Dearomatizing Claisen Rearrangements

Toby Mullins

Department of Chemistry, Imperial College London

Supervisor: Professor Donald Craig

August 2015

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy, Imperial College London
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.
Copyright Declaration

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.
Acknowledgements

Firstly I would like to thank Professor Donald Craig for his invaluable support and guidance over the course of my PhD, and RCUK and Imperial College for funding. I would also like to thank members of the DC/PP groups past and present: Joe, Rich, Simon, Bethan, Bruno, Claire, Shu, Jasprit, Jason, Daniel, Lee, Alex, Lewis and Phil. Thank you also to Lisa Haigh, Pete Haycock and Dick Sheppard for spectroscopic services.

Lastly, I want to thank my family, and especially Vicky, for their love and support over the past few years.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Ångström(s)</td>
</tr>
<tr>
<td>a</td>
<td>antarafacial</td>
</tr>
<tr>
<td>A&lt;sub&gt;ac&lt;/sub&gt;</td>
<td>unimolecular acid-catalysed alkyl bond breaking hydrolysis</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2′-azobis(2-methylpropionitrile)</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2′-bipyridyl</td>
</tr>
<tr>
<td>BSA</td>
<td>N,O-bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>BOX</td>
<td>bis(oxazoline)</td>
</tr>
<tr>
<td>°Bu</td>
<td>normal-butyl</td>
</tr>
<tr>
<td>′Bu</td>
<td>tertiary-butyl</td>
</tr>
<tr>
<td>*C</td>
<td>degree centigrade</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dCr</td>
<td>decarboxylative Claisen rearrangement</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N′-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DMA.DMA</td>
<td>dimethylacetamide dimethylacetal</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMEAD</td>
<td>di-2-methoxyethyl azodicarboxylate</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HFIP</td>
<td>hexafluoro-2-propanol</td>
</tr>
</tbody>
</table>
HMPA  hexamethylphosphoramide
IPA   propan-2-ol (iso-propyl alcohol)
IR    infrared
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  phosphino oxazole
PMB   para-methoxy benzyl
PPTS  pyridinium para-toluensulfonate
^Pr   iso-propyl
nPr   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   trifluoroacetic acid
TFAA  trifluoroacetic anhydride
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl (tosyl)</td>
</tr>
<tr>
<td>TSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
</tbody>
</table>
Stereochemical notation

The Maehr convention for indicating relative and absolute stereochemistry has been used throughout this report. Therefore, solid and broken lines are used to denote racemates, and solid and broken wedges denote absolute configuration.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>i</td>
</tr>
<tr>
<td>Declaration of Originality</td>
<td>ii</td>
</tr>
<tr>
<td>Copyright Declaration</td>
<td>iii</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>iv</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>v</td>
</tr>
<tr>
<td>Stereochemical Notation</td>
<td>viii</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>ix</td>
</tr>
</tbody>
</table>

## 1 Dearomatising Claisen rearrangements

1.1 [3,3]-sigmatropic rearrangements                                    1
1.2 Dearomatising Claisen rearrangements                                2
1.3 Dearomatising Ireland-Claisen rearrangements                        11
1.4 Dearomatising Eschenmoser-Claisen rearrangements                    12
1.5 Dearomatising Johnson-Claisen rearrangements                        21
1.6 Dearomatising aza-Claisen rearrangements                            24
1.7 Dearomatising thio-Claisen rearrangements                           31
1.8 Dearomatising iodonio-Claisen rearrangements                        36
1.9 Dearomatising Carroll rearrangements                                41

## 2 The decarboxylative Claisen rearrangement

2.1 Background                                                          43
2.2 Project aims and objectives                                          49
2.3 The decarboxylative Claisen rearrangement of furans                 51
   2.3.1 Varying the alkyl group at the benzylic position                 51
   2.3.2 Varying the electron withdrawing group                           54
   2.3.3 Furans with an aryl group at the benzylic position               55
   2.3.4 Furans substituted at the 5-position                             57
   2.3.5 Furans possessing an alkyl group at the 3-position               60
   2.3.6 Furans with an ester functionality at the 3-position             65
2.4 Conclusions                                                         66

## 3 Hinckdentine A

3.1 Background                                                          67
   3.1.1 Structure and isolation                                         67
3.1.2 Joule’s Approach 67
3.1.3 Cava’s Approach 69
3.1.4 McWhorter’s synthesis of 8-desbromohinckdentine A 72
3.1.5 Kawasaki’s synthesis of Hinckdentine A 74

3.2 Retrosynthetic Approach 77

3.3 Results and discussion 79
3.3.1 Synthesis of a model system by Friedel-Crafts acylation 79
3.3.2 Synthesis of a model system by a Passerini reaction 80
3.3.3 Synthesis of a model system by a Friedel-Crafts hydroxyalkylation 88
3.3.4 Synthesis of a model system via a cyanohydrin 96
3.3.5 Synthesis of a model system via a palladium catalysed cyclisation 96
3.3.6 dCr reaction of model system 100
3.3.7 Second generation retrosynthesis 104
3.3.8 Johnson-Claisen reactions of an indole with an alkyl protecting group 107
3.3.9 Belluš-Claisen reactions of an indole with an alkyl protecting group 107
3.3.10 Belluš-Claisen reactions of an indole with an electron-withdrawing protecting group 111
3.3.11 Eschenmoser-Claisen reactions of an indole with an electron-withdrawing protecting group 113
3.3.12 Third-generation retrosynthesis 119
3.3.13 Johnson-Claisen reactions of an indole with an electron-withdrawing protecting group 119
3.3.14 Synthesis of alternative dimethyl acetals 122
3.3.15 Ring-closing metathesis 123

3.4 Conclusions and future work 127

4 Experimental 131

5 References 249
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 $\sigma$-bond formation and $\sigma$-bond breaking (Scheme 1).

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).

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).
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).

The first example of the Claisen rearrangement was that of allyl phenol ether 1. 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.

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).
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. Schmid et al. have since shown that rearrangement can occur at room temperature in TFA as a solvent (Scheme 7). The major product of this reaction was coumaran 8, which was formed by acid-catalysed cyclisation of the Claisen rearrangement product 7.

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).
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 BCl₃ allowed the rearrangement to take place at ambient temperature in excellent yield (Scheme 9).

Reduction of the quinone functionality with sodium hydrosulfite, and then treatment with 6 equivalents of BCl₃ gave the C10 allylated product 13 in 95 % yield, with re-oxidation of the hydroquinone occurring on work up.

The use of BCl₃ 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).
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) BCl₃ gave only the cleavage product 16, whereas Et₂AlCl 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.

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, cyclohexadienone 20 was formed as a competing product (Scheme 12 and Table 2)
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.
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).\textsuperscript{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.
The use of BCl$_3$ and Et$_2$AlCl 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](image)

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](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)(^a)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eu(fod)_3</td>
<td>dichloroethane</td>
<td>80</td>
<td>48</td>
<td>14</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>N,N-diethylaniline</td>
<td>190</td>
<td>4</td>
<td>32</td>
<td>80</td>
</tr>
</tbody>
</table>

*Table 3: Conditions for Papeo’s Claisen rearrangement. *After separation 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).\(^\text{13}\)

![Scheme 17: Enantioselective aromatic Claisen rearrangement. See Table 4](image)

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 opposite configurations at the new stereocentre (Table 4, entries 1 and 4), although the *Z* isomer required a higher reaction temperature.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Ligand&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34a</td>
<td>–45</td>
<td>4 d</td>
<td></td>
<td></td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>34b</td>
<td>–45</td>
<td>24 h</td>
<td></td>
<td></td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>34a</td>
<td>–45</td>
<td>3 d</td>
<td></td>
<td></td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>34a</td>
<td>–23</td>
<td>2 d</td>
<td></td>
<td></td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>34a</td>
<td>–45</td>
<td>24 h</td>
<td></td>
<td></td>
<td>51</td>
<td>57</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ar = 4-methyphenyl = a. Ar = 3,5-bis(trifluoromethyl)phenyl = b

Based on these observations, the authors proposed a transition state by which a $\sigma$-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)

---

**Table 4**: Enantioselective aromatic Claisen rearrangement.

**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](image)

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](image)

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
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).\textsuperscript{17}

The dearomatising Eschenmoser-Claisen rearrangement of heterocycles has not been widely studied. In 1969 Eschenmoser \textit{et al}. reported the rearrangement of furfuryl alcohol 39 to give amide 40 (Scheme 22),\textsuperscript{18} and in 2007 Granik \textit{et al}. reported the similar reaction of 2-(hydroxymethyl)-benzofurans 41 (Scheme 23).\textsuperscript{19}
Granik also attempted the reaction of 3- and 2-hydroxymethylindoles \( \text{42} \) and \( \text{44} \) under the same conditions (Scheme 24). In this case, instead of the predicted [3,3] rearrangement, the only products isolated were amides \( \text{43} \) and \( \text{45} \), 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.

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 \( \text{46} \) and subsequent [3,3]-rearrangement to give C5 functionalised pyrimidines \( \text{47} \) published in 2011 by Suckling \textit{et al.} (Scheme 25).\(^\text{20}\)
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. The oxonium intermediate 49 then underwent a [3,3]-rearrangement to give carbenium 50, which was then hydrolysed to form 51.

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.
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, CF₃, OMe), 54 was the only product isolated. This observation was explained by the mechanisms given in Scheme 28.

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.

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

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) Br₂, DCM, 0 °C then (S)-1-nonen-3-ol, MeCN/DMF, 4 Å MS, rt, 4 days, 73 %; (b) (EtO)₂P(O)CH₂CN, KOtBu, 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.
Attempts to decarboxylate 65 via standard saponification methods gave the rearranged product 66 rather than the expected 2-allyloxyindolin-3-one 67 (Scheme 32). 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.

Kobayashi and Nagazaki have also utilised the dearomatising Eschenmoser-Claisen rearrangement in the synthesis of the pyrrolo[2,3-b]indole ring system. 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).
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). This procedure proved successful for a number of different allylic alcohols at room temperature, whereas propargylic alcohols required heating to reflux in dichloromethane.
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).

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). Care was needed with the isolation of 2-propenylindole-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.

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

**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](image)

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). In contrast to the Eschenmoser-Claisen rearrangement acidic catalysis is often required.
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).  

This methodology has also been extended to include indoles and applied to the synthesis of the alkaloid secodine (Scheme 40).  

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), Et₂O, 0 °C, 20 min; then HCl; (b) indole-3-glyoxyl chloride, Et₂O, 0 °C, 4 h, 90 % over two steps; (c) ClCO₂C(CH₃)₂CCl₃, Et₃N, DCM, rt, 30 min, 80 %; (d) NaBH₄, MeOH, 0 °C, 20 min, 63 %; (e) CH₂OCH₃CH₂CH₂(OMe)₂, 2,4,6-trimethylbenzoic acid, 225 °C, 100 min, 65 %; (f) Lawesson’s reagent, C₆H₆, reflux, 2 h; (g) Et₃OBF₄, DCM then NaBH₃CN, 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).

\[
\begin{array}{c}
R^1\text{C}l \quad N \quad R^2 \\
\text{Scheme 41: The aza-Claisen rearrangement}
\end{array}
\]

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.

\[
\begin{array}{c}
\text{HN} \\
\text{85} \\
\text{Scheme 42: Thermal aza-Claisen rearrangement (a) 280 °C, 3 h, sealed tube, 90 %}
\end{array}
\]

Stille \textit{et al.} carried out a study into the Lewis-acid catalysis of the rearrangement of \textit{N}-allyl aniline 86 (Scheme 43).\(^{37}\) They found that the most successful catalysts were AlCl\(_3\), ZnCl\(_2\) and BF\(_3\)·OEt\(_2\). The reaction with BF\(_3\)·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.

\[
\begin{array}{c}
\text{86} \\
\text{Scheme 43: Lewis-acid catalysed aza-Claisen rearrangement (a) AlCl}_3\text{ (1.2 equiv), xylenes, 140 °C, 8 h, } R = \text{Me} = 68 \%. \text{ } R = \text{Bn} = 15 \%
\end{array}
\]

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 starting 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).
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 \((\rightarrow)-\text{indolactam V}\) (90). When treated with 0.45 equivalents of \(\text{AlCl}_3\), allyl aniline 91 rearranged to give a mixture of open chain allyl and cyclised products (Scheme 45).

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).
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).\(^{39}\)

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).

\[\text{Scheme 46: Formation of cyclised products 93 and 94 from aza-Claisen product 92 (a) AlCl}_3, \text{ xylenes, 140 °C, sealed tube, 20 min} \]

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

\[\text{Scheme 48: Synthesis of indoles via an aza-Claisen – oxidative ring closure sequence (a) 3-bromocyclohexene, acetone, K}_2\text{CO}_3, \text{ reflux, 5 h, 90 %; (b) HCl, EtOH, reflux, 15 h, 88 %; (c) Hg(OAc)}_2, \text{ AcOH, MeOH, rt, 24 h, 80 %; (d) DDQ, xylene, reflux, 12 h, 83 %} \]
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$_3$·OEt$_2$ (Scheme 50) as part of a study into a potential acetylcholinesterase inhibitor. 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$_3$N, H$_2$O, rt, 3 h, 78% (b) BF$_3$·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), although the high temperatures required (240 – 260 °C) led to low isolated yields.

Saito and Hanzawa have since reported a rhodium catalysed variant (Scheme 52). 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.

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$_3$·OEt$_2$ catalysed rearrangement to convert $\text{N}$-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](image)

The introduction of a 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 (+)-okaramine J](image)

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](image)
Tantillo and Tambar have recently reported the enantioselective aza-Claisen rearrangement of indoles using chiral phosphoric acids (Scheme 57). 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.

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

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.

\[ \text{Figure 8: Transition state for enantioselective aza-Claisen} \]
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](image)

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

![Scheme 59: Thio-Claisen rearrangement of allyl-2-indolylsulfides](image)

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.
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

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 60: Thio-Claisen rearrangement of 3,3-disubstituted ally-2-indolysulfides (a) allyl bromide, K₂CO₃, acetone; (b) tetralin, reflux

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

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 \textbf{122} (Scheme 63). Deuterium labelling experiments confirmed that the reaction proceeded via a [3,3]-sigmatropic mechanism to give only \textbf{123}.

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme63.png}
\end{center}

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

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

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme64.png}
\end{center}

\textbf{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 \textbf{124} undergoes a dearomatising-Claisen rearrangement to give allene \textbf{125}. \textbf{125} then spontaneously undergoes tautomerisation to give \textbf{126}, which in turn undergoes a [1,5]-hydride shift to give \textbf{127}. A final electrocyclisation gives thiopyran \textbf{128}.
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.\textsuperscript{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.

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

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 pyrrolidine ring in 141 is caused by cyclisation onto the thioimidate functionality of 140 with thiol elimination (Scheme 69).
1.8 Dearomatising iodonio-Claisen rearrangements

In 1991 Ochiai et al. reported the iodonio-Claisen rearrangement of allenyliodinanes 144; formed from an $S_2'\,$ reaction between aryliodinanes 142 and propargyl silanes, germanes and stannanes 143 (Scheme 70).^57

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

Scheme 70: Iodonio-Claisen rearrangement (a) $BF_3\cdot$OEt$_2$, MgSO$_4$, DCM, $-20\,^\circ\text{C}$, 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](image)

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

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). 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.  

![Scheme 74: Solvent effects on ipso versus ortho selectivity (a) propargyl silane, BF₃·OEt₂, MgSO₄, –20 °C, 1 h, see Table 5]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Total Yield</th>
<th>ipso:ortho ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>75</td>
<td>55:45</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>59</td>
<td>53:47</td>
</tr>
<tr>
<td>3</td>
<td>hexane</td>
<td>18</td>
<td>47:53</td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>71</td>
<td>46:54</td>
</tr>
<tr>
<td>5</td>
<td>CCl₄</td>
<td>54</td>
<td>44:56</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>88</td>
<td>42:58</td>
</tr>
<tr>
<td>7</td>
<td>Et₂O</td>
<td>80</td>
<td>30:70</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>59</td>
<td>20:80</td>
</tr>
</tbody>
</table>

Table 5: Solvent effects on ipso versus ortho selectivity. <sup>a</sup>Determined by GC.

