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A Novel Method for the Synthesis of Indolo[2,1-a]isoquinolines

ANGELIQUE NATÁLIA CASSANDRA LÖTTER

2005

A Novel Method for the Synthesis of Indolo[2,1-a]isoquinolines

ANGELIQUE NATÁLIA CASSANDRA LÖTTER

Supervised by Prof. C. B. de Koning and Dr. W.A.L. van Otterlo

A thesis submitted to the Faculty of Science

University of the Witwatersrand, Johannesburg

In fulfilment of the requirements for

Degree of Master of Science

August 2005

DECLARATION

I declare that the work presented in this dissertation was carried out exclusively by myself under the supervision of Prof. C. B. de Koning and Dr. W. A. L. van Otterlo. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

Angelique Lötter

August 2005

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Most importantly I would like to thank my entire family for all their love and support, especially my mom and dad who have always been there for me through good times and bad. Tony this one is just for you.

And Thank You God for giving me the life that I have.

LIST OF ABBREVIATIONS

AIBN	Azoisobutyronitrile
Boc	*t*-Butoxycarbonyl
Boc_2O	Di-*t*-butyl-dicarbonate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethyl formamide
DNA	Deoxyribose nucleic acid
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
NaH	Sodium hydride
NMR	Nucleur magnetic resonance
NOE	Nuclear Overhauser effect
SM	Starting material
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMP	tetramethylpyridine
*p*TSA	*p*-Toluenesulfonic acid
UV	Ultra violet

ABSTRACT

Many azapolycyclic aromatic ring systems, whether they are naturally occurring or synthetically made, display important biological activities. One important class of naturally occurring azapolycyclic aromatic ring systems are the dibenzopyrrocoline alkaloids, which contain an indole ring fused to an isoquinoline moiety, where they share a common nitrogen. The basic skeleton of these alkaloids is the indolo[2,1-*a*]isoquinoline nucleus. Both the dibenzopyrrocoline alkaloids and the indolo[2,1-*a*]isoquinolines have been found to inhibit tubulin polymerization and thus possess antitumour and antileukemic activities.

In our laboratories, a variety of indolo[2,1-*a*]isoquinolines, for example 5,12-dimethyl-6-phenylindolo[2,1-*a*]isoquinoline, have been synthesized using the Suzuki-Miyaura cross coupling reaction and reaction conditions for the formation of aromatic rings ($KOBu^t$ in DMF and a light source – developed in our laboratories) as key steps. In this dissertation we discuss the synthesis of (±)-5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol and ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate using these reaction conditions as our key steps.

The syntheses commenced with the *N*-protection of isatin with a benzyl and an ethyl acetate group to afford 1-benzylindoline-2,3-dione and ethyl 2-(2,3-dioxoindolin-1-yl)acetate respectively. The next step was the synthesis of the brominated compounds 1-benzyl-2-bromo-1*H*-indole and ethyl 2-(2-bromo-1*H*-indol-1-yl)acetate by means of a functional group interconversion of the oxygen in the 3-position to two chlorine atoms, followed by hydrodehalogenation, using zinc in AcOH, and then bromination, using $POBr_3$ in CH_2Cl_2. Having obtained the brominated compounds we went on and coupled them with 2-formylphenylboronic acid using the Suzuki-Miyaura cross coupling reaction to obtain the coupled products 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde and ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate in 92 and 77% yield, respectively. Aromatisation of ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate to ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate occurred

smoothly in 2 minutes using 10 mol % $KOBu^t$ in DMF at room temperature. Using the same reaction conditions on 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde to form 6-phenylindolo-[2,1-*a*]isoquino-line resulted in (±)-5,6-dihydro-6-phenylindolo[2,1-*a*]iso-quinolin-5-ol being obtained in 75% yield (7:3 ratio of *anti*:*syn*). An attempt to dehydrate this compound using p-TSA in CH_2Cl_2 in the presence of molecular sieves was not successful. Time constraints prevented any further attempts at dehydrating (±)-5,6-dihydro-6-phenylindolo[2,1-*a*]iso-quinolin-5-ol.

In conclusion, we managed to synthesize (±)-5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol and ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate using the Suzuki-Miyaura cross coupling reaction and specific reaction conditions, using the base KO^tBu, for the formation of aromatic rings, both as key steps.

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Chapter 1: Introduction

Many naturally occurring, as well as synthetic, azapolycyclic aromatic ring systems display important biological activity and have found applications in the pharmaceutical and agricultural industries to name but a few. These compounds also known as alkaloids are mostly found in plants, but have also been isolated from mammals, salamanders, frogs and toads, mosses and fungi, marine organisms and arthropods. There are many different kinds of alkaloids and most have their biosynthetic origin from amino acids. The two largest groups of alkaloids are those made from tyrosine **1** and tryptophan **2**. Those originating from tyrosine include the isoquinoline **3** or tetrahydroisoquinoline **4** nucleus. The alkaloids made from tryptophan are almost as varied as those made from tyrosine and include the indole nucleus **5**.[1,2]

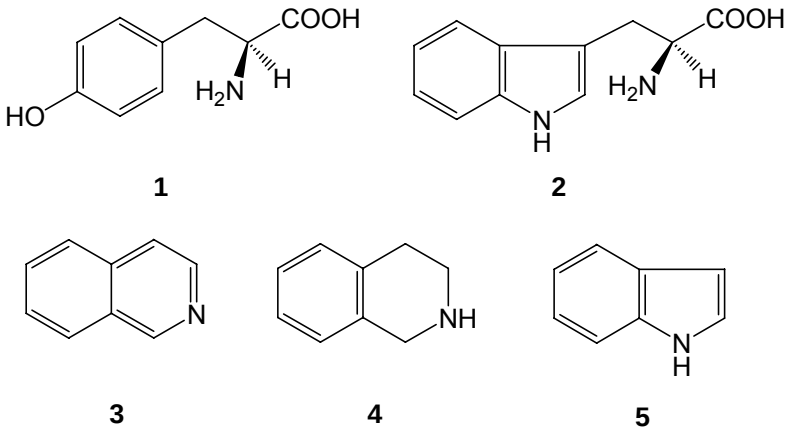
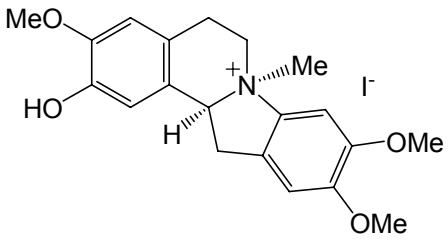
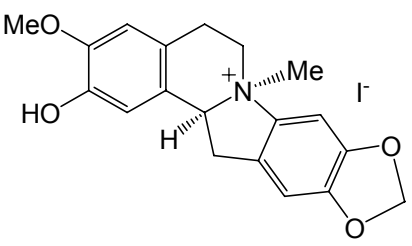


Figure 1

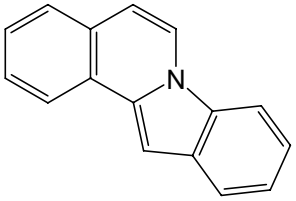
Alkaloids, such as the dibenzopyrrocoline alkaloids, cryptaustoline **6** and cryptowoline **7**, contain an indole ring fused to an isoquinoline moiety, where they share a common nitrogen atom. These alkaloids have been found to possess antitumour and antileukemic activities as well as tubulin polymerization inhibitory properties.[3] Indolo[2,1-*a*]isoquinolines **8** and related compounds, such as the pyrrolo[2,1-*a*]isoquinolines **9**, have been found to possess a similar skeleton and biological activities.[4]



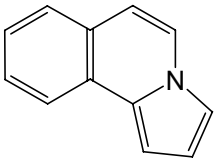
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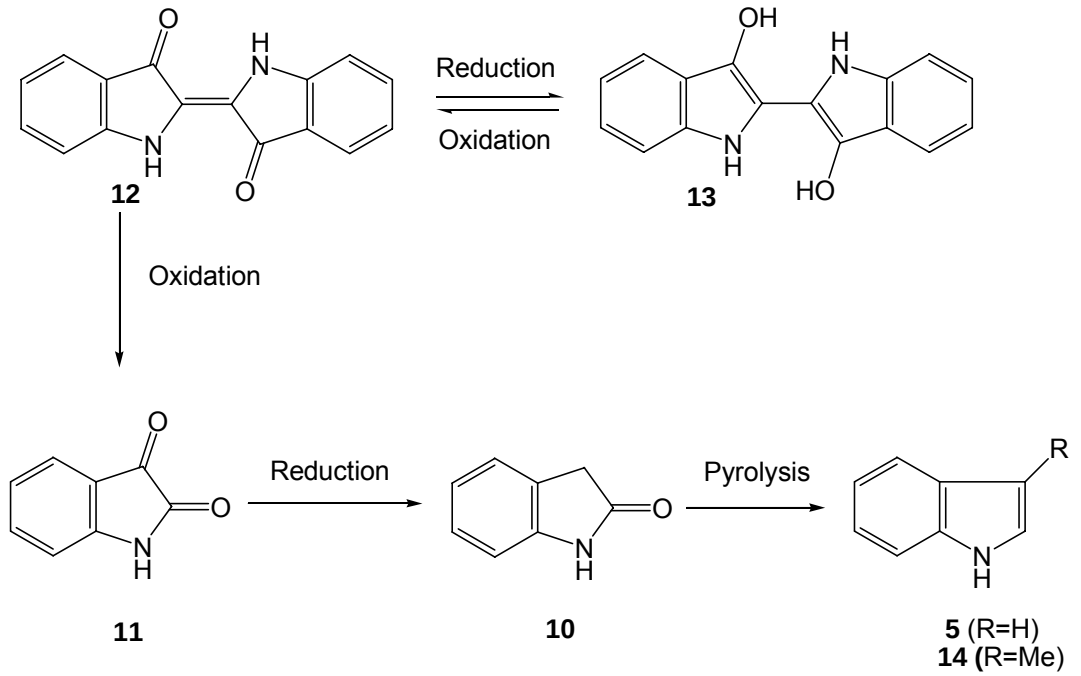
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Figure 2

Due to the broad application of polyfused heteroaromatic compounds (antimalarial, antileukemic, antitumour, antiviral, etc.), novel and more efficient methods for preparing them are of great interest to chemists and biologists.[1,2]

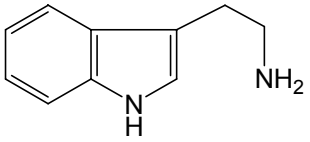
1.1. The Biological Importance of Indole and its Derivatives

Indole is a benzopyrrole in which a pyrrole ring is fused to a benzene ring through the α- and β- positions of the pyrrole. It was first obtained by Adolf von Baeyer in 1866 by pyrolysis of oxindole **10** with zinc dust.[5] The oxindole was obtained by the reduction of isatin **11** which was obtained by oxidizing the natural insoluble dark blue dye known as indigo **12**, **Scheme 1**. Indigo is used in the textile industry to give jeans their blue colour by first reducing it to its soluble salt, leucoindigo **13**. The jeans are then moistened with an aqueous solution of this salt and then exposed to air, which causes oxidation and thus precipitation of indigo in the fibres. Indole has also been isolated from certain flower oils such as jasmine and has been found to possess (when diluted) a strong pleasant odour. For this reason it has been used commercially in perfume formulations. Skatole, β-methylindole, **14** as well as indole **5** itself (when concentrated) have been found to be responsible for the foul odour of faeces.[6] Today the principal commercial source of indole is by the extraction from coal tar.[7]

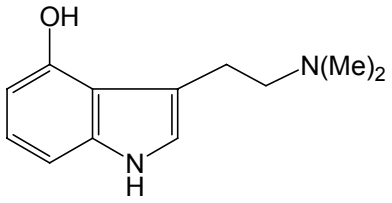


Scheme 1

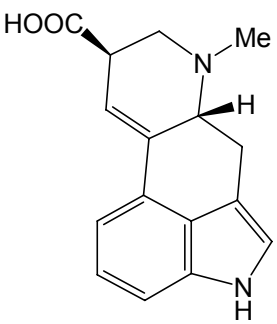
The indole alkaloids are a broad group of heterocyclic bases that contain the indole nucleus and whose structures vary in complexity. Most of these alkaloids are derived from tryptophan or the decarboxylated form of tryptophan, known as tryptamine **15**. Trytophan or tryptamine undergo biological transformations giving rise to the various alkaloids. Some derivatives of tryptamine produce psychic effects and are classified in the group of drugs known as hallucinogens. Two well-known naturally occurring hallucinogens are psilocin **16**, which is found in some species of Mexican mushrooms and lysergic acid **17**, which is found in the ergot fungus.[8] The diethylamide of lysergic acid is a synthetic drug better known as LSD **18** and is so powerful that it is capable of inducing symptoms similar to schizophrenia (**Figure 3**).[6,8,9]



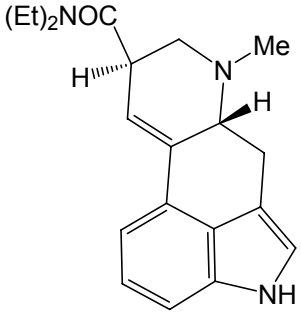
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16



17



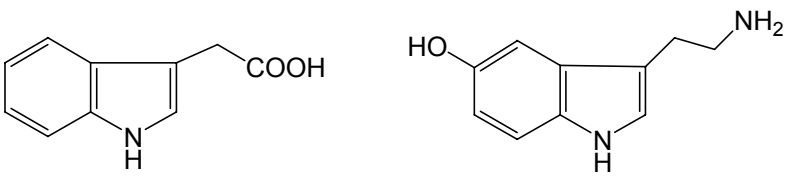
18

Figure 3

Other examples of indole-containing naturally occurring compounds, although not a comprehensive list, are:

- Indole-3-acetic acid **19** also known as auxin which is a plant growth hormone (**Figure 4**).[7]

- Seratonin **20** which is a neurotransmitter in animals as well as a hormone that affects blood pressure.[1]

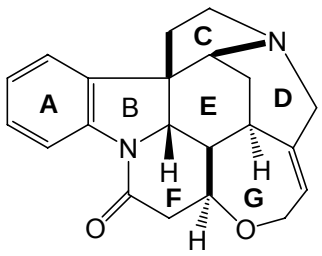


19 **20**

Figure 4

The fact that the indole alkaloids constitute such a broad group of compounds has resulted in the alkaloids being further divided into smaller groups of alkaloid families, such that compounds that are structurally similar are found together. A few different but important indole alkaloids will be discussed in the next few paragraphs.

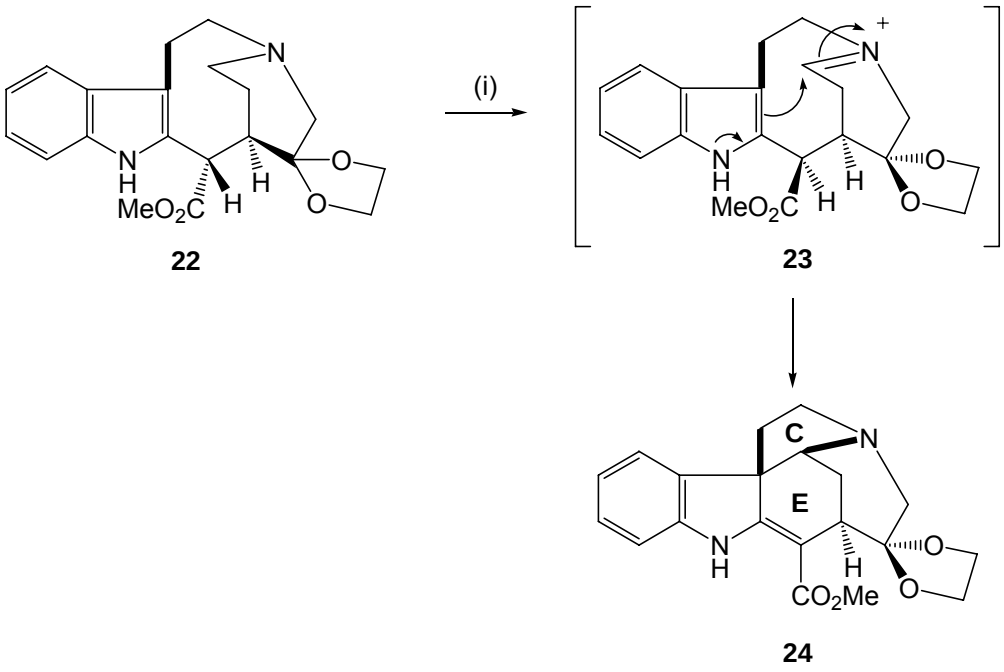
One of the most important alkaloids is strychnine **21** (**Figure 5**) which is not only the flagship compound of the family of *Strychnos* alkaloids, but is also one of the most complex alkaloid natural products (possessing seven rings and six stereogenic centers).[10] It was first isolated by Pelletier and Caventou[11] in 1818 and was one of the first alkaloids obtained in its pure form. It was also found to be the active component of an arrow poison used in South-East Asia. In therapeutic doses it has a mild analeptic effect and in lethal doses it is a convulsant, blocking postsynaptic inhibition in the spinal cord by acting as an antagonist of glycine, an inhibitory neurotransmitter. Lethal doses also lead to uncoordinated tonic convulsions (convulsions in which muscle contraction is sustained). The lethal dose for an adult human is 100 - 300 mg.[12]



21

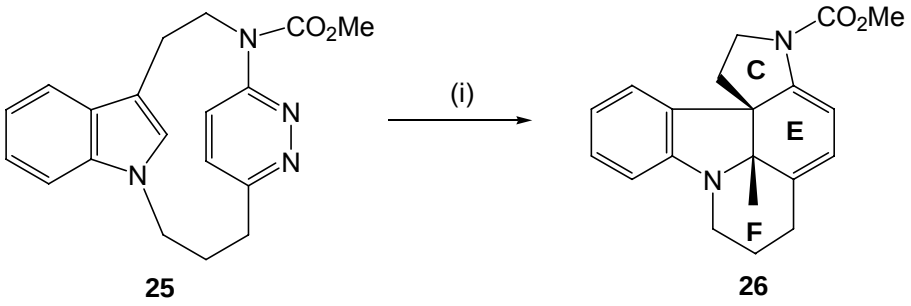
Figure 5

Many syntheses of strychnine have been reported. Magnus'[12,13] key step in the synthesis involved the transannular iminium ion cyclization of a nine-membered ring for the stereoselective construction of rings C and E, **Scheme 2**.



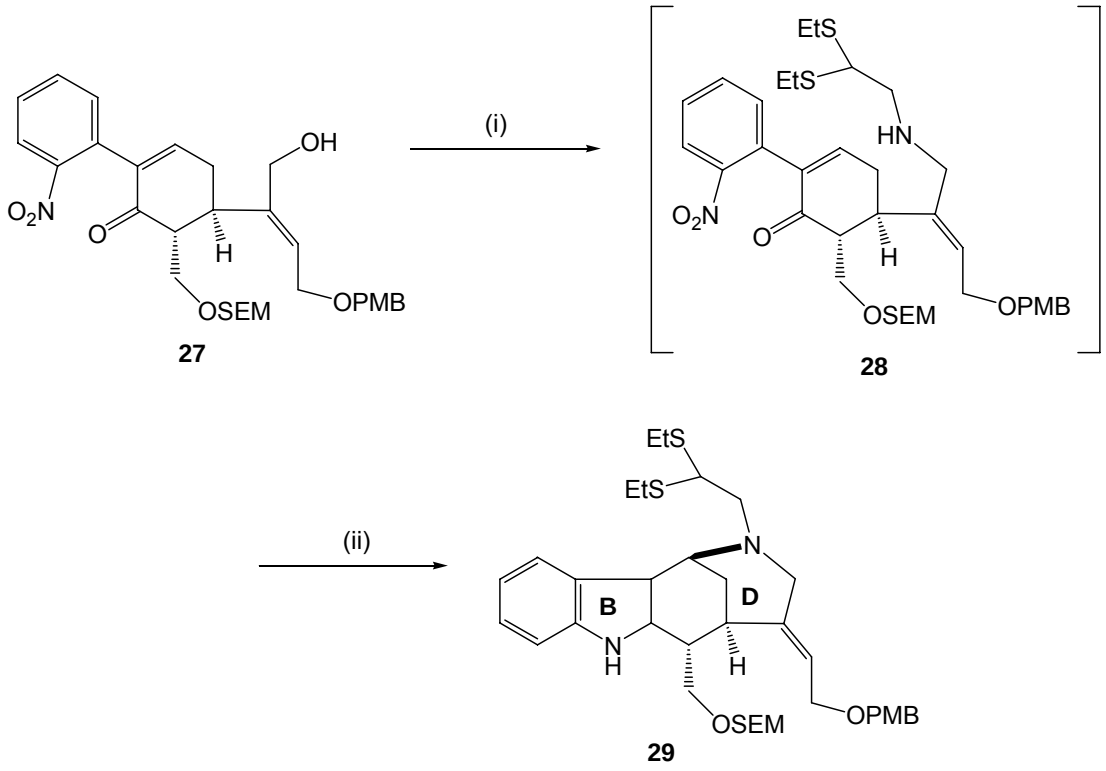
Scheme 2: (i) $Hg(OAc)_2$, CH_3COOH.

The shortest route (12-step synthesis) to date of (±)-strychnine was performed by Bodwell *et al.*[14] Their synthesis involved a transannular inverse-electron-demand Diels-Alder (IEDDA) reaction, which produced two stereogenic centers and constructed the C, E and F rings simultaneously, **Scheme 3**.



Scheme 3: (i) N,N-diethylaniline, Δ, 1 h.

Ohshima and co-workers[10] synthesized (-)-strychnine by using a zinc promoted tandem cyclisation to simultaneously construct the B and D rings, **Scheme 4**.

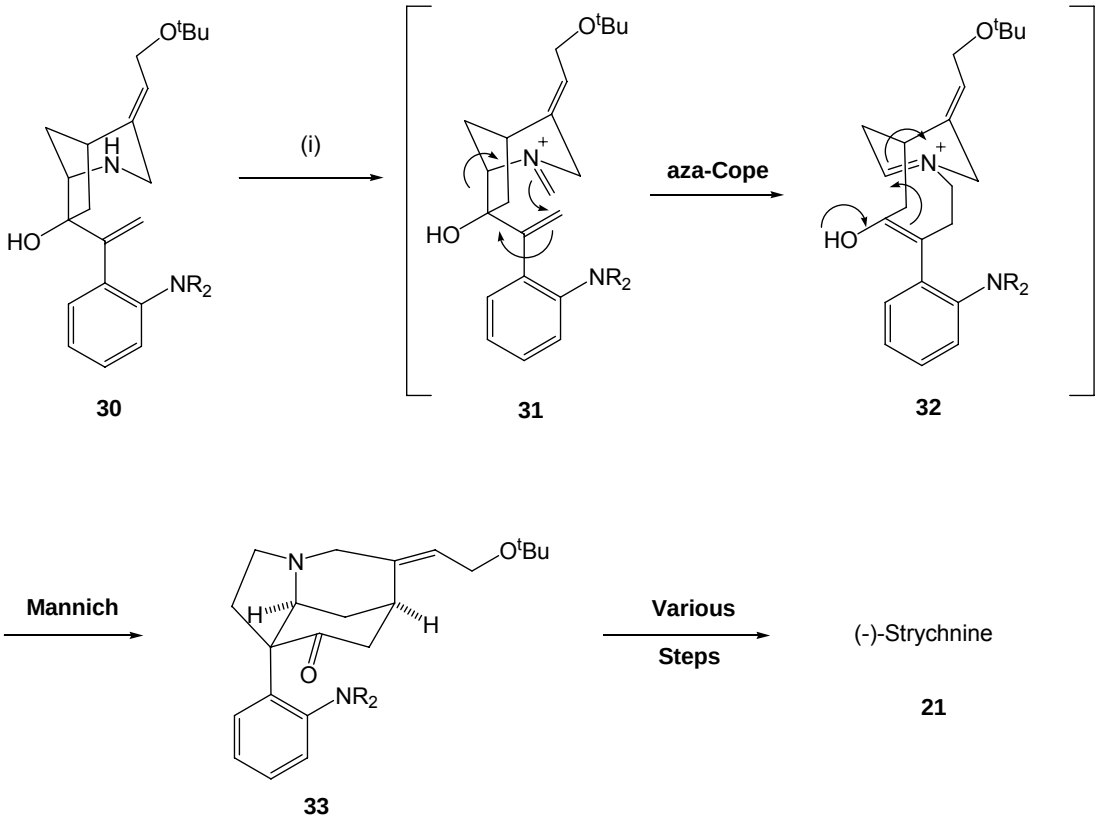


Scheme 4: (i) Tf_2O, i-Pr_2NEt, then 2,2-bis(ethylthio)ethylamine, CH_2Cl_2, -78 ºC. (ii) Zn, MeOH-aqueous NH_4Cl.

A more recent synthesis by Nakanishi and co-workers[15] involved palladium catalysis to synthesize (-)-strychnine **21**. The fact that palladium was used in the synthesis of all the rings indicates the importance of this metal as a catalyst in modern organic synthesis. Nakanishi then went on to synthesize tubifoline and dehydrotubifoline using a similar procedure.[16]

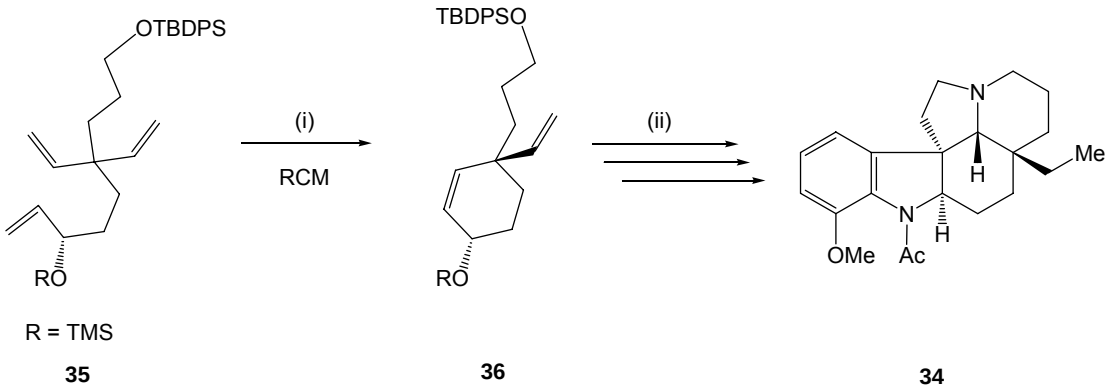
The first enantioselective route, however was accomplished by Overman *et. al* and the key to their approach was the sequential cationic aza-Cope rearrangement/Mannich cyclization.[17] Through various steps Overman synthesized the crucial compound azabicyclo[3.2.1]octane **30**, **Scheme 5**. The amine was exposed to paraformaldehyde, which resulted in the aza-Cope-Mannich cascade being triggered. First the amine was converted to the corresponding formaldiminium ion **31**, which then underwent a cationic [3,3] sigmatropic rearrangement (aza-Cope) to give **32**. This intermediate then underwent an intermolecular Mannich cyclization to obtain **33** in quantitative yield. The cyclized product then underwent a variety of conventional reactions

to yield strychnine in 25 steps with an overall yield of 3%. The biggest yield of strychnine obtained to date is 10% and was achieved by Rawal and Isawa.[18]



Scheme 5: (i) $(CH_2O)_n$, Na_2SO_4, CH_3CN, Δ.

Aspidospermine **34**, a 2,3,3-trialkylindoline alkaloid, is found in South America in an evergreen tree known as Quebracho. Aspidospermine is used as a tonic, febrifuge and anti-asthmatic for the relief of various types of dyspnoea, especially in emphysema and in asthma.[19] It has also been found to be a potential anti-HIV drug. There are many reported syntheses of this compound. A recent stereochemically controlled synthesis by Fukuda *et al.*[20] involved the use of ring closing metathesis (RCM) on **35** to form the quaternary stereogenic center of **36** as shown in **Scheme 6**.



Scheme 6: (i) 10 mol% Grubbs I, CH_2Cl_2, 48h, rt (ii) Many steps.

Vallesamidine **37** shown in **Figure 6** is a 2,2,3-trialkylindoline alkaloid and is related to aspidospermine. Vallesamidine's biological importance is unknown and its structure differs from aspidospermine in that C-19 is attached to C-2 rather then C-12. The synthesis of aspidospermine type alkaloids involve quebranchamine-type intermediates, such as **38**, and as a result, vallesamidine, containing the same stereochemistry at C-2, C-12 and C-19, it is regarded as a product of an "abnormal" cyclization.[21,22]

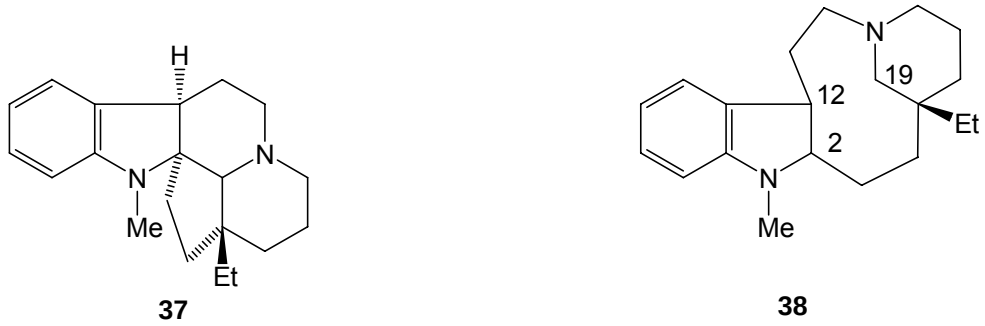
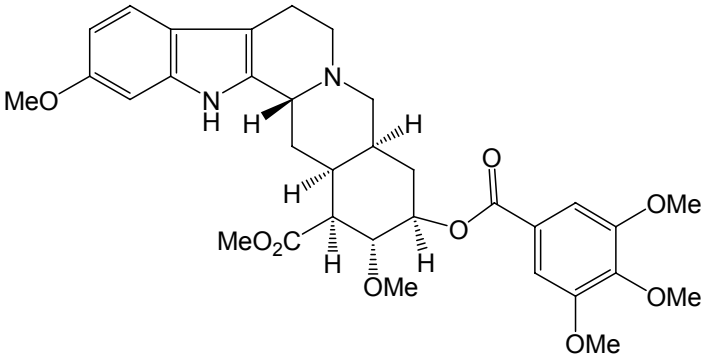


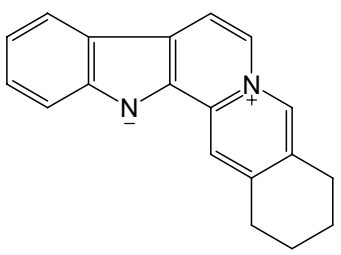
Figure 6

Another important indole alkaloid is reserpine **39**, a *Rauvolfia* alkaloid, which also falls under a family of alkaloids known as the indolo[2,3-*a*]quinolizine alkaloids. Although it is not a major drug now, it was one of the first compounds to show beneficial effects in the treatment of mental disorders and was also the forerunner of the medicinal tranquillisers.[5,7] Other indolo[2,3-*a*]quinolizine alkaloids are sempervirine **40**, serpentine **41**, alstonine **42** and alloyohimbane **43** (**Figure 7**). These compounds exhibit a combination of

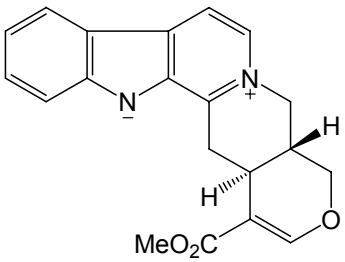
biological activity including cytostatic effects, anti-HIV, immunostimulant, sedative and antipsychotic activities.[23]



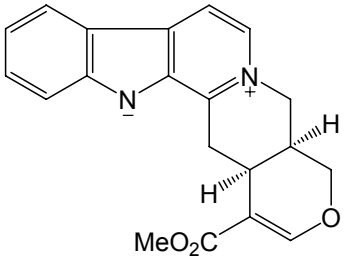
39



40



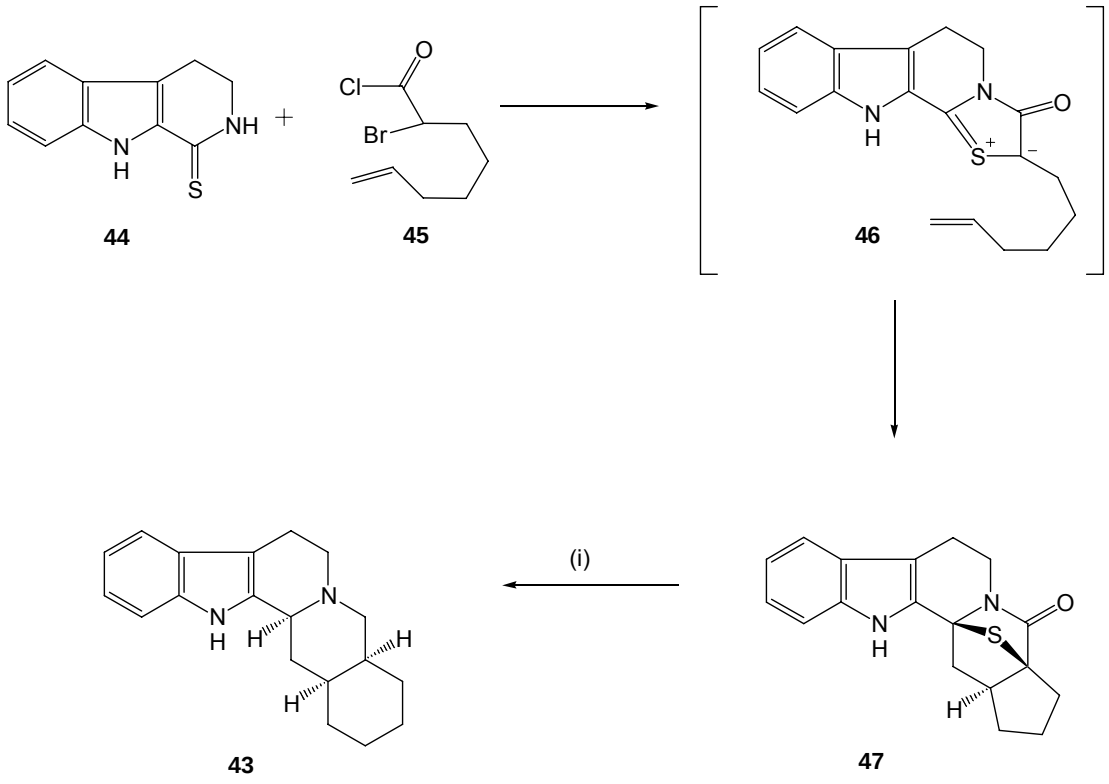
41



42

Figure 7

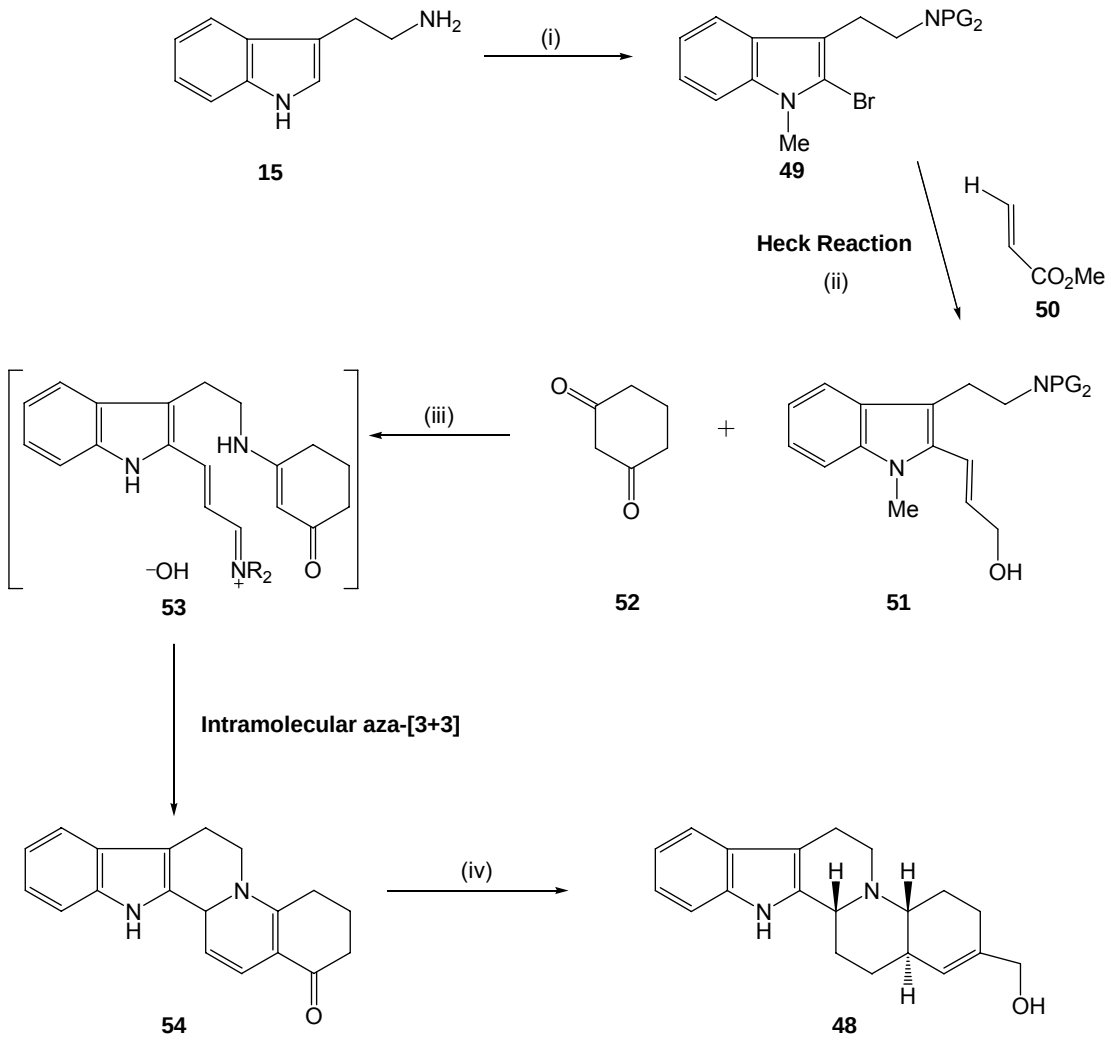
A recent synthesis of alloyohimbane **43** by Padwa and co-workers[24] involved the reaction of the thiocarboline **44** with the α-bromoacyl chloride **45** to generate the dipole thioisomünchnone **46**, **Scheme 7**. This dipole readily underwent intramolecular dipolar cycloaddition to form the cycloadduct **47** in 75% yield. Removal of the sulfur atom using Raney nickel followed by further reduction using LDA resulted in the (±)-alloyohimbane **43** being formed in 42% yield.[24, 25] Work in this area has also been done by Sainsbury.



Scheme 7: (i) (a) Ra-Ni, EtOH. (b) LAH.

