Copper(II)-Mediated Oxidative Coupling Routes to Nitrogen-Heterocycles

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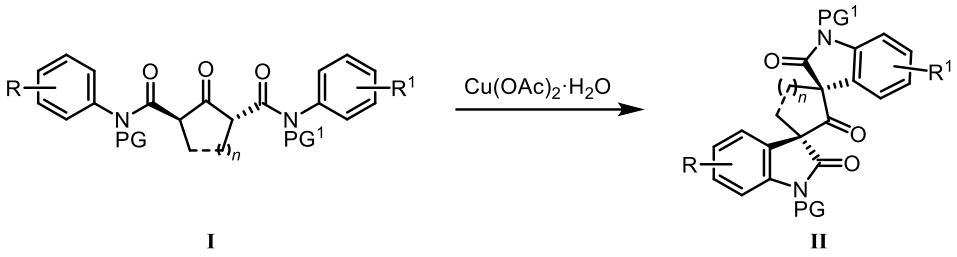
Abstract

Nitrogen-containing heterocycles have attracted considerable attention owing to their prevalence in numerous natural substances as well as their extensive applications in biology and pharmacology. In recent years, great efforts have been devoted to the elaboration of novel synthetic methodologies for the construction of *N*-heterocycles such as oxindoles and indoles.

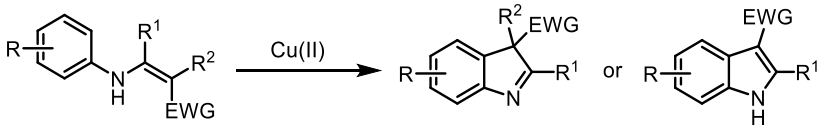
Reported in 2009 by the Taylor group, access to oxindole scaffolds has been successfully demonstrated *via* a copper(II)-mediated oxidative coupling approach. Following the same principle, the extension of this method to the formation of the more intricate bis-oxindole skeleton **II** is demonstrated *via* the double cyclisation of bis-anilides **I** using $Cu(OAc)_2 \cdot H_2O$ as oxidant (Scheme I, Chapter 2).



I **II**

Scheme I. Double copper(II)-mediated oxidative coupling approach to bis-oxindoles **II**.

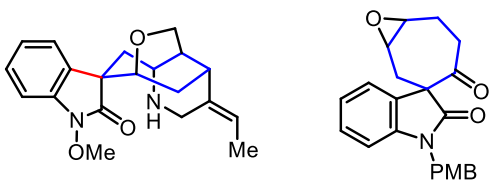
The scope of the copper(II)-mediated cyclisation to the formation of 3*H*-indoles **IV** and 1*H*-indoles **V** from *N*-aryl enamines **III** is also described (Scheme II, Chapter 3).



III **IV** ($R^2 \neq H$) **V** ($R^2 = H$)

Scheme II. Copper(II)-mediated oxidative coupling to 3*H*-indoles **IV** and 1*H*-indoles **V**.

In the last part, progress towards the total synthesis of the highly complex spirooxindole alkaloid natural product rankinidine (**VI**) is presented. Towards this end, the application of the copper(II)-mediated cyclisation for the formation of the oxindole core of rankinidine (**VII**) is presented (Chapter 4).



rankinidine (**VI**) **VII**

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Acknowledgments

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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 to oxindoles

1.1 Formation of 3,3-disubstituted oxindoles

1.1.1 Prevalence of biologically active oxindoles

Studies by the US Food and Drug Administration (US FDA) revealed that 59% of small-molecule drugs contain a nitrogen heterocycle,[1] a motif considered to be the most significant structural component of pharmaceuticals. Among the nitrogen-containing heterocycles, 3,3'-disubstituted oxindoles are versatile structural motifs found in a wide range of biologically active natural products and synthetic drugs (Figure 1.1).[2] Over the last decade, there has been significant resurgence in the synthesis of oxindoles as these structures represent excellent targets in the search for new drug candidates.[3] For example, oxindole **1** is a potent anti-cancer agent, whereas the 3-substituted 3-hydroxyoxindole is a key structural feature found in numerous alkaloid natural products (e.g. maremycin (**2**)). Similarly, 3-substituted 3-aminooxindoles such as **3**, are also an important type of structure present in a number of pharmaceutical candidates (e.g. AG-041R (**3**)).

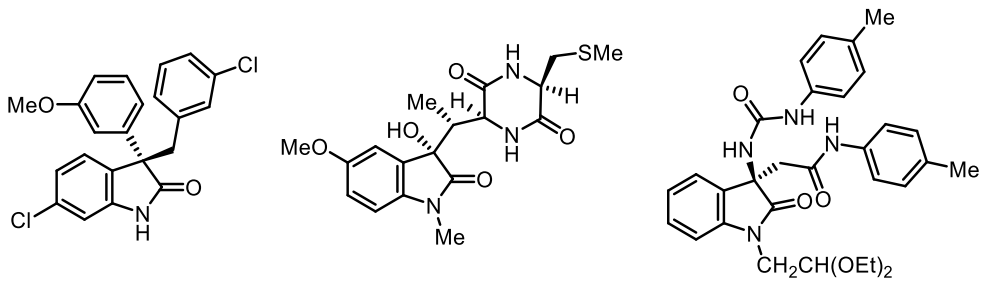
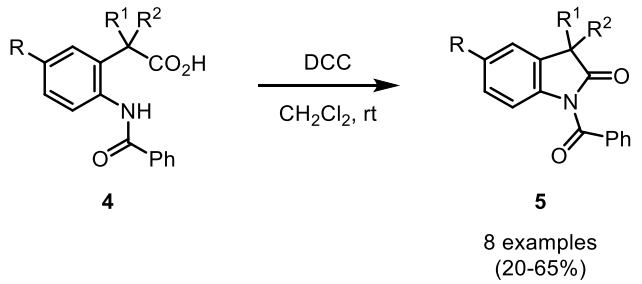


Figure 1.1. Biologically active oxindole scaffolds.

The significant biological activities observed for oxindoles emphasises the need to develop efficient synthetic strategies to access these scaffolds. Representing an important challenge for the synthetic community, numerous methods have been reported for the synthesis of oxindoles and reviewed by many groups,[2] therefore only recent and relevant examples will be discussed.

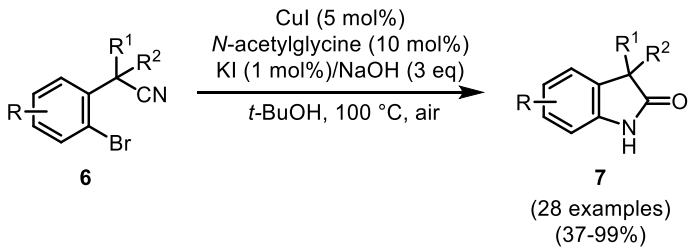
1.1.2 Synthesis of oxindoles through C–N bond formation

A convenient route to 3-substituted *N*-benzoyl oxindoles was reported by Prabhakar and co-workers.[4] The cyclisation was conducted from substrate **4**, containing both *N*-acyl-protected amine and carboxylic acid moieties using *N*,*N*'-dicyclohexylcarbodiimide (DCC) as coupling agent (Scheme 1.1). DCC-mediated dehydration of substrates **4** gave oxindoles **5** in moderate to good yields.



Scheme 1.1. Prabhakar's formation of oxindoles *via* DCC-dehydration.

A different example of a C–N disconnection strategy[5] for the formation of oxindoles was reported by the Hsieh group in 2012, which developed an intramolecular domino copper-catalysed coupling reaction from *ortho*-bromophenyl-methylenenitrile **6** to access oxindoles **7** (Scheme 1.2).[5a] The copper complex involved in the cyclisation was proposed to play two different roles by acting as a Lewis acid for the nitrile group and also by facilitating the C–N bond formation. Access to a wide range of unprotected oxindoles **7** was possible, in very high yields, with only a few exceptions.

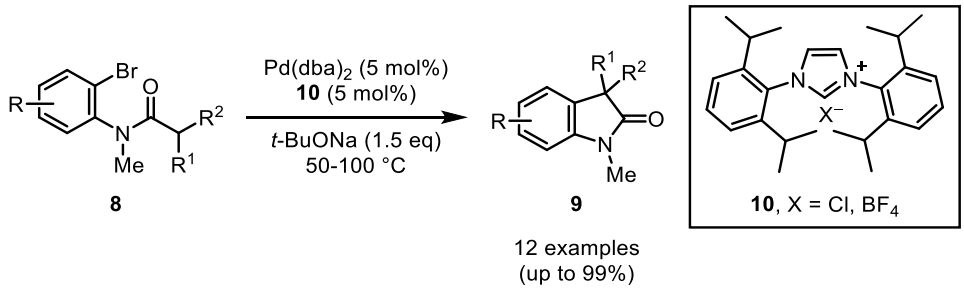


Scheme 1.2. Hsieh's copper-catalysed synthesis of oxindoles.

1.1.3 Synthesis of oxindoles through C3-C3a bond formation

1.1.3.1 A palladium-catalysed cyclisation to oxindoles

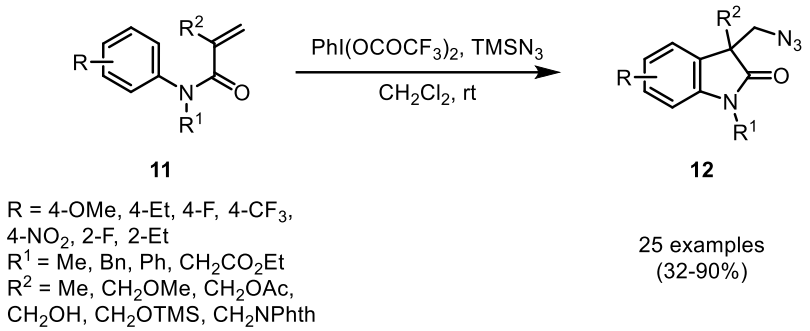
Recently, numerous methods have been reported for the synthesis of 3,3'-disubstituted oxindoles *via* a C3-C3a bond formation.[2d] The most common of these involve a palladium-mediated cyclisation of pre-functionalised linear *ortho*-halide precursors of type **8**. By way of example, the palladium-mediated cyclisation of *ortho*-bromoanilides **8** in the presence of bulky carbene ligand **10** provides access to oxindoles **9** in very good yield (Scheme 1.3).[6]



Scheme 1.3. Palladium-catalysed cyclisation of *ortho*-bromo anilides **8** to oxindoles **9**.

1.1.3.2 Antonchick's iodine-mediated cyclisation to oxindoles

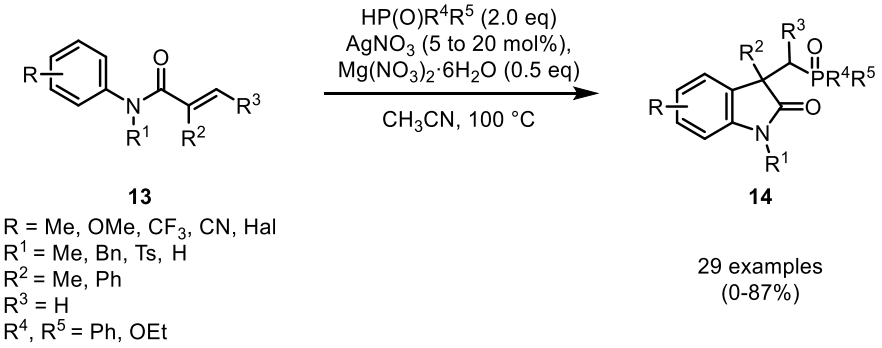
A variety of synthetic routes has been reported for the synthesis of oxindoles from *N*-arylacrylamides.[7] Recently, Antonchick *et al.* developed a different approach to obtain various oxindole derivatives by azidoarylation of alkenes.[8] Azidyl radicals, generated by oxidation of azides in the presence of hypervalent iodine(III) reagents, can easily be trapped with arenes such as compounds **11** to afford oxindoles **12** in very good yield, under metal-free reaction conditions and at ambient temperature (Scheme 1.4). Moreover, the resulting products with an appended azide group, can be used to create further molecular complexity around the privileged oxindole scaffold.



Scheme 1.4. Metal-free cyclisation for the synthesis of oxindoles **12**.

1.1.3.3 Yang's silver-catalysed route to phosphorylated oxindoles

With the same objective, Yang *et al.*, recently published a silver-catalysed carbon phosphorylation of alkenes which achieved direct cyclisation to give phosphorylated oxindoles **14**, potentially useful for insecticides or herbicides and as *P*,*O*-ligands for transition metal-catalysed reactions. Treatment of *N*-arylacrylamides **13** in the presence of silver(I) and $Mg(NO_3)_2{\cdot}6H_2O$ afforded oxindoles **14** in good yield (Scheme 1.5).[9] In the case of the *N*-unprotected and mono-substituted (R^2 = H) acrylamide, no conversion into oxindoles **14** was observed.



Scheme 1.5. Silver-catalysed carbon phosphorylation and direct C–H functionalisation to oxindoles **14**.

1.2 A copper(II)-mediated oxidative coupling route

1.2.1 The use of copper in the construction of *N*-heterocyclic compounds

In light of the biological importance of *N*-heterocycles, a range of efficient synthetic procedures for the formation of nitrogen-containing cyclic scaffolds have been developed. Recently, attention has turned to copper-mediated systems which benefit from the use of inexpensive, insensitive-to-air, non-toxic copper salts. The versatility of copper catalysts in the synthesis of five- and six-membered *N*-heterocycles, as well as fused-ring systems, was highlighted in a recent review by the Fu group.[10a] More recently, Zhang and co-workers reviewed the utility of copper in C–H functionalisation reactions for the construction of heterocycles.[10b]

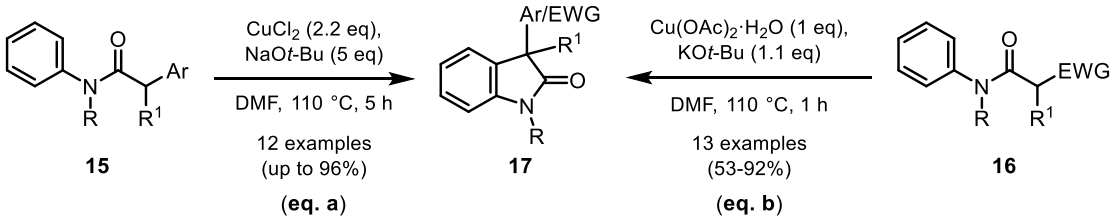
1.2.2 Copper-mediated oxidative functionalisation of C–H bonds

A review by the Stahl group highlighted the use of copper(II) as a versatile oxidant in the selective oxidation of C–H bonds.[11] By employing a source of copper(II) in combination with molecular oxygen, as a stoichiometric oxidant to regenerate the active copper(II) catalyst, many of these reactions can be performed catalytically. However, much work remains to understand the mechanism of the copper-catalysed C–H functionalisation reactions. Early studies highlighted the oxidative potential of copper(II) in a number of coupling reactions initiated by single electron transfer (SET).[12]

1.2.3 A stoichiometric Cu(II) oxidative coupling for the construction of oxindoles

A number of research groups have focused their attention on the development of improved methods for the synthesis of oxindoles *via* a direct intramolecular C–H, Ar–H coupling of non-prefunctionalised linear precursors. In 2009, Kündig and co-workers developed a copper(II) chloride-mediated cyclisation, which proceeds *via* the oxidative coupling of linear anilides **15** into oxindoles **17** in good yields (**eq. a**, Scheme 1.6).[13] The synthesis of oxindoles was performed under strictly anhydrous and inert reaction conditions. Subsequently, Taylor and co-workers developed a similar approach in which α-ester anilides **16** were converted into oxindoles **17** using a stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$ under basic conditions

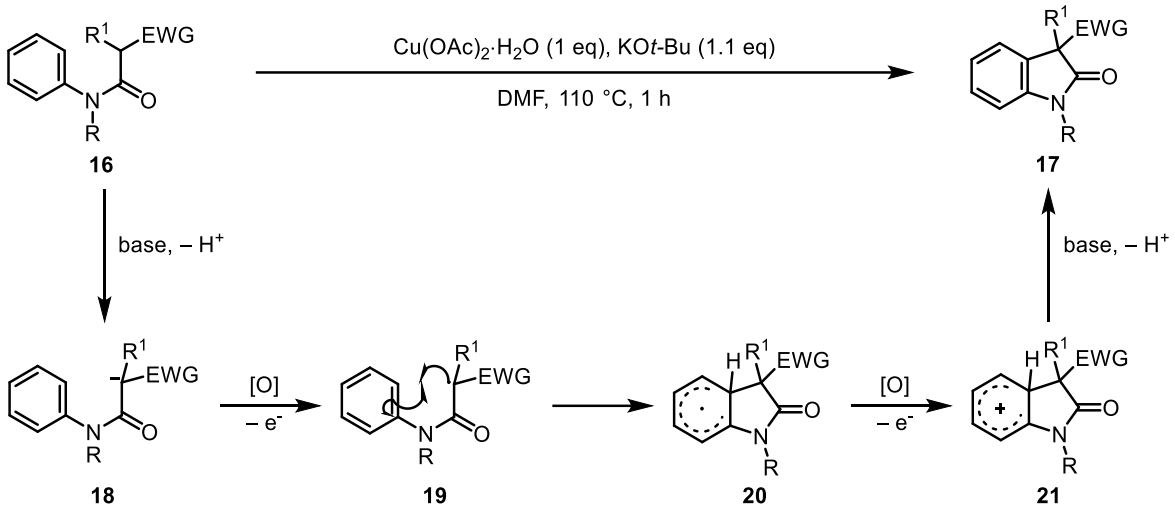
but without the need to rigorously exclude H_2O and air (**eq. b**, Scheme 1.6).[14] These procedures are valuable as an *ortho*-halo-anilide is not required for cyclisation.



Scheme 1.6. Copper(II)-mediated oxidative coupling routes to oxindoles from anilides.

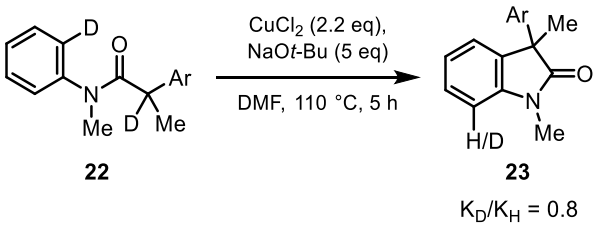
1.2.4 Proposed mechanism for the oxidative coupling route to oxindoles

The proposed mechanism for this process is depicted in Scheme 1.7. In the first step, radical **19** is formed by means of a single-electron oxidation of amide enolate **18**. At this point, intramolecular homolytic aromatic substitution affords the radical **20**, which is oxidised to generate the carbocation **21**, and upon rearomatisation, provides the oxindole product **17**.



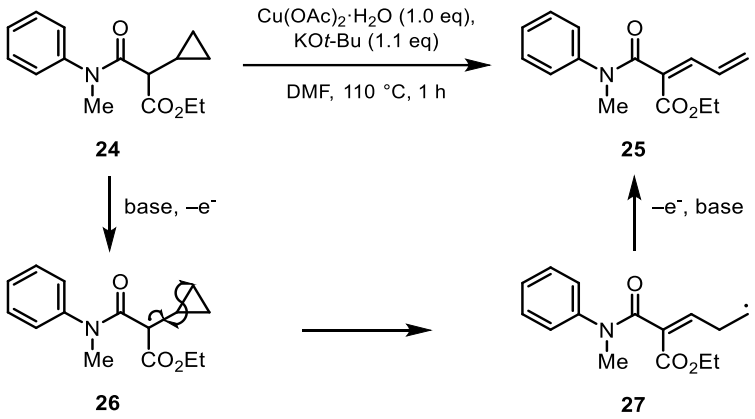
Scheme 1.7. Proposed mechanism for the copper(II)-mediated oxindole cyclisation.

In keeping with the proposed mechanism, Kundig and co-workers revealed the presence of a secondary isotope effect of $K_D/K_H = 0.8$, which indicated that the C–H bond cleavage in anilide **22** is not involved in the rate-determining step of the transformation into oxindole **23** (Scheme 1.8).[13]



Scheme 1.8. Secondary isotope effect in the copper(II) oxidative coupling.

A subsequent mechanistic study was carried out by the Taylor group using an anilide substrate containing a cyclopropyl radical probe such as **24** (Scheme 1.9).[14] Oxindole products were not formed, but instead, the dienyl anilide **25** was observed, resulting from the radical fragmentation of the cyclopropyl substituent in **26** into the radical species **27**. This information is consistent with the suggested radical amide-enolate intermediate formed in the first single-electron oxidation.

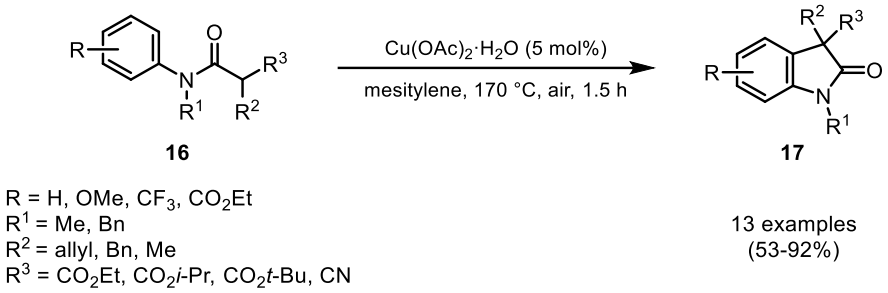


Scheme 1.9. Radical probe experiment in the copper(II) oxidative coupling reaction.

Also Kündig *et al.* confirmed the cyclisation proceeds *via* a radical pathway and determined the homolytic aromatic substitution as the rate-limiting step in the copper mediated oxindole synthesis using DFT calculations.[15]

1.2.5 A catalytic Cu(II) oxidative coupling for the construction of oxindoles

Subsequently, Taylor and co-workers reported a copper(II)-catalysed cyclisation of anilides **16** to form 3,3-disubstituted oxindoles **17** using $Cu(OAc)_2 \cdot H_2O$ (5 mol%) in boiling mesitylene under an air atmosphere (Scheme 1.10).[16] Compared to the previous conditions, the optimised catalytic conditions required no base additives, low catalyst loading, short reaction times and the reaction could be run open to air. Only a catalytic amount of copper is required for the transformation, as oxygen acts as the stoichiometric re-oxidant of the copper(I) species.



Scheme 1.10. Copper(II)-catalysed formation of 3,3-disubstituted oxindoles.

1.3 Formation of spirocyclic oxindoles

1.3.1 Prevalence of biologically active spirocyclic oxindoles

The spirocyclic oxindole moiety is remarkably important and is prevalent in many biologically active natural products, most of which have been isolated from *Apocynaceae* (oleander) and *Rubiacae* (coffee).[17] Over the last decade, there has been significant interest in the synthesis of spirocyclic oxindoles as these structures represent good targets in the search for new drug candidates.[18] Some examples of natural products **28**-**31** that contain the key ring system are outlined in Figure 1.2.

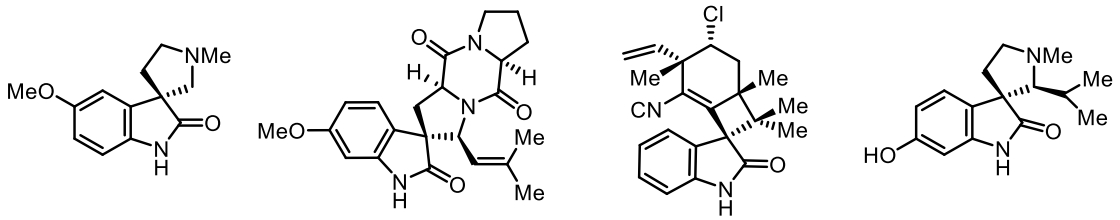
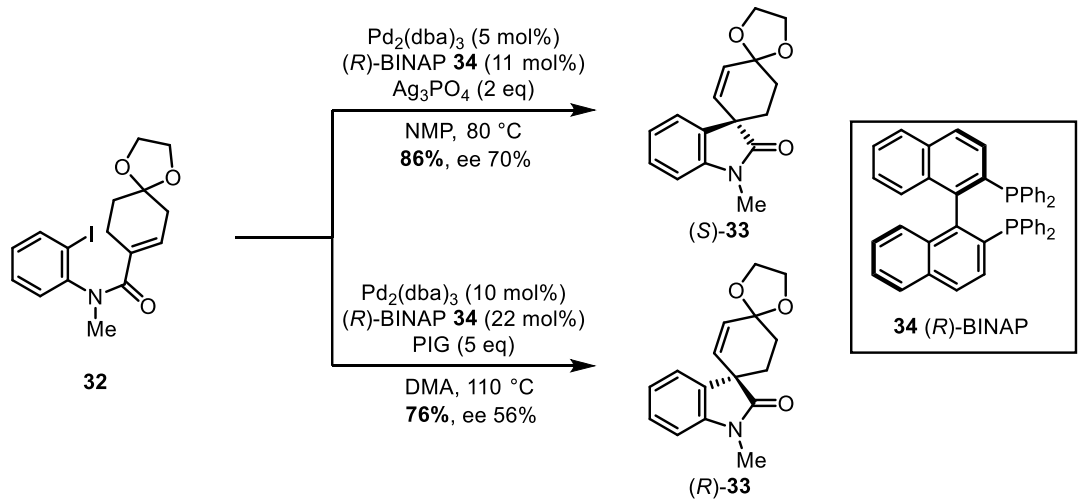


Figure 1.2. Spirocyclic oxindole alkaloids.

1.3.2 Palladium-mediated Heck cyclisation to spirocyclic oxindoles

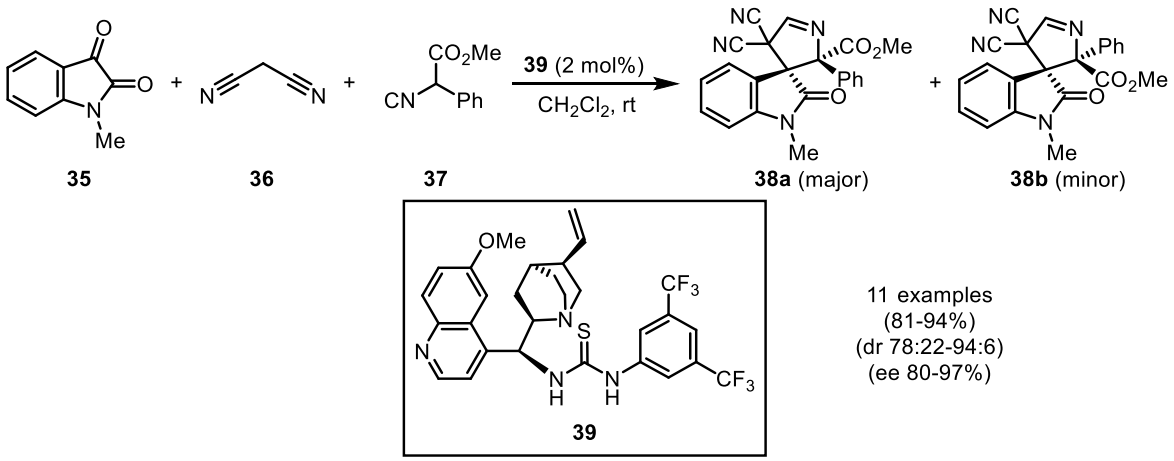
In 1998, Overman and co-workers reported the asymmetric Heck cyclisation of aryl halides **32** to prepare enantioenriched heterocycles **33** (Scheme 1.11).[19] The use of $Pd_2(dba)_3$ as a catalyst and (*R*)-BINAP (**34**) as a chiral ligand gave spirocyclic oxindoles **33** in good yields but moderate levels of enantioselectivity. The role of the additives used in the catalytic cycle was crucial for establishing the absolute configuration of the spirocyclic oxindole. While the addition of a silver salt led to the formation of the (*S*)-enantiomer, the use of a guanidine-derived additive to scavenge HI, namely 1,1,2,3,3-penta*iso*propylguanidine (PIG), resulted in the formation of the opposite enantiomer of the spirocyclic product. Thus, either enantiomer of the spirocyclic oxindole can be formed with good selectivity using a single enantiomer of a chiral diphosphine ligand.



Scheme 1.11. Overman's palladium-mediated synthesis of spirocyclic oxindoles **33**. PIG = 1,1,2,3,3-penta*iso*propylguanidine.

1.3.3 An organocatalytic asymmetric cascade reaction to spirocyclic oxindoles

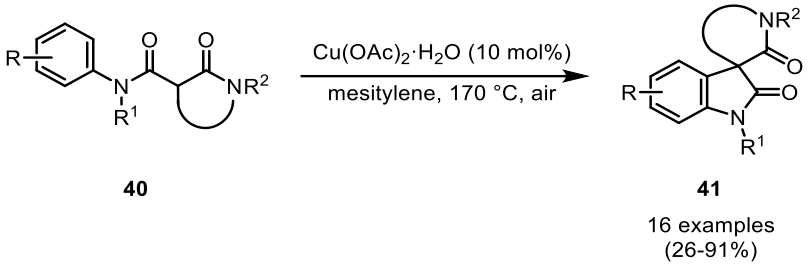
A number of excellent examples have been reported for the preparation of chiral spirooxindoles *via* organocatalytic cascade reactions.[20] In 2012, Yan *et al.* reported an organocatalytic three-component reaction of isatins **35**, malononitrile (**36**) and isocyanoacetates **37** in the presence of Takemoto's catalyst **39** which provides 3,3-dihydropyrryl-spirooxindoles **38a-b** in excellent yields and enantioselectivities (Scheme 1.12).



Scheme 1.12. Organocatalytic asymmetric cascade reaction to spirocyclic oxindoles.

1.3.4 A copper(II)-catalysed cyclisation reaction to spirocyclic oxindoles

The development of a spirooxindole cyclisation *via* a direct intramolecular C─H, Ar─H coupling methods has been studied by the Taylor group.[21] This method allows the installation of a quaternary carbon centre at the spirocyclic junction and constitutes an attractive approach for the preparation of oxindole-based natural products. As described previously, a copper(II) catalyst (10 mol%) in mesitylene at 170 °C for 30 to 90 minutes enables the cyclisation of linear substrates **40** to give spirocyclic oxindoles **41** in good yields (Scheme 1.13). The scope of the reaction was expanded by varying the size of the lactam ring (4 to 7-membered) attached to the oxindole unit at the C3 position, the nature of the *N*-protecting group as well as the benzene ring substitution pattern.



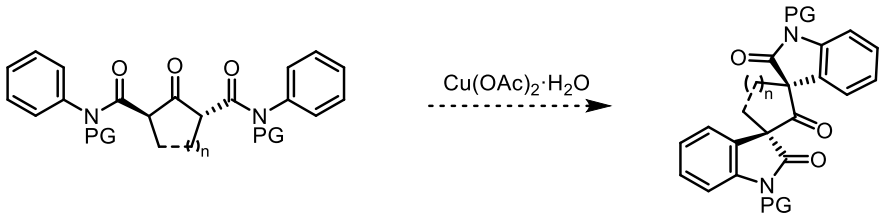
40 **41**

16 examples
(26-91%)

Scheme 1.13. Spirocyclic oxindole synthesis *via* a catalytic Cu(II)-mediated cyclisation.

1.4 Project background and aims

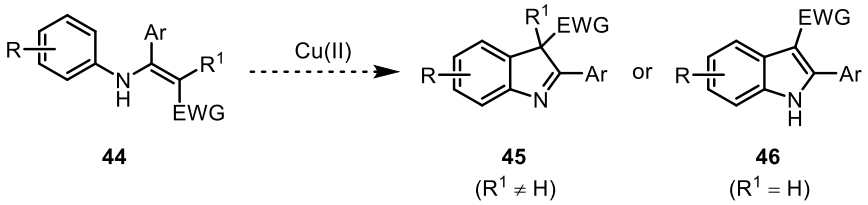
The facile entry to nitrogen-heterocycles inspired us to further demonstrate the utility of the copper(II) oxidative coupling into more complicated systems such as bis-oxindoles **43**. It was envisaged that the central core could easily be varied providing access to a range of bis-oxindoles **43** from bis-anilides **42** (Scheme 1.14). This research is discussed in Chapter 2



42 **43**

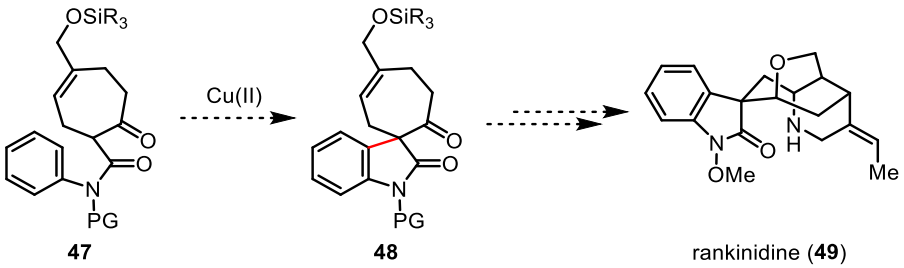
Scheme 1.14. $Cu(OAc)_2 \cdot H_2O$-mediated oxidative coupling route to bis-oxindoles **43** from bis-anilides **42**.

This route was additionally tested for the synthesis of indole derivatives, commonly found in a wide range of biologically active natural and unnatural compounds. It was proposed that the formation of 1*H*- and 3*H*-indoles would occur from the cyclisation of *N*-aryl enamines **44** to give the 3*H*-indoles **45** if $R^2 \neq H$ or the 1*H*-indoles **46** if $R^2 = H$ (Scheme 1.15). This research is discussed in Chapter 3.



Scheme 1.15. A copper(II)-mediated synthesis of 1*H*- and 3*H*-indoles.

Finally, the utility of the copper(II)-mediated oxidative coupling route was suggested as the potential key step for the total synthesis of the natural product rankinidine (**49**). Whereas the biological activity of rankinidine (**49**) has not been established yet, related natural products have shown potent medicinal properties. Access to the key spirooxindole **48** was envisioned from anilide **47**, and compound **48** appeared to be a useful intermediate for the total synthesis of rankinidine (**49**) (Scheme 1.16).



Scheme 1.16. Proposed application of the copper(II)-mediated cyclisation in the total synthesis of rankinidine (**49**).

Chapters 2–4 describe the results in each area, and each Chapter contains a more detailed introduction and discussion.

Chapter 2. The synthesis of bis-oxindole derivatives

2.1 Introduction

2.1.1 Chemical and biological importance of bis-oxindoles

Oxindoles are privileged structural motifs that exist in many natural products and synthetic compounds of biological interest.[3, 22] They have therefore attracted great attention from synthetic and medicinal chemists and as a result, a multitude of efficient methods are now available for the creation of the oxindole core.[2]

More recently, structurally challenging bis-oxindoles have emerged as potentially useful scaffolds in medicinal chemistry and diversity-oriented synthesis. With regard to medicinal applications, the novel piperidone-containing bis-spirooxindoles (**50**, Ar = 2,4-$Cl_2C_6H_3$, Figure 2.1) and (**51**, Ar = 1-naphthyl) were evaluated as potent and selective cholinesterase inhibitors, towards AChe and BuChe respectively.[23] Recently discovered, the synthetic dispirooxindole-pyrrolidine **52** has been shown to possess significant anti-bacterial and anti-cancer activities (againgst A549 human lung adenocarcinoma).[24] Of natural complexity, geleganimine B (**53**) was extracted recently from the plant *Gelsemium elegans* and exhibited neural anti-inflammatory activity.[25]

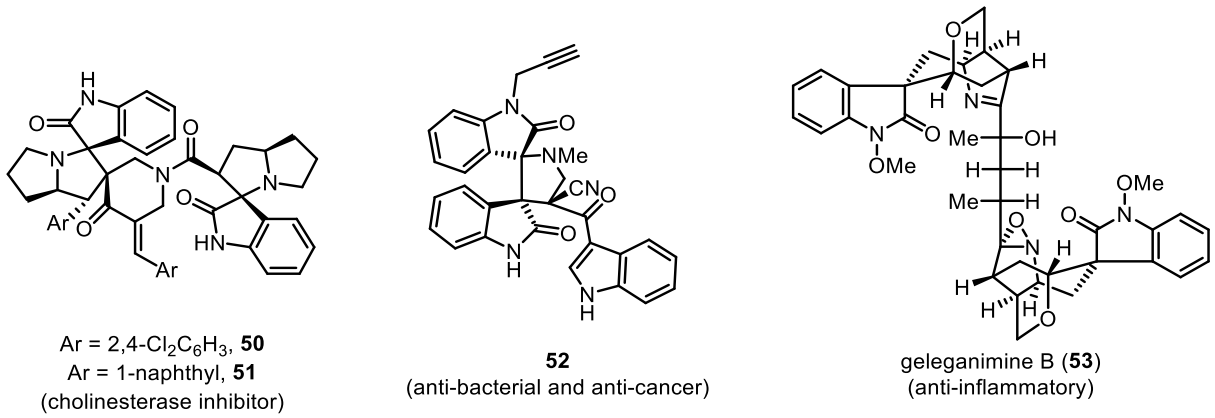
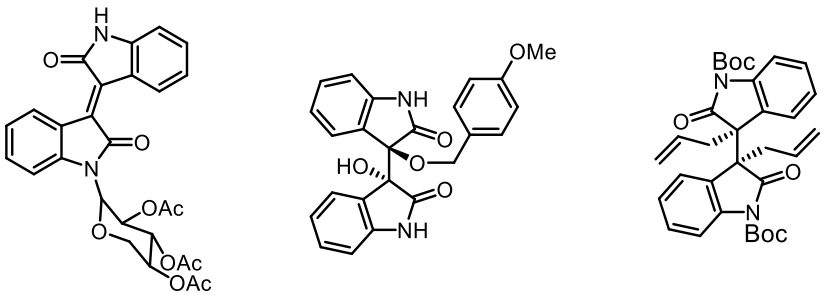


Figure 2.1. Spirocyclic bis-oxindoles as bioactive natural products and synthetic compounds.

Non-spirocyclic bis-oxindole derivatives are also important for having potent biological activities. By means of example, the anti-cancer agent Natura (**54**, Figure 2.2) has been

shown to inhibit several cyclin dependent kinases (CDKs).[26] Bis-oxindole **55** displayed considerable activity against both Gram positive and Gram negative bacteria.[27] Also of considerable interest, bis-oxindoles such as the cyclotryptamine intermediate **56**, have been widely used as useful synthetic intermediates in the synthesis of more complicated natural products.[28]



54
Natura
(anti-cancer agent)

55
(anti-bacterial)

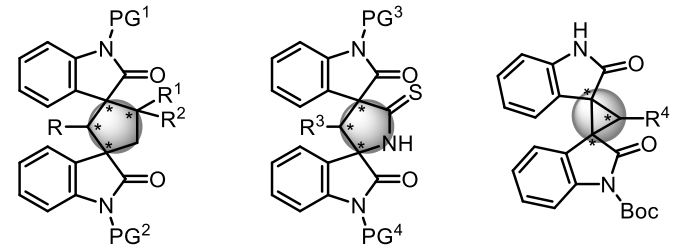
56
(cyclotryptamine intermediate)

Figure 2.2. Some biologically relevant synthetic compounds containing a bis-oxindole scaffold.

2.1.2 Formation of spirocyclic bis-oxindoles by organocatalytic processes

The significant biological activities of the bis-oxindole architecture have led to a great demand for efficient synthetic strategies for their construction. Rapid access to structurally diverse products from accessible building blocks represents a great achievement for the synthetic chemist. In that matter, a number of organocatalytic asymmetric cascade reactions have been developed for the construction of bis-spirooxindole motifs, which contain cyclopentane (**57**), thiopyrrolidine (**58**), and cyclopropane (**59**) central cores (Figure 2.3). Also, the formation of a tetrahydro-β-carboline moiety resulting from a Michael/Pictet-Spengler cascade reactions between two isatin-derived substrates was successfully accomplished using a chiral phosphoric acid as the organocatalyst.[29] The construction of a dihydrofuran linker was performed using a cinchona-derived alkaloid as the organocatalyst.[30]

While the formation of spirocyclic bis-oxindoles with high level of stereocontrol was successfully demonstrated using organocatalytic processes, they can also be prepared by photochemical [2+2]-cycloadditions,[31a] and by multicomponent reactions (MCR).[31b]



57 (spirocyclopentane bis-oxindoles)

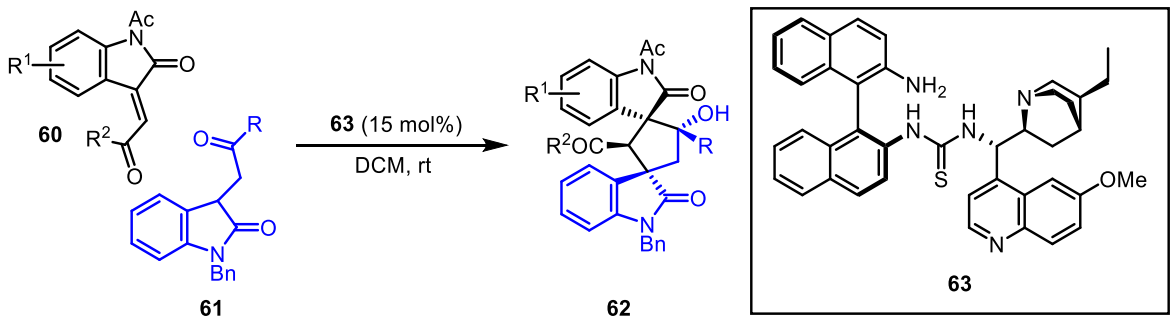
58 (spirothiopyrrolidine bis-oxindoles)

59 (spirocyclopropane bis-oxindoles)

Figure 2.3. Range of spirocyclic bis-oxindoles accessed by organocatalysis.

2.1.2.1 Synthesis of spirocyclopentane bis-oxindoles

Remarkable advances have been recently made on the enantioselective synthesis of the spirocyclopentane bis-oxindole scaffold. Initially, Barbas III *et al.* developed an organocatalytic asymmetric construction of the bis-spirooxindole motif **62** (Scheme 2.1).[32] Extraordinary levels of stereocontrol over four stereocentres were achieved from the domino Michael/aldol reaction between 3-substituted oxindoles **61** and methyleneindolinones **60**. For this purpose, the cinchona-derived catalyst **63** was designed and contained a crucial binaphthyl primary amine, a thiourea and a tertiary amine, speculating that the thiourea would bond with the oxindole unit *via* multiple hydrogen-bonding interactions. Concurrently, the ketone or ester functionalities from the methyleneindolinone were suggested to coordinate to the tertiary amine group and the binaphthyl primary amine.



61

R = Ph, 2-furanyl, 2-thiophenyl, Me
R^1 = H, 5-Hal
R^2 = C_6H_5, 4-ClC_6H_4, 2-MeC_6H_4

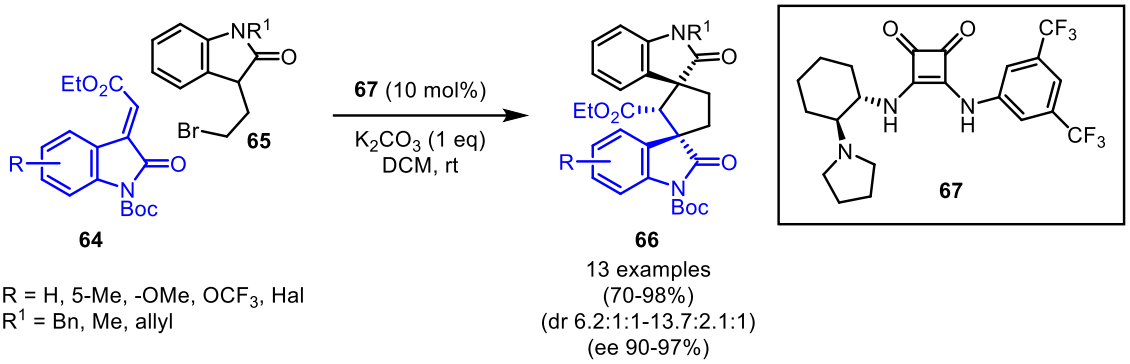
62

12 examples
(56-94%)
(dr 63:37-99:1)
(er 91:9-98:2)

63

Scheme 2.1. Barbas' organocatalytic asymmetric domino Michael/aldol approach to spirocyclic bis-oxindoles.

Subsequently, Wang and co-workers reported in 2012 a different approach to the development of spirocyclopentane bis-oxindole skeleton **66** with three contiguous stereocentres *via* an organocatalytic domino Michael/alkylation strategy, starting from methyleneindolinones **64** and 3-substituted oxindoles **65** (Scheme 2.2).[33] Their approach uses a chiral squaramide organocatalyst **67** represented in Scheme 2.2, and proceeded in good yields, enantioselectivities, but with moderate control over the relative configuration of the pentacyclic adduct **66**. However, the possibility of isolating all diastereoisomers by column chromatography ensured the synthetic utility of this process.



R = H, 5-Me, -OMe, OCF_3, Hal
R^1 = Bn, Me, allyl

13 examples
(70-98%)
(dr 6.2:1:1-13.7:2.1:1)
(ee 90-97%)

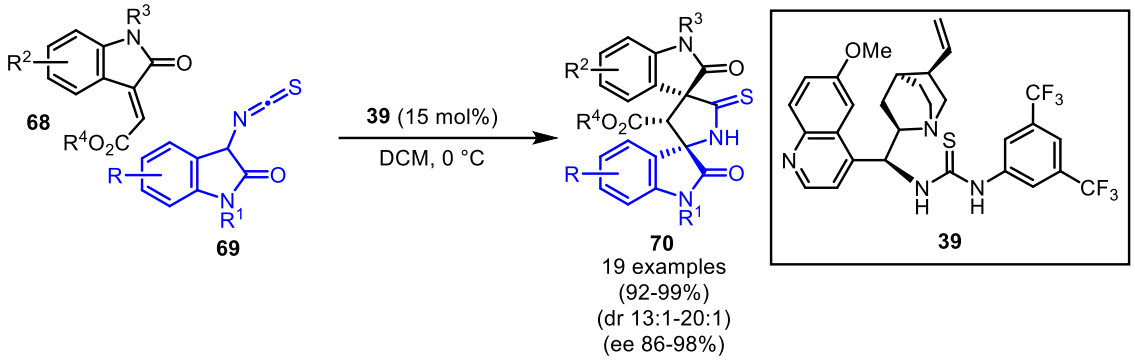
Scheme 2.2. Wang's organocatalytic asymmetric domino Michael/alkylation approach to spirocyclic bis-oxindoles.

More recently, the same group reported an organocatalytic Michael/Michael cascade for the enantioselective construction of spirocyclopentane bis-oxindoles bearing four contiguous stereocentres.[34] Better control over the diastereoselectivity of the transformation was achieved using a different organocatalyst, a chiral squaramide derived from quinidine.

2.1.2.2 Synthesis of spirothiopyrrolidine bis-oxindoles

In view of increasing the diversity in the scope of the organocatalytic asymmetric Michael/cyclisation reaction, a similar approach was investigated aiming for the formation of spirocyclic thiopyrrolidine bis-oxindoles.[35] Amongst all examples, one was reported by Wang and co-workers in 2013, in which high conversion and level of stereocontrol was obtained for the synthesis of spirothiopyrrolidine bis-oxindoles **70** from the reaction between 3-isothiocyanato oxindoles **69** and methyleneindolinones **68** using the quinine-derived organocatalyst **39** (Scheme 2.3).[35a] Looking at the extended range of spirothiopyrrolidine

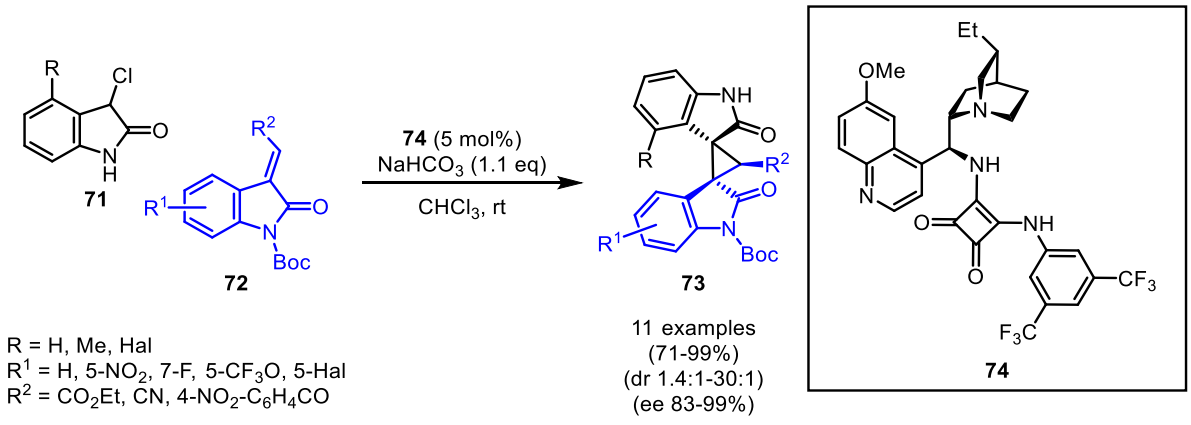
bis-oxindoles synthesised as well as the very high yields and stereocontrol reported,[35] 3-isothiocyanato oxindoles appear to represent ideal building blocks for such a process.



Scheme 2.3. Wang's organocatalytic approach to spirothiopyrrolidine bis-oxindoles.

2.1.2.3 Synthesis of spirocyclopropane bis-oxindoles

Another organocatalytic example was reported by Kanger *et al.* in 2013, who developed a one-pot asymmetric synthesis of spirocyclopropane bis-oxindoles **73** from 3-chlorooxindoles **71** and methyleneindolinone derivatives **72** (Scheme 2.4).[36] Derived from cinchona alkaloids, the squaramide organocatalyst **74** gave access to a wide range of bis-spirooxindoles with excellent yields and high levels of stereocontrol.



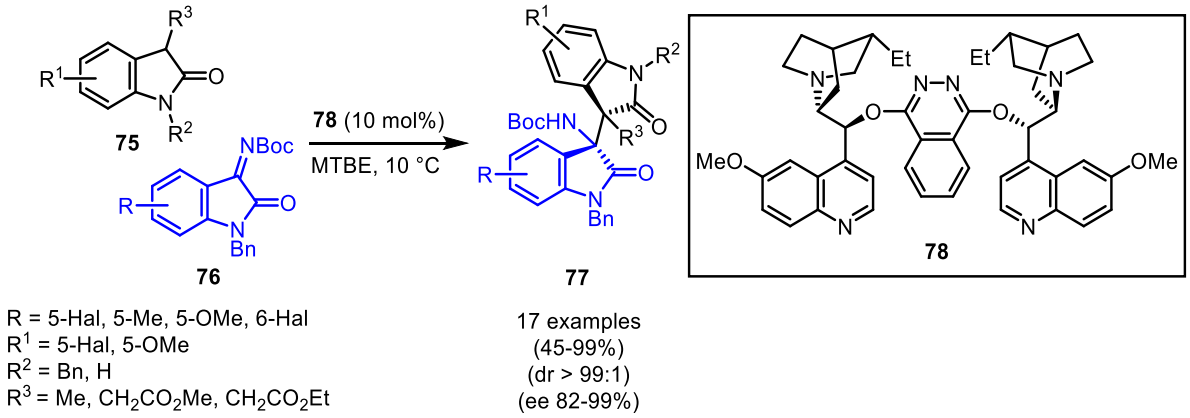
Scheme 2.4. Kanger's organocatalytic approach towards spirocyclopropane bis-oxindoles.

2.1.3 Formation of non-spirocyclic bis-oxindoles

As shown previously, the spirocyclic bis-oxindole motifs have gained broad attention from both synthetic and medicinal point of views. Non-spirocyclic bis-oxindoles have also attracted interest. Extensive studies by the group of Overman, in the area of natural product synthesis, has been undertaken, wherein the use of 3,3-linked bis-oxindole intermediates were involved.[37] Consequently, a number of asymmetric studies for the construction of this motif were also investigated.

2.1.3.1 Asymmetric addition of oxindoles to isatin-derived ketimines

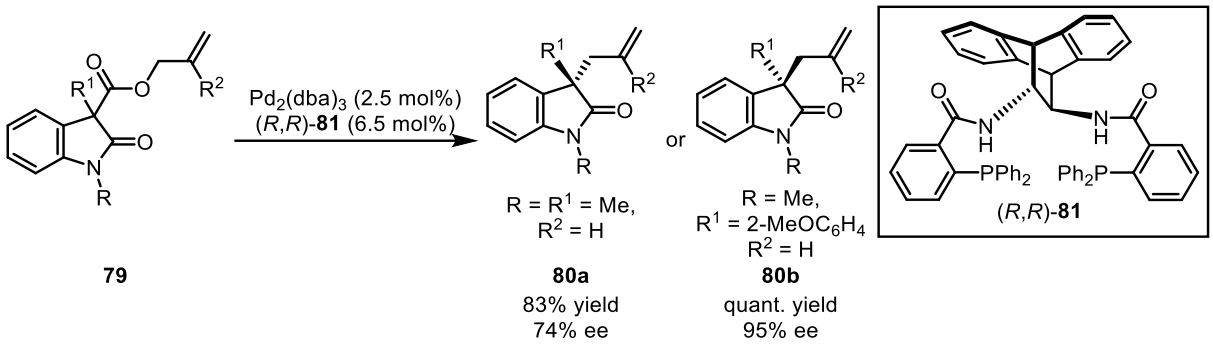
The control over the formation of enantioenriched quaternary centres is considered as one of the most powerful transformations in synthesis. One way to promote access to chiral centres is the use of organocatalysis as exemplified previously. An example was reported by Zhu and co-workers who developed a highly enantioselective synthesis of bis-oxindoles **77** with two vicinal quaternary stereocentres by means of a Lewis base promoted addition of 3-substituted oxindoles **75** to ketimines **76** (Scheme 2.5).[38] A proposed organocatalyst mode of action relied on the activation of the 3-substituted oxindoles **75**, which subsequently reacted with the imine **76** also stabilised by H-bonding within the chiral pocket of the organocatalyst **78**.



Scheme 2.5. Organocatalytic formation of bis-oxindoles **77** from 3-substituted oxindoles **75** and ketimines **76**.

2.1.3.2 Asymmetric decarboxylative allylation approach to bis-oxindoles

Access to enantioenriched oxindoles **80** *via* an asymmetric decarboxylative allylation was reported by the Taylor group in 2011. High conversions and levels of streocontrol were achieved from racemic 3,3-disubstituted oxindoles **79** using $Pd_2(dba)_3$ (2.5 mol%) and the commercially available anthracene-derived bis-phosphine **81** (6.5 mol%) as a ligand (Scheme 2.6),[39] previously utilised by Trost in his work on catalytic asymmetric allylic alkylation of ketone enolates.[40]



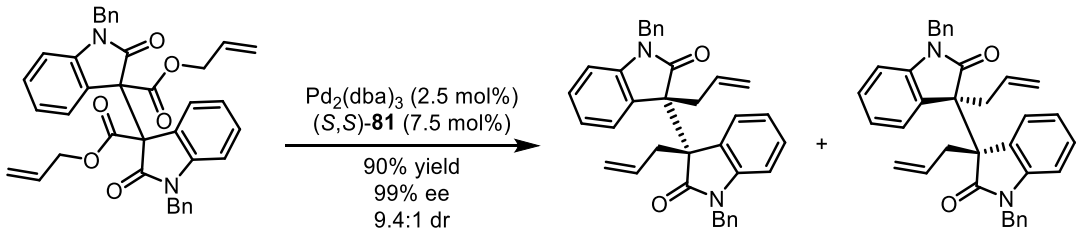
79

80a
83% yield
74% ee

80b
quant. yield
95% ee

Scheme 2.6. Taylor's asymmetric approach to enantioenriched oxindoles.

Inspired by this work, Bisai and co-workers further expanded the scope of the transformation and reported the utility of this strategy in the formation of enantioenriched bis-oxindoles **83** from racemic bis-oxindoles **82** (Scheme 2.7).[41] (*S*,*S*)-**83** has been commonly used as an intermediate for the formal synthesis of cyclotryptamine alkaloids.[37]



82
(±:meso >20:1 dr)

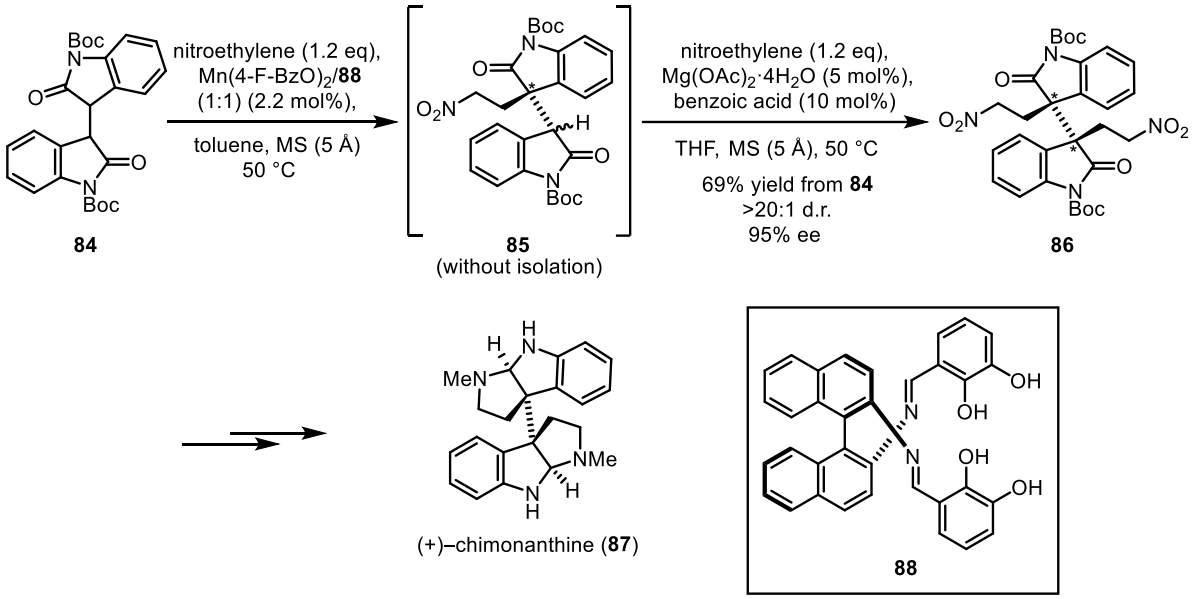
(*S*,*S*)-**83**

meso-**83**

Scheme 2.7. Bisai's extension of the asymmetric decarboxylative allylation to bis-oxindoles.

2.1.3.3 Construction of bis-oxindoles by a double Michael reaction from dihydroisoindigo and application in the total synthesis of (+)-chimonanthine (87)

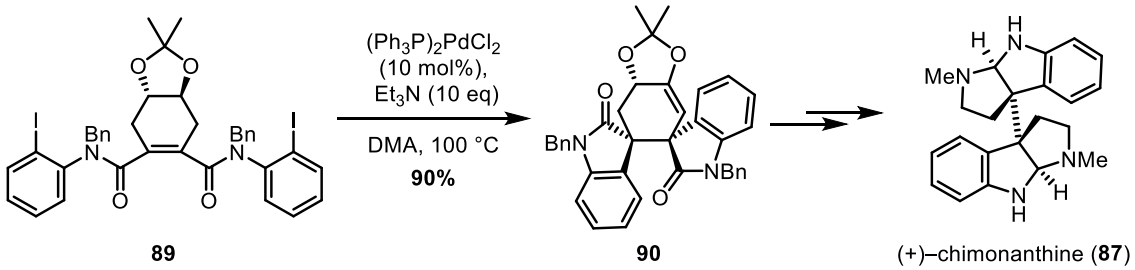
The chimonanthines are the simplest members of the indole family of alkaloids containing a hexacyclic 3a,3a'-bis-pyrrolidino[2,3b]indoline unit. All three stereochemical chimonanthines are found in nature. Amongst them, (+)-chimonanthine (**87**) was isolated from both the skin of a Colombian frog[42] and from plant sources.[43] While Overman *et al.* developed a double alkylation of dihydroisoindigo to give spirocyclic bis-oxindoles as the key step of the total synthesis of (+)-chimonantine (**87**),[37c] the group of Kanai reported a catalytic and stereoselective double Michael addition from dihydroisoindigo **84** to give bis-oxindole **86** (Scheme 2.8).[44] The one-pot double Michael reaction was investigated and the Schiff base had only moderate reactivity towards the second Michael addition, possibly explained by the severe steric hindrance from the catalyst. Consequently, the yield and the diastereoselectivity of the reaction sequence were disappointingly low (44% yield and up to 5:1 dr) but excellent enantioselectivity was generated. To solve this problem, they investigated next, a sequential Michael reaction in order to achieve a greater diastereocontrol in the second step. Not surprisingly, the chiral $Mn(4\text{-F-BzO})_2$/Schiff base catalyst **88** still afforded mono-alkylated bis-oxindole **85** with good enantiocontrol. Filtration on a pad of silica was necessary to remove the manganese catalyst. Pleasingly, treating the mono-alkylated product **85** with $Mg(OAc)_2 \cdot 4H_2O$ in presence of benzoic acid considerably improved the conversion as well as the level of diastereoselectivity. The bis-oxindole **86** represented an ideal and easy accessed target which was eventually intended for use in the total synthesis of (+)-chimonantine (**87**) as well as two other cyclotryptamine alkaloids.



Scheme 2.8. Kanai's sequential Michael reaction to bis-oxindoles **86**.

2.1.3.4 Construction of bis-oxindoles by a double palladium-catalysed Heck coupling

Interested in the formation of cyclotryptamine alkaloids, Overman and co-workers investigated several strategies to construct the hexacyclic 3a,3a'-bis-pyrrolidino[2,3b]indoline motif. Whereas earlier the focus was set on a double alkylation method from dihydroisoindigo, the construction of bis-oxindoles **90** was also undertaken by a double palladium-catalysed Heck coupling from bis-anilides **89** (Scheme 2.9).[37b] Only a single hexacyclic bis-oxindole was formed from the coupling reaction of bis-iodinated substrates **89** with $Pd(PPh_3)_2Cl_2$ (10 mol%) and excess of Et_3N. It was suggested that when the cyclohexanediol was protected as an acetonide, the oxygen substituents were locked in a diequatorial position, and consequently set the configuration of the most favoured intermediate. Also, the relative stereochemistry of **90**, in which the two oxindole units are orthogonal, was secured by single-crystal X-ray analysis. The total synthesis of (+)-chimonanthine (**87**) was also reported.[37b]



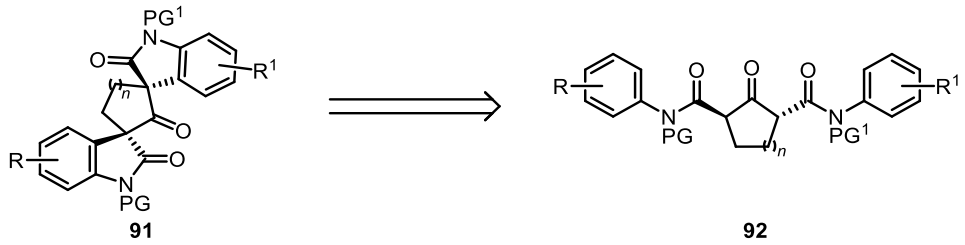
Scheme 2.9. Overman's double palladium-catalysed Heck coupling reaction to spirocyclic bis-oxindoles.

To date, this example represents the only intramolecular cyclisation process to spirocyclic bis-oxindoles.[45] While all the previous approaches relied on the synthesis of the central core from pre-existing oxindole units, this strategy focused on the formation of both oxindole motifs through a double palladium-catalysed coupling process.

2.2 Synthesis of spirocyclic bis-oxindoles

2.2.1 A copper(II)-mediated oxidative coupling approach to spirocyclic bis-oxindoles

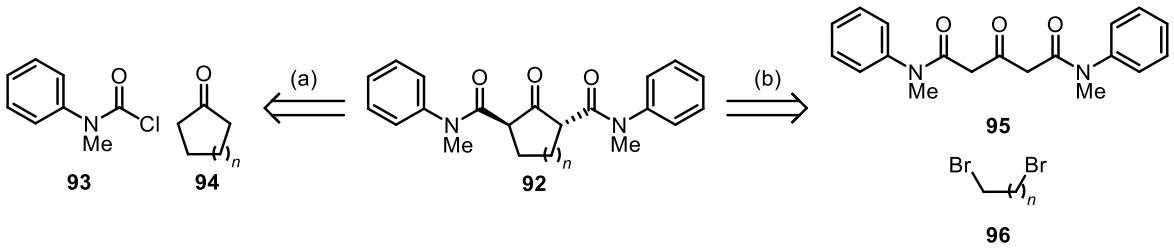
Interested by bis-oxindoles for their synthetic and biological profile, potential substrates capable of undergoing an intramolecular cyclisation under the copper(II)-mediated oxidative coupling were investigated. Following the reported synthesis of oxindoles,[14,16] spirocyclic oxindoles[21] and other heterocycles,[46] the synthesis of more structurally complex bis-oxindoles **91** with two stereogenic centres was conducted. Bis-anilide substrates were chosen as potentially amenable to perform the double C–H, Ar–H functionalisation. While Overman uses *ortho*-iodinated bis-anilide precursors as well as a palladium catalyst for the double cyclisation to proceed,[37b] the use of non-prefunctionalised bis-anilide **92** and a very inexpensive source of copper was proposed (Scheme 2.10). With regard to the already published work in the area, this work is, to the best of our knowledge, the first example representing the variation of the bis-oxindole central core.



Scheme 2.10. Expected synthesis of bis-oxindoles **91** from bis-anilide precursors **92** *via* a copper(II)-mediated double cyclisation.

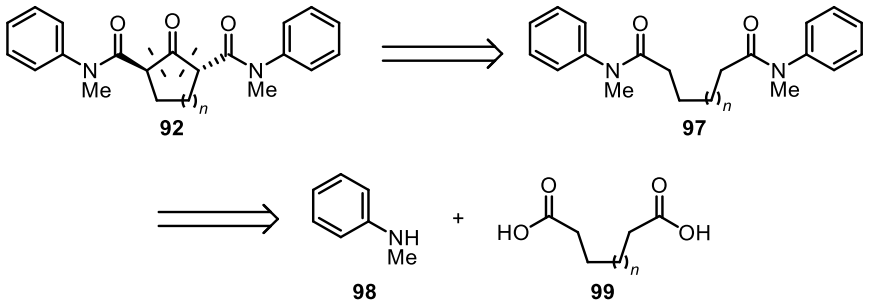
2.2.2 Strategy for the formation of cyclopentanone bis-anilide precursors

Different approaches were explored for the formation of bis-anilide precursors. To start, disconnection at the α-position of the central cyclic ketone in compound **92** was investigated but all efforts failed to give the bis-substituted product **92** from the reaction between the preformed bis-enolate of ketone **94** and carbamoyl chloride **93** (**pathway a**, Scheme 2.11). Another synthetic strategy was then proposed in which compound **92** would result from the dialkylation of tricarbonyl intermediate **95** with non-activated dibromo-alkyl derivatives **96**. Disappointingly, conversion of bis-anilide **95** to cyclic product **92** was never observed (**pathway b**, Scheme 2.11).



Scheme 2.11. Disconnection strategies for the formation of bis-anilides **92**.

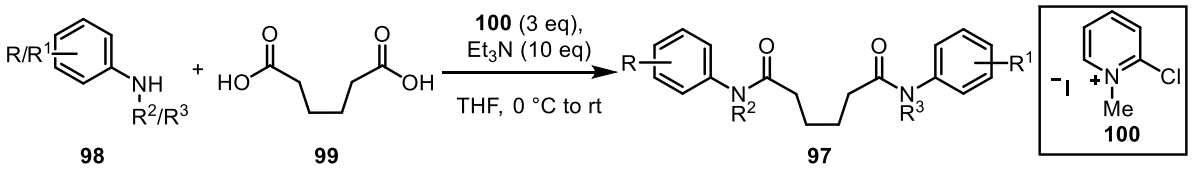
Consequently, a new approach was considered in which the formation of the bis-anilide substrate **92** would result from a formal carbon monoxide insertion between both amide moieties as depicted in the Scheme 2.12. Initial amide coupling with di-carboxylic acid **99** and *N*-methylaniline (**98**) would provide access to bis-amide **97**. Thus, the tricarbonyl bis-anilide **92** would directly arise from a novel ring closure from compound **97**.



Scheme 2. 12. Proposed route to the cyclopentanone 2,5-dicarboxamide **92**.

Using Mukaiyama's peptide coupling conditions, treatment of adipic acid with a small excess of *N*-methylaniline (**98**), 2-chloro-1-methylpyridinium iodide (**100**) and Et_3N in THF at 0 °C, gave the bis-amide **97a** in 75% yield (entry 1, Table 2.1). Due to the poor solubility of adipic acid in DCM, THF was used as the solvent for the coupling reaction. This bis-amide coupling can be performed conveniently on large scale to provide multigram quantities of precursors **97**. Symmetrical substrates **97a-d** as well as unsymmetrical substrates **97e-f** were obtained in moderate to good yields.

Table 2.1. Mukaiyama's coupling approach for the synthesis of bis-amides **97**.

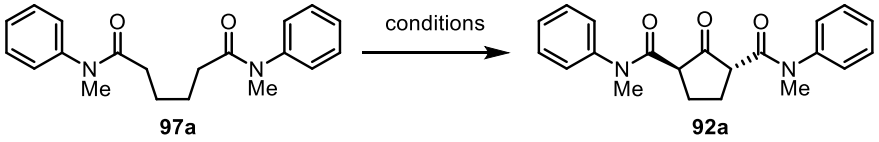


entry	R/R^1	R^2/R^3	product	yield (%)[a]
1	$R = R^1 = H$	$R^2 = R^3 = Me$	**97a**	75
2	$R = R^1 = H$	$R^2 = R^3 = Bn$	**97b**	38
3	$R = R^1 = 4\text{-Me}$	$R^2 = R^3 = Me$	**97c**	93
4	$R = R^1 = 4\text{-OMe}$	$R^2 = R^3 = Me$	**97d**	91
5	$R = 4\text{-Me}, R^1 = 4\text{-OMe}$	$R^2 = R^3 = Me$	**97e**	40[b]
6	$R = R^1 = H$	$R^2 = Me, R^3 = Bn$	**97f**	22[b]

[a] Yield of isolated product. [b] Dr. Timothy E. Hurst carried out the synthesis of both unsymmetrical substrates. **97e-f** were synthesised using a sequential addition of anilines.

A novel ring closure approach was next investigated from **97a**. Multiple coupling agents and bases were tried and the results are shown in the Table 2.2. Pleasingly, LHMDS (3 eq) in combination with CDI (1.5 eq) validated the feasibility of the ring closure reaction and afforded product **92a** in a moderate 27% yield (entry 1, Table 2.2). Replacing LHMDS with NaH dramatically lowered the yield of the reaction with only starting material recovered (entry 2). The nature of the coupling agent was also studied and the combination of diphosgene with LHMDS did not afford the cyclopentanone-derived product **92a** (entry 3). Finally, another set of conditions was tried involving the use of LDA as a base and triphosgene as the coupling agent and this gave cyclic product **92a** in 38% yield. However, the reaction never afforded bis-anilide **92a** as clean as the original conditions (entry 1). Even though compound **92a** from conditions 4 was submitted to a series of purifications by column chromatography, unidentified side-products were still observed.

Table 2.2. Optimisation of conditions for the synthesis of tricarbonyl bis-anilide **92a**



entry	base (3 eq)	coupling agent (1.5 eq)	yield (% **92a**)[a]
1	**LHMDS**	**CDI**	**27**
2	NaH	CDI	0[b,c]
3	LHMDS	diphosgene	0[b]
4	LDA	triphosgene	38[d]

[a] Unless otherwise stated all reactions were carried out in THF (0.08 M-0.12 M) at –78 °C and allowed to warm to rt once quenched by addition of NH_4Cl. [b] Only starting material was recovered. [c] The reaction was carried out at –40 °C. [d] The yield is not accurate as impurities were still present even after a series of purifications.

Full characterisation by NMR and IR spectroscopy, ESI-HRMS analysis confirmed the structure of bis-anilide **92a** obtained by the LHMDS/CDI route. The thermodynamically more stable *trans*-bis-anilide diastereoisomer **92a** was the only product obtained from the reaction. Additionally, the relative configuration of **92a** was confirmed by X-ray analysis (Figure 2.4).

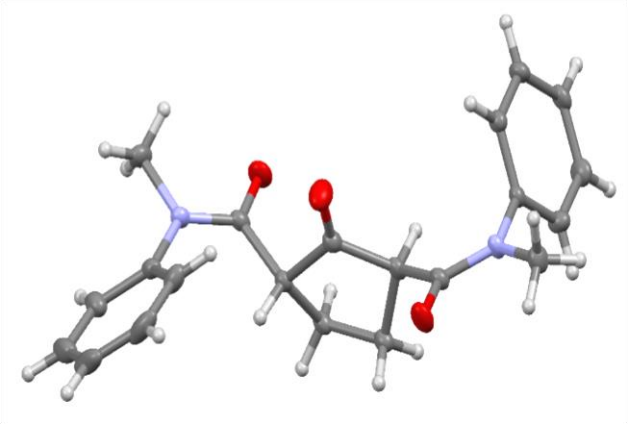
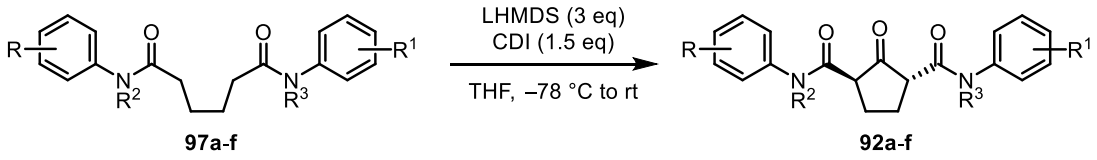


Figure 2.4. Crystal structure of *trans*-**92a** (50% probability ellipsoids, CCDC 1013303).

Then, the scope of the CDI-mediated cyclopentanone cyclisation was expanded to the range of bis-amide substrates **97a-f** (Table 2.3). Tricarbonyl cyclisation precursors **92a-f** were obtained in moderate yields.

Table 2.3. Scope of the CDI-mediated cyclopentanone cyclisation.



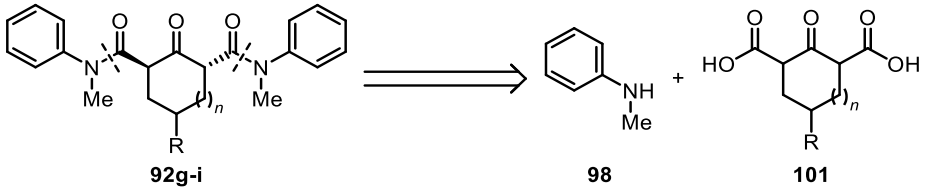
97a-f **92a-f**

entry	R/R^1	R^2/R^3	product	yield (%)[a]
1	R = R^1 = H	R^2 = R^3 = Me	**92a**	27
2	R = R^1 = H	R^2 = R^3 = Bn	**92b**	27
3	R = R^1 = 4-Me	R^2 = R^3 = Me	**92c**	18
4	R = R^1 = 4-OMe	R^2 = R^3 = Me	**92d**	17
5	R = 4-Me, R^1 = 4-OMe	R^2 = R^3 = Me	**92e**	11[b]
6	R = R^1 = H	R^2 = Me, R^3 = Bn	**92f**	20[b]

[a] Yield of isolated product. [b] Dr. Timothy E. Hurst carried out the cyclisation of both unsymmetrical substrates **92e-f**.

2.2.3 Strategies for the formation of 6- and 7-membered ring bis-anilide precursors

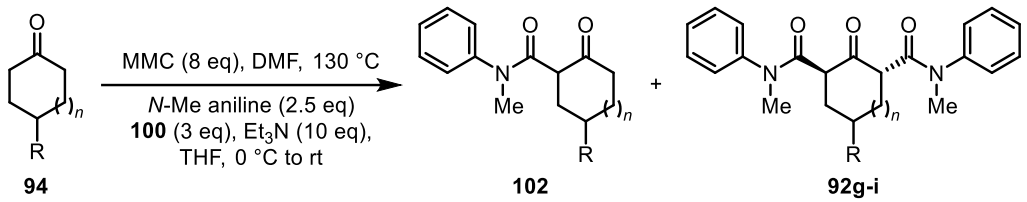
While the CDI-mediated cyclisation afforded the cyclopentanone-derived bis-anilides in moderate yields, 6- and 7-membered-related structures were not accessible by the same route. A different strategy was investigated and relied on the disconnection of both amide bonds (Scheme 2.13). It was anticipated that the cyclic di-carboxylic acid **101** would react with aniline **98** and give access to cyclisation precursors **92g-i**.



Scheme 2.13. Second strategy to access bis-anilide with larger ring size central core.

The di-carboxylic acid **101** was readily available from the reaction of cyclic ketones **94** with methyl magnesium carbonate[47] and resulted in the formation of an inseparable mixture of mono- and bis-acid (Table 2.4). A one-pot treatment of the acid mixture with aniline under Mukaiyama's conditions afforded bis-anilide **92g-i** along with a majority of mono-substituted anilide **102**, conveniently separable by column chromatography. Rapid access to bis-anilides **92g-i** was thus achieved from the one-pot MMC/Mukaiyama's coupling route.

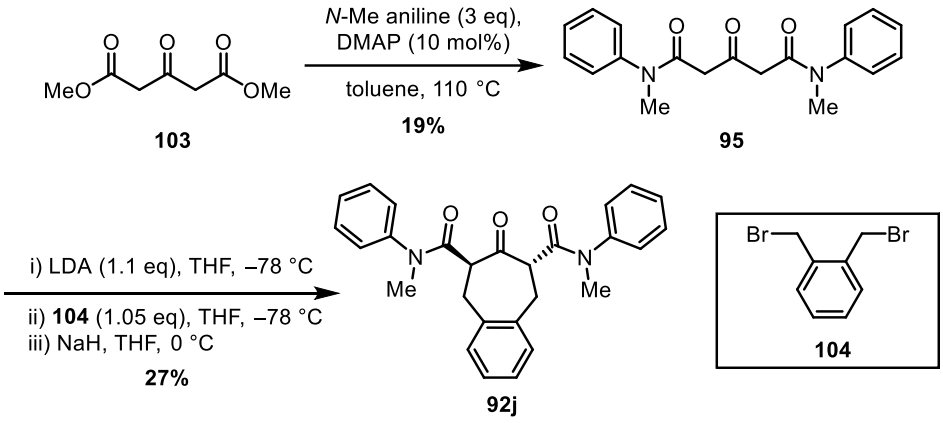
Table 2.4. Scope of the synthesis of bis-anilides.



entry	R	n	yield[a]	
			102	**92**
1	H	1	30% **102a**	14% **92g**
2	*t*-Bu	1	38% **102b**	10% **92h**
3	H	2	34% **102c**	9% **92i**

[a] Yield of isolated products. Mono-anilides **102a-c** and bis-anilides **92g-i** are separable by column chromatography.

A different strategy was developed for the formation of the 7-membered ring benzo-fused bis-anilide **92j**, mainly because of the high cost of the ketone starting material necessary for the MMC/amide bond coupling sequence. Formation of tricarbonyl bis-amide **95** was achieved in 19% yield from the diester **103** (Scheme 2.14). Treatment of the preformed dienolate of **95** with dielectrophile **104** yielded the *trans*-bis-anilide **92j** in a moderate 27% yield. This strategy was only possible with the structurally-rigid dielectrophile in order to avoid the competitive double alkylation at the same carbon atom.



Scheme 2.14. Synthesis of bis-anilide **92j**.

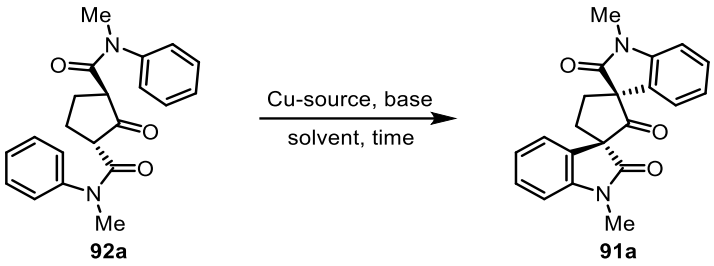
It was assumed that the five-, six-, and seven-membered ring bis-anilides were all isolated as the *trans*-bis-anilide diastereoisomers.

However, no crystal structures were obtained for the six- and seven-membered examples to confirm this assumption.

2.2.4 Preliminary studies and optimisation of the cyclisation conditions

For initial investigations, the cyclopentanone 2,5-dicarboxamide **92a** was chosen as the model substrate. The double spirocyclisation was undertaken, initially using $Cu(OAc)_2 \cdot H_2O$ in mesitylene at 170 °C, conditions optimised for the formation of mono-oxindoles.[16] After 30 min, TLC analysis indicated the complete consumption of bis-anilide **92a** but only traces of cyclised product **91a** were observed (entry 1, Table 2.5). Decreasing the temperature and carrying out the reaction in toluene at 110 °C improved the cyclisation to 24% yield (entry 2). Further reduction in temperature resulted in lower yields, even after extended reaction times (entry 3). A significant improvement was observed when employing the conditions optimised in the original study on the formation of oxindoles with stoichiometric copper.[14a] The desired spirocyclic bis-oxindole **91a** was obtained in 67% yield when the reaction was carried out in DMF at 110 °C with addition of KO*t*-Bu (2.2 eq) (entry 4). In a control experiment carried out using KO*t*-Bu (2.2 eq), in the absence of copper salt, no cyclisation took place, leading to predominantly hydrolysed and decomposed starting materials (entry 5).

Table 2.5. Optimisation of the double cyclisation reaction conditions



entry	base	Cu source	solvent	time (h)	yield (% **91a**)[a]
1	-	$Cu(OAc)_2 \cdot H_2O$ (1 eq)	mesitylene (170 °C)	0.5	<5[b]
2	-	$Cu(OAc)_2 \cdot H_2O$ (1 eq)	toluene (100 °C)	0.5	24
3	-	$Cu(OAc)_2 \cdot H_2O$ (1 eq)	toluene (80 °C)	3	17
4	**KO*t*-Bu (2.2 eq)**	**$Cu(OAc)_2 \cdot H_2O$ (2 eq)**	**DMF (110 °C)**	**0.25**	**67**
5	KO*t*-Bu (2.2 eq)	-	DMF (110 °C)	0.25	0[c]

[a] Unless otherwise stated, yield of isolated products. [b] Yield determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] No product was observed in the ^{1}H NMR spectrum of the crude reaction mixture and only traces (<5%) of starting material were observed, while products from amide hydrolysis as well as decomposition were also detected.

The double cyclisation proceeded with complete diastereoselectivity to give only the *trans*-diastereoisomer. The novel spirocyclic bis-oxindole *trans*-**91a** was fully characterised by NMR spectroscopy (see Appendix I for the ^{1}H and ^{13}C NMR spectra), IR and ESI-HRMS analysis. Also, the relative configuration was confirmed by X-ray crystallographic analysis (Figure 2.5).

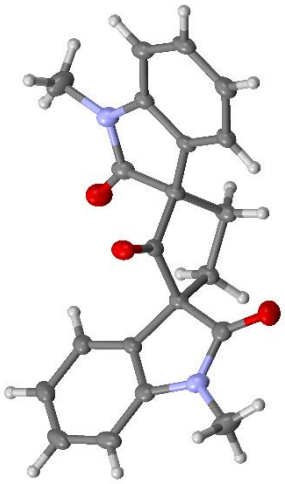


Figure 2.5. Crystal structure of *trans*-**91a** (50% probability ellipsoids, CCDC 1004040).

Owing to the C_2-symmetry of spirocyclic bis-oxindole *trans*-**91a** as well as the high diastereoselectivity of the double cyclisation, the interpretation of the ^{1}H NMR spectrum was trivial. An expansion of the aromatic region of *trans*-**91a** is shown in Figure 2.6. Only 4 peaks, integrating for two protons each were seen between 6.83 and 7.44 ppm. Also, two distinctive multiplets for each CH_2 from the cyclopentanone central core and one singlet for both Me group appeared at lower chemical shifts (see Appendix I for full ^{1}H and ^{13}C NMR spectra of *trans*-**91a**).

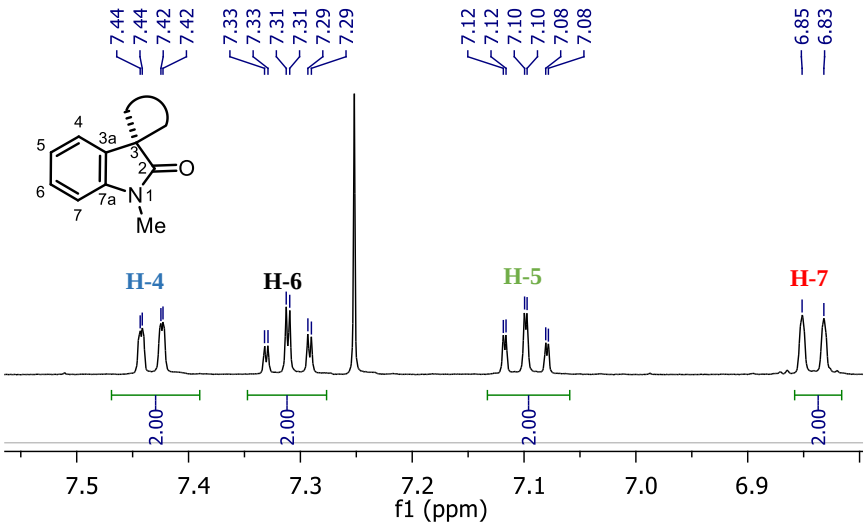
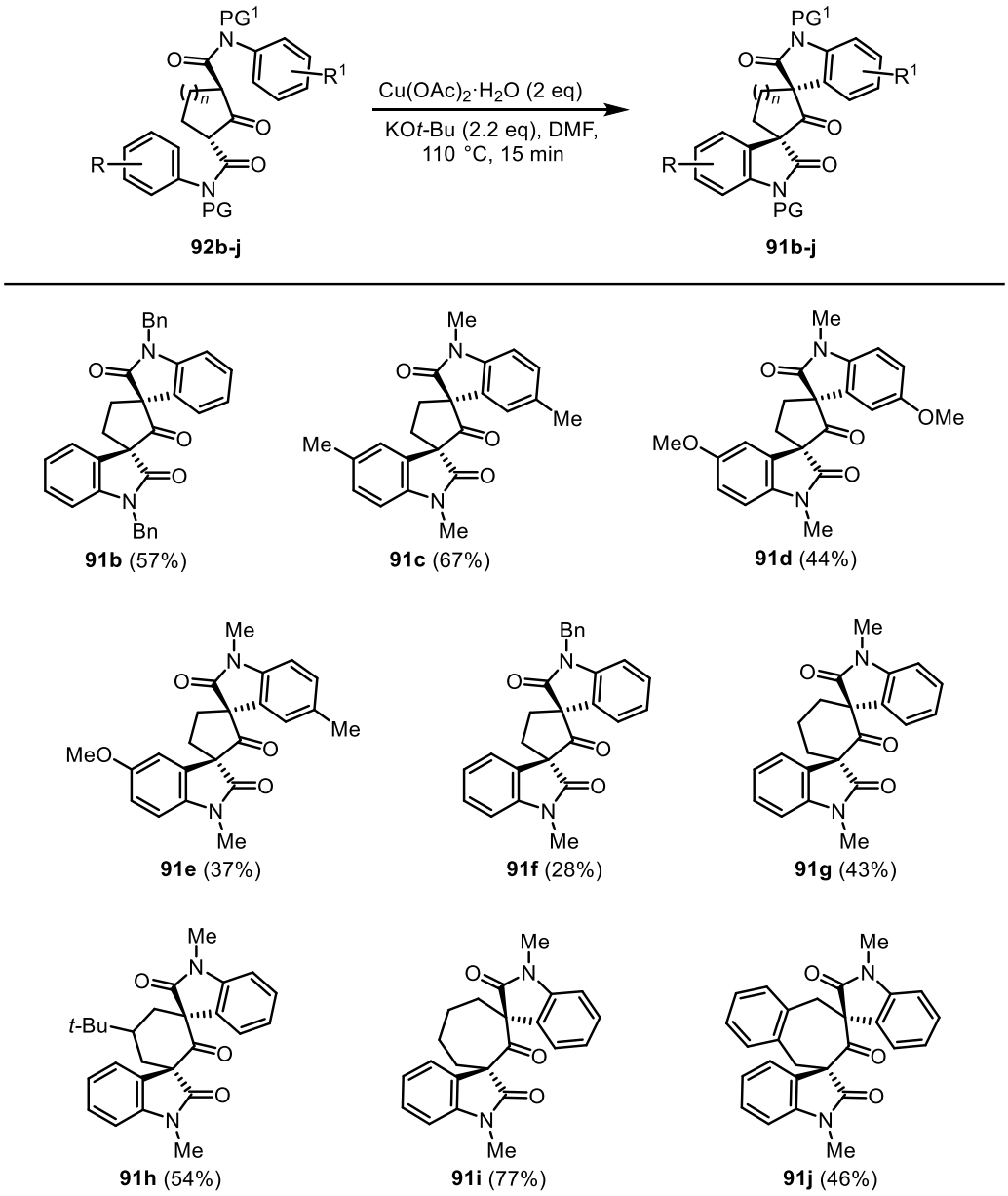


Figure 2.6. ^{1}H NMR expansion of the aromatic signals of spirocyclic bis-oxindole *trans*-**91a**.

2.2.5 Scope of the double cyclisation reaction

Having established successful conditions for the double cyclisation, further investigations on the substrate scope of this reaction using a range of substituted bis-anilides **92** were undertaken. Pleasingly, changing the substitution on the nitrogen atom did not affect the yield of the cyclisation as bis-oxindole **91b** was obtained in 57% yield (Scheme 2.15). Substitution of the aromatic ring in the *para*-position was also tolerated and both 4-Me (**91c**) and 4-OMe (**91d**) spirocyclic bis-oxindoles were formed in 67% and 44% yield, respectively. The central ring size was also varied and cyclohexanones (**91g-h**) as well as a cycloheptanone (**91i-j**) embedded between the two oxindole units were well-tolerated. All spirocyclic bis-oxindoles presented in Scheme 2.15 were obtained as single *trans*-diastereoisomers, as shown by NMR spectroscopy and X-ray analysis.



Scheme 2.15. Spirocyclic bis-oxindole substrate scope. Unsymmetrical bis-spirooxindoles **91e-f** were prepared by Dr. Timothy E. Hurst, with differences in either ring substitution (**91e**) or on the nitrogen atom (**91f**).

For the first time, great variability in the central core is possible. While other methods focussed on the elaboration of the spirocyclic central unit, our route enabled the formation of the two oxindole motifs from bis-anilide substrates that already contained the future C3-C3' spirocyclic central core. As a result, the flexibility of this approach allowed introduction of a larger range of central cores with different ring sizes. Notably, the bis-oxindole **91g-j**, containing 6- and 7-membered ring, are unprecedented structures.

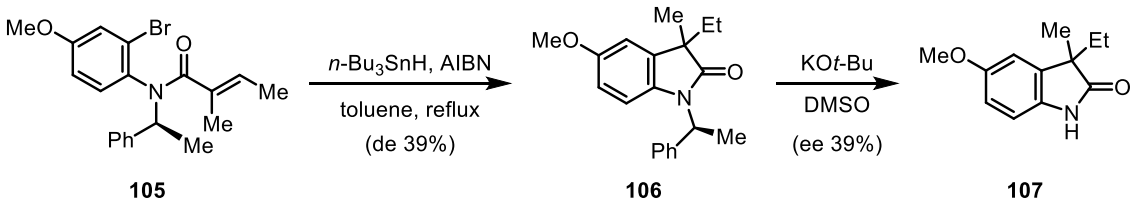
This method enabled the installation of two all-carbon quaternary centres at the oxindole 3-position in a diastereoselective manner, most likely induced by the rigidity of the cyclic core appended to both oxindole units.

The optimised conditions for the synthesis of spirocyclic bis-oxindoles required very short reaction times. Also, an inexpensive and insensitive-to-air copper(II) salt, was used to perform the one-pot double cyclisation, and the reaction was run opened to the air.

2.2.6 A copper(II)-mediated cyclisation to enantioenriched spirocyclic bis-oxindoles.

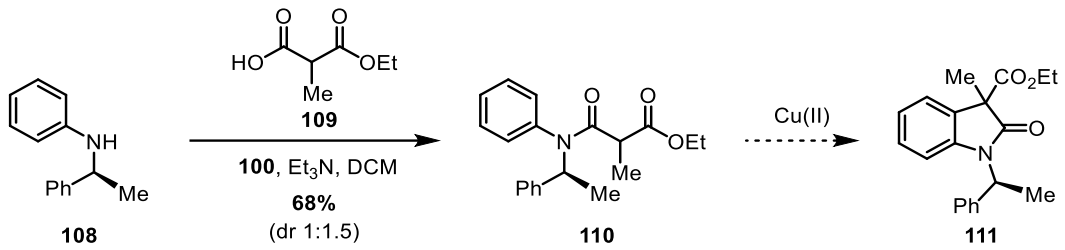
In an effort to extend the diastereoselective properties of the copper(II)-mediated double cyclisation to the formation of potentially enantioenriched bis-spirooxindoles, the introduction of a chiral auxiliary on the nitrogen of the oxindole motif was next considered.

Chiral auxiliaries on the ester have already been investigated by the Taylor group and a diastereoselective version of the oxindole cyclisation had been attempted. The use of Evans and Oppolzer chiral auxiliaries was studied. Unfortunately, neither produced the desired cyclised oxindole product. Alternatively, other chiral auxiliaries could be investigated and the auxiliary could be attached on the nitrogen atom instead. Preliminary studies on a radical cyclisation approach from *ortho*-bromo anilide **105** into a simple oxindole **106** was reported by Jones in 1989 where the use of the α-methylbenzyl group as a chiral auxiliary was reported to promote a moderate 39% ee after removal of the auxiliary to give enantioenriched oxindole **107** (Scheme 2.16).[48]



Scheme 2.16. Jones' diastereoselective formation of oxindoles.

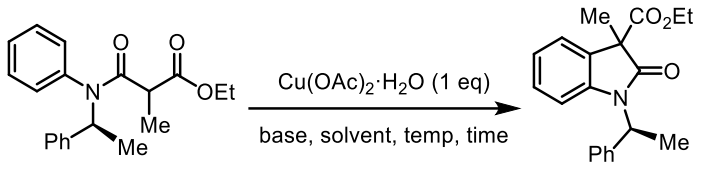
A similar approach was proposed for the diastereoselective synthesis of 3,3-disubstituted oxindoles as well as bis-oxindoles, with the hope to gain higher diastereoselectivities. The formation of 3,3-disubstituted oxindoles was first examined. The precursor **110**, bearing an (*S*)-α-methylbenzyl group, was prepared *via* a Mukaiyama amide bond coupling between readily available carboxylic acid **109**[49] and *N*-benzyl aniline **108**[50] (Scheme 2.17). From anilide **110**, the C–H, Ar–H coupling reaction should occur and hopefully enhance the resulting diastereoselectivity of the cyclisation.



Scheme 2.17. Proposed diastereoselective cyclisation to oxindole **111**.

Optimisation of the cyclisation reaction from anilide **110** into oxindole **111** was carried out and is presented below in the Table 2.6. Initially, the conditions developed for the formation of bis-oxindoles were tried (entry 1). Due to the poor yield of this reaction, the reaction conditions used for the transformation were reconsidered. Switching the solvent from DMF to toluene and carrying out the reaction at 110 °C, without base, increased the yield considerably (entry 2). Of greater importance, incorporation of the chiral auxiliary generated slight control over the diastereoselectivity of the reaction (i.e. dr 1:1.3). No consideration was given with respect to determining the absolute configuration of the major diastereoisomer **111** as all attempts at separation by column chromatography proved unsuccessful. However, this result provided encouragement for the potential achievement of greater diastereocontrol for the cyclisation of sterically more hindered spirocyclic bis-oxindoles.

Table 2.6. Optimisation of the cyclisation from anilide **110** into oxindole **111**.

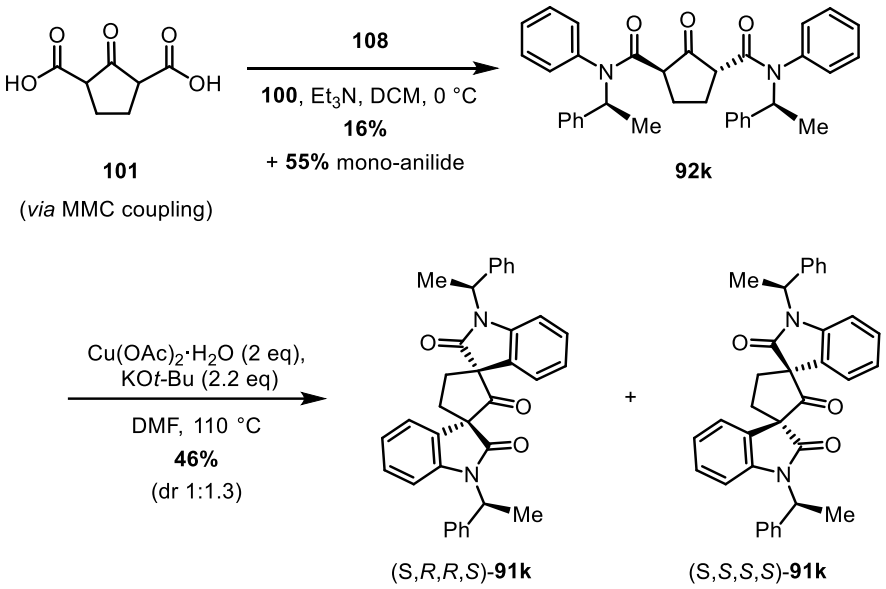


110 **111**

entry	base (eq)	solvent (temp)	time (h)	yield (% **111**)[a]	dr[b]
1	KO*t*-Bu (2.2 eq)	DMF (110 °C)	1	26	1:1.3
2	**-**	**toluene (110 °C)**	**18**	**76**	**1:1.3**
3	-	mesitylene (170 °C)	1.5	55	1:1.2

[a] Yield of isolated products. [b] dr were calculated from the integration of the ^{1}H NMR signal of both benzylic CH from the inseparable mixture of diastereoisomers after purification by column chromatography.

With regard to the previous result, attention was focused on applying this strategy to the more intricate spirocyclic bis-oxindoles with the hope of attaining superior stereocontrol over the cyclisation process. The linear bis-anilide precursor **92k**, containing the (*S*)-α-methylbenzyl chiral auxiliary on both nitrogen atoms, was prepared following the double MMC/amide coupling reactions sequence (Scheme 2.18). Cyclisation of bis-anilide **92k** under the optimised conditions delivered **91k** in 46% yield as an inseparable mixture of diastereoisomers in a 1:1.3 ratio. Unfortunately, the diastereoisomeric ratio of 1:1.3 was the same for both mono- and bis-oxindole motifs. A screening of bulkier chiral auxiliaries would be the next parameter to vary for the purpose of improving the stereocontrol of such process.



Scheme 2.18. Cyclisation of bis-anilide **92k** to give spirocyclic bis-oxindole **91k**.

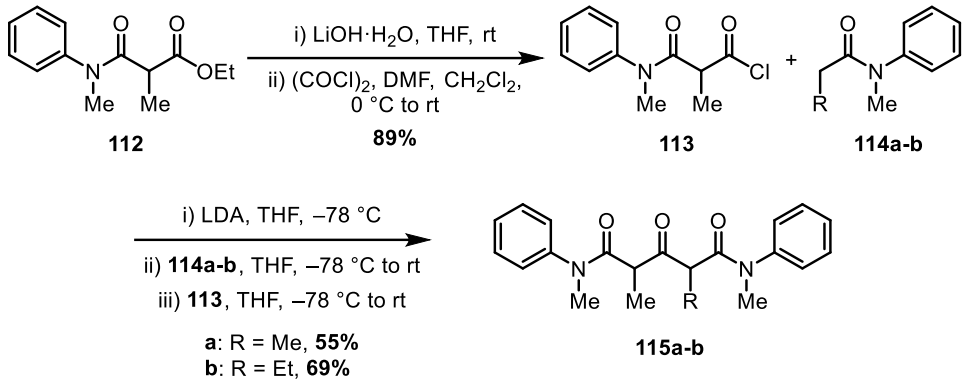
2.3 Synthesis of bis-oxindoles with an acyclic monoketone linker

To further demonstrate the scope and diversity of the double anilide cyclisation, attention turned to varying the cyclic ketone linker and applying this methodology to acyclic monoketone central core precursors. Although the linear bis-anilide would suffer from the lack of rigidity during the cyclisation compared to the cyclic central core precursors discussed earlier, a certain level of diastereocontrol during the reaction was still expected.

2.3.1 General approach for the formation of bis-anilides with an acyclic monoketone linker

For this purpose, the substrate synthesis was revised and the required cyclisation precursors were easily prepared in 3 steps. Readily available ester anilide **112** was treated with $LiOH \cdot H_2O$ and the resulting carboxylic acid transformed into acid chloride **113** using oxalyl chloride in the presence of DMF (Scheme 2.19). Acid chloride **113** was synthesised on large scale and was sufficiently stable to allow storage at –10 °C for several months without degradation. Preparation of LDA, with freshly distilled di*iso*propylamine and a titrated solution of *n*-BuLi in hexanes was treated with **114a-b** at –78 °C. The solution was stirred for 20 min and allowed to warm to 0 °C before lowering the temperature again to –78 °C. Then, the acid chloride, as a solution in THF, was slowly added and the completion of the

reaction monitored by TLC analysis. Following this procedure, access to **115a-b** was achieved in good yield as a single diastereoisomer in 55% and 69% respectively.

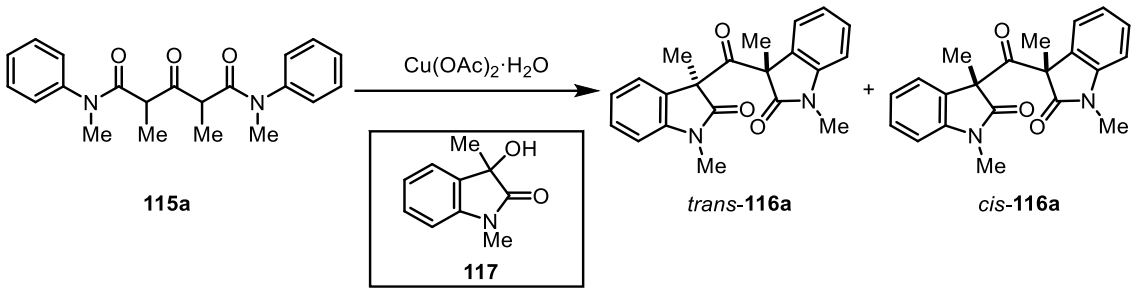


Scheme 2.19. Synthesis of bis-oxindoles with an acyclic monoketone linker.

2.3.2 Preliminary studies and optimisations of the cyclisation conditions

The efficiency of the cyclisation was tested with the symmetric precursor (**115a**, R = Me). Cyclised adduct **116a** was obtained in 65% yield as a mixture of diastereoisomers which was determined from the ^{1}H NMR spectrum of the crude mixture (entry 1, Table 2.7). Both *trans*- and *cis*-diastereomers were separable by column chromatography. However, the presence of a significant amount of side-product **117** complicated the purification (i.e. co-elution of the undesired product **117** in both diastereoisomer fractions). The contaminant **117** was identified as *N*-methyl-3-methyl-3-hydroxyoxindole, and resulted from an oxidative cleavage of either **115a** or **116a**. Pleasingly, performing the reaction without base in toluene minimised the formation of side-product **117** but also lowered the yield of the cyclisation (entry 2). Reducing the amount of time required to complete the transformation and consequently running the reaction in mesitylene at 170 °C for 30 min were sufficient to improve the yield and considerably reduce the amount of side-product **117** (entry 3). The small amount of 3-hydroxyoxindole **117** formed in this reaction was easily removed during the workup by washing with an aqueous 4.0 M NaOH solution.

Table 2.7. Optimisation of the double cyclisation to acyclic bis-oxindoles **116a**.



entry	base (eq)	solvent (temp)	time (h)	yield (%)	*trans*:*cis*-**116a**:**117**[e]
1	KO*t*-Bu (2.2 eq)	DMF (110 °C)[a]	1	65[c]	1:3:1.5
2	-	toluene (110 °C)[b]	18	48[c]	1.1:1:0.5
3	-	**mesitylene (170 °C)**[b]	**0.5**	**58**[d]	**1:1.5:traces**

[a] 2 equivalents of $Cu(OAc)_2 \cdot H_2O$ were used in the reaction. [b] 1 equivalent of $Cu(OAc)_2 \cdot H_2O$. [c] Yield after column chromatography but still contains **117**. [d] Yield of isolated products. [e] Ratio was determined from the ^{1}H NMR spectrum of the crude reaction mixture.

The novel bis-oxindoles *cis*-**116a** and *trans*-**116a** were fully characterised by NMR, IR spectroscopy, and ESI-HRMS analysis. Furthermore, the relative configuration of *trans*-**116a** was confirmed by X-ray crystallographic analysis (Figure 2.7).

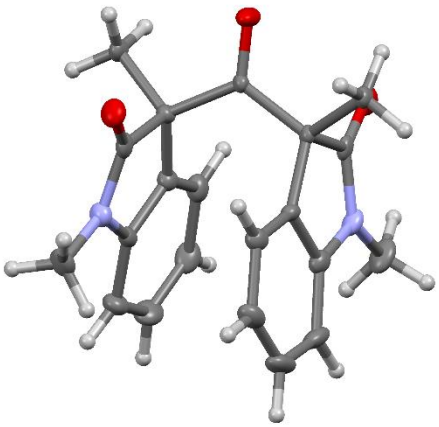


Figure 2.7. Crystal structure of *trans*-**116a** (50% probability ellipsoids, CCDC 1004039).

A very noticeable difference between both diastereoisomers was observed in the ^{1}H NMR spectra of the isolated products. Particular attention was given to the aromatic region between 6 and 8 ppm (Figure 2.8). Relying on the relative configuration determined by the

previous crystal structure (Figure 2.7), the assignment of both compounds with their respective NMR spectra was possible. The red ^{1}H NMR spectrum (a) was attributed to *cis*-**116a** (or *meso*-**116a**). The black ^{1}H NMR spectrum (b) was attributed to the *trans*-**116a**, or optically active *dl*-**116a**. The assignment of all aromatic protons were possible with 2D-NMR spectroscopy. A very different pattern was observed for the protons assigned as H-7 and H-4. While H-7 and H-4 retain very similar chemical shifts in *meso*-**116a**, H-7 was found to be particularly shielded and H-4 deshielded in *dl*-**116a**.