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

In 2012, Zhu et al. reported the formation of ortho-allylidoarenes from the reaction of iodosyl benzenes 161 and allyltrimethyl silane (Scheme 75). 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.

Scheme 75: Formation of allyiodoarenes by an iodonio-Claisen rearrangement (a) allyltrimethylsilane, BF$_3$·OEt$_2$, 2 h, see Table 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Temperature</th>
<th>162 : 163 : 164</th>
<th>Overall yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>DCM</td>
<td>−20 °C</td>
<td>0.1 : 1.0$^a$</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>DCM</td>
<td>−20 °C</td>
<td>0.3 : 0.2 : 1.0</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>CF$_3$</td>
<td>DCM</td>
<td>−20 °C</td>
<td>-</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>DCM</td>
<td>−20 °C</td>
<td>3.8 : 0.9 : 1.0</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>MeCN</td>
<td>−20 °C</td>
<td>9.1 : 2.2 : 1.0</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>DCM/MeCN (1:1)</td>
<td>−50 °C</td>
<td>10 : 1.6 : 1.0</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>O'Pr</td>
<td>DCM/MeCN (1:1)</td>
<td>−50 °C</td>
<td>8.3 : 1.6 : 1.0</td>
<td>93</td>
</tr>
</tbody>
</table>

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).
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.\textsuperscript{66}

\[ \text{Scheme 77: The Carroll rearrangement} \]

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

\[ \text{Scheme 78: Palladium catalysed Carroll rearrangement} \]

Only one example of a dearomatising Carroll rearrangement has been published to date.\textsuperscript{68} \n
\[ N\text{-Hydroxyamide 165 was converted to its O-acetoacetyl derivative 166 under standard coupling conditions.} \]
Heating to 110 °C in toluene then caused rearrangement and decarboxylation to give the ortho-substituted anilide 167 (Scheme 79).

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. In this reaction an allylic sulfonyle 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.

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

**Figure 9: The decarboxylative Claisen rearrangement**

**Scheme 80:** Dearomatising dCr of five-membered heterocycles (a) BSA, KOAc, PhMe, see Table 7
<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>100 °C, 15 h</td>
</tr>
<tr>
<td>1</td>
<td>O</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>S</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>NTs</td>
<td>67</td>
</tr>
</tbody>
</table>

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.

When the exocyclic 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).

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 ZnCl₂ (Table 8, entries 3-8). The use of other Lewis acids such as TiCl₄ and BF₃·OEt₂ resulted in either decomposition, or direct rearomatisation of 173.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>temp, solvent, additive, time</th>
<th>Product</th>
<th>Yield (%) ((\text{syn:anti}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{H}^+) (\text{O}^-) (\text{Et}^+)</td>
<td>rt, DCM, none, 2 h</td>
<td>![Product Image]</td>
<td>91 ((10:1))^a</td>
</tr>
<tr>
<td>2</td>
<td>(\text{N}^-)</td>
<td>rt, DCM, none, 3 h</td>
<td>![Product Image]</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>(\text{H}^+) (\text{O}^-)</td>
<td>0 °C, DCM, ZnCl(_2), 1 h</td>
<td>![Product Image]</td>
<td>59 ((10:1))</td>
</tr>
<tr>
<td>4</td>
<td>(\text{H}^+) (\text{O}^-) (\text{H}^+)</td>
<td>0 °C, DCM, ZnCl(_2), 1 h</td>
<td>![Product Image]</td>
<td>60 ((10:1))</td>
</tr>
<tr>
<td>5</td>
<td>(\text{H}^+) (\text{O}^-)</td>
<td>0 °C, DCM, ZnCl(_2), 1 h</td>
<td>![Product Image]</td>
<td>62 ((10:1))</td>
</tr>
<tr>
<td>6</td>
<td>(\text{H}^+) (\text{O}^-) (\text{Ph}^-)</td>
<td>0 °C, DCM, ZnCl(_2), 1 h</td>
<td>![Product Image]</td>
<td>75 ((10:1))</td>
</tr>
<tr>
<td>7</td>
<td>(\text{H}^+) (\text{O}^-) (\text{Br}^-) (\text{Ph}^-)</td>
<td>0 °C, DCM, ZnCl(_2), 1 h</td>
<td>![Product Image]</td>
<td>82 ((5:3))</td>
</tr>
<tr>
<td>8</td>
<td>(\text{H}^+) (\text{O}^-) (\text{Ph}^-)</td>
<td>0 °C, DCM, ZnCl(_2), 1 h</td>
<td>![Product Image]</td>
<td>58 ((5:1))</td>
</tr>
<tr>
<td>9</td>
<td>(\text{O}^-) (\text{Et}^-) (\text{O}^-)</td>
<td>150 °C, \textit{m}-xylene, KOAc, 16 h</td>
<td>![Product Image]</td>
<td>73 ((5:3))</td>
</tr>
</tbody>
</table>

\(^a\)Lower selectivity was observed at increased temperatures

Table 8: Reaction of bis(enol) ether 173 with electrophiles.
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.\textsuperscript{72} This pattern has also been observed in other examples of the Claisen rearrangement.\textsuperscript{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, \( -78^\circ \text{C} \), 10 min then PhCHO, \( -78^\circ \text{C} \), 1 h, 81 \%; (b) Na\textsubscript{2}(Hg), Na\textsubscript{2}HPO\textsubscript{4}, MeOH, rt, 1.5 h, 21 \%

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

Scheme 84: dCr reaction of indoles 174 (a) BSA, KOAc PhMe, \( \mu \text{w} \), 150 \(^\circ \text{C} \), see Table 9
<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>time¹</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ts</td>
<td>H</td>
<td>Ts</td>
<td>5 x 1 min</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Boc</td>
<td>H</td>
<td>Ts</td>
<td>4 x 1 min</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>Boc</td>
<td>H</td>
<td>CN</td>
<td>4 x 1 min</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Boc</td>
<td>H</td>
<td>CO₂Et</td>
<td>4 x 1 min</td>
<td>22ᵇ</td>
</tr>
<tr>
<td>5</td>
<td>Boc</td>
<td>Me</td>
<td>Ts</td>
<td>4 x 1 min</td>
<td>87ᶜ</td>
</tr>
<tr>
<td>6</td>
<td>Boc</td>
<td>Me</td>
<td>CN</td>
<td>5 x 1 min</td>
<td>82ᶜ</td>
</tr>
<tr>
<td>7</td>
<td>Boc</td>
<td>Me</td>
<td>CO₂Et</td>
<td>4 x 1 min</td>
<td>53ᶜ</td>
</tr>
</tbody>
</table>

**Table 9**: dCr reaction of indoles. ¹1 min air assisted cooling between heating cycle. ᵇExposure to silica gel resulted in re-aromatisation to the tautomeric indole. ᶜProduct 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](image)

**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.
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.

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

2.2 Project aims and objectives

The aim of the first part of this project was 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).
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](image1)

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](image2)

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](image3)
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., 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).

\[
\begin{align*}
\text{Furan} & \xrightarrow{a} \text{Ketone 185} \xrightarrow{b} \text{Alcohol 186} \\
\end{align*}
\]

**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 \( S_\text{N}2 \) reaction of a sulfinate anion with methyl bromoacetate and subsequent ester hydrolysis (Scheme 95).

\[
\begin{align*}
\text{Br} & \xrightarrow{a} \text{Tosylacetic acid 188} \\
\end{align*}
\]

**Scheme 95:** Synthesis of tosylacetic acid (a) sodium p-toluene sulfinate, DMF, rt, 24 h, 91 %; (b) LiOH, THF/H\(_2\)O, 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).

\[
\begin{align*}
\text{Alcohol 186} & \xrightarrow{a} \text{Ester 189} \\
\end{align*}
\]

**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).
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 MgSO₄ was used as a drying agent during work-up, although this can be avoided by the use of Na₂SO₄ instead. It was found necessary also to add at least 1 % Et₃N to the eluent used for silica gel chromatography. In order to record a ¹³C NMR spectrum in CDCl₃, 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>67</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>²Pr</td>
<td>80</td>
<td>13:1</td>
</tr>
</tbody>
</table>

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

---

**Scheme 97**: Synthesis of ester 192 (a) ⁶BuLi, rt, 3 h then isobutyric acid, THF, rt, 18 h, 59 %; (b) NaBH₄, MeOH, rt, 3 h, 92 %; (c) tosylacetic acid, DIC, DMAP, DCM, rt, 48 h, 84 %

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

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-aromatized 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 rearomatized 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 ($R = iPr$) with electrophiles.](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Electrophile</th>
<th>Additive</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Ts" /></td>
<td><img src="image2" alt="N" /></td>
<td>-</td>
<td><img src="image3" alt="195" /></td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td><img src="image4" alt="O" /></td>
<td><img src="image5" alt="ZnCl₂" /></td>
<td><img src="image6" alt="196" /></td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="O" /></td>
<td>-</td>
<td><img src="image8" alt="197" /></td>
<td><img src="image8" alt="197" /></td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="image9" alt="mCPBA" /></td>
<td>-</td>
<td><img src="image10" alt="198" /></td>
<td><img src="image10" alt="198" /></td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td><img src="image11" alt="I₂" /></td>
<td>-</td>
<td><img src="image8" alt="197" /></td>
<td><img src="image8" alt="197" /></td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1" alt="Ts" /></td>
<td><img src="image2" alt="N" /></td>
<td>-</td>
<td><img src="image3" alt="199" /></td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td><img src="image4" alt="O" /></td>
<td><img src="image5" alt="ZnCl₂" /></td>
<td>-</td>
<td><img src="image6" alt="200" /></td>
<td>41</td>
</tr>
</tbody>
</table>

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).
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 ¹H and ¹³C 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 ¹⁹F NMR or distinctive coupling patterns in the ¹³C NMR. It also appeared that acetamide functionality from the BSA had been incorporated in some fashion, as evidenced by the ¹H 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.

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 T₃P® 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.
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_{cl}$1 mechanism. Accordingly ester 207 was synthesised in good yield via the same method as before (Scheme 103).

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

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

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.

Scheme 105: Synthesis of ester 209 (a) $^6$BuLi, THF, 0 °C, 30 min, then $p$-cyanobenzaldehyde, rt, 16 h, 68 %; (b) tosylacetic acid, $T_{3}P$, $Et_{3}N$, rt, 18 h, 58 %

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>MeOH</td>
<td>rt</td>
<td>4 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>DIBAL</td>
<td>THF</td>
<td>0 °C</td>
<td>3 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

*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).

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 A₁ pathway.
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).

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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Time</th>
<th>Conversion$^a$</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIAD, PPh$_3$</td>
<td>DCM</td>
<td>5 days</td>
<td>18 %</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DIC, DMAP</td>
<td>DCM</td>
<td>4 days</td>
<td>100 %</td>
<td>89 %</td>
</tr>
</tbody>
</table>

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). This intermediate 220 then loses trimethylsilanol to give nitroso intermediate 221 which undergoes intramolecular condensation to yield quinoline 222.

2.3.5 Furans possessing 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. This method involved the synthesis of epoxide 223 via a Darzens reaction and subsequent thermal rearrangement to furan 224.

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 ¹H 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.

![Scheme 115](image)

**Scheme 115:** Synthesis of epoxide 223a via a Darzen’s reaction (a) methylchloroacetate, NaOMe, Et₂O, 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. ¹H NMR analysis of the crude reaction mixture showed no evidence of aromatic protons.

![Scheme 116](image)

**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.
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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Equivalents</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TSA</td>
<td>0.15</td>
<td>100 °C</td>
<td>1.5 h</td>
<td>trace&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>p-TSA</td>
<td>0.15</td>
<td>rt</td>
<td>1.5 h</td>
<td>0 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>p-TSA</td>
<td>0.15</td>
<td>rt</td>
<td>78 h</td>
<td>trace&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CSA</td>
<td>0.15</td>
<td>80 °C</td>
<td>8 h</td>
<td>trace&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>p-TSA</td>
<td>0.15</td>
<td>100 °C (μw)</td>
<td>45 min</td>
<td>trace&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>BF₃·OEt₂</td>
<td>0.15</td>
<td>rt</td>
<td>72 h</td>
<td>0 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)₂</td>
<td>0.15</td>
<td>rt</td>
<td>24 h</td>
<td>0 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>NH₄Cl</td>
<td>0.10</td>
<td>rt</td>
<td>78 h</td>
<td>0 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 14: Rearrangement of epoxide 223a with acid catalysts. All reactions carried out in toluene. *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 NH₄Cl (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](image)

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.\textsuperscript{78}

\[
\begin{align*}
\text{Scheme 119: Synthesis of 3-substituted furan 226} & \quad (a) \quad \text{t-butylamine, DIC, DMAP, DCM, rt, 2 h, 40 \%}; \\
& \quad (b) \quad \text{s-BuLi, DME, $-78$ °C, 1 h then MeI, rt, 16 h, 79 \%}
\end{align*}
\]

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).
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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent and solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 % H$_2$SO$<em>4$$</em>{(aq)}$</td>
<td>reflux</td>
<td>21 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>2M HCl$_{(aq)}$</td>
<td>rt</td>
<td>45 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>2M LiOH$_{(aq)}$ / THF</td>
<td>rt</td>
<td>120 h</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>2M LiOH$_{(aq)}$ / THF</td>
<td>50 °C</td>
<td>120 h</td>
<td>SM</td>
</tr>
</tbody>
</table>

*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).
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.

![Scheme 123: Attempted hydrolysis of quaternary ammonium salt 230](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents/solvent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$O/MeCN</td>
<td>16 h</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$O/DMF</td>
<td>69 h</td>
</tr>
<tr>
<td>3</td>
<td>KOH/ H$_2$O</td>
<td>24 h</td>
</tr>
</tbody>
</table>

**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.
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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>3 x 1 min</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>2 x 1 min</td>
</tr>
</tbody>
</table>

**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

![Figure 12: Hinckdentine A](image)

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 Approach⁸⁰

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.

![Figure 13: Joule's retrosynthesis of hinckdentine A](image)
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.

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

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

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.
3.1.3 Cava’s Approach\textsuperscript{[52]}

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).

The indolo[1,2-c]quinazoline core 243 was produced \textit{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\textsubscript{N}2 displacement with a cyanide anion. Hydrolysis of the resulting nitrile 244 and amide formation \textit{via} the acyl chloride gave the required phenyl seleno compound 241 (Scheme 129).
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 129: Synthesis of 241 (a) HOAc, EtOH, 80 °C, 6 h, 88 %; (b) MeSO₃H, P₂O₅, 85 °C, 30 min, 90 %; (c) HCO₂H, 90 °C, 1 h, 73 %; (d) Me₂NH, HCOH, HOAc, rt, 3 h, 82 %; (e) Mel, PhH, rt, 12 h, 97 %; (f) NaCN, MeCN, H₂O, reflux, 5 h, 70 %; (g) HCl, dioxane, reflux, 90 h, 80 %; (h) (COCl)₂, MeCN, DMF, rt, 5 h; 96 %; (i) PhSeCH₂CH₂NH₂, pyridine, MeCN, rt, 3 h, 30 %

Scheme 130: Formation of undesired product 245 during attempted radical cyclisation (a) AIBN, Bu₃SnH, 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).
Once again, the radical cyclisation failed and only the ethyl amide 248 was isolated (Scheme 132).

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 131: Removal of the aromaticity of the pyrimidine ring (a) NaBH₄, MeOH, reflux, 10 h, 80 %; (b) Ac₂O, pyridine, 80 °C, 30 min, 90 %

Scheme 132: Formation of undesired product 248 during attempted radical cyclisation (a) AIBN, Bu₃SnH, PhMe, reflux, 1 h, 79 %

Scheme 133: Introduction of a carbonyl group α to the indole (a) NaBH₄, MeOH, reflux, 5 h, 80 %; (b) Ac₂O, pyridine, reflux, 5 h, 91 %; (c) (COCl)₂, Et₂O, 0 °C to rt, 2 h; (d) PhSeCH₂CH₂NH₂, Et₂O, rt, 12 h, 75 % over two steps
When 250 was treated with tributyl tin hydride and AlBN 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.