The only known *β*-carboline natural product to possess a benz[*f*]indolo[2,3-*a*]quinolizine skeleton is tangutorine **48**. This alkaloid was isolated in 1999 by Che and co-workers[26] from the leaves of the *Nitraria tangutorum*. Tangutorine is related to the monoterpenoid indole alkaloids. Many of these alkaloids have been synthesized using the classic Pictet-Spengler cyclisation.[27] However a novel approach to the synthesis of tangutorine was performed by Hsung and coworkers [28] that features an intramolecular aza-[3 + 3] formal cycloaddition and a Heck coupling for constructing the C2-C3 bond. The synthesis began with the protection and bromination of tryptamine **15** to form **49**, **Scheme 8**. The Heck reaction of **49** with methyl acrylate **50**, followed by reduction and hydrolysis yielded the amino alcohol **51**. Condensation of the amino alcohol with 1,3-cyclohexanedione **52** and then oxidation with MnO_2 and reaction with an amine led to the formation of the cycloaddition precursor **53**. An intramolecular aza-[3 + 3] formal cycloaddition of **53** resulted in the pentacycle **54** being formed. Various hydrogenation and reduction methods were then

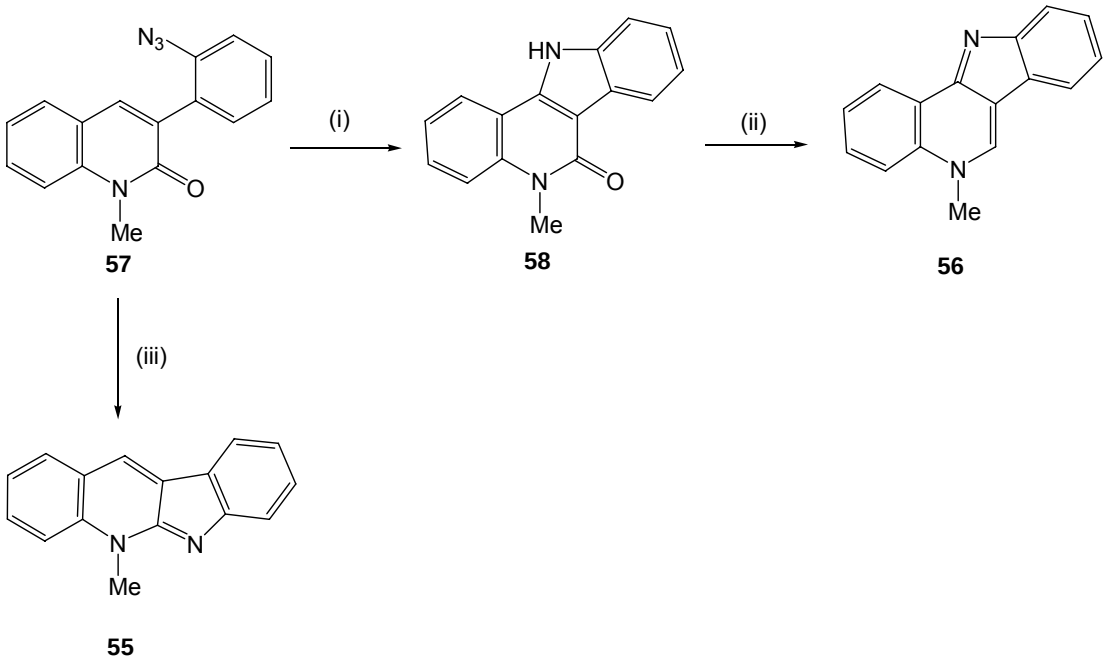
required to finally synthesize tangutorine **48** in 19 steps with an overall yield of 5.5%.



Scheme 8: (i) (a) phthalic anhydride, Et_3N, toluene, Δ (b) pyr-HBr-Br_2, CH_3Cl, THF, -10 °C (c) Boc_2O, DMAP, CH_2Cl_2, rt (ii) (a) 5 mol % $PPd(PPh_3)_4$, Cy_2NMe (1.1 Equiv.), toluene, 95 °C (b) Dibal-H, CH_2Cl_2, -78 °C, 1h (c) $NaBH_4$, *i*-PrOH/H_2O, rt then Δ, AcOH (iii) (a) Toluene, reflux (b) MnO_2, CH_2Cl_2, rt (c) $R_2^{'}NH$, Na_2SO_4, EtOAc/toluene, 95 °C (iv) (a) $Pd(OH)_2$, H_2, EtOAc (b) LHMDS, THF, -78 °C, HMPA, Mander's reagent (c) TFA, CH_2Cl_2, rt (d) $NaBH_4$, AcOH, rt, 48h (e) LAH.

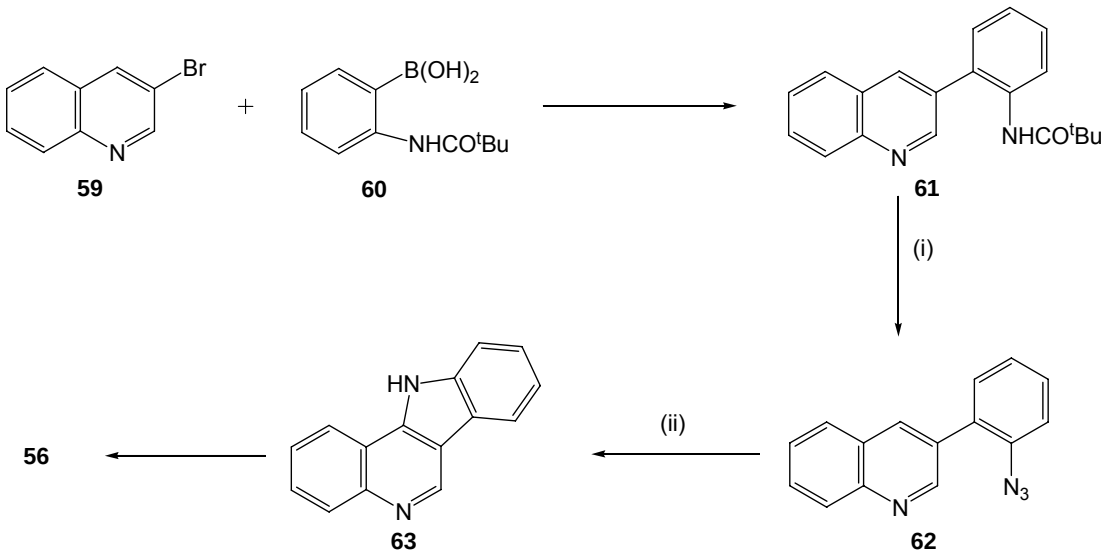
Two structurally and biosynthetically related natural products are cryptotackieine **55** and cryptosanguinolentine **56**. These two compounds were isolated from a shrub, indigenous to West Africa, which have been used in folk medicines as an antimalarial agent.[29] Cryptosanguinolentine **56** was found to possess an angular indolo[3,2-*c*]quinoline ring system, while

cryptotackieine **55** was found to possess a linear indolo[3,2-*b*]quinoline ring system. *N*-methyl derivatives of these ring systems have been reported to display antimicrobial and cytotoxic activity.[30] Fresneda *et al*.[31] synthesized these two alkaloids from 1-methyl-3-(*o*-azidophenyl)quinoline-2-one **57**, a common intermediate. Selective indolization by an intramolecular aza-Wittig reaction of **57** afforded cryptotackieine **55**, while nitrene insertion, to obtain **58**, followed by reduction afforded cryptosanguinolentine **56**, **Scheme 9**.



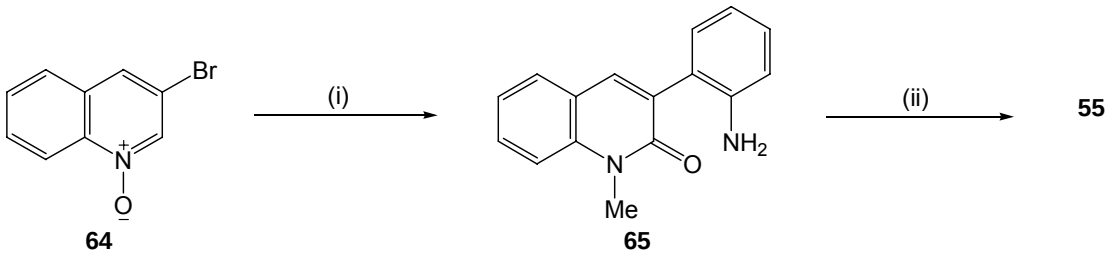
Scheme 9: (i) *o*-xylene, 150 °C (ii) Red-Al, toluene, reflux (iii) MW, Me_3P, nitrobenzene, 180 °C.

A much shorter synthesis of these two alkaloids was performed by Hajós *et al*.[32] and employed the Suzuki-Miyaura cross coupling reaction. Cross coupling of **59** and **60** to afford the phenylquinoline **61** was followed by deprotection of the amino moiety and formation of the azide **62**. Exposing the azide to high temperature resulted in ring closure to obtain **63**. Methylation of **63** resulted in cryptosanguinolentine **56**, **Scheme 10**.



Scheme 10: (i) (a) H_2SO_4 (b) HNO_2 (c) NaN_3 (ii) Δ.

In addition, cryptotackieine **55** was synthesized in 4 steps from 3-bromoquinoline-*N*-oxide **64**. The final ring closure of **65**, after coupling and deprotection, involved the condensation of the amino moiety with the oxo function of the carbostyryl ring, **Scheme 11**.[32]

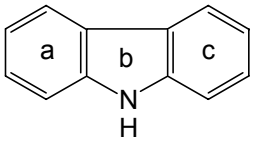


Scheme 11: (i) (a) $TsCl/K_2CO_3$ (b) MeI (c) 179 °C (ii) 174 °C.

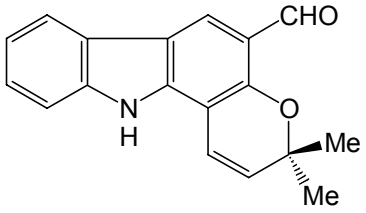
1.1.1. The Carbazoles

Carbazoles also contain the indole nucleus and have a wide range of biological activities. In 1872 carbazole **66** (**Figure 7**) was isolated from coal tar by Graebe and Glazer.[33] The first naturally occurring carbazole alkaloid to be reported was from *Murraya koenigii* and is known as murrayanine **67**. Murrayanine was found to have antibiotic properties by Chakraborty *et al.*[34] in

1965. *Murraya koenigii* is the richest known source of carbazole alkaloids and in India the leaves of this tree are used in curries.[35]



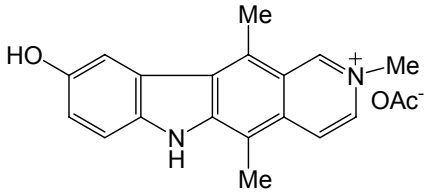
66



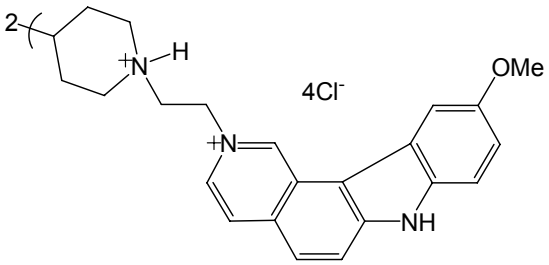
67

Figure 7

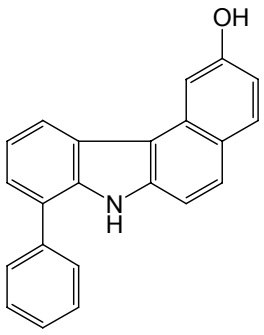
There are many different types of carbazoles depending on the type of groups and/or rings fused to them as well as the face that they are fused to. Naturally occurring as well as synthetic analogues of these carbazoles are important due to their biological activity.[4] Pyrido-fused carbazoles such as elliptinium **68** and ditercalcinium **69** for instance have been used for treating cancer (**Figure 8**).[36] Benzo[*a*]carbazoles such as **70** have been suggested as potential anti-tumour agents,[37] while the naphtho[*a*]carbazole **71** is a potential candidate for cancer treatment due to its DNA intercalative binding properties.[25,38]



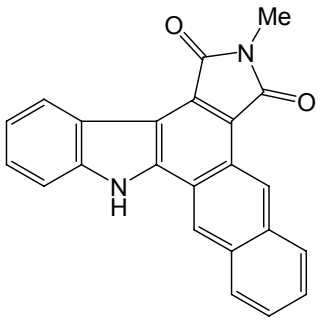
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69



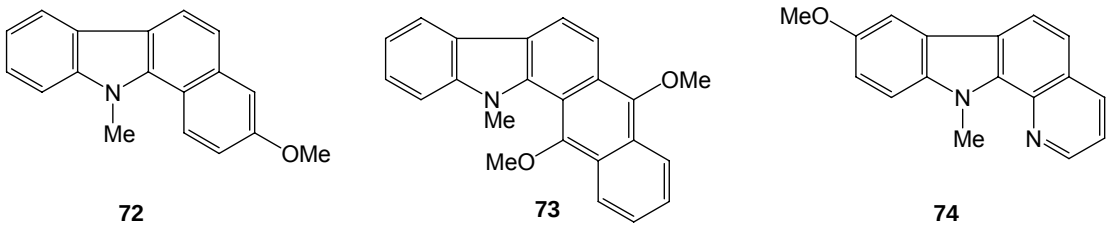
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71

Figure 8

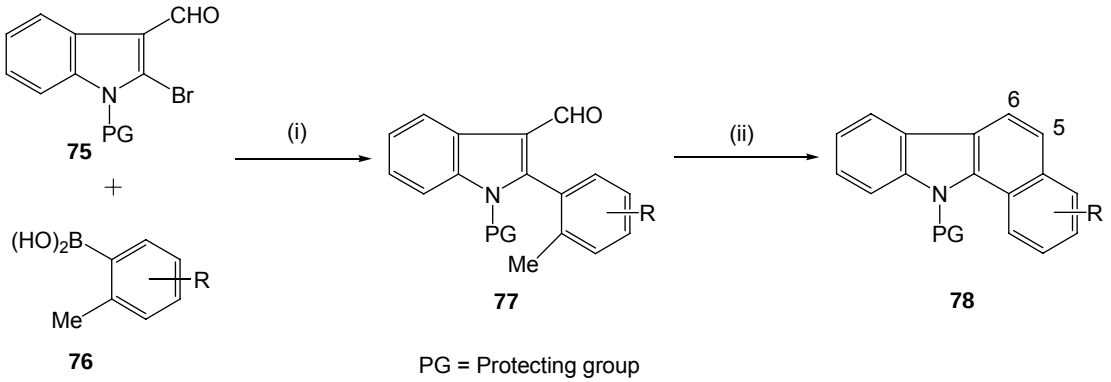
Benzo[*a*]carbazoles, naphtho[*a*]carbazole and pyrido[2,3-*a*]carbazoles such as **72, 73** and **74** respectively have previously been synthesized in our laboratories and will be discussed in the next section (**Figure 9**).



72 **73** **74**

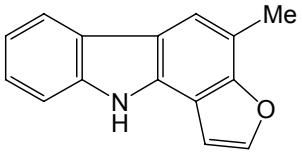
Figure 9

The method used employed the Suzuki-Miyaura cross coupling reaction of a substituted indole with a substituted aromatic molecule. The next step utilized a novel light- and base-assisted cyclization reaction to form the centrally positioned aromatic ring, i.e. the construction of the C5-C6 bond, **Scheme 12**.[4,39] These reaction conditions were shown to be very versatile in the synthesis of compounds containing the indole core.

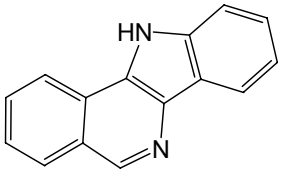


Scheme 12: (i) 10 mol % $Pd(PPh_3)_4$. aq. Na_2CO_3, DME/EtOH (ii) $KOBu^t$, hv, DMF, 70-80 °C.

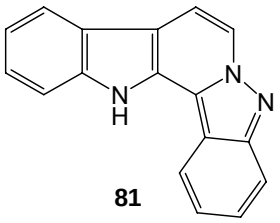
Other biologically important indole containing compounds that have been synthesized in high yields using the Suzuki-Miyaura coupling as a key step are furostifoline **79**, indolo[2,3-*c*]isoquinolines **80** and indazolo[3,2-*a*]-β-carbolines **81** (**Figure 10**).[32]



79



80

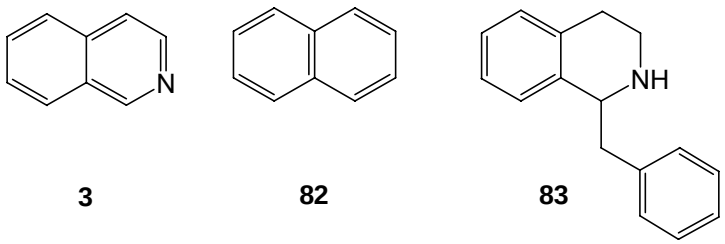


81

Figure 10

1.2. Isoquinoline, Isoquinoline Derivatives and their Biological Importance

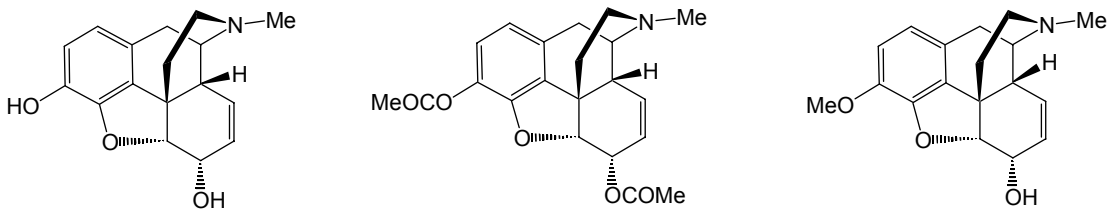
Isoquinoline **3** (**Figure 11**) is an analogue of naphthalene **82** and was discovered in 1885 as an impurity in crude quinoline coal tar. The isoquinoline nucleus is found in several hundred alkaloids of highly varied structure. Just as with the indole alkaloids, these alkaloids are divided into families where they are related structurally and by their mode of formation in the biological system. Most of the alkaloids are derivatives of 1-benzyl-1,2,3,4-tetrahydroquinoline **83** and arise in the natural organism through biological Mannich reactions.[6]



3 **82** **83**

Figure 11

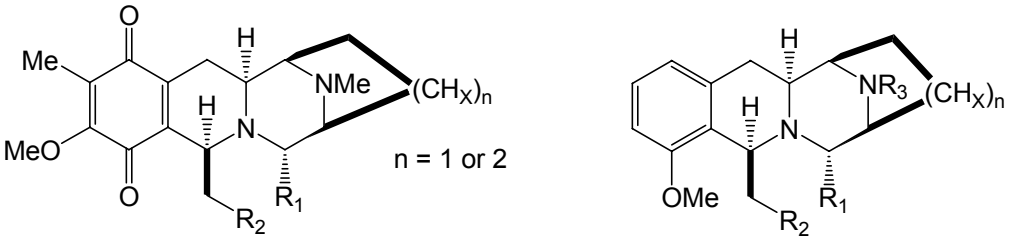
The opium poppy plant is best known for its narcotic, opium, which is found in its seed capsule. Opium was used for many centuries for its ability to alleviate pain and to induce a euphoric state when eaten or smoked.[40] The poppy capsule contains a complex mixture of alkaloids, the most important being the habit forming drug, morphine **84**, which possess a modified tetrahydroisoquinoline unit (**Figure 12**). The diacetate of morphine is heroin **85**, which is more addictive and the monomethyl ether is codeine **86**, which is less addictive and used in non-prescriptive medicine.[6]



84 **85** **86**

Figure 12

The tetrahydroisoquinoline family has been studied thoroughly over the past twenty-five years, especially the anti-tumour antibiotics. There are fifty-five natural products in this family to date.[41] The biological agents include cytotoxic agents that possess anti-tumour and anti-microbial activities. Apart from the six-membered ring containing a nitrogen, there are two core units in this family and they contain the quinone of **87** and the aromatic ring of **88** (**Figure 13**).



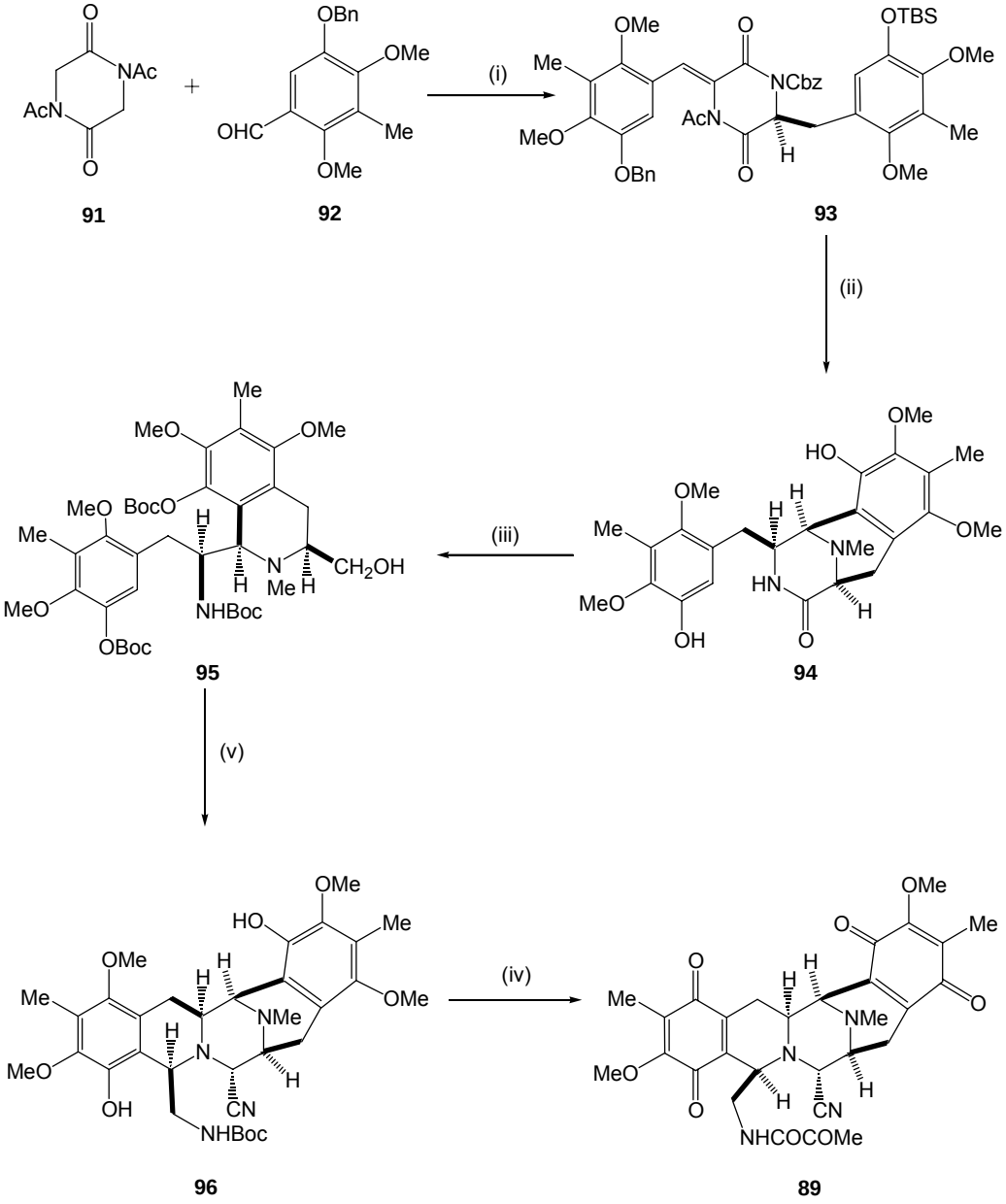
87 **88**

Figure 13

The family is classified into three families of natural products, namely the: saframycin, naphthridinomycin/bioxalomycin and quinocarcin/tetrazomine families. The saframycins and naphthridinomycins/bioxalomycins possess a quinone core while the quinocarcins/tetrazomines possess an aromatic core. A recent review by Williams and Scott describes the biological activity and chemistry of these tetrahydroisoquinoline anti-tumour antibiotics.[41] In this dissertation we will discuss the synthesis of these two core structures incorporated in saframycin A **89** and quinocarcin **90**.

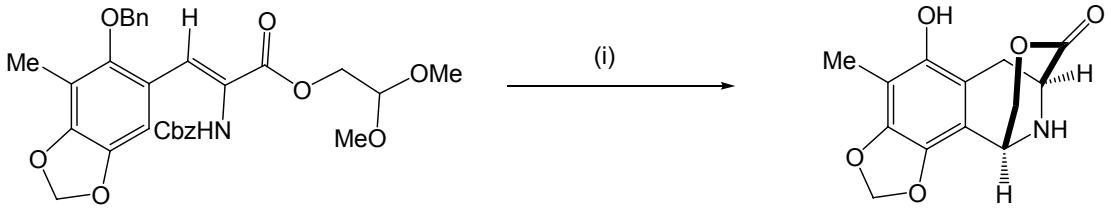
Saframycin A **89** was isolated in 1997 by Aria *et al*.[42] from *Streptomyces lavendulae* and had been found to display antitumour and antimicrobial activity. The first synthesis of (±)-saframycin A was reported by Fukuyama and co-workers in 1990.[43] The synthesis made use of the classical aldol condensation reaction of **91** and **92** to obtain the carbinolamine **93**, **Scheme 13**. Lactam **94** was then obtained via a series of reductions, cyclisations and hydrogenations of **93**. The protection of the lactam nitrogen, as the corresponding tert-butyl carbamate, activated the lactam for ring opening and followed by mild reduction afforded **95**. Deprotection followed by a Pictet-

Spengler reaction and Swern oxidation resulted in an aldehyde, which condensed with the amine to form an intermediate carbinolamine. The carbinolamine was trapped with NaCN to form the stable aminonitrile **96**. Saframycin A was finally obtained after forming an amide, using pyruvyl chloride, followed by oxidation of the hydroquinones to quinones using DDQ.



Scheme 13: (i) (a) KOBu^t, t-BuOH (b) H_2, Pd/C (c) TBSCl, Et_3N, (d) CbzCl, Et_3N, DMAP (e) **92**, KOBU^t, ^{t}BuOH (f) DBU (ii) (a) $NaBH_4$ (b) Formic acid (c) TBAF (d) H_2, Ra-Ni (e) CH_2O, $NaBH_3CN$ (iii) (a) Boc_2O, DMAP (b) $NaBH_4$ (iv) (a) TFA (b) $BocNHCH_2CHO$ (c) Swern oxidation, NaCN (v) (a) TFA (b) $MeCOCOCl$, $NaHCO_3$ (c) DDQ.

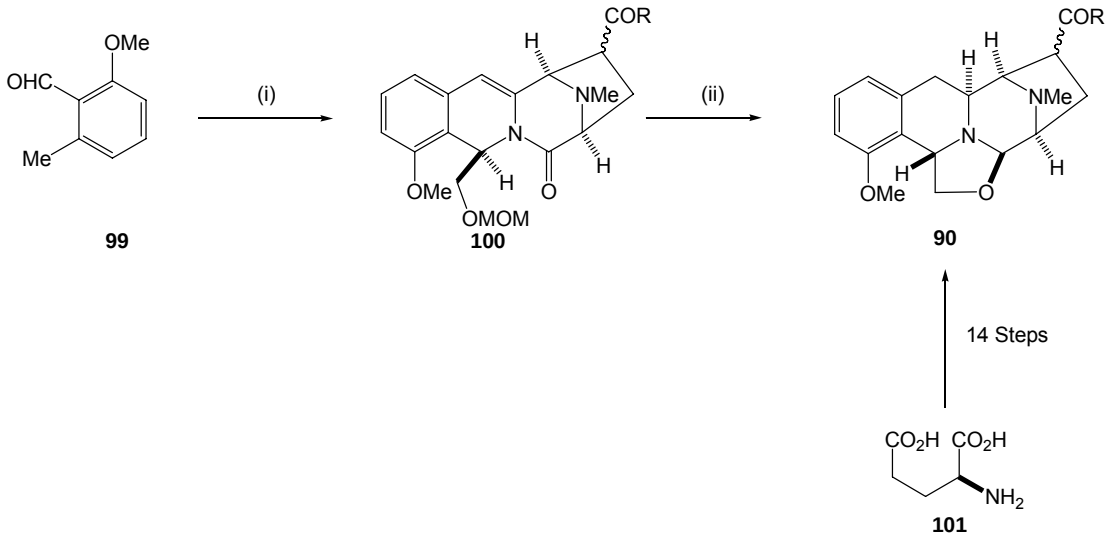
An asymmetrical synthesis of (-)-saframycin A was performed by Martinez and Corey[44] and made use of similar reaction conditions to that used by Fukuyama and Steven. The differentiating step in this synthesis was the set up of the stereochemistry of the tetrahydroisoquinoline. This step involved a rhodium-catalyzed asymmetric hydrogenation of the benzylic olefin **97**, followed by deprotection and a Pictet-Spengler cyclization to afford the tetracycle **98**, **Scheme 14**.



97 **98**

Scheme 14: (i) (a) Rh[(COD)-(R,R)-DiPAMP]$^{+}BF_4^{-}$, H_2 (b) $BF_3.OEt_2$, H_2O (c) $BF_3.OEt_2$ (d) H_2, 10 %Pd/C.

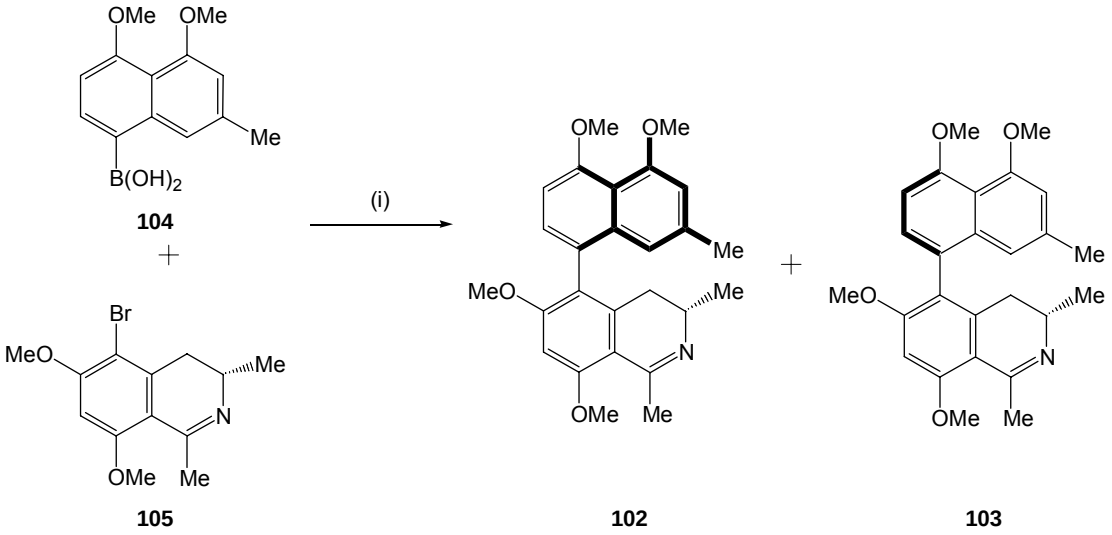
Quinocarcin **90** was isolated in 1983 from *Streptomyces melanovinaceus* by Tomita *et al*.[45] It has moderate activity against Gram-(+) bacteria such as *Staphylococcus aureus* and *Klebsiella pneumoniae*, as well as potent antitumour activity against several tumour cell lines including: St-4 gastric carcinoma, MX-1 human mammary carcinoma and P388 leukemia. The synthesis of (-)-quinocarcin has been reported. Garner *et al*.[46] published the first asymmetric synthesis and made use of chiral auxiliaries, an intermolecular 1,3-dipolar cycloaddition and an intramolecular Wittig cyclization that afforded the tetracycle **100**, from **99**, and eventually (-)-quinocarcin **90**. Unlike Garner *et al*., Tereshima[47] started their synthesis using (*S*)-glutamic acid **101** as a basis for the stereochemistry required and finally synthesized (-)-quinocarcin using classical chemistry, **Scheme 15**.[41]



Scheme 15: (i) (a) $MeSCH_2S(O)Me$, triton B, HCl, ^{t}-BuCOCl, Et_3N, $CO_2CH(Ph)CH(Me)NLi$ (b) KHMDS, trisyl azide, HOAc, $NaBH_4$ (c)H_2, Pd/C, Maleic anhydride, Ac_2O, NaOAc (d) 5N HCl, THF, MeN_3 (e) hv (f) MOMCl, *i*-Pr_2NEt, NBS, hv, PPH_3, $KOBu^t$ (ii) (a) H_2, Ra-Ni, LiOH (b) Li/NH_3, NaCN (c) TMSCl, NaI, $AgNO_3$.

The naphthylisoquinoline alkaloids have been found in two tropical plants, *Ancistrocladaceae* and *Dioncophyllaceae*.[40] There is a rapidly growing interest in these alkaloids due to them possessing both stereogenic centers and chiral axes, as well as being one of the first polyketide-derived isoquinoline alkaloids. They also display antimalarial and antiprotozoal activities *in vivo* and *in vitro*.[48]

Ancistroealaine A **102**, a naphthylisoquinoline alkaloid, had recently been found to be highly active against *Leishmania donovani*, the pathogen of visceral leishmaniasis (Kala Azar).[49] In a publication by Bringmann and co-workers the synthesis of **102** and ancistrotanzanine B **103**, using Suzuki-Miyaura coupling reactions, was reported. The naphthalene **104** and the heterocycle **105** were coupled using $Pd_2(dba)_3$ as a catalyst to afford the desired alkaloids in a 25:75 diastereomeric ratio (**102**:**103**), **Scheme 16**. The remarkable fact in this synthesis was that Suzuki-Miyaura coupling managed to work in the presence of a free imino function. The reason for this is still being investigated.[48]



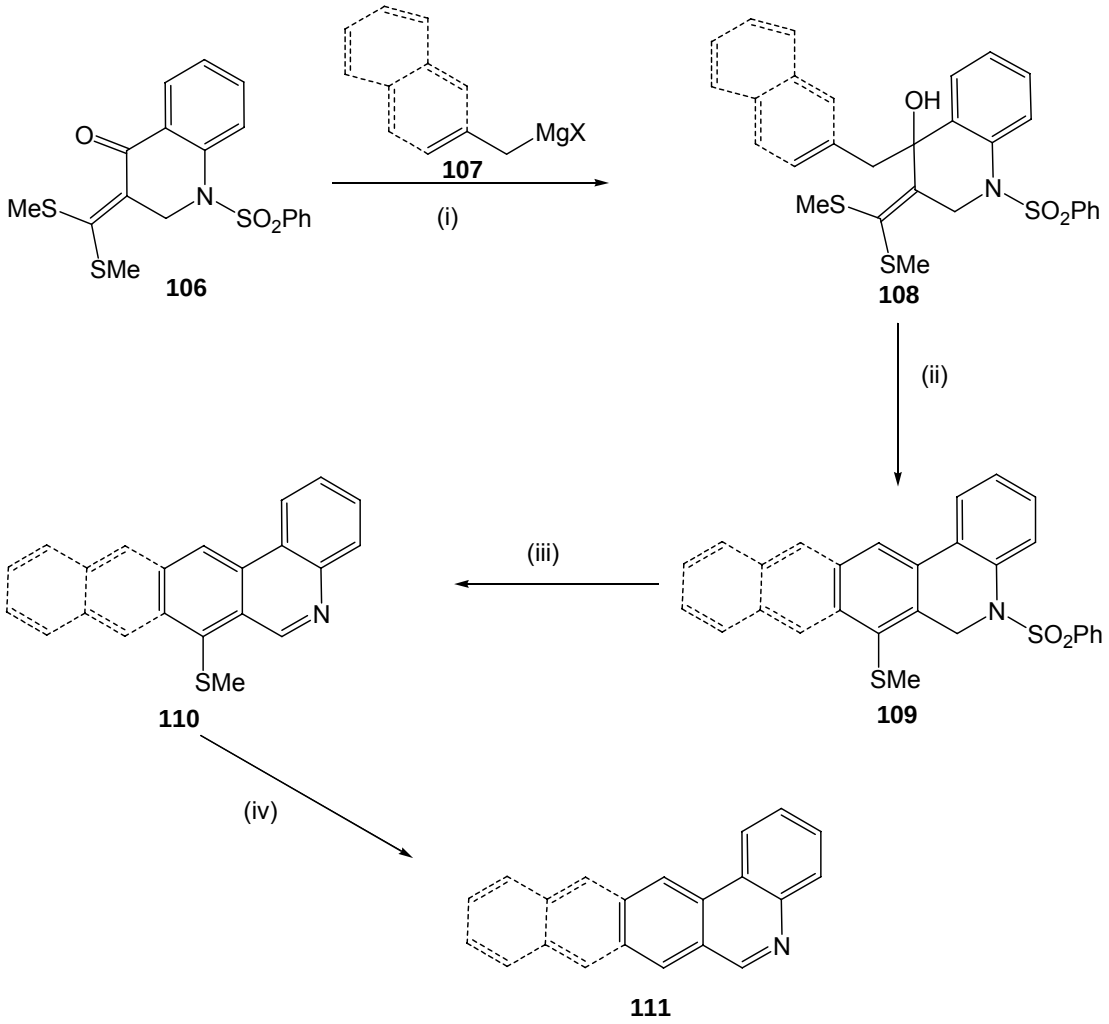
Scheme 16: (i) Toluene/H_2O, $NaHCO_3$, 5 mol % $Pd(dba)_3$.

1.2.1. The Phenanthridines

Phenanthridines and their benzo analogues are fused isoquinolines, found throughout the plant kingdom, possessing a broad range of biological properties.[50] Many phenanthridines exhibit antileukemic and antiviral activities. They have been found in the metabolites of plant families and their ring system is present in many synthetic dyestuffs.[50,51] Various methods have been employed in the synthesis of the phenanthridines including aromatic and heteroaromatic annelation[51], Bischler-Napieralski cyclization[52], and palladium-assisted coupling[50,53].

Patra *et al*.[51] synthesized a variety of substituted phenanthridines, benzo[*j*]phenanthridines and naphtha[2,1-*j*]phenanthridines, using aromatic and heteroaromatic annelation methodology, **Scheme 17**. They showed that by reacting *N*-benzenesulfonyl-3-[bis(methylthio)methylene]-1,2,3,4-tetrahydroquinoline-4-one **106** with a substituted alkene-, benzyl- or naphthyl-Grignard **107**, in ether, resulted in the formation of a carbinolacetal **108**. This carbinolacetal would undergo cyclisation in the presence of $BF_3.Et_2O$ to form dihydrophenanthridine, benzo[*j*]dihydrophenanthridine and naphtho[2,1-*j*]dihydrophenanthridines respectively **109**. These compounds were aromatized by treatment with NaOH in toluene at reflux in the presence of a

phase transfer catalyst to afford **110**. Finally dethiomethylation was performed using Raney nickel to afford substituted phenanthridines **111**.



Scheme 17: (i) Et_2O, THF (ii) $BF_3.Et_2O/C_6H_6$ (iii) $Bu_4N^+ {}^-OH$, toluene, Δ (iv) Ra-Ni.