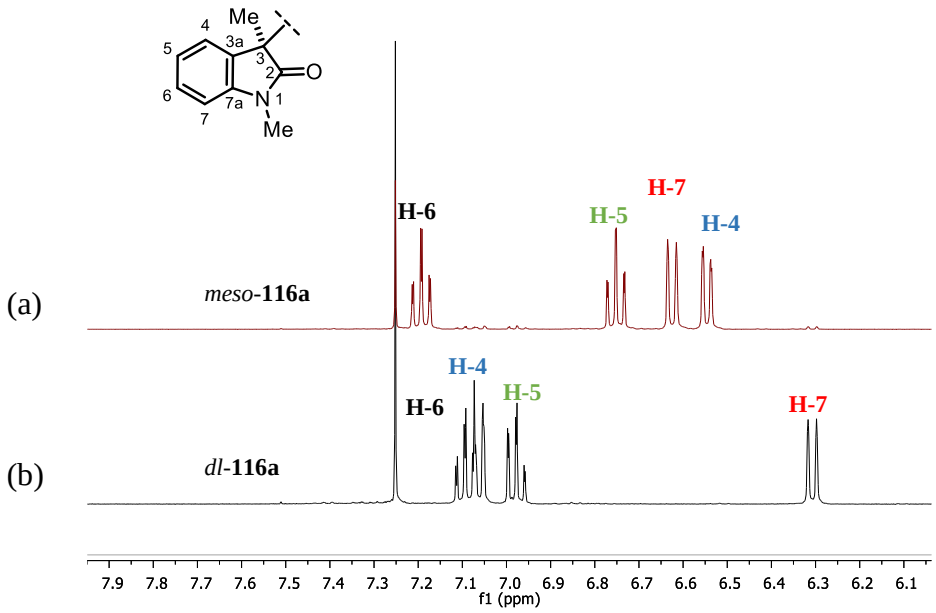
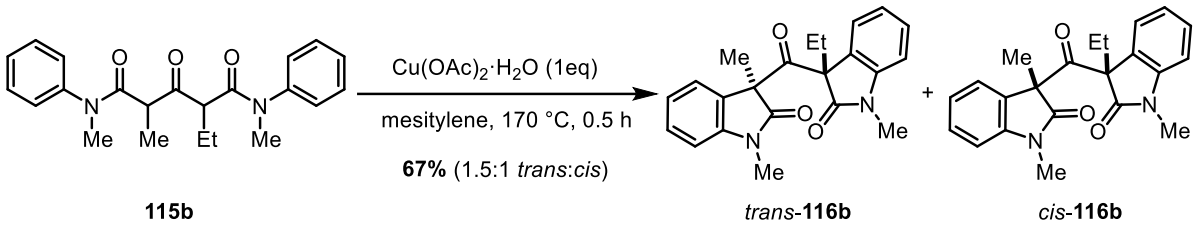


Figure 2.8. ^{1}H NMR expansion of the aromatic signals of *meso*-**116a** (a) and *dl*-**116a** (b).

2.3.3 Synthesis of an unsymmetrical bis-oxindole by double cyclisation

Unsymmetrical bis-oxindole **116b** was prepared in a similar manner (Scheme 2.20). Interestingly, changing one of the α-methyl groups in **115a** to the bulkier ethyl group (**115b**, R = Et) inverted the diastereoselectivity with *trans*-**116b** identified as the major diastereoisomer (1.5:1 *trans*-**116b**:*cis*-**116b**). Again, both compounds were separable by column chromatography.



Scheme 2.20. Synthesis of unsymmetrical bis-oxindole **116b** with a monoketone linker.

The novel bis-oxindoles *cis*-**116b** and *trans*-**116b** were fully characterised by NMR, IR spectroscopy, and ESI-HRMS analysis. In addition, the relative configurations of cis-**116b** and *trans*-**116b** (Figure 2.9) were confirmed by X-ray crystallographic analysis.

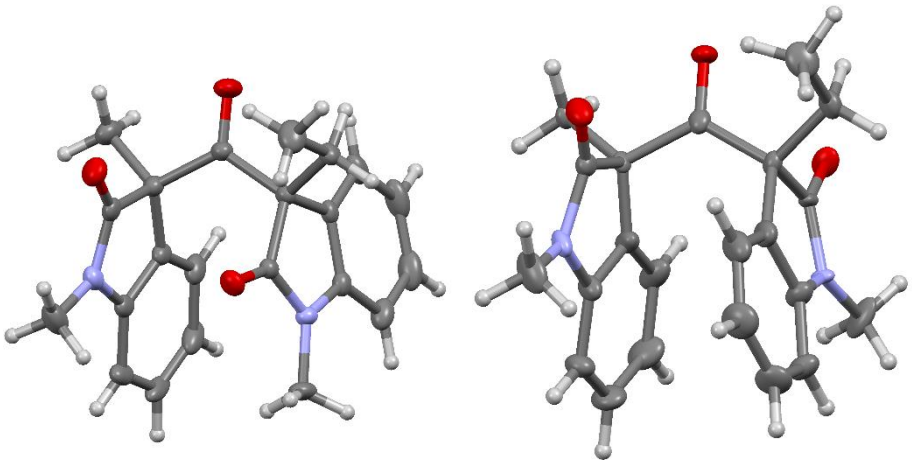


Figure 2.9. Crystal structures of *cis*-**116b** (left, CCDC 1004041) and *trans*-**116b** (right, CCDC 1016758)

Compared to the symmetrical bis-oxindole **116a**, the same trend was observed for the unsymmetrical *cis*- and *trans*-bis-oxindole diastereoisomers **116b** with regard to their respective ^{1}H NMR spectra (Figure 2.10). The red spectrum (a) shows the *cis*-bis-oxindole **116b** which now contains 8 aromatic peaks due to the fact that the cyclised product is no longer symmetrical, rendering the complete proton assignment more complex. While the majority of protons can be assigned for *cis*-**116b**, more difficulties were associated with the interpretation of the peaks in *trans*-**116b** with the exception of the shielded H-7 (black spectrum (b)).

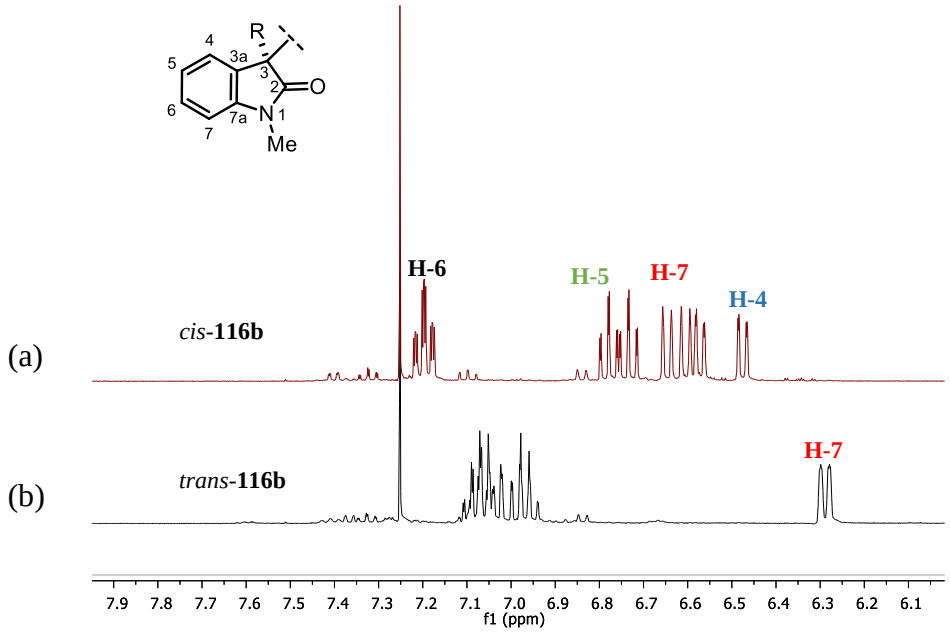


Figure 2.10. ^{1}H NMR expansion of the aromatic signals of *cis*-**116b** (a) and *trans*-**116b** (b).

The moderate diastereoselectivities observed in the synthesis of bis-oxindoles **116a-b** containing monoketone acyclic linker showed the importance of the more rigid cyclic core in spirocyclic bis-oxindoles **91a-k**, which consequently lead to complete stereocontrol over the formation of the most favoured relative *trans*-configuration.

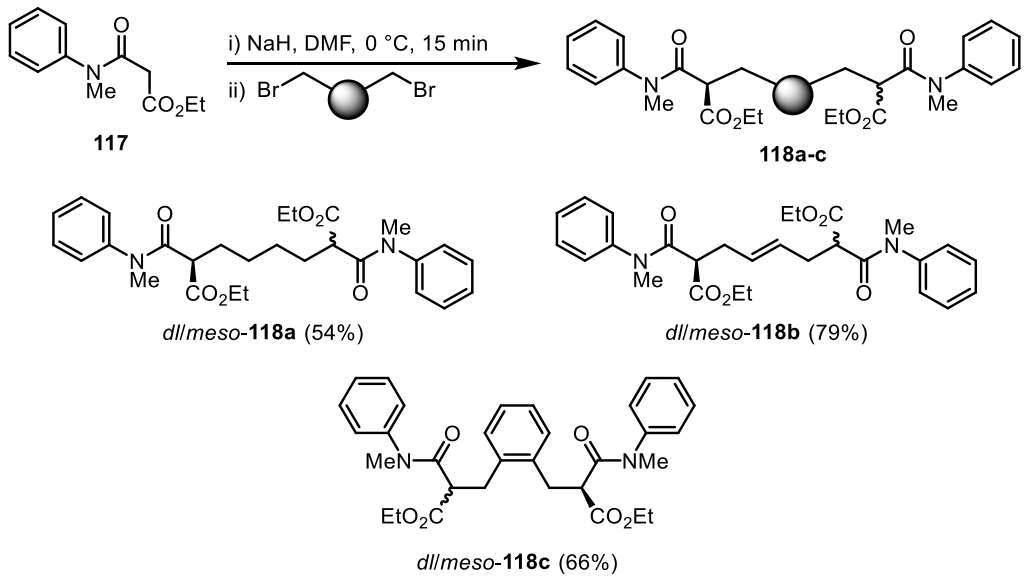
2.4 Synthesis of ester-containing bis-oxindoles

Finally, the nature of the electron-withdrawing group at C3 of both oxindole units was also varied. This specific design extended the range of linker units used for the substrate synthesis as the electron-withdrawing group would be separate from the linker.

2.4.1 General approach for the formation of bis-anilides containing ester functionalities

The one-pot synthesis of bis-anilides **118a-c** started with anilide **117**, which upon treatment with NaH generated the respective enolate. The latter was subsequently trapped with the requisite dibromide electrophile (Scheme 2.21). The diester bis-anilides **118a-c** were obtained in good yield. No diastereocontrol was observed during the substrate synthesis; this is unconsequential as the radical mechanism involved in the C–H, Ar–H functionalisation

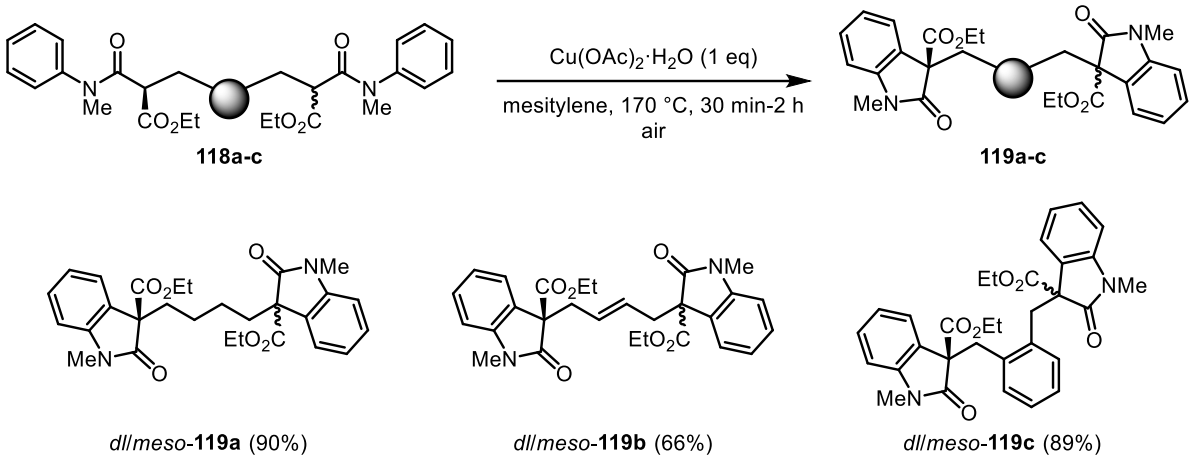
would not retain any stereogenic information. Variety in the linker was investigated and pleasingly, saturated ($(CH_2)_4$, **118a**), unsaturated ($CH_2(CH)_2CH_2$, **118b**), and benzylic (**118c**) central cores were tolerated.



Scheme 2.21. Synthesis of ester-containing bis-anilide cyclisation precursors. All compounds were obtained as a 1:1 mixture of diastereoisomers.

2.4.2 Scope of the double cyclisation reaction

With **118a-c** in hand, the double cyclisation reaction was attempted using $Cu(OAc)_2 \cdot H_2O$ (1 eq) in mesitylene at 170 °C. Pleasingly, bis-oxindole **119a** was obtained in excellent yield and short reaction time (Scheme 2.22). Whilst bis-anilide **118a** was converted into the corresponding bis-oxindole **119a** in 30 minutes, a longer reaction time (i. e. up to 2 hours) was required for the conversion of bis-anilides **118b-c** into bis-oxindoles **119b-c**. Fortunately, the yield of the reaction was not affected and the cyclised product **119b-c** were obtained in 66% and 89% yield, respectively. Unsurprisingly, all bis-oxindoles **119a-c** were obtained as an inseparable mixture of diastereoisomers (dr 1:1), owing to the flexibily of the central core.



Scheme 2.22. Synthesis of ester-containing bis-oxindoles.

2.5 Conclusion

The double cyclisation of bis-anilides has been developed using a double copper(II)-mediated C–H, Ar–H functionalisation to efficiently construct the bis-oxindole scaffold. The use of inexpensive and air-stable copper salts ensured the oxidative coupling proceeded in often good yields and with short reaction times. A variety of bis-anilides have been synthesised and afforded a large number of bis-oxindoles. The double copper(II)-mediated coupling has been shown to proceed in a diastereoselective manner for the spirocyclic bis-oxindoles giving only the *trans*-products.

A diastereoselective variant of the process has been investigated using a chiral auxiliary on the nitrogen atom of both oxindole units and a low level of stereoselectivity was induced.

Whilst the rigid central core of the spirocyclic bis-oxindoles offered a great level of diastereocontrol, very low diastereocontrol was observed for the more flexible monoketone and diester-derived bis-oxindoles.

The research described in this Chapter was recently published as a communication[51] which was subsequently followed by a full paper.[52]

Chapter 3. The synthesis of indole derivatives

3.1 Introduction to 3H-indoles

3.1.1 Chemical and biological importance of indoles

The indole scaffold is one of the most important heterocycles found in Nature.[53] Identified by Hopkins and Cole in 1901, the indole-based amino acid L-tryptophan (**120**) is involved in many aspects of human nutrition and metabolism.[54] Direct decarboxylation of L-tryptophan (**120**) by tryptophan decarboxylase (TPD) leads to tryptamine (**121**) (**eq. a**, Figure 3.1), which constitutes the skeleton of a vast number of monoterpene indole alkaloids. L-Tryptophan (**120**) is also the biogenetic precursor of 5-hydroxy-L-tryptophan (**122**) and serotonin (**123**), with amino acid **120** first hydroxylated by a tryptophan hydroxylase (TPH) and further decarboxylated to afford the 5-hydroxylated tryptamine **123** (**eq. b**, Figure 3.1).

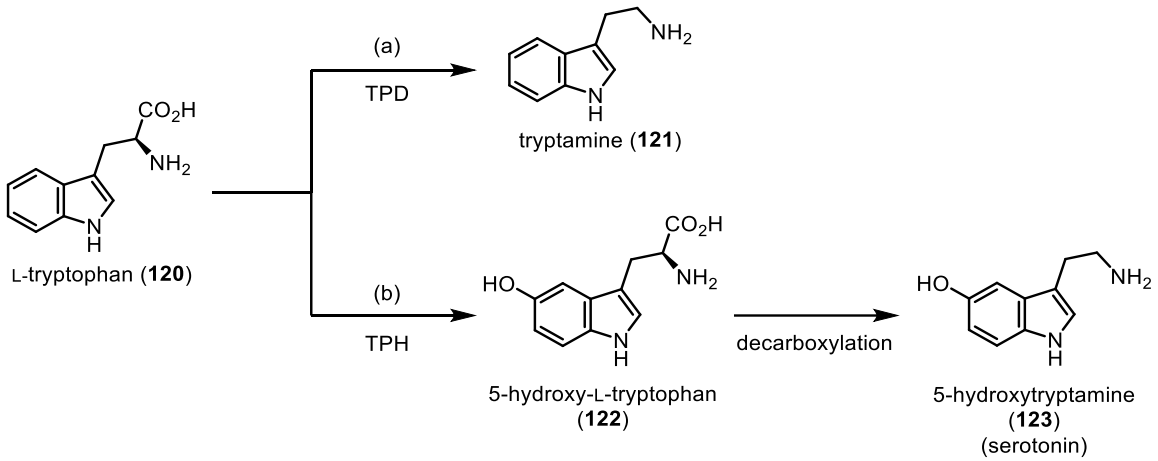


Figure 3.1. Selected examples of naturally occurring indole derivatives.

From the 1950s, the chemistry of indole started expanding significantly and several structurally diverse indoles were found to exhibit varied and potent biological activities. Nowadays, the indole scaffold appears to be one of the best represented heterocyclic motifs present in the top selling pharmaceuticals.[55] Drugs such as GlaxoSmithKline's serotonin receptor modulators sumatriptan (**124**, Imitrex) and zolmitriptan (**125**, Zomig) are representative examples (Figure 3.2). Also, plants rich in alkaloids continue to provide

diverse and novel indole-containing compounds. For example, criofolinine (**126**) was isolated from a *Malayan Tabernaemontana* species and its structure fully elucidated by Kam in 2014.[56]

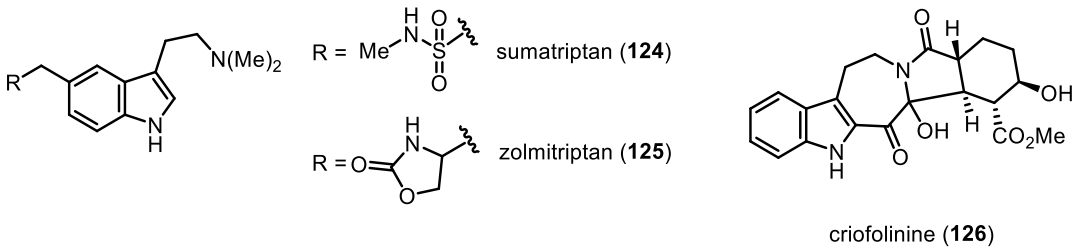


Figure 3.2. Examples of indole-containing drugs and a natural product.

Among the family of indole derivatives, 3,3-disubstituted indolenine (3*H*-indole) scaffolds have attracted considerably less attention, possibly explained by their challenging indolenine ring, which contains a reactive imine moiety, and the presence of a quaternary carbon at C3. With regard to both natural product and pharmaceutical synthesis, the indolenine structure remains a significant challenge to access. Some structurally diverse examples include flustramine C[57] (**127**, Figure 3.3), kopsifoline D[58] (**128**) and E[58] (**129**). Moreover, the synthetically interesting spiro-aziridine indolenine derivatives **130** have been shown to possess inherent antimicrobial activities against *P. diminuta* and *E. coli* (Gram-negative bacteria) and *B. subtilis* and *B. megaterium* (Gram-positive bacteria).[59] Also identified as a promising intermediate towards the formation of indoline-type natural products, 3*H*-indoles have emerged as target substrates for the synthesis of physovenine[60] (**131**) or physostigmine[61] (**132**).

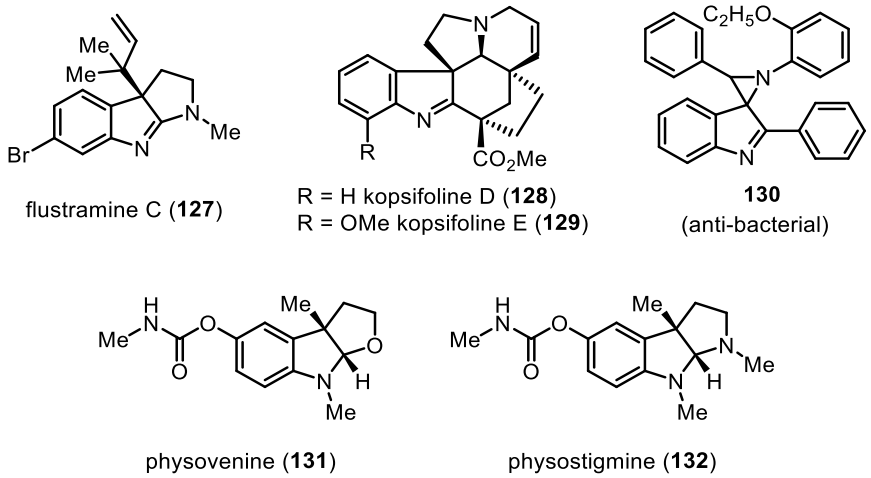


Figure 3.3. Examples of C3 quaternary indolenines and indoline compounds.

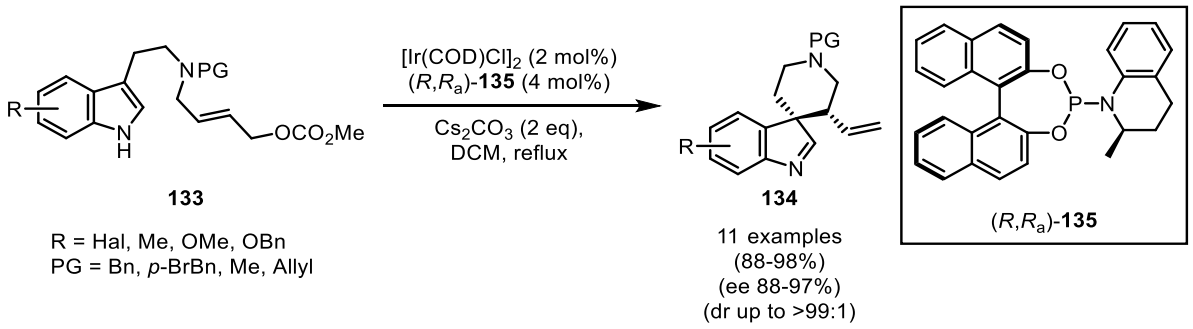
Therefore, the development of methods for the synthesis of this privileged structure still remains of interest to synthetic chemist. While many routes exist for the construction of 1*H*-indoles, fewer approaches enable the formation of indolenine products. Predominantly, the disconnection occurs *via* the dearomatisation of indoles but, recently cyclisation processes have also been reported.

3.1.2 Studies on the indolenine motif

3.1.2.1 Approaches to 3*H*-indoles by dearomatisation of indoles

The nucleophilic properties of indole are attributed to the enamine moiety which provides nucleophilic character at the C3 position. A number of approaches have been developed to exploit the nucleophilic properties of indole for the synthesis of 3*H*-indoles.

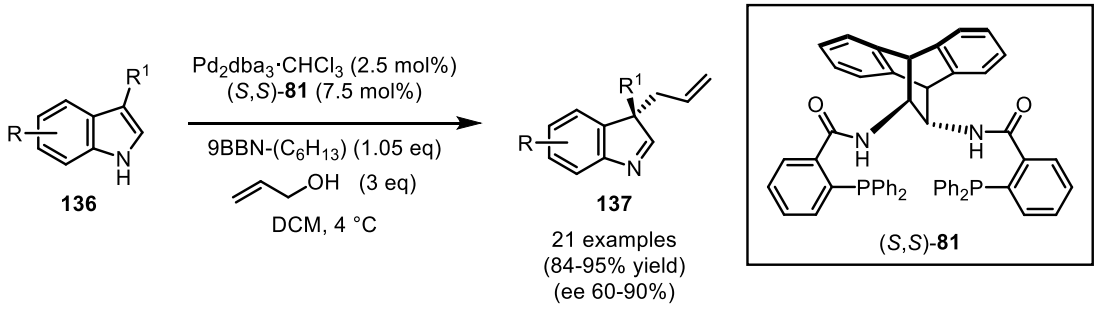
In 2010, You *et al.* developed an enantioselective method for the synthesis of spiroindolenines **134** *via* an Ir-catalysed asymmetric allylic alkylation (Scheme 3.1).[62] Readily available indoles **133** were converted into highly enantioenriched 3*H*-indoles **134**, using a well-developed Ir-catalytic system involving $[Ir(COD)Cl]_2$ and a phosphoramidite ligand **135**, with excellent yields (88-98%) and great diastereo- and enantio-control (up to >99:1 dr and 97% ee).



133 134

Scheme 3.1. Allylic alkylation route to spiroindolenines **134**.

The intermolecular dearomatisation of 3-substituted indoles to give C3-quaternary indolenines has also been investigated with non-activated electrophiles. One of the earliest examples was reported in 2006 by Trost *et al.* who examined the formation of enantioenriched indolenine derivatives **137** using a palladium-catalysed C3 allylation of 3-substituted indoles **136** (Scheme 3.2).[63] The best yields and enantioselectivities were achieved using a Pd complex formed with $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%) and Trost's anthracene-derived ligand **81** (7.5 mol%), together with 9BBN-(C_6H_{13}) (1.05 eq) and allyl alcohol (3 eq). The boron species is tightly bound to the indole nitrogen, thus promoting reaction at C3 over *N*-allylation. The nature of the substituent R^1 could vary without influencing the allylation results, and numerous alkyl side chains containing heteroatoms were tested and gave more complex indoline motifs, resulting from the intramolecular cyclisation of the appended nucleophile into the imine moiety.



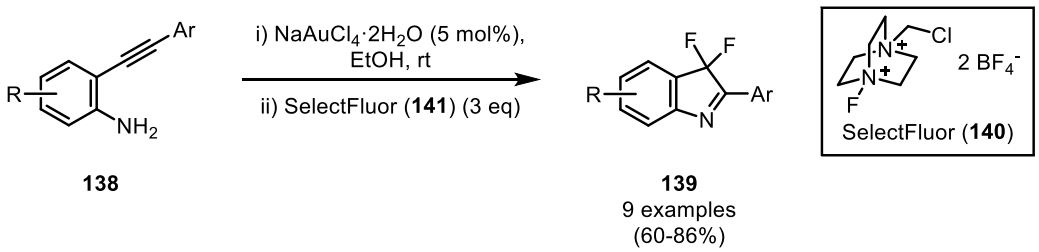
136 137

Scheme 3.2. Pd-catalysed C3 allylation to give 3*H*-indoles **137**.

Whereas the formation of the indolenine motif is well-precedented using indole precursors, only few examples exist on the cyclisation of linear substrates to 3*H*-indoles.

3.1.2.2 C–N Bond Disconnection Strategies

The formation of a C–N bond constitutes one of the most established procedures in heterocyclic chemistry.[64] Michelet and Arcadi reported in 2013 the formation of 3,3-difluorinated 3*H*-indoles **149** *via* an intramolecular gold(I)-catalysed 5-endo dig aminofluorination cyclisation of 2-alkynylanilines **138** in good to excellent yields using mild conditions (Scheme 3.3).[65] Excess of the electrophilic fluorine reagent (SelectFluor (**140**): 3 eq) was found to be crucial to promote the formation of indolenine derivatives **139**. Decreasing the amount of fluorinating agent in the reaction stopped the second fluorination from occurring and gave 1*H*-indoles exclusively. A year later, You and co-workers developed a very similar method and extended the formation of 3,3-difluorinated 3*H*-indoles *via* a silver-catalysed one-pot cyclisation/fluorination of 2-alkynylanilines.[66]

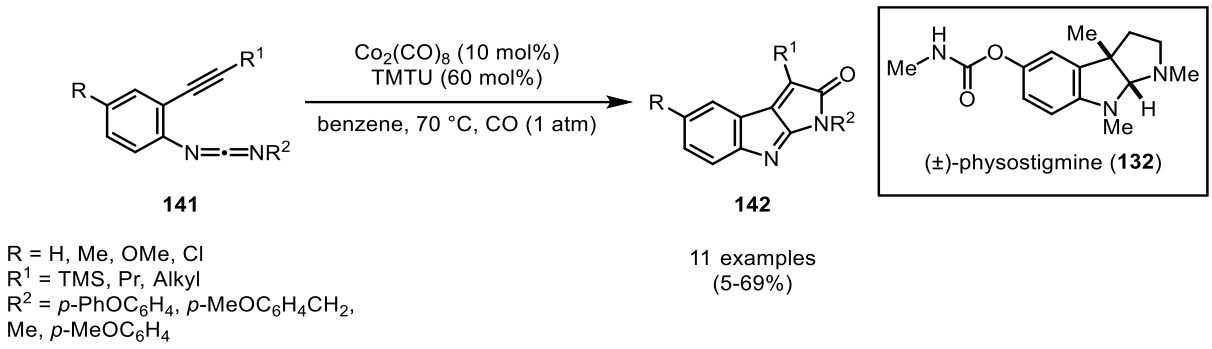


138 **139** 9 examples (60-86%)

Scheme 3.3. Synthesis of 3,3-difluorinated indoles **139** from 2-alkynylanilines **138**.

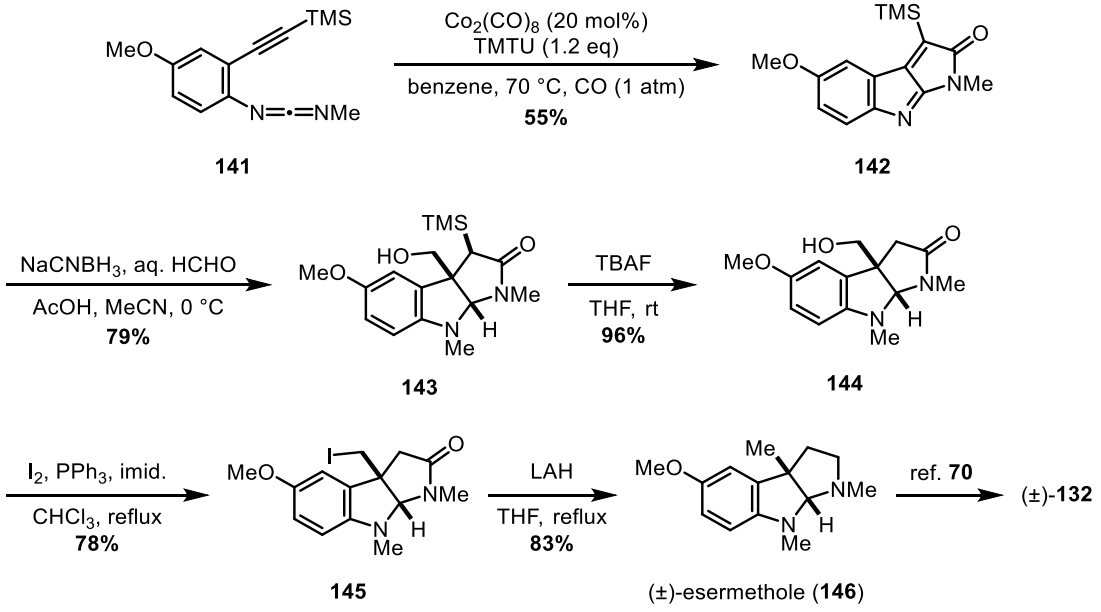
3.1.2.3 C2-C3 Bond Disconnection Strategies

A C2-C3 bond disconnection approach was developed by Mukai and co-workers in their studies towards the formal synthesis of (±)-physostigmine (**132**).[67] They have demonstrated the use of a $Co_2(CO)_8$-catalysed intramolecular aza-Pauson-Khand reaction of alkynecarbodiimide **141** to access the fused-indolenine adducts **142** (Scheme 3.4). A wide range of substitution was tolerated and afforded the 3*H*-indole derivatives in moderate to good yields.



Scheme 3.4. Aza-Pauson-Khand reaction of alkynecarbodiimides **141** to give indolenines **142**. (TMTU = tetramethylthiourea)

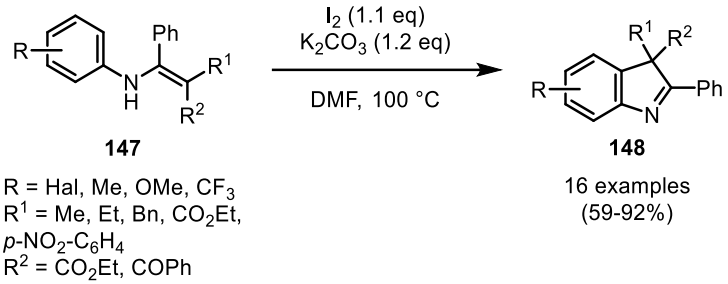
A precedented route was used to synthesise carbodiimide intermediate **141** involving the formation[68]/dehydration[69] of a urea moiety from a readily available aniline precursor. The key aza-Pauson-Khand-type step promoted the formation of the cyclic indolenine adduct **142** in 55% yield (Scheme 3.5). Treatment of indolenine **142** with $NaCNBH_3$ in the presence of aq. HCHO resulted in the reductive methylation and formed the indoline-derived product **143**. Removal of the TMS group with TBAF gave the primary alcohol **144**, which was then converted into the iodinated intermediate **145** in 78% yield. Final treatment with LAH completed the racemic total synthesis of (±)-esermethole (**146**), also completing the formal synthesis of (±)-physostigmine (**132**).[70]



Scheme 3.5. Studies towards the formal synthesis of (±)-physostigmine (**132**).

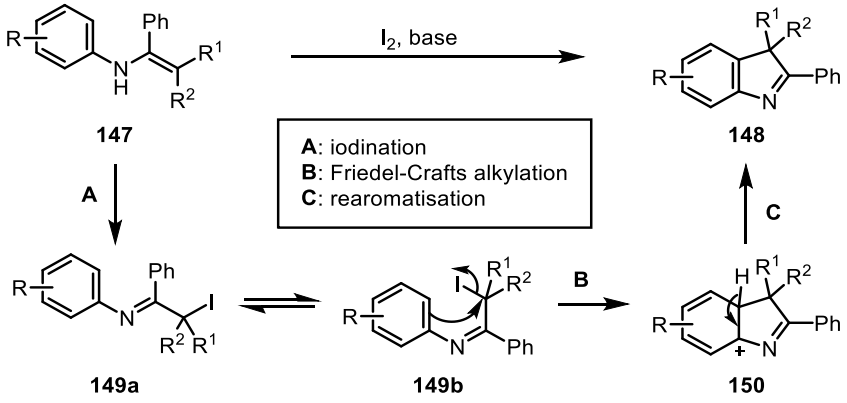
3.1.2.4 C3-C3a Bond Disconnection Strategies

To date, only one literature example refers to the cyclisation of linear precursors to give 3*H*-indoles *via* C3-C3a bond formation which make this strategy very demanding. Li and co-workers reported in 2010 an iodine-mediated oxidative coupling approach to the cyclised product **148** from readily available *N*-aryl enamines **147** in good to excellent yields (Scheme 3.6).[71]



Scheme 3.6. Iodine-mediated synthesis of 3*H*-indoles **148** from *N*-aryl enamines **147**.

Their mechanistic investigations suggest that the cyclisation occurs through a Friedel-Crafts aromatic substitution (Scheme 3.7). The iodination of enamine **147** proceeded through the formation of intermediate **149**. Then, Friedel-Crafts aromatic substitution enabled the intramolecular cyclisation by means of displacement of the iodine atom and gave the carbocation species **150**. Further rearomatisation resulted in the formation of the 3*H*-indole product **148**.



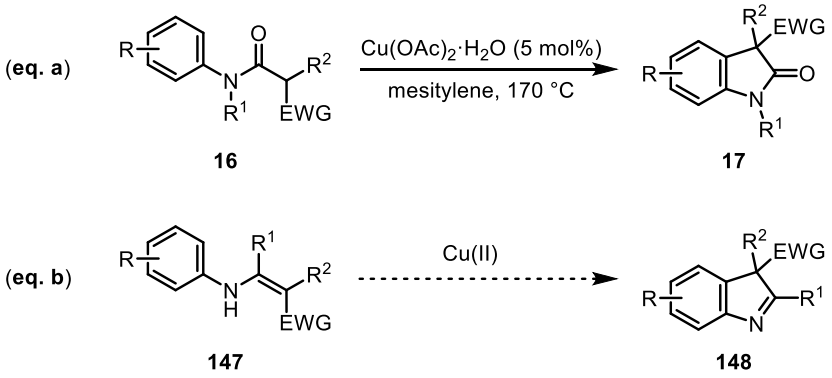
Scheme 3.7. A proposed mechanism for the formation of 3*H*-indole **148**.

3.2 A copper(II)-mediated oxidative coupling approach to 3H-indoles

3.2.1 Proposed synthetic route to 3*H*-indoles

In 2009, the Taylor group reported the cyclisation of anilide precursors **16** to oxindoles **17** *via* a copper(II)-catalysed C–H, Ar–H coupling (**eq. a**, Scheme 3.8).[16] The transformation enabled access to highly substituted oxindoles bearing a quaternary carbon at C3.

Following the continued interest in the development of new methods towards the formation of biologically relevant heterocycles, the possibility of applying the developed copper(II)-methodology to the synthesis of indole-based molecules was investigated. It was proposed that *N*-aryl enamines **147** could be cyclised into the corresponding indolenine products **148** (**eq. b**, Scheme 3.8) by means of a copper(II) oxidative coupling route.

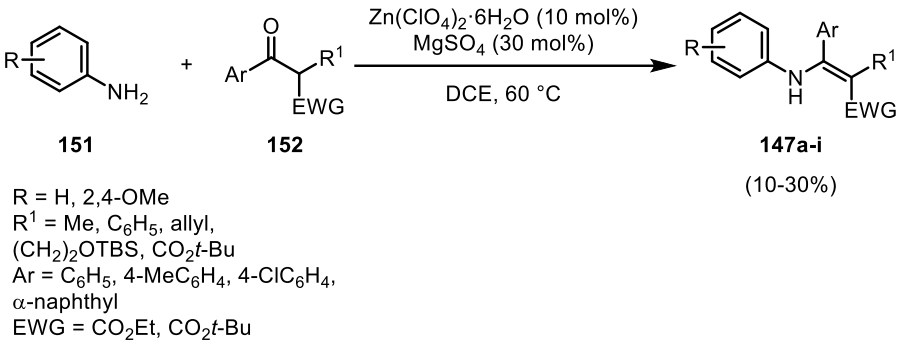


Scheme 3.8. Proposed route to 3*H*-indoles **148** from *N*-aryl enamines **147**.

3.2.2 Strategies for the formation of *N*-aryl enamines

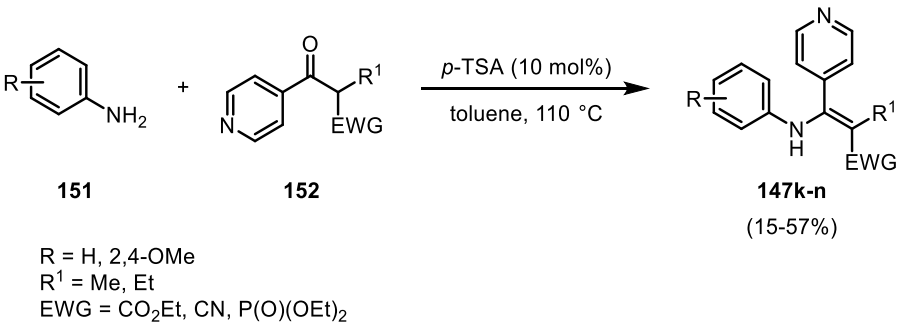
Prior to the iodine-mediated cyclisation to 3*H*-indoles, Li and co-workers proposed the synthesis of the enamine precursors **147** by means of a condensation reaction of anilines **151** with β-ketoester derivatives **152** using zinc perchlorate.[71] The addition of $MgSO_4$ was suggested to keep the reaction mixture under anhydrous conditions. Although this reaction suffers from the low nucleophilicity of the aniline compounds and causes the reaction to be sluggish, no other method has proven more successful than the latter. So, the synthesis of *N*-aryl enamines **147** using the zinc-mediated condensation between commercially available anilines **151** and readily available β-ketoesters **152** was conducted (Scheme 3.9). Not

surprisingly, condensed products **147** were obtained in poor to moderate yields ranging from 10 to 30%. The enamine **147** was purified by column chromatography, fully characterised and was in agreement with the data already reported by Li and co-workers.[71] Difficulties were observed with this route when the aromatic group at C2 was switched from a phenyl to a pyridine ring and at this point another method was considered.



Scheme 3.9. Synthetic approach to *N*-aryl enamines following Li's procedure.

A different method using a Dean & Stark apparatus was investigated for the synthesis of pyridine-substituted *N*-aryl enamines. A significant improvement was observed in the condensation process between pyridine-derived β-ketoester starting materials **152** and substituted anilines **151** to afford the resulting enamine products **147** (Scheme 3.10). The reaction took place under acid catalysis and was left overnight at reflux fitted with a Dean & Stark apparatus under an argon atmosphere.



Scheme 3.10. Dean and Stark method applied to the formation of pyridine-substituted enamines.

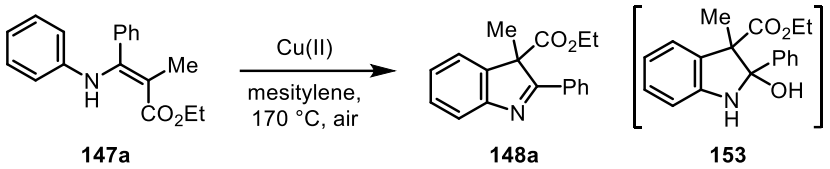
3.2.3 Preliminary studies and optimisations of the reaction conditions

With ethyl (2*Z*)-2-methyl-3-phenyl-3-(phenylamino)prop-2-enoate (**147a**) in hand, it was treated with $Cu(OAc)_2 \cdot H_2O$ (1 eq) in mesitylene at 170 °C. Pleasingly, the cyclised product **148a** was obtained and confirmed the feasibility of the proposed copper(II) oxidative coupling route to give 3*H*-indoles (entry 1, Table 3.1). However, only 21% yield of product was observed by ^{1}H NMR spectroscopy, along with a non-negligible amount of side-product **153**, which appeared to be the result of addition of water into the reactive imine functionality, consistent with the ESI-HRMS data.

This behaviour has already been observed by the group of You, who reported the formation of 3,3-disubstituted indolin-2-ols from indolenine substrates by addition of water in the reaction media.[66] Also, control of the nature of the oxygenated nucleophilic agent was possible with the use of molecular sieves. EtOH as well as benzyl and allyl alcohol were tolerated and afforded the resulting indoline-type motif.

A way to avoid the addition of water and complete the conversion of *N*-aryl enamine **147a** was next investigated. Consequently, the source of copper was switched to commercially available Cu(2-ethylhexanoate)$_2$, an anhydrous copper(II) salt, and the reaction condenser was fitted with a $CaCl_2$ drying trap. No specific care was given to set the reaction under an inert atmosphere.[16] Pleasingly, the cyclisation of **147a** occurred in an improved 78% yield (entry 2). Reduction of the amount of copper in the reaction significantly reduced the yield of the cyclisation and showed more decomposition of starting material (entry 3). It is also worth noting that this protocol requires the presence of copper. Heating the enamine precursor in mesitylene at 170 °C without the copper oxidant resulted only in the decomposition of the enamine **147a**. The 3*H*-indole **148a** was purified by column chromatography, and fully characterised. Pleasingly, the data were consistent with those already reported by Li (see Appendix I for the ^{1}H and ^{13}C NMR spectra).[71]

Table 3.1. Optimisation of the reaction conditions for the cyclisation of enamine **147a**.



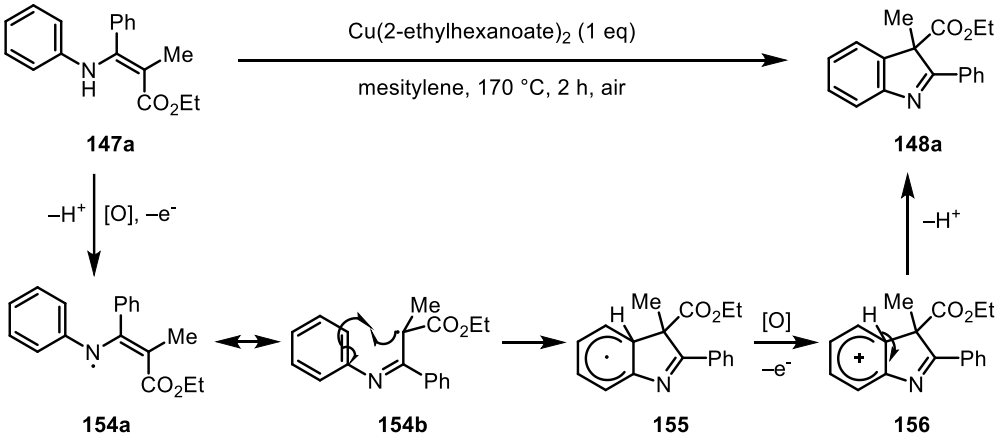
147a 148a 153

entry	Cu-source (eq)	time (h)	yield (% **148a**)
1	$Cu(OAc)_2 \cdot H_2O$ (1 eq)	2	21[a]
2	**Cu(2-ethylhexanoate)$_2$[b] (1 eq)**	**2**	**78**
3	Cu(2-ethylhexanoate)$_2$ (0.1 eq)	3	38
4	-	3	0 (decomp.)

[a] Isolated as an inseparable mixture of **148a** and **153**. According to ^{1}H NMR spectroscopy after purification and mass recovered, the yield of **148a** was determined to be 21% and **153** to be 14%.[b] Cu(2-ethylhexanoate)$_2$ = $[Me(CH_2)_3CH(Et)CO_2]_2Cu$.

3.2.4 Suggested mechanism for the formation of 3*H*-indoles

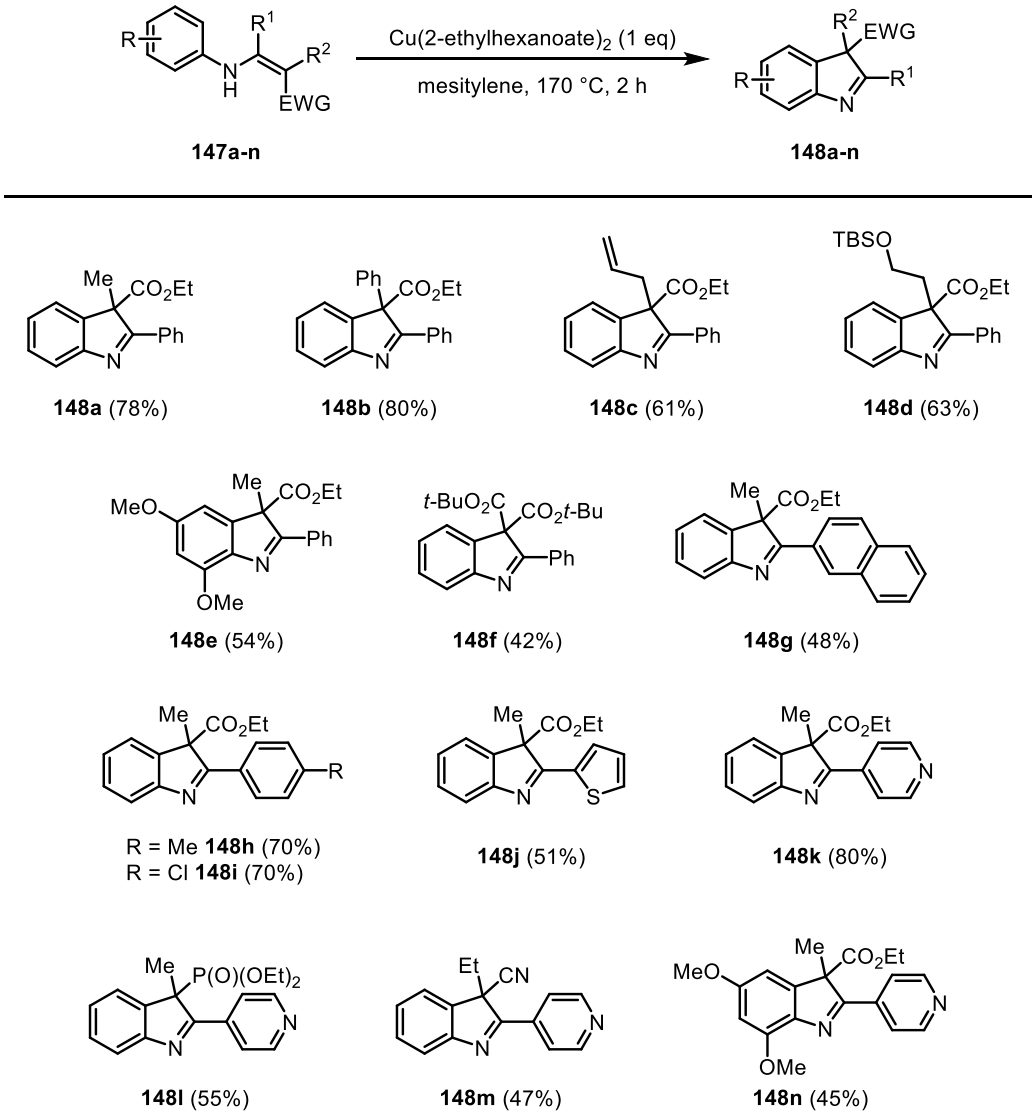
Very similar to the mechanism suggested previously for the formation of oxindoles,[14a] the oxidation of *N*-aryl enamine **147a** was suggested to give the radical intermediate **154** (Scheme 3.11). Then, homolytic aromatic substitution occurs and promotes the formation of the cyclic intermediate **155**. A second oxidation event generates the cyclohexadienyl cation **156** which rearomatises to give the 3*H*-indole **148a**.



Scheme 3.11. Suggested mechanism for the formation of 3*H*-indoles.

3.2.5 Scope of the cyclisation process

Having established successful conditions for the oxidative cyclisation on the model system **147a**, the substrate scope was then tested using a range of *N*-aryl enamines **147a-n** (Scheme 3.12). Varying the nature of the alkyl side-chain at C3 was well tolerated (R^2 = Ph, **148b**, R^2 = allyl, **148c**). The oxygen-containing substrate **148d**, of interest for the synthesis of indoline-type natural products such as physovenine (**131**, Figure 3.3), cyclised in a good 63% yield. An electron-rich aniline was also tolerated (**148e**). The alkyl group at C3 could also be replaced by a second ester functionality (**148f**).



Scheme 3.12. Scope of the cyclisation reaction to 3*H*-indoles.

Attention was predominantly focused on the nature of the aromatic ring at C2 which has not been explored by Li in the iodine-mediated cyclisation to 3*H*-indoles. Pleasingly, the cyclisation occurred and did not reduce the yield of the reaction. In fact, α-naphthyl (**148g**), 4-substituted phenyl (**148h-i**), thiophenyl (**148j**), and pyridinyl (**148k-n**) substituents were well-tolerated. The oxidative copper(II)-mediated coupling route also proceeded upon varying the nature of the electron-withdrawing group at C3 from the ethyl ester to nitrile and phosphonate moieties (**148l-m**). It should be noted that with the exception of **148a**, all cyclised products are novel compounds. A suitable crystal of the indolenine product **148h** was obtained for X-ray crystallographic analysis and conclusively confirmed its structure (Figure 3.4).

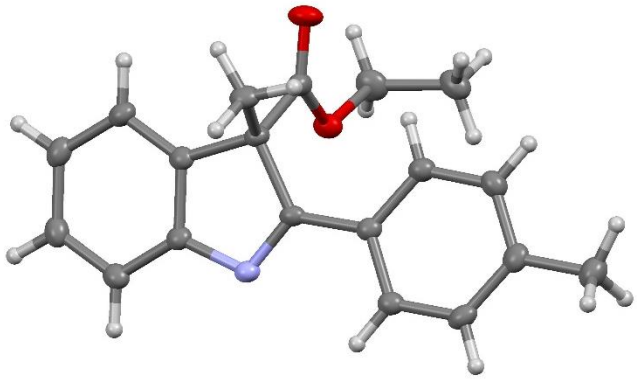
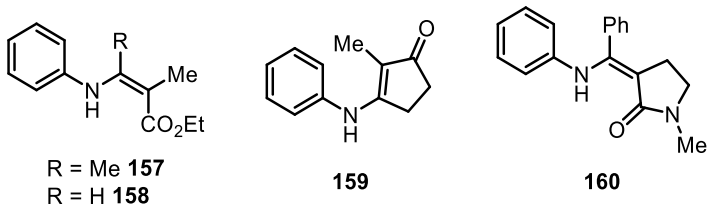


Figure 3.4. Crystal structure of **148h** (50% probability ellipsoids, CCDC 1033699).

3.2.6 Limitations of the cyclisation process

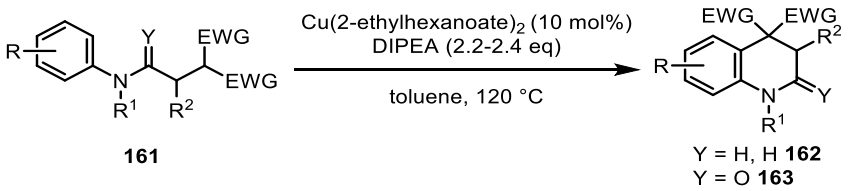
Despite the success of the cyclisation strategy for a wide range of *N*-aryl enamine precursors, this method suffered from limitations with regard to the nature of the substituents around the enamine moiety. Notably, the presence of a C2 aryl substituent appeared crucial for the oxidative coupling reaction to proceed; starting materials were recovered for substrates **157**, **158**, and **159** which had non-aromatic functional groups at C2 (Scheme 3.13). In the case of **160**, the starting material was consumed but no spirocyclic 3*H*-indole product was isolated. Steric hindrance at the spirocyclic junction may have been the problem in this specific example.



Scheme 3.13. Limitation in the scope of the cyclisation to indolenine compounds.

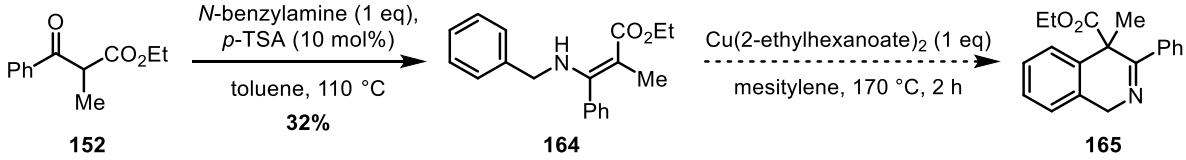
3.2.7 Studies on the cyclisation of *N*-benzyl enamine

Extended recently by the Taylor group, the copper(II)-mediated oxidative coupling route has also been applied to the synthesis of interesting scaffolds such as tetrahydroquinolines **162** and dihydro-1*H*-quinolin-2-ones **163** (Scheme 3.14).[46] Catalytic amounts of Cu(2-ethylhexanoate)$_2$ (10 mol%) along with Hünig's base (2.2-2.4 eq) were sufficient to successfully convert linear and non-functionalised precursors **161** into the corresponding cyclic products **162-163**.



Scheme 3.14. Previous approach on copper(II)-mediated cyclisation to related 6-membered ring system.

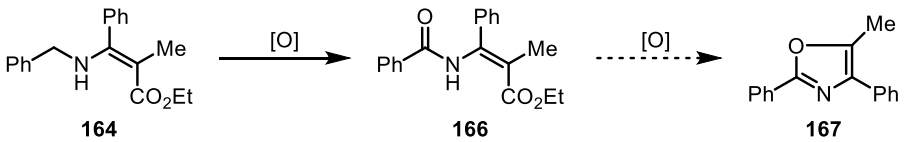
Alongside the formation of 3*H*-indoles, the copper(II)-mediated oxidative coupling route to the synthesis of 1,4-dihydroisoquinolines **165** from *N*-benzyl enamines **164** was envisioned. The investigation started with the synthesis of ethyl (2*Z*)-3-(benzylamino)-2-methyl-3-phenylprop-2-enoate (**164**) using the Dean & Stark procedure. Treatment of the β-ketoester **152** with *N*-benzylamine and *p*-TSA afforded the resulting condensed product **164** in 32% yield (Scheme 3.15).



Scheme 3.15. Proposed route for the synthesis of 1,4-dihydroisoquinolines **165**.

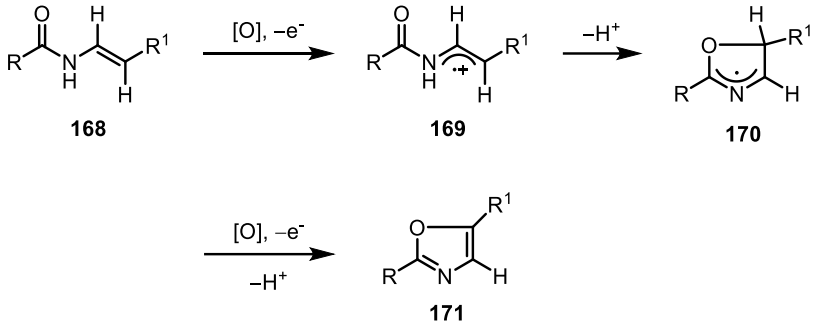
For initial investigations, the linear precursor **164** was treated with Cu(2-ethylhexanoate)$_2$ (1 eq) in mesitylene at 170 °C for 2 h. No starting material remained after 2 h by TLC and a new UV-active spot was detected. However, ESI-HMRS data were not consistent with the expected 1,4-dihydroisoquinoline **165** and indicated that the resulting product had the chemical formula $C_{16}H_{13}NO$. Analysis of the isolated product by ^{1}H NMR spectroscopy suggested the disappearance of the ester by the absence of any triplet around 1.30 ppm corresponding to the CH_3 group as well as multiplet at 4.15-4.23 ppm assigned as the CH_2 of the ethyl ester functionality. Also, ^{1}H NMR spectroscopy of the product revealed that all the aromatic protons from the starting material were retained and a new singlet at 2.61 ppm appeared which integrated for 3 protons. This singlet seemed deshielded for a methyl group, and suggested that this methyl should be adjacent to a heteroatom. Examination of all the data suggested the formation of the oxazole product **167** (Scheme 3.16). The oxazole **167** was characterised by NMR spectroscopy and ESI-HRMS analysis and the data were consistent with those already reported.[72]

Mechanistically, oxidation of substrate **164** at the benzylic position was suggested to occur first to give the enamide **166** (Scheme 3.16). A copper-catalysed aerobic oxidation from benzylamines was already reported by Fu, and afforded the corresponding amides in good yield.[73]



Scheme 3.16. Proposed oxidation of *N*-benzyl enamine.

Subsequently, the formation of the oxazole was proposed to follow an oxidative coupling pathway, already reported by the group of Buchwald,[74] and Stahl.[75] They concurrently suggested that Cu(II) could be used as a single-electron oxidant to convert enamide **168** into an enamide radical cation **169** (Scheme 3.17), which then cyclised to the radical intermediate **170**. Subsequent oxidation of the radical species **170** using Cu(II) was proposed to give the oxazole **171**. Further decarboxylation would be required, in our system, to access the oxazole product **167** from substrate **164**.



168 **169** **170** **171**

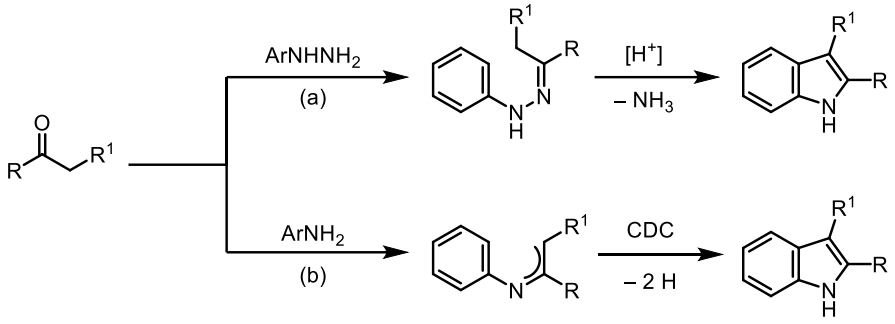
Scheme 3.17. Buchwald's reported mechanism for the formation of oxazole **171**.

3.3 Introduction to 1H-indoles

Given the success of the Cu(II)-mediated oxidative coupling route with 3*H*-indoles, the approach was extended to prepare related 1*H*-indoles.

3.3.1 Studies on the 1*H*-indole motif

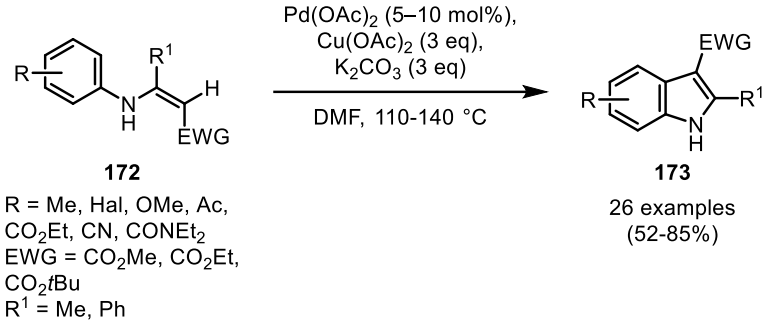
Despite a plethora of protocols to prepare 3-substituted indoles, interest still remains in new practical procedures with a low environmental impact. While classical methods such as the Fischer indole synthesis[76] (**eq. a**, Scheme 3.18) have been used for more than a hundred years, the transition metal-catalysed cyclisation of linear enamine precursors has recently emerged as a powerful alternative to access the indole motif (**eq. b**, Scheme 3.18).[77]



Scheme 3.18. a) The Fischer indole synthesis and b) Cross-Dehydrogenative Coupling (CDC) approach to 1*H*-indole synthesis.

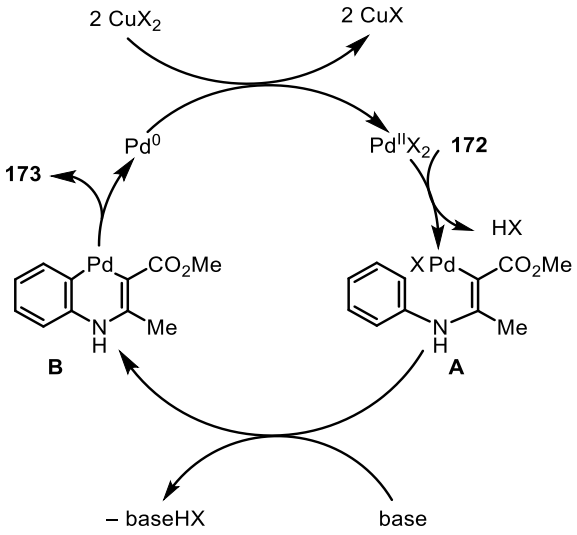
3.3.2 Glorius' approach to 1*H*-indoles

In 2008, Glorius and co-workers reported the efficient synthesis of functionalised indoles **173** using a palladium-catalysed, intramolecular oxidative coupling (Scheme 3.19).[78] A great variety of substituted anilides **172** were converted into indoles in excellent yields using $Pd(OAc)_2$ (5-10 mol%), $Cu(OAc)_2$ (3 eq) as the oxidant, and K_2CO_3 (3 eq) as the base. Importantly, removing the palladium catalyst from their reactions was detrimental to the formation of indoles as only traces of cyclised product were then observed.



Scheme 3.19. Glorius' CDC approach to 1*H*-indole derivatives.

A plausible mechanism reported by Glorius involves an initial electrophilic palladation of the nucleophilic enamine **172**, followed by deprotonation to give intermediate **A** (Scheme 3.20). Intramolecular C–H activation gives palladacycle **B** and subsequent reductive elimination generates the indole product **173** and a Pd^0 complex. The stoichiometric amount of $Cu(OAc)_2$ plays an essential role to oxidise the Pd^0 back to Pd^{II} completing the catalytic cycle.

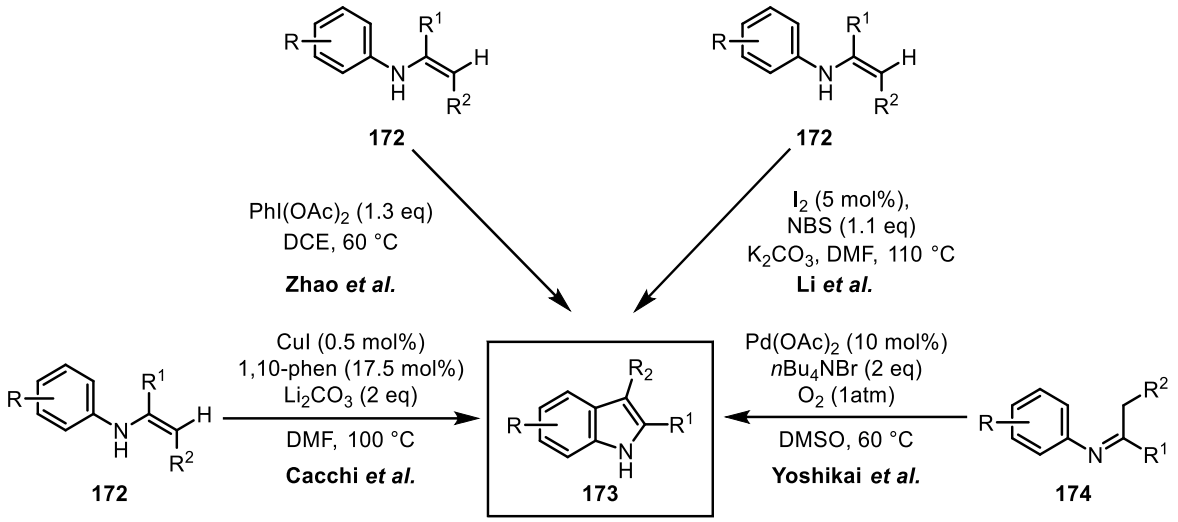


Scheme 3.20. Mechanism suggested for the cross-dehydrogenative palladium-catalysed coupling reaction to indoles **173**.

3.3.3 Other routes to 1*H*-indoles

Following Glorius' seminal report on the CDC approach to 1*H*-indoles, many groups have studied this transformation and have extended the scope of the reaction. Cacchi and co-workers accomplished the synthesis of indoles **173** from *N*-aryl enaminones **172** *via* an intramolecular copper-catalysed aryl C–H functionalisation process (Scheme 3.21).[79] Zhao *et al.* disclosed a $PhI(OAc)_2$-mediated oxidative coupling to transform *N*-aryl enamines **172** into 1*H*-indoles **173**.[80] Iodine-mediated cyclisation to 1*H*-indoles was also studied by Chan[81] and Li.[82]

Most recently, the Yoshikai group reported an expedient assembly of indole rings **173** from imine precursors **174** *via* a Pd-catalysed approach, allowing considerable broadening of the substrate scope (no need for substitution at C3, even though tolerated).[83] Their catalytic system was also found to work in the cyclisation to form pyrrole derivatives.[83b]

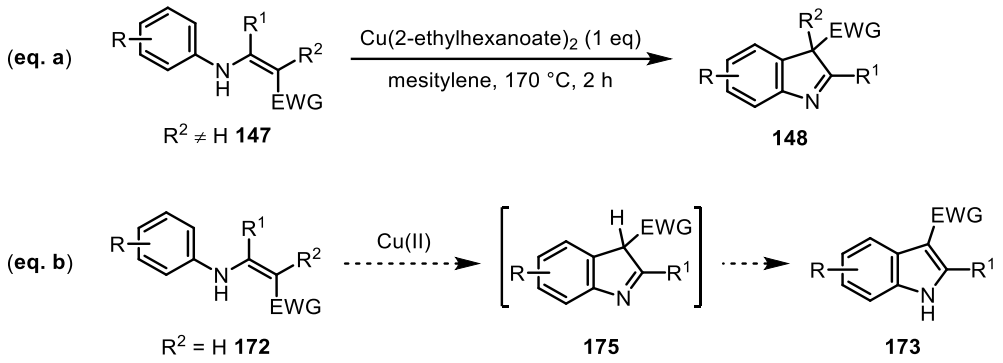


Scheme 3.21. Other routes to 1*H*-indoles from *N*-aryl enamines or imines.

3.4 A copper(II)-mediated oxidative coupling approach to 1H-indoles

3.4.1 Proposed synthetic route to 1*H*-indoles

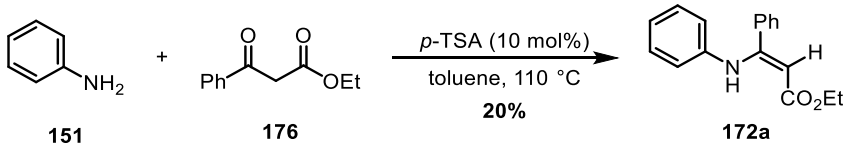
Given the success of the Cu(II)-mediated cyclisation to 3*H*-indoles (**eq. a**, Scheme 3.22), the construction of related 1*H*-indoles was envisioned (**eq. b**, Scheme 3.22). The only difference between both reactions would reside in the nature of the *N*-aryl enamines involved in the copper(II)-mediated cyclisation process. While R^2 cannot bear a hydrogen at C3 for the formation of 3*H*-indoles, it would be a requirement for the synthesis of 1*H*-indoles. It was assumed that after initial cyclisation of enamine **172**, the 3*H*-indole intermediate **175** would tautomerise and give the aromatic 1*H*-indole **173**.



Scheme 3.22. Proposed route to 1*H*-indoles from *N*-aryl enamines.

3.4.2 Preliminary studies and optimisation of the reaction conditions

Preliminary studies for the formation of indoles using a copper(II)-mediated oxidative coupling was envisioned. The readily prepared *N*-aryl enamine **172a** was used to optimise the reaction. Treatment of commercially available ethyl benzoylacetate (**176**) with aniline (**151**) in presence of a catalytic amount of *p*-TSA afforded the known enamine[78] **172a** in moderate yield (Scheme 3.23).

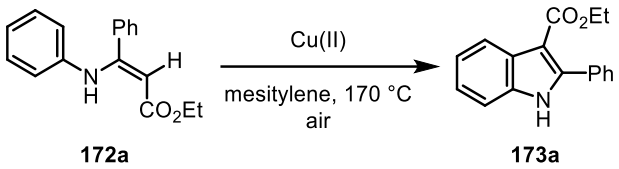


151 **176** **172a**

Scheme 3.23. Synthesis of enamine **172a** from aniline and ethyl benzoylacetate.

With practical quantities of precursor **172a** in hand, the proposed Cu(II)-mediated oxidative coupling approach for the synthesis of 1*H*-indoles was tested. The reaction of ethyl (2*Z*)-3-phenyl-3-(phenylamino)prop-2-enoate (**172a**) with Cu(2-ethylhexanoate)$_2$ gave the desired product but only in a moderate 54% yield (entry 1, Table 3.2). Varying the copper salt to Cu(OAc)$_2$·H$_2$O significantly improved the yield of the cyclisation to 69% (entry 2). As noticed earlier while optimising conditions of 3*H*-indoles, reducing the amount of copper(II) in the reaction significantly lowered the yield of the cyclisation product (entry 3). Pleasingly, when the reaction was carried out without copper salt, only decomposition of the enamine substrates was observed (entry 4). It should be noted that all reactions were carried out under air atmosphere, without a CaCl$_2$ drying trap fitted to the reaction condenser. Indole **173a** was purified by column chromatography and fully characterised. Pleasingly, the data were consistent with those reported by Glorius.[78]

Table 3.2. Optimisation of the reaction conditions for the cyclisation of enamine **172a**.



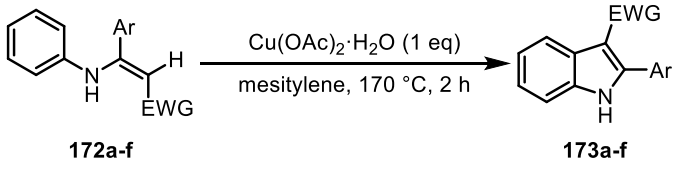
172a **173a**

entry	Cu-source (eq)	time (h)	yield (% **173a**)[a]
1	$Cu(2\text{-ethylhexanoate})_2$ (1 eq)	2	54
2	**$Cu(OAc)_2 \cdot H_2O$ (1 eq)**	**2**	**69**
3	$Cu(OAc)_2 \cdot H_2O$ (0.1 eq)	3	17
4	-	2	0 (decomp.)

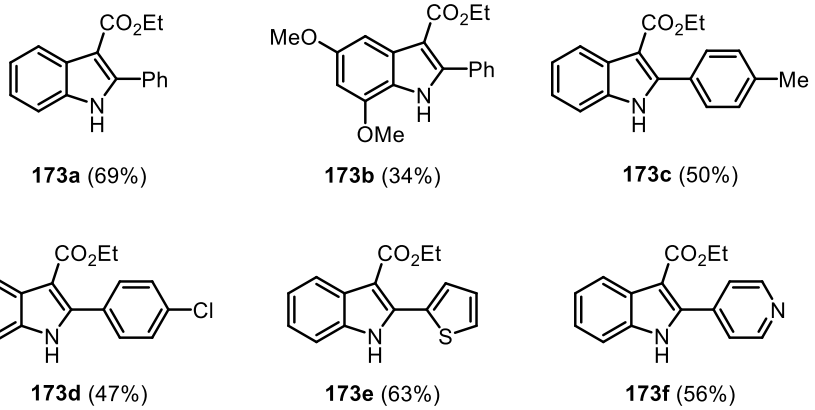
[a] Yield of isolated product.

3.4.3 Scope of the cyclisation process

Having established successful conditions for the cyclisation on the model system **172a**, the substrate scope using a variety of enamine precursors **172a-f** was investigated. Cyclisation of electron-rich enamine **172b** occurred in a moderate 34% yield (**173b**, Scheme 3.24). Different groups at C2 were also tolerated. Thus, 4-substituted phenyl (**172c-d**), 2-thiophenyl (**172e**), and 4-pyridinyl (**172f**) substrates delivered the cyclised products in good yields. Compounds **173b**, **173d-f** were novel and were fully characterised.



172a-f **173a-f**



173a (69%) **173b** (34%) **173c** (50%)

173d (47%) **173e** (63%) **173f** (56%)

Scheme 3.24. Scope of the cyclisation reaction for the formation of 1*H*-indoles.

3.5 Conclusion

An efficient oxidative coupling reaction from easily accessible *N*-aryl enamines has been clearly demonstrated and represents a facile method for the synthesis of indole-based heterocycles. A wide range of readily available β-ketoester and aniline components can be used to prepare the enamine precursors. Furthermore, this oxidative coupling method also has the advantage of employing a very inexpensive and air-stable copper salt. Reaction conditions were optimised with respect to catalyst loading, temperature, solvent and time: $Cu(2\text{-ethylhexanoate})_2$ (1 eq), mesitylene, 170 °C, 2 h, were found to be the optimal conditions for the cyclisation to proceed in high yields. Some limitations of this oxidative coupling process have been established. Notably, the design of the enamine precursor has been shown to require an aryl group at C2. The presence of a hindered pseudo-spirocyclic centre in the enamine precursor had a detrimental impact on the cyclisation. With the exception of **148a**, all cyclised products are novel compounds and were fully characterised. The structure of one indolenine product was proved by X-ray analysis.

With only minor condition changes, a range of 1*H*-indoles have also been prepared with $Cu(OAc)_2 \cdot H_2O$ as the preferred reagent. Four of these compounds were novel.

Finally, the rapid access to indole derivatives using inexpensive metal salts could be of relevance for further application in the synthesis of biologically active compounds.

The work in this Chapter has recently been published.[84]

Chapter 4. Studies towards the total synthesis of rankinidine

4.1 Introduction

4.1.1 *Gelsemium* alkaloids

The genus *Gelsemium*, which belongs to the plant family Loganiaceae, comprises three species: *Gelsemium elegans*, widespreaded over Southeast Asia, together with *Gelsemium rankinii* and *Gelsemium sempervirens*, both of which grow in the southeastern part of the United States of America. More than seventy alkaloids have been isolated from all *Gelsemium* species. These have been classified into six types according to their diverse chemical structures: sarpagine-, koumine-, humantenine-, gelsedine-, gelsemine-, and yohimbane-type alkaloids (Figure 4.1).[85] In addition to either an indole subunit, e.g. in koumidine (**177**), koumine (**178**) and sempervirine (**184**), or an oxindole motif, e.g. in humantenine (**179**), rankinidine (**49**), gelsedine (**180**), gelsemicine (**181**), gelsevirine (**182**) and gelsemine (**183**), these compounds also possess highly strained polycyclic structures to complete their complex alkaloid skeletons.

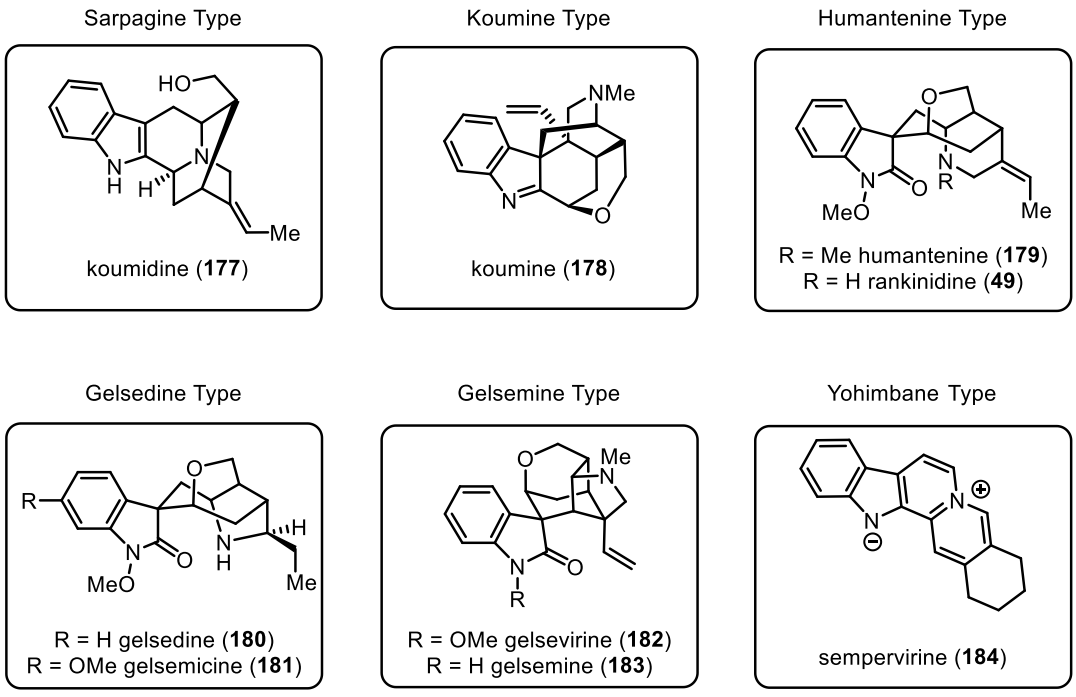


Figure 4.1. Representative *Gelsemium* alkaloid types.

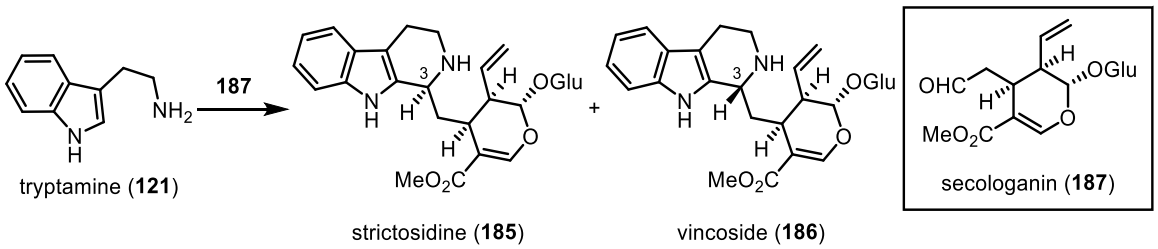
4.1.2 Biological activity of *Gelsemium* alkaloids

From a medicinal perspective, the *Gelsemium elegans* plant itself has been used in traditional Chinese medicine for certain kinds of skin ulcers. Recently, some pharmacological effects, exhibited by extracts of *G. elegans*, including analgesic,[86] anti-inflammatory,[86] and cytotoxic activities,[87] have been reported. It has been previously proved that extracts of *G. elegans* form the basis of 'Yakatsu', one of the ancient medicines stored in the Shosoin repository in Japan.[88] *G. sempervirens* and *G. rankinii* have also been used in the treatment of neuralgia and migraines, as well as spasmodic disorders such as asthma. However, in addition to their useful medicinal properties, it has been known for more than a century that these plants also cause death in both humans and livestock. Gelsemicine (**181**) (Figure 4.1) represents the first toxic component of the *G. sempervirens* extract, isolated by Chou in 1931.[89]

4.2 Biomimetic approaches to Gelsemium alkaloids

4.2.1 Biosynthesis of monoterpenoid indole alkaloids

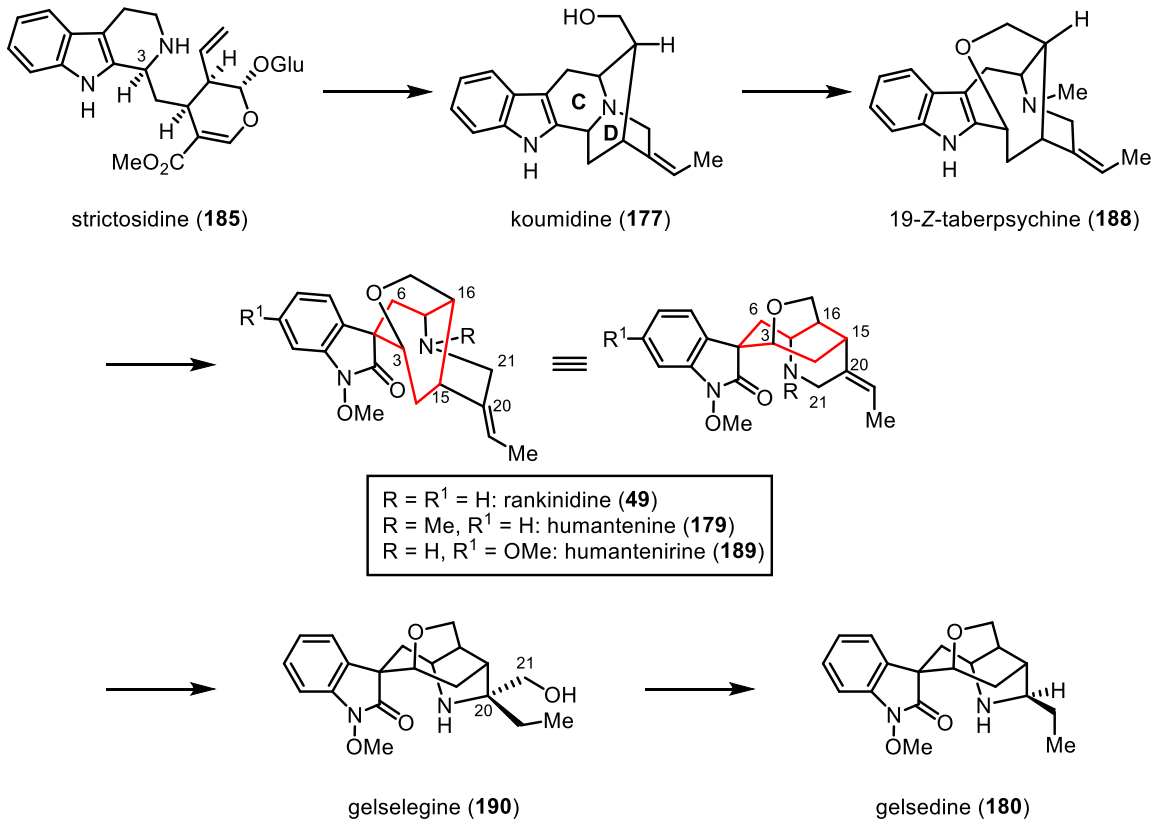
In 1979, Zenk *et al.* proposed a biosynthetic pathway towards monoterpenoid indole alkaloids **185** and **186** (Scheme 4.1). In this context, by condensation of tryptamine (**121**) with secologanin (**187**), two epimers at the C3 position, strictosidine (**185**) and vincoside (**186**), were formed.[90]



Scheme 4.1. Proposed biosynthesis of strictosidine (**185**) and vincoside (**186**).

4.2.2 Biosynthesis of *Gelsemium* alkaloids

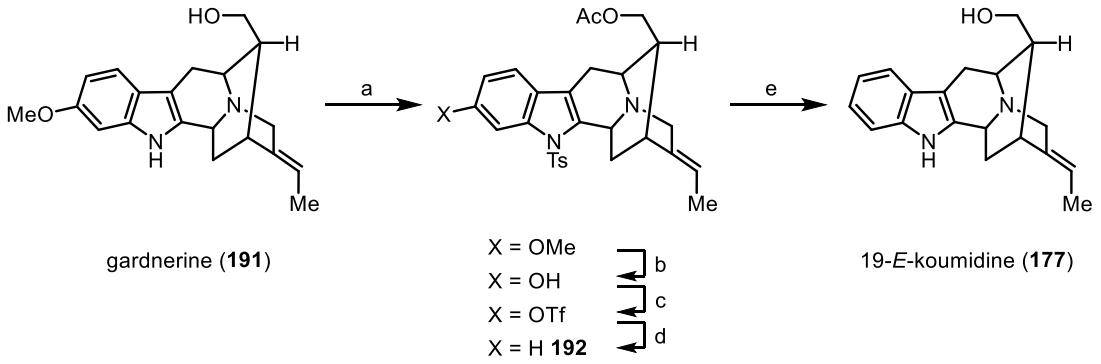
In 1988, Ponglux *et al.* extended this biosynthetic route to most types of *gelsemium* alkaloids (Scheme 4.2).[91] The intermediate strictosidine (**185**), previously reported by Zenk *et al.*, serves as a precursor to sarpagine-type indole alkaloids, such as koumidine (**177**). Metabolism of koumidine (**177**) *via* C/D ring-opening, leads to intermediate 19-*Z*-taberpsychine (**188**). Subsequently, transformation of indole **188** *via* an oxidative rearrangement to oxindole and *N*-methoxylation, gives rise to the humantenine-type alkaloids humantenine (**179**), humantenirine (**189**), and rankinidine (**49**).[92] Expanding their research to gelsedine-type alkaloids, Ponglux *et al.* proposed that gelselegine (**190**) could be derived from humantenine-type alkaloids. As such, access to gelselegine (**190**) occurs by a rearrangement of C21 to the *exo*-position in the D ring of humantenine-type oxindole alkaloids. At this point, construction of gelsedine-type alkaloids is believed to proceed by loss of the C21 carbon present in gelselegine (**190**).



Scheme 4.2. Ponglux's proposed biosynthetic route to *Gelsemium* alkaloids.

4.2.3 First synthesis of *Gelsemium* alkaloids using a biomimetic approach

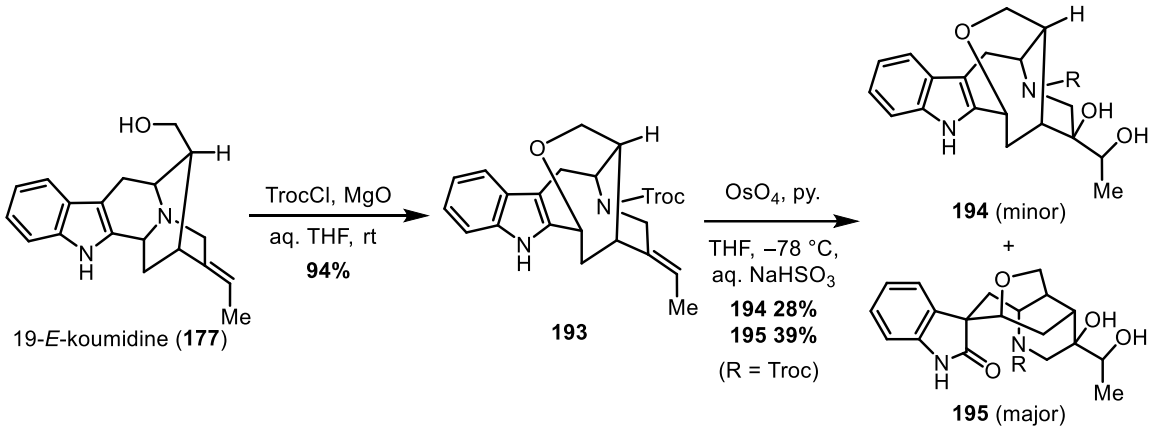
In light of Ponglux's proposed biosynthetic route to *Gelsemium* alkaloids, Takayama *et al.* reported a synthetic procedure for the conversion of the sarpagine-type indole alkaloid **191** into the oxindole alkaloids gelselegine (**190**) and gelsedine (**180**). Gardnerine (**191**) was first transformed into 19-*E*-koumidine (**177**) by a six-step sequence in 62% overall yield (Scheme 4.3).[93] Overall, this sequence involved one structural change, namely removal of the aryl methyl ether to form the intermediate **192**, following Fujita's procedure.[94]



Scheme 4.3. Conversion of gardnerine (**191**) into 19-*E*-koumidine (**177**).

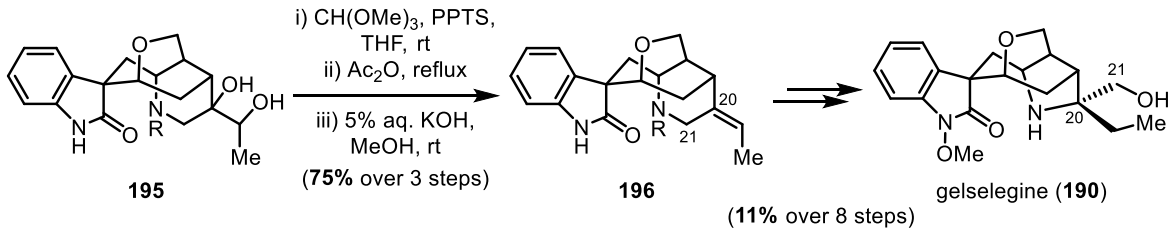
Reagents and conditions: (a) Ac_2O, py., rt, 8 h, 97%; TsCl, *n*-Bu_4NHSO_4, 50% aq. KOH-benzene, rt, 3 h, 98%; (b) $AlCl_3$, EtSH, CH_2Cl_2, −18 °C, 3 h, 91%; (c) Tf_2O, Et_3N, CH_2Cl_2, −20 °C, 10 min, 97%; (d) $Pd(OAc)_2$, DPPF, Et_3N, HCO_2H, DMF, 60 °C, 2 h, 98%; (e) LAH, THF, reflux, 6 h, 95%.

19-*E*-Koumidine (**177**) was treated with 2,2,2-trichloroethyl chloroformate in the presence of magnesium oxide in aqueous THF to generate the ring-opened compound **193** in 94% yield (Scheme 4.4).[95] Dihydroxylation of the exocyclic alkene and the indole C–C double bond in **193** with osmium tetroxide (2 eq) afforded the oxidative rearranged oxindole **195** in 39% yield as well as indole diol **194** in 28% yield where oxidation of the indole nucleus had not taken place. However, partially-reacted product **194** could be further transformed to oxindole **195** by treatment with osmium tetroxide.



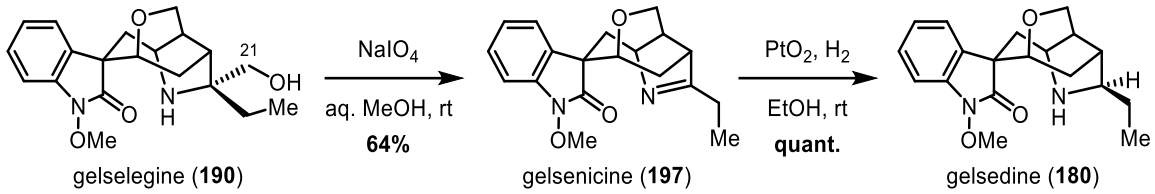
Scheme 4.4. The synthesis of *Gelsemium* alkaloids using a biomimetic route.

With the diol **195** in hand, olefin **196** was obtained *via* a three-step sequence in 75% overall yield (Scheme 4.5). More specifically, treatment of diol **195** with trimethyl orthoformate and pyridinium *p*-toluenesulfonate furnished an orthoester functionality, which was then transformed into the humantenine-type intermediate **196** following treatment with acetic anhydride and aqueous potassium hydroxide. Conversion of humantenine-type structure **196** into gelselegine (**190**) was achieved in eight more steps in 11% overall yield.



Scheme 4.5. Biomimetic synthesis of *Gelsemium* alkaloids gelselegine (**190**).

In keeping with the biosynthesis proposed by Ponglux *et al.*, the C21 carbon of gelselegine (**190**) was oxidatively cleaved with sodium periodate in 64% yield and afforded gelsenicine (**197**) (Scheme 4.6). Gelsedine (**180**) itself was then obtained by catalytic hydrogenation of the imine **197** in quantitative yield.

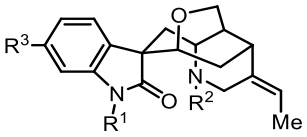


Scheme 4.6. Biomimetic synthesis of gelsenicine (**197**) and gelsedine (**180**) from gelselegine (**190**).

4.3 Humantenine-type Gelsemium alkaloids

Present in *G. elegans*, *G. rankinii*, and *G. sempervirens* species, humantenine-type alkaloids have been the subject of many investigations over several decades. In 1989, Lin *et al.* disclosed the isolation and structural elucidation of seven new humantenine-type alkaloids from *G. elegans* (Table 4.1).[96] Structurally, humantenine-type alkaloids contain a spirocyclic junction linking a strained tricyclic core appended to the oxindole unit, differing only in the substituents on the nitrogen atoms and the benzene ring.

Table 4.1. Humantenine-type alkaloids from *G. elegans*.



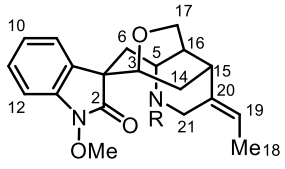
R^1	R^2	R^3	*Gelsemium* alkaloids	ref number
H	H	H	*N*-desmethoxyrankinidine	**198**
OMe	H	H	rankinidine	**49**
OMe	H	OH	11-hydroxyrankinidine	**199**
OMe	Me	H	humantenine	**179**
OMe	Me	OH	11-hydroxyhumantenine	**200**
OMe	H	OMe	humantenirine	**189**
OMe	Me	OMe	11-methoxyhumantenine	**201**

4.3.1 Rankinidine (49): a humantenine-type *Gelsemium* alkaloid

The first isolation of rankinidine (**49**) from the species *G. rankinii* was reported by Schun and Cordell in 1986.[92] Lin *et al.* then isolated rankinidine (**49**) and humantenine (**179**) from *G. elegans*.[96] Despite the occurrence of rankinidine (**49**) in both *G. rankinii*, and *G. elegans*, the biological profile of rankinidine (**49**) has not yet been established as it was found to decompose rapidly.

4.3.2 Structure elucidation

Rankinidine (**49**) was first isolated from the dried stem of *G. rankinii* as white needles.[92] The structure of the alkaloid **49** was elucidated by comparison of spectroscopic data with other humantenine-type alkaloids, previously isolated from *G. rankinii* (Figure 4.2). The IR spectrum showed absorptions at 3300, 1722, 1716, 1698, 1466, 753 cm^{-1}, and UV absorptions at 217 and 256 nm, characteristic of an oxindole nucleus. This spirocyclic oxindole **49** was assigned the molecular formula $C_{20}H_{24}N_2O_3$ by mass spectrometry and displayed a molecular ion peak at 340. Concerning the ^1H NMR spectroscopic data, comparison of rankinidine (**49**) with humantenine (**179**) revealed similar proton signals. The key difference was the disappearance of the methyl group (R = H) in rankinidine (**49**).

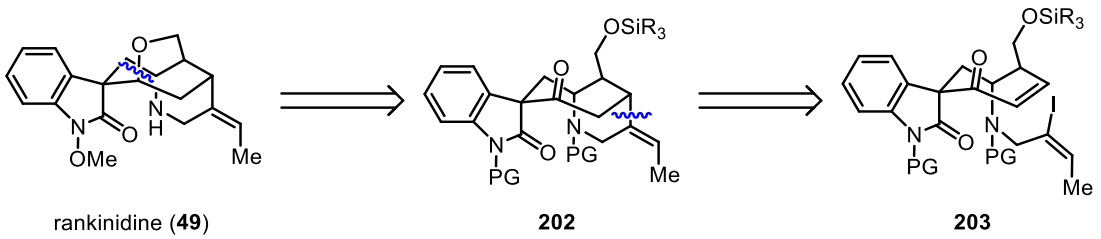


R = H rankinidine (**49**)
R = Me humantenine (**179**)

Figure 4.2. Structure elucidation of rankinidine (**49**).

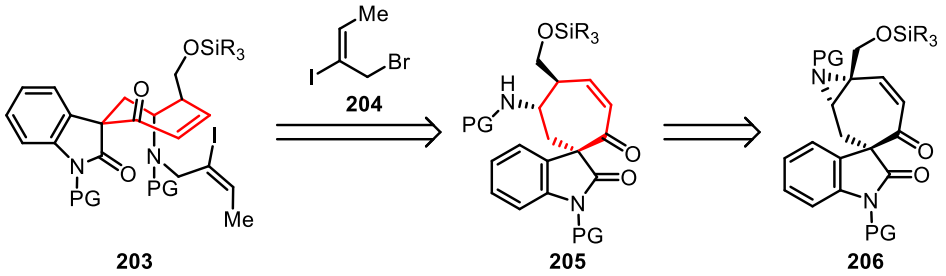
4.4 Retrosynthetic analysis and strategy

The strategy, chosen for the synthesis of rankinidine (**49**), is both novel and challenging. The copper(II)-mediated cyclisation was planned as the key step of the proposed strategy towards the total synthesis of spirocyclic oxindole **49**. However, owing to the intricate nature of this target, an earlier stage spirooxindole cyclisation was studied. Retrosynthetically, the polycyclic rankinidine (**49**) structure will be formed by an intramolecular hemiketalisation of a primary alcohol with a ketone, followed by deoxygenation, removal of all protecting groups and *N*-methoxy bond formation will be envisioned from substrate **202** (Scheme 4.7). The bridging six-membered piperidine ring will be introduced by a radical cyclisation from enone **203**.



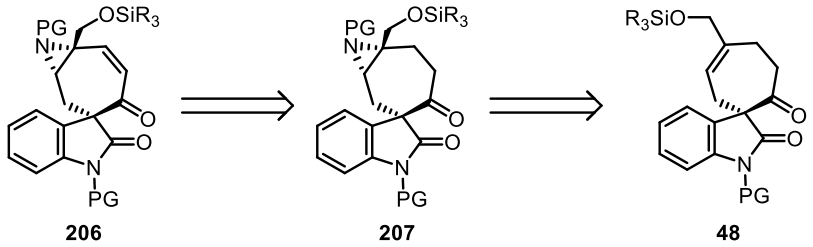
Scheme 4.7. Proposed retrosynthesis of rankinidine (**49**) from enone **203**.

The side chain used for the ring closure will be derived from the alkylation step of oxindole intermediate **205** using the readily available allyl bromide **204** (Scheme 4.8). An aziridine ring-opening will be used to introduce the alcohol-containing side-chain and the *N*-protected amine in **205** from spirooxindole **206**.



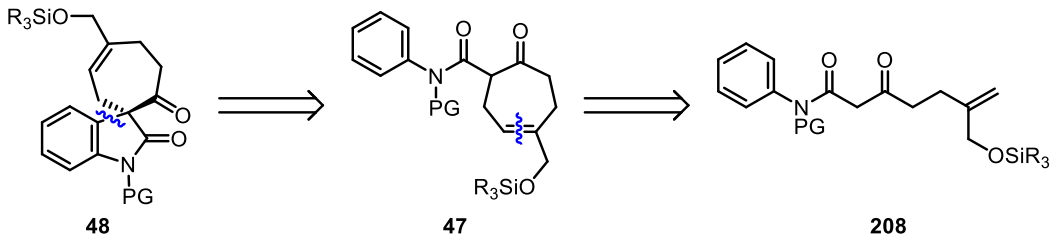
Scheme 4.8. Proposed retrosynthesis of compound **203** from intermediate **206**.

Installation of the C–C double bond in enone **206** will utilise the *in situ* formation of an enolate and a subsequent Saegusa or selenium-based oxidation process (Scheme 4.9). The aziridine **207** could be derived from the corresponding alkene **48**.



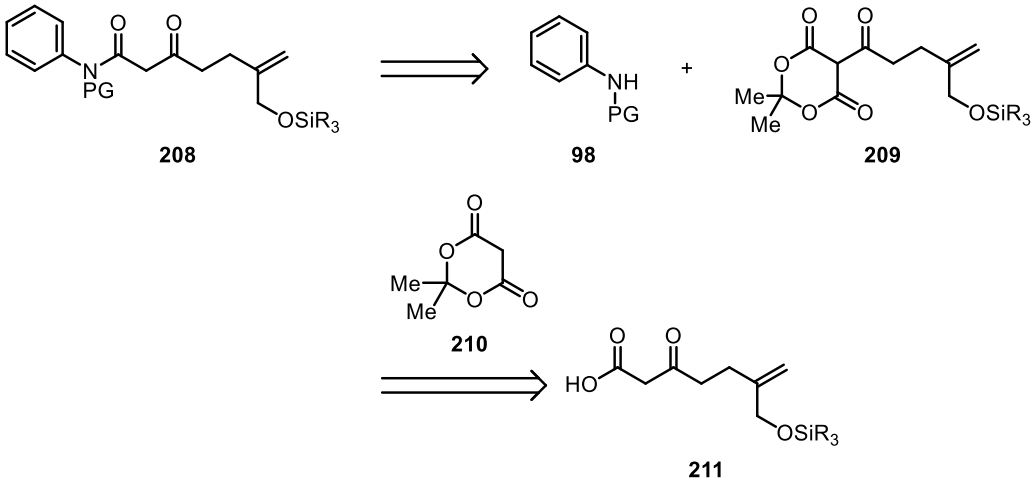
Scheme 4.9. Proposed retrosynthesis of compound **206** from the spirocyclic oxindole **48**.

The key step is the formation of the oxindole **48** utilising the copper(II)-mediated C–H, Ar–H functionalisation methodology, which is expected to proceed from anilide **47** and directly install the 3-oxindole quaternary stereogenic centre in spirocyclic oxindole **48** (Scheme 4.10). The ring-closing metathesis of diene will install the key olefin functionality in oxindole **48**. The diene intermediate will come from the installation of an allyl group in α-position of β-keto amide **208**.



Scheme 4.10. Proposed retrosynthesis of spirocyclic oxindole **48** from the anilide **208**.

Disconnection of the amide bond in anilide **208** then generates two fragments: *N*-protected aniline **98** and masked β-keto acid **209** which is expected to come from acylation of Meldrum's acid (**210**) with the corresponding carboxylic acid **211** (Scheme 4.11). The convergent nature of this synthesis and the structural features of the intermediates offer the potential to alter the order of steps at many stages in the actual synthesis.



Scheme 4.11. Proposed retrosynthesis of anilide **208** from the carboxylic acid **211**.

4.5 Rankinidine model studies

4.5.1 Model studies for the formation of spirocyclic oxindole

The feasibility of installing the spirocyclic carbocyclic junction in different 3,3-disubstituted oxindole models *via* a copper(II)-mediated C–H, Ar–H functionalisation method was initially investigated. Knowing already that a series of spirolactams could be accessed using the cyclisation process (Scheme 1.13),[21] applying the same optimised conditions for the cyclisation of 2-oxocarbocyclic-containing precursors to give spirooxindoles **212**-**214** was envisaged. The synthesis of spirocyclic oxindole **214** is particularly important as it is directly related to rankinidine (**49**) by the common 7-membered ring spiro-junction at C3 (Figure 4.3). It should be noted that this methodology should also be useful for the synthesis of Satavaptan (**215**) and this research is now on going in the Taylor group.

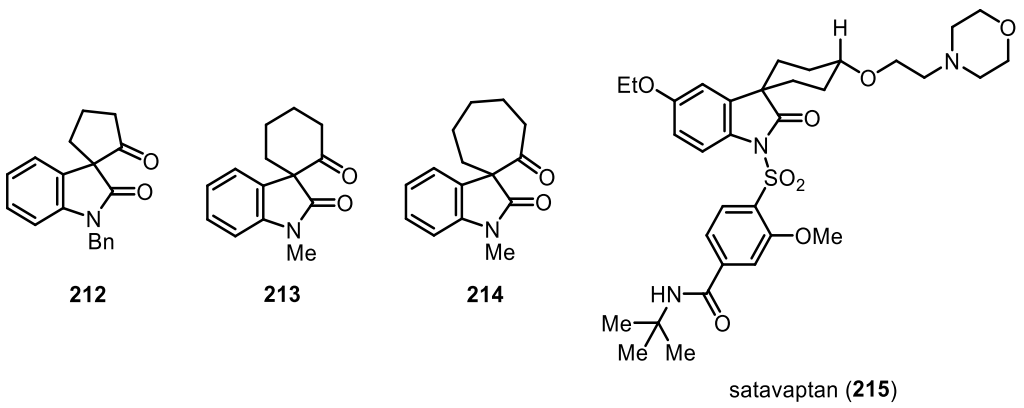
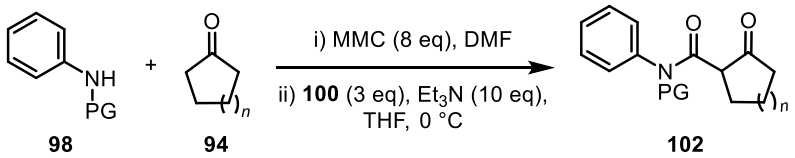


Figure 4.3. Proposed models for the copper(II)-mediated cyclisation.

4.5.1.1 Strategy for the synthesis of the anilide cyclisation precursors

A one-step MMC/amide coupling sequence was applied to the synthesis of mono-anilide **102**. As described in the previous Chapter, this strategy was also used for the formation of bis-anilide precursors (entries 1-3, Table 4.2). Conducting the reaction on larger scale was tolerated and offered sufficient amounts of anilides to test the cyclisation reactions.

Table 4.2. Substrate scope for the synthesis of anilide precursors.



98 94 102

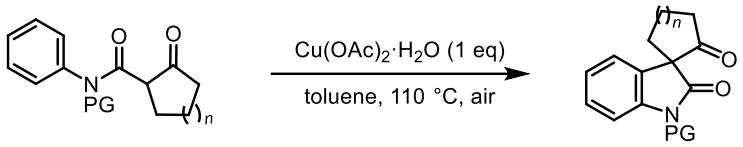
entry	PG	*n*	product	yield (%)[a]
1	Bn	1	**102d**	15
2	Me	2	**102a**	30
3	Me	3	**102c**	34

[a] Yield of isolated products. MMC = methyl magnesium carbonate.