![Scheme 134: Formation of undesired product 251 during attempted radical cyclisation (a) AIBN, Bu$_3$SnH, PhMe, reflux, 4 h, 81 %](image)

3.1.4 McWhorter’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).

![Figure 16: McWhorter’s retrosynthesis of desbromohinckdentine A](image)

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) NaNO₂, HOAc, rt, 3 h, 97 %; (c) Na₂S₂O₄, NaOH, H₂O, EtOH, reflux, 24 h, 94 %; (d) PbO₂, 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 % HCO₂H, 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) Boc₂O, DMAP CH₃CN, rt, 17 h, 96 %; (b) O₂, MeOH, - 78 °C, then Me₂S, –78 °C to rt; (c) 2,4-dimethoxybenzylamine, HOAc, NaBH₃CN, MeOH/THF, rt, 16 h, 60 % over two steps; (d) Ac₂O, pyridine, 0 °C 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 diphenylmethylenone 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).

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.

3.1.5 Kawasaki’s synthesis of Hinckdentine A

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.

![Chemical structures](image-url)

**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).
Tert-butyl carbamate protection of the aniline, followed by silyl ether cleavage, mesylation and nucleophilic displacement by NaN₃ 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 hinckdentine A (233) in 4 % yield over 19 steps.
3.2 Retrosynthetic approach

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

![Figure 18: Retrosynthetic approach to Hinckdentine A](image)

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). 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.
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 \( \alpha,\beta \)-unsaturated amide 274. Stereoselective addition of \( \text{H}_2 \) 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.

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.
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, Et2O, rt, 1 h; (b) MeOH, rt 15 min; 73 % over two steps; (c) NaH, Boc₂O, rt 2 h, 77 %; (d) NaBH₄, MeOH, rt, 50 min, 65 %; (e) cyanoacetic acid, T₃P®, Et₃N, DCM, rt, 1 h, 90 %
Using T₃P® 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).

Unfortunately, when ester 282 was subjected to standard dCr conditions (Scheme 145) extensive decomposition occurred, with no identifiable products isolated. Analysis by ¹H 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.

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). 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-acyloxyoxcarboxamide.
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).

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 Boc₂O in pyridine (Table 18, entry 14).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsCl, KOH, NBu4I</td>
<td>PhMe/H2O</td>
<td>12 h</td>
<td>rt</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>TsCl, NaOH, NBu4Br</td>
<td>PhMe/H2O</td>
<td>12 h</td>
<td>rt</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>TsCl, NaOH, NBu4Br</td>
<td>PhH/H2O</td>
<td>5 h</td>
<td>rt</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>TsF, NaOH, NBu4Br</td>
<td>PhMe/H2O</td>
<td>24 h</td>
<td>rt</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>TsF, NaOH, NBu4Br</td>
<td>PhH/H2O</td>
<td>24 h</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>TsF, NaOH, NBu4Br</td>
<td>DCM/H2O</td>
<td>24 h</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>TsF, NaOH, NBu4Br</td>
<td>THF/H2O</td>
<td>24 h</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>TsCl, NaH</td>
<td>THF</td>
<td>12 h</td>
<td>rt</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>TsCl, NaH</td>
<td>THF</td>
<td>1 h</td>
<td>85 °C</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>TsCl, NaH</td>
<td>DMF</td>
<td>1 h</td>
<td>120 °C</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>TsF, NaH</td>
<td>DMF</td>
<td>72 h</td>
<td>100 °C</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Boc₂O, NaOH, NBu4Br</td>
<td>PhMe/H2O</td>
<td>30 min</td>
<td>rt</td>
<td>54</td>
</tr>
<tr>
<td>13</td>
<td>Boc₂O, NaOH, NBu4Br</td>
<td>PhH/H2O</td>
<td>30 min</td>
<td>rt</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>Boc₂O</td>
<td>pyridine</td>
<td>5 h</td>
<td>rt</td>
<td>93</td>
</tr>
</tbody>
</table>

**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).

![Scheme 149: Attempted Passerini reaction of aldehyde 286 (a) tBuNC, cyanoacetic acid, Cu(OTf)₂, DCM, -78 °C to 50 °C](image)
In 2005, Denmark et al. reported the Passerini-type reaction of isonitriles with aldehydes to give α-hydroxyamides (Scheme 150). 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) SiCl₄ (1 equiv), catalyst, DCM, –78 °C; (b) NaHCO₃ (aq), rt]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol %)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>-</td>
<td>83</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>HMPA</td>
<td>10</td>
<td>100</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>pyridine-N-oxide</td>
<td>10</td>
<td>100</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>chiral bisphosphoramid</td>
<td>5</td>
<td>100</td>
<td>83</td>
<td>90.2/9.8</td>
</tr>
</tbody>
</table>

Table 19: Denmark’s screening of Lewis Bases. R¹ = Ph, R² = 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)

![Scheme 151: Reaction of aldehyde 286 under Denmark's "interrupted-Passerini" conditions (a) t-BuNC, Lewis base (see Table 20), SiCl₄, –78 °C; (b) NaHCO₃ (aq), 2 h, rt]

83
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.

![Scheme 152: Esterification of alcohol 287 (a) cyanoacetic acid, see Table 21](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Base</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
<th>Yield brsm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HMPA</td>
<td>4</td>
<td>52</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>HMPA</td>
<td>5.5</td>
<td>29</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>pyridine-N-oxide</td>
<td>4</td>
<td>53</td>
<td>83</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T₃P®, Et₃N</td>
<td>DCM</td>
<td>24</td>
<td>27ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N, DMAP, 2,4,6-trichlorobenzoyl chloride</td>
<td>DCM</td>
<td>48</td>
<td>43ᵃ</td>
</tr>
<tr>
<td>3</td>
<td>TFAA</td>
<td>DCM</td>
<td>20</td>
<td>40ᵃ</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃, DIAD</td>
<td>THF</td>
<td>24</td>
<td>55ᵇ</td>
</tr>
<tr>
<td>5</td>
<td>PPh₃, DMEAD</td>
<td>THF</td>
<td>36</td>
<td>57ᵃ</td>
</tr>
</tbody>
</table>

**Table 21: Esterification of 287 with cyanoacetic acid.ᵃIsolated yield.ᵇFrom analysis of ¹H 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 carbamidine conditions (Scheme 153).\(^1\) 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.

![Chemical structure of benzylisonitrile](image)

**Scheme 153:** Attempted synthesis of benzylisonitrile under phase-transfer Hoffmann carbamidine conditions (a) NaOH, CHCl₃, Et₃NBnCl, H₂O/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).

![Chemical structure of benzylamine](image)

**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).\(^2\)

![Chemical structure of dehydration reaction](image)

**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.

![Chemical Structure](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>3</td>
<td>SM consumed – no isonitrile isolated</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>10</td>
<td>SM consumed – no isonitrile isolated</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>10</td>
<td>SM consumed – no isonitrile isolated</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>10</td>
<td>SM consumed – no isonitrile isolated</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>10</td>
<td>SM consumed – no isonitrile isolated</td>
</tr>
</tbody>
</table>

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

However, the use of POCl₃ and pyridine as dehydrating reagents successfully gave benzyl isonitrile 289 in 21 % yield (Scheme 157).

![Chemical Structure](image)

**Scheme 157:** Dehydration of formamide 289 with phosphorus oxychloride (a) POCl₃, 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).
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).

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).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temperature</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIC, DMAP</td>
<td>DCM</td>
<td>72</td>
<td>rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>DIC, DMAP</td>
<td>DCM</td>
<td>5</td>
<td>90 °C (μw)</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>TFAA</td>
<td>MeCN</td>
<td>67</td>
<td>rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>DIAD, PPh₃</td>
<td>THF</td>
<td>51</td>
<td>rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>DIAD, PPh₃</td>
<td>THF</td>
<td>51</td>
<td>rt</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

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 ¹H NMR analysis of the crude reaction mixture before addition of the carboxylate indicated that the mesylate had been formed.

![Scheme 161: Attempted synthesis of ester 292 via mesylate 293](image)

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).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Lewis Acid</th>
<th>Equivalents glyoxalate</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>294</th>
<th>295</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>BF₃·OEt₂</td>
<td>1.5</td>
<td>rt</td>
<td>19</td>
<td>-</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>Cu(OTf)₂</td>
<td>4</td>
<td>-78 °C</td>
<td>4</td>
<td>55</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>-</td>
<td>4</td>
<td>rt</td>
<td>3</td>
<td>73</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>-</td>
<td>1.5</td>
<td>rt</td>
<td>24</td>
<td>89</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>benzene</td>
<td>-</td>
<td>4</td>
<td>rt</td>
<td>3.5</td>
<td>92</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>benzene</td>
<td>-</td>
<td>1.5</td>
<td>rt</td>
<td>7.5</td>
<td>82</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Table 24: Friedel-Craft hydroxylalkylation 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).
The use of the highly oxophilic Lewis Acid BF$_3$·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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc₂O</td>
<td>pyridine</td>
<td>rt</td>
<td>8</td>
<td>intractable mixture</td>
</tr>
<tr>
<td>2</td>
<td>TsCl, NaH, DMAP</td>
<td>DMF</td>
<td>rt</td>
<td>15</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Boc₂O, NaH</td>
<td>DMF</td>
<td>rt</td>
<td>94</td>
<td>SM</td>
</tr>
</tbody>
</table>

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).

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.
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).

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMB</td>
<td>-</td>
<td>DCM</td>
<td>rt</td>
<td>24 h</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>-</td>
<td>benzene</td>
<td>90 °C</td>
<td>96 h</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>PMB</td>
<td>Cu(OTf)$_2$</td>
<td>benzene</td>
<td>90 °C</td>
<td>2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>TBDPS</td>
<td>-</td>
<td>DCM</td>
<td>rt</td>
<td>70 h</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>TBDPS</td>
<td>BF$_3$·OEt$_2$</td>
<td>DCM</td>
<td>rt</td>
<td>5 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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

Scheme 172: Undesired products formed during attempted esterification of alcohol 299 (a) cyanoacetic acid, DMAP, DIC, CH$_2$Cl$_2$, 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_N$1 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 $\delta_H = 3.56$ ppm corresponding to the CH$_2$ α to the nitrile (Figure 20).

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.
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.

![Scheme 176: Synthesis of the undesired ester 294 by alcoholysis of cyanohydrin 311 (a) TMSCN, ZnI$_2$, CH$_2$Cl$_2$, rt, 3.5 h; (b) EtOH, HCl, CH$_2$Cl$_2$, rt 15 h](image)

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. 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: Synthesis of cyanoacetyl chloride (a) PCl$_5$, Et$_2$O, rt, 2.5 h, 52 %](image)
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, did not react with 4-nitrobenzaldehyde (315) by a palladium catalysed Friedel-Crafts type reaction.
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).

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

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

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).

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

![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](image)

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.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature °C</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>15 x 1 min pulses</td>
<td>36 %</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>35 min</td>
<td>60 %</td>
</tr>
</tbody>
</table>

Table 27: Attempted dCr reaction of 324

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

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

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).

![Diagram](https://example.com/diagram.png)

**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).
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.

If an amine was used, then similar problems to those encountered in the Eschenmoser-Claisen pathway would have to be overcome.
Although ketene itself may be used in the Belluš-Claisen rearrangement, more commonly the highly electrophilic dichloroketene is used. 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 25: Proposed retrosynthesis of Hinckdentine model system via a Belluš-Claisen rearrangement of an amine

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).

![Scheme 190: Attempted synthesis of alcohol 345 (a) NaH, DMF, rt, 1 h; then Mel, rt, 1 h, 78 %; (b) NaBH₄, MeOH, rt, 1 h](image)

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 morpholine-based amine was chosen due to this being the most developed example in the literature. Initial attempts to synthesise amine 346 via a reductive amination pathway failed (Scheme 191, Table 28) with only the starting aldehyde 344 being returned.

![Scheme 191: Attempted synthesis of amine 346 via a reductive amination (a) morpholine, NaBH(OAc)₃, AcOH, see Table 28](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Equiv AcOH</th>
<th>Temp</th>
<th>Time (h)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>0.1</td>
<td>rt</td>
<td>48</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>0.1</td>
<td>rt</td>
<td>48</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0.5</td>
<td>rt</td>
<td>48</td>
<td>SM recovered</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0.5</td>
<td>reflux</td>
<td>24</td>
<td>SM recovered</td>
</tr>
</tbody>
</table>

*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 %](image)

Using conditions developed within 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 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).
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).

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS-OTf</td>
<td>Et’Pr₂N</td>
<td>DCM</td>
<td>rt</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>Et’Pr₂N</td>
<td>DCM</td>
<td>rt</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TMS-OTf</td>
<td>Et’Pr₂N</td>
<td>DCM</td>
<td>rt</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>TMS-OTf</td>
<td>Et’Pr₂N</td>
<td>DCM</td>
<td>−78 °C</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>TMS-OTf</td>
<td>Et₃N</td>
<td>DCM</td>
<td>−78 °C</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>TMS-OTf</td>
<td>Et₃N</td>
<td>PhMe</td>
<td>−78 °C</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>TMS-OTf</td>
<td>Et₃N</td>
<td>PhMe</td>
<td>rt</td>
<td>120</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>TMS-OTf</td>
<td>Et₃N</td>
<td>MeCN</td>
<td>−78 °C</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 29: Conditions for dichloroketene insertion

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

Scheme 195: Formation of the formal [1,3]-rearrangement product 354 (a) morpholine, formaldehyde (37 % aq), ZnCl₂, 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).

![Scheme 196: Attempted synthesis of amine 356 via a reductive amination](image)

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 CDCl₃ in the presence of either deuterated-TFA.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reductant</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>Na(OAc)₂BH</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>Na(OAc)₂BH</td>
<td>DCM</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CF₃CO₂D</td>
<td>-</td>
<td>CDCl₃</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4 Å MS</td>
<td>-</td>
<td>CDCl₃</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 30: Screening of conditions for reductive amination of 355
(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).

\[ \text{Scheme 197: Reduction of aldehyde 355} \quad \text{(a) NaBH}_4, \text{MeOH, rt, 1 h, 98 \%} \]

$^1$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.

\[ \text{Scheme 198: Attempted Appel reaction of alcohol 357 to give iodide 358} \quad \text{(a) I}_2, \text{PPh}_3, \text{imidazole, DCM, rt, 17 h} \]

Attempts to displace an in situ formed tosylate also proved unsuccessful. 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).

\[ \text{Scheme 199: Attempted synthesis of amine 356 via displacement of a tosylate} \quad \text{(a) NaH, THF, rt, 1 h; then TsCl, rt, 1 h;} \]
\[ \text{(b) morpholine} \]

112
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-Claisen rearrangement when treated with dimethylacetamide dimethylacetal under microwave conditions (Scheme 200). As with the related dCr reaction of indoles published previously, only the exocyclic alkene was observed, with no evidence for the isomerised indole 360.

![Scheme 200: Eschenmoser-Claisen rearrangement of alcohol 357](image)

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).

![Scheme 201: Eschenmoser-Claisen rearrangement of alcohol 362](image)

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.

![Scheme 202: Eschenmoser-Claisen rearrangement of alcohol 328](image)
With these promising results in hand attention was turned to the incorporation of the benzylic side chain required for the synthesis of hinchdentine A. Indole underwent Friedel-Crafts acylation with oxalyl chloride followed by quenching with methanol and protection as the tert-butyl carbamate (Scheme 203).

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 Boc₂O, 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)

Scheme 204: Reduction of α-keto ester 367 (a) NaBH₄, rt, see Table 31

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv NaBH₄</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>α-hydroxy ester 368</th>
<th>diol 369</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>MeOH</td>
<td>45</td>
<td>41</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>THF</td>
<td>30</td>
<td>99</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>MeOH</td>
<td>90</td>
<td>-</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>

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.
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).