Benzo[*c*]phenanthridines such as nitidine **112** and fagaronine **113**, an 8,9-disubstituted planar benzophenanthridinium salt, possess anti-leukemic activity.[52] Fagaronine's anti-tumour activity has been traced to the inhibition of DNA topoisomerase and has been attributed to the conformationally rigid embedded 2-phenylnaphthalene subunit.[52,54] Other benzo[*c*]phenanthridine alkaloids of importance are chlerythrine **114**, which inhibits protein kinase C and isofagaridine **115**, which inhibits DNA topoisomerase I.[53]

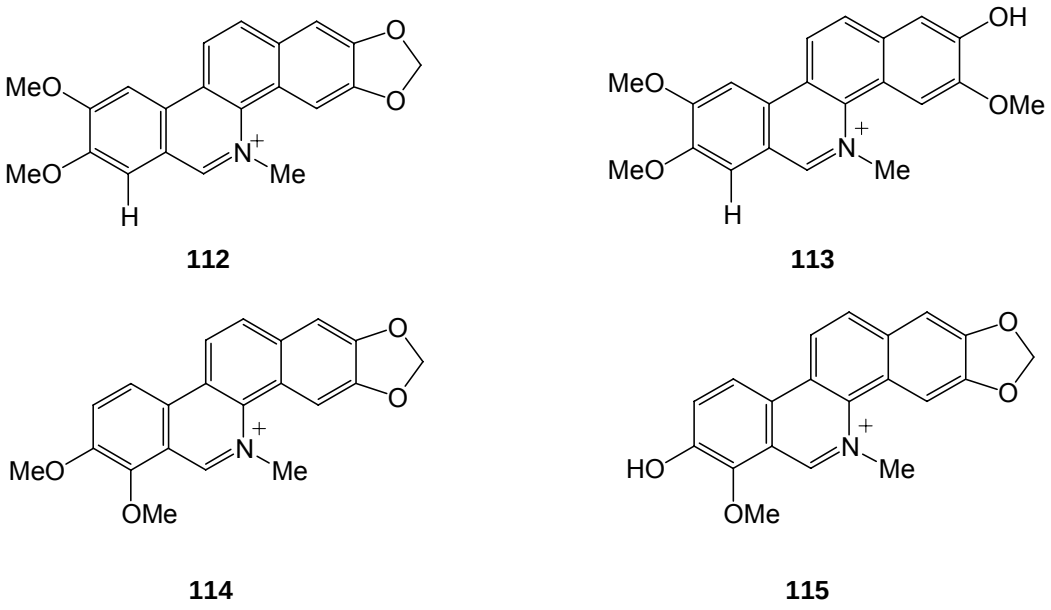
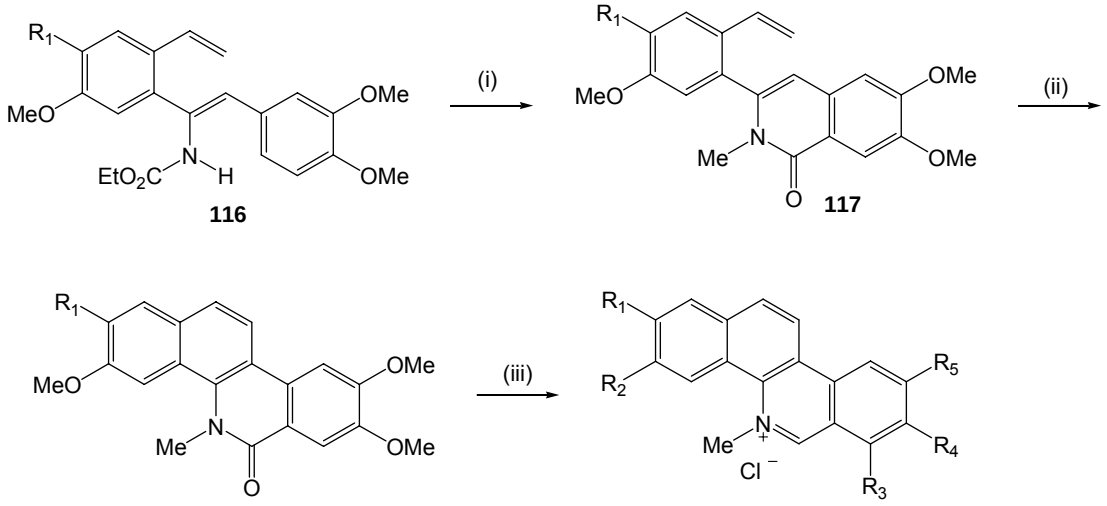


Figure 14

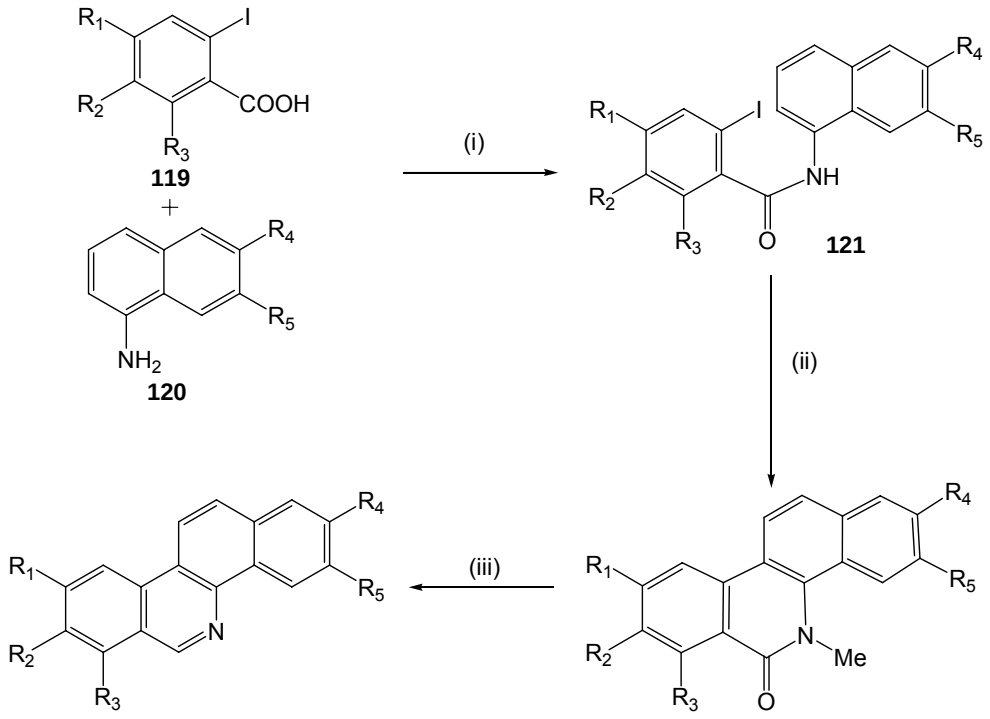
Treus *et al*.,[52] using a Bischler-Napieralski cyclization, have recently synthesized fagaronine **113**, nitidine **112** and chelerythrine **114**. Their synthesis involved reacting **116** with Tf_2O and DMAP in chloroform to yield the Bischler-Napieralski cyclized product **117**, **Scheme 17**. Oxidation with TTN (thallium trinitrate), followed by reaction with aqueous HCl, resulted in the benzo[*c*]phenanthridinone **118**. Reduction of **118** with LAH, followed by oxidation with DDQ and *O*-dealkylation with sulfuric acid afforded the naturally occurring benzo[*c*]phenanthridines.



112 Nitidine: $R_1 + R_2 = OCH_2OCH_2$, $R_3 = H$, $R_4 = R_5 = OMe$
113 Fagaronine: $R_1 = OH$, $R_2 = R_4 = R_5 = OMe$, $R_3 = H$
114 Chelerythrine: $R_1 + R_2 = OCH_2OCH_2$, $R_3 = R_4 = OMe$, $R_5 = H$

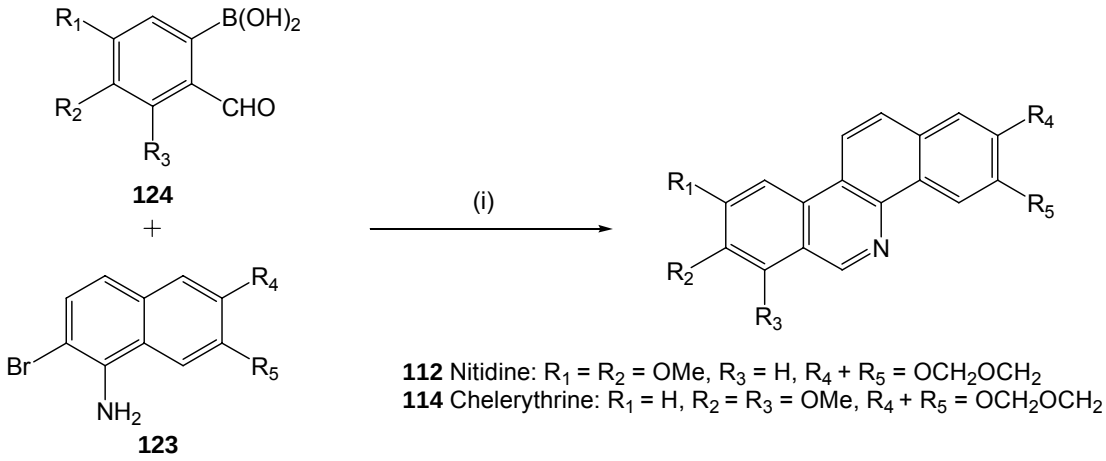
Scheme 18: (i) Tf_2O, DMAP, CH_2Cl_2, 0 °C, 1.5h (ii) (a) $Tl(NO_3)_3.3H_2O$, MeOH, rt, 5 min (b) aq. HCl, rt, 40-60 min (iii) (a) $LiAlH_4$, THF, 3h (b) DDQ, C_6H_6, 2h (c) H_2SO_4, AcOH, 2.5h.

Modern day approaches in synthesizing alkaloids, as seen previously in this dissertation, often make use of palladium as a catalyst. Chelerythrine **114** and nitidine **112** have been synthesized by Harayama[53,54] and Geen[50] under slightly different conditions. Harayama and co-workers first treated **119** and **120** with oxyalyl chloride in the presence of NEt_3 to afford the amide **121**, **Scheme 19.1**. Cyclisation of **121** to **122**, using $Pd(OAc)_2$, PPh_3 and Ag_2CO_3 in DMF, followed by reduction (LAH) and then oxidation (DDQ) resulted in the desired alkaloids. Geen synthesized the bromine **123** and boronic acid **124** compounds, which they coupled using Suzuki-Miyaura coupling methodology, **Scheme 19.2**. The aldehyde and the free amine then reacted in the presence of the base to form the desired aromatic product.



112 Nitidine: $R_1 = R_2 = OMe$, $R_3 = H$, $R_4 + R_5 = OCH_2OCH_2$
114 Chelerythrine: $R_1 = H$, $R_2 = R_3 = OMe$, $R_4 + R_5 = OCH_2OCH_2$

Scheme 19.1: (i) NEt_3 (ii) MeI, 20 mol % $Pd(OAc)_2$, PPH_3, Ag_2CO_3, DMF (iii) $LiAlH_4$ then DDQ.

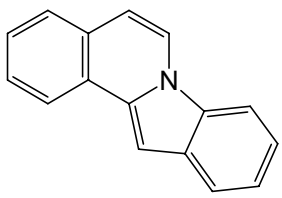


112 Nitidine: $R_1 = R_2 = OMe$, $R_3 = H$, $R_4 + R_5 = OCH_2OCH_2$
114 Chelerythrine: $R_1 = H$, $R_2 = R_3 = OMe$, $R_4 + R_5 = OCH_2OCH_2$

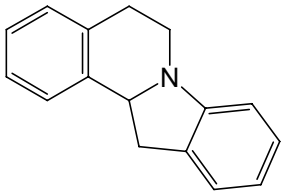
Scheme 19.2: (i) $Pd(OAc)_2$, PPh_3, DME, aq. Na_2CO_3, 21 h.

1.3. Dibenzopyrrocoline Alkaloids, Indolo[2,1-a]isoquinolines and Related Analogues

Thus far we have briefly discussed the biological importance of the indole and isoquinoline nuclei in Nature as well as in the pharmaceutical industry. We will now discuss the importance of the dibenzopyrrocoline alkaloids, the indolo[2,1-*a*]isoquinoline **8** derivatives (**Figure 15**) and related analogues as this is the main topic of this dissertation. These compounds contain an isoquinoline nucleus fused to an indole moiety where they share a common nitrogen. The dibenzopyrrocoline alkaloids form part of the isoquinoline alkaloids and tetrahydroisoquinoline family, and possess a 5,6,12,12a-tetrahydro-indolo[2,1-*a*]isoquinoline skeleton **125**.



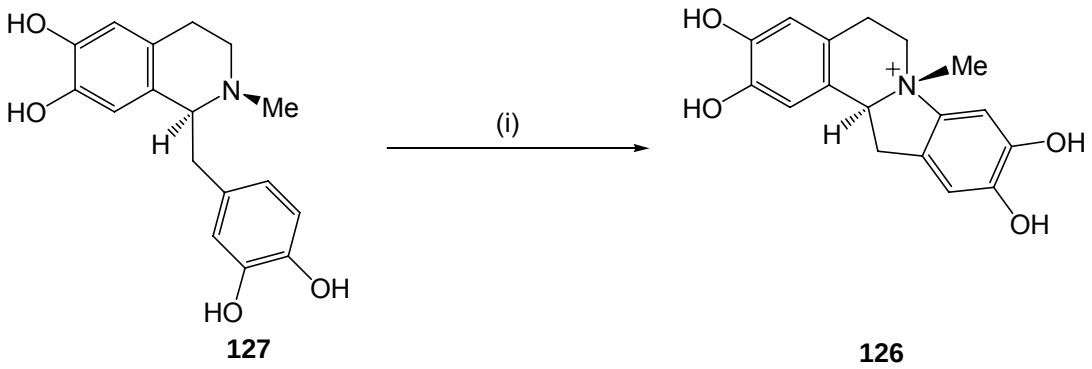
8



125

Figure 15

In 1932 Robinson and Sugasawa prepared dehydrolaudanosoline **126**, a rare dibenzopyrrocoline-type alkaloid, from the oxidative cyclization of laudanosoline **127**, **Scheme 20**.[55] Since the reaction went very smoothly they predicted that these type of alkaloids would one day be found in Nature. Two decades later, in 1952, (-)-cryptaustoline **6** and (-)-cryptowoline **7** were isolated from *Cryptocaria bowiei*, a plant indigenous to Queensland, Australia, as their water soluble iodide salts.[56] Although the biological action of these two alkaloids are uncertain they have been found to cause neurological paralysis by acting as a respiratory poison.[57,58]

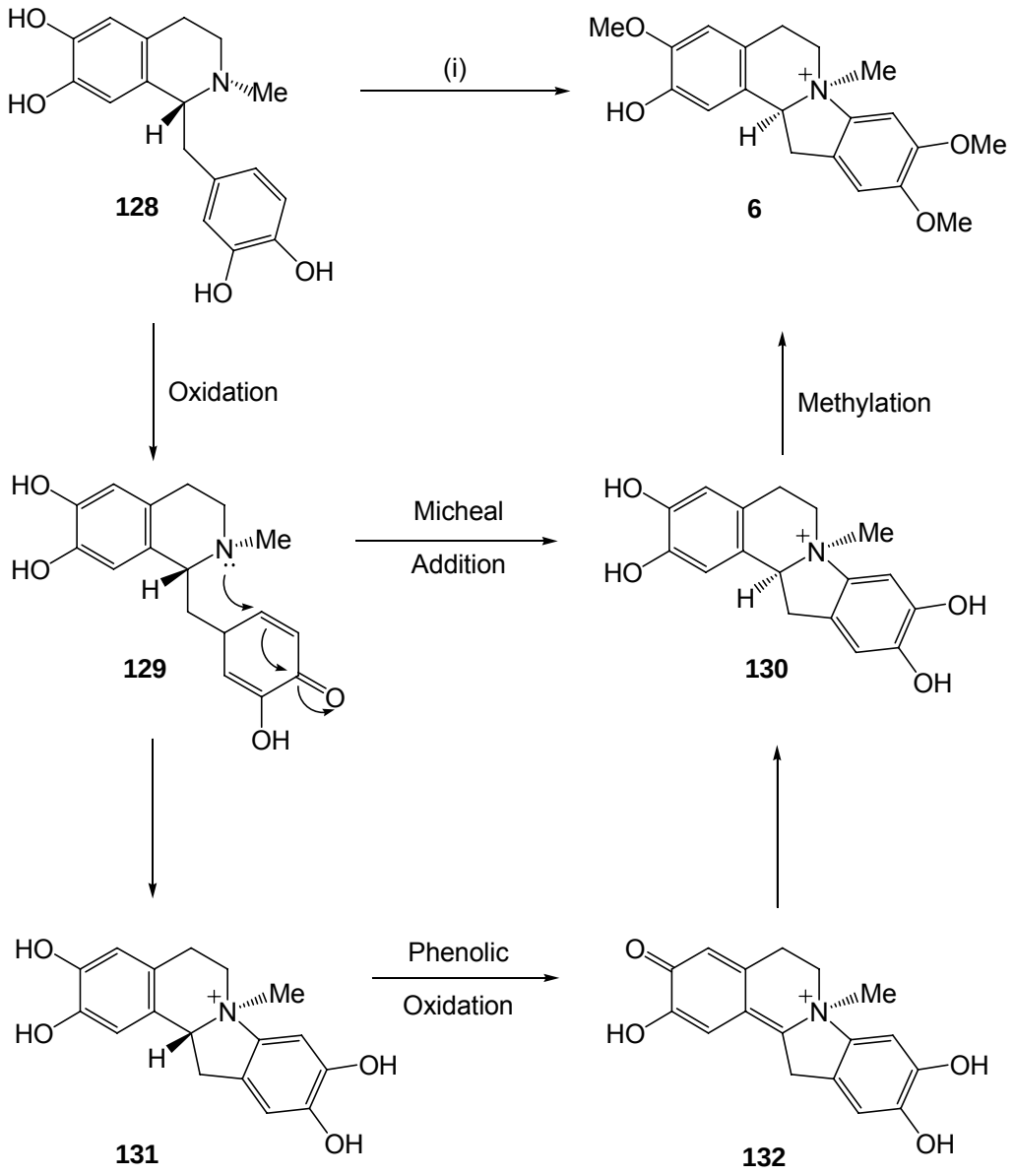


127 **126**

Scheme 20: (i) *o*-Chloranil.

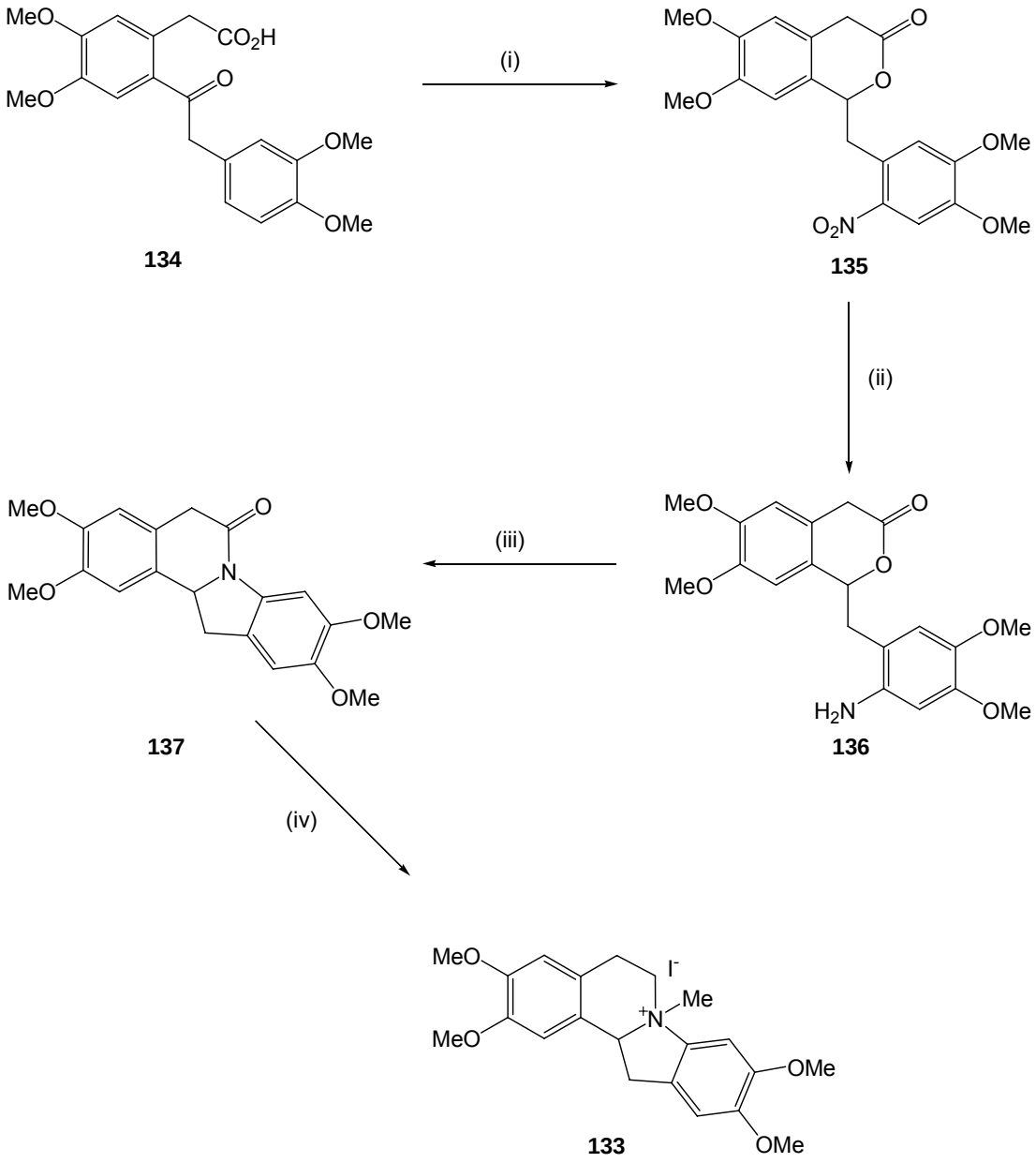
Many syntheses of (-)-cryptaustoline **6** starting from a substituted 1-benzylisoquinoline have been reported. The synthesis of (-)-cryptaustoline by Brossi *et al.*[59], starting from (+)-laudanosoline **128,** will now be discussed and is shown in **Scheme 21**. Brossi and co-workers performed an oxidative cyclisation using horse radish peroxidase-hydogen peroxide, which resulted in laudanosoline being oxidized to the intermediate Michael acceptor **129**. The cyclised product **130** then formed by way of a Michael addition. Methylation of the phenol substituents resulted in (-)-cryptaustoline **6** being obtained.[60,61]

The inversion of stereochemistry of *trans*-laudanosoline **128** to *cis*-cryptaustoline **6**, led Meyer *et. al*[58,61] to perform some kinetic studies on this synthesis. These studies showed that if the stereochemistry was retained after the Michael addition, the *trans*-fused product **131** obtained would be less stable then the *cis*-fused end product **130** due to ring strain. It was suggested that the *trans*-fused product **131** would undergo a second phenolic oxidation to the quinone methide **132**. The newly formed stereocentre would now anchor the absolute stereochemistry and allow reprotonation to obtain the more stable *cis*-fused product **130**.



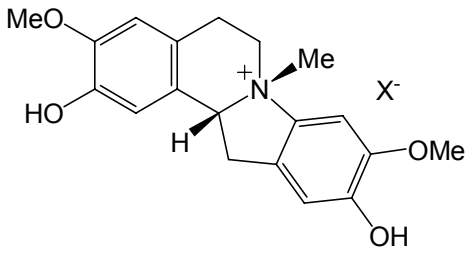
Scheme 21: (i) HRP-H_2O_2, MeI.

An asymmetric synthesis of (±)-*O*-methylcryptaustoline iodide **133**, starting from the keto acid **134**, was performed by Elliot, **Scheme 22**.[62] The keto acid was nitrated, reduced and then cyclized to the nitro lactone **135**. Reduction of the nitro group with catalytic hydrogenation using iron dust in warm acetic acid afforded the amino lactone **136**. Conversion of **136** to the lactam **137** (TFA in CH_2Cl_2) followed by reduction with BH_3·THF complex and treatment with methyl iodide gave (±)-*O*-methylcryptaustoline iodide **133**.



Scheme 22: (i) AcOH, HNO_3, 0 °C then EtOH, $NaBH_4$ (ii) Fe dust, AcOH, 60 °C, 1.5 h (iii) CH_2Cl_2-TFA, 18h then toluene, $MgSO_4$, reflux, 24h (iv) BH_3-THF, 20 h.

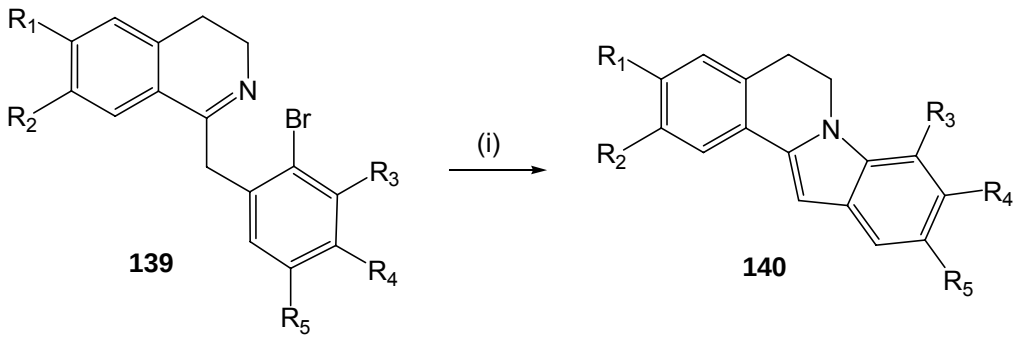
A third dibenzopyrrocoline alkaloid recently isolated from *Manglietia chingii*, a tall indigenous tree to the Guanxi and Guangdong provinces of China, was (-)-mangochinine **138** (**Figure 16**).[57] The bark of this tree has been used in Southern and South-Western China for the treatment of ulcers, as a muscle relaxant and for anti-bacterial therapy. The dibenzopyrrocoline, (-)-mangochinine, is believed to play a role in the biological activity of this bark.



138

Figure 16

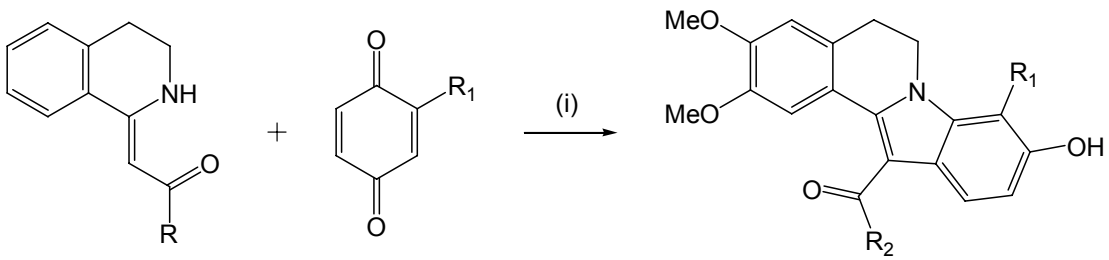
The indolo[2,1-*a*]isoquinoline derivatives contain a unique tetracyclic structure characteristic of the dibenzopyrrocoline alkaloids. Several methods for the construction of this skeleton have been reported. One well known synthesis involves the oxidative coupling of 1-benzylisoquinoline **83**.[63] Other syntheses include: (a) the cyclization of substituted 1-(2'-bromobenzyl)-3,4-dihydroisoquinolines **139** by heating at reflux in DMF in the presence of K_2CO_3 to afford **140**, **Scheme 23**.[64]



139 **140**

Scheme 23: (i) K_2CO_3, DMF, reflux.

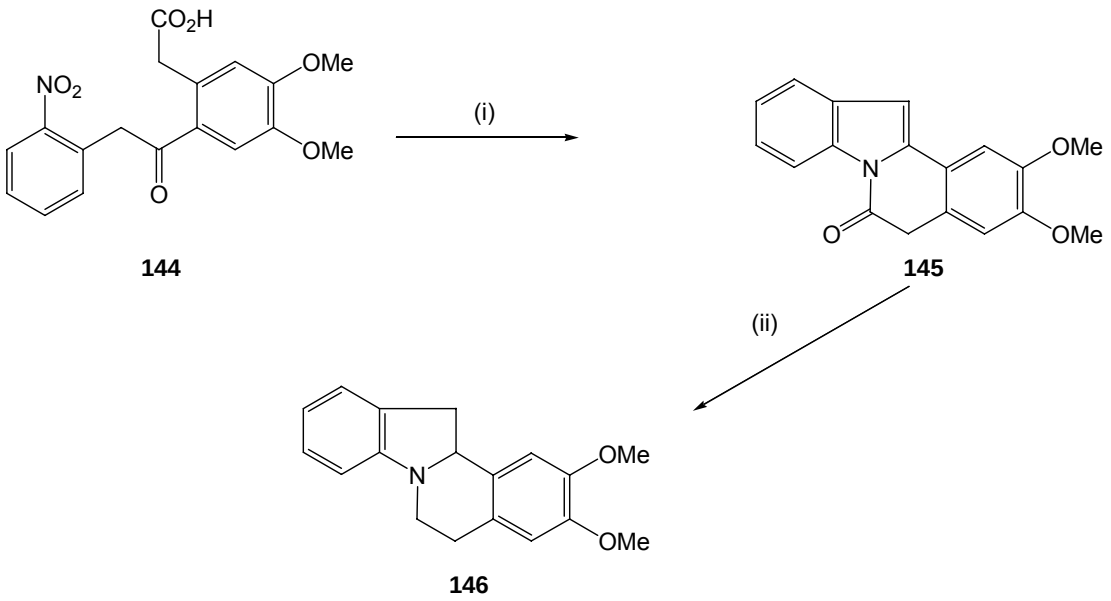
(b) the cycloannulation of **141** with *p*-benzoquinone **142** to afford **143** in a Nenitzescu-type reaction, **Scheme 24**.[65]



141 **142** **143**

Scheme 24: (i) CH_3NO_2, rt, 48 h.

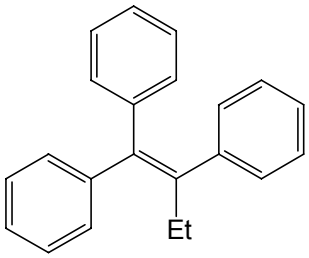
and (c) the conversion of a nitro keto acid **144** to benzopyrrocoline derivative **145**, which easily transformed into an indolo[2,1-*a*]isoquinoline **146** under reflux with zinc, **Scheme 25**.[66]



144 **145** **146**

Scheme 25: (i) MeOH, H_2SO_4 then H_2, Pd/C, MeOH/*i*-PrOH then *p*-TsOH, CH_2Cl_2 (ii) Zn, HCl, AcOH/H_2O.

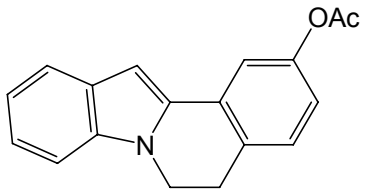
Anti-estrogens such as tamoxifen **147**, **Figure 17**, have been used in the treatment of breast cancer both in the treatment of primary breast cancer and in the advanced disease. Approximately 40% of patients with estrogen receptor positive breast tumours however, do not show a clinical response to tamoxifen treatment.[67] The fact that a large fraction of steroid hormone receptor positive tumours do not respond to or have become resistant to anti-hormonal treatment means that the development of new, improved drugs for the treatment of hormone-dependent carcinomas, such as mammary and prostatic cancer, are needed.



147

Figure 17

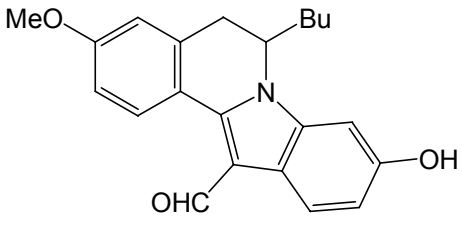
Early studies have shown that the indolo[2,1-*a*]isoquinoline structure is suitable for binding to estrogen receptors. This structure is similar to non-steroidal and steroidal estrogens and might be capable of intercalating into DNA. Recent studies have been done on acetoxy-substituted 5,6-dihydroindolo[2,1-*a*]isoquinolines **148** (**Figure 18**). These studies included their binding affinity to steroid hormone receptors, endocrine activity and cytostatic effect on hormone-independent MDA-MB 231 and hormone-dependent MCK-7 mammary tumour cells. It was found that compounds with acetoxy groups at the 3 and 10 positions, bound to steroid hormone receptors the best and at a concentration of 10^{-5}M a strong cytostatic effect was observed on both cell lines.[68]



148

Figure 18

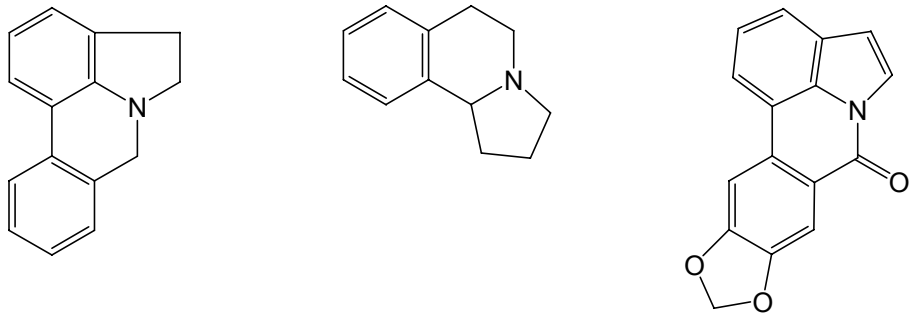
Another recent study, of a variety of hydroxy-substituted indolo[2,1-*a*]isoquinolines, showed that these compounds inhibited the growth of human mammary carcinoma cells.[3] It was suggested that the inhibition could be due to the compounds interfering with the tubulin system, which is involved in cell division. Further investigation revealed that the hydroxy-substituted indolo[2,1-*a*]isoquinolines were indeed binding to the colchicine-binding site and thereby inhibiting tubulin poymerization. The hydroxy-substituted indolo[2,1-*a*]isoquinoline that showed the highest activity was 6-butyl-12-formyl-5,6-hydro-3,9-dihydroxy indolo[2,1-*a*]isoquinoline **149** (**Figure 19**).



149

Figure 19

Two groups of compounds related to the dibenzopyrrocoline alkaloids and the indolo[2,1-*a*]isoquinolines are the pyrrolophenanthridines **150** and the pyrrolo[2,1-*a*]isoquinolines **151** (**Figure 20**). The pyrrolophenanthridines **150** also possess an isoquinoline nucleus fused to an indole moiety where they share a common nitrogen atom; however C10 is fused to C3 instead of C8. The pyrrolo[2,1-*a*]isoquinolines **151** on the other hand have an isoquinoline nucleus fused to a pyrrole moiety instead of an indole unit.

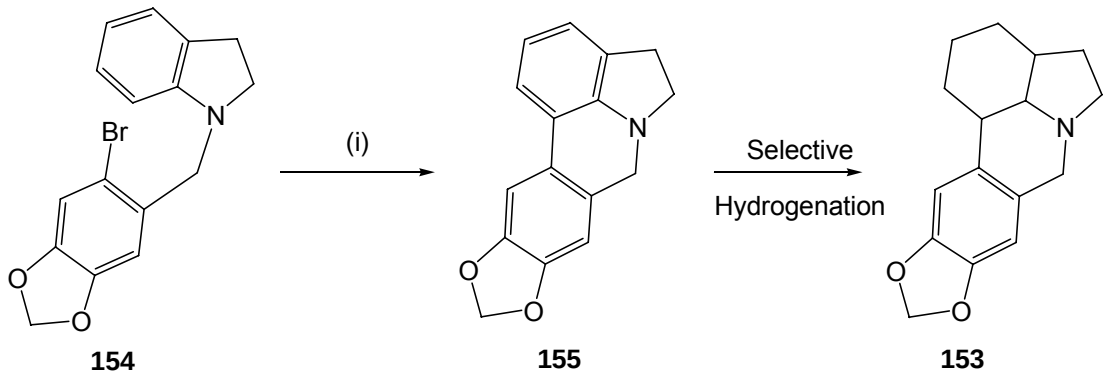


150 **151** **152**

Figure 20

Pyrrolophenanthridines have been isolated from the plants of the family *Amaryllidaceae*.[69] These alkaloids have been found to exhibit antitumour, antiviral and insect antifeeding activity. Pyrrolophenanthridones such as hippadine **152**, reversibly inhibit fertility in male rats.[70,71]

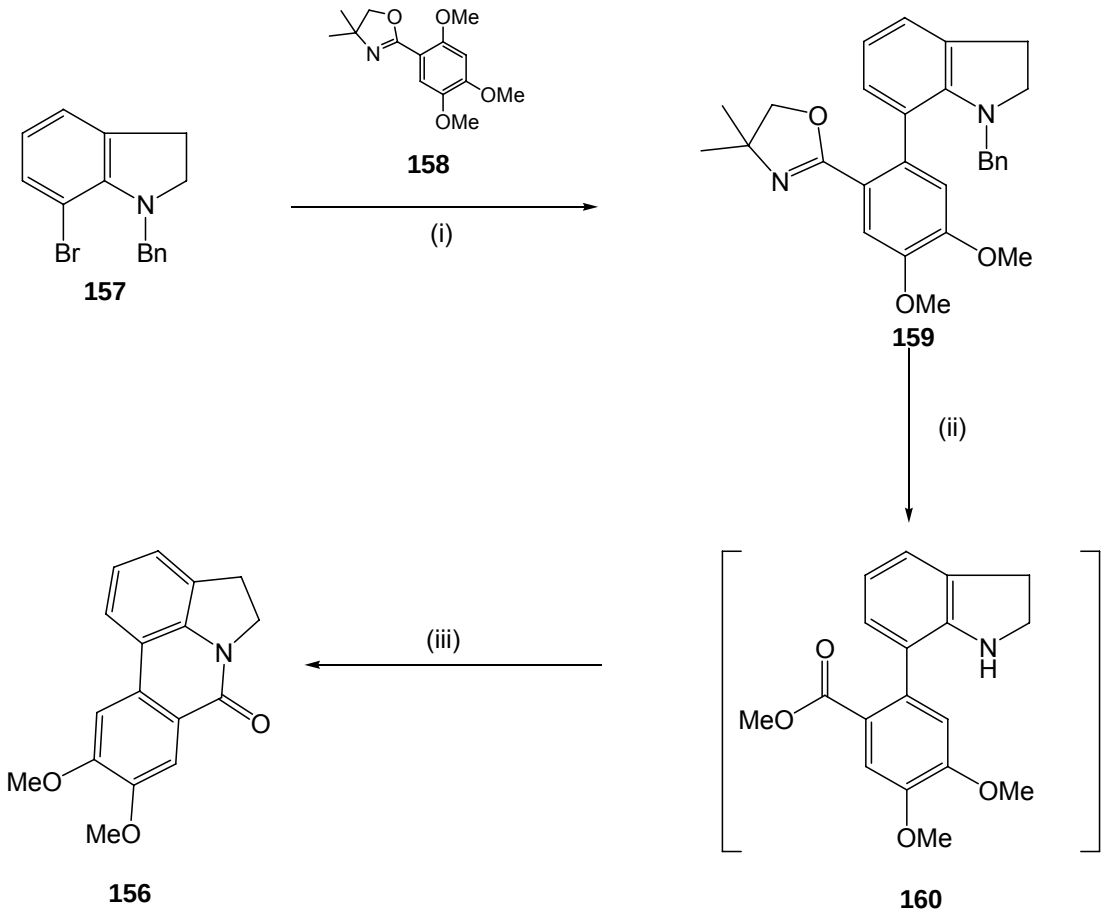
Harayama *et al.*[64] and Shao *et al.*[69] recently synthesized a variety of pyrrolophenanthridines, including (±)-γ-lycorane **153** from **154**, using Pd-mediated intramolecular biaryl coupling followed by selective hydrogenation of **155**, as shown in **Scheme 26**.



154 **155** **153**

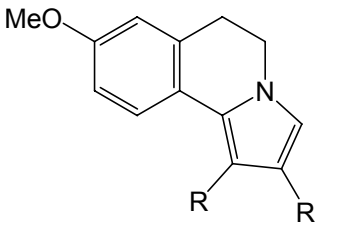
Scheme 26: (i) $Pd(OAc)_2$, P(*o*-tol)$_3$, K_2CO_3, DMF.

Oxaoassoanine **156**, a pyrrolophenanthridone, was synthesized by Meyers and Hutchings[70] by coupling an aryl Grignard (from 1-benzyl-7-bromoindole **157**) with an aryl oxazoline **158**. The biaryl compound **159** was partially hydrolysed, trans-esterified and the benzyl group removed by hydrogenation to afford a free amine **160** that spontaneously underwent acylation, with the adjacent carbomethoxyl, to the pyrrolophenanthridone **156**, **Scheme 27**.



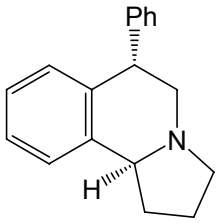
Scheme 27: (i) Mg, THF, BrF_2CCF_2Br, rt then **158**, ∆, 12-15 h (ii) 10 % H_2SO_4/EtOH, ∆, 24 h then NaOMe/MeOH, ∆, 3 h (iii) Pd/C, AcOH, MeOH, H_2.

Some of the pyrrolo[2,1-*a*]isoquinolines exhibit antineoplastic and antidepressant activities. The pyrrolo[2,1-*a*]isoquinoline bis(carbamate) **161** has recently been shown to possess antileukemic activity, *in vivo*, against P388 leukemia, **Figure 21**.[72] A recent study by Maryanoff *et al*.[73] showed that a variety of pyrrolo[2,1-*a*]isoquinolines, including 6α-phenylpyrrolo[2,1-*a*]isoquinoline **162**, inhibited serotonin (5-HT), norepinephrine and dopamine uptake in the central nervous system. As a result, these compounds can be used in the treatment of depression, obesity, obsessive-compulsive disorders and alcohol abuse.



