Rearrangements in the Indolo[2,3-*b*]quinoline System: A Novel Approach to the Synthesis of Perophoramidine and the Communesins

Thesis Presented for the degree of Doctor of Philosophy

Nicholas Voûte

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School of Chemistry

University of St Andrews

Contents

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I, Nicholas Voûte, hereby certify that this thesis, which is approximately 45000 words in length, has been written by me, that is a record of my work carried out by me and that it has not been submitted in any previous application for a higher degree.

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Abbreviations

Ac	acetyl
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
calcd	calculated
CAN	ceric ammonium nitrate
CI	chemical ionisation
COSY	proton-proton correlation spectroscopy
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec.	decomposition
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMB	dimethoxybenzyl
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	*N*,'*N*-dimethylpiperazine
DMPU	*N*,'*N*-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
E	electrophile
e.r.	enantiomeric ratio
ED_{50}	dose effecting 50% of sample
EDG	electron donating group
EI	electron impact
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl

ether	diethyl ether
g	gram(s)
HCT	human colon tumour
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IC_{50}	inhibition concentration affecting 50% of specimens
IR	infrared
J	coupling constants (in NMR spectroscopy)
LDA	lithium diisopropylamide
M	Molar, mol dm^{-3}
m	multiplet
Me	methyl
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NCS	*N*-chlorosucinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nos	*o*-nitrobenzensulfonyl
P	protecting group
PARP	Poly ADP ribose polymerase
PENDANT	polarization enhancement nurtured during attached nucleus testing
Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl

PPTS	pyridinium *p*-toluenesulfonate
q	quartet
Red-Al	sodium bis(2-methoxyethoxy)aluminiumhydride
s	singlet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TCA	trichloroacetic acid
TEOC	β-(trimethylsilyl)ethoxycarbonyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Tol	tolyl (methylphenyl)
TosMIC	tosylmethyl isocyanide
vol.	volume(s)
δ	chemical shift
µ	micro

Abstract

This thesis describes investigations directed towards developing a novel synthetic route to the natural products perophoramidine and the communesins, with particular emphasis placed on the formation of the two vicinal all-carbon quaternary centres contained in these molecules.

Chapter 1 introduces perophoramidine and the communesin group of natural products and explains how they are related to the calycanthaceous alkaloids. The isolation of perophoramidine and the communesins is outlined and their biosynthesis is discussed. Specific structural features of these natural products are highlighted before established synthetic strategies are reviewed. Chapter 1 concludes by proposing a novel synthetic route for the synthesis of perophoramidine and the communesins that involves a Claisen rearrangement in the indolo[2,3-*b*]quinoline system as a key step.

Chapter 2 describes model studies on the proposed Claisen rearrangement in an attempt to form a quaternary centre in the indolo[2,3-*b*]quinoline system. These initial studies did not result in the generation of the desired quaternary centre. However, a detailed understanding of the reactions that occur leads to the design of a new model substrate.

Chapter 3 describes studies on the revised model system that result in the formation of the desired quaternary centre using a Claisen rearrangement. The differences between the two systems are discussed before an investigation into the scope of the rearrangement is described. Chapter 3 concludes by describing an investigation into a protecting group strategy that would by required with this synthetic route.

Chapter 4 describes investigations into the formation of the second vicinal quaternary centre using a model system. The synthetic routes investigated lead to two separate methods for the formation of the desired quaternary centre.

Chapter 5 describes investigations into the effect a C-10 substituent has on the Claisen rearrangement. Additionally, an asymmetric version of the Claisen rearrangement is examined. Chapter 5 culminates in the preparation of an intermediate relevant to an asymmetric synthesis of the communesins.

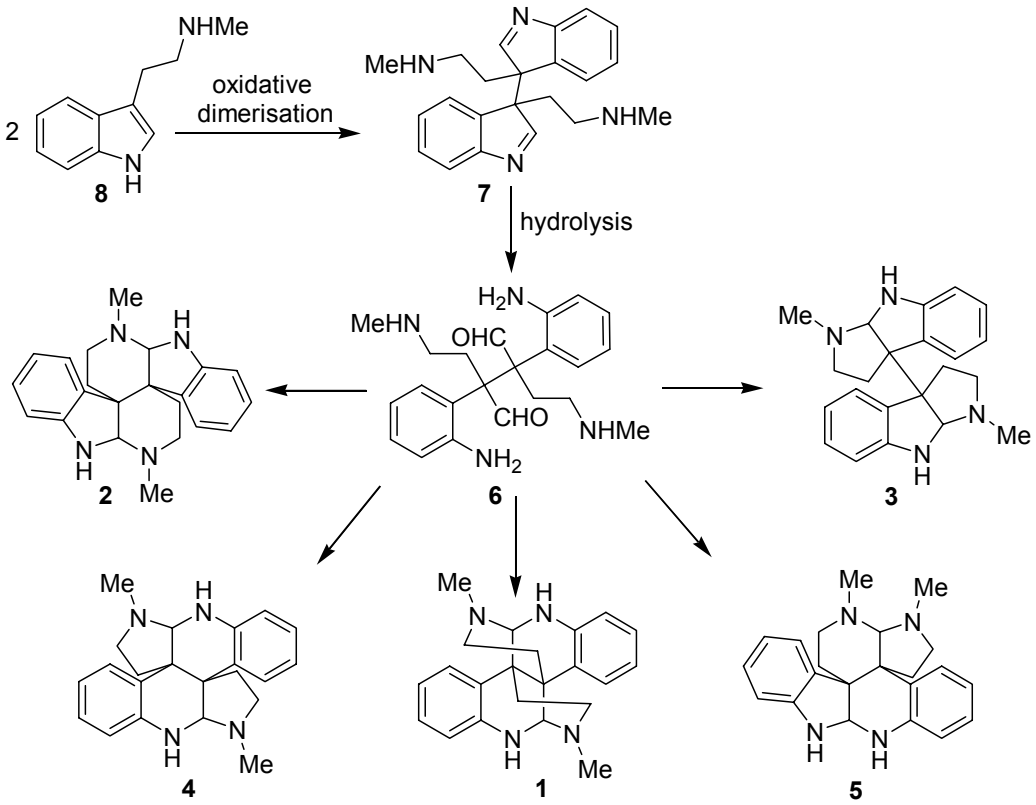
Chapter 1: Introduction

1.1 The alkaloids

Due to their diverse biological properties, the alkaloids have been utilised as medicines and poisons throughout history.[1] From ancient times the alkaloids have been used in the form of crude extracts from their natural sources. Only relatively recently has it become possible to isolate these naturally occurring compounds and to determine their precise molecular structures. An early example is the structural elucidation of the morphine alkaloids through the degradation studies conducted by Robinson and Gulland.[2] By determining their molecular structures, it became apparent that the structures of many alkaloids contain the indole ring system. These indole alkaloids have received a great amount of attention from the scientific community due to the remarkable biological properties many of these compounds display.[3] However, it is often not simply the biological properties of natural products that fascinates the synthetic chemist. The synthesis of natural products plays an integral part in gaining an understanding of chemical reactivity and in the development of new synthetic methodology. Furthermore, the total synthesis of a natural product is one of the most rigorous tests of a proposed molecular structure. The isolation, structural determination and synthesis of the indole alkaloids continues to pose new challenges to the chemist.

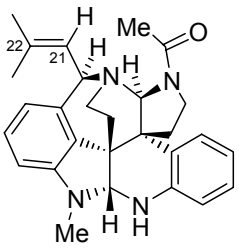
1.2 The calycanthaceous alkaloids

Following the structural determination of the natural product calycanthine, it was postulated that calycanthine represents one of the five structural isomers, **1**, **2**, **3**, **4** and **5**, that can be feasibly derived, through bis-aminal formation, from the hypothetical intermediate **6** (**Scheme 1**).[4] This intermediate **6** can be produced by hydrolysis of indolenine **7**, which can arise from the oxidative dimerisation of *N*-methyltryptamine **8**.

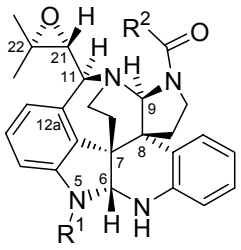


Scheme 1. The possible structural arrangements for the calycanthaceous alkaloids.

Before 1993 only three of these structural arrangements **1**, **3** and **4** were represented by, for example, the known natural products calycanthine[4,5], chimonanthine[6,7] and *iso*-calycanthine[8] respectively. Structural arrangements **2** and **5** were unknown in nature at that time. However, various natural products representing **5** have recently been discovered (natural examples of structural arrangement **2** are currently still unknown). First, the natural products communesin A (**9**) and communesin B (**10**) were isolated from a strain of *Penicillium* fungus found attached to the marine alga *Enteromorpha intestinalis* (**Figure 1**).[9] Later, communesins C (**11**) and D (**12**) were isolated from a strain of *Penicillium* fungus found living on the marine sponge *Axinella verrucosa*.[10] Subsequently, terrestrial sources also yielded natural products with the communesin parent structure. Communesin D (**12**) along with the novel communesins E (**13**) and F (**14**) were isolated from the soil inhabiting fungus *Penicillium expansum*,[11] and communesins A (**9**) and B (**10**) have been independently reported to be present in this fungus.[12] Most recently, communesins G (**15)** and H (**16**) were isolated from the psychrotolerant fungus *Penicillium rivulum*.[13]



communesin F **14**



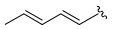
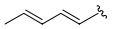
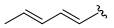
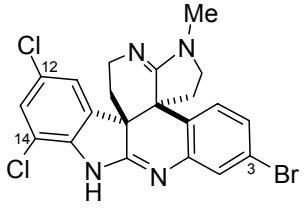
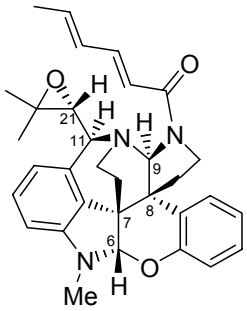
communessin		R^1	R^2
9	A	CH_3	CH_3
10	B	CH_3	
11	C	H	
12	D	CHO	
13	E	H	CH_3
15	G	CH_3	CH_2CH_3
16	H	CH_3	$CH_2CH_2CH_3$

Figure 1. The communesin family of natural products.

The eight known members of the communesin group of natural products show structural variation at the three positions R^1, R^2 and the oxidation state at the isoprene motif. All the communesins other than communesin F (**14**), which displays an unoxidised alkene of the isoprene derived motif, have a C-21-C-22 epoxide. A methyl substituent is present on the indolic nitrogen N-5 in all the communesin structures except in communesin C (**11**) and E (**13**), which are unsubstituted at this position (R^1 = H), and communesin D (**12**), which has an N-5 formyl group (R^1 = CHO). Four different R^2 substituents have been observed in the communesins. In communesin A (**9**), E (**13**) and F (**14**) R^2 is a methyl group. Whereas in communesins G (**15**) and H (**16**), R^2 is a saturated ethyl or propyl aliphatic chain. Finally, communesin B (**10**), C (**11**), and D (**12**) display an unsaturated 2,4-pentadiene chain at R^2.



perophoramidine **17**



nomofungin **18**
(original proposed structure)

Figure 2. The structure of perophoramidine and the proposed structure of nomofungin.

Moreover, structural arrangement **5** is not exclusive to the communesin family of natural products (**Figure 2**). The natural product perophoramidine (**17**), isolated from the Philippine ascidian *Perophora namei*,[14] represents an oxidised version of structure **5** and the natural product nomofungin (**18**), isolated from an unidentified fungus found on the bark of *Ficus microcarpa*, represents an appended version of structure **5**.[15]

Interestingly, communesin B (**10**) and nomofungin (**18**) display striking similarities in their proposed structure, reported spectral data (their NMR chemical shifts and coupling constants are essentially identical) and biological properties. These similarities led to the proposal that communesin B (**10**) and nomofungin (**18**) are in fact the same compound.[16] Initially, in an attempt to determine which structure correctly represented the natural product, a comparison of the ^{13}C and ^{1}H NMR chemical shifts of C-6 and H-6 with similar aminal and hemiaminal containing compounds suggested the aminal functionality present in the communesin B structure (**10**) was the most likely representation of the natural product(s) in question.[16,17] Furthermore, partial synthesis of both the nomofungin (**18**) and the communesin core structures by the research group of Stoltz,[16,17] and later by the group of Funk,[18] provided corroborating evidence in favour of the communesin B structure (**10**). The observation that there is no feasible biosynthetic pathway to nomofungin, as there is in the case of communesin B **10**, was also instrumental in the rejection of the proposed nomofungin structure (**18**).[16,17] Whilst the paper describing the isolation, structural determination and biological properties of nomofungin (**18**) was withdrawn in response to the publication of these refuting investigations, the contribution made by the authors in regard to the relative and absolute stereochemistry, and their finding on the biological properties of nomofungin/communesin B should not be ignored.[19]

1.3 Structural features of the communesins and perophoramidine

The communesins (**9-16**) and perophoramidine (**17**) all possess architecturally intriguing structures with the same core hexacyclic structure containing vicinal all-carbon quaternary stereocentres. The communesins, in contrast to perophoramidine (**17**), possess an additional azapine ring system. Perophoramidine (**17**) displays halogen substitution at C-3, C-12 and C-14, whereas the aromatic ring system of the communesins is substituted at C-12a with, presumably, an isoprene derived unit that is oxidised in most cases. The relative stereochemistry of perophoramidine (**17**), which was determined using NMR techniques,[14] is opposite to that displayed at the vicinal quaternary centres in the communesin structure: in perophoramidine the two 2C units are *trans* whereas in the communesins the two 2C units are *cis*. The first isolation report of the communesins A (**9**) and B (**10**) assigned the relative stereochemistry at all the stereocentres, other than at C-21, to be that as shown in **Figure 1** using ^{1}H-^{1}H nOe correlations.[9] The later isolation of the communesins C to H prompted

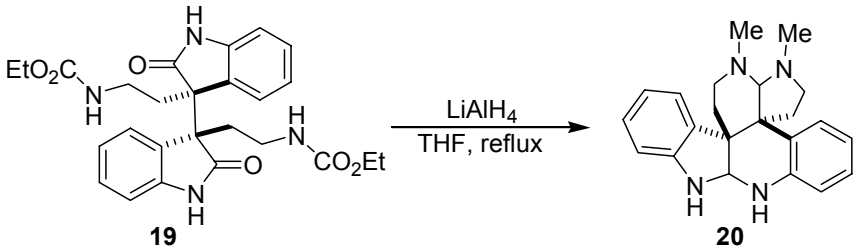
reinvestigation of the substructure's relative stereochemistry and corroborated the initial findings for communesin A (**9**) and B (**10**), therefore showing that all the communesins have the same relative stereochemistry.[10,11,13] The later investigations also assigned the relative configuration at C-21 using Murata's *J*-based configurational analysis[20] and proposed that the C-21 configuration is as depicted in **Figure 1**. The relative stereochemistry assigned to the communesins by all of these investigations is consistent with the independent stereochemical assignments made for nomofungin (**18**) (communesin B (**10**)).[15] In addition, the investigations leading to the proposed nomofungin structure (**18**) addressed the question of this compound's absolute stereochemistry and conclude, by use of the circular dichroism exciton chirality method,[21,22] that the absolute configuration is 11*S*, 7*R*, 6*S*, 9*S*, 8*R*, 21*R* (**Figure 2**).[15] However, considering that the original structural assignment of nomofungin (**18**) was incorrect, it is necessary to treat this assignment of absolute stereochemistry with caution. Despite the fact that naturally occurring perophoramidine (**17**) is reported to have an optical rotation, the absolute stereochemistry of perophoramidine has not been assigned.[14]

1.4 Biological properties of the communesins and perophoramidine

Communesin A (**9**) and, to a greater extent, communesin B (**10**) have been reported to exhibit cytotoxic activity against P-388 lymphocytic leukaemia cells (ED_{50} = 7.7 μM and 0.9 μM respectively).[9] It is proposed that the cytotoxic effect of communesin B (**10**) is achieved by disruption of the microfilament network in mammalian cells,[15] a property shared with the fungal metabolite cytochalasin D.[23] The communesins A (**9**), B (**10**), D (**12**), E (**13**), and F (**14**) have been shown to display insecticidal activity, when assayed against the larvae of silkworms, and again communesin B (**10**) showed the highest activity.[11] perophoramidine (**17**) has been shown to be cytotoxic to the HCT116 colon carcinoma cell line (IC_{50} = 60 μM) and induces apoptosis *via* PARP cleavage.[14] The communesins G (**15**) and H (**16**) have been tested in various antimicrobial, antiviral and anticancer assays but failed to show significant activity.[13]

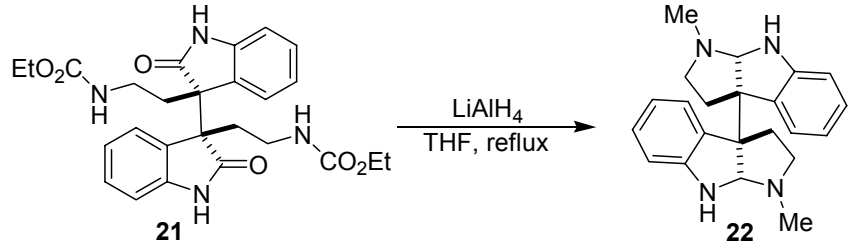
1.5 Biosynthesis of the communesins and perophoramidine

Presumably, the communesins and perophoramidine (**17**), given their structural similarities, are formed *via* similar biosynthetic pathways. Various synthetic studies have demonstrated the feasibility of a calycanthaceous alkaloid biosynthesis involving the oxidative union of two moles of tryptamine followed by bis-aminal formation.[16,17,24] Of greatest relevance to the biosynthesis of the communesins and perophoramidine is the observation, made before the isolation of these natural products, that reductive cyclisation of **19** with lithium aluminium hydride in refluxing tetrahydrofuran affords **20** (yield not reported) that displays the relative stereochemistry of perophoramidine (**17**) (**Scheme 2**).[25]



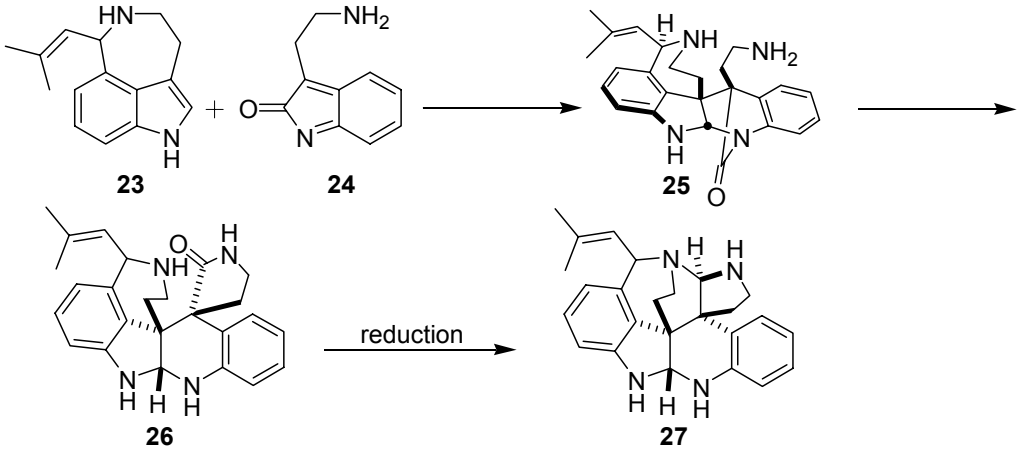
Scheme 2. Compound **20** is the only product reported from the reductive cyclisation of **19**.[25]

Surprisingly, reductive cyclisation of **21**, the C2-symmetric diastereoisomer of **19**, is reported to afford **22** and not structural arrangement **5** with the communesin relative stereochemistry (**Scheme 3**).[25] However, as the yield of **22** is not reported, it is not possible to draw the conclusion that structural arrangement **5** with the communesin relative stereochemistry cannot be formed by the reduction of **21**. Nonetheless, the observation that **20** can be formed from **19** supports the hypothesis that structural arrangement **5** can arise from the dimerisation of tryptamine derivatives in a similar way to the other calycanthaceous alkaloids.



Scheme 3. Compound **22** is the only product reported from the reductive cyclisation of **21**.[25]

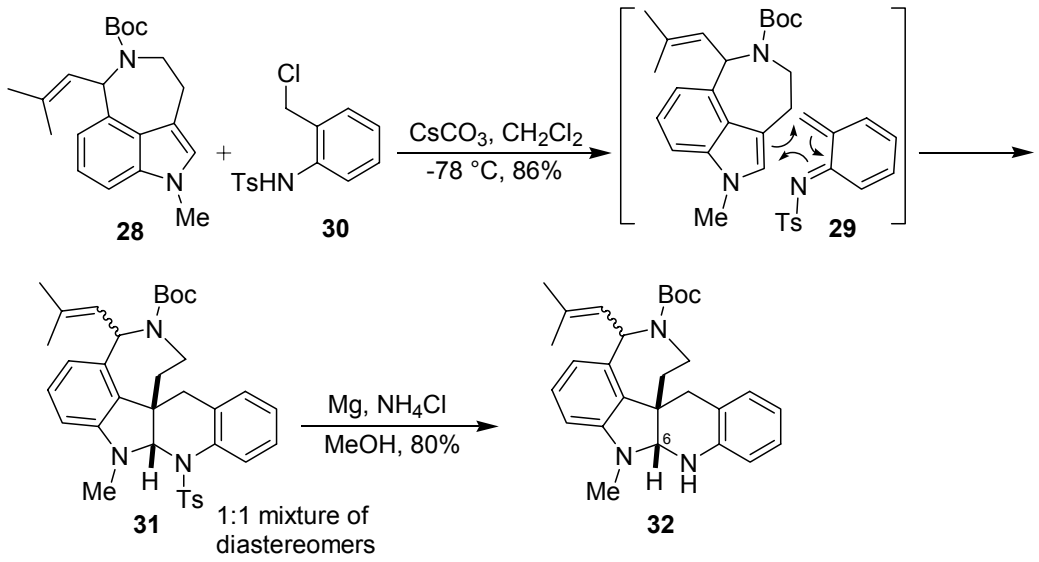
Specifically in the case of communesin biosynthesis, it has been suggested that the union of the *penicillium* fungal alkaloid aurantioclavin (**23**) with an oxidised tryptamine derivative, such as **24**, in a Diels-Alder type process would give the polycyclic cycloadduct **25** (**Scheme 4**).[16,17] The highly strained lactam of **25** would be easily opened by the primary amine to give **26** that following reduction and aminal closure would afford the communesin framework **27**.



Scheme 4. A proposed biosynthetic pathway to the communesins.[16]

Synthetic studies have been presented in support of this hypothesis.[16,17] They involve the use of a hetero-Diels-Alder reaction between *N*-Boc protected aurantioclavin **28** and the quinone methide imine **29**, generated from **30**, to form **31** as a mixture of diastereoisomers (**Scheme 5**). This study was also used to refute the nomofungin structure by comparison of H-6 and C-6 NMR chemical shifts of **32**, after the removal of the tosyl group from **31**, with those reported for communesin B (**10**)/nomofungin (**18**).[16,17]

Results from a recent detailed investigation into the biosynthesis of communesin A (**9**) and B (**10**), involving the addition of radio labelled precursors to microbial fermentation broths, support the hypothesis of a synthesis involving the dimerisation of two tryptamine based units, but do not support the idea that the construction of the isoprene unit, present in aurantioclavin, occurs prior to this dimerisation event.[26]



Scheme 5. The hetero-Diels-Alder reaction between *N*-Boc protected aurantioclavin **28** and quinone methide imine **30** demonstrates the feasibility of a similar biosynthetic pathway.[16]

It was found that when [2-^{13}C]-tryptophan was added during fermentation, the isolated communesins showed enrichment of the ^{13}C NMR signals associated with C-20 and C-17.[26] Not only is this consistent with a biosynthesis from two tryptophan derived moieties, but it also confirms the precise orientation of these units. Furthermore, the observation that ^{14}C-tryptophan and ^{3}H-methionine were incorporated into the communesins throughout production at a constant ratio suggested that these precursors were involved at approximately the same time. The incorporation of radio labels derived from ^{3}H-mevalonate and ^{14}C-tryptophan, however, did not show this constant ratio of incorporation throughout communesin production. Early in the fermentation process a high preference for tryptophan incorporation was observed, but later a preference for mevalonate was observed. These observations signify the early build up of a tryptophan based intermediate with addition of the isoprene based moiety, from mevalonate, occurring later in the biosynthesis. These results are in contrast to the hypothesis that reaction of tryptamine with aurantioclavin is an early step in communesin biosynthesis. Whilst it has been shown that methylation, with ^{3}H-methionine, and tryptamine dimerisation occur at approximately the same time, it has been suggested that dimerisation precedes methylation, based on the observation that methylation is not a crucial step in the synthesis of all the communesins.[26] However, the possible involvement of a demethylation step in the biosynthesis of communesin C (**11**) and D (**13**) has been ignored when drawing this conclusion. Indeed, the presence of the *N*-formyl group found in communesin D (**12**) could be considered as evidence for oxidative demethylation.

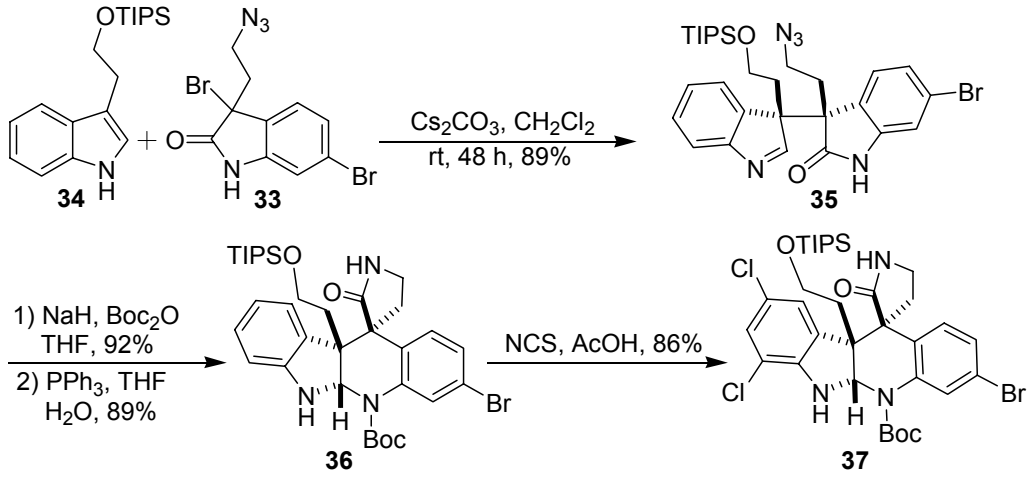
1.6 Approaches to the total synthesis of the communesins and perophoramidine

The communesin parent structure and perophoramidine (**17**) pose challenging synthetic targets. It is the two vicinal all-carbon quaternary centres, with a *trans* configuration in perophoramidine (**17**) and a *cis* configuration in the communesins, that are expected to be the most challenging aspect of any synthesis of these compounds. Generally, establishing all-carbon quaternary centres, particularly in an asymmetric manner, remains one of the key challenges of synthetic chemistry.[27-30]

Since the discovery of the communesins and perophoramidine (**17**) there have been numerous synthetic studies directed at the synthesis of these natural compounds. The first synthetic studies were not primarily concerned with the development of a total synthesis, but were mainly directed at elucidating the communesin B (**10**)/nomofungin (**18**) structure and investigating proposed biosynthetic pathways. This chapter will now outline these studies with particular attention being given to the key steps involved in the synthesis of the two vicinal quaternary centres. Many of these synthetic efforts can be described as biomimetic as they involve the union of tryptamine based moieties in either an inter- or an intramolecular fashion.

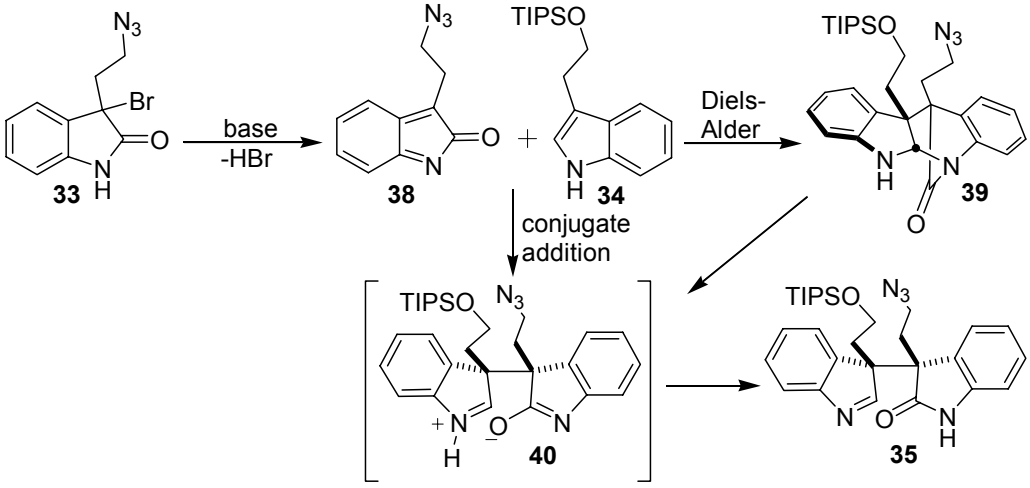
The first synthetic studies on the communesins were those published by Stoltz *et al.* detailing the reaction of Boc-protected aurantioclavin **28** with a quinone methide imine **29**.[16,17] As already stated, these studies were directed at providing corroborating evidence for the proposed biosynthetic pathway and demonstrating that the proposed nomofungin structure (**18**) was incorrect as well as developing a method for the synthesis of the natural products. As these studies have already been discussed (page 7) no further consideration will be given to them here.

Similar biomimetic approaches, reported by Funk *et al.*, have been applied to the synthesis of both perophoramidine (**17**) and the communesins, and have resulted in the first total synthesis of racemic perophoramidine (**17**).[31] The key step in Funk's synthesis of perophoramidine involves the coupling of 3-bromoindoline-2-one **33** and TIPS protected tryptophol **34** to form lactam **35** (**Scheme 6**).



Scheme 6. Key steps in the synthesis of racemic perophoramidine (**17**).[31] NCS = *N*-chlorosuccinimide, Boc = *tert*-butoxycarbonyl, TIPS = triisopropylsilyl.

After conversion of **35** to the Boc-derivative, reduction of the azide moiety causes a cascade sequence involving a transamidation and attack of the resulting Boc-protected aniline onto the indolenine ring to afford **36**. The electron rich aromatic ring of **36** was then chlorinated *ortho*- and *para*- to the indolic nitrogen to give **37**. Racemic perophoramidine (**17**) was then synthesised in eight more steps from **37**. The overall yield of perophoramidine (**17**) (twelve steps from **33**) was 10%.

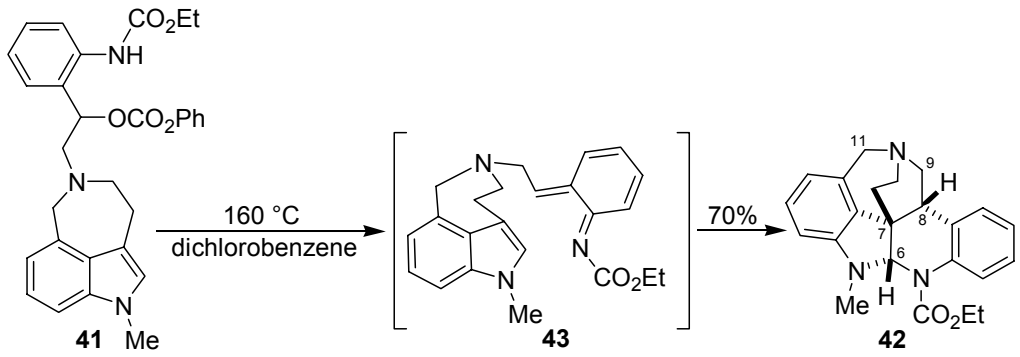


Scheme 7. Two alternative mechanisms have been suggested for the formation of **35** from **33** and **34**. TIPS = triisopropylsilyl.[33]

It has been proposed that the coupling of **33** with **34** proceeded by the initial *in situ* formation of the indole-2-one intermediate **38**, and two alternative mechanisms were suggested for the

subsequent formation of **35** (**Scheme 7**).[31] Either, a cycloaddition reaction occurs between **34** and **38** to form cycloadduct **39** that subsequently undergoes ring opening to form intermediate **40**, or a conjugate addition of **34** to **38** could directly form intermediate **40**. This second mechanism is presumably also possible in the case of the coupling of **28** with **29** (**Scheme 5**) that is reported by Stoltz *et al.* to proceed *via* a Diels-Alder type process.[16,17]

In model studies directed towards the synthesis and structural assignment of the communesins, Funk *et al.* describe an intramolecular hetero-Diels-Alder reaction used to form the core ring system and the C-7 quaternary centre (**Scheme 8**).[18] Thermolysis of carbonate **41** in dichlorobenzene gave **42** in good yield as a single diastereoisomer, presumably *via* an aza-Diels-Alder reaction of the intermediate **43**.

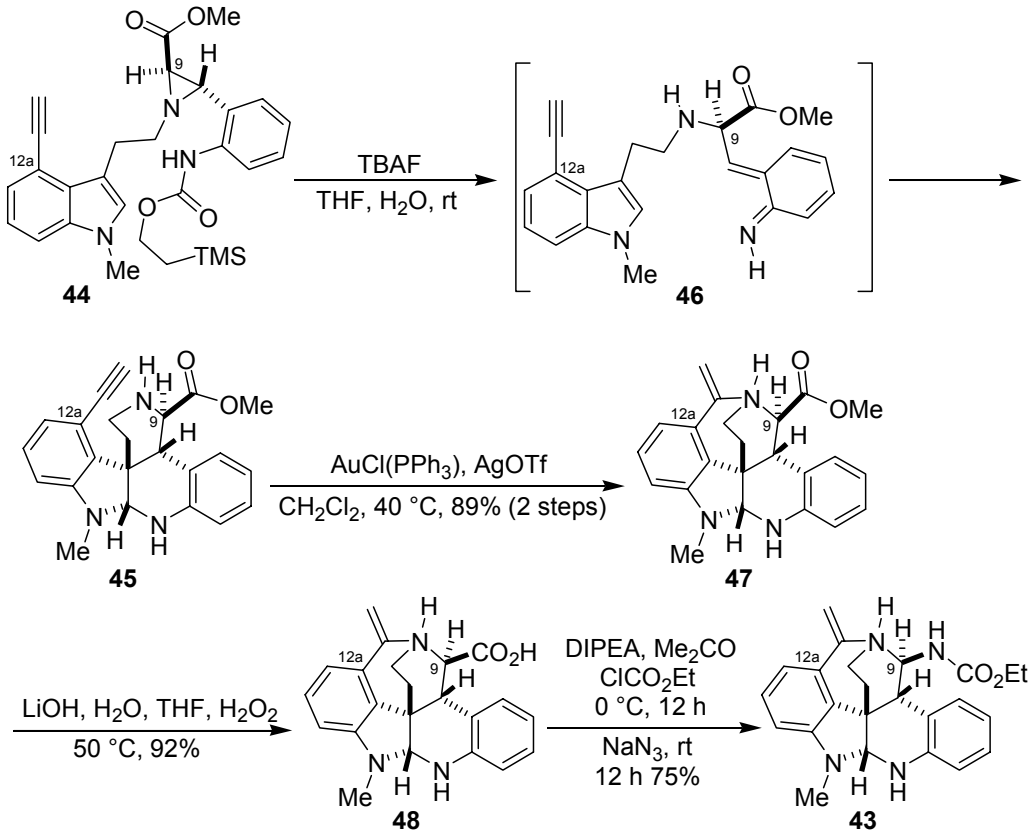


Scheme 8. An intramolecular hetero-Diels-Alder reaction is used to form the core ring system and the C-7 quaternary centre present in the communesins.[18]

In line with the study by Stoltz *et al.*, after hydrolysis of the carbamate moiety in **42**, a comparison of the C-6 and H-6 NMR chemical shifts with those of C-6 and H-6 of communesin B (**10**)/nomofungin (**18**) provided further evidence that the nomofungin structure (**18**) was incorrect. Currently, this synthetic route is not easily applicable to a total synthesis of the communesins as functionalisation of **42** at C-11, C-9 and C-8 is non-trivial.

To address this issue, a modification of this intramolecular hetero-Diels-Alder methodology was later published by Funk that involved the generation of the aza-*ortho*-xylylene by the ring opening of 2-(2-acylaminophenyl)aziridines (**Scheme 9**).[32] This method is reported to be preferable to that used previously as it allows for incorporation of a substituent at C-9 that can be used for the formation of the second aminal functionality present in the communesin structure. Additionally, in this synthesis an acetylene moiety is present at C-12a that gives a

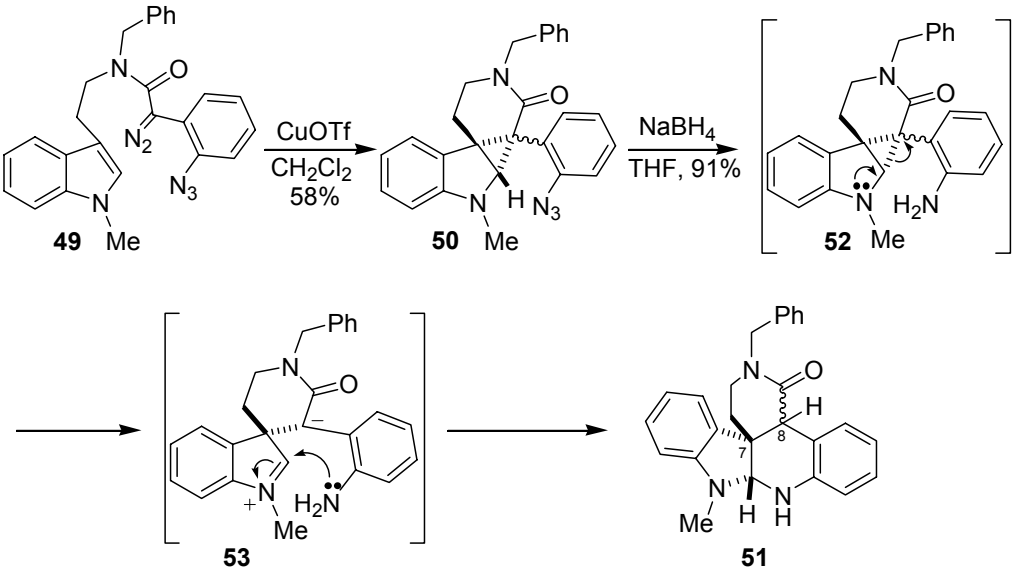
handle for the preparation of the isoprene unit. These synthetic studies culminate in the preparation of the advanced communesin intermediate **43**. Following preliminary studies on simplified substrates, it was discovered that treatment of the β-(trimethylsilyl)ethoxycarbonyl (TEOC) protected aniline **44** with tetrabutylammonium fluoride (TBAF) gave cycloadduct **45** *via* aza-*ortho*-xylylene **46**. Cycloadduct **45** was then converted to **47** using a gold catalysed intramolecular hydroamination.[33] Hydrolysis of the ester **47** to the corresponding acid **48** followed by mixed anhydride formation and treatment with sodium azide afforded **43** *via* a Curtius rearrangement that occurred with retention of configuration at C-9. It is envisaged that the C-8 quaternary centre will be formed by a C-H insertion reaction, directed from the top face to give the correct stereochemistry, of the appropriate diazo functionality.



Scheme 9. The synthesis of an advanced intermediate **43** in synthetic studies directed at the total synthesis of the communesins.[32] TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, DIPEA = *N*,*N*-diisopropylethylamine.

In model studies directed at developing a route to the communesins and perophoramidine (**17**), Qui *et al.* use an intramolecular cyclopropanation as a key step to construct the core indolo[2,3-*b*]quinoline ring system and the C-7 quaternary centre (**Scheme 10**).[34] This

approach can be, broadly speaking, classed as biomimetic as the synthesis of **49** originates from the two indole fragments tryptamine and isatin. The diazo decomposition of **49** in the presence of copper (I) triflate afforded the stable cyclopropane intermediate **50** as a mixture of diastereoisomers. Sodium borohydride reduction of the azide of **50** gave **51** after opening of the cyclopropane ring of **52** and subsequent addition of the resulting aniline functionality to the iminium ion present in **53**. The pentacycle **51** was formed as a mixture of diastereoisomers but with retention of stereochemistry at C-7. Although it is not reported, the C-8 quaternary centre is presumably formed by alkylation of the enolate derived from **51** by deprotonation of H-8.



Scheme 10. A cyclopropanation strategy for the formation of a perophoramidine and communesin core structure.[34] Tf = trifluoromethanesulfonyl.

An intermediate very similar to **51** is prepared, also from tryptamine and isatin but using a different route, in the total synthesis of racemic dehaloperophoramidine (**54**) (**Figure 3**) recently published by Rainier *et al*.[35] Whilst dehaloperophoramidine (**54**) has not been isolated from natural sources, the synthesis of **54** by the dehalogenation of naturally occurring perophoramidine (**17**), under ammonium formate catalytic transfer hydrogenolysis conditions, has been reported.[14]

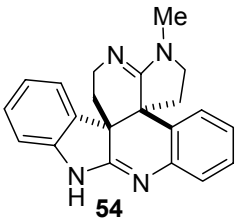
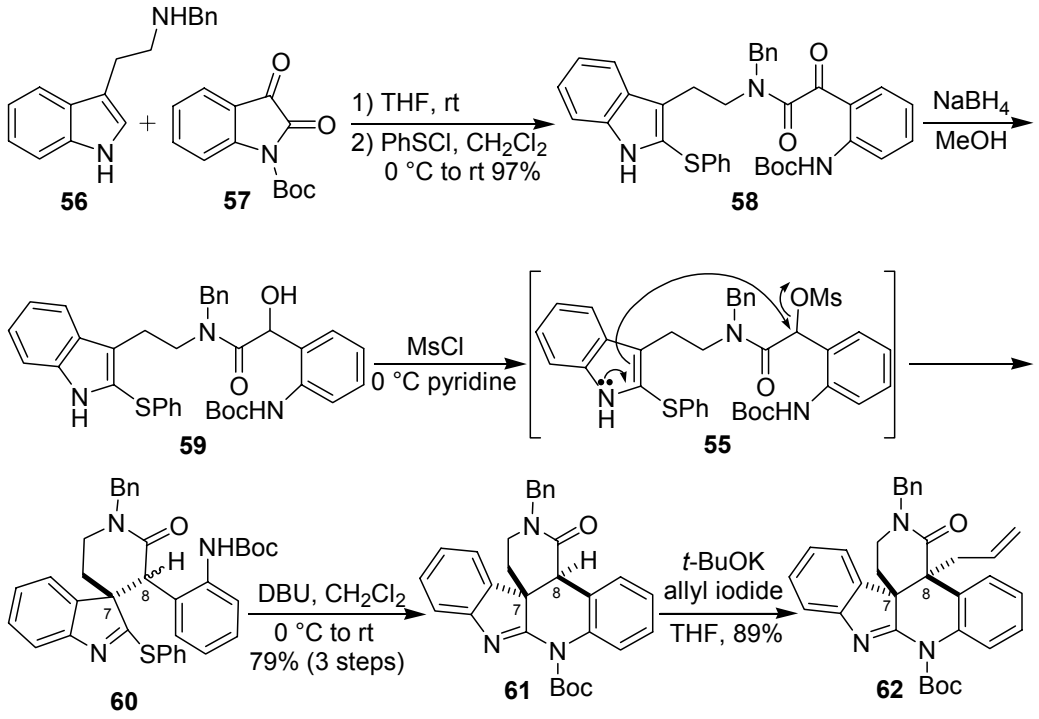


Figure 3. Dehaloperophoramidine (**54**) is not a known natural product, but it has been synthesised by the dehalogenation of naturally occurring perophoramidine (**17**).[14]

In Rainier's synthesis, which utilises thioindoles as key intermediates, the indolo[2,3-*b*]quinoline ring system and the C-7 quaternary centre are formed *via* the cyclisation of **55** followed by base treatment (**Scheme 11**).[35]

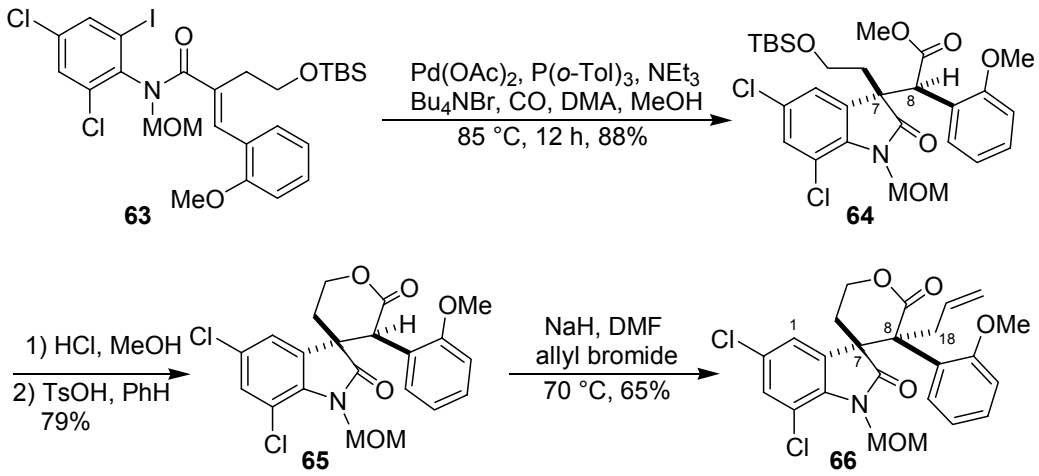


Scheme 11. Key steps in the total synthesis of dehaloperophoramidine published by Rainier *et al*.[35] Boc = *tert*-butoxycarbonyl, Ms = methanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Starting with the reaction of **56** with **57** and subsequent treatment of the product with benzenesulfenyl chloride, **58** is formed in excellent yield. After reduction of ketone **58**, alcohol **59** is treated with mesyl chloride. The thus formed mesylate **55** undergoes spontaneous cyclisation, indicating the highly nucleophilic nature that the thioether imparts upon the indole, to give **60** as a 1:1 mixture of diastereoisomers. Closure of the indolo[2,3-*b*]quinoline ring by treatment of this diastereoisomeric mixture **60** with base afforded **61** in

good yield as a single diastereoisomer (the base also causes equilibration at C-8). The C-8 quaternary centre was then formed by alkylation of **61** with allyl iodide and potassium *tert*-butoxide. X-ray crystallographic analysis established that the single diastereoisomer **62** thus generated had the perophoramidine relative stereochemistry. Dehaloperophoramidine (**54**) was synthesised in another twelve steps from **62**. The overall yield of **54** (eighteen steps from **56**) was 11%.

Weinreb *et al.* envisaged formation of the C-7 quaternary centre using a tandem intramolecular Heck/carbonylation sequence and initially explored this in model studies.[36] These model investigations were mainly directed at the synthesis of perophoramidine and the feasibility of a halogen-selective tandem Heck/carbonylation was examined. It was expected that a preferential reaction with the iodine atom in the presence of the two chlorine atoms in **63** would be possible (**Scheme 12**). Indeed, this reaction was found to proceed with a high degree of halogen selectivity and **64** was isolated in high yield as a single diastereoisomer.

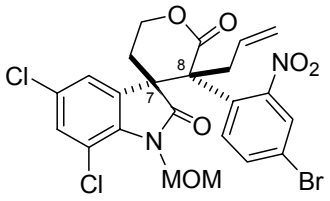


Scheme 12. The possibility of synthesising perophoramidine (**17**) using a halogen-selective tandem Heck/carbonylation reaction was explored by Weinreb *et al.* in a model system.[36] Tol = tolyl (methylphenyl), DMA = dimethylacetamide, DMF = dimethylformamide, MOM = methoxymethyl.

The relative stereochemistry at C-7 and C-8 in **64** is the result of a *syn* addition of the aryl palladium intermediate and carbon monoxide across the *E*-alkene of **63**. Removal of the silyl protecting group of **64** followed by heating of the resulting alcohol under acidic conditions afforded lactone **65** as a single diastereoisomer. Installation of the C-8 quaternary centre was achieved by allylation of the lactone enolate derived from **65** to give **66** as a single

diastereoisomer in moderate yield. Using nOe experiments (of particular note was the H-1 to H-18 enhancement), the relative stereochemistry of **66** was assigned to be that present in perophoramidine (**17**).

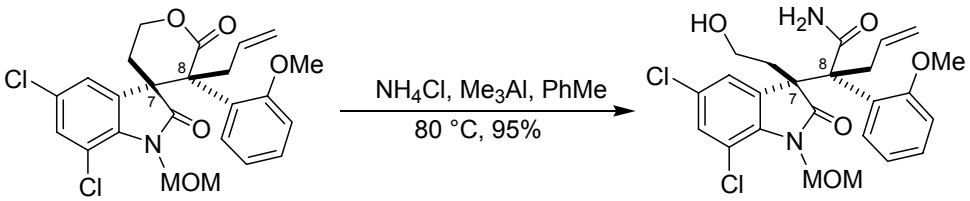
On the basis of the observed stereochemistry of **66**, a total synthesis of perophoramidine (**17**) was initiated.[37] Using a synthetic protocol similar to that used for the preparation of **66**, the suitably functionalised intermediate **67** (**Figure 4**) was prepared in low yield as a single diastereoisomer. Surprisingly, structural analysis using X-ray crystallography revealed that **66** had the communesin relative stereochemistry.



67

Figure 4. A low yielding preparation of **67** was achieved using methodology similar to that used for the preparation of **66**.[37] MOM = methoxymethyl.

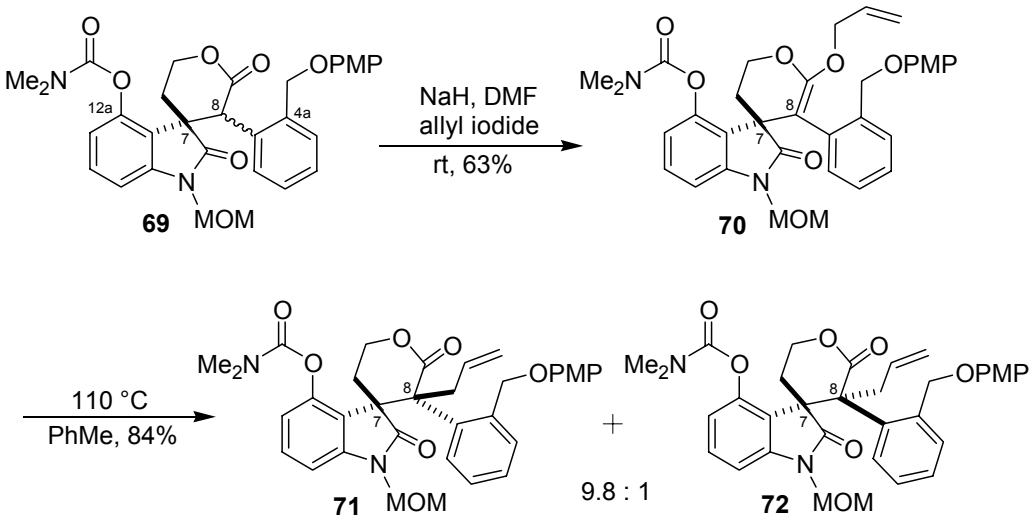
This unexpected observation led to the re-examination of compound **66** by conversion to hydroxyamide **68** allowing for an unambiguous stereochemical assignment using X-ray crystallographic analysis that had not been possible for **66** (**Scheme 13**).[37] This demonstrated that the original stereochemical assignment of **66** had been incorrect and that **66** actually had the communesin relative stereochemistry. Now, realising that it was the communesin stereochemistry that was generated by alkylation of the lactone enolate, studies towards the synthesis of perophoramidine (**17**) were discontinued and efforts towards developing a total synthesis of the communesins were initiated.[37]



66 (revised stereochemistry) **68**

Scheme 13. X-ray crystallographic analysis of **68** demonstrated that the first stereochemical assignment of **66** was incorrect.[37] MOM = methoxymethyl.

In attempts to adapt this methodology to suit a synthesis of the communesins, it was discovered that the presence of a nitro group at C-4a, which could be reduced to the corresponding amine to close the indolo[2,3-*b*]quinoline ring, caused a reduction in yield of the desired Heck/carbonylation product. A solution to this problem was to synthesise **69** that contains a protected hydroxymethyl substituent at C-4a that would allow for a late installation of the required nitrogen (**Scheme 14**). Additionally, in contrast to the attempted synthesis of perophoramidine, a substituent at C-12a was required for the construction of the isoprene based motif and the azapine ring present in the communesins.

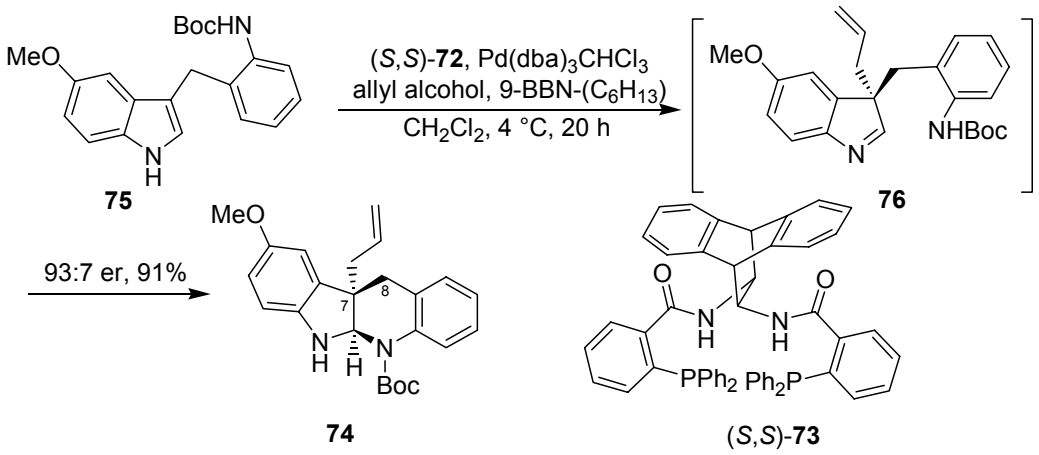


Scheme 14. The synthetic approach to perophoramidine (**17**) was adapted for the beginning of a communesin synthesis.[37] MOM = methoxymethyl, DMF = dimethylformamide, PMP = *p*-methoxyphenyl.

During attempts to allylate **69**, it was discovered that the allylation of this lactone enolate did not proceed by direct C-alkylation, but by a two step process involving *O*-allylation to form **70** followed by a Claisen rearrangement to give the C-alkylated products **71** and **72**.[37] It was found that isolation of the *O*-alkylation product **70** and subsequent separate rearrangement to **71** and **72** gave better yields than the one pot procedure used in the synthesis of **66**. In contrast to the allylation of **65**, the rearrangement of **70** was found to give mixtures of diastereoisomers **71** and **72** in a ratio that varied with different solvents. Toluene was found to give the greatest selectivity in favour of **71**.

Whilst many of the synthetic approaches discussed here have the potential to be developed into an asymmetric synthesis, the issue of asymmetry has not been addressed directly. The recent asymmetric allylation reported by Trost *et al.*, although not presented as a synthetic

strategy for the synthesis of the communesins and perophoramidine (**17**), has the potential to be used as a tool for the asymmetric synthesis of these compounds.[38] In this procedure, which was applied to various indole substrates, it was found that the anthracene derived ligand **73** in combination with a bulky borane derivative, derived from the hydroboration of 1-hexene with 9-BBN, gave the highest selectivity for *C*- versus *N*-allylation and also the highest enantiomeric ratios (**Scheme 15**). When a pendant nucleophile was present in the substrate it was found that this cyclised on to the imine under the reaction conditions to give a *cis*-fused ring system. Specifically, the indolo[2,3-*b*]quinoline ring system with a C-7 quaternary centre in **74** was generated from **75**, *via* **76**, in a 91% yield and in an enantionmeric ratio of 93:7. In the context of a communesin and perophoramidine synthesis, the fact that this methodology requires an electron rich indole for high enantiomeric ratios to be obtained, with best results being obtained with a C-12 electron donating substituent, would have to be considered. Additionally, there is no obvious handle for the generation of the C-8 quaternary centre in this system.



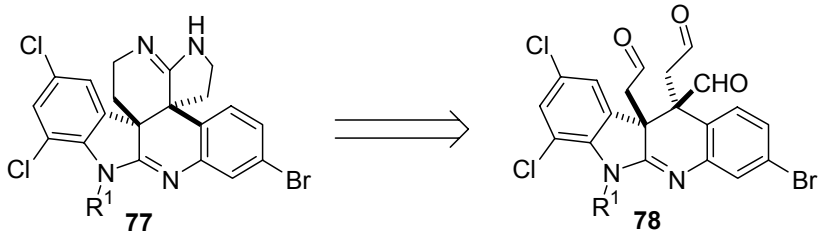
Scheme 15. The asymmetric allylation reported by Trost *et al.* could be used as the basis of an asymmetric synthesis of the communesins or perophoramidine (**17**).[38] Boc = *tert*-butoxycarbonyl, dba = dibenzylideneacetone, BBN = borabicyclo[3.3.1]nonane.

1.7 A novel approach to the synthesis of perophoramidine and the communesins

The following four chapters of this thesis describe efforts to develop a new synthetic route that is applicable to the total synthesis of both perophoramidine (**17**) and the communesin natural products. As there have been no prior methodological studies related to this current

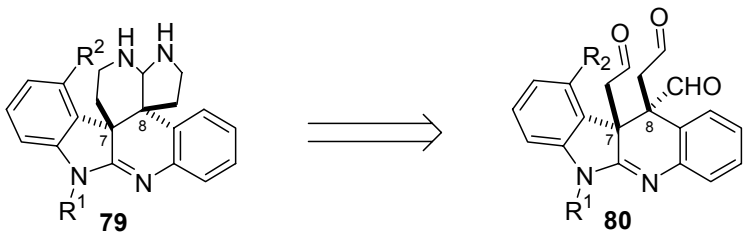
research by the Westwood group, the investigations described in this thesis have not aimed to synthesise any particular one of the natural products, but have aimed to develop an understanding of the key synthetic steps, particularly those involved with the construction of the vicinal quaternary centres, that would be used as part of a total synthesis.

Due to their significant structural differences, it was not the intention that the communesins and perophoramidine would be formed from a common intermediate. Of the structural differences between the communesins and perophoramidine that have been taken into account when attempting to develop a general strategy, the differences in the aromatic rings substituents and the relative stereochemistry at the quaternary centres C-7 and C-8 have received the greatest consideration. Whilst it is considered that the amidine and aminal units of perophoramidine (**17**) and the communesin could be constructed using similar chemistry from suitably functionalised precursors, it would be necessary to use precursors with opposing relative stereochemistry for the different natural products. For example, the construction of the amidine unit in **77**, for a perophoramidine (**17**) synthesis, will require a precursor with *trans* 2C units and suitably halogenated aromatic rings such as in **78**, or a suitably protected analogue of **78** (**Scheme 16**).



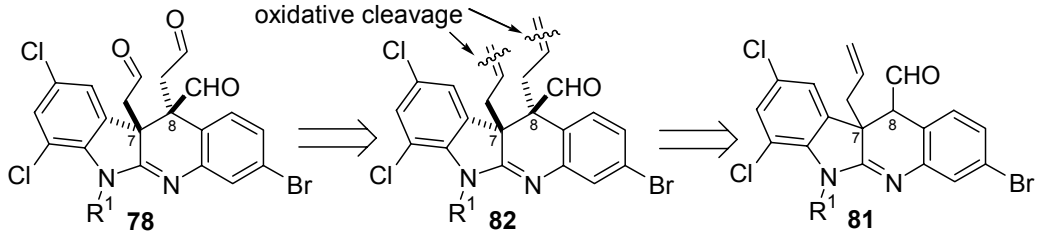
Scheme 16. Construction of the amidine functionality in perophoramidine requires *trans* 2C units. R^1 = protecting group.

On the other hand, construction of the aminal functionality in **79**, for a communesin synthesis, would require a precursor with *cis* 2C units and a substituent R^2, which would allow construction of the isoprene based moiety and the azepine ring, such as in **80** or a suitably protected analogue of **80** (**Scheme 17**).



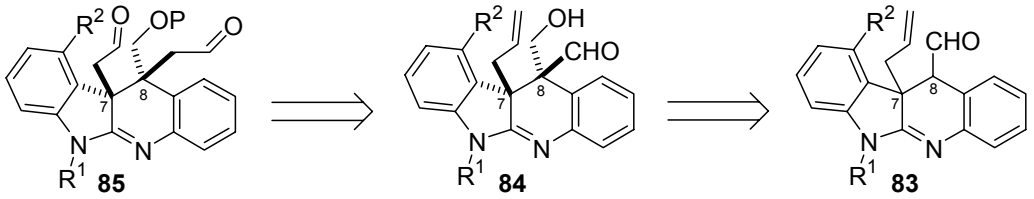
Scheme 17. Construction of the aminal functionality in the communesins requires *cis* 2C units. R^1 = protecting group.

In general, it was intended that the C-8 quaternary centre would be formed by the alkylation of a compound with a suitably acidic H-8, such as **81** for a perophoramidine (**17**) synthesis (**Scheme 18**). It was expected that the alkylation would be highly stereoselective, probably affording the configuration shown in **82**, and therefore allylation would only be suitable for a synthesis of perophoramidine. In this synthetic plan the allyl groups are considered as protected 2C units that could be developed through, preferably concurrent, oxidative cleavage.



Scheme 18. It was expected that allylation would give *trans* allyl groups and that oxidative cleavage would therefore give *trans* 2C units suitable for a perophoramidine (**17**) synthesis. R^1 = methyl or a protecting group.

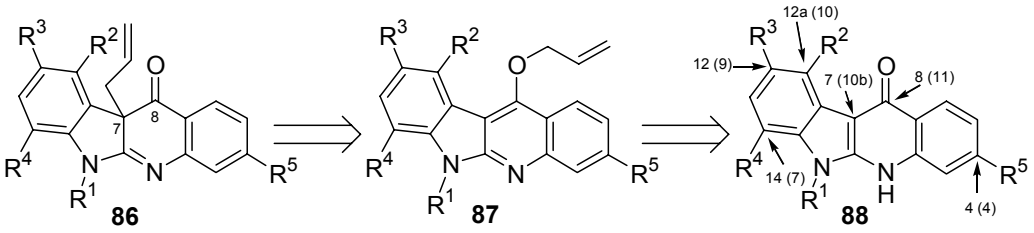
Based upon the expected approach of the electrophile opposite to the C-7 allyl group when forming the C-8 quaternary centre, a communesin synthesis would require alkylation of a compound such as **83** with a 1C electrophile, for example formaldehyde, to give **84** (**Scheme 19**). Homologation of the aldehyde moiety of **84**, after protection of the primary alcohol, into the C-8 2C unit of **85** could then be achieved using, for example, a Wittig reaction with a (methoxymethyl)triphenyl phosphonium ylide. The substituent R^1 would be either the substituent present in the final natural product (for example, a methyl group for communesin B (**10**)) or a suitable protecting group.



Scheme 19. The formation of the *cis* 2C units in the communesins would require alkylation of **83** with a 1C electrophile followed by independent manipulation of the C-8 pendant groups R^1 = methyl or a protecting group, R^2 = substituent that would give a handle for the construction of the isoprene unit and the azapine ring, P = protecting group.

Of course it is possible that alkylation at C-8 will not be *trans* selective and that the *cis* 2C relationship present in the communesins will result from allylation. Indeed, it was one of the aims of this research to establish the configuration of the C-8 stereocentre that was generated by alkylation.

It was planned that for a synthesis of both perophoramidine (**17**) and the communesins, the aldehyde that renders H-8 acidic in general structures **81** and **83** would be formed by manipulation of the ketone in general structure **86** (**Scheme 20**).



Scheme 20. Reterosynthetic plan showing the communesin natural product numbering and, in parentheses, the indolo[2,3-*b*]quinoline numbering system that will be used in subsequent chapters of this thesis.

Introduction of the ketone and the C-7 quaternary centre of **86** should be possible in a single step from allyl ether **87** using a Claisen rearrangement. It must be noted that the use of a Claisen rearrangement to generate the C-7 quaternary centre potentially allows for an asymmetric synthesis of the natural products, as asymmetric induction using the Claisen rearrangement is well known for suitably substituted allyl ethers (see Chapter 5, section 4). It was expected that allyl ether **87** would be accessible from the appropriately substituted indolo[2,3-*b*]quinolone **88**. The substituent R^1 to R^5 required in the indolo[2,3-*b*]quinoline ring system will vary with the natural product being synthesised. Whereas a synthesis of perophoramidine would require the appropriate halogen substituents at R^3, R^4 and R^5, a

synthesis of the communesins would require a substituent at R^2 that will allow construction of the isoprene based motif. For example, a bromine substituent at C-2 would allow for construction of this motif late in the synthesis using palladium based chemistry.

Due to the indolo[2,3-*b*]quinoline ring system being the core of various biologically important molecules and natural products, such as the alkaloid cryptoteckieine **89** (**Figure 5**), there are various procedures reported in the literature for the preparation of this ring system.[39-44]

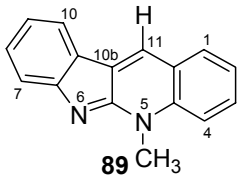


Figure 5. Structure of the natural product cryptoteckieine showing the numbering system conventionally used for the indolo[2,3-*b*]quinoline ring system.

However, there are fewer procedures reported regarding the synthesis of the required indolo[2,3-*b*]quinoline-11-one,[45] and there are no reports regarding the synthesis of the required functionalised systems. Additionally, the proposed Claisen rearrangement of the type **87** to **86** (**Scheme 20**) in the indolo[2,3-*b*]quinoline system has not been reported. Due to this limited information on the synthesis of substituted indolo[2,3-*b*]quinoline-11-one systems, in combination with the lack of information regarding the proposed Claisen rearrangement, synthetic studies were initially conducted in a model unfunctionalised indolo[2,3-*b*]quinoline system.

