# Direct Imine Acylation: The Synthesis of Diverse Heterocycles and Natural Products

Christiana Kitsiou

Doctor of Philosophy

**University of York**
**Chemistry**

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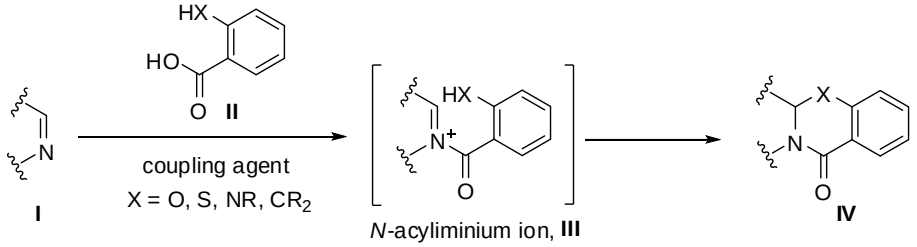
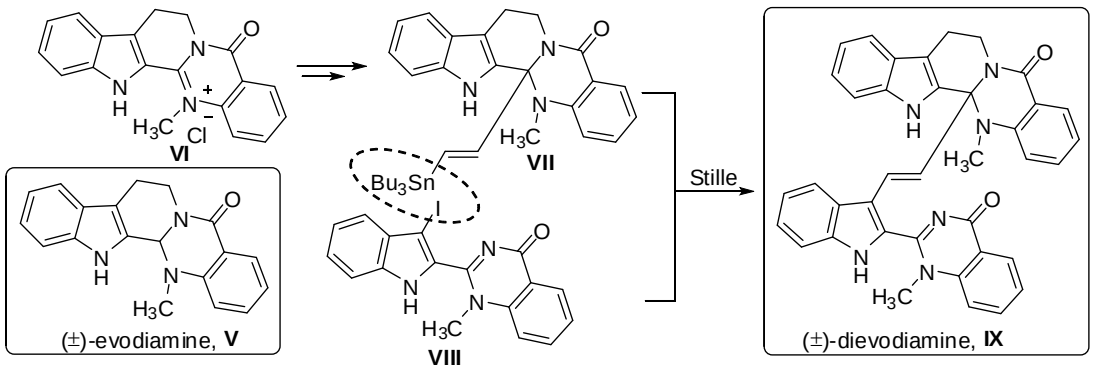
## Abstract

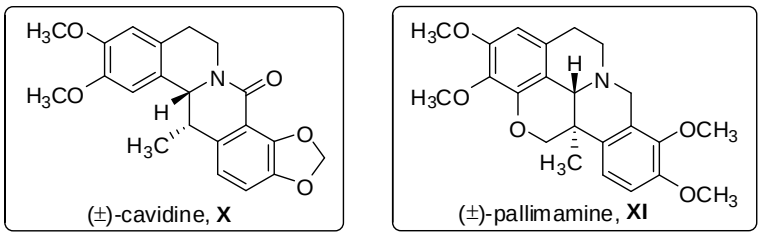
A simple and efficient procedure to prepare libraries of diverse heterocycles **IV** by the direct *N*-acylation of imines **I** with functionalised benzoic acids **II** is described. This procedure involves *N*-acyliminium ion **III** generation *via* a novel direct imine acylation (DIA) reaction followed by *in situ* intramolecular trapping by a range of nucleophiles built into the acid coupling partner. An overview of the existing methods for the synthesis and cyclisation reactions of *N*-acyliminium ions is provided (Chapter 1). The scope and limitations of the methodology are discussed thoroughly and preliminary mechanistic studies, including an *in situ* React IR study, are outlined (Chapter 2).




DIA methodology has been successfully applied in the efficient synthesis of the *Evodiae fructus* derived natural product, (±)-evodiamine **V** (Chapter 2). Efforts to apply this methodology towards the synthesis of the structurally related natural product, dievodiamine **IX**, are also described (Chapter 3). The total synthesis of (±)-dievodiamine **IX**, was completed with keys steps including organometallic addition into DHED adduct **VI** and the Stille coupling of advanced intermediates **VII** and **VIII**.




An overview of the reported synthetic approaches and biological activity of a class of protoberberine alkaloids is also provided (Chapter 4). The application of DIA methodology in the synthesis of the protoberberine alkaloid (±)-cavidine **X** is described together with preliminary studies towards the synthesis of the more complex protoberberine alkaloid, (±)-pallimamine **XI**.



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## Acknowledgements

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I am also grateful to all of the technical staff in the chemistry department, NMR, Mass Spec., glass blowing workshop, stores workers for all of their help over the years and for making York such a great place to do research. I would like also to thank the University of York Wild Fund for my PhD bursary.

Finally, special thanks to my family for their constant love and support throughout my studies. I am so lucky to have you.

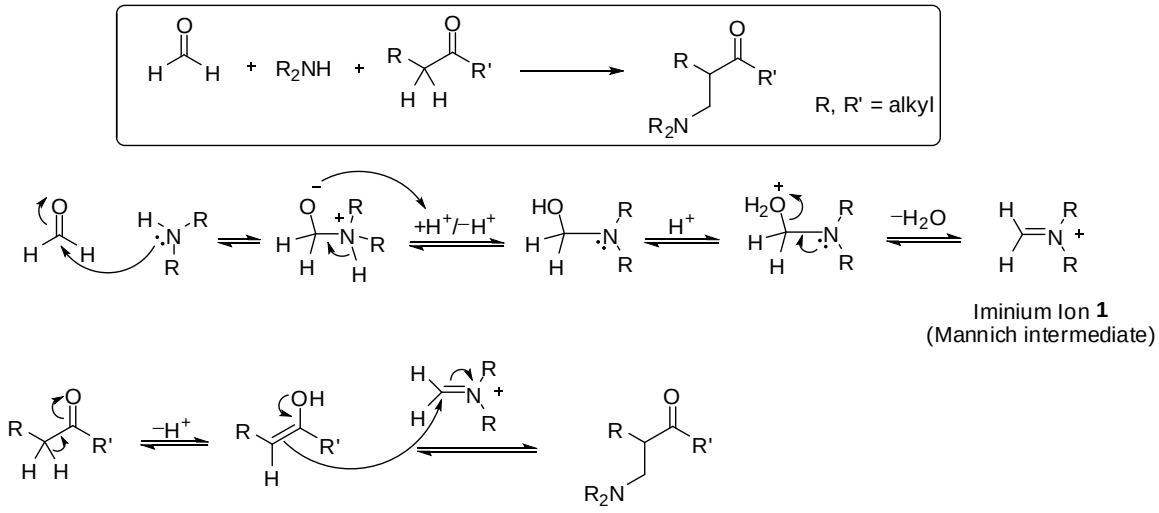
## Declaration

The research presented in this thesis was carried out at the University of York between October 2011 and December 2014. The work is, to the best of my knowledge, original except where due reference has been made to other workers. This work has not previously been presented for an award at this, or any other, University.

# Chapter 1 Introduction

## 1.1 Reactivity of Iminium *vs N*-Acyliminium Ions

Iminium ions **1** are widely used in organic synthesis as reactive species for the construction of carbon-carbon and carbon-heteroatom bonds. The well known Mannich reaction,[1] which has had an important role in synthetic organic chemistry for over 100 years, makes effective use of electrophilic iminium ions which serve as the reactive species for α-aminoalkylation reactions (Scheme 1). Moreover, the well known Pictet-Spengler[2] and Bischler-Napieralski reaction,[3] which are both subtypes of the Mannich reaction involving a cyclisation process, represent intramolecular α-aminoalkylation reactions with the iminium ions again serving as the electrophiles.




**Scheme 1**: Mannich aminoalkylation reaction

Throughout the last three decades it has been well established that substituting the nitrogen atom of the iminium species with electron-withdrawing groups renders the Mannich-intemediate **1** considerably more reactive.[4] Of the modified cations in Figure 1, the *N*-acyl derivative **2** has been most widely exploited although the use of other electronegative substituents such as esters, amides and tosyl groups has also been examined.[4b]

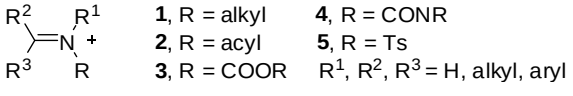
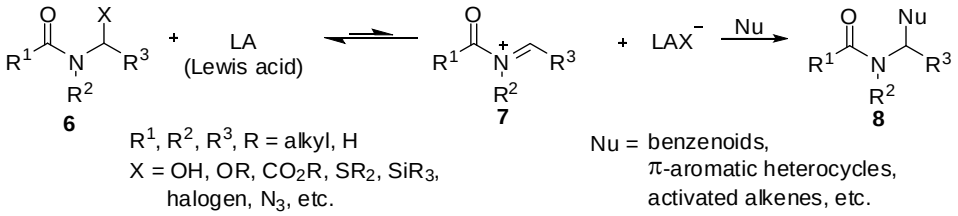



**Figure 1**: Electron-withdrawing groups at the nitrogen atom of the iminium species

The highly reactive nature of *N*-acyliminium ions requires that they are generated *in situ*; however, their transient formation has been detected in some NMR and IR spectroscopic studies.[5] In general, these intermediates are formed from more stable, isolable α-substituted acylamines of type **6** by treatment with Lewis acids or sometimes protic acids (Scheme 2). It is reported that *N*-acyliminium ions **7** exist in equilibrium with covalent adducts **6** and that the proportion of the ionic and covalent forms depends on the nature of the anion and on experimental conditions.[6] However, in the presence of suitable nucleophiles, ions of type **7** can react irreversibly to give α-substituted *N*-acylamines **8**. Note that acyclic and cyclic variants of *N*-acyliminium ions are both well established (Figure 2).[4]




**Scheme 2**: *N*-acyliminium ions **7** exist in equilibrium with covalent adducts **6**

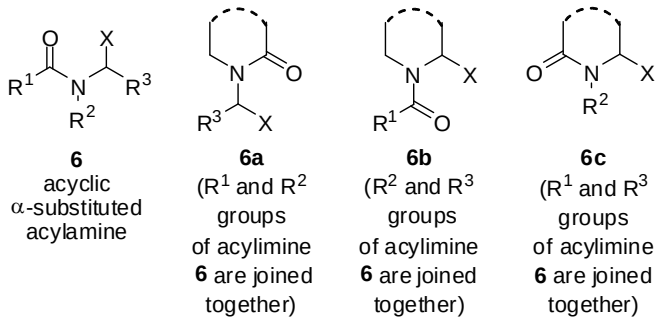
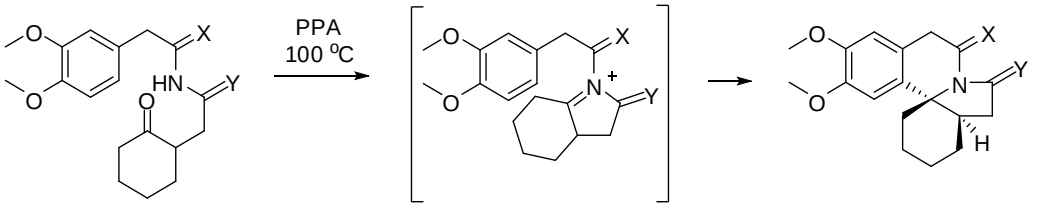



**Figure 2**: Acyclic and cyclic α-substituted acylamines

The use of *N*-acyliminium ions in heterocycle synthesis is well documented and this area has been thoroughly reviewed.[4,6] The higher reactivity profile of the *N*-acyliminium ions compared to their iminium analogues has been experimentally demonstrated. For example, while the iminium ion **10a** failed to cyclise to form the erythrinane skeleton **11a**, the analogous *N*-acyliminium species **10b** and **10c** cyclised successfully to give the erythrinane intermediates **11b** and **11c** in good yields (Scheme 3).[7]



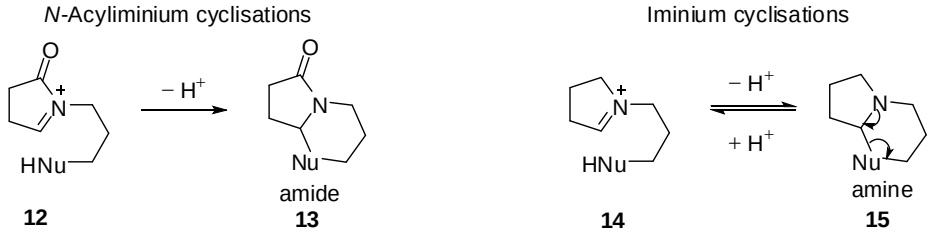

**9a** X = Y = $H_2$
**9b** X = O, Y = $H_2$
**9c** X = $H_2$, Y = O

**10a** X = Y = $H_2$
**10b** X = O, Y = $H_2$
**10c** X = $H_2$, Y = O

**11a** (X = Y = $H_2$), 0%
**11b** (X = O, Y = $H_2$), 71%
**11c** (X = $H_2$, Y = O), 65%

**Scheme 3**: The synthesis of the erythrinane intermediates **11b** and **11c**

The intramolecular reactions of *N*-acyliminium ions have received considerable attention in organic chemistry, especially for the synthesis of alkaloid natural products. The advantages of using *N*-acyliminium ions over iminium ions are plenty; in particular, the enhanced reactivity of *N*-acyliminium ions broadens the range of nucleophiles that can be used in carbon-carbon or carbon-heteroatom bond formation. In contrast, the Bischler-Napieralski and Pictet-Spengler reactions are more limited to small structural changes around the carbonyl or aromatic groups, because of the lower reactivity of the iminium intermediates.[6] In addition, *N*-acyliminium cyclisations are typically irreversible reactions.[4,6] The products of *N*-acyliminium cyclisations, which are amides, are less prone to fragmentation reactions, while the products of iminium cyclisations, which are amines, usually exist in equilibrium with the corresponding iminium ions (Scheme 4).[6]



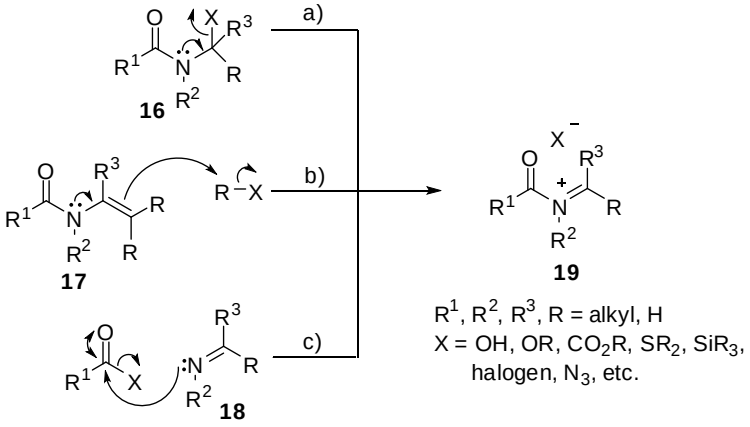

**Scheme 4**: *N*-Acyliminium cyclisations are typically irreversible reactions

An important side-reaction to be aware of in *N*-acyliminium ion chemistry is the formation of enamides *via* loss of a proton.[4a,6] This reaction may be reversible in an acidic medium, but this is not always the case. Enamides may then react as nucleophiles with the *N*-acyliminium ions still present to give dimeric structures. These problems arise if the *N*-acyliminium ion is not trapped quickly enough by the nucleophile. This may occur if the nucleophile is poorly reactive, or in the case of intramolecular reactions, if thermodynamic or stereoelectronic factors are unfavourable (e.g., formation

of large rings or anti-Baldwin products).[6] A detailed discussion on the formation of enamides from *N*-acyliminium ions is included in a following section (Section 1.2.2).

## 1.2 Generation of *N*-Acyliminium Ions

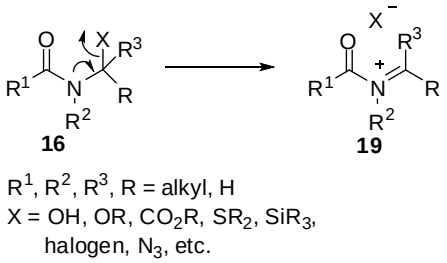
*N*-Acyliminium species can be accessed in a number of different ways, however because of their high reactivity they are always generated *in situ*. Generally, there are three major synthetic pathways: a) heterolysis of amides, bearing a leaving group on the α-carbon to nitrogen, b) electrophilic addition to enamides, c) *N*-acylation of imines (Scheme 5).[4,6]




**Scheme 5**: The three major synthetic pathways leading to *N*-acyliminium ions.

### 1.2.1 Heterolysis of Amides Bearing a Leaving Group on the α-Carbon to Nitrogen

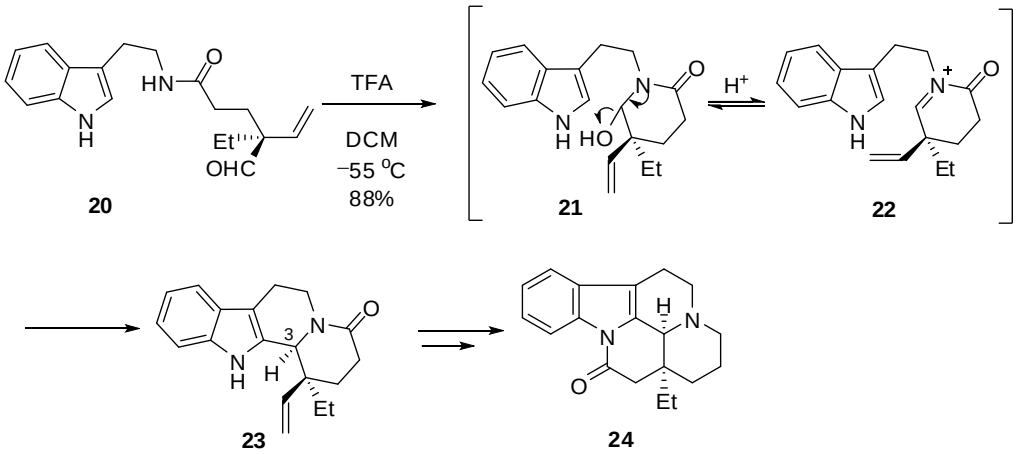
Heterolysis of α-substituted amides is by far the most common route to *N*-acyliminium ions (Scheme 6). In the majority of examples, the amide is substituted with an oxygen substituent such as hydroxyl, alkoxyl or carboxyl group; however, it can be also substituted with sulfur, silicon, halogen or nitrogen. There are several methods for the preparation of α-substituted amides, the most common of which are discussed below.




**Scheme 6**: Heterolysis of α-substituted amides

### 1.2.1.1 Reaction of Amides with Aldehydes or Ketones

Secondary amides can react with aldehydes or ketones to provide α-oxygenated intermediates which can be converted into *N*-acyliminium ions on treatment with an acid. An intramolecular example of an amide-aldehyde condensation can be seen in the synthesis of alkaloid (−)-eburnamonine **24** (Scheme 7).[8] The readily available carboxaldehyde **20** cyclised effectively under acid-catalyzed conditions to give lactam **23** *via* the formation an α-hydroxylactam **21**. Note that traces of the C(3)-epimer were also observed. Lactam **23** was then converted into the natural product **24** in 2 steps.

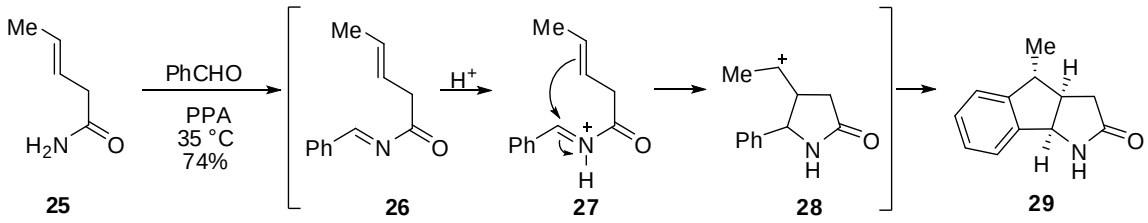



**Scheme 7**: The synthesis of lactam **23** *via* an *N*-acyliminium intermediate

An example of a ketone reacting with a secondary amide is included in the synthesis of the erythrinane skeleton **11b** and **11c** from amides **9b** and **9c** respectively as outlined in Scheme 3, Section 1.1. Note that in some cases dehydration to an enamide may take place and although in many instances this reaction can be reversible (especially under protic acid conditions), this is not always the case since enamides can further react to generate dimeric products *in situ*.[4a,6,9]

Primary amides can also react with aldehydes or ketones, to form *N*-acylimines which can then converted into *N*-acyliminium ions by reaction at nitrogen with an electrophile, usually a proton. This approach has been applied to the synthesis of lactam **29** as shown in Scheme 8; the condensation of (*E*)-3-pentanamide **25** with benzaldehyde in polyphosphoric acid afforded the tricyclic lactam **29** as a single diastereomer.[10] It is likely that *N*-acylimine **26** was formed first and then protonated under the strong acidic conditions to give the *N*-acyliminium ion **27**. A nucleophilic attack of the alkene to the *N*-acyliminium ion **27** followed by a second nucleophilic attack of the electron-rich

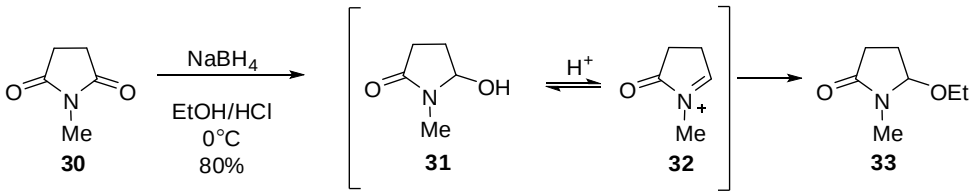
phenyl ring at the positive charged carbon of intermediate **28** then furnished the product. Note that more reactive carbonyl compounds like formaldehyde, trichloroacetaldehyde, glyoxylic acid and other α-dicarbonyl compounds are better substrates because they react with primary amides to form *N*-acylimines that are more stable and less susceptible to hydrolysis. Note also that *N*-acylimines can readily tautomerise to the corresponding enamides, therefore systems with no α-hydrogen atoms are better suited to this method of *N*-acyliminium ion formation.




**Scheme 8**: The synthesis of lactam **29** *via* an *N*-acylimine intermediate **26**

### 1.2.1.2 Regioselective Partial Reduction of Imides

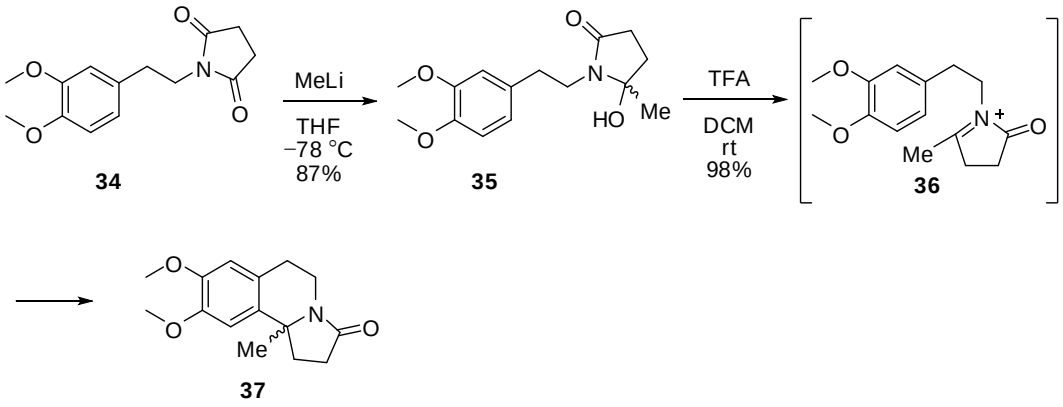
α-Oxygenated amides can be also prepared by the selective addition of hydride to one carbonyl of an imide. The main drawbacks of this conversion are the risk of overreduction or reductive ring opening. Speckamp *et al.* have developed this partial reduction of cyclic imides into a high yielding procedure by using excess sodium borohydride in ethanol (Scheme 9).[11] During the reaction, a dilute solution of hydrochloric acid in ethanol is slowly added to prevent the medium from becoming too basic, to avoid ring-opening of the product. The *N*-acyliminium ion **32** is then trapped with ethanol to give the *N*,*O*-acetal **33**. Note that problems with the regiochemistry of the reduction arise when unsymmetrical cyclic imides are used.




**Scheme 9**: Partial reduction of imide **30** with sodium borohydride

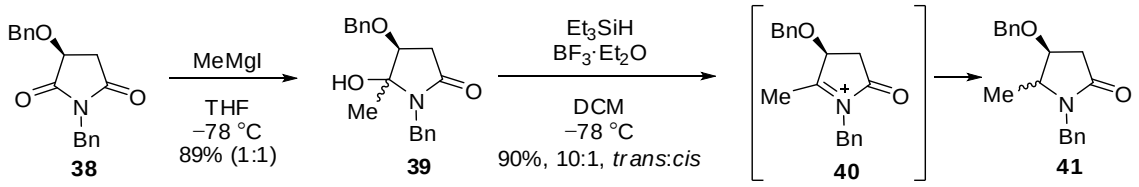
Organometallic reagents, such as Grignard and organolithium reagents, can also react with imides producing hemiaminals which are a source of *N*-acyliminium ions (Scheme 10).[12] Succinimide **34** was treated with MeLi in THF to give hemiaminal **35** in 87%

yield which was then treated with trifluoroacetic acid in dichloromethane to afford the desired tetrahydro-pyrroloisoquinolone **37** in 98% yield. Problems related with undesired ring opening were observed when bulkier organolithiums such as *n*-BuLi or PhLi were used. Note also that hemiaminals are very susceptible to dehydration making isolation and purification sometimes difficult.




**Scheme 10**: Partial reduction of symmetric succinimide **34** with an organolithium reagent

A regioselective Grignard addition to unsymmetrical cyclic imide **38** was achieved using MeMgI in THF affording hemiaminal **39** in 89% yield (Scheme 11).[13] The reductive cleavage of the carbon-oxygen bond of hemiaminal **39** to give product **41** was achieved using boron trifluoride diethyl etherate and triethylsilane, invoking the intermediacy of an *N*-acyliminium ion **40**.

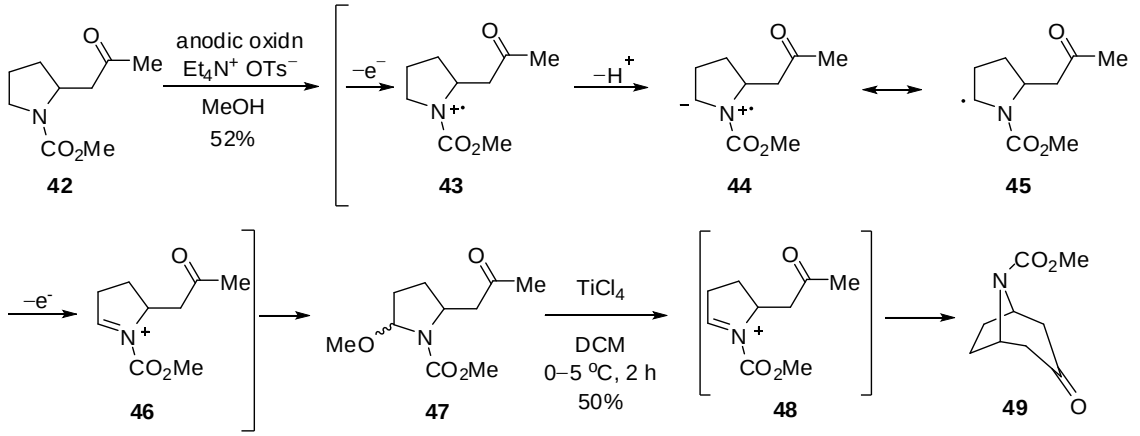



**Scheme 11**: Partial reduction of unsymmetrical imide **38** with a Grignard reagent

### 1.2.1.3 Oxidation of Amides at the Carbon α- to Nitrogen

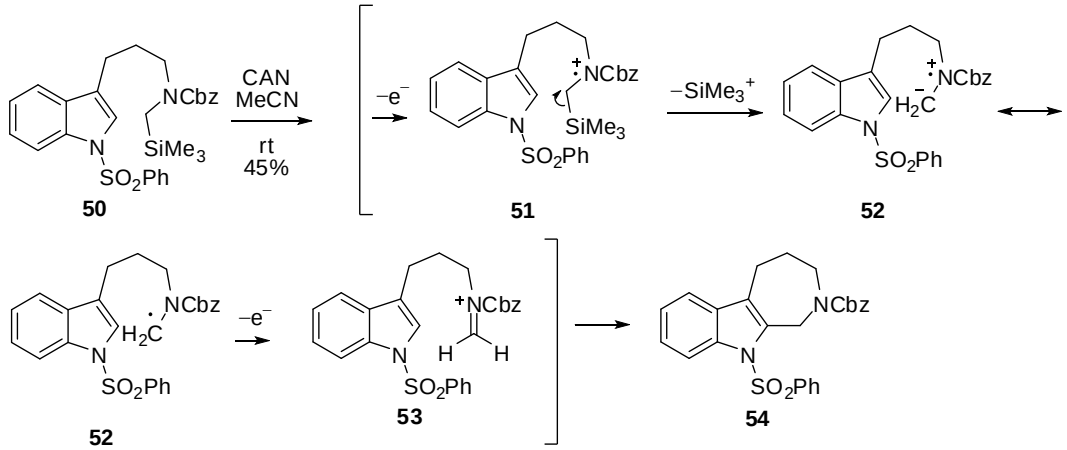
*N*-Acyliminium ions can also be obtained by the removal of hydride from the α-carbon of an amide and the most common way to effect this transformation is using electrochemical oxidation (Scheme 12).[14] The initial removal of an electron from the lone pair on nitrogen, followed by loss of a proton and another electron forms the unstable *N*-acyliminium ion **46**. This anodic oxidation was conducted in the presence of a nucleophile, MeOH, and the *N*-acyliminium ion **46** is trapped as soon as it is

generated to give the α-methoxy carbamate **47**. Treatment of the carbamate **47** with $TiCl_4$ formed the tropane alkaloid **49** *via N*-acyliminium ion intermediate **48**. Note that although this method can work well, oxidative side-products are often observed.[15]



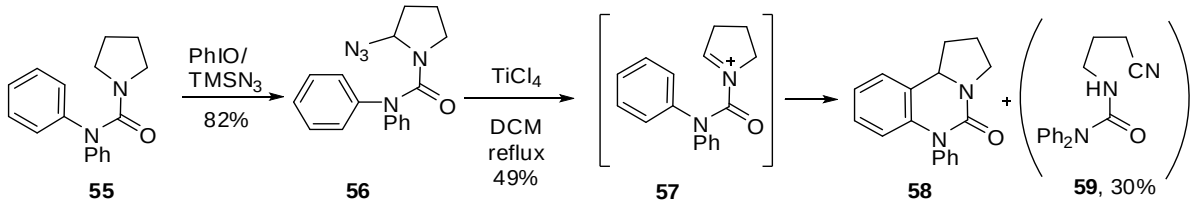

**Scheme 12**: Electrochemical oxidation of the carbamate **42**

Chemical oxidation is also possible (Scheme 13). An interesting method is to use a silane to promote oxidation at a specific site, followed by an *N*-acyliminium ion cyclisation; the high regiocontrol associated with these processes is due to the more rapid rates of tertiary aminium radical α-desilylation compared with competitive α-deprotonation.[16] For example, compound **50** was subjected to cerium(IV) oxidation which led to the generation of *N*-acyliminium ion **53** followed by cyclisation onto the 2-position of the indole to give product **54**.[17] Note that this method is intolerant of functionalities which are oxidatively unstable.



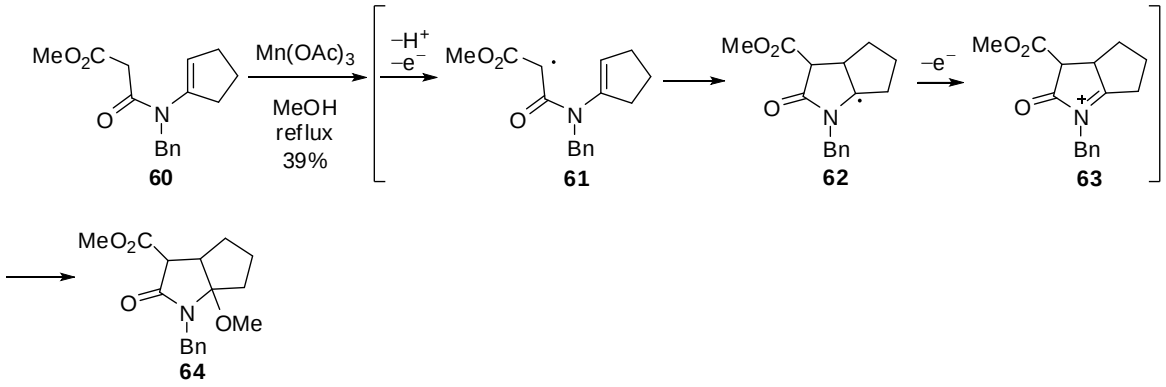

**Scheme 13**: Chemical oxidation of the carbamate **50**

The oxidation of *N*-acyl pyrrolidines with iodosylbenzene and trimethylsilyl azide produces 2-azido derivatives which are effective *N*-acyliminium ion precursors when treated with Lewis acids (Scheme 14).[18] The oxidation of pyrrolidine **55** gave 2-azido-pyrrolidine **56** in excellent yield. *N*-Acyliminium ion **57** was then formed from the α-azido derivative **56** in the presence of $TiCl_4$ and cyclised to give product **58** in 49% yield.



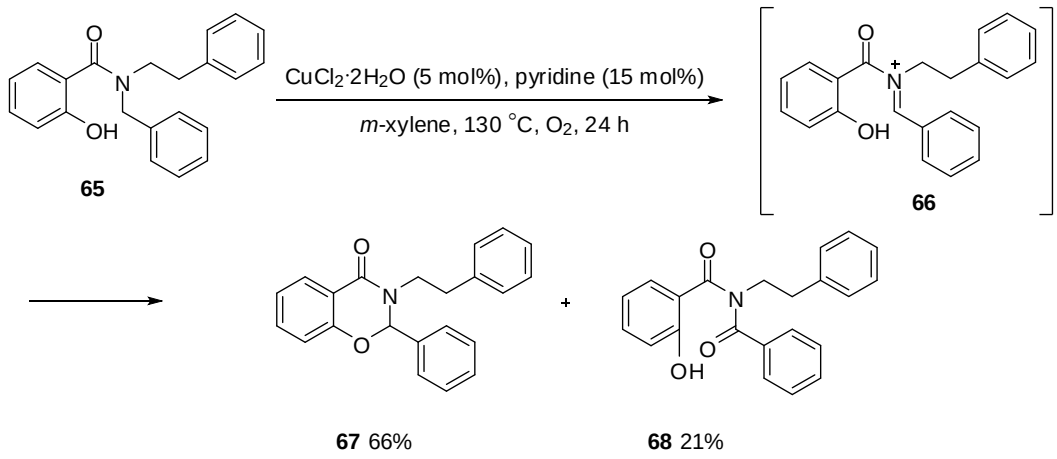

**Scheme 14**: Chemical oxidation of the *N*-acyl pyrrolidine **55** to form the α-azido derivative **56**

Chemical oxidation using $Mn(OAc)_3$ as the oxidative reagent is also possible. For example, the oxidation of the enamide **60** with $Mn(OAc)_3$ in methanol resulted in the formation of the α-methoxy amide **64** *via* an *N*-acyliminium intermediate **63** (Scheme 15).[19] In this case, the radical **61** was likely generated from the reaction of the enamide **60** with Mn(III). Cyclisation followed by subsequent oxidation by a second equivalent of Mn(III) produced the *N*-acyliminium ion **63**. The nucleophilic addition of methanol then gave the methoxy derivative **64**.




**Scheme 15**: Chemical oxidation of enamide **60** with Mn(III)

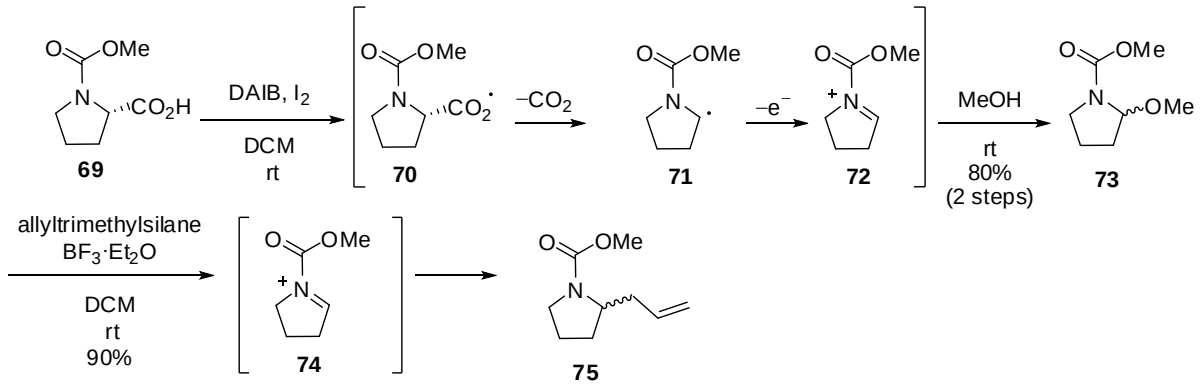
An analogous reaction, in which Cu(II) is the oxidant, was reported recently (Scheme 16).[20] A SET mechanism is proposed to form the key *N*-acyliminium ion intermediate **66**, and subsequent nucleophilic attack of the phenolate oxygen at the iminium carbon centre provided the desired dihydro-oxazinone derivative **67**. However, imide side-product **68** was also observed in the reaction mixture. The high reaction temperature (130 °C) and the imide side-products are significant drawbacks of this method.




**Scheme 16**: Chemical oxidation of amide **65** with Cu(II) catalyst

#### 1.2.1.4 Decarboxylation of α-Amido Acids

α-Oxygenated amides can be formed by the oxidative removal of a carboxylic acid group from an α-amido acid. One such method involving the use of a hypervalent iodide oxidant, is shown in Scheme 17.[21] A carboxyl radical **70** was proposed to form when α-amido acid **69** was treated with diacetoxy-iodo-benzene and iodine. This followed by loss of $CO_2$ to generate the alkyl radical **71**. The latter, being α-located to a nitrogen atom was easily oxidised by excess reagent to form an *N*-acyliminium ion **72** which was trapped by MeOH to give α-methoxy-lactam **73** in 80% yield. Lactam **73**, which is an *N*-acyliminium precursor itself, could then be trapped by various nucleophiles after elimination of the methoxy group (usually under acidic conditions). For example treatment of lactam **73** with boron trifluoride diethyl etherate and allyltrimethylsilane in dichloromethane furnished allyl-pyrrolidine **75** in 90% yield. An important drawback of this method is that side-reactions related to *N*-radical intermediates can take place.[22]



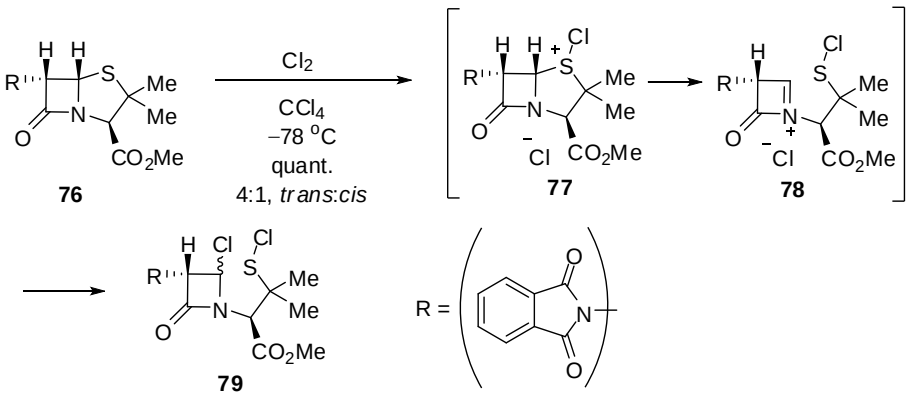

**Scheme 17**: Oxidative decarboxylation of α-amido acid **69** with DAIB/$I_2$

### 1.2.1.5 Miscellaneous

Although the heterolysis of α-oxygenated amides is the most common route to *N*-acyliminium ion intermediates, a variety of other α-substituted amides have been also employed, including α-silyl amides (Scheme 13), α-azido amides (Scheme 14) and α-amido acids (Scheme 17) as shown in the previous Sections (Sections 1.2.1.3 and 1.2.1.4). Moreover, halogen or sulfur substituents can be also effective leaving groups on the α-carbon to an amide and lead to *N*-acyliminium ion intermediates.

α-Halogenated amides are most straightforwardly prepared through the acylation of imines with acyl halides, examples of which will be given in Section 1.2.3. The major drawback of using α-halogenated amides as *N*-acyliminium ion precursors is that the elimination of HCl can be too facile, leading to their conversion into the corresponding enamides.

α-Thioalkyl amides are effective *N*-acyliminium ion precursors, however activation of the sulfur atom is required before it leaves to give the *N*-acyliminium ion intermediate. An example where an activation using chlorine gas is utilised for the electrophilic opening of the thiazolidine ring in penicillins is shown in Scheme 18.[23] The reaction of methyl 6-phthalimidopenicillanate **76** with chlorine gas, presumably proceeds through initial formation of sulfonium salt intermediate **77** and subsequent C-S bond cleavage to form the *N*-acyliminium ion **78**. The *N*-acyliminium ion **78** was then susceptible to nucleophilic attack by chloride anion to form the α-chloroamide **79**.

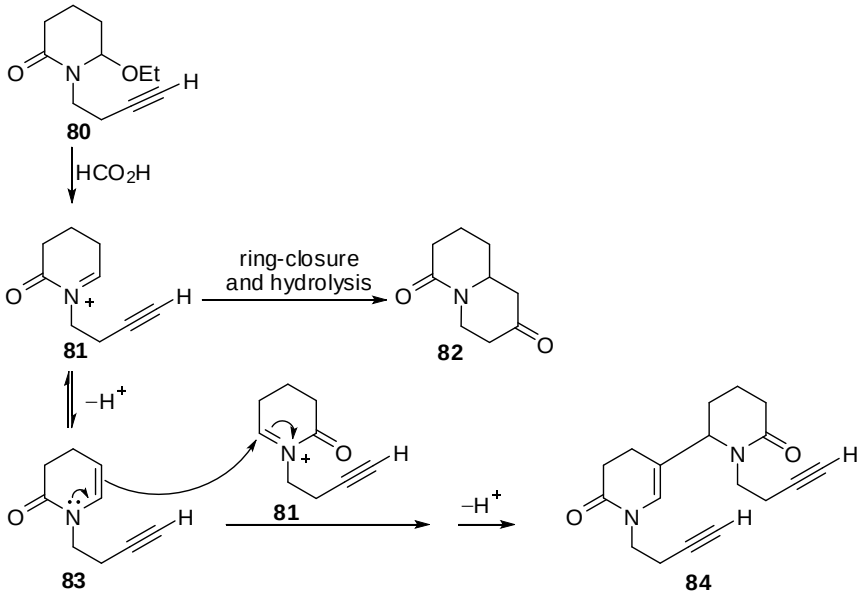



**Scheme 18**: α-Thioalkyl amides are effective *N*-acyliminium ion precursors

### 1.2.2 Electrophilic Addition to Enamides

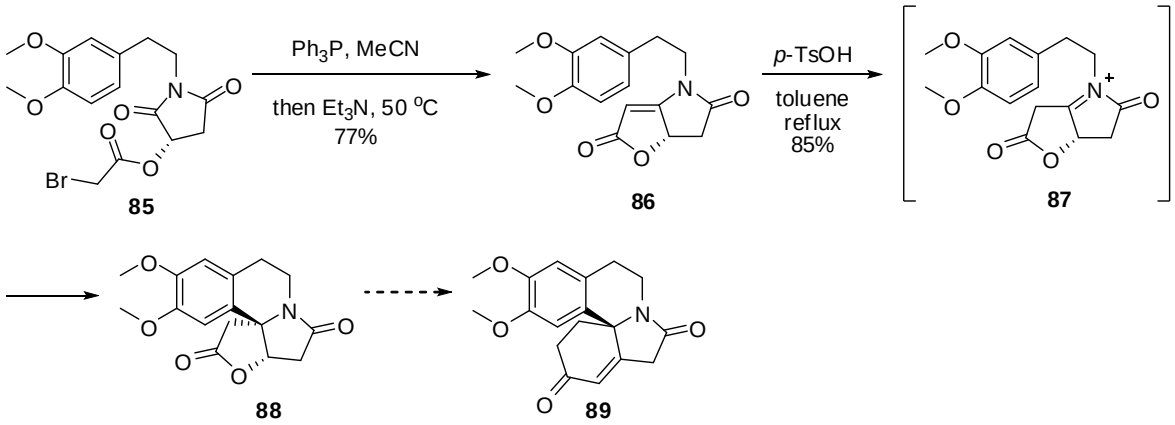
Enamides are easily obtained *via* the elimination of water or alcohol from α-hydroxyl or α-alkoxy amides or *via* the elimination of HCl from α-chloroalkyl amides. Although enamides are usually undesired intermediates in *N*-acyliminium ion chemistry, as they can lead to dimeric side-products, they can also serve as *N*-acyliminium ion precursors as their formation is usually reversible in acidic medium.

An example featuring an enamide formation which leads to an undesired dimeric side-product is illustrated in Scheme 19.[9] A 5:1 mixture of the desired cyclic product **82** and the dimer **84** is obtained when the reaction of 0.5 mmol of compound **80** was carried out in 3 mL of formic acid. However, in a more dilute solution (40 mL formic acid), the formation of the dimer **84** was not observed and only the bicyclic ketone **82** was isolated in 88% yield.



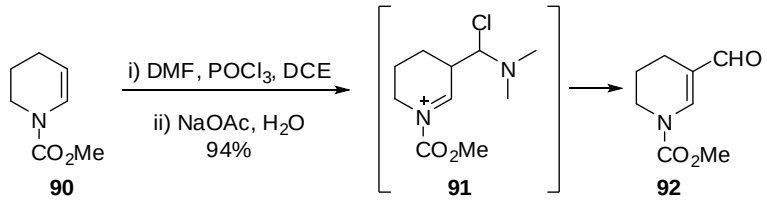

**Scheme 19**: The ring-closure of acetylene **80** to afford bicycle **82** and the enamide side-reaction which leads to dimeric product **84**

Another interesting example where an enamide serves as an *N*-acyliminium ion precursor is illustrated in Scheme 20. The conversion of imide **85** into tetracyclic isoquinoline derivative **88** was achieved *via* the enamide intermediate **86**.[24] The Wittig-type olefination of imide **85** provided enamide **86** which was then converted into *N*-acyliminium ion **87** *via* an electrophilic addition of a proton using *p*-toluenesulfonic acid in refluxing toluene. The electron-rich benzene ring then attacked the *N*-acyliminium ion **87** to generate the tetracyclic compound **88** as a single diastereoisomer. The high stereoselectivity of *N*-acyliminium ion cyclisation can be rationalised by the fact that the nucleophilic attack of the aromatic ring takes place on the side opposite to the lactone substituent to give the less-strained *cis*-fused tetracyclic isoquinoline derivative **88**. Note that compound **88** is a potential intermediate for the synthesis of the naturally occurring alkaloid 3-demethoxy-erythratidinone **89**.




**Scheme 20**: Electrophilic addition of a proton to the enamide **86** followed by an *N*-acyliminium cyclisation

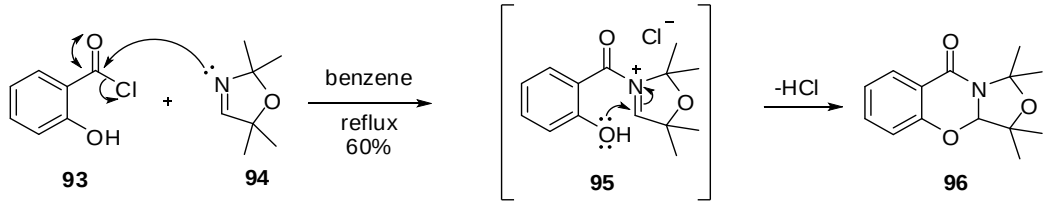
Another example of electrophilic addition reaction to enamides is the Vilsmeier reaction of the ene-carbamate **90** to give the *β*-formyl-ene-carbamate **92** (Scheme 21).[25] The reaction of ene-carbamate **90** with DMF and $POCl_3$ in 1,2-dichloroethane followed by hydrolysis gave β-formyl-ene-carbamate **92** in 94% yield, presumably *via* an *N*-acyliminium intermediate **91**.




**Scheme 21**: Electrophilic addition of a formyl group to the enamide **90** under Vilsmeier reaction conditions

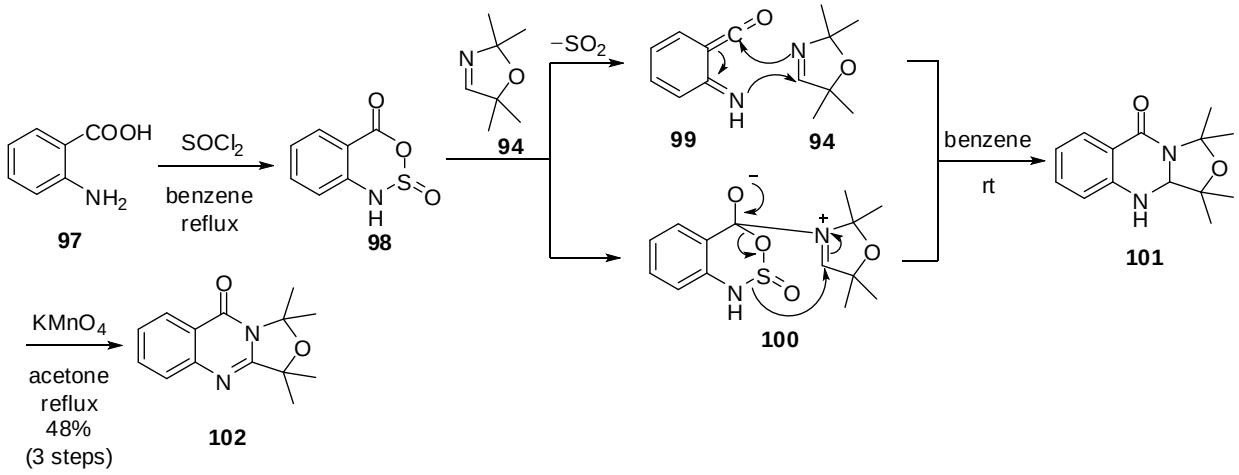
### 1.2.3 *N*-Acylation of Imines

The most direct route to *N*-acyliminium ions is *via* the *N*-acylation of imines with acid halides[26] and anhydrides.[27] For example, Johannes *et al.* showed that the treatment of salicyclic chloride **93** and 2,5-dihydrooxazole **94** in benzene at reflux afforded *N,O*-acetal **96** in 60% yield (Scheme 22).[26k] It was proposed that an *N*-acyliminium ion **95** was formed first, before the nucleophilic attack of the phenol at the imine carbon took place.




**Scheme 22**: *N*-Acylation of imine **94** with acid chloride **93**

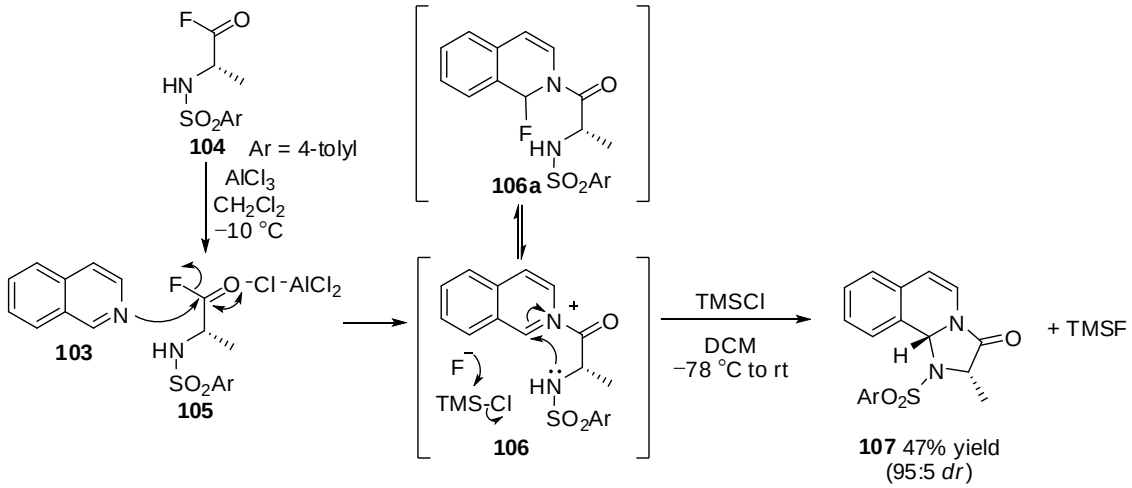
Johannes *et al.* also showed that refluxing anthranilic acid **97** in the presence of thionyl chloride gave sulfinamide anhydride **98**, which was then reacted with 2,5-dihydrooxazole **94** to give dihydroquinazoline **101** (Scheme 23).[26k] Dihydroquinazoline **101** was then subsequently oxidised to afford product **102** in 48% yield over the 3 steps. In this reaction the unstable sulfinamide anhydride **98** was formed and probably converted into the imino-ketene intermediate **99** which then reacted with 2,5-dihydrooxazole **94** in a concerted ($\pi^4+\pi^2$)-cycloaddition to form product **101**. A stepwise mechanism *via* the *N*-acyliminium ion intermediate is also possible, according to reports by Kametani *et al.*[27b,c]




**Scheme 23**: *N*-Acylation of imine **94** with sulfinamide anhydride **98**

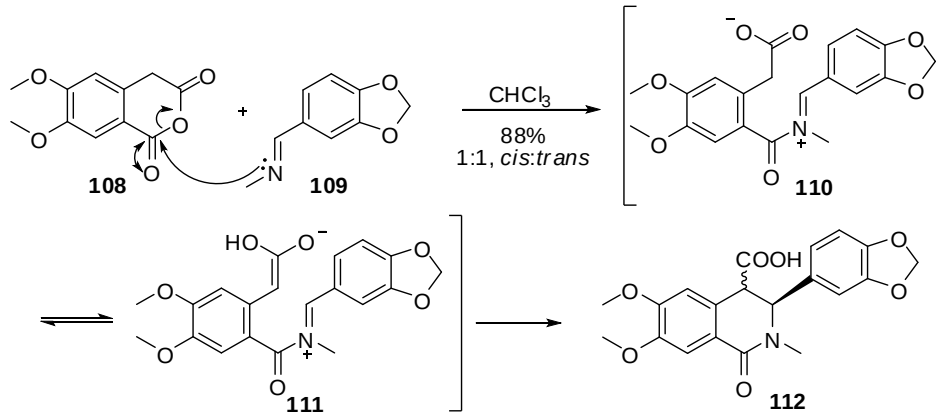
Recently, the reaction of isoquinoline **103** with α-aminoacyl fluoride **104** to afford the tricyclic product **107** *via* an *N*-acyliminium salt formation was reported (Scheme 24).[26h] Isoquinoline **103** and α-aminoacyl fluoride **104** reacted at −78 °C in dichloromethane in the presence of 0.2 equivalent of $AlCl_3$ and 1 equivalent of trimethylsilyl chloride. It was proposed that the complex of the α-aminoacyl fluoride with $AlCl_3$ (**105**) is attacked by the isoquinoline nitrogen atom, to give the *N*-acyliminium salt **106**. The salt **106** could be in an equilibrium with the corresponding covalent adduct **106a**, but the silyl

reagent trapped the fluoride ion revealing the highly reactive *N*-acyliminium ion **106**. The latter then cyclised to form the imidazolisoquinoline **107** in 47% yield (95:5 *dr*). It was reported that the yield was low due to formation of polyamides which could not be isolated and analysed.




**Scheme 24**: The reaction of isoquinoline **103** with α-aminoacyl fluoride **104**

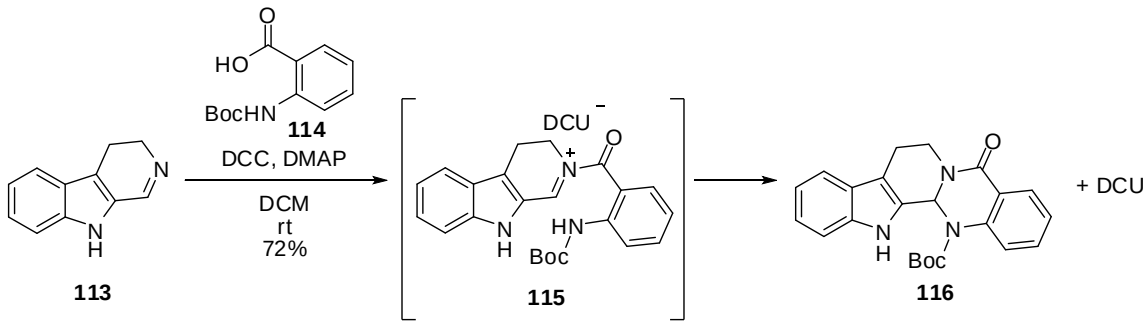
Strumberg *et al.* reported the direct acylation of imine **109** with homophthalic anhydride **108** to generate the substituted isoquinolone **112**, presumably *via* an *N*-acyliminium ion intermediate **110** (Scheme 25).[27d] The enolate **111** then trapped the *N*-acyliminium ion to give product **112** in 88% yield.




**Scheme 25**: Direct acylation of imine **109** with homophthalic anhydide **108**

As can be seen, the use of activated acids (acid chlorides, acid fluorides and anhydrides) for *N*-acyliminium generation has some precedent. However, this method suffers from limited substrate scope, as the internal nucleophile as well as other functional groups built into the coupling partners must be compatible with the acylating agent itself which is highly reactive.

To the best of our knowledge, apart from a single report, [28] which appeared after the start of this project, the direct acylation of imines with carboxylic acids is not known in the literature. This single reference reported the reaction of the dihydrocarboline **113** and carboxylic acid **114** under peptide coupling conditions (DCC/DMAP) to give *N*,*N*-acetal **116** in good yield (Scheme 26). A tandem *N*-acylation/intramolecular aza-cyclisation mechanism was proposed, involving an *N*-acyliminium cation of type **115**.




**Scheme 26**: The reaction of dihydrocarboline **113** with *N*-Boc protected carboxylic acid **114**

## 1.3 Construction of Ring Systems Using *N*-Acyliminium Cyclisations

The use of *N*-acyliminium ions in cyclisation reactions has emerged as a powerful tool for the construction of novel heterocycles and natural products.[4,6] In particular, these cyclisations have been utilised as the key carbon-carbon or carbon-heteroatom bond forming reactions in the synthesis of several pharmaceutically relevant cyclic scaffolds. Such scaffolds include the *Erythrina* alkaloid ring-systems (Schemes 3 and 20), indole alkaloid ring-systems (Scheme 7 and 13), oxazinone (Schemes 16 and 22) and quinazolinone ring-systems (Scheme 23), examples of which are given in the previous sections.

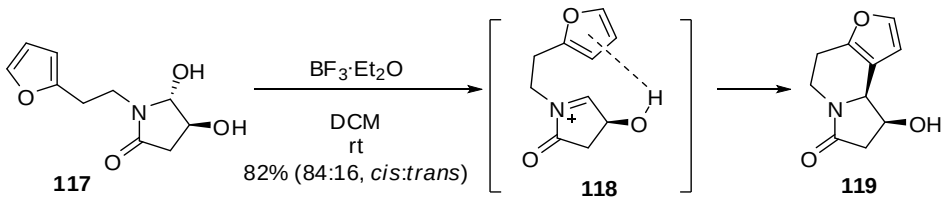
There are two important advantages of intramolecular *N*-acyliminium ion reactions over intermolecular *N*-acyliminium ion reactions. First, the generation of products from a substrate containing a relatively unreactive nucleophile, such as an unactivated

benzenoid or alkene group, is more facile and second, the stereochemical control is often better. This section is concerned exclusively with carbon-centered nucleophiles, including furan, thiophene, pyrrole, pyridine, alkene and alkyne derivatives.

### 1.3.1 Intramolecular Amidoalkylations with Aromatic π-Nucleophiles

*N*-Acyliminium cyclisations have been widely studied using aromatic π-nucleophiles.[4,6] As well as benzene rings, which are commonly used for these processes, there is a large range of other aromatic π-nucleophiles that can be also used for this purpose. Electron-rich heterocycles like indole, furan, thiophene and pyrrole, as well as a electron-deficient heterocycles such as pyridine, are effective nucleophiles in *N*-acyliminium cyclisation reactions. Examples of *N*-acyliminium cyclisations with benzene and indole nucleophiles have already been included in the previous sections (Schemes 3, 7, 10, 13, 14 and 20) and so here some additional examples with furan, thiophene, pyrrole and pyridine will be provided.

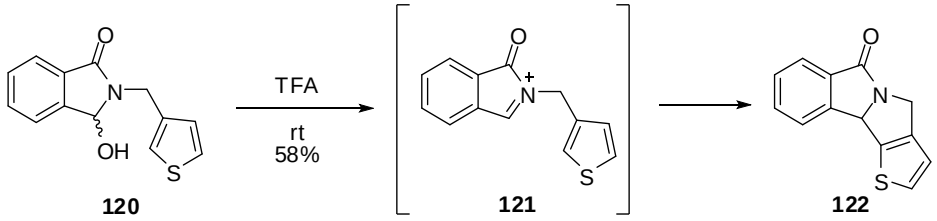
An interesting example of a highly diastereoselective *N*-acyliminium ion cyclisation which involves a tethered furan as the π-nucleophile was reported recently.[29] The fused tricyclic system **119** was formed with high *cis*-selectivity *via* *N*-acyliminium ion cyclisation of intermediate **118** which was formed from the diol **117** (Scheme 27). The Lewis acid $BF_3{\cdot}Et_2O$ in dichloromethane was used for this transformation. The *cis*-adduct formation could be attributed to an intramolecular interaction between the hydroxyl group and the electron-rich furan ring. Note that the furan reacted cleanly at the less reactive β-position as it is linked to the *N*-acyliminium ion at its α-position.




**Scheme 27**: *N*-Acyliminium cyclisation using furan as the π-nucleophile

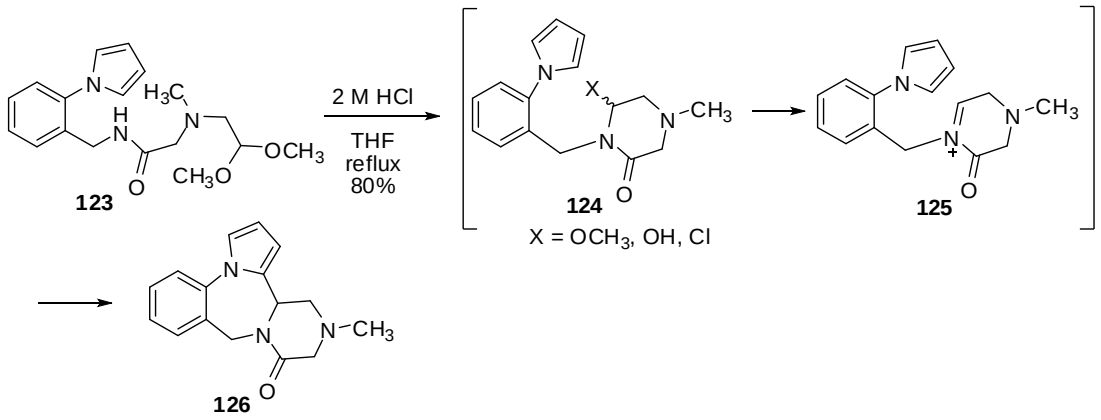
Thiophene cyclisations are usually straightforward with the reaction being favoured at the more reactive α-position of the heterocycle. Cyclisations to form strained

five-membered-ring products are possible as shown in the example below (Scheme 28); hemiaminal **120** was treated with trifluoroacetic acid to give the cyclised product **122** in 58% yield.[30]



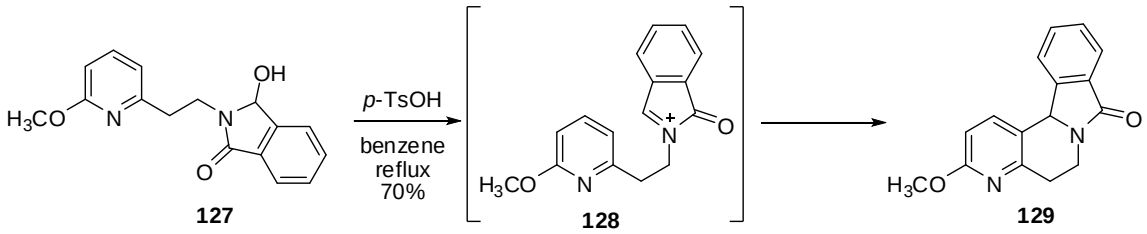

**Scheme 28**: *N*-Acyliminium cyclisation using thiophene as the π-nucleophile

*N*-Acyliminium ions linked to a pyrrole nitrogen also cyclise at the α-position. The seven-membered-ring lactam **126** was synthesised from compound **123** *via* treatment with 2 M HCl in THF (Scheme 29).[31] The reaction likely proceeds *via* intermediate **124** which forms the corresponding *N*-acyliminium ion **125** in the acidic medium. This subsequently cyclises to give lactam **126**.




**Scheme 29**: *N*-Acyliminium cyclisation using pyrrole as the π-nucleophile

Moreover, pyridines, which are electron-deficient heterocycles, can be suitable nucleophiles for *N*-acyliminium ion cyclisation reactions. Although this area is much less developed, *N*-acyliminium ion cyclisations do proceed when the pyridine nucleus is activated by electron-donating substituents such as methoxy groups. Padwa *et al.* showed that refluxing hemiaminal **127** in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid provided the tetracyclic compound **129** in good yield (Scheme 30).[32]

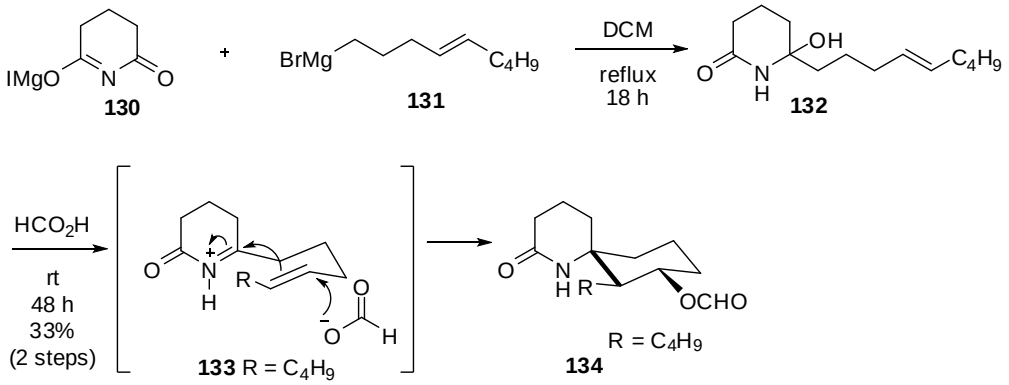



**Scheme 30**: *N*-Acyliminium cyclisation using an activated pyridine as the π-nucleophile

### 1.3.2 Intramolecular Amidoalkylations with Non-Aromatic π-Nucleophiles

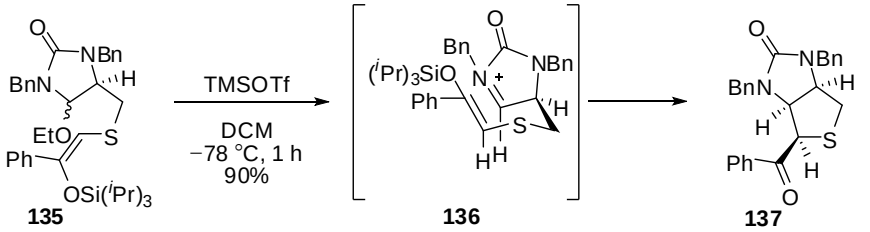
The study of the reactions of non-aromatic π-nucleophiles in *N*-acyliminium ion cylisations has been a very fruitful and diverse area of research.[4,6] *N*-Acyliminium ions are well suited to cyclisation onto alkenes, alkynes, vinyl enol ethers, vinyl silanes, allylsilanes, enols and enolates.

Alkenes and alkynes can attack *N*-acyliminium ions to furnish carbocation intermediates which can be transformed to the final products either by solvent capture, the addition of external nucleophiles or elimination. Representative examples are illustrated in previous sections (Scheme 8 and 19). An additional example where a spirocyclic system is formed from the reaction of an alkene with an *N*-acyliminium ion is shown below (Scheme 31).[33] The addition of the Grignard reagent **131** to the iodomagnesium salt of glutarimide **130** in dichloromethane afforded the hemiaminal **132** which was then treated with anhydrous formic acid to give the 6,6-spirolactam formate ester **134** as a single diastereoisomer in 33% overall yield. A chair-like transition state was proposed, with the *N*-acyliminium ion adopting a pseudo-equatorial position, permitting an anti-periplanar addition to give the desired spirocyclic amide **134** as a single diastereosiomer.




**Scheme 31**: *N*-Acyliminium cyclisation using an alkene as the π-nucleophile to form a spirocyclic system

Cyclisations of activated alkenes substituted with ether groups are also known in the literature. In particular, the condensation of silyl enol ethers with *N*-acyliminium ion intermediates is very efficient and has been used as the key step in several synthetic sequences. An interesting example is shown in Scheme 32.[34] The *Z*-isomer of the triisopropylsilyl enol ether **135** was treated with excess trimethylsilyl trifluoromethanesulfonate in dichloromethane to afford the crystalline product **137** in 90% yield as a single diastereoisomer. The same result was obtained when the *E*-isomer of enol ether **135** was used. The formation of only one diastereoisomer is rationalised by assuming that both isomers adopt a chair-like conformation prior to cyclisation, regardless of the geometry of the double bond.

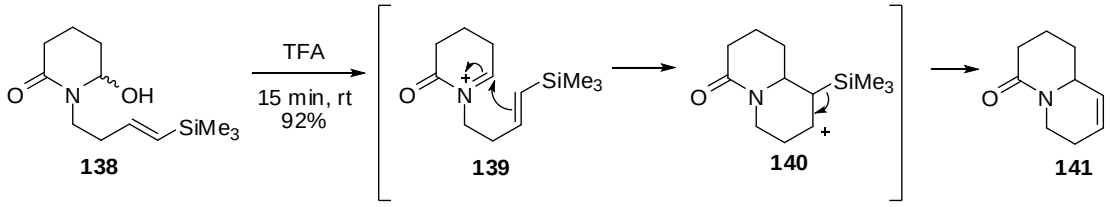



**Scheme 32**: *N*-Acyliminium cyclisation using a silyl enol ether as the π-nucleophile

Similarly, enol or enolate nucleophiles can attack the *N*-acyliminium ion effectively. Examples of *N*-acyliminium cyclisations of enols/enolates include the cyclocondensation of imines with anhydrides and the formation of tropane alkaloids from substituted pyrrolidines, as discussed in previous sections (Scheme 12 and 25).

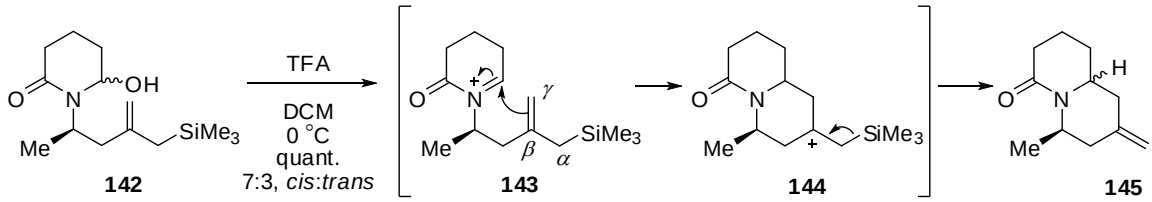
Vinylsilane nucleophiles can also participate in *N*-acyliminium ion cyclisation reactions giving adducts in good to excellent yields. In this case, the cyclisation is directed by the "β-silyl effect"; for example, hemiaminal **138** was dissolved in dry trifluoroacetic acid

and stirred for 15 minutes at rt to give quinazolizidine **141** in 92% yield exclusively (Scheme 33).[35]




**Scheme 33**: *N*-Acyliminium cyclisation using a vinylsilane as the π-nucleophile

Allylsilanes are normally good participants in *N*-acyliminium cyclisations and often engender excellent regiocontrol. The β-effect of the silicon atom is the determinant of the regiochemistry and a new carbon-carbon bond is generally formed at the vinyl carbon γ- to silicon. An example of cyclisation of a nitrogen-linked allylsilane is illustrated below (Scheme 34); hemiaminal **142** was treated with trifluoroacetic acid in dichloromethane to give product **145** in quantitative yield.[36]




**Scheme 34**: *N*-Acyliminium cyclisation using an allylsilane as the π-nucleophile

A number of *N*-acyliminium ion cyclisation reactions have been summarised, demonstrating the high utility of these processes in heterocycle synthesis. The development of a new synthetic approach to form and cyclise *in situ N*-acyliminium ion intermediates, from relatively unreactive starting materials, is the subject of this project and will be discussed in detail in the following Chapter.

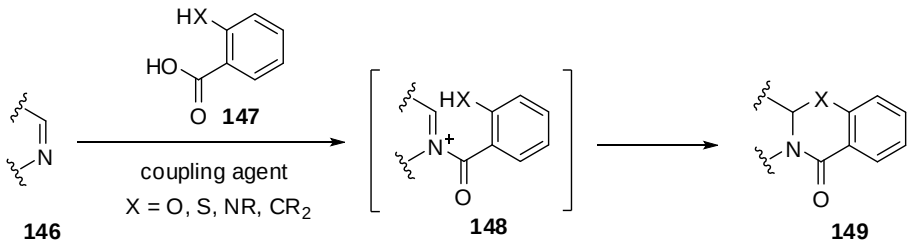
# Chapter 2 Direct Imine Acylation Methodology

## 2.1 Introduction to the Direct Imine Acylation Methodology: Project Aims

Having given an overview of existing methods for the synthesis of diverse heterocycles *via* the formation of *N*-acyliminium ions, it is clear that in the vast majority of examples, the *N*-acyliminium species is generated from a preformed system, usually *via* regioselective partial reduction[11–13] or regioselective amide oxidation.[14,15,17–20] A convergent approach to *N*-acyliminium species has also some precedent, involving the acylation of imines with acid halides[26] or anhydrides.[27] However, only a single example of the direct acylation of imines with carboxylic acids has been reported to date.[28]

It was envisioned that a novel scaffold diversity approach which involves the formation of *N*-acyliminium ions *via* the direct acylation of imines with carboxylic acids could be a valuable addition to existing methods. The access to such approach would be beneficial over the traditional methods, which typically suffer from undesirable side-reactions and harsh reaction conditions.

The concept of our Direct Imine Acylation (DIA) project is illustrated in Scheme 35. The main aim of the research was to explore the generation of an *N*-acyliminium ion **148** by acylation of an imine **146** with a functionalised carboxylic acid **147**. The *N*-acyliminium ion **148** would then be primed to undergo *in situ* cyclisation, *via* nucleophilic attack by a nucleophile or pro-nucleophile built into the acid coupling partner to give adduct **149**.



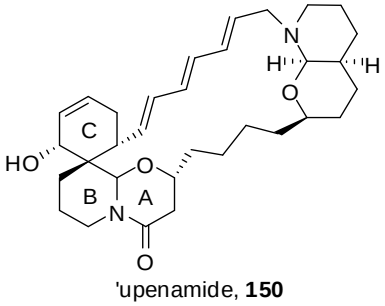

**Scheme 35**: Direct Imine Acylation (DIA) methodology

The key advantage of the direct use of carboxylic acids rather than activated derivatives (acid chlorides or anhydrides) is that it negates the need to perform and isolate these intermediates, meaning that this method is compatible with many functional groups on the acid coupling partners. In addition, many suitable acid coupling partners are

commercially available and easy to handle. These features give DIA a great potential with regards to diversity-oriented synthesis, the aim of which is the rapid access to molecular diversity from simple starting materials.[37] Once established, the aim was then to apply the DIA methodology in natural product synthesis.

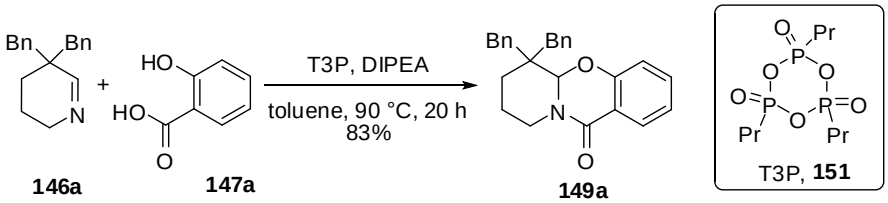
## 2.2 Initial Studies

The emergence of DIA methododology as a useful synthetic tool began during model studies, run within the group, towards the synthesis of the ABC fragment of the complex natural product, ‘upenamide **150** (Figure 3).[38] Studies conducted by Dr. Will Unsworth had shown that the coupling of the cyclic imine **146a** and salicyclic acid **147a** was really efficient, affording adduct **149a** in 83% yield after column chromatography (Scheme 36). Imine **146a** was chosen for these initial studies as it is non-volatile and cannot tautomerise to the corresponding enamine and so competing side-reactions and/or self condensation/polymerisation are negated. Propylphosphonic acid anhydride (T3P, **151**)[39] was used as the coupling agent and DIPEA as the base. T3P was chosen to effect the direct coupling, as it is nontoxic and the by-products are easily removed by aqueous extraction. The DIA reaction was performed by simply mixing the coupling partners, **146a** and **147a**, with T3P and DIPEA in toluene and heating to 90 °C for 20 h.



'upenamide, **150**

**Figure 3:** The natural product ‘upenamide **150**

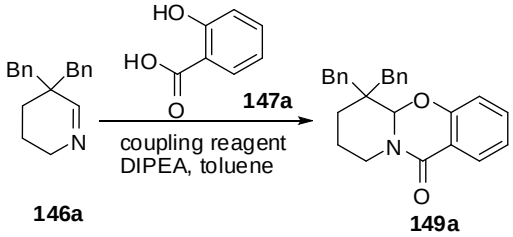


**146a** **147a** **149a**

**Scheme 36**: DIA reaction of imine **146a** with acid **147a**

Additional experiments, in which the same coupling was attempted using CDI and DCC in place of T3P, led to the formation of adduct **149a**, albeit in lower yield (Table 1, entry ii, iii). The same reaction was also tested using EDC as the coupling agent (entry iv) but it failed, most likely because of the poor solubility of EDC in toluene. Thus, T3P proved to be the most effective coupling agent but other coupling reagents can also be used in cases where T3P is either unavailable or unsuitable.

**Table 1**: Alternative coupling reagents[a]



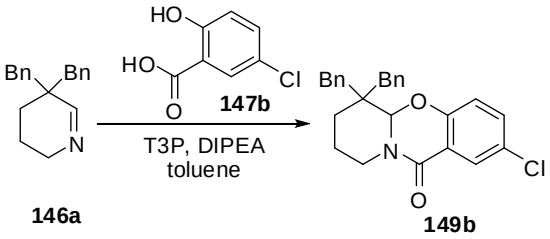

**146a** **149a**

| Entry[b] | Coupling reagent | Yield[c] |
|---|---|---|
| i | T3P | 83% |
| ii | CDI | 52% |
| iii | DCC | 77% |
| iv | EDC | 0% |

[a] This screening of conditions was conducted by Dr. Graeme Coulthard. [b] Reactions were performed on a 0.1–0.3 mmol scale using imine **146a** (1 equiv.), salicyclic acid **147a** (1.2 equiv.), coupling reagent (1.5 equiv.) and DIPEA (1.85 equiv.) in toluene at 90 °C for 20 h. [c] Isolated yield following column chromatography.

Although the above example proceeded in an excellent unoptimised yield (83%), somewhat harsh conditions (90 $^{o}$C, 20 h) had been used. Hence, in this research, it was next examined if milder conditions could give similar results (Table 2). The imine **146a** and salicyclic acid **147b** were used as the test substrates and the effect of temperature and reaction time were explored. The reaction gave full conversion to adduct **149b** when heated for 20 h at 90 °C (Table 2, entry i) while at 70 °C (entry ii), 50 °C (entry iii) and rt (entry iv) it gave lower yields. Reducing the reaction time to 1 h at 90 °C (entry v) or 70 °C (entry vi) gave 50% and 40% yield, respectively. Also the same coupling was attempted in the absence of either T3P (entry vii) or DIPEA (entry viii) but the reaction led only to the recovery of the starting materials proving that both T3P and DIPEA are necessary for the reaction to take place.

**Table 2**: Screening for optimal reaction conditions




146a 149b

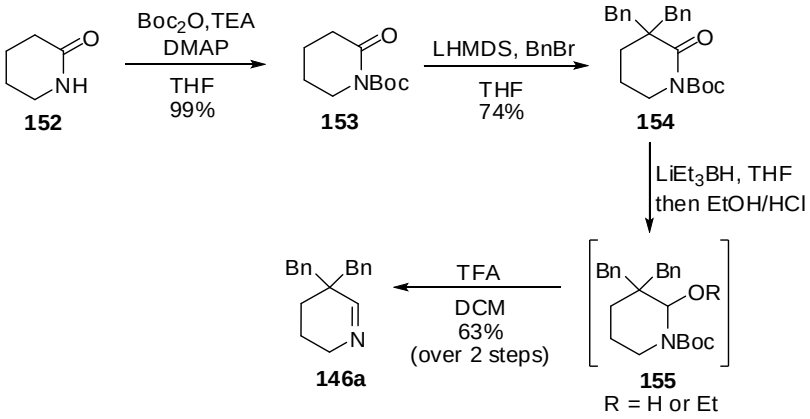
| Entry[a] | Temp. (°C) | Time (h) | Outcome (Conversion) |
|---|---|---|---|
| i | 90 | 20 | 100% |
| ii | 70 | 20 | 90% |
| iii | 50 | 20 | 70% |
| iv | rt | 20 | 20% |
| v | 90 | 1 | 50% |
| vi | 70 | 1 | 40% |
| vii[b] | 90 | 48 | No reaction |
| viii[c] | 90 | 48 | No reaction |

[a] Reactions were performed on a 0.1–0.3 mmol scale using imine **146a** (1 equiv.), salicyclic acid **147b** (1.2 equiv.), T3P (1.5 equiv.) and DIPEA (1.85 equiv.) with conditions shown unless stated. [b] The reaction was performed without the use of T3P. [c] The reaction was performed without the use of DIPEA.

## 2.3 Benzoic Acid Scope in DIA Reactions

### 2.3.1 The Synthesis of the Imine 146a

Having established optimal DIA reaction conditions, we then went on to explore DIA using a range of substituted salicyclic acid derivatives. The novel cyclic imine **146a** was synthesised on large scale and used as the test substrate to establish the acid scope. An efficient 4-step sequence, developed within the group,[40] was used to synthesise imine **146a** from piperidin-2-one **152**. Boc-Protection of piperidin-2-one **152** gave product **153** which was then benzylated to give intermediate **154** in good yield (Scheme 37). The partial reduction of product **154** with $LiEt_3BH$ (Super-Hydride$^{TM}$) followed by protecting group cleavage with trifluoroacetic acid furnished imine **146a** in 63% yield over the two steps. Note that in the current research project gram-scale quantities of high purity imine **146a** (~3g) were synthesised with the same percentage yield.

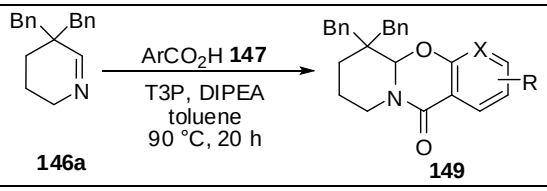



**Scheme 37**: Synthesis of imine **146a**

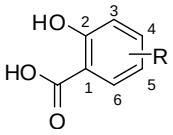
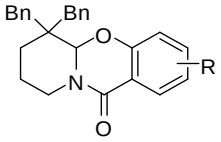
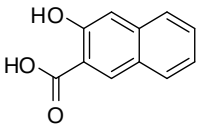
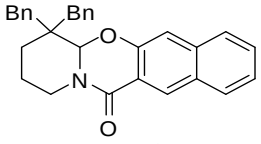
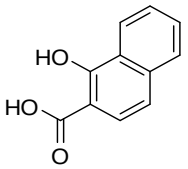
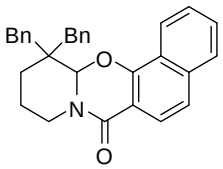
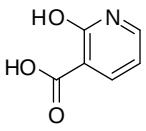
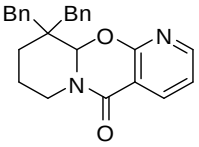
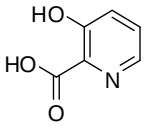
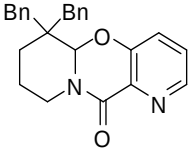
### 2.3.2 *Ortho*-Hydroxy Aromatic Acids

Commercially available salicyclic acid derivatives substituted with electron-deficient (**147b–d**), electron-donating (**147e–h**) and electron-neutral groups (**147a**) were used to afford *N*,*O*-acetals **149a–h** in excellent yields (Table 3, entries i-viii). Note that when the reaction in entry iii was performed on a large scale (3 mmol scale) it afforded product **149c** without a reduction in yield. All of these reactions were performed using the same conditions (90 °C, 20 h) with the exceptions of entries v and vii where a higher reaction temperature (120 °C) was required in order to achieve full conversion into the respective products **149e** and **149g**. We reasoned that the higher temperature is needed because the activated carboxylic acids in entries v and vii are presumably less electrophilic than the other systems tested as a result of the presence of the electron-rich methoxy groups, thus making the initial *N*-acylation slower. Naphthalene and pyridine derivatives **147i–l** are also well tolerated, affording products **149i–l** in very good yields (entries ix–xii). All of the novel products **149a–l** were fully characterised by $^{1}$H-NMR and $^{13}$C-NMR spectroscopy and by HRMS spectrometry.

**Table 3**: Acid scope in DIA with *ortho*-hydroxy aromatic acids and imine **146a**

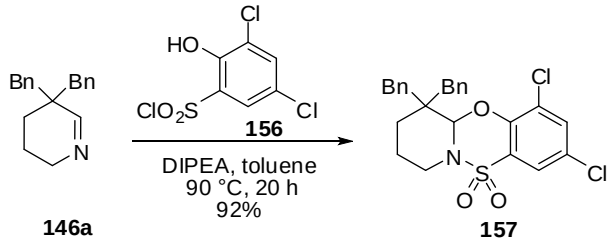



**146a** **149**

| Entry[a] | Acid | Product | Yield[b] |
|---|---|---|---|
| |  |  | |
| i | **147a**, R = H | **149a**, R = H | 83% |
| ii | **147b**, R = 5-Cl | **149b**, R = 5-Cl | 96% |
| iii[c] | **147c**, R = 5-$NO_2$ | **149c**, R = 5-$NO_2$ | 91% |
| iv | **147d**, R = 3-$NO_2$ | **149d**, R = 3-$NO_2$ | 89% |
| v[d] | **147e**, R = 4-OMe | **149e**, R = 4-OMe | 82% |
| vi | **147f**, R = 5-OMe | **149f**, R = 5-OMe | 60% |
| vii[d] | **147g**, R = 6-OMe | **149g**, R = 6-OMe | 64% |
| viii | **147h**, R = 4,6-OH | **149h**, R = 4,6-OH | 60% |
| ix |  **147i** |  **149i** | 95% |
| x |  **147j** |  **149j** | 92% |
| xi |  **147k** |  **149k** | 97% |
| xii |  **147l** |  **149l** | 63% |

[a] Reactions were performed on a 0.1–0.3 mmol scale using imine **146a** (1 equiv.), acid **147** (1.2 equiv.), T3P (1.5 equiv.) and DIPEA (1.85 equiv.) with conditions shown unless stated. [b] Isolated yield following column chromatography. [c] Reaction performed also on a 3 mmol scale and gave product **149c** in 90% yield. [d] Reaction performed at 120 °C for 20 h.

It is noteworthy that the DIA concept is not limited to acylation as demonstrated by the formation of the sulfonamide-containing dioxo(dihydro)-benzoxathiazine **157** from the reaction of the imine **146a** with the commercially available sulfonyl chloride **156**. This reaction was performed without the use of T3P (Scheme 38).

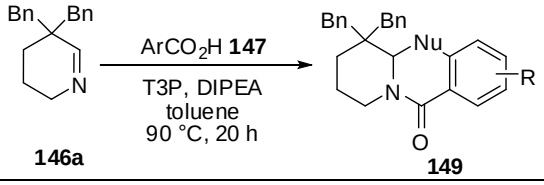



**Scheme 38**: The formation of dioxo(dihydro)-benzoxathiazine **157**.

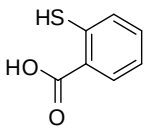
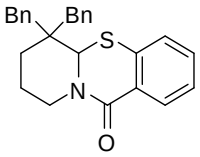
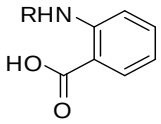
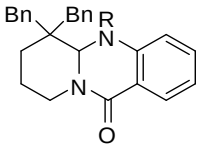
### 2.3.3 Sulfur and Nitrogen Nucleophiles

The DIA methodology is also not restricted to trapping the intermediate *N*-acyliminium ion with oxygen nucleophiles. Thiosalicyclic acid **147m** and anthranilic acids **147n** and **147o** provided thiazinone **149m** (Table 4, entry i) and diazinones **149n** and **149o** (entry ii, iii) respectively in almost quantitative yields. Interestingly, the reaction with thiosalicyclic acid **147m** could be performed in the absence of T3P giving 20% conversion to adduct **149m**. This result is not surprising since the condensation of imines with thiols has been reported previously.[26k, 41] However, no reaction was observed when T3P was excluded from the reaction of imine **146a** with *N*-methyl anthranilic acid **147n** (entry ii). The consequences of these findings have important mechanistic implications which are discussed in Section 2.8 in more detail.

**Table 4**: Acid scope in DIA with *ortho*-nitrogen and sulfur-substituted aromatic acids and imine **146a**



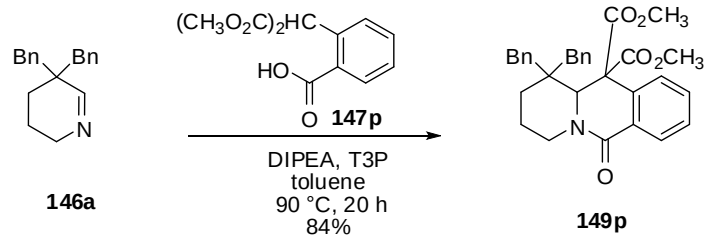

**146a** **149**

| Entry[a] | Acid | Product | Yield[b] |
|---|---|---|---|
| i[c] |  |  | 96% |
| | **147m** | **149m** | |
| |  |  | |
| ii[d] | **147n** | **149n**, R = Me | 97% |
| iii | **147o** | **149o**, R = Ph | 95% |

[a] Reactions were performed on a 0.1–0.3 mmol scale using imine **146a** (1 equiv.), benzoic acid **147** (1.2 equiv.), T3P (1.5 equiv.) and DIPEA (1.85 equiv.) with conditions shown unless stated. [b] Isolated yield following column chromatography. [c] Reaction performed in the absence of T3P gave 20% yield product. [d] Reaction performed in the absence of T3P gave 0% yield product.

### 2.3.4 Carbon Nucleophiles

We were also interested to examine the ability of DIA reaction to form C–C bonds by trapping the *N*-acyliminium ion with carbon-centered nucleophiles. Pleasingly, when the readily available diester **147p**[42] was subjected to DIA reaction conditions (T3P, DIPEA, 90 $^{o}$C, 20 h, toluene), it generated the tricyclic lactam **149p** in excellent yield (Scheme 39). Note that no product was observed when the reaction was performed in the absence of T3P.

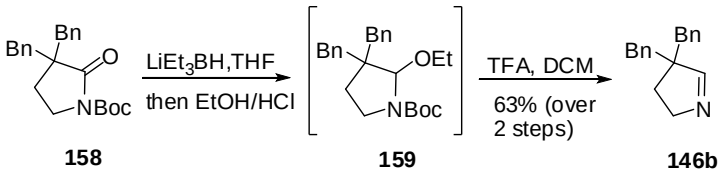



**146a** **149p**

**Scheme 39**: The synthesis of tricyclic lactam **149p**

## 2.4 Synthesis of Imine Substrates

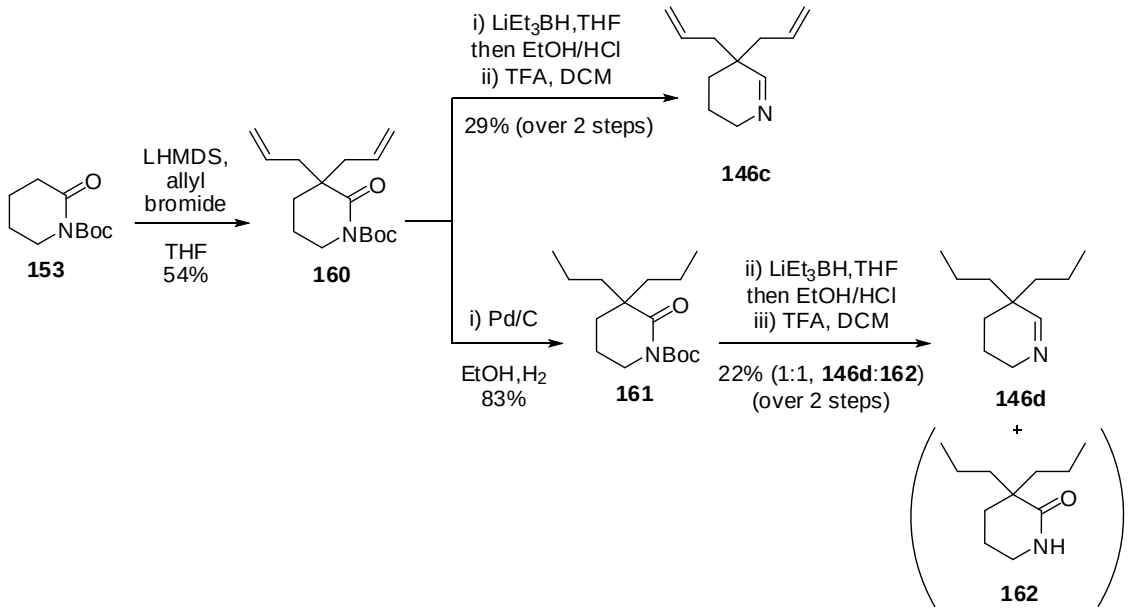
Having examined the DIA reaction using imine **146a**, we next went on to synthesise a series of cyclic imines to test the substrate scope with respect to the imine component. The cyclic imine **146b**, which was first synthesised by Dr. Will Unsworth following the same general procedure that was used to synthesise imine **146a** (Scheme 37), was prepared starting from *tert*-butyl 3,3-dibenzyl-2-oxopyrrolidine-1-carboxylate **158**.[42] The substituted pyrrolidinone **158** was synthesised in good yield *via* Boc-protection of pyrrolidinone, followed by benzylation. The partial reduction of the substituted pyrrolidinone **158** with $LiEt_3BH$ followed by Boc-cleavage gave imine **146b** in 63% yield over the two steps (Scheme 40).




**158** **159** **146b**

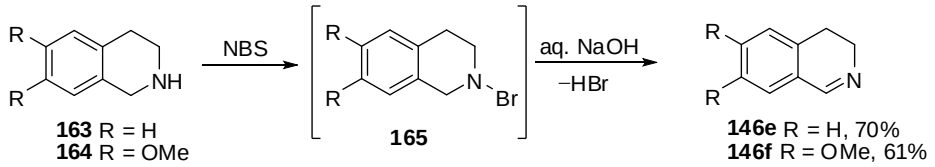
**Scheme 40**: The synthesis of imine **146b**

Two novel cyclic imines, **146c** and **146d**, were also synthesised using a similar procedure (Scheme 41). The allylation of the readily available Boc-protected lactam **153** afforded intermediate **160** which was a common intermediate for the synthesis of both imines **146c** and **146d**. Partial reduction of intermediate **160** with $LiEt_3BH$ followed by Boc-cleavage furnished imine **146c** in 29% yield over the two steps. Imine **146d** was obtained when Pd/C hydrogenation of the allyl groups of the lactam **160** was performed before the partial reduction of the lactam with $LiEt_3BH$ and the subsequent Boc-cleavage. Unfortunately, lactam **162** was observed together with imine **146d** in the $^1$H-NMR spectrum of the columned product (inseparable mixture 1:1) revealing that the $LiEt_3BH$ reduction was not complete before the trifluoroacetic acid was added.



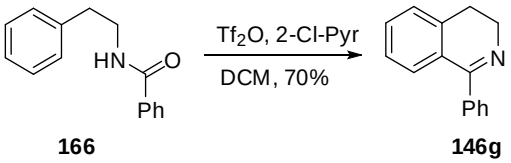

**Scheme 41**: The synthesis of imines **146c** and **146d**

The known 3,4-dihydroisoquinoline **146e** was synthesised from the corresponding 1,2,3,4-tetrahydroisoquinoline **163** based on a literature procedure (Scheme 42).[43] *N*-Bromination of amine **163** using *N*-bromosuccinimide followed by HBr elimination with aq. NaOH afforded imine **146e** in good yield. The same procedure was successfully applied to the synthesis of the known imine **146f** from 6,7-dimethythoxy-1,2,3,4-tetrahydroisoquinoline **164**.




**Scheme 42**: The synthesis of imines **146e** and **146f**

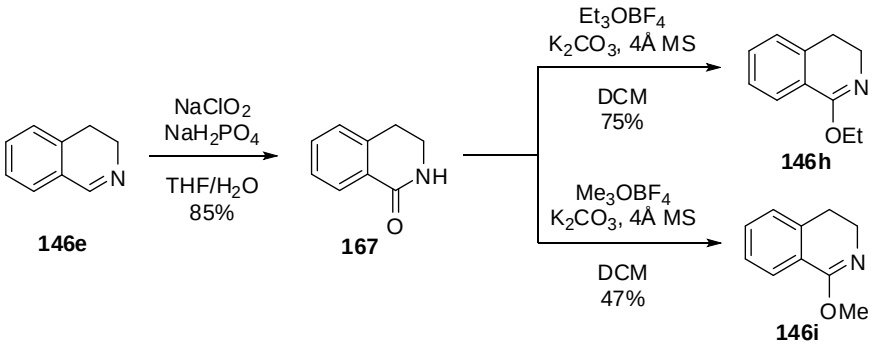
The known imine **146g** was synthesised from the corresponding amide **166**[42] under modified Bischler–Napieralski conditions following a literature procedure.[44] Amide **166** was treated with trifluoromethanesulfonic anhydride and 2-chloropyridine in dichloromethane to give imine **146g** in 70% yield (Scheme 43).




**166** **146g**

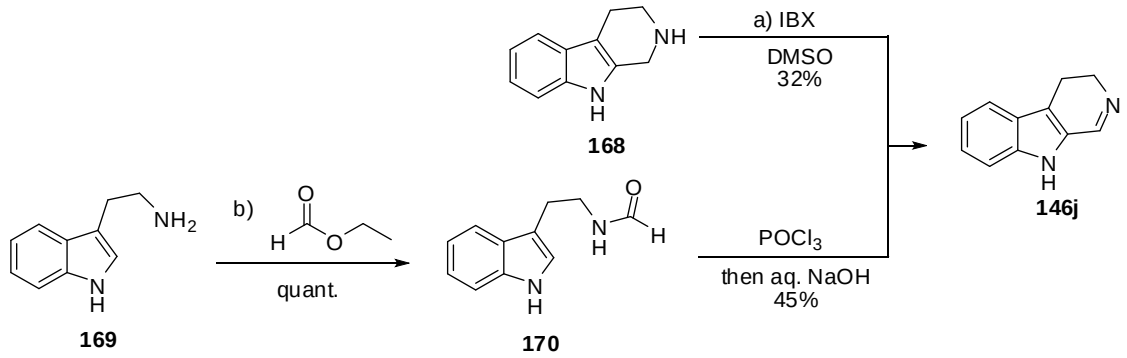
**Scheme 43**: The synthesis of imine **146g**

We have also successfully synthesised the 1-ethoxy and 1-methoxy-3,4-dihydroisoquinoline **146h** and **146i** from the 1,2,3,4-tetrahydroisoquinolin-1-one **167** using triethyloxonium and trimethyloxonium tetrafluoroborate with $K_2CO_3$ in dichloromethane, based on a literature procedure (Scheme 44).[45] The lactam **167** was synthesised from 3,4-dihydroisoquinoline **146e** *via* oxidation, using sodium chlorite under buffered conditions, following a known literature procedure.[46]



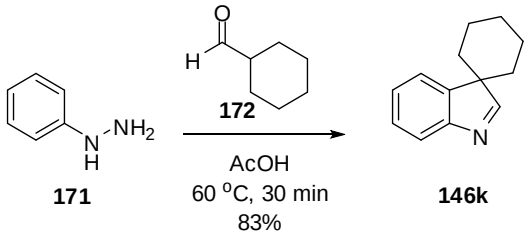

**Scheme 44**: The synthesis of imidates **146h** and **146i**

The 3*H*, 4*H*, 9*H*-pyrido[3,4-b]indole **146j** was synthesised by oxidising commercially available amine **168** using IBX following a procedure described by Nicolaou *et al.* (Scheme 45, path a).[47] However, the yield of the IBX reaction was low (our yield 32% and literature yield 40%) and an alternative way to achieve this transformation was found (Scheme 45, path b). Tryptamine **169** was treated with ethyl formate to give the known amide **170** in quantitative yield.[48] The amide **170** then underwent a Bischler–Napieralski reaction on treatment with neat $POCl_3$ to afford imine **146j**, albeit in lower yield than the one reported (our yield was 45% compared with a literature yield of 82%).[49]

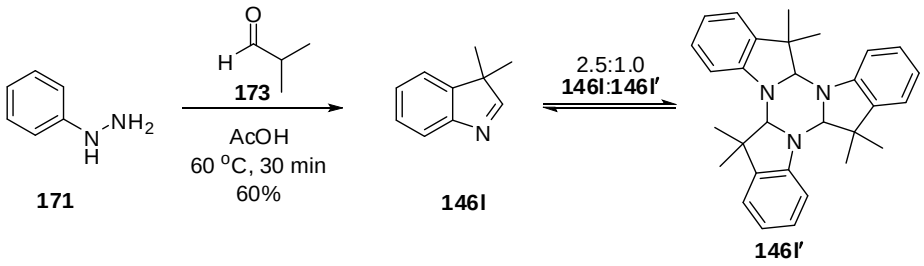



**Scheme 45**: The synthesis of imine **146j**

Two more imines were synthesised based on a procedure described by Liu *et al.*[50] A mixture of phenylhydrazine **171** and cyclohexane-carboxaldehyde **172** was heated at 60 $^{o}$C under mildly acidic conditions, a typical procedure for Fischer indole reactions, affording the known indolenine **146k** in 83% yield (Scheme 46). The same reaction conditions were applied to isobutyraldehyde **173** affording indolenine **146l** in 60% yield (Scheme 47). Note that although indolenine **146l** has been reported previously in the literature, no data has been reported to date. Interestingly, the $^{1}$H-NMR spectrum of indolenine **146l** is more complex than expected; three weak singlet resonances in the 4.95–4.26 ppm region of the spectrum were observed and are thought to be due to protons in the Ph-N-CH-N environment if the indolenine **146l** partially forms the cyclic trimer **146l′**. The formation of the cyclic trimer **146l′** from indolenine **146l** has been reported previously by Jackson *et al.*[51]




**Scheme 46**: The synthesis of imine **146k**

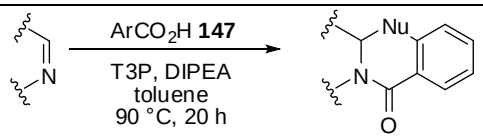



**Scheme 47**: The synthesis of imine **146l**

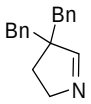
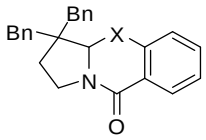
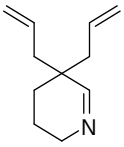
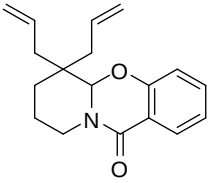
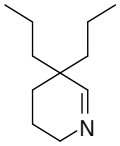
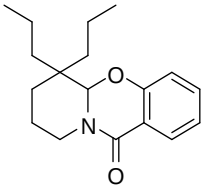
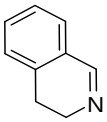
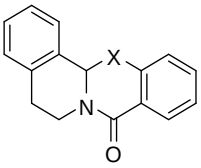
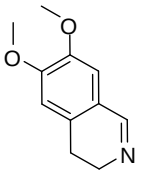
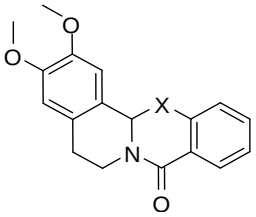
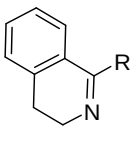
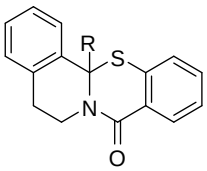
## 2.5 Imine Scope in DIA Reactions

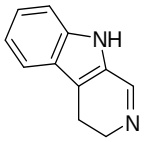
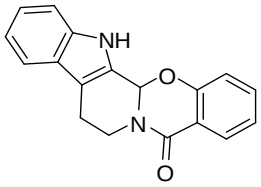
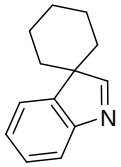
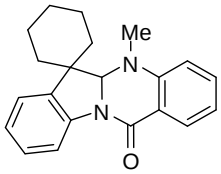
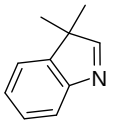
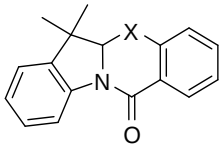
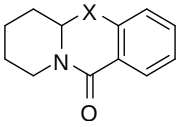
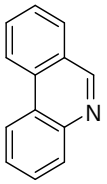
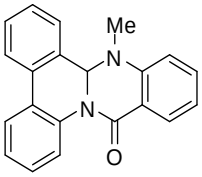
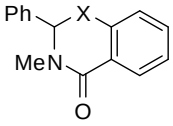
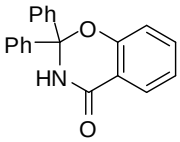
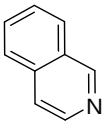
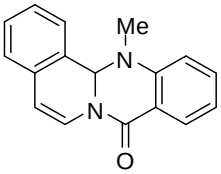
With a variety of imines in hand, we tested the coupling of each of them with various substituted benzoic acids in order to confirm that the scope of DIA methodology is versatile in terms of the imine substrate. The readily available imines **146b–n** and the commercially available imines **146o–r** were tested for their ability to undergo the DIA reaction under our standard conditions (T3P, DIPEA, 90 °C, 20 h, toluene). As can be seen in Table 5, the basic procedure is clearly very broad in scope and a diverse library of compounds, of which most are novel and which were fully characterised, has been created.

**Table 5**: Imine scope in DIA with aromatic acid derivatives




146 149

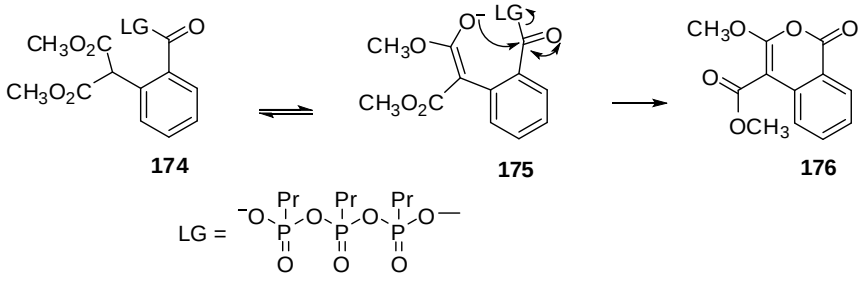
| Entry[a] | Imine | Acid | Product | Yield[b] |
|---|---|---|---|---|
| |  | |  | |
| i[c] | **146b** | **147a** | **149q** X = O | 48% |
| ii | **146b** | **147m** | **149r** X = S | 99% |
| iii | **146b** | **147n** | **149s** X = NMe | 87% |
| |  | |  | |
| iv | **146c** | **147a** | **149t** | 20% |
| |  | |  | |
| v | **146d** | **147a** | **149u** | 24% |
| |  | |  | |
| vi[c] | **146e** | **147a** | **149v** X = O | 89% |
| vii[c] | **146e** | **147m** | **149w** X = S | 97% |
| viii[f] | **146e** | **147p**[d] | **149x** X = $CH(CO_2Me)_2$ | 69% |
| |  | |  | |
| ix | **146f** | **147a** | **149y** X = O | 48% |
| x | **146f** | **147n** | **149z** X = NMe | 87% |
| |  | |  | |
| xi | **146g** R = Ph | **147m** | **149aa** R = Ph | 0% |
| xii | **146h** R = OEt | **147m** | **149ab** R = OEt | 0% |
| xiii | **146i** R = OMe | **147m** | **149ac** R = OMe | 0% |
| xiv[c] | **146m**[d] R = Me | **147m** | **149ad** R = Me | 80% |

| | | | | |
|---|---|---|---|---|
| |  | |  | |
| xv | **146j** | **147a** | **149ae** | 46% |
| |  | |  | |
| xvi | **146k** | **147n** | **149af** | 54% |
| |  | |  | |
| xvii | **146l** | **147m** | **149ag** X = S | 53% |
| xviii | **146l** | **147n** | **149ah** X = NMe | 41% |
| |  | |  | |
| xix | **146n**[d,e] | **147a** | **149ai** X = O | 7% |
| xx | **146n** | **147n** | **149aj** X = NMe | 40% |
| xxi | **146n** | **147m** | **149ak**[g] X = S | 31% |
| |  | |  | |
| xxii | **146o** | **147n** | **149al** | 8% |
| |  | |  | |
| xxiii | **146p** | **147m** | **149am** X = S | 99% |
| xxiv | **146p** | **147o** | **149an** X = NPh | 68% |
| |  | |  | |
| xxv[c] | **146q** | **147a** | **149ao** | 60% |
| |  | |  | |
| xxvi[c] | **146r** | **147n** | **149ap** | 94% |

[a] Reactions were performed on a 0.1–0.3 mmol scale using imine **146** (1 equiv.), benzoic acid **147** (1.2 equiv.), T3P (1.5 equiv.) and DIPEA (1.85 equiv.) with conditions shown unless stated. [b] Isolated yield following column chromatography. [c] Reaction performed at 120 °C for 20 h. [d] Material provided by Dr. Will Unsworth. [e] Imine **146n** was generated by de-oligomerisation of dodecahydro-4a,8a,12a-triazatriphenylene *in situ*. [f] When the reaction was performed on a 9.77 mmol scale the yield dropped to 41%. [g] Material provided by Dr. Graeme Coulthard.

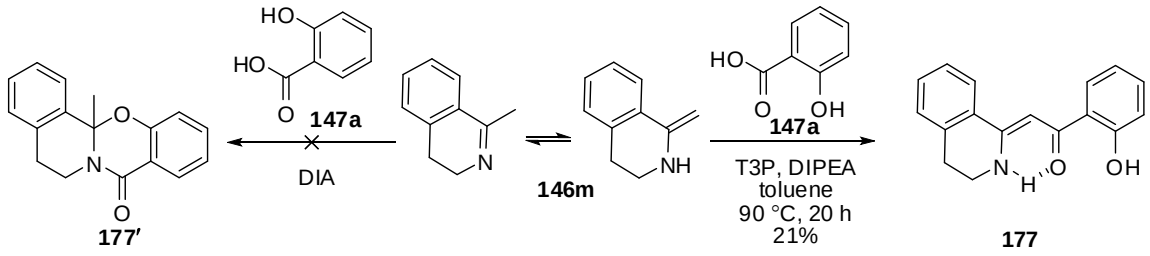
DIA reactions using the 5-membered ring imine **146b** with benzoic acids bearing *O*-, *S*- and *N*-nucleophiles were tested affording products in good yields (Table 5, entries i–iii). Note that a higher temperature was used in the salicylic acid case (entry i) as the t.l.c. analysis showed that the reaction was incomplete under the standard conditions (90 °C). Moreover, the imines **146c** and **146d** were coupled successfully with salicyclic acid **147a**, albeit in lower yield, but it is important to recognise that these reactions were unoptimised (entries iv, v).