R = $CH_2OCONHCH(CH_3)_2$

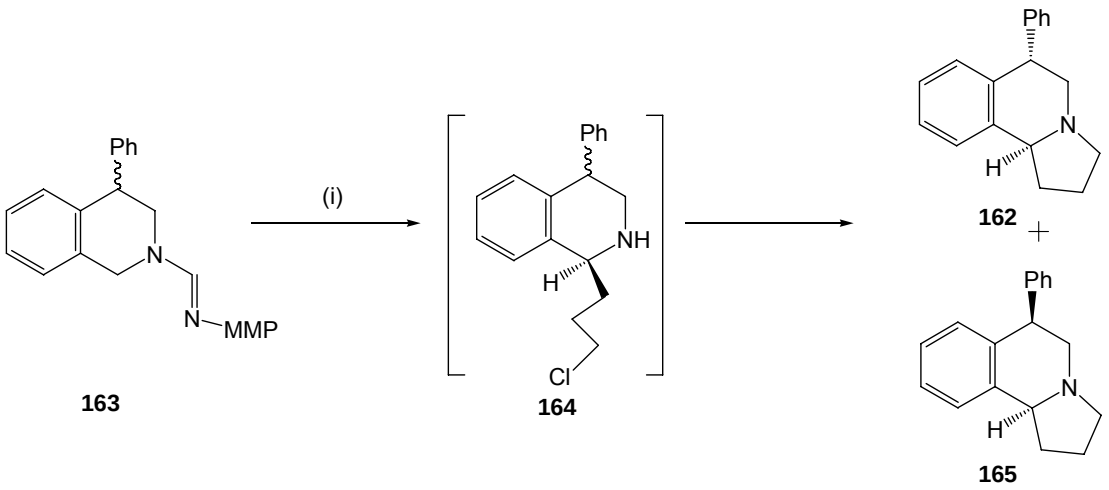
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162

Figure 21

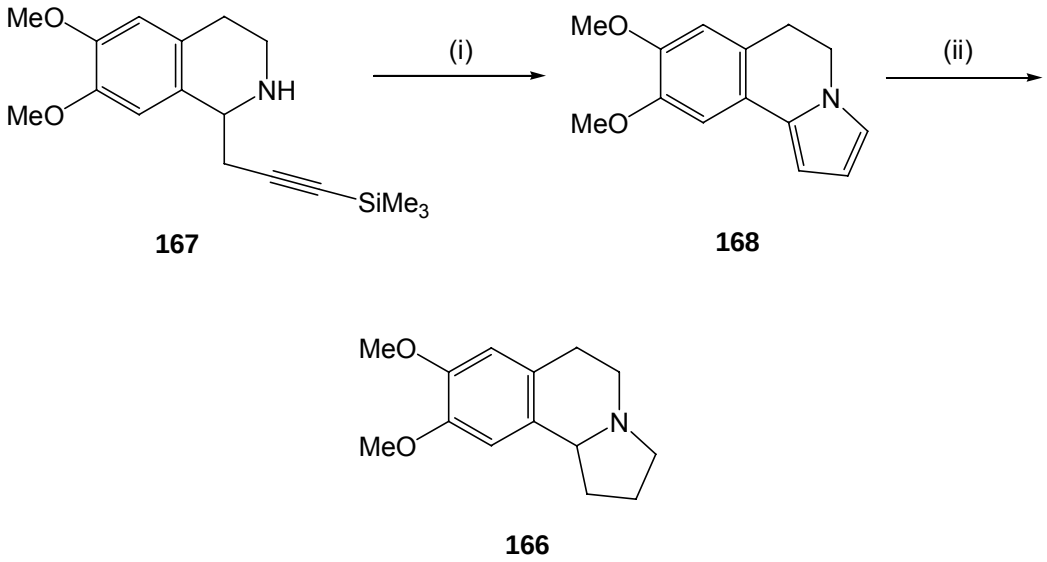
A synthesis of 6α-phenylpyrrolo[2,1-*a*]isoquinoline, using chiral formamidines, was accomplished by Meyers and Guiles.[74] The chiral formamidine formed **163** was first exposed to alkylating conditions (*s*-BuLi, 1-chloro-3-iodopropane, -100 ºC) and then to hydrazine in ethanol, in order to produce the secondary amine **164**. This amine spontaneously cyclized to form **162** and **165** in a 13:1 ratio in a greater than 80% yield as shown in **Scheme 28**.



163 **164** **162** + **165**

Scheme 28: (i) R'Li, $Cl(CH_2)_3I$ then NH_2NH_2, H_3O^+.

Chinese folk medicine for the treatment of colds, stomach aches and rheumatism often makes use the extracts of the plant *Carduus crispus.*[75] These extracts contain the pyrrolo[2,1-*a*]isoquinoline alkaloid, crispine A **166**, which displays antitumour activity. Knölker and Agarwal.[76] synthesized this natural product by means of a silver(I)-promoted oxidative cyclization of a trimethylsilyl alkyne **167** to **168**, followed by chemoselective hydrogenation as depicted in **Scheme 29**.



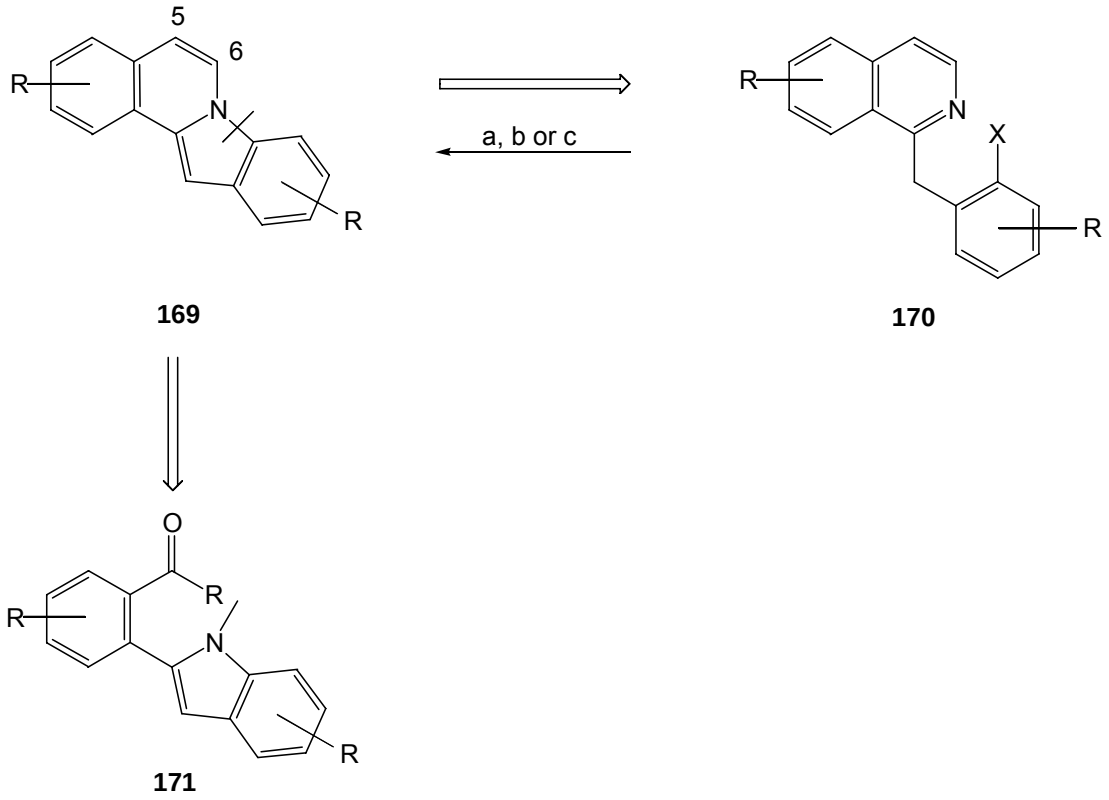
167 **168** **166**

Scheme 29: (i) AgOAc, CH_2Cl_2, rt, 14 h (ii) 5 mol % Rh/C, H_2, AcOH/MeOH, rt, 192 h.

In conclusion, it can seen that indolo[2,1-*a*]isoquinolines and related analogues possess a variety of biological activities. Although many methods have been employed in their synthesis, it is always important to improve and develop new, shorter, higher yielding methods of synthesizing these compounds. Various indolo[2,1-*a*]isoquinoline derivatives have been synthesized previously in our laboratories,[77] one of which will be discussed in the next section.

1.4. Previous Syntheses of Indolo[2,1-a]isoquinolines

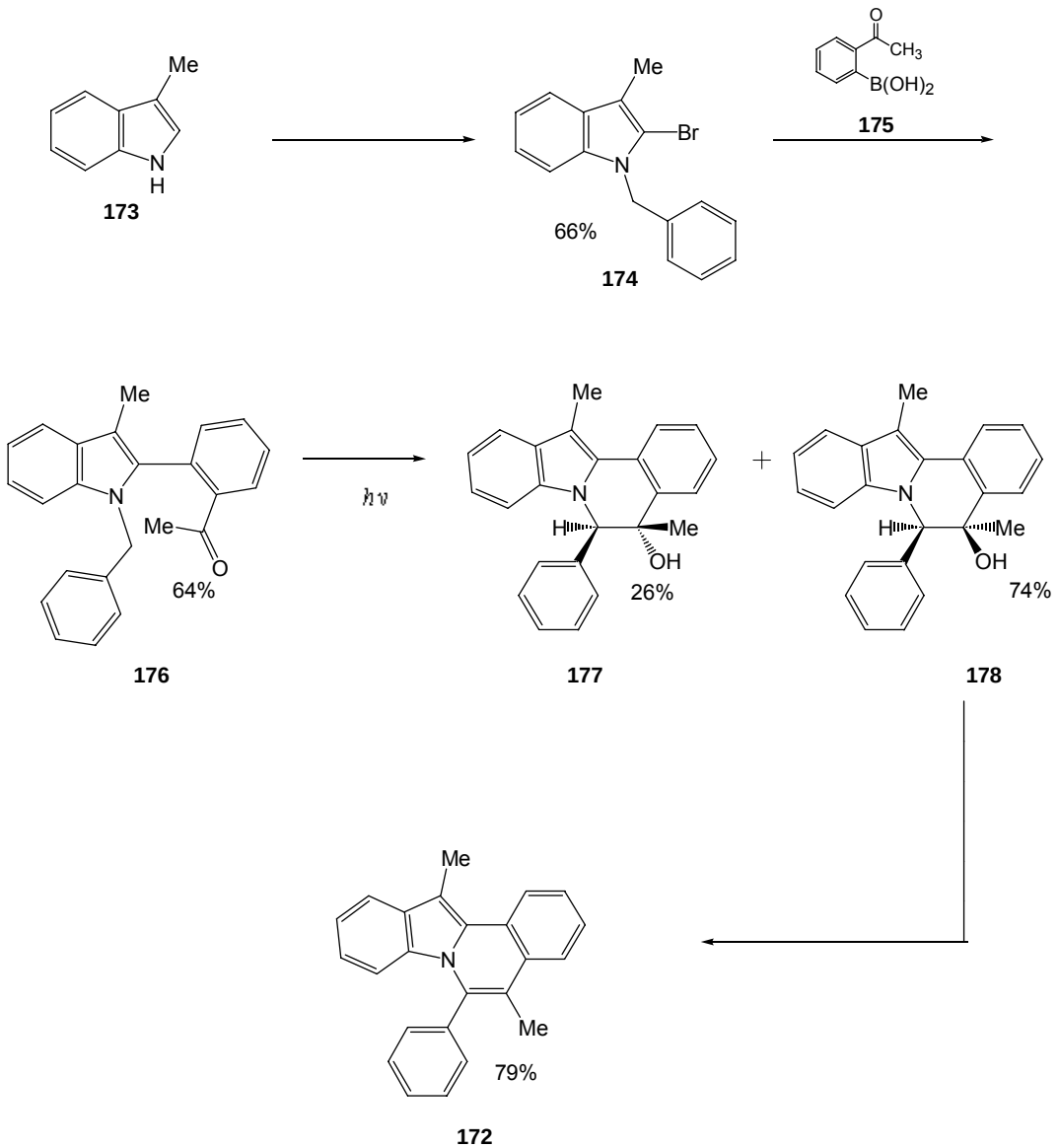
As mentioned before, many polyfused heteroaromatics are of interest due to their potential DNA intercalating and reverse transcriptase inhibiting abilities. Due to the importance of indolo[2,1-*a*]isoquinolines **8**, many methods have been employed in the formation of the indolo[2,1-*a*]isoquinoline nucleus. The most common disconnection is between the isoquinoline nitrogen and the benzene ring, which forms part of the indole nucleus. **Scheme 30** shows the retrosynthesis from the indoloisoquinoline derivative **169** to the isoquinoline derivative **170**. Radical[58,67] (a), base[53] (b) and benzyne[50] mediated (c) ring closure methods have been used in the construction of this bond.



Scheme 30: (a) X=Br, AIBN, Bu_3SnH[68,78]; (b) X=Br, K_2CO_3, DMF, reflux, 3d[63]; (c) X=Cl, nBuLi, THF, -100°C[61].

The synthesis of indolo[2,1-*a*]isoquinolines are of great interest to our research group and makes use of a novel disconnection at C-5 and C-6, shown in **Scheme 30**.

In our laboratories de Koning and co-workers have used the Suzuki-Miyaura coupling reaction[32], as well as well-developed reaction conditions discovered for the formation of aromatic rings[39,79,77] ($KOBu^t$, hv, DMF, 80 °C) to synthesise the indolo[2,1-*a*]isoquinoline derivative **172**, shown in **Scheme 31**.



Scheme 31: (i) NBS, CCl_4, 3 h then aq. NaOH, BnBr (ii) **175**, 10 mol % $Pd(PPh_3)_4$, aq. Na_2CO_3, DME (iii) $KOBu^t$, DMF, 80 °C (iv) 15 mol % TsOH, CH_2Cl_2, rt, 24 h.

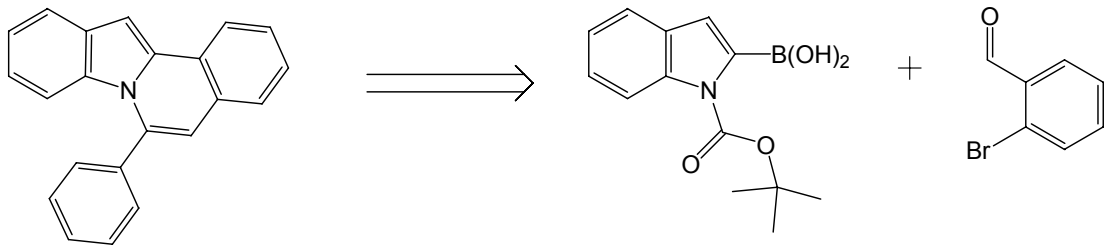
The first step of the reaction was to synthesise the 1-benzyl-2-bromo-skatole **174** using published chemistry.[80] Suzuki-Miyaura coupling of **174** with the boronic acid **175** resulted in the coupled product **176** being obtained in 64% yield. Exposure of **176** to the novel reaction conditions for forming aromatic

rings ($KOBu^t$ in DMF and a light source) resulted in the formation of diastereoisomers **177** and **178** in a 1:3 ratio. The major diastereoisomer, obtained in 74% yield, was found to be **178** by ^1H NOE NMR spectroscopy. The major diastereoisomer was exposed to 15 mol% TsOH to afford the indolo[2,1-*a*]isoquinoline derivative **172** in 79% yield.[77]

1.5. Aims

The simple reaction conditions and high yields of the synthesis described in **Scheme 31**, forms the basis of this MSc project. Using these conditions we will attempt to synthesize the indolo[2,1-*a*]isoquinoline skeleton of the dibenzopyrrocoline alkaloids **6** and **7**.

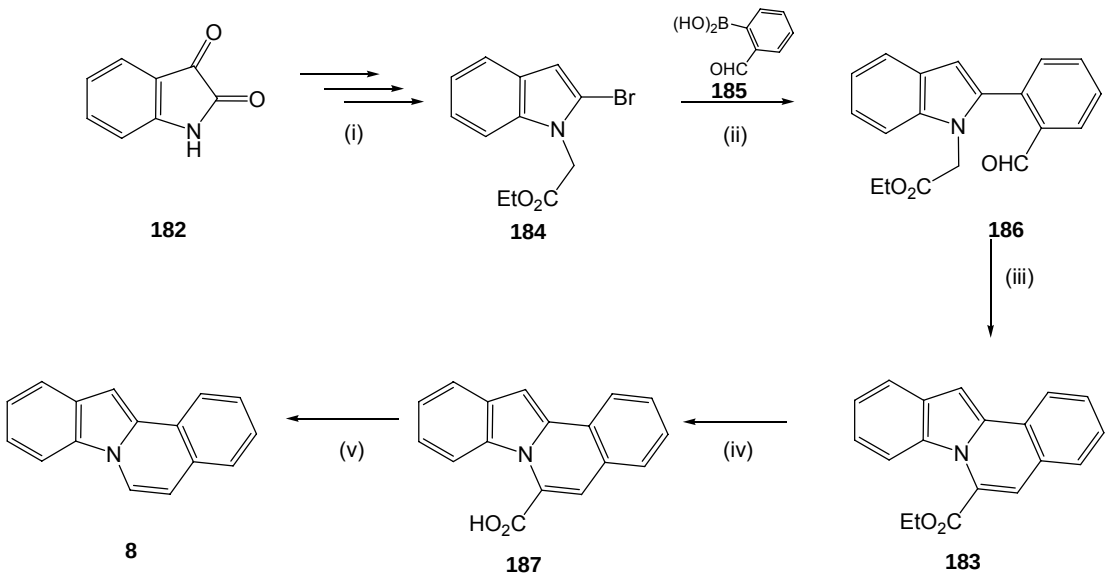
The first part of the project will involve the synthesis of the phenyl substituted indolo[2,1-*a*]isoquinoline **179**, as an extension to our previous work. Examination of the disconnection in **Scheme 32** shows that the target **179** can be disconnected to the 1-(tert-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **180** and 2-bromobenzaldehyde **181**. In **Chapter 2** the initial attempt to synthesize **179** starting from indole, the problems which occurred and the alternative employed, using isatin **182**, will be discussed.



179 **180** **181**

Scheme 32

Once **179** is successfully synthesized we will go on to synthesize ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate **183** using the same reaction conditions. Starting from isatin **182** we will first synthesize ethyl 2-(2-bromo-1*H*-indol-1-yl)acetate **184**, which can then be coupled with 2-formylphenylboronic acid **185** to form ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate **186**. Aromatisation of **186** using $KOBu^t$ in DMF at 80 °C in the presence of a light source, would afford **183**. The theory behind this is that the ester group would be easier to remove by decarboxylation than the phenyl substituent and would thus result in the formation of the indolo[2,1-*a*]isoquinoline skeleton **8** via the acid **187**, **Scheme 33**.

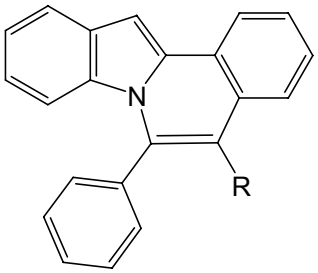


Scheme 33: (i) (a) CaH_2, $CH_3CH_2CO_2CH_2Br$, DMF, 45 °C, 24h (b) PCl_5, C_6H_6, rt, 24h (c) Zn powder (14 equiv.), AcOH, 5 min (d) $POBr_3$, CH_2Cl_2, rt (ii) $Pd(PPh_3)_4$ (10 mol %), **185**, aq. Na_2CO_3, DME, reflux (iii) $KOBu^t$, DMF, rt (iv) Δ, H^+ (v) DCC, DMAP, Bu_3SnH.

Chapter 2: Results and Discussion

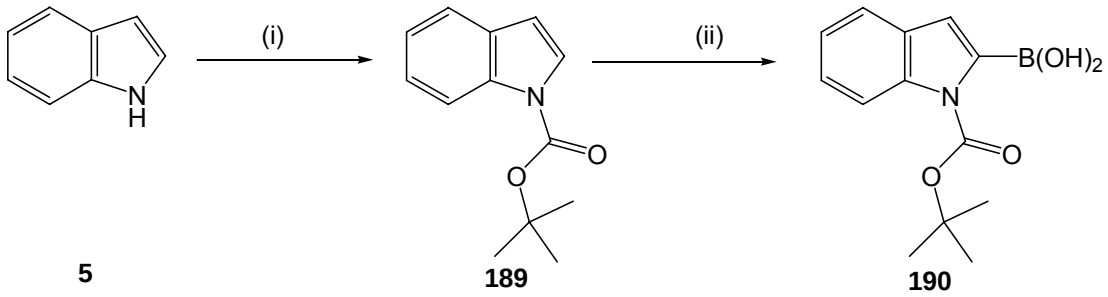
2.1. The Attempted Synthesis of 6-Phenylindolo[2,1-a]isoquinoline **179** *and 5-Methyl-6-phenylindolo[2,1-a]isoquinoline* **188**

The first two steps in the synthesis of compounds **179** and **188**, **Figure 22**, were identical to that in the literature and were performed using well-documented methodology[81,82], **Scheme 34**.



179: R = H
188: R = Me

Figure 22



5 **189** **190**

Scheme 34: (i) Boc_2O (1.3 equiv.), DMAP (5 mol %), THF, rt, 24 h. (ii) TMP (1.3 equiv.), n-BuLi (1.2 equiv.), $B(OMe)_3$ (5 equiv.), THF.

The first step involved the protection of the indole nitrogen with a Boc group to afford *tert*-butyl 1*H*-indole-1-carboxylate **189**, as we wanted to use the Boc group as a director for *n*-BuLi deprotonation and thus introduce substituents at the 2-position of the indole nucleus. We commenced the synthesis by dissolving indole in THF and then adding Boc_2O (1.3 equiv.) and DMAP (5 mol %). The reaction mixture was stirred at rt for 24 h, under nitrogen, before

it was extracted and then purified, by distillation, to afford the desired product, **189**, as a clear oil in 79% yield. The ^{1}H NMR spectrum showed a singlet at 1.66 ppm, integrating for 9 protons, which is characteristic of the three methyl groups attached to the quaternary carbon of the Boc group. The singlet at 7.89 ppm corresponding to the N-H proton had also disappeared, from the starting material, indicating that **189** had been formed.

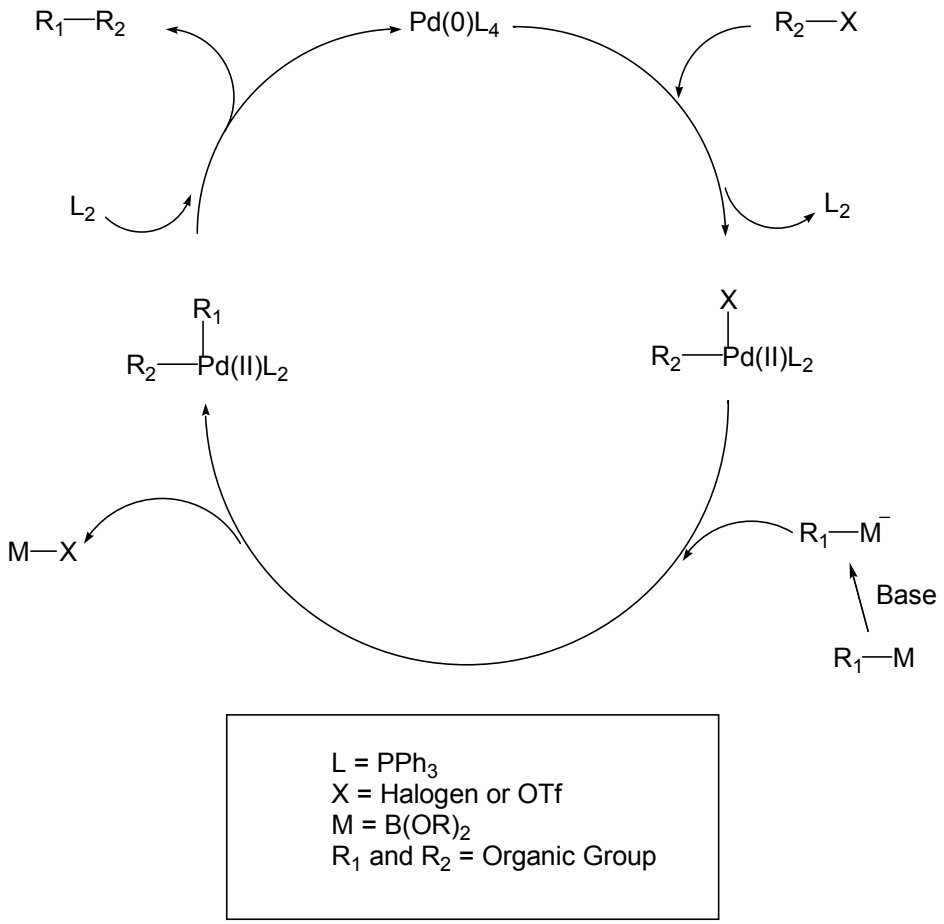
The next step was to synthesize 1-(*tert*-butoxycarbonyl)-1*H*-indolyl-2-boronic acid, **190**, by using the Boc substituent as a director to lithiate the 2-position of the indole, so that the boronic acid of **190** would be placed solely at the 2-positon.

The synthesis of **190** commenced by dissolving TMP (1.3 equiv. relative to **189**) in THF in a 2-neck, round bottom flask, equipped with a dropping funnel that contained a solution of *tert*-butyl 1*H*-indole-1-carboxylate in THF. The reaction temperature was lowered to −78 °C and *n*-BuLi (1.2 equiv.) was added dropwise using a syringe over 5 mins. After increasing the temperature to rt for 30 mins and then lowering it to −78 °C, the solution in the dropping funnel was added. The reaction was then stirred for 1.5 h at this temperature, $B(OMe)_3$ (5 equiv.) was added and the solution was stirred for a further 0.5 h at −78 °C. The reaction mixture was warmed up to r.t, acidified with a 1M aqueous HCl solution and then the organic material was extracted into ether. The organic solvent was removed to afford a 0.1 M solution, cold hexane was added and the boronic acid, **190**, precipitated out as a white solid in 65% yield. The ^{1}H NMR spectrum showed that the doublets at 6.55 ppm and 7.55 ppm, corresponding to protons 2-H and 3-H, had disappeared and that two singlets appeared at 7.50 ppm (corresponding to the 3-H proton) and 7.54 ppm (corresponding to 2×OH protons), indicating that the boronic acid, **190**, had been formed.

One of the key steps, in our synthesis of indolo[2,1-*a*]isoquinolines, used Suzuki-Miyaura coupling methodology.[83] This coupling involved a palladium catalyst, which aided in the cross coupling of a halogen or triflate and a boron-

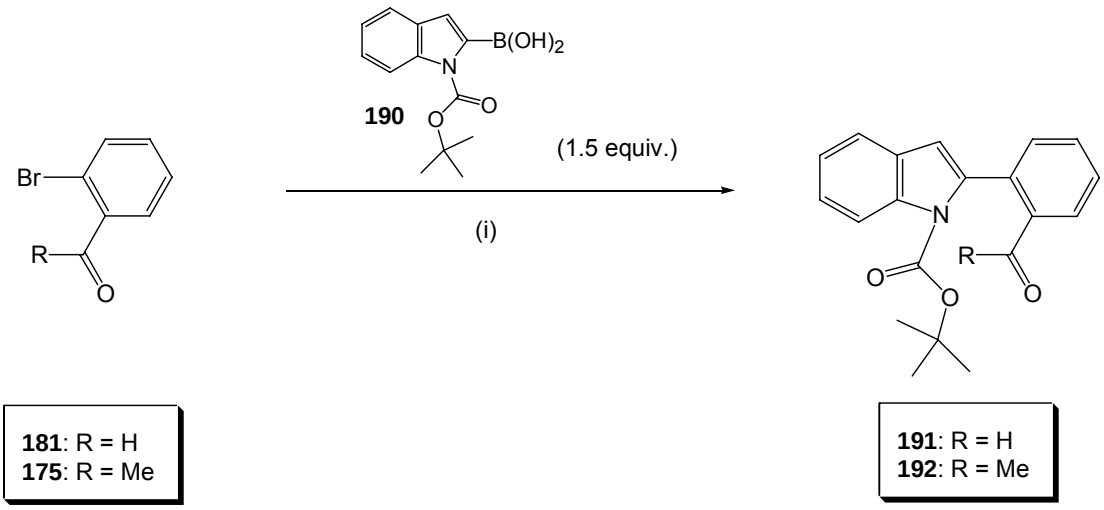
containing compound, which was a boronic acid. The methodology also makes use of a base which is believed to form the borate of the the boronic acid. **Scheme 35** shows the believed basic catalytic cycle of the palladium catalyst. First the halogen or triflate partner undergoes reaction with the Pd(0) phosphine complex by means of an oxidative addition to form a Pd(II) species. The R_1 nucleophilic species, which is the boron-containing partner in this case, is transferred from the metal to the Pd(II) complex in a step known as transmetallation. The new Pd(II) complex, having the two organic ligands bound, will then undergo reductive elimination to yield the coupled product and the Pd(0) catalyst, which is ready for another catalytic cycle.[84]

tert-Butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate, **191**, and *tert*-butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate, **192**, were synthesized using this key palladium mediated step.



Scheme 35: Catalytic cycle of Pd(0) species in Suzuki-Miyaura coupling.

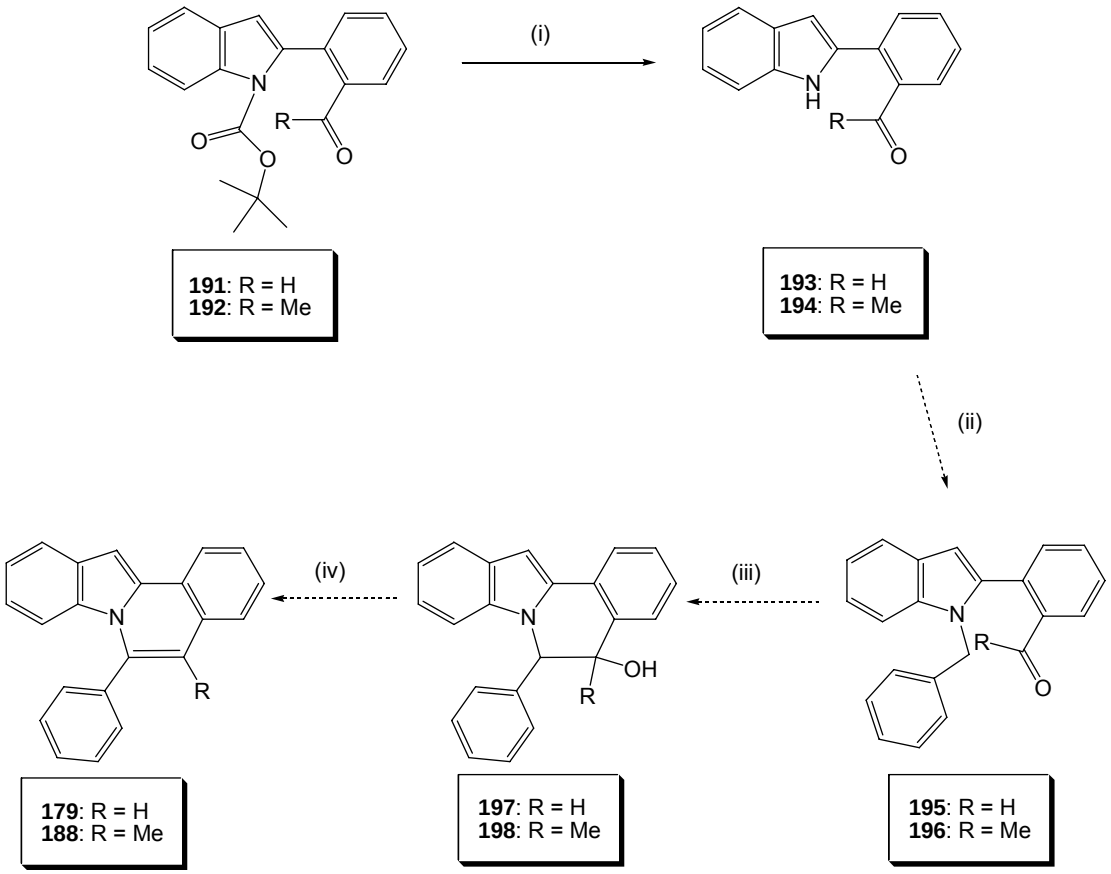
In the synthesis of, **191**, 2-bromobenzaldehyde, **181**, 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid, **190**, (1.5 equiv.) and DME were combined and degassed in a dropping funnel before being added to a round bottom flask, containing $Pd(PPh_3)_4$ (10 mol %) (**Scheme 36**). The base, a 2M Na_2CO_3 solution (5 equiv.) was degassed and added to the reaction mixture. The resulting mixture was heated under reflux for 72 h to obtain *tert*-butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate **191**, after purification by silica gel column chromatography, as a white solid in 85% yield. The two singlets at 7.50 and 7.54 ppm in the ^1H NMR spectrum of **191** had disappeared and two new singlets at 6.60 ppm (corresponding to the 3-H proton) and 10.01 ppm (corresponding to the aldehyde proton) had appeared. The triplet at 7.25 ppm and the multiplet at 7.35 ppm, integrating for two protons, were now two multiplets at 7.26-7.47 ppm and 7.51-7.66 ppm and integrated for six protons. The ^{13}C NMR spectrum showed a peak at 191.6 ppm, which is characteristic of the carbon of an aldehyde carbonyl. The spectrum also showed the presence of seven aromatic carbons bearing no hydrogen atoms, nine aromatic carbons bearing one hydrogen atom and a methyl peak at 27.5 ppm. The IR spectrum showed a carbonyl peak at 1698 cm^{-1} and an ArC=C peak at 1600 cm^{-1}. The high-resolution mass spectrum showed a molecular ion peak at *m/z* 321.1323 ($C_{20}H_{19}NO_3$ requires 321.1365), indicating that **191** had been formed. In addition, the melting point of **191** was found to be 127-128 °C.



Scheme 36: (i) $Pd(PPh_3)_4$ (10 mol %), 2M Na_2CO_3 (5 equiv.), DME, reflux, 3 days.

In the synthesis of *tert*-butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate, **192**, the same procedure as above was carried out except that 1-(2-bromophenyl)ethanone **175** was cross-coupled to **190** instead of 2-bromobenzaldehyde **181**. After purification, **192** was obtained as an orange-pink solid in 63% yield. The two singlet peaks at 7.50 and 7.54 ppm on the ^{1}H NMR spectrum had disappeared, as mentioned above; however the two new singlets formed were at 2.33 ppm (corresponding to the C**H$_3$**C=O) and at 6.48 (corresponding to the 3-H proton). The ^{13}C NMR spectrum showed a quaternary carbon corresponding to the ketone at 200.8 ppm and a peak at 28.6 ppm, corresponding to the acetyl methyl substituent. The IR spectrum was the same as mentioned above, except that there were two carbonyl peaks, one at 1731 cm^{-1} and the other at 1688 cm^{-1}. The high-resolution mass spectrum showed a molecular ion species at *m/z* 335.1530 ($C_{21}H_{21}NO_3$ requires 335.1521). The melting point of **192** was found to be 91-92 °C.

The next part of our synthesis involved the removal of the Boc protecting group on both **191** and **192**, followed by the reprotection of the free indole of 2-(1*H*-indol-2-yl)benzaldehyde **193** and 1-(2-(1*H*-indol-2-yl)phenyl)ethanone **194** with a benzyl substituent, to give **195** and **196**. In doing so we would have the methylene protons of the *N*-benzyl substituent which, being acidic, could be abstracted by means of a base. The resulting anion could then condense with the internal electrophilic aldehyde, or ketone, to afford the fused isoquinolines, **179** and **188,** after aromatisation of the intermediate alcohols, **197** and **198**, by the loss of water, **Scheme 37**.



Scheme 37: (i) Microwave, silica, 30s intervals (ii) NaH, DMF, BnBr, reflux (iii) $KOBu^t$, DMF, 80 °C, hv (iv) TsOH, CH_2Cl_2, rt.

The first attempt at removing the Boc protecting group of **191**, to form 2-(1*H*-indol-2-yl)benzaldehyde **193**, involved absorbing **191** onto silica[85], using ethyl acetate as a solvent, and then irradiating the silica in a microwave at 150 W at 30 sec. intervals. The reaction progress was monitored by TLC and after approximately 13 min. the reaction was stopped, as a mixture of products was formed and the starting material had begun to decompose. After purifying the reaction mixture by column chromatography, 30% of the starting material was recovered. The ^{1}H NMR spectrum of the only new product as shown by TLC proved to be very difficult to interpret, but it could be seen that the aldehyde proton as well as the methyl protons of the Boc group of the starting material **191** had disappeared. We speculated that as soon as the Boc protecting group was removed, the indole nitrogen condensed with the aldehyde to form **199**, **Scheme 38**.



193 **199**

Scheme 38

The ^{1}H NMR spectrum showed that the product **191** was not pure and the hydroxyl proton as well as the adjacent proton attached to the neighbouring carbon could not be detected.

The second attempt to remove the Boc protecting group of **191** involved the use of $AlCl_3$.[86] *tert*-Butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate **191** was dissolved in CH_2Cl_2 and the temperature of the resulting solution was lowered to 0 °C. $AlCl_3$ (1.3 equiv.) was added and the reaction mixture was stirred for 1h before being extracted. After purification by column chromatography, the products formed were analyzed by ^{1}H NMR spectroscopy. The spectra of all the products formed were very complicated and the products could not be readily characterized.

Due to the lack of success in deprotecting **191** under the acidic conditions used so far, we decided that we would attempt to deprotect **192**, using alternative methods. If we were successful in deprotecting the slightly less reactive ketone **192**, the same methodology could be attempted on the aldehyde **191**.

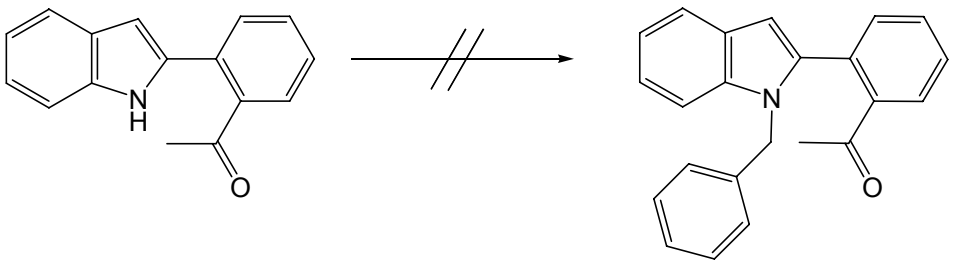
The first alternative required dissolving **192** in CH_2Cl_2 and then adding TFA (1.5 equiv.).[87] The reaction mixture was stirred for 6h at rt, treated with Na_2CO_3 and then the organic material extracted into CH_2Cl_2. After purification by silica gel column chromatography, a yellow residue was obtained that was uncharacterizable by ^{1}H NMR spectroscopy.

Since acidic conditions did not work in the removal of the Boc protecting group, we decided to use slightly basic conditions. *tert*-Butyl 2-(2-

acetylphenyl)-1*H*-indole-1-carboxylate **192** was dissolved in THF and a 6M sodium methoxide in methanol solution (3 equiv.) was added.[88] The reaction mixture was stirred for 0.5h at rt. After work up, using 1M HCl, the organic material was extracted and purified by column to afford the desired product, 1-(2-(1*H*-indole-2-yl)phenyl)ethanone **194**, as a whitish-yellow solid in 64% yield. The ^{1}H NMR spectrum showed that the peak at 1.29 ppm, corresponding to the methyl groups attached to the quaternary carbon of the Boc group, had disappeared and that the indole proton appeared as a singlet at 2.77 ppm. The splitting pattern of the aromatic protons had also changed significantly: Instead of a doublet, doublet, multiplet and singlet at 8.24, 7.73, 7.22-7.55 and 6.48 ppm respectively, there was now a multiplet, doublet, triplet, triplet, multiplet, triplet and singlet at 7.55-7.60, 7.48, 7.38, 7.29, 7.16-7.23, 7.08 and 6.53 ppm respectively. The ^{13}C NMR spectrum showed that the methyl peak at 27.4 ppm and the **C**$(CH_3)_3$ at 83.2 ppm, belonging to the Boc substituent of the starting material, had disappeared indicating that the desired deprotection was successful and that **194** had formed.

