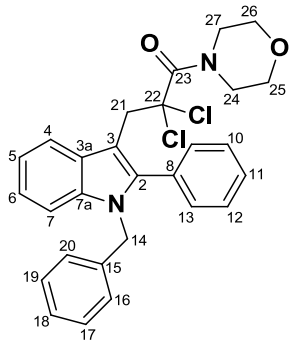
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 140.2 (**C2**), 138.3 (**C15**), 136.9 (**C7a**), 131.7 (**C8**), 130.9 (**C9** and **C13**), 128.8 (**C3a**), 128.7 (**C17** and **C19**), 128.4 (**C10** and **C12**), 127.2 (**C18**), 126.1 (**C16** and **C20**), 122.1 (**C4** or **C5** or **C6**) , 120.2 (**C7**), 119.9 (**C4** or **C5** or **C6**), 110.3 (**C4** or **C5** or **C6**), 110.0 (**C3**), 67.4 (**C23** and **C24**), {53.53, 53.47} (**C21**, **C22** and **C25**), 47.7 (**C14**)

ν_{max} (thin film)/cm^{-1}3058 (**sp^2 C-H**), 2956 (**sp^3 C-H**) 1114 (**C-O**)

ES-MS calcd for $C_{26}H_{26}N_2O$ $[M+H]^+$ 383.2123; found 383.2118

C11 is not observed, and is assumed to be overlapping with another peak in the region 128 – 130 ppm

3-(1-Benzyl-2-phenyl-1H-indol-3-yl)-2,2-dichloro-1-morpholinopropan-1-one (354)



To a solution of indole **353** (77mg, 0.201 mmol, 1.0 equiv) in DCM (2 mL) at rt was added trimethylsilyl trifluoromethanesulfonate (36 µL, 0.201 mmol, 1.0 equiv) and *N,N*-diisopropylethylamine (53 µL, 0.302 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 5 min, then dichloroacetyl chloride (23 µL, 0.242 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for a further 5 min at rt before being quenched by addition of 1M NaOH (1 mL). The solution was extracted three times with Et_2O and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave amide **354** (26 mg, 26 % yield) as a colourless oil.

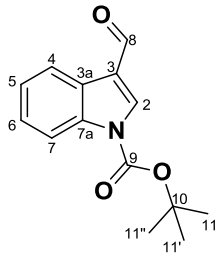
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 – 7.88 (1H, m), 7.42 – 7.34 (5H, m, H9m **H10**, **H11**, **H12** and **H13**), 7.28 – 7.19 (6H, m, **H4**, **H5**, **H6**, **H17**, **H18** and **H19**), 6.96 – 6.94 (2H, m, **H16** and **H20**), 5.28 (2H, s, **H14**), 4.04 (2H, s, **H21**), {3.94 (br. s) and 3.72 (br. s)} (8H, **H24**, **H25**, **H26** and **H27**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 164.6 (**C23**), 141.9 (**C2**), 138.1 (**C15**), 136.5 (**C7a**), 132.4 (**C8**), 131.2 (**C9** and **C13**), 129.2 (**C3a**), 128.6 (**C17** and **C19**), 128.5 (**C10** and **C12**), 128.3 (**C11**), 127.1 (**C18**), 126.1 (**C16** and **C20**), 121.9 (**C4** or **C5** or **C6**), 120.9 (**C7**), 119.8 (**C4** or **C5** or **C6**), 110.3 (**C4** or **C5** or **C6**), 106.1 (**C3**), 85.7 (**C22**), 66.7 (**C24** or **C25** or **C26** or **C27**), 66.2 (**C24** or **C25** or **C26** or **C27**), 48.7 (**C24** or **C25** or **C26** or **C27**), 47.6 (**C14**), 44.3 (**C24** or **C25** or **C26** or **C27**), 40.2 (**C21**)

ν_{max} (thin film)/cm^{-1} 1651 (**C=O**)

ES-MS calcd for $C_{28}H_{26}Cl_2N_2O_2$ $[M+H]^+$ 493.1450; found 493.1440

***Tert*-butyl 3-formyl-1H-indole-1-carboxylate (355)**[74]



To a solution of 3-formyl indole (1.00 g, 6.88 mmol, 1.0 equiv) in DCM (20 mL) at rt was added DMAP (84 mg, 0.688 mmol, 0.1 equiv), triethylamine (1.44 mL, 10.3 mmol, 1.5 equiv) and di-*tert*-butyl dicarboante (2.26 g, 10.3 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 1 h and was diluted with DCM, washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether) gave *N*-Boc indole **355** (1.51 g, 89 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.11 (1H, s, **H8**), 8.30 (1H, d, *J* = 7.5 Hz, **H7**), 8.24 (1H, s, **H2**), 8.16 (1H, d, *J* = 8.0 Hz, **H4**), 7.45 – 7.37 (2H, m, **H5** and **H6**), 1.73 (9H, s, **H11**, **H11'** and **H11''**)

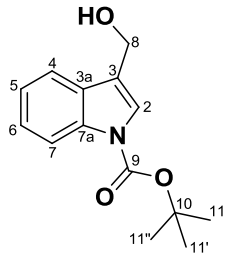
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 185.8 (**C8**), 148.8 (**C9**), 136.5 (**C2**), 136.0 (**C7a**), 126.14 (**C3a**), 126.09 (**C6**), 124.6 (**C5**), 122.1 (**C7**), 121.6 (**C3**), 115.2 (**C4**), 85.7 (**C10**), 28.1 (**C11, C11'** and **C11''**)

ν_{max} (thin film)/cm^{-1} 1741 (**C=O carbamate**), 1677 (**C=O aldehyde**)

ES-MS calcd for $C_{14}H_{15}NO_3$ $[M+MeCN+H]^+$ 287.1396; found 287.1390

These data are in accordance with the literature.[74]

***Tert*-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (357)**[74]



To a solution of aldehyde **355** (800 mg, 3.26 mmol, 1.0 equiv) in MeOH (10 mL) at 0 °C was added sodium borohydride (185 mg, 4.89 mmol, 1.5 equiv) in three portions. The reaction mixture was stirred at rt for 1 h, The reaction mixture was stirred at rt for 1 h, diluted with acetone and concentrated under reduced pressure. The residue was re-dissolved in DCM, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (25 % EtOAc in petroleum ether) gave alcohol **357** 790 mg, 98 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (1H, d, *J* = 8.0 Hz, **H7**), 7.66 (1H, d, *J* = 8.0 Hz, **H4**), 7.59 (1H, s, **H2**), 7.36 (1H, t, *J* = 8.0 Hz, **H6**), 7.28 (1H, t, *J* = 8.0 Hz, **H5**), 4.85 (2H, s, **H8**), 1.69 (9H, s, **H11**, **H11'** and **H11''**)

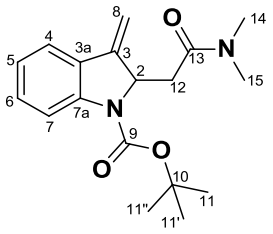
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.7 (**C9**), 135.8 (**C7a**), 129.2 (**C3a**), 124.7 (**C5**), 123.7 (**C2**), 122.7 (**C6**), 120.5 (**C3**), 119.3 (**C4**), 115.3 (**C7**), 83.8 (**C10**), 57.2 (**C8**), 28.2 (**C11**, **C11'** and **C11''**)

ν_{max} (thin film)/cm^{-1}3349 (**O-H**), 1732 (**C=O**)

A mass ion could not be generated for this compound by either CI or ES

These data are in accordance with the literature.[74]

(±)-*Tert*-butyl 2-(2-(dimethylamino)-2-oxoethyl)-3-methyleneindoline-1-carboxylate (359)



To a microwave vial containing a solution of alcohol **357** (50 mg, 0.202 mmol, 1.0 equiv) in toluene (1 mL) was added *N,N*-dimethylacetamide dimethyl acetal (177 µL, 1.21 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 5 min, cooled to rt and concentrated. Purification by silica gel chromatography (40 % EtOAc in petroleum ether) gave amide **359** (41 mg, 64 % yield) as a colourless oil.

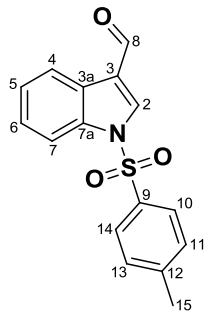
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (1H, br. s, **H7**), 7.43 (1H, d, *J* = 7.5 Hz, **H4**), 7.26 (1H, t, *J* = 8.0 Hz, **H6**), 7.00 (1H, t, *J* = 7.5 Hz, **H5**), 5.47 (1H, d, *J* = 2.5 Hz, **H8A**), 5.38 – 5.33 (1H, m, **H2**), 5.18 (1H, d, *J* = 2.5 Hz, **H8B**), 3.08 – 2.94 (7H, m, **H12A**, **H14** and **H15**), 2.64 (1H, dd, *J* = 15.0, 9.0 Hz, **H12B**), 1.58 (9H, s, **H11**, **H11'** and **H11''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.7 (**C13**), 151.5 (**C9**), 145.4 (**C3**), 143.5 (**C7a**), 129.8 (**C6**), 128.4 (**C3a**), 122.7 (**C5**), 120.6 (**C4**), 115.8 (**C7**), 103.4 (**C8**), 81.6 (**C10**), 60.9 (**C2**), 39.5 (**C12**), 37.5 (**C14** or **C15**), 35.4 (**C14** or **C15**), 28.5 (**C11**, **C11'** and **C11''**)

ν_{max} (thin film)/cm^{-1} 1698 (**C=O carbamate**), 1640 (**C=O amide**)

ES-MS calcd for $C_{18}H_{24}N_2O_3$ $[M+H]^+$ 317.1865; found 317.1872

1-Tosyl-1H-indole-3-carbaldehyde (361)[123]



To a solution of 3-formyl indole (2.00 g, 13.8 mmol, 1.0 equiv) in DCM (60 mL) at rt was added *p*-toluenesulfonyl chloride (3.14 g, 16.5 mmol, 1.2 equiv), triethylamine (2.88 mL, 20.6 mmol, 1.5 equiv) and DMAP (168 mg, 1.38 mmol, 0.1 equiv). The reaction mixture was stirred at rt for 1 h and then acidified with 1 M HCl. The solution was extracted three times with DCM and the combined organics washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave *N*-Ts indole **361** (3.40 g, 82 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.11 (1H, s, **H8**), 8.28 – 8.26 (2H, m, **H2** and **H7**), 7.91 (1H, d, *J* = 8.0 Hz, **H4**), 7.87 (2H, d *J* = 8.5 Hz, **H10** and **H14**), 7.45 - 7.35 (2H, m, **H5** and **H6**), 7.30 (2H, d, *J* = 8.5 Hz, **H11** and **H13**), 2.37 (3H, s, **H15**)