DIA reactions using imines **146e** and **146f** with benzoic acids bearing *O*-, *S*-, *N*- and *C*-nucleophiles were tested, affording a diverse range of products in moderate to excellent yield (entries vi–x). We believe that the comparative stabilities of the products may partially explain this variability in yield. For example, the DIA of 3,4-dihydroisoquinoline **146e** and acid **147a** proceeded in high yield, but the analogous reaction with the dimethoxy imine **146f** proceeded in lower yield (entries vi, ix). This may be explained by the increased propensity of the product **149y** to ring-open and thus regenerate an *N*-acyliminium ion (which can be then hydrolyzed during the aqueous work-up or column chromatography) as a result of the electron-donating groups. It is also noteworthy that when the DIA coupling of imine **146e** and acid **147p** was performed on a large scale the yield dropped from 69% to 41% and benzopyran **176** (Scheme 48) was observed in the reaction mixture and isolated in 21% yield. The benzopyran **176** was formed from the self-condensation of acid **147p**, and its formation is known in the literature *via* treatment of the corresponding acid chloride with triethylamine.[52] It is important to note that the substructure of adducts **149v–z** features heavily in natural products and pharmaceutically important compounds.[53]




**Scheme 48**: The benzopyran **176** formation

The coupling of dihydroisoquinolines substituted on C-1 (ketimines **146g**, **146m** and imidates **146h**, **146i**) was examined next. Note that the reaction of ketimines and imidates with acid halides or anhydrides has a limited precedent in the literature.[26j,27b,c] Pleasingly, ketimine **146m**, which can tautomerise to an enamine, is compatible with DIA reacting with thiosalicyclic acid **147m** to generate product **149ad** in excellent yield (entry xiv). However, the analogous reactions using benzoic acids substituted with *O*-, *N*- and *C*-nucleophiles **147a**, **147n** or **147p** (not shown in Table 5) were not successful. Interestingly, the reaction of **146m** with salicyclic acid **147a** resulted in the formation of the novel enaminone **177**, presumably *via* a *C*-acylation on the enamine tautomer of the imine (Scheme 49). This is not surprising as similar processes which proceed by imine-enamine tautomerisation, followed by *C*-acylation, have been reported previously.[54] The enaminone **177** was formed as a single geometrical isomer, thought to be the *Z*-isomer, based on comparisons with similar enaminones in the literature; the proton on the nitrogen atom of the enaminone **177** forms a H-bond with the oxygen of the carbonyl group and thus, it is characterised by a significant downfield shift ($\delta_H$/ppm 11.4) in agreement with similar observations in the literature.[54a,b]




**Scheme 49**: The synthesis of enaminone **177**

The analogous reaction with phenyl substituted ketimine **146g** (which cannot undergo such *C*-acylation) was also screened (entry xi) but this imine did not react with any of the acids most likely because of the increased steric hindrance around the imine which inhibits the requisite *N*-acylation reaction. The imidates **146h** and **146i** (entries xii, xiii) also did not react with any acid tested, further supporting the idea that the steric hindrance around the imine inhibits the DIA reaction. The contrasting reactivity of thiosalicyclic acid **147m** over the other benzoic acids (**147a**, **147n** or **147p**) (in ketimine **146m** example) indicates that an alternative mechanism possibly operates; it seems likely that in sulfur-containing systems, the nucleophilic thiol moiety attacks the imine first, before the *N*-acylation takes place. Additional support for this mechanism is found

in the fact that partial product formation (20% yield) was observed in a related example in the absence of T3P (Table 4, entry i).

Moderate to low yields were achieved when we tested the DIA reaction on imines **146j–o** (entries xv–xxii). Note that the dodecahydro-4a,8a,12a-triazatriphenylene,[55] the trimeric form of imine **146n**, successfully underwent DIA reaction (entry xix) demonstrating that even unstable imines, which are prone to oligomerization and enamine formation, can be compatible substrates in the DIA process. Dihydro-β-carboline **146j** and indolenines **146k** and **146l** were also suitable imine substrates (entries xv–xviii) further testifying to the broad scope of the DIA protocol. Traces of adduct **149al** were obtained when imine **146o** was coupled with acid **147n** (entry xxii) showing that even highly hindered imines can undergo DIA reaction partially.

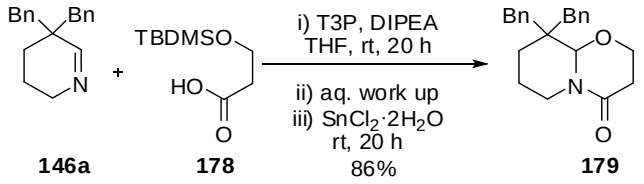
Synthetic applications of acyclic *N*-acyliminium ions are limited as they are much less stable than their cyclic analogues, particularly with respect to hydrolysis.[4,6 (a,b),26a] DIA methodology overcomes this problem by forming and trapping the unstable *N*-acyliminium ions *in situ*. Thus, the acyclic imines **146p** and **146q** were successfully coupled with acids **147a**, **147m** and **147o** to give adducts **149am–149ao** in good to excellent yields (entry xxiii–xxv). Note also that although cyclic ketimines have so far proven to be incompatible with DIA, imine **146q** which is itself a ketimine, furnished the *N*,*O*-acetal **149ao** (entry xxv) in good yield under standard DIA reaction conditions at 120 °C.

Finally, the high yielding DIA reaction of isoquinoline **146r** with anthranilic acid **147n** is important, given that it proceeds despite the loss of aromaticity (entry xxvi). Note that similar dearomatising reactions of isoquinoline **146r** to prepare related scaffolds have been previously reported.[26h,56] Unfortunately, the dearomatising DIA reaction appears not to be general as the analogous reaction of isoquinoline **146r** with acids **147a**, **147m** and **147p** (not shown in Table 5) failed to furnish any product. We also did not detect any desired products when other aromatic heterocycles containing C=N bonds (pyridine, DMAP, pyrimidine, pyrazine, oxazole, benzoxazole, thiazole, *N*-Boc imidazole and 1,3,5-triazine) were coupled with anthranilic acid **147n** under DIA reaction conditions at 120 °C.

## 2.6 DIA Methodology Variation

This project was focused on the DIA coupling between imines and aromatic acid derivatives and it demonstrated that DIA methodology is a reliable and versatile tool for the synthesis of a range of polycyclic heterocycles. However, studies within the group (conducted by Dr. Graeme Coulthard and Dr. Will Unsworth) showed that DIA is not limited to aromatic acids but is also compatible with aliphatic carboxylic acids with tethered nucleophiles.[57]

For example, the silyl-protected acid **178** was coupled with imine **146a** followed by aqueous work-up and subsequent silyl-group cleavage with $SnCl_2 \cdot 2H_2O$ to give product **179** in 86% yield (Scheme 50). The silyl protecting group is required to prevent competing *O*-acylation of the hydroxy acid analogue of **178**. Note that this was not a problem in the earlier studies due to the reduced nucleophilicity of *ortho*-substituted benzoic acids. A number of compounds have been synthesised using the above general procedure (Figure 4).




**Scheme 50**: DIA reaction between the silyl-protected acid **178** and imine **146a**

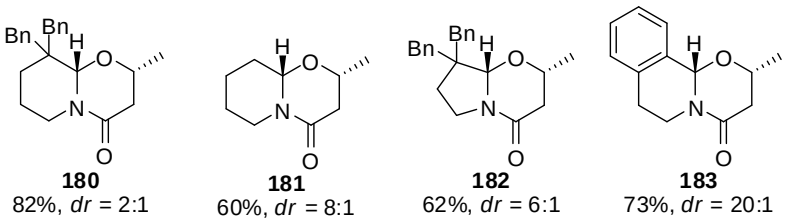
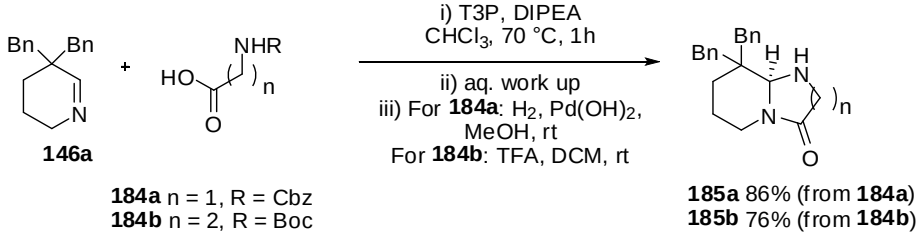



**Figure 4**: Examples of DIA products synthesised from aliphatic acids containing a tethered oxygen nucleophile

The analogous DIA process using amine-containing coupling partners was also successful. For instance, the imine **146a** was coupled with *N*-Cbz-protected amino acid **184a** and *N*-Boc-protected amino acid **184b** followed by an aqueous work-up and protecting group cleavage. This resulted in cyclisation and formation of the expected

products **185a** and **185b** in good yields (Scheme 51). A range of nitrogen-containing heterocycles have been synthesised following the same procedure as shown in Figure 5.




**Scheme 51**: DIA reaction between the acids **184a** and **184b** and imine **146a**

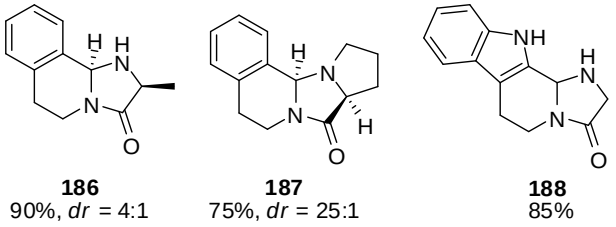
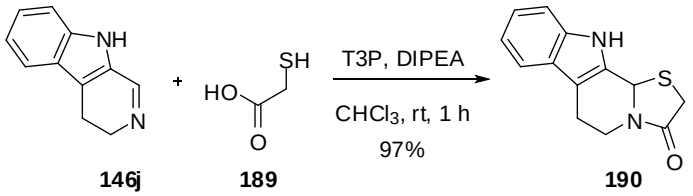



**Figure 5**: Examples of DIA products synthesised from aliphatic acids containing a tethered nitrogen nucleophile

The sulfur variant of this DIA sequence was also efficient, affording sulfur-containing heterocycles in a one-pot procedure, in this case with no protecting group required on the thiol. For example, when the thio-acid **189** was coupled with imine **146j** at rt in chloroform, thiazolidinone **190** was obtained in 97% yield (Scheme 52). Various other thiazolidinone scaffolds were synthesised in high yields following the same procedure (Figure 6).




**Scheme 52**: DIA reaction between the thio acid **189** and imine **146j**

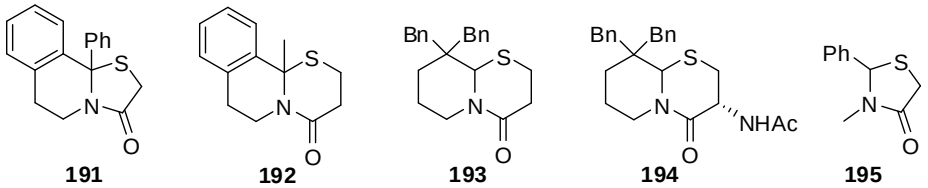
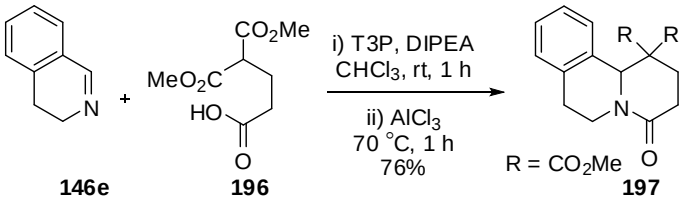



**Figure 6**: Examples of DIA products synthesised from aliphatic acids containing a tethered thiol

It was also demonstrated that carbon nucleophiles tethered on an aliphatic acid are well tolerated. In these reactions the addition of Lewis acids to the crude reaction mixture promoted cyclisation after coupling. A representative example is shown in Scheme 53; diester **196** was coupled with imine **146e** under T3P coupling conditions and then cyclised upon the addition of $AlCl_3$ to give product **197** in good yield. Note that the cyclisation step could also be promoted by using other Lewis acids like $BF_3 \cdot Et_2O$ or by using protic acids such as trifluoroacetic acid depending on the particular substrate. Many different heterocycles have been synthesised using the above procedure as shown in Figure 7.




**Scheme 53**: DIA reaction between the diester **196** and imine **146e**

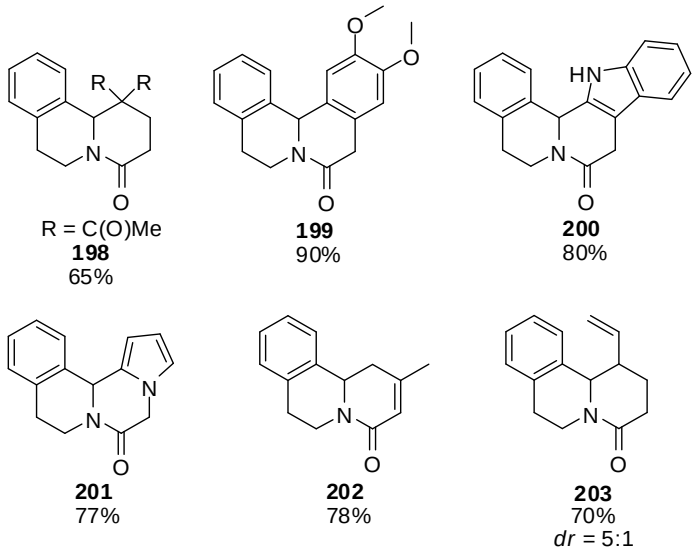
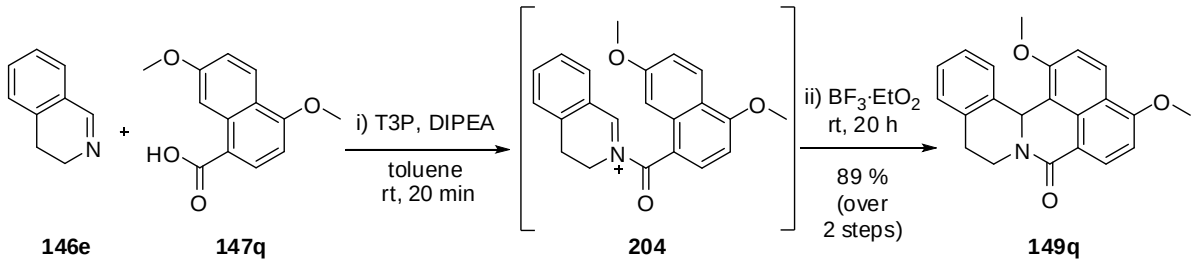



**Figure 7**: Examples of DIA products synthesised from aliphatic acids containing a tethered carbon nucleophile

The use of Lewis acids to promote the cyclisation step augured well for a similar optimisation of some DIA reactions on this project, especially for the lower yielding ones. Keen to investigate this, in this research we tested the DIA reaction of dihydroisoquinoline **146e** with dimethoxy-naphthoic acid **147q** under our standard DIA conditions (T3P, DIPEA, 90 °C, 20 h), but the reaction failed, giving back the starting materials. Pleasingly, the addition of $BF_3 \cdot Et_2O$ directly into the reaction mixture, after 20 minutes of stirring at rt, generated adduct **149q** in excellent yield (Scheme 54). The above optimisation proved to be very useful in research focused on the synthesis of the berberine natural products, cavidine **280** and pallimamine **283** (Chapter 4).

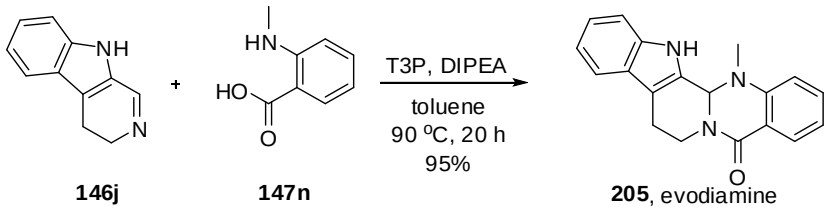



**Scheme 54**: DIA reaction of imine **146e** with acid **147q** with the aid of $BF_3 \cdot Et_2O$

## 2.7 Synthesis of Evodiamine 205

The value of DIA has been illustrated by the rapid and efficient synthesis of evodiamine **205**, a natural product isolated from *Evodia fructus*.[58] Evodiamine **205** is a known thermogenic and stimulant and is included in a number of dietary supplements, mainly to promote weight-loss. Recently, it has been shown that evodiamine **205** is a novel inhibitor of human DNA topoisomerase I.[58b] Also, SAR studies have recently shown that evodiamine analogues are highly promising anti-tumour candidates.[59] As to its biosynthesis, Yamasaki *et al.* proposed a biosynthetic pathway starting from tryptophan and anthranilic acid.[60]

Evodiamine **205**, which has most commonly been synthesised from dihydrocarboline **146j** and *N*-methylisatoic anhydride in 70–84% yield,[58b, 61] was obtained extremely efficiently using our standard DIA reaction conditions (T3P, DIPEA, toluene, 90 °C, 20 h) (Scheme 55). The readily available dihydrocarboline **146j** coupled with the *N*-methyl-anthranilic acid **147n**, in an one-pot process, to generate evodiamine **205** as a crystalline solid. All the spectral data were in full accord with those previously reported.[61]

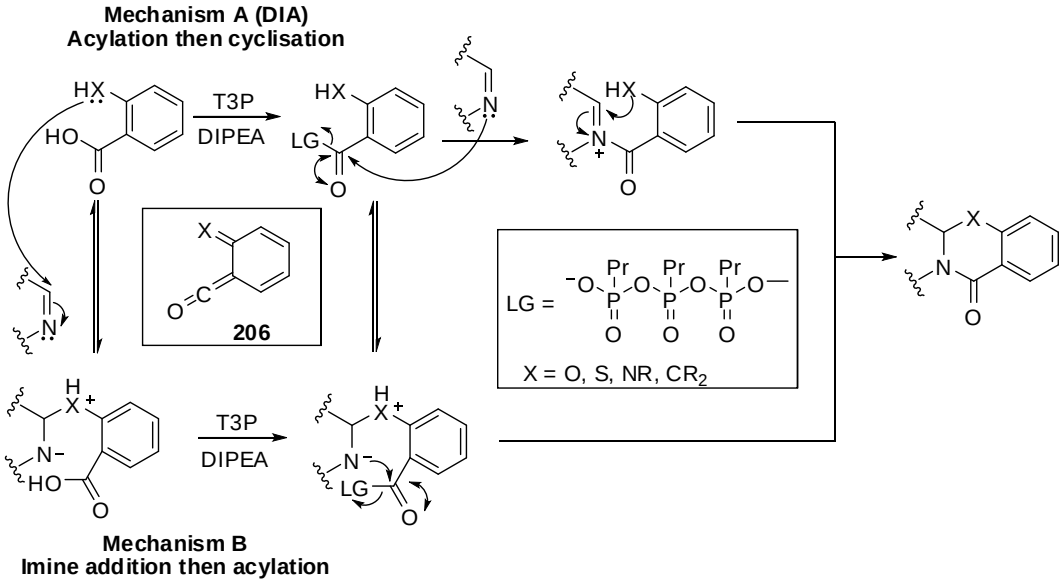



**146j** **147n** **205**, evodiamine

**Scheme 55**: The total synthesis of evodiamine **205**

## 2.8 Mechanistic Studies-ReactIR

Two mechanistic pathways were envisaged for the DIA reaction process: a) an intermolecular *N*-acylation takes place first and is followed by an intramolecular cyclisation (Mechanism A) or b) an intermolecular nucleophilic attack of the *ortho*-substituent on to the imine takes place first followed by an intramolecular acylation (Mechanism B) (Scheme 56). An added complication is that imino-ketenes **206** have been proposed for the acylation step in related anthranilic acid processes.[26k, 27b,c]



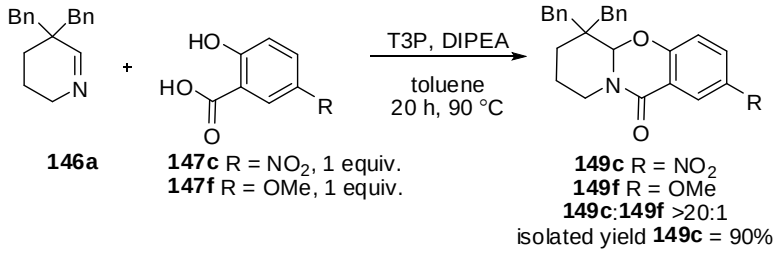

**Scheme 56**: The two possible mechanistic pathways

It is important to note that these two contrasting mechanistic pathways may operate in competition and that the exact mechanism that occurs each time may depend on the particular substrate that is involved in the process. For example, the small amount (20%) of the adduct **149m** (Table 4, entry i) that was obtained in the absence of T3P, suggests that an intermolecular nucleophilic attack on to the imine may take place first in the *S*-series (Mechanism B) as the intermolecular condensation of an imine with an unactivated carboxylic acid appears extremely unlikely. The lack of such reactivity in each of the *O*-, *N*- and *C*-series offers some support in favor of the theory that the initial step in those cases involves *N*-acylation of the imine (Mechanism A).

Further support for the mechanism A is provided by the fact that those salicyclic acid derivatives which were substituted with electron-deficient groups (Table 3, entries ii–iv)

tended to be more efficient performing the DIA reaction compared to those which were neutral (Table 3, entry i) or substituted with electron-donating groups (Table 3, entries v–viii). Therefore we reasoned that for those substrates which were electron-deficient, the electrophilicity of the analogous activated acid was increased and thus the rate of the imine acylation was accelerated resulting in higher yields. Conversely, if a condensation-type mechanism operated (Mechanism B), the addition of an electron-donating group would increase the nucleophilicity of the *ortho*-nucleophile and thus it would accelerate the rate of the intermolecular nucleophilic attack of the imine resulting in the opposite trend from the one observed.

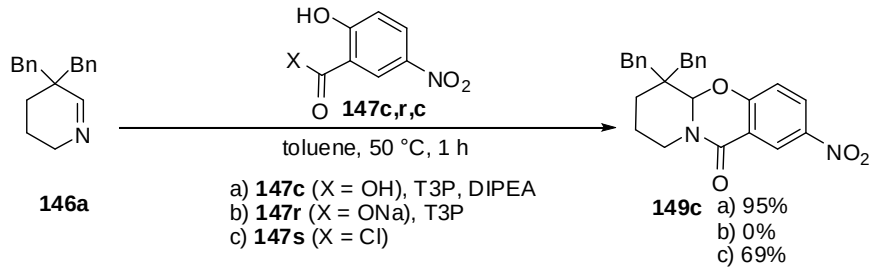
To test the above theory in a more direct way, we performed a competition experiment in the *O*-series; imine **146a** was reacted with one equivalent of acids **147c** and **147f**, in one-pot, under our standard DIA conditions (T3P, DIPEA, toluene, 90 °C, 20 h). The electron-deficient salicylic acid **147c** reacted preferentially thus supporting the DIA-type mechanism (Mechanism A); 5-$NO_2$ substituted product **149c** was formed remarkably cleanly with only traces of 5-OMe substituted **149f** observed in the $^1$H NMR spectrum of the crude material (Scheme 57).




**Scheme 57**: The competition experiment in the *O*-series

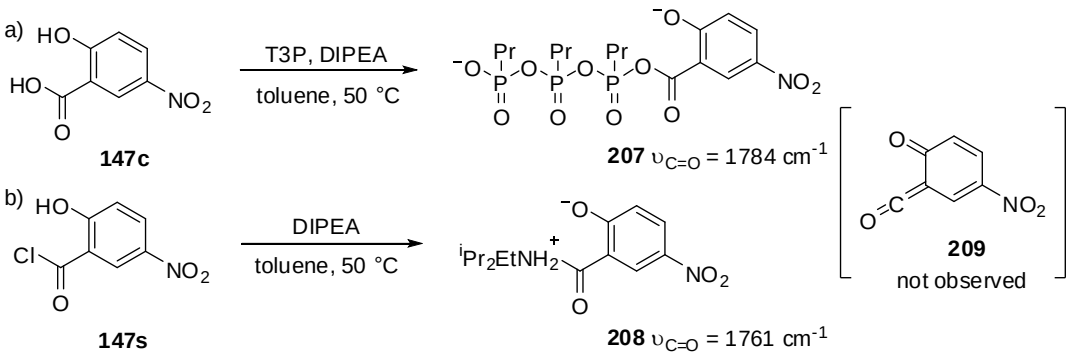
The importance of DIPEA in the process was then examined (Scheme 58). Imine **146a** reacted with acid **147c** in toluene using T3P and DIPEA to give product **149c** in 95% yield (Scheme 58, entry a). The acid **147c** was chosen as this substrate is particularly reactive (Table 3, entry iii); the reaction proceeded efficiently at 50 °C in one hour, suggesting that reaction times and temperatures of other DIA variants could be reduced similarly. Note that a lower temperature was needed to be compatible with the sensitive ReactIR probe for the ReactIR studies that would follow. We then tested the same reaction with sodium carboxylate **147r** and T3P (Scheme 58, entry b). This reaction gave back the imine **146a** indicating that the role of DIPEA is more complicated than that of a simple base to deprotonate the acid prior to its activation. In addition, the

coupling of imine **146a** and acid chloride **147s** (Scheme 58, entry c) proceeded successfully (albeit in lower yield) and that indicated that DIPEA is not essential in the cyclisation step since it was shown to proceed without the need of a base (Scheme 58c). Hence, it appeared that DIPEA might be somehow involved in the *N*-acylation step.




**Scheme 58**: Examination of the exact role of DIPEA in DIA process

With the role of DIPEA still unclear, an *in situ* ReactIR study was carried out (this study was carried out together with Dr. Will Unsworth) to examine the nature of the activated carboxylic acid. For this purpose, T3P was added to a solution of acid **147c** and DIPEA in toluene at 50 °C with *in situ* ReactIR monitoring (Scheme 59, eqn a). A rapid formation of a new carbonyl peak was observed within one minute ($\upsilon_{c=o}$ 1784 $cm^{-1}$) indicating that the conversion of acid **147c** to its activated form was complete within this time. The acid chloride analog **147s** was then reacted with DIPEA in the absence of T3P under the same reaction conditions in a second ReactIR experiment (Scheme 59, eqn b). This is also led to a rapid formation of a new carbonyl peak, within one minute, however at a lower wavenumber ($\upsilon_{c=o}$ 1761 $cm^{-1}$). This peak most likely represents the carbonyl stretch of *N*-acyl ammonium salt **208** and the fact that this stretch is not observed in the first ReactIR experiment indicates that DIPEA does not act as nucleophilic catalyst under these conditions and that the triphosphate **207** is the active acylating agent in the DIA reaction. Interestingly, no peaks were observed in the region of $\upsilon_{c=o}$ 2100-2200 $cm^{-1}$, where ketene carbonyls **209** usually appear,[62] seemingly ruling out ketene intermediates.




**Scheme 59**: An *in situ* ReactIR study was carried out to examine the nature of the activated carboxylic acid

To shed more light on the mechanism of the DIA reaction, another *in situ* ReactIR experiment was carried out on the DIA reaction of acid **147c** and imine **146a**. The results of this are shown in Figures 8 and 9. It should be noted that due to severe overlapping of the signals with wavenumbers below 1650 $cm^{-1}$ it was not possible to confidently derive any information from this region of the spectra, meaning that the fates of both the starting imine and acid could not be monitored (Figure 8). Within one minute of adding T3P to a 50 $^{o}C$ solution of imine **146a**, acid **147c** and DIPEA in toluene, three new peaks were observed and monitored. An intense peak (peak 2 = 1668 $cm^{-1}$) appeared quickly together with a much less intense peak (peak 1 = 1786 $cm^{-1}$). The intensity of peak 2 quickly began to decrease (see Figure 9) and was accompanied by the formation of a third peak (peak 3 = 1684 $cm^{-1}$). Note that the absorption for peak 2 does not appear to reach zero due to peak overlap between itself and peak 3. Peak 3 is known to represent the carbonyl stretch of the product **149c**, since a purified sample of product **149c** was tested under the same ReactIR conditions (50 $^{o}C$, toluene) and displayed the same peak at 1684 $cm^{-1}$. Peak 3 continued to increase in intensity reaching a maximum after one hour. Meanwhile, peak 1 maintained a steady low concentration before dropping away over one hour near completion of the reaction.

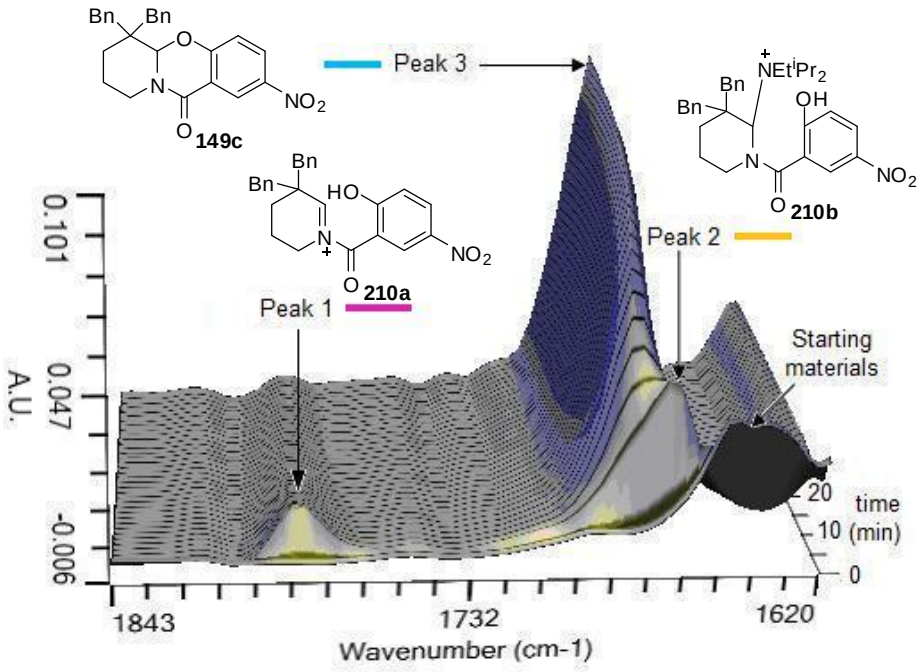



**Figure 8**: 3D ReactIR plot of atomic absorption against wavenumber and time (same time period to that shown in Figure 9 (*ca*. 70 min)

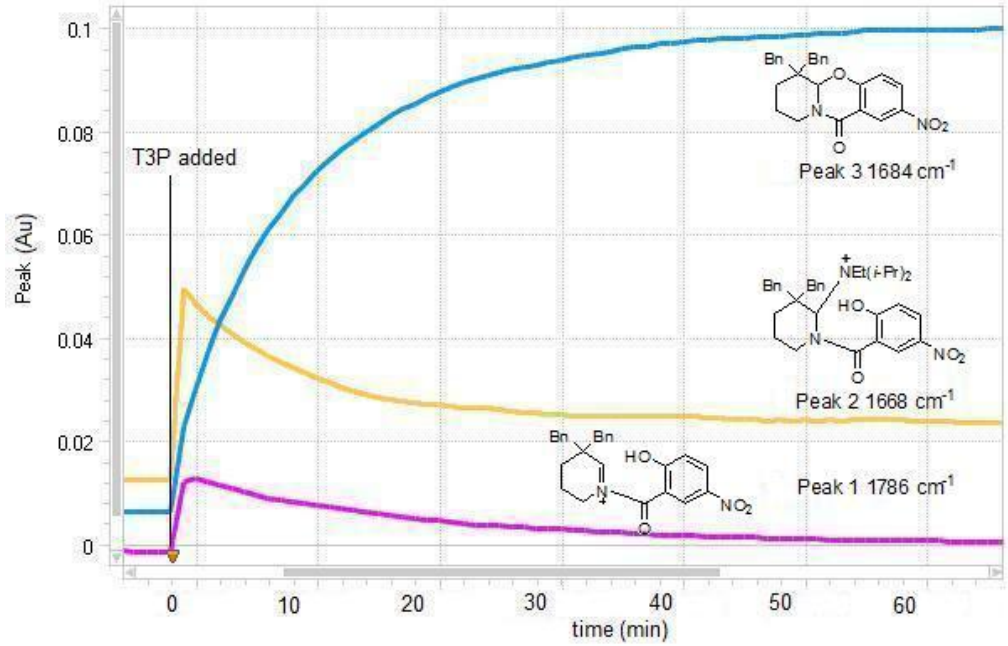
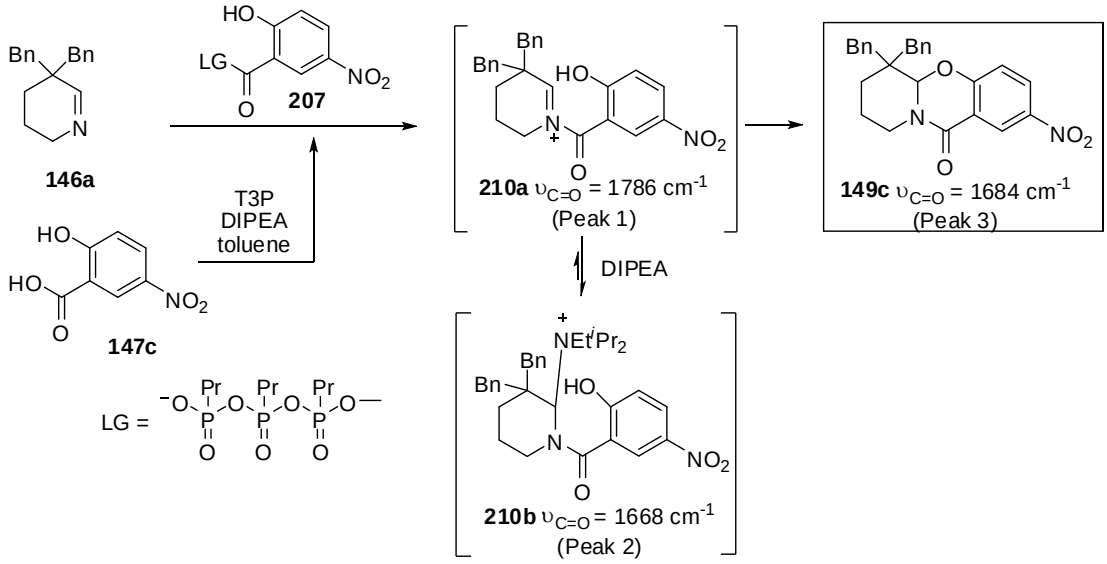



**Figure 9**: 2D ReactIR plot of atomic absorption units of the wavenumbers 1668 $cm^{-1}$ (yellow), 1684 $cm^{-1}$ (blue) and 1786 $cm^{-1}$ (pink) against time.

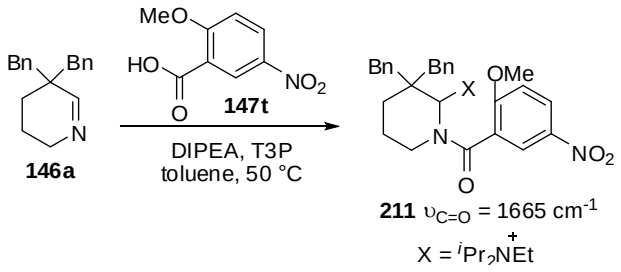
These observations suggest that an intermediate (peak 2) was formed rapidly, and slowly collapses *via* a short-lived reactive intermediate (peak 1), before reacting to give the product (peak 3). This is consistent with a mechanism where activation of

carboxylic acid **147c** to **207** takes place rapidly, but this intermediate is trapped as quickly as it is forms by imine **146a** generating the short-lived *N*-acyliminium ion **210a** (peak 1) (Scheme 60). *N*-Acyliminium ions are rarely isolable and, as such, there is no precedent for the measurement of the IR carbonyl stretches of any compounds directly comparable to **210a**. The IR stretches of the few *N*-acyliminium ions that have been measured appear in the range 1725–1810 $cm^{-1}$.[5] Therefore, the low intensity peak 1 (1786 $cm^{-1}$) is reasonable for the *N*-acyliminium ion. This reactive intermediate is then primed to undergo intramolecular cyclisation to generate the final product **149c**. However, this simple mechanism does not account for the presence of peak 2 or explain why the measured absorption of peak 1 is so low, considering that the product formation required a full hour to reach completion. It is therefore more likely that prior to cyclisation the *N*-acyliminium ion **210a** is trapped by excess DIPEA in the reaction mixture, generating the ammonium salt **210b**. Note that the wavenumber of the IR absorption of the peak representing intermediate **210b** (peak 2 = 1668 $cm^{-1}$) is not consistent with that of an *N*-acyliminium ion carbonyl stretch, which normally appears at higher wavenumbers, however is reasonable for an amide carbonyl stretch. Limited examples of ammonium adducts of *N*-acyliminium ions similar to salt **210b** have been found in the literature and have similar IR data.[63] Finally, it is likely that the formation of the intermediate **210b** is reversible, meaning that the extrusion of DIPEA can take place to regenerate the *N*-acyliminium ion **210a** which only exists in low concentration as it quickly cyclises to form the DIA product **149c** (peak 3 = 1684 $cm^{-1}$). The mechanism proposed is consistent with the persistent weak absorption of peak 1, the relatively long reaction time and the observation of peak 2 (Scheme 60).




**Scheme 60**: Proposed mechanism for the DIA reaction of imine **146a** and acid **147c**

A final ReactIR experiment was performed to provide an additional support for the above mechanism (Scheme 61). Imine **146a** reacted with *o*-anisic acid derivative **147t**, in place of salicyclic acid **147c**, under the same conditions used for the rest of the ReactIR experiments (50 $^{o}$C, toluene). This experiment was performed in expectation that product **211** (an intermediate similar to **210b**) would form, but in this case persist given that the cyclisation pathway had been negated. Within one minute after the T3P was added, the coupling was complete and a new IR peak at 1665 cm$^{-1}$, which is similar to that of intermediate **210b** (1668 cm$^{-1}$), was formed. No absorptions above 1700 cm$^{-1}$ were observed which ruled out the possibility of the coupled product existing as a discrete *N*-acyliminium ion. Thus, the carbonyl stretch of intermediate **211** most likely accounts for this peak and its rapid formation is in line with that observed for the formation of its phenol analog **210b**.




**Scheme 61**: The formation of DIPEA adduct **211**

## 2.9 Summary

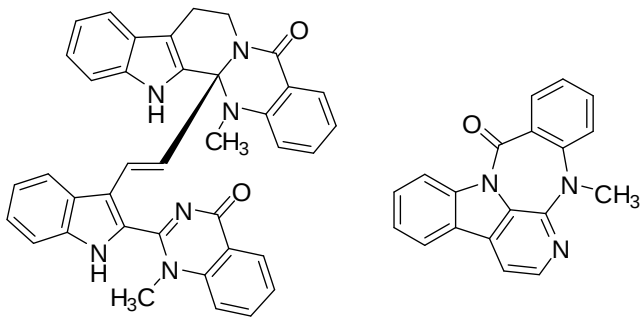
In summary, a reliable and versatile methodology has been developed based on the concept of 'Direct Imine Acylation' (DIA). This methodology uses readily available nontoxic reagents, is operationally simple, is high yielding and capable of generating a broad range of polycyclic heterocyclic scaffolds without significant optimisation. A detailed substrate scoping study of the DIA reaction using a range of imines and *ortho*-substituted benzoic acids has been completed. The versatility of this method has been shown by its compatibility with Lewis acid additives which could be added straight into the reaction mixture when the cyclisation step is slow. A rapid and efficient synthesis of the biologically important natural product evodiamine **205**, is also described. Finally, an *in situ* ReactIR study was carried out to study the DIA reaction mechanism which seems to involve an equilibrium between the *N*-acyliminium ion and an ammonium salt generated by the addition of DIPEA to the *N*-acyliminium ion.

The work described in this Chapter is included in three recent publications (Appendix II (A, B and C)).[57,64,65]

# Chapter 3 Total Synthesis of (±)-Dievodiamine 212

## 3.1 Introduction to the Natural Product (±)-Dievodiamine 212

(+)-Dievodiamine **212** was recently isolated (2010) from *Evodia fructus* together with the alkaloid evodiagine **213** (Figure 10).[66] *Evodia fructus* or *Evodia* fruits (Wu Zhu Yu) refers to the nearly ripe, dried fruit of the plant *Evodia rutaecarpa* (*Rutaceae*) that is native to China and Korea. It is classified, along with cinnamon bark, dry ginger, chilli peppers and others, as being a herb with a 'hot nature' which causes a 'warming feeling'.

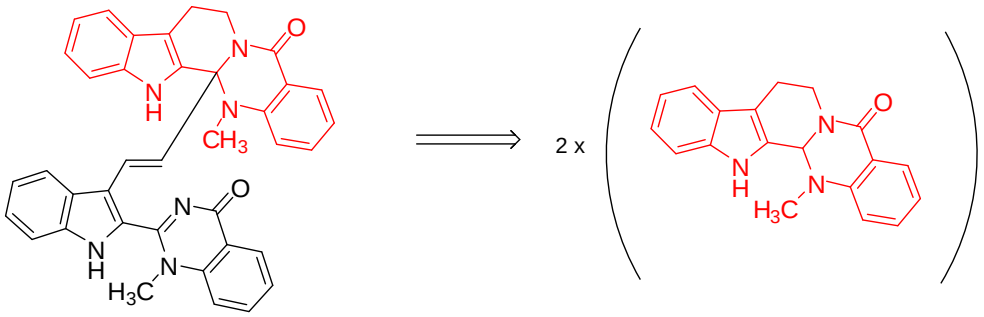



(+)-dievodiamine, **212** evodiagenine, **213**

**Figure 10**: Two new indole alkaloids, (+)-dievodiamine **212** and evodiagenine **213**

None of dievodiamine's biological properties have been reported to date, although the *Evodia* fruit is among the most popular herbal drugs in traditional Chinese medicine. *Evodia* fruit is used to treat various conditions such as gastrointestinal disorders (diarrhoea, dysentery, abdominal pain), nausea, migraine, menstrual pain, mouth ulcers, chill limbs, postpartum haemorrhage and obesity.[66, 67] The anti-inflammatory, anti-nociceptic and anti-cancer activities of *Evodia rutaecarpa* extracts have also been examined.[68]

(+)-Dievodiamine **212** was obtained as white crystals ($[\alpha]_D^{24}$ +48.86 (c 0.1, $CHCl_3$)) and its structure was elucidated by comprehensive spectroscopic analysis.[66] Its structure is closely related to evodiamine **205**, whose synthesis using DIA methodology was described in Chapter 2 (Scheme 55). Note, however, that although dievodiamine contains the basic framework of two evodiamine subunits (red and black), it is not a simple dimer of evodiamine, as its name may suggest. It does seem plausible though that evodiamine **205** is a possible biosynthetic precursor (Scheme 62).



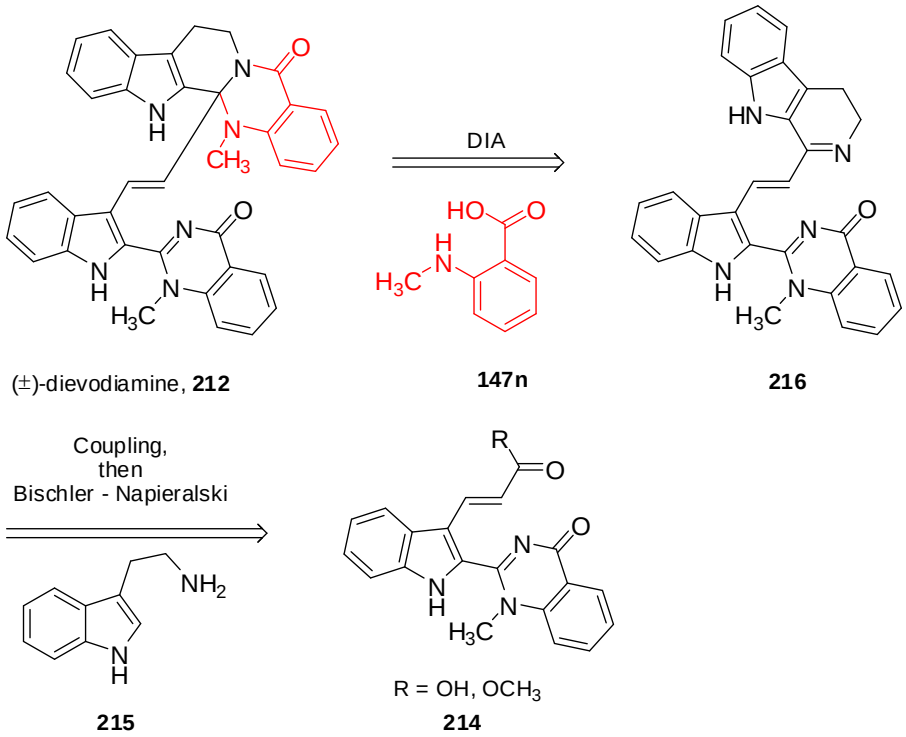

(±)-dievodiamine, **212** evodiamine, **205**

**Scheme 62**: Evodiamine **205** and dievodiamine **212**

(+)-Dievodiamine **212** belongs to a class of natural products known as bisindole alkaloids which have been extensively investigated for their interesting biology.[69] The isolation, synthesis and biological evaluation of bisindole alkaloids is an active area of research [70] with their anti-malarial properties receiving prominent attention recently.[70c,d,e] Despite this promise of potent biological activity, no synthesis of (+)-dievodiamine **212** has been reported to date.

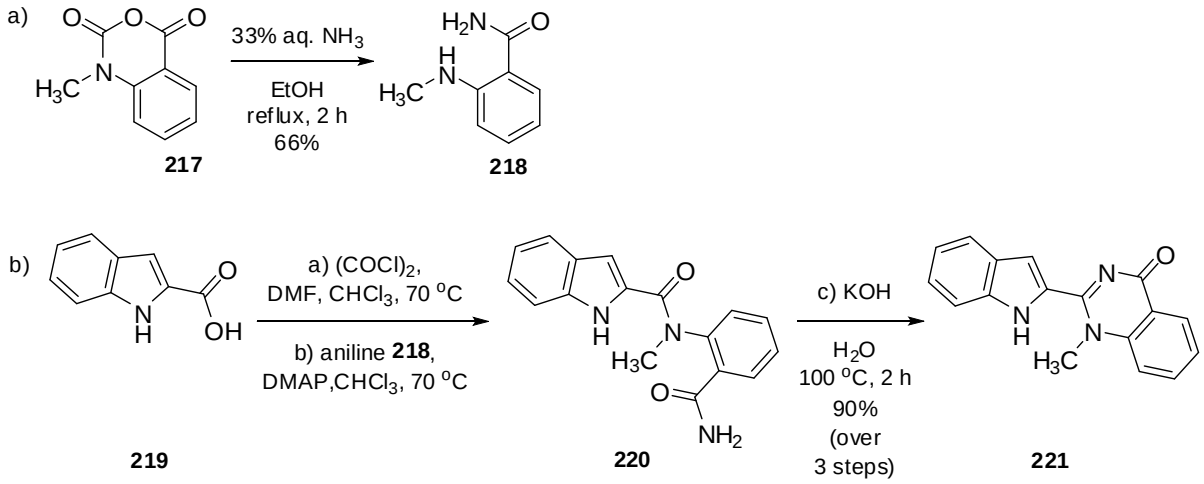
## 3.2 Linear Route to (±)-Dievodiamine 212

A route to (±)-dievodiamine **212** based on a late stage DIA reaction between imine **216** and *N*-methylanthranilic acid **147n** was investigated. It was envisioned that imine **216** could be delivered *via* coupling of the intermediate **214** with tryptamine **215** followed by Bischler-Napieralski dehydration. The initial retrosynthetic plan is shown in Scheme 63.



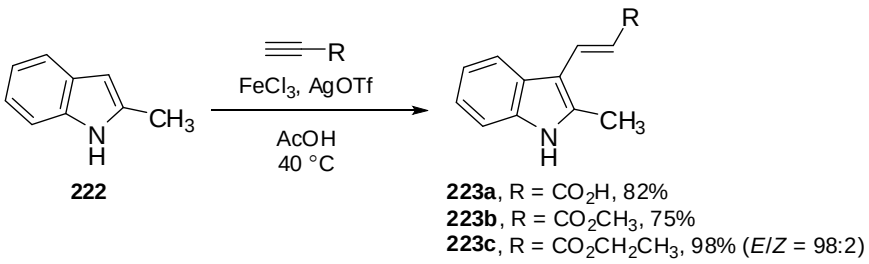

**Scheme 63**: Linear route to (±)-dievodiamine **212**

It was envisaged that the key intermediate **214** could be synthesised from indole **221** after functionalization at its C-3 position. The known aniline **218** was prepared from *N*-methylisatoic anhydride **217** *via* treatment with 33% aq. $NH_3$ (Scheme 64, eqn a).[71] The novel indole **221** was then synthesised from the commercially available indole-2-carboxylic acid **219** and aniline **218** (Scheme 64, eqn b). The acid **219** was treated with oxalyl chloride and aniline **218** to give the novel amide **220** based on a literature procedure.[72] When amide **220** was heated at reflux in aq. KOH,[73] it afforded an insoluble material which was then collected by filtration and was shown to be the novel quinazolinone **221** in excellent yield after the 3-steps sequence.

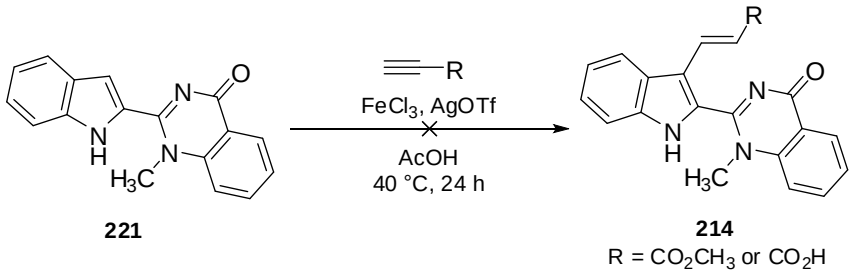



**Scheme 64**: a) The synthesis of aniline **218** from *N*-methylisatoic anhydride **217**, b) The synthesis of indole **221**

With indole **221** in hand, a number of conditions to functionalise its C-3 position were tested. A recently reported literature procedure for the regioselective synthesis of 3-indolylacrylic acid **223a** and 3-indolylacrylates **223b** and **223c** using a catalyst system of $FeCl_3$/AgOTf was examined (Scheme 65).[74] Unfortunately, the more complex indole system **221** didn't react under these conditions, and was recovered cleanly after 24 h (Scheme 66).

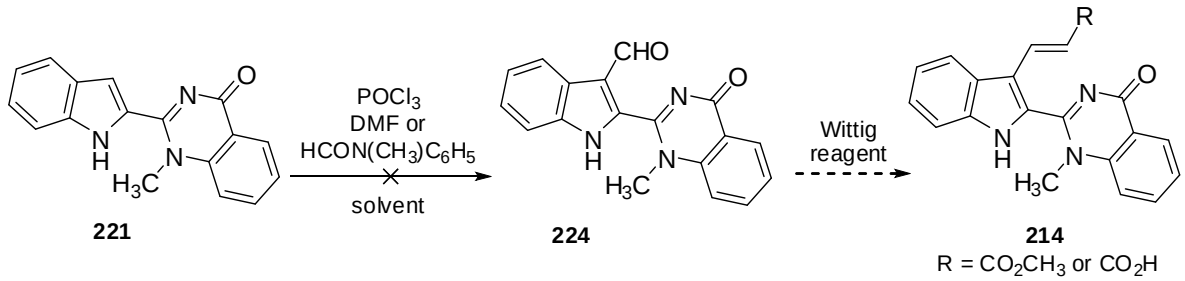



**Scheme 65**: Reported regioselective synthesis of 3-indolylacrylic acid **223a** and 3-indolylacrylates **223b** and **223c**



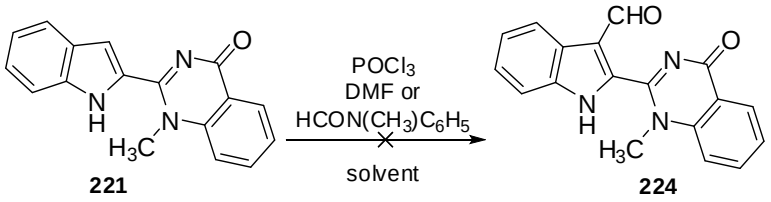

**Scheme 66**: Attempted synthesis of intermediate **214** from indole **221** under the catalytic system of $FeCl_3$/AgOTf

A Vilsmeier reaction[75] on indole **221** was attempted with a view to forming the aldehyde **224**, before performing a Wittig olefination to give intermediate **214** (Scheme 67). Unfortunately, the starting material **221** was recovered cleanly after it was treated with $POCl_3$ in DMF (Table 6, entries i, ii). Only traces of product **224** were observed in the $^1$H-NMR spectrum of the crude mixture when a stoichiometric amount of DMF was used and the solvent switched to DCE (Table 6, entry iii) and decomposition was observed when *N*-methylformanilide was used in the place of DMF (Table 6, entry iv).




**Scheme 67**: Attempted synthesis of intermediate **214** *via* aldehyde **224**

**Table 6**: Attempted Vilsmeier reaction of indole **221**

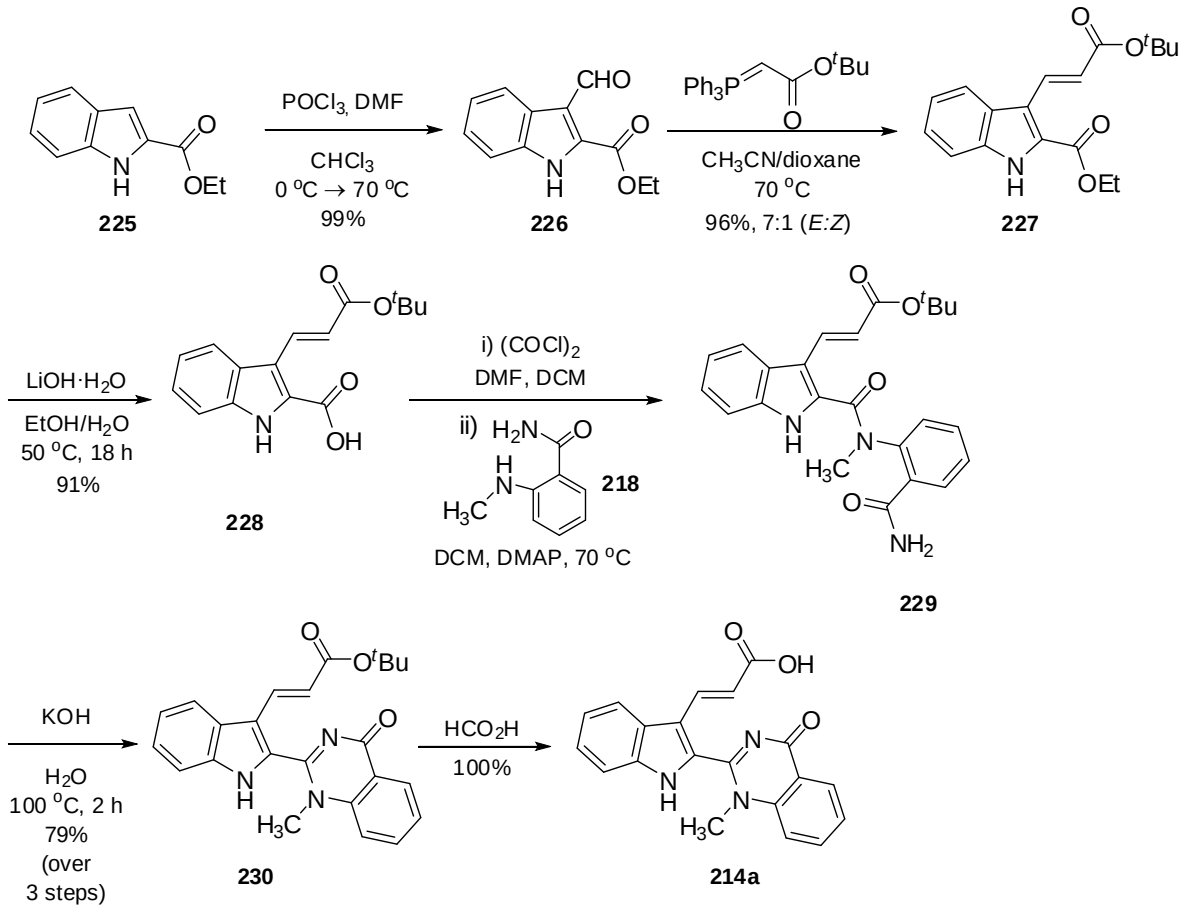



| Entry[a] | Solvent | Reagent | Temp./Time | Outcome |
|---|---|---|---|---|
| i | DMF | $POCl_3$ | 0 °C/30 min | Recovery of SM |
| ii | DMF | $POCl_3$ | 80 °C/6 h | Recovery of SM |
| iii[b] | DCE | DMF/$POCl_3$ | 80 °C/6 h | Traces of **224** |
| iv[b] | DCE | $HCON(CH_3)C_6H_5$/$POCl_3$ | 80 °C/18 h | Decomposition |

[a] Reactions were performed on a 0.4–0.8 mmol scale using indole **221** (1 equiv.) and $POCl_3$ (1.5 equiv.). [b] 1.6 Equiv. of DMF or $HCON(CH_3)C_6H_5$ were used.

The reason for the unsuccessful functionalisation at the C-3 position of indole **221** is considered to be a combination of both steric hindrance and electronic effects caused by the quinazolinone species attached at the C-2 position of the indole. Thus, it was decided to change the order of events to perform the functionalisation of the C-3 position of the indole at an earlier stage (Scheme 68). The formylation of commercially available ethyl indole-2-carboxylate **225** gave aldehyde **226** in quantitative yield based on a literature procedure.[75a,76] The Wittig reaction of aldehyde **226** followed by basic hydrolysis gave the novel compound **228**. The quinazolinone moiety present on C-2 of compound **214a** was established following the same reaction sequence we used to make intermediate **221**, *via* coupling of the acyl chloride derivative of acid **228** with aniline

**218** followed by treatment with aq. KOH. The *tert*-butyl ester **230** was then hydrolysed in formic acid to give novel acid **214a**.

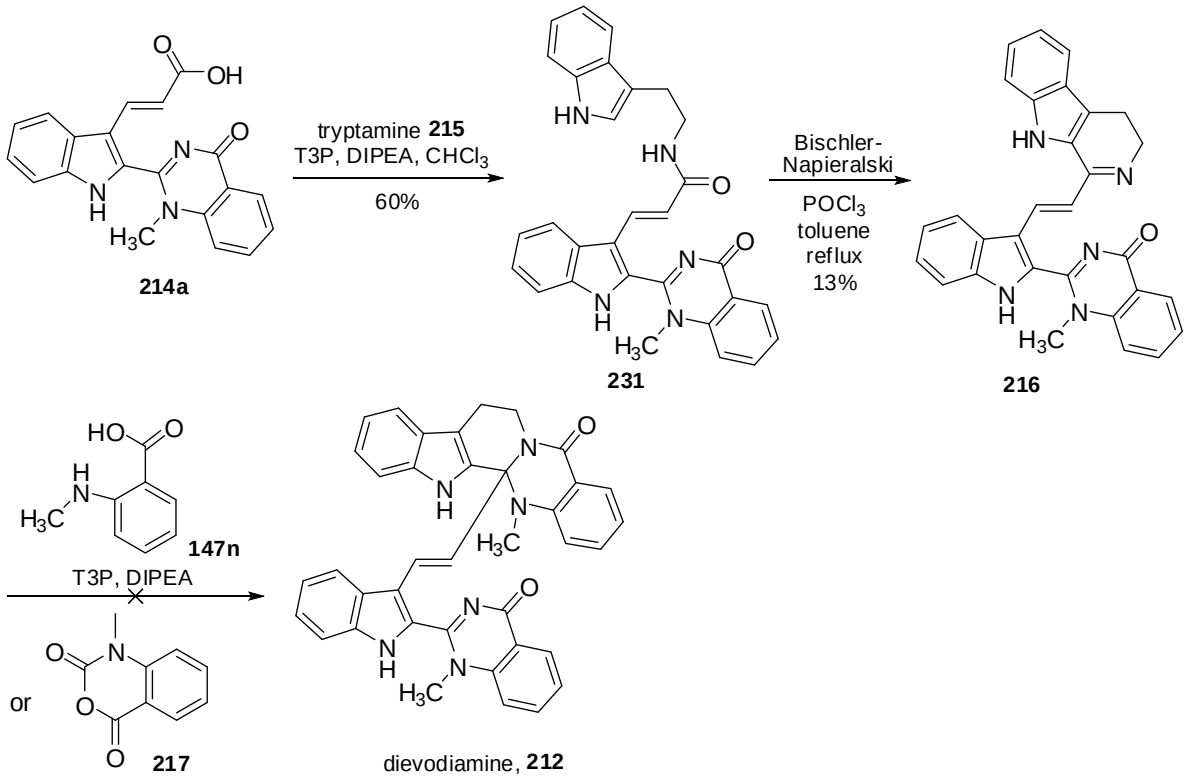



**Scheme 68**: The synthesis of the key intermediate **214a**

Having acid **214a** in hand, its conversion into the key intermediate **216** *via* amide coupling, followed by a Bischler-Napieralski reaction was examined next (Scheme 69). Pleasingly, when acid **214a** was treated with tryptamine **215**, T3P and DIPEA in chloroform, this generated intermediate **231** in good yield. [77] However, the Bischler-Napieralski reaction of intermediate **231** gave only traces of imine **216**.[77] The poor yield of the Bischler-Napieralski reaction, which was also not reproducible, was proposed to be in part due to the poor solubility of compound **231**.

The final DIA coupling was now attempted using the small amount of compound **216** available (Scheme 69), but the poor solubility of the bisindole material **216** was again problematic;[77] different solvents for the DIA coupling such as toluene, DMF, pyridine were examined, but none led to a successful result. Higher temperatures than the standard 90 °C did not prove to be beneficial either, giving back the imine **216**. Although, the coupling of anhydrides with imines is known in the literature[27] the

treatment of imine **216** with *N*-methylisatoic anhydride **217** also resulted in the recovery of imine **216**. These observations are in line with the previous results in Chapter 2 where ketimines have been proven to be mostly incompatible with the DIA protocol.



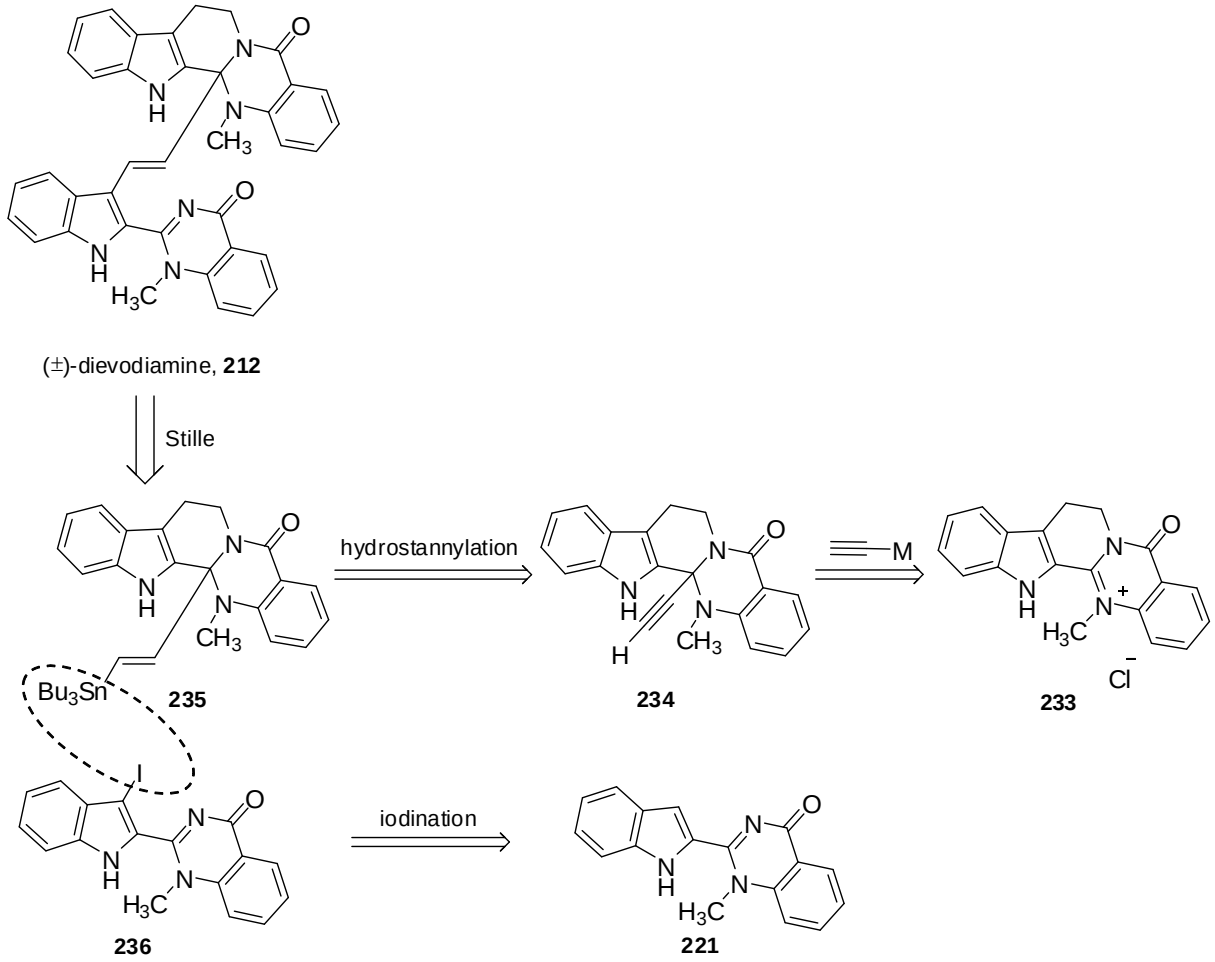

**Scheme 69**: Attempted linear generation route to synthesise (±)-dievodiamine **212**

## 3.3 Convergent Route to (±)-Dievodiamine 212

### 3.3.1 Convergent Retrosynthetic Strategy

Although we were only one step away from the synthesis of (±)-dievodiamine **212** following the linear route described above, the problems related with the poor solubility of imine **216**, as well as the low reactivity of ketimines in DIA reactions, were deemed to be too difficult to overcome. Therefore, we decided to consider alternative routes, not utilizing a DIA reaction. The unusual, although not unique,[70b] structural figure of dievodiamine **212** is its ethylene bridge linking the two indole-containing portions. This is convenient from a synthetic point of view as it potentially facilitates a convergent synthesis of dievodiamine **212** *via* the cross coupling of two evodiamine-like fragments. Therefore, we embarked on a convergent retrosynthetic strategy involving a final stage Stille coupling between the two indole-containing fragments **235** and **236** (Scheme 70). It was thought that the requisite stannane **235** could be obtained *via* the nucleophilic addition of a metallated alkyne into dehydroevodiamine hydrochloride (DHED·HCl)

**233** followed by hydrostannylation. Note that dehydroevodiamine (DHED) itself is a bioactive constituent of *Evodia rutaecarpa* which possess an interesting biological profile.[67,78] It was envisioned that the 3-iodo-indole fragment **236** could be synthesised from the readily available quinazolinone **221** *via* iodination.

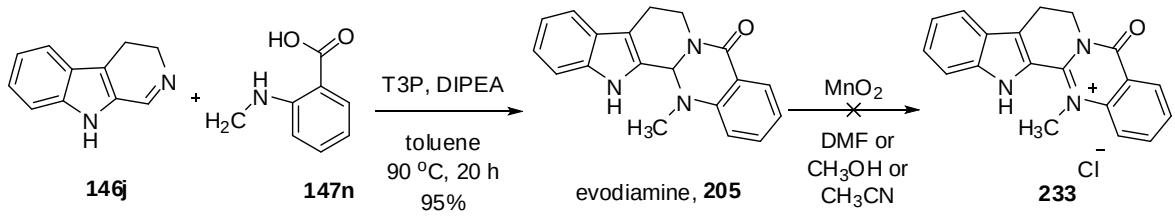



**Scheme 70**: A convergent retrosynthetic strategy to form (±)-dievodiamine **212**

## 3.4 The Synthesis of the two Indole-Containing Fragments 235 and 236

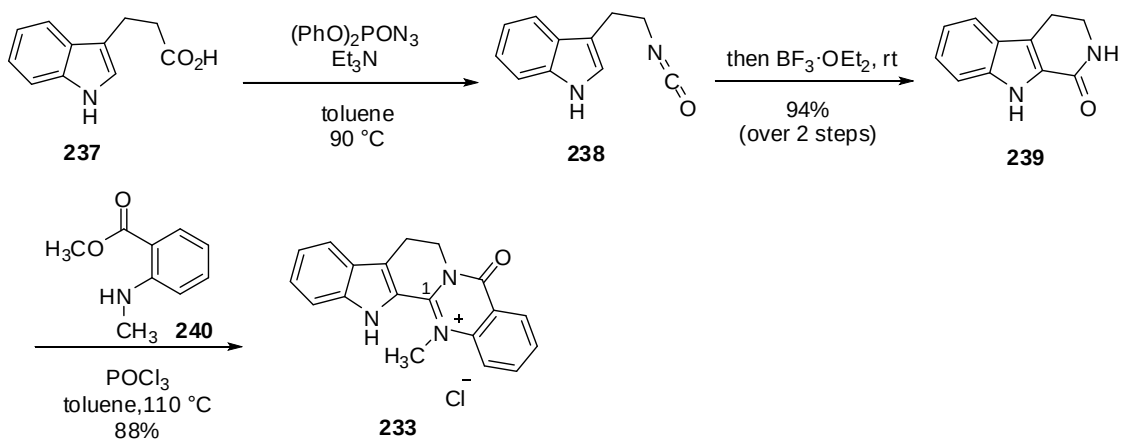
### 3.4.1 The Synthesis of the Stannane Coupling Partner 235

We first tested if the key DHED·HCl salt **233** could be obtained directly *via* the oxidation of evodiamine **205** (Scheme 71). Evodiamine **205** was synthesised *via* the DIA coupling between readily available imine **146j** and *N*-methylanthranilic acid **147n**, as described in Chapter 2, and was reacted with $MnO_2$ in different solvents. However, no oxidation was observed and complex mixtures of products were obtained.



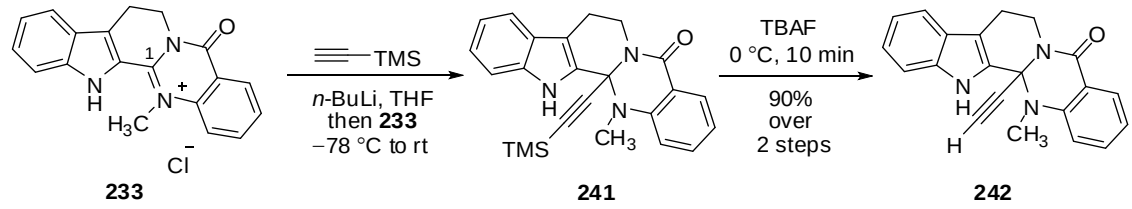

**Scheme 71**: Attempted oxidation of evodiamine **205** to the dehydroevodiamine salt (DHED·HCl) **155**

DHED·HCl salt **233** was instead synthesised from the known lactam **239** using a procedure modified from that published by Pachter *et al.* (Scheme 72).[79] Lactam **239** was synthesised from indole-3-propionic acid **237** *via* a modified Curtius rearrangement and subsequent intramolecular Friedel-Crafts acylation of the resulting isocyanate intermediate **238** following a literature procedure.[80] It was then heated with the commercially available dimethyl anthranilate **240** and $POCl_3$ in toluene to afford the DHED·HCl salt **233** in excellent yield. Note that a simple work-up was developed which involved pouring the crude reaction mixture into cold water (0 °C) and filtering the resulting yellow precipitate. The $^{13}$C-NMR chemical shift of C-1 of DHED·HCl salt **233** at low field (150.0 ppm) is characteristic.[81]



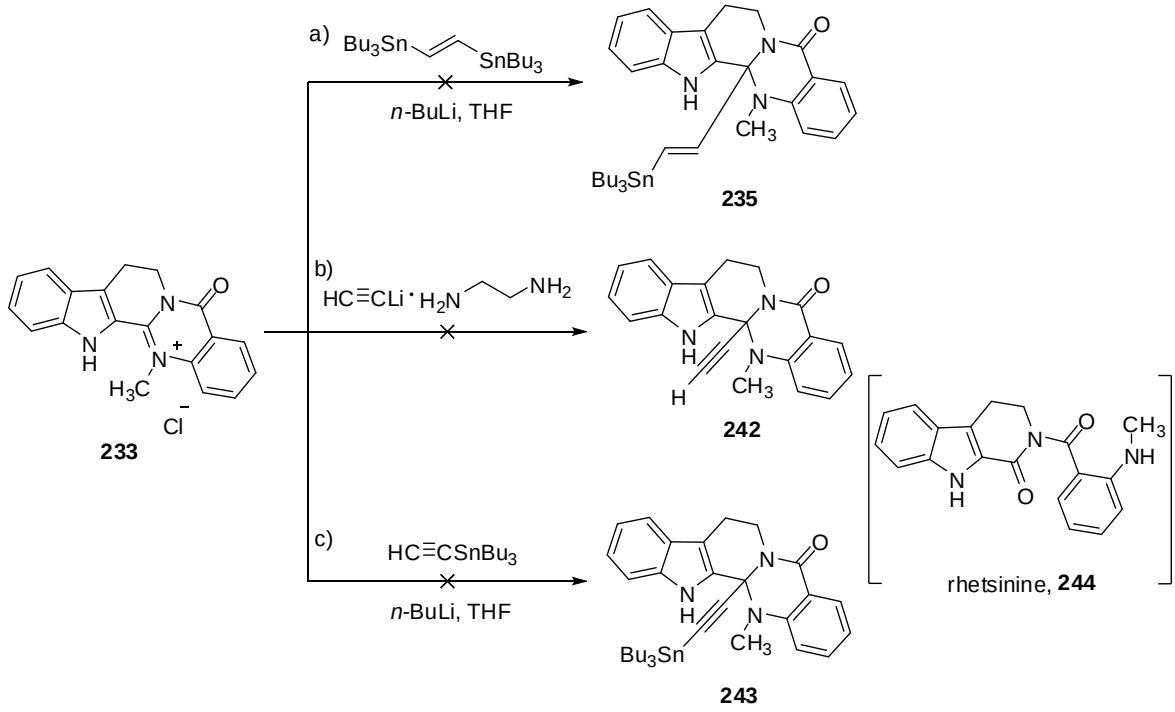

**Scheme 72**: The synthesis of dehydroevodiamine salt (DHED·HCl) **233**

It was then planned to trap the DHED·HCl salt **233** with an organometallic species. To the best of our knowledge, prior to this work, very little was known about the reactivity of DHED systems apart from limited examples of the reduction and hydrolysis of DHED adducts.[59,78] Attempts to trap the DHED·HCl salt **233** using ((trimethylsilyl)ethynyl) lithium (1.1 equiv.) in THF were made (Scheme 73). Unfortunately, only trace amounts of the alkyne **241** was isolated and the bulk of starting material recovered from the crude mixture by filtration. However, when an excess (3 equiv.) of ((trimethylsilyl)ethynyl)lithium was used, nucleophilic attack took place successfully, affording the alkyne **241** cleanly, suggesting that one equivalent of the organolithium species deprotonates the indole (or quenches the HCl) before the nucleophilic addition takes place. Note that the progress of this reaction can be monitored visually as the suspension of DHED·HCl salt **233** in THF becomes homogeneous upon completion of the reaction. Treatment of the intermediate alkyne **241** with TBAF gave the novel alkyne **242** in 90% yield over the two step sequence. Note that this is the first report of a C-C bond formation at the electrophilic C-1 position of a DHED system.



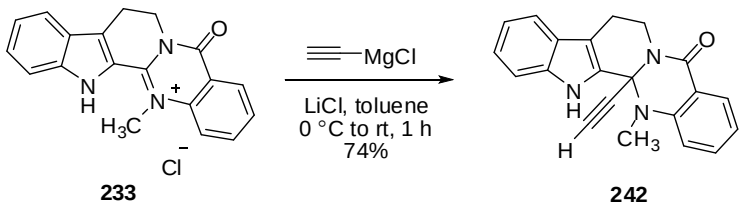

**Scheme 73**: The synthesis of alkyne **242** with ((trimethylsilyl)ethynyl)lithium

Efforts were made into shortening the route by using other organometallic reagents (Scheme 74). First, treatment of the salt **233** with bis(tributylstannyl)ethene to give organostannane **235** in one step was studied (Scheme 74, path a). However, this reaction was unsuccessful, affording a complex mixture of products. Disappointingly, the salt **233** also did not react as planned when treated with an excess of the commercially available lithium acetylide ethylenediamine complex (Scheme 74, path b) and instead hydrolysis to the known alkaloid rhetsinine **244**[79, 82] occurred after the work-up.[77] Rhetsinine **244** was also observed in the $^{1}$H-NMR spectrum of the crude mixture when salt **233** was treated with an excess of lithiated tributyl(ethynyl)stannane (Scheme 74, path c) and there was no evidence for the formation of the desired compound **243**.



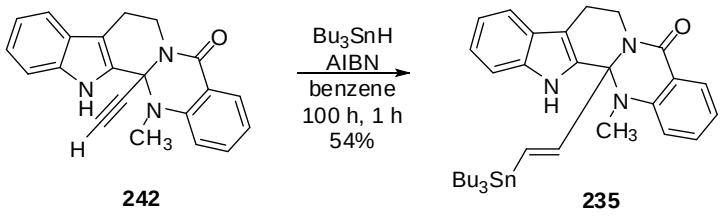

**Scheme 74**: Attempts to achieve functionalisation of DHED·HCl **233** at C-1

Attempts to trap the DHED·HCl salt **233** with the commercially available ethynylmagnesium chloride in THF were then made (Scheme 75). The initial results were disappointing giving only traces of the alkyne **242** while the bulk of the starting material remained insoluble in THF and hydrolysed to rhetsinine **244** after the work-up. Pleasingly, when the solvent was switched to toluene and lithium chloride[83] was included as an additive, alkyne **242** was isolated in 74% yield. Note that although this route does not employ a protecting group and thus is shorter, the yield is lower than the original TMS-acetylene route (see Scheme 73, 90% over the two steps).



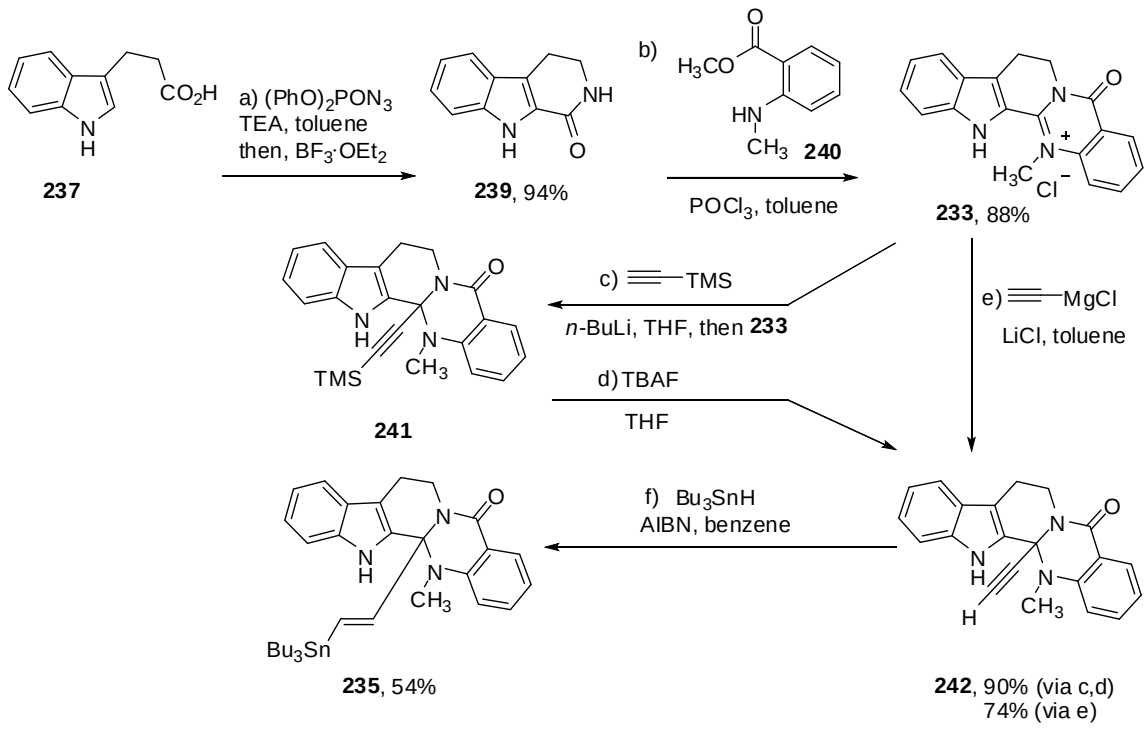

**Scheme 75**: The synthesis of alkyne **242** with ethynylmagnesium chloride

Next, the novel stannane coupling partner **235** was synthesised *via* the radical hydrostannylation of alkyne **242** with tributyltin hydride and AIBN in refluxing benzene (Scheme 76). We were pleased to find that stannane **235** was isolated as a single regio- and stereoisomer ($J$ = 18.9 Hz).




**Scheme 76**: The synthesis of stannane **235**

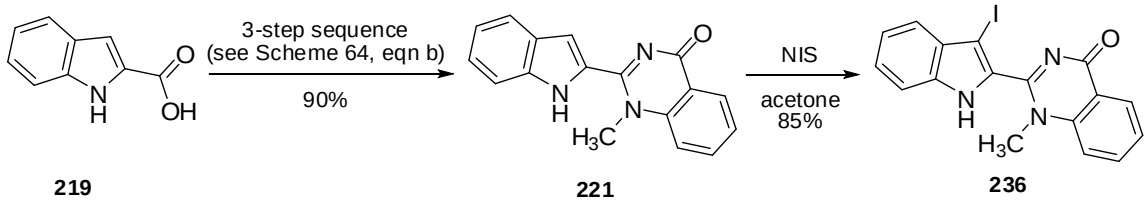
Scheme 77 shows the complete synthesis of stannane coupling partner **235** from indole acid **237**. Note that column chromatography was only used in the final step from lactam **239** and therefore the route was easy to scale-up.




**Scheme 77**: The complete synthesis of stannane coupling partner **235** from indole acid **237**

### 3.4.2 The Synthesis of the Iodide Coupling Partner 236

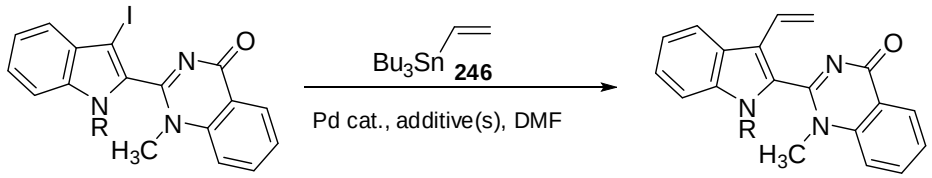
The synthesis of the novel 3-iodo-indole fragment **236** was achieved extremely efficiently by the reaction of the previously synthesised quinazolinone **221** with *N*-iodosuccinimide in acetone, based on a literature procedure (Scheme 78).[84] It is noteworthy that column chromatography was performed only at the final step of the 4-step synthesis, from indole-acid **219**, which again was advantageous during scale-up.




**Scheme 78**: The synthesis of iodide coupling partner **236** from indole-acid **219**

Having in hand the two coupling partners **235** and **236**, we moved on to establish the conditions for the final Stille coupling. Commercially available vinyl tributylstannane **246** was used in the place of stannane **235** as a test system (Table 7).

**Table 7**: Optimisation of Stille reaction of indole **236** and stannane **246**



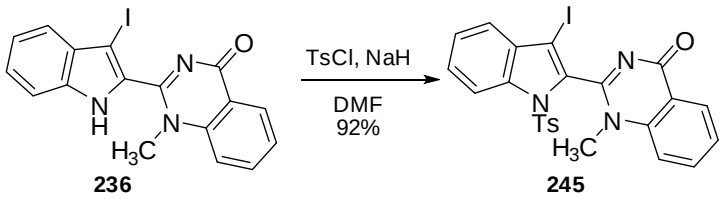

**236** R = H
**245** R = Ts

**247** R = H
**248** R = Ts

| Entry[a] | Iodide | Pd cat. | Additives (equiv.) | Temp.(°C)/ Time(h) | Outcome (Yield)[b] |
|---|---|---|---|---|---|
| i[c] | **236** | A | none | 70/20 | No reaction |
| ii | **236** | A | CsF (2), CuI (0.1) | 45/1 | No reaction |
| iii | **236** | A | CsF (2), CuI (0.1) | 80/1 | 3:2, **236:221** |
| iv | **236** | A | CsF (2), CuI (0.1) | 100/1 | Decomp. |
| v | **236** | B | $Et_4NCl$ (1.0) | 80/20 | No reaction |
| vi | **245** | B | $Et_4NCl$ (1.0) | 80/20 | **248**, 41% |
| vii | **236** | B | $Et_4NCl$ (1.0), CuI (0.1) | 80/20 | **247**, 10% |
| viii | **236** | B | $Et_4NCl$ (1.0), CuI (1.5) | 80/2 | **247**, 82% |
| ix[d] | **236** | B | $Et_4NCl$ (2.0), CuI (1.5) | 80/2 | **247**, 28% |

[a] Reactions were performed on a 0.4–0.5 mmol scale using iodide **236** or **245** (1 equiv.), stannane **246** (1.5 equiv.), Pd catalyst [A = $Pd(PPh_3)_4$, B = $PdCl_2(PPh_3)_2$] (0.05 equiv) in DMF with the additives and conditions shown unless stated. [b] Isolated yield following chromatography. [c] Reaction performed in THF. [d] Reaction performed with 0.2 equiv. of Pd catalyst B.

Heating iodide **236** at reflux with stannane **246** and $Pd(PPh_3)_4$ in THF gave no reaction (Table 7, entry i). Baldwin's conditions,[85] which exploit the synergistic effect of CuI and CsF, were also ineffective on this system, affording no product at 45 °C (entry ii) and resulted in the partial reduction of iodide **236** at 80 °C (entry iii) and eventually its decomposition at higher temperatures (entry iv). It was then tested if the addition of $Et_4NCl$ salt, which is more commonly used in Heck reactions[86] but has also found limited use in Stille reactions,[87] could be effective. However, no reaction was observed under the conditions trialled ($Pd(PPh_3)_2Cl_2$, $Et_4NCl$ at 80 °C in DMF, entry v). At that point, it was decided to test the Stille reaction on the tosylated protected iodide **245** to investigate if the nitrogen lone pair on the indole moiety is responsible for the unsuccessful results. The tosylated protected iodide **245** was synthesised from iodide **236** in high yield as shown in Scheme 79 and subjected to the same reaction conditions as those in entry v.

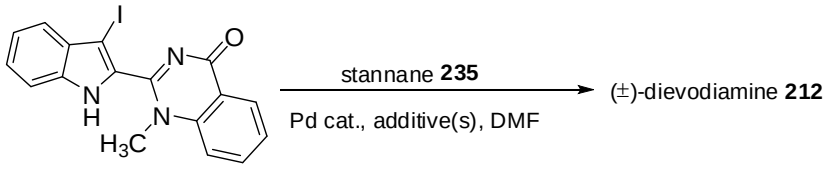



**Scheme 79**: Synthesis of the tosylated iodide **245**

Pleasingly, the novel product **248** was formed in 41% yield (entry vi) suggesting that protection of the indole moiety would be beneficial. Although this result was encouraging, an additional protection step entered in the reaction sequence which wasn't appealing and so we decided to put some more effort on the coupling of the unprotected iodide **236** before we focus wholly on the coupling of the protected iodide **245**. Copper salts are known to accelerate Stille reactions by promoting an initial transmetallation of the organostannane to generate a more reactive organocopper intermediate.[88] Pleasingly, the combination of CuI and $Et_4NCl$ with $Pd(PPh_3)_2Cl_2$ in DMF at 80 °C gave the novel product **247**, albeit in low yield (entry vii). The yield was increased dramatically by using an excess of CuI under otherwise identical conditions (82%, entry viii) but decreased significantly when a larger excess of the catalyst and $Et_4NCl$ were used (entry ix).

With the above results in mind, we embarked on the coupling of the stannane **235** with the iodide **236** to complete the total synthesis of (±)-dievodiamine **212** (Table 8). Pleasingly, when the reaction conditions developed above were applied on the real system (Table 8, entry i), (±)-dievodiamine **212** was obtained in 35% yield, but with a 20 h reaction time, showing that the coupling of iodide **236** with stannane **235** is significantly slower than the analogous test reaction with stannane **246**. Pleasingly, increasing the amounts of the catalyst to 0.2 equivalents and $Et_4NCl$ to 2 equivalents led to a reduced reaction time (2 h) and a cleaner reaction mixture to give dievodiamine **212** in a much improved yield (65%), following column chromatography and recrystallization (entry ii). A lower yield (22%) was obtained when $Et_4NCl$ was omitted (entry iii) and no product was isolated in the absence of CuI (entry iv), thus confirming the importance of both additives. Only traces of product were obtained when catalytic amount of CuI was used (entry v) or when the temperature was decreased (entry vi) or increased (entry vii). Finally, the use of $Pd(PPh_3)_2Br(NBS)$ [89] as a catalyst let to decomposition (entry viii).

**Table 8**: Optimisation of Stille reaction of indole **236** and stannane **235**




**236**

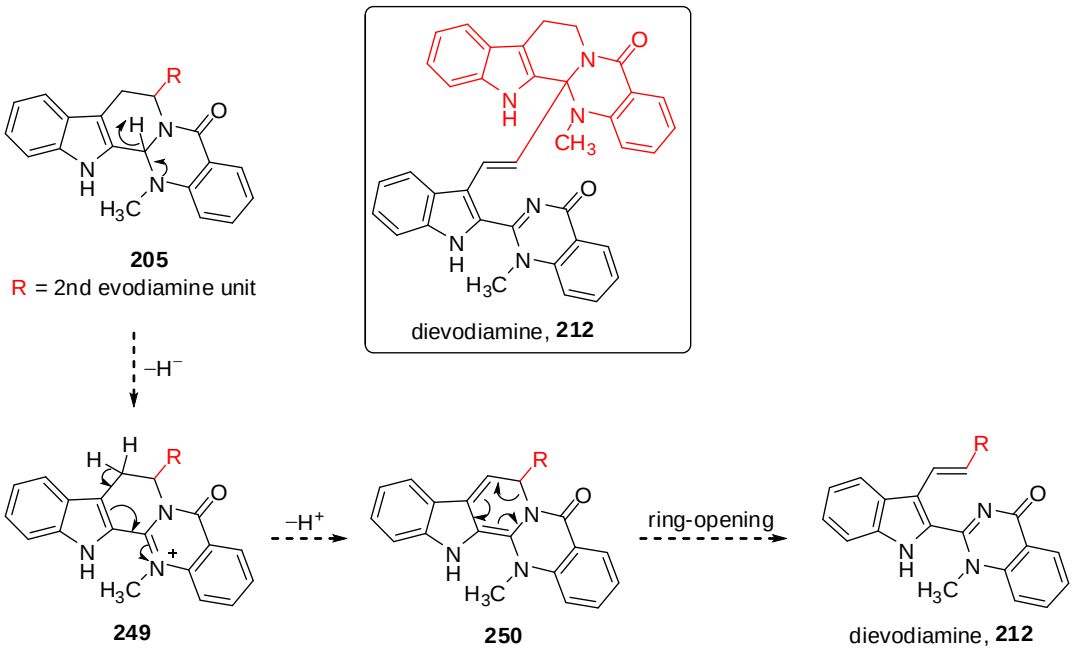
| **Entry**[a] | **Cat.** | **Additives (equiv.)** | **Temp.(°C)/ Time(h)** | **Outcome (Yield)**[b] |
|---|---|---|---|---|
| i[c] | B | $Et_4NCl$ (1.0), CuI (1.5) | 80/20 | **212**, 35% |
| ii | B | $Et_4NCl$ (2.0), CuI (1.5) | 80/2 | **212**, 65% |
| iii | B | CuI (1.5) | 80/2 | **212**, 22% |
| iv[d] | B | $Et_4NCl$ (1.0) | 80/1 | No reaction |
| v | B | $Et_4NCl$ (2.0), CuI (0.4) | 80/2 | Traces |
| vi | B | $Et_4NCl$ (2.0), CuI (1.5) | 50/2 | Traces |
| vii | B | $Et_4NCl$ (2.0), CuI (1.5) | 100/2 | Traces |
| viii | C | $Et_4NCl$ (2.0), CuI (1.5) | 50/2 | Decomp. |

[a] Reactions were performed on a 0.1–0.2 mmol scale using iodide **236** (1 equiv.), stannane **235** (1.5 equiv.), Pd catalyst [B = $PdCl_2(PPh_3)_2$, C = $Pd(PPh_3)_2Br$(NBS)] (0.2 equiv) with the additives and conditions in DMF shown unless stated. [b] Isolated yield following chromatography. [c] Reaction performed with 0.05 equiv. of Pd catalyst B. [d] Reaction performed with 0.1 equiv. of Pd catalyst B.

The first total synthesis of the (±)-dievodiamine **212** has therefore been completed. The two advanced intermediates **235** and **236** were each synthesised in four steps, in 33% and 77% yield respectively. The final Stille coupling gave the natural product in 65% yield completing the total synthesis of (±)-dievodiamine **212** in 26% over the longest linear sequence (5 steps). A considerable amount of (±)-dievodiamine **212** (~200 mg in total) has been synthesised and is available for biological testing. The spectral properties of the racemic synthetic material closely matched those reported for the natural product (Appendix I (A and B)), thus confirming its assigned structure.[66] The mp of the material was found to be 229–233 °C (no literature mp was reported[66] in the isolation paper). We predict that asymmetric induction may be possible *via* the organometallic addition of lithium acetylides to DHED·HCl salt **233** in the presence of a chiral catalyst based on literature precedent for such additions into carbonyl groups and imines.[90]

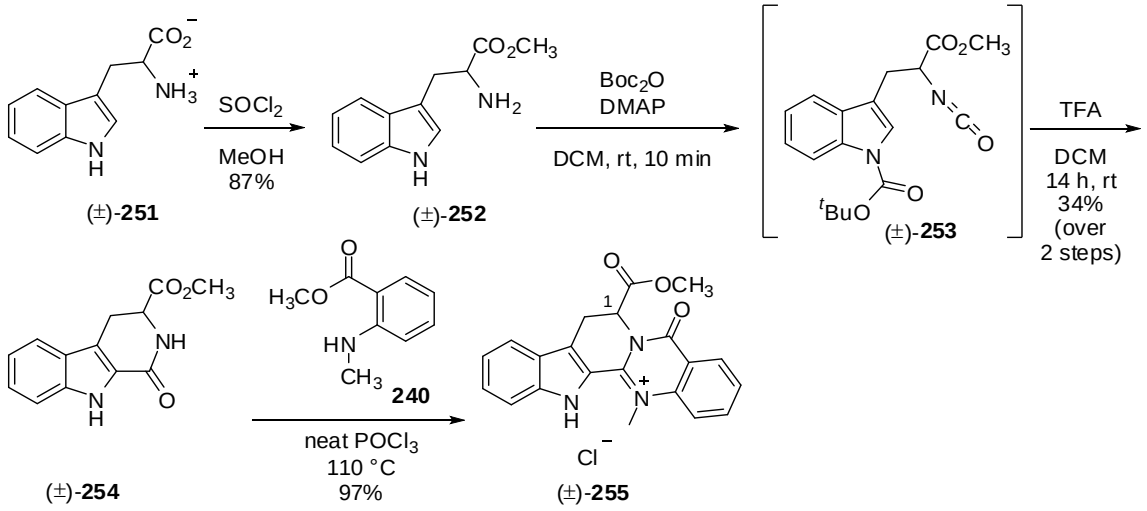
## 3.5 Attempted Biomimetic Synthesis of the Evodiamine Derived Subunit of (±)-Dievodiamine 212

Having developed a viable route to dievodiamine **212** we set out to investigate a potential biomimetic strategy leading to the natural product based on the fact that its framework contains two evodiamine subunits (red and black) (Scheme 80). It was considered that the bottom fragment of dievodiamine **212** (black) may be derived from an evodiamine unit (red) following oxidation and ring opening as shown in Scheme 80. The rearrangement shown below (**250** to **212**) may proceed *via* a 6π-azaelectrocyclic ring-opening; a similar process, in which a 6π-azaelectocyclic ring-closure is used to form a C-N bond intramolecularly, has been reported recently.[91]




**Scheme 80**: The bottom fragment of dievodiamine **212** (black) is an evodiamine unit (red) following oxidation and ring-opening

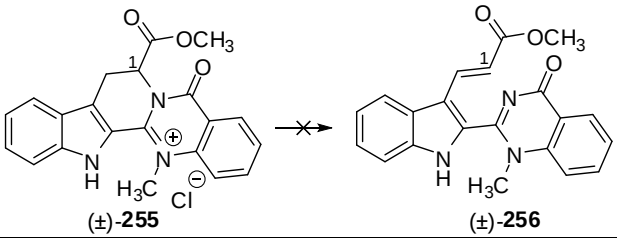
The studies were started by the formation of the DHED adduct **255** which is a simple model system of intermediate **249** (Scheme 81). *D,L*-Tryptophan **251** was treated with thionyl chloride in methanol to give tryptophan methyl ester **252**. The ester **252** was then cyclised to lactam **254** *via* the isocyanate **253** following a literature procedure;[92] the indole **252** was treated with 2.4 equivalents of Boc-anhydride and 1 equivalent of DMAP for 10 minutes before it was subjected to excess of trifluoroacetic acid to cleave the *N*-Boc protecting group and give lactam **254**. Lactam **254** was then heated at reflux with dimethyl anthranilate **240** in neat $POCl_3$ to give the novel DHED analogue **255**.




**Scheme 81**: The synthesis of the DHED analogue **255**

Once compound **255** was synthesised, different ways to effect the desired rearrangement were tested (Table 9). Heating compound **255** with DBU, resulted in decomposition while heating it with a strong base, NaH, gave the novel hydrolysis product **257** exclusively after aqueous work-up (Figure 11). Microwave irradiation of compound **255** in toluene resulted in decomposition, while simultaneous demethylation and decarboxylation took place when compound **255** was irradiated in DMF to give rutaecarpine **258**, a known alkaloid from *Evodia fructus* (Figure 11).[26j, 93]

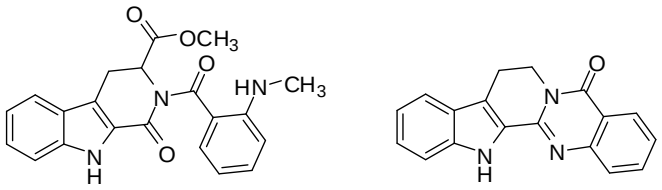
**Table 9**: Attempts to achieve the ring-opening of compound **255** to form compound **256**



(±)-**255** (±)-**256**

| Entry[a] | Solvent | Base[b] | Temp. | Time | Outcome |
|---|---|---|---|---|---|
| i | THF | DBU | 70 °C | 20 h | decomposition |
| ii | $CHCl_3$ | DBU | 70 °C | 20 h | decomposition |
| iii | THF | NaH | rt | 1.5 h | **257** (40% yield) |
| iv | toluene | – | 140 °C (MW) | 10 min | decomposition |
| v | DMF | – | 200 °C (MW) | 10 min | **258** (31% yield) |

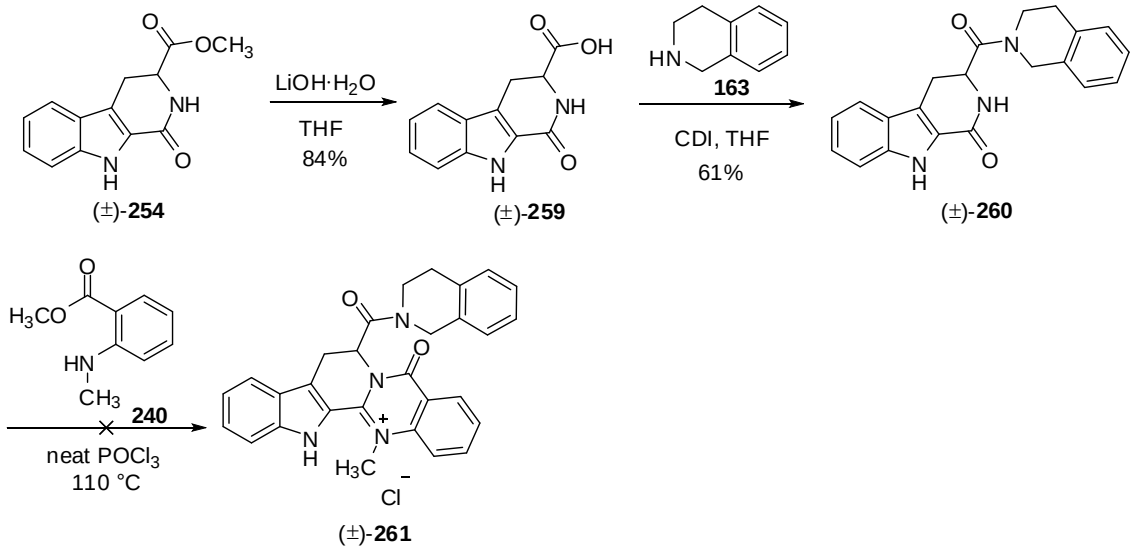
[a] Reactions were performed on a 0.1–0.3 mmol scale. [b] 1.5 Equiv. of base was used.



(±)-**257** rutaecarpine, **258**

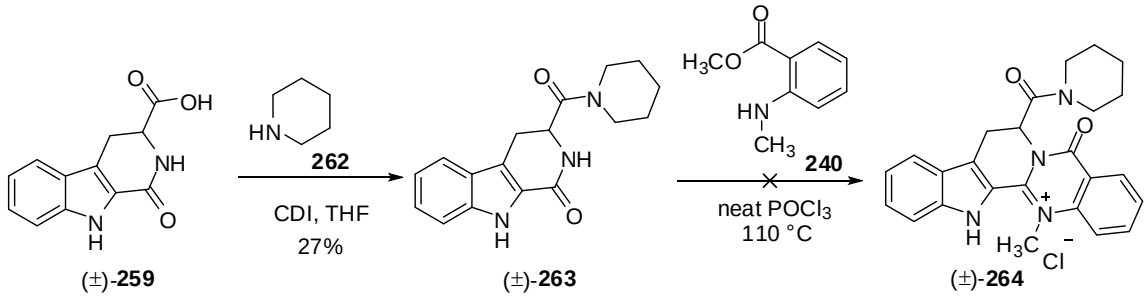
**Figure 11**: Compound **257** and rutaecarpine **258**

It was speculated that installing a bulkier group than an ester on C-1 may promote the desired transformation to take place by providing a steric driving force to the reaction. Therefore, we set out to synthesise the novel DHED analogue **261** from the readily available ester **254** (Scheme 82). The hydrolysis of ester **254** gave the corresponding acid **259** which was then converted into the amide **260** *via* coupling with tetrahydroisoquinoline **163**. However, treatment of amide **260** with dimethyl anthranilate **240** in neat $POCl_3$ didn't give any of the desired salt **261**.



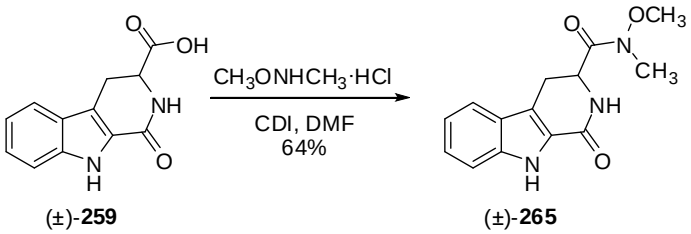
**Scheme 82**: Attempts to synthesise salt **261**

The novel lactam **263** was then synthesised from acid **259** using piperidine and CDI in THF and treated with dimethyl anthranilate **240** in neat $POCl_3$ (Scheme 83). Unfortunately, the reaction gave a complex mixture and no salt **264** was observed in the $^1$H-NMR spectrum of the crude mixture.

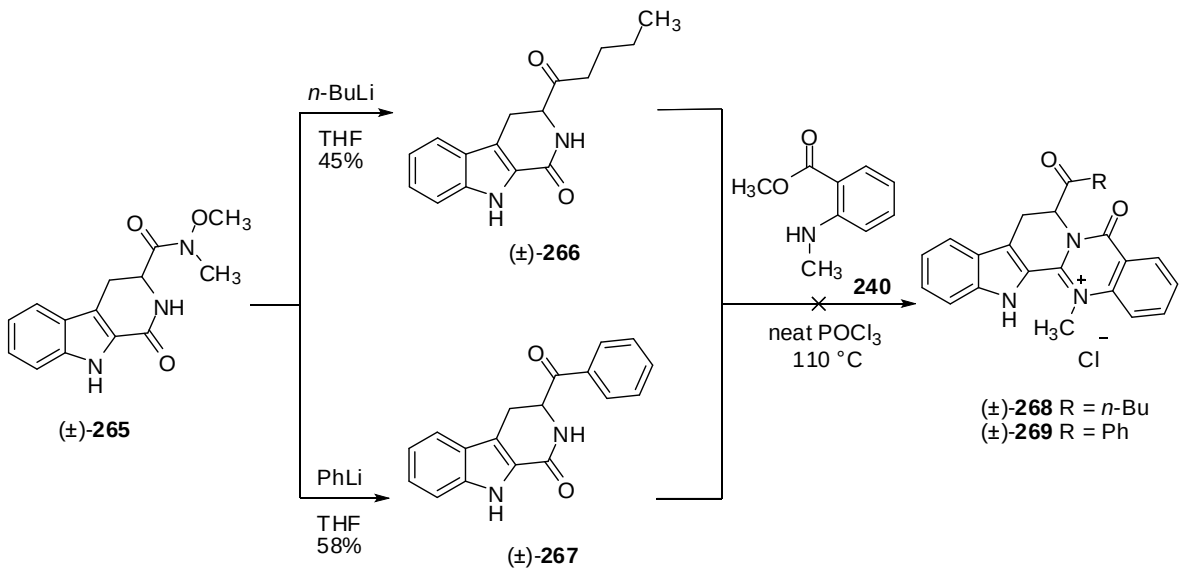



**Scheme 83**: Attempt to synthesise salt **264**

The Weinreb amide **265** was then synthesised from the acid **259** using *N*,*O*-dimethylhydroxylamine hydrochloride and CDI in DMF (Scheme 84). The treatment of the amide **265** with *n*-BuLi resulted in the formation of amide **266** while treatment with PhLi gave the amide **267** (Scheme 85). Disappointingly, neither amide **266** nor amide **267** gave the desired salts **268** and **269** when treated with dimethyl anthranilate **240** in $POCl_3$.

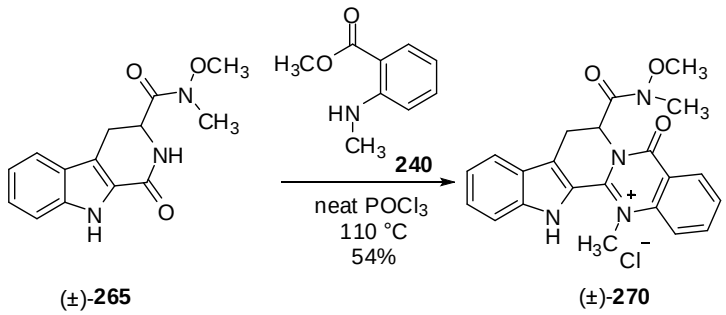



**Scheme 84**: The synthesis of Weinreb amide **265**



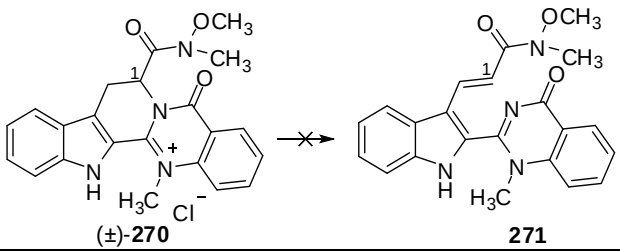

**Scheme 85**: Attempts to synthesise salts **268** and **269**

Pleasingly, when the Weinreb amide **265** was treated with dimethyl anthranilate **240** in $POCl_3$, it gave the desired DHED adduct **270** in 54% yield (Scheme 86). It was then tested if the DHED adduct **270** could undergo the desired ring-opening (Table 10). Unfortunately, heating the compound **270** with NaH at different temperatures resulted in decomposition while MW irradiation in DMF gave the novel demethylated product **272** shown in Figure 12.




**Scheme 86**: The synthesis of salt **270**

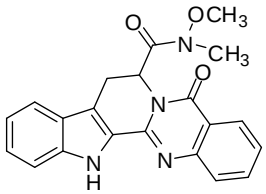
**Table 10**: Attempts to achieve the ring-opening of compound **270** to form compound **271**



(±)-**270** **271**

| Entry[a] | Solvent | Base[b] | Temp. | Time | Outcome |
|---|---|---|---|---|---|
| i | THF | NaH | rt | 4 h | decomposition |
| ii | DMF | NaH | 60 °C | 1.5 h | decomposition |
| iii | DMF | NaH | 90 °C | 20 h | decomposition |
| iv | DMF | NaH | 150 °C | 3 h | decomposition |
| v | DMF | – | 200 °C (MW) | 10 min | **272** (42% yield) |

[a] Reactions were performed on a 0.03–0.2 mmol scale. [b] 1.5 Equiv. of NaH was used.



(±)-**272**

**Figure 12**: The novel demethylated product **272**

## 3.6 Summary

The first total synthesis of (±)-dievodiamine **212** has been achieved using a Stille coupling between the two key coupling partners **235** and **236**. Each coupling partner was synthesised efficiently in just 4 steps. The brevity and efficiency of the synthesis was undoubtedly aided by the absence of protecting groups. This also imparted suitable solubility properties that enable minimisation of chromatography and thus, facilitated scale-up. Key steps include the first example of an organometallic addition into DHED adduct and the Stille coupling between the two sterically hindered components using $PdCl_2(PPh_3)_2$ and the unusual combination of $Et_4NCl$ and CuI as additives. Studies on a possible biomimetic route to dievodiamine **212** were also conducted, albeit without success.