Throughout this chapter the numbering system that is conventionally used for the complex communesin natural product structure was adopted. As the following chapters describe studies on relatively simple indolo[2,3-*b*]quinoline structures, the atoms in this ring system are numbered using the system that is conventionally used in this ring system. Specifically, from this point on in the thesis, the quaternary centres at C-7 and C-8 in the natural product will be referred to as C-10b and C-11 respectively.

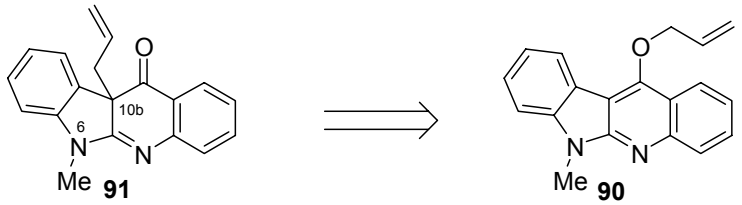
1.8 Summary

In this chapter the natural products perophoramidine (**17**) and the communesins have been introduced. The isolation, biological properties, structural features and biosynthesis of these indole alkaloids have been outlined. It has been explained how perophoramidine (**17**) and the communesins are related to the calycanthaceous alkaloids through their biosynthetic origin. A review of the literature regarding approaches to the total synthesis of perophoramidine (**17**) and the communesins has been presented, which includes many papers published since the research described in this thesis was initiated. Finally, a novel synthetic approach to these compounds was proposed that involves a Claisen rearrangement in the indolo[2,3-*b*]quinoline system as a key step. Chapter 2 will describe initial investigations into this proposed rearrangement using a model system.

Chapter 2: Investigating the Claisen Rearrangement in a Model System

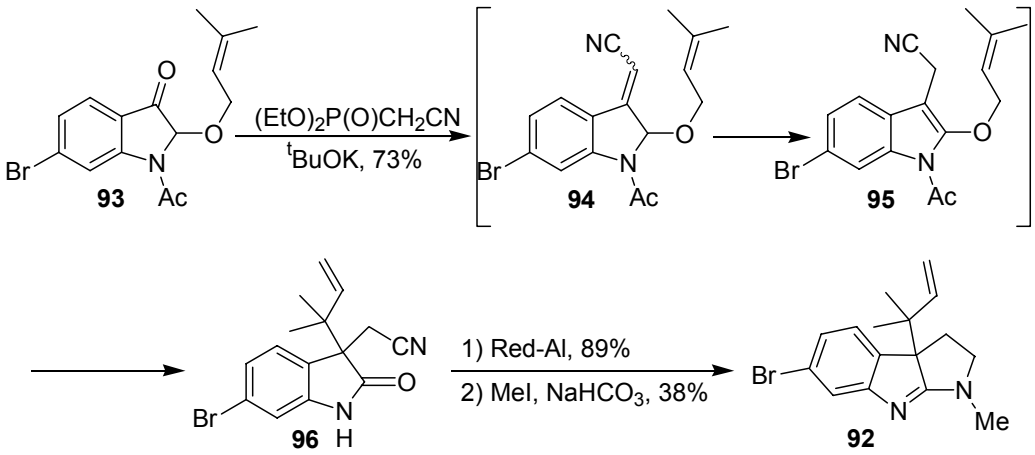
2.1 Introduction

Chapter 1 concluded by proposing a synthetic plan for a new approach to perophoramidine **17** and the communesin natural products. It was proposed that this synthetic route would initially be investigated in a model system. This chapter focuses on the preparation of **90** and on initial attempts to form the C-10b quaternary centre present in **91** using a Claisen rearrangement, which is a key transformation in the proposed synthetic route (**Scheme 21**).



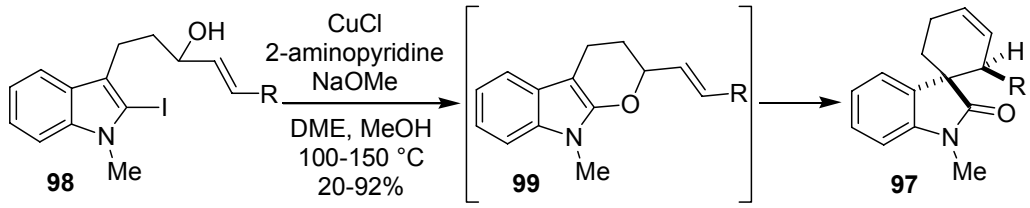
Scheme 21. The Claisen rearrangement of **90** to **91** is a key transformation in the proposed new synthesis of perophoramidine **17** and the communesins.

The conversion of **90** to **91** involves the rearrangement of an aromatic substrate to give a partially dearomatised product. Whilst there are no published examples of such Claisen rearrangements in the indolo[2,3-*b*]quinoline system, there are examples of all-carbon quaternary centre formation by the Claisen rearrangement of similar heteroaromatic substrates. Of particular relevance are the numerous reports of 2-allyloxyindoles undergoing Claisen rearrangements to give the corresponding 2-oxindole with a C-3 all-carbon quaternary centre. These rearrangements, which have been extensively studied by the group of Kawasaki, have been used in the synthesis of various hexahydropyrrolo[2,3-*b*]indole containing structures[46] including the natural products flustramine A-C,[47,48] flustramide A and B,[48] and pseudophrynaminol.[49] As an example, **Scheme 22** shows the Claisen rearrangement used as a key step in the synthesis of flustramine C (**92**).[47] In this one pot procedure, treatment of **93** with cyanomethylphosphonate forms **94** that, after isomerisation under the reaction conditions to **95**, undergoes a Claisen rearrangement to give oxindole **96** in 73% yield. Reduction followed by alkylation of the resulting pyrrolo[2,3-*b*]indole furnished the natural product, flustramine C (**92**).



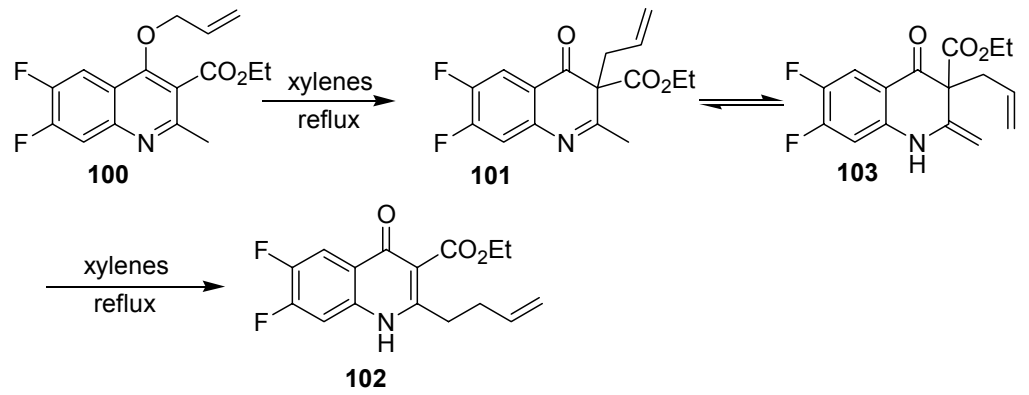
Scheme 22. Key steps in the synthesis of flustramine C (**92**).[47] Red-Al = sodium bis(2-methoxyethoxy)aluminiumhydride, Ac = acetyl.

A similar one pot protocol is used for the generation of a series of spirocyclic oxindoles **97** from 2-halo indoles **98** (**Scheme 23**).[50] After using an intramolecular Ullmann coupling to generate the pyranoindoles **99** from **98**, the pyranoindoles **99** are rearranged, under thermal conditions, to the products **97** in good yields and in greater than 9:1 diastereoisomeric ratios.



Scheme 23. A series of spirocyclic oxindoles is formed using a one pot procedure involving an intramolecular Ullmann coupling followed by a Claisen rearrangement.[50] DME = 1,2-dimethoxyethane.

Claisen rearrangements in the quinoline system that have led to the isolation of products with a disrupted aromatic system and an all-carbon quaternary centre are far less common. The only report of such a dearomatisation found in the literature describes the heating of quinoline **100** in xylenes and isolating **101** in low yield (the exact isolated yield is not reported).[51] Further heating transforms **101** to **102** *via* a Cope rearrangement of the tautomeric enamine **103** of **101** (**Scheme 24**).

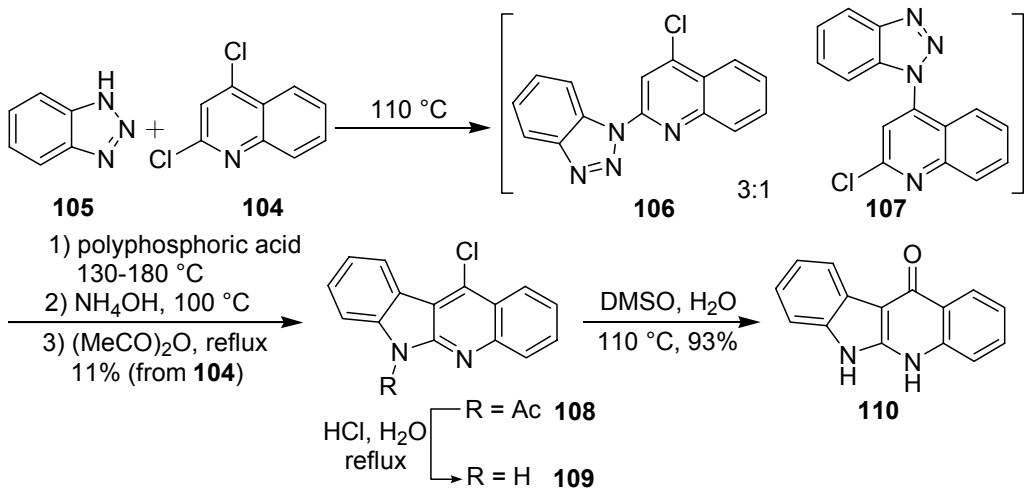


Scheme 24. It is reported that **101** has been isolated from the thermal rearrangement of **100**.[51]

In light of the literature precedent for the use of the Claisen rearrangement to form an all-carbon quaternary centre at the desired position in both the indole and the quinoline system, a synthesis of the 11-allyloxyindolo[2,3-*b*]quinoline Claisen substrate **90** was initiated.

2.2 Synthesis of 11-allyloxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline

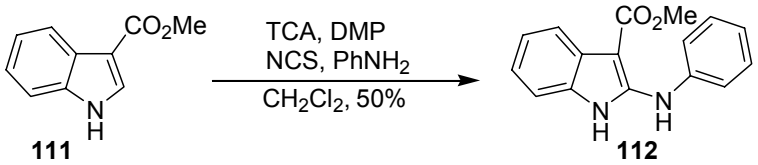
Two alternative methods for the preparation of the required indolo[2,3-*b*]quinoline-11-one system have been published.[45] As it was anticipated that gram quantities of **90** would be required, the method that appeared to be most amenable to multigram preparation was used. The alternative method involves heating of 2,4-dichloroquinoline (**104**) with benzotriazole (**104**) to give a mixture of regioisomers **106** and **107**. This mixture of isomers is treated with hot polyphosphoric acid and the desired isomer **108** is separated by crystallisation after treatment with acetic anhydride. Removal of the acetyl group with aqueous hydrochloric acid to give **109** and treatment with water in hot dimethyl sulfoxide affords the indolo[2,3-*b*]quinolone **110**.



Scheme 25. Low yielding route to indolo[2,3-*b*]quinoline-11-one **110**. Ac = acetyl, DMSO = dimethyl sulfoxide.[45]

This route to the indolo[2,3-*b*]quinoline-11-one system was considered unacceptable as it is intrinsically low yielding due to the low regiochemical selectivity of the coupling of **105** with **104**.

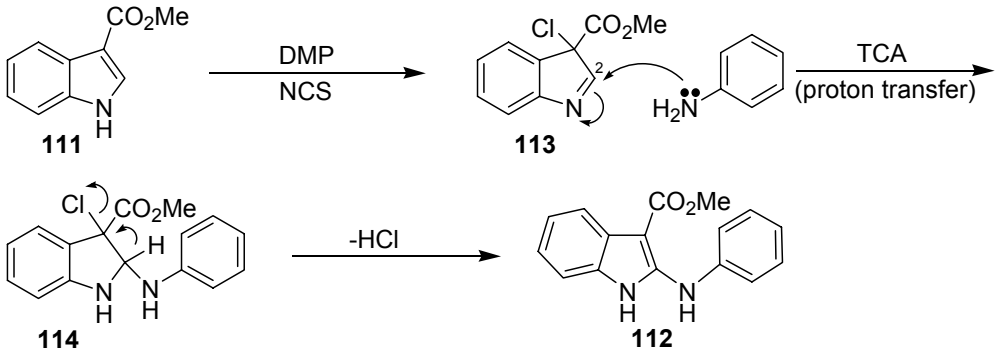
The higher yielding published route to the indolo[2,3-*b*]quinoline-11-one system involves the coupling of indoles with anilines to form the corresponding 2-aminoindoles that are subsequently cyclised to the indolo[2,3-*b*]quinoline-11-one products.[45] It was this route that was used in the current investigation. The synthesis of **110** started with the coupling of indole-3-carboxylic acid methyl ester (**111**) with aniline to form 2-aminoindole **112** (**Scheme 26**). The literature report of the synthesis of **112** describes the use of chromatography to purify **112**.[45] However, so as to avoid the use of chromatography, **112** was purified by crystallisation at the price of a small reduction in yield compared to that reported.



Scheme 26. Preparation of 2-aminoindole **112** according to the literature procedure. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

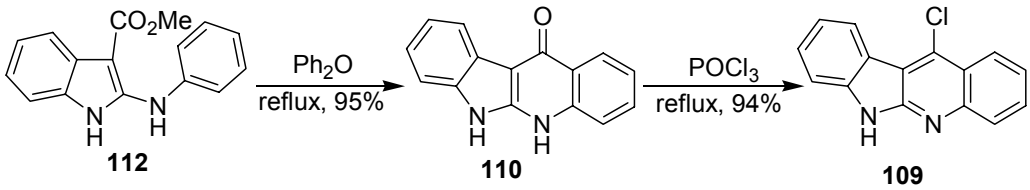
As the coupling of indole-3-carboxylic acid methyl ester (**111**) with anilines was used frequently throughout this investigation, the proposed mechanism by which the product is

formed is shown in **Scheme 27**.[52] In this mechanism it is proposed that the reaction of **111** with *N*-chlorosuccinimide (NCS) in the presence of *N*,'*N*-dimethylpiperazine (DMP) leads to the *in situ* generation of the highly reactive chloroindolenine **113**. Nucleophilic attack by aniline at C-2 of **113** gives **114** that subsequently eliminates hydrogen chloride to form the 2-aminoindole product **112**. Presumably, if addition of aniline is *syn* to the chlorine, elimination of hydrogen chloride will be *via* an E_2 mechanism as opposed to an E_1 process that would be necessitated following an addition of aniline *anti* to the chlorine of **113**.



Scheme 27. The proposed mechanism for the coupling of nucleophiles with indole-3-carboxylic acid methyl ester.[52] DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

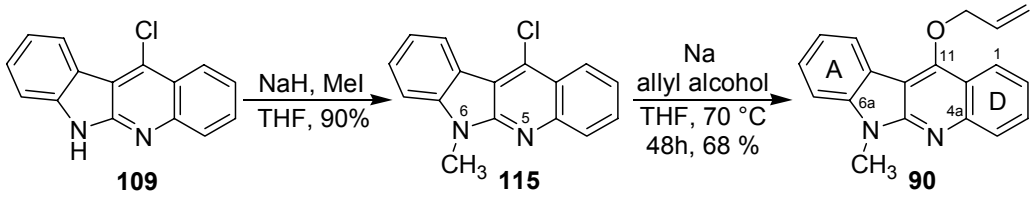
Cyclisation of **112**, with the loss of methanol, in refluxing diphenyl ether afforded **110** in excellent yield after filtration and washing with ether (**Scheme 28**).[45] The insolubility of **110** in most common solvents made purification of this compound impractical. However, crude **110** synthesised by this method, using crystallised **112**, was found to be of high purity (as determined by ^{1}H NMR) and could be used directly in the subsequent reaction. Initially when considering the synthesis of **110**, it was intended that the 11-allyloxy moiety would be installed by O-allylation of **110**, or an *N*-functionalised derivative of **110**. However, it soon became apparent that conversion of **110** to **109** was advantageous.



Scheme 28. Preparation of 11-chloro-6*H*-indolo[2,3-*b*]quinoline (**109**) according to the literature procedure.

Treatment of **110** with refluxing phosphorus oxychloride afforded chloride **109** in high yield and could be carried out on a multigram scale after modification of the literature procedure.[45] As was the case with **110**, purification of the highly insoluble chloride **109** was unfeasible and therefore crude **109**, of satisfactory purity, was used in the subsequent transformation.

The advantages of converting **110** to **109**, in regard to a synthesis of **90**, are twofold. First, with only one acidic proton present, the indolic nitrogen (N-6) of **109** was methylated using an excess of reagents to give novel compound **115**, now sufficiently soluble to allow chromatographic purification, in good yield (**Scheme 29**) (the position of the methyl group was determined after conversion of **115** to **90**). Despite the insolubility of **109** in tetrahydrofuran, tetrahydrofuran was found to be a satisfactory solvent for the methylation of **109** due to the increased solubility of the corresponding anion in this solvent. Whilst there have been reports in the literature of mixed products from the alkylation of similar substrates,[53] the methylation of **109** with sodium hydride and methyl iodide was found to be highly regioselective (no other methylated products were detectable by ^{1}H NMR). This high degree of selectivity is presumably due to the localisation of the negative charge on N-6 rather than N-5 thereby maintaining the quinoline aromatic system.



Scheme 29. Preparation of novel compounds **115** and **90**.

The second advantage of converting **110** to **109** was that the allyloxy moiety in **90** could be installed by displacement of the chlorine atom of **115** in an addition-elimination process. After two days at 70 °C, complete displacement of the chlorine in **105** with sodium allyloxide had occurred and **90** was isolated in good yield after purification by chromatography and crystallisation, which was required to achieve high purity (determined by elemental analysis and ^{1}H NMR).

The position of the methyl group in **90** could now be unequivocally assigned using a ^{1}H-^{13}C HMBC NMR experiment: a correlation was observed between the methyl protons and C-6a. C-6a was distinguished from C-4a by the absence of correlations to the protons in ring D (H-

1 to H-4), the protons in ring D (H-1 to H-4) were assigned using correlations to C-11, and C-11 was assigned on the basis of a correlation to the allylic protons. A selection of instructive correlations are shown in **Figure 6**.

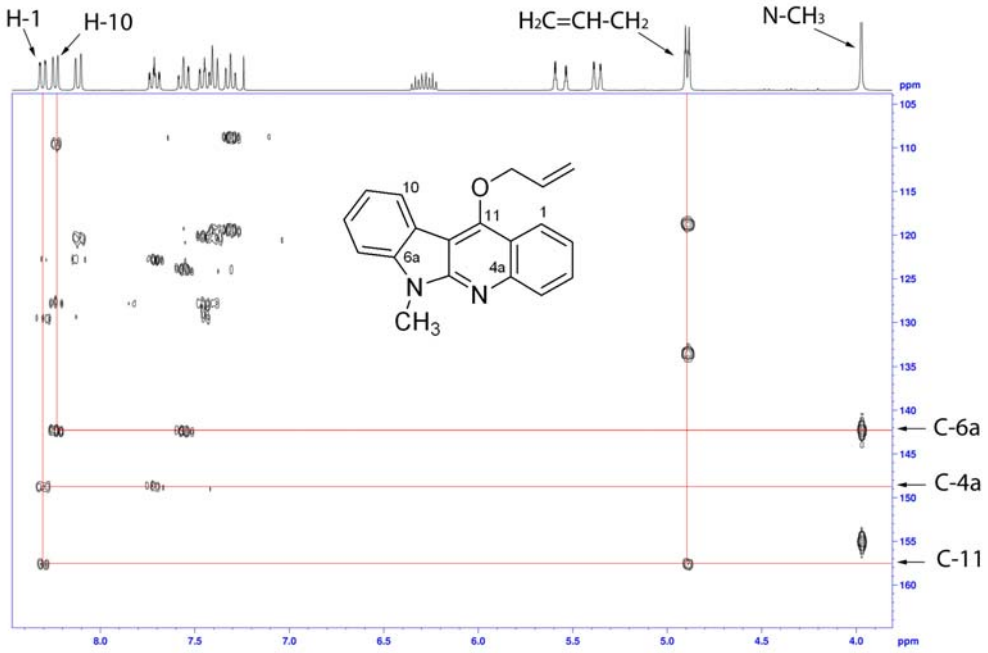
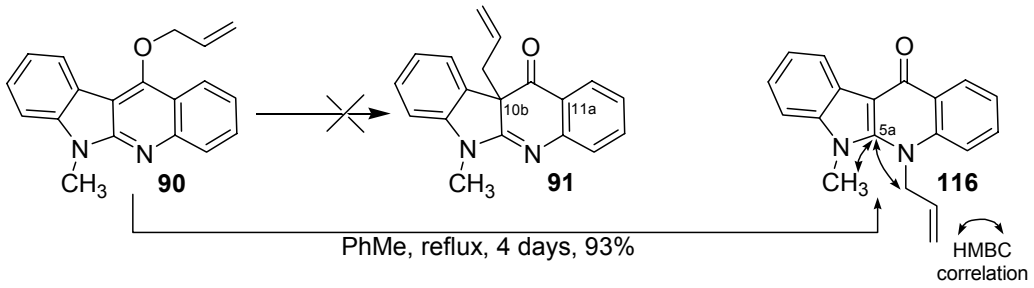


Figure 6. HMBC spectrum of **90** showing selected correlations that were used to determine the position of the methyl group.

2.3 Attempts to form the C-10b quaternary centre using a Claisen rearrangement

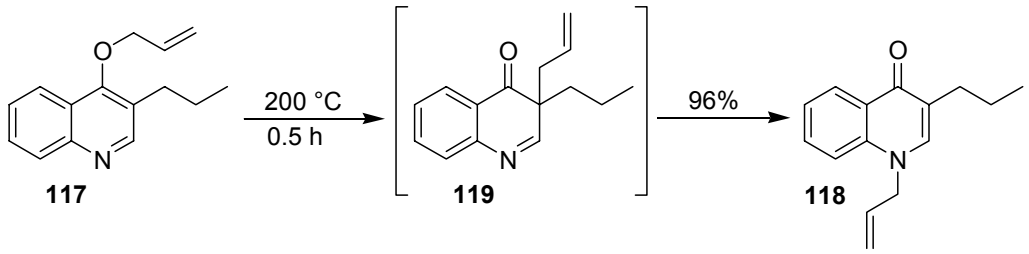
With **90** in hand, formation of a quaternary centre at C-10b by rearrangement of **90** was examined. In summary, all attempts to rearrange **90** in a variety of different solvents (including tetrahydrofuran, methanol, toluene, and trifluoroacetic acid) and at different temperatures to the desired compound **91** were unsuccessful. The only compound that could be isolated from the thermal rearrangement of **90** was a compound, more polar than **90**, with spectroscopic data consistent with structure **116**, resulting from the formal migration of the allyl group from O-11 to N-5 (**Scheme 30**). Of particular note for structural determination was the presence of a low field (173.3 ppm) quaternary (determined using the PENDANT pulse sequence) carbon signal in the ^{13}C NMR spectrum associated with **116**, consistent with a quinolone carbonyl carbon. Furthermore, inspection of the ^{1}H-^{13}C HMBC spectrum

associated with **116** revealed a mutual correlation of the α-allylic protons with C-5a and C-5a with the methyl protons, thereby indicating the close proximity of the allyl and methyl groups. In refluxing toluene, the transformation of **90** to **116** was complete after four days and **116** was isolated in 93% yield (**Scheme 30**).



Scheme 30. In refluxing toluene the transformation of **90** to **116** was found to be complete after four days.

The formation of **116** was not wholly unexpected in light of various previously published observations. For example, in addition to the formation of **101** (**Scheme 24**) and its subsequent Cope rearrangement to **102**[51] that has already been discussed on pages 25-26, a similar allyl migration has been observed in the quinoline system **117** (**Scheme 31**).[54]



Scheme 31. The formation of **118** from **117** is reported to proceed *via* a two step intramolecular process with **119** as an intermediate.[54]

It is reported that when **117** is heated without solvent, **118** is formed in near quantitative yield. Whilst it is proposed, with supporting experimental evidence gained from the rearrangement of analogues of **117**, that the transformation of **117** to **118** proceeds *via* **119** in a two step intramolecular process, a direct one step intermolecular migration is also possible. Indeed, intermolecular 1,3-migrations of alkyl groups from oxygen to nitrogen have been observed. For example, the rearrangement of 2-methoxypyridine to *N*-methyl-2-pyridone has been shown to proceed *via* an intermolecular pathway.[55]

The rearrangement of **90** to **116** can also be rationalised by either of two mechanistic pathways. First, this rearrangement could be a two step intramolecular process, Claisen rearrangement followed by an aza-Cope rearrangement,[56,57] with **91** as an intermediate. It must be noted that an intramolecular mechanism involving a Claisen rearrangement to form the C-11a substituted intermediate followed by an aza-Cope rearrangement is also possible but, as this would involve breaking the aromaticity of a benzene ring, is considered unlikely. Second, a mechanism involving cleavage of the ether bond and the consecutive intermolecular allylation of N-5, not involving the formation of **91**, can be envisaged. As only one of these mechanisms implies the existence, albeit transient, of desired **91**, it was considered important to understand the mechanisms involved in the transformation of **90** to **91**.

2.4 Investigating the allyl migration mechanism

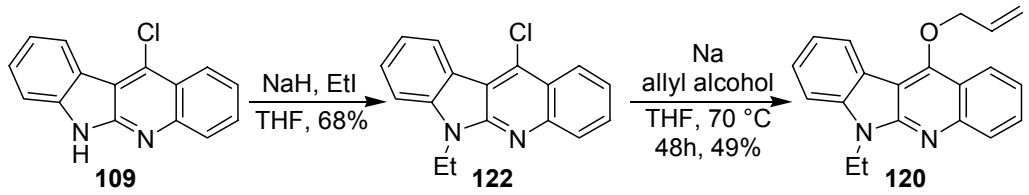
When **90** was rearranged to **116** at a range of starting concentrations no change in rate was observed (**Table 1**). This suggested that the reaction followed first order kinetics consistent with an intramolecular tandem Claisen-aza-Cope processes.

Rearangement of **90** to **116** in refluxing toluene	
Concentration of **90** (mol dm^{-3})	**116**:**90** after 12 hours*
0.25	34:66
0.05	37:63
0.01	37:63

* Calculated from integration of CH_3 peaks in the crude ^1H NMR spectrum.

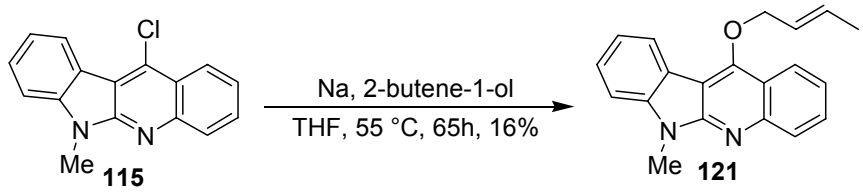
Table 1. The effect of concentration on the rate of O-11 to N-5 allyl migration.

In an attempt to gain further corroborating evidence for an intramolecular mechanism, a crossover experiment was devised. In such an experiment the "migrating" group and "fixed" group are independently labelled, thereby allowing the origin of the migrating group to be traced. It was intended that the crossover experiment would use the two structurally isomeric compounds **120** (**Scheme 32**) and **121** (**Scheme 33**). The preparation of **120** (**Scheme 32**) followed the same procedure that had been used to prepare **115** from **109**, but using ethyl iodide to form **122** from **109** (**Scheme 29**).



Scheme 32. Preparation of **120**.

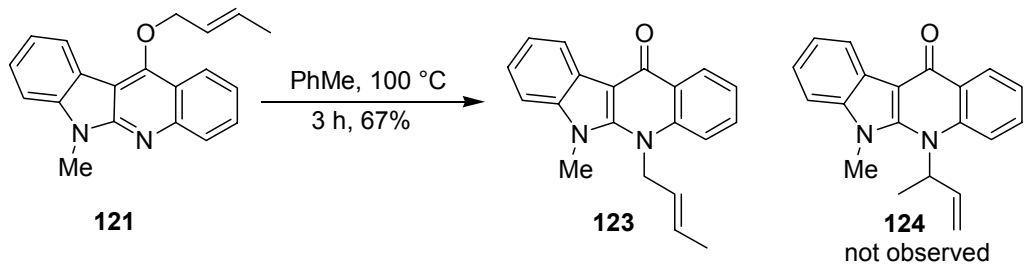
It was found that the low yielding preparation of **121** from **115** (**Scheme 33**) required a lower temperature and a longer reaction time, due to the rapid rearrangement of **121** at a higher temperature, than was required to form **90** from **115** (**Scheme 29**). No attempt was made to increase the yield of **121**, as only small quantities were required for the planned experiment.



Scheme 33. Low yielding preparation of **121**.

It was intended that the crossover experiment would involve the thermal rearrangement of **120** in the presence of **121** and that, due to the isomeric nature of **121** and **120**, any change in the molecular weight of the components in the reaction mixture would be indicative of the intermolecular transfer of the allyl or butenyl groups. That is to say, it was intended that after heating a mixture of **120** and **121** until significant rearrangement of both compounds had occurred, analysis of the crude reaction mixture by mass spectrometry would rapidly identify the presence of any crossover products with molecular weights of 316 and 288.

However, the greatly accelerated rate of rearrangement that was observed for **121** (**Scheme 34**) in relation to that of **120** invalidated the planned crossover experiment as only trace amounts of **120** would have rearranged in the time that it would take for all of **121** to be consumed.

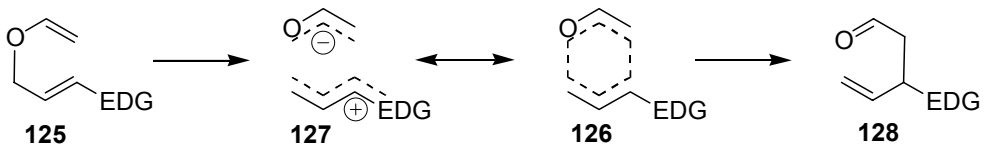


121 **123** **124** not observed

Scheme 34. The rate of rearrangement of butenyl ether **121** to **123** is faster than that observed for the corresponding allyl ether.

Despite this failure of the crossover experiment, two useful pieces of information that suggest an intramolecular mechanism involving a Claisen followed an aza-Cope rearrangement, but do not conclusively refute an intermolecular mechanism, were gained from the rearrangement of **121** (**Scheme 34**). First, it was observed that the only product formed from the thermal rearrangement of **121** was **123** and not the alternative regioisomer **124** that could be formed from an intermolecular alkylation of N-5, albeit at the more sterically hindered end of the π-allyl system. The *E*-geometry of the alkene moiety in **123** was demonstrated by ^{1}H NMR spectroscopy. The alkene protons coupling constant (^{3}J =15.8 Hz) was measured after irradiating at the methyl proton's resonance frequency, in a homonuclear decoupling experiment, so as to simplified these signals that appear as multiplets in the standard ^{1}H NMR spectrum.

Furthermore, the observation that the rate of rearrangement of the butenyl ether **121** is considerably greater than that of the allyl ether **90** also suggests an intramolecular mechanism involving a Claisen followed an aza-Cope rearrangement. This acceleration of rate is consistent with the previously documented observation that electron donating substituents at the γ-allylic position accelerate the rate of the Claisen rearrangement.[58] This effect has been rationalised in light of experimental evidence that bond breaking precedes bond formation.[59,60] Electron donating substituents at the γ-allylic position of the allyl vinyl ether **125** should lower the energy of the transition state **126** by facilitating cleavage of the C-O bond to form **127** before formation of the C-C bond in **128** (**Scheme 35**).



Scheme 35. The rate accelerating effect that electron donating groups have at the γ-allylic position has on the Claisen rearrangement has been rationalised by considering how such substituents should facilitate bond cleavage. EDG = electron donating group.

2.5 Detection of the intermediate species 91

Although an intermolecular allyl migration could not be completely ruled out, the proposed intermediacy of **91**, in the transformation of **90** to **116**, was now tenable and consideration was given to whether **91** was sufficiently stable to permit detection. Generally, the intermediate species in two step consecutive reactions reaches the highest concentration early in the reaction progress. Based on this assumption, it was reasoned that detection of **91** would be most likely early in the reaction progress before large amounts of **90** had been consumed.

After heating **90** for one hour at 100 °C, detailed analysis of the ^{1}H NMR spectrum associated with the crude reaction mixture indicated the presence of a trace quantity (approximately 0.5% in comparison to **90**) of a third compound that was neither **90** nor **116** (**Figure 7**). It was reasoned that if this additional compound was **91** it should be possible to detect a signal for C-11 of the carbonyl group at approximately 200 ppm in the ^{13}C NMR spectrum. Due to the low concentration of this compound in relation to **90** the sensitive HMBC experiment was used. Indeed, this analysis did indicate the presence of a carbon with a chemical shift of 195 ppm that correlated with a signal at 8.00 ppm in the ^{1}H dimension, presumed to be H-1 of **91**. Not only did this give further support to the proposed intermediacy of **91**, it also demonstrated that **91** was a relatively stable and long lived species.

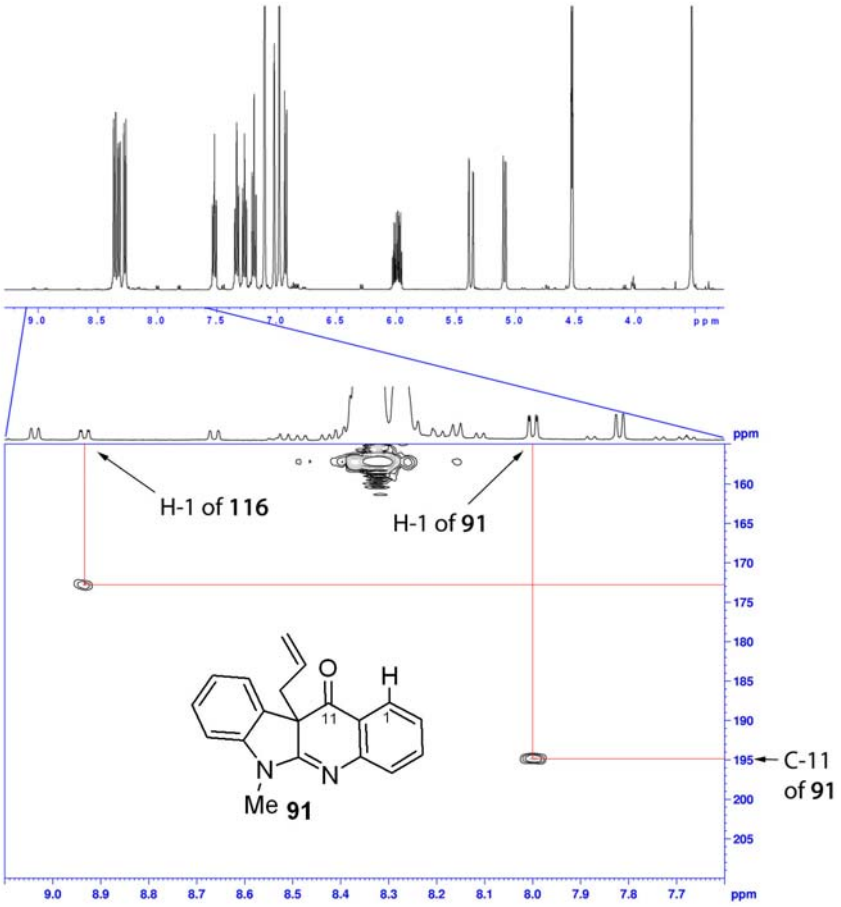


Figure 7. After heating **90** in toluene-d_8 for one hour, ^{1}H NMR and ^{1}H^{13}C HMBC spectra indicate the presence of **91**. The major peaks in the ^{1}H dimension correspond to the protons of **90**.

Being encouraged by these investigations, consideration was given as to how the concentration of this intermediate could be increased to an isolable level. A potential solution to this problem was reached by considering this two step process in terms of the relative rates (or activation energies) of the two steps involved. For **91** not to accumulate in the reaction mixture, the rate of the aza-Cope rearrangement must be significantly greater than that of the Claisen rearrangement (**Figure 8**). That is to say, the free energy of activation for the Claisen rearrangement of **90** ($\Delta G^{\ddagger}_1$) must be significantly greater than the free energy of activation for aza-Cope rearrangement ($\Delta G^{\ddagger}_2$).

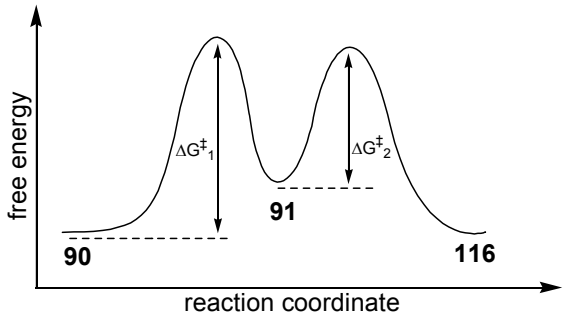


Figure 8. For intermediate **91** not to accumulate $\Delta G^{\ddagger}_1$ must be greater than $\Delta G^{\ddagger}_2$.

By rationalising the two-step process in this way it can be seen that if the relative magnitudes of the activation energies for the two steps were to be reversed so that the rate of the Claisen rearrangement is competitive with that of the aza-Cope rearrangement (either by accelerating the first step or retarding the second) the desired intermediate with a C-10b quaternary centre would accumulate in the reaction mixture (**Figure 9**).

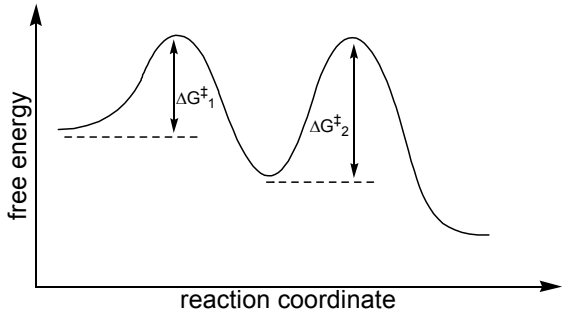
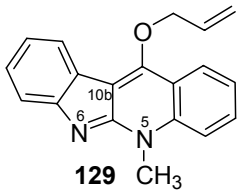


Figure 9. If $\Delta G^{\ddagger}_2$ were to be greater than $\Delta G^{\ddagger}_1$ the intermediate species would accumulate in the reaction mixture.

Initially it was proposed that the activation energy of the aza-Cope rearrangement could be increased in relation to that of the Claisen rearrangement by positioning a sterically demanding group at N-6 instead of the methyl group in **90**. Attempts were made to synthesise an analogue of **90** with a bulky triphenylmethyl group at N-6. However, as alkylation of **109** with chlorotriphenylmethane could not be achieved this approach was abandoned.

Next, consideration was given to how the activation energy to the Claisen rearrangement could be reduced. It was proposed that a reversal of the rates could be achieved by using the modified substrate **129** (**Figure 10**) in which the methyl group has been moved, in relation to

90, from N-6 to N-5. It was expected that this would have the effect of lowering the activation energy for the Claisen rearrangement whilst leaving the activation energy for the aza-Cope rearrangement essentially unchanged. The preparation and rearrangement of **129** is the subject of Chapter 3.



129

Figure 10. It was proposed that rearrangement of the modified substrate **129** would allow isolation of the intermediate Claisen product with the C-10b quaternary centre

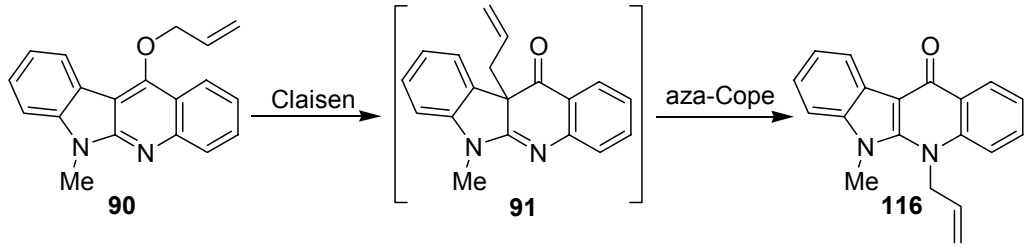
2.6 Summary and conclusions

The aim of the investigations described in this chapter was to determine the expediency of the Claisen rearrangement that is a key step in the proposed new synthesis of perophoramidine and the communesins. The synthesis of the model Claisen substrate **90** and attempts to form the C-10b quaternary centre, present in **91**, by rearrangement of this compound were described. It was found that rearrangement of **90** did not give **91** but led to the formation of **116**, the result of the formal migration of the allyl group from O-11 to N-5. After an investigation into the mechanism of this allyl migration, it was concluded that the observed rearrangement was a two step consecutive, Claisen followed by aza-Cope rearrangement, intramolecular process involving the intermediate **91**. Intermediate **91** was detected using a ^{1}H-^{13}C HMBC experiment and a rationalisation as to why **91** does not form was made based on the relative activation energies of the two steps. A modified structure **129** for the Claisen structure was proposed. Chapter 3 outlines the preparation and rearrangement of **129** before discussing the differences in chemical behaviour between **129** and **90**.

Chapter 3: A Redesigned Model System

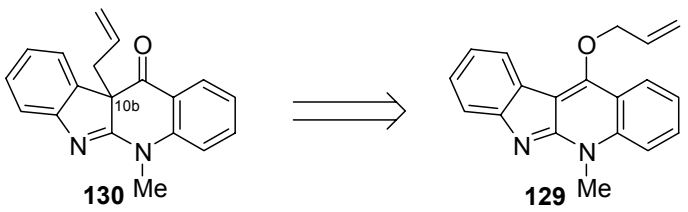
3.1 Introduction

Chapter 2 described the preparation and rearrangement of allyl ether **90**. Whilst it was found that **90** did undergo a Claisen rearrangement to form the desired compound **91**, **91** did not accumulate to an isolable quantity in the reaction mixture (**Scheme 36**). The only product that could be isolated from the rearrangement of **90** was **116**, resulting from the subsequent aza-Cope rearrangement of **91**.



Scheme 36. Claisen rearrangement and subsequent aza-Cope rearrangement of allyl ether **90**.

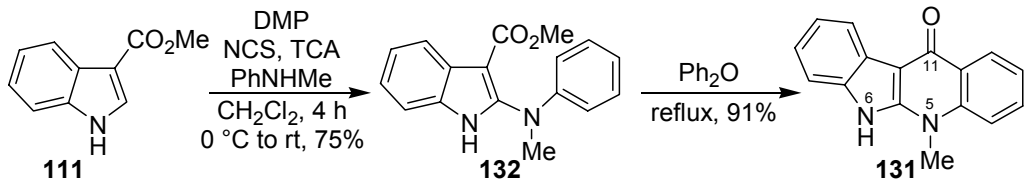
Chapter 2 concluded by proposing that if the rate of the Claisen rearrangement could be accelerated in relation to the rate of the aza-Cope rearrangement the desired intermediate would accumulate in the reaction mixture. It was further proposed that rearrangement of the modified substrate **129** should facilitate accumulation of the desired intermediate. First, this chapter focuses on the preparation of **129** and its subsequent rearrangement to **130** (**Scheme 37**). Next, an exploration into the effect that substituents at the α- and γ-allylic positions have on the Claisen and aza-Cope rearrangements is described. Finally, a limited investigation into a protecting group strategy is outlined.



Scheme 37. It was expected that the C-10b quaternary centre in **130** could be formed by rearrangement of the modified substrate **129**.

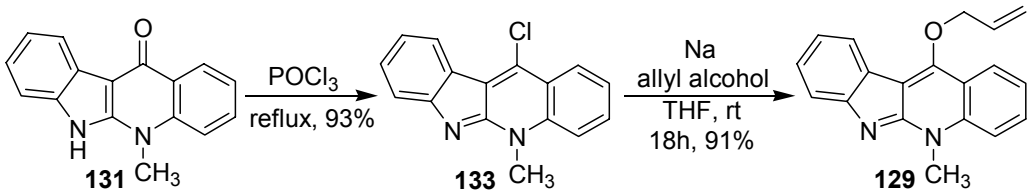
3.2 Synthesis of 11-allyloxy-6-methyl-6*H*-indolo[2,3-*b*]quinoline (129)

Using the previously reported procedure, known indolo[2,3-*b*]quinoline-11-one **131** was prepared in three steps from indole-3-carboxylic acid methyl ester (**111**) (**Scheme 38**).[45] Whilst the previous synthesis of **90** required methylation at N-6 after formation of the indolo[2,3-*b*]quinoline ring system, synthesis of **131** allowed the N-5 methyl substituent to be present from the beginning of the synthesis by using *N*-methyl aniline. Coupling of **111** with *N*-methylaniline afforded **132** that was subsequently cyclised in refluxing diphenyl ether to give **131**. Both these steps proceeded in good yield and were amenable to multigram scale preparation. Although the literature describes the use of chromatography to purify **132**, it was found that **132** could be prepared in batches of up to twenty grams when crystallisation was used as the purification method and **131** required no purification other than washing with ether.



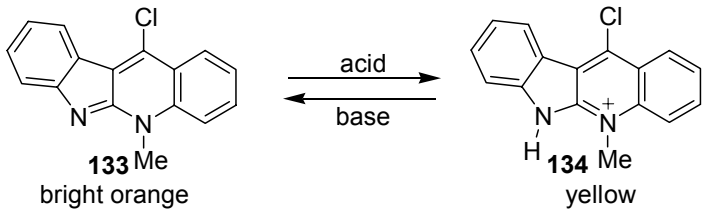
Scheme 38. Preparation of 5,6-dihydro-5-methylindolo[2,3-*b*]quinoline-11-one (**131**) acording to the literature procedure. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

Treatment of **131** with refluxing phosphorus oxychloride afforded novel chloride **133** in excellent yield (**Scheme 39**). Displacement of the chlorine atom in **133** with allyl alcohol and sodium at ambient temperature afforded the desired allyl ether **129**, again in excellent yield. Both **133** and **129** were initially purified by chromatography and it is the purified yields that are shown in **Scheme 39**. However, when a large scale preparation of **129** was later required, it was found that both steps could be conducted without purification if **131** was of high purity.



Scheme 39. Preparation of novel compounds **133** and **129**.

It is interesting to note that, unlike the 6-methyl derivatives **115** and **90**, **129** (dark yellow) and **133** (bright orange) are both highly coloured compounds, presumably due to their extensive π-electron systems delocalised over all four rings. Additionally, an interesting observation regarding colour was made during the isolation of **133** (**Scheme 40**). When **133** was a suspension in aqueous acid, after quenching any remaining phosphorus oxychloride with water, **133** was observed as a yellow solid. However, when this aqueous suspension of **133** was basified with sodium bicarbonate prior to isolation (either by extraction into dichloromethane or, for larger scale preparation, by filtration) a dramatic colour change to bright orange was observed. A rationalisation for this striking colour change is presented in **Scheme 40**. Protonation of **133**, with the π-electrons delocalised throughout all four rings, gives **134** with the π-electrons localised in two isolated conjugated systems similar to that of **115**.



Scheme 40. The extended conjugated system of **133** appears orange whereas the two isolated conjugated systems of **134** give a yellow colour.

A further experimental observation of interest is that the formation of **129** from **133** required a lower temperature and shorter reaction time than was required for the formation of **90** from **115** (page 29). To rationalise this mechanistically, if the energies of the two intermediates (**135** and **136**, **Figure 11**) in these addition-elimination processes are assumed to be approximately equal, an increased ground state energy of **133** would explain its greater lability. Presumably this difference in ground state energy is due to the stable quinoline aromaticity present in **115**, which is broken when forming **136**, that is not present in **133**. Encouragingly, this observation suggested that a similar destabilisation of **129**, in relation to

90, would potentially increase the rate of the Claisen rearrangement and facilitate the accumulation of **130**.

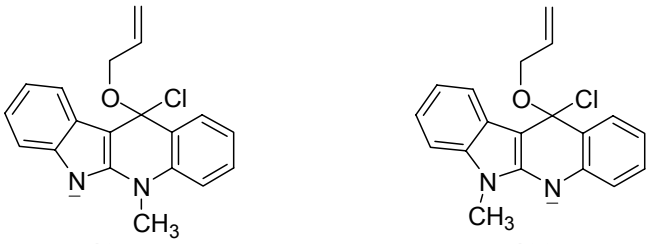
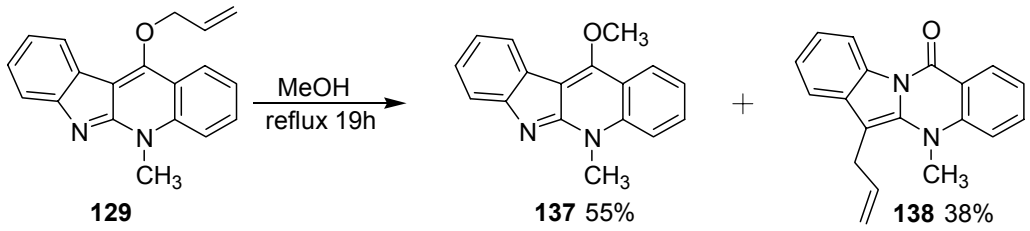


Figure 11. The two intermediate species generated by the addition of sodium allyloxide to **133** or **115** are assumed to be of approximately equal stability.

3.3 Rearrangement of 11-allyloxy-6-methyl-6*H*-indolo[2,3-*b*]quinoline (129)

Expecting a more facile rearrangement than had been observed for **90** (page 31), **129** was heated in refluxing methanol (**Scheme 41**). After nineteen hours complete consumption of **129** had occurred, and two major products were isolated from the reaction mixture.



Scheme 41. The attempted Claisen rearrangement of **129** in methanol afforded two unexpected compounds.

The more polar of the two was an orange compound that was assigned the structure of known compound **137**.[53] The structural assignment of **137** was based mainly on observations of the ^{1}H NMR spectrum that showed, in relation to **129**, a loss of the allyl group, the presence of an additional *O*-methyl group and only minor changes in the aromatic proton signals. The less polar yellow compound, which was isomeric with **129**, was assigned the structure of indolo[2,1-*b*]quinazolin-12-one **138** using ^{1}H-^{13}C HMBC and ^{1}H-^{1}H nOe experiments. Of particular value for structural determination was the observed nOe between the α-allylic and methyl protons. The structure of **138** was later confirmed by X-ray crystallography (**Figure 12**).

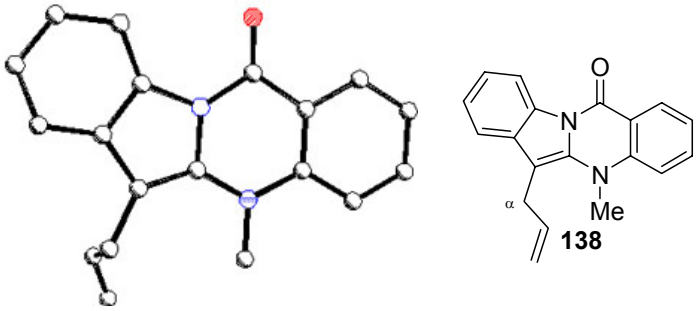
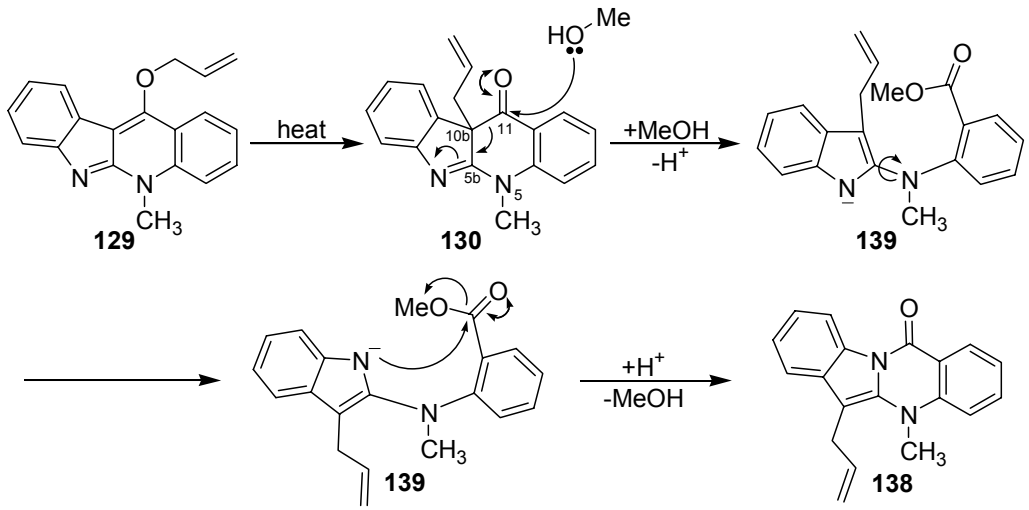


Figure 12. X-ray structure of **138**.

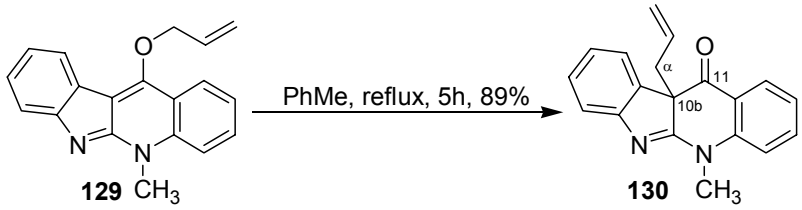
It was reasoned that the formation of **137** and **138** was a function of the nucleophilicity of methanol. However, the mechanism of formation of **138** from **129** is not as obvious as the addition-elimination process with loss of allyl alcohol that gives rise to **137**. It was believed that **138** was formed by the methanol catalysed rearrangement of **130**, generated *in situ* from **129**, and the following series of mechanistic events were proposed (**Scheme 42**). After initial rearrangement of **129** to **130**, nucleophilic attack by methanol at C-11 causes the breaking of the C-10b-C-11 bond. Subsequent rotation about the N-5-C-5b bond of **139** and intramolecular attack of the indole nitrogen at the ester, causing the loss of methanol, gives the observed product **138**.



Scheme 42. Proposed mechanism for the formation of **138**.

The use of a non-nucleophilic solvent, with a similar boiling point to that of methanol, for the rearrangement of **129** was expected to prevent the formation of both the undesired compounds, **137** and **138**. Indeed, after 4.5 days in refluxing tetrahydrofuran, **129** was found

to have undergone complete transformation to the desired product **130** with a quaternary centre at C-10b. Subjecting **90** to these same reaction conditions was shown to form only trace amounts of **116**, suggesting that the rate of the Claisen rearrangement for **129** had been significantly increased in relation to that of **90**. The use of refluxing toluene, however, for the transformation to **129** to **130** was later considered preferable as the time for complete rearrangement was reduced to five hours and only a small reduction in yield was observed due to the subsequent aza-Cope rearrangement. Under these conditions **130** was isolated in 89% yield after purification by chromatography (**Scheme 43**).



Scheme 43. High yielding formation of the quaternary centre at C-10b using a Claisen rearrangement.

Evidence that the desired compound **130** had been formed was gained from the ^{1}H NMR spectrum associated with this compound that showed the diagnostic well separated signals corresponding to the diastereotopic α-allylic protons. In the ^{13}C NMR spectrum, recorded using the PENDANT pulse sequence, the quaternary carbon signal associated with C-10b was readily distinguished at 66.2 ppm and the low field signal associated with the carbonyl carbon C-11 was observed at 192.9 ppm. Additionally, ^{13}C-^{1}H HMBC and ^{1}H-^{1}H nOe correlations, were consistent with structure **130**. Finally, the structure of **130** was confirmed by X-ray crystallography (**Figure 13**).

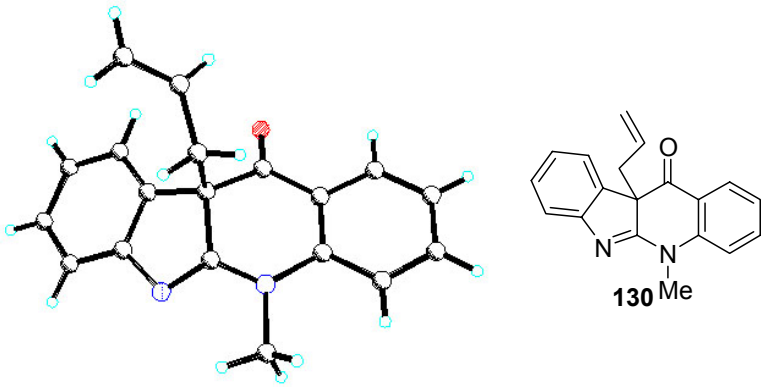
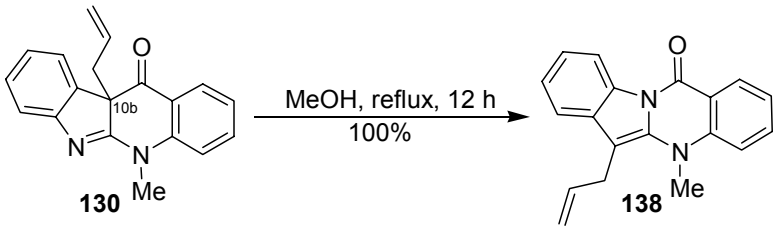


Figure 13. X-ray structure of **130**.

Now that **130** could be isolated, it was confirmed that **138** had arisen from the methanol catalysed rearrangement of **130**. Indeed, when **130** was heated in methanol at reflux a complete transformation to **138** was observed in less than twelve hours and **138** was isolated in quantitative yield (**Scheme 44**).

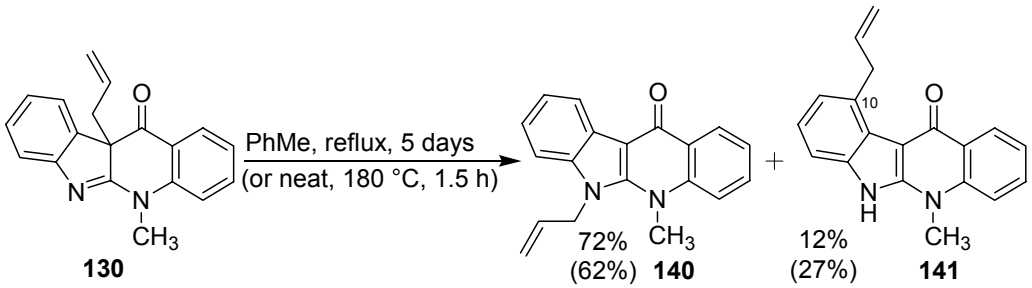


130 **138**

Scheme 44. Methanol catalysed rearrangement of **130** to **138**.

Regarding the rearrangement of **130** to **138**, it is interesting to note that there is only one report of C-10b substituted 5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-ones, similar to **130**, found in the literature.[61] These compounds are reported to have a thiomethyl substituent replacing the allyl group at C-10b of **130**. However, it was later demonstrated that the structural assignment made in this report was incorrect and that the compounds in question were in fact the corresponding indolo[2,1-*b*]quinazolin-12-ones, similar to **138**.[62] It is possible that a rearrangement similar to **130** to **138** had also occurred in this case but was not detected by the authors.[61]

Further heating of **130** in refluxing toluene for four days caused the expected aza-Cope rearrangement to **140** that was isolated in 72% yield. A minor product **141**, resulting from a Cope rearrangement of the allyl group to C-1, was also isolated in 12% yield (**Scheme 45**). It was shown that the times required for complete conversion of **129** to **140** and **90** to **116** are approximately equal, requiring about four days in refluxing toluene. This suggests that the rate of the aza-Cope rearrangements in each case are approximately equal and it is only the rate of the Claisen rearrangements that are significantly different. Heating **130** without solvent at 180 °C reduced the time for complete rearrangement to 1.5 hours, whilst also increasing the quantity of **141** formed. The separation of **140** from **141** proved to be troublesome requiring chromatography using methanol-chloroform mixtures to prevent co-elution of these compounds. It was noted that if the yield of **141** could be increased, this method of functionalising C-10 of the indolo[2,3-*b*]quinoline system could potentially be used as a step in a communesin synthesis.

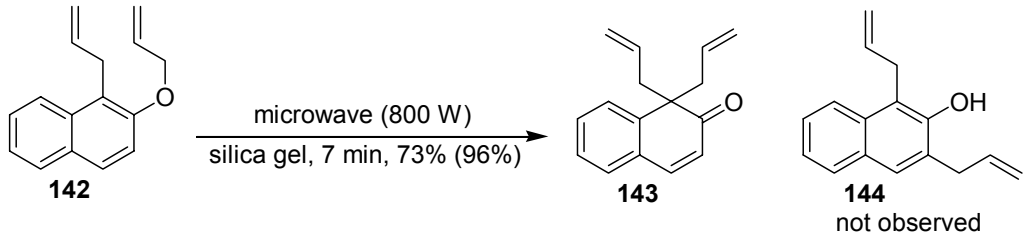


Scheme 45. Aza-Cope and Cope rearrangements of **130**.

3.4 Rationalising the difference between the two systems

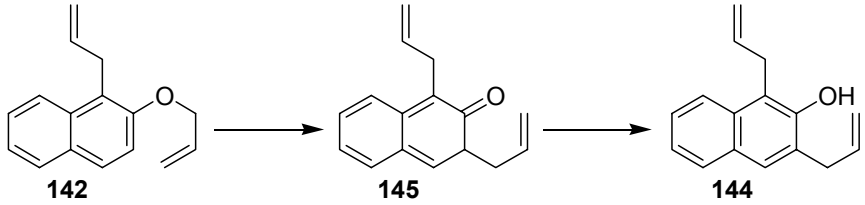
In Chapter 2 it was rationalised that the intermediate **91** did not accumulate because the rate of the aza-Cope rearrangement was significantly greater than the rate of the Claisen rearrangement, and it was proposed that by moving the methyl group from the indolic (N-6) to the quinolic (N-5) nitrogen the relative magnitudes of the two rates would be reversed. Now that a comparison of the two systems could be made and it was clear that the rate of the Claisen rearrangement had been significantly increased for **129** in comparison to that of **90** (pages 30-31), the following rationalisation was made. Whilst both **129** and **90** can be considered as complete aromatic (4n + 2) systems of 18-π-electrons (n = 4, including the nitrogen lone pair), suggesting that there is no difference in stabilisation, it is the individual aromatic components of the ring systems that are of greater importance to stability and the degree of isolated double bond character within these components must be considered.

Generally, the propensity of aromatic systems to undergo dearomatisation by a Claisen rearrangement can be considered as evidence for the isolated double bond character of the participating aromatic double bond. For example, the indole aromatic systems already discussed at the beginning of Chapter 2 undergo Claisen rearrangements with a breaking of the complete indole aromaticity but with preservation of the more stable benzene π-electron system. A further example of this is illustrated by a Claisen rearrangement in the aromatic naphthalene system (**Scheme 46**).[63,64] Rearrangement of **142** affords almost exclusively **143**, with disrupted naphthalene aromaticity, in preference to **144** with the intact naphthalene π-system.



Scheme 46. Claisen rearrangement of naphthalene **142** preferentially forms the product with disrupted naphthalene aromaticity.

This, at first sight surprising, preference for the formation of the dearomatised product can be rationalised when the individual aromatic components are considered during the two step process that forms **144** from **142** (**Scheme 47**). Claisen rearrangement of **142** to give intermediate **145** requires the breaking of the benzene aromatic system and is less favourable than formation of **143**. This shows the isolated double bond character of the naphthalene system and that the individual aromatic components must be considered when rationalising chemical behaviour.



Scheme 47. The formation of **144** necessitates an intermediate **145** with disrupted benzene aromaticity.

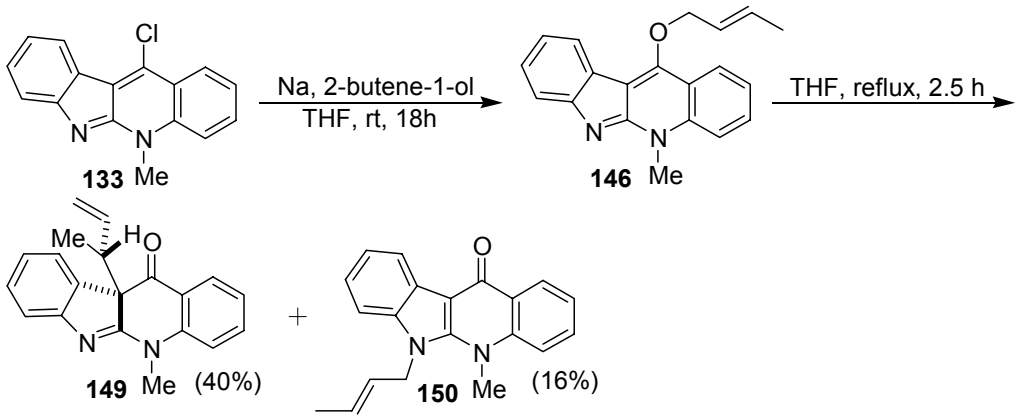
This rationalisation implies a hierarchy of aromatic stabilisation with the quinoline π-system of **129** conferring a greater degree of stabilisation than that of the complete 18-π-electron system in **90**. That is to say, **90** is more aromatic than **129** and therefore **90** is at a lower ground state energy than **129**. When the intermediates **91** and **129** are considered to be of similar ground state energy this destabilisation of **129** in relation to **90** is fundamental. A computational comparative investigation of these two system gives an interesting insight into these differences and can be read in Appendix 1.