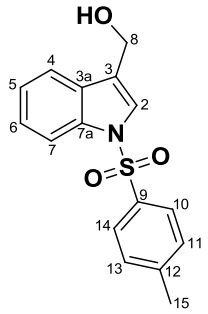
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 185.4 (**C8**), 146.2 (**C12**), 136.3 (**C2**), 135.2 (**C7a**), 134.4 (**C9**), 130.3 (**C11** and **C13**), 127.2 (**C10** and **C14**), 126.3 (**C5**), 125.1 (**C6**), 122.6 (**C7**), 122.4 (**C3**), 113.3 (**C4**), 21.7 (**C15**)

ν_{max} (thin film)/cm^{-1} 1672 (**C=O**), 1376, 1174 (**O=S=O**)

ES-MS calcd for $C_{16}H_{13}NO_3S$ $[M+H]^+$ 300.0694; found 300.0692

These data are in accordance with the literature.[123]

(1-Tosyl-1H-indol-3-yl)methanol (362)[124]



To a solution of aldehyde **361** (3.39 g, 11.3 mmol, 1.0 equiv) in MeOH (22 mL) at 0 °C was added sodium borohydride (641 mg, 17.0 mmol, 1.5 equiv) in three portions. The reaction mixture was stirred at rt for 1 h and quenched by careful addition of H_2O. The resulting solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Alcohol **362** (3.32 g, 98 % yield) was isolated as a white solid of analytical purity.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.00 (1H, d, *J* = 8.0 Hz, **H7**), 7.75 (2H, d, *J* = 8.0 Hz, **H10** and **H14**), 7.54 – 7.53 (2H, m, **H2** and **H4**), 7.34 (1H, td, *J* = 8.0, 1.0 Hz, **H6**), 7.22 (1H, td, *J* = 8.0, 1.0 Hz, **H5**), 7.12 (2H, d, *J* = 8.0 Hz, **H11** and **H13**), 4.72 (2H, s, **H8**), 2.72 (1H, br. s, **OH**), 2.25 (3H, s, **H15**)

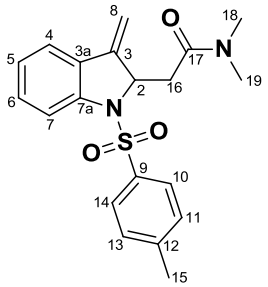
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1 (**C12**), 135.4 (**C7a**), 135.1 (**C9**), 129.9 (**C11** and **C13**), 129.5 (**C3a**), 126.8 (**C10** and **C14**), 125.0 (**C6**), 123.8 (**C2**), 123.4 (**C5**), 122.6 (**C3**), 120.0 (**C4**), 113.7 (**C7**), 56.9 (**C8**), 21.5 (**C15**)

ν_{max} (thin film)/cm^{-1} 3371 (**O-H**), 1362, 1169 (**O=S=O**)

ES-MS calcd for $C_{16}H_{15}NO_3S$ $[M+MeCN+Na]^+$ 365.0936; found 365.0928

These data are in accordance with the literature.[124]

(±)-*N,N*-Dimethyl-2-(3-methylene-1-tosylindolin-2-yl)acetamide (363)



To a microwave vial containing a solution of alcohol **362** (1.00 g, 3.32 mmol, 1.0 equiv) in toluene (16.5 mL) was added *N,N*-dimethylacetamide dimethyl acetal (2.47 mL, 19.9 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 5 min, cooled to rt and concentrated. Purification by silica gel chromatography (50 % EtOAc in petroleum ether) gave amide **363** (1.09 g, 89 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (1H, d, *J* = 8.0 Hz, **H7**), 7.61 (2H, d, *J* = 8.5 Hz, **H10** and **H14**), 7.32 – 7.27 (2H, m, **H4** and **H6**), 7.16 (2H, d, *J* = 8.5 Hz, **H11** and **H13**), 7.08 – 7.04 (1H, m, **H5**), 5.34 (1H, d, *J* = 2.5 Hz, **H8A**), 5.22 – 5.18 (1H, m, **H2**), 5.15 (1H, d, *J* = 2.5 Hz, **H8B**), 3.25 (1H, dd, *J* = 16.0, 3.5 Hz, **H16A**), 3.01 (3H, s, **H18** or **H19**), 3.00 (3H, s, **H18** or **H19**), 2.78 (1H, dd, *J* = 16.0, 9.0 Hz, **H16B**), 2.32 (3H, s, **H15**)

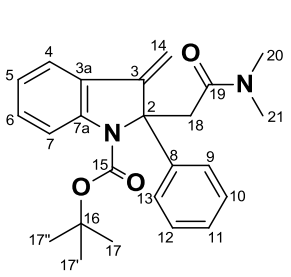
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.7 (**C17**), 145.2 (**C3**), 144.2 (**C7a**), 143.2 (**C12**), 133.8 (**C9**), 130.0 (**C4** or **C6**), 129.7 (**C11** and **C13**), 129.6 (**C3a**), 127.4 (**C10** and **C14**), 124.5 (**C5**), 121.0 (**C4** or **C6**), 116.6 (**C7**), 104.5 (**C8**), 62.9 (**C2**), 42.0 (**C16**), 37.3 (**C18** or **C19**), 35.5 (**C18** or **C19**), 21.5 (**C15**)

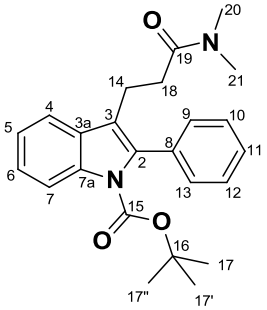
ν_{max} (thin film)/cm^{-1} 1637 (**C=O**), 1353, 1166 (**O=S=O**)

ES-MS calcd for $C_{20}H_{22}N_2O_3S$ $[M+H]^+$ 371.1429; found 371.1440

(±)-*Tert*-butyl 3-(3-(dimethylamino)-3-oxopropyl)-2-phenyl-1H-indole-1-carboxylate(364) and

***Tert*-butyl 2-(2-(dimethylamino)-2-oxoethyl)-3-methylene-2-phenylindoline-1-carboxylate (365)**





To a microwave vial containing a solution of alcohol **328** (53 mg, 0.164 mmol, 1.0 equiv) in toluene (0.8 mL) was added *N,N*-dimethylacetamide dimethyl acetal (144 μL, 0.984 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 45 min, cooled to rt and concentrated. Purification by silica gel chromatography (75 % Et_2O in DCM) gave alkene **364** (25 mg, 39 % yield) and indole **365** (7 mg, 11 % yield).

Alkene 364:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H {8.13 (br. s) and 7.72 (br. s)} (1H, **H7**), 7.47 (1H, d, *J* = 7.5 Hz, **H4**), 7.43 – 7.26 (6H, m, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 7.04 (1H, t, *J* = 7.5 Hz, **H5**), {7.47 (1H, d, *J* = 1.0 Hz), 4.68 (1H, br. s)} (**H14**), {4.33 (br.s) and 3.88 (br. s)} (1H, **H18A**), 3.38 (1H, d, *J* = 14.5 Hz, **H18B**), 3.07 (3H, s, **H20** or **H21**), 2.77 (3H, s, **H20** or **H21**), {1.53 (br. s) and 1.18 (br. s)} (9H, **H17**, **H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 168.7 (**C19**) 151.8 (**C7a**), 151.3 (**C15**), 146.4 (**C8**), 145.4 (**C3**), 130.1 (**C6**), 128.5 (**C10** and **C12**), 127.0 (**C9** and **C13**), 124.4 (**C11**), 124.0 (**C3a**), 122.8 (**C5**), 120.3 (**C4**), 115.5 (**C7**), 102.5 (**C14**), 81.1 (**C6**), 71.9 (**C2**), 40.7 (**C18**), 37.9 (**C20** or **C21**), 35.6 (**C20** or **C21**), 28.0 (**C17**, **C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 1698 (**C=O carbamate**), 1642 (**C=O amide**)

ES-MS calcd for $C_{24}H_{28}N_2O_3$ $[M+H]^+$ 393.2178; found 393.2183

Indole 365:

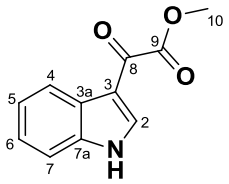
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (1H, d, *J* = 8.5 Hz, **H7**), 7.60 (1H, d, *J* = 7.5 Hz, **H4**), 7.46 – 7.30 (7H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 2.95 – 2.90 (5H, m, **H14** and (**H20** or **H21**)), 2.78 (3H, s, **H20** or **H21**), 2.51 – 2.46 (2H, m, **H18**), 1.24 (9H, s, **H17**, **H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.2 (**C19**), 150.2 (**C15**), 136.5 (**C7a**), 136.0 (**C2**), 134.3 (**C8**), 129.7 (**C19** and **C13**), 129.2 (**C3a**), 128.0 (**C10** and **C12**), 127.7 (**C11**), 124.6 (**C5** or **C6**), 122.7 (**C5** or **C6**), 119.7 (**C3**), 118.8 (**C4**), 115.4 (**C7**), 82.9 (**C16**), 37.0 (**C20** or **C21**), 35.4 (**C20** or **C21**), 33.8 (**C18**), 27.5 (**C17**, **C17'** and **C17''**), 20.0 (**C14**)

ν_{max} (thin film)/cm^{-1} 1726 (**C=O carbamate**), 1645 (**C=O amide**)

ES-MS calcd for $C_{24}H_{28}N_2O_3$ $[M+H]^+$ 393.2178; found 393.2183

Methyl 2-(1H-indol-3-yl)-2-oxoacetate (366)