Having found a successful method for the removal of the Boc substituent of **192**, we decided that we would continue with the synthesis of 5-methyl-6-phenylindolo[2,1-*a*]-isoquinoline **188**, before attempting to remove the Boc protecting group of the related substrated **191** using this method.

The next step in this synthesis was the reprotection of the indole nitrogen, using benzyl as the protecting group, to form 1-(2-(1-benzyl-1*H*-indol-2-yl)phenyl)ethanoate **196**. A solution of **194** in THF was lowered to a temperature of –20 °C and NaH (1 equiv.) was added. The solution was warmed up to rt and after stirring for 3h, benzyl bromide (1 equiv.) was added drop wise. The reaction mixture was stirred, at rt, for a further 72h before it was extracted with dichloromethane. The organic residue, after removal of the organic solvent, was purified by column chromatography. Three products were isolated but all were uncharacterizable by ^{1}H NMR spectroscopy (**Scheme 39**).



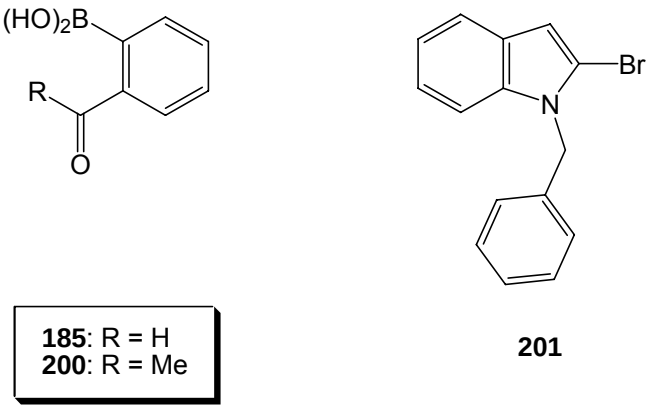
194 **196**

Scheme 39: BnBr (1 equiv.), NaH (1 equiv.), THF, -20 ˚C → r.t.

As a result of the problems encountered with the removal of the Boc group of **191** and benzylation of the indole nitrogen of **194** during the synthesis of 6-phenylindolo[2,1-*a*]isoquinoline **179** and 5-methyl-6-phenylindolo[2,1-*a*]isoquinoline **188**, it was decided that we pursue an alternative route to the synthesis of the desired products.

2.2 The Alternative route to the Synthesis of 6-Phenylindolo[2,1-a]-isoquinoline **179**

The first change in the new synthesis we wished to attempt was to swop the bromine and boronic acid groups around, hence giving compounds **185**, **200** and **201**, (**Figure 23**) as potential partners for the envisaged Suzuki-Miyaura coupling reaction. The indole would have the N-benzyl substituent in place before the coupling and thus avoid the deprotection and reprotection strategy with a benzyl group as performed previously.



185: R = H
200: R = Me

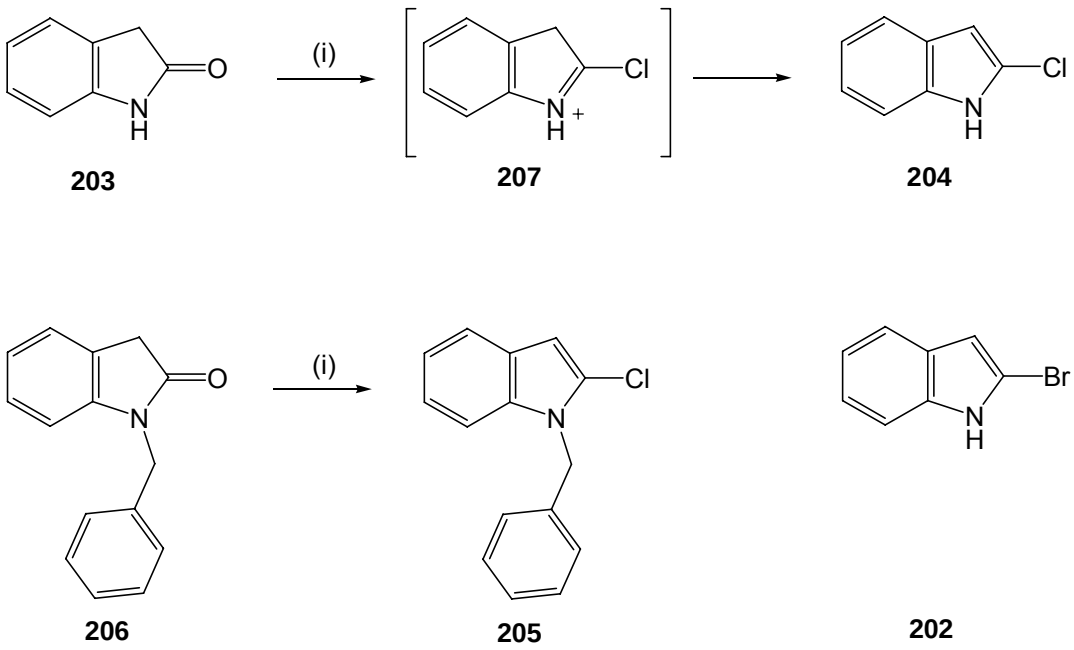
201

Figure 23

Due to the fact that 2-acetylphenyl boronic acid **200**, was not commercially available, while 2-formylphenylboronic acid **185** was, it was decided that we would only continue with the synthesis of 6-phenylindolo[2,1-*a*]-isoquinoline **179**, from 2-formylphenylboronic acid, using the alternative route.

Many chemists have synthesized 2-bromoindole **202** by using Bergman's conditions.[89] This reaction involves the use of *t*-BuLi, which is not only expensive, but *t*-BuLi also highly flammable and toxic. For these reasons it was decided that we would begin with oxindole **203**, which we hoped we could *N*-benzylate, followed by the removal of the oxygen of the oxindole and replace it with a bromine. Finally aromatisation would afford **201**. Powers[90] has synthesized 2-chloroindole **204** and *N*-benzyl-2-chloroindole **205** from oxindole **203** and *N*-benzyloxindole **206** respectively, using $POCl_3$. This

reaction involved the generation of Vilsmeier salts eg. **207** (salts of imino chlorides) by interaction of amides with phosphorus chloride, **Scheme 40**. Powers also found that *N*-benzyl-2-chloroindole was more stable then 2-chloroindole. We therefore thought that we would start by benzylating oxindole and using similar reaction conditions, using phosphorus oxybromide instead of phosphorus oxychloride, we would form **201**.

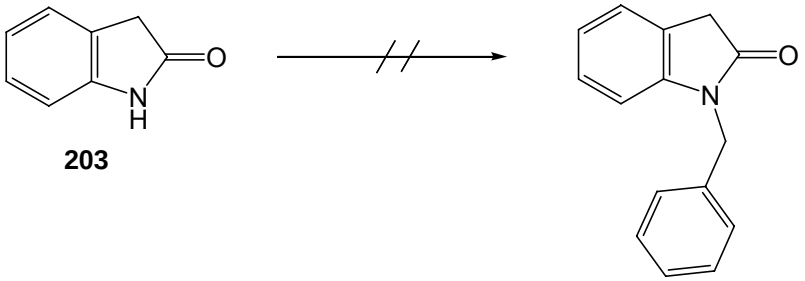


203 **207** **204**

206 **205** **202**

Scheme 40: (i) $POCl_3$, $CHCl_3$, reflux. Vilsmeier salt **207** is a protonated form of 2-chloroindole **204**.

We commenced the synthesis of **206**, by dissolving oxindole **203** in THF and then adding NaH (1 equiv.) to the solution, at rt. Benzyl bromide was added and the resulting reaction mixture was allowed to stir for 24h. The reaction was extracted, using dichloromethane, to afford a pinkish brown residue. After column purification three products were obtained, but were all uncharacterizable by ^{1}H NMR spectroscopy (**Scheme 41**).



203 **206**

Scheme 41: (i) BnBr, NaH, THF, rt (ii) BnBr, NaH, DMF, rt (iii) BnBr, K_2CO_3, DMF, microwave.

We decided to modify the procedure slightly by dissolving oxindole **203** in DMF, lowering the solution temperature to 0 °C and then adding NaH (1.1 equiv.).[91] The resulting mixture was stirred for 0.5h, at this temperature, before being allowed to warm up to rt. The reaction was stirred for 1h and benzyl bromide was added drop wise. After stirring the reaction for over 96h, the reaction was eventually aborted, as TLC indicated that only base line material, indicating probable decomposition, was present.

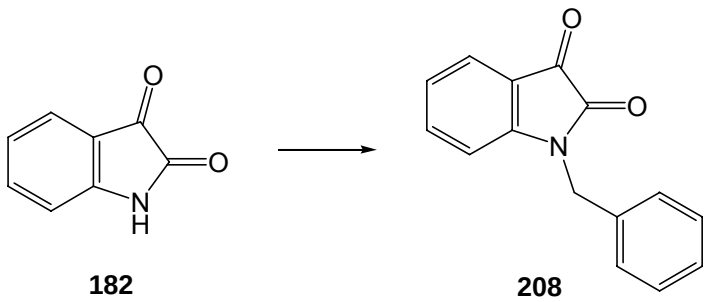
As a result of the previous two failures, we decided to attempt a different procedure. This method involved dissolving a mixture of oxindole **203**, K_2CO_3 (1 equiv.) and benzyl bromide (1.2 equiv.) in DMF and then exposing the resulting mixture to microwave radiation. The mixture was exposed for 2min. at 10 sec. intervals with a radiation of 150W. After the solution cooled, water was added and an orange precipitate formed. Purification by column chromatography afforded three products that were, once again, uncharacterizable by ^{1}H NMR spectroscopy.

Due to the reactivity of the 3-position, of oxindole **203**, it was thought that perhaps the base was not only deprotonating the nitrogen of the indole **5**, but the 3-position as well, thus resulting in a mixture of products being formed. A paper by Grunda[92] was also found, where the reactivity of the 3-position as well as the problems with benzylation of indole and oxindole, were discussed. In attempting to benzylate these two compounds, Grunda formed mono-, di- and tri-benzylated compounds, but in very low yields (less then 8%).

Looking back at Powers' work we found that he had in fact started with isatin, **182**, which had the 3-postion of oxindole blocked with a carbonyl group. We therefore decided to follow his procedure for the synthesis of 1-benzylindolin-2-one, **206**.

The first step in the synthesis of **206** was thus the *N*-benzylation of isatin. Two methods were used to synthesize 1-benzylindoline-2,3-dione **208**, **Scheme 43**. The first method used the procedure by Azizian et. al[93] and made use of microwave radiation. Isatin **182**, K_2CO_3 (1 equiv.) and benzyl bromide (3 equiv.) were dissolved in DMF and exposed to microwave radiation (150W) for 2 mins. After the resulting mixture had cooled down, water was added and an orange precipitate formed. The precipitate was collected via filtration, washed with water and recrystallised from ethanol to afford **208** as orange, needle-like crystals in 88% yield. The melting point of **208** was found to be 133-134 °C, which was relatively close to the literature value of 132-133 °C. The ^{1}H NMR spectrum included a singlet, integrating for two protons, at 4.94 ppm, which corresponded to the NC**H**$_2$Ph protons and a multiplet, integrating for five protons, between 7.25 and 7.38 ppm, corresponding to the benzyl aromatic protons. Amongst others, the ^{13}C NMR spectrum showed a peak at 44.0 ppm corresponding to N**C**H$_2$Ph carbon. The spectrum also showed the presence of an extra aromatic carbon bearing no hydrogens as well as five new aromatic carbons, bearing hydrogens, thus indicating that **208** had formed.

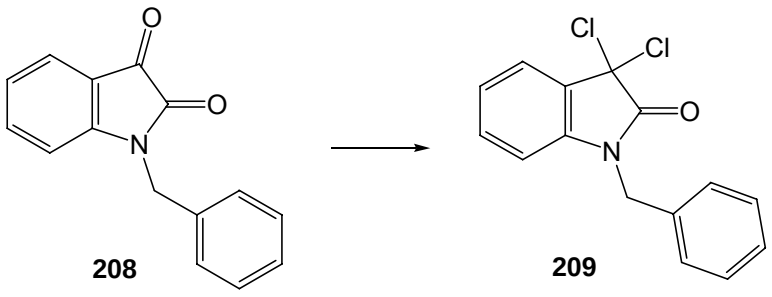
The second method used the procedure by Garden.[94] In this procedure isatin **182** and CaH_2 (1 equiv.) were dissolved in DMF. The solution was stirred for 1h at a temperature of 100 °C and then lowered to 40 °C so benzyl bromide could be added drop wise. The resulting mixture was stirred at 100 °C for a further 4 h before being poured into a 0.5M aqueous HCl solution, with vigorous stirring. An orange solid subsequently precipitated out, which was collected by filtration and purified by recrystallization from CH_2Cl_2 to afford **208** as orange needle-like crystals in 89% yield.



182 **208**

Scheme 42: (i) K_2CO_3 (1 equiv.), benzyl bromide (3 equiv.), DMF, microwave radiation, 2 min. or (ii) CaH_2 (1 equiv.) DMF, 1 h, 100 °C, then 40 °C, benzyl bromide, then 4h, 100 °C.

The next step in the synthesis of **206**, following Powers' procedure, was the functional group interconversion of the oxygen atom in the 3-position to two chlorine atoms to form 1-benzyl-3,3-dichloroindolin-2-one, **209**. PCl_5 was added to a solution of **208** in benzene. The resulting mixture was maintained at 25 °C for 24h to obtain a brown residue, after the solvent was removed, which was purified by column chromatography to afford **209** as a light yellow oil. On addition of ethanol, **209** precipitated out as a white solid in 81% yield. The melting point of **209** was found to be 125-126 °C. The ^1H NMR spectrum was slightly different to the starting material. The triplet at 7.48 ppm and the multiplet between 7.25 and 7.38 ppm now overlapped to form a multiplet between 7.22 and 7.39 ppm and integrated for 6 protons. The ^{13}C NMR spectrum had also changed slightly as the quaternary carbon corresponding to C-9 was not evident and now coincided with the signal at 124.2 ppm.

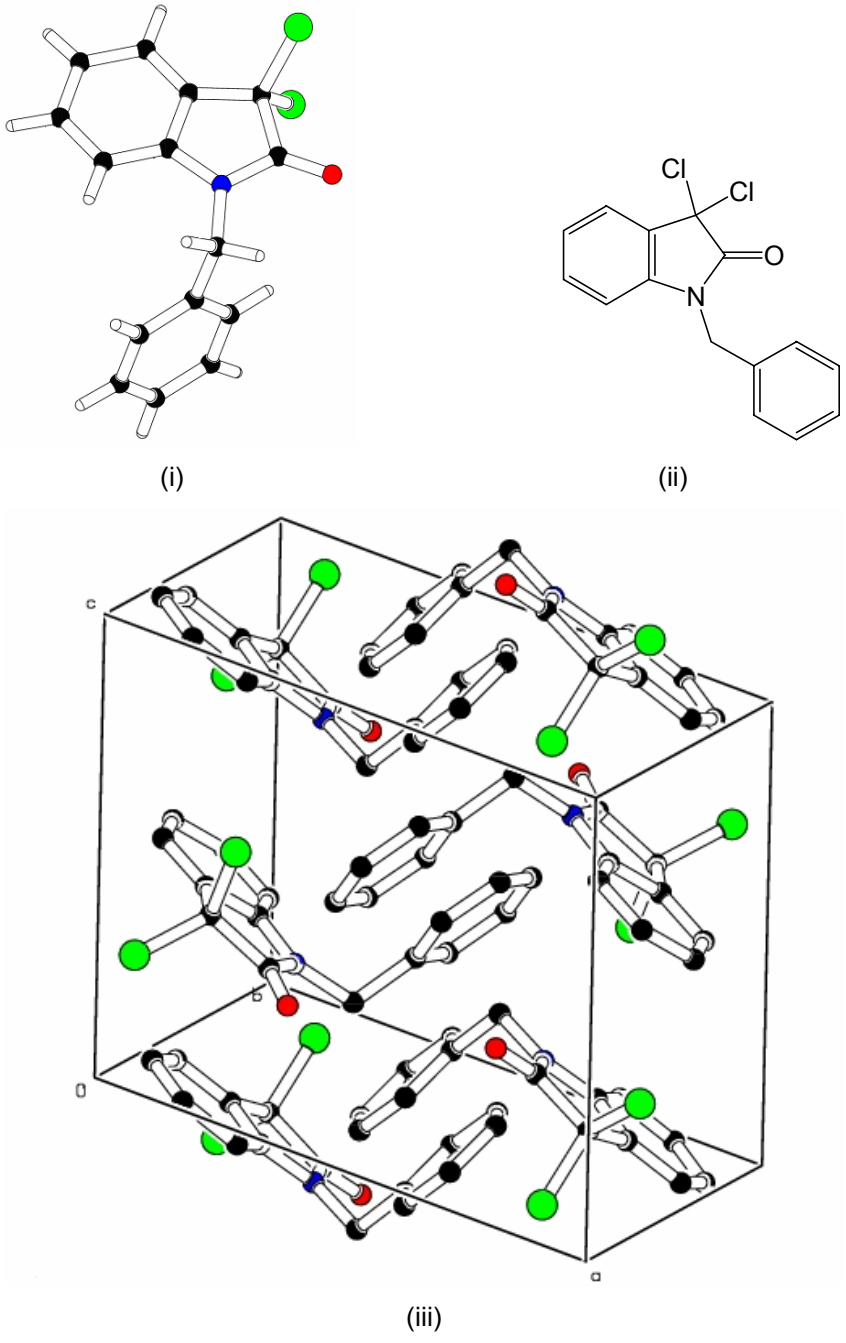


208 **209**

Scheme 43: (i) 1-benzyl-indolin-2,3-dione, benzene, PCl_5, 25 °C, 24 h.

After recrystallization of **209** from ethanol, rectangular, clear crystals were obtained and a crystal x-ray diffraction was performed, confirming that **209** had formed. The bond lengths and angles were found to be within the

average bond lengths and angles expected for this type of structure. Although the molecule itself was not centrosymmetric the crystal overall was found to be centrosymmetric (**Figure 24**).



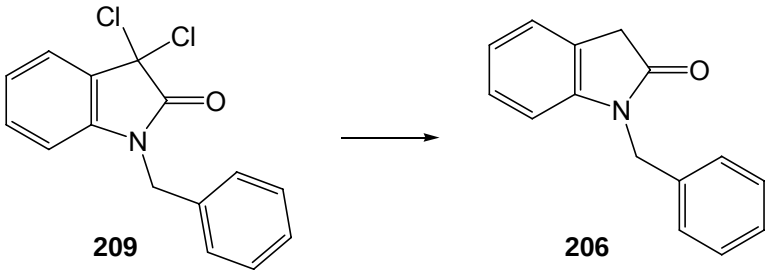
(i) (ii)

(iii)

Figure 24: (i) Crystal structure of 1-benzyl-3,3-dichloroindolin-2-one **209**. (ii) Molecular structure of **209**. (iii) Unit cell packing of **209** showing crystal is centrosymmetric.

Now that **209** had been synthesized, the next step was to form 1-benzylindolinone **206**. The first method applied was one of hydrogenation

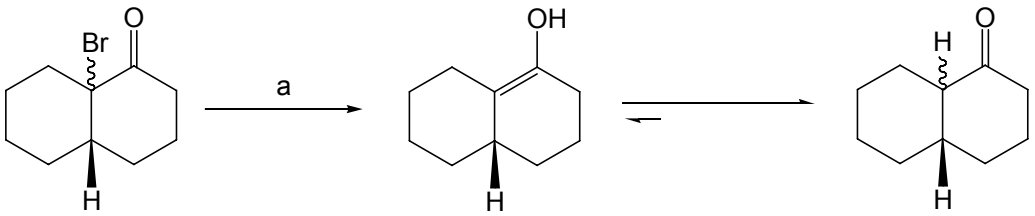
using Adams catalyst (PtO_2), in acetic acid. Adams catalyst (10 mol%) was therefor added to a solution of **209** in acetic acid (**Scheme 44**). The resulting mixture was stirred under a hydrogen atmosphere for 6h before the catalyst was removed by filteration and most of the solvent removed. The remaining acetic acid was neutralized with aqueous $NaHCO_3$ and the solution was extracted using CH_2Cl_2. The solvent was then removed and the organic residue obtained was purified by column chromatography to afford **206** as a yellow oil, that eventually, on standing, formed a white solid. Starting material was also recovered from the reaction. The yield for this reaction was variable and normally between 38 and 48%, although we did once manage to obtain **206** in 79%.



209 **206**

Scheme 44: (i) PtO_2 (10 mol%), AcOH, H_2 Atm., rt or (ii) Zn, AcOH, rt.

Zimmerman and Mais[95] did a study on the stereochemistry of the ketonization of the 1,9-enol of 1-decalone **210** and found that the debromination of α-bromoketones with zinc and a proton donor (such as acetic acid) generated unstable enols **211**, which tautomerised very readily to the ketone **212**, **Scheme 45**.



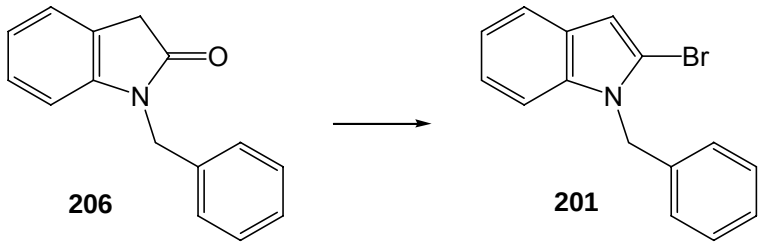
210 **211** **212**

Scheme 45: Zimmerman and co-workers' debromination with zinc and acetic acid (a) to form the unstable enol **211** that tautomerises to form the more stable ketone **212**

The second method attempted by us in order to dechlorinate **209** to afford **206** was hence Zimmerman's debromination reaction conditions. The synthesis commenced by adding activated zinc (15 equiv.) to a solution of **209** in acetic acid, over a 10 min. period. The resulting mixture was stirred for a further 10 min. before the zinc was filtered off, the solution neutralized with $NaHCO_3$ and then the organic material was extracted with diethylether. After purification by column chromatography, **206** was afforded as a white solid in 76% yield. The purification of **206** by recrystalisation was attempted using hot ethanol and dichloromethane layered with hexane, but only ethanol layered with hexane resulted in suitable crystals. The melting point was found to be 60-62 °C.

The ^{1}H NMR spectrum of 1-benzylindolin-2-one from both procedures showed a new singlet at 3.62 ppm, integrating for two protons, which corresponded to the 3-H protons. There was also a new signal in the ^{13}C NMR spectrum at 35.7 ppm, which corresponded to the carbon containing the same protons, indicating that **206** had formed.

Now that we had 1-benzylindolin-2-one **206**, the next step was to brominate the 2-positon, presumably by way of the enol, to obtain 1-benzyl-2-bromo-1*H*-indole **201** (**Scheme 46**). Various solvents, reagents known to replace a carbonyl with a halogen and additives were tried in order to try optimise the yield of this reaction. **Table 1** shows the various reaction conditions employed (all reactions were performed at reflux).



206 **201**

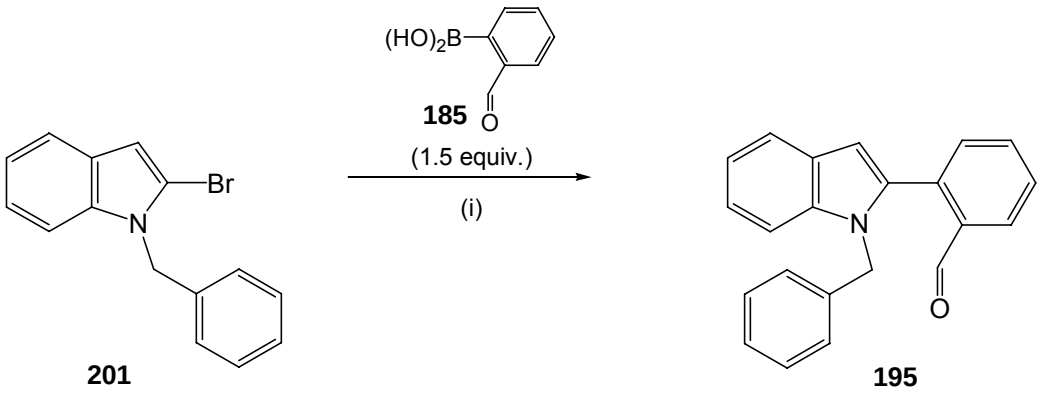
Scheme 46: See table 1 for reaction conditions

Solvent	Br Agent	Additive	Time of reflux (h)	Yield
DCM	$POBr_3$	imidazole[96]	72	50% + 20% SM
DCM	$POBr_3$	none	48	55%
DCE	$POBr_3$	none	24	-
DCE	$POBr_3$	imidazole	24	-
CH_3CN	PBr_3	none	72	7%

Table 1: DCM = dichloromethane, DCE = dichloroethane, CH_3CN = acetonitrile, $POBr_3$ = phosphorus oxybromide, PBr_3 = phosphorus tribromide, SM = starting material

From the table it can be seen that heating **206** at reflux in DCE, with and without an additive, only resulted in uncharacterizable material being isolated. In the case of **206** in CH_3CN, using PBr_3 as a brominating agent, a mixture of 5 different products were isolated. The desired product was formed in 7% yield as a white solid, while the other products formed were uncharacterizable by ^1H NMR spectroscopy. Heating 1-benzylindolin-2-one **206** at reflux in a solution of $POBr_3$ and DCM gave a much higher yield of 55%. Performing this reaction in the presence of imidazole however, resulted in 20% of the starting material being recovered and 50% of the desired product being isolated. Thus taking into account the unreacted starting material a yield of 88% of **201** was obtained. In solution **201** was found to decompose within a few hours but if left in the solid state, in a refrigerator, the compound was found to be stable for months. The melting point of **201** was found to be 87-89 °C. The ^1H NMR spectrum showed that the singlet peak at 3.62 ppm was no longer evident and a singlet, now integrating for one proton, appeared at 6.65 ppm. The ^{13}C NMR spectrum showed that the peak at 35.7 ppm, corresponding to 3-C had disappeared and a new peak, corresponding to the 3-C of the indole nucleus, at 104.5 ppm had appeared. The carbonyl peak at 175.1 ppm was no longer seen and a carbon, corresponding to the carbon attached to the bromine atom, had appeared. High-resolution mass spectroscopy showed a molecular ion species at *m/z* 285.0091 ($C_{15}H_{12}N^{79}Br$ requires 285.0153), indicating that **201** had formed. The IR spectrum showed the presence of a C-Br stretch at 691 cm^{-1} and an ArC=C stretch at 1605 cm^{-1}. There were no signals in the C=O region (1650-1750 cm^{-1}) supporting the evidence that the carbonyl had been successfully converted to the desired product **201**.

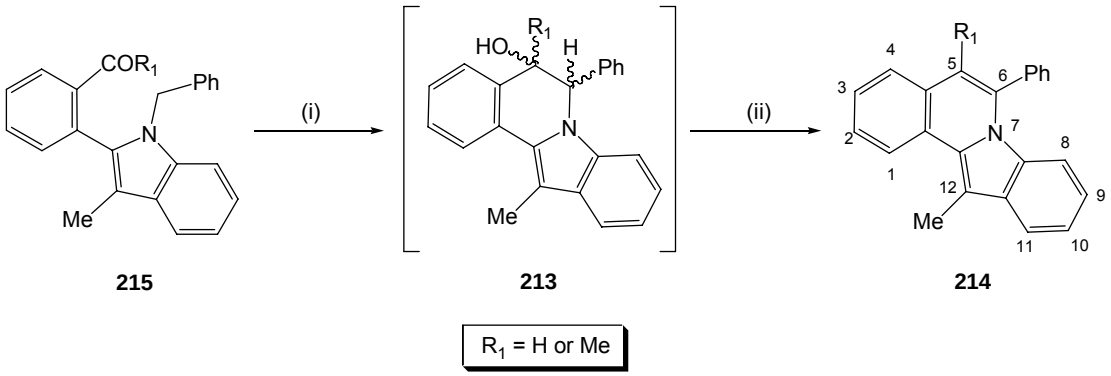
Now that the brominated compound **201** had been synthesized, the next step of the synthesis was to couple **201** with 2-formylphenylboronic acid **185**, using Suzuki-Miyaura coupling conditions. Under a nitrogen atmosphere, a solution of 1-benzyl-2-bromo-1*H*-indole **201**, 2-formylphenylboronic acid **185** (1.5 equiv.) and DME were added to a round bottom flask containing 10 mol % of $Pd(PPh_3)_4$. To the resulting mixture, a 2M Na_2CO_3 solution (5 equiv.) was added. The mixture was heated at reflux for 24h and then extracted using ethyl acetate. Once the organic solvent was removed, the residue was purified by column chromatography to afford 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde **195** as a yellow, viscous oil in 92% yield. The IR spectrum showed that the product **195** (**Scheme 47**) had formed, as there was a carbonyl carbon peak present at 1710 cm^{-1}. The ^1H NMR spectrum also showed the presence of an aldehyde proton at 9.85 ppm and the ^{13}C NMR spectrum showed the presence of an aldehyde carbon at 191.6 ppm. High resolution mass spectroscopy showed the expected molecular ion at *m/z* 311.1335 ($C_{22}H_{17}NO$ requires 311.1310).



Scheme 47: (i) $Pd(PPh_3)_4$ (10 mol%), DME, Na_2CO_3 (5 equiv.), Reflux, 24 h, 92%.

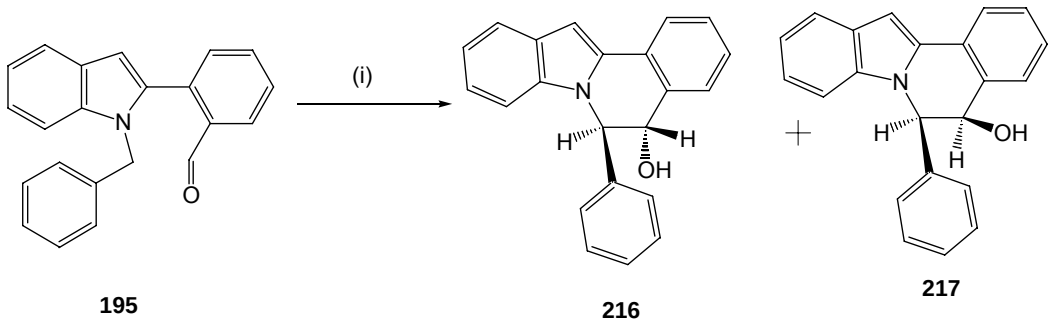
Previously, in our laboratory, it had been found that our well-developed reaction conditions for forming aromatic rings required the presence of a UV light source.[77] Other similar experiments however, showed that the light source was not always required. Using ^{t}BuOK and DMF at 80 °C co-workers were able to synthesize indolo[2,1-*a*]isoquinolines and pyrrolo[2,1-*a*]isquinolines.[4,39,77,79] In some cases however, it was found that the intermediate alcohol **213**, as shown in **Scheme 48**, was stable and an

additional step (elimination of water) had to be under taken in order to obtain the aromatic product **214**. The difference in our synthesis compared to the previous synthesis, if successful, is that the methyls substituents at the 5- and 12-positions of the product would be absent.



Scheme 48: (i) ^{t}BuOK, DMF, 80 °C (ii) 15 mol% TsOH, CH_2Cl_2, rt, 24 h.

In the synthesis of 6-phenylindolo[2,1-*a*]-isoquinoline **179**, we found that by stirring a mixture of 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde **195** and ^{t}BuOK (1.2 equiv.) in DMF, at rt for 2min, a mixture of *syn*- **216** and *anti*-5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5ol **217** diastereomers were obtained in 78% yield (**Scheme 49**). Both diastereomers were found to be yellow-green resins in a ratio of 7:3 i.e. 53% *anti* and 22% *syn*. On TLC plates the **R_f**'s were found to be quite different (0.12 difference in a 30% mixture of ethyl acetate/hexane as solvent).



Scheme 49: (i) ^{t}BuOK, DMF, rt, 2 min

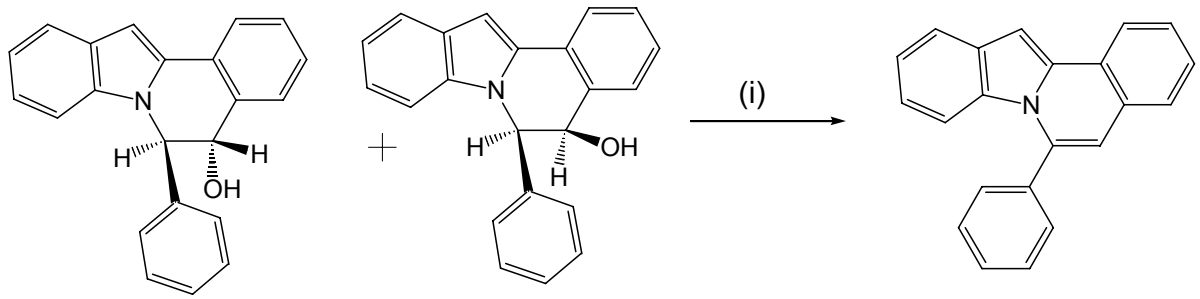
The diastereomers of **216** and **217** (**Scheme 49**) were separated by column chromatography and were analyzed by the usual methods. The IR spectra of

both revealed the presence of a broad OH peak at 3423 and 3364 cm^{-1} for the *anti*- and *syn*- diastereomers respectively. The ^{1}H NMR spectrum of the *anti*-diastereomer **216** showed that the peak at 5.26 ppm, corresponding to the methylene protons of the benzyl group, and the aldehyde proton which was visible at 9.85 ppm in the starting material had disappeared. The ^{1}H NMR spectrum however showed the presence of a hydroxyl, as a doublet, at 1.66 ppm (J = 11.0 Hz), the benzylic proton attached to the hydroxyl, as a double doublet, at 5.38 ppm (J = 7.0 and 11.0 Hz) and the benzylic proton attached to the nitrogen, as a doublet, at 5.71 ppm (J = 6.9 Hz). From the coupling constants it can be seen that the hydroxyl proton is coupled to the benzylic proton attached to the hydroxyl, which is also coupled to the benzylic proton attached to the nitrogen. The aromatic region was found to be very complicated but integrated for fourteen protons as expected. The ^{13}C NMR spectrum showed that the carbonyl carbon and the methylene carbon peaks at 191.6 and 47.6 ppm respectively had disappeared and that there were two new peaks at 59.5 and 69.5 ppm corresponding to the C-5 and C-6 respectively. The spectrum also indicated the presence of 18 aromatic carbons as expected. High resolution mass spectroscopy showed a molecular ion species at *m/z* 311.1302 ($C_{22}H_{17}NO$ requires 311.1310).

The ^{1}H NMR spectrum for the *syn*-diastereomer **217** was different and showed the presence of a very broad singlet at 2.18 ppm, corresponding to the hydroxyl proton, a slightly broad singlet at 4.91, corresponding to the benzylic proton attached to the hydroxyl and a doublet at 5.81 ppm, corresponding to the benzylic proton attached to the nitrogen (J = 1.5 Hz). Looking at the size of the coupling constant we can see that it is far smaller than the other diastereomer and thus based on this, the *anti*- and *syn*-diasteroemers were assigned. The aromatic region of the ^{1}H NMR spectrum was also fairly complicated, but the region integrated for 14 protons as expected. The C-5 and C-6 carbon peaks were found, on the ^{13}C NMR spectrum, at 62.0 and 73.9 ppm respectively. Although the spectrum showed 18 aromatic carbon signals they were at slightly different peak shifts compared to the *anti*-diastereomer **216**. High resolution mass spectroscopy

found the molecular ion for the *syn*-diastereomer **217** to be at *m/z* 311.1339, where $C_{22}H_{17}NO$ requires 311.1310.

The final step in the synthesis of 6-phenylindolo[2,1-*a*]-isoquinoline **179** was the dehydration of **216** and **217**. This step commenced by dissolving a mixture 5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol diastereomers, **216** and **217**, in CH_2Cl_2 and adding activated molecular sieves. First *p*TSA was added in order to try and dehydrate **216** and **217**, but after heating at reflux for 48h, only approximately 3% of the diastereomeric mixture had converted into another compound. A few drops of concentrated sulfuric acid were added and after 5h, a further 10 drops were added, but the conversion still had not progressed. The mixture was left stirring at reflux for a further 10h, which resulted in the reaction mixture decomposing. The dehydration of **216** and **217** were unsuccessful and 6-phenylindolo[2,1-*a*]-isoquinoline **179** was unfortunately not obtained. Clearly this is a step that can be accomplished, but time precluded attempting other methods for achieving this transformation.



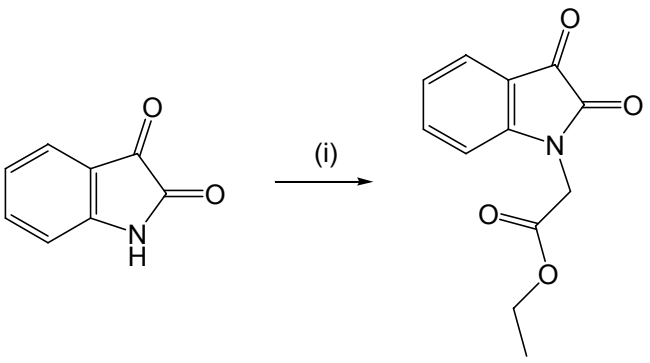
216 **217** **219**

Scheme 50: (i) p-TsOH, CH_2Cl_2, reflux 48 h.

2.3. The Synthesis of Ethyl Indolo[2,1-a]isoquinoline-6-carboxylate **183** *using the Alternative Route*

The successful synthesis of (±)-5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5ol **216/217**, starting from isatin, led us to attempt the synthesis of ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate **183** using this route.

The first step in the synthesis of **183** was the protection of isatin **182** with ethyl 2-acetate (**Scheme 51**). This was done using CaH_2 as a base on both small scale (440 mg) and large scale (10 g). Garden *et. al*[94] found that the alkylation of isatin **182**, with various protecting groups, using CaH_2 in DMF occurred more smoothly in wet DMF then in previously dried DMF, indicating that the base involved was probably the hydroxide ion and not the hydride itself. In both small scale and large-scale procedures, isatin **182** and CaH_2 (3.3 equiv. small scale and 1.0 equiv. large scale) were dissolved in wet DMF. The small-scale procedure was stirred at 45 °C for 0.5 h before adding ethyl 2-bromoacetate and then stirring for a further 24h. The large scale was stirred at 100 °C for 1h before adding ethyl 2-bromoacetate and then stirring for a further 4h. In both procedures the resulting mixture was poured into an aqueous dilute HCl solution. The small-scale reaction was extracted with ether and purified by column chromatography to obtain ethyl 2-(2,3-dioxoindolin-1-yl)acetate **218** as a bright yellow solid in 83% yield. For the large-scale reaction, **218** precipitated as a yellow solid that was purified by recrystallisation with a hexane-dichloromethane mixture, in quantitative yield. The melting point was found to be 132-133 °C. The IR spectrum showed a C=O band at 1740 cm^{-1} and an ArC=C band at 1615 cm^{-1}.



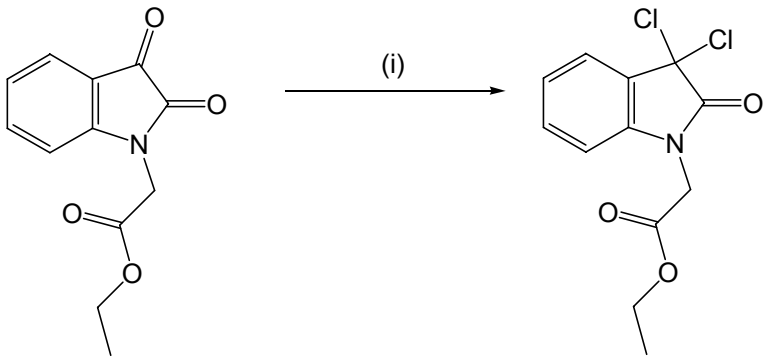
182 **218**

Scheme 51: (i) CaH_2, DMF

The ^1H NMR spectrum displayed a triplet at 1.29 ppm, corresponding to the methyl protons, a quartet at 4.25 ppm, corresponding to the methylene protons of the ethyl group and a singlet at 4.49 ppm, corresponding to the methylene protons. The aromatic region integrated for 4 protons and was made up of a doublet at 6.79 ppm, an apparent triplet at 7.16 ppm, an apparent double triplet at 7.59 ppm and a doublet at 7.66 ppm. In addition, the ^{13}C NMR spectrum showed the presence of 5 quaternary carbons and 4 aromatic protons as expected. The methyl carbon was found at 14.1 ppm, the methylene carbon attached to the nitrogen at 41.3 ppm and the methylene carbon of the ethyl group at 62.2 ppm. High-resolution mass spectroscopy showed a molecular ion species at 233.0675 ($C_{12}H_{11}NO_4$ requires 233.0688) indicating that **218** had formed.

