TOTAL SYNTHESIS OF

ANCISTROTANZANINE A

A Thesis

Submitted in Fulfillment

of the Requirements for the Degree

of

Doctor of Philosophy in Chemistry

at

The University of Adelaide

School of Chemistry and Physics

By

Jason Stewart Brusnahan

B. Sc. (Honours)

THE UNIVERSITY
OF ADELAIDE
AUSTRALIA

October 2009

'If it's not red, it's dead.'

Jason Brusnahan

Table of Contents

Chapter 5: Experimental

Abstract

This thesis describes the first total synthesis of ancistrotanzanine A, a member of the naphthylisoquinoline class of natural products. In Chapter 1 the synthetic challenges presented by the naphthylisoquinoline alkaloids are discussed and strategies that have been adopted in previous syntheses of naphthylisoquinoline alkaloids overviewed.

Chapter 2 describes the preparation of the key 5,3′-biaryl linkage via the Pinhey-Barton reaction. Studies into forming the linkage atropselectively were investigated using chiral hydrobenzoin acetal auxiliaries. This was found to have limited success with an atropisomeric ratio of 65:35 obtained. Changing the base from the achiral pyridine to the chiral brucine was also investigated and found to give no enhancement in the diastereoselectivity. From the results presented in Chapter 2, it was concluded that hydrobenzoin acetal auxiliaries were not appropriate for the diastereoselective synthesis of the key biaryl linkage of ancistrotanzanine A.

As the chiral acetal strategy outlined in Chapter 2 failed to yield an atropselective process, efforts were re-focused on a new approach to the naphthylisoquinolines. In Chapter 3, an overview of all the methods available for the synthesis of chiral 3,4-dihydroisoquinolines is provided. From this, it was decided to apply the alkylation of *o*-tolylnitriles with chiral sulfinimines, as originally developed by Davis, to the synthesis of naphthylisoquinolines. Synthesis of the *o*-tolylnitrile lead reagent was readily achieved, but it was found that the amount of lead tetraacetate had to be carefully controlled to avoid side-reactions in the Pinhey-Barton reaction. After careful optimisation, the key 5,3′-biaryl linkage was prepared in high yield. Application of the Davis methodology to the MOM protected biaryl failed, with no reaction resulting. After much experimentation, it was established that the reaction was very sensitive to steric hindrance. A successful reaction was finally achieved by changing the base to lithium diethylamide. However, it was found the diastereoselection of the alkylation was quite low when *p*-tolyl sulfinimine was used. The use of the *t*-butane sulfinimine meant that the diastereoselection was significantly improved, with a ratio of 85:15 being obtained. After 3 more steps, the total synthesis was completed and ancistrotanzanine A was obtained, as a

1:1 mixture of atropisomers. Efforts to separate the atropisomers formed failed and even the use of chiral HPLC failed to resolve the material. To complete the Chapter, two analogues of ancistrotanzanine A were prepared – the tetrahydroisoquinoline and the methoxy ether.

Chapter 4 summarises the above results and discusses the future potential of this research.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Jason Stewart Brusnahan and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Jason Stewart Brusnahan   Date: 1st of October 2009

Acknowledgements

I would like to thank Dr Jonathan Morris for his supervision and guidance throughout my Ph.D. I am grateful that he always had time to talk about my project and for the hours he has put into checking and revising this thesis. I also thank him for the extensive training he has given me both in the lab and the gym.

Thanks also must go to the past and present members of Team Morris, for making my time both enjoyable and memorable. In particular, I must thank Erin for putting up with me in the same lab for so many years and for the education in music. Thanks to Scott Walker for allowing me to pick his brain and for reading my early drafts of this thesis. Thanks Milena and Belinda for keeping the lab fun and to Emma Wiadrowski who was great support in the early days. Thanks to Hamish for continuing my research.

Thanks to the technical staff of the Chemistry Department, in particular Phil Clements for running the 600 MHz NMR experiments.

The University of Adelaide and the Department of Chemistry are gratefully acknowledged for funding.

A big thank you to my friends for all the support and fun times I've enjoyed throughout my time as a student and for reminding me just how long it's been! I especially thank Jeff and Caleb for their support during the start of my Ph.D. and the other members of the tennis team, Dion, Daniel and Jono for providing some fun and entertaining times that were a good release from the frustrations of the lab.

Thank you to my family especially Mum and Dad. Thank you for your support, continual love and encouragement throughout my studies and for giving me the opportunity to move to Adelaide to undertake further study. This means a tremendous amount to me.

Mostly, thank you Shylie for your love and support. Thanks for putting up with not seeing much of me towards the end of lab work and my frustration when experiments haven't worked. You have always helped keep me grounded and focused and I can't thank you enough.

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AIBN	2,2'-Azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
BHA	2-*t*-Butyl-4-hydroxyanisole
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl amide
Bp	Boiling point
br	Broad
Bu	Butyl
BTMA	Benzyltrimethylammonium
cat	Catalytic
CD	Circular Dichroism
Conc	Concentrated
COSY	Correlation spectroscopy
δ	Chemical shift in parts per million downfield from tetramethylsilane
d	doublet (NMR)
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[4.3.0]non-5-ene
DCC	Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride

DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine
DME	Dimethyl ether
DMF	*N*, *N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppt	1,1'-Bis(diphenylphosphanyl)ferrocenyl
ee	Enantiomeric excess
eq	equivalents
Et	Ethyl
ESI-MS	Electrospray ionisation mass spectrometry
Fmoc	Fluorenyl methyloxycarbonyl
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoric triamide
HPLC	High-pressure liquid chromatography
HRMS	High-resolution mass spectrometry
INADEQUATE	Incredible natural abundance double quantum transfer experiment
J	Coupling constant (NMR)
IR	Infrared Radiation
LDA	Lithium diisopropylamide
m	Multiplet (NMR)
Me	Methyl
MHz	Megahertz
min	Minutes

MOM	Methoxymethyl
Mp	Melting point
Ms	Methanesulfonyl
MSD	Mass spectroscopy detection
NBS	*N*-Bromosuccinimide
NOE	Nuclear Overhauser Effect
NMR	Nuclear magnetic resonance
ppm	Parts per million
Pr	Propyl
q	Quartet (NMR)
Q	Quaternary carbon
ROESY	Rotating-frame overhauser effect spectroscopy
r.t.	Room temperature
s	Singlet (NMR)
t	Triplet (NMR)
sat	Saturated
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl

Ts   *p*-Toluenesulfonyl

WSC   Water soluble carbodiimide hydrochloride

Chapter One

Introduction

1.1   General Introduction

Naturally occurring compounds have traditionally served as the source of new leads for drug discovery, forming the basis for most early medicines. The biodiversity inherent in nature provides a prolific source of structurally diverse secondary metabolites. In particular, plants have been found to be a rich source of such natural products, many of which have played a pivotal role in the development of medicinal agents for the treatment of disease. Significant drugs isolated from plants include the analgesic compound morphine and the anti cancer drug paclitaxel (Taxol®) (**Figure 1.1**).[1]
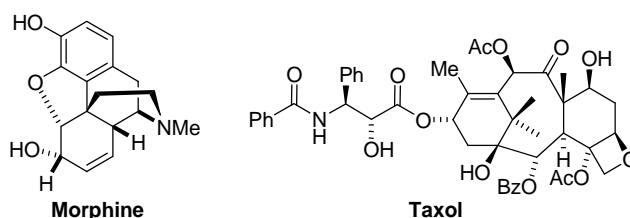

Figure 1.1   Historically significant natural products isolated from plants.

The search for new biologically active natural products from plant extracts is an ongoing and rewarding exercise. Of particular interest are plants that have been used as folk medicines, such as the plant families *Dionocophyllaceae* and *Ancistrocladus*. These plants have been used as folk medicines in West Africa and South East Asia, especially as treatments for malaria and dysentery.[2] *Dionocophyllaceae* consists of three monotypic genera, *Habropetalum, Diconophyllum,* and *Triphyophyllum. Ancistrocladaceae* contains one genus, *Ancistrocladus*, which consists of approximately 30 species that are distributed in the Indian archipelago, tropical Asia and tropical West Africa.[3,4] Over the last three decades extracts from these plant families have been analysed. Examination of these extracts has revealed that their profound biological activity is due to the presence of naphthylisoquinoline alkaloids. Over 100 naphthylisoquinoline alkaloids have now been isolated, structurally assigned and tested for their bioactivities. These biological activities include antimalarial[5-16], fungicidal[17], insect growth retardant[18] and anti-HIV[19-24] activity. The naphthylisoquinoline alkaloid dimer michellamine B was selected for preclinical drug development by the U.S. National Cancer Institute due to its potent anti-HIV

activity (**Figure 1.2**).[24] However, clinical use of michellamine B has been hampered by its potent cytotoxicity.[24]
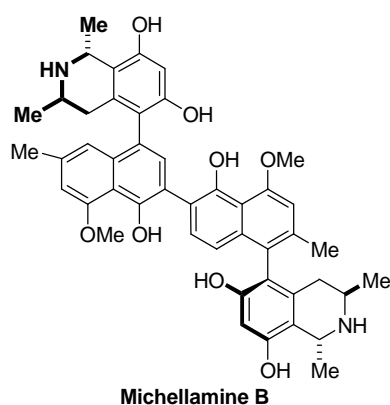

Michellamine B

Figure 1.2 The anti-HIV naphthylisoquinoline alkaloid dimer michellamine B.

As their name suggests, the naphthylisoquinoline alkaloids contain both an isoquinoline and naphthalene moiety, linked by a biaryl bond. The isoquinoline moiety normally exists as a dihydro-or tetrahydroisoquinoline with 1 or 2 stereocentres respectively. The two molecular portions can be linked in either the *ortho-* or in the *para*-positions relative to the phenolic oxygen functions in positions 1′, 3′, 6′, or 8′ and at C-5 or C-7 of the isoquinoline portion. Recently N,C-coupled naphthylisoquinoline alkaloids have also been found in Nature.[25] Shown in **Figure 1.3** are representative examples of each type of linkage, thus illustrating the structural diversity present within this class of compound.[25-30]

7,6'-linked
Dioncophylline B

7,3'-linked
Ancistrocladidine

5,1'-linked
Dioncophylline C

5,3'-linked
Ancistrotanzanine A

N-C-linked
Ancistrocladinium A

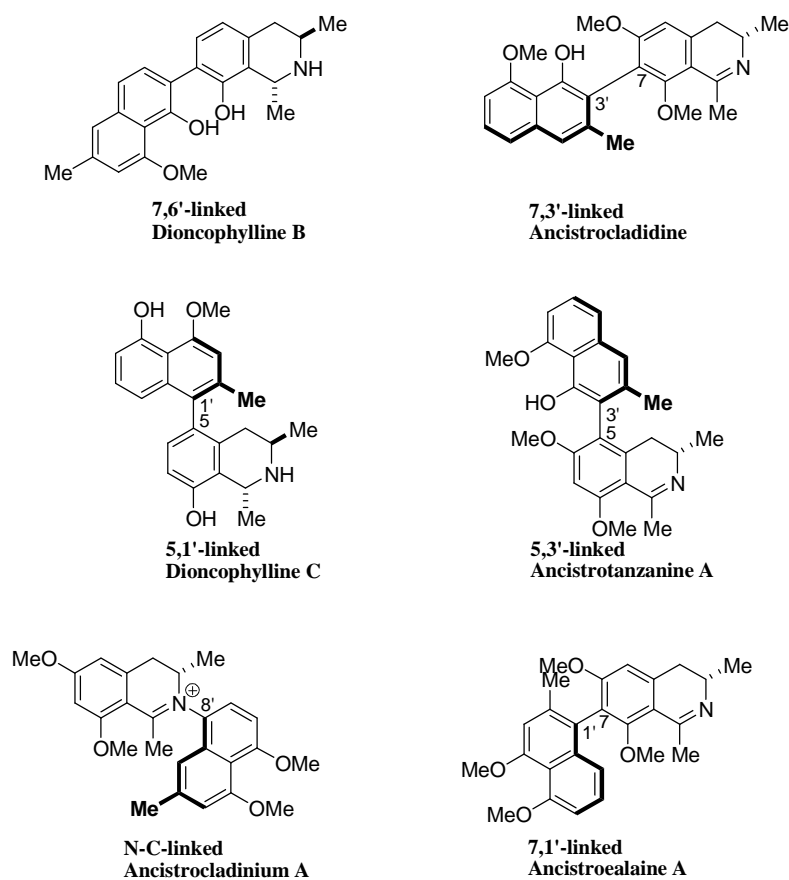**7,1'-linked**
Ancistroealaine A

Figure 1.3   Representative naphthylisoquinoline alkaloids.

It has generally been assumed that all tetrahydroisoquinoline alkaloids are derived from aromatic amino acids such as tyrosine, with the key biosynthetic step involving the Pictet-Spengler condensation reaction of 2-arylethylamines, such as dopamine **1.1**, with aldehydes or α-keto acids. For example, the biosynthetic pathway that produces the benzylisoquinoline alkaloids begins with the conversion of tyrosine into both dopamine and 4-hydroxyphenylacetaldehyde **1.2** (**Figure 1.4**).[31] Four enzymes catalyse the hydroxylation, decarboxylation and transamination reactions that yield the two intermediates. The enzyme norcoclaurine synthase catalyses the condensation of dopamine with aldehyde **1.2** to give (*S*)-norcoclaurine. The structural diversity of isoquinolines found in nature via this route originates from the variation of the aldehyde precursor and subsequent transformations of the tetrahydroisoquinoline initially formed.
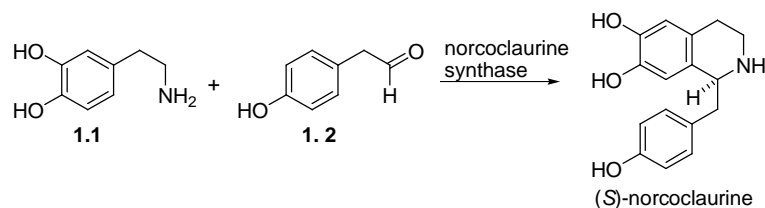
Figure 1.4   Biosynthesis of tetrahydroisoquinoline alkaloids.

The structure of dioncophylline A (**1.8**) and other naphthylisoquinoline alkaloids, however, do not fit this general biosynthetic pathway (**Scheme 1.1**).[32,33] Bringmann hypothesised that the substitution pattern of naphthylisoquinoline alkaloids strongly pointed to a biosynthetic pathway involving β-polyketides formed from acetate subunits.[33] To test this hypothesis, Bringmann and coworkers fed the presumed precursor acetate **1.3**, labeled in [$^{13}C_2$]-acetate form, to cell cultures of *T. peltatum*, which were capable of forming dioncophylline A.[32] After incubation, dioncophylline A was isolated and analyzed by 2D INADEQUATE NMR. The spectrum showed pairwise ^{13}C-^{13}C correlations originating from the acetate units being incorporated intact into the natural product **1.8**.[32] Closer examination revealed the entire carbon skeleton of both molecular halves of the dioncophylline A isolated were derived from the acetate subunits.[32] Bringmann and coworkers proposed that the naphthalene **1.6** and isoquinoline **1.7** moiety may be formed via the same β-pentaketo precursor **1.5**. According to their proposed biosynthetic hypothesis, the hexaketide molecule **1.4** would undergo aldol condensation and aromatization to provide a monocyclic diketone of type **1.5**. This diketone **1.5** can be used to form both the naphthalene and dihydroisoquinoline. Initial aldol cyclisation of diketone **1.5** would give the corresponding naphthalene portion **1.6** while reductive animation of the acetonyl keto function of **1.5**, would deliver the respective primary amine, which would condense to form the desired dihydroisoquinoline **1.7**. The two molecular halves could then be joined together by phenol-oxidative biaryl coupling, which after further reactions would yield the complete alkaloid.
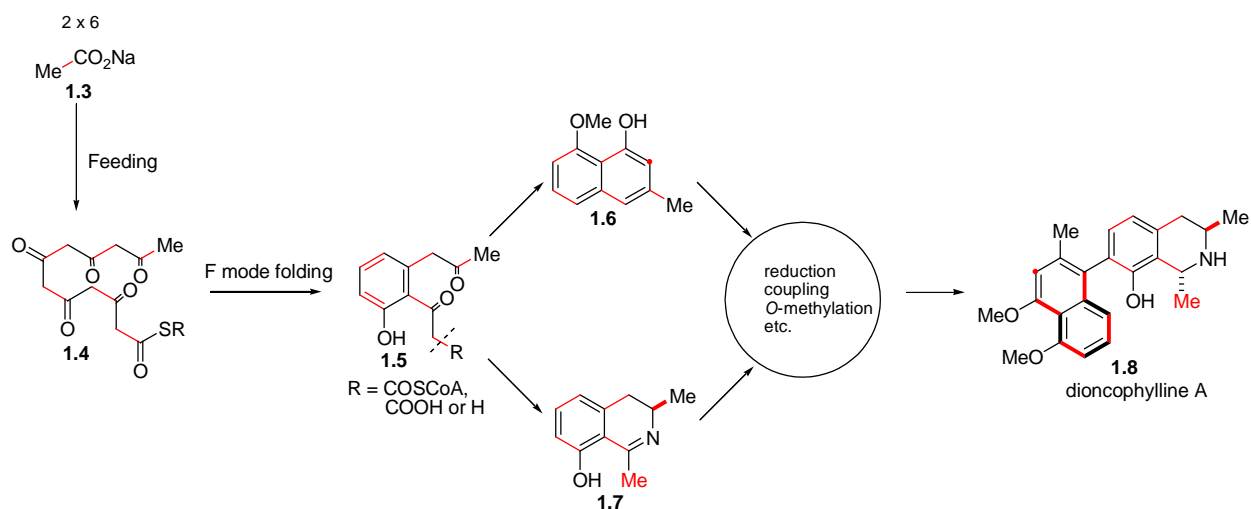
Scheme 1.1   Postulated biosynthetic pathway of the naphthylisoquinoline alkaloids dioncophylline A reported by Bringmann. The $^{13}C_2$ units are labeled in red.

Bringmann and coworkers have also conducted feeding experiments with the ^{13}C labeled isoquinoline precursor unit **1.9** using the same cell cultures of *T. peltatum* (**Figure 1.5**).[34] The INADEQUATE spectrum of the obtained dioncophylline A was found to exhibit two doublets for the $^{13}C_2$ unit of C-1 and Me-1. This confirmed that the $^{13}C_2$ labeled isoquinoline precursor **1.9** was still intact and incorporated in the isolated natural product.[34] This work constituted the first direct evidence that the two molecular portions, the naphthalene and the isoquinoline, are formed separately and are coupled to each other in an advanced form.

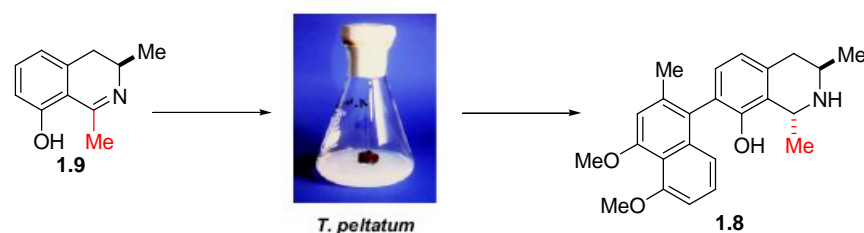**Figure 1.5** $^{13}C_2$-labeled metabolite dioncophylline A isolated from callus cultures of *T. peltatum* after feeding with $[1,1'-^{13}C_2]$-**1.9**.

The biosynthetic origin of naphthylisoquinoline alkaloids is an ongoing area of research in Bringmann's laboratories.

1.2   The Atropisomerism Phenomenon

Optical activity due to axial chirality has been known since the early 20th century and was first correctly described by Christie and Kenner in 1922.[35] Axial chirality arises from the hindered rotation around the biaryl bond due to the presence of at least two bulky substituents in the *ortho*-position of this bond.[36] The absolute axial configuration can be denoted by analysis of a Newman projection along the biaryl axis (**Figure 1.6**). After assignment of priority to the *ortho* substituents according to the Cahn-Ingold-Prelog rules, the analysis is done by following the shortest 90° path from the substituent of highest priority at the proximal ring to the highest ranking one at the distal ring. If the turn is counterclockwise the configuration is *M*, and if clockwise it is *P*.
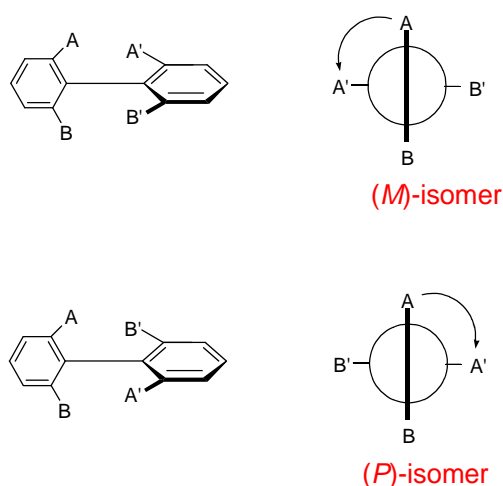

Figure 1.6   Assignment of axial chirality, where A and A′ are of higher priority than B and B′.

The other crucial precondition for atropisomerism is the rotational $\Delta G^{\ddagger}$ stability of the biaryl axis. Temperature has a profound influence on this property. For example, cooling of biaryl compounds, even those with a low degree of steric hindrance, can allow for the identification of atropisomers.[36] On the other hand, compounds that exist as single atropisomers at room temperature may undergo atropisomerisation at elevated temperatures, resulting in thermodynamically controlled equilibrium mixtures. An arbitrary definition for atropisomers is that they must have a half-life of at least 1000 s at a given temperature.[36] Consequently, the minimum free energy barrier required for rotation to occur around the axis varies with temperature.[36]

Mono-*ortho*-substituted biaryl compounds do not show atropisomerism at room temperature. Atropisomerism at room temperature can be observed for two *ortho*-substituents next to the axis, but only if both groups are bulky, as in 1,1′-binaphthalene (**1.10**) (**Figure 1.7**).[36] These bulky substituents provide enough steric repulsion against the small hydrogen atoms to cause restricted rotation about the axis in the transition state **TS-1**.[36] Tri-*ortho*-substituted biaryl compounds normally form stable atropisomers at room temperature due to the increased steric hindrance present when two substituents, other than hydrogen, try to pass one another in the transition state **TS-2**. Aldehyde **1.11** is an example of such a chiral biphenyl.[36] If the substituents are small, however, then slow rotation about the axis may occur, such as that observed for the naphthylisoquinoline alkaloid dioncophylline E **1.12**.[36] Tetra-*ortho*-substituted biaryl compounds, such as **1.13** or **1.14**, form atropisomers, which are stable even under forcing conditions. In most cases the atropisomerisation temperature is so high (for example in **1.15**) that it cannot be reached before decomposition occurs. The phenomenon of atropisomerism has been comprehensively reviewed by Bringmann, Keller and coworkers.[36]
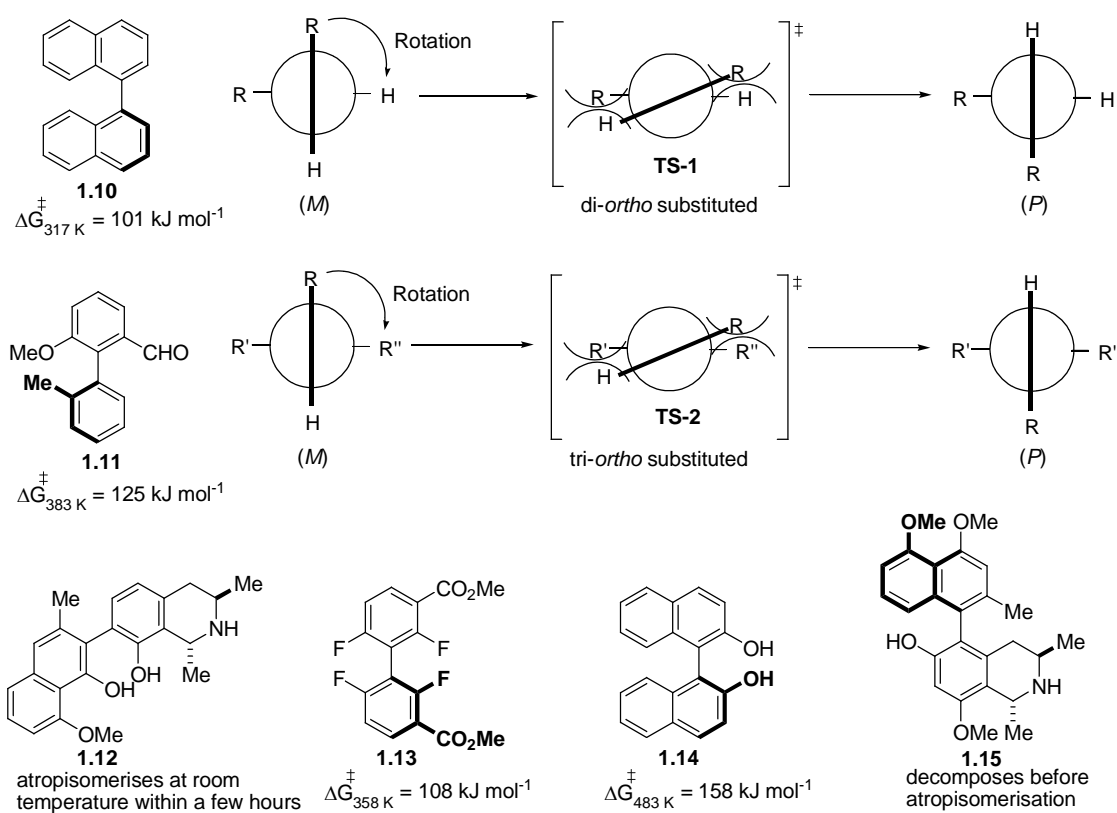

Figure 1.7   Configurational stability of di, tri and tetra-*ortho*-substituted biaryl compounds.

Given that most naphthylisoquinoline alkaloids contain either a tri-*ortho*-substituted or tetra-*ortho*-substituted biaryl linkage, the majority of these natural products exist as stable atropisomers. The stereochemistry of the biaryl axis (*M* or *P*) can be determined from Circular Dichroism (CD) experiments. The configuration of the axis is elucidated by comparison of the theoretically calculated CD spectrum with that obtained experimentally. For example, comparison of both calculated spectra for the *M*-and *P*-models of the naphthylisoquinoline alkaloid yaoundamine A (**1.16**) with the experimental CD spectrum, indicated the alkaloid to be *P*-configured about the biaryl axis (**Figure 1.8**).[37] The calculated spectrum for the *P*-isomer (**P-1.16**) matches quite well with the experimental spectrum, whereas, the theoretical spectrum of the *M*-isomer (**M-1.16**) is nearly completely opposite to the experimental spectrum.
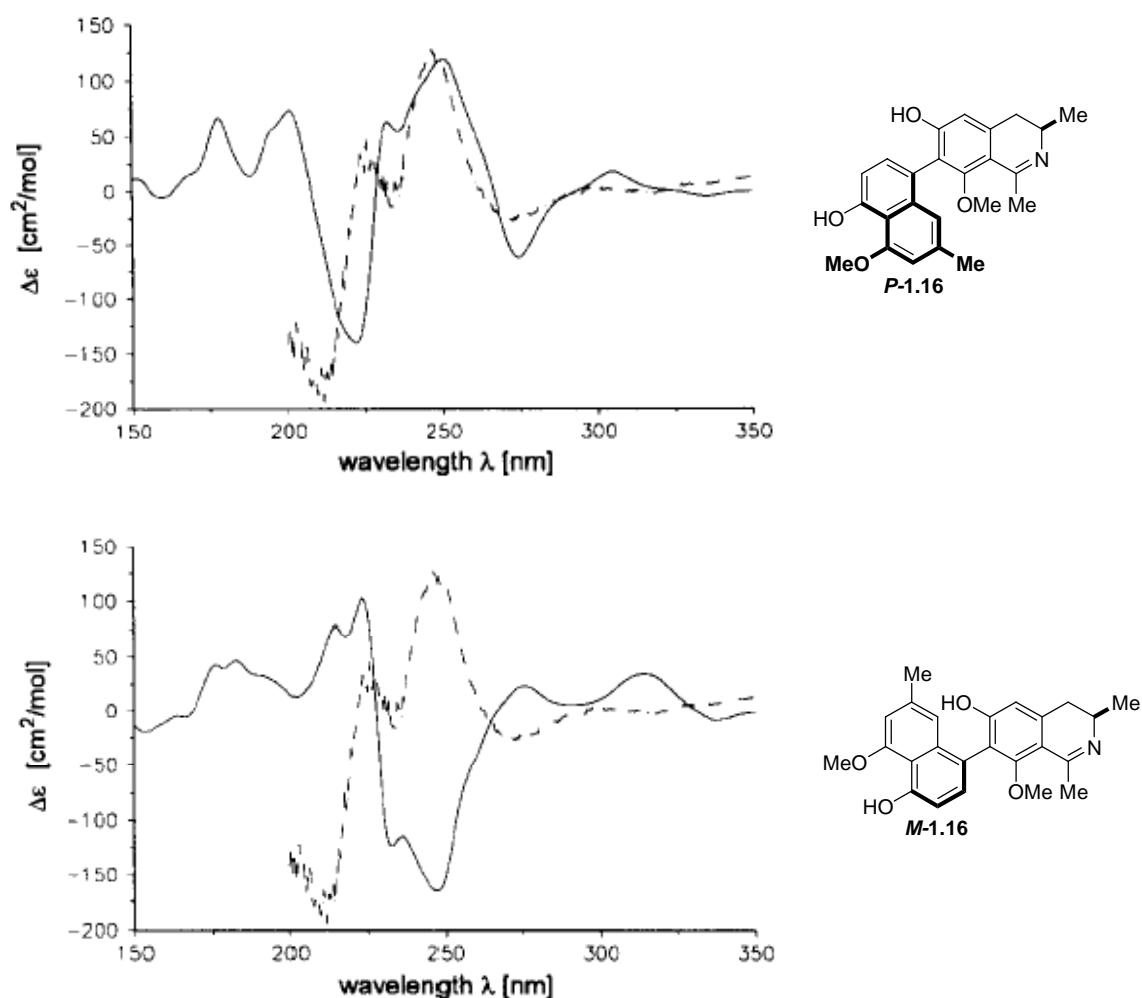

Figure 1.8   Match plot of the calculated CD spectra (-) of the yaoundamine A (*P*-atropisomer top, *M*-atropisomer bottom) with the experimental spectrum (- - -) of the alkaloid as recorded by Bringmann.[37]

1.3   Total Synthesis

The varied biological activity of naphthylisoquinoline alkaloids, coupled with their interesting architecture, has led to much interest in their total synthesis. Access to these compounds and their analogues is required to further their biomedical potential. In addition, by synthesising these challenging biologically active organic molecules the limitations of established synthetic methodology can be revealed. Along with this, situations arise that require new methods of forming and manipulating chemical bonds. As most naphthylisoquinoline alkaloids posses axial chirality, the main focus of the synthesis of these natural products is the stereoselective construction of the biaryl linkage by both *intra* and *inter*-molecular approaches. What follows is a summary of the key strategies that have been used in the total synthesis of naphthylisoquinoline alkaloids with an emphasis on the formation of the biaryl linkage atropselectively.

1.3.1   Intramolecular Approach

Bringmann reported the first total synthesis of a naphthylisoquinoline alkaloid, the 7,1′ linked *O*-methyltetradehydrotriphyophylline **1.19**, in 1984.[38] Initial attempts to perform a coupling between the bromo-naphthalene **1.17** and bromo-isoquinoline **1.18** under classical Ullmann conditions led only to trace (< 1%) amounts of mixed coupled products (**Scheme 1.2**).[38]
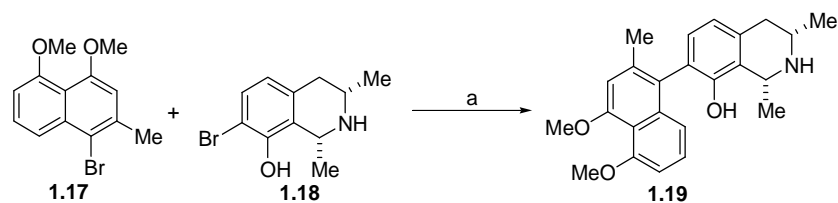
Scheme 1.2   Reagents and Yields: (a) activated copper bronze, 250 °C, <1% of mixed coupled products.

Consequently, an intramolecular coupling approach utilising a temporary ether bridge was employed (**Scheme 1.3**).[38] The ether bridge was prepared by *O*-alkylation of phenol **1.21** with bromide **1.20** under phase transfer conditions. The intramolecular aryl coupling was achieved using a photocyclisation of **1.22**, which gave biaryl **1.23** in 15% yield. Reductive ring opening of ether **1.23** gave biaryl **1.24**, which was readily converted into the racemic natural product **1.19**.
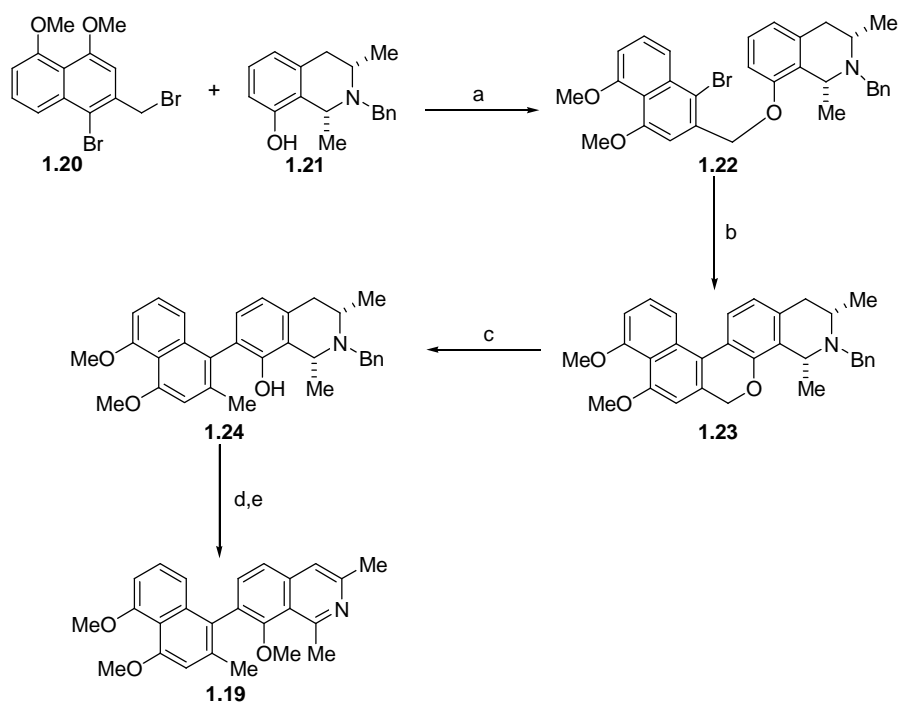
Scheme 1.3   Reagents and yields: (a) BnN(*n*-Bu)$_3$Br, CH$_2$Cl$_2$, 1M NaOH, 93%; (b) hν (254 nm), NEt$_3$, 15%; (c) Li/(C$_6$H$_5$)$_2$, THF, 78%; (d) 10% Pd/C, *trans*-decalin, reflux, 69%; (e) BnN(*n*-Bu)$_3$Br, Me$_2$SO$_4$, CH$_2$Cl$_2$, 1 M NaOH, 86%.

The use of a temporary bridge to facilitate the intramolecular aryl coupling has since been further developed by Bringmann and coworkers to allow the synthesis of optically active biaryls and has come to be known as the 'Lactone Method'.[39] The general principle of the 'lactone method' is outlined in **Scheme 1.4**. This approach uses an ester bridge such as in lactone (***M***)**-1.26**, which serves two purposes. Firstly, the ester bridge of **1.25** brings together the two coupling partners and thus allows the palladium-catalysed coupling to proceed smoothly to yield lactones such as (***M***)**-1.26**, generally in high yields. The most useful function of the ester bridge, however, is that it dramatically lowers the rotational energy barrier at the biaryl axis. Consequently, lactones of this type are configurationally unstable and exist as a mixture of rapidly interconverting atropisomers, (***M***)**-1.26** and (***P***)**-1.26**.
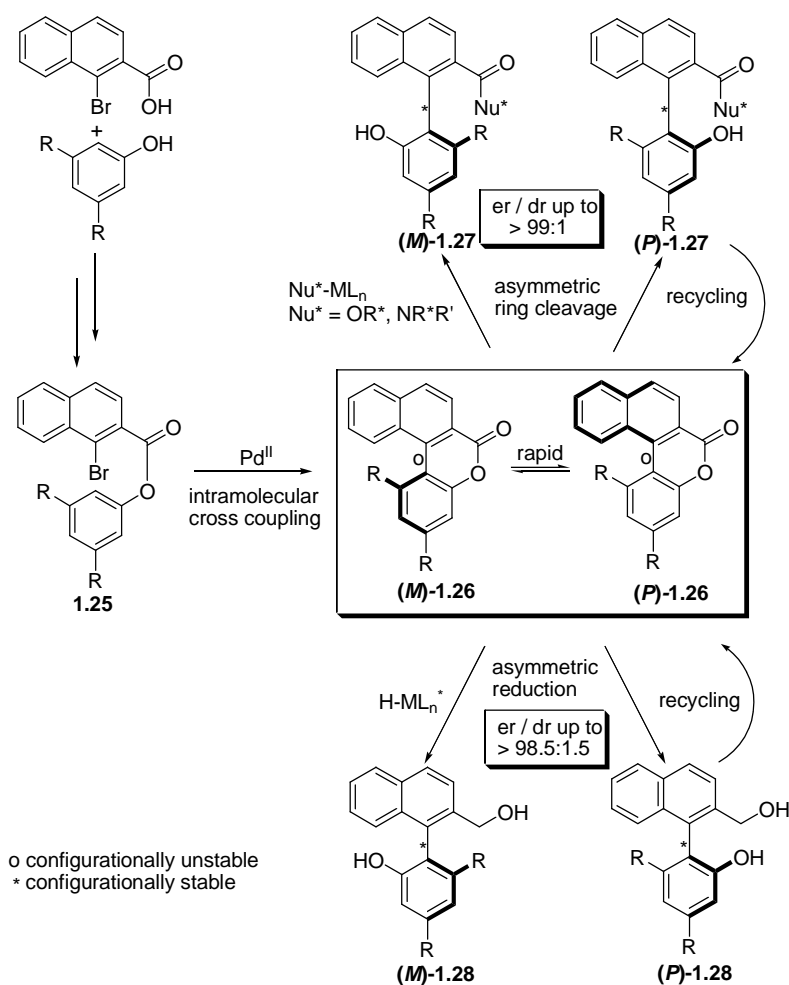
Scheme 1.4   The 'Lactone Methodology'. Preparation of axially chiral biaryls by atropselective ring cleavage of configurationally unstable lactones.

Due to the rapid equilibrium of lactones (**M**)-**1.26** and (**P**)-**1.26** the conversion of virtually all the starting material into one stereoisomer by dynamic kinetic resolution is possible. Any undesired isomer, isolated after the cleavage of the lactone bridge may be cyclised back to the lactone **1.26** and again atropselectively cleaved to the desired isomer. A major benefit of this approach is that by simply changing the cleaving reagent or catalyst to its enantiomer allows the preparation of the alternative atropisomer, from the same starting lactone intermediate. Cleavage of the lactone may be achieved with high selectivity using chiral H[40], O[41], or N-nucleophiles[42], producing configurationally stable non-racemic biaryl compounds. Upon Lewis acid activation of the lactone functionality, lactone cleavage can also be undertaken with uncharged nucleophiles, with the chiral information provided either by the chiral Lewis acid or by a chiral nucleophile.[43] Alternatively, η^6-coordination of a transition metal fragment to one of the aromatic rings of

lactone **1.26**, leads to a planar chiral activated species whose lactone bridge can be cleaved with simple achiral nucleophiles.[44]

Bringmann has applied the lactone methodology to the synthesis of range of biaryl-containing natural products and catalysts, including the total synthesis of 7,1′[45], 5,1′[46] and 5,8′[47] linked naphthylisoquinoline alkaloids. These syntheses can be exemplified by the atropdivergent total synthesis of korupensamine A and B (**Scheme 1.5**).[48] The required ester linkage in **1.31** was formed by reaction of the acid chloride **1.29** with phenol **1.30**. Intramolecular biaryl bond formation was carried out on ester **1.31** under palladium catalysis to give the biaryl lactone **1.32**. Due to the rapid interconversion of its two atrop-diastereomeric forms, reductive ring cleavage using Corey's chiral oxazaborolidene-borane system allowed either configurationally stable atropisomer (*M*)-**1.33** or (*P*)-**1.33** to be selectively generated. Biaryl (*M*)-**1.33** was then converted into the natural product korupensamine B **1.35**, while its atropisomer korupensamine A **1.34** was prepared from biaryl (*P*)-**1.33**.
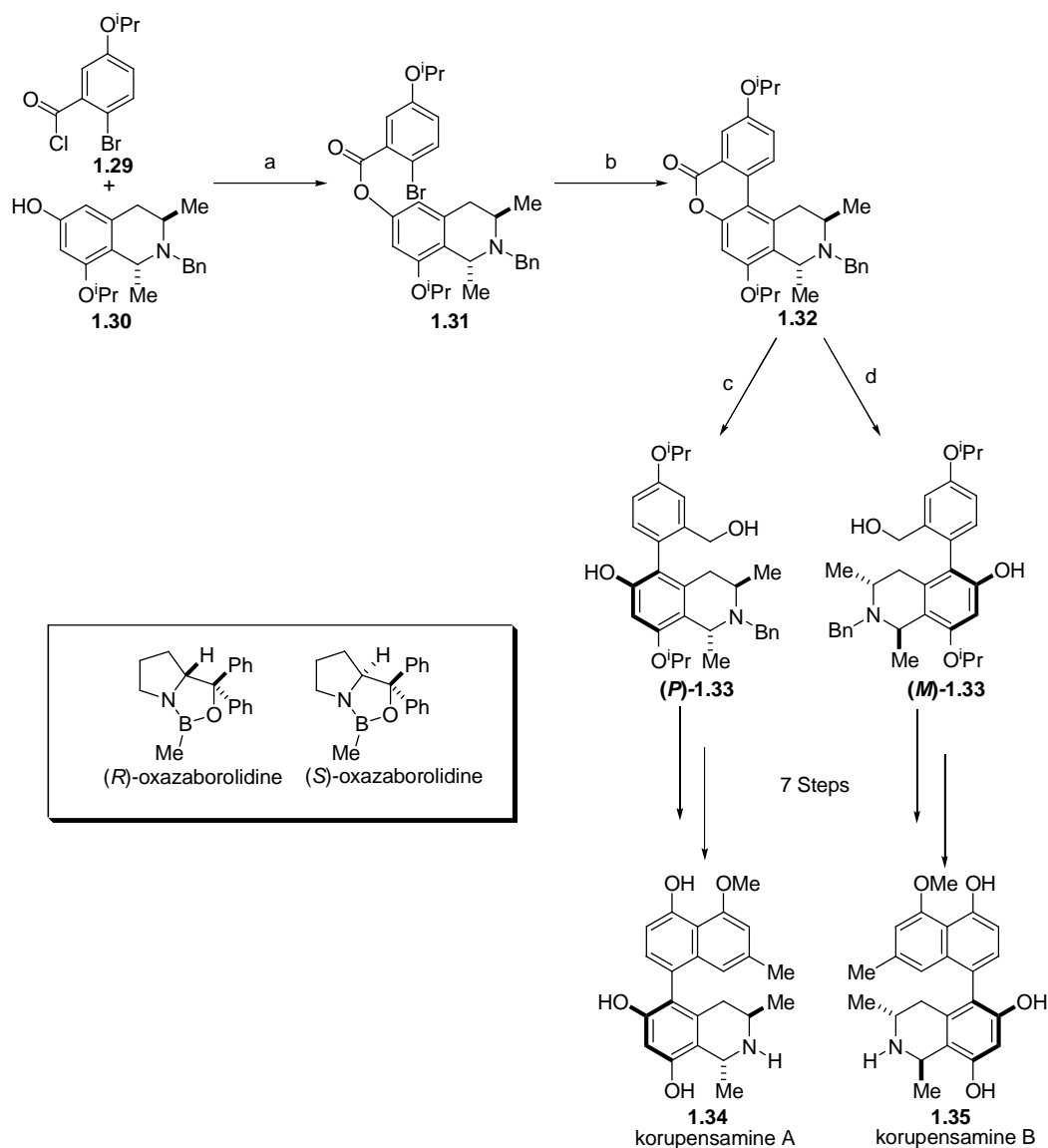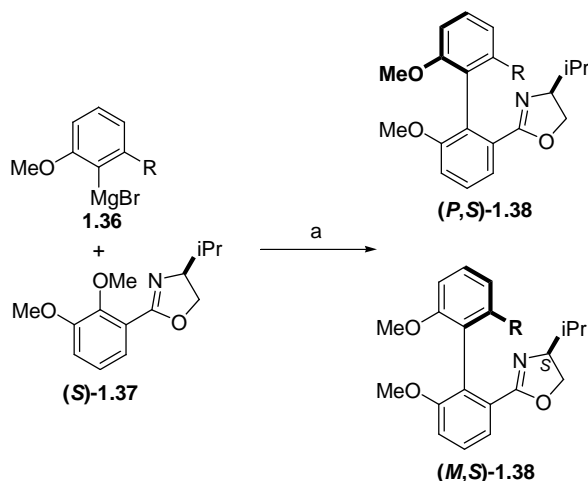
Scheme 1.5 Reagents and yields: (a) NEt$_3$, 74%; (b) 10 mol% Pd(OAc)$_2$, P(o-tolyl)$_3$, N,N-dimethylacetamide, 74%; (c) (R)-oxazaborolidine, BH$_3$, THF, 58% (M:P 6:94); (d) (S)-oxazaborolidine, BH$_3$, THF, 57% (M:P 94:6)

1.3.2   Intermolecular Approach

1.3.2.1 Application of the Meyers Biaryl Synthesis

An alternative strategy for the synthesis of naphthylisoquinoline alkaloids has been developed by Sargent and Rizzacasa using the Meyers biaryl synthesis. The Meyers biaryl synthesis allows the stereoselective construction of axially chiral biaryl compounds by nucleophilic aromatic substitution of chiral *ortho*-methoxy(oxazolinyl)arenes with aryl Grignard reagents.[49,50] The oxazoline moiety not only carries the chiral information which is transferred to the biaryl axis,

but facilitates the nucleophilic attack by stabilising the developing negative charge on the electrophile. The atropselectivity of this approach strongly depends on the relative chelating abilities of the two *ortho* substituents of the aryl Grignard reagent **1.36**.[50] For example, it was observed that regioselective nucleophilic displacement of the *ortho*-methoxy group of (*S*)-**1.37** by the aryl Grignard reagents delivered the tetra *ortho*-substituted biphenyls **1.38**, with varying atropselectivity, depending on the chelating ability of the R group (**Figure 1.9**).


R		CH$_2$OMe	CH$_2$OBn	CH$_3$	CH$_2$OTBS
Yield [%]	90	75	80	79	73
(*P,S*)-**1.38**, (*M,S*)-**1.38**	20:80	40:60	42:58	90:10	93:7

Figure 1.9   Conditions; THF reflux.

To ensure atropselectivity via this approach at least one *ortho*-substituent with complexing ability to the magnesium is required to ensure a well-defined transition state as shown in the proposed mechanism (**Scheme 1.6**). Thus, from the Table above it can been seen that if the second *ortho*-substituent R exhibited no (R = Me) or very weak (R = CH$_2$OTBS) chelating ability, then the *P* atropisomer was preferentially formed. If, however, the chelating ability of the R group was superior to that of the methoxy group (e.g. R = 1,3-dioxolan-2-yl), then intermediate **1.42** would be favoured and the *M* atropisomer formed.
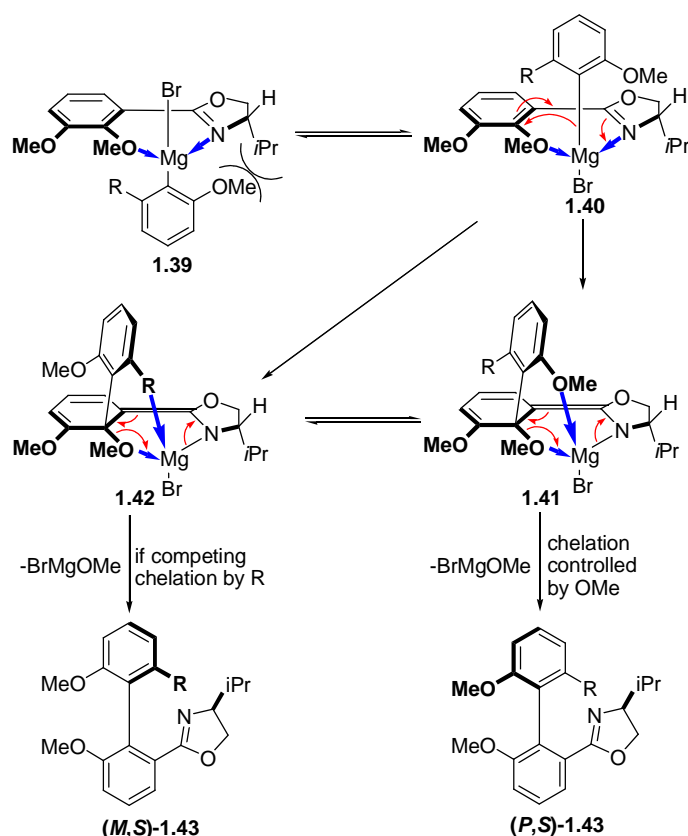
Scheme 1.6 The stereochemical control of the reaction of aryl Grignard reagents with chiral aryl oxazolines.[36,50]

Based on these results the mechanism is believed to proceed through an addition-elimination mechanism.[49,51] Initially, a chelate complex is formed between the aryl Grignard reagent and the *ortho*-methoxy(oxazolinyl)arene. Of the two possible diastereomeric arrangements, intermediate **1.40** is strongly favoured over intermediate **1.39**, as **1.40** avoids the steric repulsion of the R substituent of the oxazoline moiety with the *ortho* substituent's of the Grignard reagent. Nucleophilic addition of the Grignard reagent in **1.40** yields the aza-enolates **1.41** and **1.42**. If the R substituent does not exhibit significant chelating abilities (eg. R = Me), complexation of the methoxy group to the magnesium centre strongly favours the intermediate **1.41**. Consequently, the stereochemical alignment of the two aryl moieties is fixed, and after elimination of MeOMgBr, transferred to the biaryl axis of (***P,S***)-**1.43**. However, if R is also able to chelate to the magnesium (eg. R = 1,3-dioxolan-2-yl), the enolates are formed in ratios that reflect the relative chelating abilities of R and the methoxy group, thus allowing the alternative atropisomer to be prepared.

Rizzacasa and Sargent showed that the Meyers biaryl synthesis may be utilised in the synthesis of naphthylisoquinoline alkaloids, firstly through a racemic synthesis of dehydroancistrocladine **1.49** (**Scheme 1.7**).[52] Dehydroancistrocladine (**1.49**) is a derivative of the naphthylisoquinoline alkaloid ancistrocladisine. The required oxazoline **1.47** was prepared from bromide **1.44**. Displacement of the *ortho*-methoxy group of this oxazoline with the Grignard reagent derived from bromide **1.45** gave biaryl **1.48** in good yield. Completion of the heterocyclic system afforded dehydroancistrocladisine (**1.49**) as a mixture of atropisomers.
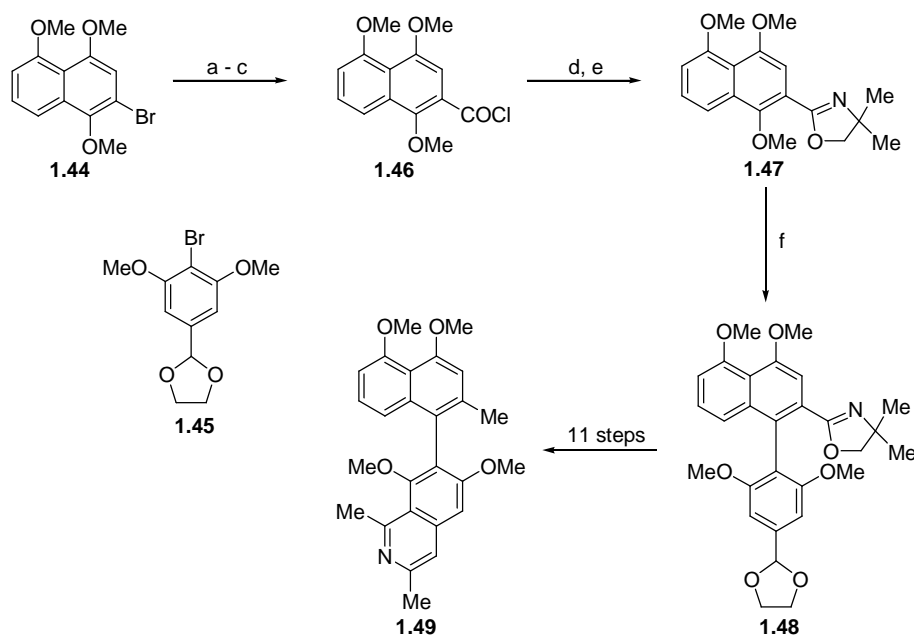
Scheme 1.7   Reagents and yields: (a) CuCN, DMF, 94%; (b) KOH, MeOH/H$_2$O, 100%; (c) (COCl)$_2$, CH$_2$Cl$_2$; (d) HOCH$_2$CMe$_2$NH$_2$, CH$_2$Cl$_2$; (e) SOCl$_2$, CH$_2$Cl$_2$, 85% over 3 steps; (f) Mg, **1.45**, THF, reflux, 81%.

The development of the chiral oxazoline-mediated coupling reaction has allowed the asymmetric synthesis of a number of naphthylisoquinoline alkaloids.[53-56] More recently, this method has been developed to allow a highly convergent approach to the total synthesis of naphthylisoquinoline alkaloids. This can be exemplified by the convergent total synthesis of (+)-*O*-methylancistrocline (**1.55**) in which the chiral biaryl linkage was constructed with high stereoselectivity using the oxazoline approach.[57] Reaction of the Grignard reagent **1.51** with the chiral naphthyloxazoline **1.50** gave the desired biaryl **1.52** as a 84:16 mixture of atropisomers, with the (*M*)-isomer, favoured. The observed stereocontrol was rationalised by considering the transition state **TS-3** in which the magnesium atom chelates preferentially to the *ortho* methoxy group rather than the methyl substituent. Expulsion of MeOMgBr gave the desired atropisomer. The mixture of biaryls

was subjected to acid treatment followed by immediate acetylation to provide the acetamides (**P**)-**1.53** and (**M**)-**1.53**, which were readily separated by flash chromatography. Reduction of (**M**)-**1.53** provided alcohol **1.54** which after conversion to the corresponding mesylate was further reduced with Zn/AcOH to furnish the natural product **1.55**.
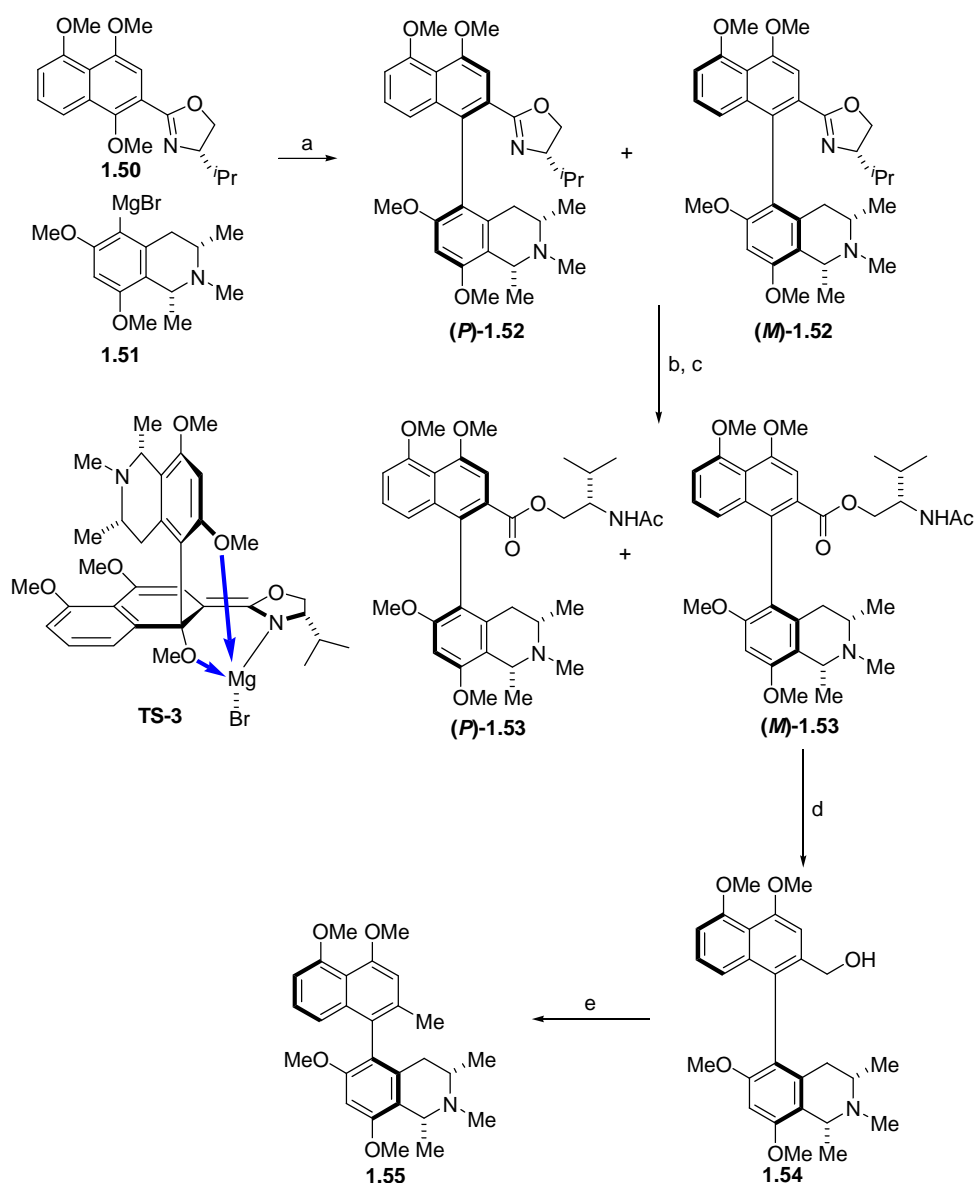
Scheme 1.8 Reagents and yields: (a) **1.51**, THF, reflux 16 h; (b) TFA, H₂O/THF; (c) Ac₂O, pyridine *P*:*M* ratio 16:84, 32% yield from **1.51**; (d) LiAlH₄, THF, rt, 22h; (e) TMSCl/ NaI, acetonitrile then Zn/HOAc, 50% from (**M**)-**1.53** (ester).

From the examples presented above, it can been seen that the Meyers methodology allows the total synthesis of naphthylisoquinoline alkaloids to be carried out atropselectively. A limitation of the strategy was reported by Sargent and coworkers in their attempt to apply this methodology to

the synthesis of the 7,3′-linked naphthylisoquinoline alkaloids.[58] The naphthalene precursor **1.56** was prepared and converted into the desired oxazoline, but unfortunately the *ortho*-methoxy group proved inert to displacement by Grignard reagents.
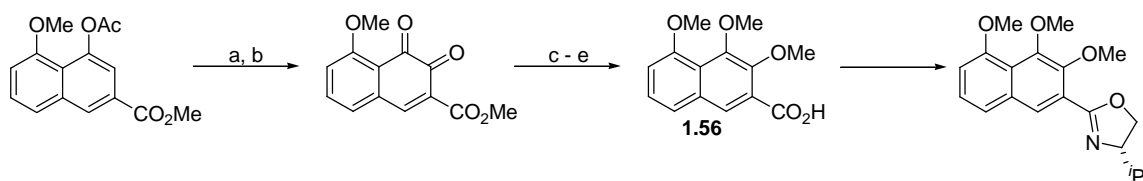

Scheme 1.9   Reagents and yields: (a) NaOMe, MeOH, 96%; (b) benzeneselenic anhydride, THF, 95%; (c) Na$_2$S$_2$O$_4$, CHCl$_3$/H$_2$O; (d) CH$_3$I, K$_2$CO$_3$, DMF, 86%; (e) NaOH, MeOH/H$_2$O, 94%.

1.3.2.2 Cross Coupling

With the development of transition metal-catalysed biaryl coupling methodology[59], many syntheses of the naphthylisoquinoline alkaloids and other related alkaloids have been completed using this concept to form the key biaryl bond.

For example, Bringmann and coworkers used a Stille cross coupling to form the key biaryl bond of the 7,6′-coupled antifungal naphthylisoquinoline alkaloid dioncophylline B (**Scheme 1.10**).[17] Coupling of stannane **1.57** with bromide **1.58** gave the biaryl compound **1.59** in 56% yield. Acid-catalysed removal of the two MOM groups and hydrogenolytic cleavage of the benzyl function afforded dioncophylline B **1.60**. Unlike the majority of naphthylisoquinoline alkaloids, dioncophylline B does not exhibit the phenomenon of axial chirality. This is a consequence of the small hydroxyl groups next to the biaryl axis causing it to be configuratively unstable and to undergo rapid atropisomeric interconversion at room temperature.
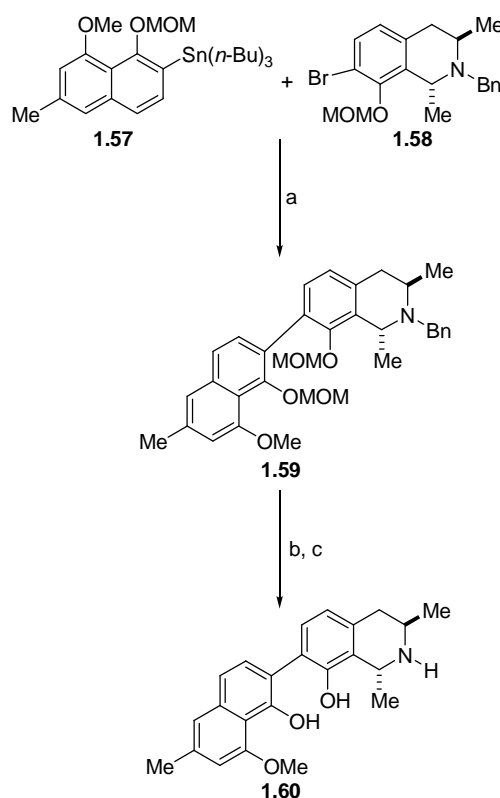
Scheme 1.10   Reagents and Yields: (a) Pd(PPh₃)₂Cl₂, PPh₃, CuBr, LiCl, DMF, 135 °C, 56%; (b) HCl, *i*PrOH,
THF, reflux, 91%; (c) Pd⁰, HCOOH, MeOH, 40 °C, 68%.