To a solution of indole (500 mg, 4.26 mmol, 1.0 equiv) in THF (14 mL) at 0 °C was added oxalyl chloride (540 µL, 6.39 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 15 min and at rt for 1 h. MeOH (1.04 mL, 25.6 mmol, 6.0 equiv) was added at rt. A slight exotherm was observed and a precipitate formed. The reaction mixture was stirred at rt for 15 min and the reaction was filtered. The filtrand was washed with petroleum ether to give α-keto ester **366** (671 mg, 78 % yield) as a pinky-yellow solid of analytical purity.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 12.43 (1H, br. s, **NH**), 8.48 (1H, d, *J* = 3.5 Hz, **H2**), 8.20 – 8.18 (1H, m, **H7**), 7.58 – 7.56 (1H, m, **H4**), 7.33 – 7.26 (2H, m, **H5** and **H6**), 3.90 (3H, s, **H10**)

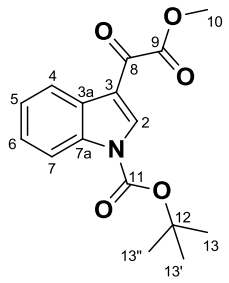
^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C 179.2 (**C8**), 164.5 (**C9**), 138.9 (**C2**), 137.2 (**C7a**), 126.0 (**C3a**), 124.3 (**C5** or **C6**), 123.3 (**C5** or **C6**), 121.6 (**C7**), 113.2, (**C4**), 112.9 (**C3**), 53.0 (**C10**)

ν_{max} (thin film)/cm^{-1} 3214 (**NH**), 1728 (**C=O ester**), 1616 (**C=O ketone**)

ES-MS calcd for $C_{11}H_9NO_3$ $[M+H]^+$ 204.0661; found 204.0659

These data are in accordance with the literature.[125]

***Tert*-butyl 3-(2-methoxy-2-oxoacetyl)-1H-indole-1-carboxylate (367)**[125]



To a solution of indole **366** (400 mg, 1.97 mmol, 1.0 equiv) in DMF (16 mL) at rt was added sodium hydride (60 % dispersion in mineral oil, 118 mg, 2.96 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 1 h and then di-*tert*-butyl dicarbonate (860 mg, 3.94 mmol, 2.0 equiv) was added. The reaction mixture was stirred for a further 2 h at rt, diluted with H_2O and extracted three times with Et_2O. The combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % Et_2O in petroleum ether) gave *N*-Boc indole **367** (419 mg, 70 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.83 (1H, s, **H2**), 8.43 – 8.41 (1H, m, **H7**), 8.20 – 8.18 (1H, m, **H4**), 7.46 – 7.39 (2H, m, **H5** and **H6**), 4.00 (3H, s, **H10**), 1.74 (9H, s, **H13**, **H13'** and **H13''**)

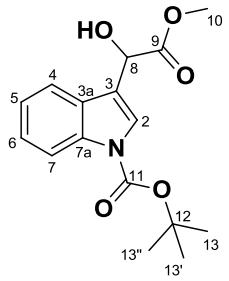
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.7 (**C8**), 162.4 (**C9**), 148.7 (**C11**), 137.2 (**C2**), 135.4 (**C7a**), 127.5 (**C3a**), 126.1 (**C5** or **C6**), 124.9 (**C5** or **C6**), 122.6 (**C7**), 116.2 (**C4**), 115.1 (**C3**), 86.0 (**C12**), 53.0 (**C10**), 28.1 (**C13**, **C13'** and **C13''**)

ν_{max} (thin film)/cm^{-1} 1745 (**C=O ester** and **carbamate**), 1666 (**C=O ketone**)

ES-MS cald for $C_{16}H_{17}NO_5$ $[M+H]^+$ 304.1185; found 304.1196

These data are in accordance with the literature.[125]

(±)-*Tert*-butyl 3-(1-hydroxy-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (368)



To a solution of ketone **367** (138 mg, 0.455 mmol, 1.0 equiv) in THF (4.5 mL) at 0 °C was added sodium borohydride (21 mg, 0.546 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 30 min and quenched by addition of water. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in petroleum ether) gave alcohol **368** (136 mg, 98 % yield) as a colourless oil.

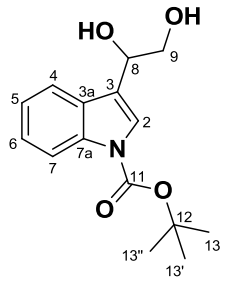
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.18 (1H, d, *J* = 8.5 Hz, **H7**), 7.69 – 7.65 (2H, m, **H2** and **H4**), 7.38 – 7.34 (1H, m, **H6**), 7.29 – 7.25 (1H, m, **H5**), 5.45 (1H, d, *J* = 5.0 Hz, **H8**), 3.80 (3H, s, **H10**), 3.46 (1H, d, *J* = 5.0 Hz, **OH**), 1.69 (9H, s, **H13**, **H13'** and **H13''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 173.8 (**C9**), 149.5 (**C11**), 135.8 (**C7a**), 128.0 (**C3a**), 124.8 (**C6**), 124.6 (**C2**), 122.9 (**C5**), 119.7 (**C4**), 118.0 (**C3**), 115.4 (**C7**), 84.0 (**C12**), 66.9 (**C8**), 53.1 (**C10**), 28.2 (**C13**, **C13'** and **C13''**)

ν_{max} (thin film)/cm^{-1} 3473 (**O-H**), 1730 (**C=O ester** and **carbamate**)

ES-MS calcd for $C_{16}H_{19}NO_5$ $[M+MeCN+Na]^+$ 369.1426; found 369.1421

(±)-*Tert*-butyl 3-(1,2-dihydroxyethyl)-1H-indole-1-carboxylate (369)



To a solution of ketone **367** (162 mg, 0.534 mmol, 1.0 equiv) in MeOH (5.5 mL) at 0 °C was added sodium borohydride (61 mg, 1.60 mmol, 3.0 equiv) in two portions. The reaction mixture was stirred at 0 °C for 10 min and at rt for 1.5 h. The reaction was quenched by careful addition of H_2O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (50 % EtOAc in petroleum ether) gave diol **369** (140 mg, 95 % yield) as a colourless oil.

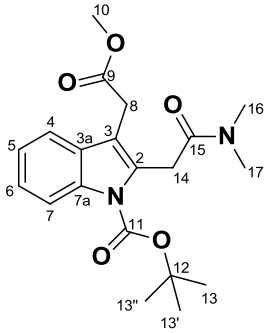
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.15 (1H, d, *J* = 8.5 Hz, **H7**), 7.62 – 7.60 (2H, m, **H2** and **H4**), 7.36 – 7.32 (1H, m, **H6**), 7.26 – 7.22 (1H, m, **H5**), 5.12 – 5.10 (1H, m, **H8**), 3.96 – 3.86 (2H, m, **H9**), 3.20 (1H, br. s, **OH**), 2.83 (1H, br. s, **OH**), 1.67 (9H, s, **H13**, **H13'** and **H13''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.7 (**C11**), 135.7 (**C7a**), 128.5 (**C3a**), 124.7 (**C6**), 123.2 (**C2**), 122.7 (**C5**), 120.2 (**C3**), 119.5 (**C4**), 115.4 (**C7**), 84.0 (**C12**), 68.7 (**C8**), 66.6 (**C9**), 28.2 (**C13**, **C13'** and **C13''**)

ν_{max} (thin film)/cm^{-1} 3376 (**O-H**), 1731 (**C=O**)

ES-MS cald for $C_{15}H_{19}NO_4$ [M-OH]$^+$ 260.1287; found 260.1280

***Tert*-butyl 2-(2-(dimethylamino)-2-oxoethyl)-3-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (371)**



To a microwave vial containing a solution of indole **368** (79 mg, 0.259 mmol, 1.0 equiv) in toluene (1.3 mL) was added *N,N*-dimethylacetamide dimethyl acetal (227 µL, 1.55 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 7 min, cooled to rt and concentrated. Purification by silica gel chromatography (65 % EtOAc in petroleum ether) gave amide **371** (21 mg, 22 % yield) as a colourless oil.

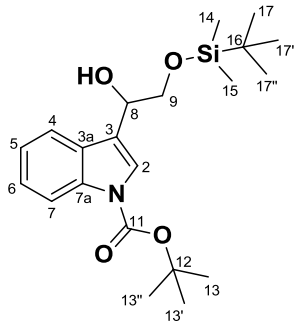
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.07 (1H, d, *J* = 7.5 Hz, **H7**), 7.54 – 7.51 (1H, m, **H4**), 7.30 – 7.22 (2H, m, **H5** and **H6**), 4.15 (2H, s, **H14**), 3.71 (2H, s, **H8**), 3.67 (3H, s, **H10**), 3.18 (3H, s, **H16** or **H17**), 3.00 (3H, s, **H16** or **H17**), 1.65 (9H, s, **H13**, **H13'** and **H13''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.6 (**C9**), 169.3 (**C15**), 150.5 (**C11**), 135.8 (**C7a**), 132.6 (**C2**), 129.3 (**C3a**), 124.0 (**C5** or **C6**), 122.5 (**C5** or **C6**), 118.2 (**C4**), 115.7 (**C7**), 113.4 (**C3**), 83.7 (**C12**), 52.1 (**C10**), 37.4 (**C16** or **C17**), 35.6 (**C16** or **C17**), 32.2 (**C14**), 30.2 (**C8**), 28.1 (**C13**, **C13'** and **C13''**)

ν_{max} (thin film)/cm^{-1} 1727 (**C=O ester** and **carbamate**), 1653 (**C=O amide**)

ES-MS calcd for $C_{20}H_{26}N_2O_5$ $[M+H]^+$ 375.1920; found 375.1935

(±)-*Tert*-butyl 3-(2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl)-1H-indole-1-carboxylate (372)



To a solution of diol **369** (160 mg, 0.577 mmol, 1.0 equiv) in DCM (5 mL) at rt was added triethylamine (97 µL, 0.692 mmol, 1.2 equiv) and DMAP (4 mg, 0.029 mmol, 0.05 equiv). The reaction was cooled to 0 °C and tert-butyldimethylsilyl chloride (91 mg, 0.606 mmol, 1.05 equiv) was added. The reaction mixture was stirred at rt for 72 h, diluted with DCM, washed with saturated $NH_4Cl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether) gave TBS-protected alcohol **372** (142 mg, 63 % yield) as a colourless oil.