3.5 Extending the scope of the Claisen rearrangement

Having established a method for the formation of the desired quaternary centre at C-10b in the indolo[2,3-*b*]quinoline system, it was considered interesting to attempt to form this quaternary centre from analogues of **129** with methyl substituents on the allyl group. This was investigated through the preparation and rearrangement of **146**, **147** and **148** (**Scheme 48**, **Scheme 49** and **Scheme 50** respectively). The rearrangement of each of these three compounds, which were prepared from **133** using methodology analogous to that used for the synthesis of **129**, will be described individually. However, in all three cases it was found that the Claisen rearrangement was significantly accelerated in relation to that observed for **129** and required only a few hours in refluxing tetrahydrofuran were required for complete consumption of the allyl ethers. Moreover, this acceleration of rate prevented the isolation of pure samples of **146**, **147** and **148** due to their rearrangement, albeit slow, at room temperature. This acceleration of the Claisen rearrangement rate can be attributed to the electron donating effect of the methyl substituents at either the α- or γ-allylic positions (see pages 34-35,).[58] The reaction conditions presented in **Scheme 48**, **Scheme 49** and **Scheme 50** are those that were optimised for the rearrangement of **148** as this was considered the most synthetically useful transformation.

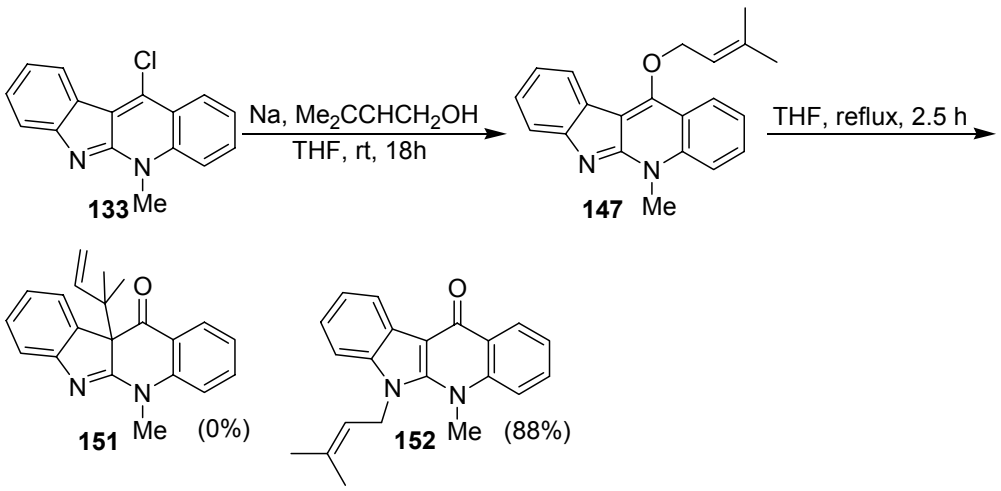
Crude **146** was synthesised from **133** using *trans*-2-butene-1-ol (**Scheme 48**). It was found that high yields of the Claisen product **149** could not be obtained by rearrangement of **146** without considerable quantities of **150** also being formed. This indicated that, in comparison to **129**, there was a disproportionate increase in the rate of the aza-Cope rearrangement in relation to the rate of the Claisen rearrangement. This additional acceleration of the aza-Cope rearrangement can be rationalised by considering the increase in steric strain that occurs on transformation of **146** to **149** and the release of steric strain that occurs on transformation of **149** to **150**. After crude **146** was heated in refluxing tetrahydrofuran for 2.5 hours, **149** was isolated in 40% yield as a single diastereoisomer. Whilst the relative stereochemistry of **149** could not be determined directly, it was assumed to be as depicted based on the premise that the Claisen rearrangement of **146** had proceeded *via* a chair transition state with the methyl group occupying an equatorial position. The signals associated with the alkene protons of **150** appear as multiplets in the ^{1}H NMR spectrum. However, selective irradiation at the methyl proton's resonance frequency (homonuclear

decoupling) allowed the ^{3}J coupling constant between the alkene protons of **150** to be measured (15.5 Hz) and the expected *trans* relationship of these protons was demonstrated.



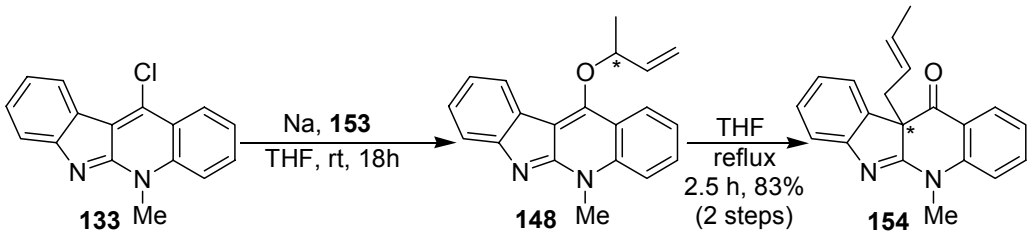
Scheme 48. Synthesis and rearrangement of **146**.

Crude **147** was synthesised from **133** using 3-methyl-2-butene-1-ol (**Scheme 49**). Whilst inspection of the ^{1}H NMR spectra associated with the crude reaction mixtures from the preparation and rearrangement of **147** did show traces of what was believed to be **151**, it was not possible to isolated this transient compound. Indeed, it was found that the only compound that could be isolated from the rearrangement of **147** was **152**. For example, after 2.5 hours at reflux **152** was isolated in a 88% yield. In this case, the disproportionate increase in the rate of the aza-Cope rearrangement in relation to the rate of the Claisen rearrangement was even more pronounced than with **146** and this is presumably due to the even greater release of steric strain on transformation of **151** to **152**.



Scheme 49. Preparation and rearrangement of **147**.

The rearrangement of **148**, formed from **133** and 3-butene-2-ol (**153**), proved to be of greater synthetic value than the rearrangement of **146** or **147** (**Scheme 50**). Indeed, **154** could be formed in high yield without any significant aza-Cope rearrangement product being observed.



Scheme 50. Preparation of **148** using 3-butene-2-ol (**153**) and rearrangement to **154**.

Of particular note is that only *E*-alkene **154** was observed and not the possible *Z*-isomer. As before the alkene geometry was determined from the ^{3}J coupling constant of the alkene protons (15.2 Hz) after homonuclear decoupling of the methyl protons. This selectivity for the *E*-alkene is important as it suggests that the Claisen rearrangement is proceeding *via* an ordered transition state, most likely a chair, in which the methyl group occupies an equatorial position (if the methyl group occupies an axial position the *Z*-alkene will result). Furthermore, this implies that the stereochemical information embedded in the chiral centre of **148** has been transferred to the newly formed chiral centre in **154**. Of course, in this racemic mixture such a chirality transfer could not be assessed. However, the fact that chirality transfer has occurred becomes significant when an enantiomerically enriched substrate is rearranged and this is the subject of section 4 in Chapter 5.

3.6 Protecting groups

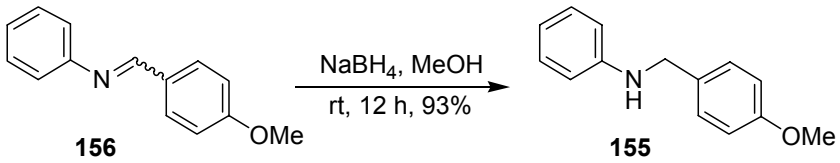
The results reported in this section were obtained in collaboration with Helmut Kraus as part of his M. Chem. Research Project, Specifically, attempts at benzyl deprotection of **161** and the preparation of **170**, **172**, **174**, and **176** were carried out in collaboration with Helmut Kraus.

As the Claisen rearrangement used to form the C-10b quaternary centre requires a substituent on the quinolic nitrogen N-5, and neither perophoramidine nor the communesins have a

substituent at this position, it was clear that an N-5 substituent that could be removed later in the synthesis was required. Whilst the development of a protection group strategy was not a primary aim of this project, some consideration was given to this matter and the synthesis of N-5 protected analogues of **130** were investigated.

Considering it desirable not to change the synthetic route that had already been developed, a protecting group that was stable to the reaction conditions used and that could be introduced at the beginning of synthesis as the appropriate *N*-substituted aniline was required. Specifically, to allow introduction at the beginning of the synthesis, the protecting group must not reduce the nucleophilic character of the aniline as would be the case with, for example, an amide protecting group. Furthermore, not only must the high temperature cyclisation in refluxing diphenyl ether be tolerated, but so must the potentially strongly acidic conditions of the phosphorus oxychloride reaction and the nucleophilic/basic nature of the sodium allyloxide. Taking these factors into account a choice was made in favour of benzyl and methoxy-substituted benzyl protecting groups. Whilst there is limited information reported in the literature regarding amidine protection,[65] there are numerous examples of amine, amide and alcohol protection strategies using these groups.[66]

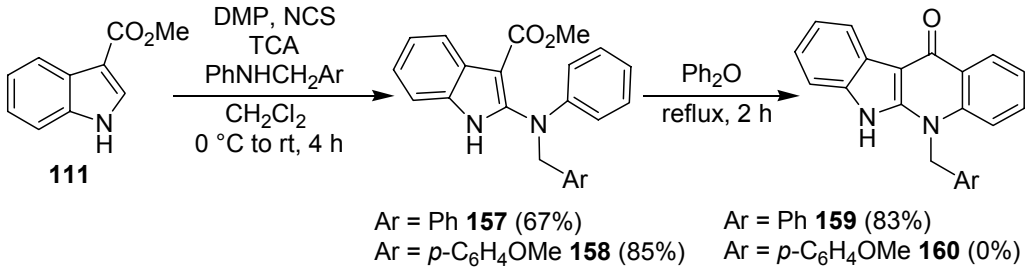
Initially considering the introduction of benzyl and *p*-methoxybenzyl (PMB) protecting groups, the methodology used for the preparation of **132** was modified to incorporate the appropriate *N*-substituted aniline. Whereas *N*-benzylaniline was commercially available, *N*-(*p*-methoxybenzyl)aniline (**155**) was synthesised in good yield by the sodium borohydride reduction of the corresponding, commercially available, imine **156** (**Scheme 51**).[67]



156 **155**

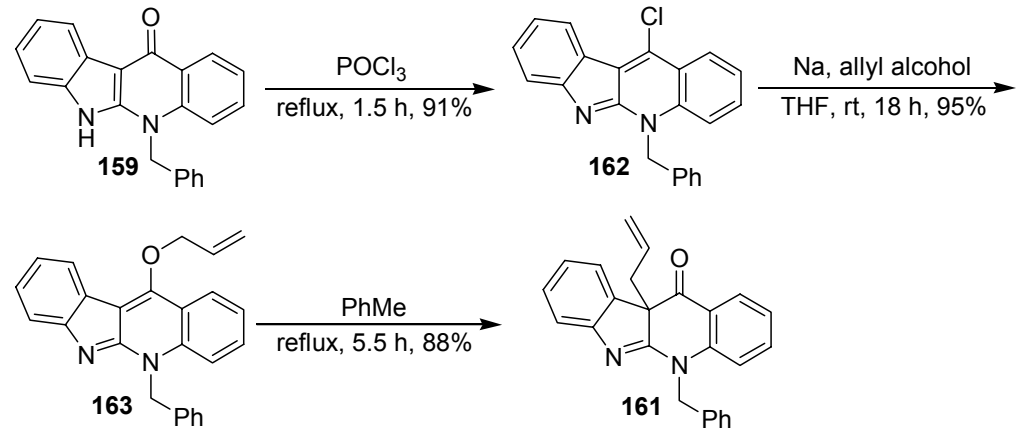
Scheme 51. Reduction of *N*-(*p*-methoxybenzylidine)aniline (**156**) to *N*-(*p*-methoxybenzyl)aniline (**155**).

It was found that **157** and **158** could both be prepared in good yield from **111** (**Scheme 52**). As was the case with **132**, **157** could be purified by crystallisation whereas **158** required chromatographic purification.



Scheme 52. Preparation of **159** and attempted preparation of **160**. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

Whilst the high temperature cyclisation of **157** proceeded smoothly to give **159** in high yield and satisfactory purity, a clean transformation of **158** to **160** could not be achieved with mixtures of compounds resulting (**Scheme 52**). The ^{1}H NMR spectrum associated with the crude ether insoluble portion of this mixture showed features consistent with loss of the PMB group: two NH signals were present at 12.30 ppm and 11.65 ppm and only traces of the signals associated with the benzyl protons of the PMB group were present. It was therefore concluded that the PMB protecting group was incompatible with the current synthetic route.

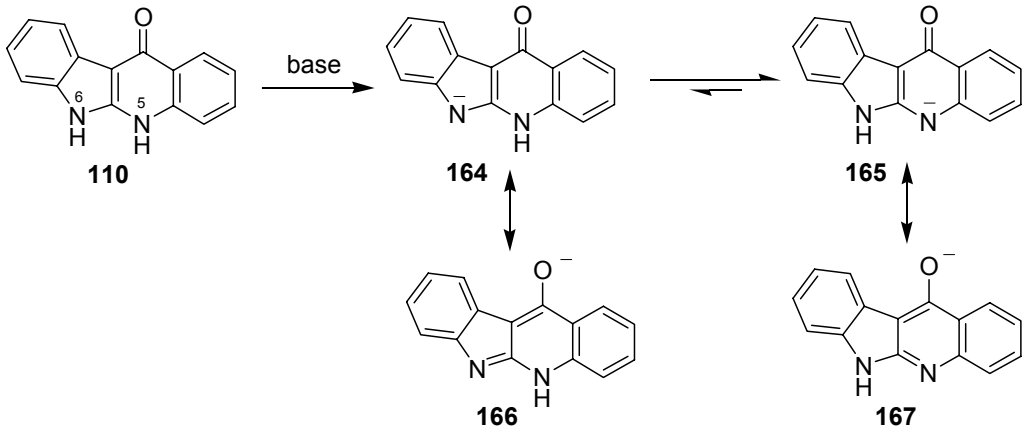


Scheme 53. Indolo[2,3-*b*]quinoline-11-one **159** was converted to **161** in an overall yield of 76%, using reaction conditions identical to those used previously.

Using a reaction sequence analogous to that used for the preparation of **130** from **132**, **159** was converted to **161** in three steps in an overall yield of 76%, *via* **162** and **163** (**Scheme 53**). The yields shown in **Scheme 53** are those involving chromatographic purification at each step. However, for large scale preparation of **161**, chromatographic purification could be carried out in the last step only if **157** was of high purity.

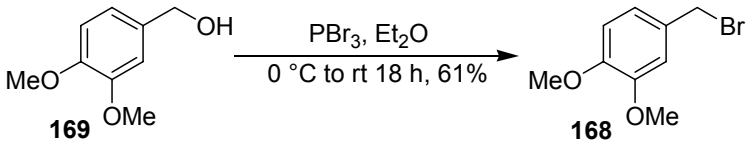
Attempts were made to remove the benzyl group from **161** using a variety of reagents (including aluminium trichloride,[68] boron trifluoride etherate,[69] vinyl chloroformate,[70] and hydrogenation with a palladium catalyst[71]) in combination with various solvents at different temperatures. In summary, all attempts at benzyl deprotection of **161** resulted in either recovery of **161** or cleavage of the allyl group to afford **159**.

Having failed to remove the benzyl group from **161**, the use of the *p*-methoxybenzyl (PMB) protecting group, and later the 3,4-dimethoxybenzyl (3,4-DMB) protecting group, was reconsidered. Whilst it was clear that incorporation of these groups prior to the high temperature cyclisation would not be possible, it was reasoned that a selective N-5 alkylation of **110** after formation of the indolo[2,3-*b*]quinoline-11-one ring system could be achieved. This proposal was based on the assumed differences in stability of the two possible mono-anions generated by deprotonation of **110** with one equivalent of base (**Scheme 54**). Removal of H-5 or H-6 from **110** gives two different anions **164** and **165** that would appear to be of approximately equal stability. However, the resonance form **166** is presumably less stable than resonance form **167**, due to the formation of the aromatic quinoline system, thereby shifting the equilibrium towards the thermodynamically more stable anion **165**/**167**.



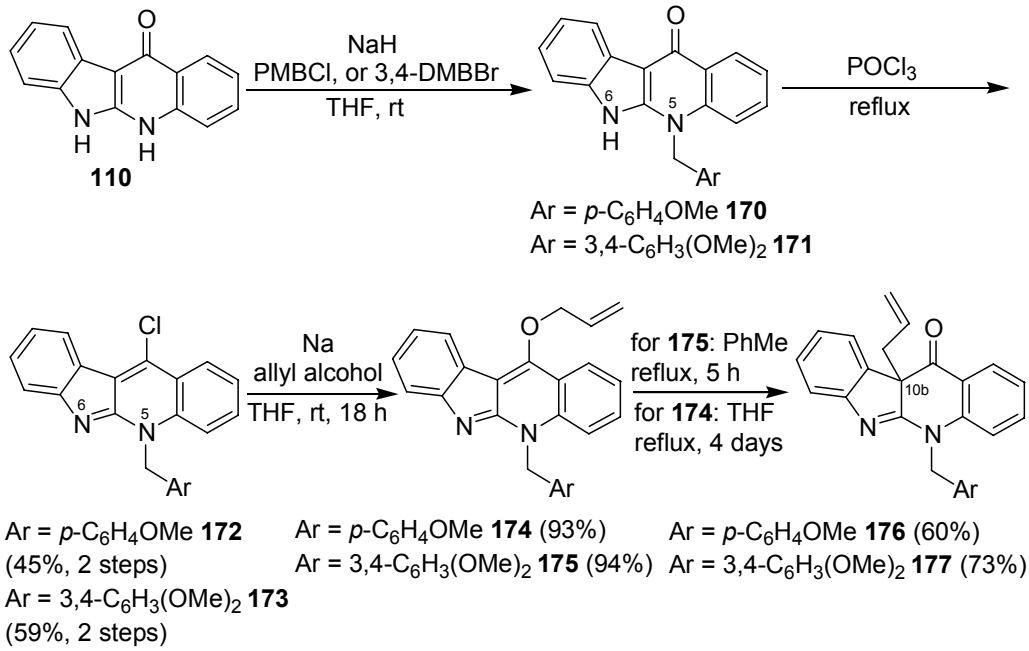
Scheme 54. It was expected that selective N-5 alkylation could be achieved *via* the presumably more stable anion **165**/**167**.

The two different electrophiles that were used for the alkylation of **110** were *p*-methoxybenzyl chloride (PMBCl), which was commercially available, and 3,4-dimethoxybenzyl bromide (3,4-DMBBr, **168**) that was prepared from 3,4-dimethoxybenzyl alcohol (**169**) and phosphorus tribromide (**Scheme 55**).[72,73]



Scheme 55. Preparation of 3,4-dimethoxybenzyl chloride (**168**).

Treatment of **110** with one equivalent of sodium hydride in tetrahydrofuran and quenching the resulting anion with either PMBCl or 3,4-DMBBr resulted in the formation of mixtures of products that could not be purified, other than by washing with ether, due to their insolubility in most solvents (**Scheme 56**). Analysis by ^{1}H NMR indicated that each of these mixtures consisted of predominantly single alkylation products that were presumed to be **170** and **171**.



Scheme 56. Preparation of PMB and 3,4-DMB protected substrates **176** and **177**. PMBCl = *p*-methoxybenzyl chloride, 3,4-DMBBr = 3,4-dimethoxybenzyl bromide.

Treatment of these mixtures with phosphorus oxychloride afforded the diagnostically orange coloured N-5 alkylated product chlorides **172** and **173** in reasonable yield, following chromatographic purification. Chloride **172** and **173** were then converted to allyl ethers **174** and **175** respectively using sodium and allyl alcohol. Claisen rearrangement to form the C-10b quaternary centre in **176** and **177** proceeded as before.

The cleavage of PMB and the more labile 3,4-DMB groups from nitrogen and oxygen is well documented.[74-78] In addition to the general methods that have been used to cleave unsubstituted benzyl groups, PMB and 3,4-DMB groups have also been cleaved from heteroatoms under oxidative conditions using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or ceric ammonium nitrate (CAN).

Attempts were made to remove the PMB and 3,4-DMB groups from **176** and **177** respectively, using the reagents trifluoroacetic acid, DDQ or CAN. However, in all cases no evidence could be found for removal of the protecting groups. As was seen with attempts to remove the benzyl group from **161**, either deallylation, recovery of the starting material, or the formation of complex mixtures of unidentifiable products was observed.

In light of these failed attempts to remove any of the N-5 protecting groups, and in particular the frequently observed deallylation of the substrates, it was considered that removal of a protecting group may be more successful later in the synthesis. No further investigations regarding a protecting group strategy were carried out.

3.7 Summary and conclusions

In Chapter 2 a modified model substrate **129** for the Claisen rearrangement was proposed. In this chapter the synthesis of **129** was outlined and it was shown that **130** containing the desired C-10b quaternary centre could successfully be formed in high yield by rearrangement of this substrate. The differences in chemical behaviour of the two allyl ethers **129** and **90** was rationalised and it was concluded that the differences in the rates of the Claisen rearrangements was due to an increased isolated double bond character of the participating aromatic bond in **129**.

An investigation into the effect of methyl substituents on the allyl group was then described and it was shown that the relative rates of the consecutive Claisen and aza-Cope rearrangements is dependent on these substituents. Furthermore, it was shown that the rearrangement of **148** gave a single *E*-alkene product **153**, indicating that a potentially synthetically useful chirality transfer had taken place. Finally, the preparation of a series of N-5 protected analogues of **130** and attempts at deprotection were outlined.

Chapter 4 describes efforts to form the C-11 quaternary centre in the indolo[2,3-*b*]quinoline system. For these studies the model compound **130** was chosen as it could be prepared on a multigram scale.

Chapter 4: Formation of the C-11 Quaternary Centre

4.1 Introduction

Chapters 2 and 3 described investigations into the formation of the C-10b quaternary centre in the indolo[2,3-*b*]quinoline system using a Claisen rearrangement. These investigations resulted in the successful formation of the C-10b quaternary centre in substrates with an N-5 substituent. The investigations described in this chapter are concerned with the formation of the second, adjacent quaternary centre at C-11 of the indolo[2,3-*b*]quinoline system. In general, the formation of vicinal all-carbon quaternary centres presents a significant challenge[27-30] and is certainly one of the most difficult aspects of a communesin or perophoramidine (**17**) synthesis. When constructing the C-11 quaternary centre the relative stereochemistry of the C-10b and C-11 has to be considered in light of the relative configurations of the natural products. As discussed in Chapter 1, perophoramidine has *trans* 2C units and the communesins have *cis* 2C units at these stereocentres. It was expected that the configuration at the C-10b quaternary centre would strongly influence the relative stereochemical outcome of transformations used to manipulate the functionality at C-11. With this in mind, one of the aims of the investigations described in this chapter was to understand how the configuration at C-10b affects the relative configuration at C-11 so as to determine the chemistry that would be required to form the correct relative stereochemistry for each of the natural products.

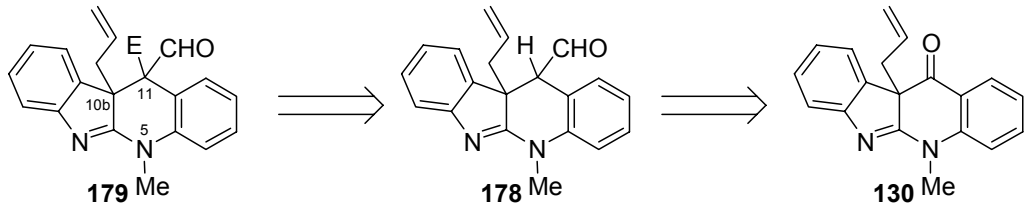
First, this chapter describes attempts at forming the C-11 quaternary centre using a route based on the alkylation of an aldehyde formed from the C-11 ketone. A modification of this procedure that results in the formation of the C-11 quaternary centre by alkylation of an ester is then described. Next, a brief investigation into the formation of the C-11 quaternary centre by opening an epoxide with organometalic reagents is outlined. Finally, formation of the C-11 quaternary centre by alkylation of a nitrile, formed from the C-11 ketone using the TosMIC reagent, is described.

All the investigations described in this chapter were conducted on the model compound **130** as this compound could be prepared in good yield on a multigram scale. Additionally, the

presence of the N-5 methyl group, as opposed to a benzyl group, aided structural determination by reducing the amount of coincidental peaks in the aromatic region of ^{1}H and ^{13}C NMR spectra.

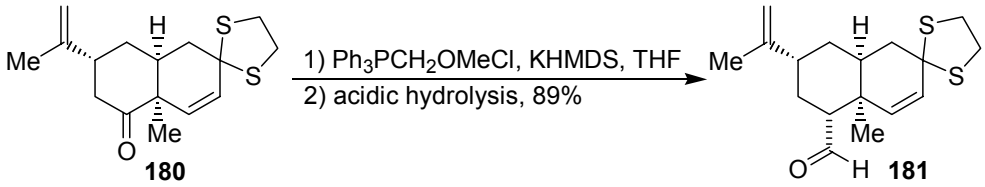
4.2 Attempts to form the C-11 aldehyde

In Chapter 1 it was proposed that the ketone resulting from the Claisen rearrangement could be manipulated in such a way so as to form a compound with an acidic hydrogen at C-11 that could be deprotonated and the resulting anion alkylated with a suitable electrophile (**Scheme 57**). Initially it was planned that conversion of the C-11 ketone of **130** to aldehyde **178** would be suitable for this purpose. It was expected that it should then be possible to alkylate **178** with a suitable electrophile to form compounds of the type **179**.



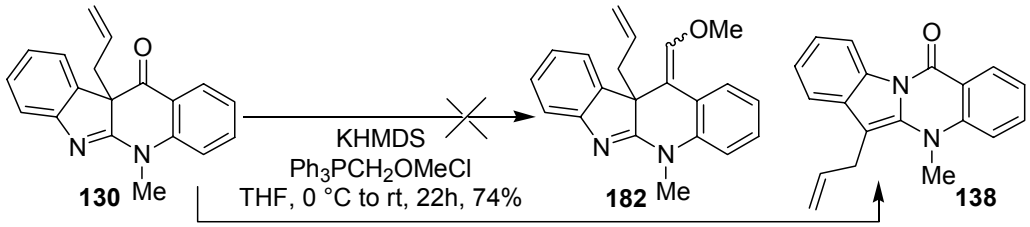
Scheme 57. Initial plan for the formation of the C-11 quaternary centre. E = electrophile.

A Wittig reaction using the phosphorane derived from (methoxymethyl)triphenyl phosphonium chloride has frequently been used to form aldehydes from ketones, *via* the corresponding easily hydrolysed enol ethers. For example, **Scheme 58** shows the high yielding conversion of ketone **180** to aldehyde **181** using this phosphorane as part of a recent synthesis of the natural product (+)-Peribysin E.[79]



Scheme 58. The phosphorane derived from (methoxymethyl)triphenyl phosphonium chloride is used to convert ketones to aldehydes.[79] HMDS = hexamethyldisilazide.

In an attempt to form the enol ether **182** that could be subsequently hydrolysed to the corresponding aldehyde **178**, **130** was treated with (methoxymethyl)triphenyl phosphonium chloride and the base potassium hexamethyldisilazide (KHMDS) in tetrahydrofuran or toluene (**Scheme 59**). The only product that could be isolated from this reaction, however, was not the expected enol ether **182**, but the rearrangement product **138** in 74% yield with 19% of **130** remaining. Analogous results were obtained when the phosphorane derived from methyltriphenyl phosphonium bromide was used.



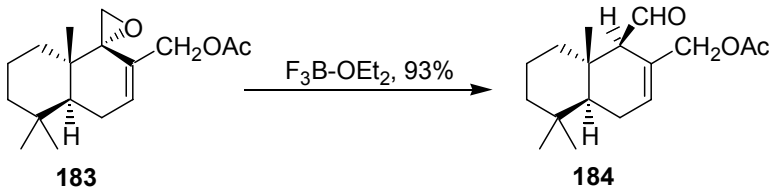
Scheme 59. An attempt to form enol ether **182** from ketone **130** using the phosphorane derived from (methoxymetyl)triphenyl phosphonium chloride. HMDS = hexamethyldisilazide.

In contrast to the previously proposed mechanism for formation of **138** from **130** in refluxing methanol (page 43), it is presumably the phosphorane that attacks the ketone and is then regenerated on formation of **138**. However, regardless of the mechanism by which **138** forms, it was clear that an alternative synthetic route was required.

From the mechanism shown in **Scheme 42** (page 43) it can be seen that if the amidine of **130** was to be reduced to the corresponding aminal, the rearrangement of **130** to **138** would not be possible. Attempts were made to prevent this unwanted rearrangement by the selective reduction of the amidine functionality present in **130** prior to reaction with the phosphorane. Whilst a selective reduction of the amidine was achieved by methylation with methyl triflate followed by brief treatment with sodium borohydride,[80] the product was found to be unstable and could not be satisfactorily purified. Alternative methods to avoid the rearrangement of **130** to **138** were considered.

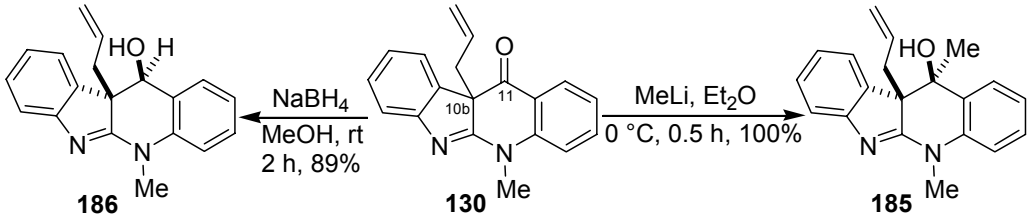
The acid catalysed rearrangement of epoxides to aldehydes and ketones is a known and frequently utilised transformation.[81] Rearrangement is often accomplished under Lewis acidic conditions and, mechanistically, involves the coordination of the Lewis acid to the epoxide followed by a 1,2-hydride migration. Boron trifluoride is a commonly used reagent

for this transformation. Epoxide **183**, for example, was transformed to aldehyde **184** in excellent yield under such conditions (**Scheme 60**).[82]



Scheme 60. Epoxide **183** is converted to aldehyde **184** in excellent yield under Lewis acidic conditions.[82]

Whilst many epoxides have been formed from ketones in one step using sulfur ylides,[83] treatment of **130** with dimethyloxosulfonium methylide afforded only **138**. With the C-11 aldehyde **178** still being the synthetic target, alternative transformations on **130** were investigated in an attempt to gain an understanding of the requirements for rearrangement to **138**. Fortunately, it was found that the reaction of **130** with sodium borohydride, Grignard or organolithium reagents did not cause rearrangement to **138** and gave the normal alcohol containing products (**Scheme 61**).



Scheme 61. Reduction or the addition of methyl lithium to **130** gave the expected alcohol containing products.

Indeed, the addition of methyl lithium to **130** afforded tertiary alcohol **185** in quantitative yield as a single diastereoisomer, and the reduction of **130** with sodium borohydride afforded alcohol **186** in high yield, also as a single diastereoisomer. The relative stereochemical assignment of **186**, which demonstrates that hydride attack had occurred on the opposite face to the allyl group, was based on X-ray crystallographic analysis (**Figure 14**). Whilst the relative stereochemistry of **185** was not determined directly, it was assumed that addition of the methyl nucleophile had also occurred on the opposite face to the allyl group to give the relative configuration shown. This proposed stereochemistry in **185** is also based on the stereochemistry of the related compound **191** prepared as described on page 62.

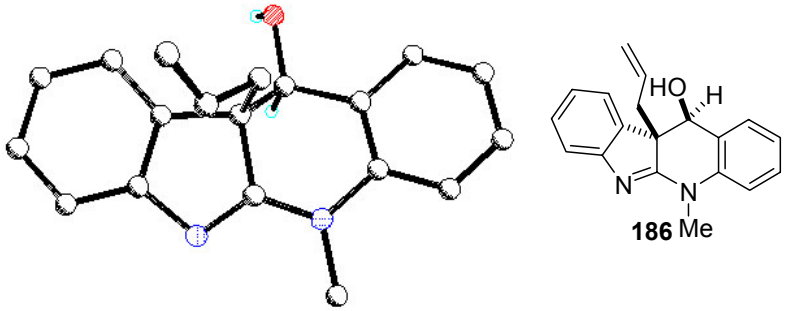
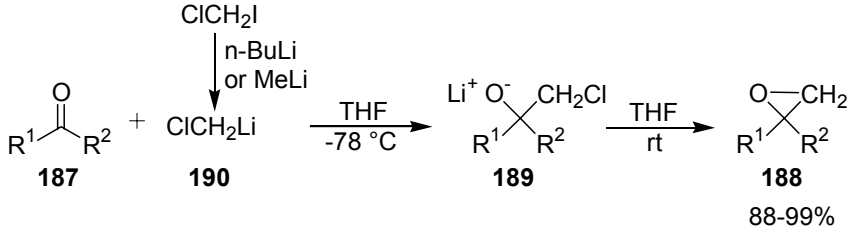


Figure 14. X-ray structure of **186**.

It is difficult to rationalise why the nucleophilic addition of the organolithium reagents, or the addition of hydride, to the carbonyl of **130** does not cause breakage of the C-10b-C-11 bond in the same way that nucleophilic attack by methanol or ylides do. One possible explanation is that C-10b-C-11 bond cleavage is prevented by prior coordination of a Lewis acidic lithium cation to the carbonyl oxygen in the case of methyl lithium, or by the coordination of boron in the case of the sodium borohydride reduction.

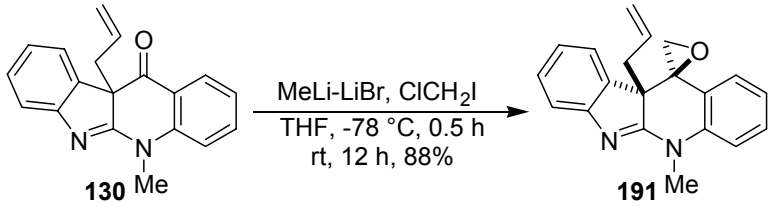
Having observed that **185** could be formed from **130** using methyl lithium without the formation of **138**, it was expected that a synthetically useful transformation involving similar chemistry would provide a route to the desired C-11 aldehyde *via* epoxidation of **130**.

A method for generating epoxides from ketones or aldehydes using an organolithium reagent has been reported in the literature (**Scheme 62**).[84] This procedure involves treating a mixture of the ketone **187** and chloroiodomethane with *n*-butyllithium or methyllithium at -78 °C. To isolate the epoxide **188**, the reaction mixture is warmed to room temperature after the addition of the alkyl lithium and quenched once the lithium alkoxide intermediate **189** has undergone ring closure. Alternatively, if the reaction is quenched immediately after formation of **189** it is possible to isolate the corresponding chlorohydrin.



Scheme 62. Epoxide formation using the highly reactive chloromethyllithium (**190**).

As all the components are mixed together, the success of this epoxide formation is indicative of the rate relationship between several fast reactions. That is to say, lithium-iodine exchange must be faster than the attack of the alkyl lithium species at the carbonyl and the attack of the chloromethyllithium (**190**) at the carbonyl must be faster than the previously reported facile decomposition of **190**.[85,86] It is reported that using methyllithium-lithium bromide complex for this epoxide formation has the advantage of increasing the rate of epoxide ring closure and reducing the amount of side products resulting from attack of the methyllithium at the carbonyl.[84]



Scheme 63. High yielding conversion of ketone **130** to epoxide **191** using chloromethyllithium.

Applying the epoxidation condition described above to **130** led to a clean transformation to epoxide **191**, as a single diastereoisomer (**Scheme 63**). Crystallisation of **191** by the slow evaporation of ether produced large (up to 3 mm), cubic, colourless crystals and allowed for multigram preparation of **191** without the use of chromatography. The relative stereochemistry of **191**, determined by X-ray crystallography (**Figure 15**), indicated that nucleophilic attack at the carbonyl had occurred, as expected, from the opposite side to the allyl group. This high degree of selectivity is presumably due to steric interactions between the reagent **190** and the allyl group.

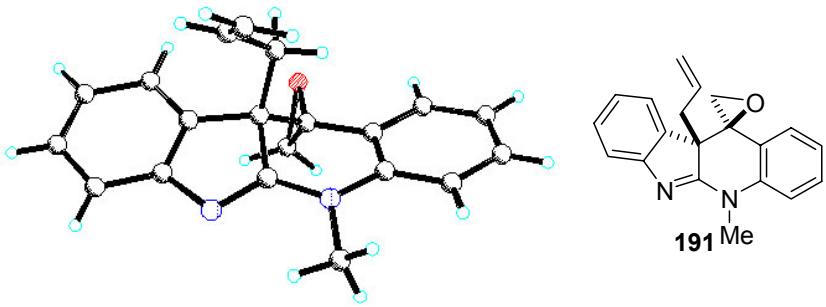
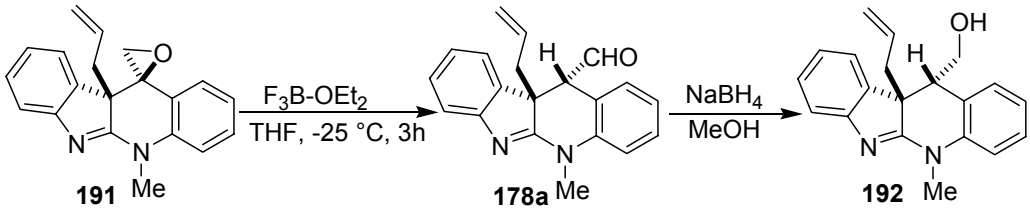


Figure 15. X-ray structure of epoxide **191**.

With epoxide **191** in hand, attempts were made to form aldehyde **178** using an acid catalysed rearrangement.[81] The transformation of **191** to **178** was attempted using a variety of Lewis and protic acids (including $MgBr_2$, F_3CO_2H, $F_3B\text{-}OEt_2$), in the solvents tetrahydrofuran or dichloromethane and using various workup procedures. In summary, aldehyde **178** could not be reproducibly prepared in satisfactory purity or yield under any of these conditions. The best results were obtained using an excess of boron trifluoride etherate in tetrahydrofuran at -25 °C (**Scheme 64**). However, even under these conditions only low yields of an impure compound, showing a diagnostic aldehyde proton doublet signal at 8.98 ppm in the ^{1}H NMR spectrum, could be isolated. This aldehyde, which rapidly decomposed to a complex mixture of compounds, was shown to have structure **178a** by reduction of a small sample with sodium borohydride to the corresponding alcohol. This impure alcohol was found to have a mass and ^{1}H NMR spectrum consistent with structure **192**.



Scheme 64. Impure samples of the unstable aldehyde **178a** ware prepared from **191**. Additional evidence that **178a** had been prepared was gained by reduction of a small sample of this impure material to **192**.

A crystal of this alcohol was grown from chloroform-hexane and analysed by X-ray crystallography thereby confirming the structure to be that of **192** (**Figure 16**). The stereochemistry of **178a** was therefore tentatively assigned as that shown.

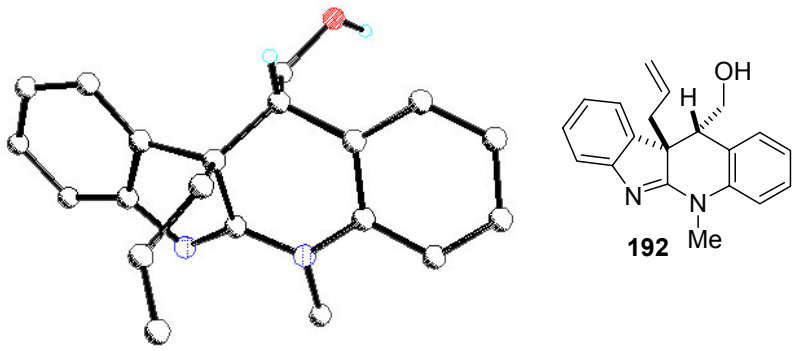
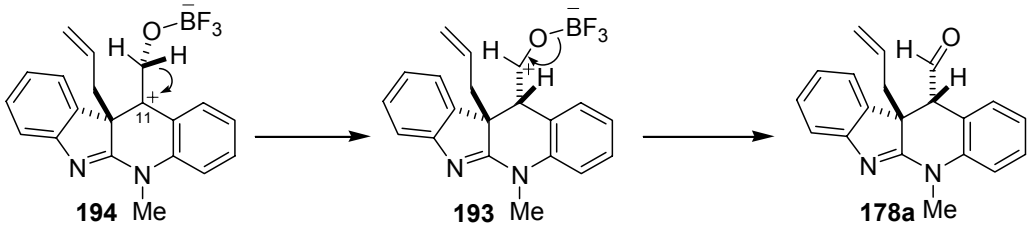


Figure 16. X-ray structure of **192**.

It is interesting to note that aldehyde **178a** is formed with retention of stereochemistry at C-11. One possible explanation for this is that the coordination of boron trifluoride to oxygen leads to the formation of a tertiary cationic centre at C-11 prior to a 1,2-hydride shift rather than the alternative concerted mechanism that would be expected to lead to inversion of configuration at C-11. The preference for the 1,2-hydride shift to take place *syn* to the allyl group to form **193** can be explained by the intermediate **194** adopting a conformation that places the oxygen in a sterically less demanding position, *anti* to the allyl group (**Scheme 65**).



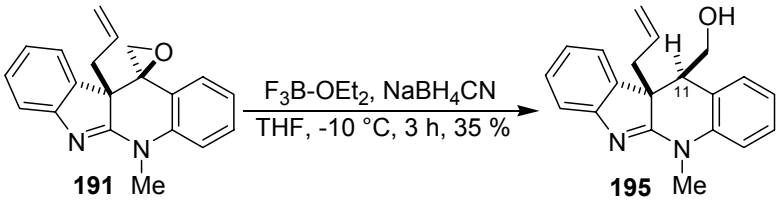
Scheme 65. After formation of the tertiary carbocation centre at C-11 a 1,2-hydride shift takes place *syn* to the allyl group with the oxygen adopting the less sterically demanding position.

An alternative explanation relies on the fact that **178a** is the thermodynamic product and **178a** results from equilibration of a mixture of diastereoisomeric aldehydes, or from the epimerisation of the single C-11 epimer of **178a** under the reaction conditions.

Attempts were made to deuterate and alkylate impure **178a** using lithium diisopropylamide in combination with methanol-d_4 or methyl iodide respectively. However, this led to the formation of complex mixtures of compounds that could not be separated and that no longer showed an aldehyde proton signal in the associated ^{1}H NMR spectrum. As aldehyde **178a** could not be prepared reproducibly, was found to decompose rapidly and could not be alkylated, alternative synthetic routes to form the C-11 quaternary centre were investigated. Initially, two routes using epoxide **191** were considered. First, it was considered that an ester functionality at C-8 would impart greater stability than the aldehyde and a synthetic sequence for the preparation of such a compound was investigated. Later, direct formation of the quaternary centre from epoxide **191** was considered.

4.3 Synthesis of ester 197

As aldehyde **178a** was found to be unsuitable as a synthetic intermediate it was considered that an oxidised analogue of this compound may have greater stability and would allow alkylation at C-11. Additionally, it was considered that the isolation of the aldehyde intermediate could be avoided by reductive opening, rather than rearrangement, of epoxide **191** to give the corresponding primary alcohol **195** (**Scheme 62**). It was expected that **195** would be a more stable intermediate compared to **178a**. That is to say, a synthetic sequence involving reductive opening of epoxide **191** to form the primary alcohol **195** followed by oxidation to the corresponding acid, involving only transient formation of aldehyde **178**, and subsequent esterification was proposed. It has been reported that the reduction of epoxides using sodium cyanoborohydride in combination with boron trifluoride etherate gives predominantly the less substituted alcohol.[87] Initial attempts to reductively open epoxide **191** using sodium cyanoborohydride in combination with sub-stoichiometric or stoichiometric amounts of boron trifluoride etherate resulted in the recovery of **191**. Treatment of epoxide **191** with sodium cyanoborohydride and an excess boron trifluoride etherate in tetrahydrofuran gave complex reaction mixtures. Attempts to separate **195** by chromatography resulted in the co-elution of compounds, but it was found that primary alcohol **195** could be isolated in low yield by crystallisation from methanol (**Scheme 66**).



Scheme 66. A low yielding conversion of epoxide **191** to primary alcohol **195**.

The structure of **195**, which is epimeric at C-11 with **192**, was determined by X-ray crystallography (**Figure 17**) and indicated that the reduction of **191** to **195** had proceeded with inversion of stereochemistry at C-11.

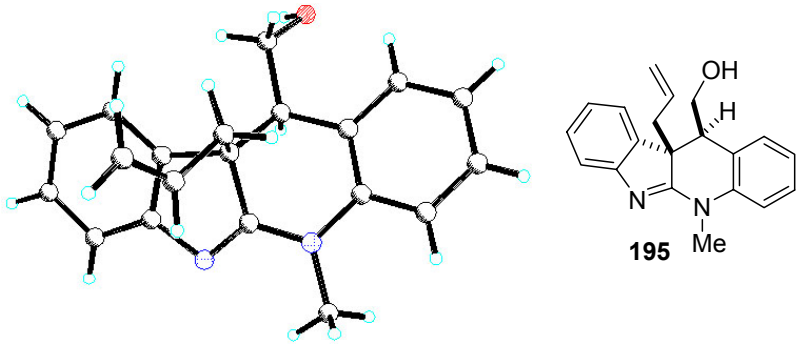


Figure 17. X-ray structure of primary alcohol **195**.

Two mechanisms leading to inversion of configuration at C-11 can be envisaged (**Figure 18**). A mechanism that involves formation of the tertiary cationic centre at C-11 followed by attack of hydride, an S_N1-like process, preferentially from the less sterically encumbered face, *anti* to the allyl group, would lead to inversion of configuration. Alternatively, a mechanism involving initial polarisation, but not actually breaking, of the C-O bond by boron trifluoride that facilitates an S_N2-like attack by hydride at C-11 would also lead to an inversion of configuration that is independent of the adjacent stereocentre. The well documented observations that the opening of epoxides with nucleophiles under acidic conditions frequently leads to inversion of configuration supports the latter of these two mechanisms.[81,88] However, it seems reasonable that the stereochemical outcome is a result of the configuration at both C-11 and C-10b and that the true mechanism is something between the two extremes of S_N1 and S_N2.

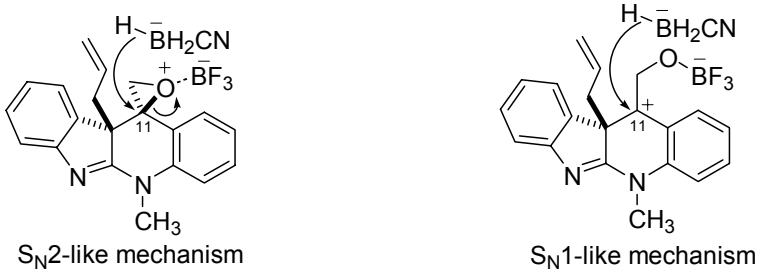
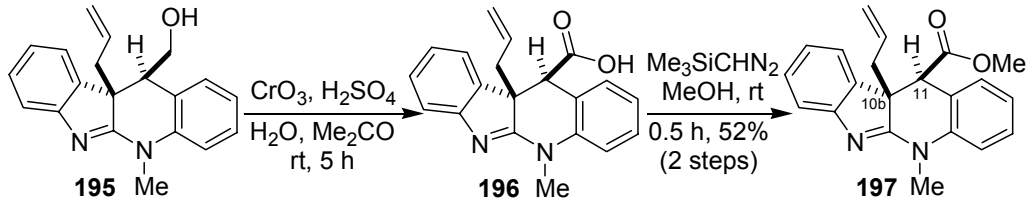


Figure 18. The two extreme mechanisms possible for the Lewis acid catalysed reductive opening of epoxide **191** will both give inversion of configuration at C-11.

The attempt to oxidise alcohol **195** to the corresponding aldehyde under the mild conditions described by Dess and Martin led to complex mixtures of products and the same problems that had been encountered previously in isolating aldehyde **178a**.[89] This suggested that it was

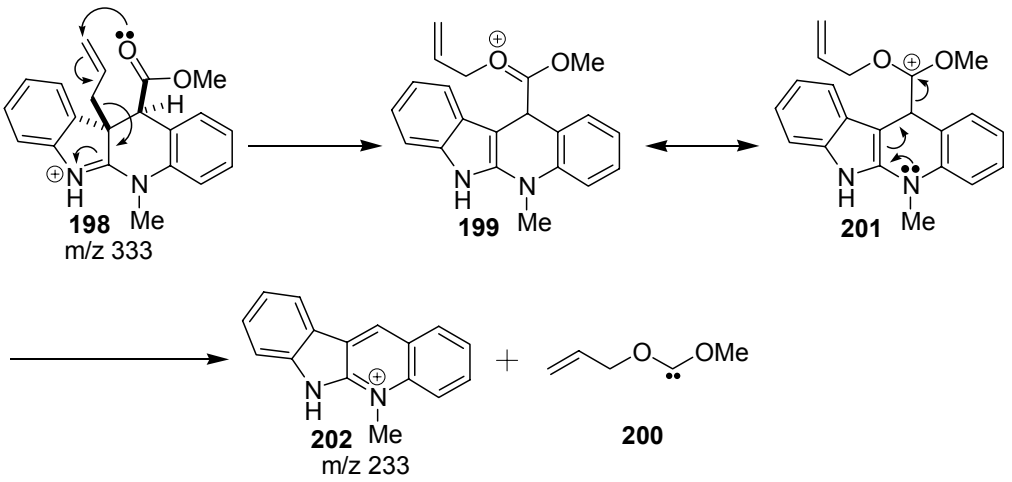
aldehyde **178** that was intrinsically unstable rather than the method of preparation that was problematic.

Now that the stable alcohol **195** could be prepared, oxidation to the corresponding carboxylic acid **196** was attempted (**Scheme 67**). Treatment of an acetone solution of **195** with chromic acid afforded carboxylic acid **196** that showed a diagnostic broad signal at 11.1 ppm in the associated ^{1}H NMR spectrum. Due to the potential zwitterionic nature of **196**, no attempt was made to purify this compound. Crude **196** was converted to the corresponding methyl ester **197** by treatment with trimethylsilyl diazomethane in methanol. From this two step procedure **197** was isolated as a single diastereoisomer in reasonable yield.



Scheme 67 Preparation of ester **197** from alcohol **195** *via* carboxylic acid **196**.

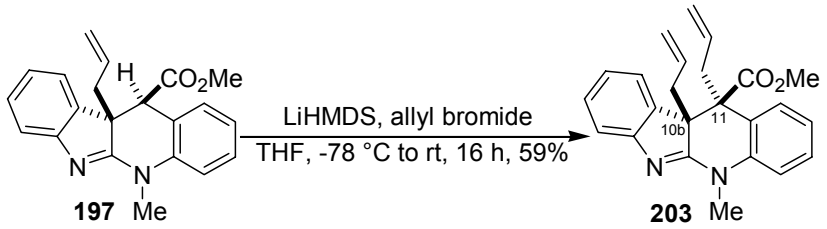
Whilst it was assumed that **197** had the same *cis* relative stereochemistry as the alcohol **195** from which it was derived, acid induced C-11 epimerisation to the thermodynamically more stable *trans* isomer could not be completely ruled out. Attempts were made to confirm the relative configuration of **197** using ^{1}H NMR nOe techniques, but no significant enhancements were observed between the allylic protons and H-11 or the ester methyl group. Although no further direct attempts were made to determine the relative stereochemistry of **197**, an interesting fragment was observed in the mass spectrum of **197** (using the electrospray ionisation method) (**Scheme 68**). A fragment with a m/z 233 (94%), arising from a loss of 100 daltons from the molecular ion m/z 333 (MH^{+}, 100%), was observed without any other fragmentation occurring. This loss of 100 daltons corresponds to a concurrent loss of both the allyl group and ester moiety. One mechanism by which this could occur, which necessitates a *cis* relationship between the two groups, involves intramolecular attack of the carbonyl oxygen lone pair at the allyl group of the protonated species **198** to give **199**, *via* a *7-endo-trig* process. Loss of the neutral carbene species **200** (100 daltons) from **201** affords **202** (m/z 233) with a highly delocalised positive charge.



Scheme 68 Following ionisation in the mass spectrometer, a simultaneous loss of the allyl and ester groups, which requires a *cis* relationship, would lead to a fragment of m/z 233.

4.4 Alkylation of the ester 197

With ester **197** in hand, alkylation of this substrate was examined. Deprotonation of **197** with the base lithium hexamethyldisilazide (LiHMDS), to generate the corresponding enolate, and quenching with allyl bromide afforded **203** (**Scheme 69**).



Scheme 69. Formation of the C-11 quaternary centre by alkylation of the enolate generated from ester **197**. HMDS = hexamethyldisilazide.

Purification by chromatography followed by crystallisation to remove a small amount of an unidentified impurity afforded a pure sample of **203** in 59% yield as a single diastereoisomer. Evidence that **203** had been formed was gained from the associated ^{1}H NMR spectrum that showed two sets of allyl group signals, and from the ^{13}C NMR spectrum that showed two quaternary carbon signals (determined using the PENDANT pulse sequence) at 58.3 ppm and 57.1 ppm, corresponding to the C-11 and C-10b all-carbon quaternary centres respectively. Finally, confirmation of the structure of **203** and unambiguous assignment of the relative

configuration at the two contiguous quaternary centres C-10b and C-11 was achieved by X-ray crystallographic analysis (**Figure 19**).

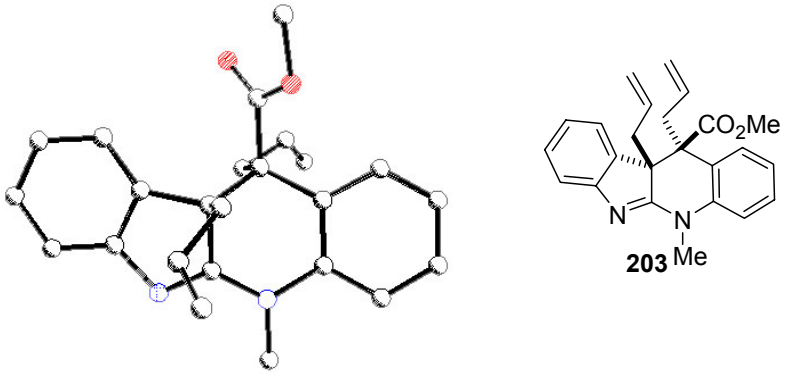
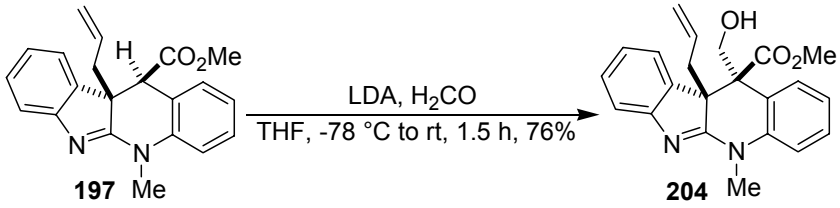


Figure 19. X-ray structure of **203** showing *trans* relationship of allyl groups.

The *trans* relationship of the two allyl groups indicated that, as expected, the electrophile had approached from the side opposite to the C-10b allyl group. This stereochemical relationship of the two allyl groups (viewed as precursors of 2C units) is that present in the perophoramidine (**17**) structure.

For a communesin synthesis it is necessary to have a one carbon unit *trans* to the C-10b allyl group. This was achieved by alkylation of the enolate generated from **197**, using lithium diisopropylamide (LDA), with formaldehyde (a one carbon electrophile) to give **204** (**Scheme 70**). Alcohol **204** was isolated in good yield after chromatographic purification and as before the presence of quaternary carbon signals at 58.8 ppm (C-11) and 55.8 ppm (C-10b) in the associated ^{13}C NMR spectrum demonstrated the presence of the two all-carbon quaternary centres.



Scheme 70. Alkylation of ester **197** with formaldehyde. LDA = lithium diisopropylamide.

X-ray crystallography was again used to show that the electrophile had approached opposite to the C-10b allyl group to give structure **204**. Now that C-11 of **204** has two pendant C1

units, independent manipulation of the ester moiety into a 2C would be required to construct the communesin relative stereochemistry. The difference in oxidation states of these two groups would seem to provide several possible methods of achieving this. For example, after protection of the primary alcohol, reduction of the ester to the corresponding aldehyde would allow for one-carbon homologation using a Wittig reaction with the phosphorane derived from (methoxymethyl)triphenyl phosphonium chloride.

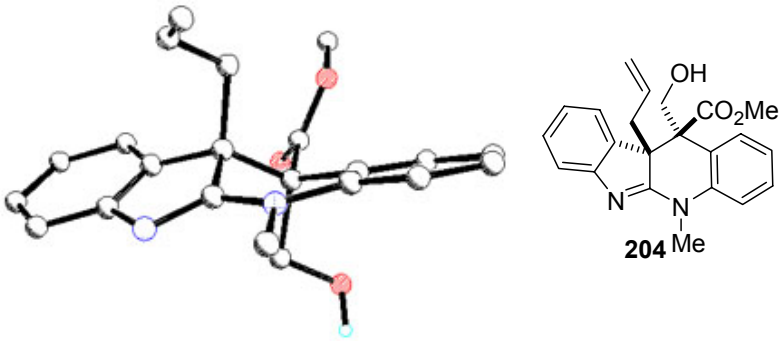
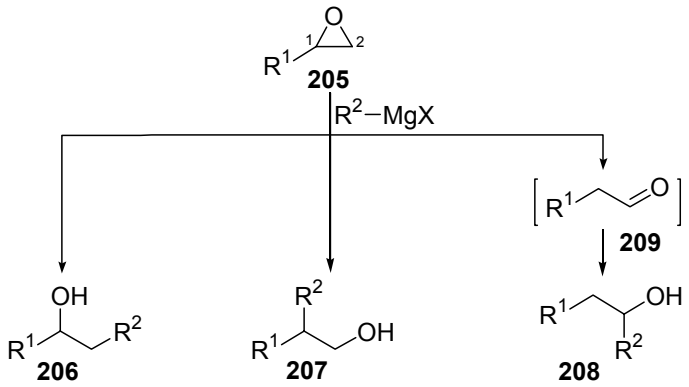


Figure 20. X-ray structure of **204**.

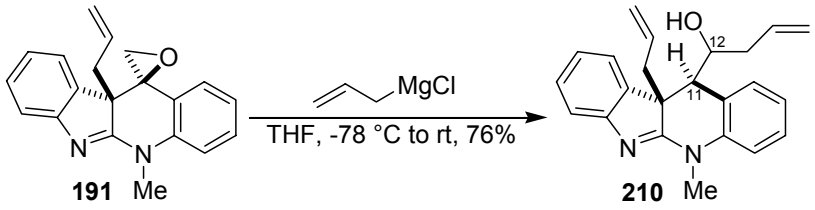
4.5 Attempts at the direct formation of the C-11 quaternary centre from epoxide 191

Attempts were made to form the C-11 quaternary centre directly from epoxide **191**. Generally, epoxides can be opened with carbon nucleophiles to form various substituted alcohols.[81] With Grignard reagents, for example, three different alcohols can be formed from the epoxides **205** (**Scheme 71**). Nucleophilic addition at the most accessible carbon will afford **206** *via* an S_N2 type process. However, addition to the more substituted carbon to form **207** is generally favoured by the Lewis acidic Grignard reagents. The formation of the **207** type product is especially likely to occur when R^1 is an electron donating group that favours the formation of a positive charge at C-1 thereby promoting a more S_N1 like process. The formation of product type **208** will be competitive with the formation of **207** as prior rearrangement to the corresponding aldehyde **209** is possible.



Scheme 71. Three major alcohol products are expected from the addition of Grignard reagents to unsymmetrical epoxides.

Based on the structural features of epoxide **191**, Grignard addition would be expected to give predominantly the **207** (or **208**) type product thereby generating the C-11 quaternary centre. Unfortunately, no evidence for the existence of the **207** type product could be found in the mixture of products formed from the reaction of allylmagnesium chloride with epoxide **191** (**Scheme 72**).



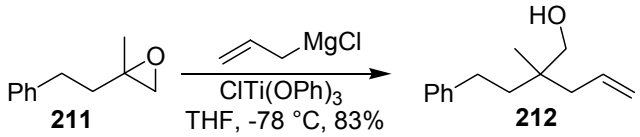
Scheme 72. Addition of allylmagnesium chloride to epoxide **191** gave mainly the product resulting from formal addition to the corresponding aldehyde.

The major component of this mixture was a compound that had spectrometric data consistent with structure **210**, resulting from Grignard addition to the *in situ* formed aldehyde. Of particular note for structural assignment was the signal corresponding to H-11 (3.15 ppm) in the associated ^{1}H NMR spectrum that would not be present for the other possible addition products (type **206** and **207**). Although no significant ^{1}H NMR nOe enhancements could be observed that would allow determination of the relative stereochemistry of **210**, it seems reasonable to suggest, based on the model used to rationalise the stereochemistry of **178a** (**Scheme 65**), that the configuration at C-11 of **210** is as depicted. The stereochemistry at C-12 is not as readily deduced and as such a tentative assignment will not be made. Additionally, purified **210** was found to contain a small amount (*ca*. 5% as determined by ^{1}H

NMR) of a second compound that could not be separated from the major compound by chromatography. This minor compound displayed ^{1}H NMR chemical shifts that were coincidental with those of the major compound in all cases other than the signal associated with H-12 (a difference of 0.22 ppm is observed for these signals between the major and minor compound). This suggests that purified **210** was predominantly a single diastereoisomer contaminated with a small amount of the corresponding C-12 epimer.

Presumably, the reason that **210** forms in preference to the **207** type product is that once the tertiary carbocation centre forms (or partially forms) at C-11, the 1,2-hydride shift to form the aldehyde is competitive with nucleophilic attack at C-11 and the steric encumbrance around C-11 slows nucleophilic attack thereby favouring the 1,2-hydride shift.

It has been reported in the literature that various organotitanium reagents react with unsymmetrical epoxides to give the more substituted product, even in the absence of highly electron donating substituents, and these reagents have been used to form all-carbon quaternary centres in a variety of substrates.[90-94] For example, epoxide **211** is reported to react with allyltitanium triphenoxide to give alcohol **212** in high yield (**Scheme 72**).[94]



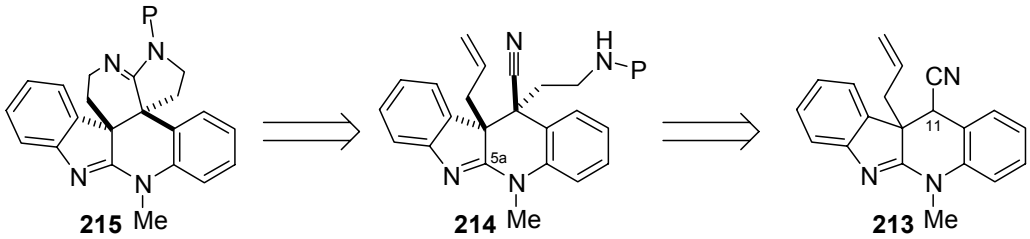
Scheme 73. Epoxide **211** is selectively opened at the more substituted carbon using allyl titanium triphenoxide.

However, reaction of epoxide **191** with the both acetylinic and allylic titanium reagents, generated from chlorotitanium triisopropoxide in combination with trimethylsilyl acetylene or allylmagnesium chloride, did not form the desired C-11 quaternary centre. With all these reagents no reaction was observed at room temperature, and at elevated temperatures decomposition to unidentified mixtures of products occurred.

4.6 Alkylation of a C-11 nitrile and the use of TosMIC

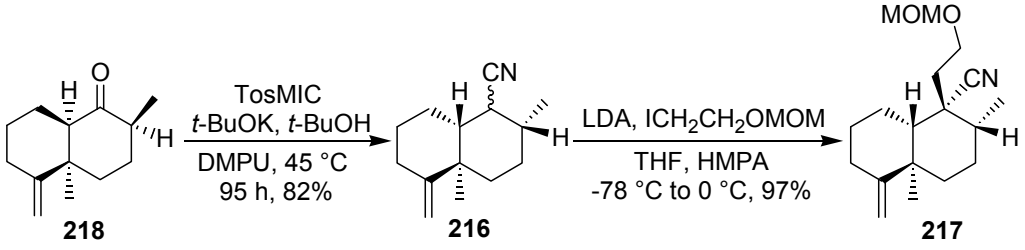
In the previous studies reported in this chapter, it was the ester functionality of **197** that rendered H-11 acidic and allowed the C-11 quaternary centre to be generated by alkylation of

the corresponding enolate. Using this method, construction of the amidine or aminal will require modification of the ester into a nitrogen containing functional group. A preferential route would involve the direct introduction of a nitrogen containing functional group that would render H-11 acidic and allow for alkylation at C-11 (**Scheme 74**). The C-11 nitrile group of **213** would render H-11 acidic and could be alkylated with a protected nitrogen containing electrophile to afford a compound of the type **214**. Both the nitrogen atoms required to construct the amidine functionality of perophoramidine would now be in place at the correct oxidation state. The amidine functionality in **215** could then presumably be constructed by oxidative cleavage of the alkene followed by reduction of the resulting aldehyde to the corresponding alcohol. Conversion of the alcohol to a leaving group could potentially lead to formation of the amidine in **215** *via* a cascade reaction, although adjustment of the C-5a amidine oxidation state may be required.[35]



Scheme 74. Alkylation of the C-11 nitrile **213** would allow for the rapid construction of the amidine functionality in **214**. P = protecting group.