The most common cross coupling method for the formation of the biaryl linkage has been the
Suzuki-Miyaura coupling. For example, the natural products korupensamine C,[60]
ancistrotanzanine B[61] and korupensamine A[62] have all been prepared using this approach. The
total synthesis of these natural products along with the development of atropselective synthesis
via the Suzuki-Miyaura approach are discussed below.

Hoye and Chen used the Suzuki-Miyaura coupling in the synthesis of ancistrobrevine C and
korupensamine C (**Scheme 1.11**). Coupling of the naphthalene **1.63** with either
tetrahydroisoquinoline fragment **1.61** or **1.62** gave the natural products as mixtures of
atropisomers, which upon deprotection, were separated by HPLC.
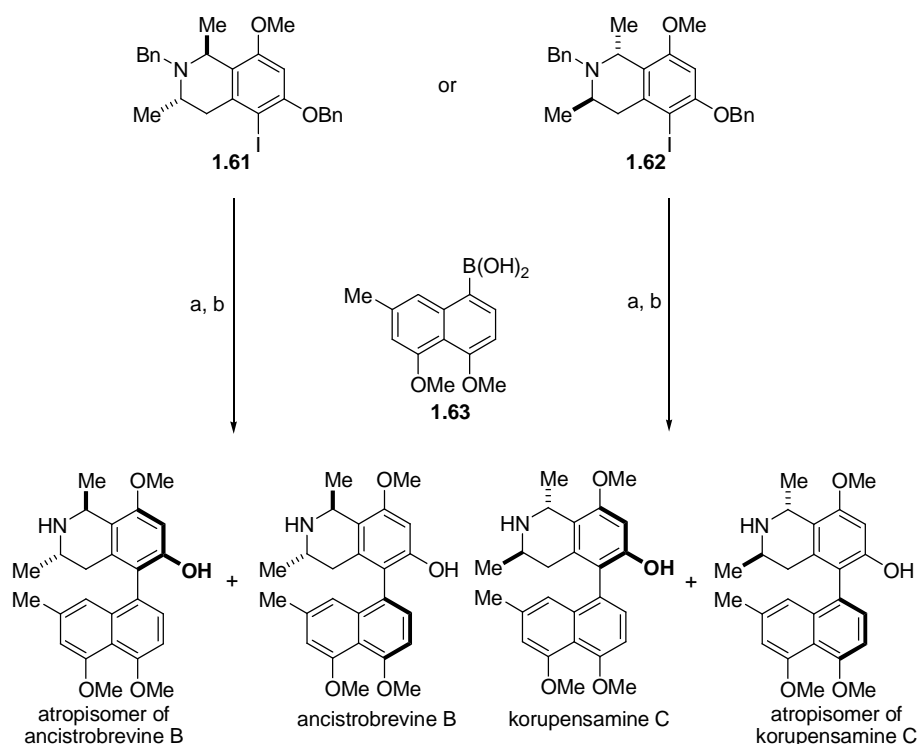
Scheme 1.11   Reagents and yields: (a) cat. Pd(PPh$_3$)$_4$, **1.63**, sat. aq. NaHCO$_3$, toluene, 71 – 76%; (b) Pd/C, H$_2$, MeOH, CH$_2$Cl$_2$, 100%.

Lipshutz and coworkers have reported a successful intermolecular cross-coupling strategy for the stereoselective preparation of the core of korupensamine A **1.34**.[63] Their approach involved the use of hydroxyl 'handles' on each of the coupling partners.[63] Coupling of these molecules under standard Suzuki conditions revealed only a slight preference for the (*P*)-isomer, indicating that steric effects alone at each of the hydroxymethyl sites in **1.64** and **1.65** were not sufficient for high diastereocontrol in the biaryl forming step (**Figure 1.10**). However, a coupling utilising an internal chelating phosphine proved more successful, affording a single diastereoisomer in 81% yield. The sole formation of the (*P*) isomer was proposed to result from the geometry of the reductive elimination from intermediate **1.68**. It was rationalised that the PPh$_2$-substituted benzoate residue is best accommodated with the phosphorous coordinated to the palladium from the bottom of the molecule, relative to the plane of the tetrahydroisoquinoline moiety. The phenyl ring of the ester and the two phenyl groups on the phosphorus combine to further block the back and underside. This causes the bulky naphthalene moiety to protrude forward over the aryl portion of the tetrahydroisoquinoline moiety. Reductive elimination would then give the observed atropisomer.
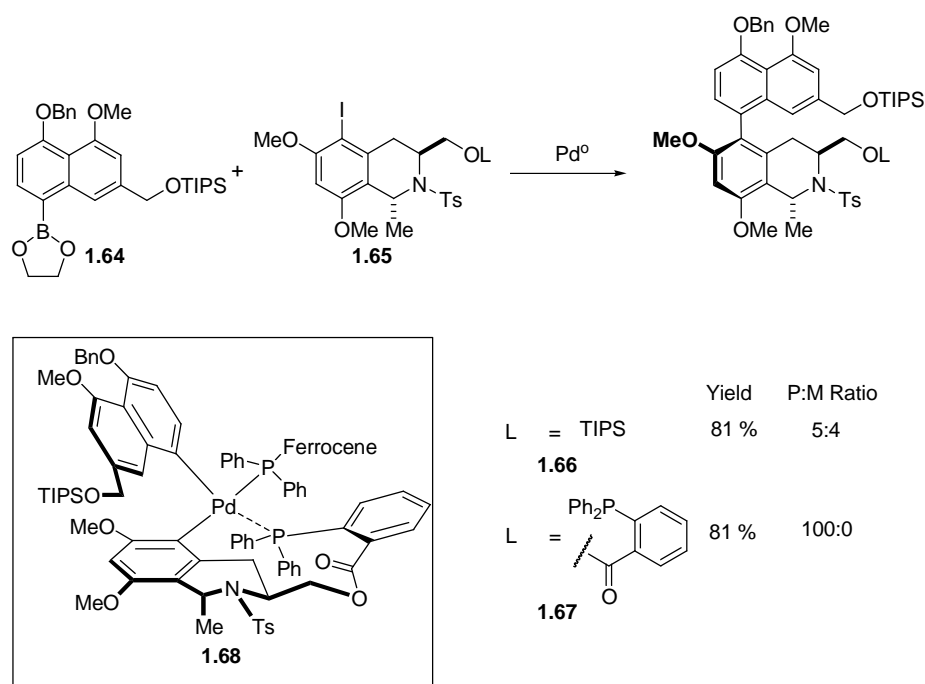
Figure 1.10   Reagents: For L = TIPS **1.66**; cat Pd(PPh$_3$)$_4$, K$_3$PO$_4$, BHT, DMF, 96 $^{\circ}$C; For **1.67**, 20 mol% Pd(dppf)Cl$_2$, K$_3$PO$_4$, BHT, DMF, 117 $^{\circ}$C.

Recently, Bringmann and coworkers have extended the Suzuki-Miyaura cross-coupling method to allow the direct synthesis of naphthylisoquinoline alkaloids through coupling the unprotected moieties directly in a stereoselective manner. This can be exemplified by the total synthesis of the naphthylisoquinoline alkaloid ancistrotanzanine B and its atrop-diastereoisomer, ancistroealaine A.[39,61] Suzuki-Miyaura cross-coupling of the boronic acid **1.63** with the chiral iodide **1.69** yielded the desired natural products. Stereoanalysis of the natural products was hampered by the fact that the two atrop-diastereoisomers were found to behave identically during chromatography, on both normal and reversed-phase silica gel. It was found that the best approach for their separation was to treat them as enantiomers. Analytical chromatography on a chiral OD-H 250 column gave the expected peaks for the diastereomeric products obtained, in a 55:45 ratio, favouring ancistroealaine A. Given the lack of internal asymmetric induction by the stereocentre at C3, the group investigated the use of chiral catalysts on influencing the atropisomeric ratio.
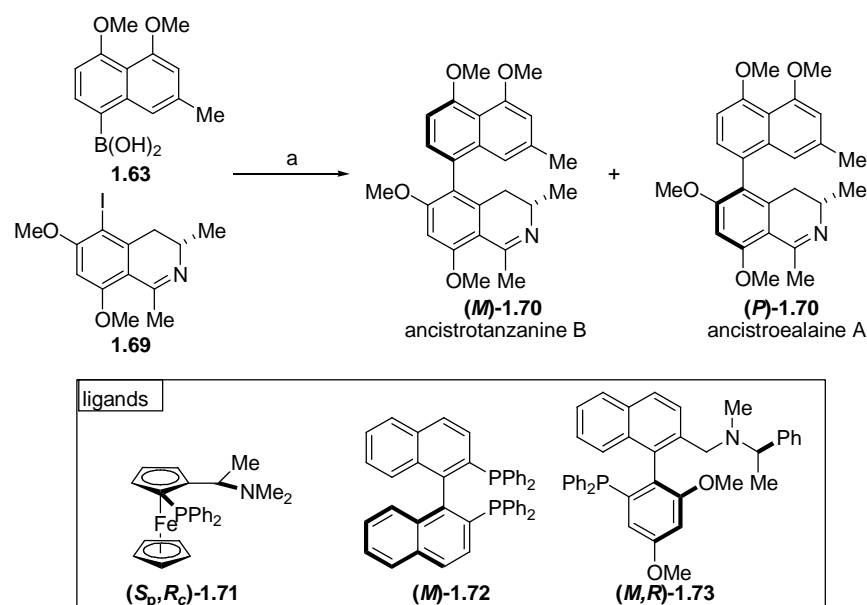
Scheme 1.12   The Suzuki cross coupling of **1.63** and **1.69**, and the chiral ligands used in Bringmann's study. Reagents: (a) catalyst, toluene, water, reflux, 16 h. Refer to table 1.1 for yields and catalyst.

Table 1.1   Yields and diastereomeric ratios obtained in the asymmetric Suzuki coupling of **1.63** and **1.69**.

Entry	Catalyst	Yield	(*M*)-**1.70**:(*P*)-**1.70**
1	Pd(PPh$_3$)$_4$	50	45:55
2	**Pd$_2$dba$_3$/(S_p,R_c)-1.71**	**38**	**75:25**
3	**Pd$_2$dba$_3$/(R_p,S_c)-ent-1.71**	**34**	**51:49**
4	Pd$_2$dba$_3$/(*M*)-**1.72**	45	61:39
5	Pd$_2$dba$_3$/(*P*)-**1.72**	50	75:25
6	Pd$_2$dba$_3$/(*M*,*R*)-**1.73**	65	63:37
7	Pd$_2$dba$_3$/(*M*,*S*)-**1.73**	89	57:43

Entries 1-5[61], entries 6-7[39]

The use of (*S*$_p$,*R*$_c$)-**1.71**, afforded the two alkaloids (*M*)-**1.70** and (*P*)-**1.70** in 38% yield and in an atropisomeric ratio of 75:25, in favour of ancistrotanzanine B. Considering this was the opposite preference to that obtained using the achiral catalyst (entry 1, **Table 1.1**), it was thought that this may be the 'mismatched' case. The group envisaged that the use of the enantiomer of (*S*$_p$,*R*$_c$)-**1.71** would give the 'matched' case and consequently an even better atropisomeric ratio, now in favour of the *P*-enantiomer. Unfortunately, use of (*R*$_p$,*S*$_c$)-**1.71** was found to give no preference to either atropisomer (entry 3). The use of other chiral ligands was found to give similar results to

(R_p,S_c)-**1.71** (**Table 1.1**). These results indicate the ability to control the atropselectivity of the Suzuki-Mayaura cross coupling by interchanging the chiral ligands is not trivial.

Alternative approaches to control the atropselectivity that do not require the use of chiral ligands have also been developed to control the atropselectivity of the Suzuki-Mayaura cross coupling reaction. One such approach is the use of planar chiral arene-chromium complexes. Planar chiral arene-chromium complexes have been utilized by Uemura and coworkers in order to control the stereoselectivity of the formation of the biaryl axis by Suzuki-Mayaura coupling (**Scheme 1.13**).[62,64] This approach is best exemplified by their synthesis of korupensamine A.[62] Coupling of the chiral planar chromium complex **1.74** with boronic acid **1.75** gave the biaryl **1.76** as a single atropisomer in excellent yield. Subsequent assembly of the heterocyclic moiety from **1.77** gave korupensamine A. Conversion of alcohol **1.76** to aldehyde **1.78** led to the discovery that **1.78** was able to undergo atropisomerism after being heated in xylene at 120 ^{o}C for 1 hour to give **1.79**. After further transformations the isopropyl protected compound **1.80** was prepared, which is the atropisomer of biaryl **1.77**. Thus, **1.80** may be converted to korupensamine B through assembly of the heterocyclic moiety using the same chemistry for the synthesis of korupensamine A.
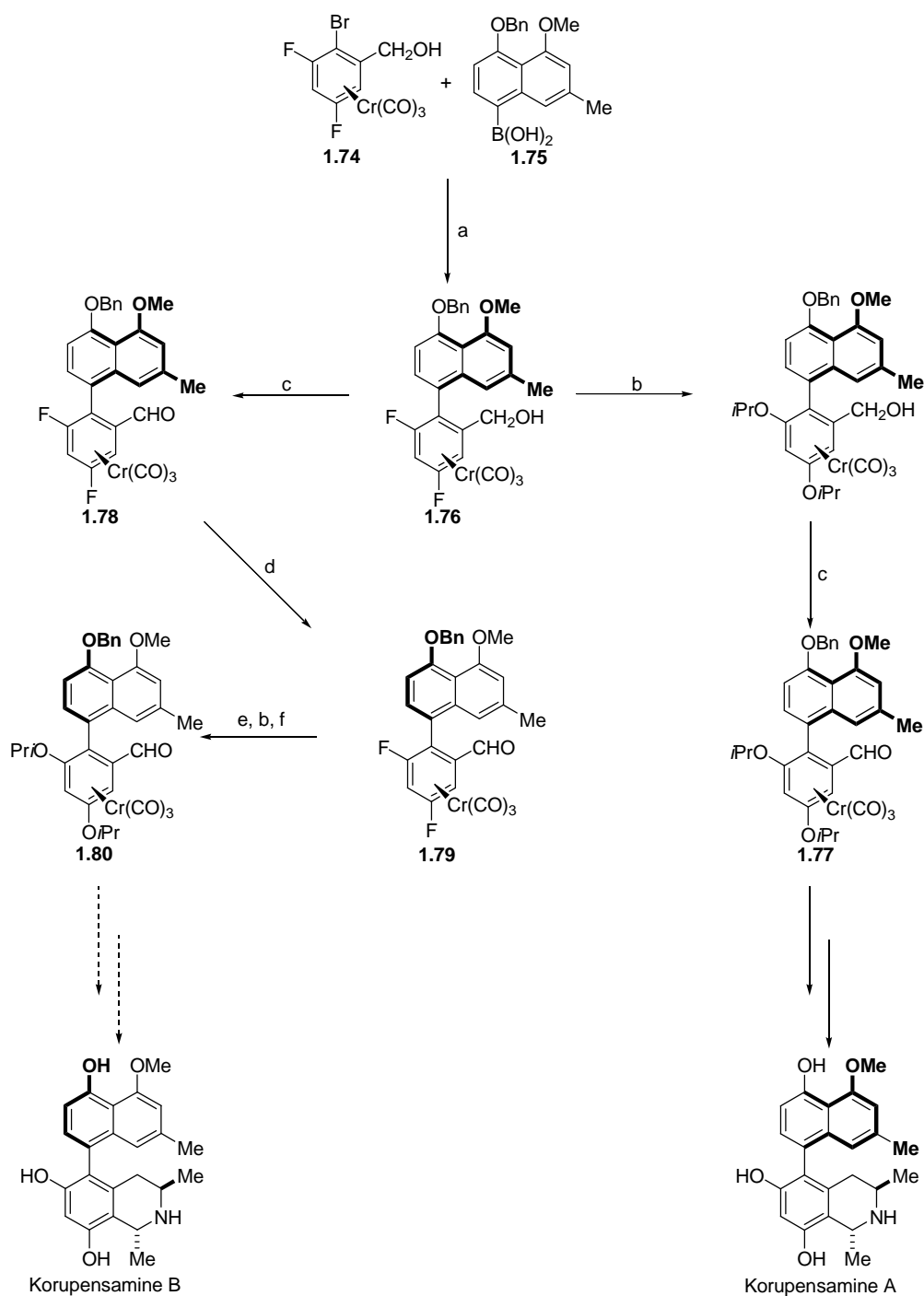
Scheme 1.13   Reagents and Yields: (a) cat. Pd(PPh$_3$)$_4$, 0.1 M aq K$_3$PO$_4$, toluene, 95 $^{\circ}$C, 74%; (b) *i*-PrOH, NaH, 18-crown-6, benzene, r.t, 93% (73% for **1.80**); (c) TFAA, DMSO, CH$_2$Cl$_2$, -78 $^{\circ}$C, then Et$_3$N, 83% for **1.77** and 87% for **1.78**; (d) xylene, 120 $^{\circ}$C, 1h, 65%; (e) CH(OMe)$_3$, *p*-TsOH, r.t. 3h, 78%; (f) 50% aq H$_2$SO$_4$, acetone, 0 $^{\circ}$C, 15 min 46%.

From examination of the aforementioned synthetic work carried out in the area of naphthylisoquinoline alkaloid synthesis, it is evident that these natural products are worthy

synthetic targets and have been the inspiration for a great deal of innovative research. Although the synthetic methods so far all allow for the atropselective total synthesis of naphthylisoquinoline alkaloids, they all require the functionalisation of both coupling partners to allow the preparation of the key biaryl linkage. This can prove troublesome for the more hindered compounds, such as the 7,3′-linked naphthylisoquinoline alkaloids, which are yet to be successfully synthesised by the approaches presented so far.

1.4 Sterically Challenging Naphthylisoquinoline Alkaloids

As mentioned above, the examples given so far have focused on the synthesis of 5,1′, 7,1′ and 5,8′ naphthylisoquinoline alkaloids. Little synthetic attention has been given to another class of naphthylisoquinoline alkaloids, the 7,3′-linked system, such as that found in ancistrocladidine (**1.81**) and ancistrotectorine (**1.82**) (**Figure 1.11**). The 7,3′-naphthylisoquinoline alkaloids present a tremendous synthetic challenge as they contain the most sterically congested biaryl bond within this group of natural products.
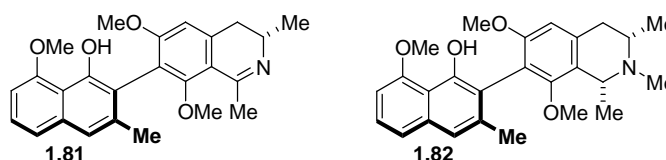

Figure 1.11   The naphthylisoquinoline alkaloids ancistrocladidine **1.81** and ancistrotectorine **1.82**.

The retrosynthesis of ancistrocladidine (**1.81**) reveals that the highly hindered biaryl system presents a significant challenge to the previously mentioned methods (**Figure 1.12**). Although numerous palladium-catalysed biaryl cross-couplings have been utilized in the synthesis of biaryls possessing one, two, or three *ortho*-substituents, a common trend in such reactions is a lowering in the yield of coupled product upon an increase in the steric bulk surrounding the resulting biaryl bond. Work by Buchwald[65] and Organ[66] has begun to rectify this; however, there are still few examples of cross-couplings resulting in products that contain four *ortho*-substituents. Consequently, cross coupling of the two moieties **1.83** and **1.84** or **1.85** and **1.86**, may prove troublesome. As mentioned in section **1.3.2.1**, oxazolines of type **1.87** were previously found to be inert to Grignard reagents. Thus the Meyers approach would appear to be inappropriate for the synthesis of 7,3′-linked naphthylisoquinoline alkaloids.
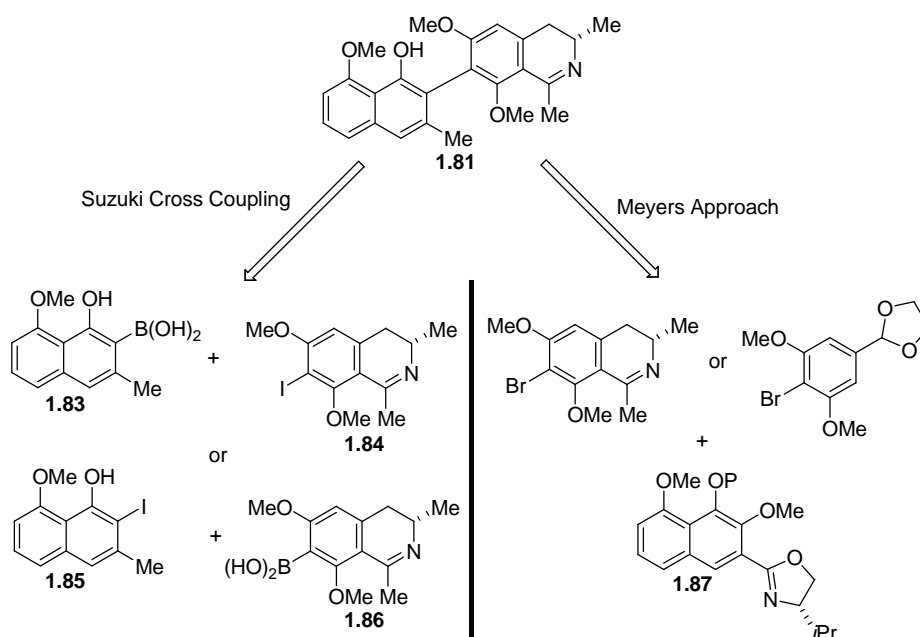
Figure 1.12   Retrosynthetic analysis of ancistrocladidine **1.81** via Suzuki cross-coupling and the Meyers approach.

At first glance, the 'lactone method' could be a viable strategy as shown in **Figure 1.13**. However, previous work has shown that the required ester bridge would need to be linked at the 8-position of the isoquinoline moiety as linkage at the 6-position gives coupled products at the 5-position of the isoquinoline moiety.[45] Consequently disconnection A would seem more appropriate. This approach requires a sterically demanding cross-coupling reaction and perhaps more importantly functionalisation of naphthol **1.89** at the C3 position would not be trivial. For example, 2-bromo-3-methyl-8-methoxy-1-naphthol has been prepared by Nishiyama and Kameoka via an eight-step sequence, in 7.5% overall yield, from (3-methoxyphenyl)-2-propanone. Although useful, the sequence required many purification steps and proceeded in low yield.[67] Use of the alternative ester **1.90** to form the lactone **1.88** would require the use of a blocking group at the C1 position of the naphthalene to prevent the coupling occurring at this position.
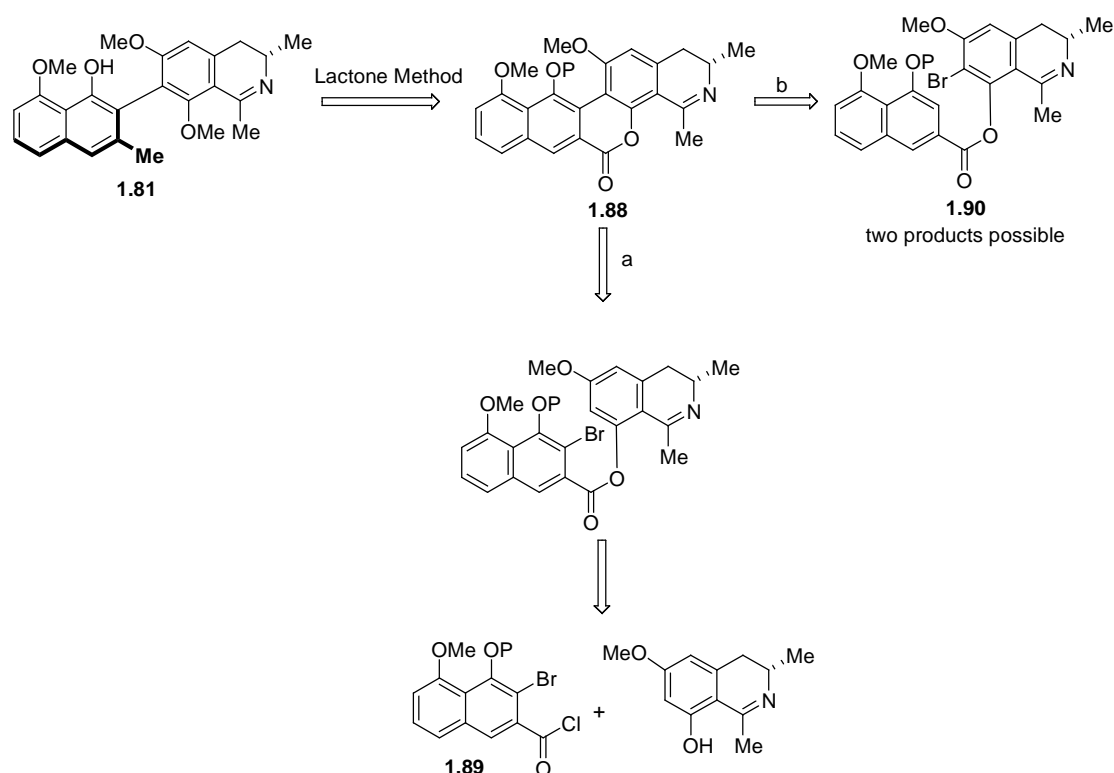
Figure 1.13   Retrosynthetic analysis of ancistrocladidine **1.81** via the 'lactone method'.

For these reasons, Morris and Bungard sought an alternative biaryl coupling methodology for the formation of the 7-3′ linkage of ancistrocladidine. They found that the *ortho*-arylation of phenols with aryllead tricarboxylates was an appropriate reaction to form the highly hindered biaryl linkage of ancistrocladidine. This work is discussed below.


1.5   Aryllead Triacetates

The *ortho*-arylation of phenols with aryllead tricarboxylates is a reaction that is known to proceed on hindered substrates in an efficient manner. The use of aryllead triacetates as electrophilic arylating agents of phenols was first recognised by Pinhey and coworkers.[68,69] It was found that reaction of mesitol (**1.91**) with aryllead **1.92** in chloroform gave the cyclohexadienones **1.93** and **1.94**. The use of equal molar amounts of pyridine was found to increase the rate of the reaction to give **1.93** and **1.94** in 90% yield in a ratio of 75:20 in favour of the *ortho*-substituted product. A variety of *ortho*-substituted phenols, and 2-methyl-1-naphthols such as **1.95**, were examined with the key observation being a marked preference for *ortho*-arylation in all cases.
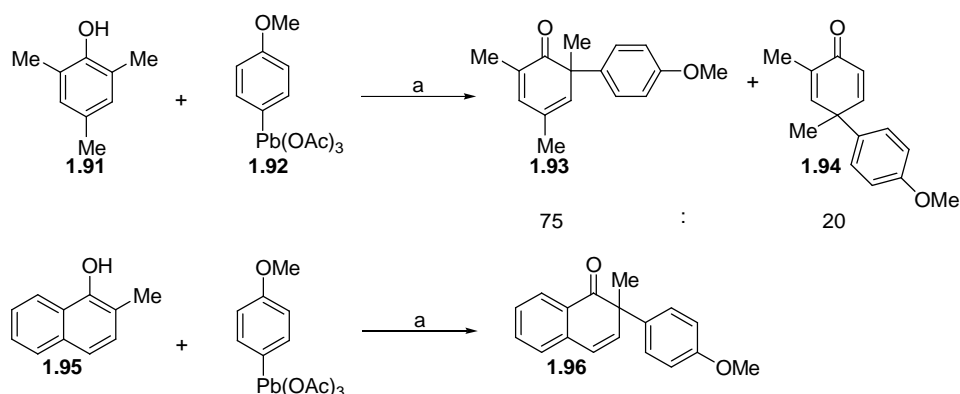
Reagents and yields: (a) pyridine, CHCl$_3$, 95% for **1.93** and **1.94**, 56% for **1.96**.

Figure 1.14   Examples of Pinhey's initial work on the reaction of aryllead tricarboxylates with phenols.

Pinhey and coworkers couldn't come to any firm conclusions about the mechanism of the observed *ortho*-arylation. They suggested that an aryloxylead intermediate such as **1.97** or **1.98** may play a key role. The existence of the aryllead intermediate **1.97** was ruled out after **1.99** failed to undergo a coupling reaction even under forcing conditions.
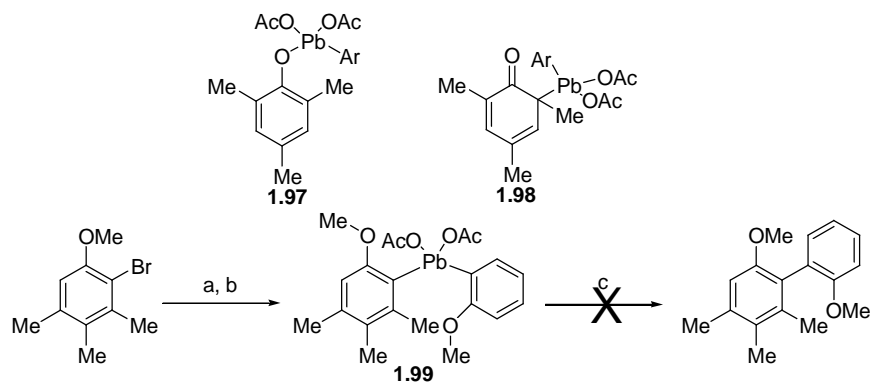
Scheme 1.14   Reagents and yields: (a) *n*-BuLi, THF, -78 °C, then B(O^{i}Pr)$_3$, H$_2$O, 72%; (b) 4-MeO-
C$_6$H$_4$Pb(OAc)$_3$, CHCl$_3$, r.t., 80%; (c) pyridine, CHCl$_3$, 60 °C, no reaction.

Using experience gained from working with arylbismuth(v) compounds that react in a similar way to aryllead compounds, Barton and coworkers studied the lead *ortho*-arylation reaction to gain further insight into the mechanism.[70] In an attempt to observe a covalent aryloxylead intermediate, 3,5-di-*t*-butylphenol **1.100** was chosen as a coupling partner for the lead reagent. It was believed that the steric constraints of this coupling partner would not allow the formation of

the final arylated product, but would allow the formation of the aryloxylead intermediate **1.101** to be detected by ¹H NMR spectroscopy.
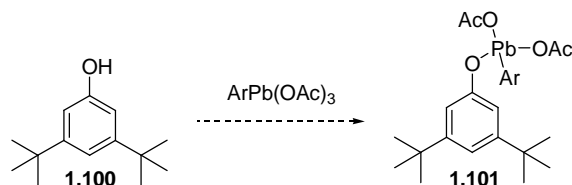

Figure 1.15   Formation of the proposed aryloxylead intermediate.

To the group's surprise, no aryloxylead intermediate was detected, but mono and di-arylation products were obtained. Optimisation of the reaction gave the highly sterically hindered diarylated product **1.102** in an astonishing 87% yield.
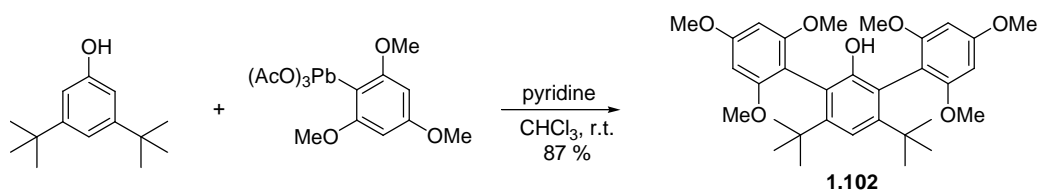

Figure 1.16   *Ortho*-arylation of a sterically hindered phenol.

More recently, work has been undertaken by Yamamoto and coworkers to extend this *ortho*-arylation methodology further in an attempt to allow the stereoselective synthesis of the biaryl linkage. Yamamoto and coworkers have shown that the asymmetric coupling of phenols using aryllead reagents is possible with chiral amines in place of pyridine.[71,72] In particular, the addition of the chiral amine brucine allowed a range of optically enriched aryl compounds to be prepared as exemplified in **Scheme 1.15**. The reaction gave high diastereoselectivity, along with moderate to good enantioselectivity.
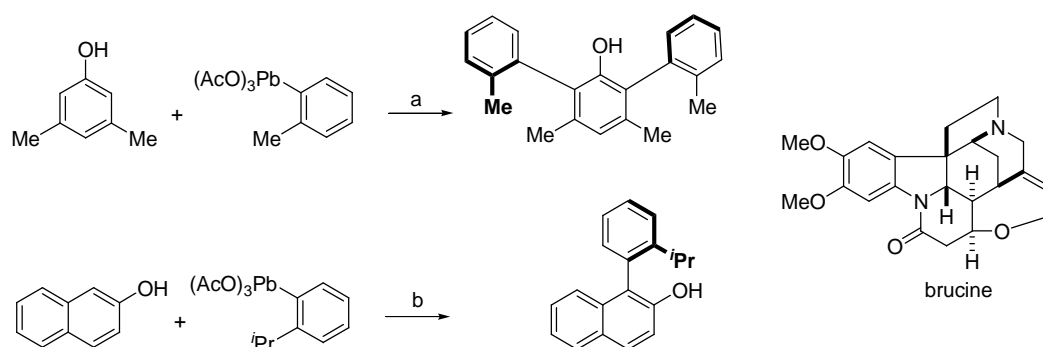
Reagents and yields: (a) toluene, *n*-BuLi, then brucine, 4Å sieves, -20 °C, 99%, 99% de; (b) toluene, *n*-BuLi, then brucine, 4Å sieves, -40 °C, 86%, 77% ee.

Scheme 1.15   Asymmetric coupling of phenols with aryllead tricarboxylates.

A possible explanation for the stereoselectivity is that brucine ligates to the lead and influences the transition state geometry such that the (*M*)-atropisomer is formed preferentially in all cases (**Figure 1.17**).
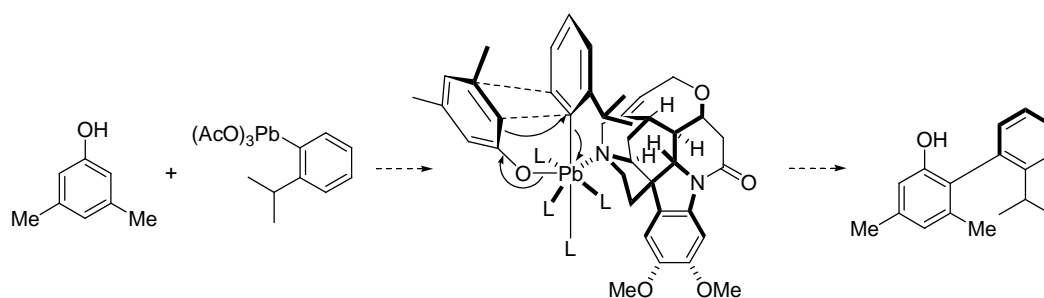
Figure 1.17   A possible transition state to account for the observed asymmetric induction.

1.6   Application of the Pinhey-Barton Reaction to the Total Synthesis of Ancistrocladidine

It can be seen from **Figure 1.18** that utilising the Pinhey-Barton reaction to form the key biaryl linkage would allow a convergent synthesis of **1.81** through the coupling of the isoquinoline unit **1.103** directly with naphthol **1.104**. Coupling of the intact isoquinoline unit would also allow an investigation into a diastereoselective Pinhey-Barton reaction using a chiral ligand such as brucine.

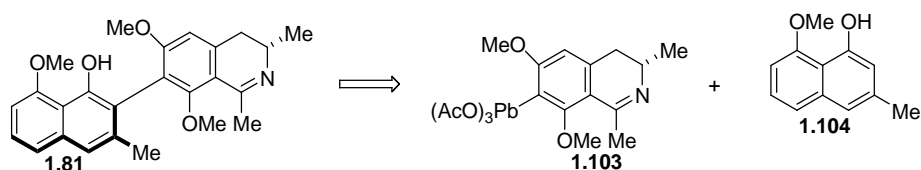**Figure 1.18**   Retrosynthesis of ancistrocladidine utilising the Pinhey-Barton reaction to form the biaryl linkage.

Organolead compounds may be prepared by two routes, either by direct plumbation or by transmetalation. The latter method is the more general route as it exhibits a greater tolerance to functionality.[73] This metal-metal exchange route is normally achieved using either a tin or boron species in the presence of catalytic amounts of mercuric salts. Therefore access to iodide **1.105** was required. Stannane **1.106** was readily prepared through halogen-lithium exchange of iodide **1.105** with *t*-BuLi and subsequent quenching with tributyltin chloride (**Scheme 1.16**). It was found, however, that exposure of stannane **1.106** to lead tetraacetate in the presence of a mercuric acetate resulted in a complex mixture, from which only starting material could be isolated. It was postulated that the lead tetraacetate may have been coordinating to the lone pair of electrons on the nitrogen atom.
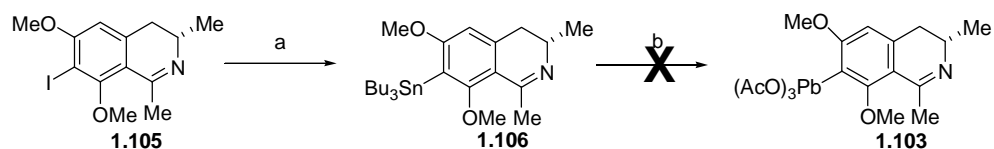
Scheme 1.16   Reagents and yields: *t* BuLi, Bu₃SnCl, THF, -95 °C to rt, 83%; b) Pb(OAc)₄, cat. Hg(OAc)₂, CH₂Cl₂, rt, 24 h, complex mixture.

With this assumption the synthesis of aryllead tetrahydroisoquinoline **1.110** was attempted. Tetrahydroisoquinoline **1.110** was selected as it is the tetrahydroisoquinoline moiety present in another 7,3′ linked naphthylisoquinoline alkaloid, ancistrotectorine (**1.82**), and thus could still be utilised in a total synthesis. *N*-Methyldihydroisoquinoline **1.107** was readily prepared by treating isoquinoline **1.105** with iodomethane in acetone. The obtained salt was reduced with DIBAL-H in dichloromethane at -78 °C to afford iodide **1.108** in a 9:1 ratio of diastereoisomers, which after chromatography afforded the *cis*-diastereoisomer in 85% yield (**Scheme 1.17**). The observed stereoselectivity for the reduction was explained by the bulky reducing agent delivering the hydride from the opposite face to the methyl group at C3. Stannane **1.109** was prepared through quenching of the lithiospecies species of **1.108** with tributyltin chloride in 56% yield. It was

found that stirring of the stannane **1.109** with lead tetraacetate and mercuric acetate at room temperature gave only recovered starting materials and a trace amount of demetalated material. Heating the reaction at 40 $^{\circ}$C resulted in complete demetallation.
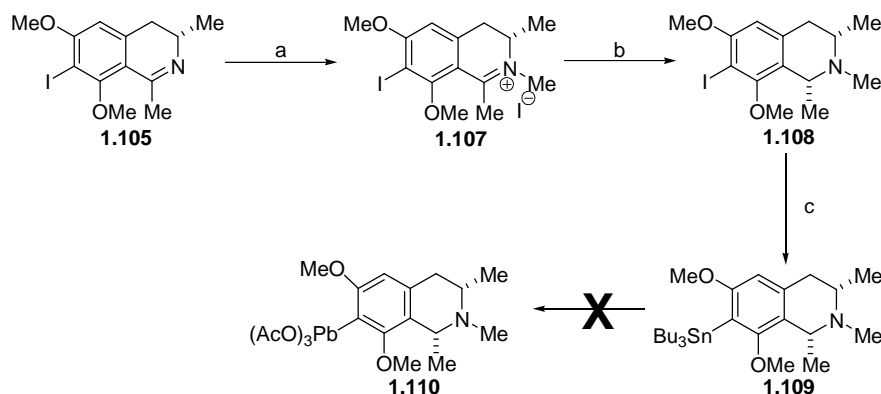
Scheme 1.17   Reagents and yields: (a) MeI, acetone, rt; (b) DIBALH, CH$_2$Cl$_2$, -78 $^{\circ}$C to r.t., 85% for 2 steps; (c) *t*-BuLi, THF, -95 $^{\circ}$C, Bu$_3$SnCl, -95 $^{\circ}$C to r.t., 83%.

Barton and coworkers have observed that arylamine **1.111** was slowly oxidised by aryllead reagent **1.112** and proposed the mechanism depicted in **Figure 1.19**.[74] Attack of the electron-rich amine on the electrophilic lead atom could form intermediate **1.113**, which following oxidation and expulsion of an acetate ion would form aryllead(II) **1.114**. Acetolysis of aryllead **1.114** then gives demetalated species **1.115** and lead(II) acetate.
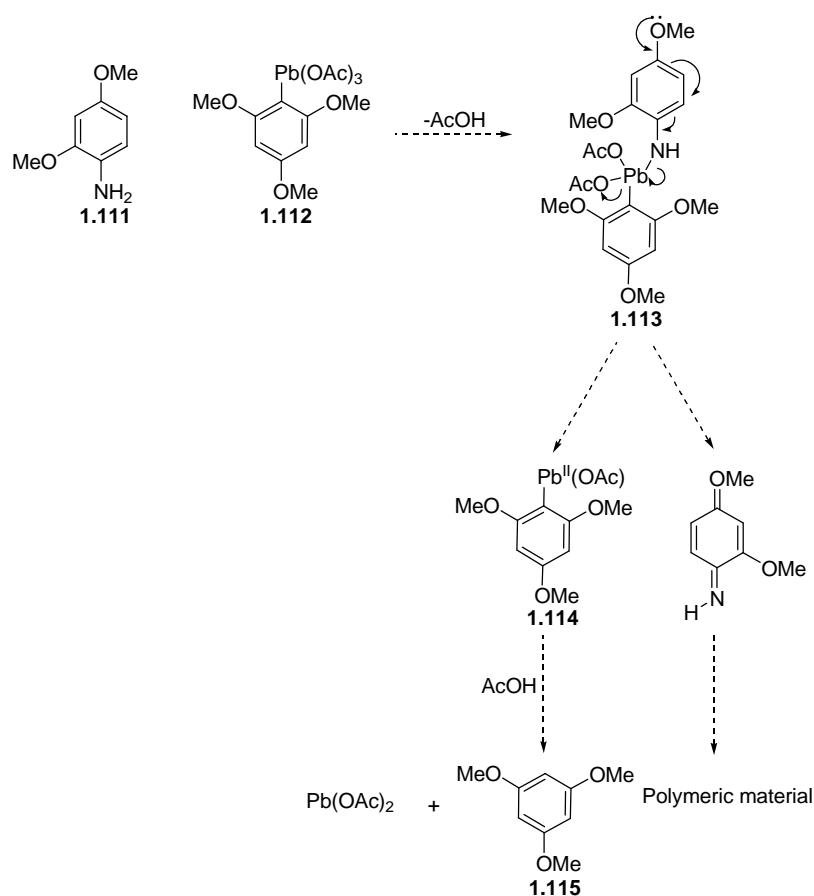
Figure 1.19   Barton and coworkers proposed mechanism for demetalation.

A similar demetallation reaction could be in operation for the tetrahydroisoquinoline lead species. Two possible solutions were explored to solve this problem. Firstly, *in situ* trapping of the aryllead species with naphthol **1.104** was investigated to see if the coupling reaction would proceed faster than the proposed oxidation. This resulted in the formation of a complex mixture from which only starting materials and demetalated species could be isolated. No trace of an *ortho*-arylated naphthol was found.

The second solution involved placing an electron-withdrawing group on the amine to draw electron density away from the nitrogen atom. A carbamate group was chosen as it could still be readily converted into an *N*-methyl derivative as required for the total synthesis of ancistrotectorine (**1.82**). Thus, stannane **1.106** was readily reduced with sodium borohydride in methanol to give amine **1.116** in 96% yield (**Scheme 1.18**). Carbamate **1.117** was prepared in 77% yield by reacting amine **1.116** with methyl chloroformate in dichloromethane and in the presence of triethylamine. Again however, reacting the carbamate under the standard conditions

for the preparation of aryllead compounds resulted in both demetalation and recovered starting material.
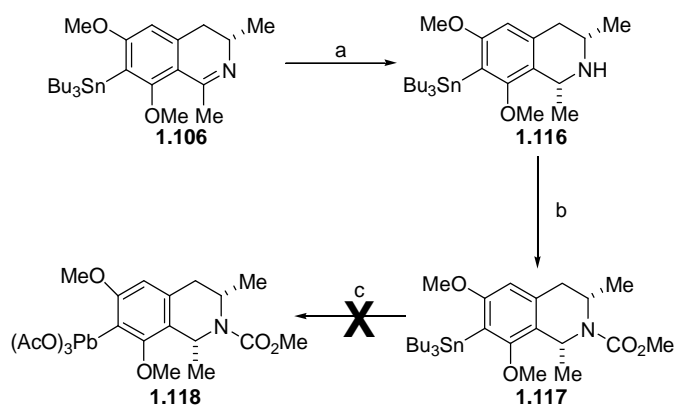
Scheme 1.18   Reagents and yields: (a) NaBH$_4$, MeOH, rt, 96%; (b) ClCO$_2$Me, NEt$_3$, CH$_2$Cl$_2$, rt, 77%; (c) Pb(OAc)$_4$, cat. Hg(OAc)$_2$, CHCl$_3$.

Given that the aryllead precursors **1.103**, **1.110** and **1.118** could not be prepared, a simpler non-nitrogen containing aryllead species was investigated that would allow the construction of the isoquinoline moiety after the formation of the biaryl linkage (**Figure 1.20**).
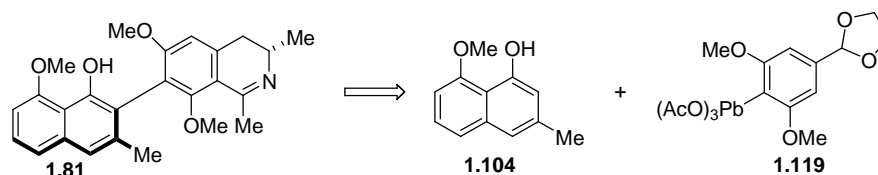
Figure 1.20   An alternative biaryl coupling with a simpler aryllead species.

Consequently, the total synthesis of ancistrocladidine required the preparation of the aryllead species **1.119**. The requisite stannane **1.121** was readily prepared through halogen-lithium exchange of iodide **1.120** with *t*-BuLi and subsequent quenching with tributyltin chloride (**Scheme 1.19**). Stirring of the stannane **1.121** with freshly purified lead tetraacetate in the presence of a catalytic amount of mercury acetate provided the aryllead triacetate **1.119** in 93% yield. Formation of the key biaryl linkage was achieved by reaction of the lead species **1.119** with naphthol **1.104** in the presence of pyridine and dichloromethane at room temperature. Hydrolysis of the crude reaction mixture afforded the desired biaryl aldehyde **1.122** in 67% yield.
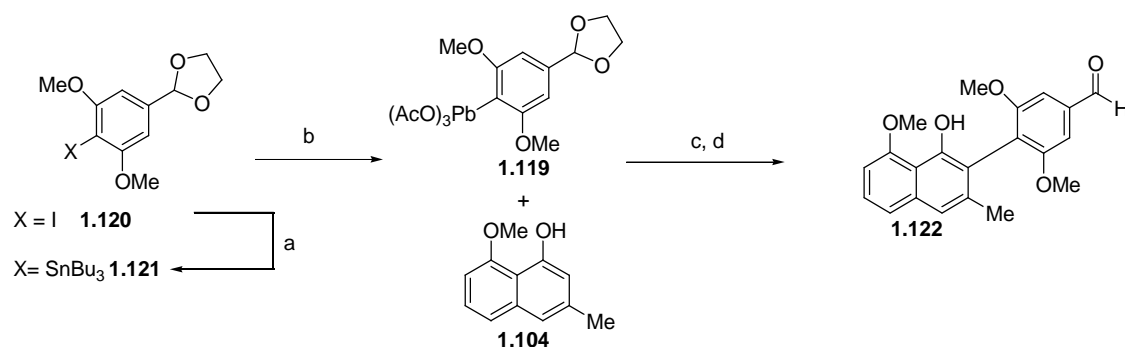
Scheme 1.19   Reagents and yields: a) *t*-BuLi, Bu$_3$SnCl, THF, -95 °C to rt, 85%; b) Pb(OAc)$_4$, cat. Hg(OAc)$_2$, CH$_2$Cl$_2$, rt, 24 h, 93%; c) pyridine, CH$_2$Cl$_2$, 24 h, rt; d) 3% v/v aqueous H$_2$SO$_4$, THF, 1 h, rt, 67%.

The aldehyde **1.122** was elaborated to the chiral amine **1.123** in a nine-step sequence as summarised in **Scheme 1.20**. A Sharpless asymmetric epoxidation was used to set the stereochemistry at C3. Bischler-Napieralski cyclisation of **1.123** was readily achieved by reaction with POCl$_3$ in the presence of 2,4,6-collidine. During the reaction, the MOM group was also cleaved thus yielding ancistrocladidine **(*M*)-1.81** along with its atropisomer **(*P*)-1.81** in a 1:1 ratio, in 74% overall yield. Separation of the atropisomers was readily achieved by recrystallisation from toluene/petroleum ether.
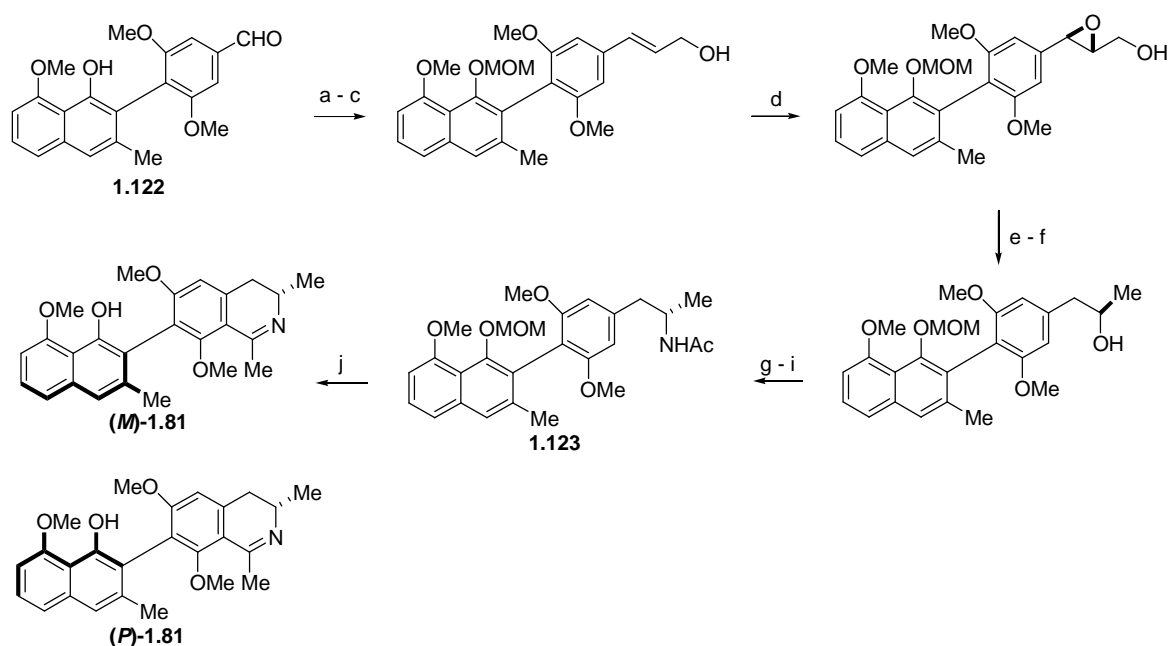
Scheme 1.20 Reagents and yields: a) MOM-Cl, NaH, THF, rt, 81%; b) NaH, (EtO)$_2$POCH$_2$CO$_2$Et, C$_6$H$_6$, 0°C to rt, 99%; c) DIBAL-H, toluene, -78 °C, 15 min, 89%; d) 5 mol% Ti(OiPr)$_4$, 6 mol% D-diisopropyltartrate, TBHP, CH$_2$Cl$_2$, -20 °C, 5 h, 80%, 90% ee; e) TsCl, NEt$_3$, DMAP, CH$_2$Cl$_2$, 1 h, 0°C, 83%; f) LiAlH$_4$, Et$_2$O, 0 °C, 2 h, 94%; g) phthalimide, DEAD, PPh$_3$, THF, rt, 16 h, 82%; h) 40% aq MeNH$_2$, EtOH reflux, 1 h, 99%; i) CH$_3$COCl, NEt$_3$, CH$_2$Cl$_2$, 0°C to rt, 97%; j) POCl$_3$, 2,4,6-collidine, CH$_3$CN, reflux, 4 h, 74% (1:1 mixture of (*M*)-**1.81** and (*P*)-**1.81**).

The formation of both atropisomers can be attributed to the loss of symmetry upon cyclisation of **1.123**, as there are two potential sites at which the electrophilic aromatic substitution can take place (**Figure 1.21**). As a result of restricted rotation about the biaryl axis, attack at either of these positions results in the formation of atropisomers.
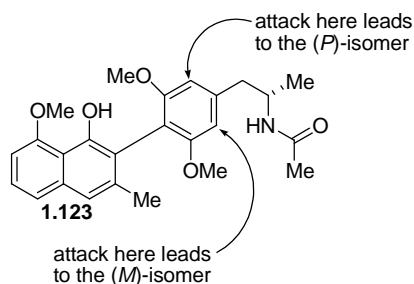

Figure 1.21   Formation of atropisomers of ancistrocladidine.

In summary, this work resulted in the first total synthesis of a 7,3′-linked naphthylisoquinoline alkaloid in 22 steps.[75,76] The key feature of the synthesis was the formation of the extremely

hindered biaryl linkage by *ortho*-arylation of a naphthol with an aryllead triacetate. The symmetrical nature of this aryllead triacetate, however, did not allow the investigation of an atropselective synthesis.

1.7   Work Described in this Thesis

Ancistrotanzanine A, an isomer of ancistrocladidine, has since been isolated. The isolation of ancistrotanzanine A gives us the opportunity to extend the Pinhey-Barton *ortho*-arylation reaction to other naphthylisoquinoline alkaloids, as discussed below.

Ancistrotanzanine A is the only example of a 5,3′-linked naphthyliosoquinoline alkaloid (**Figure 1.22**). Ancistrotanzanine A was isolated from the leaves of the East African *Ancistrocladus* species A. *tanzaniensis*, which was collected in Tanzania in the Uzungwa mountains at 1200 m above sea level. Ancistrotanzanine A was found to exhibit high antileishmanial activity against *Leishmania donovani*, the pathogen causing visceral leishmaniasis.[27]
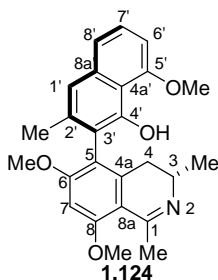

Figure 1.22   5,3′-linked naphthylisoquinoline alkaloid ancistrotanzanine A.

Analysis of the ^{1}H NMR spectrum obtained in deuterated methanol of ancistrotanzanine A revealed resonances at δ 3.90, 4.05 and 4.13 (three protons each) which were attributed to the presence of three methoxy groups. NOE effects were observed between a methoxy group at δ 3.90 and H-7 and also for the methoxy group at δ 4.13 and H-7. The remaining methoxy signal at δ 4.05 showed a NOE with the H-6′. Recording of the ^{1}H NMR in CDCl$_3$ revealed an additional OH signal at δ 9.51. HMBC correlations between the hydroxyl group proton and the aromatic methyl group to C-3′ confirmed the hydroxyl group to be located at C-4′. The aromatic protons were found to form a coupling pattern of a triplet, two doublets, and two singlets, thus excluding the biaryl axis from being located at C-6′ or C-8′, leaving only C-3′ or C-1′ for the coupling position. Of these, the latter was excluded by NOE correlations between the singlet H-1′ (δ 7.25)

with H-8′ (δ 7.38 dd, J = 7.6 Hz, 1.3 Hz) and with CH$_3$-2′ (δ 2.06). The high field ^{1}H NMR shifts of CH$_3$-2′ and OCH$_3$-6 confirmed the position of the biaryl axis to be 5,3′-coupled.

The absolute stereochemistry at C-3 of ancistrotanzanine A was determined by ruthenium-mediated oxidative degradation (**Figure 1.23**). Stereochemical analysis of the degradated products by gas chromatography was possible after derivatisation with the *R*-enantiomer of Mosher's chloride. The formation of (*S*)-3-aminobutyric acid confirmed the alkaloid to be *S*-configured at C-3.
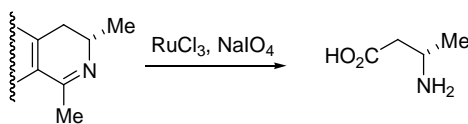

Figure 1.23   Ruthenium-mediated oxidative degradation of ancistrotanzanine A gave (*S*)-3-aminobutyric acid confirming the alkaloid to be *S*-configured at C-3.

The absolute axial configuration of ancistrotanzanine A was established by CD investigations. The experimental CD spectrum of **1.24** showed good agreement with the *M* calculated CD spectrum and was opposite to the *P* calculated CD spectrum, indicating the biaryl axis to be *M* as shown in **Figure 1.22**.

The 5,3′ biaryl bond present in ancistrotanzanine A presents the opportunity to extend the Pinhey-Barton *ortho*-arylation reaction to other naphthylisoquinoline alkaloids. Retrosynthetic analysis of ancistrotanzanine A (**1.24**) by this approach leads to the naphthol **1.104** and the aryllead species **1.125**, which unlike that required for ancistrocladidine is not symmetrical (**Figure 1.24**). This will result in atropisomers being formed immediately after the formation of the biaryl linkage, in contrast to that observed in the synthesis of ancistrocladidine. This means that the biaryl linkage may possibly be prepared in an atropselective manner.
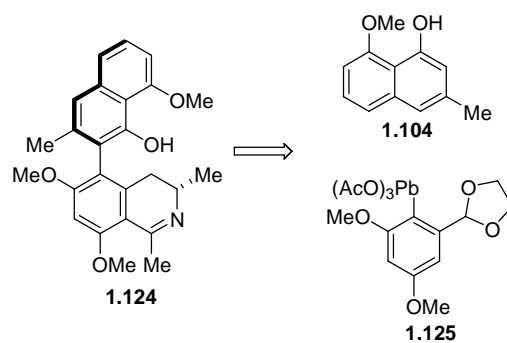
Figure 1.24   Retrosynthetic analysis of ancistrotanzanine A using the Pinhey-Barton reaction to form the key biaryl linkage.

With the above natural product target in mind the initial aims of this research were as follows:

- To investigate the use of the Pinhey-Barton strategy for the total synthesis of ancistrotanzanine A.

- To investigate the use of chiral auxiliaries and chiral ligands to control the atropselectivity during formation of the key biaryl linkage.

1.8   References

(1)   Grabley, S.; Thiericke, R. *Springer: Germany,* **1999.**

(2)   Cooper, G. P.; Record, S. J. *Yale Univ. School For. Bull.* **1931**, *147*, 27.

(3)   Bringmann, G.; Spuziak, J.; Faber, J. H.; Gulder, T.; Kajahn, I.; Dreyer, M.; Heubl, G.; Brun, R.; Mudogo, V. *Phytochemistry* **2008**, *69*, 1065.

(4)   Rizzacasa, M. A. *Studies in natural product chemistry* **1998**, *20*, 407.

(5)   Bringmann, G.; Ruedenauer, S.; Bruhn, T.; Benson, L.; Brun, R. *Tetrahedron* **2008**, *64*, 5563.

(6)   Francois, G.; Bringmann, G.; Phillipson, J. D.; Assi, L. A.; Dochez, C.; Rubenacker, M.; Schneider, C.; Wery, M.; C, W. D.; C, K. G. *Phytochemistry* **1994**, *35*, 1461.

(7)   Hallock, Y. F.; Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H., 2nd; Shaeffer, M.; Gulden, K. P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; Francois, G.; Boyd, M. R. *J. Org. Chem.* **1994**, *59*, 6349.

(8)   Bringmann, G.; D, K.; Wiesen, B.; Francois, G.; Narayanan, A. S. S.; Almeida, M. R.; Schneider, H.; Zimmermann, U. *Phytochemistry* **1996**, *43*, 1405.

(9)   Bringmann, G.; Saeb, W.; Koppler, D.; G, F. *Tetrahedron* **1996**, *52*, 13419.

(10)   Hallock, Y. F.; Manfredi, K. P.; Dai, J. R.; Cardellina, J. H., 2nd; Gulakowski, R. J.; McMahon, J. B.; Schaffer, M.; Stahl, M.; Gulden, K. P.; Bringmann, G.; Francois, G.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 677.

(11)   Bringmann, G.; Holenz, J.; Weirich, R.; Rubenacker, M.; Funke, C.; Boyd, M. R.; Gulakowski, R. J.; Francois, G. *Tetrahedron* **1998**, 497.

(12)   Bringmann, G.; Saeb, W.; God, R.; Schaffer, M.; Francois, G.; Peters, K.; Peters, E.-M.; Proksch, P.; Hostettmann, K.; Assi, L. A. *Phytochemistry* **1998**, *49*, 1667.

(13)   Bringmann, G.; Teltschik, F.; Michel, M.; Busemann, S.; Ruckert, M.; Haller, R.; Bar, S.; Robertson, S. A.; Kaminsky, R. *Phytochemistry* **1999**, *52*, 321.

(14)   Bringmann, G.; Saeb, W.; Wohlfarth, M.; Messer, K.; Brun, R. *Tetrahedron* **2000**, *56*, 5871.

(15)   Bringmann, G.; Saeb, W.; Kraus, J.; Brun, R.; Francois, G. *Tetrahedron* **2000**, *56*, 3523.

(16)   Bringmann, G.; Guenther, C.; Saeb, W.; Mies, J.; Wickramasinghe, A.; Mudogo, V.; Brun, R. *J. Nat. Prod.* **2000**, *63*, 1333.

(17)   Bringmann, G.; Günther, C.; Peters, E.; Peters, K. *Tetrahedron* **2001**, *57*, 1253.

(18)   Bringmann, G.; Holenz, J.; Wiesen, B.; Nugroho, B. W.; Proksch, P. *J. Nat. Prod.* **1997**, *60*, 342.

(19)   Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H., 2nd; McMahon, J. B.; Pannell, L. L.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 3402.

(20)   Hallock, Y. F.; Cardellina, J. H., 2nd; Schaeffer, M.; Bringmann, G.; Francois, G.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **1998**, 1729.