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)

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).

\[
\begin{align*}
\text{355} & \xrightarrow{a} \text{R} = \text{Me} - 374 \\
& \quad \text{R} = \text{iPr} - 376 \\
& \quad \text{R} = \text{Ph} - 378
\end{align*}
\]

**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,

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield addition (%)</th>
<th>Yield rearrangement (%)</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>96</td>
<td>76</td>
<td>5.2 : 1</td>
</tr>
<tr>
<td>2</td>
<td>iPr</td>
<td>80</td>
<td>76</td>
<td>4.1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>91</td>
<td>46</td>
<td>1.3 : 1</td>
</tr>
</tbody>
</table>

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

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 (R² ≠ 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).
Scheme 209: Johnson-Claisen rearrangement of alcohol 362 (a) trimethylorthoacetate, catalyst, toluene, μw, see Table 33

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Equiv. ortho ester</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>Additive</th>
<th>Equiv</th>
<th>Consumption of SM (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>0 %</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>EtCO(_2)H</td>
<td>0.1</td>
<td>42 %</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>6</td>
<td>3600</td>
<td>rt</td>
<td>EtCO(_2)H</td>
<td>0.1</td>
<td>0 %</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>(p)-NO(_2)-phenol</td>
<td>0.1</td>
<td>42 %</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>LiCl</td>
<td>0.1</td>
<td>0 %</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>AlCl(_3)</td>
<td>0.1</td>
<td>11 %</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>BF(_3)-OEt(_2)</td>
<td>0.1</td>
<td>decomp</td>
</tr>
<tr>
<td>8</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>(o)-l-benzoic acid</td>
<td>0.1</td>
<td>0 %</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>20</td>
<td>30</td>
<td>150</td>
<td>(p)-NO(_2)-phenol</td>
<td>0.1</td>
<td>42 %</td>
</tr>
<tr>
<td>10</td>
<td>PhMe</td>
<td>6</td>
<td>30</td>
<td>150</td>
<td>(p)-NO(_2)-phenol</td>
<td>0.5</td>
<td>decomp</td>
</tr>
<tr>
<td>11</td>
<td>PhMe</td>
<td>6</td>
<td>60</td>
<td>150</td>
<td>(p)-NO(_2)-phenol</td>
<td>0.1</td>
<td>46 %</td>
</tr>
<tr>
<td>12</td>
<td>PhMe</td>
<td>6</td>
<td>240</td>
<td>170</td>
<td>(p)-NO(_2)-phenol</td>
<td>0.1</td>
<td>85 %</td>
</tr>
<tr>
<td>13</td>
<td>PhMe</td>
<td>6</td>
<td>210</td>
<td>200</td>
<td>(p)-NO(_2)-phenol</td>
<td>0.1</td>
<td>100 %</td>
</tr>
</tbody>
</table>

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).

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

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 H₂O) 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 AlCl₃ 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 ¹H 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.
3.3.14 - Synthesis of alternative dimethyl acetics

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).

The standard method of forming dimethyl acetals of acetamides involves treatment with an electrophilic methylating agent, followed by treatment with methoxide. The initial 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.
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).

Amide bond formation with acrylic acid and T₃P® 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).
A ring-closing metathesis of 395 was then attempted (Scheme 216, Table 34)

![Figure 31: The alkene region of VT $^1$H NMR studies on amide 395, in d$_6$-DMSO, showing the presence of two rotamers](image-url)

Scheme 216: Attempted ring closing metathesis of diene 395 (a) see Table 34
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Equivalents</th>
<th>Concentration</th>
<th>Temp</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs II</td>
<td>0.05</td>
<td>0.02 M</td>
<td>100 °C</td>
<td>1 h</td>
<td>SM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120 °C</td>
<td>2 h</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II</td>
<td>0.05</td>
<td>0.1 M</td>
<td>100 °C</td>
<td>1 h</td>
<td>SM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120 °C</td>
<td>2 h</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Grubbs II</td>
<td>1</td>
<td>0.1 M</td>
<td>120 °C</td>
<td>90 min</td>
<td>decomp</td>
</tr>
<tr>
<td>4</td>
<td>Hoveyda-Grubbs II</td>
<td>0.2</td>
<td>0.1 M</td>
<td>100 °C</td>
<td>1 h</td>
<td>decomp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120 °C</td>
<td>2 h</td>
<td></td>
</tr>
</tbody>
</table>

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.
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. 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 217: Synthesis of diene 399 (a) DIBAL, THF, −78 °C, 1.5 h, 69 %; (b) benzylamine, K₂CO₃, 4 Å MS, benzene, rt, 16 h; (c) NaBH₄, EtOH, rt, 2 h, 73 % over two steps; (d) (a) acrylic acid, T₃P®, Et₃N, DCM, rt, 2 h 90 %

Scheme 218: Attempted ring closing metathesis of diene 399 (a) Grubbs II, Ti(OiPr)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).
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 $\varepsilon$-isomer of 373 as the major product.

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).
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. 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 F254 0.25 mm precoated aluminium plates. Product spots are visualised under UV light (λ_{max} = 254 nm) 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.

Nuclear Magnetic Resonance
^1H 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 multiplet (m). Coupling constants (J) are measured to the nearest 0.5 Hz and are presented as observed. ^13C 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 ^79Br isotope. Compounds containing chlorine are given for the ^35Cl 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.
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 Et2O, washed with saturated NaHCO3 (aq) and saturated NaCl (aq), dried over MgSO4 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, CDCl3) δH 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, CDCl3) δC 190.2 (C6), 152.7 (C2), 146.1 (C5), 116.6 (C3), 112.1 (C4), 31.7 (C7), 8.0 (C8)

νmax (thin film)/cm$^{-1}$ 1673 (C=O)

El-MS calcd for C7H8O2 [M]$^+$ 124.0524; found 124.0526

These data are in accordance with the literature.75
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 H₂O. The reaction was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

\[
\begin{align*}
\text{H NMR} & \ (400 \text{ MHz, CDCl}_3) \ \delta_H \ 7.37 \ (1\text{H, d, } J = 1.0 \text{ Hz, H₅}), \ 6.34 - 6.33 \ (1\text{H, m, H₄}), \ 6.23 \ (1\text{H, d, } J = 3.5 \text{ Hz, H₃}), \\
& \ 4.59 \ (1\text{H, t, } J = 7.0 \text{ Hz, H₆}), \ 2.37 - 2.34 \ (1\text{H, m, OH}), \ 1.93 - 1.81 \ (2\text{H, m, H₇}), \ 0.95 \ (3\text{H, t, } J = 7.5 \text{ Hz, H₈})
\end{align*}
\]

\[
\begin{align*}
\text{C NMR} & \ (101 \text{ MHz, CDCl}_3) \ \delta_C \ 156.7 \ (\text{C₂}), \ 141.8 \ (\text{C₅}), \ 110.1 \ (\text{C₄}), \ 105.9 \ (\text{C₃}), \ 69.2 \ (\text{C₆}), \ 28.6 \ (\text{C₇}), \ 9.9 \ (\text{C₈})
\end{align*}
\]

\[\nu_{\text{max}} \ (\text{thin film}) / \text{cm}^{-1} 3364 \ (\text{O-H})\]

EI-MS Calcd for C₇H₁₀O₂ [M]+ 126.0681; found 126.0679

These data are in accordance with the literature.
Methyl tosylacetate (187)

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 MgSO₄ 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.

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3) \delta \_7.74 (2\text{H}, \text{d, } J = 8.5 \text{ Hz, H5 and H9}), 7.30 (2\text{H}, \text{d, } J = 8.5 \text{ Hz, H6 and H8}) 4.06 (2\text{H}, \text{s, H3}), 3.61 (3\text{H}, \text{s, H1}), 2.37 (3\text{H}, \text{s, H10})\]

\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3) \delta_C 162.9 (C2), 145.3 (C7), 135.6 (C4), 129.7 (C6 and C8), 128.3 (C5 and C9), 60.7 (C3), 52.9 (C1), 21.5 (C10)\]

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

ES-MS calcd for C\(_{10}\)H\(_{12}\)O\(_4\)S [M-H] 227.0378; found 227.0385

These data are in accordance with the literature.
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 H₂O (550 mL) at rt. The reaction mixture was stirred at rt for 48 h, diluted with Et₂O and the phases separated. The aqueous layer was acidified to pH 1 by addition of HCl (36 %) and extracted three times with Et₂O. The combined organic layers from the second washing were dried over MgSO₄ and concentrated under reduced pressure. Recrystallization from DCM gave acid 188 (10.0 g, 86 % yield) as a white crystalline solid.

¹H NMR (400 MHz, DMSO) δH 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).

¹³C NMR (101 MHz, DMSO) δC 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).

νmax (neat)/cm⁻¹ 2954 (O-H), 1714 (C=O) 1320, 1156 (O=S=O)

ES-MS calcd for C₉H₁₀O₄S [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 H₂O, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether with 1 % Et₃N) gave ester 189 (928 mg, 70 % yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νₘₐₓ (thin film)/cm⁻¹ 1736 (C=O), 1325, 1147 (O=S=O)

ES-MS calcd for C₁₆H₁₈O₅S [M+MeCN+Na]⁺ 386.1038; found 386.1047
1-(Furan-2-yl)-2-methylpropan-1-one (190)\(^\text{75}\)

![Structural formula of 1-(Furan-2-yl)-2-methylpropan-1-one (190)](image)

To neat furan (5.10 mL, 70.0 mmol, 10 equiv) at 0 °C was added \(\text{^6}\)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 \(\text{Et}_2\text{O}\), washed with saturated \(\text{NaHCO}_3\) \text{(aq)} and saturated \(\text{NaCl}\) \text{(aq)}, dried over \(\text{MgSO}_4\) 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) C 193.6 (C6), 152.1 (C2), 146.2 (C5), 117.1 (C3), 112.1 (C4), 36.2 (C7), 18.7 (C8 and C9)

\(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 1668 (C=O)

Cl-MS calcd for \(\text{C}_8\text{H}_{10}\text{O}_2\) [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 H₂O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl (aq) dried over MgSO₄ 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, CDCl₃) 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, CDCl₃) 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)

\(\nu_{\text{max}}\) (thin film) cm\(^{-1}\) 3389 (O-H)

EI-MS calcd for C₈H₁₂O₂ [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 MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography gave ester 192 (504 mg, 84 % yield) as a pale yellow oil.

\[ \text{H NMR (400 MHz, CDCl}_3) \delta_h 7.75 (2H, d, J = 8.0 Hz, H12 and H16), 7.39 (1H, d, J = 1.0 Hz, H5), 7.33 (2H, d, J = 8.0 Hz, H13 and H15), 6.35 – 6.34 (1H, m, H4), 6.32 (1H, d, J = 3.0 Hz, H3), 5.52 (1H, d, J = 8.5 Hz, H6), 4.12 (2H, s, H10), 2.46 (3H, s, H17), 2.35 – 2.26 (1H, m, H7), \{0.97 (3H, d, J = 6.5 Hz), 0.83 (3H, d, J = 6.5 Hz)\} (H8 and H9) \]

\[ \text{C NMR (101 MHz, CDCl}_3) \delta_c 161.9 (C9), 151.0 (C2), 145.3 (C14), 142.5 (C5), 135.6 (C11), 129.8 (C13 and C15), 128.5 (C12 and C16), 110.2 (C4), 109.7 (C3), 76.0 (C6), 61.0 (C10), 31.0 (C7), 21.7 (C17), \{18.6, 18.4\} (H8 and H9) \]

\[ \nu_{max} \text{ (thin film)} / \text{cm}^{-1} 1739 (C=O), 1329, 1152 (O=S=O) \]

ES-MS calcd for C₁₇H₂₀O₅S [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 Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether with 1 % Et₃N) 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)

¹H NMR (400 MHz, CDCl₃) 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)

¹³C NMR (101 MHz, CDCl₃) 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

v_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)

![Chemical structure](image)

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 Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (10 % EtOAc in petroleum ether with 1 % Et₃N) 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).

**¹H NMR (400 MHz, CDCl₃)** 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)

**¹³C NMR (101 MHz, CDCl₃)** 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)

v_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$_2$O, 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$_3$) $\delta$ 7.66 (2H, d, $J$ = 8.5 Hz, H$_{11}$ and H$_{15}$), 7.30 (2H, d, $J$ = 8.5 Hz, H$_{12}$ and H$_{14}$), 7.27 (1H, d, $J$ = 1.5 Hz, H$_5$), 6.25 (1H, d, $J$ = 1.5 Hz, H$_4$), (4.21 (1H, d, $J$ = 14.5 Hz), 4.15 (1H, d, $J$ = 14.5 Hz) (AB system, H$_9$)), 2.68 – 2.60 (1H, m, H$_6$), 2.50 – 2.45 (1H, m, H$_{17A}$), 2.44 (3H, s, H$_{16}$), 2.24 – 2.19 (1H, m, H$_{17B}$), 2.16 (6H, s, H$_{18}$ and H$_{18'}$), 1.68 – 1.58 (1H, m, H$_{7A}$), 1.48 – 1.36 (1H, m, H$_{7B}$), 0.64 (3H, t, $J$ = 7.5 Hz, H$_8$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta_c$ 156.4 (C$_2$), 144.7 (C$_{13}$), 141.0 (C$_5$), 135.3 (C$_{10}$), 129.7 (C$_{12}$ and C$_{14}$), 128.7 (C$_{11}$ and C$_{15}$), 111.8 (C$_4$), 108.3 (C$_3$), 62.4 (C$_{17}$), 53.6 (C$_9$), 45.6 (C$_{18}$ and C$_{18'}$), 37.0 (C$_6$), 24.8 (C$_7$), 21.6 (C$_{16}$), 11.6 (C$_8$)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1316, 1143 (O=S=O)

ES-MS calcd for C$_{18}$H$_{25}$NO$_3$S [M+H]$^+$ 336.1633; found 336.1632
(±)-5-(3-(Tosylethyl)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 ZnCl₂ (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.

¹H NMR (400 MHz, CDCl₃) δ  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)

¹³C NMR (101 MHz, CDCl₃) δ  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 C₁₉H₂₄O₄S [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$_2$S$_2$O$_3$ (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, H$_{11}$ and H$_{15}$), 7.30 (2H, d, $J$ = 8.5 Hz, H$_{12}$ and H$_{14}$), 7.25 (1H, d, $J$ = 2.0 Hz, H$_5$), 6.23 (1H, d, $J$ = 2.0 Hz, H$_4$), 4.11 (2H, s, H$_9$), 2.44 (3H, s, H$_{16}$), 2.21 (2H, t, $J$ = 7.5 Hz, H$_6$), 1.40 (2H, sex., $J$ = 7.5 Hz, H$_7$), 0.80 (3H, t, $J$ = 7.5 Hz, H$_8$)

$^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 155.8 (C$_2$), 144.7 (C$_{13}$), 140.7 (C$_5$), 135.1 (C$_{10}$), 129.6 (C$_{12}$ and C$_{14}$), 128.7 (C$_{11}$ and C$_{15}$), 111.9 (C$_4$), 107.1 (C$_3$), 53.7 (C$_9$), 27.5 (C$_6$), 21.6 (C$_{16}$), 21.2 (C$_7$), 13.7 (C$_8$)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1316, 1139 (O=S=O)

EI-MS calcd for C$_{15}$H$_{16}$O$_3$S [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 $^7.65$ (2H, d, $J = 8.0$ Hz, H$_{11}$ and H$_{15}$), 7.32 (2H, d, $J = 8.0$ Hz, H$_{12}$ and H$_{14}$), 7.27 (1H, d, $J = 1.5$ Hz, H$_{5}$), 5.99 (1H, d, $J = 1.5$ Hz, H$_{4}$), 4.60 (1H, t, $J = 6.5$ Hz, H$_6$), {4.31 (1H, d, $J = 14.0$ Hz), 4.26 (1H, d, 14.0 Hz)}(AB system, H$_9$), 2.45 (3H, s, H$_{16}$), 1.92-1.80 (2H, m, H$_7$), 0.89 (3H, t, $J = 7.5$ Hz, H$_8$)

$^{13}$C NMR (101 MHz, CDCl$_3$) δ C$_{156.3}$ (C$_2$), 145.1 (C$_{13}$), 141.4 (C$_5$), 135.0 (C$_{10}$), 129.8 (C$_{12}$ and C$_{14}$), 128.6 (C$_{11}$ and C$_{15}$), 112.6 (C$_4$), 108.3 (C$_3$), 68.1 (C$_6$), 53.4 (C$_9$), 27.8 (C$_7$), 21.7 (C$_{16}$), 9.8 (C$_8$)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3502 (O-H), 1319, 1145 (O=S=O)

ES-MS calcd for C$_{15}$H$_{18}$O$_4$S [M+Na]$^+$ 317.0818; found 317.0813
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 H₂O, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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 C₁₉H₂₇NO₃S [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 H₂O, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δ 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).