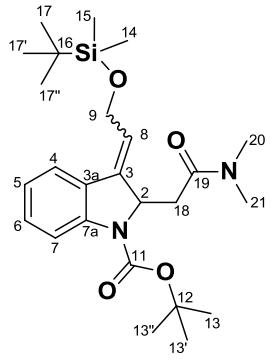
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.20 (1H, d, *J* = 8.5 Hz, **H7**), 7.67 – 7.64 (2H, m, **H2** and **H4**), 7.37 – 7.33 (1H, m, **H6**), 7.29 – 7.25 (1H, m, **H5**), 5.07 (1H, dt, *J* = 10.0, 3.0 Hz, **H8**), {3.97 (1H, dd, *J* = 10.0, 3.5 Hz), 3.81 (1H, dd, *J* = 10.0, 3.5 Hz)} (**H9**), 2.98 (1H, d, *J* = 3.0 Hz, **OH**), 1.69 (9H, s, **H13**, **H13'** and **H13''**), 0.97 (9H, s, **H17**, **H17'** and **H17''**), {0.14 (3H, s), 0.13 (3H, s)} (**H14** and **H15**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.7 (**C11**), 135.7 (**C7a**), 128.8 (**C3a**), 124.5 (**C6**), 123.2 (**C2**), 122.6 (**C5**), 119.8 (**C3**), 119.5 (**C4**), 115.4 (**C7**), 83.7 (**C12**), 68.5 (**C8**), 67.5 (**C9**), 28.2 (**C13**, **C13'** and **C13''**), 25.9 (**C17**, **C17'** and **C17''**), 18.4 (**C16**), {–5.27, –5.32} (**C14** and **C15**)

ν_{max} (thin film)/cm^{-1} 3457 (**O-H**), 1733 (**C=O**)

ES-MS calcd for $C_{21}H_{33}NO_4Si$ $[M\text{-}OH]^+$ 374.2151; found 374.2151

(*E*)-and (*Z*)-*Tert*-butyl 3-(2-(*tert*-butyldimethylsilyloxy)ethylidene)-2-(2-(dimethylamino)-2-oxoethyl)indoline-1-carboxylate (373)



To a microwave vial containing a solution of indole **372** (105 mg, 0.268 mmol, 1.0 equiv) in toluene (1.35 mL) was added *N,N*-dimethylacetamide dimethyl acetal (235 µL, 1.608 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 5 min, cooled to rt and concentrated. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alkene **373** (81 mg, 67 % yield) as a colourless oil in a 2.3 : 1 ratio of *E*:*Z* isomers (determined by comparing the integrals of signals at δ_H = 6.00 and 5.82 ppm).

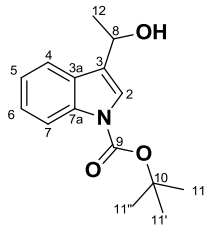
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (1H, br s, **H7**), 7.42 (1H, d, *J* = 7.5 Hz, **H4 minor**), 7.33 (1H, d, *J* = 7.5 Hz, **H4 major**), 7.27 – 7.21 (1H, m, **H6**), 7.04 – 6.97 (1H, m, **H5**), 6.02 – 5.98 (1H, m, **H8 minor**), 5.83 – 5.80 (1H, m, **H8 major**), 5.46 – 5.44 (1H, m, **H2 minor**), 5.30 – 5.27 (1H, m, **H2 major**) 4.58 – 4.52 (2H, m, **H9 major**), 4.38 – 4.30 (2H, m, **H9 minor**), 3.02 – 2.88 (7H, m, **H20**, **H21** and **H18A**), 2.69 – 2.61 (1H, m, **H18B**), 1.57 (9H, s, **H13**, **H13'** and **H13''**), 0.93 (9H, s, **H17, H17'** and **H17'' minor**), 0.92 (9H, s, **H17, H17'** and **H17'' major**) 0.12 (3H, s, **H14** or **H15 minor**), 0.11 (3H, s, **H14** or **H15 minor**), 0.10 (3H, s, **H14** or **H15 major**), 0.09 (3H, s, **H14** or **H15 major**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.6 (**C19 major**), 169.3 (**C19 minor**), 151.3 (**C11**), 144.4 (**C7a**), 136.8 (**C3**), 129.4 (**C6 minor**), 129.3 (**C6 major**), 127.6 (**C7a**), 125.2 (**C4 major**), 124.5 (**C8 major**), 122.8 (**C5 minor**), 122.7 (**C5 minor**), 120.3 (**C4 minor**), 119.6 (**C8 minor**), 115.74 (**C7 minor**), 115.66 (**C7 major**), 81.5 (**C12**), 61.5 (**C2 major**), 60.5 (**C9 minor**), 60.3 (**C9 major**), 59.3 (**C2 minor**), 39.6 (**C18**), 37.7 (**C20** or **C21 minor**), 37.5 (**C20** or **C21 major**), 35.5 (**C20** or **C21 minor**), 35.4 (**C20** or **C21 major**), 28.4 (**C13**, **C13'** and **C13''**), 26.0 (**C17, C17'** and **C17'' minor**), 25.9 (**C17, C17'** and **C17'' major**), 18.4 (**C16 minor**), 18.3 (**C16 major**), -5.1 (**C14** or **C15**), -5.2 (**C14** or **C15**)

ν_{max} (thin film)/cm^{-1} 1705 (**C=O carbamate**), 1646 (**C=O amide**)

ES-MS calcd for $C_{25}H_{40}N_2O_4Si$ $[M+H]^+$ 461.2836; found 461.2837

(±)-*Tert*-butyl 3-(1-hydroxyethyl)-1H-indole-1-carboxylate (374)[74]



To a solution of aldehyde **355** (200 mg, 0.815 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added methylmagnesium chloride (3.0 M in Et_2O, 540 µL, 1.63 mmol, 2.0 equiv) dropwise. The reaction mixture was stirred at 0 °C for 1 h before being diluted with saturated $NaCl_{(aq)}$ and EtOAc. The phases were seperated and the organic layer dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alcohol **374** (204 mg, 96 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (1H, br. d, *J* = 8.0 Hz, **H7**), 7.70 (1H, d, *J* = 8.0 Hz, **H4**), 7.56 (1H, s, **H2**), 7.35 (1H, td, *J* = 8.0, 1.0 Hz, **H6**), 7.27 (1H, td, *J* = 8.0, 1.0 Hz, **H5**), 5.18 (1H, q, *J* = 6.0 Hz, **H8**), 2.09 (1H, br. s, **OH**), 1.69 (9H, s, **H11**, **H11'** and **H11''**), 1.67 (3H, d, *J* = 6.0 Hz, **H12**)

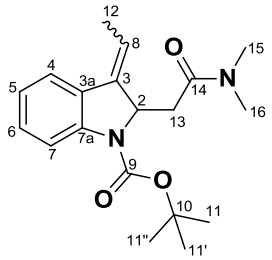
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.8 (**C9**), 135.9 (**C7a**), 128.6 (**C3a**), 125.3 (**C3**), 124.5 (**C6**), 122.6 (**C5**), 121.8 (**C2**), 119.8 (**C4**), 115.4 (**C7**), 83.7 (**C10**), 63.9 (**C8**), 28.2 (**C11, C11'** and **C11''**), 23.5 (**C12**)

ν_{max} (thin film)/cm^{-1} 3406 (**O-H**), 1730 (**C=O**)

ES-MS calcd for $C_{15}H_{19}NO_3$ $[M+MeCN+Na]^+$ 325.1528; found 325.1524

These data are in accordance with the literature.[74]

(*E*)-and (*Z*)-*Tert*-butyl 2-(2-(dimethylamino)-2-oxoethyl)-3-ethylideneindoline-1-carboxylate (375)



To a microwave vial containing a solution of indole **374** (49 mg, 0.187 mmol, 1.0 equiv) in toluene (0.95 mL) was added *N,N*-dimethylacetamide dimethyl acetal (164 µL, 1.12 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 5 min, cooled to rt and concentrated. Purification by silica gel chromatography (50 % EtOAc in petroleum ether) gave alkene **375** (47 mg, 76 % yield) as a colourless oil in a 5.2 : 1 ratio of *E*:*Z* isomers (determined by comparing the integrals of signals at δ_H = 5.98 and 5.79 ppm).

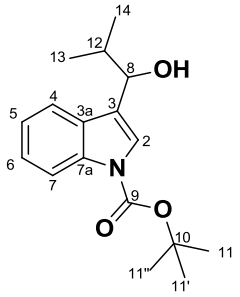
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (1H, br s, **H7**), 7.56 (1H, d, **H4**), 7.25 – 7.19 (1H, m, **H6**), 7.01 – 6.98 (1H, m, **H5**), 6.02 – 5.96 (1H, m, **H8 minor**), 5.82 – 5.76 (1H, m, **H8 major**), 5.47 – 5.44 (1H, m, **H2 minor**), 5.27 – 5.24 (**H2 major**), 3.04 – 2.89 (7H, m, **H13A**, **H15** and **H16**), 2.63 – 2.57 (1H, m, **H13B**), 2.00 (3H, d, *J* = 7.5 Hz, **H12 major**), 1.86 (3H, d, *J* = 7.5 Hz, **H12 minor**), 1.57 (9H, s, **H11**, **H11'** and **H11''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.9 (**C14 major**), 169.7 (**C14 minor**), 151.4 (**C9**), 144.2 (**C7a**), 137.0 (**C3**), 128.6 (**C6**), 124.8 (**C4**), 122.8 (**C3a**), 122.5 (**C5**), 118.8 (**C8 major**), 115.8 (**C8 minor**), 115.6 (**C7**), 81.4 (**C10**), 61.7 (**C2 major**), 59.4 (**C2 minor**), 29.2 (**C13**), 37.8 (**C15** or **C16 minor**), 37.5 (**C15** or **C16 major**), 35.5 (**C15** or **C16 minor**), 35.4 (**C15** or **C16 major**), 28.4 (**C11**, **C11'** and **C11''**), 14.6 (**C12 minor**), 14.4 (**C12 major**)

ν_{max} (thin film)/cm^{-1} 1702 (**C=O carbamate**), 1646 (**C=O amide**)

ES-MS calcd for $C_{19}H_{26}N_2O_3$ $[M+H]^+$ 331.2022; found 331.2022

(±)-*Tert*-butyl 3-(1-hydroxy-2-methylpropyl)-1H-indole-1-carboxylate (376)



To a solution of aldehyde **355** (212 mg, 0.864 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added isopropylmagnesium chloride (2.0 M in THF, 865 µL, 1.73 mmol, 2.0 equiv) dropwise. The reaction mixture was stirred at 0 °C for 1 h before being diluted with saturated $NaCl_{(aq)}$ and EtOAc. The phases were seperated and the organic layer dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether) gave alcohol **376** (199 mg, 80 % yield) as a colourless oil.