The next step was the functional group interconversion of ethyl 2-(2,3-dioxoindolin-1-yl)acetate **218** to ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate **219**. This was done as before using PCl_5 in benzene at 25 °C for 24h (**Scheme 52**). After purification by column chromatography, **219** was obtained as a white solid in quantitative yield. The melting point was found to be 115-116 °C. The IR spectrum showed the presence of a C-Cl peak at 670 cm^{-1}. The methyl and methylene peaks had the same splitting pattern and chemical shift on both the ^1H and ^{13}C NMR spectra as in compound **218**. However, the aromatic region of the ^1H NMR spectrum had changed slightly: the apparent double triplet was no longer at 7.59 ppm but instead had shifted up field slightly to 7.39 ppm. The ^{13}C NMR spectrum still had 9 aromatic carbon

signals, however the PhC=O carbon had shifted from 184.2 ppm to 73.9 ppm indicating that a change in functional group had occurred. High-resolution mass spectroscopy showed a molecular ion at m/z 287.0151 ($C_{12}H_{11}NO^{35}Cl_2$ requires 287.0116).

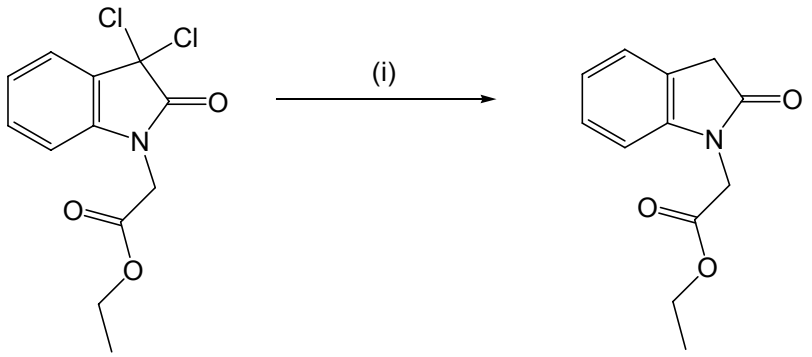


218 **219**

Scheme 52: (i) PCl_5, Benzene, 25 °C, 24 h.

The next step in the synthesis was the Zimmerman[95] dechlorination reaction using zinc in acetic acid. The dichloro compound **219** (**Scheme 53**) was dissolved in acetic acid and activated zinc (14 equiv.) was added over a 10 min period. The resulting mixture was stirred for a further 5 min. before the zinc was filtered off and most of the acetic acid removed. The remaining acetic acid was thus neutralized using a concentrated $NaHCO_3$ solution, the solution was extracted with ether and the resulting residue was purified by column chromatography to afford ethyl 2-(2-oxoindolin-1-yl)acetate **220**, as a white solid in quantitative yield. The melting point of **220** was found to be 127-129 °C. The IR spectrum had no significant changes except that instead of a broad C=O peak at 1746 cm^{-1}, there were two sharp peaks at 1740 and 1715 cm^{-1}. The ^1H NMR spectrum showed a new signal at 3.60 ppm, integrating for the 2 protons adjacent to the amide functional group. The 2 aromatic protons' signals at 7.39 and 7.66 ppm were now overlapping one another to form a multiplet between 7.23 and 7.28 ppm. The ^{13}C NMR spectrum showed the methyl and methylene carbons in the same place as before, but a new signal at 35.5 ppm, corresponding to the new methylene carbon, was now present. The spectrum also showed the presence of 8 aromatic carbons as expected.

High-resolution mass spectroscopy showed a molecular species present at *m/z* 219.0896 ($C_{12}H_{13}NO_3$ requires 219.0895).



219 **220**

Scheme 53: (i) Zn (14 equiv.), AcOH, rt, 15 min.

As in the synthesis of 1-benzyl-2-bromo-1*H*-indole **201**, the synthesis of ethyl 2-(2-bromo-1*H*-indole-1-yl)acetate **184** was performed under various reaction conditions in order to try and optimize the yield (**Scheme 54**). **Table 2** shows the reaction conditions and the results obtained (once again all reactions were performed under reflux).

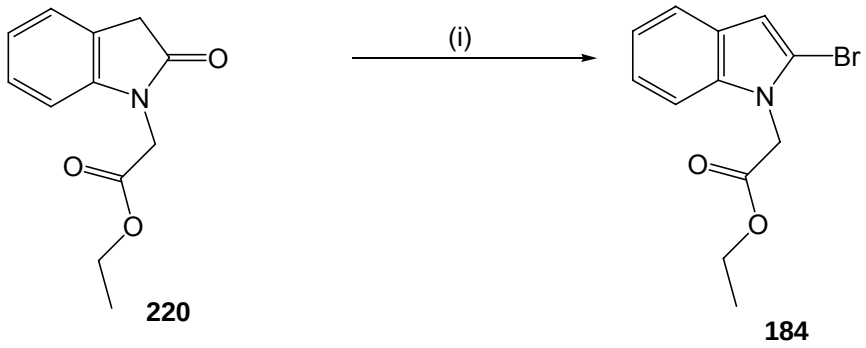
Solvent	Br Agent	Additive	Time of Reflux (h)	Yield
DCM	$POBr_3$	none	216 (9 days)	48% + 30% SM
DCM	$POBr_3$	imidazole[96]	48	40% SM
DCE	$POBr_3$	none	24	-
DCE	$POBr_3$	imidazole	48	30%
CH_3CN	PBr_3	none	96	95% SM

Table 2: DCM = dichloromethane, DCE = dichloroethane, CH_3CN = acetonitrile, $POBr_3$ = phosphorus oxybromide, PBr_3 = phosphorus tribromide, SM = starting material

From the table it can be seen that the results vary significantly with and without imidazole. Heating **220** at reflux in dichloroethane in the absence of imidazole resulted in only uncharacterizable material being isolated, while in the presence of imidazole, the product **184** was obtained in 30% yield as a white solid. Heating **220** at reflux in dichloromethane seemed to have the opposite effect. In the presence of imidazole, 40% of the starting material,

220, was recovered as well as some uncharacterizable material. In the absence of imidazole however, 30% of the starting material was recovered and 48% of the desired product was isolated (a 69% yield taking into account the recovered starting material). Heating **220** at reflux in CH_3CN, using PBr_3 as the brominating agent, seemed to have little or no effect on the starting material even after 4 days.

Analysis of ethyl 2-(2-bromo-1*H*-indole-1-yl)acetate **184** by IR spectroscopy showed the presence of a C-Br peak at 606 cm^{-1} and a carbonyl peak at 1737 cm^{-1}. A singlet at 6.63 ppm corresponding to the 3-H proton could be seen in the ^1H NMR spectrum. The carbonyl peak at 174.9 ppm and the methylene carbon signal at 35.5 ppm had disappeared and a new aromatic carbon signal at 105.1 ppm had appeared in the ^{13}C NMR spectrum. Further more, high-resolution mass spectroscopy supported the evidence that **184** had formed as a molecular ion at *m/z* 281.0052 ($C_{12}H_{12}NO_2{}^{79}Br$ requires 281.0051) was present. The melting point of **184** was found to be 61-63 °C.



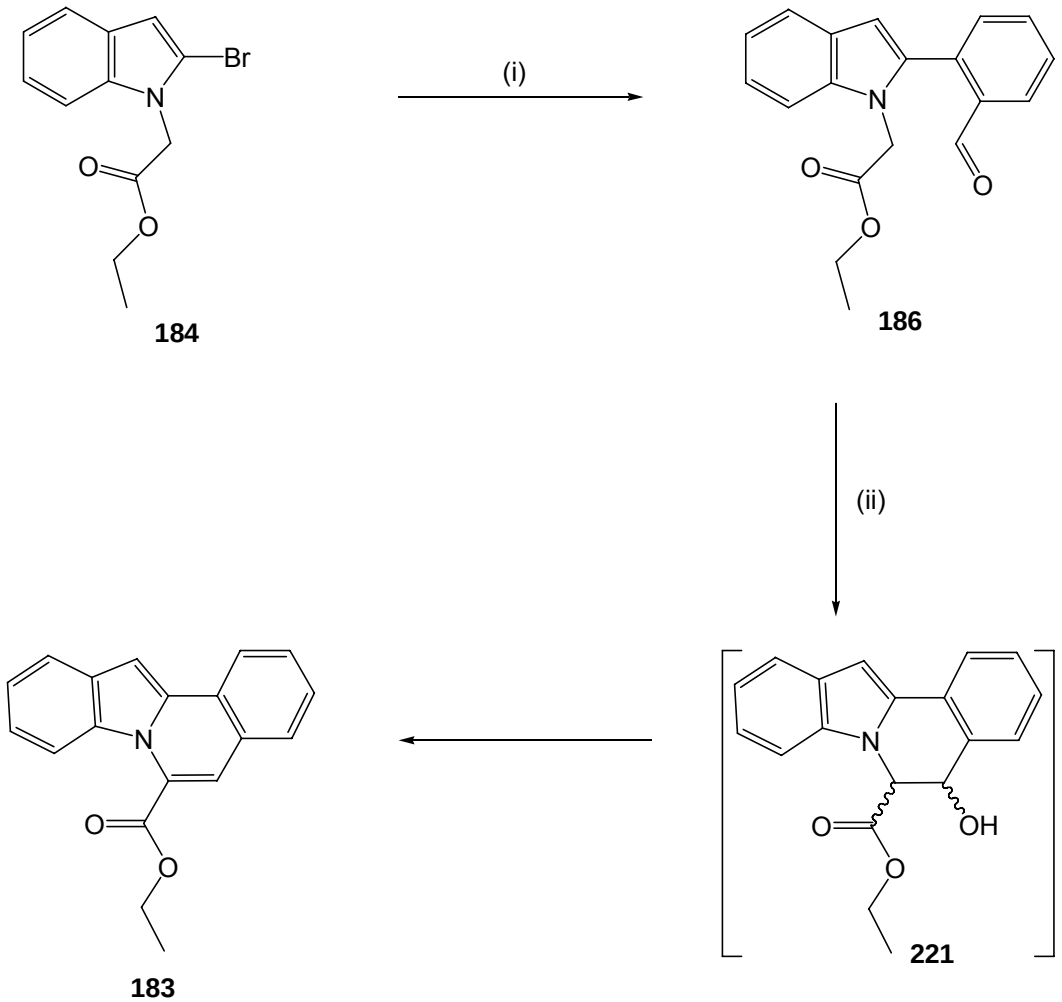
220 **184**

Scheme 54: (i) See Table 2 for reaction conditions

Now that the brominated compound **184** had been formed, the next step was to couple it with 2-formylphenylboronic acid **185** using Suzuki-Miyaura coupling conditions. Following the procedure from before, a mixture of the bromide **184**, the boronic acid **185** (1.5 equiv.), $Pd(PPh_3)_4$ (10 mol%), 2M Na_2CO_3 (5 equiv.) and DME were heated at reflux for a very short time, under a nitrogen atmosphere. Extraction of the organic material with ethyl acetate followed by the purification, by column chromatography, of the residue

afforded ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate **186** as an orange, viscous oil in 77% yield (**Scheme 55**).

IR spectroscopy showed the presence of both an aldehyde and an ester carbonyl at 1748 and 1693 cm^{-1} respectively. The ^{1}H NMR and ^{13}C NMR spectra showed the presence of an aldehyde proton and carbonyl carbon at 10.00 and 192.1 ppm respectively. In addition, high-resolution mass spectroscopy showed a molecular ion at *m/z* 307.1200 ($C_{19}H_{17}NO_3$ requires 307.1208) indicating that **186** had formed.



Scheme 55: (i) Boronic acid **185** (1.5 equiv.), $Pd(PPh_3)_4$ (10 mol%), 2M Na_2CO_3 (5 equiv.), DME, reflux, 10 min. (ii) ^{t}BuOK (10 mol%), DMF, rt, 2 min.

The final step in the synthesis of ethyl indolo[2,1-a]isoquinoline-6-carboxylate **183** was to convert ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate **186** to

183 using our well developed reaction conditions. We commenced the synthesis by adding ^{t}BuOK (10 mol%) to a solution of **186** in DMF at room temperature. The reaction was stirred at this temperature for 2 minutes before it was quenched with water and the organic material extracted with diethylether. The resulting residue was then purified by column chromatography to afford **183** as a yellow-orange solid in 59% yield. When monitoring the reaction by TLC we were able to see the formation of two new spots (presumably the diastereomeric alcohols **221** (only one spot visible - R_fs overlapping) and the dehydrated product **183**) and then the disappearance of the alcohol **221** as dehydration took place and the aromatic carboxylate **183** was formed. Just like 5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol **216** and **217**, the product **183** fluoresced intensely under UV light (**Figure 25**).

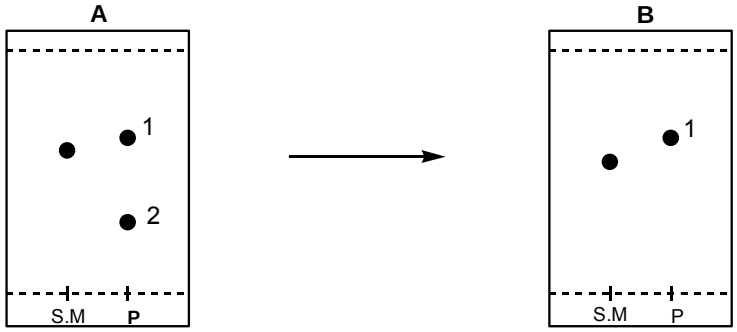


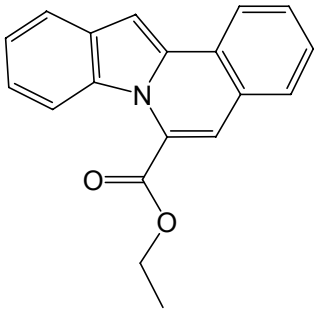
Figure 25: TLC plates showing the appearance of 2 new spots and then the disappearance of spot 2 (presumably the alcohol diastereomers) after 2 minutes. S.M = Starting Material, P = Product, A = TLC just after addition of ^{t}BuOK, B= TLC 2 minutes after adding ^{t}BuOK.

The IR spectrum showed the presence of an ArC-H stretching band at 3000 cm^{-1}, a C=O band at 1724 cm^{-1}, an ArC=C band at 1601 cm^{-1} and an Ar-H band at 738 cm^{-1}. In addition, the aldehyde proton's signal at 10.00 ppm as well as the methylene protons' signal at 4.71 ppm had disappeared in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum supported the ^{1}H NMR spectrum by showing the disappearance of the aldehyde carbonyl carbon signal at 192.1 ppm and the methylene carbon signal at 45.7 ppm. The ^{1}H NMR spectrum showed that there was another aromatic proton (the 5-H proton) present as the aromatic region integrated for ten protons and not nine as before. The ^{13}C NMR spectrum also revealed the presence of a new aromatic carbon as well as a new quaternary carbon (C-6). The high-resolution mass spectroscopy spectrum supported the NMR spectra as a molecular ion was found to be

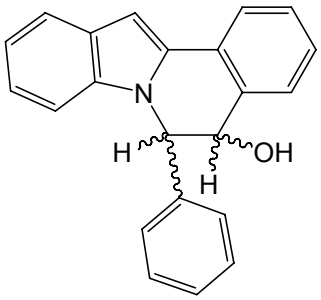
present at *m/z* 289.1081 ($C_{19}H_{15}NO_2$ requires 289.1103), indicating that **183** had successfully been synthesized. Ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate **183** was found to have a melting point of 109-110 ºC.

Chapter 3: Conclusion and Outlook

In conclusion we have managed to successfully synthesize ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate **183** and (±)-5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol **216/217**, (**Figure 26**) in moderate to high yields, using as key steps the Suzuki-Miyaura cross coupling reaction and our novel cylclisation reaction conditions (^{t}BuOK, DMF, rt).



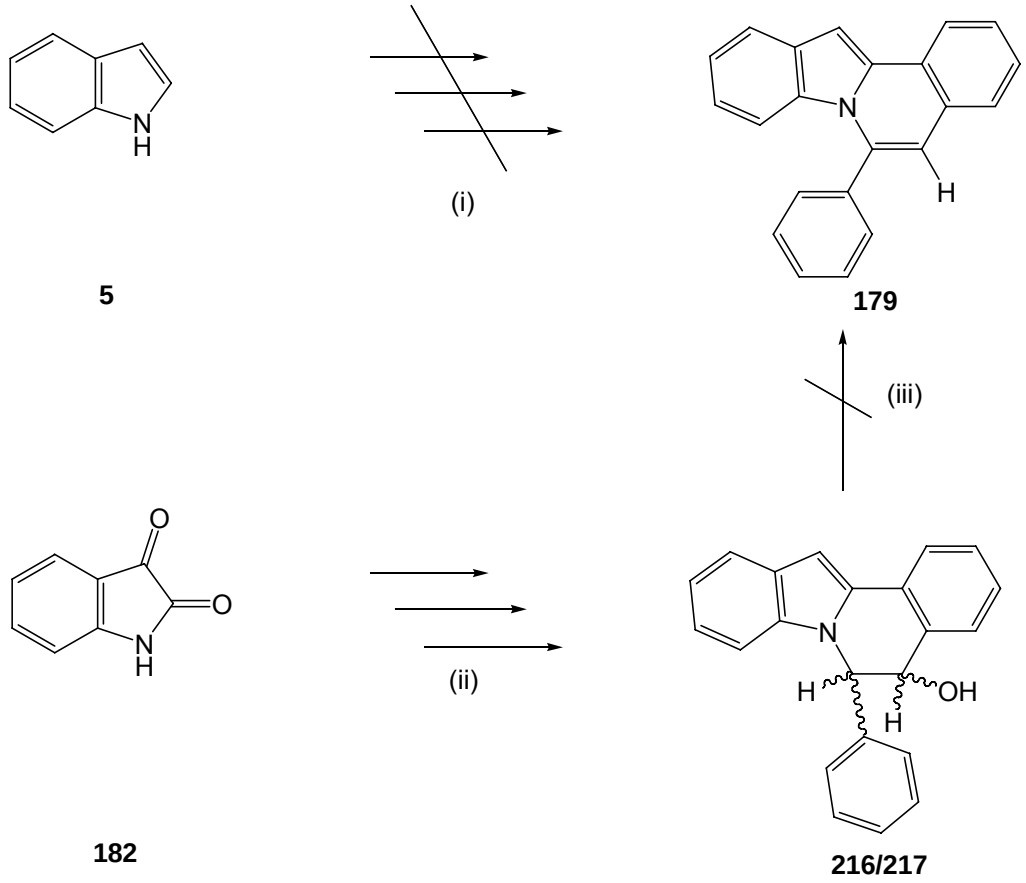
183



216/217

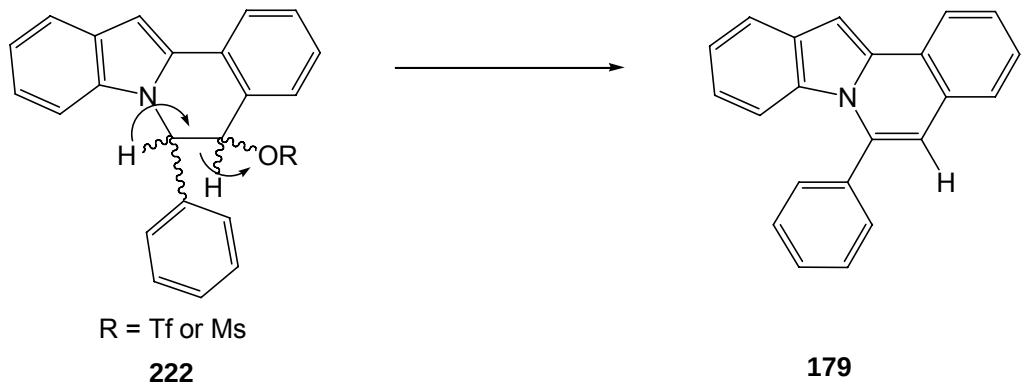
Figure 26

The initial attempted synthesis of 6-phenylindolo[2,1-*a*]isoquinoline **179**, starting from indole **5**, was found to be highly problematic i.e. removal of the Boc protecting group and reprotection of the indole nitrogen with a benzyl were difficult. The alternative route starting from isatin **182** was not only a cheaper and safer route, but was far less problematic, **Scheme 55**. The bromination reaction to afford **201** was the only moderate yielding step with a yield of approximately 55%. We managed to synthesize a mixture of diastereomers of **216/217** in 75% yield from **195**, but failed to dehydrate this compound by heating it at reflux in CH_2Cl_2 in the presence of *p*TSA and activated molecular sieves (**Scheme 56**).



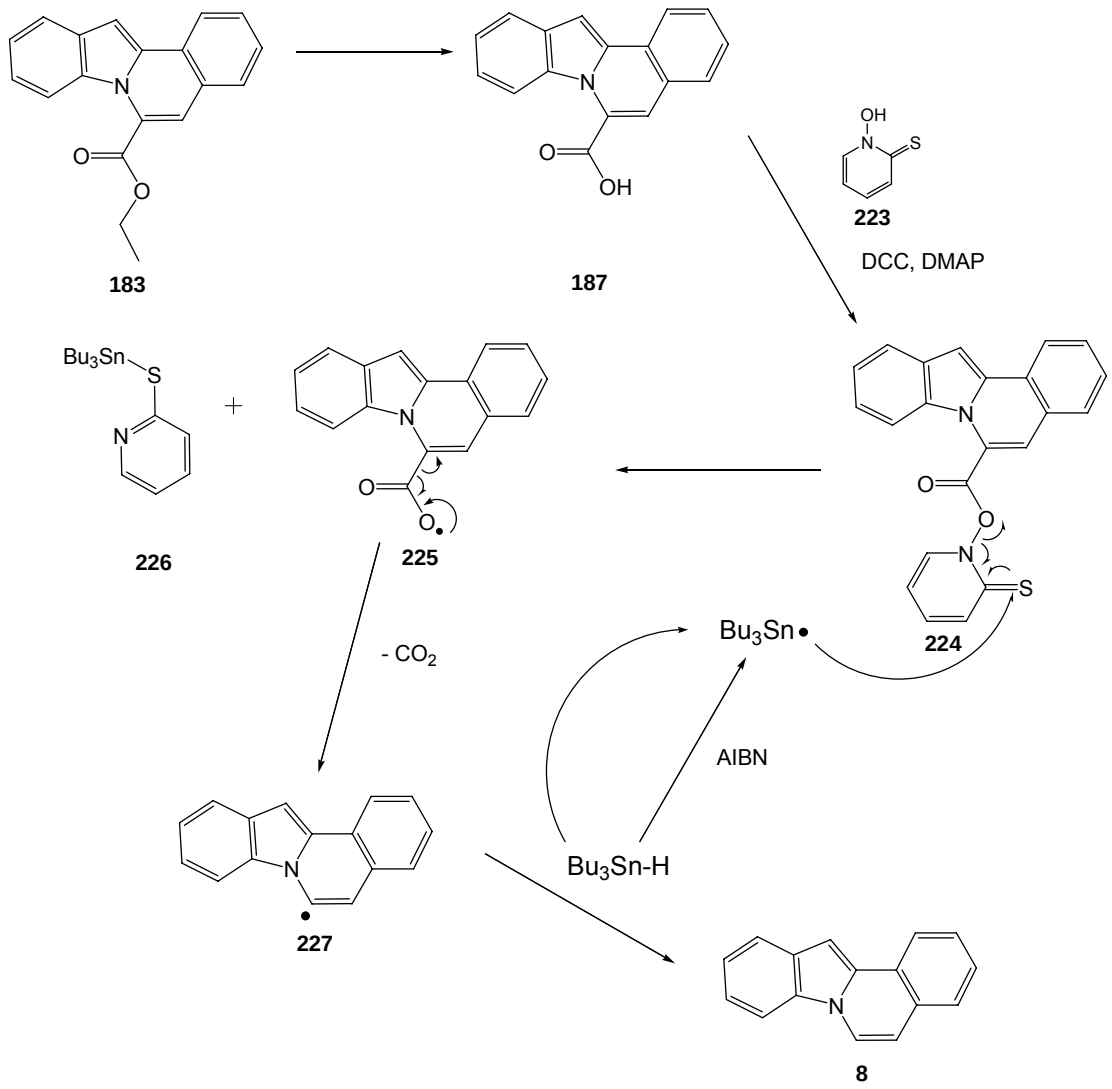
Scheme 56: (i) Initial attempted synthesis of **179** starting from indole **5**. (ii) Alternative route used to synthesize **179** starting from isatin **182**. (iii) Final step in the synthesis of **179** failed using pTSA, activated molecular sieves, CH_2Cl_2, reflux.

Alternative reaction conditions that could be used to convert **216/217** to **179** are to either repeat the reaction using another acid or to convert the hydroxyl substituent of **216/217** into a better leaving group such a mesylate (OMs) or triflate (OTf) **222**. Removal of this group should result in the formation of the desired alkene **179** as shown in **Scheme 57**.



Scheme 57

Having successfully synthesized **183** using the alternative reaction conditions (starting from isatin **182**), the next step would be to remove the ester group and obtain the indolo[2,1-*a*]isoquinoline skeleton **8** (**Schme 58**). The first step would be to convert the ester group into an acid **187**. Once the acid is obtained we could use Barton decarboxylation[97] to afford **8**. This decarboxylation involves protecting the acid OH with **223** in the presence of DCC and DMAP to form **224**, which then undergoes radical decarboxylation with Bu_3SnH to afford **8** in the presence of a radical initiator such as AIBN.



Scheme 58: Barton Decarboxylation

Chapter 4: Experimental Procedures

4.1. General Experimental Procedures

4.1.1. Purification of Solvents and Reagents

All solvents used for reactions and preparative silica gel chromatography were distilled prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl radical; dichloromethane, and dimethyl formamide from calcium hydride; benzene from sodium. Potassium tert-butoxide was sublimed prior to use. Chloroform was dried by passage through basic alumina (ICN Adsorbentien, ICN Alumina Super I). When necessary, solvents were stored over activated molecular sieves (4Å) under a nitrogen atmosphere. Unless otherwise noted, other reagents were obtained from commercial sources and used without further purification.

4.1.2. Chromatographic Separations

The R_f values quoted are for thin layer chromatography (TLC) on aluminium-backed Macherey-Nagel Alugram Sil G/UV_{254} plates pre-coated 0.25 mm silica gel 60, detection by UV-absorption. Preparative silica gel column chromatography was carried out both on wet- and dry-packed columns using Macherey-Nagel Kieselgel 60 silica gel 60 (particle size 0.063-0.200 mm) as the adsorbent. Mixtures of ethyl acetate and hexane were used as the mobile phase.

4.1.3. Spectroscopic and Physical Data

All melting points were obtained on a Reichert hot-stage microscope and are uncorrected.

^{1}H NMR (nuclear magnetic resonance) spectra were recorded on a Bruker AC-200 (200.13 MHz) or Bruker AVANCE 300 (300.13 MHz) spectrometer respectively. Spectra were recorded in deuterated chloroform ($CDCl_3$) unless otherwise specified and chemical shifts are reported in parts per million downfield from tetramethylsilane, the internal standard; coupling constants are given in Hertz. Splitting patterns are designated as “s”, “d”, “dd”, “t”, “q”, “m”, “br”, and “quat”; these symbols indicate “singlet”, “doublet”, “double doublet”, “triplet”, “quartet”, “multiplet”, “broad” and quaternary, respectively. NMR spectral data are reported as follows: chemical shift (integration of signal, description of signal, coupling constant(s) where applicable, assignment).

^{13}C NMR (^{1}H decoupled) spectra were recorded on a Bruker AC-200 (50.32 MHz) or Bruker AVANCE 300 (75.47 MHz) spectrometer respectively. Spectra were recorded in deuterated chloroform ($CDCl_3$) unless otherwise specified and chemical shifts are reported in parts per million relative to the central signal of deuterated chloroform, taken as δ 77.00.

IR (infrared) spectra were recorded on a Bruker IFS-25 Fourier Transform spectrometer. Liquid samples were recorded as thin films between sodium chloride plates, while solid samples were recorded as solutions in chloroform between sodium chloride plates. Brominated compounds were run as KBr pellets. The signals are reported on the wavenumber scale (ν/ cm^{-1}). IR spectra data are reported as follows: wavenumber (assignment).

High-resolution mass spectra (HRMS) were recorded on a VG70 MS (Mass Spectrum CC Pyramid data system), or on a VG70 SEQ (VG 11-250J or Marc II data systems). Mass spectroscopy values are reported as *m/z*.

4.1.4. Crystal Structure Data and Refinement

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program *SAINT+*. The crystal structure was solved by direct methods using SHELXL-97. Diagrams were generated using *PLATON* and *GSview*.

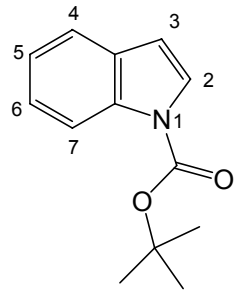
4.1.5. Other General Procedures

The term “removal of solvent under reduced pressure” refers to the use of aspirator pressure (*ca*. 25 Torr) with a Rotavapor at 40-50 ^{o}C. The term “*in vacuo*” refers to removal of solvent by rotary evaporation, followed by removal of the residual solvent at oil pump pressure (*ca*. 0.1-1.0 Torr) at ambient temperature until constant mass was achieved.

4.2. Experimental Procedures Related to Chapter 2

4.2.1. Experimental Procedures for the Attempted Synthesis of 6-Phenylindolo[2,1-*a*]isoquinoline 179 and 5-Methyl-6-phenylindolo[2,1-*a*]isoquinoline 188

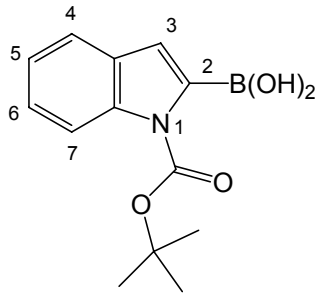
4.2.1.1. Synthesis of *tert*-Butyl 1*H*-indole-1-carboxylate 189[81]



189

Boc_2O (25.0 cm^3, 110 mmol, 1.3 equiv.) and DMAP (0.50 g, 4.1 mmol, 5 mol %) were added to a solution of indole (10 g, 85 mmol) in tetrahydrofuran (250 cm^3). The resulting mixture was stirred at room temperature for 24 h, under nitrogen. Water (50 cm^3) was added and the solution was extracted with ethyl acetate (3 × 50 cm^3). The organic layers were combined and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and purified by distillation (120 °C, 1 atm) to obtain **189** as a clear oil (14.70 g, 79%). $\mathbf{R_f}$ = 0.60 (5% ethyl acetate/hexane); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.66 (9H, s, 3×CH_3), 6.55 (1H, d, *J*=3.6 Hz, 3-H), 7.19-7.33 (2H, m, 2×ArH), 7.55 (1H, d, *J*=7.5 Hz, 4-H), 7.59 (1H, d, *J*=3.6 Hz, 2-H), 8.15 (1H, d, *J*=8.1 Hz, ArH).

4.2.1.2. Synthesis of 1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid 190[82]

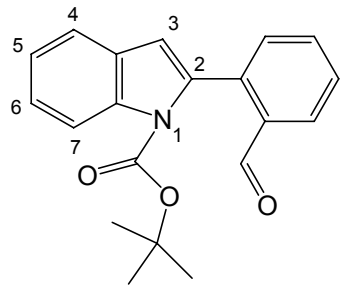


190

A 250 cm^3 round bottom flask equipped with a dropping funnel, rubber septum and nitrogen adaptor was flame dried. Tetrahydrofuran (25 cm^3 and 100 cm^3) was added to the dropping funnel and round bottom flask respectively. Tetramethylpiperidine (2.04 cm^3, 12.0 mmol, 1.3 equiv.) was added to the flask via syringe and *tert*-Butyl 1*H*-indole-1-carboxylate (2.00 g, 9.20 mmol) **189** was added to the dropping funnel. The solution was lowered to –78 ºC and butyl lithium (7.9 cm^3, 11 mmol, 1.2 equiv.) was added drop wise, via syringe, over 5 min. The solution was warmed to 0 ºC over 30 min. and then recooled to –78 ºC. The solution in the dropping funnel was now added drop wise to the flask and the resulting mixture was stirred for 1.5 h at –78 ºC. $B(OMe)_3$ (5.16 cm^3, 46.0 mmol, 5 equiv.) was added and the solution was stirred at –78 ºC for a further 30 min before allowing to warm up to room temperature. Water (150 cm^3) was added, the solution was acidified using an aqueous 1 M HCl solution and then extracted with ether (3 $\times$ 100 cm^3). The organic layers were combined, washed with brine and dried with anhydrous magnesium sulfate. The solvent was removed, *in vacuo*, until approximately 15 cm^3 remained. Cold hexane was added which resulted in 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **190** precipitated out as a white solid (1.57 g, 65%). The solid product **190** was obtained via filtration, dried overnight under nitrogen and stored in a refrigerator. $\mathbf{R_f}$ = 0.1 (20% ethyl acetate/hexane); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.74 (9H, s,

3×CH_3), 7.25 (1H, t, *J*=7.4 Hz, ArH), 7.35 (1H, m, ArH), 7.50 (1H, s, 3-H), 7.54 (2H, s, 2×OH), 7.60 (1H, d, *J*=7.6 Hz, ArH), 8.02 (1H, d, *J*=8.4 Hz, ArH).

4.2.1.3. Synthesis of *tert*-Butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate 191[83]

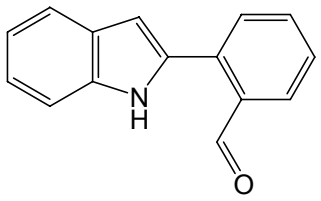


191

Tetrakis(triphenylphosphine)palladium(0) (0.53 g, 0.46 mmol, 10 mol %) was added to a 50 cm^3 flame dried, round bottom flask, equipped with a condenser and dropping funnel. The boronic acid **190** (1.80 g, 6.89 mmol, 1.5 equiv.), 2-bromobenzaldehyde (0.85 g, 4.6 mmol) and DME (12 cm^3), were combined in the dropping funnel and degassed before adding it to the flask. A 2M Na_2CO_3 solution (2.44 g, 23.0 mmol, 5 equiv.) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before heating under reflux for 72 h. Water (50 cm^3) was added and the solution was extracted with ethyl acetate (3 × 50 cm^3). The organic layers were combined and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography (2% ethyl acetate/hexane) to afford *tert*-butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate **191** as a white solid (1.26 g, 85%). $\mathbf{R_f}$ = 0.44 (10% ethyl acetate/hexane); **m.p.** 127-128 ºC; $\boldsymbol{\nu_{max}}$ ***(film)/cm*$^{-1}$**: 2980 (ArC-H), 1733 and 1698 (C=O), 1600 (ArC=C), 1160 (C-O), 768 (ArH); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.24 (9H, s, 3×CH_3), 6.60 (1H, s, 3-H), 7.26-7.47 (3H, m, 3×ArH), 7.51-7.66 (3H, m, 3×ArH), 8.01 (1H, d, *J*=7.7 Hz, ArH), 8.28

(1H, d, *J*=8.3 Hz, ArH), 10.01 (1H, s, CHO); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 27.5 (3×CH_3), 83.9 [$(CH_3)_3C$], 112.6 (3-C), 115.7 (ArCH), 120.6 (ArCH), 123.3 (ArCH), 124.9 (ArCH), 127.3 (ArCH), 128.5 (ArCH), 128.8 (ArC), 131.0 (ArCH), 133.1 (ArCH), 134.9 (ArC), 135.2 (ArC), 137.0 (ArC), 138.3 (ArC), 149.7 (NC=O), 191.6 (PhC=O); ***MS***: *m/z* (EI): 321 (M^+, 16 %), 221 (24), 193 (100), 165 (17), 57 (53), 41 (13); ***HRMS***: $C_{20}H_{19}NO_3$ requires: 321.1365, found: 321.1323.

4.2.1.4. Attempted Synthesis of 2-(1*H*-Indol-2-yl)benzaldehyde 193



193

Method 1:[85]

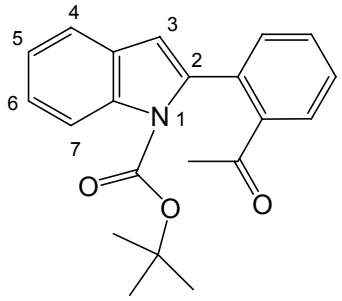
tert-Butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate (0.50 g, 1.6 mmol) **191** was absorbed onto silica in a 100 cm^3 round bottom flask by mixing silica and ethyl acetate and then evaporating the mixture to dryness on a rotary evaporator. The flask was then placed in the microwave and exposed to irradiation at 150 W for 13 min at 30 s intervals. The resulting mixture was purified by column chromatography (10% ethyl acetate/hexane) to afford starting material (0.15 g, 30%) and unidentifiable material.

Method 2:[86]

tert-Butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate (1.45 g, 4.51 mmol) **191** was dissolved in dichloromethane (70 cm^3) in a 100 cm^3 round bottom flask. The solution was lowered to 0 ºC and aluminum trichloride (0.78 g, 5.9 mmol, 1.3 equiv.) was added. After stirring for 1 h, water was added and the organic material was extracted with dichloromethane (3 × 70 cm^3). The organic layers

were combined, dried with anhydrous magnesium sulfate and the solvent removed *in vacuo*. The residue obtained was purified by column chromatography (10% ethyl acetate/ hexane) to afford only unidentifiable material.

4.2.1.5. Synthesis of *tert*-Butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate 192[83]

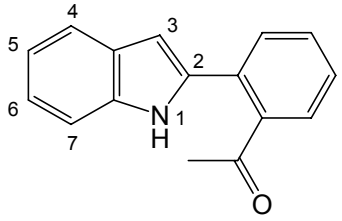


192

Triphenylphosphine palladium (0) (0.53 g, 0.46 mmol, 10 mol %) was added to a 50 cm^3 flame dried, round bottom flask, equipped with a condenser and dropping funnel. The boronic acid **190** (1.80 g, 6.89 mmol, 1.5 equiv.), 1-(2-bromophenyl)ethanone (0.92 g, 4.6 mmol) **200** and DME (12.7 cm^3, 1.1% of Na_2CO3 solution) were combined in the dropping funnel and degassed before adding to the flask. A 2M Na_2CO_3 solution (2.44 g, 23.0 mmol, 5 equiv.) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before heating at reflux for 72 h. Water (50 cm^3) was added and the solution was extracted with ethyl acetate (3 $\times$ 50 cm^3). The organic layers were combined and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography (2% ethyl acetate/hexane) to afford *tert*-butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate **192** as an orange-pink viscous oil that eventually solidified (0.97 g, 63%). $\mathbf{R_f}$ = 0.23 (10% ethyl acetate/hexane); **m.p.** 91-92 ºC; $\boldsymbol{\nu_{max}}$ ***(film)/cm^{-1}***: 2980 (ArC-H), 1731 and 1688 (C=O), 1598 (ArC=C), 1161 (C-O), 746 (ArH); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm)

= 1.29 (9H, s, 3×CH_3), 2.33 (3H, s, CH_3C=O), 6.48 (1H, s, 3-H), 7.22-7.55 (6H, m, 6×ArH), 7.73 (1H, d, *J*=7.4 Hz, ArH), 8.24 (1H, d, *J*=8.3 Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 27.4 (3×CH_3), 28.6 (CH_3C=O), 83.2 [$(CH_3)_3C$], 110.3 (3-C), 115.5 (ArCH), 120.3 (ArCH), 122.8 (ArCH), 124.3 (ArCH), 127.9 (ArCH), 128.0 (ArCH), 129.0 (ArC), 130.6 (ArCH), 130.8 (ArCH), 133.7 (ArC), 136.6 (ArC), 138.2 (ArC), 139.0 (ArC), 149.6 (NC=O), 200.8 (PhC=O); ***MS***: *m/z* (EI): 335 (M^+, 30 %), 235 (100), 220 (65), 165 (13), 57 (58), 41 (16), 30 (12); ***HRMS***: $C_{21}H_{21}NO_3$ requires: 335.1521, found: 335.1530.