νmax (thin film)/cm⁻¹ 1710 (C=O), 1312, 1139 (O=S=O)

ES-MS calcd for C₂₀H₂₆O₄S [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 H₂O, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (20 % EtOAc in petroleum ether with 1 % Et₃N) gave ester 201 (123 mg, 80 % yield) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹ 1744 (C=O)

EI-MS calcd for C₁₀H₁₁NO₃ [M]+ 193.0739; found 193.0746
(E) and (Z)-2-(2-Propylidene-2,3-dihydrofuran-3-yl)acetonitrile (202)

To a microwave vial containing 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 Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (8 % EtOAc in petroleum ether with 1 % Et₃N) 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).

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (101 MHz, CDCl₃) 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 C₉H₁₁NO [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 NaHCO₃ (aq), saturated NaCl (aq), dried over MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (2% EtOAc in petroleum ether with 1 % Et₃N) gave ester 203 (315 mg, 85 % yield) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ: 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)

¹³C NMR (101 MHz, CDCl₃) δ: 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)

¹⁹F NMR (377 MHz, CDCl₃) δ: −63.5

νₘₐₓ (thin film)/cm⁻¹ 1750 (C=O)

A mass ion could not be generated for this compound by either Cl or ES
(±)-Furan-2-yl(phenyl)methanol (204)\textsuperscript{104}

![Chemical Structure]

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\(_4\)Cl (aq) and extracted three times with Et\(_2\)O. 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\(_3\) ) \(\delta\) 7.48 – 7.45 (2H, m, H\(_8\) and H\(_{12}\)), 7.43 – 7.34 (4H, m, H\(_5\), H\(_9\), H\(_{10}\) and H\(_{11}\)), 6.36 – 6.34 (1H, m, H\(_4\)), 6.15 (1H, d, \(J = 3.0\) Hz, H\(_3\)), 5.83 (1H, d, \(J = 4.5\) Hz, H\(_6\)), 2.81 (1H, d, \(J = 4.5\) Hz, OH)

\(^{13}\)C NMR (101 MHz, CDCl\(_3\) ) \(\delta\) C 156.0 (C\(_2\)), 142.6 (C\(_5\) ), 140.9 (C\(_7\) ), 128.5 (C\(_9\) and C\(_{11}\) ), 128.1 (C\(_{10}\) ), 126.7 (C\(_8\) and C\(_{12}\) ), 110.3 (C\(_4\) ), 107.5 (C\(_3\) ), 70.1 (C\(_6\) )

\(\nu_{\text{max}}\) (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.\textsuperscript{104}
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 NH₄Cl (aq) and extracted three times with Et₂O. The combined organic layers were washed with saturated NaCl (aq) dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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).

¹³C NMR (101 MHz, CDCl₃) δ 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=NO=O)

Cl-MS calcd for C₁₁H₉NO₄ [M-OH]⁺ 202.0504; found 202.0500

These data are in accordance with the literature.
(±)-Furan-2-yl(4-nitrophenyl)methyl 2-tosylacetate (207)

![Chemical Structure](image)

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 H₂O, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δ 161.4 (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 C₂₀H₁₇NO₇S [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 NH₄Cl (aq) and extracted three times with Et₂O. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹ 3405 (OH); 2231 (C≡N)

ES-MS calcd for C₁₂H₉NO₂ [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, H$_9$, H$_{11}$, H$_{16}$ and H$_{20}$), 7.53 (2H, d, J = 8.5 Hz, H$_8$ and H$_{12}$), 7.43 – 7.42 (1H, m, H$_5$), 7.29 (2H, d, J = 7.5 Hz, H$_{17}$ and H$_{19}$), 6.86 (1H, s, H$_6$), 6.38 – 6.37 (1H, m, H$_4$), 6.28 (1H, d, J = 3.5 Hz, H$_3$), {4.22 (1H, d, J = 14.0 Hz), 4.17 (1H, d, J = 14.0 Hz) (AB system, H$_{14}$)}, 2.46 (3H, s, H$_{21}$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 161.4 (C$_{13}$), 149.6 (C$_2$), 145.6 (C$_{18}$), 144.0 (C$_5$), 141.1 (C$_7$), 135.5 (C$_{15}$), 132.4 (C$_9$ and C$_{11}$), 129.9 (C$_{17}$ and C$_{19}$), 128.5 (C$_{16}$ and C$_{20}$), 127.9 (C$_8$ and C$_{12}$), 118.4 (C$_{14}$), 112.6 (C$_{10}$), 111.2 (C$_3$), 110.6 (C$_4$), 71.4 (C$_6$), 60.9 (C$_{14}$), 21.8 (C$_{21}$).

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2230 (C=O), 1744 (C=O), 1326, 1148 (O=S=O)

ES-MS calcd for C$_{21}$H$_{17}$NO$_5$S [M-H]$^-$ 394.0749; found 394.0744
4-((3-(Tosylmethyl)furan-2-yl)methyl)benzonitrile (211)

To a microwave vial containing ester 209 (77 mg, 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 Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in petroleum ether with 1 % Et₃N) gave furan 211 (41 mg, 60 % yield) as a white solid.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹ 2257 (C≡N), 1315, 1141 (O=S=O)

ES-MS calcd for C₂₀H₂₁NO₃S [M+MeCN+H]⁺ 393.1273; found 393.1282
1-(5-Bromofuran-2-yl)ethanone (212)\textsuperscript{106}

![Chemical structure of 1-(5-Bromofuran-2-yl)ethanone (212)](image)

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.

\[^1H\text{ NMR (400 MHz, CDCl}_3\text{)}\, \delta_H\, 7.13\, (1H, d, J = 3.5\, Hz, \text{H}3),\, 6.50\, (1H, d, J = 3.5\, Hz, \text{H}4),\, 2.47\, (3H, s, \text{H}7)\]

\[^13C\text{ NMR (101 MHz, CDCl}_3\text{)}\, \delta_C\, 185.5\, (\text{C}6),\, 154.5\, (\text{C}2),\, 128.2\, (\text{C}5),\, 119.0\, (\text{C}3),\, 114.4\, (\text{C}4),\, 25.8\, (\text{C}7)\]

\(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 1656 (\(\text{C=O}\))

EI-MS calcd for \(C_6H_5BrO_2\, [M]^+\) 187.9473; found 187.9464

These data are in accordance with the literature.\textsuperscript{106}
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 H₂O (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 NaHCO₃ (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) 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)

¹³C NMR (101 MHz, CDCl₃) 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 C₁₂H₁₀O₂ [M+H]⁺ 187.0759; found 187.0755

These data are in accordance with the literature.¹⁰⁷
(±)-1-(5-Phenylfuran-2-yl)ethanol (214)\textsuperscript{107}

![Chemical structure](image)

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 then quenched with H\textsubscript{2}O. The resulting solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO\textsubscript{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.

\[ \textsuperscript{1}H \text{ NMR (400 MHz, CDCl}\textsubscript{3}) \] \( \delta \) 7.71 – 7.69 (2H, m, H\textsubscript{9} and H\textsubscript{13}), 7.43 – 7.39 (2H, m, H\textsubscript{10} and H\textsubscript{12}), 7.31 – 7.26 (1H, m, H\textsubscript{11}), 6.61 (1H, d, J = 3.5 Hz, H\textsubscript{4}), 6.34 (1H, d, J = 3.5 Hz, H\textsubscript{3}), 4.96 (1H, q, J = 6.5 Hz, H\textsubscript{6}), 2.41 (1H, s, OH), 1.62 (3H, d, J = 6.5 Hz, H\textsubscript{7})

\[ \textsuperscript{13}C \text{ NMR (101 MHz, CDCl}\textsubscript{3}) \] \( \delta \)C 157.3 (C\textsubscript{2}), 153.3 (C\textsubscript{5}), 130.8 (C\textsubscript{8}), 128.7 (C\textsubscript{10} and C\textsubscript{12}), 127.4 (C\textsubscript{11}), 123.7 (C\textsubscript{9} and C\textsubscript{13}), 107.3 (C\textsubscript{3}), 105.6 (C\textsubscript{4}), 63.8 (C\textsubscript{6}), 21.4 (C\textsubscript{7})

\( \nu_{\text{max}} \text{ (thin film)/cm}^{-1} \) 3347 (OH)

ES-MS calcd for C\textsubscript{12}H\textsubscript{12}O\textsubscript{2} [M-OH]\textsuperscript{+} 171.0810; found 171.0806

These data are in accordance with the literature.\textsuperscript{107}
To a solution of bromofuran 212 (300 mg, 1.59 mmol, 1.0 equiv) in toluene (3 mL) and H₂O (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 NaHCO₃ (aq), dried over MgSO₄ 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.

^1H NMR (400 MHz, CDCl₃) δ 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)

^13C NMR (101 MHz, CDCl₃) δc 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 C₁₂H₉NO₄ [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 H₂O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) 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)

¹³C NMR (101 MHz, CDCl₃) 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)

νₘₐₓ (thin film)/cm⁻¹ 3369 (OH), 1524, 1348 (O=N=O)

Cl-MS calcd for C₁₁H₁₁NO₄ [M-OH]⁺ 216.0661; found 216.0663

162
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 H₂O, dried over MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % EtOAc in petroleum ether with 1 % Et₃N) gave ester 218 (93 mg, 89 % yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹: 1738 (C=O), 1524, 1349 (O=N=O), 1326, 1150 (O=S=O)

ES-MS calcd for C₂₁H₁₉NO₇S [M+Na]⁺ 452.0780; found 452.0776
**N-Tert-butylfuran-2-carboxamide (225)**

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 NH₄Cl (aq), dried over MgSO₄ and concentrated. Purification by silica gel chromatography (20 % EtOAc in petroleum ether) gave amide 225 (1.41 g, 40 % yield) as a white solid.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta_H 7.36 - 7.35 (1H, m, H5), 7.01 (1H, d, J = 3.5 Hz, H3), 6.43 (1H, dd, J = 3.5, 4.0 Hz, H5), 6.19 (1H, br. s, NH), 1.42 (9H, s, H8) \]

\[ ^13C \text{ NMR (101 MHz, CDCl}_3) \delta_C 157.8 (C6), 148.8 (C2), 143.3 (C5), 113.4 (C3), 112.0 (C4), 51.4 (C7), 28.9 (C8) \]

\[ \nu_{\text{max}} \text{ (thin film)/cm}^{-1} 3298 (\text{N-H}); 1640 (\text{C=O}) \]

Cl-MS calcd for C₉H₁₃NO₂ [M+H]+ 168.1025; found 168.1020

These data are in accordance with the literature.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 n-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 reduced pressure and the residue was re-dissolved in EtOAc. This was washed with H₂O and saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) 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’’)

¹³C NMR (101 MHz, CDCl₃) 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 C₁₁H₁₇NO₂ [M+H]+ 196.1338; found 196.1329

These data are in accordance with the literature.⁷⁸
\[ N,2\text{-Dimethyl-}N\text{-}((3\text{-methylfuran-2-yl})\text{methyl})\text{propan-2-amine (229)} \] and
\[ N,N,2\text{-Trimethyl-}N\text{-}((3\text{-methylfuran-2-yl})\text{methyl})\text{propan-2-aminium iodide (230)} \]

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 \( \text{KNaC}_4\text{H}_4\text{O}_6 \) (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 \( \text{NaCl} \) (aq), dried over \( \text{MgSO}_4 \) 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.

\(^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \( \delta\) 7.30 (1H, d, \( J = 2.0 \text{ Hz, H5} \)), 6.19 (1H, d, \( J = 2.0 \text{ Hz, H4} \)), 3.51 (2H, s, \( \text{H6} \)), 2.19 (3H, s, \( \text{H9} \)), 2.04 (3H, s, \( \text{H10} \)), 1.17 (9H, s, \( \text{H8}, \text{H8'} \) and \( \text{H8''} \))

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.

\(^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \( \delta\) 7.45 (1H, d, \( J = 2.0 \text{ Hz, H5} \)), 6.36 (1H, d, \( J = 2.0 \text{ Hz, H4} \)), 4.56 (2H, s, \( \text{H6} \)), 3.12 (6H, s, \( \text{H9} \) and \( \text{H9'} \)), 2.27 (3H, s, \( \text{H10} \)), 1.67 (9H, s, \( \text{H8}, \text{H8'} \) and \( \text{H8''} \))
(±)-Furan-3-yl(phenyl)methanol (231)\textsuperscript{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\textsubscript{2}O, 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 NH\textsubscript{4}Cl (aq) and extracted three times with Et\textsubscript{2}O. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO\textsubscript{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.

\textsuperscript{1}H NMR (101 MHz, CDCl\textsubscript{3}) δ \text{H} 7.44 – 7.37 (5H, m, H\textsubscript{5}, H\textsubscript{8}, H\textsubscript{9}, H\textsubscript{11} and H\textsubscript{12}), 7.36 – 7.31 (2H, m, H\textsubscript{2} and H\textsubscript{10}), 6.36 – 6.35 (1H, m, H\textsubscript{4}), 5.76 (1H, s, H\textsubscript{6}), 2.51 (1H, br.s, OH)

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ \text{C} 143.5 (C\textsubscript{5}), 143.1 (C\textsubscript{7}), 139.8 (C\textsubscript{2}), 129.0 (C\textsubscript{3}), 128.5 (C\textsubscript{8} and C\textsubscript{12}), 127.9 (C\textsubscript{10}), 126.4 (C\textsubscript{9} and C\textsubscript{11}), 109.3 (C\textsubscript{4}), 69.5 (C\textsubscript{6})

ν\textsubscript{max} (thin film)/cm\textsuperscript{-1} 3353 (OH)

EI-MS calcd for C\textsubscript{11}H\textsubscript{10}O\textsubscript{2} [M]\textsuperscript{+} 174.0681; found 174.0675

These data are in accordance with the literature.\textsuperscript{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 H₂O, dried over MgSO₄ 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.

1H NMR (400 MHz, CDCl₃) 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)

13C NMR (101 MHz, CDCl₃) 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 C₂₀H₁₈O₅S [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 Et₂O (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 NaHCO₃ [aq]. The aqueous layer was re-extracted with DCM and the combined organic layers were dried over MgSO₄ 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.

¹H NMR (400 MHz, (CD₃)₂CO) δH 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)

¹³C NMR (101 MHz, (CD₃)₂CO) δC 182.7 (C₁₄), 165.2 (C₁₅), 148.6 (C₂), 136.1 (C₇a), 131.1 (C₈), 129.9 (C₇a), 136.1 (C₈), 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)

νmax (thin film)/cm⁻¹ 3237 (N-H), 1738 (C=O ester), 1610 (C=O ketone)

ES-MS calcd for C₁₇H₁₃NO₃ [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 1 h. 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 H₂O and the phases separated. The aqueous layer was extracted with Et₂O and the combined organic layers were washed with NH₄OH (3 % NH₃), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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’’)

¹³C NMR (101 MHz, CDCl₃) δ 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’’)

νmax (thin film)/cm⁻¹ 1740 (C=O ester and carbamate), 1647 (C=O ketone)

ES-MS calcd for C₂₂H₂₁NO₅[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 NH₄Cl (aq) and extracted with Et₂O. The combined organic layers were washed with water, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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’’)

¹³C NMR (101 MHz, CDCl₃) δc 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’’)

νₘₐₓ (thin film)/cm⁻¹ 3474 (O-H), 1729 (C=O)

ES-MS calcd for C₂₂H₂₂NO₅ [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 NaHCO₃ (aq) and extracted with EtOAc. The organic layers were washed with saturated NaHCO₃ (aq), H₂O and brine, dried over MgSO₄ and concentrated under reduced pressure to give ester 282 (1.11 g, 90 % yield) as a pale yellow foam of analytical purity.