The work described in this Chapter was published recently (Appendix II (D)).[94]

# Chapter 4 Total Synthesis of Berberine Alkaloids

## 4.1 Introduction to Protoberberine Alkaloids

### 4.1.1 Protoberberine Skeleton

Protoberberines are alkaloids based on a bis-isoquinoline skeleton as their basic building block. Most protoberberine alkaloids exist in nature either as tetrahydroprotoberberines **273** or as quaternary protoberberine salts **274** (Figure 13).[95]

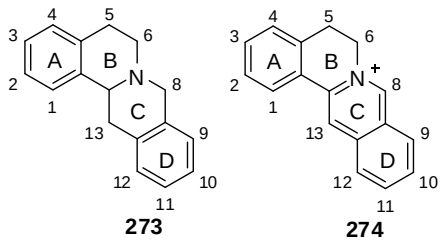



**Figure 13**: Tetrahydroprotoberberine **273** and quaternary protoberberine skeleton **274**

Such systems are usually substituted with hydroxyl, methoxy, or methylenedioxy groups at positions 2, 3, 9, 10 or 2, 3, 10, 11 and the prefix pseudo- is often used for the latter substitution pattern. Protoberberines that are substituted on the D-ring at C-12 usually take the prefix retro-. In the past, the prefix epi- was used inter-changeably for 2,3 and 9,10 substitution patterns. In some cases methyl groups are present at C-8 and C-13 and hydroxyl groups at C-5 or at C-13. More rarely, they are substituted on the A-ring at C-4 with methyl or methoxy groups. Recently, tetrahydroprotoberberines with nitro-substituents at C-1, C-4 and/or C-5 were isolated.[96] Berberine **275**, nandinine **276**, anisocycline **277**, PO-5 (alborine) **278**, coralyne **279**, cavidine **280**, thalidastine **281**, 2,9-dihydroxy-3,11-dimethoxy-1,10-dinitrotetrahydroprotoberberine **282** and pallimamine **283** are representative examples of naturally occurring protoberberines (Figure 14).[95]

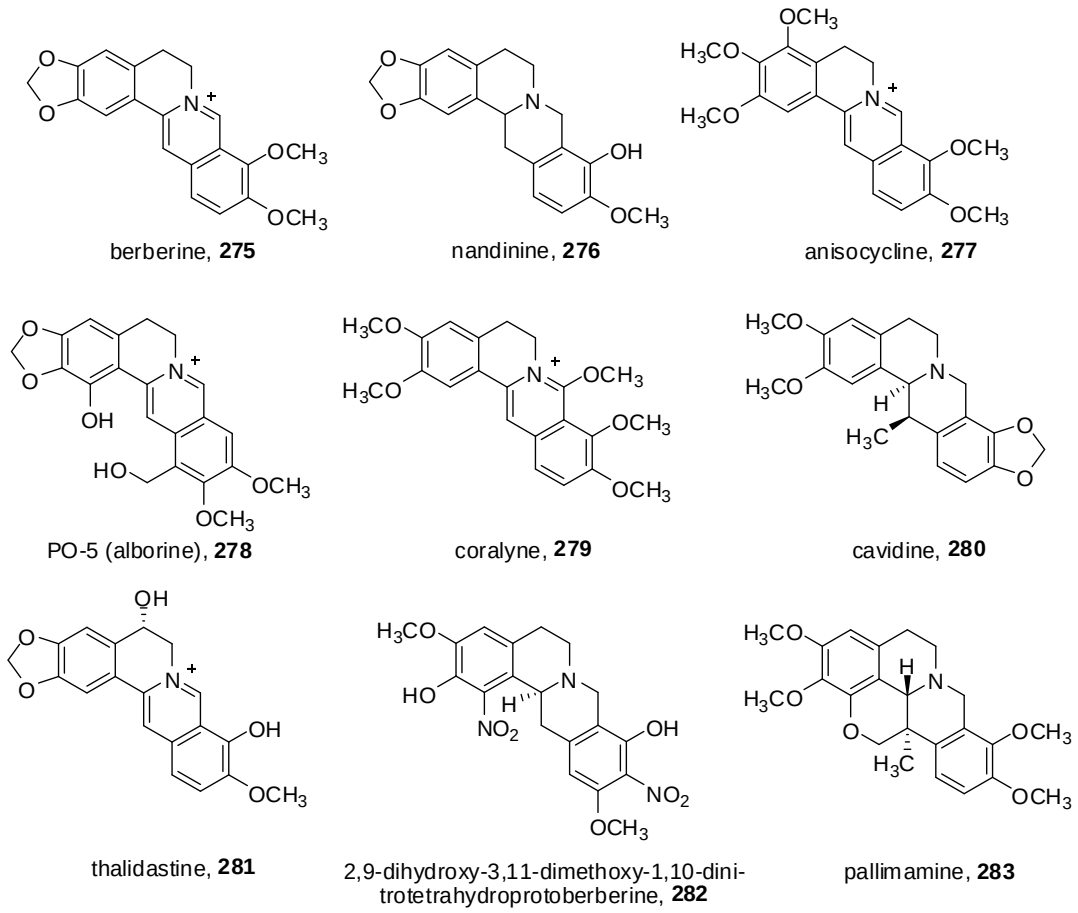
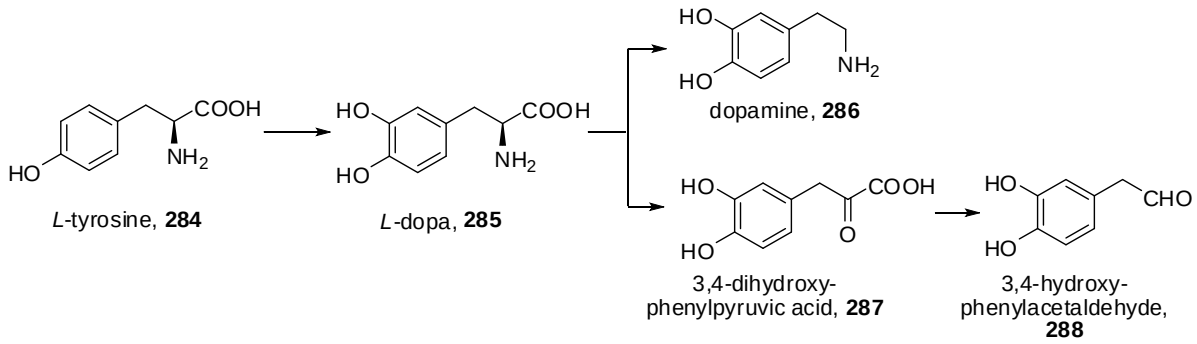


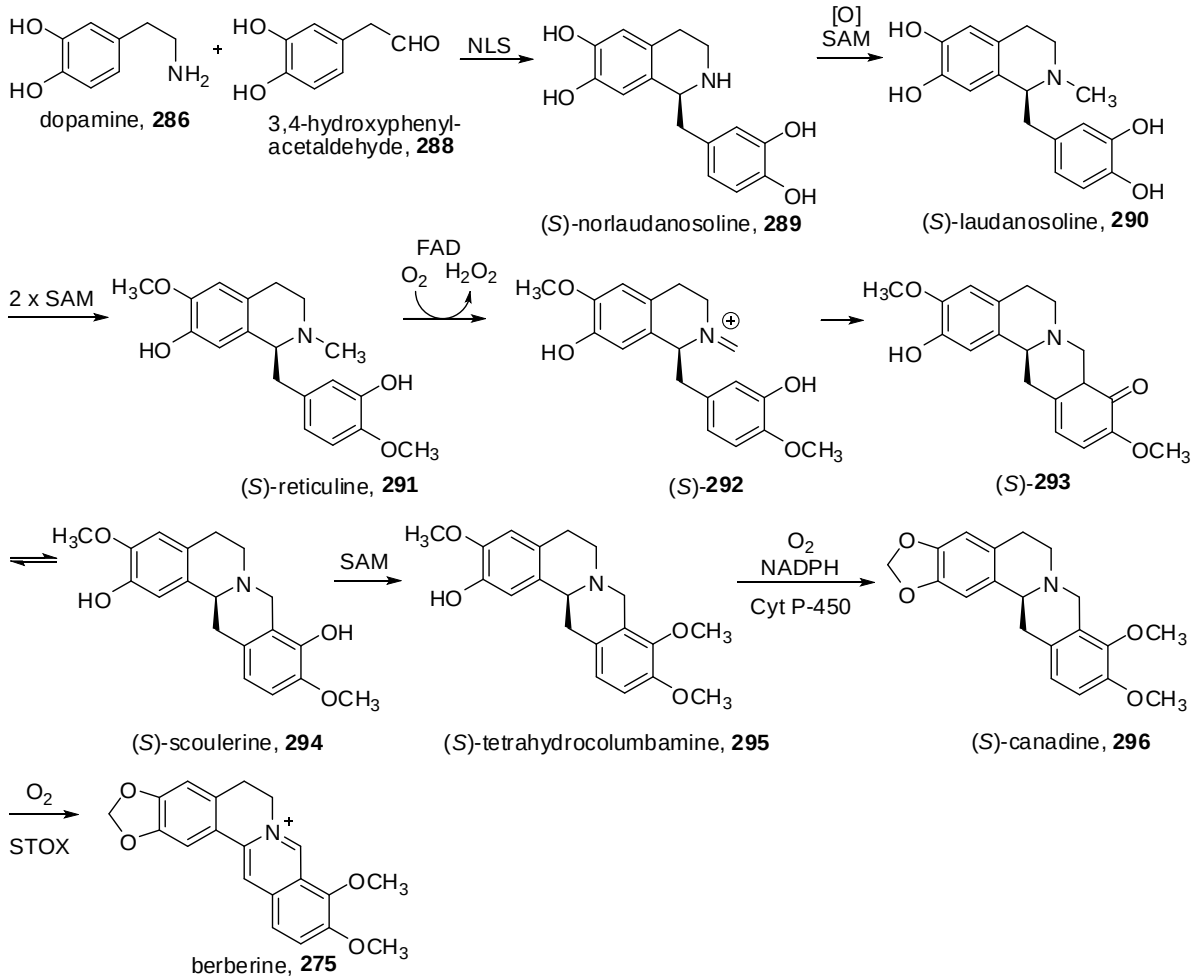

**Figure 14**: Examples of naturally occurring protoberberines

Protoberberines have been found in many plant families such as *Papaveraceae*, *Berberidaceae*, *Fumariaceae*, *Menispermaceae*, *Ranunculaceae*, *Rutaceae* and *Annonaceae*. Berberine **275** itself is probably the most widely distributed of all protoberberines alkaloids with a wide spectrum of pharmacological activities.[97] It has been shown that the amino acid tyrosine **284** is the biosynthetic precursor of berberine and it is incorporated into both the top (rings A and B) and the bottom (ring C and D) parts of the alkaloid.[98] Although not all of the individual steps of the biosynthesis have been completely established, the general sequence shown in Schemes 87 and 88 prevails in the literature.[95] Several enzymes participate in the biosynthetic pathway.[99] Dopa **285** which comes from tyrosine **284**, loses carbon dioxide to form dopamine **286** (Scheme 87). Likewise, 3,4-dihydroxyphenylpyruvic acid **287** which also comes from tyrosine **284**, loses carbon dioxide to form 3,4-hydroxyphenyl-acetaldehyde **288**. Dopamine **286** then reacts with 3,4-dihydroxyphenylacetaldehyde **288** to form norlaudanosoline **289** in a reaction similar to the Mannich reaction (Scheme 88). This reaction is catalysed by (*S*)-norlaudanosoline synthase (NLS).[100] After oxidation and methylation by *S*-adenosyl

methionine (SAM), laudanosoline **290** is formed which is then transformed to the pivotal intermediate, reticuline **291**. The formation of the berberine bridge is promoted by a berberine bridge enzyme.[101] The iminium ion **292**, undergoes a Mannich-like cyclisation to form product **293**. Product **293** undergoes keto-enol tautomerism to form scoulerine **294**, which is then methylated by SAM to form tetrahydrocolumbamine **295**. Product **295** is then oxidised to form the methylenedioxy ring from the *ortho*-methoxyphenol, with the aid of an $O_2$-, NADPH- and cytochrome P-450-dependent enzyme (canadine synthase),[102] giving canadine **296**. Canadine **296** is then oxidised to give the quaternary isoquinolinium system of berberine **275** by the (*S*)-tetrahydroprotoberberine oxidase (STOX). This happens in two separate oxidation steps, both requiring molecular oxygen. Subsequently, the berberine **275** can be converted into other protoberberines.




**Scheme 87**: The amino acid tyrosine **14** is the biosynthetic precursor of protoberberine alkaloids

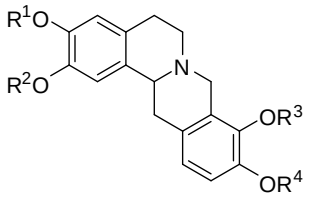



**Scheme 88**: Proposed berberine **275** biosynthesis[95,98–102]

### 4.1.2 Biological Activity

Protoberberines have been extensively investigated for their biological properties which include cytotoxic, [103] anti-fungal, [104] anti-microbial,[103b, 105] anti-flammatory,[103b, 106] and anti-malarial[107] activities. The ability of the protoberberines to act as inhibitors against topoisomerase I and II has been linked to their anti-tumour activity.[103b,108] Recently, berberine derivatives substituted with lipophilic groups had been evaluated as human cancer cell growth inhibitors.[109]

Tetrahydroprotoberberines also display a variety of biological and pharmacological properties. Tetrahydroprotoberberines possess a unique pharmacological profile as D2 dopamine receptor antagonists and D1 receptor agonists suggesting that they are potential drug candidates for the treatment of psychiatric and neurological disorders.[110] Two tetrahydroprotoberberines, **297** and **298** (Figure 15), were shown to have potential clinical use in anti-nociception (inhibition of the sensation of pain), and therefore in pain management for the recovering drug addicted patients, related to their affinity to D2 dopamine receptors.[110c] Moreover, the anti-psychotic actions of two other tetrahydroprotoberberine derivatives, **299** and **300** on animal models were reported recently, suggesting that novel lead drugs based on tetrahydroprotoberberines could potentially be used to treat schizophrenia.[110d] Additionally, studies on the anti-bacterial activities of two tetrahydroprotoberberines, **301** and **302**, were published recently.[111]

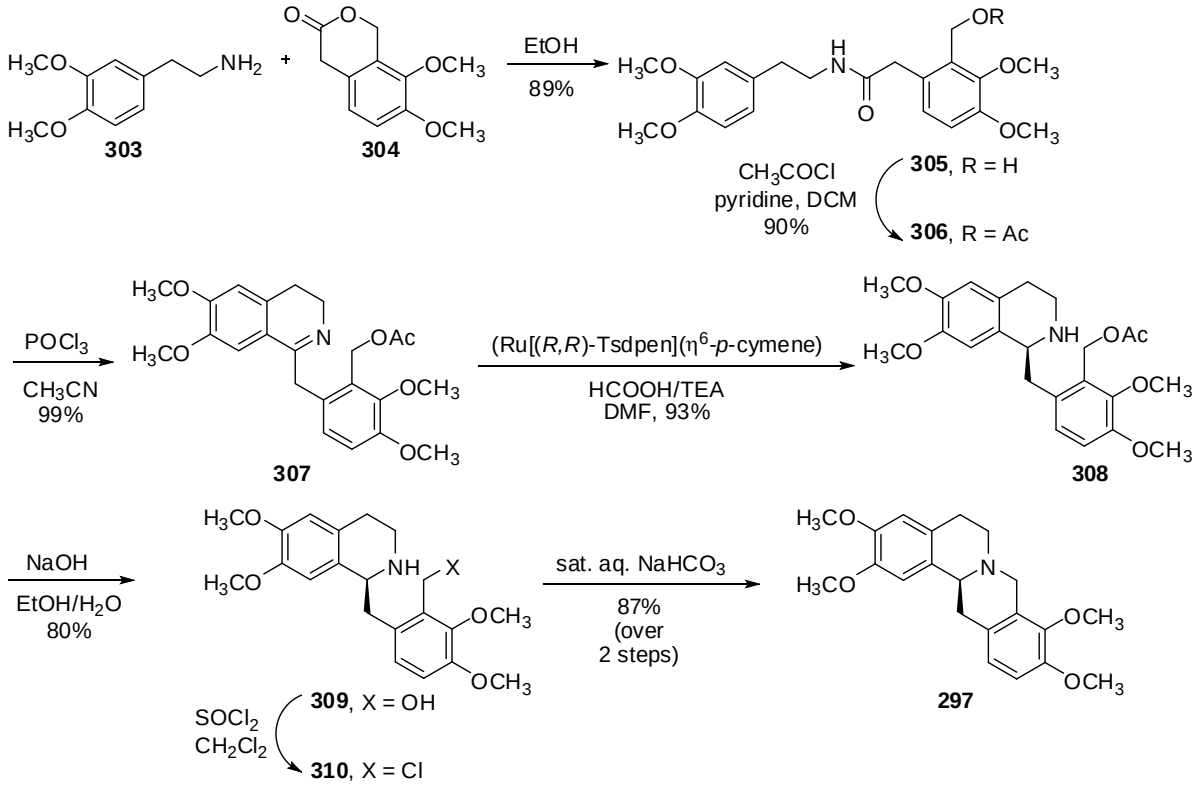



**297** $R^1 = R^2 = R^3 = R^4 = CH_3$
**298** $R^1 = R^4 = H$, $R^2 = R^3 = CH_3$
**299** $R^1 = R^2 = R^3 = Me$, $R^4 = OH$
**300** $R^1$, $R^2 = -CH_2-$, $R^3 = Me$, $R^4 = H$
**301** $R^1$, $R^2 = -CH_2-$, $R^3$, $R^4 = -CH_2-$
**302** $R^1$, $R^2 = -CH_2-$, $R^3 = R^4 = CH_3$

**Figure 15**: Tetrahydroprotoberberines **297**–**302** display a variety of biological and pharmacological activities

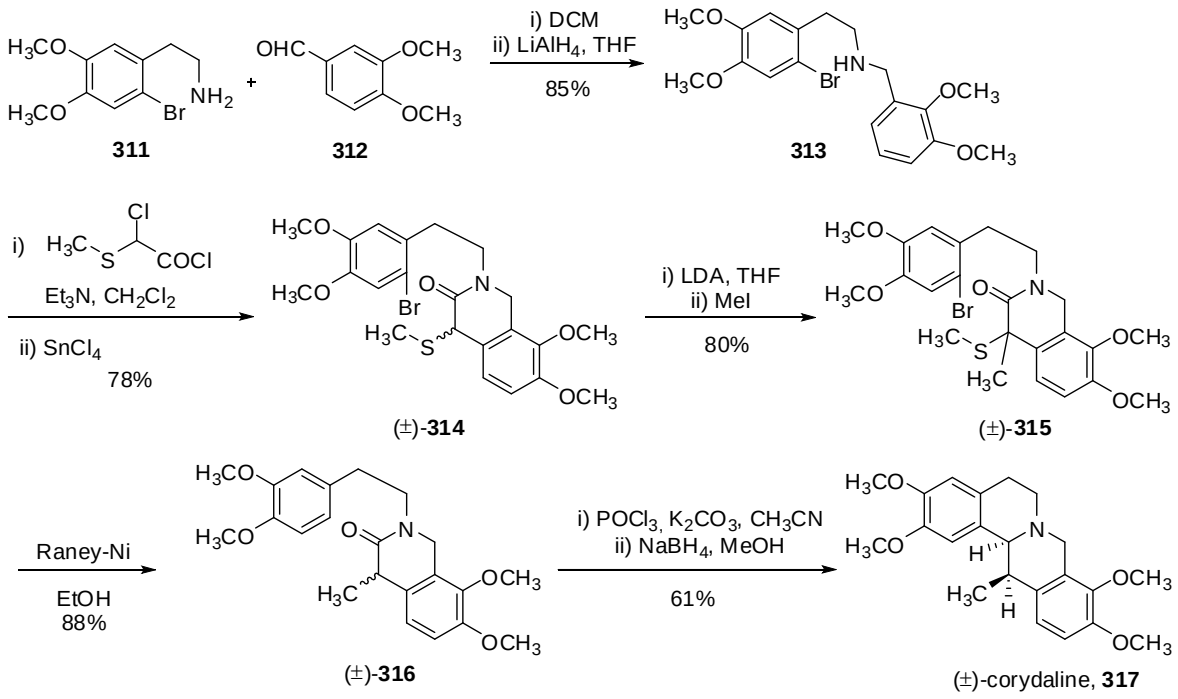
### 4.1.3 Reported Synthetic Approaches to Protoberberines

The Bischler-Napieralski reaction is one of the major approaches for the synthesis of protoberberine ring systems, usually used for the construction of the B-ring.[110d,e,112] Recently, several tetrahydroprotoberberine derivatives with diverse substituents on the A- and D-rings were synthesised using this approach, in order to test their pharmacological profiles for the treatment of schizophrenia.[110d] For example, phenylethylamine **303** and lactone **304** were heated at reflux in ethanol to give amide **305** (Scheme 89). Subsequent acylation of the alcohol species of compound **305** to generate product **306** is followed by a Bischler-Napieralski reaction to give imine **307**. Asymmetric hydrogenation catalysed by a chiral Ru-(II) complex (Noyori's catalyst)[113] followed by hydrolysis of the acetate **308** gave alcohol **309**. Closure of the C-ring was accomplished in one pot using thionyl chloride followed by aq. $NaHCO_3$ to give tetrahydroprotoberberine **297**.



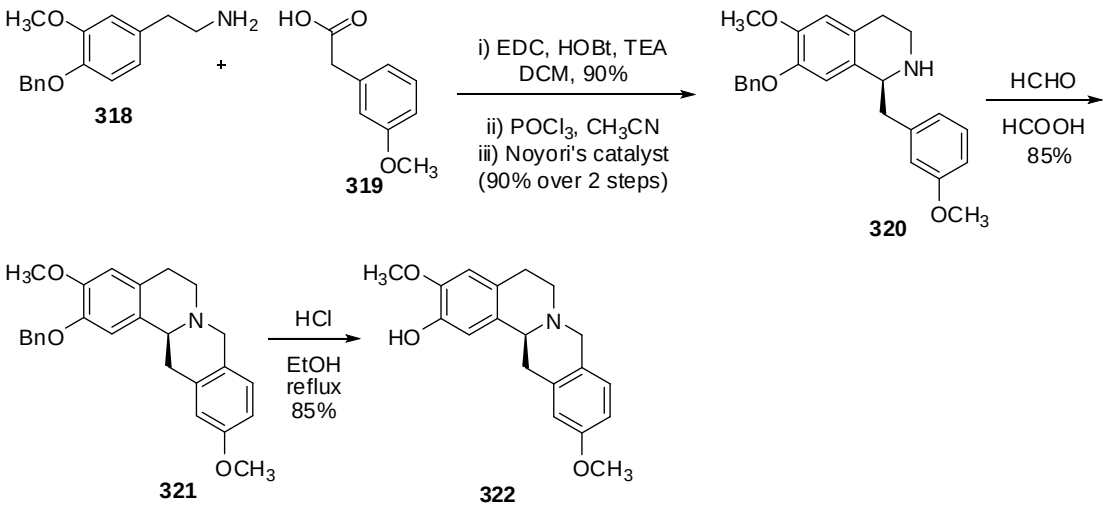

**Scheme 89**: Bischler-Napieralski reaction for the construction of the B-ring of tetrahydroprotoberberines

The Bischler-Napieralski reaction has also been used for the construction of the B-ring of 13-methyl-tetrahydroprotoberberines. [114] The condensation of 2-bromo-4,5-dimethoxy-phenylethylamine **311** with 2,3-dimethoxybenzaldehyde **312** followed by reduction with lithium aluminum hydride afforded amine **313** (Scheme 90). Acylation of the brominated amine with α-(methylthio)acetyl chloride followed by its treatment with $SnCl_4$ afforded intermediate **314** which was then treated with LDA and methyl iodide to afford lactam **315**. Treatment of lactam **315** with Raney-Ni$^{TM}$ effected the reductive cleavage of both the bromine and methylthio group to furnish compound **316**. Finally, Bischler-Napieralski reaction and subsequent $NaBH_4$ reduction provided (±)-corydaline **317**.



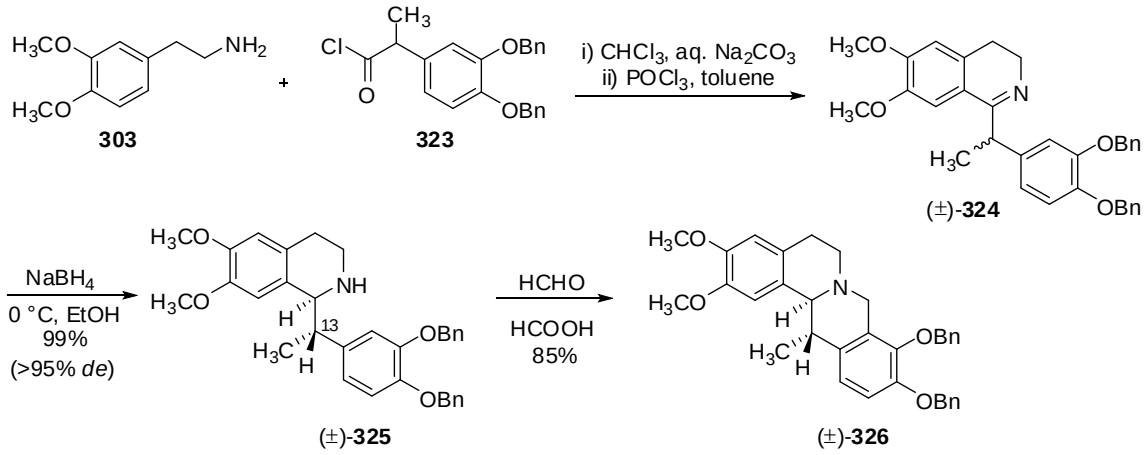

**Scheme 90**: Bischler-Napieralski reaction for the construction of the B-ring of 13-methyl-tetrahydroprotoberberines

The Pictet-Spengler sequence is also used frequently for the synthesis of the C-ring of protoberberines.[110d,e,112b] For example, piperidine **320**,[110d] which was formed *via* the condensation of phenylethylamine **318** and acid **319** using EDC, HOBt and TEA in dichloromethane followed by Bischler-Napieralski dehydration and asymmetric hydrogenation with Noyori's catalyst, as detailed previously in Scheme 89, was treated with formaldehyde in formic acid to give product **321**. Benzyl cleavage was achieved by refluxing product **321** in ethanol with concentrated HCl to give tetrahydroprotoberberine **322** in high yield (Scheme 91).




**Scheme 91**: Pictet-Spengler reaction for the synthesis of the C-ring of tetrahydroprotoberberines

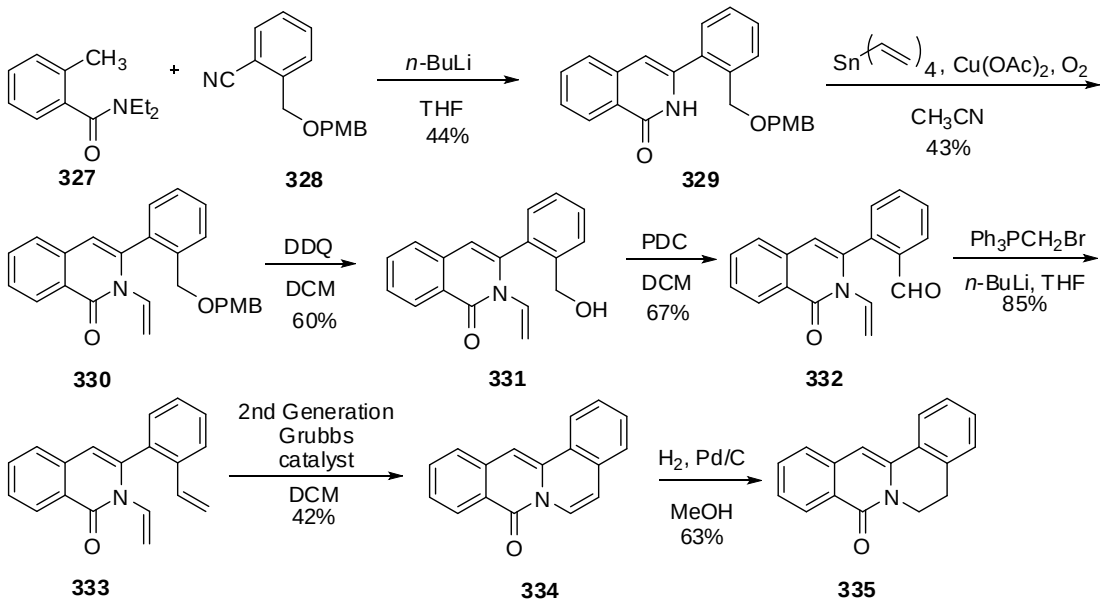
The Pictet-Spengler reaction has also been used for the construction of the C-ring of 13-methyl-tetrahydroprotoberberines (Scheme 92).[115] First, imine **324** was prepared from phenylethylamine **303** and acid chloride **323** *via* a condensation/Bischler-Napieralski cyclisation sequence. It was found that the reduction of imine **324** with sodium borohydride in ethanol at 0 °C gives benzyl-isoquinoline **325** with >95% *de* and in high yield. The C-ring of the 13-methyl-tetrahydroprotoberberine **326** was constructed *via* a Pictet-Spengler reaction of benzyl-isoquinoline **325** using formaldehyde in formic acid.




**Scheme 92**: Pictet-Spengler reaction for the synthesis of 13-methyl-tetrahydroprotoberberines

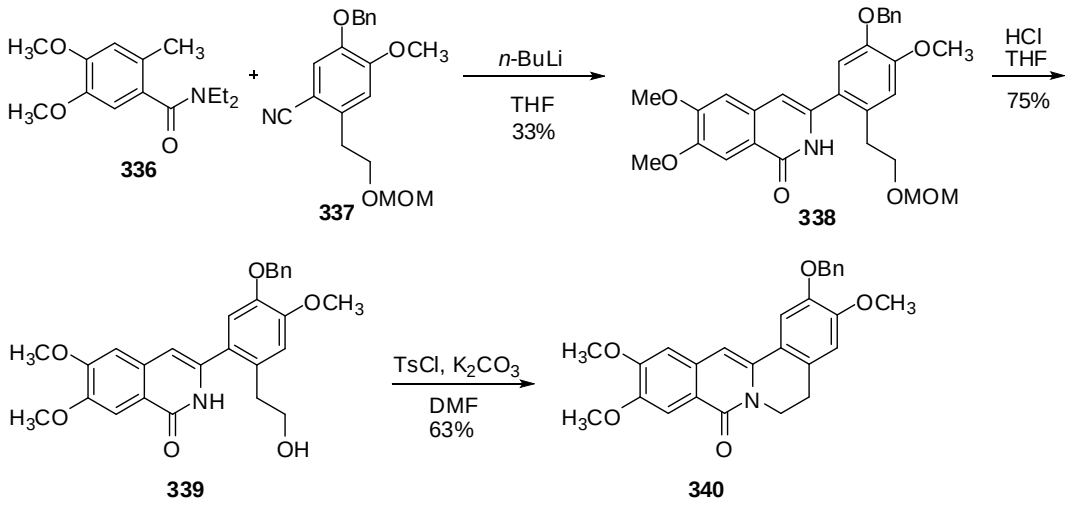
Ring closing metathesis (RCM) has been used to construct the B-ring of protoberberine alkaloids (Scheme 93).[116] *N*,*N*-Diethyl-*o*-toluamide **327** was treated with *n*-BuLi and benzonitrile **328** to afford product **329** which was then converted into compound **330** by *N*-vinylation with tetravinyltin in the presence of $Cu(OAc)_2$ under an $O_2$ atmosphere.[117]

Next, cleavage of the PMB protecting group using DDQ gave alcohol **331**. PDC oxidation of the alcohol **331** gave the corresponding aldehyde **332** which then underwent a Wittig reaction to provide the diene **333**. RCM of the diene **333** afforded the cyclised compound **334** which was selectively reduced, by catalytic hydrogenation with Pd/C under hydrogen, to give 8-oxo-protoberberine **335** in moderate yield.



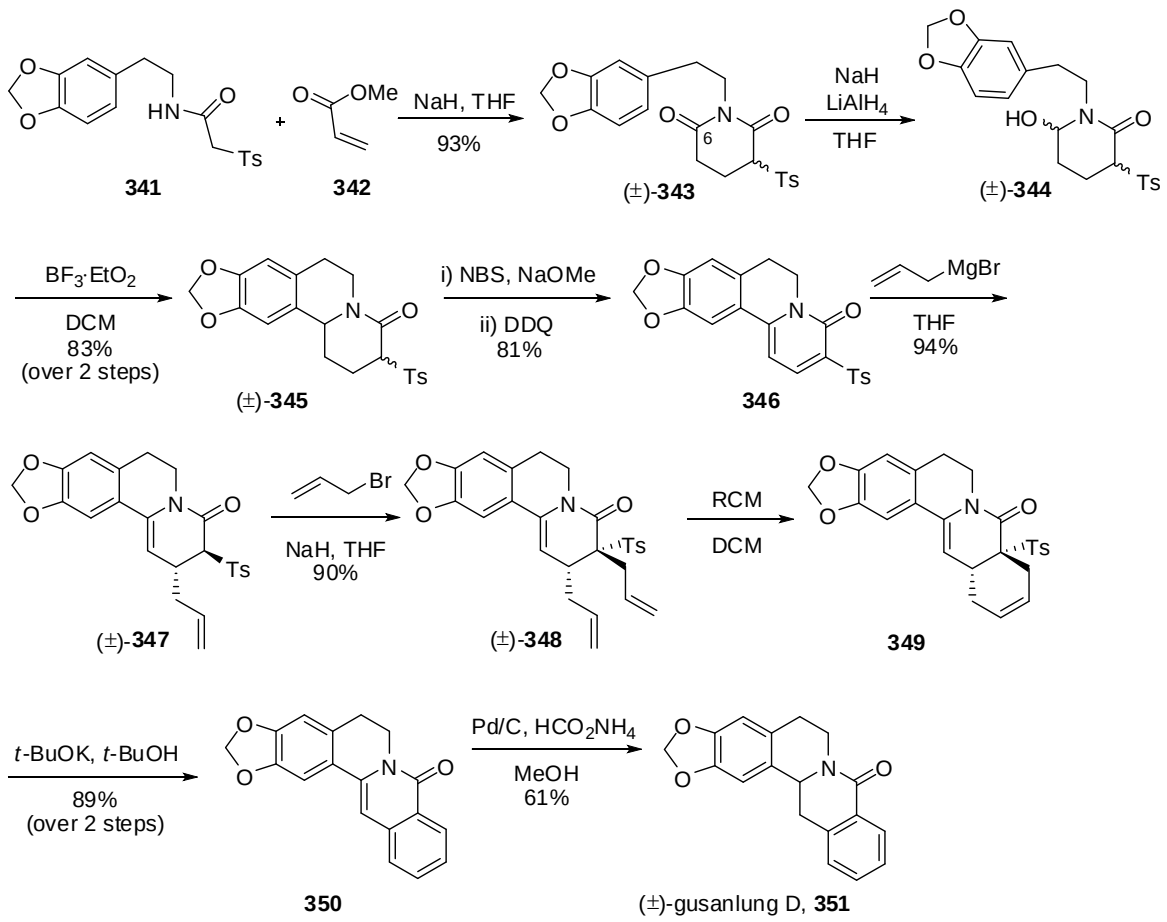

**Scheme 93**: RCM has been applied to the construction of the B-ring of 8-oxo-protoberberine alkaloids

The construction of the B-ring of 8-oxo-protoberberines *via* an $S_N2$ reaction was reported by the same group (Scheme 94).[118] The coupling reaction between *o*-toluamide **336** and benzonitrile **337** gave product **338**. Cleavage of the MOM protecting group gave alcohol **339** which was then reacted with *p*-TsCl in DMF in the presence of $K_2CO_3$ to provide 8-oxo-protoberberine **340** *via* an intramolecular $S_N2$ reaction.



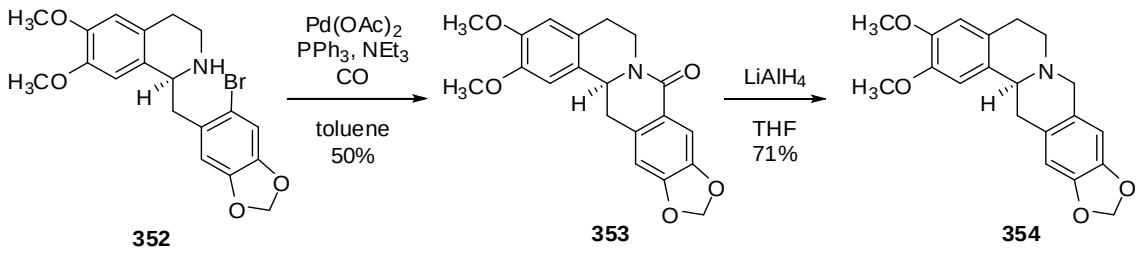
**Scheme 94**: An intramolecular $S_N2$ reaction constructs the B-ring of 8-oxo-protoberberine alkaloids

Ring closing metathesis (RCM) has also been applied to the construction of the D-ring of the protoberberine alkaloid (±)-gusanlung D, **351** (Scheme 95).[119] After the reaction of α-sulfonyl acetamide **341** with two equivalents of NaH, the resulting dianion reacted with methyl acrylate **342** to afford the cyclised product glutarimide **343**. [120] Regioselective reduction of the $C_6$-carbonyl in glutarimide **343** provided hydroxylactam **344**.[121] Without purification, hydroxylactam **344** was converted into tricyclic product **345** in the presence of $BF_3 \cdot OEt_2$, *via* an *N*-acyliminium ion intermediate. Bromination followed by dehydrobromination of product **345** using NBS and sodium methoxide gave an α,β-unsaturated lactam, which was then further oxidised to tricyclic pyridinone **346** with DDQ. 1,4-Conjugate addition of allyl magnesium bromide into adduct **346** followed by alkylation with allyl bromide produced the diallyl lactam **348**. The RCM reaction of diene **348** then furnished the D-ring of the protoberberine. Dehydrosulfonation and spontaneous oxidation formed product **350** which underwent catalytic hydrogenation with ammonium formate in the presence of Pd/C in methanol[122] to complete the synthesis of (±)-gusanlung D, **351**.



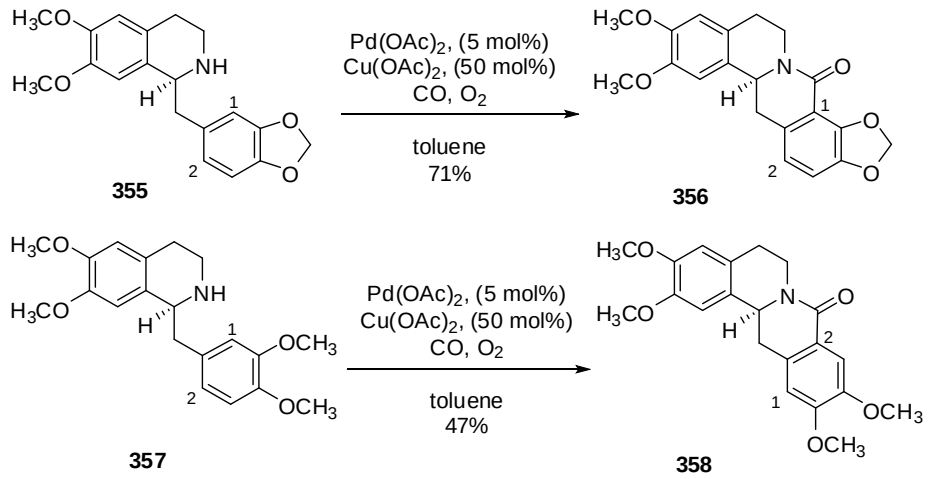

**Scheme 95**: RCM has been applied to the construction of D-ring of 8-oxo-protoberberine alkaloids

The synthesis of the tetracyclic berberine ring system has also been achieved *via* a palladium-catalysed carbonylation (Scheme 96). [123] Heating the substituted 1,2,3,4-tetrahydroisoquinoline **352** with catalytic $Pd(OAc)_2$ and triphenylphosphine under a carbon monoxide atmosphere gave adduct **353** which was reduced to the desired protoberberine **354** with lithium aluminium hydride.




**Scheme 96**: The synthesis of the tetracyclic berberine ring system has been achieved *via* a palladium-catalysed carbonylation

A different catalytic method was reported recently for the preparation of 8-oxo-protoberberines **356** and **358** in a single step, *via* a direct aromatic carbonylation using a $Pd(OAc)_2$-$Cu(OAc)_2$ catalytic system (Scheme 97).[124] The 9,10-methylenedioxy group in compound **355** chelates with the palladium species and directs *ortho*-palladation at the C-1 position, before the incorporation of CO (**359i**, Figure 16). Thus, the aromatic carbonylation of compound **355** gave 8-oxo-protoberberine **356** exclusively. In contrast, steric repulsion caused by the 9,10-dimethoxy group in compound **357** (**359ii**, Figure 16) overrides the chelation of the palladium species and the insertion of CO at the C-2 position is preferred (**359iii**, Figure 16). Thus, the aromatic carbonylation of compound **357** gave 8-oxo-protoberberine **358** as the major product.




**Scheme 97**: Direct aromatic carbonylation for the preparation of 8-oxo-protoberberines

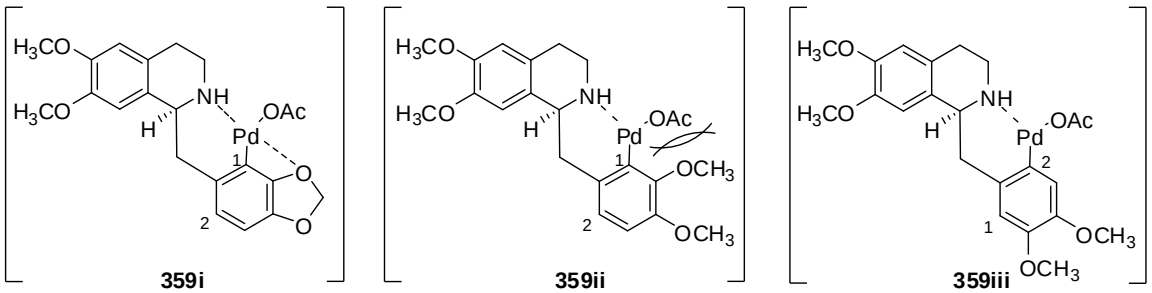
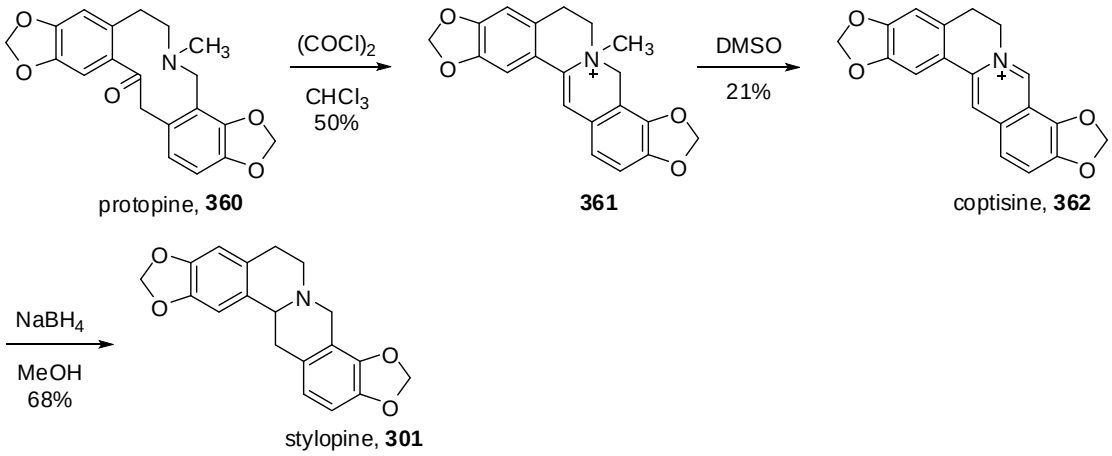



**Figure 16**: Chelation vs steric repulsion for the preparation of 8-oxo-protoberberines **356** and **358**

Recently, tetrahydroprotoberberine alkaloids have been synthesised from protopine alkaloids as the starting material.[125] The reaction of protopine **360** with oxalyl chloride provided the *N*-methyl-13,14-dehydroprotoberberine quaternary salt **361** (Scheme 98). A dimethyl sulfoxide solution of the salt **361** was heated at 120 °C to yield coptisine **362** which was then reduced with $NaBH_4$ to yield the tetrahydroprotoberberine alkaloid, stylopine **301**.




**Scheme 98**: Tetrahydroprotoberberine alkaloids were synthesised from protopine alkaloids

Other synthetic approaches to this group of alkaloids are the photocyclisation of enamides[126] (Scheme 99) and the condensation of imines with anhydrides[127] (Scheme 101) or phthalide anions (Scheme 102).[128] These approaches are discussed in detail in the following section.

## 4.2 The Total Synthesis of (±)-Cavidine 280

### 4.2.1 Introduction to the Natural Product Cavidine 280

Cavidine **280** belongs to the family of protoberberine alkaloids, specifically those known as 13-methyl-tetrahydroprotoberberine alkaloids. 13-Methyl-tetrahydroprotoberberine alkaloids constitute a group of secondary metabolites which occur in various species of *Corydalis* plants. *Corydalis* is a genus of about 350 species of herbaceous plants in the family *Papaveraceae* (poppy family),[129] and the name *Corydalis* comes from the Greek word κορυδαλός ("crested lark"), alluding to the shape of the flowers, which are native chiefly to northern temperate regions (Himalayan mountains in particular) and the high mountains of tropical eastern Africa. They are particularly diverse in China which has over 290 species, mainly distributed in Xizang Province (Tibet Autonomous Region of the Republic of China).

Extracts of *Corydalis* plants have been used in traditional Chinese medicine for the treatment of hepatitis and stomach aches.[96] It has been demonstrated that these extracts possess many pharmacological properties, including anti-bacterial, anti-viral and anti-cancer activities.[129] They can also be used for alleviating fever, rheumatic pain and to induce a fall in blood pressure.[129c] It is likely that 13-methyl-tetrahydroprotoberberines such as cavidine **280**, which are constituents of these plants, are among their biologically active constituents. In addition, a paper by Bhakuni *et al.* in 1983 details the spasmolytic activity of cavidine **280**.[130]

Cavidine **280** has been isolated from different *Corydalis* plant sources over the years. Some literature reports describe the isolation of cavidine **280** as a single (+)-enantiomer, while others report the isolation of the racemic form of cavidine **280**.[130,131,132] In 1964, Taguchi *et al.* reported the isolation of (+)- and (±)-cavidine **280** from the plant *Corydalis ambigua* together with its stereoisomer thalictrifoline **363** (Figure 17).[131] Cavidine **280** was later assigned as an optically inactive alkaloid, when isolated from *Corydalis thalictrifolia* by Manske *et al.* in 1970.[132] In 1983, the enantiomerically pure (+)-cavidine **280** was isolated from the plant *Corydalis meifolia*, together with five other tetrahydroprotoberberines.[130] It is unclear whether or not cavidine **280** is produced as a single (+)-enantiomer and then racemises, in certain plants, or if it racemises later during the isolation process.

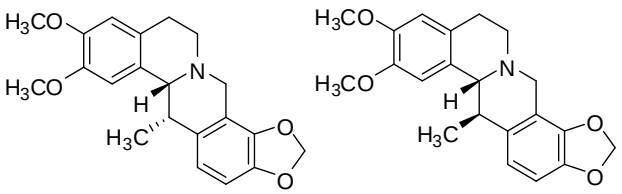



**Figure 17**: Cavidine **280** and thalictrifoline **363**

Cavidine **280** is typically referred to as the "*cis*-diastereoisomer", because the protons $H_A$ and $H_B$ are *cis* to each other while thalictrifoline **363** is referred to as the "*trans*-diastereoisomer" because these protons are *trans* (Figure 18). This should not be confused with the conformation of the quinazolidine ring system as portrayed in Figure 18; cavidine **280** adopts the *trans*-quinazolizidine conformation shown below, while thalictrifoline **363** adopts a *cis*-quinazolizidine conformation in solution in order to avoid the steric clash between the C-13 methyl group and the C-1 hydrogen atom.[127, 132]

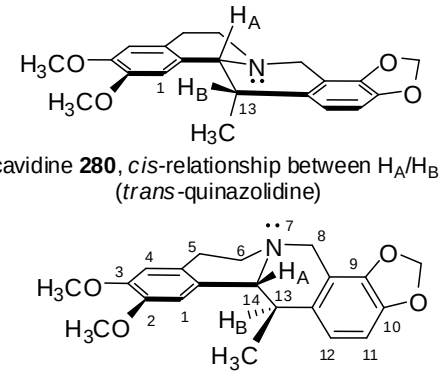



**Figure 18**: Cavidine **280** adopts the *trans*-quinazolizidine conformation and thalictrifoline **363** adopts a *cis*-quinazolizidine conformation in solution

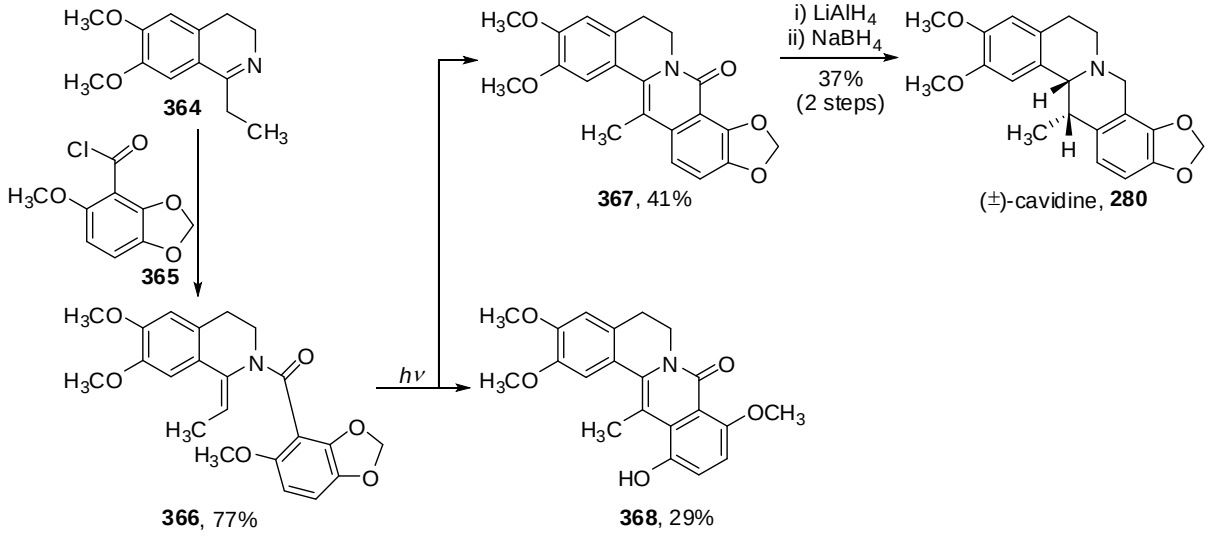
Three main differences are present in the $^1$H-NMR spectrum of the two groups of diastereoisomers.[132, 133] Firstly, the 13-methyl group appears near $\delta_H$ 1.0 ppm in *cis*-diastereoisomers (*cis* H-13 and H-14) and near $\delta_H$ 1.5 ppm in *trans*-diastereoisomers (*trans* H-13 and H-14). The 13-methyl group is deshielded in *trans*-diastereoisomers because it lies nearly in the plane of the aromatic D-ring. Secondly, the coupling constant between H-13 and H-14 in *cis*-diastereoisomers is around 3.0 Hz as expected for a dihedral angle which approaches 90°, whereas the coupling constant for the *trans*-hydrogens in *trans*-diastereoisomers is around 7.5 Hz as expected for systems in

which the dihedral angle is closer to 180°. Thirdly, the chemical shift of the equatorial C-8 proton is unusually high in the *cis*-compounds. That happens because the equatorial C-8 proton is deshielded by the aromatic D-ring, the lone pair on the adjacent nitrogen and the oxygen at C-9 and so appears at much more lower field than the axial C-8 proton.[133] This effect is not observed in the *trans*-compounds.

Full characterisation data of (±)-cavidine **280**[126b,127,129a, 134] and (±)-thalictrifoline **363**[127,134] can be found in many reports.

### 4.2.2 Reported Syntheses to Cavidine 280

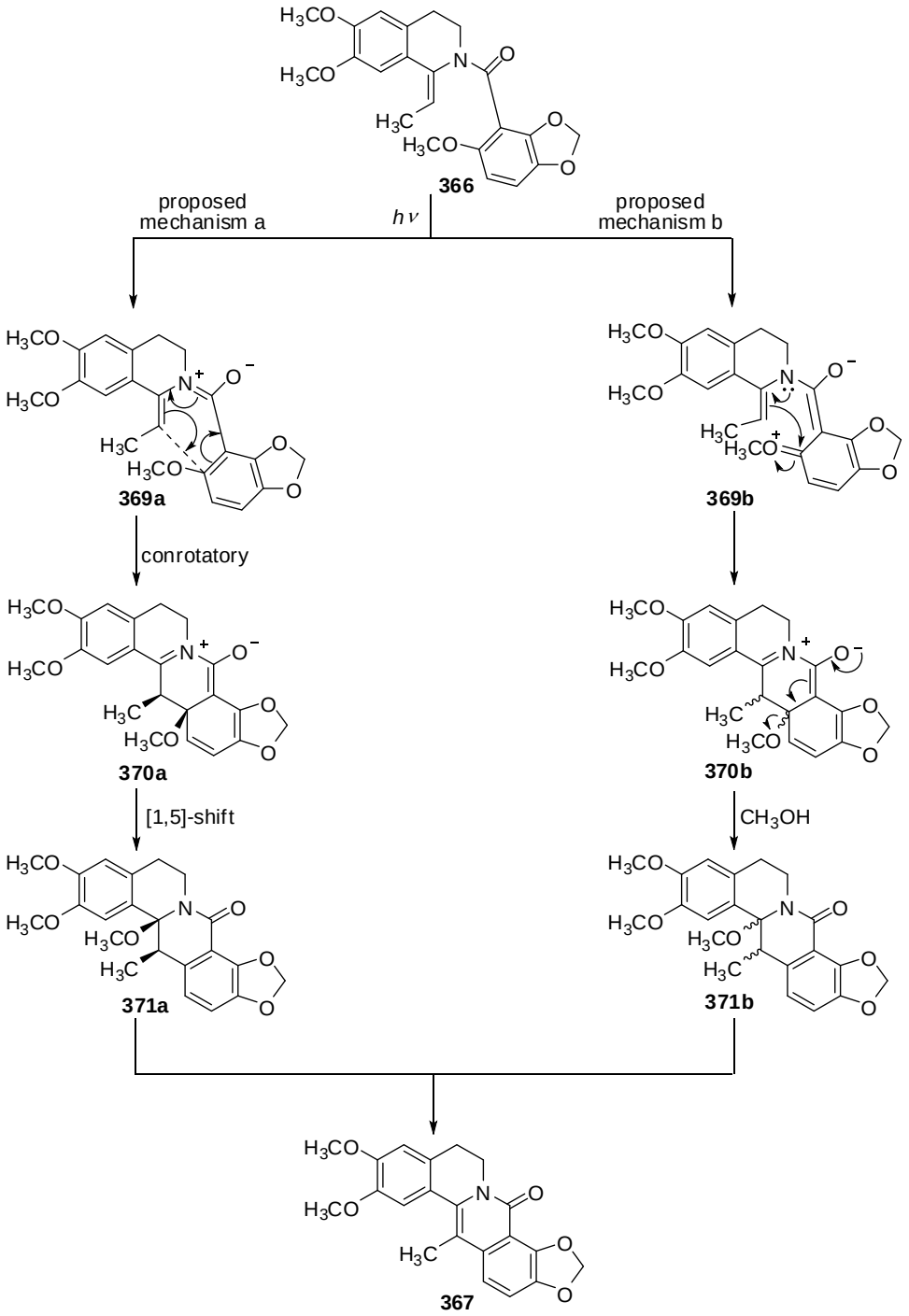
In 1975 Ninomiya *et al.* reported that the enamides prepared from 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline **364** undergo photocyclisation to form 13-methylberberin-8-ones.[126] This reaction was applied in the first total synthesis of (±)-cavidine **280** by the same group (Scheme 99).[126b] Acylation of the 3,4-dihydroisoquinoline **364** with 6-methoxy-2,3-methyldioxybenzoyl chloride **365** afforded enamide **366** in 77% yield. Irradiation of the enamide **366** in methanol afforded two photoproducts, **367** and **368**, in 41 and 29% yield respectively. Reduction of the major photoproduct **367** with lithium aluminium hydride followed by sodium borohydride afforded (±)-cavidine **280** in 37% yield (over the two steps).




**Scheme 99**: Ninomiya's synthesis of (±)-cavidine **280** *via* photocyclisation of enamide **366**

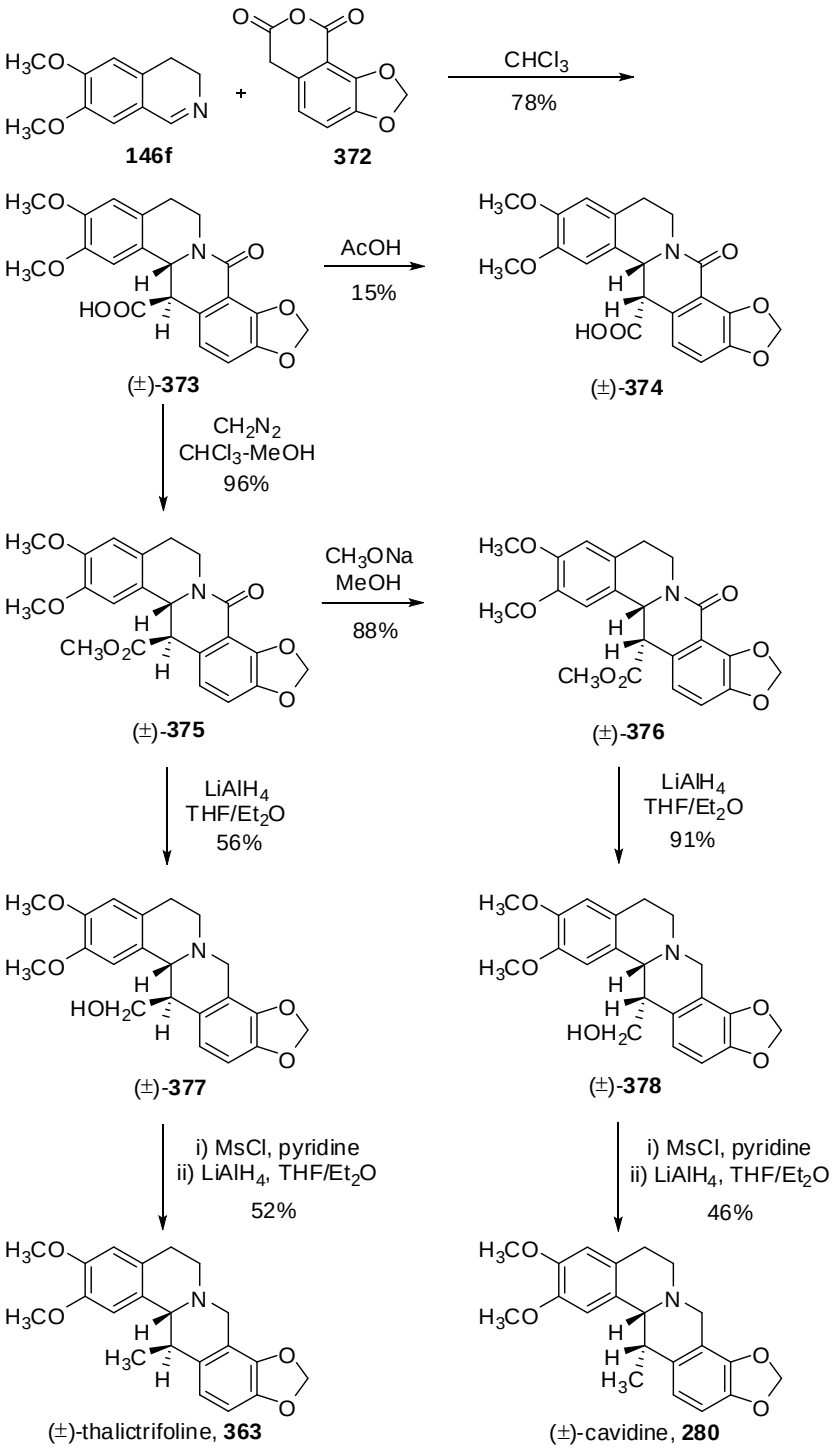
The above transformation from **366** to **367** was proposed to proceed *via* an electrocyclisation (**369a** to **370a**) followed by a [1,5]-sigmatropic shift of the methoxy-group (**370a** to **371a**) (Scheme 100, proposed mechanism a).[126b] The migrated methoxy-group in **371a** can then be eliminated to afford the lactam **367**. However, it

was speculated that it can also proceed through a stepwise cyclisation involving the electron donor *ortho*-methoxy group based on literature precedent (Scheme 100, proposed mechanism b).[135] None of these intermediates were isolated and thus no conclusive deduction about the mechanism can be drawn.




**Scheme 100**: The two possible mechanisms for the transformation from enamide **366** to lactam **367**

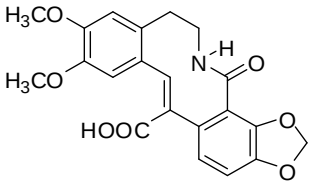
In 1981 Cushman *et al.* proposed a different synthetic approach to (±)-cavidine **280** and its stereoisomer, (±)-thalictrofoline **363** (Scheme 101).[127] The condensation of compounds **146f** and **372** in chloroform at room temperature afforded (±)-*trans*-acid **373**. Heating the acid **373** in acetic acid promotes epimerisation to generate the thermodynamically more stable (±)-*cis*-acid **374**. The (±)-*trans*-acid **373** gave the corresponding (±)-*trans* methyl ester **375** following its treatment with diazomethane and was then converted into its (±)-*cis*-isomer **376** *via* treatment with sodium methoxide in methanol. Both (±)-*trans*-ester **375** and (±)-*cis*-ester **376** were reduced to the corresponding amino alcohols (±)-**377** and (±)-**378** with lithium aluminium hydride. Mesylation of alcohols (±)-**377** and (±)-**378** and subsequent reduction of the corresponding mesylates with lithium aluminum hydride completed the synthesis, affording (±)-thalictrifoline **363** and (±)-cavidine **280** respectively.




**Scheme 101**: Cushman's synthesis of (±)-thalictifoline **363** and (±)-cavidine **280**

The first total syntheses of enantiomerically pure (+)-cavidine **280** and (+)-thalictrifoline **363** were achieved by the same group *via* chiral resolution with the aid of (−)-strychnine. The (±)-*trans*-acid **373** was treated with (−)-strychnine to give the (–)-*trans*-acid **373** as the first crop of salt crystals and (+)-*trans*-acid **373** as the second. Interestingly, heating the single enantiomer (+)-*trans*-acid **373** in refluxing acetic acid

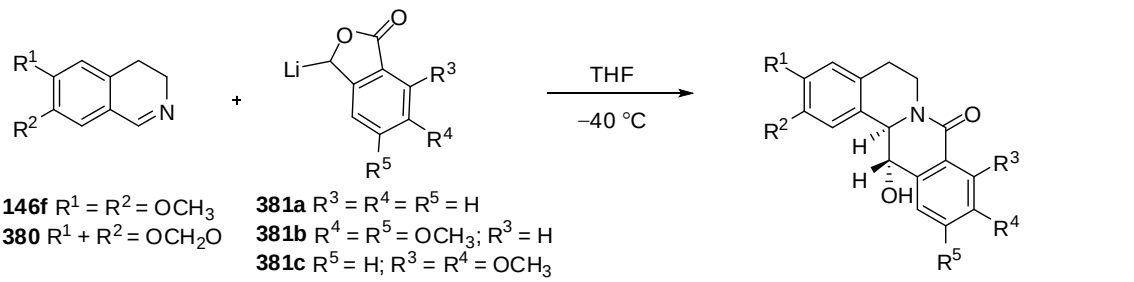
resulted in epimerisation and racemisation, affording the thermodynamically more stable (±)-*cis*-acid **374** as a racemate, suggesting that an achiral intermediate, most likely compound **379**, is involved (Figure 19). Next, (+)-*trans* methyl ester **375** was converted into its (+)-*cis*-isomer **376** without racemisation using sodium methoxide in methanol.




**379**

**Figure 19**: The achiral intermediate **379**

In 1984 Marsden *et al.* proposed a synthetic approach to 13-hydroxy-8-oxo-tetrahydroprotoberberines **382a–c** *via* a reaction between 3,4-dihydroisoquinolines **146f** or **380** and lithiated phthalide species **381a–c** (Scheme 102).[128] An initial attack of a phthalide anion at the imine carbon was followed by nitrogen attack of the phthalide carbonyl carbon to form a tetrahedral intermediate which opens to form tetrahydroprotoberberines **382a–c** in a single step.




**146f** $R^1 = R^2 = OCH_3$
**380** $R^1 + R^2 = OCH_2O$

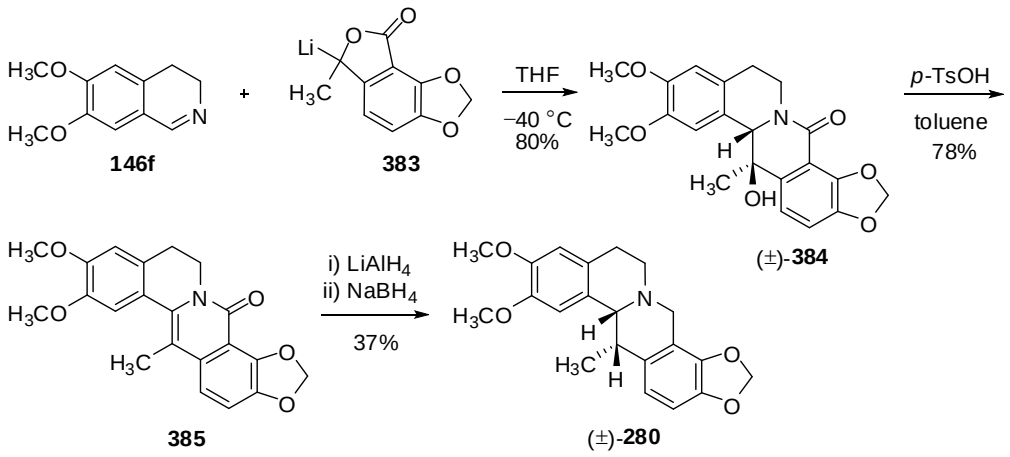
**381a** $R^3 = R^4 = R^5 = H$
**381b** $R^4 = R^5 = OCH_3$; $R^3 = H$
**381c** $R^5 = H$; $R^3 = R^4 = OCH_3$

(±)-**382a** $R^1 = R^2 = OCH_3$; $R^3 = R^4 = R^5 = H$, 61%
(±)-**382b** $R^1 = R^2 = R^4 = R^5 = OCH_3$; $R^3 = H$, 68%
(±)-**382c** $R^1 + R^2 = OCH_2O$; $R^3 = R^4 = OCH_3$; $R^5 = H$, 33%

**Scheme 102**: Marsden's synthetic approach to 13-hydroxy-8-oxo-tetrahydroprotoberberines **382a–c**

(±)-Cavidine **280** was formed from 6,7-dimethoxy-3,4-dihydroisoquinoline **146f** and 3-methylphthalide anion **383** as starting materials (Scheme 103). The reaction of dihydroisoquinoline **146f** and phthalide anion **383** was highly stereoselective and led to the formation of only one of the two possible diastereoisomers as shown in Scheme 103. Dehydration of product **384** with *p*-toluenesulfonic acid afforded compound **385**, and

finally the reduction of enamide **385** with lithium aluminium hydride, followed by sodium borohydride furnished (±)-cavidine **280**.




**Scheme 103**: Marsden's synthetic approach to (±)-cavidine **280** *via* reaction between 3,4-dihydroisoquinoline **146f** and 3-methylphthalide anion **383**

A model **386** that explains the stereospecificity of the initial reaction was proposed (Figure 20). The lone pair of the nitrogen atom of imine and the two oxygen atoms of the phthalide ring coordinate with lithium. The forth ligand may be the negative charged C-atom of another lithium phthalide or a solvent molecule. Such a model would require that cyclic imines, which are constrained in the *Z*-configuration, orient themselves with respect to the phthalide as in Figure 20 to form the *trans*-isomers exclusively.

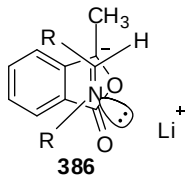
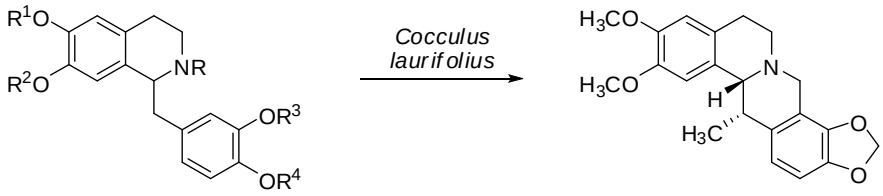



**Figure 20**: Marsden model to explain the stereospecificity of the reaction of the phthalide anion **383** and imine **146f**

The most recent synthesis of (±)-cavidine **280** was reported by Bhakuni *et al.* in 1986.[136] Bhakuni *et al.* were testing if suitably substituted 1-benzyltetrahydroisoquinolines were efficient biosynthetic precursors of *Corydalis meifolia* alkaloids. They reported that (±)-norreticuline **387a** and (±)-reticuline **387b** were metabolised by young cut branches of *Cocculus laurifolius* to furnish (±)-cavidine **280** (Scheme 104). Noteworthily, parallel work using (−)-reticuline furnished (+)-cavidine **280**.



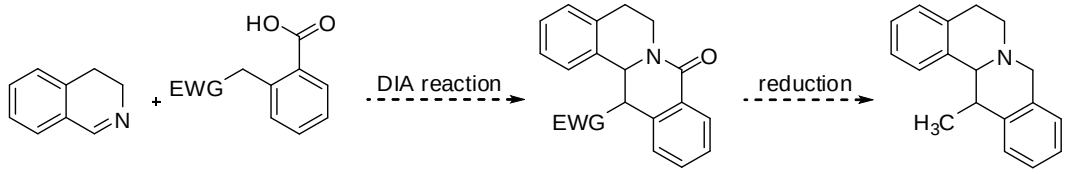

**387a**, (±)-norreticuline, R = $R^2$ = $R^3$ = H, $R^1$ = $R^4$ = $CH_3$
**387b**, (±)-reticuline, R = $R^1$ = $R^4$ = $CH_3$, $R^2$ = $R^3$ = H

(±)-cavidine, **280**

**Scheme 104**: Biosynthetic (±)-cavidine **280** from (±)-norreticuline **387a** and (±)-reticuline **387b**

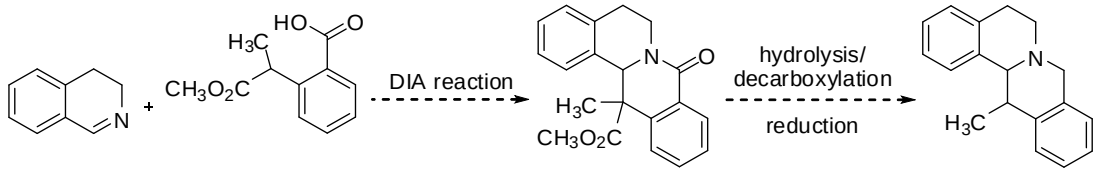
### 4.2.3 Initial Studies on (±)-Cavidine 280

Although (±)-cavidine **280** has been synthesised before, it was considered that DIA methodology would expedite an efficient convergent synthesis. The studies were started by running some test reactions to examine the efficiency of DIA coupling between the imine **146e** and acid coupling partner of type **388** (EWG = $CO_2CH_3$ or CN) (Scheme 105). If this proved successful, the reduction of DIA adduct **389** should then furnish the 13-methyl-tetrahydroprotoberberine **390**, a model system of cavidine **280**. Alternatively, the methylated coupling partner **391** could coupled with imine **146e** to give intermediate **392** which should then furnish product **390** after hydrolysis and decarboxylation followed by reduction of the amide species (Scheme 106).




**146e** **388** **389** **390**

**Scheme 105**: Initial approach to the construction of cavidine's framework using imine **146e** and acid **388**

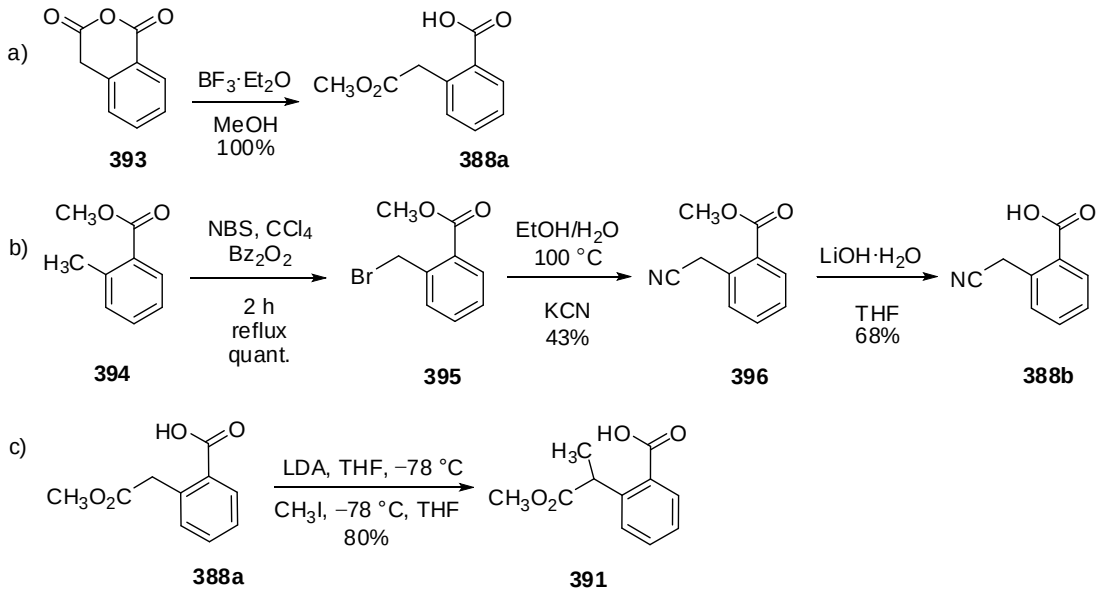



**146e** **391** **392** **390**

**Scheme 106**: Initial approach to the construction of cavidine's framework using imine **146e** and acid **391**

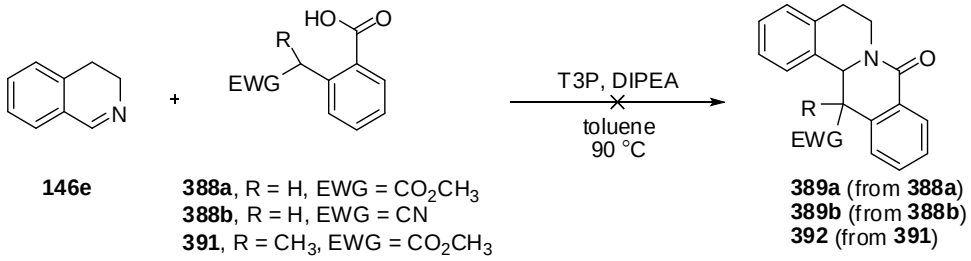
Simple literature procedures were used to synthesise acids **388a**, **388b** and **391** as shown in Scheme 107. Acid **388a** was easily formed from anhydride **393** using

$BF_3{\cdot}Et_2O$ in methanol (Scheme 107, eqn a).[137] Acid **388b** was synthesised from ester **394** *via* bromination with *N*-bromosuccinimide,[138] followed by nucleophilic substitution with cyanide[139] and ester hydrolysis (Scheme 107, eqn b). Acid **391** was synthesised *via* a LDA-promoted deprotonation of acid **388a** followed by methylation based on a literature procedure (Scheme 107, eqn c).[140]




**Scheme 107**: The synthesis of acids **388a**, **388b** and **391**

Acids **388a**, **388b** and **391** were then reacted with imine **146e** using our standard DIA coupling conditions (T3P, DIPEA, 90 °C, toluene) (Scheme 108). Unfortunately, the DIA reaction was not successful; in each case complex mixtures of products were observed in the $^1$H-NMR spectrum of the crude reaction mixture. Previous studies in our group have shown that in some cases the addition of Lewis acids to the crude reaction mixture following *N*-acylation can lead to improved yields,[57] and therefore additional optimisation reactions were performed using $BF_3{\cdot}Et_2O$ and $AlCl_3$. Disappointingly, the Lewis acid additives did not promote the formation of the expected DIA products and gave also complex mixtures.

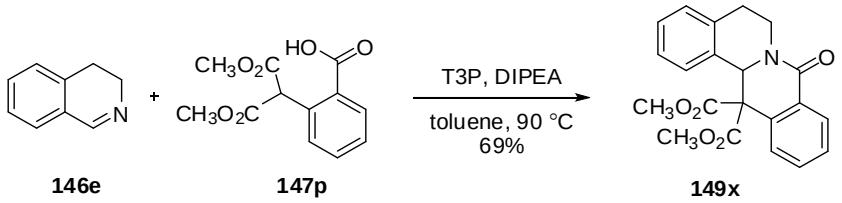



**Scheme 108**: Attempts to couple imine **146e** with acids **388a**, **388b** and **391**

The most likely explanation for these unsuccessful DIA reactions is that the α-hydrogen of esters **388a** and **391** and cyanide **388b** is not acidic enough for the intramolecular cyclisation to take place after the formation of the *N*-acyliminium ion.

### 4.2.4 The Synthesis of 13-Methyl-Tetrahydroprotoberberine 390

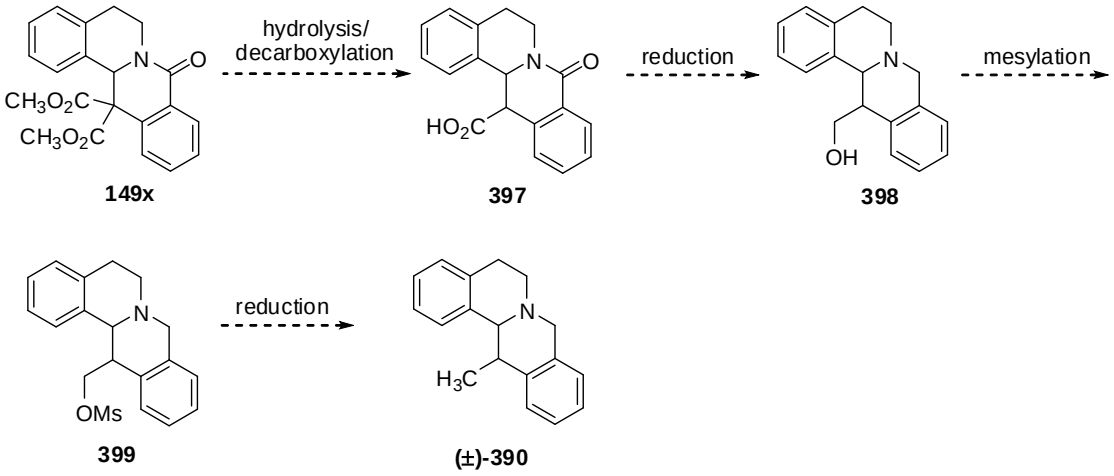
It has been already found (Chapter 2, table 5, entry viii) that diester **147p** successfully undergoes DIA coupling with imine **146e** under the standard DIA coupling conditions (T3P, DIPEA, 90 °C, toluene) giving adduct **149x** in 69% yield (Scheme 109).




**146e** **147p** **149x**

**Scheme 109**: DIA coupling between imine **146e** and diester **147p**

It was envisioned that using an approach based on that in Cushman's route[127] (Scheme 101) would then complete the synthesis of the model system, 13-methyl-tetrahydroprotoberberine **390**; ester hydrolysis and decarboxylation of diester **149x** followed by reduction and mesylation would give intermediate **399** which can be then reduced further to furnish the desired product **390** (Scheme 110).

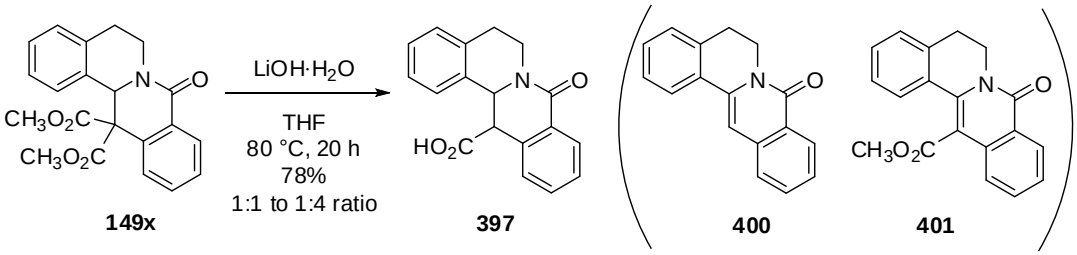



**149x** **397** **398** **399** **(±)-390**

**Scheme 110**: The synthetic approach to 13-methyl-tetrahydroprotoberberine **390**

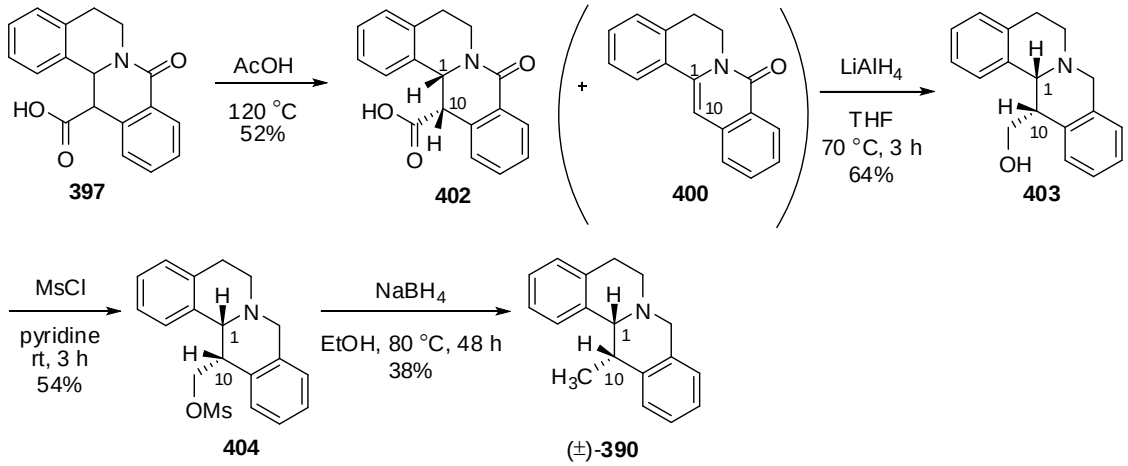
We were pleased to find that the double hydrolysis and decarboxylation of diester **149x** was achieved in 78% yield using $LiOH \cdot H_2O$ in THF at reflux (Scheme 111). Note that the purified product **397** was isolated as a mixture of two inseparable diastereoisomers

in 1:1 to 1:4 ratio (ratio varies, possibly due to epimerisation in the NMR solvent). Oxidised side-products, possibly **400** and **401**, were also observed in the mass spectrum of the crude reaction mixtures but they were not isolated at this stage.




**Scheme 111**: The double hydrolysis and decarboxylation of diester **149x**

Pleasingly, when the diasteroisomeric mixture of acid **397** was heated in AcOH at reflux, this led to isolation of the thermodynamically more stable diastereoisomer **402** in 52% yield together with the oxidised side-product **400** which was now isolated and fully characterised (Scheme 112). The double reduction of the novel acid **402** gave alcohol **403** in 64% yield which was then treated with MsCl to give mesylate **404** in 54% yield. Finally, deoxygenation of the mesylate **404** with $NaBH_4$ in refluxing ethanol, following the procedure reported by Cushman *et al.* for (±)-thalictricavine synthesis,[141] gave the 13-methyl-tetrahydroprotoberberine **390** in 38% yield. It is worth mentioning that when the deoxygenation was attempted by using $LiAlH_4$ in THF/ether, as reported by the same group during the synthesis of cavidine,[127] cleavage of the mesylate **404** back to the corresponding alcohol **403** was observed instead.



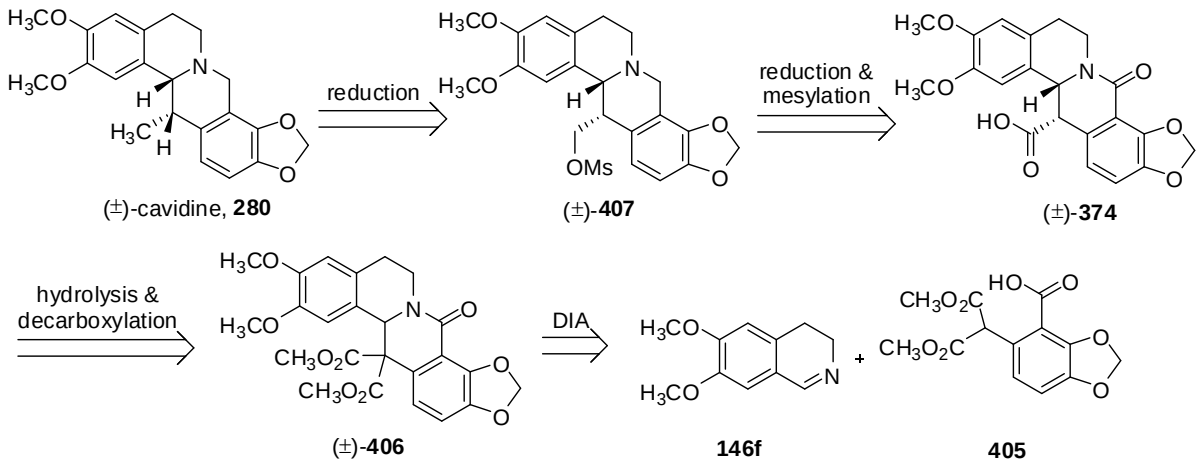

**Scheme 112**: The synthesis of 13-methyl-tetrahydroprotoberberine **390** from acid **397**

Therefore, the synthesis of the model system 13-methyl-tetrahydroprotoberberine **390** was achieved, with most of the steps not fully optimised. Note that while this compound

has been reported previously in the literature, none of its spectroscopic data were reported.[142] The stereochemistry of compounds **402** and **390** were assigned based on the *J* values of their H-1 and H-10 protons ($J_{1\text{-}10}$ = 4 Hz for **402** and $J_{1\text{-}10}$ = 3.2 Hz for **390**) which suggest that these protons are *cis*-relative to each other (see Section 4.2.1). Further support for this assignment is found in the fact that the *J* coupling constant for the novel *cis*-acid precursor **402** ($J_{1\text{-}10}$ = 4.2 Hz) matches closely with that of the methoxy-analogue acid **374** (*J* = 4.0 Hz) from Cushman's synthesis.[127]

### 4.2.5 The Total Synthesis of (±)-Cavidine 280

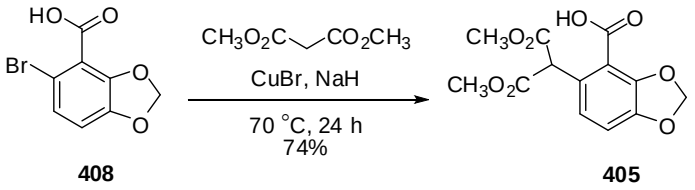
Having established an efficient synthetic sequence to make the 13-methyl-tetrahydroprotoberberine **390**, we were keen to apply the same synthetic approach to the synthesis of the alkaloid (±)-cavidine **280**. Our retrosynthetic plan is shown in Scheme 113; the DIA coupling between methylenedioxy-acid **405** and imine **146f** would generate the key intermediate **406** which would then provide (±)-cavidine **280** using a procedure modified from that of Cushman,[127] involving hydrolysis/decarboxylation, reduction, mesylation and a second reduction.



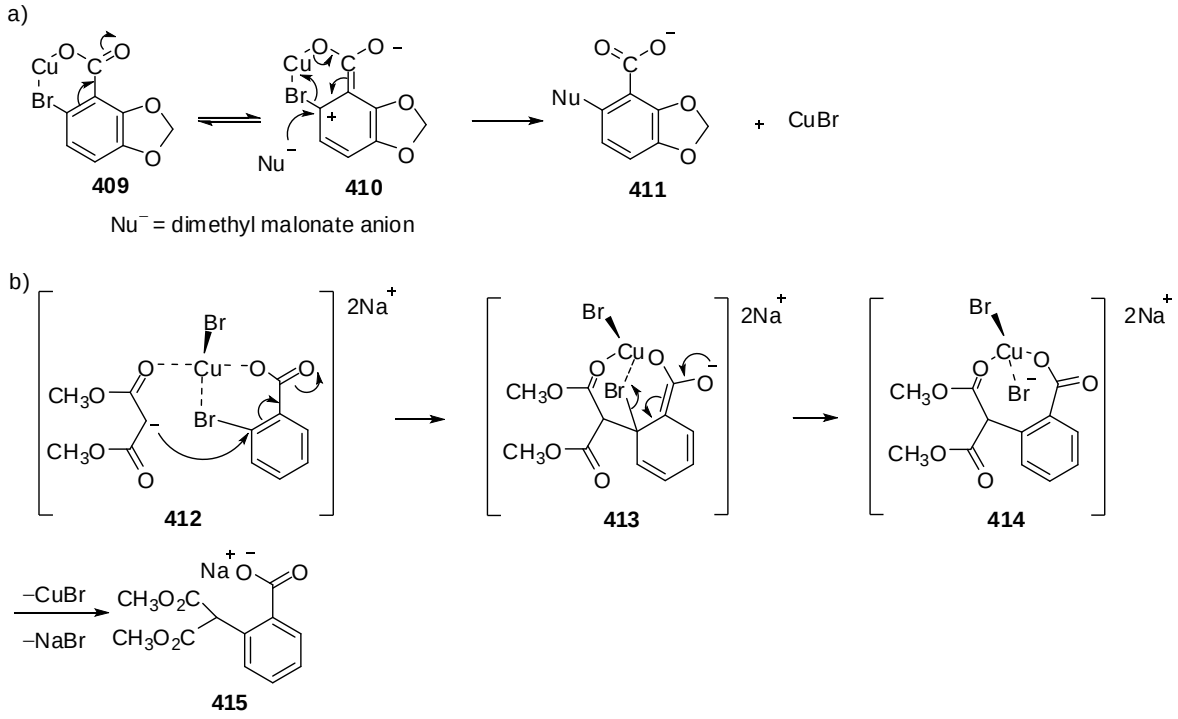

**Scheme 113**: Retrosynthesis of (±)-cavidine **280**

To begin, the novel diester **405** was synthesised from the commercially available bromide **408** based on a modified Hurtley reaction[52,143] reported by McKillop *et al.*[143c] Dimethyl malonate itself was used as the reaction solvent and the bromide **408** was heated with CuBr and NaH for 24 h to afford the novel diester **405** in 74% yield (Scheme 114). Although the mechanism of the Hurtley reaction has not been established conclusively, two possible mechanisms prevail in the literature; Mayer *et al.*[143b] proposed that a copper(I) carboxylate **409** is the key intermediate and that the

polarisation of the carbon-halogen bond is augmented by intramolecular coordination of the halogen to the copper(I) atom (Scheme 115, eqn a), while McKillop *et al.*[143c] proposed tetrahedrally coordinated copper(I) intermediates **412**–**414** (Scheme 115, eqn b).



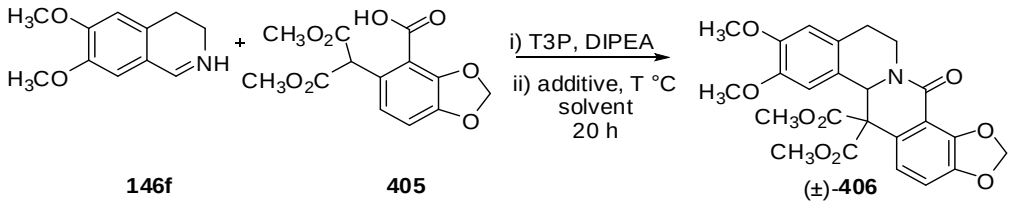

**Scheme 114**: The synthesis of diester **405**




**Scheme 115**: a) Proposed intermediates by Mayer *et al.*, b) Proposed intermediates by McKillop *et al.*

Diester **405** was then reacted with imine **146f** using the standard DIA coupling conditions (T3P, DIPEA, 90 °C, toluene). Pleasingly, the DIA coupling was successful, furnishing lactam **406**, albeit in moderate yield (39%). Additional optimisation reactions were performed using Lewis acids additives in an attempt to improve the yield (Table 11).

**Table 11**: Optimisation of DIA coupling between imine **146f** and acid **405**

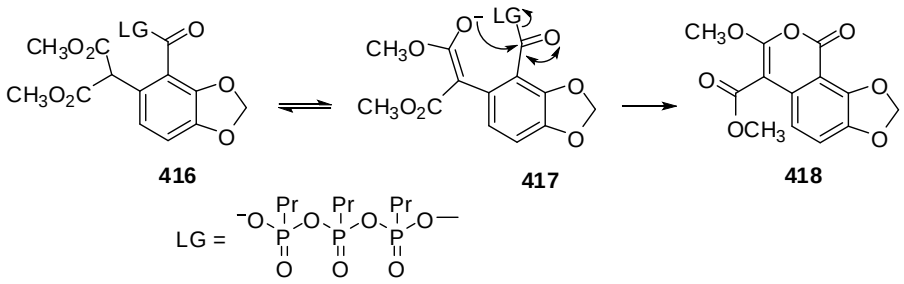



**146f** **405** (±)-**406**

| Entry[a] | Solvent | Additive | Temp. | Outcome (Yield)[b] |
|---|---|---|---|---|
| i[c] | toluene | – | 90 °C | 39% |
| ii | toluene | $BF_3{\cdot}Et_2O$ | rt | No reaction |
| iii | toluene | $BF_3{\cdot}Et_2O$ | 90 °C | 36% |
| iv | $CHCl_3$ | $AlCl_3$ | rt | 37% |
| v | $CHCl_3$ | $AlCl_3$ | 70 °C | 30% |
| vi | $CHCl_3$ | $AlCl_3$ | 50 °C | 64% |
| vii [d] | $CHCl_3$ | $BCl_3$ | rt | 69% |

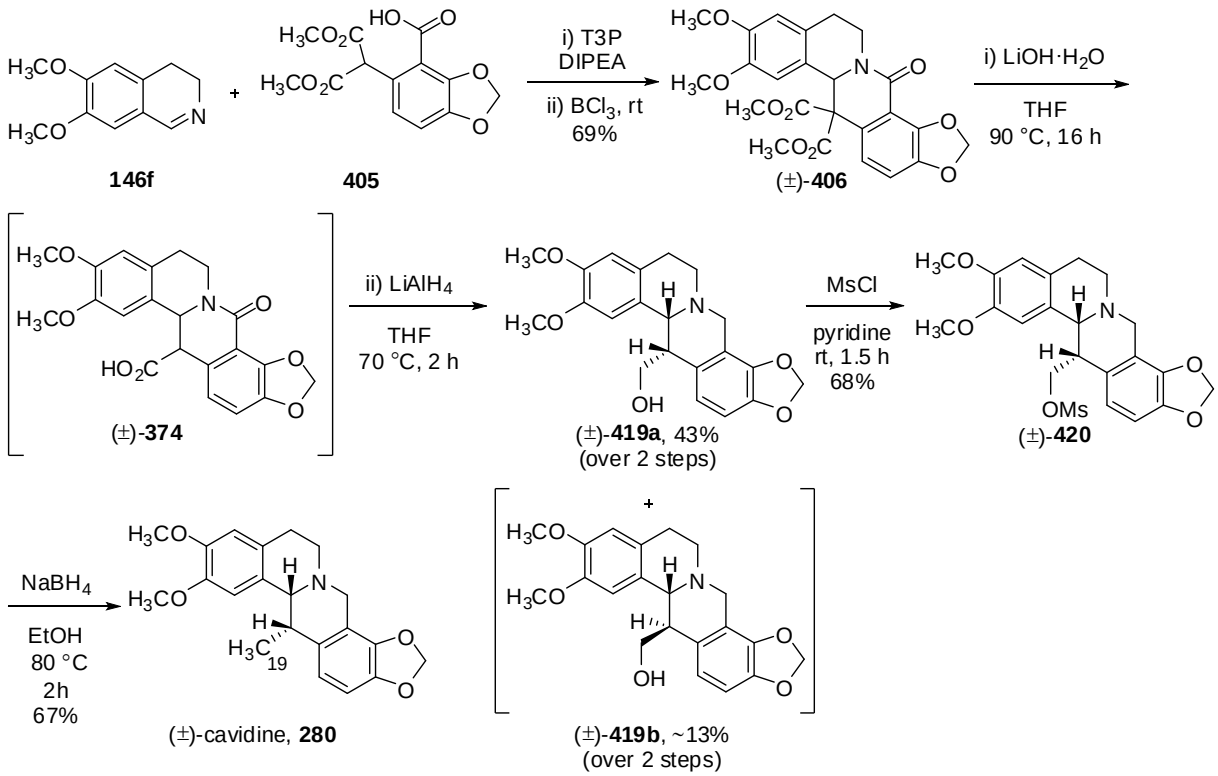
[a] Reactions were performed on a 0.1–0.3 mmol scale using imine **146f** (1 equiv.), benzoic acid **405** (1.2 equiv.), T3P (1.5 equiv.), DIPEA (1.85 equiv.) and Lewis acid additive (2 equiv.) with conditions shown unless stated. [b] Isolated yield following column chromatography. [c] The reaction was performed on a 1.21 mmol scale. [d] The reaction was performed on a 2.53 mmol scale.

Although $BF_3{\cdot}Et_2O$ proved to be an effective Lewis acid additive in previous DIA coupling reactions involving C-C bond formation,[57] it did not improve the isolated yield of product **406** (36%). However, switching the additive to $AlCl_3$ allowed product **406** to be obtained in 64% yield, after heating at 50 °C in chloroform. It is important to note that poor phase separation in the work-up was a considerable problem and the reaction was not easily reproducible. Pleasingly, this problem was overcome by using $BCl_3$ as the Lewis acid additive, to give product **406** in 69% yield. This reaction was completed at room temperature; it was also tested at 50 °C under otherwise identical conditions but as the $^1$H-NMR spectrum of the crude reaction mixture appeared to show less product **406** than the analogous rt reaction, the product was not isolated. It is also noteworthy that no competing demethylation products were observed in either $AlCl_3$ or $BCl_3$, in spite of literature precedent for such transformations on similar substrates.[144] Interestingly, the novel benzopyran **418**, formed from the self-condensation of acid **405** (Scheme 116), was observed in the $^1$H-NMR spectrum of the crude reaction mixture of most of the above DIA reactions and the compound was isolated and fully characterised. The formation of this side-product is not surprising as similar observations were reported previously (Chapter 2, Scheme 48).




**Scheme 116**: The formation of benzopyran **418**

Having optimised the DIA coupling, it was envisioned that following the same reaction sequence as for the synthesis of the model system (13-methyl-tetrahydroprotoberberine **390**, Schemes 111 and 112), would complete the synthesis of (±)-cavidine **280**. Ester hydrolysis and decarboxylation using LiOH in aqueous THF to give acid **374** was followed by reduction with $LiAlH_4$ to afford alcohol **419a** in 43% yield following column chromatography (Scheme 117). Note that in this instance, the intermediate acid **374** could not be epimerised by refluxing in AcOH and it was used as a mixture of diastereoisomers in the next step; the desired *cis*-alcohol **419a** was then separated by column chromatography (43% *cis*-alcohol **419a**, ~13% *trans*-alcohol **419b**). Also, an oxidised side-product presumed to be **419c** (Figure 21) was observed in the mass spectrum of the crude mixture but, as with *trans*-alcohol **419b**, it was difficult to isolate this compound cleanly. Finally, the formation of the natural product (±)-cavidine **280** was completed *via* mesylation and subsequent deoxygenation with $NaBH_4$ in refluxing ethanol. (±)-Cavidine **280** was synthesised in 12% overall yield and fully characterised. The characteristic $^{1}H$- and $^{13}C$-NMR chemical shifts of the methyl group of (±)-cavidine **280** at 0.94 ppm and 18.4 ppm respectively (literature values: 0.94 ppm and 18.5 ppm accordingly) distinguish (±)-cavidine **280** from its stereoisomer, thalictrifoline **363** (corresponding chemical shifts appear at 1.44 ppm and 22.4 ppm). All the spectral data were in full accord with those previously reported (Appendix I (C and D)).[127,129a,c,134]




**Scheme 117**: The total synthesis of (±)-cavidine **280**

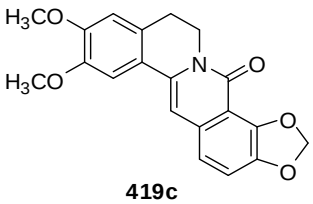



**Figure 21**: The oxidised side-product **419c**

## 4.3 Studies Towards the Synthesis of (±)-Pallimamine 283

### 4.3.1 Introduction to the Natural Product (±)-Pallimamine 283

The novel berberine alkaloid (±)-pallimamine **283** was isolated, in the form of pale yellow prisms, from the whole plant of *Corrydalis pallida var sparsimamma* in 1989 (Figure 22).[145] The plant material was collected in Nan-Shan village, Yilan-Hsier in Taiwan in July 1973. Other alkaloids isolated from the same source were protopine **360**, α-allocryptopine **421**, (±)-tetrahydropalmatine **297** and (–)-capaurimine **422** (Figure 22), all of which were previously known.

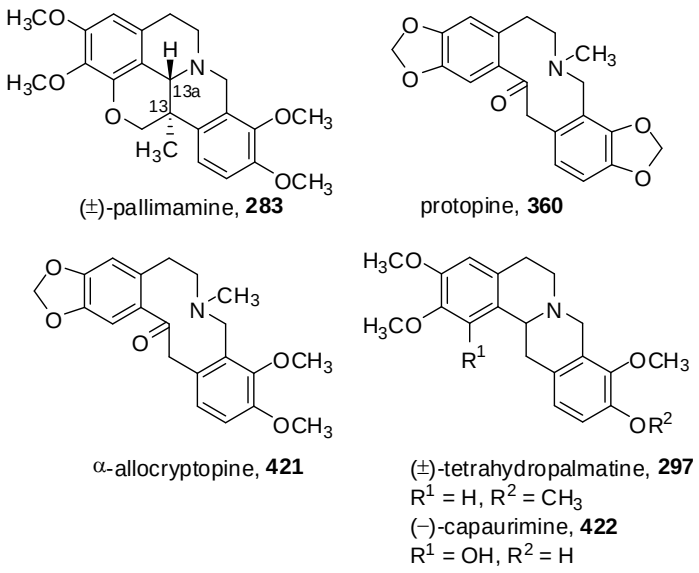


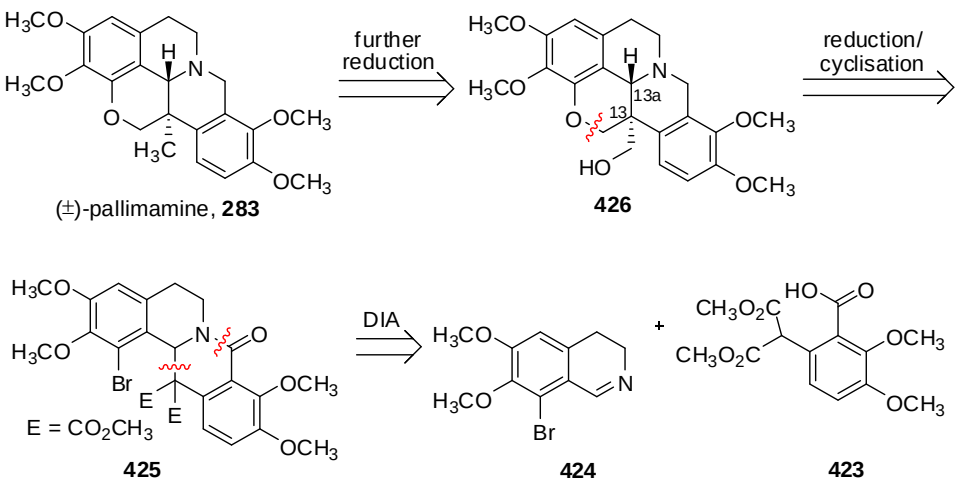

**Figure 22**: Alkaloids isolated from *Corrydalis pallida var sparsimamma*.

(±)-Pallimamine **283** was found to be racemic, unlike the other alkaloids isolated from the same plant, and it adopts a *trans*-quinazolizidine conformation. Unequivocal evidence for the structure of (±)-pallimamine **283** was provided by single crystal X-ray diffraction analysis and clearly shows that the methyl group at C-13 and the hydrogen atom at C-13a are mutually *trans*.

### 4.3.2 First Retrosynthetic Plan of (±)-Pallimamine 283

Having established an efficient synthetic sequence to make the berberine alkaloid (±)-cavidine **280**, we were keen to apply a similar retrosynthetic approach to synthesise the novel berberine alkaloid (±)-pallimamine **283**. Our first retrosynthetic strategy is shown in Scheme 118. We envisaged the synthesis of (±)-pallimamine **283** would be achieved *via* DIA reaction between the bromo-substituted

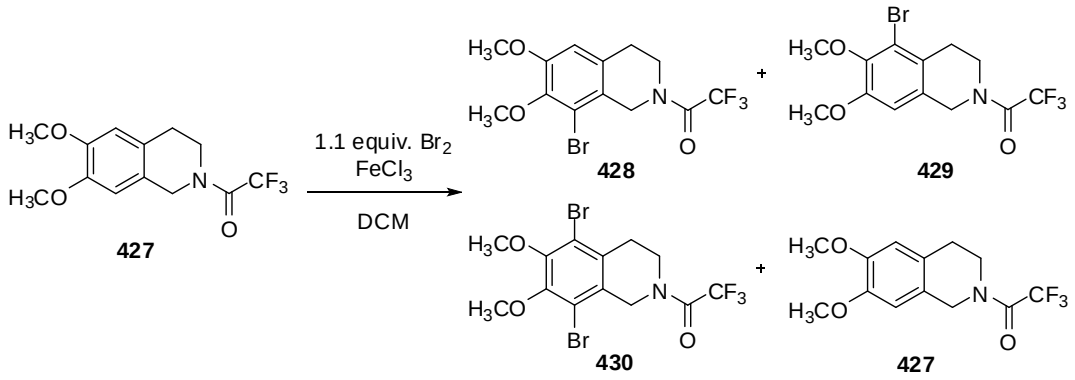
dimethoxy-dihydroisoquinoline **424** and dimethoxy-benzoic acid **423** to form the key tetracyclic-intermediate **425**. The fifth ring of (±)-pallimamine **283** would then be constructed *via* reduction of the two esters to the corresponding primary alcohols followed by an Ullman-type cyclisation between the aryl bromide and one of the newly formed primary alcohols to give intermediate **426**; at this stage, the amide may also be reduced to the corresponding tertiary amine. The reduction of the primary alcohol at C-13 to the corresponding methyl group would complete the synthesis of (±)-pallimamine **283**. It is speculated that the most stable diastereoisomer will be the one leading to the natural product (*trans*-relationship between the proton at C-13a and the methylene alcohol at C-13). First, the existence of the natural product offers reassurance that this pentacyclic system is reasonably stable. Secondly, molecular models of the two possible diasteroisomers appear to involve considerably less ring strain and steric hindrance in the desired diasteroisomer (which is based on a *trans*-decalin core) than the alternative diasteroisomer (which is based on a *cis*-decalin core). More detailed calculations would be needed to gain greater clarity on this question, but the qualitative methods described were deemed sufficient to proceed with the synthesis and test these theories synthetically.




**Scheme 118**: First retrosynthetic approach to (±)-pallimamine **283**

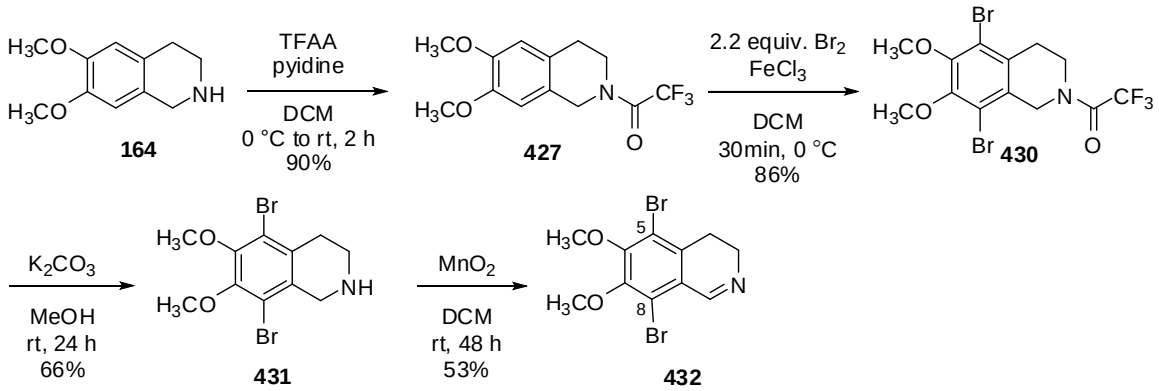
It was hoped that the required bromo-substituted dimethoxy-dihydroisoquinoline **424** could be obtained *via* bromination of the readily available amide **427** with 1.1 equivalents of bromine in the presence of $FeCl_3$.[144a] However, this reaction is not regioselective and a statistical mixture of the two possible bromo-substituted amides **428** and **429** together with the dibromo-substituted amide **430** and traces of starting

material **427** were obtained (Scheme 119).[77] All attempts to separate these compounds failed.



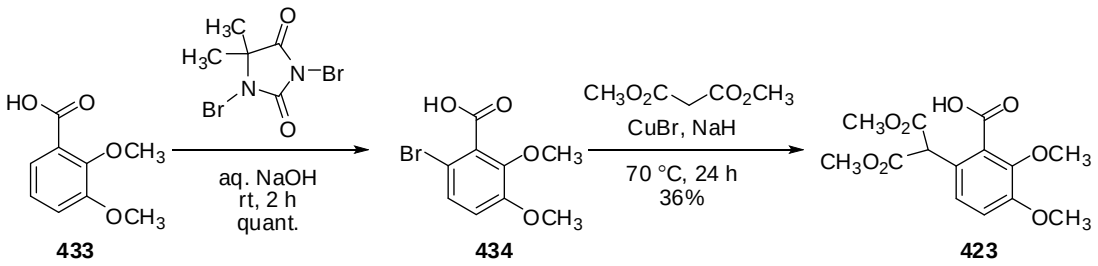

**Scheme 119**: Attempt to synthesise the monobromo amide **1**

It should be noted that the dibromo-substituted amide **430** can be easily made exclusively in high yield when amide **427** is treated with 2.2 equivalents of bromine.[144a] The presence of a second bromine atom in the dihydroisoquinoline system might even be beneficial later in the synthesis since Ullman condensation gives generally better yields with electron-poor aryl halides. Thus, it was decided to synthesise the dibromo-substituted dimethoxy-dihydroisoquinoline **432** instead, as shown in Scheme 120, and remove the extra bromine atom at C-5 later in the synthesis. The treatment of dimethoxy-tetrahydroisoquinoline **164** with trifluoroacetic anhydride gave amide **427**[42] which was then treated with 2.2 equivalents of bromine to furnish dibromo-intermediate **430** in high yield. Dibromo-intermediate **430** was then hydrolysed to the corresponding secondary amine **431** and oxidised with $MnO_2$ to give 5,8-dibromo-6,7-dimethoxy-3,4-dihydroisoquinoline **432**.