(21)   Upender, V.; Pollart, D. J.; Liu, J.; Hobbs, P. D.; Olsen, C.; Chao, W.; Bowden, B.; Crase, J. L.; Thomas, D. W.; Pandey, A.; Lawson, J. A.; Dawson, M. I. *J. Heterocyclic Chem.* **1996**, *33*, 1371.

(22)   Zhang, H.; E, Z. D.; Chen, Z. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2687.

(23)   Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L. *J. Org. Chem.* **1999**, *64*.

(24)   Boyd, M. R.; Hallock, Y. F.; Cardellina, J. H., 2nd; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W., Jr.; Bringmann, G.; Schaffer, M.; Cragg, G. M. *J. Med. Chem.* **1994**, *37*, 1740.

(25)   Bringmann, G.; Kajahn, I.; Reichert, M.; Pedersen, S. E. H.; Faber, J. H.; Gulder, T.; Brun, R.; Christensen, S. B.; Ponte-Sucre, A.; Moll, H.; Heubl, G.; Mudogo, V. *J. Org. Chem.* **2006**, *71*, 9348.

(26)   Bringmann, G.; Ruebenacker, M.; Geuder, T.; Assi, L. A. *Phytochemistry* **1991**, *30*, 3845.

(27)   Bringmann, G.; Dreyer, M.; Faber, J. H.; Dalsgaard, P. W.; Strk, D.; Jaroszewski, J. W.; Ndangalasi, H.; Mbago, F.; Brun, R.; Reichert, M.; Maksimenka, K.; Christensen, S. B. *J. Nat. Prod.* **2003**, *66*, 1159.

(28)   Govindachari, T. R.; Parthsarathy, P. C.; Desai, H. K. *Indian. J. Chem.* **1973**, *11*, 1190.

(29)   Bringmann, G.; Ruebenacker, M.; Weirich, R.; Assi, L. A. *Phytochemistry* **1992**, *31*, 4019.

(30)   Bringmann, G.; Hamm, A.; Guenther, C.; Michel, M.; Brun, R.; Mudogo, V. *J. Nat. Prod.* **2000**, *63*, 1465.

(31)   Luk, L. Y. P.; Bunn, S.; Liscombe, D. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry* **2007**, *46*, 10153.

(32)   Bringmann, G.; Wohlfarth, M.; Rischer, H.; Grune, M.; Schlauer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1464.

(33)   Bringmann, G. *Tetrahedron Lett.* **1982**, *23*, 2009.

(34)   Bringmann, G.; Mutanyatta-Comar, J.; Greb, M.; Ruedenauer, S.; Noll, T. F.; Irmer, A. *Tetrahedron* **2007**, *63*, 1755.

(35)   Christie, C. H.; Kenner, J. *J. Chem. Soc.* **1922**, *121*, 614.

(36)   Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.

(37)   Bringmann, G.; Stahl, M.; Gulden, K.-P. *Tetrahedron* **1997**, *53*, 2817.

(38)   Bringmann, G.; Jansen, J. R. *Tetrahedron Lett.* **1984**, *25*, 2537.

(39)   Bringmann, G.; Robert-Michael, P.; Petra, S.; Kristina, H.; Michaela, S.; Matthias, B. *Tetrahedron* **2004**, *60*, 4349.

(40)   Bringmann, G.; Hartung, T. *Tetrahedron* **1993**, *49*, 7891.

(41)   Bringmann, G.; Breuning, M.; Walter, R.; Wuzik, A.; Peters, K.; Peters, E.-M. *Eur. J. Org. Chem.* **1999**, 3047-3055.

(42)   Bringmann, G.; Breuning, M.; Tasler, S.; Endress, H.; Ewers, C. L. J.; Gobel, L.; Peters, K.; Peters, E.-M. *Eur. J. Org. Chem.* **1999**, *5*, 3029.

(43)   Bringmann, G.; Breuning, M.; Pfeifer, R.-M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. *J. Organomet. Chem.* **2002**, *661*, 31.

(44)   Bringmann, G.; Goebel, L.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Inorg. Chim. Acta.* **1994**, *222*, 255.

(45)   Bringmann, G.; Reuscher, H. *Tetrahedron Lett.* **1989**, *30*, 5249.

(46)   Bringmann, G.; Jansen, J. R.; Rink, H. P. *Angew. Chem.* **1986**, *98*, 917.

(47)   Bringmann, G.; Ochse, M. *Synlett* **1998**, 1294-1296.

(48)   Bringmann, G.; Ochse, M.; Goetz, R. *J. Org. Chem.* **2000**, *65*, 2069.

(49)   Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853.

(50)   Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60*, 4459.

(51)   Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989.

(52)   Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1991**, 841.

(53)   Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1991**, 278.

(54)   Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1991**, 845.

(55)   Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1991**, 2773.

(56)   Gable, R. W.; Martin, R. L.; Rizzacasa, M. A. *Aust. J. Chem.* **1995**, *48*, 2013.

(57)   Chau, P.; Czuba, I. R.; Rizzacasa, M. A.; Bringmann, G.; Gulden, K.-P.; Schaffer, M. *J. Org. Chem.* **1996**, *61*, 7101.

(58)   Comber, M. F.; Morris, J. C.; Sargent, M. V. *Aust. J. Chem.* **1998**, *51*, 19.

(59)   Meijere, A. d.; Diederich, F. *Metal-Catalysed Cross-Coupling Reactions, 2nd Completely Revised and Enlarged Edition*; WILEY-VCH GmBH and Co. KGaA, Weinheim, 2004.

(60)   Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097.

(61)   Bringmann, G.; Hamm, A.; Schraut, M. *Org. Lett.* **2003**, *5*, 2805.

(62)   Watanabe, T.; Tanaka, Y.; Shoda, R.; Sakamoto, R.; Kamikawa, K.; Uemura, M. *J. Org. Chem.* **2004**, *69*, 4152.

(63)   Lipshutz, B. H.; Keith, J. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3530.

(64)   Kamikawa, K.; Watanabe, T.; Daimon, A.; Uemura, M. *Tetrahedron* **2000**, *56*, 2325.

(65)   Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(66)   Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angewandte Chemie, Int. Ed.* **2009**, *48*, 2383.

(67)   Nishiyama, T.; Kameoka, H. *Chem. Express* **1991**, *109*, 6.

(68)   Bell, H. C.; Pinhey, J. T.; Rowe, B. A. *Aust. J. Chem.* **1979**, *32*, 1551.

(69)   Pinhey, J. T.; Rowe, B. A. *Aust. J. Chem.* **1979**, *32*, 1561.

(70)   Barton, D. H. R.; Donnelly, D. M. X.; Guiry, P. J.; Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2921.

(71)   Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365.

(72)   Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.

(73)   P. Kozyrod, R.; Pinhey, J. T. *Tetrahedron Lett.* **1983**, *24*, 1301.

(74)   Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2095.

(75)   Bungard, C. J.; Morris, J. C. *J. Org. Chem.* **2006**, *71*, 7354.

(76)   Bungard, C. J.; Morris, J. C. *Org. Lett.* **2002**, *4*, 631.

Chapter Two

Studies into a Diastereoselective Pinhey-Barton Reaction

2.1   Application of the Pinhey-Barton Reaction to the Total Synthesis of Ancistrotanzanine A

The key feature of the Morris and Bungard synthesis of ancistrocladidine was the formation of the highly hindered biaryl linkage by *ortho*-arylation of a naphthol with an aryllead triacetate.[1,2] However, the symmetry of this aryllead triacetate did not allow an investigation into an atropselective synthesis. As a result of restricted rotation about the central biaryl bond, cyclisation of amide **1.23** at either of the two sites, as indicated below, results in the formation of atropisomers (**Figure 2.1**).
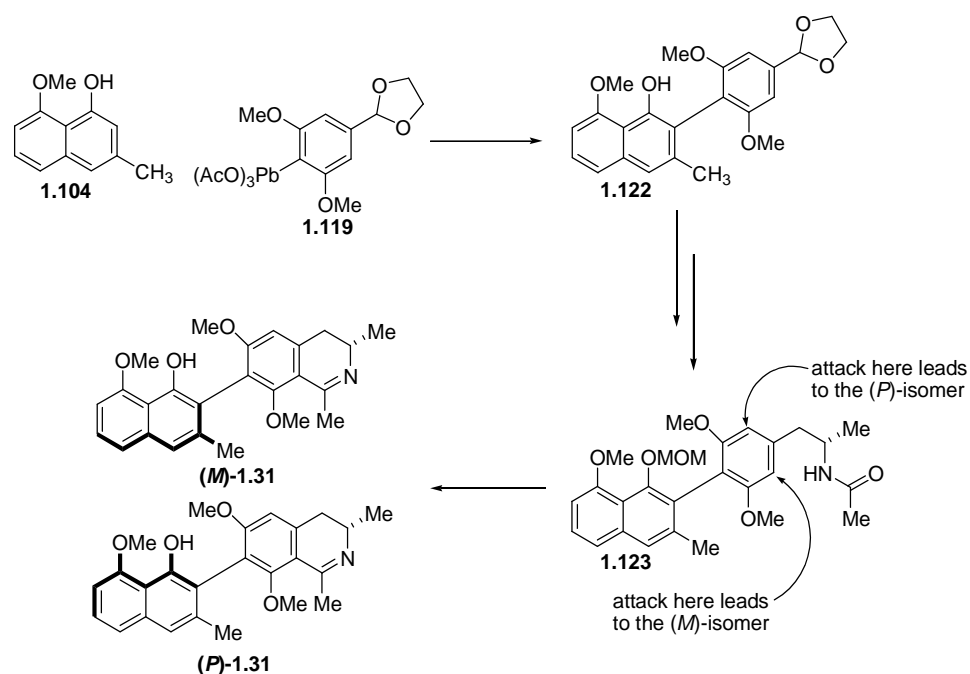

Figure 2.1   Formation of atropisomers in the synthesis of ancistrocladidine.

A synthesis of ancistrotanzanine A using a similar strategy would require the coupling of the aryllead species **2.1** with naphthol **1.104**. Unlike the aryllead species used for the synthesis of ancistrocladidine, this aryllead species lacks symmetry. Consequently, *ortho*-arylation of naphthol **1.104** with aryllead **2.1** would result in formation of biaryl **2.2** as a 1:1 mixture of atropisomers (**Figure 2.2**). A total synthesis of ancistrotanzanine A would allow an investigation into an atropselective synthesis of a naphthylisoquinoline alkaloid via the Pinhey-Barton approach developed by Morris and Bungard.
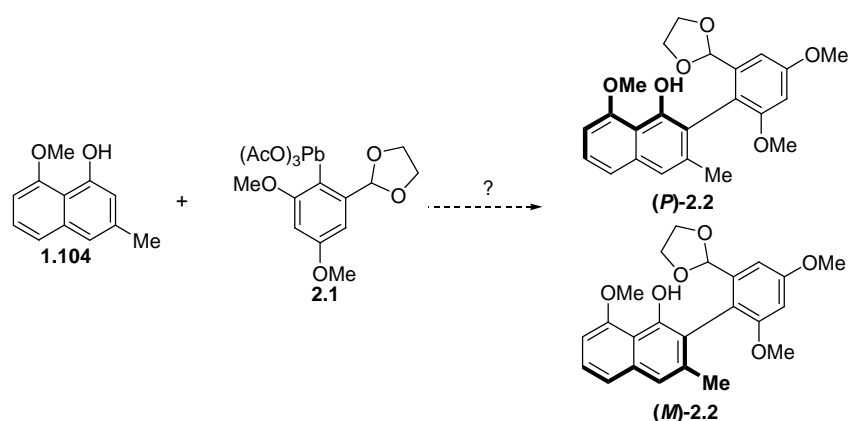
Figure 2.2   The *ortho*-arylation of naphthol **1.104** with aryllead **2.1** would result in the formation of biaryl **2.2** as a 1:1 mixture of atropisomers.

Pinhey observed that the coupling of phenols with aryllead triacetates is facilitated by the participation of excess pyridine or analogous bases in chloroform. Using this observation Yamamoto investigated the use of alternative base additives with the aim to find a chiral amine base that would allow an efficient asymmetric synthesis of the biaryl bond via the Pinhey-Barton reaction.[3,4] What follows is a brief explanation of this work and how it could be applied to an atropselective synthesis of ancistrotanzanine A.

2.2   Search for a chiral ligand

Yamamoto and coworkers began with a search for an efficient synthesis of 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol **2.5** by the Pinhey-Barton reaction using chiral amines in place of pyridine (**Scheme 2.1**).[4] Before using chiral amines, the group investigated the effect of achiral primary, secondary and tertiary amines on the coupling reaction of 3,5-dimethylphenol **2.5** with (2-isopropylphenyl)lead triacetate **2.4** (**Scheme 2.1**).
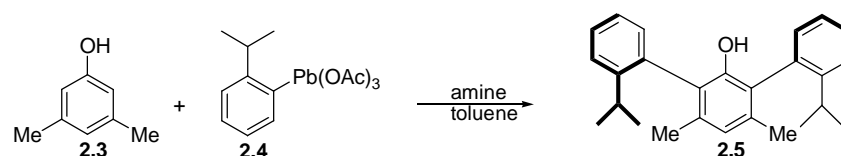
Scheme 2.1   Coupling reaction performed by Yamamoto and coworkers with a range of amines. For reaction conditions see **Table 2.1.**
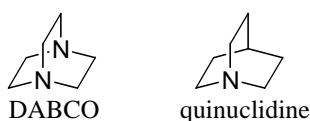
Entry	Amine	Yield
1	i-PrNH$_2$	75
2	(i-Pr)$_2$NH	0
3	(i-Pr)$_2$NEt	0
4	Et$_3$N	0
5	DABCO	78
6	quinuclidine	95

The reaction was performed using **2.3** (1.0 equivalent), aryllead compound **2.4** (3.0 equivalent) and amine (3.0 equivalent) at r.t. for 2 h.[4]

Table 2.1   Effect of the amine on the ligand coupling of **2.3** with **2.4**.

As seen in Table 2.1, the use of a primary amine gave the biaryl **2.5** in good yield, whereas secondary amines and tertiary amines, such as triethylamine, were found not to promote the ligand coupling. However, it was observed that the conformationally restricted tertiary amines DABCO and quinuclidine exhibited excellent reactivity, with the biaryl **2.5** obtained in high yield.

Having established that both primary and conformationally restricted tertiary amines may be used to promote the *ortho*-arylation reaction, the group investigated an asymmetric version of the reaction using a range of chiral bases (**Figure 2.3**). The use of chiral primary amines **2.6** and **2.7** were found to give no selectivity. Bidentate amines (such as **2.8** and **2.9**) gave low selectivity and incomplete consumption of the starting phenol. Quinuclidine derivatives with an oxygen functional group at the β-position also resulted in poor yields and poor selectivity.
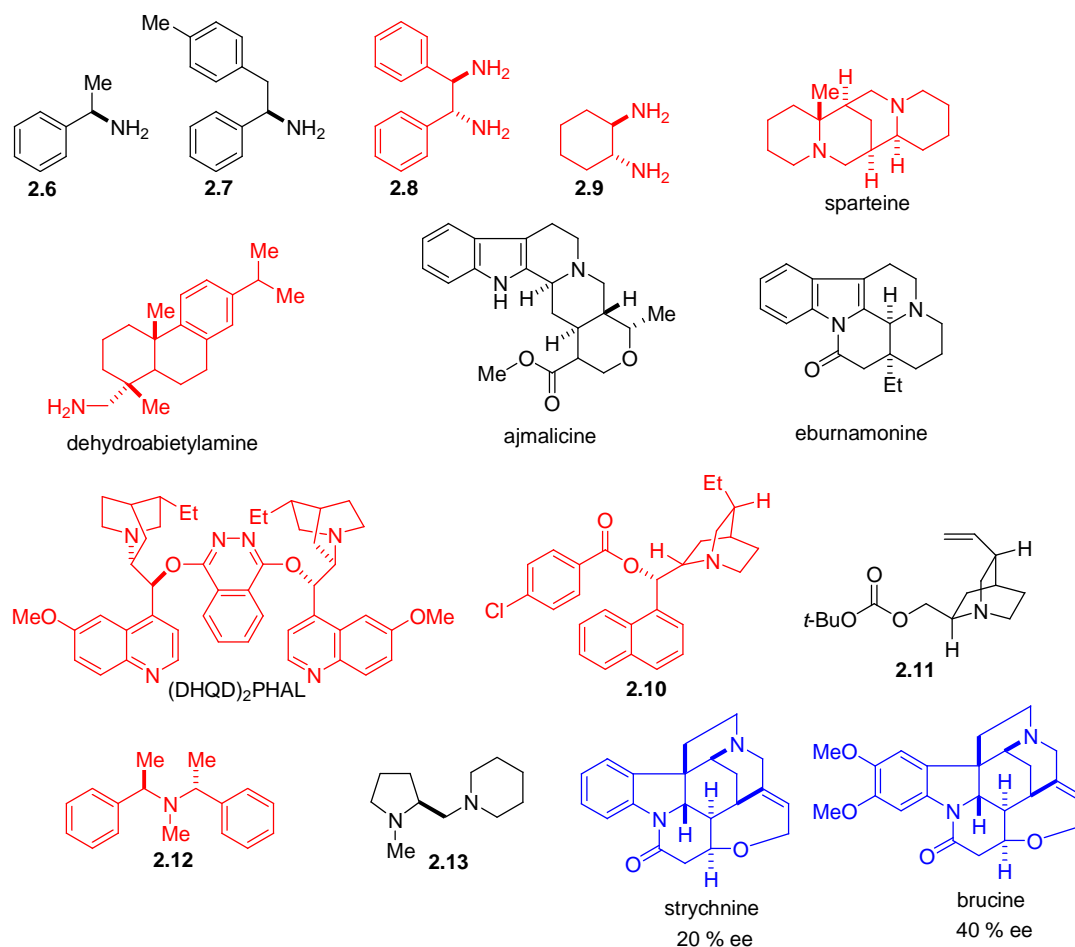
Figure 2.3 Chiral bases screened by Yamamoto and coworkers in search of an asymmetric reaction Pinhey-Barton reaction.[4] The bases in black gave no atropselectivity. The base in red gave some atropselectivity (<10% ee). Bases in blue gave the best atropselectivity.

The chiral base brucine, which contains a conformationally restricted tertiary amine moiety, was found to give the best result of the screened chiral bases (92%, 40% ee), (**Scheme 2.2**). Interestingly, strychnine which lacks the methoxy functional groups of brucine, gave both a lower yield (32%) and lower ee (20%).
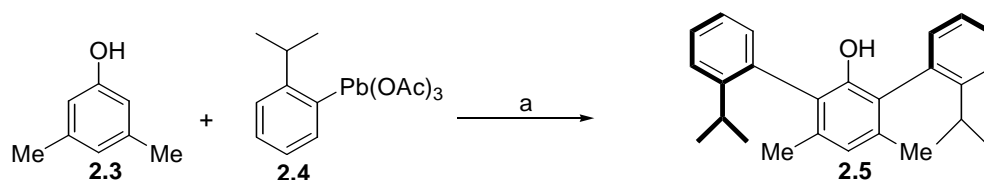

Scheme 2.2 Reagents and Yields: 1.0 equivalent of **2.3**, 2.5 equivalents of aryllead **2.4**, 3.0 equivalents of brucine, toluene r.t., 92%, 40% ee.

Having established that the use of brucine was high yielding and gave some atropselectivity, Yamamoto and coworkers studied the effect of solvent on the reaction. It was found that while

dichloromethane, tetrahydrofuran and toluene gave comparable yields of the biaryl **2.5**, the use of toluene as the solvent led to the highest atropselectivity.

Acetic acid, a by-product of the reaction, reacts with brucine to form a salt, which retards brucine's ability to promote the ligand coupling. Consequently, a large excess (up to 6 equivalents) of brucine was necessary. However, due to the high toxicity of brucine (LD_{50} (oral, rat) 1 mg kg^{-1}) methods were sought to avoid having to use a large excess of brucine. The use of 4Å molecular sieves allowed the coupling reaction to reach completion with the use of less brucine. The group also examined the effect of metallating phenol **2.3** as its lithium, sodium and or potassium salt. Indeed, performing the reaction with lithium phenoxide **2.14**, at low temperatures (-20 ^{o}C or -40 ^{o}C) was found to increase the ee of the reaction from 40 to 61% (**Scheme 2.3**). The reaction conditions were optimised and are summarised below (**Scheme 2.3**).
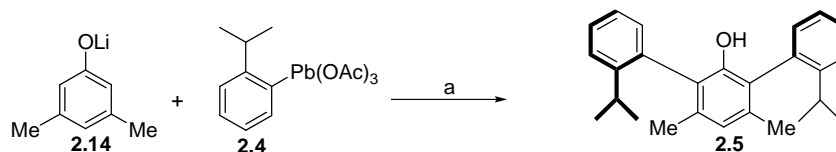
Scheme 2.3   Reagents and yields: (a) 1.0 eq of **2.14**, 2.5 eq of aryllead **2.4**, 2.0 eq of brucine, 3 g/mmol 4Å molecular sieves, toluene, -20 ^{o}C, 21 h (99%, 61% ee).

Given that strychnine lacks methoxy substituents on the aromatic ring and gave a lower ee, it was suspected by Yamamoto that the methoxy groups played a key role in the enantioselectivity of brucine. Consequently, the group investigated the effect of two other brucine derivatives on the atropselectivity of the reaction (**Figure 2.4**). Use of the benzyloxy-substituted brucine gave the same selectivity achieved from the use of brucine, whereas silyl-protected brucine was found to be a poor ligand with incomplete conversion of the starting substrates and no enhancement in the selectivity.
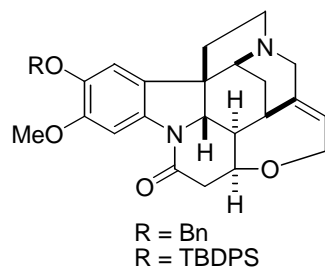
R = Bn
R = TBDPS

Figure 2.4   Derivatives of brucine tested to investigate the extent that the methoxy groups of brucine affected the *ortho*-arylation reaction.

The high diastereo- and enantioselectivity of the brucine mediated *ortho*-arylation Pinhey-Barton reaction is presumably a result of brucine coordinating to the lead center and promoting ligand coupling. A plausible mechanism for the asymmetric ligand coupling was proposed by Yamamoto and is shown below.
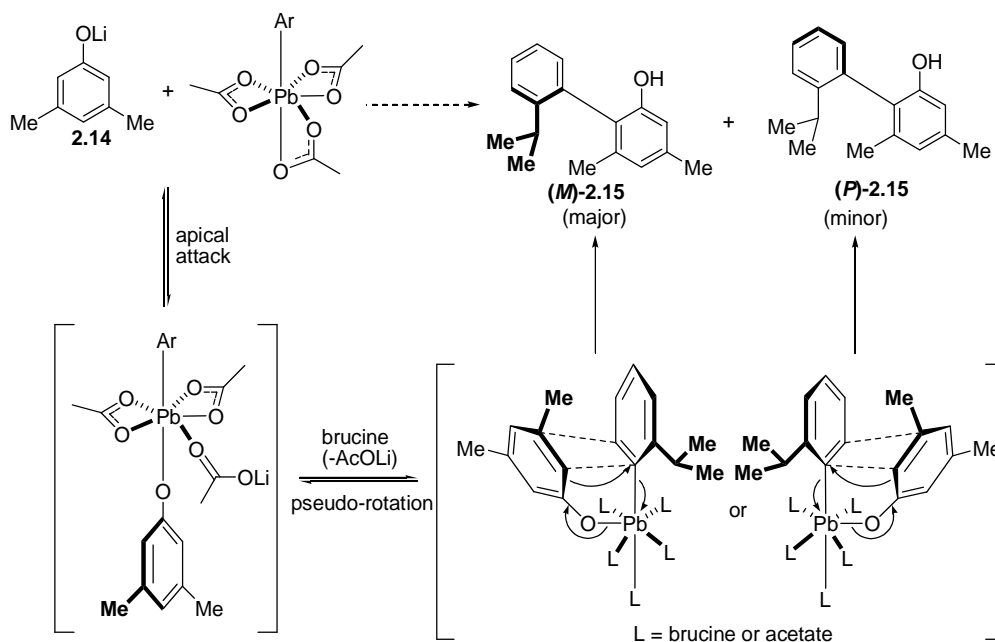
Figure 2.5   Proposed mechanism for the selectivity observed during the coupling reaction.

Yamamoto suggested that the lithium phenoxide coordinates to an apical position of lead and the resulting lithium acetate may undergo ligand exchange with brucine. Both the configuration and conformation of this complex may be controlled by the steric effect of brucine during pseudorotation. Finally, oxidative coupling occurs to give **(*M*)-2.15** as the major isomer.

Given the results from the above work, it was envisaged that brucine may also allow for the atropselective coupling of naphthol **1.104** and the aryllead species **2.1** that is required for the synthesis of ancistrotanzanine A. However, the sole use of brucine to control the atropselectivity of the reaction presents some issues. Brucine is extremely toxic, which would cause safety concerns for scaling up of the synthesis. In addition, (+)-brucine is not available from natural sources, thus limiting the ability of this approach to selectively generate either atropisomer.

With these concerns in mind an alternative strategy for controlling the atropselectivity was sought. Reviewing other strategies that have been used for the synthesis of optically active biaryl compounds reveals that the use of a chiral auxiliary has proven to be both popular and effective.[5-7] However, placing a chiral auxiliary on the naphthol unit would require its deletion at a later stage of the synthesis, thus increasing the number of steps required for the total synthesis of ancistrotanzanine A. On the other hand the acetal functionality of the aryllead **2.1** would be an attractive option in facilitating the transfer of the chiral information, given its ease of removal after the formation of the biaryl linkage and its location next to the biaryl bond. The auxiliary used would have to be bulky enough to ensure one atropisomer is formed preferentially, by causing a steric clash during the transition state proposed by Yamamoto. The phenyl groups of the acetal (**R,R**)-**2.16** would appear to be a reasonable way of achieving the steric environment required to give one atropisomer over the other (**Figure 2.6**). Acetals of type **2.16** can be prepared from hydrobenzoin chiral diols which are readily available in both enantiomeric forms, thus potentially allowing the preparation of either atropisomer simply by interchanging the auxiliary with its enantiomer. This potentially would allow a diastereoselective synthesis of the biaryl axis of ancistrotanzanine A.
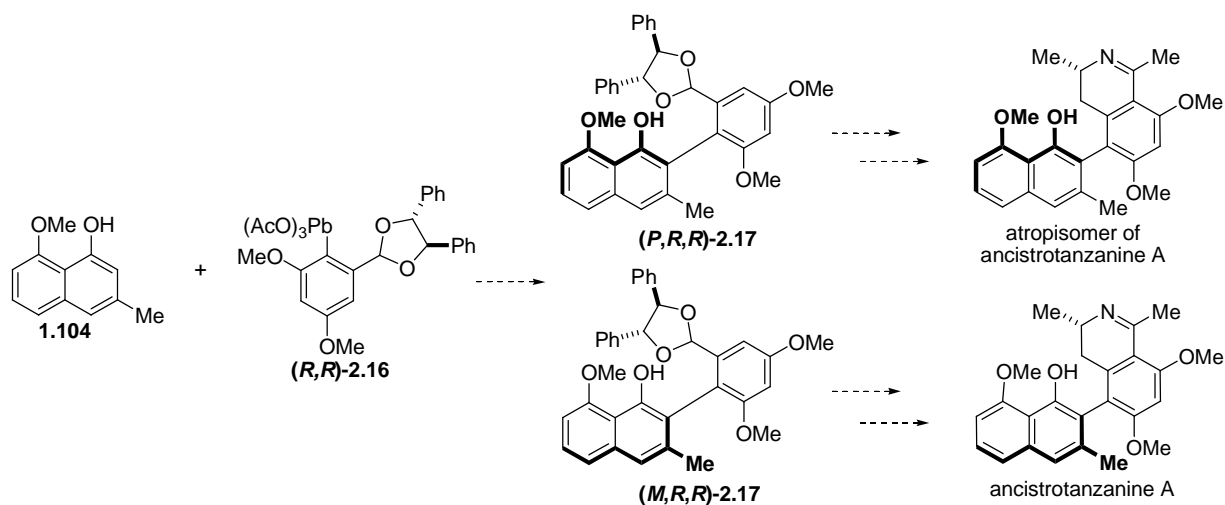
Figure 2.6   Reaction of naphthol **1.104** with aryllead (**R,R**)-**2.16** would result in the formation of diastereoisomers (**P,R,R**)-**2.17** and (**M,R,R**)-**2.17**.

2.3   Combining the 'Lactone Method' with the Pinhey-Barton Reaction

One issue regarding the diastereoselective Pinhey-Barton strategy is that the deprotection of the acetal functionality of biaryl **2.17** would give aldehyde **2.18**, which may react further to give hemiacetal **2.19** (**Figure 2.7**). This would presumably result in the biaryl axis being racemised but on the other hand, it does present the possibility of combining the *ortho*-arylation Pinhey-Barton strategy with the 'lactone method', which is discussed below.
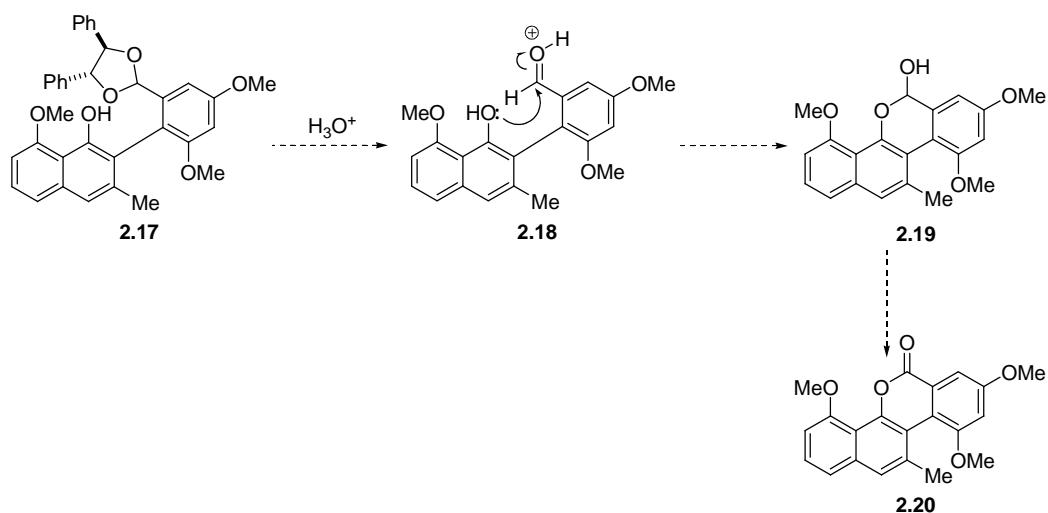

Figure 2.7   Deprotection of the acetal functionality may result in formation of hemiacetal **2.19** which could be used to prepare lactone **2.20**.

The 'lactone method' has been shown to be highly successful for the preparation of optically active biaryl compounds.[8] The use of this strategy in the synthesis of ancistrotanzanine A would require the successful formation of the biaryl axis via the *intra*-molecular palladium coupling of the requisite bromide **2.21** (**Figure 2.8**). Given the highly steric environment, however, this may be difficult to achieve.
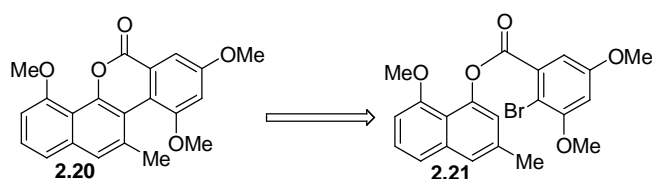

Figure 2.8 The required lactone for the synthesis of the ancistrotanzanine A via the lactone method and the requisite bromide **2.21**.

Use of the Pinhey-Barton strategy to prepare the biaryl axis may allow the use of the lactone method given the close proximity of the hydroxyl group to the aldehyde. The close proximity of these two groups may result in the formation of hemiacetal **2.19** under the acidic conditions used to deprotect the acetal functionality as shown in **Figure 2.9**. Oxidation of the hemiacetal to the lactone **2.20** should be possible. Dynamic kinetic resolution of the lactone **2.20** would then be able to give either atropisomer as discussed in Section 1.3.1.
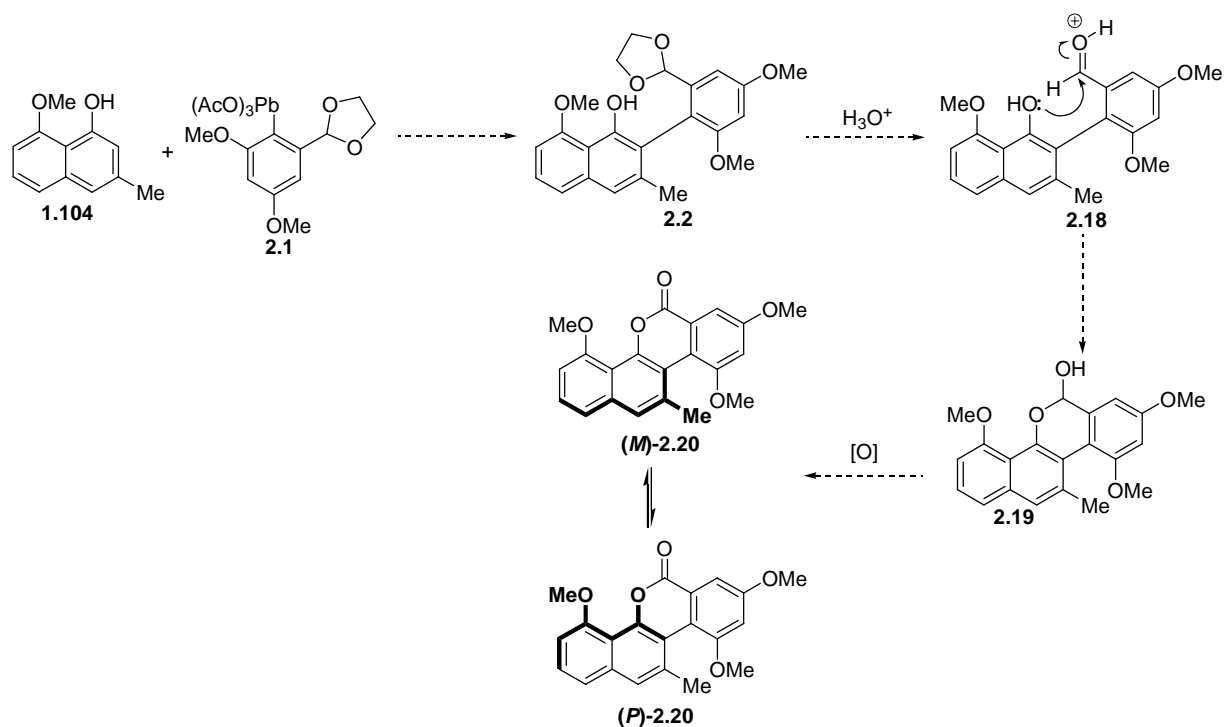
Figure 2.9   Mechanism for the possible formation of hemiacetal **2.19** which may then be oxidized to lactone **2.20**.

Hence, before investigating a diastereoselective Pinhey-Barton reaction, it was deemed appropriate to investigate the preparation of the achiral aryllead triacetate species **2.1** and its coupling with naphthol **1.104** with an aim of preparing lactone **2.20**.

2.4   Preparation of the Aryllead Species 2.1

As mentioned previously, aryllead triacetates are conveniently prepared by reaction of lead tetraacetate in the presence of a catalytic amount of a mercury(II) salt from aryl stannanes. Thus, to prepare aryllead triacetate **2.1** we require stannane **2.22**, which may be prepared by halogen/metal exchange of the known bromide **2.23**, and quenching this species with tributyltin chloride (**Figure 2.10**).
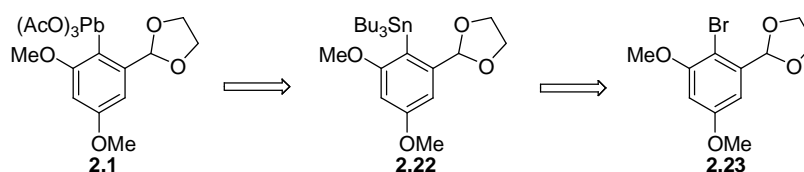

Figure 2.10   Retrosynthesis of the aryllead precursor **2.1**.

As reported by Rizzacasa and Sargent bromide **2.23** was prepared from aldehyde **2.24** by bromination of 3,5-dimethoxybenzaldehyde[9] **2.24**, followed by acetal formation with 1,2-ethanediol under Dean Stark conditions.[10] Stannane **2.22** was readily prepared in 71% yield by halogen/lithium exchange of bromide **2.23** with t-BuLi at -95 $^{\circ}$C in tetrahydrofuran, followed by quenching of the lithiospecies with tributyltin chloride (**Scheme 2.4**).
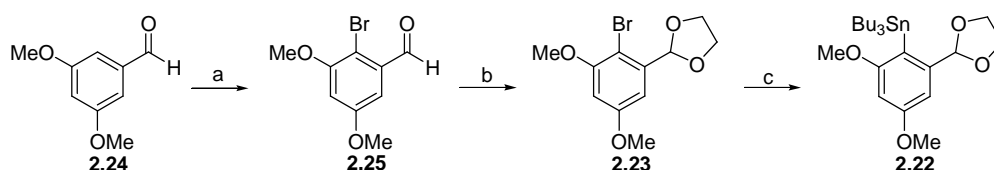
Scheme 2.4   Reagents and yields; (a) 1.04 eq Br$_2$ solution in acetic acid (3.34 M) acetic acid, 15 $^{\circ}$C, 30 min, 77%; (b) 1.5 eq 1,2-ethanediol, benzene, Dean Stark, 88% (c) 2.2 eq t-BuLi, THF, -95 $^{\circ}$C, then 1.1 eq ClSnBu$_3$, -95 $^{\circ}$C to r.t., o.n., 71%.

Exposure of the stannane **2.22** to the standard aryllead forming conditions gave a promising result. After successive washings of the crude material with petroleum spirit, analysis of the ^{1}H NMR spectrum revealed that the desired aryllead compound **2.1** had been prepared, along with a trace of demetallated material **2.26**. Integration of the resonances of the C-H protons of the acetal groups of the two compounds, δ 6.23 (aryllead) and δ 5.77 (demetallated), showed the ratio to be 88:12.
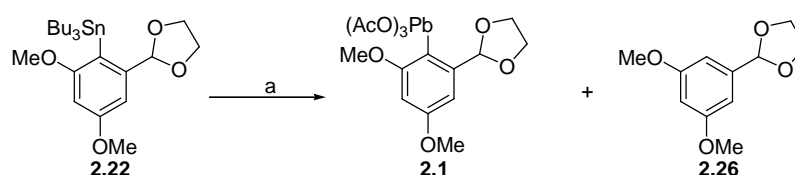
Scheme 2.5   Reagents and yields: (a) 1.5 eq Pb(OAc)$_4$, cat Hg(OOCCF$_3$)$_2$, CH$_2$Cl$_2$, r.t., 88% **2.1**, 12% demetallated **2.26**.

A small sample was purified for characterisation purposes. Although full spectroscopic data could not be obtained for this compound as a result of decomposition under mass spectroscopic analysis, the ^{1}H NMR and ^{13}C NMR spectra are quite diagnostic. In particular the carbon signals at δ 100.7, 101.3 and 104.4 exhibit characteristic ^{207}Pb-satellites at 204 Hz, 105 Hz and 300 Hz either side of the parent peak respectively as shown in **Figure 2.11**.
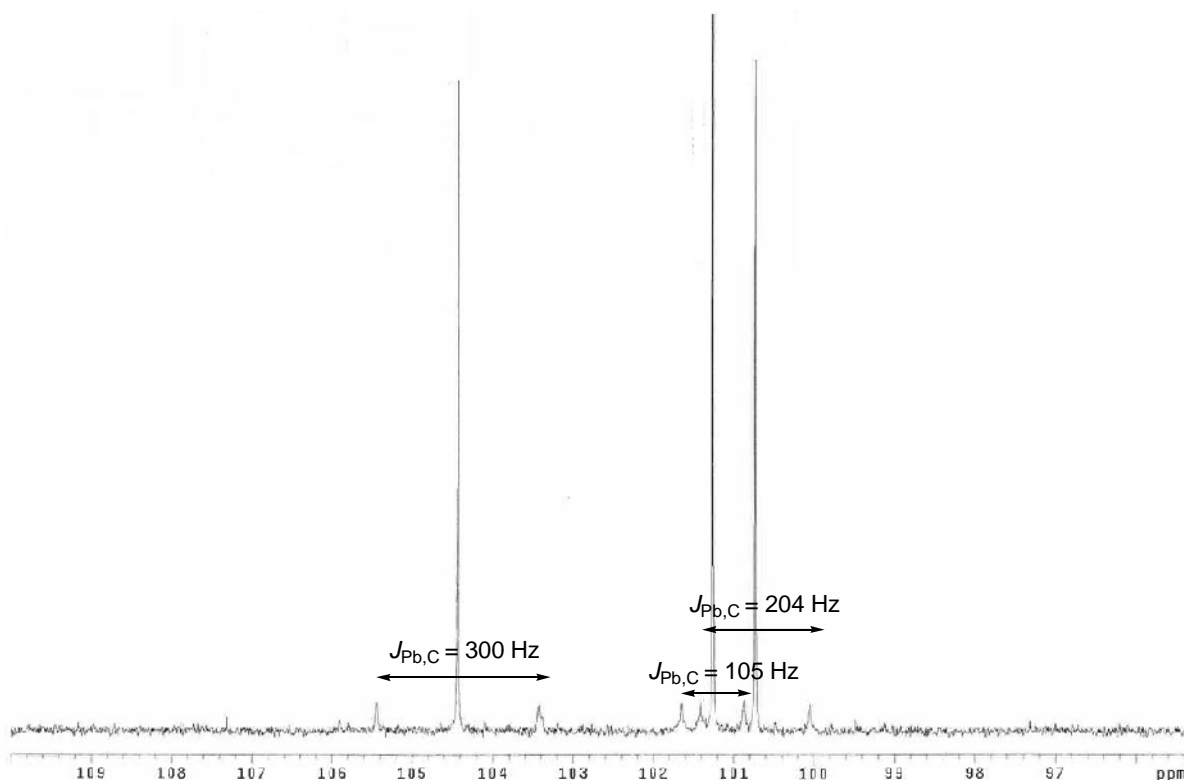
Figure 2.11   Expansion of the 150 MHz ^{13}C NMR spectrum of aryllead tricarboxylate **2.1** showing the ^{207}Pb-satellites.

2.5   Formation of the 5,3′-Biaryl Bond

The naphthol coupling partner **1.104**, which is the same naphthol used in the synthesis of ancistrocladidine, was readily prepared by the method reported by Morris and Bungard[11] (**Scheme 2.6**). Alcohol **2.27** was prepared as reported by Hoshino and coworkers.[12] It was then treated with 1.5 equivalents of triflate anhydride in pyridine to afford the triflate **2.28** in 95% yield. Reaction of the triflate **2.28** with *n*-BuLi in the presence of 1,1-diethoxyethylene at -95 $^{\circ}$C followed by acidic work up afforded the required benzocyclobutenone **2.29** in 69% yield. Alkynylation of the benzocyclobutenone was achieved by reaction of lithiated propargyl chloride in tetrahydrofuran, to give the benzocyclobutenol **2.30** in 63% yield. Hydroxyl-directed reduction of the acetylene **2.30** with lithium aluminium hydride gave the allenic alcohol **2.31**, which upon thermolysis afforded the naphthol **1.104** in 88% yield.
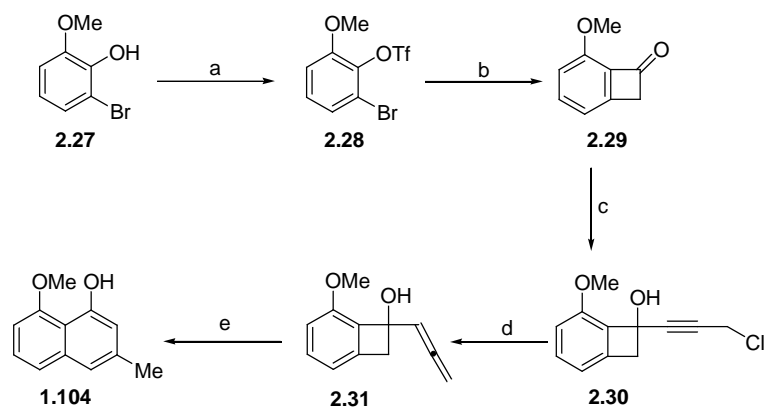
Scheme 2.6   Reagents and yields: a) 1.5 eq Tf$_2$O, pyridine, 0 ^{o}C to r.t., 95%; b) 2 eq *n*-BuLi, 2 eq 1,1-
diethoxyethylene, THF, -95 ^{o}C to r.t., then 3% aqueous sulfuric acid, 69% c) 1.3 eq 3-chloro-1-
propynyllithium, THF, -60 ^{o}C, 63%; d) 2 eq, LiAlH$_4$, THF, 0 ^{o}C, 84%; e) toluene, reflux, 88%.

Having established access to sufficient quantities of the aryllead triacetate **2.1** and naphthol **1.104** investigation of the coupling of the two precursors could now be undertaken. Stirring of a solution of the crude aryllead triacetate **2.1** with naphthol **1.104** and pyridine in dry dichloromethane resulted in the formation of a new product of lower R$_f$ by TLC analysis. The reaction was found to be complete after stirring for 24 hours. After purification by flash chromatography, the new compound was determined to be the desired *ortho*-arylated naphthol **2.2**. The ^{1}H NMR spectrum showed that the resonance of the methyl signal of the naphthalene was shifted upfield from δ 2.41 to δ 2.10 due to shielding from the newly attached ring system. The resonance at δ 9.43 confirmed the presence of a hydroxyl group hydrogen bonded to a methoxy group. This type of resonance has been observed for similar compounds.[1,2] The singlet at δ 7.22 was found to exhibit a NOE interaction with the methyl group on the naphthalene ring and was attributed to H4′. A long range coupling ([3]*J*) from C5′ to H4′ was observed in the HMBC spectrum. The COSY spectrum confirmed that H5′, H6′ and H7′ were an ABX spin system. The ROESY spectrum revealed that H7′ δ 6.70 was found to exhibit a NOE with the methoxy group δ 3.97 of the naphthol. This data confirms that the arylation occurred *ortho* to the hydroxyl group. Confirmation that the acetal functionality was still present was confirmed by the singlet at δ 5.43 integrating to 1 H and the multiplets at δ 3.78 and δ 4.40 both integrating to 2 H.
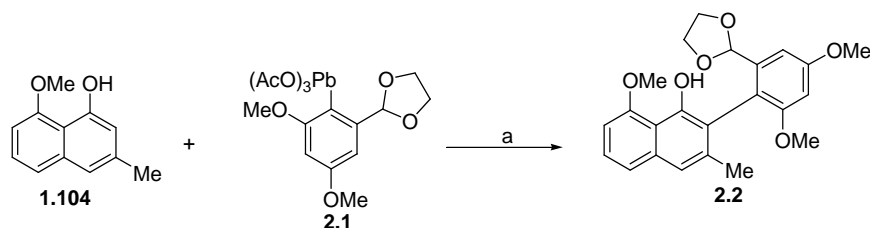
Scheme 2.7   Reagents and yields; (a) 3 eq pyridine, CH_2Cl_2, r.t. 24 h, 55%.

Having established that the arylation of the naphthol had given the desired product the preparation of lactone **2.20**, was investigated. It was deemed appropriate to use Jones' reagent as it was envisaged that these acidic conditions would remove the acetal functionality, oxidise the aldehyde and then facilitate the formation of the requisite lactone. It should be noted that the formation of the hemiacetal **2.19** would require free rotation to occur around the biaryl axis, to allow the carbonyl group to come into the plane of the attacking hydroxyl nucleophile. With the hemiacetal prepared *in situ* oxidation of the lactol should occur immediately, thus yielding the desired lactone. Reacting acetal **2.2** with chromium oxide in the presence of acid gave an orange precipitate. The ^1H NMR spectrum of the crude reaction material showed a complex mixture of products, but the desired lactone **2.20** could not be isolated, nor the aldehyde or acid.
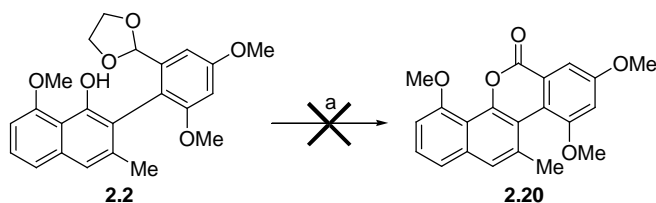
Scheme 2.8   Reagents: (a) 1.3 eq CrO_7, H_2SO_3, acetone/water, 2 h.

Given the above result the acetal functionality was first removed by stirring in THF/aqueous sulfuric acid to determine if the hemiacetal would be formed under these conditions. The ^1H NMR spectrum of the crude reaction material indicated that the hemiacetal **2.19** had not formed. The signals at δ 9.55 and δ 9.66 are indicative of a hydrogen bonded phenol and aldehyde group respectively.

To circumvent any problems with the conditions required for the Bischler-Napieralski cyclisation that is required to complete the total synthesis, the free hydroxyl group was protected as its methoxymethyl ether. This was readily achieved using sodium hydride in *N,N-*

dimethylformamide followed by the addition of methoxymethyl chloride, gave the protected biaryl aldehyde **2.32** in quantitative yield (**Scheme 2.9**).
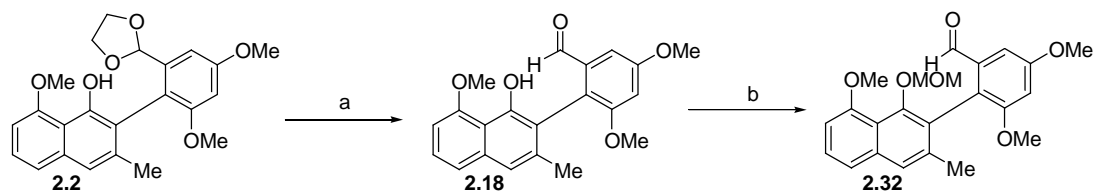
Scheme 2.9 Reagents and yields: (a) 3% aq H_2SO_4/THF, r.t., 91%; (b) 2 eq NaH, DMF, 5 eq MOMCl, r.t., 100%.

Attempts to oxidise **2.32** to the acid or lactone failed. Given the lack of success of forming either the hemiacetal or the lactone **2.20** it was decided to stop investigating the 'lactone method' and return to the diastereoselective Pinhey-Barton reaction.

2.6   Investigations into a Diastereoselective Pinhey-Barton Reaction

An investigation into the use of chiral phenyl acetals to allow an asymmetric Pinhey-Barton reaction requires the synthesis of aryllead (***R,R***)-**2.16**. Thus, stannane (***R,R***)-**2.33** was required which could be prepared in a similar manner to the achiral stannane **2.22** presented earlier.
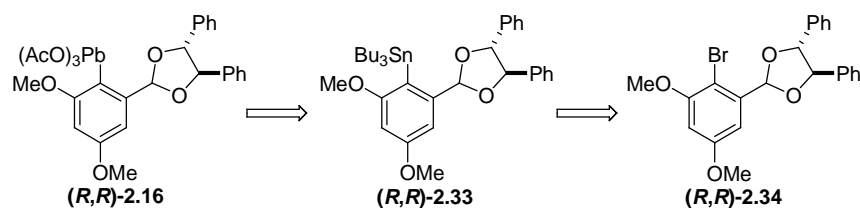
Figure 2.12 Retrosynthesis of the aryllead (***R,R***)-**2.16** required for a diastereoselective synthesis.

Reaction of aldehyde **2.25** with (*R,R*)-hydrobenzoin, in the presence of a catalytic amount of *p*-toluenesulfonic acid, in benzene under Dean-Stark conditions afforded the requisite bromide (***R,R***)-**2.34** in 92% yield. Lithium-halogen exchange of bromide (***R,R***)-**2.34** with *t*-BuLi at –95 °C followed by quenching with tributyltin chloride gave a new product, with the reaction found to be complete after allowing the reaction to warm to room temperature overnight. The ^{1}H NMR spectrum of the crude reaction material revealed the desired stannane and a trace of suspected

demetalated material **2.35**. Purification by flash chromatography, using silica gel as the stationary phase, was found to only afford the demetalated material **2.35** in quantitative yield, with no trace of the stannane. An authentic sample of acetal **2.35** was prepared and the ^{1}H NMR spectrum found to match that of the suspected demetalated material obtained (**Scheme 2.10**).

X = Br **2.25**   X = Br (**R,R**)-**2.34**
X = H **2.24**   X = H **2.35**
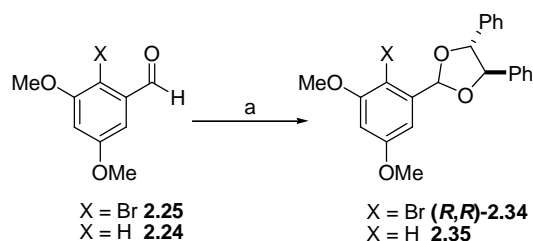
Scheme 2.10   Reagents and Yields Reagents: (a) 1.5 eq *(R,R)*-(+)-hydrobenzoin, cat. *p*-toluenesulfonic acid, benzene, Dean-Stark conditions, 92% for (**R,R**)-**2.34**, 96% for **2.35**.

It was found that purification of the stannane (**R,R**)-**2.33** by flash chromatography with silica gel had to be performed eluting with 1% triethylamine in the eluting solvent to obtain the acid sensitive stannane in 59% yield (**Scheme 2.11**).

(**R,R**)-**2.34**   (**R,R**)-**2.33**
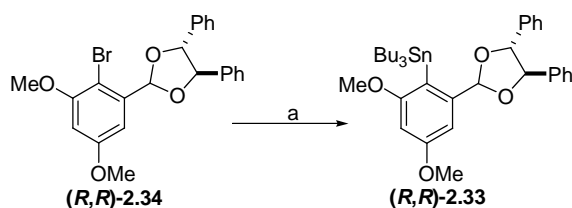
Scheme 2.11   Reagents and Yields: (a) 2.2 eq *t*-BuLi, THF, -95 ^{o}C, 1.5 eq ClSnBu$_3$, -95 ^{o}C to r.t., 59%.

Exposure of stannane (**R,R**)-**2.33** to freshly dried lead tetraacetate in dry dichloromethane yielded a mixture of aryllead (**R,R**)-**2.16** and demetalated material in a 86:14 ratio. Eventually, it was established that the optimal conditions for the synthesis of the aryllead species (**R,R**)-**2.16** were 2 equivalents of freshly dried lead tetraacetate, which gave the aryllead species in 90% yield (**Scheme 2.12**).
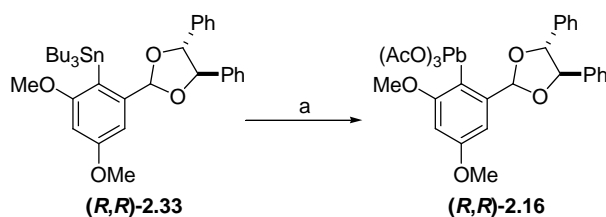
Scheme 2.12   Reagents and yields: (a) 2 eq Pb(OAc)$_4$, cat Hg(OOCCF$_3$)$_2$, CH$_2$Cl$_2$, r.t., 90%.

Having access to sufficient quantities of the chiral aryllead triacetate allowed the investigation into a diastereoselective Pinhey-Barton *ortho*-arylation reaction. Reaction of the aryllead species **(R,R)-2.16** with naphthol **1.104** under the standard conditions gave a promising result. The ^{1}H NMR spectrum of the crude reaction material revealed no trace of the starting aryllead species or naphthol but showed the presence of two new products. Purification by flash chromatography yielded the inseparable atropisomers **(P,R,R)-2.17** and **(M,R,R)-2.17** in 71% yield. The relative ratio of the atropisomers was observed to be 41:59 through integration of the resonances due to the C-H proton of the acetal groups corresponding to the two atropisomers at δ 5.93 (major) and δ 5.98 (minor). From this spectrum, it was not possible to determine which atropisomer (*M*) or (*P*) was favoured.
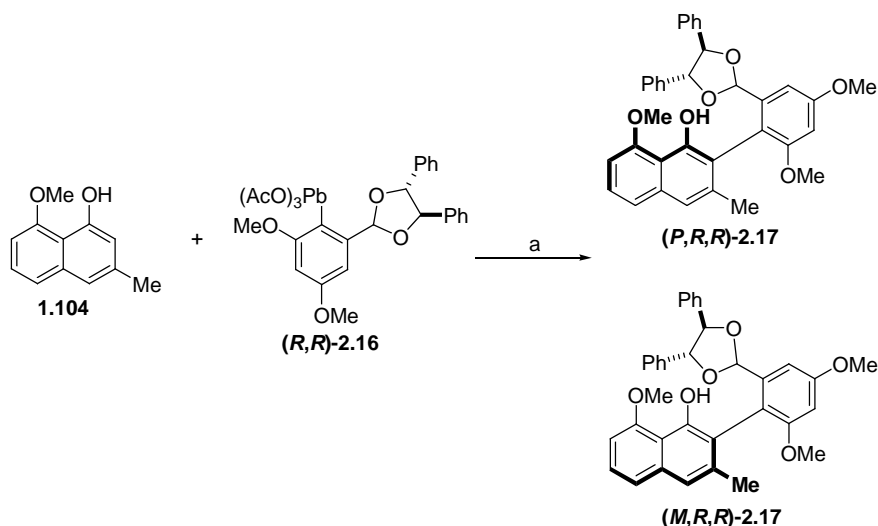
Scheme 2.13   Reagents and yields: (a) 3 eq pyridine, CH$_2$Cl$_2$, r.t., 71% (relative atropisomeric ratio 41:59).

Removal of the acetal functionality by stirring **(R,R)-2.17** in aqueous sulfuric acid and tetrahydrofuran was found to yield the previously prepared aldehyde **2.18** (**Scheme 2.14**).
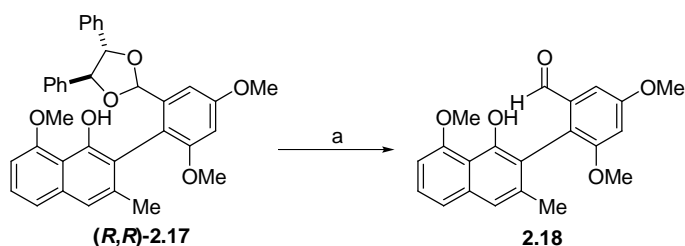
Scheme 2.14   Reagents and yields: (a) 3% aq H_2SO_4/THF, r.t., 85%.

Given that there seemed to be a slight preference for one atropisomer over the other with the use of only the chiral auxiliary, the reaction was repeated using similar conditions to that reported by Yamamoto, with the chiral base brucine used in place of the achiral base pyridine. Addition of *n*-BuLi to the naphthol at 0 °C in toluene generated the lithium salt. This was cooled to –78 °C, and brucine, 4Å sieves, and aryllead (***R,R***)-**2.16** were added sequentially. TLC analysis confirmed the reaction to be complete after stirring for 4 hours at -78 °C (**Scheme 2.15**). The fast reaction rate observed here is in contrast to that observed by Yamamoto, where warming of the reaction (usually to -40 °C or -20 °C) was necessary to increase the rate of the arylation and reaction times of 20 hours usually required.[3,4] The ^{1}H NMR spectrum of the crude reaction material showed the biaryl (***R,R***)-**2.17** to be in a 39:61 ratio of atropisomers. This suggests that the use of brucine gave no enhancement to the atropselectivity of the reaction.
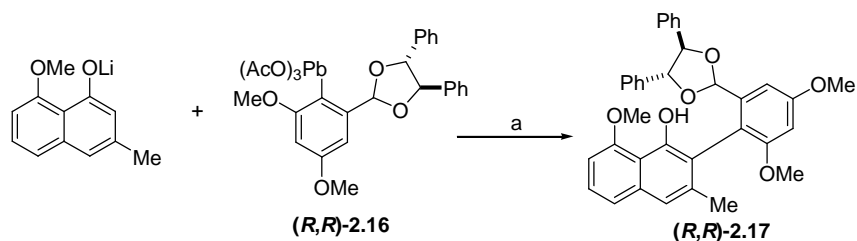
Scheme 2.15   Reagents and yields: (a) 2 eq brucine, 1.5 g/mol crushed 4Å sieves, toluene -78 °C, 4 h, 36% (relative atropisomeric ratio 39:61).

The lack of selectivity from the use of brucine may be a result of a spatial mismatch occurring with the use of the (*R*, *R*)-auxiliary during the ligand coupling intermediate proposed by Yamamoto. Hence, the (*S*, *S*)-auxiliary was also investigated to determine if a 'matched' situation would arise yielding a single atropisomer. The stannane (***S,S***)-**2.33** was readily prepared by employing similar conditions to that used for the preparation of the (***R,R***)-**2.33** and is summarised below (**Scheme 2.16**). The optical rotations obtained for both the bromide (***S,S***)-**2.34** and

stannane **(S,S)-2.33** were found to be opposite to that of the (R,R)-enantiomers. Conversion of the stannane to the aryllead **(S,S)-2.16** was achieved in comparable yield to that of the (R,R)-aryllead and the two enantiomers had identical ^{1}H NMR spectroscopic data.
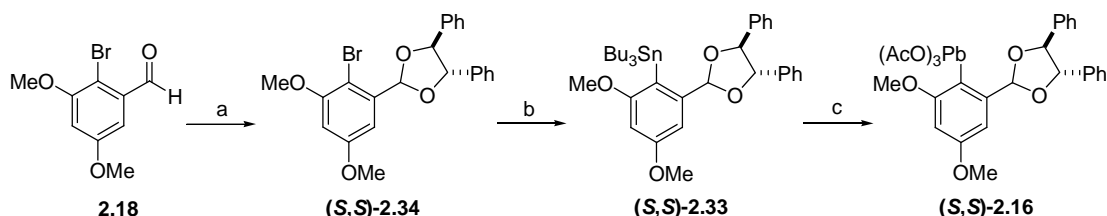
Scheme 2.16   Reagents and Yields: (a) 1.5 eq *(S,S)*-(+)-hydrobenzoin, *p*-toluenesulfonic acid, benzene, Dean-Stark conditions, 89%; (b) 2.2 eq *t*-BuLi, THF, -95 ^{o}C, 1.5 eq ClSnBu$_3$, -95 ^{o}C to r.t., 57% (c) 2 eq Pb(OAc)$_4$, cat Hg(OOCCF$_3$)$_2$, CH$_2$Cl$_2$, r.t., 98%.