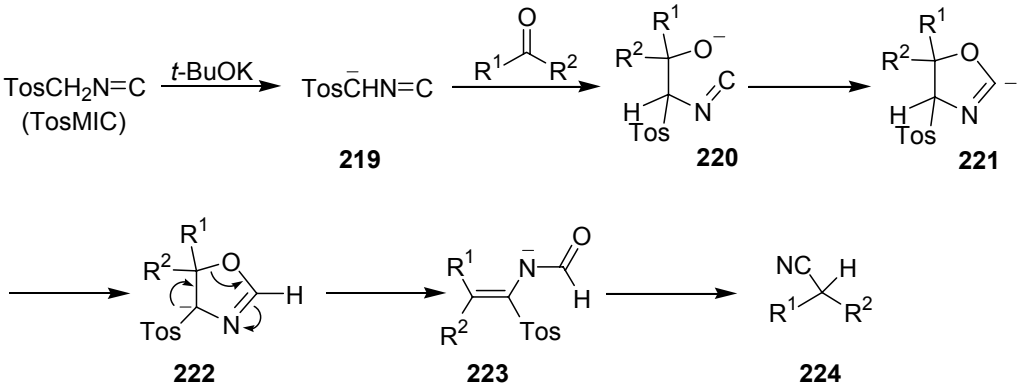
An example of alkylation α to a nitrile to create an all-carbon quaternary centre is illustrated in **Scheme 75**.[95] As part of the total synthesis of the diterpenoids (-)-kolavenol and (-)-agelasine B, the diastereoisomeric mixture of nitriles **216** was alkylated to give a single diastereoisomer **217** in excellent yield.



Scheme 75. Conversion of ketone **218** to nitrile **216** and subsequent alkylation in the synthesis of diterpenoids (-)-kolavenol and (-)-agelasine B.[95] TosMIC = tosylmethyl isocyanide, DMPU = *N*,'*N*-dimethylpropyleneurea, LDA = lithium diisopropylamide, MOM = methoxymethyl, HMPA = hexamethylphosphoramide.

Also of interest in this total synthesis is the one step procedure that is used to generate nitrile **216** from ketone **218** (**218** undergoes a base promoted epimerisation of both of the two carbon centres adjacent to the carbonyl prior to reaction). The reagent used in this case is tosylmethyl isocyanide (TosMIC) and is been reported to add a one carbon unit to a ketone as in cyanohydrin formation, without the simultaneous formation of an α-hydroxy group.[96] Such a one step reductive cyanation has clear advantages over a multi-step protocol.

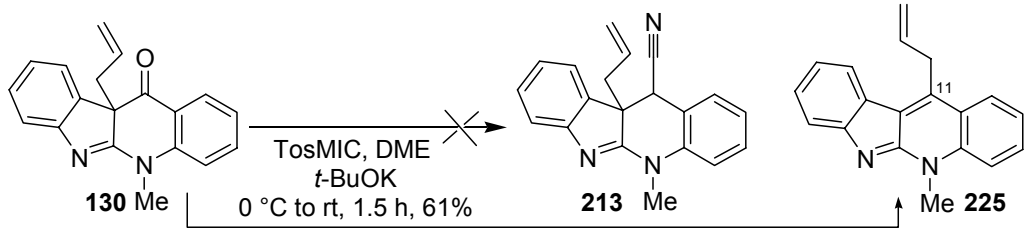
Mechanistically, it has been proposed that the formation of nitriles from ketones using TosMIC, under basic condition, involves attack of **219** at the carbonyl carbon to form anion **220** prior to the formation of the oxazolidine ring of **221** (**Scheme 76**).[97] Alternatively, formation of **221** by a one step cycloaddition has been suggested.[98] Following proton exchange, it is proposed that **222** ring opens to give **223**. Evidence has been presented in support of the proposed intermediacy of **221** and **223**. For example, acidification of the reaction mixture before complete formation of the nitrile has, in some cases, allowed for the isolation of protonated **221** and **223** and when these were resubjected to the basic reaction conditions nitriles **224** resulted.[96,97] However, whilst it is reported that *tert*-butoxide is involved, less experimental evidence is available regarding the mechanism of nitrile **224** formation from intermediate **223** and only speculative mechanistic pathways have been suggested.[96]



Scheme 76. Proposed mechanism for the reductive cyanation using TosMIC (tosylmethyl isocyanide).

In an attempt to prepare the C-11 quaternary centre using a two step protocol similar to that shown in **Scheme 75**, the reductive cyanation conditions using TosMIC were applied to ketone **130**.[96] Interestingly, but somewhat frustratingly, the expected nitrile **213** (**Scheme 77**)

could not be isolated from the mixture of products formed by the treatment of **130** with TosMIC in the presence of potassium *tert*-butoxide.



Scheme 77. The attempted reductive cyanation of ketone **130** using TosMIC resulted in the formation of **25** as the major product. TosMIC = tosylmethyl isocyanide, DME = 1,2-dimethoxyethane.

This mixture of products was found to consist predominantly of a bright orange coloured (of note for structural assignment) compound that showed spectroscopic data consistent with structure **225**. Of particular note was the high field (33.0 ppm) methylene carbon signal in the associated ^{13}C NMR spectrum suggesting that the allyl group was attached to a carbon atom rather than a hetero-atom. Furthermore, the position of the allyl group was demonstrated through correlations in the associated ^{1}H-^{13}C HMBC spectrum (**Figure 21**).

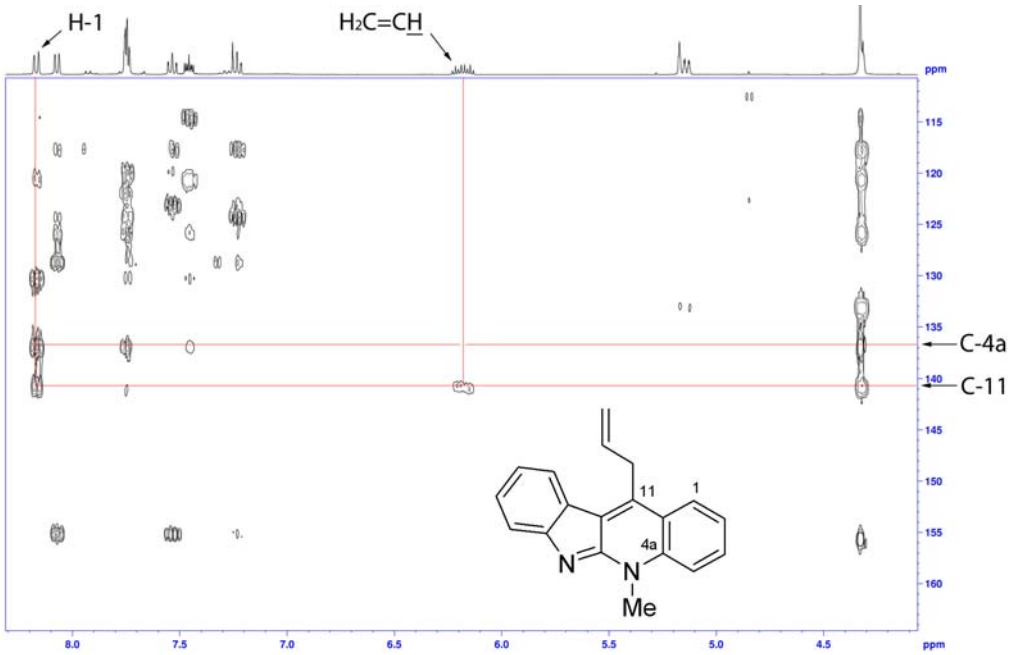
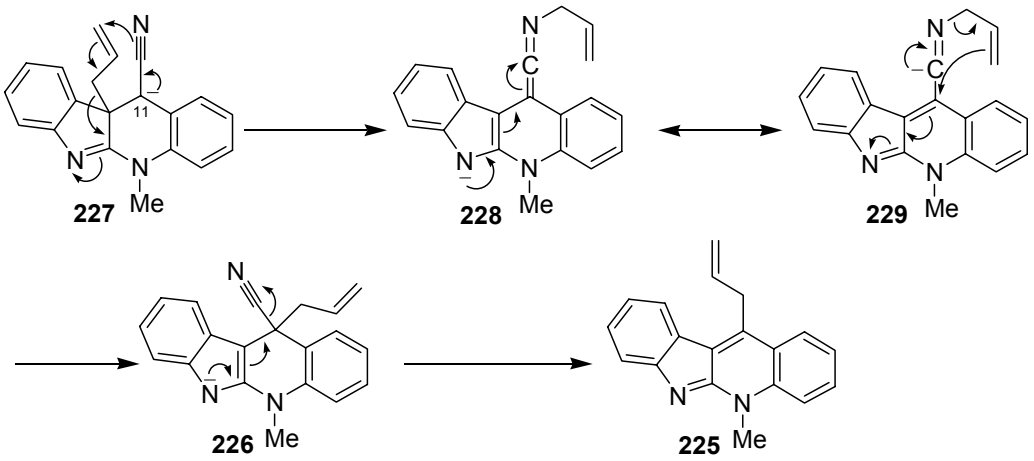


Figure 21. HMBC spectrum of **225** showing selected correlations used in determining the position of the allyl group.

Whilst an investigation into the mechanism and attempts to identify any intermediates involved in the formation of **225** would be interesting, such an investigation was not undertaken due to time constraints. In addition, a full understanding of the mechanism was considered to be unnecessary for devising a method to avoid the formation of **225**. That is to say, integral involvement of the allyl group is required regardless of the precise mechanistic details, and manipulation of the allyl group prior to the reductive cyanation procedure would, presumably, prevent the formation of **225**. However, before these further synthetic studies are discussed two possible mechanisms will be outlined.

Generally, there are two opposing mechanistic pathways that could lead to the formation of **225** from **130**. Either the desired nitrile **213** forms and subsequently undergoes a further reaction to form **225** under the basic reaction conditions (**Scheme 78**), or **213** never forms and the path leading to the formation of **225** is divergent at an intermediate point in the nitrile forming mechanism. Which of these two is correct could, in principle, be identified by the preparation of nitrile **213** using a synthetic route other than that involving TosMIC, and subjecting **213** to basic reaction conditions.

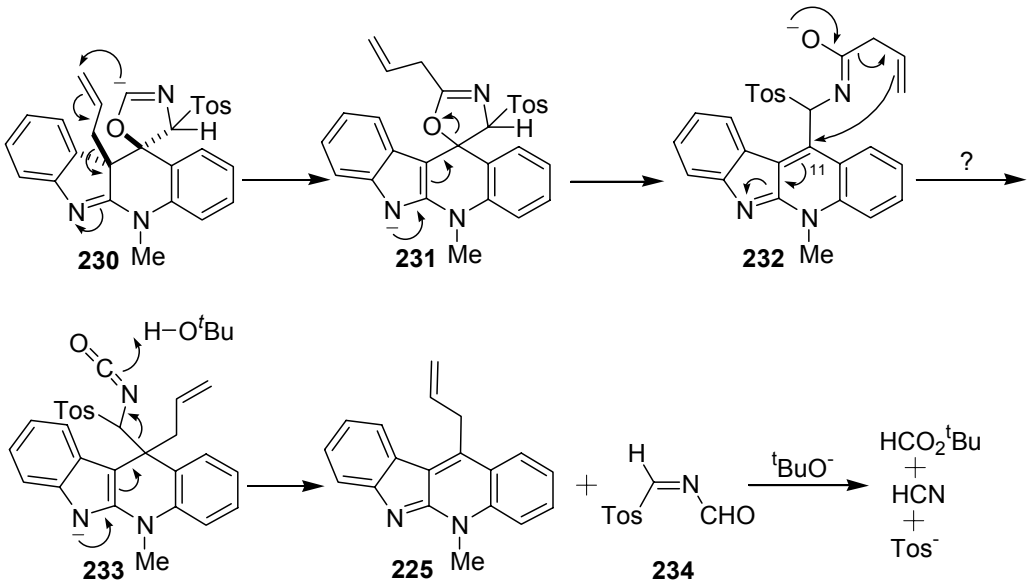


Scheme 78. A possible mechanistic pathway to **225** that requires the initial formation of the nitrile.

The first of these general mechanisms can be rationalised by the more concise, once formation of **227** has occurred, sequence of events (**Scheme 78**). Whilst it is easy to see how the loss of cyanide from **226** would give **225**, it is harder to understand how **226** could arise. Formation of **226** *via* a direct 5-*endo*-*trig* attack of the C-11 anion of **227** at the alkene seems less likely than the 7-*endo*-*trig* attack through nitrogen that would form **228** before rearrangement to **226** *via* **229**. However, this attack of the nitrogen at the allyl group also

seems implausible as the nitrile of **227**, with a planar anionic centre C-11, and allyl group of **227** are presumably in a perpendicular conformation. If the formation of **226** from **227** was to proceed by an intermolecular mechanism, the intramolecular proximity of the two groups would be irrelevant to attack. However, as attack at the allyl group by the enolate derived from ester **197** was not observed, an intermolecular mechanism was considered unlikely in this case.

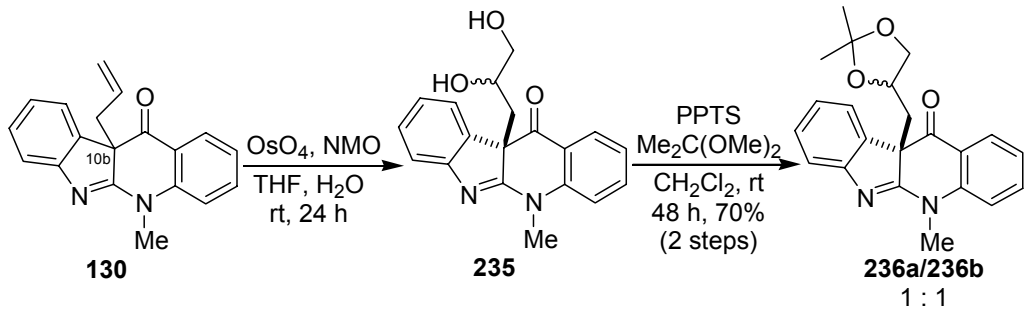
A mechanism that does not necessitate the formation of the nitrile **227** can also be envisaged (**Scheme 78**). In this mechanism, attack of the TosMIC anion at the less sterically encumbered face of ketone **130** would give **230** after proton exchange. The carbanion of **230** could then attack the allyl group to give **231**, rather than ring opening and ultimately forming nitrile **213**. Breaking of the C-O bond then places the negative charge on the oxygen of **232**. Attack of the allyl group at C-11 could in principle form isocyanate **233**, however the cleavage of the C-C bond that would be required seems unlikely. Isocyanate **233** then decomposes, with protonation, to give **225** and the formamide derivative **234**. Presumably nucleophilic attack by *tert*-butoxide converts **234** to hydrogen cyanide, *tert*-butyl formate and *p*-toluene sulfinate. However, none of these by products would be diagnostic of this mechanism as *tert*-butyl formate and *p*-toluene sulfinate are generated during nitrile formation and hydrogen cyanide is also generated in the mechanism depicted in **Scheme 78**.



Scheme 79. A mechanism for the formation of **223** that does not require the initial formation of the nitrile **211**.

It was reasoned that if the allyl group of **130** could no longer participate in the formation of **225**, it should be possible to synthesise the desired C-11 nitrile group using the reductive cyanation. Whilst it was stated in Chapter 1 that development of the allyl group would preferentially be a late synthetic step, allowing for a concurrent manipulation of two allyl groups, development of the C-10b allyl group of **130** directly after the Claisen rearrangement would be synthetically advantageous in light of the observed formation of **225**. Additionally, in the proposed synthetic route involving the α-alkylation of the nitrile it was ultimately intended that alkylation with a 2C nitrogen containing electrophile would be used to introduce the 2C unit, rather than allylation.

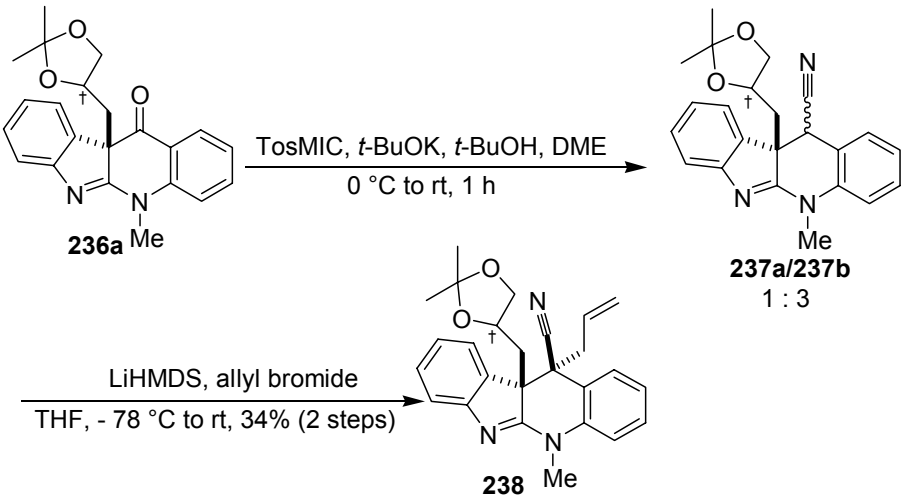
Wishing to test the idea that the reductive cyanation could be carried out once the allyl group had been removed, using a short synthetic route, **130** was treated with osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO). These conditions for dihydroxylation afforded a mixture of insoluble compounds that displayed a signal in the associated mass spectrum (m/z 345, MNa^+) consistent with the formation of **235** (**Scheme 80**). Making no attempt to separate the diastereoisomers or at purification other that trituration with ether, crude **235** was suspended in dichloromethane and converted to acetonides **236a**/**236b** by pyridinium *p*-toluenesulfonate (PPTS) catalysed transacetalation with 2,2-dimethoxypropane. The acetonides **236a**/**236b**, now sufficiently soluble to allow purification by chromatography, were formed as a 1:1 mixture of diastereoisomers in a combined yield of 70% (calculated over two steps). Although complete separation of this diastereoisomeric mixture using chromatography was not achieved, small samples that were predominantly single isomers could be obtained through careful chromatography.



Scheme 80. After dihydroxylation of alkene **130**, the vicinal hydroxyl groups of **235** were protected as the corresponding acetonide. NMO = *N*-methylmorpholine *N*-oxide, PPTS = pyridinium *p*-toluenesulfonate.

As oxidative cleavage of both diastereoisomers of **235** would lead to the same aldehyde, both diastereoisomers of **235** would be suitable synthetic intermediates and in principle could be transformed in one pot. However, from a practical perspective, working simultaneously with the diastereoisomeric mixtures proved to be troublesome and led to greatly reduced yields, due to difficulties with isolation in the subsequent synthetic steps. Therefore, the reaction sequence presented in **Scheme 80** shows transformations conducted on a sample of **236a** that was predominantly one diastereoisomer (the less polar of the two).

After subjecting **236a** to the reductive cyanation conditions used previously, the crude reaction mixture thus obtained was subjected to chromatography and a mixture of compounds that was believed to consist of predominantly nitriles **237a** and **237b**, epimeric at C-11, was separated. The spectrometric observations that led to this conclusion were that the mass spectrum (using the chemical ionisation method) showed a strong peak at m/z 374 (MH^+) consistent with the molecular formula of **237**. In addition, a diagnostic nitrile absorption at 2243 cm^{-1} was observed in the IR spectrum. The ^1H NMR spectrum clearly showed the presence of two compounds both displaying the distinctive H-11 singlets that were well separated at 4.15 ppm and 4.09 ppm (integrating to in a 1:3 ratio respectively). These diastereoisomers could not be separated from one another or from the minor impurities present in this mixture. This mixture of diastereoisomers **237a** and **237b** was treated with lithium hexamethyldisilazide (LiHMDS) and the resulting red coloured anion was quenched with allyl bromide. Whilst allyl bromide was not ultimately intended to be used in a natural product synthesis, it was used in this case to rapidly determine the expediency of this route. A compound that has spectrometric data consistent with structure **238** was separated from the crude reaction mixture by chromatography.



Scheme 81. Formation of nitrile **237** and allylation with allyl bromide. TosMIC = tosylmethyl isocyanide, DME = 1,2-dimethoxyethane, HMDS = hexamethyldisilazide. † = single unknown configuration.

Of particular importance in determining that **238** was the C- and not the N-alkylated product was the presence of the characteristic nitrile absorption at 2243 cm^{-1} in the IR spectrum associated with this compound. Additionally, the ^{13}C NMR spectrum (recorded using the PENDANT pulse sequence) of **238** showed two high field quaternary carbon signals at 55.3 ppm and 49.5 ppm associated with the C-10b and C-11 quaternary centres respectively. As crystals of **238** could not be obtained, the assignment of the relative stereochemistry at C-10b and C-11 is an assumption based on the previously observed alkylation of ester **197** when X-ray crystallography was used to demonstrate that the electrophile had approached from the face opposite to the C-10b allyl group.

4.7 Summary and conclusion

The aim of the model investigations described in this chapter was to develop methods for the formation of the second all-carbon quaternary centre at C-11 by manipulation of the C-11 ketone of **130**. It was also necessary to determine the C-10b/C-11 relative stereochemistry that would be formed at these vicinal quaternary centres. By achieving these aims, these investigations have been successful and have culminated in the preparation of three key compounds (**Figure 22**). However, whilst the relative stereochemical assignment of **203** and **204** was based on X-ray crystallography, the stereochemical assignment of **236** was tentative.

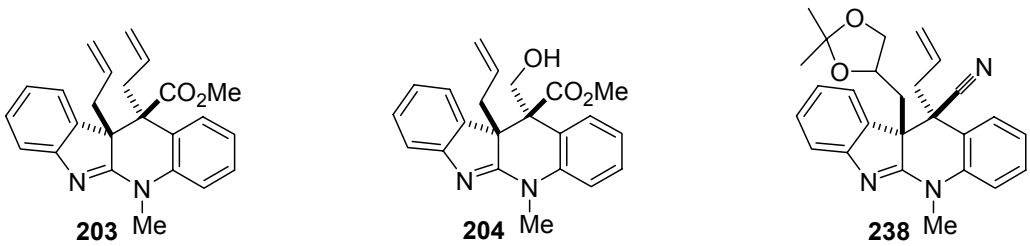


Figure 22. Key compounds containing the vicinal quaternary centres at C-10b and C-11 contained within the natural products perophoramidine (**17**) and the communesins.

Unfortunately, both of the successful synthetic routes to the C-11 quaternary centre from the ketone **130** are low yielding. In the case of the ester route, it is the inelegant reductive opening of the epoxide that reduces the overall yield of this sequence. To determine whether this reaction could be optimised, or perhaps whether a different route to the ester would be superior, would require further investigation. Whilst none of the by-products from this reductive epoxide opening could be identified, it is possible that the allyl group is involved in side reactions and that prior development of the allyl group may lead to a cleaner transformation.

The two step procedure from ketone **130** to the C-11 quaternary centre using TosMIC, whilst very concise, required development of the allyl group before the reductive cyanation could be achieved. Furthermore, although the dihydroxylation and protection procedure provided a rapid method for removing the alkene functionality from the substrate so as to test a hypothesis, it would clearly be impractical as part of a total synthesis due to the formation of diastereoisomeric mixtures that are difficult to isolate. This problem could be overcome by either devising a synthetic route in which the alcohol stereocentre is destroyed immediately after formation by, for example, cleavage of the diol with sodium periodate or lead tetraacetate, or by creating diol **235** as a single diastereoisomer using, for example, a matched asymmetric dihydroxylation.[99] Cleavage of diol **235** to give the corresponding aldehyde was attempted using both sodium periodate, which led to complex mixtures of products, and lead tetraacetate, which afforded small amounts of an aldehyde product. Attempts at asymmetric dihydroxylation[99] of **130** resulted in complete recovery of **130**. Both these studies were discontinued due to time constraints. Due to the approach of electrophiles opposite to the C-10b allyl group in the alkylations described, it is clear that at present these synthetic procedures are more suited to a synthesis of perophoramidine (**17**) rather than to a synthesis of the communesins and as such a synthesis of perophoramidine (**17**) has been initiated using

the methods described in this report (see Appendix 2). On the other hand, this alkylation selectivity does not preclude a communesin synthesis. Indeed, all that would be required is the independent manipulation of the two C-11 C1 units present in **203** and this is easily envisaged due to the differences in oxidation state.

The investigations described in Chapter 5 return to the rearrangements of indolo[2,3-*b*]quinolines and consider the effect of a substituent at C-10 with the aim of initiating a synthesis of the communesin natural products. Studies into developing of an asymmetric version of the Claisen rearrangement are also outlined.

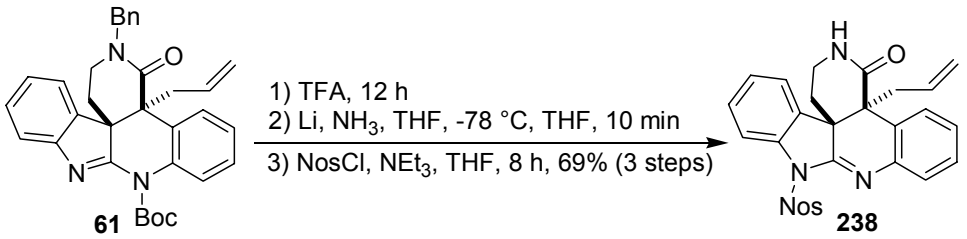
Chapter 5: Asymmetric Formation of the C-10b Quaternary Centre and the Effect of Bromine at C-10

5.1 Introduction

Chapter 3 outlined the structural features required for the formation of the C-10b quaternary centre in the indolo[2,3-*b*]quinoline system using a Claisen rearrangement. Chapter 4 described investigations that resulted in two successful methods for the formation of the adjacent quaternary centre at C-11. In both these chapters investigations have been conducted on model compounds and no consideration has been given to the possible effect that substituents, which are required for the construction of the natural products, may have on the Claisen rearrangement. For example, the substituent required for the construction of the isoprene based moiety (page 4) in the communesins, at C-10 of the indolo[2,3-*b*]quinoline ring system, may accelerate the aza-Cope rearrangement in relation to the Claisen rearrangement through steric interactions, as was observed in the case of **146** and **147**, (pages 49-50).

It was shown in Chapter 4 that the relative stereochemistry at the C-11 quaternary centre was controlled by the configuration at C-10b. Therefore, the asymmetric generation of the C-10b quaternary centre would allow an asymmetric synthesis of the natural products. This is certainly the case for perophoramidine (**17**) as there are only two stereocentres present.

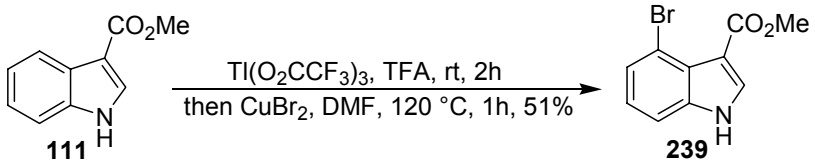
Initially, this chapter describes the synthesis and subsequent Claisen rearrangement of the 11-allyloxy-10-bromoindolo[2,3-*b*]quinoline system. After having successfully formed the C-10b quaternary centre in this system, the development of an asymmetric version of the Claisen rearrangement in this system is described. A benzyl protecting group on N-5 was chosen for these investigations. This choice was made as the benzyl group can be incorporated at the beginning of the synthesis and therefore makes for a shorter and higher yielding synthetic route. Additionally, it must be noted that the debenzylation of a similar substrate has been achieved.[35] Amide **61** was converted to **238** using a dissolving metal reduction as part of a recent synthesis of (±)-dehaloperophoramidine (**54**) (**Scheme 82**).



Scheme 82. Cleavage of a benzyl group under dissolving-metal conditions was used as part of a recent synthesis of (±)-dehaloperophoramidine.[35] TFA = trifluoroacetic acid, Nos = *o*-nitrobenzensulfonyl, Boc = *tert*-butoxycarbonyl.

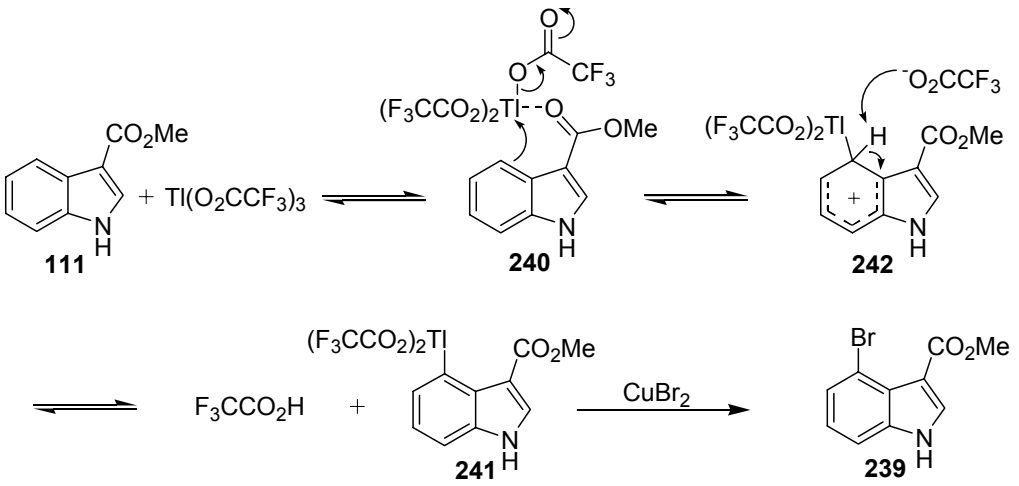
5.2 Synthesis and rearrangement of 11-alyloxy-10-bromo-5-benzyl-5*H*-indolo[2,3-*b*]quinoline (255)

The synthesis of 10-bromoindolo[2,3-*b*]quinolones using the previously developed methodology required the use of 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**239**). Ester **239** is not commercially available and only one method for its synthesis is described in the literature.[100,101] This method, which has been used for the synthesis of range of 4-halo indoles, involves conversion of **111** to the corresponding organothallium compound with thallium (III) trifluoroacetate in trifluoroacetic acid followed by treatment with a solution of copper (II) bromide in *N*,*N*-dimethylformamide. As **239** could be formed in one step from commercially available **111** in moderate yield, this thalliation method was successfully used to prepare **239** for initial studies (**Scheme 83**).



Scheme 83. Directed bromination using thallium trifluoroacetate. TFA = trifluoroacetic acid, DMF = dimethylformamide.

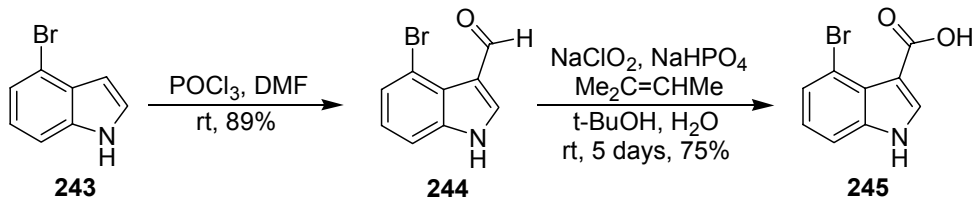
It has been reported that, mechanistically, this electrophilic aromatic thallation is directed by the initial formation of the substrate-electrophile complex **240** followed by a reversible electrophilic aromatic substitution with loss of trifluoroacetic acid to give **241** *via* **242** (**Scheme 84**).[102]



Scheme 84. Bromination with $CuBr_2$ is preceded by a directed electrophilic thalliation.

There are several drawbacks associated with this thalliation procedure that make multi-gram preparation of **239**, which would be required for a synthesis of the communesins, impractical. The thallium reagent, which is used in greater than stoichiometric quantities, and the waste that is generated are toxic and difficult to separate from the product. Furthermore, the product **239** and starting substrate **111**, which remained in the crude product, required careful chromatography to achieve separation. The literature method for the purification of **239**, involving elution from a silica column with dichloromethane-methanol (99:1, v/v), was found to be unsuitable leading to the elution of **111**, **239** and metal salts in the first few fractions.[100] Better results were obtained when ethyl acetate-hexane mixtures were used for chromatography.

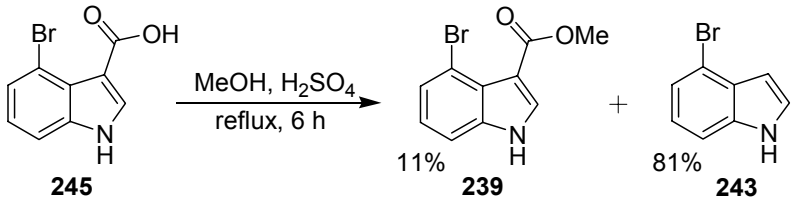
As a synthesis that allowed multigram preparation of **239** was required, a three step protocol involving formylation, oxidation and esterification starting from 4-bromoindole (**243**) was considered. Utilising the Vilsmeier-Haack reaction, **243** was converted to the known aldehyde **244**[100] in good yield (**Scheme 85**).



Scheme 85. Formylation of 4-bromoindole and subsequent oxidation. DMF = *N*,*N*-dimethylformamide.

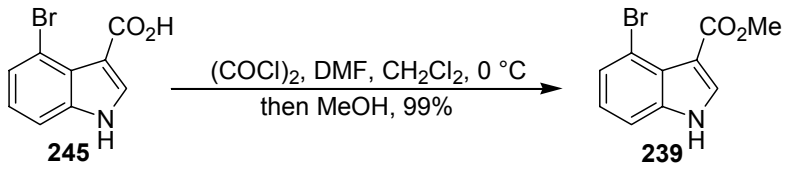
The oxidation of **244** to **245** using sodium chlorite in the presence of 2-methyl-2-butene[103] is reported in the literature but no preparation, isolation, purification or spectroscopic data is reported.[100] Nonetheless, it was eventually found that the transformation of **244** to **245** required a large excess of reagents and a reaction time of five days at room temperature. Purification of **245** was achieved by extracting an intensely blue impurity from an aqueous solution of **245** at high pH with dichloromethane, followed by the addition of aqueous hydrochloric acid to precipitate protonated **245** of sufficient purity for the subsequent transformation.

Whilst the esterification of the 4-iodo analogue of **245** using diazomethane is reported in the literature,[101] the conversion of **245** to **239** is unknown. So as to avoid the use of diazomethane, the conversion of **245** to **239** was attempted using methanol and a catalytic amount of sulfuric acid with heating at reflux (**Scheme 86**). This method provided **239** in low yield together with the major product **243**, resulting from the decarboxylation of **245**. Attempts to form **239** from **245** at lower temperatures under acidic conditions gave similar results.



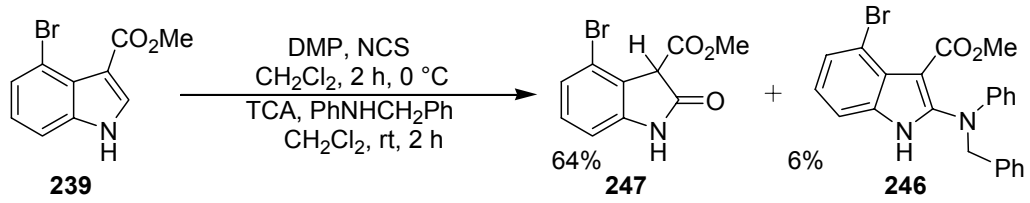
Scheme 86. Esterification in refluxing acidic MeOH resulted mainly in the decarboxylation of **245**.

A revised reaction procedure led to a much higher yielding conversion of **245** to **239**. The sequential treatment of **245** with oxalyl chloride followed by methanol, without isolation of the intermediate acid chloride, afforded **239** in nearly quantitative yield (**Scheme 87**).



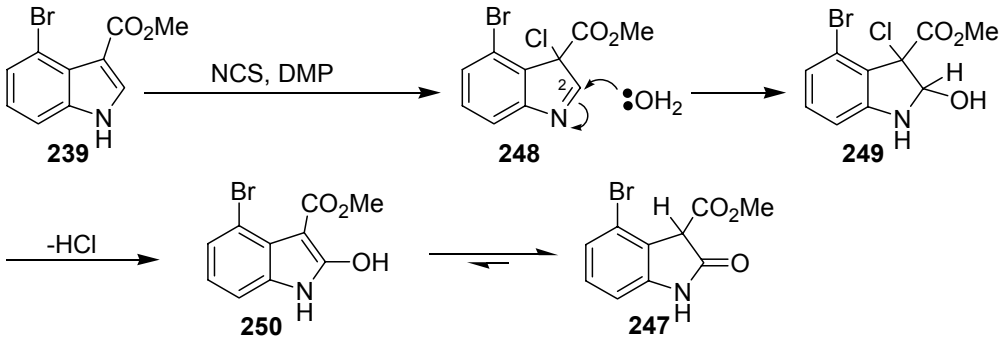
Scheme 87. High yielding esterification using oxalyl chloride and methanol. DMF = *N*,*N*-dimethylformamide.

Now that **239** could be synthesised in high yield on a multi-gram scale without the use of chromatography, attention was turned to the coupling of **239** with *N*-benzyl aniline. Subjecting **239** to the same reaction conditions that had been used for the synthesis of **157** (pages 51-52) afforded only small quantities of the expected 2-aminoindole **246** with 2-oxindole **247** being the major product (**Scheme 88**).



Scheme 88. Attempted coupling of **239** with *N*-benzylaniline. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

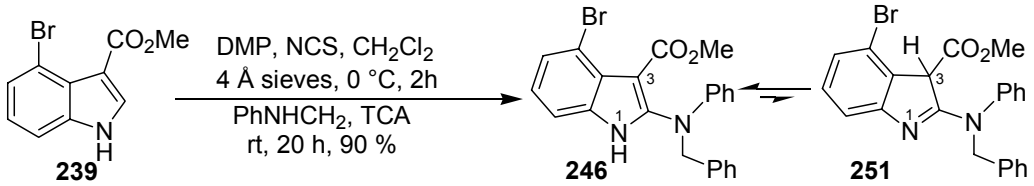
Presumably, **247** results from the nucleophilic attack of water rather than the aniline at C-2 of the intermediate chloroindolenine **248**, followed by elimination of hydrogen chloride from **249** to give **250** (**Scheme 89**) (cf. page 28).



Scheme 89. Proposed mechanism of formation of oxindole **247**. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide.

In an attempt to increase the yield of **246**, it was considered that the attack of water on **248** could have occurred either before the addition of *N*-benzylaniline to the reaction or at the workup stage, when significant amounts of **248** remained. If the latter was to be the case, extending the reaction time after the addition of *N*-benzylaniline would be expected to increase the yield of **246**. Whilst extending the reaction time did improve the yield of **246**, consistently high yields could only be achieved when powdered molecular sieves were also

added to the reaction mixture (**Scheme 90**). This suggests that **248** is very sensitive to the presence of water under the conditions in which it is formed, although the reason for this is unclear.



Scheme 90. Coupling of **239** with *N*-benzylaniline. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

The ^{1}H NMR ($CDCl_3$) spectrum of purified **246** showed additional peaks that could not be attributed to structure **246** alone (**Figure 23**). This complication of the ^{1}H NMR spectrum was assigned to the existence of the 1*H*- and 3*H*-indole tautomers, **246** and **251**, in an 8:2 ratio.

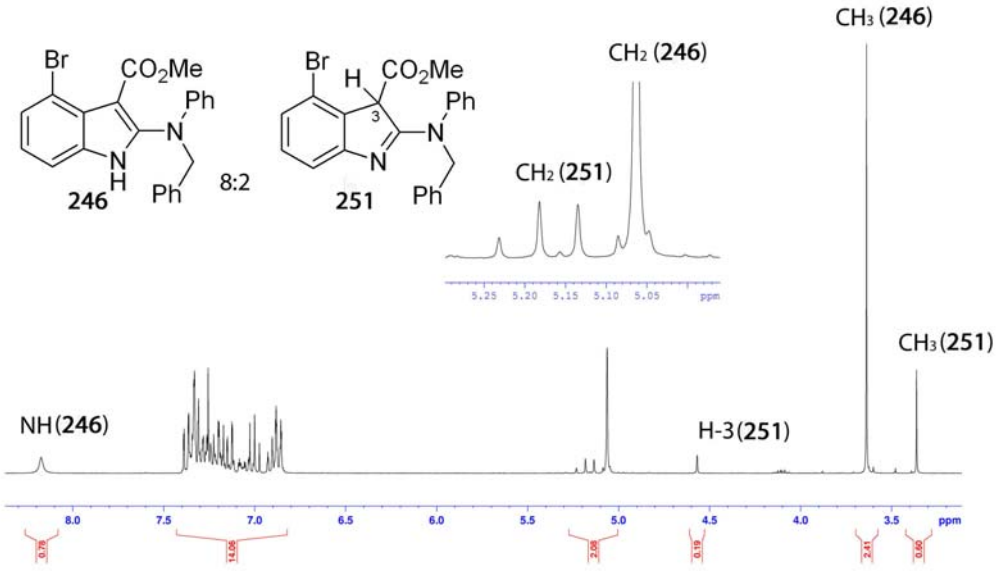


Figure 23. ^{1}H NMR spectrum ($CDCl_3$) showing presence of 3*H*-indole tautomer of **246**.

The presence of the 3*H*-indole tautomer **251**, which was not observed for **157**, can be rationalised using a steric explanation. A steric interaction between the bromine and the ester moiety leads to a destabilisation of the 1*H*-indole tautomer **246** in relation to the 3*H*-indole tautomer **251**. This steric interaction with bromine is diminished in **251** due to the sp^3 hybridisation of C-3 that places the ester moiety out of the plane with respect to the bromine

atom. Inspection of the carbonyl infrared absorption frequency associated with **111**, **239**, **157** and **246**/**251** was instructive and suggested a close proximity of the bromine and ester moiety, thereby supporting this steric based rationalisation (**Table 2**).

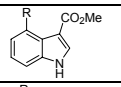
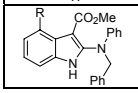
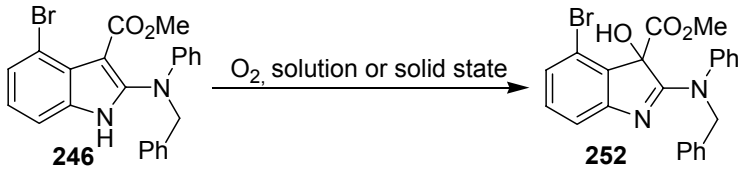
	Carbonyl IR absorption frequency (KBr, cm^{-1})	
	R = H	R = Br
	1669 (**111**)	1695 (**239**)
	1669 (**157**)	1672 (**246**/**251**)

Table 2. A comparison of the carbonyl IR absorption frequencies of **111**, **238**, **157** and **246**.

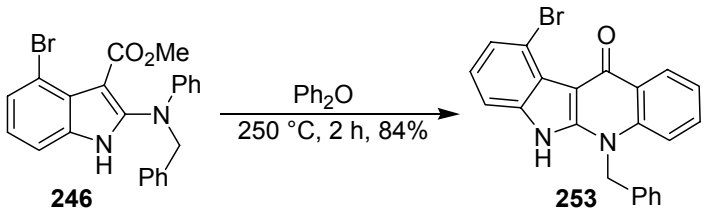
The carbonyl absorption frequency associated with **239** is 26 cm^{-1} greater than that of **111** suggesting that the close proximity to bromine had changed the conformation of the ester moiety and reduced the carbonyl conjugation with the indole π-electrons. A similar, but smaller magnitude, difference was seen for **246**/**251** and **157**. In this case, the bulky *N*-benzyl and *N*-phenyl groups of **246**/**251** presumably prevent the ester moiety from twisting out of plane with the bromine atom leading to a smaller change in absorption frequency. Whilst this rationalisation is tentative, it was clear that the C-2 substituent played a role in the stabilisation of the 3*H*-tautomer **251** as the 3*H*-tautomer of **157** was not observed.

A further complication related to the synthesis of **246** arose from the propensity of **246** to undergo a rapid autoxidation to **252** (**Scheme 91**). In less than five days a complete and clean transformation of **246** to **252** was observed in either the solid state or in solution. It remains challenging to rationalise why this oxidation was observed for **246** but not for **157**. However, it appeared plausible that the difference in propensity to oxidation of **246** and **157** was related to the presence of the 3*H*-indole tautomer **251**. The presence of tautomer **251** together with traces of **252**, which were always present in samples of **246**, made the use of ^{13}C NMR spectroscopy an impractical characterisation technique for **246**.



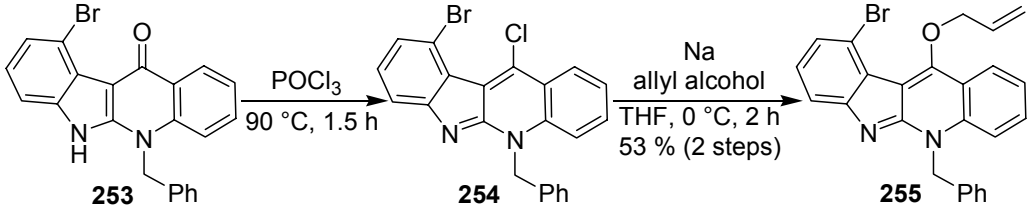
Scheme 91. 2-Aminoindole **246** was found to undergo a rapid autoxidation to **252**.

Due to the oxidation of **246** to **252**, **246** was used immediately after preparation and the cyclisation of **246** to **253** (**Scheme 92**) was conducted under an argon atmosphere that had been unnecessary for previous cyclisations (*cf*. page 40 and 52).



Scheme 92. High temperature cyclisation of **246** to **253**.

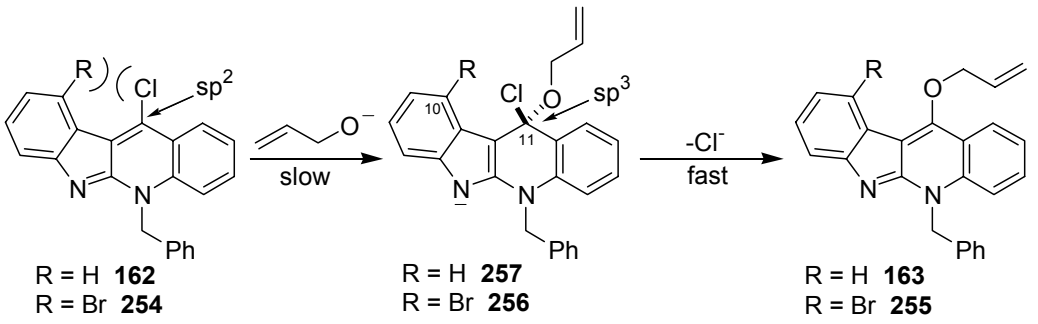
As previously described, treatment of **253** with phosphorus oxycholoride afforded **254** (**Scheme 93**). However, **254** was found to be more susceptible to nucleophilic displacement of the chlorine than previously prepared compounds **133** and **162** (pages 40 and 52). Purification of **254** proved to be counterproductive leading to reduced yields of **254** due to its conversion back to **253**. Crude **254** was therefore used in the reaction with sodium allyloxide to synthesise **255** in an acceptable yield over the two steps.



Scheme 93. Reaction of **253** with phosphorus oxychloride and subsequent reaction with sodium allyloxide proceeds in acceptable yield over two steps.

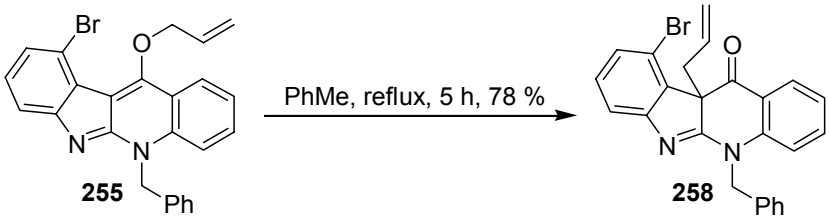
In contrast to the non-brominated substrate **162** that required a reaction time of 18 hours at room temperature for conversion to **163** (page 52), the conversion of **254** to **255** required only two hours at 0 °C. This increase in rate for the nucleophilic aromatic substitution was rationalised by considering the effect of a steric, and possibly electronic, interaction between Cl-11 and Br-10 in **254** (**Scheme 94**). The ring system of **254** is planar, with all carbons sp^2 hybridised. There is a repulsion between Cl-11 and Br-10 that is reduced, in the rate limiting step, on formation of the sp^3 centre at C-11 in the intermediate species **256** (a similar release of steric strain does not occur on the formation of **257** from **162**). Whilst this repulsion is regained between O-11 and Br-10 in **255**, it is important to note that changes in the rate

limiting (slow) step effect the overall rate. Furthermore, there is a net reduction in steric repulsion on transformation of **254** to **255** as oxygen has a smaller atomic radius than chlorine.



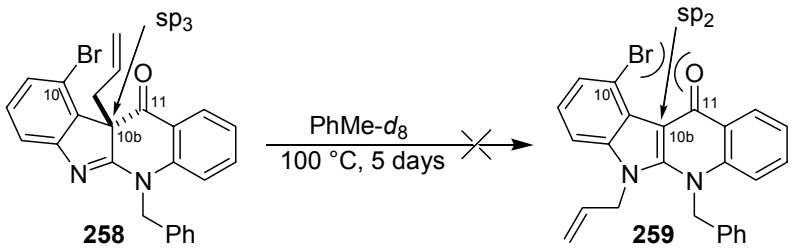
Scheme 94. When R = Br, as opposed to R = H, there is a reduction in steric and electronic repulsion on formation of the sp^3 centre at C-11 during the rate limiting step.

With **255** in hand, the formation of **258** using the Claisen rearrangement was examined (**Scheme 95**). Uneventfully, in refluxing toluene **255** was found to undergo rearrangement to **258** in approximately the same time that was required for the transformation of **163** to **161** (page 52) and **258** was isolated in 78% yield.



Scheme 95. The Claisen rearrangement of the brominated substrate proceeds under the same conditions that were required for the non-brominated substrate.

However, when **258** was heated in toluene-d_8 at 100 °C for five days, conditions that had been shown to cause significant aza-Cope rearrangement of **130** and **161**, no significant change in the ^{1}H NMR spectrum of **258** was observed (**Scheme 96**). Therefore the presence of a Br-10 substituent had not accelerated the aza-Cope rearrangement as had been anticipated (page 83), but it had caused a retardation of this process.



Scheme 96. Steric repulsion between Br-10 and O-11 in **258** increases the energy barrier associated with the aza-Cope rearrangement to **259**.

To understand how the Br-10 substituent exerts this effect a rationalisation that considers the interaction between bromine and oxygen, similar to that used previously (page 87), can be evoked (**Scheme 96**). In **258** C-10b is sp^3 hybridised placing the allyl group and ketone in a position synclinal to Br-10. Rearrangement of **258** to **259** would move O-11 into an eclipsing position with Br-10 resulting in repulsion between O-11 and Br-10. A comparison of the carbonyl infrared absorption frequencies of **111** and **239** (page 88) suggests a close proximity of the Br-10 and O-11 in **239** and presumably this is also the case for **258**. It was expected that a comparison of the X-ray crystal structures of **161** and **258** would further support this rationalisation by showing a difference in the relative position of O-11 in the two compounds (**Figure 24**). However, the crystal structures of these two compounds showed no significant difference in the position of O-11.

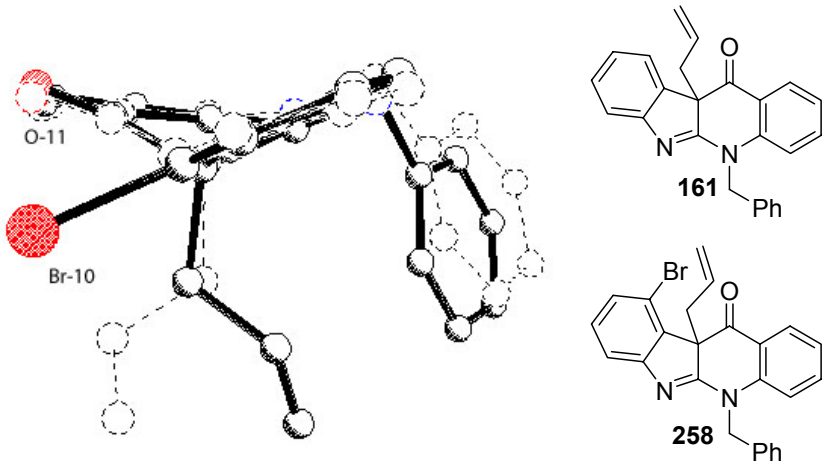
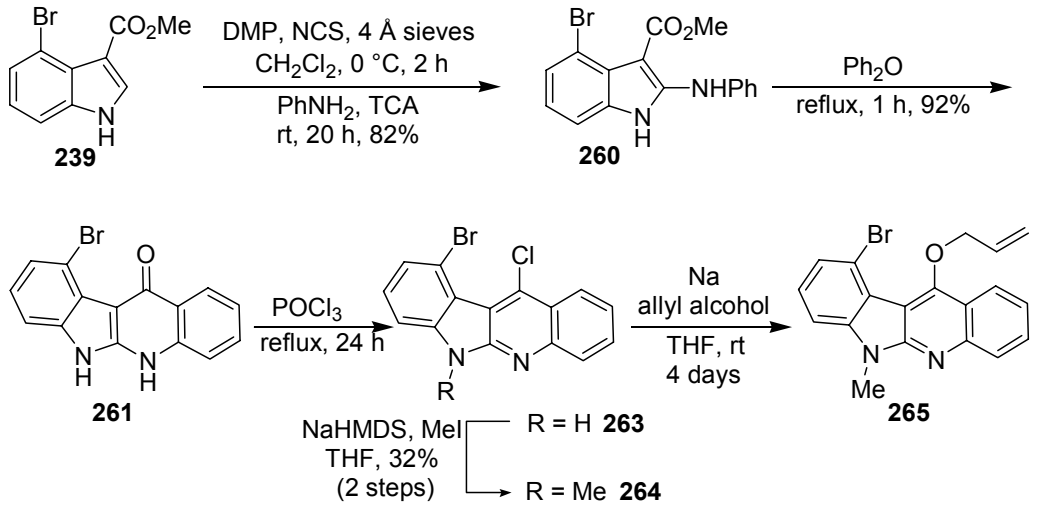


Figure 24. Overlaid X-ray structures of **161** (dotted lines) and **258** (solid lines) showing no significant difference in the relative positions of O-11 in the two structures.

5.3 Re-examination of the N-6 substituted system

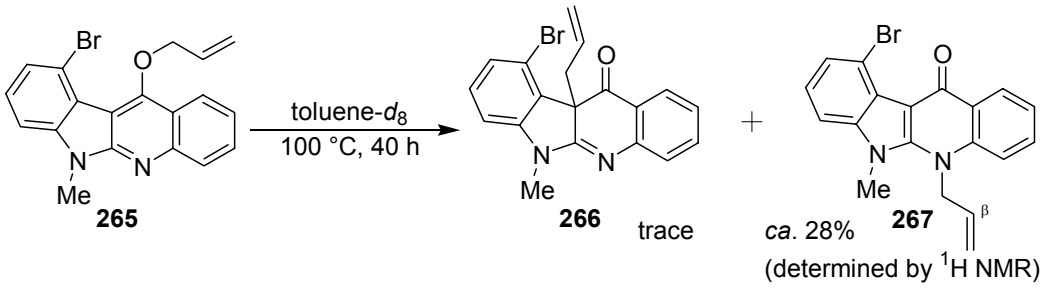
This observed retardation of the aza-Cope rearrangement of **258**, caused by the presence of Br-10, led to the reconsideration of the initial, N-6 substituted, model system discussed in Chapter 2. It was rationalised that the presence of a 10-Br-substituent may also slow the rate of the aza-Cope rearrangement in this system leading to the accumulation of the intermediate compound. If this were to be the case, positioning a methyl substituent at N-6 would have the advantage of avoiding the use of a protecting group strategy in a synthesis of communesin A (**9**), B (**10**), F (**14**), G (**15**) or H (**16**). This initial system was revisited and synthesised with a Br-10 substituent.

Coupling of **239** with aniline, to give **260**, followed by cyclisation in refluxing phenyl ether afforded **261** in high yield (**Scheme 97**). It was found that the conversion of **261** to **262** by treatment with phosphorus oxychloride required longer reaction times than had previously been used for the conversion of **110** to **109** (page 28) and only impure samples of **263** could be obtained. Crude **263**, which could not be purified due to its insolubility in most solvents, was methylated with sodium hexamethyldisilazide (NaHMDS) and methyl iodide in tetrahydrofuran to give **264** that was isolated in 32% yield (calculated for two steps from **261**) after purification by chromatography. The use of NaHMDS for the methylation of **263** was found to give better results than sodium hydride that had been used previously for the methylation of **109** (page 29). It was found that the displacement of the chlorine from **264** proceeded more readily than had been observed for **115** (page 29) and could be achieved at room temperature. After four days at room temperature **264** was found to have undergone a complete reaction with sodium allyloxide in tetrahydrofuran. Unfortunately, **265** could not be separated from a second product of as yet undetermined structure (*ca*. 30%, determined by ^{1}H NMR) and as such **265** was characterised by ^{1}H NMR only. Nevertheless, as the signals associated with the allyl moiety of **265** were clearly visible and not coincidental with any of the peaks associated with the contaminant, the contaminated sample of **265** was considered suitable for further investigation.



Scheme 97. Synthesis of 11-allyloxy-10-bromo-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**5.25**). DMP = *N*,'*N*-dimethylpiperazine, NCS = N-chlorosuccinimide, TCA = trichloroacetic acid, HMDS = hexamethyldisilazide.

The contaminated sample of **265** was heated in toluene-d_8 at 100 °C and analysed by ^{1}H NMR (**Scheme 98**). After 18 hours and later at 40 hours, only trace amounts of the diastereotopic allylic protons that are characteristic of **266** were observed. The observation that there were only small changes in the chemical shift of the allylic proton signals and that the multiplicity of the β-allylic proton signal was similar to that observed for **116** (see Appendix 3) indicated that the formation of **267** was the major outcome (**Figure 25**). Unfortunately, this result was not significantly different from the thermal rearrangement of **90** (page 31) and as such no further investigation was conducted on this system.



Scheme 98. Allyl ether **265** was heated in toluene-d_8 and the reaction was monitored by ^{1}H NMR.

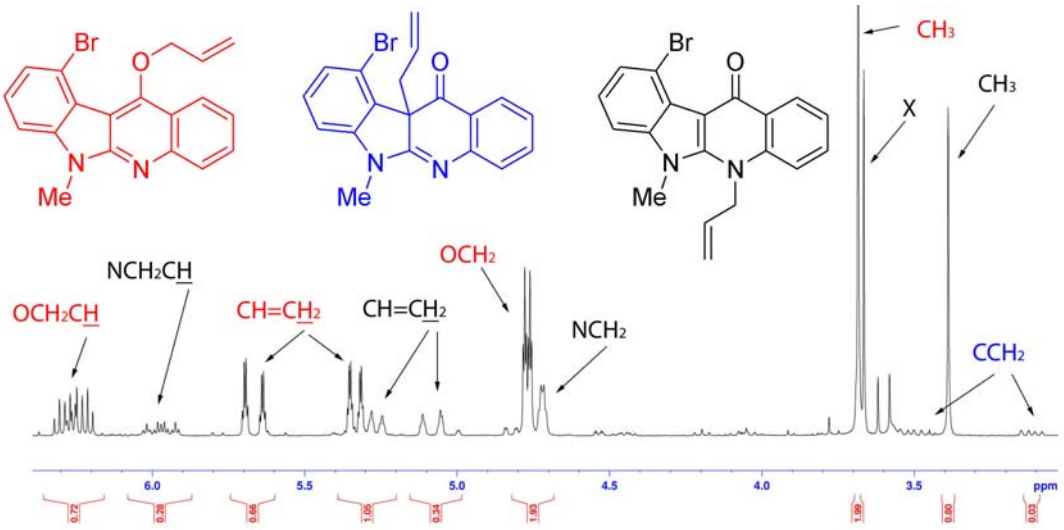


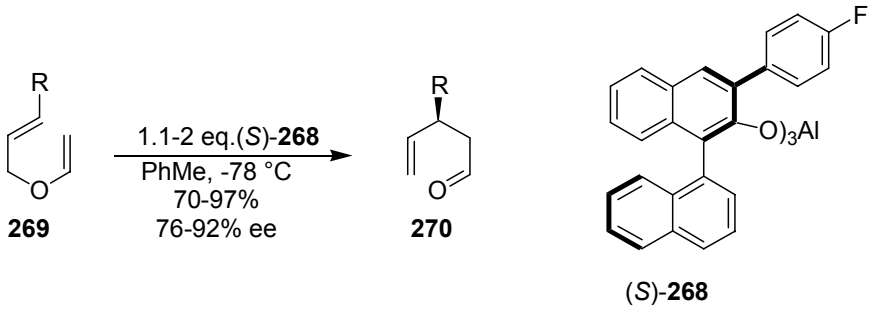
Figure 25. Section of the ^{1}H NMR spectrum showing signals corresponding to the allyl group protons of **265** **266** and **267**. This spectrum was recorded after heating **265** for 40 hours at 100 °C in toluene-d_8. X = signal associated with contaminant of undetermined structure.

It is hard to say why a retardation of the aza-Cope rearrangement is observed for **258** and not for **266**. One possible explanation is that in the N-5 substituted systems there is only a small difference between the magnitudes of the Claisen and aza-Cope rearrangement's rates with the Claisen rearrangement being faster. The presence of the Br-10 substituent reinforces this difference by slowing the aza-Cope rearrangement. For the N-6 substituted system, if the rate of the aza-Cope rearrangement is already much greater than that of the Claisen rearrangement, the effect the Br-10 substituent has on the aza-Cope rearrangement may not be sufficient to reverse the magnitudes of the rates for the two steps. That is to say, even with a Br-10 substituent in **265**, the rate of the aza-Cope rearrangement is still significantly greater than that of the Claisen rearrangement.

5.4 Asymmetric formation of the C-10b quaternary centre

The asymmetric generation of chiral centres using the Claisen rearrangement can be achieved by using an achiral substrate with an external chiral activator, such as a chiral Lewis acid, or by intramolecular chirality transfer using a chiral substrate.[104,105] Asymmetric induction using sub-stoichiometric quantities of chiral Lewis acids in combination with achiral allyl vinyl ethers has not been achieved on a diverse range of substrates and often requires specific functionality on the allyl vinyl ethers.[106-108] The frequent failure to use sub-stoichiometric

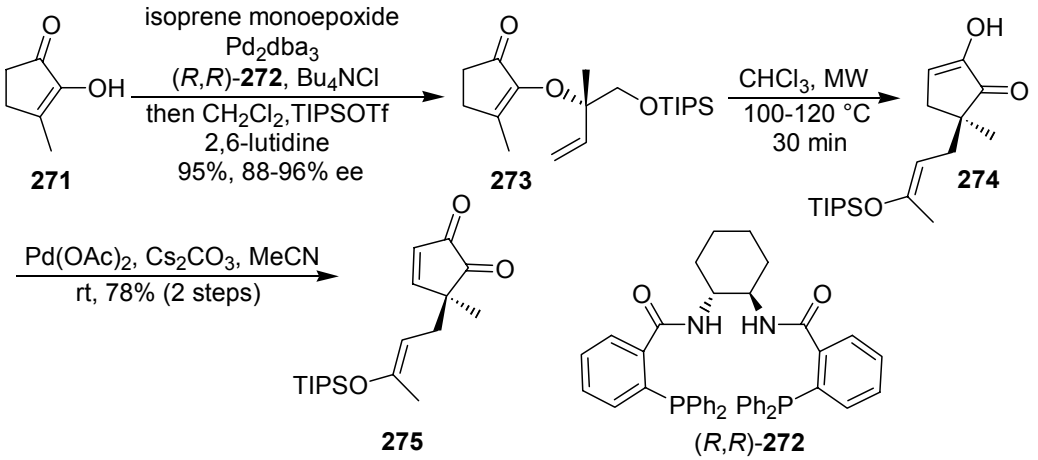
quantities of chiral Lewis acids to catalyse the Claisen rearrangement arises from the fact that coordination of the Lewis acid to the carbonyl oxygen of the product is stronger than coordination to the ether oxygen of the substrate.[105] That is to say, the product is a stronger Lewis base than the starting substrate and therefore leads to product inhibition of the catalyst. However, regardless of this problem, chiral Lewis acids have been used in greater than stoichiometric quantities to good effect on a range of substrates. For example, the chiral aluminum complex (*R*)-**268** has been used to promote the Claisen rearrangement of aliphatic substrates of the type **269** to give γ,δ-unsaturated aldehydes **270** in high yield and good enantiomeric ratios (**Scheme 99**).[109]



269 **270** (*S*)-**268**

Scheme 99. The aluminium complex (*R*)-**268** has been used to catalyse the Claisen rearrangement of a range of allyl vinyl ethers. R = benzyl, cyclohexyl, *t*-butyl or trimethylsilyl.

Alternatively, if the allyl vinyl ether substrate is chiral due to substituents at the α-allylic position, chirality can be efficiently transferred to the newly formed chiral centres through the highly ordered transition state of the Claisen rearrangement. To illustrate the use of this chirality transfer method in natural product synthesis, the first three steps used in a recent synthesis of (-)-terpestacin are presented in **Scheme 100**.[110]

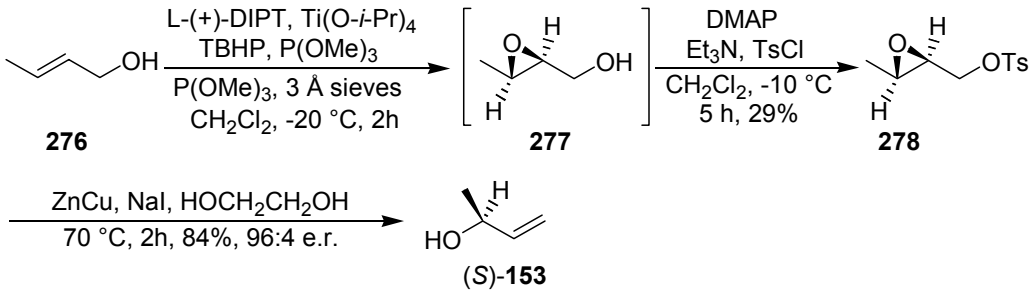


Scheme 100. A key step in the recent synthesis of (-)-terpestacin involves chirality transfer using a Claisen rearrangement. dba = dibenzylideneacetone, TIPS = triisopropylsilyl, MW = microwave irradiation.

In this synthesis of (-)-terpestacin, an asymmetric allylic alkylation[111] of 3-methyl-1,2-cyclopentanedione (**271**) with racemic isoprene monoepoxide in the presence (*R*,*R*)-**272** is used to generate **273** with high enantioselectivity. The chirality at the α-allylic position of **273** is then transferred completely (it is not reported how this was assessed) to the newly formed quaternary centre in **274** using a Claisen rearrangement under microwave (MW) conditions. After Saegusa oxidation[112] of **274**, **275** is isolated in 78% yield over two steps.