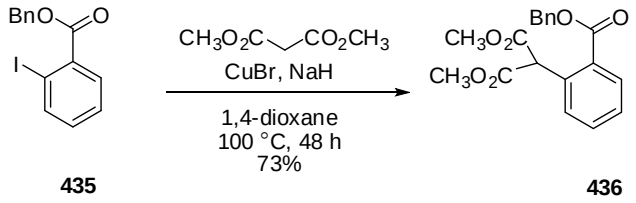

**Scheme 120**: Synthesis of 5,8-dibromo-6,7-dimethoxy-3,4-dihydroisoquinoline **432**

Having imine **432** in hand, we embarked on the synthesis of the acid coupling partner **423** (Scheme 121). To begin, the commercially available 2,3-dimethoxybenzoic acid **433** was brominated using 1,3-dibromo-5,5-dimethylhydantoin following a known literature procedure.[146] Bromide **434** was then converted into the novel diester **423** in 36% yield *via* a modified Hurtley reaction.[143c–e]



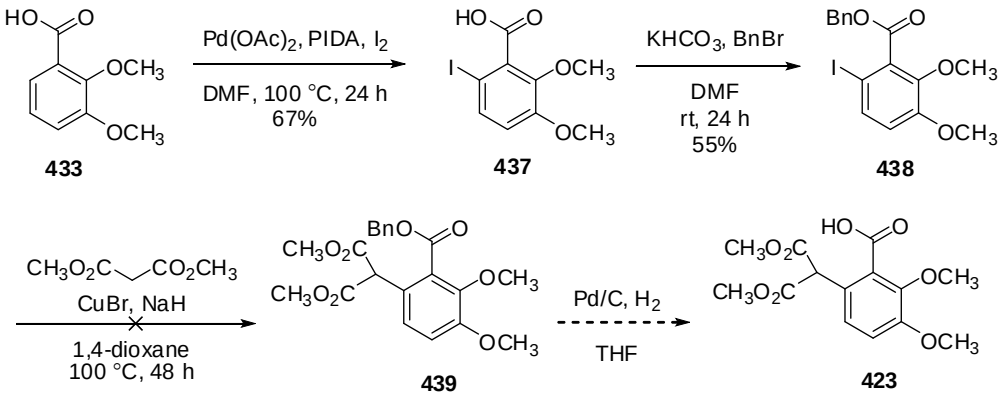

**Scheme 121**: Synthesis of the acid coupling partner **423**

The yield for the Hurtley reaction was somewhat disappointing and also, was not easily reproductible, prompting us to seek an alternative way to synthesise the required diester **423** in better yield. Clive *et al.*[147] reported the formation of diester **436** from the benzyl-protected iodobenzoic acid **435** using 1,4-dioxane as a solvent and stoichiometric amount of dimethyl malonate (Scheme 122). Intrigued by this report, we were keen to test this reaction in our system.



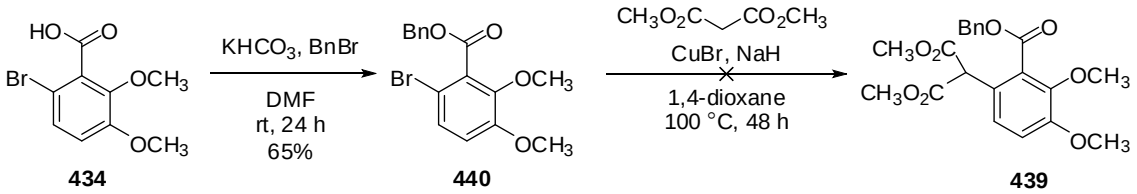

**Scheme 122**: Clive's reported synthesis of diester **436**

6-Iodo-2,3-dimethoxybenzoic acid **437** was synthesised from commercially available 2,3-dimethoxybenzoic acid **433** *via* a carboxylate-directed C-H iodination following the procedure of Yu *et al.* (Scheme 123).[148] It was then benzylated using BnBr and $KHCO_3$ to give the novel iodide **438** based on another literature procedure.[149] Unfortunately, iodide **438** did not react when treated with NaH, CuBr and dimethyl malonate in 1,4-dioxane; not even traces of diester **439** were observed in the $^1$H-NMR spectrum of the crude reaction mixture and the bulk of the starting material **438** was recovered cleanly.




**Scheme 123**: Attempted alternative synthesis of **423**

It was then tested whether the bromide-analogue **440** could be converted into the corresponding diester **439** in the same way (Scheme 124). The readily available bromide **434** was benzylated to give the novel bromide **440**,[149] however when treated with NaH, CuBr and dimethyl malonate in 1,4-dioxane again no product formation was observed and the bulk of the starting material **440** was recovered cleanly.

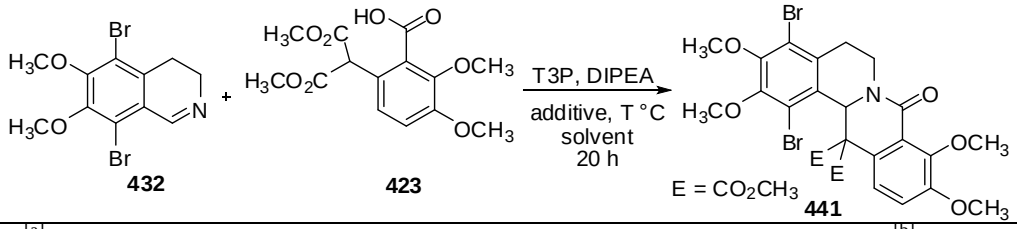



**Scheme 124**: Attempted synthesis of diester **439**

It is important to note that there is no literature precedent for *ortho*-halogenated benzoic acids substituted with electron-donating groups undergoing halogen/dialkyl malonate exchange under the Hurtley reaction conditions (NaH, CuBr and dimethyl malonate).[143] All the substituted *ortho*-halogenated benzoic acids in the literature that successfully undergo halogen/dialkyl malonate exchange are substituted with electron-withdrawing groups and so may proceed *via* nucleophilic aromatic substitution processes.[150]

Having failed to find a higher yielding route to dimethoxy-acid **423**, we reverted to the first synthetic route. Thus, the DIA reaction of the dimethoxy-acid **423** with imine **432**, was tested, and pleasingly the DIA adduct **441** was successfully synthesised in 38% yield using $AlCl_3$ as the Lewis acid at 50 °C (Table 12).

**Table 12**: Optimisation of DIA coupling between imine **432** and acid **423**



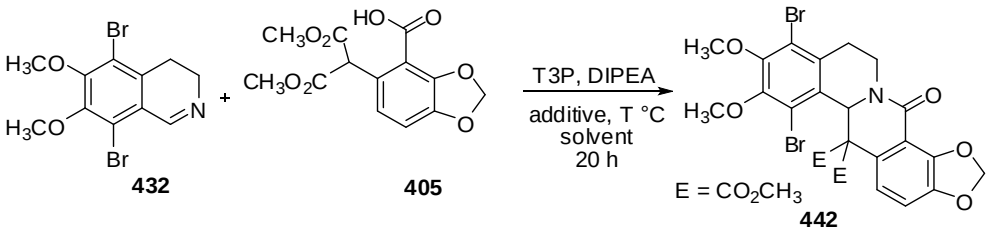

**432** + **423** → **441**

| Entry[a] | Solvent | Additive | Temp. | Outcome (yield)[b] |
|---|---|---|---|---|
| i | toluene | – | 90 °C | Complex mixture, small product formation |
| ii | $CHCl_3$ | $AlCl_3$ | 50 °C | 38% |
| iii | toluene | $AlCl_3$ | 90 °C | Complex mixture |
| iv | $CHCl_3$ | $AlCl_3$ | rt | Complex mixture, small product formation |
| v | $CHCl_3$ | $BF_3{\cdot}Et_2O$ | 50 °C | Complex mixture |

[a] Reactions were performed on 0.05–0.20 mmol scale using imine **432** (1 equiv.), benzoic acid **423** (1.2 equiv.), T3P (1.5 equiv.), DIPEA (1.85 equiv.) and Lewis acid additive (2 equiv.) with conditions shown, unless stated. [b] Isolated yield following column chromatography.

The DIA coupling between the methylenedioxy-acid **405** and imine **432** has been also tested for comparison (Table 13). Pleasingly, the DIA reaction using either $AlCl_3$ or $BCl_3$ as additives gave adduct **442** in reasonable yields (31-41%). Note that the yields were lower compared to related DIA reactions, possibly because the dibromo-imine **432** is more sterically hindered than previous DIA coupling partners.

**Table 13**: Optimisation of DIA coupling between imine **432** and acid **405**




**432** + **405** → **442**

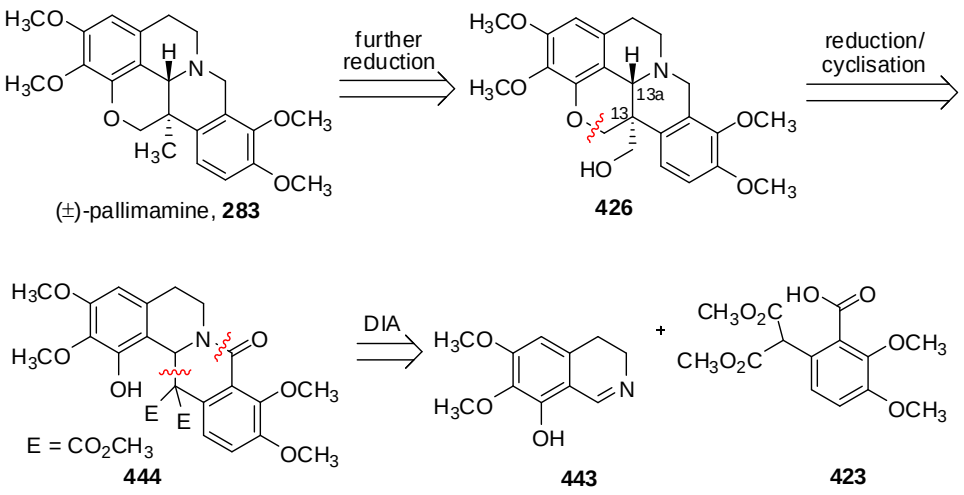
| Entry[a] | Solvent | Additive | Temp | Outcome (yield)[b] |
|---|---|---|---|---|
| i | $CHCl_3$ | $AlCl_3$ | 50 °C | 41% |
| ii | toluene | $BCl_3$ | 80 °C | 39% |
| iii | $CHCl_3$ | $BCl_3$ | rt | 31% |

[a] Reactions were performed on 0.1–0.2 mmol scale using imine **432** (1 equiv.), benzoic acid **405** (1.2 equiv.), T3P (1.5 equiv.), DIPEA (1.85 equiv.) and Lewis acid additive (2 equiv.) with conditions shown, unless stated. [b] Isolated yield following column chromatography.

### 4.3.3 Second Retrosynthetic Plan of (±)-Pallimamine 283

Once the key DIA adduct **441** was formed, our work should have next focused on the construction of the fifth ring of (±)-pallimamine **283** *via* reduction of the two esters followed by an Ullman-type cyclisation. However this was not pursued, as a slightly different retrosynthetic approach under investigation concurrently was proving to be more promising. This strategy uses a hydroxyl-substituted imine **443** as starting material in the place of the dibromo-substituted imine **432** (Scheme 125).

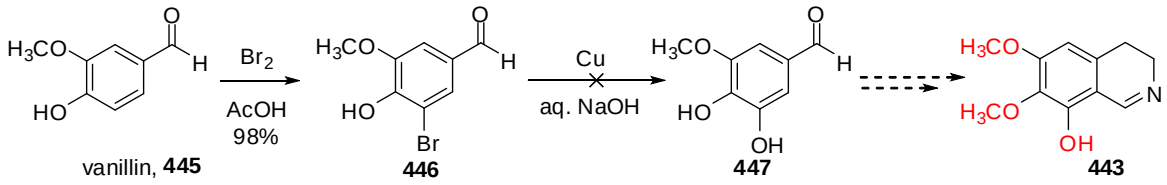
It was envisaged that the key intermediate **444** would be formed *via* an initial DIA reaction between the hydroxyl-substituted imine **443** and the dimethoxy-benzoic acid **423**. The fifth ring of (±)-pallimamine **283** would then be constructed *via* reduction of the two esters to yield the corresponding primary alcohols. The conversion of these alcohols into better leaving groups followed by an $S_N2$ reaction with the phenol should furnished the fifth ring of (±)-pallimamine **283**. Further reduction of the primary alcohol at C-13 to the corresponding methyl group would furnish the natural product.




**Scheme 125**: Second retrosynthetic approach of (±)-pallimamine **283**

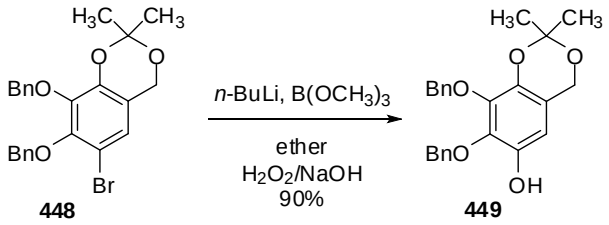
There are a number of reports in the literature which use vanillin **445** as a precursor for phenyl ring systems with methoxy, methoxy, hydroxyl sequential substitution patterns.[151] Thus, we set out to prepare the required 8-hydroxyl-6,7-dimethoxy-3,4-dihydroisoquinoline **443** from vanillin **445** (Scheme 126). The synthesis started with the selective bromination of vanillin **445** using bromine in AcOH following a literature procedure.[151a–c,e] Although the reaction of the aldehyde **446** with copper powder in

the presence of aqueous sodium hydroxide to afford the catechol **447** is a known reaction,[151c–e] no product was observed in our hands.



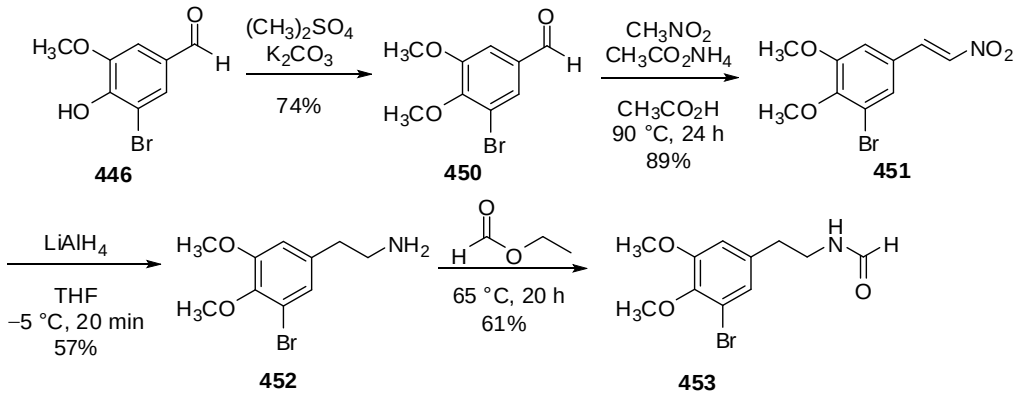

**Scheme 126**: Attempted synthesis of hydroxyl-substituted imine **443** starting from vanillin **445**

A paper by Nicolaou *et al.* reported the conversion of bromo-species into phenolic species *via* a borate intermediate (Scheme 127).[152] The readily available bromide **448** was treated with $B(OCH_3)_3$ and *n*-BuLi to give phenol **449** after an oxidative work-up with $H_2O_2$ in aqueous NaOH.



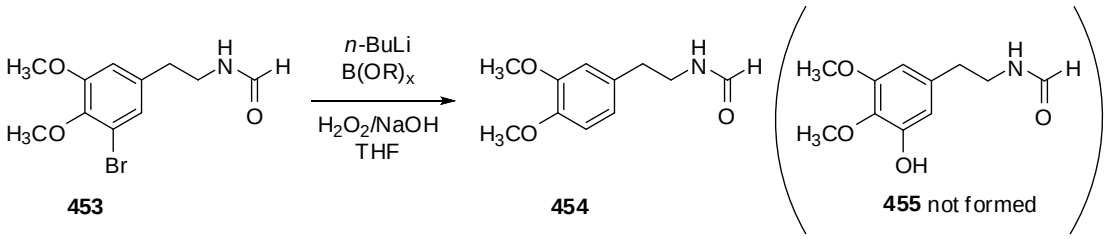

**Scheme 127**: Conversion of bromo-species **448** to phenolic species **449** *via* a borate intermediate

Intrigued by the above report, we decided to test this reaction on our system. First, we methylated intermediate **446** with dimethyl sulfate and $K_2CO_3$ following a literature procedure (Scheme 128).[153] The resulting 3-bromo-4,5-dimethoxybenzaldehyde **450** was then reacted with nitromethane and ammonium acetate in a Henry reaction, followed by a subsequent dehydration to give the novel nitro-compound **451** in 89% based on a literature procedure.[112] Reduction of compound **451** with lithium aluminum hydride at −5 °C gave the corresponding ethanamine **452** in 57% yield. Note that debromination occurs together with the reduction, when the nitro-compound **451** was treated with lithium aluminum hydride at higher temperatures (e.g. 70 °C, rt). Amine **452** was then treated with ethyl formate to give the novel formamide **453** in 61% yield.




**Scheme 128**: Synthesis of the formamide **453** from vanillin **446**

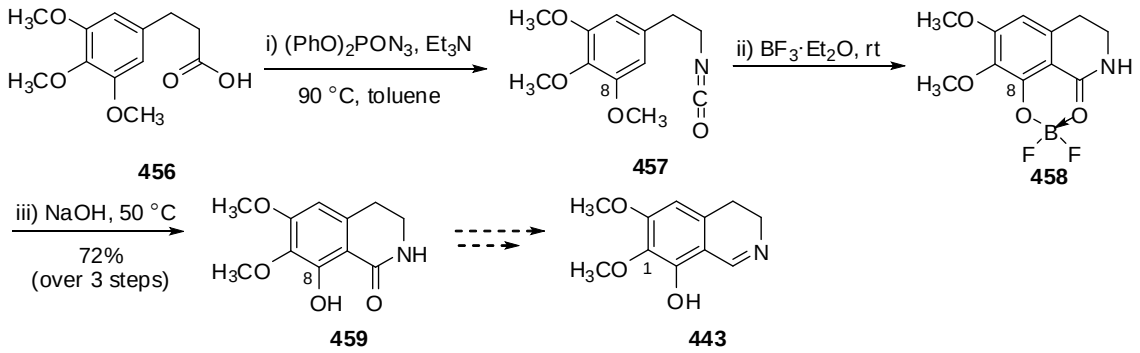
Having bromo-substituted formamide **453** in hand, we tested if we could convert it into the corresponding hydroxyl-substituted formamide **455** using Nicolaou's conditions (Scheme 129).[152] Phenylformamide **453** was treated with trimethyl borate and *n*-BuLi to give the debrominated phenylformamide **454** rather than the phenolic formamide **455** after the oxidative work-up. The same disappointing results were observed when triisopropyl borate and isopropoxyboronic acid pinacol ester [$^{i}$PrOBPin] were used. These results signify that the lithium-halogen exchange took place but the borate formation and the subsequent oxidation did not.




**Scheme 129**: Attempt to convert bromo-substituted formamide **453** into hydroxyl-substituted formamide **455** *via* a borate intermediate

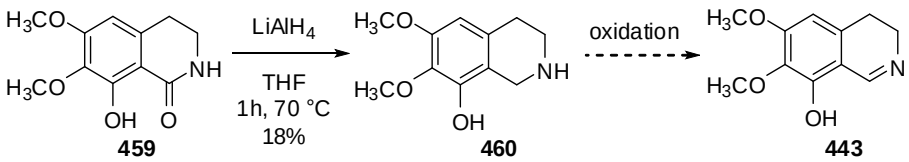
Due to the previous observations, it was decided to consider an alternative way to prepare imine **443** (Scheme 130). We discovered that lactam **459** could be synthesised from carboxylic acid **456** *via* a known literature procedure.[80] The isocyanate intermediate **457**, generated from the carboxylic acid **456** *via* a modified Curtius rearrangement, was captured by the electron-rich tethered aromatic ring in the presence of concentrated $BF_3 \cdot Et_2O$ to generate the $BF_2$-complex **458**. Caggiano *et al.* obtained an X-ray structure of the $BF_2$-complex **458** which revealed that the $BF_2$-group is strongly coordinated to the Lewis basic lactam in a six-membered ring rearrangement

explaining the selectivity of demethylation at C-8.[80] The $BF_2$-complex **458** was then hydrolysed *via* a basic work-up to give lactam **459** in high yield.




**Scheme 130**: Synthesis of lactam **459** from carboxylic acid **456**

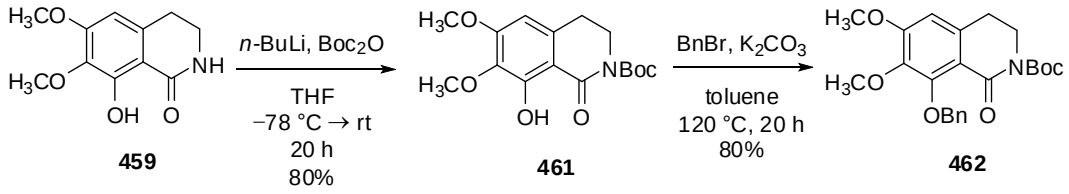
Lactam **459** constituted a convenient precursor to imine **443** as it contained a phenyl ring system with the required substitution pattern (methoxy, methoxy, hydroxy) already established in its structure. To begin, it was tested whether the imine **443** could be synthesised *via* the reduction of lactam **459** with lithium aluminum hydride and subsequent oxidation (Scheme 131). Following the reaction of lactam **459** with lithium aluminum hydride in THF at reflux an additional methylene group peak (3.84–3.82 ppm, 2H, m, $CH_2$) was observed in $^1$H-NMR spectrum of the purified product suggesting the formation of the amine **460**. However, mass spectrometry failed to show the expected mass peak and also the product was difficult to isolate cleanly due to its high polarity. The poor yields and the inconsistent product quality suggested that protection of the phenol and/or the amide species of intermediate **459** would be useful.




**Scheme 131**: Attempt to synthesise imine **443** *via* the reduction of the corresponding lactam **459** and subsequent oxidation

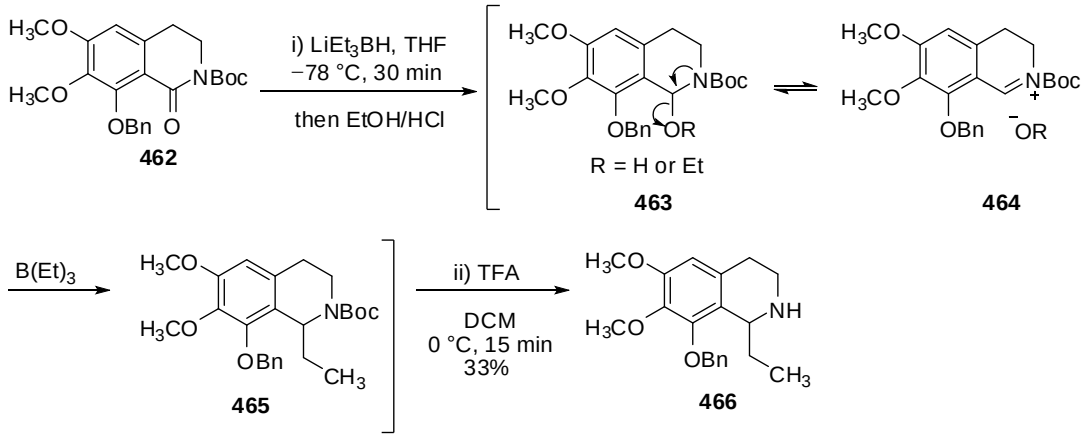
Thus, we developed an orthogonal protecting group strategy as shown in Scheme 132. Lactam **459** was treated with *n*-BuLi and 1 equivalent of di-*tert*-butyl dicarbonate to give the novel *N*-Boc protected lactam **461** exclusively in 80% yield. The *N*-Boc protected lactam **461** was then heated at reflux with BnBr and $K_2CO_3$ in toluene, based

on a literature procedure,[154] to give the orthogonally protected novel lactam **462** in 80% yield.




**Scheme 132**: Synthesis of the orthogonally protected lactam **462**

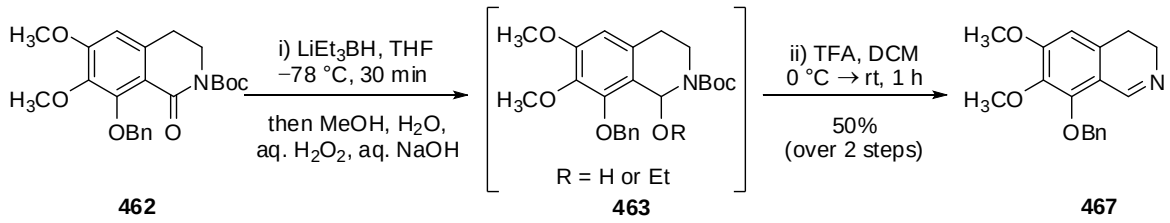
In Chapter 2 we detailed a reaction procedure for the synthesis of imines from the corresponding *N*-Boc protected lactams *via* a partial reduction with Super-Hydride™ and subsequent Boc-cleavage with TFA (Scheme 37, Section 2.3.1). Interestingly, when this reaction sequence was applied to lactam **462**, ethylated amine **466** was the only product observed (Scheme 133). It is speculated that the *N,O*-acetal derivative **463**, which is presumed to form after partial reduction with Super-Hydride,™ collapses to an *N*-acyliminium ion **464** during the work-up and is then trapped by triethylborane present in the crude reaction mixture. Boc-cleavage then revealed the cyclic amine **466**.




**Scheme 133**: Synthesis of the cyclic amine **466**

A paper by Robertson *et al.* came to our attention reporting an oxidative work-up for *L*-selectride reductions of ketones and lactols.[155] In this report, quenching the *L*-selectride reactions by the sequential addition of methanol, water and an aqueous solution of $H_2O_2$ and NaOH provided purer products, avoiding borane-related side-products. We were pleased to find that the application of this oxidative work-up to our Super-Hydride™ reduction, followed by Boc cleavage with TFA, gave imine **467** in a good yield over the two steps (50%) (Scheme 134). Under the conditions described above, any borane present in the reaction mixture is likely to be oxidised to the

corresponding borate, and thus does not react as a nucleophile to trap the *N*-acyliminium ion as in the original procedure.



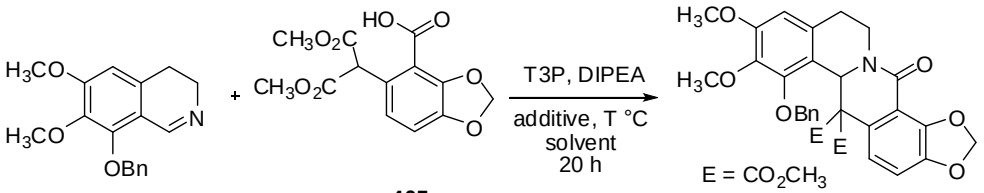

**462** **463** **467**

**Scheme 134**: Synthesis of the imine **467**

### 4.3.4 Synthesis of the Key DIA Intermediates 468 and 469

Having imine **467** in hand, we moved on to test the key DIA coupling required for the synthesis of pallimamine **283**. Methylenedioxy acid **405**, which was synthesised in ample amounts during the cavidine synthesis described previously (see Section 4.2.5), was used as the test substrate to perform a screen for the optimal DIA reaction conditions (Table 14). The DIA coupling of acid **405** and imine **467** under our standard DIA reaction conditions (T3P, DIPEA, 90 °C, 20 h, toluene) was not successful, furnishing a complex mixture of products (Table 14, entry i), while a complex mixture was also obtained when the temperature was decreased to rt, along with some starting material (entry ii). As was demonstrated before, the addition of Lewis acid to the crude reaction mixture often promotes the DIA coupling, hence different Lewis acids were tested for this purpose. Although $BCl_3$ proved to be the most effective additive for the key DIA coupling in cavidine synthesis, giving DIA adduct **406** in 69% yield, it did not have similar success for the synthesis of the DIA adduct **468**, which was isolated in just 21% yield (entry iii). Pleasingly, switching the additive to $AlCl_3$ allowed product **468** to be obtained in a more respectable 50% yield, after heating at 50 °C in chloroform (entry iv).

**Table 14**: Optimisation of DIA coupling between imine **467** and acid **405**

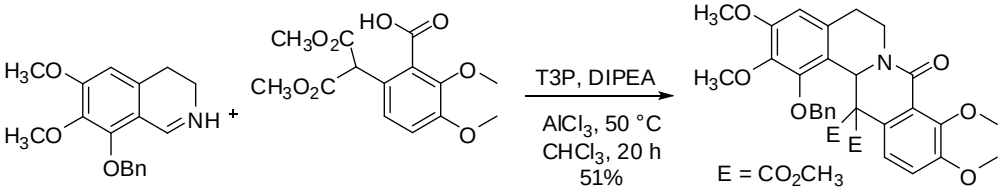



**467** **405** **468**

| Entry[a] | Solvent | Additive | Temp | Outcome (Yield)[b] |
|---|---|---|---|---|
| i | toluene | – | 90 °C | Complex mixture |
| ii | toluene | – | rt | Starting material & complex mixture |
| iii | $CHCl_3$ | $BCl_3$ | rt | 21% |
| iv | $CHCl_3$ | $AlCl_3$ | 50 °C | 50% |

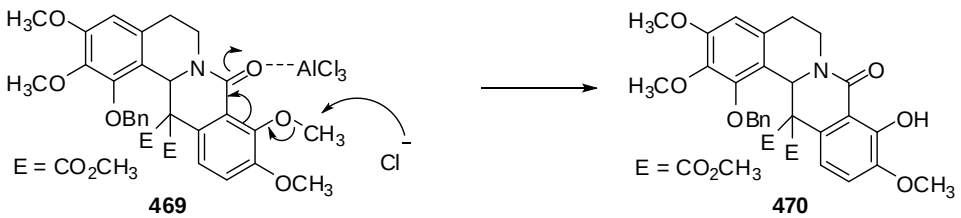
[a] Reactions were performed on 0.1–0.8 mmol scale using imine **467** (1 equiv.), acid **405** (1.2 equiv.), T3P (1.5 equiv.) and DIPEA (1.85 equiv.) with conditions shown, unless stated. The Lewis acid additive (2 equiv.) was added after stirring the reaction at rt for 20 minutes. [b] Isolated yield following column chromatography.

At this stage the project was passed on to a collaborator (Dr Will Unsworth) for further investigation. Pleasingly, the optimised DIA conditions were successful on the pallimamine system; the key coupled intermediate **469** was obtained in 51% yield when the requisite dimethoxy acid **423** was coupled with imine **467** using the optimised conditions ($AlCl_3$, 50 °C, chloroform) (Scheme 135). It is noteworthy that a small amount of demethylated product **470** was also observed in the reaction mixture, in line with literature precedent for such transformations on similar substrates (Scheme 136).[144]




**467** **423** **469**

**Scheme 135**: Synthesis of the key DIA intermediate **469**




**469** **470**

**Scheme 136**: The formation of the demethylated product **470**

## 4.4 Summary

A new synthetic approach for the synthesis of tetrahydroprotoberine alkaloids, which utilises DIA coupling reaction as a key step, has been successfully developed. The synthesis of 13-methyl-tetrahydroprotoberberine **390**, a model system of the natural product cavidine **280**, has been achieved using a DIA reaction between the imine **146e** and the diester **147p** as the key step. The synthesis was then completed using an approach based on that in Cushman's route;[127] double hydrolysis and decarboxylation followed by reduction, mesylation and deoxygenation with $NaBH_4$ gave the tetrahydroprotoberberine **390** in good yield.

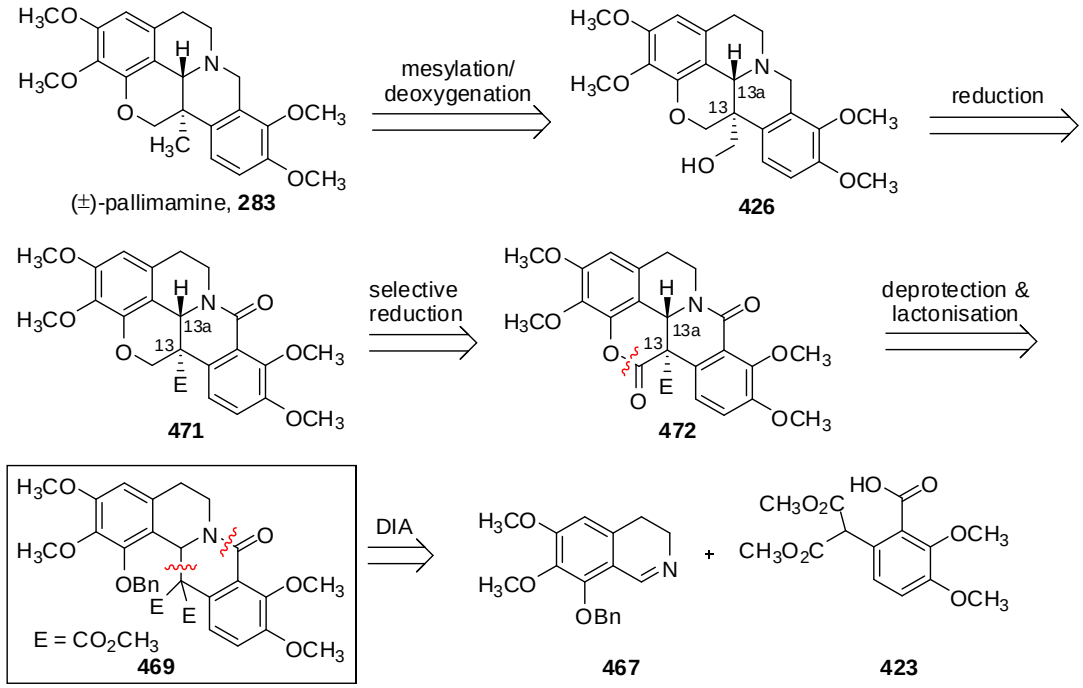
The total synthesis of (±)-cavidine **280** has also been completed; in this instance the DIA coupling between the imine **146f** and the novel diester **405** was low yielding under the standard conditions, but was improved significantly by using a Lewis acid additive. The fact that the coupling reagents (T3P and DIPEA) are compatible with Lewis acid additives is important as this allows such one-pot optimisation processes to be developed, further expanding the scope of the methodology. The efficient convergent synthesis of (±)-cavidine **280** described in this Chapter was included in a recent publication (Appendix II (C)).[65]

Finally, the DIA coupling between the novel trisubstituted dihydroisoquinoline **467** and the novel diesters **405** and **423** has been achieved, highlighting the potential application of the DIA methodology towards the synthesis of the berberine alkaloid (±)-pallimamine **283** which has never been prepared to date. The completion of this synthesis is ongoing in the Taylor group.

# Chapter 5 Future Plans and Perspectives

## 5.1 Total Synthesis of Pallimamine 283

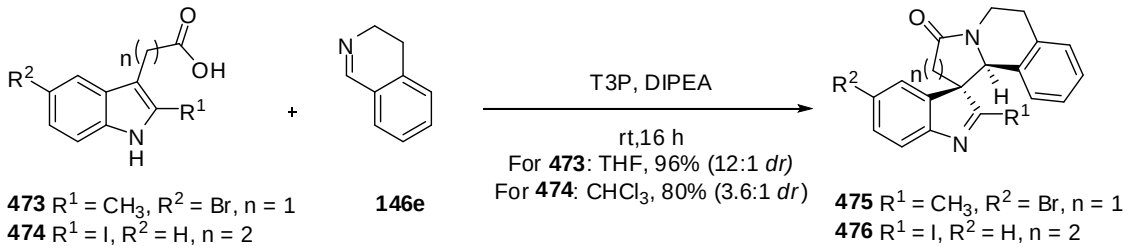
With the synthesis of the key DIA intermediate **469** achieved, efforts to complete the synthesis of (±)-pallimamine **283** are ongoing within the group (Scheme 137). It is envisioned that the condensation of phenol, after cleavage of the benzyl group in the DIA adduct **469**, with one of the two diastereoisotopic esters will give intermediate **472**. Subsequent selective reduction of lactone **472**, to afford the corresponding ether, will then give pentacyclic intermediate **471**. Finally, it is hoped that following the same reaction sequence as that used during the synthesis of (±)-cavidine **280** (reduction, mesylation and deoxygenation), will complete the synthesis of (±)-pallimamine **283**.




**Scheme 137**: Current retrosynthetic plan for the synthesis of (±)-pallimamine **283**

## 5.2 Synthesis of Spirocycles and β-Lactams Using DIA Methodology

Parallel work currently under investigation in the Taylor group[156] has uncovered the potential of DIA for the synthesis of spirocyclic scaffolds and also β-lactams. For example, the substituted 2-methylindole **473** reacted with the isoquinoline **146e** under DIA reaction conditions (T3P, DIPEA, THF, rt, 16 h) to give the spirocycle **475** in excellent yield (Scheme 138). Similarly, the substituted 2-iodoindole **474** reacted with isoquinoline **146e** to generate the spirocycle **476** again in excellent yield (Scheme 137).



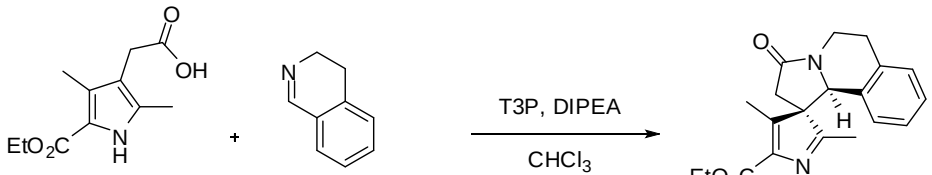

**473** $R^1 = CH_3$, $R^2$ = Br, n = 1
**474** $R^1$ = I, $R^2$ = H, n = 2

**146e**

**475** $R^1 = CH_3$, $R^2$ = Br, n = 1
**476** $R^1$ = I, $R^2$ = H, n = 2

**Scheme 138**: Synthesis of spirocycles **475** and **476** using DIA reaction conditions

Moreover, pyrrole substrates are well tolerated, giving spirocycles in good yields (Scheme 139). For instance, the substituted pyrrole **477** and isoquinoline **146e** were coupled under DIA coupling conditions to give product **478** in 62% yield. Note that spirocyclic scaffolds are being increasingly utilised in drug discovery, due to increasing interest in fragments with greater three-dimensionality.[157]



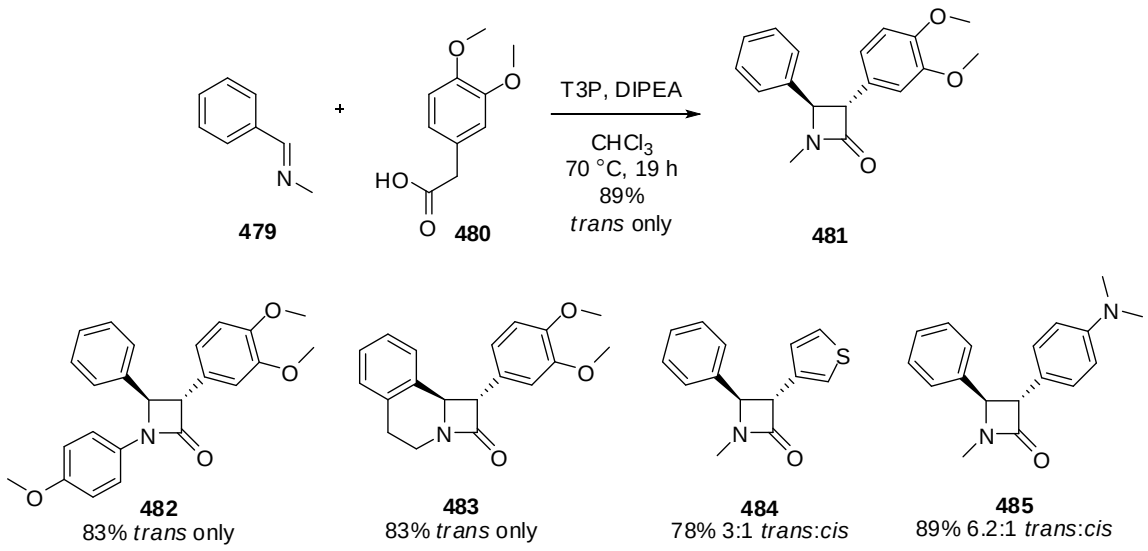

**477**

**146e**

**478**

**Scheme 139**: Synthesis of spirocycle **478** using DIA reaction conditions

In addition, a range of β-lactam scaffolds have been synthesised efficiently (Scheme 140).[158] For example, the reaction of imine **479** and acid **480** under DIA coupling conditions gave β-lactam **481** in 89% yield. This augurs well for a potential use of DIA reaction in antibiotic drug discovery.[159]

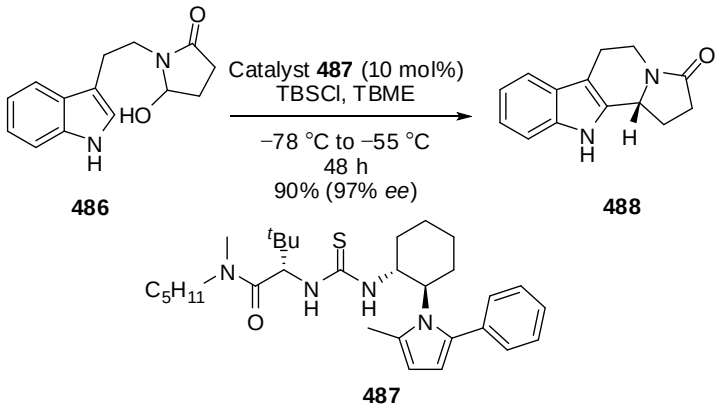



**Scheme 140**: Synthesis of β-lactams **481–485** using DIA reaction conditions

Further investigation of the above reactions and their use in target synthesis is ongoing.

## 5.3 Asymmetric Induction

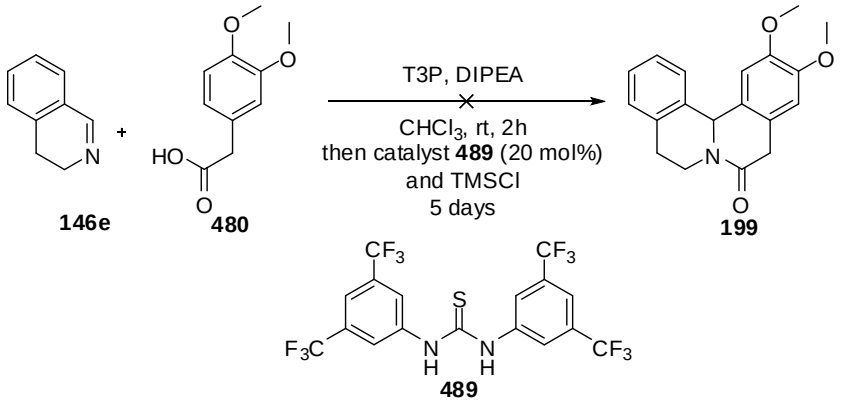
Recently, *N*-acyliminium ions have been demonstrated to engage successfully in asymmetric catalytic reactions.[160,161] Jacobsen's studies in this area led to the discovery that chiral thiourea catalysts can promote highly enantioselective acyl-Pictet-Spengler and Mannich-type reactions to provide products in high enantiomeric excess.[161] A representative example, which involves a chiral thiourea catalyst **487** in the presence of TMSCl, is shown in Scheme 141.[161g]




**Scheme 141**: Asymmetric cyclisation catalysed by thiourea catalyst **487**

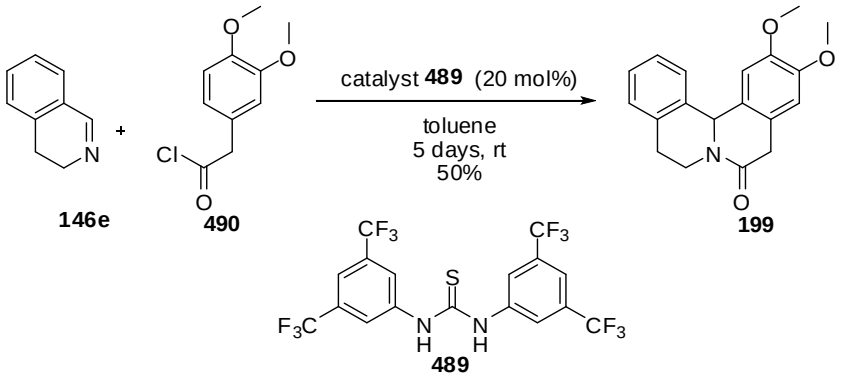
Inspired by the above Jacobsen's work, preliminary studies to impart asymmetric induction in DIA were conducted within the group (Dr. Graeme Coulthard). To begin,

imine **146e** and acid **480** were treated with T3P and DIPEA in chloroform for two hours before catalyst **489** and TMSCl were added (Scheme 142). Disappointingly, no product was observed in the $^{1}$H-NMR spectrum of the crude mixture, even after 5 days.



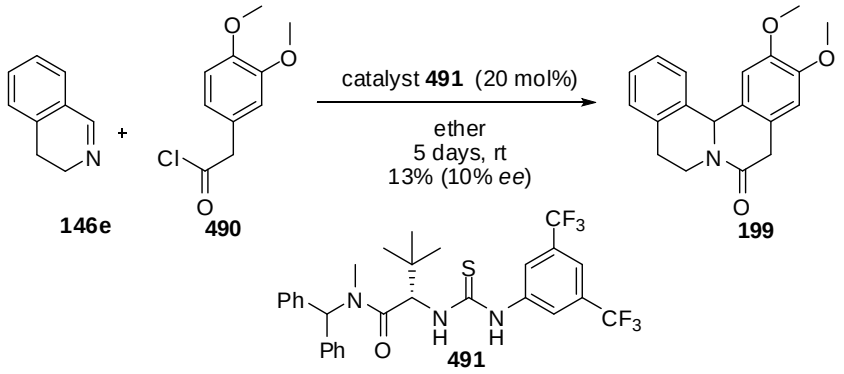

**Scheme 142**: Attempt to achieve DIA reaction of imine **146e** and acid **480** in the presence of catalyst **489**

Pleasingly, when acyl chloride **490**, imine **146e**, and catalyst **489** were dissolved in toluene and the mixture was stirred for 5 days at rt, compound **199** was isolated in 50% yield, after column chromatography (Scheme 143).




**Scheme 143**: DIA reaction of imine **146e** with acid chloride **490** using catalyst **489**

It was then hoped that asymmetric induction could be achieved when a chiral thiourea catalyst was used in the place of the catalyst **489**. Pleasingly, some enantiomeric excess was achieved after a short screen of different chiral thiourea catalysts and solvents (10% *ee* using catalyst **491** in ether, Scheme 144). This proves that this strategy is viable in principal but further investigation of these reactions is required to provide a synthetically useful procedure.




**Scheme 144**: The coupling of imine **146e** with acid chloride **490** using the chiral catalyst **491** in ether.

In conclusion, it has been demonstrated that DIA methodology is a reliable and versatile tool for the synthesis of diverse heterocycles. It has been also demonstrated that this procedure can be applied successfully in target synthesis. In future, efforts will continue to investigate the possibility of performing the reaction asymmetrically, and further applications in target synthesis will also be pursued.

# Chapter 6 Experimental

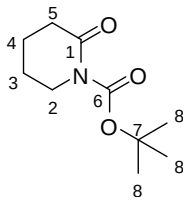
## General Information

Except where stated, all reagents were purchased from commercial sources and used without further purification. All reactions were performed in oven-dried glassware under an atmosphere of argon unless specified otherwise. Where necessary, solvents (THF, toluene, dichloromethane, ether) were dried on an Innovative Technology Inc. PureSolv® solvent purification system by passing the solvent through activated alumina and copper catalyst columns, as appropriate. In some reactions, anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. Anhydrous benzene was obtained by distillation over calcium hydride and stored over 4 Å molecular sieves. Petrol refers to the fractions of petroleum ether which boil between 40 °C and 60 °C. Aqueous solutions are saturated unless specified otherwise. Alkyllithium reagents were titrated against *N*-benzylbenzamide before use. Reaction temperatures of −78 °C were achieved using dry ice/acetone mixtures and reaction temperatures of −5 °C were achieved using salt/ice mixtures. Flash column chromatography was carried out using slurry packed Fluka silica gel ($SiO_2$), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Thin-layer chromatography (t.l.c) was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic *p*-anisaldehyde as appropriate. NMR spectra were recorded on a Jeol ECX-400 NMR or Jeol ECS400 spectrometer operating 400 MHz ($^1$H) and 100 MHz ($^{13}$C) respectively. All spectra was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). Couplings constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad or combinations of these. Where coincident coupling constants have been observed in the NMR spectru m, the apparent multiplicity of the proton resonance concerned is reported. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HSQC and HMBC experiments where required. The residual solvent peak, $\delta_H$ 7.26 and $\delta_C$ 77.0 for $CDCl_3$ and $\delta_H$ 2.50 and $\delta_C$ 39.50 for $(CD_3)_2SO$ was used as a reference. Infrared spectra (IR) were recorded on a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film or Perkin Elmer FT-IR spectrometer dispersed from either $CH_2Cl_2$ or $CDCl_3$. High Resolution Mass Spectra (HRMS) were obtained by University of York

Mass spectrometer service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. An FTIR analyser, ReactIR 4000 with a MCT detector, a KBr bean splitter and an ATR probe (DiComp) were used for all ReactIR experiments. The probe was fitted to a 50 mL glass round bottom flask containing a magnetic stirrer bar to provide agitation. A nitrogen purge was maintained on tha system throughout the experiment, and a nitrogen background was used in computing the absorbance spectra. Each spectrum represents 256 co-added scans measured at a spectral resolution of 4 $cm^{-1}$ in the 4000–650 $cm^{-1}$ range with the Happ-Genzel apodisation function. All numbering on the structures below is for the benefit of structure characterisation and does not conform to IUPAC rules.

## Reaction Procedures and Compound Characterisation

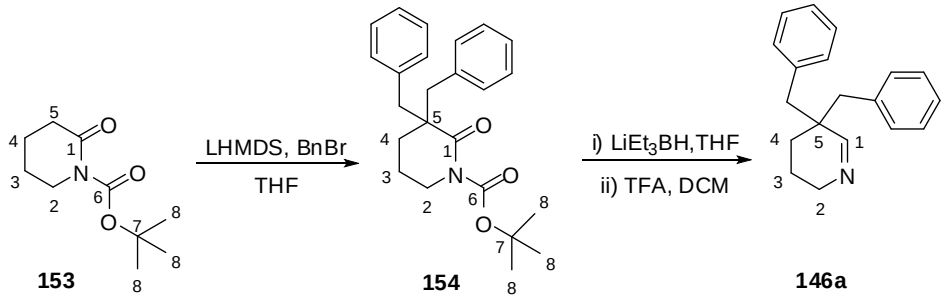
### *tert*-Butyl 2-oxopiperidine-1-carboxylate (153):[162]




Triethylamine (14.1 mL, 100 mmol), DMAP (0.616 g, 5.04 mmol) and $Boc_2O$ (16.5 g, 75.6 mmol) were added to a solution of the piperidin-2-one **152** (5.00 g, 50.4 mmol) in THF (250 mL). The solution was stirred at rt for 24 h. The mixture was washed with sat. aq. $NH_4Cl$ (350 mL), extracted with ethyl acetate (3 × 200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 10:1→1:1 petrol:ethyl acetate) afforded compound **153** as a colourless solid (8.27 g, 82%); $R_f$ 1.7 (1:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 3.64 (2H, t, *J* = 4.9 Hz, H-2), 2.50 (2H, t, *J* = 7.2 Hz, H-5), 1.81–1.79 (4H, m, H-3,4), 1.51 (9H, s, H-8). Obtained data in accord with those reported in the literature.[162]

Lab Notebook Reference: CHK 1/1 p.2

**5, 5-Dibenzyl-2,3,4,5-tetrahydropyridine (146a):**




This compound was first synthesised by Dr. Will Unsworth.

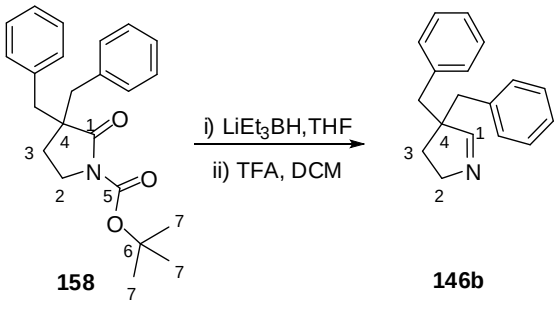
To a solution of *tert*-butyl 2-oxopiperidine-1-carboxylate **153** (4.0 g, 20.1 mmol) in THF (80 mL) at −78 °C was added LHMDS (48.2 mL, 48.2 mmol, 1 M solution in THF) and the resulting solution was stirred at −78 °C for 1 h. Benzyl bromide (5.74 mL, 48.2 mmol) was then added and the mixture warmed to rt and stirred at this temperature for 2 h, before the reaction was quenched by the addition of sat. aq. $NH_4Cl$ (200 mL), extracted with ethyl acetate (3 × 200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 20:1→7:3 petrol:ethyl acetate) afforded the 3,3-dibenzylpiperidin-2-one **154** as a colourless solid (5.70 g, 74%, mixture of rotamers (ratio 4:1)); [$\nu_{max}$ (thin film)/$cm^{-1}$ 3029, 2979, 2934, 1766, 1715, 1633, 1495, 1455, 1393, 1368; $\delta_H$ (400 MHz, $CDCl_3$) 7.27–7.17 (10H, m, ArH, both), 3.50 (2H, d, *J* = 13.0 Hz, C*H*HPh, minor), 3.38 (2H, d, *J* = 13.2 Hz, C*H*HPh, major), 3.17 (2H, t, *J* = 5.9 Hz, H-2, major), 2.73 (2H, t, *J* = 5.8 Hz, H-2, minor), 2.64 (2H, d, *J* = 13.2 Hz, CH*H*Ph, major) 2.60 (2H, d, *J* = 13.0 Hz, CH*H*Ph, minor), 1.59 (9H, s, H-8, major), 1.53 (9H, s, H-8, minor), 1.72–1.69 (2H, m, H-4, both), 1.39–1.33 (2H, m, H-3, both); $\delta_C$ (100 MHz, $CDCl_3$) 176.1 (C-1 major), 173.6 (C-1 minor), 153.1 (C-6 both), 138.2 (Ar C major), 137.4 (Ar C minor), 130.9 (Ar CH major), 130.9 (Ar CH minor), 128.2 ( Ar CH major), 128.1 (Ar CH minor), 126.7 (Ar CH major), 126.5 (Ar CH minor), 82.6 (C-7 both), 48.4 (C-5 both), 47.6 (C-2 major), 46.0 (C-2 minor), 46.0 (C-*C*$H_2$Ph major), 45.9 (C-*C*$H_2$Ph minor), 28.2 (C-4 minor), 28.2 (C-4 major), 28.1 (C-8 both) 20.0 (C-3 major), 19.9 (C-3 minor); HRMS ($ESI^+$): Found: 380.2234; $C_{24}H_{30}NO_3$ ($MH^+$) Requires: 380.2220 (−3.7 ppm error)]; A portion of the 3,3-dibenzylpiperidin-2-one **154** (6.66 g, 17.5 mmol) was next dissolved in THF (180 mL) and cooled to −78 °C. Super-Hydride™ (52.4 mL, 27.9 mmol, 1 M solution in THF) was added dropwise over 5 min and stirring continued at −78 °C for a further 30 min after the addition was complete. The excess reducing agent was quenched by the

addition of 10:1 ethanol:conc. aq. HCl (180 mL) and the resulting mixture diluted with dichloromethane (2000 mL), washed with water (1000 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was used directly to the next step without further purification; A 1:1 mixture of DCM:TFA (60 mL), that had been pre-cooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 min. The majority of the volatile organics were then quickly removed *in vacuo*, before the crude residue was dissolved in dichloromethane (1000 mL), washed with sat. aq. $NaHCO_3$ (400 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1→1:2 petrol:ethyl acetate) afforded compound **146a** as a colourless solid (2.87 g, 63%); $R_f$ 0.15 (1:1 petrol:ethyl acetate); mp 63–65 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 1645, 1602, 1493, 1453, 1265, 1194, 1059, 939; $\delta_H$ (400 MHz, $CDCl_3$) 7.73 (1H, br s, H-1), 7.31–7.20 (6H, m, ArH), 7.17–7.12 (4H, m, ArH), 3.10 (2H, td, *J* = 5.7, 2.5 Hz, H-2), 2.86 (2H, d, *J* = 13.4 Hz, C*H*HPh), 2.65 (2H, d, *J* = 13.4 Hz, CH*H*Ph), 1.58–1.54 (2H, m, H-4), 1.30–1.24 (2H, m, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 168.8 (C-1), 137.1 (Ar C), 130.4 (Ar CH), 128.1 (Ar CH), 126.4 (Ar CH), 48.9 (C-2), 45.0 (C-*C*$H_2$Ph), 42.4 (C-5), 27.2 (C-4), 18.7 (C-3); HRMS (ESI$^+$): Found: 264.1742; $C_{19}H_{22}N$ ($MH^+$) Requires: 264.1747 (2.8 ppm error).

[20% overall yield starting from *tert*-butyl 2-oxopiperidine-1-carboxylate **153**]

Lab Notebook Reference: CHK 1/2 p.4 and CHK 1/3 p.29

**4,4-Dibenzyl-3,4-dihydro-2*H*-pyrrole (146b):**



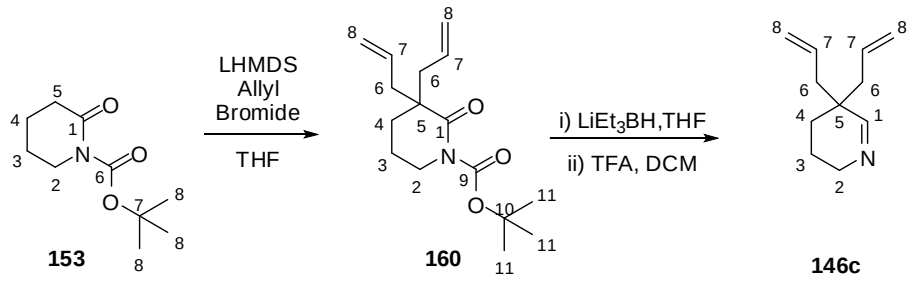

This compound was first synthesised by Dr. Will Unsworth.

The *tert*-butyl 3,3-dibenzyl-2-oxopyrrolidine-1-carboxylate **158**[42] was dissolved in THF (85 mL) and cooled to −78 °C. Super-Hydride™ (24.6 mL, 24.6 mmol, 1 M solution in THF) was added dropwise over 5 min and stirring continued at −78 °C for a further 30

min after the addition was complete. The excess reducing agent was quenched by the addition of 10:1 ethanol:conc. aq. HCl (88 mL) and the resulting mixture diluted with dichloromethane (1000 mL), washed with water (500 mL), dried over $MgSO_4$ and concentrated *in vacuo*. A 1:1 mixture of DCM:TFA (28 mL), that had been pre-cooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 min. The majority of the volatile organics were then quickly removed *in vacuo*, before the crude residue was dissolved in dichloromethane (500 mL), washed with sat. aq. $NaHCO_3$ (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 2:1→1:1 petrol:ethyl acetate) afforded compound **146b** as a colourless oil (1.60 g, 79%); $\nu_{max}$ (thin film)/$cm^{-1}$ 2980, 2956, 1600, 1578, 1472, 1432, 1081, 1194, 743, 691; $\delta_H$ (400 MHz, $CDCl_3$) 7.48 (1H, br s, H-1), 7.31–7.21 (6H, m, ArH), 7.16–7.12 (4H, m, ArH), 3.27 (td, *J* = 7.2, 2.3 Hz, H-2), 2.95 (2H, d, *J* = 13.4 Hz, C*H*HPh), 2.87 (2H, d, *J* = 13.4 Hz, CH*H*Ph), 1.77 (2H, t, *J* = 7.2 Hz, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 172.3 (C-1), 137.5 (Ar C), 130.2 (Ar CH), 128.2 (Ar CH), 126.4 (Ar CH), 60.9 (C-2), 58.7 (C-4), 43.8 (C-*C*$H_2$Ph), 31.0 (C-3); HRMS ($ESI^+$): Found: 250.1586; $C_{18}H_{20}N$ ($MH^+$) Requires: 250.1590 (0.7 ppm error).

Lab Notebook Reference: CHK 1/45 p.66

**5,5-Bis(prop-2-en-1-yl)-2,3,4,5-tetrahydropyridine (146c):**



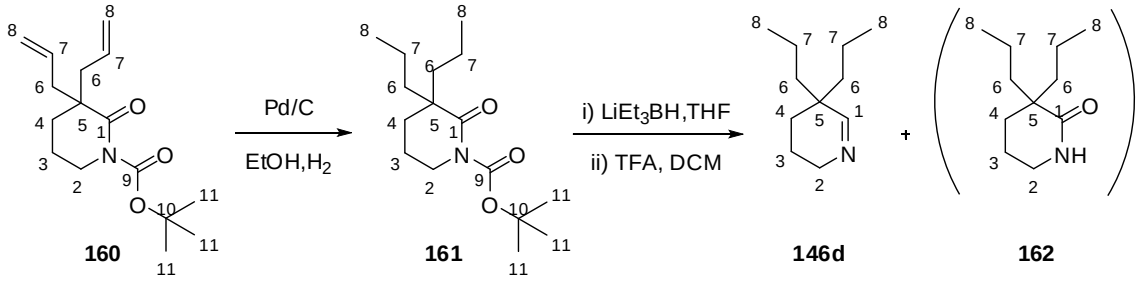

To a solution of *tert*-butyl 2-oxopiperidine-1-carboxylate **153** (6.00 g, 30.2 mmol) in THF (120 mL) at −78 °C was added LHMDS (72.36 mL, 72.36 mmol, 1 M solution in THF) and the resulting solution was stirred at −78 °C for 1 h. Allyl bromide (6.26 mL, 72.36 mmol) was then added and the mixture warmed to rt and stirred at this temperature for 2 h, before the reaction was quenched by the addition of sat. aq. $NH_4Cl$ (100 mL), extracted with ethyl acetate (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 10:1→5:1 petrol:ethyl acetate) afforded the *tert*-butyl 2-oxo-3,3-bis(prop-2-en-yl)piperidine-1-carboxylate **160** as a yellow oil (4.58 g, 54%); $R_f$ 0.51 (5:1 petrol:ethyl acetate); [$\delta_H$

(400 MHz, $CDCl_3$) 5.80–5.70 (2H, m, H-7), 5.10–5.04 (4H, m, H-8), 3.56 (2H, t, *J* = 6.3 Hz, H-2), 2.49 (2H, dddd, *J* = 13.6, 6.9, 1.1, 1.1 Hz, H-6a), 2.25 (2H, dd, 13.6, 7.9 Hz, H-6b), 1.83–1.77 (2H, m, H-4), 1.75–1.72 (2H, m, H-3), 1.50, (9H, s, H-11); $\delta_C$ (100 MHz, $CDCl_3$) 176.1 (C-1), 153.7 (C-9), 133.8 (C-7), 118.7 (C-8), 82.6 (C-10), 48.0 (C-5), 47.3 (C-2), 42.9 (C-6), 30.1 (C-4), 28.1 (C-11), 20.0 (C-3)]. A portion of the compound **160** (1.43 g, 5.13 mmol) was next dissolved in THF (50 mL) and cooled to −78 °C. Super-Hydride™ (15.4 mL, 15.4 mmol, 1 M solution in THF) was added dropwise over 5 min and stirring continued at −78 °C for a further 30 min after the addition was complete. The excess reducing agent was quenched by the addition of 10:1 ethanol:conc. aq. HCl (40 mL) and the resulting mixture diluted with dichloromethane (40 mL), washed with water (80 mL), dried over $MgSO_4$ and concentrated *in vacuo*. A 1:1 mixture of DCM:TFA (15 mL), that had been pre-cooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 min. The majority of the volatile organics were then quickly removed *in vacuo*, before the crude residue was dissolved in dichloromethane (40 mL), washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:2 petrol:ethyl acetate→pure ethyl acetate) afforded compound **146c** as a yellow oil (0.41 g, 29%); $R_f$ 0.11 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2889, 1656, 1416, 1352, 1261, 1109, 981, 902; $\delta_H$ (400 MHz, $CDCl_3$) 7.48 (1H, br s, H-1), 5.78–5.67 (2H, m, H-7), 5.10–5.03 (4H, m, H-8), 3.44–3.43 (2H, m, H-2), 2.13–2.10 (4H, m, H-6), 1.57–1.51 (4H, m, H-3,4); $\delta_C$ (100 MHz, $CDCl_3$) 168.8 (C-1), 133.3 (C-7), 118.5 (C-8), 49.2 (C-2), 42.0 (C-6), 39.4 (C-5), 28.0 (C-3/4), 18.9 (C-3/4); HRMS ($ESI^+$): Found: 164.1437; $C_{11}H_{18}N$ ($MH^+$) Requires: 164.1434 (−2.2 ppm error).

[13% overall yield starting from *tert*-butyl 2-oxopiperidine-1-carboxylate **153**]

Lab Notebook Reference: CHK 1/4 p. 14 and CHK 1/8 p.18

**5,5-Dipropyl-2,3,4,5-tetrahydropyridine (146d):**



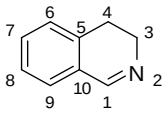

The *tert*-butyl 2-oxo-3,3-bis(prop-2-en-yl)piperidine-1-carboxylate **160** (150 mg, 0.535 mmol) was dissolved in ethanol (6 mL) and treated with Pd/C (25 mg, 5% w/w on activated carbon). The reaction mixture was then allowed to stir under a positive pressure of hydrogen (balloon) overnight at room temperature. The solution was filtered through Celite™ and concentrated under reduce pressure to give *tert*-butyl 2-oxo-3,3-dipropylpiperidine-1-carboxylate **161** as colourless oil (126 mg, 83%); [$\delta_H$ (400 MHz, $CDCl_3$) 3.58 (2H, t, *J* = 5.6 Hz, H-2), 1.82–1.76 (2H, m, H-3), 1.72–1.70 (2H, m, H-4), 1.66–1.58 (2H, m, H-6a), 1.49 (9H, s, H-11, overlapping), 1.51–1.42 (2H, m, H-6b, overlapping), 1.32–1.22 (4H, m, H-7), 0.88 (6H, m, H-8); $\delta_C$ (100 MHz, $CDCl_3$) 177.2 (C-1), 153.8 (C-9), 82.2 (C-10), 48.1 (C-2), 47.2 (C-5), 40.9 (C-4), 31.1 (C-6/7), 28.0 (C-11), 20.3 (C-6/7), 17.3 (C-3), 14.6 (C-8)]. A portion of the compound **161** (1.2 g, 4.26 mmol) was next dissolved in THF (50 mL) and cooled to −78 °C. Super-Hydride™ (12.8 mL, 12.8 mmol, 1 M solution in THF) was added dropwise over 5 min and stirring continued at −78 °C for a further 30 min after the addition was complete. The excess reducing agent was quenched by the addition of 10:1 ethanol:conc. aq. HCl (33.3 mL) and the resulting mixture diluted with dichloromethane (33.3 mL), washed with water (66.7 mL), dried over $MgSO_4$ and concentrated *in vacuo*. A 1:1 mixture of DCM:TFA (12.5 mL), that had been pre-cooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 min. The majority of the volatile organics were then quickly removed *in vacuo*, before the crude residue was dissolved in dichloromethane (33.3 mL), washed with sat. aq. $NaHCO_3$ (16.7 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:2 petrol:ethyl acetate→pure ethyl acetate) afforded an inseparable mixture 1:1 of compound **146d** and 3,3-dipropylpiperidin-2-one **162** (153 mg, 22%); $R_f$ 0.4 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1633, 1466, 1444, 1389, 1330, 1292, 1188, 1092;

5,5-Dipropyl-2,3,4,5-tetrahydropyridine (**146d**): $\delta_H$ (400 MHz, $CDCl_3$) 7.42 (1H, s, H-1), 3.42–3.39 (2H, m, H-2), 1.74–1.18 (12H, m, H-3,4,6,7), 0.87–0.83 (6H, m, H-8); $\delta_C$ (100 MHz, $CDCl_3$) 170.5 (C-1), 49.2 (C-2), 40.5 (C-3,4,6,7), 39.4 (C-5), 28.5 (C-3,4,6,7), 19.4 (C- C-3,4,6,7), 16.9 (C-3,4,6,7), 14.6 (C-8); HRMS ($ESI^+$): Found: 168.1748; $C_{11}H_{22}N$ ($MH^+$) Requires: 168.1747 (−0.8 ppm error).

3,3-Dipropylpiperidin-2-one (**162**): $\delta_H$ (400 MHz, $CDCl_3$) 6.21 (1H, br s, N*H*), 3.22–3.19 (2H, m, H-2), 1.74–1.18 (12H, m, H-3,4,6,7), 0.87–0.83 (6H, m, H-8); $\delta_C$ (100 MHz, $CDCl_3$) 177.4 (C-1), 44.6 (C-5), 42.6 (C-2), 41.1 (C-3,4,6,7), 29.6 (C-3,4,6,7), 20.0 (C-3,4,6,7), 17.4 (C-3,4,6,7), 14.8 (C-8). Obtained data in accord with those reported in the literature.[163]

Lab Notebook Reference: CHK 1/7 p.13 and CHK 1/10 p.22

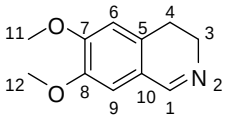
**3,4-Dihydroisoquinoline (146e):**[43]




To a stirred solution of 1,2,3,4-tetrahydroisoquinoline **163** (10.2 g, 76.6 mmol) in dichloromethane (150 mL) was added slowly *N*-bromosuccinimide (15.0 g, 84.3 mmol) under ice-cooling. After stirring for 30 min, 30% NaOH (50 mL) was added to the reaction mixture. The resulting solution was stirred at rt for 1 h. Water (150 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **146e** as an orange oil (6.81 g, 70%); $R_f$ 0.29 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, t, *J* = 2.2 Hz, H-1), 7.36 (1H, ddd, *J* = 7.2, 7.2, 1.8 Hz, H-7/8), 7.32–7.26 (2H, m, ArH), 7.16 (1 H, d, *J* = 7.2 Hz H-6/9), 3.78 (2H, td, *J* = 8.1, 2.2 Hz, H-3), 2.75 (2H, t, *J* = 8.1 Hz, H-4), $\delta_C$ (100 MHz, $CDCl_3$) 160.1 (C-1), 136.1 (C-10), 130.9 (C-8), 128.3 (C-5), 127.2 (C-9), 126.9 (C-6/7), 127.0 (C-6/7), 47.2 (C-3), 24.8 (C-4). Obtained data in accord with those reported in the literature.[164]

Lab Notebook Reference: CHK 1/35 p.53

**6,7-Dimethoxy-3,4-dihydroisoquinoline (146f):**[43]

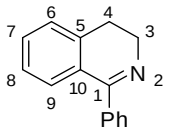



To a solution 6,7-dimethythoxy-1,2,3,4-tetrahydroisoquinoline **164** (105mg, 0.545 mmol) in dichloromethane (2.43 mL) at 0 °C is added *N*-bromosuccinimide (107 mg, 0.600 mmol). After stirring for 30 mins at 0 °C, 30% aq. NaOH (1 mL) is added and the mixture is stirred for an additional 60 mins at rt. The organic layer is separated, washed with water (1.2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, pure ethyl acetate→ethyl acetate, 5% MeOH) afforded compound **146f** as a brown oil (64.0 mg, 61%); $R_f$ 0.29 (9:1 ethyl acetate: MeOH); $\delta_H$ (400 MHz, $CDCl_3$) 8.22 (1H, s, H-1), 6.80 (1H, s, H-6/9), 6.66 (1H, s, H-6/9), 3.90 (3H, s, H-11/12), 3.88 (3H, s, H-11/12), 3.71 (2H, t, *J* = 7.7 Hz, H-3), 2.67

(2H, t, $J$ = 7.7 Hz, H-4); HRMS ($ESI^+$): Found: 192.1026; $C_{11}H_{14}NO_2$ ($MH^+$) Requires: 192.1019 (−3.1 ppm error). Obtained data in accord with those reported in the literature.[165]

Lab Notebook Reference: CHK 2/117 p.170

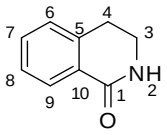
**1-Phenyl-3,4-dihydroisoquinoline (146g):**[44]




Trifluoromethanesulfonic anhydride (3.63 mL, 21.2 mmol) was added via syringe over 1 min to a stirred mixture of amide **166**[42] (3.38 g, 19.2 mmol) and 2-chloropyridine (2.18 mL, 23.1 mmol) in dichloromethane (100 mL) at −78 °C. After 5 min, the reaction mixture allowed to warm slowly to rt. The reaction vessel was placed into a preheated oil bath at 45 °C and maintained at that temperature for 2 h. Then the reaction mixture was allowed to cool to rt and was diluted with dichloromethane (50 mL). Then aq. NaOH (60 mL, 1 M) was introduced to neutralize the trifluoromethanesulfonate salts and the layers were separated. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 2:1 petrol:ethyl acetate→1:1 petrol:ethyl acetate) afforded compound **146g** as an orange oil. (2.12 g, 70%); $R_f$ 0.31 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 7.62–7.59 (2H, m, ArH), 7.44–7.35 (4H, m, ArH), 7.28–7.20 (3H, m, ArH), 3.87–3.83 (2H, m, H-3), 2.78–2.71 (2H, m, H-4), $\delta_C$ (100 MHz, $CDCl_3$) 167.0 (C-1), 138.8 (Ar C), 138.6 (Ar C), 130.4 (Ar CH), 129.1 (Ar CH), 128.6 (Ar CH), 128.5 (Ar C), 127.9 (Ar CH), 127.7 (Ar CH), 127.2 (Ar CH), 126.4 (Ar CH), 47.4 (C-3), 26.1 (C-4). Obtained data in accord with those reported in the literature.[44]

Lab Notebook Reference: CHK 1/27 p.44

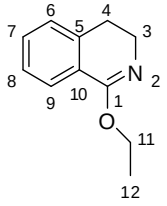
**1,2,3,4-Tetrahydroisoquinolin-1-one (167):**[46]




An aqueous solution of $NaH_2PO_4$ (1.54 mL, 1.54 mmol, 1.0 M) was added to a solution of $NaClO_2$ (464 mg, 5.13 mmol) in THF (4.0 mL). To the resulting pale yellow solution, was added a solution of imine **146e** (134 mg, 1.02 mmol) in THF (1.6 mL) dropwise over 5–10 min. The mixture was vigorously stirred for 5 mins. Then, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (30 mL), 10% $Na_2S_2O_3$ (10 mL) and brine (10 mL). The organic layer was dried over $Mg_2SO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→ethyl acetate→ethyl acetate, 5% MeOH) afforded compound **167** as a colourless solid (94.9 mg, 63%); $R_f$ 0.11 (1:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* = 7.6 Hz, H-6/9), 7.77 (1H, br s, N*H*), 7.34 (1 H, dd, *J* = 7.6, 7.6 Hz, H-7/8), 7.25 (1 H, dd, *J* = 7.6, 7.6 Hz, H-7/8), 7.11 (1 H, d, *J* = 7.6 Hz, H-6/9), 3.47 (2H, td, *J* = 6.4, 2.9 Hz, H-3), 2.88 (2H, t, *J* = 6.4 Hz, H-4); HRMS ($ESI^+$): Found: 148.0759; $C_9H_{10}NO$ ($MH^+$) Requires: 148.0757 (−1.3 ppm error). Obtained data in accord with those reported in the literature.[46]

Lab Notebook Reference: CHK 2/96 p.144

**1-Ethoxy-3,4-dihydroisoquinoline (146h):**[45]

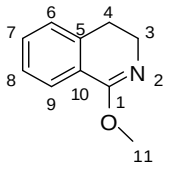



To a solution of 1,2,3,4-tetrahydroisoquinolin-1-one **167** (90.3 mg, 0.614 mmol) in dichloromethane (7.57 mL) was added triethyloxonium tetrafluoroborate (272 mg, 1.84 mmol), $K_2CO_3$ (339 mg, 2.45 mmol) and 4 Å MS (313 mg). The mixture was stirred at rt for 1 h. The organic layer was diluted in ethyl acetate (10 mL), washed with sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **146h** as colourless oil (80.6 mg, 75%). Compound **146h** was used without further purification; $\delta_H$ (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* = 7.6 Hz H-6/9), 7.31–7.26 (1H, m,

H-7/8), 7.21–7.18 (1H, m, H-7/8), 7.11 (1H, d, *J* = 7.4 Hz, H-6/9), 4.18 (2H, q, *J* = 7.1 Hz, H-11), 3.57 (2H, t, *J* = 7.0 Hz, H-3), 2.68 (2H, t, *J* = 7.0 Hz, H-4), 1.31 (3H, t, *J* = 7.1 Hz, H-12). The salt of this compound with methyl-hydrogen sulphate is known, but no spectroscopic data was reported.[166]

Lab Notebook Reference: CHK 2/97 p.146

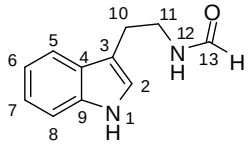
**1-Methoxy-3,4-dihydroisoquinoline (146i):**[45]




To a solution of 1,2,3,4-tetrahydroisoquinolin-1-one **167** (534 mg, 3.62 mmol) in dichloromethane (45 mL) was added trimethyloxonium tetrafluoroborate (1.14 g, 7.71 mmol), $K_2CO_3$ (2.00 g, 14.5 mmol) and 4 Å MS (1.85 g). The mixture was stirred at rt for 1 h. The organic layer was diluted in ethyl acetate (50 mL), washed with sat. aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide 484 mg of crude material. Purification by column chromatography ($SiO_2$, 2:1 petrol:ethyl acetate→ethyl acetate) afforded compound **146i** as a yellow oil (277 mg, 47%); $R_f$ 0.34 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 7.59 (1H, d, *J* = 7.6 Hz, H-6/9), 7.30–7.27 (1H, m, H-7/8), 7.22–7.18 (1H, m, H-7/8), 7.11 (1H, d, *J* = 7.5 Hz, H-6/9), 3.78 (1H, s, H-11), 3.59 (2H, t, *J* = 7.1 Hz, H-3), 2.69 (2H, t, *J* = 7.1 Hz, H-4). This compound has been reported previously in the literature, but no data was reported.[45]

Lab Notebook Reference: CHK 2/99 p.150

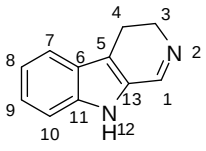
***N*-[2-(1*H*-Indol-3-yl)ethyl]formamide (170):**[48]



A solution of tryptamine **169** (2 g, 12.5 mol) in ethyl formate (15.9 mL, 0.198 mol) was heated at reflux for 24 h. The solvent was evaporated under reduced pressure to give compound **170** as a brown oil (2.46 g, quantitative); $R_f$ 0.5 (ethyl acetate, 10 % MeOH); [$\delta_H$ (400 MHz, DMSO-$d_6$) 10.84 (1H, br s, H-13), 8.10 (1H, br s, N*H*), 8.03 (1H, br s, N*H*), 7.54 (1H, d, *J* = 7.9, 1.1 Hz, H-5/8), 7.35 (1H, dd, *J* = 8.1, 1.0 Hz, H-5/8), 7.17 (1H, d, *J* = 2.3 Hz, H-2), 7.07 (1 H, ddd, *J* = 8.1, 7.0, 1.1 Hz, H-6/7), 6.99 (1H, ddd, *J* = 7.9, 7.0, 1.0 Hz, H-6/7), 3.42–3.46 (2H, m, H-11), 2.85 (2H, t, *J* = 7.2 Hz, H-10); $\delta_C$ (100 MHz, DMSO-$d_6$) 161.0 (C-13), 136.2 (C-4/9), 127.1 (C-4/9), 122.7 (C-2), 120.9 (C-6/7), 118.2 (C-6/7), 118.2 (C-5/8), 111.5 (C-3), 111.3 (C-5/8), 38.0 (C-11), 25.1 (C-10). Obtained data in accord with those reported in the literature.[48]

Lab Notebook Reference: CHK 2/91 p.137.

**3*H*, 4*H*, 9*H*-Pyrido[3,4-b]indole (146j):**



**Procedure A:**[47]

IBX (95.5 mg, 0.341 mmol) was dissolved in DMSO (0.5 mL) with vigorous stirring for 30 min at rt. This IBX solution was then added to a solution of amine **168** (53.4 mg, 0.310 mmol) in DMSO (0.5 mL) and allowed to stir at rt for 20 min. The mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ (1 mL) and then basified with saturated aq. $NaHCO_3$ (1 mL). Following extraction with ethyl acetate (5 mL), the organic phase was washed with water (2 × 10 mL) and brine (10 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, DCM, 1% MeOH→DCM, 2% MeOH→DCM, 5% MeOH→DCM, 10% MeOH) afforded compound **146j** as an orange solid (580 mg, 32%); $R_f$ 0.51 (5:1 DCM:MeOH).

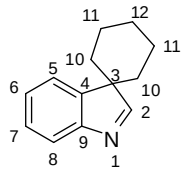
**Procedure B:**[49]

*N*-[2-(1*H*-Indol-3-yl)ethyl]formamide **170** (1.85 g, 9.84 mmol) was added in small portions with rapid stirring under argon, in phosphorus oxychloride (5.00 mL, 53.2 mmol). The reaction mixture was kept at rt by means of an ice-water bath. Stirring was continued until complete disappearance of the starting material (60 min). The bright yellow suspension was slowly poured into anhydrous diethyl ether with rapid stirring (30 mL). The hydrochloride salt of compound **146j** which precipitated was then collected by filtration and washed several times with ether. Recrystallization of the solid in a mixture of ethyl acetate and 95% ethanol afforded the pure salt of compound **146j**. The latter was dissolved in water (50 mL) and the solution was made basic by slow addition of aq. NaOH (1 M), leading to precipitation of compound **146j**. The mixture was extracted with ether (3 × 50 mL), the organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure, leaving compound **146j** as a pale yellow amorphous solid (757 mg, 45%); $R_f$ 0.09 (ethyl acetate).

$\delta_H$ (400 MHz, DMSO-$d_6$) 8.36 (1 H, t, *J* = 2.3 Hz, H-1), 7.56 (1H, dd, *J* = 7.9, 1.1 Hz, H-7/10 ), 7.40 (1 H, dd, *J* = 8.2, 0.8 Hz, H-7/10), 7.19 (1H, ddd, *J* = 8.2, 7.0, 1.1 Hz, H-8/9), 7.04 (1 H, ddd, *J* = 7.9, 7.0, 0.8 Hz, H-8/9), 3.78 (2 H, td, *J* = 8.6, 2.3 Hz, H-3), 2.80 (2 H, t, *J* = 8.6 Hz, H-4). Obtained data in accord with those reported in the literature.[47]

Lab Notebook Reference: CHK 1/38 p.59 (Procedure A) and CHK 2/94 p.145 (Procedure B)

**Spiro[cyclohexane-1,3'-indole] (146k):**[50]

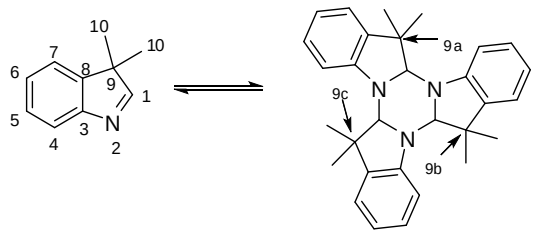



A mixture of phenylhydrazine **171** (0.165 mL, 1.68 mmol) and cyclohexanecarbaldehyde **172** (0.205 mL, 1.68 mmol) in AcOH (16.8 mL) was stirred at 60 °C for 30 min. The solvent was removed *in vacuo*. Purification by column chromatography ($SiO_2$, pure petrol→10:1 petrol: ethyl acetate) afforded compound **146k** as a brown solid (258 mg, 83%); $R_f$ 0.14 (9:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 8.36 (1H,

s, H-2), 7.64 (1H, dd, *J* = 7.5, 1.1 Hz, H-8/5), 7.39 (1H, dd, *J* = 7.5, 1.3 Hz, H-5/8), 7.33 (1 H, ddd, *J* = 7.5, 7.5, 1.3 Hz, H-6/7), 7.24 (1H, ddd, *J* = 7.5, 7.5, 1.1 Hz, H-6/7), 1.93–1.55 (10H, m, H-10,11,12 ); HRMS ($ESI^+$): Found: 186.1269; $C_{13}H_{16}N$ ($MH^+$) Requires: 186.1277 (3.7 ppm error). Obtained data in accord with those reported in literature.[167]

Lab Notebook Reference: CHK 2/115 p.168

**3,3-Dimethyl-3*H*-indole (146l):**[50,51]




**146l** **146l′**

A mixture of phenylhydrazine **171** (0.496 mL, 5.04 mmol) and isobutyraldehyde **173** (0.458 mL, 5.04 mmol) in AcOH (50.4 mL, 0.880 mol) was stirred at 60 °C for 30 min. The solvent was removed *in vacuo*. Purification by column chromatography ($SiO_2$, pure petrol→19:1→10:1 petrol:ethyl acetate) afforded compound **146l** as a yellow solid (437 mg, 60%); $R_f$ 0.23 (5:2 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2917, 2818, 1493, 1578, 1454, 1432, 1367, 1253, 895, 729; $\delta_H$ (400 MHz, $CDCl_3$) (The NMR spectrum is complex since compound **146l** is present in the monomeric form as well as in the trimer form **146l′**, in ratio 2.5:1).

Monomer **146l**: $\delta_H$ (400 MHz, $CDCl_3$) 8.03 (1H, s, H-1), 7.65–7.62 (1H, m, ArH), 7.36–7.32 (2H, m, ArH), 7.29–7.25 (1H, m, ArH), 1.37 (6H, s, H-10); $\delta_C$ (100 MHz, $CDCl_3$) 180.1 (C-1), 154.2 (C-3/8), 144.8 (C-3/8), 127.6 (Ar CH), 126.2 (Ar CH), 121.1 (Ar CH), 121.1 (Ar CH), 53.5 (C-9) 21.6 (C-10).

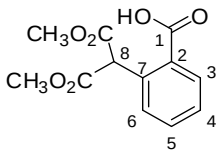
Trimer **146l′**: $\delta_H$ (400 MHz, $CDCl_3$) 7.21–7.15 (2H, m, ArH), 7.10–6.99 (3 H, m, ArH), 6.87 (1H, ddd, *J* = 7.5, 7.5, 0.9 Hz, ArH), 6.78 (1H, ddd, *J* = 7.4, 7.4, 0.9 Hz, ArH), 6.66 (1H, ddd, *J* = 7.4, 7.4, 0.9 Hz, ArH), 6.56 (1H, ddd, *J* = 7.4, 8.2, 1.5 Hz, ArH), 6.49 (1H, d, *J* = 8.0 Hz, ArH), 6.22 (1H, d, *J* = 7.8 Hz, ArH), 5.66 (1H, d, *J* = 8.0 Hz, ArH), 4.95 (1H, s, PhNC*H*N), 4.46 (1H, s, PhNC*H*N), 4.26 (1H, s, PhNC*H*N), 1.64 (3H, s, C*H*$_3$), 1.40 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.33 (6H, s, 2x C*H*$_3$), 1.24 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 150.5 (Ar C), 148.6 (Ar C), 145.8 (Ar C), 140.8 (Ar C), 138.3

(Ar C), 137.0 (Ar C), 129.3 (Ar CH), 127.3 (Ar CH), 126.4 (Ar CH), 123.6 (Ar CH), 122.2 (Ar CH), 120.8 (Ar CH), 119.5 (Ar CH), 119.0 (Ar CH), 117.7 (Ar CH), 115.0 (Ar CH), 107.1 (Ar CH), 105.1 (Ar CH), 88.8 (PhN*C*HN), 86.9 (Ph-N*C*HN), 83.0 (PhN*C*HN), 47.2 (C-9a/b/c), 44.1 (C-9a/b/c), 42.9 (C-9a/b/c), 31.7 (C-*CH*$_3$), 29.7 (C-*CH*$_3$), 28.4 (C-*CH*$_3$), 23.6 (C-*CH*$_3$), 21.5 (C-*CH*$_3$), 20.0 (C-*CH*$_3$); HRMS (ESI$^+$): Found: 146.0964; $C_{10}H_{12}N$ ($MH^+$) Requires: 146.0964 (−0.1 ppm error).

These compounds have been reported previously in the literature, but no spectroscopic data were reported.[50,51]

Lab Notebook Reference: CHK 2/120 p.175

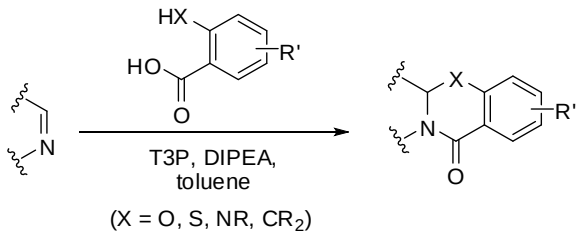
**2-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)benzoic acid (147p):**[52]




Sodium hydride (2.40 g, 60.0 mmol, 60 % in mineral oil) was added portionwise to a rapidly stirred cold suspension (0 °C) of 2-bromobenzoic acid (5.05 g, 25.1 mmol), copper bromide (360 mg, 2.51 mmol) and dimethyl malonate (50.2 mL). After the addition of the sodium hydride had been completed, the mixture was stirred for 10 min at rt and then for 1.5 h at 70 °C. The suspension, which had turned to a solid mass, was dissolved in water (50 mL), washed with ether (3 × 50 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 8:1→1:1→1:2 petrol:ethyl acetate) afforded compound **147p** as a white solid (5.80 g, 92%); $R_f$ 0.7 (2:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 8.15 (1H, d, *J* = 7.9 Hz, H-3/6), 7.61 (1H, ddd, *J* = 7.6, 7.6, 1.5 Hz, H-4/5), 7.48–7.44 (2H, m, H-3/6, 4/5), 5.83 (1H, s, H-8), 3.79 (6H, s, $CO_2C*H*_3$); HRMS (ESI$^+$): Found: 275.0526 $C_{12}H_{12}NaO_6$ ($MNa^+$) Requires: 275.0526 (−0.1 ppm error). Obtained data in accord with those reported in the literature.[147]

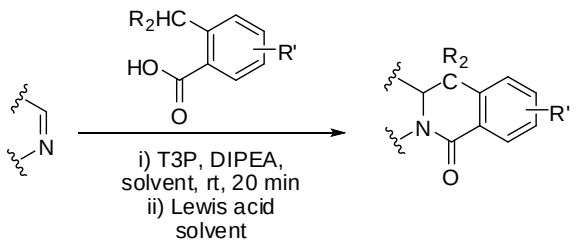
Lab Notebook Reference: CHK 4.247 p.51

**General DIA procedure A:**



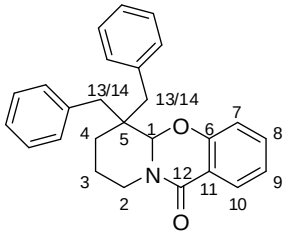

To a solution of imine (1 mmol) and acid (1.2 mmol) in dry toluene (10 mL) was added sequentially DIPEA (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was heated at either 50 °C, 90 °C or 120 °C in a sealable tube for the specified time, before cooling to rt and pouring into sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL), concentrated *in vacuo* and purified by column chromatography.

**General DIA procedure B:**




To a solution of imine (1 mmol) and acid (1.2 mmol) in chloroform (10 mL) was added sequentially DIPEA (1.85 mmol) and T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at rt in a sealable tube for 20 min before adding a Lewis acid ($BF_3{\cdot}Et_2O$ or $AlCl_3$ or $BCl_3$) (2 mmol) and stirred at rt or 50 °C for the specified time. The reaction mixture was poured into sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with dichloromethane (for $BF_3{\cdot}Et_2O$ and $BCl_3$) or ethyl acetate (for $AlCl_3$) (3 × 30 mL). The combined organic extracts were washed with brine (for $AlCl_3$), concentrated *in vacuo* and purified by column chromatography.

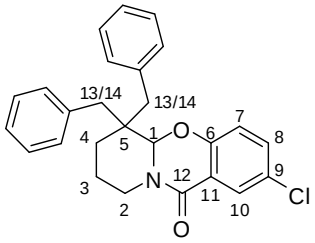
**6,6-Dibenzyl-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzoxazin-11-one (149a):**




Synthesised using general DIA procedure A from imine **146a** (45.0 mg, 0.171 mmol), acid **147a** (28.3 mg, 0.205 mmol), DIPEA (55.0 μL, 0.316 mmol) and T3P (163 mg, 0.256 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded cmpound **149a** as a colourless oil (54.5 mg, 83%); $R_f$ 0.29 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1640, 1588, 1448, 1310, 1212, 1053, 896, 742; $\delta_H$ (400 MHz, $CDCl_3$) 7.94 (1H, dd, *J* = 7.7, 1.7 Hz, H-10), 7.49 (1H, ddd, *J* = 8.3, 7.3, 1.7 Hz, H-8), 7.35–7.05 (12H, m, ArH, H-7,9), 5.09 (1H, s, H-1), 4.71–4.64 (1H, m, H-2eq), 3.23 (1H, d, *J* = 13.4 Hz, C*H*HPh-13), 3.22 (1H, d, *J* = 13.7 Hz, C*H*HPh-14), 2.91 (1H, d, *J* = 13.7 Hz, CH*H*Ph-14), 2.48–2.40 (2H, m, H-2ax, CH*H*Ph-13), 2.19–2.05 (1H, m, H-3a), 1.64–1.56 (2H, m, H-3b,4a), 1.42–1.32 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 162.6 (C-12), 156.1 (C-6), 137.2 (Ar C), 136.4 (Ar C), 134.3 (C-8), 131.1 (Ar CH), 131.1 (C-10), 128.1 (Ar CH), 126.5 (Ar CH), 122.0 (C-7/9), 116.1 (C-11), 115.7 (C-7/9), 89.2 (C-1), 42.4 (C-5), 41.8 (C-2), 41.4 (C-13), 35.8 (C-14), 27.6 (C-4), 19.6 (C-3); HRMS ($ESI^+$): Found: 384.1940 (3.5 ppm error); $C_{26}H_{26}NO_2$ ($MH^+$) Requires: 384.1958 Found: 348.1940 (4.6 ppm error).

Lab Notebook Reference: CHK 1/16 p.32

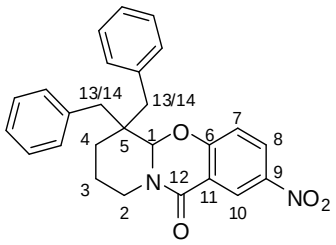
**6,6-Dibenzyl-2-chloro-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzoxazin-11-one (149b):**




Synthesised using general DIA procedure A from imine **146a** (66.9 mg, 0.254 mmol), acid **147b** (52.6 mg, 0.305 mmol), DIPEA (81.9 μL, 0.470 mmol) and T3P (242 mg, 0.381 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded compound **149b** as a white solid (46.7 mg, 96%); mp 198–201 °C; $R_f$ 0.29 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1668, 1608, 1475, 1441, 1325, 1283, 704; $\delta_H$ (400 MHz, $CDCl_3$) 7.90 (1H, d, *J* = 2.7 Hz, H-10), 7.42 (1H, dd, *J* = 8.8, 2.7 Hz, H-8), 7.34–7.20 (9H, m, ArH), 7.11–7.09 (1H, m, ArH), 7.05 (1H, d, *J* = 8.8 Hz, H-7), 5.09 (1H, s, H-1), 4.68–4.62 (1H, m, H-2eq), 3.21–3.16 (2H, m, C*H*HPh-13, C*H*HPh-14), 2.86 (1H, d, *J* = 13.5 Hz, CH*H*Ph-14), 2.49–2.40 (2H, m, H-2ax, CH*H*Ph-13), 2.18–2.04 (1H, m, H-3a), 1.65–1.56 (2H, m, H-3b,4a), 1.42–1.31 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 161.4 (C-12), 154.5 (C-6), 137.0 (Ar C), 136.3 (Ar C), 134.2 (C-8), 131.0 (Ar CH), 131.0 (Ar CH), 128.1 (Ar CH), 128.1 (Ar CH), 127.7 (C-10) 127.3 (C-9), 126.6 (Ar CH), 126.6 (Ar CH), 117.3 (C-11), 117.2 (C-7), 89.5 (C-1), 42.5 (C-2), 42.0 (C-13), 41.4 (C-5), 35.8 (C-14), 27.6 (C-4), 19.5 (C-3); HRMS ($ESI^+$): Found: 418.1585; $C_{26}H_{25}{}^{35}ClNO_2$ ($MH^+$) Requires: 418.1568 (−3.9 ppm error).

Lab Notebook Reference: CHK 1/5 p.9

**6,6-Dibenzyl-2-nitro-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzoxazin-11-one (149c) :**



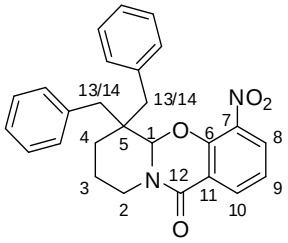

Synthesised using general DIA procedure A from imine **146a** (37.0 mg, 0.141 mmol), acid **147c** (30.9 mg, 0.169 mmol), DIPEA (45.5 μL, 0.261 mmol) and T3P (135 mg, 0.212 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149c** as a colourless oil (55.0 mg, 91%).

Also synthesised using general DIA procedure A from imine **146a** (33.0 mg, 0.125 mmol), acid **147c** (27.6 mg, 0.150 mmol), DIPEA (40.3 μL, 0.231 mmol) and T3P (119 mg, 0.188 mmol) in toluene (1.3 mL) at 50 °C for 2 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149c** as a colourless oil (51.0 mg, 95%).

$R_f$ 0.8 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1646, 1597, 1571, 1503, 1459, 1426, 1321, 1268, 693; $\delta_H$ (400 MHz, $CDCl_3$) 8.83 (1H, d, *J* = 2.8 Hz, H-10), 8.36 (1H, dd, *J* = 9.2, 2.8 Hz, H-8), 7.35–7.19 (9H, m, ArH), 7.14–7.10 (2H, m, H-7, ArH), 5.26 (1H, s, H-1), 4.76–4.70 (1H, m, H-2eq), 3.18 (1H, d, *J* = 13.5 Hz, C*H*HPh-13, overlapping), 3.17 (1H, d, *J* = 13.5 Hz, C*H*HPh-14, overlapping), 2.78 (1H, d, *J* = 13.5 Hz, CH*H*Ph-14), 2.52–2.43 (2H, m, H-2ax, CH*H*Ph-13), 2.17–2.04 (1H, m, H-3a), 1.68–1.58 (2H, m, H-3b,4a), 1.47–1.35 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 160.4 (C-12), 159.5 (C-6), 142.5 (C-9), 136.3 (Ar C), 135.9 (Ar C), 130.9 (Ar CH) , 131.0 (Ar CH), 129.5 (C-8), 128.3 (Ar CH), 128.2 (Ar CH), 126.8 (Ar CH), 126.7 (Ar CH), 124.6 (C-10), 116.7 (C-7), 115.8 (C-11), 90.4 (C-1), 43.0 (C-5), 42.2 (C-2), 41.3 (C-13), 35.6 (C-14), 27.8 (C-4), 19.6 (C-3); HRMS ($ESI^+$): Found: 429.1817; $C_{26}H_{25}N_2O_4$ ($MH^+$) Requires: 429.1809 (−1.8 ppm error).

Lab Notebook Reference: CHK 1/55 and CHK/WPU 1241

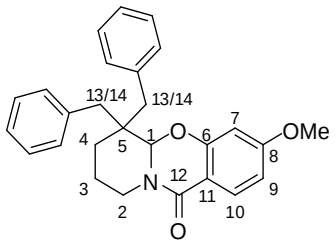
**6,6-Dibenzyl-4-nitro-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzoxazin-11-one (149d):**




Synthesised using general DIA procedure A from imine **146a** (56.1 mg, 0.213 mmol), acid **147d** (46.9 mg, 0.256 mmol), DIPEA (68.6 μL, 0.394 mmol) and T3P (204 mg, 0.320 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded compound **149d** as a colourless oil (81.1 mg, 89%); $R_f$ 0.43 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1647, 1589, 1506, 1449, 1311, 1275; $\delta_H$ (400 MHz, $CDCl_3$) 8.24 (1H, dd, *J* = 7.7, 1.7 Hz, H-10), 8.19 (1H, dd, *J* = 8.2, 1.7 Hz, H-8), 7.34–7.13 (11H, m, H-9, ArH), 5.31 (1H, s, H-1), 4.75–4.68 (1H, m, H-2eq), 3.35 (1H, d, *J* = 13.4 Hz, C*H*HPh-13), 3.17 (1H, d, *J* = 13.4 Hz, C*H*HPh-14), 2.85 (1H, d, *J* = 13.4 Hz, CH*H*Ph-14), 2.53–2.42 (2H, m, H-2ax, CH*H*Ph-13), 2.18–2.05 (1H, m, H-3a), 1.68–1.59 (2H, m, H-3b,4a), 1.50–1.40 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 159.4 (C-12), 150.2 (C-6), 137.0 (C-7), 136.4 (Ar C), 136.1 (Ar C), 133.7 (C-10), 131.2 (Ar CH), 131.0 (Ar CH), 130.2 (C-8), 128.2 (Ar CH), 126.6 (Ar CH), 121.0 (C-9), 118.2 (C-11), 90.6 (C-1), 43.2 (C-2), 42.2 (C-13), 40.9 (C-5), 35.6 (C-14), 27.6 (C-4), 19.6 (C-3); HRMS ($ESI^+$): Found: 429.1827; $C_{26}H_{25}N_2O_4$ ($MH^+$) Requires: 429.1809 (−4.3 ppm error).

Lab Notebook Reference: CHK 1/11 p.23

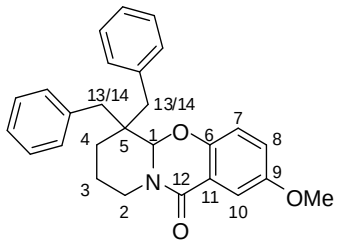
**6,6-Dibenzyl-3-methoxy-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3] benzoxazin-11-one (149e):**




Synthesised using general DIA procedure A from imine **146a** (31.2 mg, 0.118 mmol), acid **147e** (23.9 mg, 0.142 mmol), DIPEA (38.0 μL, 0.219 mmol) and T3P (113 mg, 0.178 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **149e** as a white solid (40.0 mg, 82%); mp 158–162 °C; $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1635, 1593, 1562, 1473, 1423, 1381, 1352, 1257, 1181; $\delta_H$ (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* = 8.6 Hz, H-10), 7.34–7.19 (8H, m, ArH), 7.13–7.09 (2H, m, ArH), 6.63–6.56 (2H, m, H-7,9), 5.06 (1H, s, H-1), 4.67–4.60 (1H, m, H-2eq), 3.90 (3H, s, OMe) 3.24–3.19 (2H, m, C*H*HPh-13,14), 2.89 (1H, d, *J* = 13.7 Hz, CH*H*Ph-14 ), 2.45–2.37 (2H, m, H-2ax, CH*H*Ph-13), 2.16–2.03 (1H, m, H-3a), 1.63–1.54 (2H, m, H-3b,4a), 1.42–1.28 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 164.8 (C-12), 163.0 (C-8), 157.8 (C-6), 137.5 (Ar C), 136.6 (Ar C), 131.2 (Ar CH), 131.2 (Ar CH), 129.7 (C-10), 128.2 (Ar CH), 128.2 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 109.5 (C-11), 109.0 (C-7/9), 100.2 (C-7/9), 89.5 (C-1), 55.8 (C-OMe), 42.5 (C-2), 41.8 (C-13), 41.5 (C-5), 35.9 (C-14), 27.8 (C-4), 19.8 (C-3); HRMS ($ESI^+$): Found: 414.2076; $C_{27}H_{28}NO_3$ ($MH^+$) Requires: 414.2064 (−2.9 ppm error).

Lab Notebook Reference: CHK 1/42 p.77

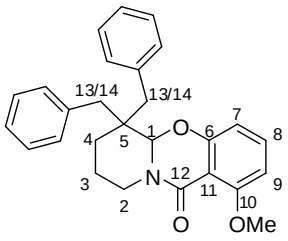
**6,6-Dibenzyl-2-methoxy-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3] benzoxazin-11-one (149f):**




Synthesised using general DIA procedure A from imine **146a** (37.0 mg, 0.141 mmol), acid **147f** (28.4 mg, 0.169 mmol), DIPEA (45.5 μL, 0.261 mmol) and T3P (135 mg, 0.212 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149f** as a colourless solid (35.0 mg, 60%). mp 108–109 °C; $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1471, 1447, 1431, 1413, 1375, 1309, 1264, 1193, 692; $\delta_H$ (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* = 2.6 Hz, H-10), 7.33–7.16 (8H, m, ArH), 7.11–7.02 (4H, m, ArH), 5.01 (1H, s, H-1), 4.67–4.60 (1H, m, H-2eq), 3.81 (3H, s, OMe) 3.22–3.18 (2H, m, C*H*HPh-13,14), 2.92 (1H, d, *J* = 13.9 Hz, CH*H*Ph-14), 2.48–2.40 (2H, m, H-2ax, CH*H*Ph-13), 2.17–2.05 (1H, m, H-3a), 1.66–1.55 (2H, m, H-3b,4a), 1.38–1.28 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 163.1 (C-12), 154.6 (C-6), 150.2 (C-9), 137.3 (Ar C), 136.5 (Ar C), 131.1 (Ar CH), 131.0 (Ar CH), 128.1 (Ar CH), 126.4 (Ar CH), 126.4 (Ar CH), 122.4 (C-7/8), 116.9 (C-7/8), 116.5 (C-11), 109.9 (C-10), 89.1 (C-1), 55.9 (C-OMe), 42.2 (C-5), 41.9 (C-1), 41.5 (C-13), 35.9 (C-14), 27.6 (C-4), 19.5 (C-3); HRMS ($ESI^+$): Found: 414.2074; $C_{27}H_{28}NO_3$ ($MH^+$) Requires: 414.2064. (−0.6 ppm error).

Lab Notebook Reference: CHK/WPU 125

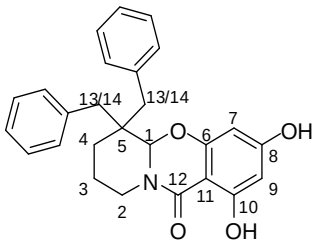
**6,6-Dibenzyl-1-methoxy-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3] benzoxazin-11-one (149g):**




Synthesised using general DIA procedure A from imine **146a** (50.1 mg, 0.190 mmol), acid **147g** (38.3 mg, 0.228 mmol), DIPEA (61.3 μL, 0.352 mmol) and T3P (182 mg, 0.286 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **149g** as a white solid (51 mg, 64%); mp 186–187 °C; $R_f$ 0.29 (1:1 ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1581, 1560, 1457, 1432, 1248, 1090; $\delta_H$ (400 MHz, $CDCl_3$) 7.37 (1H, dd, *J* = 8.3, 8.3 Hz, H-8), 7.03-7.14 (8H, m, ArH), 7.10–7.05 (2H, m, ArH), 6.72 (1H, d, *J* = 8.3 Hz, H-7/9), 6.60 (1H, d, *J* = 8.3 Hz, H-7/9), 4.95 (1H, s, H-1), 4.67–4.60 (1H, m, H-2eq), 3.91 (3H, s, OMe) 3.23 (1H, d, *J* = 13.8 Hz, C*H*HPh-13), 3.19 (1H, d, *J* = 13.4 Hz, C*H*HPh-14), 2.90 (1H, d, *J* = 13.8 Hz, CH*H*Ph-13), 2.47–2.37 (2H, m, H-2ax, CH*H*Ph-14), 2.17–2.04 (1H, m, H-3a), 1.65–1.53 (2H, m, H-3b,4a), 1.35–1.24 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 162.1 (C-12), 160.7 (C-10), 158.3 (C-6), 137.5 (Ar C), 136.6 (Ar C) , 134.3 (C-8), 131.1 (Ar CH), 128.1 (Ar CH), 126.4 (Ar CH), 126.3 (Ar CH), 108.4 (C-7/9), 109.5 (C-11), 105.4 (C-7/9), 88.4 (C-1), 56.3 (C-OMe), 42.0 (C-5), 41.5 (C-2), 41.4 (C-14), 36.0 (C-13), 27.5 (C-4), 19.6 (C-3); HRMS ($ESI^+$): Found: 414.2075; $C_{27}H_{28}NO_3$ ($MH^+$) Requires: 414.2064 (−2.8 ppm error).

Lab Notebook Reference: CHK 1/15 p.28

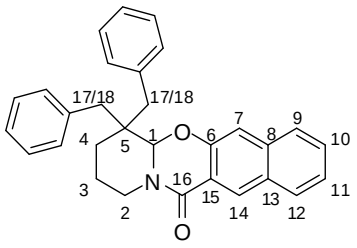
**6,6-Dibenzyl-1,3-dihydroxy-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1*b*][1,3] benzoxazin-11-one (149h):**




Synthesised using general DIA procedure A from imine **146a** (41.3 mg, 0.157 mmol), acid **147h** (35.7 mg, 0.188 mmol), DIPEA (50.9 μL, 0.290 mmol) and T3P (151 mg, 0.235 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→2:1 petrol:ethyl acetate) afforded compound **149h** as a white solid (39.0 mg, 60%); mp 135–136 °C; $R_f$ 0.57 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3269, 1619, 1589, 1491, 1471, 1441, 1293, 1257, 1137; $\delta_H$ (400 MHz, $CDCl_3$) 12.10 (1H, br s, O*H*), 7.35–7.20 (8H, m, ArH), 7.10–7.06 (2H, m, ArH), 6.09 (1H, d, *J* = 2.0 Hz, H-7/9), 6.01 (1H, d, *J* = 2.0 Hz, H-7/9), 5.48 (1H, br s, O*H*), 4.96 (1H, s, H-1), 4.55–4.47 (1H, m, H-2eq), 3.18 (1H, d, *J* = 13.7 Hz, C*H*HPh-13), 3.17 (1H, d, *J* = 13.4 Hz, C*H*HPh-14), 2.90 (1H, d, *J* = 13.7 Hz, CH*H*Ph-13), 2.46–2.37 (2H, m, H-2ax, CH*H*Ph-14), 2.15–2.05 (1H, m, H-3a), 1.67–1.55 (2H, m, H-3b,4a), 1.37–1.22(1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 167.0 (C-12), 162.8 (C-8/10), 162.8 (C-8/10), 157.5 (C-6), 137.0 (Ar C), 136.3 (Ar C), 131.0 (Ar CH), 128.2 (Ar CH), 128.2 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 97.2 (C-11), 95.2(C-7/9), 93.8 (C-7/9), 88.9 (C-1), 42.1 (C-5), 41.4 (C-2), 41.1 (C-14), 35.7 (C-13), 27.4 (C-4), 19.4 (C-3); HRMS ($ESI^+$): Found: 416.1847; $C_{26}H_{26}NO_4$ ($MH^+$) Requires: 416.1856 (2.3 ppm error).

Lab Notebook Reference: CHK 1/22 p.40

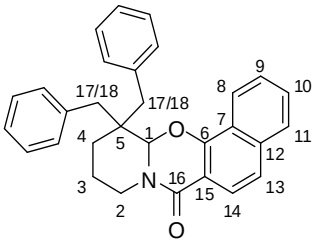
**4,4-Dibenzyl-2,3,4,4a-tetrahydro-1*H*,12*H*-naphtho[2,3-*e*]pyrido[2,1-*b*][1,3]oxazin-12-one (149i):**




Synthesised using general DIA procedure A from imine **146a** (56.2 mg, 0.214 mmol), acid **147i** (48.2 mg, 0.256 mmol), DIPEA (69.0 μL, 0.396 mmol) and T3P (204 mg, 0.321 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 7:1→5:1 petrol:ethyl acetate) afforded compound **149i** as a white solid (88.4 mg, 95%); mp 204–205 °C; $R_f$ 0.37 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1640, 1608, 1580, 1491, 1438, 1388, 1338, 1264, 1233, 869; $\delta_H$ (400 MHz, $CDCl_3$) 8.53 (1H, s, H-14), 7.89 (1H, d, *J* = 8.2, ArH), 7.80 (1H, d, *J* = 8.2, ArH), 7.56–7.48 (1H, m, ArH), 7.48 (1H, s, H-7) 7.42–7.37 (1H, m, ArH), 7.34–7.16 (10H, m, ArH), 5.16 (1H, s, H-1), 4.80–4.74 (1H, m, H-2eq), 3.29 (1H, d, *J* = 13.4 Hz, C*H*HPh-17), 3.21 (1H, d, *J* = 13.7 Hz, C*H*HPh-18), 2.91 (1H, d, *J* = 13.7 Hz CH*H*Ph-18), 2.52 (1H, ddd, *J* = 12.6, 12.6, 2.9 Hz, H-2ax), 2.45 (1H, d, *J* = 13.4 Hz, CH*H*Ph-17), 2.22–2.08 (1H, m, H-3a), 1.66–1.56 (2H, m, H-3b,4a), 1.45–1.35 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 162.3 (C-16), 152.6 (C-6), 137.3 (Ar C), 136.9 (Ar C), 136.6 (Ar C), 131.3 (Ar CH), 131.1 (C-14), 129.9 (Ar C), 129.6 (Ar C), 129.2 (Ar C), 128.7 (Ar CH), 128.3 (Ar CH), 128.2 (Ar CH), 126.7 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 124.8 (Ar CH), 117.1 (Ar C), 110.8 (C-7), 89.2 (C-1), 43.0 (C-5), 42.3 (C-2), 41.7 (C-17), 35.8 (C-18), 27.9 (C-4), 19.9 (C-3); HRMS ($ESI^+$): Found: 434.2126; $C_{30}H_{28}NO_2$ ($MH^+$) Requires: 434.2115 (−2.6 ppm error); Elemental Analysis: calculated for $C_{30}H_{27}NO_2$ requires C, 83.11; H, 6.28; N, 3.23; found C, 82.84; H, 6.33; N, 3.27.