¹H NMR (400 MHz, CDCl₃) δ 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'’)

¹³C NMR (101 MHz, CDCl₃) δ 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 (C3a), 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 C₂₅H₂₅N₂O₆ [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 POCl₃ (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 NaHCO₃ (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.

¹H NMR (400 MHz, (CD₃)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)

¹³C NMR (101 MHz, (CD₃)₂SO) δC 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 C₁₅H₁₁NO [M+H]+ 222.0919, found 222.0909

mp = 237 – 239 °C
Tert-butyl 3-formyl-2-phenyl-1H-indole-1-carboxylate (286)\textsuperscript{109}

[Chemical structure image]

To a stirring solution of 3-formyl-2-phenyl indole 285 (2.00 g, 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\textsubscript{2}Cl\textsubscript{2} : EtOAc : hexane) to give N-Boc indole 286 (2.74 g, 94 % yield) as a yellow solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ \textsubscript{H} 9.75 (1H, s, H\textsubscript{14}), 8.44 – 8.42 (1H, m, H\textsubscript{7}), 8.27 – 8.24 (1H, m, H\textsubscript{4}), 7.54 – 7.48 (5H, m, H\textsubscript{9}, H\textsubscript{10}, H\textsubscript{11}, H\textsubscript{12} and H\textsubscript{13}), 7.47 - 7.40 (2H, m, H\textsubscript{5} and H\textsubscript{6}), 1.30 (9H, s, H\textsubscript{17}, H\textsubscript{17}’ and H\textsubscript{17}’’

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ \textsubscript{C} 188.2 (C\textsubscript{14}), 149.9 (C\textsubscript{15}), 149.2 (C\textsubscript{2}), 136.3 (C\textsubscript{7a}), 131.0 (C\textsubscript{8}), 130.1 ((C\textsubscript{9} and C\textsubscript{13} or (C\textsubscript{10} and C\textsubscript{12})), 129.3 (C\textsubscript{11}), 128.1 ((C\textsubscript{9} and C\textsubscript{13} or (C\textsubscript{10} and C\textsubscript{12})), 126.0 (C\textsubscript{6}), 125.5 (C\textsubscript{3a}), 124.8 (C\textsubscript{5}), 122.0 (C\textsubscript{7}), 119.8 (C\textsubscript{3}), 114.9 (C\textsubscript{4}), 85.0 (C\textsubscript{16}), 27.4 (C\textsubscript{17}, C\textsubscript{17}’ and C\textsubscript{17}’’)

ν\textsubscript{max} (thin film)/cm\textsuperscript{-1} 1737 (C=O carbamate), 1664 (C=O aldehyde)

El-MS calcd for C\textsubscript{20}H\textsubscript{19}NO\textsubscript{3} [M]\textsuperscript{+} 321.1365; found 321.1365

mp = 175-176 °C (lit. 178-179 °C)

These data are in accordance with the literature.\textsuperscript{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 NaHCO₃ (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 MgSO₄ 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.

1H NMR (400 MHz, CDCl₃) 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'')

13C NMR (101 MHz, CDCl₃) 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'')

νmax (thin film)/cm⁻¹ 3340 (OH), 1729 (C=O ester and carbamate), 1657 (C=O amide)

EI-MS calcd for C₂₅H₃₀N₂O₄ [M]+ 422.2206; found 422.2196
(±)-Tert-butyl 3-(2-(tert-butyramino)-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 NaHCO₃ (aq), dried over MgSO₄, 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.

¹H NMR (400 MHz, CDCl₃) δH 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’’).

¹³C NMR (101 MHz, CDCl₃) δc 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)

νmax (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_{3}O_{5}[M+Na]^+ 512.2161; found 512.2166
**N-Benzylformamide (290)**

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.

\[
\begin{align*}
{^1H} \text{ NMR} (400 \text{ MHz, CDCl}_3) &\delta \ H8 \ \text{major rotamer}, \ 8.20 \ (1H, s), \ H8 \ \text{minor rotamer}, \ 8.12 \ (1H, d, J = 12.0 \text{ Hz}), \\
&7.40 - 7.23 \ (5H, m, H2, H3, H4, H5, H6), \ 6.38 \ (1H, br. s, NH \ \text{major rotamer}), \ 6.17 \ (1H, br. s. NH \ \text{minor rotamer}), \\
&4.44 \ (2H, d, J = 6.0 \text{ Hz}), \ H7 \ \text{major rotamer}, \ 4.37 \ (2H, d, J = 6.5 \text{ Hz}, \ H7 \ \text{minor rotamer})
\end{align*}
\]

\[
{^{13}C} \text{ NMR} (101 \text{ MHz, CDCl}_3) \delta \ C8 \ \text{minor rotamer}, \ 164.7 \ (C8 \ \text{major rotamer}), \ 161.2 \ (C8 \ \text{major rotamer}), \ 137.6 \ (C1 \ \text{major rotamer}), \ 137.5 \ (C1 \ \text{minor rotamer}), \ {128.9, \ 128.7, \ 127.9, \ 127.8, \ 127.6, \ 127.0} \ (C2-C6 \ \text{major and minor}), \\
&45.6 \ (C7 \ \text{minor rotamer}) \ 42.1 \ (C7 \ \text{major rotamer})
\]

\[\nu_{\max} \ (\text{thin film})/\text{cm}^{-1} \ 1664 \ (C=O)\]

EI-MS calcd for C₈H₉NO [M]⁺ 135.0684; found 135.0684

These data are in accordance with the literature.
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 POCl₃ (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 CH₂Cl₂. The combined organic layers were dried over MgSO₄ 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.

\[ \text{N} \quad \text{C} \]

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.

\[^{1}\text{H NMR (400 MHz, CDCl}_3] \delta_7.46 – 7.36 (5H, m, H2, H3, H4, H5 and H6), 4.68 (2H, s, H7)\]

\[^{13}\text{C NMR (101 MHz, CDCl}_3] 157.7 \{t, J = 5.0 \text{ Hz, NC}, 132.4 \{C1\}, \{129.0, 128.5, 126.6 \{C2-C6\}, 45.6 \{t, J = 7.0 \text{ Hz, C7} \}\]

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 NaHCO₃ (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 MgSO₄ 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.

1H NMR (400 MHz, CDCl₃) 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’’)

13C NMR (101 MHz, CDCl₃) 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 C28H28N2O4 [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 NaHCO₃ (aq), H₂O, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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'')

¹³C NMR (101 MHz, CDCl₃) δC 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)

v_max (thin film)/cm⁻¹ 1737 (C=O ester and carbamate), 1668 (C=O amide)

(±)-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$_3$)$_2$SO) $\delta_H$ 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$_3$)$_2$SO) $\delta_C$ 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)

$\nu_{\text{max}}$ (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$_2$O (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$_6$D$_6$) δ$_H$ 7.77 (2H, d, $J = 8.5$ Hz, H$_7$ and H$_7'$), 7.32 (4H, dd, $J = 8.0, 1.5$ Hz, H$_9$, H$_{13}$, H$_9'$ and H$_{13}'$), 7.13-7.11 (2H, m, H$_4$ and H$_4'$), 7.07 – 6.98 (12H, m, NH, H$_5$, H$_6$, H$_{10}$, H$_{11}$, H$_{12}$, NH', H$_5'$, H$_6'$, H$_{10}'$, H$_{11}'$ and H$_{12}'$), 6.06 (1H, s, H$_{14}$), 3.69 (2H, q, $J = 7.0$ Hz, H$_{16}$), 0.72 (3H, t, $J = 7.0$ Hz, H$_{17}$)

$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ$_C$ 172.8 (C$_{15}$), 135.99, (C$_2$ or C$_8$), 135.96 (C$_2$ or C$_8$), 133.2 (C$_{7a}$), 128.8 (C$_9$ and C$_{13}$), 128.7 (C$_{3a}$), 128.0 (C$_{10}$ and C$_{12}$), 127.4 (C$_{11}$), 121.9 (C$_4$), 121.2 (C$_7$), 119.9 (C$_5$ or C$_6$), 110.8 (C$_5$ or C$_6$), 110.3 (C$_3$), 60.4 (C$_{16}$), 42.1 (C$_{14}$), 13.7 (C$_{17}$)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3398 (N-H), 1720 (C=O)

ES-MS calcd for C$_{32}$H$_{26}$N$_2$O$_2$ [M+Na]$^+$ 493.1892; found 493.1906
1-Benzyl-2-phenyl-1H-indole (298)\textsuperscript{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\textsubscript{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.

\[^{1}\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta H 7.75 - 7.71 (1H, m, H7), 7.51 - 7.48 (2H, m, H9 and H13), 7.46 - 7.40 (3H, m, H10, H11 and H12), 7.35 - 7.18 (6H, m, H4, H5, H6, H17, H18 and H19), 7.09 (2H, d, J = 7.0 Hz, H16 and H20), 6.71 (1H, s, H3), 5.42 (2H, s, H14)\]

\[^{13}\text{C} \text{ NMR} (101 \text{ MHz, CDCl}_3) \delta C 141.9 (C2), 138.3 (C15), 138.0 (C7a), 132.7 (C8), 129.3 (C9 and C13), 128.8 (C17 and C19), 128.6 (C10 and C12), 128.3 (C3a), 128.1 (C11), 127.2 (C18), 126.0 (C16 and C20), 121.9 (C4 or C5 or C6), 120.6 (C7), 120.2 (C4 or C5 or C6), 110.6 (C4 or C5 or C6), 102.4 (C3), 47.8 (C14)\]

\(\nu_{max} \text (\text{thin film})/\text{cm}^{-1} 3062, 3029 (\text{sp}^2 \text{C-H}), 2925 (\text{sp}^3 \text{C-H})\)

EI-MS calcd for C\textsubscript{21}H\textsubscript{17}N [M]\textsuperscript{+} 283.1361; found 283.1370

These data are in accordance with the literature.\textsuperscript{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)

$\nu_{\text{max}}$ (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 NaHCO₃ (aq), saturated NH₄Cl (aq) and H₂O, dried over MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography gave protected alcohol 300 (1.02 g, 36 % yield) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ, 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’)

¹³C NMR (101 MHz, CDCl₃) δC 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)

Cl-MS calcd for C₈H₂₀O₂Si [M+NH₄]⁺ 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 MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (DCM) gave aldehyde 301 (156 mg, 20 % yield) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) 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’)

¹³C NMR (101 MHz, CDCl₃) 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)

Cl-MS calcd for C₈H₁₈O₂Si [M+NH₄]⁺ 192.1420; found 192.1426
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 NH₄Cl (aq), and extracted with Et₂O. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δc 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)

νₘₐₓ (thin film)/cm⁻¹ 3393 (O-H)

EI-MS calcd for C₁₀H₁₄O₃ [M]⁺ 182.0943; found 182.0936

These data are in accordance with the literature.

112
2-(4-Methoxybenzoyloxy)acetaldehyde (303)\textsuperscript{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\textsubscript{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.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ \textsubscript{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)

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ \textsubscript{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\textsubscript{max} (thin film)/cm\textsuperscript{-1} 1733 (C=O)

EI-MS calcd for C\textsubscript{10}H\textsubscript{12}O\textsubscript{3} [M]\textsuperscript{+} 180.0786; found 180.0789

These data are in accordance with the literature.\textsuperscript{113}
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$_2$O and extracted with Et$_2$O. The combined organic layers were washed with 5 % LiCl$_{\text{aq}}$, H$_2$O, saturated NaCl$_{\text{aq}}$, 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 $^1$H 7.76 – 7.73 (4H, m, H$_5$, H$_9$, H$_5'$ and H$_9'$), 7.49 – 7.40 (6H, m, H$_6$, H$_7$, H$_8$, H$_6'$, H$_7'$ and H$_8'$), 5.98 (1H, ddt, $J = 17.0$, 10.5, 4.0 Hz, H$_2$), 5.44 (1H, dq, $J = 17.0$, 2.0 Hz, H$_{1A}$), 5.17 (1H, dq, $J = 10.5$, 2.0 Hz, H$_{1B}$), 4.27 (2H, dt, $J = 4.0$, 2.0 Hz, H$_3$), 1.13 (9H, s, H$_{11}$, H$_{11'}$ and H$_{11''}$)

$^{13}$C NMR (101 MHz, CDCl$_3$) δ $^{13}$C 137.1 (C$_2$), 135.6 (C$_5$, C$_9$, C$_5'$ and C$_9'$), 133.8 (C$_4$ and C$_4'$), 129.7 (C$_7$ and C$_7'$), 127.7 (C$_6$, C$_8$, C$_6'$ and C$_8'$), 114.0 (C$_1$), 64.7 (C$_3$), 26.9 (C$_{11}$, C$_{11'}$ and C$_{11''}$), 19.3 (C$_{10}$)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1646 (C=O), 1110 (Si-O)

Cl-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)

To a solution of alkene 304 (8.00 g, 27.0 mmol, 1.0 equiv) in DCM (300 mL) at –78 °C was passed O₃/O₂ (1.3 mmol O₃/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 N₂ 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.

¹H NMR (400 MHz, CDCl₃) δ 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’’)

¹³C NMR (101 MHz, CDCl₃) δ 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 C₁₈H₂₂O₂Si [M+NH₄]⁺ 316.1733; found 316.1740

These data are in accordance with the literature.
(±)-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 NaHCO₃ [aq] and H₂O, dried over MgSO₄ 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

¹H NMR (400 MHz, CDCl₃) δH 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).

¹³C NMR (101 MHz, CDCl₃) δC 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).

νₘₐₓ (thin film)/cm⁻¹ 1744 (C=O), 1099 (C-O ether)

ES-MS calcd for C₂₇H₂₇NO₃ [M+Na]⁺ 436.1889; found 436.1888
Oxazolidinone 307

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta_c$ 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)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1759 (C=N), 1698 (C=O)

ES-MS calcd for C$_{30}$H$_{31}$N$_3$O$_2$ [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 NaHCO₃ (aq) and H₂O, dried over MgSO₄ 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, CDCl₃) 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, CDCl₃) 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').

¹³C NMR (101 MHz, CDCl₃) 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)

El-MS calcd for C₈H₁₆N₂O₄ [M]^+ 204.1110; found 204.1117
Cyanoacetic acid chloride (310)\textsuperscript{116}

\[
\begin{array}{c}
\text{N} \\
\text{3} \\
\text{O} \\
\text{2} \\
\text{Cl} \\
\text{1}
\end{array}
\]

To an ice-cooled solution of cyanoacetic acid (5.00 g, 58.8 mmol, 1.0 equiv) in Et\textsubscript{2}O (30 mL) in a two-necked round bottom flask fitted with a vigereux condenser was added PCl\textsubscript{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\textsubscript{3}) \(\delta_H = 4.03\) (2H, s, H2).

\(^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta_C = 164.0\) (C1), 77.1 (C3), 35.5 (C2).

\(v_{\text{max}}\) (thin film)/cm\(^{-1}\) = 1790 (C=O)

EI-MS calcd for [C\textsubscript{3}H\textsubscript{2}NOCl]\textsuperscript{+} 102.9825; found 102.9810.
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 Cul (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$_2$O (20 mL), and extracted with Et$_2$O. 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 7.60 – 7.58 (2H, m, H$_{10}$ and H$_{14}$), 7.44 – 7.38 (4H, m, H$_3$, H$_{11}$, H$_{12}$ and H$_{13}$), 7.22 – 7.18 (1H, m, H$_5$), 6.80 – 6.76 (2H, m, H$_4$ and H$_6$), 4.32 (2H, br. s, NH$_2$)

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 147.8 (C$_1$), 132.2 (C$_3$), 131.5 (C$_{10}$ and C$_{14}$), 129.8 (C$_5$), 128.5 (C$_{11}$ and C$_{13}$), 128.3 (C$_{12}$), 123.4 (C$_9$), {118.0, 114.4 (C$_4$ and C$_6$)}, 108.0 (C$_2$), 94.8 (C$_8$), 86.0 (C$_7$)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3468, 3370 (NH$_2$ assymetric and symmetric stretch); 2207 (C≡C stretch)

CI-MS calcd 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)\textsuperscript{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\textsubscript{2}O, dried over MgSO\textsubscript{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.