The freshly prepared aryllead triacetate **(S,S)-2.16** was reacted with naphthol **1.104**, using pyridine to promote the reaction. The ^{1}H NMR spectrum of the crude reaction material indicated that the atropisomeric ratio of the minor biaryl to the major biaryl was 35:65. Resolution of the two biaryls was again unachievable by flash chromatography.
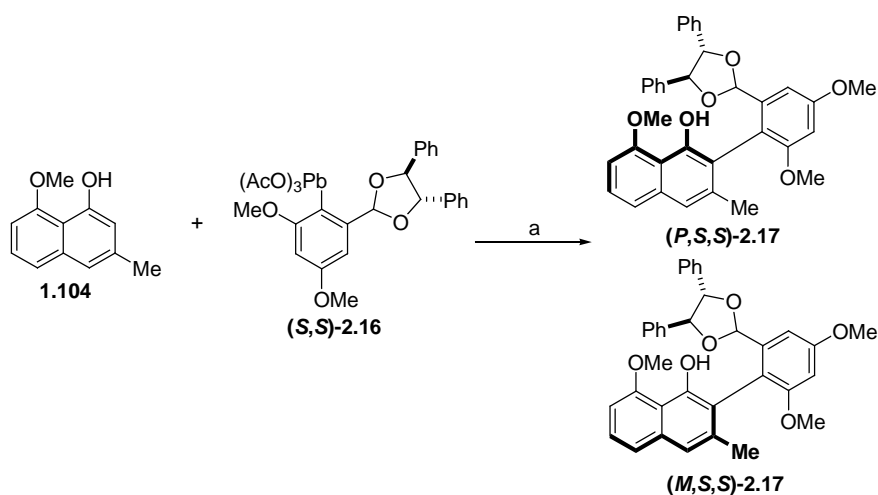
Scheme 2.17   Reagents and yields: (a) 3 eq pyridine, CH$_2$Cl$_2$, r.t., 50% (relative atropisomeric ratio 35:65).

Although it was not possible to determine which atropisomer was favoured over the other (i.e. *M* or *P*) it is interesting to note that it appears the use of a chiral acetal auxiliary has the potential to allow the synthesis of either atropisomer. For instance, assuming the (R,R)-aryllead species favoured the formation of the (M)-biaryl **(R,R)-2.17**, then this would be the major compound

observed by ^{1}H NMR analysis. Arylation of naphthol **1.104** with aryllead species (*S,S*)-**2.16** resulted in the diastereomers (*M,S,S*)-**2.17** and (*P,S,S*)-**2.17** being formed. These diastereoisomers are enantiomers of (*P,R,R*)-**2.17** and (*M,R,R*)-**2.17** respectively, as shown in **Figure 2.13**. Consequently, the enantiomeric pairs should have the same ^{1}H NMR spectra. Considering the ^{1}H NMR spectrum of the biaryl compounds obtained using the aryllead (*S,S*)-**2.16** showed that the major diastereoisomer had the same chemical shifts as the major diastereoisomer obtained from the use of the (*R,R*)-**2.16** aryllead, then these products must be enantiomers. This suggests the two auxiliaries give the opposite stereoisomer at the biaryl axis with one of the biaryls *M* and the other being *P*. This was a promising result, as it implies that the use of chiral acetals may be used to prepare either atropisomer if the appropriate conditions to achieve this in greater atropselectivity could be found.
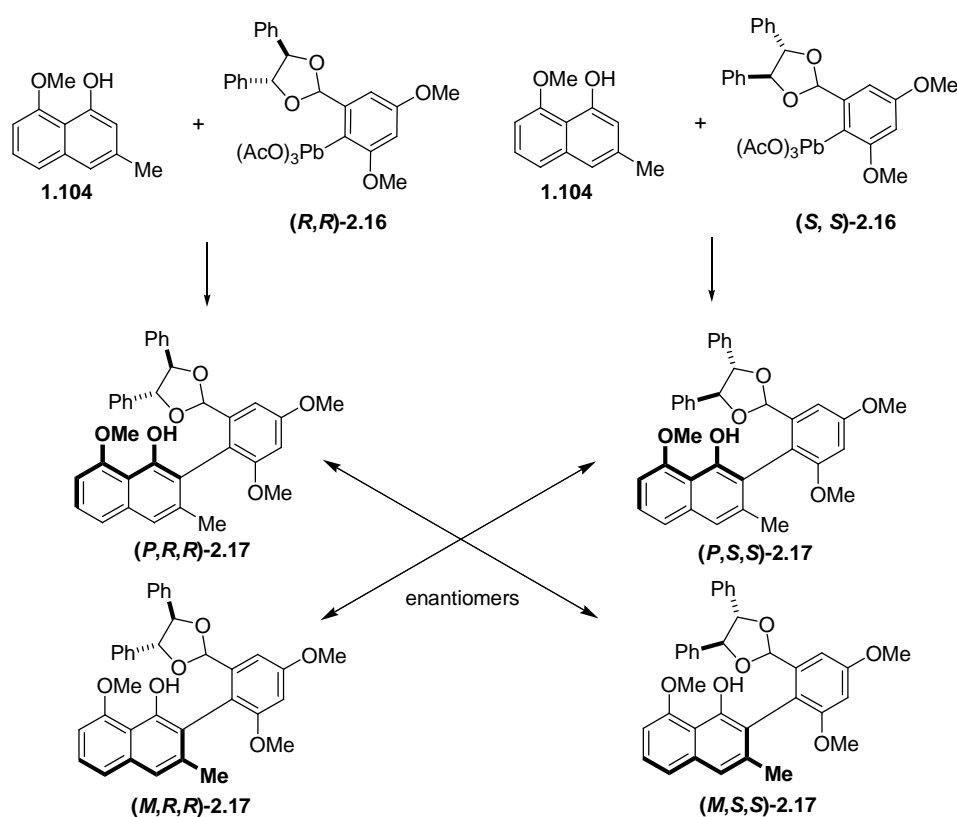

Figure 2.13 The enantiomeric pairs obtained through *ortho*-arylation of naphthol **1.104** with aryllead (*R,R*)-**2.16** or (*S,S*)-**2.16**.

To test if a matched situation would occur with brucine and aryllead (*S,S*)-**2.16**, the arylation was repeated using brucine. Unfortunately, no improvement in the relative ratio of the

diastereoisomers was observed with a ratio of 41:59 obtained when performing the arylation at room temperature. Repeating the experiment with the lithium salt of the naphthol at -78 $^{\circ}$C also proved disappointing with the same selectivity observed.
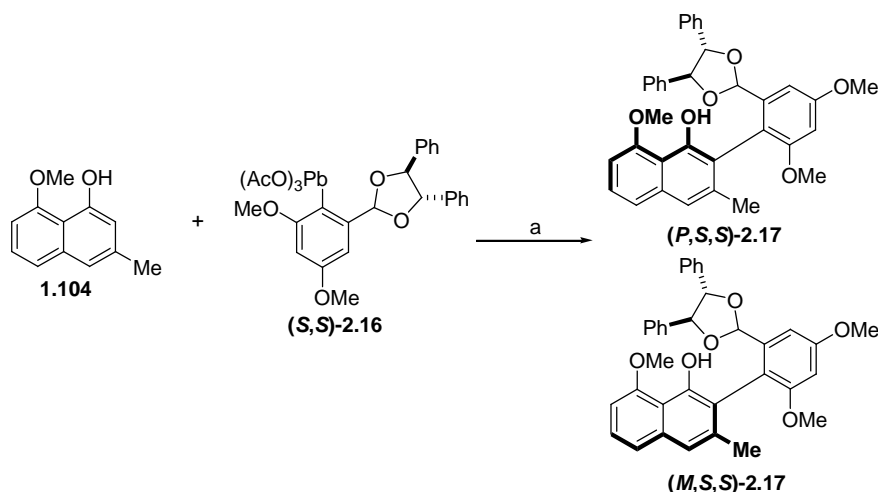
Scheme 2.18 Reagents and yields: (a) brucine, CH$_2$Cl$_2$, r.t., 53% (41:59) or *n*-BuLi, toluene, brucine, 4Å sieves, -78 $^{\circ}$C, 51% (relative atropisomeric ratio 41:59).

2.7 Conclusions

In summary, the key 5,3′ biaryl linkage has been successfully formed via the Pinhey-Barton reaction to yield biaryl **2.18**, which is required for the total synthesis of ancistrotanzanine A. Preliminary studies into controlling the atropselectivity of the reaction using a chiral auxiliary were found to have limited success. Studies into the use of the chiral base brucine in place of pyridine were also undertaken, with no enhancement in atropselectivity observed. From the results presented in this Chapter, it is concluded that while the hydrobenzoin acetal auxiliaries gave some selectivity, it wasn't high enough to be useful. As the diastereoisomers weren't separable, it was decided, due to time constraints, to stop examining this further.
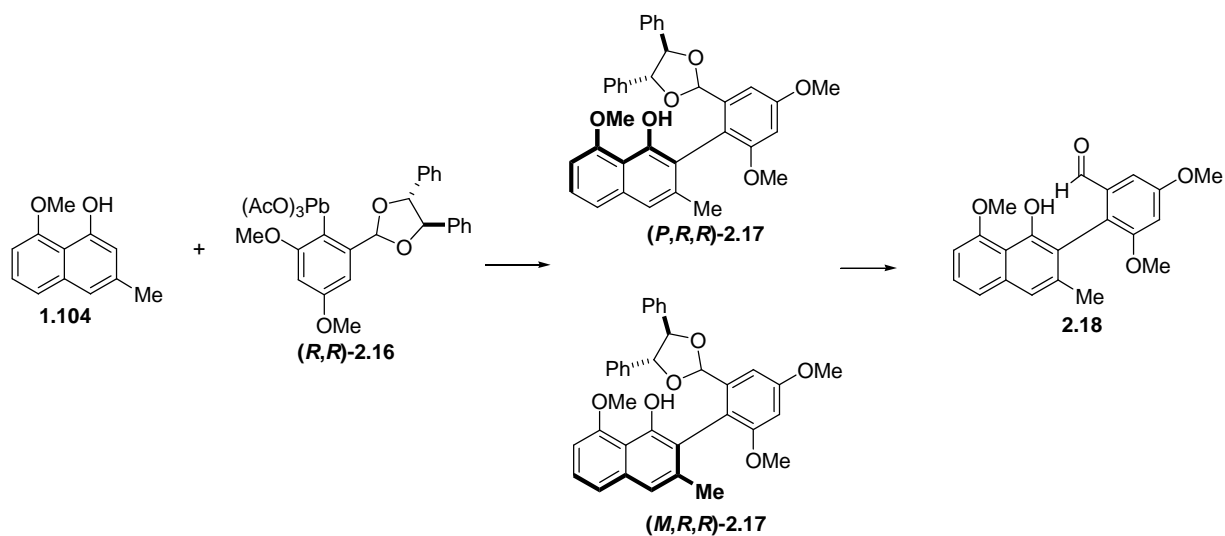
Acetal	Base	Yield	Relative Ratio of Atropisomers
(R,R)	Pyridine	71%	41:59
(R,R)	Brucine	36%	39:61
(S,S)	Pyridine	50%	35:65
(S,S)	Brucine	51%	41:59

Table 2.2 Summary of the conditions studied for the atropselective synthesis of biaryl **2.17**. For reaction conditions see section 2.6.

Although it should be possible to complete the total synthesis of ancistrotanzanine A from aldehyde **2.32**, using the Morris and Bungard endgame, this would afford the natural product as a mixture of atropisomers and take a further 9 steps (**Figure 2.14**). Hence, it was decided to put this work on hold and explore alternative methods for the synthesis of the isoquinoline moiety that were compatible with the Pinhey-Barton synthesis of the biaryl axis for ancistrotanzanine A. These studies are presented in Chapter 3.
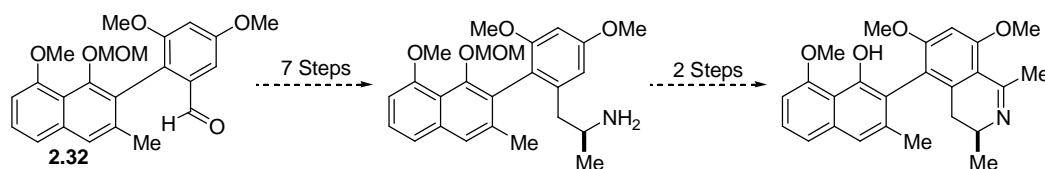
Figure 2.14 Proposed route to the total synthesis of ancistrotanzanine A, where 9 steps are still required to complete the synthesis from aldehyde **2.32**, which was prepared as a mixture of atropisomers.

2.8 References

(1)   Bungard, C. J.; Morris, J. C. *Org. Lett.* **2002**, *4*, 631.

(2)   Bungard, C. J.; Morris, J. C. *J. Org. Chem.* **2006**, *71*, 7354.

(3)   Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.

(4)   Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365.

(5)   Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853.

(6)   Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60*, 4459.

(7)   Gable, R. W.; Martin, R. L.; Rizzacasa, M. A. *Aust. J. Chem.* **1995**, *48*, 2013.

(8)   Bringmann, G.; Robert-Michael, P.; Petra, S.; Kristina, H.; Michaela, S.; Matthias, B. *Tetrahedron* **2004**, *60*, 4349.

(9)   Borchardt, R. T.; Sinhababu, A. K. *J. Org. Chem.* **1981**, *46*, 5021.

(10)   Rizzacasa, M. A.; Sargent, M. V.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 79.

(11)   Bungard, C. J.; Morris, J. C. *J. Org. Chem.* **2002**, *67*, 2361.

(12)   Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877.

Chapter Three

The Total Synthesis of Ancistrotanzanine A

Ancistrotanzanine A, like all the other naphthylisoquinoline alkaloids, contains both an isoquinoline and naphthalene moiety, linked by a biaryl bond. While it would be possible to use the exact same strategy to prepare ancistrotanzanine A as was used to synthesis ancistrocladidine, it was felt an alternative approach to the isoquinoline moiety could lead to a more efficient synthesis. What follows is a review of the methods available to prepare the isoquinoline moiety found in naphthylisoquinoline alkaloids.

3.1   Strategies Utilised in the Synthesis of 3,4-Dihydroisoquinolines

The isoquinoline moiety found in most naphthylisoquinoline alkaloids contain a *meta*-oxygenation pattern at C6 and C8 as shown in **Figure 3.1**. The method most widely used for the synthesis of such 3,4-dihydroisoquinolines is the Bischler-Napieralski cyclisation.[1] Corresponding tetrahydroisoquinolines may be derived from the appropriate 3,4-dihydroisoquinoline or the 3,4-dihydroisoquinolinium salt by reduction with metal hydrides. The Pictet-Spengler reaction has been utilised to directly assemble the tetrahydroisoquinoline moiety.[1] The key intermediate for the preparation of all of these heterocycles is the amphetamine **3.1** (**Figure 3.1**). What follows is a summary of some of the synthetic strategies used for the stereoselective synthesis of the amphetamine intermediate **3.1** that may be compatible with the Pinhey-Barton total synthesis approach.
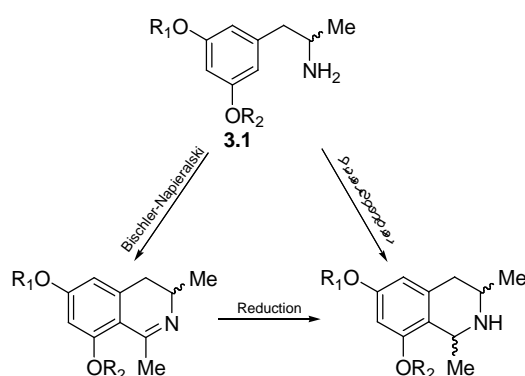

Figure 3.1   Synthetic approaches towards the synthesis of isoquinolines.

3.1.1   Introduction of the Nitrogen Functionality *via* the Henry Reaction

As part of their work towards the total synthesis of naphthylisoquinoline alkaloids, Bringmann and coworkers have pioneered a popular route to chiral 3,4-dihydroisoquinolines such as (*S*)-**3.6** and tetrahydroisoquinolines such as (*S,S*)-**3.7**.[2] The method involves the introduction of the nitrogen functionality *via* the Henry reaction. Reduction of nitrostyrene **3.2** with iron powder gave the ketone **3.3**, which upon reaction with (*S*)-methylbenzylamine gave the chiral imine **3.4**. Stereoselective hydrogenation with Raney nickel, followed by deprotection, liberated the chiral amine (*S*)-**3.5**, which was readily converted into the desired dihydroisoquinoline (*S*)-**3.6** under Bischler-Napieralski cyclisation conditions. With the appropriate metal hydride, stereoselective reduction of the imine can also be achieved, to give the *cis*-or-*trans* tetrahydroisoquinoline with both excellent selectivity and yield.
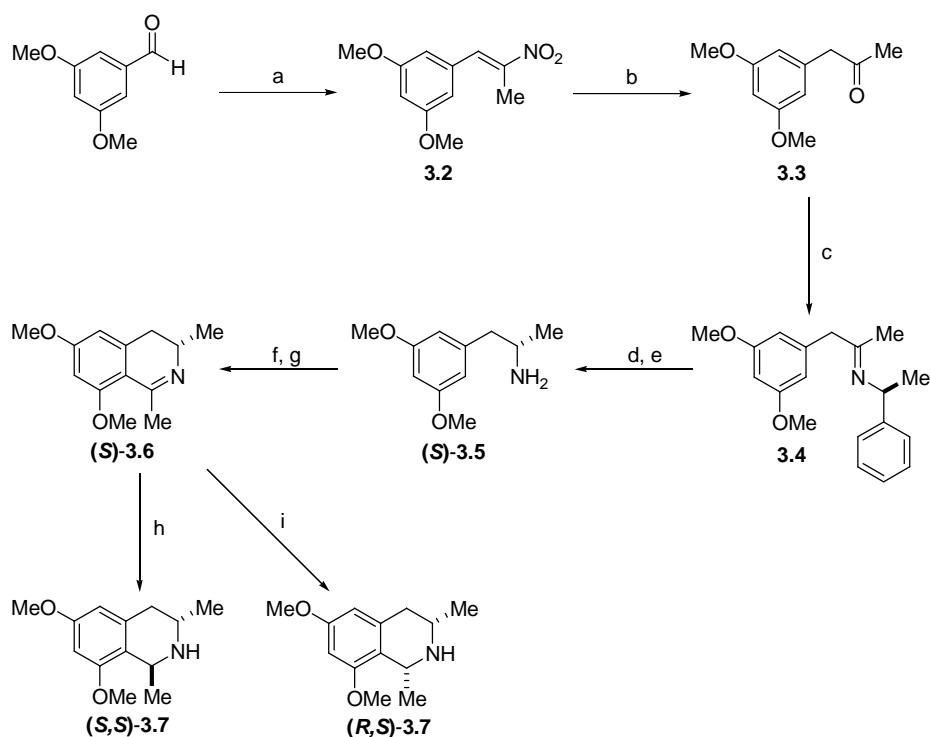
Scheme 3.1   Reagents and yields: (a) NH$_4$OAc, HOAc, EtNO$_2$; (b) Fe/HOAc; (c) (*S*)-1-phenylethylamine, toluene; (d) Raney Ni, EtOH; (e) H$_2$, Pd-C, MeOH, 84%, 92% de; (f) AcCl, NEt$_3$, CH$_2$Cl$_2$; (g) POCl$_3$, CH$_3$CN, 76%; (h) LiAlH$_4$/AlMe$_3$, THF, 85%, 92% de; (i) NaBH$_4$, 82%, 95% de.

3.1.2 Introduction of Chirality *via* the Reaction of Grignard Reagents with Chiral Electrophiles

An alternative and shorter sequence for the preparation of the enantiomerically pure amphetamine building block has been developed by Hoye and Chen.[3] The method involves the ring opening of the optically active aziridine **3.9** (prepared in 3 steps from alanine, not shown) with the aromatic Grignard reagent derived from commercially available chloride **3.8** (**Scheme 3.2**). Deprotection of the toluenesulfinamide group yielded the enantiomerically pure amphetamine (**R**)-**3.5**, which was readily converted to the dihydroisoquinoline (**R**)-**3.6** by the standard acetylation/cyclisation protocol. Reduction gave the *cis*-configured tetrahydroisoquinoline (**S**,**R**)-**3.7**, which was smoothly converted into an appropriately functionalised *N*-methyl derivative **3.10**. This approach is the shortest route to the key chiral amphetamine building block.
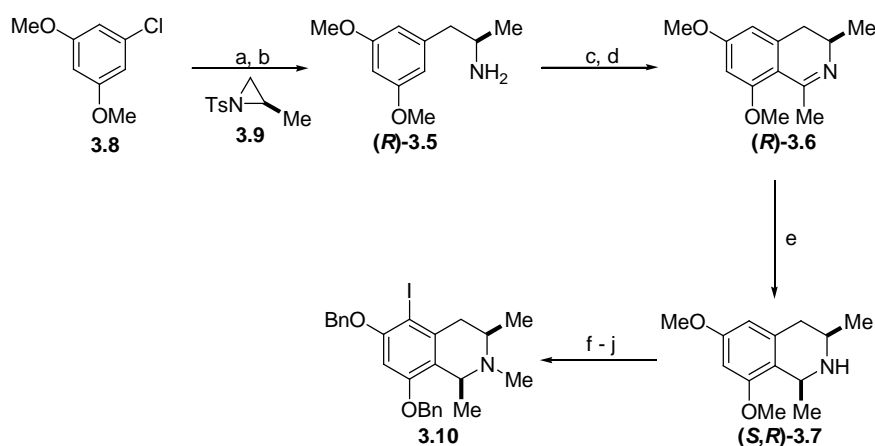
Scheme 3.2 Reagents and yields: (a) Mg, THF, CuBr•SMe$_2$, **3.9**, 100%; (b) Na/NH$_3$, 79%; (c) Ac$_2$O, NEt$_3$, 99%; (d) POCl$_3$, CH$_3$CN, 82%; (e) H$_2$, Pd/C, 93%; (f) BBr$_3$, CH$_2$Cl$_2$, 99%; (g) 2.1 eq TESCl, NEt$_3$, CH$_2$Cl$_2$, ClCO$_2$Et, TBAF, THF, 87%; (h) BnBr, K$_2$CO$_3$, 72%; (i) LiAlH$_4$, 94%; (j) I$_2$, Ag$_2$SO$_4$, EtOH, 80%.

3.1.3 Introduction of Chirality *via* Functionalisation of Double Bonds

The Sharpless asymmetric epoxidation has been used to introduce the appropriate stereochemistry first by the group of Rao[4] and then by Morris and Bungard.[5,6] To illustrate this

approach, in their total synthesis of ancistrocladidine, Morris and Bungard set the stereochemistry at C3 of the required amphetamine intermediate **1.123** by employing a Katsuki-Sharpless epoxidation.[5,6] The required allylic alcohol **3.11** was prepared in three steps from the biaryl aldehyde **1.122** in 71% overall yield (**Scheme 3.3**). Epoxide **3.12** was obtained in 80% yield and 90% ee using the standard Sharpless catalytic conditions. Recrystallisation gave enriched **3.12** in greater than 95% ee. Tosylation of **3.12** gave the primary tosylate, which after concomitant cleavage and ring opening of the epoxide by LiAlH$_4$ afforded alcohol **3.13** in 94% yield. The nitrogen functionality was introduced through reaction of alcohol **3.13** with phthalimide under Mitsunobu conditions, followed by hydrolysis of the phthalimide group with aqueous ethanolic methylamine. Following acetylation of chiral amphetamine, Bischler-Napieralski cyclisation was readily achieved by reaction of **1.123** with POCl$_3$ in the presence of 2,4,6-collidine.
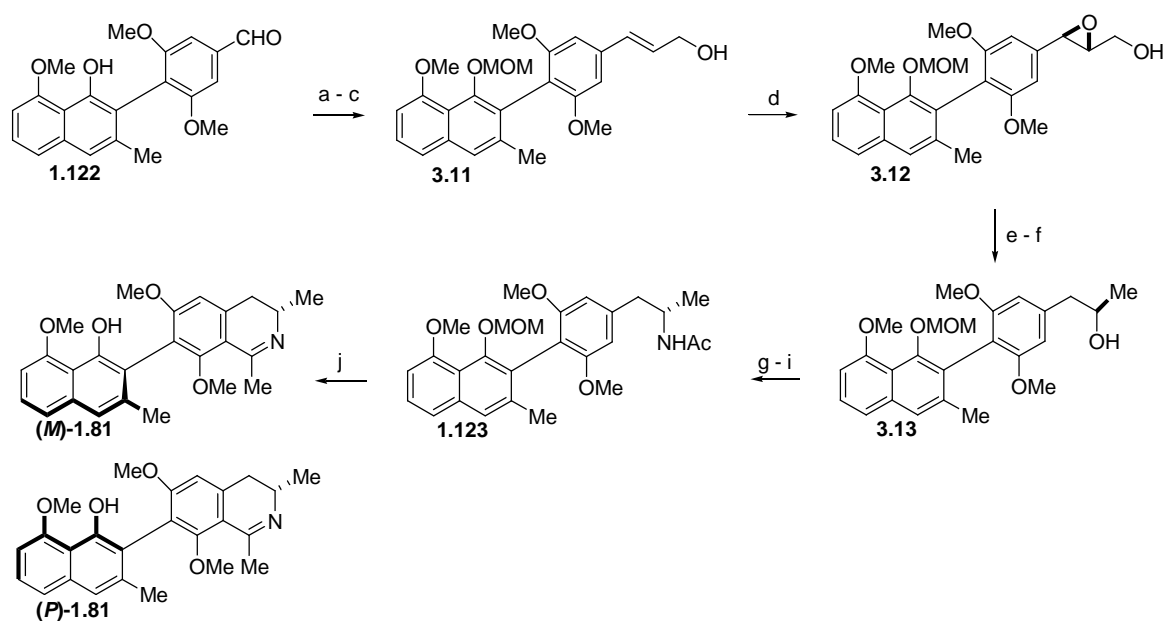

Scheme 3.3   Reagents and yields: (a) MOM-Cl, NaH, THF, rt, 81%; (b) NaH, (EtO)$_2$POCH$_2$CO$_2$Et, C$_6$H$_6$, 0°C to rt, 99%; (c) DIBAL-H, toluene, -78 °C, 15 min, 89%; (d) 5 mol% Ti(O *i*-Pr)$_4$, 6 mol% D-diisopropyl tartrate, TBHP, DCM, -20 °C, 5 h, 80%, 90% ee; (e) TsCl, NEt$_3$, DMAP, DCM,1 h, 0°C, 83%; (f) LiAlH$_4$, Et$_2$O, 0 °C, 2 h, 94%; (g) phthalimide, DEAD, PPh$_3$, THF, rt, 16 h, 82%; (h) 40% aq MeNH$_2$, EtOH reflux, 1 h, 99%; (i) CH$_3$COCl, NEt$_3$,CH$_2$Cl$_2$, 0 °C to rt, 97%; (j) POCl$_3$, 2,4,6-collidine, CH$_3$CN, reflux, 4 h, 74% (1:1 mixture of atropisomers).

3.1.4   Introduction of Chirality using Chiral Sulfinimines

Davis and coworkers have reported a sulfinimine-mediated asymmetric synthesis of 6,8-dimethoxy-3,4-dihydroisoquinolines.[7] The approach utilises the chiral sulfinamide (**R**)-**3.16** as the key intermediate, which was prepared with high diastereoselectivity by the addition of the laterally lithiated nitrile **3.14** to chiral sulfinimine **3.15** (**Scheme 3.4**). Davis rationalised that the high stereoselectivity was a result of the reaction proceeding via a chair-like transition state **TS-3.1**. The *o*-quinonedimethane structure derived from the nitrile anion chelates through the lithium cation to the sulfinyl oxygen and approaches the *si*-face of the sulfinimine via a six-membered chair-like transition state. Treatment of the sulfinamide (**R**)-**3.16** with excess methyl lithium followed by acidification results in cyclisation and formation of the dihydroisoquinoline (**R**)-**3.6**. This strategy has yet to be utilised in the total synthesis of naphthylisoquinoline alkaloids.
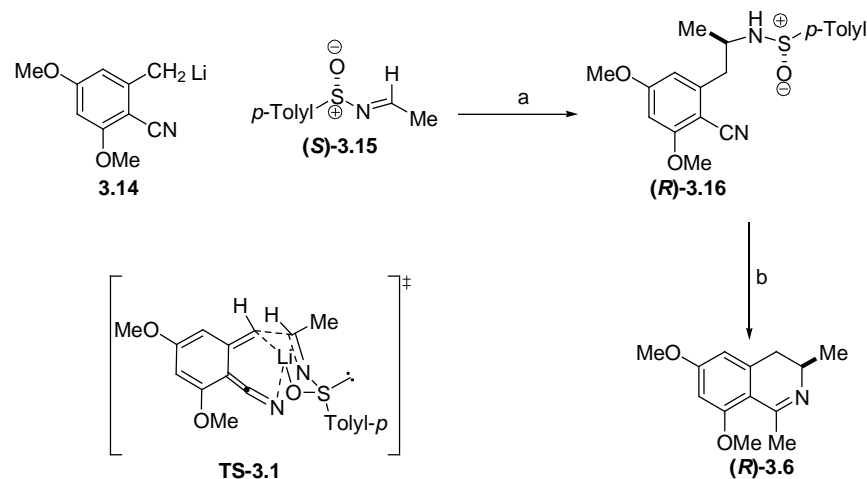
Scheme 3.4   Reagents and yields: a) LDA, diglyme, -78 °C then **3.15**, 68%; b) MeLi, then 2 N HCl, 65%.

3.2   Which of these Methods is most Applicable for the Total Synthesis of Ancistrotanzanine A?

What follows is a discussion on the application of each of the dihydroisoquinoline syntheses described above for the total synthesis of ancistrotanzanine A. To be able to carry out each of the dihydroisoquinoline syntheses, access to the following biaryls is required (**Figure 3.2**).
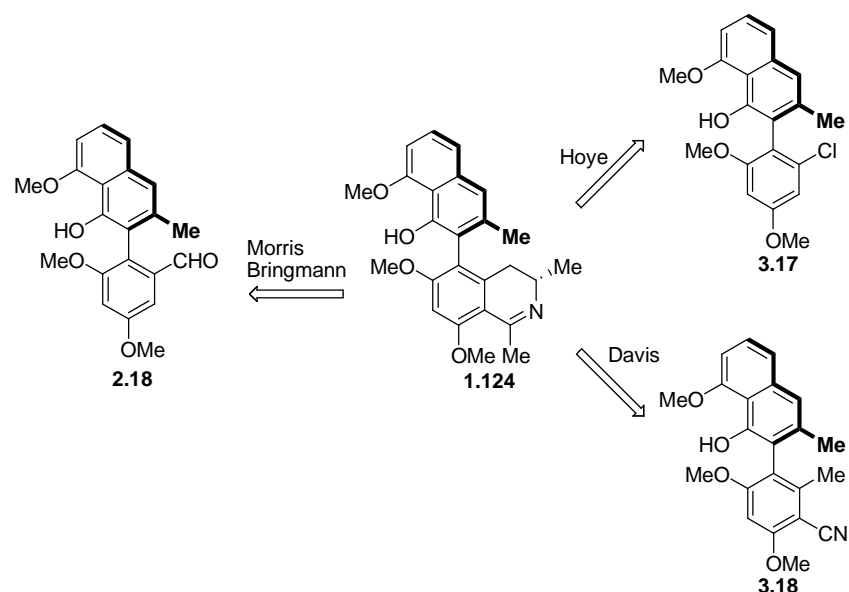
Figure 3.2   Retrosynthesis of ancistrotanzanine A using the various dihydroisoquinoline methods mentioned in Section 3.1.

The Morris and Bungard approach requires the biaryl **2.18**, already synthesised in Chapter 2 (Section 2.5). As mentioned at the end of that Chapter the synthesis of the isoquinoline moiety by this approach is quite long (9 steps). If the Bringmann protocol was used instead, the synthesis would be only 5 steps.

The Hoye and Davis strategies are both short synthetic sequences. The two methods also lead to the exciting possibility of being able to explore some new chemistry and to test the limits of the Pinhey-Barton total synthesis strategy. Application of the Hoye strategy to the total synthesis of ancistrotanzanine A requires the preparation of biaryl **3.17** (**Figure 3.2**). This biaryl contains a high degree of steric hindrance near the chlorine and consequently the required Grignard reagent may prove troublesome to prepare. While this strategy would be interesting to pursue, it was felt to be too "high-risk".

The Davis method requires the preparation of biaryl **3.18**. The chiral sulfinimine required for the alkylation of the biaryl **3.18** can be prepared in 1 step from the commercially available chiral sulfinamide. The implementation of the Davis methodology to prepare the isoquinoline moiety of ancistrotanzanine A, coupled with the Pinhey-Barton reaction to form the key biaryl **3.18,** is

given below (**Figure 3.3**). It can be seen that this approach allows the isoquinoline moiety to be prepared in only 3 steps after formation of the biaryl bond. If this strategy was successful, this would allow one of the shortest total synthesis of a naphthylisoquinoline alkaloid reported. Thus, it was decided that the Davis approach would be used for the total synthesis of ancistrotanzanine A. As mentioned previously, the Davis protocol has never been used in a total synthesis of naphthylisoquinoline alkaloids.
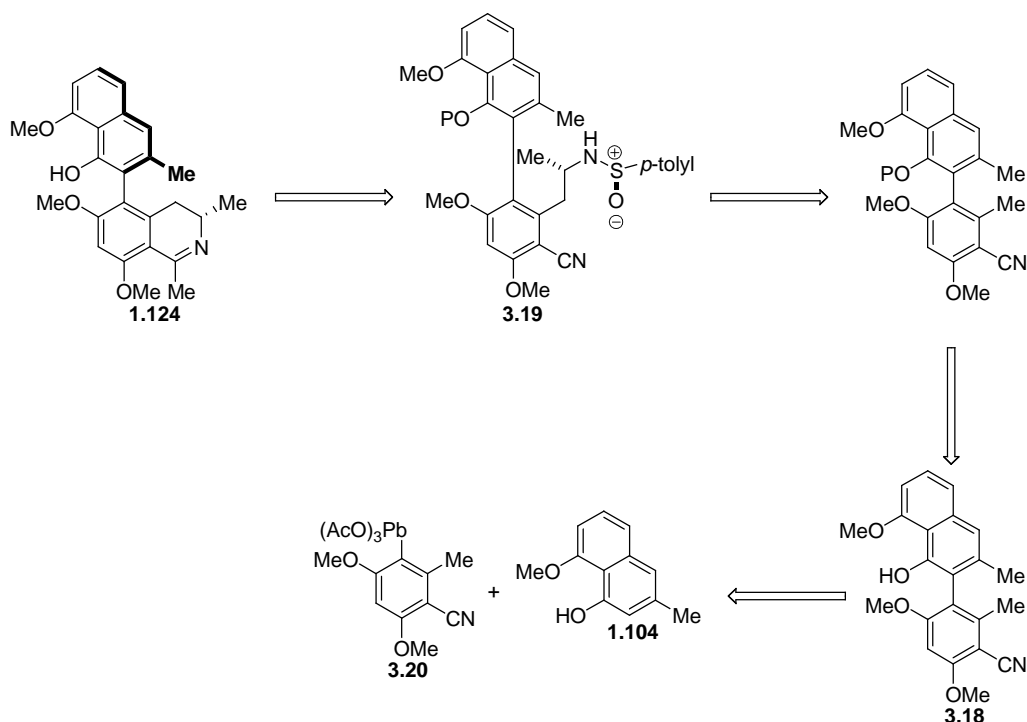
Figure 3.3   Retrosynthetic analysis of ancistrotanzanine A using the Pinhey-Barton reaction to form the key biaryl linkage and the Davis methodology to form the isoquinoline moiety.

Having decided that the Davis methodology was the most appropriate for the total synthesis of ancistrotanzanine A, studies into the preparation of the required aryllead species **3.20** were undertaken.

3.3   Preparation of the Aryllead Triacetate 3.20

As noted earlier the most common preparation of aryllead compounds is the use of tin-lead transmetallation. Consequently stannane **3.21** was required for the synthesis of aryllead **3.20** (**Figure 3.4**). Access to stannanes can be achieved by either tin-halogen exchange using

palladium catalysis,[8] or by the reaction of aryl organometallic (Grignard or lithium) reagent with aryl halides. Our initial efforts focused on the palladium process as it was felt that it would be the milder method.
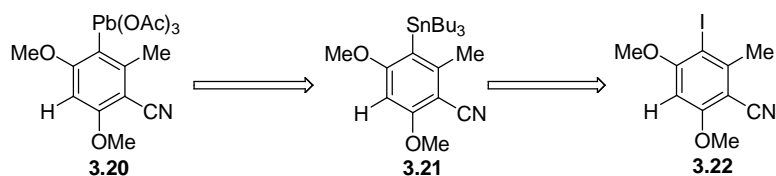
Figure 3.4   Retrosynthesis of the aryllead species required for the synthesis of the isoquinoline moiety of ancistrotanzanine A via the shorter Davis methodology.

A range of conditions have been employed to achieve the formation of the carbon-tin bond via palladium catalysis.[8,9] Masuda and co-workers have reported that aryl iodides may be converted to aryl stannanes using palladium-catalysed cross-coupling with tributyltin hydride (**Scheme 3.5**).[9] Dimer byproducts are not formed under these conditions.

3.23 R_1 = OMe   **3.26** R_1 = OMe, 94 %
3.24 R_1 = NH$_2$ **3.27** R_1 = NH$_2$, 73 %
3.25 R_1 = CO$_2$Et   **3.28** R_1 = CO$_2$Et, 86 %
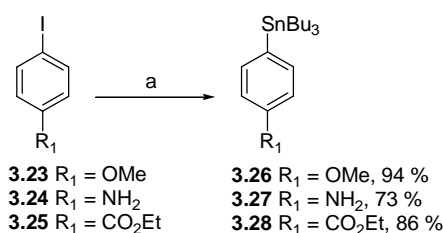
Scheme 3.5   Reagents: (a) cat (3 mol%) PdCl$_2$(PMePh$_2$)$_2$, 3 eq KOAc, 2 eq HSnBu$_3$, NMP, r.t. 16 h; for R_1 = CO$_2$Et the reaction was heated at 50 $^{\circ}$C.

Masuda and coworkers found that bis(tributyltin) is produced *in situ* using their conditions and proceeded by the shown in **Figure 3.5**. The use of bis(tributyltin) in place of tributyltin hydride resulted in the formation of the desired stannanes without any loss of yield. It was also observed that the palladium catalyst PdCl$_2$(PPh$_3$)$_2$ worked almost as well as PdCl$_2$(PMePh$_2$)$_2$ with only a slight reduction in yield.[9]
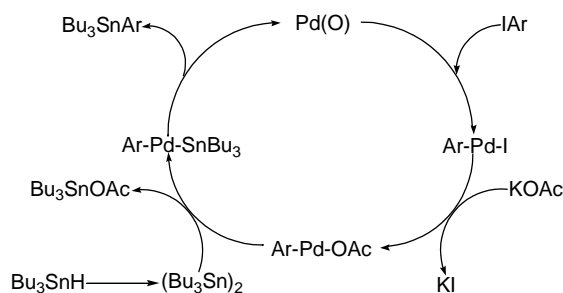
Figure 3.5 Proposed catalytic cycle of tin-halogen exchange using the conditions developed by Masuda and co-workers.

With the above methodology in mind, stannane **3.21** could be prepared from the palladium-catalysed cross-coupling of iodide **3.22** with bistributyltin, as shown in **Figure 3.6**, but to do this the preparation of iodide **3.22** requires the addition of iodine regioselectively at C5 of the known nitrile **3.29**[7].
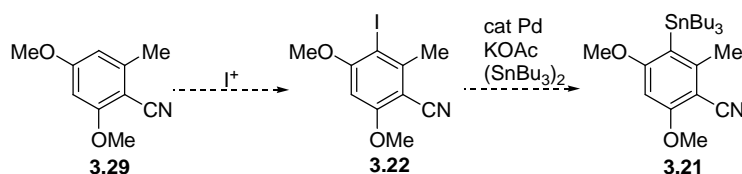
Figure 3.6 Proposed synthesis of stannane **3.21** using the methodology developed by Masuda.

Although commercially available, nitrile **3.29** was readily prepared as described by Davis (**Scheme 3.6**). Reaction of orcinol (**3.30**) with methyl iodide gave the known dimethyl ether **3.31**[10] in 82% yield. Bromination of **3.31** with *N*-bromosuccinimide gave bromide **3.32** in 84% yield, which upon reaction with copper cyanide in *N,N*-dimethylformamide at reflux yielded the nitrile **3.29** in 86% yield.
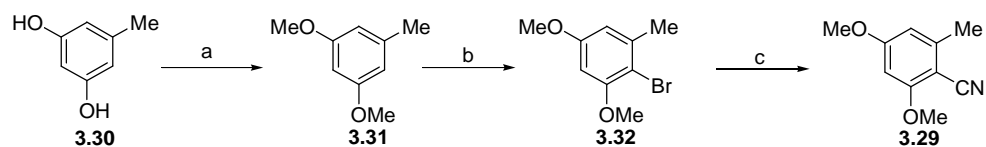
Scheme 3.6 Reagents and yields: a) 5.2 eq K$_2$CO$_3$, 3.5 eq MeI, acetone, reflux, 82%; b) 1.02 eq *N*-bromosuccinimide, chloroform, reflux, 84%; c) 1.4 eq CuCN, *N,N*-dimethylformamide, reflux, 86%.

Pleasingly, the 300 MHz ^{1}H NMR spectrum of the crude reaction mixture obtained from iodination of nitrile **3.29** confirmed the presence of only one aromatic resonance at δ 6.28 and the absence of any starting material (**Scheme 3.7**). This indicated that the iodination had occurred either at C5 or C3 and not at both positions. The chemical shift of the methoxy groups were almost identical at δ 3.94 and δ 3.95 respectively, with the methyl resonance shifted downfield (δ 2.62) compared to the starting material (δ 2.49). The 2D ROESY spectrum exhibited a NOE correlation between the aromatic signal and at least one of the methoxy groups. Due to the close proximity of the methoxy resonances it was not possible to distinguish if the correlation was due to just one or both of the methoxy groups. Moreover, no NOE correlation was observed for the methyl resonance with the aromatic resonance. The heteronuclear multiple bond connectivity (HMBC) spectrum was found to exhibit many long range correlations through the ring system, which made it difficult to confirm the structure. It was decided to convert the iodide to the stannane to see if the stannane was more amenable to structural elucidation.
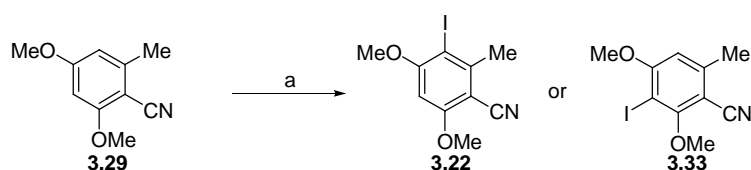
Scheme 3.7   Reagents and yields: (a) 1.02 eq I$_2$, 2 eq Ag$_2$SO$_4$, ethanol, 0 ^{o}C to r.t., 81%.

Conversion of the iodide **3.22** to the corresponding stannane **3.21** using the standard conditions reported by Masuda at room temperature gave no product. Heating the reaction mixture to 60 ^{o}C was found necessary to promote the reaction and conversion found to be complete after stirring at this temperature overnight (**Scheme 3.8**). Purification of the product from tin residues proved tedious, with sequential columns required to afford the pure stannane in low yield (30%). Changing of the reaction solvent from *N*-methylpyrrolidone to *N,N*-dimethylformamide provided an improved yield (45%).
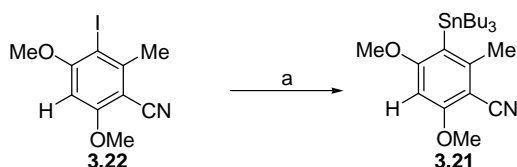
Scheme 3.8   Reagents and yields: a) 3 eq KOAc, 2 eq (Bu$_3$Sn)$_2$, 0.1 mol% PdCl$_2$(PPh$_3$)$_2$, *N,N*-dimethylformamide, 60 ^{o}C, 45%.

The 600 MHz ^{1}H NMR spectrum of stannane **3.21** proved to be much more amenable to structural elucidation than that of iodide **3.22**. The resonances of the methoxy groups were now resolved, appearing at δ 3.92 and δ 3.81 respectively (**Figure 3.7**). The aromatic resonance showed a NOE correlation with both of the methoxy protons, in the ROESY spectrum. No such effect was observed for the methyl group with the aromatic resonance, thus confirming that the desired stannane **3.21** had been prepared and that the iodine had been delivered to C5.
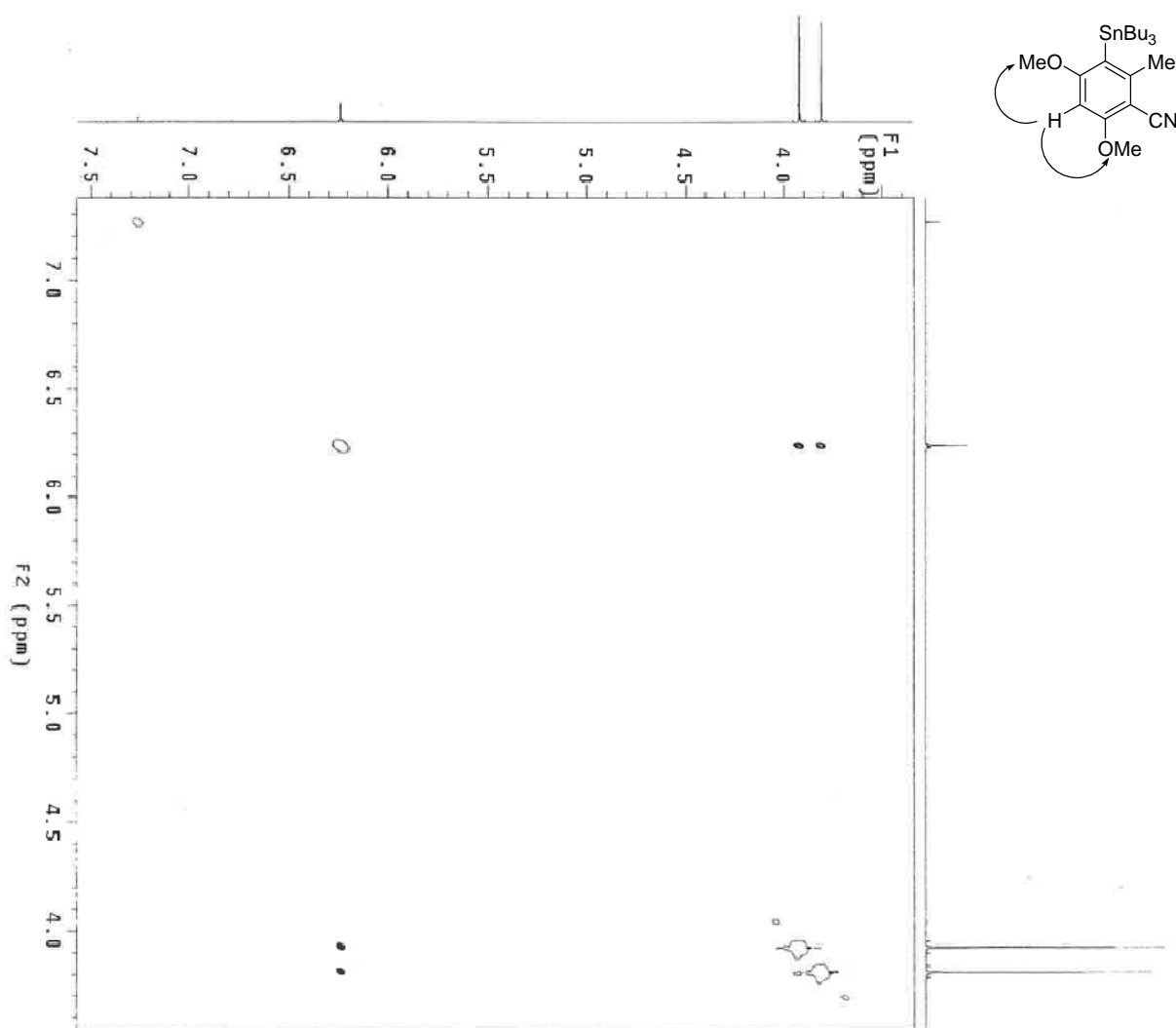

Figure 3.7   Portion of the ROESY spectra indicating the NOE of the aromatic hydrogen with the two methoxy protons for the stannane **3.21**.

Given the modest yield obtained from the synthesis of the stannane via the palladium chemistry, it was decided to examine the alternate transmetallation conditions. It was envisaged that the lithium-halogen exchange would occur faster than nucleophilic attack of the nitrile or deprotonation of the methyl group. Reaction of iodide **3.22** with 2 equivalents of *tert*-butyllithium followed by quenching with tributyltin chloride was found to give a mixture of products. The 300 MHz ^{1}H NMR spectrum of the crude reaction material showed a mixture of the desired stannane **3.21**, unreacted starting material, and demetalated material. No trace of any product resulting from the formation of nucleophilic attack at the nitrile group was observed. Purification of the crude mixture by flash chromatography on silica gel afforded the stannane in 62% yield. Further elution afforded the unreacted starting material (18%) and demetalated material (16%). Careful optimisation of the reaction conditions was carried out by gradually increasing the equivalents of *tert*-butyllithium. It was subsequently found that the optimal conditions for the preparation of the stannane **3.21** were to use 2.5 equivalents of *tert*-butyllithium and quenching with 1.25 equivalents of tributyltin chloride as summarised in **Scheme 3.9**. This resulted in a 75% yield of the stannane **3.21** and a trace (less than 5%) of de-iodinated material **3.29**.
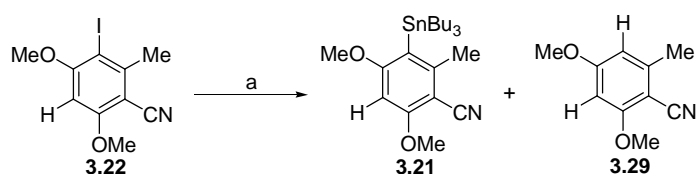
Scheme 3.9   Reagents and Yield: (a) 2.5 eq *t*-BuLi, 1.25 eq ClSnBu$_3$, THF, - 95 ^{o}C - r.t., o.n., 75%.

With sufficient quantities of the stannane now available, in only three steps from a commercially available starting material, investigation into the synthesis of the aryllead triacetate **3.20** could be pursued.

Exposure of the stannane **3.21** to the standard aryllead forming conditions gave a promising result. Analysis of the 300 MHz ^{1}H NMR spectrum of the reaction mixture revealed a new product, as well as traces of demetallated material **3.29**. Successive washings of the residue with petroleum ether gave the aryllead species **3.20**. However, the integration of the acetate signal (δ 2.13) in the ^{1}H NMR spectrum revealed that the material was not 100% pure, with there being

significantly more acetate protons present in the spectrum than there should have been. Presumably this is a result of an excess of lead tetraacetate. Attempts to remove the excess reagent were not successful, so it was decided to utilise the crude material in the Pinhey-Barton *ortho*-arylation reaction.
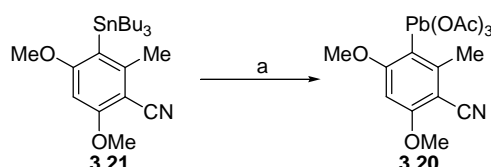
Scheme 3.10   Reagents; (a) 2.0 eq Pb(OAc)$_4$, cat Hg(OOCCF$_3$)$_2$, dichloromethane, r.t., 24 h.

3.4   Formation of the 5,3′-Biaryl Linkage

With the aryllead triacetate successfully prepared, studies on the coupling of this compound with naphthol **1.104** were investigated. Stirring of a solution of aryllead triacetate **3.20** with **1.104** and pyridine at room temperature for 24 hours resulted in the formation of two new products (**Scheme 3.11**). The two compounds were separated by flash column chromatography.
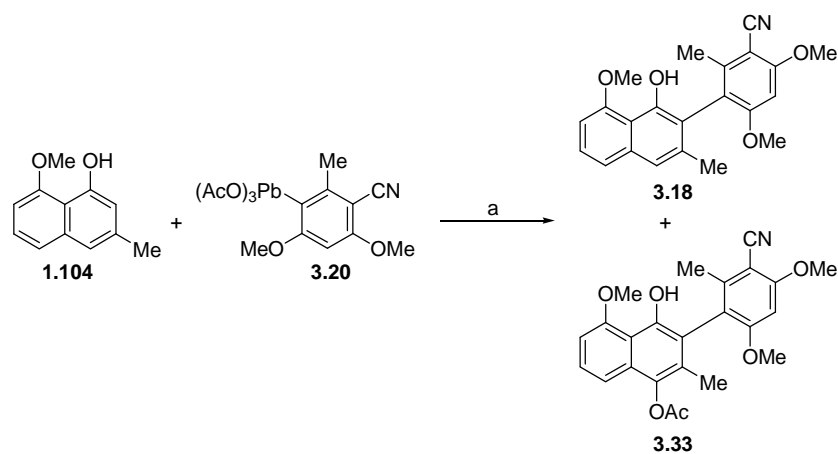
Scheme 3.11   Reagents and yields: (a) 3 eq pyridine, CH$_2$Cl$_2$, 24 h, r.t., **3.18** 44%, **3.33** 21%.

The first compound eluted was determined to be the desired *ortho*-arylated naphthol **3.18**, with the ^{1}H NMR spectrum confirming the presence of 3 methoxy groups, 2 methyl groups and only 5 aromatic hydrogens. The resonance of the methyl signal of the naphthalene was shifted upfield

form δ 2.41 to δ 2.03 due to the shielding effect of the newly attached ring system. This was also observed for the methyl resonance at C6 from the aryllead species (δ 2.18 from δ 2.73). The resonance due to H4′ was found to exhibit a NOE with the methyl signal at δ 2.03 (**Figure 3.8**). A long range (J^3) coupling was present from C5′ to H4′ in the HMBC spectrum. The COSY spectrum confirmed that H5′ (δ 7.28-7.37) was coupled to H6′ (δ 7.28-7.37) and H7′ (δ 6.74). H7′ was found to exhibit a NOE with the methoxy resonance on the naphthalene (δ 4.01). The infrared spectrum confirmed the presence of both the phenol (3400 cm^{-1}) and nitrile (2210 cm^{-1}) functionalities.
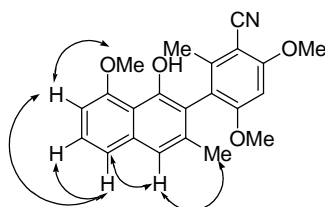
Figure 3.8   Correlations observed in the 2D NMR spectra of **3.18**.

The second compound collected from the column was similar to that of the desired product, but the H4′ resonance in the aromatic portion of the ^{1}H NMR spectrum was absent. In addition, there was a new singlet at δ 2.44, which integrated to 3H. From this information and the mass spectral data, it was evident that the new compound was acetate **3.33** (**Scheme 3.11**).

Lead tetraacetate is known to acetoxylate phenols, a reaction which has become known as the Wessely acetoxylation.[11] For example, Pinhey and coworkers required a number of 2-acetoxy-2-alkylnaphthalene-1(2H)-ones of type **3.35**, which they proposed may be prepared by the Wessely acetoxylation (**Figure 3.9**).
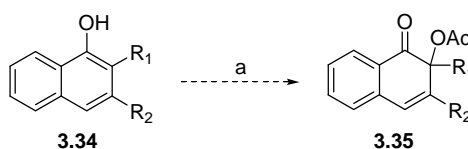
Figure 3.9   Proposed formation of 2-acetoxy-2-alkylnaphthalene-1(2H)-ones by the Wessely acetoxylation: (a) Pb(OAc)$_4$, acetic acid.

As a model study Pinhey and coworkers investigated the Wessely acetoxylation of 1-naphthol.[11] To their surprise, they found that 1-naphthol (**3.36**) had a strong preference for acetoxylation at C4 rather than C2, with acetate **3.37** obtained in 43% yield compared to 28% yield for ketone **3.38**.
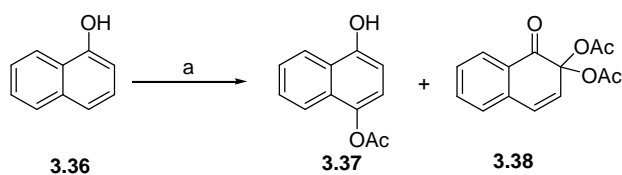
Scheme 3.12   Reagents and yields: (a) 2 eq Pb(OAc)$_4$, acetic acid, **3.37** 43%, **3.38** 28%.

Based on the above result, it would appear that a similar reaction may be taking place during the coupling reaction of aryllead **3.20** and naphthol **1.104**. Given that the ^{1}H NMR spectrum of the aryllead triacetate showed an increase in the integration of the acetate group resonance, it is likely that the excess lead tetraacetate is the culprit. This is a surprising result as no such byproduct was observed in the earlier aryllead chemistry described in this thesis and that reported by Bungard.

Accordingly, reinvestigation into the synthesis of the aryllead triacetate was undertaken with the amount of lead tetraacetate used being limited. Reducing the equivalents of lead tetraacetate to one was found to give a slight increase in demetalated material, but still a comparable yield of the desired aryllead precursor. However, optimal results were obtained, with a slight excess of lead tetraacetate (1.1 equivalents) followed by recrystallisation of the crude product from dichloromethane and petroleum spirit to give pure aryllead **3.20** as indicated by the ^{1}H NMR spectrum.
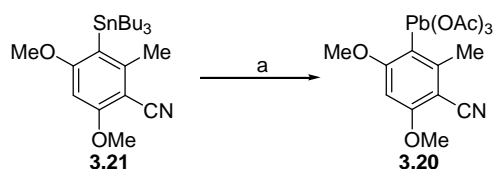
Scheme 3.13   Reagents and yields: (a) 1.1 eq Pb(OAc)$_4$, cat Hg(OOCCF$_3$)$_2$, dichloromethane, r.t., 81%.

Although full spectroscopic data could not be obtained for this compound as a result of decomposition under mass spectroscopic analysis and limited solubility in suitable NMR solvents, the 600 MHz ^{1}H NMR spectrum is quite diagnostic (**Figure 3.10**). In particular, both the aromatic signal at δ 6.41 and the methyl signal at δ 2.73 have characteristic ^{207}Pb-satellities at 113 Hz and 15 Hz, either side of the parent peaks respectively.
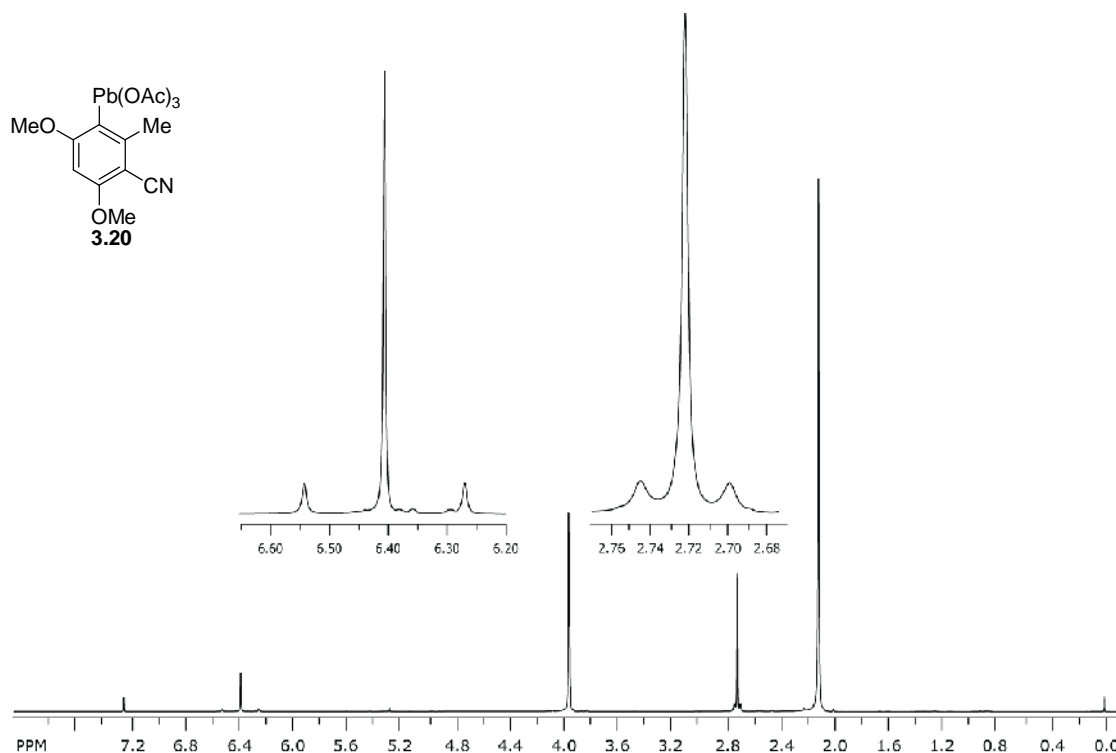
Figure 3.10   600 MHz ^{1}H NMR spectrum of aryllead triacetate **3.20**.

Pleasingly, use of this material in the coupling reaction was found to give the arylated product in higher yield (77%) with no trace of the acetate byproduct (**Scheme 3.14**).
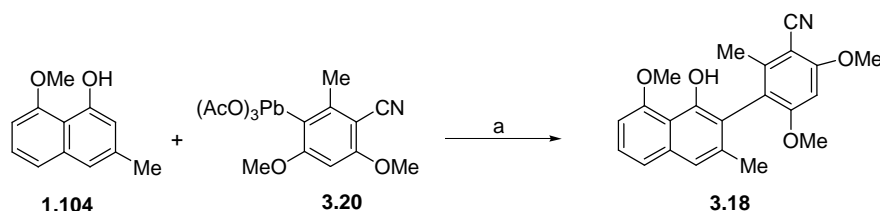
Scheme 3.14   Reagents and yields: (a) 3 eq pyridine, CH$_2$Cl$_2$, 24 h, r.t., 77%.

3.5   Investigation into the Resolution of Biaryl 3.18

Having established the chemistry required for the formation of the 5,3′-biaryl linkage, attention was now focused on the possibility of resolving the atropisomers. The successful resolution of the atropisomers would allow the preparation of both (*M*)-ancistrotanzanine A and the (*P*)-atropisomer, which is not found in nature. The separation of the atropisomers would also mean that complications with determining the selectivity of the alkylation reaction used for setting the C3 stereocentre of the isoquinoline moiety would be avoided. This work was carried out in conjunction with Milena Czyz.