Of the two methods discussed above, the chirality transfer method was considered to be the most suitable for the asymmetric construction of the indolo[2,3-*b*]quinoline C-10b quaternary centre in this current investigation. In Chapter 3 it was shown that the Claisen rearrangement of **148** proceeded smoothly to give *E*-alkene **154** as the only observed product (page 50). This suggested that, if the Claisen rearrangement had proceeded exclusively *via* a chair transition state, the methyl group always adopts the equatorial position and complete chirality transfer had taken place in the rearrangement of racemic **148**. However, for this chirality transfer to be of synthetic value an enantiomerically enriched substrate must be used. Additionally, due to the planned oxidative cleavage of the resulting alkene (see page 20), the methyl group is redundant in its final position. To test this chirality transfer in the 10-brominated system and to potentially provide an asymmetric approach towards the commumesins, a synthesis of enantiomerically enriched (*S*)-(+)-3-butene-2-ol ((*S*)-**153**) was required.

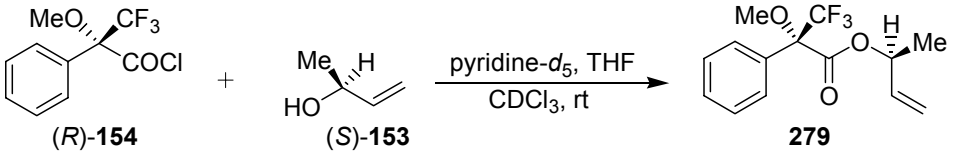
Enantiomerically enriched (*S*)-**153** was synthesised using literature procedures starting from *trans*-2-butene-1-ol (**276**) (**Scheme 101**).[113,114] Sharpless asymmetric epoxidation of **276** with *tert*-butyl hydroperoxide (TBHP), in the presence of L-(+)-diisopropyl tartrate (DIPT), followed by the *in situ* tosylation of the resulting epoxide **277** afforded (2*S*,3*S*)-(-)-epoxytosylate **278** in high chemical and optical purity after repeated crystallisation in accordance with the literature precedent.[113] The optical purity of **278** synthesised by this method was assessed by comparison of the optical rotation with a literature value. It is reported that the (2*R*,3*R*)-(-)-enantiomer of **278** with an enantiomeric purity of >99:1 e.r., determined by ^{1}H NMR analysis in combination with a chiral shift reagent, has an optical rotation of $[\alpha]^{25}_D = +34.2$.[113] The optical rotation of (2*S*,3*S*)-**278** was recorded to be $[\alpha]^{20}_D = -38.6$ suggesting that the optical purity of (2*S*,3*S*)-(-)-**278** was also of >99:1 e.r.



Scheme 101. Synthesis of enantiomerically enriched (*S*)-(+)-3-butene-2-ol. DIPT = diisopropyl tartrate, TBHP = *tert*-butyl hydroperoxide, DMAP = 4-dimethylaminopyridine, Ts = *p*-toluenesulfonyl.

Treatment of **278** with sodium iodide and zinc-copper couple in ethylene glycol led to the formation of (*S*)-**153** in good yield.[114] It is proposed that, mechanistically, this reaction involves the reaction of **278** with sodium iodide to form the corresponding epoxy iodide that subsequently undergoes reductive elimination to give (*S*)-**153** *via* a radical mechanism.[115] Due to the volatility of (*S*)-**153**, ethylene glycol was used as the solvent in this reaction and the product was separated by distillation at atmospheric pressure. By stirring a tetrahydrofuran solution of (*S*)-**153** with 3 Å molecular sieves, the water that had co-distilled with (*S*)-**153** was removed. However, the tetrahydrofuran could not be separated from the volatile (*S*)-**153** and in subsequent reactions (*S*)-**153** was used as a solution in tetrahydrofuran. The concentration of (*S*)-**153** in tetrahydrofuran was determined by analysis of the ^{1}H NMR spectrum associated with this tetrahydrofuran solution and was found to be *ca*. 2.7 M. The enantiomeric purity of (*S*)-**153** was determined by formation of an ester of

(*S*)-**153** with the chiral derivatising reagent (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPACl, (R)-**154**) (**Scheme 102**).[116]



Scheme 102. Determination of enatiomeric purity of (S)-**153** by the formation of an ester with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

Using ^{1}H NMR, the diastereoisomeric composition of **279**, which is related to the enantiomeric composition of (*S*)-**153**, was determined by integration of the methyl doublet in **279** that showed a large chemical shift non-equivalence (**Figure 26**). Using this method it was found that (*S*)-**153** had been formed with an enantiomeric purity of 96:4 e.r. For comparison, this derivatisation and ^{1}H NMR analysis was also conducted on commercially available racemic-**153**, using identical reaction conditions. This showed the expected 1:1 ratio of diastereoisomers, suggesting that under these conditions a kinetic resolution had not taken place.

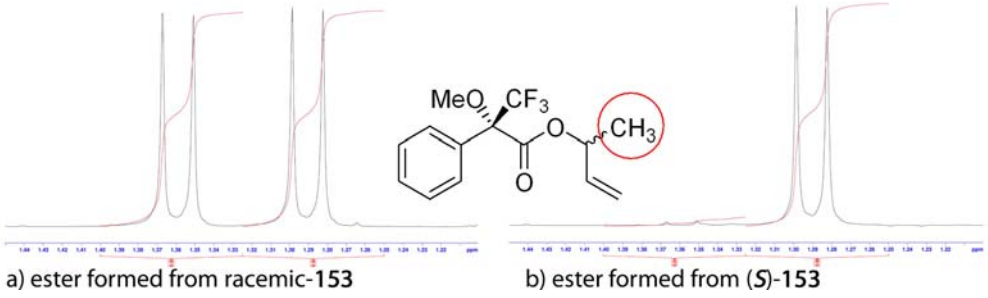


Figure 26. Analysis of the MTPA esters formed from a) racemic-**153** and b) (*S*)-**153** by ^{1}H NMR demonstrated that (*S*)-**153** had been formed in 96:4 e.r.

The formation of **279** not only allowed the enantiomeric purity of (*S*)-**153** to be determined, but it also allowed the relative stereochemistry of **279**, and therefore the absolute stereochemistry of (*S*)-**153**, to be confirmed by using the model developed by Mosher (**Figure 27**).[117] In this model, the differences in ^{1}H NMR chemical shifts of the methyl and vinyl protons for the two possible diastereoisomeric esters **279** and **280**, formed from (*R*)-**154** with racemic-**153**, results from the time weighted average preferential shielding of these groups by the π cloud of the α-phenyl substituent of the acid moiety. It is assumed that the

trifuoromethyl group eclipses the carbonyl and that the allylic proton is located in the same relative position in each of the two diastereoisomers. In the (*S*,*S*)-diastereoisomer **279** the methyl group will be more shielded than the methyl group of the (*S*,*R*)-diastereoisomer **280**, and will therefore resonate at lower chemical shift. For the esters **279** derived from (*S*)-**153**, the major diastereoisomer did indeed show a lower chemical shift for the methyl group protons of the alcohol derived moiety (**Figure 26b**). This supported the view that (*S*)-**153** had been prepared and not (*R*)-**153**.

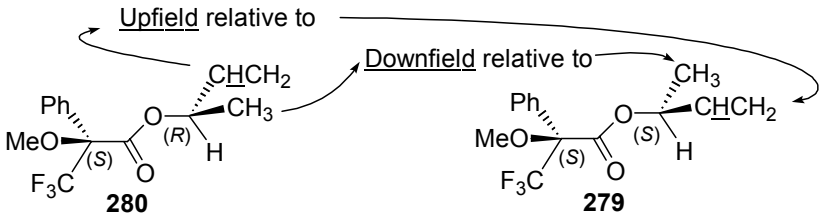
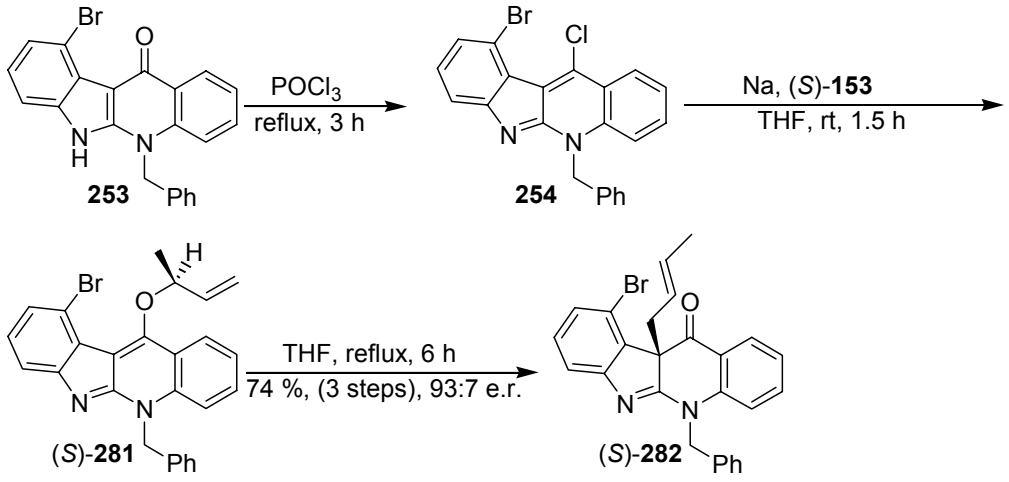


Figure 27. Comparison of the relative ^{1}H NMR chemical shifts for the two esters **280** and **279** formed from (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and racemic-**153** allows the relative stereochemistry to be determined.

With (*S*)-**153** in hand, the enantiomerically enriched allyl vinyl ether (*S*)-**281** could be synthesised (**Scheme 103**). Treatment of crude **254** with the sodium alkoxide generated from (*S*)-**153** afforded (*S*)-**281** that was not purified due to its observed slow rearrangement at room temperature (cf. page 48). After heating crude (*S*)-**281** in tetrahydrofuran at reflux for six hours, (*S*)-**282** was isolated in 74% yield (calculated over three steps). For comparison, racemic-**282** was also prepared using identical conditions using commercially available racemic-**153**.



Scheme 103. Synthesis of enatiomerically enriched (*S*)-**282**.

The enantiomeric purity of (*S*)-**282** was determined using the chiral lanthanide shift reagent $Eu(hfc)_3$ (hfc = heptafluorohydroxymethylene-(+)-camphorato) (**Figure 28**).[118] The addition of $Eu(hfc)_3$ in small portions to (*S*)-**282** in $CDCl_3$ led to a good separation of the signal in the ^1H NMR spectrum associated with H-1 of (*S*)-**282**. The enantiomeric purity of (*S*)-**282** was measured by integration of these separated signals and was determined to be 93:7 e.r. It must be noted, however, that enantiomeric ratios determined using lanthanide chiral shift reagents have been reported to be most accurate in the region of 70:30 e.r. to 80:20 e.r. with significant errors reported above these values.[119] Attempts were made to determine the enatiomeric purity of (*S*)-**282** with greater accuracy using chiral HPLC. Unfortunately, using a variety of solvent systems in combination with both normal and reversed phase columns, the two enantiomers could not be satisfactorily separated.

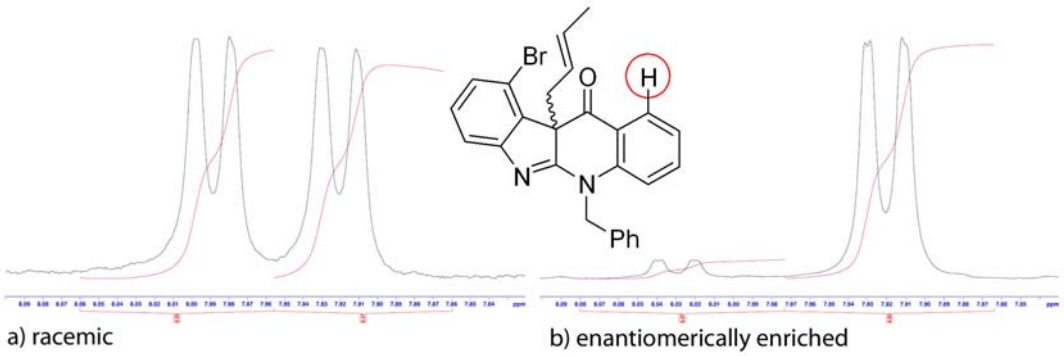


Figure 28. Analysis of a) racemic-**282** and b) enantiomerically enriched (*S*)-**282** using the chiral lanthanide shift reagent $Eu(hfc)_3$ in combination with ^1H NMR demonstrated that the enatiomeric purity of (*S*)-**282** was 93:7 e.r.

The enantiomeric ratio of 93:7 measured for (*S*)-**282** is consistent with a small loss of enantiomeric purity in relation to (*S*)-**153** (96:4 e.r.). This could be due to the Claisen rearrangement proceeding, to a minor extent, *via* a mechanistic pathway other than the expected chair transition state (**Figure 29**). A boat transition state with the methyl group occupying the equatorial position would give a reversal of the absolute configuration at C-10b whilst maintaining the *E*-geometry of the resulting alkene. Alternatively, a mechanism that involves bond breaking preceding bond formation (see page 35) could also account for some loss of optical purity.

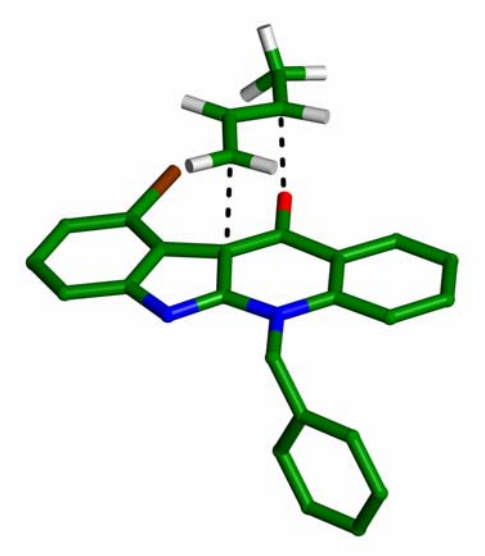


Figure 29. Claisen rearrangement of (*S*)-**281** *via* a chair transition state with the methyl group occupying a equatorial position will give the *S*-configuration at C-10b and the *E*-alkene of (*S*)-**282**.

Based on the proposed transition state shown in **Figure 29**, it was expected that using (*S*)-**153** would afford the (*S*)-absolute configuration at C-10b of the indolo[2,3-*b*]quinoline system. Crystals of (*S*)-**282** grown from ethyl acetate/hexane were analysed by X-ray crystallography and the absolute configuration was established by anomalous dispersion effects in diffraction measurements (**Figure 30**). By this method the (*S*)-configuration of the molecules in the crystal analysed was demonstrated. This crystallographic analysis suggests, but does not prove, that the bulk sample is predominantly of the expected (*S*)-configuration.

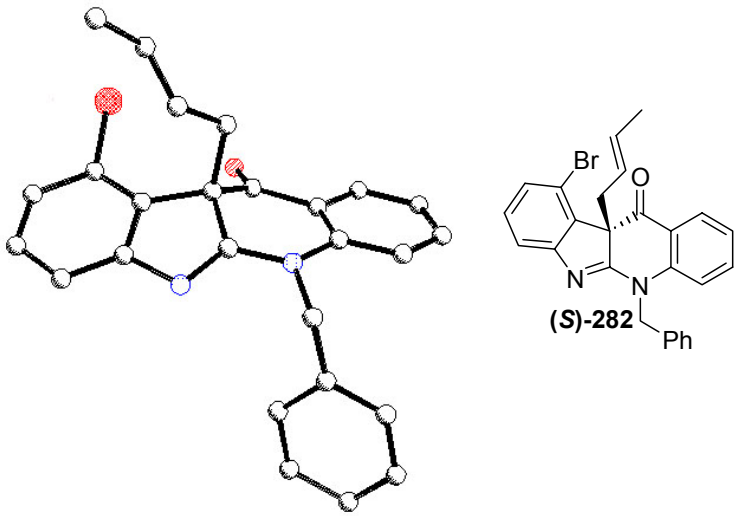


Figure 30. X-ray structure of (*S*)-**281**. The absolute configuration was demonstrated by anomalous dispersion effects in diffraction measurements.

5.5 Summary and Conclusions

The investigations described in this chapter were aimed at extending the methodology described in Chapter 2. First, the effect of a substituent at position C-10 of the indolo[2,3-*b*]quinoline system was explored with the aim of extending the methodology so as to be applicable to a communesin synthesis. A high yielding route to 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**239**), which was required for the synthesis of the 10-bromoindolo[2,3-*b*]quinoline system, was established. It was found that the chemistry that had been used previously for the synthesis of the indolo[2,3-*b*]quinoline ring system and for the generation of the C-10b quaternary centre was also applicable to the synthesis of compounds with a Br-10 substituent.

Various differences in the chemical reactivity between the system discussed in this chapter and the model system discussed in Chapter 2 were observed. The most important of these was that the presence of the Br-10 substituent did not accelerate the aza-Cope rearrangement of **258** as expected, but actually retarded this process. Based on this observation, a modified N-6 substituted system was investigated. Unfortunately, rearrangement of **265** did not lead to the accumulation of significant quantities of **266**.

Finally, the asymmetric construction of the C-10b quaternary centre was explored. It was shown that by using an enantiomerically enriched chiral secondary alcohol for the synthesis of the allyl ether (*S*)-**280**, the chirality could be transferred to the newly formed stereocentre at C-10b through the ordered transition state of the Claisen rearrangement. By using this technique (*S*)-**281** was prepared in good yield. In regard to a communesin synthesis, (*S*)-**281** has functionality a positions C-10, C-10b and C-11 that would allow asymmetric construction of the communesin natural products.

Whist the investigations presented in this chapter are far from a complete communesin synthesis, it is clear that this route is applicable to a synthesis of these compounds. Furthermore, this is the first asymmetric strategy directed at a synthesis of the communesins that incorporates functionality at all the positions necessary for the construction of the rest of the natural products.

Chapter 6: Experimental

6.1 General procedures

Chemical reagents were obtained from either Alfa Aesar-Avocardo/Lancaster or Aldrich and were used as received unless otherwise stated. All reactions were performed in oven-dried glassware, under a positive pressure of argon. THF was dried by refluxing with sodium-benzophenone under an argon atmosphere and was collected by distillation. CH_2Cl_2 was dried by refluxing with CaH_2 under an argon atmosphere and was collected by distillation. Alcohols used for the formation of alkoxides were dried either by standing over 4 Å molecular sieves or by distillation from sodium under an argon atmosphere. Aniline, *N*-methylaniline and *N*,'*N*-dimethylpiperazine were all dried by distillation from KOH. $NaHCO_{3(aq)}$ and $NH_4Cl_{(aq)}$ refers to saturated solutions. The following were used for cooling reaction mixtures:

-ice/water (0 °C)

-ice/acetone (-10 °C)

-dry ice/acetone (-78 °C)

-A cryocool machine was used for all other temperature below 0 °C

Thin-layer chromatography was performed using glass plates coated with silica gel (with fluorescent indicator UV_{254}). Developed plates were air-dried and analysed under a UV lamp (254/365 nm). Flash chromatography was performed using silica gel (40-63 μm, Fluorochem).

Melting points were recorded in open capillaries using an Electrothermal 9100 melting point apparatus. Values are quoted to the nearest 1 °C and are uncorrected.

Optical rotations were measured on a Perkin Elmer Model 341 Polarimeter using a 2 ml solution cell with a 10 cm path length. The concentration (c) is expressed in g/dm^3.

Elemental microanalysis for carbon, hydrogen and nitrogen were performed within the School of Chemistry at the University of St Andrews.

Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT spectrometer. Absorption maxima are reported in wavenumbers (cm^{-1}) and intensities are quoted as strong (s), medium (m), weak (w), and broad (br). Assignment of absorptions is only given if was used for structural determination.

Low and high-resolution mass spectra were recorded using either electron impact (EI), chemical ionisation (CI), or electrospray (ESI) ionisation methods and using time-of-flight mass analysis operating in positive mode. Only the molecular ion(s) and major fragment peaks (>20%) are reported. The intensities (%) are given in parentheses.

Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker Advance 300 (^{1}H, 300; ^{13}C, 75 MHz), Bruker Advance 400 (^{1}H, 400; ^{13}C, 101 MHz), or Bruker Advance 500 (^{1}H, 500; ^{13}C, 125 MHz). ^{13}C NMR spectra were recorded using the PENDANT pulse sequence and peaks are assigned and either C, CH, CH_2 or CH_3. Assignment of peaks in the ^{13}C NMR spectrum to specific carbon atoms is only given if the peak was of particular importance for structural determination. All NMR spectra ware acquired using the deuterated solvent as the lock and the residual solvent or TMS (tetramethylsilane) as the internal reference. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz. The multiplicity used in the assignment of ^{1}H NMR spectra is indicated by the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), dt (doublet of triplets), q (quartet), m (multiplet), and br (broad). Peaks were assigned with the aid of the two-dimensional NMR spectroscopic techniques COSY, HSQC, and HMBC.

General method A: General procedure for the synthesis of 2-Phenylamino-1*H*-indole-3-carboxylic acid methyl esters

N-Chlorosuccinimide (1.1 equiv.) and *N*,'*N*-dimethylpiperazine (0.55 equiv.) were added to a stirred solution of indole-3-carboxylic acid methyl ester (**111**) (1 equiv.) in CH_2Cl_2 (1 vol.), cooled to 0 °C and maintained under an argon atmosphere. The reaction mixture was stirred at 0 °C for 2 hours. A mixture of the trichloroacetic acid (0.25 equiv.) and the appropriate

aniline (2 equiv) in CH_2Cl_2 (1 vol.) was added before allowing the reaction mixture to warm to room temperature. After 2 hours, the reaction mixture was sequentially washed with 10% $NaHCO_{3(aq)}$ (0.5 vol.), 1.0 M hydrochloric acid (0.5 vol.), and water (0.5 vol.). The CH_2Cl_2 solution was dried ($MgSO_4$), filtered through a pad of silica and the solvent was removed by evaporation at reduced pressure. The crude products were purified either by crystallisation from CH_2Cl_2/hexane or by flash chromatography.

General method B: General procedure for the synthesis of 5,6-dihydroindolo[2,3-*b*]quinolin-11-ones from 2-phenylamino-1*H*-indole-3-carboxylic acid methyl esters

The appropriate phenylamino-1*H*-indole-3-carboxylic acid methyl ester was heated in Ph_2O under reflux. After allowing the reaction mixture to return to room temperature, the solid insoluble product was collected by filtration and washed with ether until a fine powder resulted that was free of Ph_2O.

General method C: General procedure for the synthesis of 11-chloro-5*H*-indolo[2,3-*b*]quinolines from 5,6-dihydroindolo[2,3-*b*]quinolin-11-ones

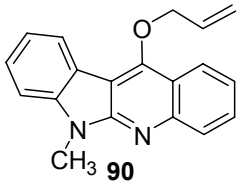
A mixture of the appropriate 5,6-dihydroindolo[2,3-*b*]quinolin-11-one and $POCl_3$ (1 vol.) were heated at reflux, under an argon atmosphere, and then cooled to room temperature. The excess $POCl_3$ was removed by evaporation at reduced pressure and the residue was added to crushed ice/water (*ca*. 1 vol.). The mixture was basified with a saturated $NaHCO_{3(aq)}$ until all the yellow solids had turned orange. The aqueous suspension was then extracted with CH_2Cl_2 (3 x 2 vol.). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was removed by evaporation at reduced pressure. Alternatively, for large scale preparation, the product can be collected by filtration after the addition of $NaHCO_{3(aq)}$.

General method D: General procedure for the synthesis of 11-alkyloxy-5*H*-indolo[2,3-*b*]quinolines from 11-chloro-5*H*-indolo[2,3-*b*]quinolines

Alkoxides were formed by slowly adding the appropriate alcohol, at a rate that maintained a steady reaction, to sodium in THF with stirring and under an argon atmosphere. When all the sodium had dissolved, the alkoxide was added *via* cannula to a stirred mixture of the appropriate 11-chloro-5*H*-indolo[2,3-*b*]quinoline in THF (1 vol.). The reaction mixture was then stirred at room temperature, under an argon atmosphere, for 18 hours. After adding a saturated solution of $NH_4Cl_{(aq)}$ (0.1 vol.), the solvent was removed by evaporation at reduced pressure and the residue was partitioned between water (1 vol.) and CH_2Cl_2 (1 vol.). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 1 vol.). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was removed by evaporation at reduced pressure. Purification by chromatography afforded the pure product.

6.2 Preparation of individual compounds and characterisation data

Preparation of 11-allyloxy-6-methyl-6*H*-indolo[2,3-*b*]quinoline (90)

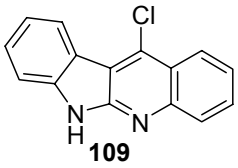


90

A solution of the alkoxide generated from allyl alcohol (25.5 ml, 375 mmol) and sodium (2.6 g, 196 mmol) in THF (70 ml) was added to 11-chloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**115**) (3.50 g, 13.1 mmol) in THF (25 ml), maintained under an argon atmosphere, and the reaction mixture heated at 70 °C (bath temperature). After 48 hours the reaction was cooled to room temperature and $NH_4Cl_{(aq)}$ (10 ml) was added. The excess allyl alcohol and THF were evaporated at reduced pressure and the residue was partitioned between water (25 ml) and CH_2Cl_2 (25 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 25 ml). All the CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (10% to 20% EtOAc/hexane) followed by crystallised from EtOAc/hexane to afford the title compound **90** as pale yellow crystals (1.47g, 5.10 mmol, 68%). Mp 75-76 ^{o}C; Anal. calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 78.86; H, 5.66; N, 9.72;

IR (KBr) ν_{max}: 3057 (w), 2928 (w), 1638 (s), 1608 (s), 1570 (m), 1492 (s), 1474 (m), 1428 (m), 1395 (s), 1292 (s), 1245 (m), 1099 (m), 993 (w), 922 (w), 765 (s), 742 (s) cm^{-1}; MS (ESI) m/z 288 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{19}H_{16}N_2O$ 288.1262, found 288.1263; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.5, 1.1 Hz, 1H, H-1), 8.24 (d, *J* = 7.5 Hz, 1H, H-10), 8.12 (d, *J* = 8.5 Hz, 1H, H-4), 7.72 (ddd, *J* = 8.5, 7.0, 1.1 Hz, 1H, H-3), 7.56 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H, H-8), 7.45 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, H-2), 7.39 (d, *J* = 8.0 Hz, 1H, H-7), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H, H-9), 6.29 (ddt, *J* = 17.0 Hz, 10.5 Hz, 5.5 Hz, 1H, C<u>H</u>=CH_2), 5.56 (dq, *J* = 17.0, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 5.37 (dq, *J* = 10.5, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 4.89 (td *J* = 5.5, 1.5 Hz, 2H, OCH_2), 3.97 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (C), 154.8 (C), 148.6 (C), 142.2 (C), 133.4 (CH), 129.4 (CH), 127.8 (CH), 127.7 (CH), 123.8 (CH), 122.71 (CH), 122.68 (CH), 120.7 (CH), 120.1 (C), 119.3 (C), 118.6 (CH_2), 109.4 (C), 108.6 (CH), 75.2 (CH_2), 28.0 (CH_3).

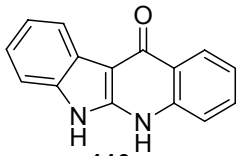
Preparation of 11-chloro-6*H*-indolo[2,3-*b*]quinoline (109)[45]



109

5,6-Dihydroindolo[2,3-*b*]quinolin-11-one (**110**) (13.7 g, 58.5 mmol) was refluxed in $POCl_3$ (300 ml) for 3 hours and then cooled to room temperature. The excess $POCl_3$ was evaporated at reduced pressure and the residue was added to chipped ice/water (*ca* 150 ml). The mixture was made basic (*ca* pH 9) by the addition of saturated $NaHCO_3$ solution and the yellow solids were collected by filtration. After washing with water, the product was thoroughly dried to afford the title compound **109** in sufficient purity for the next step (13.9 g, 55.1 mmol, 94%). Spectroscopic data was in accordance with that published in the literature.[45] Mp 307-315 °C (dec.) (lit.[45] 314-316 °C (dec.)); ^1H NMR (300 MHz, DMSO-d_6) δ 12.11 (br s, 1H, NH), 8.59 (d, *J* = 7.8 Hz, 1H, H-10), 8.54 (dd, *J* = 8.4, 1.1 Hz, 1H, H-1), 8.37 (dd, *J* = 8.4, 1.0 Hz, 1H, H-4), 7.91-7.80 (m, 1H, H-3), 7.71-7.50 (m, 3H, H-7, H-2, H-8), 7.41-7.31 (m, 1H, H-9).

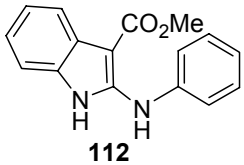
Preparation of 5,6-dihydroindolo[2,3-*b*]quinolin-11-one (110)[45]



110

Prepared from 2-phenylamino-1*H*-indole-3-carboxylic acid methyl ester (**112**) (17.5 g, 65.7 mmol) in Ph_2O (90 ml) with a reaction time of 3.5 hours using general method B. The title compound **110** was obtained as a light brown solid (14.6 g, 62.3 mmol, 95%). Spectroscopic data was in accordance with that published in the literature.[45] Mp > 400 °C (lit.[45] > 360 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (br s, 2H, 2 x NH), 8.29 (d, J = 7.7 Hz, 1H, H-10), 8.19 (d, J = 7.9 Hz, 1H, H-1), 7.63-7.58 (m, 1H, H-3), 7.48-7.42 (m, 1H, H-9), 7.15-7.31 (m, 3H, H-2, H-4, H-8); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7 (C, C-11), 145.7 (C), 138.7 (C), 135.4 (C), 131.1 (CH), 125.7 (CH), 124.2 (C), 123.9 (C), 123.0 (CH), 121.8 (CH), 121.2 (CH), 120.4 (CH), 117.8 (CH), 111.3 (CH), 102.2 (C).

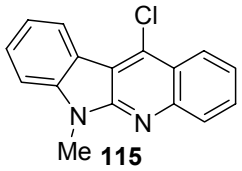
Preparation of 2-phenylamino-1*H*-indole-3-carboxylic acid methyl ester (112)[45]



112

Prepared from indole-3-carboxilic acid methyl ester (**111**) (25.9 g, 148 mmol) in CH_2Cl_2 (600 ml) and aniline (26.9 ml, 295 mmol) using general method A. The crude product was crystallised twice from CH_2Cl_2/hexane to afford the title compound **112** as a pale yellow crystals (19.8 g, 74.4 mmol, 50%). Spectroscopic data was in accordance with that published in the literature.[45] Mp 121-122 °C (lit.[45] 121-122 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H, NH), 8.22 (s, 1H, NH), 7.46-7.38 (m, 2H, 2 x ArH), 7.80 (d, J = 7.7, 1H, ArH), 7.30-7.24 (m, 2H, 2 x ArH), 7.22-7.10 (m, 3H, 3 x ArH), 7.08-7.03 (m, 1H, ArH), 3.93 (s, 3H, CH_3).

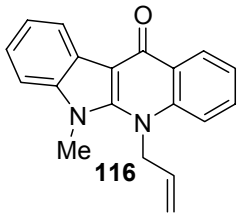
Preparation of 11-chloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline (115)



115

Sodium hydride (1.58 g of a 60% dispersion in oil, 39.5 mmol) was added to a stirred suspension of 11-chloro-6*H*-indolo[2,3-*b*]quinoline (**109**) (2.00 g, 7.93 mmol) in THF (70 ml), maintained under an argon atmosphere. When effervescence ceased, methyl iodide (2.50 ml, 40.1 mmol) was added and the reaction mixture was heated at 50 °C (bath temperature) for 1 hour. After cooling the reaction mixture to room temperature, $NH_4Cl_{(aq)}$ (20 ml) was added and the solvent was evaporated at reduced pressure. The residue was partitioned between CH_2Cl_2 (30 ml) and water (30 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 30 ml). All the CH_2Cl_2 extracts were combined, then dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (10% to 20% EtOAc/Hexane) to afford the title compound **115** as a pale yellow crystalline solid (1.89 g, 7.09 mmol, 90%). Mp 141-142 ^oC; IR (KBr) ν_{max}: 1603 (s), 1560 (m), 1489 (m), 1470 (m), 1422 (m), 1393 (s), 1322 (m), 1260 (m), 1121 (w), 1073 (w), 944 (w), 863 (w), 763 (m), 749 (s), 629 (m) cm^{-1}; MS (ESI) m/z 267 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{16}H_{12}N_2{}^{35}Cl$ 267.0689, found 267.0681; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 7.5 Hz, 1H, H-10), 8.39 (dd, *J* = 8.3, 1.2 Hz, 1H, H-1), 8.11 (d, *J* = 8.3 Hz, 1H, H-4), 7.74 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H, H-3), 7.60 (ddd, *J* = 8.3, 7.5, 1.2 Hz, 1H, H-8), 7.53 (ddd, *J* = 8.3, 6.8, 1.0 Hz, 1H, H-2), 7.38 (d, *J* = 8.3 Hz, 1H, H-7), 7.33 (td, *J* = 7.5, 0.8 Hz, 1H, H-9), 3.95 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (C), 147.0 (C), 142.8 (C), 135.7 (C), 129.5 (CH), 128.6 (CH), 127.9 (CH), 124.3 (CH), 124.2 (CH), 123.7 (CH), 122.4 (C), 120.4 (CH),119.8 (C), 115.6 (C), 108.6 (CH), 27.9 (CH_3).

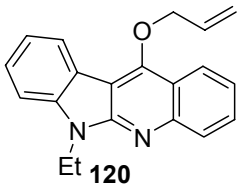
Preparation of 5,6-dihydro-5-allyl-6-methylindolo[2,3-*b*]quinolin-11-one (116)



116

A mixture of 11-allyloxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**90**) (200 mg, 0.694 mmol) and PhMe (10 ml) were heated at reflux under an argon atmosphere for 4 days. After cooling the reaction mixture to room temperature, the PhMe was evaporated at reduced pressure and the crude product was purified by flash chromatography (50% to 80% EtOAc/Hexane) to afford the title compound **116** as a colourless crystalline solid (186 mg, 0.645 mmol, 93%). Mp 196-197 ^{o}C; IR (KBr) ν_{max}: 1613 (m, C=O), 1591 (s), 1535 (s), 1510 (s), 1467 (m), 1396 (w), 1242 (m), 1126 (w), 929 (w), 751 (s) cm^{-1}; MS (EI) m/z 288 (M^+, 13), 247 (44), 219 (26), 86 (65), 84 (100); HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O$ 288.1263, found 288.1255; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 7.5, 0.7 Hz, 1H, H-10), 8.40 (dd, *J* = 7.9, 1.6 Hz, 1H, H-1), 7.44 (td, *J* = 8.7, 1.6 Hz, 1H, H-3), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H, H-9), 7.16-7.26 (m, 3H, H-4, H-2, H-8), 6.97 (d, *J* = 8.0 Hz, 1H, H-7), 6.28 (m, 1H, C<u>H</u>=CH$_2$), 5.43 (m, 1H, CH=C<u>H</u>$_2$), 5.15 (m, 1H, CH=C<u>H</u>$_2$), 4.92 (m, 2H, NCH$_2$), 3.74 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C, C-11), 147.4 (C, C-5a), 140.5 (C), 137.4 (C), 133.6 (CH), 131.2 (CH), 126.0 (CH), 125.1 (C), 123.5 (C), 123.2 (CH), 122.4 (CH), 122.2 (CH), 121.2 (CH), 118.2 (CH$_2$), 115.6 (CH), 108.9 (CH), 104.4 (C), 51.7 (CH$_2$), 32.8 (CH$_3$).

Preparation of 11-allyloxy-6-ethyl-6*H*-indolo[2,3-*b*]quinoline (120)

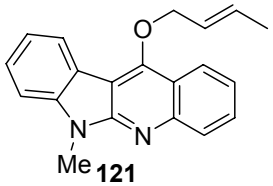


120

A solution of the alkoxide generated from allyl alcohol (31.5 ml, 463 mmol) and sodium (1.60 g, 69.5 mmol) in THF (10 ml) was added to 11-chloro-5-ethyl-5*H*-indolo[2,3-*b*]quinoline (**122**) (1.30 g, 4.63 mmol) in THF (15 ml), maintained under an argon atmosphere, and the reaction mixture heated at 70 °C (bath temperature). After 48 hours the reaction was cooled to room temperature and $NH_4Cl_{(aq)}$ (10 ml) was added. The excess allyl alcohol and THF were evaporated at reduced pressure and the residue was partitioned

between water (25 ml) and CH_2Cl_2 (25 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 25 ml). All the CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The resided was purified by flash chromatography (5% to 15% EtOAc/hexane) and then crystallized from EtOH to give the title compound **120** as pale yellow crystals (686 mg, 2.27 mmol, 49%). M.p.77-78 °C; Anal. calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.16; H, 6.15; N, 9.20; IR (KBr) ν_{max}: 1636 (m), 1607 (m), 1570 (w), 1489 (m), 1471 (m), 1407 (s), 1375 (m), 1277 (m), 1232 (m), 1177 (w), 1104 (m), 971 (w), 932 (w), 751 (s), 650 (w), 583 (w), 465 (w) cm^{-1}; MS (EI) m/z 302 (M^+, 18), 261 (100), 205 (25); HRMS (EI) m/z calcd for $C_{20}H_{18}N_2O$ 302.1419 found 302.1419; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.5, 1.5 Hz, 1H, H-1), 8.26 (d, *J* = 7.8 Hz, 1H, H-10), 8.12 (d, *J* = 8.7 Hz, 1H, H-4), 7.71 (ddd, *J* = 8.7, 6.8, 1.5 Hz, 1H, H-3), 7.56 (ddd, *J* = 8.3, 7.4, 1.2 Hz, 1H, H-8), 7.41-7.48 (m, 2H, H-2, H-7), 7.31 (ddd, *J* = 7.8, 7.4, 0.8 Hz, 1H, H-9), 6.30 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1H, C<u>H</u>=CH_2), 5.58 (dq, *J* = 17.3, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 5.38 (dq, *J* = 10.5, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 4.90 (dt, *J* = 5.5, 1.2 Hz, 2H, OCH_2), 4.58 (q, *J* = 7.2 Hz, 2H, NCH_2), 1.51 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (C), 154.1 (C), 148.5 (C), 141.1 (C), 133.3 (CH), 129.2 (CH), 127.7 (CH), 127.4 (CH), 123.9 (CH), 122.52 (CH), 122.46 (CH), 120.1 (CH), 119.9 (C), 119.3 (C), 118.4 (CH_2), 109.3 (C), 108.6 (CH), 75.1 (CH_2), 36.3 (CH_2), 13.8 (CH_3).

Preparation of 11-(*E*-but-2-enyloxy)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (121)

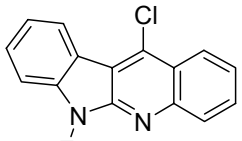


121

A solution of the alkoxide generated from *E*-2-butene-1-ol (31.8 ml, 375 mmol) and sodium (1.29 g, 56.2 mmol) in THF (10 ml) was added to 11-chloro-6-methyl-5*H*-indolo[2,3-*b*]quinoline (**115**) (1.00 g, 3.75 mmol) in THF (15 ml), maintained under an argon atmosphere, and the reaction mixture was heated at 55 °C (bath temperature). After 65 hours the reaction was cooled to room temperature and $NH_4Cl_{(aq)}$ (10 ml) was added. The excess alcohol and THF were evaporated at reduced pressure and the residue was partitioned between water (20 ml) and CH_2Cl_2 (20 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2. All the CH_2Cl_2 extracts were combined, dried ($MgSO_4$),

and the solvent was evaporated at reduced pressure to leave an oily residue. The residue was purified by flash chromatography (3% to 6% EtOAc/hexane) followed by crystallization from MeOH/water to afford the title compound **121** as a colourless crystalline solid (188 mg, 0.622 mmol, 17%); Mp 60-61 °C; Anal. calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.19; H, 6.11; N, 8.91; IR (KBr) ν_{max}: 1637 (s), 1610 (s), 1571 (m), 1491 (s), 1475 (m), 1397 (s), 1337 (m), 1322 (m), 1289 (s), 1243 (m), 1186 (w), 1124 (w), 1097 (m), 976 (s), 953 (m), 752 (s), 741 (s), 645 (w), 462 (w) cm^{-1}; MS (ESI) m/z 303 (MH^+, 38), 249 (100); HRMS (ESI) m/z calcd for $C_{20}H_{19}N_2O$ 303.1497 found 303.1493; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.4, 1.2 Hz, 1H, H-1), 8.27 (d, *J* = 7.5 Hz, 1H, H-10), 8.12 (d, *J* = 8.4 Hz, 1H, H-4), 7.72 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H, H-3), 7.58 (ddd, *J* = 8.2, 7.4, 1.0 Hz, 1H, H-8), 7.46 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H, H-2), 7.43 (d, *J* = 8.2 Hz, 1H, H-7), 7.33 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H, H-9), 5.97 (m, 2H, $CH_2C\underline{H}=C\underline{H}$), 4.84 (d, *J* = 5.0 Hz, 2H, OCH_2), 4.00 (s, 3H, NCH_3), 1.78 (d, *J* = 1.5 Hz, 3H, $CHC\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (C), 155.1 (C), 148.9 (C), 142.4 (C), 131.9 (CH), 129.6 (CH), 127.9 (CH), 127.8 (CH), 126.7 (CH), 124.1 (CH), 123.1 (CH), 122.8 (CH), 120.6 (CH), 120.5 (C), 119.6 (C), 118.8 (CH_2), 109.7 (C), 108.8 (CH), 75.7 (CH_2), 28.3 (CH_3), 18.3 (CH_3).

Preparation of 11-chloro-6-ethyl-6*H*-indolo[2,3-*b*]quinoline (122)

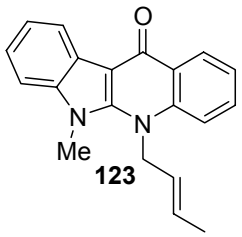


122

Sodium hydride (1.58 g of a 60% dispersion in oil, 39.6 mmol) was added to a stirred suspension of 11-chloro-6*H*-indolo[2,3-*b*]quinoline (**109**) (2.00 g, 7.93 mmol) in THF (70 ml), maintained under an argon atmosphere. When effervescence ceased, ethyl iodide (3.18 ml, 39.6 mmol) was added and the reaction mixture was heated at 50 °C (bath temperature) for 3 hours. After cooling the reaction mixture to room temperature, $NH_4Cl_{(aq)}$ (20 ml) was added and the THF was evaporated at reduced pressure. The residue was partitioned between CH_2Cl_2 (30 ml) and water (30 ml), then filtered to remove unreacted starting material (260 mg, 1.03 mmol, 13%). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 30 ml). All the CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatograph (5% to 10% EtOAc/hexane) to afford title compound **122** as a yellow

crystalline solid (1.50 g, 5.34 mmol, 68%). Mp 133-134 °C; IR (KBr) ν_{max}: 1632 (w), 1603 (s), 1561 (w), 1485 (m), 1470 (m), 1400 (s), 1380 (w), 1321 (w), 1260 (w), 1233 (m), 1153 (w), 1132 (w), 760 (m), 743 (s), 628 (w), 464 (m) cm^{-1}; MS (ESI) m/z 281 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{17}H_{14}N_2Cl$ 281.0847 found 281.0846; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (m, 1H, H-10), 8.41 (m, 1H, H-1), 8.12 (m, 1H, H-4), 7.74 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H, H-3), 7.60 (ddd, *J* = 7.9, 7.5, 1.3 Hz, 1H, H-8), 7.53 (ddd, *J* = 8.3, 6.8, 1.0 Hz, 1H, H-2), 7.43 (d, *J* = 7.9 Hz, 1H, H-7), 7.33 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H, H-9), 4.57 (q, *J* = 7.2 Hz, 2H, CH_2), 1.49 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2 (C), 147.3 (C), 142.2 (C), 135.9 (CH), 129.7 (CH), 128.9 (CH), 128.2 (CH), 124.7 (CH), 124.4 (CH), 124.0 (CH), 122.7 (C), 120.5 (CH), 120.4, (C), 116.0 (C), 109.1 (CH), 36.7 (CH_2), 14.1 (CH_3).

Preparation of 5-(*E*-but-2-enyloxy)-6-methyl-5,6-dihydroindolo[2,3-*b*]quinolin-11-one (123)

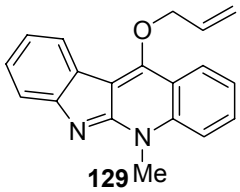


123

11-(*E*-but-2-enyloxy)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**121**) (12 mg, 0.0397 mmol) and PhMe (0.8 ml) were heated at 100 °C for 3 hours. The PhMe was evaporated at reduced pressure and the residue was purified by flash chromatography (30% to 50% EtOAc/hexane) to give the title compound **123** as a colourless crystalline solid (8 mg, 0.0265 mmol, 67%). Mp 164-165 °C; IR (KBr) ν_{max}: 1618 (s, C=O), 1593 (s), 1577 (m), 1534 (s), 1509 (s), 1466 (m), 1391 (w), 1350 (w), 1316 (w), 1238 (m), 1126 (w), 1041 (w), 976 (w), 879 (w), 748 (s), 672 (w) cm^{-1}; MS (EI) m/z 302 (M^+, 20), 247 (100), 219 (46); HRMS (EI) m/z calcd for $C_{20}H_{18}N_2O$ 302.1419 found 302.1418 ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 7.7, 0.8 Hz, 1H, H-10), 8.39 (dd, *J*, = 7.9, 1.2 Hz, 1H, H-1), 7.41 (ddd, *J* = 8.5, 6.9, 1.2, 1H, H-3), 7.14-7.30 (m, 4H, H-9, H-8, H-4, H-2), 6.92 (d, *J* = 8.2 Hz, 1H, H-7), 5.83 (m, 1H, C<u>H</u>CH_3), 5.52 (m, 1H, CH_2C<u>H</u>), 4.80 (m, 2H, CH_2), 3.70 (s, 3H, NCH_3), 1.72 (dd, *J* = 1.6, 6.7 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (C), 147.6 (C), 140.8 (C), 137.7 (C), 131.4 (CH), 129.4 (CH), 126.5 (CH), 126.3 (CH), 125.4 (C), 123.8 (C), 123.5 (CH), 122.6 (CH),

122.5 (CH), 121.5 (CH), 115.9 (CH), 109.1 (CH), 104.7 (C), 52.1 (CH_2), 33.2 (CH_3), 18.2 (CH_3).

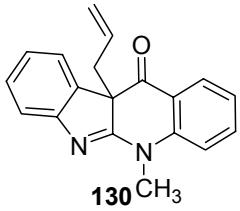
Preparation of 11-allyloxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (129)



129

Prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**133**) (1.50 g, 5.62mmol) in THF (30 ml), with the alkoxide generated from allyl alcohol (7.50 ml, 110 mmol) and sodium (650 mg, 28.3 mmol) in THF (10 ml), using general method D. The crude product was purified by flash chromatograph (80% EtOAc/hexane) to afford the title compound **129** as a dark yellow solid (1.46 g, 5.06 mmol, 90%). Mp 93-94 ^{o}C; IR (KBr) ν_{max}: 1643 (s), 1571 (s), 1522 (m), 1492 (s), 1460 (m), 1352 (m), 1283 (s), 1240 (s), 1177 (m) 1149 (m), 1118 (m), 1098 (m), 1059 (m), 965 (w), 909 (w), 750 (s), 661 (w), 595 (w), 468 (w) cm^{-1}; MS (CI) m/z 289 (MH^+, 100), 249 (27); HRMS (CI) m/z calcd for $C_{19}H_{17}N_2O$ 289.1341 found 289.1339; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H, H-1), 8.08 (d, *J* = 8.0 Hz, 1H, H-10), 7.63-7.77 (m, 3H, H-7, H-3, H-4), 7.52 (td, *J* = 8.0, 1.0 Hz, 1H, H-8), 7.40 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, H-2), 7.24 (td, *J* = 8.0, 1.0 Hz, 1H, H-9), 6.23 (ddt, *J* = 17.0, 10.5, 1.5, 1H, C<u>H</u>=CH_2), 5.54 (dq, *J* = 17.0, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 5.35 (dq, *J* = 10.5, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 4.92 (dt, *J* = 5.5, 1.5 Hz, 2H, OCH_2), 4.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (C), 156.6 (C), 153.9 (C), 138.1 (C), 132.8 (CH), 130.9 (CH), 128.3 (CH), 124.3 (CH), 123.2 (CH), 122.5 (C), 121.6 (CH), 120.0 (CH), 118.8 (CH_2), 117.9 (C), 117.5 (CH), 116.4 (C), 114.2(CH), 75.1 (CH_2), 33.0 (CH_3).

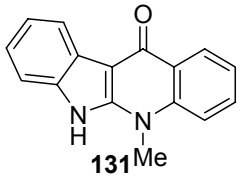
Preparation of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (130)



130

A solution of 11-allyloxy-5-methyl-6*H*-indolo[2,3-*b*]quinoline (**129**) (1.46 g, 5.06 mmol) and PhMe (50 ml) was refluxed under an argon atmosphere for 5 hours. After cooling to room temperature, the PhMe was evaporated at reduced pressure and the residue was purified by flash chromatography (10% to 20% EtOAc/hexane) to afford the title compound **130** as a bright yellow crystalline solid (1.30 g, 4.51 mmol, 89%). Crystals suitable for X-ray analysis were obtained from EtOAc/hexane. Mp 94-95 ^{o}C; Anal. calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.09; H, 5.33; N, 9.56; IR (KBr) ν_{max}: 3070 (w), 2901 (w), 1692 (s, C=O), 1560 (s), 1471 (s), 1386 (s), 1344 (m), 1296 (m), 1207 (m), 1167 (m), 1068 (w), 1038 (w), 985 (w), 922 (m), 844 (m), 777 (s), 762 (s), 670 (m), 676 (m), 629 (w), 504 (w), 468 (w) cm^{-1}; MS (ESI) m/z 289 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{19}H_{17}N_2O$ 289.1341 found 289.1346; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8, 1.4 Hz, H-1), 7.70 (d, *J* = 7.3 Hz, 1H, H-10), 7.63 (ddd, *J* = 8.8, 7.3, 1.4 Hz, 1H, H-3), 7.42 (d, *J* = 7.3 Hz, 1H, H-7), 7.35 (td, *J* = 7.3, 1.3 Hz, 1H, H-8), 7.12-7.19 (m, 3H, H-4, H-9, H-2), 5.28-5.42 (m, 1H, C<u>H</u>=CH_2), 4.99 (m, 1H, CH=C<u>H</u>$_2$), 4.83 (m, 1H, CH=C<u>H</u>$_2$), 3.72 (s, 3H, CH_3), 2.80 (dd, *J* = 13.2, 6.8 Hz, 1H, CCH_2), 2.46 (dd, *J* = 13.2, 7.8 Hz, 1H, CCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9 (C, C-11), 172.4 (C, C-5a), 153.6 (C), 145.4 (C), 140.0 (CH), 133.1 (C), 130.4 (CH), 128.9 (CH), 128.6 (CH), 124.7 (CH), 123.3 (CH), 122.5 (CH), 120.3 (CH_2), 119.0 (C), 118.7 (CH), 114.6 (CH), 66.2 (C, C-10b), 45.1 (CH_2), 33.2 (CH_3).

Preparation of 5,6-dihydro-5-methylindolo[2,3-*b*]quinolin-11-one (131)[45]

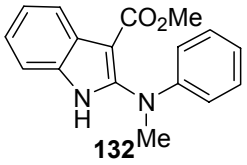


131

Prepared from 2-(methylphenylamino)-1*H*-indole-3-carboxylic acid methyl ester (**132**) (17.0 g, 60.6 mmol) in Ph_2O (80 ml), with a reaction time of 2.5 hours, using general method B.

The title compound **131** was obtained as a light brown micro crystalline solid (13.8 g, 55.6 mmol, 91%). Spectroscopic data was in accordance with that published in the literature.[45] Mp >400 °C (lit.[45] >360 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.07 (br s, 1H, NH), 8.39 (dd, *J* = 8.3, 1.4 Hz, 1H, H-10), 8.22-8.18 (m, 1H, H-1), 7.82-7.71 (m, 2H, H-3, H-9), 7.50-7.46 (m, 1H, H-8), 7.39 (ddd, *J* = 7.9, 6.3, 1.7 Hz, 1H, H-2), 7.31-7.18 (m, 2H, H-4, H-7), 3.98 (s, 3H, CH_3).

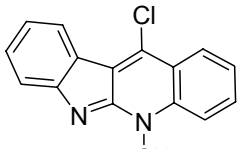
Preparation of 2-(methylphenylamino)-1*H*-indole-3-carboxylic acid methyl ester (132)[45]



132

Prepared from indole-3-carboxilic acid methyl ester (**111**) (18.8 g, 107 mmol) in CH_2Cl_2 (440 ml) and *N*-methylaniline (23.4 ml, 216 mmol) using general method A. The crude product was crystallised from CH_2Cl_2/hexane to afford the title compound **132** as colourless crystals (22.6 g, 80.6 mmol, 75%). Spectroscopic data was in accordance with that published in the literature.[45] Mp 144-146 °C (lit.[45] 146-147 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (broad s, 1H, NH), 8.17-8.10 (m, 1H, ArH), 7.31-7.19 (m, 5H, 5 x ArH), 6.94-6.83 (m, 3H, 3 x ArH), 3.84 (s, 3H, OCH_3), 3.47 (s, 3H, NCH_3).

Preparation of 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (133)

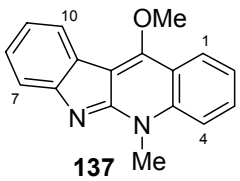


133

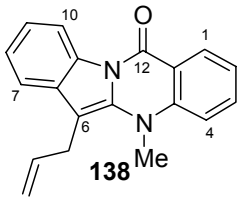
Prepared from 5,6-dihydro-6-methylindolo[2,3-*b*]quinolin-11-one (**131**) (7.80 g, 31.4 mmol) and $POCl_3$ (70 ml), with a reaction time of 1 hour, using general method C. Following isolation by extracting into CH_2Cl_2, the crude product was purified by flash chromatography (80% to 100% EtOAc/hexane) to afford the title compound **133** as a bright orange solid (7.80 g, 29.2 mmol, 93%). Mp 182-183 ^{o}C; IR (KBr) ν_{max}: 1632 (m), 1610 (m), 1572 (s), 1523 (s), 1491 (s) , 1438 (s), 1272 (s), 1235 (s), 1193 (w), 1139 (w), 1076 (m), 950 (w), 887 (w), 850 (w), 751 (s), 598 (w), 465 (w) cm^{-1}; MS (ESI) m/z 267 (MH^+, 100); HRMS (ESI) m/z calcd

for $C_{16}H_{12}N_2Cl$ 267.0689 found 267.0688; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42-8.47 (m, 2H, H-10, H-1), 7.72-7.84 (m, 3H, H-7, H-3, H-4), 7.49-7.62 (m, 2H, H-8, H-2), 7.26-7.31 (m, 1H, H-9), 4.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (C), 155.2 (C), 137.1 (C), 136.0 (C), 131.2 (CH), 129.9 (CH), 126.2 (CH), 125.0 (C), 124.1 (CH), 124.0 (C), 122.4 (CH), 120.4 (CH), 119.3 (C), 117.8 (CH), 114.4 (CH), 33.3 (CH_3).

Preparation of 11-methoxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (137) and 6-Allyl-5-methyl-5*H*-indolo[2,1-*b*]quinazolin-12-one (138)



137

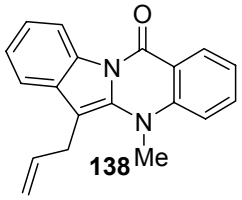


138

11-Allyloxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**129**) (80.0 mg, 0.277 mmol) and MeOH (4.0 ml) were heated at reflux for 19 hours. The reaction mixture was cooled to room temperature and the MeOH was evaporated at reduced pressure. The residue was purified by flash chromatograph and two compounds were isolated. The first, bright yellow crystalline solid, compound to be eluted (25% EtOAc/hexane) was 6-allyl-5-methyl-5*H*-indolo[2,1-*b*]quinazolin-12-one (**138**) (30 mg, 0.104 mmol, 38%). Crystals suitable for X-ray analysis were obtained from MeOH. Mp 160-161 °C; Anal. calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.04; H, 5.54; N, 9.75; IR (KBr) ν_{max}: 1673 (s, C=O), 1618 (s), 1585 (s), 1491 (s), 1463 (m), 1397 (m), 1371 (m), 1253 (w), 1170 (w), 1073 (w), 1020 (w), 912 (m), 879 (m), 775 (w), 738 (s), 684 (w) cm^{-1}; MS (CI) m/z 289 (MH^+, 100); HRMS (CI) m/z calcd for $C_{19}H_{17}N_2O$ 289.1341 found 289.1341; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.72 (m, 1H, H-10), 8.29 (dd, *J* = 7.8, 1.5 Hz, 1H, H-1), 7.57 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H, H-3), 7.34-7.38 (m, 1H, H-7), 7.28 (td, *J* = 7.3, 1.3 Hz, 1H, H-8), 7.18-7.24 (m, 1H, H-9), 7.02-7.12 (m, 2H, H-2, H-4), 6.01-6.14 (ddt, *J* = 16.9, 10.1, 5.1 Hz, 1H, C<u>H</u>=CH_2), 5.13 (dq, *J* = 10.1, 1.7 Hz, 1H, CH=C<u>H</u>$_2$), 5.04 (dq, *J* = 16.9, 1.7 Hz, 1H, CH=C<u>H</u>$_2$), 3.73 (s, 1H, CH_3), 3.69 (dt, *J* = 5.1, 1.7 Hz, 1H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C, C-12), 142.6 (C), 136.8 (CH), 135.6 (C), 134.6 (CH), 131.1 (C), 129.8 (C), 128.7 (CH), 124.2 (CH), 121.5 (CH), 120.4 (CH), 116.3 (CH), 116.14 (CH), 116.09 (CH_2), 114.0 (C), 112.5 (CH), 92.5 (C, C-6), 36.2 (CH_3), 28.8 (CH_2).

The second, orange solid, compound to be eluted (EtOAc) was 11-methoxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**137**) (40 mg, 0.152 mmol, 55%). Spectroscopic data was in accordance with that published in the literature.[53] Mp 183-186 °C (lit.[53] 184-186°C); MS (ESI) m/z 263 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{17}H_{15}N_2O$ 263.1184 found 263.1180; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.0, 0.9 Hz, 1H, H-1), 8.14 (d, *J* = 7.7, 1H, H-10), 7.82-7.71 (m, 3H, H-7, H-3, H-4), 7.54 (ddd, *J* = 8.3, 8.0, 1.0, 1H, H-8), 7.46 (ddd, *J* = 8.0, 6.5, 1.3 Hz, 1H, H-2), 7.27 (ddd, *J* = 8.0, 7.7, 1.0 Hz, 1H, H-9), 4.33 (s, 3H, OCH_3/NCH_3), 4.31 (s, 3H, OCH_3/NCH_3).

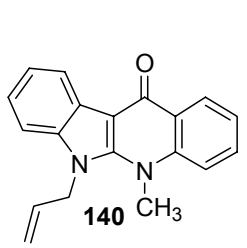
Preparation of 6-allyl-5-methyl-5*H*-indolo[2,1-*b*]quinazolin-12-one (138)



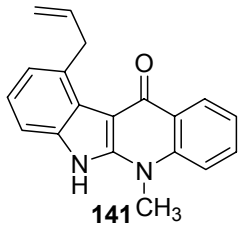
138

5,10b-Dihydro-10b-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (**130**) (25mg, 0.0867 mmol) and MeOH (2.5 ml) were heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and the MeOH was evaporated at reduced pressure to afford the title compound **138** as a bright yellow crystalline solid (25 mg, 0.0867 mmol, 100%). Spectroscopic data was identical to that of **138** prepared by the above procedure.

Preparation of 5,6-dihydro-6-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (140) and 5,6-dihydro-10-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (141)



140



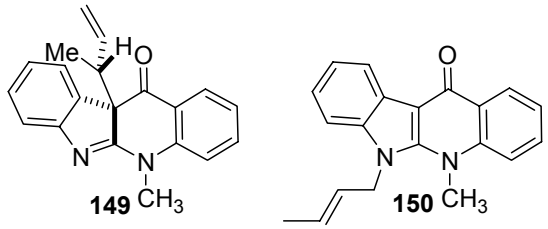
141

5,10b-Dihydro-10b-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (**130**) (200 mg, 0.694 mmol) and PhMe (10 ml) were heated at reflux, under an argon atmosphere, for 4 days. After cooling the reaction mixture to room temperature, the PhMe was evaporated at reduced pressure and the residue was purified by flash chromatography. The first, colourless

crystaline solid, compound to be eluted (1% MeOH/$CHCl_3$) was 5,6-dihydro-6-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (**140**) (143 mg, 0.496 mmol, 72%). Mp 187-188 ^oC; IR (KBr) ν_{max}: 1619 (s, C=O), 1594 (s), 1509 (s) , 1467 (s), 1384 (m), 1311 (m), 1242 (s), 1158 (m), 1125 (m), 1039 (m), 1014 (w), 983 (w), 925 (m), 878 (m), 740 (s), 675 (m), 654 (w), 584 (w), 545 (m), 452 (w) cm^{-1}; MS (EI) m/z 288 (M^+, 12), 247 (42), 86 (66), 84 (100); HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O$ 288.1263 found 288.1268; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 8.0, 1.5 Hz, 1H, H-10), 8.43 (dd, *J* = 8.0, 1.5 Hz, 1H, H-1), 7.49 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, H-3), 7.12-7.30 (m, 4H, H-9 H-8, H-4, H-2), 7.00 (d, *J* = 8.0 Hz, 1H, H-7), 6.05-6.18 (m, 1H, C<u>H</u>=CH_2), 5.30-5.37 (m, 1H, CH=C<u>H</u>$_2$), 5.08-5.17 (m, 1H, CH=C<u>H</u>$_2$), 4.72-4.76 (m, 2H, NCH_2), 3.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C, C-11), 148.5 (C, C-5a), 141.3 (C), 137.5 (C), 132.9 (CH), 131.2 (CH), 126.3 (CH), 125.5 (C), 124.0 (C), 123.5 (CH), 122.6 (CH), 122.4 (CH), 121.3 (CH), 117.9 (CH_2), 115.4 (CH), 109.4 (CH), 105.0 (C), 49.2 (CH_2), 37.1 (CH_3).

The second, colourless crystaline solid, compound to be eluted (2% MeOH/$CHCl_3$) was 5,10b-dihydro-10-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (**141**) (24 mg, 0.0832 mmol, 12%). Mp 270-280 °C (dec.); IR (KBr) ν_{max}: 3052 (br s, N-H), 1617 (s, C=O), 1576 (s), 1546 (s), 1510 (s), 1433 (m), 1380 (m), 1303 (m), 1273 (m), 1217 (w), 1165 (w), 1133 (w), 1057 (w), 997 (w), 911 (w), 875 (m), 787 (w), 753 (s), 708 (w), 625 (w), 490 (w) cm^{-1}; MS (ESI) m/z 311 (MNa^+, 100); HRMS (ESI) m/z calcd for $C_{19}H_{16}N_2ONa$ 311.1160 found 311.1154; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 12.08 (s, 1H, NH), 8.42 (d, *J* = 8.0 Hz, 1H, H-1), 7.70-7.78 (m, 2H, H-4, H-3), 7.36 (ddd, *J* = 8.0, 6.5, 1.0 Hz, 1H, H-2), 7.32 (dd, *J* = 7.5, 1.0 Hz, 1H, H-9), 7.20 (t, *J* = 7.5 Hz, 1H, H-8), 7.00 (d, *J* = 7.5 Hz, 1H, H-7), 6.02-6.12 (m, 1H, C<u>H</u>=CH_2), 4.96-5.02 (m, 1H, CH=C<u>H</u>$_2$), 4.87-4.91 (m, 1H, CH=C<u>H</u>$_2$), 4.52 (d, *J* = 6.5 Hz, 2H, C<u>H</u>$_2$CH=CH_2), 3.96 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ170.7 (C, C-11), 147.3 (C), 140.3 (CH), 138.7 (C), 135.5 (C, C-10), 133.8 (C), 131.2 (CH), 126.5 (CH), 124.9 (C), 123.3 (CH), 123.1 (C), 122.7 (CH), 121.6 (CH), 114.8 (CH), 113.8 (CH_2), 108.7 (CH), 103.1 (C), 39.6 (CH_2), 33.2 (CH_3).