Lab Notebook Reference: CHK 1/12 p.23

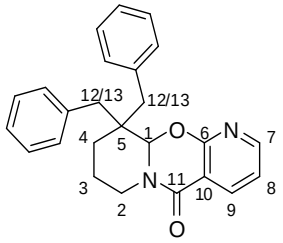
**12,12-Dibenzyl-10,11,12,12a-tetrahydro-7*H*,9*H*-naphtho[2,1-*e*]pyrido[2,1-*b*][1,3]oxazin-7-one (149j):**




Synthesised using general DIA procedure A from imine **146a** (50.6 mg, 0.192 mmol), acid **147j** (43.5 mg, 0.231 mmol), DIPEA (62.0 μL, 0.356 mmol) and T3P (183 mg, 0.288 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 7:1 petrol:ethyl acetate) afforded compound **147j** as colourless oil (76.7 mg, 92%); $R_f$ 0.37 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1626, 1574, 1491, 1442, 1418, 1380, 1264, 1237; $\delta_H$ (400 MHz, $CDCl_3$) 9.58 (1H, d, *J* = 8.6, ArH), 7.98 (1H, d, *J* = 8.8, ArH), 7.79 (1H, d, *J* = 8.1, ArH), 7.61 (1H, ddd, *J* = 8.6, 6.9, 1.3 Hz, ArH), 7.43 (1H, ddd, *J* = 8.1, 6.9, 1.3 Hz, ArH), 7.35–7.15 (9H, m, ArH), 7.12–7.07 (2H, m, ArH), 5.12 (1H, s, H-1), 4.74–4.66 (1H, m, H-2eq), 3.32 (1H, d, *J* = 13.7 Hz, C*H*HPh-17), 3.26 (1H, d, *J* = 13.4 Hz, C*H*HPh-18), 3.00 (1H, d, *J* = 13.7 Hz, CH*H*Ph-17), 2.51 (1H, *J* = 13.4 Hz, CH*H*Ph-18, overlapping), 2.55 (1H, ddd, *J* = 13.2, 13.2, 3.95 Hz, H-2ax, overlapping), 2.25–2.10 (1H, m, H-3a), 1.70–1.60 (2H, m, H-3b,4a), 1.42–1.32 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 165.0 (C-16), 157.3 (C-6), 137.5 (Ar C), 136.7 (Ar C), 136.0 (C-14), 132.1 (Ar C), 131.2 (Ar CH), 130.1 (Ar C), 129.0 (Ar CH), 128.5 (Ar CH), 128.3 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 126.3 (Ar CH), 124.7 (Ar CH), 117.0 (Ar CH), 107.9 (Ar CH), 88.8 (C-1), 41.9 (C-5), 41.7 (C-1), 41.7 (C-18), 36.3 (C-17), 27.6 (C-4), 19.6 (C-3); HRMS ($ESI^+$): Found: 434.2138; $C_{30}H_{28}NO_2$ ($MH^+$) Requires: 434.2115 (−5.0 ppm error).

Lab Notebook Reference: CHK 1/13 p.24

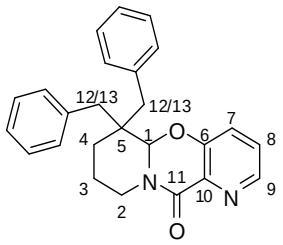
**10,10-Dibenzyl-8,9,10,10a-tetrahydro-5*H*,7*H*-dipyrido[2,1-*b*:3',2'-*e*][1,3]oxazin-5-one (149k):**




Synthesised using general DIA procedure A from imine **146a** (43.5 mg, 0.165 mmol), acid **147k** (27.6 mg, 0.198 mmol), DIPEA (53.3 μL, 0.306 mmol) and T3P (158 mg, 0.248 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1→3:1 petrol:ethyl acetate) afforded compound **147k** as a colourless oil (61.7 mg, 97%); $R_f$ 0.37 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1642, 1575, 1471, 1450, 1415, 1394, 1318, 1231; $\delta_H$ (400 MHz, $CDCl_3$) 8.41 (1H, dd, *J* = 4.9, 1.8 Hz, H-7), 8.28 (1H, dd, *J* = 7.5, 1.8 Hz, H-9), 7.33–7.17 (10H, m, ArH), 7.10 (1H, dd, *J* = 7.5, 4.9 Hz, H-8), 5.29 (1H, s, H-1), 4.73–4.65 (1H, m, H-2eq), 3.34 (1H, d, *J* = 13.5 Hz, C*H*HPh-12), 3.16 (1H, d, *J* = 13.5 Hz, C*H*HPh-13), 2.87 (1H, d, *J* = 13.5 Hz, CH*H*Ph-13 ), 2.39 (1H, ddd, *J* = 13.3, 13.3, 3.9 Hz, H-2ax), 2.34 (1H, *J* = 13.5 Hz, CH*H*Ph-12), 2.17–2.03 (1H, m, H-3a), 1.67–1.55 (2H, m, H-3b,4a), 1.46–1.36 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 161.4 (C-11), 160.9 (C-6), 152.8 (C-7), 137.8 (C-9), 136.7 (Ar C), 136.2 (Ar C), 131.2 (Ar CH), 130.9 (Ar CH), 128.2 (Ar CH), 126.5 (Ar CH), 119.0 (C-8), 110.7 (C-10), 89.5 (C-1), 42.9 (C-5), 42.2 (C-2), 41.1 (C-12), 35.3 (C-13), 27.6 (C-4), 19.7 (C-3); HRMS ($ESI^+$): Found: 407.1734 (1.0 ppm error); $C_{25}H_{24}N_2NaO_2$ ($MNa^+$) Requires: 407.1730, Found: 385.1907; $C_{25}H_{25}N_2O_2$ ($MH^+$) Requires: 385.1911 (−0.9 ppm error).

Lab Notebook Reference: CHK 1/28 p.45

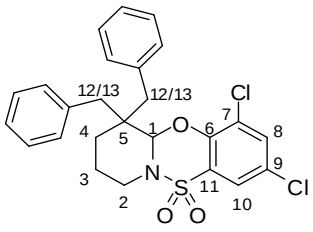
**6,6-Dibenzyl-6,7,8,9-tetrahydro-5a*H*,11*H*-dipyrido[2,1-*b*:2',3'-*e*][1,3]oxazin-11-one (149l):**




Synthesised using general DIA procedure A from imine **146a** (43 mg, 0.163 mmol), acid **147l** (27.2 mg, 0.196 mmol), DIPEA (52.6 μL, 0.302 mmol) and T3P (156 mg, 0.245 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→petrol:ethyl acetate→pure ethyl acetate→ethyl acetate, 10% MeOH) afforded compound **149l** as an orange oil (39.1 mg, 63%); $R_f$ 0.23 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1654, 1450, 1415, 1382, 1314, 1228, 718; $\delta_H$ (400 MHz, $CDCl_3$) 8.47–8.43 (1H, m, H-9), 7.49–7.40 (2H, m, H-7,8), 7.34–7.19 (8H, m, ArH) 7.12–7.06 (2H, m, ArH), 5.19 (1H, s, H-1), 4.80–4.73 (1H, m, H-2eq), 3.25–3.17 (2H, m, C*H*HPh-12,13), 2.86 (1H, d, *J* = 13.7 Hz, CH*H*Ph-12/13), 2.55–2.42 (2H, m, H-2ax, CH*H*Ph-12/13), 2.17–2.04 (1H, m, H-3a), 1.64–1.56 (2H, m, H-3b,4a), 1.42–1.32 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 161.3 (C-11), 153.6 (C-6), 144.5 (C-9), 136.9 (Ar C), 136.3 (Ar C), 133.7 (C-10), 131.1 (Ar CH), 131.1 (Ar CH), 128.4 (C-8), 128.3 (Ar CH), 128.3 (Ar CH), 126.8 (Ar CH), 126.7 (Ar CH), 124.3 (C-7), 89.9 (C-1), 42.7 (C-5), 42.5 (C-2), 41.5 (C-12), 35.9 (C-13), 27.8 (C-4), 19.6 (C-3); HRMS ($ESI^+$): Found: 385.1906; $C_{25}H_{25}N_2O_2$ ($MH^+$) Requires: 385.1911 (−1.1 ppm error).

Lab Notebook Reference: CHK 1/32 p.52

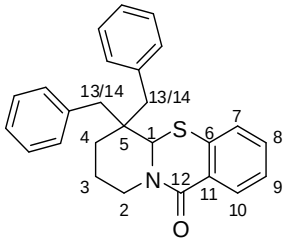
**10,10-Dibenzyl-1,3-dichloro-8,9,10,10a-tetrahydro-7*H*-pyrido[1,2 *b*] [4,1,2] benzoxathiazine 5,5-dioxide (157):**




To a solution of imine **146a** (45.3 mg, 0.172 mmol) and 3,5-dichloro-2-hydroxybenzenesulfonic chloride **156** (53.9 mg, 0.206 mmol) in dry toluene (1.5 mL) was added DIPEA (55.4 μL, 0.318 mmol). The resulting solution was heated at 90 °C in a sealable tube for 20 h, before cooling to rt and pouring into sat. aq. $NaHCO_3$ (3 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL), and the organic extracts combined, concentrated *in vacuo* and purified by column chromatography ($SiO_2$, 3:1→2:1 petrol:ethyl acetate) affording compound **157** as white solid (77.9 mg, 93%); mp 188–191 °C; $R_f$ 0.57 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1431, 1337, 1217, 1161, 944, 690; $\delta_H$ (400 MHz, $CDCl_3$) 7.64 (1H, d, *J* = 2.5 Hz, H-8/10), 7.59 (1H, d, *J* = 2.5 Hz, H-8/10), 7.46–7.24 (10H, m, ArH) 5.50 (1H, s, H-1), 3.65–3.61 (1H, m, H-2eq), 3.11 (1H, d, *J* = 14.2 Hz, C*H*HPh-12), 3.00 (1H, d, *J* = 14.2 Hz, CH*H*Ph-12), 2.98 (1H, d, *J* = 14.7 Hz, C*H*HPh-13), 2.88 (1H, d, *J* = 14.7 Hz, CH*H*Ph-13), 2.79–2.72 (1H, m, H-2ax), 2.14–2.01 (1H, m, H-3a), 1.82–1.65 (2H, m, H-3b,4a), 1.57–1.50 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 146.9 (C-6), 136.4 (Ar C), 136.3 (Ar C), 134.3 (C-8/10), 131,0 (Ar CH), 130.9 (Ar CH), 128.4 (Ar CH), 129.4 (Ar CH), 127.2 (Ar CH), 126.8 (Ar CH), 124.4 (C-8/10), 124.1 (Ar C), 123.9 (C-11) 90.0 (C-1), 42.2 (C-5), 41.9 (C-2), 39.6 (C-12), 35.3 (C-13), 27.6 (C-4), 19.5 (C-3); HRMS ($ESI^+$): Found: 488.0861; $C_{25}H_{24}{}^{35}Cl_2NO_3S$ ($MH^+$) Requires: 488.0848 (−2.5 ppm error).

Lab Notebook Reference: CHK 2/132 p.194

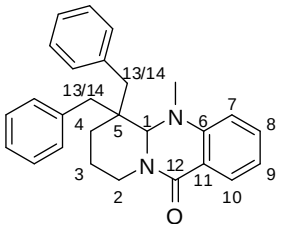
**6,6-Dibenzyl-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzothiazin-11-one (149m):**




Synthesised using general DIA procedure A from imine **146a** (50.1 mg, 0.190 mmol), acid **147m** (35.2 mg, 0.228 mmol), DIPEA (61.3 μL, 0.352mmol) and T3P (182 mg, 0.286 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded compound **149m** as a white solid (72.5 mg, 96%); mp 182–184 °C; $R_f$ 0.57 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1616, 1566, 1471, 1433, 1396, 1266, 896; $\delta_H$ (400 MHz, $CDCl_3$) 8.18 (1H, dd, *J* = 7.9, 0.9 Hz, H-10), 7.38–7.16 (9H, m, ArH), 7.13–7.07 (4H, m, ArH), 4.96 (1H, ddd, *J* = 12.9, 2.1, 2.1 Hz, H-2eq), 4.63 (1H, s, H-1), 3.19 (1H, d, *J* = 13.7 Hz, C*H*HPh-13), 2.90 (1H, d, *J* = 13.1 Hz, C*H*HPh-14), 2.67 (1H, d, *J* = 13.1 Hz, CH*H*Ph-14), 2.53 (1H, ddd, *J* = 12.9, 12.9, 2.6 Hz, H-2ax), 2.26 (1H, d, *J* = 13.7 Hz, CH*H*Ph-13), 2.20–2.07 (1H, m, H-3a), 1.77–1.70 (1H, m, H-4a), 1.64–1.50 (2H, m, H-3b,4b); $\delta_C$ (100 MHz, $CDCl_3$) 162.6 (C-12), 137.0 (Ar C), 136.5 (Ar C), 134.1 (Ar C) 134.1 (Ar C), 132.3 (Ar CH), 131.2 (Ar CH), 131.1 (Ar CH), 130.5 (C-10), 128.4 (Ar CH), 128.2 (Ar CH), 126.7 (Ar CH), 126.6 (Ar CH), 125.8 (Ar CH), 65.5 (C-1), 48.0 (C-2), 47.2 (C-5), 40.9 (C-13), 36.5 (C-14), 30.5 (C-4), 21.6 (C-3); HRMS ($ESI^+$): Found: 400.1739; $C_{26}H_{26}NOS$ ($MH^+$) Requires: 400.1730 (−2.3 ppm error).

Lab Notebook Reference: CHK 1/14 p.24

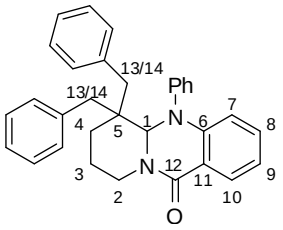
**6,6-Dibenzyl-5-methyl-5,5a,6,7,8,9-hexahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (149n):**




Synthesised using general DIA procedure A from imine **146a** (39.0 mg, 0.148 mmol), acid **147n** (26.9 mg, 0.178 mmol), DIPEA (47.7 μL, 0.273 mmol) and T3P (141 mg, 0.222 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149n** as a colourless oil (72.0 mg, 97%); $R_f$ 0.55 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1623, 1580, 1471, 1452, 1432, 1397, 1280, 1253; $\delta_H$ (400 MHz, $CDCl_3$) 7.97 (1H, dd, *J* = 7.7, 1.3 Hz, H-10), 7.45–7.40 (1H, m, ArH), 7.30–7.14 (8H, m, ArH), 7.07–6.98 (4H, m, ArH), 4.87 (1H, ddd, *J* = 12.8, 2.4, 2.4 Hz, H-2eq), 4.33 (1H, s, H-1), 3.16 (3H, s, C*H*$_3$), 3.05 (1H, d, *J* = 13.5 Hz, C*H*HPh-13), 2.81 (1H, d, *J* = 13.2 Hz, C*H*HPh-14), 2.49 (1H, ddd, *J* = 12.8, 12.8, 2.9 Hz, H-2ax), 2.45 (1H,d, *J* = 13.5 Hz, CH*H*Ph-13), 2.23 (1H, d, *J* = 13.2 Hz, CH*H*Ph-14), 2.15–2.01 (1H, m, H-3a), 1.68–1.62 (1H, m, H-4a), 1.56–1.45 (2H, m, H-3b,4b); $\delta_C$ (100 MHz, $CDCl_3$) 162.1 (C-12), 150.3 (C-6), 137.7 (Ar C), 137.6 (Ar C), 133.4 (Ar CH), 131.5 (Ar CH), 131.1 (Ar CH), 128.1 (Ar CH), 128. 0 (Ar CH), 126.5 (Ar CH), 126.3 (Ar CH), 122.0 (Ar CH), 121.4 (C-11), 120.7 (Ar CH), 82.1 (C-1), 48.2 (C-*C*H$_3$), 48.0 (C-5), 44.8 (C-2), 40.9 (C-13), 37.1 (C-14), 31.1 (C-4), 21.7 (C-3); HRMS ($ESI^+$): Found: 397.2286; $C_{27}H_{29}N_2O$ ($MH^+$) Requires: 397.2274 (−2.9 ppm error).

Lab Notebook Reference: CHK/WPU 1222

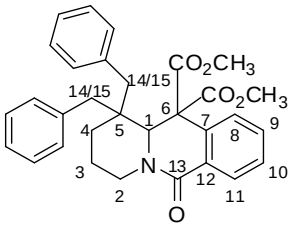
**6,6-Dibenzyl-5-phenyl-5,5a,6,7,8,9-hexahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (149o):**




Synthesised using general DIA procedure A from imine **146a** (38.0 mg, 0.144 mmol), acid **147o** (36.9 mg, 0.173 mmol), DIPEA (46.4 μL, 0.266 mmol) and T3P (137 mg, 0.216 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 2:1 petrol:ethyl acetate) afforded compound **149o** as a white solid (63.0 mg, 95%); $R_f$ 0.59 (ethyl acetate); mp 177–178 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1579, 1469, 1451, 1431, 1410, 1362, 1280, 1198, 739, 693; $\delta_H$ (400 MHz, $CDCl_3$) 8.05 (1H, dd, *J* = 7.7, 1.5 Hz, H-10), 7.62–7.57 (2H, m, ArH), 7.52–7.46 (2H, m, ArH), 7.40–7.20 (5H, m, ArH), 7.13–6.92 (7H, m, ArH), 6.35 (2H, d, *J* = 7.3 Hz, ArH), 5.21 (1H, s, H-1), 4.94 (1H, ddd, 12.7, 2.1, 2.1 Hz, H-2eq), 3.27 (1H, d, *J* = 13.9 Hz, C*H*HPh-13), 3.02 (1H, d, *J* = 13.2 Hz, C*H*HPh-14), 2.58 (1H, d, 13.2 Hz, CH*H*Ph-14, overlapping), 2.52 (1H, ddd, 12.7, 12.7, 2.95 Hz, H-2ax, overlapping), 2.52 (1H, d, 13.9 Hz, CH*H*Ph-13) 2.15–2.04 (1H, m, H-3a), 1.62–1.55 (1H, m, H-4a), 1.51–1.44 (1H, m, H3b), 1.19–1.09 (1H, m, H-4b); $\delta_C$ (100 MHz, $CDCl_3$) 162.4 (C-12), 151.2 (C-6), 147.8 (Ar C), (Ar C), 137.5 (Ar C), 137.3 (Ar CH), 133.2 (Ar CH), 131.4 (Ar CH), 131.1 (Ar CH), 130.1 (Ar CH), 128.9 (Ar CH), 128.4 (Ar CH), 128.1 (Ar CH), 127.9 (Ar CH), 127.0 (Ar CH), 126.4 (Ar CH), 126.1 (Ar CH), 121.8 (Ar CH), 119.8 (C-11), 119.7 (Ar CH), 81.4 (C-1), 47.9 (C-5), 45.1 (C-2), 38.5 (C-13), 36.6 (C-14), 30.9 (C-4), 21.4 (C-3); HRMS ($ESI^+$): Found:459.2436; $C_{32}H_{31}N_2O$ ($MH^+$) Requires: 459.2431 (−1.2 ppm error).

Lab Notebook Reference: CHK/WPU 1230

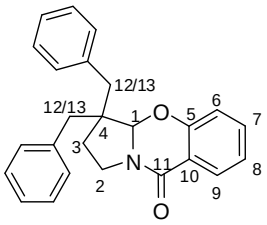
**Dimethyl 1,1-dibenzyl-6-oxo-1,3,4,11a-tetrahydro-2*H*-pyrido[1,2-*b*]isoquinoline-11, 11 (6*H*)-dicarboxylate (149p):**




Synthesised using general DIA procedure A from imine **146a** (38.0 mg, 0.144 mmol), acid **147p** (46.3 mg, 0.173 mmol), DIPEA (46.4 μL, 0.266 mmol) and T3P (137 mg, 0.216 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149p** as a yellow solid (62.0 mg, 97%); $R_f$ 0.72 (ethyl acetate); mp 160–163 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1711, 1624, 1577, 1448, 1412, 1235, 1210, 1163, 731, 692; $\delta_H$ (400 MHz, $CDCl_3$) 8.16 (1H, dd, *J* = 7.7, 1.4 Hz, H-11), 7.65 (1H, dd, *J* = 8.0, 1.0 Hz, H-8), 7.57–7.52 (1H, ddd, *J* = 8.0, 7.5, 1.4 Hz, H-9), 7.43 (1H, ddd, 7.7, 7.5, 1.0 Hz, H-10), 7.25–7.12 (6H, m, ArH), 7.04–7.00 (2H, m, ArH), 6.95–6.92 (2H, m, ArH), 5.17 (1H, s, H-1), 4.64 (1H, ddd, *J* = 12.6, 6.6, 6.6 Hz, H-2a), 3.98 (3H, s, C*H*$_3$), 3.69 (3H, s, C*H*$_3$), 2.85 (1H, ddd, *J* = 12.6, 5.9, 5.9 Hz, H-2b) 2.75 (1H, d, *J* = 13.2 Hz, C*H*HPh-14), 2.58 (1H, d, *J* = 14.6 Hz, C*H*HPh-15), 2.46 (1H, d, *J* = 14.6 Hz, CH*H*Ph-15), 2.43 (1H, d, *J* = 13.2 Hz, CH*H*Ph-14), 1.69–1.58 (1H, m, H-3a), 1.55–1.46 (1H, m, H-4a), 1.41–1.36 (1H, m, H-4b), 0.99–0.89 (1H, m, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 169.6 (C-*C*$O_2CH_3$), 169.0 (C-*C*$O_2CH_3$), 162.3 (C-13), 137.9 (Ar C), 137.7 (Ar C), 133.4 (Ar C), 131.9 (C-9), 131.3 (Ar CH), 130.7(Ar CH), 129.8 (C-8), 128.6 (C-10), 128.4 (Ar CH), 128.0 (Ar C), 128.0 (Ar CH), 127.7 (C-11), 126.4 (Ar CH), 126.4 (Ar CH), 63.2 (C-1), 60.0 (C-6), 53.9 (C-*C*$H_3$), 53.2 (C-*C*$H_3$), 44.8 (C-2), 44.5 (C-5), 40.5 (C-14), 39.9 (C-15), 33.5 (C-3), 20.0 (C-4); HRMS ($ESI^+$): Found: 498.2278; $C_{31}H_{32}NO_5$ ($MH^+$) Requires: 498.2275 (−0.7 ppm error).

Lab Notebook Reference: CHK/WPU 1246

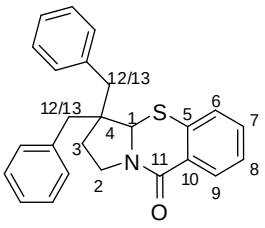
**3,3-Dibenzyl-1,2,3,3a-tetrahydro-9*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-9-one (149q):**




Synthesised using general DIA procedure A from imine **146b** (33.2 mg, 0.133 mmol), acid **147a** (22.1 mg, 0.160 mmol), DIPEA (42.9 μL, 0.246 mmol) and T3P (127 mg, 0.200 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1 petrol:ethyl acetate) afforded compound **149q** as a yellow oil (23.7 mg, 48%); $R_f$ 0.27 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2980, 1647, 1587, 1446, 1412, 1329, 1195, 1083, 1059, 693; $\delta_H$ (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J* = 7.7, 1.7 Hz, H-9), 7.40 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz, H-7), 7.28–7.13 (8H, m, ArH), 7.07–7.00 (4H, m, ArH), 5.21 (1H, s, H-1), 3.49–3.37 (2H, m, H-2), 2.95 (1H, d, *J* = 14.1, C*H*HPh-12, overlapping), 2.96 (1H, d, *J* = 13.8 Hz, C*H*HPh-13, overlapping), 2.89 (1H, d, *J* = 14.1 Hz, CH*H*Ph-12), 2.73 (1H, d, *J* = 13.8 Hz, CH*H*Ph-13), 1.81 (1H, ddd, *J* = 13.3, 6.7, 1.4 Hz, H-3eq), 1.62–1.56 (1H, m, H-3ax); $\delta_C$ (100 MHz, $CDCl_3$) 161.3 (C-11), 157.2 (C-5), 137.4 (Ar C), 136.4 (Ar C), 134.0 (Ar CH), 131.0 (Ar CH), 130.9 (Ar CH), 128.4 (Ar CH), 128.4 (Ar CH), 127.9 (C-9), 126.8 (Ar CH), 126.8 (Ar CH), 122.7 (Ar CH), 119.3 (C-10), 116.7 (Ar CH), 90.5 (C-1), 48.0 (C-4), 40.8 (C-2), 40.2 (C-13), 37.9 (C-12), 26.4 (C-3); HRMS ($ESI^+$): Found: 370.1792; $C_{25}H_{24}NO_2$ ($MH^+$) Requires: 370.1802 (2.7 ppm error).

Lab Notebook Reference: CHK 1/17 p.79

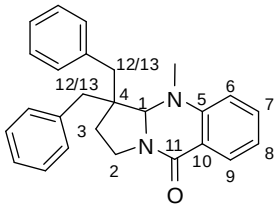
**3,3-Dibenzyl-1,2,3,3a-tetrahydro-9*H*-pyrrolo[2,1-*b*][1,3]benzothiazin-9-one (149r):**




Synthesised using general DIA procedure A from imine **146b** (49.5 mg, 0.199 mmol), acid **147m** (36.74 mg, 0.238 mmol), DIPEA (64.0 μL, 0.367 mmol) and T3P (189 mg, 0.298 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded compound **149r** as a white solid (66.4 mg, 87%); $R_f$ 0.8 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2874, 1620, 1567, 1424, 1387, 732, 694; $\delta_H$ (400 MHz, $CDCl_3$) 8.00 (1H, d, *J* = 7.7 Hz, H-9), 7.32–7.25 (5H, m, ArH), 7.20–7.13 (7H, m, ArH), 6.98 (1H, d, *J* = 8.0 Hz, H-6), 4.91 (1H, s, H-1), 3.77–3.72 (1H, m, H-2a), 3.67–3.60 (1H, m, H-2b), 3.10 (1H, d, *J* = 13.6 Hz, C*H*HPh-12), 2.83 (1H, d, *J* = 14.0 Hz, C*H*HPh-13), 2.78 (1H, d, *J* = 14.0 Hz, CH*H*Ph-13), 2.77 (1H, d, *J* = 13.6 Hz, CH*H*Ph-12), 1.78 (1H, ddd, *J* = 12.3, 5.8, 0.9 Hz, H-3eq), 1.51–1.42 (1H, m, H-3ax); $\delta_C$ (100 MHz, $CDCl_3$) 163.4 (C-11), 137.1 (Ar C), 135.8 (Ar C), 134.8 (C-5), 131.8 (Ar CH), 130.9 (Ar CH), 130.6 (Ar CH), 129.9 (C-9), 129.8 (C-10), 128.4 (Ar CH), 127.7 (Ar CH), 126.9 (Ar CH), 126.8 (Ar CH), 126.0 (Ar CH), 65.8 (C-1), 49.8 (C-4), 44.1 (C-2), 41.1 (C-12), 39.4 (C-13), 27.1 (C-3); HRMS ($ESI^+$): Found: 386.1574; $C_{25}H_{24}NOS$ ($MH^+$) Requires: 386.1573 (−0.2 ppm error).

Lab Notebook Reference: CHK 1/52 p.76

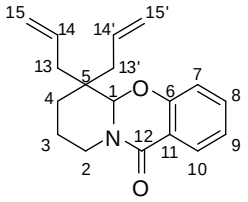
**3,3-Dibenzyl-4-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (149s):**




Synthesised using general DIA procedure A from imine **146b** (34.0 mg, 0.136 mmol), acid **147n** (24.8 mg, 0.164 mmol), DIPEA (43.8 μL, 0.252 mmol) and T3P (130 mg, 0.204 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149s** as a colourless oil (52.0 mg, 87%); $R_f$ 0.68 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1677, 1626, 1464, 1381, 1292, 1244; $\delta_H$ (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J* = 7.5, 1.7 Hz, H-9), 7.42 (1H, ddd, *J* = 8.4, 7.5, 1.7 Hz, H-7), 7.35–7.20 (5H, m, ArH), 6.90 (1H, ddd, *J* = 7.5, 7.5, 0.9 Hz, H-8), 6.85 (1H, dd, *J* = 8.4, 0.9 Hz, H-6), 4.70 (1H, s, H-1), 3.54–3.46 (2H, m, H-2), 3.24 (3H, s, C*H*$_3$), 3.19 (1H, d, *J* = 14.3 Hz, C*H*HPh-12), 3.17 (1H, d, *J* = 14.1 Hz, C*H*HPh-13), 2.97 (1H, d, *J* = 14.1 Hz, CH*H*Ph-13), 2.90 (1H, d, *J* = 14.3 Hz, CH*H*Ph-12), 1.84–1.65 (2H, m, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 162.5 (C-11), 149.9 (C-10), 137.5 (Ar C), 136.2 (Ar C), 133.6 (C-7), 131.4 (Ar CH), 131.0 (Ar CH), 128.4 (Ar CH), 128.1 (C-9), 126.9 (Ar CH), 126.8 (Ar CH), 119.1 (C-8), 117.7 (C-5), 112.7 (C-6), 77.9 (C-1), 50.0 (C-4), 42.4 (C-12), 41.1 (C-2), 37.7 (C-13), 35.3 (C-*C*H$_3$), 28.1 (C-3); HRMS ($ESI^+$): Found: 405.1934; $C_{26}H_{26}N_2NaO$ ($MNa^+$) Requires: 405.1937 (0.7 ppm error).

Lab Notebook Reference: CHK/WPU 1247

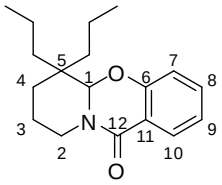
**6,6-Di[(1*E*)-prop-1-en-1-yl]-6,7,8,9-tetrahydro-5a*H*,11*H* pyrido [2,1*b*] [1,3] benzoxazin-11-one (149t):**




Synthesised using general DIA procedure A from imine **146c** (43.0 mg, 0.263 mmol), acid **147a** (43.6 mg, 0.316 mmol), DIPEA (84.8 μL, 0.487 mmol) and T3P (251 mg, 0.395 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate) afforded compound **149t** as a colourless oil (14.4 mg, 20%); $R_f$ 0.57 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2893, 1643, 1614, 1588, 1566, 1448, 1380, 1353, 1307, 1265, 745; $\delta_H$ (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J* = 7.7, 1.7 Hz, H-10), 7.41 (1H, ddd, *J* = 8.2, 7.3, 1.7 Hz, H-8), 6.89 (1H, ddd, *J* = 7.7, 7.3, 1.0 Hz, H-9), 6.90 (1H, d, *J* = 8.2, 1.0 Hz, H-7), 5.96–5.72 (2H, m, H-14,14'), 5.18 (1H, s, H-1), 5.18–5.06 (4H, m, H-15,15'), 4.64–4.58 (1H, m, H-2eq), 2.66 (1H, ddd, 13.5, 13.5, 4.0 Hz, H-2ax), 2.50 (1H, dd, *J* = 14.4, 8.0 Hz, H-13a), 2.40 (1H, dd, 14.1, 8.4 Hz, H-13'a), 2.28 (1H, dd, *J* = 14.4, 7.0 Hz, H-13b), 2.22 (1H, dd, J = 14.1, 7.2 Hz, H-13'b), 1.78–1.65 (2H, m, H-3), 1.48–1.36 (2H, m, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 163.1 (C-12), 156.2 (C-6), 134.1 (C-8), 133.5 (C-14/14'), 133.2 (C-14/14'), 128.0 (C-10), 121.9 (C-9), 118.9 (C-15), 118.5 (C-15'), 116.3 (C-11), 115.7 (C-7), 90.8 (C-1), 41.8 (C-2), 40.7 (C-5), 40.7 (C-13'), 29.5 (C-13) (C-4), 18.7 (C-3); HRMS ($ESI^+$): Found: 284.1652; $C_{18}H_{22}NO_2$ ($MH^+$) Requires: 284.1645 (−2.4 ppm error) .

Lab Notebook Reference: CHK 1/21 p.36

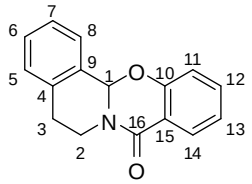
**6,6-Dipropyl-6,7,8,9-tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzoxazin-11-one (149u):**




Synthesised using general DIA procedure A from imine **146d** (1:1 mixture of imine **146d** and lactam **162**) (36.2 mg, 0.216 mmol), acid **147a** (35.9 mg, 0.260 mmol), DIPEA (69.7 μL, 0.400 mmol) and T3P (206 mg, 0.324 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded compound **149u** as a colourless oil (14.7 mg, 24%); $R_f$ 0.43 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2828, 1643, 1588, 1567, 1448, 1416, 1382, 1355, 1308, 1265, 1148; $\delta_H$ (400 MHz, $CDCl_3$) 7.91 (1H, dd, *J* = 7.6, 1.7 Hz, H-10), 7.39 (1H, ddd, *J* = 8.2, 7.6, 1.7 Hz, H-8), 7.02 (1H, ddd, *J* = 7.6, 7.6, 1.0 H-9), 6.86 (1H, dd, *J* = 8.2, 1.0 Hz, H-7), 5.13 (1H, s, H-1), 4.63–4.57 (1H, m, H-2eq), 2.68 (1H, ddd, *J* = 13.1, 13.1, 4.4 Hz, H-2ax), 1.72–1.20 (12H, m, 6 × C*H*$_2$), 0.95–0.85 (6H, m, 2 × C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 163.1 (C-12), 156.4 (C-6), 134.0 (C-8), 127.9 (C-10), 121.7 (C-9), 116.3 (C-11), 115.7 (C-7), 92.3 (C-1), 41.9 (C-2), 41.3 (C-5), 39.4 (C-*C*H$_2$), 31.5 (C-*C*H$_2$), 30.5 (C-*C*H$_2$), 19.0 (C-*C*H$_2$), 16.9 (C-*C*H$_2$), 16.0 (C-*C*H$_2$), 15.1 (C-*C*H$_3$), 15.0 (C-*C*H$_3$); HRMS ($ESI^+$): Found: 288.1954; $C_{18}H_{26}NO_2$ ($MH^+$) Requires: 288.1958 (1.3 ppm error) .

Lab Notebook Reference: CHK 1/30 p.47

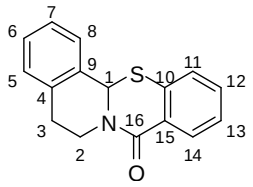
**5,13a-Dihydro-6*H*,8*H*-isoquinolino[1,2-*b*][1,3]benzoxazin-8-one (149v):**




Synthesised using general DIA procedure A from imine **146e** (30.0 mg, 0.229 mmol), acid **147a** (37.9 mg, 0.275 mmol), DIPEA (73.8 μL, 0.424 mmol) and T3P (219 mg, 0.344 mmol) in toluene (2.3 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1 petrol:ethyl acetate) afforded compound **149v** as a colourless oil (51.0 mg, 89%); $\nu_{max}$ (thin film)/$cm^{-1}$ 1643, 1588, 1446, 1395, 1211, 1014, 746; $\delta_H$ (400 MHz, $CDCl_3$) 8.03 (1H, dd, *J* = 7.7, 1.5 Hz, H-14), 7.62–7.58 (1H, m, ArH), 7.48 (1H, ddd, 8.3, 7.4, 1.7 Hz, ArH), 7.41–7.35 (2H, m, ArH), 7.28–7.24 (1H, m, ArH), 7.15 (1H, ddd, *J* = 7.7, 7.5, 1.0 Hz, ArH), 7.07 (1H, dd, *J* = 8.2, 0.9 Hz, ArH), 6.28 (1H, s, H-1), 4.52 (1H, ddd *J* = 12.8, 4.4, 4.4 Hz, H-2eq), 3.42 (1H, ddd, 12.8, 10.7, 3.8 Hz, H-2ax), 3.10 (1H, ddd, *J* = 15.7, 10.7, 4.4 Hz, H-3ax), 2.86 (1H, ddd, 15.7, 4.4, 3.8 Hz, H-3eq); $\delta_C$ (100 MHz, $CDCl_3$) 163.1 (C-16), 157.6 (C-10), 136.2 (C-4/9), 134.3 (Ar CH), 130.8 (Ar CH), 129.5 (C-4/9), 128.7 (Ar CH), 128.6 (Ar CH), 128.2 (Ar CH), 127.3 (Ar CH), 122.8 (Ar CH), 118.8 (C-15), 116.6(Ar CH), 84.1 (C-1), 38.3 (C-2), 28.6 (C-3); HRMS ($ESI^+$): Found: 252.1021; $C_{16}H_{14}NO_2$ ($MH^+$) Requires: 252.1019 (−0.9 ppm error).

Lab Notebook Reference: CHK 1/19 p.34

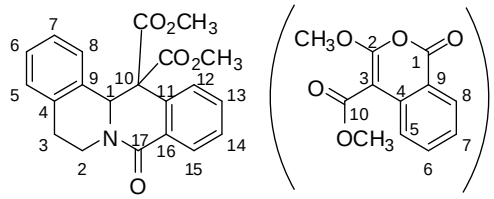
**13a-Methyl-5, 13a-dihydro-6*H*, 8*H*-isoquinolino[1,2-*b*][1,3]benzothiazin-8-one (149w):**




Synthesised using general DIA procedure A from imine **146e** (37.7 mg, 0.287 mmol), acid **147m** (53.2 mg, 0.345 mmol), DIPEA (92.6 μL, 0.532 mmol) and T3P (274 mg, 0.431 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149w** as a white solid (74.4 mg, 97%); $R_f$ 0.8 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1664, 1656, 1618, 1579, 1434, 1358, 1290, 1216, 1126, 731; $\delta_H$ (400 MHz, $CDCl_3$) 8.19 (1H, ddd, *J* = 7.7, 1.5, 0.6 Hz, H-14), 7.44–7.24 (7H, m, ArH), 6.24 (1H, s, H-1), 4.83–4.79 (1H, m, H-2eq), 3.24–3.11 (2H, m, H-2ax,3a), 3.00–2.93 (1H, m, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 164.9 (C-16), 137.8 (Ar C), 136.4 (Ar C), 131.8 (Ar CH), 131.2 (Ar CH), 130.8 (Ar C), 129.1 (Ar C), 128.9 (Ar CH), 128.6 (Ar CH), 127.7 (Ar CH), 127.3 (Ar CH), 127.0 (Ar CH), 126.3 (Ar CH), 60.7 (C-1), 40.7 (C-2), 29.6 (C-3); HRMS ($ESI^+$): Found: 268.0785; $C_{16}H_{14}NOS$ ($MH^+$) Requires: 268.0791 (2.2 ppm error).

Lab Notebook Reference: CHK 1/46 p.72

**Dimethyl 8-oxo-5,13a-dihydro-6H-isoquino[3,2-*a*]isoquinoline-13,13(8*H*)-dicarboxylate (149x):**



**149x** **176**

**Small scale**: Synthesised using general DIA procedure A from imine **146e** (25.0 mg, 0.191 mmol), acid **147p** (57.4 mg, 0.229 mmol), DIPEA (61.6 μL, 0.353 mmol) and T3P (182 mg, 0.287 mmol) in toluene (1.9 mL) at 90 °C in a sealable tube for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149x** as a colourless oil (48.0 mg, 69%).

**Large scale**: : Synthesised using general DIA procedure A from imine **146e** (1.28 g, 9.77 mmol), acid **147p** (2.96 mg, 11.7 mmol), DIPEA (3.15 μL, 18.1 mmol) and T3P (9.33 g, 14.7 mmol, 50% solution in THF) in toluene (51 mL) at 90 °C in a sealable tube for 20 h. Purification by column chromatography ($SiO_2$, 5:1→4:1→3:1→1:1 petrol:ethyl acetate) afforded compound **149x** as a yellow solid (1.48 mg, 41%) together with compound **176** as a side product (0.755 mg, 21%).

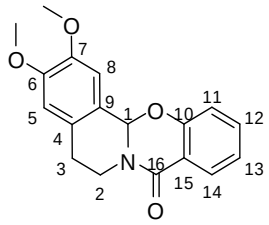
Dimethyl 8-oxo-5,13a-dihydro-6H-isoquino[3,2-a]isoquinoline-13,13(8*H*)-dicarboxylate (**149x**): mp 85–87 °C; $R_f$ 0.5 (ethyl acetate); νmax (thin film)/$cm^{-1}$ 1710, 1627, 1437, 1384, 1234, 716; $\delta_H$ (400 MHz, $CDCl_3$) 8.19 (1H, dd, *J* = 7.7, 1.8 Hz, H-15), 7.56–7.46 (2H, m, ArH), 7.30–7.14 (5H, m, ArH), 5.71 (1H, s, H-1), 4.88 (1H, ddd, *J* = 12.4, 4.3, 2.1 Hz, H-2eq), 3.90 (3H, s, C$H_3$), 3.49 (3H, s, C$H_3$), 3.15–3.07 (1H, m, H-3a), 2.97 (1H, ddd, *J* = 12.4, 12.4, 2.5 Hz, H-2ax), 2.81–2.74 (1H, m, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 170.2 (C-*C*$O_2CH_3$), 166.8 (C-*C*$O_2CH_3$), 164.3 (C-17), 139.0 (Ar C), 137.2 (Ar C), 132.3 (Ar CH), 132.0 (Ar C), 128.9 (Ar CH), 128.9 (Ar CH), 128.7 (Ar CH), 128.3 (Ar C), 127.9 (Ar CH), 127.7 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 66.1 (C-10), 61.2 (C-1), 53.1 (C-*C*$H_3$), 53.0 (C-*C*$H_3$), 39.9 (C-2), 29.6 (C-3); HRMS ($ESI^+$): Found: 366.1342; $C_{21}H_{20}NO_5$ ($MH^+$) Requires: 366.1336 (−1.8 ppm error).

Methyl-3-methoxy-1-oxo-1*H*-isochromene-4-carboxylate (**176**): mp 90–103 °C; νmax (thin film)/$cm^{-1}$ 2966, 1739, 1698, 1602, 1698, 1485, 1365, 1313, 1245, 1220, 1078, 1050, 1013, 784, 750, 734, 683; $\delta_H$ (400 MHz, $CDCl_3$) 8.19 (1H, d, *J* = 8.0 zHz, ArH), 8.01 (1H, d, *J* = 8.3 Hz, ArH), 7.68 (1H, m, ArH), 7.35 (1H, m, ArH), 4.10 (3H,

s,C$H_3$), 3.91 (3H, s, C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 165.2 (C-10), 159.5 (C-1/2), 159.3 (C-1/2), 137.4 (C-4/9), 135.6 (Ar CH), 129.9 (Ar CH), 125.8 (Ar CH), 124.1 (Ar CH), 116.1 (C-4/9), 89.0 (C-3), 56.7 (C-11/12), 52.0 (C-11/12); HRMS ($ESI^+$): Found: 257.0427 $C_{12}H_{10}NaO_5$ ($MNa^+$) Requires: 257.0420 (−2.7 ppm error); This compound has been reported previously in the literature, but the available NMR data were obtained in a DMSO-$d_6$ solution.[52]

Lab Notebook Reference: CHK/WPU 1249 (small scale) and CHK 4.257 p.70 (large scale)

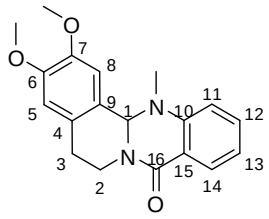
**2,3-Dimethoxy-5,13a-dihydro-6*H*,8*H*-isoquinolino[1,2-*b*][1,3]benzoxazin-8-one (149y):**




Synthesised using general DIA procedure A from imine **146f** (66.6 mg, 0.348 mmol), acid **147a** (57.7 mg, 0.418 mmol), DIPEA (112 μL, 0.644 mmol) and T3P (332 mg, 0.522 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate) afforded compound **149y** as a white oil (51.6 mg, 48%); $R_f$ 0.33 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1587, 1494, 1446, 1394, 1247, 1209, 1095; $\delta_H$ (400 MHz, $CDCl_3$) 8.03 (1H, dd, *J* = 7.8, 1.7 Hz, H-14), 7.48 (1H, ddd, *J* = 8.2, 7.3, 1.7 Hz, H-12), 7.16 (1H, ddd, *J* = 7.8, 7.3, 0.5 Hz, H-13), 7.08 (1H, dd, *J* = 8.2, 0.5 Hz, H-11), 7.03 (1H, s, H-5/8), 6.71 (1H, s, C-5/8), 6.23 (1H, s, H-1) 4.58 (1H, ddd, *J* = 12.8, 4.8, 3.5 Hz, H-2eq), 3.95 (3H, s, OC$H_3$), 3.92 (3H, s, OC$H_3$), 3.33 (1H, ddd, *J* = 12.8, 11.3, 3.5 Hz, H-2ax), 3.05 (1H, ddd, *J* = 15.6, 11.3, 4.8 Hz, H-3ax), 2.77 (1H, ddd, *J* = 15.6, 3.5, 3.5 Hz, H-3eq); $\delta_C$ (100 MHz, $CDCl_3$) 163.1 (C-16), 157.6 (C-10), 150.0 (C-6/7), 148.4 (C-6/7), 134.2 (C-12) , 129.1 (Ar C), 128.7 (C-14), 122.8 (C-13), 122.4 (Ar C), 118.8 (C-15), 116.6 (C-11), 111.0 (C-5/8), 110.6 (C-5/8), 84.2 (C-1), 56.2 (C-$C$H$_3$), 56.1 (C-$C$H$_3$), 38.4 (C-2), 28.1 (C-3); HRMS ($ESI^+$): Found: 312.1242; $C_{18}H_{18}NO_4$ ($MH^+$) Requires: 312.1230 (−3.7 ppm error).

Lab Notebook Reference: CHK 2/123 p.179

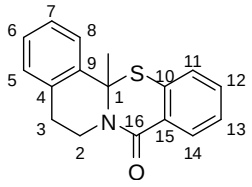
**2,3-Dimethoxy-13-methyl-5,6,13,13a-tetrahydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (149z):**




Synthesised using general DIA procedure A from imine **146f** (76.9 mg, 0.402 mmol), acid **147n** (73.0 mg, 0.483 mmol), DIPEA (130 μL, 0.744 mmol) and T3P (384 mg, 0.603 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate) afforded compound **149z** as a colourless oil (114 mg, 87%); $R_f$ 0.54 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1583, 1492, 1446, 1401, 1342, 1318, 1241, 1215, 1094, 1001, 746; $\delta_H$ (400 MHz, $CDCl_3$) 8.07–8.04 (1H, m, H-14), 7.47–7.42 (1H, m, H-12), 7.13–7.09 (2H, m, H-11,13), 6.87 (1H, s, H-5/8), 6.67 (1H, s, H-5/8), 5.66 (1H, m, H-1), 4.64 (1H, ddd, *J* = 12.8, 5.0, 2.7 Hz, H-2eq), 3.89 (3H, s, OC$H_3$), 3.88 (3H, s, OC$H_3$), 3.20–3.13 (1H, m, H-2ax), 2.95–2.87 (1H, m, H-3a), 2.78–2.71 (1H, m, H-3b), 2.47 (3H, s, NC$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 164.6 (C-16), 151.2 (C-6/7/10), 149.1 (C-6/7/10), 148.3 (C-6/7/10), 133.0 (C-12), 129.7 (Ar C), 128.9 (C-14), 123.7 (Ar C), 122.9 (Ar C), 122.8 (C-11/13), 121.0 (C-11/13), 111.0 (C-5/8), 110.8 (C-5/8), 71.3 (C-1), 56.2 (C-$C$H$_3$), 56.0 (C-$C$H$_3$), 39.1 (C-NCH$_3$), 36.0 (C-2), 28.3 (C-3); HRMS ($ESI^+$): Found: 325.1535; $C_{19}H_{21}N_2O_3$ ($MH^+$) Requires: 325.1547 (3.7 ppm error).

Lab Notebook Reference: CHK 2/122 p.178

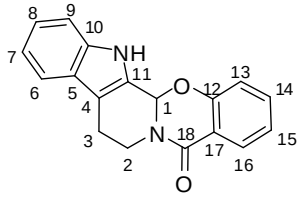
**5,13a-Dihydro-6*H*,8*H*-isoquinolino[1,2-*b*][1,3]benzothiazin-8-one (149ad):**




Synthesised using general DIA procedure A from imine **146m** (40.0 mg, 0.275 mmol), acid **147m** (51.0 mg, 0.330 mmol), DIPEA (88.7 μL, 0.510 mmol) and T3P (263 mg, 0.413 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) afforded **149ad** as an orange oil (58.5 mg, 80%); $R_f$ 0.34 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2879, 1657, 1618, 1609, 1564, 1422, 1366, 1332, 1275, 1231, 732; $\delta_H$ (400 MHz, $CDCl_3$) 8.15 (1H, ddd, *J* = 7.8, 1.5, 0.5 Hz, H-14), 7.42 (1H, dd, *J* =7.8, 1.6 Hz, ArH), 7.35 (1H, ddd, *J* = 7.7, 7.7, 1.6 Hz, ArH), 7.30–7.15 (5H, m, ArH), 5.04 (1H, ddd, 12.6, 9.7, 1.9 Hz, H-2eq), 3.03 (1H, ddd, *J* = 15.4, 12.6, 9.7 Hz, H-3ax), 2.93 (1H, ddd, *J* = 12.6, 12.6, 2.8 Hz, H-2ax, overlapping), 2.86 (1H, ddd, *J* = 15.4, 2.8, 1.9 Hz, H-3eq, overlapping), 1.91 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 163.6 (C-16), 135.8 (Ar C), 135.4 (Ar C), 134.8 (Ar C), 132.1 (Ar CH), 130.9 (C-14), 129.4 (Ar CH), 128.2 (Ar C), 128.1 (Ar CH), 127.3 (Ar CH), 127.1 (Ar CH), 126.2 (Ar CH), 126.1 (Ar CH), 65.9 (C-1), 37.3 (C-2), 29.7 (C-3), 28.5 (C-*C*H$_3$); HRMS ($ESI^+$): Found: 282.0950; $C_{17}H_{15}NOS$ ($MH^+$) Requires: 282.0947 (−1.0 ppm error).

Lab Notebook Reference: CHK 1/53 p.82

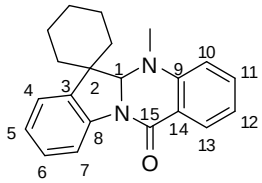
**7,8,13,13b-Tetrahydro-5*H*-indolo[2',3':3,4]pyrido[2,1-*b*][1,3]benzoxazin-5-one (149ae):**




Synthesised using general DIA procedure A from β-carboline **146j** (26.8 mg, 0.157 mmol), acid **147a** (26.1 mg, 0.189 mmol), DIPEA (50.7 μL, 0.291 mmol) and T3P (150 mg, 0.236 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, DCM, 1% MeOH→DCM, 2% MeOH→DCM, 4% MeOH→DCM, 7% MeOH→DCM, 9% MeOH) afforded compound **149ae** as a white oil (14.4 mg, 46%); $R_f$ 0.43 (DCM, 1% MeOH); $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, br s, N*H*), 8.06 (1H, dd, *J* = 7.9, 1.7 Hz, ArH), 7.61 (1H, d, *J* = 7.9, ArH), 7.49 (1H, ddd, 8.2, 7.3, 1.7 Hz, ArH), 7.43 (1H, ddd, *J* = 8.2, 0.9, 0.9 Hz, ArH), 7.29 (1H, ddd, *J* = 7.1, 7.1, 1.2 Hz, ArH), 7.21–7.15 (2H, m, ArH), 7.04 (1H, d, *J* = 8.2 Hz, ArH), 6.48 (1H, s, H-1), 4.94 (1H, ddd, *J* = 13.1, 5.1, 2.3, H-2eq), 3.32 (1H, ddd, *J* = 13.1, 10.8, 4.9 Hz, H-2ax), 3.09–2.94 (2H, m, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 163.1 (C-18), 156.8 (C-12), 137.2 (Ar C), 134.3 (Ar CH), 128.9 (Ar CH), 127.1 (Ar C), 126.0 (Ar C), 123.8 (Ar CH), 123.1 (Ar CH), 120.4 (Ar CH), 119.4 (Ar CH), 118.7 (Ar C), 116.4 (Ar CH), 113.8 (Ar C), 111.7 (Ar CH), 81.2 (C-1), 39.2 (C-2), 20.3 (C-3); Obtained data in accord with those reported in literature.[26j]

Lab Notebook Reference: CHK 1/40 p.73

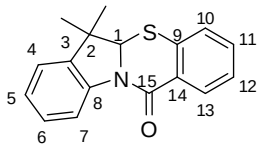
**5'-Methyl-5',5a'-dihydro-12'*H*-spiro[cyclohexane-1,6'-indolo[2,1-*b*]quinazolin]-12'-one (149af):**




Synthesised using general DIA procedure A from imine **146k** (41.3 mg, 0.223 mmol), acid **147n** (40.5 mg, 0.268 mmol), DIPEA (71.7 μL, 0.412 mmol) and T3P (212.6 mg, 0.334 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 19:1 petrol:ethyl acetate) afforded compound **149af** as a colourless oil (38.3 mg, 54%); $R_f$ 0.59 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2883, 2812, 1635, 1581, 1460, 1406, 1387, 1300, 1251, 1193, 1153, 740; $\delta_H$ (400 MHz, $CDCl_3$) 8.34 (1H, dd, *J* = 7.9, 1.1 Hz, H-13), 8.07 (1H, dd, *J* = 7.8, 1.7 Hz, H-7), 7.64 (1H, dd, *J* = 7.6, 1.1 Hz, H-10 ), 7.44 (1H, ddd, *J* = 8.4, 7.6, 1.7 Hz, H-5), 7.30 (1H, ddd, *J* = 7.9, 7.6, 1.1 Hz, H-12), 7.10 (1H, ddd, *J* = 7.6, 7.6, 1.1 Hz, H-11), 6.93 (1H, ddd, *J* = 7.8, 7.6, 0.9 Hz, H-6), 6.87 (1H, dd, *J* = 8.4, 0.9 Hz, H-4), 4.92 (1H, s, H-1), 3.09 (3H, s, C*H*$_3$), 2.12–1.32 (10 H, m, C*H*$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 161.2 (C-15), 149.6 (Ar C), 139.6 (Ar C), 138.6 (Ar C), 134.1 (C-5), 128.6 (C-7), 127.9 (C-12), 124.8 (C-10), 124.2 (C-11), 119.3 (C-6) , 117.5 (C-13), 116.9 (Ar C), 113.0 (C-4), 85.3 (C-1), 48.8 (C-2), 36.8 (C-*C*H$_3$), 33.1 (C-*C*H$_2$), 28.9 (C-*C*H$_2$), 25.4 (C-*C*H$_2$), 23.4 (C-*C*H$_2$), 20.6 (C-*C*H$_2$); HRMS ($ESI^+$): Found: 341.1618; $C_{21}H_{22}N_2NaO$ ($MNa^+$) Requires: 341.1624 (1.7 ppm error).

Lab Notebook Reference: CHK 2/118 p.174

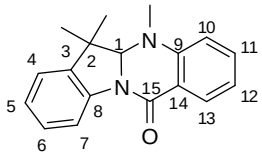
**6,6-Dimethyl-5a,6-dihydro-12*H*-indolo[2,1-b][1,3]benzothiazin-12-one (149ag):**



Synthesised using general DIA procedure A from imine **146l** (38.8 mg, 0.267 mmol), acid **147m** (49.4 mg, 0.321 mmol), DIPEA (86.1 μL, 0.494 mmol) and T3P (255 mg, 0.401 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 19:1 petrol:ethyl acetate) afforded compound **149ag** as a colourless oil (39.7 mg, 53%); $R_f$ 0.76 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 2918, 1625, 1572, 1457, 1369, 1310, 1269, 1143, 1078, 739; $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, ddd, *J* = 8.1, 1.0, 0.6 Hz, H-13), 8.22 (1H, ddd, *J* = 7.8, 1.5, 0.5 Hz, ArH), 7.44–7.28 (4H, m, ArH), 7.21 (1H, ddd, *J* = 7.5, 1.4, 0.6 Hz, ArH), 7.14 (1H, ddd, *J* = 7.4, 7.4, 1.1 Hz, ArH), 5.43 (1H, s, H-1), 1.53 (1H, s, C*H*$_3$), 1.45 (1H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 162.1 (C-15), 140.2 (Ar C), 138.5 (Ar C), 135.1 (Ar C), 132.1 (Ar CH), 130.4 (Ar CH), 130.4 (Ar C), 128.3 (Ar CH), 127.8 (Ar CH), 126.4 (Ar CH), 124.6 (Ar CH), 121.8 (Ar CH), 116.3 (C-13), 73.4 (C-1), 44.2 (C-2), 27.6 (C-*C*H$_3$), 26.4 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 282.0958; $C_{17}H_{16}NOS$ ($MH^+$) Requires: 282.0947 (−3.8 ppm error).

Lab Notebook Reference: CHK 2/126 p.182

**5,6,6-Trimethyl-5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-one (149ah):**

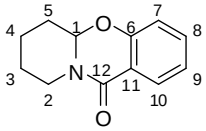


Synthesised using general DIA procedure A from imine **146l** (31.8 mg, 0.219 mmol), acid **147n** (39.7 mg, 0.263 mmol), DIPEA (70.6 μL, 0.405 mmol) and T3P (210 mg, 0.329 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 19:1 petrol:ethyl acetate) afforded compound **149ah** as a colourless oil (25.0 mg, 41%); $R_f$ 0.64 (5:2 petrol:ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 2924, 1636, 15577, 1461, 1435, 1409, 1390, 741; $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, dd, *J* = 8.0, 1.1 Hz, H-13), 8.10 (1H, dd, *J* = 7.8, 1.7 Hz, H-7), 7.45 (1H, ddd, *J* = 8.4, 7.3, 1.7 Hz, H-5), 7.31–7.27 (1H, m, H-12), 7.21 (1H, dd, *J* = 7.5, 1.4 Hz, H-10), 7.13 (1H,

ddd, *J* = 7.5, 7.5, 1.1 Hz, H-11), 6.96 (1H, ddd, *J* = 7.8, 7.3, 0.8 Hz, H-6), 6.88 (1H, d, *J* = 8.4 Hz, H-4), 4.98 (1H, s, H-1), 3.02 (3H, s, NC$H_3$), 1.70 (3H, s, C$H_3$), 1.34 (3H, s, C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 160.9 (C-15), 149.5 (Ar C), 139.0 (Ar C), 138.8 (Ar C), 134.0 (Ar CH) , 128.6 (Ar CH), 128.2 (C-12), 124.5 (C-11), 121.6 (C-10), 119.3 (Ar CH), 116.8 (Ar C), 116.8 (C-13), 112.4 (Ar CH), 85.2 (C-1), 46.0 (C-2), 34.8 (C-N$CH_3$), 26.0 (C-$CH_3$), 23.3 (C-$CH_3$); HRMS ($ESI^+$): Found: 279.1492; $C_{18}H_{19}N_2O$ ($MH^+$) Requires: 279.1492 (−0.1 ppm error).

Lab Notebook Reference: CHK 2/121 p.177

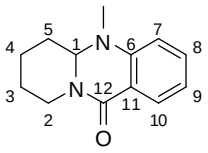
**6,7,8,9-Tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzoxazin-11-one (149ai):**




Synthesised using general DIA procedure A from imine **146n** (28.0 mg, 0.250 mmol), acid **147a** (55.8 mg, 0.404 mmol), DIPEA (108 μL, 0.623 mmol) and T3P (321 mg, 0.505 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate) afforded compound **149ai** as a white oil (4.3 mg, 7%); $R_f$ 0.57 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2901, 1643, 1587, 1564, 1448, 1391, 1311, 1262, 1242, 748; $\delta_H$ (400 MHz, $CDCl_3$) 7.94 (1H, dd, *J* = 7.6, 1.6 Hz, H-10), 7.42 (1H, ddd, *J* = 8.3, 7.6, 1.6 Hz, H-8), 7.07 (1H, ddd, *J* = 7.6, 7.6, 0.8 Hz, H-9), 6.90 (1H, dd, *J* = 8.3, 0.8 Hz, H-7), 5.21 (1H, dd, *J* = 9.88, 4.18 Hz, H-1), 4.51–4.46 (1H, m, H-2eq), 2.78 (1H, ddd, *J* = 13.6, 13.6, 3.5 Hz, H-2ax), 2.26–2.22 (1H, m, H-5a), 1.96–1.93 (1H, m, H-3/4), 1.86–1.81 (2H, m, H-5b, H3/4), 1.63–1.42 (2H, m, H-3/4); $\delta_C$ (100 MHz, $CDCl_3$) 163.4 (C-12), 156.6 (C-6), 134.0 (C-8), 128.1 (C-10), 122.2 (C-9), 117.5 (C-11), 116.0 (C-7), 85.9 (C-1), 41.3 (C-2), 31.4 (C-5), 23.5 (C-3/4), 21.2 (C-3/4); HRMS ($ESI^+$): Found: 204.1020; $C_{12}H_{14}NO_2$ ($MH^+$) Requires: 204.1019 (−0.6 ppm error) .

Lab Notebook Reference: CHK 1/18 p.33

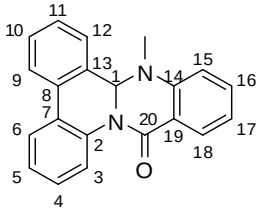
**5-Methyl-5,5a,6,7,8,9-hexahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (149aj):**



Synthesised using general DIA procedure A from dodecahydo-4a,8a,12a-triazatriphenylene **146n** (26.1 mg, 0.173 mmol), acid **147n** (43.0 mg, 0.173 mmol), DIPEA (55.7 μL, 0.320 mmol) and T3P (165 mg, 0.260 mmol) in toluene (1.7 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149aj** as a colourless oil (15.0 mg, 40%); $R_f$ 0.39 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1624, 1581, 1463, 1449, 1290, 1156; $\delta_H$ (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J* = 7.6, 1.7 Hz, H-10), 7.32 (1H, ddd, *J* = 8.3, 7.6, 1.7 Hz, H-8), 6.76 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz, H-9), 6.51 (1H, dd, *J* = 8.3, 1.0 Hz, H-7), 4.83–4.76 (1H, m, H-2eq), 4.64 (1H, dd, *J* = 10.6, 2.4 Hz, H-1), 2.88 (3H, s, C*H*$_3$), 2.67–2.60 (1H, m, H-2ax), 2.02–1.95 (1H, m, H-3/4/5), 1.82–1.55 (5H, m, H-3,4,5); $\delta_C$ (100 MHz, $CDCl_3$) 162.6 (C-12), 146.4 (C-6), 133.9 (C-8), 128.8 (C-10), 117.4 (C-9), 114.8 (C-11), 111.0 (C-7), 78.1 (C-1), 45.0 (C-2), 34.8 (C-*C*H$_3$), 28.3 (C-3/4/5), 24.7 (C-3/4/5), 24.4 (C-3/4/5); HRMS ($ESI^+$): Found: 217.1340; $C_{13}H_{17}N_2O$ ($MH^+$) Requires: 217.1335 (−2.1 ppm error).

Lab Notebook Reference: CHK/WPU 1255

**9-Methyl-8b, 9-dihydro-14*H*-quinazolino [3,2 -*f*]phenanthridin-14-one (149al):**

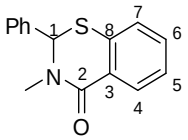


Synthesised using general DIA procedure A from phenanthridine **146o** (45.6 mg, 0.254 mmol), acid **147n** (46.2 mg, 0.305 mmol), DIPEA (82.0 μL, 0.471 mmol) and T3P (243 mg, 0.382 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **149al** as a yellow oil (6.6 mg, 8%); $R_f$ 0.8 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2875, 2808, 1635, 1583, 1482, 1460, 1417, 1365; $\delta_H$ (400 MHz, $CDCl_3$) 7.91 (1H, dd, *J* = 7.6, 2.9 Hz, ArH), 7.42 (1H, dd, *J* = 7.7, 1.6 Hz, ArH), 7.75 (1H, dd, *J* = 7.6, 0.7 Hz,

ArH, ), 7.66 (1H, dd, *J* = 7.7, 1.5 Hz, ArH), 7.48–7.37 (4H, m, ArH), 7.26 (1H, ddd, *J* = 7.5, 7.5, 1.1 Hz, ArH), 7.06 (1H, d, *J* =7.4 Hz, ArH), 6.86 (1H, d, *J* = 8.2 Hz, ArH), 6.80 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz, ArH) 5.74 (1H, s, H-1), 3.37 (3H, s, NC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 164.3 (C-20), 149.4 (Ar C), 139.2 (Ar C), 135.2 (Ar C), 134.0 (Ar CH), 132.9 (Ar C), 129.3 (Ar CH), 128.8 (Ar CH), 128..4 (Ar CH), 128.0 (Ar CH), 127.4 (Ar C), 127.1 (Ar CH), 126.6 (Ar CH), 124.9 (Ar CH), 124.0 (Ar CH), 122.5 (Ar CH), 118.1 (Ar CH), 115.3 (Ar C), 112.1 (Ar CH), 75.4 (C-1), 38.8 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 313.1334; $C_{21}H_{17}N_2O$ ($MH^+$) Requires: 313.1335 (0.5 ppm error).

Lab Notebook Reference: CHK 2/85 p.127

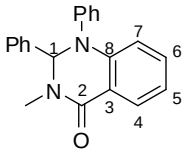
**3-Methyl-2-phenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-one (149am):**




Synthesised using general DIA procedure A from imine **146p** (51.8 mg, 0.435 mmol), acid **147m** (80.43 mg, 0.522 mmol), DIPEA (140 μL, 0.804 mmol) and T3P (415 mg, 0.652 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 2:1 petrol:ethyl acetate) afforded compound **149am** as an orange solid (11.5 mg, 99%); mp 77–79 °C [Lit. mp 79–81 °C];[168] $R_f$ 0.37 (2:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 8.16 (1H, dd, *J* = 7.7, 1.6 Hz, H-4), 7.33–7.19 (7H, m, ArH), 7.09 (1H, dd, *J* = 7.7, 1.3 Hz, H-7), 5.64 (1H, s, H-1), 3.25 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 164.2 (C-2), 138.4 (Ar C), 132.9 (Ar C), 132.0 (Ar CH), 130.0 (C-4), 128.8 (Ar C), 128.6 (Ar CH), 128.4 (Ar CH), 127.3 (Ar CH), 126.2 (Ar CH), 126.2 (Ar CH), 63 (C-1), 36.0 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 256.0794; $C_{15}H_{14}NOS$ ($MH^+$) Requires: 256.0791 (−1.3 ppm error). This compound has been reported previously in the literature, but no NMR data was reported.[168]

Lab Notebook Reference: CHK 1/48 p.69

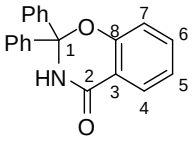
**3-Methyl-1,2-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one (149an):**




Synthesised using general DIA procedure A from imine **146p** (24.6 μL, 0.200 mmol), acid **147o** (51.2 mg, 0.240 mmol), DIPEA (64.5 μL, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149an** as a white solid (43.0 mg, 68%); mp 220–223 °C; $R_f$ 0.57 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1581, 1471, 1373, 1279, 1238, 1207; $\delta_H$ (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J* = 7.9, 1.2 Hz, H-4), 7.37–7.24 (8H, m, ArH), 7.19–7.13 (3H, m, ArH), 6.96 (1H, ddd, *J* = 7.9, 7.9, 1.1 Hz, H-5), 6.85 (1H, dd, *J* = 8.2, 1.1 Hz, H-7), 5.96 (1H, s, H-1), 3.18 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 162.8 (C-2), 146.1 (Ar C), 143.9 (Ar C), 139.3 (Ar C), 133.0 (Ar CH), 129.8 (Ar CH), 128.9 (Ar CH), 128.8 (Ar CH), 128.6 (Ar CH), 126.5 (Ar CH), 124.8 (Ar CH), 123.3 (Ar CH), 121.3 (Ar CH), 120.5 (Ar C), 118.8 (Ar CH), 80.0 (C-1), 34.3 (C-*C*H$_3$); HRMS ($ESI^+$): Found: 315.1493; $C_{21}H_{19}N_2O$ ($MH^+$) Requires: 315.1492 (−0.5 ppm error).

Lab Notebook Reference: CHK/WPU 1239

**2,2-Diphenyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (149ao):**

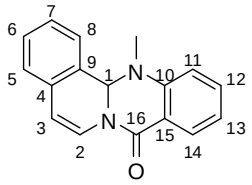



Synthesised using general DIA procedure A from imine **146q** (35.6 μL, 0.200 mmol), acid **147a** (33.1 mg, 0.240 mmol), DIPEA (64.5 μL, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **147ao** as a white solid (36.0 mg, 60%); mp 220–223 °C; $R_f$ 0.60 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1647, 1627, 1589, 1448, 1354, 1219; $\delta_H$ (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J* = 7.9, 1.5 Hz, H-4), 7.52–7.48 (4H, m, ArH), 7.44–7.34 (7H, m, ArH), 7.05–6.98 (2H, m, ArH), 6.72 (1H, br s, N*H*); $\delta_C$ (100 MHz, $CDCl_3$) 162.6 (C-2), 156.0 (C-8), 141.3 (C-Ph), 134.8 (Ar CH), 129.1 (Ar CH), 128.5 (Ar CH), 127.8 (Ar CH), 127.1 (Ar CH), 122.3

(Ar CH), 118.0 (C-3), 117.5 (Ar CH), 92.0 (C-1); HRMS ($ESI^+$): Found: 302.1174; $C_{20}H_{16}NO_2$ ($MH^+$) Requires: 302.1176 (0.6 ppm error)

Lab Notebook Reference: CHK/WPU 1240

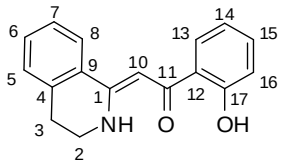
**13-Methyl-13,13a-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (149ap):**




Synthesised using general DIA procedure A from isoquinoline **146r** (29.8 μL, 0.250 mmol), acid **147n**, (45.4 mg, 0.300 mmol), DIPEA (80.6 μL, 0.463 mmol) and T3P (239 mg, 0.375 mmol) in toluene (2.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded compound **149ap** as a colourless oil (62.0 mg, 94%); $R_f$ 0.80 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1618, 1581, 1432, 1395, 1362, 1304, 1238, 1154, 884; $\delta_H$ (400 MHz, $CDCl_3$) 8.08 (1H, dd, *J* = 8.2, 1.5 Hz, H-14), 7.53 (1H, ddd, *J* = 8.1, 7.3, 1.6 Hz, ArH), 7.44 (1H, d, *J* = 7.1 Hz, ArH), 7.40 (1H, d, *J* = 8.0 Hz, H-2), 7.30–7.18 (4H, m, ArH), 7.05 (1H, dd, *J* = 7.4, 1.7 Hz, ArH), 6.44 (1H, s, H-1), 5.71 (1H, d, *J* = 8.0 Hz, H-3), 2.63 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 162.0 (C-16), 150.5 (C-10), 134.2 (Ar CH), 131.7 (Ar C), 129.3 (Ar CH), 129.2 (Ar CH), 127.8 (Ar CH), 127.3 (Ar CH), 126.7 (Ar C), 125.7 (Ar CH), 124.1 (Ar CH), 123.5 (Ar C), 123.3 (C-2), 122.8 (Ar CH), 106.0 (C-3), 72.1 (C-1), 36.7 (C-*C*H$_3$); HRMS ($ESI^+$): Found: 263.1176; $C_{17}H_{15}N_2O$ ($MH^+$) Requires: 263.1179 (1.1 ppm error) .

Lab Notebook Reference: CHK/WPU 1257

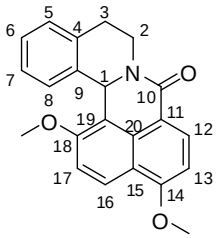
**1-(2-Hydroxyphenyl)-2-[(1*Z*)-1,2,3,4-tetrahydroisoquinolin-1-ylidene]ethan-1-one (177):**




Synthesised using general DIA procedure A from imine **146m** (32.0 mg, 0.220 mmol), acid **147a** (36.5 mg, 0.264 mmol), DIPEA (71.1 μL, 0.408 mmol) and T3P (211 mg, 0.331 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1→3:1→2:1 petrol:ethyl acetate) afforded compound **177** as a coloureless oil (12.4 mg, 21%); $R_f$ 0.50 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2879, 1588, 1572, 1532, 1462, 1304, 1269, 1133; $\delta_H$ (400 MHz, $CDCl_3$) 11.37 (1H, s, N*H*), 7.83 (1H, d, *J* = 7.8 Hz, ArH), 7.77 (1H, dd, *J* = 8.0, 1.4 Hz, ArH), 7.46 (1H, ddd, *J* = 7.4, 7.4, 1.4 Hz, ArH), 7.40–7.32 (2H, m, ArH), 7.28–7.26 (1H, m, ArH), 6.94 (1H, dd, *J* = 8.3, 1.2 Hz, ArH), 6.86–6.82 (1H, m, ArH), 6.36 (1H, s, H-10), 3.60–3.56 (1H, m, H-2), 2.99 (1H, t, *J* = 6.7 Hz, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 190.9 (C-11), 162.0 (C-17), 159.1 (C-1), 136.7 (C-4/9), 133.3 (Ar CH), 131.5 (Ar CH), 129.1 (C-4/9), 128.4 (Ar CH), 127.5 (Ar CH), 127.3 (Ar CH), 125.8 (Ar CH), 121.0 (C-12), 118.2 (Ar CH), 118.2 (Ar CH), 85.7 (C-10), 38.8 (C-2), 28.2 (C-3); HRMS ($ESI^+$): Found: 266.1169; $C_{17}H_{16}NO_2$ ($MH^+$) Requires: 266.1176 (2.6 ppm error).

Lab Notebook Reference: CHK 1/20 p.35

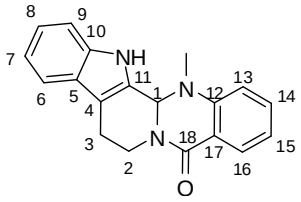
**11,14-Dimethoxy-5,14b-dihydro-6*H*,8*H*-benzo[de]isoquino[1,2-*a*]isoquinolin-8-one (149q):**



Synthesised using general DIA procedure B from imine **146e** (53.4 mg, 0.407 mmol), acid **147q** (113 mg, 0.489 mmol), DIPEA (131 μL, 0.753 mmol), T3P (388 mg, 0.611 mmol) and $BF_3{\cdot}Et_2O$ (0.250 mL, 2.04 mmol) in toluene (2.5 mL) at rt for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **149q** as a pink solid (125 mg, 89%); mp 242–248 °C; $R_f$ 0.2 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2944, 2845, 1638, 1586, 1518, 1461, 1412, 1349, 1261, 1242, 1186, 1055, 1048, 1093, 736; $\delta_H$ (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* = 9.2 Hz, ArH), 8.24 (1H, d, *J* = 8.1 Hz, ArH), 7.38 (1H, d, *J* = 9.2 Hz, ArH), 7.20–7.12 (2H, m, ArH), 6.96 (1H, t, *J* = 7.8 Hz, ArH), 6.75 (1H, d, *J* = 8.1 Hz, ArH), 6.49 (1H, d, *J* = 7.8 Hz, ArH), 6.22 (1H, s, H-1), 4.70 (1H, ddd, *J* = 13.5, 7.1, 6.6 Hz, H-2a), 4.03 (3H, s, C*H*$_3$), 3.97 (3H, s, C*H*$_3$), 3.61 (1H, ddd, *J* = 13.5, 7.1, 7.1 Hz, H-2b), 3.34 (1H, ddd, *J* = 16.1, 7.1, 7.1 Hz, H-3a), 3.07 (1H, ddd, *J* = 16.1, 7.1, 6.6 Hz, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 163.7 (C-10), 158.5 (C-14/18), 154.4 (C-14/18), 138.0 (Ar C), 135.6 (Ar C), 130.7 (Ar C), 128.9 (Ar CH), 128.5 (Ar CH), 127.2 (Ar CH), 125.7 (Ar CH), 123.9 (Ar CH), 123.6 (Ar CH), 119.3 (Ar C), 116.7 (Ar C), 113.7 (Ar C), 111.2 (Ar CH), 102.1 (Ar CH), 55.9 (C-*C*H$_3$), 55.7 (C-1), 55.6 (C-*C*H$_3$), 42.3 (C-2), 27.2 (C-3); HRMS ($ESI^+$): Found: 346.1440; $C_{22}H_{20}INO_3$ ($MH^+$) Requires: 346.1438 (0.6 ppm error).

Lab Notebook Reference: CHK 4/240 p.44

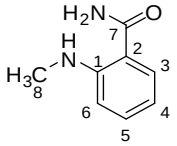
**Evodiamine (205):**




Synthesised using general DIA procedure A from *β*-carboline **146j** (34.0 mg, 0.200 mmol), acid **147n** (36.2 mg, 0.240 mmol), DIPEA (64.5 μL, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) afforded evodiamine **205** as a pale yellow solid (58.0 mg, 95%); mp 262–264 ºC [Lit. mp 268–270 $^{o}$C];[27b] $R_f$ 0.5 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 2285, 1602, 1485, 1365, 1287, 1258, 1207, 1147 ; $\delta_H$ (400 MHz, DMSO-$d_6$) 11.08 (1H, br s, N*H*), 7.80 (1H, dd, *J* = 7.9, 1.6 Hz, ArH), 7.51–7.45 (2H, m, ArH), 7.36 (1H, dd, *J* = 7.9, 0.6 Hz, ArH), 7.12–6.94 (4H, m, ArH), 6.13 (1H, s, H-1), 4.64 (1H, ddd, *J* = 12.7, 4.5, 4.5 Hz, H-2eq), 3.21 (1H, ddd, 12.7, 12.7, 4.8, H-2ax), 2.96–2.87 (1H, m, H-3a), 2.88 (3H, s, C*H*$_3$), 2.83–2.76 (1H, m, H-3b); $\delta_C$ (100 MHz, DMSO-$d_6$) 164.3 (C-18), 148.8 (Ar C), 136.5 (Ar C), 133.5 (Ar CH), 130.6 (Ar C), 128.0 (Ar CH), 126.0 (Ar C), 121.9 (Ar CH), 120.3 (Ar CH), 119.3 (Ar C), 118.9 (Ar CH), 118.2 (Ar CH), 117.5 (Ar CH), 111.7 (Ar CH), 111.5 (Ar C), 69.8 (C-1), 40.8 (C-2), 36.4 (C-*C*H$_3$), 19.5 (C-3); HRMS (ESI$^+$): Found: 304.1445; $C_{19}H_{18}N_3O$ (MH$^+$) Requires: 304.1444 (−0.1 ppm error). Obtained data in accord with those reported in the literature.[61]

Lab Notebook Reference: CHK 2/98 p.148

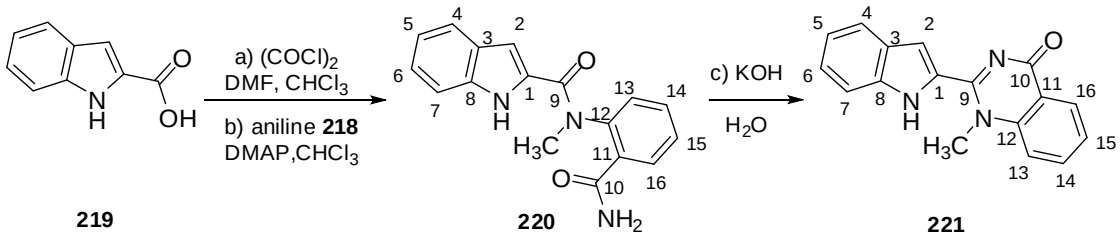
**2-(Methylamino)benzamide (218):**[71]



To a stirred suspension of *N*-methylisatoic anhydride **217** (10.0 g, 56.0 mmol) in ethanol (40 mL) was added dropwise 33% aq. $NH_3$ (10 mL). After addition, the solution was refluxed at 88 °C for 2 h. On cooling, a solid formed which was then collected by filtration and washed several times with cooled ethanol (5.58 g, 66%); $\delta_H$ (400 MHz, $CDCl_3$) 7.84–7.79 (br s, N*H*$_2$), 7.33–7.39 (2H, m, ArH), 6.70 (1H, d, *J* = 8.1 Hz, ArH), 6.59 (1H, dd, *J* = 8.1, 8.1 Hz, ArH), 5.74–5.71 (br s, N*H*), 2.88 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.2 (C-7), 151.1 (Ar C), 133.6 (Ar CH), 128.2 (Ar CH), 114.4 (Ar CH), 112.9 (Ar C), 111.4 (Ar CH), 29.6 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 151.0867; $C_8H_{11}N_2O$ ($MH^+$) Requires: 151.0866 (−0.3 ppm error). Obtained data in accord with those reported in the literature.[71]

Lab Notebook Reference: CHK 1/61 p.91

**2-(1*H*-Indol-2-yl)-1-methyl-1,4-dihydroquinazolin-4-one (221):**

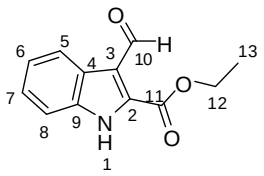



To a solution of indole-2-carboxylic acid **219** (5.00 g, 31.0 mmol) in chloroform, (350 mL) oxalyl chloride (4.42 mL, 52.3 mmol) and 2 drops of DMF were added. The reaction was heated to reflux (70 °C) for 1 h. Then the solvent was evaporated to dryness *in vacuo* to give indole-2-carbonyl chloride (6.79 g). The residue was taken up with chloroform (763 mL) and DMAP (462 mg, 3.78 mmol) and aniline **218** (16.0 g, 107 mmol) were added. The reaction mixture was stirred at 70 °C for 1 h, before quenching with water (800 mL). Following extraction with dichloromethane (3 × 800 mL), the organic phase was washed with water (2 × 500 mL) and brine (500 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo* affording amide **220** as an orange solid (10.4 g). [mp 185–188 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3128, 1643,

1596, 1550, 1497, 1400, 1371, 1322, 738, 723; $\delta_H$ (400 MHz, DMSO-$d_6$) 11.51 (1H, br s, N*H*), 7.69 (1H, br, N*H*), 7.64–7.62 (1H, m, ArH), 7.55–7.52 (2H, m, ArH), 7.39–7.36 (3H, m, ArH, H-2), 7.27 (1H, d, *J* = 7.3 Hz, ArH), 7.10 (1H, dd, *J* = 7.3, 7.3 Hz, ArH), 6.90 (1H, dd, *J* = 7.3, 7.3 Hz, ArH), 5.28 (1H, br, N*H*), 3.35 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 168.9 (C-9), 162.0 (C-10), 142.2 (Ar C), 136.1 (Ar C), 135.8 (Ar C), 131.7 (Ar CH), 130.8 (Ar C), 130.3 (Ar CH), 129.3 (Ar CH), 128.9 (Ar CH), 127.4 (Ar C), 122.0 (C-2), 119.9 (Ar CH), 112.6 (Ar CH), 39.09 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 294.1236; $C_{17}H_{16}N_3O_2$ ($MH^+$) Requires: 294.1237 (0.4 ppm error)]. The crude product was added in 1 M aq. KOH (13.6 g in 242 mL in water, 242 mmol) and was stirred for 1 h at 105 °C. The resultant solid was isolated by filtration and washed with cold water (800 mL), 10 % aq. HCl (300 mL), ether (300 mL) and dried *in vacuo*, affording compound **221** as a yellow solid. (7.69 g, 90 %); mp decompose at 210 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 1604, 1576, 1498, 1482, 1464, 1422, 1410, 1365, 1324, 1241, 1129; $\delta_H$ (400 MHz, DMSO-$d_6$) 12.02 (br, 1H, N*H*), 8.13 (1H, dd, *J* = 7.9, 1.4, ArH), 8.13 (1H, dd, *J* = 7.9, 1.4, ArH), 7.91 (1H, ddd, *J* = 8.4, 7.0, 1.6, ArH), 7.83 (1H, d, *J* = 8.4 Hz, ArH), 7.69 (1H, dd, *J* = 7.9, 0.7, ArH), 7.60–7.55 (2H, m, ArH), 7.30–7.25 (2H, m, ArH/H-2), 7.10 (1H, ddd, *J* = 7.9, 7.0, 1.0 Hz, ArH), 4.09 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 167.1 (C-9/10), 154.4 (C-9/10), 142.2 (Ar C), 136.8 (Ar C), 134.0 (Ar CH), 129.2 (Ar C), 127.9 (Ar C), 126.9 (Ar CH), 126.1 (Ar CH), 124.3 (C-2), 121.6 (Ar CH), 120.1 (Ar C), 119.9 (Ar CH), 117.1 (Ar CH), 112.6 (Ar CH), 108.8 (Ar CH), 38.3 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 276.1134; $C_{17}H_{14}N_3O$ ($MH^+$) Requires: 276.1131 (−0.9 ppm error).

Lab Notebook Reference: CHK 2/135 p.197

**Ethyl 3-formyl-1*H*-indole-2-carboxylate (226):**[75a,76]

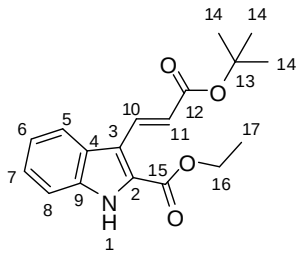



$POCl_3$ (2.71 mL, 29.1 mmol) was added dropwise to a stirred solution of DMF (7.9 mL, 102 mmol) at 0 °C to obtain the chloroiminium ion. A solution of indole **225** (5.00 g, 26.4 mmol) in DMF (8 mL, 102 mmol) and chloroform (30 mL) was added to the vessel containing the formylating agent and the resulting mixture was stirred

at rt for 1 h and at 70 °C for 4 h. The chloroform was removed *in vacuo* and then the reaction mixture was poured into cold water (100 mL) and neutralized with 2 M NaOH. The yellow precipitate was collected by filtration to give product **226** as a yellow powder (5.6 g, 99%); $R_f$ 0.8 (1:1, petrol:ethyl acetate); $\delta_H$ (400 MHz, DMSO-$d_6$) 10.61 (1H, s, H-10), 8.24 (1H, dd, *J* = 8.0, 1.1 Hz, H-5/8), 7.57 (1H, dd, *J* = 8.3, 1.1 Hz, H-5/8), 7.39 (1H, ddd, *J* = 8.3, 7.1, 1.1 Hz, H-6/7), 7.30 (1H, ddd, *J* = 8.0, 7.1, 1.1 Hz, H-6/7), 4.45 (2H, q, *J* = 7.1 Hz, H-12), 1.40 (3H, t, *J* = 7.1 Hz, H-13); $\delta_C$ (100 MHz, DMSO-$d_6$) 187.5 (C-10), 160.1 (C-11), 135.7 (Ar C), 132.6 (Ar C), 125.9 (Ar CH), 124.7 (Ar C), 123.4 (Ar CH), 122.3 (Ar CH), 118.3 (Ar C), 113.1 (Ar CH), 61.8 (C-12), 14.0 (C-13); Obtained data in accord with those reported in the literature.[76]

Lab Notebook Reference: CHK 2/82 p.120

**Ethyl 3-[(1*E*)-3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-1*H*-indole-2-carboxylate (227):**

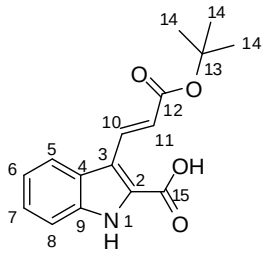



A magnetically stirred solution of [(*tert*-butoxycarbonyl)ethenyl]triphenyl phosphorane (4.07 g, 10.8 mmol) and ethyl 3-formyl-1*H*-indole-2-carboxylate **226** (1.81 g, 8.32 mmol) in a 1:1 mixture of $CH_3CN$/dioxane (43 mL) was heated at 70 °C for 17 h under nitrogen atmosphere. The solvent was evaporated under reduced pressure and the crude residue purified by column chromatography ($SiO_2$, 2:1→1:1 petrol:ethyl acetate) to give compound **227** as a white solid (2.52 g, 96%) (only *E*-isomer was observed); $R_f$ 0.8 (2:1 petrol:ethyl acetate); mp 148–151 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3254, 2929, 1657, 1595, 1546, 1487, 1437, 1417, 1313, 1276, 1234, 1124; $\delta_H$ (400 MHz, $CDCl_3$) 8.50 (1H, d, *J* = 16.3 Hz, H-10), 7.97 (1H, dd, *J* = 8.2, 1.0 Hz, H-5/8), 7.54 (1H, ddd, *J* = 8.3, 1.0, 1.0 Hz, H-5/8), 7.39–7.34 (1H, m, H-6/7), 7.23 (1H, ddd, *J* = 8.2, 7.0, 1.0 Hz, H-6/7), 6.52 (1H, d, *J* = 16.3 Hz, H-11), 4.41 (2H, q, *J* = 7.1 Hz, H-16), 1.51 (9H, s, H-14), 1.40 (3H, t, *J* = 7.1 Hz, H-17); $\delta_C$ (100 MHz, DMSO-$d_6$) 166.1 (C-12), 160.8 (C-15), 136.6 (C-10), 136.4 (Ar C), 127.0 (Ar C),

125.4 (Ar CH), 124.7 (Ar C), 122.0 (Ar CH), 121.6 (Ar CH), 118.8 (C-11), 115.4 (Ar C), 113.2 (Ar CH), 79.5 (C-13), 61.1 (C-16), 27.9 (C-14), 14.1 (C-17); HRMS ($ESI^+$): Found: 316.1546; $C_{18}H_{22}NO_4$ ($MH^+$) Requires: 316.1543 (−0.5 ppm error).

Lab Notebook Reference: CHK 2/83 p.122.

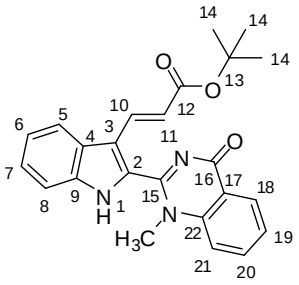
**3-[(1*E*)-3-(*tert*-Butoxy)-3-oxoprop-1-en-1-yl]-1*H*-indole-2-carboxylic acid (228):**




To a round bottom flask containing ester **227** (1.79 g, 5.68 mmol) in a 1:1 mixture of EtOH/$H_2O$ (57 mL), LiOH·$H_2O$ (714 mg, 17.0 mmol) was added. The reaction mixture was stirred at 50 °C for 1 h. The ethanol was removed *in vacuo* and the crude was dissolved in water (100 mL) and then acidified with 10% aq. HCl. The precipitate was collected by filtration to give product **228** as a yellow solid (1.49 g, 91%) mp 185–190 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3363, 3296, 2983, 1679, 1623, 1315, 1290, 1210, 1148, 1130, 986, 863, 849, 739; $\delta_H$ (400 MHz, $CDCl_3$) 12.28 (1H, s, COO*H*), 8.55 (1H, d, *J* = 16.4 Hz, H-10), 7.95 (1H, d, *J* = 8.2 Hz, H-5/8), 7.51 (1H, d, *J* = 8.2 Hz, H-5/8), 7.36–7.33 (1H, m, H-6/7), 7.24–7.20 (1H, m, H-6/7), 6.49 (1H, d, *J* = 16.4 Hz, H-11), 3.35 (1H, br s, N*H*), 1.47 (9H, s, H-14); $\delta_C$ (100 MHz, $CDCl_3$) 166.3 (C-12), 162.4 (C-15), 137.0 (C-10), 136.4 (Ar C), 128.3 (Ar C), 125.1 (Ar CH), 124.8 (Ar C), 121.9 (Ar CH), 121.5 (Ar CH), 117.9 (C-11), 114.9 (Ar C), 113.2 (Ar CH), 79.4 (C-13), 27.9 (C-14); HRMS ($ESI^+$): Found: 310.1039; $C_{16}H_{17}NaO_4$ ($MNa^+$) Requires: 310.1050 (3.0 ppm error).

Lab Notebook Reference: CHK 2/84 p.131

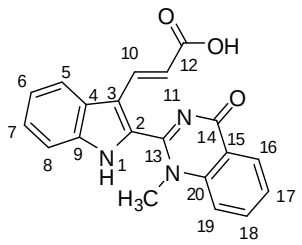
***tert*-Butyl (2*E*)-3-[2-(1-methyl-4-oxo-1,4-dihydroquinazolin-2-yl)-1*H*-indol-3-yl]prop-2-enoate (230):**



To a solution of indole-2-carboxylic acid derivative **228** (740 mg, 2.58 mmol) in chloroform (50 mL), oxalyl chloride (0.654 mL, 17.7 mmol) and 2 drops of DMF were added. The reaction was heated to reflux (70 °C) for 1 h. Then the solvent was evaporated to dryness *in vacuo* to give indole-2-carbonyl chloride. The residue was taken up with chloroform (52 mL) and DMAP (31.5 mg, 0.258 mmol) and aniline **218** (1.16 g, 7.74 mmol) were added. The reaction mixture was stirred at 70 °C for 1 h, before quenching with water (120 mL). Following extraction with dichloromethane (3 × 120 mL), the organic phase was washed with water (2 × 80 mL) and brine (80 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo* affording amide **229**. The crude product was added in 3.5 M aq. KOH (926 mg in 4.7 mL water, 16.5 mmol) and was stirred for 1 h at 105 °C. The resultant solid was isolated by filtration and washed with cold water (120 mL), 10 % aq. HCl (50 mL) and dried *in vacuo*, affording compound **230** as a yellow solid (818 mg, 79%); mp 215–223 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2971, 1705, 1622, 1600, 1511, 1493, 1440, 1396, 1365, 1324, 1296, 1252, 1144, 1072; $\delta_H$ (400 MHz, DMSO-$d_6$) 8.21 (1H, dd, *J* = 7.9, 1.4 Hz, ArH), 8.03–7.95 (2H, m, ArH), 7.88 (1H, d, *J* = 8.4, ArH), 7.78 (1H, d, *J* = 16.1 Hz, H-10), 7.69–7.65 (1H, m, ArH), 7.60–7.58 (1H, m, ArH), 7.40–7.36 (1H, m, ArH), 7.31–7.27 (1H, m, ArH), 6.44 (1H, d, *J* = 16.1 Hz, H-11), 3.67 (3H, s, $CH_3$), 1.45 (9H, s, H-14); $\delta_C$ (100 MHz, DMSO-$d_6$) 166.2 (C-12), 154.2 (C-15/16), 141.4 (C-15/16), 136.6 (C-10), 135.9 (Ar CH), 134.5 (Ar CH), 131.5 (Ar CH), 131.4 (Ar C), 128.8 (Ar CH) , 128.7 (Ar CH), 127.2 (Ar C), 124.5 (Ar CH), 122.0 (Ar C), 121.0 (Ar C), 119.9 (Ar C), 117.0 (C-11), 116.5 (Ar CH), 112.9 (Ar CH), 112.2 (Ar C), 79.5 (C-13), 37.9 (C-*C*$H_3$), 27.8 (C-14); HRMS ($ESI^+$): Found: 402. 1801; $C_{24}H_{24}N_3O_3$ ($MH^+$) Requires: 402.1812 (2.8 ppm error).

Lab Notebook Reference: CHK 2/89 p.133 and CHK 2/90 p.135

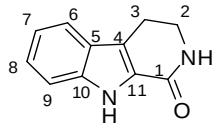
**(2*E*)-3-[2-(1-Methyl-4-oxo-1,4-dihydroquinazolin-2-yl)-1*H*-indol-3-yl)prop-2-enoic acid (214a):**




To a round bottom flask containing ester **230** (3.15 g, 7.85 mmol), formic acid (105 mL) was added at rt. The reaction mixture was stirred at 50 °C for 1 h. Then the solvent was evaporated to dryness *in vacuo* to give compound **214a** as a yellow solid (2.71 g, 100 %); mp 220–223 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3206, 2820, 1679, 1604, 1588, 1521, 1494, 1429, 1415, 1398, 1320, 1302, 1206; $\delta_H$ (400 MHz, $CDCl_3$) 12.48 (1H, br s, COOH), 8.20 (1H, d, *J* = 7.9 Hz, ArH), 8.02 (1H, d, *J* = 8.1 Hz, ArH), 7.97–7.93 (1H, m, ArH), 7.85 (1H, d, *J* = 8.4 Hz, ArH), 7.79 (1H, d, *J* = 16.1 Hz, H-10), 7.67–7.57 (2H, m, ArH), 7.39–7.35 (1H, m, ArH), 7.31–7.27 (1H, m, ArH), 6.46 (1H, *J* = 16.1 Hz, H-11), 3.66 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 168.6 (C-12), 154.9 (C-13/14), 142.0 (C-13/14), 137.1 (Ar C), 136.8 (C-10), 135.0 (Ar CH), 133.4 (Ar C), 132.1 (Ar C), 127.8 (Ar CH), 127.4 (Ar CH), 125.2 (Ar C), 124.9 (Ar CH), 122.5 (Ar CH), 121.4 (Ar CH), 120.4 (Ar C), 117.5 (Ar CH), 116.6 (C-11), 113.4 (Ar CH), 112.6 (Ar CH), 38.2 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 346.1180; $C_{20}H_{16}N_3O_3$ (MH$^+$) Requires: 346.1186 (1.3 ppm error).

Lab Notebook Reference: CHK/WPU 1348

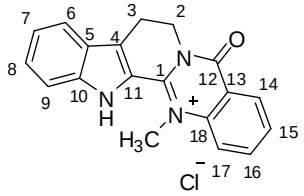
**1*H*, 2*H*, 3*H*, 4*H*, 9*H*-Pyrido[3,4-*b*]indol-1-one (239):**[80]




Dimethylphosphoryl azide (3.42 mL, 15.8 mmol) was added dropwise to a stirred solution of indole-3-propionic acid **237** (3.00 g, 15.8 mmol) and $NEt_3$ (2.06 mL, 15.8 mmol) in toluene (48 mL) at rt under $N_2$. The reaction was then heated with stirring at 90 °C for 90 min. Most of the solvent was removed under reduced pressure to afford mobile oil. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (7.95 mL, 193 mmol) was added dropwise to the rapidly stirred mixture, which was then warmed to rt and stirred for 16 h. The reaction was basified with 1 M aq. NaOH (to pH = 10) and ethyl acetate (64 mL) was added. The rapidly stirred mixture was heated at 50 °C for 1 h, until all the crude material was dissolved. The reaction mixture was cooled to rt and extracted with ethyl acetate (3 × 100 mL), washed with brine (100 mL), and then dried over $MgSO_4$. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **239** as a colorless oil (2.78 g, 94%); $R_f$ 0.3 (ethyl acetate); $\delta_H$ (400 MHz, DMSO-$d_6$) 11.59 (1H, br s, N*H*), 7.59–7.57 (2H, m, H-6/9, N*H*), 7.38 (1H, d, *J* = 8.2 Hz, H-6/9), 7.21 (1H, dd, *J* = 8.2, 7.0 Hz, H-7/8), 7.05 (1H, dd, *J* = 8.2, 7.0 Hz, H-7/8), 3.50 (2H, t, *J* = 7.0 Hz, H-2), 2.91 (2H, t, *J* = 7.0 Hz, H-3); HRMS ($ESI^+$): Found:187.0861; $C_{11}H_{11}N_2O$ ($MH^+$) Requires: 187.0866 (2.4 ppm error); Obtained data in accord with those reported in the literature.[80]

Lab Notebook Reference: CHK 3/140 p.8

**Dehydroevodiamine hydrochloride (233):**[79]

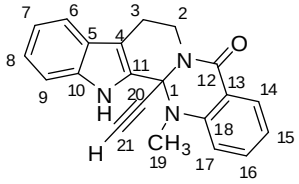



To a round bottom flask containing lactam **239** (8.85 g, 47.5 mmol) in toluene (400 mL), dimethyl athranilate **240** (9.27 mL, 63.2 mmol) was added at rt. Then $POCl_3$ (29.4 mL, 316 mmol) was added and the resulting pale orange solution was heated at 110 °C for 1 h before pouring carefully into ice cold water (2 L). The resultant precipitate was

isolated by filtration, washed with water (1 L) and collected with methanol, concentrated and dried under high vacuum, affording compound **233** as a yellow solid (16.1 g, 88%); mp 204–207 °C (Lit. mp 215–218 °C);[81] $\nu_{max}$ (thin film)/cm$^{-1}$ 1703, 1544, 1499, 1425, 1335, 1207, 1103, 769, 683, 520; $\delta_H$ (400 MHz, DMSO-d$_6$) 8.35 (1H, dd, *J* = 7.9, 1.5 Hz, H-14), 8.20–8.11 (2H, m, H-16,17), 7.88 (1H, d, *J* = 8.1 Hz, H-6), 7.82–7.78 (1H, m, H-15), 7.73 (1H, d, *J* = 8.3 Hz, H-9), 7.52 (1H, ddd, *J* = 8.3, 6.9, 1.0 Hz, H-8), 7.27 (1H, ddd, *J* = 8.1, 6.9, 1.0 Hz, H-7), 4.47 (2H, t, *J* = 6.7 Hz, H-2), 4.41 (3H, s, C*H*$_3$), 3.33 (2H, t, *J* = 6.7 Hz, H-3); $\delta_C$ (100 MHz, DMSO-d$_6$) 158.2 (C-12), 150.0 (C-1), 141.4 (C-10), 139.6 (C-18), 136.6 (C-16), 130.1 (C-4), 128.7 (C-8), 128.6 (C-15), 127.7 (C-14), 123.3 (C-5), 121.6 (C-7), 121.5 (C-6), 120.1 (C-11), 118.7 (C-13), 118.5 (C-17), 113.6 (C-9), 42.0 (C-2), 41.0 (C-*C*H$_3$), 18.5 (C-3); HRMS (ESI$^+$): Found: 302.1274; $C_{19}H_{16}N_3O$ (MH$^+$) Requires: 302.1288 (4.7 ppm error). Obtained data in accord with those reported in the literature.[81]

Lab Notebook Reference: CHK 3/141 p.16

**13b-Ethynyl-14-methyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(7*H*)-one (242):**




**Procedure A:**

*n*-BuLi (2.78 mL, 4.44 mmol, 1.6 M in hexanes) was added to a solution of trimethylsilylacetylene (0.84 mL, 5.92 mmol) in THF (15 mL) at −78 °C and the mixture was stirred for 30 min. The resulting ((trimethylsilyl)ethynyl) lithium solution was then added to a suspension of DHED salt **233** (500 mg, 1.48 mmol) in THF (15 mL) at −78 °C *via* cannula. The mixture was stirred at −78 °C for 30 min and then allowed to stir at rt for another 30 min before quenching with water (30 mL). Following extraction with dichloromethane (3 x 30 mL), the organic phase was washed with water (2 × 20 mL) and brine (20 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo* affording aklyne **241** as an orange solid (634 g). The crude material was used directly to the next step without further purification. TBAF (1 M, 1.78 mL, 1.78 mmol)

was added to the solution of alkyne **241** at 0 °C in THF (15.8 mL) and the resulting solution was stirred at 0 °C for 10 min. Then, the reaction mixture was poured into the water, extracted with ether (3 x 30 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo* affording compound **242** as an orange solid (435 mg, 90%).

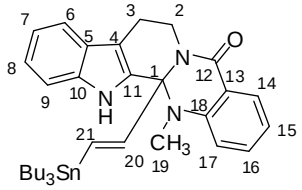
**Procedure B:**

Ethynylmagnesium chloride (0.750 mL, 0.375 mmol) was added to a stirred suspension of DHED salt **233** (42.2 mg, 0.125 mmol) in toluene (1.5 mL) at 0 °C. Then LiCl (16.9 mg, 0.400 mmol) was added. The reaction mixture was stirred for 5 mins at 0 °C and then allowed to warm at rt and stirred for an additional 1 h before quenching with water (20 mL). Following extraction with dichloromethane (3 x 20 mL), the organic phase was washed with water (2 × 20 mL) and brine (20 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo* affording compound **242** as an orange solid (30.3 mg, 74%).

$R_f$ 0.4 (3:1 petrol:ethyl acetate); mp 220–223 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3194, 1597, 1554, 1443, 1397, 1329, 1294, 1243, 1219, 740, 717; $\delta_H$ (400 MHz, DMSO-$d_6$) 11.64 (1H, br s, N*H*), 7.98 (1H, dd, *J* = 7.7, 1.5 Hz, ArH), 7.64–7.59 (2H, m, ArH), 7.46 (1H, d, *J* = 8.1 Hz, ArH), 7.31–7.21 (3H, m, ArH), 7.1 (1H, ddd, *J* = 7.1, 7.1, 1.0 Hz, ArH), 4.90–4.86 (1H, m, H-2a), 3.60 (1H, s, H-21), 3.10–2.99 (2H, m, H-2b,3a), 2.87–2.78 (1H, m, H-3b), 2.58 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 162.8 (C-12), 148.7 (Ar C), 136.9 (Ar C), 133.6 (Ar CH), 128.5 (Ar C), 127.8 (Ar CH), 125.1 (Ar CH), 123.0 (Ar CH), 122.6 (Ar CH), 121.8 (Ar C), 121.2 (Ar CH), 119.1 (Ar CH), 118.9 (Ar CH), 111.9 (Ar C), 111.8 (Ar C), 82.0 (C-1/20), 75.1 (C-1/20), 69.7 (C-21), 38.0 (C-2), 36.9 (C-*C*H$_3$), 20.1 (C-3); HRMS ($ESI^+$): Found: 328.1453; $C_{21}H_{18}N_3O$ ($MH^+$) Requires: 328.1444 (2.5 ppm error).

Lab Notebook Reference: CHK 2/134 p.196 (Procedure A) and CHK 3/180 p.61 (Procedure B)

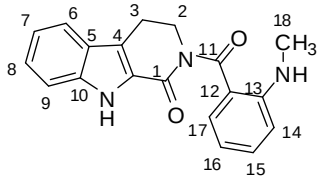
**14-Methyl-13b-[(*E*)-2-(tributylstannyl)vinyl]-8,13,13b,14-tetrahydroindolo [2',3':3,4] pyrido[2,1-*b*]quinazolin-5(7*H*)-one (235):**




Tributyltin hydride (1.02 mL, 3.77 mmol) was added to a mixture of alkyne **242** (1.00 g, 3.05 mmol) and AIBN (94.2 mg, 0.611 mmol) in degassed anhydrous benzene (15 mL). The rapidly stirred suspension was heated at 100 °C for 1 h. The solvent was removed *in vacuo*. Purification by column chromatography ($SiO_2$, pure petrol→19:1 petrol:ethyl acetate→10:1 petrol:ethyl acetate) afforded compound **235** as an orange oil. (1.02 g, 54 %) (only *E*-isomer); $R_f$ 0.5 (3:1 petrol:ethyl acetate); mp 148–154 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2911, 2879, 2826, 2808, 1607, 1581, 1446, 1399, 1280; $\delta_H$ (400 MHz, $CDCl_3$) 8.11 (1H, br s, N*H*), 8.03 (1H, dd, *J* = 7.8, 1.4 Hz, ArH), 7.59 (1H, d, *J* = 8.0 Hz, ArH), 7.45–7.40 (2H, m, ArH), 7.28–7.24 (1H, m, ArH), 7.19–7.11 (3H, m, ArH), 6.18 (1H, d, *J* = 18.9 Hz, H-20/21), 5.97 (1H, d, *J* = 18.9 Hz, H-20/21), 5.16 (1H, ddd, *J* = 12.9, 4.9, 1.6 Hz, H-2eq), 3.21 (1H, ddd, *J* = 12.9, 11.5, 4.4 Hz, H-2ax), 3.03–2.88 (2H, m, H-3a,b), 2.45 (3H, s, H-19), 1.27–1.08 (12H, m, *n*-Bu (C*H*$_2$)), 0.81–0.77 (9H, m, *n*-Bu (C*H*$_3$)), 0.72–0.68 (6H, m, *n*-Bu (C*H*$_2$)); $\delta_C$ (100 MHz, $CDCl_3$) 163.7 (C-12), 152.3 (Ar C), 144.7 (C-20/21), 136.7 (Ar C), 132.9 (Ar CH), 130.5 (C-20/21), 130.3 (Ar CH), 128.4 (Ar CH), 126.3 (Ar C), 125.0 (Ar C), 124.3 (Ar CH), 123.9 (Ar CH), 123.0 (Ar CH), 120.0 (Ar CH), 119.0 (Ar CH), 113.2 (Ar C), 111.4 (Ar C), 100.0 (C-1), 40.1 (C-19), 38.8 (C-2), 28.9 (*n*-Bu (*C*H$_2$)), 27.2 (*n*-Bu (*C*H$_2$)), 20.7 (C-3), 13.7 (*n*-Bu (*C*H$_3$)), 9.5 (n-Bu (*C*H$_2$)); HRMS ($ESI^+$): Found: 620.2641; $C_{33}H_{46}N_3O^{120}Sn$ ($MH^+$) Requires: 620.2664 (2.7 ppm error).