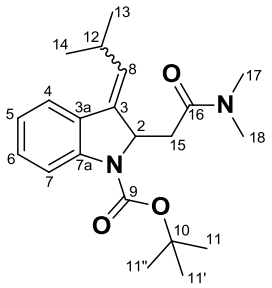
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (1H, d, *J* = 8.5 Hz, **H7**), 7.69 (1H, d, *J* = 8.0 Hz, **H4**), 7.55 (1H, s, **H2**), 7.36 – 7.32 (1H, m, **H6**), 7.27 – 7.23 (1H, m, **H5**), 4.68 (1H, dd, *J* = 7.0, 2.5 Hz, **H8**), 2.25 (1H, octet, *J* = 7.0 Hz, **H12**), 1.87 (1H, br. s, **OH**), 1.70 (9H, s, **H11**, **H11'** and **H11''**), 1.09 (3H, d, *J* = 7.0 Hz, **H13** or **H14**), 0.94 (3H, d, *J* = 7.0 Hz, **H13** or **H14**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.8 (**C9**), 135.8 (**C7a**), 128.9 (**C3a**), 124.5 (**C6**), 123.3 (**C3**), 123.1 (**C2**), 122.5 (**C5**), 120.1 (**C4**), 115.4 (**C7**), 83.7 (**C10**), 73.8 (**C8**), 34.0 (**C12**), 28.2 (**C11**, **C11'** and **C11''**), {19.5, 18.3} (**C13** and **C14**)

ν_{max} (thin film)/cm^{-1} 3449 (**O-H**), 1732 (**C=O**)

CI-MS calcd for $C_{17}H_{23}NO_3$ $[M\text{-}OH]^+$ 272.1651; found 272.1662

(*E*)-and (*Z*)-*Tert*-butyl 2-(2-(dimethylamino)-2-oxoethyl)-3-(2-methylpropylidene)indoline-1-carboxylate (376)



To a microwave vial containing a solution of indole **375** (87 mg, 0.301 mmol, 1.0 equiv) in toluene (1.5 mL) was added *N,N*-dimethylacetamide dimethyl acetal (263 µL, 1.80 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 5 min, cooled to rt and concentrated. Purification by silica gel chromatography (40 % EtOAc in petroleum ether) gave alkene **376** (47 mg, 76 % yield) as a colourless oil in a 4.1 : 1 ratio of *E*:*Z* isomers (determined by comparing the integrals of signals at δ_H = 7.51 and 7.36 ppm).

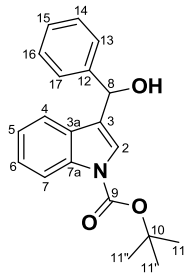
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87 (1H, br. s, **H7**), 7.51 (1H, d, *J* = 8.0 Hz, **H4 major**), 7.36 (1H, d, *J* = 8.0 Hz, **H4 minor**), 7.23 – 7.16 (1H, m, **H6**), 7.01 – 6.95 (1H, m, **H5**), 5.70 – 5.67 (m, **H8 minor**), 5.46 – 5.44 (m, **H8 major** and **H2 minor**), 5.20 – 5.17 (m, **H2 major**), 3.08 – 2.82 (8H, m, **H12**, **H15A**, **H17** and **H18**), 2.61 – 2.55 (1H, m, **H15B**), 1.56 (9H, s, **H11**, **H11'** and **H13''**), 1.11 – 1.04 (6H, m, **H13** and **H14**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.8 (**C16 major**), 169.6 (**C16 minor**), 151.6 (**C9 minor**), 151.3 (**C9 major**), 144.2 (**C7a**), 133.7 (**C3**), 132.4 (**C8 major**), 128.8 (**C6 major**), 128.6 (**C6 minor**), 128.3 (**C8 minor**), 127.8 (**C3a**), 124.5 (**C4 major**), 122.8 (**C5 minor**), 122.6 (**C5 major**), 119.8 (**C4 minor**), 115.8 (**C7**), 81.3 (**C10**), 62.0 (**C2 major**), 59.3 (**C2 minor**), 39.5 (**C15**), 37.82 (**C17** or **C18 major**), 37.76 (**C17** or **C18 minor**), 35.5 (**C17** or **C18 minor**), 35.4 (**C17** or **C18 minor**), 28.4 (**C11**, **C11'** and **C11''**), 27.2 (**C12**), 23.3 (**C13** or **C14 minor**), 23.0 (**C13** or **C14 minor**), 22.8 (**C13** or **C14 major**), 22.7 (**C13** or **C14 major**)

ν_{max} (thin film)/cm^{-1} 1703 (**C=O carbamate**), 1641 (**C=O amide**)

ES-MS calcd for $C_{21}H_{30}N_2O_3$ $[M+H]^+$ 359.2335; found 359.2330

(±)-*Tert*-butyl 3-(hydroxy(phenyl)methyl)-1H-indole-1-carboxylate (378)



To a solution of aldehyde **355** (210 mg, 0.856 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added phenylmagnesium bromide (3.0 M in Et_2O, 570 µL, 1.71 mmol, 2.0 equiv) dropwise. The reaction mixture was stirred at 0 °C for 1 h before being diluted with saturated $NaCl_{(aq)}$ and EtOAc. The phases were seperated and the organic layer dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alcohol **378** (252 mg, 91 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (1H, br. d, *J* = 8.0 Hz, **H7**), 7.54 – 7.46 (4H, m, **H2**, **H4**, **H13** and **H17**), 7.41 – 7.31 (4H, m, **H6**, **H14**, **H15** and **H16**), 7.19 (1H, t, *J* = 8.0 Hz, **H5**), 6.08 (1H, d, *J* = 2.5 Hz, **H8**), 2.45 (1H, br. s, **OH**), 1.70 (9H, s, **H11**, **H11'** and **H11''**)

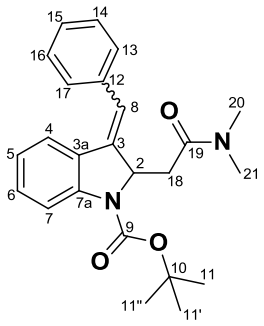
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.8 (**C9**), 142.5 (**C12**), 136.0 (**C7a**), 128.6 (**C14** and **C16**), 127.9 (**C15**), 126.7 (**C13** and **C17**), 124.6 (**C6**), 123.7 (**C3**), 123.6 (**C2**), 122.6 (**C5**), 120.1 (**C4**), 115.3 (**C7**), 83.8 (**C10**), 70.4 (**C8**), 28.2 (**C11**, **C11'** and **C11''**)

C3a is not observed and is assumed to be overlapping with the signal at 128.6 ppm from the HMBC experiment.

ν_{max} (thin film)/cm^{-1} 3423 (**O-H**), 1731 (**C=O**)

ES-MS calcd for $C_{20}H_{21}NO_3$ $[M\text{-}OH]^+$ 306.1494; found 306.1497

(*E*)-and (*Z*)--*Tert*-butyl 3-benzylidene-2-(2-(dimethylamino)-2-oxoethyl)indoline-1-carboxylate (379)



To a microwave vial containing a solution of indole **378** (71 mg, 0.220 mmol, 1.0 equiv) in toluene (1 mL) was added *N,N*-dimethylacetamide dimethyl acetal (193 µL, 1.32 mmol, 6.0 equiv). The reaction was exposed to microwave irradiation at 150 °C for 5 min, cooled to rt and concentrated. Purification by silica gel chromatography (30 % EtOAc in petroleum ether) gave alkene **379** (40 mg, 46 % yield) as a colourless oil in a 1.3 : 1 ratio of *E*:*Z* isomers (determined by comparing the integrals of signals at δ_H = 7.06 and 6.75 ppm).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (1H, br. s, **H7**), 7.61 – 7.56 (1H, m, **H4**), 7.45 – 7.18 (6H, m, **H6**, **H13**, **H14**, **H15**, **H16** and **H17**), 7.06 (1H, t, *J* = 7.5 Hz, **H5 minor**), 6.89 (1H, s, **H8 minor**), 6.75 (1H, t, *J* = 7.5 Hz, **H5 major**), 6.71 (1H, s, **H8 major**), 5.94 – 5.92 (1H, m, **H2 minor**), 5.44 – 5.43 (**H2 major**), 3.04 – 2.74 (8H, m, **H8**, **H20** and **H21**), 1.61 (9H, s, **H11**, **H11'** and **H11''**)

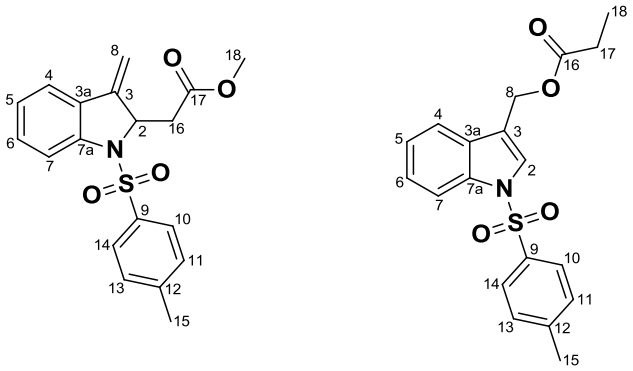
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.8 (**C19 major**), 169.5 (**C19 minor**), 151.7 (**C9 minor**), 151.3 (**C9 major**), 142.7 (**C7a**), 138.3 (**C3 minor**), 138.1 (**C3 major**), 137.2 (**C12**), 136.1 (**C3a major**), 130.4 (**C3a minor**), 129.7 (**C6 minor**), 129.6 (**C6 major**), 128.8 (**C13** and **C17 major**), 128.7 (**C4 major**), 128.5 (**C14** and **C16 minor**), 128.4 (**C14** and **C16 major**), 127.3 (**C13** and **C17 minor**), 124.1 (**C15**), 123.0 (**C5 minor**), 122.6 (**C8 major**), 122.2 (**C5 major**), 119.8 (**C4 minor**), 118.7 (**C8 minor**), 116.2 (**C7 minor**), 115.8 (**C7 major**), 81.9 (**C10 major**), 81.6 (**C10 minor**), 62.1 (**C2 major**), 60.2 (**C2 minor**), 40.0 (**C18**), 37.7 (**C20** or **C21**) 35.6 (**C20** or **C21 major**), 35.4 (**C20** or **C21 minor**), 28.5 (**C11**, **C11'** and **C11''**)

ν_{max} (thin film)/cm^{-1} 1702 (**C=O carbamate**), 1642 (**C=O amide**)

ES-MS calcd for $C_{24}H_{28}N_2O_3$ $[M+H]^+$ 393.2178; found 393.2190

(±)-Methyl 2-(3-methylene-1-tosylindolin-2-yl)acetate (386) and

(1-Tosyl-1H-indol-3-yl)methyl propionate (387)



Method 1

To a microwave vial containing a solution of indole **362** (100 mg, 0.332 mmol, 1.0 equiv) in toluene (1.6 mL) was added trimethylorthoacetate (253 µL, 1.99 mmol, 6.0 equiv) and propionic acid (1 drop). The reaction was exposed to microwave irradiation at 150 °C for 30 min, cooled to rt and concentrated. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave alkene **386** (12 mg, 10 % yield) as a colourless oil, indole **387** (14 mg, 12 % yield) as a colourless oil and recovered starting material **362** (52 mg, 52 % yield).