\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) & \delta_{H} 7.70 (2H, d, J = 8.5 Hz, H_{16} and H_{20}), 7.66 (1H, d, J = 7.5 Hz, H_{5} or H_{6}), 7.52 – 7.47 (2H, m, H_{10} and H_{14}), 7.42 – 7.38 (4H, m, H_{3}, H_{11}, H_{12} and H_{13}), 7.34 – 7.30 (1H, m, H_{5} or H_{6}), 7.25 (1H, br. s. NH), 7.19 (2H, d, 8.0 Hz, H_{17} and H_{19}) 7.09 (1H, dt, J = 7.5, 1.0 Hz, H_{4}), 2.36 (3H, s, H_{21}) \\
\text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3) & \delta_{C} 144.1 (C_{18}), 137.5 (C_{1}), 136.1 (C_{15}), 132.0 (C_{3}), 131.6 (C_{10} and C_{14}), 129.6 (C_{17} and C_{19}), 129.1 (C_{12}), 128.6 (C_{11} and C_{13}), 127.3 (C_{16} and C_{20}), 124.6 (C_{4}), 122.0 (C_{9}), 120.4 (C_{5} or C_{6}), 114.7 (C_{2}), 96.2 (C_{8}), 83.7 (C_{7}), 21.6 (C_{21})
\end{align*}

One carbon signal (C_{5}/C_{6}) is not observed, and is assumed to be overlapping with the peak at 129.6 ppm from the HSQC experiment.

\begin{align*}
\nu_{\text{max}} \text{(thin film)/cm}^{-1} & 1338, 1163 (O=\text{S}=\text{O}) \\
\text{ES-MS calcd for C}_{21}\text{H}_{17}\text{NO}_{2}\text{S} [M+H]^+ & 348.1058; \text{found 348.1062}
\end{align*}

These data are in accordance with the literature.\textsuperscript{117}
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) \textbf{318} (213 mg, 63 % yield) as a yellow solid.

$^1$H NMR (400 MHz, (CD$_3$)$_2$SO) $\delta$ 9.14 (2H, d, $J = 5.5$ Hz, H$_6$ and H$_6'$), 8.60 (2H, d, $J = 8.0$ Hz, H$_3$ and H$_3'$), 8.38 (2H, td, $J = 8.0$, 1.5 Hz, H$_4$ and H$_4'$), 7.83 (2H, td, $J = 5.5$, 1.5 Hz, H$_5$ and H$_5'$)

$^{13}$C NMR (101 MHz, (CD$_3$)$_2$SO) $\delta$ C 156.9 (C$_2$ and C$_2'$), 150.2 (C$_6$ and C$_6'$), 141.8 (C$_4$ and C$_4'$), 127.8 (C$_5$ and C$_5'$), 124.4 (C$_3$ and C$_3'$)
To a solution of PdCl$_2$(bipy) 318 (134 mg, 0.402 mmol, 1.0 equiv) in H$_2$O (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$_2$O$_5$ under vacuum overnight to give ([bpy]Pd$^{2+}$(H$_2$O)$_2$.OTf)$_2$ 319 (210 mg, 88 % yield) as a brown solid

$^1$H NMR (500 MHz, (CD$_3$)$_2$SO) 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$_3$)$_2$SO) 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$_3$)$_2$SO) 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-isopropyltartrate (2.23 g, 9.50 mmol, 3.3 equiv) in H2O (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 MgSO4 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)Pd2+(H2O)2]2–(OTf)2 (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.

1H NMR (400 MHz, CDCl3) 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)

13C NMR (101 MHz, CDCl3) 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.

νmax (thin film)/cm⁻¹3502 (O-H), 1730 (C=O), 1374, 1177 (O=S=S)

ES-MS calcd for C26H25NO5S [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)

$\nu_{\max}$ (thin film)/cm$^{-1}$ 1370, 1171 (O=S=O)

ES-MS calcd for C$_{21}$H$_{17}$NO$_2$S [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 KNaC₄H₄O₆ (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 MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography gave diol 322 (848 mg, 80 % yield) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ, 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)

¹³C NMR (101 MHz, CDCl₃) δ, 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 C₂₃H₂₁NO₄S [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 mmol, 1.05 equiv) was added. The reaction mixture was stirred at rt for 21 h, diluted with DCM, washed with saturated NH₄Cl (aq) and H₂O, dried over MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (30 % Et₂O in petroleum ether) gave protected alcohol 323 (976 mg, 90 % yield) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δ 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.
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 NaHCO₃ (aq), saturated NaCl (aq), dried over MgSO₄ 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, CDCl₃) 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, CDCl₃) 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).

$\nu_{\text{max}}$ (thin film)/cm⁻¹ 2264 (C=O), 1745 (C=O)

ES-MS calcd for C₂₉H₂₆N₂O₆S [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 NaHCO₃ (aq), saturated NaCl (aq), dried over MgSO₄ 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.

1H NMR (400 MHz, CDCl₃) δ 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)

13C NMR (101 MHz, CDCl₃) δ 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 C₃₂H₃₆N₂O₅Si [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, 0.009 mmol, 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$_2$SO$_4$ 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: 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: 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.

$\nu_{\text{max}}$ (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$_{33}$H$_{28}$N$_3$O$_6$S [M+Na]$^+$ 594.1675; found 594.1693
(Z)-2-Isoproxy-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, 0.009 mmol, 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 Na₂SO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ, 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)

¹³C NMR (101 MHz, CDCl₃) δ, 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.

νmax (thin film)/cm⁻¹ 3367 (N-H), 2209 (C=O), 1681, 1627 (β-enamino ester), 1377, 1176 (O=S=O)

ES-MS calcd for C₃₄H₃₉N₃O₅Si [M+H]⁺ 630.2458; found 630.2466
Tert-butyl 3-(hydroxymethyl)-2-phenyl-1H-indole-1-carboxylate (328)\textsuperscript{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 H₂O, dried over MgSO₄ and concentrated under reduced pressure. Purification by silica gel chromatography gave alcohol 328 (1.45 g, 96 % yield) as a colourless oil.

\textsuperscript{1}H NMR (400 MHz, CDCl₃) δ\textsubscript{H} 8.29 (1H, d, \textit{J} = 8.0 Hz, H7), 7.77 (1H, d, \textit{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’’)

\textsuperscript{13}C NMR (101 MHz, CDCl₃) δ\textsubscript{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’’)

\textit{v}_{max} (thin film)/cm\textsuperscript{-1} 3372 (O-H), 1728 (C=O)

ES-MS calcd for C\textsubscript{20}H\textsubscript{21}NO\textsubscript{3} [M+H]\textsuperscript{+} 324.1600; found 324.1588

These data are in accordance with the literature.\textsuperscript{74}
**Tert-butyl 3-((2-cyanoacetoxy)methyl)-2-phenyl-1H-indole-1-carboxylate (183)**

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 NaHCO₃ (aq), saturated NaCl (aq), dried over MgSO₄ 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, CDCl₃) δ 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, CDCl₃) δ 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)

$${v}_{max}$$ (thin film)/cm⁻¹ 1731 (C=O)

ES-MS calcd for C₂₃H₂₂N₂O₄[M+H]⁺ 391.1658; found 391.1667

These data are in accordance with the literature.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 Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (15 % EtOAc in petroleum ether with 1 % Et₃N) gave alkene 184 (202 mg, 37 % yield) as a white solid.

¹H NMR (400 MHz, CDCl₃) 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″)

¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₂₂N₂O₂ [M+H]⁺ 347.1760; found 347.1754

These data are in accordance with the literature.⁷⁴
1-Methyl-1H-indole-3-carbaldehyde (344)

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 careful addition of H₂O, and was extracted three times with EtOAc. The combined organic layers were washed with 5 % LiCl (aq), saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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 C₁₀H₉NO [M+H]⁺ 160.0762; found 160.0751

These data are in accordance with the literature.

210
1-Methyl-1H-indole (347)\textsuperscript{121}

![Indole structure]

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\textsubscript{4}Cl\textsuperscript{(aq)}. The solution was extracted three times with Et\textsubscript{2}O, and the combined organic layers were washed with saturated NaCl\textsuperscript{(aq)}, dried over MgSO\textsubscript{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.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.76 (1H, d, \(J = 8.0\) Hz, H\textsubscript{7}), 7.43 (1H, d, \(J = 8.5\) Hz, H\textsubscript{4}), 7.37 – 7.33 (1H, m, H\textsubscript{5}), 7.26 – 7.22 (1H, m, H\textsubscript{6}), 7.14 (1H, d, \(J = 3.0\) Hz, H\textsubscript{2}), 6.61 (1H, d, \(J = 3.0\) Hz, H\textsubscript{3}), 3.86 (3H, s, H\textsubscript{8})

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 136.8 (C\textsubscript{7a}), 128.9 (C\textsubscript{2}), 128.6 (C\textsubscript{3a}), 121.6 (C\textsubscript{5}), 121.0 (C\textsubscript{7}), 119.4 (C\textsubscript{6}), 109.3 (C\textsubscript{4}), 101.0 (C\textsubscript{3}), 32.9 (C\textsubscript{8})

\(\nu\)\textsuperscript{\text{max}} (thin film)/\text{cm}^{-1} 3053 (sp\textsuperscript{2} C-H); 2941 (sp\textsuperscript{3} C-H)

EI-MS calcd for C\textsubscript{9}H\textsubscript{9}N [M]\textsuperscript{+} 131.0735; found 131.0733

These data are in accordance with the literature.\textsuperscript{121}

---

\textsuperscript{121} Reference number for literature citation.
4-((1-Methyl-1H-indol-3-yl)methyl)morpholine (346)\textsuperscript{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\textsubscript{2}O, 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\textsubscript{2}O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO\textsubscript{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.

\begin{align*}
^{1}H\text{ NMR}\ (400 \text{ MHz, CDCl}_3)\ &\delta\text{H} 7.83 (1H, d, J = 8.0 \text{ Hz, H7}),\ 7.37 (1H, d, J = 8.0 \text{ Hz, H4}),\ 7.32 – 7.29 (1H, m, H5), \\
&\quad 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 \text{ and H12}),\ 2.59 – 2.57 (4H, m, H10 \text{ and H13})
\end{align*}

\begin{align*}
^{13}C\text{ NMR}\ (101 \text{ MHz, CDCl}_3)\ &\delta\text{C} 137.1 (\text{C7a}),\ 128.5 (\text{C2}),\ 121.7 (\text{C5}),\ 119.7 (\text{C7}),\ 119.1 (\text{C6}),\ 110.7 (\text{C3}),\ 109.2 (\text{C4}),\ 67.2 (\text{C11} \text{ and C12}),\ 54.0 (\text{C9}),\ 53.7 (\text{C10} \text{ and C13}),\ 32.7 (\text{C8})
\end{align*}

\(\nu_{\text{max}}\ (\text{thin film})/\text{cm}^{-1}:\ 3051 (\text{sp}^{2} \text{C-H})\),\ 2953 (\text{sp}^{3} \text{C-H}),\ 1113 (\text{C-O})

ES-MS calcd for C\textsubscript{14}H\textsubscript{18}N\textsubscript{2}O [M+H]\textsuperscript{+}: 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\textsuperscript{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 Et2O and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO4 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.

1H NMR (400 MHz, CDCl3) δH 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)

13C NMR (101 MHz, CDCl3) δC 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)

νmax (thin film)/cm⁻¹ 1652 (C=O)

ES-MS calcd for C16H15Cl2N2O2 [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 H₂O, 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 H₂O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃ δ, 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹ 3058 (sp² C-H), 2956 (sp³ C-H) 1114 (C-O)

ES-MS calcd for C₂₆H₂₆N₂O [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
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 Et₂O and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

\[ \text{1H NMR (400 MHz, CDCl₃) } \delta \text{H 7.90 – 7.88 (1H, m), 7.42 – 7.34 (5H, m, H9m H10, H11, H12 and H13), 7.28 – 7.19 (6H, m, H4, H5, H6, H17, H18 and H19), 6.96 – 6.94 (2H, m, H16 and H20), 5.28 (2H, s, H14), 4.04 (2H, s, H14), 3.94 (br. s) and 3.72 (br. s)} \text{ (8H, H24, H25, H26 and H27)} \]

\[ \text{13C NMR (101 MHz, CDCl₃) } \delta_c 164.6 \text{ (C23), } 141.9 \text{ (C2), } 138.1 \text{ (C15), } 136.5 \text{ (C7a), } 132.4 \text{ (C8), } 131.2 \text{ (C9 and C13), } 129.2 \text{ (C3a), } 128.6 \text{ (C17 and C19), } 128.5 \text{ (C10 and C12), } 128.3 \text{ (C11), } 127.1 \text{ (C18), } 126.1 \text{ (C16 and C20), } 121.9 \text{ (C4 or C5 or C6), } 120.9 \text{ (C7), } 119.8 \text{ (C4 or C5 or C6), } 110.3 \text{ (C4 or C5 or C6), } 106.1 \text{ (C3), } 85.7 \text{ (C22), } 66.7 \text{ (C24 or C25 or C26 or C27), } 66.2 \text{ (C24 or C25 or C26 or C27), } 48.7 \text{ (C24 or C25 or C26 or C27), } 47.6 \text{ (C14), } 44.3 \text{ (C24 or C25 or C26 or C27), } 40.2 \text{ (C21)} \]

\[ \nu_{\text{max}} \text{ (thin film)/cm}^{-1} \text{ 1651 (C=O)} \]

ES-MS calcd for C₂₈H₂₆Cl₂N₂O₂ [M+H]^+ 493.1450; found 493.1440
**Tert-butyl 3-formyl-1H-indole-1-carboxylate (355)**

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$_3$) $\delta$ 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$_3$) $\delta$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'')

$\nu_{\text{max}}$ (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.
**Tert-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (357)**

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 H₂O, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ: 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’’)

¹³C NMR (101 MHz, CDCl₃) δ: 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<sub>max</sub> (thin film)/cm<sup>-1</sup> 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$_3$) $\delta$ 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$_3$) $\delta$ 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’’)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1698 (C=O carbamate), 1640 (C=O amide)

ES-MS calcd for C$_{18}$H$_{24}$N$_2$O$_3$ [M+H]$^+$ 317.1865; found 317.1872
1-Tosyl-1H-indole-3-carbaldehyde (361)\textsuperscript{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-toluene sulfonyl 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 \textsubscript{(aq)}, dried over MgSO\textsubscript{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.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\)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)

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\)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)

\(v_{\text{max}}\) (thin film)/cm\textsuperscript{-1} 1672 (C=O), 1376, 1174 (O=S=O)

ES-MS calcd for C\textsubscript{16}H\textsubscript{13}NO\textsubscript{3}S \([\text{M+H}]^+\) 300.0694; found 300.0692

These data are in accordance with the literature.\textsuperscript{123}
(1-Tosyl-1H-indol-3-yl)methanol (362)\textsuperscript{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\textsubscript{2}O. The resulting solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl\textsubscript{(aq)}, dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Alcohol 362 (3.32 g, 98 % yield) was isolated as a white solid of analytical purity.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta_{H} 8.00 (1H, d, J = 8.0 Hz, H_{7}), 7.75 (2H, d, J = 8.0 Hz, H_{10} and H_{14}), 7.54 – 7.53 (2H, m, H_{2} and H_{4}), 7.34 (1H, td, J = 8.0, 1.0 Hz, H_{6}), 7.22 (1H, td, J = 8.0, 1.0 Hz, H_{5}), 7.12 (2H, d, J = 8.0 Hz, H_{11} and H_{13}), 4.72 (2H, s, H_{8}), 2.72 (1H, br. s, OH), 2.25 (3H, s, H_{15})

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta_{C} 145.1 (C_{12}), 135.4 (C_{7a}), 135.1 (C_{9}), 129.9 (C_{11} and C_{13}), 129.5 (C_{3a}), 126.8 (C_{10} and C_{14}), 125.0 (C_{6}), 123.8 (C_{2}), 123.4 (C_{5}), 122.6 (C_{3}), 120.0 (C_{4}), 113.7 (C_{7}), 56.9 (C_{8}), 21.5 (C_{15})

\(\nu_{\text{max}}\) (thin film)/cm\textsuperscript{-1} 3371 (O-H), 1362, 1169 (O=S=O)

ES-MS calcd for C\textsubscript{16}H\textsubscript{15}NO\textsubscript{3}S [M+MeCN+Na]\textsuperscript{+} 365.0936; found 365.0928

These data are in accordance with the literature.\textsuperscript{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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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)

\(\nu\)max (thin film)/cm\(^{-1}\) 1637 (C=O), 1353, 1166 (O=S=O)

ES-MS calcd for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_3\)S [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 % Et₂O in DCM) gave alkene 364 (25 mg, 39 % yield) and indole 365 (7 mg, 11 % yield).