Covalently bound chiral auxiliaries have been used for the resolution of chiral biaryl compounds. For example, the successful resolution of racemic atropisomeric C_3-cyclotriveratrylene derivatives were achieved through the use of (*R*)-(+)-2-phenoxypropionic acid.[12] Accordingly, it was decided to examine whether (*R*)-(+)-2-phenoxypropionic acid could be used for the resolution of the racemic biaryl **3.18** (**Figure 3.11**).
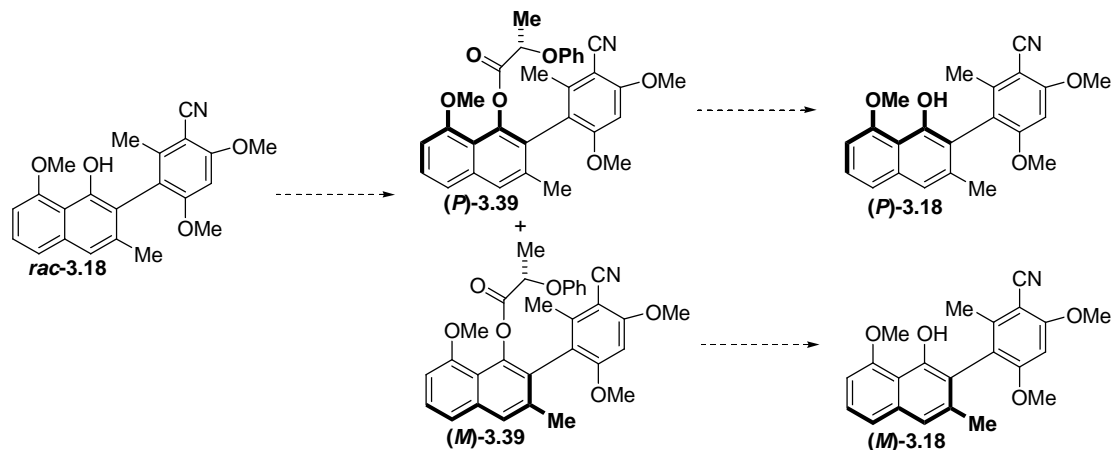
Figure 3.11   Proposed resolution of biaryl **3.18** with (*R*)-(+)-2-phenoxypropionic acid.

Reacting naphthol **3.18** with (*R*)-(+)-2-phenoxypropionic acid under DCC-DMAP coupling conditions in dichloromethane was found to give no reaction with only starting material observed in the 300 MHz ^{1}H NMR spectrum of the crude reaction material (**Scheme 3.15**).
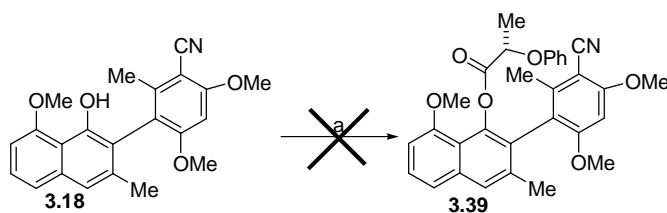
Scheme 3.15   Reagents: (a) 1.5 eq (*R*)-(+)-2-phenoxypropionic acid, 0.11 eq DMAP, 1.1 eq DCC, *N*,*N*-dimethylformamide, 0 °C to r.t., 48 h, (no reaction).

In an effort to determine if steric hindrance was responsible for the lack of reactivity of the naphthol **3.18** the preparation of ester **3.41** from simple naphthol **1.104** was investigated using similar conditions to that above. Surprisingly, the ester was not formed. It was subsequently found that deprotonation of the hydrogen bonded hydroxyl group with sodium hydride in *N*,*N*-dimethylformamide followed by quenching with the acid chloride **3.40** was required to afford the ester **3.41** in 89% yield (**Scheme 3.16**).
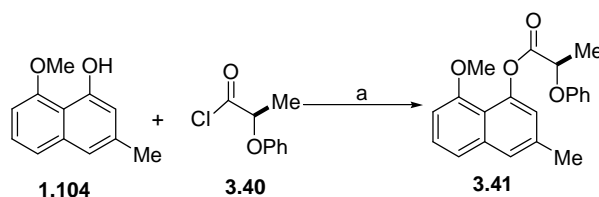
Scheme 3.16   Reagents and yields: (a) 2 eq NaH, 0 °C, 20 min, DMF, then **3.40**, 0 °C to r.t. o.n., 89%.

Having successfully prepared the chiral ester **3.41**, use of the above conditions were explored on the real system. The ^{1}H NMR spectrum of the crude material revealed mainly starting naphthol **3.18** and a trace of an unidentifiable product. Separation of the new product from the starting material was not possible by both chromatography and recrystallisation. Given the lack of success at forming the requisite ester an alternative resolving agent was sought.

Fuji and coworkers reported the resolution of a racemic mixture of binaphthalenediol **3.42** with various resolving agents such as *N*-protected amino acids, (-)-menthyl chloroformate and cholesteryl chloroformate.[13] They observed by TLC analysis that Boc-Ala-OH, Boc-Val-OH, Boc-Ile-OH and Boc-Met-OH showed large separation. With its low cost, the use of Boc-Ala-OH was selected for the resolution of binaphthalenediol (**Scheme 3.17**). Condensation of racemic

3.42 and Boc-Ala-OH was achieved using WSC/DMAP conditions and afforded a diastereomeric mixture of (*P*)-**3.43** and (*M*)-**3.43**. After separation by flash chromatography, hydrolysis of the ester afforded (*P*)-**3.42** and (*M*)-**3.42** in 92 and 91% yield respectively.
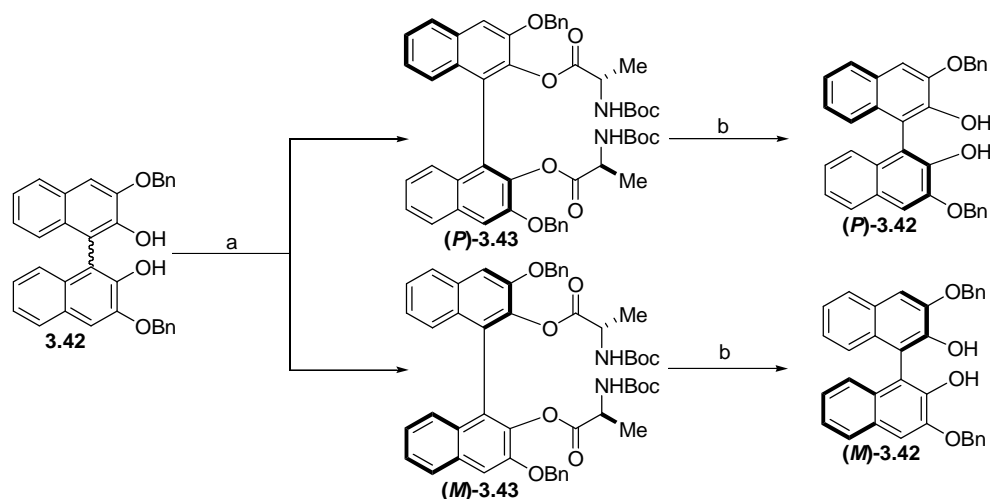
Scheme 3.17   Reagents and yields: (a) 2.5 eq Boc-Ala-OH, 3.0 eq WSC·HCl, 0.04 eq DMAP, o.n. then crystallisation and column chromatography, (*P*)-**3.43** (45%), (*M*)-**3.43**   (48%); (b) 3 eq 3 M NaOH, THF, 60 °C, 11 h, (*P*)-**3.42** (92%), (*M*)-**3.42** (91%).

Accordingly, use of Boc-Ala-OH and Fmoc-Ala-OH for the resolution of naphthol **3.18** was investigated (**Scheme 3.18**). However, using similar conditions to that reported by Fuji resulted in no reaction. Changing to sodium hydride in *N*,*N*-dimethylformamide to deprotonate the hydroxyl group followed by quenching with the appropriate acid chloride also was found to give no reaction. Changing the solvent to dimethyl sulfoxide also proved futile.
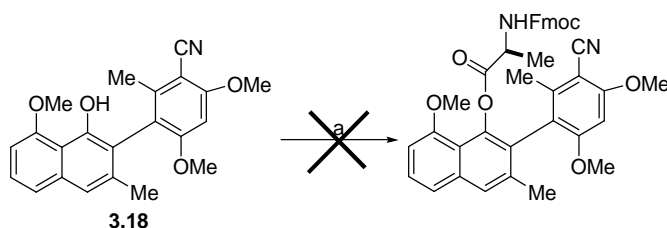
Scheme 3.18   Reagents and yields: (a) 2 eq NaH, *N*,*N*-dimethylformamide (or dimethyl sulfoxide), 0 °C 20 min then 5 eq Fmoc-Ala-Cl, *N*,*N*-dimethylformamide, 0 °C to r.t. (no reaction).

It is suspected that the lack of reactivity of biaryl **3.18** is due to the steric bulk *ortho* to the hydroxyl group interfering with the approaching resolving agent. Given the lack of success of resolving the atropisomeric mixture it was decided to explore other options.

3.6 Investigation into an Atropselective Pinhey-Barton Reaction

Given the lack of success of resolving the biaryl **3.18**, attention was focused on carrying out an atropselective Pinhey-Barton reaction. Based on Yamamoto's work on similar systems[14], it was envisaged that use of the chiral ligand brucine would promote an atropselective Pinhey-Barton reaction and this work is summarised below.

Interestingly, the use of brucine in place of pyridine under the standard reactions conditions was found to give a higher yield of the desired 5,3′-biaryl product **3.18** (83%). Given that Yamamoto and coworkers found the highest enantioselectivities of their coupling reactions were obtained when the reaction was performed at lower temperatures and with lithiated phenols, these conditions were investigated. The lithiated naphthol was prepared by reaction of naphthol **1.104** with *n*-butyl lithium in toluene at 0 ^{o}C. Coupling of the lithiated naphthol with the aryllead species **3.20** in the presence of brucine and 4Å molecular sieves at -78 ^{o}C gave the biaryl **3.18** in 66% yield (**Scheme 3.19**).
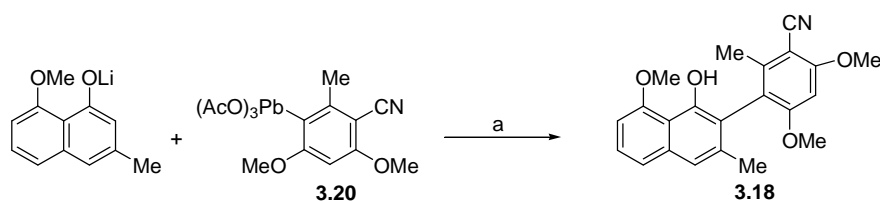
Scheme 3.19 Reagents and yields: (a) 2 eq brucine, 1.5 g/mol crushed 4Å sieves, toluene, -78 ^{o}C, 6 h, 66%.

In an attempt to determine if any stereoselectivity had occurred with the use of the chiral ligand brucine, the three differently coupled biaryls were analysed by HPLC using a Chiralcel OD-H column. Unfortunately, despite extensive experimentation, baseline separation of the two atropisomers was not possible. Consequently the determination of any stereoselectivity proved inconclusive. It is worth noting that Yamamoto and coworkers were successful using HPLC

analysis of similar products with the same chiral column to determine their ee values, however base line separation of the naphthol coupled products sometimes required up to three columns linked in series.[14] Not having the facilities to perform such an experiment, it was decided to carry the pyridine coupled material through to ancistrotanzanine A. This would afford ancistrotanzanine A as a 1:1 mixture of atropisomers. Following the successful completion of the synthesis, the brucine coupled material would then be taken through the total synthesis. If atropselection had occurred, a change in the ratio of the atropisomers would be observed, thus indicating if brucine had any effect on the atropselectivity of the Pinhey-Barton reaction.

3.7   Studies of the Key Alkylating Step

The synthesis of the isoquinoline moiety employing the methodology reported by Davis and coworkers involves the diastereoselective addition of the laterally lithiated nitrile **3.14** to sulfinimine **3.15** as shown before in **Scheme 3.4**. In order to circumvent any problems associated with the presence of a free hydroxyl group, it was protected as its MOM ether. This protecting group was chosen as it would be readily cleaved in the final stages of the synthesis under the acidic conditions used for the formation of the isoquinoline moiety. The protection was achieved using sodium hydride in *N,N*-dimethylformamide to deprotonate the naphthol **3.18**, followed by addition of MOM-Cl to yield the protected product in 91% yield (**Scheme 3.20**).
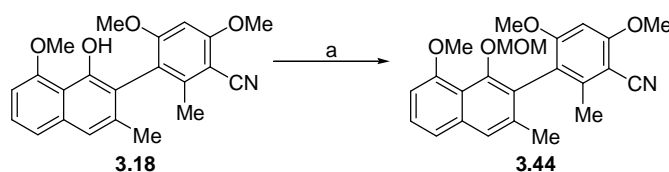
Scheme 3.20   Reagents and yield: (a) 2 eq NaH, *N,N*-dimethylformamide, 5 eq MOM-Cl, r.t., o.n., 91%.

Examination of the 600 MHz ^{1}H NMR spectrum revealed the presence of the diagnostic resonances due to the CH_2 group of the protecting group as two doublets at δ 4.77 and δ 4.96 respectively. The two doublets is due to the stereo-axis present in the molecule causing the CH_2 protons to be diastereotopic. A resonance due to the new methoxy group was observed at δ 2.86. Comparison to the spectrum of the starting material indicated that the hydrogen bound alcohol resonance at δ 9.48 was no longer present.

Davis and coworkers reported that use of sulfinimine (*S*)-**3.15** gave the (*R*)-stereochemistry at C3 for the 3,4-dihydroisoquinoline. This is the opposite to that required for ancistrotanzanine A. However, the (*S*)-sulfinamide is cheaper and accordingly initial studies of the alkylation of biaryl **3.18** were undertaken using the sulfinimine (*S*)-**3.15**. The completion of the synthesis would result in a total synthesis of *ent*-ancistrotanzanine A and its diastereoisomer, as shown below (**Figure 3.12**).
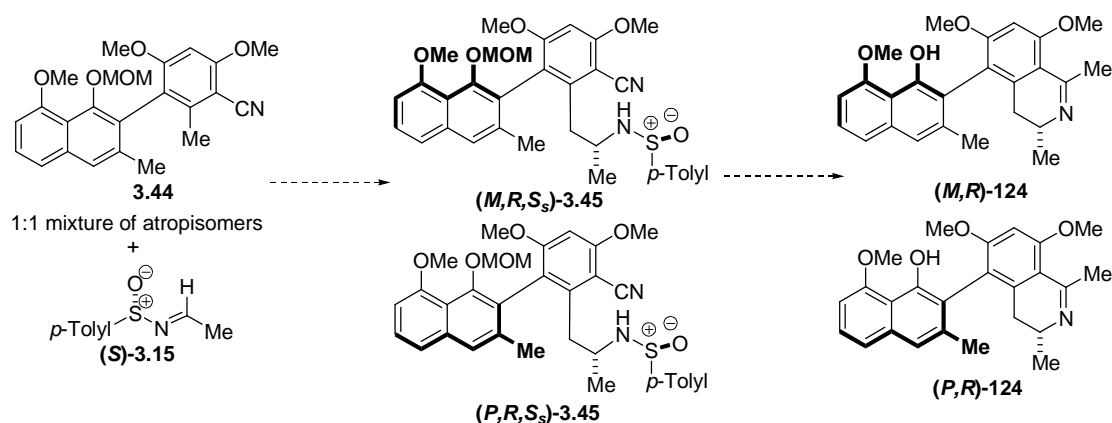
Figure 3.12 Alkylation with the (*S*)-sulfinimine would give the (*R*)-stereochemistry at C3 and result in a total synthesis of *ent*-ancistrotanzanine A (***P,R***)-**124** and its atropisomer (***M,R***)-**124**.

The known sulfinimine (*S*)-**3.15** was readily prepared by condensation of the corresponding sulfinamide (*S*)-**3.45**, with acetaldehyde in the presence of 4Å molecular sieves as reported by Davis[7] (**Scheme 3.21**).
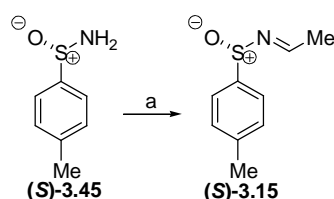
Scheme 3.21 Reagents and yields: (a) 3 eq acetaldehyde, 4Å molecular sieves, dichloromethane r.t, 93%.

With sufficient quantities of the biaryl **3.44** and the sulfinimine (*S*)-**3.15**, studies into the alkylation reaction using the conditions reported by Davis were undertaken. Treatment of biaryl **3.44** with lithium diisopropylamide in diglyme at –78 °C followed by the addition of a solution of

sulfinimine (*S*)-**3.15** in diglyme, was found to give no reaction (**Scheme 3.22**). Examination of the 300 MHz ^{1}H NMR spectrum of the crude reaction material revealed only starting material present with no trace of the desired product. The starting material was recovered in quantitative yield after purification by flash chromatography.
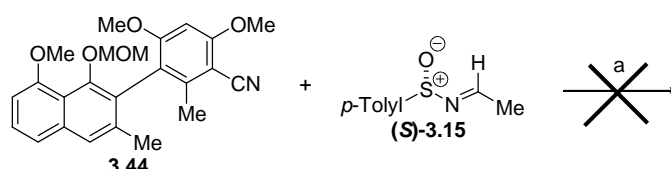
Scheme 3.22   Reagents: (a) i. 2 eq LDA, digylme, -78 ^{o}C, 0.5 h, ii. 1.1 eq (*S*)-**3.15**, diglyme, –78 ^{o}C, 0.5 h (no reaction).

Davis and coworkers have also reported successful alkylations using tetrahydrofuran as the solvent, albeit in lower yield. However, repeating our reaction, but using tetrahydrofuran, gave no trace of the desired product with only starting material recovered. Given the lack of success in either solvent reported by Davis, it was suspected that either the substrate, with its highly hindered reaction site, or the base was responsible for the lack of reactivity. Investigations into the latter were undertaken, with a range of bases screened.

The use of NaHMDS as the base in place of LDA to generate the required enolate was studied in both tetrahydrofuran and diglyme. Unfortunately, no trace of the desired product was observed in the ^{1}H NMR spectrum of the crude reaction material from either reaction. The use of sodium hydride was investigated to deprotonate the methyl group in dimethylsulfoxide, but these conditions were also found to give no reaction.

Schwesinger phosphazene bases, such as P4-*t*Bu **3.46**, give rise to 'naked' anions *in situ* and are known in some cases to give rate enhancement and higher diastereoselectivities.[15] Thus, it was deemed appropriate to use such a base to investigate if solvent coordination to the enolate was the cause for the lack of reactivity. However, the use of P4-*t*Bu, in place of LDA, proved futile.
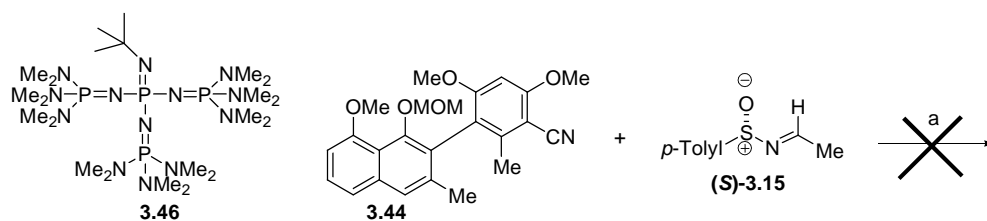
Scheme 3.23   Reagents and yields: (a) i. 2 eq P4-*t*Bu, THF, -78 °C, 0.5 h, ii. 1.1 eq (*S*)-**3.15**, diglyme, –78 °C, 0.5 h (no reaction).

Having had no success with changing the base, it was suspected that the substrate may be the issue. Closer inspection of the reaction site gives rise to the possibility that the MOM protecting group may be coordinating to the lithium species generated *in situ*. This may result in the reaction site being effectively shielded from the sulfinimine. Thus, an alternative protecting group was investigated. The *iso*-propyl group was deemed appropriate given its lack of a secondary coordinating oxygen group compared to that of the MOM protecting group. The protection proceeded smoothly and the conditions are given in **Scheme 3.24**.
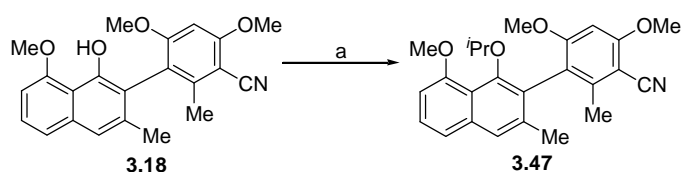
Scheme 3.24   Reagents and yield: (a) 2 eq NaH, DMF, r.t., 30 min, then 5 eq 2-bromopropane, r.t. o.n., 83%.

Examination of the 300 MHz ^{1}H NMR spectrum revealed the presence of the diagnostic resonances due to the methyl groups of the isopropyl group as two doublets at δ 0.86 and δ 1.06. The presence of two doublets can again be attributed to the rigid biaryl axis causing the methyl groups to appear in different chemical environments. The resonance of the CH proton of the isopropyl group appeared as a multiplet at δ 3.89-3.97.

Unfortunately, subjecting the isopropyl biaryl **3.47** to the alkylating conditions reported by Davis and coworkers, using both diglyme and tetrahydrofuran, gave only starting material in quantitative yield.

Given the issues we had encountered, it was decided to return to the simpler system reported by Davis to see if we could solve the issues we were having.

3.8   Reinvestigation of the Davis Methodology

It was deemed appropriate, given the lack of success discussed in Section 3.7, to re-examine the alkylation of *o*-tolylnitrile **3.29** with sulfinimine (*S*)**-3.15** as reported by Davis.[7] Lithiation of the *o*-tolylnitrile **3.29** was undertaken using LDA as the base in diglyme at -78 °C. After the addition of the (*S*)-sulfinimine the reaction was monitored by TLC analysis and the reaction found to be complete after stirring for 30 minutes (**Scheme 3.25**). Examination of the 300 MHz ¹H NMR spectrum of the crude reaction mixture revealed a promising result, with the presence of the diagnostic doublets of the methyl group at δ 1.33 (major diastereoisomer) and 1.38 (minor diastereoisomer). The spectroscopic data of the major diastereoisomer (*R*,*S*ₛ)**-3.16** matched that reported by Davis and coworkers. However, the minor diastereoisomer (*S*,*S*ₛ)**-3.16** was more prominent, with the de obtained being only 80%, compared to the 97% reported by Davis. Separation of the diastereoisomers was not possible by flash chromatography. Changing the reaction solvent from diglyme to tetrahydrofuran resulted in no reduction in yield or selectivity. Despite our best efforts, we weren't able to reproduce the selectivity reported by Davis.
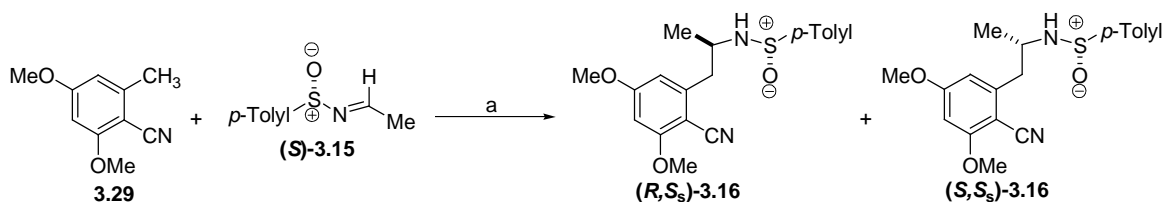
Scheme 3.25   Reagents and yield: (a) 2 eq LDA, diglyme or THF, - 78 °C 30 min, then 1.2 eq (*S*)**-3.15**, -78 °C, 30 mins, 64%.

Reaction of the 90:10 mixture of sulfinamides **3.16** with four equivalents of methyl lithium followed by treatment with acid was found to yield a single product by TLC analysis. The 300 MHz ¹H NMR spectrum of the purified material confirmed that the desired isoquinoline **3.6** had been prepared. As expected, the optical rotation of the prepared isoquinoline **3.6** as its

hydrochloric salt ($[\alpha]_D^{25} = +106$) was lower than that obtained by Davis ($[\alpha]_D^{25} = +139$). This is clearly due to the drop in diastereoselectivity of the alkylation step.
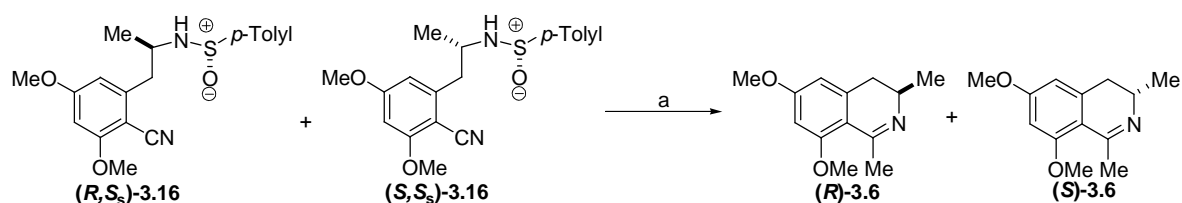
Scheme 3.26   Reagents and yield: (a) 4 eq MeLi, THF, - 78 °C to r.t., 1 h, then 2N HCl, 2 h, 62%.

Although the diastereoselectivity reported by Davis and coworkers could not be achieved, the success of the alkylation on the *o*-tolylnitrile indicated that the reaction was being carried out appropriately. Having satisfied ourselves that the chemistry was valid, it was decided that an investigation into the sensitivity of the alkylation to steric hindrance was required.

By comparing the *o*-tolylnitrile **3.29** to the substrate **3.44** required for the synthesis of ancistrotanzanine A it can be seen that there is a large increase in the steric environment *ortho* to the reaction site (**Figure 3.13**). It was shown in Section 3.7 that biaryl **3.44** was unreactive when the alkylation conditions reported by Davis were used. The lack of reactivity of this substrate would appear to be a consequence of the increased steric hindrance surrounding the reaction site. Davis and coworkers had not studied the effect or limitations that steric hindrance had on the alkylation reaction. Thus, it was deemed appropriate to study the limitations of the alkylation reaction with regard to steric hindrance *ortho* to the reaction site on simpler model systems, such as iodide **3.22** and the biaryl **3.48**.
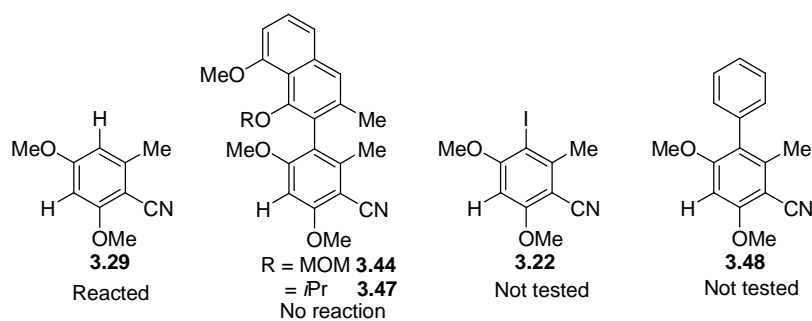
Figure 3.13   *o*-Tolylnitrile substrates.

With the ready availability of iodide **3.22** it was deemed appropriate to investigate the above alkylation on this substrate. Quenching the lithium enolate of **3.22** with the sulfinimine (*S*)-**3.15** at –78 °C gave a promising result. Analysis of the 300 MHz ^{1}H NMR spectrum of the crude reaction material confirmed that the alkylation had preceded with the diagnostic resonances of the methyl groups at δ 1.39 and δ 1.46 of the two diastereoisomers. It was observed that the presence of the iodide had no adverse effect on the stereoselectivity of the alkylation with a 90:10 ratio of diastereoisomers again obtained. However, the yield of the alkylated product was much lower at 44%. This decrease in yield is perhaps due to the increase in steric bulk provided by the iodine *ortho* to the reaction site.
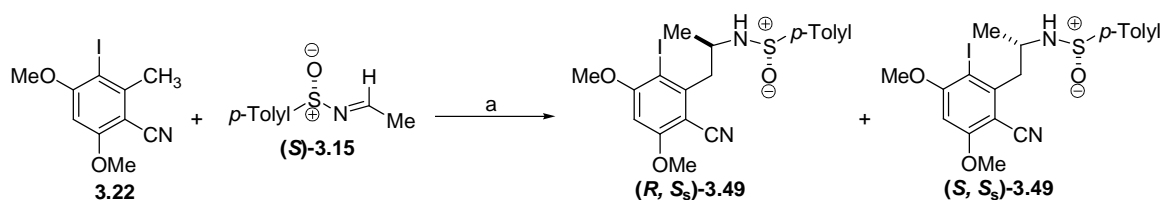
Scheme 3.27   Reagents and yield: (a) 2 eq LDA, THF, -78 °C, 0.5 h, then 1.2 eq (*S*)-**3.15**, -78 °C, 0.5 h, 44%.

To further probe the limits of the alkylation reaction to steric hindrance and to have a model that closely resembled the structure of biaryls **3.44** and **3.47**, investigation of the alkylation of the biaryl **3.48** was deemed appropriate. The synthesis of biaryl **3.48** was readily achieved by Suzuki coupling of commercially available phenyl boronic acid **3.49** and iodide **3.22** in 66% yield (**Scheme 3.28**). A major byproduct was the deiodonated material **3.29**, which was isolated in 30% yield.
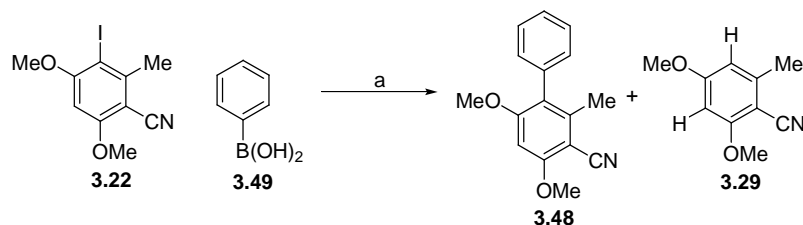
Scheme 3.28   Reagents and yield: (a) cat PdCl$_2$(PPh$_3$), 1.6 eq phenylboronic acid, 4.0 eq NaHCO$_3$, DME/H$_2$O (1:1), 70 °C, o.n., **3.48** 66%, **3.29** 30%.

Subjecting the model system biaryl **3.48** to the standard alkylating conditions yielded an interesting result. Examination of the 300 MHz ^{1}H NMR spectrum revealed the presence of a substantial amount of unreacted starting material and also resonances similar to that of the previous alkylated products. Purification by flash chromatography afforded the desired product in a modest 33% yield and 80% de. Under the same reaction conditions the unsubstituted nitrile **3.29** was found to afford the alkylated product in 64% yield, almost a two fold greater yield than that obtained for the model system. Given the only difference in the model system is the aryl group *ortho* to the reaction site, the increased steric bulk was again thought to be responsible for the low yield.
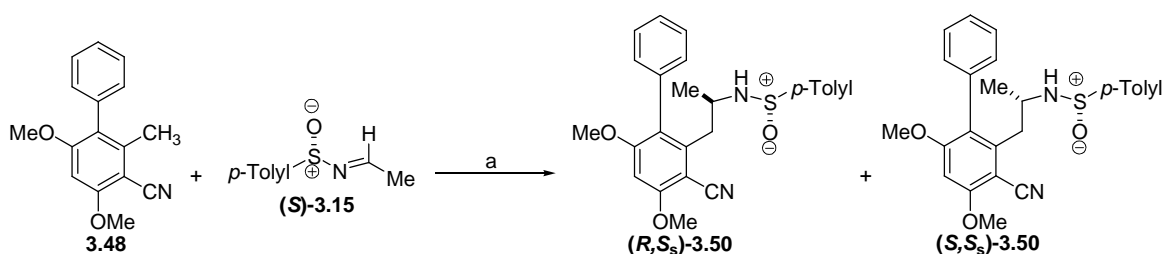
Scheme 3.29   Reagents and yield: (a) 2 eq LDA, THF, then 1.3 eq (*S*)-**3.15**, -78 ^{o}C, 30 mins, 32%.

As we were unable to change the steric environment of the substrate in the real system (biaryl **3.44)** it was decided to examine the steric bulk of the base used to generate the enolate. It was suspected that the use of the bulky reagent LDA was resulting in the incomplete generation of the required lithiated species for the model system (biaryl **3.48**). Lithium diethylamide, which was readily available, was considered a potential candidate as it has similar properties to LDA, but is less bulky. Pleasingly, use of lithium diethylamide for the alkylation of the model biaryl **3.48** was found to give more than a two fold increase in the yield of alkylated product, with no change in the diastereoselectivity (**Scheme 3.30**). Application of lithium diethylamide to the alkylation of iodide **3.22** also gave an increase in the yield from 44% to 73% with only a small deviation in the diastereoselectivity (76% compared to 80%).
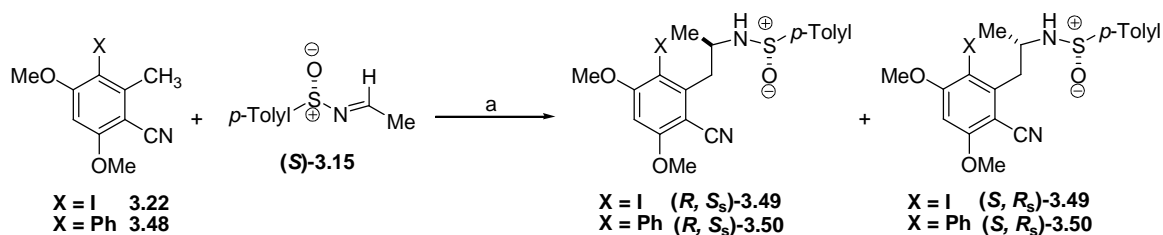
Scheme 3.30   Reagents and yield: (a) 4 eq LiNEt$_2$, diglyme, -78 $^{\circ}$C, 30 mins, then (*S*)-**3.15**, -78 $^{\circ}$C, 30 min, 77%
for X = I, 68% for X = Ph.

The improved yields obtained with the use of lithium diethylamide for alkylation of both the
iodide **3.22** and the model biaryl **3.48** prompted the study of these conditions on the alkylation of
the real system. These studies are discussed below.

3.9   The Total Synthesis of *ent*-Ancistrotanzanine A

Having established that lithium diethylamide was an appropriate base to be used in place of LDA,
attention was now focused on applying these conditions to the real system. Dropwise addition of
the biaryl **3.44** to a solution of lithium diethylamide in dry diglyme at -78 $^{\circ}$C resulted in a deep
red coloured solution and after stirring for 30 minutes at -78 $^{\circ}$C a solution of the sulfinimine (*S*)-
3.15 in diglyme at -78 $^{\circ}$C was added. Disappointingly the 600 MHz ^{1}H NMR spectrum of the
crude reaction material confirmed that no reaction had occurred with only the presence of starting
material being observed.

However, changing the solvent to tetrahydrofuran gave a promising result. Thirty minutes after
the addition of the sulfinimine, TLC analysis indicated the presence of a new product. The 600
MHz ^{1}H NMR spectrum of the crude residue obtained revealed a complex mixture, consisting of
starting biaryl and promisingly new resonances similar to that observed for the previous alkylated
products reported in Section 3.8. The four doublets (*J* = 6.6 Hz) at δ 1.00, 1.07, 1.13, 1.26 were
quite diagnostic, indicating that the alkylation was proceeding. The reaction conditions were
optimised with 4 equivalents of lithium diethylamide found to be necessary for the complete
consumption of the starting material, as summarised in **Scheme 3.31**. The mixture of
diastereoisomers was found to be inseparable by flash chromatography on silica gel.
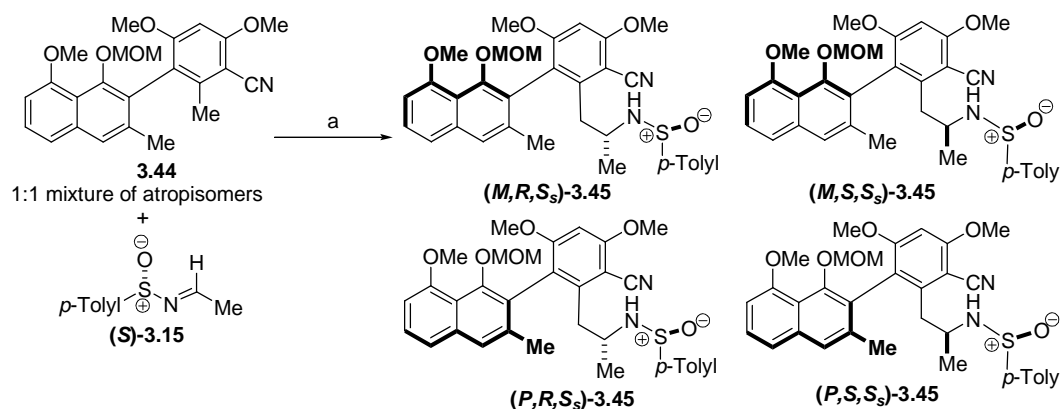
Scheme 3.31   Reagents and yield: (a) 4 eq LiNEt$_2$, THF, **3.44**, -78 ^{o}C, 30 mins, then 1.2 eq (**S**)-**3.15**, -78 ^{o}C, 30 min, 50%.

Examination of the 600 MHz ^{1}H NMR spectrum of the purified material confirmed the presence of 4 diagnostic multiplets in the region of δ 3.26-3.56. These are indicative C-H resonances from the newly attached alkyl chain as observed in the previous alkylated products. The four separate resonances, along with the four methyl resonances, confirmed that the obtained product was a mixture of diastereoisomers as shown above. Although separation of the diastereoisomers was not possible by chromatography the results from the model studies would suggest that the major diastereoisomers from the above reaction would most likely result from the formation of (***M,R,S***$_s$)-**3.45** and (***P,R,S***$_s$)-**3.45** with the minor diastereoisomers being (***M,S,S***$_s$)-**3.45** and (***P,S,S***$_s$)-**3.45**. From integration of the methyl signals at δ 1.00, 1.07, 1.13, and 1.26 of the 600 MHz ^{1}H NMR spectrum the ratio of the major diastereoisomers to that of the minor diastereoisomers was found to be 68:32. The selectivity is much less than that obtained for the model studies in Section 3.8, where the selectivity observed was usually 90:10.

Having established the chemistry required for the formation of the key alkylated product, albeit with low selectivity, attention was focused on completing the synthesis of the *ent*-ancistrotanzanine A and its diastereoisomer.

Treatment of sulfinamide **3.45** with 5 eq of methyl lithium, followed by the addition of acid, afforded *ent*-ancistrotanzanine A (***M,R***)-**1.124** and its atropisomer (***P,R***)-**1.124** in 49% yield (**Scheme 3.32**). The 600 Hz ^{1}H NMR spectrum showed resonances at 9.44 and 9.46, which are

indicative of hydrogen bound naphthol protons revealing that cleavage of the methoxymethyl protecting group had also occurred.
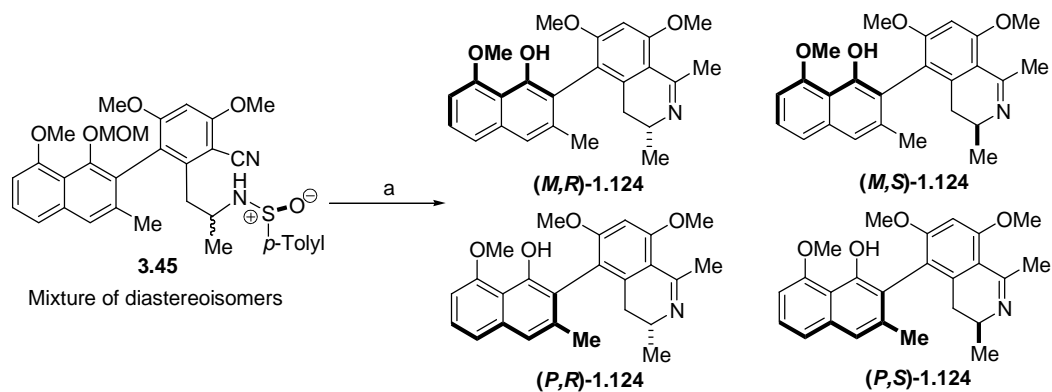
Scheme 3.32   Reagents and yield: (a) 5 eq MeLi, THF, -78 °C to r.t., 1 h, then 2N HCl 2 h, r.t., 49%.

Although the yield of the cyclisation step is modest it is worth noting that four operations were undertaken in one step. Firstly insertion of the methyl functionality at C1 was accomplished followed by removal of the sulfur auxiliary and cyclisation to give the isoquinoline moiety. Cleavage of the MOM protecting group was also achieved, under the reaction conditions to afford the natural product.

Even though the synthesis of *ent*-ancistrotanzanine A was quite short, the inability to control the selectivity of the alkylation posed a problem. Given both the lack of selectivity observed during the model studies in Section 3.8 and the low yield obtained for the alkylation of the real system (only 50%) an alternative sulfur auxiliary was sought. These studies are presented below.

3.10   Investigation of an Alternate Sulfur Auxiliary

In their studies towards the asymmetric synthesis of *β*-amino acids, Ellmann and coworkers used *tert*-butane sulfinyl imines, such as (*S*)-**3.51**, to facilitate the transfer of the chiral information (**Scheme 3.33**).[16] A range of metal enolate species and solvents were explored to determine their effect on both the yield and diastereofacial selectivity of the enolate addition, to the *tert*-butane sulfinyl imine. It was observed that the greatest stereoselectivity occurred using the titanium enolate, prepared by transmetallation of the corresponding lithium enolate with ClTi(O-*i*Pr)$_3$. The

stereoselectivity observed was rationalised by the proposed Zimmerman-Traxler-type six-membered transition state **TS-3.2**. Given the success that Ellmann and others have had with diastereoselective enolate additions to *tert*-butane sulfinyl imines[16-18] it was envisaged that an auxiliary of this type would also be applicable for the alkylation of *o*-tolylnitriles.
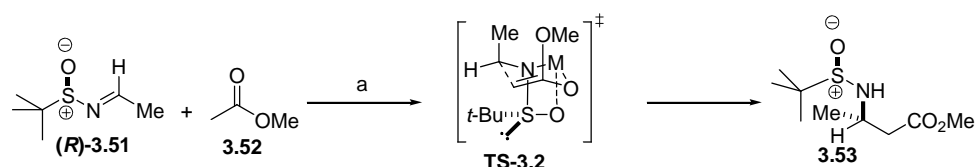
Scheme 3.33   Reagents and yields: (a) 1 eq LDA, 2 eq ClTi(O-^{i}Pr)$_3$, THF, -78 ^{o}C, 94%, dr 99:1.

The (*R*)-*tert*-butane sulfinyl imine was readily prepared in high yield by condensation with acetaldehyde in the presence of 4Å molecular sieves (**Scheme 3.34**).
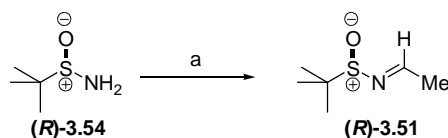
Scheme 3.34   Reagents and yields: (a) 3.0 eq acetaldehyde, 4Å sieves, dichloromethane, r.t., 86%.

Alkylation of the *o*-tolylnitrile was undertaken, using lithium diisopropylamide as the base to generate the required laterally lithiated nitrile species (**Scheme 3.35**). Inspection of the 300 MHz ^{1}H NMR spectrum of the crude product showed the presence of the diagnostic multiplets due to the CH$_2$ and CH protons at δ 2.81-2.98 and δ 3.59-3.68 respectively. The singlet at δ 1.08 (*tert*-butyl group) and the doublet at δ 1.36 (methyl group) was further evidence that the desired alkylated product was prepared. Further analysis of the spectrum indicated that the product was prepared as a single diastereoisomer with no trace of the minor diastereoisomer observed. Thus, the selectivity obtained using the *tert*-butyl sulfur auxiliary was greatly improved from the 90:10 diastereoisomeric ratio obtained when the *p*-tolyl-sulfur auxiliary was used to set the stereocentre (Section 3.8).
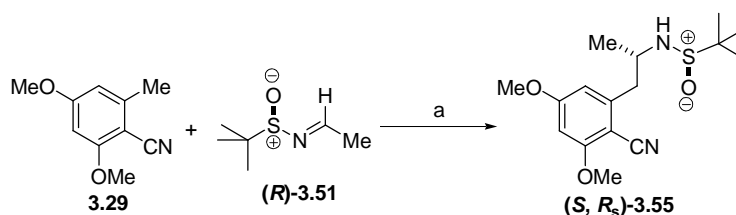
Scheme 3.35 Reagents and Yield: (a) 2 eq LDA, 1.2 eq (**R**)-**3.51**, THF, -78 °C, 72%.

Given that alkylation of the real system was found to require the use of the smaller base lithium diethylamide, the above experiment was repeated using this base to generate the lithium enolate species. Lithium diethylamide was found to give only a slight reduction in yield and no change to the diastereoselectivity of the alkylated product (**Scheme 3.36**).
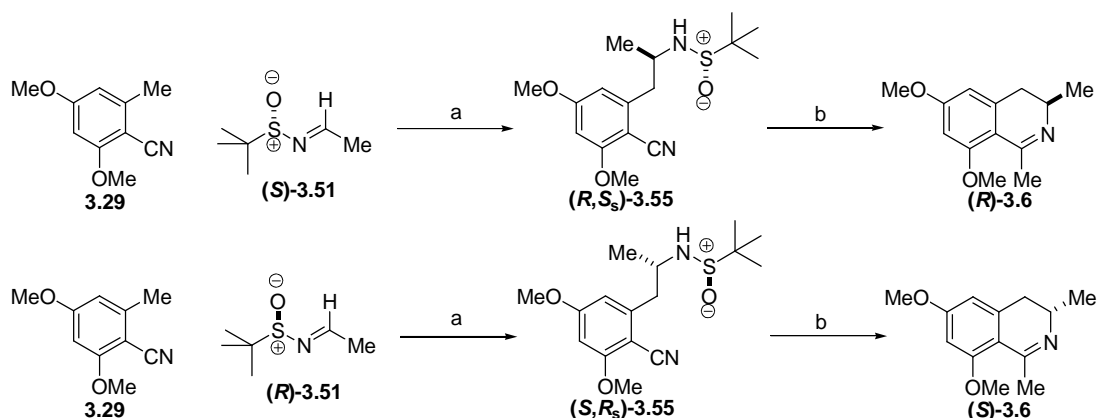
Scheme 3.36 Reagents and yields: (a) 2 eq LiNEt$_2$, 1.2 eq (**R**)-**3.51** or 1.2 eq (**S**)-**3.51**, THF, -78 °C, 68-71%; (b) 4 eq MeLi, THF, -78 °C then r.t., 2N HCl, 50-74%.

The alkylation of nitrile **3.29** was also studied with the enantiomer (**S**)-**3.51**. The alkylated product obtained was found to have the opposite optical rotation to that observed when the sulfinimine (**R**)-**3.51** was used. To confirm the absolute stereochemistry of the alkylated products (**S**,**R**$_s$)-**3.55** and (**R**,**S**$_s$)-**3.55** they were both converted to their known dihydroisoquinolines. Reaction of each of the alkylated products with methyl lithium followed by stirring with acid afforded the corresponding dihydroisoquinolines in greater yield than that obtained with the *p*-toluene sulfinimine auxiliary. Optical rotations of the hydrochloride salts of both enantiomers were in strong agreement with the reported literature data[7,19] and confirmed that the (**R**)-*tert*-

butane sulfinyl imine gave the (*S*)-stereochemistry at C3 and that the (*S*)-*tert*-butane sulfinyl imine gave the (*R*)-stereochemistry at C3.

It is interesting to note the difference in the 300 MHz ^{1}H NMR spectrum of isoquinoline **3.6** as the free base compared to its hydrochloride salt (**Figure 3.14**). It can be seen from the two spectra that the formation of the isoquinoline hydrochloric salt results in a large downfield shift of the singlet for the methyl group at C1 from 2.41 to 2.95. There is also a large downfield shift for the proton at C3 (multiplet) from 3.26-3.33 to 4.01-4.12 and the signals for the protons at C4 are also shifted.
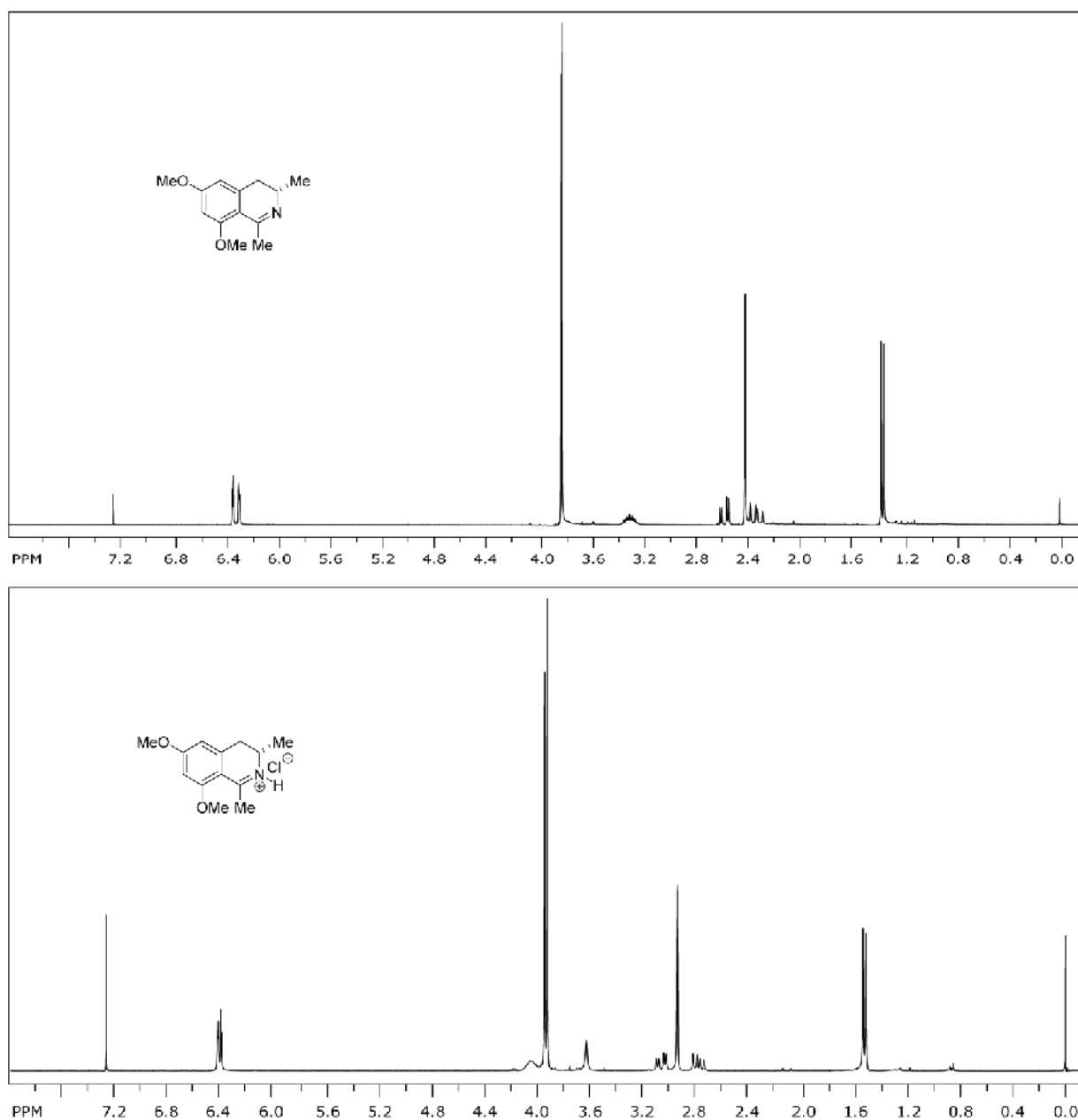
Figure 3.14   300 MHz ^{1}H NMR of the isoquinoline **3.6** as the free base (top) and as the hydrochloric salt (below).

Having established that the *tert*-butyl sulfur auxiliary gave greater selectivity for the alkylation of *o*-tolylnitrile **3.29** than the use of the *p*-tolyl auxiliary, attention was focused on applying the chemistry successfully on the real system with the expectation that the selectivity of the alkylation step would be enhanced.

3.11   The Total Synthesis of Ancistrotanzanine A

The stereochemistry at C3 of the isoquinoline moiety of ancistrotanzanine A is *S*. From the results above, alkylation of the biaryl **3.44** with the (*R*)-*tert*-butane sulfinyl imine should give the required stereoselectivity. After reacting the generated anion with sulfinimine (***R***)-**3.51**, a new product was obtained (**Scheme 3.37**). Examination of the 600 MHz ^{1}H NMR spectrum of the product revealed the presence of the diagnostic methyl doublets ($J = 6.0$ Hz) at δ 0.90, 1.03, 1.10, and 1.17. Comparison to the starting material spectrum indicated that the methyl resonance at 2.18 was no longer present. From integration of both the *tert*-butyl group peaks and the methyl group peaks previously mentioned it was observed that the ratio of the major diastereoisomers, presumably (***M,S,R***$_s$)-**3.56** and (***P,S,R***$_s$)-**3.56**, to that of the minor diastereoisomers, (***M,R,R***$_s$)-**3.56** and (***P,R,R***$_s$)-**3.56**, was 85:15.
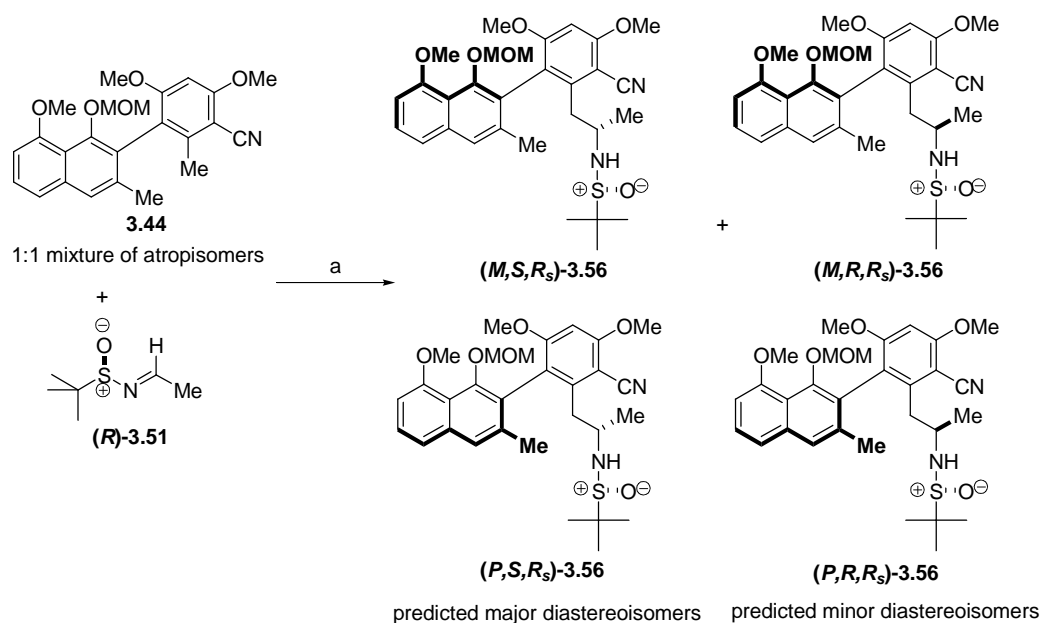
Scheme 3.37   Reagents and yields: (a) 3 eq LiNEth$_2$, THF, 0.5 h, - 78 ^{o}C, then 1.3 eq (***R***)-**3.51**, THF, -78 ^{o}C, 2 h, 75%.

Separation of the diastereoisomers was not possible by flash chromatography with the ratio of diastereoisomers preserved after purification. The 600 MHz ^{1}H NMR spectrum of the pure material is shown below confirming the product to be a mixture of four diastereoisomers (**Figure 3.15**).
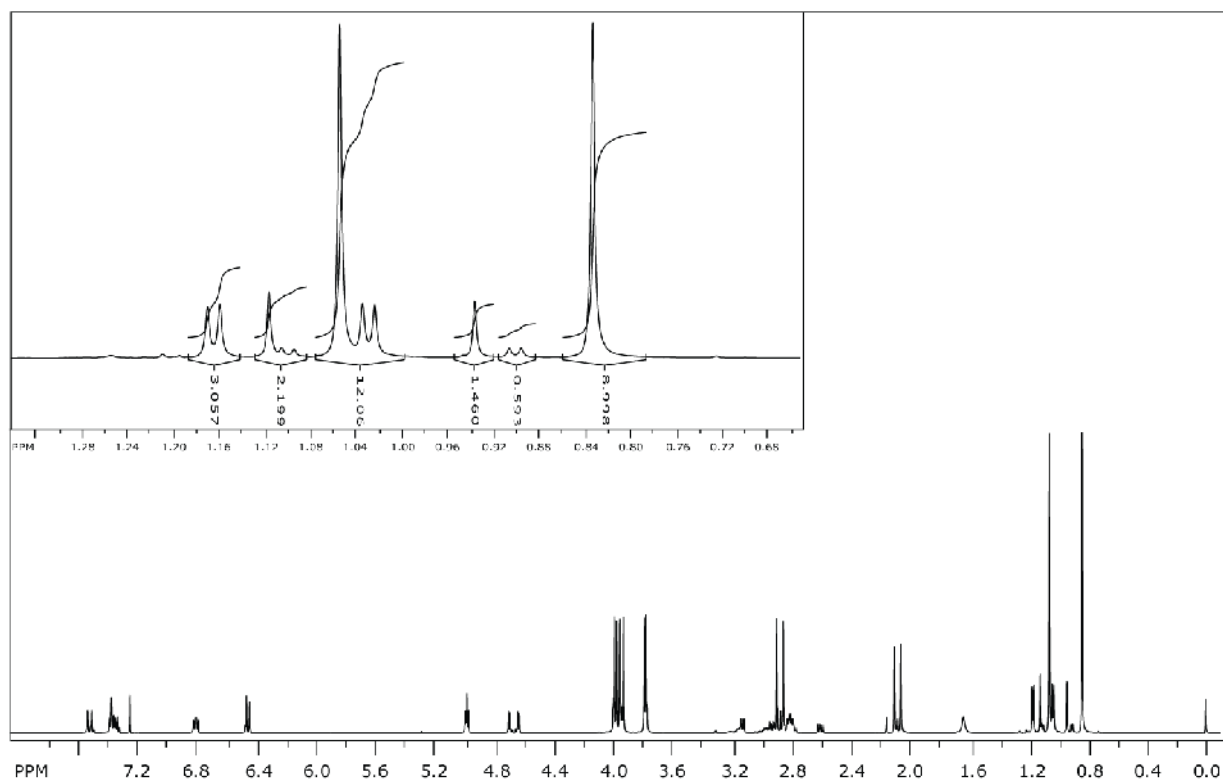
Figure 3.15   600 MHz ^{1}H NMR spectrum of **3.56** indicating the presence of four diastereoisomers.

Having successfully prepared the alkylated product **3.56**, the final steps of the synthesis was studied. Treatment of sulfinamide **3.56** with methyl lithium followed by acidification afforded the natural product, as a mixture of atropisomers in 77% yield (**Scheme 3.38**). This was much higher than the yield obtained with the *p*-toluene sulfur auxiliary (49%).
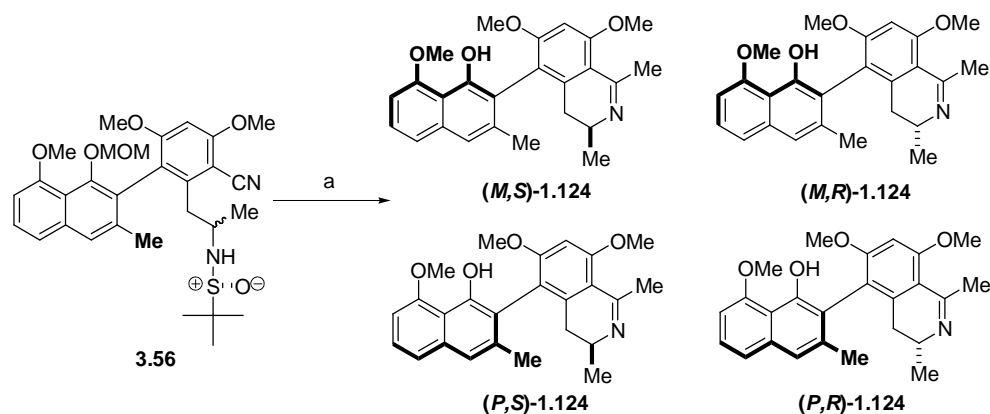
Scheme 3.38   Reagents and Yields; (a) 5 eq MeLi, THF, -78 °C to r.t. 1 h, then 2 M HCl, 2 h, 77%.

The 600 MHz ^{1}H NMR spectrum of the obtained natural product was found to match that obtained when the *p*-toluene auxiliary was used (**Figure 3.16**). Isoquinolines (***M,S***)-**1.124** and (***P,R***)-**1.124** are an enantiomeric pair as are (***P,S***)-**1.124** and (***M,R***)-**1.124**. This results in the ^{1}H NMR spectrum appearing to only contain two atropisomers and not the four stereoisomers that have been prepared. The aromatic portion of the spectrum exhibits the same coupling pattern reported by Bringmann and coworkers for ancistrotanzanine A.[20] The presence of both atropisomers causes the peaks to appear broader as a result of overlapping from the similar resonances.
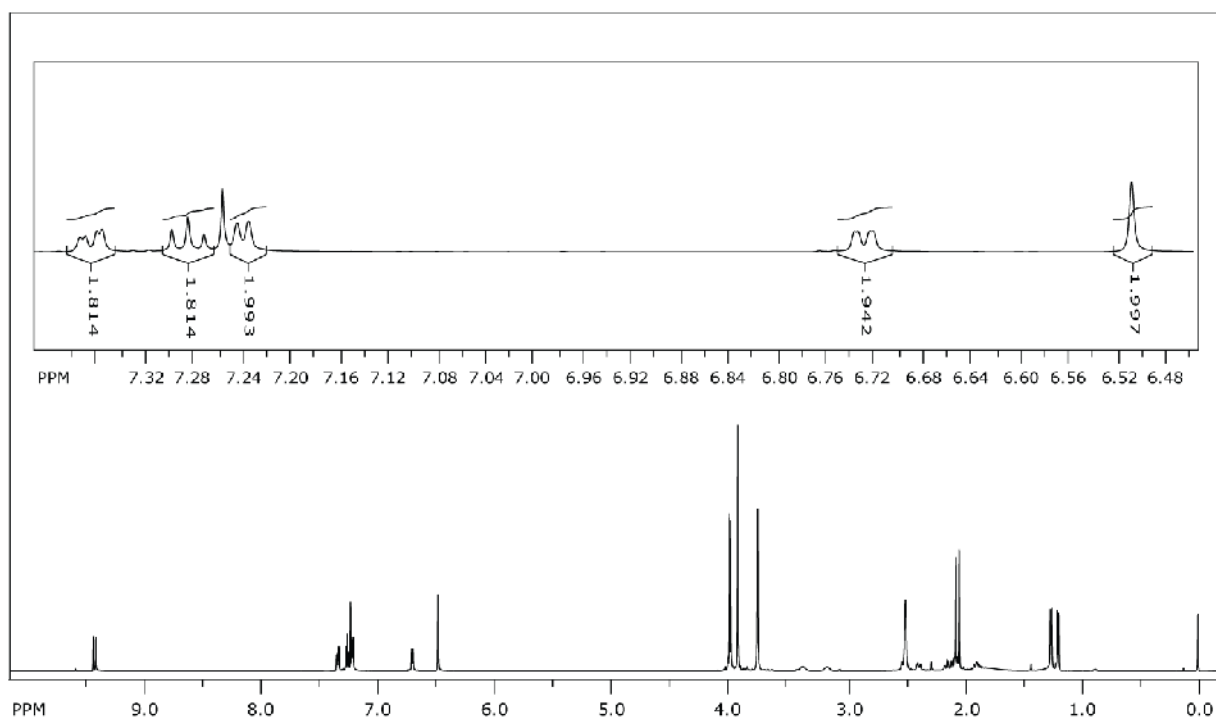
Figure 3.16 600 MHz ^{1}H NMR spectrum of the synthetically prepared ancistrotanzanine A (1:1 mixture of atropisomers) in CDCl$_3$.