4.5.1.2 A copper(II)-mediated oxidative coupling to *N*-methoxyoxindoles

The copper(II)-mediated C–H, Ar–H oxidative coupling reaction was next examined. Pleasingly, the cyclisation proceeded in good yields (entries 1-3, Table 4.3). $Cu(OAc)_2 \cdot H_2O$ (1 eq) in toluene at 110 °C gave the best cyclisation results. The 7-membered ring cyclisation of rankinidine model system **102c**, was investigated in more detail. Remarkably, lowering the temperature to 50 °C and extending the reaction time to 12 h still gave spirooxindole **214** in 12% yield. With regard to a potential asymmetric synthesis of rankinidine (**49**), dropping the temperature of the reaction may maximise the opportunity to induce stereoselectivity during the copper(II)-mediated cyclisation process to the spirooxindole. Of interest for the formal synthesis of satavaptan (**215**), the cyclohexanone-containing spirocyclic oxindole **213** was obtained in 65% yield, confirming the viability of the proposed route.

Table 4.3. Scope and optimisation of the oxidative cyclisation process.



102 **212-214**

entry	PG	*n*	product	yield (%)[a]
1	Bn	1	**212**	56
2	Me	2	**213**	65
3	Me	3	**214**	66[b]

[a] Yield of isolated products. [b] A test reaction was carried out and lowering the temperature to 50 °C and extending the reaction time to 12 h still gave spirooxindole **214** in 12% yield.

Thus, access to the spirocyclic oxindole core utilising the copper(II)-mediated radical cyclisation methodology was successfully investigated and a number of model compounds were prepared successfully.

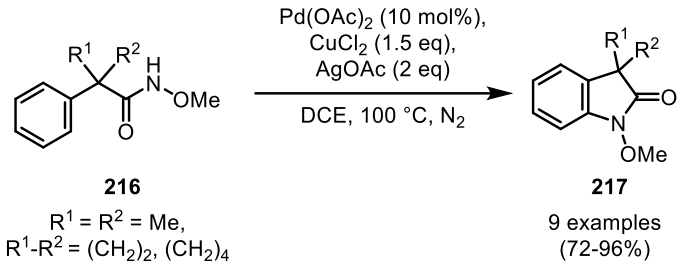
4.5.2 Studies towards the *N*-methoxyoxindole scaffold

N-Alkoxyoxindoles are versatile building blocks, found in a wide range of alkaloids such as gelsedine-type[85] or notoamide-type.[97] These scaffolds represent excellent targets in the search for new drug candidates. For example, *N*-hydroxyoxindole derivatives have been found to be active against sclerosis.[98] They have also been studied as alternative coupling reagents for peptide bond formation.[99] Only a few methods have been described so far for the synthesis of this feature.[100]

4.5.2.1 Cyclisation processes for the formation of *N*-methoxyoxindoles

Of particular interest, *N*-methoxyoxindoles **217**, a key structural feature of rankinidine (**49**), were synthesised for the first time by Kikugawa *et al.* in 1984 *via* electrophilic aromatic substitution with a nitrenium ion generated from *N*-chloro-*N*-methoxyamides.[101] Although this method is widely used, the outcome is strongly dependent on the substitution pattern of

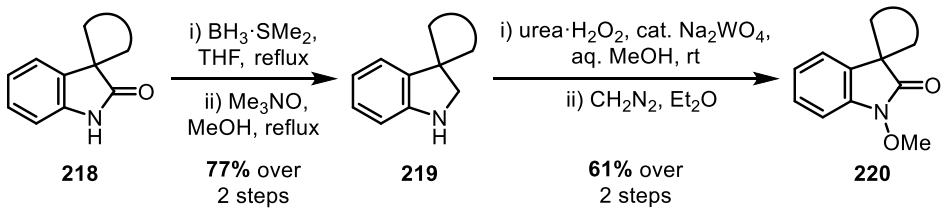
the phenyl ring. *N*-Methoxyoxindole **217** can also be prepared by copper-catalysed intramolecular *N*-arylation of hydroxamates.[102] In 2008, Yu *et al.* disclosed a C−H amination procedure for the preparation of β-, γ-, and δ-lactams employing Pd-catalysed C−H activation reactions (Scheme 4.12).[103] Treatment of hydroxamates **216** with $Pd(OAc)_2$ (10 mol%), $CuCl_2$ (1.5 eq) and AgOAc (2 eq) afforded *N*-methoxyoxindoles **217** in good yields (72-96%).



Scheme 4.12. Lactamisation of aryl C–H, and N–H bonds to afford *N*-methoxyoxindoles.

4.5.2.2 The synthesis of *N*-methoxyoxindoles from unprotected oxindoles

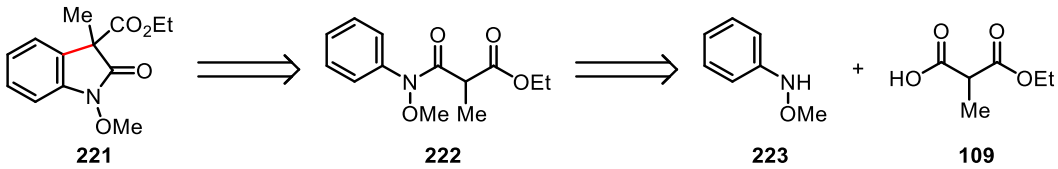
Of particular relevance, Sakai *et al.* reported the oxidation of unprotected oxindole **218** to give *N*-methoxyoxindole **220** *via* intermediate **219** in a four-step sequence in 47% overall yield (Scheme 4.13).[95b] Lactam **218** was reduced with $BH_3{\cdot}SMe_2$ and the resultant amine **219** was oxidised using a urea-hydrogen peroxide complex, in the presence of sodium tungstate.[104] Subsequent *O*-methylation with diazomethane yielded the *N*-methoxyoxindole **220** in 61% overall yield from indoline **219**.



Scheme 4.13. Sakai's synthesis of *N*-methoxyoxindole.

4.5.2.3 A copper(II)-mediated cyclisation process to *N*-methoxyoxindoles

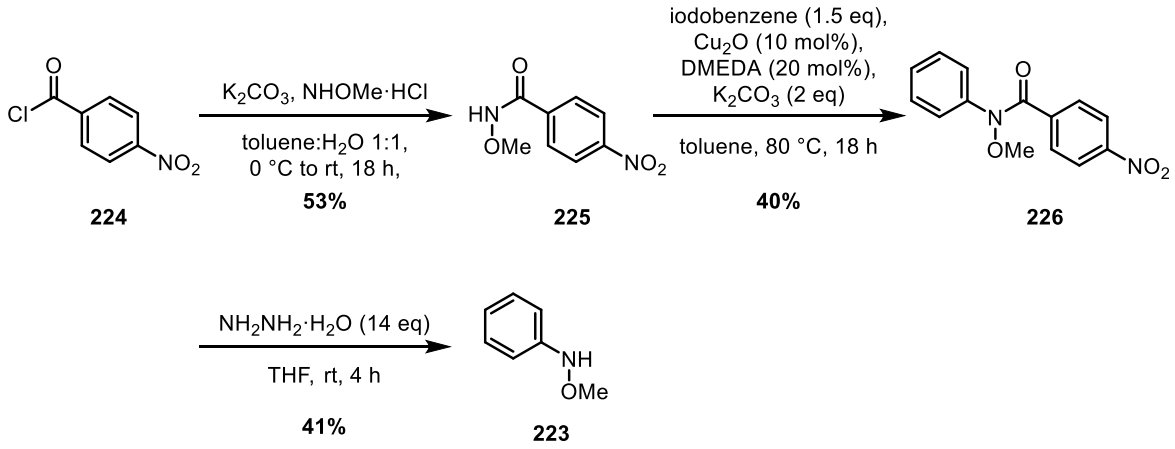
We decided to investigate a different approach for the formation of *N*-methoxyoxindoles *via* a copper(II) oxidative coupling process from anilide precursors (Scheme 4.14). It was envisaged that *N*-methoxyoxindole **221** would potentially be accessed using a copper(II)-mediated oxidative process from anilide **222**. Disconnection of the anilide **222** at the amide functionality would lead to *N*-methoxyaniline **223** and the respective carboxylic acid **109**.



Scheme 4.14. Preliminary disconnection strategy to *N*-methoxyoxindole.

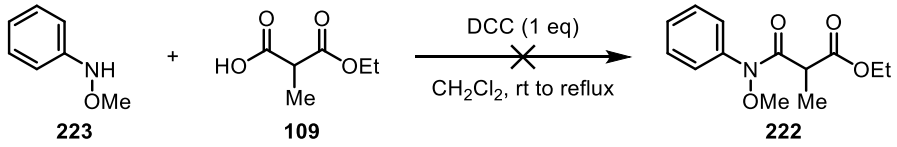
4.5.2.4 Initial studies for the synthesis of anilide 222 from *N*-methoxyaniline

Initial studies towards the preparation of oxindole **221** commenced with the synthesis of readily available *N*-methoxyaniline **223**.[105] The requisite 4-nitrobenzo-*O*-methyl hydroxamic acid **225** was obtained in good yield by acylation of methoxylamine with acid chloride **224** (Scheme 4.15). Then, a copper(I)-catalysed C−N bond formation between hydroxamate **225** and iodobenzene afforded **226** in 40% yield.[106] The resulting *N*-aryl hydroxamate **226** was successfully converted into *O*-methyl-*N*-phenylhydroxylamine (**223**) *via* hydrazinolysis.



Scheme 4.15. Synthesis of *O*-methyl-*N*-phenylhydroxylamine (**223**).

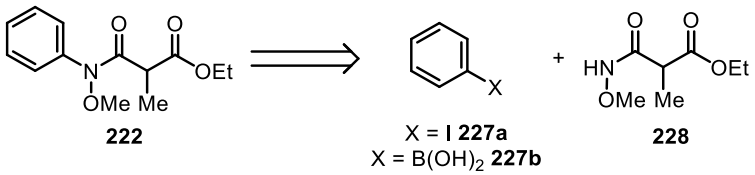
With compound *O*-methyl-*N*-phenylhydroxylamine (**223**) in hand, the amide coupling between aniline **223** and 3-ethoxy-2-methyl-3-oxopropanoic acid (**109**) was next investigated (Scheme 4.16). Aniline **223** was added to a mixture of acid **109** and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in dichloromethane. Disappointingly, no reaction was observed after 24 h. Further heating also failed to promote the reaction, and instead led to decomposition of the starting material.



Scheme 4.16. Attempts towards the synthesis of anilide **222**.

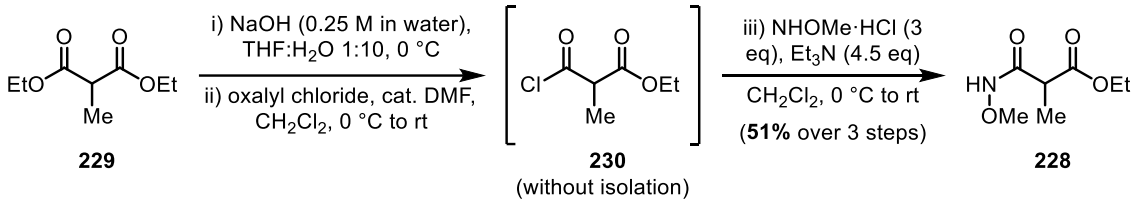
4.5.2.5 Revised route towards the synthesis of *N*-methoxyanilide

Given the synthetic difficulties encountered with the formation of anilide **222** discussed above, the focus was transferred to a different disconnection approach whereby *N*-methoxyanilide **222** would result from the cross-coupling of *O*-alkyl hydroxamates **228** with aryl iodides **227a** or phenylboronic acid **227b** (Scheme 4.17).



Scheme 4.17. Retrosynthetic analysis for the synthesis of anilide **222**.

Hydrolysis of commercially available diethyl methylmalonate (**229**) and treatment of the resulting mono-acid with oxalyl chloride afforded the acid chloride **230** (Scheme 4.18). The acid chloride **230** was successfully converted into the corresponding hydroxamate **228** in 51% yield *via* slow addition of acid chloride **230** into a cooled solution of methoxylamine (3 eq) and triethylamine (4.5 eq). Alternative conditions using DCC, T_3P and Mukaiyama's coupling agent were unsuccessful.

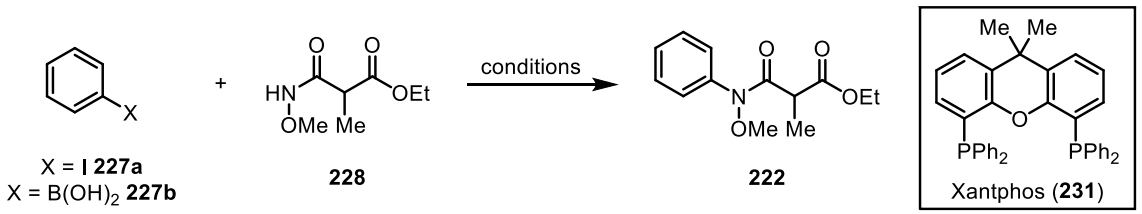


Scheme 4.18. Synthesis of hydroxamate **228**.

Access to practical quantities of hydroxamate **228** was crucial in order to be able to thoroughly examine a number of methods for the preparation of substrate **222**. Initial investigations examined C−N cross-coupling of hydroxamate **228** with iodobenzene (entry 1, Table 4.4) using the procedure developed by Katkevics.[102, 106] The desired anilide **222** was isolated in 33% yield. An alternative approach, first reported by Chan and Lam in 1998,[107] using a source of copper(II) and arylboronic acid, was next explored. However, the isolated yield was lowered to 23% (entry 2, Table 4.4). Reported by Tomkinson *et al.*, the use of palladium(II) was found to promote C−N cross coupling in the presence of Xantphos (1.5 mol%), with a low catalyst loading (1 mol%).[108a] Unfortunately, a lower yield was observed using Tomkinson's procedure (entry 3, Table 4.4). CuI was also used as the C−N cross-coupling promotor, but no improvement in yield was observed (entry 4, Table 4.4).[108b] Subsequently, a one-pot coupling reaction/cyclisation sequence, using a stoichiometric amount of $Cu(OAc)_2{\cdot}H_2O$, was investigated (entries 5-6, Table 4.4). By heating the reaction to 110 °C in DMF or 120 °C in toluene, with or without addition of base, the amide bond

formation and concomitant cyclisation to oxindole product **221** was unsuccessful. Traces of anilide **222** was observed in both cases.

Table 4.4. Optimisation for the synthesis of anilide **222**.



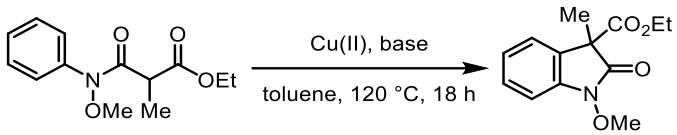
entry	catalyst (mol%)	ligand (mol%)	base[e]	solvent (°C)	yield (%)[f]
1[a]	Cu_2O (10)	DMEDA (20)[c]	K_2CO_3	toluene (80)	33
2[b]	$Cu(OAc)_2$ (100)	-	-	DMF (60)	23
3[a]	$Pd(OAc)_2$ (1)	Xantphos (**231**) (1.5)	Cs_2CO_3	1,4-dioxane (80)	11
4[a]	CuI (5)	1,10-phen (50)[d]	Cs_2CO_3	DMF (80)	10
5[b]	$Cu(OAc)_2{\cdot}H_2O$ (100)	-	piperidine	DMF (110)	8
6[b]	$Cu(OAc)_2{\cdot}H_2O$ (100)	-	-	toluene (120)	7

[a] The reaction was carried out using 1.2 to 3 eq of **227a**. [b] The reaction was carried out using 1.2 eq of **227b**. [c] DMEDA = *N*,*N'*-dimethylethylenediamine. [d] 1,10-phen = 1,10-phenanthroline. [e] An excess of base was used in the reaction (5 to 10 eq). [f] Yield of isolated product.

4.5.2.6 Copper(II)-mediated cyclisation of 222 to give *N*-methyloxindole 221

With sufficient quantities of *N*-methoxyanilide **222** prepared *via* the Cu_2O method, the proposed cyclisation to oxindole **221** was investigated. Using a stoichiometric amount of $Cu(OAc)_2{\cdot}H_2O$ in toluene under air at reflux, the presence of cyclised product **221** was detected in the ^1H NMR spectrum of the unpurified reaction mixture (entry 1, Table 4.5). Despite all efforts, oxindole **221** was found to be inseparable from the starting material **222**. Although, replacing the copper source by Cu(II) 2-ethylhexanoate enhanced the conversion of the cyclisation to completion, unfortunately the isolated yield for both catalytic (entry 2) or stoichiometric (entry 3) procedures, was particularly poor owing to partial decomposition.

Table 4.5. Attempts towards the synthesis of *N*-methoxyoxindole **221**.



222 **221**

entry	copper source (mol%)	base (eq.)	yield (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$ (100)	-	20[c]
2	Cu(2-ethylhexanoate)$_2$ (10)[a]	DIPEA (2)	15
3	Cu(2-ethylhexanoate)$_2$ (200)	DIPEA (5)	17

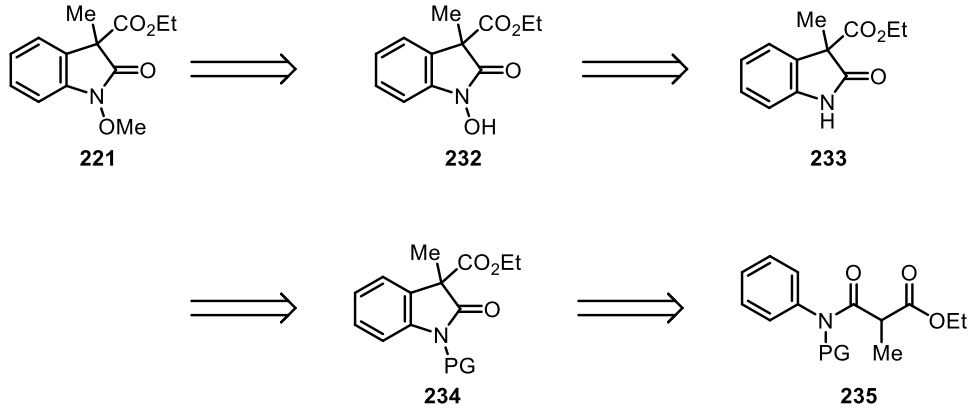
[a] Cu(2-ethylhexanoate)$_2$ = $[Me(CH_2)_3CH(Et)CO_2]_2Cu$. [b] Unless otherwise stated, yield of isolated product. [c] The conversion was not complete even after 18 h, the yield represents the inseparable mixture of **222**:**221** in a 5:1 ratio, respectively.

The novel oxindole **221** was fully characterised by NMR, IR spectroscopy, and ESI-HRMS analysis. ^{1}H NMR spectroscopy showed a characteristic deshielded methyl group appearing as a singlet at 4.04 ppm, in accordance with the predicted high chemical shift nature of the *N*-OMe group.

4.5.3 A new one-pot oxidation/methylation sequence to *N*-methoxyoxindoles

4.5.3.1 Lactam oxidation of unprotected oxindoles

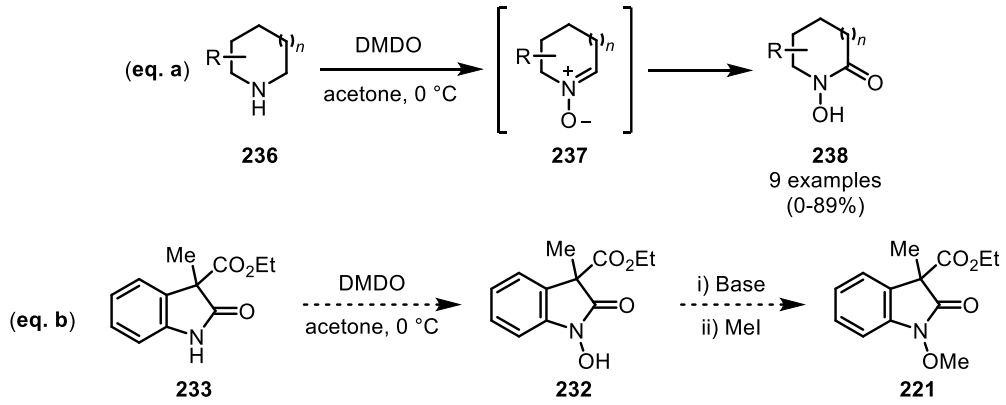
The cyclisation reaction conditions were revised, and an alternative route to *N*-methoxyoxindole **221** was proposed in which the targeted oxindole could be obtained by oxidation of the unprotected lactam **233** to afford the hydroxamic acid **232**, followed by a methylation step (Scheme 4.19). Formation of protected oxindole **234** could utilise the Cu(II)-mediated cyclisation route from anilide **235**.



Scheme 4.19. Revised route towards *N*-methoxyoxindole **221**.

4.5.3.2 Undheim's oxidation of cyclic amines for the synthesis of hydroxamic acids

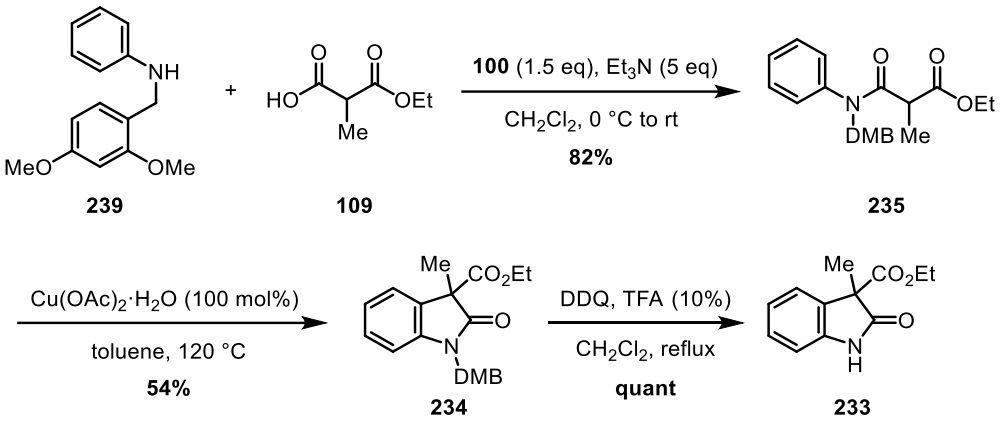
Undheim has reported that a number of cyclic secondary amines **236** can be oxidised to the corresponding hydroxamic acids **238** *via* intermediates **237** using dimethyldioxirane as the sole oxidant (**eq. a**, Scheme 4.20).[100b] Indeed, dioxiranes have become well established as remarkable oxidants, capable of highly selective oxidations, including epoxidations and electrophilic *O*-insertion into non-activated C─H bonds.[109] It was proposed that unprotected oxindole **233** could be oxidised with DMDO to yield the corresponding hydroxamic acid **232** (**eq. b**, Scheme 4.20). Subsequent methylation of the hydroxamic acid **232** could provide access to the desired *N*-methoxyoxindole **221**. More recently, Grainger *et al.* reported an iron-mediated peroxide oxidation of nitroxides to the protected *N*-OMe products.[110]



Scheme 4.20. Undheim's DMDO oxidation of cyclic secondary amines (**eq. a**). Proposed route towards *N*-methoxyoxindole **221** following Undheim's procedure (**eq.b**).

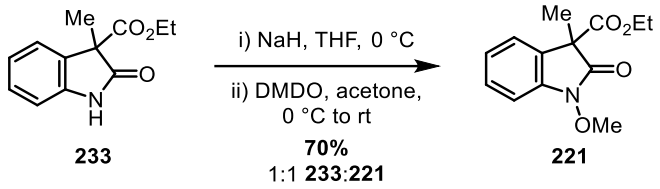
4.5.3.3 Attempted oxidation of unprotected oxindole 233

Readily available *N*-(2,4-dimethoxybenzyl)aniline[111] (**239**) was subjected to Mukaiyama's coupling conditions and afforded anilide **235** in good yield (Scheme 4.21). Next, *N*-(2,4-dimethoxybenzyl)oxindoles **234** was prepared using the copper-mediated cyclisation step to give *N*-protected oxindole **234** in moderate yield. Finally, deprotection of the oxindole, following Trost's procedure,[112] afforded oxindole **233** in quantitative yield.



Scheme 4.21. Synthesis of unprotected oxindole **233**.

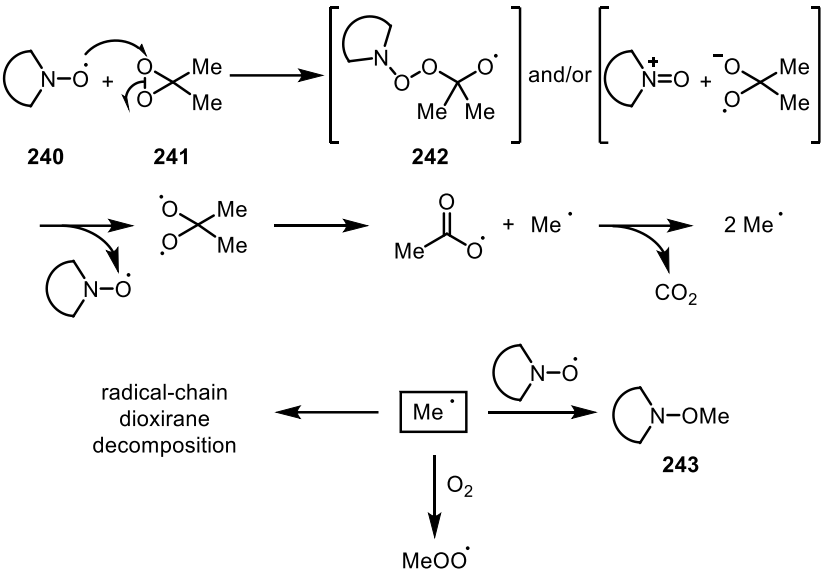
Initially, a solution of unprotected oxindole **233** in acetone was treated with a solution of DMDO (0.05 to 0.07 M in acetone) at 0 °C. After warming to room temperature, the reaction mixture was stirred for a further 18 h, but the oxidation of lactam **233** was not observed. However, when oxindole **233** was added to a preformed suspension of NaH in THF and subsequently treated with a dilute solution of DMDO at 0 °C, analysis of the unpurified material by ^{1}H NMR spectroscopy, after 18 h, showed the presence of the unexpected *N*-methoxyoxindole **221** (Scheme 4.22). Differentiated from oxindole **233** by the appearance of a shifted singlet assigned to the methoxy group at 4.04 ppm, the ^{1}H NMR spectrum of the unpurified reaction mixture revealed incomplete oxidation, indicated by the presence of recovered starting material. Pleasingly, no evidence of decomposition was detected. Despite all efforts, the separation of both compounds was unsuccessful and led to the recovery of a mixture of starting material **233** and product **221** in a 1:1 ratio.



Scheme 4.22. Synthesis of *N*-methoxyoxindole.

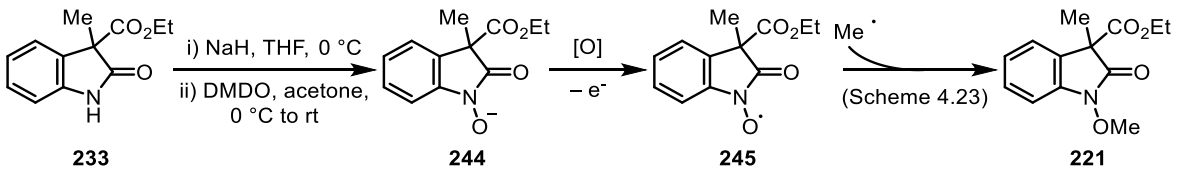
4.5.3.4 Proposed mechanism for the formation of *N*-methoxyoxindole 221

The radical reactivity of dioxiranes is well-known. In 1991, Adam and co-workers reported the reaction of dioxiranes with a nitroxide to produce methyl radicals, readily trapped by the radical scavenger.[113] In agreement, the group of Minisci suggested that the homolytic decomposition of the dioxirane occurred in the presence of an aminoxyl radical such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). When TEMPO was used as a trapping agent for radicals during the oxidation of alkanes with dimethyldioxirane, no resulting alcohols or ketones were observed. Instead, the main reaction product arose from the trapping of a methyl radical.[114] In their studies on the reaction of aminoxyl with dioxiranes, Curci *et al.* have also found that these radical species react readily with dioxiranes and indeed, promote their radical decomposition (Scheme 4.23).[115] The formation of **242** could be envisaged by homolytic substitution between the aminoxyl **240** and the dioxirane **241** O–O bond, affording the radical intermediate **242**. Driven by the release of CO_2, two methyl radicals can be generated and subsequently trapped by the radical scavenger **240** to give access to the *N*-methoxy product **243**.



Scheme 4.23. Curci's proposed radical decomposition of DMDO in presence of an aminoxyl radical.

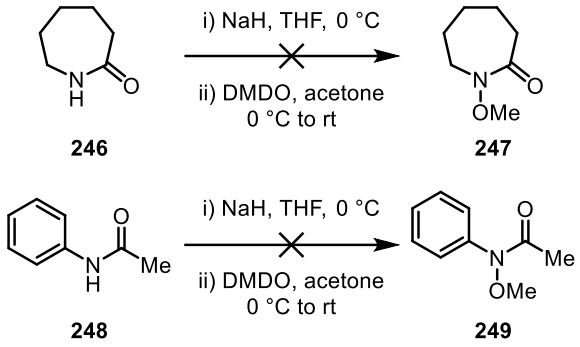
In light of Undheim's oxidation of cyclic secondary amine to hydroxamic acid (**eq. a**, Scheme 4.20) and Curci's rationalisation on the radical decomposition of DMDO in the presence of aminoxyl derivatives, a plausible mechanism for the one-pot oxidation/methylation sequence is proposed in Scheme 4.24. First the base is expected to deprotonate the lactam **233**, which consequently triggers the first oxidation by DMDO and form the *N*-oxide intermediate **244** (Scheme 4.24). Oxidation of *N*-oxide **244** was suggested to give the reactive aminoxyl **245**, which would promote the radical decomposition of DMDO and generate methyl radicals. Eventually, the aminoxyl scavenger would trap a methyl radical and lead to *N*-methoxyoxindole **221**.



Scheme 4.24. Proposed mechanism for the formation of *N*-methoxyoxindole.

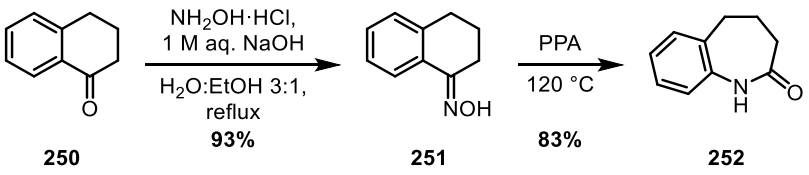
4.5.3.5 Scope and optimisation of the oxidation/methylation reaction

The scope and optimisation of the reaction conditions was investigated in order to gain deeper understanding of this promising oxidation process. Two model substrates were chosen for initial investigations, commercially available ε-caprolactam (**246**) and acetanilide (**248**). However, neither afforded their respective oxidised products **247** and **249** when treated with NaH/DMDO and resulted in the recovery of starting material (Scheme 4.25).



Scheme 4.25. Attempted oxidation of model substrates **246** and **248**.

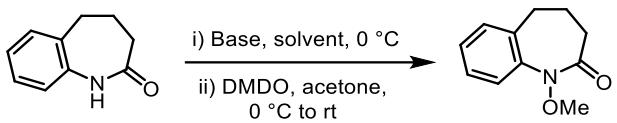
Attention then moved to the application of this method to the benzo-fused 7-membered lactam **252**. The use of lactam **252** as a model system is also beneficial since the *N*-methoxy product **253** has previously been fully characterised. Following the reported procedure,[116] tetralone (**250**) was treated with the HCl salt of hydroxylamine in the presence of sodium hydroxide which afforded the oxime **251** in 93% yield (Scheme 4.26). At this point, Beckmann rearrangement of substrate **251** gave access to benzo-fused caprolactam **252** in 83% yield.



Scheme 4.26. Synthesis of the benzo-fused caprolactam model **252**.

With practical quantities of precursor **252** in hand, optimisation of the oxidation reaction was next envisioned (Table 4.6). Gratifyingly, the *N*-methoxyoxindole product **253** was observed. Significant differences in yield were observed by altering the number of equivalents of DMDO added to the reaction (entries 1-5, Table 4.6). The use of 1.5 eq of dioxirane was found to give the best result (entry 3). Subsequent addition of MeOH, 15 min after addition of DMDO did not improve the ratio of starting material to product, suggesting that the methyl group is not coming from the presence of MeOH in the reaction mixture (entry 5). Interestingly, replacing THF with DMF did affect the reaction (entry 6) but not in favour of the product **253**. The use of DBU as an organic base was tried but no reaction was observed (entry 8). However, the ratio was significantly improved using different inorganic bases (entries 8-9). Indeed, the use of NaHMDS in place of NaH, improved the ratio to 1.5:1 **252**:**253**. For comparison, switching from DMDO to *m*-CPBA (entry 10) resulted in the exclusive recovery of starting material. Pleasingly, the data for compound **253** were consistent with those already reported by Togo.[117]

Table 4.6. Optimisation of the oxidation/methylation steps by DMDO.



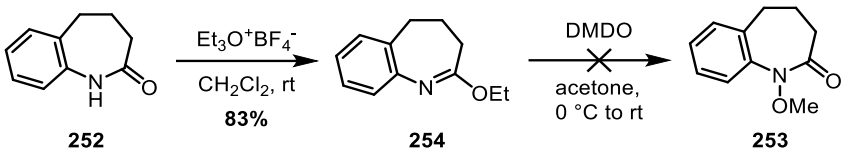
252 **253**

entry	base (eq)	solvent	eq of DMDO	ratio (**252**:**253**)[b]
1	NaH (2.1)	THF	0.5	23:1
2	NaH (2.3)	THF	1	6:1
3	NaH (1.3)	THF	1.5	3:1[c]
4	NaH (1.5)	THF	2	7:1
5	NaH (1.05)	THF[a]	3	11:1
6	NaH (1.05)	DMF	1.5	18:1
7	DBU (1.05)	toluene	1.5	**252**
8	LHMDS (2)	THF	1.5	2.5:1
9	NaHMDS (2)	THF	1.5	1.5:1
10	NaH (2.6)	THF	*m*-CPBA (1.2)	**252**

[a] MeOH (0.5 mL) was added 15 min after DMDO was added to the reaction. [b] Unless otherwise stated, ratio of **252**:**253** calculated using the ^{1}H NMR of the unpurified reaction mixture. [c] Purification by column chromatography of the separable mixture afforded the lactam **252** and *N*-methoxylactam **253**, in 59% and 18% yields, respectively.

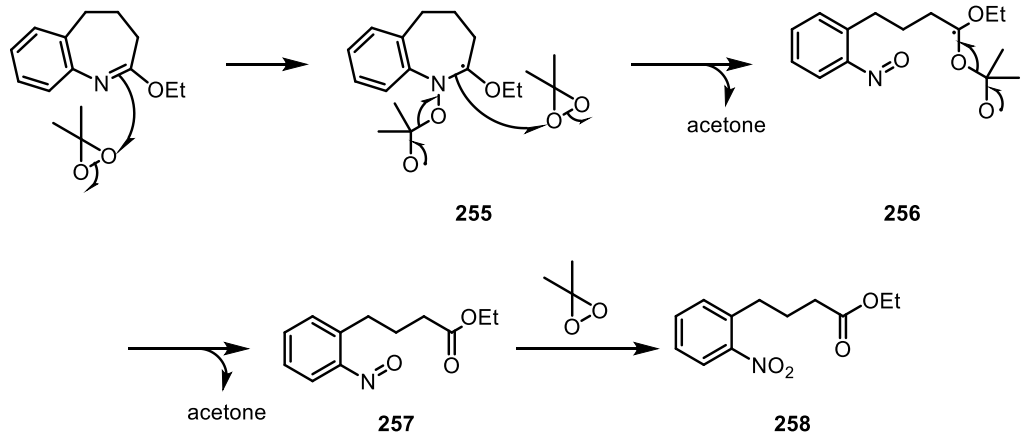
4.5.3.6 Suggested DMDO oxidation route to *N*-methoxycaprolactam 253

Reported by Aue *et al.*, peracid oxidation of an imino ether promoted the formation of the corresponding hydroxamic acid albeit in low yield.[118] Therefore imidate **254** was prepared from lactam **252**,[119] and treated with DMDO; however, the formation of the *N*-methoxy product **253** was not observed (Scheme 4.27).



Scheme 4.27. Proposed dimethyldioxirane oxidation of imidate **254**.

Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy showed the presence of lactam **252**, resulting from hydrolysis, as well as another side-product. The molecular formula of the sodium salt was established as $C_{12}H_{15}NNaO_4$ through ESI-HRMS analysis, suggesting that over-oxidation had taken place since three extra oxygen atoms were present. 1D and 2D NMR spectroscopic data were consistent with the cleavage of the amide functionality and rationalised by the loss of the proton from the amide at 7.88 ppm. Besides, a new signal at 173.1 ppm in the ^{13}C NMR spectrum suggested the presence of an ester functionality (an IR stretch at 1729 cm^{-1} was also observed). Two characteristic N–O stretching bands were identified respectively at 1524 and 1345 cm^{-1} which suggested that the product was ester **258**. Comparison with the known methyl ester[120] equivalent of **258** confirmed the structure of the latter. Reviewed by Murray,[121] dimethyldioxirane can oxidise primary amines to nitro compounds. Mechanistically, the process is believed to involve a succession of oxygen atom transfers. Although, unprecedented, it is proposed that the transformation of imino ether **254** to afford the *ortho*-nitro phenyl compound **258** took place using a similar pathway. The first equivalent of DMDO could oxidise the imidate nitrogen to give the radical intermediate **255** (Scheme 4.28). Driven by the loss of acetone and the excess of DMDO, the lactam ring could open and lead to intermediate **256**. With an excess of DMDO in the reaction mixture, the nitroso functionality present in intermediate **257** could be oxidised further to the nitro compound **258**.



Scheme 4.28. Proposed mechanism for the formation of the *ortho*-nitro ethyl ester **258**.

As a result of the prevalence of the *N*-methoxyoxindole feature in *Gelsemium* alkaloids, the development of a new methodology for the oxidation of the oxindole nucleus would be of considerable value. Further investigations will be required to gain more insight into the mechanism of the above processes. To date, this is the only method that consists of a one-pot oxidation/methylation sequence for the synthesis of *N*-methoxyoxindoles, although further optimisation will be required to improve the transformation into a useful synthetic procedure.

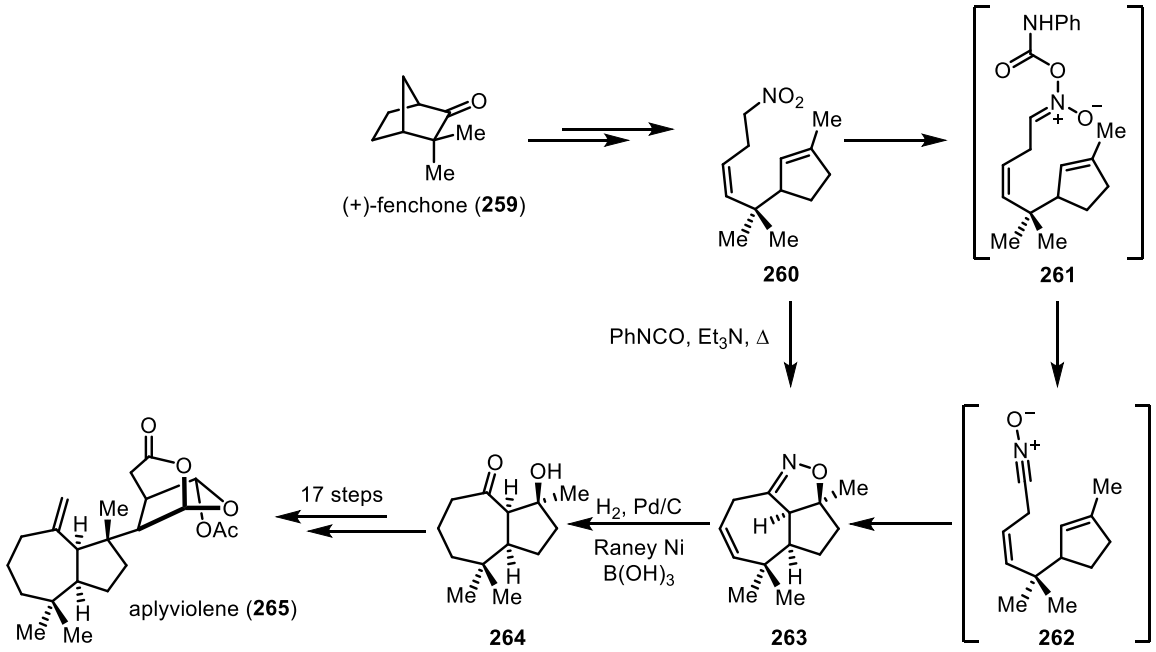
4.6 Progress towards the total synthesis of rankinidine (49)

4.6.1 A seven-membered ring formation by a cycloaddition route

In the preliminary studies, cyclisation of the preformed cycloheptanone was used to generate the rankinidine core structure **214**. However, formation of the required functionalised cycloheptanone cyclisation precursor appeared problematic. Therefore, the focus was turned to the formation of the requisite seven-membered ring by ring-closure of precursors already bearing the required functionalities. Reviewed by Enders *et al.* in 2013, compounds containing a seven-membered ring are commonly found in the cores of naturally occurring compounds.[122] In comparison with five- or six-membered ring formation, methods available to construct seven-membered carbocycles are limited which makes them challenging targets for synthetic chemists. With respect to the structure of rankinidine (**49**), the challenging target contains a seven-membered carbocycle embedded in a tricyclic core. Two disconnection approaches will be presented, which consist of cycloaddition and a ring-closing metathesis approaches.

4.6.1.1 Overman's 7-membered ring closure to (−)-aplyviolene (265)

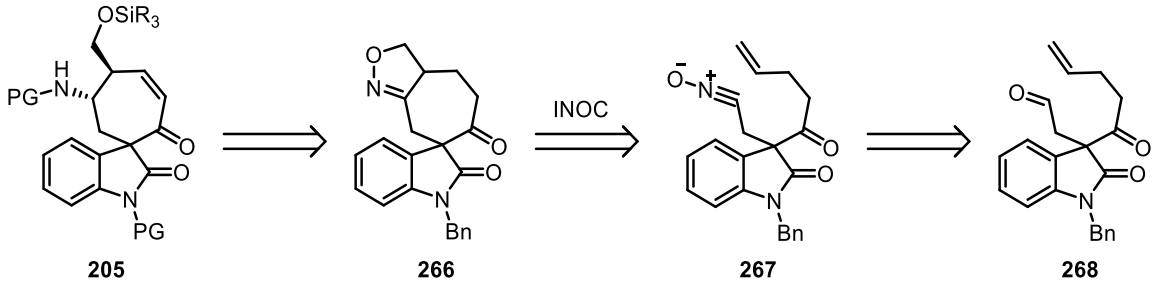
Reported by Overman *et al.* in the total synthesis of (−)-aplyviolene (**265**) in 2012,[123] the construction of seven-membered carbocycles was accomplished by a cycloaddition/fragmentation reaction. Overman's strategy started with the synthesis of precursor **260**, obtained in seven steps from inexpensive commercially available (+)-fenchone (**259**) (Scheme 4.29). Treatment of intermediate **260** with phenylisocyanate and a base promoted the synthesis of isoxazoline **263** *via* an Intramolecular Nitrile Oxide-Olefin Cycloaddition (INOC) reaction, proceeding through intermediates **261** and **262**. Fragmentation of the new isoxazoline ring was performed by hydrogenation and gave access to the β-hydroxy ketone product **264** which was converted into the natural product aplyviolene (**265**) in 17 further steps.



Scheme 4.29. Overman's strategy for the total synthesis of aplyviolene (**265**).

4.6.1.2 Proposed retrosynthetic pathway for the formation of spirooxindole 205

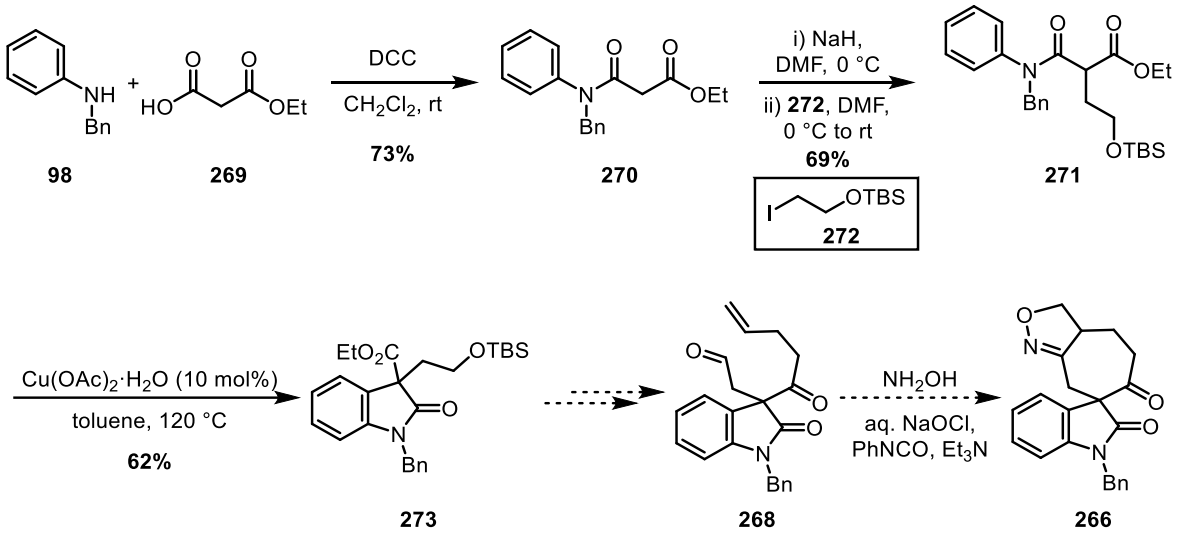
It was anticipated that a similar approach could be used to prepare spirocyclic oxindole **205**, potentially a key intermediate in the synthesis of rankinidine (**49**). Retrosynthetically, enone formation and fragmentation of the isoxazoline motif in intermediate **266** would give access to spirooxindole **205**. Cycloadduct **266** would arise from nitrile oxide **267** which itself could be achieved by treatment of aldehyde **268** with hydroxylamine as depicted in Scheme 4.30. Our copper(II) chemistry would be employed to prepare oxindole **268**.



Scheme 4.30. Proposed retrosynthetic pathway to afford spirooxindole **205**.

4.6.1.3 Synthesis of 3,3-disubstituted oxindole 273

The synthesis of 1,3-dipolar cycloaddition precursor **268** was first required. Anilide **270** was prepared by amide coupling between aniline **98** and the carboxylic acid **269** in 73% yield using *N,N'*-dicyclohexylcarbodiimide as the coupling agent (Scheme 4.31). Pleasingly, insertion of a 2-carbon containing side chain was achieved *via* alkylation of substrate **270** with alkyl iodide **272** in good yield. Oxindole formation from anilide **271** using a copper(II)-mediated oxidative coupling process led to the cyclised product **273** in 62% yield.



Scheme 4.31. Synthesis of oxindole **273**.

4.6.1.4 Attempted synthesis of INOC precursor 268

With oxindole **273** in hand, the installation of the keto alkene side chain present in compound **268** was explored by transformation of the ester functionality. Initial investigation of ester hydrolysis to form the corresponding carboxylic acid **274**, using sodium hydroxide afforded a complex mixture of products (Figure 4.4). Using milder conditions, the hydrolysis of ester **273**, followed by *in situ* addition of oxalyl chloride to form acid chloride **275** was attempted (suitable for a Grignard addition in a later stage). However, conversion into oxindole **275** was not observed but decomposition of starting material was detected by ^{1}H NMR spectroscopic analysis. Reduction of the ester **273** to the corresponding alcohol **276** with DIBAL-H was also attempted. However, both the amide and ester functionalities were

reduced to the known indole **277** in low yield. ^{1}H NMR spectroscopic data were consistent with those already published.[124]

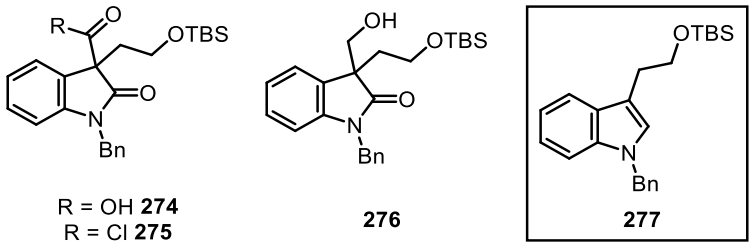
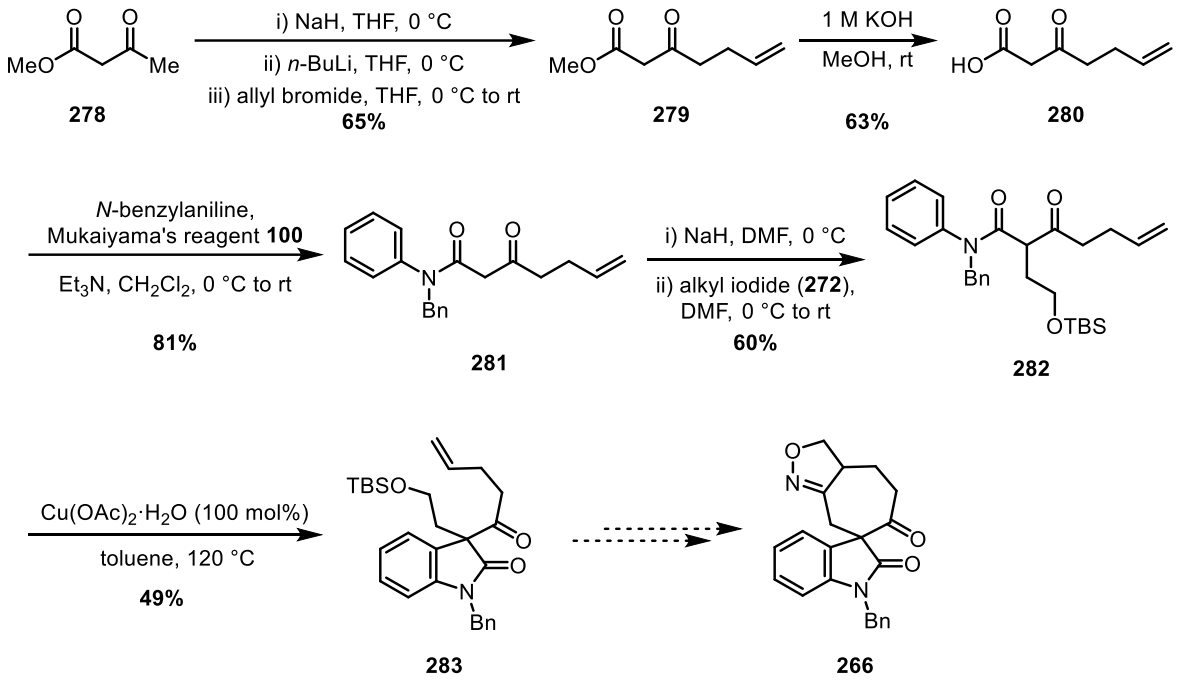


Figure 4.4. Attempted synthesis of oxindoles **274**-**276**. Synthesis of indole **277**.

4.6.2 An alternative strategy for the synthesis of oxindole 268

4.6.2.1 Synthesis of oxindole 283

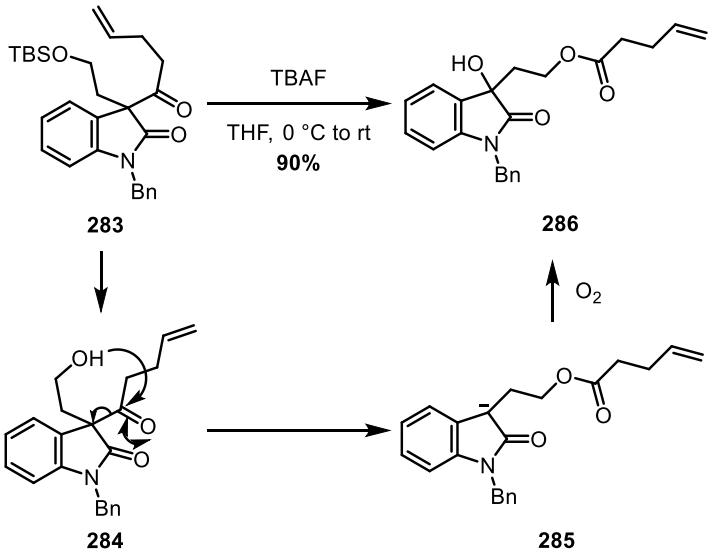
It became apparent that the ester functionality in oxindole **273** had to be replaced. The synthesis was adapted by changing the ester with the requisite keto alkene side chain. In this context, the synthesis began with the functionalisation of methyl acetoacetate (**278**). Alkylation of the preformed β-keto ester dianionic species with allyl bromide furnished compound **279** in 65% yield (Scheme 4.32).[125] Basic hydrolysis to give the carboxylic acid **280**, followed by amide coupling using Mukaiyama's procedure led to anilide **281**. Alkylation of β-keto amide **281** with *tert*-butyl(2-iodoethoxy)dimethylsilane (**272**) provided access to the cyclisation precursor **282** in 60% yield. Finally, the copper(II)-mediated cyclisation proceeded with moderate efficiency. 3,3-Disubstituted oxindole **283** was fully characterised by IR, NMR spectroscopy and ESI-HRMS analysis.



Scheme 4.32. Synthesis of 3,3-disubstituted oxindole **283**.

4.6.2.2 Attempted access to aldehyde intermediate 268

Desilylation/oxidation of protected alcohol **283** was required next. For initial investigations, oxindole **283** was treated with a solution of tetrabutylammonium fluoride. As expected, deprotection of the silyl alcohol took place, however ESI-HRMS data were not consistent with the expected product **284**, supporting a molecular formula of $C_{22}H_{23}NNaO_4$, 16 units (also an atom of oxygen) higher than the expected oxindole **284**. Analysis of the isolated product by ^{13}C NMR spectroscopy showed an absence of a signal corresponding to a ketone at ~ 200 ppm and a new signal in the ester region at 172.8 ppm was observed. The presence of a quaternary carbon at 75.2 ppm suggested that the product should still be a di-substituted oxindole, but the value had shifted 9 ppm downfield compared to the starting material (quaternary carbon at 66.2 ppm). A broad IR stretch at 3369 cm^{-1} suggested the presence of a hydroxyl group. The spectroscopic data were consistent with the structure **286**. Mechanistically, formation of the primary alcohol **284** promoted the direct rearrangement to the anionic intermediate **285** which by means of aerial oxidation gave the 3-substituted-3-hydroxy-2-oxindole **286** with high efficiency (Scheme 4.33).



Scheme 4.33. Proposed mechanism for the formation of di-substituted oxindole **286**.

Conclusive evidence for the structure was obtained by single crystal X-ray diffraction analysis of the product **286** (Figure 4.5).

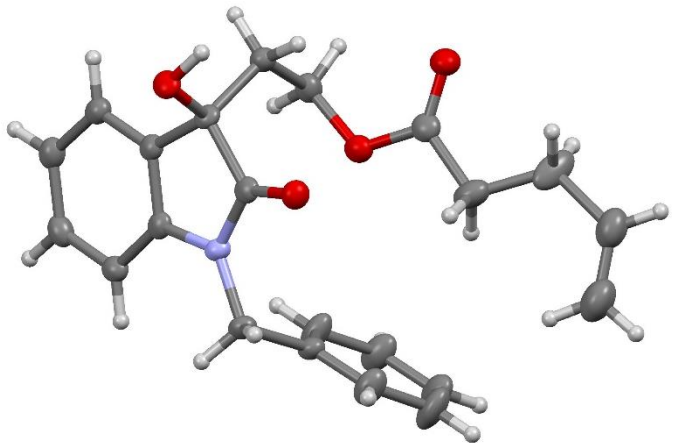
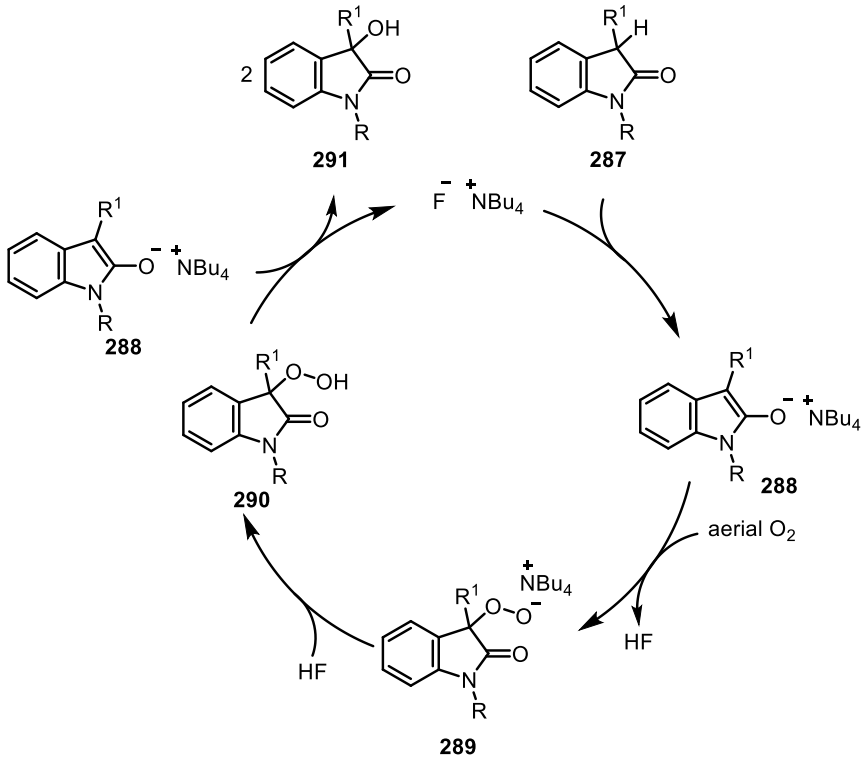


Figure 4.5. Crystal structure of **286** (50% probability ellipsoids, CCDC 1049570).

Support for this mechanism is provided by the report of Buckley *et al.*, who developed a method of hydroxylation at the C3 position of mono-substituted oxindoles using aerial oxidation in combination with TBAF.[126] In their case, the formation of 3-hydroxy-oxindole **291** is reported to proceed *via* the catalytic cycle shown in the Scheme 4.34. Treatment of oxindole **287** with TBAF afforded the tetrabutylammonium enolate **288**. Addition of O_2 promoted the peroxide anion **289** formation. Recombination with a molecule of HF gave

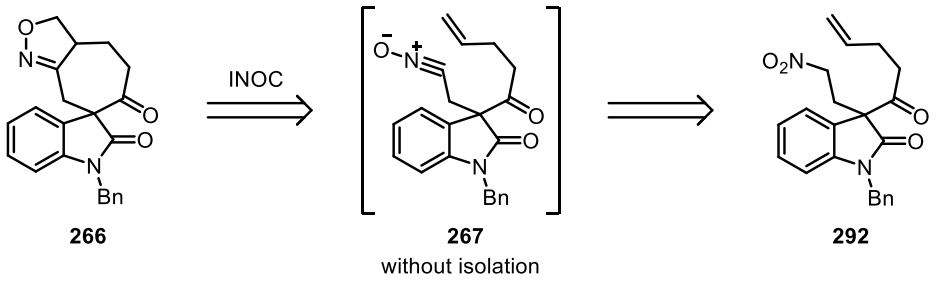
peroxide **290** and regenerated TBAF, able to re-enter a new catalytic cycle. Then, they proposed the cleavage of the O–O bond by addition of a second enolate **288** which led to two molecules of the hydroxylated product **291**.



Scheme 4.34. Buckley's proposed catalytic cycle for the formation of 3-hydroxyoxindole **291**.

4.6.3 Proposed access to cycloaddition adduct 266 from nitro alkene precursor

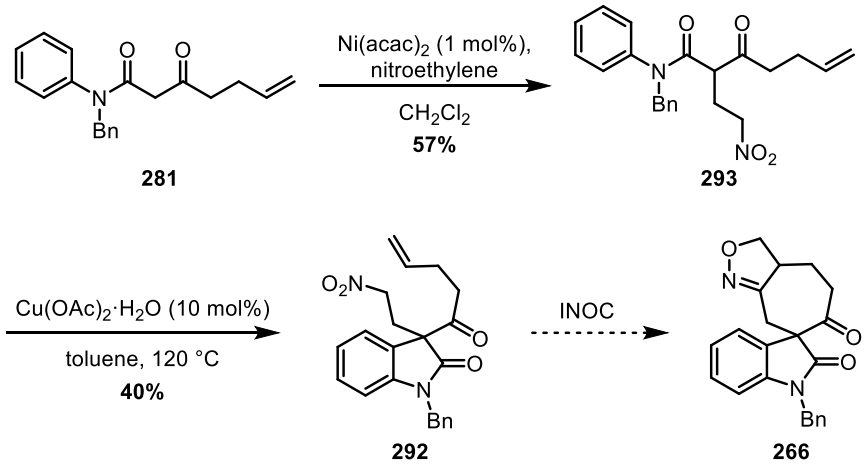
In light of these results and in search of a more efficient method for preparing the cycloaddition precursor **267**, the use of an alternative method was next investigated as shown in Scheme 4.35. The nickel-catalysed Michael addition of β-dicarbonyls developed by Nelson *et al.* in 1980 inspired an attempt to perform the conjugate addition of β-keto amide **281** into nitroethylene.[127] The nitrile oxide precursor **267** can be formed directly from the nitro group present in oxindole **292** as shown previously by Overman in the synthesis of aplyviolene (**265**) (Scheme 4.29).



Scheme 4.35. Proposed retrosynthetic pathway to cycloadduct **266**.

4.6.3.1 Synthesis of nitro alkene precursor 292

Nitroethylene was formed by distillation of a mixture of 2-nitroethanol and phthalic anhydride heated at 180 °C (DrySyn heating block) under vacuum (106-107 mm Hg). The distillate was dried over $CaCl_2$ and could be stored in the freezer for a reasonable period of time. Addition of nitroethylene to a premixed solution of **281** with a catalytic amount of $Ni(acac)_2$ afforded product **293** in moderate yield (Scheme 4.36). Copper(II)-mediated cyclisation of anilide substrate **293** gave access to the desired INOC precursor **292** in 40% yield, which was fully characterised.

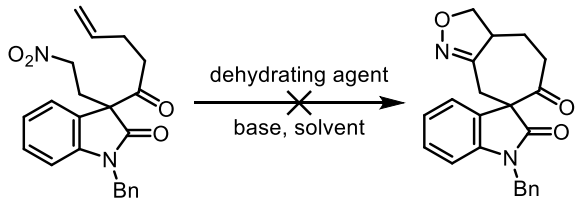


Scheme 4.36. Synthesis of the cycloaddition precursor **292**.

4.6.3.2 Attempted INOC cycloaddition

With oxindole **292** in hand, the cycloaddition reaction to form the tetracyclic spirooxindole **266** was attempted. Initially, Overman's procedure, shown previously in Scheme 4.29, was applied, however, decomposition of the starting material was observed (entry 1, Table 4.7). Dehydration of the nitro group in oxindole **292** was next envisioned using phosphorus oxychloride, and triethylamine.[128] Disappointingly, decomposition of starting material was also observed (entry 2). Reported by Basel and Hassner in 1997,[129] the dehydration conditions using $(Boc)_2O$ in the presence of DMAP appeared to offer a milder alternative to other methods because of the innocuous nature of the side-products (*t*-BuOH and CO_2). Applying these conditions to nitro-containing oxindole **292** did not afford the corresponding cyclised product **266**. Instead, unreacted starting material was recovered after purification (entry 3).

Table 4.7. Attempted INOC cyclisation from nitro-containing oxindole **292**.



292 **266**

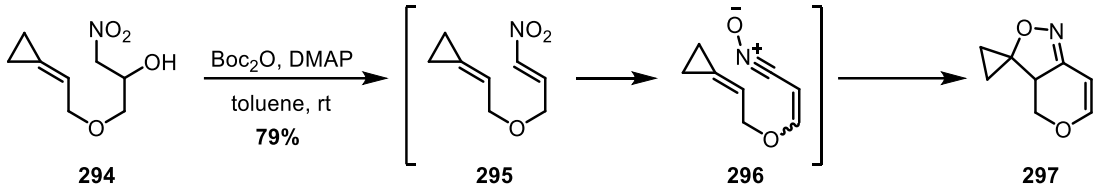
entry	dehydrating agent (eq)	base (eq)	solvent (°C)	time (h)	yield (% **266**)
1	PhNCO (3)	Et_3N (5)	toluene (110)	1	0[a]
2	$POCl_3$ (3)	Et_3N (5)	$CHCl_3$ (rt)	1	0[a]
3	Boc_2O (2.5)	DMAP (0.1)	toluene (90)	18	0[b]

[a] Only decomposition was observed. [b] Decomposition was observed, however some starting material was also recovered.

4.6.3.3 Investigation of the INOC reaction with a different substrate

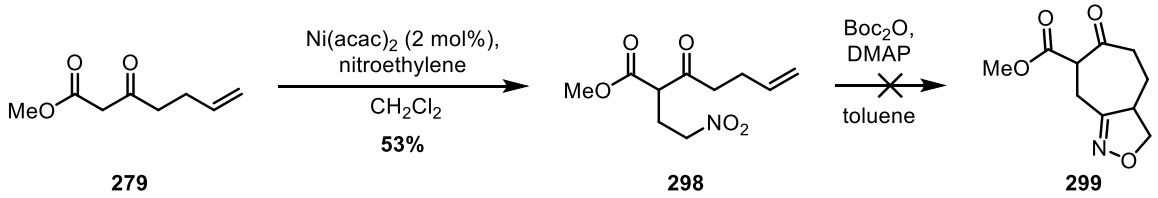
The synthesis of a simpler substrate was envisaged, in order to further investigate the cycloaddition reaction. Reported in the total synthesis of gelsemoxonine by Carreira *et al.* in 2013,[130] intermediate **294** was treated with Boc_2O in the presence of DMAP and delivered isoxazoline **297**. Alcohol activation followed by elimination to give intermediate **295**,

formation of nitrile oxide **296**, and intramolecular dipolar cycloaddition was proposed to give access to tricyclic product **297** (Scheme 4.37).



Scheme 4.37. Carreira's INOC reaction strategy.

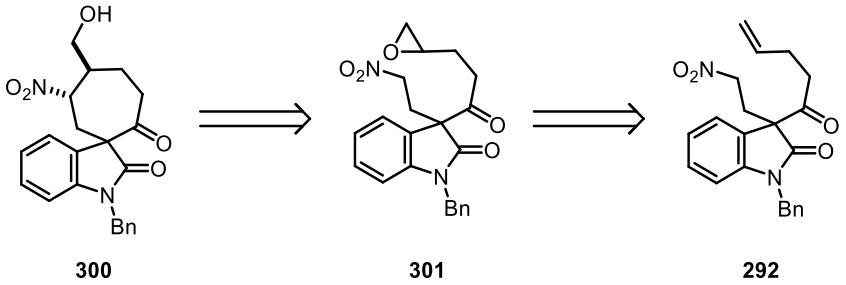
An alternative INOC precursor **298** was synthesised using the previous strategy. Readily available β-keto ester **279** was alkylated by 1,4-conjugate addition into nitroethylene in the presence of nickel(II) to give intermediate **298** in 53% yield (Scheme 4.38). Subjecting the precursor **298** to Carreira's cycloaddition reaction conditions were unsuccessful. Unfortunately, ^{1}H NMR spectroscopy of the unpurified reaction mixture did not show the desired bicyclic product **299**, but instead, decomposition was observed. Dehydration of substrate **298** was attempted with phenyl isocyanate, but decomposition was again detected.



Scheme 4.38. Synthesis of compound nitro-alkene derivative **298**.

4.6.4 Suggested 7-membered ring closure by epoxide ring-opening

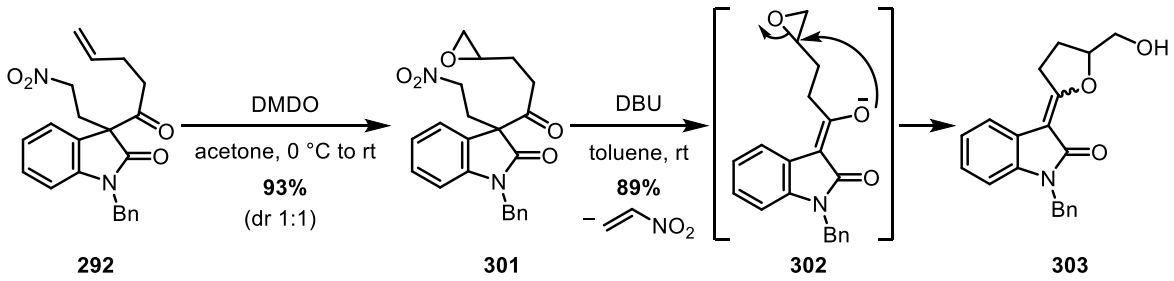
With the cycloaddition reaction proving problematic, an approach consisting of epoxide ring-opening of oxindole **301** towards the key intermediate **300** was investigated (Scheme 4.39). It was anticipated that upon deprotonation of the alpha position of the nitro group, the anion would directly undergo epoxide ring-opening to give the seven-membered spirooxindole **300**. Oxirane **301** should be available from the epoxidation of the terminal alkene present in the INOC precursor **292**.



Scheme 4.39. Proposed synthetic route to spirocyclic oxindole **300**.

4.6.4.1 Attempted synthesis of spirocyclic oxindole 300

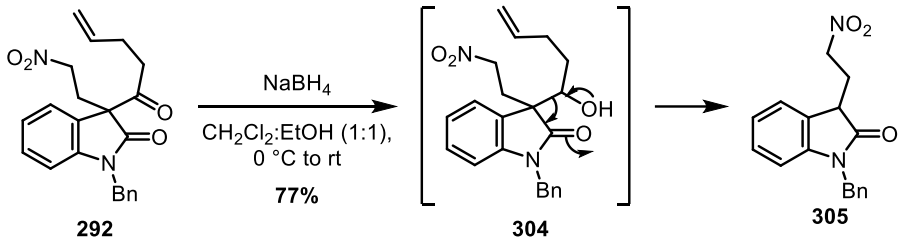
Alkene **292** was treated with DMDO to give the terminal oxirane **301** in good yield as an inseparable mixture of diastereoisomers in a 1:1 ratio (Scheme 4.40). Formation of the 7-membered ring was then investigated. Surprisingly, when DBU was used as base, loss of nitroethylene was observed by ESI-HRMS analysis. The 1D and 2D NMR spectroscopic data of the product were consistent with this observation and suggested the presence of three CH_2 and one CH left as found in the undesired cyclised product **303**. Considering literature precedent on THF ring formation by epoxide ring-opening *via* enolate formation, the enolate regioselectivity can be explained based on stereoelectronic effects.[131, 132] Indeed, formation of a five-membered ring by carbon alkylation of an enolate is unfavourable as the approach of the electrophile will take place perpendicularly to the plane of the enolate **302**. Accordingly, reaction at the enolate oxygen is preferred. It also appeared that the cyclisation resulted in the oxirane ring-opening at the sterically more hindered central carbon, liberating primary alcohol **303** over the six-membered secondary alcohol. The geometry of the exocyclic double bond was not confirmed (the formation of both *E*-[131] and *Z*-isomers[132] have been reported).



Scheme 4.40. Proposed formation of 3-methyleneoxindole **303**.

4.6.4.2 Reduction of the ketone functionality in oxindole 292

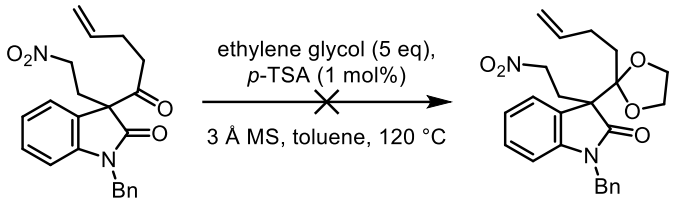
In response to these unexpected results, reduction of the ketone with $NaBH_4$ was attempted to suppress this unwanted side reaction (Scheme 4.41). Unfortunately, loss of the keto-alkene side chain was suggested by ESI-HRMS analysis. The molecular formula of the sodium salt of the product was established as $C_{17}H_{16}N_2NaO_3$. The ^1H and ^{13}C NMR spectroscopic data showed an absence of a ketone at ~ 200 ppm and a new CH signal at 72.5 ppm identified as a doublet of doublets (J = 8.4, 5.3 Hz) at 3.63 ppm in the ^1H NMR spectrum. Two characteristic N–O stretching bands were identified respectively at 1550 and 1345 cm^{-1} which suggested that the product is oxindole **305**. Mechanistically, hydride reduction to give the secondary alcohol **304**, followed by a retro-aldol-type reaction affords the 3-substituted oxindole **305** in good yield.



Scheme 4.41. Formation of the unexpected mono-substituted oxindole **305**.

4.6.4.3 Acetal protection of the ketone functionality in oxindole 292

To overcome the formation of the product **305**, attention was turned to the acetal protection of the ketone **292** (Scheme 4.42). Analysis of the unpurified material by ^1H NMR spectroscopy after treatment of ketone **292** with an excess of ethylene glycol in the presence of *p*-toluenesulfonic acid showed no trace of the desired oxindole **306** but only recovery of starting material **292**.



292 **306**

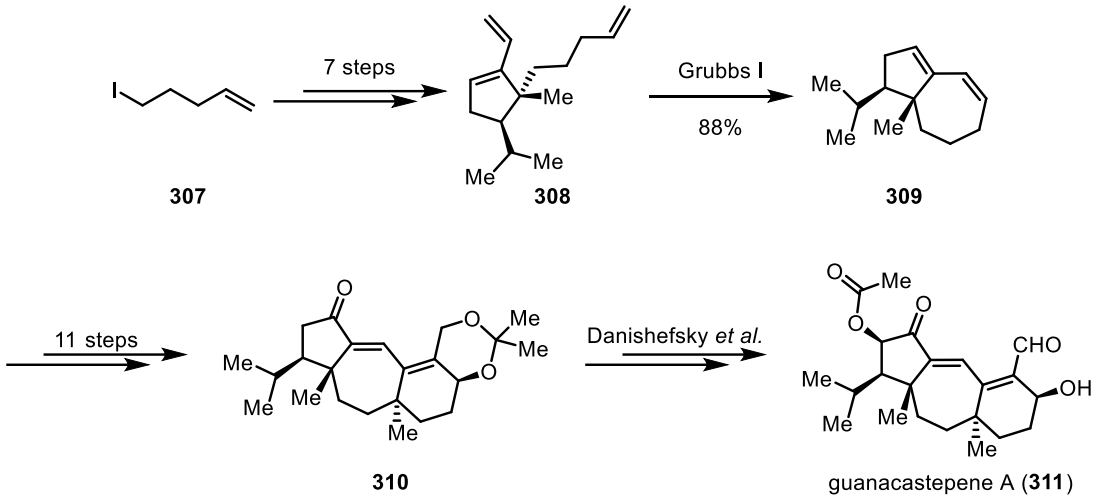
Scheme 4.42. Attempted acetal protection of the ketone **292**.

After unsuccessful attempts to promote seven-membered ring-closing using a range of approaches, attention turned to an alternative disconnection strategy, wherein the cyclisation of the carbocyclic ring system would take place *via* Grubbs ring-closing metathesis.

4.6.5 Ring-closing metathesis strategy

4.6.5.1 Snider's 7-membered ring-closing metathesis towards guanacastepene A (311)

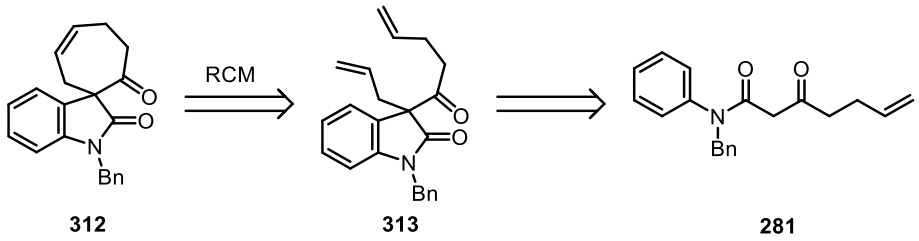
Whilst attention had initially focused on a cycloaddition disconnection, ring-closing metathesis was proposed as a new approach to construct the seven-membered carbocyclic system. The metathesis reaction has been reported to be an excellent method to promote the formation of medium sized ring systems.[122] In the formal synthesis of (±)-guanacastepene A (**311**), Snider *et al.* reported the construction of the central seven-membered ring by ring-closing metathesis using the first generation Grubbs catalyst (Scheme 4.43).[133] Precursor **308** was completed in a seven-step sequence from iodo alkene **307**. To complete the formal synthesis of advanced intermediate **310**,[134] eleven more steps were required from compound **309**.



Scheme 4.43. Snider's formal synthesis of guanacastepene A (**311**).

4.6.5.2 Proposed retrosynthetic pathway to cycloadduct 312

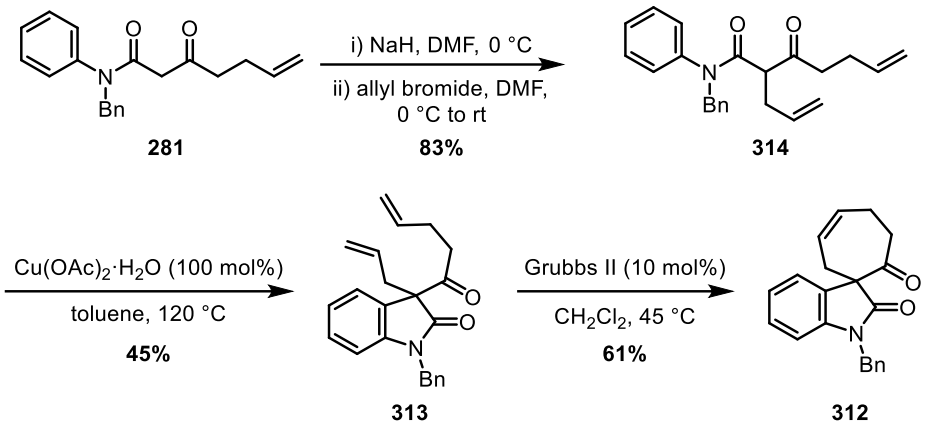
It was envisaged that cycloadduct **312**, containing an alkene for further functionalisation, could be prepared from diene **313**. Alkylation of β-keto amide **281**, followed by the copper(II)-mediated oxidative coupling would give access to the metathesis precursor **313** (Scheme 4.44).



Scheme 4.44. Retrosynthetic analysis for the formation of spirocyclic oxindole **312**.

4.6.5.3 Synthesis of spirocyclic oxindole 312

Having prepared substrate **281** on large scale, alkylation with allyl bromide afforded anilide **314** in 83% yield (Scheme 4.45). The following key copper(II)-mediated oxidative coupling step proceeded to give the oxindole **313** in moderate yield. Pleasingly, subjecting oxindole **313** to diene metathesis produced the desired spirofused tricyclic product **312** in 61% yield.

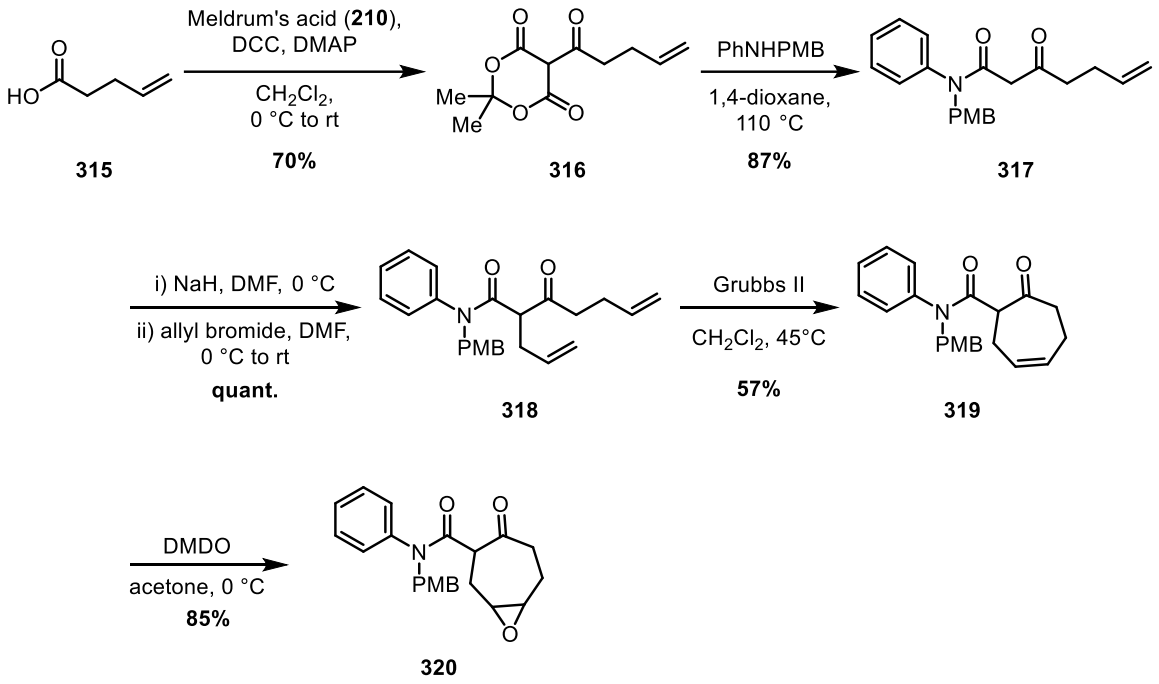


281 **314** **313** **312**

Scheme 4.45. Synthesis of spirocyclic oxindole **312** *via* ring-closing metathesis.

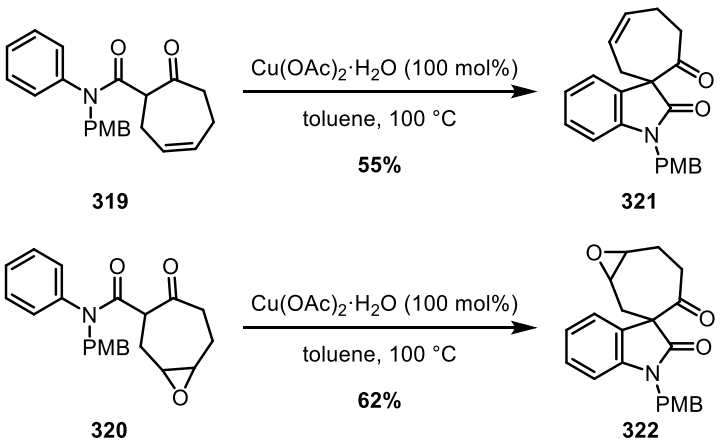
4.6.5.4 Meldrum's acid variant

Next, the synthetic route was shortened and a more easily removed *N*-protecting group was employed. Acylation of Meldrum's acid (**210**) with commercially available and inexpensive carboxylic acid **315** using DCC as the coupling agent gave access to the masked β-keto acid **316** in good yield (Scheme 4.46).[135] Heating compound **316** to reflux in 1,4-dioxane, with *N*-protected aniline afforded the corresponding amide **317** in excellent yield. The synthesis was pursued using the same route developed previously and through a three-step sequence afforded the advanced oxindole precursor **319**. Epoxide **320** was also prepared as a potential cyclisation precursor.



Scheme 4.46. Optimised synthesis of cyclisation precursors **319** and **320**.

The formation of oxindoles was then investigated (Scheme 4.47). However, both substrates **319** and **320** suffered from the issue of anilide hydrolysis. Consequently, the temperature of the reaction was decreased to 100 °C and afforded spirocyclic oxindoles **321** and **322**, in 55% and 62% yield, respectively. Both compounds were fully characterised and the ^{1}H NMR data for the alkene/epoxide were diagnostic (**321**, δ 5.68-5.66 ppm; **322**, δ 3.01-317 ppm).

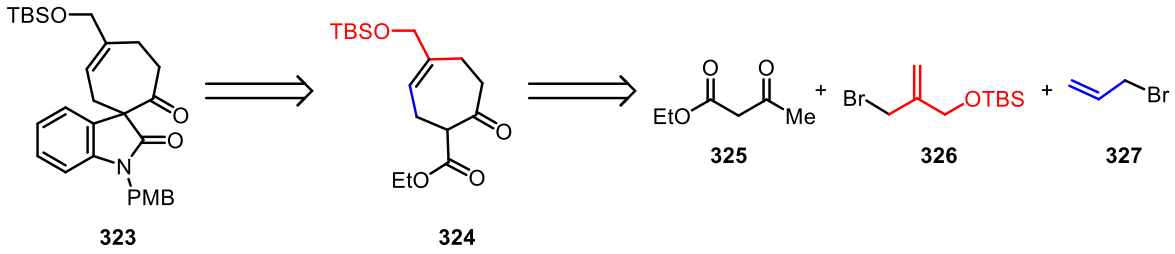


Scheme 4.47. Synthesis of spirocyclic oxindoles **321** and **322**.

4.6.6 Preliminary functionalisation around the alkene functionality

4.6.6.1 Retrosynthetic studies towards spirocyclic oxindole 323

The reactivity of the seven-membered ring in spirooxindole **322** was tested in preliminary studies, but unfortunately both enone formation and epoxide ring-opening have not been successful. Consequently, introduction of a functionalised alkene at an earlier stage was investigated. To this end, the synthesis of the seven-membered ring spirocyclic oxindole **323** was proposed (Scheme 4.48). Initially, the spirocyclic oxindole could be formed from β-keto ester **324** *via* an ester hydrolysis, amide bond formation and copper(II)-mediated cyclisation sequence. The formation of ester **324** could be achieved from metathesis of the respective diene, which in turn could be synthesised *via* a double alkylation process between ethyl acetoacetate (**325**) and two different allyl bromide building blocks **326** and **327**.

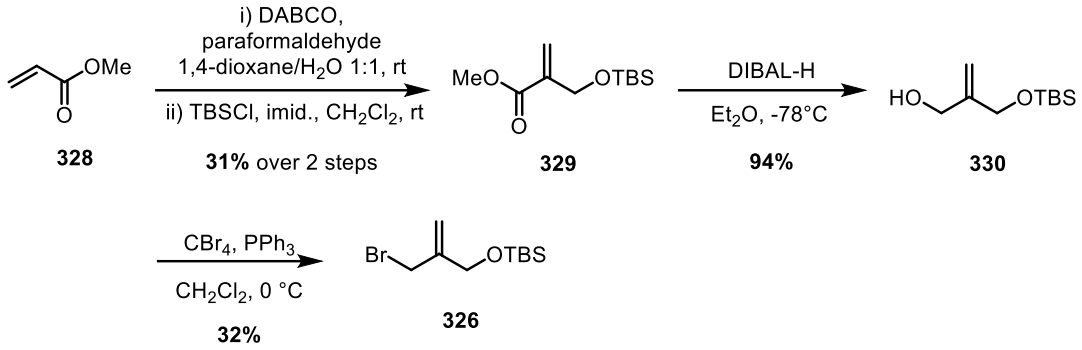


323 **324** **325** **326** **327**

Scheme 4.48. Retrosynthetic pathway to spirocyclic oxindole **323**.

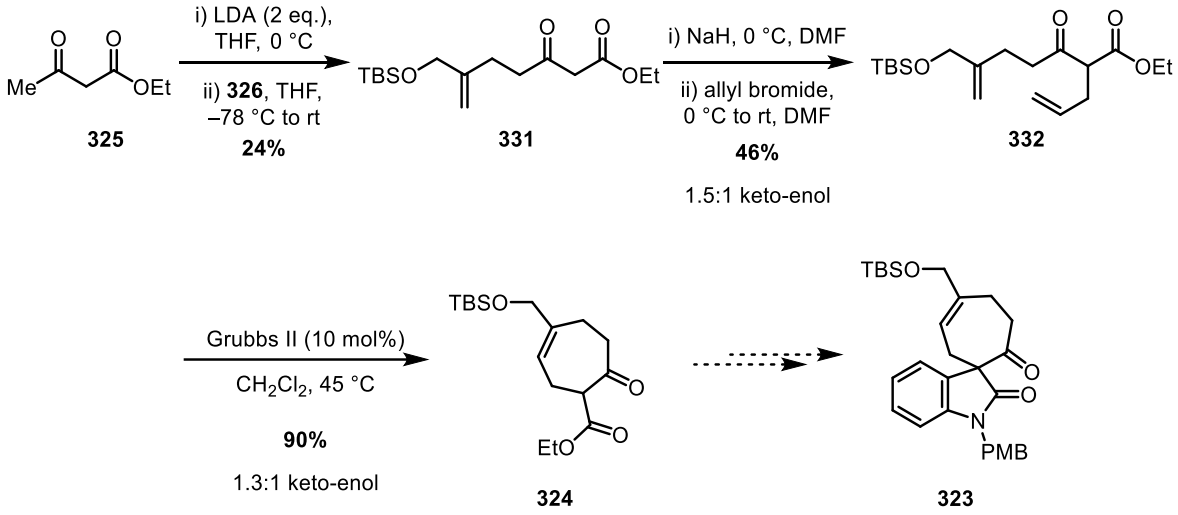
4.6.6.2 Attempted synthesis of spirocyclic oxindole 323

The synthesis of allyl bromide **326** began following a well-established protocol.[136] Specifically, Baylis-Hillman reaction between methyl acrylate (**328**) and paraformaldehyde, followed by primary alcohol protection afforded α,β-unsaturated methyl ester **329** in 31% over two steps (Scheme 4.49). DIBAL-H reduction of the ester **329** gave the primary alcohol **330**, the treatment of the alcohol with triphenylphosphine and tetrabromomethane gave the bromo alkyl product **326**.



Scheme 4.49. Synthesis of allyl bromide building block **326**.

With allyl bromide **326** in hand, alkylation of ethyl acetoacetate (**325**) was carried out in moderate yield using LDA (2 eq) and gave access to β-keto ester **331** (Scheme 4.50). Diene **332** was obtained *via* a second alkylation procedure with allyl bromide and yielded metathesis precursor **332** as a mixture of keto-enol tautomers in a 1.5:1 ratio, respectively. The ring-closing metathesis was performed using the second generation Grubbs catalyst and gave the expected seven-membered ring product **324** as a 1.3:1 mixture of keto-enol tautomers, respectively. Ester hydrolysis and amide coupling followed by a key copper(II)-mediated cyclisation step would potentially afford the advanced intermediate **323**. Unfortunately, at this stage investigation had to be stopped due to lack of time.



Scheme 4.50. Synthesis of β-keto ester **324**.

4.7 Conclusion

An efficient synthetic route to the complex natural product rankinidine (**49**), which utilises the copper(II)-mediated radical cyclisation methodology has been investigated. The synthesis of model substrates was successfully undertaken. Disappointingly, when the oxidative coupling was applied to the synthesis of *N*-methoxyoxindole, the cyclisation proved more difficult, mainly due to decomposition. An alternative approach, based on dioxirane-mediated oxidation of unprotected oxindole proved to be a more successful route to access the *N*-methoxyoxindole scaffold. Unfortunately, this transformation proved difficult to optimise.

An intramolecular cycloaddition approach to more advanced rankinidine precursors proved unsuccessful but a reliable and readily scalable route to spirooxindole **322** was undertaken. Further studies (cycloheptenone **324**) were also successful. These result should form the basis for future studies towards the synthesis of rankinidine (**49**).

Chapter 5. Final conclusions and future work

5.1 The synthesis of bis-oxindole derivatives

In light of the work developed by the Taylor group in the area of copper(II)-mediated cyclisations to oxindoles, the extension of this method to the synthesis of the structurally more challenging bis-oxindoles has been successfully demonstrated. A great diversity has been observed in the nature of the central core between both oxindole units, going from a rigid system containing cyclic ketones to a more flexible system containing linear mono-ketone, and di-ester linkers (Figure 5.1). Whereas complete diastereocontrol was observed for the formation of the spirocyclic bis-oxindoles, the introduction of more flexible moieties in the linker has been shown to be detrimental in maintaining the diastereoselectivity.

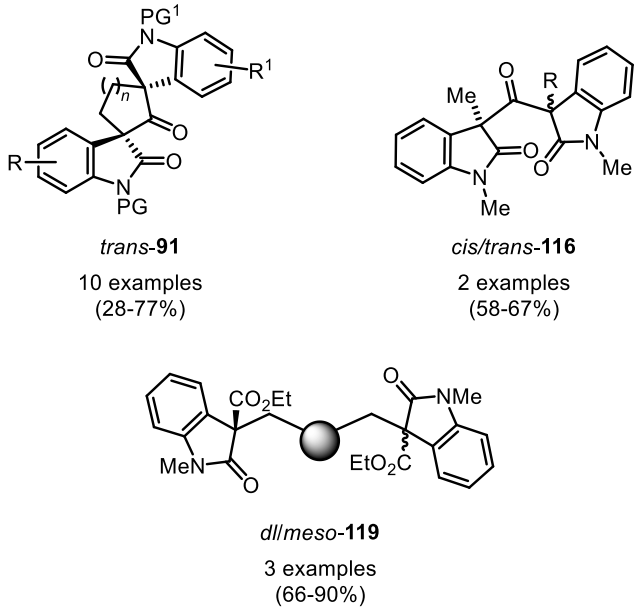
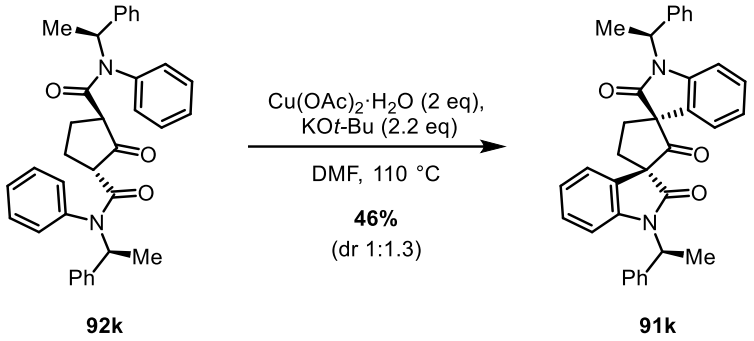


Figure 5.1. Substrate scope in the copper(II)-mediated formation of bis-oxindoles.

Asymmetric studies, relying on the introduction of a chiral auxiliary on the nitrogen of the spirocyclic bis-oxindole precursors **92k** has been investigated (Scheme 5.1), but further research is needed in this area.



Scheme 5.1. Asymmetric studies in the formation of spirocyclic bis-oxindoles.

Future work in this area will focus on the introduction of bulkier chiral auxiliaries on the nitrogen and study the impact on the copper(II)-mediated double cyclisation of spirocyclic bis-oxindole substrates. A range of α-chiral amines could be tested in order to gain higher diastereocontrol (Figure 5.2).

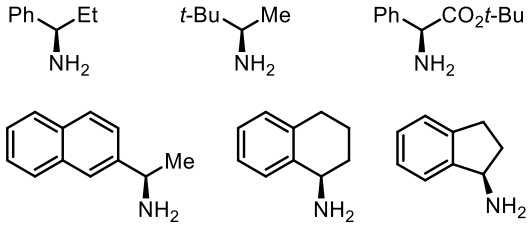
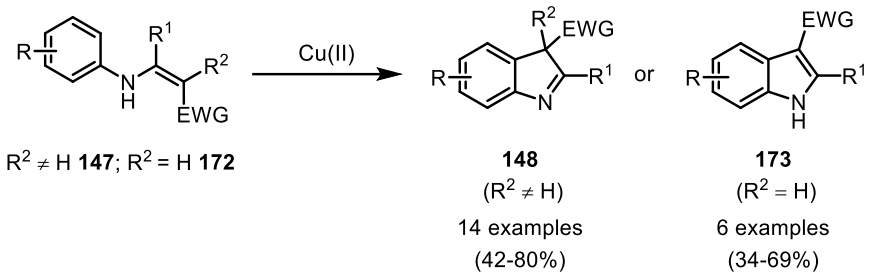


Figure 5.2. Examples of α-chiral amines.

5.2 The synthesis of indole derivatives

The extension of the copper(II)-mediated oxidative coupling has been successfully applied to the synthesis of indole derivatives. The construction of 3*H*-indoles **148** and 1*H*-indoles **173** has been undertaken through the cyclisation of simple and readily available *N*-aryl enamines (Scheme 5.2). A wide range of cyclised products has been obtained using a copper salt as oxidant.

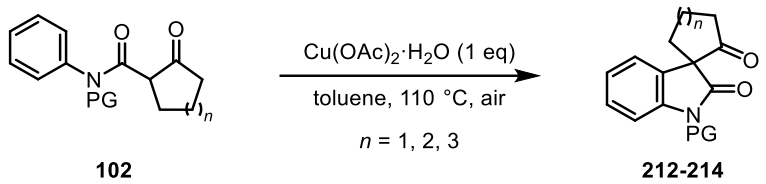


Scheme 5.2. A copper(II)-mediated synthesis of 3*H*- and 1*H*-indoles.

The extension of the substrate scope to simpler *N*-aryl enamines could be tested. Also, imine precursors instead of enamines will potentially give access to a larger range of indole derivatives. The total synthesis of biologically potent indoline natural products would present an opportunity to apply this copper(II)-mediated methodology.

5.3 Studies towards the total synthesis of rankinidine (49)

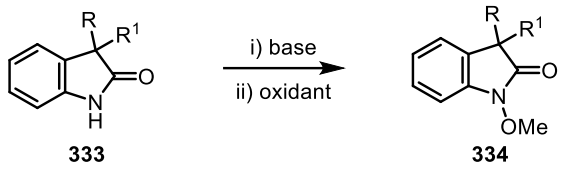
Application of the copper(II)-mediated oxidative coupling to underpin a synthetic approach to the spirocyclic oxindole rankinidine (**49**) has been studied. Access to spirocyclic ketone oxindoles containing 5-, 6-, and 7-membered rings has shown promising results for the viability of the proposed application. Further investigations on the asymmetric synthesis of spirocyclic ketone oxindoles could be also envisioned.



Scheme 5.3. Synthesis of spirocarbocyclic oxindoles *via* a copper(II) oxidative coupling route.

Concerning the formation of *N*-methoxyoxindoles, a one-pot oxidation/methylation sequence using DMDO as oxidant showed great promise (Scheme 5.4). However, the poor conversion of this transformation needs to be improved to make it synthetically useful. Having already screened a number of different conditions for this reaction, the nature of the oxidant could next be investigated. To gain deeper understanding of the mechanism, either

the influence of a deuterium labelled dioxirane oxidant or the addition of a radical promotor could be investigated.

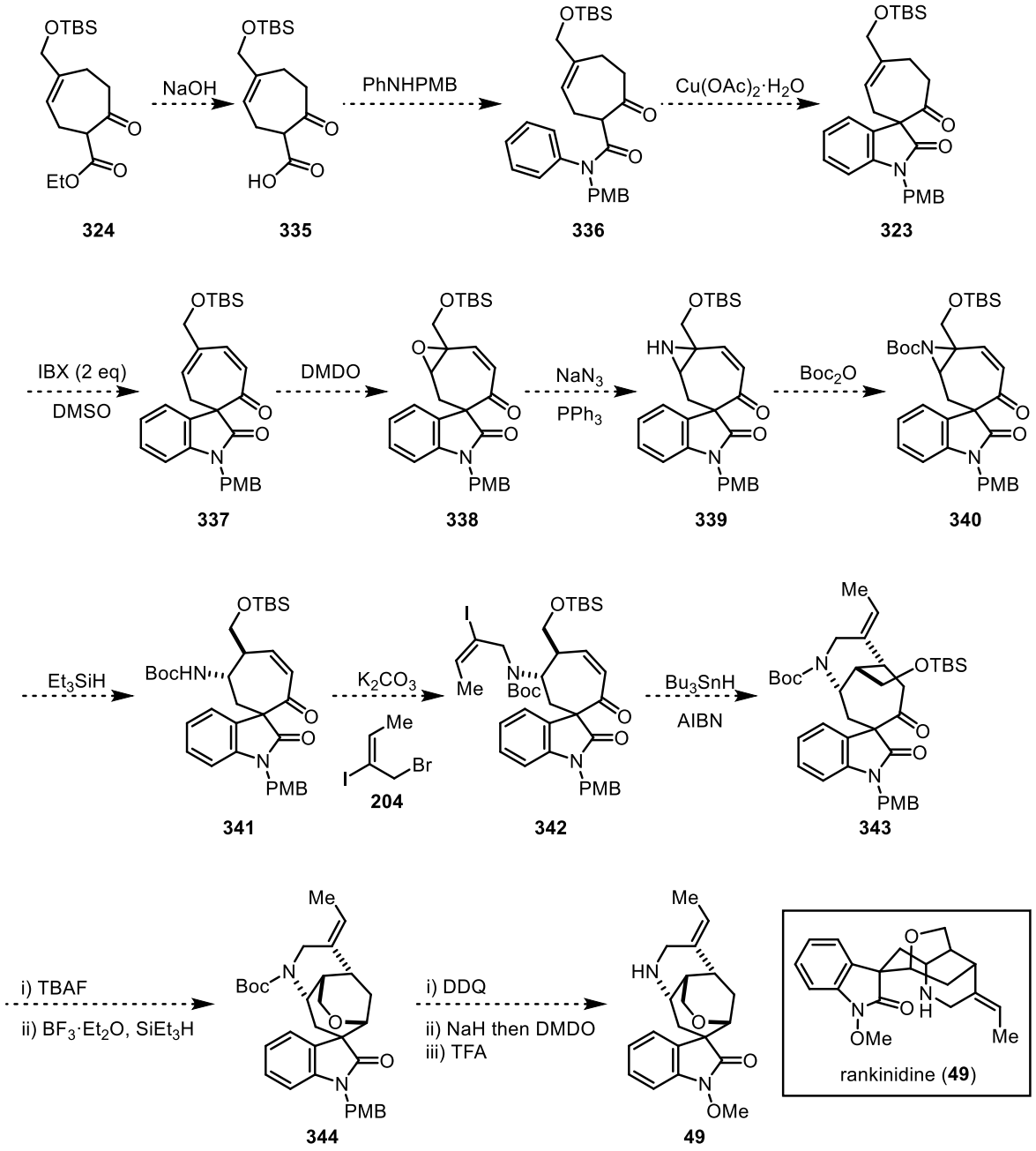


333 **334**

Scheme 5.4. Optimisation of the transformation of unprotected oxindole **333** to *N*-methoxyoxindole **334**.

A possible synthetic route to the natural product rankinidine (**49**) is proposed in Scheme 5.5 and the preparation of the functionalised 7-membered ring compound **324** will hopefully pave the way to complete the synthesis of rankinidine (**49**) in future studies.

The formation of compound **324** was achieved in 3 steps. Ester hydrolysis, amide coupling with *N*-4-methoxybenzylaniline, copper(II) cyclisation, enone formation, followed by *N*-protected aziridine formation and opening will provide an alternative key intermediate **341**. From intermediate **341**, the amino functionality is expected to react with *E*-1-bromo-2-iodobut-2-ene in a S_N2 manner and afford the iodoalkene **342** on treatment with base. Intramolecular radical cyclisation will then directly generate the tetracyclic structure **343**. Finally, deprotection of the primary alcohol in spirooxindole **343** will result in intramolecular hemiketalisation, whereas reduction of the ensuing hemiketal, followed by oxindole deprotection, DMDO oxidation/methylation sequence and nitrogen protecting group removal will provide the natural product rankinidine (**49**).



Scheme 5.5. Forward synthesis towards rankinidine (**49**).

Chapter 6. Experimental

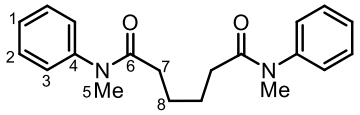
6.1 General experimental

All reactions were performed under an atmosphere of argon unless specified otherwise. Acetonitrile, dichloromethane, tetrahydrofuran, diethyl ether and toluene were dried on an Innovative Technology Pure Solv solvent purification system. Anhydrous tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone ketyl. All other reagents and solvents were from commercial sources and used without further purification. Aqueous solutions are saturated unless specified otherwise. Thin layer chromatography (TLC) was carried out on Merck plastic-backed plates (Fluka Kieselgel 60 F254) and visualised by ultra-violet irradiation (254 nm) and by staining with aqueous acidic ceric ammonium molybdate(IV) or potassium permanganate solutions as appropriate. Aldrich silica gel (60, 0.040-0.063 mm) was used for flash column chromatography. All melting points were taken on a Gallenkamp apparatus. ^{1}H NMR spectra were recorded on a Jeol ECX-400 MHz or Jeol ECS-400 MHz spectrometer and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). The coupling constants are quoted to the nearest 0.1 Hz (s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, m = multiplet, br = broad) and are reported as measured splittings on each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) signal was used as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz on a Jeol ECX-400 MHz or Jeol ECS-400 MHz spectrometer. The central reference of $CDCl_3$ (δ_C = 77.0 ppm, t) was used as reference. ^{13}C spectra were verified using DEPT experiments. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR and the nearest 0.1 ppm for ^{13}C NMR. Structural assignment was aided by the use of DEPT, COSY, HSQC and HMBC spectroscopy. High Resolution Mass Spectra were recorded using a Bruker MicrOTOF spectrometer and errors are reported in ppm. IR spectra were recorded on a Jasco FT/IR-4100 spectrometer. Samples were prepared as a neat film. All numbering of the structures below is for characterisation purposes and does not conform to IUPAC rules.

6.2 The synthesis of bis-oxindole derivatives

6.2.1 General procedure A: Double Mukaiyama's amide bond coupling

N,*N'*-Dimethyl-*N*,*N*'-diphenyladipamide (**97a**)

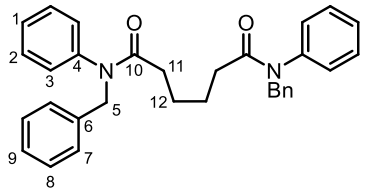


97a

To a stirred solution of adipic acid (1.01 g, 6.84 mmol) in THF (100 mL) was added *N*-methylaniline (1.85 mL, 17.1 mmol), 2-chloro-1-methylpyridinium iodide (5.24 g, 20.5 mmol), and Et_3N (9.52 mL, 68.4 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred overnight. Then, a solution of aq. HCl (10%, 100 mL) was added. The aqueous phase was extracted with EtOAc (2 × 80 mL), washed with water (2 × 80 mL) and brine (2 × 80 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude yellow oil was then purified by column chromatography (SiO_2, Hexane/EtOAc, 1:4) to give the title compound **97a** (1.66 g, 75%) as a yellow solid; mp. 68-70 °C; R_f 0.34 (EtOAc); ν_{max} (cm^{-1}) 2948, 1650, 1592, 1494, 1454, 1417, 1385, 1325, 1288, 1266, 1113, 1039, 776, 699, 566; δ_H (400 MHz; $CDCl_3$) 7.35 (4 H, t, *J* = 7.4 Hz, H-2), 7.28 (2 H, t, *J* = 7.4 Hz, H-1), 7.08 (4 H, d, *J* = 7.4 Hz, H-3), 3.18 (6 H, s, H-5), 1.94 (4 H, br s, H-7), 1.42 (4 H, br s, H-8); δ_C (100 MHz; $CDCl_3$) 172.9 (C-6), 144.2 (C-4), 129.8 (C-2), 127.8 (C-1), 127.4 (C-3), 37.3 (C-5), 33.9 (C-7), 25.2 (C-8); Found (ESI): $[MNa]^+$ 347.1731; $C_{20}H_{24}N_2NaO_2$ requires $[MNa]^+$ 347.1730, 0.2 ppm.