Alkene 364:

1H NMR (400 MHz, CDCl₃) δH {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), 1.53 (br. s) and 1.18 (br. s) (9H, H17, H17’ and H17’’)

13C NMR (101 MHz, CDCl₃) δC 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 C₂₄H₂₈N₂O₃ [M+H]⁺ 393.2178; found 393.2183

Indole 365:

1H NMR (400 MHz, CDCl₃) δH 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’’)

222
$^{13}$C NMR (101 MHz, CDCl$_3$) δc 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)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1726 (C=O carbamate), 1645 (C=O amide)

ES-MS calcd for C$_{24}$H$_{28}$N$_{2}$O$_{3}$ [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.

$\text{H NMR (400 MHz, (CD}_3\text{)}_2\text{SO)} \delta \text{H} 12.43 \text{ (1H, br. s, NH)}, 8.48 \text{ (1H, d, } J = 3.5 \text{ Hz, H2)}, 8.20 - 8.18 \text{ (1H, m, H7), 7.58 - 7.56 \text{ (1H, m, H4)}, 7.33 - 7.26 \text{ (2H, m, H5 and H6)}, 3.90 \text{ (3H, s, H10)}$

$\text{C NMR (101 MHz, (CD}_3\text{)}_2\text{SO)} \delta \text{C} 179.2 \text{ (C8)}, 164.5 \text{ (C9)}, 138.9 \text{ (C2)}, 137.2 \text{ (C7a)}, 126.0 \text{ (C3a)}, 124.3 \text{ (C5 or C6), 123.3 \text{ (C5 or C6), 121.6 \text{ (C7), 113.2 \text{ (C4), 112.9 \text{ (C3), 53.0 \text{ (C10)}}}$

$\nu_{\text{max}} \text{ (thin film)}/\text{cm}^{-1} 3214 \text{ (NH), 1728 \text{ (C=O ester), 1616 \text{ (C=O ketone)}}$

$\text{ES-MS calcd for C}_{11}\text{H}_{9}\text{NO}_3 \text{ [M+H]}^+ 204.0661; \text{ found 204.0659}$

These data are in accordance with the literature.$^{125}$
**Tert-butyl 3-(2-methoxy-2-oxoacetyl)-1H-indole-1-carboxylate (367)**

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$_2$O and extracted three times with Et$_2$O. 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$_2$O in petroleum ether) gave N-Boc indole 367 (419 mg, 70 % yield) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 8.83 (1H, s, H$_2$), 8.43 – 8.41 (1H, m, H$_7$), 8.20 – 8.18 (1H, m, H$_4$), 7.46 – 7.39 (2H, m, H$_5$ and H$_6$), 4.00 (3H, s, H$_{10}$), 1.74 (9H, s, H$_{13}$, H$_{13}'$ and H$_{13}''$)

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 178.7 (C$_8$), 162.4 (C$_9$), 148.7 (C$_{11}$), 137.2 (C$_2$), 135.4 (C$_{7a}$), 127.5 (C$_{3a}$), 126.1 (C$_5$ or C$_6$), 124.9 (C$_5$ or C$_6$), 122.6 (C$_7$), 116.2 (C$_4$), 115.1 (C$_3$), 86.0 (C$_{12}$), 53.0 (C$_{10}$), 28.1 (C$_{13}$, C$_{13}'$ and C$_{13}''$)

$\nu_{max}$ (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.
(±)-Tert-buty l 3-(1-hydroxy-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (368)

![Chemical Structure](image)

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 MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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”)

¹³C NMR (101 MHz, CDCl₃) δ 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 C₁₆H₁₉NO₅ [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 H₂O and extracted three times with EtOAc. The combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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’’)

¹³C NMR (101 MHz, CDCl₃) δc 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 C₁₅H₁₉NO₄ [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 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’’)

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1727 (C=O ester and carbamate), 1653 (C=O amide)

ES-MS calcd for C$_{20}$H$_{26}$N$_2$O$_5$ [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 NH₄Cl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δ 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 C₂₁H₃₃NO₄Si [M-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 δH = 6.00 and 5.82 ppm).

1H NMR (400 MHz, CDCl3) δH 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)

13C NMR (101 MHz, CDCl3) δC 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)

νmax (thin film)/cm⁻¹ 1705 (C=O carbamate), 1646 (C=O amide)

ES-MS calcd for C25H40N2O4Si [M+H]⁺ 461.2836; found 461.2837
(±)-Tert-buty 3-(1-hydroxyethyl)-1H-indole-1-carboxylate (374)\textsuperscript{74}

![Chemical Structure](image)

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\textsubscript{2}O, 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\textsubscript{aq} and EtOAc. The phases were separated and the organic layer dried over MgSO\textsubscript{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.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ\textsubscript{H} 8.17 (1H, br. d, J = 8.0 Hz, H\textsubscript{7}), 7.70 (1H, d, J = 8.0 Hz, H\textsubscript{4}), 7.56 (1H, s, H\textsubscript{2}), 7.35 (1H, td, J = 8.0, 1.0 Hz, H\textsubscript{6}), 7.27 (1H, td, J = 8.0, 1.0 Hz, H\textsubscript{5}), 5.18 (1H, q, J = 6.0 Hz, H\textsubscript{8}), 2.09 (1H, br. s, OH), 1.69 (9H, s, H\textsubscript{11}, H\textsubscript{11}' and H\textsubscript{11}"), 1.67 (3H, d, J = 6.0 Hz, H\textsubscript{12})

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ\textsubscript{C} 149.8 (C\textsubscript{9}), 135.9 (C\textsubscript{7a}), 128.6 (C\textsubscript{3a}), 125.3 (C\textsubscript{3}), 124.5 (C\textsubscript{6}), 122.6 (C\textsubscript{5}), 121.8 (C\textsubscript{2}), 119.8 (C\textsubscript{4}), 115.4 (C\textsubscript{7}), 83.7 (C\textsubscript{10}), 63.9 (C\textsubscript{8}), 28.2 (C\textsubscript{11}, C\textsubscript{11}' and C\textsubscript{11}"), 23.5 (C\textsubscript{12})

ν\textsubscript{max} (thin film)/cm\textsuperscript{-1} 3406 (O-H), 1730 (C=O)

ES-MS calcd for C\textsubscript{15}H\textsubscript{19}NO\textsubscript{3} [M+MeCN+Na]\textsuperscript{+} 325.1528; found 325.1524

These data are in accordance with the literature.\textsuperscript{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).

^1H NMR (400 MHz, CDCl₃) 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’’).

^13C NMR (101 MHz, CDCl₃) 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 C₁₉H₂₈N₂O₃ [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 separated and the organic layer dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹ 3449 (O-H), 1732 (C=O)

CI-MS calcd for C₁₇H₂₃NO₃ [M-OH]⁺ 272.1651; found 272.1662
(E)- and (Z)-Tert-butyl 2-(2-(dimethylamino)-2-oxoethyl)-3-(2-methylpropyldene)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 \( \delta_H = 7.51 \) and 7.36 ppm).

\[ \text{ES-MS calcd for } C_{21}H_{30}N_2O_3 [M+H]^+ 359.2335; \text{ found } 359.2330 \]

\( ^1 \text{H NMR (400 MHz, CDCl}_3 \) \( \delta_H 7.87 \) (1H, br. s, H7), 7.51 (1H, d, \( J = 8.0 \text{ Hz, H4 major} \), 7.36 (1H, d, \( J = 8.0 \text{ Hz, H4 minor} \), 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)

\( ^{13} \text{C NMR (101 MHz, CDCl}_3 \) \( \delta_C 169.8 \) (C16 major), 169.6 (C16 minor), 151.6 (C9 minor), 151.3 (C9 major), 144.2 (C7a), 133.7 (C3), 132.4 (C8 minor), 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)

\( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 1703 (C=O carbamate), 1641 (C=O amide)
(±)-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 Et₂O, 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 separated and the organic layer dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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’’)

¹³C NMR (101 MHz, CDCl₃) δC 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.

νmax (thin film)/cm⁻¹ 3423 (O-H), 1731 (C=O)

ES-MS calcd for C₂₀H₂₁NO₃ [M-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 \( \delta_H = 7.06 \) and 6.75 ppm).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H \) 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\(_3\)) \( \delta_C \) 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”)

\( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 1702 (C=O carbamate), 1642 (C=O amide)

ES-MS calcd for C\(_{24}\)H\(_{30}\)N\(_2\)O\(_3\) [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 $^1$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 $^{13}$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)
\( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 1735 (C=O), 1356, 1169 (O=S=O)

ES-MS calcd for \( \text{C}_{19}\text{H}_{19}\text{NO}_{4}\text{S} \) [M+H]\(^{+}\) 358.1113; found 358.1127

**Indole 387**

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.01 (1H, d, \( J = 8.0 \) Hz, H\(_7\)), 7.81 (2H, d, \( J = 8.5 \) Hz, H\(_{10}\) and H\(_{14}\)), 7.65 (1H, s, H\(_2\)), 7.59 (1H, d, \( J = 8.0 \) Hz, H\(_4\)), 7.39 – 7.35 (1H, m, H\(_6\)), 7.31 – 7.25 (3H, m, H\(_5\), H\(_{11}\) and H\(_{13}\)), 5.27 (2H, s, H\(_8\)), 2.41 – 2.33 (5H, m, H\(_{15}\) and H\(_{17}\)), 1.17 (3H, t, \( J = 7.5 \) Hz, H\(_{18}\))

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 174.3 (C\(_{16}\)) 145.1 (C\(_{12}\)), 135.18 (C\(_7\)a or C\(_9\)), 135.16 (C\(_7\)a or C\(_9\)), 130.0 (C\(_{11}\) and C\(_{13}\)), 129.5 (C\(_3\)a), 126.9 (C\(_{10}\) and C\(_{14}\)), 125.6 (C\(_2\)), 125.1 (C\(_6\)), 123.4 (C\(_5\)), 119.8 (C\(_4\)), 117.5 (C\(_3\)), 113.7 (C\(_7\)), 57.7 (C\(_8\)), 27.5 (C\(_{17}\)), 21.6 (C\(_{15}\)), 9.1 (C\(_{18}\))

\( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 1734 (C=O), 1371, 1171 (O=S=O)

ES-MS calcd for \( \text{C}_{19}\text{H}_{19}\text{NO}_{4}\text{S} \) [M+H]\(^{+}\) 358.1113; found 358.1120
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\textsubscript{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.

\textsuperscript{1}{H} NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) H 7.76 (1H, d, \(J = 8.0\) Hz, H\textsubscript{7}), 7.59 (2H, d, \(J = 8.5\) Hz, H\textsubscript{10} and H\textsubscript{14}), 7.33 – 7.22 (7H, m, H\textsubscript{4}, H\textsubscript{6}, H\textsubscript{20}, H\textsubscript{21}, H\textsubscript{22}, H\textsubscript{23} and H\textsubscript{24}), 7.18 (2H, d, \(J = 8.5\) Hz, H\textsubscript{11} and H\textsubscript{13}), 7.10 – 7.06 (1H, m, H\textsubscript{5}), 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)\} (H\textsubscript{8}), 5.02 – 4.98 (1H, m, H\textsubscript{2}), \{4.51 (1H, dd, \(J = 14.5, 6.0\) Hz), 4.39 (1H, dd, \(J = 14.5, 6.0\) Hz)\} (AB system, H\textsubscript{18}), \{3.09 (1H, dd, \(J = 15.0, 4.0\) Hz), 2.75 (1H, dd, \(J = 15.0, 7.5\) Hz)\} (H\textsubscript{16}), 2.36 (3H, s, H\textsubscript{15})

\textsuperscript{13}{C} NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) C 169.1 (C\textsubscript{17}), 144.5 (C\textsubscript{12}), 144.1 (C\textsubscript{3}), 143.2 (C\textsubscript{7a}), 138.0 (C\textsubscript{19}), 133.4 (C\textsubscript{9}), 130.2 (C\textsubscript{6}), 129.8 (C\textsubscript{11} and C\textsubscript{13}), 129.5 (C\textsubscript{3a}), \{128.7, 127.8\} (C\textsubscript{20}, C\textsubscript{21}, C\textsubscript{23} and C\textsubscript{24}), 127.4 (C\textsubscript{10} and C\textsubscript{14}), 124.8 (C\textsubscript{5}), 121.1 (C\textsubscript{4}), 116.8 (C\textsubscript{7}), 104.4 (C\textsubscript{8}), 63.0 (C\textsubscript{2}), 44.5 (C\textsubscript{16}), 43.7 (C\textsubscript{18}), 21.6 (C\textsubscript{15})

C22 is not observed and is assumed to be overlapping with the peak at 127.4 from the HSQC and HMBC experiments.

\(\nu\)\textsubscript{max} (thin film)/cm\textsuperscript{-1} 3300 (N-H), 1648 (C=O), 1354, 1167 (O=S=O)

ES-MS calcd for C\textsubscript{25}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+} 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 H₂O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 Mhz, CDCl₃) δ 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)

¹³C NMR (101 MHz, CDCl₃) δC 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)

νmax (thin film)/cm⁻¹ 3327 (NH), 1242, 1034 (C-O)

ES-MS calcd for C₁₅H₁₇NO [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 MgSO₄ 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.

³¹H NMR (400 MHz, CDCl₃) δH 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).

¹³C NMR (101 MHz, CDCl₃) δC 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)

νₘₐₓ (thin film)/cm⁻¹ 1642 (C=O), 1242, 1030 (C-O)

ES-MS calcd for C₁₇H₁₉NO₂ [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/CO₂ 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 MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δH 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)

¹³C NMR (101 MHz, CDCl₃) δc 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 C₁₈H₁₇NO₃S [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 H₂O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δₗ 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)

¹³C NMR (101 MHz, CDCl₃) δₑ 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)

νₘₙₙ (thin film)/cm⁻¹ 3331 (N-H), 1353, 1166 (O=S=O)

ES-MS calcd for C₂₅H₂₉N₂O₂S [M+H]⁺ 419.1793; found 419.1794
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 NaHCO₃ (aq), saturated NaCl (aq), dried over MgSO₄ 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.

^1H NMR (400 MHz, CDCl₃) δH 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), 7.10 - 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, minor, 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), 4.86 (d, J = 2.0 Hz) (H8), 3.93 – 3.86 (m), 3.55 – 3.48 (m) and 3.33 – 3.23 (m) (H17), 1.97 – 1.90 (1H, m, H16B minor) and 1H6B minor), 1.97 – 1.90 (1H, m, H16B major)

^13C NMR (101 MHz, CDCl₃) δC 166.9 (C25 minor), 166.3 (C25 major), 164.5 (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)
$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1646 (C=O), 1353, 1166 (O=S=O)

ES-MS calcd for $C_{28}H_{28}N_{2}O_{3}S$ [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 KNaC4H4O6 (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 MgSO4 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.

1H NMR (400 MHz, CDCl3) 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’’)

13C NMR (101 MHz, CDCl3) 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 C22H23NO3 [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 H2O. The solution was extracted three times with EtOAc and the combined organic layers were washed with saturated NaCl (aq), dried over MgSO4 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.

1H NMR (400 MHz, CDCl3) δH 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'')

13C NMR (101 MHz, CDCl3) δC 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'')

νmax (thin film)/cm⁻¹ 1698 (C=O)

ES-MS calcd for C29H32N2O2 [M+H]+ 441.2542; found 441.2547
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 NaHCO₃ (aq), saturated NaCl (aq), dried over MgSO₄ 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, CDCl₃) δ: 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, CDCl₃) δ: 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 C₃₂H₃₄N₂O₃ [M+H]⁺ 495.2648; found 495.2650
5 References


(117) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. J. Org. Chem. 2007, 72 (15), 5731–5736.