Bringmann and coworkers recorded the ^{1}H NMR spectrum in deuterated methanol. Consequently, the deuterated chloroform was removed under reduced pressure and the residue dissolved in deuterated methanol. Surprisingly, the resonance due to the methyl group at C1 was absent in the 600 MHz ^{1}H NMR spectrum as shown in **Figure 3.17**.
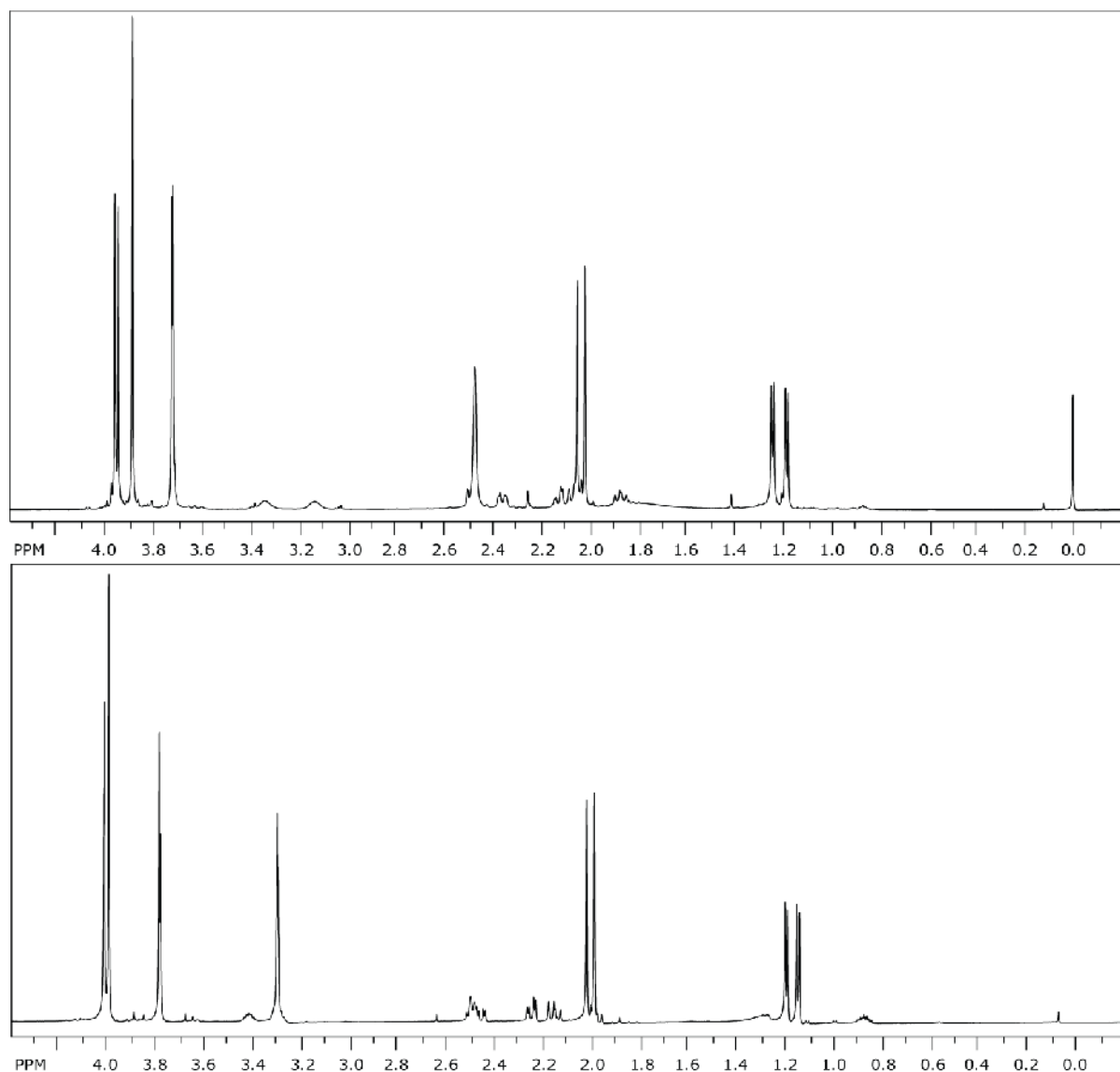
Figure 3.17   Expansion of the 600 MHz ^{1}H NMR spectra of ancistrotanzanine A in deuterated chloroform (top) and then obtained in deuterated methanol (below) revealing the absence of the C1 methyl resonance.

The deuterated chloroform originally used most likely contained a trace of hydrochloric acid. The presence of a catalytic amount of acid could catalyse the reaction shown in **Figure 3.18**. Protonation of the nitrogen atom leads to the activated species **3.57**, which activates the methyl group at C1 for deprotonation leading to an intermediate of type **3.59**. **3.59** is then readily deuterated and the process continues until all three hydrogens of the methyl group at C1 are replaced with deuterium. Consequently, the conversion of sulfinamide **3.56** to ancistrotanzanine

A was repeated and the ^{1}H NMR spectrum was recorded in d_4-MeOH, with no $CDCl_3$ used. The 600 MHz ^{1}H NMR revealed the presence of the methyl group, confirming that the acid in the $CDCl_3$ had indeed catalysed the proposed reaction below.
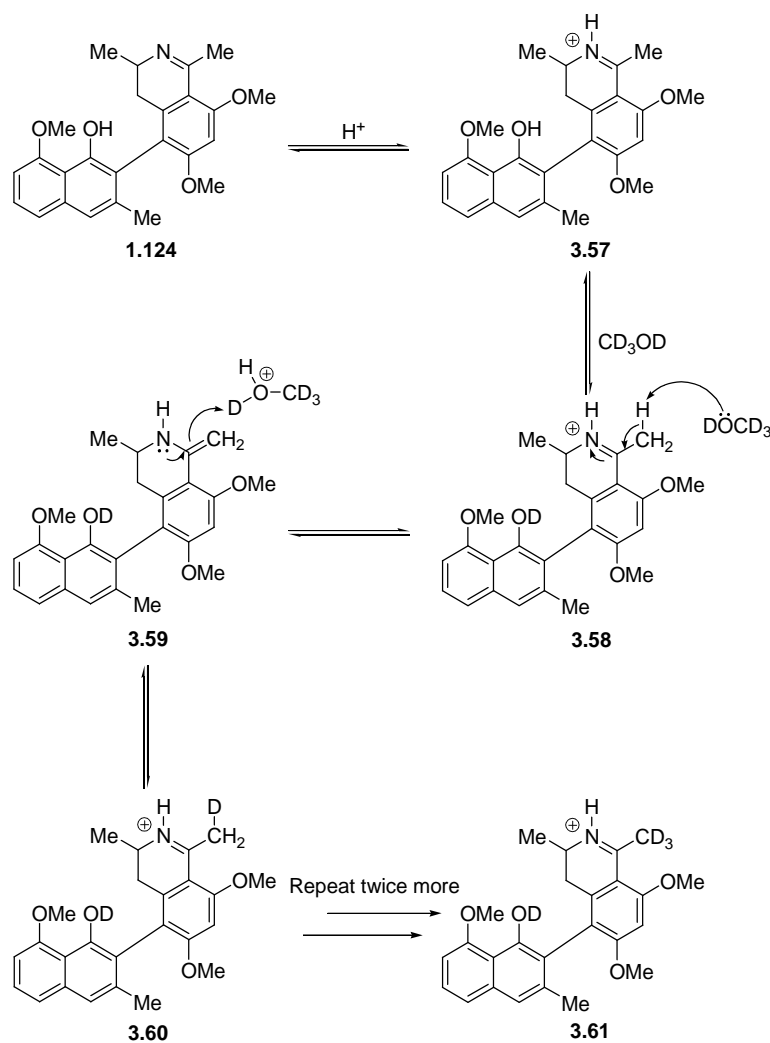
Figure 3.18   Proposed mechanism of hydrogen- deuterium exchange of the methyl group an C1.

Interestingly, the ^{1}H NMR spectrum of ancistrotanzanine A recorded in d_4-MeOH did not match that provided by Bringmann and coworkers. Closer examination of the isolation of ancistrotanzanine A revealed that the plant extracts were dissolved in dichloromethane and resolved using preparative HPLC with a Symmetry C_{18} column eluting with acetonitrile (with 0.05% trifluoroacetic acid) and water (with 0.05% trifluoroacetic acid).[20] There was no indication

that the sample of ancistrotanzanine A that was isolated had been neutralised to give the free base. In Section 3.10 it was found that the conversion of 3,4-dihydroisoquinolines to the corresponding salt can cause a dramatic shift in the ^{1}H NMR spectrum when compared to the free base. Thus, it was suspected that the data reported was in fact that of the trifluoroacetic acid salt of the natural product and not of the free base. Thus, the trifluoroacetic acid salt of ancistrotanzanine A was prepared by adding two drops of the acid to a solution of ancistrotanzanine A in dichloromethane. Removal of the solvent under reduced pressure afforded a brown gum. The 600 MHz ^{1}H NMR spectrum obtained in deuterated methanol resulted in a spectrum matching that reported by Bringmann and coworkers. **Figure 3.19** shows an expansion of the 600 MHz ^{1}H NMR spectrum obtained of the salt and that of the free base, showing the difference in the chemical shifts.
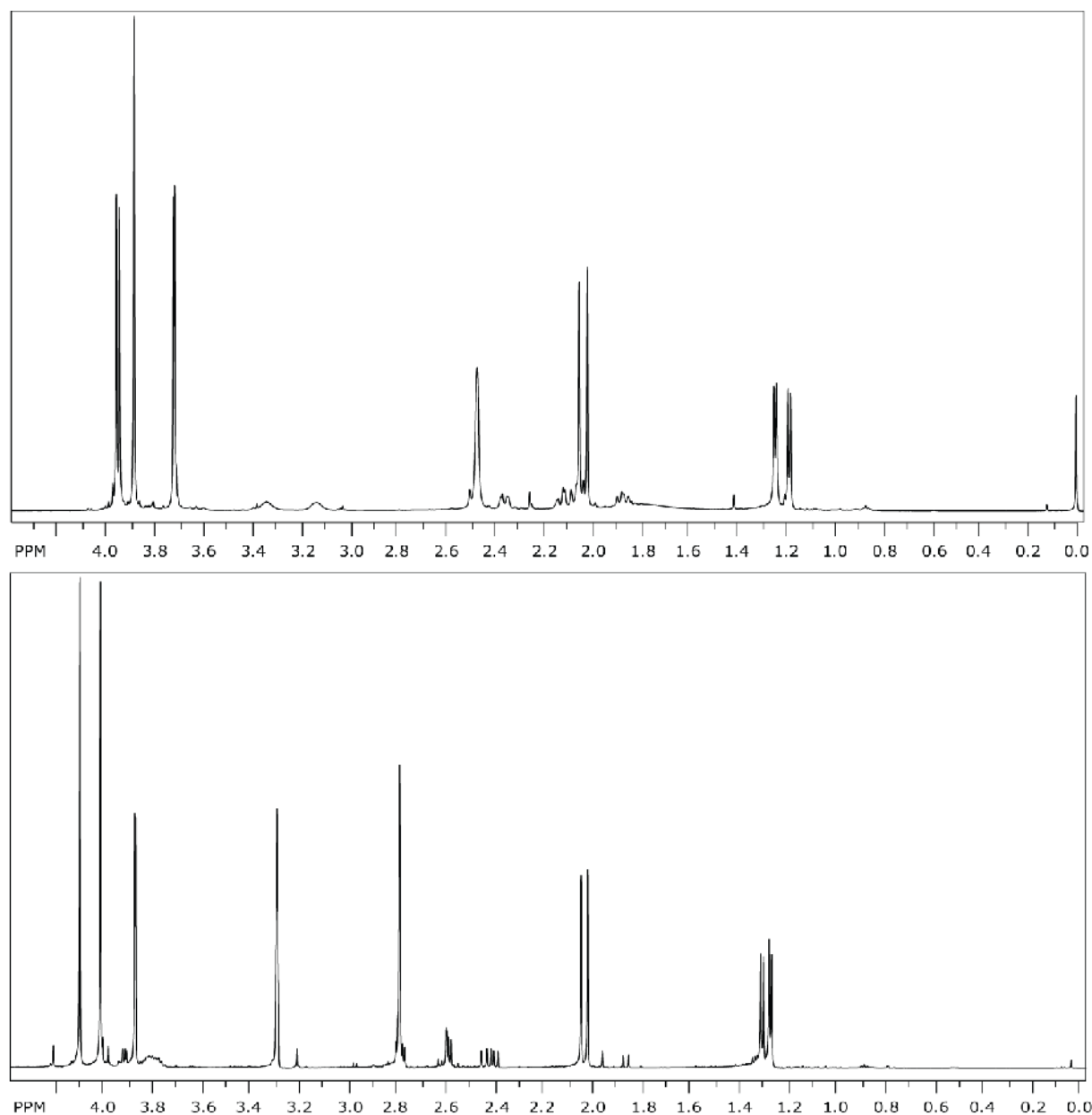
Figure 3.19   Expansion of the 600 MHz NMR spectra of ancistrotanzanine A as the free base in deuterated
chloroform (top) and as the TFA salt in deuterated methanol (below).

Having established that ancistrotanzanine A had been successfully prepared, efforts were focused
on the possibility of separating the atropisomers. HPLC analysis was undertaken with a
Symmetry C_{18} column and eluted with acetonitrile (with 0.05% trifluoroacetic acid) and water
(with 0.05% trifluoroacetic acid) with the gradient reported by Bringmann and coworkers. These
conditions, unfortunately, resulted in no baseline separation of the atropisomers with only one

peak observed with a retention time of 28.23 min. However, comparison to an authentic sample of ancistrotanzanine A was possible with Bringmann and coworkers providing 1 mg of ancistrotanzanine A for HPLC analysis. The retention time observed for the natural ancistrotanzanine A sample was found to be 28.22 min, within experimental error of the synthetic sample.

Given the lack of success at separating the atropisomers of ancistrotanzanine A with an achiral column use of a chiral OC-D column was investigated. Despite extensive experimentation, no separation was possible. Given their extensive experience and analytical resources a sample of the synthetic material was given to the Bringmann laboratory and they have analysed it with a number of chiral analytical HPLC columns. Unfortunately, despite their best efforts, no baseline separation was possible.

With the lack of success using HPLC, recrystallisation of the material was investigated. This also proved futile with no enhancement of either atropisomer observed after recrystallisation.

Given the lack of success of separating the atropisomers and having established that the stereocentre at C3 could be prepared with reasonable selectivity, investigations into the alkylation of the brucine coupled biaryls was undertaken. It was envisaged that if brucine had caused some atropselectivity then a change in the ratio of the atropisomers of ancistrotanzanine A from 1:1 would be observed. These results are presented in Section 3.12.

3.12   Studies into the Atropselectivity of the Brucine Coupled Biaryls

In Section 3.6 the preparation of "chiral" biaryl **3.44** was discussed. The reaction involved brucine promoted coupling of lithiated naphthol **1.104** with the aryllead species **3.20** at -78 $^{\circ}$C and is shown again here (**Scheme 3.39**). HPLC analysis was used to investigate if any atropselectivity had occurred, however, despite much experimentation, baseline separation could not be achieved. It was decided to now investigate if any atropselection had occurred by converting this material into ancistrotanzanine A. If atropselection had occurred, we would

observe a change in the 1:1 ratio of atropisomers of ancistrotanzanine A. We would also see a change in the atropisomeric ratio of the alkylated product.
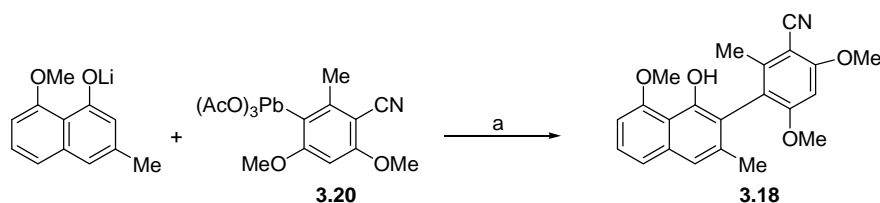
Scheme 3.39   Reagents and yields: (a) 2 eq brucine, 1.5 g/mol crushed 4Å sieves, toluene, -78 $^{\circ}$C, 6 h, 66%.

Alkylation of "chiral" biaryl **3.44** occurred in comparable yield to that obtained when the achiral coupled biaryl was used. Comparison of the 600 MHz ^{1}H NMR spectrum of the product to that obtained when the achiral material was used showed no change in the ratio of the atropisomers. Indeed, when the material was converted to ancistrotanzanine A a 1:1 mixture of atropisomers was observed. This was a surprising result as it was expected that some change in the ratio would be observed if brucine had resulted in some atropselectivity in the Pinhey-Barton reaction.

Reasons as to why we have not seen any atropselectivity through the use of brucine is unclear. A possible explanation is that the use of brucine to cause asymmetric induction in these systems may not be appropriate. This is supported in Chapter 2 where the use of brucine gave rise to no change in the ratio of atropisomers.

A more interesting possibility for the apparent lack of atropselectivity may be the result of racemisation of the biaryl during deprotonation. Given the close proximity of the MOM protecting group it is possible that it chelates to the lithium (**Figure 3.20**). Once the ring is formed it may lower the energy barrier of rotation, much like the lactone bridge in Bringmann's 'lactone method'. This would allow rotation about the biaryl axis and racemisation of the axis. Thus, any atropselectivity obtained from the brucine promoted ligand coupling reaction would be lost. In Section 3.14, this issue is explored further.
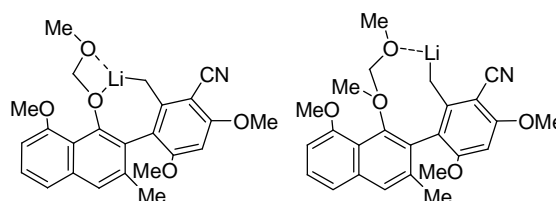
Figure 3.20   Chelating of the MOM protecting group during the alkylation of the biaryl **3.44** may result in a
lowering of the energy barrier for rotation around the biaryl axis.

Given these setbacks, it was decided to study the reduction of the imine of the isoquinoline
moiety. It was envisaged that the extra stereocentre present in the analogue would cause a greater
interaction between the compound and the chiral phase of the HPLC columns used for analysis,
thus perhaps facilitating the separation of the atropisomers (**Figure 3.21**). This compound could
also aid Bringmann's structure elucidation studies.

3.62
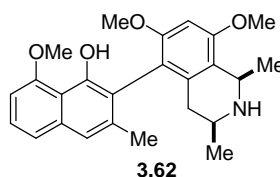
Figure 3.21   Proposed analogue of ancistrotanzanine A to be prepared to aid in biologically active natural
product structure elucidation studies undertaken by Bringmann and coworkers.

Ancistrotanzanine B **1.70** was isolated from the same plant extracts that gave ancistrotanzanine A
and has high biological activity[20]. It is a regio-isomer of methoxy protected ancistrotanzanine A
3.63 and to further aid the structure elucidation studies, it was deemed appropriate to prepare the
methoxy analogue of ancistrotanzanine A (**Figure 3.22**).

3.63

OMe protected ancistrotanzanine A

(**M**)-**1.70**

Ancistrotanzanine B
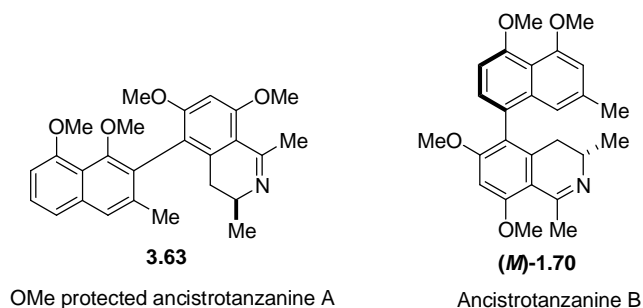
Figure 3.22   The proposed methoxy analogue of ancistrotanzanine A and the natural product ancistrotanzanine
B.

The preparation of these analogues of ancistrotanzanine A are discussed in the following sections.

3.13   Synthesis of the Tetrahydroisoquinoline Analogue of Ancistrotanzanine A

There are many methods available for the stereoselective reduction of 3.4-dihydroisoquinolines to give either the *cis* or *trans* configuration of the methyl groups at C1 and C3. It is well documented that reduction of 3,4-dihydroisoquinolines with sodium borohydride in methanol gives the *cis*-configured tetrahydroisoquinoline.[2,7] The use of the bulky reducing agent diisobutylaluminum hydride has also been shown to give the desired *cis*-selectivity when used for the reduction of isoquinolinium salts such as **3.65** (**Scheme 3.40**).[6] The observed selectivity is a result of the reducing agent delivering a hydride from the opposite face with respect to the methyl group at C3.
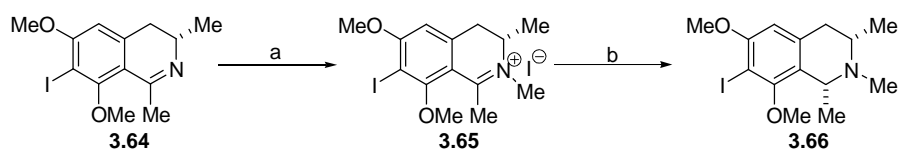
Scheme 3.40   Reagents and yield: (a) MeI, acetone, r.t.; (b) DIBAL, dichloromethane, -78 °C to r.t., 85% for 2 steps.

Using a combination of lithium aluminum hydride and trimethyl aluminium gives the *trans*-tetrahydroisoquinoline as a result of pre-coordination of the bulky trimethyl aluminium to the lone pair on nitrogen. This bulky group would sit away from the methyl at C3, thus blocking this face and forcing the hydride to be delivered from the same side as the methyl group (**Scheme 3.41**).
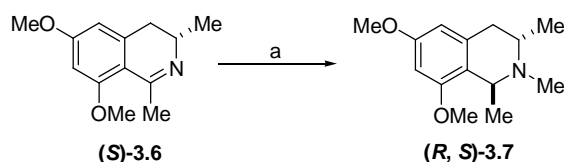
Scheme 3.41   Reagents and yield: (a) LiAlH$_4$/AlMe$_3$, THF, 85%, 92% de.

Given the *cis*-tetrahydroisoquinoline would have the methyl groups at C1 and C3 on the same face it was envisaged that this may cause a greater interaction between the compound and the chiral phase of the HPLC columns used for analytical purposes, thus facilitating the separation of the atropisomers. Stirring of ancistrotanzanine A in methanol with sodium borohydride overnight was found to result in a new product by TLC analysis. Examination of the 600 Mz ^{1}H NMR spectrum of the cude material confirmed the presence of two new resonances at δ 1.45 (C3 methyl appearing as a triplet due to overlap of the two doublets from the atropisomers) and at δ 4.31 (due to the new H at C1). Purification of the crude material by flash chromatography on reverse phase silica gel afforded the mixture of tetrahydroisoquinolines **3.62** in 98% yield (**Scheme 3.42**).
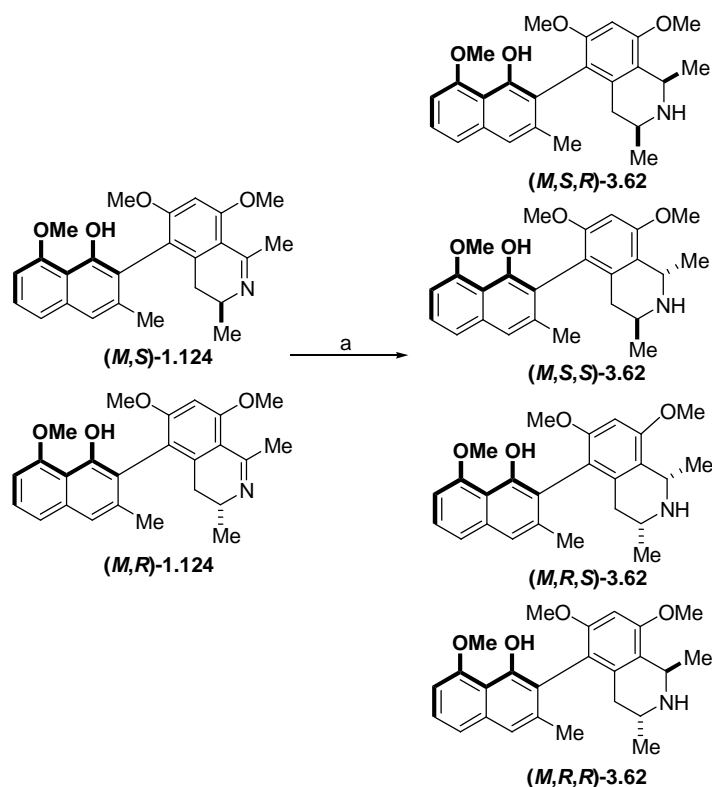
Scheme 3.42   Reagents and Yields (a) 6.0 eq NaBH$_4$, methanol, 0 °C for 30 min then r.t. o.n. (98%, 95:5 mixture of *cis/trans*). Please note that the ancistrotanzanine A used was a 1:1 mixture of atropisomers but for simplicity only one atropisomer is shown.

The 600 MHz ^{1}H NMR spectrum of the pure tetrahydroisoquinoline is shown in **Figure 3.23**. As can be seen the spectrum is quite complicated due to the presence of atropisomers and the minor *trans*-product. It is thought that the major product is *cis* due to the literature precedent that the conditions used to reduce the imine are known to give the *cis*-configuration as discussed earlier. Further evidence that the major compound is the *cis*-isomer, is that the ^{1}H NMR spectroscopic data for similar tetrahydroisoquinolines substituted at the 5 position shows that the CH hydrogen at C1 appears at lower chemical shift compared to the *trans*-diastereoisomer.[3] The ROESY spectrum of the mixture also indicated a weak correlation between the proton at C1 and the proton at C3, thus confirming that the major product is the *cis*-isomer and its atropisomer.
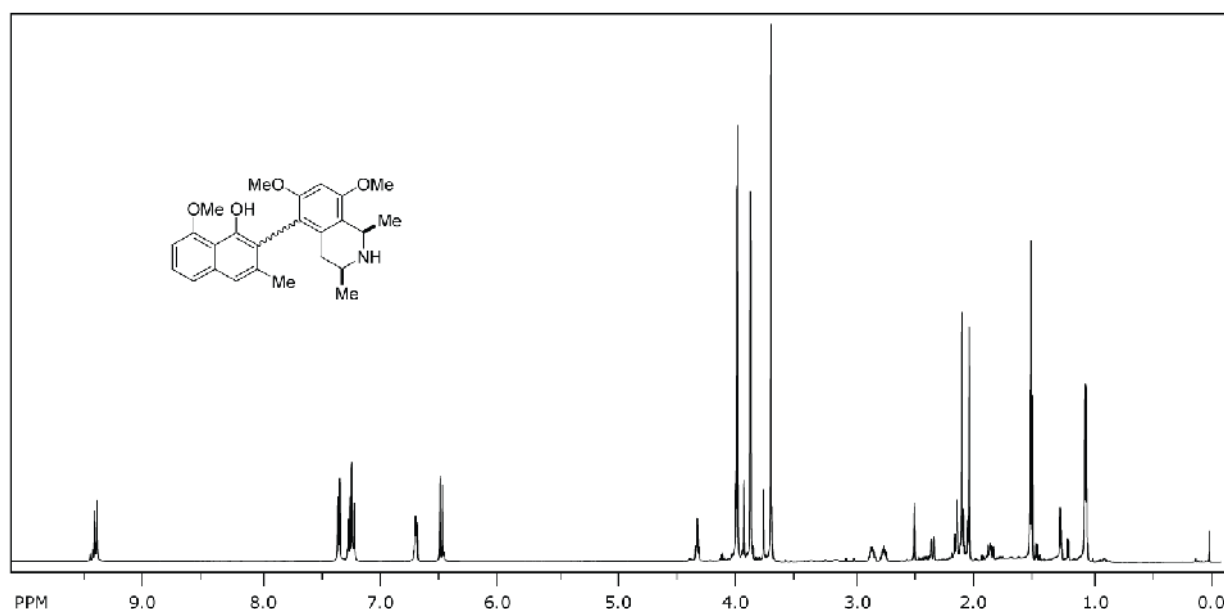
Figure 3.23   600 MHz ^{1}H NMR spectrum of the tetrahydroisoquinoline analogue of ancistrotanzanine A.

3.14   Synthesis of Methoxyancistrotanzanine A

The synthesis of methoxy protected analogue of ancistrotanzanine A should be readily prepared as a 1:1 mixture of atropisomers by using the same chemistry used in the synthesis of ancistrotanzanine A. The only difference to the sequence is that a methoxy protecting group has to be used in place of the MOM protecting group. Given that brucine was found to give no stereoselectivity, but a greater yield of the desired biaryl compound, the room temperature brucine coupling conditions were used to prepare the coupled biaryl **3.18** for the synthesis of

biaryl **3.67**. Protection of the hydroxyl functionality as the methoxy derivative was readily achieved using similar conditions to the MOM protection, but quenching with iodomethane in place of MOM-Cl, to give the methoxy ether protected product **3.67** in 95% yield (**Scheme 3.43**).
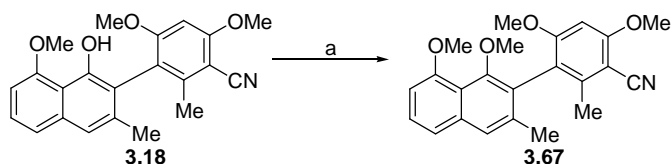
Scheme 3.43 Reagents and yields: (a) 2 eq NaH tetrahydrofuran, r.t., 30 min then 5 eq iodomethane, r.t., o.n., 95%.

Having prepared the methoxy protected product studies into the application of the alkylating conditions were pursued. Reaction of biaryl **3.67** under the standard alkylation conditions gave a new product. The 300 MHz ^{1}H NMR spectrum of the crude reaction material indicated the desired product to be present. Interestingly, integration of the *tert*-butyl groups indicated that the ratio of atropisomers was not 1:1, but in fact 63:37. After purification by flash chromatography, the ^{1}H NMR spectrum of the pure material indicated that the ratio of the major atropisomers was still 63:37 (**Scheme 3.44**). This is in stark contrast to that obtained for the MOM protected biaryl alkylated products, where the atropisomeric ratio of the major alkylated products was always 1:1.
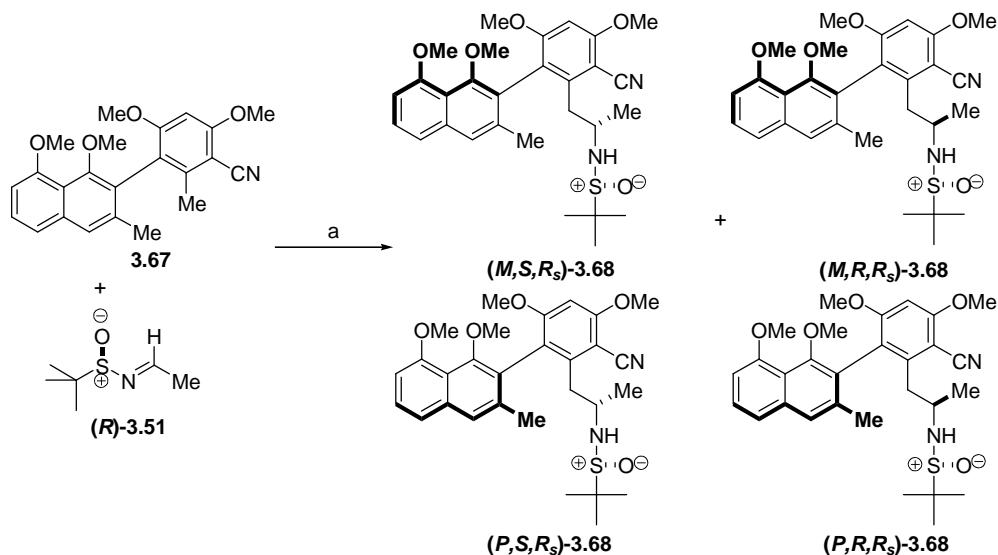
Scheme 3.44 Reagents and yields: (a) 3 eq LiNEth$_2$, tetrahydrofuran, 0.5 h, - 78 ^{o}C, then 1.3 eq (**R**)-**3.51**, tetrahydrofuran, -78 ^{o}C, 2 h, 67%.

In Section 3.12 it was suggested that the MOM protecting group of biaryl **3.44** may coordinate to the lithium during the alkylation reaction. This may lower the energy barrier for free rotation to occur around the biaryl axis, thus causing racemisation of the axis. Given there is only one site for coordination to the lithium for the methoxy group in biaryl **3.67** free rotation about the biaryl linkage may not be favoured. Consequently, any atropselectivity gained during brucine promoted ligand coupling would be retained. As this may be the case here, this surprising result is currently under investigation in our laboratory.

Reaction of sulfinamide **3.68** as a mixture of atropisomers with methyl lithium followed by stirring in acid afforded the desired methoxy protected analogue of ancistrotanzanine A (**Scheme 3.45**). The atropisomeric ratio was observed to still be 63:37 from the 300 MHz ^{1}H NMR spectrum of **3.63** from integration of the C3 protons of the respective atropisomers.
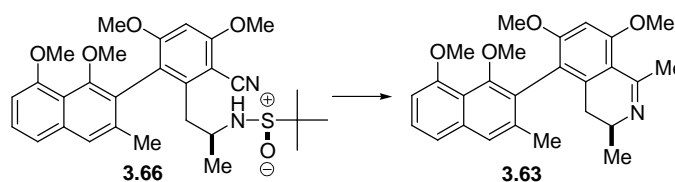
Scheme 3.45   Reagents and yields: (a) 5 eq methyl lithium, tetrahydrofuran, -78 ^{o}C – r.t., 1 h, then 2 M hydrochloric acid, r.t, 2 h, 37%.

Samples of the synthetically prepared ancistrotanzanine A (**1.124**), the tetrahydroisoquinoline **3.62** and the methoxy protected derivative **3.63** have been sent for biological testing and we are currently waiting on these results.

3.15   Conclusions

The first total synthesis of the naphthylisoquinoline alkaloid ancistrotanzanine A has been achieved. A key step of the total synthesis was the formation of the highly steric 5-3′-biaryl linkage via the Pinhey–Barton reaction. After much work the optimal conditions for the alkylation of biaryl **3.18** were found, which allowed the isoquinoline methodology developed by Davis to be successfully implemented for the completion of the synthesis. It was found that use

of the *tert*-butyl auxiliary of **3.51** gave greater diastereoselectivity for this key step, compared to the *p*-tolyl auxiliary of **3.15**.

Although the synthesis of ancistrotanzanine A was not able to be achieved atropselectively, this work constitutes one of the shortest syntheses of a naphthylisoquinoline alkaloid reported thus far in the literature and is summarised in **Scheme 3.46**.
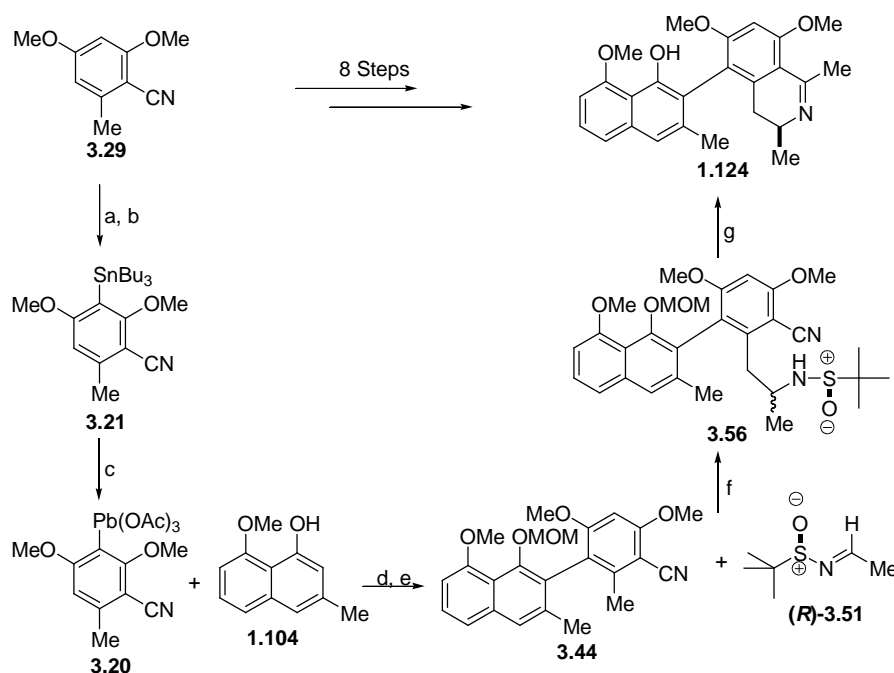
Scheme 3.46 Reagents and yields: (a) 1.02 eq I$_2$, 2 eq Ag$_2$SO$_4$, ethanol, 0 ^{o}C to r.t., 81%; (b) 2.5 eq *t*-BuLi, 1.25 eq ClSnBu$_3$, THF, - 95 ^{o}C - r.t., o.n., 75%; (c) 1.1 eq Pb(OAc)$_4$, cat HgOAc, dichloromethane, r.t., 81%; (d) 3 eq pyridine, CH$_2$Cl$_2$, 24 h, r.t., 77%; (e) 2 eq NaH, *N,N*-dimethylformamide, 5 eq MOM-Cl, r.t., o.n., 91%; (f) 3 eq LiNEt$_2$, THF, 0.5 h, - 78 ^{o}C, then (***R***)-**3.51**, THF, -78 ^{o}C, 2 h, 75% (g) 5 eq MeLi, THF, -78 ^{o}C to r.t. 1 h, then 2 M HCl, 2 h, 77%.

3.16 References

(1)   Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(2)   Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 913.

(3)   Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L.; Priest, O. P. *J. Org. Chem.* **1999**, *64*, 7184.

(4)   Rao, A. V. R.; Gurjar, M. K.; Ramana, D. V.; Chheda, A. K. *Heterocycles* **1996**, *43*, 1.

(5)   Bungard, C. J.; Morris, J. C. *Org. Lett.* **2002**, *4*, 631.

(6)   Bungard, C. J.; Morris, J. C. *J. Org. Chem.* **2006**, *71*, 7354.

(7)   Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901.

(8)   Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3855.

(9)   Murata, M.; Watanabe, S.; Masuda, Y. *Synlett* **2000**, 1043.

(10)   Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 2068.

(11)   Greenland, H.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1986**, *39*, 2067.

(12)   Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc* **1985**, *107*, 1299.

(13)   Tsubaki, K.; Morikawa, H.; Tanaka, H.; Fuji, K. *Tetrahedron*: *Asymmetry* **2003**, *14*, 1393.

(14)   Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc* **2002**, *124*, 5365.

(15)   Solladie-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343.

(16)   Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.

(17)   Chen, X.-Y.; Qui, X.-L.; Qing, F.-L. *Tetrahedron* **2008**, *64*, 2301.

(18)   Cogan, D. A.; Guangcheng, L.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.

(19)   Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.

(20)   Bringmann, G.; Dreyer, M.; Faber, J. H.; Dalsgaard, P. W.; Strk, D.; Jaroszewski, J. W.; Ndangalasi, H.; Mbago, F.; Brun, R.; Reichert, M.; Maksimenka, K.; Christensen, S. B. *J. Nat. Prod.* **2003**, *66*, 1159.

Chapter Four

Summary and Future Work

4.1   Summary and Future Work

In a study that has resulted in the total synthesis of ancistrotanzanine A (**1.24**), a 5,3′-linked naphthylisoquinoline alkaloid, several key issues were explored. Firstly, as described in Chapter 2, the key 5,3′ biaryl linkage was successfully formed via the Pinhey-Barton reaction to yield biaryl **2.18**, shown below. Studies into a diastereoselective Pinhey-Barton reaction using chiral hydrobenzoin acetal auxiliaries were found to have limited success. Changing the base from the achiral pyridine to the chiral brucine also gave no enhancement in the diastereoselectivity. From the results presented in Chapter 2, it was concluded that hydrobenzoin acetal auxiliaries were not appropriate for the diastereoselective synthesis of biaryl **2.17**.
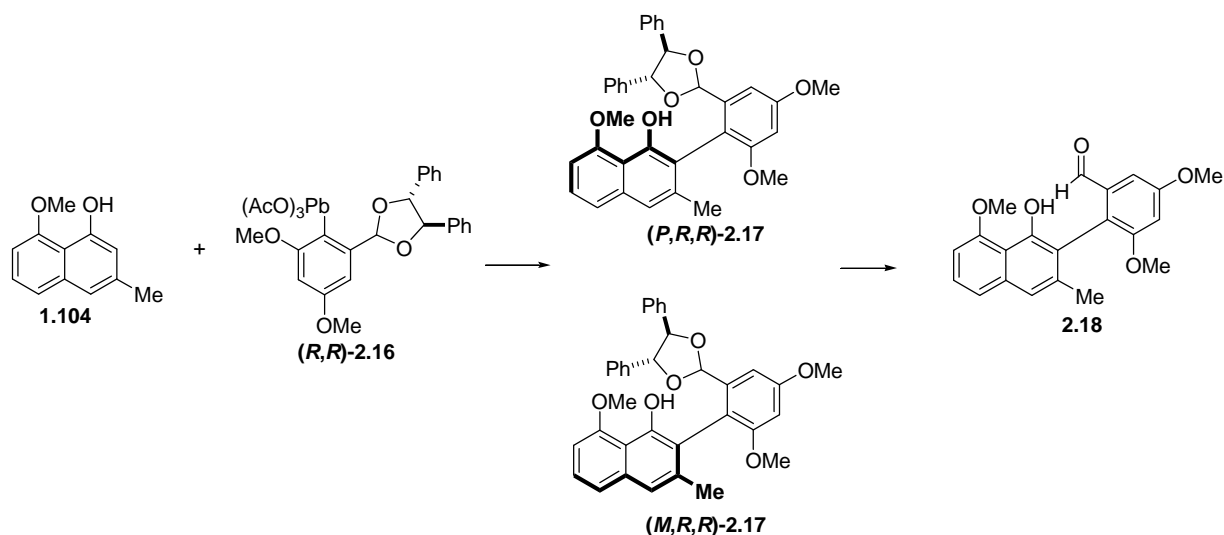
Acetal	Base	Yield	Relative Ratio of Atropisomers
(R,R)	Pyridine	71%	41:59
(R,R)	Brucine	36%	39:61
(S,S)	Pyridine	50%	35:65
(S,S)	Brucine	51%	41:59

Table 4.1   Summary of the conditions studied for the atropselective synthesis of biaryl **2.17**. For reaction conditions see section 2.6.

The search for alternative chiral bases to pyridine and alternative chiral auxiliaries is an ongoing area of research in our laboratories. In particular, the synthesis of chiral pyridine derivatives, such

as these illustrated in **Figure 4.1,** is being investigated and once prepared will be tested for asymmetric coupling of phenols with arylleads. If successful, the use of chiral pyridine derivatives has the advantage that the chiral pyridines may be accessed as either enantiomer, and thereby potentially allows the preparation of either atropisomer.
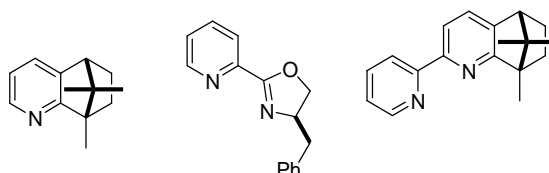
Figure 4.1   Examples of chiral pyridine derivatives being prepared in our group.

As the chiral acetal strategy outlined in Chapter 2 failed to yield an atropselective process, efforts were re-focused on a new approach to the naphthylisoquinolines. In Chapter 3, an overview of all the methods available for the synthesis of chiral 3,4-dihydroisoquinolines was provided. From this, it was decided to apply the alkylation of *o*-tolylnitriles with chiral sulfinimines, as originally developed by Davis, to the synthesis of naphthylisoquinolines. Ancistrotanzanine A was selected as the target as it had only recently been isolated and synthetic access would allow investigation into the biomedical potential.

Synthesis of the *o*-tolylnitrile lead reagent was readily achieved, but it was found that the amount of lead tetraacetate had to be carefully controlled to avoid side-reactions in the Pinhey-Barton reaction. After careful optimisation, the biaryl **3.18** was obtained in 77% yield. Application of the Davis methodology to the MOM protected biaryl **3.44** failed, with no reaction resulting. After much experimentation, it was established that the reaction was very sensitive to steric hindrance. A successful reaction was finally achieved by changing the base to lithium diethylamide. However, it was found the diastereoselection of the alkylation was quite low when *p*-tolyl sulfinimine was used. The use of the *t*-butane sulfinimine meant that the diastereoselection was significantly improved, with a ratio of 85:15 being obtained. After 3 more steps, the total synthesis was completed and ancistrotanzanine A was obtained, albeit as a 1:1 mixture of atropisomers. Efforts to separate the atropisomers formed failed and even the use of chiral HPLC failed to resolve the material.

To help overcome this issue, resolution of the Pinhey-Barton product was examined, but as the phenol was sterically hindered it was not possible to do this. The Pinhey-Barton reaction was carried out in the presence of brucine with the hope that the reaction could be atropselective. As the atropisomers could not be resolved by chiral HPLC, the material was carried through the synthesis. Surprisingly, there appeared to be no atropselection as the final material was still a 1:1 mixture.

To complete the Chapter, two analogues were prepared – the tetrahydroisoquinoline and the methoxy ether. It had been hoped that the tetrahydroisoquinoline would be easier to separate by chiral HPLC, but this did not prove to be the case.

From all of this work, it can be seen that application of the Davis methodology, with the use of the *t*-butane auxiliary, does allow for a rapid synthesis of the target molecule. However, the stereoselectivity of the alkylation process is not high enough and does limit the work that can be done on the biological activity. To overcome this, it is proposed that an alternate strategy should be explored as summarised in **Figure 4.2**.
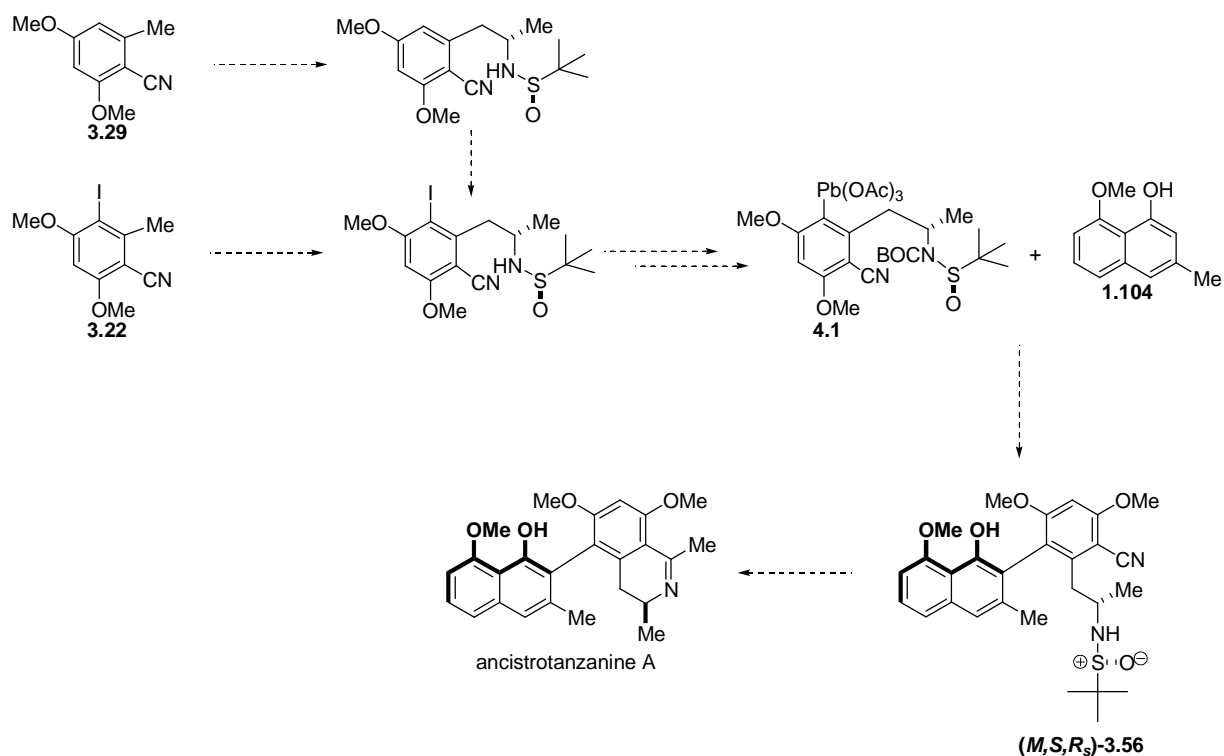
Figure 4.2   Proposed stereoselective synthesis of ancistrotanzanine A.

The alkylation of the model systems have already been shown to be very stereoselective and thus, allow for the C3 stereochemistry to be set. With this chiral material, the aryl lead species **4.1** could be prepared. As discussed in Chapter One the preparation of nitrogen containing aryllead species can be troublesome, but in their synthetic studies on diazonamide A, Konopelski and coworkers found the tyrosine fragment **4.2** readily underwent tin-lead exchange to give aryllead tricarboxylate **4.3** in 85% yield (**Scheme 4.1**).[1] This seems to be a reasonable precedent for this process.
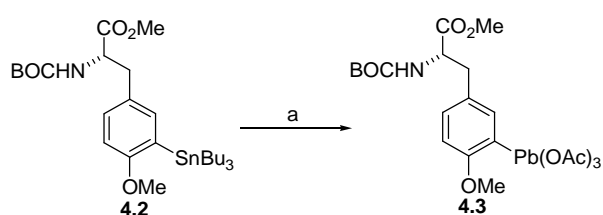
Scheme 4.1   Reagents and Yields: (a) Pb(OAc)$_4$, cat Hg(OAc)$_2$, CHCl$_3$, 40 °C, 85%.

The subsequent Pinhey-Barton arylation reaction and cyclisation protocol should afford ancistrotanzanine A. As the lead species is a single enantiomer, the Pinhey-Barton reaction will yield diastereomers and indeed, it may be possible to get some atropselectivity in the reaction. This strategy is currently being examined by the Morris group.

As discussed in this thesis, the application of the Davis chemistry appears to be susceptible to steric hindrance and indeed, this complicated the total synthesis of ancistrotanzanine A. However, many of the naphthylisoquinoline alkaloids do not have substituents at the C5 position and as such, this complication will not exist. Examining the synthesis of one of these alkaloids will allow us to determine the utility of the strategy. Dioncophylline E is an interesting target as it has excellent biological activity, it does not exhibit atropisomerism and it has yet to be synthesised.[2] It would be a good testing ground for the suitability of this strategy as a general method for synthesising the naphthylisoquinoline alkaloids.

To synthesise dioncophylline E, access to sulfinamide **4.4** is required. Sulfinamide **4.4** could be prepared from alkylation of biaryl **4.5** (**Figure 4.3**). Given the reduced steric environment at the reaction site of **4.5** the alkylation should proceed smoothly, unlike that observed for the total

synthesis of ancistrotanzanine A. The biaryl **4.5** could be generated by coupling naphthol **1.104** with aryllead **4.6**.
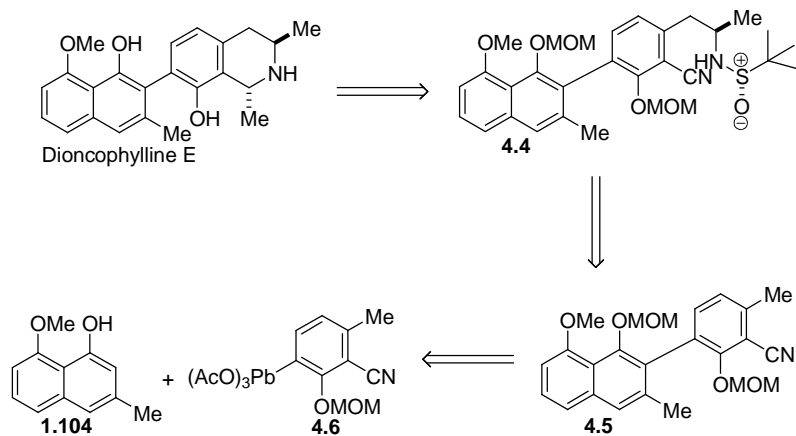
Figure 4.3   Retrosynthesis of dioncophylline E.

4.2   References

(1)   Konopelski, J. P.; Hottenroth, J. M.; Oltra, E. A.; Veliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609.

(2)   Bringmann, G.; Messer, K.; Wolf, K.; Muhlbacher, J.; Grune, M.; Brun, R.; Louis, A. M. *Phytochemistry* **2002**, *60*, 389.

Chapter Five

Experimental

5.1 General Experimental

Unless otherwise stated all reactions were performed in dry glassware under an atmosphere of oxygen free argon. After filtration of solutions to remove the drying agents, the solvents were removed under reduced pressure on a Büchi rotary evaporator and residue solvent was removed under high vacuum.

Physical and Spectroscopic Techniques

Melting points were obtained on a Reichert Thermovar Kofler apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Gemini 300 (300 MHz) or a Varian Unity Inova (600 MHz) spectrometer, with both running vNMR 6.1c software. Chemical shifts are reported in parts per million (ppm) on the δ scale. Chemical shifts in $CDCl_3$ were referenced relative to tetramethylsilane (TMS) (0 ppm) for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Chemical shifts in D_6C_6 were referenced relative to residue C_6D_5H (7.16 ppm) for ^{1}H NMR and C_6D_6 (128.4 ppm) for ^{13}C NMR. Chemical shifts in CD_3OD were referenced relative to residue CD_2HOH (3.31 ppm) for ^{1}H NMR and CD_3OD (49.2 ppm) for ^{13}C NMR. Chemical shifts in $(CD_3)_2CO$ were referenced relative to residue CD_3COCD_2H (2.05 ppm) for ^{1}H NMR and $(CD_3)_2CO$ (29.9 ppm) for ^{13}C NMR. Peak assignments are consistent with 2D NMR and/ or DEPT experiments. IR spectra were recorded on a Perkin Elmer FT-IR BX spectrophotometer, either as Nujol mulls, or neat with NaCl plates. ESI-MS were performed by direct injection into a Finnigan classic LC-Q mass spectrometer. HRMS were performed at Monash University, Australia. Elemental analysis was performed at the University of Otago, Dunedin Campus. Optical rotations were measured on an Atago AP-100 polarimeter. Samples were prepared in either a 5 mL or 10 mL volumetric flask at the stated concentration (g/100 mL) and in the stated spectrophotometric grade solvent. Measurements were taken at 589 nm (sodium D line), and at the stated temperature either in a 1 dm or 2 dm path length optical cell. Values are quoted as specific rotations calculated according to the following formula (**Figure 5.1**).

$$[a]_D^t = \frac{100a}{1c}$$

$[a]_D^t$ = specific rotation at t ^{o}C

α   = number of degress

l   = path length

c   = concentration in g/100 mL

Figure 5.1   Formula for calculation of specific rotation.

Chromatography

Analytical thin layer chromatography (TLC) was conducted on Merck, aluminium-backed silica plates 60 F_{254}, and visualised under short-wave ultraviolet light and stained with either a potassium permanganate or vanilla dip. Flash chromatography was routinely performed using Scharlau GE0048 silica gel 60 (0.04 – 0.06 mm), following published guidelines.[1] Where stated, reversed-phase flash chromatography employed Waters Preparative C_{18} reversed-phase silica (55-105 μm), which was recycled by successive washings with DMSO, CH_2Cl_2, MeOH + 1% TFA and MeOH.

Solvents and Reagents

Unless otherwise stated, reagents were purchased from commercial sources and used without further purification. Solvents were purified according to well established procedures.[2] In particular, dichloromethane, toluene, pyridine, *N,N*-diethylamine and *N,N*-diisopropylamine were freshly distilled from calcium hydride before use. Diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone before use. *N,N*-Dimethylformamide was dried by standing over 4Å molecular sieves for two periods of 24 h, before being stored under dry argon over fresh 4Å sieves. Ethanol was dried in a similar way to *N,N*-dimethylformamide, however 3Å sieves were used. Petroleum ether used had a boiling point of 40-60 ^{o}C. *n*-Butyllithium in hexanes , *t*-butyllithium in pentanes and methyllithium in diethyl ether were purchased from Aldrich and titrated with *N-o*-tolylpivalamide in THF as described by Suffert.[3] MOM-Cl was prepared by the

literature procedure[4] and stored in the freezer. Lead tetraacetate was dried over potassium hydroxide under vacuum for 2 h prior to use. 2-Bromo-6-methoxyphenol was prepared as described by Hoshino.[5]

Analytical HPLC

Analytical HPLC for the measurements of both the synthetic sample and natural sample of ancistrotanzanine A and biaryl **3.18** were carried out on a *Finnigan* HPLC system, with a Thermo Finnigan LCQ Deca XP[Plus] Ultra-Sensitive Ion trap LC/MS System with ESI probes and APCI probes and Surveyor LC pumps, autosampler and photodiode array detector.

5.2 Experiments Described in Chapter 2

2-Bromo-3,5-dimethoxybenzaldehyde (2.25)[6]
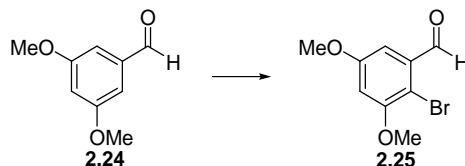
A solution of bromine in acetic acid (3.34 M, 3.0 mL, 10.0 mmol) was added dropwise to a solution of aldehyde **2.24** (1.60 g, 9.6 mmol) in acetic acid (20 mL) at 15 °C (ice bath) and stirred at this temperature for 30 min. The reaction was quenched with water (200 mL) where upon the product precipitated as a white solid. The solid was collected by filtration, then dissolved in dichloromethane and the organic solution washed successively with saturated aqueous sodium bicarbonate solution, water, saturated brine solution and dried (MgSO$_4$). The solvent was removed under reduced pressure to give the bromide **2.25** as a white solid (1.81 g, 77%).

Mp: 114-116 °C, Lit (115-116 °C).[6]

^{1}H NMR (300 MHz, CDCl$_3$): δ 3.86 [s, 3H], 3.92 [s, 3H], 6.72 [d, J = 2.9 Hz, 1H], 7.05 [d, J = 2.9 Hz, 1H], 10.42 [s, 1H].[6]

2-(2-Bromo-3,5-dimethoxyphenyl)-1,3-dioxolane (2.23)[7]
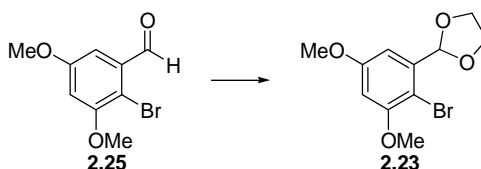
A solution of the aldehyde **2.25** (5.18 g, 21.1 mmol), 1,2-ethanediol (1.97 g, 31.7 mmol), and *p*-toluenesulfonic acid (300 mg, 1.6 mmol) in benzene (100 mL) was heated at reflux under Dean-Stark conditions for 16 h. After this time diethyl ether (100 mL) and saturated aqueous sodium bicarbonate solution (50 mL) were added. After separation, the organic extract was washed with water, saturated brine solution and dried over MgSO$_4$. The solvent was removed under reduced pressure to give a white precipitate. Purification by flash chromatography on silica gel, eluting with 10% ethyl acetate/ petroleum ether, gave **2.23** as a white solid (5.37 g, 88%).

Mp: 83-84 °C, Lit (84-84.5 °C).[7]

^{1}H NMR (300 MHz, CDCl$_3$): δ 3.83 [s, 3H], 3.87 [s, 3H], 4.03-4.12 [m, 2H], 4.13-4.22 [m, 2H], 6.13 [s, 1H], 6.51 [d, J = 3.0 Hz, 1H], 6.80 [d, J = 3.0 Hz, 1H]. [7]

(2-(1,3-Dioxolan-2-yl)-4,6-dimethoxyphenyl)tributylstannane (2.22)
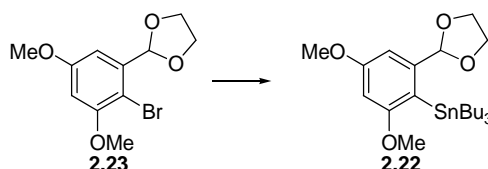
A solution of *t*-BuLi in pentane (1.1 M, 8.1 mL, 8.9 mmol) was added dropwise *via* syringe to a stirred solution of bromide **2.23** (1.146 g, 4.0 mmol) in dry THF (30 mL) at –95 °C. The resulting solution was stirred at –95 °C for 15 min and tributyltin chloride (1.2 mL, 4.4 mmol) was added dropwise and the reaction allowed to warm slowly to r.t. overnight. The resulting solution was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 3). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/petroleum ether, to give the title compound as a colourless oil (1.41 g, 71%).

^{1}H NMR (600 MHz, C$_6$D$_6$): δ 0.95 [t, J = 7.6 Hz, 9H, CH$_3$ of *n*-Bu], 1.21-1.33 [m, 6H, 1''-CH$_2$ of *n*-Bu], 1.42-1.49 [m, 6H, 3''-CH$_2$ of *n*-Bu], 1.64-1.77 [m, 6H, 2''-CH$_2$ of *n*-Bu], 3.28 [s, 3H, 4'-OMe], 3.42 [s, 3H, 6'-OMe], 3.36 [m, 2H, 4'-or-5'-CH$_2$ of acetal], 3.64 [m, 2H, 4'-or-6'-CH$_2$ of acetal], 5.93 [s, 1H, 2'-CH], 6.39 [d, J = 2.4 Hz, 1H, 5-ArH], 7.24 [d, J = 2.4 Hz, 1H, 3-ArH].
^{13}C NMR (150 MHz, C$_6$D$_6$): 12.4 (1''-C *n*-Bu), 14.0 (4''-C *n*-Bu), 27.9 (3''-C *n*-Bu), 29.7 (2''-C *n*-Bu), 54.8 (4-C-OMe and 6-C-OMe), 65.0 (4'-C and 5'-C), 98.4 (5-C), 103.4 (3-C), 104.6 (2'-C), 120.9 (1-C), 147.7 (2-C), 162.3 (6-C), 165.4 (4-C).
ESI-MS: 443 (M$^+$-Bu) 100%.
HRMS: Calcd for C$_{23}$H$_{41}$O$_4$^{120}Sn (MH$^+$) 501.2027, found 501.2025.