Lab-book No PD/8/44.

N,*N'*-Dibenzyl, *N*,*N'*-diphenyladipamide (**97b**)

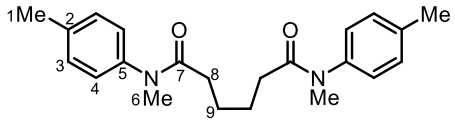


97b

Adipic acid (0.508 g, 3.47 mmol), *N*-benzylaniline (1.61 g, 8.78 mmol), 2-chloro-1-methylpyridinium iodide (2.66 g, 10.4 mmol), and Et_3N (4.83 mL, 34.7 mmol) in THF (50 mL) were subjected to general procedure A. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1 to Hexane/EtOAc, 2:1) to give the title compound **97b** (0.630 g, 38%) as a colourless solid; mp. 64-66 °C; R_f 0.15 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 1655, 1595, 1495, 1454, 1398, 1259, 1203, 1079, 1017, 700; δ_H (400 MHz; $CDCl_3$) 7.31 – 7.26 (6 H, m, H_{Ar}), 7.24 – 7.20 (6 H, m, H_{Ar}), 7.18 – 7.13 (4 H, m, H_{Ar}), 6.90 (4 H, dd, *J* = 6.4, 3.1 Hz, H_{Ar}), 4.83 (4 H, s, H-5), 1.98 (4 H, br s, H-11), 1.50 (4 H, br s, H-12); δ_C (100 MHz; $CDCl_3$) 172.7 (C-10), 142.4 (C_{Ar}), 137.7 (C_{Ar}), 129.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.0 (CH_{Ar}), 127.4 (CH_{Ar}), 53.0 (C-5), 34.2 (C-11), 25.1 (C-12); Found (ESI): $[MNa]^+$ 499.2337; $C_{32}H_{32}N_2NaO_2$ requires $[MNa]^+$ 499.2356, 3.8 ppm.

Lab-book No PD/9/39.

N,*N*'-Dimethyl-*N*,*N*'-di-4-tolyladipamide (**97c**)



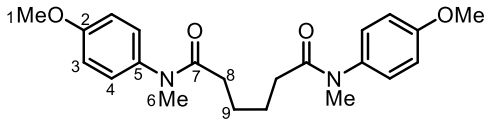
97c

Adipic acid (0.503 g, 3.44 mmol), *N*-methyl-*p*-toluidine (1.09 mL, 8.60 mmol), 2-chloro-1-methylpyridinium iodide (2.63 g, 10.3 mmol), and Et_3N (4.79 mL, 34.4 mmol) in THF (50 mL) were subjected to general procedure A. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:3) to give the title compound **97c** (1.13 g, 93%) as a pale yellow solid; mp. 81-83 °C; R_f 0.23 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1650, 1612, 1513, 1418, 1382, 1290, 1119, 1021, 826, 724, 559; δ_H (400 MHz; $CDCl_3$) 7.17 (4 H, d, *J* = 8.1 Hz, H-3), 6.98 (4 H, d, *J* = 8.1 Hz, H-4), 3.18 (6 H, s, H-6), 2.36 (6 H, s, H-1), 1.96 (4 H, br s, H-8), 1.43 (4 H, br s, H-9); δ_C (100 MHz; $CDCl_3$) 173.1 (C-7), 141.6 (C-5), 137.7

(C-2), 130.4 (C-3), 127.1 (C-4), 37.4 (C-6), 33.9 (C-8), 25.2 (C-9), 21.2 (C-1); Found (ESI): $[MNa]^+$ 375.2033; $C_{22}H_{28}N_2NaO_2$ requires $[MNa]^+$ 375.2043, 2.8 ppm.

Lab-book No PD/9/27.

N,*N*'-Dimethyl-*N*,*N*'-di-4-methoxyphenyladipamide (**97d**)



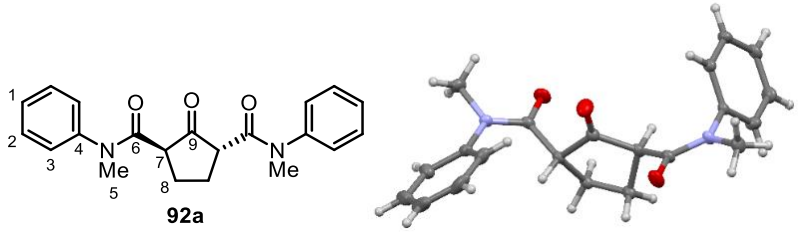
97d

Adipic acid (0.503 g, 3.44 mmol), 4-methoxy-*N*-methylaniline (1.19 g, 8.67 mmol), 2-chloro-1-methylpyridinium iodide (2.63 g, 10.3 mmol), and Et_3N (4.79 mL, 34.4 mmol) in THF (50 mL) were subjected to general procedure A. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:4) to give the title compound **97d** (1.20 g, 91%) as a colourless solid; mp. 85-87 °C; R_f 0.21 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1646, 1584, 1508, 1443, 1383, 1291, 1243, 1170, 1106, 1119, 1029, 837, 734; δ_H (400 MHz; $CDCl_3$) 6.99 (4 H, d, *J* = 8.9 Hz, H-4), 6.85 (4 H, d, *J* = 8.9 Hz, H-3), 3.78 (6 H, s, H-1), 3.14 (6 H, s, H-6), 1.92 (4 H, t, *J* = 6.1 Hz, H-8), 1.44 – 1.38 (4 H, m, H-9); δ_C (100 MHz; $CDCl_3$) 173.2 (C-7), 158.8 (C-2), 137.0 (C-5), 128.4 (C-4), 114.9 (C-3), 55.5 (C-1), 37.4 (C-6), 33.8 (C-8), 25.2 (C-9); Found (ESI): $[MNa]^+$ 407.1937; $C_{22}H_{28}N_2NaO_4$ requires $[MNa]^+$ 407.1941, 1.0 ppm.

Lab-book No PD/9/40.

6.2.2 General procedure B: CDI-mediated cyclisation

trans-bis(*N*-Methyl-*N*-phenyl)-2-oxo-cyclopentane-1,3-dicarboxamide (**92a**)



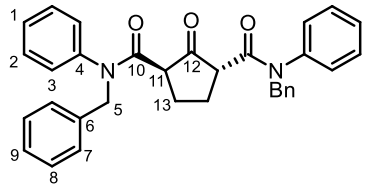
92a

To a stirred solution of *N*,*N*'-dimethyl-*N*,*N*'-diphenyladipamide (0.502 g, 1.54 mmol) in THF (20 mL) was added LiHMDS (1.0 M in THF, 4.62 mL, 4.62 mmol) at −78 °C. The reaction mixture was stirred for 15 min and a solution of CDI (0.376 g, 2.31 mmol) in THF (20 mL) was then added slowly at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and a sat. aq. solution of NH_4Cl (20 mL) was added. The reaction mixture was allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic portions were washed with water (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The brown crude residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:1) to give the title compound **92a** (0.148 g, 27%) as a colourless solid; mp. 130-132 °C; R_f 0.42 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1804, 1740, 1655, 1633, 1593, 1496, 1454, 1386, 1299, 1191, 1122, 1093, 930, 892, 773, 699, 562; δ_H (400 MHz; $CDCl_3$) 7.42 – 7.36 (4 H, m, H-2), 7.36 – 7.30 (2 H, m, H-1), 7.26 (4 H, d, *J* = 7.1 Hz, H-3), 3.23 (6 H, s, H-5), 3.23 – 3.19 (2 H, m, H-7), 2.18 – 2.05 (4 H, m, H-8); δ_C (100 MHz; $CDCl_3$) 209.9 (C-9), 169.3 (C-6), 143.4 (C-4), 130.1 (C-2), 128.4 (C-1), 127.4 (C-3), 53.2 (C-7), 37.7 (C-5), 26.4 (C-8); Found (ESI): $[MNa]^+$ 373.1529; $C_{21}H_{22}N_2NaO_3$ requires $[MNa]^+$ 373.1523, 1.6 ppm. CCDC 1013303 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/8/48.

trans-bis(*N*-Benzyl-*N*-phenyl)-2-oxo-cyclopentane-1,3-dicarboxamide (**92b**)

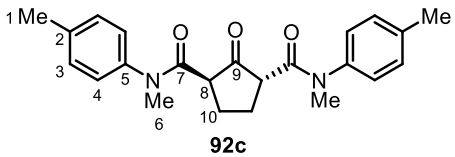


92b

N,*N'*-Dibenzyl-*N*,*N'*-diphenyladipamide (0.416 g, 0.873 mmol), LiHMDS (1.0 M in THF, 2.62 mL, 2.62 mmol), and CDI (0.212 g, 1.31 mmol) in THF (20 mL + 5 mL) were subjected to general procedure B. Purification by column chromatography (SiO_2, Hexane/EtOAc, 4:1 to 2:1) afforded the title compound **92b** (0.120 g, 27%) as a colourless solid; mp. 115-117 °C; R_f 0.16 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 1744, 1651, 1595, 1495, 1398, 1265, 1109, 1019, 732, 699; δ_H (400 MHz; $CDCl_3$) 7.33 – 7.28 (6 H, m, H_{Ar}), 7.26 – 7.21 (6 H, m, H_{Ar}), 7.16 (4 H, dd, *J* = 7.5, 1.7 Hz, H_{Ar}), 7.07 (4 H, br s, H_{Ar}), 4.90 (2 H, d, *J* = 14.4 Hz, H-5a), 4.83 (2 H, d, *J* = 14.4 Hz, H-5b), 3.27 – 3.19 (2 H, m, H-11), 2.21 – 2.12 (4 H, m, H-13); δ_C (100 MHz; $CDCl_3$) 209.5 (C-12), 169.6 (C-10), 141.7 (C_{Ar}), 137.0 (C_{Ar}), 129.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 127.5 (CH_{Ar}), 53.4 (C-11), 53.3 (C-5), 26.5 (C-13); Found (ESI): $[MNa]^+$ 525.2157; $C_{33}H_{30}N_2NaO_3$ requires $[MNa]^+$ 525.2149, 1.6 ppm.

Lab-book No PD/9/22.

trans-bis(*N*-Methyl-*N*-4-tolyl)-2-oxo-cyclopentane-1,3-dicarboxamide (**92c**)



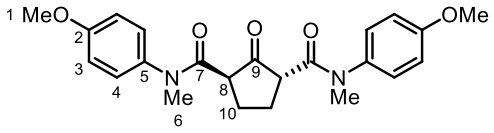
92c

N,*N*'-Dimethyl-*N*,*N*'-di-4-tolyladipamide (0.468 g, 1.33 mmol), LiHMDS (1.0 M in THF, 3.99 mL, 3.99 mmol), and CDI (0.325 g, 2.00 mmol) in THF (20 mL + 5 mL) were subjected to general procedure B. Purification by column chromatography (SiO_2, Hexane/EtOAc, 1:1) afforded the title compound **92c** (0.092 g, 18%) as a colourless solid; mp. 133-135 °C; R_f 0.48 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1745, 1646, 1614, 1514, 1420, 1380, 1303, 1268, 1107, 912, 824, 722, 560; δ_H (400 MHz; $CDCl_3$) 7.21 – 7.08 (8 H, m, H-3, H-4), 3.25 – 3.21 (2 H, m, H-8), 3.20 (6 H, s, H-6), 2.34 (6 H, s, H-1), 2.16 – 2.04 (4 H, m, H-10); δ_C (100 MHz; $CDCl_3$) 209.9 (C-9), 169.4 (C-7), 140.9 (C-5), 138.3 (C-2), 130.6 (C-3), 127.1 (C-4),

53.1 (C-8), 37.7 (C-6), 26.3 (C-10), 21.2 (C-1); Found (ESI): $[MNa]^+$ 401.1828; $C_{23}H_{26}N_2NaO_3$ requires $[MNa]^+$ 401.1836, 1.8 ppm.

Lab-book No PD/9/29.

trans-bis(*N*-Methyl-*N*-4-methoxyphenyl)-2-oxo-cyclopentane-1,3-dicarboxamide (**92d**)



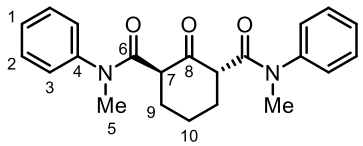
92d

N,*N*'-Dimethyl-*N*,*N*'-di-4-methoxyphenyladipamide (0.535 g, 1.39 mmol), LiHMDS (1.0 M in THF, 4.17 mL, 4.17 mmol), and CDI (0.340 g, 2.10 mmol) in THF (20 mL + 5 mL) were subjected to general procedure B. Purification by column chromatography (SiO_2, Hexane/EtOAc, 1:1) afforded the title compound **92d** (0.095 g, 17%) as a colourless solid; mp. 132-134 °C; R_f 0.42 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1743, 1645, 1583, 1509, 1443, 1381, 1292, 1245, 1170, 1030, 838, 732; δ_H (400 MHz; $CDCl_3$) 7.16 (4 H, br d, J = 5.7 Hz, H_{Ar}), 6.87 (4 H, dd, J = 7.5, 1.5 Hz, H_{Ar}), 3.80 (6 H, s, H-1), 3.26 – 3.21 (2 H, m, H-8), 3.20 (6 H, s, H-6), 2.17 – 2.03 (4 H, m, H-10); δ_C (100 MHz; $CDCl_3$) 210.0 (C-9), 169.6 (C-7), 159.3 (C-2), 136.2 (C-5), 128.5 (CH_{Ar}), 115.1 (CH_{Ar}), 55.6 (C-1), 53.1 (C-8), 37.8 (C-6), 26.3 (C-10); Found (ESI): $[MNa]^+$ 433.1741; $C_{23}H_{26}N_2NaO_5$ requires $[MNa]^+$ 433.1734, 1.6 ppm.

Lab-book No PD/9/41.

6.2.3 General procedure C: Double MMC carboxylation/Mukaiyama's coupling

trans-bis(*N*-Methyl-*N*-phenyl)-2-oxo-cyclohexane-1,3-dicarboxamide (**92g**)



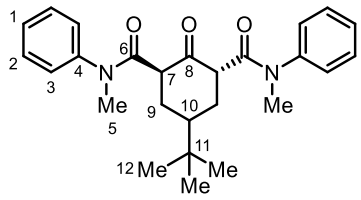
92g

Cyclohexanone (0.210 mL, 2.04 mmol) was added to a solution of methyl magnesium carbonate (2.0 M in DMF, 8.15 mL, 16.3 mmol). The reaction mixture was stirred for 6 h at 130 °C. The reaction was allowed to cool to room temperature and HCl (10% solution in

water) was added slowly until the pH media became acidic. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (4 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of mono- and bis-acids. To a stirred solution of the crude acid mixture (0.175 g, 0.938 mmol) in CH_2Cl_2 (17 mL) was added *N*-methylaniline (0.254 mL, 2.34 mmol), 2-chloro-1-methylpyridinium iodide (0.720 g, 2.82 mmol) and Et_3N (1.31 mL, 9.38 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. HCl (10% solution in water, 10 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of mono- and bis-anilides. Purification by column chromatography (SiO_2, Hexane/EtOAc, 3:1 to Hexane/EtOAc, 1:4) afforded the monoanilide product **102a** (0.065 g, 30%) as a yellow oil and the title compound **92g** (0.048 g, 14%) as a colourless solid; mp. 158-160 °C; R_f 0.19 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1713, 1651, 1595, 1495, 1451, 1422, 1381, 1304, 1074, 920, 774, 729, 701; δ_H (400 MHz; $CDCl_3$) 7.33 – 7.29 (6 H, m, H-1, H-2), 7.06 – 7.02 (4 H, m, H-3), 3.25 (6 H, s, H-5), 2.94 (2 H, dd, *J* = 13.2, 5.5 Hz, H-7), 2.33 – 2.18 (2 H, m, H-9a), 1.91 (2 H, dd, *J* = 13.2, 2.7 Hz, H-9b), 1.86 – 1.79 (1 H, m, H-10a), 1.37 – 1.22 (1 H, m, H-10b); δ_C (100 MHz; $CDCl_3$) 201.9 (C-8), 168.6 (C-6), 143.8 (C-4), 129.8 (C-2), 127.9 (C-1), 127.1 (C-3), 54.8 (C-7), 37.7 (C-5), 30.0 (C-9), 22.9 (C-10); Found (ESI): $[MNa]^+$ 387.1682; $C_{22}H_{24}N_2NaO_3$ requires $[MNa]^+$ 387.1679, 0.8 ppm.

Lab-book No PD/9/20.

5-*tert*-Butyl-*trans*-bis(*N*-methyl-*N*-phenyl)-2-oxo-cyclohexane-1,3-dicarboxamide (**92h**)



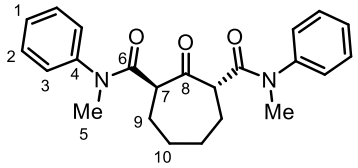
92h

4-*tert*-Butylcyclohexanone (0.216 g, 1.40 mmol) and methyl magnesium carbonate (2.0 M in DMF, 5.6 mL, 11.2 mmol) were subjected to general procedure C. The mixture of crude mono- and bis-acids was subsequently treated with *N*-methylaniline (0.320 mL, 2.99 mmol), 2-chloro-1-methylpyridinium iodide (0.917 g, 3.60 mmol) and Et_3N (1.67 mL, 12.0 mmol) following general procedure C. Purification by column chromatography (SiO_2, Hexane/EtOAc, 2:1) afforded the monoanilide product **102b** (0.131 g, 38%) as a brown oil

and the title compound **92h** (0.051 g, 10%) as a foamy colourless solid; mp. 81-83 °C; R_f 0.42 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1716, 1658, 1596, 1495, 1386, 1124, 1073, 775, 702; δ_H (400 MHz; $CDCl_3$) 7.32 – 7.29 (6 H, m, H-1, H-2), 7.06 – 7.02 (4 H, m, H-3), 3.24 (6 H, s, H-5), 2.97 (2 H, dd, *J* = 12.7, 5.4 Hz, H-7), 2.15 – 2.02 (2 H, m, H-9a), 1.96 – 1.86 (2 H, m, H-9b), 1.27 – 1.16 (1 H, m, H-10), 0.83 (9 H, s, H-12); δ_C (100 MHz; $CDCl_3$) 202.3 (C-8), 168.8 (C-6), 143.7 (C-4), 129.8 (C-2), 127.9 (C-1), 127.1 (C-3), 54.3 (C-7), 44.3 (C-10), 37.8 (C-5), 32.8 (C-11), 31.3 (C-9), 27.6 (C-12); Found (ESI): $[MNa]^+$ 443.2293; $C_{26}H_{32}N_2NaO_3$ requires $[MNa]^+$ 443.2305, 2.8 ppm.

Lab-book No PD/9/37.

trans-bis(*N*-Methyl-*N*-phenyl)-2-oxo-cycloheptane-1,3-dicarboxamide (**92i**)

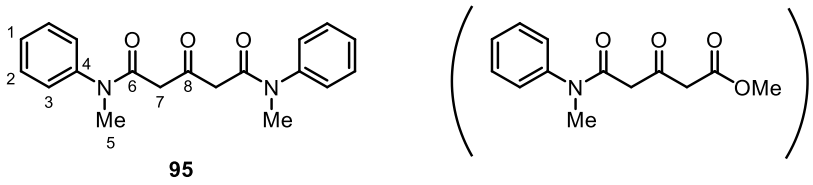


92i

Cycloheptanone (0.190 g, 1.70 mmol) and methyl magnesium carbonate (2.0 M in DMF, 6.8 mL, 13.6 mmol) were subjected to general procedure C. The mixture of crude mono- and bis-acids was subsequently treated with *N*-methylaniline (0.240 mL, 2.19 mmol), 2-chloro-1-methylpyridinium iodide (0.670 g, 2.62 mmol) and Et_3N (1.22 mL, 8.75 mmol) in CH_2Cl_2 (20 mL) following general procedure C. Purification by column chromatography (SiO_2, Hexane/EtOAc, 2:1 to Hexane/EtOAc, 1:2) afforded the monoanilide product **102c** (0.073 g, 34%) as a yellow oil and the title compound **92i** (0.029 g, 9%) as a yellow oil; R_f 0.22 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1709, 1650, 1595, 1495, 1452, 1419, 1381, 1118, 774, 729, 701; δ_H (400 MHz; $CDCl_3$) 7.30 – 7.25 (2 H, m, H-1), 7.22 (4 H, t, *J* = 7.4 Hz, H-2), 6.96 (4 H, d, *J* = 7.4 Hz, H-3), 3.21 (6 H, s, H-5), 3.16 (2 H, dd, *J* = 6.7, 4.0 Hz, H-7), 2.00 – 1.89 (2 H, m, H-10a), 1.88 – 1.77 (2 H, m, H-9a), 1.60 – 1.47 (2 H, m, H-9b), 1.46 – 1.32 (2 H, m, H-10b); δ_C (100 MHz; $CDCl_3$) 204.5 (C-8), 169.7 (C-6), 143.9 (C-4), 129.9 (C-2), 128.1 (C-1), 127.6 (C-3), 54.9 (C-7), 37.6 (C-5), 28.2 (C-9), 27.1 (C-10); Found (ESI): $[MNa]^+$ 401.1847; $C_{23}H_{26}N_2NaO_3$ requires $[MNa]^+$ 401.1836, 2.8 ppm.

Lab-book No PD/9/25.

N,*N'*-Dimethyl-3-oxo-*N*,*N'*-diphenylpentanediamide (**95**)

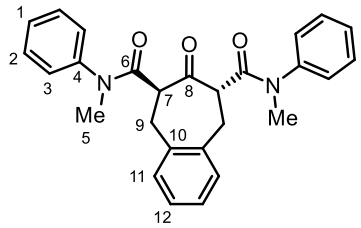


95

To a stirred solution of dimethyl 1,3-acetonedicarboxylate (1.00 mL, 6.93 mmol) in toluene (100 mL) was added *N*-methylaniline (2.25 mL, 20.8 mmol), and 4-(dimethylamino)pyridine (0.085 g, 0.693 mmol). The reaction mixture was stirred overnight at 110 °C and allowed to cool to room temperature. Toluene was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:1) and give the monoanilide product (0.932 g, 54%) as a brown oil and the title compound **95** (0.429 g, 19%) as a brown solid; mp. 74-76 °C; R_f 0.24 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1724, 1651, 1594, 1495, 1379, 1347, 1120, 774, 700; δ_H (400 MHz; $CDCl_3$) 7.43 – 7.37 (4 H, m, H_{Ar}), 7.36 – 7.29 (2 H, m, H_{Ar}), 7.20 – 7.14 (4 H, m, H_{Ar}), 3.33 (4 H, s, H-7), 3.24 (6 H, s, H-5); δ_C (100 MHz; $CDCl_3$) 199.1 (C-8), 166.7 (C-6), 143.5 (C-4), 130.0 (CH_{Ar}), 128.3 (CH_{Ar}), 127.3 (CH_{Ar}), 49.2 (C-7), 37.4 (C-5); Found (ESI): $[MNa]^+$ 347.1350; $C_{19}H_{20}N_2NaO_3$ requires $[MNa]^+$ 347.1366, 4.7 ppm.

Lab-book No PD/7/48.

trans-6-*N*,8-*N*-Dimethyl-7-oxo-6-*N*,8-*N*-diphenyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6,8-dicarboxamide (**92j**)



92j

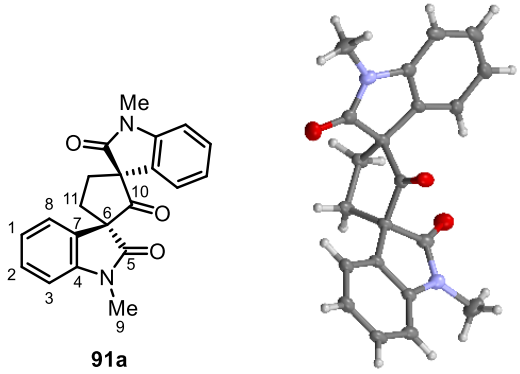
To a stirred solution of di*iso*propylamine (0.104 mL, 0.740 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 0.310 mL, 0.775 mmol). The reaction mixture was stirred at 0 °C for 15 min and cooled to –78 °C. A solution of *N*,*N'*-dimethyl-3-oxo-*N*,*N'*-diphenylpentanediamide (0.229 g, 0.705 mmol) in THF (2 mL) was added and the reaction mixture was stirred for 30 min, allowed to warm to room temperature and stirred for a further 30 min. It was then cooled to –78 °C and a solution of α,α'-dibromo-*o*-xylene (0.198 g, 0.751 mmol) in THF (2 mL) was slowly added at –78 °C. The reaction was warmed to room temperature and stirred for 1 h then cooled to 0 °C and NaH (0.031 g, 0.775 mmol) was

added. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by addition of NH_4Cl (20 mL). The two phases were separated and the resulting aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Hexane/EtOAc, 2:1) afforded the title compound **92j** (0.080 g, 27%) as a foamy colourless solid; mp. 60-62 °C; R_f 0.48 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1699, 1650, 1595, 1494, 1380, 1117, 911, 772, 727, 699; δ_H (400 MHz; $CDCl_3$) 7.40 (4 H, t, *J* = 7.5 Hz, H-2), 7.32 (2 H, t, *J* = 7.5 Hz, H-1), 7.14 (4 H, d, *J* = 7.5 Hz, H-3), 7.10 (4 H, br s, H-11, H-12), 4.07 (2 H, dd, *J* = 8.1, 5.2 Hz, H-7), 3.16 (6 H, s, H-5), 3.11 (2 H, dd, *J* = 14.8, 8.1 Hz, H-9a), 2.97 (2 H, dd, *J* = 14.8, 5.2 Hz, H-9b); δ_C (100 MHz; $CDCl_3$) 204.0 (C-8), 168.9 (C-6), 143.3 (C-4), 137.5 (C-10), 130.0 (C-2), 129.5 (CH_{Ar}), 128.2 (C-1), 127.5 (C-3), 127.4 (CH_{Ar}), 55.4 (C-7), 37.8 (C-5), 34.1 (C-9); Found (ESI): $[MNa]^+$ 449.1829; $C_{27}H_{26}N_2NaO_3$ requires $[MNa]^+$ 449.1836, 1.5 ppm.

Lab-book No PD/9/85.

6.2.4 General procedure D: Spirocyclisation reaction

trans-1,1''-Dimethyl-1,1'',2,2''-tetrahydrodispiro[indole-3,1'-cyclopentane-3',3''-indole]-2,2',2''-trione (**91a**)



91a

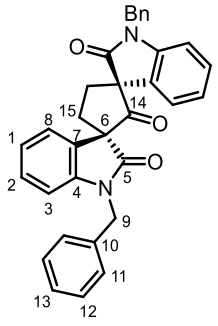
To a stirred solution of bis-anilide **92a** (0.027 g, 0.078 mmol) in DMF (3 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.032 g, 0.161 mmol) and KO*t*-Bu (0.019 g, 0.168 mmol). The reaction mixture was stirred at 110 °C for 15 min and allowed to cool to room temperature. An aq. solution of 10% NH_4OH (2 × 5 mL) was added and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with water (4 × 5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. ^1H NMR of the crude

reaction mixture showed only the *trans*-diastereoisomer **91a**. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91a** (0.018 g, 67%) as a colourless solid; mp. 184-186 °C; R_f 0.42 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1751, 1704, 1612, 1493, 1471, 1370, 1347, 1266, 1070, 885, 752; δ_H (400 MHz; $CDCl_3$) 7.43 (2 H, dd, *J* = 7.6, 1.2 Hz, H-8), 7.31 (2 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.10 (2 H, td, *J* = 7.6, 1.2 Hz, H-1), 6.84 (2 H, d, *J* = 7.6 Hz, H-3), 3.21 (6 H, s, H-9), 3.15 – 3.10 (2 H, m, H-11a), 2.78 – 2.72 (2 H, m, H-11b); δ_C (100 MHz; $CDCl_3$) 208.0 (C-10), 175.0 (C-5), 144.4 (C-4), 129.8 (C-7), 129.1 (C-2), 124.3 (C-8), 123.6 (C-1), 108.4 (C-3), 63.7 (C-6), 32.4 (C-11), 26.6 (C-9); Found (ESI): $[MNa]^+$ 369.1213; $C_{21}H_{18}N_2NaO_3$ requires $[MNa]^+$ 369.1210, 0.8 ppm. CCDC 1004040 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/8/88.

trans-1,1''-Dibenzyl-1,1'',2,2''-tetrahydrodispiro[indole-3,1'-cyclopentane-3',3''-indole]-2,2',2''-trione (**91b**)



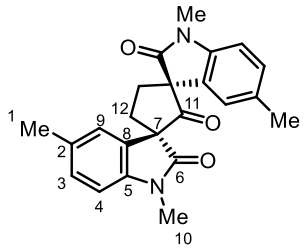
91b

Bis-anilide **92b** (0.015 g, 0.029 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.012 g, 0.058 mmol) and KO*t*-Bu (0.007 g, 0.064 mmol) in DMF (1.5 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91b** (0.008 g, 57%) as a pale yellow solid; mp. 115-117 °C; R_f 0.50 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 1740, 1703, 1612, 1488, 1467, 1455, 1359, 1311, 1178, 873, 752, 734; δ_H (400 MHz; $CDCl_3$) 7.48 (2 H, dd, *J* = 7.6, 1.0 Hz, H-8), 7.34 – 7.30 (4 H, m, H_{Ar}), 7.30 – 7.27 (6 H, m, H_{Ar}), 7.19 (2 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.07 (2 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.70 (2 H, d, *J* = 7.6 Hz, H-3), 5.02 (2 H, d, *J* = 15.9 Hz, H-9a), 4.83 (2 H, d,

J = 15.9 Hz, H-9b), 3.26 – 3.15 (2 H, m, H-15a), 2.93 – 2.81 (2 H, m, H-15b); δ_C (100 MHz; $CDCl_3$) 208.0 (C-14), 175.2 (C-5), 143.5 (C-4), 135.3 (C-10), 129.8 (C-7), 129.1 (C-2), 129.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.1 (CH_{Ar}), 124.4 (C-8), 123.7 (C-1), 109.5 (C-3), 63.8 (C-6), 43.9 (C-9), 32.5 (C-15); Found (ESI): $[MNa]^+$ 521.1825; $C_{33}H_{26}N_2NaO_3$ requires $[MNa]^+$ 521.1836, 2.0 ppm.

Lab-book No PD/9/24.

trans-1,1",5,5"-Tetramethyl-1,1",2,2"-tetrahydrodispiro[indole-3,1'-cyclopentane-3',3"-indole]-2,2',2"-trione (**91c**)

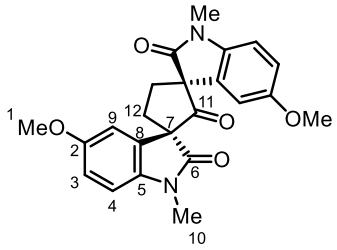


91c

Bis-anilide **92c** (0.040 g, 0.105 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.044 g, 0.219 mmol) and KO*t*-Bu (0.026 g, 0.230 mmol) in DMF (4 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91c** (0.026 g, 67%) as a colourless solid; mp. 197-199 °C; R_f 0.60 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1751, 1701, 1624, 1602, 1499, 1349, 1271, 1069, 918, 811; δ_H (400 MHz; $CDCl_3$) 7.24 (2 H, dd, *J* = 1.3, 0.6 Hz, H-9), 7.10 (2 H, ddd, *J* = 7.9, 1.3, 0.6 Hz, H-3), 6.72 (2 H, d, *J* = 7.9 Hz, H-4), 3.19 (6 H, s, H-10), 3.17 – 3.04 (2 H, m, H-12a), 2.77 – 2.64 (2 H, m, H-12b), 2.33 (6 H, s, H-1); δ_C (100 MHz; $CDCl_3$) 208.4 (C-11), 175.0 (C-6), 142.1 (C-5), 133.3 (C-2), 129.8 (C-8), 129.3 (C-3), 125.1 (C-9), 108.1 (C-4), 63.8 (C-7), 32.5 (C-12), 26.6 (C-10), 21.2 (C-1); Found (ESI): $[MNa]^+$ 397.1506; $C_{23}H_{22}N_2NaO_3$ requires $[MNa]^+$ 397.1523, 4.1 ppm.

Lab-book No PD/9/36.

trans-5,5"-Dimethoxy-1,1"-dimethyl-1,1",2,2"-tetrahydrodispiro[indole-3,1'-cyclopentane-3',3"-indole]-2,2',2"-trione (**91d**)

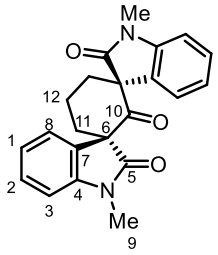


91d

Bis-anilide **92d** (0.042 g, 0.102 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.041 g, 0.206 mmol) and KO*t*-Bu (0.026 g, 0.228 mmol) in DMF (4 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1 to Hexane/EtOAc, 2:1) to give the title compound **91d** (0.018 g, 44%) as a colourless solid; mp. 180-182 °C; R_f 0.46 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1749, 1701, 1600, 1497, 1469, 1435, 1354, 1288, 1039, 811; δ_H (400 MHz; $CDCl_3$) 7.07 (2 H, d, *J* = 2.6 Hz, H-9), 6.83 (2 H, dd, *J* = 8.4, 2.6 Hz, H-3), 6.74 (2 H, d, *J* = 8.4 Hz, H-4), 3.79 (6 H, s, H-1), 3.18 (6 H, s, H-10), 3.15 – 3.03 (2 H, m, H-12a), 2.79 – 2.67 (2 H, m, H-12b); δ_C (100 MHz; $CDCl_3$) 207.9 (C-11), 174.7 (C-6), 156.7 (C-2), 137.9 (C-5), 130.8 (C-8), 114.1 (C-3), 111.1 (C-9), 108.8 (C-4), 64.1 (C-7), 56.0 (C-1), 32.5 (C-12), 26.6 (C-10); Found (ESI): $[MNa]^+$ 429.1433; $C_{23}H_{22}N_2NaO_5$ requires $[MNa]^+$ 429.1421, 2.9 ppm.

Lab-book No PD/9/45.

trans-1,1"-Dimethyl-1,1",2,2"-tetrahydrodispiro[indole-3,1'-cyclohexane-3',3"-indole]-2,2',2"-trione (**91g**)



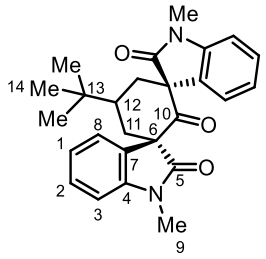
91g

Bis-anilide **92g** (0.033 g, 0.091 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.037 g, 0.187 mmol) and KO*t*-Bu (0.023 g, 0.202 mmol) in DMF (3 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91g** (0.014 g, 43%) as a colourless solid; mp. 210-212 °C; R_f 0.64 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 1705, 1688, 1610, 1494, 1471, 1372, 1348, 1266, 1105,

753; δ_H (400 MHz; $CDCl_3$) 7.57 (2 H, dd, *J* = 7.4, 1.2 Hz, H-8), 7.28 (2 H, td, *J* = 7.4, 1.2 Hz, H-2), 7.07 (2 H, td, *J* = 7.4, 1.2 Hz, H-1), 6.79 (2 H, d, *J* = 7.4 Hz, H-3), 3.17 (6 H, s, H-9), 2.50 (6 H, br s, H-11, H-12); δ_C (100 MHz; $CDCl_3$) 203.2 (C-10), 175.8 (C-5), 143.9 (C-4), 132.9 (C-7), 128.7 (C-2), 124.4 (C-8), 123.4 (C-1), 108.3 (C-3), 62.3 (C-6), 33.5 (C-11), 26.6 (C-9), 17.1 (C-12); Found (ESI): $[MNa]^+$ 383.1370; $C_{22}H_{20}N_2NaO_3$ requires $[MNa]^+$ 383.1366, 0.9 ppm.

Lab-book No PD/9/21.

5-*tert*-Butyl-*trans*-1,1"-dimethyl-1,1",2,2"-tetrahydrodispiro[indole-3,1'-cyclohexane-3',3"-indole]-2,2',2"-trione (**91h**)

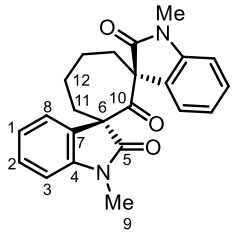


91h

Bis-anilide **92h** (0.045 g, 0.108 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.044 g, 0.219 mmol) and KO*t*-Bu (0.026 g, 0.228 mmol) in DMF (4.5 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91h** (0.024 g, 54%) as a colourless solid; mp. 152-154 °C; R_f 0.48 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1707, 1690, 1651, 1610, 1494, 1470, 1371, 1346, 1263, 753; δ_H (400 MHz; $CDCl_3$) 7.86 (1 H, dd, *J* = 7.6, 1.2 Hz, H-8a), 7.34 (1 H, dd, *J* = 7.6, 1.2 Hz, H-8b), 7.28 (1 H, td, *J* = 7.6, 1.2 Hz, H-2a), 7.28 (1 H, td, *J* = 7.6, 1.2 Hz, H-2b), 7.08 (1 H, td, *J* = 7.6, 1.2 Hz, H-1a), 7.07 (1 H, td, *J* = 7.6, 1.2 Hz, H-1b), 6.81 (1 H, d, *J* = 7.6 Hz, H-3a), 6.78 (1 H, d, *J* = 7.6 Hz, H-3b), 3.19 (3 H, s, H-9a), 3.14 (3 H, s, H-9b), 3.05 – 2.95 (1 H, m, H-12), 2.48 (1 H, t, *J* = 13.1 Hz, H-11a), 2.34 (2 H, d, *J* = 8.8 Hz, H-11b), 2.19 (1 H, d, *J* = 14.9 Hz, H-11a), 0.96 (9 H, s, H-14); δ_C (100 MHz; $CDCl_3$) 203.9 (C-10), 176.4 (C-5a), 175.5 (C-5b), 143.9 (C-4a), 143.8 (C-4b), 133.9 (C-7a), 132.7 (C-7b), 128.8 (C-2a), 128.6 (C-2b), 124.7 (C-8a), 124.0 (C-8b), 123.5 (C-1a), 123.3 (C-1b), 108.4 (C-3a), 108.2 (C-3b), 63.3 (C-6a), 61.9 (C-6b), 37.5 (C-12), 35.8 (C-11a), 35.6 (C-11b), 32.6 (C-13), 27.3 (C-14), 26.7 (C-9a), 26.5 (C-9b); Found (ESI): $[MNa]^+$ 439.2011; $C_{26}H_{28}N_2NaO_3$ requires $[MNa]^+$ 439.1992, 4.2 ppm.

Lab-book No PD/9/42.

trans-1,1''-Dimethyl-1,1'',2,2''-tetrahydrodispiro[indole-3,1'-cycloheptane-3',3''-indole]-2,2',2''-trione (**91i**)

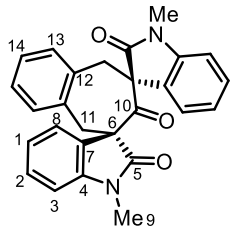


91i

Bis-anilide **92i** (0.025 g, 0.065 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.028 g, 0.138 mmol) and KO*t*-Bu (0.016 g, 0.146 mmol) in DMF (2.5 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91i** (0.019 g, 77%) as a colourless solid; mp. 196-198 °C; R_f 0.69 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1701, 1682, 1608, 1493, 1470, 1373, 1347, 1260, 1126, 1079, 947, 753, 729; δ_H (400 MHz; $CDCl_3$) 7.36 (2 H, d, *J* = 7.6 Hz, H-8), 7.23 (2 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.02 (2 H, td, *J* = 7.6, 1.2 Hz, H-1), 6.76 (2 H, d, *J* = 7.6 Hz, H-3), 3.20 (6 H, s, H-9), 2.85 (2 H, br s, H-11a), 2.43 (2 H, br t, *J* = 9.0 Hz, H-12a), 2.07 – 1.94 (4 H, m, H-11b, H-12b); δ_C (100 MHz; $CDCl_3$) 174.9 (C-5), 142.8 (C-4), 132.0 (C-7), 128.5 (C-2), 125.3 (C-8), 122.9 (C-1), 108.2 (C-3), 67.9 (C-6), 33.9 (C-11), 26.5 (C-9), 24.2 (C-12); Found (ESI): $[MNa]^+$ 397.1510; $C_{23}H_{22}N_2NaO_3$ requires $[MNa]^+$ 397.1523, 3.1 ppm.

Lab-book No PD/9/33.

trans-1,1''-Dimethyl-1,1'',2,2'',7',9'-hexahydro-5'*H*-dispiro[indole-3,6'-benzo[7]annulene-8',3''-indole]2,2'',7'-trione (**91j**)



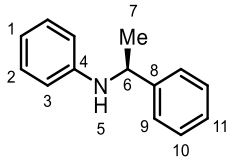
91j

Bis-anilide **92j** (0.031 g, 0.073 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.030 g, 0.151 mmol) and KO*t*-Bu (0.019 g, 0.170 mmol) in DMF (2 mL) were subjected to general procedure D. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **91j** (0.014 g, 46%) as a yellow solid; mp. 214-216 °C; R_f 0.50 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1710, 1678, 1609, 1493, 1471, 1370, 1347, 1261, 1077, 1023, 910, 798,

752; δ_H (400 MHz; $CDCl_3$) 7.33 (2 H, dd, *J* = 5.4, 3.3 Hz, H-14), 7.26 (2 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.16 (2 H, dd, *J* = 5.4, 3.3 Hz, H-13), 7.04 (2 H, d, *J* = 7.6 Hz, H-8), 6.98 (2 H, td, *J* = 7.6, 1.2 Hz, H-1), 6.81 (2 H, d, *J* = 7.6 Hz, H-3), 3.65 (2 H, d, *J* = 14.7 Hz, H-11a), 3.46 (2 H, d, *J* = 14.7 Hz, H-11b), 3.17 (6 H, s, H-9); δ_C (100 MHz; $CDCl_3$) 205.2 (C-10), 174.9 (C-5), 143.9 (C-4), 135.9 (C-12), 132.5 (C-7), 130.8 (C-13), 128.8 (C-2), 127.7 (C-14), 125.0 (C-8), 123.1 (C-1), 108.3 (C-3), 65.7 (C-6), 38.0 (C-11), 26.5 (C-9); Found (ESI): $[MNa]^+$ 445.1527; $C_{27}H_{22}N_2NaO_3$ requires $[MNa]^+$ 445.1523, 1.1 ppm.

Lab-book No PD/9/87.

N-[(1*S*)-1-phenylethyl]aniline[50] (**108**)



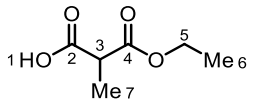
(*S*)-**108**

A mixture of iodobenzene (1.12 mL, 10.0 mmol), (*S*)-phenylethylamine (1.29 mL, 10.0 mmol), K_2CO_3 (2.77 g, 20.0 mmol), CuI (0.190 g, 1.00 mmol) and L-proline (0.234 g, 2.03 mmol) in DMSO (10 mL) was heated at 60 °C for 18 h. The cooled mixture was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual oil was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1) to afford the title compound (*S*)-**108** (0.432 g, 22%) as a clear oil; R_f 0.54 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.36 (2 H, d, *J* = 7.4 Hz, CH_{Ar}), 7.31 (2 H, t, *J* = 7.4 Hz, CH_{Ar}), 7.22 (1 H, tt, *J* = 7.4, 1.0 Hz, CH_{Ar}), 7.09 (1 H, d, *J* = 7.4 Hz, CH_{Ar}), 7.07 (1 H, d, *J* = 7.4 Hz, CH_{Ar}), 6.63 (1 H, tt, *J* = 7.4, 1.0 Hz, CH_{Ar}), 6.50 (2 H, dd, *J* = 8.6, 1.0 Hz, CH_{Ar}), 4.48 (1 H, q, *J* = 6.7 Hz, H-6), 4.01 (1 H, br s, H-5), 1.51 (3 H, d, *J* = 6.7 Hz, H-7).

Data are consistent with literature values.[50]

Lab-book No PD/10/61.

3-Ethoxy-2-methyl-3-oxopropanoic acid[137] (**109**)



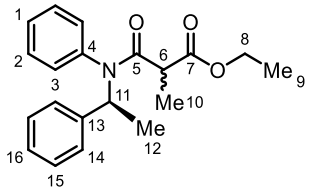
109

Diethyl methylmalonate (4.00 g, 23.0 mmol) was dissolved in a mixture of THF:H_2O (1:10, 880 mL). The reaction mixture was cooled to 0 °C, then NaOH (0.25 M in water, 120 mL) was added. The reaction mixture was stirred for 1 h, acidified with an aq. sol. of HCl (10%, 5 mL) to bring the pH to 2. The solution was saturated with brine (10 g), extracted with EtOAc (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound **109** (3.02 g, quant.), which was used in the next step without further purification; R_f 0.4 (Petrol/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 10.19 (1 H, br s, H-1), 4.21 (2 H, q, *J* = 7.1 Hz, H-5), 3.47 (1 H, q, *J* = 7.3 Hz, H-3), 1.45 (3 H, d, *J* = 7.3 Hz, H-7), 1.27 (3 H, t, *J* = 7.1 Hz, H-6).

Analytical data are consistent with literature values.[137]

Lab-book No PD/5/14.

Ethyl 2-methyl-2{phenyl[(1*S*)-1-phenylethyl]carbamoyl}acetate (**110**)



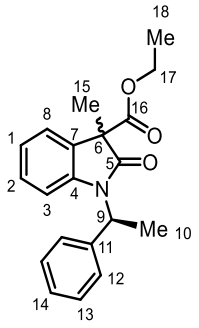
110

To a stirred solution of *N*-[(1*S*)-1-phenylethyl]aniline (**108**) (0.101 g, 0.514 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C the readily available 3-ethoxy-2-methyl-3-oxopropanoic acid (**109**) (0.066 g, 0.453 mmol), 2-chloro-1-methylpyridinium iodide (0.167 g, 0.654 mmol) and Et_3N (0.298 mL, 2.14 mmol). The resulting yellow mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature and stirred for a further 1 h. HCl (10% solution in water, 5 mL) was added, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual oil was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) to afford the title compound **110** (0.148 g, 68%) as a thick colourless oil in a 1:1.5 **110/110'** ratio of inseparable diastereoisomers; R_f 0.22 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 2981, 2939, 1741, 1652, 1594,

1495, 1451, 1391, 1341, 1311, 1233, 1190, 1081, 1030, 779, 699, 572; δ_H (400 MHz; $CDCl_3$) 7.39 (1 H, t, *J* = 7.4 Hz, CH_{Ar}), 7.29 (1.6 H, td, *J* = 7.4, 0.7 Hz, CH_{Ar}), 7.26 – 7.23 (4 H, m, CH_{Ar}), 7.16 (0.6 H, d, *J* = 7.4 Hz, CH_{Ar}), 7.14 (0.4 H, d, *J* = 7.4 Hz, CH_{Ar}), 7.11 (0.8 H, d, *J* = 8.1 Hz, CH_{Ar}), 7.07 (0.6 H, d, *J* = 7.4 Hz, CH_{Ar}), 6.36 (0.6 H, q, *J* = 7.2 Hz, H-11'), 6.36 – 6.30 (0.6 H, m, CH_{Ar}), 6.30 (0.4 H, q, *J* = 7.2 Hz, H-11), 6.23 (0.4 H, d, *J* = 7.4 Hz, CH_{Ar}), 4.12 (0.4 H, q, *J* = 7.1 Hz, H-8), 4.12 (0.4 H, q, *J* = 7.1 Hz, H-8), 4.05 (0.6 H, dd, *J* = 10.8, 7.1 Hz, H-8'), 3.99 (0.6 H, dd, *J* = 10.8, 7.1 Hz, H-8'), 3.15 (1 H, pent, *J* = 7.1 Hz, H-6), 1.44 (1.2 H, d, *J* = 7.2 Hz, H-12), 1.39 (1.8 H, d, *J* = 7.2 Hz, H-12'), 1.32 (1.8 H, d, *J* = 7.1 Hz, H-10'), 1.25 (1.2 H, d, *J* = 7.1 Hz, H-10), 1.25 (1.2 H, t, *J* = 7.1 Hz, H-9), 1.15 (1.8 H, t, *J* = 7.1 Hz, H-9'); δ_C (100 MHz; $CDCl_3$) 171.0 and 170.9 (C-7), 169.92 and 169.89 (C-5), 141.0 and 140.9 (C-13), 138.0 and 137.9 (C-4), 130.6 (CH_{Ar}), 129.0 (CH_{Ar}), 128.60 and 128.56 (CH_{Ar}), 128.23 and 128.16 (CH_{Ar}), 128.1 (CH_{Ar}), 127.62 and 127.57 (CH_{Ar}), 61.2 and 61.1 (C-8), 52.5 and 52.0 (C-11), 44.6 and 44.5 (C-6), 17.1 and 16.9 (C-12), 14.21 and 14.17 (C-9 or C-10), 14.12 and 14.07 (C-9 or C-10); Found (ESI): $[MNa]^+$ 348.1562; $C_{20}H_{23}NNaO_3$ requires $[MNa]^+$ 348.1570, 2.5 ppm.

Lab-book No PD/10/36.

Ethyl 3-methyl-2-oxo-1-[(1*S*)-1-phenylethyl]-2,3-dihydro-1*H*-indole-3-carboxylate (**111**)



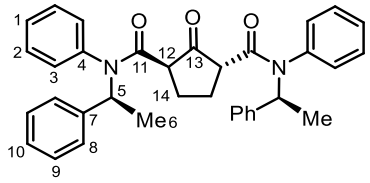
111

To a stirred solution of anilide **110** (0.028 g, 0.085 mmol) in toluene (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.018 g, 0.089 mmol). The reaction mixture was stirred at 110 °C for 18 h and allowed to cool to room temperature. The copper salt was removed by addition of an aq. sol. of NH_4OH (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Hexane/EtOAc, 9:1) to give the title compound **111** (0.021 g, 76%) as a yellow oil in a 1:1.3 **111/111'** mixture of diastereoisomers, inseparable by column chromatography; R_f 0.23 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 2982, 2936, 1741, 1714, 1607,

1484, 1467, 1350, 1237, 1190, 1112, 1019, 752, 698; δ_H (400 MHz; $CDCl_3$) 7.41 – 7.37 (1 H, m, H_{Ar}), 7.35 – 7.26 (4 H, m, H_{Ar}), 7.23 (0.45 H, d, *J* = 7.4 Hz, H-8), 7.22 (0.55 H, d, *J* = 7.4 Hz, H-8'), 7.08 – 7.01 (1 H, m, H_{Ar}), 6.96 (0.45 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.96 (0.55 H, td, *J* = 7.6, 1.0 Hz, H-1'), 6.49 (0.45 H, d, *J* = 7.6 Hz, H-3), 6.45 (0.55 H, d, *J* = 7.6 Hz, H-3'), 5.92 (0.55 H, q, *J* = 7.2 Hz, H-9'), 5.83 (0.45 H, q, *J* = 7.2 Hz, H-9), 4.24 – 4.13 (1.1 H, m, H-17'), 4.12 – 4.02 (0.9 H, m, H-17), 1.85 (1.35 H, d, *J* = 7.2 Hz, H-10), 1.82 (1.65 H, d, *J* = 7.2 Hz, H-10'), 1.72 (1.35 H, s, H-15), 1.71 (1.65 H, s, H-15'), 1.20 (1.65 H, t, *J* = 7.1 Hz, H-18'), 1.15 (1.35 H, t, *J* = 7.1 Hz, H-18); δ_C (100 MHz; $CDCl_3$) 175.5 and 175.4 (C-5), 171.4 and 170.0 (C-16), 141.7 and 141.5 (C-4), 139.1 and 139.0 (C-11), 130.6 and 130.5 (C-7), 128.8 and 128.7 (CH_{Ar}), 128.56 and 128.55 (C-2), 127.54 and 127.45 (CH_{Ar}), 126.7 and 126.6 (CH_{Ar}), 123.01 and 122.97 (C-8), 122.52 and 122.50 (C-1), 111.4 and 111.1 (C-3), 62.1 and 62.0 (C-17), 55.01 and 54.99 (C-6), 49.5 and 48.8 (C-9), 20.0 and 19.7 (C-15), 16.2 and 16.1 (C-10), 13.94 and 13.92 (C-18); Found (ESI): $[MNa]^+$ 346.1406; $C_{20}H_{21}NNaO_3$ requires $[MNa]^+$ 346.1414, 2.1 ppm.

Lab-book No PD/10/65.

trans-2-Oxo-1-*N*,3-*N*-diphenyl-1-*N*,3-*N*-bis[(1*S*)-1-phenylethyl]cyclopentane-1,3-dicarboxamide (**92k**)



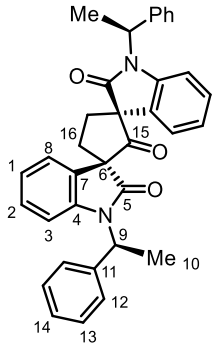
92k

Cyclopentanone (0.44 mL, 5.00 mmol) was added to a solution of methyl magnesium carbonate (2.0 M in DMF, 20.0 mL, 40.0 mmol). The reaction mixture was stirred for 6 h at 130 °C and was allowed to cool to room temperature and HCl (10% solution in water) was added slowly until the pH media became acidic. The aqueous was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (4 × 10 mL) and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of mono- and bis-acids. To a stirred solution of the crude acid mixture (0.124 g, 0.722 mmol) in CH_2Cl_2 (7 mL) was added *N*-[(1*S*)-1-phenylethyl]aniline (**108**) (0.308 g, 1.56 mmol), 2-chloro-1-methylpyridinium iodide (0.553 g, 2.17 mmol) and Et_3N (1.00 mL, 7.22 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. HCl (10% in water, 20 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL),

dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of mono- and bis-anilides. Purification by column chromatography (SiO_2, Hexane/EtOAc, 6:1 to 2:1) afforded the monoanilide product (0.121 g, 55%) as a clear oil and the title compound **92k** (0.062 g, 16%) as a foamy colourless solid and 1:1 mixture of inseparable diastereoisomers; mp. 47-49 °C; R_f 0.30 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 2973, 1741, 1642, 1594, 1494, 1451, 1392, 1345, 1230, 1085, 778, 700; δ_H (400 MHz; $CDCl_3$) 7.34 – 7.11 (18 H, m, H_{Ar}), 6.52 (1 H, d, *J* = 7.5 Hz, H_{Ar}), 6.20 (1 H, q, *J* = 7.2 Hz, H-5a), 6.17-6.13 (1 H, m, H_{Ar}), 6.16 (1 H, q, *J* = 7.2 Hz, H-5b), 3.02 – 2.95 (2 H, m, H-12), 2.12 – 2.08 (2 H, m, H-14a), 2.07 – 1.96 (2 H, m, H-14b), 1.42 (3 H, d, *J* = 7.2 Hz, H-6a), 1.38 (3 H, d, *J* = 7.2 Hz, H-6b); δ_C (100 MHz; $CDCl_3$) 209.8 and 208.8 (C-13), 169.5 and 169.3 (C-11), 140.9 and 140.5 (C-7), 137.9 and 137.7 (C-4), 131.4 and 131.1 (CH_{Ar}), 129.9 and 129.5 (CH_{Ar}), 128.74 and 128.67 (CH_{Ar}), 128.19 and 128.14 (CH_{Ar}), 128.1 (2 × CH_{Ar}), 127.6 and 127.5 (CH_{Ar}), 54.1 and 54.0 (C-12), 52.7 and 52.5 (C-5), 26.6 and 26.5 (C-14), 17.3 and 17.2 (C-6); Found (ESI): $[MNa]^+$ 553.2468; $C_{35}H_{34}N_2NaO_3$ requires $[MNa]^+$ 553.2462, 1.2 ppm.

Lab-book No PD/10/62.

trans-1,1''-bis[(1*S*)-1-Phenylethyl]-1,1'',2,2''-tetrahydrodispiro[indole-3,1'-cyclopentane-3',3''-indole]-2,2',2''-trione (**91k**)



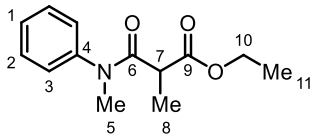
91k

To a stirred solution of bis-anilide **92k** (0.036 g, 0.068 mmol) in DMF (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.028 g, 0.139 mmol) and KO*t*-Bu (0.017 g, 0.149 mmol). The reaction mixture was stirred at 110 °C for 15 min and allowed to cool to room temperature. An aq. solution of 10% NH_4OH (2 × 5 mL) was added and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with water (4 × 5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) to give the title compound **91k** (0.016 g, 46%) as a colourless solid, in a 1:1.3 **91k**/**91k'** mixture of diastereoisomers,

inseparable by column chromatography; mp. 66-68 °C; R_f 0.31 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2981, 1755, 1700, 1608, 1484, 1466, 1348, 1310, 1254, 1052, 850, 752, 697; δ_H (400 MHz; $CDCl_3$) 7.50 – 7.45 (2 H, m, CH_{Ar}), 7.36 – 7.26 (10 H, m, CH_{Ar}), 7.10 – 7.00 (4 H, m, CH_{Ar}), 6.51 (1.1 H, d, *J* = 7.1 Hz, H-3'), 6.44 (0.9 H, dd, *J* = 7.1, 0.7 Hz, H-3), 5.78 (1 H, pent, *J* = 7.1 Hz, H-9), 3.26 – 3.16 (2 H, m, H-16a), 2.94 – 2.83 (2 H, m, H-16b), 1.84 (3 H, d, *J* = 7.2 Hz, H-10a), 1.84 (3 H, d, *J* = 7.2 Hz, H-10b); δ_C (100 MHz; $CDCl_3$) 208.1 and 208.0 (C-15), 175.2 and 175.1 (C-5), 142.5 and 142.4 (C-4), 139.0 and 138.6 (C-11), 130.2 and 130.1 (C-7), 128.8 (CH_{Ar}), 128.6 (C-2), 127.6 and 127.5 (CH_{Ar}), 126.6 (CH_{Ar}), 124.4 and 124.3 (C-8), 123.24 and 123.19 (C-1), 111.2 and 111.0 (C-3), 63.8 and 63.6 (C-6), 49.6 and 49.2 (C-9), 32.7 and 32.3 (C-16), 16.5 and 16.3 (C-10); Found (ESI): $[MNa]^+$ 549.2162; $C_{35}H_{30}N_2NaO_3$ requires $[MNa]^+$ 549.2149, 2.4 ppm.

Lab-book No PD/10/73.

Ethyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate[14a] (**112**)



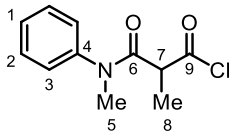
112

To a stirred solution of 3-ethoxy-2-methyl-3-oxopropanoic acid (**109**) (2.41 g, 16.4 mmol) in CH_2Cl_2 (100 mL) was added at 0 °C, *N*-methylaniline (1.94 mL, 18.0 mmol), 2-chloro-1-methylpyridinium iodide (6.23 g, 24.5 mmol), and Et_3N (11.3 mL, 0.726 mmol). The reaction mixture was stirred at 0 °C for 30 min and allowed slowly to warm to room temperature and stirred for a further 2 h. A solution of HCl (10% in water, 75 mL) was added and the organic phase was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic portions were washed with water (2 × 75 mL) and brine (2 × 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude yellow oil was then purified by column chromatography (SiO_2, Hexane/EtOAc, 6:1) to give the title compound **112** (3.26 g, 77%) as a yellow oil; R_f 0.42 (Hexane/EtOAc, 3:1); δ_H (400 MHz; $CDCl_3$) 7.44 – 7.39 (2 H, m, H-2), 7.38 – 7.33 (1 H, m, H-1), 7.23 (2 H, m, H-3), 4.09 (1 H, dq, *J* = 14.0, 7.1 Hz, H-10a), 4.08 (1 H, dq, *J* = 14.0, 7.1 Hz, H-10b), 3.38 (1 H, q, *J* = 7.1 Hz, H-7), 3.28 (3 H, s, H-5), 1.28 (3 H, d, *J* = 7.1 Hz, H-8), 1.21 (3 H, t, *J* = 7.1 Hz, H-11).

Data are consistent with literature values.[14a]

Lab-book No PD/4/59.

2-Methyl-3-(methyl(phenyl)amino)-3-oxopropanoyl chloride (**113**)



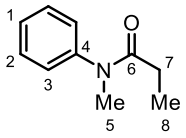
113

To a stirred solution of ethyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate (**112**) (3.26 g, 13.8 mmol) in THF (50 mL) was added a solution of $LiOH{\cdot}H_2O$ (2.32 g, 55.2 mmol) in water (10 mL). The reaction mixture was stirred overnight at room temperature, then a solution of HCl was added until acidic (pH ~ 2-3). The aqueous phase was extracted with EtOAc (2 × 50 mL), washed with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

The crude acid (2.84 g, 13.7 mmol) was dissolved in CH_2Cl_2 (50 mL). The solution was cooled to 0 °C and $(COCl)_2$ (1.17 mL, 13.8 mmol) and cat. DMF were added. The reaction mixture was stirred for 30 min and allowed to warm to room temperature and stirred for a further 3 h. Then, the reaction mixture was quenched with NH_4Cl (50 mL), extracted with CH_2Cl_2 (2 × 50 mL), washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title acid chloride **113** (2.75 g, 89%) as a green solid. The acid chloride was stored in the freezer and stable when kept at –10 °C for several months; δ_H (400 MHz; $CDCl_3$) 7.51 – 7.45 (2 H, m, H-2), 7.44 – 7.39 (1 H, m, H-1), 7.28 (2 H, d, *J* = 7.3 Hz, H-3), 3.84 (1 H, q, *J* = 6.9 Hz, H-7), 3.33 (3 H, s, H-5), 1.37 (3 H, d, *J* = 6.9 Hz, H-8).

Lab-book No PD/8/49.

N-Methyl-*N*-phenylpropionamide[138] (**114a**)



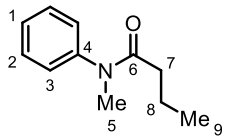
114a

To a stirred solution of *N*-methylaniline (1.19 mL, 11.0 mmol) in EtOAc (20 mL) at 0 °C was added propionyl chloride (1.00 mL, 11.5 mmol) and Et_3N (1.68 mL, 12.1 mmol). The reaction mixture was stirred for 1 h at 0 °C, warmed to room temperature and stirred for a further 2 h. A solution of aq. HCl (10%, 20 mL) was added and the organic phase was extracted with EtOAc (2 × 20 mL), washed with water (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound **114a** (1.48 g, 82%) as an off-white crystalline solid; mp. 54-56 °C (lit.[138] 57-59 °C); R_f 0.54 (Hexane/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 7.40 (2 H, t, *J* = 7.4 Hz, H-2), 7.32 (1 H, t, *J* = 7.4 Hz, H-1), 7.19 – 7.14 (2 H, m, H-3), 3.25 (3 H, s, H-5), 2.07 (2 H, q, *J* = 7.5 Hz, H-7), 1.03 (3 H, t, *J* = 7.5 Hz, H-8).

Data are consistent with literature values.[138]

Lab-book No PD/4/49.

N-Methyl-*N*-phenylbutyramide[139] (**114b**)



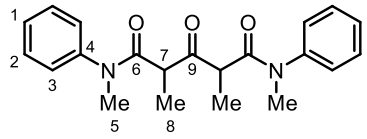
114b

To a stirred solution of *N*-methylaniline (0.542 mL, 5.00 mmol) in EtOAc (10 mL) at 0 °C was added butyryl chloride (0.545 mL, 5.25 mmol) and Et_3N (0.765 mL, 5.50 mmol). The reaction mixture was stirred for 1 h at 0 °C, warmed to room temperature and stirred for a further 2 h. A solution of aq. HCl (10%, 20 mL) was added and the organic phase was extracted with EtOAc (2 × 10 mL), washed with water (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound **114b** (0.633 g, 71%) as an orange oil; R_f 0.53 (Hexane/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 7.42 – 7.34 (2 H, m, H-2), 7.34 – 7.25 (1 H, m, H-1), 7.18 – 7.09 (2 H, m, H-3), 3.23 (3 H, s, H-5), 2.00 (2 H, t, *J* = 6.5 Hz, H-7), 1.55 (2 H, dd, *J* = 13.0, 6.5 Hz, H-8), 0.79 (3 H, t, *J* = 6.5 Hz, H-9).

Data are consistent with literature values.[139]

Lab-book No PD/8/64B.

bis(*N*-Methyl-*N*-phenyl) 1,3-dimethyl-1,3-acetonedicarboxamide (**115a**)

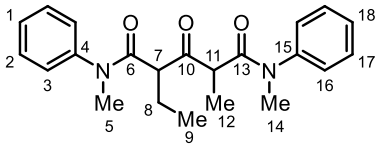


115a

To a stirred solution of freshly distilled di*iso*propylamine (0.083 mL, 0.589 mmol) in THF (4 mL) at −10 °C was added *n*-BuLi (2.28 M in hexanes, 0.258 mL, 0.589 mmol). The reaction mixture was stirred for 15 min and cooled to −78 °C. A solution of anilide **114a** (0.087 g, 0.535 mmol) in THF (1 mL) was added at −78 °C, stirred for 20 min and allowed to warm to 0 °C. The reaction mixture was cooled to −78 °C and a solution of acid chloride **113** (0.134 g, 0.589 mmol) in THF (1 mL) was added. The resulting yellow mixture was stirred for 2 h at −78 °C, allowed to warm to room temperature and stirred for a further 1 h. The reaction solution was quenched with NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic portions were washed with water (2 × 5 mL) and brine (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The brown crude residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:1) to give the title compound **115a** (0.103 g, 55%) as a colourless solid; mp. 80-82 °C; R_f 0.22 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1707, 1655, 1594, 1495, 1452, 1416, 1383, 1262, 1124, 1097, 1073, 1003, 785, 771, 698, 568, 530; δ_H (400 MHz; $CDCl_3$) 7.36 (4 H, t, *J* = 7.4 Hz, H-2), 7.29 (2 H, t, *J* = 7.4 Hz, H-1), 7.23 (4 H, d, *J* = 7.4 Hz, H-3), 3.46 (2 H, q, *J* = 7.0 Hz, H-7), 3.22 (6 H, s, H-5), 0.97 (6 H, d, *J* = 7.0 Hz, H-8); δ_C (100 MHz; $CDCl_3$) 203.5 (C-9), 170.7 (C-6), 143.5 (C-4), 130.0 (C-2), 128.2 (C-1), 127.6 (C-3), 49.0 (C-7), 37.8 (C-5), 14.3 (C-8); Found (ESI): $[MNa]^+$ 375.1676; $C_{21}H_{24}N_2NaO_3$ requires $[MNa]^+$ 375.1679, 0.9 ppm. Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.38; H, 6.96; N, 8.06.

Lab-book No PD/8/94.

bis(*N*-Methyl-*N*-phenyl) 1-methyl,3-ethyl-1,3-acetonedicarboxamide (**115b**)

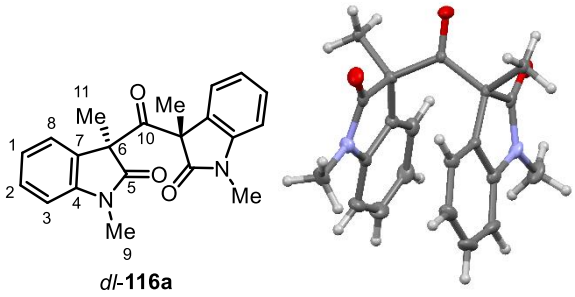


115b

To a stirred solution of freshly distilled di*iso*propylamine (0.060 mL, 0.429 mmol) in THF (2 mL) at −10 °C was added *n*-BuLi (2.5 M in hexanes, 0.180 mL, 0.450 mmol). The reaction mixture was stirred for 15 min and cooled to −78 °C. A solution of anilide **114b** (0.073 g, 0.409 mmol) in THF (1 mL) was added at −78 °C, the reaction stirred for 20 min and allowed to warm to 0 °C. The reaction mixture was cooled to −78 °C and a solution of 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoyl chloride (**113**) (0.113 g, 0.501 mmol) in THF (1 mL) was added. The resulting yellow mixture was stirred for 2 h at −78 °C, allowed to warm to room temperature and stirred for a further 1 h. The reaction solution was quenched with NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic portions were washed with water (2 × 5 mL) and brine (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The brown crude residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:1) to give the title compound **115b** (0.104 g, 69%) as an orange oil; R_f 0.54 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1717, 1649, 1594, 1495, 1454, 1381, 1297, 1123, 774, 701; δ_H (400 MHz; $CDCl_3$) 7.44 – 7.38 (6 H, m, H_{Ar}), 7.32 (4 H, t, *J* = 8.2 Hz, H_{Ar}), 3.69 (1 H, q, *J* = 7.0 Hz, H-11), 3.33 (1 H, dd, *J* = 8.0, 5.9 Hz, H-7), 3.27 (3 H, s, H-5 or H-14), 3.24 (3 H, s, H-5 or H-14), 1.72 – 1.60 (1 H, m, H-8a), 1.43 – 1.35 (1 H, m, H-8b), 0.99 (3 H, d, *J* = 7.0 Hz, H-12), 0.69 (3 H, t, *J* = 7.4 Hz, H-9); δ_C (100 MHz; $CDCl_3$) 203.1 (C-10), 170.9 (C-6 or C-13), 169.5 (C-6 or C-13), 143.7 (C-4 or C-15), 143.5 (C-4 or C-15), 129.9 (CH_{Ar}), 128.1 (CH_{Ar}), 127.81 and 127.78 (CH_{Ar}), 57.1 (C-7), 48.2 (C-11), 37.8 (C-5), 23.4 (C-8), 13.9 (C-12), 12.3 (C-9); Found (ESI): $[MNa]^+$ 389.1843; $C_{22}H_{26}N_2NaO_3$ requires $[MNa]^+$ 389.1836, 2.0 ppm.

Lab-book No PD/8/86.

dl-3-(1,3-Diethyl-2-oxo-2,3-dihydro-1*H*-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (*dl*-**116a**)



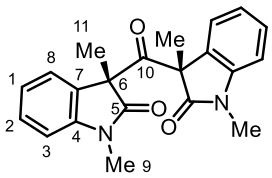
dl-**116a**

To a stirred solution of bis-anilide **115a** (0.036 g, 0.101 mmol) in mesitylene (3.5 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.021 g, 0.105 mmol). The reaction mixture was stirred for 30 min at reflux. Mesitylene was removed *in vacuo*. The resulting brown residue was diluted with EtOAc (5 mL) and washed twice with a 10% aq. solution of NH_4OH (2 × 5 mL) and 4.0 M solution of NaOH (3 × 5 mL). The ^1H NMR of the unpurified reaction mixture showed a mixture of diastereoisomers in a ratio of 1:1.5 *dl*-**116a**:*meso*-**116a**. Purification by column chromatography (SiO_2, Hexane/EtOAc, 4:1) gave first the title diastereoisomer *dl*-**116a** (0.010 g, 27%) as a colourless solid; mp. 262-264 °C; R_f 0.42 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1728, 1706, 1611, 1492, 1469, 1374, 1345, 1120, 1028, 768, 752; δ_H (400 MHz; $CDCl_3$) 7.10 (2 H, td, *J* = 7.6, 1.1 Hz, H-2), 7.06 (2 H, dd, *J* = 7.6, 1.1 Hz, H-8), 6.98 (2 H, td, *J* = 7.6, 1.1 Hz, H-1), 6.31 (2 H, d, *J* = 7.6 Hz, H-3), 2.78 (6 H, s, H-9), 1.48 (6 H, s, H-11); δ_C (100 MHz; $CDCl_3$) 196.3 (C-10), 174.1 (C-5), 144.1 (C-4), 129.0 (C-2), 127.8 (C-7), 125.5 (C-8), 122.2 (C-1), 107.9 (C-3), 62.1 (C-6), 26.3 (C-9), 22.7 (C-11); Found (ESI): $[MNa]^+$ 371.1350; $C_{21}H_{20}N_2NaO_3$ requires $[MNa]^+$ 371.1366, 4.3 ppm. CCDC 1004039 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/8/97A/2A.

meso-3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (*meso*-**116a**)

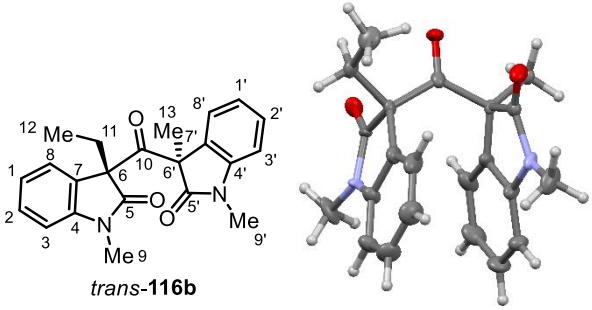


meso-**116a**

The diastereoisomer *meso*-**116a** (0.011 g, 31%) was then isolated by column chromatography (SiO_2, Hexane/EtOAc, 4:1) as a colourless solid; mp. 170-172 °C; R_f 0.25 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1731, 1717, 1608, 1490, 1468, 1374, 1344, 1120, 1032, 761, 542; δ_H (400 MHz; $CDCl_3$) 7.20 (2 H, td, *J* = 7.6, 1.2 Hz, H-2), 6.76 (2 H, td, *J* = 7.6, 1.2 Hz, H-1), 6.63 (2 H, d, *J* = 7.6 Hz, H-3), 6.55 (2 H, dd, *J* = 7.6, 1.2 Hz, H-8), 2.91 (6 H, s, H-9), 1.50 (6 H, s, H-11); δ_C (100 MHz; $CDCl_3$) 197.9 (C-10), 174.2 (C-5), 144.4 (C-4), 129.1 (C-2), 128.6 (C-7), 123.9 (C-8), 122.3 (C-1), 108.3 (C-3), 61.3 (C-6), 26.4 (C-9), 22.9 (C-11); Found (ESI): $[MNa]^+$ 371.1372; $C_{21}H_{20}N_2NaO_3$ requires $[MNa]^+$ 371.1366, 1.6 ppm.

Lab-book No PD/8/97A/2C.

trans-3-(3-Ethyl-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (*trans*-**116b**)



trans-**116b**

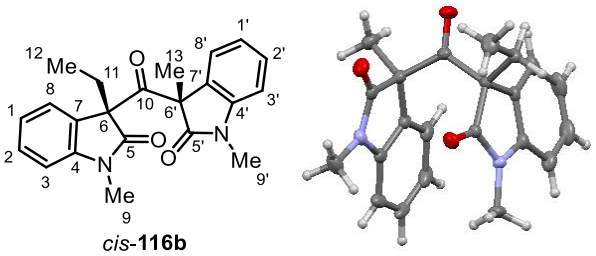
To a stirred solution of bis-anilide **115b** (0.051 g, 0.140 mmol) in mesitylene (4 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.028 g, 0.140 mmol). The reaction mixture was stirred for 30 min at 170 °C (Drysyn heating block). Mesitylene was removed *in vacuo*. The resulting brown residue was diluted with EtOAc (5 mL) and washed twice with a 10% aq. solution of NH_4OH (2 × 5 mL) and 4.0 M solution of NaOH (3 × 5 mL). ^1H NMR of the crude reaction showed a mixture of diastereoisomers in a ratio of 1.5:1 *trans*-**116b**:*cis*-**116b**. Purification by column chromatography (SiO_2, Hexane/EtOAc, 4:1 to 1:1) gave first the title diastereoisomer *trans*-**116b** (0.021 g, 41%) as a colourless solid; mp. 200-202 °C; R_f 0.42 (Hexane/EtOAc, 1:1);

ν_{max} (cm^{-1}) 1724, 1701, 1609, 1489, 1461, 1369, 1346, 1259, 1160, 1101, 765; δ_H (400 MHz; $CDCl_3$) 7.11 – 7.05 (3 H, m, H_{Ar}), 7.03 (1 H, dd, *J* = 7.6, 1.2 Hz, H_{Ar}), 7.01 – 6.93 (2 H, m, H_{Ar}), 6.29 (2 H, d, *J* = 7.6 Hz, H-3, H-3'), 2.80 (3 H, s, H-9'), 2.79 (3 H, s, H-9), 2.21 (1 H, dq, *J* = 14.8, 7.4 Hz, H-11a), 2.10 (1 H, dq, *J* = 14.8, 7.4 Hz, H-11b), 1.47 (3 H, s, H-13), 0.42 (3 H, t, *J* = 7.4 Hz, H-12); δ_C (100 MHz; $CDCl_3$) 196.1 (C-10), 174.2 (C-5), 173.2 (C-5'), 144.9 (C-4'), 144.0 (C-4), 129.0 (C-2 or C-2'), 128.9 (C-2 or C-2'), 127.9 (C-7'), 126.0 (C-8 or C-8'), 125.4 (C-7), 125.2 (C-8 or C-8'), 122.1 (C-1 or C-1'), 121.9 (C-1 or C-1'), 107.9 (C-3 or C-3'), 107.7 (C-3 or C-3'), 67.2 (C-6), 62.3 (C-6'), 29.1 (C-11), 26.4 (C-9 or C-9'), 26.2 (C-9 or C-9'), 22.8 (C-13), 7.8 (C-12); Found (ESI): $[MNa]^+$ 385.1525; $C_{22}H_{22}N_2NaO_3$ requires $[MNa]^+$ 385.1523, 0.7 ppm. CCDC 1016758 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/8/93/2A.

cis-3-(3-Ethyl-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (*cis*-**116b**)



cis-**116b**

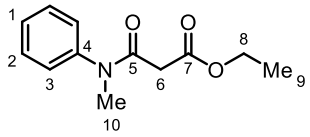
The diastereoisomer *cis*-**116b** (0.013 g, 26%) was then isolated by column chromatography (SiO_2, Hexane/EtOAc, 1:1) as a colourless solid; mp. 155-157 °C; R_f 0.23 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1727, 1712, 1611, 1493, 1470, 1372, 1347, 1259, 1161, 1102, 755; δ_H (400 MHz; $CDCl_3$) 7.20 (1 H, td, *J* = 7.6, 1.2 Hz, H-2 or H-2'), 7.19 (1 H, td, *J* = 7.6, 1.2 Hz, H-2 or H-2'), 6.78 (1 H, td, *J* = 7.6, 1.2 Hz, H-1), 6.73 (1 H, td, *J* = 7.6, 1.2 Hz, H-1'), 6.65 (1 H, d, *J* = 7.6 Hz, H-3'), 6.60 (1 H, d, *J* = 7.6 Hz, H-3), 6.57 (1 H, dd, *J* = 7.6, 1.2 Hz, H-8), 6.48 (1 H, dd, *J* = 7.6, 1.2 Hz, H-8'), 2.94 (3 H, s, H-9'), 2.85 (3 H, s, H-9), 2.18 (1 H, dq, *J* = 14.8, 7.4 Hz, H-11a), 2.09 (1 H, dq, *J* = 14.8, 7.4 Hz, H-11b), 1.48 (3 H, s, H-13), 0.47 (3 H, t, *J* = 7.4 Hz, H-12); δ_C (100 MHz; $CDCl_3$) 197.7 (C-10), 174.2 (C-5), 173.3 (C-5'), 145.0

(C-4'), 144.6 (C-4), 129.1 (C-2 or C-2'), 129.1 (C-2 or C-2'), 128.6 (C-7'), 126.6 (C-7), 124.3 (C-8 or C-8'), 123.7 (C-8 or C-8'), 122.2 (C-1, C-1'), 108.4 (C-3 or C-3'), 108.1 (C-3 or C-3'), 66.2 (C-6), 61.6 (C-6'), 29.6 (C-11), 26.5 (C-9 or C-9'), 26.2 (C-9 or C-9'), 22.9 (C-13), 7.7 (C-12); Found (ESI): $[MNa]^+$ 385.1518; $C_{22}H_{22}N_2NaO_3$ requires $[MNa]^+$ 385.1523, 1.3 ppm. CCDC 1004041 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/8/93/2C.

Ethyl 3-(*N*-methyl-*N*-phenylamino)-3-oxopropionate[140] (**117**)



117

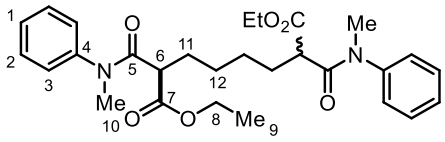
To a stirred solution of commercially available 3-ethoxy-3-oxopropanoic acid in CH_2Cl_2 (100 mL) at 0 °C, was added *N*-methylaniline (6.50 mL, 60.1 mmol), 2-chloro-1-methylpyridinium iodide (20.8 g, 81.9 mmol), and Et_3N (38.0 mL, 273 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature and stirred for a further 2 h. A solution of HCl (10% in water, 100 mL) was added and the organic phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic portions were washed with water (2 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude yellow oil was then purified by column chromatography (SiO_2, Hexane/EtOAc, 1:1) to give the title compound **117** (12.0 g, 99%) as a yellow oil; R_f 0.37 (Hexane/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 7.41 (2 H, t, *J* = 7.3 Hz, H-2), 7.35 (1 H, t, *J* = 7.3 Hz, H-1), 7.22 (2 H, d, *J* = 7.3 Hz, H-3), 4.11 (2 H, q, *J* = 7.1 Hz, H-8), 3.29 (3 H, s, H-10), 3.19 (2 H, s, H-6), 1.21 (3 H, t, *J* = 7.1 Hz, H-9).

Data are consistent with literature values.[140]

Lab-book No PD/4/58.

6.2.4 General procedure E: dialkylation reaction

dl/meso-1,8-Diethyl 2,7-bis[*N*-methyl(*N*-phenyl)carbamoyl]octanedioate (*dl/meso*-**118a**)

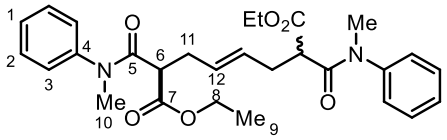


118a

To a stirred suspension of NaH (60% in mineral oil, 0.107 g, 2.66 mmol) in DMF (20 mL) was added ethyl 3-(*N*-methyl-*N*-phenylamino)-3-oxopropionate (**117**) (0.490 g, 2.22 mmol) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and 1,4-dibromobutane (0.131 mL, 1.11 mmol) was then added at 0 °C. The reaction was stirred at room temperature overnight. The reaction mixture was quenched by addition of an aq. sol. of NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic portions were washed with water (4 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound *dl/meso*-**118a** (0.298 g, 54%) as a colourless oil in a 1:1 mixture of diastereoisomers, inseparable by column chromatography; R_f 0.25 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1733, 1655, 1595, 1496, 1382, 1181, 1116, 1026, 919, 774, 729, 700; δ_H (400 MHz; $CDCl_3$) 7.42 – 7.36 (4 H, m, H-2), 7.36 – 7.29 (2 H, m, H-1), 7.21 – 7.16 (4 H, m, H-3), 4.14 – 4.00 (4 H, m, H-8), 3.27 (3 H, s, H-10a), 3.26 (3 H, s, H-10b), 3.23 (1 H, t, *J* = 5.7 Hz, H-6a), 3.21 (1 H, t, *J* = 5.7 Hz, H-6b), 1.85 – 1.67 (4 H, m, H-11), 1.20 (6 H, t, *J* = 7.1 Hz, H-9), 1.16 – 0.96 (4 H, m, H-12); δ_C (100 MHz; $CDCl_3$) 170.1 (C-7), 169.2 and 169.1 (C-5), 143.5 (C-4), 129.9 (C-2), 128.3 (C-1), 127.8 (C-3), 61.2 (C-8), 49.1 (C-6), 37.7 (C-10), 29.4 and 29.3 (C-11), 27.41 and 27.40 (C-12), 14.2 (C-9); Found (ESI): $[MNa]^+$ 519.2461; $C_{28}H_{36}N_2NaO_6$ requires $[MNa]^+$ 519.2466, 0.8 ppm.

Lab-book No PD/9/66.

dl/meso-1,8-Diethyl (4*E*)-2,7-bis[methyl(phenyl)carbamoyl]oct-4-enedioate (*dl/meso*-**118b**)

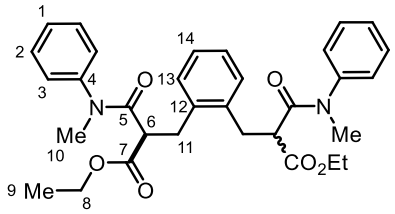


118b

NaH (60% in mineral oil, 0.110 g, 2.75 mmol), 3-(*N*-methyl-*N*-phenylamino)-3-oxopropionate (**117**) (0.491 g, 2.22 mmol), and *trans*-1,4-dibromo-2-butene (0.234 g, 1.09 mmol) in DMF (20 mL) were subjected to general procedure E. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound *dl/meso*-**118b** (0.434 g, 79%) as a colourless waxy oil in a 1:1 mixture of diastereoisomers, inseparable by column chromatography; R_f 0.18 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1734, 1655, 1595, 1496, 1382, 1255, 1183, 1156, 1116, 1027, 774, 729, 700; δ_H (400 MHz; $CDCl_3$) 7.41 – 7.34 (4 H, m, H-2), 7.33 – 7.27 (2 H, m, H-1), 7.21 – 7.12 (4 H, m, H-3), 5.23 – 5.19 (2 H, m, H-12), 4.10 – 4.00 (4 H, m, H-8), 3.30 (1 H, dd, *J* = 5.9, 3.1 Hz, H-6a), 3.28 (1 H, dd, *J* = 5.9, 3.1 Hz, H-6b), 3.24 (3 H, s, H-10a), 3.21 (3 H, s, H-10b), 2.58 – 2.35 (4 H, m, H-11), 1.18 (3 H, t, *J* = 7.1 Hz, H-9a), 1.18 (3 H, t, *J* = 7.1 Hz, H-9b); δ_C (100 MHz; $CDCl_3$) 169.61 and 169.55 (C-7), 168.6 and 168.5 (C-5), 143.5 and 143.4 (C-4), 129.9 (C-2), 129.1 and 129.0 (C-12), 128.2 (C-1), 127.9 and 127.8 (C-3), 61.2 (C-8), 49.0 and 48.9 (C-6), 37.72 and 37.66 (C-10), 32.5 (C-11), 14.1 (C-9); Found (ESI): $[MNa]^+$ 517.2310; $C_{28}H_{34}N_2NaO_6$ requires $[MNa]^+$ 517.2309, 0.3 ppm.

Lab-book No PD/9/71.

dl/meso-Ethyl 2-[(2-{3-ethoxy-2-[methyl(phenyl)carbamoyl]-3-oxopropyl}phenyl)methyl]-2-[methyl(phenyl)carbamoyl]acetate (*dl/meso*-**118c**)



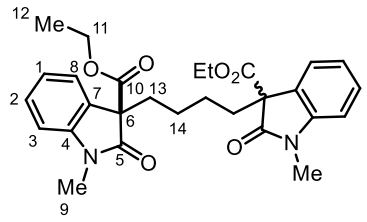
118c

NaH (60% in mineral oil, 0.111 g, 2.70 mmol), 3-(*N*-methyl-*N*-phenylamino)-3-oxopropionate (**117**) (0.499 g, 2.25 mmol), and dibromo-*o*-xylene (0.300 g, 1.13 mmol) in DMF (20 mL) were subjected to general procedure E. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound *dl/meso*-**118c** (0.406 g, 66%) as a white solid in a 1:1 mixture of diastereoisomers, inseparable by column chromatography; mp. 86-88 °C; R_f 0.23 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1740, 1654, 1595, 1495, 1382, 1259, 1183, 1116, 1026, 728, 700; δ_H (400 MHz; $CDCl_3$) 7.23 – 7.13 (7 H, m, H_{Ar}), 7.12 – 7.05 (3 H, m, H_{Ar}), 7.01 – 6.95 (1 H, m, H_{Ar}), 6.60 (3 H, br s, H_{Ar}), 4.14 – 4.03 (4 H, m, H-8), 3.43 (1 H, dd, *J* = 8.9, 6.1 Hz, H-6a), 3.38 (1 H, dd, *J* = 11.4, 4.1 Hz, H-6b), 3.10 (3 H, s, H-10a), 3.08 (3 H, s, H-10b), 2.87 (1 H, d, *J* = 6.1 Hz, H-11a), 2.86 (1 H, d, *J* = 8.9 Hz, H-11a'), 2.80 (1 H, dd, *J* = 13.6, 11.4 Hz, H-11b), 2.51 (1 H, dd, *J* = 13.6, 4.1 Hz, H-11b'), 1.21 (6 H, t, *J* = 7.1 Hz, H-9); δ_C (100 MHz; $CDCl_3$) 169.4 and 169.2 (C-7), 168.5 (C-5), 143.1 and 142.9 (C-4), 136.9 and 136.7 (C-12), 130.8 and 130.6 (CH_{Ar}), 129.58 and 129.55 (CH_{Ar}), 128.2 and 128.1 (CH_{Ar}), 127.6 and 127.4 (CH_{Ar}), 127.1 and 126.8 (CH_{Ar}), 61.40 and 61.36 (C-8), 50.0 and 49.2 (C-6), 37.5 and 37.3 (C-10), 31.6 and 31.5 (C-11), 14.12 and 14.07 (C-9); Found (ESI): $[MNa]^+$ 567.2475; $C_{32}H_{36}N_2NaO_6$ requires $[MNa]^+$ 567.2466, 1.6 ppm. Anal. Calcd. for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.03; H, 6.58; N, 4.88.

Lab-book No PD/9/70.

6.2.5 General procedure F: double cyclisation of di-ester containing bis-oxindoles

dl/meso-Ethyl 3-{4-[3-(ethoxycarbonyl-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]butyl}-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (*dl/meso*-**119a**)

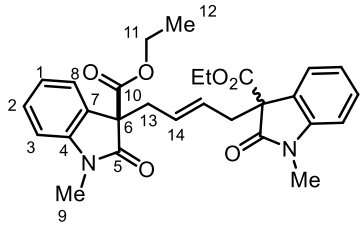


119a

To a stirred solution of bis-anilide *dl/meso*-**118a** (0.060 g, 0.121 mmol) in mesitylene (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.024 g, 0.121 mmol). The reaction mixture was stirred for 30 min at 170 °C and allowed to cool to room temperature. Mesitylene was removed and the residue was diluted with EtOAc (5 mL), and washed with an aq. sol. of NH_4OH (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Hexane/EtOAc, 3:1) to give the title compound *dl/meso*-**119a** (0.054 g, 90%) as a yellow solid in a 1:1 mixture of diastereoisomers, inseparable by column chromatography; mp. 145-147 °C; R_f 0.35 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1736, 1709, 1609, 1492, 1470, 1372, 1346, 1223, 1081, 1020, 750, 727; δ_H (400 MHz; $CDCl_3$) 7.29 (1 H, td, *J* = 7.4, 1.2 Hz, H-2a), 7.28 (1 H, td, *J* = 7.4, 1.2 Hz, H-2b), 7.16 (1 H, dd, *J* = 7.4, 1.2 Hz, H-8a), 7.15 (1 H, dd, *J* = 7.4, 1.2 Hz, H-8b), 7.04 (1 H, td, *J* = 7.4, 1.2 Hz, H-1a), 7.02 (1 H, td, *J* = 7.4, 1.2 Hz, H-1b), 6.80 (2 H, t, *J* = 8.3 Hz, H-3), 4.13 – 4.02 (4 H, m, H-11), 3.20 (3 H, s, H-9a), 3.18 (3 H, s, H-9b), 2.15 – 2.00 (4 H, m, H-13), 1.12 (3 H, t, *J* = 7.1 Hz, H-12a), 1.10 (3 H, t, *J* = 7.1 Hz, H-12b), 0.99 – 0.73 (4 H, m, H-14); δ_C (100 MHz; $CDCl_3$) 174.3 and 174.2 (C-5), 169.4 (C-10), 144.1 (C-4), 129.1 and 129.0 (C-2), 128.1 and 128.0 (C-7), 123.37 and 123.36 (C-8), 123.0 and 122.8 (C-1), 108.3 (C-3), 61.9 (C-11), 59.5 and 59.4 (C-6), 34.0 and 33.9 (C-13), 26.47 and 26.45 (C-9), 23.63 and 23.55 (C-14), 13.99 and 13.98 (C-12); Found (ESI): $[MNa]^+$ 515.2153; $C_{28}H_{32}N_2NaO_6$ requires $[MNa]^+$ 515.2153, 0.1 ppm.

Lab-book No PD/9/69B.

dl/meso-Ethyl 3-[(2*E*)-4-[3-(ethoxycarbonyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]but-2-en-1-yl]-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (*dl/meso*-**119b**)

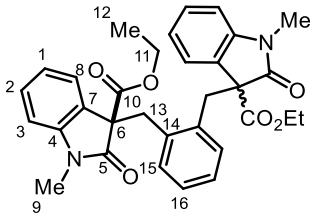


119b

Bis-anilide *dl/meso*-**118b** (0.049 g, 0.100 mmol), and $Cu(OAc)_2 \cdot H_2O$ (0.020 g, 0.100 mmol) in mesitylene (2 mL) were subjected to general procedure F. The reaction mixture was stirred at 170 °C for 2 h. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound *dl/meso*-**119b** (0.032 g, 66%) as a yellow solid in a 1:1 mixture of diastereoisomers, inseparable by column chromatography; mp. 130-132 °C; R_f 0.35 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 1736, 1711, 1609, 1493, 1470, 1372, 1347, 1223, 1086, 1021, 750, 729; δ_H (400 MHz; $CDCl_3$) 7.28 (2 H, td, *J* = 7.6, 1.1 Hz, H-2), 7.14 – 7.09 (2 H, m, H-8), 7.04 – 6.98 (2 H, m, H-1), 6.79 (2 H, d, *J* = 7.6 Hz, H-3), 5.02 (1 H, dd, *J* = 4.4, 3.6 Hz, H-14a), 4.94 (1 H, d, *J* = 3.6 Hz, H-14b), 4.11 – 4.00 (4 H, m, H-11), 3.21 (3 H, s, H-9a), 3.14 (3 H, s, H-9b), 2.80 (2 H, td, *J* = 14.1, 3.2 Hz, H-13a), 2.69 – 2.55 (2 H, m, H-13b), 1.10 (3 H, t, *J* = 7.1 Hz, H-12a), 1.09 (3 H, t, *J* = 7.1 Hz, H-12b); δ_C (100 MHz; $CDCl_3$) 173.6 and 173.5 (C-5), 169.0 and 168.9 (C-10), 144.2 and 144.1 (C-4), 129.0 (C-2), 127.9 and 127.61 (C-14), 127.56 and 127.49 (C-7), 123.7 and 123.5 (C-8), 122.8 and 122.7 (C-1), 108.5 and 108.3 (C-3), 61.9 (C-11), 59.3 and 59.1 (C-6), 37.20 and 37.16 (C-13), 26.6 and 26.5 (C-9), 14.0 (C-12); Found (ESI): $[MNa]^+$ 513.1997; $C_{28}H_{30}N_2NaO_6$ requires $[MNa]^+$ 513.1996, 0.1 ppm.

Lab-book No PD/9/78.

dl/meso-Ethyl 3-[(2-{[ethoxycarbonyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]methyl}phenyl)methyl]-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (*dl/meso*-**119c**)



119c

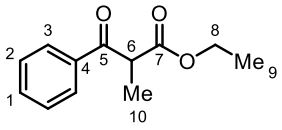
Bis-anilide *dl/meso*-**118c** (0.060 g, 0.111 mmol), and $Cu(OAc)_2 \cdot H_2O$ (0.024 g, 0.120 mmol) in mesitylene (3 mL) were subjected to general procedure F. The reaction mixture was stirred at 170 °C for 2 h. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound *dl/meso*-**119c** (0.048 g, 89%) as a colourless solid in a 1:1 mixture of diastereoisomers, inseparable by column chromatography; mp. 113-115 °C; R_f 0.42 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 1735, 1710, 1609, 1492, 1470, 1372, 1351, 1222, 1095, 1060, 1021, 751, 728; δ_H (400 MHz; $CDCl_3$) 7.24 (1 H, d, *J* = 7.4 Hz, H-8a), 7.18 (1 H, t, *J* = 7.4 Hz, H-2a), 7.14 (1 H, t, *J* = 7.4 Hz, H-2b), 7.08 (1 H, d, *J* = 7.4 Hz, H-8b), 6.98 (1 H, t, *J* = 7.4 Hz, H-1a), 6.95 (1 H, t, *J* = 7.4 Hz, H-1b), 6.74 – 6.68 (2 H, m, H-16), 6.68 – 6.63 (2 H, m, H-15), 6.54 (1 H, d, *J* = 7.4 Hz, H-3a), 6.50 (1 H, d, *J* = 7.4 Hz, H-3b), 4.15 (4 H, dq, *J* = 14.4, 7.2 Hz, H-11), 3.64 (1 H, d, *J* = 14.2 Hz, H-13a), 3.39 (1 H, d, *J* = 14.2 Hz, H-13a'), 3.33 (1 H, d, *J* = 14.2 Hz, H-13b), 3.18 (1 H, d, *J* = 14.2 Hz, H-13b'), 2.93 (3 H, s, H-9a), 2.91 (3 H, s, H-9b), 1.17 (3 H, t, *J* = 7.1 Hz, H-12a), 1.15 (3 H, t, *J* = 7.1 Hz, H-12b); δ_C (100 MHz; $CDCl_3$) 173.8 and 173.7 (C-5), 169.3 and 169.2 (C-10), 144.0 and 143.4 (C-4), 134.1 and 133.8 (C-14), 129.9 and 129.7 (C-15), 129.1 and 129.0 (C-2), 127.4 and 127.1 (C-7), 126.1 and 126.0 (C-16), 124.4 and 124.2 (C-8), 122.4 and 122.3 (C-1), 108.03 and 108.01 (C-3), 62.1 and 62.0 (C-11), 61.0 and 60.9 (C-6), 35.94 and 35.87 (C-13), 26.2 (C-9), 14.0 (C-12); Found (ESI): $[MNa]^+$ 563.2163; $C_{32}H_{32}N_2NaO_6$ requires $[MNa]^+$ 563.2153, 1.9 ppm. Anal. Calcd. for $C_{32}H_{32}N_2O_6$: C, 71.09; H, 5.97; N, 5.18. Found: C, 70.73; H, 6.02; N, 5.06.

Lab-book No PD/9/86.

6.3 The synthesis of indole derivatives

6.3.1 General procedure G: alkylation step

Ethyl 2-methyl-3-oxo-3-phenylpropanoate[71] (**152a**)



152a

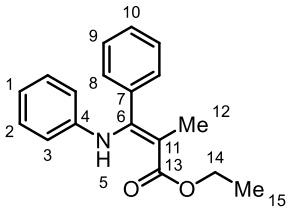
To a stirred solution of ethyl benzoylacetate (0.866 mL, 5.00 mmol) in DMF (5 mL) was added K_2CO_3 (1.04 g, 7.50 mmol) and iodomethane (0.343 mL, 5.50 mmol). The reaction mixture was heated at 60 °C for 3 h and allowed to cool to room temperature. The resulting yellow suspension was quenched with water (50 mL) and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) and afforded the title compound **152a** (1.03 g, 99%) as a yellow oil; R_f 0.27 (Hexane/EtOAc, 9:1); δ_H (400 MHz; $CDCl_3$) 7.99 – 7.94 (2 H, m, H-3), 7.60 – 7.54 (1 H, m, H-1), 7.50 – 7.43 (2 H, m, H-2), 4.36 (1 H, q, *J* = 7.1 Hz, H-6), 4.13 (2 H, q, *J* = 7.1 Hz, H-8), 1.48 (3 H, d, *J* = 7.1 Hz, H-10), 1.15 (3 H, t, *J* = 7.1 Hz, H-9).

Data are consistent with literature values.[71]

Lab-book No PD/7/78.

6.3.2 General procedure H: Zn-mediated condensation approach to *N*-aryl enamines

Ethyl (2*Z*)-2-methyl-3-phenyl-3-(phenylamino)prop-2-enoate[71] (**147a**)



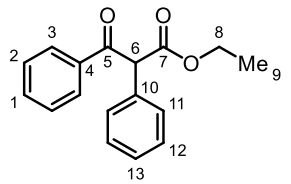
147a

To a stirred solution of ethyl 2-methyl-3-oxo-3-phenylpropanoate (**152a**) (1.03 g, 4.99 mmol) in 1,2-dichloroethane (2.5 mL) was added aniline (0.910 mL, 9.99 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.093 g, 0.250 mmol) and $MgSO_4$ (0.184 g, 1.53 mmol). The reaction mixture was stirred at 60 °C for 18 h and allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) to give the title compound **147a** (0.418 g, 30%) as a pale yellow solid; mp. 67-69 °C; R_f 0.58 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 3224, 2991, 1638, 1568, 1497, 1247, 1137, 1029, 777, 709; δ_H (400 MHz; $CDCl_3$) 10.92 (1 H, br s, H-5), 7.34 – 7.31 (3 H, m, H_{Ar}), 7.25 – 7.22 (2 H, m, H_{Ar}), 7.03 – 6.94 (2 H, m, H-2), 6.79 (1 H, t, *J* = 7.4 Hz, H-1), 6.52 (2 H, d, *J* = 7.8 Hz, H-3), 4.24 (2 H, q, *J* = 7.1 Hz, H-14), 1.68 (3 H, s, H-12), 1.34 (3 H, t, *J* = 7.1 Hz, H-15); Found (ESI): $[MH]^+$ 282.1483; $C_{18}H_{20}NO_2$ requires $[MH]^+$ 282.1489, 2.0 ppm.

Data are consistent with literature values (no reported melting point).[71]

Lab-book No PD/7/82.

Ethyl 3-oxo-2,3-diphenylpropanoate[141] (**152b**)



152b

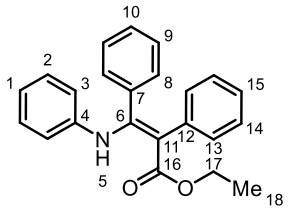
To a stirred solution of di*iso*propylamine (0.924 mL, 6.59 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M in hexanes, 2.76 mL, 6.90 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and cooled to –78 °C, then ethyl phenylacetate (1.00 mL, 6.27 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. Benzoyl chloride (0.765

mL, 6.59 mmol) was then added at –78 °C and the reaction was allowed to warm to room temperature and stirred for 18 h. The resulting yellow solution was quenched with sat. aq. NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1 to 9:1) to give the title compound **152b** (1.40 g, 83%) as a colourless solid; mp. 63-65 °C (Lit.[142] 89-90 °C); R_f 0.36 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.95 (2 H, dd, *J* = 8.3, 1.2 Hz, H_{Ar}), 7.55 – 7.49 (1 H, m, H_{Ar}), 7.45 – 7.38 (4 H, m, H_{Ar}), 7.37 – 7.32 (2 H, m, H_{Ar}), 7.32 – 7.26 (1 H, m, H_{Ar}), 5.60 (1 H, s, H-6), 4.21 (1 H, q, *J* = 7.1 Hz, H-8a), 4.21 (1 H, q, *J* = 7.1 Hz, H-8b), 1.23 (3 H, t, *J* = 7.1 Hz, H-9).

Data are consistent with literature values.[141, 142]

Lab-book No PD/9/91.

Ethyl (2*Z*)-2,3-diphenyl-3-(phenylamino)prop-2-enoate (**147b**)

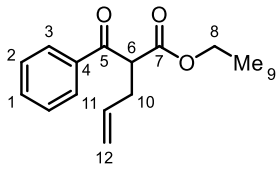


147b

Ethyl 3-oxo-2,3-diphenylpropanoate (**152b**) (0.168 g, 0.625 mmol), aniline (0.114 mL, 1.25 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.012 g, 0.031 mmol) and $MgSO_4$ (0.023 g, 0.187 mmol) in 1,2-dichloroethane (1.5 mL) were subjected to general procedure H. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **147b** (0.056 g, 26%) as a pale yellow oil; R_f 0.69 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3197, 2987, 1645, 1590, 1566, 1415, 1256, 1205, 1129, 1025, 793, 696, 571; δ_H (400 MHz; $CDCl_3$) 11.33 (1 H, br s, H-5), 7.09 – 6.97 (12 H, m, H_{Ar}), 6.87 (1 H, td, *J* = 7.4, 1.0 Hz, H-1), 6.62 (2 H, d, *J* = 7.8 Hz, H-3), 4.21 (2 H, q, *J* = 7.1 Hz, H-17), 1.24 (3 H, t, *J* = 7.1 Hz, H-18); δ_C (100 MHz; $CDCl_3$) 170.6 (C-16), 158.1 (C-6), 140.5 (C-4), 137.3 (C-12), 134.8 (C-7), 133.0 (CH_{Ar}), 130.4 (CH_{Ar}), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (CH_{Ar}), 127.1 (CH_{Ar}), 125.5 (CH_{Ar}), 123.0 (C-1), 122.6 (C-3), 102.9 (C-11), 60.0 (C-17), 14.6 (C-18); Found (ESI): $[MNa]^+$ 366.1462; $C_{23}H_{21}NNaO_2$ requires $[MNa]^+$ 366.1465, 0.8 ppm.

Lab-book No PD/9/95.

Ethyl 2-benzoylpent-4-enoate[143] (**152c**)



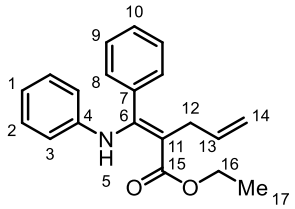
152c

Ethyl benzoylacetate (1.22 mL, 7.00 mmol), allyl bromide (0.666 mL, 7.70 mmol), and K_2CO_3 (1.45 g, 10.5 mmol) in DMF (10 mL) were subjected to general procedure G. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 9:1) to give the title compound **152c** (0.803 g, 49%) as a colourless oil; R_f 0.50 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, d, *J* = 7.5 Hz, H-3), 7.60 – 7.54 (1 H, m, H-1), 7.49 – 7.42 (2 H, m, H-2), 5.86 – 5.73 (1 H, m, H-11), 5.10 (1 H, dd, *J* = 17.1, 1.2 Hz, H-12a), 5.02 (1 H, dd, *J* = 10.2, 1.2 Hz, H-12b), 4.38 (1 H, t, *J* = 7.2 Hz, H-6), 4.12 (2 H, q, *J* = 7.1 Hz, H-8), 2.76 – 2.71 (2 H, m, H-10), 1.14 (3 H, td, *J* = 7.1, 1.2 Hz, H-9).

Data are consistent with literature values.[143]

Lab-book No PD/10/48.