4.2.1.6. Synthesis of 1-(2-(1*H*-Indole-2-yl)phenyl)ethanone 194



194

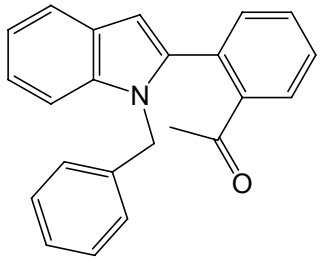
Method 1:[87]

tert-Butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate **192** (0.20 g, 0.60 mmol) was dissolved in dichloromethane (20 cm^3) in a 50 cm^3 round bottom flask. Trifluoroacetic acid (0.07 cm^3, 0.9 mmol, 1.5 equiv.) was added and the solution went from clear to light yellow. The solution was stirred at room temperature for 6 h before it was treated with $NaHCO_3$ and then extracted with dichloromethane (3 × 20 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow residue that contained a variety of unidentifiable products.

Method 2:[88]

tert-Butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate **192** (0.20 g, 0.60 mmol) was dissolved in THF (0.60 cm^3) in a 50 cm^3 round bottom flask. A 6.5 M solution of NaOMe in methanol (0.28 cm^3, 1.8 mmol, 3 equiv.) was added and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was worked up using 0.1 M HCl (5 cm^3) and extracted with ether (3 × 5 cm^3). The organic layers were combined, dried with anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The yellow residue obtained was purified by column chromatography (10% ethyl acetate/hexane) to afford 1-(2-(1*H*-indole-2-yl)phenyl)ethanone **194** as a whitish yellow solid (0.090 g, 64%). $\mathbf{R_f}$ = 0.32 (10% ethyl acetate/hexane); **m.p.** ; ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.95 (3H, s, CH_3C=O), 2.77 (1H, bs, NH), 6.53 (1H, s, 3-H), 7.08 (1H, t, *J*=7.5 Hz, ArH), 7.16-7.23 (1H, m, ArH), 7.29 (1H, t, *J*=7.5 Hz, ArH), 7.38 (1H, t, *J*=7.4 Hz, ArH), 7.48 (1H, d, *J*= 7.4 Hz, ArH), 7.55-7.60 (3H, m, 3×ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 24.9 (CH_3C=O), 89.0 (ArC), 93.3 (3-C), 110.5 (ArCH), 120.0 (ArCH), 120.7 (ArCH), 121.7 (ArCH), 122.4 (ArCH), 122.7 (ArCH), 127.8 (ArCH), 129.6 (ArCH), 130.9 (ArC), 133.0 (ArC), 133.6 (ArC), 139.9 (ArC), 198.8 (PhC=O);

4.2.1.7. Attempted Synthesis of 1-(2-(1-Benzyl-1*H*-indol-2-yl)phenyl)-ethanoate 196



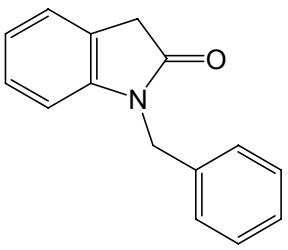
196

At –20 ºC, NaH (0.013 g, 0.18 mmol, 1 equiv.) was added to a solution of 1-(2-(1-benzyl-1*H*-indol-2-yl)phenyl)ethanoate **194** (0.060 g, 0.18 mmol) in THF (5 cm^3). The solution was warmed up to room temperature and stirred for 3h before benzyl bromide (0.02 cm^3, 0.2 mmol, 1 equiv.) was added drop wise. The resulting mixture was stirred for 72 h. Dichloromethane (5 cm^3) was

added and the solution was washed with water (3×5 cm^3). The organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to afford a yellow residue. The residue was purified by column chromatography (5% ethyl acetate/hexane) to afford 3 unidentifiable products.

4.2.2. Experimental Procedures for the Alternative route to the Synthesis of *6-Phenylindolo[2,1-a]-isoquinoline* 179

4.2.2.1. Attempted Synthesis of 1-Benzylindolin-2-one 206[91]



206

Method 1:

Oxindole **203** (0.25 g, 1.9 mmol) was dissolved in THF (25.0 cm^3) before adding NaH (0.094g, 2.1 mmol, 1.1 equiv.) at room temperature. Benzyl bromide (0.24 cm^3, 2.0 mmol, 1.1 equiv.) was added and the mixture was stirred for 24 h. Dichloromethane (25 cm^3) was added and the solution was washed with water (3 $\times$ 25 cm^3). The organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to afford a pinkish brown residue. The residue was purified by column chromatography (5→10→20% ethyl acetate/hexane) to afford 3 unidentifiable products.

Method 2:

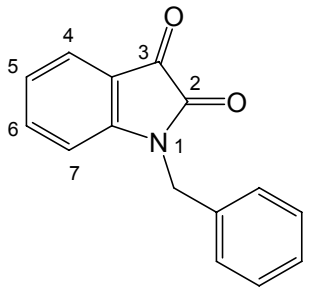
Oxindole **203** (0.25 g, 1.9 mmol) was dissolved in DMF (20.09 cm^3) in a 50 cm^3 round bottom flask. The solution was lowered to 0 ºC and NaH (0.094 g, 2.1 mmol, 1.1 equiv.) was added. The resulting mixture was stirred at 0 ºC for 30 min. and then warmed up to room temperature. The solution was stirred for a further 1 h before benzyl bromide (0.24 cm^3, 2.0 mmol, 1.05 equiv.) was added drop wise. After stirring for a long period of time, the reaction was

eventually aborted, as TLC (30% ethyl acetate/hexane) only detected base line material.

Method 3:

A mixture of oxindole **203** (0.25 g, 1.9 mmol), potassium carbonate (0.26 g, 1.9 mmol, 1 equiv.) and benzyl bromide (0.27 cm^3, 2.3 mmol, 1.2 equiv.) were dissolved in DMF (1.50 cm^3) in a 10 cm^3 beaker. The resulting mixture was exposed to microwave radiation (150 W) for 2 min. at 10 sec. intervals. The solution was allowed to cool and water (5 cm^3) was added. The resulting orange precipitate was filtered off, dried *in vacuo* and purified by column chromatography (10% ethyl acetate/hexane) to afford 3 unidentifiable products.

4.2.2.2. Synthesis of 1-Benzylindoline-2,3-dione 208[90]



208

Method 1:

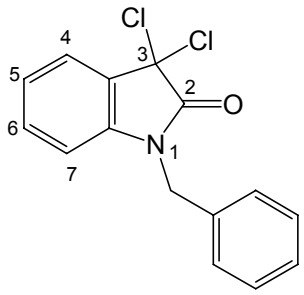
A mixture of isatin **182** (2.21 g, 15.0 mmol), potassium carbonate (3.00 g, 15.0 mmol, 1 equiv.) and benzyl bromide (5.34 cm^3, 45.0 mmol, 3 equiv.) were dissolved in DMF (9.00 cm^3) in a 100 cm^3 beaker. The resulting mixture was exposed to microwave radiation (150 W) for 2 min. at 30 sec. intervals. The solution was allowed to cool and water (50 cm^3) was added. The resulting orange precipitate was filtered off and washed with water. The crude product was recrystallised from ethanol to afford 1-benzylindoline-2,3-dione **208** as orange needle-like crystals (2.00 g, 88%). $\mathbf{R}_f$ = 0.42 (30% ethyl

acetate/hexane); **m.p.** 133-134 ºC; ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 4.94 (2H, s, CH_2), 6.78 (1H, d, *J*=7.9 Hz, ArH), 7.09 (1H, t, *J*=7.6 Hz, ArH), 7.25-7.38 (5H, m, 5×ArH), 7.48 (1H, dt, *J*=1.2 and 7.8Hz, ArH), 7.61 (1H, d, *J*=7.5Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 44.0 (CH_2), 110.0 (ArCH), 117.6 (ArC), 123.8 (ArCH), 125.3 (ArCH), 127.4 (2×ArCH), 128.1 (ArCH), 129.0 (2×ArCH), 134.5 (ArC), 138.3 (ArCH), 150.7 (ArC), 158.2 (2-C), 183.2 (3-C).

Method 2:

Isatin **182** (8.00 g, 54.0 mmol) and CaH_2 (2.29 g, 54.0 mmol, 1 equiv.) were dissolved in DMF (27.0 cm^3) in a 50 cm^3 round bottom flask. The solution was stirred at 100 ºC for 1 h and then cooled to 40 ºC so that benzyl bromide (7.10 cm^3, 60.0 mmol, 1.1 equiv.) could be added slowly. The resulting mixture was heated to 100 ºC for 4 h and then allowed to cool to room temperature. The solution was poured into a 0.5 M HCl solution (200 cm^3), with vigorous stirring, which resulted in an orange precipitate. The precipitate was filtered off and washed with water. The crude product was further purified by recrystalisation with dichloromethane layered with hexane to afford 1-benzylindoline-2,3-dione **208** as orange needle-like crystals (11.44 g, 89%).

4.2.2.3. Synthesis of 1-Benzyl-3,3-dichloroindolin-2-one 209

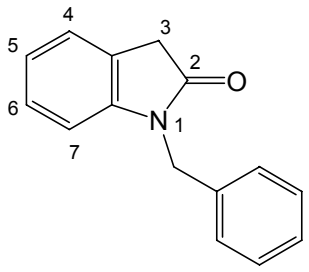


209

The dione **208** (6.40 g, 27.0 mmol) was dissolved in benzene (70 cm^3) in a 100 cm^3 round bottom flask. Phosphorus pentachloride (12.80 g, 62.10 mmol, 2.3 equiv.) was added and the solution was warmed to 25 ºC for 24 h. The

solvent was removed *in vacuo* to obtain a yellow brown residue, which was further purified by column chromatography (5% ethyl acetate/hexane) to afford 1-benzyl-3,3-dichloroindolin-2-one **209** as a light yellow oil. On addition of ethanol the chlorinated product **209** precipitated out as a white solid (6.37g, 81%). $\mathbf{R}_f$ = 0.58 (30% ethyl acetate/hexane); **m.p.** 125-126 ºC; ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 4.94 (2H, s, CH_2), 6.72 (1H, d, *J*=7.9 Hz, ArH), 7.14 (1H, t, *J*=7.6 Hz, ArH), 7.22-7.39 (6H, m, 6×ArH), 7.64 (1H, d, *J*=7.5Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 44.5 (CH_2), 110.1 (3-C), 124.2 (ArCH), 124.9 (ArCH), 127.1 (2×ArCH), 128.1 (ArCH), 129.0 (2×ArCH), 129.3 (ArC), 131.8 (ArCH), 134.4 (ArC), 139.8 (ArC), 169.2 (2-C).

4.2.2.4. Synthesis of 1-Benzylindolin-2-one 206



206

Method 1:

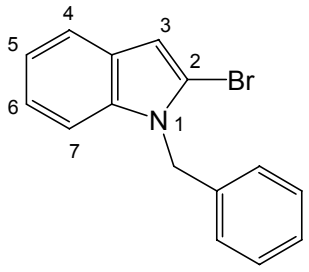
In a 10 cm^3 round bottom flask, 1-benzyl-3,3-dichloroindolin-2-one **209** (0.20 g, 0.68 mmol) was dissolved in acetic acid (5 cm^3). Adams catalyst (PtO_2, 0.02 g, 10 mol %) was added and the solution was degassed before exposing it to a hydrogen atmosphere for 6 h. The catalyst was filtered off and most of the acetic acid was removed *in vacuo*. A concentrated $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dichloromethane (3 × 10 cm^3). The organic layers were combined, dried with anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (20% ethyl acetate/hexane) to afford

1-benzylindolin-2-one **206** as a light yellow oil that eventually solidified into a white solid (0.12 g, 79%) (38-48% yield and recovered starting material).

Method 2:

In a 250 cm^3 round bottom flask, 1-benzyl-3,3-dichloroindolin-2-one **209** (3.00 g, 10.3 mmol) was dissolved in acetic acid (90 cm^3). Activated zinc (10.00 g, 154.5 mmol, 15 equiv.) was added over a 10 min. period and the resulting mixture was stirred for a further 10 min, at room temperature. The zinc was filtered off and washed with acetic acid and ethyl acetate. Most of the solvent was removed *in vacuo* and concentrated $NaHCO_3$ was added until effervescence stopped. The solution was extracted with diethylether (3 × 50 cm^3), the organic layers combined and the solvent dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the resulting residue was purified by column chromatography (20% ethyl acetate/hexane) to afford 1-benzylindolin-2-one **206** as a white solid (1.75 g, 76%); $\mathbf{R_f}$ = 0.40 (30% ethyl acetate/hexane); **m.p.** 60-62 ºC; ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 3.62 (2H, s, 3-H), 4.91 (2H, s, CH_2), 6.72 (1H, d, *J*=7.8 Hz, ArH), 7.00 (1H, t, *J*=7.5 Hz, ArH), 7.16 (1H, t, *J*=7.8 Hz, ArH), 7.21-7.34 (6H, m, 6×ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 35.7 (3-C), 43.7 (CH_2), 109.0 (ArCH), 122.3 (ArCH), 124.3 (ArCH), 124.4 (ArC), 127.3 (2×ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.7 (2×ArCH), 135.9 (ArC), 144.3 (ArC), 175.1 (2-C).

4.2.2.5. Synthesis of 1-Benzyl-2-bromo-1*H*-indole 201[90,96]



201

Method 1

Phosphorus oxybromide (0.19 g, 0.68 mmol, 1.5 equiv.) was added to a solution of 1-benzylindolin-2-one **206** (0.10 g, 0.45 mmol) in dichloromethane (10.00 cm^3). The resulting mixture was stirred at reflux for 1 h. The solution was cooled to room temperature and imidazole (0.04 g, 0.5 mmol, 1.2 equiv.) was added before refluxing for a further 48 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dicholoromethane (3 × 30 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting orange residue was purified by column chromatography (2% ethyl acetate/hexane) to afford the brominated compound **201** as a white solid (0.07 g, 88%) and starting material (0.02 g, 20%); **m.p.** 87-89 ºC; ***ν_{max} (film)/cm^{-1}***: 3000 (ArC-H), 1605 (ArC=C), 780 (ArH), 691 (C-Br); ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 5.41 (2H, s, CH_2), 6.65 (1H, s, 3-H), 7.06-7.13 (4H, m, 4×ArH), 7.20-7.28 (4H, m, 4×ArH), 7.55 (1H, dd, *J*=2.2 and 6.4 Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 48.1 (CH_2), 104.5 (3-C), 109.0 (ArCH), 113.5 (ArC), 119.8 (ArCH), 120.3 (ArCH), 122.0 (ArCH), 126.4 (2×ArCH), 127.5 (ArCH), 128.2 (ArC), 128.7 (2×ArCH), 136.7 (ArC), 137.0 (ArC); ***MS***: *m/z* (EI): 285 (M^+, 42 %), 204 (11), 91 (100), 65 (9); ***HRMS***: $C_{15}H_{12}N^{79}Br$ requires: 285.0153, found: 285.0091.

Method 2

Phosphorus oxybromide (0.16 g, 0.54 mmol, 1.2 equiv.) was added to a solution of 1-benzylindolin-2-one **206** (0.10 g, 0.45 mmol) in dichloromethane (10.0 cm^3). The resulting mixture was stirred at reflux for 72 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dicholoromethane (3 × 30 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting residue was purified by column chromatography (2% ethyl acetate/hexane) to afford the brominated compound **201** as a white solid (0.07 g, 55%).

Method 3

Phosphorus oxybromide (0.19 g, 0.64 mmol, 1.5 eq) was added to a solution of 1-benzylindolin-2-one **206** (0.10 g, 0.45 mmol) in dichloroethane (5.0 cm^3). The resulting mixture was stirred at reflux for 24 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dicholoromethane (3 $\times$ 30 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting residue was purified by column chromatography (2% ethyl acetate/hexane) to afford 2 uncharacterizable compounds.

Method 4

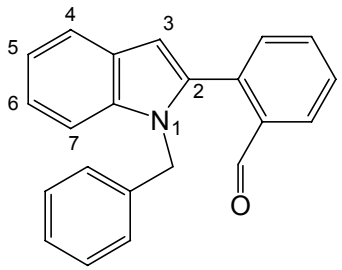
Phosphorus oxybromide (0.19 g, 0.68 mmol, 1.5 equiv.) was added to a solution of 1-benzylindolin-2-one **206** (0.10 g, 0.45 mmol) in dichloroethane (5.0 cm^3). The resulting mixture was stirred at reflux for 1 h. The solution was cooled to room temperature and imidazole (0.04 g, 0.5 mmol, 1.2 equiv.) was added before refluxing for a further 48 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dicholoromethane (3 $\times$ 30 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting residue was purified by column chromatography (2% ethyl acetate/hexane) to afford uncharacterizable material.

Method 5

Phosphorus bromide (0.05 cm^3, 0.6 mmol, 1.2 equiv.) was added to a solution of 1-benzylindolin-2-one **206** (0.10 g, 0.45 mmol) in CH_3CN (5.0 cm^3). The resulting mixture was stirred at reflux for 72 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dicholoromethane (3 $\times$ 30 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting residue was purified by column chromatography (2%

ethyl acetate/hexane) to afford the brominated compound **201** as a white solid (0.09 g, 7%) and 4 uncharacterizable compounds.

4.2.2.6. Synthesis of 2-(1-Benzyl-1*H*-indol-2-yl)benzaldehyde 195[83]

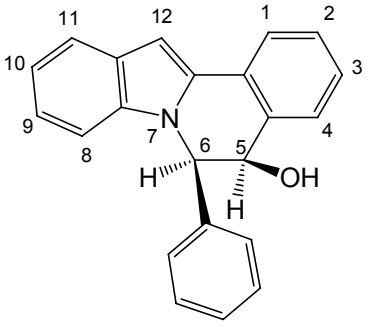


195

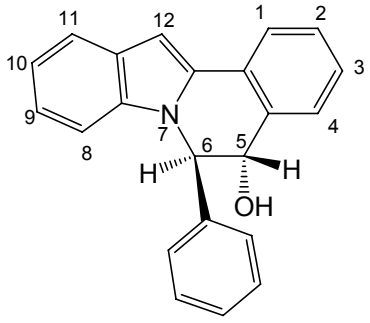
Tetrakis(triphenylphosphine)palladium(0) (0.10 g, 0.087 mmol, 10 mol %) was added to a 50 cm^3 flame dried, round bottom flask, equipped with a condenser and dropping funnel. The bromide **201** (0.25 g, 0.87 mmol), 2-formylphenylboronic acid **185** (0.15 g, 1.3 mmol, 1.5 equiv.) and DME (2.4 cm^3, 1.1% of Na_2CO_3 solution) were combined in the dropping funnel and degassed before adding to the flask. A 2M Na_2CO_3 solution (0.46 g, 4.4 mmol, 5 equiv.) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before refluxing for 24 h. Water (10 cm^3) was added and the solution was extracted with ethyl acetate (3 $\times$ 20 cm^3). The organic layers were combined and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (2% ethyl acetate/hexane) to afford 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde **195** as a yellow, viscous oil (0.25 g, 92%). $\mathbf{R}_f$ = 0.74 (30% ethyl acetate/hexane); $\boldsymbol{\nu}_{max}$ ***(film)/cm^{-1}***: 3060 (ArC-H), 1710 (C=O), 1550 (ArC=C), 750 (ArH); ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 5.26 (2H, s, CH_2), 6.63 (1H, s, 3-H), 6.83 (2H, dd, *J*=3.9 and 5.3 Hz, 2×ArH), 7.16-7.27 (5H, m, 5×ArH), 7.32 (1H, d, *J*=8.0 Hz, ArH), 7.40 (1H, dd, *J*=1.2 and 7.4 Hz, ArH), 7.50-7.61 (2H, m, 2×ArH), 7.69 (1H, dd, *J*=1.1 and 6.9Hz, ArH), 8.01

(1H, dd, *J*=1.4 and 7.6 Hz, ArH), 9.85 (1H, s, CHO); ***[13]C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 47.6 (CH_2), 106.8 (3-C), 110.4 (ArCH), 120.5 (ArCH), 120.8 (ArCH), 122.7 (ArCH), 126.1 (2×ArCH), 127.4 (ArCH), 127.5 (ArCH), 127.9 (ArC), 128.7 (2×ArCH), 129.0 (ArCH), 131.4 (ArCH), 133.2 (ArCH), 135.4 (ArC), 135.5 (ArC), 135.8 (ArC), 137.4 (ArC), 137.8 (ArC), 191.6 (C=O); ***MS***: *m/z* (EI): 311 (M^+, 33 %), 283 (58), 282 (65), 221 (19), 220 (100), 206 (39), 182 (53), 181 (72), 180 (20), 153 (20), 152 (30), 91 (87), 86 (27), 84 (41), 76 (15), 57 (22), 43 (18); ***HRMS***: $C_{22}H_{17}NO$ requires: 311.1310, found: 311.1335.

4.2.2.7. Synthesis of 5,6-Dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol 216 and 217[77]



216



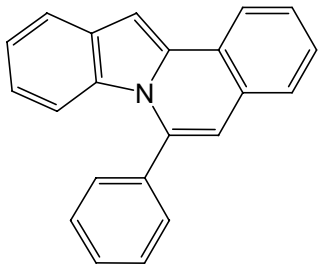
217

To a solution of 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde **195** (0.20 g, 0.64 mmol) in DMF (20 cm^3) was added ^tBuOK (0.086 g, 0.77 mmol, 1.2 equiv.) and the resulting mixture was stirred for 2 min. at room temperature. The solution was quenched with H_2O (40 cm^3) and the organic layer was extracted with ether (3 × 40 cm^3). After the organic layers were combined and dried, the solvent was removed *in vacuo*. The residue obtained was purified by column chromatography (2→5% ethyl acetate/ hexane) to afford the *anti*- and *syn*-diastereomers **216** and **217** as yellow-green resins in a 7:3 ratio (53% *anti* and 22% *syn*). $\mathbf{R_f}$ (*syn*) **216** = 0.49 (30% ethyl acetate/hexane); $\boldsymbol{\nu_{max}}$ ***(film)/cm^{-1}***: 3548 (NH), 3423 (OH), 3060 (ArC-H), 1605 (ArC=C), 747 (ArH);

^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.66 (1H, d, *J*= 11.0 Hz, OH), 5.38 (1H, dd, *J*=7.0 Hz and 11.0 Hz, C*H*-OH), 5.71 (1H, d, *J*=6.9 Hz, NC*H*), 6.84 (2H, m, 2×ArH), 6.92 (1H, s, ArH), 6.97-7.05 (5H, m, 5×ArH), 7.11-7.21 (2H, m, 2×ArH), 7.29 (1H, t, *J*=7.4 Hz, ArH), 7.38 (1H, d, *J* = 7.8 Hz, ArH), 7.54 (1H, dd, *J*=2.2 and 6.4Hz, ArH), 7.75 (1H, d, *J* = 7.6 Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 59.5 (*C*OH), 69.5 (N*C*H), 97.4 (ArCH), 109.4 (ArCH), 120.5 (ArCH), 120.8 (ArCH), 122.3 (ArCH), 123.9 (ArCH), 125.0 (ArCH), 127.3 (ArC), 127.9 (2×ArCH), 128.0 (ArCH), 128.1 (ArCH), 128.4 (ArCH), 128.6 (2×ArCH), 129.1 (ArC), 133.4 (ArC), 134.5 (ArC), 135.0 (ArC), 136.4 (ArC); ***MS***: *m/z* (EI): 311 (M^+, 100 %), 310 (18), 283 (17), 282 (47), 280 (14), 234 (17), 220 (42), 206 (41), 204 (30), 178 (15), 165 (18), 155 (14), 91 (20); ***HRMS***: $C_{22}H_{17}NO$ requires: 311.1310, found: 311.1302.

R_f (*anti*) **217** = 0.36 (30% ethyl acetate/hexane); ***ν_{max} (film)/cm^{-1}***: 3364 (OH), 3058 (ArC-H), 1607 (ArC=C), 747 (ArH); ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 2.18 (1H, bs, OH), 4.91 (1H, s, C*H*-OH), 5.81 (1H, d, *J*=1.5 Hz, NC*H*), 6.70 (2H, dd, *J*=2.6 and 6.6 Hz, 2×ArH), 6.97 (1H, s, ArH), 7.00-7.09 (5H, m, 5×ArH), 7.12-7.18 (3H, m, 3×ArH), 7.29-7.35 (1H, m, ArH), 7.58-7.60 (1H, m, ArH), 7.79 (1H, d, *J*=7.7 Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 62.0 (*C*OH), 73.9 (N*C*H), 97.6 (ArCH), 109.6 (ArCH), 120.5 (ArCH), 120.9 (ArCH), 122.4 (ArCH), 124.4 (ArCH), 125.9 (2×ArCH), 127.7 (ArCH), 128.0 (ArC), 128.1 (ArCH), 128.7 (2×ArCH), 129.1 (ArC), 129.7 (ArCH), 129.9 (ArCH), 131.0 (ArC), 133.7 (ArC), 137.4 (ArC), 137.8 (ArC); ***MS***: *m/z* (EI): 311 (M^+, 100 %), 310 (20), 283 (18), 282 (47), 280 (14), 234 (18), 220 (42), 217 (14), 206 (42), 204 (31), 178 (16), 165 (19), 155 (15), 91 (21); ***HRMS***: $C_{22}H_{17}NO$ requires: 311.1310, found: 311.1339.

4.2.2.8. Attempted Synthesis of 6-Phenylindolo[2,1-*a*]isoquinoline 179[4]

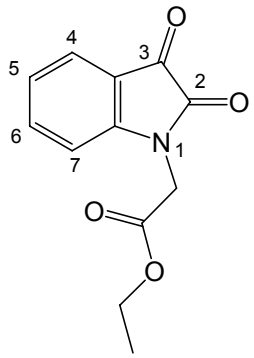


179

To a solution of 5,6-dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ol **222** (0.15 g, 0.48 mmol) in CH_2Cl_2 (50.0 cm^3) was added 21 activated pieces of molecular sieves followed by *p*TSA (0.02 g, 72 mmol, 15 mol %). The reaction mixture was stirred for 24 h at room temperature before a further 15 mol % of *p*TSA was added and the solution stirred at reflux for another 24 h. At this time TLC indicated that only about 3% of the diastereomeric mixture had converted into another compound. Concentrated H_2SO_4 (10 drops over 5 h) was added to the reaction mixture and the solution was stirred at reflux for 15 h, at which point TLC indicated that the reaction mixture had decomposed.

4.2.2. Experimental Procedures for the Synthesis of Ethyl Indolo[2,1-*a*]isoquinoline-6-carboxylate 183 Using the Alternative Route

4.2.3.1. Synthesis of Ethyl 2-(2,3-dioxoindolin-1-yl)acetate 218[94]



218

Small Scale:

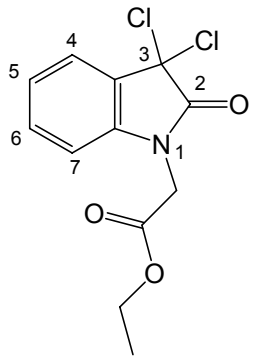
Isatin **182** (0.44 g, 0.30 mmol) and CaH_2 (0.42 g, 10 mmol, 3.3 equiv.) were dissolved in DMF (5.0 cm^3) in a 20 cm^3 round bottom flask. The solution was stirred at 45 ºC for 0.5hand then cooled to room temperature so that ethyl 2-bromoacetate (1.00 cm^3, 9.00 mmol, 3 equiv.) could be added slowly. The resulting mixture was warmed to 45 ºC for a further 24 h. The solution was cool to room temperature and neutralized with an aqueous 1 M HCl solution. The organic layer was extracted with ether (3 × 20 cm^3), the organic layers were combined and dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue obtained was purified by column chromatography (hexane→2%→5% ethyl acetate/hexane) to afford ethyl 2-(2,3-dioxoindolin-1-yl)acetate **218** as a bright, yellow solid (0.58 g, 83%). $\mathbf{R_f}$ = 0.24 (30% ethyl acetate/hexane); **m.p.** 132-133 ºC; $\boldsymbol{\nu_{max}}$ ***(film)/cm*$^{-1}$**: 2983 (ArC-H), 1740 (C=O), 1615 (ArC=C), 1210 (C-O), 757 (ArH); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.29 (3H, t, *J*=7.1 Hz, CH_3), 4.25 (2H, q, *J*=7.1 Hz, OCH_2)

4.49 (2H, s, NCH_2), 6.79 (1H, d, *J*=7.9 Hz, ArH), 7.16 (1H, t, *J*=7.5 Hz, ArH), 7.57-7.62 (1H, dt, *J*=1.2 and 7.8 Hz, ArH), 7.66 (1H, d, *J*=7.5 Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 14.1 (CH_3), 41.3 (NCH_2), 62.2 (OCH_2), 110.1 (ArCH), 117.7 (ArC), 124.1 (ArCH), 125.6 (ArCH), 138.4 (ArCH), 150.3 (ArC), 158.0 (2-C), 166.7 (CO_2Et), 182.4 (3-C); ***MS***: *m/z* (EI): 233 (M^+, 35 %), 132 (100), 77 (24), 51 (9); ***HRMS***: $C_{12}H_{11}NO_4$ requires: 233.0688, found: 233.0675.

Large Scale:

Isatin **182** (10.00 g, 68.00 mmol) and CaH_2 (2.86 g, 68.0 mmol, 1 equiv.) were dissolved in DMF (35.0 cm^3) in a 50 cm^3 round bottom flask. The solution was stirred at 100 ºC for 1hand then cooled to 40 ºC so that ethyl 2-bromoacetate (22.62 cm^3, 204.0 mmol, 3 equiv.) could be added slowly. The resulting mixture was heated to 100 ºC for 4 h and then allowed to cool to room temperature. The solution was poured into a 0.5 M HCl solution (200 cm^3), with vigorous stirring, which resulted in a yellow precipitate. The precipitate was filtered off and washed with water. The crude product was further purified by recrystalisation with hexane layered dichloromethane to afford ethyl 2-(2,3-dioxoindolin-1-yl)acetate **218** as yellow crystals in quantitative yield.

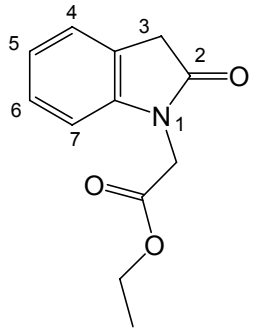
4.2.3.2. Synthesis of ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate 219[90]



219

The dione **218** (2.50 g, 10.7 mmol) was dissolved in benzene (40 cm^3) in a 100 cm^3 round bottom flask. Phosphorus pentachloride (5.00 g, 24.6 mmol, 2.3 equiv.) was added and the solution was warmed to 25 ºC for 24 h. The solvent was removed *in vacuo* to obtain a light, yellow residue, which was further purified by column chromatography (hexane→2% ethyl acetate/hexane) to afford ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate **219** as a white solid (3.10 g, 100%). $\mathbf{R_f}$ = 0.43 (30% ethyl acetate/hexane); **m.p.** 115-116 ºC; $\boldsymbol{\nu_{max}}$ ***(film)/cm*$^{-1}$**: 2984 (ArC-H), 1746 (C=O), 1613 (ArC=C), 1102 (C-O), 752 (ArH), 670 (C-Cl); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.26 (3H, t, *J*=7.1 Hz, CH_3), 4.23 (2H, q, *J*=7.1 Hz, O*C*H_2) 4.48 (2H, s, N*C*H_2), 6.77 (1H, d, *J*=7.9 Hz, ArH), 7.19 (1H, t, *J*=7.7 Hz, ArH), 7.39 (1H, dt, *J*=1.0 and 7.8 Hz, ArH), 7.66 (1H, d, *J*=7.5 Hz, ArH); ^{13}***C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 14.0 (CH_3), 41.8 (N*C*H_2), 62.1 (O*C*H_2), 73.9 (ArCH), 109.1 (ArCH), 124.5 (ArCH), 125.0 (ArCH), 129.0 (ArC), 131.8 (ArCH), 139.4 (ArC), 166.4 (2-C), 168.9 (CO_2Et); ***MS***: *m/z* (EI): 287 (M^+, 39 %), 254 (37), 252 (100), 216 (23), 214 (36), 188 (11), 186 (18), 173 (23), 151 (21), 89 (18); ***HRMS***: $C_{12}H_{11}NO^{35}Cl_2$ requires: 287.0116, found: 287.0151.

4.2.3.3. Synthesis of Ethyl 2-(2-oxoindolin-1-yl)acetate 220

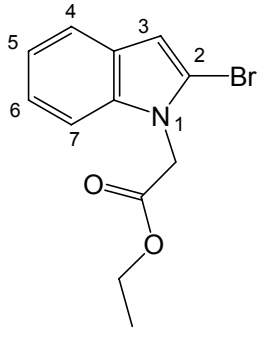


220

In a 20 cm^3 round bottom flask, ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate **219** (0.15 g, 0.52 mmol) was dissolved in acetic acid (5 cm^3). Activated zinc (0.50 g, 7.3 mmol, 14 equiv.) was added over a 10 min. period and the

resulting mixture was stirred for a further 5 min, at room temperature. The zinc was filtered off and washed with acetic acid and ethyl acetate. Most of the solvent was removed *in vacuo* and concentrated $NaHCO_3$ was added until effervescence stopped. The solution was extracted with ether (3×20 cm^3), the organic layers combined and the solvent dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the resulting residue was purified by column chromatography (2%→5% ethyl acetate/hexane) to afford ethyl 2-(2-oxoindolin-1-yl)acetate **220** as a white solid in quantitative yield; $\mathbf{R_f}$ = 0.09 (30% ethyl acetate/hexane); **m.p.** 127-129 ºC; $\boldsymbol{\nu_{max}}$ ***(film)/cm^{-1}***: 2985 (ArC-H), 1740 and 1715 (C=O), 1615 (ArC=C), 1114 (C-O), 757 (ArH); ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.27 (3H, t, *J*=7.1 Hz, CH_3), 3.60 (2H, s, 3-H), 4.22 (2H, q, *J*=7.1 Hz, OCH_2) 4.47 (2H, s, NCH_2), 6.70 (1H, d, *J*=7.8 Hz, ArH), 7.05 (1H, t, *J*=7.5 Hz, ArH), 7.23-7.28 (2H, m, 2×ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 14.1 (CH_3), 35.5 ($ArCH_2$), 41.3 (NCH), 61.7 (OCH_2), 108.1 (ArCH), 122.7 (ArCH), 124.2 (ArC), 124.5 (ArCH), 127.9 (ArCH), 142.8 (ArC), 167.6 (CO_2Et), 174.9 (NCO); ***MS***: *m/z* (EI): 219 (M^+, 45 %), 146 (49), 119 (11), 118 (100), 91 (39), 65 (14), 43 (12), 21 (24); ***HRMS***: $C_{12}H_{13}NO_3$ requires: 219.0895, found: 219.0896.

4.2.3.4. Synthesis of Ethyl 2-(2-bromo-1*H*-indol-1-yl)acetate 184[90,96]



184

Method 1

Phosphorus oxybromide (0.60 g, 2.2 mmol, 1.2 equiv.) was added to a solution of ethyl 2-(2-oxoindolin-1-yl)acetate **220** (0.40 g, 1.8 mmol) in dichloromethane (40 cm^3). The resulting mixture was stirred at reflux for 9 days. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dichloromethane (3 × 50 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting purple residue was purified by column chromatography (2% ethyl acetate/hexane) to afford the brominated compound **184** as a white solid (0.25 g, 89%) and starting material (0.12 g, 30%); **m.p.** 61-63 ºC; ***ν_{max} (film)/cm^{-1}***: 2999 (ArC-H), 1737 (C=O), 1625 (ArC=C), 1111 (C-O), 784 (ArH), 606 (C-Br); ***^{1}H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.23 (3H, t, *J*=7.2 Hz, CH_3), 4.19 (2H, q, *J*=7.1 Hz, OC*H_2*), 4.87 (2H, s, NC*H*), 6.63 (1H, s, 3-H), 7.08-7.21 (3H, m, 3×ArH) 7.53 (1H, d, *J*=7.7 Hz, ArH); ***^{13}C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 14.1 (CH_3), 46.0 (NCH), 61.7 (OCH_2), 105.1 (3-C), 109.0 (ArCH), 113.4 (ArC), 120.0 (ArCH), 120.6 (ArCH), 122.2 (ArCH), 128.1 (ArC), 136.9 (ArC), 167.9 (C=O); ***MS***: *m/z* (EI): 281 (M^+, 19 %), 213 (15), 210 (35), 208 (36), 201 (35), 143 (12), 129 (19), 128 (10), 127 (18), 115 (66), 87 (15), 81 (41), 69 (14), 43 (21), 41 (100), 39 (13), 29 (42), 28 (18), 27 (10); ***HRMS***: $C_{12}H_{12}NO_2{}^{79}Br$ requires: 281.0051, found: 281.0052.

Method 2

Phosphorus oxybromide (0.19 g, 0.69 mmol, 1.5 equiv.) was added to a solution of ethyl 2-(2-oxoindolin-1-yl)acetate **220** (0.10 g, 0.46 mmol) in dichloromethane (10.0 cm^3). The resulting mixture was stirred at reflux for 1 h and imidazole (0.04 g, 0.6 mmol, 1.2 equiv.) was added. The solution was stirred at reflux for a further 48 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dichloromethane (3 × 50 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting

residue was purified by column chromatography (2% ethyl acetate/hexane) to afford starting material **220** (0.05 g, 40%) and uncharacterizable material.

Method 3

Phosphorus oxybromide (0.19 g, 0.69 mmol, 1.5 equiv.) was added to a solution of ethyl 2-(2-oxoindolin-1-yl)acetate **220** (0.10 g, 0.46 mmol) in dichloroethane (5.0 cm^3). The resulting mixture was stirred at reflux for 24 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dichloromethane (3 $\times$ 50 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting purple residue was purified by column chromatography (2% ethyl acetate/hexane) to afford 2 uncharacterizable compounds.

Method 4

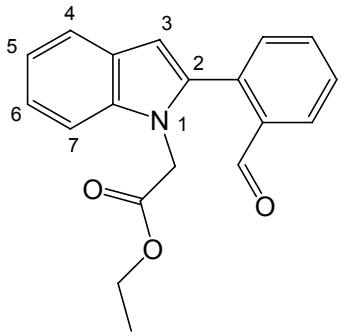
Phosphorus oxybromide (0.19 g, 0.69 mmol, 1.5 equiv.) was added to a solution of ethyl 2-(2-oxoindolin-1-yl)acetate **220** (0.10 g, 0.46 mmol) in dichloroethane (5.0 cm^3). The resulting mixture was stirred at reflux for 1 h and imidazole (0.04 g, 0.6 mmol, 1.2 equiv.) was added. The solution was stirred at reflux for a further 48 h. A 2M $NaHCO_3$ solution was added until effervescence stopped and the solution was extracted with dichloromethane (3 $\times$ 50 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting residue was purified by column chromatography (2% ethyl acetate/hexane) to afford the brominated compound **184** as a white solid (0.04 g, 30%).

Method 5

Phosphorus bromide (0.05 cm^3, 0.6 mmol, 1.2 eq) was added to a solution of ethyl 2-(2-oxoindolin-1-yl)acetate **220** (0.10 g, 0.46 mmol) in CH_3CN (5.0 cm^3). The resulting mixture was stirred at reflux for 96 h. A 2M $NaHCO_3$

solution was added until effervescence stopped and the solution was extracted with dicholoromethane (3 × 30 cm^3). The organic layers were combined, washed with brine and dried with anhydrous $MgSO_4$ before removing the solvent *in vacuo*. The resulting residue was purified by column chromatography (2% ethyl acetate/hexane) to afford starting material **220** (0.095 g, 95%).