2-(1,3)-Dioxolan-2-yl)-4,6-dimethoxypheyl)triacetate lead (2.1)
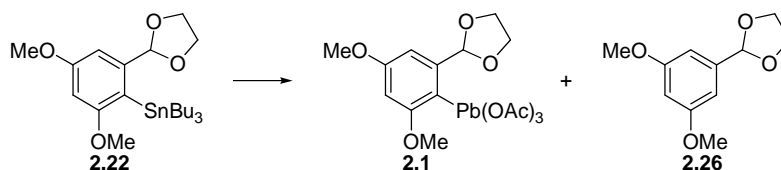
A solution of stannane **2.22** (0.875 g, 1.75 mmol) in dry dichloromethane (15 mL) was added via cannula to a solution of lead tetraacetate (1.17 g, 2.63 mmol) and mercury trifluoroacetate (60 mg, 0.14 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred at r.t. for 18 h, whilst protected from light. After this time the orange reaction mixture was filtered through a plug of Celite with dichloromethane (150 mL). The solvent was removed under reduced pressure and the residue washed with petroleum ether (x 4) to give a light yellow solid (1.46 g). This was found to consist of a mixture of **2.1** and **2.26** in a 88:12 ratio by integration of the two acetal C-H protons (δ 6.23 and 5.77) in the ^{1}H NMR spectrum. Due to stability concerns the mixture was used immediately in the next reaction. Recrystallisation of a small amount of the mixture (50 mg) from petroleum spirit/dichloromethane (1:1) gave 25 mg of pure **2.1**.

^{1}**H NMR** (600 MHz, CDCl$_3$): δ 2.09 [s, 9H], 3.83 [s, 3H], 3.90 [s, 3H], 3.97-4.11 [m, 4H], 6.23 [s, 1H], 6.56 [d, J = 4.0 Hz, 1H], 6.72 [d, J = 4.0 Hz, 1H].

^{13}**C NMR** (150 MHz, CDCl$_3$): δ 20.7, 55.9, 56.8, 65.0, 100.7, 101.2, 104.4, 141.1, 142.4 158.7, 163.7, 178.2.

2-Bromo-6-methoxyphenyl trifluoromethanesulfonate (2.28)[8]
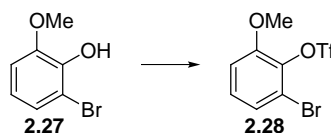
Triflic anhydride (12.6 mL, 74.6 mmol) was added dropwise via syringe to a solution of phenol **2.27**[5] (10.1 g, 49.7 mmol) in dry pyridine (30 mL) at 0 °C. The reaction was stirred at this temperature for 5 min, and then allowed to warm to r.t. overnight. The resulting solution was poured into water (100 mL) and extracted with diethyl ether (x 3). The combined organic extracts were washed in turn with 10% aqueous hydrochloric acid solution, water, saturated brine solution and dried (MgSO$_4$). The solvent was removed under reduced pressure to afford an oil, which was purified by bulb-to-bulb distillation (95 °C @ 3 mm/Hg) to afford the triflate as a yellow oil (15.8 g, 95%).

^{1}**H NMR** (300 MHz, CDCl$_3$): δ 3.91 [s, 3H], 6.79 [dd, J = 1.2, 5.3 Hz, 1H], 7.14-7.26 [m, 2H].[8]

6-Methoxycyclobutabenzen-1-one (2.29)[8]
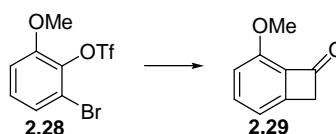
A stirred solution of triflate **2.28** (8.49 g, 25.3 mmol) and 1,1-diethoxyethylene (6.68 mL, 50.6 mmol) in dry THF (125 mL) was cooled to –95 °C. A solution of *n*-BuLi in hexanes (2.1 M, 24.1 mL, 50.6 mmol) was added dropwise via syringe and the resulting mixture stirred at –95 °C for 30 min and then allowed to warm to r.t. overnight. The resulting acetal was hydrolysed *in situ* by addition of 3% aqueous H_2SO_4 solution (40 mL), followed by vigorous stirring at r.t. for 3 h. The resulting solution was poured into water, and extracted with diethyl ether (*x* 3). The combined organic extracts were washed in turn with saturated aqueous sodium bicarbonate solution, water and saturated brine solution. The organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give an oily residue. Purification by flash chromatography on silica gel, eluting with 10% ethyl acetate/ petroleum ether, gave **2.29** as a yellow solid (2.60 g, 69%).

Mp: 33-34 °C, Lit (34-35 °C).[8]

^{1}H NMR (300 MHz CDCl$_3$): δ 3.93 [s, 2H], 4.11 [s, 3H], 6.80 [d, *J* = 8.4 Hz, 1H], 7.02 [d, *J* = 7.2 Hz, 1H], 7.43 [dd, *J* = 8.4, 7.2 Hz, 1H].[8]

1-(3-Chloropropynyl)-6-methoxybenzocyclobuten-1-ol (2.30)[8]
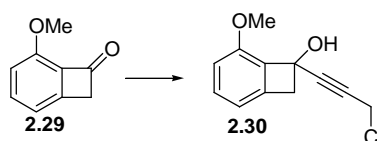
A solution of *n*-BuLi in hexanes (2.1 M, 3.8 mL, 7.98 mmol) was added dropwise to propargyl chloride (0.68 mL, 7.90 mmol) in dry ether (5 mL) at –95 °C. The resulting mixture was stirred at -95 °C for 20 min. A pre-cooled (-78 °C) solution of benzocyclobutenone **2.29** (907 mg, 6.12 mmol) in dry THF (8 mL) was added dropwise *via* cannula. The reaction was allowed to warm slowly to -60 °C over 1 h, and was maintained at this temperature for a further 3 h. After this time saturated aqueous ammonium chloride solution (20 mL) was slowly added. The mixture was then allowed to warm to room temperature and extracted with ethyl acetate (*x* 4). The organic layers were combined and washed with water, saturated brine solution and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude product, which was purified by flash

chromatography on silica gel, eluting with 20% ethyl acetate/petroleum ether, to give **2.30** as a yellow viscous oil (852 mg, 63%).[8]

¹H NMR (300 MHz); δ 2.59 [br s, 1H], 3.42 [d, *J* = 13.8 Hz, 1H], 3.74 [d, *J* = 14.1 Hz, 1H], 4.05 [s, 3H], 4.18 [s, 2H], 6.72-6.76 [m, 2H], 7.23-7.28 [m, 1H].[8]

6-Methoxy-1-propadienylbenzocyclobuten-1-ol (2.31)[8]
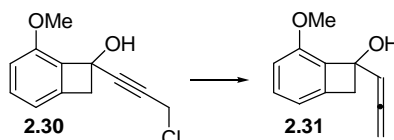
A solution of acetylene **2.30** (788 mg, 3.54 mmol) in dry THF (10 mL) was added dropwise to a suspension of LiAlH₄ (268 mg, 7.06 mmol) in dry THF (20 mL) at 0 °C. The resulting solution was allowed to warm to r.t. and stirred for 30 min. The reaction was cooled to 0 °C and quenched *via* the dropwise addition of 1 M aqueous hydrochloric acid solution (10 mL). Water (10 mL) was added and the product extracted with ethyl acetate (*x* 4). The organic fractions were combined and washed with water, saturated brine solution and dried (MgSO₄). The solvent was removed under reduced pressure to give **2.31** as a yellow oil (560 mg, 84%).

¹H NMR (300 MHz, CDCl₃): δ 2.59 [br s, 1H], 3.33 [d, *J* = 14.4 Hz, 1H], 3.51 [d, *J* = 14.4 Hz, 1H], 3.91 [s, 3H], 4.98 [m, 2H], 5.67 [dd, *J* = 6.6, 6.6 Hz, 1H], 6.69-6.75 [m, 2H], 7.19-7.25 [m, 1H].[8]

8-Methoxy-3-methylnaphthalen-1-ol (1.104)[8]
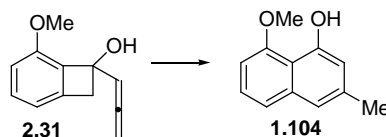
A solution of the allenic alcohol **2.31** (560 mg, 2.98 mmol) in dry toluene (8 mL) was heated at reflux for 4 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel eluting with 20% ethyl acetate/ petroleum ether to afford the title compound as a white solid (493 mg, 88%).

Mp: 93-94 °C, Lit (93-94 °C).[8]

¹H NMR (300 MHz, CDCl₃): δ 2.41 [s, 3H], 4.02 [s, 3H], 6.68 [dd, J = 7.2, 1.2 Hz, 1H], 6.73 [d, J = 1.5 Hz, 1H], 7.08 [br s, 1H], 7.22-7.33 [m, 2H], 9.23 [s, 1H].[8]

2-(2-1,3-Dioxolan-2-yl)-4,6-dimethoxyphenyl)-8-methoxy-3-methylnaphthalen-1-ol (2.2)
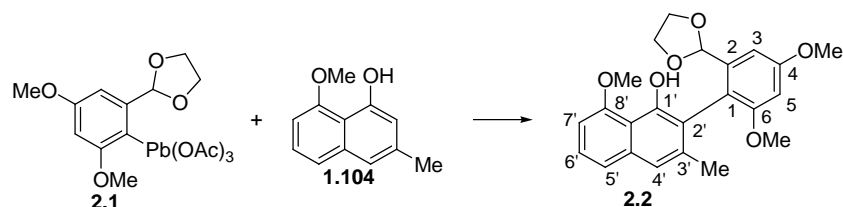
Dry pyridine (0.56 mL, 6.9 mmol) was added dropwise to a solution of crude aryllead compound **2.1** (1.36 g, 2.1 mmol) and naphthol **1.104** (0.435 g, 2.3 mmol) in dry dichloromethane (25 mL). The reaction was stirred at r.t, protected from light, for 24 h. After this time saturated aqueous ammonium chloride solution was added and the aqueous layer was extracted with dichloromethane (x 4). The combined organic extracts were washed with water, saturated brine solution and dried (MgSO₄). Removal of the solvent under reduced pressure gave a yellow oil, which was purified by flash chromatography on silica gel, eluting with 40% ethyl acetate/petroleum ether, to give **2.2** as a white solid (0.47 g, 55%).

Mp: 234-235 °C.

¹H NMR (600 MHz, CDCl₃): δ 2.10 [s, 3H, *Me*], 3.69 [s, 3H, 6-O*Me*], 3.78-3.80 [m, 2H, C*H*₂], 3.89 [s, 3H, 4-O*Me*], 3.97 [s, 3H, 8'-O*Me*], 4.04-4.08 [m, 2H, C*H*₂], 5.43 [s, 1H, C-*H*], 6.60 [d, J = 2.4 Hz, 1H, 5-Ar-*H*], 6.70 [dd, J = 0.6 Hz, J = 7.2 Hz, 1H, 7'-Ar-*H*], 6.88 [d, J = 2.4, 1H, 3-Ar-*H*], 7.22 [s, 1H, 4'-Ar-*H*], 7.26-7.29 [m, 1H, 6'-Ar-*H*], 7.35 [dd, J = 0.6 Hz, J = 8.4 Hz, 1H, 5'-Ar-*H*], 9.43 [s, 1H, O*H*].

¹³C NMR (150 MHz, CDCl₃): 20.6 (*Me*), 55.4 (4-O*Me*), 55.86 (6-O*Me*), 55.88 (8'-O*Me*), 65.0 (*C*H₂), 65.4 (*C*H₂), 100.1 (5-Ar-*C*), 101.6 (C-H), 101.7 (3-Ar-*C*), 103.0 (7-Ar-*C*), 113.3 (8a-Ar-*C*), 118.1 (3'-Ar-*C*), 118.3 (4'-Ar-*C*), 119.2 (4-Ar-*C*), 121.2 (5'-Ar-*C*), 125.3 (6-Ar-*C*), 136.1 (4a-Ar-*C*) 138.1 (2-Ar-*C*), 139.0 (2'-Ar-*C*), 151.0 (1'-Ar-*C*), 156.2 (8-*Ar*-OMe), 157.9 (6'-*Ar*-OMe), 160.2. (4'-*Ar*-OMe).

IR (Nujol Mull): 3380, 1600, 1584 cm⁻¹.

ESI-MS: 397 (100%).

Analysis: Calcd for C 69.68, H 6.10, Found C 69.98, H 6.22.

2-(1-Hydroxy-8-methoxy-3-methylnaphthalen-2-yl)-3,5-dimethoxybenzaldehyde (2.18)
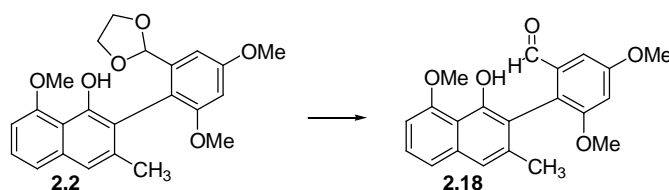
Aqueous sulfuric acid (3%, 10 mL) was added in one portion to a solution of acetal compound **2.2** (206 mg, 0.52 mmol) in tetrahydrofuran (25 mL). The reaction mixture was stirred vigorously at r.t. for 2 h and then extracted with ethyl acetate (*x* 4) and the organic extracts combined. These extracts were washed with saturated aqueous sodium bicarbonate solution, water, brine and dried (MgSO$_4$). Removal of the solvent under reduced pressure afforded a residue, which was purified by flash chromatography on silica gel, eluting with dichloromethane, to give **2.18** as a light yellow solid (164 mg, 91%).

Mp: 67-69 $^{\circ}$C.

^{1}H NMR (300 MHz, CDCl$_3$): δ 2.04 [s, 3H], 3.74 [s, 3H], 3.91 [s, 3H], 3.99 [s, 3H], 6.74 [dd, *J* = 1.2, 7.5 Hz, 1 H], 6.83 [d, *J* = 2.7 Hz, 1H], 7.18 [d, *J* = 2.7 Hz, 1H], 7.28-7.39 [m, 3H], 9.55 [s, 1H], 9.66 [s, 1H].

^{13}C NMR (75 MHz , CDCl$_3$): 20.6, 55.6, 56.0, 100.5, 103.6, 105.3, 113.1, 115.5, 117.2, 118.8, 121.2, 124.4, 126.0, 135.6, 136.3, 138.0, 151.6, 156.1, 158.5, 160.3, 192.6.

IR (Nujol Mull): 1573, 1602, 1632, 1691, 3338 cm^{-1}.

ESI-MS: 353 (50%), 335 (100%), 320 (75%).

HRMS: Calcd for C$_{21}$H$_{21}$O$_5$ (M+H) 353.13890, found 353.13892.

3,5-Dimethoxy-2-(8-methoxy-1-(methoxymethoxy)-3-methylnaphthalen-2-yl)benzaldehyde (2.32)
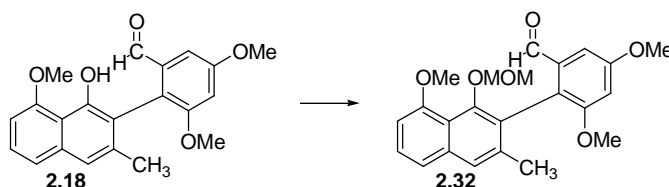
A solution of naphthol **2.18** (93 mg, 0.26 mmol) in dry *N,N*-dimethylformamide (3 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.52 mmol) in dry *N,N*-dimethylformamide (3 mL). The reaction was stirred for 1 h at r.t. resulting in a turbid

red solution. Methoxymethyl chloride (0.1 mL, 1.3 mmol) was added dropwise and the reaction stirred at r.t. overnight. The reaction was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 4). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 30% ethyl acetate/petroleum spirit, to give the title compound as a white solid (106 mg, 100%).

Mp: 112-113 ^{o}C.

^{1}H NMR (600 MHz, CDCl$_3$): δ 2.04 [s, 3H, Me], 2.78 [s, 3H, OMe of MOM], 3.76 [s, 3H, 5-OMe], 3.91 [s, 3H, 3-OMe], 3.94 [s, 3H, 8'-OMe], 4.81 [d, *J* = 6.6 Hz, 1H, CH$_2$ of MOM], 4.97 [d, *J* = 6.6 Hz, 1H, CH$_2$ of MOM], 6.78 [d, *J* = 2.4 Hz, 1H, 4-H], 6.83 [dd, *J* = 1.2, 7.2 Hz, 1H 7'-H], 7.17 [d, *J* = 2.4 Hz, 1H, 6-H], 7.36-7.41 [m, 2H, 5'-H and 6-H'], 7.52 [s, 1H, 4'-H], 9.64 [s, 1H].

^{13}C NMR (150 MHz, CDCl$_3$): δ 20.8 (Me), 55.65 (3-OMe), 56.00 (5-OMe), 56.02 (8'-OMe), 56.15 (O-CH$_2$-O*Me*), 100.1 (6-C), 100.8 (CH$_2$), 104.5 (4-C), 105.4 (7'-C), 118.3 (4a'-C), 120.6 (5'-C), 124.4 (4'-C), 125.4 (2-C), 125.6 (3'-C), 126.4 (6'-C), 135.8 (1-C), 136.8 (2'-C), 137.2 (8a-C), 151.4 (1'-C), 155.8 (8'-C), 159.0 (3-C), 160.2 (5-C), 192.1 (C=O).

IR (Neat): 1696, 1602, 1565 cm^{-1}.

ESI-MS: 419 (100%).

HRMS: Calcd for C$_{23}$H$_{24}$NaO$_6$ (MNa$^+$) 419.1471, found 419.1465.

(4*R*,5*R*)-2-(2-Bromo-3,5-dimethoxyphenyl)-4,5-diphenyl-1,3-dioxolane (2.34)
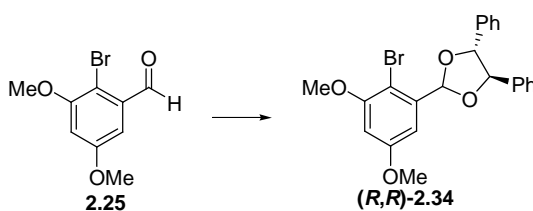
A solution of the aldehyde **2.25** (0.402 g, 1.6 mmol), (*R*,*R*)-(+)-hydrobenzoin (0.514 g, 2.4 mmol), and *p*-toluenesulfonic acid (5 mg, 0.03 mmol) in benzene (40 mL) was heated at reflux under Dean-Stark conditions for 24 h. After this time the reaction mixture was cooled to r.t., and saturated aqueous sodium bicarbonate solution (40 mL) and ethyl acetate (30 mL) were added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution, dried (MgSO$_4$) and the solvent removed under reduced pressure to give a white solid. Purification by flash

chromatography on silica gel, eluting with 20% ethyl acetate/petroleum spirit, gave **(*R,R*)-2.34** as a white solid (0.653 g, 92%).

$[\alpha]_D^{22\,^\circ C} = +16$ (0.5, CHCl$_3$).

Mp: 39-40 $^\circ$C

^{1}H NMR (600 MHz, CDCl$_3$): δ 3.83 [s, 3H], δ 3.86 [s, 3H], δ 4.97-5.00 [m, 2H], δ 6.54 [d, *J* = 3.0 Hz, 1H], δ 6.68 [s, 1H], δ 7.06 [d, *J* = 3.0 Hz, 1H], δ 7.26-7.37 [m, 10H].

^{13}C NMR (150 MHz, CDCl$_3$): 55.6 (OMe), 56.4 (OMe), 85.2 (C-H), 87.1 (C-H), 100.6 (C-H), 103.4 (Ar-H), 103.8 (C), 103.9 (Ar-H), 126.2 (Ar-H), 126.9 (Ar-H), 128.2 (Ar-H), 128.5 (Ar-H), 128.5 (Ar-H), 128.6 (Ar-H), 136.4 (Q), 138.2 (Q), 138.4 (Q), 156.8 (Q), 159.8 (Q).

ESI-MS: (M^{81}BrNa$^+$) 465 (96%) , (M^{79}BrNa$^+$) 463 (100%), 247 (47%),245 (50%).

HRMS: Calcd for C$_{23}$H$_{21}$^{79}BrNaO$_4$ (MNa$^+$) 463.0521, found 463.0511.

Tributyl (2-((4*R*,5*R*)-4,5-diphenyl-1,3-dioxolane-2-yl))-4,6-dimethoxyphenyl)stannane (2.33)
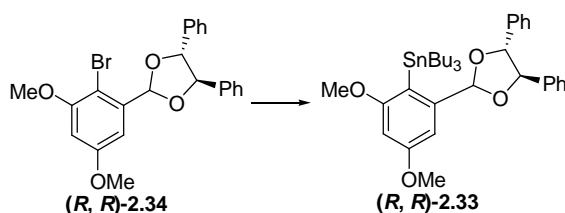
A solution of *t*-BuLi in pentane (1.3 M, 2.5 mL, 3.3 mmol) was added dropwise *via* syringe to a stirred solution of bromide **(*R,R*)-2.34** (0.653 g, 1.5 mmol) in dry tetrahydrofuran (25 mL) at –95 $^\circ$C. The resulting bright yellow solution was stirred at –95 $^\circ$C for 15 min and tributyltin chloride (0.61 mL, 2.25 mmol) added dropwise. The reaction was allowed to warm slowly to r.t. overnight. The resulting solution was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 3). Evaporation of the organic extracts under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel, eluting with 5% ethyl acetate/petroleum ether and 1% triethylamine, to give the title compound as a colourless oil (0.573 g, 59%).

$[\alpha]_D^{23} = +30$ (0.5, CHCl$_3$).

^{1}H NMR (600 MHz, (CD$_3$)$_2$CO): δ 0.83-0.85 [m, 9H], δ 1.10-1.12 [m, 6H], 1.28-1.35 [m, 6H], 1.51-1.56 [m, 6H], 3.82 [s, 3H], 3.86 [s, 3H], 4.94-4.97 [m, 2H], 6.30 [s, 1H], 6.56 [d, *J* = 2.4 Hz, 1H], 7.15 [d, *J* = 2.4 Hz, 1H], 7.34-7.39 [m, 10H].

^{13}**C NMR** (150 MHz, (CD$_3$)$_2$CO): δ 12.3, 13.7, 27.9, 29.6, 55.2, 55.5, 85.8, 87.7, 98.1, 104.1, 105.6, 105.7, 120.7, 127.2, 127.6, 128.8, 128.99, 129.02, 137.2, 138.9, 148.0, 162.6, 165.7.

ESI-MS: (MNa$^+$) 675 (100%), 413 (25%), 323 (25%), 267 (20%).

HRMS: Calcd for C$_{35}$H$_{48}$NaO$_4$^{127}Sn (MNa$^+$) 675.2472; found 675.2467.

(2-((4*R*,5*R*)-4,5-Diphenyl-1,3-dioxolane-2-yl))-4,6-dimethoxyphenyl)lead triacetate (2.16)
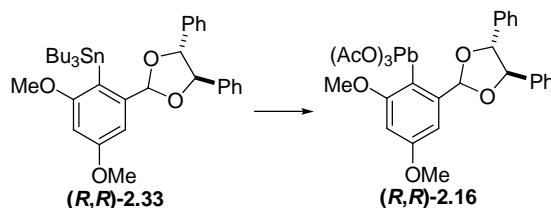
Method 1 (using 1.2 equivalents of lead tetraacetate)

A solution of stannane **(*R,R*)-2.33** (228 mg, 0.35 mmol) in dry dichloromethane (3 mL) was added via cannula to a solution of lead tetraacetate (206 mg, 0.42 mmol) and mercury trifluoroacetate (9 mg, 0.02 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at r.t. for 24 h whilst protected from light. After this time the orange reaction mixture was filtered through a plug of Celite with dichloromethane (30 mL). The solvent was removed under reduced pressure to give a residue, which was washed with petroleum ether (*x* 4) to give a light yellow solid (239 mg). This was found to consist of a mixture of **(*R,R*)-2.16** and **(*R,R*)-2.36** in a ratio of 86% aryllead and 14% demetalated by integration of the CH protons of the acetal group of the two compounds at δ 6.36 and δ 6.68.

Method 2 (using 2 equivalents of lead tetraacetate)

A solution of stannane **(*R,R*)-2.33** (0.463g, 0.71 mmol) in dry dichloromethane (10 mL) was added via cannula to a solution of lead tetraacetate (0.630 mg, 1.42 mmol) and mercury trifluoroacetate (17 mg, 0.05 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred at r.t. for 24 h whilst protected from light. After this time the orange reaction mixture was filtered through a plug of Celite with dichloromethane (50 mL). The solvent was removed under reduced pressure to give a light yellow precipitate, which was washed with petroleum ether (*x* 4) to give the title compound as a light yellow solid (481 mg, 90%).

^{1}**H NMR** (300 MHz, CDCl$_3$): δ 1.8-2.15 [br s, 9H], 3.85 [s, 3H], 3.92 [s, 3H], 4.97-5.07 [m, 2H], 6.63 [d, *J* = 2.7 Hz, 1H], 6.68 [s, 1H], 6.85 [d, *J* = 2.7 Hz, 1H], 7.19-7.40 [m, 10H].

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.3, 20.4, 55.9, 56.8, 86.0, 87.5, 100.9, 101.7, 105.0, 126.7, 126.9, 128.58, 128.64, 128.9, 135.1, 136.2, 140.2, 158.7, 163.2, 178.0.

(4*R*,5*R*)-2-(3,5-Dimethoxyphenyl)-4,5-diphenyl-1,3-dioxolane (2.35)
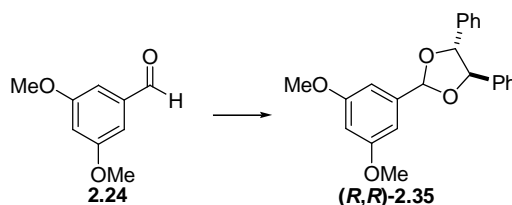
A solution of the aldehyde **2.24** (0.258 g, 1.6 mmol), (*R,R*)-(+)-hydrobenzoin (0.514 g, 2.4 mmol), and *p*-toluenesulfonic acid (5 mg, 0.03 mmol) in benzene (40 mL) was heated at reflux under Dean-Stark conditions for 16 h. After this time the reaction mixture was cooled to r.t., saturated sodium bicarbonate solution (20 mL) and ethyl acetate (10 mL) were added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution, dried (MgSO$_4$) and the solvent removed under reduced pressure to give a white solid. This was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate/petroleum spirit, to give **(*R,R*)-2.35** as a viscous oil (0.555 g, 96%).

$[\alpha]_D^{23^0 C} = +30$ (0.5, CHCl$_3$)

^{1}H NMR (300 MHz, CDCl$_3$): δ 3.83 [s, 6H], 4.90-4.97 [m, 2H], 6.36 [s, 1H], 6.52 [t, *J* = 2.1 Hz, 1H], 6.84 [d, *J* = 2.1 Hz, 2H], 7.29-7.39 [m, 10H].

^{13}C NMR (75 MHz, CDCl$_3$): δ 55.4 (OMe) , 85.1 (CH), 87.1 (CH), 101.4 (CH), 104.3 (Ar-H), 126.4 (Ar-H), 126.9 (Ar-H), 128.2 (Ar-H), 128.51 (Ar-H), 128.55 (Ar-H), 136.4, 137.8, 140.6, 160.9.

ESI-MS: (MNa$^+$) 385 (100%).

HRMS: Calcd for C$_{23}$H$_{23}$O$_4$ (MH$^+$) 363.15963, found 363.15940.

2-(2-((4*R*,5*R*)-4,5-Diphenyl-1,3-dioxolane-2-yl)-8-methoxy-3-methylnaphthalen-1-ol (2.17)
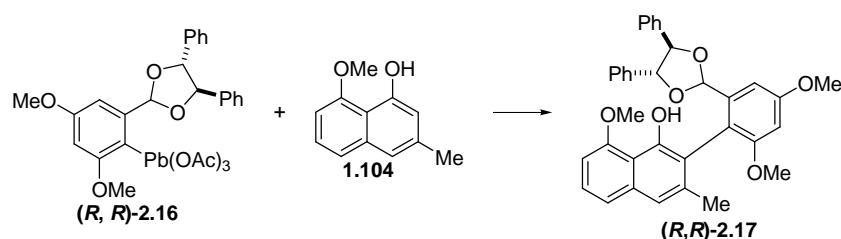
Method 1 (Use of pyridine to promote the reaction.)

A solution of naphthol **1.104** (45 mg, 0.24 mmol) in dry dichloromethane (2 mL) was added via cannula to a solution of crude aryllead **(R,R)-2.16** (0.212 mg, 0.24 mmol) in dry dichloromethane (2 mL), followed directly by the addition of dry pyridine (0.06 mL, 0.72 mmol). The reaction was stirred at r.t. for 24 h at which time it was quenched with saturated aqueous ammonium chloride (10 mL) and the aqueous layer was extracted with dichloromethane (*x* 3). The combined organic extracts were washed successively with 10% aqueous hydrochloric acid solution, water, saturated brine solution and then dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow solid. Purification by flash chromatography on silica gel eluting with 40% ethyl acetate/ petroleum ether gave **(R,R)-2.17** as a yellow solid (93 mg, 71%). Integration of the acetal C-H protons (δ 5.93 and 5.98) showed the diastereoisomers to be in a 41:59 ratio.

Method 2 (Use of brucine to promote the reaction.)

A solution of *n*-BuLi in hexanes (0.15 mL, 1.9 M, 0.28 mmol) was added dropwise to a solution of naphthol **1.104** (0.53 g, 0.28 mmol) in dry toluene (4 mL) at 0 ^{o}C. The light orange solution was stirred at 0 ^{o}C for 15 mins and then cooled to -78 ^{o}C. Brucine (0.221 g, 0.56 mmol), aryllead **(R,R)-2.16** (0.210 g, 0.28 mmol) and crushed 4Å sieves were then added sequentially and the reaction mixture stirred at -78 ^{o}C for 4 h. After this time the reaction mixture was filtered through a plug of Celite with dichloromethane (25 mL) and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography, eluting with 60% ethyl acetate/petroleum spirit, to give the title compound as a light yellow solid (0.56 mg, 36%). Integration of the acetal C-H protons at δ 5.93 and 5.98 showed the diastereoisomers to be in a 39:61 ratio.

Mp: 71 – 75 ^{o}C

All spectroscopic data matched that of the (*S,S*)-coupled product and is given for this compound.

(4*S*,5*S*)-2-(2-Bromo-3,5-dimethoxyphenyl)-4,5-diphenyl-1,3-dioxolane ((*S*,*S*)-2.34)
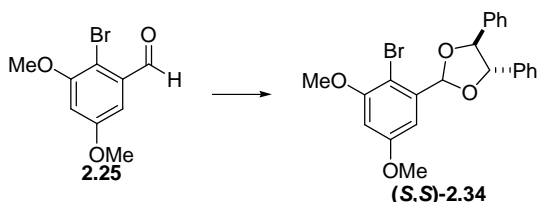
A solution of the aldehyde **2.25** (0.41 g, 1.7 mmol), (*S*,*S*)-(-)-hydrobenzoin (0.56 g, 2.6 mmol), and *p*-toluenesulfonic acid (5 mg, 0.03 mmol) in benzene (40 mL) was heated at reflux under Dean-Stark conditions for 24 h. After this time the reaction mixture was cooled to r.t., saturated aqueous sodium bicarbonate solution (40 mL) and ethyl acetate (30 mL) were added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated aqueous brine solution, dried (MgSO₄) and the solvent removed under reduced pressure to give a white solid. This was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate/petroleum spirit to give **(*S*,*S*)-2.34** as a white solid (0.653 g, 89%).

All spectroscopic data matched that obtained for the (*R*, *R*)-enantiomer.

$[\alpha]_D^{22^0 C}$ = - 16 (0.5, CHCl₃)

Mp: 43-44 °C

All spectroscopic data matched that of the (*R*, *R*)-enantiomer.

Tributyl-(2-((4*S*,5*S*)-4,5-diphenyl-1,3-dioxolane-2-yl))-4,6-dimethoxyphenyl)stannane ((*S*, *S*)-2.33)
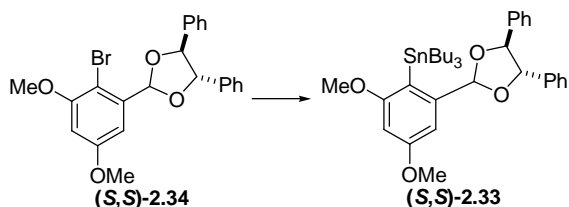
A solution of *t*-BuLi in pentane (1.2 M, 1.7 mL, 2.0 mmol) was added dropwise *via* syringe to a stirred solution of bromide **(*S*,*S*)-2.34** (0.402 g, 0.9 mmol) in dry tetrahydrofuran (25 mL) at –95 °C. The resulting bright yellow solution was stirred at –95 °C for 15 min and tributyltin chloride

(0.38 mL, 1.4 mmol) added dropwise. The reaction was allowed to warm slowly to r.t. overnight. The resulting solution was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 3). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel, eluting with 5% ethyl acetate/petroleum ether and 1% triethylamine, to give the title compound as a colourless oil (0.373 g, 57%).

$[\alpha]_D^{23^0 C}$ = - 20 (0.5, CHCl$_3$)

All spectroscopic data matched that obtained for the (*R*,*R*)-enantiomer.

(2-((4*S*,5*S*)-4,5-Diphenyl-1,3-dioxolane-2-yl))-4,6-dimethoxyphenyl)lead triacetate ((*S*,*S*)-2.16)
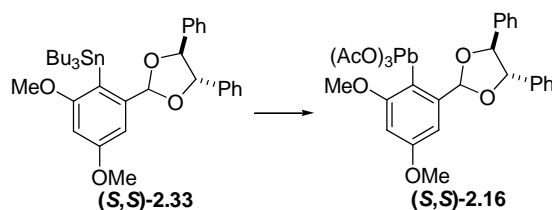
A solution of stannane **(*S*, *S*)-2.33** (0.348 g, 0.53 mmol) in dry dichloromethane (6 mL) was added via cannula to a solution of lead tetraacetate (470 mg, 1.06 mmol) and mercury trifluoroacetate (13 mg, 0.03 mmol) in dry dichloromethane (6 mL). The reaction mixture was stirred at r.t. for 24 h whilst protected from light. After this time the orange reaction mixture was filtered through a plug of Celite with dichloromethane (40 mL). The solvent was removed under reduced pressure to give a light yellow precipitate which was washed with petroleum ether (*x* 4) to give the title compound as a light yellow solid (387 mg, 98%).

All spectroscopic data matched that obtained for the (*R*,*R*) enantiomer.

2-(2-((4*S*,5*S*)-4,5-Diphenyl-1,3-dioxolane-2-yl)-8-methoxy-3-methylnaphthalen-1-ol ((*S*,*S*)-2.17)
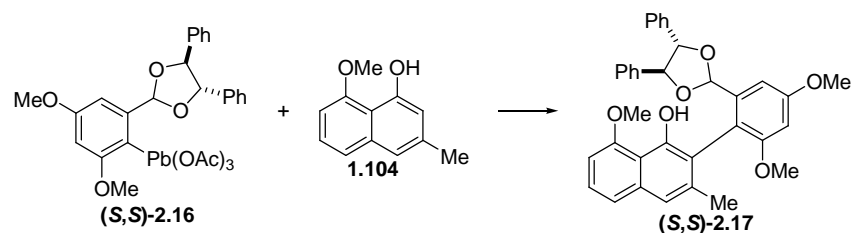
Method 1 (Pyridine coupled.)

A solution of naphthol **1.104** (24 mg, 0.13 mmol) in dichloromethane (2 mL) was added *via* cannula to a solution of aryllead (*S*,*S*)-**2.16** (141 mg, 0.19 mmol) in dry dichloromethane (2 mL). Dry pyridine (0.05 mL, 0.57 mmol) was added and the reaction stirred at r.t. for 24 h at which time it was quenched with saturated aqueous ammonium chloride solution (5 mL) and the aqueous layer extracted with dichloromethane (*x* 3). The combined organic extracts were washed successively with 10% aqueous hydrochloric acid solution, water, saturated brine solution and then dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow solid. Purification by flash chromatography on silica gel, eluting with 40% ethyl acetate/petroleum ether, gave (*S*,*S*)-**2.17** as a white solid (36 mg, 50%). Integration of the acetal C-H protons (δ 5.93 and 5.98) showed the diastereoisomers to be in a 35:65 ratio.

Method 2 (brucine promoted at room temperature.)

A solution of naphthol **1.104** (19 mg, 0.1 mmol) in dry dichloromethane (2 mL) was added to a solution of the aryllead compound (*S*,*S*)-**2.16** (73 mg, 0.1 mmol) and brucine (118 g, 0.3 mmol) in dry dichloromethane (2 mL). The reaction was stirred at r.t., protected from light, for 24 h. After this time the yellow reaction mixture was filtered through a plug of Celite with dichloromethane (10 mL) and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography, eluting with 60% ethyl acetate/petroleum spirit, to give the title compound as a light yellow solid (29 mg, 53%). Integration of the acetal C-H protons (δ 5.93 and 5.98) showed the diastereoisomers to be in a 41:59 ratio.

Method 3 (brucine promoted at -78 °C.)

A solution of *n*-BuLi in hexanes (0.16 mL, 2.2 M, 0.36 mmol) was added dropwise to a solution of naphthol **1.104** (0.68 g, 0.36 mmol) in dry toluene (4 mL) at 0 °C. The light orange solution was stirred at 0 °C for 15 mins and then cooled to -78 °C. Brucine (0.284 g, 0.72 mmol), aryllead (*S*,*S*)-**2.16** (0.268 g, 0.36 mmol) and crushed 4Å sieves (1.1 g) were then added sequentially and the reaction mixture stirred at -78 °C for 4 h. After this time the reaction mixture was filtered

through a plug of Celite with dichloromethane (25 mL) and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography, eluting with 60% ethyl acetate/petroleum spirit, to give the title compound as a light yellow solid (0.99 g, 51%). Integration of the acetal C-H protons (δ 5.93 and 5.98) showed the diastereoisomers to be in a 41:59 ratio.

Mp: 89-92 ^{o}C.

^{1}H NMR (mixture of diastereoisomers 300 MHz, CDCl$_3$): δ 2.11 [s, 3H, major diastereoisomer], 2.20 [s, 3H, minor diastereoisomer], 3.74 [s, 6H, both diastereoisomers], 3.94 [s, 6H, both diastereoisomers], 3.97 [s, 3H, minor diastereoisomer], 4.00 [s, 3H, major diastereoisomer], 4.61-4.72 [m, 2H, both diastereoisomers], 4.89-4.92 [m, 2H, both diastereoisomers], 5.93 [s, 1H, major diastereoisomer], 5.98 [s, 1H, minor diastereoisomer], 6.67-6.75 [m, 6H, both diastereoisomers], 6.91-7.43 [m, unable to give an accurate integration due to CDCl$_3$ peak, both diastereoisomers], 9.48 [s, 1H minor diastereoisomer], 9.56 [s, 1H, major diastereoisomer].

^{13}C NMR (mixture of diastereoisomers 75 MHz, CDCl$_3$): δ 20.68, 26.71, 55.37, 55.41, 55.8, 55.90, 55.95, 56.0, 84.2, 84.8, 86.6, 86.7, 99.9, 100.0, 102.0, 102.1, 102.2, 102.4, 103.06, 103.11, 113.3, 113.4, 118.2, 118.3, 118.5, 118.7, 119.0, 119.2, 121.17, 121.2, 125.2, 125.48, 125.52, 125.6, 126.9, 127.0, 127.1, 127.2, 127.3, 127.5, 128.18, 128.23, 128.28, 128.33, 128.5, 128.6, 136.2, 136.3, 137.46, 137.53, 137.8, 138.1, 138.8, 139.2, 139.6, 139.7, 150.8, 151.3, 156.16, 156.22, 158.0, 158.1, 160.3.

IR (Nujol Mull): 1582, 1607, 3382 cm^{-1}.

ESI-MS: 571 (100%), 353 (25%), 267 (30%), 265 (25%).

HRMS: Cald for C$_{35}$H$_{32}$NaO$_6$ (MNa^{+}) 571.2097, found 571.2094.

5.3 Experiments described in Chapter 3

3,5-Dimethoxytoluene (3.31)[9]
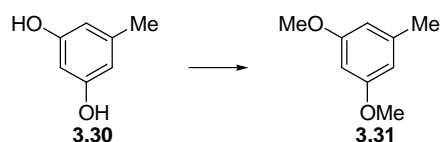
Iodomethane (82 g, 0.88 mol), orcinol (31.0 g, 0.25 mol) and anhydrous potassium carbonate (180 g, 1.3 mmol) were dissolved in acetone (500 mL) and heated to reflux overnight. The solvent was removed under reduced pressure and the precipitate dissolved in water (800 mL) and extracted with ethyl acetate (*x* 3). The organic extracts were washed with 10% aqueous potassium hydroxide solution, water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave the title compound as an orange oil (31.1 g, 82%).

^{1}H NMR (300 MHz, CDCl$_3$): δ 2.30 [s, 3H], 3.76 [s, 6H], 6.28 [dd, *J* = 2.1, 2.1 Hz, 1H], 6.34 [d, *J* = 2.1 Hz, 2H].[9]

2-Bromo-3,5-Dimethoxytoluene (3.32)[10]

Toluene **3.31** (2.44 g, 16.0 mmol) and *N*-bromosuccinimide (2.86 g, 16.2 mmol) were dissolved in anhydrous chloroform (60 mL) and the reaction mixture heated at reflux for 16 hours. The reaction mixture was then cooled to r.t. and water (40 mL) added. The aqueous layer was extracted with chloroform (*x* 3) and the organic extracts combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a light pink precipitate, which was purified by flash chromatography on silica gel eluting with 20% ethyl acetate/ petroleum ether to give **3.32** as a white solid (3.12g, 84%).

Mp: 52-53 ^{o}C, Lit (55 ^{o}C)[10]
^{1}H NMR (300 MHz, CDCl$_3$): δ 2.39 [s, 3H], 3.79 [s, 3H], 3.86 [s, 3H], 6.34 [d, *J* = 2.7 Hz, 1H], 6.44 [d, *J* = 2.7 Hz, 1H].[10]

2,4-Dimethoxy-6-methylbenzonitrile (3.29)[10]
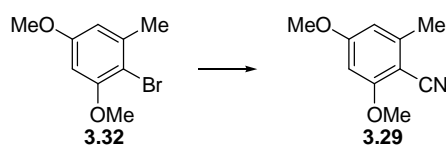
Bromide **3.32** (1.66 g, 7.2 mmol) was dissolved in dry *N,N*-dimethylformamide (40 mL) and CuCN (0.91 g 10.1 mmol) added in one portion. The solution was heated to 120 °C for 16 h after which time the reaction mixture was cooled and poured into a mixture of 1,2-diaminoethane (30 mL) in water (250 mL). The mixture was extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 20% ethyl acetate/ petroleum ether to give **3.29** as a white solid (1.1 g, 86%).

Mp: 70-71 °C, Lit (68 °C)[10]

^{1}H NMR (300 MHz, CDCl$_3$): δ 2.47 [s, 3H], 3.84 [s, 3H], 3.88 [s, 3H], 6.29 [d, *J* = 2.4 Hz, 1H], 6.38 [d, *J* = 2.4 Hz, 1H].[10]

3-Iodo-4,6-dimethoxy-2-methylbenzonitrile (3.22)
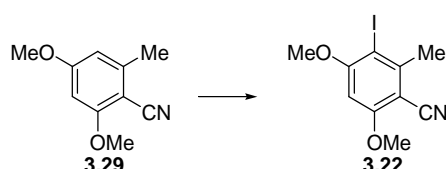
A solution of iodine (2.52 g, 10 mmol) in ethanol (10 mL) was added dropwise to a mixture of nitrile **3.29** (1.73 g, 9.8 mmol) and silver sulfate (6.11 g, 19.6 mmol) in dry ethanol (50 mL) at 0 °C over 0.5 h. The yellow reaction mixture was allowed to warm to r.t. and stirred at this temperature for 16 h. After this time the white mixture was filtered through a plug of Celite with dichloromethane (150 mL) and the solvent removed under reduced pressure to give a white cake. This was dissolved in dichloromethane (100 mL) and washed with 10% aqueous sodium thiosulfate solution, water, saturated brine solution and dried (MgSO$_4$). Concentration and purification by flash chromatography on silica gel eluting with 20% ethyl acetate/ petroleum ether gave **3.22** as a white powder (2.40 g, 81%).

Mp: 165-166 °C.

IR (Nujol Mull): 2207 cm^{-1}.

¹H NMR (600 MHz, CDCl₃): δ 2.65 [s, 3H], 3.94 [s, 3H], 3.95 [s, 3H], 6.28 [s, 1H].

¹³C NMR (150 MHz, CDCl₃): δ 27.5, 56.7, 56.7, 82.3, 92.2, 95.4, 115.9, 147.3, 162.2, 163.6.

ESI-MS: 304 (100%)

Analysis: Calcd for C 39.63, H 3.33, N 4.62, I 41.87, Found C 39.91, H 3.58, N 4.58, I 41.67.

4,6-Dimethoxy-2-methyl-3-(tributylstannyl)benzonitrile (3.21)
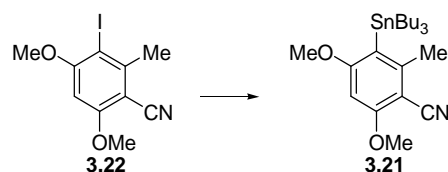
Method 1 (Use of a palladium catalyst.)

Iodide **3.22** (1.50 g, 4.96 mmol) was dissolved in dry *N,N*-dimethylformamide (15 mL) under an atmosphere of Ar. To the mixture was added PdCl₂(PPh₃)₂ (348 mg, 0.5 mmol) and KOAc (1.46 g, 14.9 mmol) consecutively in one portion. The Ar flow was stopped and the yellow reaction mixture frozen (liquid N₂) and then evacuated under reduced pressure for 3 min. The evacuation was ceased and the reaction mixture allowed to thaw. This was repeated two more times and once thawed again the Ar atmosphere returned. Bistributyltin (5.0 mL, 9.92 mmol) was added dropwise *via* syringe and the reaction mixture heated at 60 °C for 16 h. The black reaction mixture was cooled to r.t. and filtered through a plug of Celite with ethyl acetate (150 mL). The organic extract was washed with water (*x* 3), saturated brine solution and dried (MgSO₄). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 20% ethyl acetate/petroleum ether, to give **3.21** as a clear oil (1.04 g, 45%).

Method 2 (Use of halogen-lithium exchange.)

A solution of *t*-BuLi in pentane (1.5 M, 5.9 mL, 8.8 mmol) was added dropwise *via* syringe to a stirred solution of the iodide **3.22** (1.07 g, 3.5 mmol) in dry tetrahydrofuran (50 mL) at -95 °C. The resulting orange solution was stirred at -95 °C for 15 min and then tributyltin chloride (1.2 mL, 4.4 mmol) was slowly added and the reaction allowed to warm slowly to r.t. overnight. The resulting solution was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO₄). Evaporation of the solvent under reduced pressure gave the

crude product, which was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate/petroleum spirit, to give the title compound as a colourless oil (1.23 g, 75%).

IR (Neat): 2207 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.84-0.92 [m, 9H, 4'-CH$_3$], 0.99-1.01 [m, 6H, 1'-CH$_2$], 1.29-1.34 [m, 6H, 3'-CH$_2$], 1.42-1.52 [m, 6H, 2'-CH$_2$], 2.48 [s, 3H, 2-CH$_3$], 3.81 [s, 3H, 4 or 6-OMe], 3.92 [s, 3H, 4 or 6-OMe], 6.23 [s, 1H, 5-Ar-H].

^{13}C NMR (150 MHz, CDCl$_3$): δ 12.0 (1'-C), 13.6 (4'-C), 23.4 (2-CH$_3$), 27.3 (3'-C), 29.1 (2'-C), 55.3 (4 or 6-OMe), 55.8 (4 or 6 OMe), 90.8 (5-C), 95.5 (1-C), 117.1 (CN), 122.5 (3-C), 151.0 (2-C), 164.5 (4 or 6-C), 167.8 (4 or 6-C).

ESI-MS: 410 (100%), 354 (30%), 296 (75%).

HRMS cald for C$_{22}$H$_{37}$NNaO$_2$^{120}Sn (MNa$^+$) 490.1744, found 490.1738.

(3-Cyano-4,6-dimethoxy-2-methylphenyl)lead triacetate (3.20)
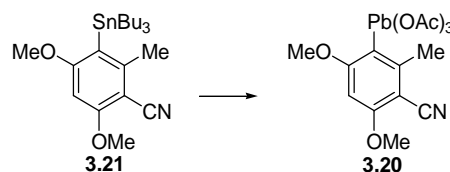
To a solution of lead tetraacetate (0.842 g, 1.9 mmol) and mercury trifluroacetate (0.04 g, 0.1 mmol) in dry dichloromethane (9 mL) was added a solution of stannane **3.21** (0.792 g, 1.7 mmol) in dry dichloromethane (9 mL) via cannula. The reaction mixture was stirred at r.t. overnight. whilst protected from light. After this time the orange reaction mixture was filtered through a plug of Celite with dichloromethane (150 mL). The solvent was removed under reduced pressure to give a light yellow precipitate, which was recrystallised from dichloromethane and petroleum spirit (1:4) to give pure aryllead **3.20** as a light yellow solid (0.772 g, 81%).

IR (Neat): 2207 cm^{-1}

^{1}H NMR (600 MHz, CDCl$_3$): δ 2.13 [s, 9H], δ 2.73 [s, 3H], 3.97 [s, 3H], 3.98 [s, 3H], 6.41 [s, 1H].

^{13}C NMR (150 MHz, CDCl$_3$): 19.5, 20.0, 56.8, 57.0, 93.2, 98.6, 115.2, 145.0, 148.9, 162.5, 166.0, 180.4.

3-(1-Hydroxy-8-methoxy-3-methylnaphthalen-2-yl)-4,6-dimethoxy-2-methylbenzonitrile (3.18)
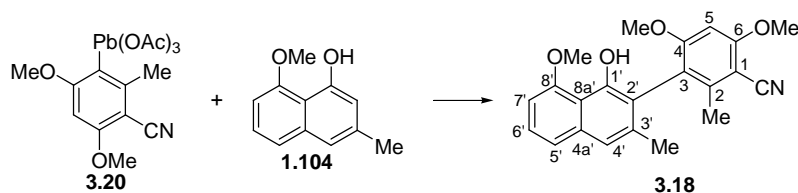
Method 1 (Crude aryllead used with pyridine as the promoter)

Dry pyridine (0.6 mL, 7.4 mmol) was added dropwise to a solution of crude aryllead species **3.20** (1.19 g, 2.1 mmol) and naphthol **1.104** (0.401 g, 2.1 mmol) in dry dichloromethane (20 mL). The reaction was stirred at r.t., protected from light, for 24 h. After this time saturated aqueous ammonium chloride solution was added and the aqueous layer extracted with dichloromethane (*x* 4). The combined organic extracts were washed with 1 M hydrochloric acid solution, water, saturated brine solution and dried (MgSO$_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 50% ethyl acetate/petroleum spirit, to give **3.18** as a bright yellow solid (0.334 g, 44%). Further elution of the column with 70% ethyl acetate/petroleum spirit afforded **3.33** as a yellow solid (0.181 g, 21%).

Data for 3.18

Mp: 227-228 $^{\circ}$C.

IR (Neat): 1584, 2210, 3400 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ 2.03 [s, 3H, 3'-Me], 2.18 [s, 3H, 2-Me], 3.77 [s, 3H, 4 or 6-OMe], 3.98 [s, 3H, 4 or 6-OMe], 4.01 [s, 3H, 8'-OMe], 6.45 [s, 1H, 5-Ar-H], 6.74 (d, *J* = 7.8 Hz, 1H, 7'-Ar-H), 7.24 [s, 1H, 4'-Ar-H], 7.28-7.31 [m, 1H, 6'-Ar-H], 7.36-7.37 [m, 1H, 5'-Ar-H], 9.48 [br s, 1H, OH].

^{13}C NMR (150 MHz, CDCl$_3$): δ 18.2 (2-Me), 20.1 (3'-Me), 55.92 (OMe), 55.95 (OMe), 56.01 (OMe), 92.6 (5-C), 95.0 (3-C), 103.4 (7'-C), 113.4 (8a'-C), 116.7 (CN), 118.0 (2'-C), 118.9 (4'-C), 119.5 (1-C), 121.2 (5'-C), 125.8 (6'-C), 136.2 (4a'-C), 137.5 (3'-C), 143.7 (3-C), 151.0 (1'-C), 156.1 (8'-C), 161.5 (4 or 6-C), 162.8 (4 or 6-C).

ESI-MS: 364 (100%).

HRMS: Calcd for C$_{22}$H$_{22}$NO$_4$ (MH$^+$) 364.1549, found 364.1553.

HPLC Analysis:

- Chiralcel OD-H (*Daicel*, 4.6 *x* 250 mm)

  Eluants: *iso*-propanol/*n*-hexane (different gradients)

  Result: always one peak, no separation.

Data for 3.33
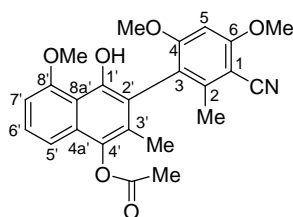
Mp: 223-224 ^{0}C.

IR (Nujol Mull): 3361, 2290, 1726, 1633, 1586 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ1.86 [s, 3H, 3'-Me], 2.19 [s, 3H, 2-Me], 2.44 [s, 3H, Me of OAc], 3.77 [s, 3H, 4 or 6-OMe], 3.98 [s, 3H, 4 or 6-OMe], 4.02 [s, 3H, 8'-OMe], 6.44 [s, 1H, 5-Ar-H], 6.79 (dd, *J* = 1.5, 6.9 Hz, 1H, 7'-Ar-H), 7.33-7.37 [m, 2H, 5' and 6'-Ar-H], 9.47 [br s, 1H, OH].

^{13}C NMR (150 MHz, CDCl$_3$): δ 13.6 (3'-Me), 18.3 (2-Me), 20.1 (Me of OAc), 55.9 (OMe), 56.0 (OMe), 56.2 (OMe), 92.6 (5-C), 95.0 (3-C), 104.2 (7'-C), 113.8 (8a'-C), 114.8 (5'-C), 116.6 (CN), 117.7 (2'-C), 118.8 (1-C), 126.6 (6'-C), 128.9 (3'-C), 129.1 (4a'-C), 136.9 (4'-C), 143.9 (2-C), 149.2 (1'-C), 156.4 (8'-C), 161.6 (4 or 6-C), 163.0 (4 or 6-C), 169.3 (C=O).

ESI-MS: 422 (100%).

HRMS: Calcd for C$_{24}$H$_{24}$NO$_6$ (MH$^+$) 422.1604, found 422.1612.

Method 2 (Pyridine used as the promoter and pure aryllead.)

Dry pyridine (0.31 mL, 3.9 mmol) was added dropwise to a solution of aryllead **3.20** (0.73 g, 1.3 mmol) and naphthol **1.104** (0.25 g, 1.3 mmol) in dry dichloromethane (24 mL). The reaction was stirred at r.t., protected from light, for 24 h. After this time saturated aqueous ammonium chloride solution was added and the aqueous layer extracted with dichloromethane (*x* 4). The combined organic extracts were washed with 1 M hydrochloric acid solution, water, saturated brine solution and dried (MgSO$_4$). The solvent was removed under reduced pressure and the residue purified by

flash chromatography, eluting with 50% ethyl acetate/petroleum spirit, to give the title compound as a bright yellow solid (0.36 g, 77%).

Method 3 (Use of brucine to promote the reaction at room temperature)

To a solution of the aryllead compound **3.20** (0.56 g, 1.0 mmol) and brucine (1.18 g, 3.0 mmol) in dry dichloromethane (9 mL) was added a solution of naphthol **1.104** (0.19 1.0 mmol) in dry dichloromethane (9 mL). The reaction was stirred at r.t., protected from light, for 24 h. After this time the yellow reaction mixture was filtered through a plug of Celite with dichloromethane (80 mL) and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography, eluting with 50% ethyl acetate/petroleum spirit, to give the title compound as a bright yellow solid (0.31 g, 85%).

Method 4 (Use of brucine to promote the reaction and lithiation of the naphthol)

A solution of *n*-BuLi in hexanes (0.92 mL, 1.8 M, 1.66 mmol) was added dropwise to a solution of naphthol **1.104** (0.31 g, 1.66 mmol) in dry toluene (22 mL) at 0 °C. The light orange solution was stirred at 0 °C for 15 mins and then cooled to -78 °C. Brucine (1.31 g, 3.22 mmol), aryllead **3.20** (0.931 mg, 1.66 mmol) and crushed 4Å sieves were then added sequentially and the reaction mixture stirred at -78 °C for 6.5 h. After this time the reaction mixture was filtered through a plug of Celite with dichloromethane (150 mL) and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography, eluting with 50% ethyl acetate/petroleum spirit, to give the title compound as a bright yellow solid (0.40 g, 66%).

(*R*)-1-Methoxy-6-methylnaphthalen-8-yl-2-phenoxypropanoate (3.41)
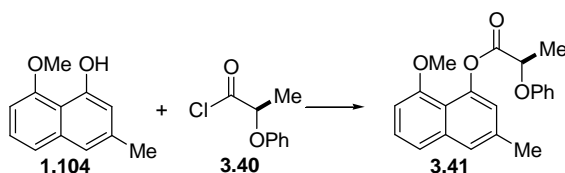
A solution of naphthol **1.104** (100 mg, 0.53 mmol) in dry *N*,*N*-dimethylformamide (3 mL) was added dropwise via cannula to a suspension of sodium hydride (60%, 44 mg, 1.1 mmol) in dry *N*,*N*-dimethylformamide (3 mL) under an Ar atmosphere at 0 °C. The red reaction mixture was stirred for 20 mins at 0 °C at which time the acid chloride **3.40** (294 mg, 1.6 mmol) was added

dropwise via syringe. The orange reaction mixture was stirred for 21 h at r.t. and then poured into a saturated aqueous sodium bicarbonate solution (20 mL). The mixture was extracted with ethyl acetate (*x* 3) and the organic extracts combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a brown oil, which was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate/petroleum ether, to give **3.41** as a light yellow solid (0.161 g, 89%). A small sample was recrystallised from 20% ethyl acetate/petroleum spirit to give **3.41** as a crystalline solid.

Mp: 99-100 $^{\circ}$C.

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.87 [d, *J* = 6.9 Hz, 3H], 2.41 [s, 3H], 3.79 [s, 3H], 5.10 [q, *J* = 6.9 Hz, 1H], 6.73-6.76 [m, 2H], 7.00-7.10 [m, 3H], 7.28-7.37 [m, 4H], 7.44-7.45 [m, 1H].

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.4 (CH$_3$), 21.2 (CH$_3$), 55.5 (OMe), 73.4 (CH), 105.2 (Ar-H), 115.9 (Ar-H), 117.2, 120.3 (Ar-H), 121.1 (Ar-H), 121.8 (Ar-H), 125.8 (Ar-H), 126.5 (Ar-H) 129.6 (Ar-H), 135.9, 136.9, 145.8, 155.2, 157.8, 171.0 (C=O).

ESI-MS: (MNa$^+$) 359 (100%).

$[\alpha]_D^{23^{\circ}C}$ = +420 (0.1, CHCl$_3$).

Analysis: Calcd for C 74.98, H 5.99, Found C 74.69, H 5.94.

4,6-Dimethoxy-3-(8-methoxy-1-(methoxymethyl)-3'-methylnaphthalen-2-yl)-2-methylbenzonitrile (3.44)
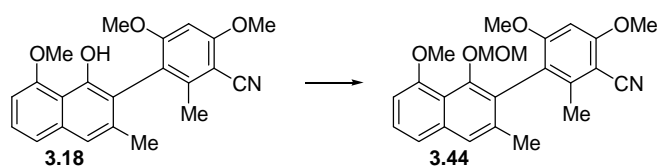
A solution of naphthol **3.18** (303 mg, 0.83 mmol) in dry *N,N*-dimethylformamide (7 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 100 mg, 2.5 mmol) in dry *N,N*-dimethylformamide (8 mL). The reaction was stirred for 1 h at r.t. resulting in a turbid red solution. MOM-Cl (0.32 mL, 4.2 mmol) was added dropwise and the reaction stirred at r.t. overnight. The reaction was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 4). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 50% ethyl acetate/petroleum spirit, to give the title compound as a white solid (309 mg, 91%).

**Mp**: 154-155 ^{o}C.

IR (Solution in CHCl$_3$): 2403, 1585, 1522 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ 2.03 [s, 3H, 3'-Me], 2.18 [s, 3H, 2-Me], 2.86 [s, 3H, OMe of MOM], 3.76 [s, 3H, OMe], 3.95 [s, 3H, OMe], 3.99 [s, 3H, OMe], 4.77 [d, J = 6.0 Hz, 1H, CH of MOM], 4.96 [d, J = 6.0 Hz, 1H, CH of MOM], 6.42 [s, 1H, 5-Ar-H], 6.82 [dd, J= 1.5, 15.0 Hz, 1H, 7'-Ar-H], 7.34-7.39 [m, 2H, 5' and 6'-Ar-H], 7.51 [s, 1H, 4' Ar-H].

^{13}C NMR (150 MHz, CDCl$_3$): δ 18.7 (2-Me), 20.2 (3'-Me), 55.9 (OMe), 56.02 (OMe), 56.06 (OMe), 56.14 (OMe), 92.1 (5-C), 94.4 (3-C), 100.5 (CH$_2$), 105.3 (7'-C), 116.6 (CN), 118.7 (8a'-C), 120.5 (5'-C), 120.7 (1-C), 124.6 (4'-C), 126.2 (6'-C), 127.8 (3'-C), 136.2 (2'-C), 137.0 (4a'-C), 143.9 (2-C), 150.6 (1'-C), 155.8 (8'-C), 162.0 (4 or 6-C), 162.9 (4 or 6-C).

ESI-MS: 376 (100%), 408 (45%).