Ethyl (2*Z*)-2-[phenyl(phenylamino)methylidene]pent-4-enoate (**147c**)



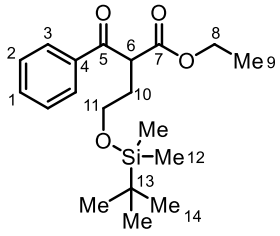
147c

Ethyl 2-benzoylpent-4-enoate (**152c**) (0.261 g, 1.12 mmol), aniline (0.205 mL, 2.25 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.057 g, 0.152 mmol) and $MgSO_4$ (0.040 g, 0.336 mmol) in 1,2-dichloroethane (2 mL) were subjected to general procedure H. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1) to give the title compound **147c** (0.049 g, 14%) as a colourless oil; R_f 0.6 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3073, 2977, 1648, 1610, 1593, 1572, 1358, 1265, 1204, 1171, 1126, 1025, 910, 778, 692; δ_H (400 MHz; $CDCl_3$) 11.13 (1 H, br s, H-5), 7.33 – 7.29 (3 H, m, H-9 and H-10), 7.29 – 7.21 (2 H, m, H-8), 6.99 (2 H, t, *J* = 7.9 Hz, H-2), 6.82 (1 H, t, *J* = 7.3 Hz, H-1), 6.54 (2 H, d, *J* = 8.0 Hz, H-3), 5.81 (1 H, ddt, *J* = 16.8, 10.1, 5.8 Hz, H-13), 4.89 (1 H, dd, *J* = 10.1, 1.4 Hz, H-14a), 4.82 (1 H, dd, *J* = 16.8, 1.4 Hz, H-14b), 4.25 (2 H, q, *J* = 7.1 Hz, H-16), 2.80 (2 H, d, *J* = 5.8 Hz, H-12), 1.32 (3 H, t, *J* = 7.1 Hz, H-17); δ_C (100 MHz; $CDCl_3$) 171.2 (C-15), 157.7 (C-6), 140.8 (C-4),

138.9 (C-13), 135.1 (C-7), 129.2 (C-8), 128.8 (C-10), 128.6 (C-2), 128.4 (C-9), 122.6 (C-1), 122.1 (C-3), 113.8 (C-14), 96.7 (C-11), 59.7 (C-16), 32.2 (C-12), 14.6 (C-17); Found (ESI): $[MH]^+$ 308.1641; $C_{20}H_{22}NO_2$ requires $[MH]^+$ 308.1645, 1.5 ppm.

Lab-book No PD/10/52.

Ethyl 2-benzoyl-4[(*tert*-butyldimethylsilyl)oxy]butanoate (**152d**)

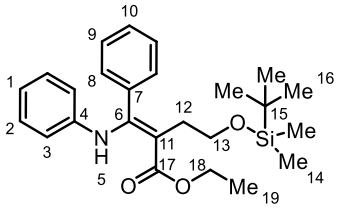


152d

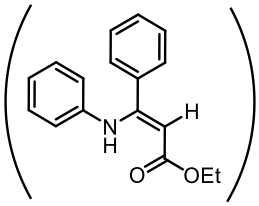
Ethyl benzoylacetate (0.866 mL, 5.00 mmol), *tert*-butyl(2-iodoethoxy)dimethylsilane (1.54 mL, 5.38 mmol), and K_2CO_3 (1.04 g, 7.50 mmol) in DMF (10 mL) were subjected to general procedure G. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **152d** (0.901 g, 51%) as a colourless oil; R_f 0.56 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2951, 2931, 2862, 1740, 1687, 1253, 1195, 1159, 1096, 1002, 948, 833, 775, 690; δ_H (400 MHz; $CDCl_3$) 8.06 – 7.99 (2 H, m, H-3), 7.60 – 7.53 (1 H, m, H-1), 7.50 – 7.43 (2 H, m, H-2), 4.66 (1 H, dd, *J* = 7.3, 6.5 Hz, H-6), 4.15 (2 H, q, *J* = 7.1 Hz, H-8), 3.67 (2 H, t, *J* = 5.8 Hz, H-11), 2.27 – 2.13 (2 H, m, H-10), 1.17 (3 H, t, *J* = 7.1 Hz, H-9), 0.87 (9 H, s, H-14), 0.01 (3 H, s, H-12a), –0.02 (3 H, s, H-12b); δ_C (100 MHz; $CDCl_3$) 195.9 (C-5), 170.1 (C-7), 136.2 (C-4), 133.5 (C-1), 128.9 (C-2 or C-3), 128.7 (C-2 or C-3), 61.4 (C-8), 60.5 (C-11), 50.3 (C-6), 32.1 (C-10), 26.0 (C-14), 18.3 (C-13), 14.1 (C-9), –5.4 (C-12a), –5.5 (C-12b); Found (ESI): $[MNa]^+$ 373.1791; $C_{19}H_{30}NaO_4Si$ requires $[MNa]^+$ 373.1806, 3.8 ppm.

Lab-book No PD/9/94.

Ethyl (2*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-[phenyl(phenylamino)methylidene]butanoate (**147d**)



147d

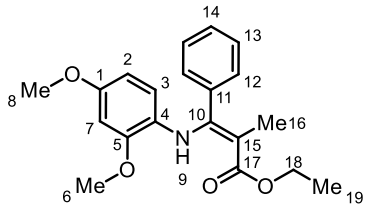


172a

Ethyl 2-benzoyl-4[(*tert*-butyldimethylsilyl)oxy]butanoate (**152d**) (0.344 g, 0.981 mmol), aniline (0.179 mL, 1.96 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.030 g, 0.081 mmol) and $MgSO_4$ (0.040 g, 0.332 mmol) in 1,2-dichloroethane (3 mL) were subjected to general procedure H. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1 to 19:1) to give the title compound **147d** (0.044 g, 10%) as a yellow oil along with the by-product **172a** (0.021 g, 8%) inseparable by column chromatography; R_f 0.66 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2959, 2927, 2854, 1653, 1612, 1594, 1573, 1503, 1267, 1210, 1171, 1132, 1086, 1025, 1038, 835, 774, 749, 699; δ_H (400 MHz; $CDCl_3$) 11.19 (1 H, br s, H-5), 7.34 – 7.31 (3 H, m, H_{Ar}), 7.28 – 7.24 (2 H, m, H_{Ar}), 7.00 – 6.95 (2 H, m, H-2), 6.82 (1 H, t, *J* = 7.4 Hz, H-1), 6.51 (2 H, d, *J* = 7.7 Hz, H-3), 4.26 (2 H, q, *J* = 7.1 Hz, H-18), 3.57 – 3.47 (2 H, m, H-13), 2.39 – 2.32 (2 H, m, H-12), 1.35 (3 H, t, *J* = 7.1 Hz, H-19), 0.83 (9 H, s, H-16), −0.07 (6 H, s, H-14); δ_C (100 MHz; $CDCl_3$) 171.3 (C-17), 158.6 (C-6), 140.6 (C-4), 135.0 (C-7), 129.4 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (CH_{Ar}), 122.7 (CH_{Ar}), 122.3 (CH_{Ar}), 122.2 (CH_{Ar}), 94.5 (C-11), 63.6 (C-13), 59.7 (C-18), 31.3 (C-12), 26.1 (C-16), 18.5 (C-15), 14.7 (C-19), −5.2 (C-14); Found (ESI): $[MNa]^+$ 448.2288; $C_{25}H_{35}NNaO_3Si$ requires $[MNa]^+$ 448.2278, 2.1 ppm.

Lab-book No PD/9/97.

Ethyl (2*Z*)-3[(2,4-dimethoxyphenyl)amino]-2-methyl-3-phenylprop-2-enoate (**147e**)

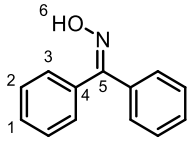


147e

Ethyl 2-methyl-3-oxo-3-phenylpropanoate (**152a**) (0.431 g, 2.09 mmol), 2,4-dimethoxyaniline (0.642 mL, 4.19 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.039 g, 0.104 mmol) and $MgSO_4$ (0.083 g, 0.691 mmol) in 1,2-dichloroethane (3 mL) were subjected to general procedure H. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **147e** (0.151 g, 21%) as a light brown solid; mp. 75-77 °C; R_f 0.38 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2935, 1648, 1608, 1572, 1512, 1249, 1205, 1122, 1034, 832, 776, 703; δ_H (400 MHz; $CDCl_3$) 10.65 (1 H, br s, H-9), 7.30 – 7.26 (3 H, m, H_{Ar}), 7.22 – 7.18 (2 H, m, H_{Ar}), 6.34 (1 H, d, *J* = 2.7 Hz, H-7), 6.10 (1 H, d, *J* = 8.8 Hz, H-3), 5.99 (1 H, dd, *J* = 8.8, 2.7 Hz, H-2), 4.24 (2 H, q, *J* = 7.1 Hz, H-18), 3.81 (3 H, s, H-6 or H-8), 3.64 (3 H, s, H-6 or H-8), 1.65 (3 H, s, H-16), 1.33 (3 H, t, *J* = 7.1 Hz, H-19); δ_C (100 MHz; $CDCl_3$) 171.5 (C-17), 157.1 (C-10), 156.1 (C-1 or C-5), 152.6 (C-1 or C-5), 136.0 (C-11), 129.3 (C-12 or C-13), 128.4 (C-14), 128.2 (C-12 or C-13), 123.8 (C-4), 123.4 (C-3), 103.2 (C-2), 98.7 (C-7), 92.9 (C-15), 59.5 (C-18), 55.8 (C-6 or C-8), 55.4 (C-6 or C-8), 14.7 (C-19), 14.4 (C-16); Found (ESI): $[MNa]^+$ 364.1522; $C_{20}H_{23}NNaO_4$ requires $[MNa]^+$ 364.1519, 0.6 ppm.

Lab-book No PD/9/96.

N-(Diphenylmethylidene)hydroxylamine[144]



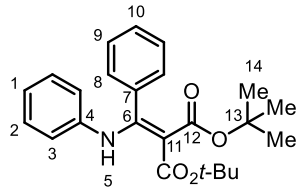
To a stirred solution of benzophenone (1.82 g, 10.0 mmol) in MeOH (15 mL) was added $NH_2OH \cdot HCl$ (1.11 g, 16.0 mmol) and NaOAc (1.64 g, 20.0 mmol) in water (20 mL). The reaction mixture was stirred at reflux overnight and allowed to cool to room temperature. Water (20 mL) was added, the aqueous phase was extracted with EtOAc (20 mL) and separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Hexane/EtOAc, 6:1) afforded the title compound (0.976 g, 50%) as a colourless solid; mp. 139-141 °C (Lit.[144] 140 °C); R_f 0.52

(Hexane/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 8.63 (1 H, br s, H-6), 7.48 – 7.39 (7 H, m, H_{Ar}), 7.38 – 7.29 (3 H, m, H_{Ar}).

Data are consistent with literature values.[144]

Lab-book No PD/11/5.

1,3-Di-*tert*-butyl 2-[phenyl(phenylamino)methylidene]propanedioate (**147f**)



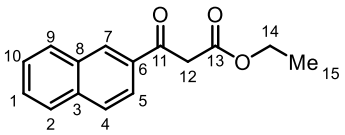
147f

To a stirred solution of benzophenone oxime (0.099 g, 0.500 mmol) in toluene (6 mL) was added Et_3N (0.070 mL, 0.500 mmol) and triflic anhydride (0.126 mL, 0.750 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 5 min and the preformed di-*tert*-butyl malonate sodium salt (1.50 mmol) in THF (2 mL) was introduced *via* cannula at –78 °C. The reaction mixture, that turned instantly yellow, was allowed to warm to room temperature, and stirred for 1 h. NH_4OH (10 mL) was added and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Hexane/EtOAc, 19:1) afforded the title compound **147f** (0.100 g, 51%) as a colourless oil; R_f 0.52 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2977, 2932, 1717, 1652, 1594, 1572, 1501, 1366, 1280, 1253, 1164, 1133, 851, 698; δ_H (400 MHz; $CDCl_3$) 10.87 (1 H, br s, H-5), 7.42 – 7.17 (5 H, m, H-8, H-9, H-10), 7.11 – 6.93 (2 H, m, H-2), 6.88 (1 H, t, *J* = 7.5 Hz, H-1), 6.61 (2 H, d, *J* = 7.8 Hz, H-3), 1.52 (9 H, s, H-14a), 1.18 (9 H, s, H-14b); δ_C (100 MHz; $CDCl_3$) 167.9 (C-12a), 166.6 (C-12b), 158.6 (C-6), 139.5 (C-4), 134.0 (C-7), 129.3 (C-10), 129.1 (C-8 or C-9), 128.6 (C-2), 128.3 (C-8 or C-9), 123.8 (C-1), 123.2 (C-3), 101.5 (C-11), 80.6 (C-13a), 80.2 (C-13b), 28.6 (C-14a), 27.6 (C-14b); Found (ESI): $[MH]^+$ 396.2156; $C_{24}H_{30}NO_4$ requires $[MH]^+$ 396.2169, 3.4 ppm.

Lab-book No PD/11/8.

6.3.3 General procedure I: Formation of β-ketoester

Ethyl 3-(naphthalen-2-yl)-3-oxopropanoate[145]

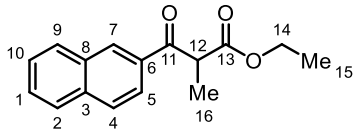


To a stirred suspension of NaH (60% in dispersion in oil, 1.20 g, 50.8 mmol) in THF (10 mL) was added diethylcarbonate (4.85 mL, 40.0 mmol) and the reaction mixture was brought to reflux. Then, 2-acetonaphthone (1.70 g, 10.0 mmol) was added dropwise. The suspension was stirred for 3 h, and allowed to cool to room temperature. Glacial acetic acid (1 mL), followed by aq. sol. of HCl (10%, 20 mL) were added to the reaction mixture. The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with aq. sol. of $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a brown oil, which was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) to afford the title compound (2.23 g, 92%) as a yellow oil; R_f 0.45 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 8.43 (1 H, d, *J* = 1.3 Hz, H_{Ar}), 8.00 (1 H, dd, *J* = 8.6, 1.8 Hz, H_{Ar}), 7.95 (1 H, d, *J* = 7.8 Hz, H_{Ar}), 7.88 (2 H, d, *J* = 8.8 Hz, H_{Ar}), 7.60 (1 H, ddd, *J* = 8.2, 7.0, 1.4 Hz, H_{Ar}), 7.55 (1 H, ddd, *J* = 8.2, 7.0, 1.4 Hz, H_{Ar}), 4.22 (2 H, q, *J* = 7.1 Hz, H-14), 4.10 (2 H, s, H-12), 1.25 (3 H, t, *J* = 7.1 Hz, H-15).

Data are consistent with literature values.[145]

Lab-book No PD/11/19.

Ethyl 2-methyl-3-(naphthalen-2-yl)-3-oxopropanoate[146] (**152g**)



152g

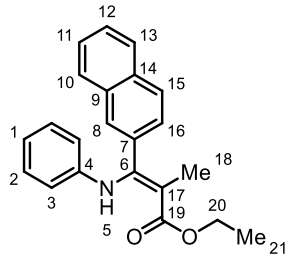
Ethyl 3-(naphthalen-2-yl)-3-oxopropanoate (1.01 g, 4.17 mmol), iodomethane (0.285 mL, 4.59 mmol), and K_2CO_3 (0.868 g, 6.28 mmol) in DMF (10 mL) were subjected to general procedure G. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **152g** (0.833 g, 78%) as a pale yellow oil; R_f 0.38 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 8.50 (1 H, s, H_{Ar}), 8.02 (1 H, dd, *J* = 8.8, 1.8 Hz, H_{Ar}), 7.96 (1 H, d, *J* = 8.3 Hz, H_{Ar}), 7.89 (1 H, d, *J* = 8.8 Hz, H_{Ar}), 7.86 (1 H, d, *J* = 8.3 Hz, H_{Ar}), 7.60 (1 H, ddd, *J* = 8.1, 7.0, 1.5 Hz, H_{Ar}), 7.55 (1 H, ddd, *J* = 8.1, 7.0, 1.5 Hz, H_{Ar}),

4.53 (1 H, q, *J* = 7.0 Hz, H-12), 4.15 (1 H, q, *J* = 7.1 Hz, H-14a), 4.14 (1 H, q, *J* = 7.1 Hz, H-14b), 1.54 (3 H, d, *J* = 7.0 Hz, H-16), 1.15 (3 H, t, *J* = 7.1 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 195.9 (C-11), 171.1 (C-13), 135.8 (C_{Ar}), 133.3 (C_{Ar}), 132.6 (C_{Ar}), 130.5 (CH_{Ar}), 129.8 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 127.9 (CH_{Ar}), 127.0 (CH_{Ar}), 124.2 (CH_{Ar}), 61.5 (C-14), 48.5 (C-12), 14.1 (C-15 or C-16), 14.0 (C-15 or C-16).

Data are consistent with literature values.[146]

Lab-book No PD/11/22.

Ethyl (2*Z*)-2-methyl-3-(naphthalen-2-yl)-3-(phenylamino)prop-2-enoate (**147g**)

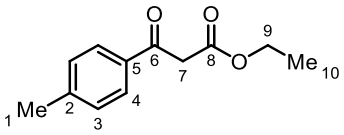


147g

Ethyl 2-methyl-3-(naphthalen-2-yl)-3-oxopropanoate (**152g**) (0.198 g, 0.773 mmol), aniline (0.141 mL, 1.55 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.029 g, 0.077 mmol) and $MgSO_4$ (0.028 g, 0.232 mmol) in 1,2-dichloroethane (2 mL) were subjected to general procedure H. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1) to give the title compound **147g** (0.032 g, 13%) as a colourless solid; mp. 80-82 °C; R_f 0.60 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3228, 2979, 1649, 1592, 1576, 1499, 1256, 1238, 1137, 1112, 822, 748; δ_H (400 MHz; $CDCl_3$) 11.01 (1 H, br s, H-5), 7.89 – 7.74 (4 H, m, H_{Ar}), 7.58 – 7.45 (2 H, m, H_{Ar}), 7.35 (1 H, dd, *J* = 8.4, 1.7 Hz, H_{Ar}), 6.97 – 6.88 (2 H, m, H-2), 6.75 (1 H, t, *J* = 7.4 Hz, H-1), 6.57 (2 H, d, *J* = 7.6 Hz, H-3), 4.27 (2 H, q, *J* = 7.1 Hz, H-20), 1.72 (3 H, s, H-18), 1.36 (3 H, t, *J* = 7.1 Hz, H-21); δ_C (100 MHz; $CDCl_3$) 171.6 (C-19), 155.9 (C-6), 141.2 (C-4), 133.1 (C-9, C-14), 133.0 (C-7), 129.1 (CH_{Ar}), 128.6 (C-2), 128.4 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 127.0 (CH_{Ar}), 126.8 (CH_{Ar}), 126.4 (CH_{Ar}), 122.2 (C-1), 121.6 (C-3), 95.2 (C-17), 59.8 (C-20), 14.7 (C-21), 14.4 (C-18); Found (ESI): $[MH]^+$ 332.1644; $C_{22}H_{22}NO_2$ requires $[MH]^+$ 332.1645, 0.3 ppm.

Lab-book No PD/11/26.

Ethyl 3-(4-methylphenyl)-3-oxopropanoate[145]

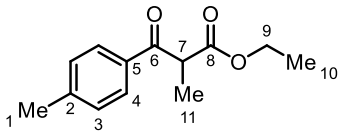


4-Methylacetophenone (1.34 mL, 10.0 mmol), diethylcarbonate (4.85 mL, 40.0 mmol) and NaH (60% in dispersion in oil, 1.21 g, 50.4 mmol) in THF (10 mL) were subjected to general procedure I. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound (1.84 g, 89%) as a yellow oil in a 4:1 mixture of keto-enol tautomers; R_f 0.33 (Hexane/EtOAc, 6:1); δ_H (400 MHz; $CDCl_3$, **Keto**) 7.82 (2 H, dd, *J* = 8.2, 2.0 Hz, H_{Ar}), 7.25 (2 H, dd, *J* = 8.2, 2.0 Hz, H_{Ar}), 4.19 (2 H, qd, *J* = 7.1, 2.0 Hz, H-9), 3.95 (2 H, d, *J* = 1.9 Hz, H-7), 2.40 (3 H, d, *J* = 2.4 Hz, H-1), 1.24 (3 H, td, *J* = 7.1, 2.0 Hz, H-10); δ_H (400 MHz; $CDCl_3$, **Enol**) 12.58 (1 H, s, OH), 7.65 (2 H, dd, *J* = 8.3, 2.0 Hz, H_{Ar}), 7.20 (2 H, dd, *J* = 8.3, 2.0 Hz, H_{Ar}), 5.61 (1 H, d, *J* = 1.7 Hz, H-7), 4.24 (2 H, qd, *J* = 7.1, 2.0 Hz, H-9), 2.37 (3 H, d, *J* = 2.3 Hz, H-1), 1.31 (3 H, td, *J* = 7.2, 2.1 Hz, H-10).

Data are consistent with literature values.[145]

Lab-book No PD/10/49.

Ethyl 2-methyl-3-(4-methylphenyl)-3-oxopropanoate[146] (**152h**)



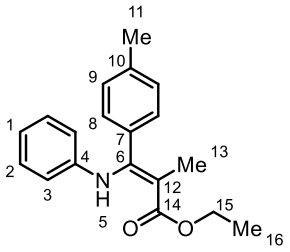
152h

Ethyl 3-(4-methylphenyl)-3-oxopropanoate (1.19 g, 5.77 mmol), iodomethane (0.395 mL, 6.35 mmol), and K_2CO_3 (1.20 g, 8.65 mmol) in DMF (10 mL) were subjected to general procedure G. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **152h** (0.906 g, 71%) as a colourless oil; R_f 0.33 (Hexane/EtOAc, 6:1); δ_H (400 MHz; $CDCl_3$) 7.86 (2 H, d, *J* = 8.0 Hz, H_{Ar}), 7.24 (2 H, d, *J* = 8.0 Hz, H_{Ar}), 4.33 (1 H, q, *J* = 7.1 Hz, H-7), 4.12 (2 H, q, *J* = 7.1 Hz, H-9), 2.39 (3 H, s, H-1), 1.46 (3 H, dd, *J* = 7.1, 1.1 Hz, H-11), 1.15 (3 H, td, *J* = 7.1, 1.1 Hz, H-10).

Data are consistent with literature values.[146]

Lab-book No PD/10/53.

Ethyl (2*Z*)-2-methyl-3-(4-methylphenyl)-3-(phenylamino)prop-2-enoate (**147h**)

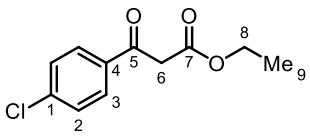


147h

Ethyl 2-methyl-3-(4-methylphenyl)-3-oxopropanoate (**152h**) (0.296 g, 1.34 mmol), aniline (0.245 mL, 2.68 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.053 g, 0.141 mmol) and $MgSO_4$ (0.054 g, 0.444 mmol) in 1,2-dichloroethane (2 mL) were subjected to general procedure H. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1) to give the title compound **147h** (0.045 g, 11%) as a colourless oil; R_f 0.6 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 3218, 2979, 1649, 1594, 1578, 1498, 1250, 1171, 1128, 1034, 1015, 826, 780, 733, 692; δ_H (400 MHz; $CDCl_3$) 10.92 (1 H, br s, H-5), 7.13 (4 H, s, H-8 and H-9), 7.02 – 6.96 (2 H, m, H-2), 6.80 (1 H, t, *J* = 7.4 Hz, H-1), 6.54 (2 H, d, *J* = 7.6 Hz, H-3), 4.24 (2 H, q, *J* = 7.1 Hz, H-15), 2.34 (3 H, s, H-11), 1.70 (3 H, s, H-13), 1.34 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 171.6 (C-14), 156.3 (C-6), 141.3 (C-4), 138.6 (C-10), 132.6 (C-7), 129.4 (C-8 or C-9), 129.2 (C-8 or C-9), 128.5 (C-2), 122.1 (C-1), 121.6 (C-3), 94.5 (C-12), 59.7 (C-15), 21.5 (C-11), 14.7 (C-16), 14.3 (C-13); Found (ESI): $[MH]^+$ 296.1640; $C_{19}H_{22}NO_2$ requires $[MH]^+$ 296.1645, 1.7 ppm.

Lab-book No PD/10/56.

Ethyl 3-(4-chlorophenyl)-3-oxopropanoate[147]



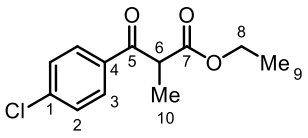
4-Chloroacetophenone (1.30 mL, 10.0 mmol), diethylcarbonate (4.85 mL, 40.0 mmol) and NaH (60% in dispersion in oil, 1.22 g, 50.8 mmol) in THF (10 mL) were subjected to general procedure I. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound (2.03 g, 90%) as a yellow oil in a 3:1 mixture of keto-enol tautomers; R_f 0.38 (Hexane/EtOAc, 6:1); δ_H (400 MHz; $CDCl_3$, **Keto**) 7.93 – 7.80 (2 H, m, H_{Ar}), 7.54 – 7.40 (2 H, m, H_{Ar}), 4.21 – 4.14 (2 H, m, H-8), 3.96 – 3.91 (2 H, m, H-6), 1.26 – 1.18 (3 H, m, H-9); δ_H (400 MHz; $CDCl_3$, **Enol**) 12.84 – 12.31 (1 H, m, OH), 7.71 – 7.65 (2

H, m, H_{Ar}), 7.39 – 7.33 (2 H, m, H_{Ar}), 5.87 – 5.46 (1 H, m, H-6), 4.28 – 4.22 (2 H, m, H-8), 1.34 – 1.28 (3 H, m, H-9).

Data are consistent with literature values.[147]

Lab-book No PD/10/50.

Ethyl 3-(4-chlorophenyl)-2-methyl-3-oxopropanoate[148] (**152i**)



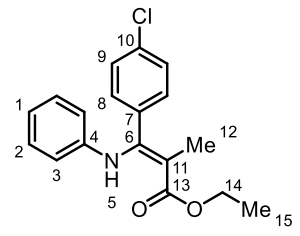
152i

Ethyl 3-(4-chlorophenyl)-3-oxopropanoate (1.71 g, 7.54 mmol), iodomethane (0.517 mL, 8.30 mmol), and K_2CO_3 (1.56 g, 11.3 mmol) in DMF (15 mL) were subjected to general procedure G. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **152i** (1.45 g, 80%) as a colourless oil; R_f 0.29 (Hexane/EtOAc, 6:1); δ_H (400 MHz; $CDCl_3$) 7.94 – 7.87 (2 H, m, H_{Ar}), 7.47 – 7.40 (2 H, m, H_{Ar}), 4.30 (1 H, qd, *J* = 7.0, 1.4 Hz, H-6), 4.17 – 4.08 (2 H, m, H-8), 1.49 – 1.43 (3 H, m, H-10), 1.18 – 1.12 (3 H, m, H-9); δ_C (100 MHz; $CDCl_3$) 194.7 (C-5), 170.7 (C-7), 140.0 (C-4), 134.3 (C-1), 130.1 (CH_{Ar}), 129.1 (CH_{Ar}), 61.6 (C-8), 48.5 (C-6), 14.0 (C-9 or C-10), 13.7 (C-9 or C-10).

Data are consistent with literature values.[148]

Lab-book No PD/10/54.

Ethyl (2*Z*)-3-(4-chlorophenyl)-2-methyl-3-(phenylamino)prop-2-enoate (**147i**)



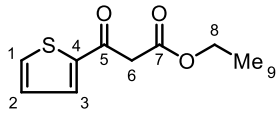
147i

Ethyl 3-(4-chlorophenyl)-3-oxopropanoate (**152i**) (0.334 g, 1.39 mmol), aniline (0.253 mL, 2.77 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.058 g, 0.155 mmol) and $MgSO_4$ (0.062 g, 0.518 mmol) in 1,2-dichloroethane (2 mL) were subjected to general procedure H. The residue was purified

by column chromatography (SiO_2, Hexane/EtOAc, 49:1) to give the title compound **147i** (0.086 g, 20%) as a colourless oil; R_f 0.64 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 3228, 2980, 1651, 1592, 1578, 1498, 1477, 1250, 1132, 1090, 1012, 835, 781, 750, 693; δ_H (400 MHz; $CDCl_3$) 10.83 (1 H, br s, H-5), 7.30 (2 H, d, *J* = 8.3 Hz, H-9), 7.19 (2 H, d, *J* = 8.3 Hz, H-8), 7.05 – 6.99 (2 H, m, H-2), 6.83 (1 H, t, *J* = 7.4 Hz, H-1), 6.54 (2 H, d, *J* = 7.5 Hz, H-3), 4.24 (2 H, q, *J* = 7.1 Hz, H-14), 1.68 (3 H, s, H-12), 1.34 (3 H, t, *J* = 7.1 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 171.4 (C-13), 154.8 (C-6), 140.9 (C-4), 134.6 (C-10), 134.1 (C-7), 131.0 (C-8), 128.8 (C-2 or C-9), 128.7 (C-2 or C-9), 122.5 (C-1), 122.0 (C-3), 95.2 (C-11), 59.9 (C-14), 14.6 (C-15), 14.3 (C-12); Found (ESI): $[MNa]^+$ 338.0901; $C_{18}H_{18}ClNNaO_2$ requires $[MNa]^+$ 338.0918, 5.0 ppm.

Lab-book No PD/10/57.

Ethyl 3-oxo-3-(thiophen-2-yl)propanoate[149]

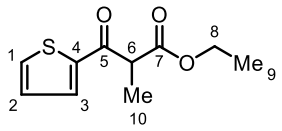


To a stirred solution of thiophene-2-carboxylic acid (1.28 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (1.73 g, 12.0 mmol), DMAP (2.46 g, 20.1 mmol) and DCC (2.27 g, 11.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The dicyclohexylurea was then filtered off, and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated *in vacuo* and the residue was dissolved in absolute EtOH (60 mL). The solution was then treated with a solution of *p*-TSA (4.67 g, 24.5 mmol) in absolute EtOH (15 mL) and heated at reflux for 1 h. EtOH was removed *in vacuo* and the residue was dissolved with EtOAc (50 mL). The organic extracts were washed with water (50 mL), aq. sat. $NaHCO_3$ (50 mL), aq. HCl (10%, 50 mL), and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica (SiO_2, Hexane/EtOAc, 9:1) to give the title compound (1.81 g, 91%) as an orange oil; R_f 0.31 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.72 (1 H, dd, *J* = 3.8, 1.0 Hz, H-3), 7.68 (1 H, dd, *J* = 4.9, 1.0 Hz, H-1), 7.13 (1 H, dd, *J* = 4.9, 3.8 Hz, H-2), 4.19 (2 H, q, *J* = 7.2 Hz, H-8), 3.90 (2 H, s, H-6), 1.24 (3 H, t, *J* = 7.2 Hz, H-9).

Data are consistent with literature values.[149]

Lab-book No PD/10/6.

Ethyl 2-methyl-3-oxo-3-(thiophen-2-yl)propanoate[150] (**152j**)



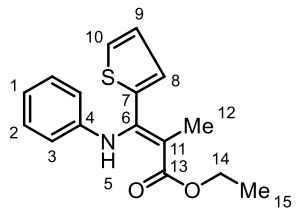
152j

To a stirred suspension of NaH (60% in dispersion in oil, 0.117 g, 2.94 mmol) in DMF (25 mL) was added ethyl 3-oxo-3-(thiophen-2-yl)propanoate (0.530 g, 2.67 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and iodomethane (0.183 mL, 2.94 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature and stirred for a further 1 h, then quenched by slow addition of water (30 mL) at 0 °C. The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (4 × 20 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude yellow oil which was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) and afforded the title compound **152j** (0.282 g, 53%) as a colourless oil; R_f 0.32 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.77 (1 H, dd, *J* = 3.9, 1.1 Hz, H-3), 7.67 (1 H, dd, *J* = 4.9, 1.1 Hz, H-1), 7.13 (1 H, dd, *J* = 4.9, 3.9 Hz, H-2), 4.21 (1 H, q, *J* = 7.1 Hz, H-6), 4.15 (2 H, q, *J* = 7.1 Hz, H-8), 1.49 (3 H, d, *J* = 7.1 Hz, H-10), 1.19 (3 H, t, *J* = 7.1 Hz, H-9).

Data are consistent with literature values.[150]

Lab-book No PD/10/8.

Ethyl (2*Z*)-2-methyl-3-(phenylamino)-3-(thiophen-2-yl)prop-2-enoate (**147j**)



147j

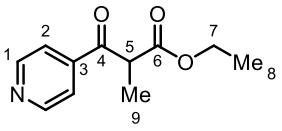
To a stirred solution of ethyl 2-methyl-3-oxo-3-(thiophen-2-yl)propanoate (**152j**) (0.194 g, 0.914 mmol) in AcOH (0.262 mL, 4.57 mmol) was added an excess of aniline (0.416 mL, 4.57 mmol). The reaction mixture was stirred at 80 °C for 5 h and allowed to cool to room temperature. Water (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by

column chromatography (SiO_2, Hexane/EtOAc, 99:1 to 19:1) and afforded the title compound **147j** (0.029 g, 11%) as a yellow oil; R_f 0.25 (Hexane/EtOAc, 8:1); ν_{max} (cm^{-1}) 2982, 1735, 1654, 1612, 1594, 1498, 1250, 1215, 1116, 853, 779, 757, 711, 696; δ_H (400 MHz; $CDCl_3$) 10.61 (1 H, br s, H-5), 7.43 (1 H, dd, *J* = 5.0, 0.7 Hz, H-10), 7.40 (1 H, dd, *J* = 3.7, 0.7 Hz, H-8), 7.05 (2 H, t, *J* = 7.8 Hz, H-2), 7.00 (1 H, dd, *J* = 5.0, 3.7 Hz, H-9), 6.85 (1 H, t, *J* = 7.8 Hz, H-1), 6.63 (2 H, d, *J* = 7.8 Hz, H-3), 4.23 (2 H, q, *J* = 7.1 Hz, H-14), 1.87 (3 H, s, H-12), 1.33 (3 H, t, *J* = 7.1 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 171.9 (C-13), 149.8 (C-6), 143.1 (C-7), 141.7 (C-4), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 127.8 (CH_{Ar}), 126.9 (C-9), 122.4 (C-1), 121.3 (C-3), 98.1 (C-11), 60.0 (C-14), 14.6 (C-12 or C-15), 14.2 (C-12 or C-15); Found (ESI): $[MH]^+$ 288.1048; $C_{16}H_{18}NO_2S$ requires $[MH]^+$ 288.1053, 1.5 ppm.

Lab-book No PD/10/13.

6.3.4 General procedure J: Formation of α-substituted β-ketoesters

Ethyl 2-methyl-3-oxo-3-(pyridin-4-yl)propanoate (**152k**)



152k

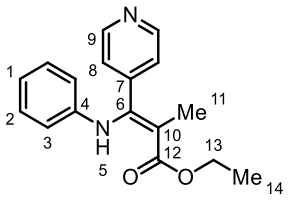
To a stirred solution of 4-ethyl picolinate (0.749 mL, 5.00 mmol) in THF (15 mL) was added ethyl propionate (1.15 mL, 10.0 mmol) at –40 °C. A solution of LHMDS (1.0 M in THF, 10.5 mL, 10.5 mmol) was quickly added. The reaction mixture was stirred at –40 °C for 30 min and allowed to warm to room temperature and stirred for 20 min. Then acetic acid (1 mL) was slowly added at 0 °C and the reaction mixture precipitated. $NaHCO_3$ (15 mL) was then added to the flask. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1 to 2:1) to give the title compound **152k** (0.966 g, 93%) as a yellow oil; R_f 0.08 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2985, 2942, 1732, 1698, 1595, 1556, 1454, 1408, 1376, 1338, 1222, 1180, 1073, 1036, 967, 838, 658; δ_H (400 MHz; $CDCl_3$) 8.76 (2 H, d, *J* = 6.0 Hz, H-1), 7.69 (2 H, d, *J* = 6.0 Hz, H-2), 4.26 (1 H, q, *J* = 7.0 Hz, H-5), 4.09 (2 H, q, *J* = 7.1 Hz, H-7), 1.44 (3 H, d, *J* = 7.0 Hz, H-9), 1.10 (3 H, t, *J* = 7.1 Hz, H-8); δ_C (100 MHz; $CDCl_3$) 195.4 (C-4), 170.1 (C-6), 151.1 (C-1), 142.0 (C-3), 121.4 (C-2), 61.8 (C-7), 48.7 (C-

5), 14.0 (C-8 or C-9), 13.3 (C-8 or C-9); Found (ESI): $[MNa]^+$ 230.0786; $C_{11}H_{13}NNaO_3$ requires $[MNa]^+$ 230.0788, 0.8 ppm.

Lab-book No PD/11/35.

6.3.5 General procedure K: Dean and Stark approach to enamine precursors

Ethyl (2*Z*)-2-methyl-3-(phenylamino)-3-(pyridin-4-yl)prop-2-enoate (**147k**)

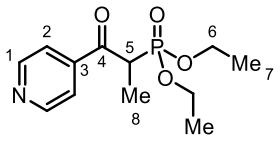


147k

To a stirred solution of ethyl 2-methyl-3-oxo-3-(pyridin-4-yl)propanoate (**152k**) (0.186 g, 0.898 mmol) in toluene (8 mL) was added aniline (0.082 mL, 0.898 mmol) and *p*-TSA (0.017 g, 0.090 mmol). The flask was fitted with a Dean & Stark apparatus, and stirred overnight at 110 °C. The resulting yellow reaction mixture was cooled to room temperature and toluene was removed. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) to give the title compound **147k** (0.130 g, 51%) as a colourless solid; mp. 58-60 °C; R_f 0.36 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 3242, 2980, 1653, 1591, 1577, 1499, 1257, 1145, 1034, 833; δ_H (400 MHz; $CDCl_3$) 10.75 (1 H, br s, H-5), 8.57 (2 H, dd, *J* = 4.4, 1.6 Hz, H-9), 7.17 (2 H, dd, *J* = 4.4, 1.6 Hz, H-8), 7.07 – 6.96 (2 H, m, H-2), 6.84 (1 H, t, *J* = 7.4 Hz, H-1), 6.56 (2 H, d, *J* = 7.8 Hz, H-3), 4.23 (2 H, q, *J* = 7.1 Hz, H-13), 1.67 (3 H, s, H-11), 1.32 (3 H, t, *J* = 7.1 Hz, H-14); δ_C (100 MHz; $CDCl_3$) 171.2 (C-12), 153.0 (C-6), 150.1 (C-9), 143.8 (C-7), 140.4 (C-4), 128.8 (C-2), 124.5 (C-8), 123.1 (C-1), 122.4 (C-3), 95.7 (C-10), 60.1 (C-13), 14.6 (C-14), 14.2 (C-11); Found (ESI): $[MH]^+$ 283.1435; $C_{17}H_{19}N_2O_2$ requires $[MH]^+$ 283.1441, 2.0 ppm.

Lab-book No PD/11/38.

Diethyl [1-oxo-1-(pyridin-4-yl)propan-2-yl]phosphonate (**152l**)

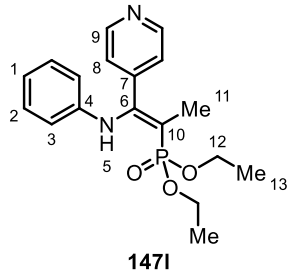


152l

4-Ethyl picolinate (0.375 mL, 2.50 mmol), diethyl ethylphosphonate (0.811 mL, 5.00 mmol), LHMDS (1.0 M in THF, 5.25 mL, 5.25 mmol) in THF (10 mL) were subjected to general procedure J. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 49:1) to give the title compound **152l** (0.585 g, 86%) as a yellow oil; R_f 0.27 (CH_2Cl_2/MeOH, 24:1); ν_{max} (cm^{-1}) 3474, 2984, 2942, 1693, 1409, 1234, 1049, 1021, 796; δ_H (400 MHz; $CDCl_3$) 8.78 (2 H, br s, H-1), 7.87 – 7.63 (2 H, m, H-2), 4.16 – 3.99 (5 H, m, H-5 and H-6), 1.56 – 1.44 (3 H, m, H-8), 1.30 – 1.23 (3 H, m, H-7a), 1.19 – 1.13 (3 H, m, H-7b); δ_C (100 MHz; $CDCl_3$) 196.1 (d, *J*(C-P) = 5.4 Hz, C-4), 150.8 (C-1), 142.9 (C-3), 121.7 (C-2), 63.0 (d, *J*(C-P) = 7.4 Hz, C-6a), 62.9 (d, *J*(C-P) = 6.9 Hz, C-6b), 42.1 (d, *J*(C-P) = 128.6 Hz, C-5), 16.4 (d, *J*(C-P) = 5.9 Hz, C-7a), 16.2 (d, *J*(C-P) = 5.9 Hz, C-7b), 11.8 (d, *J*(C-P) = 6.8 Hz, C-8); Found (ESI): $[MH]^+$ 272.1045; $C_{12}H_{19}NO_4P$ requires $[MH]^+$ 272.1046, 0.4 ppm.

Lab-book No PD/11/41.

Diethyl [(1*Z*)-1-(phenylamino)-1-(pyridin-4-yl)prop-1-en-2-yl]phosphonate (**147l**)



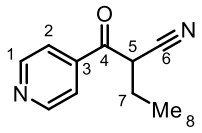
147l

Diethyl [1-oxo-1-(pyridin-4-yl)propan-2-yl]phosphonate (**152l**) (0.231 g, 0.852 mmol), aniline (0.078 mL, 0.852 mmol), and *p*-TSA (0.016 g, 0.085 mmol) in toluene (8 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1 to 1:2) to give the title compound **147l** (0.045 g, 15%) as a colourless solid; mp. 84-86 °C; R_f 0.35 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 3253, 2982, 1593, 1582, 1497, 1361, 1049, 1020, 959, 872, 837, 798, 750; δ_H (400 MHz; $CDCl_3$) 9.50 (1 H, br s, H-5), 8.57 (2 H, dd, *J* = 4.4, 1.6 Hz, H-9), 7.21 (2 H, dd, *J* = 4.4, 1.6 Hz, H-8), 7.02 – 6.90 (2 H, m, H-2), 6.78 (1 H, t, *J* = 7.4 Hz, H-1), 6.51 (2 H, d, *J* = 7.7 Hz, H-3), 4.18 – 4.03 (4 H, m, H-12), 1.63 (3 H, d, *J*(H-P) = 14.0 Hz, H-11), 1.35 (6 H, t, *J* = 7.1 Hz, H-13); δ_C (100

MHz; $CDCl_3$) 153.4 (d, *J*(C-P) = 10.7 Hz, C-6), 150.1 (C-9), 144.0 (d, *J*(C-P) = 19.1 Hz, C-7), 141.5 (C-4), 128.7 (C-2), 124.5 (C-8), 122.1 (C-1), 121.3 (C-3), 91.7 (d, *J*(C-P) = 178.2 Hz, C-10), 61.7 (C-12a), 61.6 (C-12b), 16.5 (C-13a), 16.4 (C-13b), 14.6 (d, *J*(C-P) = 7.4 Hz, C-11); Found (ESI): $[MNa]^+$ 369.1342; $C_{18}H_{23}N_2NaO_3P$ requires $[MNa]^+$ 369.1339, 0.9 ppm.

Lab-book No PD/11/43.

2-(Pyridine-4-carbonyl)butanenitrile (**152m**)

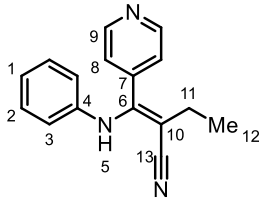


152m

4-Ethyl picolinate (0.375 mL, 2.50 mmol), butyronitrile (0.435 mL, 5.00 mmol), LHMDS (1.0 M in THF, 5.25 mL, 5.25 mmol) in THF (10 mL) were subjected to general procedure J. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1 to 1:2) to give the title compound **152m** (0.427 g, 98%) as a thick yellow oil; R_f 0.20 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 2975, 2939, 2203, 1707, 1603, 1559, 1460, 1411, 1342, 1233, 1159, 1066, 1003, 829, 685; δ_H (400 MHz; $CDCl_3$) 8.87 (2 H, dd, *J* = 4.4, 1.6 Hz, H-1), 7.74 (2 H, dd, *J* = 4.4, 1.6 Hz, H-2), 4.22 (1 H, dd, *J* = 8.1, 5.6 Hz, H-5), 2.09 – 2.00 (2 H, m, H-7), 1.17 (3 H, t, *J* = 7.4 Hz, H-8); δ_C (100 MHz; $CDCl_3$) 190.6 (C-4), 151.4 (C-1), 140.1 (C-3), 121.4 (C-2), 116.4 (C-6), 41.9 (C-5), 23.2 (C-7), 11.5 (C-8); Found (ESI): $[MH]^+$ 175.0864; $C_{10}H_{11}N_2O$ requires $[MH]^+$ 175.0866, 0.9 ppm.

Lab-book No PD/11/44.

(2*Z*)-2-[(Phenylamino)(pyridin-4-yl)methylidene]butanenitrile (**147m**)



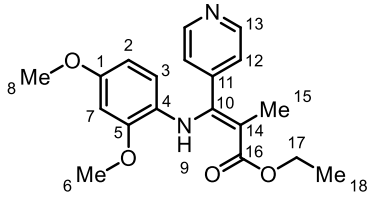
147m

2-(Pyridine-4-carbonyl)butanenitrile (**152m**) (0.453 g, 2.60 mmol), aniline (0.237 mL, 2.60 mmol), and *p*-TSA (0.053 g, 0.280 mmol) in toluene (10 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound **147m** (0.343 g, 53%) as a colourless solid; mp. 100-102 °C;

R_f 0.35 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 3303, 2972, 2194, 1593, 1583, 1546, 1496, 1363, 1246, 909, 834, 747, 729, 692; δ_H (400 MHz; $CDCl_3$) 8.55 (2 H, dd, *J* = 4.5, 1.7 Hz, H-9), 7.37 (2 H, dd, *J* = 4.5, 1.7 Hz, H-8), 7.11 – 7.05 (2 H, m, H-2), 6.91 (1 H, t, *J* = 7.4 Hz, H-1), 6.59 (2 H, d, *J* = 7.7 Hz, H-3), 6.46 (1 H, br s, H-5), 2.34 (2 H, q, *J* = 7.5 Hz, H-11), 1.25 (3 H, t, *J* = 7.5 Hz, H-12); δ_C (100 MHz; $CDCl_3$) 150.6 (C-6), 150.1 (C-9), 142.5 (C-7), 140.1 (C-4), 129.2 (C-2), 124.3 (C-8), 123.4 (C-1), 121.0 (C-3), 120.8 (C-13), 93.3 (C-10), 22.2 (C-11), 12.6 (C-12); Found (ESI): $[MH]^+$ 250.1340; $C_{16}H_{16}N_3$ requires $[MH]^+$ 250.1339, 0.5 ppm.

Lab-book No PD/11/45.

Ethyl (2*Z*)-3-[(2,4-dimethoxyphenyl)amino]-2-methyl-3-(pyridin-4-yl)prop-2-enoate (**147n**)



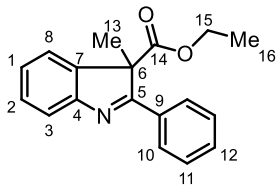
147n

Ethyl 2-methyl-3-oxo-3-(pyridin-4-yl)propanoate (**152k**) (0.258 g, 1.24 mmol), 2,4-dimethoxyaniline (0.190 g, 1.24 mmol), and *p*-TSA (0.024 g, 0.124 mmol) in toluene (10 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 4:1) to give the title compound **147n** (0.240 g, 57%) as an orange solid; mp. 88-90 °C; R_f 0.12 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 3243, 2980, 2939, 1731, 1704, 1652, 1609, 1577, 1513, 1254, 1208, 1135, 1034, 832, 780; δ_H (400 MHz; $CDCl_3$) 10.37 (1 H, br s, H-9), 8.51 (2 H, dd, *J* = 4.4, 1.6 Hz, H-13), 7.10 (2 H, dd, *J* = 4.4, 1.6 Hz, H-12), 6.28 (1 H, d, *J* = 2.6 Hz, H-7), 6.26 (1 H, d, *J* = 8.7 Hz, H-3), 6.03 (1 H, dd, *J* = 8.7, 2.6 Hz, H-2), 4.22 (2 H, q, *J* = 7.1 Hz, H-17), 3.76 (3 H, s, H-6 or H-8), 3.64 (3 H, s, H-6 or H-8), 1.60 (3 H, s, H-15), 1.31 (3 H, t, *J* = 7.1 Hz, H-18); δ_C (100 MHz; $CDCl_3$) 171.3 (C-16), 157.1 (C-1 or C-5), 154.7 (C-10), 153.4 (C-1 or C-5), 149.8 (C-13), 144.2 (C-11), 125.2 (C-7), 124.2 (C-12), 122.8 (C-4), 103.3 (C-2), 98.9 (C-3), 93.3 (C-14), 59.8 (C-17), 55.6 (C-6 or C-8), 55.4 (C-6 or C-8), 14.7 (C-15 or C-18), 14.3 (C-15 or C-18); Found (ESI): $[MNa]^+$ 365.1473; $C_{19}H_{22}N_2NaO_4$ requires $[MNa]^+$ 365.1472, 0.4 ppm.

Lab-book No PD/11/63.

6.3.6 General procedure L: Cu(II)-mediated cyclisation to 3*H*-indoles

Ethyl 3-methyl-2-phenyl-3*H*-indole-3-carboxylate (**148a**)



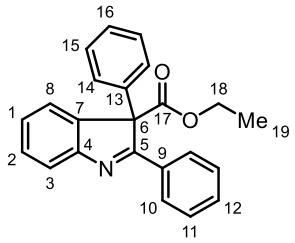
148a

To a stirred solution of ethyl (2*Z*)-2-methyl-3-phenyl-3-(phenylamino)prop-2-enoate (**147a**) (0.053 g, 0.187 mmol) in mesitylene (5 mL) was added Cu(2-ethylhexanoate)$_2$ (0.066 g, 0.187 mmol). The flask was fitted with a condenser and a $CaCl_2$ drying trap. The reaction was stirred and heated at 170 °C (Drysyn heating block) for 2 h. The resulting green solution was allowed to cool to room temperature. NH_4OH (10 mL) was added, the aqueous phase was extracted twice with EtOAc (2 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The brown residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 99:1) to give the title compound **148a** (0.041 g, 78%) as a colourless oil; R_f 0.28 (Hexane/EtOAc, 9:1); ν_{max} (cm^{-1}) 2983, 2935, 1728, 1531, 1444, 1236, 1221, 1101, 1012, 1004, 754, 728, 513; δ_H (400 MHz; $CDCl_3$) 7.98 – 7.94 (2 H, m, H-10), 7.71 (1 H, dd, *J* = 7.6, 1.0 Hz, H-3), 7.49 – 7.45 (3 H, m, H-11 and H-12), 7.42 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.40 – 7.37 (1 H, m, H-8), 7.26 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 4.12 (1 H, dq, *J* = 10.8, 7.1 Hz, H-15a), 3.97 (1 H, dq, *J* = 10.8, 7.1 Hz, H-15b), 1.71 (3 H, s, H-13), 0.97 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 178.1 (C-5), 171.6 (C-14), 154.9 (C-4), 141.8 (C-7), 132.0 (C-9), 131.2 (C-12), 129.1 (C-2), 128.9 (C-11), 128.4 (C-10), 126.4 (C-1), 121.4 (C-3 or C-8), 121.2 (C-3 or C-8), 62.2 (C-6), 61.9 (C-15), 21.1 (C-13), 13.8 (C-16); Found (ESI): $[MNa]^+$ 302.1153; $C_{18}H_{17}NNaO_2$ requires $[MNa]^+$ 302.1151, 0.5 ppm.

Data are consistent with literature values.[71]

Lab-book No PD/9/9.

Ethyl 2,3-diphenyl-3*H*-indole-3-carboxylate (**148b**)

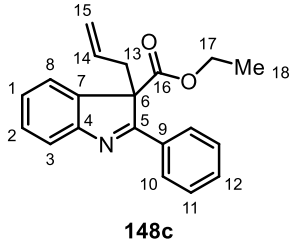


148b

Ethyl (2*Z*)-2,3-diphenyl-3-(phenylamino)prop-2-enoate (**147b**) (0.052 g, 0.152 mmol), Cu(2-ethylhexanoate)$_2$ (0.054 g, 0.155 mmol) in mesitylene (5 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 19:1) afforded the title compound **148b** (0.042 g, 80%) as a colourless oil; R_f 0.40 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3068, 2983, 1732, 1534, 1495, 1456, 1445, 1264, 1229, 1192, 1026, 765, 745, 693; δ_H (400 MHz; $CDCl_3$) 7.92 (2 H, dd, *J* = 8.4, 1.4 Hz, H-10), 7.73 (1 H, d, *J* = 7.6 Hz, H-3), 7.42 – 7.30 (7 H, m, H_{Ar}), 7.26 – 7.19 (4 H, m, H_{Ar}), 4.17 (1 H, dq, *J* = 10.8, 7.1 Hz, H-18a), 4.04 (1 H, dq, *J* = 10.8, 7.1 Hz, H-18b), 0.99 (3 H, t, *J* = 7.1 Hz, H-19); δ_C (100 MHz; $CDCl_3$) 177.3 (C-5), 169.3 (C-17), 154.8 (C-4), 142.5 (C-7), 136.8 (C_{Ar}), 132.7 (C_{Ar}), 130.9 (CH_{Ar}), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.9 (CH_{Ar}), 128.3 (CH_{Ar}), 127.8 (CH_{Ar}), 127.4 (CH_{Ar}), 126.8 (CH_{Ar}), 123.4 (CH_{Ar}), 121.3 (C-3), 71.6 (C-6), 62.1 (C-18), 13.8 (C-19); Found (ESI): $[MNa]^+$ 364.1306; $C_{23}H_{19}NNaO_2$ requires $[MNa]^+$ 364.1308, 0.5 ppm.

Lab-book No PD/9/98.

Ethyl 2-phenyl-3-(prop-2-en-1-yl)-3*H*-indole-3-carboxylate (**148c**)



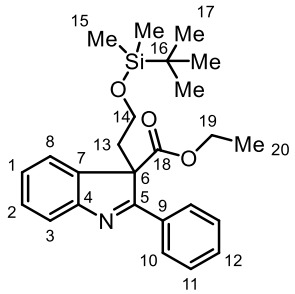
148c

Ethyl (2*Z*)-2-[phenyl(phenylamino)methylidene]pent-4-enoate (**147c**) (0.047 g, 0.154 mmol), Cu(2-ethylhexanoate)$_2$ (0.054 g, 0.153 mmol) in mesitylene (2 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 49:1) afforded the title compound **148c** (0.029 g, 61%) as a yellow oil; R_f 0.38 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 3064, 2980, 1726, 1532, 1445, 1266, 1224, 1075, 1032, 1020, 922, 756, 692; δ_H (400 MHz; $CDCl_3$) 7.97 – 7.92 (2 H, m, H-10), 7.69 (1 H, d,

J = 7.6 Hz, H-3), 7.49 – 7.44 (3 H, m, H-11 and H-12), 7.42 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.38 (1 H, d, *J* = 7.6 Hz, H-8), 7.27 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 5.02 – 4.83 (1 H, m, H-14), 4.73 – 4.56 (2 H, m, H-15), 4.13 (1 H, dq, *J* = 10.8, 7.1 Hz, H-17a), 3.99 (1 H, dq, *J* = 10.8, 7.1 Hz, H-17b), 3.27 (1 H, ddt, *J* = 14.0, 6.8, 1.1 Hz, H-13a), 3.06 (1 H, dd, *J* = 14.0, 7.6 Hz, H-13b), 0.98 (3 H, t, *J* = 7.1 Hz, H-18); δ_C (100 MHz; $CDCl_3$) 176.4 (C-5), 171.1 (C-16), 155.8 (C-4), 139.4 (C-7), 132.6 (C-9), 131.1 (C-12), 130.2 (C-14), 129.2 (C-2), 128.8 (C-11), 128.2 (C-10), 126.3 (C-1), 121.7 (C-8), 121.1 (C-3), 119.2 (C-15), 66.3 (C-6), 61.9 (C-17), 38.7 (C-13), 13.8 (C-18); Found (ESI): $[MH]^+$ 306.1485; $C_{20}H_{20}NO_2$ requires $[MH]^+$ 306.1489, 1.2 ppm.

Lab-book No PD/10/55.

Ethyl 3-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-2-phenyl-3*H*-indole-3-carboxylate (**148d**)



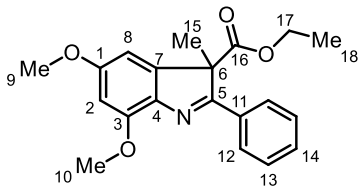
148d

The contaminated mixture (0.061 g of a mixture of ethyl (2*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-[phenyl(phenylamino)methylidene]butanoate (**147d**) and **172a**) that contained **147d** (0.041 g, 0.095 mmol), Cu(2-ethylhexanoate)$_2$ (0.050 g, 0.142 mmol) in mesitylene (5 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 49:1 to 8:1) afforded the title compound **148d** (0.025 g, 63%) as a yellow oil; R_f 0.54 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2955, 2930, 2857, 1729, 1533, 1464, 1445, 1253, 1224, 1108, 1091, 1013, 835, 764, 692; δ_H (400 MHz; $CDCl_3$) 7.97 – 7.93 (2 H, m, H-10), 7.69 (1 H, d, *J* = 7.6 Hz, H-3), 7.47 – 7.44 (3 H, m, H-11 and H-12), 7.41 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.37 (1 H, d, *J* = 7.6 Hz, H-8), 7.25 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 4.10 (1 H, dq, *J* = 10.8, 7.1 Hz, H-19a), 3.96 (1 H, dq, *J* = 10.8, 7.1 Hz, H-19b), 2.99 (1 H, ddd, *J* = 10.3, 9.0, 6.8 Hz, H-14a), 2.93 (1 H, ddd, *J* = 10.3, 9.0, 5.0 Hz, H-14b), 2.80 (1 H, ddd, *J* = 13.8, 8.8, 5.0 Hz, H-13a), 2.68 (1 H, ddd, *J* = 13.8, 8.8, 6.8 Hz, H-13b), 0.95 (3 H, t, *J* = 7.1 Hz, H-20), 0.63 (9 H, s, H-17), –0.31 (3 H, s, H-15a), –0.33 (3 H, s, H-15b); δ_C (100 MHz; $CDCl_3$) 176.9 (C-5), 171.1 (C-18), 155.7 (C-4), 139.2 (C-7), 132.7 (C-9), 131.1 (C-12), 129.2 (C-2), 128.8 (C-11), 128.2 (C-10), 126.3 (C-1), 121.7 (C-8), 121.2 (C-3), 64.9 (C-6), 61.9 (C-19), 58.3 (C-14), 37.2 (C-13), 25.8 (C-17), 18.2 (C-16),

13.8 (C-20), −5.72 (C-15); Found (ESI): $[MH]^+$ 424.2305; $C_{25}H_{34}NO_3Si$ requires $[MH]^+$ 424.2302, 0.5 ppm.

Lab-book No PD/10/4.

Ethyl 5,7-dimethoxy-3-methyl-2-phenyl-3*H*-indole-3-carboxylate (**148e**)

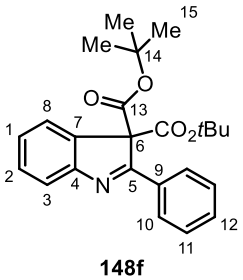


148e

Ethyl (2*Z*)-3[(2,4-dimethoxyphenyl)amino]-2-methyl-3-phenylprop-2-enoate (**147e**) (0.151 g, 0.443 mmol), Cu(2-ethylhexanoate)$_2$ (0.155 g, 0.443 mmol) in mesitylene (10 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 8:1 to 6:1) afforded the title compound **148e** (0.081 g, 54%) as a thick colourless oil; R_f 0.21 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2937, 1727, 1597, 1526, 1433, 1453, 1377, 1320, 1231, 1200, 1100, 1048, 831, 773, 694; δ_H (400 MHz; $CDCl_3$) 7.95 – 7.91 (2 H, m, H-12), 7.41 – 7.37 (3 H, m, H-13 and H-14), 6.53 (1 H, d, *J* = 2.2 Hz, H-8), 6.50 (1 H, d, *J* = 2.2 Hz, H-2), 4.11 (1 H, dq, *J* = 10.8, 7.1 Hz, H-17a), 4.00 (3 H, s, H-9 or H-10), 3.94 (1 H, dq, *J* = 10.8, 7.1 Hz, H-17b), 3.81 (3 H, s, H-9 or H-10), 1.67 (3 H, s, H-15), 0.95 (3 H, t, *J* = 7.1 Hz, H-18); δ_C (100 MHz; $CDCl_3$) 174.3 (C-5), 171.7 (C-16), 160.3 (C-1 or C-3), 152.3 (C-1 or C-3), 144.8 (C-7), 137.0 (C-4), 132.3 (C-11), 130.4 (C-14), 128.6 (C-13), 128.0 (C-12), 99.4 (C-2), 98.4 (C-8), 62.5 (C-6), 61.8 (C-17), 56.3 (C-9 or C-10), 55.9 (C-9 or C-10), 21.5 (C-15), 13.8 (C-18); Found (ESI): $[MH]^+$ 340.1540; $C_{20}H_{22}NO_4$ requires $[MH]^+$ 340.1543, 1.0 ppm.

Lab-book No PD/9/100.

3,3-Di-*tert*-butyl 2-phenyl-3*H*-indole-3,3-dicarboxylate (**148f**)

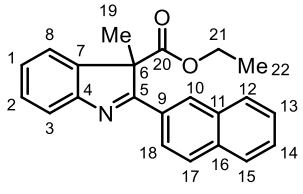


148f

1,3-Di-*tert*-butyl 2-[phenyl(phenylamino)methylidene] propanedioate (**147f**) (0.047 g, 0.120 mmol), Cu(2-ethylhexanoate)$_2$ (0.043 g, 0.122 mmol) in mesitylene (3 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 19:1) afforded the title compound **148f** (0.020 g, 42%) as a colourless solid; mp. 95-97 °C; R_f 0.41 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2978, 2934, 1724, 1457, 1369, 1247, 1142, 835, 767, 690; δ_H (400 MHz; $CDCl_3$) 8.10 (2 H, dd, *J* = 7.8, 1.4 Hz, H-10), 7.66 (1 H, d, *J* = 7.7 Hz, H-3), 7.63 (1 H, d, *J* = 7.7 Hz, H-8), 7.46 – 7.40 (4 H, m, H-2, H-11, and H-12), 7.28 (1 H, td, *J* = 7.7, 1.1 Hz, H-1), 1.29 (18 H, s, H-15); δ_C (100 MHz; $CDCl_3$) 172.6 (C-5), 164.8 (C-13), 155.7 (C-4), 136.1 (C-7), 133.1 (C-9), 130.9 (C-12), 129.6 (C-2), 129.4 (C-10) 128.1 (C-11), 126.6 (C-1), 123.6 (C-8), 121.1 (C-3), 83.5 (C-14), 75.5 (C-6), 27.6 (C-15); Found (ESI): [MNa]$^+$ 416.1819; $C_{24}H_{27}NNaO_4$ requires [MNa]$^+$ 416.1832, 3.1 ppm; Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.37; H, 6.90; N, 3.23.

Lab-book No PD/11/14.

Ethyl 3-methyl-2-(naphthalen-2-yl)-3*H*-indole-3-carboxylate (**148g**)



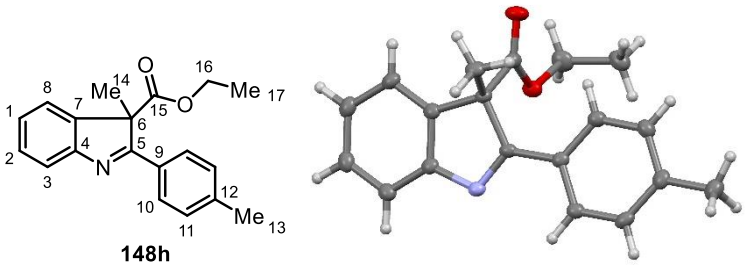
148g

Ethyl (2*Z*)-2-methyl-3-(naphthalen-2-yl)-3-(phenylamino)prop-2-enoate (**147g**) (0.025 g, 0.076 mmol), Cu(2-ethylhexanoate)$_2$ (0.027 g, 0.077 mmol) in mesitylene (2 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 19:1) afforded the title compound **148g** (0.012 g, 48%) as a yellow oil; R_f 0.48 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2981, 1729, 1531, 1457, 1241, 1221, 1102, 1013, 861, 767, 751; δ_H (400 MHz; $CDCl_3$) 8.27 (1 H, d, *J* = 1.6 Hz, H_{Ar}), 8.22 (1 H, dd, *J* = 8.5, 1.6 Hz, H_{Ar}), 7.93 (2 H, d, *J* = 8.5 Hz, H_{Ar}), 7.89 – 7.84 (1 H, m, H_{Ar}), 7.75 (1 H, d, *J* = 7.6 Hz, H-3), 7.58 – 7.54 (1 H, m, H_{Ar}), 7.54 – 7.50 (1 H, m, H_{Ar}), 7.44 (1 H, td, *J* = 7.6,

1.1 Hz, H-2), 7.42 (1 H, dd, *J* = 7.6, 1.1 Hz, H-8), 7.28 (1 H, td, *J* = 7.6, 1.1 Hz, H-1), 4.14 (1 H, dq, *J* = 10.8, 7.1 Hz, H-21a), 3.98 (1 H, dq, *J* = 10.8, 7.1 Hz, H-21b), 1.79 (3 H, s, H-19), 0.96 (3 H, t, *J* = 7.1 Hz, H-22); δ_C (100 MHz; $CDCl_3$) 178.1 (C-5), 171.8 (C-20), 155.1 (C-4), 142.0 (C-7), 134.6 (C_{Ar}), 133.1 (C_{Ar}), 129.6 (C_{Ar}), 129.1 (2 × CH_{Ar}), 129.0 (CH_{Ar}), 128.6 (CH_{Ar}), 127.84 (CH_{Ar}), 127.77 (CH_{Ar}), 126.8 (CH_{Ar}), 126.5 (C-1), 125.1 (CH_{Ar}), 121.4 (C-8), 121.3 (C-3), 62.2 (C-6), 61.9 (C-21), 21.4 (C-19), 13.9 (C-22); Found (ESI): $[MH]^+$ 330.1473; $C_{22}H_{20}NO_2$ requires $[MH]^+$ 330.1489, 4.8 ppm.

Lab-book No PD/11/33.

Ethyl 3-methyl-2-(4-methylphenyl)-3*H*-indole-3-carboxylate (**148h**)



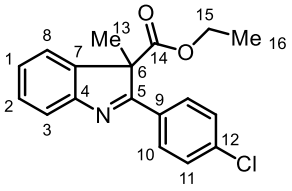
148h

Ethyl (2*Z*)-2-methyl-3-(4-methylphenyl)-3-(phenylamino)prop-2-enoate (**147h**) (0.042 g, 0.142 mmol), Cu(2-ethylhexanoate)$_2$ (0.050 g, 0.144 mmol) in mesitylene (2 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 49:1) afforded the title compound **148h** (0.030 g, 70%) as a yellow solid; mp. 75-77 °C; R_f 0.41 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 2982, 2936, 1730, 1530, 1510, 1466, 1377, 1238, 1222, 1102, 826, 768, 754; δ_H (400 MHz; $CDCl_3$) 7.85 (2 H, d, *J* = 8.3 Hz, H-10), 7.69 (1 H, d, *J* = 7.6 Hz, H-3), 7.41 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.37 (1 H, d, *J* = 7.6 Hz, H-8), 7.27 (2 H, d, *J* = 8.3 Hz, H-11), 7.23 (1 H, td, *J* = 7.6, 1.2 Hz, H-1), 4.11 (1 H, dq, *J* = 10.8, 7.1 Hz, H-16a), 3.97 (1 H, dq, *J* = 10.8, 7.1 Hz, H-16b), 2.41 (3 H, s, H-13), 1.70 (3 H, s, H-14), 0.97 (3 H, t, *J* = 7.1 Hz, H-17); δ_C (100 MHz; $CDCl_3$) 178.1 (C-5), 171.8 (C-15), 155.1 (C-4), 141.8 (C-7 or C-9), 141.7 (C-7 or C-9), 129.6 (C-11), 129.4 (C-12), 129.0 (C-2), 128.4 (C-10), 126.1 (C-1), 121.3 (C-8), 121.0 (C-3), 62.1 (C-6), 61.8 (C-16), 21.6 (C-13), 21.2 (C-14), 13.8 (C-17); Found (ESI): $[MH]^+$ 294.1501; $C_{19}H_{20}NO_2$ requires $[MH]^+$ 294.1489, 4.1 ppm. CCDC 1033699 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/10/59.

Ethyl 2-(4-chlorophenyl)-3-methyl-3*H*-indole-3-carboxylate (**148i**)

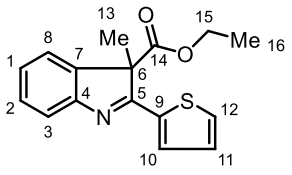


148i

Ethyl (2*Z*)-3-(4-chlorophenyl)-2-methyl-3-(phenylamino)prop-2-enoate (**147i**) (0.064 g, 0.202 mmol), Cu(2-ethylhexanoate)$_2$ (0.071 g, 0.202 mmol) in mesitylene (2 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 49:1) afforded the title compound **148i** (0.045 g, 70%) as a yellow oil; R_f 0.38 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 2982, 2936, 1729, 1591, 1529, 1491, 1402, 1267, 1236, 1220, 1092, 1013, 995, 840, 755, 725; δ_H (400 MHz; $CDCl_3$) 7.90 (2 H, d, *J* = 8.6 Hz, H-10), 7.70 (1 H, d, *J* = 7.6 Hz, H-3), 7.44 (2 H, d, *J* = 8.6 Hz, H-11), 7.42 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.38 (1 H, d, *J* = 7.6 Hz, H-8), 7.29 – 7.25 (1 H, m, H-1), 4.11 (1 H, dq, *J* = 10.7, 7.1 Hz, H-15a), 3.97 (1 H, dq, *J* = 10.7, 7.1 Hz, H-15b), 1.69 (3 H, s, H-13), 0.98 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 176.9 (C-5), 171.4 (C-14), 154.8 (C-4), 141.8 (C-7), 137.4 (C-9 or C-12), 130.6 (C-9 or C-12), 129.6 (C-10), 129.2 (C-2 and C-11), 126.6 (C-1), 121.4 (C-3 or C-8), 121.3 (C-3 or C-8), 62.1 (C-6), 62.0 (C-15), 21.0 (C-13), 13.9 (C-16); Found (ESI): $[MH]^+$ 314.0931; $C_{18}H_{17}ClNO_2$ requires $[MH]^+$ 314.0942, 1.2 ppm.

Lab-book No PD/10/60.

Ethyl 3-methyl-2-(thiophen-2-yl)-3*H*-indole-3-carboxylate (**148j**)



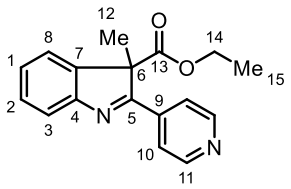
148j

Ethyl (2*Z*)-2-methyl-3-(phenylamino)-3-(thiophen-2-yl)prop-2-enoate (**147j**) (0.019 g, 0.068 mmol), Cu(2-ethylhexanoate)$_2$ (0.025 g, 0.070 mmol) in mesitylene (2 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 9:1) afforded the title compound **148j** (0.010 g, 51%) as a yellow oil;

R_f 0.14 (Hexane/EtOAc, 8:1); ν_{max} (cm^{-1}) 2982, 2934, 1730, 1687, 1545, 1509, 1465, 1427, 1240, 1223, 1105, 1013, 855, 768, 754, 716; δ_H (400 MHz; $CDCl_3$) 7.67 (1 H, d, *J* = 7.6 Hz, H-3), 7.53 (1 H, dd, *J* = 5.0, 0.7 Hz, H-12), 7.44 (1 H, dd, *J* = 3.8, 0.7 Hz, H-10), 7.40 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.36 (1 H, dd, *J* = 7.6, 1.0 Hz, H-8), 7.24 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 7.13 (1 H, dd, *J* = 5.0, 3.8 Hz, H-11), 4.11 (1 H, dq, *J* = 10.8, 7.1 Hz, H-15a), 3.99 (1 H, dq, *J* = 10.8, 7.1 Hz, H-15b), 1.75 (3 H, s, H-13), 1.00 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 172.8 (C-5), 171.2 (C-14), 155.1 (C-4), 141.4 (C-7), 137.2 (C-9), 130.5 (C-12), 129.8 (C-10), 129.1 (C-2), 128.3 (C-11), 126.2 (C-1), 121.5 (C-8), 121.0 (C-3), 62.6 (C-6), 62.0 (C-15), 22.0 (C-13), 13.9 (C-16); Found (ESI): $[MH]^+$ 286.0905; $C_{16}H_{16}NO_2S$ requires $[MH]^+$ 286.0896, 3.2 ppm.

Lab-book No PD/10/14.

Ethyl 3-methyl-2-(pyridin-4-yl)-3*H*-indole-3-carboxylate (**148k**)

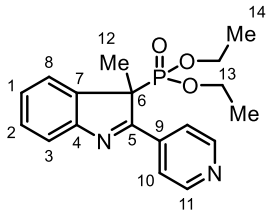


148k

Ethyl (2*Z*)-2-methyl-3-(phenylamino)-3-(pyridin-4-yl)prop-2-enoate (**147k**) (0.059 g, 0.207 mmol), Cu(2-ethylhexanoate)$_2$ (0.073 g, 0.208 mmol) in mesitylene (3 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 2:1) afforded the title compound **148k** (0.046 g, 80%) as a yellow oil; R_f 0.11 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 2983, 2936, 1730, 1595, 1524, 1238, 1223, 1102, 1012, 829, 771, 757; δ_H (400 MHz; $CDCl_3$) 8.74 (2 H, br s, H-11), 7.77 (2 H, dd, *J* = 4.8, 1.3 Hz, H-10), 7.74 (1 H, d, *J* = 7.6 Hz, H-3), 7.44 (1 H, td, *J* = 7.6, 1.1 Hz, H-2), 7.41 (1 H, d, *J* = 7.6 Hz, H-8), 7.31 (1 H, td, *J* = 7.6, 1.1 Hz, H-1), 4.10 (1 H, dq, *J* = 10.9, 7.1 Hz, H-14a), 3.97 (1 H, dq, *J* = 10.9, 7.1 Hz, H-14b), 1.69 (3 H, s, H-12), 0.97 (3 H, t, *J* = 7.1 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 176.0 (C-5), 170.9 (C-13), 154.4 (C-4), 150.6 (C-11), 141.8 (C-7), 139.0 (C-9), 129.3 (C-2), 127.5 (C-1), 122.0 (C-3, C-8, or C-10), 121.9 (C-3, C-8, or C-10), 121.6 (C-3, C-8, or C-10), 62.2 (C-6), 62.1 (C-14), 20.5 (C-12), 13.8 (C-15); Found (ESI): $[MH]^+$ 281.1280; $C_{17}H_{17}N_2O_2$ requires $[MH]^+$ 281.1285, 1.6 ppm.

Lab-book No PD/11/40.

Diethyl [3-methyl-2-(pyridin-4-yl)-3*H*-indol-3-yl]phosphonate (**148l**)

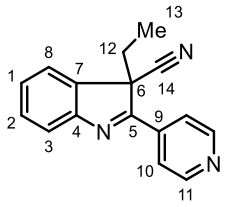


148l

Diethyl [(1*Z*)-1-(phenylamino)-1-(pyridin-4-yl)prop-1-en-2-yl]phosphonate (**147l**) (0.026 g, 0.074 mmol), Cu(2-ethylhexanoate)$_2$ (0.027 g, 0.077 mmol) in mesitylene (2 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, CH_2Cl_2/MeOH, 99:1 to 24:1) afforded the title compound **148l** (0.014 g, 55%) as a yellow oil; R_f 0.11 (CH_2Cl_2/MeOH, 49:1); ν_{max} (cm^{-1}) 2981, 2933, 1595, 1247, 1043, 1019, 971, 773; δ_H (400 MHz; $CDCl_3$) 8.77 (2 H, br s, H-11), 8.21 (2 H, br s, H-10), 7.76 (1 H, d, *J* = 7.6 Hz, H-3), 7.68 (1 H, d, *J* = 7.6 Hz, H-8), 7.46 (1 H, t, *J* = 7.6 Hz, H-2), 7.36 (1 H, t, *J* = 7.6 Hz, H-1), 4.00 – 3.62 (4 H, m, H-13a and H-13b), 1.92 (3 H, d, *J*(H-P) = 17.8 Hz, H-12), 1.11 (3 H, t, *J* = 7.1 Hz, H-14a), 0.99 (3 H, t, *J* = 7.1 Hz, H-14b); δ_C (100 MHz; $CDCl_3$) 175.0 (C-5), 154.6 (d, *J*(C-P) = 6.6 Hz, C-4), 150.2 (d, *J*(C-P) = 4.7 Hz, C-11), 150.1 (d, *J*(C-P) = 5.4 Hz, C-7), 139.7 (d, *J*(C-P) = 5.7 Hz, C-9), 129.2 (d, *J*(C-P) = 1.5 Hz, C-2), 127.6 (d, *J*(C-P) = 5.6 Hz, C-10), 127.1 (d, *J*(C-P) = 2.3 Hz, C-1), 124.6 (d, *J*(C-P) = 2.7 Hz, C-8), 121.8 (C-3), 63.9 (d, *J*(C-P) = 7.5 Hz, C-13a), 63.5 (d, *J*(C-P) = 7.4 Hz, C-13b), 59.7 (d, *J*(C-P) = 129.2 Hz, C-6), 18.7 (d, *J*(C-P) = 6.4 Hz, C-12), 16.3 (d, *J*(C-P) = 5.6 Hz, C-14a), 16.1 (d, *J*(C-P) = 6.3 Hz, C-14b); Found (ESI): $[MH]^+$ 345.1360; $C_{18}H_{22}N_2O_3P$ requires $[MH]^+$ 345.1363, 0.8 ppm.

Lab-book No PD/11/46.

3-Ethyl-2-(pyridin-4-yl)-3*H*-indole-3-carbonitrile (**148m**)

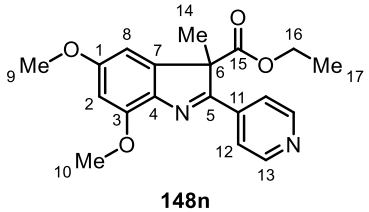


148m

(2*Z*)-2-[(Phenylamino)(pyridin-4-yl)methylidene]butanenitrile (**147m**) (0.041 g, 0.166 mmol), Cu(2-ethylhexanoate)$_2$ (0.058 g, 0.164 mmol) in mesitylene (5 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 2:1) afforded the title compound **148m** (0.019 g, 47%) as a yellow oil; R_f 0.19 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 3039, 2972, 2933, 2237, 2223, 1686, 1595, 1529, 1458, 1410, 1266, 827, 750, 767; δ_H (400 MHz; $CDCl_3$) 8.83 (2 H, br s, H-11), 8.07 (2 H, dd, *J* = 4.8, 1.3 Hz, H-10), 7.77 (1 H, d, *J* = 7.7 Hz, H-3), 7.62 (1 H, d, *J* = 7.5 Hz, H-8), 7.54 (1 H, td, *J* = 7.7, 1.2 Hz, H-2), 7.44 (1 H, td, *J* = 7.5, 1.2 Hz, H-1), 2.48 (1 H, dq, *J* = 14.8, 7.4 Hz, H-12a), 2.13 (1 H, dq, *J* = 14.8, 7.4 Hz, H-12b), 0.67 (3 H, t, *J* = 7.4 Hz, H-13); δ_C (100 MHz; $CDCl_3$) 170.4 (C-5), 154.4 (C-4), 151.0 (C-11), 138.0 (C-9), 136.7 (C-7), 130.6 (C-2), 128.4 (C-1), 122.9 (C-8), 122.7 (C-3), 121.7 (C-10), 118.0 (C-14), 52.6 (C-6), 30.9 (C-12), 7.9 (C-13); Found (ESI): $[MH]^+$ 248.1177; $C_{16}H_{14}N_3$ requires $[MH]^+$ 248.1182, 2.1 ppm.

Lab-book No PD/11/48.

Ethyl 5,7-dimethoxy-3-methyl-2-(pyridin-4-yl)-3*H*-indole-3-carboxylate (**148n**)



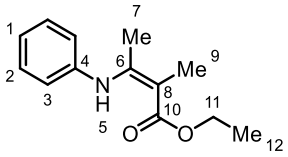
148n

Ethyl (2*Z*)-3-[(2,4-dimethoxyphenyl)amino]-2-methyl-3-(pyridin-4-yl)prop-2-enoate (**147n**) (0.063 g, 0.183 mmol), Cu(2-ethylhexanoate)$_2$ (0.064 g, 0.183 mmol) in mesitylene (5 mL) were subjected to general procedure L at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 1:1) afforded the title compound **148n** (0.028 g, 45%) as an orange oil; R_f 0.08 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 2937, 1731, 1592, 1456, 1317, 1235, 1153, 1049, 829; δ_H (400 MHz; $CDCl_3$) 8.68 (2 H, br s, H-13), 7.77 (2 H, dd, *J* = 4.8, 1.3 Hz, H-12), 6.55 (1 H, d, *J* = 2.2 Hz, H-8), 6.51 (1 H, d, *J* = 2.2 Hz, H-2), 4.13 (1 H, dq, *J* = 10.8, 7.1 Hz, H-16a), 4.02 (3 H, s, H-9 or H-10), 3.96 (1 H, dq, *J* = 10.8, 7.1 Hz,

H-16b), 3.84 (3 H, s, H-9 or H-10), 1.68 (3 H, s, H-14), 0.98 (3 H, t, *J* = 7.1 Hz, H-17); δ_C (100 MHz; $CDCl_3$) 171.9 (C-5), 171.1 (C-15), 161.4 (C-1 or C-3), 153.0 (C-1 or C-3), 150.5 (C-13), 145.1 (C-7), 139.1 (C-11), 136.6 (C-4), 121.5 (C-12), 99.5 (C-2), 98.6 (C-8), 62.5 (C-6), 62.2 (C-16), 56.4 (C-9 or C-10), 56.0 (C-9 or C-10), 21.0 (C-14), 13.9 (C-17); Found (ESI): $[MH]^+$ 341.1488; $C_{19}H_{21}N_2O_4$ requires $[MH]^+$ 341.1496, 2.4 ppm.

Lab-book No PD/11/65.

Ethyl (2*Z*)-2-methyl-3-(phenylamino)but-2-enoate[151] (**157**)



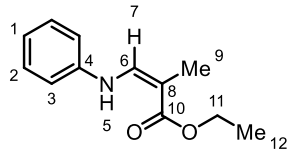
157

A mixture of ethyl 2-methylacetoacetate (2.83 mL, 20.0 mmol), aniline (1.82 mL, 20.0 mmol), and cerium ammonium nitrate (0.552 g, 1.00 mmol) in EtOH (20 mL) was stirred at room temperature overnight. Water was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The organic phase was washed with water (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 99:1) to give the title compound **157** (0.832 g, 19%) as an orange oil; R_f 0.56 (Hexane/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 10.93 (1 H, br s, H-5), 7.29 (2 H, t, *J* = 7.9 Hz, H-2), 7.09 (1 H, t, *J* = 7.4 Hz, H-1), 7.01 (2 H, d, *J* = 7.4 Hz, H-3), 4.17 (2 H, q, *J* = 7.1 Hz, H-11), 2.02 (3 H, s, H-7 or H-9), 1.85 (3 H, s, H-7 or H-9), 1.30 (3 H, t, *J* = 7.1 Hz, H-12).

Data are consistent with literature values.[151]

Lab-book No PD/9/82.

Ethyl (2*Z*)-2-methyl-3-(phenylamino)prop-2-enoate (**158**)

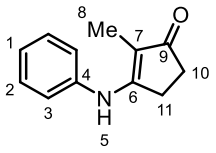


158

To a stirred solution of ethyl 2-methyl-3-oxopropanoate (1.01 g, 7.76 mmol) in EtOH (60 mL) was added aniline (0.547 g, 6.00 mmol). The reaction mixture was stirred at 80 °C for 1 h and allowed to cool to room temperature. EtOH was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 9:1) to give the title compound **158** (0.510 g, 41%) as a colourless oil; R_f 0.28 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3317, 2982, 1731, 1683, 1643, 1600, 1497, 1239, 1109, 750, 691; δ_H (400 MHz; $CDCl_3$) 7.91 (1 H, dd, *J* = 13.3, 1.2 Hz, H-7), 7.31 – 7.21 (2 H, m, H-2), 6.98 – 6.89 (3 H, m, H-1 and H-3), 4.19 (2 H, q, *J* = 7.1 Hz, H-11), 1.84 (3 H, d, *J* = 1.0 Hz, H-9), 1.29 (3 H, t, *J* = 7.1 Hz, H-12); δ_C (100 MHz; $CDCl_3$) 169.3 (C-10), 141.3 (C-4), 137.4 (C-6), 129.7 (C-2), 122.0 (C-1), 115.2 (C-3), 99.5 (C-8), 59.9 (C-11), 14.7 (C-12), 9.9 (C-9); Found (ESI): $[MNa]^+$ 228.0997; $C_{12}H_{15}NNaO_2$ requires $[MNa]^+$ 228.0995, 1.0 ppm.

Lab-book No PD/10/95.

2-Methyl-3-(phenylamino)cyclopent-2-en-1-one (**159**)



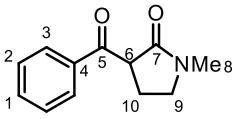
159

To a stirred solution of 2-methyl-1,3-cyclopentanedione (0.507 g, 4.52 mmol) in toluene (50 mL) was added aniline (0.407 mL, 4.46 mmol) and *p*-TSA (0.025 g, 0.131 mmol). The condenser was fitted with a Dean & Stark apparatus and the reaction mixture was heated at 110 °C for 18 h. The reaction mixture was neutralised by addition of solid K_2CO_3, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, CH_2Cl_2/MeOH, 19:1) afforded the title compound **159** (0.754 g, 89%) as a light brown solid; mp. 180-182 °C; R_f 0.36 (CH_2Cl_2/MeOH, 19:1); ν_{max} (cm^{-1}) 3178, 3032, 2925, 1707, 1607, 1593, 1543, 1396, 1276, 1065, 770; δ_H (400 MHz; $CDCl_3$) 7.40 – 7.32 (2 H, m, H-2), 7.18 (1 H, t, *J* = 7.5 Hz, H-1), 7.15 – 7.12 (2 H, m, H-3), 6.68 (1 H, br s, H-5), 2.72 – 2.63 (2 H, m, H-10), 2.45 – 2.34 (2 H, m, H-11), 1.69 (3 H, t, *J* = 1.4 Hz, H-8); δ_C (100 MHz; $CDCl_3$) 203.6 (C-

9), 169.8 (C-6), 138.9 (C-4), 129.5 (C-2), 125.3 (C-1), 123.0 (C-3), 111.5 (C-7), 33.3 (C-11), 26.2 (C-10), 6.8 (C-8); Found (ESI): $[MH]^+$ 188.1069; $C_{12}H_{14}NO$ requires $[MH]^+$ 188.1070, 0.7 ppm.

Lab-book No PD/9/12.

3-Benzoyl-1-methylpyrrolidin-2-one[152]

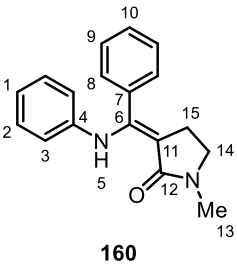


To a stirred solution of *N*-methyl-2-pyrrolidinone (0.500 mL, 5.19 mmol) in THF (40 mL) was added at −78 °C, benzoyl chloride (0.630 mL, 5.44 mmol) and LHMDS (1.0 M in THF, 10.6 mL, 10.6 mmol). The reaction mixture, which immediately turned yellow, was stirred for 1 h at −78 °C. Then, the reaction mixture was quenched by addition of an aq. sol. of HCl (10%, 20 mL) and allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Hexane/EtOAc, 1:1) afforded the title compound (0.980 g, 93%) as a yellow oil; R_f 0.21 (Hexane/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 8.15 – 8.05 (2 H, m, H-3), 7.61 – 7.52 (1 H, m, H-1), 7.49 – 7.43 (2 H, m, H-2), 4.54 – 4.38 (1 H, m, H-6), 3.66 – 3.49 (1 H, m, H-9a or H-10a), 3.42 – 3.34 (1 H, m, H-9a or H-10a), 2.88 – 2.79 (3 H, m, H-8), 2.66 – 2.52 (1 H, m, H-9b or H-10b), 2.32 – 2.14 (1 H, m, H-9b or H-10b).

Data are consistent with literature values.[152]

Lab-book No PD/11/8.

(3*Z*)-1-Methyl-3-[phenyl(phenylamino)methylidene]pyrrolidin-2-one (**160**)



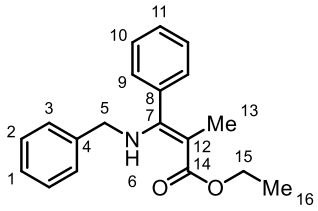
160

3-Benzoyl-1-methylpyrrolidin-2-one (0.508 g, 2.50 mmol), aniline (0.228 mL, 2.50 mmol), and *p*-TSA (0.036 g, 0.189 mmol) in toluene (50 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 3:1) to give

the title compound **160** (0.355 g, 51%) as a yellow solid; mp. 99-101 °C; R_f 0.57 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 3200, 2930, 2871, 1639, 1596, 1494, 1427, 1398, 1281, 1245, 1084, 1073, 751, 701; δ_H (400 MHz; $CDCl_3$) 10.31 (1 H, br s, H-5), 7.38 – 7.27 (5 H, m, H_{Ar}), 7.03 – 6.92 (2 H, m, H-2), 6.74 (1 H, t, *J* = 7.4 Hz, H-1), 6.52 (2 H, d, *J* = 7.6 Hz, H-3), 3.37 – 3.24 (2 H, m, H-14), 2.89 (3 H, s, H-13), 2.69 – 2.54 (2 H, m, H-15); δ_C (100 MHz; $CDCl_3$) 172.1 (C-12), 147.4 (C-6), 142.0 (C-4), 135.9 (C-7), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.63 (CH_{Ar}), 128.58 (CH_{Ar}), 121.0 (C-1), 120.1 (C-3), 101.8 (C-11), 47.2 (C-14), 29.8 (C-13), 23.4 (C-15); Found (ESI): $[MH]^+$ 279.1493; $C_{18}H_{19}N_2O$ requires $[MH]^+$ 279.1492, 0.2 ppm.

Lab-book No PD/9/30.

Ethyl (2*Z*)-3-(benzylamino)-2-methyl-3-phenylprop-2-enoate (**164**)

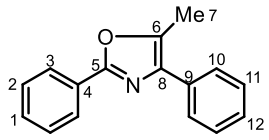


164

To a stirred solution of ethyl 2-methyl-3-oxo-3-phenylpropanoate (**152a**) (0.419 g, 2.03 mmol) in toluene (10 mL) was added benzylamine (0.222 mL, 2.03 mmol) and *p*-TSA (0.042 g, 0.221 mmol). The reaction mixture was stirred at 110 °C overnight with a Dean & Stark apparatus fitted on the reaction condenser. Then, the reaction mixture was allowed to cool to room temperature. Solvent was removed and the residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **164** (0.191 g, 32%) as a colourless oil; R_f 0.42 (Hexane/EtOAc, 8:1); ν_{max} (cm^{-1}) 3266, 2937, 1737, 1686, 1646, 1582, 1450, 1266, 1133, 777, 698; δ_H (400 MHz; $CDCl_3$) 9.40 (1 H, br s, H-6), 7.40 – 7.34 (3 H, m, H_{Ar}), 7.29 – 7.23 (2 H, m, H-2), 7.22 – 7.17 (1 H, m, H-1), 7.16 – 7.06 (4 H, m, H_{Ar}), 4.23 – 4.15 (2 H, m, H-15), 4.01 (2 H, d, *J* = 6.4 Hz, H-5), 1.49 (3 H, s, H-13), 1.30 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 171.6 (C-14), 162.0 (C-7), 140.0 (C-4), 133.6 (C-8), 128.8 (CH_{Ar}), 128.63 (CH_{Ar}), 128.57 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 127.0 (CH_{Ar}), 89.8 (C-12), 59.2 (C-15), 48.5 (C-5), 14.8 (C-16), 14.2 (C-13); Found (ESI): $[MH]^+$ 296.1641; $C_{19}H_{22}NO_2$ requires $[MH]^+$ 296.1645, 1.2 ppm.

Lab-book No PD/10/28.

5-Methyl-2,4-diphenyl-1,3-oxazole (**167**)



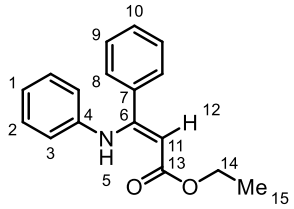
167

To a stirred solution of ethyl (2*Z*)-3-(benzylamino)-2-methyl-3-phenylprop-2-enoate (**164**) (0.044 g, 0.148 mmol) in mesitylene (4 mL) was added Cu(2-ethylhexanoate)$_2$ (0.054 g, 0.154 mmol). The reaction mixture was stirred at 170 °C for 1 h and allowed to cool to room temperature. NH_4OH (5 mL) was added, the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **167** (0.013 g, 37%) as a yellow oil; R_f 0.46 (Hexane/EtOAc, 6:1); δ_H (400 MHz; $CDCl_3$) 8.12 – 8.05 (2 H, m, H_{Ar}), 7.77 – 7.71 (2 H, m, H_{Ar}), 7.50 – 7.40 (5 H, m, H_{Ar}), 7.36 – 7.27 (1 H, m, H_{Ar}), 2.61 (3 H, s, H-7).

Data are consistent with literature values.[72]

Lab-book No PD/10/30.

Ethyl (2*Z*)-3-phenyl-3-(phenylamino)prop-2-enoate[78] (**172a**)



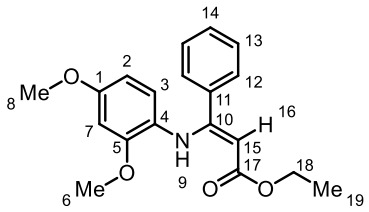
172a

To a solution of ethyl benzoylacetate (0.495 mL, 2.86 mmol) in toluene (15 mL) was added aniline (0.261 mL, 2.86 mmol) and *p*-TSA (0.055 g, 0.290 mmol). The flask was fitted with a Dean & Stark apparatus, and stirred overnight at 110 °C. The reaction mixture was allowed to cool to room temperature. Solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 49:1) to give the title compound **172a** (0.151 g, 20%) as a colourless solid; mp. 52-54 °C (Lit.[153] 67-68 °C); R_f 0.62 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 10.29 (1 H, br s, H-5), 7.36 – 7.26 (5 H, m, H_{Ar}), 7.13 – 7.02 (2 H, m, H-2), 6.90 (1 H, t, *J* = 7.4 Hz, H-1), 6.65 (2 H, *J* = 7.7 Hz, H-3), 4.99 (1 H, s, H-12), 4.20 (2 H, q, *J* = 7.1 Hz, H-14), 1.31 (3 H, t, *J* = 7.1 Hz, H-15).

Data is consistent with literature values.[78, 153]

Lab-book No PD/10/20.

Ethyl (2*Z*)-3-[(2,4-dimethoxyphenyl)amino]-3-phenylprop-2-enoate (**172b**)

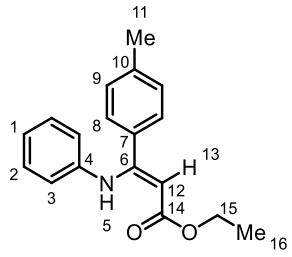


172b

Ethyl benzoylacetate (0.283 g, 1.47 mmol), 2,4-dimethoxyaniline (0.227 g, 1.48 mmol), and *p*-TSA (0.028 g, 0.147 mmol) in toluene (10 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) to give the title compound **172b** (0.091 g, 19%) as a yellow oil; R_f 0.32 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3263, 2976, 2836, 1653, 1609, 1587, 1573, 1516, 1463, 1439, 1418, 1329, 1277, 1207, 1157, 1098, 1037, 911, 794, 774, 699; δ_H (400 MHz; $CDCl_3$) 10.07 (1 H, br s, H-9), 7.32 – 7.22 (5 H, m, H_{Ar}), 6.39 (1 H, d, *J* = 2.7 Hz, H-7), 6.22 (1 H, d, *J* = 8.7 Hz, H-3), 6.06 (1 H, dd, *J* = 8.7, 2.7 Hz, H-2), 4.91 (1 H, s, H-16), 4.19 (2 H, q, *J* = 7.1 Hz, H-18), 3.81 (3 H, s, H-6 or H-8), 3.67 (3 H, s, H-6 or H-8), 1.29 (3 H, t, *J* = 7.1 Hz, H-19); δ_C (100 MHz; $CDCl_3$) 170.3 (C-17), 159.7 (C-10), 156.6 (C-1 or C-5), 152.4 (C-1 or C-5), 136.6 (C-11), 129.2 (C-14), 128.3 (C-12 or C-13), 128.2 (C-12 or C-13), 123.9 (C-3), 123.0 (C-4), 103.3 (C-2), 98.9 (C-7), 89.7 (C-15), 59.2 (C-18), 55.8 (C-6 or C-8), 55.5 (C-6 or C-8), 14.7 (C-19); Found (ESI): $[MNa]^+$ 350.1363; $C_{19}H_{21}NNaO_4$ requires $[MNa]^+$ 350.1363, 0.1 ppm.

Lab-book No PD/11/62.

Ethyl (2*Z*)-3-(4-methylphenyl)-3-(phenylamino)prop-2-enoate (**172c**)

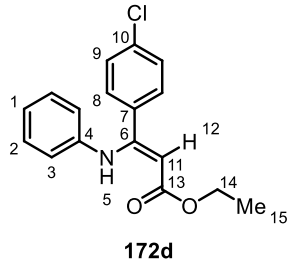


172c

Ethyl 3-(4-methylphenyl)-3-oxopropanoate (0.275 g, 1.33 mmol), aniline (0.122 mL, 1.33 mmol), and *p*-TSA (0.029 g, 0.152 mmol) in toluene (5 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **172c** (0.045 g, 12%) as a colourless oil; R_f 0.70 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3252, 2978, 1655, 1615, 1585, 1596, 1285, 1165, 1102, 1037, 828, 794, 692; δ_H (400 MHz; $CDCl_3$) 10.28 (1 H, br s, H-5), 7.26 – 7.21 (2 H, m, H-8), 7.12 – 7.02 (4 H, m, H-2, and H-9), 6.90 (1 H, t, *J* = 7.4 Hz, H-1), 6.67 (2 H, d, *J* = 7.5 Hz, H-3), 4.98 (1 H, s, H-13), 4.20 (2 H, q, *J* = 7.1 Hz, H-15), 2.32 (3 H, s, H-11), 1.31 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 170.3 (C-14), 159.3 (C-6), 140.7 (C-4), 139.7 (C-10), 133.1 (C-7), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (CH_{Ar}), 122.9 (C-1), 122.3 (C-3), 90.9 (C-13), 59.3 (C-15), 21.4 (C-11), 14.6 (C-16); Found (ESI): $[MH]^+$ 282.1489; $C_{18}H_{20}NO_2$ requires $[MH]^+$ 282.1489, 0.1 ppm.

Lab-book No PD/11/9.

Ethyl (2*Z*)-3-(4-chlorophenyl)-3-(phenylamino)prop-2-enoate (**172d**)



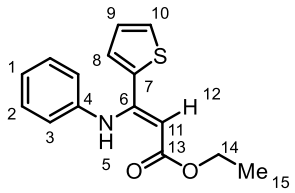
172d

Ethyl 3-(4-chlorophenyl)-3-oxopropanoate (0.188 g, 0.829 mmol), aniline (0.076 mL, 0.829 mmol), and *p*-TSA (0.018 g, 0.096 mmol) in toluene (5 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **172d** (0.039 g, 16%) as a colourless oil; R_f 0.58 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3253, 2979, 1656, 1612, 1597, 1584, 1564, 1500, 1478, 1441, 1362, 1280, 1165, 1090, 1035, 837, 796, 748; δ_H (400 MHz; $CDCl_3$) 10.24 (1 H, br s, H-5), 7.54 – 7.16 (4 H, m, H-8 and H-9), 7.19 – 7.00 (2 H, m, H-2), 6.92 (1 H, t, *J* = 7.4 Hz,

H-1), 6.65 (2 H, d, *J* = 7.5 Hz, H-3), 4.96 (1 H, s, H-12), 4.20 (2 H, q, *J* = 7.2 Hz, H-14), 1.30 (3 H, t, *J* = 7.2 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 170.0 (C-13), 157.8 (C-6), 140.2 (C-4), 135.5 (C-7 or C-10), 134.5 (C-7 or C-10), 129.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 123.3 (C-1), 122.5 (C-3), 91.6 (C-11), 59.5 (C-14), 14.6 (C-15); Found (ESI): $[MNa]^+$ 324.0759; $C_{17}H_{16}ClNNaO_2$ requires $[MNa]^+$ 324.0762, 0.8 ppm.

Lab-book No PD/11/6.

Ethyl (2*Z*)-3-(phenylamino)-3-(thiophen-2-yl)prop-2-enoate (**172e**)

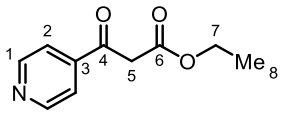


172e

Ethyl 3-oxo-3-(thiophen-2-yl)propanoate (0.257 g, 1.30 mmol), aniline (0.118 mL, 1.30 mmol), and *p*-TSA (0.025 g, 0.131 mmol) in toluene (5 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 19:1) to give the title compound **172e** (0.019 g, 5%) as a colourless oil; R_f 0.48 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3250, 2979, 1735, 1656, 1595, 1498, 1484, 1428, 1364, 1270, 1220, 1167, 1043, 696; δ_H (400 MHz; $CDCl_3$) 10.10 (1 H, br s, H-5), 7.29 (1 H, dd, *J* = 5.0, 1.2 Hz, H-10), 7.18 – 7.11 (2 H, m, H-2), 7.02 (1 H, dd, *J* = 3.7, 1.2 Hz, H-8), 6.98 (1 H, t, *J* = 7.4 Hz, H-1), 6.91 (1 H, dd, *J* = 5.0, 3.7 Hz, H-9), 6.81 (2 H, d, *J* = 7.5 Hz, H-3), 5.18 (1 H, s, H-12), 4.19 (2 H, q, *J* = 7.1 Hz, H-14), 1.30 (3 H, t, *J* = 7.1 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 170.0 (C-13), 152.1 (C-6), 140.7 (C-4), 137.7 (C-7), 128.9 (C-8), 128.8 (C-2), 127.7 (C-10), 127.3 (C-9), 123.7 (C-1), 123.1 (C-3), 91.3 (C-11), 59.5 (C-14), 14.6 (C-15); Found (ESI): $[MH]^+$ 274.0890; $C_{15}H_{16}NO_2S$ requires $[MH]^+$ 274.0896, 2.2 ppm.

Lab-book No PD/11/12.

Ethyl 3-oxo-3-(pyridin-4-yl)propanoate[154]

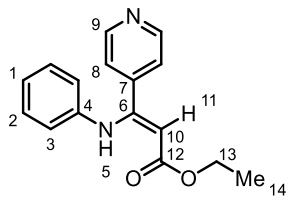


4-Ethyl picolinate (0.750 mL, 5.00 mmol), ethyl acetate (3.43 mL, 35.0 mmol), LHMDS (1 M in THF, 10.0 mL, 10.0 mmol) in THF (10 mL) were subjected to general procedure I. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 1:1) to give the title compound (0.795 g, 82%) as a colourless crystalline solid in a 1:3 keto-enol mixture; mp. 46-48 °C (Lit.[155] 57.5-58 °C); R_f 0.42 (Hexane/EtOAc, 1:2); δ_H (400 MHz; $CDCl_3$, **Keto**) 8.91 – 8.79 (2 H, m, H-1), 7.80 – 7.64 (2 H, m, H-2), 4.21 (2 H, q, *J* = 7.1 Hz, H-7), 3.98 (2 H, s, H-5), 1.25 (3 H, t, *J* = 7.1 Hz, H-8); δ_H (400 MHz; $CDCl_3$, **Enol**) 12.43 (1 H, s, OH), 8.70 (2 H, dd, *J* = 4.7, 1.5 Hz, H-1), 7.60 (2 H, dd, *J* = 4.6, 1.5 Hz, H-2), 5.76 (1 H, s, H-5), 4.28 (2 H, q, *J* = 7.2 Hz, H-7), 1.34 (3 H, t, *J* = 7.2 Hz, H-8).

Data is consistent with literature values.[155]

Lab-book No PD/11/49.

Ethyl (2*Z*)-3-(phenylamino)-3-(pyridin-4-yl)prop-2-enoate (**172f**)



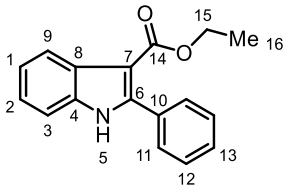
172f

Ethyl 3-oxo-3-(pyridin-4-yl)propanoate (0.234 g, 1.21 mmol), aniline (0.110 mL, 1.21 mmol), and *p*-TSA (0.023 g, 0.121 mmol) in toluene (10 mL) were subjected to general procedure K. The residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 2:1) to give the title compound **172f** (0.115 g, 35%) as a yellow oil; R_f 0.40 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 3260, 2979, 1659, 1615, 1583, 1547, 1501, 1481, 1441, 1408, 1279, 1168, 1034, 834, 795, 748, 693; δ_H (400 MHz; $CDCl_3$) 10.19 (1 H, br s, H-5), 8.53 (2 H, d, *J* = 6.0 Hz, H-9), 7.21 (2 H, d, *J* = 6.0 Hz, H-8), 7.09 (2 H, t, *J* = 7.8 Hz, H-2), 6.94 (1 H, t, *J* = 7.4 Hz, H-1), 6.65 (2 H, d, *J* = 7.9 Hz, H-3), 5.02 (1 H, s, H-11), 4.20 (2 H, q, *J* = 7.1 Hz, H-13), 1.30 (3 H, t, *J* = 7.1 Hz, H-14); δ_C (100 MHz; $CDCl_3$) 169.8 (C-12), 156.1 (C-6), 150.2 (C-9), 144.0 (C-7), 139.7 (C-4), 128.9 (C-2), 123.7 (C-1), 122.6 (C-3 or C-8), 122.5 (C-3 or C-8), 92.7 (C-10), 59.7 (C-13), 14.5 (C-14); Found (ESI): $[MH]^+$ 269.1288; $C_{16}H_{17}N_2O_2$ requires $[MH]^+$ 269.1285, 1.4 ppm.

Lab-book No PD/11/51.