Preparation of rac-(1'*R*,10b*S*)-5,10b-dihydro-10b-(1'-methylallyl)-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (149) and 5,6-dihydro-6-(*E*-but-2-enyl)-5-methylindolo[2,3-*b*]quinolin-11-one (150)

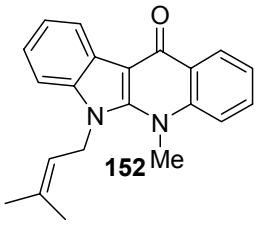


149 **150**

Crude 11-(*E*-but-2-enyloxy)-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**146**) was prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**133**) (200 mg, 0.750mmol) in THF (10 ml), with the alkoxide generated from *trans*-2-butene-1-ol (0.51 ml, 6.01 mmol) and sodium (35 mg, 1.52 mmol) in THF (0.5 ml), using general method D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.2, 1.3 Hz, 1H, H-1), 8.11 (d, *J* = 7.5 Hz, 1H, H-10), 7.72-7.83 (m, 3H, H-7, H-3, H-4), 7.46-7.56 (m, 2H, H-8, H-2), 7.24-7.29 (m, 1H, H-9), 5.91-5.96 (m, 1H, $CH_2C\underline{H}$), 5.66-5.70 (m, 1H, $C\underline{H}CH_3$), 4.89-4.92 (m, 2H, CH_2), 4.35 (s, 3H, NCH_3), 1.76-1.78 (m, 3H $CHC\underline{H}_3$). Crude **145** was dissolved in THF (10 ml) and the mixture was heated at reflux for 2.5 hours. The reaction was cooled to room temperature and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography. The first, bright yellow crystalline solid, compound to be eluted ($CHCl_3$) was rac-(1'*R*,10b*S*)-5,10b-dihydro-10b-(1-methylallyl)-5-methylindolo[2,3-*b*]quinolin-11-one (**149**) (91 mg, 0.301 mmol, 40%). Mp 123-124 ^{o}C (dec.); IR (KBr) ν_{max}: 3080 (w), 2977 (w), 2932 (w), 1698 (s, C=O), 1559 (s), 1470 (s), 1469 (s), 1388 (s), 1342 (w), 1304 (m), 1206 (m), 1194 (m), 1156 (m), 1122 (w), 1066 (m), 1036 (m), 970 (w), 920 (m), 872 (m), 857 (m), 801 (w), 763 (s), 748 (s), 700 (m), 644 (w), 524 (w), 456 (w) cm^{-1}; MS (CI) m/z 303 (MH^+, 68), 249 (100); HRMS (CI) m/z calcd for $C_{20}H_{19}N_2O$ 303.1497 found 303.1488; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.5 1.5 Hz, H-10), 7.58-7.64 (m, 2H, H-1, H-3), 7.33-7.43 (m, 2H, H-7, H-8), 7.10-7.17 (m, 3H, H-9, H-4, H-2), 5.79 (ddd, *J* = 17.0, 10.5, 8.5 Hz, 1H, $C\underline{H}=CH_2$), 5.11 (ddd, *J*=10.5, 1.5, 1.0 Hz, 1H, CH_2), 4.78 (dt, *J* = 17.0, 1.5 Hz, 1H, CH_2), 3.73 (s, 3H, NCH_3), 2.83-2.92 (m, 1H, $C\underline{H}CH_3$), 0.56 (d, *J* = 7.0 Hz, 3H, $CHC\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3 (C, C-11), 172.1 (C), 154.6 (C), 145.2 (C), 136.7 (CH), 135.7 (CH), 130.8 (C), 129.0 (CH), 128.5 (CH), 125.6 (CH), 123.0 (CH), 122.6 (CH), 119.8 (C), 118.5 (CH), 117.7 (CH_2), 114.5 (CH), 70.5 (C, C-10b), 46.3 (CH), 33.2 (CH_3), 14.1 (CH_3).

The second, colourless crystalline solid, compound to be eluted (1% MeOH/$CHCl_3$) was 5,6-dihydro-6-(*E*-but-2-enyl)-5-methylindolo[2,3-*b*]quinolin-11-one (**150**). Mp 165-166 ^oC; Anal. calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.11; H, 5.80; N, 9.15; IR (KBr) ν_{max}: 3053 (w), 2915 (w), 1617 (s, C=O), 1590 (s), 1538 (s), 1506 (s), 1461 (s), 1394 (m), 1362 (m), 1323 (m), 1285 (m), 1262 (m), 1189 (m), 1168 (w), 1125 (m), 1069 (w), 1036 (m), 981 (m), 927 (w), 879 (m), 753 (s), 675 (w), 606 (w), 542 (w), 487 (w), 456 (w) cm^{-1}; MS (CI) m/z 303 (MH^+, 100); HRMS (CI) m/z calcd for $C_{20}H_{19}N_2O$ 303.1497 found 303.1488; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 8.5, 2.0 Hz, 1H, H-1), 8.50 (d, *J* = 7.5, 1H, H-10), 7.52 (ddd, *J* = 8.5, 7.5, 2.0 Hz, 1H, H-3), 7.16-7.32 (m, 4H, H-8, H-4, H-2, H-9), 7.08 (d, *J* = 8.0 Hz, 1H, H-7), 5.69-5.79 (m, 1H, $CH_2C\underline{H}$), 5.54-5.67 (m, 1H, $C\underline{H}CH_3$), 4.68-4.73 (m, 2H, CH_2), 3.90 (s, 3H, NCH_3), 1.72 (dd, *J* = 6.5, 1.5 Hz, 3H, $CHC\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (C, C-11), 148.5 (C, C-5a), 141.4 (C), 137.6 (C), 131.2 (CH), 129.0 (CH), 126.4 (CH), 125.7 (CH), 125.6 (C), 124.1 (C), 123.4 (CH), 122.6 (CH), 122.4 (CH), 121.4 (CH), 115.4 (CH), 109.5 (CH), 105.1 (C), 48.5 (CH_2), 37.3 (CH_3, NCH_3), 17.9 (CH_3, $CH\underline{C}H_3$).

Preparation of 5,6-dihydro-5-methyl-6-(3-methyl-2-butenyl)indolo[2,3-*b*]quinolin-11-one (152)

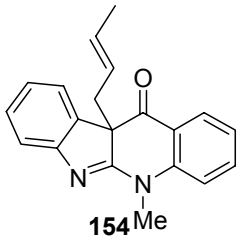


152

Crude 5-methyl-11-(3-methyl-2-butenyloxy)-5*H*-indolo[2,3-*b*]quinoline (**147**) was Prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**133**) (200 mg, 0.750mmol) in THF (10 ml), with the alkoxide generated from 3-methyl-2-butene-1-ol (0.61 ml, 6.09 mmol) and sodium (35 mg, 1.52 mmol) in THF (0.5 ml), using general method D. ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.2, 1.0 Hz, 1H, H-1), 8.15 (d, *J* = 7.3 Hz, 1H, H-10), 7.68-7.77 (m, 3H, H-7, H-3, H-4), 7.40-7.55 (m, 2H, H-8, H-2), 7.20-7.28 (m, 1H, H-9), 5.71-5.77 (m, 1H, $CH_2C\underline{H}$), 4.97 (d, *J* = 7.1, 2H, CH_2), 4.31 (s, 3H, NCH_3), 1.81 (s, 3H, CCH_3), 1.68 (s, 3H, CCH_3). Crude **147** was dissolved in THF (10 ml) and the mixture was heated at reflux for 2.5 hours. The reaction was cooled to room temperature and the solvent was evaporated at

reduced pressure. The residue was purified by flash chromatography (1% MeOH/$CHCl_3$) to afford the title compound **152** as a colourless crystalline solid (208 mg, 0.657, 88%). Mp 220-221 ^oC; Anal. calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.50; H, 6.28; N, 8.78; IR (KBr) ν_{max}: 3057 (w), 2980 (w), 2912 (w), 1621 (s, C=O), 1594 (s), 1539 (s), 1509 (s), 1460 (s), 1389 (w), 1372 (m), 1327 (m), 1264 (m), 1211 (w), 1182 (m), 1155 (w), 1039 (m), 984 (w), 926 (w), 880 (m), 745 (s), 673 (w), 610 (w), 488 (w), 463 (w) cm^{-1}; MS (ESI) m/z 339 (MNa^+, 100); HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2ONa$ 339.1473 found 339.1470; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45-8.50 (m, 2H, H-1, H-10), 7.50 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H, H-3), 7.17-7.30 (m, 4H, H-8, H-4, H-2, H-9), 7.05 (d, *J* = 8.0 Hz, 1H, H-7), 5.30-5.34 (m, 1H, C<u>H</u>$C(CH_3)_2$), 4.66 (d, *J* = 5.0 Hz, 2H, NCH_2), 3.83 (s, 3H, NCH_3), 1.81 (s, 3H, $C(CH_3)_2$), 1.78 (d, *J* = 1.0 Hz, 3H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ173.4 (C, C-11), 148.3 (C, C-5a), 141.4 (C), 137.5 (C), 136.2 (C), 131.1 (CH), 126.4 (CH), 125.5 (C), 124.1 (C), 123.3 (CH), 122.5 (CH), 122.4 (CH), 121.5 (CH), 120.4 (CH), 115.3 (CH), 109.3 (CH), 105.0 (C), 45.7 (CH_2), 37.6 (CH_3), 25.7 (CH_3), 18.6 (CH_3).

Preparation of 5,10b-dihydro-10b-(*E*-but-2-enyl)-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (154)

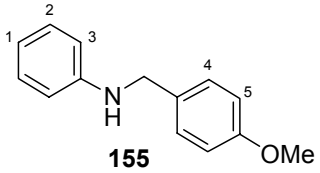


154

Crude 5-methyl-11-(1-methylallyloxy)-5*H*-indolo[2,3-*b*]quinoline (**148**) was prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**133**) (100 mg, 0.375 mmol) in THF (5 ml), with the alkoxide generated from 3-buten-2-ol (0.25 ml, 2.91 mmol) and sodium (20 mg, 0.870 mmol) in THF (0.5 ml), using general method D. ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.4, 1.4 Hz, 1H, H-1), 8.11 (d, *J* = 7.7 Hz, 1H, H-10), 7.69-7.78 (m, 3H, H-7, H-3, H-4), 7.53 (ddd, *J* = 8.2, 7.7, 1.7 Hz, 1H, H-8), 7.42 (ddd, *J* = 8.4, 6.4, 1.6 Hz, 1H, H-2), 7.22-7.27 (m, 1H, H-9), 6.10 (ddd, *J* = 17.2, 10.5, 6.4 Hz, 1H, C<u>H</u>$=CH_2$), 5.32-5.41 (m, 1H, C<u>H</u>CH_3), 5.18 (dt, *J* = 17.2, 1.1 Hz, 1H, CH=C<u>H</u>$_2$), 5.08 (dt, *J* = 10.5, 1.1 Hz, 1H, CH=C<u>H</u>$_2$), 4.33 (s, 3H, NCH_3), 1.60 (d, *J* = 10.4 Hz, 3H, CHC<u>H</u>$_3$). Crude **148** was dissolved in THF and heated at reflux for 2.5 hours under an argon atmosphere. The reaction mixture was cooled

to room temperature and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (10 to 20% EtOAc/hexane) to afford the title compound **154** as a bright yellow crystalline solid (94 mg, 0.311 mmol, 83%). Mp 114-116 ^{o}C; IR (KBr) ν_{max}: 3027 (w), 2936 (w), 1693 (s, C=O), 1559 (s), 1472 (s), 1453 (s), 1387 (m), 1344 (w), 1289 (m), 1204 (m), 1164 (m), 1121 (w), 1054 (w), 1016 (w), 964 (m), 845 (w), 764 (s), 746 (s), 690 (w), 654 (w), 583 (w), 504 (w) cm^{-1}; MS (EI) m/z 302 (M^+, 28), 248 (100), 219 (45); HRMS (EI) m/z calcd for $C_{20}H_{18}N_2O$ 302.1419 found 302.1426; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.5 Hz, 1H, H-1), 7.67 (d, *J* = 7.5 Hz, 1H, H-10), 7.62 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, H-8), 7.14 (d, *J* = 7.5 Hz, 1H, H-4), 7.34 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, H-3), 7.11-7.17 (m, 3H, H-2, H-7, H-9), 5.17-5.29 (m, 1H, C<u>H</u>CH$_3$), 4.96-5.07 (m, 1H, CH$_2$C<u>H</u>), 3.72 (s, 3H, NCH$_3$), 2.72 (dd, *J* = 13.0, 6.5 Hz, 1H, CH$_2$), 2.36 (dd, *J* = 13.0, 8.0 Hz, 1H, CH$_2$), 1.52 (d, *J* = 6.5 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (C, C=O), 172.6 (C), 153.5 (C), 145.4 (C), 135.9 (CH), 133.4 (C), 131.4 (CH), 128.8 (CH), 128.5 (CH), 124.7 (CH), 123.1 (CH), 122.7 (CH), 122.4 (CH), 119.2 (C), 118.6 (C), 114.5 (CH), 66.6 (C, C-10b), 44.4 (CH$_2$), 33.1 (CH$_3$), 18.0 (CH$_3$).

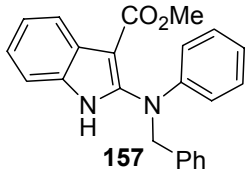
Preparation of *N*-(*p*-methoxybenzyl)aniline (155)[67]



155

$NaBH_4$ (3.78 g, 100 mmol) was added to a stirred solution of (*E*)-*N*-[(4-methoxyphenyl)methylene]benzenamine (**156**) and MeOH (80 ml). After 12 hours, water (20 ml) was added and the MeOH was evaporated at reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 20 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and the CH_2Cl_2 was evaporated at reduced pressure. The residue was crystallised from hexane to afford the title compound **155** as colourless crystals (5.00 g, 23.5 mmol, 93%). Spectroscopic data was in accordance with that published in the literature.[67] Mp 58-60 ^{o}C (lit.[67] 61-62 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.32 (m, 2H, 2 x H-4), 7.14-7.21 (m, 2H, 2 x H-2), 6.86-6.91 (m, 2H, 2 x H-3), 6.72 (tt, *J* = 7.2, 1.0 Hz, 1H, H-1), 6.62 (m, 2H, 2 x H-5), 4.25 (s, 2H, CH_2), 3.94 (br s, 1H, NH), 3.80 (s, 3H, CH_3).

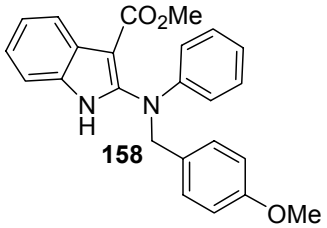
Preparation of 2-(benzylphenylamino)-1*H*-indole-3-carboxylic acid methyl ester (157)



157

Prepared from indole-3-carboxilic acid methyl ester (**111**) (24.8 g, 142 mmol) in CH_2Cl_2 (440 ml) and *N*-benzylaniline (51.9 g, 283 mmol) using general method A. The crude product was crystallised from CH_2Cl_2/hexane to afford the title compound **157** as colourless crystals (33.6 g, 94.3 mmol, 67%). Mp 165-166 ^oC; IR (KBr) ν_{max}: 3270 (br s, N-H), 1669 (s, C=O), 1599 (m), 1543 (s), 1498 (s), 1443 (s), 1421 (m), 1338 (m), 1273 (m), 1212 (s), 1115 (m), 1085 (m), 1061 (m), 1016 (w), 790 (w), 747 (s), 728 (m), 696 (m), 636 (w), 503 (w) cm^{-1}; MS (ESI) m/z 379 (MNa^+, 100); HRMS (ESI) m/z calcd for $C_{23}H_{20}N_2O_2Na$ 379.1422 found 379.1427; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (br s, 1H, NH), 8.11-8.15 (m, 1H, ArH), 7.16-7.37 (m, 10H, 10 x ArH), 6.83-6.91 (m, 3H, 3 x ArH), 5.13 (s, 2H, NCH_2), 3.80 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C), 147.3 (C), 147.2 (C), 138.9 (C), 132.1 (C), 129.4 (2 x CH), 128.9 (2 x CH), 127.3 (CH), 126.99 (2 x CH), 126.81 (C), 123.0 (CH), 122.1 (CH), 121.8 (CH), 120.9 (CH), 116.9 (2 x CH), 110.8 (CH), 98.8 (C), 56.7 (CH_2), 51.0 (CH_3).

Preparation of 2-[(4-methoxybenzyl)phenylamino]-1*H*-indole-3-carboxylic acid methyl ester (158)

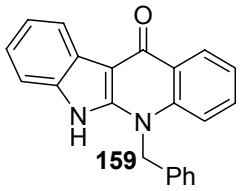


158

Prepared from indole-3-carboxilic acid methyl ester (**111**) (1.88 g, 10.8 mmol) in CH_2Cl_2 (50 ml) and *N*-(*p*-methoxybenzyl)aniline (**155**) (4.59 g, 21.5 mmol) using general method A. The crude product was purified by flash chromatography (5% to 10% EtOAc/hexane) to afford the title compound **158** as colourless crystalline solid (3.54 g, 9.16 mmol, 85%). Mp 158-159 ^oC; IR (KBr) ν_{max}: 3284 (br s, N-H), 2949 (m), 1668 (s, C=O), 1560 (m), 1542 (s), 1499 (s), 1443 (s), 1246 (s), 1124 (s), 944 (m), 878 (m), 870 (m), 748 (s), 693 (s), 633 (m), 504 (w), 436 (w) cm^{-1}; MS (CI) m/z 387 (MH^+, 52), 386 (73), 266 (24), 235 (47), 121 (100); HRMS (CI) m/z calcd for $C_{24}H_{23}N_2O_3$ 387.1709 found 387.1705; ^1H NMR (300 MHz, $CDCl_3$) δ

8.33 (s, 1H, NH), 8.11-8.15 (m, 1H, ArH), 7.15-7.25 (m, 7H, 8 x ArH), 6.77-6.90 (m, 5H, 5 x ArH), 5.04 (s, 2H, CH_2), 3.78 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C), 158.8 (C), 147.3 (C), 132.1 (C), 130.8 (C), 129.4 (2 x CH), 128.3 (2 x CH), 126.8 (C), 122.9 (CH), 122.1 (CH), 121.7 (CH), 120.9 (CH), 117.1 (2 x CH), 114.2 (2 x CH), 110.7 (CH), 98.7 (C), 56.0 (CH_2), 55.4 (CH_3), 51.1 (CH_3).

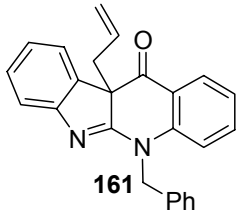
Preparation of 5,6-dihydro-5-benzylindolo[2,3-*b*]quinolin-11-one (159)



159

Prepared from 2-(benzylphenylamino)-1*H*-indole-3-carboxylic acid methyl ester (**157**) (17.0 g, 94.0 mmol) in Ph_2O (150 ml), with a reaction time of 2 hours, using general method B. The title compound **159** was obtained as a light brown micro crystalline solid (25.3 g, 78.0 mmol, 83%). Mp *ca*. 300 ^oC (dec.); IR (KBr) ν_{max}: 3061 (br m N-H), 1609 (s, C=O), 1576 (s), 1514 (s), 1460 (s), 1392 (m), 1242 (m), 1138 (w), 1053 (w), 1021 (w), 871 (w), 751 (m), 730 (m), 682 (m), 623 (m), 533 (m) 447 (w) cm^{-1}; MS (CI) m/z 325 (MH^+, 100), 235 (51); HRMS (CI) m/z calcd for $C_{22}H_{17}N_2O$ 325.1341, found 325.1348; ^1H NMR (400 MHz,$(CD_3)_2SO$) δ 12.25 (s, 1H, NH), 8.41 (dd, *J* = 8.4, 1.3 Hz, 1H, ArH), 8.23-8.26 (m, 1H, ArH), 7.57-7.64 (m, 2H, 2 x ArH), 7.43-7.46 (m, 1H, ArH), 7.16-7.46 (m, 8H, 8 x ArH), 5.81 (s, 2H, CH_2); ^{13}C NMR (101 MHz,$(CD_3)_2SO$) δ 171.7 (C), 147.0 (C), 138.4 (C), 135.8 (C), 134.8 (C), 131.3 (CH), 128.9 (2 x CH), 127.5 (CH), 126.0 (2 x CH), 126.0 (CH), 124.9 (C), 124.1 (C), 122.9 (CH), 121.9 (CH), 121.3 (CH), 120.2 (CH), 115.6 (CH), 110.9 (CH), 102.3 (C), 48.6 (CH_2).

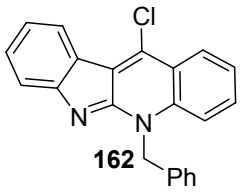
Preparation of 5,10b-dihydro-10b-allyl-5-benzyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (161)



161

A solution of 11-allyloxy-5-benzyl-6*H*-indolo[2,3-*b*]quinoline (**163**) (5.50 g, 15.1 mmol) and PhMe (200 ml) was refluxed under an argon atmosphere for 5.5 hours. After cooling to room temperature, the PhMe was evaporated at reduced pressure and the residue was purified by flash chromatography (10% to 20% EtOAc/hexane) to afford the title compound **161** as a bright yellow crystalline solid (4.82 g, 13.2 mmol, 88%). Crystals suitable for X-ray analysis were obtained from EtOAc/hexane. Mp 137-138 ^{o}C; IR (KBr) ν_{max}: 1692 (m, C=O), 1601 (w), 1558 (s), 1484 (w), 1467 (s), 1452 (m), 1390 (w), 1339 (w), 1293 (w), 1202 (w), 1023 (w), 926 (w) 844 (w), 757 (m), 734 (w), 705 (m) cm^{-1}; MS (EI) m/z 364 (M^+, 23), 323 (100), 273 (20), 178 (22); HRMS (EI) m/z calcd for $C_{25}H_{20}N_2O$ 364.1576, found 364.1570; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.7, 1.7 Hz, 1H, H-1), 7.72 (dd, *J* = 7.4, 1.2 Hz, 1H, H-10), 7.24-7.49 (m, 8H, 8 x ArH), 7.01-7.50 (m, 3H, 3 x ArH), 5.91 (d, *J* = 16.8 Hz, 1H, HCH_2), 5.34-5.48 (m, 1H, C<u>H</u>=CH_2), 5.12 (d, *J* = 16.8 Hz, 1H, HCH_2), 4.99-5.03 (m, 1H, CH=C<u>H</u>$_2$), 4.82-4.89 (m, 1H, CH=C<u>H</u>$_2$), 2.92 (dd, *J* = 13.6, 7.0 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.55 (dd, *J* = 13.6, 7.7 Hz, 1H, C<u>H</u>$_2$CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9 (C, C-11), 172.2 (C), 153.6 (C), 144.8 (C), 136.4 (C), 135.9 (CH), 133.4 (C), 130.3 (CH), 129.1 (2 x CH), 129.0 (CH), 128.5 (CH), 127.7 (CH), 126.8 (2 x CH), 124.8 (CH), 123.4 (CH), 122.7 (CH), 120.5 (CH_2), 119.3 (C), 118.9 (CH), 115.6 (CH), 66.2 (C, C-10b), 49.7 (CH_2), 45.1 (CH_2).

Preparation of 11-chloro-5-benzyl-5*H*-indolo[2,3-*b*]quinoline (162)

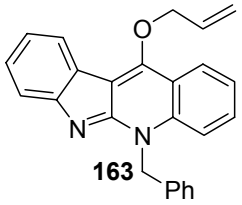


162

Prepared from 5,6-dihydro-6-benzylindolo[2,3-*b*]quinolin-11-one (**159**) (6.84 g, 21.1 mmol) and $POCl_3$ (100 ml), with a reaction time of 1 hour, using general method C. Following

isolation by extracting into CH_2Cl_2, the crude product was purified by flash chromatography (50% to 100% EtOAc/hexane) to afford the title compound **162** as a bright orange solid (6.58 g, 19.2 mmol, 91%). Mp 220-222 ^oC; IR (KBr) ν_{max}: 2920 (w), 1632 (m), 1611 (m), 1560 (s), 1523 (s), 1492 (s), 1438 (s), 1397 (m), 1267 (m), 1233 (m), 1141 (w), 1088 (w), 964 (w), 944 (w), 851 (w), 751 (s), 699 (m) cm^{-1}; MS (CI) m/z 343 (MH^+, 100), HRMS (CI) m/z calcd for $C_{22}H_{16}N_2{}^{35}Cl$ 343.1002, found 343.0998; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.7 Hz, 1H, ArH), 8.41 (d, *J* = 8.3 Hz, 1H, ArH), 7.73 (d, *J* = 8.0 Hz, 1H, ArH), 7.56-7.64 (m, 3H, 3 x ArH), 7.41-7.46 (m, 1H, ArH), 7.17-7.32 (m, 6H, 6 x ArH), 6.15 (s, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C), 155.5 (C), 136.53 (C), 136.45 (C), 135.6 (C), 131.2 (CH), 130.0 (CH), 129.1 (2 x CH), 127.8 (CH), 126.7 (2 x CH), 126.3 (CH), 125.3 (C), 124.4 (C), 124.1 (CH), 122.5 (CH), 120.6 (CH), 119.6 (C), 118.1 (CH), 115.4 (CH), 49.7 (CH_2).

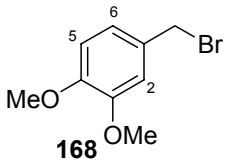
Preparation of 11-allyloxy-5-benzyl-5*H*-indolo[2,3-*b*]quinoline (163)



Prepared from 11-chloro-5-benzyl-5*H*-indolo[2,3-*b*]quinoline (**162**) (6.50 g, 19.0 mmol) in THF (100 ml), with the alkoxide generated from allyl alcohol (45.0 ml, 662 mmol) and sodium (2.18 mg, 94.8 mmol) in THF (20 ml), using general method D. The crude product was purified by flash chromatograph (80% to 100% EtOAc/hexane) to afford the title compound **163** as a dark yellow solid. Mp 147-148 ^oC; IR (KBr) ν_{max}: 1641 (m), 1563 (m), 1516 (s), 1494 (s), 1441 (s), 1407 (w), 1319 (m), 1284 (s), 1239 (s), 1168 (m), 1146 (s), 1100 (m), 970 (w), 931 (m), 751 (s), 695 (w) cm^{-1}; MS (CI) m/z 365 (MH^+, 100), 325 (83); HRMS (CI) m/z calcd for $C_{25}H_{21}N_2O$ 365.1654, found 365.1650; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (ddd, *J* = 7.9, 1.0, 1.0 Hz, 1H, H-1), 8.16 (d, *J* = 7.7 Hz, 1H, H-10), 7.77 (d, *J* = 8.0 Hz, 1H, ArH), 7.61-7.63 (m, 2H, ArH), 7.54 (dd, *J* = 7.4, 8.7 Hz, 1H, ArH), 7.37-7.42 (m, 1H, ArH), 7.20-7.30 (m, 6H, 6 x ArH), 6.29 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H, $OCH_2C\underline{H}$), 6.19 (s, 2H, NCH_2), 5.59 (dq, *J* = 17.2, 1.5 Hz, 1H, $CH{=}C\underline{H_2}$), 5.41 (dq, *J* = 10.5, 1.5 Hz, 1H, $CH{=}C\underline{H_2}$), 5.02 (dt, *J* = 5.6, 1.5 Hz, 1H, OCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 157.0 (C), 154.4 (C), 137.7 (C), 136.0 (C), 133.0 (CH), 131.0 (CH), 129.0 (2 x CH), 128.5 (CH), 127.7

(CH), 126.8 (2 x CH), 124.6 (CH), 123.4 (CH), 123.0 (C), 121.8 (CH), 120.2 (CH), 119.0 (CH_2), 118.5 (C), 118.0 (CH), 116.7 (C), 115.3 (CH), 75.3 (CH_2), 49.5 (CH).

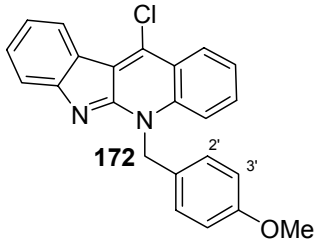
Preparation of 3,4-dimethoxybenzyl bromide (168)[72]



168

A solution of PBr_3 (6.29 ml, 66.6 mmol) and Et_2O (20 ml) was slowly added to a stirred solution of 3,4-dimethoxybenzyl alcohol (**169**) (5.63 g, 33.5 mmol) in Et_2O (50 ml) at 0 °C, maintained under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and, after 12 hours, water (100 ml) was cautiously added. When the vigorous reaction had subsided, the Et_2O was separated and the aqueous phase was further extracted with Et_2O (3 x 50 ml). The Et_2O extracts were combined, dried ($MgSO_4$) and the Et_2O was evaporated at reduced pressure. The residue was crystallised from EtOAc/hexane to afford the title compound **168** as colourless crystals (4.72 g, 20.4 mmol, 61%) Spectroscopic data was in accordance with that published in the literature.[73] Mp: 47-49 °C (lit.[73] 50-51 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6), 6.91 (d, *J* = 2.0 Hz, 1H, H-2), 6.81 (d, *J* = 8.2 Hz, 1H, H-5), 4.51 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3).

Preparation of 11-chloro-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (172)

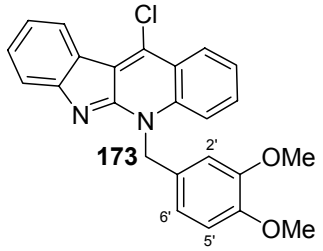


172

Sodium hydride (80 mg of a 60% dispersion in oil, 2.00 mmol) was added to a stirred suspension of 5,6-dihydroindolo[2,3-*b*]quinolin-11-one (**110**) (469 mg, 2.00 mmol) in THF (30 ml), maintained under an argon atmosphere. When effervescence ceased, *p*-methoxybenzyl chloride (0.4 ml, 3.00 mmol) and tetrabutyl ammonium iodide (222 mg, 0.601 mmol) were added and the reaction mixture was stirred at room temperature for 4 days. $NH_4Cl_{(aq)}$ (20 ml) was added and the THF was evaporated at reduced pressure. The residue

was collected by filtration and washed with water (50 ml) and CH_2Cl_2 (100 ml) to afford crude 5,6-dihydro-5-(*p*-methoxybenzyl)indolo[2,3-*b*]quinolin-11-one (**170**) as a colourless solid (420 mg). A portion of crude **170** (150 mg) and $POCl_3$ (4 ml) were heated at reflux for 1.5 hours, under an argon atmosphere. After cooling the reaction mixture to room temperature, the excess $POCl_3$ was evaporated at reduced pressure and $NaHCO_{3(aq)}$ (150 ml) was added to the residue. The aqueous suspension was then extracted with CH_2Cl_2 (3 x 70 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatography (60% to 100% EtOAc/hexane) to afford the title compound **172** as a bright orange solid (120 mg, 0.322 mmol, 76%). Mp 207-208 ^oC; IR (KBr) ν_{max}: 2925 (w), 1631 (W), 1610 (m), 1561 (m), 1515 (s), 1491 (s), 1439 (m), 1397 (w), 1249 (s), 1232 (m), 1178 (w), 1140 (w), 1079 (w) 1031 (w), 816 (w), 748 (s) cm^{-1}; MS (ESI) m/z 395 (MNa^+, 100), 373 (MH^+, 43); HRMS (ESI) m/z calcd for $C_{23}H_{18}N_2O^{35}Cl$ 373.1108, found 373.1108; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.6 Hz, 1H, H-10), 8.41 (d, *J* = 8.3 Hz, 1H, H-1), 7.47 (d, *J* = 8.1 Hz, 1H, H-7), 7.56-7.66 (m, 3H, H-3, H-4, H-8), 7.41-7.47 (m, 1H, H-2), 7.30 (t, *J* = 7.5 Hz, H-9), 7.14-7.19 (m, 2H, 2 x H-2'), 6.75-6.81 (m, 2H, 2 x H-3'), 6.09 (s, 2H, CH_2), 3.72 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C), 155.9 (C), 155.5 (C), 136.5 (C), 131.2 (CH), 129.9 (CH), 128.2 (2 x CH), 127.7 (C), 126.3 (CH), 125.3 (C), 124.3 (C), 124.1 (CH), 122.4 (CH), 120.5 (CH), 119.6 (C), 118.1 (CH), 115.4 (CH), 114.5 (2 x CH), 55.4 (CH_3), 49.2 (CH_2).

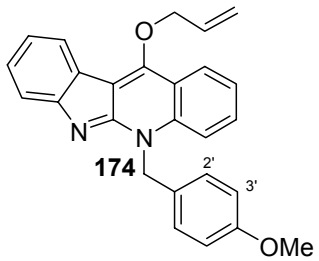
Preparation of 11-chloro-5-(3,4-dimethoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (173)



Sodium hydride (205 mg of a 60% dispersion in oil, 5.12 mmol) was added to a stirred suspension of 5,6-dihydroindolo[2,3-*b*]quinolin-11-one (**110**) (1.00 g, 4.27 mmol) in THF (30 ml), maintained under an argon atmosphere. When effervescence ceased, a solution of 3,4-dimethoxybenzyl bromide (**168**) (1.48 g, 6.40 mmol) and THF (5 ml) was added and the reaction mixture was stirred at room temperature for 24 hours. $NH_4Cl_{(aq)}$ (5 ml) was added and the THF was evaporated at reduced pressure. The residue was washed with water and

was then, after decanting the water, pulverised under Et_2O until a fine powder resulted. The product was collected by filtration and washed with Et_2O to afford crude 5,6-dihydro-5-(3,4-dimethoxybenzyl)indolo[2,3-*b*]quinolin-11-one (**171**) as a light brown solid (1.50 g). A portion of crude **161** (500 mg) and $POCl_3$ (5 ml) were heated at reflux for 1.5 hours, under an argon atmosphere. After allowing the reaction mixture to cool to room temperature, the excess $POCl_3$ was evaporated at reduced pressure and $NaHCO_{3(aq)}$ (30 ml) was added to the residue. The aqueous suspension was extracted with CH_2Cl_2 (3 x 30 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatography (80% to 100% EtOAc) to afford the title compound **173** as a bright orange solid (340 mg, 0.844 mmol, 59%). Mp 217-218 ^oC; IR (KBr) ν_{max}: 1637 (w), 1608 (w), 1561 (m), 1519 (s), 1491 (m), 1438 (m), 1283 (m), 1262 (m), 1231 (m), 1141 (m), 1077 (w), 1026 (w), 754 (m) cm^{-1}; MS (ESI) m/z 403 (MH^+, 100), 151 (26) HRMS (ESI) m/z calcd for $C_{25}H_{20}N_2O_2{}^{35}Cl$ 403.1213, found 403.1201; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.6 Hz, 1H, H-10), 8.43 (d, *J* = 8.0 Hz, 1H, H-1), 7.75 (d, *J* = 7.6 Hz, 1H, H-7), 7.65-7.70 (m, 2H, H-3, H-4), 7.59 (td, *J* = 7.6, 1.2 Hz, 1H, H-8), 7.46 (ddd, *J* = 8.0, 6.0, 2.3 Hz, 1H, H-2), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H, H-9), 6.90 (d, *J* = 1.3 Hz, 1H, H-2'), 6.68-6.75 (m, 2H, H-5', H-6'), 6.10 (s, 2H, CH_2), 3.80 (s, 3H, CH_3), 3.74 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C), 155.5 (C), 149.6 (C), 148.7 (C), 136.6 (C), 136.5 (C), 131.2 (CH), 129.9 (CH), 128.2 (C), 126.3 (CH), 125.3 (C), 124.3 (C), 124.1 (CH), 122.5 (CH), 120.6 (CH), 119.6 (C), 119.1 (CH), 118.1 (CH), 115.4 (CH), 111.5 (CH), 110.3 (CH), 56.1 (CH_3), 56.0 (CH_3), 49.6 (CH_2).

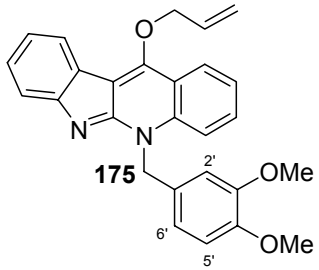
Preparation of 11-allyloxy-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (174)



Prepared from 11-chloro-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (**172**) (110 mg, 0.300 mmol) in THF (5 ml), with the alkoxide generated from allyl alcohol (0.70 ml, 10.5 mmol) and sodium (35 mg, 1.50 mmol) in THF (5 ml), using general method D. The crude product was purified by flash chromatograph (60% to 80% EtOAc/hexane) to afford the title

compound **174** as a dark yellow solid (110 g, 0.279 mmol, 93%). Mp 133-134 ^{o}C; IR (KBr) ν_{max}: 1643 (s), 1561 (s), 1513 (s), 1251 (s), 1033 (m), 875 (w), 751 (s), 466 (m) cm^{-1}; MS (CI) m/z 395 (MH^+, 100), 275 (100), 235 (94), 121 (99); HRMS (CI) m/z calcd for $C_{26}H_{23}N_2O_2$ 395.1760, found 395.1761; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4, Hz, 1H, H-1), 8.14 (d, *J* = 7.9 Hz, 1H, H-10), 7.78 (d, *J* = 8.4 Hz, 1H, H-7), 7.50-7.62 (m, 3H, H-3, H-4, H-8), 7.13-7.39 (m, 4H, H-2, H-9, 2 x H-2'), 6.74-6.78 (m, 2H, 2 x H-3'), 6.26 (ddt, *J* = 17.0, 10.5, 1.5, 1H, C<u>H</u>=CH_2), 6.09 (s, 2H, NCH_2), 5.56 (dq, *J* = 17.0, 1.3 Hz, 1H, CH=C<u>H</u>$_2$), 5.38 (dq, *J* = 10.5, 1.3 Hz, 1H, CH=C<u>H</u>$_2$), 4.98 (dt, *J* = 5.7, 1.3 Hz, 2H, OCH_2), 3.69 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (C), 158.9 (C), 156.9 (C), 154.3 (C), 137.7 (C), 133.0 (CH), 130.9 (CH), 128.5 (CH), 128.2 (2 x CH), 128.1 (C), 124.5 (CH), 123.3 (CH), 122.9 (C), 121.7 (CH), 120.2 (CH), 118.9 (CH_2), 118.4 (C), 117.9 (CH), 116.7 (C), 115.3 (CH), 114.3 (2 x CH), 75.3 (CH_2), 55.3 (CH_3), 48.9 (CH_2).

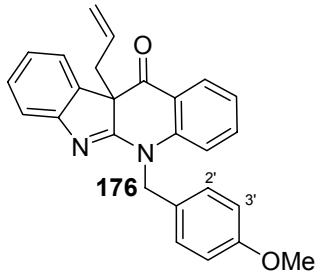
Preparation of 11-allyloxy-5-(3,4-dimethoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (175)



Prepared from 11-chloro-5-(3,4-dimethoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (**173**) (320 mg, 0.794 mmol) in THF (15 ml), with the alkoxide generated from allyl alcohol (1.90 ml, 27.9 mmol) and sodium (91 mg, 3.79 mmol) in THF (5 ml), using general method D. The crude product was purified by flash chromatograph (60% to 80% EtOAc/hexane) to afford the title compound **175** as a dark yellow solid (316 g, 0.744 mmol, 94%). Mp 146-148 ^{o}C; IR (KBr) ν_{max}: 2935 (w), 1639 (m), 1613 (m), 1565 (s), 1516 (s), 1493 (s), 1439 (s), 1346 (m), 1314 (m), 1285 (s), 1238 (s), 1201 (m), 1140 (s), 1099 (m), 1028 (s), 936 (w), 757 (s), 467 (w) cm^{-1}; MS (ESI) m/z 425 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3$ 425.1865, found 425.1876; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.2 Hz, 1H, H-1), 8.15 (d, *J* = 7.5 Hz, 1H, H-10), 7.78 (d, *J* = 7.5 Hz, 1H, H-7), 7.61-7.71 (m, 2H, H-3, H-4), 7.56 (td, *J* = 7.5, 1.2 Hz, 1H, H-8), 7.40 (ddd, *J* = 8.2, 6.5, 1.6 Hz, 1H, H-2), 7.30 (td, *J* = 7.5, 1.0, 1H, H-9), 6.90 (s, 1H, H-2'), 6.72-6.74 (m, 2H, H-5', H-6'), 6.28 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H, C<u>H</u>=CH_2),

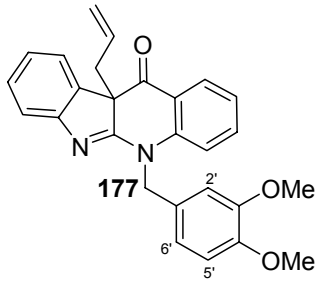
6.11 (s, 2H, NCH_2), 5.57 (dq, *J* = 17.2, 1.3, 1.3 Hz, 1H, CH=C$\underline{H}_2$), 5.40 (dq, *J* = 10.5, 1.3, 1.3 Hz, 1H, CH=C$\underline{H}_2$), 5.01 (dt, *J* = 5.6, 1.3 Hz, 1H, OCH_2), 3.80 (s, 3H, CH_3), 3.74 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (C), 157.0 (C), 154.4 (C), 149.5 (C), 148.6 (C), 137.8 (C), 133.0 (CH), 131.0 (CH), 128.6 (C), 128.5 (CH), 124.6 (CH), 123.3 (CH), 123.0 (C), 121.8 (CH), 120.2 (CH), 119.1 (CH), 119.0 (CH_2), 118.4 (C), 118.0 (CH), 116.8 (C), 115.4 (CH), 111.4 (CH), 110.4 (CH), 75.3 (CH_2), 56.1 (CH_3), 56.0 (CH_3), 49.3 (CH_2).

Preparation of 5,10b-dihydro-10b-allyl-5-(*p*-methoxybenzyl)-10b*H*-indolo[2,3-*b*]quinolin-11-one (176)



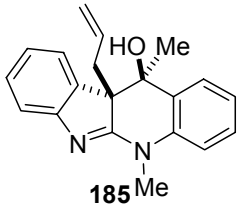
A mixture of 11-allyloxy-5-(*p*-methoxybenzyl)-5*H*-indolo[2,3-*b*]quinoline (**174**) (110 mg, 0.279 mmol) and THF (10 ml) was heated at reflux for 4 days, under an argon atmosphere, and was then cooled to room temperature. The THF was evaporated at reduced pressure and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford the title compound **176** as a bright yellow crystalline solid (66 mg, 0.167 mmol, 60%) Mp 121-122 ^{o}C; IR (KBr) ν_{max}: 2959 (w), 1691 (s), 1455 (s), 1470 (s), 1249 (s), 1024 (m), 928 (m), 846 (m), 760 (s), 506 (m) cm^{-1}; MS (CI) m/z 395 (MH^+, 48), 275 (75), 235 (55), 121 (100); HRMS (CI) m/z calcd for $C_{26}H_{23}N_2O_2$ 395.1760, found 395.1752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.6 Hz, H-1), 7.70-7.73 (m, 1H, H-10), 7.28-7.51 (m, 5H, H-3, H-7, H-8, 2 x H-3'), 7.06-7.19 (m, 3H, H-4, H-9, H-2), 6.84-6.89 (m, 2H, 2 x H-3'), 5.80 (d, *J* = 16.2 Hz, 2H, NCH_2), 5.33-5.47 (m, 1H, C$\underline{H}$=CH_2), 5.10 (d, *J* = 16.2 Hz, 2H, NCH_2), 4.99-5.03 (m, 1H, CH=C$\underline{H}_2$), 4.81-4.88 (m, 1H, CH=C$\underline{H}_2$), 3.78 (s, 3H, CH_3), 2.90 (dd, *J* = 13.1, 6.7 Hz, 1H, C$\underline{H}_2$CH=CH_2), 2.53 (dd, *J* = 13.1, 7.8 Hz, 1H, C$\underline{H}_2$CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (C, C-11), 172.3 (C), 159.2 (C), 153.7 (C), 144.8 (C), 135.8 (CH), 133.4 (C), 130.3 (CH), 129.0 (CH), 128.5 (CH), 128.3 (C), 128.2 (2 x CH), 124.8 (CH), 123.3 (CH), 122.6 (CH), 120.5 (CH_2), 119.3 (C), 118.9 (CH), 115.6 (CH), 114.5 (2 x CH), 66.2 (C, C-10b), 55.5 (CH_3), 49.2 (CH_2), 45.1 (CH_2).

Preparation of 5,10b-dihydro-10b-allyl-5-(3,4-dimethoxybenzyl)-10b*H*-indolo[2,3-*b*]quinolin-11-one (177)



A solution of 11-allyloxy-5-(3,4-dimethoxybenzyl)-6*H*-indolo[2,3-*b*]quinoline (**175**) (290 mg, 0.683 mmol) and PhMe (20 ml) was refluxed under an argon atmosphere for 5 hours. After cooling to room temperature, the PhMe was evaporated at reduced pressure and the residue was purified by flash chromatography (10% to 20% EtOAc/hexane) to afford the title compound **177** as a bright yellow crystalline solid (211 mg, 0.497 mmol, 73%). Mp 132-135 ^{o}C; IR (KBr) ν_{max}: 2936, (w), 1693 (s, C=O), 1594 (m), 1557 (s), 1516 (s), 1470 (s), 1390 (m), 1257 (s), 1140 (m), 1140 (m), 1026 (m), 927 (w), 851 (w), 761 (s), 702 (w) cm^{-1}; MS (ESI) m/z 447 (MNa^+, 100), 425 (MH^+, 12); HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3$ 425.1865, found 425.1862; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.8 Hz, 1H, H-1), 7.72 (d, *J* = 7.4 Hz, 1H, H-10), 7.49 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H, H-3), 7.42 (d, *J* = 7.5 Hz, 1H, H-7), 7.35 (td, *J* = 7.5, 1.3 Hz, 1H, H-8), 7.07-7.20 (m, 3H, H-4, H-9, H-2), 6.89-6.96 (m, 2H, H-2', H-6'), 6.82 (d, *J* = 8.2, 1H, H-5'), 5.83 (d, *J* = 16.5, 1H, NCH_2), 5.36-5.51 (m, 1H, C<u>H</u>=CH_2), 5.07 (d, *J* = 16.5 Hz, 1H, NCH_2), 4.98-5.03 (m, 1H, CH=C<u>H</u>$_2$), 4.80-4.88 (m, 1H, CH=C<u>H</u>$_2$), 3.85 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 2.91 (dd, *J* = 13.0, 7.1 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.53 (dd, *J* = 13.0, 7.4, 1H, C<u>H</u>$_2$CH=CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9 (C, C-11), 172.2 (C), 153.6 (C), 149.6 (C), 148.6 (C), 144.8 (C), 135.9 (CH), 133.3 (C), 130.2 (CH), 129.0 (CH), 128.8 (C), 128.5 (CH), 124.9 (CH), 123.4 (CH), 122.7 (CH), 120.5 (CH_2), 119.2 (C), 119.0 (CH), 118.9 (CH), 115.6 (CH), 111.5 (CH), 110.2 (CH), 66.2 (C, C-10b), 56.1 (2 x CH_3), 49.5 (CH_2), 45.0 (CH_2).

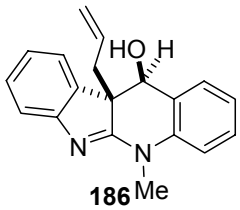
Preparation of rac-(10b*S*,11*S*)-10b-allyl-5,11-dimethyl-5,11-dihydro-10b*H*-indolo[2,3-b]quinoline-11-ol (185)



185

MeLi (0.20 ml of a 1.6 M solution in Et_2O, 0.320 mmol) was added to a solution of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**130**) (46 mg, 0.160 mmol) and Et_2O (1 ml) cooled to 0 ºC, maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm to room temperature and $NH_4Cl_{(aq)}$ (0.5 ml) was added. The Et_2O was separated and the aqueous phase was further extracted with Et_2O (3 x 5 ml). The Et_2O extracts were combined, dried ($MgSO_4$), and the Et_2O was evaporated at reduced pressure to afford the title compound **185** as colourless crystalline solid (49 mg, 0.160 mmol, 100%). Mp 94-95 ^oC; IR (KBr) ν_{max}: 3241 (br m, O-H), 2974 (m), 1554 (s), 1470 (m), 1402 (m), 1293 (w), 1201 (m), 1154 (m), 1123 (m), 1075 (w), 927 (m), 814 (w), 759 (s), 679 (w), 658 (w), 505 (w) cm^{-1}; MS (CI) m/z 305 (MH^+, 96), 304 (M^+, 100), 263 (33); HRMS (CI) m/z calcd for $C_{20}H_{21}N_2O$ 305.1654 found 305.1641; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.5, 1.3 Hz, 1H, H-1), 7.40 (d, *J* = 7.3 Hz, 1H, H-10), 7.24-7.34 (m, 3H, H-3, H-7, H-8), 7.11 (ddd, *J* = 8.5, 7.5, 1.3 Hz, 1H, H-2), 6.98-7.05 (m, 2H, H-4, H-9), 5.19-7.05 (m, 1H, C<u>H</u>=CH_2), 4.73-4.82 (m, 2H, CH=C<u>H_2</u>), 3.59 (s, 3H, NCH_3), 7.27 (dd, *J* = 13.5, 7.1 Hz, 1H, C<u>H_2</u>CH=CH_2), 2.45 (dd, *J* = 13.5, 7.4 Hz, 1H, C<u>H_2</u>CH=CH_2), 2.34 (s, 1H, OH), 1.18 (s, 3H, CC<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 156.2 (C), 139.3 (C), 135.8 (C), 133.2 (CH), 131.9 (C), 128.9 (CH), 128.8 (CH), 124.8 (CH), 123.4 (CH), 122.9 (CH), 122.7 (CH), 118.5 (CH_2), 117.5 (CH), 114.2 (CH), 76.1 (C, C-11), 61.0 (C, C-10b), 36.6 (CH_2), 32.7 (CH_3), 26.5 (CH_3).

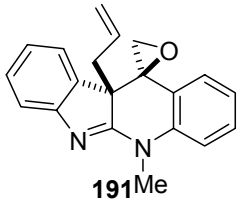
Preparation of rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,3-b]quinoline-11-ol (186)



186

$NaBH_4$ (164 mg, 4.34 mmol) was added to a solution of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**130**) (250 mg, 0.867 mmol) and MeOH (10 ml). After 2 hours, water (2 ml) was added and the MeOH was evaporated at reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 5 ml). The combined extracts were dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatography (10% to 20% EtOAc/hexane) the afford the title compound **186** as a colourless crystalline solid (224 mg, 0.771 mmol, 89%). Crystals suitable for X-ray analysis were obtained from EtOH. Mp 181-182 ^oC; IR (KBr) ν_{max}: 3416 (m, br, O-H), 3076 (m), 1557 (s), 1491 (s), 1468 (m), 1455 (s), 1399 (s), 1339 (m), 1305 (m), 1214 (m), 1189 (m), 1125 (m), 1056 (m), 1015 (m), 912 (m), 841 (w), 754 (s) 694 (m), 659 (w), 501 (w), 488 (w), 434 (w) cm^{-1}; MS (CI) m/z 291 (MH^+, 100), 273 (27), 249 (31), 233 (22); HRMS (CI) m/z calcd for $C_{19}H_{19}N_2O$ 291.1497, found 291.1496; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 7.6, 1.3, 1.0 Hz, 1H, H-1), 7.47 (d, *J* = 7.3 Hz, 1H, H-10), 7.24-7.38 (m, 3H, H-3, H-7, H-8), 7.13 (td, *J* = 7.6, 1.0 Hz, 1H, H-2), 6.99-7.05 (m, 2H, H-4, H-9), 5.12-5.26 (m, 1H, C<u>H</u>=CH_2), 4.98 (d, *J* = 7.3 Hz, 1H, C<u>H</u>OH), 4.71-4.78 (m, 2H, CH=C<u>H_2</u>), 3.57 (s, 3H, CH_3), 2.94 (d, *J* = 7.3 Hz, 1H, OH), 2.63 (dd, *J* = 13.7, 7.1 Hz, 1H, CCH_2), 2.32 (dd, *J* = 13.7, 7.7 Hz, 1H, CCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C), 155.8 (C), 140.1 (C), 137.2 (C), 132.7 (CH), 128.94 (CH), 128.87 (CH), 126.7 (C), 125.8 (CH), 123.1 (CH), 123.0 (CH), 122.6 (CH), 118.5 (CH_2), 117.5 (CH), 114.3 (CH), 72.1 (CH, C-11), 57.0 (C, C-10b), 33.6 (CH_2), 32.9 (CH_3).

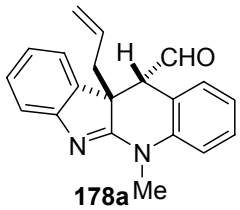
Preparation of rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinolin-11-spiro-2'-oxirane (191)



191

MeLi-LiBr (15.0 ml of a 1.5 M solution, 22.5 mmol) was slowly added, over a period of 20 minutes, to a mixture of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**130**) (5.40 g, 18.7 mmol), chloroiodomethane (1.70 ml, 23.9 mmol) and THF (75 ml) at -78 °C, maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm the room temperature and stirring was continued for 12 hours. $NH_4Cl_{(aq)}$ was added and the solvent was evaporated at reduced pressure. Water (40 ml) and Et_2O (40 ml) were added to the residue. The Et_2O was separated and the aqueous phase was further extracted with Et_2O (3 x 40 ml). The combined Et_2O extracts were dried ($MgSO_4$) and filtered through a plug of silica. The Et_2O solution of the crude product was then placed in an open flask and allowed to slowly evaporate at ambient temperature and pressure until nearly dry (*ca*. 10 ml Et_2O remaining). There was thus obtained the title compound **191** as large colourless crystals (4.98 g, 16.5 mmol, 88%). Crystals form Et_2O were suitable for X-ray analysis. Mp 119-120 ^oC; IR (KBr) ν_{max}: 3062 (w), 2988 (w), 1558 (s), 1493 (s), 1470 (s), 1451 (s), 1398 (s), 1298 (m), 1212 (s), 1124 (m), 1040 (m), 1016 (m), 961 (w), 918 (m), 899 (m), 845 (w), 755 (s), 663 (m), 634 (w), 501 (w) cm^{-1}; MS (ESI) m/z 303 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{20}H_{19}N_2O$ 303.1497, found 303.1492; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.40 (m, 5H, 5 x ArH), 6.97-7.11 (m, 3H, 3 x ArH), 5.18-5.32 (m, 1H, C<u>H</u>=CH_2), 4.73-4.85 (m, 2H, CH=C<u>H</u>$_2$), 3.64 (s, 3H, CH_3), 3.06 (d, *J* = 5.5 Hz, 1H, OCH_2), 2.75 (dd, *J* = 13.0, 6.5 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.57 (dd, *J* = 13.5, 8.0 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.51 (d, *J* = 5.5 Hz, 1H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 155.6 (C), 141.7 (C), 134.2 (C), 132.0 (CH), 129.6 (CH), 129.0 (CH), 124.0 (CH), 123.3 (C), 123.2 (CH), 122.9 (2 x CH), 118.8 (CH_2), 118.0 (CH), 114.2 (CH), 60.3 (C, C-11), 55.0 (C, C-10b), 53.8 (CH_2 (signal inverted in PENDANT spectrum)), 38.4 (CH_2), 32.9 (CH_3).

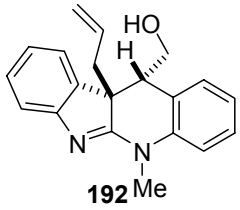
Preparation of rac-(10b*R*,11*R*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carbaldehyde (178a)



178a

F_3BOEt_2 (0.84 ml, 6.69 mmol) was slowly added, over a period of 0.5 hours, to a solution of rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinolin-11-spiro-2'-oxirane (**191**) (400 mg, 1.32 mmol) in THF (10 ml) at -25 °C under an argon atmosphere. After 3 hours, $NH_{3(g)}$ was bubbled into the reaction mixture for 5 minutes and then water (5 ml) was added. The THF was evaporated at reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3 x 5 ml). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatograph (10% to 25% EtOAc/hexane) to afford an impure sample of the title compound **178a** as a colourless oil that rapidly turned black (82 mg). IR (film) ν_{max}: 3075 (w), 298 (w), 1723 (s, C=O), 1617 (w), 1558 (s), 1493 (m), 1471 (s), 1454 (s), 1400 (m), 1297 (w), 1214 (m), 1133 (w), 925 (w), 954 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, *J* = 4.2 Hz, 1H, CHO), 7.19-7.42 (m, 5H, 5 x ArH), 7.00-7.15 (m, 3H, 3 x ArH), 5.41-5.56 (m, 1H, C<u>H</u>=CH_2), 5.02-5.07 (m, 1H, CH=C<u>H</u>$_2$), 4.79-4.86 (m, 1H, CH=C<u>H</u>$_2$), 3.98 (d, *J* = 4.2 Hz, 1H, C<u>H</u>CHO), 3.66 (s, 3H, CH_3), 2.47 (dd, *J* = 13.5, 8.2 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.34 (dd, *J* = 13.5, 6.9 Hz, 1H, C<u>H</u>$_2$CH=CH_2).

Preparation of rac-(10b*R*,11*R*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline (192)

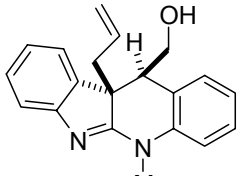


192

A sample of impure rac-(10b*R*,11*R*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carbaldehyde (**178a**) (7 mg) was dissolved in MeOH (0.5 ml) and $NaBH_4$ (5 mg, 0.132 mmol) was added. After 2 hours, water (0.5 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 1 ml). The combined extracts were dried ($MgSO_4$) and the

solvent was evaporated at reduced pressure to give the title compound **192** as a colourless solid (7 mg). A crystal suitable for X-ray analysis was obtained from $CDCl_3$/hexane. IR (film) ν_{max}: 3192 (br s, O-H), 1556 (s), 1493 (s), 1469 (s), 1455 (s), 1403 (m), 1219 (m), 1132 (w), 1063 (m), 922 (w), 753 (s), 737 (s), cm^{-1}; MS (CI) m/z 304 (M^+, 100), 233 (68); HRMS (CI) m/z calcd for $C_{20}H_{20}N_2O$ 304.1576, found 304.1577; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.36 (m, 5H, 5 x ArH), 6.99-7.08 (m, 3H, 3 x ArH), 5.38-5.52 (m, 1H, C<u>H</u>=CH_2), 4.94-4.98 (m, 1H, CH=C<u>H</u>$_2$), 4.74-4.81 (m, 1H, CH=C<u>H</u>$_2$), 3.61 (s, 3H, CH_3), 3.51 (dd, *J* = 14.2, 8.4 Hz, 1H, C<u>H</u>$_2$OH), 3.31-3.39 (m, 2H, C<u>H</u>C<u>H</u>$_2$OH), 2.47 (dd, *J* = 13.4, 7.8 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.25 (dd, *J* = 13.4, 7.2 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 1.70 (m, 1H, OH).

Preparation of rac-(10b*R*,11*S*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline (195)

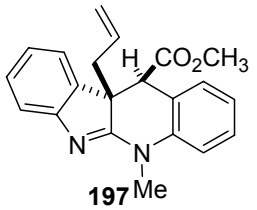


195

A stirred mixture of rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinolin-11-spiro-2'-oxirane (**191**) (560 mg, 1.84 mmol) and $NaBH_3CN$ (291 mg, 4.63 mmol) in THF (20 ml), maintained under an argon atmosphere, was cooled to -10 °C. A solution of F_3BOEt_2 (0.51 ml, 4.06 mmol) in THF (5 ml) was added over a period of 20 min. After 2 hours, an additional portion of F_3BOEt_2 (0.12 ml, 0.955 mmol) in THF (1 ml) was added and stirring was continued for 1 hour at -10 °C. $NaHCO_{3(aq)}$ (50 ml) was added and the reaction mixture was allowed to warm to room temperature. The aqueous solution was extracted with CH_2Cl_2 (4 x 30 ml), the combined extracts were washed with brine (50 ml), dried ($MgSO_4$), and the CH_2Cl_2 was evaporated at reduced pressure. The residue was crystallised from MeOH/water to afford the title compound **195** as a colourless crystalline solid (196 mg, 0.644 mmol, 35%). Crystals from MeOH were suitable for X-ray analysis. Mp 190-191 ^oC; Anal. calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.99; H, 6.66; N, 9.53; IR (KBr) ν_{max}: 3201 (br s, O-H), 2928 (m), 2876 (m), 1616 (m), 1557 (s), 1495 (s), 1472 (s), 1456 (s), 1401 (s), 1316 (m), 1222 (s), 1139 (w), 1105 (m), 1051 (s), 986 (m), 931 (m), 809 (w), 758 (m) 652 (w), 499 (w) cm^{-1}; MS (CI) m/z 305 (MH^+, 83), 304 (M^+, 100), 233 (54); HRMS (CI) m/z calcd for $C_{20}H_{20}N_2O$ 304.1576, found 304.1569; ^1H NMR

(300 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, H-1), 7.23-7.26 (m, 4H, 4 x ArH), 6.98-7.14 (m, 3H, 3 x ArH), 4.96-5.10 (m, 1H, C<u>H</u>=CH_2), 4.62-4.73 (m, 3H, CH=C<u>H</u>$_2$ and C<u>H</u>$_2$OH), 4.39-4.48 (m, 1H, C<u>H</u>$_2$OH), 3.58 (s, 3H, CH_3), 3.07-3.12 (m, 1H, C<u>H</u>CH_2OH), 2.35-2.38 (m, 2H, C<u>H</u>$_2$CH=CH_2), 2.01 (dd, *J* = 7.5, 3.5, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 156.0 (C), 141.4 (C), 136.7 (C), 132.6 (CH), 128.8 (CH), 128.2 (CH), 127.4 (CH), 125.4 (C), 123.7 (CH), 123.2 (CH), 122.3 (CH), 118.2 (CH_2), 117.4 (CH), 114.6 (CH), 61.7 (CH_2, CH_2OH), 54.3 (C, C-10b), 44.2 (CH, C-11), 35.0 (CH_2), 33.1 (CH_3).

Preparation of rac-(10b*R*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (197)

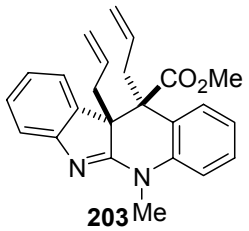


197

A solution of rac-(10b*R*,11*S*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline (**195**) (470 mg, 1.54 mmol) in acetone (20 ml) was added to a stirred mixture of CrO_3 (772 mg, 7.72 mmol) and celite (2.00 g) in 1.5 M H_2SO_4 (10 ml). After 5 hours, *i*-PrOH (2.0 ml, 26 mmol) was added and stirring was continued for 0.5 hours. The reaction mixture was filtered through celite and the celite was washed with EtOAc (50 ml). Brine (50 ml) was added to the filtrate followed by sufficient $NaHCO_{3(aq)}$ to neutralise (pH 7) the aqueous phase. The EtOAc was separated and the aqueous phase was further extracted with EtOAc (4 x 50 ml). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure to afford crude **196**. Crude **196** was dissolved in MeOH (20 ml) and Me_3SiCHN_2 (1.54 ml of a 2.0 M solution in Et_2O, 3.08 mmol) was added. After stirring for 0.5 hours, AcOH (0.5 ml) was added and stirring was continued for an additional 0.5 hours. The solvent was evaporated at reduced pressure and the residue was partitioned between $NaHCO_{3(aq)}$ (10 ml) and CH_2Cl_2 (10 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (5% EtOAc/hexane) to afford the title compound **197** as a colourless crystalline solid (267 mg, 0.803 mmol, 52%). Mp 137-138 ^{o}C; IR (KBr) ν_{max}: 2951 (w), 1740 (s, C=O), 1618 (m), 1560 (s), 1495 (m), 1470 (s), 1400 (m), 1215 (m), 1161

(m), 921 (w), 751 (m) cm^{-1}; MS (ESI) m/z 333 (MH^+, 100), 233 (94); HRMS (ESI) m/z calcd for $C_{21}H_{21}N_2O_2$ 333.1603, found 333.1599; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.38 (m, 3H, 3 x ArH), 6.99-7.12 (m, 4H, 4 x ArH), 4.97-5.11 (m, 1H, C<u>H</u>=CH_2), 4.66-4.76 (m, 2H, CH=C<u>H</u>$_2$), 4.09 (s, 1H, C<u>H</u>CO_2CH_3), 3.94 (s, 3H, OCH_3), 3.61 (s, 3H, NCH_3), 2.87 (dd, *J* = 14.0, 6.5 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.55 (dd, *J* = 14.0, 8.0 Hz, 1H, C<u>H</u>$_2$CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C, C=O), 172.0 (C), 156.0 (C), 141.0 (C), 136.4 (C), 132.4 (CH), 129.2 (CH), 129.0 (CH), 127.5 (CH), 123.0 (CH), 122.7 (CH), 122.4 (CH), 121.2 (C), 118.4 (CH_2), 117.6 (CH), 114.8 (CH), 53.3 (C, C-10b), 52.2 (CH_3), 49.2 (CH, C-11), 34.7 (CH_2), 33.0 (CH_3).

Preparation of rac-(10b*R*,11*S*)-10b,11-diallyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (203)

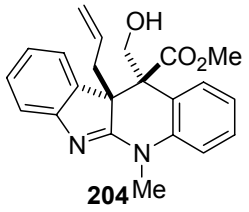


203

LiHMDS (0.36 ml of a 1.0 M solution in THF, 0.36 mmol) was added to a solution of rac-(10b*R*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (**197)** (60 mg, 0.181 mmol) in THF (2 ml) at -78 °C, maintained under an argon atmosphere. The reaction mixture was warmed to 0 °C and then, after 1 hour, cooled to -78 °C. Allyl bromide (0.047 ml, 0.543 mmol) was added and the reaction mixture was slowly warmed to room temperature. After 16 hours, $NH_4Cl_{(aq)}$ (0.3 ml) was added and the THF was evaporated at reduced pressure. The residue was partitioned between water (1 ml) and CH_2Cl_2 (2 ml), the CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 2 ml). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The crude product was purified by flash chromatography (5% to 15% EtOAc/hexane) followed by crystallisation from EtOAc/hexane to afford the title compound **203** as a colourless crystalline solid (39 mg, 0.105 mmol, 59%). Crystals form EtOAc/hexane were suitable for X-ray analysis. Mp 171-173 ^oC; IR (KBr) ν_{max}: 2984 (w), 2955 (w), 1728 (s, C=O), 1617 (m), 1562 (s), 1495 (w), 1468 (m), 1455 (m), 1400 (m), 1316 (w), 1292 (w), 1233 (s), 1220 (s), 935 (w), 759 (s) cm^{-1}; MS (ESI) m/z 373

(MH^+, 100); HRMS (ESI) m/z calcd for $C_{24}H_{25}N_2O_2$ 373.1916, found 373.1907; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.24 (m, 3H, 3 x ArH), 6.97-7.06 (m, 5H, 5 x ArH), 5.32-5.47 (m, 1H, C(10b)CH_2C<u>H</u>), 4.93-5.07 (m, 1H, C(11)CH_2C<u>H</u>), 4.57-4.84 (m, 4H, C(10b)CH_2CH=C<u>H</u>$_2$ and C(11)CH_2CH=C<u>H</u>$_2$), 3.96 (s, 3H, OCH_3), 3.61 (s, 3H, NCH_3), 2.76 (dd, *J* = 13.6, 8.2 Hz, 1H, C(10b)CH_2), 2.63 (dd, *J* = 13.9, 7.0 Hz, 1H, C(11)CH_2), 2.39 (dd, *J* = 13.6, 6.2 Hz, 1H, C(10b)CH_2), 2.03 (dd, *J* = 13.9, 7.0 Hz, 1H, C(11)CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (C, C=O), 171.7 (C), 156.3 (C), 140.0 (C), 134.7 (C), 133.3 (CH), 132.3 (CH), 131.3 (CH), 129.0 (CH), 128.7 (CH), 123.7 (C), 122.9 (CH), 122.6 (CH), 121.9 (CH), 119.0 (CH_2), 118.5, (CH_2), 117.5 (CH), 114.5 (CH), 58.3(C, C-11), 57.1 (C, C-10b), 52.2 (CH_3), 38.5 (CH_2), 38.1 (CH_2), 33.0 (CH_3).