4.2.3.5. Synthesis of Ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate 186[83]

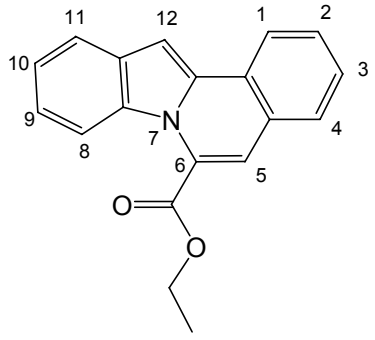


186

Tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.089 mmol, 10 mol %) was added to a 50 cm^3 flame dried, round bottom flask, equipped with a condenser and dropping funnel. The bromide **184** (0.25 g, 0.89 mmol), 2-formylphenylboronic acid **185** (0.20 g, 1.1 mmol, 1.5 equiv.) and DME (2.6 cm^3, 1.1% of Na_2CO_3 solution) were combined in the dropping funnel and degassed before adding to the flask. An aqueous 2M Na_2CO_3 solution (0.47 g, 4.45 mmol, 5 equiv.) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before refluxing for 10 min. Water (10 cm^3) was added and the solution was extracted with ethyl acetate (3 × 20 cm^3). The organic layers were combined and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (2% ethyl acetate/hexane) to afford ethyl 2-(2-(2-

formylphenyl)-1*H*-indol-1-yl)acetate **186** as an orange, viscous oil (0.21 g, 77%). $\mathbf{R}_f$ = 0.59 (30% ethyl acetate/hexane); $\boldsymbol{\nu}_{max}$ ***(film)/cm*$^{-1}$**: 2982 (ArC-H), 1748 and 1693 (C=O), 1600 (ArC=C), 1200 (C-O), 766 (ArH); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.15 (3H, t, *J*=7.1 Hz, CH_3), 4.10 (2H, q, *J*=7.1 Hz, OCH_2) 4.71 (2H, s, NCH_2), 6.63 (1H, s, 3-H), 7.18-7.33 (3H, m, 3×ArH), 7.51 (1H, d, *J*=7.6 Hz, ArH), 7.59 (1H, t, *J*=7.4 Hz, ArH), 7.68 (2H, ddd, *J*=1.5, 4.2 and 7.4 Hz, 2×ArH), 8.08 (1H, dd, *J*=1.1 and 7.7 Hz, ArH), 10.0 (1H, s, CHO); ^{13}***C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 14.0 (CH_3), 45.7 (NCH_2), 61.7 (OCH_2), 107.1 (3-H), 109.3 (ArCH), 120.9 (ArCH), 121.0 (ArCH), 123.0 (ArCH), 127.9 (ArC), 129.2 (ArCH), 131.5 (ArCH), 133.3 (ArCH), 135.2 (ArC), 135.4 (ArC), 135.8 (ArC), 137.9 (ArC), 168.3 (CO_2Et), 192.1 (CHO); ***MS***: *m/z* (EI): 307 (M^+, 65 %), 279 (33), 278 (39), 250 (24), 235 (13), 234 (47), 233 (25), 220 (19), 219 (23), 210 (12), 207 (20), 206 (54), 205 (43), 204 (47), 203 (15), 192 (13), 182 (36), 181 (100), 178 (20), 177 (14), 165 (19), 153 (31), 152 (49), 151 (23), 150 (16), 149 (56), 136 (24), 102 (12), 86 (34), 84 (45), 77 (19), 76 (23), 51 (10), 47 (12), 29 (12); ***HRMS***: $C_{19}H_{17}NO_3$ requires: 307.1208, found: 307.1200.

4.2.3.6. Synthesis of Ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate 183[77]



183

To a solution of ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate **186** (0.15 g, 0.49 mmol) in DMF (15 cm^3) was added ^{t}BuOK (0.006 g, 0.05 mmol, 10 mol %) at room temperature. The resulting mixture was stirred for 2 min. before it was quenched with water (25 cm^3) and then extracted with ether (3 × 25 cm^3).

The organic layers were combined, dried with $MgSO_4$ and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (2% ethyl acetate hexane) to afford ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate **183** (0.083 g, 59%) as a yellow-orange solid. $\mathbf{R}_f$ = 0.65 (30% ethyl acetate/hexane); **m.p.** 109-110 ºC; $\boldsymbol{\nu_{max}}$ ***(film)/cm*$^{-1}$**: 3000 (ArC-H), 1724 (C=O), 1601 (ArC=C), 738 (ArH); ^{1}***H NMR*** (300 MHz; $CDCl_3$; Me_4Si): δ_H (ppm) = 1.41 (3H, t, *J*=7.1 Hz, CH_3), 4.51 (2H, q, *J*=7.1 Hz, OCH_2), 7.12 (1H, s, 12-H), 7.17-7.26 (3H, m, 3×ArH), 7.36 (1H, t, *J*=7.4 Hz, ArH), 7.49 (2H, dd, *J*=7.7 and 18.9 Hz, 2×ArH), 7.61 (1H, d, *J*=8.2 Hz, ArH), 7.74 (1H, d, *J*=7.6 Hz, ArH), 8.07 (1H, d, *J*=7.9 Hz, ArH); ^{13}***C NMR*** (75 MHz, $CDCl_3$): δ_C (ppm) = 14.2 (CH_3), 62.2 (OCH_2), 95.4 (ArCH), 113.8 (ArCH), 115.2 (ArCH), 120.7 (ArCH), 121.0 (ArCH), 122.2 (ArCH), 123.4 (ArCH), 126.9 (ArC), 127.3 (ArC), 127.7 (ArCH), 127.8 (ArCH), 128.8 (ArC), 129.2 (ArC), 129.3 (ArC), 131.7 (ArC), 135.5 (ArC), 164.1 (OC=O); ***MS***: *m/z* (EI): 289 (M^+, 100 %), 261 (67), 216 (19), 187 (5), 131 (7), 108 (8); ***HRMS***: $C_{19}H_{15}NO_2$ requires: 289.1103, found: 289.1081.

Chapter 5: References

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Appendix

Appendix I – Crystal Data for 1-Benzyl-3,3-dichloroindolin-2-one 209

Empirical formula	C15 H11 Cl2 N O
Formula weight	292.15
Temperature	293(2) K
Wavelength	0.71073 A
Unit cell dimensions	a = 10.4847(13) A, b = 14.4641(18) A c = 9.2203(11) A α = 90°, β = 107.244(2)°, γ= 90°
Crystal system	Monoclinic
Volume	1335.4(3) $Å^3$
Z, Calculated density	4, 1.453 Mg/m^3
Absorption coefficient	0.475 mm^{-1}
F(000)	600
Theta range for data collection	2.03 to 28.28°
Limiting indices	-13<=h<=11, -19<=k<=18, -11<=l<=12
Reflections collected / unique	8978 / 3284 [R(int) = 0.0281]
Completeness to theta = 28.28	99.3%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3284 / 0 / 216
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0321, wR2 = 0.0828
R indices (all data)	R1 = 0.0431, wR2 = 0.0878
Largest diff. peak and hole	0.341 and -0.361 e.A^-3

Table 1: Crystal data and structure refinement for 1-Benzyl-3,3-dichloro-indolin-2-one **209**

Atom	x	y	z	U(eq)
o(1)	3766(1)	281(1)	2989(1)	44(1)
c(1)	579(1)	1988(1)	4981(2)	32(1)
c(2)	436(2)	2942(1)	5118(2)	35(1)
c(3)	1279(2)	3552(1)	4691(2)	33(1)
c(4)	2286(1)	3242(1)	4101(2)	29(1)
c(5)	2416(1)	2295(1)	3965(1)	24(1)
c(6)	1577(1)	1676(1)	4402(1)	c25(1)
c(7)	2017(1)	720(1)	4159(2)	28(1)
c(8)	3161(1)	878(1)	3430(2)	29(1)
c(9)	4395(1)	2252(1)	2903(2)	31(1)
c(10)	5491(1)	2649(1)	4216(2)	26(1)
c(11)	5813(2)	3582(1)	4255(2)	35(1)
c(12)	6839(2)	3937(1)	5458(2)	43(1)
c(13)	7547(2)	3362(1)	6610(2)	41(1)
c(14)	7237(2)	2431(1)	6577(2)	38(1)
c(15)	6207(1)	2076(1)	5390(2)	31(1)
n(1)	3342(1)	1812(1)	3408(1)	26(1)
cl(1)	2707(1)	120(1)	5914(1)	39(1)
cl(2)	745(1)	27(1)	2934(1)	39(1)

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1-Benzyl-3,3-dichloroindolin-2-one **209**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Bond	Bond Length
O(1)-c(8)	1.2103(17)
C(1)-c(6)	1.3838(19)
C(1)-c(2)	1.398(2)
C(1)-h(1)	0.983(17)
C(2)-c(3)	1.386(2)
C(2)-h(2)	0.931(19)
C(3)-c(4)	1.397(2)
C(3)-h(3)	1.013(17)
C(4)-c(5)	1.3853(19)
C(4)-h(4)	0.932(16)
C(5)-c(6)	1.3966(18)
C(5)-n(1)	1.4110(17)
C(6)-c(7)	1.4947(19)
C(7)-c(8)	1.5560(19)
C(7)-cl(2)	1.7807(13)
C(7)-cl(1)	1.7887(14)
C(8)-n(1)	1.3644(18)
C(9)-n(1)	1.4651(17)
c(9)-c(10)	1.5133(19)
c(9)-h(9a)	0.959(17)
c(9)-h(9b)	0.980(17)
c(10)-c(11)	1.388(2)
c(10)-c(15)	1.393(2)
c(11)-c(12)	1.394(2)
c(11)-h(11)	0.917(18)
c(12)-c(13)	1.379(3)
c(12)-h(12)	0.94(2)
c(13)-c(14)	1.384(2)
c(13)-h(13)	0.97(2)
c(14)-c(15)	1.388(2)
c(14)-h(14)	0.945(19)
c(15)-h(15)	0.943(17)

Table 3: Bond lengths [A] for 1-Benzyl-3,3-dichloroindolin-2-one **209**

Bond	Bond Angle
c(6)-c(1)-c(2)	118.05(13)
c(6)-c(1)-h(1)	120.4(10)
c(2)-c(1)-h(1)	121.5(10)
c(3)-c(2)-c(1)	120.58(14)
c(3)-c(2)-h(2)	117.7(12)
c(1)-c(2)-h(2)	121.7(12)
c(2)-c(3)-c(4)	121.69(14)
c(2)-c(3)-h(3)	116.7(9)
c(4)-c(3)-h(3)	121.5(9)
c(5)-c(4)-c(3)	117.31(13)
c(5)-c(4)-h(4)	122.1(10)
c(3)-c(4)-h(4)	120.6(10)
c(4)-c(5)-c(6)	121.38(12)
c(4)-c(5)-n(1)	128.31(12)
c(6)-c(5)-n(1)	110.31(11)
c(1)-c(6)-c(5)	121.00(13)
c(1)-c(6)-c(7)	131.46(13)
c(5)-c(6)-c(7)	107.51(11)
c(6)-c(7)-c(8)	103.96(11)
c(6)-c(7)-cl(2)	114.14(9)
c(8)-c(7)-cl(2)	109.69(9)
c(6)-c(7)-cl(1)	111.92(9)
c(8)-c(7)-cl(1)	107.77(9)
cl(2)-c(7)-cl(1)	109.06(7)
o(1)-c(8)-n(1)	127.77(13)
o(1)-c(8)-c(7)	125.99(13)
n(1)-c(8)-c(7)	106.23(11)
n(1)-c(9)-c(10)	112.07(11)
n(1)-c(9)-h(9a)	106.1(10)
c(10)-c(9)-h(9a)	110.9(10)
n(1)-c(9)-h(9b)	108.1(10)
c(10)-c(9)-h(9b)	110.8(10)
h(9a)-c(9)-h(9b)	108.8(13)
c(11)-c(10)-c(15)	119.15(13)
c(11)-c(10)-c(9)	120.73(13)
c(15)-c(10)-c(9)	120.11(13)
c(10)-c(11)-c(12)	120.18(15)
c(10)-c(11)-h(11)	119.1(11)
c(12)-c(11)-h(11)	120.7(11)
c(13)-c(12)-c(11)	120.21(15)
c(13)-c(12)-h(12)	121.6(12)
c(11)-c(12)-h(12)	118.1(12)

Table 4

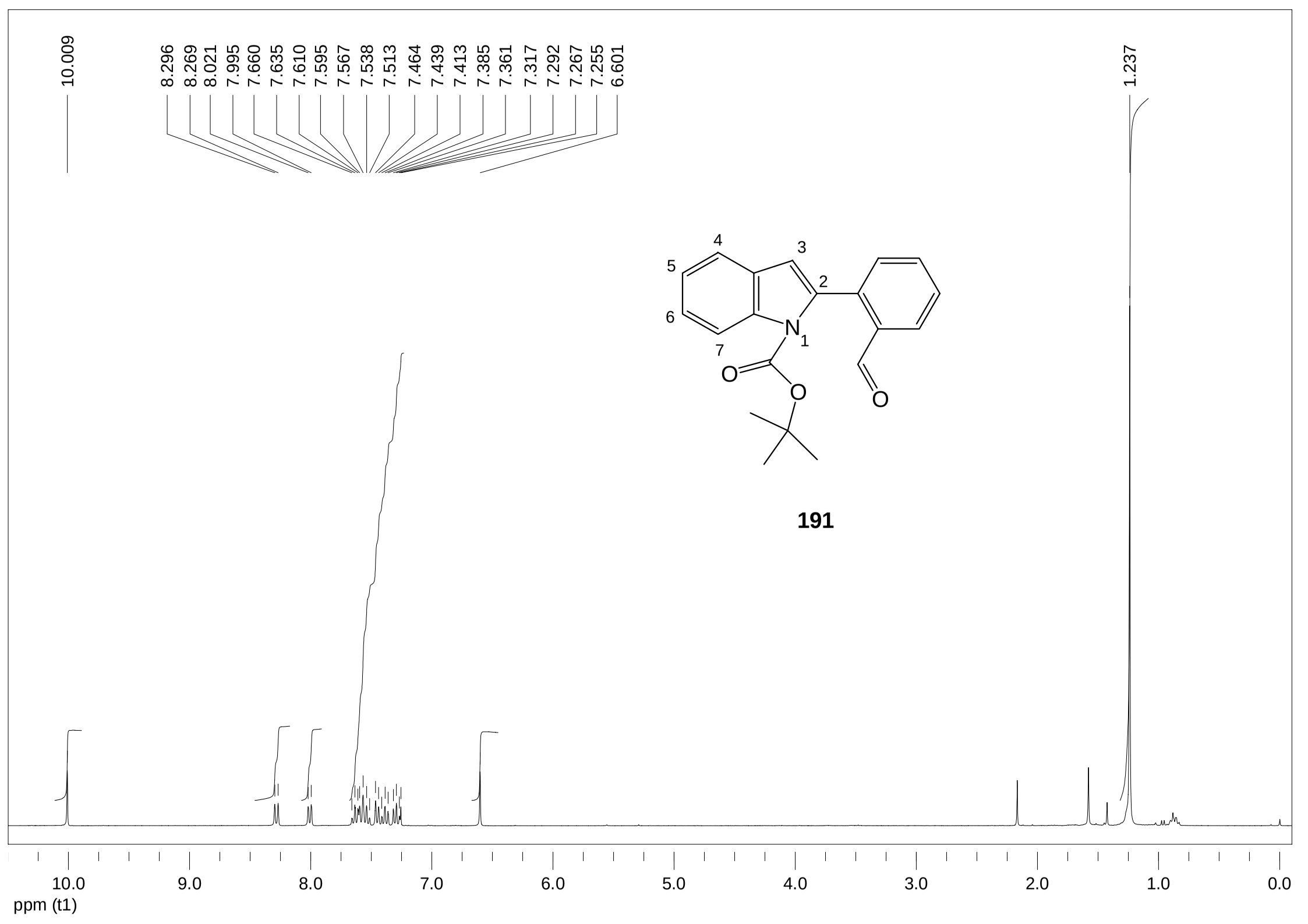
Bond	Bond Angle
c(12)-c(13)-c(14)	120.01(15)
c(12)-c(13)-h(13)	120.3(11)
c(14)-c(13)-h(13)	119.7(11)
c(13)-c(14)-c(15)	120.02(15)
c(13)-c(14)-h(14)	122.5(11)
c(15)-c(14)-h(14)	117.5(11)
c(14)-c(15)-c(10)	120.43(14)
c(14)-c(15)-h(15)	121.6(10)
c(10)-c(15)-h(15)	118.0(10)
c(8)-n(1)-c(5)	111.83(11)
c(8)-n(1)-c(9)	123.75(12)
c(5)-n(1)-c(9)	124.40(11)

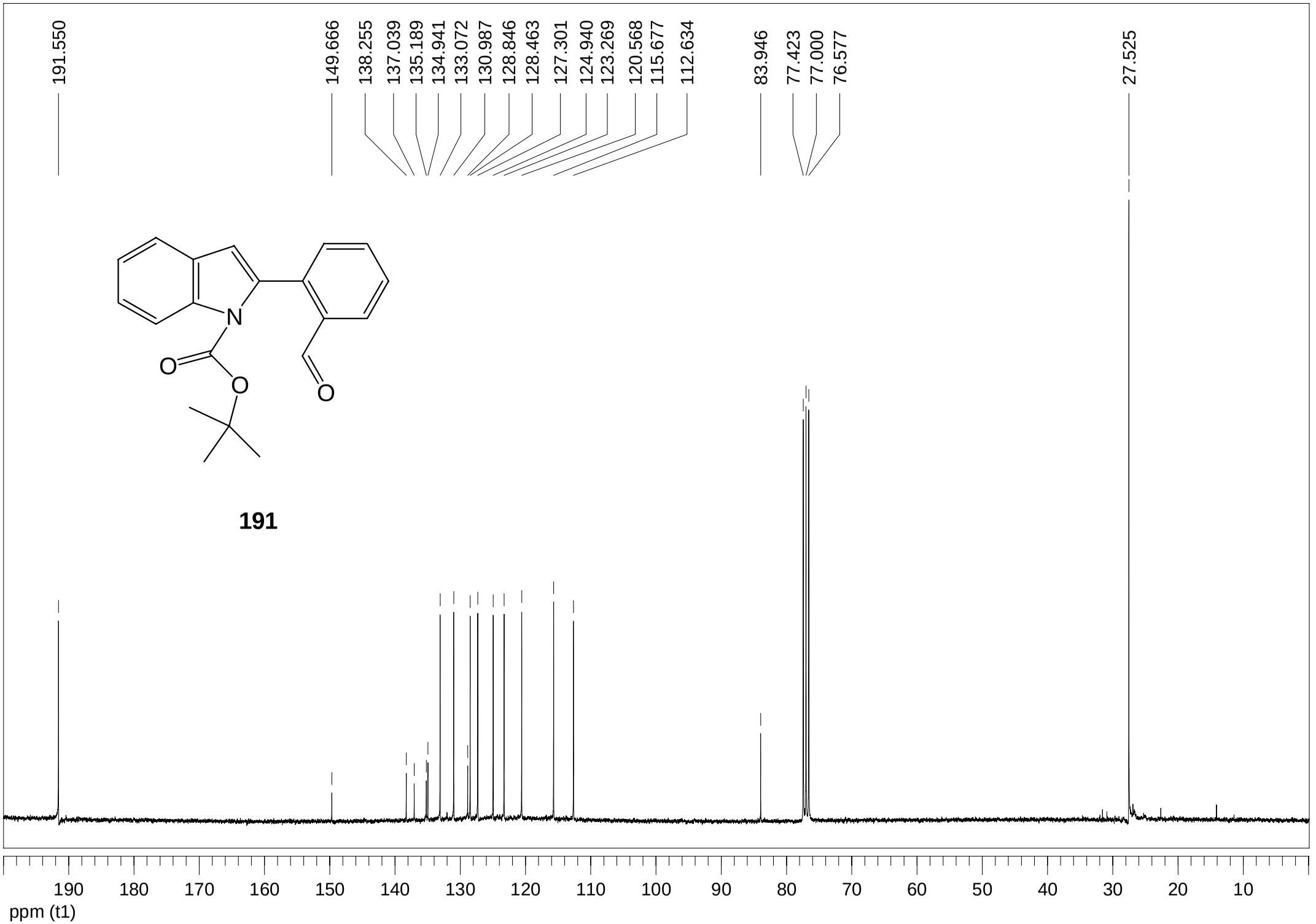
Table 4 Continued: Bond angles [degrees] for 1-Benzyl-3,3-dichloroindolin-2-one **209**

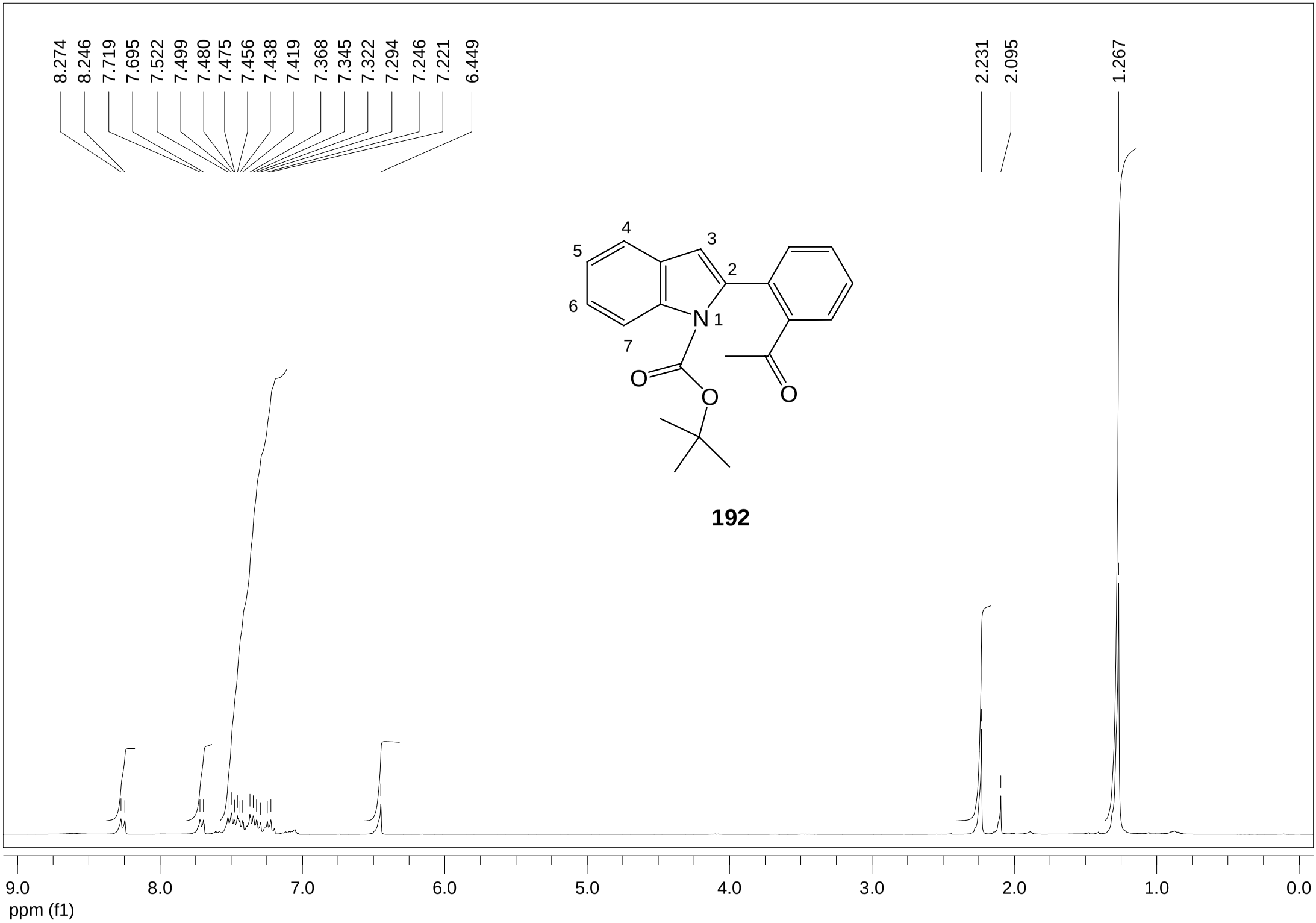
Bond	Bond Angle
c(6)-c(1)-c(2)-c(3)	-0.3(2)
c(1)-c(2)-c(3)-c(4)	0.6(2)
c(2)-c(3)-c(4)-c(5)	-0.3(2)
c(3)-c(4)-c(5)-c(6)	-0.10(19)
c(3)-c(4)-c(5)-n(1)	179.95(12)
c(2)-c(1)-c(6)-c(5)	-0.1(2)
c(2)-c(1)-c(6)-c(7)	177.75(14)
c(4)-c(5)-c(6)-c(1)	0.29(19)
n(1)-c(5)-c(6)-c(1)	-179.75(12)
c(4)-c(5)-c(6)-c(7)	-177.99(12)
n(1)-c(5)-c(6)-c(7)	1.97(14)
c(1)-c(6)-c(7)-c(8)	178.48(14)
c(5)-c(6)-c(7)-c(8)	-3.49(13)
c(1)-c(6)-c(7)-cl(2)	59.00(18)
c(5)-c(6)-c(7)-cl(2)	-122.96(10)
c(1)-c(6)-c(7)-cl(1)	-65.48(17)
c(5)-c(6)-c(7)-cl(1)	112.56(10)
c(6)-c(7)-c(8)-o(1)	-176.75(14)
cl(2)-c(7)-c(8)-o(1)	-54.30(18)
cl(1)-c(7)-c(8)-o(1)	64.32(16)
c(6)-c(7)-c(8)-n(1)	3.86(14)
cl(2)-c(7)-c(8)-n(1)	126.32(10)
cl(1)-c(7)-c(8)-n(1)	-115.06(10)
n(1)-c(9)-c(10)-c(11)	-122.02(14)
n(1)-c(9)-c(10)-c(15)	59.21(17)
c(15)-c(10)-c(11)-c(12)	-0.2(2)
c(9)-c(10)-c(11)-c(12)	-178.95(13)
c(10)-c(11)-c(12)-c(13)	0.6(2)
c(11)-c(12)-c(13)-c(14)	-0.3(2)
c(12)-c(13)-c(14)-c(15)	-0.4(2)
c(13)-c(14)-c(15)-c(10)	0.8(2)
c(11)-c(10)-c(15)-c(14)	-0.5(2)
c(9)-c(10)-c(15)-c(14)	178.28(13)
o(1)-c(8)-n(1)-c(5)	177.75(14)
c(7)-c(8)-n(1)-c(5)	-2.88(14)
o(1)-c(8)-n(1)-c(9)	-3.7(2)
c(7)-c(8)-n(1)-c(9)	175.62(11)
c(4)-c(5)-n(1)-c(8)	-179.37(13)
c(6)-c(5)-n(1)-c(8)	0.67(15)
c(4)-c(5)-n(1)-c(9)	2.1(2)
c(6)-c(5)-n(1)-c(9)	-177.82(12)
c(10)-c(9)-n(1)-c(8)	-107.47(15)
c(10)-c(9)-n(1)-c(5)	70.85(17)

Table 5: Torsion angles [degrees] for 1-Benzyl-3,3-dichloroindolin-2-one **209**

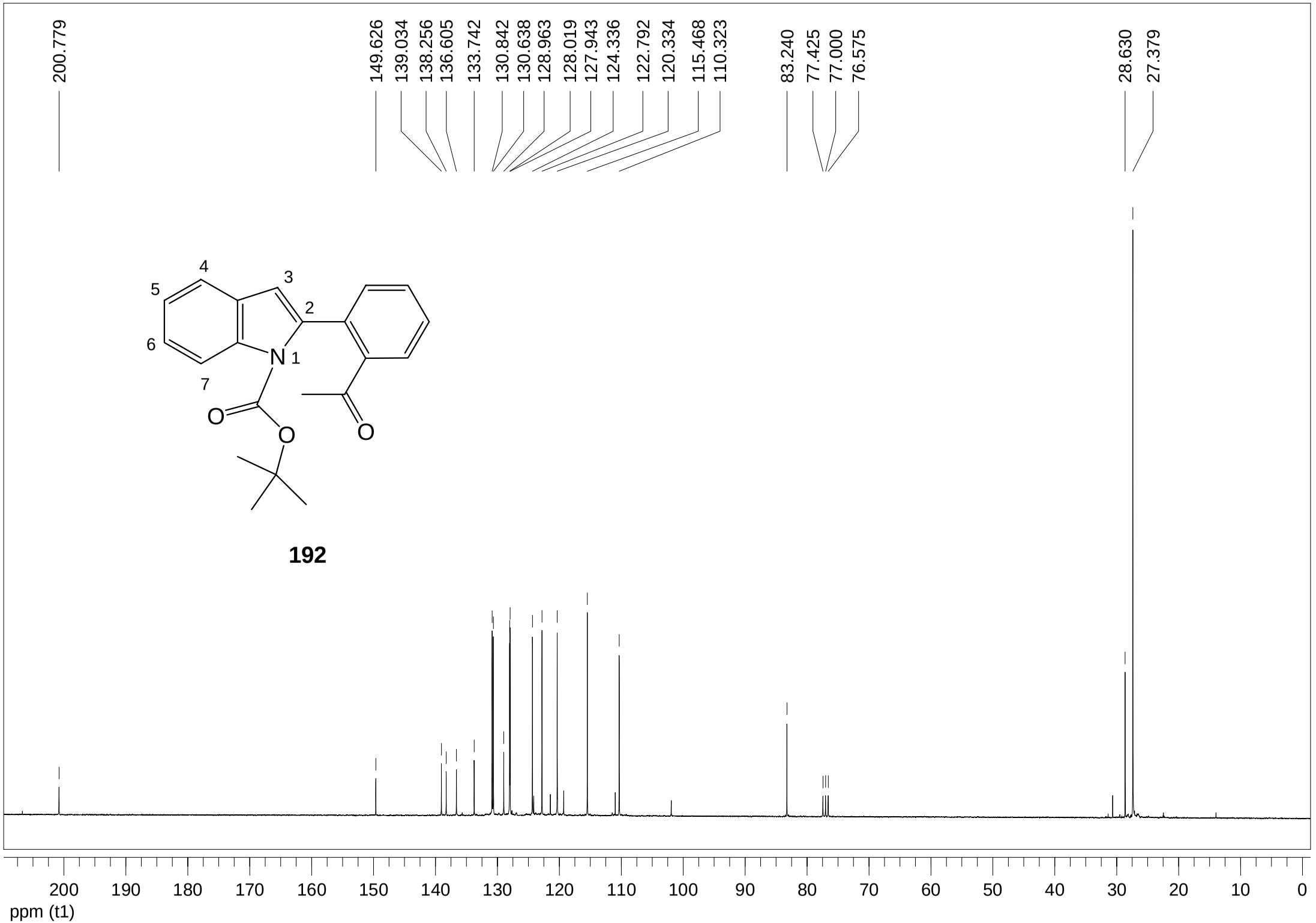
Appendix II – Selected NMR Spectra


10.009
8.296
8.269
8.021
7.995
7.660
7.635
7.610
7.595
7.567
7.538
7.513
7.464
7.439
7.413
7.385
7.361
7.317
7.292
7.267
7.255
6.601
1.237
4
3
5
2
6
N
1
7
O
O
O
191
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

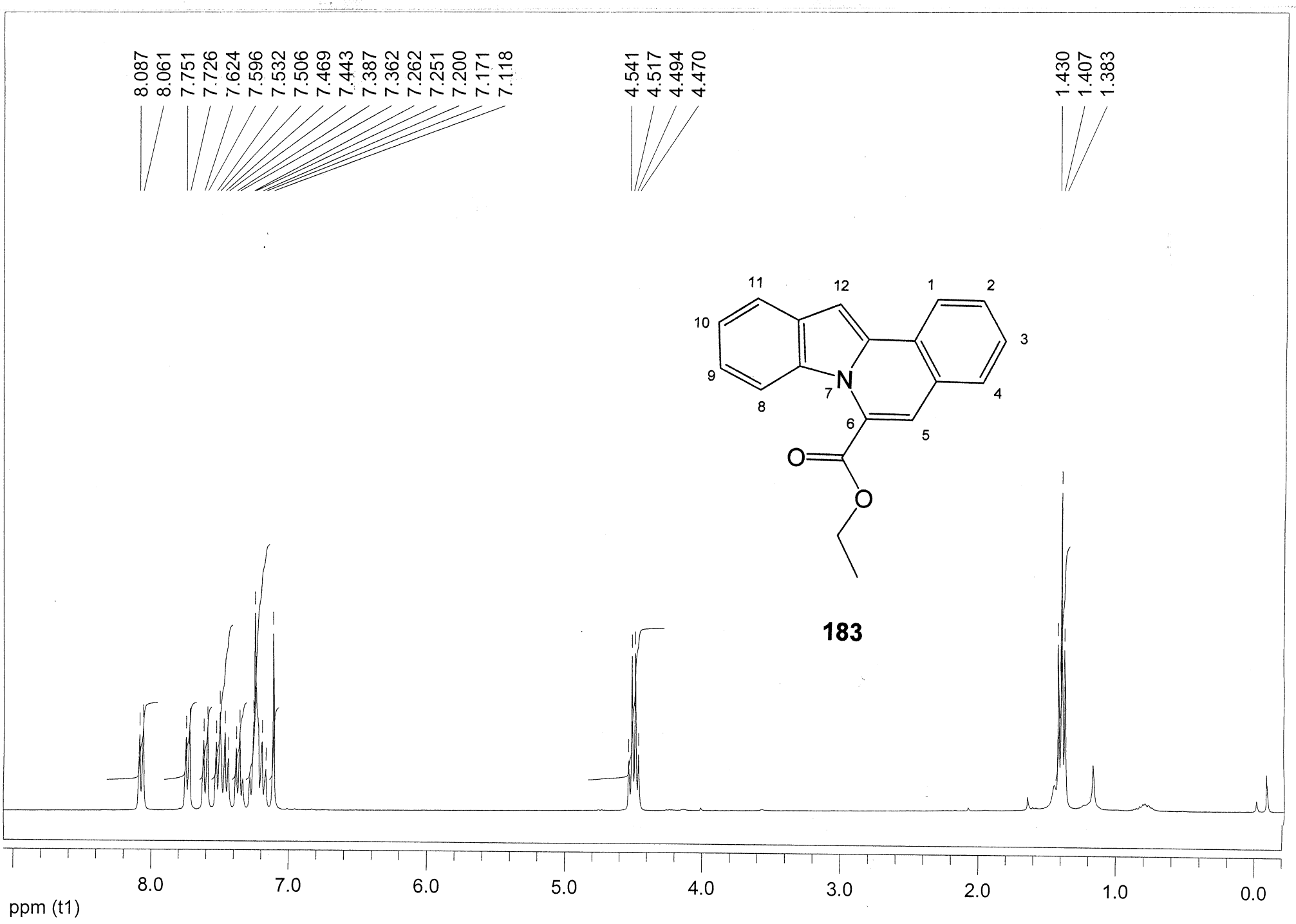

191.550
149.666
138.255
137.039
135.189
134.941
133.072
130.987
128.846
128.463
127.301
124.940
123.269
120.568
115.677
112.634
83.946
77.423
77.000
76.577
27.525
N
O
O
O
191
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


8.274
8.246
7.719
7.695
7.522
7.499
7.480
7.475
7.456
7.438
7.419
7.368
7.345
7.322
7.294
7.246
7.221
6.449
2.231
2.095
1.267
4
3
5
2
6
N 1
7
O
O
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

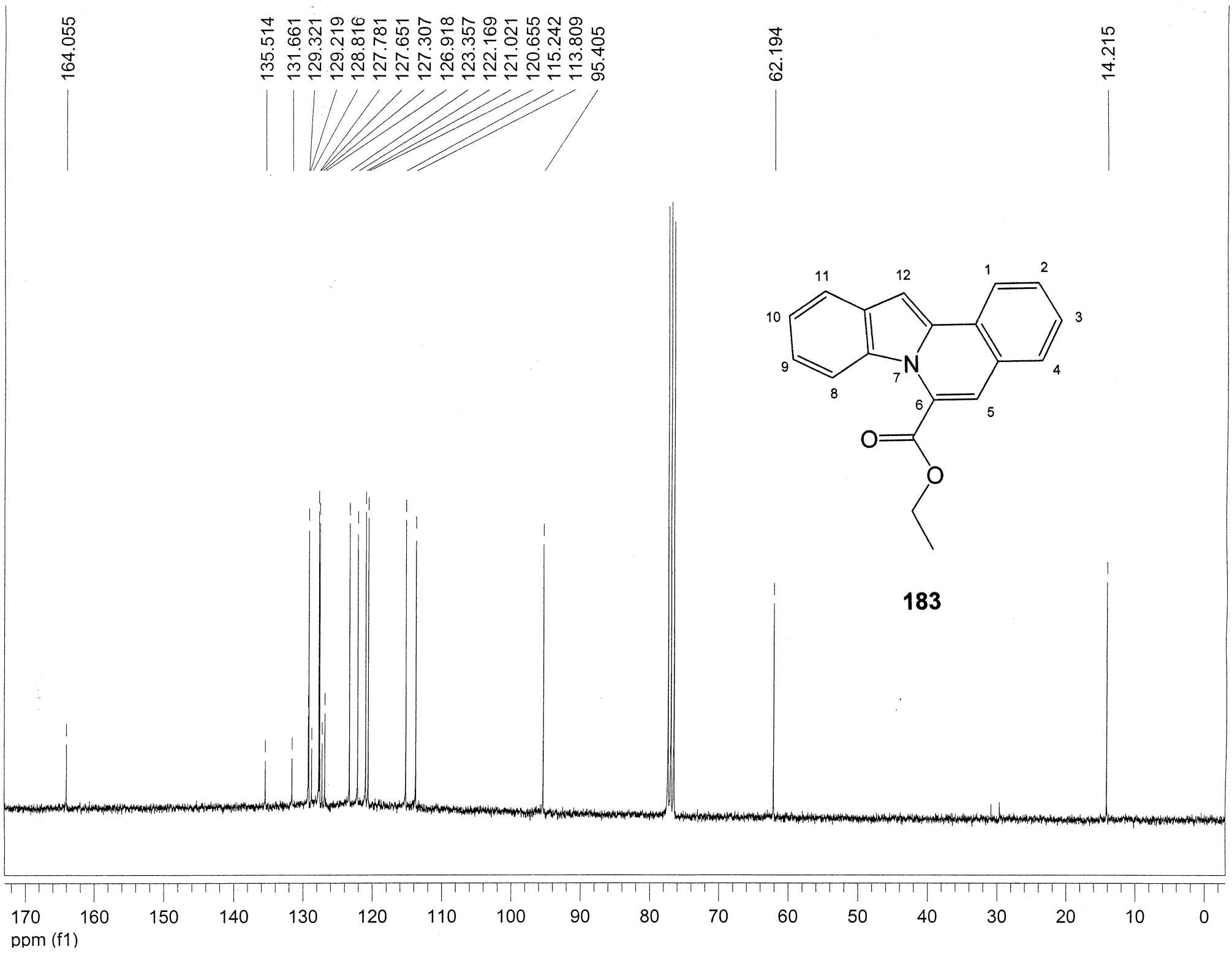
192


200.779
149.626
139.034
138.256
136.605
133.742
130.842
130.638
128.963
128.019
127.943
124.336
122.792
120.334
115.468
110.323
83.240
77.425
77.000
76.575
28.630
27.379
4
3
5
2
6
N 1
7
O
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)

192


8.087
8.061
7.751
7.726
7.624
7.596
7.532
7.506
7.469
7.443
7.387
7.362
7.262
7.251
7.200
7.171
7.118
4.541
4.517
4.494
4.470
1.430
1.407
1.383
11
12
1
2
10
3
9
N
7
4
8
6
5
O
O
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

183


164.055
135.514
131.661
129.321
129.219
128.816
127.781
127.651
127.307
126.918
123.357
122.169
121.021
120.655
115.242
113.809
95.405
62.194
14.215
11
12
1
2
10
3
9
N
7
4
8
6
5
O
O
183
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)