6.3.7 General procedure M: Cu(II)-mediated cyclisation to 1*H*-indoles

Ethyl 2-phenyl-1*H*-indole-3-carboxylate (**173a**)



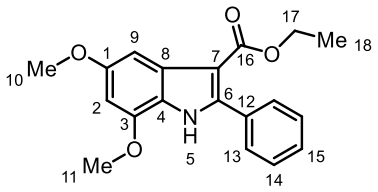
173a

To a stirred solution of ethyl (2*Z*)-3-phenyl-3-(phenylamino)prop-2-enoate (**172a**) (0.016 g, 0.059 mmol) in mesitylene (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.012 g, 0.058 mmol). The reaction mixture was stirred at 170 °C for 2 h and allowed to cool to room temperature. NH_4OH (5 mL) was added and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, Hexane/EtOAc, 8:1) and afforded the title compound **173a** (0.011 g, 69%) as a colourless solid; mp. 134-136 °C (Lit.[156] 150-152 °C); R_f 0.26 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 8.50 (1 H, br s, H-5), 8.39 – 8.09 (1 H, m, H_{Ar}), 7.78 – 7.57 (2 H, m, H_{Ar}), 7.47 – 7.43 (3 H, m, H_{Ar}), 7.41 – 7.36 (1 H, m, H_{Ar}), 7.29 – 7.25 (2 H, m, H_{Ar}), 4.30 (2 H, q, J = 7.1 Hz, H-15), 1.31 (3 H, t, J = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 165.4 (C-14), 144.5 (C_{Ar}), 135.2 (C_{Ar}), 132.2 (C_{Ar}), 129.7 (CH_{Ar}), 129.3 (CH_{Ar}), 128.2 (CH_{Ar}), 127.7 (C_{Ar}), 123.3 (CH_{Ar}), 122.3 (CH_{Ar}), 122.2 (CH_{Ar}), 111.0 (CH_{Ar}), 104.9 (C-7), 59.8 (C-15), 14.4 (C-16).

Data are consistent with literature values.[78, 155]

Lab-book No PD/11/7.

Ethyl 5,7-dimethoxy-2-phenyl-1*H*-indole-3-carboxylate (**173b**)

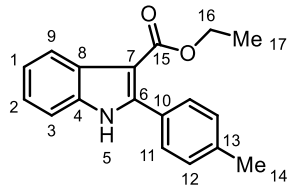


173b

Ethyl (2*Z*)-3-[(2,4-dimethoxyphenyl)amino]-3-phenylprop-2-enoate (**172b**) (0.061 g, 0.185 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.037 g, 0.185 mmol) in mesitylene (2 mL) were subjected to general procedure M at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 8:1) afforded the title compound **173b** (0.020 g, 34%) as a yellow oil; R_f 0.42 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 3276, 2938, 2836, 1683, 1595, 1528, 1485, 1454, 1420, 1291, 1202, 1155, 1044, 829, 697; δ_H (400 MHz; $CDCl_3$) 8.56 (1 H, br s, H-5), 7.65 – 7.62 (2 H, m, H_{Ar}), 7.45 – 7.41 (3 H, m, H_{Ar}), 7.29 (1 H, d, *J* = 2.1 Hz, H-9), 6.39 (1 H, d, *J* = 2.1 Hz, H-2), 4.28 (2 H, q, *J* = 7.1 Hz, H-17), 3.91 (3 H, s, H-10 or H-11), 3.89 (3 H, s, H-10 or H-11), 1.27 (3 H, t, *J* = 7.1 Hz, H-18); δ_C (100 MHz; $CDCl_3$) 165.6 (C-16), 156.8 (C-1 or C-3), 146.3 (C-1 or C-3), 143.8 (C-6 or C-12), 132.4 (C-6 or C-12), 129.7 (C-13 or C-14), 129.2 (C-15), 128.2 (C-13 or C-14), 127.1 (C-8), 121.1 (C-4), 105.1 (C-7), 95.4 (C-2 or C-9), 95.1 (C-2 or C-9), 59.7 (C-17), 55.9 (C-10 or C-11), 55.6 (C-10 or C-11), 14.4 (C-18); Found (ESI): $[MNa]^+$ 348.1209; $C_{19}H_{19}NNaO_4$ requires $[MNa]^+$ 348.1206, 0.9 ppm.

Lab-book No PD/11/64.

Ethyl 2-(4-methylphenyl)-1*H*-indole-3-carboxylate (**173c**)



173c

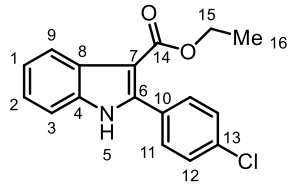
Ethyl (2*Z*)-3-(4-methylphenyl)-3-(phenylamino)prop-2-enoate (**172c**) (0.039 g, 0.138 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.036 g, 0.142 mmol) in mesitylene (2 mL) were subjected to general procedure M at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 9:1) afforded the title compound **173c** (0.019 g, 50%) as a colourless solid; mp. 144-146 °C (Lit.[156] 165-167 °C); R_f 0.30 (Hexane/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 8.53 (1 H, br s, H-5), 8.28 – 8.12 (1 H, m, H_{Ar}), 7.54 (2 H, d, *J* = 8.1 Hz, H_{Ar}), 7.37 – 7.34 (1 H, m, H_{Ar}), 7.27 – 7.22 (4 H, m, H_{Ar}), 4.30 (2 H, q, *J* = 7.1 Hz, H-16), 2.39 (3 H, s, H-14), 1.33 (3 H, t, *J* = 7.1 Hz, H-17); δ_C (100 MHz; $CDCl_3$) 165.5 (C-15), 144.8 (C-6), 139.4 (C-

13), 135.1 (C_{Ar}), 129.5 (C-11 or C-12), 129.1 (C_{Ar}), 128.9 (C-11 or C-12), 127.8 (C_{Ar}), 123.1 (CH_{Ar}), 122.2 (CH_{Ar}), 122.1 (CH_{Ar}), 111.0 (CH_{Ar}), 104.6 (C-7), 59.8 (C-16), 21.5 (C-14), 14.5 (C-17). Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 76.96; H, 6.20; N, 4.81.

Data are consistent with literature values.[156]

Lab-book No PD/11/39.

Ethyl 2-(4-chlorophenyl)-1*H*-indole-3-carboxylate (**173d**)

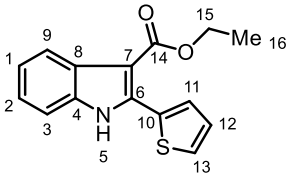


173d

Ethyl (2*Z*)-3-(4-chlorophenyl)-3-(phenylamino)prop-2-enoate (**172d**) (0.033 g, 0.109 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.028 g, 0.110 mmol) in mesitylene (2 mL) were subjected to general procedure M at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 9:1) afforded the title compound **173d** (0.015 g, 47%) as a colourless solid; mp. 135-137 °C; R_f 0.35 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3281, 2980, 1667, 1484, 1439, 1278, 1213, 1128, 1091, 1045, 1015, 841, 830, 790, 726, 753; δ_H (400 MHz; $CDCl_3$) 8.56 (1 H, br s, H-5), 8.25 – 8.11 (1 H, m, H_{Ar}), 7.62 – 7.56 (2 H, m, H-11 or H-12), 7.43 – 7.39 (2 H, m, H-11 or H-12), 7.39 – 7.34 (1 H, m, H_{Ar}), 7.31 – 7.26 (2 H, m, H_{Ar}), 4.31 (2 H, q, *J* = 7.1 Hz, H-15), 1.33 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 165.3 (C-14), 143.2 (C_{Ar}), 135.5 (C_{Ar}), 135.3 (C_{Ar}), 131.1 (C-11 or C-12), 130.5 (C_{Ar}), 128.6 (C-11 or C-12), 127.6 (C_{Ar}), 123.6 (CH_{Ar}), 122.42 (CH_{Ar}), 122.41 (CH_{Ar}), 111.1 (CH_{Ar}), 105.3 (C-7), 60.0 (C-15), 14.5 (C-16); Found (ESI): $[MNa]^+$ 322.0596; $C_{17}H_{14}ClNNaO_2$ requires $[MNa]^+$ 322.0605, 2.8 ppm.

Lab-book No PD/11/37.

Ethyl 2-(thiophen-2-yl)-1*H*-indole-3-carboxylate (**173e**)

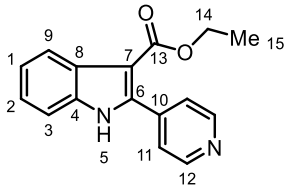


173e

Ethyl (2*Z*)-3-(phenylamino)-3-(thiophen-2-yl)prop-2-enoate (**172e**) (0.014 g, 0.050 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.013 g, 0.050 mmol) in mesitylene (2 mL) were subjected to general procedure M at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 8:1) afforded the title compound **173e** (0.009 g, 63%) as a yellow oil; R_f 0.30 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 3292, 2936, 1668, 1490, 1455, 1439, 1419, 1341, 1274, 1203, 1121, 1110, 854, 788, 752, 703; δ_H (400 MHz; $CDCl_3$) 8.57 (1 H, br s, H-5), 8.25 – 8.15 (1 H, m, H_{Ar}), 7.73 (1 H, dd, *J* = 3.8, 1.3 Hz, H-11), 7.48 (1 H, dd, *J* = 5.2, 1.3 Hz, H-13), 7.38 (1 H, dd, *J* = 6.2, 2.9 Hz, H_{Ar}), 7.29 – 7.26 (2 H, m, H_{Ar}), 7.15 (1 H, dd, *J* = 5.2, 3.8 Hz, H-12), 4.42 (2 H, q, *J* = 7.1 Hz, H-15), 1.44 (3 H, t, *J* = 7.1 Hz, H-16); δ_C (100 MHz; $CDCl_3$) 165.4 (C-14), 137.3 (C_{Ar}), 135.2 (C_{Ar}), 132.7 (C_{Ar}), 129.6 (C-11), 128.1 (C-13), 127.8 (C_{Ar}), 127.6 (C-12), 123.8 (CH_{Ar}), 122.5 (CH_{Ar}), 122.4 (CH_{Ar}), 111.0 (CH_{Ar}), 105.2 (C-7), 60.2 (C-15), 14.7 (C-16); Found (ESI): $[MH]^+$ 272.0731; $C_{15}H_{14}NO_2S$ requires $[MH]^+$ 272.0740, 3.2 ppm.

Lab-book No PD/11/53.

Ethyl 2-(pyridin-4-yl)-1*H*-indole-3-carboxylate (**173f**)



173f

Ethyl (2*Z*)-3-(phenylamino)-3-(pyridin-4-yl)prop-2-enoate (**172f**) (0.049 g, 0.181 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.045 g, 0.181 mmol) in mesitylene (2 mL) were subjected to general procedure M at 170 °C for 2 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 1:2) afforded the title compound **173f** (0.027 g, 56%) as an orange solid; mp. 181-183 °C; R_f 0.08 (Hexane/EtOAc, 1:1); ν_{max} (cm^{-1}) 3273, 2978, 2928, 1697, 1605, 1490, 1444, 1332, 1276, 1211, 1131, 1048, 788, 753; δ_H (400 MHz; $CDCl_3$) 10.12 (1 H, br s, H-5), 8.63 (2 H, br s, H-12), 8.23 (1 H, dd, *J* = 6.4, 2.9 Hz, H_{Ar}), 7.61 (2 H, d, *J* = 3.3 Hz, H-11), 7.47 – 7.42 (1 H, m, H_{Ar}), 7.32 – 7.28 (2 H, m, H_{Ar}), 4.34 (2 H, q, *J* = 7.1 Hz, H-14), 1.35 (3 H, t, *J* = 7.1 Hz, H-15); δ_C (100 MHz; $CDCl_3$) 165.2 (C-13), 149.3 (C_{Ar}), 140.9 (C_{Ar}),

135.94 (C_{Ar}), 135.93 (C_{Ar}), 129.3 (CH_{Ar}), 127.4 (CH_{Ar}), 124.1 (CH_{Ar}), 122.54 (CH_{Ar}), 122.53 (CH_{Ar}), 111.6 (CH_{Ar}), 106.2 (C-7), 60.2 (C-14), 14.4 (C-15); Found (ESI): $[MH]^+$ 267.1131; $C_{16}H_{15}N_2O_2$ requires $[MH]^+$ 267.1128, 1.2 ppm; Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 71.85; H, 5.58; N, 10.10.

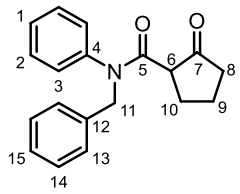
Lab-book No PD/11/54.

6.4 Studies towards the total synthesis of rankinidine

6.4.1 Model studies for spirocyclic oxindole formation

6.4.1.1 General procedure N: One-step MMC/amide coupling route

N-Benzyl-2-oxo-*N*-phenylcyclopentane-1-carboxamide (**102d**)



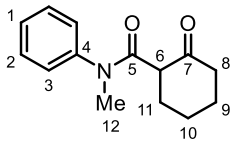
102d

Cyclopentanone (0.290 g, 2.26 mmol) was added to a solution of methyl magnesium carbonate (2.0 M in DMF, 9.04 mL, 18.1 mmol). The reaction mixture was stirred for 6 h at 130 °C. The reaction was allowed to cool to room temperature and an aq. sol. of HCl (10%, 10 mL) was added slowly until the pH media became acidic. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (4 × 10 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of mono- and bis-acids. To a stirred solution of the crude acid mixture in CH_2Cl_2 (17 mL) was added *N*-benzylaniline (0.154 mL, 0.831 mmol), 2-chloro-1-methylpyridinium iodide (0.255 g, 0.997 mmol) and Et_3N (0.462 mL, 3.32 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. HCl (10% solution in water, 10 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of mono- and bis-anilides. Purification by column chromatography (SiO_2, Hexane/EtOAc, 4:1) afforded the title compound **102d** (0.043 g, 15%) as a colourless solid; mp. 97-99 °C; R_f 0.27 (Hexane/EtOAc, 1:2); ν_{max} (cm^{-1}) 2966, 1739, 1644, 1595, 1495, 1405, 700; δ_H (400 MHz; $CDCl_3$) 7.32 – 7.27 (3 H, m, H_{Ar}), 7.27 – 7.23 (3 H, m, H_{Ar}), 7.23 – 7.18 (2 H, m, H_{Ar}), 7.13 (2 H, br s, H_{Ar}), 5.01 (1 H, d, *J* = 14.4 Hz, H-11a), 4.82 (1 H, d, *J* = 14.4 Hz, H-11b), 3.08 (1 H, dd, *J* = 10.2, 9.2 Hz, H-6), 2.48 – 2.36 (1 H, m, H-10a), 2.35 – 2.16 (2 H, m, H-8a, H-9a), 2.14 – 2.03 (2 H, m, H-8b, H-10b), 1.77 – 1.58 (1 H, m, H-9b); δ_C (100 MHz; $CDCl_3$) 214.8 (C-7), 170.1 (C-5), 142.1 (C_{Ar}), 137.1 (C_{Ar}), 129.6 (CH_{Ar}), 128.7 (2 × CH_{Ar}), 128.5

(CH_{Ar}), 128.3 (CH_{Ar}), 127.4 (CH_{Ar}), 53.3 (C-11), 52.9 (C-6), 38.6 (C-8), 28.4 (C-10), 21.1 (C-9); Found (ESI): $[MNa]^+$ 316.1297; $C_{19}H_{19}NNaO_2$ requires $[MNa]^+$ 316.1308, 3.4 ppm.

Lab-book No PD/9/22.

N-Methyl-2-oxo-*N*-phenylcyclohexane-1-carboximide (**102a**)

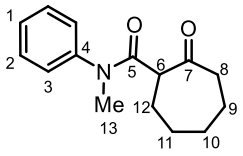


102a

Cyclohexanone (0.210 mL, 2.04 mmol) and methyl magnesium carbonate (2.0 M in DMF, 8.15 mL, 16.3 mmol) were subjected to general procedure N. The mixture of crude mono- and bis-acids was subsequently treated with *N*-methylaniline (0.254 mL, 2.34 mmol), 2-chloro-1-methylpyridinium iodide (0.720 g, 2.82 mmol) and Et_3N (1.31 mL, 9.38 mmol) following general procedure N. Purification by column chromatography (SiO_2, Hexane/EtOAc, 3:1 to Hexane/EtOAc, 1:4) afforded the monoanilide product **102a** (0.065 g, 30%) as a yellow oil; R_f 0.52 (Hexane/EtOAc, 1:4); ν_{max} (cm^{-1}) 2941, 2865, 1710, 1652, 1595, 1495, 1450, 1421, 1382, 1126, 775, 702; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.35 (2 H, m, H-2), 7.34 – 7.31 (1 H, m, H-1), 7.15 (2 H, dd, *J* = 8.2, 1.3 Hz, H-3), 3.28 (3 H, s, H-12), 3.21 (1 H, dd, *J* = 11.7, 5.9 Hz, H-6), 2.44 – 2.37 (1 H, m, H-8a), 2.16 (1 H, ddd, *J* = 15.4, 12.9, 3.6 Hz, H-11a), 2.04 – 1.94 (2 H, m, H-8b, H-11b), 1.94 – 1.83 (2 H, m, H-9a, H-10a), 1.78 – 1.64 (1 H, m, H-9b), 1.51 – 1.37 (1 H, m, H-10b); δ_C (100 MHz; $CDCl_3$) 207.5 (C-7), 169.7 (C-5), 143.8 (C-4), 129.9 (C-2), 128.2 (C-1), 127.3 (C-3), 55.3 (C-6), 41.7 (C-8), 37.5 (C-12), 30.5 (C-11), 26.9 (C-9), 23.8 (C-10); Found (ESI): $[MNa]^+$ 254.1149; $C_{14}H_{17}NNaO_2$ requires $[MNa]^+$ 254.1151, 0.8 ppm.

Lab-book No PD/9/20/2a.

N-Methyl-2-oxo-*N*-phenylcycloheptane-1-carboxamide (**102c**)



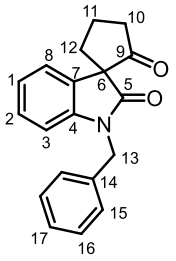
102c

Cycloheptanone (0.190 g, 1.70 mmol) and methyl magnesium carbonate (2.0 M in DMF, 6.80 mL, 13.6 mmol) were subjected to general procedure N. The mixture of crude mono- and bis-acids was subsequently treated with *N*-methylaniline (0.240 mL, 2.19 mmol), 2-chloro-1-methylpyridinium iodide (0.668 g, 2.62 mmol) and Et_3N (1.22 mL, 8.75 mmol) following general procedure N. Purification by column chromatography (SiO_2, Hexane/EtOAc, 6:1) gave the title compound **102c** (0.073 g, 34%) as a colourless oil; R_f 0.23 (Hexane/EtOAc, 6:1); ν_{max} (cm^{-1}) 2884, 1678, 1624, 1570, 1472, 1359, 1097; δ_H (400 MHz; $CDCl_3$) 7.45 – 7.29 (3 H, m, H-1, H-2), 7.22 – 7.16 (2 H, m, H-3), 3.45 (1 H, dd, *J* = 10.6, 3.9 Hz, H-6), 3.25 (3 H, s, H-13), 2.55 (1 H, ddd, *J* = 14.6, 11.6, 3.3 Hz, H-8a), 2.14 – 2.04 (1 H, m, H-8b), 2.02 – 1.92 (1 H, m, H-11a), 1.92 – 1.81 (2 H, m, H-12), 1.80 – 1.71 (2 H, m, H-9a, H-10a), 1.40 – 1.03 (3 H, m, H-9b, H-10b, H-11b); δ_C (100 MHz; $CDCl_3$) 210.9 (C-7), 170.6 (C-5), 143.6 (C-4), 129.9 (C-2), 128.2 (C-1), 128.0 (C-3), 56.6 (C-6), 43.3 (C-8), 37.6 (C-13), 29.6 (C-10), 28.6 (C-12), 28.4 (C-11), 24.6 (C-9); Found (ESI): $[MH]^+$ 246.1497; $C_{15}H_{20}NO_2$ requires $[MH]^+$ 246.1489, 3.2 ppm.

Lab-book No PD/9/25.

6.4.1.2 General procedure O: Copper(II)-mediated cyclisation to spirocyclic oxindoles

1'-Benzyl-1',2'-dihydrospiro[cyclopentane-1,3'-indole]-2',5-dione (**212**)



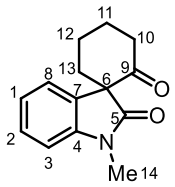
212

To a stirred solution of *N*-benzyl-2-oxo-*N*-phenylcyclopentane-1-carboxamide (**102d**) (0.011 g, 0.039 mmol) in toluene (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.010 g, 0.052 mmol).

The reaction was stirred and heated at 110 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature. NH_4OH (10 mL) was added, the aqueous phase was extracted twice with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, Hexane/EtOAc, 6:1) to give the title compound **212** (0.006 g, 56%) as a colourless oil; R_f 0.19 (Hexane/EtOAc, 4:1); ν_{max} (cm^{-1}) 2969, 1747, 1702, 1611, 1489, 1466, 1360, 1183, 1107, 754, 697; δ_H (400 MHz; $CDCl_3$) 7.34 – 7.24 (5 H, m, H_{Ar}), 7.16 (1 H, td, *J* = 7.7, 1.3 Hz, H-2), 7.09 (1 H, dd, *J* = 7.2, 1.2 Hz, H-8), 7.00 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.69 (1 H, d, *J* = 7.9 Hz, H-3), 5.00 (1 H, d, *J* = 15.8 Hz, H-13a), 4.80 (1 H, d, *J* = 15.8 Hz, H-13b), 2.79 – 2.70 (1 H, m, CH_2), 2.70 – 2.61 (1 H, m, CH_2), 2.60 – 2.48 (2 H, m, CH_2), 2.46 – 2.37 (1 H, m, CH_2), 2.32 – 2.19 (1 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 212.7 (C-9), 175.4 (C-5), 143.5 (C-4), 135.4 (C-14), 130.5 (C-7), 128.9 (CH_{Ar}), 128.7 (C-2), 127.7 (CH_{Ar}), 127.1 (CH_{Ar}), 123.0 (C-1), 122.6 (C-8), 109.6 (C-3), 63.1 (C-6), 43.9 (C-13), 38.4 (CH_2), 34.2 (CH_2), 20.4 (CH_2); Found (ESI): $[MNa]^+$ 314.1154; $C_{19}H_{17}NNaO_2$ requires $[MNa]^+$ 314.1151, 0.8 ppm.

Lab-book No PD/11/11.

1’-Methyl-1’-2’-dihydrospiro[cyclohexane-1,3’-indole]-2’,6-dione (**213**)



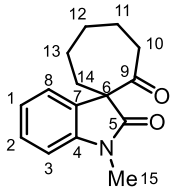
213

N-Methyl-2-oxo-*N*-phenylcyclohexane-1-carboximide (**102a**) (0.016 g, 0.068 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.014 g, 0.071 mmol) in toluene (2 mL) were subjected to general procedure O at 110 °C for 3 h. The residue was purified by flash chromatography (SiO_2, Hexane/EtOAc, 6:1) to give the title compound **213** (0.010 g, 65%) as a colourless oil; R_f 0.38 (Hexane/EtOAc, 2:1); ν_{max} (cm^{-1}) 2940, 2867, 1730, 1697, 1613, 1494, 1471, 1373, 1348, 1127, 754; δ_H (400 MHz; $CDCl_3$) 7.30 (1 H, td, *J* = 7.6, 1.1 Hz, H-2), 7.28 (1 H, d, *J* = 7.3 Hz, H-8), 7.09 (1 H, td, *J* = 7.5, 0.9 Hz, H-1), 6.83 (1 H, d, *J* = 7.8 Hz, H-3), 3.19 (3 H, s, H-14), 3.05 (1 H, ddd, *J* = 14.2, 10.5, 5.5 Hz, CH_2), 2.58 (1 H, dt, *J* = 14.2, 5.5 Hz, CH_2), 2.41 (1 H, dtt, *J* = 14.2, 10.5, 4.0 Hz, CH_2), 2.27 – 2.13 (2 H, m, CH_2), 2.08 (1 H, ddd, *J* = 14.2, 10.5, 4.0 Hz, CH_2), 2.03 – 1.92 (1 H, m, CH_2), 1.90 – 1.81 (1 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 205.4 (C-9), 174.4 (C-5), 143.3 (C-4), 129.5 (C-7), 128.8 (C-2), 124.7 (C-8),

122.8 (C-1), 108.5 (C-3), 63.8 (C-6), 39.9 (CH_2), 37.4 (CH_2), 27.0 (CH_2), 26.6 (C-14), 20.4 (CH_2); Found (ESI): $[MNa]^+$ 252.0998; $C_{14}H_{15}NNaO_2$ requires $[MNa]^+$ 252.0995, 1.1 ppm.

Lab-book No PD/11/10.

1'-Methyl-1',2'-dihydrospiro[cycloheptane-1,3'-indole]-2',7-dione (**214**)



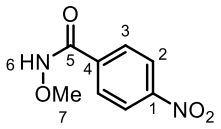
214

N-Methyl-2-oxo-*N*-phenylcycloheptane-1-carboxamide (**102c**) (0.037 g, 0.152 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.030 g, 0.152 mmol) in toluene (4 mL) were subjected to general procedure O at 110 °C for 1.5 h. Purification by column chromatography (SiO_2, Hexane/EtOAc, 4:1) gave the title compound **214** (0.024 g, 66%) as a colourless oil; R_f 0.34 (Hexane/EtOAc, 3:1); ν_{max} (cm^{-1}) 2889, 1703, 1668, 1585, 1471, 1447, 1352, 1325; δ_H (400 MHz; $CDCl_3$) 7.29 (1 H, td, *J* = 7.7, 1.2 Hz, H-2), 7.25 (1 H, ddd, *J* = 7.7, 1.2, 0.5 Hz, H-8), 7.06 (1 H, td, *J* = 7.7, 1.2 Hz, H-1), 6.83 (1 H, d, *J* = 7.7 Hz, H-3), 3.19 (3 H, s, H-15), 3.09–3.01 (1 H, m, H-10a), 2.78–2.67 (1 H, m, H-10b), 2.31 (1 H, dd, *J* = 14.8, 9.1 Hz, H-14a), 2.17 – 2.09 (1 H, m, H-12a), 2.07 – 1.95 (1 H, m, H-14b), 1.94 – 1.84 (1 H, m, H-11a), 1.84 – 1.73 (4 H, m, H-13, H-12b, H-11b); δ_C (100 MHz; $CDCl_3$) 207.6 (C-9), 175.3 (C-5), 143.5 (C-4), 130.8 (C-7), 128.7 (C-2), 123.6 (C-8), 122.7 (C-1), 108.6 (C-3), 65.6 (C-6), 42.3 (C-10), 34.8 (C-14), 30.9 (C-13), 26.8 (C-11), 26.5 (C-15), 25.4 (C-12); Found (ESI): $[MH]^+$ 244.1334; $C_{15}H_{18}NO_2$ requires $[MH]^+$ 244.1332, 0.8 ppm.

Lab-book No PD/4/7.

6.4.2 Studies towards the formation of the *N*-methoxyoxindole scaffold

N-Methoxy-4-nitrobenzamide[157] (**225**)



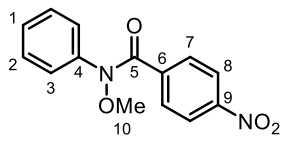
225

To a stirred solution of methoxylamine hydrochloride (0.232 g, 2.78 mmol) in a mixture of water:toluene (1:1, 20 mL) was added $KHCO_3$ (0.470 g, 2.53 mmol). The reaction was cooled to 0 °C and 4-nitrobenzoyl chloride (0.698 g, 5.06 mmol) was added. The reaction mixture was stirred for 1 h, then allowed to warm to room temperature. The solution was stirred for 18 h at room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound **225** (0.288 g, 53%) as a colourless powder; mp. 165-167 °C (Lit.[157] 176–177 °C); R_f 0.21 (Petrol/EtOAc, 1:1); δ_H (400 MHz, DMSO-d_6) 12.06 (1 H, s, H-6), 8.28 (2 H, d, J = 8.9 Hz, H-2), 7.95 (2 H, d, J = 8.9 Hz, H-3), 3.71 (3 H, s, H-7).

Analytical data are consistent with literature values.[157]

Lab-book No PD/4/97.

N-Methoxy-4-nitro-*N*-phenylbenzamide[105] (**226**)



226

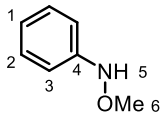
A Schlenk tube was charged with hydroxamate **225** (0.400 g, 2.04 mmol), Cu_2O (0.031 g, 0.214 mmol), K_2CO_3 (0.563 g, 4.08 mmol) and flushed with argon. Then, iodobenzene (0.343 mL, 3.06 mmol), DMEDA (0.040 mL, 0.372 mmol) and toluene (15 mL) were added. The reaction mixture was stirred at 80 °C overnight and allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (10 mL). A sat. aq. solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and water (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 4:1) to give the title compound **226** (0.218

g, 40%) as a yellow oil; R_f 0.63 (Petrol/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 8.23 (2 H, d, *J* = 8.7 Hz, H-8), 7.69 (2 H, d, *J* = 8.7 Hz, H-7), 7.41 (1 H, t, *J* = 7.8 Hz, H-1), 7.35 – 7.29 (2 H, m, H-3), 7.10 (2 H, t, *J* = 7.8 Hz, H-2), 3.66 (3 H, br s, H-10).

Analytical data are consistent with literature values.[105]

Lab-book No PD/4/99.

O-Methyl-*N*-phenylhydroxylamine[105] (**223**)



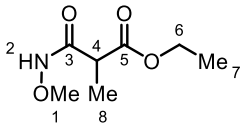
223

The *N*-methoxyanilide **226** (0.086 g, 0.316 mmol) was treated with hydrazine hydrate (0.223 mL, 4.59 mmol) in THF (9 mL). The reaction mixture was stirred at room temperature until the reaction was complete. *n*-Hexane (9 mL) was added and the solution concentrated using a steam of nitrogen. Solid by-products were removed by filtration, washed with Et_2O (9 mL) and concentrated *in vacuo* to give **223** (0.016 g, 41%) as a yellow oil. The product was sufficiently pure to use in the next step without purification; R_f 0.65 (Petrol/EtOAc, 3:1); δ_H (400 MHz; $CDCl_3$) δ 7.32 – 7.23 (2 H, m, H_{Ar}), 7.03 (1 H, br s, H-5), 6.99 – 6.90 (3 H, m, H_{Ar}), 3.77 (3 H, s, H-6).

Analytical data are consistent with literature values.[105]

Lab-book No PD/5/3.

Ethyl 3-(methoxyamino)-2-methyl-3-oxopropanoate (**228**)



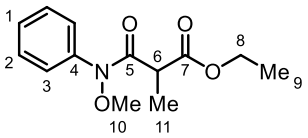
228

To a stirred solution of 3-ethoxy-2-methyl-3-oxopropanoic acid (**109**) (1.11 g, 7.55 mmol) in CH_2Cl_2 (20 mL) was added oxalyl chloride (0.99 mL, 11.3 mmol) and a drop of DMF at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and allowed to warm to room temperature. The solvent was removed *in vacuo* and the crude acid chloride **230** was used in the next step without further purification. Acid chloride **230** was dissolved in CH_2Cl_2 (30

mL) and added at 0 °C, *via* a syringe pump (10 mL/h), to a stirred solution of Et_3N (3.55 mL, 25.5 mmol) and methoxylamine (1.41 g, 16.9 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 °C for a further 10 min and then quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated, and the aqueous was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with water (2 × 40 mL) and brine (2 × 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 1:1) to give the title compound **228** (0.512 g, 51%) as a colourless oil; R_f 0.21 (Petrol/EtOAc, 1:1); ν_{max} (cm^{-1}) 3202, 1662, 1739, 1455, 1187, 1092, 1033, 932; δ_H (400 MHz; $CDCl_3$) 9.27 (1 H, br s, H-2), 4.18 (1 H, q, *J* = 7.1, H-6a), 4.18 (1 H, q, *J* = 7.1, H-6b), 3.76 (3 H, br s, H-1), 3.24 (1 H, q, *J* = 7.0 Hz, H-4), 1.44 (3 H, d, *J* = 7.0 Hz, H-8), 1.26 (3 H, t, *J* = 7.1, H-7); δ_C (100 MHz; $CDCl_3$) 172.2 (C-5), 170.6 (C-3), 64.4 (C-1), 61.9 (C-6), 45.0 (C-4), 15.5 (C-8), 14.1 (C-7); Found (ESI): $[MNa]^+$ 198.0732; $C_7H_{13}NNaO_4$ requires $[MNa]^+$ 198.0737, 2.3 ppm.

Lab-book No PD/5/32.

Ethyl 3-(methoxy(phenyl)amino)-2-methyl-3-oxopropanoate (**222**)

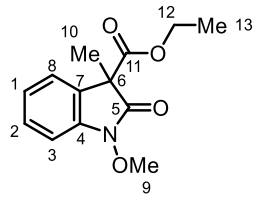


222

To a stirred solution of hydroxamate **228** (0.144 g, 0.819 mmol) in toluene (5 mL) was added Cu_2O (0.020 g, 0.137 mmol), *N,N'*-dimethylethylenediamine (0.021 mL, 0.200 mmol), iodobenzene (0.076 mL, 0.675 mmol) and K_2CO_3 (0.234 g, 1.70 mmol). The reaction mixture was heated at 80 °C and held for 16 h. The resulting brown suspension was filtered through Celite®, washed with EtOAc (10 mL), and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, Petrol/EtOAc, 8:1) to give the title compound **222** (0.068 g, 33%) as a colourless oil; R_f 0.42 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1711, 1660, 1569, 1467, 1433, 1343, 1292, 1254, 1190, 1161, 1062, 1044, 1016, 746, 683; δ_H (400 MHz; $CDCl_3$) 7.47 (2 H, d, *J* = 7.8 Hz, H-3), 7.40 (2 H, t, *J* = 7.8 Hz, H-2), 7.27 – 7.23 (1 H, m, H-1), 4.30 – 4.10 (2 H, m, H-8), 3.85 (1 H, br s, H-6), 3.69 (3 H, s, H-10), 1.46 (3 H, d, *J* = 7.0 Hz, H-11), 1.27 (3 H, t, *J* = 7.1 Hz, H-9); δ_C (100 MHz; $CDCl_3$) 172.2 (C-7), 170.8 (C-5), 137.9 (C-4), 129.0 (C-2), 126.8 (C-1), 123.1 (C-3), 61.9 (C-10), 61.3 (C-8), 44.7 (C-6), 14.3 (C-11), 13.6 (C-9); Found (ESI): $[MNa]^+$ 274.1044; $C_{13}H_{17}NNaO_4$ requires $[MNa]^+$ 274.1050, 2.1 ppm.

Lab-book No PD/5/31.

Ethyl 1-methoxy-3-methyl-2-oxoindoline-3-carboxylate (**221**)

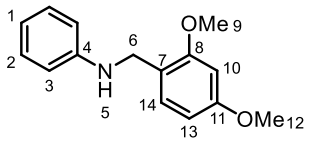


221

To a stirred solution of ethyl 3-(methoxy(phenyl)amino)-2-methyl-3-oxopropanoate (**222**) (0.024 g, 0.097 mmol) in toluene (5 mL) was added Cu(2-ethylhexanoate)$_2$ (0.068 g, 0.194 mmol) and Hünig's base (0.084 mL, 0.485 mmol). The reaction mixture was stirred at 110 °C for 2 h, and allowed to cool to room temperature. NH_4OH (5 mL) was added and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (2 × 5 mL), brine (2 × 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, Petrol/EtOAc, 8:1) to give the title compound **221** (0.004 g, 17%) as a colourless oil; R_f 0.64 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1746, 1733, 1615, 1466, 1324, 1240, 1112, 1039, 751; δ_H (400 MHz; $CDCl_3$) 7.34 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.25 (1 H, ddd, *J* = 7.6, 1.2, 0.6 Hz, H-8), 7.09 (1 H, td, *J* = 7.6, 1.2 Hz, H-1), 7.01 (1 H, dd, *J* = 7.6, 1.2 Hz, H-3), 4.17 (1 H, dq, *J* = 10.8, 7.1 Hz, H-12a), 4.08 (1 H, dq, *J* = 10.8, 7.1 Hz, H-12b), 4.04 (3 H, s, H-9), 1.68 (3 H, s, H-10), 1.15 (3 H, t, *J* = 7.1 Hz, H-13); Found (ESI): $[MH]^+$ 250.1073; $C_{13}H_{16}NO_4$ requires $[MH]^+$ 250.1074, 0.5 ppm.

Lab-book No PD/5/39.

N-(2,4-Dimethoxybenzyl)aniline[111] (**239**)



239

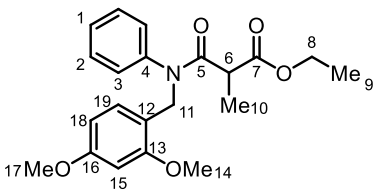
A solution of aniline (3.00 mL, 32.9 mmol) and 2,4-dimethoxybenzaldehyde (5.58 g, 33.6 mmol) in toluene (40 mL) was stirred at 165 °C for 18 h under a Dean & Stark apparatus. After cooling to room temperature, the solvent was removed under reduced pressure and the crude imine (8.15 g, quant) was used in the next step without further purification.

The crude imine was dissolved in CH_2Cl_2/EtOH (40 mL, 1:1) and cooled to 0 °C. Sodium borohydride (2.15 g, 56.8 mmol) was added portionwise to the solution and the reaction mixture then allowed to stir at room temperature for 12 h. The reaction mixture was then poured into ice. An aq. sol. of HCl (0.1 M, 2 mL) was added. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound **239** (7.91 g, 96%) as a colourless solid; mp. 76-78 °C (Lit.[111] 99-100 °C); R_f 0.5 (Petrol/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.19 (1 H, d, *J* = 8.2 Hz, H-14), 7.16 (2 H, dd, *J* = 8.6, 7.3 Hz, H-2), 6.70 (1 H, dt, *J* = 7.3, 1.0 Hz, H-1), 6.65 (2 H, dd, *J* = 8.6, 1.0 Hz, H-3), 6.47 (1 H, d, *J* = 2.4 Hz, H-10), 6.42 (1 H, dd, *J* = 8.2, 2.4 Hz, H-13), 4.24 (2 H, s, H-6), 3.82 (3 H, s, H-9 or H-12), 3.79 (3 H, s, H-9 or H-12).

Analytical data are consistent with literature values.[111]

Lab-book No PD/6/16.

Ethyl 3-((2,4-dimethoxybenzyl)(phenyl)amino)-2-methyl-3-oxopropanoate (**235**)



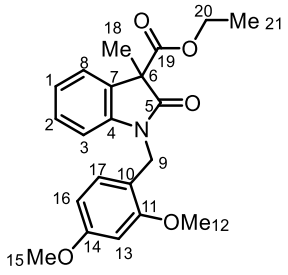
235

To a stirred solution of 3-ethoxy-2-methyl-3-oxopropanoic acid (**109**) (0.322 g, 2.18 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *N*-(2,4-dimethoxybenzyl)aniline (**239**) (0.564 g, 2.29 mmol), 2-chloro-1-methylpyridinium iodide (0.843 g, 3.27 mmol) and Et_3N (1.52 mL, 10.9 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and

then quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, Petrol/EtOAc, 5:1) gave the title compound **235** (0.661 g, 82%) as a clear oil; R_f 0.20 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1740, 1656,1613, 1594, 1507, 1495, 1455, 1399, 1207, 1182, 701; δ_H (400 MHz; $CDCl_3$) 7.32 – 7.23 (5 H, m, H-1, H-2 and H-3), 7.03 (1 H, dd, *J* = 8.2, 2.4 Hz, H-19), 6.41 (1 H, dd, *J* = 8.2, 2.4 Hz, *H*-18), 6.30 (1 H, d, *J* = 2.4 Hz, H-15), 4.95 (1 H, *J* = 14.4 Hz, H-11a), 4.82 (1 H, *J* = 14.4 Hz, H-11b), 4.09 (2 H, q, *J* = 7.1 Hz, H-8), 3.77 (3 H, s, H-14 or H-17), 3.50 (3 H, s, H-14 or H-17), 3.35 (1 H, q, *J* = 7.1 Hz, H-6), 1.31 (3 H, d, *J* = 7.1 Hz, H-10), 1.22 (3 H, t, *J* = 7.1 Hz, H-9); δ_C (100 MHz; $CDCl_3$) 171.0 (C-7), 170.0 (C-5), 160.3 (C-13 or C-16), 158.5 (C-13 or C-16), 142.2 (C-4), 131.0 (C-1), 129.3 (C-2), 128.7 (C-3), 128.1 (C-19), 117.9 (C-12), 104.2 (C-18), 98.2 (C-15), 61.2 (C-8), 55.4 (C-14 or C-17), 55.1 (C-14 or C-17), 47.1 (C-11), 44.0 (C-6), 14.3 (C-10), 14.2 (C-9); Found (ESI): $[MH]^+$ 372.1800; $C_{21}H_{26}NO_5$ requires $[MH]^+$ 372.1805, 1.5 ppm.

Lab-book No PD/5/92.

Ethyl 1-(2,4-dimethoxybenzyl)-3-methyl-2-oxoindoline-3-carboxylate (**234**)



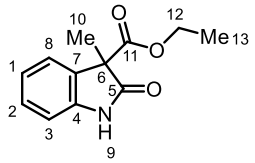
234

To a stirred solution of ethyl 3-((2,4-dimethoxybenzyl)(phenyl)amino)-2-methyl-3-oxopropanoate (**235**) (0.560 g, 1.50 mmol) in toluene (30 mL) at room temperature was added $Cu(OAc)_2 \cdot H_2O$ (0.300 g, 1.50 mmol). The reaction mixture was heated at reflux and held for 18 h. The solvent was removed *in vacuo*. The brown residue was diluted with EtOAc (50 mL), filtered through Celite® and washed with EtOAc (2 × 50 mL). The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 6:1) to give the title compound **234** (0.300 g, 54%) as a thick yellow oil; R_f 0.42 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1738, 1713, 1610, 1508, 1466, 1262, 1208, 1121, 1034, 751; δ_H (400 MHz; $CDCl_3$) 7.23 (1 H, ddd, *J* = 7.8, 1.3, 0.5 Hz, H-8), 7.19 (1 H, td, *J* = 7.8, 1.3 Hz, H-2), 7.07 (1 H, d, *J* = 8.4 Hz, H-17), 7.00 (1 H, td, *J* = 7.8, 1.3 Hz, H-1), 6.78 (1 H, d, *J* = 7.8 Hz, H-3), 6.46 (1 H, d, *J* = 2.4 Hz,

H-13), 6.35 (1 H, dd, *J* = 8.4, 2.4 Hz, H-16), 4.98 (1 H, d, *J* = 16.6 Hz, H-9a), 4.81 (1 H, d, *J* = 16.6 Hz, H-9b), 4.18 (1 H, dq, *J* = 10.8, 7.1 Hz, H-20a), 4.08 (1 H, dq, *J* = 10.8, 7.1 Hz, H-20b), 3.87 (3 H, s, H-12 or H-15), 3.76 (3 H, s, H-12 or H-15), 1.70 (3 H, s, H-18), 1.16 (3 H, t, *J* = 7.1 Hz, H-21); δ_C (100 MHz; $CDCl_3$) 175.6 (C-19), 170.0 (C-5), 160.4 (C-11 or C-14), 158.1 (C-11 or C-14), 143.1 (C-4), 130.3 (C-7), 129.0 (C-2), 128.8 (C-17), 122.8 (C-8), 122.7 (C-1), 116.0 (C-10), 109.7 (C-3), 104.4 (C-16), 98.4 (C-13), 62.0 (C-20), 55.5 (C-12 or C-15), 55.4 (C-12 or C-15), 55.2 (C-6), 38.0 (C-9), 20.0 (C-18), 14.0 (C-21); Found (ESI): $[MNa]^+$ 392.1471; $C_{21}H_{23}NNaO_5$ requires $[MNa]^+$ 392.1468, 0.7 ppm.

Lab-book No PD/5/96.

Ethyl 3-methyl-2-oxoindoline-3-carboxylate (**233**)



233

To a solution of oxindole **234** (0.253 g, 0.685 mmol) in CH_2Cl_2:water (22 mL, 10:1) was added DDQ (0.784 g, 3.42 mmol) and trifluoroacetic acid (0.166 mL, 2.04 mmol) at room temperature. The reaction was then heated at reflux for 2 d. The reaction mixture was poured into sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, Petrol/EtOAc, 5:1 to Petrol/EtOAc, 3:1) to give the title compound **233** (0.237 g, quant.) as a colourless solid; mp. 73-75 °C; R_f 0.22 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1675, 1599, 1579, 1503, 1460, 1423, 1262, 1213, 1028, 829; δ_H (400 MHz; $CDCl_3$) 9.34 (1 H, br s, H-9), 7.23 (2 H, d, *J* = 7.8 Hz, H-2, H-8), 7.03 (1 H, td, *J* = 7.8, 1.0 Hz, H-1), 6.96 (1 H, dd, *J* = 7.8, 1.0 Hz, H-3), 4.14 (2 H, dq, *J* = 10.8, 7.1 Hz, H-12), 1.69 (3 H, s, H-10), 1.15 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz; $CDCl_3$) 178.1 (C-11), 169.8 (C-5), 141.1 (C-4), 130.9 (C-7), 129.1 (C-2), 123.3 (C-8), 122.9 (C-1), 110.5 (C-3), 62.1 (C-12), 55.8 (C-6), 20.2 (C-10), 14.0 (C-13); Found (ESI): $[MH]^+$ 220.0958; $C_{12}H_{14}NO_3$ requires $[MH]^+$ 220.0968, 4.4 ppm. Anal. Calcd. for $C_{12}H_{14}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.56; H, 5.91; N, 6.22.

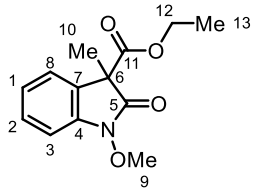
Lab-book No PD/5/98.

6.4.2.1 Preparation of DMDO (241)

A three necked 2 L round-bottomed flask (RBF) was equipped with an air condenser, and connected to a 2 necked 100 mL RBF cooled to –78 °C, with the latter connected to vacuum. The 2 L RBF was charged with $NaHCO_3$ (48 g), water (40 mL), and acetone (25 mL). In a dropping funnel (attached to the 3 necked RBF) was introduced water (30 mL) and acetone (30 mL). Then, oxone (4 × 22.5 g) was added in 4 portions. Vigorous stirring was continued for 1 h while a slight vacuum is applied to the 2 necked RBF. A yellow solution of dimethyldioxirane in acetone was collected in the receiving flask. The DMDO was allowed to reach 0 °C, dried with anhydrous K_2CO_3, and the solution was flushed with Ar and stored in the freezer. The concentration of DMDO was determined by titration as follows: 25 mL of 0.02 M aq. sol. of $Na_2S_2O_3$ (0.496 g of $Na_2S_2O_3 \cdot 5H_2O$ in 100 mL of H_2O) was placed in a 25 mL burette. A 100 mL Erlenmeyer flask was charged with water (20 mL), glacial acetic acid (1 mL), a freshly prepared solution of sodium iodide (10 mL, 10 g of NaI in 50 mL of water) and then the solution of DMDO (2 mL) was added. The resulting dark yellow solution was titrated with the 0.02 M aq. sol. of $Na_2S_2O_3$ until it turned colourless. The concentration was calculated according to the following equation [(molarity of titrant) × (mL of titrant)]/[(mL of DMDO solution) × 2] and the concentration was included between 0.05 and 0.07 M.

Lab-book No PD/2/88.

Ethyl 1-methoxy-3-methyl-2-oxoindoline-3-carboxylate (**221**)



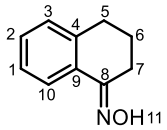
221

To a stirred suspension of NaH (60% in mineral oil, 0.002 g, 0.070 mmol) in THF (1 mL) at 0 °C was added oxindole **233** (0.008 g, 0.042 mmol) as a solution in THF (1 mL). The reaction mixture was stirred for 10 min and then DMDO (0.05-0.07 M in acetone, 1.85 mL) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. A solution of sat. aq. NH_4Cl (2 mL) was added. The aqueous portion was extracted with EtOAc (2 mL), washed with brine (2 × 2 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2,

Petrol/EtOAc, 6:1) to give an inseparable 1:1 mixture of starting material **233**, and the title compound **221** (0.006 g, 70%); R_f 0.64 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1746, 1733, 1615, 1466, 1324, 1240, 1112, 1039, 751; δ_H (400 MHz; $CDCl_3$) 7.34 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.25 (1 H, ddd, *J* = 7.6, 1.2, 0.6 Hz, H-8), 7.09 (1 H, td, *J* = 7.6, 1.2 Hz, H-1), 7.01 (1 H, dd, *J* = 7.6, 1.2 Hz, H-3), 4.17 (1 H, dq, *J* = 10.8, 7.1 Hz, H-12a), 4.08 (1 H, dq, *J* = 10.8, 7.1 Hz, H-12b), 4.04 (3 H, s, H-9), 1.68 (3 H, s, H-10), 1.15 (3 H, t, *J* = 7.1 Hz, H-13); Found (ESI): $[MH]^+$ 250.1073; $C_{13}H_{16}NO_4$ requires $[MH]^+$ 250.1074, 0.5 ppm.

Lab-book No PD/6/6.

3,4-Dihydronaphthalen-1(2*H*)-one oxime[116] (**251**)



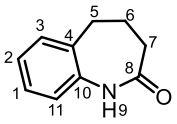
251

To a stirred solution of $NH_2OH{\cdot}HCl$ (3.50 g, 50.4 mmol) in water (21 mL) was added a solution of NaOH (10% in water, 14 mL). Then, α-tetralone (3.51 g, 23.9 mmol) in EtOH (7 mL) was added and the reaction mixture was heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature. Water (30 mL) was added and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic portions were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude oxime **251** (3.58 g, 93%) as a pale yellow solid, which was used in the next step without further purification; R_f 0.32 (Petrol/EtOAc, 9:1); δ_H (400 MHz; $CDCl_3$) 8.70 (1 H, br s, H-11), 7.88 (1 H, dd, *J* = 7.4, 1.5 Hz, H_{Ar}), 7.27 (1 H, dt, *J* = 7.4, 1.5 Hz, H_{Ar}), 7.21 (1 H, td, *J* = 7.4, 1.5 Hz, H_{Ar}), 7.15 (1 H, dd, *J* = 7.4, 1.5 Hz, H_{Ar}), 2.83 (2 H, t, *J* = 6.2 Hz, H-7), 2.76 (2 H, t, *J* = 6.2 Hz, H-5), 1.88 (2 H, pent, *J* = 6.2 Hz, H-6).

Analytical data are consistent with literature values.[116]

Lab-book No PD/6/28.

4,5-Dihydro-1*H*-benzo[b]azepin-2(3*H*)-one[116] (**252**)



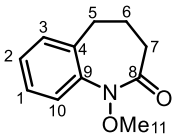
252

A mixture of oxime **251** (3.58 g, 22.2 mmol) was placed in a 100 mL flask with polyphosphoric acid (≥83% phosphate (as P_2O_5) basis, 52.4 g). The reaction mixture was stirred and heated at 120 °C. The viscosity of the mixture decreased as the temperature reached 120 °C. The reaction was heated for 1 h and allowed to return to room temperature. The mixture was poured onto ice, then the aqueous phase was extracted with EtOAc (50 mL). The organic phase was washed with NaOH (2.0 M in water, 50 mL). The combined organic portions were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the lactam **252** (2.98 g, 83%). The crude solid was used in the next step without further purification; R_f 0.21 (CH_2Cl_2/EtOAc, 9:1); mp. 110-112 °C (Lit.[116] 142-143 °C); δ_H (400 MHz; $CDCl_3$) 7.88 (1 H, br s, H-9), 7.24 – 7.20 (2 H, m, H_{Ar}), 7.13 (1 H, td, *J* = 7.6, 1.3 Hz, H_{Ar}), 6.98 (1 H, d, *J* = 7.6 Hz, H_{Ar}), 2.80 (2 H, t, *J* = 7.2 Hz, H-5), 2.35 (2 H, t, *J* = 7.2 Hz, H-7), 2.23 (2 H, pent, *J* = 7.2 Hz, H-6).

Analytical data are consistent with literature values.[116]

Lab-book No PD/6/29.

1-Methoxy-4,5-dihydro-1*H*-benzo[b]azepin-2(3*H*)-one[157a] (**253**)



253

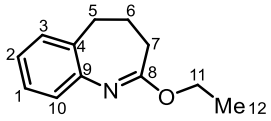
To a stirred solution of NaH (60% in mineral oil, 0.007 g, 0.172 mmol) in THF (1 mL) at 0 °C was added 4,5-dihydro-1*H*-benzo[b]azepin-2(3*H*)-one (**252**) (0.020 g, 0.121 mmol) as a solution in THF (1 mL). The reaction mixture was stirred for 10 min then DMDO (0.055 M in acetone, 3.20 mL, 0.180 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. A solution of sat. aq. NH_4Cl (5 mL) was added. The aqueous phase was extracted with EtOAc (5 mL), and the organic layer washed with brine (2 × 3 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting separable mixture was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 9:1) to

give the starting material **252** (11.8 mg, 59%) as a colourless solid, and the title compound **253** (0.004 g, 18%), as a colourless oil; R_f 0.41 (EtOAc/Petrol, 3:1); δ_H (400 MHz, $CDCl_3$) δ 7.44 (1 H, d, *J* = 8.2 Hz, H-10), 7.34 (1 H, ddd, *J* = 8.2, 5.2, 3.9 Hz, H-1), 7.21 (1 H, dd, *J* = 3.9, 1.2 Hz, H-2 or H-3), 7.22 (1 H, dd, *J* = 5.2, 1.2 Hz, H-2 or H-3), 3.79 (3 H, s, H-11), 2.78 (2 H, t, *J* = 7.1 Hz, H-5), 2.29 (1 H, td, *J* = 7.1, 1.1 Hz, H-7), 2.20 (2 H, td, *J* = 7.1, 1.1 Hz, H-6).

Analytical data are consistent with literature values.[157a]

Lab-book No PD/6/30.

(*E*)-2-Ethoxy-4,5-dihydro-3*H*-benzo[b]azepine[119] (**254**)



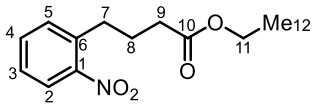
254

To a stirred solution of 4,5-dihydro-1*H*-benzo[b]azepin-2(3*H*)-one (**252**) (0.073 g, 0.462 mmol) in CH_2Cl_2 (5 mL) was added dropwise triethyloxonium tetrafluoroborate (0.091 g, 0.478 mmol) as a solution in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 d at room temperature. A sat. aq. solution of $NaHCO_3$ (5 mL) was added and the mixture was stirred for 30 min. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic portions were washed with water (2 × 5 mL), and brine (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product **254** (0.071 g, 83%) as an oil, which was used in the next step without further purification; R_f 0.31 (CH_2Cl_2/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 7.24 – 7.18 (2 H, m, H_{Ar}), 7.16 – 7.10 (1 H, m, H_{Ar}), 6.98 – 6.94 (1 H, m, H_{Ar}), 4.30 (2 H, q, *J* = 7.1 Hz, H-11), 2.59 – 2.53 (2 H, m, CH_2), 2.40 – 2.34 (2 H, m, CH_2), 2.28 – 2.18 (2 H, m, CH_2), 1.37 (3 H, t, *J* = 7.1 Hz, H-12).

Analytical data are consistent with literature values.[119]

Lab-book No PD/6/46.

Ethyl 4-(2-nitrophenyl)butanoate (**258**)



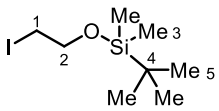
258

To a stirred solution of imino ether **254** (0.034 g, 0.159 mmol) in acetone (1 mL) was added at 0 °C, DMDO (0.07 M, 3.2 mL, 0.224 mmol) in solution in acetone. The reaction mixture was allowed to warm to room temperature and stirred overnight. Acetone was removed under vacuum. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 6:1) to give the title compound **258** (0.013 g, 33%), along with 4,5-dihydro-1*H*-benzo[b]azepin-2(3*H*)-one (**252**) (0.012 g, 47%). Ethyl 4-(2-nitrophenyl)butanoate (**258**) was isolated as an orange oil; R_f 0.91 (CH_2Cl_2/EtOAc, 4:1); ν_{max} (cm^{-1}) 2983, 1729, 1524, 1345, 1248, 1181, 1155, 1024, 857, 786, 741; δ_H (400 MHz; $CDCl_3$) 7.88 (1 H, d, *J* = 8.1 Hz, H-2), 7.51 (1 H, t, *J* = 7.5 Hz, H-4), 7.35 (2 H, m, H-3 and H-5), 4.12 (2 H, q, *J* = 7.1 Hz, H-11), 2.91 (2 H, t, *J* = 7.3 Hz, H-7), 2.37 (2 H, t, *J* = 7.3 Hz, H-9), 1.98 (2 H, pent, *J* = 7.3 Hz, H-8), 1.25 (3 H, t, *J* = 7.1 Hz, H-12); δ_C (100 MHz; $CDCl_3$) 173.1 (C-10), 149.4 (C-1), 136.5 (C-6), 132.9 (C-2), 132.0 (C-4), 127.2 (C-5), 124.7 (C-3), 60.4 (C-11), 33.8 (C-9), 32.1 (C-7), 25.8 (C-8), 14.2 (C-12); Found (ESI): $[MNa]^+$ 260.0892; $C_{12}H_{15}NNaO_4$ requires $[MNa]^+$ 260.0893, 0.6 ppm.

Lab-book No PD/6/47.

6.4.3 Progress towards the total synthesis of rankinidine (49)

tert-Butyl(2-iodoethoxy)dimethylsilane[158] (**272**)



272

To a suspension of NaH (60% in mineral oil, 1.22 g, 30.5 mmol) in THF (60 mL) at 0 °C was added ethylene glycol (1.70 mL, 30.5 mmol). The reaction mixture was stirred for 2 h at room temperature. Then, *tert*-butyldimethylsilyl chloride (4.60 g, 30.5 mmol) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with a sat. aq. solution of NH_4Cl (60 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic portions were washed with water (2 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to

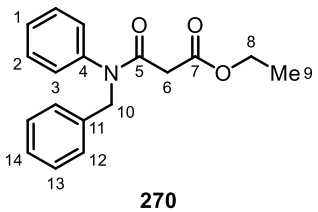
give the mono-protected alcohol (5.29 g, 98%) as a clear oil. The residue was used in the next step without further purification.

To a solution of the alcohol (5.29 g, 30.0 mmol), imidazole (3.09 g, 45.4 mmol) and PPh_3 (10.2 g, 38.9 mmol) in THF (150 mL) was added iodine (9.14 g, 36.0 mmol) at 0 °C, over 20 min. The resulting dark mixture was stirred for 40 min at room temperature. The reaction was quenched with a mixture of sat. aq. $Na_2S_2O_3$:NH_4Cl (1:1, 150 mL), and the aqueous layer was extracted with EtOAc (2 × 75 mL). The triphenylphosphine oxide by-product was precipitated out using Et_2O (75 mL) and hexane (75 mL), then filtered off. Concentration and column chromatography (SiO_2, 100% petrol) gave the title compound **272** (6.31 g, 73%) as a clear oil; R_f 0.90 (Petrol/EtOAc, 4:1); δ_H (400 MHz; $CDCl_3$) 3.83 (2 H, t, *J* = 7.0 Hz, H-2), 3.20 (2 H, t, *J* = 7.0 Hz, H-1), 0.90 (9 H, s, H-5), 0.08 (6 H, s, H-3).

Analytical data are consistent with literature values.[158]

Lab-book No PD/5/2.

Ethyl 3-(benzyl(phenyl)amino)-3-oxopropanoate[159] (**270**)



270

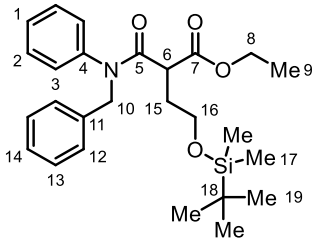
To a solution of *N*-benzylaniline (3.46 mL, 20.0 mmol) in CH_2Cl_2 (100 mL) was added successively monoethyl malonate (2.64 g, 20.0 mmol) and DCC (4.13 g, 20.0 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was filtered through a short pad of silica and the filtrate was concentrated *in vacuo*. The residue was treated with $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Petrol/EtOAc, 6:1) gave the title compound **270** (4.32 g, 73%) as a thick and colourless oil; R_f 0.44 (Petrol/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 7.35 – 7.19 (8 H, m, H_{Ar}), 7.05 – 6.97 (2 H, m, H_{Ar}), 4.91 (2 H, s, H-10), 4.12 (2 H, q, *J* = 7.2 Hz, H-8), 3.21 (2 H, s, H-6), 1.23 (3 H, t, *J* = 7.2 Hz, H-9).

Analytical data are consistent with literature values.[159]

Lab-book No PD/5/4.

6.4.3.1 General procedure P: alkylation of β-amido esters

Ethyl 2-(benzyl(phenyl)carbamoyl)-4-(*tert*-butyldimethylsilyloxy)butanoate (**271**)

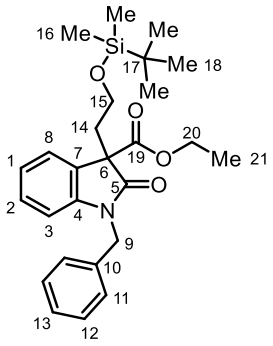


271

To a stirred solution of NaH (60% in mineral oil, 0.142 g, 3.36 mmol) in DMF (50 mL) was added anilide **270** (1.00 g, 3.36 mmol) at 0 °C. The reaction mixture was stirred for 15 min and alkyl iodide **272** (0.963 g, 3.35 mmol) was added slowly. The resulting light green solution was stirred for 30 min and then allowed to warm to room temperature where it slowly turned yellow. The reaction mixture was stirred overnight and quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with water (5 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude pale yellow oil was then purified by column chromatography (SiO_2, Petrol/EtOAc, 9:1) to give the title compound **271** (1.06 g, 69%) as a yellow oil; R_f 0.62 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 2910, 1714, 1636, 1473, 1378, 1237, 1080, 823, 765, 689; δ_H (400 MHz; $CDCl_3$) 7.31 – 7.18 (8 H, m, H_{Ar}), 7.05 – 7.00 (2 H, m, H_{Ar}), 5.05 (1 H, d, J = 14.3 Hz, H-10a), 4.76 (1 H, d, J = 14.3 Hz, H-10b), 4.09 (2 H, q, *J* = 7.1 Hz, H-8), 3.59 (2 H, t, *J* = 5.7 Hz, H-16), 3.57 (1 H, t, *J* = 6.8 Hz, H-6), 2.08 (2 H, dt, *J* = 6.8, 5.7 Hz, H-15), 1.20 (3 H, t, *J* = 7.1 Hz, H-9), 0.78 (9 H, s, H-19), −0.05 (3 H, s, H-17a), −0.08 (3 H, s, H-17b); δ_C (100 MHz; $CDCl_3$) 170.3 (C-7), 169.1 (C-5), 141.8 (C-11 or C-4), 137.4 (C-11 or C-4), 129.6 (CH_{Ar}), 128.8 (2 × CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.5 (CH_{Ar}), 61.2 (C-8), 60.5 (C-16), 53.4 (C-10), 45.8 (C-6), 32.6 (C-15), 26.0 (C-19), 18.3 (C-18), 14.1 (C-9), −5.3 (C-17); Found (ESI): $[MH]^+$ 456.2541; $C_{26}H_{38}NO_4Si$ requires $[MH]^+$ 456.2565, 4.8 ppm.

Lab-book No PD/5/5.

Ethyl 1-benzyl-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2-oxoindoline-3-carboxylate (**273**)

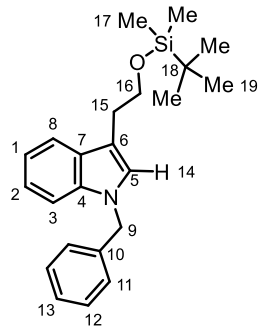


273

To a stirred solution of anilide **271** (0.510 g, 1.12 mmol) in toluene (50 mL) at room temperature was added $Cu(OAc)_2 \cdot H_2O$ (0.022 g, 0.112 mmol). The reaction mixture was heated at reflux and held for 22 h. The solvent was removed *in vacuo*. The brown residue was diluted with EtOAc (50 mL), filtered through Celite® and washed with EtOAc (2 × 50 mL). The filtrate was concentrated *in vacuo* and the crude product was then purified by column chromatography (SiO_2, Petrol/EtOAc, 9:1) to give the title compound **273** (0.312 g, 62%) as a pink oil; R_f 0.61 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 2910, 1715, 1694, 1585, 1466, 1445, 1340, 1201, 1086, 823; δ_H (400 MHz; $CDCl_3$) 7.36 – 7.26 (5 H, m, H_{Ar}), 7.23 (1 H, dd, *J* = 7.6 Hz, H-8), 7.17 (1 H, td, *J* = 7.6, 0.8 Hz, H-2), 7.00 (1 H, td, *J* = 7.6, 0.8 Hz, H-1), 6.67 (1 H, d, *J* = 7.6 Hz, H-3), 5.20 (1 H, d, *J* = 15.9 Hz, H-9a), 4.65 (1 H, d, *J* = 15.9 Hz, H-9b), 4.17 (1 H, dq, *J* = 10.8, 7.1 Hz, H-20a), 4.07 (1 H, dq, *J* = 10.8, 7.1 Hz, H-20b), 3.49 (2 H, ddd, *J* = 13.3, 6.7, 3.3 Hz, H-15), 2.63 (1 H, dt, *J* = 13.9, 7.5 Hz, H-14a), 2.53 (1 H, ddd, *J* = 13.9, 6.7, 5.4 Hz, H-14b), 1.16 (3 H, t, *J* = 7.1 Hz, H-21), 0.77 (9 H, s, H-18), −0.11 (3 H, s, H-16a), −0.12 (3 H, s, H-16b); δ_C (100 MHz; $CDCl_3$) 174.4 (C-19), 169.5 (C-5), 143.4 (C-4), 135.8 (C-10), 128.9 (C-2), 128.7 (C-12), 127.8 (C-7), 127.6 (C-13), 127.3 (C-11), 123.6 (C-8), 122.7 (C-1), 109.4 (C-3), 62.1 (C-20), 59.0 (C-15), 57.8 (C-6), 43.9 (C-9), 36.1 (C-14), 25.9 (C-18), 18.3 (C-17), 13.9 (C-21), −5.50 (C-16); Found (ESI): $[MH]^+$ 454.2391; $C_{26}H_{36}NO_4Si$ requires $[MH]^+$ 454.2408, 1.7 ppm.

Lab-book No PD/5/6.

1-Benzyl-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1*H*-indole (**277**)



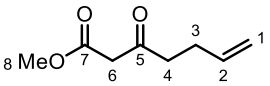
277

To a stirred solution of oxindole **273** (0.098 g, 0.216 mmol) in Et_2O (5 mL) was added DIBAL-H (1.0 M in hexanes, 0.240 mL, 0.237 mmol) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, then warmed to room temperature and stirred for a further 2 h. MeOH (1 mL), followed by water (1 mL) was added slowly to the reaction mixture. The aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, Petrol/EtOAc, 50:1) to give the title compound **277** (0.008 g, 11%) as a colourless oil; R_f 0.71 (Petrol/EtOAc, 9:1); δ_H (400 MHz; $CDCl_3$) 7.61 (1 H, ddd, *J* = 7.7, 1.2 Hz, H_{Ar}), 7.31 – 7.23 (2 H, m, H_{Ar}), 7.28 (2 H, d, *J* = 7.1 Hz, H_{Ar}), 7.16 (1 H, t, *J* = 7.7 Hz, H_{Ar}), 7.12 – 7.07 (1 H, m, H_{Ar}), 7.11 (2 H, d, *J* = 7.7 Hz, H_{Ar}), 6.96 (1 H, s, H-14), 5.27 (2 H, s, H-9), 3.87 (2 H, t, *J* = 7.4 Hz, H-16), 2.99 (2 H, t, *J* = 7.4 Hz, H-15), 0.89 (9 H, s, H-19), 0.02 (6 H, s, H-17).

Analytical data are consistent with literature values.[124]

Lab-book No PD/5/10.

Methyl 3-oxohept-6-enoate[160] (**279**)



279

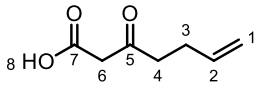
To a suspension of NaH (60% in mineral oil, 1.10 g, 27.5 mmol) in THF (100 mL) at 0 °C was added methyl acetoacetate (2.80 mL, 26.1 mmol). The reaction mixture was stirred for 30 min and *n*-BuLi (24.4 mL, 39.1 mmol) was slowly added. After 10 min, allyl bromide (3.46 mL, 28.7 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and then quenched with sat. aq. NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL). The resulting solution was dried ($MgSO_4$), filtered and

concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 99:1 to Petrol/EtOAc, 20:1) to give the title compound **279** (2.61 g, 65%) as a colourless oil; R_f 0.82 (Petrol/EtOAc, 1:1); δ_H (400 MHz; $CDCl_3$) 5.79 (1 H, ddt, *J* = 16.7, 10.2, 6.5 Hz, H-2), 5.09 – 4.95 (2 H, m, H-1), 3.73 (3 H, s, H-8), 3.45 (2 H, s, H-6), 2.64 (2 H, t, *J* = 7.0 Hz, H-4), 2.34 (2 H, td, *J* = 7.0, 6.5 Hz, H-3).

Analytical data are consistent with literature values.[160]

Lab-book No PD/5/59.

3-Oxohept-6-enoic acid[161] (**280**)



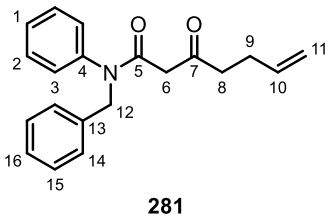
280

To a stirred solution of the ester **279** (2.06 g, 13.2 mmol) in MeOH (50 mL) at room temperature was added a solution of KOH (1.0 M in water, 13.2 mmol). The reaction mixture was stirred at room temperature for 2 h. After removal of MeOH, the reaction was acidified with 10% aq. HCl (30 mL) to pH 3 and extracted with EtOAc. The organic portion was washed with sat. aq. NH_4Cl (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the acid **280** (1.53 g, 63%) as a colourless oil. The crude acid **280** was used in the next step without further purification; δ_H (400 MHz; $CDCl_3$) 11.79 (1 H, br s, H-8), 5.79 (1 H, ddt, *J* = 16.8, 10.2, 6.5 Hz, H-2), 5.09 – 4.98 (2 H, m, H-1), 3.51 (2 H, s, H-6), 2.67 (2 H, t, *J* = 7.3 Hz, H-4), 2.42 – 2.30 (2 H, m, H-3).

Analytical data are consistent with literature values.[161]

Lab-book No PD/5/60.

N-Benzyl-3-oxo-*N*-phenylhept-6-enamide (**281**)



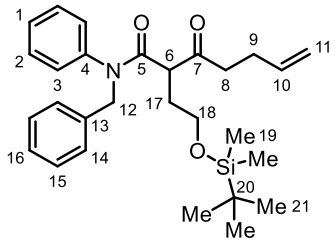
281

To a stirred solution of acid **280** (1.53 g, 10.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added *N*-benzylaniline (1.95 mL, 11.3 mmol), 2-chloro-1-methylpyridinium iodide (4.13 g, 16.2 mmol) and Et_3N (7.50 mL, 54.0 mmol). The reaction mixture was allowed to warm to room

temperature, stirred for 4 h, and then quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with water (2 × 50 mL) and brine (2 × 50 mL). The resulting solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 3:1) to give the title compound **281** (3.02 g, 81%) as an orange oil; R_f 0.35 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1720, 1651, 1594, 1495, 1393, 1273, 914, 730, 697; δ_H (400 MHz; $CDCl_3$) 7.33 – 7.21 (8 H, m, H_{Ar}), 6.97 (2 H, dd, *J* = 6.5, 3.0 Hz, H_{Ar}), 5.70 (1 H, ddt, *J* = 16.8, 10.4, 6.4 Hz, H-10), 4.98 – 4.92 (2 H, m, H-11), 4.91 (2 H, s, H-12), 3.30 (2 H, s, H-6), 2.42 (2 H, t, *J* = 7.0 Hz, H-8), 2.22 (2 H, td, *J* = 7.0, 6.4 Hz, H-9); δ_C (100 MHz; $CDCl_3$) 203.7 (C-7), 141.9 (C-5), 137.0 (C_{Ar}), 136.8 (C-10), 129.8 (C_{Ar}), 129.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 128.52 (CH_{Ar}), 128.48 (CH_{Ar}), 127.6 (CH_{Ar}), 115.5 (C-11), 53.1 (C-12), 49.5 (C-6), 42.3 (C-8), 27.5 (C-9); Found (ESI): $[MH]^+$ 308.1642; $C_{20}H_{22}NO_2$ requires $[MH]^+$ 308.1645, 0.9 ppm.

Lab-book No PD/5/62.

N-Benzyl-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3-oxo-*N*-phenylhept-6-enamide (**282**)



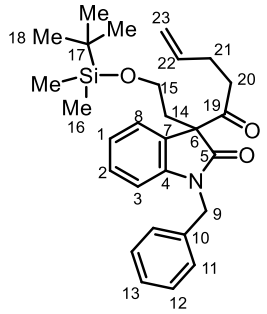
282

N-Benzyl-3-oxo-*N*-phenylhept-6-enamide (**281**) (0.484 g, 1.58 mmol), NaH (0.072 g, 1.73 mmol), *tert*-Butyl(2-iodoethoxy)dimethylsilane (0.480 g, 1.66 mmol) in DMF (15 mL) were subjected to general procedure P at 0 °C for 18 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 6:1) to give the title compound **282** (0.436 g, 60%) as a colourless oil; R_f 0.57 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1692, 1633, 1473, 1372, 1236, 1080, 823, 690; δ_H (400 MHz; $CDCl_3$) 7.32 – 7.28 (3 H, m, H_{Ar}), 7.27 – 7.23 (3 H, m, H_{Ar}), 7.21 – 7.17 (2 H, m, H_{Ar}), 6.96 – 6.92 (2 H, m, H_{Ar}), 5.66 (1 H, ddt, *J* = 16.9, 10.3, 6.5 Hz, H-10), 4.95 – 4.91 (2 H, m, H-11), 4.90 (2 H, s, H-12), 3.67 (1 H, dd, *J* = 8.2, 5.4 Hz, H-6), 3.63 – 3.50 (2 H, m, H-18), 2.36 (1 H, ddd, *J* = 17.0, 8.4, 5.7 Hz, H-8a), 2.18 – 2.09 (3 H, m, H-9, H-17a), 2.03 (1 H, ddd, *J* = 17.0, 8.4, 5.7 Hz, H-8b), 1.90 (1 H, ddt, *J* = 13.4, 8.2, 5.4 Hz, H-17b), 0.81 (9 H, s, H-21), −0.02 (3 H, s, H-19a), −0.04 (3 H, s, H-19b); δ_C (100 MHz; $CDCl_3$) 205.9 (C-7), 169.1 (C-5), 141.6 (C_{Ar}), 137.4 (C_{Ar}), 137.0 (C-10), 129.7 (CH_{Ar}), 129.1 (CH_{Ar}), 128.9 (CH_{Ar}), 128.53 (CH_{Ar}), 128.48 (CH_{Ar}), 127.5 (CH_{Ar}), 115.3 (C-11), 60.7 (C-18), 53.42

(C-6), 53.39 (C-12), 40.3 (C-8), 32.4 (C-17), 27.5 (C-9), 26.0 (C-21), 18.3 (C-20), −5.3 (C-19a), −5.3 (C-19b); Found (ESI): $[MH]^+$ 466.2773; $C_{28}H_{40}NO_3Si$ requires $[MH]^+$ 466.2772, 0.2 ppm.

Lab-book No PD/5/65.

1-Benzyl-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3-pent-4-enoylindolin-2-one (**283**)

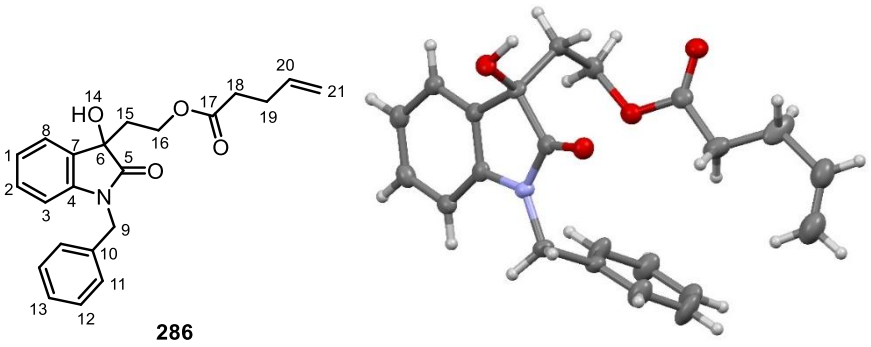


283

N-Benzyl-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3-oxo-*N*-phenylhept-6-enamide (**282**) (0.035 g, 0.080 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.015 g, 0.080 mmol) in toluene (3 mL) were subjected to general procedure O at 110 °C for 18 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 8:1) to give the title compound **283** (0.018 g, 49%) as a colourless oil; R_f 0.41 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1718, 1681, 1583, 1463, 1443, 1336, 822, 687; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.26 (5 H, m, H_{Ar}), 7.22 (1 H, td, *J* = 7.6, 1.3 Hz, H-2), 7.12 (1 H, ddd, *J* = 7.6, 1.3, 0.5 Hz, H-8), 7.03 (1 H, td, *J* = 7.6, 1.3 Hz, H-1), 6.82 (1 H, d, *J* = 7.6 Hz, H-3), 5.58 (1 H, ddt, *J* = 12.4, 10.4, 4.6 Hz, H-22), 5.08 (1 H, d, *J* = 15.4 Hz, H-9a), 4.79 (1 H, d, *J* = 15.4 Hz, H-9b), 4.88 – 4.83 (2 H, m, H-23), 3.43 (2 H, t, *J* = 6.9 Hz, H-15), 2.55 – 2.44 (3 H, m, H-14, H-20a), 2.24 – 2.09 (3 H, m, H-20b, H-21), 0.77 (9 H, s, H-18), −0.11 (3 H, s, H-16a), −0.12 (3 H, s, H-16b); δ_C (100 MHz; $CDCl_3$) 202.1 (C-19), 175.1 (C-5), 143.5 (C-4), 136.7 (C-22), 135.8 (C-10), 129.01 (C-2), 128.95 (C-11), 127.9 (C-13), 127.7 (C-12), 127.1 (C-7), 124.3 (C-8), 123.0 (C-1), 115.3 (C-23), 109.5 (C-3), 64.6 (C-6), 59.2 (C-15), 44.3 (C-9), 37.7 (C-20), 35.8 (C-14), 27.4 (C-21), 25.9 (C-18), 18.3 (C-17), −5.5 (C-16a), −5.5 (C-16b); Found (ESI): $[MNa]^+$ 486.2440; $C_{28}H_{37}NNaO_3Si$ requires $[MNa]^+$ 486.2435, 1.0 ppm.

Lab-book No PD/5/43

2-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl pent-4-enoate (**286**)



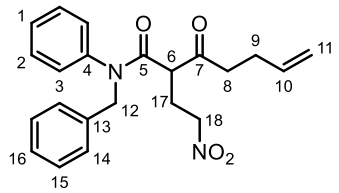
286

To a stirred solution of oxindole **283** (0.075 g, 0.162 mmol) in THF (8 mL) at 0 °C was added TBAF (1.0 M in THF, 0.18 mL, 0.178 mmol). The reaction mixture was stirred for 10 min and allowed to warm to room temperature. After 1 h, the reaction was complete by TLC. The solvent was removed under vacuum and the residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 3:1) to give the title compound **286** (0.053 g, 90%) as a crystalline solid; mp. 57-59 °C; R_f 0.5 (Petrol/EtOAc, 1:1); ν_{max} (cm^{-1}) 3369, 1705, 1614, 1467, 1356, 1172, 1103, 1079, 752, 697; δ_H (400 MHz; $CDCl_3$) 7.39 (1 H, dd, *J* = 7.6, 1.0 Hz, H-8), 7.35 – 7.26 (5 H, m, H_{Ar}), 7.21 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.07 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.71 (1 H, d, *J* = 7.6 Hz, H-3), 5.73 (1 H, ddt, *J* = 16.5, 10.3, 6.1 Hz, H-20), 5.02 – 4.94 (2 H, m, H-21), 4.93 (1 H, d, *J* = 15.7 Hz, H-9a), 4.83 (1 H, d, *J* = 15.7 Hz, H-9b), 4.23 (1 H, dt, *J* = 11.5, 6.4 Hz, H-16a), 4.05 (1 H, dt, *J* = 11.5, 6.4 Hz, H-16b), 2.39 (2 H, t, *J* = 6.4 Hz, H-15), 2.27 – 2.12 (4 H, m, H-18, H-19); δ_C (100 MHz; $CDCl_3$) 177.6 (C-5), 172.8 (C-17), 142.6 (C-4), 136.7 (C-20), 135.4 (C-10), 130.0 (C-2), 129.5 (C-7), 129.0 (C-11), 127.9 (C-13), 127.3 (C-12), 124.2 (C-8), 123.4 (C-1), 115.6 (C-21), 109.8 (C-3), 75.2 (C-6), 59.8 (C-16), 44.0 (C-9), 37.1 (C-15), 33.2 (C-18), 28.7 (C-19); Found (ESI): $[MNa]^+$ 388.1520; $C_{22}H_{23}NNaO_4$ requires $[MNa]^+$ 388.1523, 0.7 ppm. CCDC 1049570 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane in which a few drops of dichloromethane were added.

Lab-book No PD/5/69.

N-Benzyl-2-(2-nitroethyl)-3-oxo-*N*-phenylhept-6-enamide (**293**)

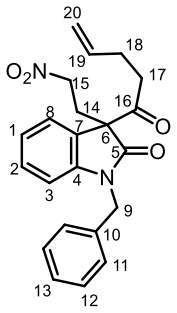


293

To a stirred solution of anilide **281** (0.971 g, 3.16 mmol) in CH_2Cl_2 (40 mL) at room temperature was added freshly distilled nitroethylene (0.227 mL, 3.32 mmol) and $Ni(acac)_2$ (0.008 g, 0.030 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 6:1) to give the title compound **293** (0.740 g, 62%) as a pale yellow oil; R_f 0.30 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1720, 1652, 1595, 1551, 1495, 1399, 701; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.34 (3 H, m, H_{Ar}), 7.30 – 7.24 (3 H, m, H_{Ar}), 7.18 (2 H, dd, *J* = 7.2, 2.4 Hz, H_{Ar}), 6.95 – 6.91 (2 H, m, H_{Ar}), 5.66 (1 H, ddt, *J* = 17.5, 9.8, 6.4 Hz, H-10), 4.97 – 4.90 (2 H, m, H-11), 4.97 (1 H, d, *J* = 14.0 Hz, H-12a), 4.82 (1 H, d, *J* = 14.0 Hz, H-12b), 4.50 (1 H, ddd, *J* = 13.3, 7.2, 6.0 Hz, H-18a), 4.42 (1 H, ddd, *J* = 13.3, 7.2, 6.0 Hz, H-18b), 3.50 (1 H, t, *J* = 6.6 Hz, H-6), 2.41 (2 H, ddd, *J* = 7.2, 6.6 Hz, H-17), 2.31 (1 H, dd, *J* = 10.2, 7.6 Hz, H-8a), 2.21 – 2.13 (3 H, m, H-8b, H-9); δ_C (100 MHz; $CDCl_3$) δ 203.9 (C-7), 172.1 (C-5), 168.0 (C_{Ar}), 141.0 (C_{Ar}), 136.8 (C-10), 136.5 (CH_{Ar}), 130.2 (CH_{Ar}), 128.7 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 127.8 (CH_{Ar}), 115.7 (C-11), 73.3 (C-18), 53.5 (C-12), 53.3 (C-6), 40.5 (C-8), 27.4 (C-9), 26.1 (C-17); Found (ESI): $[MH]^+$ 381.1795; $C_{22}H_{25}N_2O_4$ requires $[MH]^+$ 381.1809, 3.7 ppm.

Lab-book No PD/5/76.

1-Benzyl-3-(2-nitroethyl)-3-pent-4-enoylindolin-2-one (**292**)

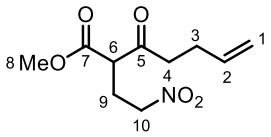


292

N-Benzyl-2-(2-nitroethyl)-3-oxo-*N*-phenylhept-6-enamide (**293**) (0.079 g, 0.208 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.005 g, 0.021 mmol) in toluene (4 mL) were subjected to general procedure O at 110 °C for 18 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 8:1) to give the title compound **292** (0.026 g, 40%) as a pale yellow oil; R_f 0.40 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1722, 1704, 1609, 1552, 1487, 1381, 1361, 1171, 753, 699; δ_H (400 MHz; $CDCl_3$) 7.37 – 7.31 (4 H, m, H_{Ar}), 7.32 – 7.26 (2 H, m, H_{Ar}), 7.10 – 7.04 (2 H, m, H_{Ar}), 6.90 (1 H, d, *J* = 7.9 Hz, H-3), 5.54 (1 H, ddt, *J* = 17.1, 10.3, 6.3 Hz, H-19), 5.05 (1 H, d, *J* = 15.4 Hz, H-9a), 4.86 (1 H, d, *J* = 15.4 Hz, H-9b), 4.85 (1 H, dq, *J* = 10.3, 1.5 Hz, H-20a), 4.82 (1 H, dq, *J* = 17.1, 1.5 Hz, H-20b), 4.36 (1 H, dd, *J* = 8.6, 6.5 Hz, H-15a), 4.36 (1 H, dd, *J* = 8.6, 6.5 Hz, H-15b), 2.98 (1 H, ddd, *J* = 14.4, 8.6, 6.5 Hz, H-14a), 2.73 (1 H, ddd, *J* = 14.4, 8.6, 6.5 Hz, H-14b), 2.42 (1 H, ddd, *J* = 17.5, 8.0, 6.0 Hz, H-17a), 2.26 – 2.17 (1 H, m, H-18a), 2.17 – 2.10 (1 H, m, H-18b), 2.06 (1 H, ddd, *J* = 17.5, 8.0, 6.0 Hz, H-17b); δ_C (100 MHz; $CDCl_3$) 200.7 (C-16), 173.9 (C-5), 143.1 (C-4), 136.1 (C-19), 135.2 (C-10), 130.1 (C-2), 129.0 (C-11), 128.2 (C-13), 127.6 (C-12), 125.8 (C-7), 123.81 (C-8), 123.76 (C-1), 115.5 (C-20), 110.1 (C-3), 70.7 (C-15), 63.3 (C-6), 44.4 (C-9), 37.6 (C-17), 29.8 (C-14), 27.1 (C-18); Found (ESI): $[MH]^+$ 379.1650; $C_{22}H_{23}N_2O_4$ requires $[MH]^+$ 379.1652, 0.5 ppm.

Lab-book No PD/5/79.

Methyl 2-(2-nitroethyl)-3-oxohept-6-enoate (**298**)

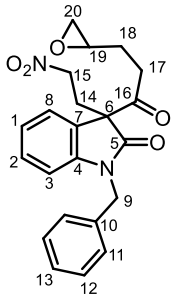


298

To a stirred solution of methyl 3-oxohept-6-enoate **279** (0.205 g, 1.31 mmol) in CH_2Cl_2 (10 mL) was added freshly distilled nitroethylene (106 mbar, 140-150 °C (oil bath temperature)) and $Ni(acac)_2$ (0.006 g, 0.020 mmol). The reaction mixture was stirred at room temperature and held for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 8:1) to give the title compound **298** (0.160 g, 53%) as a colourless oil; R_f 0.41 (Petrol/EtOAc, 4:1); ν_{max} (cm^{-1}) 1743, 1715, 1554, 1436, 1383, 1363, 1247, 1174, 1000, 918; δ_H (400 MHz; $CDCl_3$) 5.77 (1 H, ddt, *J* = 16.8, 10.2, 6.5 Hz, H-2), 5.03 (1 H, dd, *J* = 16.8, 1.2 Hz, H-1a), 4.99 (1 H, dd, *J* = 10.2, 1.2 Hz, H-1b), 4.43 (2 H, dt, *J* = 13.9, 7.1 Hz, H-10), 3.75 (3 H, s, H-8), 3.69 (1 H, t, *J* = 7.1 Hz, H-6), 2.76 (1 H, dt, *J* = 17.7, 7.4 Hz, H-4a), 2.63 (1 H, dt, *J* = 17.7, 7.1 Hz, H-4b), 2.56 – 2.40 (2 H, m, H-9), 2.34 (2 H, ddd, *J* = 7.1, 7.4, 6.5 Hz, H-3); δ_C (100 MHz; $CDCl_3$) 202.9 (C-5), 168.8 (C-7), 136.4 (C-2), 115.9 (C-1), 72.9 (C-10), 54.8 (C-6), 53.0 (C-8), 41.8 (C-4), 27.5 (C-3), 25.0 (C-9); Found (ESI): $[MNa]^+$ 252.0837; $C_{10}H_{15}NNaO_5$ requires $[MNa]^+$ 252.0842, 2.2 ppm.

Lab-book No PD/6/45.

1-Benzyl-3-(2-nitroethyl)-3-(3-(oxiran-2-yl)propanoyl)indolin-2-one (**301**)



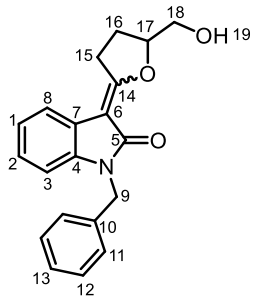
301

To a stirred solution of oxindole **292** (0.019 g, 0.050 mmol) in acetone (1 mL) at 0 °C was added DMDO (0.06 M solution in acetone, 3.30 mL, 0.202 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for 30 min. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 3:1) to give the title compound **301** (0.018 g, 93%) as a colourless oil and inseparable mixture of diastereoisomers in a 1:1 ratio; R_f 0.2 (Petrol/EtOAc, 4:1); ν_{max}

(cm^{-1}) 1723, 1702, 1608, 1553, 1486, 1381, 1349, 1172, 755, 700; δ_H (400 MHz; $CDCl_3$) 7.38 – 7.28 (6 H, m, H_{Ar}, H-8), 7.13 – 7.07 (2 H, m, H-1, H-2), 6.92 (1 H, d, *J* = 7.8 Hz, H-3), 5.04 (0.5 H, d, *J* = 15.4 Hz, H-9a), 5.04 (0.5 H, d, *J* = 15.4 Hz, H-9a'), 4.93 (0.5 H, d, *J* = 15.4 Hz, H-9b), 4.91 (0.5 H, d, *J* = 15.4 Hz, H-9b'), 4.36 (2 H, t, *J* = 7.6 Hz, H-15), 2.98 (1 H, ddd, *J* = 15.2, 7.6 Hz, H-14a), 2.80 – 2.69 (2 H, m, H-19, H-14b), 2.63 (1 H, dd, *J* = 6.3, 4.8 Hz, H-20a), 2.47 (1 H, ddt, *J* = 18.2, 8.0, 6.2 Hz, H-17a), 2.31 (1 H, dd, *J* = 4.8, 2.7 Hz, H-20b), 2.14 (1 H, ddd, *J* = 18.2, 8.0, 6.2 Hz, H-17b), 1.96 – 1.78 (1 H, m, H-18a), 1.65 – 1.43 (1 H, m, H-18b); δ_C (100 MHz; $CDCl_3$) 200.92 and 200.91 (C-16), 173.93 and 173.88 (C-5), 143.23 and 143.21 (C-4), 135.20 and 135.19 (C-10), 130.3 (C-8), 129.2 (C-12), 128.3 (C-13), 127.73 and 127.72 (C-11), 125.84 and 125.82 (C-7), 124.0 (C-2), 123.87 and 123.86 (C-1), 110.3 (C-3), 70.7 (C-15), 63.4 and 63.3 (C-6), 51.0 and 50.8 (C-19), 47.1 and 46.9 (C-20), 44.5 (C-9), 34.9 and 34.4 (C-17), 29.93 and 29.88 (C-14), 26.1 and 25.9 (C-18); Found (ESI): $[MNa]^+$ 417.1423; $C_{22}H_{22}N_2NaO_5$ requires $[MNa]^+$ 417.1421, 0.5 ppm.

Lab-book No PD/6/3.

(*Z*)-1-Benzyl-3-(5-(hydroxymethyl)dihydrofuran-2(3*H*)-ylidene)indolin-2-one (**303**)



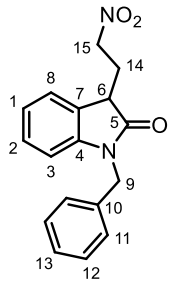
303

To a stirred solution of oxindole **301** (0.014 g, 0.040 mmol) in toluene (1 mL) was added DBU (0.007 mL, 0.050 mmol). The reaction mixture was stirred overnight at room temperature. The toluene was removed under vacuum and the residue was treated with water (1 mL) and extracted with EtOAc (2 × 2 mL). The combined organic portions were washed with brine (2 × 2 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc/Petrol, 4:1) to give the title compound **303** (0.006 g, 89%) as a colourless oil; R_f 0.40 (EtOAc); ν_{max} (cm^{-1}) 3405, 1722, 1681, 1611, 1467, 1349, 1244, 1185, 1140, 1098, 961, 751, 735, 698; δ_H (400 MHz; $CDCl_3$) 7.66 (1 H, dd, *J* = 7.6, 1.2 Hz, H-8), 7.32 – 7.24 (4 H, m, H_{Ar}), 7.22 (1 H, dd, *J* = 8.3, 4.2 Hz, H_{Ar}), 7.06 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 6.99 (1 H, td, *J* = 7.6, 1.2 Hz, H-1), 6.71 (1 H, d, *J* = 7.6 Hz, H-3), 4.98 (2 H, s, H-9), 4.87 (1 H, tdd, *J* = 7.3, 5.2, 3.1 Hz, H-17), 4.02 (1 H, ddd, *J* = 12.6, 6.0, 3.1 Hz, H-18a), 3.79 (1 H, ddd, *J* = 12.6, 6.0, 5.2 Hz, H-18b), 3.64 (1 H, ddd, *J* = 19.1,

9.5, 4.9 Hz, H-15a), 3.33 (1 H, ddd, *J* = 19.1, 9.5, 8.1 Hz, H-15b), 2.29 (1 H, dddd, *J* = 12.6, 9.5, 7.3, 4.9 Hz, H-16a), 2.11 (1 H, dddd, *J* = 12.6, 9.5, 8.0, 7.3 Hz, H-16b), 1.94 (1 H, br t, *J* = 6.0 Hz, H-19); δ_C (100 MHz; $CDCl_3$) 171.7 (C-14), 169.1 (C-5), 139.3 (C-4), 137.0 (C-10), 128.7 (CH_{Ar}), 127.4 (CH_{Ar}), 127.3 (CH_{Ar}), 125.9 (C-2), 122.6 (C-7), 122.1 (C-8), 121.7 (C-1), 108.2 (C-3), 100.3 (C-6), 86.3 (C-17), 64.3 (C-18), 43.4 (C-9), 31.1 (C-16), 24.5 (C-15); Found (ESI): $[MNa]^+$ 344.1245; $C_{20}H_{19}NNaO_3$ requires $[MNa]^+$ 344.1263, 4.4 ppm.

Lab-book No PD/6/7.

1-Benzyl-3-(2-nitroethyl)indolin-2-one (**305**)

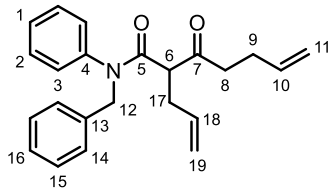


305

To a stirred solution of oxindole **292** (0.017 g, 0.045 mmol) in CH_2Cl_2:EtOH (2 mL, 1:1) at 0 °C was added $NaBH_4$ (0.003 g, 0.067 mmol). After 30 min the ice bath was removed and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into ice, extracted with EtOAc (2 × 2 mL), washed with water (2 mL) and brine (2 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 6:1) to give the title compound **305** (0.010 g, 77%) as a colorless oil; R_f 0.45 (Petrol/EtOAc, 4:1); ν_{max} (cm^{-1}) 1703, 1613, 1550, 1489, 1467, 1382, 1362, 1169, 752, 698; δ_H (400 MHz; $CDCl_3$) 7.35 – 7.26 (6 H, m, H_{Ar}, H-8), 7.21 (1 H, t, *J* = 7.8 Hz, H-2), 7.05 (1 H, t, *J* = 7.8 Hz, H-1), 6.76 (1 H, d, *J* = 7.8 Hz, H-3), 4.90 (2 H, s, *H*-9), 4.76 (1 H, ddd, *J* = 14.2, 7.7, 6.0 Hz, H-15a), 4.62 (1 H, ddd, *J* = 14.2, 7.7, 6.0 Hz, H-15b), 3.63 (1 H, dd, *J* = 8.4, 5.3 Hz, H-6), 2.75 (1 H, dtd, *J* = 14.2, 7.7, 5.3 Hz, H-14a), 2.50 (1 H, ddt, *J* = 14.2, 8.4, 6.0 Hz, H-14b); δ_C (100 MHz; $CDCl_3$) 176.7 (C-5), 143.5 (C-4), 135.7 (C-10), 129.3 (CH_{Ar}), 129.0 (C-8), 128.1 (C-2), 127.4 (CH_{Ar}), 127.0 (CH_{Ar}), 124.0 (C-7), 123.0 (C-1), 109.5 (C-3), 72.5 (C-6), 44.4 (C-9), 42.3 (C-15), 28.9 (C-14); Found (ESI): $[MNa]^+$ 319.1052; $C_{17}H_{16}N_2NaO_3$ requires $[MNa]^+$ 319.1053, 0.4 ppm.

Lab-book No PD/6/17.

2-Allyl-*N*-benzyl-3-oxo-*N*-phenylhept-6-enamide (**314**)

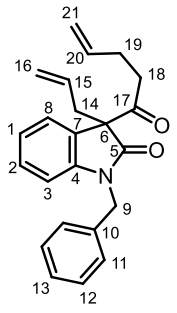


314

N-Benzyl-3-oxo-*N*-phenylhept-6-enamide (**281**) (0.242 g, 0.790 mmol), NaH (0.035 g, 0.870 mmol), allyl bromide (0.072 mL, 0.830 mmol) in DMF (8 mL) were subjected to general procedure P at 0 °C for 2 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 6:1) to give the title compound **314** (0.227 g, 83%) as a colourless oil; R_f 0.45 (Petrol/EtOAc, 3:1); ν_{max} (cm^{-1}) 1717, 1650, 1594, 1495, 1392, 1255, 914, 699; δ_H (400 MHz; $CDCl_3$) 7.36 – 7.30 (3 H, m, H_{Ar}), 7.28 – 7.23 (3 H, m, H_{Ar}), 7.21 – 7.17 (2 H, m, H_{Ar}), 6.95 – 6.91 (2 H, m, H_{Ar}), 5.77 – 5.59 (2 H, m, H-10, H-18), 5.07 – 4.90 (4 H, m, H-11, H-19), 4.89 (2 H, s, H-12) 3.39 (1 H, dd, *J* = 8.4, 5.9 Hz, H-6), 2.66 (1 H, dddt, *J* = 15.4, 8.4, 7.1, 1.2 Hz, H-17a), 2.48 (1 H, dddt, *J* = 15.4, 7.1, 5.9, 1.2 Hz, H-17b), 2.44 – 2.37 (1 H, m, H-8a), 2.30 – 2.21 (1 H, m, H-8b), 2.24 – 2.09 (2 H, m, H-9); δ_C (100 MHz; $CDCl_3$) 204.9 (C-7), 168.8 (C-5), 141.6 (C_{Ar}), 137.2 (C_{Ar}), 137.0 (C-10), 135.0 (C-18), 129.8 (CH_{Ar}), 129.1 (CH_{Ar}), 129.0 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.6 (CH_{Ar}), 117.4 (C-19), 115.3 (C-11), 56.9 (C-6), 53.4 (C-12), 40.3 (C-8), 33.6 (C-17), 27.4 (C-9); Found (ESI): $[MH]^+$ 348.1967; $C_{23}H_{26}NO_2$ requires $[MH]^+$ 348.1958, 2.5 ppm.

Lab-book No PD/5/64.

3-Allyl-1-benzyl-3-pent-4-enoylindolin-2-one (**313**)



313

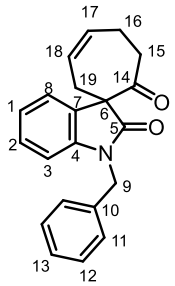
2-Allyl-*N*-benzyl-3-oxo-*N*-phenylhept-6-enamide (**314**) (0.356 g, 1.03 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.208 g, 1.03 mmol) in toluene (20 mL) were subjected to general procedure O at 110 °C for 18 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 8:1) to give the title compound **313** (0.090 g, 45%) as a colourless oil; R_f 0.50 (Petrol/EtOAc, 5:1); ν_{max} (cm^{-1}) 1723, 1707, 1609, 1486, 1466, 1349, 1173, 752, 699; δ_H

(400 MHz; $CDCl_3$) 7.36 – 7.27 (5 H, m, H_{Ar}), 7.22 (1 H, td, *J* = 7.5, 1.3 Hz, H-2), 7.15 (1 H, ddd, *J* = 7.5, 1.3, 0.5 Hz, H-8), 7.04 (1 H, td, *J* = 7.5, 1.3 Hz, H-1), 6.79 (1 H, d, *J* = 7.5 Hz, H-3), 5.66 – 5.55 (1 H, m, H-20), 5.30 (1 H, dddd, *J* = 16.5, 10.1, 8.2, 6.4 Hz, H-15), 5.04 (1 H, ddd, *J* = 16.5, 3.1, 1.2 Hz, H-16a), 4.99 (1 H, d, *J* = 15.6 Hz, H-9a), 4.92 (1 H, d, *J* = 15.6 Hz, H-9b), 4.91 – 4.82 (3 H, m, H-16b, H-21), 3.02 (1 H, ddt, *J* = 13.8, 6.4, 1.2 Hz, H-14a), 2.92 (1 H, dd, *J* = 13.8, 8.2 Hz, H-14b), 2.56 – 2.46 (1 H, m, H-18a), 2.28 – 2.12 (3 H, m, H-18b, H-19); δ_C (100 MHz; $CDCl_3$) 202.0 (C-17), 174.7 (C-5), 143.5 (C-4), 136.6 (C-20), 135.6 (C-10), 131.6 (C-15), 129.2 (C-2), 128.9 (C-11), 127.9 (C-13), 127.7 (C-12), 127.0 (C-7), 124.2 (C-8), 123.2 (C-1), 119.6 (C-16), 115.4 (C-21), 109.6 (C-3), 66.2 (C-6), 44.2 (C-9), 38.2 (C-18), 37.7 (C-14), 27.3 (C-19); Found (ESI): $[MNa]^+$ 368.1673; $C_{23}H_{23}NNaO_2$ requires $[MNa]^+$ 368.1621, 1.7 ppm.

Lab-book No PD/5/73.

6.4.3.2 General procedure Q: Ring-closing metathesis to 7-membered ring systems

(*Z*)-1'-Benzylspiro[cyclohept[3]ene-1,3'-indoline]-2',7-dione (**312**)



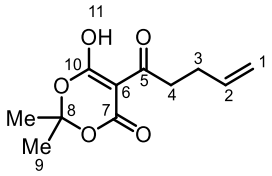
312

To a degassed solution of **313** (0.090 g, 0.220 mmol) (purged three times with nitrogen and vacuum) in CH_2Cl_2 (50 mL) was added Grubbs 2nd generation catalyst (0.022 g, 0.030 mmol) then, the reaction was heated at 45 °C. After 5 h, the reaction mixture was complete by TLC and was allowed to cool to room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 6:1) to give the title compound **312** (0.050 g, 61%) as a clear oil; R_f 0.25 (Petrol/EtOAc, 6:1); ν_{max} (cm^{-1}) 1716, 1669, 1586, 1464, 1443, 1328, 1172, 753, 699; δ_H (400 MHz; $CDCl_3$) 7.34 – 7.21 (6 H, m, H_{Ar}, H-8), 7.18 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.00 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.70 (1 H, d, *J* = 7.6 Hz, H-3), 5.97 – 5.80 (2 H, m, H-17, H-18), 4.95 (1 H, d, *J* = 15.9 Hz, H-9a), 4.84 (1 H, d, *J* = 15.9 Hz, H-9b), 3.66 – 3.58 (1 H, m, H-15a), 3.43 (1 H, ddd, *J* = 15.4, 4.4, 1.8 Hz, H-19a), 2.78 – 2.67 (2 H, m, H-15b, H-16a), 2.65 – 2.50 (1 H, m, H-16b),

2.38 (1 H, dd, *J* = 15.4, 7.5 Hz, H-19b); δ_C (100 MHz; $CDCl_3$) 206.5 (C-14), 174.2 (C-5), 142.8 (C-4), 135.5 (C-10), 131.0 (C-17), 128.92 (C-11), 128.89 (C-7), 128.8 (C-2), 127.7 (C-12), 127.1 (C-13), 125.6 (C-18), 124.2 (C-8), 122.9 (C-1), 109.6 (C-3), 67.8 (C-6), 43.9 (C-9), 39.0 (C-15), 31.4 (C-19), 27.7 (C-16); Found (ESI): $[MH]^+$ 318.1488; $C_{21}H_{20}NO_2$ requires $[MH]^+$ 318.1489, 0.3 ppm.

Lab-book No PD/5/74.

5-(1-Hydroxypent-4-enylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**316**)

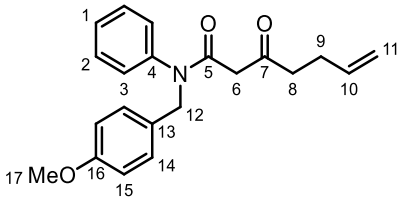


316

A solution of DCC (4.74 g, 23.0 mmol) in CH_2Cl_2 (10 mL) was added slowly to a stirred solution of Meldrum's acid (3.01 g, 20.9 mmol), 4-pentenoic acid (2.13 mL, 20.9 mmol), and 4-(dimethylamino)pyridine (2.81 g, 23.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The suspension was filtered through Celite®, and then washed with CH_2Cl_2 (50 mL). The filtrate was washed subsequently with 10% aq. HCl (50 mL). The aqueous phase was extracted twice with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with water (2 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc) to give the title compound **316** (3.32 g, 70%) as a yellow oil; R_f 0.21 (EtOAc/Petrol, 4:1); ν_{max} (cm^{-1}) 1739, 1665, 1574, 1408, 1282, 1154, 1031, 919; δ_H (400 MHz; $CDCl_3$) 5.84 (1 H, ddt, *J* = 16.9, 10.2, 6.6 Hz, H-2), 5.08 (1 H, dtd, *J* = 16.9, 1.4, 1.3 Hz, H-1a), 5.02 (1 H, dtd, *J* = 10.2, 1.4, 1.3 Hz, H-1b), 3.19 (2 H, dd, *J* = 7.7, 6.6 Hz, H-4), 2.48 (1 H, ddd, *J* = 6.6, 6.6, 1.4 Hz, H-3a), 2.45 (1 H, ddd, *J* = 7.7, 6.6, 1.4 Hz, H-3b), 1.72 (6 H, s, H-9); δ_C (100 MHz; $CDCl_3$) 197.2 (C-5), 170.6 (C-10), 160.3 (C-7), 136.1 (C-2), 116.3 (C-1), 105.0 (C-8), 91.7 (C-6), 35.1 (C-4), 29.9 (C-3), 26.9 (C-9); Found (ESI): $[MNa]^+$ 249.0742; $C_{11}H_{14}NaO_5$ requires $[MNa]^+$ 249.0733, 3.6 ppm.