Lab Notebook Reference: CHK 3/139 p.20

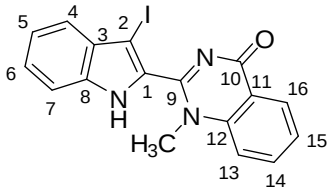
**Rhetsinine (244):**[79]




*n*-BuLi (0.555 mL, 0.888 mmol, 1.6 M in hexanes) was added to a solution of tributyl(ethynyl)stannane (0.343 mL, 1.18 mmol) in THF (3 mL) at −78 °C and the mixture was stirred for 30 min. The resulting ((tributylstannyl)ethynyl)lithium solution was then added to a suspension of DHED salt **233** (100 mg, 0.296 mmol) in THF (3 mL) at −78 °C *via* cannula. The mixture was stirred at −78 °C for 30 min and then allowed to stir at rt for another 30 min before quenching with water (20 mL). Following extraction with dichloromethane (3 x 20 mL), the organic phase was washed with water (2 × 20 mL) and brine (20 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo* affording compound **244** as an orange solid (488 mg, 52%); mp 160–168 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3270, 2932, 1652, 1620, 1609, 1573, 1552, 1516, 1483, 1280; $\delta_H$ (400 MHz, $CDCl_3$) 11.76 (1H, br s, N*H*), 7.70 (1H, d, *J* = 8.0 Hz, ArH), 7.41 (1H, d, *J* = 8.3 Hz, ArH), 7.34–7.29 (3H, m, ArH), 7.12 (1H, ddd, *J* = 8.0, 7.9, 0.8 Hz, ArH), 6.92–6.89 (1H, m), 6.70 (1H, d, *J* = 8.3 Hz, ArH), 6.49 (1H, 7.9, 7.9, 0.8 Hz, ArH), 4.11 (2H, t, *J* = 6.2 Hz, H-2), 3.18 (2H, t, *J* = 6.2 Hz, H-3), 2.81 (3H, d, *J* = 5 Hz, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 175.2 (C-11), 161.6 (C-1), 150.2 (Ar C), 138.9 (Ar C), 134.0 (Ar CH), 132.0 (Ar CH), 126.6 (Ar C), 126.2 (Ar CH), 125.0 (Ar C), 123.0 (Ar C), 121.4 (Ar CH), 120.6 (Ar CH), 117.5 (Ar C), 114.7 (Ar CH), 113.3 (Ar CH), 111.4 (Ar CH), 47.4 (C-2), 30.1 (C-*C*H$_3$), 21.1 (C-3); HRMS ($ESI^+$): Found: 302.1297; $C_{19}H_{16}N_3O$ ($MH^+$) Requires: 302.1288 (−3.0 ppm error). Obtained data in accord with those reported in the literature (only Mass spectrometry and IR spectroscopy data available).[79]

Lab Notebook Reference: CHK 3/157 p.33

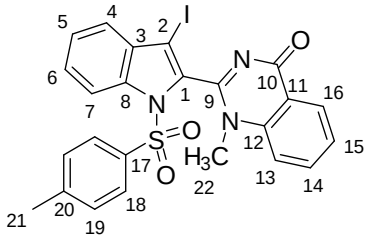
**2-(3-Iodo-1*H*-indol-2-yl)-1-methyl-1,4-dihydroquinazolin-4-one (236):**




To a solution of quinazolinone **221** (4.00 g, 14.5 mmol) in acetone (500 mL) was added *N*-iodosuccinimide (3.43 g, 15.3 mmol). After stirring for 2 h at rt, sat. aq. $Na_2S_2O_3$ (300 mL) was added and the mixture was stirred for an additional 5 min at rt. The resulting precipitate was isolated by filtration and washed with cold water (1 L). The resulting white solid was collected and dried *in vacuo*. Purification by column chromatography ($SiO_2$, DCM→DCM, 1% MeOH→DCM, 2% MeOH→ DCM, 4% MeOH) afforded compound **236** as a white solid (4.94 g, 85%); $R_f$ 0.5 (18:1 DCM:MeOH); mp 214–219 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1572, 1503, 1469, 1445, 1425, 1410, 1377, 1353, 1157, 1129, 1057, 755; $\delta_H$ (400 MHz, DMSO-$d_6$) 12.41 (1H, br, N*H*), 8.22 (1H, dd, *J* = 8.0, 1.6 Hz, ArH), 7.99 (1H, ddd, *J* = 8.4, 7.1, 1.6 Hz, ArH), 7.91 (1H, dd, *J* = 8.4, 1.0 Hz, ArH), 7.69 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, ArH), 7.55 (1H, dd, *J* = 8.2, 0.9 Hz, ArH), 7.47 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 7.37 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, ArH), 7.27 (1H, ddd, *J* = 8.0, 7.0, 0.9 Hz, ArH), 3.81 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 167.8 (C-9/10), 155.8 (C-9/10), 141.9 (Ar C), 136.7 (Ar CH), 134.9 (Ar C), 133.1 (Ar C), 130.2 (Ar C), 127.8 (Ar CH), 127.3 (Ar CH), 124.9 (Ar CH), 121.5 (Ar CH), 121.5 (Ar CH), 120.4 (Ar C), 117.5 (Ar CH), 113.1 (Ar CH), 62.8 (C-2), 38.0 (C-*C*H$_3$); HRMS ($ESI^+$): Found: 402.0090; $C_{17}H_{13}IN_3O$ ($MH^+$) Requires: 402.0098 (1.9 ppm error); Elemental Analysis: calculated for $C_{17}H_{12}IN_3O$ requires C, 50.89; H, 3.01; N, 10.47; found C, 51.43; H, 2.98; N, 10.24

Lab Notebook Reference: CHK 2/137 p.201

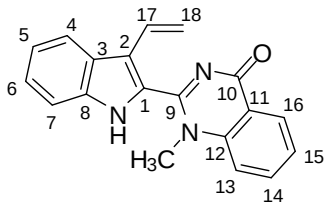
**2-[3-Iodo-1-(4-methylbenzenesulfonyl)-1*H*-indol-2-yl]-1-methyl-1,4 dihydroquinazolin-4-one (245):**




To a solution of iodide **236** (3.00 g, 7.48 mmol) in DMF (25 mL) was added sodium hydride (449 mg, 11.2 mmol, 60% dispersion in mineral oil) at 0 °C. After stirring for 10 min at 0 °C, tosyl chloride (2.14 g, 11.2 mmol) was added. The mixture was stirred for an additional 30 min at rt before quenching with water (800 mL). The resulting precipitate was isolated by filtration and washed with cold water (1 L). The resulting white solid was collected (DCM soluble) and dried *in vacuo*. Purification by column chromatography ($SiO_2$, DCM→DCM, 1% MeOH→DCM, 1% MeOH) afforded compound **245** as a colourless oil (3.80 g, 92%); $R_f$ 0.6 (10:0.2 DCM:MeOH); $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1573, 1503, 1470, 1444, 1426, 1410, 1377, 1353, 1157; $\delta_H$ (400 MHz, $CDCl_3$) 8.28 (1H, d, *J* = 7.9, 1.4, ArH), 8.09–8.07 (3H, m, ArH), 8.04–8.00 (1H, m, ArH), 7.94 (1H, d, *J* = 8.3 Hz, ArH), 7.73 (1H, ddd, *J* = 7.9, 7.9, 0.9, ArH), 7.60 (1H, ddd, *J* = 8.5, 8.5, 1.5 Hz, ArH), 7.56–7.44 (4H, m, ArH), 3.72 (3H, s, H-22), 2.37 (3H, s, H-21); $\delta_C$ (100 MHz, $CDCl_3$) 168.3 (C-9/10), 155.4 (C-9/10), 147.4 (Ar C), 141.8 (Ar C), 135.0 (Ar CH), 134.0 (Ar C), 133.8 (Ar C), 132.0 (Ar C), 131.2 (Ar C), 128.6 (Ar CH), 128.5 (Ar CH), 128.4 (Ar CH), 128.0 (Ar CH), 126.1 (Ar CH), 123.6 (Ar CH), 123.6 (Ar CH), 120.7 (Ar C), 117.9 (Ar CH), 115.1 (Ar CH), 76.8 (C-2), 37.2 (C-22), 22.0 (C-21); HRMS ($ESI^+$): Found: 577.9997; $C_{24}H_{19}IN_3NaO_3S$ ($MNa^+$) Requires: 578.0006 (1.5 ppm error).

Lab Notebook Reference: CHK 2/137 p.201

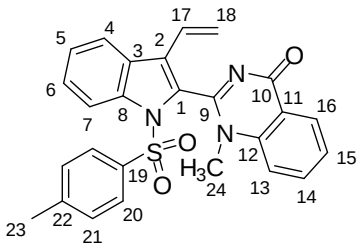
**2-(3-Ethenyl-1*H*-indol-2-yl)-1-methyl-1,4-duhydroquinazolin-4-one (247):**




$NEt_4Cl$ (82.5 mg, 0.498 mmol) was added to a Schlenk tube under Ar and flame dried *in vacuo*. Iodide **236** (200 mg, 0.498 mmol), stannane **246** (273 mg, 0.748 mmol) and $PdCl_2(PPh_3)_2$ (17.4 mg, 0.0249 mmol) were then added to the Schlenk tube under Ar. Degassed DMF (4 mL) was added and the reaction mixture was stirred at rt until everything dissolved. The rapidly stirred mixture was then heated at 80 °C for 10 min before CuI (142.5 mg, 0.748 mmol) was added. The reaction mixture was stirred at 80 °C for 2 h, before cooling to rt and quenching with water (20 mL). Following extraction with dichloromethane (3 × 20 mL), the organic phase was washed with water (20 mL) and then dried over $MgSO_4$. Purification by column chromatography (10% $K_2CO_3$ in $SiO_2$,[169] DCM→DCM, 2% MeOH→DCM, 3% MeOH) afforded compound **247** as a yellow solid (89 mg, 82%); mp 182–186 °C; $R_f$ 0.6 (DCM, 10% MeOH); $\nu_{max}$ (thin film)/$cm^{-1}$ 3109, 2923, 1629, 1605, 1519, 1492, 1448, 1397, 1339, 1260, 765, 748; $\delta_H$ (400 MHz, DMSO-$d_6$) 12.00 (1H, br s, N*H*), 8.17 (1H, d, *J* = 7.7 Hz, ArH), 7.98 (1H, d, *J* = 8.0 Hz, ArH), 7.92 (1H, dd, *J* = 8.4, 8.5 Hz, ArH), 7.81 (1H, d, *J* = 8.4 Hz, ArH), 7.61 (1H, dd, *J* = 8.5, 7.7 Hz, ArH), 7.51 (1H, d, *J* = 8.1 Hz, ArH), 7.30 (1H, dd, *J* = 8.1, 7.9 Hz, ArH), 7.19 (1H, dd, *J* = 8.0, 7.9 Hz, ArH), 6.90 (1H, dd, *J* = 17.8, 11.5 Hz, H-17), 5.73 (1H, dd, *J* = 17.8, 1.2 Hz, H-18a), 5.27 (1H, dd, *J* = 11.5, 1.2 Hz, H-18b), 3.70 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 167.3 (C-9/10), 155.2 (C-9/10), 141.6 (Ar C), 136.4 (Ar C), 134.1 (Ar CH), 128.8 (C-17), 128.7 (Ar CH), 127.1 (Ar CH), 126.4 (Ar CH), 124.8 (Ar C), 123.7 (Ar CH), 120.7 (Ar CH), 120.6 (Ar C), 119.8 (Ar C), 116.9 (Ar CH), 114.7 (Ar C), 113.5 (C-18), 112.3 (Ar CH), 37.3 (C-*C*H$_3$); HRMS ($ESI^+$): Found: 302.1286; $C_{19}H_{16}N_3O$ ($MH^+$) Requires: 302.1288 (0.8 ppm error).

Lab Notebook Reference: CHK 3/152 p.27

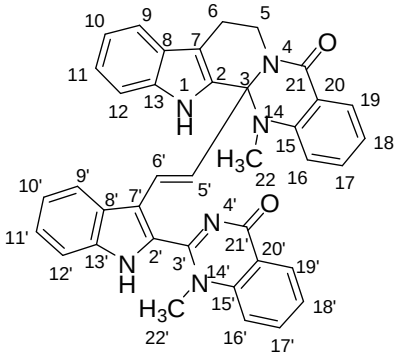
**2-[3-Ethenyl-1-(4-methylbenzenesulfonyl)-1*H*-indol-2-yl]-1-methyl-1,4-dihydroquinazolin-4-one (248):**



$NEt_4Cl$ (59.7 mg, 0.360 mmol) was added to a Schlenk tube under Ar and flame dried *in vacuo*. Iodide **163** (200 mg, 0.360 mmol) and stannane **162** (172 mg, 0.541 mmol) and $PdCl_2(PPh_3)_2$ (12.6 mg, 0.0170 mmol) were then added to the Schlenk tube under Ar. Degassed DMF (4 mL) was added and the reaction mixture was stirred at rt until everything dissolved. The rapidly stirred mixture was then heated at 80 °C for 20 h before cooling and quenching with water (20 mL). Following extraction with ethyl acetate (3 × 20 mL), the organic phase was washed with water (20 mL) and then dried over $MgSO_4$. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded the title compound as a colourless oil. (70 mg, 41%); $R_f$ 0.3 (Ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2910, 2879, 1625, 1580, 1502, 1472, 1446, 1431, 1416, 1376, 1355, 1159; $\delta_H$ (400 MHz, $CDCl_3$) 8.47 (1H, ddd, *J* = 8.0, 1.6, 0.5 Hz, ArH), 8.13 (1H, ddd, *J* = 8.4, 1.0, 0.8 Hz, ArH), 7.91–7.88 (2H, m, ArH), 7.85–7.79 (2H, m, ArH), 7.58 (1H, ddd, *J* = 8.0, 7.2, 1.0 Hz, ArH), 7.52 (1H, d, *J* = 8.7 Hz, ArH), 7.44 (1H, ddd, *J* = 8.5, 7.3, 1.3 Hz, ArH), 7.34 (1H, ddd, *J* = 8.0, 7.3, 1.1 Hz, ArH), 7.24–7.22 (2H, m, ArH), 6.73 (1H, dd, *J* = 17.9, 11.6 Hz, H-17), 5.81 (1H, dd, *J* = 17.9, 1.0 Hz, H-18b), 5.43 (1H, dd, *J* = 11.6, 1.0 Hz, H-18a), 3.68 (3H, s, H-24), 2.30 (3H, s, H-23); $\delta_C$ (100 MHz, $CDCl_3$) 168.8 (C-9/1-), 154.7 (C-9/10), 145.7 (Ar C), 141.4 (Ar C), 135.7 (Ar C), 134.2 (Ar CH), 133.6 (Ar C), 129.9 (Ar CH), 128.8 (Ar CH), 128.6 (Ar C), 127.9 (Ar C), 127.8 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 126.2 (C-17), 124.6 (Ar CH), 122.7 (Ar C), 121.4 (Ar CH), 120.4 (Ar C), 119.5(C-18), 115.2 (Ar CH), 114.7 (Ar CH), 36.3 (C-24), 21.6 (C-23); HRMS ($ESI^+$): Found: 456.1358; $C_{26}H_{22}N_3O_3S$ ($MH^+$) Requires: 456.1376 (4.0 ppm error).

Lab Notebook Reference: CHK 3/138 p.3

**(±)-Dievodiamine (212):**

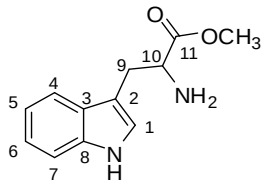


$NEt_4Cl$ (82.5 mg, 0.498 mmol) was added to a Schlenk tube under Ar and flame dried *in vacuo*. Iodide **236** (100 mg, 0.249 mmol), stannane **235** (231 mg, 0.374 mmol) and first batch of $PdCl_2(PPh_3)_2$ (17.4 mg, 0.0249 mmol) were then added to the Schlenk tube under Ar. Degassed DMF (2.5 mL) was added and the reaction mixture was stirred at rt until everything dissolved. The rapidly stirred mixture was then heated at 80 °C for 10 min. A second batch of $PdCl_2(PPh_3)_2$ (17.4 mg, 0.0249 mmol) and CuI (71.2 mg, 0.374 mmol) were then added. The reaction mixture was stirred at 80 °C for 2 h, before cooling and quenching with water (20 mL). Following extraction with ethyl acetate (3 × 20 mL), the organic phase was then dried over $MgSO_4$. Purification by column chromatography ($SiO_2$, DCM→DCM, 1% MeOH→DCM, 2% MeOH) followed by recrystallisation (DCM/hexane) afforded (±)-dievodiamine **212** as a pale yellow solid. (98 mg, 65%); $R_f$ 0.6 (DCM, 10 % MeOH); mp 229–233 °C (no Lit. mp has been reported); $\nu_{max}$ (thin film)/$cm^{-1}$ 3216, 3057, 2928, 1629, 1604, 1522, 1490, 1446, 1396, 1396, 1355, 1299, 1262, 1174, 1150, 733, 761. 703, 693; $\delta_H$ (400 MHz, DMSO-$d_6$) 12.00 (1H, br s, N*H*), 11.42 (1H, br s, N*H*), 8.18 (1H, d, *J* = 7.9 Hz, H-19'), 7.93 (1H, t, *J* = 8.3, 7.2 Hz, H-17'), 7.78 (1H, d, *J* = 7.7 Hz, H-19), 7.70–7.64 (2H, m, H-9',18'), 7.55–7.50 (2H, m, H-9,16'), 7.43 (1H, d, *J* = 8.1 Hz, H-12'), 7.37–7.32 (2H, m, H-12,17), 7.23 (1H, t, *J* = 8.1, 7.4 Hz, H-11'), 7.17–7.03 (5H, m, H-11,10',16,10,18), 6.55 (1H, d, *J* = 16.0 Hz, H-6'), 6.35 (1H, d, *J* = 16.0 Hz, H-5'), 4.91–4.88 (1H, m, H-5eq), 3.28 (3H, s, H-22'), 3.16–3.10 (1H, m, H-5ax), 2.95–2.91 (1H, m, H-6eq), 2.82–2.73 (1H, m, H-6ax), 2.47 (3H, m, H-22); $\delta_C$ (100 MHz, DMSO-$d_6$) 167.3 (C-21'), 162.6 (C-21), 154.9 (C-3'), 149.1 (C-15), 141.4 (C-15'), 136.8 (C-13), 136.3 (C-12'), 134.1 (C-17') , 133.2 (C-17), 130.7 (C-2), 128.9 (C-2'), 128.4 (C-5'), 127.5 (C-19), 127.1 (C-19'), 126.5 (C-18'), 125.5 (C-8), 124.5 (C-8'), 123.8 (C-11'), 123.3 (C-18), 122.9 (C-20), 122.4 (C-16), 122.2 (C-11), 121.5

(C-6'), 120.7 (C-10'), 120.3 (C-9'), 119.9 (C-20'), 118.9 (C-10), 118.6 (C-9), 116.9 (C-16'), 112.8 (C-7'), 112.4 (C-12'), 111.7 (C-12), 111.2 (C-7), 72.6 (C-3), 38.7 (C-22), 38.6 (C-5), 36.8 (C-22'), 20.2 (C-6); HRMS ($ESI^+$): Found: 625.2307; $C_{38}H_{30}N_6NaO_2$ ($MNa^+$) Requires: 625.2322 (2.4 ppm error).

Lab Notebook Reference: CHK 3/150 p. 25

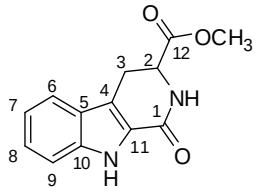
**Methyl 2-amino-3-(1*H*-indol-3-yl)propanoate (252):**[170]




To a suspension of tryptophan **251** (6.24 g, 30.6 mmol) in methanol (61.2 mL), $SOCl_2$ (5.36 mL, 73.4 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 20 h at rt. The solvent was evaporated and the residue was dissolved in water (100 mL) and basified to pH = 8 by adding sat. aq. $K_2CO_3$. The ester was extracted with dichloromethane (3 × 200 mL) and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure yielding compound **252** as a colourless oil (5.80 g, 87%); $\delta_H$ (400 MHz, $CDCl_3$) 8.18 (1H, br, N*H*), 7.62 (1H, dd, *J* = 7.9 Hz, H-4/7), 7.35 (1H, ddd, *J* = 8.1, 1.0, 1.1 Hz, H-4/7), 7.20 (1H, dd, *J* = 8.1, 7.0, 1.1 Hz, H-5/6), 7.13 (1H, ddd, *J* = 7.9, 7.0, 1.0 Hz, H-5/6), 7.06 (1H, d, *J* = 2.3 Hz, H-1), 3.84 (1H, dd, *J* = 4.8, 7.7 Hz, H-10), 3.72 (3H, s, OC*H*$_3$), 3.29 (1H, ddd, *J* = 14.4, 4.8, 0.7 Hz, H-9a), 3.06 (1H, ddd, *J* = 14.4, 7.7, 0.7 Hz, H-9b), 1.58 (1H, br, N*H*$_2$); HRMS ($ESI^+$): Found: 219.1126; $C_{12}H_{15}N_2O_2$ ($MH^+$) Requires: 219.1128 (0.9 ppm error). Obtained data in accord with those reported in the literature.[170]

Lab Notebook Reference: CHK 3/171 p.49

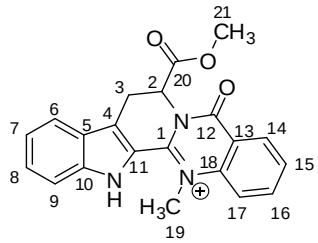
**Methyl 1-oxo-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]indole-3-carboxylate (254):**[92]




A solution of methyl 2-amino-3-(1*H*-indol-3-yl)propanoate **252** (207 mg, 0.947 mmol) in dichloromethane (1.3 mL) was added to a solution of DMAP (116 mg, 0.947 mmol) and $(Boc)_2O$ (496 mg, 2.27 mmol) in dichloromethane (1.3 mL) and the reaction mixture was stirred for 10 minutes at rt. TFA (0.725 mL, 9.47 mmol) was added and the reaction mixture was stirred for 1 h before quenching with sat. aq. $NaHCO_3$ (10 mL). Following extraction with dichloromethane (3 × 10 mL), the organic phase was washed with brine (10 mL) and then dried over $MgSO_4$. Purification by column chromatography ($SiO_2$, 2:1→1:1→1:2 petrol:ethyl acetate→pure ethyl acetate) afforded compound **254** as a yellow solid (120 mg, 52%); mp 183–186 °C; $R_f$ 0.4 (1:2 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3190, 2908, 1704, 1640, 1596, 1465, 1430, 1351, 1309, 1205, 1138; $\delta_H$ (400 MHz, $CDCl_3$) 9.34 (1H, br, N*H*), 7.61 (1H, dd, *J* = 8.0, 1.2 Hz, H-6/9), 7.46 (1H, dd, *J* = 8.2, 0.9 Hz, H-6/9), 7.34 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, H-7/8), 7.18 (1H, ddd, *J* = 8.0, 7.0, 0.9 Hz, H-7/8), 6.18 (1H, br N*H*), 4.58 (1H, ddd, *J* = 9.8, 6.0, 1.9 Hz, H-2), 3.82 (3H, s, OC*H*$_3$), 3.47 (1H, dd, *J* = 16.2, 6.0, H-3eq), 3.30 (1H, dd, *J* = 16.2, 9.8 Hz, H-3ax); $\delta_C$ (100 MHz, $CDCl_3$) 172.2 (C-1/12), 171.1 (C-1/12), 161.6 (Ar C), 137.5 (Ar C), 125.6 (C-7/8), 120.6 (C-7/8), 120.4 (C-6/9), 117.7 (Ar C), 112.6 (C-6/9), 99.9 (Ar C), 55.0 (C-2), 53.0 (C-O*C*H$_3$), 24.1 (C-3); HRMS ($ESI^+$): Found: 245.0925; $C_{13}H_{13}N_2O_3$ ($MH^+$) Requires: 245.0921 (−1.9 ppm error). This compound has been reported previously in the literature but no data were obtained.[92]

Lab Notebook Reference: CHK 3/166 p.100

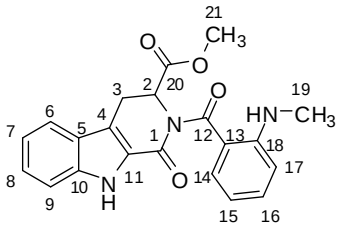
**7-(Methoxycarbonyl)-14-methyl-5-oxo-5,7,8,13-tetrahydroindolo [2',3':3,4] pyrido[2,1-*b*] quinazolin-14-ium (255):**



To a round bottom flask containing methyl 1-oxo-1*H*, *2H*, *3H*, *4H*, *9H*-pyrido[3,4-b]indole-3-carboxylate **254** (217 mg, 0.887 mmol), methyl athranilate **240** (0.130 mL, 0.887 mmol) was added at rt. Then $POCl_3$ (1.33 mL, 14.2 mmol) was added and the resulting solution was heated at 110 °C for 1 h before pouring carefully into ice cold water (100 mL). The resultant precipitate was isolated by filtration, washed with water (200 mL) and collected with dichloromethane, concentrated and dried under high vacuum, affording compound **255** as a yellow solid (299 mg, 85%); mp 80–85 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1710, 1611, 1553, 1500, 1428, 1361, 1340, 1204, 1131, 1102; $\delta_H$ (400 MHz, $CDCl_3$) 8.38 (1H, dd, *J* = 7.9, 1.4 Hz, ArH), 8.26–8.18 (2H, m, ArH), 7.93 (1H, d, *J* = 8.1 Hz, ArH), 7.88–7.84 (1H, m, ArH), 7.75 (1H, d, *J* = 8.3 Hz, ArH), 7.53 (ddd, *J* = 8.3, 6.9, 1.0 Hz, ArH), 7.27 (ddd, *J* = 8.1, 6.9, 1.0 Hz, ArH), 6.42 (dd, *J* = 6.7, 1.4 Hz, H-2), 4.49 (3H, s, H-19), 4.00 (1H, dd, *J* = 17.4, 1.4, H-3eq), 3.58 (1H, dd, *J* = 17.4, 6.7 Hz, H-3ax), 3.53 (3H, s, H-21); $\delta_C$ (100 MHz, $CDCl_3$) 168.4 (C-20), 157.6 (C-12), 148.8 (C-1), 142.0 (Ar C), 139.6 (Ar C), 137.5 (Ar CH), 129.4 (Ar CH), 129.3 (Ar CH), 128.1 (Ar C), 127.5 (Ar CH), 123.5 (Ar C), 122.1 (Ar CH), 121.7 (Ar CH), 119.2 (Ar CH), 119.2 (Ar C), 117.9 (Ar C), 113.9 (Ar CH), 53.6 (C-2), 53.3 (C-21), 41.6 (C-19), 21.7 (C-3); HRMS ($ESI^+$): Found: 360.1327; $C_{21}H_{18}N_3O_3$ ($MH^+$) Requires: 360.1343 (4.3 ppm error).

Lab Notebook Reference: CHK 3/169 p.47

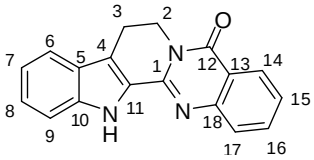
**Methyl 2-[2-(methylamino)benzoyl]-1-oxo-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*] indole-3-carboxylate (257):**




Sodium hydride (91.7 mg, 2.29 mmol, 60% dispersion in mineral oil) was added in a suspension of the salt **255** (605 mg, 11.5 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then was stirred at rt for 1.5 h. The resultant precipitate was isolated by filtration, washed with water (100 mL), concentrated and dried under high vacuum, affording compound **257** as a brown solid (241 mg, 40%); $\nu_{max}$ (thin film)/$cm^{-1}$ 3293, 3054, 2950, 1713, 1740, 1670, 1611, 1555, 1502, 1429, 1363, 1261, 1216, 1175, 749 ; $\delta_H$ (400 MHz, $CDCl_3$) 9.24 (1H, br, N*H*), 7.63 (1H, d, *J* = 8.0 Hz, ArH), 7.42 (1H, dd, *J* = 8.0, 1.6 Hz, ArH), 7.39–7.31 (2H, m, ArH), 7.24 (1H, d, *J* = 8.4 Hz, ArH), 7.18 (1H, ddd, *J* = 8.0, 6.9, 1.0 Hz, ArH), 6.75 (1H, d, *J* = 8.4 Hz, ArH), 6.53 (1H, ddd, *J* = 8.0, 7.1, 1.1 Hz, ArH), 5.20 (1H, dd, *J* = 6.0, 2.5 Hz, H-2), 3.69 (3H, s, H-21), 3.64–3.60 (2H, m, H-3), 2.93 (3H, d, *J* = 5.0 Hz, H-19); $\delta_C$ (100 MHz, $CDCl_3$) 172.1 (C-1/12/20), 171.6 (C-1/12/20), 170.9 (C-1/12/20), 151.0 (Ar C), 134.7 (Ar CH), 132.3 (Ar CH), 127.0 (Ar C), 126.3 (Ar CH), 126.1 (Ar C), 124.9 (Ar C), 121.1 (Ar C), 120.9 (Ar CH), 120.7 (Ar CH), 118.8 (Ar C), 114.4 (Ar CH), 111.2 (Ar CH), 100.0 (Ar CH), 59.2 (C-2), 53.0 (C-21), 29.7 (C-19), 24.5 (C-3); HRMS ($ESI^+$): Found: 400.1287; $C_{21}H_{19}N_3NaO_4$ ($MH^+$) Requires: 400.1268 (−4.9 ppm error).

Lab Notebook Reference: CHK 3/182 p.68

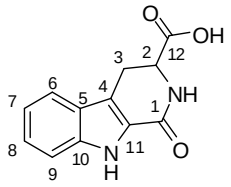
**Rutaecarpine (258):**



Salt **255** (30.0 mg, 0.076 mmol) was diluted in DMF (1 mL) and irradiated under microwave heating (200 watts, 200 °C) for 10 min. The solvent was evaporated to afford rutaecarpine **258** as a white solid (6.70 mg, 31%); $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 3337, 2926, 1651, 1595, 1470, 1401, 1327, 1229, 159, 127; $\delta_H$ (400 MHz, $CDCl_3$) 9.48 (1H, br, N*H*), 8.32 (1H, dd, *J* = 8.0, 1.4 Hz, ArH), 7.71 (1H, ddd, *J* = 8.2, 6.9, 1.4 Hz, ArH), 7.67–7.63 (2H, m, ArH), 7.43 (1H, ddd, *J* = 8.0, 6.9, 1.4 Hz, ArH), 7.38 (1H, d, *J* = 8.1 Hz, ArH), 7.32 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, ArH), 7.18 (1H, ddd, *J* = 8.0, 6.9, 1.1 ArH), 4.60 (2H, t, *J* = 6.9 Hz, H-2), 3.24 (2H, t, *J* = 6.9 Hz, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 161.6 (C-12), 147.4 (Ar C), 145.0 (Ar C), 138.3 (Ar C), 134.4 (Ar CH), 127.2 (Ar CH), 127.1 (Ar C), 126.5 (Ar CH), 126.2 (Ar CH), 125.7 (Ar C), 125.6 (Ar CH), 121.1 (Ar C), 120.6 (Ar CH), 120.1 (Ar CH), 118.4 (Ar C), 112.1 (Ar CH), 41.1 (C-2), 19.6 (C-3); HRMS (ESI$^+$): Found: 288.1134; $C_{18}H_{14}N_3O$ ($MH^+$) Requires: 288.1131 (-0.8 ppm error); Obtained data in accord with those reported in the literature.[26j]

Lab Notebook Reference: CHK 3/173 p.51

**1-Oxo-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (259):**

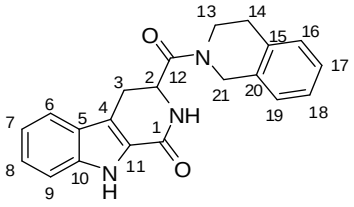


To a round bottom flask containing ester **254** (2.08 g, 8.52 mmol) in THF (25.6 mL), $LiOH{\cdot}H_2O$ (1.07 g, 25.6 mmol) in water (25.6 mL) was added at rt. The reaction mixture was stirred for 10 min. The yellow solution was dissolved in water (50 mL), washed with dichloromethane (100 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer, was extracted with ethyl acetate (3 × 100 mL), and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*, affording compound **259** as a yellow solid (1.65 g, 84%); mp 234–237 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3322, 1614,

1469, 1402, 1308, 1212, 1001; $\delta_H$ (400 MHz, $CDCl_3$) 11.64 (1H, br s, COO*H*), 7.67 (1H, d, *J* = 3.9 Hz, N*H*), 7.60 (1H, d, *J* = 7.9 Hz, H-6/9), 7.37 (1H, d, *J* = 8.2 Hz, H-6/9), 7.21 (1H, ddd, *J* = 8.2, 7.0, 1.0 Hz, H-7/8), 7.05 (1H, ddd, *J* = 7.9, 7.0, 1.0 Hz, H-7/8), 4.34–4.31 (1H, m, H-2), 3.32–3.23 (2H, m, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 173.8 (C-12), 161.5 (C-1), 137.0 (Ar C), 126.8 (Ar C), 124.8 (Ar CH), 124.1 (Ar C), 120.1 (Ar CH), 119.5 (Ar CH), 115.3 (Ar C), 112.4 (Ar CH), 53.9 (C-2), 23.4 (C-3); HRMS ($ESI^+$): Found: 231.0765; $C_{12}H_{11}N_2O_3$ ($MH^+$) Requires: 231.0764 (−0.6 ppm error).

Lab Notebook Reference: CHK 4/198 p.6

**3-(1,2,3,4-Tetrahydroisoquinoline-2-carbonyl)-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]-1-one (260):**

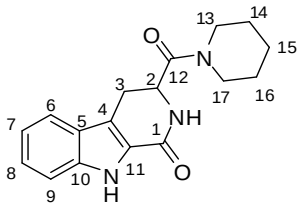



CDI (59.3 mg, 0.366 mmol) was added in a suspension of acid **259** (84.3 mg, 0.366 mmol) in THF (0.59 mL). The resulting solution was stirred for 1.5 h at rt after which 1,2,3,4-tetrahydroisoquinoline **163** (46.5 μL) was added. The resulting solution was stirred for 24 h at rt and then was concentrated to dryness. The reaction mixture was diluted in ethyl acetate (10 mL) and washed with $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 2:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **260** as a white solid (77.3 mg, 61%); mp 107–110°C; $R_f$ 0.2 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3190, 2884, 1635, 1625, 1559, 1431, 1309, 1266, 1211, 1138, 895; NMR spectra showed rotameric broadening; $\delta_H$ (400 MHz, $CDCl_3$) 10.73 (1H, br s, N*H*), 7.55–7.49 (2H, m, ArH), 7.27–7.10 (6H, m, ArH), 6.76 (1H, br s, N*H*), 5.01–4.95 (1H, m, H-2), 4.84–4.66 (2H, m, C$H_2$), 3.82–3.76 (2H, m, C$H_2$), 3.32–3.13 (2H, m, C$H_2$), 2.97–2.89 (2H, m, C$H_2$); Some of the $^{13}$C-NMR peaks were doubled due to rotameric broadening; $\delta_C$ (100 MHz, $CDCl_3$) 168.9 (C-1/12), 162.0 (C-1/12), 137.9 (Ar C), 134.7 (Ar C), 133.4 (Ar C), 132.6 (Ar C), 131.7 (Ar C), 129.1 (Ar CH), 128.3 (Ar CH), 127.3 (Ar CH), 126.7 (Ar CH), 126.6 (Ar CH), 126.5 (Ar CH), 126.5 (Ar CH), 125.9 (Ar CH), 125.1 (Ar C), 124.7 (Ar CH),

120.2 (Ar CH), 119.8 (Ar CH), 116.9 (Ar C), 113.0 (Ar CH), 54.4 (C-2), 47.4 (C-21), 45.1 (C-21'), 43.2 (C-13/14), 41.0 (C-13'/14'), 29.4 (C-13/14), 28.1 (C-13'/14'), 24.6 (C-3); HRMS ($ESI^+$): Found: 346.1558; $C_{21}H_{20}N_3O_2$ ($MH^+$) Requires: 346.1550 (−2.3 ppm error).

Lab Notebook Reference: CHK 3/199 p.86

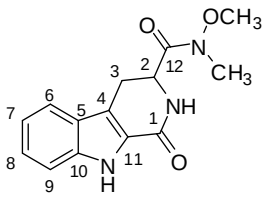
**3-(Piperidine-1-carbonyl)-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]indol-1-one (263):**




CDI (142 mg, 0.876 mmol) was added in a suspension of acid **259** (202 mg, 0.876 mmol) in THF (1.41 mL). The resulting solution was stirred for 1 h at rt. Piperidine **262** (0.086 mL, 0.876 mmol) was then added and the resulting solution was stirred for 24 h. The reaction mixture was quenched with water (10 mL) at −78 °C and extracted with dichloromethane (20 mL). The organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **263** as a yellow oil (70.9 mg, 27%); $\nu_{max}$ (thin film)/$cm^{-1}$ 3244, 2941, 1638, 1487, 1449, 1330, 1248, 1330, 1186, 727; $\delta_H$ (400 MHz, $CDCl_3$) 10.45 (1H, br s, N*H*), 7.55 (1H, d, *J* = 8.1 Hz, ArH), 7.48 (1H, d, *J* = 8.3 Hz, ArH), 7.31–7.27 (1H, m, ArH), 7.16–7.11 (1H, m, ArH), 6.47 (1H, br, N*H*), 4.90 (1H, ddd, *J* = 12.2, 5.4 Hz, H-2), 3.64–3.49 (4H, m, H-13,17), 3.26–3.11 (2H, m, H-3), 1.70–1.51 (6H, m, H-14,15,16); HRMS ($ESI^+$): Found: 298.1541; $C_{17}H_{20}N_3O_2$ ($MH^+$) Requires: 298.1550 (2.9 ppm error).

Lab Notebook Reference: CHK 4/219 p.19

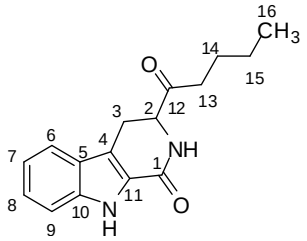
***N*-Methoxy-*N*-methyl-1-oxo-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]indol-3-carboxamide (265):**




To a stirred solution of acid **259** (1.27 g, 5.52 mmol) in DMF (8.5 mL), CDI (1.34 g, 8.27 mmol) was added at rt. The resulting suspension was stirred at rt for 1 h, before *N*,*O*-dimethylhydroxylamine hydrochloride (861 mg, 8.83 mmol) was added. The orange solution was stirred at rt for 48 h. The reaction mixture was diluted in ethyl acetate (20 mL) and washed with 10% aq. HCl. The acidic aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic extracts were washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was washed with water (6 × 50 mL) affording compound **265** as a yellow solid without any further purification (966 mg, 64%); mp 75–85 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3228, 1655, 1550, 1488, 1370, 1324, 1281, 1154, 980, 743, 507; $\delta_H$ (400 MHz, $CDCl_3$) 9.86 (1H, br, N*H*), 7.58 (1H,dd, *J* = 8.0, 1.1 Hz, H-6/9), 7.47 (1H, dd, *J* = 8.2, 0.9 Hz, H-6/9), 7.30 (1H, ddd, *J* = 8.2, 7.0, 1.1 Hz, H-7/8), 7.15 (1H, ddd, *J* = 8.0, 7.0, 0.9 Hz, H-7/8), 6.28 (1H, br, N*H*), 4.87 (1H, dd, *J* = 10.9, 5.5 Hz, H-2), 3.78 (3H, s, OC$H_3$), 3.50 (1H, dd, *J* = 15.9, 5.5 Hz, H-3eq), 3.29 (3H, s, C$H_3$), 3.18 (1H, dd, 15.9, 10.9 Hz, H-3ax); $\delta_C$ (100 MHz, $CDCl_3$) 171.0 (C-1/12), 170.4 (C-1/12), 161.8 (Ar C), 137.6 (Ar C), 125.2 (Ar CH), 125.0 (Ar C), 120.3 (Ar CH), 120.1 (Ar CH), 117.6 (Ar C), 112.7 (Ar CH), 61.6 (C-O*C*$H_3$), 54.5 (C-2), 32.6 (C-*C*$H_3$), 23.9 (C-3); HRMS ($ESI^+$): Found: 274.1182; $C_{14}H_{16}N_3O_3$ ($MH^+$) Requires: 274.1186 (1.4 ppm error).

Lab Notebook Reference: CHK 4/211 p.10

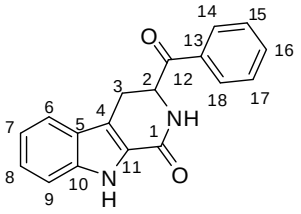
**3-Pentanoyl-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]indol-1-one (266):**




To a stirred solution of Weinreb amide **265** (298 mg, 1.09 mmol) in THF (13.1 mL), *n*-BuLi (2.05 mL, 3.28 mmol, 1.6 M solution in hexanes) was added at −78 °C. The resulting solution was stirred for 15 min at −78 °C and then for additional 15 min at −40 °C. The reaction mixture was quenched with water (20 mL) at −40 °C and extracted with dichloromethane (30 mL). The organic extracts were washed with sat. aq. $NH_4Cl$ (30 mL), brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate) afforded compound **266** as a brown oil (134 mg, 45%); $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3225, 2937, 1649, 1620, 1488, 1415, 1326, 1282, 908, 129, 627, 480; $\delta_H$ (400 MHz, $CDCl_3$) 10.69 (1H, br, N*H*), 7.58 (1H, d, *J* = 8.0 Hz, ArH), 7.50 (1H, d, *J* = 8.3 Hz, ArH), 7.31–7.26 (1H, m, ArH), 7.16–7.12 (1H, m, ArH), 6.88 (1H, br s, N*H*), 4.53 (1H, dd, *J* = 11.3, 5.7 Hz, H-2), 3.48 (1H, dd, *J* = 15.6, 5.7, H-3eq), 3.16 (1H, dd, *J* = 15.6, 11.3 Hz, H-3ax), 2.69–2.52 (2H, m, H-13), 1.66–1.58 (2H, m, H-14), 1.37–1.26 (2H, m, H-15), 0.93–0.89 (3H, m, H-16); $\delta_C$ (100 MHz, $CDCl_3$) 206.5 (C-12), 161.9 (C-1), 137.9 (Ar C), 126.3 (Ar C), 125.3 (Ar CH), 124.8 (Ar C), 120.4 (Ar CH), 119.9 (Ar CH), 117.3 (Ar C), 113.0 (Ar CH), 61.6 (C-2), 38.2 (C-13), 25.4 (C-14), 24.0 (C-3), 22.2 (C-15), 13.8 (C-16); HRMS ($ESI^+$): Found: 271.1440; $C_{16}H_{19}N_2O_2$ ($MH^+$) Requires: 271.1441 (0.4 ppm error).

Lab Notebook Reference: CHK 4/214 p.14

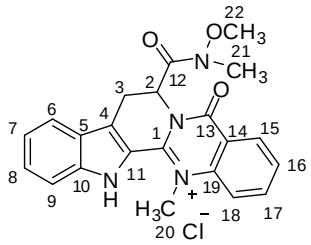
**3-Benzoyl-1*H*, 2*H*, 3*H*, 4*H*, 9*H*-pyrido[3,4-*b*]indol-1-one (267):**




To a stirred solution of Weinreb amide **265** (156 mg, 0.569 mmol) in THF (5.7 mL), PhLi (1.26 mL, 2.28 mmol, 1.8 M solution in ether) was added at −78 °C. The resulting solution was stirred for 3.5 h at −78 °C. The reaction mixture was quenched with water (10 mL) at −78 °C and extracted with dichloromethane (20 mL). The organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate) afforded compound **267** as a yellow solid (95.6 mg, 58%); mp 218–220 °C; $R_f$ 0.6 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3249, 2932, 1691, 1658, 1489, 1448, 1331, 1227, 1156, 746, 695, 665; $\delta_H$ (400 MHz, $CDCl_3$) 9.72 (1H, br, N*H*), 7.97–7.95 (1H, m, ArH), 7.70-7.65 (1H, m, ArH), 7.58–7.42 (4H, m, ArH), 7.36–7.28 (2H, m, ArH), 7.13 (1H, ddd, *J* =8.0, 7.0, 1.0 Hz, ArH), 6.44 (1H, br s, N*H*), 5.55 (1H, ddd, *J* = 12.0, 5.6, 1.4 Hz, H-2), 3.51 (1H, dd, *J* = 16.3, 5.6 Hz, H-3eq), 3.12 (1h, dd, *J* = 16.3, 12.0 Hz, H-3ax); $\delta_C$ (100 MHz, $CDCl_3$) 196.2 (C-12), 161.7 (C-1), 134.1 (Ar CH), 134.0 (Ar C), 129.1 (Ar CH), 128.5 (Ar CH), 128.1 (Ar CH), 126.8 (Ar C), 126.1 (Ar CH), 125.8 (Ar C), 125.4 (Ar CH), 124.9 (Ar C), 120.5 (Ar CH), 120.1 (Ar CH), 117.2 (Ar C), 112.7 (Ar CH), 58.7 (C-2), 25.9 (C-3) HRMS ($ESI^+$): Found: 291.1140; $C_{18}H_{15}N_2O_2$ ($MH^+$) Requires: 291.1128 (−4.1 ppm error).

Lab Notebook Reference: CHK 4/218 p.20

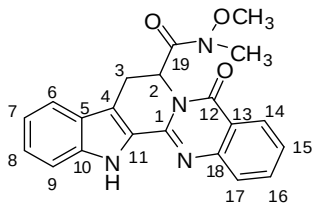
**7-[Methoxy(methyl)carbamoyl]-14-methyl-5-oxo-5,7,8,13-tetrahydroindolo [2',3':3,4] pyrido[2,1-*b*] quinazolin-14-ium (270):**



To a round bottom flask containing Weinreb amide **265** (101 mg, 0.371 mmol), methyl athranilate **240** (0.054 mL, 0.371 mmol) was added at rt. Then $POCl_3$ (0.557 mL, 5.96 mmol) was added and the resulting solution was heated at 110 °C for 1 h before pouring carefully into ice cold water (40 mL). The resultant precipitate was isolated by filtration, washed with water (100 mL) and collected with methanol, concentrated and dried under high vacuum, affording compound **270** as a brown solid (84.9 mg, 54%); mp 178–182 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1703, 1604, 1544, 1499, 1426, 1335, 1256, 1207, 1103, 1175, 1049, 769; $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, dd, *J* = 7.9, 1.2 Hz, ArH), 8.27–8.18 (2H, m, ArH), 7.90 (1H, d, *J* = 8.0 Hz, ArH), 7.85 (1H, dd, *J* = 7.9, 7.9 Hz, ArH), 7.73 (1H, d, *J* = 8.1 Hz, ArH), 7.53-7.50 (1H, m, ArH), 7.25 (1H, dd, *J* = 8.0, 7.8 Hz, ArH), 6.44–6.42 (1H, m, H-2), 4.51 (3H, s, H-20), 4.51 (3H, s, H-22), 3.81–3.77 (2H, m, H-3), 3.05 (3H, s, H-21); $\delta_C$ (100 MHz, $CDCl_3$) 166.3 (C-12), 157.8 (C-13), 150.4 (C-1), 141.9 (Ar C), 139.5 (Ar C), 137.5 (Ar CH), 129.3 (Ar CH), 128.9 (Ar CH), 127.9 (Ar CH), 125.6 (Ar C), 123.7 (Ar C), 121.9 (Ar CH), 121.5 (Ar CH), 119.8 (Ar C), 119.1 (Ar CH), 117.6 (Ar C), 113.8 (Ar CH), 61.6 (C-22), 52.5 (C-2), 41.8 (C-20), 32.0 (C-21), 21.7 (C-3); HRMS ($ESI^+$): Found: 389.1599; $C_{22}H_{21}N_4O_3$ ($MH^+$) Requires: 389.1608 (2.3 ppm error).

Lab Notebook Reference: CHK 4/216 p.13

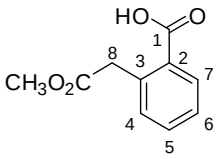
***N*-Methoxy-*N*-methyl-5-oxo-5,7,8,13-tetrahydroindolo[2',3':3,4]pyrido[2,1-*b*] quinazoline-7-carboxamide (272):**



Salt **270** (14.4 mg, 0.034 mmol) was diluted in DMF (1.5 mL) and irradiated under microwave heating (200 watts, 200 °C) for 10 min. The reaction mixture was diluted in dichloromethane (10 mL) and washed with water (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **272** (5.2 mg, 42%); $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3299, 2938, 1663, 1595, 1550, 1471, 1291, 1235, 1172, 770, 734, 696; $\delta_H$ (400 MHz, $CDCl_3$) 9.17 (1H, br s, N*H*), 8.24 (1H, d, *J* = 7.9 Hz, ArH), 7.75–7.69 (2H, m, ArH), 7.57 (1H, d, *J* = 8.0 Hz, ArH), 7.43–7.39 (2H, m, ArH), 7.29 (1H, ddd, *J* = 8.2, 7.0, 1.0 Hz, ArH), 7.15 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, ArH), 6.37 (1H, dd, *J* = 7.0, 2.4 Hz, H-2), 4.03 (3H, s, OC*H*$_3$), 3.60 (2H, m, H-3), 3.18 (3H, s, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.2 (C-19), 162.1 (C-12), 156.7 (Ar C), 147.9 (Ar C), 142.8 (Ar C), 138.3 (Ar C), 132.8 (Ar C), 134.7 (Ar CH), 127.3 (Ar C), 127.1 (Ar CH), 127.0 (Ar CH), 126.3 (Ar CH), 125.9 (Ar CH), 120.9 (Ar CH), 119.9 (Ar CH), 113.5 (Ar C), 112.2 (Ar CH), 61.7 (C-O*C*H$_3$), 51.7 (C-2), 32.3 (C-*C*H$_3$), 22.6 (C-3); HRMS ($ESI^+$): Found: 375.1451; $C_{21}H_{19}N_4O_3$ ($MH^+$) Requires: 375.1452 (0.3 ppm error).

Lab Notebook Reference: CHK 4/225 p.28

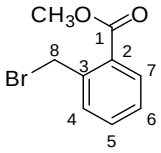
**2-(2-Methoxy-2-oxoethyl) benzoic acid (388a):**[137]




To a well stirred solution of anhydride **393** (500 mg, 3.08 mmol) in methanol (2 mL, 49.4 mmol), $BF_3{\cdot}Et_2O$ (0.285 mL, 2.31 mmol) was added dropwise. The reaction mixture was stirred 24 h and was added to sat. aq. $NaHCO_3$ (25 mL) and extracted with ether (3 × 30 mL) to remove the traces of any unreacted anhydride. The aqueous layer was neutralised with conc. aq. HCl at 0 °C and extracted with ether (3 × 30 mL). The organic phase was washed with brine (3 × 30 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to give compound **388a** (600 mg, quantitative) as a white solid; No futher purification was required; $R_f$ 0.5 (ethyl acetate, 10 % MeOH); $\delta_H$ (400 MHz, $CDCl_3$) 8.20 (1H, dd, *J* = 7.7, 1.4 Hz, H-7), 7.55 (1H, ddd, *J* = 7.7, 7.7, 1.4 Hz, H-5), 7.41 (1H, ddd, *J* = 7.7, 7.7, 1.1 Hz, H-6), 7.29 (1H, dd, *J* = 7.7, 1.1 Hz, H-4), 4.07 (2H, s, H-8), 3.71 (3H, s, OC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.4 (C-1/9), 172.0 (C-1/9), 136.8 (C-2), 133.3 (C-6), 132.4 (C-7), 131.9 (C-4), 128.5 (C-3), 127.6 (C-5), 52.0 (C-O*C*H$_3$), 40.6 (C-8); HRMS ($ESI^+$): Found: 217.0473; $C_{10}H_{10}NaO_4$ ($MNa^+$) Requires: 217.0471 (−0.8 ppm error). Obtained data in accord with those reported in the literature.[137]

Lab Notebook Reference: CHK 1/36 p.54

**Methyl 2-(bromomethyl)benzoate (395):**[138]

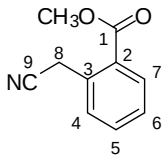



*N*-Bromosuccinimide (9.35 g, 50.0 mmol) was added to a solution of methyl 2-methylbenzoate **394** (7.5g, 50.0 mmol) in carbon tetrachloride (100 mL) and the mixture was refluxed with catalytic amount of benzoyl peroxide (2.43 g, 10 mmol) for 24 h. After cooling to rt, the precipitate was removed by filtration and the filtrate was concentrate under vaccum to give compound **395** as a white solid (11.4 g, quantitative); $\delta_H$ (400 MHz, $CDCl_3$) 8.07–8.05 (1H, m, ArH), 7.98–7.95 (1H, m, ArH), 7.53–7.44

(1H, m, ArH), 7.37–7.34 (1H, m, ArH), 4.97 (2H, s, H-8), 3.94 (3H, s, OC$H_3$). Obtained data in accord with those reported in the literature.[171]

Lab Notebook Reference: CHK 4/237 p.42

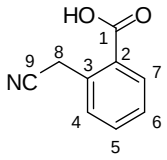
**Methyl 2-(cyanomethyl)benzoate (396):**[139]




The benzyl bromide **395** (459 mg, 2.00 mmol) was diluted in ethanol (15.0 mL) and KCN (261.1 mg, 4.01 mmol) in boiled water (2.5 mL) was added. The mixture was heated under reflux at 70 °C for 1.5 h. The resulting solution poured into sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with ether (2 × 20 mL), dried over $MgSO_4$ concentrated *in vacuo* and purified by column chromatography ($SiO_2$, 9:1→7:1 petrol:ethyl acetate) to afford compound **396** (152 mg, 43%); $R_f$ 0.3 (7:1 ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2961, 2251, 1715, 1605, 1493, 1450, 1435, 1261, 1194, 1138, 1080, 971, 739, 707; $\delta_H$ (400 MHz, $CDCl_3$) 8.06 (1H, d, *J* = 7.9 Hz, ArH), 7.57–7.56 (2H, m, ArH), 7.44–7.40 (1H, m, ArH), 4.22 (2H, s, H-8), 3.92 (3H, s, OC$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 166.8 (C-1), 133.2 (Ar CH), 132.1 (Ar C), 131.7 (Ar CH), 130.3 (Ar CH), 128.4 (Ar CH), 128.4 (Ar C), 118.0 (C-9), 52.4 (C-O*C*$H_3$), 23.3(C-8); HRMS ($ESI^+$): Found: 198.0524 $C_{10}H_9NaO_2$ ($MNa^+$) Requires: 198.0525 (0.8 ppm error). Obtained data in accord with those reported in the literature.[172]

Lab Notebook Reference: CHK 4/242 p.46

**2-(Cyanomethyl)benzoic acid (388b):**

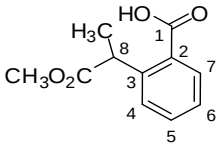



To a round bottom flask containing ester **396** (151.4 mg, 0.864 mmol) in THF (2.6 mL), $LiOH·H_2O$ (108.8 mg, 2.59 mmol) in water (2.6 mL) was added at rt. The reaction mixture was stirred for 1 h. The solution was dissolved in water (20 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer, was extracted with ethyl acetate (3 × 20 mL), and the organic extracts were dried over $MgSO_4$ and concentrated *in*

*vacuo*, affording compound **388b** as a yellow solid (94.9 mg, 68%); mp 149–152 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 2973, 2827, 2647, 2252, 1671, 1577, 1500, 1577, 1454, 1411, 1399, 1311, 1292, 1281, 1266, 1081, 912, 739, 674; $\delta_H$ (400 MHz, $CDCl_3$) 8.22 (1H, d, *J* = 7.3 Hz, ArH), 7.68–7.62 (2H, m, ArH), 7.52–7.47 (1H, m, ArH), 4.27 (2H, s, H-8); $\delta_C$ (100 MHz, $CDCl_3$) 171.4 (C-1), 134.22 (Ar CH), 132.8 (Ar C), 132.6 (Ar CH), 130.4 (Ar CH), 128.8 (Ar CH), 127.0 (Ar C), 117.7 (C-9), 23.4 (C-8); HRMS (ESI$^+$): Found: 184.0370 $C_9H_7NaO_2$ ($MNa^+$) Requires: 184.0369 (−0.8 ppm error). This compound has been reported previously in the literature but no data were obtained.[173]

Lab Notebook Reference: CHK 4/243 p.47

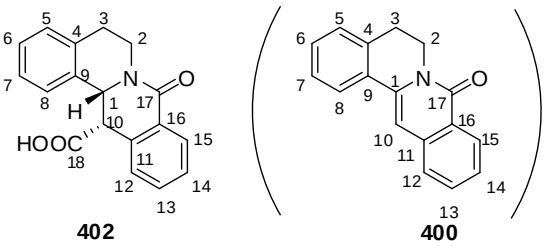
**2-(1-Methoxy-1-oxopropan-2-yl)benzoic acid (391):**




A solution of diisopropylamine (0.362 mL, 2.59 mL) in THF (6.15 mL) under Ar atm was cooled to −78 °C and *n*-BuLi (1.62 mL, 2.59 mmol) was added. The solution was stirred for 30 min at −78 °C before the acid **388a** (202 mg, 1.04 mmol) in THF (6.15 mL) was added dropwise. The solution was stirred for 2 h at −78 °C and then iodomethane (0.129, 2.08 mmol) was added dropwise and the solution was stirred for 48 h. The reaction mixture was quenched with sat. aq. $NH_4Cl$ (20 mL), extracted with ether (3 × 20 mL) dried over $MgSO_4$ and concentrated *in vacuo*, affording compound **391** as a yellow solid(174 mg, 80 %); mp 65–67 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 2986, 2953, 1724, 1693, 1602, 1577, 1492, 1454, 1407, 1377, 1301, 1212, 1143, 1090, 1059, 861, 762, 710, 646, 555; $\delta_H$ (400 MHz, $CDCl_3$) 8.07 (1H, dd, *J* = 7.9, 1.4 Hz, ArH), 7.56 (1H, ddd, *J* = 7.6, 7.6, 1.5 Hz, ArH), 7.41–7.34 (2H, m, ArH), 4.78 (1H, q, *J* = 7.1 Hz, H-8), 3.67 (3H, s, OC*H*$_3$), 1.55 (3H, d, *J* = 7.1 Hz, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 175.2 (C-1/9), 172.6 (C-1/9), 143.1 (Ar C), 133.5 (Ar CH), 131.8 (Ar CH), 128.7 (Ar CH), 128.0 (Ar C), 127.1(Ar CH), 52.2 (C-O*C*H$_3$), 42.0 (C-8), 18.5 (C-*C*H$_3$); HRMS (ESI$^+$): Found: 231.0632 $C_{11}H_{12}NaO_4$ ($MNa^+$) Requires: 231.0628 (−1.6 ppm error).

Lab Notebook Reference: CHK 4/259 p.63

***cis*-5-Oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13-carboxylic acid (402):**



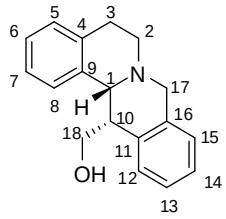

To a round bottom flask containing diester **149x** (1.48 g, 4.05 mmol) in THF (12.2 mL), $LiOH{\cdot}H_2O$ (510 mg, 12.2 mmol) in water (12.2 mL) was added at rt. The reaction mixture was stirred for 24 h at 80 °C. The solution was dissolved in water (50 mL), washed with dichloromethane (100 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography ($SiO_2$, 3:1→2:1→1:1 petrol:ethyl acetate) to afford a mixture of diastereosisomers as a yellow solid (930 mg, 78%); A solution of the two diasteroisomers (138.4 mg, 0.472 mmol) in acetic acid (18.2 mL) was refluxed at 120 °C for 24 h. The solvent was evaporated *in vacuo* and purification by column chromatography ($SiO_2$, 3:1→2:1 petrol:ethyl acetate) afforded compound **402** as a single diastereoisomer (72.6 mg, 52%) together with compound **400** as a side product (14 mg, 10%).

*cis*-8-Oxo-5,8,13,13a-tetrahydro-6H-isoquino[3,2-a]isoquinoline-13-carboxylic acid (**402**): $R_f$ 0.4 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3268, 2925, 2556, 1725, 1624, 1602, 1575, 1465, 1427, 1364, 1340, 1303, 1258, 1169, 909, 796, 733; $\delta_H$ (400 MHz, $CDCl_3$) 8.12 (1H, dd, *J* = 7.6, 1.5 Hz, ArH), 7.51–7.41 (2H, m, ArH), 7.38–7.37 (1H, m, ArH), 7.26–7.25 (2H, m, ArH), 7.22–7.18 (1H, m, ArH), 7.11 (1H, d, *J* = 7.4 Hz, ArH), 6.60–6.51 (1H, br s, COO*H*), 5.22 (1H, d, *J* = 4.2 Hz, H-1), 4.91–4.88 (1H, m, H-2a), 4.19 (1H, d, *J* = 4.2 Hz, H-10), 2.99–2.95 (2H, m, H-2b,3a), 2.70–2.66 (1H, m, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 172.7 (C-18), 164.0 (C-17), 136.6 (Ar C), 134.6 (Ar C), 133.0 (Ar C), 132.2 (Ar CH), 129.2 (Ar CH), 129.1 (Ar C), 129.0 (Ar CH), 128.8 (Ar CH), 127.7 (Ar CH), 127.3 (Ar CH), 126.9 (Ar CH), 126.1 (Ar CH), 56.4 (C-1), 50.8 (C-10), 38.9 (C-2), 28.7(C-3); HRMS ($ESI^+$): Found: 270.0886; $C_{17}H_{13}NNaO$ ($MNa^+$) Requires: 270.0889 (0.7 ppm error).

7,8-Dihydro-5*H*-azatetraphen-5-one (**400**): mp 120–124 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3063, 2944, 1646, 1619, 1595, 1491, 1466, 1403, 1341, 1315 1252, 1167, 765; $\delta_H$ (400 MHz, $CDCl_3$) 8.44 (1H, d, *J* = 8.1 Hz, ArH), 7.87-7.83 (1H, m, ArH), 7.65 (1H, ddd, *J* = 7.9, 6.9, 1.3 Hz, ArH), 7.59 (1H, d, *J* = 7.9 Hz, ArH), 7.47 (1H, ddd, *J* = 8.1, 6.9, 1.3 Hz, ArH), 7.38-7.37 (2H, m, ArH), 7.29-7.27 (1H, m, ArH), 7.05 (1H, s, H-10), 4.39 (2H, t, *J* = 6.2 Hz, H-2), 3.03 (2H, t, *J* = 6.2 Hz, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 162.2 (C-17), 137.4 (Ar C), 136.5 (Ar C), 136.4 (Ar C), 132.3 (Ar CH), 130.2 (Ar C), 129.3 (Ar CH), 128.0 (Ar CH), 128.0 (Ar CH), 127.4 (Ar CH), 126.6 (Ar CH), 126.2 (Ar CH), 125.0 (Ar CH), 124.9 (Ar C), 102.9 (C-10), 39.6 (C-2), 28.6 (C-3); HRMS (ESI$^+$): Found: 248.1074; $C_{17}H_{14}NO$ ($MH^+$) Requires: 248.1070 (−1.7 ppm error). Obtained data in accord with those reported in the literature.[174]

Lab Notebook Reference: CHK 4/263 p.76 and CHK 4/275 p.86

***cis*-7,8,12b,13-Tetrahydro-5*H*-6-azatetraphen-13-ylmethanol (403):**

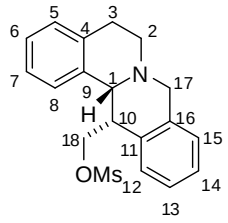



The *cis*-acid **402** (305, 1.04 mmol) was added to a solution of $LiAlH_4$ (197 mg, 5.20 mmol) in THF (66 mL). The reaction mixture was heated at 70 °C for 24 h before it was cooled to 0 °C and decomposed by addition of water (0.197 mL), 15 % NaOH (0.197 mL) and water (0.592 mL). The aluminates were filtered and washed with ethyl acetate. The combined filtrates were dried and evaporated. Purification by column chromatography ($SiO_2$, 4:1→3:1 petrol:ethyl acetate) yield **403** as a brown oil (177 mg, 64%); $R_f$ 0.6 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 3263, 3024, 2905, 2760, 1494, 1454, 1360, 1285, 1141, 1105, 1084, 1043, 1032, 998, 776; $\delta_H$ (400 MHz, $CDCl_3$) 7.31–7.12 (8H, m, ArH), 4.16–4.11 (2H, m, H-1,17a), 3.79–3.72 (2H, m H-17b,18a), 3.62 (1H, ddd, *J* = 10.4, 2.8, 1.5 Hz, H-18b), 3.32–3.17 (3H, m, H-3a,2a, 10), 2.78–2.74 (1H, m, H-3b), 2.60 (1H, ddd, *J* = 12.1, 10.9, 2.9 Hz, H-2b); $\delta_C$ (100 MHz, $CDCl_3$) 136.7 (Ar C), 135.5 (Ar C), 134.7 (Ar C), 134.7 (Ar C), 129.2 (Ar CH), 128.5 (Ar CH), 126.8 (Ar CH), 126.6 (Ar CH), 126.4 (Ar CH), 126.4 (Ar CH), 125.8 (Ar CH), 125.7 (Ar CH), 65.6 (C-18), 63.6 (C-1), 58.3 (C-17), 51.0 (C-

2), 44.2 (C-10), 29.3 (C-3); HRMS ($ESI^+$): Found: 266.1547; $C_{18}H_{20}INO$ ($MH^+$) Requires: 266.1539 (−3.1 ppm error).

Lab Notebook Reference: CHK 4/276 p.90

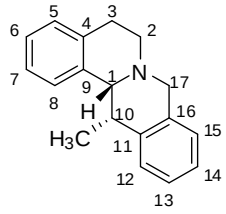
***cis*-7,8,12b,13-Tetrahydro-5*H*-6-azatetraphen-13-ylmethyl methanesulfonate (404):**




Methanesulfonyl chloride (49.3 μL, 0.637 mmol) was added to a solution of alcohol **403** (52.8 mg, 0.200 mmol) in pyridine (1.27 mL). The reaction mixture was stirred at rt for 3 h and then quenched with water (10 mL). The mixture was extracted with ether (3 × 20 mL). The organic extract was dried and evaporated. Purification by column chromatography ($SiO_2$, 5:1→3:1 petrol:ethyl acetate) yield mesylate **404** as a brown oil (36.6 mg, 54%); $R_f$ 0.6 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3437, 2925, 2854, 1642, 1491, 1459, 1328, 1174, 1040, 767; $\delta_H$ (400 MHz, $CDCl_3$) 7.34–7.31 (2H, m, ArH), 7.26–7.17 (4H, m, ArH), 7.15–7.12 (2H, m ArH), 4.24–4.23 (2H, m, H-18), 4.12 (1H, d, *J* = 15.3 Hz, H-17a), 3.99 (1H, br s, H-1), 3.74 (1H, d, *J* = 15.3 Hz, H-17b), 3.66–3.62 (1H, m, H-10), 3.18–3.12 (2H, m, H-2a,3a), 3.73–2.68 (1H, m, H-3b), 2.64–2.58 (1H, m, H-2b), 2.49 (3H, s, C*H*$_3$(Ms)); $\delta_C$ (100 MHz, $CDCl_3$) 135.8 (Ar C), 135.3 (Ar C), 134.6 (Ar C), 130.2 (Ar CH), 129.0 (Ar CH), 127.2 (Ar CH), 126.5 (Ar CH), 126.4 (Ar CH), 126.3 (Ar CH), 126.3 (Ar CH), 126.1 (Ar CH), 125.9 (Ar C), 72.2 (C-18), 61.7 (C-1), 58.4 (C-17), 50.9 (C-2), 43.9 (C-10), 36.3 (C-*C*H$_3$(Ms)), 29.5 (C-3); HRMS ($ESI^+$): Found: 344.1310; $C_{19}H_{22}NO_3S$ ($MH^+$) Requires: 344.1315 (1.4 ppm error).

Lab Notebook Reference: CHK 4/278 p.93

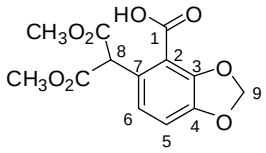
***cis*-13-Methyl-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene (390):**




The mesylate **404** (36.7 mg, 0.107 mmol) was suspended in 95% EtOH (6.6 mL) and $NaBH_4$ (62.5 mg, 1.65 mmol) was added to the stirred mixture. The mixture was refluxed at 80 °C for 48 h and then poured into water (20 mL). The aqueous phase was extracted with chloroform (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate) yielded compound **390** as a colourless oil (10 mg, 38%); $R_f$ 0.6 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3022, 2965, 2907, 2798, 2750, 1494, 1452, 1391, 1362, 1337, 1283, 1250, 1150, 1112, 1035, 1022, 907, 759, 734, 726; $\delta_H$ (400 MHz, $CDCl_3$) 7.26–7.08 (8H, m, ArH), 4.05 (1H, d, *J* = 15.0 Hz, H-17a), 3.86 (1H, d, *J* = 3.2 Hz, H-1), 3.71 (1H, d, *J* = 15.0 Hz, H-17b), 3.36 (1H, qd, *J* = 7.0, 3.2 Hz, H-10), 3.22–3.14 (2H, m, H-2a,3a), 2.72–2.59 (2H, m, H-2b,3b), 0.98 (3H, d, *J* = 7.0 Hz, C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 141.4 (Ar C), 136.7 (Ar C), 136.0 (Ar C), 134.1 (Ar C), 128.9 (Ar CH), 128.7 (Ar CH), 126.2 (Ar CH), 126.1 (Ar CH), 126.0 (Ar CH), 125.8 (Ar CH), 125.7 (Ar CH), 125.7 (Ar CH), 63.5 (C-1), 58.9 (C-17), 51.1 (C-2), 38.7 (C-10), 29.7 (C-3), 18.3 (C-*C*$H_3$); HRMS ($ESI^+$): Found: 250.1582; $C_{18}H_{20}N$ ($MH^+$) Requires: 250.1590 (3.4 ppm error). This compound has been reported previously in the literature, but no data were reported.[142]

Lab Notebook Reference: CHK 5/283 p.2

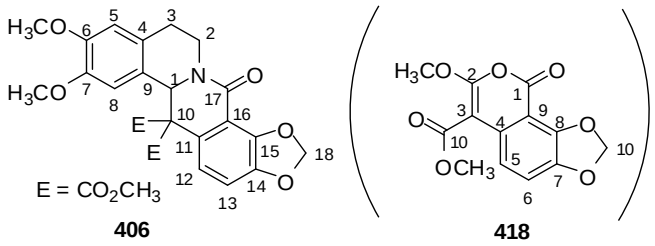
**5-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-2*H*-1,3-benzodioxole-4-carboxylic acid (405):**




Sodium hydride (419 mg, 10.5 mmol, 60 % in mineral oil) was added portionwise to a rapidly stirred cold suspension (0 °C) of 5-bromobenzo[1,3]dioxole-4-carboxylic acid **408** (1.00 g, 4.37 mmol), copper bromide (62.6 mg, 0.437 mmol) and dimethyl malonate (17.3 mL). After the addition of the sodium hydride had been completed, the mixture was stirred for 10 min at rt and then for 20 h at 70 °C. The suspension, which had turned to a solid mass, was dissolved in water (30 mL), washed with ether (3 × 80 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer, was extracted with ethyl acetate (3 × 100 mL), and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 5:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **405** as a colourless solid (1.01 g, 74%); $R_f$ 0.1 (1:1 petrol:ethyl acetate); mp 88–93 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2912, 2877, 1704, 1688, 1456, 1431, 1216, 1137, 1039, 1012; $\delta_H$ (400 MHz, $CDCl_3$) 6.95 (1H, d, *J* = 8.2 Hz H-5/6), 6.88 (1H, d, *J* = 8.2 Hz, H-5/6), 6.11 (2H, s, H-9), 5.53 (1H, s, H-8), 3.76 (6H, s, $CO_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.2 (C-1), 168.5 (C-$CO_2CH_3$), 149.7 (Ar C), 148.5 (Ar C), 127.1 (Ar C), 123.9 (C-5/6), 111.9 (C-5/6), 102.5 (C-9), 100.0 (Ar C), 54.2 (C-8), 53.0 (C-$CO_2CH_3$); HRMS ($ESI^+$): Found: 319.0424; $C_{13}H_{12}NaO_8$ ($MNa^+$) Requires: 319.0424 (0.2 ppm error); Elemental Analysis: calculated for $C_{13}H_{12}O_8$ requires C, 52.71; H, 4.08; found C, 52.15; H, 4.07.

Lab Notebook Reference: CHK 2/127 p.187

**Dimethyl 8,9-dimethoxy-14-oxo-11,12-dihydro-6a*H*-[1,3]dioxolo[4,5-*h*]isoquino [2,1-*b*] isoquinoline-6,6(14*H*)-dicarboxylate (406):**




**406** **418**

Synthesised using general DIA procedure A from imine **146f** (230 mg, 1.21 mmol), acid **405** (408 mg, 1.38 mmol), DIPEA (315 μL, 1.81 mmol) and T3P (1.42 g, 2.23 mmol) in toluene (5.8 mL) at 90 °C for 20 h. Purification by column chromatography ($SiO_2$, 4:1→2:1→1:1 petrol:ethyl acetate→pure ethyl acetate→ethyl acetate, 5% MeOH) afforded compound **406** as a yellow oil (214 mg, 38%) together with traces of compound **418**.

Synthesised using general DIA procedure B from imine **146f** (34.3 mg, 0.179 mmol), acid **405** (63.7 mg, 0.215 mmol), DIPEA (57.6 μL, 0.331 mmol), T3P (171 mg, 0.269 mmol) and $AlCl_3$ (47.7 mg, 0.358 mmol) in chloroform (1 mL) at 50 °C for 20 h. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) to afford compound **406** as a yellow oil (54.2 mg, 64%).

Synthesised using general DIA procedure B from imine **146f** (484 mg, 2.53 mmol), acid **405** (900 mg, 3.04 mmol), DIPEA (0.815 mL, 4.68 mmol), T3P (2.42 g, 3.80 mmol) and $BCl_3$ (5.10 mL, 5.10 mmol, 1.0 M solution in DCM) in chloroform (25 mL) at rt for 20 h. Purification by column chromatography ($SiO_2$, 1:1→1:2 petrol:ethyl acetate) to afford compound **406** as a yellow solid (819 mg, 69%).

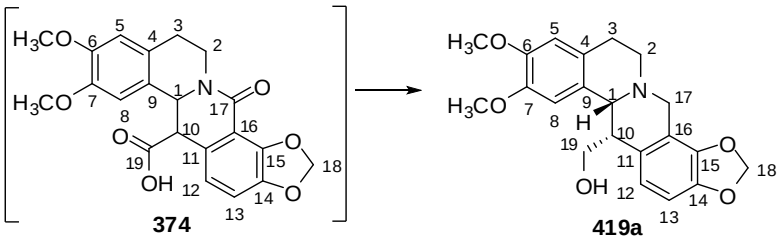
Dimethyl 8,9-dimethoxy-14-oxo-11,12-dihydro-6a*H*-[1,3]dioxolo[4,5-h]isoquino [2,1-b] isoquinoline-6,6(14*H*)-dicarboxylate (**406**): mp 152–156 C; $R_f$ 0.4 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2908, 1707, 1626, 1588, 1494, 1440, 1412, 1103, 1029, 718; $\delta_H$ (400 MHz, $CDCl_3$) 6.91 (1H, d, *J* = 8.1 Hz, H-12/13), 6.81 (1H, s, H-5/8), 6.69 (1H, s, H-5/8), 6.54 (1H, d, *J* = 8.1 Hz, H-12/13), 6.22 (1H, d, *J* = 1.3 Hz, H-18a), 6.10 (1H, d, 1.3 Hz, H-18b), 5.58 (1H, s, H-1), 4.85–4.78 (1H, m, H-2eq), 3.88 (3H, s, OC$H_3$), 3.87 (3H, s, OC$H_3$), 3.80 (3H, s, $CO_2CH_3$), 3.51 (3H, s, $CO_2CH_3$), 2.92–2.87 (2H, m, H-2ax, H-3a), 2.67–2.64 (1H, m, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 170.1 (C-$CO_2CH_3$), 167.0 (C-$CO_2CH_3$), 162.0 (C-17), 149.0 (Ar C), 148.3 (Ar C), 148.2 (Ar C), 147.1 (Ar C),

131.6 (Ar C), 130.3 (Ar C), 123.1 (Ar C), 120.1 (Ar CH), 112.2 (Ar C), 111.1 (Ar CH), 110.9 (Ar CH), 110.7 (CH), 102.7 (C-18), 65.9 (C-10), 61.2 (C-1), 55.9 (C-O*C*H$_3$), 55.7 (C-O*C*H$_3$), 53.0 (C-CO$_2$*C*H$_3$), 52.9 (C-CO$_2$*C*H$_3$), 39.3 (C-2), 28.9 (C-3). HRMS (ESI$^+$): Found: 470.1454; $C_{24}H_{24}NO_9$ (MH$^+$) Requires: 470.1446 (−1.7 ppm error).

Methyl-7-methoxy-9-oxo-9*H*-[1,3]dioxolo[4,5-h]isochromene-6-carboxylate (**418**): $\nu_{max}$ (thin film)/cm$^-$ 2936, 1752, 1699, 1633, 1601, 1584, 1483, 1435, 1353, 1266, 1100, 1063, 1032, 955, 813; $\delta_H$ (400 MHz, $CDCl_3$) 7.43 (1H, d, *J* = 8.6 Hz, H-5/6), 7.17 (1H, d, *J* = 8.6 Hz, H-5/6), 6.22 (2H, s, H-10), 4.07 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 165.6 (C-1/2/10), 158.1 (C-1/2/10), 156.1 (C-1/2/10), 149.2 (Ar C), 146.2 (Ar C), 130.2 (Ar C), 127.2 (Ar C), 116.9 (C-5/6), 116.0 (C-5/6), 115.6 (Ar C), 103.3 (C-10), 57.1 (C-O*C*H$_3$), 52.3 (C-O*C*H$_3$); HRMS (ESI$^+$): Found: 301.0330 $C_{13}H_{10}NaO_7$ (MNa$^+$) Requires: 301.0319 (−3.6 ppm error).

Lab Notebook Reference: CHK 2/129 p.189, CHK 5/290 p.11 and CHK 5/345 p.79

***cis*-2,3-Dimethoxy-9,10-(methylenedioxy)-13-(hydroxymethyl)-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene (419a):**

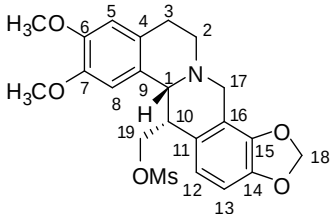



To a round bottom flask containing diester **406** (106.5 mg, 0.227 mmol) in THF (0.7 mL), LiOH·H$_2$O (28.6 mg, 0.681 mmol) in water (0.7 mL) was added at rt. The reaction mixture was stirred for 16 h at 90 °C. The solution was dissolved in water (10 mL), washed with dichloromethane (10 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer, was extracted with ethyl acetate (3 × 20 mL), and the organic extracts were dried over MgSO$_4$ and concentrated *in vacuo* to give a crude mixture of acid **374** (64.2 mg); [complex due to diastereoisomers and rotamers; $\delta_H$ (400 MHz, $CDCl_3$) 6.89–6.79 (2H, m, H-12,13), 6.71 (1H, br s, H-5/8 ), 6.62 (1H, br s, H-5/8), 6.13–6.02 (2H, m, H-18), 5.19–5.10 (1H, m, H-1/10), 4.93–4.81 (1H, m, H-1/10), 3.66–3.71 (6H, group of br singlets, 2 × OC*H*$_3$), 3.02–2.87 (2H, m, H-2), 2.71–2.58 (2H, m, H-3)]. The crude mixture was then added to a solution of LiAlH$_4$ (30.7 mg, 0.808 mmol) in

THF (10 mL) and heated at 70 °C for 2 h, before it was cooled to 0 °C and quenched by the sequential addition of water (0.031 mL), 15 % NaOH (0.031 mL) and water (0.092 mL). The aluminates were filtered and washed with ethyl acetate. The remaining solids were then collected and refluxed in ethyl acetate for 2 h and filtered a second time. The combined filtrates were dried with $MgSO_4$ and evaporated. Purification by column chromatography ($SiO_2$, 1:1 petrol: ethyl acetate→ethyl acetate) yield compound **419a** as a yellow solid (35.7 mg, 43%); $R_f$ 0.6 (ethyl acetate); mp 145–147 °C (Lit. mp 193-195 °C);[127] $\nu_{max}$ (thin film)/$cm^{-1}$ 3261, 2924, 1609, 1516, 1462, 1360, 1257, 1232, 11209, 1138, 1044; $\delta_H$ (400 MHz, $CDCl_3$) 6.78 (2H, s, H-5,8), 6.64 (1H, br s, H-12/13), 6.61 (1H, br s, H-12/13), 6.01 (1H, d, *J* =1.5 Hz, H-18a), 5.95 (1H, d, *J* = 1.5 Hz, H-18b), 4.14 (1H, d, *J* = 15.2 Hz, H-17a), 4.00 (1H, br s, H-1), 3.88 (3H, s, OC*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 3.75 (1H, dd, *J* = 10.4, 2.0 Hz, H-19a), 3.58–3.54 (1H, m, H-19b), 3.53 (1H, d, *J* = 15.2 Hz, H-17b), 3.19–3.15 (3H, m, H-10,2), 2.68–2.56 (2H, m, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 147.8 (Ar C), 147.8 (Ar C), 145.5 (Ar C), 143.1 (Ar C), 131.0 (Ar C), 127.9 (Ar C), 126.3 (Ar C), 120.9 (C-5/8), 117.2 (Ar C), 111.5 (C-12/13), 108.4 (C-12/13), 107.4 (C-5/8), 101.2 (C-18), 66.0 (C-19), 63.4 (C-1), 56.1 (C-O*C*H$_3$), 55.9 (C-O*C*H$_3$), 53.0 (C-17), 51.2 (C-2), 43.9 (C-10), 29.0 (C-3); HRMS ($ESI^+$): Found: 370.1632; $C_{21}H_{24}NO_5$ ($MH^+$) Requires: 370.1649 (4.4 ppm error). Obtained data in accord with those reported in the literature.[127]

*cis*-2,3-Dimethoxy-9,10-(methylenedioxy)-13-(hydroxymethyl)-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene (**419b**): $\delta_H$ (400 MHz, $CDCl_3$) 6.78 (1H, d, *J* = 8.0 Hz, H-12/13), 6.69 (1H, d, *J* = 8.0 Hz, H-12/13), 6.59 (2H, br s, H-5/8), 5.89 (1H, d, *J* =1.5 Hz, H-18a), 5.88 (1H, d, *J* = 1.5 Hz, H-18b), 4.37 (1H, br s, H-1), 4.21 (1H, dd, *J* = 10.3, 3.0 Hz, H-19a), 3.99 (1H, dd, *J* = 10.3, 3.0 Hz, H-19b), 3.83 (1H, d, *J* = 15.8 Hz, H-17a), 3.82 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 3.61 (1H, d, *J* = 15.8 Hz, H-17b), 3.39 (2H, m, H-10,2), 3.24 (1H, m, H-2), 3.09 (1H, m, H-3a), 2.73 (1H, m, H-3b); $\delta_C$ (100 MHz, $CDCl_3$) 147.9 (Ar C), 147.1 (Ar C), 145.4 (Ar C), 143.3 (Ar C), 127.4 (Ar C), 126.6 (Ar C), 126.0 (Ar C), 120.9 (C-12/13), 117.0 (Ar C), 111.8 (C-5/8), 108.9 (C-5/8), 107.2 (C-12/13), 101.1 (C-18), 70.1 (C-19), 59.6 (C-1), 55.9 (C-O*C*H$_3$), 55.8 (C-O*C*H$_3$), 48.5 (C-2), 43.7 (C-17), 40.1 (C-10), 29.9 (C-3);

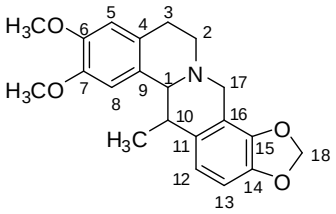
Lab Notebook Reference: CHK 5/356 p.94***cis*-2,3-Dimethoxy-9,10-(methylenedioxy)-13-(methanesulfonylmethyl)-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene (420):**[127]




Methanesulfonyl chloride (23.8 μL, 0.308 mmol) was added to a solution of alcohol **419a** (35.5 mg, 0.096) in pyridine (1 mL). The reaction mixture was stirred at rt for 1.5 h and then quenched with water (10 mL). The mixture was extracted with ether (3 × 20 mL). The organic extract was dried and evaporated. Purification by column chromatography ($SiO_2$, 2:1→1:1 hexene:ethyl acetate→ethyl acetate) afforded the mesylate as a yellow oil (25.5 mg, 68%); $R_f$ 0.9 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2936, 1517, 1462, 1353, 1334, 1172, 1142, 1041, 955, 730; $\delta_H$ (400 MHz, $CDCl_3$) 6.84 (1H, d, *J* = 8.0 Hz, H-12/13), 6.75 (1H, s, H-5/8), 6.73 (1H, d, *J* = 8.0 Hz, H-12/13), 6.61 (1H, s, H-5/8), 6.00 (1H, d, *J* = 1.4 Hz, H-18a), 5.97 (1H, s, *J* = 1.4 Hz, H-18b), 4.22–4.08 (3H, m, H-1, $CH_2$), 3.92–3.86 (2H, m, C$H_2$), 3.90 (3H, s, OC$H_3$), 3.88 (3H, s, OC$H_3$), 3.56–3.52 (2H, m, H-10, $CH_2$), 3.11–3.00 (2H, m, C$H_2$), 2.63–2.55 (1H, m, $CH_2$), 2.62 (3H, s, $CH_3$(Ms)); $\delta_C$ (100 MHz, $CDCl_3$) 147.8 (Ar C), 147.4 (Ar C), 145.3 (Ar C), 142.9 (Ar C), 132.9 (Ar C), 128.1 (Ar C), 126.3 (Ar C), 126.1 (Ar C), 123.1 (Ar CH), 111.4 (Ar CH), 108.5 (Ar CH), 106.7 (Ar CH), 101.4 (C-18), 72.4 (C-19), 61.5 (C-1), 56.2 (C-OC$H_3$), 56.0 (C-OC$H_3$), 53.2 (C-17), 51.2 (C-2), 43.7 (C-10), 36.8 (C-C$H_3$(Ms)), 29.2 (C-3); HRMS ($ESI^+$): Found: 448.1427; $C_{22}H_{26}NO_7S$ ($MH^+$) Requires: 448.1424 (−1.3 ppm error). Obtained data in accord with those reported in the literature.[127]

Lab Notebook Reference: CHK 5/297 p.22

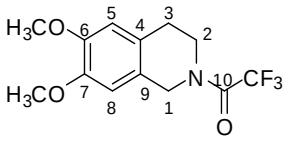
**(±)-Cavidine (280):**[141]




The mesylate **420** (22.4 mg, 0.058 mmol) was dissolved in 95% ethanol (3.5 mL) and $NaBH_4$ (32.8 mg, 0.867 mmol) was added to the stirred mixture. The mixture was refluxed at 80 °C for 2 h and then poured into water (15 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and evaporated to yield the crude product. Purification by column chromatography ($SiO_2$, 5:1 hexane:ethyl acetate) afforded cavidine **280** as a white solid (13.6 mg, 67%); $R_f$ 0.4 (1:1 hexane:ethyl acetate); mp 180–184 °C (Lit. mp 188–189 °C);[127] $\nu_{max}$ (thin film)/$cm^{-1}$ 2909, 2757, 1514, 1457, 1333, 1356, 1254, 1228, 1042, 729; $\delta_H$ (400 MHz, $CDCl_3$) 6.72 (1H, d, *J* = 8.0 Hz, H-13), 6.68 (1H, s, H-8), 6.67 (1H, d, *J* = 8.0 Hz, H-12), 6.61 (1H, s, H-5), 5.97 (1H, d, *J* = 1.5 Hz, H-18a), 5.93 (1H, d, *J* = 1.5 Hz, H-18b), 4.09 (1H, d, *J* = 15.3 Hz, H-17a), 3.88 (3H, s, OC$H_3$), 3.88 (3H, s, OC$H_3$), 3.73 (1H, br s, H-1), 3.50 (1H, d, *J* = 15.3 Hz, H-17b), 3.28–3.22 (1H, m, H-10), 3.16–3.07 (2H, m, H-2a,3a), 2.63–2.57 (2H, m, H-2b,3b), 0.94 (3H, d, *J* = 6.9 Hz, C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 147.6 (C-6), 147.1 (C-7), 144.6 (C-15), 143.0 (C-14), 135.9 (C-11), 128.3 (C-4), 128.26 (C-9), 121.2 (C-12), 116.8 (C-16), 111.1 (C-5), 108.5 (C-8), 106.7 (C-13), 101.0 (C-18), 63.1 (C-1), 56.1 (C-O$CH_3$), 55.8 (C-O$CH_3$), 53.3 (C-17), 51.2 (C-2), 38.5 (C-10), 29.3 (C-3), 18.4 (C-$CH_3$); HRMS ($ESI^+$): Found: 354.1683; $C_{21}H_{24}NO_4$ ($MH^+$) Requires: 354.1700 (4.3 ppm error). Obtained data in accord with those reported in the literature.[127,129a,c,134]

Lab Notebook Reference: CHK 6/359 p.1

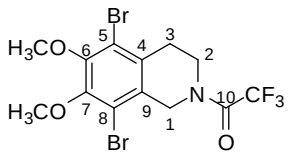
**1-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-2,2,2-trifluoroethanethan-1-one (427):**[144a]



This material was provided by Dr. Will Unsworth as a 2:1 mixture of rotamers and the characterisation data of the major and minor rotamer are provided here for reference:

major: $\delta_H$ (400 MHz, $CDCl_3$) 6.62 (1H, s, H-5/6), 6.62 (1H, s, H-5/6), 4.72 (2H, s, H-1), 3.89–3.81 (2H, m, H-2), 3.87 (3H, s, OC$H_3$), 3.86 (3H, s, OC$H_3$), 2.90–2.87 (2H, m, H-3); minor: $\delta_H$ (400 MHz, $CDCl_3$) 6.65 (1H, s, H-5/6), 6.56 (1H, s, H-5/6), 4.67 (2H, s, H-1), 3.89–3.81 (2H, m, H-2), 3.87 (3H, s, OC$H_3$), 3.86 (3H, s, OC$H_3$), 2.88–2.85 (2H, m, H-3); HRMS ($ESI^+$): Found: 312.0823; $C_{13}H_{14}F_3NNaO_3$ ($MNa^+$) Requires: 312.0818 (−1.7 ppm error). Obtained data in accord with those reported in the literature.[144a]

**1-(5,8-Dibromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-2,2,2-trifluoroethanethan-1-one (430):**[144a]

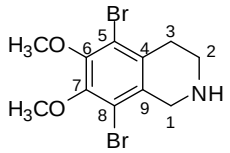


A round bottom flask was charged with trifluoroacetamide **427** (2 g, 6.91 mmol) and $FeCl_3$ (2.33 g, 14.4 mmol) in dichloromethane (13.5 mL). The resulting mixture was cooled to 0 °C. To the flask was added $Br_2$ (0.780 mL, 15.2 mL) in dichloromethane (7.36 mL) dropwise over 15 min. The reaction mixture was stirred at 0 °C for 30 min. To the flask was added dichloromethane (30 mL) followed by crushed ice. The mixture was stirred vigorously and extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (30 mL), sat. aq. $NaS_2O_3$ (30 mL), brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduce pressure to give compound **430** as a solid (2.67 g, 86% crude yield), which was used without further purification. NMR spectra showed rotameric broadening; $\delta_H$ (400 MHz, $CDCl_3$) 4.72 (2H, couple of singlets, C$H_2$), 3.90–3.80 (8H, m, C$H_2$, C$H_3$), 2.96–

2.90 (2H, m, C$H_2$); HRMS (ESI$^+$): Found: 467.9057; $C_{13}H_{12}{}^{79}Br_2F_3NNaO_3$ ($MNa^+$) Requires: 467.9028 (−1.7 ppm error). Obtained data in accord with those reported in the literature.[144a]

Lab Notebook Reference: CHK 5/299 p.24

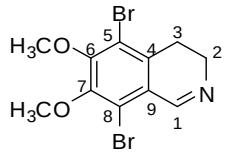
**5,8-Dibromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (431):**[144a]




A round bottom flask was charged with crude trifluoroacetamide **430** (2.67 g, 5.97 mmol), methanol (24.7 mL) and dichloromethane (6.20 mL). To the suspension was added $K_2CO_3$ (2.48 g, 17.9 mmol) and the mixture was stirred vigorously for 24 h at rt. $K_2CO_3$ was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and the solution was washed with water (50 mL), brine (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude secondary amine **431** (1.38 g, 66% crude yield) which was used for the next reaction without further purification. $\delta_H$ (400 MHz, $CDCl_3$) 3.92 (2H, br s, C$H_2$), 3.88 (3H, s, C$H_3$), 3.87 (3H, s, C$H_3$), 3.10–3.07 (2H, m, C$H_2$), 2.71–2.70 (2H, m, C$H_2$); HRMS (ESI$^+$): Found: 349.9373; $C_{11}H_{14}{}^{79}Br_2NO_2$ ($MH^+$) Requires: 349.9386 (3.2 ppm error). Obtained data in accord with those reported in the literature.[144a]

Lab Notebook Reference: CHK 5/300 p.25

**5,8-Dibromo-6,7-dimethoxy-3,4-dihydroisoquinoline (432):**[144a]

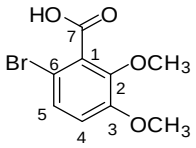



A round bottom flask was charged with crude amine **431** (1.38 g, 3.96 mmol), dichloromethane (37 mL) and manganese oxide (7.46 g, 85.7 mmol). The resulting mixture was stirred vigorously at rt for 48 h. The reaction mixture was filtered through Celite$^{TM}$ pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, 7:1→5:1→3:1 petrol:ethyl acetate) to

provide compound **432** as an orange oil (730 mg, 53%); $R_f$ 0.3 (1:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 8.58 (1H, br s, H-1), 3.93 (3H, s, OC$H_3$), 3.88 (3H, s, OC$H_3$), 3.74 (2H, t, *J* = 7.5 Hz, H-2), 2.75 (2H, t, *J* = 7.5 Hz, H-3); HRMS ($ESI^+$): Found: 347.9232; $C_{11}H_{12}{}^{79}Br_2NO_2$ ($MH^+$) Requires: 347.9229 (−1.2 ppm error). Obtained data in accord with those reported in the literature.[144a]

Lab Notebook Reference: CHK 5/303 p.27

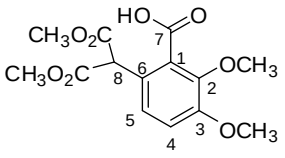
**6-Bromo-2,3-dimethoxybenzoic acid (434):**[146]




In an ice bath, 2,3-dimethoxybenzoic acid **433** (10 g, 54.9 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (8.63g, 30.2 mmol) were added to 0.7 M NaOH (86 mL). The reaction mixture was stirred at rt for 1 h, then 1 M HCl (150 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried with $MgSO_4$ and concentrated to give compound **434** as a solid (14.3 g, quantitative), which was used without further purification; $\delta_H$ (400 MHz, $CDCl_3$) 11.46 (1H, br s, COO*H*), 7.21 (1H, d, *J* = 8.9 Hz, H-4/5), 6.81 (1H, d, *J* = 8.9 Hz, H-4/5), 3.88 (3H, s, OC$H_3$), 3.82 (3H, s, OC$H_3$); HRMS ($ESI^+$): Found: 282.9575; $C_9H_9{}^{79}BrNaO_4$ ($MNa^+$) Requires: 282.9576 (0.6 ppm error). Obtained data in accord with those reported in the literature.[146]

Lab Notebook Reference: CHK 5/301 p.26

**6-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-2,3-dimethoxybenzoic acid (423):**

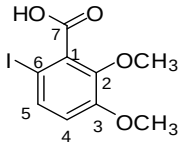



Sodium hydride (748 mg, 18.7 mmol, 60 % in mineral oil) was added portionwise to a rapidly stirred cold suspension (0 °C) of 6-bromo-2,3-dimethoxybenzoic acid **434** (2 g, 7.66 mmol), copper bromide (110 mg, 0.766 mmol) and dimethyl malonate (30 mL). After the addition of the sodium hydride had been completed, the mixture was stirred for 10 min at rt and then for 20 h at 70 °C. The suspension, which had turned to a solid

mass, was dissolved in water (60 mL), washed with ether (3 × 160 mL) and then acidified with 10% hydrochloric acid. The acidic aqueous layer, was extracted with ethyl acetate (3 × 200 mL) and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 10:1→2:1→1:1 petrol:ethyl acetate→ethyl acetate) afforded compound **423** as a white solid (870 mg, 36%); $R_f$ 0.47 (DCM, 2% MeOH); mp 104-108 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3223, 2955, 1735, 1581, 1494, 1438, 1264, 1150, 1055; $\delta_H$ (400 MHz, $CDCl_3$) 7.22 (1H, d, *J* = 8.7 Hz H-4/5), 7.08 (1H, d, *J* = 8.7 Hz, H-4/5), 5.36 (1H, s, H-8), 3.99 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$), 3.78 (6H, s, $CO_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.0 (C-7), 167.3 (C-*C*$O_2$Me), 152.3 (Ar C), 147.6 (Ar C), 126.5 (C-4/5), 125.5 (Ar C), 124.8 (Ar C), 115.2 (C-4/5), 62.2 (C-O*C*$H_3$), 56.0 (C-O*C*$H_3$), 54.2 (C-8), 52.9 (C-$CO_2$*C*$H_3$); HRMS ($ESI^+$): Found: 335.0728; $C_{14}H_{16}NaO_8$ ($MNa^+$) Requires: 335.0737 (2.9 ppm error).

Lab Notebook Reference: CHK 5/305 p.30

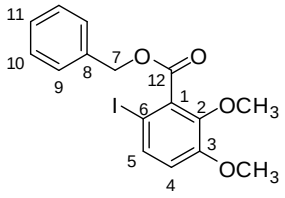
**6-Iodo-2,3-dimethoxybenzoic acid (437):**[148]




In a a round bottom flask, acid **433** (2.52g, 13.9 mmol), $Pd(OAc)_2$ (156 mg, 0.693 mmol), iodobenzene diacetate (4.46 g, 13.9 mmol) and $I_2$ (3.52 g, 13.9 mmol) were dissolved in DMF (69 mL) under air atmosphere. The reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to rt and 10% aq. $Na_2CO_3$ (350 mL) was added. The organic layer was separated and the aqueous layer was washed with ether (2 × 350 mL). The aqueous layer was acidified with 2 M HCl, extracted with ethyl acetate (3 × 700 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($SiO_2$, 7:1→5:1→3:1→2:1 petrol:ethyl acetate) to afford compound **437** as a white solid (2.86 g, 67%); $R_f$ 0.26 (9:1 DCM:MeOH); $\delta_H$ (400 MHz, $CDCl_3$) 10.55 (1H, br s, COO*H*), 7.49 (1H, d, *J* = 8.7 Hz, H-4/5), 6.73 (1H, d, *J* = 8.7 Hz, H-4/5), 3.91 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$); HRMS ($ESI^+$): Found: 330.9445; $C_9H_9INaO_4$ (MNa) Requires: 330.9438 (−2.7 ppm error). Obtained data in accord with those reported in the literature.[175]

Lab Notebook Reference: CHK 5/329 p.59

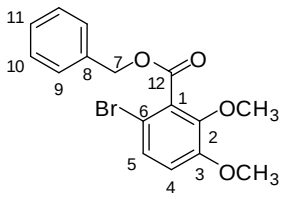
**Benzyl 6-iodo-2,3-dimethoxybenzoate (438):**




To a solution of 6-iodo-2,3-dimethoxybenzoic acid **437** (397.7 mg, 1.29 mmol) in DMF (2.8 mL) were added $KHCO_3$ (194 mg, 1.94 mmol) and benzyl bromide (184 μL, 1.55 mmol) and the mixture was stirred at rt for 1.5 h. The reaction mixture was quenched with water (20 mL) and extracted with ether (3 × 30 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($SiO_2$, 10:1 petrol:ethyl acetate) to afford compound **438** as a colourless oil (489 mg, 55%); $R_f$ 0.45 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2940, 1733, 1571, 1472, 1412, 1294, 1264, 1154, 1054, 1003; $\delta_H$ (400 MHz, $CDCl_3$) 7.50–7.48 (2H, m, ArH), 7.45 (1H, d, *J* = 8.7 Hz, H-4/5), 7.39–7.31 (3H, m, Ar-H), 6.68 (1H, d, *J* = 8.7 Hz, H-4/5), 5.40 (2H, s, H-7), 3.83 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 166.8 (C-12), 152.9 (Ar C), 146.8 (Ar C), 135.2 (Ar C), 134.2 (C-4/5), 128.6 (C-9/10/11), 128.5 (Ar C), 128.4 (C-9/10/11), 128.3 (C-9/10/11), 115.1 (C-4/5), 79.3 (C-6), 67.6 (C-7), 61.6 (C-O*C*H$_3$), 55.9 (C-O*C*H$_3$); HRMS ($ESI^+$): Found: 420.9916; $C_{16}H_{15}INaO_4$ ($MNa^+$) Requires: 420. 9907 (−2.4 ppm error).

Lab Notebook Reference: CHK 5/330 p.57

**Benzyl 6-bromo-2,3-dimethoxybenzoate (440):**

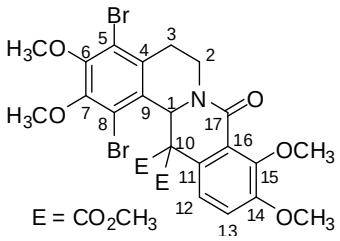



To a solution of 6-bromo-2,3-dimethoxybenzoic acid **434** (239.8 mg, 0.919 mmol) in DMF (2 mL) were added $KHCO_3$ (138 mg, 1.38 mmol) and benzyl bromide (112 μL, 0.938 mmol) and the mixture was stirred at rt for 1.5 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The

organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($SiO_2$, 7:1 petrol:ethyl acetate) to afford compound **440** as a colourless oil (209.3 mg, 65%); $R_f$ 0.57 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2940, 2839, 1732, 1576, 1473, 1414, 1372, 1295, 1261, 1218, 1156, 1052, 1003; $\delta_H$ (400 MHz, $CDCl_3$) 7.48–7.45 (2H, m, ArH), 7.40–7.31 (3H, m, ArH), 7.22 (1H, d, *J* = 8.8 Hz, H-4/5), 6.81 (1H, d, *J* = 8.8 Hz, H-4/5), 5.41 (2H, s, H-7), 3.83 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 165.7 (C-12), 152.0 (Ar C), 146.9 (Ar C), 135.2 (Ar C), 131.1 (Ar C), 128.5 (C-9/10/11), 128.4 (C-9/10/11), 128.3 (C-9/10/11), 127.8 (C-4/5), 114.5 (C-4/5), 108.8 (C-6), 67.5 (C-7), 61.6 (C-O*C*H$_3$), 56.0 (C-O*C*H$_3$); HRMS ($ESI^+$): Found: 373.0043; $C_{16}H_{15}{}^{79}BrNaO_4$ ($MNa^+$) Requires: 373.0046 (0.4 ppm error).

Lab Notebook Reference: CHK 5/327 p.54

**13,13-Dimethyl 9,12-dibromo-3,4,10,11-tetramethoxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (441):**

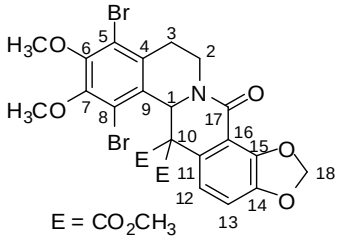



Synthesised using general DIA procedure B from imine **432** (41.5 mg, 0.119 mmol), acid **423** (44.6 mg, 0.143 mmol), DIPEA (38.3 μL, 0.220 mmol), T3P (114 mg, 0.179 mmol) and $AlCl_3$ (31.7 mg, 0.238 mmol) in chloroform (1.5 mL) at rt for 20 h. Purification by column chromatography ($SiO_2$, 3:1→1:1 petrol:ethyl acetate) afforded compound **441** as a yellow oil (29.1 mg, 38%); $R_f$ 0.4 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2941, 1742, 1657, 1486, 1455, 1423, 1393, 1301, 1272, 1223, 1025; $\delta_H$ (400 MHz, $CDCl_3$) 7.20 (1H, d, *J* = 8.8 Hz, H-12/13), 7.07 (1H, d, *J* = 8.8 Hz, H-12/13), 5.99 (1H, s, H-1), 4.91 (1H, ddd, *J* = 13.0, 5.3, 1.8 Hz, H-2eq), 4.05 (3H, s, OC*H*$_3$), 3.96 (3H, s, OC*H*$_3$), 3.93 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 3.68 (3H, s, $CO_2C$*H*$_3$), 3.55 (3H, s, $CO_2C$*H*$_3$), 3.34 (1H, ddd, *J* = 16.5, 12.9, 5.3 Hz, H-3ax), 3.05 (1H, ddd, *J* = 16.5, 3.4, 1.8 Hz, H-3eq), 2.76 (1H, ddd, *J* = 13.0, 12.9, 3.4 Hz, H-2ax); $\delta_C$ (100 MHz, $CDCl_3$) 167.8 (*C*$O_2CH_3$), 166.5 (*C*$O_2CH_3$), 162.0 (C-17), 153.7 (Ar C), 150.9 (Ar C), 149.8 (Ar C), 148.8 (Ar C), 139.0 (Ar C), 129.3 (Ar C), 128.5 (Ar C), 124.7

(C-12/13), 123.8 (Ar C), 120.1 (Ar C), 119.2 (Ar C), 114.8 (C-12/13), 64.6 (C-10), 61.7 (C-O$CH_3$), 60.8 (C-1), 60.7 (C-O$CH_3$), 60.2 (C-O$CH_3$), 56.0 (C-O$CH_3$), 53.1 (C-$CO_2CH_3$), 52.9 (C-$CO_2CH_3$), 38.7 (C-2), 30.6 (C-3); HRMS ($ESI^+$): Found: 663.9804; $C_{25}H_{25}{}^{79}Br_2NNaO_9$ ($MNa^+$) Requires: 663.9788 (−2.3 ppm error).

Lab Notebook Reference: CHK 5/307 p.32

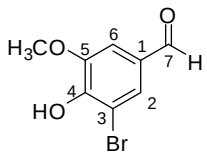
**13,13-Dimethyl 9,12-dibromo-10,11-dimethoxy-3,4-methylenedioxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (442):**




Synthesised using general DIA procedure B from imine **432** (42.1 mg, 0.121 mmol), acid **405** (43.1 mg, 0.146 mmol), DIPEA (39.2 μL, 0.224 mmol), T3P (115.8 mg, 0.182 mmol) and $AlCl_3$ (32.4 mg, 0.243 mmol) in chloroform (1 mL) at 50 °C for 20 h. Purification by column chromatography ($SiO_2$, 5:1→3:1 petrol:ethyl acetate) afforded compound **442** as a colourless oil (31.3 mg, 41%); $R_f$ 0.38 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2948, 2870, 1743, 1642, 1448, 1404, 1299, 1253, 1238, 1221, 1021; $\delta_H$ (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* = 8.7 Hz, H-12/13), 7.06 (1H, d, *J* = 8.7 Hz, H-12/13), 6.02 (1H, s, H-1), 5.99 (2H, s, H-18), 4.76 (1H, ddd, *J* = 12.8, 4.7, 1.7 Hz, H-2eq), 3.97 (3H, s, OC$H_3$), 3.87 (3H, s, OC$H_3$), 3.71 (3H, s, $CO_2CH_3$), 3.52 (3H, s, $CO_2CH_3$), 3.49–3.44 (1H, m, H-2ax), 3.06 (1H, ddd, 16.3, 3.1, 1.7 Hz, H-3eq), 2.82 (1H, ddd, *J* =12.8, 12.8, 3.1 Hz, H-3ax); $\delta_C$ (100 MHz, $CDCl_3$) 167.7 ($CO_2CH_3$), 167.3 ($CO_2CH_3$), 165.9 (C-17), 152.6 (Ar C), 150.9 (Ar C), 148.8 (Ar C), 143.9 (Ar C), 138.9 (Ar C), 130.9 (Ar C), 127.8 (Ar C), 127.8 (Ar C), 121.7 (C-12/13), 120.0 (C-12/13), 119.3 (Ar C), 112.2 (Ar C), 99.9 (Ar C), 78.4 (C-18), 63.3 (C-10), 60.9 (C-O$CH_3$), 60.7 (C-O$CH_3$), 59.9 (C-1), 53.3 (C-$CO_2CH_3$), 53.0 (C-$CO_2CH_3$), 39.5 (C-2), 30.5 (C-3); HRMS ($ESI^+$): Found: 647.9496; $C_{24}H_{21}{}^{79}Br_2NNaO_9$ (MNa) Requires: 647.9475 (−3.1 ppm error).