Method 2

To a microwave vial containing a solution of indole **271** (1.81 g, 6.00 mmol, 1.0 equiv) in toluene (15 mL) was added trimethylorthoacetate (4.57 mL, 36.0 mmol, 6.0 equiv) and 4-nitrophenol (83 mg, 0.600 mmol, 0.1 equiv). The reaction was exposed to microwave irradiation at 200 °C for 3.5 h, cooled to rt and concentrated. Purification by silica gel chromatography (DCM) gave alkene **386** (285 mg, 13% yield) as a colourless oil.

Alkene 386

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (1H, d, *J* = 8.0 Hz, **H7**), 7.61 (2H, d, *J* = 8.0 Hz, **H10** and **H14**), 7.35 – 7.30 (2H, m, **H4** and **H6**), 7.20 (2H, d, *J* = 8.0 Hz, **H11** and **H13**), 7.11 – 7.07 (1H, m, **H5**), 5.38 (1H, d, *J* = 2.5 Hz, **H8A**), 5.01 – 4.96 (2H, m, **H2** and **H8B**), 3.75 (3H, s, **H18**), {3.22 (1H, dd, *J* = 16.0, 4.0 Hz), 2.84 (1H, dd, *J* = 16.0, 8.0 Hz)} (**H16**), 2.37 (3H, s, **H15**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.9 (**C17**), 144.8 (**C3**), 144.3 (**C12**), 143.3 (**C7a**), 133.8 (**C9**), 130.2 (**C6**), 129.7 (**C11** and **C13**), 129.3 (**C3a**), 127.3 (**C10** and **C14**), 124.6 (**C5**), 121.0 (**C4**), 116.7 (**C7**), 103.8 (**C8**), 62.4 (**C2**), 51.8 (**C18**), 42.6 (**C16**), 21.6 (**C15**)

v_{max} (thin film)/cm^{-1} 1735 (**C=O**), 1356, 1169 (**O=S=O**)

ES-MS calcd for $C_{19}H_{19}NO_4S$ $[M+H]^+$ 358.1113; found 358.1127

Indole 387

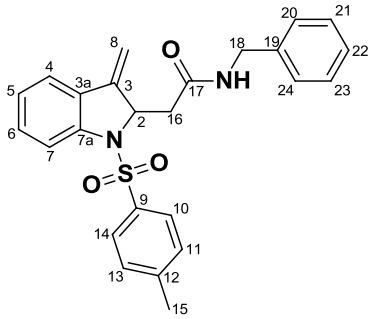
^1H NMR (400 MHz, $CDCl_3$) δ_H 8.01 (1H, d, *J* = 8.0 Hz, **H7**), 7.81 (2H, d, *J* = 8.5 Hz, **H10** and **H14**), 7.65 (1H, s, **H2**), 7.59 (1H, d, *J* = 8.0 Hz, **H4**), 7.39 – 7.35 (1H, m, **H6**), 7.31 – 7.25 (3H, m, **H5**, **H11** and **H13**), 5.27 (2H, s, **H8**), 2.41 – 2.33 (5H, m, **H15** and **H17**), 1.17 (3H, t, *J* = 7.5 Hz, **H18**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.3 (**C16**) 145.1 (**C12**), 135.18 (**C7a** or **C9**), 135.16 (**C7a** or **C9**), 130.0 (**C11** and **C13**) , 129.5 (**C3a**), 126.9 (**C10** and **C14**), 125.6 (**C2**), 125.1 (**C6**), 123.4 (**C5**), 119.8 (**C4**), 117.5 (**C3**), 113.7 (**C7**), 57.7 (**C8**), 27.5 (**C17**), 21.6 (**C15**), 9.1 (**C18**)

v_{max} (thin film)/cm^{-1} 1734 (**C=O**), 1371, 1171 (**O=S=O**)

ES-MS calcd for $C_{19}H_{19}NO_4S$ $[M+H]^+$ 358.1113; found 358.1120

(±)-*N*-Benzyl-2-(3-methylene-1-tosylindolin-2-yl)acetamide (388)



To a solution of benzylamine (86 µL, 0.791 mmol, 1.1 equiv) in DCM (2.5 mL) at rt was added trimethylaluminium (2.0 M in hexane, 395 µL, 0.791 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at rt for 15 min then a solution of ester **386** (257 mg, 0.719 mmol, 1.0 equiv) in DCM (2.5 mL) was added dropwise. The reaction mixture was stirred at rt for a further 48 h and was carefully quenched by addition of 2M HCl. The solution was extracted with DCM, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (35 % EtOAc in petroleum ether) gave amide **388** (188 mg, 55 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (1H, d, *J* = 8.0 Hz, **H7**), 7.59 (2H, d, *J* = 8.5 Hz, **H10** and **H14**), 7.33 – 7.22 (7H, m, **H4**, **H6**, **H20**, **H21**, **H22**, **H23** and **H24**), 7.18 (2H, d, *J* = 8.5 Hz, **H11** and **H13**), 7.10 – 7.06 (1H, m, **H5**), 6.10 (1H, br. t, *J* = 6.0 Hz, **NH**), {5.40 (1H, d, *J* = 2.5 Hz), 5.07 (1H, d, *J* = 2.5 Hz)} (**H8**), 5.02 – 4.98 (1H, m, **H2**), {4.51 (1H, dd, *J* = 14.5, 6.0 Hz), 4.39 (1H, dd, *J* = 14.5, 6.0 Hz)} (AB system, **H18**), {3.09 (1H, dd, *J* = 15.0, 4.0 Hz), 2.75 (1H, dd, *J* 15.0, 7.5 Hz)} (**H16**), 2.36 (3H, s, **H15**)

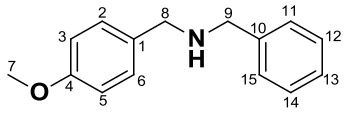
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.1 (**C17**), 144.5 (**C12**), 144.1 (**C3**), 143.2 (**C7a**), 138.0 (**C19**), 133.4 (**C9**), 130.2 (**C6**), 129.8 (**C11** and **C13**), 129.5 (**C3a**), {128.7, 127.8} (**C20**, **C21**, **C23** and **C24**), 127.4 (**C10** and **C14**), 124.8 (**C5**), 121.1 (**C4**), 116.8 (**C7**), 104.4 (**C8**), 63.0 (**C2**), 44.5 (**C16**), 43.7 (**C18**), 21.6 (**C15**)

C22 is not observed and is assumed to be overlapping with the peak at 127.4 from the HSQC and HMBC experiments.

ν_{max} (thin film)/cm^{-1} 3300 (**N-H**), 1648 (**C=O**), 1354, 1167 (**O=S=O**)

ES-MS calcd for $C_{25}H_{24}N_2O_3S$ $[M+H]^+$ 433.1586; found 433.1591

***N*-Benzyl-1-(4-methoxyphenyl)methanamine (390)**



To freshly crushed and activated 4Å molecular sieves at rt was added benzene (20 mL), potassium carbonate (138 mg, 1.00 mmol, 0.5 equiv), 4-methoxybenzylamine (261 µL, 2.00 mmol, 1.0 equiv) and benzaldehyde (193 µL, 1.90 mmol, 0.95 equiv). The reaction mixture was stirred at rt overnight and filtered through Celite®. The filter cake washed with DCM and the combined organic layers were concentrated under reduced pressure. The residue was redissolved in EtOH (20 mL) and sodium borohydride (151 mg, 4.00 mmol, 2.0 equiv) was added in three portions at 0 °C. The reaction mixture was stirred at rt for 2 h and then quenched by careful addition of H_2O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (70 % EtOAc in petroleum ether) gave secondary amine **390** (410 mg, 95 % yield) as a colourless oil.

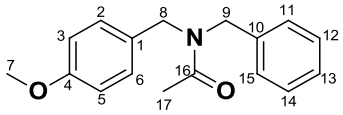
^{1}H NMR (400 Mhz, $CDCl_3$) δ_H 7.40 – 7.35 (4H, m, **H11**, **H12**, **H14** and **H15**), 7.32 – 7.29 (3H, m, **H2**, **H6** and **H13**), 6.92 (2H, d, *J* = 8.5 Hz, **H3** and **H5**), 3.84 (5H, s, **H7** and **H9**), 3.79 (2H, s, **H8**), 1.64 (1H, br. s, **NH**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.7 (**C4**), 140.5 (**C10**), 132.5 (**C1**), 129.4 (**C2** and **C6**), {128.4, 128.2} (**C11**, **C12**, **C13** and **C14**), 127.0 (**C13**), 113.8 (**C3** and **C5**), 55.3 (**C7**), 53.1 (**C9**), 52.6 (**C8**)

ν_{max} (thin film)/cm^{-1} 3327 (**NH**), 1242, 1034 (**C-O**)

ES-MS calcd for $C_{15}H_{17}NO$ $[M+H]^+$ 228.1388; found 228.1391

***N*-Benzyl-N-(4-methoxybenzyl)acetamide (391)**



To a solution of amine **390** (375 mg, 1.64 mmol, 1.0 equiv) in DCM (10 mL) at rt was added triethylamine (275 µL, 1.98 mmol, 1.2 equiv), DMAP (20 mg, 0.164 mmol, 0.1 equiv) and acetic anhydride (187 µL, 1.98 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 3 h, diluted with DCM, washed with 2M HCl, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography gave amide **391** (420 mg, 95 % yield) as a colourless oil.

This product was observed as a mixture of two rotamers in the NMR spectrum.