Lab-book No PD/7/1.

N-(4-Methoxybenzyl)-3-oxo-*N*-phenylhept-6-enamide (**317**)

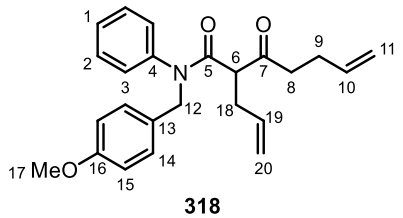


317

To a stirred solution of masked β-keto acid **316** (2.16 g, 9.55 mmol) in 1,4-dioxane (14 mL) was added *N*-(4-methoxybenzyl)aniline (2.04 g, 9.55 mmol). The reaction mixture was stirred for 4 h at 110 °C, then the solvent was removed *in vacuo* and the residual oil was purified by column chromatography (SiO_2, Petrol/EtOAc, 5:1) to give the title compound **317** (2.81 g, 87%) as a yellow oil; R_f 0.31 (Petrol/EtOAc, 4:1); ν_{max} (cm^{-1}) 1720, 1651, 1594, 1512, 1395, 1244, 1175, 1033, 821, 701; δ_H (400 MHz; $CDCl_3$) 7.32 – 7.28 (3 H, m, H-1, H-2), 7.12 (2 H, d, *J* = 8.7 Hz, H-14), 6.94 (2 H, dd, *J* = 6.5, 3.1 Hz, H-3), 6.78 (2 H, d, *J* = 8.7 Hz, H-15), 5.70 (1 H, ddt, *J* = 16.8, 10.2, 6.6 Hz, H-10), 4.94 (1 H, dd, *J* = 16.8, 1.5 Hz, H-11a), 4.91 (1 H, dd, *J* = 10.2, 1.5 Hz, H-11b), 4.83 (2 H, s, H-12), 3.76 (3 H, s, H-17), 3.27 (2 H, s, H-6), 2.41 (2 H, t, *J* = 7.1 Hz, H-8), 2.21 (2 H, td, *J* = 7.1, 6.6 Hz, H-9); δ_C (100 MHz; $CDCl_3$) 203.7 (C-7), 166.7 (C-5), 159.0 (C-16), 141.9 (C-13), 136.8 (C-10), 130.3 (C-14), 129.7 (C-2), 129.2 (C-4), 128.6 (C-3), 128.5 (C-1), 115.4 (C-11), 113.8 (C-15), 55.3 (C-17), 52.5 (C-12), 49.5 (C-6), 42.3 (C-8), 27.5 (C-9); Found (ESI): $[MNa]^+$ 360.1561; $C_{21}H_{23}NNaO_3$ requires $[MNa]^+$ 360.1570, 2.6 ppm.

Lab-book No PD/7/2.

N-(4-Methoxybenzyl)-2-(2-methylallyl)-3-oxo-*N*-phenylhept-6-enamide (**318**)



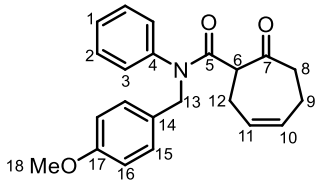
318

N-(4-Methoxybenzyl)-3-oxo-*N*-phenylhept-6-enamide (**317**) (2.58 g, 7.65 mmol), NaH (0.336 g, 8.41 mmol), allyl bromide (0.695 mL, 8.03 mmol) in DMF (100 mL) were subjected to general procedure P at 0 °C for 18 h. Purification by column chromatography (SiO_2, Petrol/EtOAc, 6:1) gave the title compound **318** (3.21 g, quant.) as a light yellow oil; R_f 0.43 (Petrol/EtOAc, 4:1); ν_{max} (cm^{-1}) 1717, 1650, 1613, 1594, 1512, 1394, 1302, 1245, 1176, 1033, 916, 702; δ_H (400 MHz; $CDCl_3$) 7.34 – 7.29 (3 H, m, H-1, H-2), 7.09 (2 H, d, *J* = 8.6 Hz, H-14), 6.90 (2 H, dd, *J* = 6.6, 3.1 Hz, H-3), 6.77 (2 H, d, *J* = 8.6 Hz, H-15), 5.75 –

5.58 (2 H, m, H-10, H-19), 5.05 – 4.90 (4 H, m, H-11, H-20), 4.82 (2 H, s, H-12), 3.77 (3 H, s, H-17), 3.35 (1 H, dd, *J* = 8.4, 5.9 Hz, H-6), 2.64 (1 H, ddd, *J* = 15.3, 8.4, 7.2 Hz, H-18a), 2.47 (1 H, ddd, *J* = 15.3, 7.2, 5.9 Hz, H-18b), 2.42 – 2.35 (1 H, m, H-8a), 2.29 – 2.21 (1 H, m, H-8b), 2.22 – 2.14 (2 H, m, H-9); δ_C (100 MHz; $CDCl_3$) 204.9 (C-7), 168.7 (C-5), 159.1 (C-16), 141.5 (C-13), 137.0 (C-10), 135.1 (C-19), 130.4 (C-14), 129.8 (C-2), 129.4 (C-4), 129.2 (C-3), 128.5 (C-1), 117.3 (C-20), 115.3 (C-11), 113.8 (C-15), 56.9 (C-6), 55.3 (C-17), 52.8 (C-12), 40.3 (C-8), 33.6 (C-18), 27.4 (C-9); Found (ESI): $[MNa]^+$ 400.1878; $C_{24}H_{27}NNaO_3$ requires $[MNa]^+$ 400.1883, 1.4 ppm.

Lab-book No PD/7/11.

(*Z*)-*N*-(4-Methoxybenzyl)-7-oxo-*N*-phenylcyclohept-3-enecarboxamide (**319**)

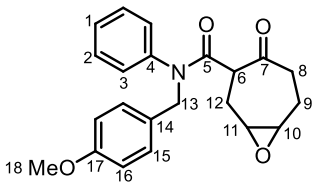


319

N-(4-Methoxybenzyl)-2-(2-methylallyl)-3-oxo-*N*-phenylhept-6-enamide (**318**) (0.493 g, 1.33 mmol), Grubbs 2nd generation catalyst (0.052 g, 0.067 mmol), in CH_2Cl_2 (100 mL) were subjected to general procedure Q at 45 °C for 1 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 5:1 to Petrol/EtOAc, 2:1) to give the title compound **319** (0.264 g, 57%) as a colourless oil; R_f 0.42 (Petrol/EtOAc, 4:1); ν_{max} (cm^{-1}) 1709, 1661, 1648, 1594, 1512, 1396, 1244, 1176, 1033, 702; δ_H (400 MHz; $CDCl_3$) 7.30 – 7.26 (3 H, m, H-1, H-2), 7.12 (2 H, d, *J* = 8.7 Hz, H-15), 6.94 (2 H, dd, *J* = 5.8, 3.8 Hz, H-3), 6.77 (2 H, d, *J* = 8.7 Hz, H-16), 5.68 – 5.56 (2 H, m, H-10, H-11), 4.88 (1 H, d, *J* = 14.2 Hz, H-13a), 4.77 (1 H, d, *J* = 14.2 Hz, H-13b), 3.80 (1 H, dd, *J* = 11.9, 3.9 Hz, H-6), 3.75 (3 H, s, H-18), 2.79 – 2.71 (1 H, m, H-12a), 2.67 (1 H, dd, *J* = 14.9, 7.3 Hz, H-8a), 2.43 – 2.34 (1 H, m, H-12b), 2.08 – 2.02 (2 H, m, H-9), 2.01 – 1.93 (1 H, m, H-8b); δ_C (100 MHz; $CDCl_3$) 209.2 (C-7), 169.5 (C-5), 159.0 (C-17), 141.6 (C-4), 130.2 (C-15), 129.6 (CH_{Ar}), 129.4 (C-14), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.4 (C-10 or C-11), 128.2 (C-10 or C-11), 113.8 (C-16), 55.3 (C-6 or C-18), 55.2 (C-6 or C-18), 52.5 (C-13), 42.2 (C-8), 28.4 (C-12), 23.9 (C-9); Found (ESI): $[MNa]^+$ 372.1573; $C_{22}H_{23}NNaO_3$ requires $[MNa]^+$ 372.1570, 0.7 ppm.

Lab-book No PD/7/13.

N-(4-Methoxybenzyl)-4-oxo-*N*-phenyl-8-oxabicyclo[5.1.0]octane-3-carboxamide (**320**)

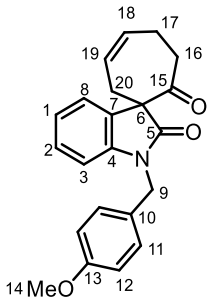


320

To a stirred solution of (*Z*)-*N*-(4-methoxybenzyl)-7-oxo-*N*-phenylcyclohept-3-enecarboxamide (**319**) (0.122 g, 0.348 mmol) in acetone (2 mL) at 0 °C was added a solution of DMDO (0.06 M in acetone, 11.05 mL, 0.696 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature for a further 1 h. The solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc/Petrol 2:1) to give the title compound **320** (0.108 g, 85%) as a colourless oil and inseparable mixture of 1:1.5 diastereoisomers **320**:**320'**; R_f 0.11 (Petrol/EtOAc, 2:1); ν_{max} (cm^{-1}) 1710, 1657, 1594, 1594, 1512, 1396, 1244, 1176, 1031, 730, 702; δ_H (400 MHz; $CDCl_3$) 7.31 – 7.26 (3 H, m, H-1, H-2), 7.14 – 7.06 (2 H, m, H-15), 6.92 – 6.84 (2 H, m, H-3), 6.80– 6.74 (2 H, m, H-16), 4.84 (1 H, d, *J* = 14.3 Hz, H-13a, H-13a'), 4.77 (0.4 H, d, *J* = 14.3 Hz, H-13b), 4.75 (0.6 H, d, *J* = 14.3 Hz, H-13b'), 3.75 (3 H, s, H-18), 3.66 – 3.58 (1 H, m, H-6), 3.17 (1 H, td, *J* = 4.6, 1.7 Hz, H-11), 3.06 – 3.01 (1 H, m, H-10), 2.54 – 2.34 (2 H, m, H-12), 2.09 (0.6 H, ddd, *J* = 12.1, 7.5, 4.4 Hz, H-8a'), 2.01 – 1.93 (2 H, m, H-9), 1.82 (1.4 H, ddd, *J* = 12.1, 9.8, 4.4 Hz, H-8a, H-8b, H-8b'); δ_C (100 MHz; $CDCl_3$) 209.3 and 207.4 (C-7), 168.9 and 168.7 (C-5), 159.0 (C-17), 141.3 and 141.2 (C-4), 130.2 and 130.1 (C-15), 129.74 and 129.70 (C-2), 129.4 (C-1), 129.31 and 129.26 (C-14), 128.5 (C-3), 113.8 (C-16), 55.3 (C-18), 54.4 (C-11), 54.0 and 53.3 (C-10), 52.6 and 52.5 (C-13), 51.7 and 51.4 (C-6), 38.0 and 36.3 (C-8), 28.6 and 27.3 (C-12), 24.0 and 22.7 (C-9); Found (ESI): $[MNa]^+$ 388.1504; $C_{22}H_{23}NNaO_4$ requires $[MNa]^+$ 388.1519, 3.9 ppm.

Lab-book No PD/7/14.

(*Z*)-1'-(4-Methoxybenzyl)spiro[cyclohept[3]ene-1,3'-indoline]-2',7-dione (**321**)

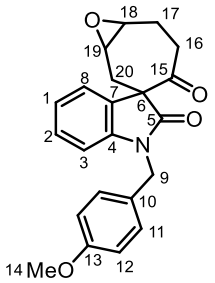


321

(*Z*)-*N*-(4-Methoxybenzyl)-7-oxo-*N*-phenylcyclohept-3-enecarboxamide (**319**) (0.023 g, 0.067 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.018 g, 0.094 mmol) in toluene (2 mL) were subjected to general procedure O at 100 °C for 1.5 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc 6:1) to give the title compound **321** (0.013 g, 55%) as a colourless solid; mp. 125-127 °C; R_f 0.27 (Petrol/EtOAc, 4:1); ν_{max} (cm^{-1}) 1697, 1610, 1514, 1487, 1466, 1352, 1248, 1178, 1033, 750; δ_H (400 MHz; $CDCl_3$) 7.28 (1 H, dd, *J* = 7.6, 1.0 Hz, H-8), 7.20 (2 H, d, *J* = 8.7 Hz, H-11), 7.17 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 6.99 (1 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.83 (2 H, d, *J* = 8.7 Hz, H-12), 6.72 (1 H, d, *J* = 7.6 Hz, H-3), 5.95 – 5.80 (2 H, m, H-18, H-19), 4.88 (1 H, d, *J* = 15.5 Hz, H-9a), 4.77 (1 H, d, *J* = 15.5 Hz, H-9b), 3.76 (3 H, s, H-14), 3.60 (1 H, dd, *J* = 14.2, 8.1 Hz, H-16a), 3.41 (1 H, ddd, *J* = 15.4, 4.7, 2.2 Hz, H-20a), 2.76 – 2.65 (2 H, m, H-16b, H-17a), 2.63 – 2.50 (1 H, m, H-17b), 2.35 (1 H, dd, *J* = 15.4, 7.4 Hz, H-20b); δ_C (100 MHz; $CDCl_3$) 206.6 (C-15), 174.2 (C-5), 159.1 (C-13), 142.9 (C-4), 131.0 (C-18 or C-19), 130.6 (C-7), 128.8 (C-2), 128.5 (C-11), 127.5 (C-10), 125.6 (C-18 or C-19), 124.2 (C-8), 122.8 (C-1), 114.3 (C-12), 109.6 (C-3), 67.8 (C-6), 55.3 (C-14), 43.4 (C-9), 39.0 (C-16), 31.4 (C-20), 27.7 (C-17); Found (ESI): $[MNa]^+$ 370.1410; $C_{22}H_{21}NNaO_3$ requires $[MNa]^+$ 370.1414, 1.1 ppm.

Lab-book No PD/7/17.

1'-(4-Methoxybenzyl)-8-oxaspiro[bicyclo[5.1.0]octane-3,3'-indoline]-2',4-dione (**322**)

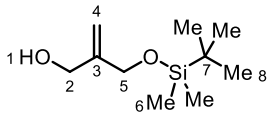


322

N-(4-Methoxybenzyl)-4-oxo-*N*-phenyl-8-oxabicyclo[5.1.0]octane-3-carboxamide (**320**) (0.024 g, 0.067 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.016 g, 0.085 mmol) in toluene (2 mL) were subjected to general procedure O at 100 °C for 1.5 h. The residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 3:1) to give the title compound **322** (0.015 g, 62%) as a slightly yellow oil and inseparable mixture of diastereoisomers in a 1:3 ratio of **322**:**322'**; R_f 0.48 (Petrol/EtOAc, 1:1); ν_{max} (cm^{-1}) 1698, 1611, 1514, 1488, 1466, 1362, 1248, 1178, 1033, 751; δ_H (400 MHz; $CDCl_3$) 7.55 (1 H, dd, *J* = 7.6, 1.0 Hz, H-8), 7.20 (1 H, td, *J* = 7.6, 1.0 Hz, H-2), 7.17 (2 H, d, *J* = 8.8 Hz, H-11), 7.08 (0.75 H, td, *J* = 7.6, 1.0 Hz, H-1'), 7.02 (0.25 H, td, *J* = 7.6, 1.0 Hz, H-1), 6.83 (2 H, d, *J* = 8.8 Hz, H-12), 6.73 (1 H, d, *J* = 7.6 Hz, H-3), 4.94 – 4.74 (1 H, m, H-9a, H-9a'), 4.76 (0.75 H, d, *J* = 15.6 Hz, H-9b'), 4.76 (0.25 H, d, *J* = 15.6 Hz, H-9b), 3.75 (3 H, s, H-14), 3.43 (1 H, ddd, *J* = 6.9, 3.9, 2.4 Hz, H-19), 3.31 (1 H, dt, *J* = 3.9, 2.8 Hz, H-18), 3.19 (1 H, dd, *J* = 8.4, 3.0 Hz, H-16a), 3.13 (1 H, dd, *J* = 15.7, 2.4 Hz, H-20a), 2.54 – 2.47 (3 H, m, H-16b, H-17), 2.41 (1 H, dd, *J* = 15.7, 6.9 Hz, H-20b); δ_C (100 MHz; $CDCl_3$) 204.0 (C-15), 173.9 (C-5), 159.2 (C-13), 142.9 (C-4), 130.3 (C-7), 129.2 and 128.8 (C-2), 128.53 and 128.45 (C-11), 127.4 (C-10), 125.6 and 123.9 (C-8), 123.4 and 122.9 (C-1), 114.3 (C-12), 110.1 and 109.5 (C-3), 64.8 and 63.8 (C-6), 55.3 (C-14), 55.2 and 53.9 (C-18), 54.3 and 53.5 (C-19), 43.54 and 43.46 (C-9), 36.5 and 35.8 (C-16), 33.1 and 32.8 (C-20), 25.9 and 24.9 (C-17); Found (ESI): $[MNa]^+$ 386.1369; $C_{22}H_{21}NNaO_4$ requires $[MNa]^+$ 386.1363, 1.6 ppm.

Lab-book No PD/7/16.

2-((*tert*-Butyldimethylsilyloxy)methyl)prop-2-en-1-ol[136a] (**330**)



330

To a stirred solution of paraformaldehyde (1.50 g, 50.0 mmol) and methyl acrylate (13.5 mL, 150 mmol) in a mixture of 1,4-dioxane:water (25 mL, 1:1) was added DABCO (5.21 g, 50.0 mmol). The reaction mixture was stirred overnight at room temperature. Water (20 mL) and Et_2O (20 mL) were added to the mixture. The aqueous phase was separated and extracted with Et_2O (2 × 20 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

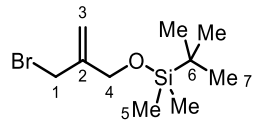
To a stirred solution of methyl 2-(hydroxymethyl)acrylate (4.55 g, 35.0 mmol) in dry CH_2Cl_2 (100 mL) was added imidazole (5.99 g, 88.0 mmol) and *tert*-butyldimethylsilyl chloride (6.33 g, 42.0 mmol). The reaction mixture was stirred at room temperature for 2 h and subsequently quenched with a solution of sat. aq. $NaHCO_3$ (100 mL). The organic layer was separated by extraction with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a colourless oil which was purified by column chromatography (SiO_2, Petrol/EtOAc, 99:1) to give the ester (5.13 g, 64%) as a colourless oil. (*Lab-book No PD/6/59*)

To a stirred solution of ester (5.13 g, 22.3 mmol) in Et_2O (180 mL) at −78 °C was added a solution of di*iso*butylaluminum hydride (1.0 M in hexanes, 67.0 mL, 67.0 mmol) dropwise. After 2 h, the reaction mixture was quenched with sat. aq. Rochelle's salt (100 mL). The reaction mixture was diluted with EtOAc (100 mL) and allowed to warm to room temperature. After stirring overnight, the organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound **330** (4.18 g, 94%) as a clear oil which was used in the next step without further purification; R_f 0.11 (Petrol/EtOAc, 9:1); 5.08 (1 H, dd, *J* = 2.0, 1.2 Hz, H-4a), 5.07 (1 H, dd, *J* = 2.0, 1.2 Hz, H-4b), 4.23 (2 H, s, H-5), 4.15 (2 H, s, H-2), 0.90 (9 H, s, H-8), 0.07 (6 H, s, H-6).

Analytical data are consistent with literature values.[136a]

Lab-book No PD/6/60

(2-(Bromomethyl)allyloxy)*tert*-butyldimethylsilane[162] (**326**)



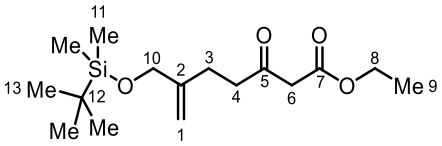
326

To a stirred solution of allylic alcohol **330** (1.02 g, 4.94 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added tetrabromomethane (3.28 g, 9.88 mmol) and PPh_3 (2.59 g, 9.88 mmol). The reaction mixture was stirred for 30 min and allowed to warm to room temperature, then stirred for a further 2 h, and subsequently quenched with a sat. aq. solution of NH_4Cl (20 mL). The aqueous layer was separated, and extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a colourless oil which was purified by column chromatography (SiO_2, Petrol/EtOAc, 99:1) to give the title compound **326** (0.420 g, 32%) as a colourless oil; R_f 0.80 (Petrol/EtOAc, 9:1); δ_H (400 MHz; $CDCl_3$) 5.25 (1 H, dq, *J* = 2.0, 1.2 Hz, H-3a), 5.20 (1 H, dq, *J* = 2.0, 1.2 Hz, H-3b), 4.26 (2 H, t, *J* = 1.2 Hz, H-4), 4.00 (2 H, s, H-1), 0.91 (9 H, s, H-7), 0.09 (6 H, s, H-5).

Analytical data are consistent with literature values.[162]

Lab-book No PD/6/68.

Ethyl 6-((*tert*-butyldimethylsilyloxy)methyl)-3-oxohept-6-enoate (**331**)



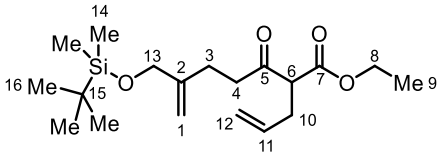
331

To a stirred solution of di*iso*propylamine (0.420 mL, 3.02 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in hexanes, 1.97 mL, 3.16 mmol) at 0 °C. The pale yellow solution was held at 0 °C for 20 min and cooled to −78 °C, then ethyl acetoacetate (0.180 mL, 1.44 mmol) was added and the reaction was stirred at −78 °C for 15 min before the subsequent addition of (2-(bromomethyl)allyloxy)*tert*-butyldimethylsilane (**326**) (0.400 g, 1.51 mmol) as a solution in THF (1 mL). The reaction mixture was stirred for 1 h at −78 °C, warmed to room temperature, and stirred for 4 h. An aq. sat. sol. of NH_4Cl (5 mL) was added. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 20:1) to

give the title compound **331** (0.107 g, 24%) as a colourless oil; R_f 0.40 (Petrol/EtOAc, 9:1); ν_{max} (cm^{-1}) 2955, 2930, 2857, 1472, 1463, 1252, 1084, 834, 775, 669; δ_H (400 MHz; $CDCl_3$) 5.04 (1 H, dd, *J* = 2.6, 1.2 Hz, H-1a), 4.79 (1 H, dd, *J* = 2.6, 1.2 Hz, H-1b), 4.19 (2 H, q, *J* = 7.0 Hz, H-8), 4.06 (2 H, s, H-10), 3.44 (2 H, s, H-6), 2.73 (2 H, t, *J* = 8.2 Hz, H-4), 2.30 (2 H, t, *J* = 8.2 Hz, H-3), 1.27 (3 H t, *J* = 7.0 Hz, H-9), 0.90 (9 H, s, H-13), 0.05 (6 H, s, H-11); δ_C (100 MHz; $CDCl_3$) 203.1 (C-5), 167.3 (C-7), 147.0 (C-2), 109.3 (C-1), 66.1 (C-10), 61.5 (C-8), 49.4 (C-6), 41.4 (C-4), 26.2 (C-3), 26.0 (C-13), 18.4 (C-12), 14.2 (C-9), −5.3 (C-11); Found (ESI): $[MNa]^+$ 337.1803; $C_{16}H_{30}NaO_4Si$ requires $[MNa]^+$ 337.1806, 0.7 ppm.

Lab-book No PD/6/70.

Ethyl 2-allyl-6-[(*tert*-butyldimethylsilyloxy)methyl]-3-oxohept-6-enoate (**332**)



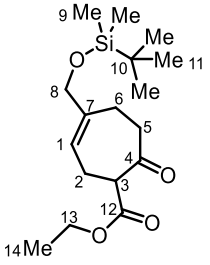
332

Ethyl 6-[(*tert*-butyldimethylsilyloxy)methyl]-3-oxohept-6-enoate (**331**) (0.089 g, 0.280 mmol), NaH (0.012 g, 0.310 mmol), allyl bromide (0.026 g, 0.300 mmol) in DMF (8 mL) were subjected to general procedure P at 0 °C for 2 h. The crude pale yellow oil was then purified by column chromatography (SiO_2, Petrol/EtOAc, 40:1) to give the title compound **332** (0.045 g, 46%) as a colourless oil in a 1.5:1 mixture of keto-enol tautomers, respectively; R_f 0.38 (Petrol/EtOAc, 20:1); ν_{max} (cm^{-1}) 2956, 2930, 2857, 1743, 1716, 1472, 1253, 1112, 837, 777; δ_H (400 MHz; $CDCl_3$, **Keto**) 5.72 (1 H, ddt, *J* = 17.0, 10.2, 6.9 Hz, H-11), 5.11 – 5.04 (2 H, m, H-12), 5.04 – 5.03 (1 H, m, H-1a), 4.77 (1 H, dd, *J* = 2.7, 1.3 Hz, H-1b), 4.17 (2 H, dq, *J* = 10.8, 7.1 Hz, H-8), 4.05 (2 H, s, H-13), 3.53 (1 H, t, *J* = 7.4 Hz, H-6), 2.74 (1 H, t, *J* = 7.6 Hz, H-4a), 2.68 (1 H, t, *J* = 7.6 Hz, H-4b), 2.58 (2 H, dd, *J* = 7.4, 6.9 Hz, H-10), 2.27 (2 H, t, *J* = 7.6 Hz, H-3), 1.25 (3 H, t, *J* = 7.1 Hz, H-9), 0.89 (9 H, s, H-16), 0.05 (6 H, s, H-14); δ_C (100 MHz; $CDCl_3$, **Keto**) 204.0 (C-5), 169.3 (C-7), 147.2 (C-2), 134.4 (C-11), 117.6 (C-12), 109.2 (C-1), 66.1 (C-13), 61.5 (C-8), 58.6 (C-6), 40.6 (C-4), 32.3 (C-10), 26.1 (C-3), 26.0 (C-16), 18.4 (C-15), 14.2 (C-9), −5.3 (C-14); δ_H (400 MHz; $CDCl_3$, **Enol**) 5.60 (1 H, ddt, *J* = 16.6, 10.4, 7.3 Hz, H-11), 5.17 (1 H, dd, *J* = 2.6, 1.2 Hz, H-1a), 5.07 – 5.04 (2 H, m, H-12), 4.82 (1 H, dd, *J* = 2.6, 1.2 Hz, H-1b), 4.17 (2 H, dq, *J* = 10.8, 7.1 Hz, H-8), 3.93 (2 H, s, H-13), 2.76 – 2.58 (6 H, m, H-3, H-4, H-10), 1.25 (3 H, t, *J* = 7.1 Hz, H-9), 0.88 (9 H, s, H-16), 0.03 (6 H, s, H-14); δ_C (100 MHz; $CDCl_3$, **Enol**) 204.5 (C-5), 171.9 (C-7), 143.7 (C-2), 132.6 (C-11), 119.1 (C-12), 113.3 (C-1), 66.1 (C-13), 63.2 (C-6), 61.5 (C-

8), 40.6 (C-4), 36.4 (C-10), 34.3 (C-3), 26.0 (C-16), 18.4 (C-15), 14.1 (C-9), −5.3 (C-14); Found (ESI): $[MNa]^+$ 377.2107; $C_{19}H_{34}NaO_4Si$ requires $[MNa]^+$ 377.2119, 3.1 ppm.

Lab-book No PD/6/72.

Ethyl 4-{[(*tert*-butyldimethylsilyl)oxy]methyl}-7-oxocyclohept-3-ene-1-carboxylate (**324**)



324

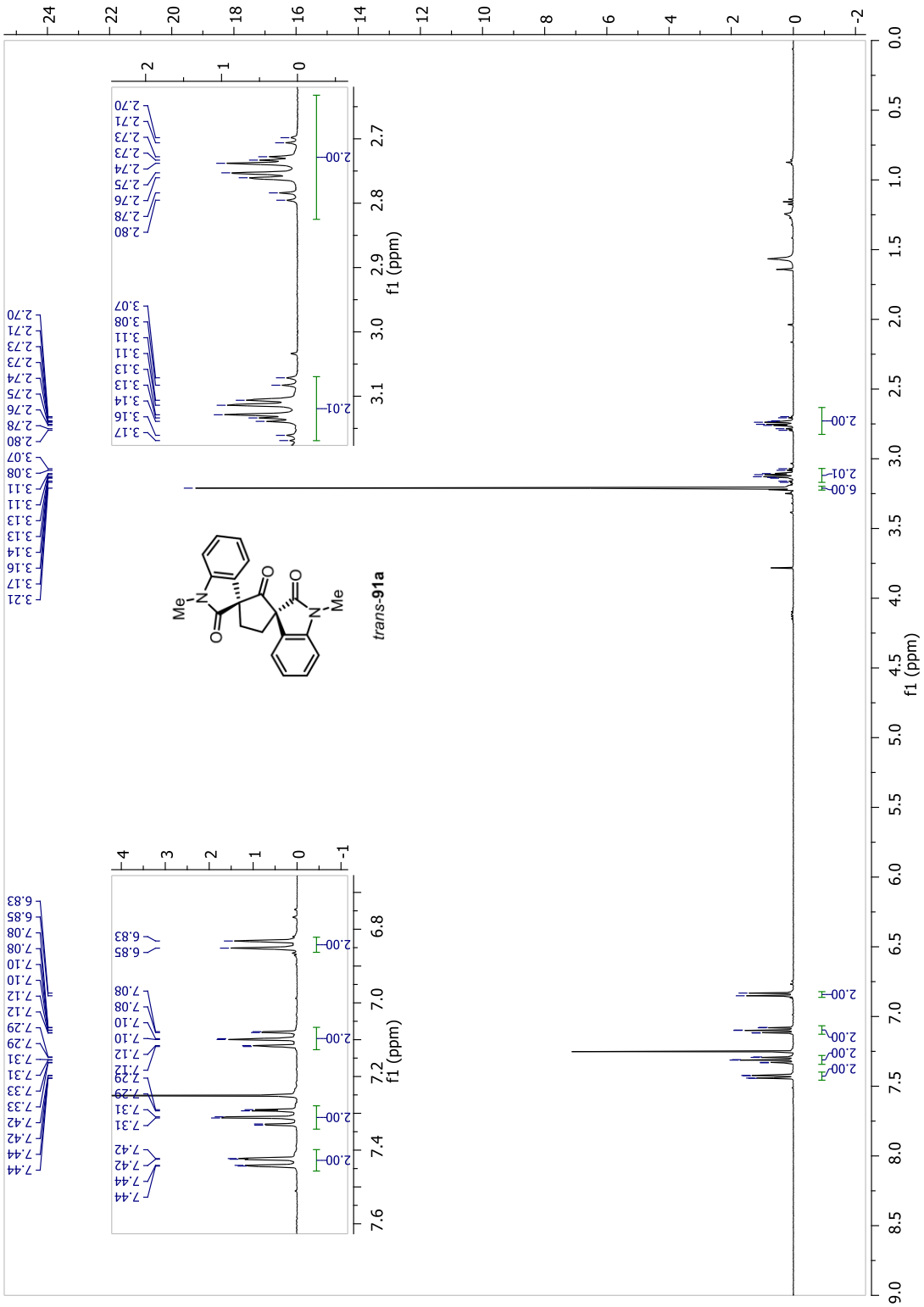
To a stirred and degassed solution of diene **332** (0.043 g, 0.120 mmol) in CH_2Cl_2 (20 mL) was added 2nd generation Grubbs catalyst (0.011 g, 0.012 mmol). The reaction mixture was stirred for 1 h at reflux during which a colour change from light red to brown was observed. The reaction was allowed to cool to room temperature, then the solvent was removed under vacuum and the crude residue was purified by column chromatography (SiO_2, Petrol/EtOAc, 20:1) to give the title compound **324** (0.035 g, 90%) as a colourless oil and as a respective 1.3:1 mixture of keto-enol tautomers, respectively; R_f 0.32 (Petrol/EtOAc, 9:1); ν_{max} (cm^{-1}) 2955, 2930, 2857, 1745, 1714, 1464, 1362, 1252, 1153, 1096, 1069, 836, 777; δ_H (400 MHz; $CDCl_3$, **Keto**) 5.77 (1 H, t, *J* = 6.5 Hz, H-1), 4.25 (2 H, q, *J* = 7.1 Hz, H-13), 4.03 (2 H, s, H-8), 3.74 (1 H, dd, *J* = 10.6, 3.8 Hz, H-3), 3.13 (1 H, dd, *J* = 15.7, 6.5 Hz, H-5a), 2.95 – 2.90 (2 H, m, H-6), 2.76 (1 H, dd, *J* = 15.7, 6.5 Hz, H-5b), 2.30 – 2.24 (2 H, m, H-2), 1.25 (3 H, t, *J* = 7.1 Hz, H-14), 0.88 (9 H, s, H-11), 0.04 (6 H, s, H-9); δ_C (100 MHz; $CDCl_3$, **Keto**) 207.5 (C-4), 169.9 (C-12), 141.4 (C-7), 121.3 (C-1), 67.6 (C-8), 61.7 (C-13), 57.6 (C-3), 41.9 (C-5), 39.0 (C-6), 26.5 (C-2), 25.9 (C-11), 18.4 (C-10), 14.2 (C-14), −5.3 (C-9); δ_H (400 MHz; $CDCl_3$, **Enol**) 5.41 (1 H, td, *J* = 5.7, 2.1 Hz, H-1), 4.19 (2 H, q, *J* = 7.1 Hz, H-13), 4.13 (2 H, s, H-8), 2.95 – 2.92 (1 H, m, H-5a), 2.88 – 2.86 (2 H, m, H-6), 2.75 – 2.69 (1 H, m, H-5b), 2.16 (2 H, s, H-2), 1.28 (3 H, t, *J* = 7.1 Hz, H-14), 0.88 (9 H, s, H-11), 0.04 (6 H, s, H-9); δ_C (100 MHz; $CDCl_3$, **Enol**) 202.9 (C-4), 172.9 (C-12), 141.6 (C-7), 121.3 (C-1), 65.8 (C-3), 61.7 (C-13), 61.2 (C-8), 41.9 (C-5), 38.9 (C-6), 25.9 (C-11), 24.5 (C-2), 18.4 (C-10), 14.1 (C-14), −5.3 (C-9); Found (ESI): $[MNa]^+$ 349.1800; $C_{17}H_{30}NaO_4Si$ requires $[MNa]^+$ 349.1806, 1.6 ppm.

Lab-book No PD/6/73.

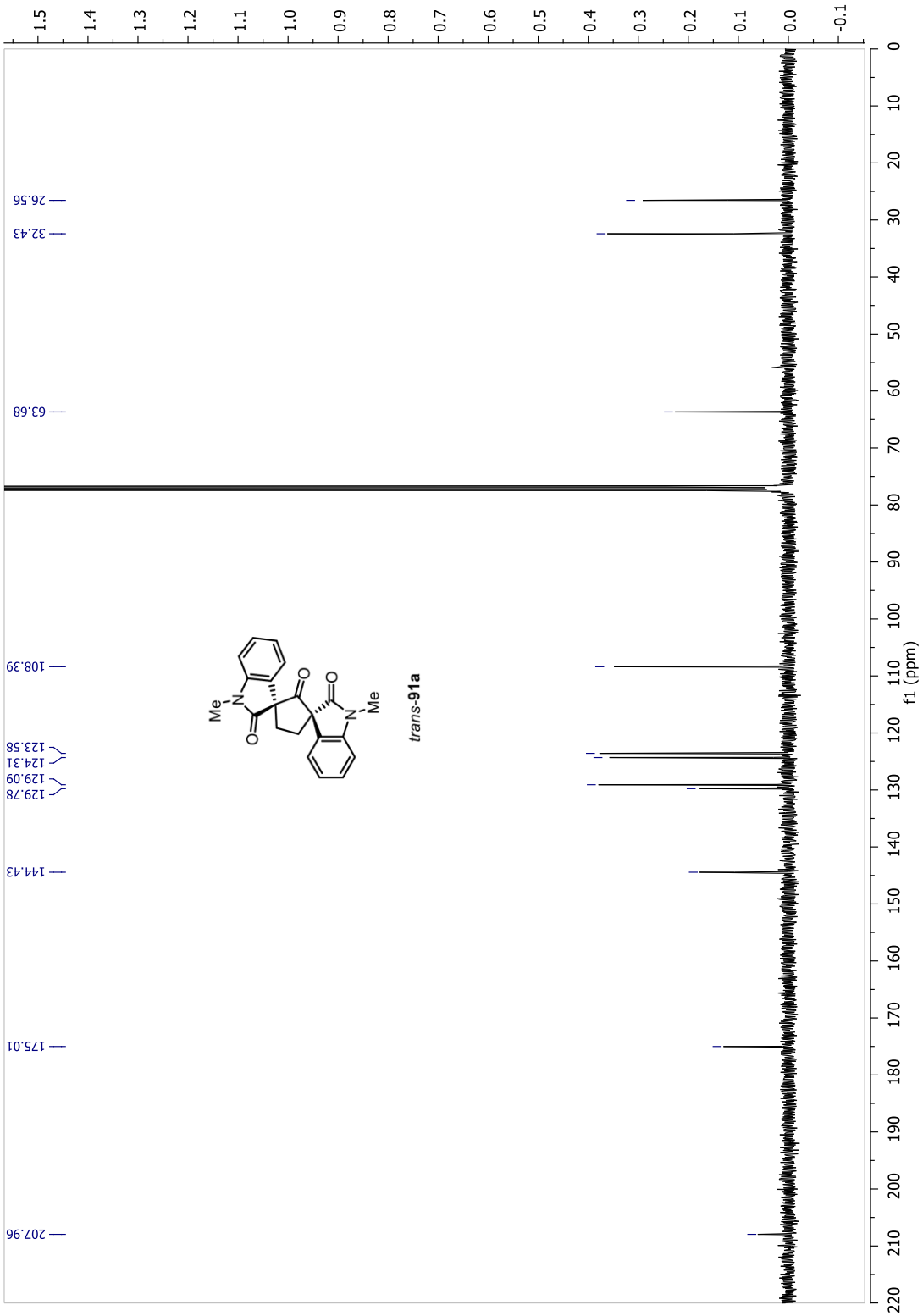
Appendices

Appendix I: Representative NMR spectra

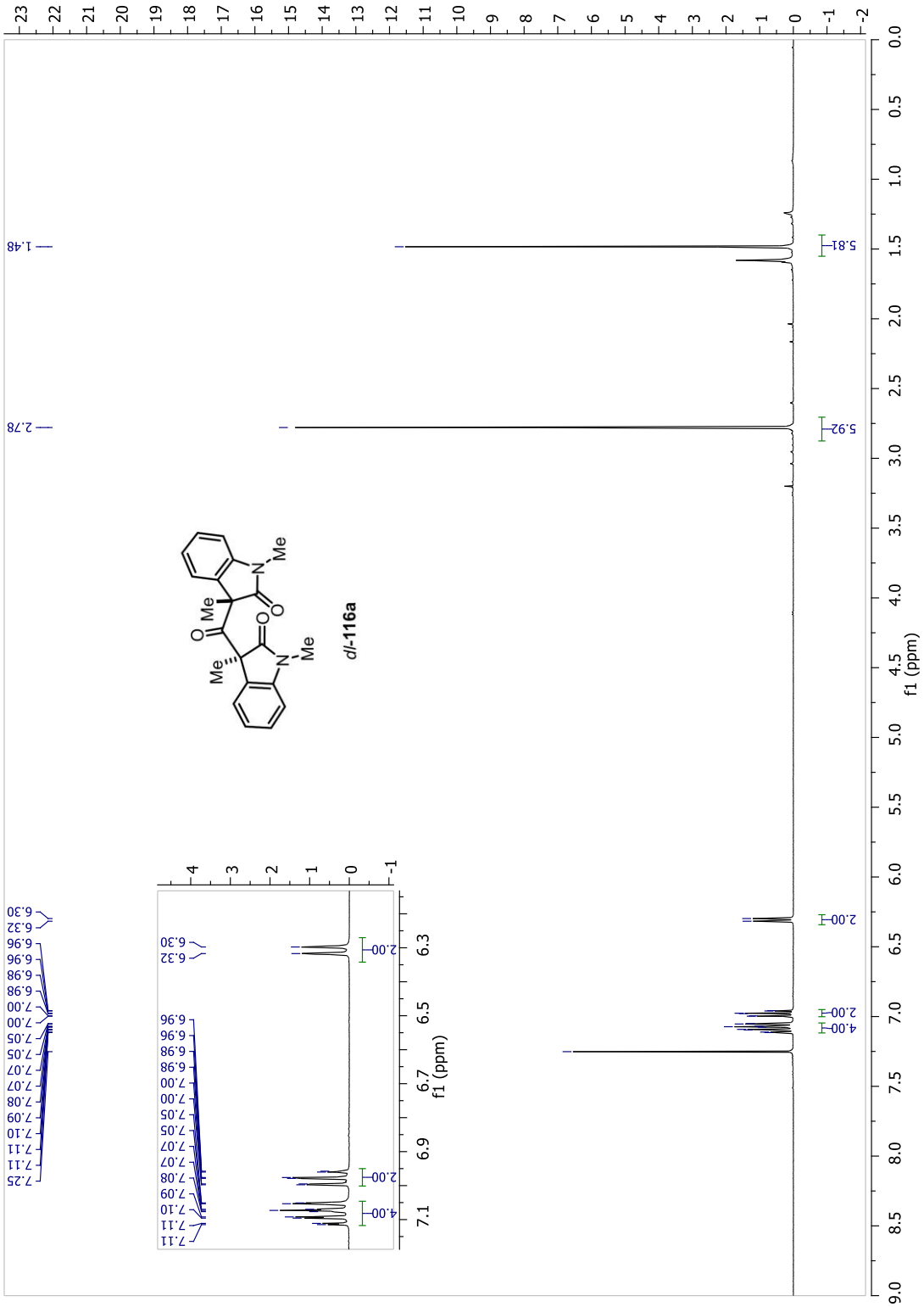
^{1}H NMR spectrum of spirocyclic bis-oxindole *trans*-91a (400 MHz; $CDCl_3$)



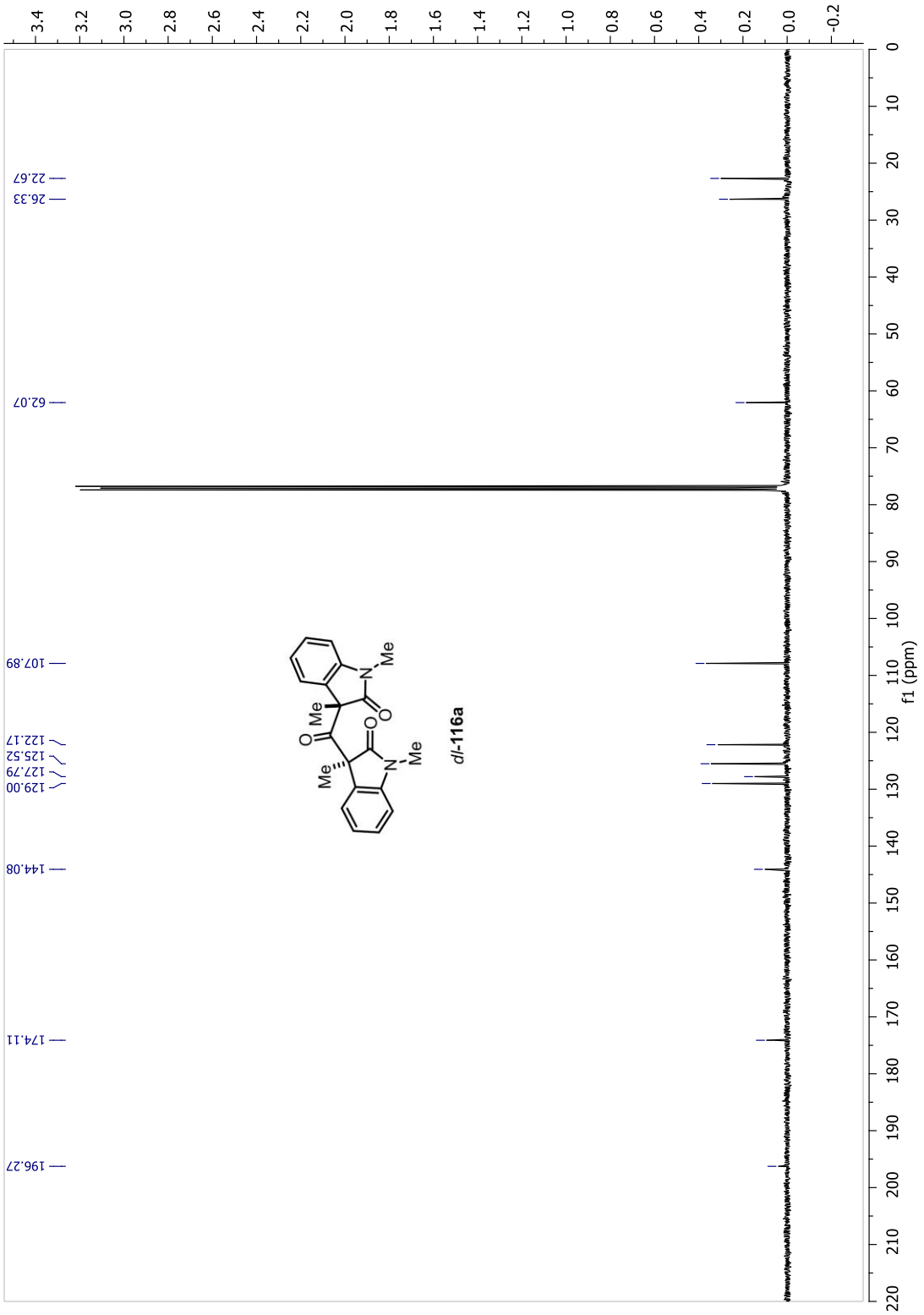
^{13}C NMR spectrum of spirocyclic bis-oxindole *trans*-91a (100 MHz; $CDCl_3$)



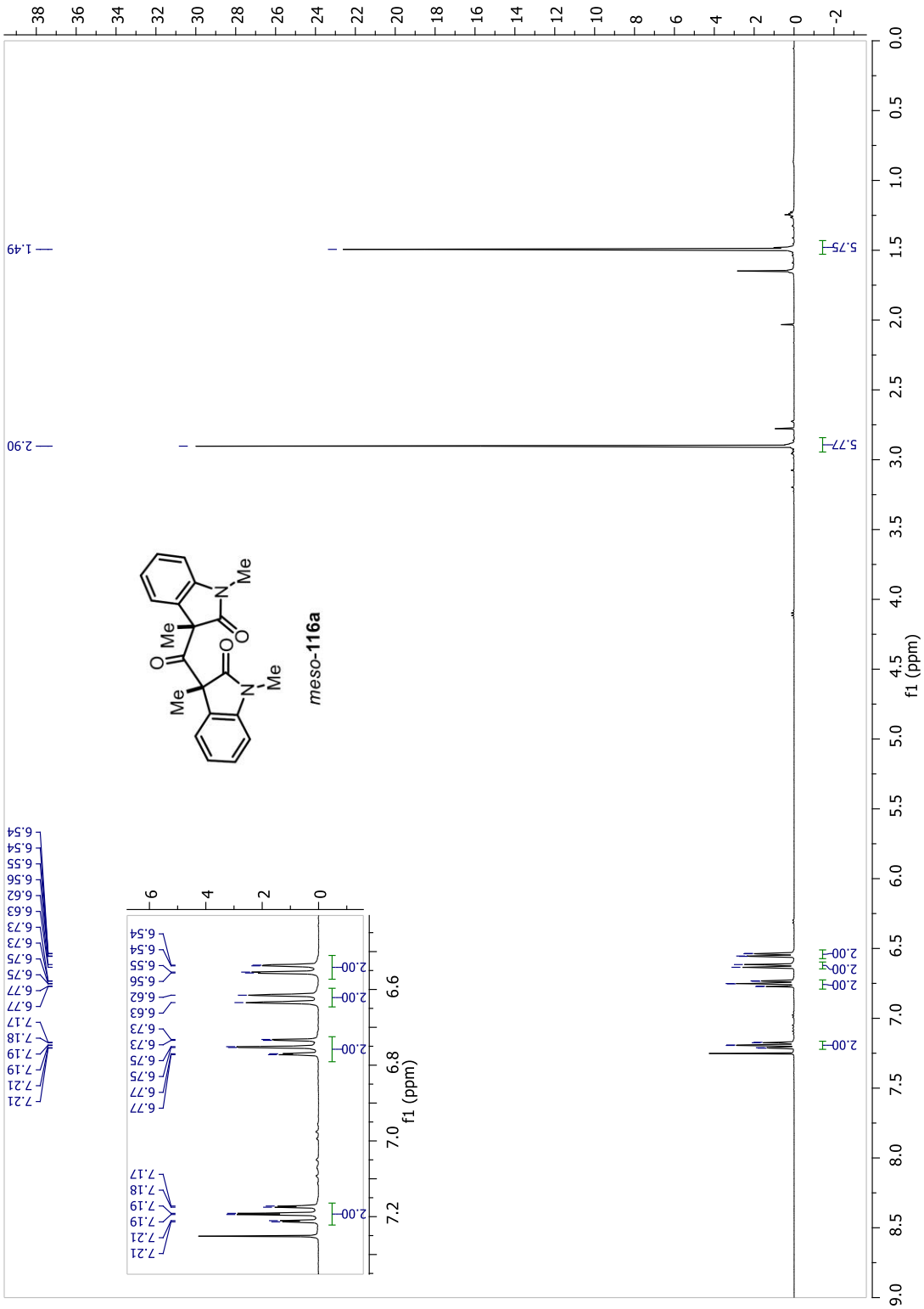
^{1}H NMR spectrum of bis-oxindole *dl*-116a (400 MHz; $CDCl_3$)



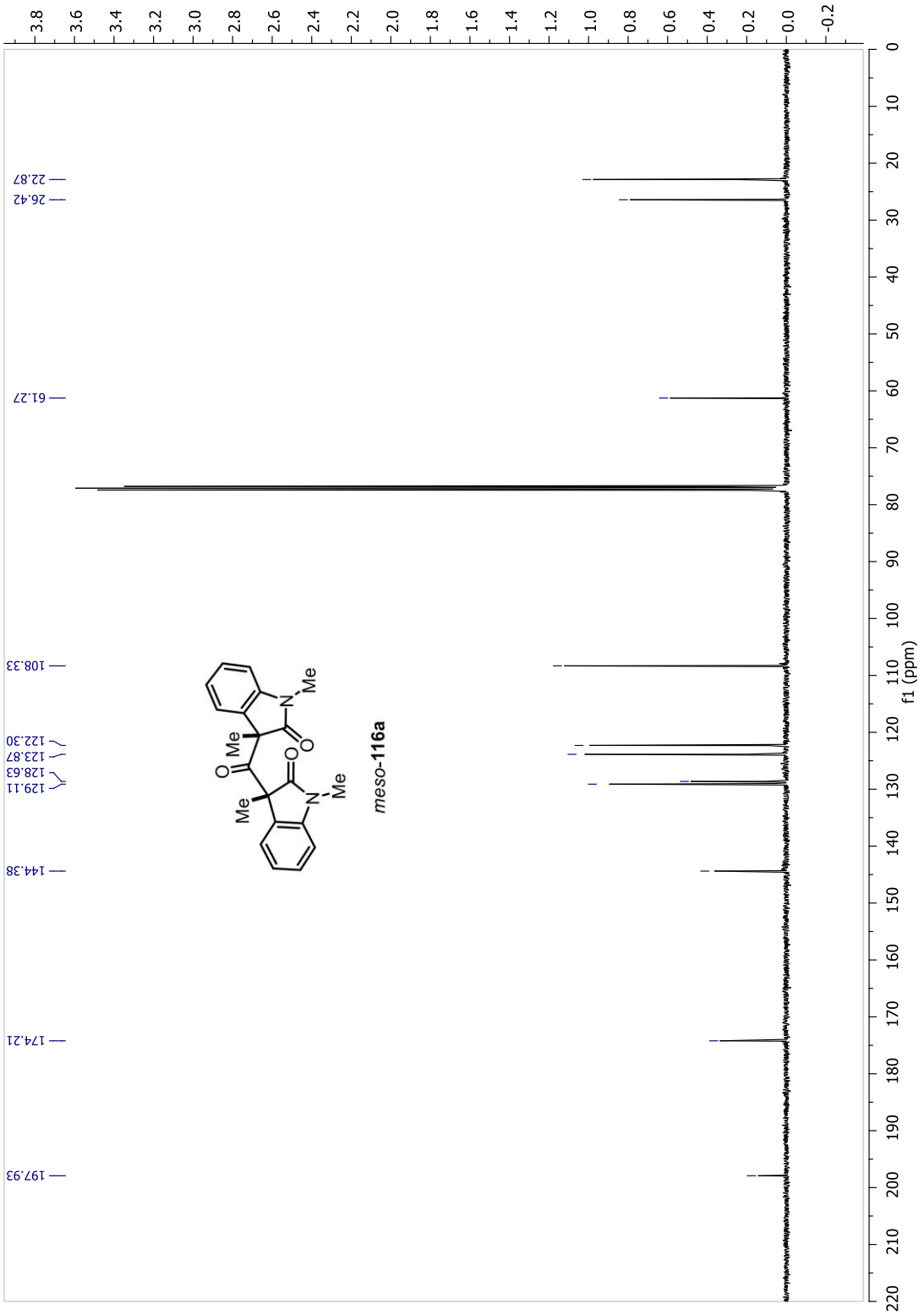
^{13}C NMR spectrum of bis-oxindole *dl*-116a (100 MHz; $CDCl_3$)



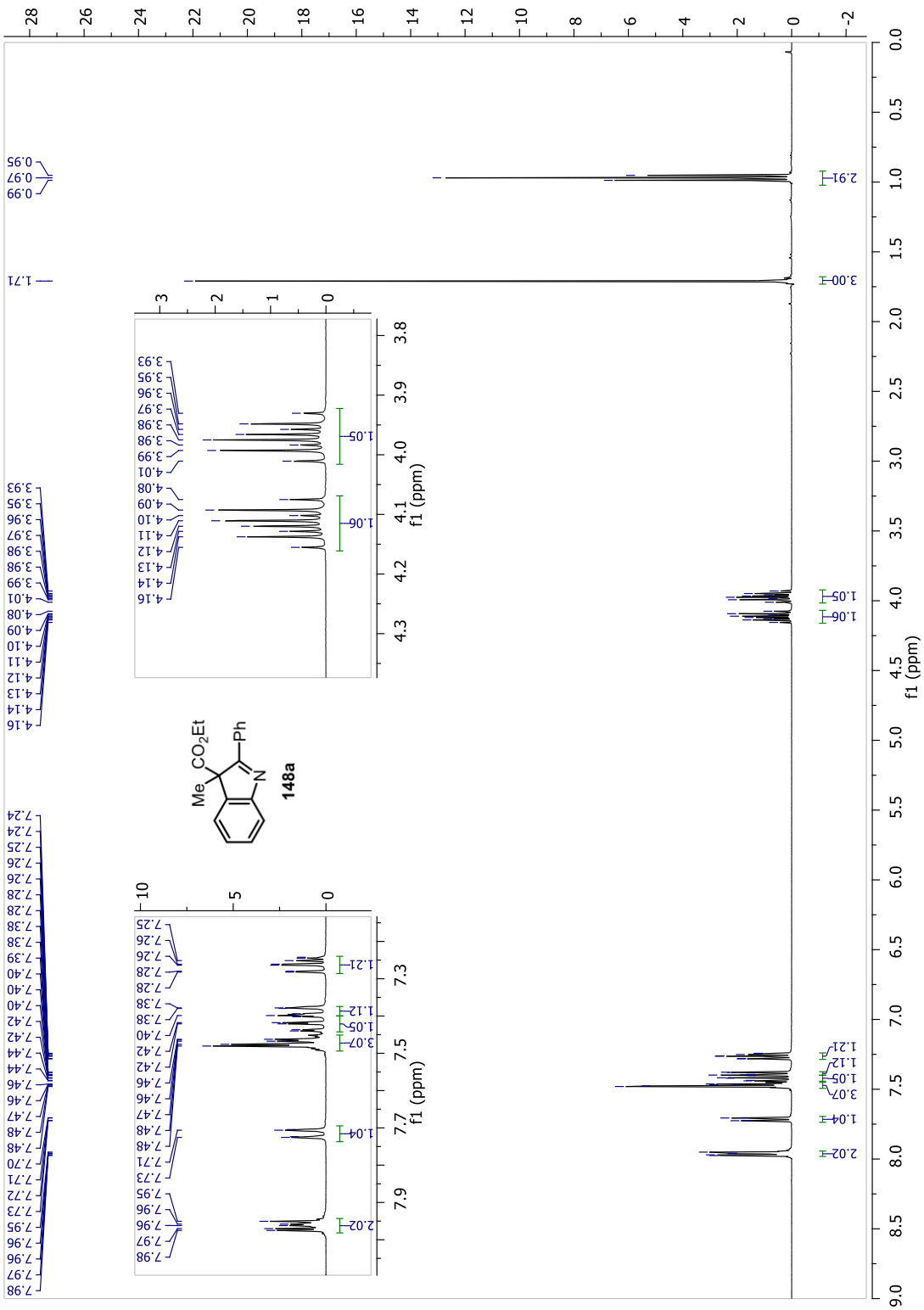
^{1}H NMR spectrum of bis-oxindole *meso*-116a (400 MHz; $CDCl_3$)



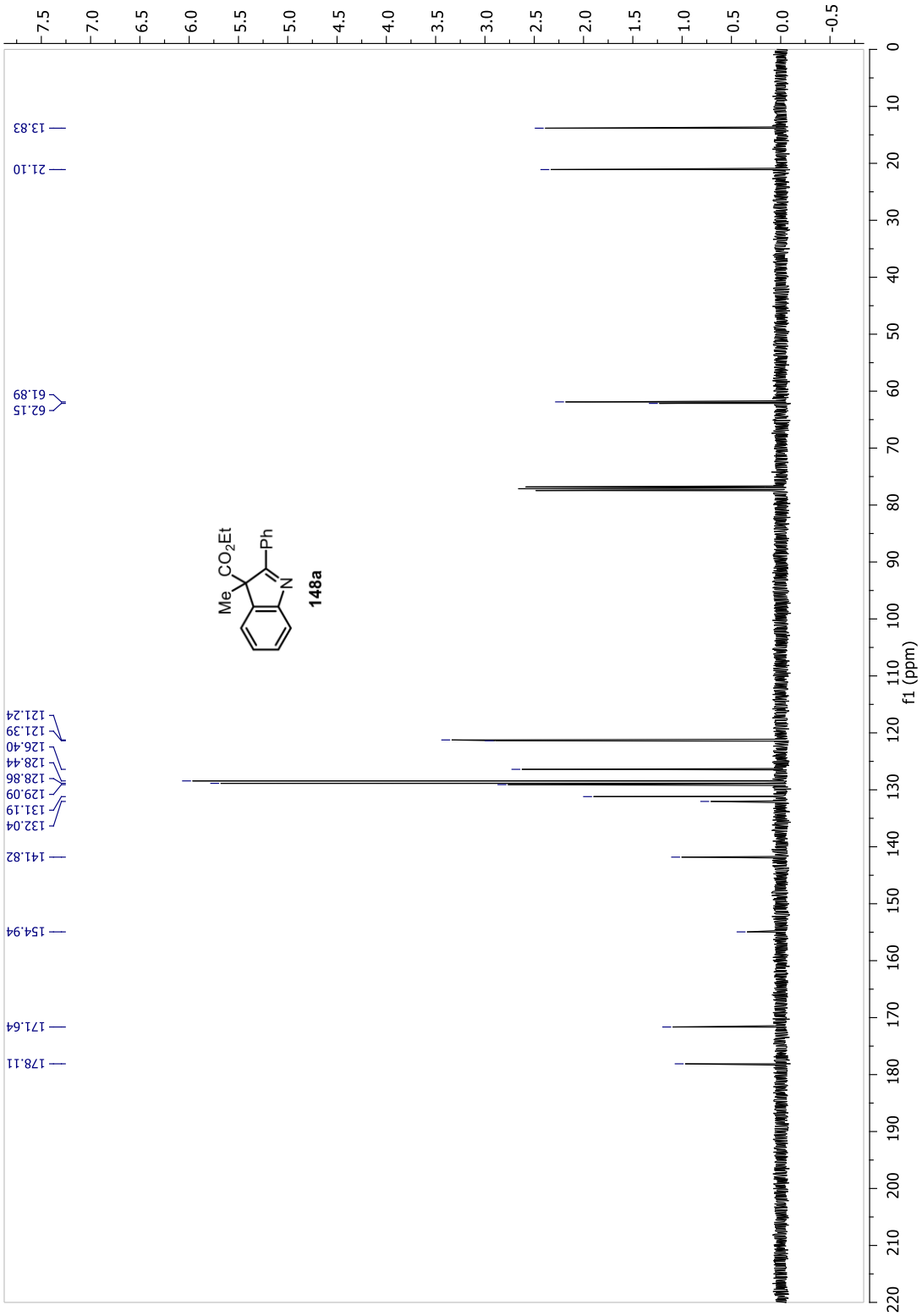
^{13}C NMR spectrum of bis-oxindole *meso*-116a (100 MHz; $CDCl_3$)



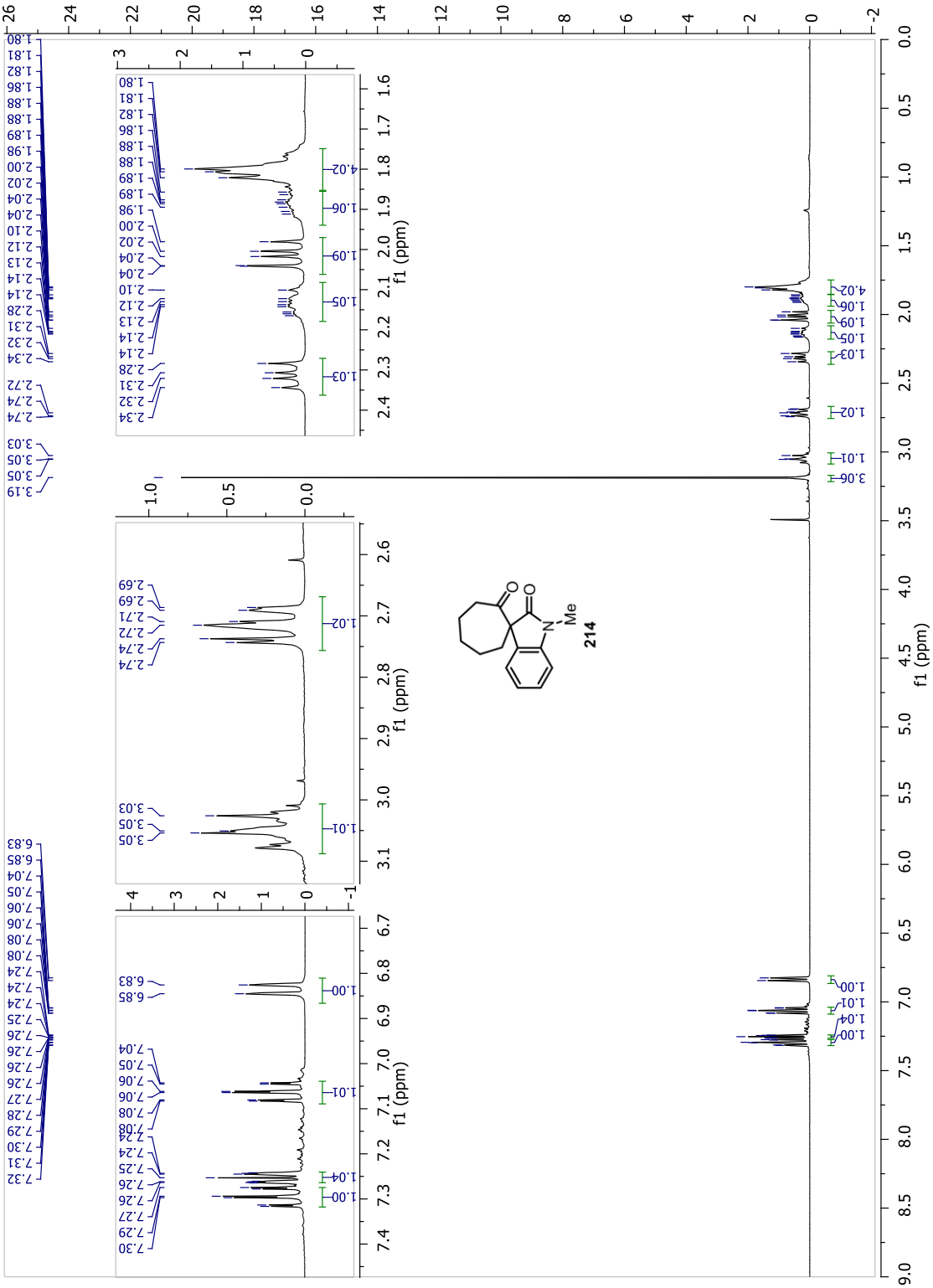
^{1}H NMR spectrum of 3*H*-indole 148a (400 MHz; $CDCl_3$)



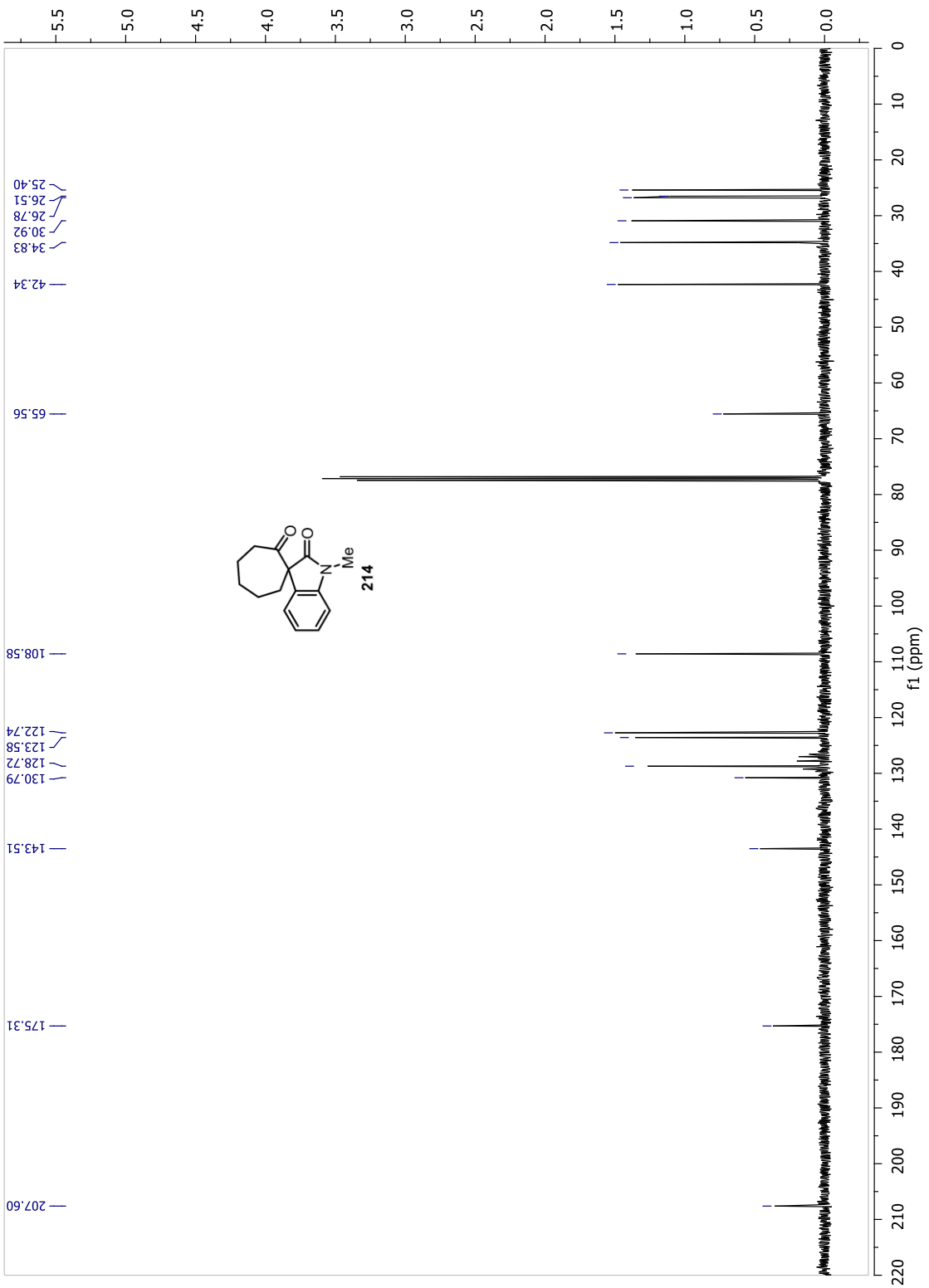
^{13}C NMR spectrum of 3*H*-indole 148a (100 MHz; $CDCl_3$)



^{1}H NMR spectrum of spirooxindole 214 (400 MHz; $CDCl_3$)

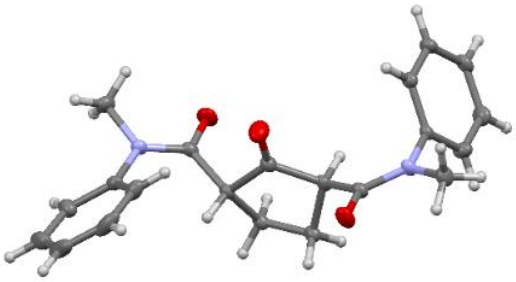


^{13}C NMR spectrum of spirooxindole 214 (100 MHz; $CDCl_3$)



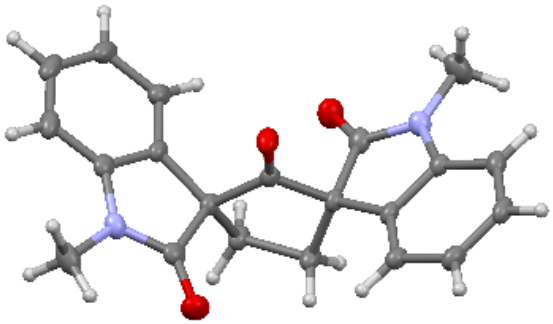
Appendix II: Crystallographic data

Compound 92a (CCDC 1013303)



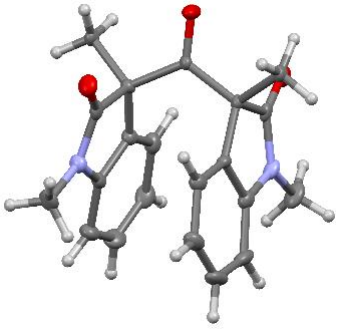
Identification code	rjkt1410	
Empirical formula	$C_{21}H_{22}N_2O_3$	
Formula weight	350.40	
Temperature/K	110.05(10)	
Crystal system	monoclinic	
Space group	$P2_1/n$	
a/Å	8.75713(16)	α = 90°
b/Å	15.9322(2)	β = 108.2987(19)°
c/Å	13.1649(2)	γ = 90°
Volume/Å^3	1743.89(5)	
Z	4	
ρ_{calc}g/cm^3	1.335	
μ/mm^{-1}	0.090	
F(000)	744.0	
Crystal size/mm^3	0.1835 × 0.16 × 0.1458	
Radiation	MoKα (λ = 0.71073)	
2Θ range for data collection/°	6.058 to 59.996	
Index ranges	-11 ≤ h ≤ 12, -22 ≤ k ≤ 22, -18 ≤ l ≤ 18	
Reflections collected	20689	
Independent reflections	5098 [R_{int} = 0.0289, R_{sigma} = 0.0227]	
Data/restraints/parameters	5098/0/237	
Goodness-of-fit on F^2	1.044	
Final R indexes [I>=2σ (I)]	R_1 = 0.0496, wR_2 = 0.1284	
Final R indexes [all data]	R_1 = 0.0570, wR_2 = 0.1340	
Largest diff. peak/hole / e Å^{-3}	0.53/-0.42	

Compound 91a (CCDC 1004040)



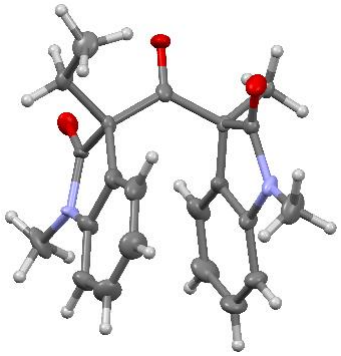
Identification code	rjkt1403
Empirical formula	$C_{21}H_{18}N_2O_3$
Formula weight	346.37
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.1668(10)
b/Å	13.0868(3)
c/Å	18.4536(8)
α/°	90
β/°	114.242(7)
γ/°	90
Volume/Å^3	3339.8(3)
Z	8
ρ_{calc}mg/mm^3	1.378
m/mm^{-1}	0.093
F(000)	1456.0
Crystal size/mm^3	0.4761 × 0.2122 × 0.0636
Radiation	MoKα (λ = 0.7107)
2Θ range for data collection	5.888 to 60.218°
Index ranges	$-12 \leq h \leq 20$, $-18 \leq k \leq 10$, $-25 \leq l \leq 25$
Reflections collected	10277
Independent reflections	6553 [R_{int} = 0.0282, R_{sigma} = 0.0483]
Data/restraints/parameters	6553/0/473
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.0478, wR_2 = 0.1092
Final R indexes [all data]	R_1 = 0.0716, wR_2 = 0.1228
Largest diff. peak/hole / e Å^{-3}	0.27/-0.21

Compound *dl*-116a (CCDC 1004039)



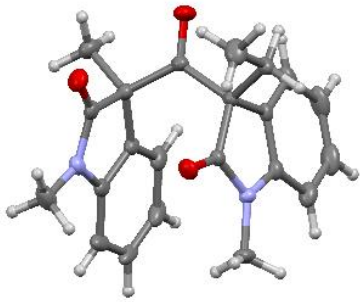
Identification code	rjkt1231	
Empirical formula	$C_{21}H_{20}N_2O_3$	
Formula weight	348.39	
Temperature/K	110.00(10)	
Crystal system	orthorhombic	
Space group	$Pna2_1$	
a/Å	27.4231(9)	α = 90°
b/Å	7.8100(2)	β = 90°
c/Å	16.1403(4)	γ = 90°
Volume/Å^3	3456.85(16)	
Z	8	
ρ_{calc}mg/mm^3	1.339	
m/mm^{-1}	0.090	
F(000)	1472.0	
Crystal size/mm^3	0.1696 × 0.093 × 0.0709	
2Θ range for data collection	5.8 to 55.12°	
Index ranges	$-35 \leq h \leq 32$, $-8 \leq k \leq 10$, $-21 \leq l \leq 20$	
Reflections collected	12994	
Independent reflections	7464[R(int) = 0.0267]	
Data/restraints/parameters	7464/1/477	
Goodness-of-fit on F^2	1.073	
Final R indexes [I>=2σ (I)]	R_1 = 0.0497, wR_2 = 0.1151	
Final R indexes [all data]	R_1 = 0.0583, wR_2 = 0.1201	
Largest diff. peak/hole / e Å^{-3}	0.35/-0.27	
Flack parameter	-0.7(9)	

Compound *trans*-116b (CCDC 1016758)



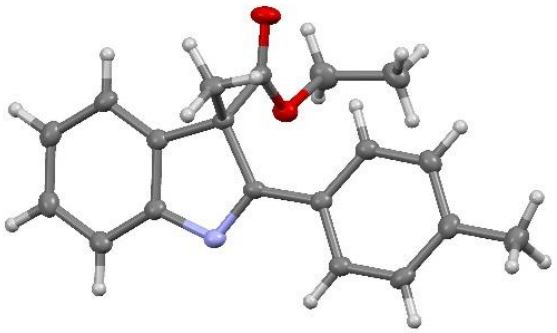
Identification code	rjkt1404	
Empirical formula	$C_{22}H_{22}N_2O_3$	
Formula weight	362.41	
Temperature/K	110.05(10)	
Crystal system	monoclinic	
Space group	$P2_1/c$	
a/Å	7.7526(3)	α = 90°
b/Å	16.2826(7)	β = 96.448(5)°
c/Å	14.5413(8)	γ = 90°
Volume/Å^3	1823.97(15)	
Z	4	
ρ_{calc}g/cm^3	1.320	
μ/mm^{-1}	0.088	
F(000)	768.0	
Crystal size/mm^3	0.1956 × 0.0941 × 0.0393	
Radiation	MoKα (λ = 0.71073)	
2Θ range for data collection/°	5.638 to 60.7	
Index ranges	-10 ≤ h ≤ 10, -22 ≤ k ≤ 22, -20 ≤ l ≤ 18	
Reflections collected	14503	
Independent reflections	4976 [R_{int} = 0.0592, R_{sigma} = 0.0632]	
Data/restraints/parameters	4976/43/314	
Goodness-of-fit on F^2	1.057	
Final R indexes [I>=2σ (I)]	R_1 = 0.0928, wR_2 = 0.2206	
Final R indexes [all data]	R_1 = 0.1533, wR_2 = 0.2563	
Largest diff. peak/hole / e Å^{-3}	0.31/-0.29	

Compound *cis*-116b (CCDC 1004041)



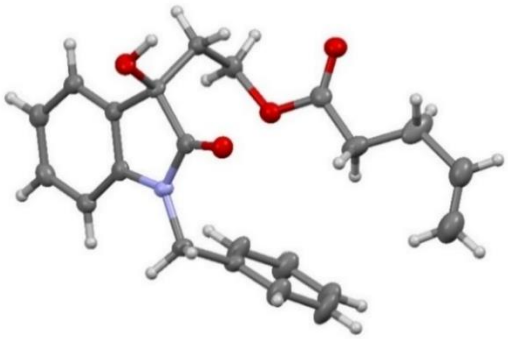
Identification code	rjkt1405	
Empirical formula	$C_{22}H_{22}N_2O_3$	
Formula weight	362.41	
Temperature/K	110.05(10)	
Crystal system	orthorhombic	
Space group	Pbca	
a/Å	9.00239(19)	α = 90°
b/Å	14.4646(3)	β = 90°
c/Å	27.9468(6)	γ = 90°
Volume/Å^3	3639.13(13)	
Z	8	
ρ_{calc}mg/mm^3	1.323	
m/mm^{-1}	0.089	
F(000)	1536.0	
Crystal size/mm^3	0.257 × 0.2069 × 0.1358	
Radiation	MoKα (λ = 0.71073)	
2Θ range for data collection	5.812 to 52.682°	
Index ranges	$-11 \le h \le 11$, $-18 \le k \le 18$, $-34 \le l \le 34$	
Reflections collected	24004	
Independent reflections	3719 [R_{int} = 0.0296, R_{sigma} = 0.0142]	
Data/restraints/parameters	3719/0/248	
Goodness-of-fit on F^2	1.132	
Final R indexes [I>=2σ (I)]	R_1 = 0.0519, wR_2 = 0.1370	
Final R indexes [all data]	R_1 = 0.0547, wR_2 = 0.1392	
Largest diff. peak/hole / e Å^{-3}	0.42/-0.30	

Compound 148h (CCDC 1033699)



Identification code	rjkt1416	
Empirical formula	$C_{19}H_{19}NO_2$	
Formula weight	293.35	
Temperature/K	109.9(2)	
Crystal system	triclinic	
Space group	P-1	
a/Å	8.6704(8)	α = 82.390(6)°
b/Å	8.8590(6)	β = 67.841(8)°
c/Å	11.4799(8)	γ = 72.612(7)°
Volume/Å^3	779.15(11)	
Z	2	
ρ_{calc}g/cm^3	1.250	
μ/mm^{-1}	0.642	
F(000)	312.0	
Crystal size/mm^3	0.1685 × 0.1242 × 0.0297	
Radiation	CuKα (λ = 1.54184)	
2Θ range for data collection/°	8.318 to 134.148	
Index ranges	-10 ≤ h ≤ 10, -10 ≤ k ≤ 10, -13 ≤ l ≤ 13	
Reflections collected	9975	
Independent reflections	2788 [R_{int} = 0.0319, R_{sigma} = 0.0283]	
Data/restraints/parameters	2788/0/202	
Goodness-of-fit on F^2	1.032	
Final R indexes [I>=2σ (I)]	R_1 = 0.0392, wR_2 = 0.0991	
Final R indexes [all data]	R_1 = 0.0479, wR_2 = 0.1055	
Largest diff. peak/hole / e Å^{-3}	0.25/-0.23	

Compound 286 (CCDC 1049570)



Identification code	rjkt1308	
Empirical formula	$C_{22}H_{23}NO_4$	
Formula weight	365.41	
Temperature/K	110	
Crystal system	monoclinic	
Space group	$P2_1/c$	
a/Å	11.5049(4)	$\alpha = 90°$
b/Å	8.7499(3)	$\beta = 97.701(3)°$
c/Å	18.8298(7)	$\gamma = 90°$
Volume/Å^3	1878.44(11)	
Z	4	
ρ_{calc}mg/mm^3	1.292	
m/mm^{-1}	0.089	
F(000)	776.0	
Crystal size/mm^3	0.1482 × 0.0609 × 0.032	
2Θ range for data collection	6 to 55.9°	
Index ranges	$-12 \le h \le 14$, $-11 \le k \le 9$, $-14 \le l \le 22$	
Reflections collected	5931	
Independent reflections	3705[R(int) = 0.0270]	
Data/restraints/parameters	3705/3/258	
Goodness-of-fit on F^2	1.079	
Final R indexes [I>=2σ (I)]	$R_1 = 0.0571$, $wR_2 = 0.1079$	
Final R indexes [all data]	$R_1 = 0.0891$, $wR_2 = 0.1254$	
Largest diff. peak/hole / e Å^{-3}	0.22/-0.23	

Appendix III: *Org. Lett.* **2014**, *16*, 4900-4903

Organic LETTERS

Letter

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Copper-Mediated Construction of Spirocyclic Bis-oxindoles via a Double C−H, Ar−H Coupling Process

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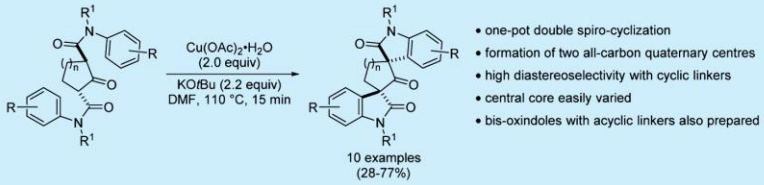
Supporting Information



ABSTRACT: A double C−H, Ar−H coupling process for the conversion of bis-anilides into spirocyclic bis-oxindoles, enabling the concomitant formation of two all-carbon quaternary centers at oxindole 3-positions in a diastereoselective manner, is described. The optimum cyclization conditions utilize stoichiometric $Cu(OAc)_2 \cdot H_2O$/KO*t*Bu in DMF at 110 °C and have been applied to prepare a range of structurally diverse bis-spirooxindoles in fair to good yields (28−77%); the method has also been extended to prepare bis-oxindoles linked by a functionalized acyclic carbon chain.

Over the past decade, there has been a significant resurgence of interest in oxindoles, as these structures represent validated targets in the search for new drug candidates and form the cornerstone of numerous alkaloids of biological interest.[1] More recently, bis-oxindoles have attracted considerable attention (Figure 1). For example,

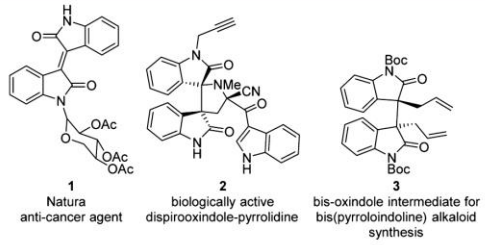
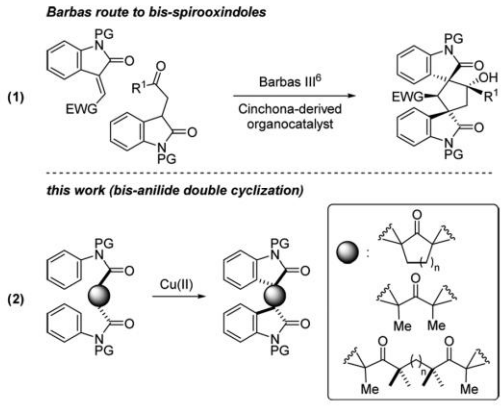


Figure 1. Examples of bis-oxindole targets.

Natura (**1**) is representative of a family of isoindigo-based anticancer agents (CDK inhibitors)[2] and compound **2** is typical of a range of dispirooxindole-pyrrolidine derivatives recently shown to possess significant antibacterial and anticancer activities (against A549 human lung adenocarcinoma).[3] Moreover, bis-oxindoles have long been employed as precursors of bis(pyrroloindoline) alkaloids,[4] most recently with compound **3** being used as a cornerstone for the synthesis of a diverse range of cyclotryptamine alkaloids.[4d]

Many synthetic strategies have been established to access the oxindole motif,[5] but only limited examples have been reported to date on bis-oxindoles, probably because of their highly functionalized polycyclic skeletons, particularly those containing multiple spiro-quaternary carbon centers. The majority of approaches rely on the linking together of preformed oxindoles,[2−4] a strategy most beautifully illustrated by Barbas who developed an organocatalytic asymmetric Michael addition/aldol cascade reaction between 3-substituted oxindoles and methyleneindolinones which proceeds with excellent diastereo- and enantiocontrol (Scheme 1, eq 1).[6] Related variants have subsequently been reported[7] but all commence with preformed oxindoles and all produce bis-oxindole

Scheme 1. Strategies for the Synthesis of Bis-oxindoles



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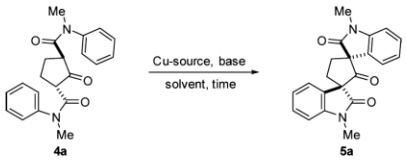
products linked at the 3,3-positions by another 5-membered ring generated in a formal [3 + 2]-cyclization process.[8]

Our objective was to establish a more general route to bis-oxindoles (Scheme 1, eq 2) which would utilize readily accessible bis-anilide precursors[9] and would be applicable to the formation of a range of diverse bis-oxindole products with, for the first time, great variability in the linking central core units. As shown, the plan was to utilize a copper(II)-mediated bis-anilide cyclization approach (a formal C−H, Ar−H coupling) based on the chemistry devised for the preparation of oxindoles[10,11] and related heterocycles[12] by the groups of Taylor and Kündig in 2009. Herein, we wish to disclose the success of this approach to access a range of bis-spirooxindoles featuring central core units of different ring sizes and, in addition, functionalized acyclic linker units.

The cyclopentanone 2,5-dicarboxamide **4a** was chosen as the bis-anilide for preliminary studies (Table 1). Compound **4a** was prepared in two steps by amide coupling between adipic acid and *N*-methylaniline followed by a novel ring closure using carbonyldiimidazole (CDI; see Supporting Information for details). The thermodynamically more stable *trans*-bis-anilide diastereoisomer was the only product of the reaction (confirmed by X-ray crystallography).[13] The double spirocyclization was then investigated, initially using $Cu(OAc)_2·H_2O$ in mesitylene at 170 °C, conditions optimized for the formation of simple oxindoles.[10b,c] However, only traces of cyclized product **5a** were detected under these conditions (Table 1, entry 1). Carrying out the reaction in toluene at reflux gave a useful 24% yield (entry 2) but further reductions in temperature resulted in lower yields, even after extended reaction times (e.g., entry 3). However, changing to $Cu(OAc)_2·H_2O$ and KO*t*Bu in DMF (conditions employed in our original study[10a]) gave the desired spirocyclic bis-oxindole **5a** in a gratifying 67% yield (entry 4). This double cyclization proceeded with complete diastereoselectivity to give only the *trans*-diastereoisomer illustrated, in which the two oxindole units are orthogonal (confirmed by X-ray crystallographic analysis, Figure 2).[14]

Having established successful conditions for the double cyclization on the model system **4a**, we went on to test the substrate scope using a range of substituted bis-anilides **4**.[15] First we ensured that the procedure was compatible with *N*-benzyl protection and found that adduct **5b** was formed in 57% yield. Substitution of the aromatic rings was studied next, and both 4-methyl- and 4-methoxy-substitution was well tolerated giving **5c** and **5d**, respectively. Unsymmetrical bis-oxindoles were also prepared with either differential ring substitution (**5e**) or differential *N*-protection (**5f**). Variation of the central ring size was also explored.[15] Thus, a cyclohexanone (**5g**) and a substituted cyclohexanone example (**5h**) were prepared, as were a 7-membered ring-containing bis-oxindole (**5i**, obtained in 77% yield) and a benzo-fused cycloheptanone example (**5j**). The yields of the cyclization products varied (28−77%), but it should be noted that all of the procedures in Scheme 2 used the standard conditions developed in Table 1 and none were optimized. It should also be noted that all of products in Scheme 2 were obtained as single *trans*-diastereoisomers.

Table 1. Optimization of the Reaction Conditions



entry	base	Cu source	solvent (temp)	time (h)	yield
1	–	$Cu(OAc)_2·H_2O$ (1.0 equiv)	mesitylene (170 °C)	0.5	<5%
2	–	$Cu(OAc)_2·H_2O$ (1.0 equiv)	toluene (100 °C)	0.5	24%
3	–	$Cu(OAc)_2·H_2O$ (1.0 equiv)	toluene (80 °C)	3	17%
4	**KO*t*Bu (2.2 equiv)**	**$Cu(OAc)_2·H_2O$[a] (2.0 equiv)**	**DMF (110 °C)**	**0.25**	**67%**

[a]In a control experiment carried out using KO*t*Bu (2.2 equiv) but without $Cu(OAc)_2·H_2O$, no product was observed in the ^1H NMR spectrum of the crude reaction mixture. Instead, residual starting material and products from amide hydrolysis as well as decomposition were observed.

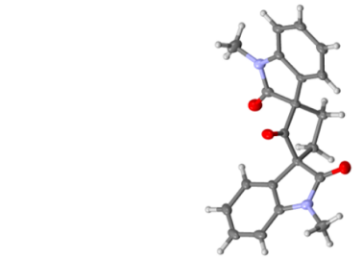
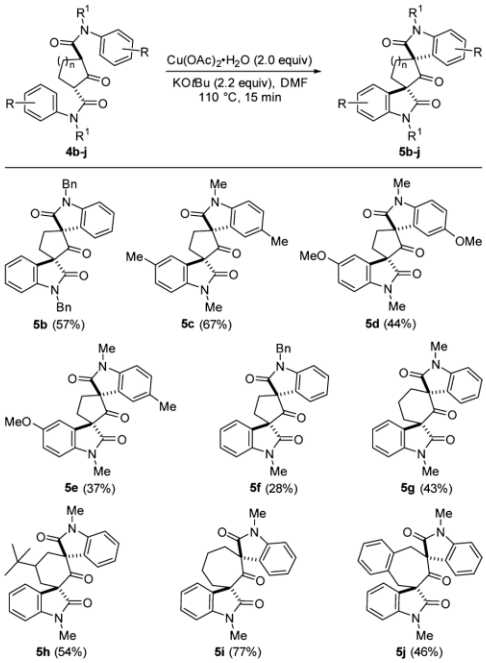


Figure 2. Crystal structure of **5a** (50% probability ellipsoids).

Scheme 2. Bis-spirooxindole Substrate Scope



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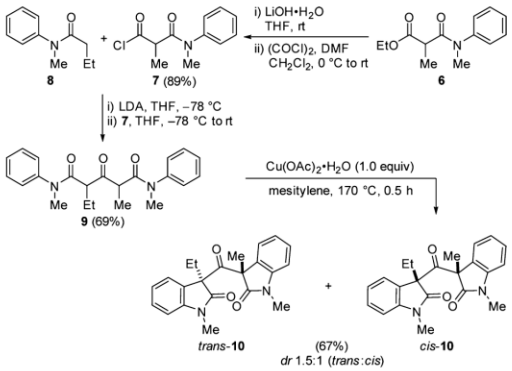
To further demonstrate the scope and versatility of the double anilide cyclization procedure, attention switched to the use of acyclic linker units. Initial studies were carried out on bis-anilide **9**, readily prepared as shown in Scheme 3. Thus, acid

Scheme 3. Bis-oxindole Synthesis with an Acyclic Linker



chloride **7** was synthesized from the respective ester anilide **6** in 89% yield over two steps. The enolate of **8** was trapped with acid chloride **7** and afforded bis-anilide **9** in 69% yield. In this case, the strongly basic procedure was not required, and treatment of precursor **9** with $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in mesitylene at 170 °C for 30 min afforded the desired bisoxindole **10** in 67% yield.[16] The keto-linked bis-oxindole **10** was obtained as a mixture of diastereoisomers (1.5:1 *trans*/*cis*) which were separable by column chromatography. The relative configurations of the diastereoisomeric products were determined by X-ray crystallography (Figure 3) indicating that the *trans*-isomer **10** was the major product.[17]

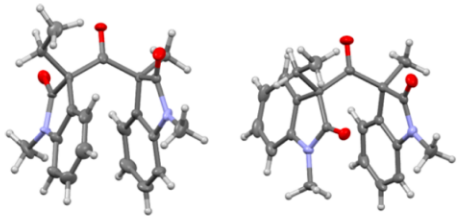


Figure 3. Crystal structures of *trans*-**10** (left) and *cis*-**10** (right).

Having established that this Cu(II) method could be employed to prepare bis-oxindoles with a keto-functionalized one-carbon linker, we sought to further extend the reaction scope (Scheme 4).

Compounds **11a–c** were easily obtained from the corresponding diacid chlorides using similar procedures to those employed in Scheme 3. Cyclization again occurred efficiently using $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in mesitylene at 170 °C, and again mixtures of diastereoisomers were produced. The diastereoisomers of bis-oxindole **12a**, linked by a three-carbon dicarbonyl chain, were separable, and the structures confirmed by X-ray analysis (Figure 4).[18] We also varied the linker chain length introducing an aromatic ring (**12b**) and prepared the adamantane-linked example **12c** using a similar procedure.

Scheme 4. Bis-oxindole Synthesis with Di-ketone Linkers

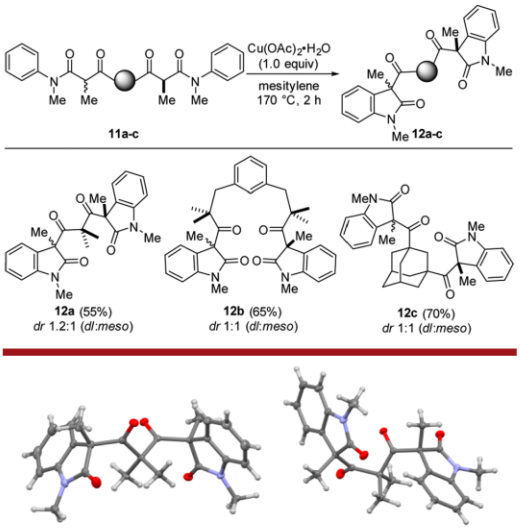


Figure 4. Crystal structures of DL-**12a** (left) and *meso*-**12a** (right).

In conclusion, we have developed a concise strategy to access a diverse range of spirocyclic bis-oxindoles using a one-pot, double Cu(II)-mediated bis-anilide cyclization by double C–H, Ar–H coupling. This method allows the installation of two all-carbon quaternary centers at the oxindole 3-position in a diastereoselective manner and great variability in the linking central core units for the first time. The method has been extended to prepare a number of bis-oxindoles linked by a functionalized acyclic carbon chain. We are currently investigating the use of chiral auxiliaries in these processes as well as exploring applications in target synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(13) X-ray data for **4a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1013303), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.
(14) X-ray data for **5a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1004040), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.
(15) The cyclopentanone precursors were prepared using the procedure described for **4a**; the 6- and 7-membered ring precursors **4g−j** were synthesized from cyclohexanone or -heptanone *via* double carboxylation with methyl magnesiumcarbonate: Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598. This was followed by double Mukaiyama amide coupling (see Supporting Information for details).
(16) The previous conditions $(Cu(OAc)_2{\cdot}H_2O$, KO*t*Bu in DMF at 110 °C) were tried; however, the yield of the product was inferior (~54%). This drop in yield is mainly due to formation of oxidative cleavage byproducts, namely *N*-methyl-3-alkyl-3-hydroxyoxindoles. Formation of these byproducts is minimized under the $Cu(OAc)_2{\cdot}H_2O$/toluene conditions.
(17) X-ray data for *cis*- and *trans*-**10** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1004041 and 1016758), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.
(18) X-ray data for *meso*-**12a** and *dl*-**12a** have been deposited with the Cambridge Crystallographic Data Centre (*meso*-**12a**: CCDC 1013389, DL-**12a**: CCDC 1013390), which can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif. See Supporting Information for crystallographic details.

Appendix IV: *Tetrahedron* **2015**, doi: 10.1016/j.tet.2015.02.060

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Tetrahedron xxx (2015) 1–13

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Substrate scope in the copper-mediated construction of bis-oxindoles via a double C–H/Ar–H coupling process

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Dedicated to the memory of Alan Katritzky: inspirational giant of heterocyclic chemistry, collaborator, and friend

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C–H Functionalisation

ABSTRACT

The synthesis of bis-oxindoles via the copper(II)-mediated double cyclisation of linear bis-anilides is described. $Cu(OAc)_2 \cdot H_2O$ was identified as an efficient and inexpensive catalyst for this process. In contrast to previous methods, which rely on the synthesis of the central core from existing oxindole building blocks, this new approach focusses on concurrent formation of both oxindole rings from a simple linear precursor, allowing the formation of bis-oxindoles containing a diverse range of cyclic and acyclic linkers using a single synthetic method.

1. Introduction

The oxindole motif has long been the subject of considerable attention due to its prevalence in natural and unnatural compounds with varied and extensive biological activities.[1] More recently, bis-oxindoles have emerged as interesting yet synthetically challenging targets owing to their complex polycyclic architecture. Some biologically active spirocyclic bis-oxindoles include the synthetic anti-bacterial/anti-cancer spirooxindole-pyrrolidine **1**,[2] naturally occurring anti-inflammatory geleganimine B **2**,[3] and cholinesterase inhibitor **3** (Fig. 1).[4] Non-spirocyclic bis-oxindole **4** has also been shown to possess potent anti-bacterial activity against both Gram positive and Gram negative organisms.[5] Moreover, bis-oxindoles (e.g., **5**) have been used extensively as key intermediates in the total synthesis of the cyclotryptamine[6] and related[7] alkaloids.

Given the demonstrated utility of bis-oxindoles, coupled with the synthetic challenge of preparing complex polycyclic scaffolds containing multiple stereogenic centres, it is not surprising that a number of approaches to these intriguing heterocycles have been reported.[8] Some representative examples of bis-spirooxindoles, containing various core ring sizes and linkers, are shown in Fig. 2. These have been prepared by cascade reactions[9] (e.g., **6**, **8**, and **9**), photochemical [2+2]-cycloadditions[10] (e.g., **7**), and by condensation onto isatin-based imines[11] (e.g., **10**). It is noteworthy that excellent control over both relative and absolute stereochemistry can often be achieved in such systems.

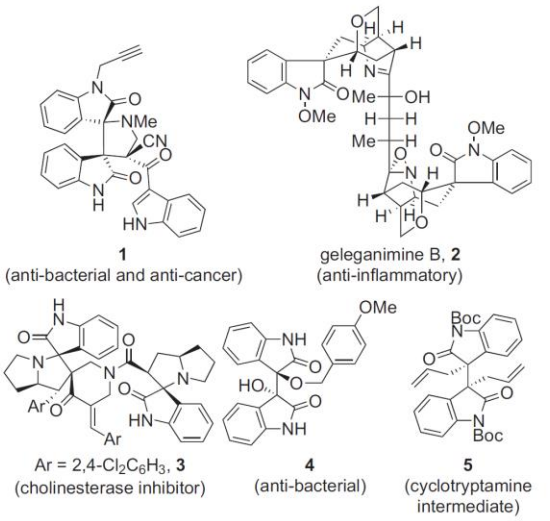

Fig. 1. Examples of valuable bis-oxindoles.

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http://dx.doi.org/10.1016/j.tet.2015.02.060
0040-4020/

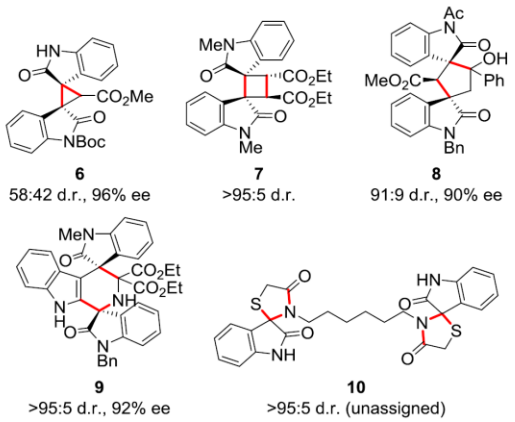
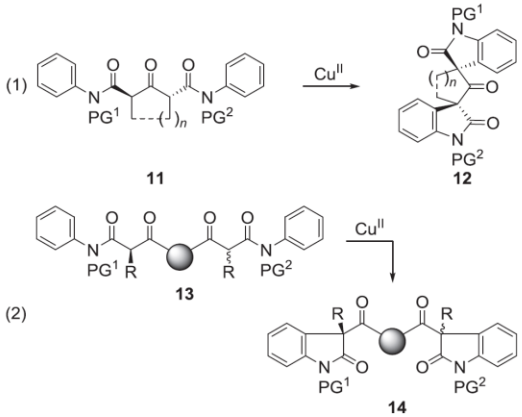


Fig. 2. Examples of bis-spirooxindoles prepared by elaboration of pre-formed oxindoles. Bonds formed in the cyclisation process are shown in red.

However, regardless of the structural diversity of bis-oxindoles that can be accessed via these different synthetic manifolds, the previous approaches all rely on a single overall strategy: i.e., synthesis of the central core from pre-existing oxindole building blocks, often derived from isatin.

We have previously demonstrated the efficient synthesis of oxindoles from linear anilides in high yield via a copper(II)-mediated formal C–H/Ar–H coupling reaction,[12] and subsequently reported preliminary studies, which took advantage of this method to provide access to bis-spirooxindoles with complete control of diastereoselectivity (Scheme 1, Eq. 1).[13] We now wish to disclose full results on the copper(II)-mediated double cyclisation of readily available linear bis-anilides, which offers a fundamentally different approach to the synthesis of bis-oxindoles by simultaneous formation of both oxindole rings around an existing central linker (Scheme 1, Eqs. 1 and 2). In this fashion, we are able to prepare spirocyclic bis-oxindoles with full control over the size of the core ring system, as well as bis-oxindoles connected by diverse acyclic linkers, using a single synthetic method. In addition to detailed experimental procedures, 15 previously unreported cyclisations are included in this publication.

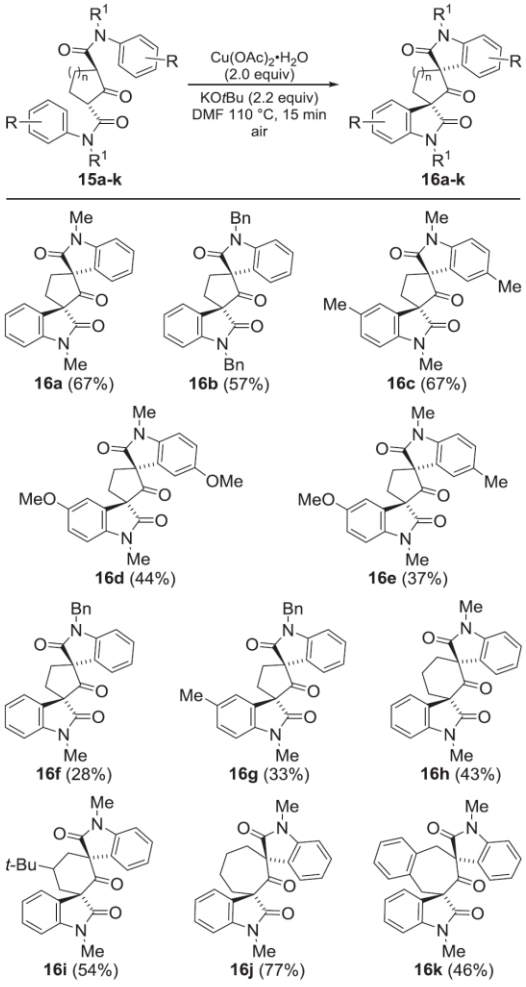


Scheme 1. Bis-anilide double cyclisation strategy for the synthesis of bis-oxindoles.

2. Results and discussion

2.1. Synthesis of spirocyclic bis-oxindoles

In our preliminary studies,[13] we focussed on the synthesis of spirocyclic bis-oxindoles **16a**–**k** by the copper-mediated double cyclisation of linear bis-anilides **15a**–**k** in moderate to good yields (Scheme 2). These results are reproduced here, and warrant only brief comment. Optimisation studies carried out for the cyclisation of cyclopentanone 2,5-dicarboxamide **15a** showed that the preferred reaction conditions involved $Cu(OAc)_2 \cdot H_2O$ (2.2 equiv) and KO*t*Bu (2.2 equiv) in DMF at 110 °C for 15 min, delivering the desired bis-spirooxindole **16a** in 67% isolated yield and as a single diastereomer. The *trans*-relationship of the carboxamides present in both the linear bis-anilide **15a** and bis-oxindole **16a** was confirmed unambiguously by X-ray crystallography (Fig. 3). We also examined the scope of this copper-mediated double cyclisation, exemplified by the synthesis of symmetrical (**16b**–**d**) and un-



Scheme 2. Substrate scope in the synthesis of spirocyclic bis-oxindoles. All compounds were isolated as single diastereomers.

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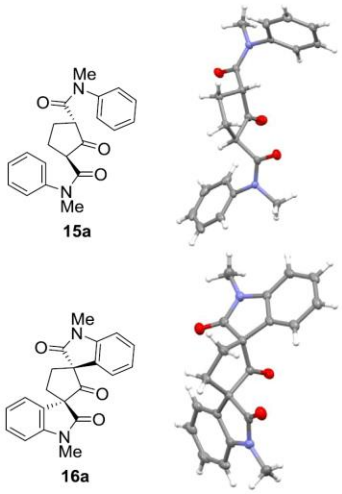


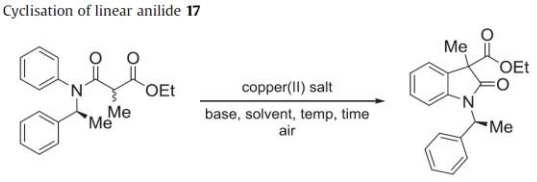
Fig. 3. Crystal structures of *trans*-cyclopentanone 2,5-dicarboxamide **15a** and spirocyclic bis-oxindole **16a** (50% probability ellipsoids).

symmetrical (**16e**–**g**, differentiated by both ring substitution and nitrogen protecting group) bis-oxindoles, as well as those containing varying core ring sizes (**16h**–**k**). Key features of this method include the inexpensive copper salt used, the short reaction time, broad diversity in the cyclic linker, and high diastereoselectivity observed in the cyclisation.