Lab Notebook Reference: CHK 5/333 p.62

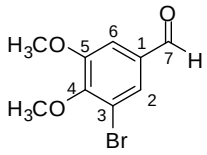
**3-Bromo-4-hydroxy-5-methoxybenzaldehyde (446):**[151a-c,e]




A round bottom flask was charged with vanillin **445** (5.00 g, 32.9 mmol) and glacial acetic acid (30 mL) was added. Vanillin **445** was dissolved to form a pale yellow solution. Neat bromine (1.85 mL, 36.2 mL) was added dropwise to the stirring solution to produce a deep red-orange solution. The reaction was stirred for 1 h to result in the formation of a bright yellow participate when nearing completion. The reaction mixture was poured onto cold water (0 °C, 60 mL) resulting in further precipitation of a pale yellow solid. The solid was collected by filtration, washed with cold water and dried *in vacuo* to afford compound **446** as a yellow solid (6.96 g, 91%). The crude was used to the next step without further purification; $\delta_H$ (400 MHz, $CDCl_3$) 9.79 (1H, s, H-7), 7.64 (1H, d, *J* = 1.7 Hz, H-2/6), 7.36 (1H, d, *J* = 1.7 Hz, H-2/6), 6.51 (1H, s, O*H*), 3.99 (3H, s, OC$H_3$); HRMS (ESI$^+$): Found: 252.9476; $C_8H_7{}^{79}BrNaO_3$ ($MNa^+$) Requires: 252.9471 (−2.1 ppm error). Obtained data in accord with those reported in the literature.[151e]

Lab Notebook Reference: CHK 6/369 p.11

**3-Bromo-4,5-dimethoxybenzaldehyde (450):**[153]

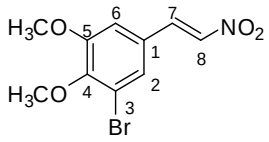



To a round bottom flask containing 3-bromo-4-hydroxy-5-methoxybenzaldehyde **446** (7.44, 32.2 mmol) in acetone (70 mL), anhydrous $K_2CO_3$ (11.1 g, 80.5 mmol) was added. To the stirring mixture was added $Me_2SO_4$ (7.62 g, 80.5 mmol) and the reaction was stirred vigorously at rt for 16 h. $K_2CO_3$ was removed by filtration and the filtrate was washed with acetone (2 × 70 mL) and methanol (70 mL). The combined filtrate was concentrated under reduced pressure to an orange oil and purified by column chromatography ($SiO_2$, 10:1 petrol:ethyl acetate) to afford compound **450** as a yellow oil (5.96 g, 74%); $R_f$ 0.25 (1:1 petrol:ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 9.83 (1H, s, H-7),7.64 (1H, d, *J* = 1.8 Hz, H-2/6), 7.38 (1H, d, *J* = 1.8 Hz, H-2/6), 3.94 (3H,

s, OC$H_3$), 3.93 (3H, s, OC$H_3$); HRMS (ESI$^+$): Found: 266.9620; $C_9H_9{}^{79}BrNaO_3$ ($MNa^+$) Requires: 266.9627 (1.8 ppm error). Obtained data in accord with those reported in the literature.[153]

Lab Notebook Reference: CHK 6/373 p.35

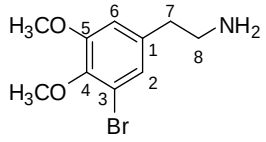
**1-Bromo-2,3-dimethoxy-5[(*E*)-2-nitroethenyl]benzene (451):**[112]




To a solution of 3-bromo-4,5-dimethoxybenzaldehyde **450** (3.54 g, 14.4 mmol) in acetic acid (12 mL) was added nitromethane (2.34 mL, 43.3 mmol) and ammonium acetate (1.11 g, 14.4 mmol). The mixture was heated to 90 °C for 24 h. The cooled mixture was quenched with cold water (80 mL) to favor the precipitation of a solid. The solid was collected by filtration and washed with more cold water. The filtrate was extracted with ethyl acetate (3 × 80 mL). The solid and the combined organic layers were dried *in vacuo* and purified by column chromatography ($SiO_2$, 8:1 petrol:ethyl acetate) to afford compound **451** as a yellow solid (3.72 g, 89%); $R_f$ 0.67 (7:1 petrol:ethyl acetate); mp 85–88 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3114, 2940, 1630, 1593, 1554, 1504, 1488, 1414, 1357, 1321, 1283, 1239, 1046; $\delta_H$ (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 13.7 Hz, H-7), 7.51 (1H, d, *J* = 13.7 Hz, H-8), 7.37 (1H, d, *J* = 2 Hz, H-2/6), 6.98 (1H, d, *J* = 2 Hz, H-2/6), 3.92 (3H, s, OC$H_3$), 3.92 (3H, s, OC$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 154.0 (Ar C), 149.7 (Ar C), 137.5 (C-7), 137.1 (C-8), 126.8 (Ar C), 126.3 (C-2/6), 118.5 (Ar C), 111.4 (C-2/6), 60.9 (C-O$CH_3$), 56.2 (C-O$CH_3$); HRMS (ESI$^+$): Found: 287.9862; $C_{10}H_{11}{}^{79}BrNO_4$ ($MH^+$) Requires: 287.9866 (2.6 ppm error). This compound has been reported previously in the literature, but no spectral data are reported to date.[176]

Lab Notebook Reference: CHK 6/377 p.20

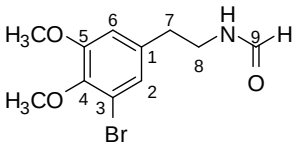
**2-(3-Bromo-4,5-dimethoxyphenyl)ethan-1-amine (452):**




1-Bromo-2,3-dimethoxy-5[(*E*)-2-nitroethenyl]benzene **451** (132.5 mg, 0.460 mmol) was dissolved in THF (2 mL) at −5 °C (salt/ice water) and $LiAlH_4$ (52.4 mg, 1.38 mmol) was added portionwise. The reaction mixture was stirred for 20 min before it was acidified with HCl 1 M to pH = 1. The aqueous layer was extracted with dichloromethane (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound **452** was used to the next step without further purification (68.1 mg, 57% crude yield); $\nu_{max}$ (thin film)/$cm^{-1}$ 3363, 2999, 2935, 2835, 2665, 1591, 1515, 1463, 1417, 1261, 12351141, 1026; $\delta_H$ (400 MHz, $CDCl_3$) 6.98 (1H, s, H-2/6), 6.70 (1H, s, H-2/6), 3.84 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.15 (2H, t, *J* = 7.0 Hz, H-8), 2.80 (2H, t, *J* = 7.0 Hz, H-7); $\delta_C$ (100 MHz, $CDCl_3$) 153.7 (Ar C), 145.0 (Ar C), 136.5 (Ar C), 124.8 (C-2/6), 117.7 (Ar C), 112.4 (C-2/6), 60.6 (C-O*C*$H_3$), 56.2 (C-O*C*$H_3$), 54.6 (C-8), 32.8 (C-7); HRMS ($ESI^+$): Found: 260.0275; $C_{10}H_{15}{}^{79}BrNO_2$ ($MH^+$) Requires: 260.0281 (2.1 ppm error). This compound has been reported previously in the literature, but no spectral data are reported to date.[176]

Lab Notebook Reference: CHK 6/390 p.39

***N*-[2-(3-Bromo-4,5-dimethoxyphenyl)ethyl]formamide (453):**

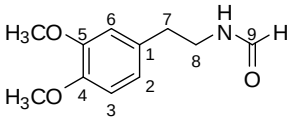



2-(3-Bromo-4,5-dimethoxyphenyl)ethan-1-amine **452** (1.02 g, 3.92 mmol) was dissolved in ethyl formate (40 mL). The reaction mixture was stirred for 20 h at 65 °C. The solvent was evaporated and the residue was purified by column chromatography ($SiO_2$, 1:1→1:3→1:5 petrol:ethyl acetate→pure ethyl acetate) to afford compound **453** as a colourless oil (689 mg, 61%); $R_f$ 0.58 (9:1 ethyl acetate:MeOH); $\nu_{max}$ (thin film)/$cm^{-1}$ 3287, 2875, 2936, 1659, 1596, 1566, 1515, 1488, 1463, 1414, 1384, 1271, 12341140, 1044, 999; $\delta_H$ (400 MHz, $CDCl_3$) 8.13 (1H, s, H-9), 6.95 (1H, d, *J* = 1.9 Hz, H-2/6), 6.67 (1H, d, *J* = 1.9 Hz, H-2/6), 5.81 (1H, br s, N*H*), 3.84 (3H, s,

OC$H_3$), 3.81 (3H, s, OC$H_3$), 3.52 (2H, q, $J$ = 6.9 Hz, H-8), 2.76 (2H, t, $J$ = 6.9 Hz, H-7); $\delta_C$ (100 MHz, $CDCl_3$) 161.3 (C-9), 153.8 (Ar C), 145.2 (Ar C), 135.8 (Ar C), 124.7 (C-2/6), 117.7 (Ar C), 112.2 (C-2/6), 60.7 (C-O*C*H$_3$), 56.2 (C-O*C*H$_3$), 39.1 (C-8), 35.2 (C-7); HRMS (ESI$^+$): Found: 310.0054; $C_{11}H_{14}{}^{79}BrNNaO_3$ (MNa$^+$) Requires: 310.0049 (−1.5 ppm error)

Lab Notebook Reference: CHK 6/394 p.45

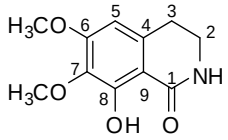
***N*-[2-(3,4-Dimethoxyphenyl)ethyl]formamide (454):**




To a solution of *N*-[2-(3-bromo-4,5-dimethoxyphenyl)ethyl]formamide **453** (135 mg, 0.467 mmol) in THF was added *n*-BuLi (0.411 mL, 1.03 mmol) dropwise at –78 °C and the resulting reaction mixture was stirred at –78 °C for 2 h. $B(OMe)_3$ (0.156 mL, 1.40 mmol) was then added dropwise and the mixture was allowed to warm to 0 °C over a period of 1 h. A cooled solution of $H_2O_2$ (0.238 mL, 2.34 mmol, 35% w/w) in 10% aq. NaOH (89.6 mg, 2.24 mmol) was added and the reaction mixture was stirred at 0 °C for 0.5 h. The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ to give the crude compound **454** (94.2 mg, 96%); $R_f$ 0.58 (9:1 ethyl acetate:MeOH); $\delta_H$ (400 MHz, $CDCl_3$) 8.13 (1H, s, H-9), 6.80 (1H, d, $J$ = 8.0 Hz, ArH), 6.74–6.71 (2H, m, ArH), 5.67 (1H, br s, N*H*), 3.86 (3H, s, OC$H_3$), 3.85 (3H, s, OC$H_3$), 3.54 (2H, q, $J$ = 6.8 Hz, H-8), 2.78 (2H, t, 6.8 Hz, H-7); HRMS (ESI$^+$): Found: 232.0944; $C_{11}H_{15}NNaO_3$ (MNa$^+$) Requires: 232.0944 (−0.1 ppm error); Obtained data in accord with those reported in the literature.[177]

Lab Notebook Reference: CHK 6/392 p.42

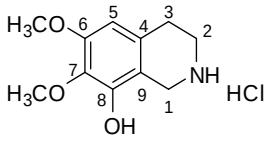
**8-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-one (459):**[80]




Diphenyl azide (8.96 mL, 0.0420 mol) was added dropwise to a stirred solution of carboxylic acid **456** (10.0 g, 0.0420 mol) and triethylamine (5.80 mL, 0.0420 mol) in toluene (125 mL) at rt. The reaction was then stirred at 90 °C for 1.5 h. Most of the solvent was removed *in vacuo* to afford a mobile oil. The flask was cooled to 0 °C under nitrogen atmosphere and $BF_3{\cdot}OEt_2$ (20.8 mL) was added dropwise. The reaction mixture was stirred for 20 h at rt before it was quenched with 1 M NaOH to pH = 10. Ethyl acetate (300 mL) was added and the rapidly stirred mixture was heated for 1 h at 50 °C solvating all the crude material. The mixture was cooled to rt, the layers separated and the aqueous fraction further extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude product. Column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) gave compound **459** (7.34 g, 80%) as a white solid; $R_f$ 0.4 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 12.37 (1H, s, O*H*), 6.45 (1H, br s, N*H*), 6.25 (1H, s, H-5), 3.88 (3H, s, OC$H_3$), 3.86 (3H, s, OC$H_3$), 3.52 (2H, dt, *J* = 6.7, 2.7 Hz, H-2), 2.90 (2H, t, *J* = 6.7 Hz, H-3); HRMS ($ESI^+$): Found: 246.0736; $C_{11}H_{13}NNaO_4$ ($MNa^+$) Requires: 246.0737 (0.2 ppm error); Elemental Analysis: calculated for $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.20; H, 5.95; N, 6.17. Obtained data in accord with those reported in the literature.[80]

Lab Notebook Reference: CHK 6/396 p.71

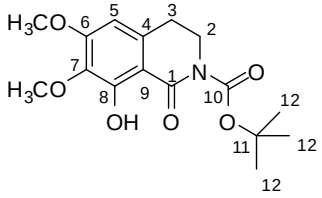
**6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-8-ol hydrochloride (460):**




8-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-one **459** (146 mg, 0.453 mmol) was dissolved in THF (7.7 mL) at rt and $LiAlH_4$ (99.2 mg, 2.61 mmol) was added portionwise. The reaction mixture was stirred for 1 h at 70 °C before it was poured in to water (20 mL) and acidified with HCl 1 M to pH = 1. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, DCM→DCM, 5% MeOH→DCM, 8% MeOH) afforded compound **460** as a colourless oil (24.5 mg, 18%); $R_f$ 0.5 (9:1, DCM:MeOH); $\delta_H$ (400 MHz, $CDCl_3$) 12.32 (1H, br s, O*H*), 6.26 (1H, s, H-5), 6.09 (1H, br s, N*H*), 3.89 (3H, s, OC$H_3$), 3.88 (3H, s, OC$H_3$), 3.84–3.82 (2H, m, H-1), 3.54–3.53 (2H, m, H-2), 2.93–2.90 (2H, m, H-3). Note that mass spec failed to show the expected mass peak. This compound has been reported previously in the literature.[178]

Lab Notebook Reference: CHK 6/398 p.51

***tert*-Butyl 8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (461):**

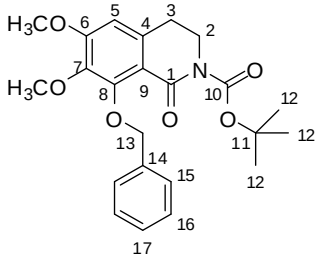



*n*-BuLi (11.0 mL, 27.6 mmol, 2.5 M in hexanes) was added in a stirred solution of amide **459** (2.05 g, 9.18 mL) in dry THF (110 mL) at −78 °C. After 10 minutes a solution of $Boc_2O$ (2.21 g, 10.1 mmol) in THF (28 mL) was transferred *via* syringe at −78 °C. The reaction mixture was then allowed to warm to rt and left to stir for 20 h. The reaction was quenched with sat. aq. $NH_4Cl$ (100 mL) at rt. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate→pure ethyl acetate) to afford compound

**461** as colorless crystals (2.35 g, 80%); $R_f$ 0.6 (1:1 petrol:ethyl acetate); mp 115–117 °C; νmax (thin film)/cm−1 3007, 2977, 2941, 1711, 1643, 1575, 1450, 1420, 1368, 1291, 1254, 1228; $\delta_H$ (400 MHz, $CDCl_3$) 12.24 (1H, s, O*H*), 6.23 (1H, s, H-5), 3.90 (2H, t, *J* = 6.3 Hz, H-2), 3.88 (3H, s, OC$H_3$), 3.83 (3H, s, OC$H_3$), 2.90 (2H, t, *J* = 6.3 Hz, H-3), 1.55 (9H, s, H-12); $\delta_C$ (100 MHz, $CDCl_3$) 169.3 (C-1), 157.5 (Ar C), 157.2 (Ar C), 152.0 (Ar C), 136.1 (Ar C), 135.2 (Ar C), 106.3 (Ar C), 101.6 (C-5), 83.6 (C-11), 60.6 (C-O*C*$H_3$), 55.9 (C-O*C*$H_3$), 44.6 (C-2), 28.4 (C-12), 27.9 (C-3); HRMS ($ESI^+$): Found: 346.1248; $C_{16}H_{21}NNaO_6$ ($MNa^+$) Requires: 346.1261 (3.3 ppm error); Elemental Analysis: calculated for $C_{16}H_{21}NO_6$ requires C, 59.43; H, 6.55; N, 4.33; found C, 59.66; H, 6.46; N, 4.25

Lab Notebook Reference: CHK 6/427 p.85

***tert*-Butyl 8-(benzyloxy)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (462):**

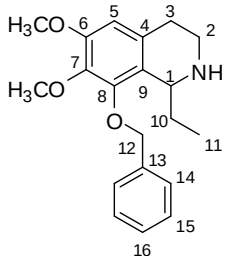



Amide **461** (115 mg, 0.355 mmol) and benzyl bromide (0.063 mL, 0.532 mmol) were dissolved in toluene (3 mL). $K_2CO_3$ was added and the reaction mixture was stirred at 120 °C for 20 h. The reaction was cooled to rt before it was quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) to afford compound **462** as colourless oil (118 mg, 80%); $R_f$ 0.5 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2977, 2936, 1761, 1708, 1592, 1489, 1454, 1423, 1379, 1309, 1279, 1248, 1146, 1121; $\delta_H$ (400 MHz, $CDCl_3$) 7.59–7.57 (2H, m, ArH), 7.36–7.26 (3H, m, ArH), 6.47 (1H, s, H-5), 5.16 (2H, s, H-13), 3.98 (3H, s, OC$H_3$), 3.83 (3H, s, OC$H_3$, overlapping), 3.81 (2H, t, *J* = 6.2 Hz, H-2, overlapping), 2.84 (2H, t, *J* = 6.2 Hz, H-3), 1.57 (9H, s, H-12); $\delta_C$ (100 MHz, $CDCl_3$) 161.2 (C-1), 156.4 (Ar C), 154.3 (Ar C), 152.6 (C-10), 142.4 (Ar C), 137.4 (Ar C), 137.0 (Ar C), 129.0 (Ar CH), 128.1 (Ar CH), 127.8 (Ar CH), 117.7 (Ar C), 105.6 (C-5), 82.6 (C-11), 75.8 (C-13), 61.0

(C-O*C*H$_3$), 56.0 (C-O*C*H$_3$), 44.1 (C-2), 29.5 (C-3), 28.0 (C-12); HRMS (ESI$^+$): Found: 436.1728; $C_{23}H_{27}NNaO_6$ (MNa$^+$) Requires: 436.1731 (0.5 ppm error).

Lab Notebook Reference: CHK 6/421 p.84

**8-(Benzyloxy)-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (466):**

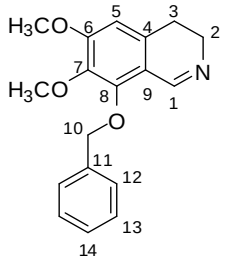



Compound **462** (118 mg, 0.285 mmol) was dissolved in THF (3 mL) and cooled to −78 °C. Super-Hydride$^{TM}$ (0.428 mL, 0.428 mmol, 1 M solution in THF) was added dropwise and stirring continued for 30 min at −78 °C. The excess reducing agent was quenched by the addition of 10:1 EtOH:conc. aq. HCl (3 mL) and the resulting mixture diluted with dichloromethane (33 mL), washed with water (17 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was used directly to the next step without further purification. A 1:1 mixture of DCM:TFA (2 mL), that had been pre-cooled to 0 °C, was added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 min. The majority of the volatile organics were then removed *in vacuo*, before the crude residue was dissolved in dichloromethane (17 mL), washed with sat. aq. $NaHCO_3$ (7 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate→ethyl acetate, 5 % MeOH→ ethyl acetate, 10 % MeOH) afforded compound **466** as yellow oil (30.9 mg, 33%); $R_f$ 0.2 (DCM, 10 % MeOH); $\nu_{max}$ (thin film)/cm$^{-1}$ 2935, 1674, 1602, 1494, 1453, 1424, 1374, 1346, 1277, 1199, 1117, 1027; $\delta_H$ (400 MHz, $CDCl_3$) 7.44–7.42 (2H, m, ArH), 7.41–7.30 (3H, m, ArH), 6.42 (1H, s, H-5), 5.68 (1H, br s, N*H*), 5.19 (1H, d, *J* = 11.2 Hz, H-12a), 5.01 (1H, d, *J* = 11.2 Hz, H-12b), 4.11 (1H, dd, *J* = 9.4, 2.9 Hz, H-1), 3.85 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.28–3.22 (1H, m, H-2a), 3.15–3.09 (1H, m, H-2b), 2.96–2.87 (1H, m, H-3a), 2.83–2.76 (1H, m, H-3b), 1.93–1.85 (1H, m, H-10a), 1.79–1.70 (1H, m H-10b), 0.97 (3H, t, *J* = 7.4 Hz, H-11); $\delta_C$ (100 MHz, $CDCl_3$) 152.5 (Ar C), 149.4 (Ar C), 140.4 (Ar C), 137.6 (Ar C), 128.6 (Ar C), 128.4 (Ar CH), 128.0 (Ar CH), 127.9 (Ar CH), 122.4 (Ar C), 107.3 (C-5), 74.9 (C-12), 60.9 (C-O*C*H$_3$), 55.9 (C-O*C*H$_3$), 53.1 (C-1), 37.7 (C-2), 27.2 (C-3/10), 27.0 (C-

3/10), 11.0 (C-11); HRMS ($ESI^+$): Found: 328.1894; $C_{20}H_{26}NO_3$ ($MH^+$) Requires: 328.1907 (4.0 ppm error).

Lab Notebook Reference: CHK 6/428 p.86

**8-(Benzyloxy)-6,7-dimethoxy-3,4-dihydroisoquinoline (467):**

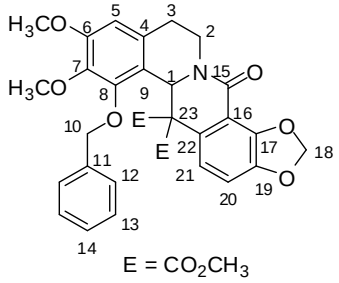



Compound **462** (102 mg, 0.247 mmol) was dissolved in THF (2.6 mL) and cooled to −78 °C. Super-Hydride$^{TM}$ (0.371 mL, 0.371 mmol, 1 M solution in THF) was added dropwise and stirring continued for 30 min at −78 °C. The excess reducing agent was quenched at −78 °C by the sequential addition of methanol (0.213 mL), water (0.107 mL), aq. $H_2O_2$ solution 30% w/v (0.107 mL) and aq. NaOH solution 6 M (0.107 mL). Stirring was continued while the mixture warmed to rt. The resulting mixture was then diluted with water (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ solution (10 mL), sat. aq $Na_2CO_3$ solution (10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was used directly to the next step without further purification. A 1:1 mixture of DCM:TFA (2 mL), that had been pre-cooled to 0 °C, was added immediately to the crude product and the resulting solution was left to stir for 1 h at rt. The majority of the volatile organics were then removed *in vacuo*, before the crude residue was dissolved in dichloromethane (20 mL), washed with sat. aq. $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, 1:1 ethyl acetate:petrol→2:1 ethyl acetate:petrol→pure ethyl acetate) afforded compound **467** as colourless oil (37.1 mg, 50%); $R_f$ 0.15 (9:1 ethyl acetate:MeOH); $\nu_{max}$ (thin film)/$cm^{-1}$ 2938, 1619, 1597, 1570, 1492, 1454, 1427, 1379, 1348, 1311, 1234, 1123, 1093, 1191; $\delta_H$ (400 MHz, $CDCl_3$) 8.49 (1H, br s, H-1), 7.44–7.42 (2H, m, ArH), 7.39–7.30 (3H, m, ArH), 6.47 (1H, s, H-5), 5.13 (2H, s, H-10), 3.89 (3H, s, OC$H_3$ ), 3.87 (3H, s, OC$H_3$), 3.63 (2H, t, $J$ = 7.8 Hz, H-2), 2.60 (2H, t, $J$ = 7.8 Hz, H-3); $\delta_C$ (100 MHz, $CDCl_3$) 155.8 (Ar C), 155.4 (C-1), 150.5 (Ar C), 140.4 (Ar C), 136.8 (Ar C), 133.3 (Ar C), 128.4 (Ar CH), 128.4 (Ar CH), 128.2

(Ar CH), 115.8 (Ar C), 106.4 (C-5), 76.1 (C-10), 61.0 (C-O*C*H$_3$), 56.0 (C-O*C*H$_3$), 46.8 (C-2), 25.3 (C-3); HRMS (ESI$^+$): Found: 298.1427; $C_{18}H_{20}NO_3$ ($MH^+$) Requires: 298.1438 (3.7 ppm error).

Lab Notebook Reference: CHK 6/431 p.94

**13,13-Dimethyl 12-(benzyloxy)-10,11-dimethoxy-3,4-methylenedioxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (468):**

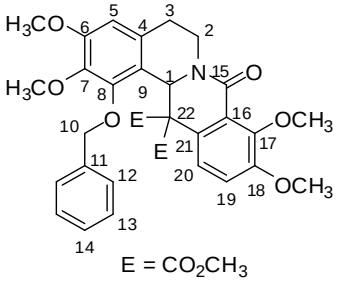



Synthesised using general DIA procedure B from imine **467** (59.3 mg, 0.199 mmol), acid **405** (70.9 mg, 0.239 mmol), DIPEA (64.3 μL, 0.369 mmol), T3P (190 mg, 0.299 mmol) and $AlCl_3$ (53.2 mg, 0.399 mmol) in chloroform (2 mL) at 50 °C for 20 h. Purification by column chromatography ($SiO_2$, 3:1→2:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded compound **468** as a colourless oil (56.8 mg, 50%) $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 2951, 2248, 1741, 1656, 1600, 1496, 1461, 1428, 1346, 1309, 1235, 1124, 1043; $\delta_H$ (400 MHz, $CDCl_3$) 7.96–7.17 (5H, m, Ar-H), 6.91 (1H, d, *J* = 8.4 Hz, H-20/21), 6.83 (1H, d, *J* = 8.4 Hz, H-20/21), 6.53 (1H, s, H-5), 6.21 (1H, d, *J* = 1.3 Hz, H-18a), 6.12 (1H, d, *J* = 1.3 Hz, H-18b), 5.23 (1H, s, H-1), 4.91 (1H, d, *J* = 10.8 Hz, H-10a), 4.77 (1H, d, *J* = 10.8 Hz, H-10b), 4.76–4.72 (1H, m, H-2eq), 3.89 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 3.51 (3H, s, $CO_2CH_3$), 3.45 (3H, s, $CO_2CH_3$), 3.36–3.28 (1H, m, H-3a), 2.57–2.50 (2H, m, H-2ax,3b); $\delta_C$ (100 MHz, $CDCl_3$) 168.7 (C-*C*$O_2CH_3$), 166.6 (C-*C*$O_2CH_3$), 161.9 (C-15), 152.7 (Ar C), 150.3 (Ar C), 148.5 (Ar C), 147.6 (Ar C), 139.6 (Ar C), 136.4 (Ar C), 136.1 (Ar C), 129.5 (Ar CH), 129.4 (Ar C), 128.4 (Ar CH), 128.1 (Ar CH), 124.0 (C-20/21), 117.7 (Ar C), 112.5 (Ar C), 110.7 (C-20/21), 107.3 (C-5), 102.5 (C-18), 75.7 (C-10), 64.2 (C-23), 60.9 (C-O*C*H$_3$), 56.8 (C-1), 55.7 (C-O*C*H$_3$), 52.8 (C-$CO_2$*C*H$_3$), 52.5 (C-$CO_2$*C*H$_3$), 39.5 (C-2), 29.8 (C-3); HRMS (ESI$^+$): Found: 576.1883; $C_{31}H_{30}NO_{10}$ ($MH^+$) Requires: 576.1864 (−3.3 ppm error).

Lab Notebook Reference: CHK 7/443 p.11

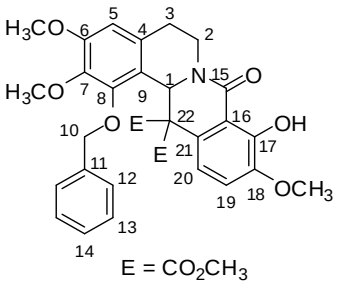
The following compounds (compounds **469** and **470**) were prepared by Dr. Will Unsworth and their characterisation data are provided below for reference:

**13,13-Dimethyl 12-(benzyloxy)-3,4,10,11-tetramethoxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (469):**




mp 70–72 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 2949, 1740, 1654, 1602, 1580, 1453, 1487, 1424, 1308, 1272, 1236, 1124, 1068; $\delta_H$ (400 MHz, $CDCl_3$) 7.26–7.22 (1H, m, ArH), 7.18–7.11 (4H, m, Ar-H), 7.04 (2H, br s, H-19/10), 6.53 (1H, s, H-5), 5.09, (1H, s, H-1), 4.90 (1H, d, *J* = 11.0 Hz, H-10a), 4.81 (1H, ddd, *J* = 13.3, 5.3, 2.5 Hz, H-2eq), 4.77 (1H, d, *J* = 11.0 Hz, H-10b), 4.03 (3H, s, OC*H*$_3$), 3.93 (3H, s, OC*H*$_3$), 3.89 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 3.53 (3H, s, $CO_2C$*H*$_3$), 3.48 (3H, s, $CO_2C$*H*$_3$), 3.33 (1H, ddd, *J* = 13.3, 13.3, 4.1 Hz, H-3ax), 2.56–2.48 (2H, m, H-2ax, 3eq); $\delta_C$ (100 MHz, $CDCl_3$) 168.8 (*C*$O_2CH_3$), 166.7 (*C*$O_2CH_3$), 162.2 (C-15), 153.2 (Ar C), 152.7 (Ar C), 150.3 (Ar C), 149.2 (Ar C), 139.6 (Ar C), 136.3 (Ar C), 136.1 (Ar C), 129.9 (Ar C), 129.5 (Ar CH), 128.5 (Ar CH), 128.1 (Ar CH), 126.0 (C-19/20), 123.3 (Ar C), 117.9 (Ar C), 114.5 (C-19/20), 107.3 (C-5), 75.7 (C-10), 64.6 (C-22), 61.5 (C-O*C*H$_3$), 60. 9 (C-O*C*H$_3$), 56.2 (C-1), 55.9 (C-O*C*H$_3$), 55.7 (C-O*C*H$_3$), 52.8 (C-$CO_2$*C*H$_3$), 52.6 (C-$CO_2$*C*H$_3$), 39.1 (C-2), 29.7 (C-3); HRMS (ESI$^+$): Found: 592.2183; $C_{32}H_{34}NO_{10}$ (MH$^+$) Requires: 592.2177 (1.0 ppm error).

**13,13-Dimethyl 12-(benzyloxy)-4-hydroxy-3,10,11-trimethoxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (470):**




mp 93–95 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 2951, 1739, 1638, 1602, 1582, 1496, 1454, 1436, 1360, 1345, 1310, 1234, 1260, 1123, 1068; $\delta_H$ (400 MHz, $CDCl_3$) 7.28–7.23 (1H, m, Ar-H), 7.21–7.13 (4H, m, Ar-H), 6.98 (1H, d, *J* = 8.6 Hz, H-19/20), 6.80 (1H, d, *J* = 8.6 Hz, H-19/20), 6.54 (1H, s, H-5), 5.04, (1H, s, H-1), 4.92 (1H, d, *J* = 11.0 Hz, H-10a), 4.79 (1H, d, *J* = 11.0 Hz, H-10b), 4.62 (1H, ddd, *J* = 13.1, 5.1, 2.7 Hz, H-2eq), 3.93 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 3.58 (3H, s, $CO_2C$*H*$_3$), 3.45 (3H, s, $CO_2C$*H*$_3$), 3.43–3.34 (1H, m, H-3a), 2.57–2.48 (2H, m, H-2ax, 3b); $\delta_C$ (100 MHz, $CDCl_3$) 168.7 (*C*$O_2CH_3$), 168.3 (*C*$O_2CH_3$), 166.7 (C-15), 152.7 (Ar C), 151.1 (Ar C), 150.2 (Ar C), 148.0 (Ar C), 139.7 (Ar C), 136.0 (Ar C), 136.0 (Ar C), 129.7 (Ar CH), 128.5 (Ar CH), 128.1 (Ar CH), 127.5 (Ar C), 120.5 (C-19/20), 117.6 (Ar C), 114.6 (C-19/20), 110.8 (Ar C), 107.4 (C-5), 75.7 (C-10), 63.5 (C-22), 61.0 (C-O*C*$H_3$), 56.7 (C-1), 55.9 (C-O*C*$H_3$), 55.8 (C-O*C*$H_3$), 52.9 (C-$CO_2$*C*$H_3$), 52.5 (C-$CO_2$*C*$H_3$), 39.7 (C-2), 29.7 (C-3); HRMS (ESI$^+$): Found: 578.2007; $C_{31}H_{32}NO_{10}$ ($MH^+$) Requires: 578.2021 (−2.4 ppm error).

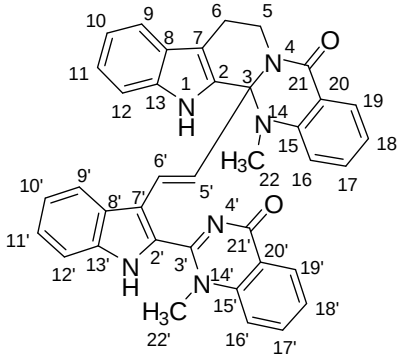
# Appendices

## Appendix I: NMR Comparison Tables

A. Comparison table of the $^1$H NMR data of the natural ($\delta_H$ ref)[66] and synthetic ($\delta_H$ exp) (±)-dievodiamine **212**.

| The $^1$H NMR data of (±)-dievodiamine 212 (DMSO-$d_6$ at 300 MHz ) | | | | |
|---|---|---|---|---|
| | $\delta_H$ ref | | $\delta_H$ exp[a] | |
| NH | 11.92 | 1H, br s | 12.00 | 1H, br s |
| NH | 11.34 | 1H, br s | 11.42 | 1H, br s |
| 19' | 8.16 | 1H, d, *J* = 6.6 Hz | 8.18 | 1H, d, *J* = 7.9 Hz |
| 17' | 7.88 | 1H, t, *J* = 8.4, 7.8 Hz | 7.93 | 1H, t, *J* = 8.3, 7.2 Hz |
| 19 | 7.74 | 1H, d, *J* = 7.5 Hz | 7.78 | 1H, d, *J* = 7.7 Hz |
| 9' | 7.64 | 1H, d, *J* = 8.1 Hz | 7.70–7.64 | 2H, m |
| 18' | 7.60 | 1H, t, *J* = 7.8, 6.6 Hz | | |
| 9 | 7.51 | 1H, t, *J* = 7.8 Hz | 7.55–7.50 | 2H, m |
| 16' | 7.46 | 1H, t, *J* = 8.4 Hz | | |
| 12' | 7.40 | 1H, d, *J* = 8.1 Hz | 7.43 | 1H, d, *J* = 8.1 Hz |
| 12 | 7.33 | 1H, d, *J* = 8.1 Hz | 7.37–7.32 | 2H, m |
| 17 | 7.28 | 1H, t, *J* = 8.1, 7.2 Hz | | |
| 11' | 7.21 | 1H, t, *J* = 8.1, 7.2 Hz | 7.23 | 1H, t, *J* = 8.1, 7.4 Hz |
| 11 | 7.13 | 1H, t, *J* = 8.1, 7.5 Hz | 7.17–7.03 | 5H, m |
| 10' | 7.11 | 1H, t, *J* = 8.1, 7.2 Hz | | |
| 16 | 7.07 | 1H, t, *J* = 7.8, 7.5 Hz | | |
| 10 | 7.05 | 1H, t, *J* = 7.2, 7.5 Hz | | |
| 18 | 7.01 | 1H, t, *J* = 7.2, 7.5 Hz | | |
| 6' | 6.54 | 1H, d, *J* = 16.0 Hz | 6.55 | 1H, d, *J* = 16.0 Hz |
| 5' | 6.31 | 1H, d, J = 16.0 Hz | 6.35 | 1H, d, J = 16.0 Hz |
| 5eq | 4.86 | 1H, dd, *J* = 12.6, 3.9, 3.7 Hz | 4.91–4.88 | 1H, m |
| 22' | 3.26 | 3H, s | 3.28 | 3H, s |
| 5ax | 3.08 | 1H, dt, *J* = 12.6, 4.5, 5.1 Hz | 3.16–3.10 | 1H, m |
| 6eq | 2.90 | 1H, dd, *J* = 11.1, 3.9, 5.1 Hz | 2.95–2.91 | 1H, m |
| 6ax | 2.76 | 1H, dt, *J* = 11.1, 3.7, 4.5 Hz | 2.82–2.73 | 1H, m |
| 22 | 2.47 | 3H, s | 2.47 | 3H, s |

[a] Solvent reference peak at $\delta_H$ 2.50



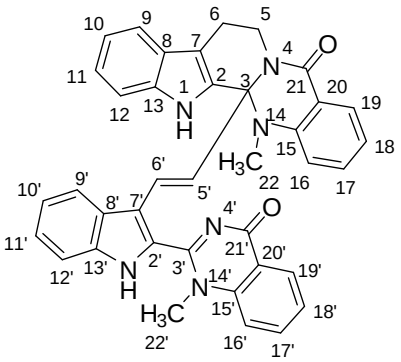
**212**

B. Comparison table of the $^{13}C$ NMR data of the natural ($\delta_C$ ref)[66] and synthetic ($\delta_C$ exp) (±)-dievodiamine **212**.

| The $^{13}C$ NMR data of (±)-dievodiamine 212 (DMSO-$d_6$ at 300 MHz) | | | |
|---|---|---|---|
| | $\delta_C$ ref | $\delta_C$ exp[a] | $\Delta\delta_C$ |
| 21' | 167.6 | 167.3 | +0.3 |
| 21 | 163.0 | 162.6 | +0.4 |
| 3' | 155.3 | 154.9 | +0.4 |
| 15 | 149.5 | 149.1 | +0.4 |
| 15' | 141.8 | 141.4 | +0.4 |
| 13 | 137.2 | 136.8 | +0.4 |
| 12' | 136.7 | 136.3 | +0.4 |
| 17' | 134.4 | 134.1 | +0.3 |
| 17 | 133.5 | 133.2 | +0.3 |
| 2 | 131.0 | 130.7 | +0.3 |
| 2' | 129.2 | 128.9 | +0.3 |
| 5' | 128.8 | 128.4 | +0.4 |
| 19 | 127.9 | 127.5 | +0.4 |
| 19' | 127.5 | 127.1 | +0.3 |
| 18' | 126.8 | 126.5 | +0.3 |
| 8 | 125.9 | 125.5 | +0.4 |
| 8' | 125.0 | 124.5 | +0.5 |
| 11' | 124.2 | 123.8 | +0.4 |
| 18 | 123.6 | 123.3 | +0.3 |
| 20 | 123.1 | 122.9 | +0.2 |
| 16 | 122.7 | 122.4 | +0.3 |
| 11 | 122.5 | 122.2 | +0.3 |
| 6' | 121.9 | 121.5 | +0.4 |
| 10' | 121.0 | 120.7 | +0.3 |
| 9' | 120.6 | 120.3 | +0.3 |
| 20' | 120.3 | 119.9 | +0.4 |
| 10 | 119.3 | 118.9 | +0.4 |
| 9 | 119.0 | 118.6 | +0.4 |
| 16' | 117.1 | 116.9 | +0.4 |
| 7' | 113.2 | 112.8 | +0.4 |
| 12' | 112.7 | 112.4 | +0.3 |
| 12 | 112.1 | 111.7 | +0.4 |
| 7 | 111.6 | 111.2 | +0.4 |
| 3 | 76.6 | 76.2 | +0.4 |
| 22 | 39.1 | 38.7 | +0.4 |
| 5 | 38.9 | 38.6 | +0.3 |
| 22' | 37.1 | 36.8 | +0.3 |
| 6 | 20.6 | 20.2 | +0.4 |

[a] Solvent reference peak at $\delta_C$ 39.50

Note that all of $^{13}C$-NMR peaks for the synthetic material were all *ca.* 0.3–0.4 ppm lower than those of the natural product. Given that all of the resonances differed to approximately the same degree, we believe that it is highly likely that the difference is caused by a difference in the reference peak of the NMR spectra. (We referenced DMSO-$d_6$ at $\delta_C$ 39.50 for the centre of the septet)

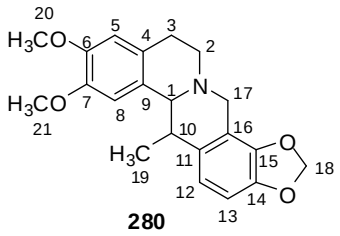


**212**

C. Comparison table of the $^{1}$H NMR data of the natural ($\delta_H$ ref)[129c] and synthetic ($\delta_H$ exp) (±)-cavidine **280**.

| **The $^{1}$H NMR data of (±)-cavidine 280 ($CDCl_3$ at 300 MHz)** | | | | |
|---|---|---|---|---|
| | $\delta_H$ ref | | $\delta_H$ exp[a] | |
| H-13 | 6.71 | 1H, d, *J* = 8.0 Hz | 6.72 | 1H, d, *J* = 8.0 Hz |
| H-8 | 6.68 | 1H, s | 6.68 | 1H, s |
| H-12 | 6.67 | 1H, d, *J* = 8.0 Hz | 6.67 | 1H, d, *J* = 8.0 Hz |
| H-5 | 6.61 | 1H, s | 6.61 | 1H, s |
| H-18a | 5.96 | 1H, d, *J* = 1.6 Hz | 5.97 | 1H, d, *J* = 1.5 Hz |
| H-18b | 5.92 | 1H, d, *J* = 1.6 Hz | 5.93 | 1H, d, *J* = 1.5 Hz |
| H-17a | 4.07 | 1H, d, *J* = 15.6 Hz | 4.09 | 1H, d, *J* = 15.3 Hz |
| H-20/21 | 3.87 | 3H, s | 3.88 | 3H, s |
| H-20/21 | 3.87 | 3H, s | 3.88 | 3H, s |
| H-1 | 3.73 | 1H, br s | 3.73 | 1H, br s |
| H-17b | 3.50 | 1H, d, *J* = 15.6 Hz | 3.50 | 1H, d, *J* = 15.3 Hz |
| H-10 | 3.25 | 1H, m | 3.28–3.22 | 1H, m |
| H-2a,3a | 3.12 | 2H, m | 3.16–3.07 | 2H, m |
| H-2b,3b | 2.60 | 2H, m | 2.63–2.57 | 2H, m |
| H-19 | 0.94 | 3H, d, *J* = 7.0 Hz | 0.94 | 3H, d, *J* = 6.9 Hz |

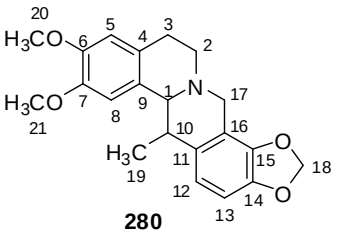
[a] Solvent reference peak at $\delta_H$ 7.26




**280**

D. Comparison table of the $^{13}C$ NMR data of the natural ($\delta_C$ ref)[134] and synthetic ($\delta_C$ exp) (±)-cavidine **280**.

| **The $^{13}C$ NMR data of (±)-cavidine 280 ($CDCl_3$ at 300 MHz)** | | | |
|---|---|---|---|
| | $\delta_C$ ref | $\delta_C$ exp[a] | $\Delta\delta_C$ |
| 6 | 147.9 | 147.6 | −0.3 |
| 7 | 147.3 | 147.1 | −0.2 |
| 15 | 144.8 | 144.6 | −0.2 |
| 14 | 143.2 | 143.0 | −0.2 |
| 11 | 136.1 | 135.9 | −0.2 |
| 4 | 128.5 | 128.3 | −0.2 |
| 9 | 128.5 | 128.3 | −0.2 |
| 12 | 121.3 | 121.2 | −0.1 |
| 16 | 116.9 | 116.8 | −0.1 |
| 5 | 111.3 | 111.1 | −0.2 |
| 8 | 108.8 | 108.5 | −0.3 |
| 13 | 106.8 | 106.7 | −0.1 |
| 18 | 101.1 | 101.0 | −0.1 |
| 1 | 63.2 | 63.1 | −0.1 |
| 20/21 | 56.1 | 56.1 | – |
| 20/21 | 55.9 | 55.8 | −0.1 |
| 17 | 53.4 | 53.3 | −0.1 |
| 2 | 51.3 | 51.2 | −0.1 |
| 10 | 38.7 | 38.5 | −0.2 |
| 3 | 29.3 | 29.3 | 0.0 |
| 19 | 18.5 | 18.4 | −0.1 |



**280**

[a] Solvent reference peak at $\delta_C$ 77.0

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# Direct Imine Acylation: Rapid Access to Diverse Heterocyclic Scaffolds

**William P. Unsworth, Christiana Kitsiou, and Richard J. K. Taylor***

*Department of Chemistry, University of York, Heslington, York, YO10 5DD, U. K.*

*richard.taylor@york.ac.uk*

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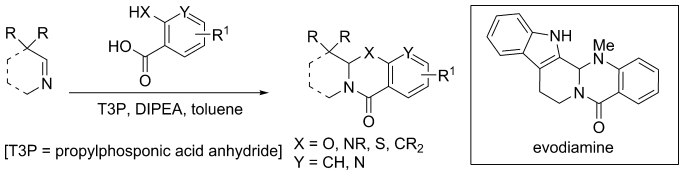
## ABSTRACT

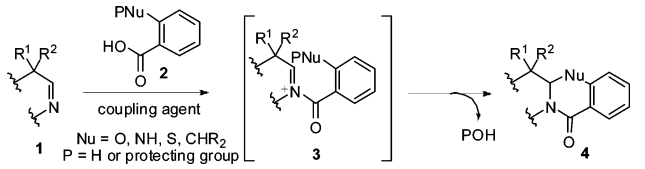



**A simple and efficient procedure to prepare a range of diverse heterocycles by the direct acylation of imines using a variety of functionalized benzoic acids is described. The methodology features a novel method for *N*-acyliminium ion generation followed by in situ intramolecular trapping by oxygen-, nitrogen-, sulfur- and carbon-based nucleophiles. Preliminary mechanistic studies, using ReactIR, are also reported.**

New methods for the synthesis of polycyclic heterocycles are invaluable in the pharmaceutical and agrochemical industries.[1] The potential of such methodology is at its greatest when it facilitates the synthesis of a diverse range of substrate classes, is high yielding and operationally simple, and results in a rapid increase in molecular complexity from simple readily available starting materials.[2,3]

We report a novel scaffold diversity approach built around the concept of direct imine acylation (DIA) as illustrated in Scheme 1. It was planned that acylation of an imine (**1**) with a suitably functionalized carboxylic acid (**2**) would generate an *N*-acyliminium ion (**3**) in anticipation that a nucleophile or pronucleophile built into the acid coupling partner would initiate in situ cyclization. We now report the successful implementation of the DIA approach using functionalized benzoic acids to generate a range of diverse heterocycles (**4**).

**Scheme 1.** Direct Imine Acylation




The use of *N*-acyliminium ions in heterocycle synthesis is well documented,[4] but in the vast majority of examples, the *N*-acyliminium species are generated from preformed systems, usually by a regioselective partial imide reduction or a regioselective amide oxidation.[4] The key advantage to our convergent approach is the direct use of a carboxylic acid (rather than activated derivatives)[5,6] in *N*-acyliminium generation allowing a range of *ortho*-functional groups to be tolerated. The ready availability of starting materials and the convergent nature of the process gives DIA great potential, particularly with regards to diversity-oriented synthesis.[2]

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008 and references therein.

(2) (a) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104. (b) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149. (c) Lipkus., A. R.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F., III; Schenck, R. J; Trippe, A. J. *J. Org. Chem.* **2008**, *73*, 4443.

(3) (a) Taylor, R. J. K.; Reid, M.; Foot, J. S.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851. (b) Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260. (c) Klein, J. E. M. N.; Perry, A.; Pugh., D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446 and references therein.

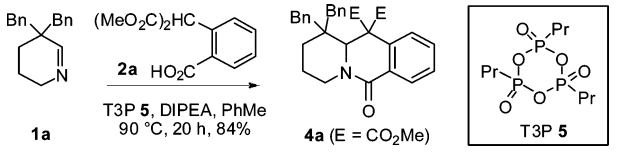
(4) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 1985. 4367. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(5) For early examples using acid chlorides, acyl fluorides, anhydrides, etc., see (a) Ziegler, E.; Hanus, H. D. *Monatsh. Chem.* **1965**, *96*, 411. (b) Ziegler, E.; Kollenz, G.; Kappe, T. *Monatsh. Chem.* **1968**, *99*, 804. (c) Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186. (d) Castagnioli, N., Jr. *J. Org. Chem.* **1969**, *34*, 3187.

10.1021/ol303073b 
**Published on Web 12/24/2012**

The viability of the DIA concept was established using the novel cyclic imine **1a** and the benzoic acid **2a** (Scheme 2). Propylphosphonic acid anhydride (T3P, **5**)[7] in toluene was chosen to effect the direct coupling, as it is nontoxic and the byproducts are easily removed by aqueous extraction.[8]

**Scheme 2.** Reaction of Imine **1a** with Acid **2a**



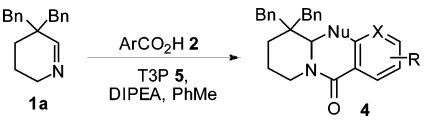

We were delighted to observe the efficient formation of tricyclic lactam **4a** in 84% yield after chromatography. Additional experiments in which the same coupling was attempted in the absence of either DIPEA or T3P led only to the recovery of the starting materials, with no evidence of the cyclized product **4a**.

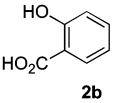
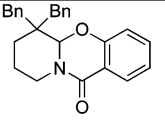
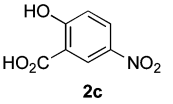
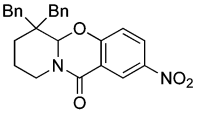
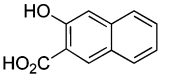
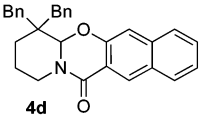
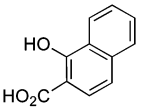
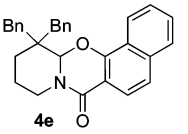
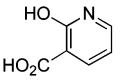
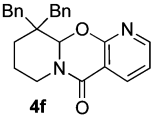
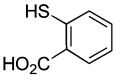
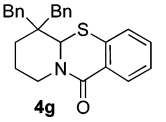
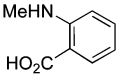
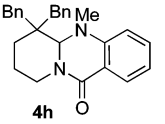
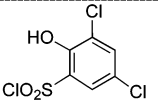
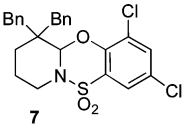
We then went on to explore DIA using a range of substituted benzoic acid derivatives (**2b**–**2h**, Table 1). As can be seen, salicylic acid derivatives are extremely well tolerated, affording products in excellent yields (Table 1, entries i–vi).[9] The DIA methodology is not restricted to the trapping of the intermediate *N*-acyliminium salt with carbon and oxygen nucleophiles. For example, under the standard T3P conditions, treatment of imine **1a** with thiosalicylic acid **2g** gave thiazinone **4g** (entry vii), and *N*-methyl anthranilic acid **2h** underwent cyclization to the diazine **4h** (entry viii), both in near quantitative yields. The final example in Table 1 (entry ix) illustrates that the DIA concept need not be limited to acylation, as demonstrated by the formation of sulfonamide-containing dioxo(dihydro)-benzoxathiazine **7** from reaction of imine **1a** with commercially available sulfonyl chloride **6**.

We next went on to confirm that the scope of this methodology is equally versatile in terms of the imine substrate (Table 2). First, 3,4-dihydroisoquinoline (**1b**) gave adducts **4i** and **4j** in reasonable and excellent yields, respectively (entries i and ii); this substructure features heavily in natural products and in pharmaceutically important compounds,[10] and applications of this DIA sequence in target synthesis are anticipated. Further diversity can be achieved by varying the ring size of the imine, as demonstrated by the DIA reaction of the disubstituted 1-pyrroline **1c** affording adduct **4k** in excellent yield (entry iii).

Synthetic applications of acyclic *N*-acyliminium salts are limited as they are much less stable than their cyclic analogues, particularly with respect to hydrolysis.[4,11]

**Table 1.** Acid Scope in Direct Imine Acylation/Cyclization[a]




| entry | acylating agent | product | yield[b] |
|---|---|---|---|
| i |  **2b** |  **4b** | 83%[c],[d] |
| ii |  **2c** |  **4c** | 91% |
| iii | | | 90%[e] |
| iv |  **2d** |  **4d** | 95% |
| v |  **2e** |  **4e** | 92% |
| vi |  **2f** |  **4f** | 97% |
| vii |  **2g** |  **4g** | 96%[f] |
| viii |  **2h** |  **4h** | 97%[c] |
| ix |  **6** |  **7** | 92%[g] |

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using T3P, DIPEA in PhMe at 90 °C for 20 h. [b] Isolated yields after purification by column chromatography. [c] Reaction performed in the absence of T3P gave 0% yield of product. [d] Reaction performed in the absence of DIPEA gave 0% yield of product. [e] Reaction performed on a 3 mmol scale under the standard conditions. [f] Reaction performed in the absence of T3P gave 20% yield of product. [g] Compound **6** was stirred with imine **1a** and DIPEA in PhMe at 90 °C for 20 h.

(6) For more recent examples using acid chlorides, acyl fluorides, anhydrides, etc., see (a) Strumberg, D.; Pommier, Y.; Paull, K.; Jayaraman, M.; Nagafuji, P.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 446. (b) Sieck, O.; Ehwald, M.; Liebscher, J. *Eur. J. Org. Chem.* **2005**, *4*, 663. (c) Chen, Z.; Hu, G.; Chen, J.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. *Bioorg. Med. Chem.* **2009**, *17*, 2351. (d) Johannes, K.; Martens, J. *Tetrahedron* **2010**, *66*, 242 and references therein.

(7) Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed.* **1980**, *19*, 133.

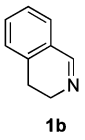
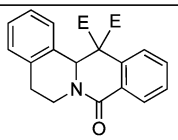
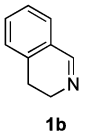
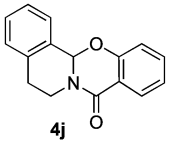
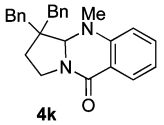
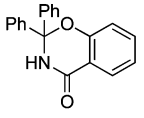
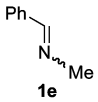
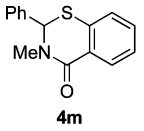
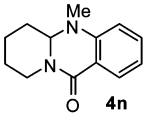
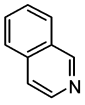
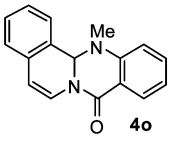
(8) Successful coupling was also achieved using T3P, HATU or DCC, each with DIPEA, in refluxing $CHCl_3$ or toluene at 90 °C.

(9) After the completion of this work, a single example of *N*-acyliminium ion formation by direct carboxylic acid coupling to imines was reported using DCC/DMAP to couple a substituted benzoic acid to dihydrocarboline: Pin, F.; Comesse, S.; Daïch, A. *Tetrahedron* **2011**, *67*, 5564.

(10) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341 and references therein.

(11) Böhme, H.; Hartke, K. *Chem. Ber.* **1963**, *96*, 600.

**Table 2.** Imine Scope in Direct Imine Acylation/Cyclization[a]

| entry | imine | acid | product | yield[b] |
|---|---|---|---|---|
| i |  **1b** | **2a** |  **4i** (E = $CO_2Me$) | 69% |
| ii |  **1b** | **2b** |  **4j** | 89% |
| iii[c] |  **1c** | **2h** |  **4k** | 87% |
| iv |  **1d** | **2b** |  **4l** | 60% |
| v |  **1e** | **2g** |  **4m** | 99% |
| vi |  **1f** | **2h** |  **4n** | 40% |
| vii |  **1g** | **2h** |  **4o** | 94% |

[a] Reactions were performed on a 0.1−0.3 mmol scale using T3P, DIPEA in PhMe at 90 °C for 20 h. [b] Isolated yields after purification by column chromatography. [c] Imine **1f** was generated by deoligomerization of dodecahydro-4a,8a,12a-triazatriphenylene in situ.

DIA technology overcomes this problem by forming and trapping the unstable *N*-acyliminium ions in situ, and so acylic imines **1d** and **1e** undergo DIA reactions giving adducts **4l** and **4m** (entries iv and v). Dodecahydro-4a,8a,12a-triazatriphenylene, the trimeric form of imine **1f**,[12] was employed directly in a DIA procedure with anthranilic acid **2h** to produce diazine **4n** (entry vi), demonstrating that even unstable imines, which are prone to oligomerization and enamine formation, can be compatible with the DIA protocol. Finally (entry vii), we demonstrated that isoquinoline (**1g**) could be successfully employed in a DIA coupling with anthranilic acid **2h**, overcoming loss of aromaticity,[13] to afford the tetracyclic nitrogen heterocycle **4o** in 94% yield. This example indicates that DIA will not be limited to simple imines. It should also be noted that, for comparison purposes, all reactions were carried out using the standard conditions and that optimization should lead to an increase in yield in the majority of cases.

Two extreme mechanistic pathways could be envisaged for these processes: (i) *N*-acylation takes place first and is followed by an intramolecular cyclization (as we have assumed, Scheme 1), or (ii) nucleophilic addition of the *ortho*-substituent onto the imine occurs first, followed by intramolecular acylation. An added complication is that imino-ketene intermediates have been proposed for the acylation step in related anthranilic acid processes.[5c,6d] Of course, it is not unreasonable that the exact mechanism is substrate-dependent, or that more than one mechanism may operate in competition. However, the fact that no reaction occurs with most examples in the absence of the T3P coupling agent provides corroboration for the theory that the initial step involves *N*-acylation of the imine.[14] To shed more light on the process, an in situ ReactIR study was carried out to study the DIA reaction of imine **1a** with 5-nitro-salicylic acid **2c**.[15] A more detailed analysis is included in the Supporting Information, but this ReactIR study rules out a ketene intermediate and is consistent with a process involving (i) rapid carboxylic acid activation, (ii) imine *N*-acylation generating a short-lived *N*-acyliminium ion **3c** (Peak 1, Figures 1 and 2), (iii) reversible trapping of the iminium intermediate by excess DIPEA in the reaction mixture, affording an ammonium salt **8** (Peak 2, Figures 1 and 2), and (iv) regeneration of the *N*-acyliminium intermediate **3c** and cyclization to give the product **4c** (Peak 3, Figures 1 and 2).

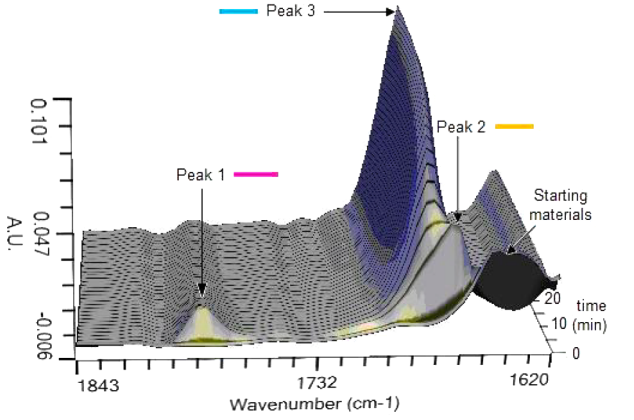



**Figure 1.** 3D ReactIR plot of atomic absorption against wavenumber and time.

(12) (a) Schöpf, C.; Komzak, A.; Braun, F.; Jacobi, E.; Bormuth, M.-L.; Bullnheimer, M.; Hagel, I. *Liebigs Ann.* **1948**, *559*, 1. (b) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936.

(13) Sieck, O.; Ehwald, M.; Liebscher, J. *Tetrahedron Lett.* **2000**, *29*, 5479.

(14) With thiosalicylic acid **2g** (Table 1, entry vi) a small amount (20%) of coupled product **4g** was observed in the absence of T3P, and so some intermolecular imine addition may be taking place in this system.

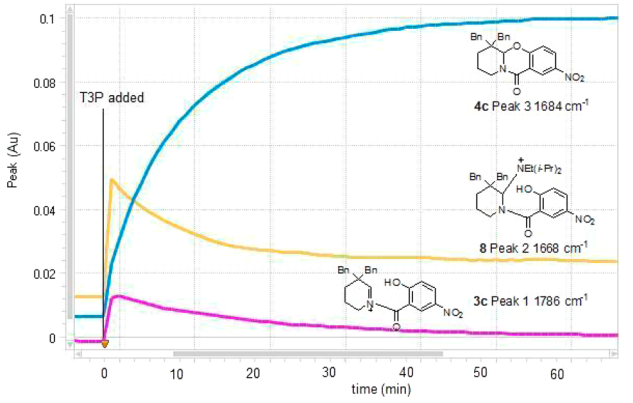



**Figure 2.** 2D ReactIR plot of atomic absorption units of the wavenumbers 1786, 1668 and 1684 $cm^{-1}$ against time.

Finally, the value of DIA has been illustrated by the rapid and efficient synthesis of evodiamine (**9**), a natural product isolated from *Evodiae fructus*.[16] Evodiamine has been shown to reduce fat uptake in animal studies[16b] and has been included in some dietary preparations, particularly in the Chinese herbal weight loss supplement, Wu-Chu-Yu. More recently, it has been demonstrated that evodiamine is a novel inhibitor of human DNA topoisomerase I.[16c] Starting from dihydrocarboline **1h**,[17] treatment with *N*-methyl anthranilic acid **2h** and T3P under standard DIA conditions produced evodiamine (**9**) in a one-pot process in 95% yield as a crystalline product (Scheme 3).

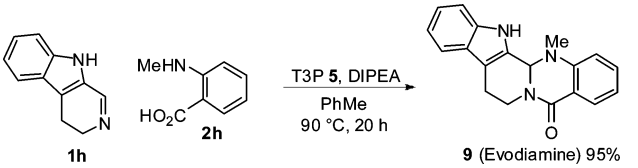
In summary, DIA methodology has been shown to be a reliable and versatile tool for the synthesis of a range of polycyclic heterocyclic scaffolds. The procedure uses readily available nontoxic reagents, is operationally simple and is relatively insensitive to both water and air. Crucially, the in situ generation and trapping of the transient *N*-acyliminium ion avoids the need to isolate unstable *N*-acyliminium ion precursors. The mild nature of the reagents used

(15) Acid **2c** was chosen, as this substrate was found to be particularly reactive; a lower temperature was needed to be compatible with the ReactIR probe, and this reaction proceeded efficiently in 1 h at 50 °C.

(16) (a) Nakasato, T.; Asada., S.; Murai., K. *J. Pharm. Soc. Jpn.* **1962**, *82*, 619. (b) Kobayashi, Y.; Nakano, Y.; Kizaki, M.; Hoshikuma, K.; Yokoo, Y.; Kamiya, T. *Planta Med.* **2001**, *67*, 628. (c) Dong, G.; Sheng, C. S.; Wang, S.; Miao, Z.; Yao, J.; Zhang, W. *J. Med. Chem.* **2010**, *53*, 7521.

(17) Nicolaou, K. C.; Mathison, C. J. N.; Maonagnon., T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077.

**Scheme 3.** Application of DIA to Prepare Evodiamine




for the *N*-acylation is important in this regard, as they have been shown to be compatible with unprotected nucleophiles, which may not survive the typically much harsher conditions used in most of the existing procedures for *N*-acyliminium ion generation. The potential substrate scope is very large, and in most cases the isolated yields were found to be very high under identical conditions, suggesting that diverse targeted libraries of compounds should be readily synthesized using DIA, requiring little or no optimization. It is also worth noting that while for the purpose of the publication, column chromatography was used to ensure analytically pure products were obtained, in the majority of cases no discernible byproducts from the reagents, or reaction side-products, were observable in the $^1$H NMR spectra of the unpurified products. We are confident that in time the reactions described will be further optimized and augmented with new variants, as well as finding use in target synthesis.[18]

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**Supporting Information Available.** Synthetic procedures, ReactIR details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Unsworth, W. P.; Gallagher, K. A.; Jean, M.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Org. Lett.* **2012**, DOI: dx.doi.org/10.1021/ol3030764.

The authors declare no competing financial interest.

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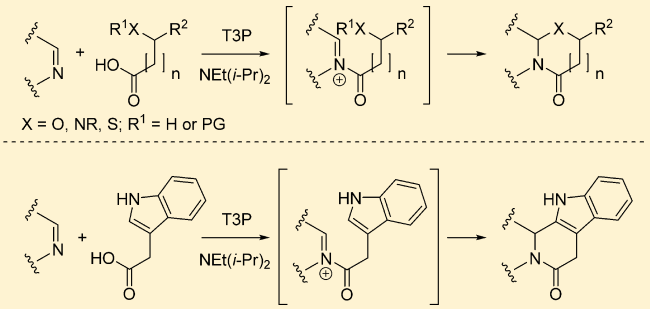
# Direct Imine Acylation for Molecular Diversity in Heterocyclic Synthesis

William P. Unsworth, Graeme Coulthard, Christiana Kitsiou, and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

Supporting Information

**ABSTRACT:** Imines and carboxylic acids have been directly coupled using propylphosphonic acid anhydride and NEt($i$-Pr)$_2$ to give $N$-acyliminium ions, which were intramolecularly trapped with oxygen, nitrogen, sulfur, and carbon nucleophiles to provide a wide range of structurally diverse heterocycles.



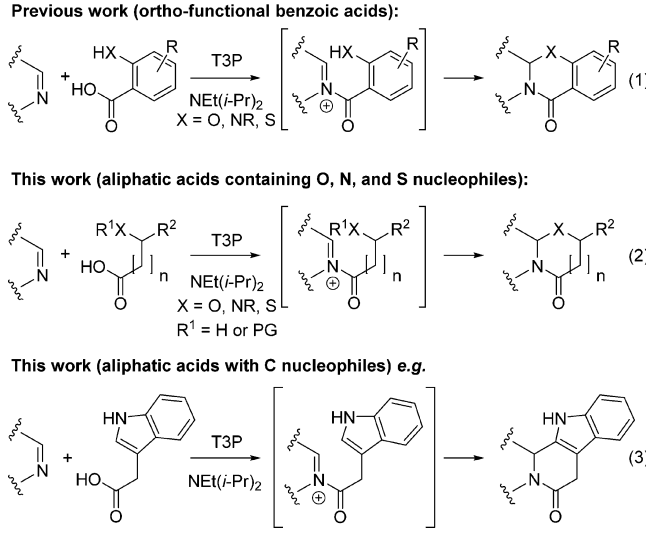

## INTRODUCTION

Heterocycles are important structures in the pharmaceutical, agrochemical, and fine chemical industries.[1,2] Much recent attention has focused on diversity-oriented synthesis[3−5] to expand the variety of structures, including heterocycles, populating unexplored "chemical space" to aid the discovery of novel lead compounds.[6]

The chemistry of $N$-acyliminium ions is well established,[7−9] and the formation of $N$-acyliminium ions by the direct acylation of imines with acid halides[10−21] and anhydrides[22−24] has some precedent. However, apart from a single example,[25] previous to our recent disclosures,[26,27] the direct acylation of imines with carboxylic acids was not known. We reported[26] that imines can be coupled, using propylphosphonic acid anhydride (T3P) and NEt($i$-Pr)$_2$,[28] to benzoic acids in a direct imine acylation (DIA) reaction to generate $N$-acyliminium ions, which were then trapped intramolecularly with a range of nucleophilic ortho substituents on the benzoic acids (Scheme 1, eq 1). This provided a range of polycyclic heterocycles, and the methodology was applied to the synthesis of the natural product evodiamine. However, this methodology was limited to benzoic acids containing nucleophilic heteroatoms in the ortho position. To date, only a single example of DIA using an aliphatic carboxylic acid has been reported.[27] We considered that the direct coupling of imines and aliphatic carboxylic acids containing nucleophiles, or pronucleophiles, would allow access to a far greater variety of heterocyclic structures using this simple coupling procedure.

Herein we report results which establish that DIA methodology has an extremely wide scope and is applicable to aliphatic carboxylic acids containing oxygen, nitrogen, and sulfur nucleophiles (Scheme 1, eq 2). Of particular note is the use of aliphatic acids containing carbon pronucleophiles such as active methylenes, aromatic groups, and alkenes, enabling structural diversity to be generated via carbon−carbon bond formation (Scheme 1, eq 3).

**Scheme 1. Direct Imine Acylation (DIA)**




## RESULTS AND DISCUSSION

To establish the validity of the DIA protocol with aliphatic acids, we investigated the reaction of imine **1a** with hydroxy acid **2a** and its TBDMS-protected analogue **2b** (Scheme 2). The reaction of hydroxy acid **2a** led to the formation of the desired heterocycle **3a**, but in low yield. This appeared to be due to competing $O$-acylation of the hydroxy acid; note that this was not a problem in our previous work, when ortho-

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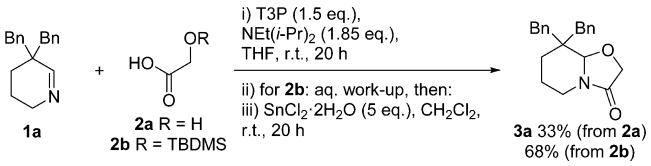
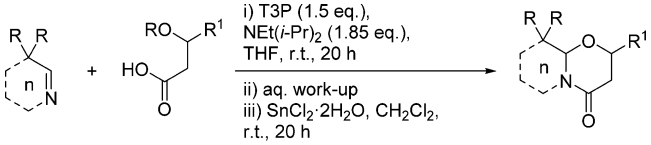
**Scheme 2. DIA with Aliphatic Carboxylic Acids**




substituted benzoic acids were used due to their reduced nucleophilicity. To avoid *O*-acylation, the silyl-protected acid **2b** was coupled with **1a** and following aqueous workup a mixture of products was obtained, presumably arising from the reaction of the *N*-acyliminium ion with water in the workup. The unpurified product mixture was then treated with $SnCl_2 \cdot 2H_2O$[29,30] in $CH_2Cl_2$ at room temperature, which resulted in concomitant silyl cleavage and cyclization, affording product **3a** in 68% yield, a significant improvement over the unprotected variant.

The scope of this improved protocol was then explored (Table 1). The coupling of imine **1a** with TBDMS-protected 3-hydroxypropanoic acid **2c** and methyl-substituted acid **2d** provided the required heterocycles in good yield (Table 1, entries 1 and 2). We also investigated the range of imines tolerated in the DIA reaction (Table 1). The majority of the imines tested as DIA substrates are stable, nonenolizable imines; however, unsubstituted imine **1b** (which exists largely as a trimer[31]) was a suitable substrate (entry 3), showing that imines which are prone to oligomerization are compatible. The five-membered-ring imine **1c** and tetrahydroisoquinoline derivative **1d** both reacted successfully, giving products **3e,f** (entries 4 and 5). Precedent for *N*-acyliminium chemistry using acyclic precursors is extremely sparse due to their propensity to hydrolyze.[11] However, the use of DIA conditions allowed the acyclic imine **1e** to be effectively employed (entry 6); in this case, the use of anhydrous triflic acid, rather than $SnCl_2 \cdot 2H_2O$, reduced unwanted hydrolysis, promoting a one-pot deprotection and cyclization. In this example, chloroform, rather than $CH_2Cl_2$, was used to effect cyclization because it has a higher reflux temperature and the analogous process in $CH_2Cl_2$ (either at room temperature or 45 °C) was low yielding. The *N*-acylation was also performed in chloroform, to avoid having to perform a solvent switch. It is noteworthy that the T3P coupling can be performed in a number of solvents with little impact on the efficiency of the process; high-yielding DIA reactions performed in toluene, $CH_2Cl_2$, chloroform, and THF have all been reported, previously[26,27] and herein. This flexibility in terms of the solvent for the *N*-acylation is important in examples in which additional reagents are required to effect cyclization (e.g. Table 4), as the solvent that is most compatible with the requisite additives can be used. Either $CH_2Cl_2$ or chloroform was used in the majority of subsequent examples for reasons of convenience, as they could be used as obtained commercially with no additional drying. The stereochemical assignments of the major diastereoisomers shown are based on NMR analysis, on literature precedent, and by analogy to our previous work.[27,29,32,33] This direct imine acylation with aliphatic carboxylic acids gives rise to a range of previously unreported structures, the core of which is present in compounds which have recently found use as herbicides.[34]

**Table 1. DIA and Intramolecular Cyclization with Oxygen Nucleophiles**[b]




| Entry | Imine | Acid | Product | Yield (%) |
|---|---|---|---|---|
| 1 | 1a | 2c | 3b | 86 |
| 2 | 1a | 2d | 3c (d.r. = 2:1) | 82 |
| 3 | 1b | 2d | 3d (d.r. = 8:1) | 60 |
| 4 | 1c | 2d | 3e (d.r. = 6:1) | 62 |
| 5 | 1d | 2d | 3f (d.r. = 20:1) | 73[a] |
| 6 | 1e | 2d | 3g (d.r. = 12:1) | 65[b] |

[a]No intermediate workup carried out. [b]The following reaction conditions were used in this reaction: (i) T3P, $NEt(i\text{-}Pr)_2$, $CHCl_3$, 70 °C, 1 h; (ii) TfOH, room temperature, 1 h (one pot).

The analogous DIA process using amine-containing coupling partners was investigated next (Table 2). Three imines were reacted with commercially available *N*-Boc or *N*-Cbz-protected amino acids. As with the oxygen variant, following the T3P coupling, an aqueous workup was carried out. This was followed by cleavage of the *N*-protecting group (using TFA in $CH_2Cl_2$ for Boc cleavage or $H_2/Pd(OH)_2$ in MeOH for Cbz cleavage), resulting in cyclization and formation of the expected nitrogen-containing heterocycles in excellent yields. Both $\alpha$- and $\beta$-amino acids were suitable substrates (entries 1 and 2), and substitution on the amino acid was fully compatible (entry 3). It was found that secondary amines were effective nucleophiles, as evidenced by the use of *N*-Boc-(*S*)-proline (entry 4). Other imines were compatible with the procedure, including $\beta$-carboline **1f** (entry 5). Note that, in all of these examples, the *N*-acylation was performed at reflux, rather than at room temperature. This is not because the *N*-acylation is slower in this system but because the higher temperature also promotes partial cyclization before protecting group cleavage. It was found that this higher temperature led to higher overall yields for the two-step sequence in comparison to the case where the coupling was carried out at room temperature. The assigned syn stereochemistry of the major diastereoisomers of **5c,d** is based on analogy with the work of Liebscher[35] and, for **5d**, a NOESY correlation.

The sulfur variant of this DIA sequence is extremely efficient, affording *S*-containing heterocycles in high yields in a one-pot procedure with no protecting group required on the thiol (Table 3). The reactions proceeded at room temperature and


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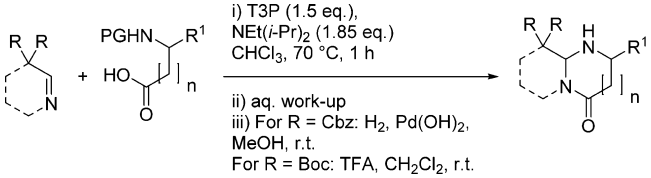
**Table 2. DIA and Intramolecular Cyclization with Nitrogen Nucleophiles**



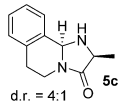
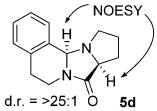
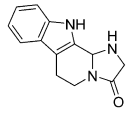
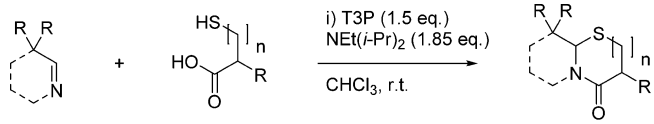
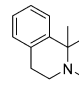
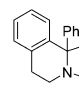
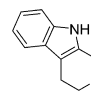

| Entry | Imine | Acid | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **4a** |  **5a** | 86 |
| 2 |  **1a** |  **4b** |  **5b** | 76 |
| 3 |  **1d** |  **4c** |  d.r. = 4:1 **5c** | 90 |
| 4 |  **1d** |  **4d** |  d.r. = >25:1 **5d** | 75 |
| 5 |  **1f** |  **4a** |  **5e** | 85 |

**Table 3. DIA and Intramolecular Cyclization with Sulfur Nucleophiles**




| Entry | Imine | Acid | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **6a** |  **7a** | 90 |
| 2 |  **1a** |  **6b** |  d.r. = 4:1 **7b** | 89 |
| 3 |  **1g** |  **6a** |  **7c** | 89 |
| 4 |  **1h** |  **6c** |  **7d** | 93 |
| 5 |  **1f** |  **6c** |  **7e** | 97 |
| 6 |  **1e** |  **6c** |  **7f** | 93 |

are both reliable and high-yielding in comparison with known syntheses of related heterocyclic systems.[36] Variation in the sulfur-containing carboxylic acid is tolerated, as 3-mercaptopropionic acid **6a**, *N*-acetyl-L-cysteine **6b**, and thioglycolic acid **6c** (entries 1−4) were suitable substrates. The reactions of ketone-derived imines **1g,h** (entries 3 and 4) are particularly noteworthy, as these imines do not undergo DIA in any of the other reaction systems tested (i.e. carboxylic acids bearing *O*-, *N*-, or *C*-nucleophiles). This suggests that an alternative mechanism, which was proposed in our previous communication,[26] is likely to operate, whereby the nucleophilic thiol attacks the imine before *N*-acylation in these examples. 3,4-Dihydro-*β*-carboline **1f** (entry 5) was also a suitable imine substrate, as was the acyclic imine *N*-benzylidenemethylamine **1e**, which gave the adduct **7f** in 93% yield (entry 6). The thiazolidinone scaffold is important in medicinal chemistry and present in numerous biologically active compounds,[37] and this DIA methodology allows ready access to structurally diverse thiazolidinone-containing substructures.

The value of this methodology is further enhanced by the ability to form C−C bonds by trapping the *N*-acyliminium ion with various carbon-centered nucleophiles (Table 4). In these reactions a one-pot process was achieved by using a Lewis acid to effect cyclization after the coupling (Table 4). Carboxylic acids tethered to a diester or diketone (entries 1 and 2) were used to generate an *N*-acyliminium ion, which cyclized upon the addition of $AlCl_3$. Keen to extend the scope of carbon nucleophiles, we investigated electron-rich aromatic systems, including 3,4-dimethoxyphenyl, indole, pyrrole, and dimethoxynaphthyl systems (entries 3−6). These substrates also provided the expected products in good to excellent yields, with $BF_3{\cdot}OEt_2$ used to effect cyclization.

Finally, we explored the possibility that carboxylic acids containing olefins could be successfully utilized and were pleased to find that an alkene (entry 7) and an allylsilane (entry 8) were compatible, using either TFA or $BF_3{\cdot}OEt_2$ as the activating agent. The core substructures of **9a−c** are prevalent in a number of natural products,[38−40] and the heterocyclic core of **9e** is present in aldose reductase inhibitors.[41] Thus, DIA of imines with aliphatic carboxylic acids, and subsequent cyclization, can be considered to be of high importance in the synthesis of medicinally important frameworks.

In conclusion, we have demonstrated that a range of imines can be directly coupled with carboxylic acids using T3P and NEt(*i*-Pr)$_2$ to give *N*-acyliminium ions which can be intramolecularly trapped with oxygen, nitrogen, sulfur, and carbon nucleophiles. These reactions enable a range of diverse heterocyclic structures to be generated. Investigations into asymmetric variants are ongoing, as are applications in target synthesis.

## EXPERIMENTAL SECTION

**Preparation of Substrates for the DIA Reactions.** The following substrates were commercially available and used as supplied: *N*-benzylidenemethylamine **1e**, the amino acids **4a−d**, the thioacids **6a−c**, (3,4-dimethoxyphenyl)acetic acid **8c**, 3-indoleacetic acid **8d**, and 4,7-dimethoxy-1-naphthoic acid **8f**. The following substrates were prepared according to literature procedures: imines **1a−d**,[26] Me-isoquinoline imine **1g**,[42] Ph-isoquinoline imine **1h**,[43] TBDMS-


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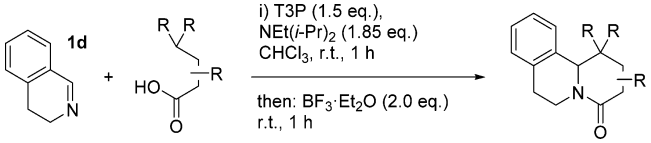
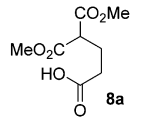
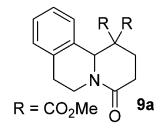
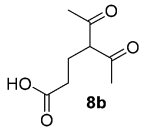
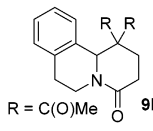
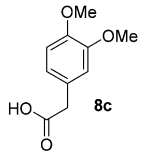
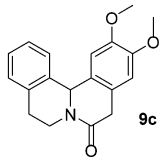
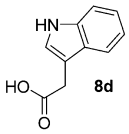
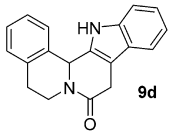
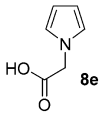
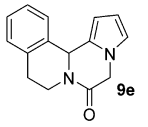
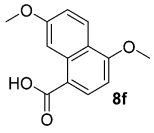
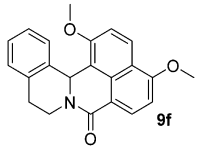
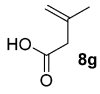
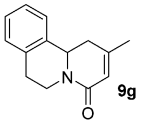
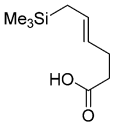
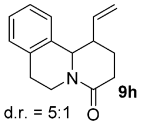
**Table 4. DIA and Intramolecular Cyclization with Carbon Nucleophiles**




| Entry | Acid | Product | Yield (%) |
|---|---|---|---|
| 1 |  8a |  R = $CO_2Me$ 9a | 76[a] |
| 2 |  8b |  R = C(O)Me 9b | 65[a] |
| 3 |  8c |  9c | 90 |
| 4 |  8d |  9d | 80 |
| 5 |  8e |  9e | 77 |
| 6 |  8f |  9f | 89[b] |
| 7 |  8g |  9g | 78[c] |
| 8 |  8h |  d.r. = 5:1 9h | 70 |

[a]$AlCl_3$ (2.0 equiv) used instead of $BF_3{\cdot}OEt_2$ and reaction run at 70 °C. [b]Toluene used in place of $CHCl_3$, coupling time 20 min and cyclization time 20 h. [c]$CH_2Cl_2$ used in place of $CHCl_3$, TFA used in place of $BF_3{\cdot}OEt_2$, and reaction run at 45 °C.

protected 3-hydroxypropanoic acid **2b**,[44] TBDMS-protected 4-hydroxybutanoic acid **2c**, TBDMS-protected 3-hydroxybutanoic acid **2d**,[45] 2-(methoxycarbonyl)pentanedioic acid 1-methyl ester **8a**,[46] and 3-methyl-3-butenonic acid **8g**.[47]

**4-Acetyl-5-oxohexanoic Acid (8b).** The title compound was prepared by modified literature procedures. According to the procedure of Shrout and Lightner,[48] ethyl acrylate (2.00 g, 2.16 mL, 20.0 mmol), 2,4-pentanedione (8.00 g, 8.22 mL, 79.9 mmol), and $K_2CO_3$ (1.38 g, 9.99 mmol) were stirred together at 37 °C for 20 h. The mixture was filtered through a sintered-glass funnel, and the solids were washed with $CH_2Cl_2$ (2 × 10 mL). The filtrate was concentrated in vacuo until excess 2,4-pentanedione was removed (judged by TLC). This provided ethyl 4-acetyl-5-oxohexanoate (3.18 g, 79%) as a pale yellow liquid: $R_f$ 0.80 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2984, 2940, 1727, 1699, 1608, 1421, 1359, 1249, 1182, 1152, 1027; $\delta_H$ (400 MHz, $CDCl_3$) data for keto form 3.74 (1H, t, $J$ = 6.9), 4.14 (2H, q, $J$ = 7.0), 2.33−2.27 (2H, m), 2.21 (6H, s), 2.19−2.12 (2H, m), 1.26 (3H, t, $J$ = 7.0), data for enol form 16.78 (1H, s), 4.15 (2H, q, $J$ = 7.2), 2.63−2.57 (2H, m), 2.42−2.36 (2H, m), 2.17 (6H, s), 1.27 (3H, t, $J$ = 7.2); HRMS (ESI) $m/z$ calcd 201.1121 for $C_{10}H_{17}O_4$ ($MH^+$), found 201.1113. Ethyl 4-acetyl-5-oxohexanoate (500 mg, 2.50 mmol) was dissolved in THF/$H_2O$ (1/1, 10 mL) and stirred at room temperature. Concentrated $H_2SO_4$ (1.25 mL) was added and the reaction mixture stirred at room temperature for 14 h. The reaction mixture was diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (1/1 petroleum ether/ethyl acetate) gave 4-acetyl-5-oxohexanoic acid (**8b**; 224 mg, 52%) as a clear, colorless oil: $R_f$ 0.25 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) data for keto form 3.76 (1H, t, $J$ = 7.0), 2.41−2.35 (2H, m), 2.22 (6H, s), 2.19−2.12 (2H, m), data for enol form 16.78 (1H, s), 2.66−2.59 (2H, m), 2.50−2.43 (2H, m), 2.18 (6H, s); HRMS (ESI) $m/z$ calcd 173.0808 for $C_8H_{13}O_4$ ($MH^+$), found 173.0812.

**1*H*-Pyrrol-1-ylacetic Acid (8e).** The title compound was prepared using a modified procedure of Mitchell and co-workers;[49] glycine ethyl ester hydrochloride (2.50 g, 17.9 mmol) and sodium acetate (2.45 g, 29.9 mmol) were placed in a round-bottomed flask. Water (12.5 mL) and acetic acid (25 mL) were then added, followed by 2,5-dimethoxytetrahydrofuran (2.37 g, 2.32 mmol, 17.9 mmol). The resulting mixture was stirred at 100 °C for 4 h and then cooled. The reaction mixture was poured into water (50 mL) and washed with EtOAc (30 mL). The aqueous phase was neutralized with solid $Na_2CO_3$ and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with water (50 mL) before being dried ($MgSO_4$), filtered, and concentrated to give a crude material which was purified by column chromatography (4/1 petroleum ether/ethyl acetate) to give ethyl 1*H*-pyrrol-1-ylacetate (1.79 g, 65%) as a brown oil: $R_f$ 0.56 (4/1 petroleum ether/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2985, 2939, 1748, 1500, 1297, 1188, 1091, 1025, 722; $\delta_H$ (400 MHz, $CDCl_3$) 6.68 (2H, t, $J$ = 2.1), 6.22 (2H, t, $J$ = 2.1), 4.64 (2H, s), 4.24 (2H, q, $J$ = 7.1), 1.3 (3H, t, $J$ = 7.1); $\delta_C$ (100 MHz, $CDCl_3$) 168.7 (C═O), 121.7 (2 × CH), 109.0 (2 × CH), 61.5 ($CH_2$), 51.8 ($CH_2$), 14.1 ($CH_3$); MS (ESI) $m/z$ 154.09 ($MH^+$) and 176.07 ($MNa^+$). Ethyl 1*H*-pyrrol-1-ylacetate (1.0 g, 6.528 mmol) was dissolved in THF/$H_2O$ (20 mL) and cooled to 0 °C. NaOH (1.31 g, 32.6 mmol) was added and the reaction mixture stirred at 0 °C for 30 min before being washed with $CH_2Cl_2$ (20 mL). The aqueous phase was acidified with concentrated HCl and extracted with $CH_2Cl_2$ (3 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated to give 1*H*-pyrrol-1-ylacetic acid (**8e**; 775 mg, 95%), as brown solids: $R_f$ 0.26 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3074 (br), 2968, 2935, 1726, 1505, 1390, 1297, 1092, 727; $\delta_H$ (400 MHz, $CDCl_3$) 9.31 (1H, br s), 6.67 (2H, t, $J$ = 2.1), 6.24 (2H, t, $J$ = 2.1), 4.71 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 174.9 (C═O), 121.8 (2 × CH), 109.3 (2 × CH), 50.3 ($CH_2$); MS (ESI) $m/z$ 126.06 ($MH^+$) and 148.04 ($MNa^+$).

**(*E*)-/(*Z*)-6-(Trimethylsilyl)hex-4-enoic Acid (8h).** The title compound was prepared using a modified procedure of Wardrop;[50] 4-pentenoic acid (500 mg, 510 μL, 4.99 mmol) and allyltrimethylsilane (1.71 g, 2.38 mL, 1.50 mmol) were dissolved in $CH_2Cl_2$ (10 mL). Hoveyda-Grubbs II catalyst (78.2 mg, 0.125 mmol) was added and the resulting solution stirred at reflux for 5 h. The reaction mixture was filtered through Celite and the filtrate concentrated to provide the crude product. Purification by column chromatography (4/1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petroleum ether/$Et_2O$) gave the acid **8h** (461 mg, 50%) as a clear, colorless oil, as an approximately 2.8:1 mixture of isomers: $R_f$ 0.2 (4/1 petroleum ether/$Et_2O$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2954, 1709, 1412, 1247, 1153, 966, 837; $\delta_H$ (400 MHz, $CDCl_3$) data for major isomer 5.53−5.43 (1H, m), 5.30−5.20 (1H, m), 2.44−2.37 (2H, m), 2.37−2.27 (2H, m), 1.41 (2H, dd, $J$ = 7.9 0.9), −0.02 (9H, s), data for minor isomer 5.53−5.43 (1H, m), 5.30−5.20 (1H, m), 2.44−2.37 (2H, m), 2.37−2.27 (2H, m), 1.50 (2H, dd, $J$ = 8.8, 1.2), 0.01 (9H, s); $\delta_C$ (100 MHz, $CDCl_3$) data for major isomer 179.9 (C═O), 128.1 (CH), 125.9 (CH), 34.6 ($CH_2$), 27.9 ($CH_2$), 22.7 ($CH_2$), −2.1 (3 × $CH_3$), data for minor isomer 179.9 (C═O), 127.4 (CH), 124.6 (CH), 34.2 ($CH_2$), 22.3 ($CH_2$), 18.5 ($CH_2$), −1.8 (3 × $CH_3$); HRMS (ESI) $m/z$ calcd 209.0968 for $C_9H_{18}NaO_2Si$ ($MNa^+$), found 209.0962.

**General Procedures for the DIA Reactions.** *General DIA Procedure A (Table 1).* To a solution of imine (1 mmol) and TBDMS-protected carboxylic acid (1.2 mmol) in THF (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at room temperature for 20 h, before it was poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL), washed with water (30 mL), and concentrated in vacuo. The crude residue was then dissolved in $CH_2Cl_2$ (10 mL), $SnCl_2 \cdot 2H_2O$ (5 mmol) was added, and the mixture was stirred at room temperature for 20 h. The reaction was quenched by the addition of excess solid $K_2CO_3$, and the mixture was then stirred for 5 min, filtered, and concentrated in vacuo. Purification by column chromatography (see individual entries for the solvents used for chromatography) afforded the *N*,*O*-acetal product.

*General DIA Procedure B (Table 2, Entries 1, 3, and 5).* To a solution of imine (1 mmol) and Cbz-protected amino acid (1.2 mmol) in $CHCl_3$ (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at 70 °C for 1 h, before it was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL), washed with water (30 mL), concentrated in vacuo, and passed through a short silica column, with 1/1 petroleum ether/ethyl acetate as eluent. The crude residue was then dissolved in methanol (10 mL) in a round-bottomed flask that was purged with argon. Palladium hydroxide on carbon (70 mg/mmol of imine, 20 wt %, 50% water) was then added and the flask evacuated and back-filled with hydrogen several times. The mixture was stirred under a small positive pressure of hydrogen (balloon) for 1 h, before the hydrogen was evacuated and the reaction flask back-filled with argon. The reaction mixture was then filtered through Celite, rinsed with methanol, and concentrated in vacuo, which afforded the product without the need for further purification.

*General DIA Procedure C (Table 2, Entries 2 and 4).* To a solution of imine (1 mmol) and Boc-protected amino acid (1.2 mmol) in $CHCl_3$ (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at 70 °C for 1 h, before it was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL), washed with water (30 mL), and concentrated in vacuo. The crude residue was then dissolved in $CH_2Cl_2$ (5 mL) and cooled to 0 °C, and TFA (5 mL) was added. The reaction mixture was warmed to room temperature and stirred for 15 min, before the solvent and TFA were removed in vacuo. The residue was dissolved in $CH_2Cl_2$ (50 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (25 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (see individual entries for the solvents used for chromatography) afforded the product.

*General DIA Procedure D (Table 3).* To a solution of imine (1 mmol) and thiol-carboxylic acid (1.2 mmol) in $CHCl_3$ (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at room temperature for 1 h, before it was poured into 10% aqueous $K_2CO_3$ (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL), and the extract was washed with water (30 mL) and concentrated in vacuo. Purification by column chromatography (see individual entries for the solvents used for chromatography) afforded the product.

*General DIA Procedure E (Table 4).* Imine **1d** (100 mg, 0.762 mmol) and the appropriate carboxylic acid (0.915 mmol) were dissolved in $CHCl_3$ (4 mL) in a microwave vial and stirred at room temperature. NEt(*i*-Pr)$_2$ (182 mg, 246 μL, 1.410 mmol) and T3P (364 mg, 1.14 mmol, 728 mg of a 50% solution in THF) were added via syringe. The reaction mixture was stirred at room temperature, 45 °C, or 70 °C for 1 h. The appropriate acid or Lewis acid (1.525 mmol) was added and the reaction mixture stirred at room temperature, 45 °C, or 70 °C for a further 1 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material, which was purified by column chromatography (see individual entries for the solvents used for chromatography).

**8,8-Dibenzyltetrahydro-2*H*-oxazolo[3,2-*a*]pyridin-3(5*H*)-one (3a; Scheme 1).** The compound was synthesized using general DIA procedure A from imine **1a** (24.9 mg, 0.0963 mmol) and acid **2b** (22.0 mg, 0.116 mmol). Purification by column chromatography (4/1 petroleum ether/ethyl acetate) afforded the title compound **3a** as a colorless oil (21.0 mg, 68%): $R_f$ 0.60 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1713, 1445, 1287, 1084, 703; $\delta_H$ (400 MHz, $CDCl_3$) 7.34−7.18 (8H, m), 7.08−7.04 (2H, m), 4.81 (1H, s), 4.37 (1H, d, $J$ = 15.5) and 4.33 (1H, d, $J$ = 15.5, AB system), 4.15−4.10 (1H, m), 2.96 (1H, d, $J$ = 13.5), 2.92 (1H, d, $J$ = 13.5), 2.72 (1H, d, $J$ = 13.5), 2.60−2.51 (1H, m), 2.38 (1H, d, $J$ = 13.5), 2.04−1.92 (1H, m), 1.60−1.53 (2H, m), 1.28−1.18 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) 168.2 (C), 137.1 (C), 136.4 (C), 131.1 (CH), 130.8 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 126.4 (CH), 91.7 (CH), 68.3 ($CH_2$), 41.9 (C), 41.3 ($CH_2$), 38.8 ($CH_2$), 34.0 ($CH_2$), 26.8 ($CH_2$), 19.6 ($CH_2$); HRMS ($ESI^+$): $m/z$ calc. 344.1621 for $C_{21}H_{23}NNaO_2$ ($MNa^+$), found 344.1630.

**9,9-Dibenzylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one (3b; Table 1, Entry 1).** The compound was synthesized using general DIA procedure A from imine **1a** (53.0 mg, 0.201 mmol) and acid **2c** (49.2 mg, 0.241 mmol). Purification by column chromatography (4/1 → 2/1 petroleum ether/ethyl acetate) afforded the title compound **3b** as a colorless oil (58.0 mg, 86%): $R_f$ 0.65 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2898, 1625, 1471, 1422, 1391, 1261, 1114, 1015, 720; $\delta_H$ (400 MHz, $CDCl_3$) 7.33−7.18 (8H, m), 7.10−7.06 (2H, m), 4.74−4.67 (1H, m), 4.33 (1H, s), 4.25 (1H, dd, $J$ = 11.0, 6.4), 3.76−3.69 (1H, m), 3.08 (1H, d, $J$ = 13.1), 3.00 (1H, d, $J$ = 13.5), 2.86 (1H, d, $J$ = 13.5), 2.77−2.68 (1H, m), 2.38−2.20 (3H, m), 2.05−1.89 (1H, m), 1.54−1.46 (2H, m), 1.35−1.25 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 167.3 (C), 137.7 (C), 137.0 (C), 130.9 (CH), 130.9 (CH), 128.0 (CH), 127.9 (CH), 126.2 (CH), 126.2 (CH), 88.9 (CH), 62.3 ($CH_2$), 41.7 ($CH_2$), 41.4 (C), 40.1 ($CH_2$), 35.2 ($CH_2$), 33.1 ($CH_2$), 27.8 ($CH_2$), 20.2 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 336.1958 for $C_{22}H_{26}NO_2$ ($MH^+$), found 336.1953.

**9,9-Dibenzyl-2-methylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one (3c; Table 1, Entry 2).** The compound was synthesized using general DIA procedure A from imine **1a** (65.0 mg, 0.247 mmol) and acid **2d** (64.6 mg, 0.296 mmol). Purification by column chromatography (2/1 → 1/1 petroleum ether/ethyl acetate) afforded the title compound **3c** as a colorless oil (71.0 mg, 82%) as a 2/1 (A/B) mixture of diastereoisomers: $R_f$ 0.55 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2941, 1658, 1463, 1451, 1358, 1280, 1142, 703; $\delta_H$ (400 MHz, $CDCl_3$) 7.33−7.16 and 7.14−7.05 (20H, m, 10 from A and 10 from B), 4.76−4.64 (2H, m, A and B), 4.36 (1H, s, A), 4.32 (1H, s, B), 3.85−3.77 (1H, m, B), 3.10 (1H, d, $J$ = 13.2, B), 3.05−2.94 (3H, m, 2 from A and B), 2.89−2.77 (3H, m, 2 from A and B), 2.40−2.18 (7H, m, 3 from A and 4 from B), 2.01−1.89 (2H, m, A and B), 1.55−1.45 (4H, m, A and B), 1.42 (3H, d, $J$ = 6.2, B), 1.38−1.28 (2H, m, A and B), 1.25 (3H, d, $J$ = 6.6, A); $\delta_C$ (100 MHz, $CDCl_3$) 167.6 (C, B), 166.4 (C, A), 137.9 (C, A and B), 137.2 (C, B), 137.0 (C, A), 131.1 (CH, A), 131.0 (CH, B), 131.0 (CH, A), 130.9 (CH, B), 128.0 (CH, A), 128.0 (CH, B), 127.9 (CH, B), 127.8 (CH, A), 126.3 (CH, A), 126.2 (CH, B), 126.2 (CH, A and B), 88.6 (CH, B), 83.4 (CH, A), 68.8 (CH, B), 67.1 (CH, A), 41.7 (C, A), 41.6 (C, B), 41.5 ($CH_2$, B), 41.3 ($CH_2$, A), 40.2 ($CH_2$, B), 40.1 ($CH_2$, B), 39.8 ($CH_2$, A), 37.9 ($CH_2$,


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A), 35.3 ($CH_2$, B), 35.2 ($CH_2$, A), 28.0 ($CH_2$, A), 27.9 ($CH_2$, B), 21.1 ($CH_2$, B), 20.4 ($CH_2$, A), 20.2 ($CH_2$, B), 17.2 ($CH_2$, A); HRMS ($ESI^+$) $m/z$ calcd 350.2115 for $C_{23}H_{28}NO_2$ ($MH^+$), found 350.2104.

**2-Methylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one (3d; Table 1, Entry 3).** The compound was synthesized using general DIA procedure A from dodecahydro-4a,8a,12a-triazatriphenylene (the trimer of imine **1b**; 50.0 mg, 0.201 mmol) and acid **2d** (131 mg, 0.603 mmol). Purification by column chromatography (2/1 → 1/1 petroleum ether/ethyl acetate → ethyl acetate) afforded the title compound **3d** as a pale yellow oil (61.0 mg, 60%) as an 8/1 (A/B) mixture of diastereoisomers: $R_f$ 0.20 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 4.77−4.70 (1H, m, B), 4.70−4.66 (2H, m, A and B), 4.62−4.57 (1H, m, A), 4.26−4.18 (1H, m, B), 3.91−3.82 (1H, m, A), 2.55−2.18 (6H, m, 3 from A and 3 from B), 2.04−1.64 (6H, m, 3 from A and 3 from B), 1.55−1.30 (6H, m, 3 from A and 3 from B), 1.27 (6H, d, $J$ = 6.2, 3 from A and 3 from B); $\delta_C$ (100 MHz, $CDCl_3$) 166.8 (C, A and B), 88.2 (CH, A), 83.9 (CH, B), 69.5 (CH, A), 65.8 (CH, B), 41.1 ($CH_2$, B), 40.1 ($CH_2$, A), 39.8 ($CH_2$, A), 39.1 ($CH_2$, B), 32.8 ($CH_2$, A), 32.0 ($CH_2$, B), 24.8 ($CH_2$, B), 24.5 ($CH_2$, A), 23.4 ($CH_2$, B), 22.6 ($CH_2$, A), 21.0 ($CH_3$, A), 19.8 ($CH_3$, B). Spectral data are in accord with those reported in the literature.[11]

**8,8-Dibenzyl-2-methyltetrahydro-2*H*-pyrrolo[2,1-*b*][1,3]-oxazin-4(3*H*)-one (3e; Table 1, Entry 4).** The compound was synthesized using general DIA procedure A from imine **1c** (50.0 mg, 0.201 mmol) and acid **2d** (48.2 mg, 0.221 mmol). Purification by column chromatography (2/1 → 1/1 petroleum ether/ethyl acetate) afforded the title compound **3e** as a colorless oil (42.0 mg, 62%) as a 6/1 (A/B) mixture of diastereoisomers: $R_f$ 0.40 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2930, 1644, 1455, 1391, 1126, 757, 703; $\delta_H$ (400 MHz, $CDCl_3$) 7.34−7.16 (16H, m, 8 from A and 8 from B), 7.08−7.03 (4H, m, 2 from A and 2 from B), 4.74 (1H, s, B), 4.64 (1H, s, A), 4.52−4.47 (1H, m, B), 3.95−3.87 (1H, m, A), 3.60−3.43 (2H, m, A and B), 3.30−3.19 (2H, m, A and B), 2.91 (1H, d, $J$ = 13.7, A), 2.86 (1H, d, $J$ = 13.7, B), 2.79−2.61 (7H, m, 3 from A and 4 from B), 2.39 (1H, dd, $J$ = 17.6, 4.0, A), 2.26−2.09 (2H, m, A and B), 1.77−1.67 (2H, m, A and B), 1.57−1.45 (2H, m, A and B), 1.42 (3H, d, $J$ = 6.0, A), 1.34 (3H, d, $J$ = 6.6, B); $\delta_C$ (100 MHz, $CDCl_3$) 166.7 (C, A and B), 137.6 (C, B), 137.5 (C, A), 136.7 (C, A), 136.6 (C, B), 130.9 (CH, B), 130.8 (CH, A), 128.2 (CH, A and B), 128.1 (CH, A and B), 126.6 (CH, B), 126.5 (CH, A), 126.5 (CH, A and B), 90.4 (CH, A), 84.0 (CH, B), 72.0 (CH, A), 69.1 (CH, B), 47.4 (C, B), 47.1 (C, A), 40.7 ($CH_2$, B), 40.4 ($CH_2$, A and B), 39.9 ($CH_2$, A), 38.6 ($CH_2$, A), 37.3 ($CH_2$, A and B), 37.0 ($CH_2$, B), 24.9 ($CH_2$, B), 24.7 ($CH_2$, A), 21.4 ($CH_3$, A), 19.7 ($CH_3$, B); HRMS ($ESI^+$) $m/z$ calcd 336.1958 for $C_{22}H_{26}NO_2$ ($MH^+$), found 336.1958.

**2-Methyl-2,3,6,7-tetrahydro[1,3]oxazino[2,3-*a*]isoquinolin-4(11b*H*)-one (3f; Table 1, Entry 5).** To a solution of imine **1d** (210 mg, 1.60 mmol) and TBDMS-protected carboxylic acid **2d** (419 mg, 1.92 mmol) in $CH_2Cl_2$ (11.1 mL) were added sequentially $NEt(i\text{-}Pr)_2$ (0.520 mL, 2.96 mmol) and then T3P (1.53 g, 2.40 mmol, 50% solution in THF). The resulting solution was stirred at room temperature for 20 h. $SnCl_2{\cdot}2H_2O$ (2.49 mmol, 11.2 mmol) was then added directly to the reaction mixture, which was stirred at room temperature for a further 24 h. The reaction was quenched by the addition of 10% aqueous $K_2CO_3$, and the mixture was diluted with water (50 mL), extracted with $CH_2Cl_2$ (3 × 50 mL), washed with water (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **3f** as a colorless oil (254 mg, 73%) as a 20/1 (A/B) mixture of diastereoisomers: $R_f$ 0.40 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2800, 1650, 1463, 1391, 1374, 1307, 1166, 1123, 747; $\delta_H$ (400 MHz, $CDCl_3$; data for the major diastereoisomer A only) 7.51−7.47 (1H, m), 7.28−7.22 (2H, m), 7.14−7.09 (1H, m), 5.86 (1H, s), 4.67−4.60 (1H, m), 4.20−4.10 (1H, m), 3.09−2.92 (1H, m), 2.73−2.67 (1H, m), 2.52 (1H, dd, $J$ = 17.2, 3.7), 2.37 (1H, dd, $J$ = 17.2, 11.4), 1.37 (3H, d, $J$ = 6.2); $\delta_C$ (100 MHz, $CDCl_3$) 166.2 (C), 134.8 (C), 133.5 (C), 128.3 (CH), 128.2 (CH), 126.6 (CH), 126.0 (CH), 84.1 (CH), 70.3 (CH), 39.3 ($CH_2$), 37.4 ($CH_2$), 27.8 ($CH_2$), 21.1 ($CH_3$); HRMS ($ESI^+$) $m/z$ calcd 240.0995 for $C_{13}H_{15}NNaO_2$ ($MNa^+$), found 240.0991.

Characteristic NMR data for the minor diastereoisomer B: $\delta_H$ (400 MHz, $CDCl_3$) 5.98 (1H, s); $\delta_C$ (100 MHz, $CDCl_3$) 82.3 (CH).

**3,6-Dimethyl-2-phenyl-1,3-oxazinan-4-one (3g; Table 1, Entry 6).** To a solution of imine **1e** (98.0 μL, 0.795 mmol) and TBDMS-protected carboxylic acid **2d** (208 mg, 0.954 mmol) in chloroform (5.5 mL) were added sequentially DIPEA (0.260 mL, 1.47 mmol) and then T3P (1759 mg, 1.19 mmol, 50% solution in THF). The resulting solution was heated to reflux for 1 h and then cooled to 0 °C. Triflic acid (0.700 mL, 7.95 mmol) was then added directly to the reaction mixture, which was warmed to room temperature and stirred for a further 1 h. The reaction was quenched by the addition of 1 M aqueous NaOH (25 mL), extracted with $CH_2Cl_2$ (3 × 50 mL), washed with water (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **3g** as a colorless oil (106 mg, 65%) as a 12/1 (A/B) mixture of diastereoisomers: $R_f$ 0.25 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3432, 1643, 1456, 1389, 1350, 1301, 1152, 755, 701; $\delta_H$ (400 MHz, $CDCl_3$) 7.42−7.35 (10H, m, 5 from A and 5 from B), 5.81 (1H, s, B), 5.58 (1H, s, A), 4.14−4.05 (1H, m, A), 3.93−3.85 (1H, m, B), 2.87 (3H, s, B), 2.58 (3H, s, A), 2.55−2.51 (4H, m, 2 from A and 2 from B), 1.32 (3H, d, $J$ = 6.1, A), 1.15 (3H, d, $J$ = 6.1, B); $\delta_C$ (100 MHz, $CDCl_3$; data for the major diastereoisomer A only) 167.9 (C), 137.5 (C), 129.8 (CH), 128.9 (CH), 127.5 (CH), 90.9 (CH), 70.7 (CH), 40.0 ($CH_2$), 29.8 ($CH_3$), 21.1 ($CH_3$); HRMS ($ESI^+$) $m/z$ calcd 206.1176 for $C_{12}H_{16}NO_2$ ($MH^+$), found 206.1176.

**8,8-Dibenzylhexahydroimidazo[1,2-*a*]pyridin-3(5*H*)-one (5a; Table 2, Entry 1).** Synthesis using general DIA procedure B from imine **1a** (27.0 mg, 0.103 mmol) and protected amino acid **4a** (25.9 mg, 0.124 mmol) afforded the title compound **5a** as a colorless oil (28.5 mg, 86%): $R_f$ 0.25 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3344 (br), 2940, 1680, 1452, 1293, 910; $\delta_H$ (400 MHz, $CDCl_3$) 7.34−7.10 (8H, m), 7.08−6.98 (2H, m), 4.30 (1H, s), 4.15 (1H, dd, $J$ = 12.8, 4.8), 3.69 (1H, d, $J$ = 15.8), 3.55 (1H, d, $J$ = 15.8), 2.99 (1H, d, $J$ = 13.5), 2.86 (1H, d, $J$ = 13.0), 2.79 (1H, d, $J$ = 13.0), 2.57−2.48 (1H, m), 2.37 (1H, d, $J$ = 13.5), 2.05−1.90 (1H, m), 1.63−1.50 (2H, m), 1.35−1.20 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 182.5 (C), 137.4 (C), 137.1 (C), 131.0 (CH), 130.9 (CH), 128.3 (CH), 128.3 (CH), 126.6 (CH), 126.5 (CH), 76.7 (CH), 49.3 ($CH_2$), 43.0 (C), 41.8 ($CH_2$), 39.5 ($CH_2$), 34.1 ($CH_2$), 27.9 ($CH_2$), 20.1 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 321.1961 for $C_{21}H_{25}N_2O$ ($MH^+$), found 321.1955.

**9,9-Dibenzylhexahydro-1*H*-pyrido[1,2-*a*]pyrimidin-4(6*H*)-one (5b; Table 2, Entry 2).** The compound was synthesized using general DIA procedure C from imine **1a** (53.0 mg, 0.201 mmol) and acid **4b** (49.2 mg, 0.241 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate → ethyl acetate) afforded the title compound **5b** as a pale yellow solid (82.0 mg, 76%): $R_f$ 0.65 (ethyl acetate); mp 102−104 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3344 (br), 2943, 1632, 1454, 1360, 1280, 910; $\delta_H$ (400 MHz, $CDCl_3$) 7.34−7.17 (10H, m), 4.78−4.72 (1H, m), 3.92 (1H, s), 3.30−3.24 (1H, m), 3.17 (1H, d, $J$ = 13.1), 3.01 (1H, d, $J$ = 13.1), 2.86−2.79 (1H, m), 2.62 (1H, d, $J$ = 13.1), 2.44−2.36 (3H, m), 2.27−2.17 (1H, m), 1.98−1.85 (1H, m), 1.53−1.40 (2H, m), 1.36−1.25 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (C), 137.2 (C), 137.1 (C), 131.0 (CH), 130.9 (CH), 128.2 (CH), 127.8 (CH), 126.5 (CH), 126.3 (CH), 75.2 (CH), 42.0 ($CH_2$), 41.2 (C), 40.8 ($CH_2$), 40.1 ($CH_2$), 36.4 ($CH_2$), 34.6 ($CH_2$), 29.6 ($CH_2$), 20.4 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 335.2118 for $C_{22}H_{27}N_2O$ ($MH^+$), found 335.2107.

**(2*S*)-2-Methyl-1,2,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-3(10b*H*)-one (5c; Table 2, Entry 3).** Synthesis using general DIA procedure B from imine **1d** (57.0 mg, 0.434 mmol) and protected amino acid **4c** (116 mg, 0.521 mmol) afforded the title compound **5c** as a colorless oil (79 mg, 90%) as a 4/1 (A/B) mixture of diastereoisomers: $R_f$ 0.10 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3406 (br), 1682, 1439, 1354, 1306, 737; $\delta_H$ (400 MHz, $CDCl_3$) 7.51−7.14 (8H, m, 4 from A and 4 from B), 5.70 (1H, s, B), 5.57 (1H, s, A), 4.20−4.13 (2H, m, A and B), 3.75−3.64 (2H, m, A and B), 3.27−3.14 (2H, m, A and B), 3.03−2.92 (2H, m, A and B), 2.84−2.73 (2H, m, A and B), 1.44 (3H, d, $J$ = 6.8, B), 1.37 (3H, d, $J$ = 6.8, A); $\delta_C$ (100 MHz, $CDCl_3$) 173.4 (C, A and B), 134.2 (C, B), 134.0 (C, A), 133.8 (C, A and B), 129.2 (CH, A), 129.1 (CH, B), 128.6 (CH, B), 128.4 (CH, A),


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127.2 (CH, A), 127.1 (CH, B), 125.4 (CH, A), 125.4 (CH, B), 69.7 (CH, B), 69.6 (CH, A), 56.4 (CH, A), 55.9 (CH, B), 37.2 ($CH_2$, B), 36.8 ($CH_2$, A), 28.3 ($CH_2$, A), 27.9 ($CH_2$, B), 16.4 ($CH_3$, B), 15.9 ($CH_2$, A); HRMS ($ESI^+$) $m/z$ calcd 203.1179 for $C_{12}H_{15}N_2O$ ($MH^+$), found 203.1174.

**(8a*S*)-5,6,8a,9,10,11-Hexahydropyrrolo[1′,2′:3,4]imidazo-[2,1-*a*]isoquinolin-8(12a*H*)-one (5d; Table 2, Entry 4).** The compound was synthesized using general DIA procedure C from imine **1d** (57.0 mg, 0.434 mmol) and acid **4d** (106 mg, 0.521 mmol). Purification by column chromatography (100/1 → 50/1 ethyl acetate/methanol) afforded the title compound **5d** as a colorless oil (74.0 mg, 75%): $R_f$ 0.10 (100/1 ethyl acetate/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3442, 2967, 1694, 1650, 1433, 1368, 1303, 1199, 1057, 748; $\delta_H$ (400 MHz, $CDCl_3$) 7.44 (1H, d, $J$ = 7.5), 7.31−7.23 (2H, m), 7.14 (1H, d, $J$ = 7.3), 5.82 (1H, s), 4.25 (1H, ddd, $J$ = 13.2, 5.7, 1.5), 3.94 (1H, dd, $J$ = 8.6, 4.6), 3.11−3.02 (1H, m), 2.92−2.74 (2H, m), 2.59−2.53 (1H, m), 2.23−2.07 (2H, m), 1.95−1.87 (1H, m), 1.76−1.67 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) 174.6 (C), 134.8 (C), 131.7 (C), 129.2 (CH), 127.9 (CH), 127.3 (CH), 127.0 (CH), 73.4 (CH), 66.4 (CH), 48.1 ($CH_2$), 36.9 ($CH_2$), 29.0 ($CH_2$), 25.4 ($CH_2$), 24.3 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 229.1335 for $C_{14}H_{17}N_2O$ ($MH^+$), found 229.1335; $[\alpha]_D^{22}$ −21.0° ($c$ 0.9, $CHCl_3$).

**5,6,11,11b-Tetrahydro-1*H*-imidazo[1′,2′:1,2]pyrido[3,4-*b*]-indol-3(2*H*)-one (5e; Table 2, Entry 5).** The compound was synthesized using general DIA procedure B from imine **1f** (35.0 mg, 0.206 mmol) and protected amino acid **4a** (51.7 mg, 0.247 mmol), affording the title compound **5e** as a colorless oil (40 mg, 85%): $R_f$ 0.10 (100/1 ethyl acetate/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3141 (br), 1643, 1424, 1285, 734; $\delta_H$ (400 MHz, $d_6$-DMSO) 11.09 (1H, br s), 7.39 (1H, d, $J$ = 7.9), 7.31 (1H, d, $J$ = 7.9), 7.05 (1H, dd, $J$ = 7.9, 6.7), 6.95 (1H, dd, $J$ = 7.9, 6.7), 5.71 (1H, s), 4.19−4.13 (1H, m), 3.42 (1H, d, $J$ = 15.8), 3.20−3.08 (2H, m), 2.73−2.65 (1H, m); $\delta_C$ (100 MHz, $d_6$-DMSO) 173.1 (C), 136.3 (C), 132.8 (C), 126.2 (C), 121.5 (CH), 118.6 (CH), 118.2 (CH), 111.5 (CH), 107.7 (C), 69.6 (CH), 49.6 ($CH_2$), 37.4 ($CH_2$), 20.4 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 228.1131 for $C_{13}H_{14}N_3O$ ($MH^+$), found 228.1134.