Preparation of rac-(10b*R*,11*S*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (204)

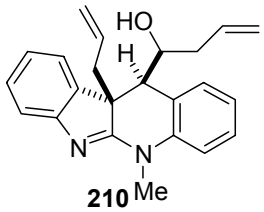


204

n-BuLi (0.27 ml of a 1.46 M solution, 0.394 mmol) was added to a mixture of *i*-Pr_2NH (0.058 ml, 0.412 mmol) and THF (1 ml) at -78 °C, maintained under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and then, after 0.5 hours, was cooled to -78 °C before a solution of rac-(10b*R*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (**197**) (65 mg, 0.196 mmol) in THF (2 ml) was added. The reaction mixture was warmed to -10 °C and after 1 hour formaldehyde, generated by heating paraformaldehyde (59 mg) to 150 °C, was bubbled through the vigorously stirred reaction mixture. The reaction mixture was then allowed to warm to room temperature and was stirred for 1 hour. $NH_4Cl_{(aq)}$ (0.5 ml) was added and the THF was evaporated at reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 4 ml) and the combined CH_2Cl_2 extracts were dried ($MgSO_4$). The CH_2Cl_2 was evaporated at reduced pressure and the residue was purified by flash chromatography (20% to 40% EtOAc/hexane) to afford the title compound **204** as colourless crystals (55 mg, 0.152 mmol, 76%). Crystals suitable for X-ray analysis were obtained from EtOAc/hexane. Mp 202-203 ^{o}C; Anal. calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.92; H, 6.11; N,

7.89; IR (KBr) ν_{max}: 3240 (br m, O-H), 2954 (w), 1733 (s, C=O), 1618 (m), 1561 (s), 1497 (m), 1470 (m), 1455 (m), 1406 (m), 1311 (m), 1235 (s), 1162 (w), 1116 (m), 1066 (m), 923 (w), 805 (w), 760 (s), 731 (m), 643 (w) cm^{-1}; MS (ESI) m/z 385 (MNa^+, 100); HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_3Na$ 385.1528, found 385.1527; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H, ArH), 7.25-7.28 (m, 2H, 2 x ArH), 6.97-7.15 (m, 5H, 5 x ArH), 4.92-5.07 (m, 1H, C<u>H</u>=CH_2), 4.67-4.79 (m, 2H, CH=C<u>H</u>$_2$), 4.01 (s, 3H, OCH_3), 3.91 (dd, *J* = 11.6, 6.6 Hz, 1H, C<u>H</u>$_2$OH), 3.59 (s, 3H, NCH_3), 3.38 (dd, *J* = 11.6, 8.0 Hz, 1H, C<u>H</u>$_2$OH), 2.77 (dd, *J* = 13.6, 7.9 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 2.51 (dd, *J* = 13.6, 6.6 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 1.75 (dd, *J* = 6.6, 8.0 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (C, C=O), 171.5 (C) 155.9 (C), 140.4 (C), 134.3 (C), 131.7 (CH), 131.0 (CH), 129.2 (CH), 129.2 (CH), 122.8 (CH), 122.7 (CH), 122.53 (C), 122.50 (CH), 118.9 (CH_2), 117.7 (CH), 114.8 (CH), 64.3 (CH_2), 58.8 (C, C-11), 55.8 (C, C-10b), 52.6 (CH_3), 38.7 (CH_2), 33.0 (CH_3).

Preparation of rac-(10b*R*,11*S*)-1-(10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-yl)but-3-en-1-ol (210)

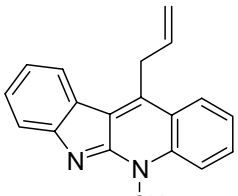


210

Allylmagnesium chloride (0.25 ml of a 2.0 M solution in THF, 0.500 mmol) was added to a solution of rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinolin-11-spiro-2'-oxirane (**191**) (101 mg, 0.334 mmol) in THF (1.5 ml) cooled to -78 °C and maintained under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and, after 3 hours, $NH_4Cl_{(aq)}$ (0.5 ml) was added. The THF was evaporated at reduced pressure and the residue was partitioned between CH_2Cl_2 (5 ml) and water (5ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 5 ml). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatograph (10% EtOAc/hexane) to afford the title compound **210** as a colourless crystalline solid (88 mg, 0.255 mmol, 76%). Mp 182-183 ^oC; IR (KBr) ν_{max}: 3233 (br m), 3076 (w), 2927 (w), 1615 (m), 1557 (s), 1470 (s), 1455 (s), 1400 (s), 1317 (w), 1273 (w), 1215 (s), 1182 (w), 1049 (w), 922 (m), 758 (s), 714 (w) cm^{-1}; MS (ESI) m/z 345 (MH^+, 100); HRMS (ESI) m/z calcd for $C_{23}H_{25}N_2O$

345.1967, found 345.1975; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H, H-1), 7.24-7.35 (m, 4H, 4 x ArH), 7.00-7.10 (m, 3H, 3 x ArH), 5.77-5.91 (m, 1H, $HOCHCH_2C\underline{H}$), 5.18-5.27 (m, 2H, $HOCHCH_2CH=C\underline{H}_2$), 4.97-5.11 (m, 1H, $CCH_2C\underline{H}$), 4.73-4.80 (m, 1H, $C\underline{H}OH$), 4.61-4.71 (m, 2H, $CCH_2CH=C\underline{H}_2$), 3.60 (s, 3H, CH_3), 3.15 (s, 1H, $C\underline{H}CHOH$), 2.85-2.96 (m, 1H, $HOCHC\underline{H}_2$), 2.71 (dd, *J* = 13.9, 6.5 Hz, 1H, 1H, $CC\underline{H}_2$), 2.44-2.55 (m, 2H, $HOCHC\underline{H}_2$ and $CC\underline{H}_2$), 2.07 (d, *J* = 3.6 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 156.8 (C), 142.2 (C), 136.6 (C), 134.8 (CH), 133.2 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 124.2 (CH), 123.5 (C), 122.4 (CH), 122.2 (CH), 119.4 (CH_2), 117.9 (CH_2), 117.4 (CH), 115.3 (CH), 70.6 (CH), 55.9 (C, C-10b), 45.5 (CH, C-11), 42.0 (CH_2), 35.6 (CH_2), 33.2 (CH_3).

Preparation of 11-allyl-5-methyl-5*H*-indolo[2,3-*b*]quinoline (225)

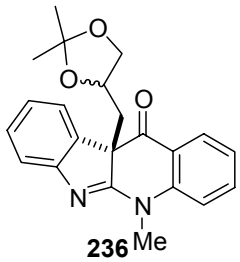


225

t-BuOK (0.83 ml of a 1.0 M solution in *t*-BuOH, 0.830 mmol) was added to a stirred mixture of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**130**) (100 mg, 0.347 mmol), TosMIC (88 mg, 0.451 mmol) and DME (2.5 ml) that was cooled to 0 °C and maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 hour. Water (2 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml). The combined extracts were washed with brine (10 ml) and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (50% to 80% EtOAc/hexane) to afford the title compound **225** as an orange solid (57 mg, 0.209 mmol, 61%). Mp 125-127 ^{o}C; IR (KBr) ν_{max}: 3049 (w), 1627 (s), 1608 (m), 1565 (s), 1525 (s), 1492 (s), 1455 (s), 1418 (s), 1286 (s), 1237 (s), 1173 (m), 1135 (m), 1080 (m), 996 (w), 939 (m), 834 (m), 751 (s), 662 (w), 595 (m), 466 (m) cm^{-1}; MS (EI) m/z 272 (M^+, 100), 255 (20), 84 (46); HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O$ 272.1313, found 272.1317; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.2 Hz, 1H, H-1), 8.08 (d, *J* = 7.5 Hz, 1H, H-10), 7.73-7.78 (m, 3H, H-7, H-3, H-4), 7.54 (t, *J* = 7.5 Hz, 1H, H-8), 7.45-7.49 (m, 1H, H-2), 7.24 (t, *J* = 7.5 Hz, 1H, H-9), 6.19 (ddt, *J* = 16.4, 10.4, 5.6 Hz, 1H, $C\underline{H}=CH_2$), 5.13-5.18 (m, 2H, $CH=C\underline{H}_2$), 4.31-4.35 (m, 5H, CH_3,

$C\underline{H}_2CH=CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C, C-6a), 155.3 (C, C-5a), 141.0 (C, C-11), 137.1 (C, C-4a), 133.3 (CH), 130.4 (CH), 128.9 (CH), 126.0 (CH), 124.3 (C), 123.3 (CH), 122.0 (CH), 120.8 (C), 120.0 (CH), 117.82 (CH_2), 117.79 (CH), 114.7 (CH), 33.3 (CH_3), 33.0 (CH_2).

Preparation of rac-(10b*R*,4'*R*)-10b-(2',2'-dimethyl[1,3]dioxolan-4'-ylmethyl)-5-methyl-5,10b-dihydroindolo[2,3-b]quinolin-11-one and rac-(10b*R*,4'*S*)-10b-(2',2'-dimethyl[1,3]dioxolan-4'-ylmethyl)-5-methyl-5,10b-dihydroindolo[2,3-b]quinolin-11-one



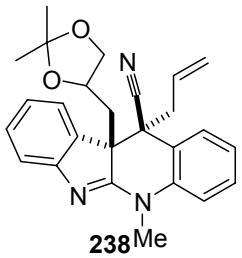
236

Osmium tetroxide (3.26 ml of a 2.5% solution in *t*-BuOH) was added to a vigorously stirred solution of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**130**) (1.50 g, 5.20 mmol) and NMO (1.28 g, 10.9 mmol) in THF/water (9:1, 40 ml). After 24 hours a saturated solution of sodium sulphite (90 ml) was added and stirring was continued for 0.5 hours before the reaction mixture was extracted with CH_2Cl_2 (3 x 150 ml). The combined CH_2Cl_2 extracts were washed with brine (200 ml), dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was triturated with Et_2O and the yellow solids were collected by filtration to afford crude **235** (1.47 g). MS (ESI) m/z 345 (MNa^+, 100). 2,2-dimethoxypropane (9.57 ml, 78.0 mmol) and PPTS (1.31 g, 5.21 mmol) were added to a stirred suspension of crude **235** in CH_2Cl_2 (100 ml), maintained under an argon atmosphere. After 2 days, when all the solids had gone into solution, $NaHCO_{3(aq)}$ (50 ml) was added and the CH_2Cl_2 was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 25 ml). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (5% to 10% EtOAc/hexane) to yield the title compound **236** as a 1:1 mixture of diastereomers (1.32 g, 3.64 mmol, 70%). Whilst complete separation of the diastereomers could not be achieved, small highly enriched samples of each diastereomer could be obtained (122 mg of the less polar isomer and 50 mg of the more polar) by careful flash chromatography.

Less polar isomer (**236a**): IR (film) ν_{max}: 2986 (m), 2937 (w), 1694 (s, C=O), 1563 (s), 1471 (s), 1454 (s), 1387 (m), 1296 (w), 1210 (m), 1156 (m), 1059 (m), 915 (w), 858 (w), 758 (m), 512 (w) cm^{-1}; MS m/z (CI) 363 (MH^+, 100), 261 (20); HRMS (CI) m/z calcd for $C_{22}H_{23}N_2O_3$ 363.1709, found 363.1698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.3 Hz, 1H, H-1), 7.70 (d, *J* = 7.2 Hz 1H, H-10), 7.58 (t, *J* = 7.8 Hz, 1H, H-3), 7.43 (d, *J* = 7.6 Hz, 1H, H-7), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H, H-8), 7.06-7.18 (m, 3H, H-9, H-4, H-2), 3.69 (s, 3H, NCH_3), 3.51-3.58 (m, 1H, OCH), 3.27 (dd, *J* = 8.6, 6.0 Hz 1H, OCH_2), 3.01 (dd, *J* = 8.6, 6.0 Hz 1H, OCH_2), 2.45 (dd, *J* = 13.5, 5.5 Hz 1H, OCH_2), 2.18 (dd, *J* = 13.5, 7.1 Hz 1H, OCH_2), 1.22 (s, 3H, CCH_3), 1.17 (s, 3H, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2 (C, C-11), 172.3 (C), 153.9 (C), 145.4 (C), 136.1 (CH), 132.4 (C), 129.3 (CH), 128.6 (CH), 124.7 (CH), 123.4 (CH), 122.3 (CH), 118.8 (CH), 118.4 (C), 114.5 (CH), 108.4 (C, $\underline{C}Me_2$), 72.0 (CH), 69.3 (CH_2), 64.4 (C, C-10b), 44.6 (CH_2), 33.3 (CH_3), 26.8 (CH_3), 25.6 (CH_3).

More polar isomer (**236b**): IR (film) ν_{max}: 2986 (m), 2937 (w), 1696 (s), 1471 (s), 1454 (m), 1386 (m), 1296 (w), 1209 (m), 1159 (m), 1060 (m), 917 (w), 854 (w), 758 (m), 514 (w) cm^{-1}; MS (CI) m/z 363 (MH^+, 100), 261 (24); HRMS (CI) m/z calcd for $C_{22}H_{23}N_2O_3$ 363.1709, found 363.1700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.3, 1.5 Hz, 1H, H-1), 7.77 (d, *J* = 7.4 Hz, 1H, H-10), 7.61 (td, *J* = 8.0, 1.5 Hz, 1H, H-3), 7.34-7.44 (m, 2H, H-7, H-8), 7.11-7.21 (m, 3H, H-9, H-4, H-2), 3.82-3.91 (m, 2H, OCH, OCH_2), 3.71 (s, 3H, NCH_3), 3.26-3.33 (m, 1H, OCH_2), 2.51 (dd, *J* = 13.5, 5.8 Hz, 1H, CCH_2), 1.88 (dd, *J* = 13.5, 6.1 Hz, 1H, CCH_2), 1.89 (s, 3H, CCH_3), 1.15 (s, 3H, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1 (C, C-11), 173.0 (C), 153.7 (C), 145.0 (C), 135.8 (CH), 133.0 (C), 129.2 (CH), 128.9 (CH), 125.0 (CH), 123.5 (CH), 122.7 (CH), 119.5 (C), 118.9 (CH), 114.6 (CH), 109.0 (C, $\underline{C}$-Me_2), 72.1 (CH), 69.3 (CH_2), 64.6 (C, C-10b), 45.6 (CH_2), 33.3 (CH_3), 26.8 (CH_3), 25.4 (CH_3).

Preparation of rac-(10b*R*,11*S*)-11-allyl-10b-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-5-methyl-5,11-dihydro-10b*H*-indolo[2,3-b]quinolin-11-carbonitrile (238)

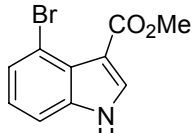


238

t-BuOK (0.73 ml of a 1.0 M solution in *t*-BuOH, 0.730 mmol) was added to a stirred mixture of **236a** (110 mg, 0.304 mmol), TosMIC (77 mg, 0.396 mmol) and DME (2.5 ml), cooled to 0 °C and maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 0.5 hour. Water (2 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml). The combined extracts were washed with brine (10 ml) and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (5% to 10% EtOAc/hexane) to afford a sample that was predominantly **237** as a mixture of diastereomers (* = minor isomer) that could not be separated (59 mg). IR (KBr) ν_{max}: 2985 (m), 2934 (w), 2243 (w, C≡N), 1562 (s), 1496 (s), 1471 (s), 1457 (s), 1401 (m), 1380 (m), 1370 (m), 1300 (w), 1213 (s), 1152 (m), 1060 (m), 857 (w), 830 (w), 756 (s), 650 (w), 510 (w) cm^{-1}; MS (CI) m/z 374 (MH^+, 100), 316 (20); HRMS (CI) m/z calcd for $C_{23}H_{24}N_3O_2$ 374.1869, found 374.1858; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.52 (m, 2H, 2 x ArH, 2 x ArH*), 6.99-7.37 (m, 6H, 6 x ArH, 6 x ArH*), 4.16 (s, 0.75H, CHCN), 4.09 (s, 0.25H, CHCN*), 3.60 (s, 0.75H, NCH_3*), 3.53 (s, 2.25H, NCH_3), 3.32-3.44 (m, 1H, CHO, CHO*), 3.12-3.19 (m, 1H, CH_2O, CH_2O*), 2.98 (dd, *J* = 8.6, 6.5 Hz, 0.75H, CH_2O), 2.89 (dd, *J* = 8.5, 6.5 Hz, 0.75H, CH_2O*), 2.15-2.22 (m, 1H, CCH_2, CCH_2*), 2.02 (dd, *J* = 13.4, 5.6 Hz, 0.75H, CCH_2), 1.69 (dd, *J* = 13.4, 6.3 Hz, 0.25H, CCH_2*), 1.08-1.11 (m, 6H, $C(CH_3)_2$, $C(CH_3)_2$*). This mixture of diastereomers (59 mg) was dissolved in THF (1 ml) and cooled to -78 °C, under an argon atmosphere. LiHMDS (0.24 ml of a 1.0 M solution in THF) was added and the reaction mixture was warmed to 0 °C for 0.5 hours. The orange reaction mixture was then cooled to -78 °C and allyl bromide (27 μl, 0.312 mmol) was added. After stirring -78 °C for 2 hours, the reaction mixture slowly warmed to room temperature and stirred for a further 16 hours. $NH_4Cl_{(aq)}$ (0.5 ml) was added and the solvent was evaporated at reduced pressure. The residue was partitioned between CH_2Cl_2 (1 ml) and water (1 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 1 ml). The combined extracts

were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by chromatography (5% to 10% EtOAc/hexane) to afford the title compound **238** as a colourless oil (43 mg, 0.104 mmol, 34%). IR (film) ν_{max}: 2985 (w), 2934 (w), 2241 (w, C≡N), 1564 (s), 1495 (m), 1470 (m), 1454 (m), 1401 (m), 1211 (m), 1155 (w), 1064 (m), 926 (w), 754 (m), 951 (w) cm^{-1}; MS (EI) m/z 413 (M^+, 70), 314 (44), 257 (100); HRMS (EI) m/z calcd for $C_{26}H_{27}N_3O_2$ 413.2103, found 413.1998; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H, H-10), 7.31-7.43 (m, 4H, 4 x ArH), 7.03-7.12 (m, 3H, 3 x ArH), 5.38-5.49 (m, 1H, C<u>H</u>=CH_2), 5.01-5.05 (m, 1H, CH=C<u>H</u>$_2$), 4.82-4.87 (m, 1H, CH=C<u>H</u>$_2$), 3.61 (s, 3H, NCH_3), 3.43-4.39 (m, 1H, HCO), 3.26 (dd, *J* = 8.5, 6.1 Hz, 1H, CH_2O), 3.06 (dd, *J* = 8.5, 6.6 Hz, 1H, CH_2O), 2.39 (dd, *J*= 13.8, 6.7 Hz, 1H, C<u>H</u>$_2$CHO), 2.24-2.33 (m, 2H, C<u>H</u>$_2$CHO, C<u>H</u>$_2$CH=CH_2), 2.18 (dd, *J* = 13.8, 7.0 Hz, 1H, C<u>H</u>$_2$CH=CH_2), 1.18 (s, 3H, CCH_3), 1.15 (s, 3H, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C), 156.4 (C), 138.8 (C), 133.3 (C), 130.7 (CH), 130.20 (CH), 130.17 (CH), 129.3 (CH), 123.4 (CH), 123.0 (CH), 122.5 (CH), 121.0 (CH_2), 120.5 (C), 119.6 (C), 118.2 (CH), 115.3 (CH), 108.5 (C), 72.2 (CH), 69.6 (CH_2), 55.3 (C, C-10b), 49.5 (C, C-11), 38.9 (CH_2), 38.6 (CH_2), 33.0 (CH_3), 26.9 (CH_3), 25.7 (CH_3).

Preparation of 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (239)



239

Method 1:[100]

A solution of indole-3-carboxylic acid methyl ester (**111**) (2.15 g, 12.3 mmol) and TFA (20 ml) was added to a mixture of thallium trifluoroacetate (10.0 g, 18.4 mmol) and TFA (20 ml), and the reaction mixture was stirred for 2 hours at room temperature. After evaporation of the TFA at reduced pressure, a solution of copper (II) bromide (11 g, 49.2 mmol) in DMF (70 ml) was added to the residue and the reaction mixture was stirred at 120 °C for 1 hour. The reaction mixture was cooled to room temperature and CH_2Cl_2 (100 ml) was added. The insoluble precipitate was removed by filtration through celite and the filtrate was washed with brine (2 x 200 ml), dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatograph (5% to 15% EtOAc/hexane) to afford the title compound **239** as tan crystalline solid (1.61 g, 6.34 mmol, 51%). Spectroscopic data was in accordance with that published in the literature.[100] Mp 123-124 °C (lit.[100] 125-126 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (br, s, 1H, NH), 7.89 (d, *J* = 3.1 Hz, 1H, H-2), 7.48

(dd, *J* = 8.0, 0.8 Hz, 1H, H-5/H-7), 7.37 (dd, *J* = 8.0, 0.8 Hz, 1H, H-5/H-7), 7.09 (t, *J* = 8.0, 8.0 Hz, 1H, H-6), 3.91 (s, 3H, CH_3).

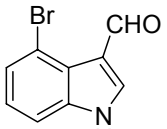
Method 2:

4-Bromo-1*H*-indole-3-carboxylic acid (**245**) (500 mg, 2.08 mmol), H_2SO_4 (1 drop) and MeOH (25 ml) were heated at reflux under an argon atmosphere for 6 hours. $NaHCO_{3(aq)}$ (5 ml) was added and the MeOH was evaporated at reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 10 ml) and the combined extracts were dried ($MgSO_4$). The CH_2Cl_2 was evaporated at reduced pressure and the residue was purified by flash chromatography. The first compound to be eluted (10% EtOAc/hexane) was 4-bromoindole (**243**) as a colourless oil (330 mg, 1.68 mmol, 81%). Spectroscopic data was identical to that of commercially available 4-bromoindole. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H, NH), 7.25-7.36 (m, 3H, H-2, H-5, H-7), 7.05 (dd, *J* = 7.9, 7.9 Hz, 1H, H-6), 6.60-6.63 (m, 1H, H-3). The second compound to be eluted (20% EtOAc/hexane) was 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**239**) as a tan crystalline solid (58 mg, 0.228 mmol, 11%). Spectroscopic data was identical to that of **239** prepared by method 1.

Method 3:

A mixture of 4-bromo-1*H*-indole-3-carboxylic acid (**245**) (1.10 g, 4.58 mmol) and oxalyl chloride (0.48 ml, 5.50 mmol) in CH_2Cl_2 (25 ml) was cooled to 0 °C, under an argon atmosphere. DMF (0.35 ml, 4.52 mmol) was added over a period of 0.5 hours. After 1.5 hours, when effervescence had ceased, MeOH (5 ml, 123 mmol) was added and the reaction mixture was allowed to warm to room temperature. Water (40 ml) was added and the mixture was made basic (pH 10) by the addition of 15% $NaOH_{(aq)}$. The CH_2Cl_2 was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The combined CH_2Cl_2 extracts were washed with 0.5 M NaOH (20 ml), brine (20 ml) and dried ($MgSO_4$). Removal of the solvent afforded the title compound **239** as a tan solid of sufficient purity for subsequent reactions (1.15 g, 4.53 mmol, 99%). Spectroscopic data was identical to that of **239** prepared by method 1.

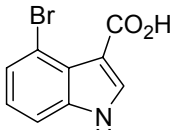
Preparation of 4-bromo-1*H*-indole-3-carbaldehyde (244)



244

A solution of 4-Bromoindole (5.00 g, 25.5 mmol) in DMF (10 ml) was added dropwise to a stirred mixture of $POCl_3$ (5.9 ml, 63.3 mmol) and DMF (10 ml). The temperature of the reaction mixture was maintained at 35-40 °C for 45 min and then the reaction mixture was added to ice (ca. 50 g) and water (100 ml). NaOH (13 g) in water (60 ml) was added over a period of 0.5 hours. The mixture was boiled for 5 min and then cooled rapidly to 50 °C. The product was collected by filtration and washed with water to afford the title compound **244** as colourless crystals (5.07 g, 22.6 mmol, 89%). Spectroscopic data was in accordance with that published in the literature.[100] Mp 182-185 °C (lit.[100] 185-187 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H, CHO), 9.32 (br, s, 1H, NH), 8.12 (d, *J* = 3.3 Hz, 1H, H-2), 7.51 (dd, *J* = 8.0, 0.9 Hz, 1H, H-5/H-7), 7.46 (dd, *J* = 8.0, 0.9 Hz, 1H, H-5/H-7), 7.16 (t, *J* = 8.0, 1H Hz, H-6).

Preparation of 4-bromo-1*H*-indole-3-carboxylic acid (245)

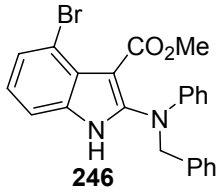


245

A solution of $NaClO_2$ (24.2 g, 268 mmol) and $NaHPO_4.H_2O$ (41.9g, 304 mmol) in water (320 ml) was added to a mixture of 4-bromo-1*H*-indole-3-carbaldehyde (**244**) (4.00 g, 17.9 mmol), 2-methyl-2-butene (47.0 ml, 444 mmol) and *t*-BuOH (200 ml). The reaction mixture was vigorously stirred for 5 days. The *t*-BuOH was evaporated at reduced pressure and, after the addition of water (200 ml), the aqueous residue was extracted with EtOAc (4 x 80 ml). The combined EtOAc extracts were washed with brine (100 ml) and then the EtOAc was evaporated at reduced pressure. The residue was dissolved in 0.5 M $NaOH_{(aq)}$ (300 ml) and the resulting basic solution was repeatedly extracted with CH_2Cl_2 (*ca*. 10 x 50 ml) until the aqueous phase was no longer blue. After filtering the aqueous solution through celite, concentrated hydrochloric acid was added to the filtrate until the solution was acidic (*ca*. pH 5) and the product had crystallised. The product was collected by filtration and washed with water to afford the title compound **245** as a tan crystalline solid (3.20 g, 13.3 mmol, 75%).

Mp 189-190 °C (dec.); IR (KBr) ν_{max}: 3371 (s, N-H), 2931 (br m, O-H), 1675 (s), 1563 (w), 1517 (m), 1447 (m), 1425 (m), 1355 (w), 1329 (w), 1307 (m), 1256 (w), 1192 (m), 1143 (w), 1021 (w), 910 (w), 764 (m), 730 (w), 653 (w), 612 (w), 566 (w) cm^{-1}; MS (EI) m/z 241 ($^{81}BrM^+$, 15), 239 ($^{79}BrM^+$, 15), 197 (90), 195 (100), 116 (49); HRMS (EI) m/z calcd for $C_9H_6NO_2{}^{79}Br$ 238.9582, found 238.9584; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 11.49 (br, s, 1H, NH/OH), 11.20 (br, s, 1H, NH/OH), 8.06 (d, *J* = 3.0 Hz, 1H, H-2), 7.53 (dd, *J* = 8.0, 0.9 Hz, 1H, H-5/H-7), 7.39 (dd, *J* = 8.0, 0.9 Hz, 1H, H-5/H-7), 7.09 (t, *J* = 8.0 Hz, 1H, H-6); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 164.9 (C), 139.3 (C), 134.6 (CH), 127.5 (CH), 125.7 (C), 124.4 (CH), 114.3 (C), 112.4 (CH), 109.5 (C).

Preparation of 2-(benzylphenylamino)-4-bromoindole-3-carboxylic acid methyl ester (246)

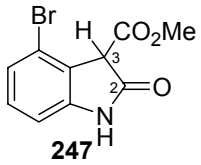


246

N-Chlorosuccinimide (116 mg, 0.869 mmol) and *N*,*N*'-dimethylpiperazine (0.059ml, 0.436 mmol) were added to a mixture of 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**239**) (200 mg, 0.787 mmol) and powdered 4 Å molecular sieves (400 mg) in CH_2Cl_2 (4 ml) at 0 °C, maintained under an argon atmosphere. After stirring for 2 hours a solution of *N*-benzylaniline (288 mg, 1.57 mmol) and trichloroacetic acid (32 mg 0.196 mmol) in CH_2Cl_2 (4 ml) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 20 hours. The molecular sieves were removed by filtration and the filtrate was washed sequentially with 1.0 M $HCl_{(aq)}$ (4 ml), $NaHCO_{3(aq)}$ (4 ml) and water (4 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (5% to 10% EtOAc/hexane) to afford the title compound **246** as a colourless crystalline solid (310 mg, 0.712 mmol, 90%). Mp 156-157 °C; IR (KBr) ν_{max}: 3267 (br s, N-H), 1672 (s, C=O), 1599 (m), 1543 (s), 1498 (s), 1446 (s), 1325 (s), 1253 (s), 1172 (s), 1127 (s), 1083 (m), 1029 (w), 950 (w), 772 (s), 743 (s), 690 (s), 622 (w), 506 (w), 459 (w), 437 (w) cm^{-1}; MS (CI) m/z 434 ($^{79}BrM^+$,86), 435 ($^{79}BrMH^+$,97), 436 ($^{81}BrM^+$, 100), 437 ($^{81}BrMH^+$, 85), 405 (25), 403 (26), 356 (40); HRMS (CI) m/z calcd for $C_{23}H_{20}N_2O_2{}^{81}Br$ 437.0688, found 437.0678; The NMR data presented

shows both the 3*H**- and 1*H*-indole tautomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 0.8H, NH), 6.85-7.39 (m, 13H, 7.5 x ArH, 7.5 ArH*), 5.22 (d, *J* = 14 Hz, 0.2H, CH_2*), 5.12 (d, *J* = 14 Hz, 0.2H, CH_2*), 4.58 (s, 0.2H, H-3*), 3.65 (s, 2.4H, CH_3), 3.37 (s, 0.6H, CH_3*).

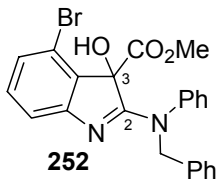
Preparation of 4-bromo-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid methyl ester (247)



247

The above procedure was carried out without the addition of molecular sieves and with a reaction time of 2 hours after the addition of *N*-benzylaniline using 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**239**) (100 mg, 0.394 mmol). After workup, the crude product was purified by flash chromatograph (10% to 30% EtOAc/hexane). The first product to be eluted was **246** (11 mg, 0.0253 mmol, 6%). The second product to be eluted was the title compound **247** as a colourless crystalline solid (68 mg, 0.252 mmol, 64%). Mp 151-153 °C; IR (KBr) ν_{max}: 3247 (br m), 1749 (s), 1715 (s), 1617 (m), 1586 (w), 1453 (m), 1298 (m), 1251 (m), 1167 (m), 1021 (w), 942 (w), 773 (w), 722 (w) cm^{-1}; MS (ESI) m/z 292 ($^{79}BrMNa^{+}$,100), 294 ($^{81}BrMNa^{+}$, 80); HRMS (ESI) m/z calcd for $C_{10}H_8NO_3{}^{81}BrNa$ 293.9565, found 293.9572; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H, NH), 7.14-7.22 (m, 2H, 2 x ArH), 6.89 (dd, *J* = 6.9, 1.7 Hz, 1H, ArH), 4.46 (s, 1H, H-3), 3.83 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 166.1 (C, C-2), 143.5 (C), 131.2 (CH), 126.6 (CH), 125.5 (C), 120.2 (C), 109.6 (CH), 55.0 (CH, C-3), 53.7 (CH_3).

Preparation of 2-(benzylphenylamino)-4-bromo-3-hydroxy-3*H*-indole-3-carboxylic acid methyl ester (252)

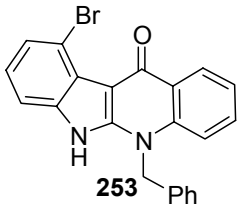


252

Samples of 2-(benzylphenylamino)-4-bromoindole-3-carboxylic acid methyl ester (**246**) were found to undergo complete autoxidation to the title compound **252** in less than 5 days.

Colourless crystalline solid. Mp 156-158 °C; IR (KBr) ν_{max}: 3478 (br m, O-H), 1747 (s, C=O), 1558 (s), 1496 (m), 1454 (m), 1430 (s), 1249 (s), 1167 (m), 1103 (m), 1018 (w), 946 (w), 905 (w), 782 (m), 753 (w), 700 (m), 515 (w) cm^{-1}; MS (CI) m/z 451 ($^{79}BrMH^+$,100), 453 ($^{81}BrMH^+$, 85); HRMS (CI) m/z calcd for $C_{23}H_{20}N_2O_3{}^{79}Br$ 451.0657, found 451.0652; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04-7.37 (m, 12H, 12 x ArH), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H, ArH), 5.28 (d, *J* = 14.5 Hz, 1H, CH_2), 4.97 (d, *J* = 14.5 Hz, 1H, CH_2), 3.72 (s, 1H, OH), 3.60 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (C, C=O), 169.7 (C, C-2), 158.4 (C), 140.3 (C), 136.7 (C), 134.0 (C), 132.2 (CH), 130.1 (CH), 129.0 (2 x CH), 128.9 (4 x CH), 128.6 (2 x CH), 127.8 (CH), 125.9 (CH), 116.9 (C), 116.6 (CH), 84.0 (C, C-3), 57.2 (CH_2), 53.9 (CH_3).

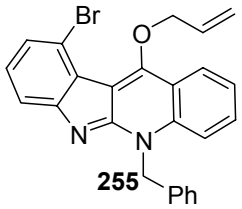
Preparation of 5,6-dihydro-5-benzyl-10-bromoindolo[2,3-*b*]quinolin-11-one (253)



253

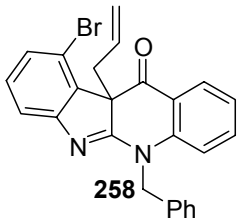
A solution of 2-(benzylphenylamino)-indole-3-carboxylic acid methyl ester (**246**) (310 mg, 0.712 mmol) in Ph_2O (2.5 ml) was heated at 250 °C, under an argon atmosphere, for 2 hours. After cooling to room temperature the formed solids were collected by filtration and washed with Et_2O to yield the title compound **253** as a light brown crystalline solid (241 mg, 0.598 mmol, 76%). Mp *ca*. 320 ^oC (dec.); IR (KBr) ν_{max}: 3031 (br s, N-H), 1616 (s, C=O), 1546 (s), 1508 (s), 1454 (m), 1431 (m), 1371 (m), 1325 (m), 1115 (m), 1053 (m), 871 (m), 755 (s), 739 (m), 692 (m), 538 (m), 505 (w), 458 (w) cm^{-1}; MS (CI) m/z 402 ($^{79}BrM^+$,60), 403 ($^{79}BrMH^+$,85), 404 ($^{81}BrM^+$, 78), 405 ($^{81}BrMH^+$, 60), 325 (70), 315 (87), 314 (100), 313 (90), 312 (89), 234 (35); HRMS (CI) m/z calcd for $C_{22}H_{16}N_2O^{79}Br$ 403.0446 found 403.0436; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 12.46 (s, 1H, NH), 8.39 (d, *J* = 8.0 Hz, 1H, H-1), 7.12-7.64 (m, 11H, 11 x ArH) 5.77 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 170.5 (C, C-11), 147.6 (C), 138.1 (C), 136.7 (C), 135.7 (C), 131.5 (CH), 128.9 (2 x CH), 127.5 (CH), 126.7 (CH), 126.6 (CH), 126.0 (2 x CH), 125.6 (C), 124.5 (C), 124.2 (CH), 122.0 (CH), 115.2 (CH), 112.7 (C), 110.3 (CH), 101.2 (C), 48.6 (CH_2).

Preparation of 11-allyloxy-5-benzyl-10-bromo-5*H*-indolo[2,3-*b*]quinoline (255)



5,6-Dihydro-5-benzyl-10-bromoindolo[2,3-*b*]quinolin-11-one (**253**) (110 mg, 0.273 mmol) and $POCl_3$ (2 ml) were heated at 90 °C for 1.5 hours, under an argon atmosphere, and then cooled to room temperature. The $POCl_3$ was evaporated at reduced pressure, with the final traces being removed by the addition and evaporation of a small amount of PhMe. THF (1 ml) was added to the residue and the mixture was cooled to 0 °C, under an argon atmosphere. A solution of the alkoxide generated from sodium (31 mg, 1.35 mmol) and allyl alcohol (0.50 ml, 7.33 mmol) in (THF 0.5 ml) was added and the reaction mixture was stirred for 2 hours. $NH_4Cl_{(aq)}$ (0.5 ml) was added and the solvent was evaporated at reduced pressure. The residue was partitioned between CH_2Cl_2 (2 ml) and water (2ml). The CH_2Cl_2 was separated and the residue was further extracted with CH_2Cl_2 (3 x 2 ml). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the CH_2Cl_2 was evaporated at reduced pressure. The residue was purified by flash chromatography (20% to 50% EtOAc/hexane) to afford the title compound **255** as an orange solid (63 mg, 0.142 mmol, 53%). Mp 143-145 ^oC; IR (KBr) ν_{max}: 1625 (s), 1561 (s), 1518 (s), 1491 (s), 1453 (w), 1408 (w), 1276 (m), 1260 (m), 1177 (w), 1141 (w), 952 (w), 869 (w), 754 (m) cm^{-1}; MS (CI) m/z 445 ($^{81}BrMH^+$, 100), 443 ($^{79}BrMH^+$, 95), 403 (30), 364 (27), 91 (23); HRMS (CI) m/z calcd for $C_{25}H_{20}N_2O^{79}Br$ 443.0759 found 443.0753; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33-8.36 (m, 1H, H-1), 7.59-7.69 (m, 3H, 3 x ArH), 7.19-7.49 (m, 8H, 8 x ArH), 6.15-6.28 (m, 3H, C<u>H</u>=CH_2, NCH_2), 5.49 (dq, *J* = 17.0, 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 5.32 (dq, *J* = 10.5, 1.5 Hz, 1H CH=C<u>H</u>$_2$), 4.86 (dt, *J* = 5.5, 1.5 Hz, 2H, OCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (C), 158.4 (C), 156.4 (C), 137.8 (C), 135.9 (C), 132.7 (CH), 131.6 (CH), 129.5 (CH), 129.1 (2 x CH), 127.8 (CH), 126.8 (2 x CH), 125.7 (CH), 125.4 (CH), 124.0 (C), 122.1 (CH), 119.1 (CH_2), 118.9 (C), 117.0 (CH), 116.71 (C), 116.67 (C), 115.3 (CH), 77.9 (CH_2), 49.6 (CH_2).

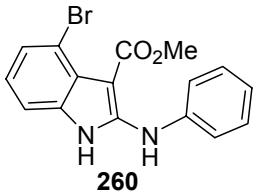
Preparation of 5,10b-dihydro-10b-allyl-5-benzyl-10-bromo-10b*H*-indolo[2,3-*b*]quinolin-11-one (258)



258

11-Allyloxy-5-benzyl-10-bromo-5*H*-indolo[2,3-*b*]quinoline (**255**) (37 mg, 0.0835 mmol) and PhMe were heated at reflux for 5 hours, under an argon atmosphere, and then cooled to room temperature. The PhMe was evaporated at reduced pressure. The residue was purified by flash chromatography (5% to 10% EtOAc/hexane) to afford the title compound **258** as a bright yellow crystalline solid (29 mg, 0.0654 mmol, 78%). Crystals suitable for X-ray analysis were obtained from EtOAc/hexane. Mp 175-177 ^{o}C; IR (KBr) ν_{max}: 1697 (m, C=O), 1603 (w), 1559 (s), 1467 (s), 1417 (m), 1280 (w), 1211 (w), 1040 (w), 926 (w), 854 (w), 783 (w), 758 (m), 702 (w) cm^{-1}; MS (ESI) m/z 467 (^{81}BrMNa^{+}, 84), 465 (^{79}BrMNa^{+}, 100); HRMS (ESI) m/z calcd for $C_{25}H_{20}N_2O^{79}Br$ 443.0759 found 443.0751; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.5 Hz 1H, H-1), 7.02-7.50 (m, 11H, 11 x ArH), 5.84 (d, *J* = 17 Hz, 1H, NCH_2), 4.95-5.17 (m, 3H, NCH_2, C<u>H</u>=C<u>H$_2$</u>), 4.82-4.87 (m, 1H, CH=C<u>H$_2$</u>), 3.57 (dd, *J* = 13.5, 6.5 Hz, 1H, C<u>H$_2$</u>CH=CH$_2$), 2.93 (dd, *J* = 13.5, 6.5 Hz, 1H, C<u>H$_2$</u>CH=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (C, C-11), 171.2 (C), 156.6 (C), 144.3 (C), 136.2 (C), 135.6 (CH), 131.7 (C), 130.6 (CH), 129.8 (CH), 129.1 (2 x CH), 128.7 (CH), 128.2 (CH), 127.8 (CH), 126.9 (2 x CH), 123.1 (CH), 120.3 (CH_2), 120.2 (C), 119.1 (C), 117.8 (CH), 115.5 (CH), 69.3 (C, C-10b), 50.1 (CH_2), 39.1 (CH_2).

Preparation of 4-bromo-2-phenylamino-1H-indole-3-carboxylic acid methyl ester (260)

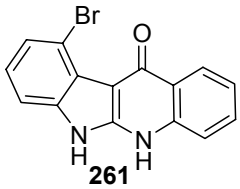


260

N-Chlorosuccinimide (711 mg, 5.32 mmol) and *N*,*N*'-dimethylpiperazine (0.36ml, 2.66 mmol) were added to a mixture of 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**239**) (1.23 g, 4.84 mmol) and powdered 4 Å molecular sieves (2 g) in CH_2Cl_2 (30 ml) at 0 °C, maintained under an argon atmosphere. After stirring for 2 hours a solution of aniline (0.88

ml, 9.68 mmol) and trichloroacetic acid (198 mg, 1.21 mmol) in CH_2Cl_2 (30 ml) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 20 hours. The molecular sieves were removed by filtration and the filtrate was washed sequentially with 1.0 M $HCl_{(aq)}$ (15 ml), $NaHCO_{3(aq)}$ (15 ml) and water (15 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was crystallised from EtOAc/hexane to afford the title compound **260** as a colourless crystalline solid (1.37 g, 3.97 mmol, 82%). Mp 172-173 ^oC; IR (KBr) ν_{max}: 3328 (m, N-H), 3269 (m, N-H), 1650 (s, C=O), 1590 (s), 1572 (s), 1494 (m), 1476 (m), 1446 (m), 1430 (m), 1369 (s), 1306 (m), 1253 (s), 1189 (m), 1131 (m), 1095 (m), 964 (w), 917 (w), 810 (w), 763 (s), 740 (m), 695 (m), 633 (w), 528 (w) cm^{-1}; MS (EI) m/z 346 ($^{81}BrM^+$, 18), 344 ($^{79}BrM^+$, 21), 314 (91), 312 (100), 205 (57); HRMS (EI) m/z calcd for $C_{16}H_{13}N_2O_2{}^{81}Br$ 346.0140, found 346.0148; ^1H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H, NH), 8.25 (s, 1H, NH), 7.36-7.46 (m, 3H, 3 x ArH), 7.18-7.28 (m, 3H, 3 x ArH), 7.06 (dd, *J* = 7.9, 0.8 Hz, 1H, ArH), 6.86 (dd, *J* = 7.8, 7.8 Hz, 1H, ArH), 3.91 (s, 1H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C), 150.4 (C), 138.3 (C), 133.5 (C), 130.5 (2 x CH), 128.4 (CH), 125.5 (CH), 125.4 (C), 122.3 (2 x CH), 121.9 (CH), 112.6 (C), 109.1 (CH), 87.1 (C), 50.5 (CH_2).

Preparation of 10-bromo-5,6-dihydroindolo[2,3-*b*]quinolin-11-one (261)

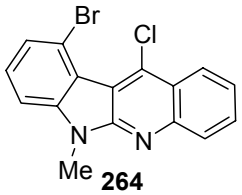


261

Prepared from 4-bromo-2-phenylamino-1H-indole-3-carboxylic acid methyl ester (**260**) (300 mg, 0.869 mmol) in Ph_2O (2 ml), with a reaction time of 1.5 hours, using general method B. The title compound **261** was obtained as a light brown solid (235 mg, 0.750 mmol, 86%). Mp *ca*. 360 (dec.) ^oC; IR (KBr) ν_{max}: 3333 (s, N-H), 3053 (m, br, N-H), 1636 (s), 1584 (s), 1530 (s), 1478 (m), 1455 (m), 1337 (w), 1311 (w), 1191 (w), 1112 (w), 1021 (w), 885 (w), 758 (m), 740 (m), 584 (m) cm^{-1}; MS (EI) m/z 314 ($^{81}BrM^+$, 88), 312 ($^{79}BrM^+$, 100), 205 (24); HRMS (EI) m/z calcd for $C_{15}H_9N_2O^{79}Br$ 311.9898, found 311.9894; ^1H NMR (400 MHz,$(CD_3)_2SO$) δ 12.06 (s, 2H, 2 x NH), 8.25 (d, *J* = 7.5 Hz, 1H, H-1), 7.57-7.64 (m, 2H, H-3, H-4), 7.45 (d, *J* = 7.8 Hz, 1H, H-9/H-7), 7.36 (d, *J* = 7.8 Hz, 1H, H-9/H-7), 7.27 (t, *J* = 7.5, Hz, 1H, H-2), 7.10 (t, *J* = 7.8 Hz, 1H, H-8); ^{13}C NMR (101 MHz,$(CD_3)_2SO$) δ 171.1 (C, C-

11), 146.0 (C), 137.8 (C), 136.9 (C), 131.0 (CH), 126.2 (CH), 126.0 (CH), 124.31 (C), 124.26 (C), 123.9 (CH), 121.5 (CH), 116.9 (CH), 112.6 (C), 110.1 (CH), 100.6 (C).

Preparation of 10-bromo-11-chloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline (264)

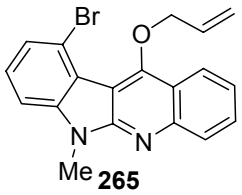


264

10-Bromo-5,6-dihydroindolo[2,3-*b*]quinolin-11-one (**261**) (500 mg, 1.45 mmol) was refluxed in $POCl_3$ (5 ml) for 24 hours and then cooled to room temperature. The excess $POCl_3$ was evaporated at reduced pressure and the residue was added to chipped ice/water (*ca* 20 ml). The mixture was made basic (*ca* pH 9) by the addition of saturated $NaHCO_3$ solution and the solids were collected by filtration. After washing with water, the product was thoroughly dried to afford crude **263** as a mustard coloured solid (570 mg). A portion of crude **263** (300 mg) was suspended in THF (10 ml) under an argon atmosphere and cooled to 0 °C. NaHMDS (1.81 ml, of a 1.0 M solution in THF) was added. After all the solids had gone into solution, methyl iodide (0.14 ml, 2.26 mmol) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 18 hours, $NH_4Cl_{(aq)}$ (0.5 ml) was added and the solvent was evaporated at reduced pressure. Water (10 ml) and CH_2Cl_2 (10 ml) were added to the residue and the mixture was filtered through celite. The CH_2Cl_2 was separated and the aqueous residue was further extracted with CH_2Cl_2 (3 x 15 ml). The combined CH_2Cl_2 extract were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (15% EtOAc/hexane) to afford the title compound **264** as a pale yellow crystalline solid (110 mg, 0.318 mmol, 35%). Mp 202-204 ^oC; IR (KBr) ν_{max}: 1590 (s), 1563 (m), 1478 (m), 1383 (m), 1303 (m), 1249 (w), 863 (w), 811 (w), 773 (s), 757 (s), 744 (m), 630 (m) cm^{-1}; MS (EI) m/z 346 ($^{81}BrM^+$, 100), 344 ($^{79}BrM^+$, 69), 135 (25), 115 (27), 98 (39), 91 (57), 73 (92), 60 (76); HRMS (EI) m/z calcd for $C_{16}H_{10}N_2{}^{35}Cl^{79}Br$ 343.9716, found 343.9716; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, J = 8.6, 1.0 Hz, 1H, H-1), 8.07 (d, J = 8.5 Hz, 1H, H-4), 7.77 (ddd, J = 8.5, 6.8, 1.0 Hz, 1H, H-3), 7.51-7.61 (m, 2H, H-8, H-2), 7.34-7.44 (m, 2H, H-7, H-9), 3.98 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C), 146.9 (C), 144.9 (C), 136.2 (C), 130.3 (CH), 129.4 (CH), 127.5

(CH), 127.3 (CH), 125.6 (CH), 124.1 (CH), 123.3 (C), 119.8 (C), 117.2 (C), 115.2 (C), 107.8 (CH), 28.3 (CH_3).

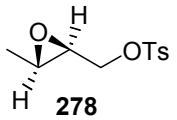
Preparation of 11-allyloxy-10-bromo-6-methyl-6*H*-indolo[2,3-*b*]quinoline (265)



265

A solution of the alkoxide generated from allyl alcohol (0.53 ml, 7.79 mmol) and sodium (60 mg, 2.61 mmol) in THF (0.5 ml) was added to 10-bromo-11-chloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**264**) (90 mg, 0.260 mmol) in THF (1 ml), maintained under an argon atmosphere. and the reaction mixture was stirred at room temperature for 4 days. $NH_4Cl_{(aq)}$ (0.5 ml) was added and the solvent was evaporated at reduced pressure. The residue was partitioned between water (1 ml) and CH_2Cl_2 (2 ml). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 2 ml). All the CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (10% to 20% EtOAc/hexane) to afford the title compound as **265** as a pale yellow solid (95 mg). This compound could not be separated from a contaminant of undetermined structure (*ca*. 30%, determined by ^{1}H NMR). However, the peaks associated with the title compound **265** were readily distinguished. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.4, 1.5 Hz, 1H, H-1), 8.08 (d, *J* = 8.9 Hz, 1H, H-4), 7.34 (td, *J* = 8.9, 1.5 Hz, 1H, H-3), 7.53 (dd, J = 7.3, 1.3 Hz, 1H, H-7), 7.32-7.50 (m, 3H, H-8, H-2, H-9), 6.23 (ddt, *J* = 16.9, 10.5, 5.4 Hz, 1H, C<u>H</u>=CH_2), 5.52 (dq, J = 16.9, 1.5 Hz, 1H, CH=C<u>H_2</u>), 5.31 (dq, *J* = 10.5, 1.5 Hz, 1H, CH=C<u>H_2</u>), 4.79 (dt, *J* = 5.4, 1.5 Hz, 2H, CH_2), 3.97 (s, 3H, CH_3).

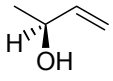
Preparation of (-)-(2*S*,3*S*)-3-methyl-2-(4-methylbenzenesulfonate)-2-oxiranemethanol (278)[113]



278

CH_2Cl_2 (200 ml) was added to crushed activated 3 Å molecular sieves (3.0 g), maintained under a argon atmosphere, in a 1 L flask and the mixture was cooled to -20 °C. L-(+)-Diisopropyl tartrate (1.42 g, 6.00 mmol), (*E*)-2-buten-1-ol (7.21 g, 100 mmol), and Ti(O-*i*-Pr)$_4$ (1.42 g, 5.00 mmol) were added sequentially. After stirring at -20 °C for 15 min, *tert*-butyl hydroperoxide (36.4 ml of a 5.5 M solution in nonane, 200 mmol) was added and the reaction mixture was stirred at -20 °C for 2 hours. Trimethyl phosphite (18.9 ml, 160 mmol) was added carefully, so as not to allow the temperature to rise above -20 °C. Triethylamine (20.6 ml, 141 mmol), DMAP (1.47 g, 12.0 mmol), and *p*-toluenesulfonyl chloride (19.1 g 100 mmol) as a solution in CH_2Cl_2 (250 ml) were then added. After stirring at -10 °C for 10 hours, the reaction mixture was filtered through celite. The filtrate was washed with 10% tartaric acid solution (200 ml), $NaHCO_{3(aq)}$ (200 ml), brine (200 ml) and then dried ($MgSO_4$). After removal of the CH_2Cl_2 by evaporation at reduced pressure, the remaining volatile material was removed by Kugelrohr distillation (40-50 °C, 0.1 mmHg). The residue was then crystallised three times from Et_2O/hexane to afford the title compound **278** as colourless crystals (7.05 g, 29.1 mmol, 29%). Spectroscopic data was in accordance with that published in tha literature.[113] Mp 61-62 °C (lit.[113] 61.5-62.0 °C); $[\alpha]^{20}_D$ -38.6 (c 3.60, $CHCl_3$) (lit.[113] $[\alpha]^{25}_D$ +34.2 (c 3.29, $CHCl_3$) for (*R*,*R*)-enantiomer of >99:1 e.r.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.82 (m, 2H, ArH), 7.33-7.38 (m, 2H, ArH), 4.18 (dd, *J* = 11.3, 3.9 Hz, 1H, CH_2), 3.98 (dd, *J* = 11.3, 5.7 Hz, 1H, CH_2), 2.84-2.94 (m, 2H, C<u>H</u>OC<u>H</u>), 2.46 (s, 3H, $ArCH_3$), 1.30 (d, *J* = 5.2 Hz, 3H, CHC<u>H</u>$_3$).

Preparation of (*S*)-(+)-3-butene-2-ol (*S*)-153



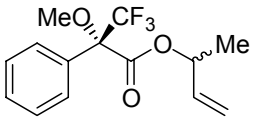
(*S*)-**153**

A solution of (-)-(2*S*,3*S*)-3-Methyl-2-(4-methylbenzenesulfonate)-2-oxiranemethanol (**278**) (6.38 g, 26.3 mmol) in ethylene glycol (30 ml) was added to a mixture of zinc-copper couple (3.19 g) and sodium iodide (11.8g, 79.0 mmol) in ethylene glycol (60 ml). The reaction

mixture was heated at 70 °C and stirred for 2 hours. After allowing the reaction mixture to cool to room temperature, the insoluble material was removed by filtration through a silica plug (positive pressure) and filtrate was fractionally distilled. The fractions between 86-94 °C were collected as (*S*)-(+)-3-butene-2-ol ((*S*)-**153**) (1.60 g, 22.2 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 17.2, 10.4, 5.8 Hz, 1H, C<u>H</u>=CH_2), 5.21 (dt, *J* = 17.2, 1.4 Hz, 1H, CH=C<u>H</u>$_2$), 5.05 (dt, *J* = 10.4, 1.4 Hz, 1H, CH=C<u>H</u>$_2$), 4.24-4.34 (m, 1H, C<u>H</u>OH), 2.19 (d, *J* = 10.4 Hz, 1H, OH).

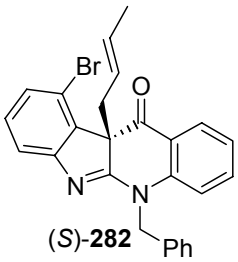
Removal of water: (*S*)-(+)-3-butene-2-ol was dissolved in THF and stirred with 3 Å molecular sieves (800 mg) for 3 days. The molecular sieves were removed by filtration and washed with THF. The filtrate and washings were combined and the concentration of (*S*)-(+)-3-butene-2-ol in THF was determined by ^{1}H NMR (*ca*. 2.7 M).

Determination of enantiomeric purity by formation of MTPA esters:



The following procedure was carried out for both racemic 3-butene-2-ol and (*S*)-(+)-3-butene-2-ol. Pyridine-d_5 (150 μl), (*R*)-(-)-MTPACl (13 μl, 0.0700 mmol), and 3-butene-2-ol (19 μl of a 2.7 M solution in THF) were added sequentially to a dry, argon flushed, NMR tube. After 0.5 hours, $CDCl_3$ (0.6 ml) was added. Analysis by ^{1}H NMR indicated that all the 3-butene-2-ol had been consumed. 3-dimethylamino-1-propylamine (12 μl, 0.0961 mmol) was added and after 5 min the reaction mixture was diluted with Et_2O (3 ml). The Et_2O solution was washed sequentially with dilute hydrochloric acid (0.5 M, 1.0 ml), $NaHCO_{3(aq)}$ (1 ml), and brine (1 ml), and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure and to afford the MTPA ester of 3-butene-2-ol as a colourless oil. The NMR data presented is for the racemic material showing both the (*S*,*S*)-diastereomer* and the (*S*,*R*)-diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.54 (m, 2H, ArH, ArH*), 7.38-7.42 (m, 3H, 1.5 x ArH, 1.5 x ArH*), 5.72-5.94 (m, 1H, C<u>H</u>=CH_2, C<u>H</u>=CH_2*), 5.56-5.63 (m, 1H, OCH, OCH*), 5.15-5.37 (m, 2H, CH=C<u>H</u>$_2$, CH=C<u>H</u>$_2$*), 3.56-3.58 (m, 1.5H, OCH_3), 3.54-3.56 (m, 1.5H, OCH_3*), 1.43 (d, *J* = 6.6 Hz, 1.5H, CHC<u>H</u>$_3$), 1.36 (d, *J* = 6.6 Hz, 1.5H, CHC<u>H</u>$_3$*); ^{19}F NMR (376 MHz, $CDCl_3$) -71.56 (s, 1.5F, CF_3*), -71.60 (s, 1.5F, CF_3). Analysis of the MTPA ester formed from (*S*)-(+)-3-butene-2-ol by ^{1}H NMR indicated the presence of 4% of the (*S*,*R*)-diastereomer.

Preparation of (*S*)-(-)-5-benzyl-10-bromo-10b-(*E*-but-2-enyl)-5*H*-indolo[2,3-*b*]quinolin-11-one ((*S*)-282)



(*S*)-**282**

A mixture of 5,6-dihydro-5-benzyl-10-bromoindolo[2,3-*b*]quinolin-11-one (**253**) (200 mg, 0.496 mmol) and $POCl_3$ (3 ml) were heated at reflux for 3 hours, under an argon atmosphere. After the excess $POCl_3$ had been evaporated at reduced pressure (the addition and evaporation of a small amount of dry PhMe was used to remove the last remaining traces of $POCl_3$), CH_2Cl_2 (10 ml) and $NaHCO_{3(aq)}$ (10 ml) were added and the mixture was stirred until completely orange with no remaining yellow solids. The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 10 ml). The extracts were combined, dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The resulting bright orange residue was dissolved in THF (10 ml), under an argon atmosphere, and the alkoxide generated from (*S*)-(+)-3-buten-2-ol (1.50 ml of a 2.7 M solution in THF, 0.556 mmol) and sodium (34 mg, 1.48 mmol) in THF (5 ml) was added. After stirring for 1.5 hours, $NH_4Cl_{(aq)}$ (0.5 ml) was added and the solvent was evaporated at reduced pressure. The residue was partitioned between CH_2Cl_2 (5 ml) and water (5 ml), the CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 5 ml), the extracts were combined, dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The residue was dissolved in THF and heated at reflux under an argon atmosphere for 6 hours. The THF was evaporated at reduced pressure and the crude product was purified by flash chromatography (10% EtOAc/hexane) to yield the title compound (*S*)-**282** as a bright yellow crystalline solid (167 mg, 0.364 mmol, 74%, $[\alpha]^{20}_D$ -347.1 (c 5.80, $CHCl_3$)). This material was crystallised from Et_2O/hexane to give a sample for X-ray analysis. Mp 124-125 ^oC; IR (KBr) ν_{max}: 1700 (s, C=O), 1602 (m), 1560 (s), 1467 (s), 1415 (s), 1391 (m), 1323 (w), 1240 (m), 1212 (m), 1163 (w), 1042 (w), 965 (m), 856 (m), 785 (m), 765 (s), 693 (m), 533 (w) cm^{-1}; MS (CI) m/z 456 ($^{79}BrM^+$, 30), 457 ($^{79}BrMH^+$, 42), 458 ($^{81}BrM^+$, 41), 459 ($^{81}BrMH^+$, 39), 405 (65), 403 (100), 325 (75); HRMS (CI) m/z calcd for $C_{26}H_{22}N_2O^{79}Br$ 457.0915 found 457.0915; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.0, 1.5 Hz, 1H, H-1), 7.00-7.51 (m, 11H, 11 x ArH), 5.85 (d, *J* = 16.5 Hz, 1H, NCH_2), 5.31-5.46 (m, 1H, C<u>H</u>CH_3), 5.04 (d, *J* = 16.5 Hz, 1H,

NCH_2), 4.63-4.78 (m, 1H, $CH_2C\underline{H}$), 3.49 (dd, J = 13.5, 7.0 Hz, 1H, $C\underline{H_2}CH$), 2.86 (dd, J = 13.5, 7.5 Hz, 1H, $C\underline{H_2}CH$), 1.37 (dd, J = 6.5, 1.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2 (C, C-11), 171.4 (C), 156.6 (C), 144.3 (C), 136.4 (C), 135.5 (CH), 132.0 (C), 131.3 (CH), 130.5 (CH), 129.0 (2 x CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 126.9 (2 x CH), 123.0 (CH), 122.2 (CH), 120.4 (C), 119.0 (C), 117.7 (CH), 115.4 (CH), 69.7 (C, C-10b), 50.1 (CH_2), 38.4 (CH_2), 17.9 (CH_3).

Conclusions

The investigations presented in this thesis were directed at developing a new synthetic route to perophoramidine and the communesin group of natural products. These investigations focused mainly on the rearrangements in the indolo[2,3-*b*]quinoline system. It was discovered that the relative rates of the Claisen rearrangement and subsequent aza-Cope rearrangement of 11-allyloxyindolo[2,3-*b*]quinolines could be controlled through the positioning of a substituent on either N-5 or N-6 of this ring system. When the substituent was placed on N-6 it was found that the rate of the aza-Cope rearrangement is greater than the rate of the Claisen rearrangement and the intermediate compound does not accumulate. Conversely, when the substituent is placed on N-5 the situation is reversed so that the Claisen rearrangement is faster than the aza-Cope rearrangement and the intermediate accumulates in the reaction mixture. By controlling the rates of these consecutive rearrangements in this way it was possible to prepare compounds containing the desired C-10b quaternary centre in high yield.

This is a truly novel approach to synthesising perophoramidine and the communesins. Furthermore, whilst the dearomatisation of aromatic systems using Claisen rearrangements has occasionally been applied to natural product synthesis,[47-49,120-122] such control of a two step process by altering the degree of aromatic stabilisation is, to the best of our knowledge, without precedent in natural product synthesis.

Through the use of model studies conducted on one of the substrates prepared using the Claisen rearrangement, it was shown that the adjacent quaternary centre at C-11 could also be successful constructed. This further demonstrated that this synthetic methodology is applicable to the synthesis of perophoramidine and the communesins. Through these studies a significant body of information was generated that will be used in the design of synthetic routes to perophoramidine and the communesins. Furthermore, the intermediate (*S*)-**281** was prepared that can be used directly as part of an asymmetric synthesis of the communesin natural products.

In general, the aim of the research described in this thesis was to develop a new method for the construction of the vicinal all-carbon quaternary centres contained in the natural products perophoramidine and the communesins. In conclusion the aims of this research have been achieved.

Future Work

The results presented in this thesis enable the development of new synthetic projects. Many of the investigations reported in this thesis have been conducted on model compounds and the chemistry that has been developed will be applied to the synthesis of perophoramidine (**17**) and the communesins by using the appropriately substituted indolo[2,3-*b*]quinoline ring systems. Indeed, such synthetic projects have already been initiated.

With regard to a communesin synthesis, it is intended that the ketone of (*S*)-**282** with by converted to the C-11 quaternary centre by using the methods described in Chapter 4. The Br-10 substituent will be used to construct the isoprene motif by using, for example, a Heck reaction with methyl acrylate. This would give the correct number of carbon atoms for the isoprene motif and the necessary functionality for construction of the azapine ring.

Synthetic studies directed at a perophoramidine will use the appropriate halogen substituted ring system (see appendix 2) and it is intended that the methods involving the formation and alkylation of the C-11 nitrile described in Chapter 4 will be used in this synthesis.

Appendix 1: A computational investigation into the rearrangement of 90 and 129

The computational investigations described in this section were conducted by Prof. Douglas Philp.

In order to better understand the differences in chemical behaviour between the two systems **90** and **129** the rearrangement sequences for both compounds were investigated at the B3LYP/6-31G(d,p) level of theory. Initially, lowest energy conformations of **90**, **91**, **116** were located using molecular mechanics calculations. Guess structures for the transition states linking **90** and **91** and **91** and **116** were then generated by the linear synchronous transit method and refined using the AM1 method. These crude guesses were then used as input structures for the DFT calculations. All of the transition states located for the two rearrangements have the classical chair-like structure. Vibrational frequency analysis and intrinsic reaction coordinate (IRC) calculations verified that all of the transition state structures located were valid and energies for each species on the reaction pathways were extracted by standard methods.

The calculated barrier for the conversion of **90** into **91** is 27.3 kcalmol^{-1} (**Figure 31**). Significantly, intermediate **91** is calculated to be 6.7 kcalmol^{-1} higher in energy than **90**. The computed barrier for the conversion of intermediate **91** into **116** is significantly lower (23.0 kcalmol^{-1}) than that for the first rearrangement. These calculations are consistent with the efficient conversion of **90** to **116** *via* intermediate **91** with the first step being rate limiting so as **91** would never accumulate in the reaction mixture as a result of the relatively fast second rearrangement.