2.2. Towards a copper-mediated cyclisation approach to enantioenriched spirocyclic bis-oxindoles

In a new aspect to this work, we wished to explore the potential of extending the diastereoselective copper-mediated double cyclisation to the enantioselective synthesis of spirocyclic bis-oxindoles. Jones and McCarthy have reported the use of the α-methylbenzyl group as a chiral auxiliary on nitrogen in the radical cyclisation of *N*-arylacrylamides to give enantioenriched 3,3-disubstituted oxindoles, albeit in a moderate 39% ee after removal of the auxiliary.[14] It was anticipated that a similar approach might be successful in our process. To test this hypothesis, model linear anilide **17** bearing an (*S*)-α-methylbenzyl group was prepared in 68% yield via Mukaiyama coupling of the requisite aniline and carboxylic acid. The copper-mediated cyclisation of **17** was then carried out under several different sets of conditions to examine the effect on the diastereoselectivity of the reaction (Table 1). In the event, the highest chemical yield of **18** was observed in toluene at 110 °C (entry 2). Of greater import, a slight bias in favour of one diastereomer was observed in all cases, providing encouragement for the potential success of this approach in the synthesis of the sterically more encumbered bis-spirooxindoles.

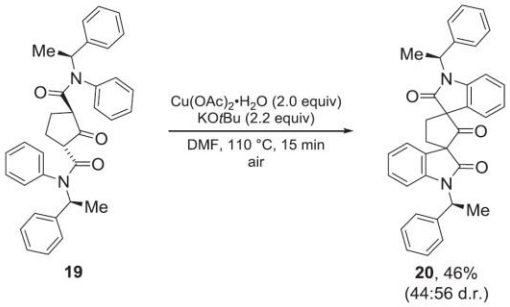
Table 1
Cyclisation of linear anilide **17**



17 **18**

Entry	Conditions	Yield (%)	dr
1	$Cu(OAc)_2 \cdot H_2O$ (1 equiv), KO*t*Bu, DMF, 110 °C, 1 h	26	44:56
2	$Cu(OAc)_2 \cdot H_2O$ (1 equiv), toluene, 110 °C, 18 h	76	44:56
3	$Cu(OAc)_2 \cdot H_2O$ (1 equiv), mesitylene, 170 °C, 1.5 h	55	45:55

The linear bis-anilide precursor **19** containing the (*S*)-α-methylbenzyl chiral auxiliary on both nitrogen atoms was therefore prepared in analogous fashion to **15a**. Cyclisation of **19** under the optimised conditions for bis-spirooxindole formation delivered **20** in 46% yield as an inseparable mixture of diastereomers in a 44:56 ratio (Scheme 3), similar to **18** above.



19 **20**, 46% (44:56 d.r.)

Scheme 3. Cyclisation of linear bis-anilide **19**.

Despite the rather disappointing diastereoselectivity imparted by the (*S*)-α-methylbenzyl group, these preliminary results show promise for future improvement through optimisation of the chiral auxiliary and reaction conditions.

2.3. Synthesis of bis-oxindoles with an acyclic monoketone linker

Having established the utility of the double cyclisation of linear bis-anilides for the synthesis of spirocyclic bis-oxindoles, attention turned to expanding the scope of this method to include substrates containing an acyclic linker. The required cyclisation precursors were easily prepared in three steps from known ester **21** (Scheme 4).[12a] Thus, saponification of the ester moiety in **21** followed by treatment with oxalyl chloride delivered acid chloride **22**, which was sufficiently stable to allow storage at −10 °C for several months without degradation. Treatment of anilides **23a**–**c** with LDA, followed by addition of the acid chloride **22** delivered the target linear bis-anilides **24a**–**c** in 40–69% yield. Crucially, this stepwise strategy provided access to unsymmetrical substrates differentiated by ring substitution (**24b**, R^1=Me), and at the carbonyl α-position (**24c**, R^2=Et).

Cyclisation of **24a** in the presence of $Cu(OAc)_2 \cdot H_2O$ (2 equiv) and KO*t*Bu (2.2 equiv) in DMF at 110 °C for 1 h delivered the desired bisoxindole **25a** as a mixture of diastereomers, along with significant quantities of an oxidative cleavage by-product, namely *N*-methyl 3-hydroxy-3-methyloxindole **26** (*trans*-**25a**/*cis*-**25a**/**26** molar ratio=1:3:1). Pleasingly, formation of this by-product can be minimised by performing the reaction without base in mesitylene at 170 °C for 30 min, giving bis-oxindole **25a** as a separable 40:60 mixture of *trans*/*cis*-diastereomers in 58% combined yield. The small amount of hydroxyindole **26** formed in this reaction was easily removed during the workup by washing with 4 M NaOH solution. Unsymmetrical bisoxindole **25b** was prepared in similar fashion. Interestingly, changing one of the α-methyl groups to the bulkier ethyl group (**25c**, R^2=Et) prompted a change in selectivity,

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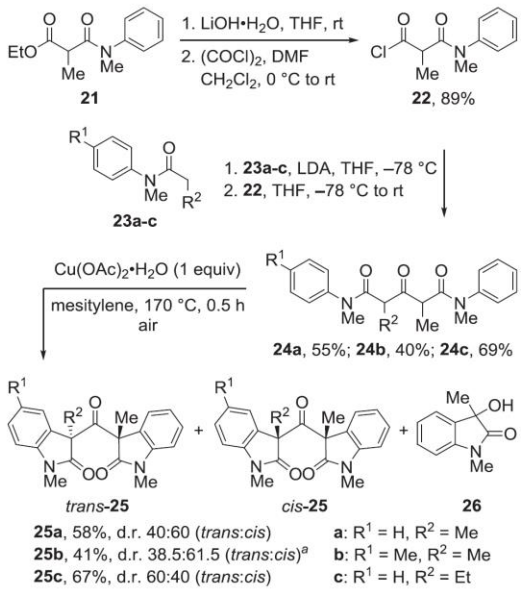

Scheme 4. Synthesis of bis-oxindoles with an acyclic monoketone linker. [a]2 equiv of $Cu(OAc)_2 \cdot H_2O$ was used with a reaction time of 3 h.

with *trans*-**25c** isolated as the major product. The relative stereochemistries in *trans*-**25a**, *trans*-**25c** and *cis*-**25c** were all confirmed by X-ray crystallography (Fig. 4).

The moderate diastereoselectivities observed in the synthesis of bis-oxindoles **25a**–**c** containing a flexible acyclic linker highlights the key role played by the more rigid cyclic core in spirocyclic bis-oxindoles **16a**–**k**, which serves to more efficiently relay stereochemical information during the cyclisation, leading to the complete diastereoselectivity observed in the latter case.

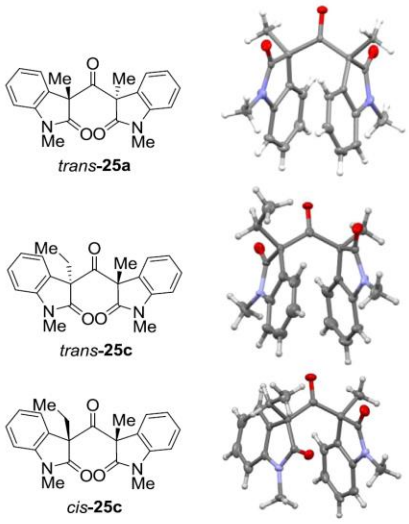

Fig. 4. Crystal structures of *trans*-**25a**, *trans*-**25c** and *cis*-**25c** (50% probability ellipsoids).

2.4. Synthesis of bis-oxindoles with diketone linkers

With the synthesis of bis-oxindoles separated by a one-carbon ketone linker established via this copper-mediated double cyclisation, we next sought to extend the scope to incorporate linkers of varying chain lengths. The required linear substrates were easily prepared via reaction of diacid chlorides **27** with 2.4 equiv of the enolate derived from anilides **23** (Scheme 5). This flexible approach provided rapid access to cyclisation precursors containing a diverse array of central linkers incorporating various aliphatic chains (**28a**–**d**), an adamantane (**28e**) and aromatic rings (**28f**–**j**). In most cases an inseparable 50:50 mixture of *dl*/*meso*-diastereomers was obtained, which is inconsequential for the subsequent cyclisation. The exception was malonate-derived substrate **28a**, where the diastereomers were separable by column chromatography, giving *meso*-**28a** and *dl*-**28a** in 32% and 27% yields, respectively. The relative stereochemistry in *meso*-**28a** and *dl*-**28a** was assigned based on the characteristic signals for the *gem*-dimethyl group in the ^{1}H NMR spectrum (2×3H singlets at δ_H 1.42 and 1.23 for *meso*-**28a**, 1×6H singlet at δ_H 1.21 for *dl*-**28a**). In addition, the structure of *dl*-**28a** was confirmed by X-ray crystallography (Fig. 5).

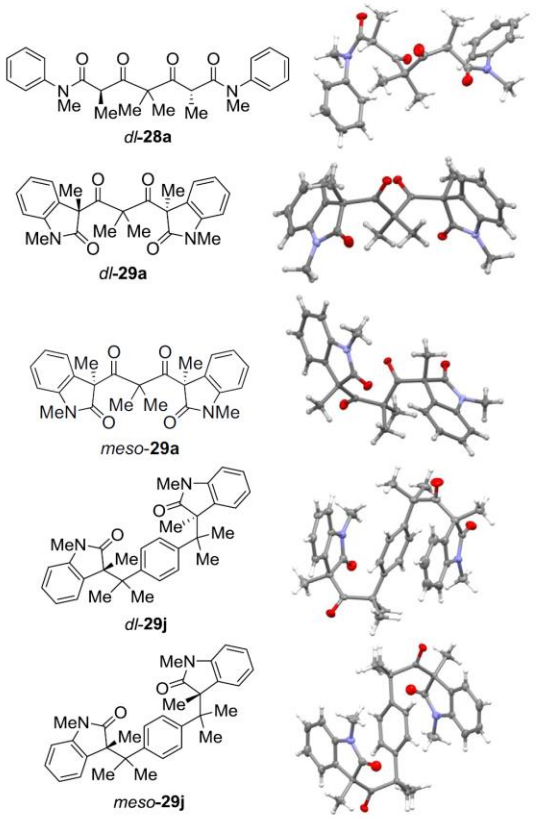

Fig. 5. Crystal structures of *dl*-**28a**, *dl*-**29a**, *meso*-**29a**, *dl*-**29j** and *meso*-**29j** (50% probability ellipsoids).

As expected, cyclisation of *meso*-**28a** occurred smoothly on heating in the presence of $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in mesitylene, giving a separable 44:56 mixture of *meso*-**29a** and *dl*-**29a** in a combined 55% yield (Scheme 6). The same result was obtained

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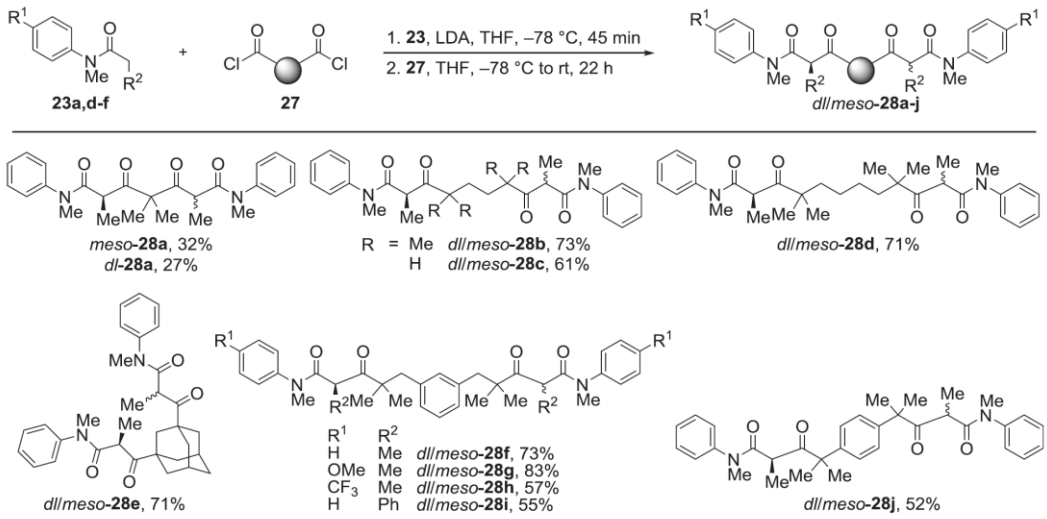
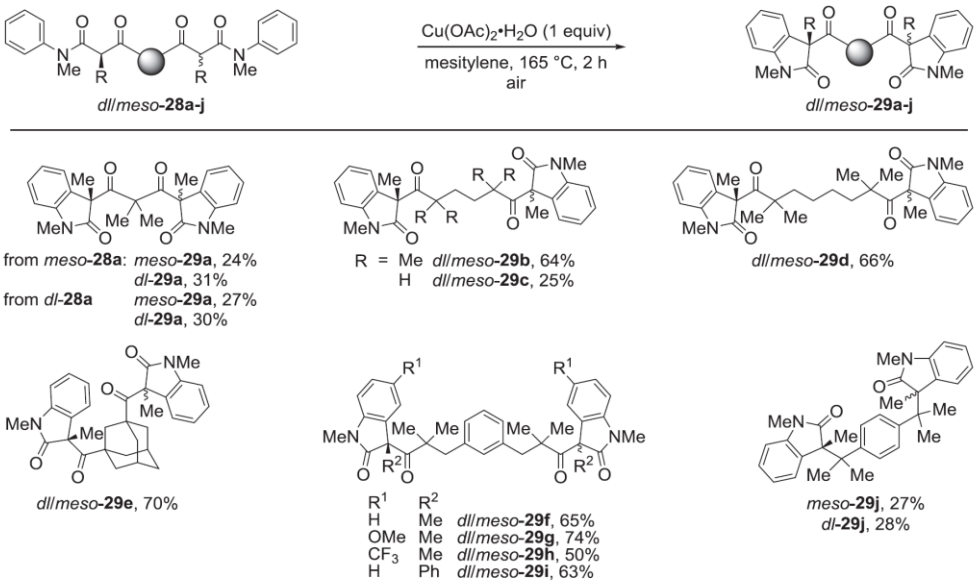


Scheme 5. Synthesis of bis-oxindole linear precursors. With the exception of **28a**, all compounds were isolated as an inseparable 50:50 mixture of *dl*/*meso*-diastereomers.

when *dl*-**28a** was used as the substrate. Once again, the structures of *meso*-**29a** and *dl*-**29a** were confirmed by the characteristic ^{1}H NMR signals for the *gem*-dimethyl group, as well as by X-ray crystallography (Fig. 5). Variation in the aliphatic linker chain length was also tolerated, delivering bis-oxindoles **29b**–**d** as mixtures of diastereomers. Replacement of the *gem*-dimethyl groups in **29b** with methylene groups (**29c**, R=H) results in a significant reduction in yield, highlighting the preference for substitution at the carbonyl α-positions to avoid decomposition.

More complex linkers were also well tolerated, exemplified by the synthesis of adamantane **29e** in 70% yield. Bis-oxindoles **29f**–**i**, incorporating an aromatic linker derived from the well-known rhodium ligand α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid (H_2esp),[15] could be also prepared in similar fashion. It is noteworthy that substitution on the aromatic ring with both electron-donating (**29g**, R^1=OMe) and electron-withdrawing groups (**29h**, R^1=CF_3), or replacement of the oxindole C-3/C-3′ methyl groups with an aromatic ring (**29i**, R^2=Ph) all resulted in successful cyclisation reactions. Aromatic-linked bis-oxindoles *meso*-**29j** and *dl*-**29j** proved separable by column chromatography. However, determination of the relative stereochemistry proved difficult by NMR spectroscopy alone, necessitating their characterisation by X-ray crystallography (Fig. 5).



Scheme 6. Synthesis of bis-oxindoles with diketone linkers. With the exception of **29a** and **29j**, all compounds were isolated as an inseparable 50:50 mixture of *dl*/*meso*-diastereomers.

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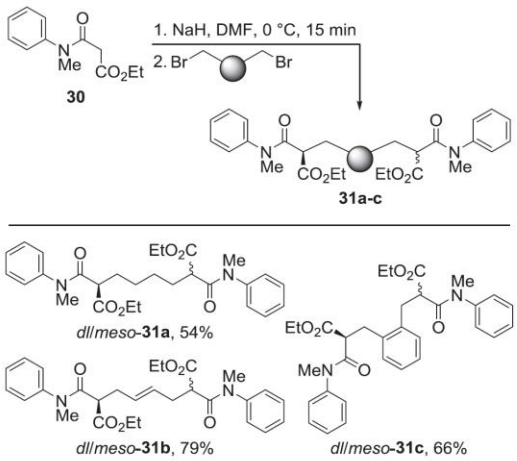
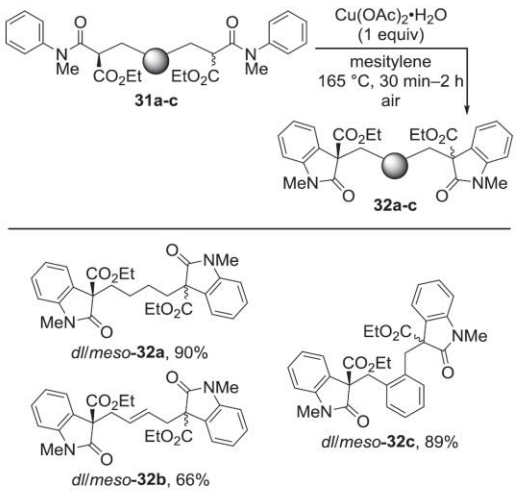


Scheme 7. Synthesis of ester-containing linear precursors. All compounds were isolated as an inseparable 50:50 mixture of *dl*/*meso*-diastereomers.

2.5. Synthesis of ester-containing bis-oxindoles

In a final new aspect to this work, we wished to explore the effect of moving the required electron-withdrawing group from the linker into the C-3 position of the oxindole. The required linear precursors **31a**–**c** were rapidly prepared from anilide **30** by deprotonation with NaH followed by introduction of the requisite dibromide (Scheme 7).

In the event, cyclisation of **31a**–**c** under the optimised conditions delivered bis-oxindoles containing aliphatic (**32a**), olefinic (**32b**) and aromatic (**32c**) linkers in good to excellent yield (Scheme 8).



Scheme 8. Synthesis of ester-containing bis-oxindoles. All compounds were isolated as an inseparable 50:50 mixture of *dl*/*meso*-diastereomers.

3. Conclusions

In conclusion, we have developed a concise synthesis of bis-oxindoles from linear bis-anilides via a copper(II)-mediated formal C–H/Ar–H coupling process. Highlights of this method include the inexpensive copper salt used, the short reaction times and the complete diastereoselectivity observed in the synthesis of spirocyclic bis-oxindoles containing various core ring sizes. Furthermore, we are able to prepare bis-oxindoles connected by diverse acyclic linkers using this single synthetic method.

This simple double cyclisation represents a fundamentally different approach to the synthesis of bis-oxindoles by simultaneous formation of both oxindole rings around an existing central linker. We anticipate that this method should find ready application in the synthesis of complex bis-oxindoles, efforts towards which are underway in our laboratory.

4. Experimental

4.1. General information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous solvents (CH_2Cl_2, toluene, DMF) were obtained from an Innovative Technologies solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. NMR spectra were recorded on a JEOL spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 ($CHCl_3$) and δ_C 77.0 ($CDCl_3$) was used as a reference. Coupling 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. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded neat on a Perkin–Elmer Spectrum Two FTIR-ATR spectrometer. Mass-spectra (low- and high-resolution) were obtained using electrospray ionisation (ESI) on a Micro-TOF spectrometer. Melting points were recorded in capillary tubes on a Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on silica gel 60F254 pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aq potassium permanganate, ethanolic *p*-anisaldehyde or ammonium molybdate as appropriate. Flash column chromatography was carried out using slurry packed silica gel (SiO_2), 35–75 Dm particle size, 60 Å pore size, under a light positive pressure, eluting with the specified solvent system.

4.2. General procedure 1 for the formation of spirocyclic bis-oxindoles 16a–k

To a stirred solution of the bis-anilide **15** (1 equiv) in DMF (0.02–0.06 M) were added $Cu(OAc)_2 \cdot H_2O$ (2 equiv) and KO*t*Bu (2.2 equiv). The reaction mixture was stirred at 110 °C for 15 min under an atmosphere of air and allowed to cool to room temperature. An aq solution of 10% NH_4OH (2×5 mL) was added and the aqueous phase was extracted with EtOAc (2×5 mL). The combined organic phases were washed with water (4×5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The ^{1}H NMR spectrum of the crude reaction mixture showed only the *trans*-diastereoisomer present. The residue was purified by column chromatography (SiO_2, hexane/EtOAc) to give the *title compound* **16**.

*4.2.1. (trans)-1,1″-Dimethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**16a**).* Bis-anilide **15a** (27.4 mg, 0.078 mmol), $Cu(OAc)_2 \cdot H_2O$ (32.2 mg, 0.161 mmol) and KO*t*Bu (18.8 mg, 0.168 mmol) in DMF (3 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16a** (18.2 mg, 67%) as a colourless solid, mp 184–186 °C; R_f 0.42 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 1751, 1704, 1612, 1493, 1471, 1370, 1347, 1266, 1070, 885, 752; δ_H (400 MHz, $CDCl_3$) 7.43 (2H, dd, J=7.6,

1.2 Hz, C*H*), 7.31 (2H, td, *J*=7.6, 1.2 Hz, C*H*), 7.10 (2H, td, *J*=7.6, 1.2 Hz, C*H*), 6.84 (2H, d, *J*=7.6 Hz, C*H*), 3.21 (6H, s, CH_3), 3.15–3.10 (2H, m, CH_2), 2.78–2.72 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 208.0 (*C*), 175.0 (*C*), 144.4 (*C*), 129.8 (*C*), 129.1 (*C*H), 124.3 (*C*H), 123.6 (*C*H), 108.4 (*C*H), 63.7 (*C*), 32.4 (CH_2), 26.6 (CH_3); HRMS (ESI): MNa^+, found 369.1213. $[C_{21}H_{18}N_2NaO_3]^+$ requires 369.1210. CCDC 1004040 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*4.2.2. (trans)-1,1″-Dibenzyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**16b**).* Bis-anilide **15b** (14.7 mg, 0.029 mmol), $Cu(OAc)_2 \cdot H_2O$ (11.6 mg, 0.058 mmol) and KO*t*Bu (7.22 mg, 0.064 mmol) in DMF (1.5 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16b** (8.2 mg, 57%) as a pale yellow solid, mp 115–117 °C; R_f 0.50 (hexane/EtOAc, 2:1); ν_{max} (ATR, cm^{-1}) 1740, 1703, 1612, 1488, 1467, 1455, 1359, 1311, 1178, 873, 752, 734; δ_H (400 MHz, $CDCl_3$) 7.48 (2H, dd, *J*=7.6, 1.0 Hz, C*H*), 7.34–7.30 (4H, m, C*H*), 7.30–7.27 (6H, m, C*H*), 7.19 (2H, td, *J*=7.6, 1.0 Hz, C*H*), 7.07 (2H, td, *J*=7.6, 1.0 Hz, C*H*), 6.70 (2H, d, *J*=7.6 Hz, C*H*), 5.02 (2H, d, *J*=15.9 Hz, CH_2), 4.83 (2H, d, *J*=15.9 Hz, CH_2), 3.26–3.15 (2H, m, CH_2), 2.93–2.81 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 208.0 (*C*), 175.2 (*C*), 143.5 (*C*), 135.3 (*C*), 129.8 (*C*), 129.1 (*C*H), 129.0 (*C*H), 127.8 (*C*H), 127.1 (*C*H), 124.4 (*C*H), 123.7 (*C*H), 109.5 (*C*H), 63.8 (*C*), 43.9 (CH_2), 32.5 (CH_2); HRMS (ESI): MNa^+, found 521.1825. $[C_{33}H_{26}N_2NaO_3]^+$ requires 521.1836.

*4.2.3. (trans)-1,1″,5,5″-Tetramethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**16c**).* Bis-anilide **15c** (39.8 mg, 0.105 mmol), $Cu(OAc)_2 \cdot H_2O$ (43.7 mg, 0.219 mmol) and KO*t*Bu (25.8 mg, 0.230 mmol) in DMF (4 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16c** (26.2 mg, 67%) as a colourless solid, mp 197–199 °C; R_f 0.60 (hexane/EtOAc, 1:2); ν_{max} (ATR, cm^{-1}) 1751, 1701, 1624, 1602, 1499, 1349, 1271, 1069, 918, 811; δ_H (400 MHz, $CDCl_3$) 7.24 (2H, dd, *J*=1.3, 0.6 Hz, C*H*), 7.10 (2H, ddd, *J*=7.9, 1.3, 0.6 Hz, C*H*), 6.72 (2H, d, *J*=7.9 Hz, C*H*), 3.19 (6H, s, CH_3), 3.17–3.04 (2H, m, CH_2), 2.77–2.64 (2H, m, CH_2), 2.33 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 208.4 (*C*), 175.0 (*C*), 142.1 (*C*), 133.3 (*C*), 129.8 (*C*), 129.3 (*C*H), 125.1 (*C*H), 108.1 (*C*H), 63.8 (*C*), 32.5 (CH_2), 26.6 (CH_3), 21.2 (CH_3); HRMS (ESI): MNa^+, found 397.1506. $[C_{23}H_{22}N_2NaO_3]^+$ requires 397.1523.

*4.2.4. (trans)-5,5″-Dimethoxy-1,1″-dimethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**16d**).* Bis-anilide **15d** (41.7 mg, 0.102 mmol), $Cu(OAc)_2 \cdot H_2O$ (41.1 mg, 0.206 mmol) and KO*t*Bu (25.6 mg, 0.228 mmol) in DMF (4 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1 to hexane/EtOAc, 2:1) to give the *title compound* **16d** (18.3 mg, 44%) as a colourless solid, mp 180–182 °C; R_f 0.46 (hexane/EtOAc, 1:2); ν_{max} (ATR, cm^{-1}) 1749, 1701, 1600, 1497, 1469, 1435, 1354, 1288, 1039, 811; δ_H (400 MHz, $CDCl_3$) 7.07 (2H, d, *J*=2.6 Hz, C*H*), 6.83 (2H, dd, *J*=8.4, 2.6 Hz, C*H*), 6.74 (2H, d, *J*=8.4 Hz, C*H*), 3.79 (6H, s, CH_3), 3.18 (6H, s, CH_3), 3.15–3.03 (2H, m, CH_2), 2.79–2.67 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 207.9 (*C*), 174.7 (*C*), 156.7 (*C*), 137.9 (*C*), 130.8 (*C*), 114.1 (*C*H), 111.1 (*C*H), 108.8 (*C*H), 64.1 (*C*), 56.0 (CH_3), 32.5 (CH_2), 26.6 (CH_3); HRMS (ESI): MNa^+, found 429.1433. $[C_{23}H_{22}N_2NaO_5]^+$ requires 429.1421.

*4.2.5. (trans)-5-Methoxy-1,1″,5″-trimethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole-2,2′,2″-trione (**16e**).* Bis-anilide **15e** (51.0 mg, 0.130 mmol), $Cu(OAc)_2 \cdot H_2O$ (52.0 mg, 0.260 mmol), and KO*t*Bu (32.0 mg, 0.286 mmol) in DMF (4 mL) were subjected to general procedure 1. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1 to 1:1) to give the *title compound* **16e** (19.0 mg, 37%) as a colourless solid, mp 176–178 °C; R_f 0.48 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2940, 1749, 1691, 1601, 1496, 1465, 1433, 1349, 1310, 1287, 1216, 1172, 1067, 1040, 1022, 845; δ_H (400 MHz, $CDCl_3$) 7.23–7.22 (1H, m, C*H*), 7.12–7.09 (2H, m, C*H*), 6.84 (1H, dd, *J*=8.4, 2.5 Hz, C*H*), 6.74 (1H, d, *J*=8.4 Hz, C*H*), 6.72 (1H, d, *J*=7.9 Hz, C*H*), 3.80 (3H, s, CH_3), 3.19 (3H, s, CH_3), 3.18 (3H, s, CH_3), 3.16–3.06 (2H, m, CH_2), 2.77–2.68 (2H, m, CH_2), 2.34 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 208.1 (*C*), 174.8 (*C*), 174.7 (*C*), 156.6 (*C*), 142.0 (*C*), 137.7 (*C*), 133.1 (*C*), 130.8 (*C*), 129.5 (*C*), 129.3 (*C*H), 124.9 (*C*H), 113.9 (*C*H), 111.1 (*C*H), 108.7 (*C*H), 108.0 (*C*H), 63.9 (*C*), 63.7 (*C*), 55.9 (CH_3), 32.4 (CH_2), 32.3 (CH_2), 26.5 (CH_3), 26.4 (CH_3), 21.1 (CH_3); HRMS (ESI): MH^+, found 391.1655. $[C_{23}H_{23}N_2O_4]^+$ requires 391.1652.

*4.2.6. (trans)-1-Benzyl-1″-methyl-di-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**16f**).* Bis-anilide **15f** (0.107 g, 0.250 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.100 g, 0.500 mmol), and KO*t*Bu (62.0 mg, 0.550 mmol) in DMF (4 mL) were subjected to general procedure 1. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound* **16f** (29.1 mg, 28%) as a colourless solid, mp 92–94 °C; R_f 0.53 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2934, 1752, 1697, 1610, 1488, 1466, 1345, 1309, 1253, 1176, 1079, 1030; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, dd, *J*=7.4, 0.7 Hz, C*H*), 7.46 (1H, dd, *J*=7.4, 0.7 Hz, C*H*), 7.36–7.23 (6H, m, C*H*), 7.19 (1H, td, *J*=7.8, 1.2 Hz, C*H*), 7.12 (1H, td, *J*=7.6, 0.8 Hz, C*H*), 7.07 (1H, td, *J*=7.6, 0.8 Hz, C*H*), 6.86 (1H, d, *J*=7.7 Hz, C*H*), 6.70 (1H, d, *J*=7.7 Hz, C*H*), 4.99 (1H, d, *J*=15.9 Hz, CH_2), 4.85 (1H, d, *J*=15.9 Hz, CH_2), 3.23 (3H, s, CH_3), 3.20–3.12 (2H, m, CH_2), 2.87–2.77 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 207.9 (*C*), 175.2 (*C*), 174.8 (*C*), 144.3 (*C*), 143.4 (*C*), 135.2 (*C*), 129.7 (*C*), 129.6 (*C*), 129.0 (*C*H), 128.90 (*C*H), 128.86 (*C*H), 127.6 (*C*H), 127.0 (*C*H), 124.3 (*C*H), 124.2 (*C*H), 123.52 (*C*H), 123.49 (*C*H), 109.3 (*C*H), 108.3 (*C*H), 63.65 (*C*), 63.61 (*C*), 43.8 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 26.5 (CH_3); HRMS (ESI): MNa^+, found 445.1516. $[C_{27}H_{22}N_2NaO_3]^+$ requires 445.1523.

*4.2.7. (trans)-1″-Benzyl-1,5-dimethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**16g**).* Bis-anilide **15g** (0.116 g, 0.263 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.105 g, 0.526 mmol), and KO*t*Bu (65.0 mg, 0.579 mmol) in DMF (8 mL) were subjected to general procedure 1. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 1:4 to 1:1) to give the *title compound* **16g** (37.8 mg, 33%) as a colourless solid, mp 102–104 °C; R_f 0.51 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2942, 1753, 1701, 1605, 1498, 1466, 1348, 1310, 1253, 1175, 1080, 1059, 1030; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J*=7.3, 0.6 Hz, C*H*), 7.34–7.29 (4H, m, C*H*), 7.27–7.23 (2H, m, C*H*), 7.19 (1H, td, *J*=7.7, 1.3 Hz, C*H*), 7.14–7.11 (1H, m, C*H*), 7.07 (1H, td, *J*=7.7, 0.9 Hz, C*H*), 6.74 (1H, d, *J*=7.9 Hz, C*H*), 6.68 (1H, d, *J*=7.7 Hz, C*H*), 5.00 (1H, d, *J*=16.0 Hz, CH_2), 4.85 (1H, d, *J*=16.0 Hz, CH_2), 3.25–3.09 (2H, m, CH_2), 3.20 (3H, s, CH_3), 2.86–2.74 (2H, m, CH_2), 2.35 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 208.1 (*C*), 175.3 (*C*), 174.7 (*C*), 143.4 (*C*), 141.9 (*C*), 135.1 (*C*), 133.2 (*C*), 129.8 (*C*), 129.5 (*C*), 129.3 (*C*H), 128.8 (*C*H), 127.6 (*C*H), 126.9 (*C*H), 124.8 (*C*H), 124.3 (*C*H), 123.5 (*C*H), 109.3 (*C*H), 108.0 (*C*H), 63.7 (*C*), 63.6 (*C*), 43.7 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 26.4 (CH_3), 21.1 (CH_3); HRMS (ESI): MNa^+, found 459.1662. $[C_{28}H_{24}N_2NaO_3]^+$ requires 459.1679.

*4.2.8. (trans)-1,1″-Dimethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclohexane-3′,3″-indole]-2,2′,2″-trione (**16h**).* Bis-anilide **15h** (33.3 mg, 0.091 mmol), $Cu(OAc)_2 \cdot H_2O$ (37.4 mg, 0.187 mmol) and KO*t*Bu (22.7 mg, 0.202 mmol) in DMF (3 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16h** (14.2 mg, 43%) as a colourless solid, mp 210–212 °C; R_f 0.64 (hexane/EtOAc, 1:4); ν_{max} (ATR, cm^{-1}) 1705, 1688, 1610, 1494, 1471, 1372, 1348, 1266, 1105, 753; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, dd, *J*=7.4, 1.2 Hz, C*H*), 7.28 (2H, dd, *J*=7.4, 1.2 Hz, C*H*), 7.07 (2H, td, *J*=7.4, 1.2 Hz, C*H*), 6.79 (2H,

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d, J=7.4 Hz, C*H*), 3.17 (6H, s, CH_3), 2.50 (6H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 203.2 (*C*), 175.8 (*C*), 143.9 (*C*), 132.9 (*C*), 128.7 (CH), 124.4 (*C*H), 123.4 (CH), 108.3 (*C*H), 62.3 (*C*), 33.5 (CH_2), 26.6 (CH_3), 17.1 (CH_2); HRMS (ESI): MNa^+, found 383.1370. $[C_{22}H_{20}N_2NaO_3]^+$ requires 383.1366.

*4.2.9. 5-tert-Butyl-(trans)-1,1″-dimethyl-1,1″,2,2″-tetrahydrodispiro [indole-3,1′-cyclohexane-3′,3″-indole]-2,2′,2″-trione (**16i**).* Bis-anilide **15i** (45.4 mg, 0.108 mmol), $Cu(OAc)_2 \cdot H_2O$ (43.8 mg, 0.219 mmol) and KO*t*Bu (25.6 mg, 0.228 mmol) in DMF (4.5 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16i** (24.1 mg, 54%) as a colourless solid, mp 152–154 °C; R_f 0.48 (hexane/EtOAc, 1:2); ν_{max} (ATR, cm^{-1}) 1707, 1690, 1651, 1610, 1494, 1470, 1371, 1346, 1263, 753; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, dd, J=7.6, 1.2 Hz, C*H*), 7.34 (1H, dd, J=7.6, 1.2 Hz, C*H*), 7.28 (1H, dd, J=7.6, 1.2 Hz, C*H*), 7.28 (1H, dd, J=7.6, 1.2 Hz, C*H*), 7.08 (1H, td, J=7.6, 1.2 Hz, C*H*), 7.07 (1H, td, J=7.6, 1.2 Hz, C*H*), 6.81 (1H, d, J=7.6 Hz, C*H*), 6.78 (1H, d, J=7.6 Hz, C*H*), 3.19 (3H, s, CH_3), 3.14 (3H, s, CH_3), 3.05–2.95 (1H, m, C*H*), 2.48 (1H, t, J=13.1 Hz, CH_2), 2.34 (2H, d, J=8.8 Hz, CH_2), 2.19 (1H, d, J=14.9 Hz, CH_2), 0.96 (9H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 203.9 (*C*), 176.4 (*C*), 175.5 (*C*), 143.9 (*C*), 143.8 (*C*), 133.9 (*C*), 132.7 (*C*), 128.8 (*C*H), 128.6 (CH), 124.7 (*C*H), 124.0 (CH), 123.5 (*C*H), 123.3 (CH), 108.4 (*C*H), 108.2 (CH), 63.3 (*C*), 61.9 (*C*), 37.5 (*C*H), 35.8 (CH_2), 35.6 (CH_2), 32.6 (*C*), 27.3 (CH_3), 26.7 (CH_3), 26.5 (CH_3); HRMS (ESI): MNa^+, found 439.2011. $[C_{26}H_{28}N_2NaO_3]^+$ requires 439.1992.

*4.2.10. (trans)-1,1″-Dimethyl-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cycloheptane-3′,3″-indole]-2,2′,2″-trione (**16j**).* Bis-anilide **15j** (24.5 mg, 0.065 mmol), $Cu(OAc)_2 \cdot H_2O$ (27.5 mg, 0.138 mmol) and KO*t*Bu (16.4 mg, 0.146 mmol) in DMF (2.5 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16j** (18.8 mg, 77%) as a colourless solid, mp 196–198 °C; R_f 0.69 (hexane/EtOAc, 1:2); ν_{max} (ATR, cm^{-1}) 1701, 1682, 1608, 1493, 1470, 1373, 1347, 1260, 1126, 1079, 947, 753, 729; δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, J=7.6 Hz, C*H*), 7.23 (2H, td, J=7.6, 1.2 Hz, C*H*), 7.02 (2H, td, J=7.6, 1.2 Hz, C*H*), 6.76 (2H, d, J=7.6 Hz, C*H*), 3.20 (6H, s, CH_3), 2.85 (2H, br s, CH_2), 2.43 (2H, br t, J=9.0 Hz, CH_2), 2.07–1.94 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 174.9 (*C*), 142.8 (*C*), 132.0 (*C*), 128.5 (*C*H), 125.3 (*C*H), 122.9 (CH), 108.2 (*C*H), 67.9 (*C*), 33.9 (CH_2), 26.5 (CH_3), 24.2 (CH_2); HRMS (ESI): MNa^+, found 397.1510. $[C_{23}H_{22}N_2NaO_3]^+$ requires 397.1523.

*4.2.11. (trans)-1,1″-Dimethyl-1,1″,2,2″,7′,9′-hexahydro-5′H-dispiro [indole-3,6′-benzo[7]annulene-8′,3″-indole]2,2″,7′-trione (**16k**).* Bis-anilide **15k** (31.1 mg, 0.073 mmol), $Cu(OAc)_2 \cdot H_2O$ (30.2 mg, 0.151 mmol) and KO*t*Bu (19.1 mg, 0.170 mmol) in DMF (2 mL) were subjected to general procedure 1. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to give the *title compound* **16k** (14.3 mg, 46%) as a yellow solid, mp 214–216 °C; R_f 0.50 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 1710, 1678, 1609, 1493, 1471, 1370, 1347, 1261, 1077, 1023, 910, 798, 752; δ_H (400 MHz, $CDCl_3$) 7.33 (2H, dd, J=5.4, 3.3 Hz, C*H*), 7.26 (2H, td, J=7.6, 1.2 Hz, C*H*), 7.16 (2H, dd, J=5.4, 3.3 Hz, C*H*), 7.04 (2H, d, J=7.6 Hz, C*H*), 6.98 (2H, td, J=7.6, 1.2 Hz, C*H*), 6.81 (2H, d, J=7.6 Hz, C*H*), 3.65 (2H, d, J=14.7 Hz, CH_2), 3.46 (2H, d, J=14.7 Hz, CH_2), 3.17 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.2 (*C*), 174.9 (*C*), 143.9 (*C*), 135.9 (*C*), 132.5 (*C*), 130.8 (*C*H), 128.8 (CH), 127.7 (*C*H), 125.0 (CH), 123.1 (*C*H), 108.3 (CH), 65.7 (*C*), 38.0 (CH_2), 26.5 (CH_3); HRMS (ESI): MNa^+, found 445.1527. $[C_{27}H_{22}N_2NaO_3]^+$ requires 445.1523.

4.3. Synthesis of bis-oxindoles 18 and 20 bearing chiral auxiliaries

*4.3.1. Ethyl 3-methyl-2-oxo-1-[(1S)-1-phenylethyl]-2,3-dihydro-1H-indole-3-carboxylate (**18**).* To a stirred solution of anilide **17** (27.7 mg, 0.085 mmol) in toluene (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (17.7 mg, 0.089 mmol). The reaction mixture was stirred at 110 °C for 18 h under an atmosphere of air and allowed to cool to room temperature. The copper salt was removed by addition of an aq soln of NH_4OH (5 mL). The aqueous phase was extracted with EtOAc (2×5 mL). The combined organic extracts were washed with water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1) to give the *title compound* **18** (44:56, 21.0 mg, 76%) as a yellow oil; R_f 0.23 (hexane/EtOAc, 6:1); ν_{max} (ATR, cm^{-1}) 2982, 2936, 1741, 1714, 1607, 1484, 1467, 1350, 1237, 1190, 1112, 1019, 752, 698; δ_H (400 MHz, $CDCl_3$) 7.41–7.37 (1H, m, C*H*), 7.35–7.26 (4H, m, C*H*), 7.23 (0.45H, d, J=7.4 Hz, C*H*), 7.22 (0.55H, d, J=7.4 Hz, C*H*), 7.08–7.01 (1H, m, C*H*), 6.96 (0.45H, td, J=7.6, 1.0 Hz, C*H*), 6.96 (0.55H, td, J=7.6, 1.0 Hz, C*H*), 6.49 (0.45H, d, J=7.6 Hz, C*H*), 6.45 (0.55H, d, J=7.6 Hz, C*H*), 5.92 (0.55H, q, J=7.2 Hz, C*H*), 5.83 (0.45H, q, J=7.2 Hz, C*H*), 4.24–4.13 (1.1H, m, CH_2), 4.12–4.02 (0.9H, m, CH_2), 1.85 (1.35H, d, J=7.2 Hz, CH_3), 1.82 (1.65H, d, J=7.2 Hz, CH_3), 1.72 (1.35H, s, CH_3), 1.71 (1.65H, s, CH_3), 1.20 (1.65H, t, J=7.1 Hz, CH_3), 1.15 (1.35H, t, J=7.1 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 175.5 and 175.4 (*C*), 171.4 and 170.0 (*C*), 141.7 and 141.5 (*C*), 139.1 and 139.0 (*C*), 130.6 and 130.5 (*C*), 128.8 and 128.7 (*C*H), 128.56 and 128.55 (CH), 127.54 and 127.45 (CH), 126.7 and 126.6 (*C*H), 123.01 and 122.97 (CH), 122.52 and 122.50 (CH), 111.4 and 111.1 (CH), 62.1 and 62.0 (CH_2), 55.01 and 54.99 (*C*), 49.5 and 48.8 (*C*H), 20.0 and 19.7 (CH_3), 16.2 and 16.1 (CH_3), 13.94 and 13.92 (CH_3); HRMS (ESI): MNa^+, found 346.1406. $[C_{20}H_{21}NNaO_3]^+$ requires 346.1414.

*4.3.2. 1,1″-Bis[(1S)-1-phenylethyl]-1,1″,2,2″-tetrahydrodispiro[indole-3,1′-cyclopentane-3′,3″-indole]-2,2′,2″-trione (**20**).* To a stirred solution of bis-anilide **19** (35.9 mg, 0.068 mmol) in DMF (2 mL) was added $Cu(OAc)_2 \cdot H_2O$ (27.7 mg, 0.139 mmol) and KO*t*Bu (16.7 mg, 0.149 mmol). The reaction mixture was stirred at 110 °C for 15 min under an atmosphere of air and allowed to cool to room temperature. An aq solution of 10% NH_4OH (2×5 mL) was added and the aqueous phase was extracted with EtOAc (2×5 mL). The combined organic phases were washed with water (4×5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 8:1) to give the *title compound* **20** (44:56, 16.4 mg, 46%) as a colourless solid, mp 66–68 °C; R_f 0.31 (hexane/EtOAc, 4:1); ν_{max} (ATR, cm^{-1}) 2981, 1755, 1700, 1608, 1484, 1466, 1348, 1310, 1254, 1052, 850, 752, 697; δ_H (400 MHz, $CDCl_3$) 7.50–7.45 (2H, m, C*H*), 7.36–7.26 (10H, m, C*H*), 7.10–7.00 (4H, m, C*H*), 6.51 (1.1H, d, J=7.1 Hz, C*H*), 6.44 (0.9H, dd, J=7.1, 0.7 Hz, C*H*), 5.78 (2H, pent, J=7.1 Hz, C*H*), 3.26–3.16 (2H, m, CH_2), 2.94–2.83 (2H, m, CH_2), 1.84 (3H, d, J=7.2 Hz, CH_3), 1.84 (3H, d, J=7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 208.1 and 208.0 (*C*), 175.2 and 175.1 (*C*), 142.5 and 142.4 (*C*), 139.0 and 138.6 (*C*), 130.2 and 130.1 (*C*), 128.8 (*C*H), 128.6 (*C*H), 127.6 and 127.5 (*C*H), 126.6 (CH), 124.4 and 124.3 (CH), 123.24 and 123.19 (CH), 111.2 and 111.0 (CH), 63.8 and 63.6 (*C*), 49.6 and 49.2 (*C*H), 32.7 and 32.3 (CH_2), 16.5 and 16.3 (CH_3); HRMS (ESI): MNa^+, found 549.2162. $[C_{35}H_{30}N_2NaO_3]^+$ requires 549.2149.

4.4. General procedure 2 for the synthesis of monoketone linked bis-oxindoles 25a–c

To a stirred solution of bis-anilide **24** (1 equiv) in mesitylene (0.03–0.1 M) was added $Cu(OAc)_2 \cdot H_2O$ (1 equiv). The reaction mixture was stirred for 30 min at 170 °C (Drysyn heating block) under an atmosphere of air. Mesitylene was removed in vacuo. The resulting residue was diluted with EtOAc (5 mL) and washed twice with a 10% aq solution of NH_4OH (2×5 mL) and 4 M solution of NaOH (3×5 mL). The ^1H NMR spectrum of the crude reaction showed a mixture of diastereoisomers present. Purification by column chromatography (SiO_2, hexane/EtOAc) gave the *title compound* **25**.

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*4.4.1. dl-3-(1,3-Diethyl-2-oxo-2,3-dihydro-1H-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (dl-**25a**) and meso-3-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (meso-**25a**).* Bis-anilide **24a** (35.7 mg, 0.101 mmol), and $Cu(OAc)_2 \cdot H_2O$ (21.0 mg, 0.105 mmol) in mesitylene (3.5 mL) were submitted to general procedure 2. The ^1H NMR spectrum of the crude reaction showed a mixture of diastereoisomers in a ratio of 40:60 *dl*-**25a**/*meso*-**25a**. Purification by column chromatography (SiO_2, hexane/EtOAc, 4:1) gave first *dl*-**25a** (9.6 mg, 27%) as a white solid, mp 262–264 °C; R_f 0.42 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 2932, 1728, 1706, 1611, 1492, 1469, 1446, 1374, 1345, 1120, 1028, 988, 768, 752; δ_H (400 MHz, $CDCl_3$) 7.10 (2H, td, *J*=7.6, 1.1 Hz, C*H*), 7.06 (2H, dd, *J*=7.6, 1.1 Hz, C*H*), 6.98 (2H, td, *J*=7.6, 1.1 Hz, C*H*), 6.31 (2H, d, *J*=7.6 Hz, CH), 2.78 (6H, s, CH_3), 1.48 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 196.3 (*C*), 174.1 (*C*), 144.1 (*C*), 129.0 (CH), 127.8 (*C*), 125.5 (CH), 122.2 (CH), 107.9 (CH), 62.1 (*C*), 26.3 (CH_3), 22.7 (CH_3); HRMS (ESI): MNa^+, found 371.1350. $[C_{21}H_{20}N_2NaO_3]^+$ requires 371.1366. CCDC 1004039 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The diastereoisomer *meso*-**25a** (10.9 mg, 31%) was then isolated by column chromatography (SiO_2, hexane/EtOAc, 4:1) as a white solid, mp 170–172 °C; R_f 0.25 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 1731, 1717, 1608, 1490, 1468, 1374, 1344, 1120, 1032, 761, 542; δ_H (400 MHz, $CDCl_3$) 7.20 (2H, td, *J*=7.6, 1.2 Hz, C*H*), 6.76 (2H, td, *J*=7.6, 1.2 Hz, C*H*), 6.63 (2H, d, *J*=7.6 Hz, C*H*), 6.55 (2H, dd, *J*=7.6, 1.2 Hz, C*H*), 2.91 (6H, s, CH_3), 1.50 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 197.9 (*C*), 174.2 (*C*), 144.4 (*C*), 129.1 (CH), 128.6 (*C*), 123.9 (CH), 122.3 (CH), 108.3 (CH), 61.3 (*C*), 26.4 (CH_3), 22.9 (CH_3); HRMS (ESI): MNa^+, found 371.1372. $[C_{21}H_{20}N_2NaO_3]^+$ requires 371.1366.

*4.4.2. trans/cis-3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-indole-3-carbonyl)1,3,5-trimethyl-2,3-dihydro-1H-indol-2-one (trans/cis-**25b**).* Bis-anilide **24b** (89.0 mg, 0.243 mmol), and $Cu(OAc)_2 \cdot H_2O$ (97.0 mg, 0.486 mmol) in mesitylene (2.4 mL) were submitted to general procedure 2, with a reaction time of 3 h. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give *trans*/*cis*-**25b** (38.5:61.5, 36.2 mg, 41%) as a colourless solid, mp 143–145 °C; R_f 0.20 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2929, 1714, 1694, 1604, 1502, 1490, 1468, 1445, 1421, 1368, 1342, 1257, 1185, 1146, 1118, 1027; δ_H (400 MHz, $CDCl_3$) 7.22 (0.615H, td, *J*=7.8, 1.1 Hz, C*H*), 7.19 (0.385H, td, *J*=7.8, 1.1 Hz, C*H*), 7.00–6.96 (1H, m, C*H*), 6.84 (0.615H, td, *J*=7.5, 0.8 Hz, C*H*), 6.75 (0.385H, td, *J*=7.5, 0.8 Hz, C*H*), 6.71 (0.615H, dd, *J*=7.4, 0.8 Hz, C*H*), 6.62 (0.385H, d, *J*=7.8 Hz, C*H*), 6.58 (0.615H, d, *J*=7.8 Hz, C*H*), 6.54 (1H, d, *J*=7.9 Hz, C*H*), 6.51 (0.385H, d, *J*=7.9 Hz, C*H*), 6.34 (0.385H, s, C*H*), 6.17 (0.615H, s, C*H*), 2.96 (1.85H, s, CH_3), 2.90 (1.15H, s, CH_3), 2.87 (1.15H, s, CH_3), 2.81 (1.85H, s, CH_3), 2.12 (1.15H, s, CH_3), 2.05 (1.85H, s, CH_3), 1.50 (1.85H, s, CH_3), 1.49 (1.15H, s, CH_3), 1.48 (1.15H, s, CH_3), 1.47 (1.85H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 197.9 (*C*), 174.3 and 174.09 (*C*), 174.06 and 173.9 (*C*), 144.3 and 144.1 (*C*), 142.2 and 142.0 (*C*), 131.63 and 131.58 (*C*), 129.4 and 129.3 (CH), 129.0 and 128.9 (CH), 128.8 and 128.51 (*C*), 128.48 and 128.2 (*C*), 124.9 and 124.7 (CH), 123.7 and 123.6 (CH), 122.22 and 122.19 (CH), 108.2 and 108.1 (CH), 107.8 and 107.7 (CH), 61.4 and 61.2 (*C*), 61.1 and 61.0 (*C*), 26.5 and 26.34 (CH_3), 26.29 and 26.2 (CH_3), 22.73 and 22.71 ($2\times CH_3$), 20.91 and 20.87 (CH_3); HRMS (ESI): MNa^+, found 385.1514. $[C_{22}H_{22}N_2NaO_3]^+$ requires 385.1523.

*4.4.3. trans-3-(3-Ethyl-1-methyl-2-oxo-2,3-dihydro-1H-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (trans-**25c**) and cis-3-(3-ethyl-1-methyl-2-oxo-2,3-dihydro-1H-indole-3-carbonyl)-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (cis-**25c**).* Bis-anilide **24c** (51.3 mg, 0.140 mmol) and $Cu(OAc)_2 \cdot H_2O$ (28.0 mg, 0.140 mmol) in mesitylene (4 mL) were subjected to general procedure 2. The ^1H NMR spectrum of the crude reaction showed a mixture of diastereoisomers in a ratio of 60:40 *trans*-**25c**/*cis*-**25c**. Purification by column chromatography (SiO_2, hexane/EtOAc, 4:1 to hexane/EtOAc, 1:1) gave first *trans*-**25c** (20.8 mg, 41%) as a colourless solid, mp 200–202 °C; R_f 0.42 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 1724, 1701, 1609, 1489, 1461, 1369, 1346, 1259, 1160, 1101, 765; δ_H (400 MHz, $CDCl_3$) 7.11–7.05 (3H, m, C*H*), 7.03 (1H, dd, *J*=7.6, 1.2 Hz, C*H*), 7.01–6.93 (2H, m, C*H*), 6.29 (2H, d, *J*=7.6 Hz, C*H*), 2.80 (3H, s, CH_3), 2.79 (3H, s, CH_3), 2.21 (1H, dq, *J*=14.8, 7.4 Hz, CH_2), 2.10 (1H, dq, *J*=14.8, 7.4 Hz, CH_2), 1.47 (3H, s, CH_3), 0.42 (3H, t, *J*=7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 196.1 (*C*), 174.2 (*C*), 173.2 (*C*), 144.9 (*C*), 144.0 (*C*), 129.0 (CH), 128.9 (CH), 127.9 (*C*), 126.0 (CH), 125.4 (*C*), 125.2 (CH), 122.1 (CH), 121.9 (CH), 107.9 (CH), 107.7 (CH), 67.2 (*C*), 62.3 (*C*), 29.1 (CH_2), 26.4 (CH_3), 26.2 (CH_3), 22.8 (CH_3), 7.8 (CH_3); HRMS (ESI): MNa^+, found 385.1525. $[C_{22}H_{22}N_2NaO_3]^+$ requires 385.1523. CCDC 1016758 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The diastereoisomer *cis*-**25c** (13 mg, 26%) was then isolated by column chromatography (SiO_2, hexane/EtOAc, 1:1) as a colourless solid, mp 155–157 °C; R_f 0.23 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 1727, 1712, 1611, 1493, 1470, 1372, 1347, 1259, 1161, 1102, 755; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, td, *J*=7.6, 1.2 Hz, C*H*), 7.19 (1H, td, *J*=7.6, 1.2 Hz, C*H*), 6.78 (1H, td, *J*=7.6, 1.2 Hz, C*H*), 6.73 (1H, td, *J*=7.6, 1.2 Hz, C*H*), 6.65 (1H, d, *J*=7.6 Hz, C*H*), 6.60 (1H, d, *J*=7.6 Hz, C*H*), 6.57 (1H, dd, *J*=7.6, 1.2 Hz, C*H*), 6.48 (1H, dd, *J*=7.6, 1.2 Hz, C*H*), 2.94 (3H, s, CH_3), 2.85 (3H, s, CH_3), 2.18 (1H, dq, *J*=14.8, 7.4 Hz, CH_2), 2.09 (1H, dq, *J*=14.8, 7.4 Hz, CH_2), 1.48 (3H, s, CH_3), 0.47 (3H, t, *J*=7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 197.7 (*C*), 174.2 (*C*), 173.3 (*C*), 145.0 (*C*), 144.6 (*C*), 129.12 (CH), 129.10 (CH), 128.6 (*C*), 126.6 (*C*), 124.3 (CH), 123.7 (CH), 122.2 (CH), 108.4 (CH), 108.1 (CH), 66.2 (*C*), 61.6 (*C*), 29.6 (CH_2), 26.5 (CH_3), 26.2 (CH_3), 22.9 (CH_3), 7.7 (CH_3); HRMS (ESI): MNa^+, found 385.1518. $[C_{22}H_{22}N_2NaO_3]^+$ requires 385.1523. CCDC 1004041 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.5. General procedure 3 for the formation of diketone linked bis-oxindoles 29a–j

A solution of bis-anilide **28** (1 equiv) and $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in mesitylene (0.1 M) was heated at 165 °C for 2 h under an atmosphere of air, then cooled to room temperature. Saturated NH_4Cl (15 mL) was added and the aqueous phase extracted with EtOAc (3×15 mL). The combined organics were washed with 10% NH_4OH (15 mL), 4 M NaOH (3×15 mL), and saturated brine (15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc) to give the *title compound* **29**.

*4.5.1. meso-1,3-Bis(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2-dimethylpropane-1,3-dione (meso-**29a**) and dl-1,3-bis(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2-dimethylpropane-1,3-dione (dl-**29a**)*

*4.5.1.1. From dl-N,N′-2,4,4,6-hexamethyl-3,5-dioxo-N,N′-diphenylheptanedicarboxamide (dl-**28a**).* Bis-anilide *dl*-**28a** (0.180 g, 0.426 mmol) and $Cu(OAc)_2 \cdot H_2O$ (85.0 mg, 0.426 mmol) in mesitylene (4.3 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give *meso*-**29a** (47.6 mg, 27%) as a colourless solid, mp 159–161 °C; R_f 0.50 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2936, 1721, 1705, 1694, 1667, 1607, 1492, 1470, 1445, 1366, 1343, 1256, 1121, 1099, 1082, 1027, 990; δ_H (400 MHz, $CDCl_3$) 7.40 (2H, dd, *J*=7.5, 0.8 Hz, C*H*), 7.34 (2H, td, *J*=7.8, 1.1 Hz, C*H*), 7.06 (2H, td, *J*=7.5,

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0.8 Hz, C*H*), 6.88 (2H, d, *J*=7.8 Hz, C*H*), 3.25 (6H, s, CH_3), 1.57 (6H, s, CH_3), 0.98 (3H, s, CH_3), 0.94 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 203.4 (*C*), 175.6 (*C*), 142.9 (*C*), 130.2 (*C*), 128.9 (*C*H), 124.8 (*C*H), 122.9 (*C*H), 108.3 (*C*H), 64.5 (*C*), 60.4 (*C*), 26.6 (CH_3), 24.3 (CH_3), 23.4 (CH_3), 22.7 (CH_3); HRMS (ESI): MH^+, found 419.1972. $[C_{25}H_{27}N_2O_4]^+$ requires 419.1965. CCDC 1013389 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The diastereoisomer *dl*-**29a** (53.7 mg, 30%) was then isolated as a colourless solid, mp 128–130 °C; R_f 0.40 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2930, 1697, 1657, 1609, 1492, 1470, 1447, 1372, 1346, 1260, 1117, 1094, 1028, 976; δ_H (400 MHz, $CDCl_3$) 7.33 (2H, td, *J*=7.7, 1.2 Hz, C*H*), 7.29 (2H, dd, *J*=7.5, 0.7 Hz, C*H*), 7.10 (2H, td, *J*=7.6, 0.9 Hz, C*H*), 6.85 (2H, d, *J*=7.7 Hz, C*H*), 3.24 (6H, s, CH_3), 1.57 (6H, s, CH_3), 0.89 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 204.0 (*C*), 175.8 (*C*), 142.8 (*C*), 129.7 (*C*), 128.9 (*C*H), 124.4 (*C*H), 123.1 (*C*H), 108.3 (*C*H), 64.5 (*C*), 60.5 (*C*), 26.5 (CH_3), 23.8 (CH_3), 21.2 (CH_3); HRMS (ESI): MH^+, found 419.1975. $[C_{25}H_{27}N_2O_4]^+$ requires 419.1965. CCDC 1013390 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*4.5.1.2. From meso-N,N′-2,4,4,6-hexamethyl-3,5-dioxo-N,N′-diphenylheptanedicarboxamide (meso-**28a**).* Bis-anilide *meso*-**28a** (0.148 g, 0.350 mmol) and $Cu(OAc)_2 \cdot H_2O$ (70.0 mg, 0.350 mmol) in mesitylene (3.5 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give *meso*-**29a** (35.4 mg, 24%) as a colourless solid, followed by *dl*-**29a** (45.2 mg, 31%) as a colourless solid.

*4.5.2. dl/meso-1,6-Bis(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2,5,5-tetramethylhexane-1,6-dione (dl/meso-**29b**).* Bis-anilide *dl/meso*-**28b** (0.215 g, 0.436 mmol) and $Cu(OAc)_2 \cdot H_2O$ (87.0 mg, 0.436 mmol) in mesitylene (4.4 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 1:9 to 1:4) to give the *title compound dl/meso*-**29b** (50:50, 0.136 g, 64%) as a colourless solid, mp 182–184 °C; R_f 0.57 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2972, 1706, 1688, 1608, 1491, 1471, 1373, 1346, 1259, 1118, 1098, 1029, 983; δ_H (400 MHz, $CDCl_3$) 7.34–7.29 (2H, m, C*H*), 7.05–7.02 (4H, m, C*H*), 6.88 (2H, d, *J*=7.9 Hz, C*H*), 3.27 (6H, s, CH_3), 1.50 (6H, s, CH_3), 1.31–1.25 (2H, m, CH_2), 1.09–0.99 (2H, m, CH_2), 0.90 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.77 (3H, s, CH_3), 0.76 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 207.66 and 207.65 (*C*), 176.3 and 176.2 (*C*), 143.4 (*C*), 129.8 and 129.7 (*C*), 128.9 (*C*H), 123.50 and 123.46 (*C*H), 122.80 and 122.78 (*C*H), 108.6 (*C*H), 60.8 (*C*), 49.5 and 49.4 (*C*), 35.7 and 35.5 (CH_2), 26.5 (CH_3), 24.3 (CH_3), 24.0 (CH_3), 23.44 and 23.43 (CH_3), 23.4 (CH_3); HRMS (ESI): MH^+, found 489.2746. $[C_{30}H_{37}N_2O_4]^+$ requires 489.2748.

*4.5.3. dl/meso-1,6-Bis(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)hexane-1,6-dione (dl/meso-**29c**).* Bis-anilide *dl/meso*-**28c** (0.218 g, 0.500 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.100 g, 0.500 mmol) in mesitylene (5 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29c** (50:50, 52.9 mg, 25%) as a colourless solid, mp 120–122 °C; R_f 0.19 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2937, 1719, 1689, 1608, 1491, 1475, 1374, 1348, 1258, 1160, 1119, 1099, 1061, 1035, 985; δ_H (400 MHz, $CDCl_3$) 7.34–7.28 (2H, m, C*H*), 7.08–7.02 (4H, m, C*H*), 6.89 (2H, d, *J*=8.0 Hz, C*H*), 3.263 (3H, s, CH_3), 3.259 (3H, s, CH_3), 2.28–2.21 (2H, m, CH_2), 1.97–1.89 (2H, m, CH_2), 1.51 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.24–1.16 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 202.8 and 202.7 (*C*), 175.9 (*C*), 143.6 (*C*), 129.3 (*C*), 129.0 (*C*H), 123.33 and 123.31 (*C*H), 123.134 and 123.129 (*C*H), 108.52 and 108.51 (*C*H), 61.6 (*C*), 37.8 and 37.7 (CH_2), 26.5 (CH_3), 22.4 and 22.3 (CH_2), 19.0 and 18.9 (CH_3); HRMS (ESI): MNa^+, found 455.1931. $[C_{26}H_{28}N_2NaO_4]^+$ requires 455.1941.

*4.5.4. dl/meso-1,8-Bis(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2,7,7-tetramethyloctane-1,8-dione (dl/meso-**29d**).* Bis-anilide *dl/meso*-**28d** (0.250 g, 0.480 mmol) and $Cu(OAc)_2 \cdot H_2O$ (96.0 mg, 0.480 mmol) in mesitylene (4.8 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29d** (50:50, 0.164 g, 66%) as a colourless solid, mp 109–111 °C; R_f 0.25 (hexane/EtOAc, 3:1); ν_{max} (ATR, cm^{-1}) 2938, 1718, 1687, 1609, 1493, 1467, 1449, 1374, 1342, 1261, 1119, 1101, 1030, 981; δ_H (400 MHz, $CDCl_3$) 7.31 (2H, tdd, *J*=7.1, 2.0, 1.2 Hz, C*H*), 7.04–7.00 (4H, m, C*H*), 6.86 (2H, d, *J*=7.7 Hz, C*H*), 3.252 (3H, s, CH_3), 3.247 (3H, s, CH_3), 1.49 (6H, s, CH_3), 1.42–1.32 (2H, m, CH_2), 1.27–1.19 (2H, m, CH_2), 0.93–0.77 (4H, m, CH_2), 0.88 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.79 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 208.0 and 207.9 (*C*), 176.2 (*C*), 143.3 (*C*), 129.8 (*C*), 128.8 (*C*H), 123.273 and 123.269 (*C*H), 122.8 (*C*H), 108.5 (*C*H), 60.8 (*C*), 49.7 (*C*), 40.89 and 40.86 (CH_2), 26.4 (CH_3), 24.91 and 24.87 (CH_2), 24.5 and 24.38 (CH_3), 24.36 and 24.28 (CH_3), 23.4 (CH_3); HRMS (ESI): MNa^+, found 539.2859. $[C_{32}H_{40}N_2NaO_4]^+$ requires 539.2880.

*4.5.5. dl/meso-3-[3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-indole-3-carbonyl)adamantane-1-carbonyl]-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (dl/meso-**29e**).* Bis-anilide *dl/meso*-**28e** (0.206 g, 0.400 mmol) and $Cu(OAc)_2 \cdot H_2O$ (80.0 mg, 0.400 mmol) in mesitylene (4 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29e** (0.143 g, 70%) as a colourless solid, mp 173–174.5 °C; R_f 0.34 (hexane/EtOAc, 1:3); ν_{max} (ATR, cm^{-1}) 2930, 1707, 1685, 1608, 1491, 1470, 1447, 1372, 1342, 1258, 1171, 1119, 1099, 1043, 1022; δ_H (400 MHz, $CDCl_3$) 7.34 (2H, tt, *J*=7.7, 1.5 Hz, C*H*), 7.07–6.99 (2H, m, C*H*), 6.94 (1H, dd, *J*=7.0, 0.6 Hz, C*H*), 6.91–6.88 (2H, m, C*H*), 6.82 (1H, d, *J*=7.3 Hz, C*H*), 3.29 (3H, s, CH_3), 3.27 (3H, s, CH_3), 1.80–1.76 (1H, m, C*H*), 1.74–1.68 (1H, m, C*H*), 1.64–1.52 (3H, m, CH_2), 1.46–1.43 (3H, m, CH_2), 1.45 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.38–1.30 (5H, m, CH_2), 1.27–1.23 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 206.7 and 206.6 (*C*), 176.1 and 176.0 (*C*), 143.6 and 143.4 (*C*), 129.71 and 129.66 (*C*), 129.0 and 128.9 (*C*H), 123.1 (*C*H), 122.97 and 122.95 (*C*H), 108.8 and 108.7 (*C*H), 60.58 and 60.55 (*C*), 49.1 and 48.9 (*C*), 39.2 and 39.1 (CH_2), 37.52 and 37.47 (CH_2), 36.9 (CH_2), 36.6 (CH_2), 34.99 and 34.98 (CH_2), 27.84, 27.82 and 27.80 (*C*H), 26.6 and 26.5 (CH_3), 23.13 and 23.05 (CH_3); HRMS (ESI): MNa^+, found 533.2421. $[C_{32}H_{34}N_2NaO_4]^+$ requires 533.2411.

*4.5.6. dl/meso-3-[2-({3-[3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2-dimethyl-3-oxopropyl]phenyl}methyl)-2-methylpropanoyl]-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (dl/meso-**29f**).* Bis-anilide *dl/meso*-**28f** (0.145 g, 0.255 mmol) and $Cu(OAc)_2 \cdot H_2O$ (51.0 mg, 0.255 mmol) in mesitylene (2.6 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29f** (50:50, 93.2 mg, 65%) as a colourless oil, R_f 0.60 (hexane/EtOAc, 3:2); ν_{max} (ATR, cm^{-1}) 2972, 2930, 1710, 1690, 1608, 1491, 1467, 1447, 1372, 1341, 1257, 1118, 1097, 1030, 984; δ_H (400 MHz, $CDCl_3$) 7.27 (2H, tt, *J*=7.8, 1.3 Hz, C*H*), 7.06 (1H, td, *J*=7.6, 3.3 Hz, C*H*), 6.90–6.83 (6H, m, C*H*), 6.69–6.63 (3H, m, C*H*), 3.27 (6H, s, CH_3), 2.89 (1H, d, *J*=13.2 Hz, CH_2), 2.88 (1H, d, *J*=13.2 Hz, CH_2), 2.56 (1H, d, *J*=13.2 Hz, CH_2), 2.55 (1H, d, *J*=13.2 Hz, CH_2), 1.53 (3H, s, CH_3), 1.52 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.74 (3H, s, CH_3), 0.72 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 207.38 and

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207.37 (*C*), 176.3 (*C*), 143.09 and 143.08 (*C*), 136.7 (*C*), 133.62 and 133.59 (*C*H), 129.54 and 129.52 (*C*), 128.88 and 128.85 (*C*H), 128.63 and 128.62 (*C*H), 127.1 (*C*H), 123.02 and 122.98 (*C*H), 122.79 and 122.78 (*C*H), 108.4 (*C*H), 60.9 (*C*), 50.60 and 50.57 (*C*), 45.77 and 45.76 (CH_2), 26.4 (CH_3), 24.9 and 24.8 (CH_3), 23.4 (CH_3), 22.6 and 22.5 (CH_3); HRMS (ESI): MNa^+, found 587.2876. $[C_{36}H_{40}N_2NaO_4]^+$ requires 587.2880.

*4.5.7. dl/meso-5-Methoxy-3-[2-({3-[3-(5-methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2-dimethyl-3-oxopropyl]phenyl} methyl)-2-methylpropanoyl]-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (dl/meso-**29g**).* Bis-anilide *dl/meso*-**28g** (0.305 g, 0.485 mmol) and $Cu(OAc)_2 \cdot H_2O$ (97.0 mg, 0.485 mmol) in mesitylene (4.9 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29g** (50:50, 0.223 g, 74%) as a colourless solid, mp 60–62 °C; R_f 0.09 (hexane/EtOAc, 3:1); ν_{max} (ATR, cm^{-1}) 2970, 2931, 1703, 1689, 1598, 1497, 1469, 1433, 1369, 1348, 1288, 1235, 1202, 1173, 1106, 1036, 985; δ_H (400 MHz, $CDCl_3$) 7.04 (1H, td, *J*=7.7, 3.4 Hz, C*H*), 6.85–6.82 (2H, m, C*H*), 6.76 (2H, dt, *J*=8.6, 1.8 Hz, C*H*), 6.72 (2H, d, *J*=8.6 Hz, C*H*), 6.65 (0.5H, s, C*H*), 6.64 (0.5H, s, C*H*), 6.40 (1H, d, *J*=2.4 Hz, C*H*), 6.37 (1H, d, *J*=2.4 Hz, C*H*), 3.68 (3H, s, CH_3), 3.67 (3H, s, CH_3), 3.22 (6H, s, CH_3), 2.82 (2H, d, *J*=12.7 Hz, CH_2), 2.58 (2H, d, *J*=12.7 Hz, CH_2), 1.49 (6H, s, CH_3), 0.88 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.75 (3H, s, CH_3), 0.72 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 207.6 and 207.5 (*C*), 176.01 and 176.00 (*C*), 156.1 (*C*), 136.64 and 136.63 (*C*), 136.56 and 136.55 (*C*), 133.53 and 133.52 (*C*H), 130.90 and 130.87 (*C*), 128.92 and 128.89 (*C*H), 126.99 and 126.96 (*C*H), 113.0 (*C*H), 110.4 and 110.3 (*C*H), 108.8 (*C*H), 61.22 and 61.21 (*C*), 55.6 (CH_3), 50.59 and 50.56 (*C*), 45.53 and 45.52 (CH_2), 26.5 (CH_3), 24.4 and 24.2 (CH_3), 23.6 (CH_3), 23.0 and 22.8 (CH_3); HRMS (ESI): MNa^+, found 647.3106. $[C_{38}H_{44}N_2NaO_6]^+$ requires 647.3092.

*4.5.8. dl/meso-5-(Trifluoromethyl)-3-[2-({3-[3-(5-(trifluoromethyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,2-dimethyl-3-oxopropyl]phenyl}methyl)-2-methylpropanoyl]-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (dl/meso-**29h**).* Bis-anilide *dl/meso*-**28h** (0.211 g, 0.300 mmol) and $Cu(OAc)_2 \cdot H_2O$ (60.0 mg, 0.300 mmol) in mesitylene (3 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29h** (50:50, 0.106 g, 50%) as a colourless solid, mp 68–70 °C; R_f 0.12 (hexane/EtOAc, 3:1); ν_{max} (ATR, cm^{-1}) 2971, 1717, 1694, 1620, 1503, 1471, 1452, 1372, 1343, 1324, 1288, 1254, 1215, 1157, 1115, 1067, 1025, 984; δ_H (400 MHz, $CDCl_3$) 7.54 (2H, d, *J*=8.2 Hz, C*H*), 7.05–7.01 (2H, m, C*H*), 6.98 (1H, s, C*H*), 6.91 (2H, d, *J*=8.2 Hz, C*H*), 6.83–6.80 (2H, m, C*H*), 6.64–6.62 (1H, m, C*H*), 3.294 (3H, s, CH_3), 3.292 (3H, s, CH_3), 2.88 (2H, d, *J*=13.2 Hz, CH_2), 2.55 (1H, d, *J*=13.2 Hz, CH_2), 2.54 (1H, d, *J*=13.2 Hz, CH_2), 1.55 (3H, s, CH_3), 1.54 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.73 (3H, s, CH_3), 0.72 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 206.6 (*C*), 176.4 (*C*), 146.0 (*C*), 136.46 and 136.45 (*C*), 133.32 and 132.29 (*C*H), 130.22 and 130.18 (*C*), 128.9 (*C*H), 127.32 and 127.31 (*C*H), 126.6 (q, *J*=4.0 Hz, *C*H), 125.2 (q, *J*=32.1 Hz, *C*), 123.9 (q, *J*=272 Hz, *C*), 120.11 and 120.07 (q, *J*=3.7 Hz, *C*H), 108.3 (*C*H), 60.6 (*C*), 50.9 and 50.8 (*C*), 45.64 and 45.58 (CH_2), 26.7 (CH_3), 24.9 and 24.6 (CH_3), 23.7 (CH_3), 22.8 and 22.6 (CH_3); HRMS (ESI): MNa^+, found 723.2620. $[C_{38}H_{38}F_6N_2NaO_4]^+$ requires 723.2628.

*4.5.9. dl/meso-3-[2-({3-[3-(2,2-Dimethyl-3-(1-methyl)-2-oxo-3-phenyl-2,3-dihydro-1H-indol-3-yl)-3-oxopropyl]phenyl}methyl)-2-methylpropanoyl]-1-methyl-3-phenyl-2,3-dihydro-1H-indol-2-one (dl/meso-**29i**).* Bis-anilide *dl/meso*-**28i** (0.208 g, 0.300 mmol) and $Cu(OAc)_2 \cdot H_2O$ (60.0 mg, 0.300 mmol) in mesitylene (3 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 9:1 to 4:1) to give the *title compound dl/meso*-**29i** (50:50, 0.131 g, 63%) as a colourless solid, mp 105–107 °C; R_f 0.28 (hexane/EtOAc, 3:1); ν_{max} (ATR, cm^{-1}) 2970, 1709, 1693, 1608, 1490, 1469, 1446, 1368, 1341, 1253, 1129, 1076, 1055, 1022; δ_H (400 MHz, $CDCl_3$) 7.34 (1H, td, *J*=7.7, 1.2 Hz, C*H*), 7.33 (1H, td, *J*=7.7, 1.2 Hz, C*H*), 7.29–7.26 (6H, m, C*H*), 7.20–7.16 (4H, m, C*H*), 7.07 (0.5H, d, *J*=7.4 Hz, C*H*), 7.03 (0.5H, d, *J*=7.4 Hz, C*H*), 6.96 (1H, td, *J*=7.6, 0.6 Hz, C*H*), 6.93 (1H, td, *J*=7.6, 0.6 Hz, C*H*), 6.91–6.81 (6H, m, C*H*), 6.68–6.66 (1H, m, C*H*), 3.192 (3H, s, CH_3), 3.188 (3H, s, CH_3), 2.92 (1H, d, *J*=12.9 Hz, CH_2), 2.90 (1H, d, *J*=12.9 Hz, CH_2), 2.75 (1H, d, *J*=12.9 Hz, CH_2), 2.71 (1H, d, *J*=12.9 Hz, CH_2), 1.13 (3H, s, CH_3), 1.12 (3H, s, CH_3), 0.82 (3H, s, CH_3), 0.80 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 207.3 and 207.2 (*C*), 174.6 (*C*), 143.97 and 143.95 (*C*), 138.0 (*C*), 136.72 and 136.69 (*C*), 133.8 and 133.7 (*C*H), 129.5 and 129.4 (*C*H), 129.2 and 129.1 (*C*H), 128.5 (*C*H), 128.1 (*C*H), 127.8 (*C*H), 127.13 and 127.11 (*C*H), 126.00 and 125.99 (*C*H), 125.5 and 125.4 (*C*), 122.8 and 122.7 (*C*H), 108.63 and 108.61 (*C*H), 70.40 and 70.39 (*C*), 51.24 and 51.17 (*C*), 45.5 and 45.3 (CH_2), 26.66 and 26.65 (CH_3), 24.9 and 24.5 (CH_3), 22.5 and 22.2 (CH_3); HRMS (ESI): MNa^+, found 711.3170. $[C_{46}H_{44}N_2NaO_4]^+$ requires 711.3193.

*4.5.10. meso-3-(2-{4-[2-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)propan-2-yl]phenyl}propan-2-yl)-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (meso-**29j**) and dl-3-(2-{4-[2-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)propan-2-yl]phenyl}propan-2-yl)-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (dl-**29j**).* Bis-anilide *dl/meso*-**28j** (0.189 g, 0.350 mmol) and $Cu(OAc)_2 \cdot H_2O$ (70.0 mg, 0.350 mmol) in mesitylene (3.5 mL) were subjected to general procedure 3. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 1:9 to 1:4) to give the *title compound meso*-**29j** (49.7 mg, 27%) as a colourless solid, mp 213–214 °C; R_f 0.34 (hexane/EtOAc, 3:1); ν_{max} (ATR, cm^{-1}) 2979, 1691, 1606, 1490, 1471, 1450, 1374, 1343, 1251, 1118, 1095, 1033, 999; δ_H (400 MHz, $CDCl_3$) 7.12 (2H, td, *J*=7.6, 1.2 Hz, C*H*), 6.98 (2H, dd, *J*=7.3, 0.9 Hz, C*H*), 6.89 (2H, td, *J*=7.5, 0.7 Hz, C*H*), 6.43 (4H, s, C*H*), 6.37 (2H, d, *J*=7.7 Hz, C*H*), 2.66 (6H, s, CH_3), 1.53 (6H, s, CH_3), 1.48 (6H, s, CH_3), 1.36 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 206.9 (*C*), 175.7 (*C*), 142.4 (*C*), 139.1 (*C*), 130.3 (*C*), 128.4 (*C*H), 126.7 (*C*H), 123.2 (*C*H), 122.5 (*C*H), 107.9 (*C*H), 60.7 (*C*), 53.2 (*C*), 29.2 (CH_3), 25.9 (CH_3), 24.1 (CH_3), 24.0 (CH_3); HRMS (ESI): MNa^+, found 559.2565. $[C_{34}H_{36}N_2NaO_4]^+$ requires 559.2567. CCDC 1031379 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The diastereoisomer *dl*-**29j** (53.1 mg, 28%) was then isolated as a colourless solid, mp 195–196 °C; R_f 0.22 (hexane/EtOAc, 3:1); ν_{max} (ATR, cm^{-1}) 2978, 1704, 1692, 1609, 1493, 1471, 1449, 1373, 1343, 1256, 1121, 1032, 997; δ_H (400 MHz, $CDCl_3$) 7.08 (2H, td, *J*=7.6, 1.2 Hz, C*H*), 6.93 (2H, dd, *J*=7.4, 0.6 Hz, C*H*), 6.83 (2H, td, *J*=7.4, 0.6 Hz, C*H*), 6.43 (4H, s, C*H*), 6.34 (2H, d, *J*=7.7 Hz, C*H*), 2.68 (6H, s, CH_3), 1.62 (6H, s, CH_3), 1.47 (6H, s, CH_3), 1.30 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 206.9 (*C*), 175.8 (*C*), 142.3 (*C*), 139.2 (*C*), 130.1 (*C*), 128.3 (*C*H), 126.7 (*C*H), 123.2 (*C*H), 122.4 (*C*H), 107.9 (*C*H), 60.6 (*C*), 53.3 (*C*), 29.1 (CH_3), 25.9 (CH_3), 24.2 (CH_3), 23.8 (CH_3); HRMS (ESI): MNa^+, found 559.2566. $[C_{34}H_{36}N_2NaO_4]^+$ requires 559.2567. CCDC 1031380 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.6. General procedure 4 for the formation of di-ester-containing bis-oxindoles 32a–c

To a stirred solution of bis-anilide **31** (1 equiv) in mesitylene (0.04–0.06 M) was added $Cu(OAc)_2 \cdot H_2O$ (1 equiv). The reaction mixture was stirred for 30 min to 2 h at 170 °C under an atmosphere of air and allowed to cool to room temperature. Mesitylene

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was removed, the residue was diluted with EtOAc (5 mL), and washed with an aq soln of NH_4OH (5 mL). The aqueous phase was extracted with EtOAc (2×5 mL). The combined organic extracts were washed with water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 3:1) to give the *title compound* **32**.

*4.6.1. dl/meso-Ethyl 3-{4-[3-(ethoxycarbonyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]butyl}-1-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate (dl/meso-**32a**).* Bis-anilide *dl/meso*-**31a** (60.1 mg, 0.121 mmol) and $Cu(OAc)_2 \cdot H_2O$ (24.2 mg, 0.121 mmol) in mesitylene (2 mL) were subjected to general procedure 4. The reaction mixture was stirred at 170 °C for 30 min. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 3:1) to give the *title compound dl/meso*-**32a** (50:50, 53.9 mg, 90%) as a yellow solid, mp 145–147 °C; R_f 0.35 (hexane/EtOAc, 1:2); ν_{max} (ATR, cm^{-1}) 1736, 1709, 1609, 1492, 1470, 1372, 1346, 1223, 1081, 1020, 750, 727; δ_H (400 MHz, $CDCl_3$) 7.29 (1H, td, J=7.4, 1.2 Hz, C*H*), 7.28 (1H, td, J=7.4, 1.2 Hz, C*H*), 7.16 (1H, dd, J=7.4, 1.2 Hz, C*H*), 7.15 (1H, dd, J=7.4, 1.2 Hz, C*H*), 7.04 (1H, td, J=7.4, 1.2 Hz, C*H*), 7.02 (1H, td, J=7.4, 1.2 Hz, C*H*), 6.80 (2H, t, J=8.3 Hz, C*H*), 4.13–4.02 (4H, m, CH_2), 3.20 (3H, s, CH_3), 3.18 (3H, s, CH_3), 2.15–2.00 (4H, m, CH_2), 1.12 (3H, t, J=7.1 Hz, CH_3), 1.10 (3H, t, J=7.1 Hz, CH_3), 0.99–0.73 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 174.3 and 174.2 (*C*), 169.4 (*C*), 144.1 (*C*), 129.1 and 129.0 (CH), 128.1 and 128.0 (*C*), 123.37 and 123.36 (CH), 123.0 and 122.8 (CH), 108.3 (CH), 61.9 (CH_2), 59.5 and 59.4 (*C*), 34.0 and 33.9 (CH_2), 26.47 and 26.45 (CH_3), 23.63 and 23.55 (CH_2), 13.99 and 13.98 (CH_3); HRMS (ESI): MNa^+, found 515.2153. $[C_{28}H_{32}N_2NaO_6]^+$ requires 515.2153.

*4.6.2. dl/meso-Ethyl 3-[(2E)-4-[3-(ethoxycarbonyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]but-2-en-1-yl]-1-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate (dl/meso-**32b**).* Bis-anilide *dl/meso*-**31b** (49.4 mg, 0.100 mmol), and $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.100 mmol) in mesitylene (2 mL) were subjected to general procedure 4. The reaction mixture was stirred at 170 °C for 2 h. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 2:1) to give the *title compound dl/meso*-**32b** (50:50, 32.3 mg, 66%) as a yellow solid, mp 130–132 °C; R_f 0.35 (hexane/EtOAc, 1:1); ν_{max} (ATR, cm^{-1}) 1736, 1711, 1609, 1493, 1470, 1372, 1347, 1223, 1086, 1021, 750, 729; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, td, J=7.6, 1.1 Hz, C*H*), 7.14–7.09 (2H, m, C*H*), 7.04–6.98 (2H, m, C*H*), 6.79 (2H, d, J=7.6 Hz, C*H*), 5.02 (1H, dd, J=4.4, 3.6 Hz, C*H*), 4.94 (1H, d, J=3.6 Hz, C*H*), 4.11–4.00 (4H, m, CH_2), 3.21 (3H, s, CH_3), 3.14 (3H, s, CH_3), 2.80 (2H, td, J=14.1, 3.2 Hz, CH_2), 2.69–2.55 (2H, m, CH_2), 1.10 (3H, t, J=7.1 Hz, CH_3), 1.09 (3H, t, J=7.1 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 173.6 and 173.5 (*C*), 169.04 and 168.94 (*C*), 144.2 and 144.1 (*C*), 129.0 (CH), 127.9 and 127.61 (CH), 127.56 and 127.49 (*C*), 123.7 and 123.5 (CH), 122.8 and 122.7 (CH), 108.5 and 108.3 (CH), 61.9 and 61.8 (CH_2), 59.3 and 59.1 (*C*), 35.64 and 35.57 (CH_2), 26.6 and 26.5 (CH_3), 14.0 (CH_3); HRMS (ESI): MNa^+, found 513.1997. $[C_{28}H_{30}N_2NaO_6]^+$ requires 513.1996.

*4.6.3. dl/meso-Ethyl 3-[(2-{[(ethoxycarbonyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]methyl}phenyl)methyl]-1-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate (dl/meso-**32c**).* Bis-anilide *dl/meso*-**31c** (60.2 mg, 0.111 mmol), and $Cu(OAc)_2 \cdot H_2O$ (24.0 mg, 0.120 mmol) in mesitylene (3 mL) were subjected to general procedure 4. The reaction mixture was stirred at 170 °C for 2 h. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 2:1) to give the *title compound dl/meso*-**32c** (50:50, 48.3 mg, 89%) as a white solid, mp 113–115 °C; R_f 0.42 (hexane/EtOAc, 1:2); ν_{max} (ATR, cm^{-1}) 1735, 1710, 1609, 1492, 1470, 1372, 1351, 1222, 1095, 1060, 1021, 751, 728; δ_H (400 MHz, $CDCl_3$) 7.24 (1H, d, J=7.4 Hz, C*H*), 7.18 (1H, t, J=7.4 Hz, C*H*), 7.14 (1H, t, J=7.4 Hz, C*H*), 7.08 (1H, d, J=7.4 Hz, C*H*), 6.98 (1H, t, J=7.4 Hz, C*H*), 6.95 (1H, t, J=7.4 Hz, C*H*), 6.74–6.68 (2H, m, C*H*), 6.68–6.63 (2H, m, C*H*), 6.54 (1H, d, J=7.4 Hz, C*H*), 6.50 (1H, d, J=7.4 Hz, C*H*), 4.15 (4H, dq, J=14.4, 7.2 Hz, CH_2), 3.64 (1H, d, J=14.2 Hz, CH_2), 3.39 (1H, d, J=14.2 Hz, CH_2), 3.33 (1H, d, J=14.2 Hz, CH_2), 3.18 (1H, d, J=14.2 Hz, CH_2), 2.93 (3H, s, CH_3), 2.91 (3H, s, CH_3), 1.17 (3H, t, J=7.1 Hz, CH_3), 1.15 (3H, t, J=7.1 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 173.8 and 173.7 (*C*), 169.3 and 169.2 (*C*), 144.0 and 143.4 (*C*), 134.1 and 133.8 (*C*), 129.9 and 129.7 (CH), 129.1 and 129.0 (CH), 127.4 and 127.1 (*C*), 126.1 and 126.0 (CH), 124.4 and 124.2 (CH), 122.4 and 122.3 (CH), 108.03 and 108.01 (CH), 62.1 and 62.0 (CH_2), 61.0 and 60.9 (*C*), 35.94 and 35.87 (CH_2), 26.2 (CH_3), 14.0 (CH_3); HRMS (ESI): MNa^+, found 563.2163. $[C_{32}H_{32}N_2NaO_6]^+$ requires 563.2153.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.02.060.

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Appendix V: *Eur. J. Org. Chem.* **2015**, 2333-2336

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SHORT COMMUNICATION

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A Copper-Mediated Oxidative Coupling Route to 3*H*- and 1*H*-Indoles from *N*-Aryl-enamines

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Keywords: Heterocycles / 1*H*-Indole / 3*H*-Indole / Copper-mediated coupling / Cyclization

A facile copper(II)-mediated C–H bond oxidation and C–C bond formation procedure has been applied to the synthesis of indole derivatives. Intramolecular oxidative coupling of 3,3-disubstituted enamines proceeded using a non-expensive and air-stable copper salt, Cu(2-ethylhexanoate)$_2$, to afford the corresponding C-3 quaternary indolenine products in good to excellent yields. 1*H*-Indoles can be prepared in a similar manner but in this case, $Cu(OAc)_2{\cdot}H_2O$ has been found to be the preferred oxidant.

Introduction

Indole derivatives are commonly found in a range of biologically active natural (**1**,[1a] **2**,[1b] **3**,[1b] and **4**;[1c] Figure 1) and unnatural compounds such as the antibacterial agent **5**.[1d] Among the family of indoles, 3,3-disubstituted indolenine (3*H*-indole) skeletons have attracted considerable attention, possibly explained by their challenging indolenine ring and the presence of a quaternary C-3 atom. Moreover, 3*H*-indoles have been employed as precursors for the synthesis of indoline natural products, such as physovenine (**4**; Figure 1).[2]

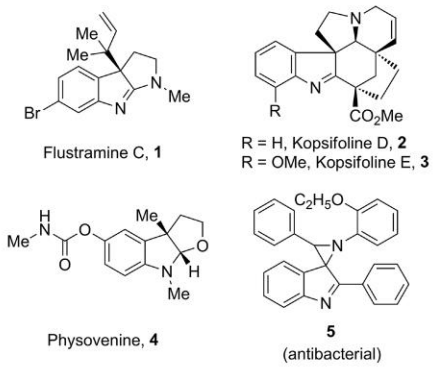
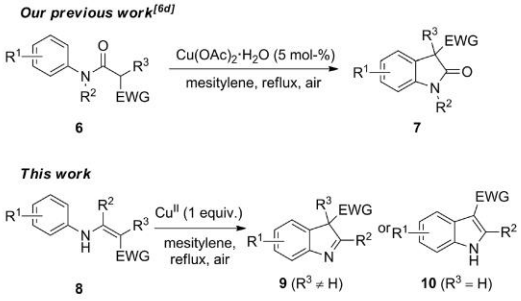


Figure 1. Examples of C-3 quaternary indolenines and indoline compounds.

Therefore, the development of synthetic methods for this privileged structure has been explored by many researchers, most often by the dearomatisation of indoles.[3] Recently, a number of approaches have been developed for the synthesis of 3*H*-indole derivatives relying on more challenging intramolecular cyclisation processes.[4] Of particular relevance to this work, Li and co-workers recently reported an iodine-mediated synthesis of 3*H*-indoles by the intramolecular cyclisation of enamines.[5]

Following our continued interest in the development of new approaches for the formation of biologically relevant heterocycles[6] (first started in 2009 with the discovery of the Cu^{II}-mediated cyclisation to oxindoles; Scheme 1), we have expanded the scope of such cyclisation processes to various indole-containing heterocycles. Herein, we report that *N*-aryl-enamines are excellent substrates for the synthesis of C-3 quaternary indolenines and 3-substituted indoles by Cu^{II}-mediated oxidative coupling.



Scheme 1. Copper-mediated cyclisation approach to 3*H*- and 1*H*-indoles.

Results and Discussion

Initial experiments, summarised in Table 1, were carried out using the readily available enamine[5] **8a** prepared from

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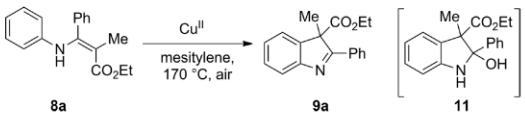
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500112.

the corresponding aniline and β-dicarbonyl compound. The cyclisation was then investigated, initially using $Cu(OAc)_2 \cdot H_2O$ in mesitylene at 170 °C, conditions optimised for our preliminary results on the formation of oxindoles.[6d] However, only 21% yield (estimated by ^{1}H NMR analysis after purification) of cyclised product **9a** was formed (Entry 1). The low yield of the reaction appeared to be the result of addition of water to the reactive enamine functionality giving **11**. To overcome this issue, we switched the source of copper to commercially available Cu(2-ethylhexanoate)$_2$ and fitted the reaction condenser with a $CaCl_2$ drying trap, but still under air. Pleasingly, the cyclisation of **8a** occurred in an improved 78% yield (Entry 2). However, reduction of the amount of copper in the reaction significantly reduced the yield of the cyclisation (Entry 3). It is also worth noting that this protocol does require the presence of copper. Heating of the enamine precursor in mesitylene at 170 °C resulted only in the decomposition of **8a** (Entry 4). Based on literature precedent,[5,6] we assume that cyclisation occurs by initial deprotonation followed by copper-mediated oxidative radical generation and then homolytic aromatic substitution.

Table 1. Optimisation of the reaction conditions for the cyclisation of **8a** to **9a**.

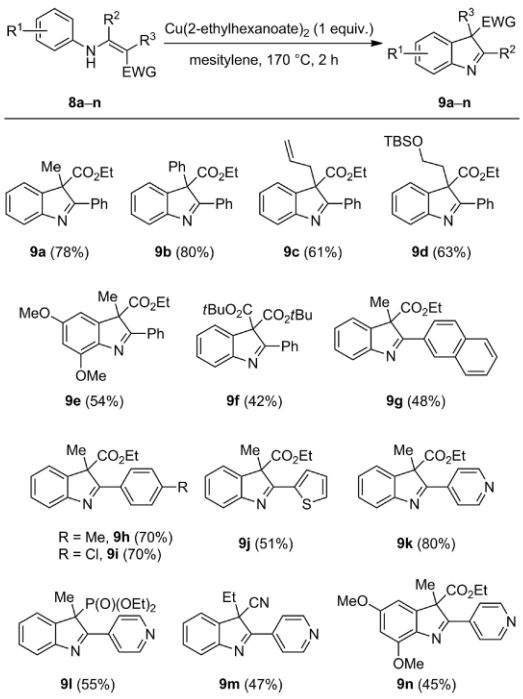


8a **9a** **11**

Entry	Cu-source (eq)	Time [h]	Yield of **9a** [%]
1	$Cu(OAc)_2 \cdot H_2O$ (1 equiv.)[a]	2	21[c]
2	Cu(2-ethylhex)$_2$[b] (1 equiv.)	2	78
3	Cu(2-ethylhex)$_2$ (0.1 equiv.)	3	38
4	–	3	0 (decomp.)

[a] When toluene (at 110 °C) was used in place of mesitylene, only decomposition was observed by ^{1}H NMR spectroscopy. [b] Cu(2-ethylhexanoate)$_2$ = $[Me(CH_2)_3CH(Et)CO_2]_2Cu$. [c] Isolated as an inseparable mixture of **9a** and **11**. According to ^{1}H NMR spectroscopy after purification and the mass recovered, **9a** was estimated at 21% and **11** at 14%.

Using these optimal conditions, the scope of the process in terms of substrate structure was examined (Scheme 2). Varying the nature of the alkyl side-chain at C-3 was well tolerated (R^3 = Ph, **9b**; R^3 = allyl, **9c**). The oxygen-containing substrate **9d**, interesting for the synthesis of indoline-type natural products such as physovenine (**4**; Figure 1), cyclised in a good 63% yield. Substitution of the aromatic ring showed that an electron-rich aniline was also well tolerated (**9e**). The alkyl group at C-3 could also be replaced by another ester functionality (**9f**). Varying the nature of the electron-withdrawing group at C-3 was also well tolerated (**9l**–**9m**) as was the nature of the aromatic ring at C-2 (**9g**–**9n**). It should be noted that for the first time, the Cu^{II}-mediated cyclisation conditions offer the possibility of changing the nature of the aromatic ring at C-2 as well as the electron-withdrawing group at C-3. With the exception of **9a**, all cyclised products are novel compounds and were fully characterised. Also, we were able to obtain a suitable crystal of the indolenine product **9h** for X-ray crystallographic analysis and conclusively confirmed its structure (Figure 2).



Scheme 2. Scope of the cyclisation reaction to 3*H*-indoles.

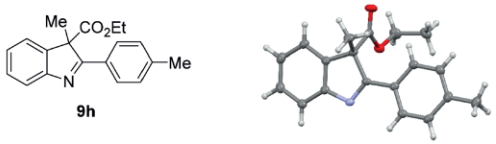
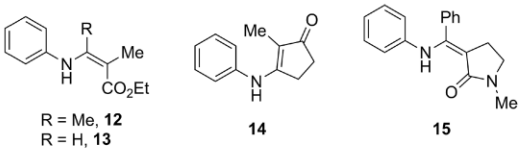


Figure 2. Crystal structure of **9h** (50% probability ellipsoids).

It should be noted that the method failed for substrates **12**–**14**, where starting materials were recovered (Scheme 3). The presence of a C-2 aryl substituent therefore appears crucial. In the case of **15**, the starting material was consumed, but no spirocyclic 3*H*-indole product was isolated. For this example, steric hindrance may have been the problem. It should also be noted that we were unable to prepare cyclisation precursors in which the EWG substituent was replaced, for example, by an aromatic substituent (presumably due to rapid hydrolysis).

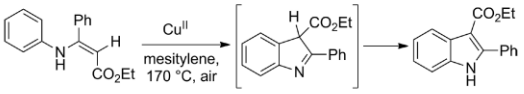


Scheme 3. Substrates not affording indole products.

Given the success of the Cu^{II} route with 3*H*-indoles, we briefly extended its use to prepare related 1*H*-indoles.[7] Whereas classical synthetic methods such as the Fischer indole synthesis has been used for more than a hundred years, transition metal catalysed cyclisation of linear enamine precursors by a cross-dehydrogenative coupling (CDC) process, has emerged as a powerful alternative over the past several decades.[8] An important example was reported by Glorius and co-workers, who developed a palladium(II)-catalysed oxidative cyclisation reaction of *N*-aryl-enamines derived from aniline and β-dicarbonyl compounds to afford 1*H*-indoles.[8i]

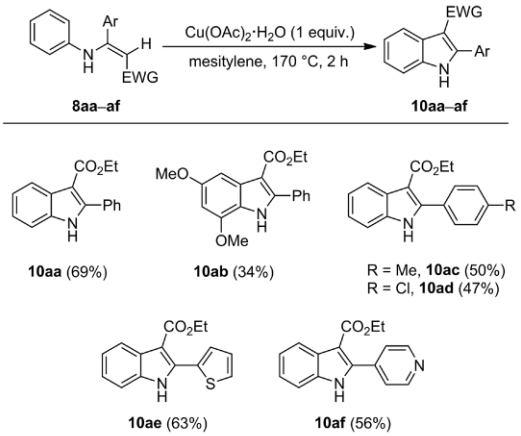
With the aim of obtaining 3-substituted indoles, we attempted to apply our Cu^{II}-mediated protocol to trisubstituted enamines (which after the initial cyclisation should spontaneously tautomerise from the 3*H*-indole **9aa** to 1*H*-indole **10aa**). The reaction of readily available ethyl (2*Z*)-3-phenyl-3-(phenylamino)prop-2-enoate[8i] (**8aa**) with Cu(2-ethylhexanoate)$_2$ gave the desired indole product **10aa** but only in a moderate 54% yield (Table 2, Entry 1). Switching the copper salt from Cu(2-ethylhexanoate)$_2$ to Cu(OAc)$_2$·H$_2$O significantly increased the yield to 69% (Entry 2). Reducing the amount of copper in the reaction dramatically lowered the yield (Entry 3), as observed before with the indolenine example **9a** (Table 1, Entry 3). Also, a similar result was observed when the reaction was carried out without copper and only decomposition was detected (Entry 4).

Table 2. Optimisation of the reaction conditions for the cyclisation of **8aa** to **10aa**.



Entry	Cu source (equiv.)	Time [h]	Yield of **10aa** [%]
1	Cu(2-ethylhex)$_2$ (1)	2	54
2	Cu(OAc)$_2$·H$_2$O (1)	2	69
3	Cu(OAc)$_2$·H$_2$O (0.1)	3	17
4	–	2	0 (decomp.)

Having established successful conditions for the cyclisation of the model system **8aa**, we went on to test the substrate scope using a range of enamine precursors **8ab**–**af**. A substrate with electron-donating substituents was prepared and converted into the indole product (**10ab**; Scheme 4). Different groups at C-2 were also tolerated. Thus, 4-substituted phenyl (**10ac**–**10ad**), 2-thiophenyl (**10ae**), and 4-pyridinyl (**10af**) substrates delivered the cyclised products in good yields.



Scheme 4. Scope of the cyclisation reaction to 1*H*-indoles.

Conclusions

We have developed a highly efficient oxidative coupling process by employing inexpensive and air-stable copper salts. The current protocol conveniently affords structurally diverse indole derivatives including 3,3-disubstituted indolenines and 3-substituted indoles from readily available aniline-derived enamines. Further studies to apply these processes in target synthesis are in progress.

Experimental Section

Representative Example. Synthesis of 9a: To a stirred solution of ethyl (2*Z*)-2-methyl-3-phenyl-3-(phenylamino)prop-2-enoate (**8a**) (0.053 g, 0.187 mmol) in mesitylene (5 mL) was added Cu(2-ethylhexanoate)$_2$ (0.066 g, 0.187 mmol). The flask was fitted with a condenser and a $CaCl_2$ drying trap. The reaction mixture was stirred and heated to 170 °C (Drysyn heating block) for 2 h. The resulting green solution was cooled to room temperature. NH_4OH (10 mL) was added, the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The brown residue was purified by column chromatography (SiO_2; hexane/EtOAc, 99:1) to give the title compound **9a** (0.041 g, 78%) as a colourless oil. R_f = 0.28 (hexane/EtOAc, 9:1). IR: $\tilde{\nu}_{max}$ = 2983, 2935, 1728, 1531, 1444, 1236, 1221, 1101, 1012, 1004, 754, 728, 513 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.94 (m, 2 H, C*H*), 7.71 (dd, *J* = 7.6, 1.0 Hz, 1 H, C*H*), 7.49–7.45 (m, 3 H, C*H*), 7.42 (td, *J* = 7.6, 1.0 Hz, 1 H, C*H*), 7.40–7.37 (m, 1 H, C*H*), 7.26 (td, *J* = 7.6, 1.0 Hz, 1 H, C*H*), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1 H, CH_2), 3.97 (dq, *J* = 10.8, 7.1 Hz, 1 H, CH_2), 1.71 (s, 3 H, CH_3), 0.97 (t, *J* = 7.1 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (*C*), 171.6 (*C*), 154.9 (*C*), 141.8 (*C*), 132.0 (*C*), 131.2 (*C*H), 129.1 (*C*H), 128.9 (*C*H), 128.4 (*C*H), 126.4 (*C*H), 121.4 (*C*H), 121.2 (*C*H), 62.2 (*C*), 61.9 (CH_2), 21.1 (CH_3),

13.8 (CH_3) ppm. MS (ESI): calcd. for $C_{18}H_{17}NNaO_2$ $[MNa]^+$ 302.1151; found 302.1153; Δ = 0.5 ppm.

CCDC-1033699 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data of the products, and copies of the ^1H and ^{13}C NMR spectra.

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Abbreviations

1,10-phen	1,10-phenanthroline
9-BBN	9-borabicyclo[3.3.1]nonane
acac	acetylacetone
Ac	acetyl
Ac_2O	acetic anhydride
AChe	acetylcholinesterase
Ar	aryl
AIBN	2,2-azobis*iso*butyronitrile
aq	aqueous
atm	atmosphere
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BuChe	butyrylcholinesterase
Bz	benzoyl
cat	catalytic
m-CPBA	*meta*-chloroperbenzoic acid
cod	cyclooctadiene
CDC	cross-dehydrogenative coupling
CDI	1,1′-carbonyldiimidazole
CDK	cyclin dependent kinases
COSY	correlation spectroscopy
CSA	camphor-10-sulfonic acid
δ	chemical shift

DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	di*iso*butylaluminium hydride
DIPEA	*N*,*N*'-di*iso*propylethylamine
DMA	*N*,*N'*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMB	2,4-dimethoxybenzyl
DMDO	dimethyldioxirane
DMEDA	*N*,*N'*-dimethylethylenediamine
DMF	*N*,*N'*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropylene urea
DMSO	dimethyl sulfoxide
DPPF	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalent(s)
er	enantiomeric ratio
ESI-HRMS	electrospray ionisation-high resolution mass spectrometry
Et	ethyl
EWG	electron withdrawing group

g	gram(s)
h	hour(s)
hal	halogenated
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HSQC	heteronuclear single quantum correlation
Hz	Hertz(s)
imid	imidazole
INOC	Intramolecular Nitrile oxide-Olefin Cycloaddition
IR	infrared
J	coupling constant in Hz
L	litre(s)
LAH	lithium aluminium hydride
LDA	lithium di*iso*propylamide
LHMDS	lithium hexamethyldisilazane (or LiHMDS)
m	meter(s)
m/z	mass to charge ratio
M	molar
MCR	multicomponent reactions
Me	methyl
MMC	methyl magnesium carbonate
MS	mass spectrometry or molecular sieves
MTBE	methyl *tert*-butyl ether
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
p-TSA	*para*-toluenesulfonic acid

Petrol	petroleum ether (fraction which boils at 40-60 °C)
PG	protecting groups
Ph	phenyl
Phth	phthaloyl
PIG	1,1,2,3,3-penta*iso*propylguanidine
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium *para*-toluenesulfonate
py	pyridine
quant.	quantitative
R	alkyl group (undefined)
RBF	round-bottomed flask
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
rt	room temperature
sat	saturated
SET	single-electron transfer
T3P	propane phosphonic acid anhydride
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl (or TBDMS)
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMTU	tetramethylthiourea
TPD	Tryptophan decarboxylase
TPH	Tryptophan hydroxylase
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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