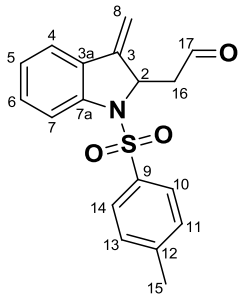
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.094 (7H, m, **H2**, **H6**, **H11**, **H12**, **H13**, **H14** and **H15**), 6.93 (2H, d, *J* = 8.5 Hz, **H3** and **H5 minor**), 6.87 (2H, d, *J* = 8.5 Hz, **H3** and **H5 major**), 4.60 (2H, s, **H9 minor**), 4.56 (2H, s, **H8 major**), 4.45 (2H, s, **H9 major**), 4.40 (2H, s, **H8 minor**), 3.84 (3H, s, **H7 minor**), 3.82 (3H, s, **H7 major**), 2.26 (3H, s, **H17 minor**), 2.22 (3H, s, **H17 major**).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.1 (**C16 minor**), 171.0 (**C16 major**), 159.1 (**C4 minor**), 159.0 (**C4 major**), 137.4 (**C10 minor**), 136.5 (**C10 major**), 129.8 (**C2** and **C6 major**), 129.5 (**C1 minor**), 129.0 (**C12** and **C14 major**), 128.6(**C12** and **C14 minor**), 128.3 (**C11** and **C15 minor**), 128.2 (**C1 major**), 127.8 (**C2** and **C6 minor**), 127.6 (**C13 minor**), 127.4 (**C13 major**), 126.4 (**C11** and **C15 major**), 114.4 (**C3** and **C5 minor**), 114.0 (**C3** and **C5 major**), 55.4 (**C7 minor**), 55.3 (**C7 major**), 50.5 (**C8 minor**), 50.2 (**C9 major**), 47.7 (**C9 minor**), 47.3 (**C8 major**), 21.8 (**C17**)

ν_{max} (thin film)/cm^{-1}1642 (**C=O**), 1242, 1030 (**C-O**)

ES-MS calcd for $C_{17}H_{19}NO_2$ $[M+H]^+$ 270.1494; found 270.1491

(±)-2-(3-Methylene-1-tosylindolin-2-yl)acetaldehyde (393)



To a solution of amide **363** (1.09 g, 2.94 mmol, 1.0 equiv) in THF (30 mL) at –42 °C (MeCN/CO_2 bath) was added DIBAL-H (1.0 M in hexanes, 6.47 mL, 2.2 equiv) dropwise. The reaction mixture was stirred at –42 °C for 6 h and then quenched by addition of EtOH (20 mL) at –42 °C. The solution was stirred for a further 15 min at –42 °C then was warmed to rt and 2M $HCl_{(aq)}$ (40 mL) was added. The solution was extracted three times with EtOAc, and the combined organic layers were washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave aldehyde **393** (587 mg, 61 % yield) as a pale yellow oil.

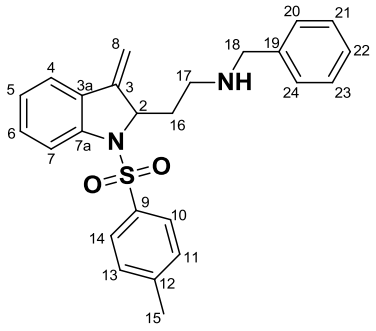
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.81 (1H, m, **H17**), 7.78 (1H, d, *J* = 8.5 Hz, **H7**), 7.58 (2H, d, *J* = 8.5 Hz, **H10** and **H14**), 7.33- 7.29 (2H, m, **H4** and **H6**), 7.19 (2H, d, *J* = 8.5 Hz, **H11** and **H13**), 7.07 (1H, t, *J* = 7.5 Hz, **H5**), 5.39 (1H, d, *J* = 2.0 Hz, **H8A**), 5.05 – 5.01 (1H, m, **H2**), 4.95 (1H, d, *J* = 2.0 Hz, **H8B**), {3.19 (1H, ddd, *J* = 18.0, 4.0, 2.0 Hz), 3.09 (1H, ddd, *J* = 18.0, 6.5, 1.5 Hz)} (AB system, **H16**), 2.34 (3H, s, **H15**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.8 (**C17**), 144.7 (**C7a**), 144.5 (**C12**), 143.4 (**C3**), 133.5 (**C9**), 130.4 (**C6**), 129.8 (**C11** and **C13**), 129.1 (**C3a**), 127.3 (**C10** and **C14**), 124.8 (**C5**), 121.1 (**C4**), 116.7 (**C7**), 104.1 (**C8**), 60.8 (**C2**), 51.5 (**C16**), 21.6 (**C15**)

ν_{max} (thin film)/cm^{-1} 1742 (**C=O**), 1354, 1168 (**O=S=O**)

ES-MS calcd for $C_{18}H_{17}NO_3S$ $[M+MeCN+Na]^+$ 391.1092; found 391.1100

(±)-*N*-Benzyl-2-(3-methylene-1-tosylindolin-2-yl)ethanamine (394)



To freshly crushed and activated 4Å molecular sieves at rt was added a solution of aldehyde **393** (500 mg, 1.53 mmol, 1.0 equiv) in benzene (15 mL), potassium carbonate (106 mg, 0.765 mmol, 0.5 equiv) and benzylamine (200 µL, 1.84 mmol, 1.2 equiv). The reaction mixture was stirred at rt overnight and filtered through Celite®. The filter cake washed with DCM and the combined organic layers were concentrated under reduced pressure. The residue was redissolved in EtOH (15 mL) and sodium borohydride (116 mg, 3.06 mmol, 2.0 equiv) was added in three portions at 0 °C. The reaction mixture was stirred at rt for 1.5 h and then quenched by careful addition of H_2O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5 % MeOH in DCM) gave secondary amine **394** (463 mg, 72 % yield) as a colourless oil.

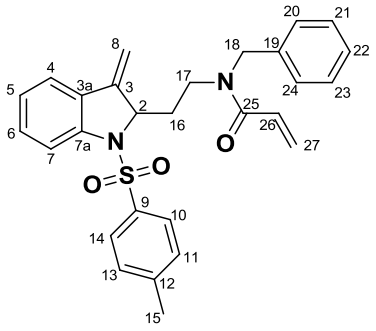
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (1H, d, *J* = 8.5 Hz, **H7**), 7.52 (2H, d, *J* = 8.5 Hz, **H10** and **H14**), 7.35 – 7.24 (7H, m, **H4**, **H6**, **H20**, **H21**, **H22**, **H23** and **H24**), 7.15 (2H, d, *J* = 8.5 Hz, **H11** and **H13**), 7.11 – 7.07 (1H, m, **H5**), 5.34 (1H, d, *J* = 2.0 Hz, **H8A**), 4.90 (1H, d, *J* = 2.0 Hz, **H8B**), 4.79 – 4.75 (1H, m, **H2**), {3.84 (1H, d, *J* = 13.0 Hz), 3.78 (1H, d, *J* = 13.0 Hz)} (AB system, **H18**), 2.98 – 2.92 (1H, m, **H17A**), 2.80 – 2.74 (1H, m, **H17B**), 2.34 (3H, s, **H15**), 2.24 – 2.16 (1H, m, **H16A**), 2.07 – 2.00 (2H, m, **H16B** and **NH**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1 (**C7a**), 144.1 (**C12**), 143.6 (**C3**), 140.1 (**C19**), 134.0 (**C9**), 130.4 (**C3a**), 130.0 (**C22**), 129.6 (**C11** and **C13**), 128.4 (**C20** and **C24**, or **C21** and **C23**), 128.3 (**C20** and **C24**, or **C21** and **C23**), 127.3 (**C10** and **C14**), 127.0 (**C6**), 124.8 (**C5**), 121.0 (**C4**), 117.7 (**C7**), 103.4 (**C8**), 64.9 (**C2**), 54.1 (**C18**), 44.1 (**C17**), 37.6 (**C16**), 21.6 (**C15**)

ν_{max} (thin film)/cm^{-1} 3331 (**N-H**), 1353, 1166 (**O=S=O**)

ES-MS calcd for $C_{25}H_{26}N_2O_2S$ $[M+H]^+$ 419.1793; found 419.1794

(±)-*N*-Benzyl-N-(2-(3-methylene-1-tosylindolin-2-yl)ethyl)acrylamide (395)



To a solution of amine **394** (38 mg, 0.091 mmol, 1.0 equiv) in DCM (1 mL) at rt was added acrylic acid (10 µL, 0.136 mmol, 1.5 equiv), propylphosphonic anhydride (50 % w/w in EtOAc, 90 µL, 0.136 mmol, 1.5 equiv) and triethylamine (25 µL, 0.182 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 2 h and diluted with DCM. The solution was washed with saturated $NaHCO_{3\ (aq)}$, saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (35 % EtOAc in petroleum ether) gave amide **395** (42 mg, 98 % yield).

This product was observed as a mixture of two rotamers in the NMR spectrum.