**9,9-Dibenzylhexahydropyrido[2,1-*b*][1,3]thiazin-4(6*H*)-one (7a; Table 3, Entry 1).** The compound was synthesized using general DIA procedure D from imine **1a** (25.0 mg, 0.0950 mmol) and thioacid **6a** (9.9 μL, 0.247 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7a** as a colorless oil (30 mg, 90%): $R_f$ 0.60 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2941, 1642, 1454, 1360, 1327, 1185, 912; $\delta_H$ (400 MHz, $CDCl_3$) 7.34−7.16 (10H, m), 5.00−4.94 (1H, m), 4.40 (1H, s), 3.10−2.91 (4H, m), 2.88−2.74 (3H, m), 2.40 (1H, d, $J$ = 14.0), 2.28−2.18 (1H, m), 2.06−1.94 (1H, m), 1.62−1.49 (2H, m), 1.40−1.30 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 169.6 (C), 137.4 (C), 136.4 (C), 131.0 (CH), 130.9 (CH), 128.1 (CH), 128.0 (CH), 126.5 (CH), 126.4 (CH), 64.9 (CH), 44.8 ($CH_2$), 44.3 (C), 42.0 ($CH_2$), 36.6 ($CH_2$), 35.5 ($CH_2$), 29.9 ($CH_2$), 23.0 ($CH_2$), 20.1 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 352.1730 for $C_{22}H_{26}NOS$ ($MH^+$), found 352.1728.

***N*-((3*R*)-9,9-Dibenzyl-4-oxooctahydropyrido[2,1-*b*][1,3]-thiazin-3-yl)acetamide (7b; Table 3, Entry 2).** The compound was synthesized using general DIA procedure D from imine **1a** (34 mg, 0.129 mmol) and thioacid **6b** (25.3 mg, 0.155 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7b** as a colorless oil (47 mg, 89%) as a 4/1 (A/B) mixture of diastereoisomers: $R_f$ 0.2 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3260, 2894, 1608, 1419, 720; $\delta_H$ (400 MHz, $CDCl_3$) 7.35−7.15 (18H, m, 8 from A and 10 from B), 7.05 (2H, d, $J$ = 6.6, A), 6.94−6.91 (1H, m, B, NH), 6.78−6.75 (1H, m, A, NH), 4.89−4.82 (2H, m, A and B), 4.64−4.52 (2H, m, A and B), 4.49 (1H, s, B), 4.16 (1H, s, A), 3.49−3.40 (2H, m, A and B), 3.24−3.18 (2H, m, A and B), 3.05−2.97 (3H, m, A), 2.96−2.82 (2H, m, B), 2.67−2.60 (1H, m, B), 2.42−2.30 (4H, m, 2 from A and 2 from B), 2.02 (3H, s, B), 2.01 (3H, s, A), 2.00−1.90 (2H, m, A and B), 1.64−1.52 (4H, m, 2 from A and 2 from B), 1.45−1.35 (1H, m, A), 1.35−1.25 (1H, m, B); $\delta_C$ (100 MHz, $CDCl_3$) 170.6 (C, A), 170.4 (C, B), 169.0 (C, B), 168.2 (C, A), 137.2 (C, B), 136.7 (C, A), 136.3 (C, A), 135.9 (C, B), 131.0 (CH, A and B), 130.9 (CH, A and B), 128.2 (CH, 2 from A and 1 from B), 128.0 (CH, B), 126.6 (CH, A), 126.5 (CH, B), 65.0 (CH, B), 63.5 (CH, A), 53.3 (CH, B), 52.3 (CH, A), 46.5 ($CH_2$, A), 46.2 (C, A), 45.5 ($CH_2$, B), 43.3 (C, B), 42.1 ($CH_2$, A), 41.1 ($CH_2$, B), 37.0 ($CH_2$, A), 36.2 ($CH_2$, B), 29.7 ($CH_2$, A), 29.6 ($CH_2$, B), 28.1 ($CH_2$, A), 26.9 ($CH_2$, B), 23.3 ($CH_3$, A), 23.2 ($CH_3$, B), 21.2 ($CH_2$, A), 21.0 ($CH_2$, B); HRMS ($ESI^+$) $m/z$ calcd 409.1944 for $C_{24}H_{29}N_2O_2S$ ($MH^+$), found 409.1945.

**11b-Methyl-2,3,6,7-tetrahydro[1,3]thiazino[2,3-*a*]-isoquinolin-4(11b*H*)-one (7c; Table 3, Entry 3).** The compound was synthesized using general DIA procedure D from imine **1g** (57.0 mg, 0.393 mmol) and thioacid **6a** (41.0 μL, 0.471 mmol). Purification by column chromatography (1/1 → 1/2 petroleum ether/ethyl acetate) afforded the title compound **7c** as a colorless oil (82 mg, 89%): $R_f$ 0.10 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1607, 1372, 1330, 1067, 751; $\delta_H$ (400 MHz, $CDCl_3$) 7.43 (1H, d, $J$ = 7.5), 7.26−7.17 (2H, m), 7.12 (1H, d, $J$ = 7.3), 5.10 (1H, ddd, $J$ = 13.0, 4.9, 1.7), 3.24 (1H, ddd, $J$ = 15.6, 9.9, 5.1), 3.03−2.93 (1H, m), 2.87−2.67 (4H, m), 2.04 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 168.0 (C), 139.1 (C), 134.1 (C), 129.1 (CH), 127.4 (CH), 126.7 (CH), 126.1 (CH), 65.3 (C), 36.7 ($CH_2$), 33.8 ($CH_2$), 30.5 ($CH_3$), 29.1 ($CH_2$), 22.5 ($CH_2$); HRMS ($ESI^+$) $m/z$ calcd 234.0947 for $C_{13}H_{16}NOS$ ($MH^+$), found 234.0948.

**10b-Phenyl-5,6-dihydro-2*H*-thiazolo[2,3-*a*]isoquinolin-3-(10b*H*)-one (7d; Table 3, Entry 4).** The compound was synthesized using general DIA procedure D from imine **1h** (58.0 mg, 0.280 mmol) and thioacid **6c** (23.3 μL, 0.336 mmol). Purification by column chromatography (3/1 petroleum ether/ethyl acetate) afforded the title compound **7d** as a colorless oil (73 mg, 93%): $R_f$ 0.30 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1653, 1380, 1271, 1157, 739; $\delta_H$ (400 MHz, $CDCl_3$) 7.50−7.46 (1H, m), 7.33−7.13 (8H, m), 4.12 (1H, ddd, $J$ = 13.0, 7.0, 4.6), 3.98 (1H, d, $J$ = 15.5), 3.73 (1H, d, $J$ = 15.5), 3.17 (1H, ddd, $J$ = 13.0, 9.0, 6.0), 3.06−3.00 (1H, m), 2.64 (1H, ddd, $J$ = 16.3, 6.0, 4.6); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (C), 144.0 (C), 138.8 (C), 133.4 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 126.8 (CH), 126.4 (CH), 73.4 (C), 38.1 ($CH_2$), 34.3 ($CH_2$), 27.1 ($CH_3$); HRMS ($ESI^+$) $m/z$ calcd 282.0947 for $C_{17}H_{16}NOS$ ($MH^+$), found 282.0954.

**5,6,11,11b-Tetrahydrothiazolo[3′,2′:1,2]pyrido[3,4-*b*]indol-3(2*H*)-one (7e; Table 3, Entry 5).** The compound was synthesized using general DIA procedure D from imine **1f** (35.0 mg, 0.206 mmol) and thioacid **6c** (17.2 μL, 0.247 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7e** as a colorless oil (49 mg, 97%): $R_f$ 0.35 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3168, 1624, 1420, 1302, 1214, 885; $\delta_H$ (400 MHz, $d_6$-DMSO) 11.51 (1H, br s), 7.40 (1H, d, $J$ = 7.7), 7.29 (1H, d, $J$ = 8.1), 7.07−7.03 (1H, m), 6.98−6.94 (1H, m), 6.22 (1H, s), 4.34 (1H, dd, $J$ = 13.2, 4.4), 3.81 (1H, d, $J$ = 15.2), 3.57 (1H, d, $J$ = 15.2), 3.19−3.11 (1H, m), 2.78−2.62 (2H, m); $\delta_C$ (100 MHz, $d_6$-DMSO) 170.1 (C), 137.0 (C), 132.6 (C), 126.5 (C), 122.3 (CH), 119.5 (CH), 118.9 (CH), 112.0 (CH), 107.8 (C), 56.1 (CH), 40.9 ($CH_2$), 33.5 ($CH_2$), 21.2 ($CH_3$); HRMS ($ESI^+$) $m/z$ calcd 245.0743 for $C_{13}H_{13}N_2OS$ ($MH^+$), found 245.0753.

**3-Methyl-2-phenylthiazolidin-4-one (7f; Table 3, Entry 6).** The compound was synthesized using general DIA procedure D from imine **1e** (90.8 mg, 0.726 mmol) and thioacid **6c** (84.3 mg, 63.8 μL, 0.915 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7f** as a colorless oil (173 mg, 93%): $R_f$ 0.35 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3031, 2922, 1670, 1389, 697; $\delta_H$ (400 MHz, $CDCl_3$) 7.44−7.34 (3H, m), 7.33−7.28 (2H, m), 5.52 (1H, d, $J$ = 2.1), 3.84 (1H, dd, $J$ = 15.4, 2.1), 3.72 (1H, d, $J$ = 15.4), 2.74 (3H, s); $\delta_C$ (100 MHz, $CHCl_3$) 171.13 (C═O), 139.12 (C), 129.1 (2 × CH), 129.0 (2 × CH), 126.8 (CH), 65.3 (CH), 32.9 ($CH_2$), 30.1 ($CH_3$); HRMS ($ESI^+$) $m/z$ calcd 194.0634 for $C_{10}H_{12}NOS$ ($MH^+$), found 194.0630. These data were consistent with those reported in the literature.[12]

**Dimethyl 4-Oxo-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]-isoquinoline-1,1(2*H*,11b*H*)-dicarboxylate (9a, Table 4, entry 1).** Imine **1d** (50 mg, 0.381 mmol) and carboxylic acid **8a** (93 mg, 0.457 mmol) were dissolved in $CHCl_3$ (2 mL) in a microwave vial. $NEt(i\text{-}Pr)_2$ (91.1 mg, 123 μL, 0.705 mmol) and T3P (182 mg, 0.572 mmol, 364 mg of a 50% solution in THF) were added via syringe. The


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reaction mixture was stirred at 70 °C for 1 h. $AlCl_3$ (102 mg, 0.762 mmol) was added and the reaction mixture stirred at 70 °C for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (ethyl acetate) gave the title compound **9a** (92 mg, 76%) as a yellow solid: mp 130−133 °C (from $CHCl_3$); $R_f$ 0.48 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2952, 2874, 1741, 1713, 1668, 1399, 1276, 1159, 1078, 759; $\delta_H$ (400 MHz, $CDCl_3$) 7.27−7.12 (4H, m), 5.49 (1H, m), 4.67−4.55 (1H, m), 3.82 (3H, s), 3.36 (3H, s), 2.94−2.83 (2H, m), 2.77−2.65 (1H, m), 2.66−2.43 (4 H, m); $\delta_C$ (100 MHz, $CDCl_3$) 171.2 (C═O), 170.9 (C═O), 169.1 (C═O), 137.5 (C), 132.9 (C), 128.3 (CH), 127.4 (CH), 126.5 (CH), 126.1 (CH), 60.1 (C), 59.0 (CH), 53.1 ($CH_3$), 52.5 ($CH_3$), 39.7 ($CH_2$), 29.5 ($CH_2$), 28.7 ($CH_2$), 28.7 ($CH_2$); HRMS (ESI) $m/z$ calcd 318.1336 for $C_{17}H_{20}NO_5$ ($MH^+$), found 318.1335.

**1,1′-(4-Oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-1,1-diyl)diethanone (9b; Table 4, Entry 2).** The compound was synthesized using general DIA procedure E (at 70 °C and with $AlCl_3$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8b** (158 mg, 0.915 mmol). Purification by column chromatography (ethyl acetate) gave the *title compound* **9b** (141 mg, 65%) as a colorless solid: mp 146−147 °C (from petroleum ether/EtOAc); $R_f$ 0.25 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3014, 2947, 2921, 1687, 1660, 1464, 1402, 1356, 1186, 1136, 759; $\delta_H$ (400 MHz, $CDCl_3$) 7.26−7.20 (1H, m), 7.20−7.14 (2H, m), 7.09−7.04 (1H, m), 5.67 (1H, s), 4.36 (1H, dt, $J$ = 12.7, 5.8), 3.18−3.09 (1H, m), 2.87 (2H, *app* t, $J$ = 6.6), 2.59−2.40 (3H, m), 2.38−2.29 (1H, m), 2.28 (3H, s), 1.82 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 204.2 (C═O), 203.8 (C═O), 170.3 (C═O), 137.2 (C), 133.8 (C), 129.0 (CH), 127.9 (CH), 126.6 (CH), 125.5 (CH), 71.2 (C), 56.2 (CH), 40.3 ($CH_2$), 29.1 ($CH_2$), 28.2 ($CH_3$), 28.0 ($CH_2$), 26.8 ($CH_3$), 24.2 ($CH_2$); HRMS (ESI) $m/z$ calcd 286.1438 for $C_{17}H_{20}NO_3$ ($MH^+$), found 286.1430.

**2,3-Dimethoxy-8,9-dihydro-5*H*-isoquinolino[1,2-*a*]isoquinolin-6(13b*H*)-one (9c; Table 4, Entry 3).** The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8c** (179 mg, 0.915 mmol). Purification by column chromatography (ethyl acetate) gave the title compound **9c** (212 mg, 90%) as a yellow solid: mp 175−177 °C (from EtOAc/MeOH) (lit.[13] mp 141−142 °C (from EtOH/petroleum ether)); $R_f$ 0.30 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2932, 1629, 1520, 1461, 1251, 758, 601; $\delta_H$ (400 MHz, $CDCl_3$) 7.31−7.28 (3H, m), 7.03 (1H, d, $J$ = 7.3), 6.73 (1H, s), 6.57 (1H, s), 5.64 (1H, s), 4.61 (1H, ddd, $J$ = 13.0, 6.2, 5.2), 3.91 (3H, s), 3.80 (3H, s), 3.60 (1H, d, $J$ = 18.9), 3.51 (1H, d, $J$ = 18.9), 3.29 (1H, ddd, $J$ = 13.0, 8.8, 5.2), 3.03 (1H, ddd, $J$ = 15.4, 8.8, 6.2), 2.91 (1H, app dt, $J$ = 15.9, 5.2); $\delta_C$ (100 MHz, $CDCl_3$) 169.5 (C═O), 148.7 (C), 147.4 (C), 136.0 (C), 135.7 (C), 128.8 (CH), 127.6 (CH), 126.1 (CH), 125.8 (CH), 125.3 (C), 125.2 (C), 110.3 (CH), 109.7 (CH), 59.0 (CH), 56.0 ($CH_3$), 56.0 ($CH_3$), 40.9 ($CH_2$), 37.3 ($CH_2$), 28.1 ($CH_2$); HRMS (ESI) $m/z$ calcd 310.1438 for $C_{19}H_{20}NO_3$ ($MH^+$), found 310.1437.

**5,6,14,14b-Tetrahydroindolo[2′,3′:3,4]pyrido[2,1-*a*]isoquinolin-8(9*H*)-one (9d; Table 4, Entry 4).** The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8d** (160 mg, 0.915 mmol). Purification by column chromatography (ethyl acetate) gave the title compound **9d** (176 mg, 80%) as a light brown solid: mp decomposition noted at 205 °C (from EtOAc/MeOH); $R_f$ 0.51 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3063, 2953, 1603, 1454, 1226, 1216, 756, 738, 710; $\delta_H$ (400 MHz, $CDCl_3$) 11.51 (1H, s), 7.50−7.43 (2H, m), 7.30−7.13 (5H, m), 7.04 (1H, ddd, $J$ = 7.9, 7.0, 0.9), 6.02 (1H, s), 4.25 (1H, *app* dt, $J$ = 12.8, 6.4), 3.67 (1H, dd, $J$ = 20.7, 2.4), 3.47 (1H, dd, $J$ = 20.7, 2.4), 3.48−3.39 (1H, m), 3.13−2.94 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) 167.1 (C═O), 137.7 (C), 137.0 (C), 135.4 (C), 128.5 (CH), 128.3 (C), 127.6 (CH), 126.2 (CH), 125.5 (C), 124.3 (CH), 121.8 (CH), 118.9 (CH), 118.3 (CH), 111.4 (CH), 105.0 (C), 54.9 (CH), 41.9 ($CH_2$), 29.2 ($CH_2$), 27.1 ($CH_2$); HRMS (ESI) $m/z$ calcd 289.1335 for $C_{19}H_{17}N_2O$ ($MH^+$), found 289.1334.

**8,9-Dihydro-5*H*-pyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoquinolin-6(13b*H*)-one (9e; Table 4, Entry 5).** The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8e** (115 mg, 0.915 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) gave the title compound **9e** (140 mg, 77%) as a brown oil: $R_f$ 0.65 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2944, 2897, 1651, 1448, 1427, 1317, 908, 724; $\delta_H$ (400 MHz, $CDCl_3$); 7.41−7.35 (1H, m), 7.31−7.24 (2H, m), 7.24−7.19 (1H, m), 6.70 (1H, dd, $J$ = 2.6, 1.6), 6.23 (1H, dd, $J$ = 3.6, 2.6), 5.99 (1H, ddd, $J$ = 3.6, 1.6, 1.0), 5.90 (1H, s), 4.76 (1H, ddd, $J$ = 12.6, 5.4, 3.6), 4.69 (1H, d, $J$ = 17.1), 4.62 (1H, d, $J$ = 17.1), 3.22−3.13 (1H, m), 3.12−3.01 (1H, m), 2.86 (1H, app dt, $J$ = 15.8, 3.6); $\delta_C$ (100 MHz, $CDCl_3$) 165.3 (C═O), 134.8 (C), 133.5 (C), 129.0 (CH), 127.6 (CH), 126.3 (CH), 125.5 (CH), 119.2 (CH), 108.9 (CH), 105.7 (CH), 54.2 (CH), 48.9 ($CH_2$), 40.4 ($CH_2$), 28.2 ($CH_2$); HRMS (ESI) $m/z$ calcd 239.1179 for $C_{15}H_{15}N_2O$ ($MH^+$), found 239.1179.

**11,14-Dimethoxy-5,6-dihydrobenzo[*de*]isoquinolino[1,2-*a*]isoquinolin-8(14b*H*)-one (9f; Table 4, Entry 6).** Imine **1d** (53.4 mg, 0.407 mmol) and carboxylic acid **8f** (113 mg, 0.489 mmol) were dissolved in toluene (2.5 mL). $NEt(i\text{-}Pr)_2$ (97.3 mg, 131 μL, 0.753 mmol) and T3P (194 mg, 0.611 mmol, 386 mg of a 50% solution in THF). The resulting solution was stirred at room temperature for 20 min. $BF_3{\cdot}Et_2O$ (0.25 mL, 2.04 mmol) was added and the reaction mixture stirred at room temperature for 20 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (4/1 petroleum ether/ethyl acetate → 1/1 petroleum ether/ethyl acetate → EtOAc) gave the title compound **9f** (125 mg, 89%) as a pink solid: mp 242−248 °C; $R_f$ 0.31 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2944, 2845, 1638, 1586, 1518, 1461, 1412, 1349, 1261, 1242, 1186, 1055, 1048, 1093, 736; $\delta_H$ (400 MHz, $CDCl_3$); 8.30 (1H, d, $J$ = 9.2), 8.24 (1H, d, $J$ = 8.1), 7.38 (1H, d, $J$ = 9.2), 7.20−7.12 (2H, m), 6.96 (1H, t, $J$ = 7.8), 6.75 (1H, d, $J$ = 8.1), 6.49 (1H, d, $J$ = 7.8), 6.22 (1H, s), 4.70 (1H, ddd, $J$ = 13.5, 7.1, 6.6), 4.03 (3H, s), 3.97 (3H, s), 3.61 (1H, ddd, $J$ = 13.5, 7.1, 7.1), 3.34 (1H, ddd, $J$ = 16.1, 7.1, 7.1), 3.07 (1H, ddd, $J$ = 16.1, 7.1, 6.6); $\delta_C$ (100 MHz, $CDCl_3$) 163.7 (C═O), 158.5 (C), 154.4 (C), 138.0 (C), 135.6 (C), 130.7 (C), 128.9 (CH), 128.5 (CH), 127.2 (CH), 125.7 (CH), 123.9 (CH), 123.6 (CH), 119.3 (C), 116.7 (C), 113.7 (C), 111.2 (CH), 102.1 (CH), 55.9 ($CH_3$), 55.7 (CH), 55.6 ($CH_3$), 42.3 ($CH_2$), 27.2 ($CH_2$); HRMS (ESI) $m/z$ calcd 346.1438 for $C_{22}H_{20}NO_3$ ($MH^+$), found 346.1440.

**2-Methyl-6,7-dihydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (9g; Table 4, Entry 7).** Imine **1d** (38 mg, 0.290 mmol) and 3-methylbut-3-enoic acid **8g** (34.8 mg, 0.348 mmol) were dissolved in $CH_2Cl_2$ (2.9 mL). $NEt(i\text{-}Pr)_2$ (69.3 mg, 93.5 μL, 0.536 mmol) and T3P (13.8 mg, 0.435 mmol, 27.7 mg of a 50% solution in THF) were added, and the reaction mixture was stirred at 45 °C for 1 h. TFA (165 mg, 111 μL, 1.449 mmol) was added and the reaction mixture stirred at 45 °C overnight. The reaction was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined aqueous layers were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (2/1 petroleum ether/ethyl acetate) gave the title compound **9g** (48 mg, 78%) as a colorless oil: $R_f$ 0.52 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2974, 2936, 2909, 2851, 1670, 1623, 1415, 1299, 760; $\delta_H$ (400 MHz, $CDCl_3$) 7.26−7.15 (4H, m), 5.88 (1H, app dq, $J$ = 2.6, 1.4), 4.83−4.72 (2H, m), 3.00−2.75 (3H, m), 2.59 (1H, dd, $J$ = 17.1, 4.9), 2.43−2.31 (1H, m), 1.99 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 165.4 (C═O), 150.2 (C), 135.9 (C), 134.9 (C), 129.0 (CH), 126.7 (CH), 126.6 (CH), 125.6 (CH), 120.7 (CH), 54.3 (CH), 38.6 ($CH_2$), 37.7 ($CH_2$), 29.5 ($CH_2$), 22.7 ($CH_3$); HRMS (ESI) $m/z$ calcd 214.1226 for $C_{14}H_{16}NO$ ($MH^+$), found 214.1223.

**1-Vinyl-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4-(11b*H*)-one (9h; Table 4, Entry 8).** The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and


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carboxylic acid **8h** (170 mg, 0.915 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) gave the title compound **9h** (122 mg, 70%) as a clear, colorless oil, as a 5/1 (A/B) mixture of diastereoisomers: $R_f$ 0.39 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 2933, 2870, 1635, 1461, 1433, 1409, 1360, 1286, 1248, 916, 741; $\delta_H$ (400 MHz, $CDCl_3$) data for major diastereoisomer 7.26−7.10 (4H, m), 5.53 (1H, ddd, $J$ = 17.6, 10.1, 7.3), 4.97 (3H, m), 4.91 (1H, d, $J$ = 3.4), 3.17−3.11 (1H, m), 2.88−2.67 (3H, m), 2.61 (1H, ddd, $J$ = 18.0, 11.6, 7.0), 2.53 (1H, ddd, $J$ = 18.0, 7.3, 2.8), 2.26−2.14 (1H, m), 2.09−2.00 (1H, m), data for minor diastereoisomer 7.26−7.10 (4H, m), 6.05 (1H, ddd, $J$ = 17.5, 10.3, 7.3), 5.26 (1H, dt, $J$ = 17.5, 1.2), 5.24 (1H, dt, $J$ = 10.3, 1.1), 4.56 (1H, d, $J$ = 7.3), 4.39 (1H, dt, $J$ = 12.6, 5.6), 3.22−3.16 (1H, m), 3.10−3.00 (1H, m), 2.88−2.67 (3H, m), 2.44−2.31 (1H, m), 1.97−1.78 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) data for major diastereoisomer 169.7 (C═O), 135.8 (C), 134.4 (CH), 128.8 (CH), 126.5 (CH), 126.3 (CH), 126.2 (CH), 118.0 ($CH_2$), 60.0 (CH), 42.3 (CH), 38.5 ($CH_2$), 29.1 ($CH_2$), 28.1 ($CH_2$), 25.7 ($CH_2$), one quaternary carbon signal not observed, data for minor diastereoisomer 140.2 (CH), 136.5 (C), 134.9 (C), 128.5 (CH), 127.2 (CH), 126.1 (CH), 125.0 (CH), 116.4 ($CH_2$), 59.6 (CH), 41.9 ($CH_2$), 41.7 (CH), 30.6 ($CH_2$), 28.5 ($CH_2$), 26.2 ($CH_2$), carbonyl signal not observed; HRMS (ESI) $m/z$ calcd 228.1383 for $C_{15}H_{18}NO$ ($MH^+$), found 228.1386.

## ■ ASSOCIATED CONTENT

### Supporting Information

Text giving general experimental details and figures giving $^1$H and $^{13}$C spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail for R.J.K.T.: richard.taylor@york.ac.uk.


### Notes

The authors declare no competing financial interest.

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# Substrate scope in the direct imine acylation of *ortho*-substituted benzoic acid derivatives: the total synthesis (±)-cavidine

Christiana Kitsiou, William P. Unsworth, Graeme Coulthard, Richard J.K. Taylor *

*University of York, Heslington, York YO10 5DD, UK*

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Evodiamine

ABSTRACT

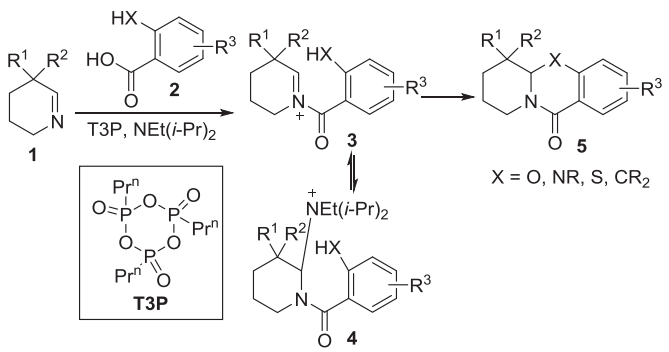
The direct imine acylation (DIA) and subsequent cyclisation of a range of imines with *ortho*-substituted benzoic acid derivatives is described. Variation in the coupling reagents, imine and benzoic acid were all examined. The DIA procedure was also applied in the total synthesis of (±)-cavidine.



## 1. Introduction

The controlled synthesis of diverse heterocycles is crucial in both the pharmaceutical and agrochemical industries.[1] Novel methods that expedite their synthesis are therefore of great importance, especially those which furnish a range of diverse scaffolds whose biological activity has not previously been well-examined. Such diversity-oriented-synthesis[2] has attracted widespread interest in recent years as a strategy to accelerate the discovery of new therapeutically important compounds.

In order for these methods to be widely adopted by the synthetic community, both in industry and in academia, various conditions must be satisfied: the new methods must be reliable, operationally simple, high yielding and crucially be capable of generating a broad range of structures without significant optimisation. Our research group recently reported one such method, based on the concept of 'Direct Imine Acylation' (DIA).[3] This methodology centres on a novel way to generate *N*-acyliminium ions and their subsequent reaction with tethered nucleophiles. The initial communication focused on the direct coupling of a range of imines (**1**) with *ortho*-substituted benzoic acids (**2**) using propylphosphonic acid anhydride (T3P)[4] and NEt(*i*-Pr)$_2$ (DIPEA) to activate the benzoic acid towards nucleophilic attack by the imine nitrogen to form the key *N*-acyliminium ion **3** (Scheme 1). An accompanying mechanistic study, in which the progress of the reaction was monitored in situ by IR spectroscopy using ReactIR™, shed further light on the process. It is proposed that the *N*-acyliminium ion **3** exists only briefly and is trapped by excess DIPEA in the reaction mixture, affording ammonium salt **4**. This process is reversible and so the extrusion of DIPEA results in the regeneration of the *N*-acyliminium ion **3**, which is subsequently trapped by the *ortho*-nucleophile in a one-pot process, driving the equilibrium towards the formation of the desired heterocyclic product **5**.




**Scheme 1.** Direct imine acylation.

* Corresponding author. E-mail address: tet@york.ac.uk (R.J.K. Taylor).

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Diversity was initially examined both in terms of the imine **1** and the benzoic acid derivative **2**. Most notably, the methodology was shown to be compatible with phenols, anilines, thiols and carbon pro-nucleophiles as the *ortho*-substituent on the benzoic acid (**2**, X=O, NMe, S, $C(CO_2Me)_2$). Furthermore, we more recently disclosed preliminary results, which demonstrate that DIA is also compatible with aliphatic carboxylic acids.[5] Protected aliphatic alcohols, protected amines, thiols and a range of carbon pro-nucleophiles can also be tethered to the carboxylic acid and react with the *N*-acyliminium ion using broadly similar conditions to those described above, dramatically increasing the range of heterocyclic scaffolds accessible. DIA has also been used in target synthesis; the total synthesis of evodiamine **6**[3,6] was completed in high yield (95%, see later) and DIA methodology was also used to construct the spirooxoquinolizidinone ring system of the proposed structures of the complex marine natural product 'upenamide **7** (Fig. 1).[7]

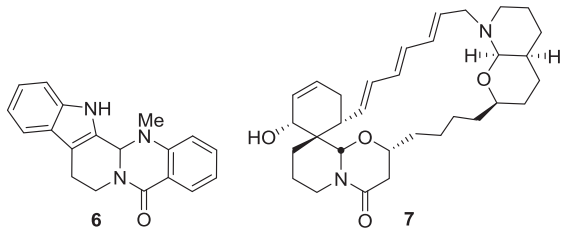



**Fig. 1.** The structure of evodiamine **6** and one of the proposed structures of 'upenamide **7**.

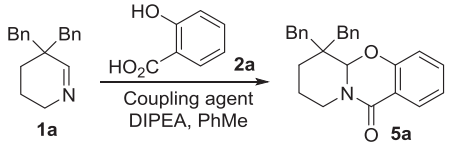
Herein we report extended substrate scoping studies for DIA using benzoic acid derivatives. We also describe the application of DIA in the total synthesis of the natural product (±)-cavidine.

## 2. Results and discussion

In our initial communication, all of the DIA reactions reported were performed by simply mixing the imine, carboxylic acid, T3P and DIPEA in toluene and heating to 90 °C in most cases, or 120 °C if t.l.c. analysis indicated that the reaction was incomplete after 20 h. All of the reagents were used as supplied, without drying or purification, and it was not necessary to exclude air from the reaction. We have since discovered that both CDI and DCC may be used in place of T3P in the reaction of imine **1a** with salicylic acid **2a** (Table 1, entries 1–3). The same reaction was also tested using EDC as the coupling reagent but this failed, most likely because of the poor solubility of EDC in toluene. Thus, the highest yield was obtained using our original T3P conditions, but it is important to note that other coupling reagents can also be used, in cases where T3P is either unavailable or unsuitable.

The scope of the T3P-meditated DIA conditions described above (Table 1, entry 1) was first tested with regard to the acid coupling partner **2** (Table 2). Note that examples reported in our prior communication are indicated with an asterisk and that the majority of the new examples led to the formation of novel compounds.

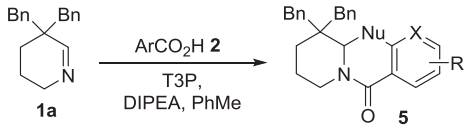
**Table 1**
Alternative coupling reagents[a]

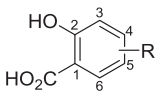
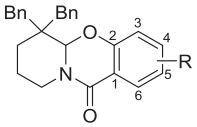
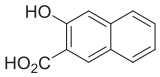
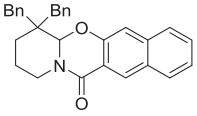
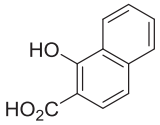
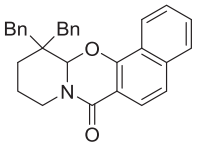
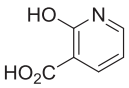
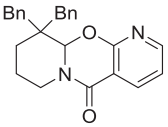
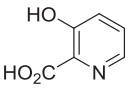
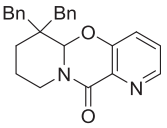
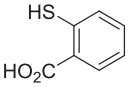
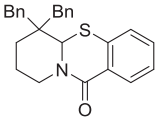
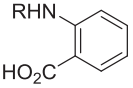
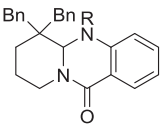



| Entry | Coupling agent | Yield[b] |
|---|---|---|
| 1 | T3P | 83% |
| 2 | CDI | 52% |
| 3 | DCC | 77% |
| 4 | EDC | 0% |

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imine **1a** (1 equiv), salicylic acid **2a** (1.2 equiv), coupling reagent (1.5 equiv), DIPEA (1.85 equiv) in PhMe at 90 °C for 20 h.
[b] Isolated yields after purification by column chromatography.

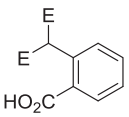
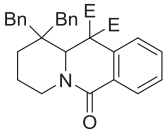
**Table 2**
Benzoic acid scope in DIA with imine **1a**[a]




| Entry | Acylating agent | Product | Yield[b] |
|---|---|---|---|
| |  |  | |
| 1 | **2a** R=H | **5a** R=H | 83%*[c,d] |
| 2 | **2b** R=3-$NO_2$ | **5b** R=3-$NO_2$ | 89% |
| 3 | **2c** R=5-$NO_2$ | **5c** R=5-$NO_2$ | 91%* |
| 4 | **2c** | **5c** | 90%*[e] |
| 5 | **2d** R=5-Cl | **5d** R=5-Cl | 96% |
| 6 | **2e** R=4-OMe | **5e** R=4-OMe | 82%[f] |
| 7 | **2f** R=5-OMe | **5f** R=5-OMe | 60% |
| 8 | **2g** R=6-OMe | **5g** R=6-OMe | 64%[f] |
| 9 | **2h** R=4,6-OH | **5h** R=4,6-OH | 60% |
| |  |  | |
| 10 | **2i** | **5i** | 95%* |
| |  |  | |
| 11 | **2j** | **5j** | 92%* |
| |  |  | |
| 12 | **2k** | **5k** | 97%* |
| |  |  | |
| 13 | **2l** | **5l** | 63% |
| |  |  | |
| 14 | **2m** | **5m** | 96%*[g] |
| |  |  | |
| 15 | **2n** R=Me | **5n** R=Me | 97%*[c] |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Acylating agent | Product | Yield[b] |
|---|---|---|---|
| 16 | **2o** R=Ph | **5o** R=Ph | 95% |
| |  |  | |
| 17 | **2p** E=$CO_2$Me | **5p** E=$CO_2$Me | 84%*[c] |

*Entries highlighted with an asterisk were reported in the earlier communication (see Ref. 3).

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imine **1a** (1 equiv), benzoic acid **2a**–**p** (1.2 equiv), T3P (1.5 equiv), DIPEA (1.85 equiv) in PhMe at 90 °C for 20 h.

[b] Isolated yields after purification by column chromatography.

[c] Reaction performed in the absence of T3P gave 0% yield of product.

[d] Reaction performed in the absence of DIPEA gave 0% yield of product.

[e] Reaction performed on a 3 mmol scale under the standard conditions.

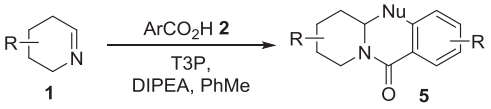
[f] Reaction performed at 120 °C for 20 h.

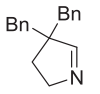
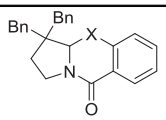
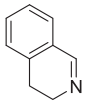
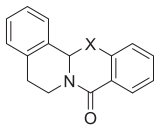
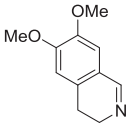
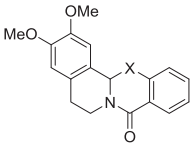
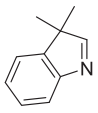
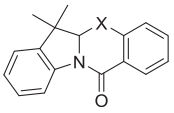
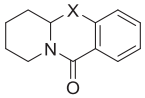
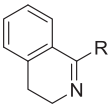
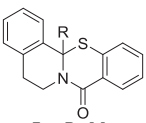
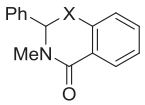
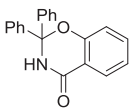
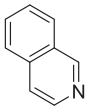
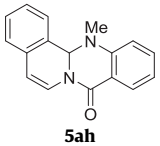
[g] Reaction performed in the absence of T3P gave 20% yield of product.

Imine **1a** was reacted with a wide range of salicylic acid derivatives **2a**–**h**[3] using the standard DIA procedure, affording *N*,*O*-acetals **5a**–**h** in good to excellent yields (Table 2, entries 1–9). All of these reactions were performed using the same conditions with the exceptions of entries 6 and 8; in both of these cases a higher reaction temperature (120 °C) was required in order to achieve full conversion into the respective products **5e** and **5g**. The initial N-acylation appears to be significantly slower in these two examples, which is unsurprising as the activated carboxylic acid is presumably less electrophilic than the other systems tested as a result of the presence and position of the electron-rich methoxy groups. Naphthalene and pyridine derivatives **2i**–**l** are also well tolerated, affording products **5i**–**l** again in good to excellent yields (entries 10–13). Clearly, *ortho*-hydroxy aromatics are excellent substrates, but the real strength of the DIA procedure is its versatility, which is demonstrated by the similarly efficient reactions of thiosalicylic acid **2m** and anthranilic acids **2n** and **2o** (entries 14–16). Perhaps most impressively, diester **2p** also takes part in DIA, demonstrating that C–C bond formation can also be achieved in very good yield (entry 17). Crucially, all of these examples were performed using the standard reaction conditions and are unoptimised, highlighting the operational simplicity of the process and its significant potential for the rapid synthesis of diverse compound libraries for biological screening.

The substrate scope with respect to the imine component was next examined (Table 3). The requisite imines **1a**–**k** were either generated as described in our previous reports, were available commercially or were made via literature methods.[3,5,8,9] The basic procedure is clearly very broad in scope, with a range of imines compatible; DIA reactions using imines **1b**–**e** and benzoic acid derivatives bearing *O*-, *S*-, *N*- and *C*-nucleophiles were tested, affording a diverse range of products in moderate to excellent yields (Table 3, entries 1–10). The yields for some of these reactions are lower than for those using imine **1a**, but it is important to recognise that all of these reactions are unoptimised and the only change made to the reaction conditions was to increase the temperature to 120 °C if t.l.c. analysis showed that the reaction was incomplete under the standard conditions (90 °C). We believe that the comparative stabilities of the products may partially explain this variability in yield. For example, the DIA of 3,4-dihydroisoquinoline **1c** and acid **2a** proceeded in high yield but the analogous reaction with the dimethoxy imine **1d** proceeded in lower yield (entries 4 and 7), which may be explained by the increased propensity for the product **5w** to ring-open (and thus regenerate the intermediate *N*-acyliminium ion) as a result of the two electron-donating groups. Greater reversibility in the cyclisation step would not only lead to an increased reaction time, but may also

**Table 3**
Imine scope in DIA with benzoic acid derivatives[a]




| Entry | Imine | Acid | Product | Yield[b] |
|---|---|---|---|---|
| |  | |  | |
| 1 | **1b** | **2a** | **5q** X=O | 48%[c] |
| 2 | **1b** | **2m** | **5r** X=S | 99% |
| 3 | **1b** | **2n** | **5s** X=NMe | 87%* |
| |  | |  | |
| 4 | **1c** | **2a** | **5t** X=O | 89%*[c] |
| 5 | **1c** | **2m** | **5u** X=S | 97%[c] |
| 6 | **1c** | **2p** | **5v** X=CH($CO_2$Me)$_2$ | 69%*[c] |
| |  | |  | |
| 7 | **1d** | **2a** | **5w** X=O | 48% |
| 8 | **1d** | **2n** | **5x** X=NMe | 87% |
| |  | |  | |
| 9 | **1e** | **2m** | **5y** X=S | 53% |
| 10 | **1e** | **2n** | **5z** X=NMe | 41% |
| |  | |  | |
| 11 | **1f**[d] | **2m** | **5aa** X=S | 31% |
| 12 | **1f** | **2n** | **5ab** X=NMe | 40%* |
| |  | |  | |
| 13 | **1g** R=Me | **2m** | **5ac** R=Me | 80%[c] |
| 14 | **1h** R=Ph | **2m** | **5ad** R=Ph | 0% |
| |  | |  | |
| 15 | **1i** | **2m** | **5ae** X=S | 99%* |
| 16 | **1i** | **2o** | **5af** X=NPh | 68% |
| |  | |  | |
| 17 | **1j** | **2a** | **5ag** | 60%*[c] |
| |  | |  | |
| 18 | **1k** | **2n** | **5ah** | 94%* |

*Entries highlighted with an asterisk were reported previously (see Ref. 3).

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imines **1b**–**k** (1 equiv), benzoic acid **2a**–**p** (1.2 equiv), T3P (1.5 equiv), DIPEA (1.85 equiv) in PhMe at 90 °C for 20 h.

[b] Isolated yields after purification by column chromatography.

[c] Reaction performed at 120 °C for 20 h.

[d] Imine **1f** was generated by de-oligomerisation of dodecahydro-4a,8a,12a-triazatriphenylene in situ.

lead to hydrolysis of the product during aqueous work-up and during column chromatography. Nonetheless, significant quantities of material were isolated in all cases and indeed some of the yields (e.g., entries 2–5, 8) were excellent and comparable with those reported in Table 2.

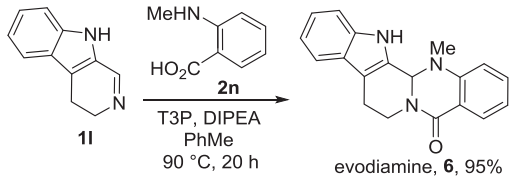
The coupling of imine **1f** was examined next. This imine, which exists primarily in its trimeric form dodecahydro-4a,8a,12a-triazatriphenylene,[9] is known to oligomerise and so must be generated in situ. Nevertheless, it reacted with acids **2m** and **2n** under the standard DIA conditions to form products **5aa** and **5ab**, albeit in moderate yield (entries 11 and 12). Note that none of the imine systems **1a**–**e** can tautomerise to enamines and it is significant that this comparatively unstable imine is also compatible with the standard DIA procedure.

Ketimine **1g** (which also is able to tautomerise to an enamine) is compatible with DIA, reacting with thiosalicylic acid **2m**, generating product **5ac** in good yield (entry 13). However, the analogous reactions using benzoic acids substituted with *O*-, *N*- and *C*-nucleophiles (**2a**, **2n** and **2p**, not shown in the table) did not furnish the expected products. Instead, C-acylation took place preferentially (presumably via the enamine tautomer of the imine), resulting in the predominant formation of *Z*-enaminones.[10] The analogous reaction with phenyl substituted ketimine **1h** (which cannot undergo such C-acylation) was also screened but this imine did not react at all with thiosalicylic acid **2m** (entry 14) or indeed with any of the benzoic acid derivatives **2a**, **2n** or **2p** (not shown in the table). This result is in line with previous studies, which also found that ketimines fail to undergo DIA with carboxylic acids bearing *O*-, *N*- or *C*-nucleophiles and this is most likely because the increased steric hindrance around the imine inhibits the requisite N-acylation reaction. The contrasting reactivity of thiosalicylic acid **2m** has intriguing mechanistic implications and is consistent with our previous work. Of the two successful DIA-type reactions of ketimines that were reported previously,[7] both involved thiol-substituted carboxylic acids, indicating that an alternative mechanism most likely operates. Thus, it seems likely that in sulfur-containing systems the nucleophilic thiol moiety attacks the imine carbon first, before intramolecular N-acylation takes place.[7] Additional support for this mechanism is found in the fact that partial product formation (20% yield) was observed in a related example even in the absence of T3P (Table 1, entry 14).

A significant advantage to DIA is its ability to generate acyclic *N*-acyliminium ions, which are far less stable than their cyclic analogues, particularly with respect to hydrolysis.[11] This means that *N*-acyliminium ion precursors are difficult to prepare and handle, but DIA technology overcomes this by forming the unstable *N*-acyliminium ions in situ, and trapping them in one pot. This is exemplified by the formation of DIA products **5ae**–**ag** in good to excellent yields from commercially available acylic imines **1i** and **1j** (entries 15–17). Note also that imine **1j** is a ketimine; *N*-substituted ketimines have so far proven to be incompatible with DIA but pleasingly this substituted ketimine furnished *N*,*O*-acetal **5ag** in good yield under standard DIA conditions at 120 °C (entry 17).

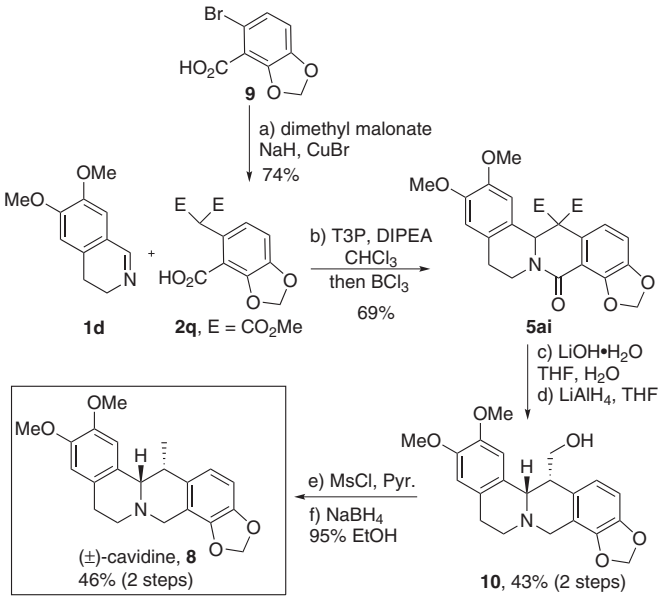
The high yielding DIA reaction of isoquinoline **1k** with anthranilic acid **2n** is significant given that it proceeds despite the loss of aromaticity (entry 18). Unfortunately, this dearomatising DIA reaction appears not to be general; the analogous reactions of isoquinoline **1k** with acids **2a**, **2m** and **2p** under identical conditions all failed to furnish any product. Other aromatic heterocycles containing C=N bonds (quinolone, pyridine, DMAP, pyrimidine, pyrazine, oxazole, thiazole, *N*-Boc imidazole and 1,3,5-triazine) were also examined under DIA conditions at 120 °C with anthranilic acid **2n** but no products were isolated in any case. Note that similar dearomatising reactions of isoquinolines have been reported,[12] and that the degree of aromaticity in the precursor is likely to be crucial in the outcome of these reactions.

Finally, the formation of the natural product evodiamine **6** from dihydrocarboline **1l** and anthranilic acid **2n** is a particularly noteworthy example (Scheme 2). Evodiamine is a key component in various weight-loss supplements and also is known to inhibit DNA topoisomerase I.[13] Its synthesis in 95% yield from two easily available coupling partners highlights well the potential of DIA in target synthesis.




**Scheme 2.** The total synthesis of evodiamine **6**.

Additional biologically important targets are also being pursued, e.g., cavidine **8**, a member of a large family of alkaloids known as protoberberines[14] with extremely broad biological activity.[15] Cavidine was first isolated from a *Corydalis* plant in 1964 by Taguchi[16] and its structure was later assigned by Manske.[17] Its synthesis has been completed previously,[18] but nonetheless, we considered that DIA methodology would expedite an efficient convergent synthesis (Scheme 3).




**Scheme 3.** The total synthesis of (±)-cavidine **8**.

To begin, commercially available bromide **9** was converted into the novel dimethyl malonate derivative **2q** via a known method based on the Hurtley reaction.[19] Acid **2q** was then reacted with imine **1d** using our standard DIA coupling conditions. We were pleased that the DIA was successful on this more complex system, furnishing lactam **5ai** in moderate yield (39%). Previous studies in our group have shown that in some cases, the addition of Lewis acids to the crude reaction mixture following N-acylation can lead to improved yields,[5] and therefore additional optimisation reactions were performed. The most common additive used in the DIA reactions reported to date is $BF_3 \cdot OEt_2$, but on this system it did not improve the isolated yield of product **5ai** (36%). However, switching the additive to $BCl_3$ (2 equiv) allowed product **5ai** to be obtained in 69% yield at RT in chloroform.[20] Importantly, the work-up for this reaction was straightforward and this result is easily

reproducible. It is also noteworthy that no competing demethylation products were observed.

The synthesis was then completed using an approach based on that in Cushman's route.[18c] Ester hydrolysis and decarboxylation using LiOH in aqueous THF followed by reduction with $LiAlH_4$, afforded alcohol **10** as a single diastereoisomer following column chromatography. Mesylation, followed by deoxygenation with $NaBH_4$ in refluxing ethanol[21] then completed the synthesis, affording (±)-cavidine **8**, the spectral data of which were in full accord with those previously reported (Scheme 3).[14j,k,18c]

## 3. Conclusion

A detailed substrate scoping study of the DIA reactions of a range of imines and *ortho*-substituted benzoic acids has been completed. The reaction has been shown to be very broad in scope, proceeds under operationally simple conditions and generally affords the desired product in good to excellent yield without optimisation of the reaction conditions. This should result in DIA being used for the construction of diverse compound libraries for biological evaluation. The total synthesis of (±)-cavidine was also completed; in this instance the DIA was low yielding under the standard conditions, but could be improved significantly by using a Lewis acid additive. The fact that the coupling reagents (T3P and DIPEA) are compatible with Lewis acid additives is significant as this allows such one-pot optimisation processes to be performed easily. The success of this example also augurs well for the similar optimisation of other DIA reactions (especially the lower yielding cases) further expanding its wide scope. This in turn is expected to lead to DIA being widely used in the synthesis of other biologically important natural product/drug targets.

## 4. Experimental section

### 4.1. General

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous dichloromethane and toluene were obtained from an Innovative Technology Pure Solv solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. Flash column chromatography was carried out using slurry packed silica gel ($SiO_2$), 35–70 μm, 60 Å, under light positive pressure eluting with the specified solvent system. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 $F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic *p*-anisaldehyde as appropriate. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Jeol ECX-400 NMR or Jeol ECS400 spectrometer operating 400 MHz and 100 MHz, respectively, or on a Bruker DRX500 spectrometer, operating at 500 MHz and 125 MHz, respectively. All spectra was acquired at 295 K. Chemical shifts ($\delta$) are quoted in parts per million (ppm). The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; multiplet; br, broad or combinations of these. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. The residual solvent peaks, $\delta_H$ 7.26 and $\delta_C$ 77.0 for $CDCl_3$ were used as references. Infrared spectra (IR) were recorded on a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either $CH_2Cl_2$ or $CDCl_3$. High Resolution Mass Spectra (HRMS) were obtained by University of York Mass spectrometer Service, using ionisation (ESI) on a Bruker Daltonics, MicrOTOF spectrometer. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Compounds **1i**–**k**, **2a**–**o** were all purchased from Sigma–Aldrich and used as supplied. Compounds **1a**,[3] **1b**,[3] **1c**,[8a] **1d**,[8b] **1e**,[8c] **1f**,[9] **1g**,[8d] **1h**,[8e] **1l**,[8f] **2p**,[3,22] **5a**,[3] **5c**,[3] **5d**,[3] **5i**–**k**,[3] **5m**,[3] **5n**,[3] **5p**,[3] **5s**,[3] **5t**,[3] **5v**,[3] **5ab**,[3] **5ae**,[3] **5ag**,[3] **5ah**,[3] **6**[3] were prepared using literature procedures.

### 4.2. General procedure for the DIA reaction

To a solution of imine (1 mmol) and acid (1.2 mmol) in dry toluene (10 mL) was added sequentially DIPEA (1.85 mmol) and then T3P (1.5 mmol, 50% in THF). The resulting solution was heated at 90 °C or 120 °C in a sealable tube for the specified time, before cooling to RT and pouring into satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with DCM (3×30 mL), concentrated in vacuo and purified by column chromatography.

*4.2.1. 6,6-Dibenzyl-4-nitro-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3]benzoxazin-11-one (**5b**).* Synthesised using the general DIA procedure from imine **1a** (56.1 mg, 0.213 mmol), acid **2b** (46.9 mg, 0.256 mmol), DIPEA (68.6 μL, 0.394 mmol) and T3P (204 mg, 0.320 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5b** as a colourless oil (81.1 mg, 89%); $R_f$ 0.43 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1647, 1589, 1506, 1449, 1311, 1275; $\delta_H$ (400 MHz, $CDCl_3$) 8.24 (1H, dd, *J*=7.7, 1.7 Hz), 8.19 (1H, dd, *J*=8.2, 1.7 Hz), 7.34–7.13 (11H, m, H-9), 5.31 (1H, s), 4.75–4.68 (1H, m), 3.35 (1H, d, *J*=13.4 Hz), 3.17 (1H, d, *J*=13.4 Hz), 2.85 (1H, d, *J*=13.4 Hz), 2.53–2.42 (2H, m), 2.18–2.05 (1H, m), 1.68–1.59 (2H, m), 1.50–1.40 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 159.4, 150.2, 137.0, 136.4, 136.1, 133.7, 131.2, 131.0, 130.2, 128.2, 126.6, 121.0, 118.2, 90.6, 43.2, 42.2, 40.9, 35.6, 27.6, 19.6; HRMS ($ESI^+$): Found: 429.1827; $C_{26}H_{25}N_2O_4$ ($MH^+$) Requires: 429.1809 (−4.3 ppm error).

*4.2.2. 6,6-Dibenzyl-2-chloro-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3]benzoxazin-11-one (**5d**).* Synthesised using the general DIA procedure from imine **1a** (66.9 mg, 0.254 mmol), acid **2d** (52.6 mg, 0.305 mmol), DIPEA (81.9 μL, 0.470 mmol) and T3P (242 mg, 0.381 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5d** as a white solid (46.7 mg, 96%); mp 198–201 °C; $R_f$ 0.29 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1668, 1608, 1475, 1441, 1325, 1283, 704; $\delta_H$ (400 MHz, $CDCl_3$) 7.90 (1H, d, *J*=2.7 Hz), 7.42 (1H, dd, *J*=8.8, 2.7 Hz), 7.34–7.20 (9H, m), 7.11–7.09 (1H, m), 7.05 (1H, d, *J*=8.8 Hz), 5.09 (1H, s), 4.68–4.62 (1H, m), 3.21–3.16 (2H, m), 2.86 (1H, d, *J*=13.5 Hz), 2.49–2.40 (2H, m), 2.18–2.04 (1H, m), 1.65–1.56 (2H, m), 1.42–1.31 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 161.4, 154.5, 137.0, 136.3, 134.2, 131.0, 131.0, 128.1, 128.1, 127.7, 127.3, 126.6, 126.6, 117.3, 117.2, 89.5, 42.5, 42.0, 41.4, 35.8, 27.6, 19.5; HRMS ($ESI^+$): Found: 418.1585; $C_{26}H_{25}^{35}ClNO_2$ ($MH^+$) Requires: 418.1568 (−3.9 ppm error).

*4.2.3. 6,6-Dibenzyl-3-methoxy-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3] benzoxazin-11-one (**5e**).* Synthesised using the general DIA procedure from imine **1a** (31.2 mg, 0.118 mmol), acid **2e** (23.9 mg, 0.142 mmol), DIPEA (38.0 μL, 0.219 mmol) and T3P (113 mg, 0.178 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (3:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded **5e** as a white solid (40.0 mg, 82%); mp 158–162 °C; $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1635, 1593, 1562, 1473, 1423, 1381, 1352, 1257, 1181; $\delta_H$ (400 MHz, $CDCl_3$) 7.85 (1H, d, *J*=8.6 Hz), 7.34–7.19 (8H, m), 7.13–7.09 (2H, m), 6.63–6.56 (2H, m), 5.06 (1H, s), 4.67–4.60 (1H, m), 3.90 (3H, s), 3.24–3.19 (2H, m), 2.89 (1H, d, *J*=13.7 Hz), 2.45–2.37 (2H, m), 2.16–2.03 (1H, m), 1.63–1.54 (2H, m), 1.42–1.28 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 164.8, 163.0, 157.8, 137.5, 136.6, 131.2, 131.2, 129.7, 128.2, 128.2, 126.6, 126.5, 109.5, 109.0, 100.2, 89.5, 55.8, 42.5, 41.8,

41.5, 35.9, 27.8, 19.8; HRMS ($ESI^+$): Found: 414.2076; $C_{27}H_{28}NO_3$ ($MH^+$) Requires: 414.2064 (−0.6 ppm error).

*4.2.4. 6,6-Dibenzyl-2-methoxy-6,7,8,9-tetrahydro-5aH,11H-pyrido [2,1-b][1,3] benzoxazin-11-one (**5f**).* Synthesised using the general DIA procedure from imine **1a** (37.0 mg, 0.141 mmol), acid **2f** (28.4 mg, 0.169 mmol), DIPEA (45.5 μL, 0.261 mmol) and T3P (135 mg, 0.212 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **5f** as a colourless solid (35.0 mg, 60%); mp 108–109 °C; $R_f$ 0.7 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1471, 1447, 1431, 1413, 1375, 1309, 1264, 1193, 692; $\delta_H$ (400 MHz, $CDCl_3$) 7.41 (1H, d, *J*=2.6 Hz), 7.33–7.16 (8H, m), 7.11–7.02 (4H, m), 5.01 (1H, s), 4.67–4.60 (1H, m), 3.81 (3H, s), 3.22–3.18 (2H, m), 2.92 (1H, d, *J*=13.9 Hz), 2.48–2.40 (2H, m), 2.17–2.05 (1H, m), 1.66–1.55 (2H, m), 1.38–1.28 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 163.1, 154.6, 150.2, 137.3, 136.5, 131.1, 131.0, 128.1, 126.4, 126.4, 122.4, 116.9, 116.5, 109.9, 89.1, 55.9, 42.2, 41.9, 41.5, 35.9, 27.6, 19.5; HRMS ($ESI^+$): Found: 414.2074; $C_{27}H_{28}NO_3$ ($MH^+$) Requires: 414.2064 (−2.8 ppm error).

*4.2.5. 6,6-Dibenzyl-1-methoxy-6,7,8,9-tetrahydro-5aH,11H-pyrido [2,1-b][1,3] benzoxazin-11-one (**5g**).* Synthesised using the general DIA procedure from imine **1a** (50.1 mg, 0.190 mmol), acid **2g** (38.3 mg, 0.228 mmol), DIPEA (61.3 μL, 0.352 mmol) and T3P (182 mg, 0.286 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (3:1→1:1 petrol:ethyl acetate→pure ethyl acetate) afforded **5g** as a white solid (51.0 mg, 64%); mp 186–187 °C; $R_f$ 0.29 (1:1 ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1581, 1560, 1457, 1432, 1248, 1090; $\delta_H$ (400 MHz, $CDCl_3$) 7.37 (1H, dd, *J*=8.3, 8.3 Hz), 7.03–7.14 (8H, m), 7.10–7.05 (2H, m), 6.72 (1H, d, *J*=8.3 Hz), 6.60 (1H, d, *J*=8.3 Hz), 4.95 (1H, s), 4.67–4.60 (1H, m), 3.91 (3H, s), 3.23 (1H, d, *J*=13.8 Hz), 3.19 (1H, d, *J*=13.4 Hz), 2.90 (1H, d, *J*=13.8 Hz), 2.47–2.37 (2H, m), 2.17–2.04 (1H, m), 1.65–1.53 (2H, m), 1.35–1.24 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 162.1, 160.7, 158.3, 137.5, 136.6, 134.3, 131.1, 128.1, 126.4, 126.3, 108.4, 109.5, 105.4, 88.4, 56.3, 42.0, 41.5, 41.4, 36.0, 27.5, 19.6; HRMS ($ESI^+$): Found: 414.2075; $C_{27}H_{28}NO_3$ ($MH^+$) Requires: 414.2064 (−2.8 ppm error).

*4.2.6. 6,6-Dibenzyl-1,3-dihydroxy-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3] benzoxazin-11-one (**5h**).* Synthesised using the general DIA procedure from imine **1a** (41.3 mg, 0.157 mmol), acid **2h** (35.7 mg, 0.188 mmol), DIPEA (50.9 μL, 0.290 mmol) and T3P (151 mg, 0.235 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (3:1→2:1 petrol:ethyl acetate) afforded **5h** as a white solid (39.0 mg, 60%); mp 135–136 °C; $R_f$ 0.57 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3269, 1619, 1589, 1491, 1471, 1441, 1293, 1257, 1137; $\delta_H$ (400 MHz, $CDCl_3$) 12.10 (1H, br s), 7.35–7.20 (8H, m), 7.10–7.06 (2H, m), 6.09 (1H, d, *J*=2.0 Hz), 6.01 (1H, d, *J*=2.0 Hz), 5.48 (1H, br s), 4.96 (1H, s), 4.55–4.47 (1H, m), 3.18 (1H, d, *J*=13.7 Hz), 3.17 (1H, d, *J*=13.4 Hz), 2.90 (1H, d, *J*=13.7 Hz), 2.46–2.37 (2H, m), 2.15–2.05 (1H, m), 1.67–1.55 (2H, m), 1.37–1.22 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 167.0, 162.8, 162.8, 157.5, 137.0, 136.3, 131.0, 128.2, 128.2, 126.6, 126.5, 97.2, 95.2, 93.8, 88.9, 42.1, 41.4, 41.1, 35.7, 27.4, 19.4; HRMS ($ESI^+$): Found: 416.1847; $C_{26}H_{26}NO_4$ ($MH^+$) Requires: 416.1856 (2.3 ppm error).

*4.2.7. 6,6-Dibenzyl-6,7,8,9-tetrahydro-5aH,11H-dipyrido[2,1-b:2′,3′-e][1,3]oxazin-11-one (**5l**).* Synthesised using the general DIA procedure from imine **1a** (43.0 mg, 0.163 mmol), acid **2l** (27.2 mg, 0.196 mmol), DIPEA (52.6 μL, 0.302 mmol) and T3P (156 mg, 0.245 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (3:1→petrol:ethyl acetate→pure ethyl acetate→ethyl acetate, 10% MeOH) afforded **5l** as an orange oil (39.1 mg, 63%); $R_f$ 0.23 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1654, 1450, 1415, 1382, 1314, 1228, 718; $\delta_H$ (400 MHz, $CDCl_3$) 8.47–8.43 (1H, m), 7.49–7.40 (2H, m), 7.34–7.19 (8H, m), 7.12–7.06 (2H, m), 5.19 (1H, s), 4.80–4.73 (1H, m), 3.25–3.17 (2H, m), 2.86 (1H, d, *J*=13.7 Hz), 2.55–2.42 (2H, m), 2.17–2.04 (1H, m), 1.64–1.56 (2H, m), 1.42–1.32 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 161.3, 153.6, 144.5, 136.9, 136.3, 133.7, 131.1, 131.1, 128.4, 128.3, 128.3, 126.8, 126.7, 124.3, 89.9, 42.7, 42.5, 41.5, 35.9, 27.8, 19.6; HRMS ($ESI^+$): Found: 385.1906; $C_{25}H_{25}N_2O_2$ ($MH^+$) Requires: 385.1911 (−1.1 ppm error).

*4.2.8. 6,6-Dibenzyl-5-phenyl-5,5a,6,7,8,9-hexahydro-11H-pyrido [2,1-b]quinazolin-11-one (**5o**).* Synthesised using the general DIA procedure from imine **1a** (38.0 mg, 0.144 mmol), acid **2o** (36.9 mg, 0.173 mmol), DIPEA (46.4 μL, 0.266 mmol) and T3P (137 mg, 0.216 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (2:1 petrol:ethyl acetate) afforded **5o** as a white solid (63.0 mg, 95%); $R_f$ 0.59 (ethyl acetate); mp 177–178 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1579, 1469, 1451, 1431, 1410, 1362, 1280, 1198, 739, 693; $\delta_H$ (400 MHz, $CDCl_3$) 8.05 (1H, dd, *J*=7.7, 1.5 Hz), 7.62–7.57 (2H, m), 7.52–7.46 (2H, m), 7.40–7.20 (5H, m), 7.13–6.92 (7H, m), 6.35 (2H, d, *J*=7.3 Hz), 5.21 (1H, s), 4.94 (1H, ddd, *J*=12.7, 2.1, 2.1 Hz), 3.27 (1H, d, *J*=13.9 Hz), 3.02 (1H, d, *J*=13.2 Hz), 2.58 (1H, d, *J*=13.2 Hz), 2.52 (1H, ddd, *J*=12.7, 12.7, 3.0 Hz), 2.52 (1H, d, *J*=13.9 Hz), 2.15–2.04 (1H, m), 1.62–1.55 (1H, m), 1.51–1.44 (1H, m), 1.19–1.09 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 162.4, 151.2, 147.8, 137.5, 137.3, 133.2, 131.4, 131.1, 130.1, 128.9, 128.4, 128.1, 127.9, 127.0, 126.4, 126.1, 121.8, 119.8, 119.7, 81.4, 47.9, 45.1, 38.5, 36.6, 30.9, 21.4; HRMS ($ESI^+$): Found: 459.2436; $C_{32}H_{31}N_2O$ ($MH^+$) Requires: 459.2431 (−1.2 ppm error).

*4.2.9. 3,3-Dibenzyl-1,2,3,3a-tetrahydro-9H-pyrrolo[2,1-b][1,3]benzoxazin-9-one (**5q**).* Synthesised using general the DIA procedure from imine **1b** (33.2 mg, 0.133 mmol), acid **2a** (22.1 mg, 0.160 mmol), DIPEA (42.9 μL, 0.246 mmol) and T3P (127 mg, 0.200 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (3:1 petrol:ethyl acetate) afforded **5q** as a yellow oil (23.7 mg, 48%); $R_f$ 0.27 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2980, 1647, 1587, 1446, 1412, 1329, 1195, 1083, 1059, 693; $\delta_H$ (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J*=7.7, 1.7 Hz), 7.40 (1H, ddd, *J*=8.2, 7.4, 1.7 Hz), 7.28–7.13 (8H, m), 7.07–7.00 (4H, m), 5.21 (1H, s), 3.49–3.37 (2H, m), 2.95 (1H, d, *J*=14.1), 2.96 (1H, d, *J*=13.8 Hz), 2.89 (1H, d, *J*=14.1 Hz), 2.73 (1H, d, *J*=13.8 Hz), 1.81 (1H, ddd, *J*=13.3, 6.7, 1.4 Hz), 1.62–1.56 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 161.3, 157.2, 137.4, 136.4, 134.0, 131.0, 130.9, 128.4, 128.4, 127.9, 126.8, 126.8, 122.7, 119.3, 116.7, 90.5, 48.0, 40.8, 40.2, 37.9, 26.4; HRMS ($ESI^+$): Found: 370.1792; $C_{25}H_{24}NO_2$ ($MH^+$) Requires: 370.1802 (2.7 ppm error).

*4.2.10. 3,3-Dibenzyl-1,2,3,3a-tetrahydro-9H-pyrrolo[2,1-b][1,3]benzothiazin-9-one (**5r**).* Synthesised using general the DIA procedure from imine **1b** (49.5 mg, 0.199 mmol), acid **2m** (36.7 mg, 0.238 mmol), DIPEA (64.0 μL, 0.367 mmol) and T3P (189 mg, 0.298 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5r** as a white solid (66.4 mg, 87%); $R_f$ 0.80 (3:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2874, 1620, 1567, 1424, 1387, 732, 694; $\delta_H$ (400 MHz, $CDCl_3$) 8.00 (1H, d, *J*=7.7 Hz), 7.32–7.25 (5H, m), 7.20–7.13 (7H, m), 6.98 (1H, d, *J*=8.0 Hz), 4.91 (1H, s), 3.77–3.72 (1H, m), 3.67–3.60 (1H, m), 3.10 (1H, d, *J*=13.6 Hz), 2.83 (1H, d, *J*=14.0 Hz), 2.78 (1H, d, *J*=14.0 Hz), 2.77 (1H, d, *J*=13.6 Hz), 1.78 (1H, ddd, *J*=12.3, 5.8, 0.9 Hz), 1.51–1.42 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 163.4, 137.1, 135.8, 134.8, 131.8, 130.9, 130.6, 129.9, 129.8, 128.4, 127.7, 126.9, 126.8, 126.0, 65.8, 49.8, 44.1, 41.1, 39.4, 27.1; HRMS ($ESI^+$): Found: 386.1574; $C_{25}H_{24}NOS$ ($MH^+$) Requires: 386.1573 (−0.2 ppm error).

*4.2.11. 13a-Methyl-5,13a-dihydro-6H, 8H-isoquinolino[1,2-b][1,3] benzothiazin-8-one (**5u**).* Synthesised using the general DIA

procedure from imine **1c** (37.7 mg, 0.287 mmol), acid **2m** (53.2 mg, 0.345 mmol), DIPEA (92.6 μL, 0.532 mmol) and T3P (274 mg, 0.431 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **5u** as a white solid (74.4 mg, 97%); $R_f$ 0.80 (2:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1664, 1656, 1618, 1579, 1434, 1358, 1290, 1216, 1126, 731; $\delta_H$ (400 MHz, $CDCl_3$) 8.19 (1H, ddd, *J*=7.7, 1.5, 0.6 Hz), 7.44–7.24 (7H, m), 6.24 (1H, s), 4.83–4.79 (1H, m), 3.24–3.11 (2H, m), 3.00–2.93 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 164.9, 137.8, 136.4, 131.8, 131.2, 130.8, 129.1, 128.9, 128.6, 127.7, 127.3, 127.0, 126.3, 60.7, 40.7, 29.6; HRMS ($ESI^+$): Found: 268.0611; $C_{16}H_{13}NNaOS$ ($MNa^+$) Requires: 290.0610 (−0.2 ppm error).

*4.2.12. 2,3-Dimethoxy-5,13a-dihydro-6H,8H-isoquinolino[1,2-b][1,3]benzoxazin-8-one (**5w**).* Synthesised using the general DIA procedure from imine **1d** (66.6 mg, 0.348 mmol), acid **2a** (57.7 mg, 0.418 mmol), DIPEA (112 μL, 0.644 mmol) and T3P (332 mg, 0.522 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (1:1 petrol:ethyl acetate) afforded **5w** as a white solid (51.6 mg, 48%); $R_f$ 0.33 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1641, 1587, 1494, 1446, 1394, 1247, 1209, 1095; $\delta_H$ (400 MHz, $CDCl_3$) 8.03 (1H, dd, *J*=7.8, 1.7 Hz), 7.48 (1H, ddd, *J*=8.2, 7.3, 1.7 Hz), 7.16 (1H, ddd, *J*=7.8, 7.3, 0.5 Hz), 7.08 (1H, dd, *J*=8.2, 0.5 Hz), 7.03 (1H, s), 6.71 (1H, s), 6.23 (1H, s), 4.58 (1H, ddd, *J*=12.8, 4.8, 3.5 Hz), 3.95 (3H, s), 3.92 (3H, s), 3.33 (1H, ddd, *J*=12.8, 11.3, 3.5 Hz), 3.05 (1H, ddd, *J*=15.6, 11.3, 4.8 Hz), 2.77 (1H, ddd, *J*=15.6, 3.5, 3.5 Hz); $\delta_C$ (100 MHz, $CDCl_3$) 163.1, 157.6, 150.0, 148.4, 134.2, 129.1, 128.7, 122.8, 122.4, 118.8, 116.6, 111.0, 110.6, 84.2, 56.2, 56.1, 38.4, 28.1; HRMS ($ESI^+$): Found: 334.1058; $C_{18}H_{17}NNaO_4$ ($MNa^+$) Requires: 334.1050 (−2.6 ppm error).

*4.2.13. 2,3-Dimethoxy-13-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[1,2-b]quinazolin-8-one (**5x**).* Synthesised using the general DIA procedure from imine **1d** (76.9 mg, 0.402 mmol), acid **2n** (73.0 mg, 0.483 mmol), DIPEA (130 μL, 0.744 mmol) and T3P (384 mg, 0.603 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (1:1 petrol:ethyl acetate) afforded **5x** as a colourless oil (114 mg, 87%); $R_f$ 0.54 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1583, 1492, 1446, 1401, 1342, 1318, 1241, 1215, 1094, 1001, 746; $\delta_H$ (400 MHz, $CDCl_3$) 8.07–8.04 (1H, m), 7.47–7.42 (1H, m), 7.13–7.09 (2H, m), 6.87 (1H, s), 6.67 (1H, s), 5.66 (1H, m), 4.64 (1H, ddd, *J*=12.8, 5.0, 2.7 Hz), 3.89 (3H, s), 3.88 (3H, s), 3.20–3.13 (1H, m), 2.95–2.87 (1H, m), 2.78–2.71 (1H, m), 2.47 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 164.6, 151.2, 149.1, 148.3, 133.0, 129.7, 128.9, 123.7, 122.9, 122.8, 121.0, 111.0, 110.8, 71.3, 56.2, 56.0, 39.1, 36.0, 28.3; HRMS ($ESI^+$): Found: 347.1361; $C_{19}H_{21}N_2NaO_3$ ($MNa^+$) Requires: 347.1366 (1.6 ppm error).

*4.2.14. 6,6-Dimethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]benzothiazin-12-one (**5y**).* Synthesised using the general DIA procedure from imine **1e** (38.8 mg, 0.267 mmol), acid **2m** (49.4 mg, 0.321 mmol), DIPEA (86.1 μL, 0.494 mmol) and T3P (255 mg, 0.401 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (19:1 petrol:ethyl acetate) afforded **5y** as a colourless oil (39.7 mg, 53%); $R_f$ 0.76 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2918, 1625, 1572, 1457, 1369, 1310, 1269, 1143, 1078, 739; $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, ddd, *J*=8.1, 1.0, 0.6 Hz), 8.22 (1H, ddd, *J*=7.8, 1.5, 0.5 Hz), 7.44–7.28 (4H, m), 7.21 (1H, ddd, *J*=7.5, 1.4, 0.6 Hz), 7.14 (1H, ddd, 7.4, 7.4, 1.1 Hz), 5.43 (1H, s, H-1), 1.53 (3H, s), 1.45 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 162.1, 140.2, 138.5, 135.1, 132.1, 130.4, 130.4, 128.3, 127.8, 126.4, 124.6, 121.8, 116.3, 73.4, 44.2, 27.6, 26.4; HRMS ($ESI^+$): Found: 282.0958; $C_{17}H_{16}NOS$ ($MH^+$) Requires: 282.0947 (−3.8 ppm error).

*4.2.15. 5,6,6-Trimethyl-5a,6-dihydroindolo[2,1-b]quinazolin-12(5H)-one (**5z**).* Synthesised using the general DIA procedure from imine **1e** (31.8 mg, 0.219 mmol), acid **2n** (39.7 mg, 0.263 mmol), DIPEA (70.6 μL, 0.405 mmol) and T3P (210 mg, 0.329 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (19:1 petrol:ethyl acetate) afforded **5z** as a colourless oil (25.0 mg, 41%); $R_f$ 0.64 (5:2 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2924, 1636, 1577, 1461, 1435, 1409, 1390, 741; $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, dd, *J*=8.0, 1.1 Hz), 8.10 (1H, dd, *J*=7.8, 1.7 Hz), 7.45 (1H, ddd, *J*=8.4, 7.3, 1.7 Hz), 7.31–7.27 (1H, m), 7.21 (1H, dd, *J*=7.5, 1.4 Hz), 7.13 (1H, ddd, 7.5, 7.5, 1.1 Hz), 6.96 (1H, ddd, *J*=7.8, 7.3, 0.8 Hz), 6.88 (1H, d, *J*=8.4 Hz), 4.98 (1H, s), 3.02 (3H, s), 1.70 (3H, s), 1.34 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 160.9, 149.5, 139.0, 138.8, 134.0, 128.6, 128.2, 124.5, 121.6, 119.3, 116.8, 116.8, 112.4, 85.2, 46.0, 34.8, 26.0, 23.3; HRMS ($ESI^+$): Found: 279.1492; $C_{18}H_{19}N_2O$ ($MH^+$) Requires: 279.1492 (−0.1 ppm error).

*4.2.16. 6,7,8,9-Tetrahydro-5aH,11H-pyrido[2,1-b][1,3]benzothiazin-11-one (**5aa**).*[23] Synthesised using the general DIA procedure from imine **1f** (47.3 mg, 0.190 mmol), acid **2m** (105 mg, 0.683 mmol), DIPEA (184 μL, 0.510 mmol) and T3P (544 mg, 0.854 mmol) in toluene (2 mL) at 90 °C for 20 h. Purification by column chromatography (5:0.5:0.5 petrol:ethyl acetate:$CH_2Cl_2$) afforded **5aa** as a white solid (39.0 mg, 31%); $R_f$ 0.76 (ethyl acetate); mp 52–54 °C (literature 53.5–54.5 °C);[23] $\nu_{max}$ (thin film)/$cm^{-1}$ 3062, 2939, 2858, 1635, 1440, 1275, 1204, 920, 742; $\delta_H$ (400 MHz, $CDCl_3$) 8.16 (1H, dd, *J*=7.7, 1.2 Hz), 7.35 (1H, ddd, *J*=7.7, 7.7, 1.2 Hz), 7.23 (1H, ddd, *J*=7.7, 7.7, 1.2 Hz), 7.18 (1H, dd, *J*=7.7, 1.2 Hz), 4.83 (1H, dd, *J*=10.8, 3.8 Hz), 4.50–4.59 (1H, m), 2.98 (1H, ddd, *J*=13.5, 11.8, 4.0 Hz), 2.10–2.01 (1H, m), 2.01–1.88 (2H, m), 1.87–1.75 (1H), 1.74–1.49 (2H, m); $\delta_C$ (100 MHz, CDCl3); 164.7, 134.8, 131.9, 130.6, 127.7, 126.4, 125.8, 59.0, 44.5, 31.9, 23.7, 23.1; HRMS ($ESI^+$): Found: 220.0792; $C_{12}H_{14}NOS$ ($MH^+$) Requires: 220.0791 (−0.8 ppm error).[23]

*4.2.17. 5,13a-Dihydro-6H,8H-isoquinolino[1,2-b][1,3]benzothiazin-8-one (**5ac**).* Synthesised using the general DIA procedure from imine **1g** (40.0 mg, 0.275 mmol), acid **2m** (51.0 mg, 0.330 mmol), DIPEA (88.7 μL, 0.510 mmol) and T3P (263 mg, 0.413 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5ac** as an orange oil (58.5 mg, 80%); $R_f$ 0.34 (5:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2879, 1657, 1618, 1609, 1564, 1422, 1366, 1332, 1275, 1231, 732; $\delta_H$ (400 MHz, $CDCl_3$) 8.15 (1H, ddd, *J*=7.8, 1.5, 0.5 Hz), 7.42 (1H, dd, *J*=7.8, 1.6 Hz), 7.35 (1H, ddd, *J*=7.7, 7.7, 1.6 Hz), 7.30–7.15 (5H, m), 5.04 (1H, ddd, 12.6, 9.7, 1.9 Hz), 3.03 (1H, ddd, *J*=15.4, 12.6, 9.7 Hz), 2.93 (1H, ddd, *J*=12.6, 12.6, 2.8 Hz), 2.86 (1H, ddd, *J*=15.4, 2.8, 1.9 Hz), 1.91 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 163.6, 135.8, 135.4, 134.8, 132.1, 130.9, 129.4, 128.2, 128.1, 127.3, 127.1, 126.2, 126.1, 65.9, 37.3, 29.7, 28.5; HRMS ($ESI^+$): Found: 304.0766; $C_{17}H_{15}NNaOS$ ($MNa^+$) Requires: 304.0767 (0.3 ppm error).

*4.2.18. 3-Methyl-1,2-diphenyl-2,3-dihydroquinazolin-4(1H)-one (**5af**).* Synthesised using the general DIA procedure from imine **1i** (24.6 μL, 0.200 mmol), acid **2o** (51.2 mg, 0.240 mmol), DIPEA (64.5 μL, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **5af** as a white solid (43.0 mg, 68%). Mp 220–223 °C; $R_f$ 0.57 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 1625, 1581, 1471, 1373, 1279, 1238, 1207; $\delta_H$ (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J*=7.9, 1.2 Hz), 7.37–7.24 (8H, m), 7.19–7.13 (3H, m), 6.96 (1H, ddd, *J*=7.9, 7.9, 1.1 Hz), 6.85 (1H, dd, *J*=8.2, 1.1 Hz), 5.96 (1H, s), 3.18 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 162.8, 146.1, 143.9, 139.3, 133.0, 129.8, 128.9, 128.8, 128.6, 126.5, 124.8, 123.3, 121.3, 120.5, 118.8, 80.0, 34.3; HRMS ($ESI^+$): Found: 315.1493; $C_{21}H_{19}N_2O$ ($MH^+$) Requires: 315.1492 (−0.5 ppm error).

*4.2.19. 5-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-1,3-benzodioxole-4-carboxylic acid (**2q**).* Sodium hydride (60% in mineral oil, 419 mg,

10.5 mmol) was added portionwise to a rapidly stirred cold suspension (0 °C) of 5-bromobenzo[1,3]dioxole-4-carboxylic acid **9** (1.00 g, 4.37 mmol), cuprous bromide (62.6 mg, 0.437 mmol) and dimethyl malonate (17.3 mL). After the addition of the sodium hydride had been completed, the mixture was stirred for 10 min at rt and then for 20 h at 70 °C. The suspension, which had turned to a solid mass, was dissolved in water (30 mL), washed with ether (3×80 mL) and then acidified with 10% HCl. The acidic aqueous layer, was extracted with ethyl acetate (3×100 mL), and the organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (5:1→pure ethyl acetate) afforded **2q** as a colourless solid (1.01 g, 74%); $R_f$ 0.1 (1:1 petrol:ethyl acetate); mp 88–93 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2912, 2877, 1704, 1688, 1456, 1431, 1216, 1137, 1039, 1012; $\delta_H$ (400 MHz, $CDCl_3$) 6.95 (1H, d, *J*=8.2 Hz), 6.88 (1H, d, *J*=8.2 Hz), 6.11 (2H, s), 5.53 (1H, s), 3.76 (6H, s); $\delta_C$ (100 MHz, $CDCl_3$) 169.2, 149.7, 148.5, 127.1, 123.9, 111.9, 107.3, 102.5, 100.0, 54.2, 53.0; HRMS ($ESI^+$): Found: 319.0424; $C_{13}H_{12}NaO_8$ ($MNa^+$) Requires: 319.0424 (0.2 ppm error).

*4.2.20. Dimethyl 8,9-dimethoxy-14-oxo-11,12-dihydro-6aH-[1,3]dioxolo[4,5-h]isoquino [2,1-b] isoquinoline-6,6(14H)-dicarboxylate (**5ai**).* To a solution of imine **1d** (484 mg, 2.53 mmol), and acid **2q** (900 mg, 3.04 mmol) in chloroform (25 mL) was added sequentially DIPEA (0.815 mL, 4.68 mmol) and T3P (2.42 g, 3.80 mmol, 50% solution in THF). The resulting solution was stirred for 20 min at rt before $BCl_3$ (5.10 mL, 5.10 mmol, 1.0 M solution in DCM) was added. The resulting solution was stirred at rt for 20 h before it was poured into satd aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (3×100 mL), dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography (1:1→1:2 petrol:ethyl acetate) to afford **5ai** as a yellow solid (819 mg, 69%); $R_f$ 0.5 (ethyl acetate); mp 152–156 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2908, 1707, 1626, 1588, 1494, 1440, 1412, 1103, 1029, 718; $\delta_H$ (400 MHz, $CDCl_3$) 6.91 (1H, d, *J*=8.1 Hz), 6.81 (1H, s), 6.69 (1H, s), 6.54 (1H, d, *J*=8.1 Hz), 6.22 (1H, d, *J*=1.3 Hz), 6.10 (1H, d, 1.3 Hz), 5.58 (1H, s), 4.85–4.78 (1H, m), 3.88 (3H, s), 3.87 (3H, s), 3.80 (3H, s), 3.51 (3H, s), 2.92–2.87 (2H, m), 2.67–2.64 (1H, m); $\delta_C$ (100 MHz, $CDCl_3$) 170.1, 167.0, 162.0, 149.0, 148.3, 148.2, 147.1, 131.6, 130.3, 123.1, 120.1, 112.2, 111.1, 110.9, 110.7, 102.7, 65.9, 61.2, 55.9, 55.7, 53.0, 52.9, 39.3, 28.9; HRMS ($ESI^+$): Found: 470.1454; $C_{24}H_{24}NO_9$ ($MH^+$) Requires: 470.1446 (−1.7 ppm error).

*4.2.21. (±)-cis-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)13-(hydroxymethyl) tetrahydro protoberberine (**10**).* To a round bottom flask containing diester **5ai** (106.5 mg, 0.227 mmol) in THF (0.7 mL), lithium hydroxide monohydrade (28.6 mg, 0.681 mmol) in water (0.7 mL) was added at rt. The reaction mixture was stirred for 16 h at 90 °C. The solution was diluted with water (10 mL), washed with DCM (10 mL) and then acidified with 10% aq HCl. The acidic aqueous layer was then extracted with ethyl acetate (3×20 mL), and the organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude reaction mixture was then added to a solution of $LiAlH_4$ (30.7 mg, 0.808 mmol) in THF (10 mL) and heated at 70 °C for 2 h, before it was cooled to 0 °C and quenched by the sequential addition of water (0.031 mL), 15% aq NaOH (0.031 mL) and water (0.092 mL). The resulting solids were removed by filtration and washed with EtOAc. The solids were then collected and refluxed in EtOAc for 2 h and filtered a second time. The combined filtrates were dried with $MgSO_4$ and evaporated. Purification by column chromatography (1:1 petrol:ethyl acetate→EtOAc) afforded **10** as a yellow solid; (35.7 mg, 43%); $R_f$ 0.6 (ethyl acetate); mp: 145–147 °C (literature 193–195 °C);[18c] $\nu_{max}$ (thin film)/$cm^{-1}$ 3261, 2924, 1609, 1516, 1462, 1360, 1257, 1232, 1209, 1138, 1044; $\delta_H$ (400 MHz, $CDCl_3$) 6.78 (2H, s), 6.64 (1H, br s), 6.61 (1H, br s), 6.01 (1H, d, *J*=1.5 Hz), 5.95 (1H, d, *J*=1.5 Hz), 4.14 (1H, d, *J*=15.2 Hz), 4.00 (1H, br s), 3.88 (3H, s), 3.66 (3H, s), 3.75 (1H, dd, *J*=10.4, 2.0 Hz), 3.58–3.54 (1H, m), 3.53 (1H, d, *J*=15.2 Hz), 3.19–3.15 (3H, m), 2.68–2.56 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) 147.8, 147.8, 145.5, 143.1, 131.0, 127.9, 126.3, 120.9, 117.2, 111.5, 108.4, 107.4, 101.2, 66.0, 63.4, 56.1, 55.9, 53.0, 51.2, 43.9, 29.0; HRMS ($ESI^+$): Found: 370.1632; $C_{21}H_{24}NO_5$ ($MH^+$) Requires: 370.1649 (4.4 ppm error); Obtained data in accord with those reported in the literature.[18c]

*4.2.22. (±)-cis-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)13-(methanesulfoxymethyl) tetrahydro protoberberine.* Methanesulfonyl chloride (23.8 μL, 0.308 mmol) was added to a solution of alcohol **10** (35.5 mg, 0.096) in pyridine (1 mL). The reaction mixture was stirred at rt for 1.5 h and then quenched with water (10 mL). The mixture was extracted with $Et_2O$ (3×20 mL). The organic extract was dried and evaporated. Purification by column chromatography (2:1→1:1 hexene:ethyl acetate→EtOAc) afforded the *title compound* as a yellow oil (25.5 mg, 68%); $R_f$ 0.9 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2936, 1517, 1462, 1353, 1334, 1172, 1142, 1041, 955, 730; $\delta_H$ (400 MHz, $CDCl_3$) 6.84 (1H, d, *J*=8.0 Hz), 6.75 (1H, s), 6.73 (1H, d, *J*=8.0 Hz), 6.61 (1H, s), 6.00 (1H, d, *J*=1.4 Hz), 5.97 (1H, d, *J*=1.4 Hz), 4.22–4.08 (3H, m), 3.92–3.86 (2H, m), 3.90 (3H, s), 3.88 (3H, s), 3.56–3.52 (2H, m), 3.11–3.00 (2H, m), 2.63–2.55 (1H, m), 2.62 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 147.8, 147.4, 145.3, 142.9, 132.9, 128.1, 126.3, 1261, 123.1, 111.4, 108.5, 106.7, 101.4, 72.4, 61.5, 56.2, 56.0, 53.2, 51.2, 43.7, 36.8, 29.2; HRMS ($ESI^+$): Found: 448.1427; $C_{22}H_{26}NO_7S$ ($MH^+$) Requires: 448.1424 (−1.3 ppm error).

*4.2.23. (±)-Cavidine (**8**).* To a solution of (±)-*cis*-2,3-dimethoxy-8-oxo-9,10-(methylenedioxy)13-(methanesulfoxymethyl) tetrahydro protoberberine (22.4 mg, 0.058 mmol) in 95% EtOH (3.5 mL) was added $NaBH_4$ (32.8 mg, 0.867 mmol). The resulting mixture was heated at reflux (80 °C) for 2 h and then poured into $H_2O$ (15 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3×20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to yield the crude product. Purification by column chromatography (5:1 hexane:ethyl acetate) afforded cavidine **8** as a white solid (13.6 mg, 67%); $R_f$ 0.4 (1:1 hexane:ethyl acetate); mp: 180–184 °C (literature 188–189 °C) $\nu_{max}$ (thin film)/$cm^{-1}$ 2909, 2757, 1514, 1457, 1333, 1356, 1254, 1228, 1042, 729; $\delta_H$ (400 MHz, $CDCl_3$) 6.72 (1H, d, *J*=8.0 Hz), 6.68 (1H, s), 6.67 (1H, d, *J*=8.0 Hz), 6.61 (1H, s), 5.97 (1H, d, *J*=1.5 Hz), 5.93 (1H, d, *J*=1.5 Hz), 4.09 (1H, d, *J*=15.3 Hz), 3.88 (3H, s), 3.88 (3H, s), 3.73 (1H, br s), 3.50 (1H, d, *J*=15.3 Hz), 3.28–3.22 (1H, m), 3.16–3.07 (2H, m), 2.63–2.57 (2H, m), 0.94 (3H, d, *J*=6.9 Hz); $\delta_C$ (100 MHz, $CDCl_3$) 147.6, 147.1, 144.6, 143.0, 135.9, 128.3, 128.3, 121.2, 116.8, 111.1, 108.5, 106.7, 101.0, 63.1, 56.1, 55.8, 53.3, 51.2, 38.5, 29.3, 18.4; HRMS ($ESI^+$): Found: 354.1683; $C_{21}H_{24}NO_4$ ($MH^+$) Requires: 354.1700 (4.3 ppm error); Obtained data in accord with those reported in the literature.[14j,k,18c]

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D.

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# An Expedient Protecting-Group-Free Total Synthesis of (±)-Dievodiamine

**William P. Unsworth,* Christiana Kitsiou, and Richard J. K. Taylor***

*Department of Chemistry, University of York, Heslington, York, YO10 5DD, U.K.*

*william.unsworth@york.ac.uk; richard.taylor@york.ac.uk*

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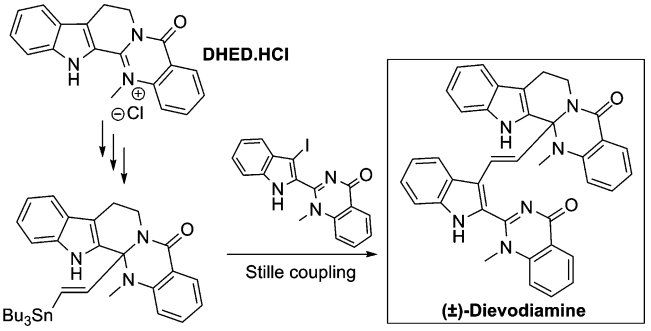
## ABSTRACT




**The first total synthesis of the *Evodia rutaecarpa* derived natural product dievodiamine is described. The convergent synthesis was performed without protecting groups, delivering a route that is short and high yielding and uses limited chromatography. Key steps include organometallic addition into a DHED adduct and the Stille coupling of two advanced intermediates to complete the synthesis.**

In recent years, protecting-group-free methods have received widespread attention as ways to improve the efficiency of synthesis. Furthermore, such an approach provides an 'opportunity for invention', as the development of novel synthetic methodology becomes necessary.[1] Herein we report the successful application of these principles in the first total synthesis of (±)-dievodiamine **1**.

Dievodiamine was recently isolated from *Evodia rutaecarpa*.[2] None of its biological properties have been reported, although the *Evodia* fruits are used in numerous traditional Chinese remedies to treat a wide range of conditions including headaches, abdominal pain, migraine, chill limbs, postpartum hemorrhage, nausea, inflammation, and cancer.[2] Its structure is closely related to evodiamine **2**, another *Evodia rutaecarpa* derived natural product, which was recently synthesized by our group using direct imine acylation methodology.[3] Evodiamine is a known thermogenic and stimulant and is included in a number of dietary supplements, principally used to promote weight loss. In addition, more recent studies have shown that it binds to a diverse range of proteins; its therapeutic potential against a number of diseases, including cancer, Alzheimer's disease, and cardiovascular disease, and its ability to inhibit human DNA topoisomerase I have been reported and reviewed.[4] Furthermore, a recent SAR study has shown evodiamine analogues to be highly promising antitumor candidates.[5] Dievodiamine **1** is not a simple dimer of evodiamine, as its name may suggest, but it does contain the basic framework of two evodiamine subunits (following oxidation and ring opening) suggesting that evodiamine **2** is a likely biosynthetic precursor.[6] Bisindole alkaloids constitute a major class of natural products, and their interesting biology has been well documented.[7] The isolation, synthesis, and biological evaluation of bisindole alkaloids remains a highly

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active area of research[8] with their potential antimalarial properties in particular receiving prominent attention recently.[8c–e] An unusual, although not unique,[8b] structural feature of dievodiamine is the ethylene bridge linking the two indole-containing portions. This is convenient from a synthetic viewpoint, as it provides a handle for a convergent synthesis, via the cross-coupling of two evodiamine-like fragments (Figure 1). With this in mind, and in view of the diverse biological profile of evodiamine and related compounds, we decided to embark on the total synthesis of (±)-dievodiamine, to confirm the reported structure and to enable its therapeutic potential to be better examined.

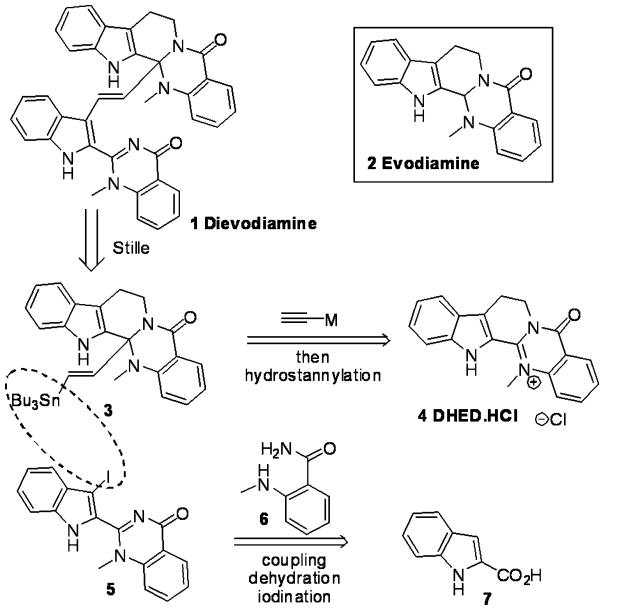



**Figure 1.** Retrosynthetic strategy.

Our convergent retrosynthetic strategy hinged upon the Stille reaction of two indole-containing fragments **3** and **5**. It was thought that the requisite stannane **3** could be obtained via the novel addition of a metalated alkyne into dehydroevodiamine hydrochloride (DHED·HCl, **4**), itself an alkaloid derived from *Evodia rutaecarpa*, followed by hydrostannylation. It was hoped that the 3-iodo-indole fragment **5** could be synthesized from 2-(methylamino)-benzamide **6** and commercially available indole-2-carboxylic acid **7** (Figure 1).

The synthesis began with the conversion of indole **8** into known lactam **9**[9] via a Curtius rearrangement and subsequent electrophilic aromatic substitution (Scheme 1). This was then converted to DHED·HCl **4** by heating with dimethyl anthranilate **10** and $POCl_3$, using a procedure modified from that of Decker.[10] In our hands, a particularly convenient purification was developed; the crude reaction mixture was poured into water, and the resulting precipitate was removed by filtration, rinsed with water, and dried, affording the desired quinazolinium salt **4** as a yellow solid in high yield. It was then planned to trap this adduct with an organometallic species. However, surprisingly little is known about the reactivity of DHED systems[11] and, to the best of our knowledge, there are no reports of C–C bond formation at the electrophilic carbon of any DHED. To test this idea, a small excess of ((trimethylsilyl)ethynyl)lithium was added to a suspension of DHED·HCl **4** in THF at −78 °C and allowed to warm to RT before quenching with water. As expected, only a trace amount of alkyne **11** was isolated, with the bulk of the starting material **4** recovered by filtration of the crude reaction mixture. In contrast, when 3 equiv of ((trimethylsilyl)ethynyl)lithium were used all of the starting material **4** was consumed and **11** was isolated cleanly, suggesting that 1 equiv of the organolithium species must deprotonate the indole, before the requisite nucleophilic addition takes place. Conveniently, the progress of the reaction could be monitored visually, as the mixture became homogeneous upon completion of the reaction. Following aqueous workup and treatment of the intermediate alkyne **11** with TBAF, alkynyl dihydroquinazolinone **12** was isolated in 90% yield over the two-step sequence. Of course, the TMS group present during this sequence necessitates a separate cleavage step and therefore does not satisfy the ideals of a protecting group-free synthesis. Thus, the same transformation was attempted using an excess of a lithium acetylide ethylenediamine complex. This was unsucessful, but the use of an excess of commercially available ethynylmagnesium chloride did give product **12**. Initial results were disappointing, however, as under the conditions described above the desired alkyne **12** was only isolated in trace amounts, with the bulk of the material remaining insoluble as the reaction progressed and was lost during aqueous workup. The poor solubility of DHED·HCl **4** was thought to be a limiting factor in this reaction, and pleasingly, when the solvent was switched to toluene, and lithium chloride[12] was included as an additive, alkyne **12** was isolated in a much improved yield following a single, truly protecting-group-free transformation. Finally, hydrostannylation with tributyltin hydride and AIBN in refluxing benzene completed the synthesis of stannane coupling partner **3**, which was isolated as a single regio- and stereoisomer in reasonable yield. It should be noted that column chromatography was only used in the final step of either of these three- or four-step sequences from lactam **9**.

(8) (a) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329. (b) Vougogiannopoulou, K.; Fokialakis, N.; Aligiannis, N.; Cantrell, C.; Skaltsounis, A.-L. *Org. Lett.* **2010**, *12*, 1908. (c) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864. (d) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706. (e) Vallakati, R.; May, J. A. *Synlett* **2012**, 2577. (f) Vallakati, R.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 6936. (g) Welch, T. R.; Williams, R. M. *Tetrahedron* **2013**, *69*, 770.

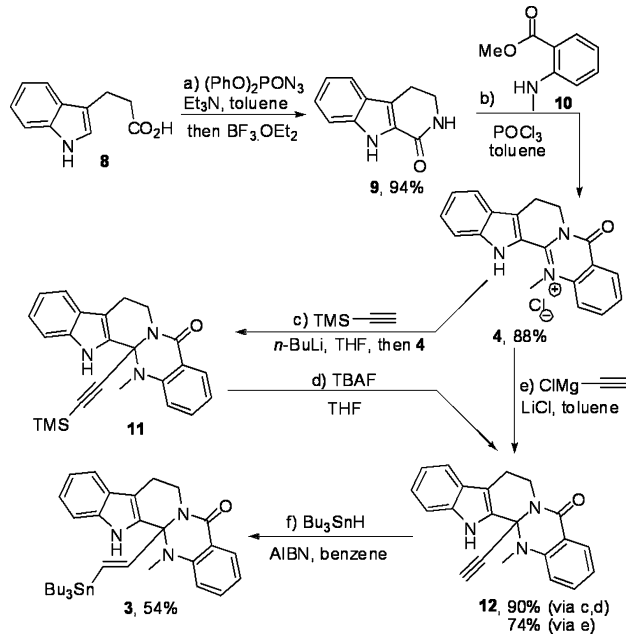
(9) Judd, K. E.; Mahon, M. F.; Caggiano, L. *Synthesis* **2009**, 2809.

(10) Decker, M. *Eur. J. Med. Chem.* **2005**, *40*, 305.

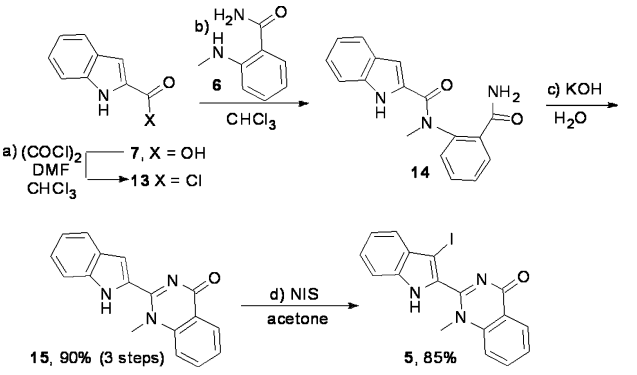
(11) Limited examples of reduction or hydrolysis reactions of DHED adducts can be found in refs 5 and 10.

(12) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

**Scheme 1.** Synthesis of Stannane **3**



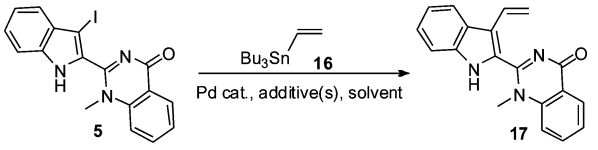

**Scheme 2.** Synthesis of Indole **5**




The synthesis of iodide coupling partner **5** was achieved extremely efficiently from commercially available indole-2-carboxylic acid **7**. Acid chloride formation was followed by reaction with aniline **6**[13] to form amide **14**, which was then heated at reflux in aqueous KOH.[14] The insoluble material was then collected by filtration, affording quinazolinone **15** in excellent yield over the three-step sequence. The synthesis of indole **5** was completed by reaction with *N*-iodosuccinimide in acetone, affording the desired product **5** in 77% overall yield from **7** (Scheme 2) following column chromatography. Note that this was the only chromatography required throughout the four-step synthesis, which could be performed on a multigram scale. The limited use of chromatography is an important feature in the syntheses of both coupling partners **3** and **5**, especially during scale-up. Unprotected indoles are often difficult to handle due to their relatively low solubility in many organic solvents, but pleasingly, we were instead able to exploit this property to our advantage by developing efficient workup conditions that may not have been possible had protecting groups been employed on the indole nitrogen atoms.

Conditions for the final Stille coupling were established using vinyl tributylstannane **16** with iodide **5** (Table 1). First, no reaction was observed following their treatment with $Pd(PPh_3)_4$ in refluxing THF (entry i). Baldwin's conditions,[15] which exploit the synergistic effect of CuI and CsF along with $Pd(PPh_3)_4$ in DMF, were also ineffective on this system, affording no product at 45 °C (entry ii) and led only to the partial reduction of iodide **5** (entry iii) and its eventual decomposition (entry iv) at elevated temperatures. The additive $Et_4NCl$, which is more commonly used as an additive in Heck reactions,[16] has found limited use in related Stille reactions,[17] but under the conditions trialled ($Et_4NCl$, $PdCl_2(PPh_3)_2$ at 80 °C in DMF, entry v) no reaction was observed. It was considered that the reason for the poor reactivity of **5** may be due to its steric bulk inhibiting the transmetalation step. Copper salts are known to accelerate sluggish Stille couplings by promoting an initial transmetalation of the organostannane to generate a more reactive organocopper intermediate.[18] Pleasingly when the additives CuI and $Et_4NCl$ were

**Table 1.** Optimization of Stille Conditions[a]




| entry | cat. | additives (equiv) | temp (°C)/ time (h) | outcome (yield)[c] |
|---|---|---|---|---|
| i[b] | A | none | 70/20 | no reaction |
| ii | A | CsF (2), CuI (0.1) | 45/1 | no reaction |
| iii | A | CsF (2), CuI (0.1) | 80/1 | 3:2 **15:5** |
| iv | A | CsF (2), CuI (0.1) | 100/1 | decomp. |
| v | B | $Et_4NCl$ (1.0) | 80/20 | no reaction |
| vi | B | $Et_4NCl$ (1.0), CuI (0.1) | 80/20 | **17** (10%) |
| vii | B | $Et_4NCl$ (1.0), CuI (1.5) | 80/2 | **17** (81%) |

[a] Reactions were performed on a 0.2−0.5 mmol scale using iodide **5** (1.0 equiv), stannane **16** (1.5 equiv), and a Pd catalyst [A = $Pd(PPh_3)_4$ or B = $PdCl_2(PPh_3)_2$, 0.05 equiv], with the additives and conditions shown, in DMF unless stated. [b] Reaction performed in THF. [c] Isolated yield following column chromatography.

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combined with $PdCl_2(PPh_3)_2$ and heated at 80 °C in DMF (entry vi), this led to the isolation of a small quantity of coupled product **17**. Furthermore, the yield was increased dramatically by using an excess of CuI (81%, entry vii).

Focus then switched to completing the synthesis of (±)-dievodiamine **1** (Scheme 3). The coupling of iodide **5** with stannane **3** was slower than with test substrate **17**, but nonetheless, the desired coupled product **1** was obtained in 35% yield using the conditions developed above with a 20 h reaction time. Furthermore, increasing the amounts of $PdCl_2(PPh_3)_2$ and $Et_4NCl$ (0.2 and 2.0 equiv respectively) led to a reduced reaction time (2 h) and a cleaner reaction mixture, allowing the target compound to be isolated in a much improved 65% yield following column chromatography and recrystallization.[19] The spectral properties of the synthetic material ($^1H$ and $^{13}C$ NMR data, IR, mass spectrum)[20] closely matched those reported for the natural product, with the $^{13}C$ NMR data being particularly conclusive (see Supporting Information), thus confirming its assigned structure.[2]

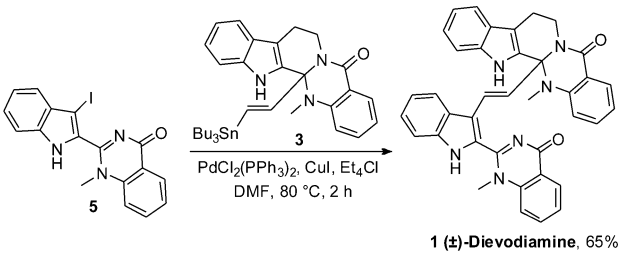
The first total synthesis of (±)-dievodiamine **1** has therefore been completed. The two key coupling partners **3** and **5** were each synthesized in just four steps, in 33% and 77% yield respectively, and the final Stille coupling completed the synthesis of this potentially valuable natural product in 65% yield. The brevity and efficiency of the synthesis was undoubtedly aided by the absence of protecting groups.

(18) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(19) A lower yield (22%) was obtained when $Et_4NCl$ was omitted under otherwise identical conditions, and no product was isolated in the absence of CuI, thus confirming the importance of both additives.

(20) We also obtained a melting point for **1**, but no literature melting point has been reported for comparison.

**Scheme 3.** Total Synthesis of (±)-Dievodiamine




Not only did this help to reduce the total number of steps, but also imparted suitable solubility properties that enabled us to minimize chromatography, thus facilitating scale-up. Key steps include the first example of an organometallic addition into a DHED adduct and a Stille reaction in which two sterically hindered components coupled using $PdCl_2(PPh_3)_2$ and the unusual combination of $Et_4NCl$ and CuI as additives. Future work will focus on testing the biological properties of dievodiamine and, if these results show promise, performing SAR studies on related analogues.

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**Supporting Information Available.** Synthetic procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

## Abbreviations

| | |
|---|---|
| Å | Ångstrom |
| AIBN | azobisisobutyronitrile |
| aq. | aqueous |
| Ar | aryl |
| ax | axial |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bu | butyl |
| Bz | benzoyl |
| CAN | cerium(IV) ammonium nitrate |
| cat. | catalyst |
| Cbz | carboxybenzyl |
| CDI | carbonyl diimidazole |
| conc. | concentrated |
| *p*-cymene | 4-isopropyltoluene |
| DAIB | diacetoxy-iodo-benzene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexyl carbodiimide |
| DCE | 1,1-dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| *de* | diastereomeric excess |
| DMAP | *N*,*N*-dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DIPEA | *N*,*N*-diisopropylethylamine |
| *dr* | diastereomeric ratio |
| EDC | 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide |
| *ee* | enantiomeric excess |
| eq | equatorial |
| eqn | equation |
| equiv. | equivalent(s) |
| ESI | electrospray ionisation |
| Et | ethyl |
| EWG | electron-withdrawing group |
| FAD | flavin adenine dinucleotide |
| h | hour(s) |
| HRMS | high resolution mass spectrometry |
| *i* | *iso* |
| IBX | 2-iodoxybenzoic acid |
| IR | infrared |
| LDA | lithium diisopropylamide |
| LG | leaving group |
| LHMDS | lithium bis(trimethylsilyl)amide |
| Lit. | literature |
| *m* | *meta* |
| M | molar |
| $M^+$ | parent molecular ion (in mass spectrometry) |
| Me | methyl |
| min | minute(s) |
| MOM | methoxymethyl |
| mp | melting point |
| MS | molecular sieves |
| Ms | methanesulfonyl (mesyl) |
| MW | microwave irradiation |
| *m/z* | mass/charge ratio |
| *n* | *normal* |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| NBS | *N*-bromosuccinimide |
| NIS | *N*-iodosuccinimide |
| NLS | (*S*)-norlaudanosoline synthase |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| *o* | *ortho* |
| OAc | acetate |
| OMs | methanesulfonate (mesylate) |
| OTf | trifluoromethanesulfonate (triflate) |
| *p* | *para* |
| PDC | pyridinium dichromate |
| Ph | phenyl |
| PMB | *p*-methoxybenzyl |
| PPA | polyphosphoric acid |
| Pr | propyl |
| quant. | quantitative |
| $R_f$ | retention factor |
| rt | room temperature |
| SAM | *S*-adenosyl methionine |
| sat. | saturated |
| SET | single-electron-transfer |
| STOX | (*S*)-tetrahydroprotoberberine oxidase |
| *t* | *tert* |
| TBAF | *tetra*-*n*-butylammonium fluoride |
| TBDMS | *tert*-butyldimethylsilyl |
| TBME | *tert*-butyl methyl ether |
| TEA | triethylamine |
| temp. | temperature |
| TFA | trifluoroacetic acid |
| Tf | trifluoromethanesulfonyl (triflyl) |
| THF | tetrahydrofuran |
| t.l.c | thin-layer chromatography |
| TMS | trimethylsilyl |
| Tsdpen | *N*-tosyl-1,2-diphenylethylenediamine |
| Ts | *p*-toluenesulfonyl (tosyl) |
| T3P | propane phosphonic acid anhydride |

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