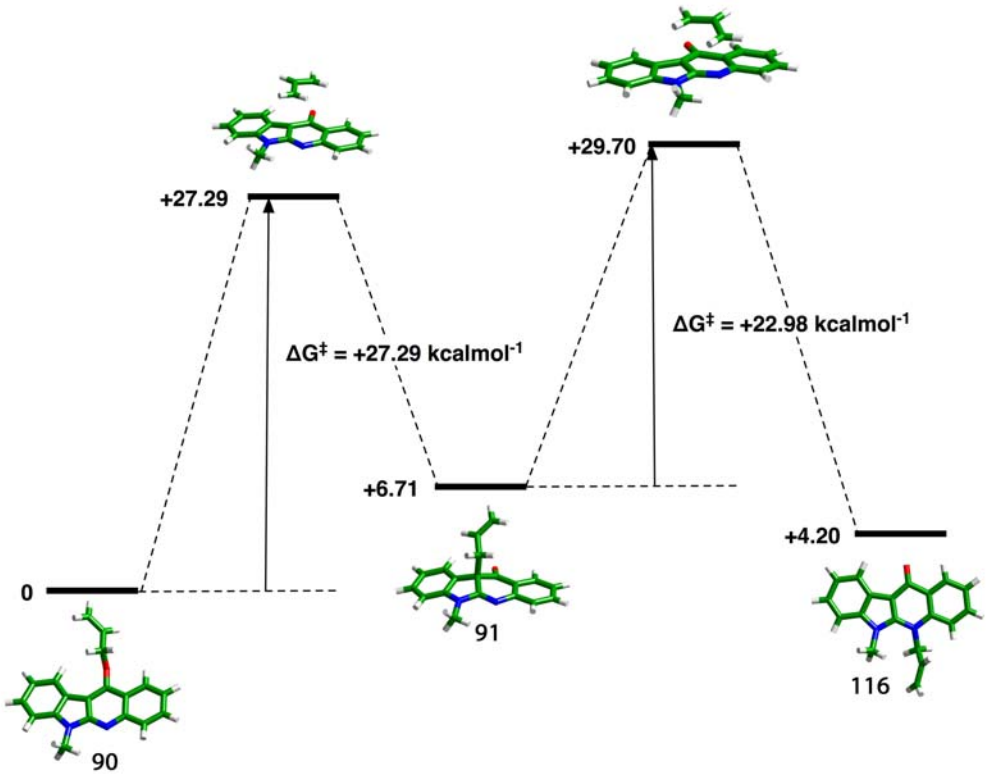


Figure 31. Calculated energy barriers (B3LYP/6-31G(d,p)) for the conversion of **90** to **91** and the conversion of **91** to **116**.

The reaction sequence **129** to **130** to **139** was also investigated at the B3LYP/6-31G(d,p) level of theory using the methodology outlined above. As before, all of the transition states located for the two rearrangements have the classical chair-like structure and vibrational frequency analysis and intrinsic reaction coordinate (IRC) calculations verified that all of the transition state structures located were valid and energies for each species on the reaction pathways were extracted by standard methods.

The calculated barrier for the conversion of **129** into **130** is 25.2 kcalmol^{-1} and the process is now essentially thermoneutral, with **130** being just 0.3 kcalmol^{-1} higher in energy than **129**. (**Figure 32**). The computed barrier for the conversion of **130** into **139** (26.8 kcalmol^{-1}) is now higher than that for the conversion of **129** into **130**.

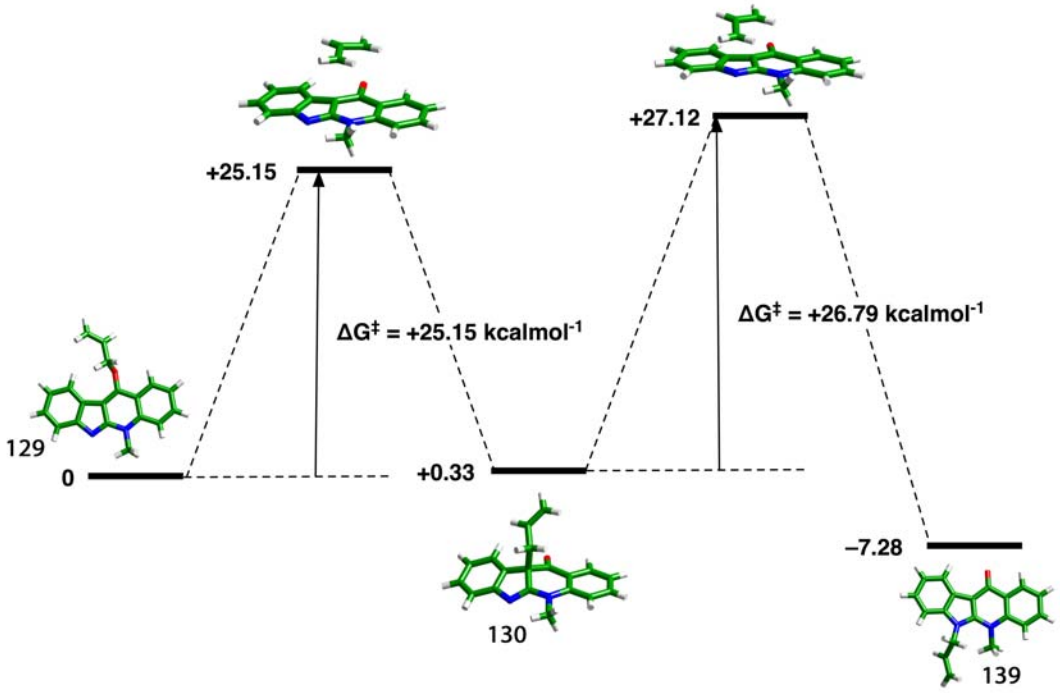


Figure 32. Calculated energy barriers (B3LYP/6-31G(d,p)) for the conversion of **129** to **130** and the conversion of **130** to **139**.

A comparison of the free energies of all of the compounds (**90**, **91**, **116**, **129**, **130** and **139**) is instructive (**Figure 33**). Taking **90** as the zero point, both **91** and **130** have relatively similar energies (+6.7 and +10.4 kcalmol^{-1}, respectively), as do the two *N*-allyl compounds **116** and **139** (+4.2 and +2.7 kcalmol^{-1}, respectively). By contrast, **90** is calculated to be 10.1 kcalmol^{-1} more stable than **129**. This is consistent with the rationalisation that it is the predominantly the difference in ground state energy between **90** and **129** that causes the differences in chemical behaviour.

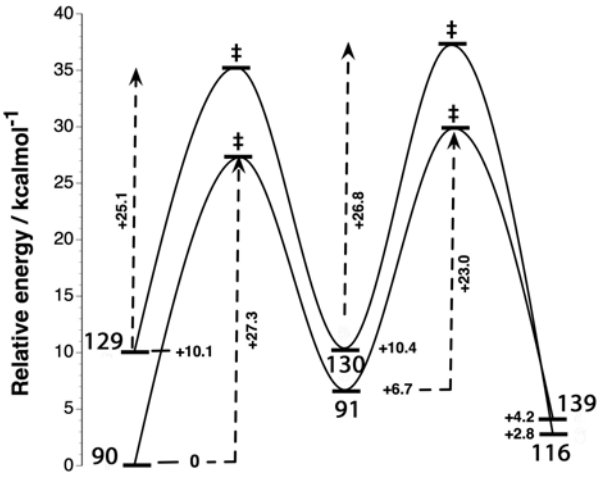
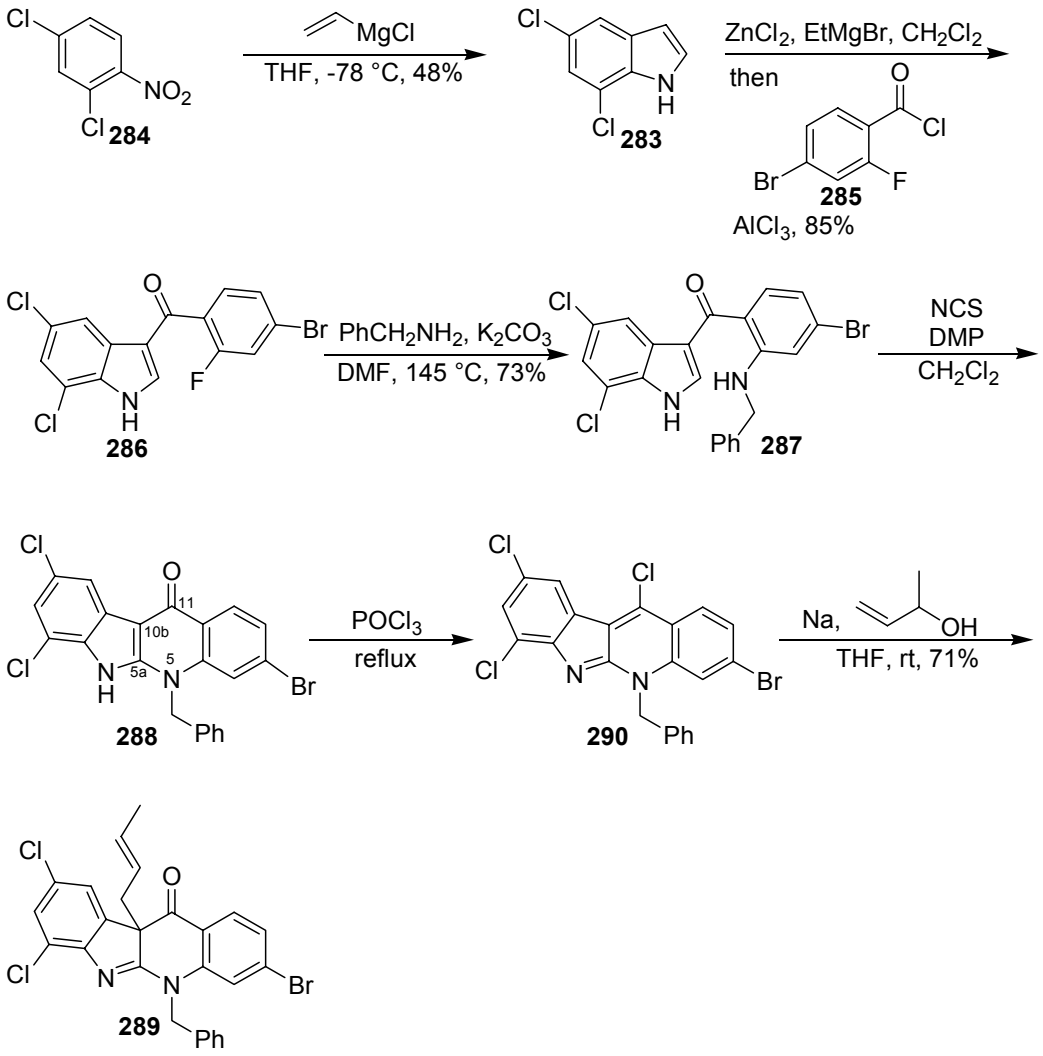


Figure 33. A comparison of the free energies of all of the compounds, taking **90** as the zero point, supports the idea that it is the difference in ground state energy between **90** and **129** that accounts for the differences in chemical behaviour.

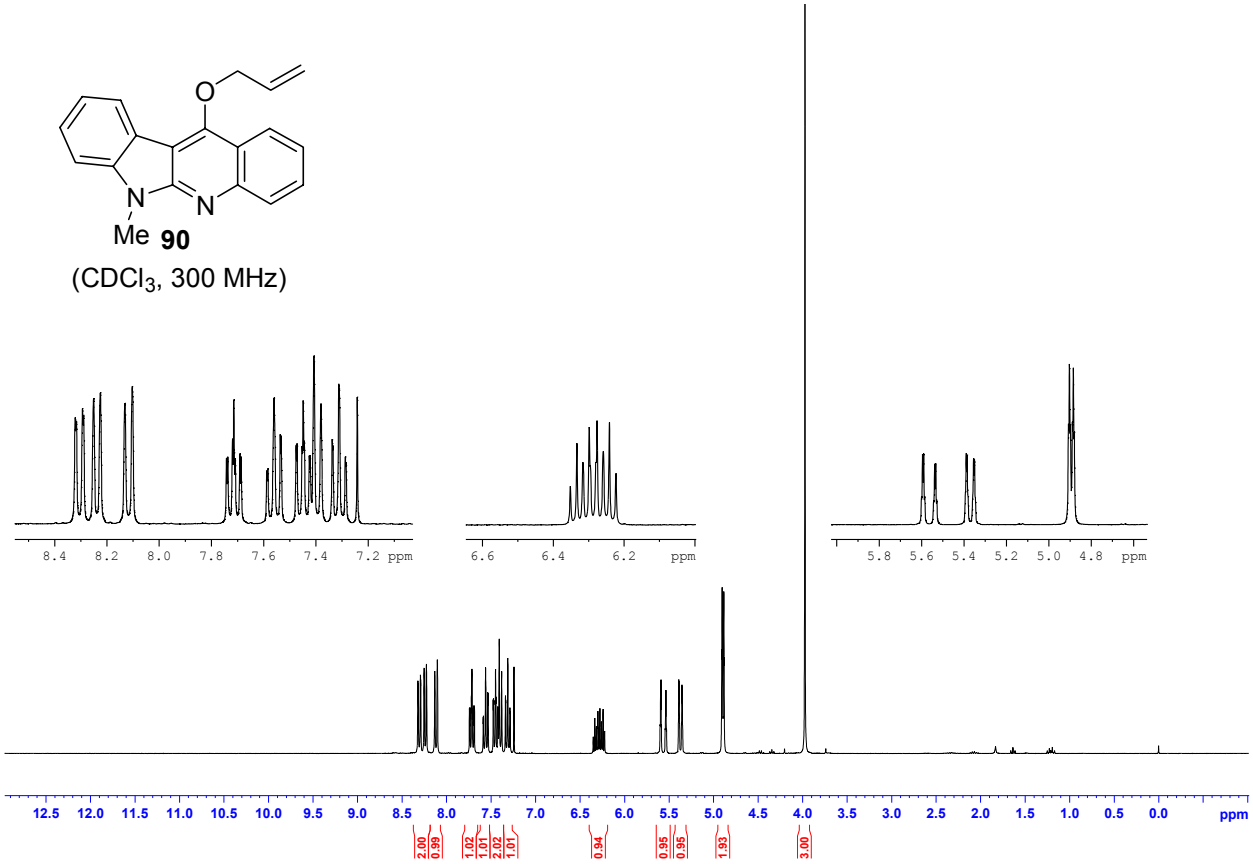
Appendix 2: The start of a perophoramidine synthesis

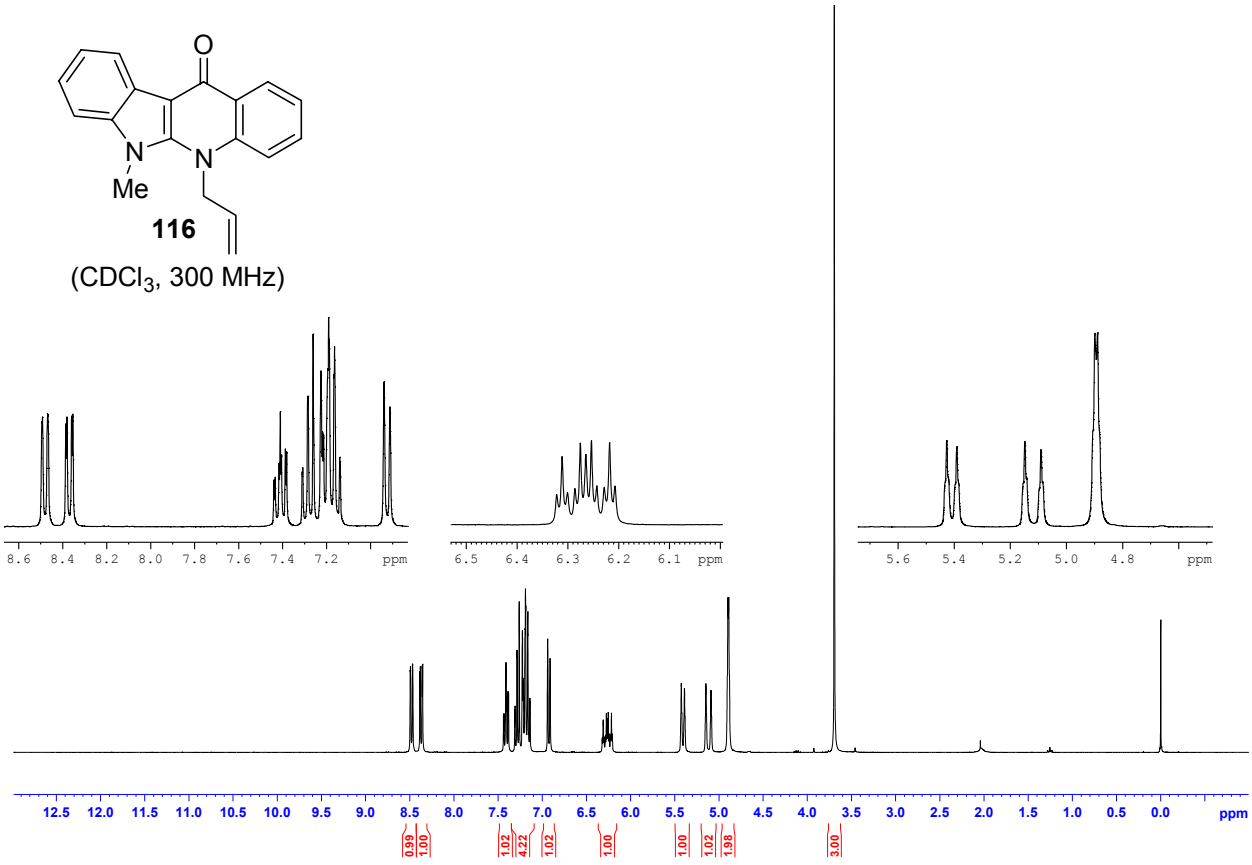
A synthesis of perophoramidine (**17**) has been initiated by Dr Edward Makiyi using the chemistry described in this thesis (**Scheme 104**). The synthesis starts with the synthesis of 5,7-dichlorindole (**283**) from 2,4-dichloro-1-nitrobenzene (**284**) according to the literature procedure.[123] 5,7-Dichloroindole (**283**) was then coupled with **285** before displacement of the fluorine atom, which takes place in preference to displacement of the bromine atom, in **286** with *N*-benzylaniline to afford **287**. Closure of the indolo[2,3-*b*]quinoline-11-one ring system of **288** was then accomplished by treatment of **287** with *N*-chlorosucinimide in a procedure similar to that described frequently throughout this thesis. In this synthesis, by forming the C-10b-C-11 bond prior to the N-5-C-5a bond it was possible to avoid potential problems of regioselectivity that would have arisen if the indolo[2,3-*b*]quinoline-11-one ring system had been formed using the chemistry previously described. Formation of the C-10b quaternary centre in **289** was then achieved using the same reaction sequence that had been used in the model system, *via* chloride **290**. It is interesting to note that the Claisen rearrangement in this sequence takes place at room temperature and no heating is required to form **280**.

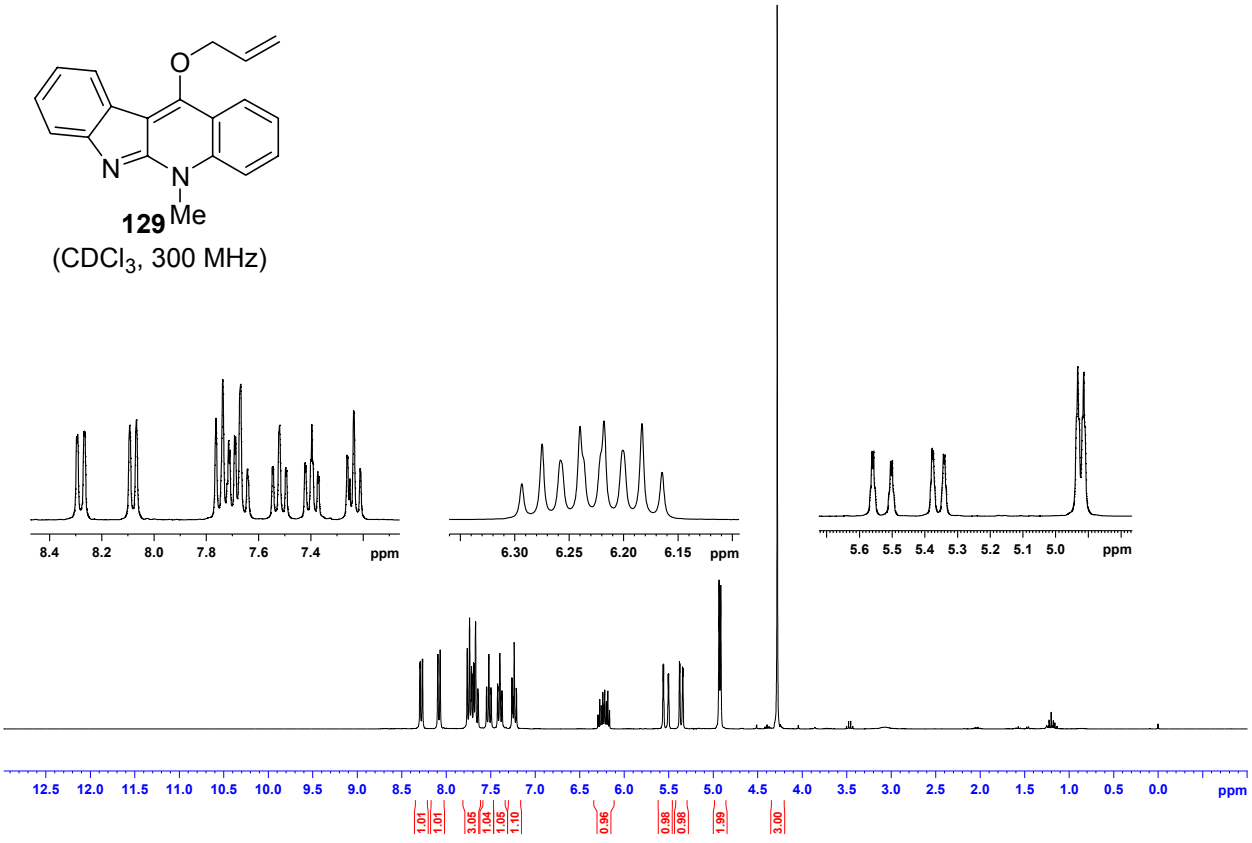


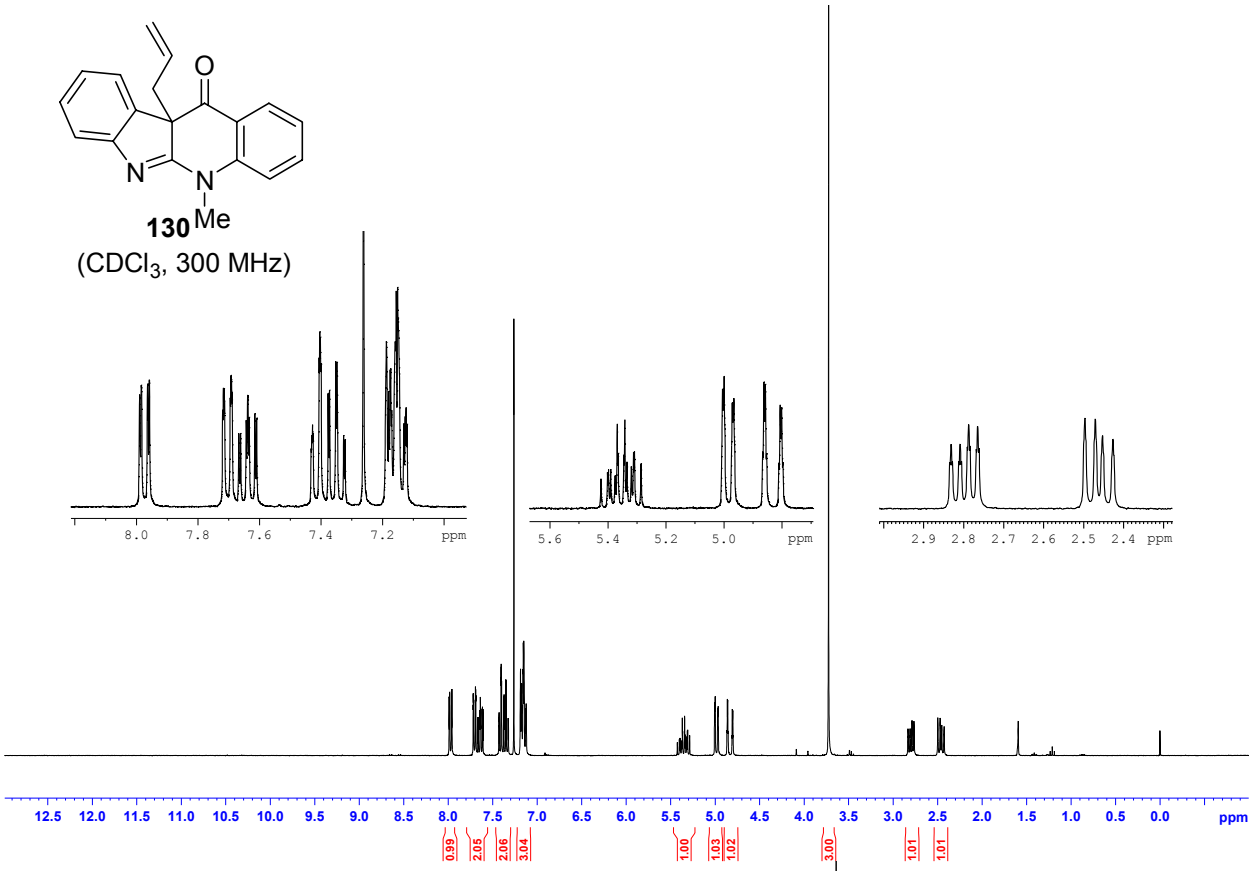
Scheme 104. A perophoramidine synthesis has been initiated using the chemistry developed in this thesis. DMP = *N*,'*N*-dimethylpiperazine, NCS = *N*-chlorosucinimide, TCA = trichloroacetic acid.

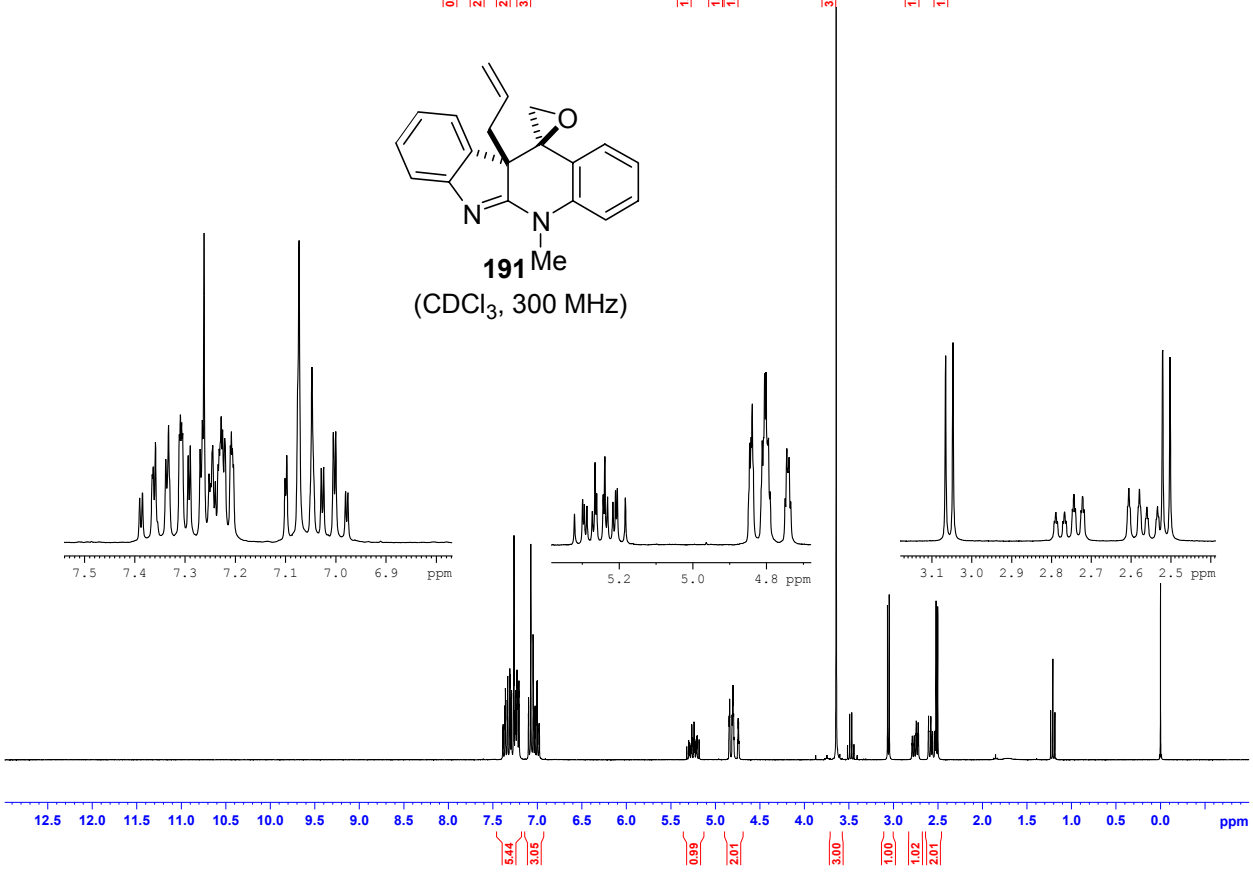
Appendix 3: ^{1}H NMR Spectra of Key Novel Compounds

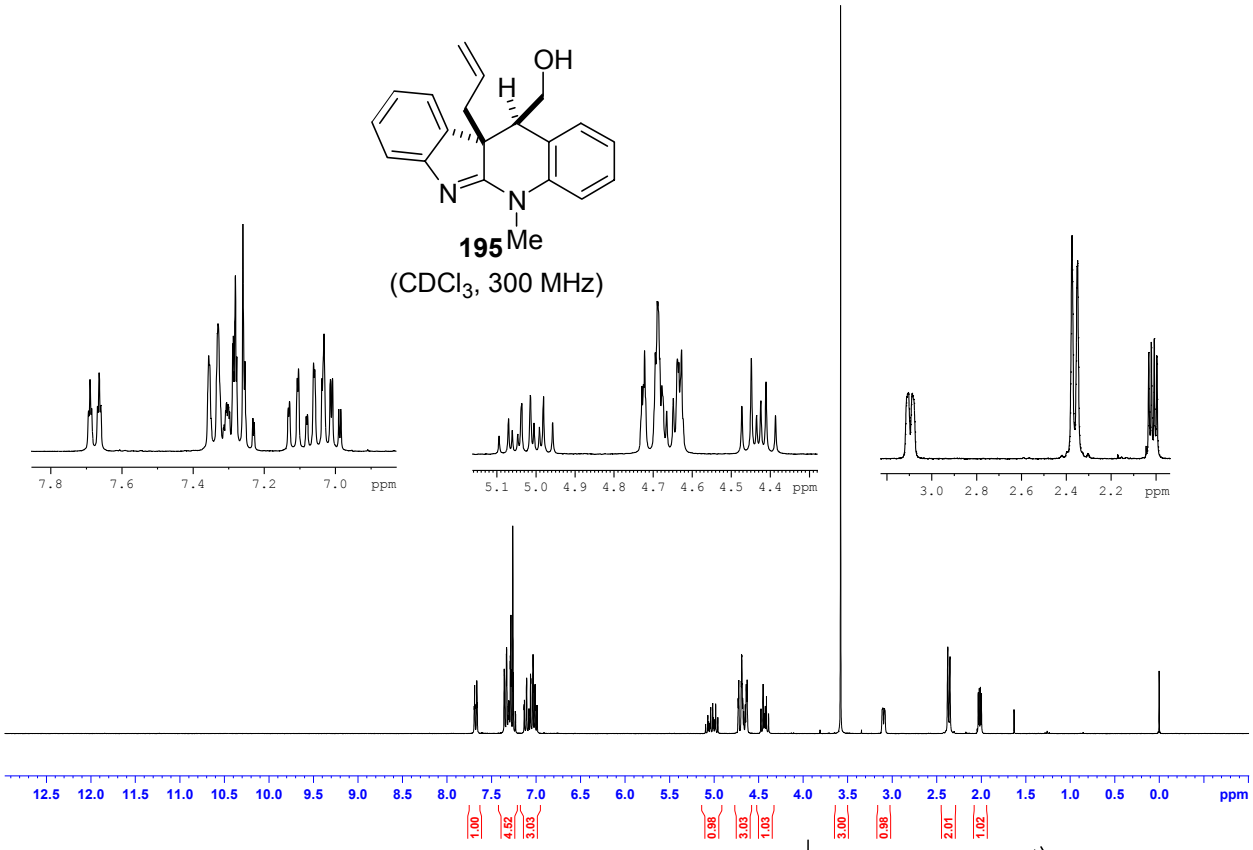


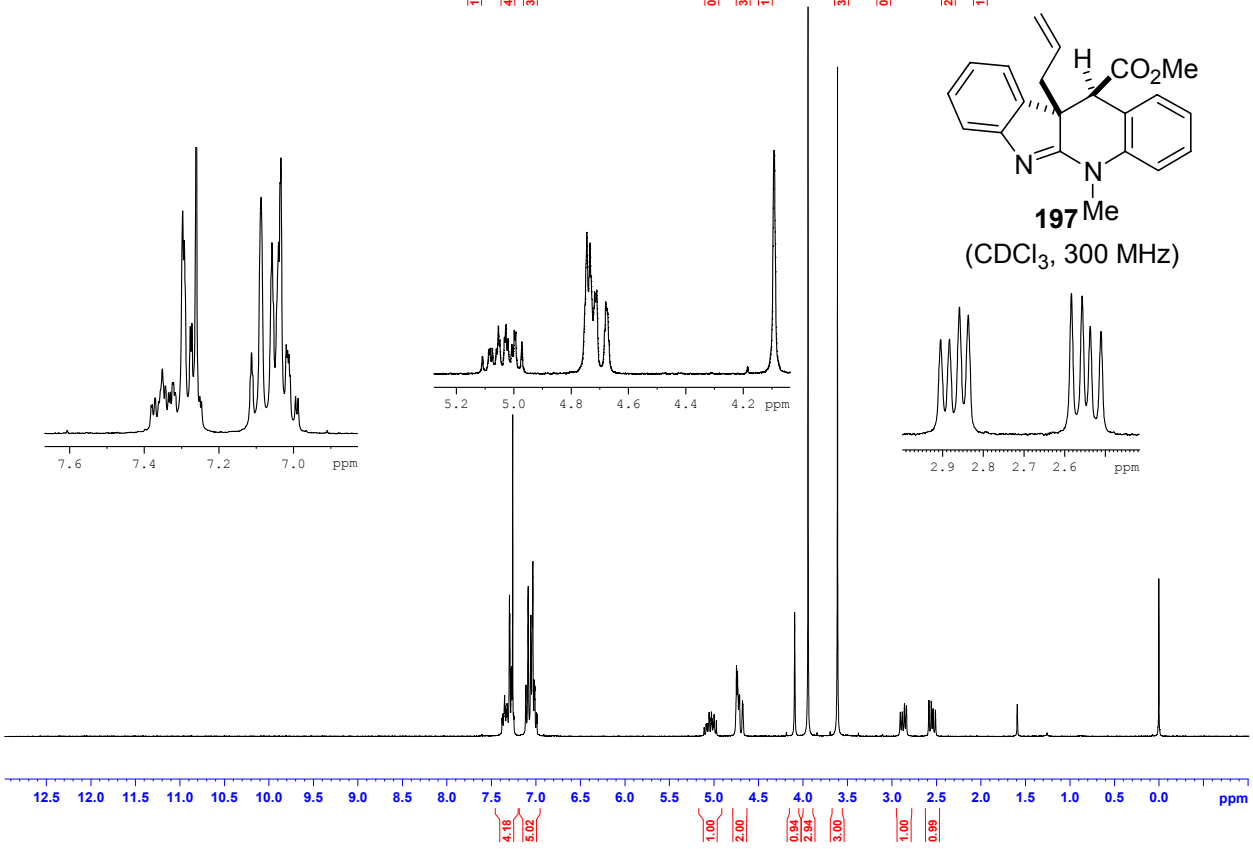

O
N
Me
N
116
(CDCl3, 300 MHz)
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 ppm
6.5 6.4 6.3 6.2 6.1 ppm
5.6 5.4 5.2 5.0 4.8 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99 1.00 1.02 4.22 1.02 1.00 1.00 1.02 1.98 3.00

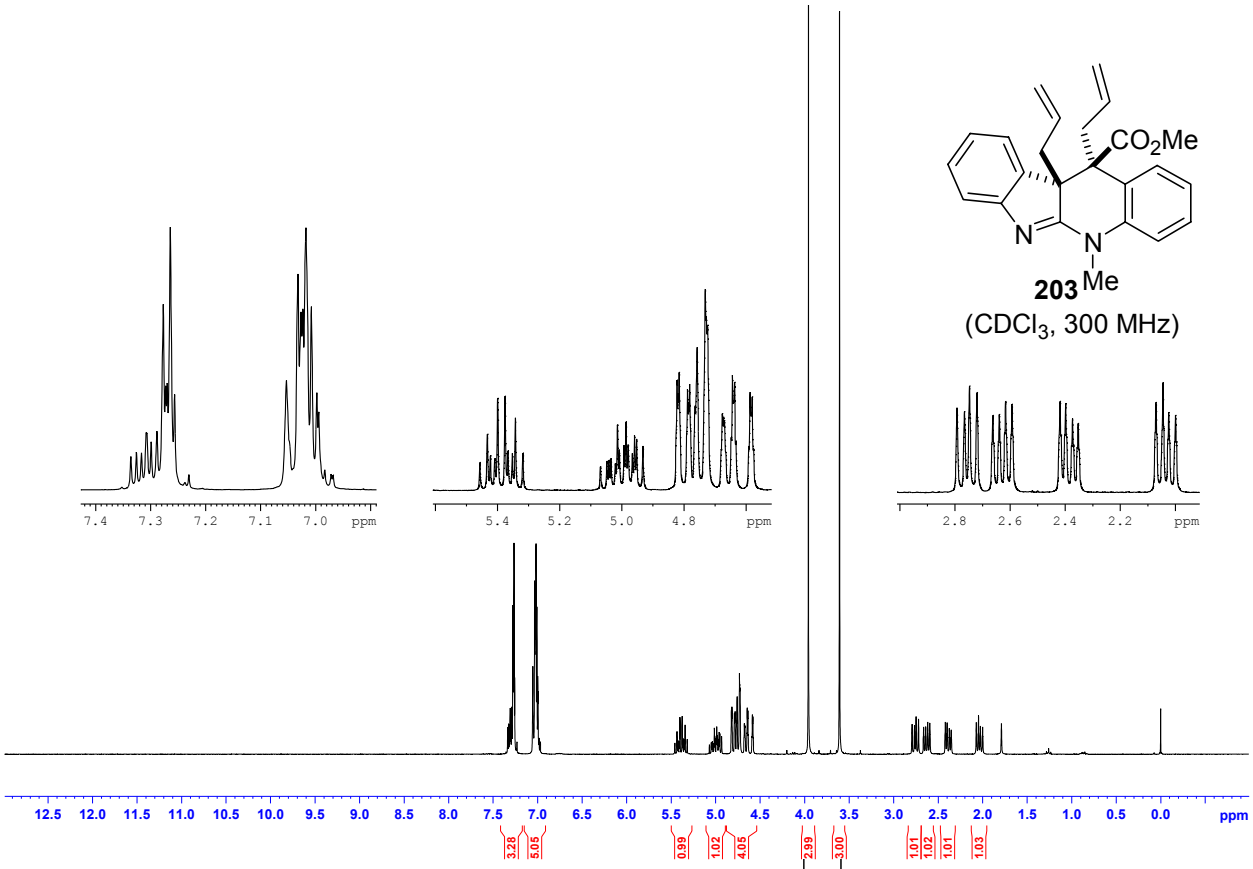

O
N
N
Me
129
(CDCl3, 300 MHz)
8.4 8.2 8.0 7.8 7.6 7.4 ppm
6.30 6.25 6.20 6.15 ppm
5.6 5.5 5.4 5.3 5.2 5.1 5.0 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.01 1.01 3.05 1.04 1.05 1.10 0.96 0.98 0.98 1.99 3.00

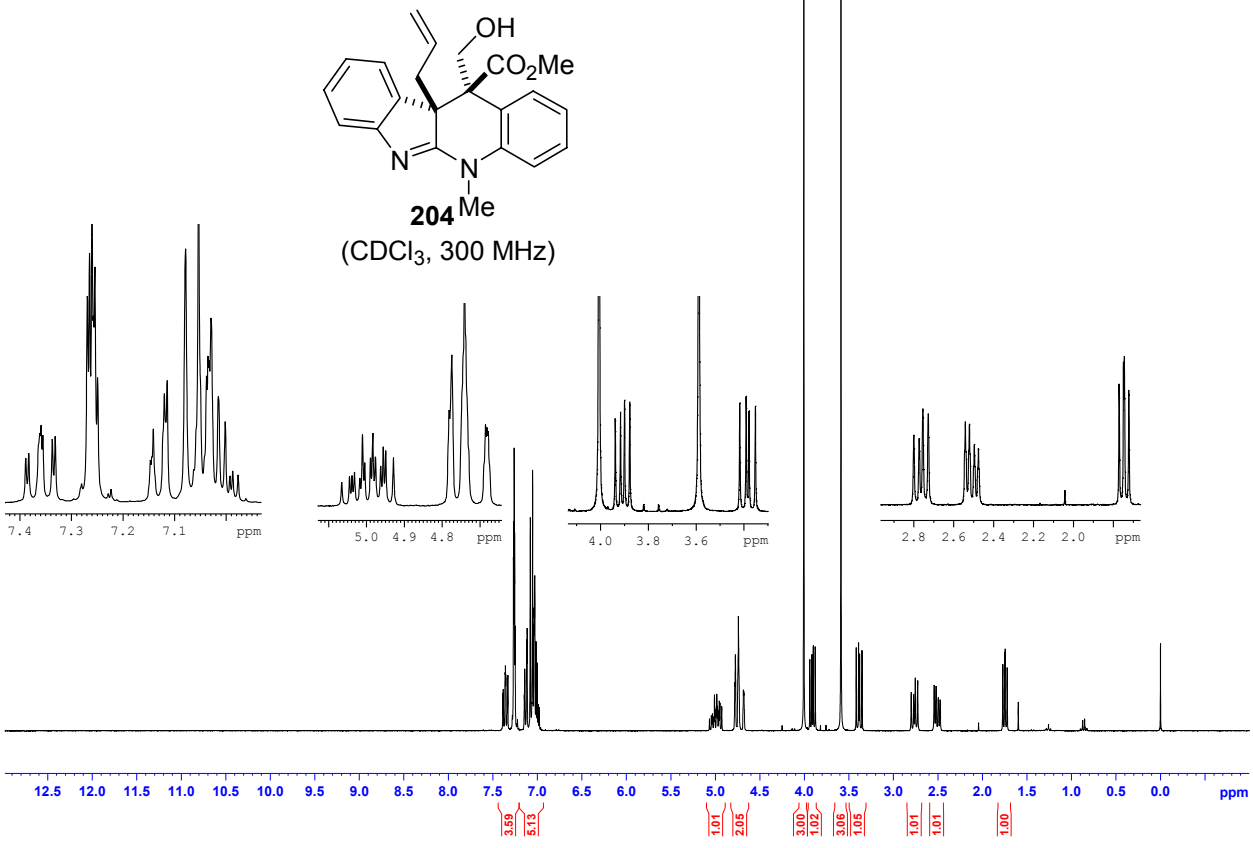

O
N
N
Me
130
(CDCl3, 300 MHz)
8.0 7.8 7.6 7.4 7.2 ppm
5.6 5.4 5.2 5.0 ppm
2.9 2.8 2.7 2.6 2.5 2.4 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99 2.05 2.06 3.04 1.00 1.03 1.02 3.00 1.01 1.01

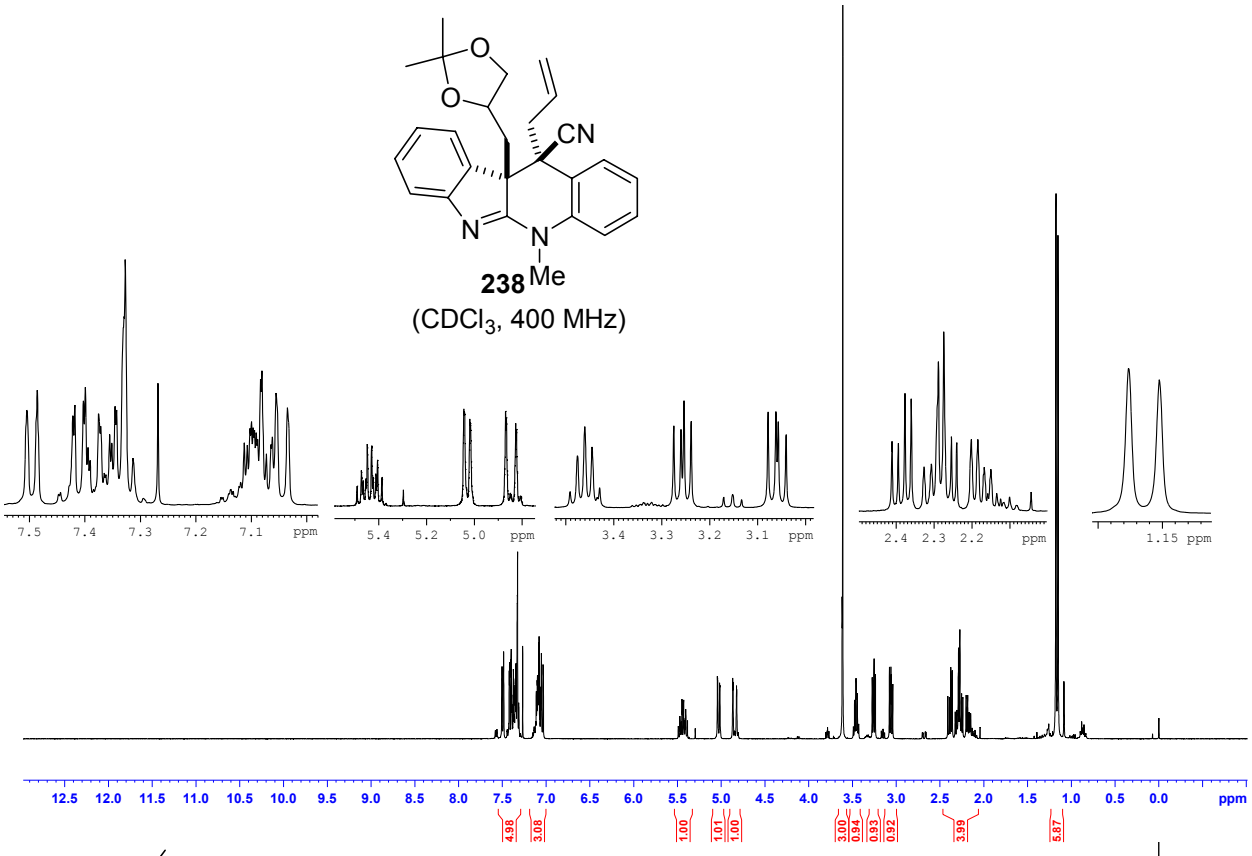

O
N
N
Me
191
(CDCl3, 300 MHz)
7.5 7.4 7.3 7.2 7.1 7.0 6.9 ppm
5.2 5.0 4.8 ppm
3.1 3.0 2.9 2.8 2.7 2.6 2.5 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
5.44 3.05 0.99 2.01 3.00 1.00 1.02 2.01

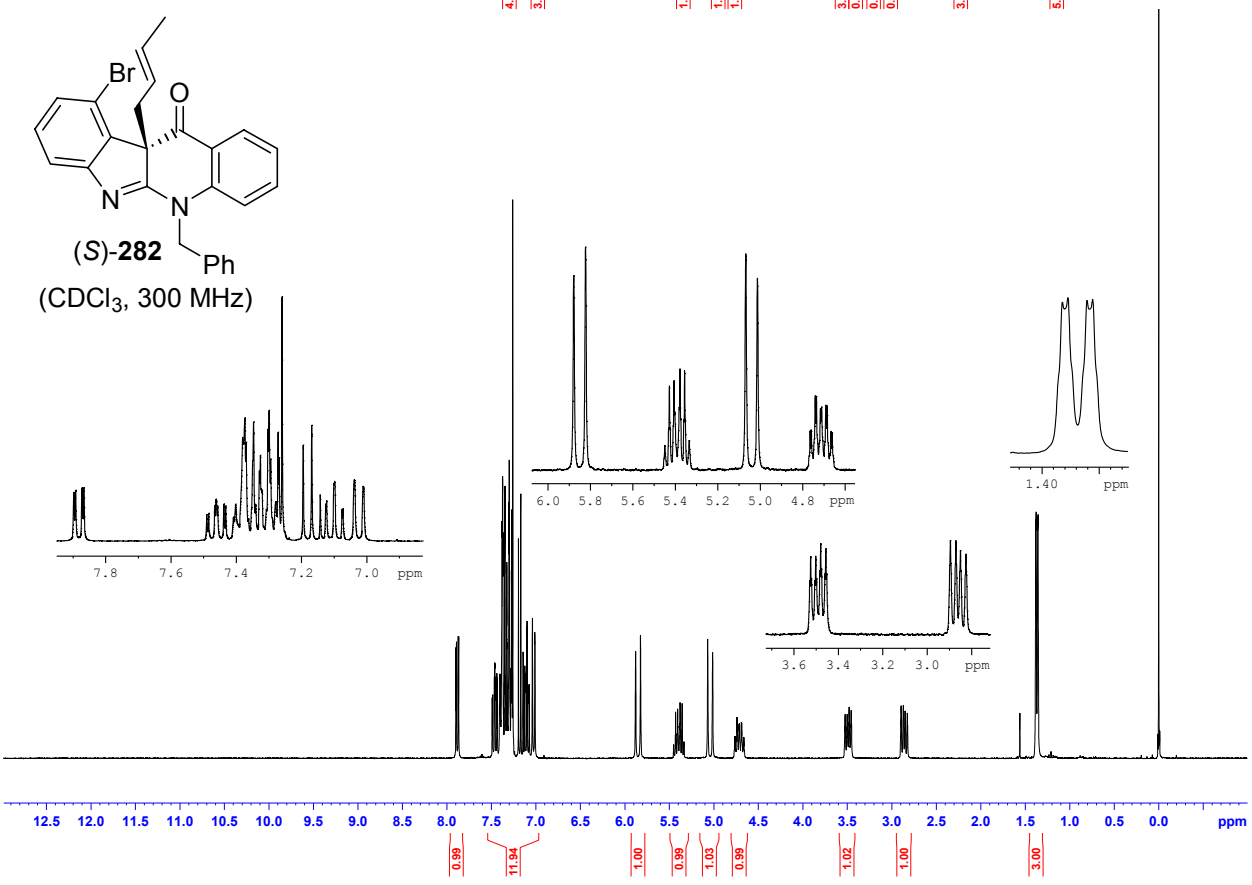

OH
H
N
N
Me
195
(CDCl3, 300 MHz)
7.8 7.6 7.4 7.2 7.0 ppm
5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 ppm
3.0 2.8 2.6 2.4 2.2 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 4.52 3.03 0.98 3.03 1.03 3.00 0.98 2.01 1.02


H
CO2Me
N
N
Me
197
(CDCl3, 300 MHz)
7.6 7.4 7.2 7.0 ppm
5.2 5.0 4.8 4.6 4.4 4.2 ppm
2.9 2.8 2.7 2.6 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
4.18 5.02 1.00 2.00 0.94 2.94 3.00 1.00 0.99


CO2Me
N
N
Me
203
(CDCl3, 300 MHz)
7.4 7.3 7.2 7.1 7.0 ppm
5.4 5.2 5.0 4.8 ppm
2.8 2.6 2.4 2.2 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.28 5.05 0.99 1.02 4.05 2.99 3.00 1.01 1.02 1.01 1.03


OH
CO2Me
N
N
Me
204
(CDCl3, 300 MHz)
7.4 7.3 7.2 7.1 ppm
5.0 4.9 4.8 ppm
4.0 3.8 3.6 ppm
2.8 2.6 2.4 2.2 2.0 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.59 5.13 1.01 2.05 3.00 1.02 3.06 1.05 1.01 1.01 1.00


O
O
CN
N
N
Me
238
(CDCl3, 400 MHz)
7.5 7.4 7.3 7.2 7.1 ppm
5.4 5.2 5.0 ppm
3.4 3.3 3.2 3.1 ppm
2.4 2.3 2.2 ppm
1.15 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
4.98
3.08
1.00
1.01
1.00
3.00
0.94
0.93
0.92
3.99
5.87


Br
O
N
N
Ph
(S)-282
(CDCl3, 300 MHz)
7.8 7.6 7.4 7.2 7.0 ppm
6.0 5.8 5.6 5.4 5.2 5.0 4.8 ppm
1.40 ppm
3.6 3.4 3.2 3.0 ppm
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99
11.94
1.00
0.99
1.03
0.99
1.02
1.00
3.00

Appendix 4: Crystallographic Data

Crystal data and structure refinement for 6-allyl-5-methyl-5*H*-indolo[2,1-*b*]quinazolin-12-one (138)

Identification code	nvnw3	
Empirical formula	$C_{19}H_{16}N_2O$	
Formula weight	288.34	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 11.332(3) Å	α = 90°.
	b = 17.217(4) Å	β = 107.218(7)°.
	c = 7.5306(19) Å	γ = 90°.
Volume	1403.4(6) $Å^3$	
Z	4	
Density (calculated)	1.365 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	608	
Crystal size	0.2000 x 0.0300 x 0.0300 mm^3	
Theta range for data collection	2.22 to 25.31°.	
Index ranges	-13<=h<=13, -16<=k<=20, -7<=l<=9	
Reflections collected	8730	
Independent reflections	2532 [R(int) = 0.0589]	
Completeness to theta = 25.00°	98.9 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9872	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2532 / 0 / 201	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0510, wR2 = 0.1329	
R indices (all data)	R1 = 0.0593, wR2 = 0.1400	
Largest diff. peak and hole	0.241 and -0.324 $e.Å^{-3}$	

Crystal data and structure refinement for 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (130)

Identification code	nvnw2	
Empirical formula	$C_{19}H_{16}N_2O$	
Formula weight	288.34	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.803(2) Å	α= 69.857(9)°.
	b = 11.370(3) Å	β= 76.385(9)°.
	c = 14.533(3) Å	γ = 75.170(11)°.
Volume	1450.7(6) $Å^3$	
Z	4	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	608	
Crystal size	0.20 x 0.15 x 0..15 mm^3	
Theta range for data collection	3.03 to 25.34°.	
Index ranges	-11<=h<=11, -7<=k<=13, -17<=l<=17	
Reflections collected	8213	
Independent reflections	4769 [R(int) = 0.0517]	
Completeness to theta = 25.00°	91.7 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.3123	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4769 / 0 / 400	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2sigma(I)]	R1 = 0.0663, wR2 = 0.1551	
R indices (all data)	R1 = 0.0866, wR2 = 0.1712	
Largest diff. peak and hole	0.275 and -0.327 $e.Å^{-3}$	

Crystal data and structure refinement for 5,10b-dihydro-10b-allyl-5-benzyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (161)

Identification code	nvnw11	
Empirical formula	$C_{25}H_{20}N_2O$	
Formula weight	364.43	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.8504(11) Å	α = 89.003(9)°.
	b = 9.4200(13) Å	β = 74.988(6)°.
	c = 11.6217(15) Å	γ = 84.933(9)°.
Volume	932.2(2) $Å^3$	
Z	2	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	384	
Crystal size	0.2000 x 0.1000 x 0.0500 mm^3	
Theta range for data collection	2.17 to 25.34°.	
Index ranges	-10<=h<=10, -9<=k<=11, -13<=l<=12	
Reflections collected	6101	
Independent reflections	3209 [R(int) = 0.0252]	
Completeness to theta = 25.00°	94.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8433	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3209 / 0 / 255	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.1000	
R indices (all data)	R1 = 0.0485, wR2 = 0.1066	
Extinction coefficient	0.030(7)	
Largest diff. peak and hole	0.228 and -0.201 $e.Å^{-3}$	

Crystal data and structure refinement for rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,3-b]quinoline-11-ol (186)

Identification code	nvnw14	
Empirical formula	$C_{19}H_{18}N_2O$	
Formula weight	290.35	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.5564(10) Å	α = 108.091(3)°.
	b = 11.5496(13) Å	β = 95.188(2)°.
	c = 12.9057(15) Å	γ = 90.667(2)°.
Volume	1488.3(3) $Å^3$	
Z	4	
Density (calculated)	1.296 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	616	
Crystal size	0.1300 x 0.1000 x 0.1000 mm^3	
Theta range for data collection	1.67 to 25.34°.	
Index ranges	-12<=h<=12, -13<=k<=13, -15<=l<=13	
Reflections collected	9720	
Independent reflections	5124 [R(int) = 0.0191]	
Completeness to theta = 25.00°	94.7 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9424	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5124 / 2 / 408	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0390, wR2 = 0.0916	
R indices (all data)	R1 = 0.0458, wR2 = 0.0977	
Largest diff. peak and hole	0.197 and -0.191 $e.Å^{-3}$	

Crystal data and structure refinement for rac-(10b*S*,11*S*)-10b-allyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinolin-11-spiro-2'-oxirane (191)

Identification code	nvnw6	
Empirical formula	$C_{20}H_{18}N_2O$	
Formula weight	302.36	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Rhombohedral	
Space group	R-3	
Unit cell dimensions	a = 24.708(4) Å	α = 90°.
	b = 24.708(4) Å	β = 90°.
	c = 13.524(2) Å	γ = 120°.
Volume	7150.0(19) $Å^3$	
Z	18	
Density (calculated)	1.264 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	2880	
Crystal size	0.150 x 0.100 x 0.030 mm^3	
Theta range for data collection	2.86 to 25.34°.	
Index ranges	-23<=h<=29, -25<=k<=29, -13<=l<=16	
Reflections collected	13581	
Independent reflections	2823 [R(int) = 0.0368]	
Completeness to theta = 25.34°	97.2 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.6569	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2823 / 0 / 210	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0712, wR2 = 0.2014	
R indices (all data)	R1 = 0.0800, wR2 = 0.2129	
Largest diff. peak and hole	2.318 and -0.332 $e.Å^{-3}$	

Crystal data and structure refinement for rac-(10b*R*,11*R*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline (192)

Identification code	nvnw4	
Empirical formula	$C_{20}H_{20}N_2O$	
Formula weight	304.38	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.121(2) Å	α = 90°.
	b = 11.403(2) Å	β = 90°.
	c = 17.486(5) Å	γ = 90°.
Volume	1619.2(7) $Å^3$	
Z	4	
Density (calculated)	1.249 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	648	
Crystal size	0.1000 x 0.0300 x 0.0100 mm^3	
Theta range for data collection	2.13 to 25.35°.	
Index ranges	-9<=h<=6, -10<=k<=13, -20<=l<=18	
Reflections collected	10586	
Independent reflections	2923 [R(int) = 0.0677]	
Completeness to theta = 25.35°	99.0 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.5286	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2923 / 1 / 215	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0832, wR2 = 0.2077	
R indices (all data)	R1 = 0.1104, wR2 = 0.2310	
Absolute structure parameter	-4(4)	
Extinction coefficient	0.022(6)	
Largest diff. peak and hole	0.330 and -0.251 $e.Å^{-3}$	

Crystal data and structure refinement for rac-(10b*R*,11*S*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline (195)

Identification code	nvnw5	
Empirical formula	$C_{20}H_{20}N_2O$	
Formula weight	304.38	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 12.742(4) Å	α = 90°.
	b = 14.828(3) Å	β = 90°.
	c = 16.748(4) Å	γ = 90°.
Volume	3164.4(14) $Å^3$	
Z	8	
Density (calculated)	1.278 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	1296	
Crystal size	0.2000 x 0.1000 x 0.0200 mm^3	
Theta range for data collection	2.43 to 25.31°.	
Index ranges	-11<=h<=15, -14<=k<=17, -19<=l<=19	
Reflections collected	18917	
Independent reflections	2869 [R(int) = 0.0633]	
Completeness to theta = 25.31°	99.5 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.4324	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2869 / 1 / 215	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0543, wR2 = 0.1317	
R indices (all data)	R1 = 0.0630, wR2 = 0.1380	
Extinction coefficient	0.0048(11)	
Largest diff. peak and hole	0.231 and -0.245 $e.Å^{-3}$	

Crystal data and structure refinement for rac-(10b*R*,11*S*)-10b,11-diallyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (203)

Identification code	nvnw7	
Empirical formula	$C_{24}H_{24}N_2O_2$	
Formula weight	372.45	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.9672(14) Å	α = 90°.
	b = 14.623(3) Å	β = 94.361(6)°.
	c = 16.505(3) Å	γ = 90°.
Volume	1917.2(6) $Å^3$	
Z	4	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	792	
Crystal size	0.100 x 0.100 x 0.100 mm^3	
Theta range for data collection	3.05 to 25.35°.	
Index ranges	-7<=h<=9, -17<=k<=17, -15<=l<=19	
Reflections collected	10822	
Independent reflections	3315 [R(int) = 0.0500]	
Completeness to theta = 25.35°	94.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.5182	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3315 / 0 / 256	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.0941	
R indices (all data)	R1 = 0.0549, wR2 = 0.1001	
Largest diff. peak and hole	0.237 and -0.213 $e.Å^{-3}$	

Crystal data and structure refinement for rac-(10b*R*,11*S*)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10b*H*-indolo[2,5-*b*]quinoline-11-carboxylic acid methyl ester (204)

Identification code	nvnw9	
Empirical formula	$C_{22}H_{22}N_2O_3$	
Formula weight	362.42	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.338(5) Å	α = 90°.
	b = 10.644(5) Å	β = 90°.
	c = 16.851(8) Å	γ = 90°.
Volume	1854.3(15) $Å^3$	
Z	4	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	768	
Crystal size	0.1000 x 0.0500 x 0.0500 mm^3	
Theta range for data collection	2.26 to 25.37°.	
Index ranges	-12<=h<=12, -12<=k<=12, -20<=l<=20	
Reflections collected	18221	
Independent reflections	3349 [R(int) = 0.0654]	
Completeness to theta = 25.00°	98.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8279	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3349 / 1 / 252	
Goodness-of-fit on F^2	1.093	
Final R indices [I>2sigma(I)]	R1 = 0.0589, wR2 = 0.1315	
R indices (all data)	R1 = 0.0651, wR2 = 0.1362	
Absolute structure parameter	1.6(16)	
Extinction coefficient	0.0085(18)	
Largest diff. peak and hole	0.225 and -0.229 $e.Å^{-3}$	

Crystal data and structure refinement for 5,10b-dihydro-10b-allyl-5-benzyl-10-bromo-10b*H*-indolo[2,3-*b*]quinolin-11-one (258)

Identification code	nvnw10	
Empirical formula	$C_{25}H_{19}BrN_2O$	
Formula weight	443.33	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 30.457(10) Å	α = 90°.
	b = 8.162(2) Å	β = 122.791(12)°.
	c = 18.382(5) Å	γ = 90°.
Volume	3841(2) $Å^3$	
Z	8	
Density (calculated)	1.533 Mg/m^3	
Absorption coefficient	2.160 mm^{-1}	
F(000)	1808	
Crystal size	0.030 x 0.030 x 0.010 mm^3	
Theta range for data collection	2.62 to 25.35°.	
Index ranges	-34<=h<=36, -9<=k<=9, -18<=l<=21	
Reflections collected	10780	
Independent reflections	3401 [R(int) = 0.1102]	
Completeness to theta = 25.00°	97.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8220	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3401 / 0 / 263	
Goodness-of-fit on F^2	1.095	
Final R indices [I>2sigma(I)]	R1 = 0.0569, wR2 = 0.0731	
R indices (all data)	R1 = 0.0963, wR2 = 0.0815	
Largest diff. peak and hole	0.489 and -0.597 $e.Å^{-3}$	

Crystal data and structure refinement for (*S*)-(-)-5-benzyl-10-bromo-10b-(*E*-but-2-enyl)-5*H*-indolo[2,3-*b*]quinolin-11-one ((*S*)-282)

Identification code	nvnw13	
Empirical formula	$C_{26}H_{21}BrN_2O$	
Formula weight	457.36	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 8.7486(17) Å	α = 101.33(3)°.
	b = 9.3067(19) Å	β = 99.93(3)°.
	c = 13.714(3) Å	γ = 90.56(3)°.
Volume	1077.4(4) $Å^3$	
Z	2	
Density (calculated)	1.410 Mg/m^3	
Absorption coefficient	1.928 mm^{-1}	
F(000)	468	
Crystal size	0.1000 x 0.1000 x 0.0800 mm^3	
Theta range for data collection	2.23 to 25.28°.	
Index ranges	-10<=h<=10, -11<=k<=7, -16<=l<=16	
Reflections collected	6436	
Independent reflections	4997 [R(int) = 0.0640]	
Completeness to theta = 25.00°	93.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.6056	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4997 / 3 / 545	
Goodness-of-fit on F^2	1.003	
Final R indices [I>2sigma(I)]	R1 = 0.0621, wR2 = 0.1269	
R indices (all data)	R1 = 0.0775, wR2 = 0.1376	
Absolute structure parameter	-0.005(14)	
Extinction coefficient	0.022(2)	
Largest diff. peak and hole	1.054 and -0.516 e.$Å^{-3}$	

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