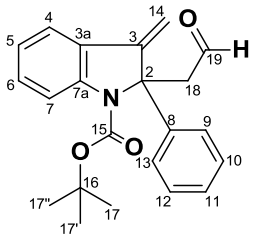
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (1H, d, *J* = 8.0 Hz, **H7 major**), 7.75 (1H, d, *J* = 8.0 Hz, **H7 minor**), 7.55 (2H, d, *J* = 8.0 Hz, **H10 major** and **H14 major**), 7.52 (2H, d, *J* = 8.0 Hz, **H10 minor** and **H14 minor**), 7.38 – 7.15 (9H, m, **H4**, **H6**, **H11**, **H13**, **H20**, **H21**, **H22**, **H23** and **H24**), 7.10 – 7.05 (1H, m, **H5**), 6.70 (1H, dd, *J* = 16.5, 10.5 Hz, major, **H26 major**) 6.55 (1H, dd, *J* = 16.5, 10.5 Hz, **H26 minor**), 6.49 – 6.39 (1H, m, **H27A**), 5.79 (1H, dd, *J* = 10.5, 2.0 Hz, **H27B major**), 5.68 (1H, dd, *J* = 10.5, 2.0 Hz, **H27B minor**), {5.43 – 5.42 (m), 5.15 (d, *J* = 2.0 Hz) and 4.86 (d, *J* = 2.0 Hz)} (**H8**), 4.80 – 4.71 (1H, m, **H18A**), 4.65 – 4.53 (2H, m, **H2** and **H18B**), {3.93 – 3.86 (m), 3.55 – 3.48 (m) and 3.33 – 3.23 (m)} (**H17**), 2.59 – 2.50 (1H, m, **H16A major**), 2.35 – 2.23 (5H, m, **H15**, **H16A minor** and **H16B minor**), 1.97 – 1.90 (1H, m, **H16B major**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.9 (**C25 minor**), 166.3 (**C25 major**), 144.5 (**C12 major**), 144.2 (**C12 minor**), 144.13 (**C3 major** or **C7a major**), 144.07 (**C3 major** or **C7a major**), 143.8 (**C3 minor**), 143.6 (**C7a minor**), 137.7 (**C19 major**), 137.0 (**C19 minor**), 133.7 (**C9 minor**), 133.4 (**C9 major**), 130.6 (**Ar-C**), 130.0 (**Ar-C**), 129.7 (**Ar-C**), 129.6 (**Ar-C**), 129.4 (**C3a**), 128.9 (**C27 major**), 128.6 (**Ar-C**), 128.4 (**C27 minor**), 127.9 (**Ar-C**), 127.6 (**C26 major**), 127.4 (**C26 minor**), 127.3 (**C10** and **C14**), 126.6 (**Ar-C**), 124.8 (**C5 major**), 124.7 (**C5 minor**), 121.0 (**Ar-C**), 117.1 (**C17 minor**), 116.9 (**C17 major**), 103.8 (**C8 minor**), 102.8 (**C8 major**), 64.6 (**C2 minor**), 64.2 (**C2 major**), 51.3 (**C18 minor**), 49.3 (**C18 major**), 42.2 (**C17 minor**), 42.0 (**C17 major**), 35.8 (**C16 major**), 34.4 (**C16 minor**), 21.6 (**C15**)

ν_{max} (thin film)/cm^{-1} 1646 (**C=O**), 1353, 1166 (**O=S=O**)

ES-MS calcd for $C_{28}H_{28}N_2O_3S$ $[M+H]^+$ 473.1899; found 473.1900

(±)-*Tert*-butyl 3-methylene-2-(2-oxoethyl)-2-phenylindoline-1-carboxylate (397)



To a solution of nitrile **184** (192 mg, 0.554 mmol, 1.0 equiv) in toluene (2.5 mL) at –78 °C was added DIBAL-H (1.0 M in hexanes, 609 µL, 0.609 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at –78 °C for 1.5 h and then carefully quenched by addition of EtOH (2.5 mL). The reaction mixture was stirred at –78 °C for a further 15 min and then warmed to rt and diluted with saturated $KNaC_4H_4O_{6\ (aq)}$ and the resulting biphasic mixture stirred overnight. The phases were separated and the aqueous phase was re-extracted with EtOAc. The combined organic layers were washed with saturated $NaCl_{\ (aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether) gave aldehyde **397** (133 mg, 69 % yield) as a colourless oil.

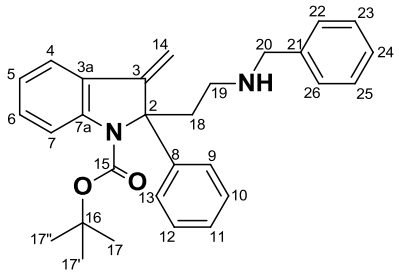
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.54 (1H, s, **H19**), 8.15 (1H, br. s, **H7**), 7.50 (1H, d, *J* = 7.5 Hz, **H4**), 7.42 – 7.21 (6H, **H6**, **H9**, **H10**, **H11**, **H12** and **H13**), 7.11 (1H, t, *J* = 7.5 Hz, **H5**), 5.58 (1H, s, **H14A**), 4.83 (1H, s, **H14B**), 3.81 (1H, br. s, **H18A**), 3.27 (1H, dd, *J* = 15.5, 2.0 Hz, **H18B**), 1.19 (9H, br. s, **H17**, **H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 200.5 (**C19**), 151.1 (**C15**), 150.7 (**C7a**), 144.8 (**C3**), 130.9 (**C6**), 128.8 (**C10** and **C12**), 128.5 (**C8**), 127.5 (**C11**), 126.4 (**C3a**), 124.0 (**C9** and **C13**), 123.4 (**C5**), 120.9 (**C4**), 115.8 (**C7**), 104.0 (**C14**), 82.0 (**C16**), 71.2 (**C2**), 51.9 (**C18**), 27.9 (**C17**, **C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 1702 (**C=O**)

ES-MS calcd for $C_{22}H_{23}NO_3$ $[M+H]^+$ 350.1756; found 350.1762

(±)-*Tert*-butyl 2-(2-(benzylamino)ethyl)-3-methylene-2-phenylindoline-1-carboxylate (398)



To freshly crushed and activated 4Å molecular sieves at rt was added a solution of aldehyde **397** (105 mg, 0.300 mmol, 1.0 equiv) in benzene (3 mL), potassium carbonate (21 mg, 0.150 mmol, 0.5 equiv) and benzylamine (40 µL, 0.361 mmol, 1.2 equiv). The reaction mixture was stirred at rt overnight and filtered through Celite®. The filter cake washed with DCM and the combined organic layers were concentrated under reduced pressure. The residue was redissolved in EtOH (4 mL) and sodium borohydride (23 mg, 0.600 mmol, 2.0 equiv) was added in three portions at 0 °C. The reaction mixture was stirred at rt for 2 h and then quenched by careful addition of H_2O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl $_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (5 % MeOH in DCM) gave secondary amine **398** (96 mg, 73 % yield) as a colourless oil.

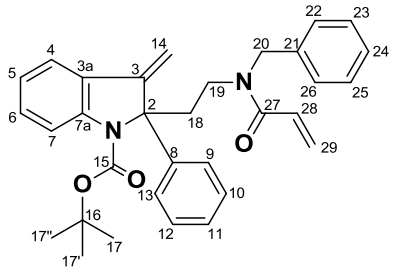
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (1H, br. s, **H7**), 7.46 (1H, d, *J* = 7.5 Hz, **H4**), 7.39 – 7.23 (11H, m), 7.08 (1H, t, *J* = 7.5 Hz, **H5**), 5.49 (1H, s, **H8A**), 4.75 (1H, s, **H8B**), 3.73 (2H, s, **H20**), 3.13 (1H, br. s, **H18A**), 2.71 – 2.59 (2H, m, **H19**), 2.47 – 2.40 (1H, m, **H18B**), {1.46 (br. s) and 1.17 (br. s)} (9H, **H17**, **H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.5 (**C15**), 146.6 (**C7a**), 145.2 (**C3**), 140.3 (**C21**), 130.4 (**C6**), 128.43 ((**C10** and **C12**) or (**C23** and **C25**)), 128.40 ((**C10** and **C12**) or (**C23** and **C25**)), 128.2 (**C8**), 128.0 (**C22** and **C26**), 127.3 (**C3a**), 126.9 (**C11** or **C24**), 126.8 (**C11** or **C24**), 124.3 (**C9** and **C13**), 122.9 (**C5**), 120.5 (**C4**), 115.6 (**C7**), 102.5 (**C14**), 81.2 (**C16**), 73.1 (**C2**), 54.1 (**C20**), 44.5 (**C19**), 39.4 (**C18**), 27.9 (**C17**, **C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 1698 (**C=O**)

ES-MS calcd for $C_{29}H_{32}N_2O_2$ $[M+H]^+$ 441.2542; found 441.2547

(±)-*Tert*-butyl 2-(2-(N-benzylacrylamido)ethyl)-3-methylene-2-phenylindoline-1-carboxylate (399)



To a solution of amine **398** (71 mg, 0.161 mmol, 1.0 equiv) in DCM (1.6 mL) at rt was added acrylic acid (17 µL, 0.242 mmol, 1.5 equiv), propylphosphonic anhydride (50 % w/w in EtOAc, 154 µL, 0.242 mmol, 1.5 equiv) and triethylamine (45 µL, 0.322 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 2 h and diluted with DCM. The solution was washed with saturated $NaHCO_{3\ (aq)}$, saturated $NaCl_{(aq)}$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in petroleum ether) gave amide **399** (72 mg, 90 % yield).

This product was observed as a mixture of two rotamers in the NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.11 (1H, br. s, **H7**), 7.47 (1H, d, *J* = 7.5 Hz, **H4**), 7.37 – 7.03 (12H, m, **H5**, **H6**, **H9**, **H10**, **H11**, **H12**, **H13**, **H22**, **H23**, **H24**, **H25** and **H26**), 6.67 – 6.40 (2H, m, **H28** and **H29A**), 5.77 – 5.67 (1H, m, **H29B**), 5.53 (1H, s, **H14A**), 4.82 – 4.47 (3H, m, **H14B** and **H20**), 3.53 – 3.12 (3H, m, **H18A** and **H19**), 2.63 – 2.36 (1H, m, **H18B**) {1.48 (br. s) and 1.16 (br. s)} (9H, **H17**, **H17'** and **H17''**)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.7 (**C27 minor**), 166.1 (**C27 major**), 151.4 (**C15 major**), 150.8 (**C15 minor**), 145.7 (**C7a**), 137.5 (**C3**), 137.0 (**C21**) , 130.8 (**C6**), 130.4 (**C8**), 129.0 (**C29**), 128.9 (**Ar-C**), 128.64 (**C22 minor** and **C26 minor**) , 128.57 (**Ar-C**), 128.5 (**C22 major** and **C26 major**), 127.9 (**Ar-C**), 127.7 (**Ar-C**), 127.5 (**Ar-C**), 127.3 (**Ar-C**), 127.2 (**C28**), 126.9 (**Ar-C**), 126.8 (**C3a**), 126.4 (**Ar-C**), 124.1 (**Ar-C**), 124.0 (**Ar-C**), 123.3 (**Ar-C**), 123.0 (**Ar-C**), 120.7 (**C4**), 115.7 (**C7 major**), 115.5 (**C7 minor**), 103.1 (**C14 minor**), 102.4 (**C14 major**), 81.8 (**C16 major**), 81.3 (**C16 minor**), 72.8 (**C2 minor**), 72.5 (**C2 major**), 49.2 (**C20**), 42.8 (**C19**), 37.9 (**C18 major**), 37.8 (**C18 minor**), 27.9 (**C17**, **C17'** and **C17''**)

ν_{max} (thin film)/cm^{-1} 1701 (**C=O carbamate**), 1650 (**C=O amide**)

ES-MS calcd for $C_{32}H_{34}N_2O_3$ $[M+H]^+$ 495.2648; found 495.2650

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