HRMS: Calcd for C$_{24}$H$_{25}$NNaO$_5$ (MNa$^+$) 430.1630, found 430.1624.

(*S*)-(+)-*N*-(Ethene)-*p*-toluenesulfinimine ((*S*)-3.15)[11]
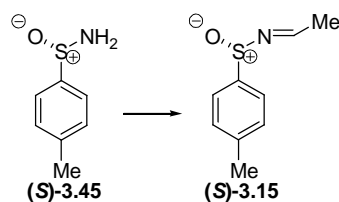
Acetaldehyde (0.43 g, 9.7 mmol) and 4Å molecular sieves (12 g) were added in one portion to a solution of sulfinamide (*S*)-3.45 (0.50 g, 3.2 mmol) in dry dichloromethane (15 mL) and the mixture stirred at r.t. for 24 h. After this time ethyl acetate (20 mL) was added and the mixture filtered through a plug of Celite. The brown cake was washed thoroughly with ethyl acetate (80 mL) and the solvent removed *in vacuo* to yield (*S*)-3.15 as a yellow oil (0.54 g, 93%), which was used without further purification.

^{1}H NMR (300 MHz, CD$_3$Cl): δ 2.20 [d, J = 5.1 Hz, 3H], 2.40 [s, 3H], 7.31 [d, J = 8.1 Hz, 2H], 7.56 [d, J = 8.1 Hz, 2H], 8.24 [q, J = 5.1 Hz, 1H][11]

$[\alpha]_D^{25}$ = +418 (1.2, CHCl$_3$)[11]

3-(1-Isopropoxy-8-methoxy-3-methylnaphthalen-2-yl)-4,6-dimethoxy-2-methylbenzonitrile (3.47)
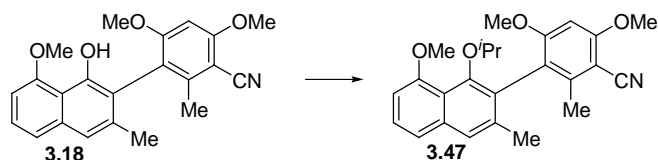
A solution of naphthol **3.18** (220 mg, 0.61 mmol) in dry *N,N*-dimethylformamide (5 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 50 mg, 1.25 mmol) in dry *N,N*-dimethylformamide (5 mL). The reaction was stirred for 1 h at r.t. resulting in a turbid red solution. 2-Bromopropane (0.26 mL, 3.05 mmol) was added dropwise and the reaction stirred at r.t. overnight. The reaction was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 50% ethyl acetate/petroleum spirit, to give the title compound as a white solid (205 mg, 83%).

Mp: 83-85 °C.

IR (Nujol Mull): 2402, 1587, 1522 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.86 [d, *J* = 6.0 Hz, 3H], 1.06 [d, *J* = 6.0 Hz, 3H], 2.02 [s, 3H], 2.19 [s, 3H], 3.78 [s, 3H], 3.89-3.97 [m, 1H], 3.93 [s, 3H], 4.00 [s, 3H], 6.41 [s, 1H], 6.79 [dd, *J* = 2.4, 4.2 Hz, 1H], 7.32-7.34 [m, 2H], 7.45 [d, *J* = 0.6 Hz, 1H].

^{13}C NMR (150 MHz, CDCl$_3$): δ 18.8, 20.1, 21.9, 22.1, 55.6, 55.64, 55.9, 76.1, 91.9, 94.7, 105.3, 116.7, 120.1, 120.3, 120.9, 123.7, 126.1, 127.7, 136.5, 136.8, 144.0, 151.9, 156.5, 161.5, 162.8.

ESI-MS: 428 (100%), 406 (60%), 364 (45%), 322 (25%).

HRMS: Calcd for C$_{25}$H$_{28}$NO$_4$ (MH$^+$) 406.2018, found 406.2019.

(S_s,R)-(+)-*N*-[1-Methyl-2-(4,6-dimethoxybenzonitrile)-ethyl-*p*-toluenesulfinamide (3.16)[10]
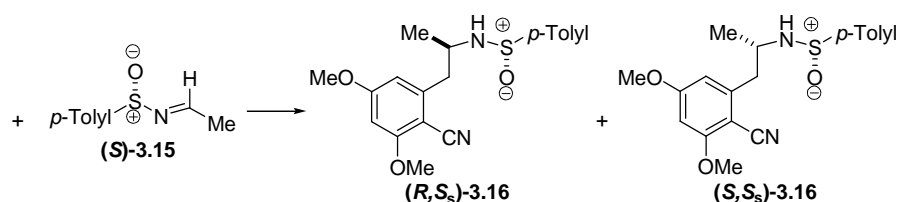
Method 1 (use of diglyme as the solvent.)

Diglyme (10 mL) was added to a freshly prepared solution of lithium *N,N*-diisopropylamide in tetrahydrofuran (1.7 M, 1.76 mL, 3.0 mmol) and the mixture cooled to -78 $^{\circ}$C. A solution of the *o*-tolylnitrile **3.29** (0.266 g, 1.5 mmol) in dry diglyme (6 mL) was then added dropwise at -78 $^{\circ}$C. The now deep red solution was stirred at -78 $^{\circ}$C for 0.5 h. After this time sulfinimine **(S)-3.15** (0.308 g, 1.7 mmol) in dry diglyme (2 mL) at -78 $^{\circ}$C was added dropwise via cannula to give an orange solution. After stirring for 0.5 h at -78 $^{\circ}$C saturated aqueous ammonium chloride solution (20 mL) was added and the mixture was extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow gum, which was purified by flash chromatography on silica gel eluting with 50% ethyl acetate/ petroleum ether to give **3.16** as a white solid (0.344 g, 64%). ^{1}H NMR analysis showed the diastereoisomeric ratio to be 90:10 through integration of the methyl protons at δ 1.33 and δ 1.38 respectively.

Method 2 (use of tetrahydrofuran in place of diglyme as the solvent.)

A solution of *n*-BuLi in hexanes (1.2 mL, 2.1 M, 2.6 mmol) was added to a solution of dry *N,N*-diisopropylamine (0.37 mL, 2.6 mmol) in dry tetrahydrofuran (3 mL) at -78 $^{\circ}$C and the solution allowed to warm to r.t. over 20 mins. The solution was then cooled to -78 $^{\circ}$C and a solution of the *o*-tolylnitrile **3.29** (0.235 g, 1.3 mmol) in dry tetrahydrofuran (6 mL) then added dropwise at -78 $^{\circ}$C. The now deep red solution was stirred at -78 $^{\circ}$C for 0.5 h. After this time sulfinimine **(S)-3.15** (0.253 mg, 1.4 mmol) in dry tetrahydrofuran (2 mL) at -78 $^{\circ}$C was added dropwise via cannula to give an orange solution. After stirring for 0.5 h at -78 $^{\circ}$C saturated aqueous ammonium chloride was added (20 mL) and the mixture was extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow gum, which was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate/ petroleum ether, to give **3.16** as a white solid (0.294 g, 63%). ^{1}H NMR analysis showed the diastereoisomeric ratio to be 90:10 through integration of the methyl protons at δ 1.33 and δ 1.38 respectively.

Method 3 (use of lithium diethylamide as the base.)

A solution of *n*-BuLi in hexanes (1.0 mL, 2.1 M, 2.2 mmol) was added to a solution of dry *N,N*-diethylamine (0.23 mL, 2.2 mmol) in dry tetrahydrofuran (2 mL) at -78 $^{\circ}$C and the solution

allowed to warm to r.t. over 20 mins. Diglyme (10 mL) was added to the yellow solution to give an orange solution, which was then cooled to -78 °C. A solution of the *o*-tolylnitrile **3.29** (0.202 g, 1.1 mmol) in dry diglyme (5 mL) was added dropwise at -78 °C. The now deep red solution was stirred at -78 °C for 0.5 h. After this time sulfinimine **(*S*)-3.15** (0.218 mg, 1.2 mmol) in dry diglyme (2 mL) at -78 °C was added dropwise via cannula to give an orange solution. After stirring for 0.5 h at -78 °C saturated aqueous ammonium chloride was added (20 mL) and the mixture was extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow gum, which was purified by flash chromatography on silica gel eluting with 50% ethyl acetate/ petroleum ether to give **3.16** as a mixture of diastereoisomers as a white solid (0.312 g, 79%). ^{1}H NMR analysis revealed the diastereoisomeric ratio to be 90:10 through integration of the methyl protons at δ 1.33 and δ 1.38 respectively.

^{1}**H NMR** (300 MHz, mixture of diastereoisomer, CDCl$_3$): δ 1.33 [d, *J* = 6.3 Hz, 3H, major diastereoisomer], 1.38 [d, *J* = 6.3 Hz, 3H, minor diastereoisomer], 1.89 [br s, 2H, both diastereoisomers], 2.40 [s, 6H, both diastereoisomers], 2.91-3.18 [m, 4H, both diastereoisomers], 3.74 [s, 3H, minor diastereoisomer], 3.76-3.81 [m, 2H, both diastereoisomers], 3.86 [s, 3H, major diastereoisomer], 3.89 [s, 3H, minor diastereoisomer], 3.90 [s, 3H, major diastereoisomer], 6.13 [d, *J* = 2.2 Hz, 1H, minor diastereoisomer], 6.31 [d, *J* = 2.2 Hz, 1H, minor diastereoisomer], 6.40 [d, *J* = 2.3 Hz, 1H, major diastereoisomer], 6.51 [d, *J* = 2.3 Hz, 1H, major diastereoisomer], 7.16 [d, *J* = 8.4 Hz, 2H, minor diastereoisomer], 7.29 [d, *J* = 8.2 Hz, 2H, major diastereoisomer], 7.39 [d, *J* = 8.2 Hz, 2 H, minor diastereoisomer], 7.52 [d, *J* = 8.2 Hz, 2H, major diastereoisomer] $[\alpha]_D^{25\,^0C}$ = +22 (1.3, CHCl$_3$)

### (3*R*)-(+)-6,8-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline (3.6)
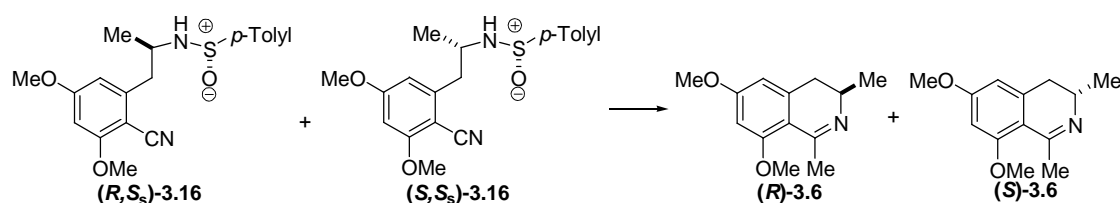
A solution of methyllithium in ether (4.8 mL, 1 M, 4.8 mmol) was added to a solution of sulfinamide **3.16** (428 mg, 1.2 mmol) in dry tetrahydrofuran (10 mL) at -78 °C. The resulting deep red solution was allowed to warm to r.t. over 1 h. Hydrochloric acid (2 M, 20 mL) was added and the reaction mixture stirred vigorously for 2 h. After this time the yellow solution was brought to a pH of 10 with 10% aqueous sodium hydroxide solution and extracted with ethyl acetate (x 4). The organic extracts were combined and washed with water, saturated brine solution and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a pink gum, which was purified by flash chromatography on silica gel, eluting with ethyl acetate with 1% triethylamine, to give **3.6** as a light orange gum (163 mg, 62%). The ^1H NMR data matched that of the isoquinoline obtained from the use of the *tert*-butyl sulfur auxiliary and is given there.

Preparation of the hydrochloride salt.

The gum was converted to its hydrochloric salt at 0 °C using concentrated HCl (2 mL) in methanol (10 mL). The solid that formed was collected and recrystallised from petroleum ether/ dichloromethane.

$[\alpha]_D^{25} = + 106$ (0.9, methanol), (lit.[10], +139 (c 0.6, methanol))

(S$_s$,R)-(+)-*N*-[1-Methyl-2-(3-Iodo-4,6-dimethoxybenzonitrile)-ethyl-*p*-toluenesulfinamide (3.49)
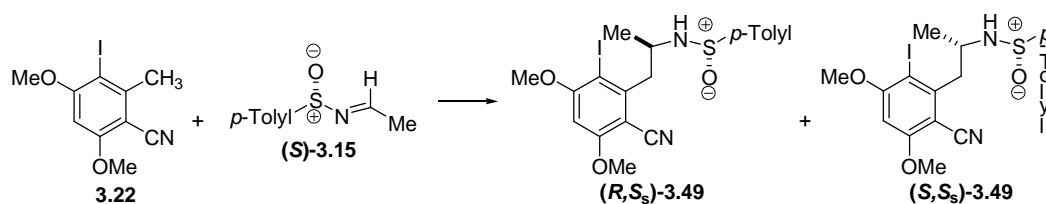
Method 1 (Tetrahydrofuran and LDA.)

A solution of *n*-BuLi in hexanes (0.55 mL, 2.2 M, 1.2 mmol) was added to a solution of dry *N,N*-diisopropylamine (0.17 mL, 1.2 mmol) in dry tetrahydrofuran (2 mL) at -78 °C and the solution allowed to warm to r.t. over 20 mins. The yellow solution was then cooled to -78 °C and a solution of the iodide **3.22** (0.171 g, 0.6 mmol) in dry tetrahydrofuran (10 mL) at -78 °C added dropwise. The now deep red solution was stirred at -78 °C for 0.5 h. After this time sulfinimine **(S)-3.15** (0.135 mg, 0.7 mmol) in dry tetrahydrofuran (4 mL) at -78 °C was added dropwise via cannula to give a yellow solution. After stirring for 0.5 h at -78 °C saturated aqueous ammonium

chloride solution was added (15 mL) and the mixture extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow oil, which was purified by flash chromatography on silica gel eluting with 50% ethyl acetate/ petroleum ether to give **3.49** as an inseparable mixture of diastereoisomers as a white solid (0.127 g, 44%). ^{1}H NMR analysis showed the diastereoisomeric ratio to be 90:10 through integration of the methyl protons at δ 1.39 and δ 1.46 respectively.

Method 2 (Diglyme and lithium diethylamide.)

A solution of *n*-BuLi in hexanes (0.63 mL, 2.1 M, 1.32 mmol) was added to a solution of dry diethylamine (0.14 mL, 1.32 mmol) in dry diglyme (2 mL) at -78 ^{o}C and the solution allowed to warm to r.t. over 20 mins. The orange solution was then cooled to -78 ^{o}C and a solution of the iodide **3.22** (0.100 g, 0.33 mmol) in dry diglyme (5 mL) at -78 ^{o}C added dropwise. The now deep red solution was stirred at -78 ^{o}C for 0.5 h. After this time sulfinimide (*S*)-**3.15** (65 mg, 0.36 mmol) in dry diglyme (2 mL) at -78 ^{o}C was added dropwise via cannula to give an orange solution. After stirring for 0.5 h at -78 ^{o}C saturated aqueous ammonium chloride solution (10 mL) was added and the mixture was extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a pink gum which was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate/ petroleum ether, to give **3.49** as a white solid (0.117 g, 73%). ^{1}H NMR analysis showed the diastereoisomeric ratio to be 88:12 through integration of the methyl protons at δ 1.39 and δ 1.46 respectively.

Mp: 72-75 ^{o}C.

^{1}H NMR (mixture of diastereoisomers, 600 MHz, CDCl$_3$): δ 1.39 [d, *J* = 6.0 Hz, 3H, major diastereoisomer], 1.46 [d, *J* = 6.3 Hz, 3H, minor diastereoisomer], 1.63 [br s, 2H, both diastereoisomers], 2.35 [s, 3H, minor diastereoisomer], 2.39 [s, 3H, major diastereoisomer] 2.87-3.12 [m, 2H, minor diastereoisomer], 3.13-3.33 [m, 2H, major diastereoisomer], 3.92-4.15 [m, 14 H, both diastereoisomers], 6.30 [s, 1H, minor diastereoisomer], 6.37 [s, 1H, major diastereoisomer], 7.01 [d, *J* = 7.8 Hz, 2H, minor diastereoisomer], 7.19 [d, *J* = 7.8 Hz, 2H, minor diastereoisomer], 7.23 [d, *J* = 7.8 Hz, 2H, major diastereoisomer], 7.40 [d, *J* = 7.8 Hz, 2H, major diastereoisomer].
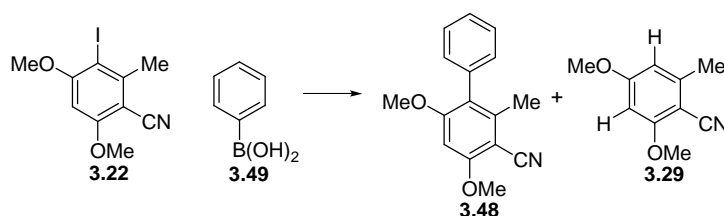
^{13}**C NMR** (mixture of diastereoisomers, 75 MHz, CDCl$_3$): δ 21.2, 23.6, 24.7, 29.5, 47.1, 47.6, 48.3, 52.2, 56.2, 56.6, 56.7, 82.7, 82.8, 92.4, 92.8, 96.3, 96.4, 116.2, 125.4, 129.0, 129.2, 140.4, 141.0, 142.0, 146.7, 147.3, 162.0, 162.3, 163.3, 163.5.

IR (nujol mull): 3179, 2216, 1576 cm^{-1}.

ESI-MS: 507 (100%).

HRMS: Calcd for C$_{19}$H$_{21}$IN$_2$O$_3$SNa (MNa$^+$) = 507.0215, Found 507.0211.

3-Phenyl-4,6-dimethoxy-2-methylbenzonitrile (3.48)

A mixture of iodide **3.22** (0.500 g, 1.65 mmol), phenyl boronic acid (0.322 g, 2.64 mmol), PdCl$_2$(PPh$_3$)$_2$ (21 mg, 0.03 mmol) and sodium bicarbonate (0.555g, 6.6 mmol) were dissolved in a mixture of dimethyl ether (15 mL) and water (15 mL) and heated to 70 $^{\circ}$C for 16 h. The orange mixture was cooled to r.t. and the solvents removed under reduced pressure. The orange precipitate was dissolved in dichloromethane and washed with water, saturated brine solution and dried over MgSO$_4$. Removal of the solvent under reduced pressure gave an orange solid, which was purified by flash chromatography on silica gel, eluting with 30% ethyl acetate/petroleum ether, to give **3.48** as a light orange solid (0.276 g, 66%) and **3.29** as a white solid (0.088 g, 30%).

Mp: 147-148 $^{\circ}$C.

^{1}**H NMR** (300 MHz, CDCl$_3$): δ 2.21 [s, 3H], 3.77 [s, 3H], 4.00 [s, 3H], 6.41 [s, 1H], 7.11-7.15 [m, 2H], 7.33-7.45 [m, 3H].
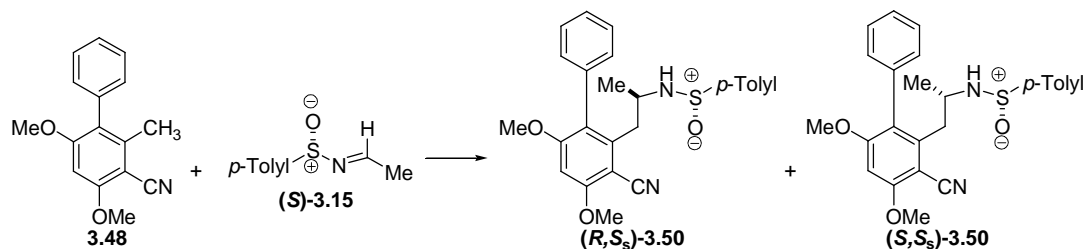
^{13}**C NMR** (75 MHz, CDCl$_3$): δ 19.2, 56.0, 56.2, 92.6, 94.7, 116.8, 124.5, 127.4, 128.4, 130.4, 135.9, 142.6, 161.5, 162.8.

IR (Solution in CHCl$_3$): 2219 cm^{-1}

ESI-MS: 276 (100%)

HRMS: Calculated for: C$_{16}$H$_{15}$NNaO$_2$ (MNa$^+$) 276.1000; Found 276.0999.

(S_s,R)-(+)-N-[1-Methyl-2-(3-benzene-4,6-dimethoxybenzonitrile)-ethyl-p-toluenesulfinamide (3.50)

Method 1 (Tetrahydrofuran and LDA)

A freshly prepared solution of lithium *N,N*-diisopropylamide (2.1 M, 0.8 mmol), in dry tetrahydrofuran (2 mL) was cooled to -78 °C and a solution of the *o*-tolylnitrile **3.48** (100 mg, 0.4 mmol) in dry tetrahydrofuran added dropwise via cannula. After stirring for 0.5 h, **(S)-3.15** (94 mg, 0.5 mmol) in dry tetrahydrofuran (2 mL) at -78 °C was added dropwise via cannula and the solution stirred for 0.5 h. At this time the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO_4). Removal of the solvent under reduced pressure gave an orange solid, which was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate/ petroleum ether, to give **3.50** as a light orange solid (55 mg, 32%). ^{1}H NMR analysis showed the diastereoisomeric ratio to be 90:10 through integration of the methyl protons at δ 1.06 and δ 1.12 respectively.

Method 2 (Diglyme and lithium diethylamide.)

A solution of *n*-BuLi in hexanes (0.67 mL, 2.1 M, 1.4 mmol) was added to a solution of dry diethylamine (0.14 mL, 1.4 mmol) in dry diglyme (2 mL) at -78 °C and the solution allowed to warm to r.t. over 20 mins. The solution was cooled to -78 °C and *o*-tolylnitrile **3.48** (89 mg, 0.35 mmol) in dry diglyme (2 mL) added dropwise via cannula. The now deep red solution was stirred at -78 °C for 0.5 h. After this time sulfinimine **(S)-3.15** (76 mg, 0.42 mmol) in dry diglyme (2 mL) at -78 °C was added dropwise via cannula to give an orange solution. The reaction mixture was stirred for 0.5 h at -78 °C and saturated aqueous ammonium chloride added (20 mL) and the mixture extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO_4). Removal of the solvent under reduced pressure gave an orange solid, which was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate/ petroleum ether, to give **3.50** as a light orange solid (103 mg, 68%). ^{1}H

NMR analysis showed the diastereoisomeric ratio to be 90:10 through integration of the methyl protons at δ 1.06 and δ 1.12 respectively.

Mp: 78-79 °C.

IR (Solution in CHCl$_3$): 2220 cm^{-1}

^{1}H NMR (300 MHz, mixture of diastereoisomers, CDCl$_3$): δ 1.06 [d, J = 6.6 Hz, 3H, major diastereoisomer], 1.12 [d, J = 6.6 Hz, 3H, minor diastereoisomer], 2.37 [s, 3H, minor diastereoisomer], 2.39 [s, 3H, major diastereoisomer], 2.58-2.60 [m, 2H, minor diastereoisomer], 2.78-2.92 [m, 2H, major diastereoisomer], 3.44-3.56 [m, 2H, both diastereoisomers], 3.65 [d, J = 9.3 Hz, 1H, major diastereoisomer], 3.77 [s, 3H, minor diastereoisomer], 3.79 [s, 3H, major diastereoisomer], 4.03 [s, 6H, both diastereoisomers], 6.45 [s, 1H, minor diastereoisomer], 6.49 [s, 1H, major diastereoisomer], 7.01-7.15 [m, 4H, both diastereoisomers], 7.17-7.25 [m, 4H, both diastereoisomers], 7.29-7.48 [m, 10H, both diastereoisomers].

^{13}C NMR (75 MHz, mixture of diastereoisomers, CDCl$_3$): δ 21.2, 21.3, 23.9, 24.9, 40.1, 40.6, 50.2, 52.7, 55.8, 55.9, 56.1, 92.8, 93.0, 95.5, 117.0, 152.0, 125.4, 125.5, 126.0, 127.4, 127.6, 127.9, 128.2, 128.3, 128.5, 129.0, 129.3, 129.9, 130.1, 130.2, 130.3, 130.7, 131.1, 134.8, 135.1, 140.5, 141.0, 141.1, 142.3, 142.9, 143.2, 161.4, 161.6, 162.6, 162.7.

ESI-MS: (MNa$^+$) 457 (100%).

HRMS: Calculated for C$_{25}$H$_{27}$N$_2$O$_3$S (MH$^+$) 435.17424, found 435.17413.

Alkylation of tolylnitrile 3.44
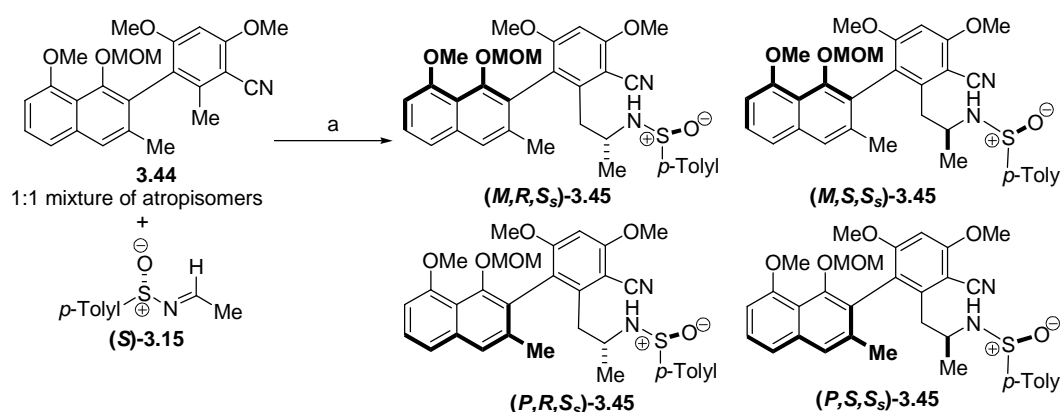
A solution of *n*-BuLi in hexanes (0.7 mL, 2.0 M, 1.4 mmol) was added to a solution of dry diethylamine (0.14 mL, 1.4 mmol) in dry tetrahydrofuran (2 mL) at -78 °C and the solution

allowed to warm to r.t. over 20 mins. The pale yellow solution was cooled to -78 °C and a solution of the biaryl **3.44** (1:1 mixture of atropisomers, 140 mg, 0.34 mmol) in dry tetrahydrofuran (4 mL) added dropwise. The now deep red solution was stirred at -78 °C for 0.5 h. After this time sulfinimine (*S*)-**3.15** (80 mg, 0.44 mmol) in dry tetrahydrofuran (2 mL) at -78 °C was added dropwise via cannula to give a orange solution, which was stirred at -78 °C for 0.5 h. After this time saturated aqueous ammonium chloride solution was added (20 mL) and the mixture was extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a brown gum, which was purified by flash chromatography on silica gel, eluting with 70% ethyl acetate/ petroleum ether, to give **3.45** as a mixture of diastereoisomers and as a white gum (100 mg, 50%).

IR (Neat): 3253, 2217, 1914, 1730, 1621, 1590 cm^{-1}.

**^{1}H NMR** (600 MHz, CDCl$_3$): δ 1.00 [d, *J* = 6.6 Hz, 3H, major atropisomer], 1.07 [d, *J* = 6.6 Hz, 3H, minor atropisomer], 1.13 [d, *J* = 6.6 Hz, 3H, major atropisomer], 1.26 [d, *J* = 6.6 Hz, 3H, minor atropisomer], 1.83 [s, 3H, minor atropisomer], 2.02 [s, 3H, major atropisomer], 2.04 [s, 3H, minor atropisomer], 2.19 [s, 3H, major atropisomer], 2.35 [s, 3H, major atropisomer], 2.37 [s, 3H, minor atropisomer], 2.40 [s, 3H, major atropisomer], 2.41 [s, 3H, minor atropisomer], 2.67-2.74 [m, 2H if ,major, 4H if minor], 2.76-2.84 [m, 2H if major, 4H if minor], 2.82 [s, 3H, minor atropisomer], 2.88 [s, 3H, major atropisomer], 2.91 [s, 3H, major atropisomer], 2.92 [s, 3H, minor atropisomer], 3.03 [dd, *J* = 6.6, 13.2 Hz, 1H, major atropisomer], 3.26-3.34 [m, 1H, major atropisomer], 3.35-3.42 [m, 1H, minor atropisomer], 3.43-3.50 [m, 1H, major atropisomer], 3.51-3.56 [m, 1H, minor atropisomer], 3.75 [s, 3H, minor atropisomer], 3.77 [s, 3H, minor atropisomer], 3.80 [s, 3H, major atropisomer], 3.82 [s, 3H, major atropisomer], 3.91 [s, 3H, minor atropisomer], 3.94 [s, 3H, minor atropisomer], 3.96 [s, 6H, major atropisomers], 4.01 [s, 3H, minor atropisomer], 4.02 [s, 3H, minor atropisomer], 4.03 [s, 3H, major atropisomer], 4.06 [s, 3H, major atropisomer], 4.59 [d, *J* = 5.4 Hz, 1H, minor atropisomer], 4.64 [d, *J* = 5.4 Hz, 1H, minor atropisomer], 4.66 [d, *J* = 5.4 Hz, 1H, major atropisomer], 4.71 [d, *J* = 5.4 Hz, 1H, major atropisomer], 4.92-4.93 [m, 1H, minor atropisomer], 4.99 [d, *J* = 5.4 Hz, 1H, major atropisomer], 5.02 [d, *J* = 5.4 Hz, 1H, major atropisomer], 6.46 [s, 2H, minor atropisomer], 6.50 [s, 1H, major atropisomer], 6.54 [s, 1H, major atropisomer], 6.80-6.86 [m, 4H, all atropisomers], 7.08-7.22 [m, 8H, all atropisomers], 7.33-7.56 [m, 8H, all atropisomers].

^{13}**C NMR** (150 MHz, CDCl$_3$): δ 14.1, 19.9, 20.2, 20.3, 21.2, 21.3, 22.8, 23.3, 23.9, 24.9, 30.5, 40.8, 40.9, 41.5, 41.9, 49.6, 50.1, 52.1, 53.1, 55.8, 56.06, 56.14, 56.3, 56.4, 56.7, 60.3, 65.5, 92.8, 92.9, 93.0, 95.5, 96.2, 100.3, 100.4, 105.4, 405.5, 105.8, 116.2, 117.0, 117.2, 118.6, 118.7, 118.9, 120.46, 120.52, 120.6, 120.8, 121.1, 124.8, 124.9, 125.1, 125.2, 125.5, 125.6, 126.1, 126.4, 127.1, 128.8, 129.1, 129.2, 129.3, 129.6, 130.8, 136.2, 136.4, 136.7, 136.93, 137.02, 137.13, 140.5, 140.68, 140.73, 141.0, 142.6, 143.9, 144.1, 144.3, 144.6, 149.6, 150.2, 155.89, 155.91, 162.1, 162.2, 162.3, 163.04, 163.1.

ESI-MS: 611 (100%) (MNa$^+$).

HRMS: Calcd for C$_{33}$H$_{37}$N$_2$O$_6$S (MH$^+$) 589.2372, found 589.2364.

Ent-**Ancistrotanzanine A ((*P*,*R*)-1.124)**
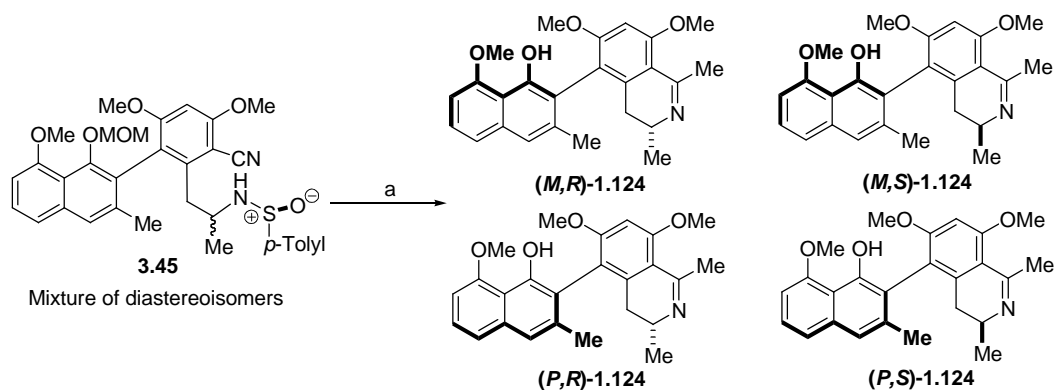
A solution of methyl lithium (0.4 mL, 0.4 mmol, 1 M in diethyl ether) was added to a solution of **3.45** (48 mg, 0.08 mmol), in dry tetrahydrofuran (2 mL) at -78 ^{0}C and the orange reaction mixture allowed to warm to r.t. over 1.5 h. 2 M Aqueous hydrochloric acid (5 mL) was added and the reaction stirred for a further 2 h. The reaction mixture was brought to pH 10 by the addition of 10% aqueous sodium hydroxide solution and extracted with diethyl ether (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (Na$_2$SO$_4$). Removal of the solvent *in vacuo* afforded a brown gum, which was purified by flash chromatography on reverse phase silica gel, eluting with methanol, to give *ent*-ancistrotanzanine A as a mixture of atropisomers (16 mg, 49%). All spectroscopic data matched that obtained for ancistrotanzanine A and its atropisomer prepared via the *t*-Bu sulfur auxiliary.

(*R*)-(-)-*N*-(Ethene)-*t*-butylsulfinimine ((*R*)-3.51)[12]
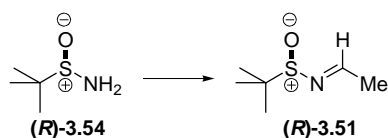
(*R*)-3.54   (*R*)-3.51

Acetaldehyde (0.54 g, 12.3 mmol) was added in one portion to a solution of sulfinamide **(*R*)-3.54** (0.50 g, 4.1 mmol) in dry dichloromethane (30 mL). Crushed 4Å molecular sieves (12 g) were then added in one portion and the mixture stirred at r.t. for 24 h. After this time ethyl acetate (20 mL) was added and the mixture filtered through a plug of Celite. The brown cake was washed thoroughly with ethyl acetate (80 mL) and the solvent removed *in vacuo* to yield **(*R*)-3.51** as a yellow oil (0.52 g, 86%)

¹H NMR (300 MHz, CDCl₃): δ 1.20 [s, 9H], 2.24 [d, *J* = 5.1 Hz, 3H], 8.09 [q, *J* = 5.1 Hz, 1H][12]

$[\alpha]_D^{25}$ = -372 (1.1, CHCl₃)

(*S*)-(+)-*N*-(Ethene)-*t*-butylsulfinimine (3.51)
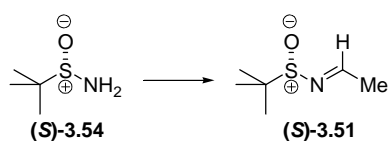
(*S*)-3.54   (*S*)-3.51

Acetaldehyde (0.54 g, 12.3 mmol) was added in one portion to a solution of sulfinamide **(*S*)-3.54** (0.50 g, 4.1 mmol) in dry dichloromethane (30 mL). Crushed 4Å molecular sieves (12 g) were then added in one portion and the mixture stirred at r.t. for 24 hours. After this time ethyl acetate (20 mL) was added and the mixture filtered through a plug of Celite. The brown cake was washed thoroughly with ethyl acetate (80 mL) and the solvent removed *in vacuo* to yield **(*S*)-3.51** as a yellow oil (0.58 g, 96%). The ¹H NMR data matched that of the enantiomer above.

$[\alpha]_D^{25}$ = + 327 (0.92, CHCl₃)

(R_s,S)-(+)-*N*-[1-Methyl-2-(4,6-dimethoxybenzonitrile)-ethyl-*t*-butylsulfinamide ((R_s,S)-3.55)

3.29   (*R*)-3.51   (*S*,R_s)-3.55
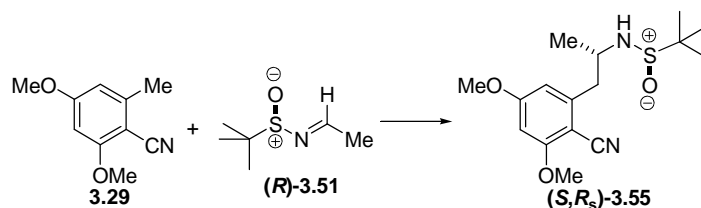
A solution of *n*-BuLi in hexanes (1.2 mL, 1.9 M, 2.3 mmol) was added to a solution of dry *N,N*-diethylamine (0.23 mL, 2.3 mmol) in dry tetrahydrofuran (2 mL) at -78 °C and the solution allowed to warm to r.t. over 20 mins. The reaction mixture was cooled to -78 °C and a solution of the *o*-tolylnitrile **3.29** (0.200 g, 1.1 mmol) in dry tetrahydrofuran (9 mL) added dropwise to give a deep red solution. The reaction was stirred at -78 °C for 0.5 h after which a solution of sulfinimine (*R*)-**3.51** (183 mg, 1.3 mmol) in dry tetrahydrofuran (6 mL) at -78 °C was added dropwise via cannula to give an orange solution. After stirring for 0.5 h at -78 °C saturated aqueous ammonium chloride solution was added (20 mL) and the mixture extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a yellow gum, which was purified by flash chromatography on silica gel, eluting with ethyl acetate, to give **3.55** as a white gum (0.251 g, 68%).

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.08 [s, 9H], 1.36 [d, *J* = 6.6 Hz, 3H], 2.81-2.98 [m, 2H], 3.11 [d, *J* = 7.8 Hz, 1H], 3.59-3.68 [m, 1H], 3.82 [s, 3H], 3.85 [s, 3H], 6.30 [d, *J* = 2.1, 1H], 6.42 [d, *J* = 2.1 Hz, 1H].

^{13}C NMR (75 MHz, CDCl$_3$): 22.3 (CH$_3$), 23.1 (CH$_3$), 43.1 (CH$_2$), 54.4 (CH), 55.7 (OMe), 55.7 (C-*t*Bu), 60.0 (OMe), 95.3 (Q), 96.4 (Ar-H), 107.2 (Ar-H) 116.4 (Q), 146.0 (Q), 163.1 (Ar-OMe), 163.9 (Ar-OMe).

IR (Neat): 3320, 2217 1604, 1581, 1462 cm^{-1}.

ESI-MS: 347 (100), 291 (20).

HRMS: Calcd for C$_{16}$H$_{24}$IN$_2$O$_3$SNa (MNa$^+$) = 347.1405, Found 347.1404.

$[\alpha]_D^{25}$ = -3.7 (4.3, CHCl$_3$).

(S$_s$,R)-(+)-*N*-[1-Methyl-2-(4,6-dimethoxybenzonitrile)-ethyl-*t*-butylsulfinamide ((S$_s$,R)-3.55)
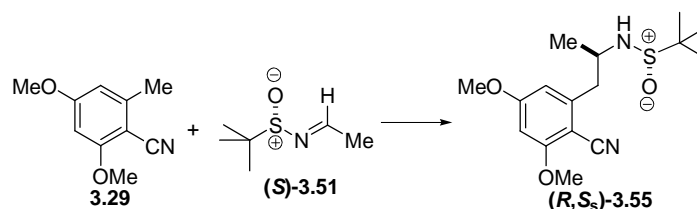
A solution of *n*-BuLi (0.6 mL, 1.9 M, 1.1 mmol) was added to a solution of dry *N,N*-diethylamine (0.12 mL, 1.1 mmol) in dry tetrahydrofuran (1 mL) at -78 °C and the solution allowed to warm to

r.t. over 20 mins. The reaction mixture was cooled to -78 ^{o}C and a solution of the *o*-tolylnitrile **3.29** (0.100 g, 0.57 mmol) in dry tetrahydrofuran (5 mL) added dropwise to give a deep red solution. The reaction was stirred at -78 ^{o}C for 0.5 h after which time a solution of sulfinimine **(*S*)-3.51** (92 mg, 0.6 mmol) in dry tetrahydrofuran (3 mL) at -78 ^{o}C was added dropwise via cannula to give an orange solution. After stirring for 0.5 h at -78 ^{o}C saturated aqueous ammonium chloride solution was added (20 mL) and the mixture extracted with ethyl acetate (*x* 3). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure g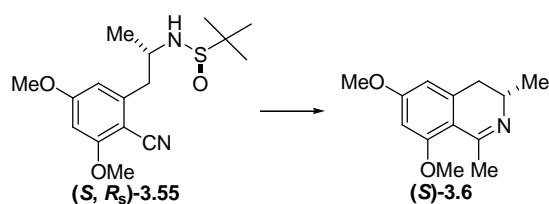ave a yellow gum, which was purified by flash chromatography on silica gel, eluting with ethyl acetate, to give **(*S*$_s$,*R*)-3.55** as a white gum (0.132 g, 71%). The ^{1}H NMR data matched that of the enantiomer, **(*R*$_s$,*S*)-3.55**.

$$[\alpha]_D^{25\,^oC} = +3.7 \ (3.5, \ CHCl_3)$$

All spectroscopic data matched that of the (R$_s$,S)-enantiomer.

(3*S*)-(-)-6,8-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline ((*S*)-3.6)

A solution of methyl lithium in diethyl ether (2.4 mL, 1 M, 2.4 mmol) was added to a solution of sulfinamide **(*S*$_s$,*R*)-3.55** (196 mg, 0.6 mmol) in dry tetrahydrofuran (5 mL) at -78 ^{o}C. The resulting deep red solution was allowed to warm to r.t. over 1 h. Hydrochloric acid (2 M, 5 mL) was added and the reaction mixture stirred vigorously for 2 h. After this time the yellow solution was brought to a pH of 10 with aqueous sodium hydroxide (2M) and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (Na$_2$SO$_4$). Removal of the solvent under reduced pressure gave a pink gum, which was purified by flash chromatography on silica gel, eluting with ethyl acetate and 1% triethylamine, to give **(*S*)-3.6** as a light pink gum (97 mg, 74%).

^{1}H NMR (300 MHz, free base, CDCl$_3$): δ 1.36 [d, J = 6.9 Hz, 3H], 2.31 [dd, J = 15.6, 13.1 Hz, 1 H], 2.41 [s, 3H], 2.58 [dd, J = 15.6, 4.2 Hz, 1H], 3.26-3.33 [m, 1H], 3.83 [s, 6H], 6.31 [d, J = 2.4 Hz, 1 H], 6.35 [d, J = 2.4 Hz, 1H].

^{13}C NMR (75 MHz, free base, CDCl$_3$): δ 21.9, 27.6, 35.2, 51.3, 55.3, 97.1, 104.1, 113.2, 142.4, 158.9, 161.7, 162.9.

A small sample of the gum was converted to its hydrochloride salt at 0 ^{o}C using concentrated HCl (2 mL) in methanol (10 mL). The solid that formed was collected and recrystallised from petroleum ether/dichloromethane.

Data for the hydrochloride salt.

Mp: 194-195 ^{o}C (lit.[10] 190-191 ^{0}C).

$[\alpha]_1^{25^0 C}$ = -138 (1.0, methanol), (lit.[13], -141 (c 0.9, methanol)).

^{1}H NMR (300 MHz, HCl salt, CDCl$_3$): δ 1.51 [d, J = 6.6 Hz, 3H], 2.76 [dd, J = 16.5 Hz, 8.7 Hz, 1 H], 2.95 [s, 3H], 3.05 [dd, J = 16.5, 5.7 Hz, 1H], 3.64 [br s, 1H], 3.94 [s, 3H], 3.96 [s, 3H], 4.01-4.12 [m, 1H], 6.42 [d, J = 2.1 Hz, 1 H], 6.44 [d, J = 2.1 Hz, 1H].[13]

(3R)-(+)-6,8-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline ((R)-3.6)
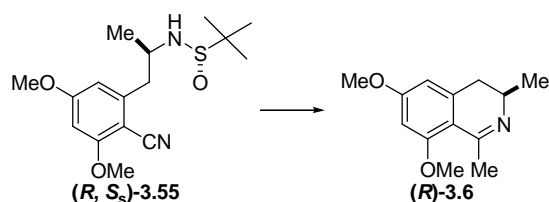
A solution of methyl lithium in diethyl ether (1.9 mL, 1 M, 1.9 mmol) was added to a solution of sulfinamide **(R$_s$,S)-3.55** (157 mg, 0.5 mmol) in dry tetrahydrofuran (4 mL) at -78 ^{o}C. The resulting deep red solution was allowed to warm to r.t. over 1 h. Hydrochloric acid (2 M, 4 mL) was added and the reaction mixture stirred vigorously for 2 h. After this time the yellow solution was brought to a pH of 10 with aqueous sodium hydroxide (2M) and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (Na$_2$SO$_4$). Removal of the solvent under reduced pressure gave a pink gum, which was purified by flash chromatography on silica gel, eluting with ethyl acetate and 1% triethylamine, to give **(R)-3.6** as a light pink gum (54 mg, 50%).

A small sample of the gum was converted to its hydrochloride salt at 0 ^{o}C using concentrated HCl (2 mL) in methanol (10 mL). The solid that formed was collected and recrystallised from petroleum ether/dichloromethane.
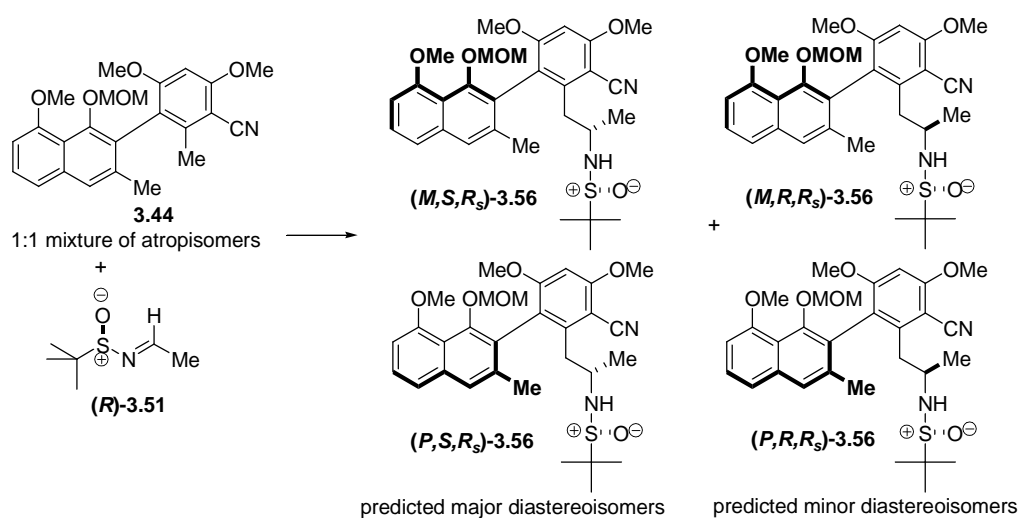
Data for the hydrochloride salt.

Mp: 190-191 ^{o}C (lit.[10] 190-191 ^{0}C).

$[\alpha]_1^{25^{o}C} = +130$ (1.0, methanol), (lit.[10], +139 (c 0.6, methanol)).

Alkylation of 3.44 with *t*-Bu sulfinimine

predicted major diastereoisomers   predicted minor diastereoisomers

A solution of *n*-BuLi in hexanes (1.75 mL, 1.8 M, 3.2 mmol) was added to a solution of dry diethylamine (0.33 mL, 3.2 mmol) in dry tetrahydrofuran (6 mL) at -78 ^{o}C and the solution allowed to warm to r.t. over 20 mins. The pale yellow solution was cooled to -78 ^{o}C and a solution of the biaryl **3.44** (426 mg, 1.05 mmol) in dry tetrahydrofuran (11 mL) was added dropwise. The now deep red solution was stirred at -78 ^{o}C for 0.5 h. After this time sulfinimine **(*R*)-3.51** (202 mg, 1.4 mmol) in dry tetrahydrofuran (6 mL) at -78 ^{o}C was added dropwise via cannula. After stirring for 2 h at -78 ^{o}C the reaction was quenched with saturated aqueous sodium bicarbonate solution and the mixture extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave an orange gum, which was purified by flash chromatography on silica gel eluting with ethyl acetate to give **3.56** as a white solid (426 mg, 75%).

**Mp**: 171-174 °C.

IR (Neat): 3249, 2216, 1625, 1456 cm⁻¹.

¹H NMR (600 MHz, mixture of atropisomers, CDCl₃); δ 0.83 [s, 9H, major diastereoisomer], 0.90 [d, J = 6.0 Hz, 3H, minor diastereoisomer], 0.94 [s, 9H, minor diastereoisomer], 1.03 [d, J = 6.0 Hz, 3H, major diastereoisomer], 1.06 [s, 9H, major diastereoisomer], 1.10 [d, J = 6.0 Hz, 3H, minor diastereoisomer], 1.12 [s, 9H, minor diastereoisomer], 1.17 [d, J = 6 Hz, 3H, minor diastereoisomer], 2.06 [s, 3H, major diastereoisomer], 2.08 [s, 3H, minor diastereoisomer], 2.10 [s, 3H, major diastereoisomer], 2.16 [s, 3 H, minor diastereoisomer], 2.58-2.62 [m, 2H, all diastereoisomers], 2.76-3.02 [m, 22H, all diastereoisomers], 3.12-3.22 [m, 4H, all diastereoisomers], 3.77-3.79 [m, 12H, all diastereoisomers], 3.93-4.00 [m, 24 H, all diastereoisomers], 4.63-4.71 [m, 4H, all diastereoisomers], 4.97-5.00 [m, 4H, all diastereoisomers], 6.46-6.48 [m, 4H, all diastereoisomers], 6.81-6.84 [m, 4H, all diastereoisomers], 7.34-7.40 [m, 8H, all diastereoisomers], 7.51-7.55 [m, 4H, all diastereoisomers].

¹³C NMR (150 MHz, mixture of atropisomers, CDCl₃); δ 20.2, 20.3, 20.9, 22.0, 22.2, 22.4, 22.5, 23.0, 25.2, 41.1, 41.6, 42.0, 50.4, 50.6, 53.2, 54.7, 55.1, 55.2, 55.3, 55.77, 55.79, 56.0, 56.1, 56.17, 56.21, 56.4, 56.5, 92.7, 92.96, 93.05, 93.3, 95.7, 96.5, 100.4, 105.2, 105.4, 105.7, 106.0, 117.3, 117.7, 118.8, 119.0, 120.56, 120.63, 120.7, 120.8, 121.1, 125.0, 125.1, 126.3, 126.4, 127.0, 127.1, 136.3, 136.6, 137.0, 137.2, 144.1, 144.8, 149.6, 150.1, 155.9, 162.16, 162.19, 162.7, 162.9, 163.2.

ESI-MS: 577 (100%).

HRMS: Calculated for C₃₀H₃₈N₂NaO₆S (MNa⁺) 577.2348, found 577.2350.

Ancistrotanzanine A ((*M,S*)-1.124)
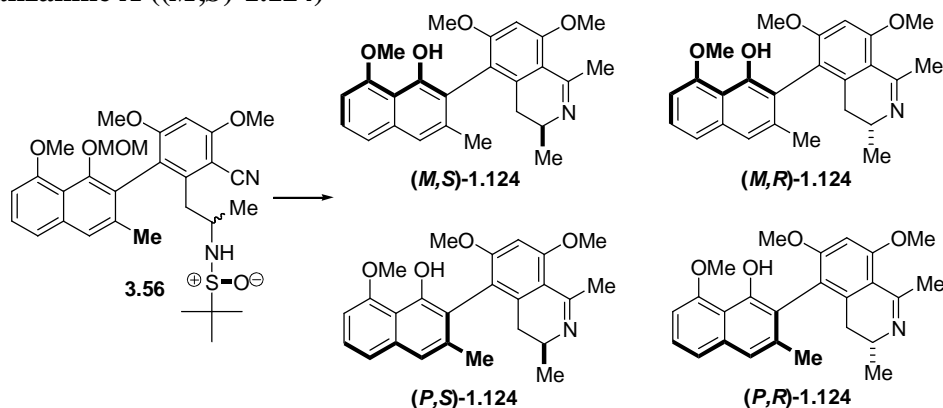
A solution of methyllithium in ether (1.6 mL, 1 M, 1.6 mmol) was added to a solution of sulfinamide **3.56** (179 mg, 0.32 mmol) in dry tetrahydrofuran (4 mL) at -78 $^{\circ}$C. The resulting deep red solution was allowed to warm to r.t. over 1 h. Hydrochloric acid (2 M, 10 mL) was added and the reaction mixture stirred vigorously for 2 h. After this time the yellow solution was brought to a pH of 10 with 10% aqueous sodium hydroxide solution and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a brown smear, which was purified by flash chromatography on reverse phase silica gel, eluting with methanol, to give ancistrotanzanine A (*M, S*)-**1.124** as a light yellow solid (100 mg, 77%) as a 1:1 mixture of atropisomers from integration of the methyl signals at 1.20 and 1.25.

Mp: 181-184 $^{\circ}$C

IR (Neat): 3342, 3164, 2725, 2688, 2358, 2324, 1711, 1633, 1580 cm^{-1}.

^{1}H NMR (600 MHz, mixture of atropisomers, CDCl$_3$); δ 1.20 [d, *J* = 6.6 Hz, 3H, one atropisomer], 1.25 [d, *J* = 6.6 Hz, 3H, one atropisomer], 1.86-1.94 [m, 1H, one atropisomer], 2.04-2.18 [m, 2H, one atropisomer], 2.05 [s, 3H, one atropisomer], 2.08 [s, 3H, one atropisomer], 2.36 [m, 1H, one atropisomer], 2.49 [s, 6H, both atropisomers], 3.12-3.23 [m, 1H, one atropisomer], 3.33-3.42 [m, 1H, one atropisomer], 3.77 [s, 3H, one atropisomer], 3.78 [s, 3H, one atropisomer], 3.94 [s, 6H, both atropisomers], 4.00 [s, 3H, one atropisomer], 4.02 [s, 3H, one atropisomer], 6.51 [s, 2H, both atropisomers], 6.72 [dd, *J* = 1.8, 7.8 Hz, 2H, both atropisomers], 7.24 [s, 1H, one atropisomer], 7.25 [s, 1H, one atropisomer], 7.29 [t, *J* = 7.8 Hz, 2H, both atropisomers], 7.37 [dd, *J* = 3.0, 7.8 Hz, 2H both atropisomers], 9.44 [s, 1H, one atropisomer], 9.46 [s, 1H, one atropisomer].

^{13}C NMR (150 MHz, mixture of atropisomers, CDCl$_3$); δ 20.3, 20.4, 21.4, 22.3, 27.6, 31.7, 31.9, 55.42, 55.43, 55.71, 55.75, 55.99, 56.01, 93.8, 93.9, 103.26, 103.33, 113.42, 113.45, 118.6, 118.7, 121.2, 125.56, 125.59, 136.1, 137.7, 138.2, 140.9, 141.5, 150.9, 151.5, 156.1, 156.2.

ESI-MS 406 (100%).

HRMS: Calculated for $C_{25}H_{28}NO_4$ (MH$^+$) 406.2018, found 406.2014.

Spectroscopic data for the ^{1}H NMR Data of the trifluroacetic acid salt.

IR (Neat): 3374, 2953, 2923, 2852, 2363, 2313, 1778, 1738, 1671, 1633, 1611 cm^{-1}.

¹H NMR (600 MHz, mixture of atropisomers, CD$_3$OD); δ 1.27 [d, J = 6.8 Hz, 3H, one atropisomer], 1.30 [d, J = 6.8 Hz, 3H, one atropisomer], 2.02 [s, 3H, one atropisomer], 2.06 [s, 3H, one atropisomer], 2.38-2.47 [m, 1H, one atropisomer], 2.55-2.63 [m, 2H, one atropisomer], 2.76-2.81 [m, 1H, one atropisomer], 2.79 [s, 6H both atropisomers], 3.76-3.86 [m, 2H, both atropisomer], 3.877 [s, 3H, one atropisomer], 3.881 [s, 3H, one atropisomer], 4.02 [s, 6H, both atropisomers], 4.11 [s, 6H, both atropisomers], 6.79 [s, 2H, both atropisomers], 6.87 [d J = 7.0 Hz, 2H, both atropisomers], 7.23 [s, 2H, both atropisomer], 7.30-7.36 [m, 4H, both atropisomers].

¹³C NMR (150 MHz, CD$_3$OD); 18.5, 18.6, 20.8, 25.28, 25.34, 33.1, 33.2, 57.22, 57.24, 57.41, 57.43, 96.2, 105.48, 105.50, 109.45, 109.53, 115.1, 118.06, 118.12, 120.5, 120.6, 121.0, 121.2, 122.6, 128.0, 138.4, 138.5, 138.8, 141.6, 141.9, 152.8, 153.2, 158.04, 158.06, 161.8, 166.72, 166.74, 168.0, 176.26, 176.33.

HPLC Analysis: Analytical HPLC for the measurements of both the synthetic sample and natural sample of ancistrotanzanine A were measured on an achiral analytical Symmetry-C$_{18}$ (*Waters*, 4.6 *x* 250 mm) column with the eluents in acetonitrile/water (+ 0.05% trifluoroacetic acid using a linear gradient (0 min 20% A, 25 min 55% A) with a flow rate of 1.0 mL/min. This gave a retention time of 28.93 min for the synthetic sample of ancistrotanzanine A and a retention time of 28.92 min for the natural sample of ancistrotanzanine A.

Analytical HPLC for the resolution of the synthetic ancistrotanzanine A sample was carried out on a *Jasco* HPLC-system, and was conducted by Tobias Buettner in Professor Gerhard Bringmann's laboratory in Wurzburg.

The sample was measured on two achiral columns:

- Chromolith (*Waters*, 4.6 *x* 100 mm)
- Symmetry-C$_{18}$ (*Waters*, 4.6 *x* 250 mm)

    Eluants in both cases: acetonitrile/water + 0.05% trifluoroacetic acid (different gradients)

    Results: always one peak, no separation

And two chiral columns:

- Chiral-OD-H (*Daicel*, 4.6 *x* 250 nm)

    Eluents: *iso*-propanol/*n*-hexane (different gradients)

- Chiral-OD-RH (*Daicel*, 4.6 *x* 250 nm)

  Eluents: acetonitrile/water + 0.05% trofluoroacetic acid (different gradients)

        iso-propanol/methanol (different gradients, several isocratic runs)

  Results: always one peak, no separation

2-((1*R*,3*S*)-1,2,3,4-Tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinolin-5-yl)-8-methoxy-3-methylnaphthalen-1-ol (3.62)
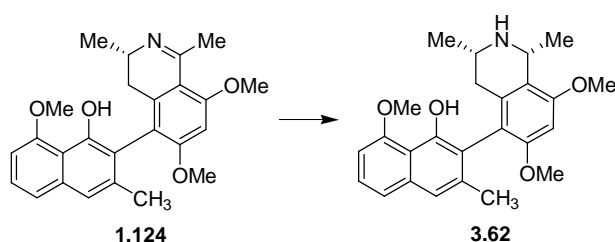
Sodium borohydride (18 mg, 0.48 mmol) was added in one portion to a solution of ancistrotanzanine A (**1.124**) (1:1 mixture of atropisomers, 34 mg, 0.08 mmol) in methanol (9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then warmed to r.t. o.n. The mixture was filtered through a plug of Celite with dichloromethane (10 mL) and the solvent removed under reduced pressure. Purification by flash chromatography on reverse phase silica gel, eluting with methanol, afforded the title compound as a yellow solid (33 mg, 98% yield) as a mixture of diastereoisomers. Due to the complexity of the ^{1}H NMR data, the chemical shifts are given without integration.

Mp: 99-102 °C.

IR (Nujol Mull): 3370, 3172, 1633, 1609, 1567 cm^{-1}.

^{1}**H NMR** (600 MHz, mixture of diastereoisomers, CDCl$_3$): δ 1.03-1.06 [m], 1.20 [d, *J* = 6.7 Hz], 1.23-1.27 [m], 1.43 [d, *J* = 6.7 Hz], 1.45 [d, *J* = 6.7 Hz], 1.82-187 [m], 2.03-2.19 [m], 2.32-2.35 [m], 2.49 [s], 2.71-2.78 [m], 2.81-2.88 [m], 3.70 [s], 3.76 [s], 3.77 [s], 3.87 [s], 3.88 [s], 3.93 [s], 3.98 [s], 3.99 [s], 4.31-4.34 [m], 4.37-4.41 [m], 6.48 [s], 6.50 [s], 6.70-6.71 [m], 7.23-7.29 [m], 7.35-7.36 [m], 9.36 [br s], 9.42 [br s], 9.44 [br s], 9.46 [br s].

^{13}**C NMR** (150 MHz, mixture of atropisomers, CDCl$_3$): 14.2, 20.2, 20.3, 20.4, 20.5, 21.0, 21.46, 21.49, 22.3, 22.5, 22.6, 22.8, 23.0, 23.1, 27.6, 27.7, 29.7, 31.7, 31.9, 35.4, 36.8, 42.1, 42.2, 47.4, 48.2, 48.4, 49.7, 49.8, 51.1, 51.5, 54.95, 54.99, 55.12, 55.37, 55.66, 55.7, 55.8, 55.90, 55.94, 55.96, 55.98, 56.09, 56.4, 60.3, 93.4, 93.68, 93.76, 93.86, 94.0, 103.0, 103.1, 103.23, 103.30, 112.9, 113.3, 113.4, 113.5, 113.6, 116.4, 116.8, 117.1, 118.4, 118.5, 118.6, 118.7, 119.7, 119.9, 121.0, 121.2, 121.5, 125.2, 125.5, 125.6, 135.5, 135.91, 135.94, 136.0, 136.9, 137.6, 137.7,

138.11, 138.16, 138.46, 140.86, 141.4, 150.2, 150.9, 151.3, 151.5, 155.5, 155.6, 156.1, 156.9, 157.05, 157.07, 158.5, 158.6, 159.47, 159.53.

ESI-MS: (MNa$^+$) 430 (100%).

HRMS: Calcd for $C_{25}H_{30}NO_4$ (MH$^+$) 408.2175, found 408.2169.

Analytical HPLC for the resolution of the *cis*-tertrahydro analogue was carried out on a *Jasco* HPLC-system, and was conducted by Tobias Buettner in Professor Gerhard Bringmann's laboratory in Wurzburg.

The sample was measured on two achiral columns:

- Chromolith (*Waters*, 4.6 *x* 100 mm)

- Symmetry-C$_{18}$ (*Waters*, 4.6 *x* 250 mm)

  Eluants in both cases: acetonitrile/water + 0.05% trifluoroacetic acid (different gradients)

  Results: always one peak, no separation.

And two chiral colums:

- Chiral-OD-H (*Daicel*, 4.6 *x* 250 nm)

  Eluents: *iso*-propanol/*n*-hexane (different gradients)

- Chiral-OD-RH (*Daicel*, 4.6 *x* 250 nm)

  Eluents: acetonitrile/water + 0.05% trofluoroacetic acid (different gradients)

     iso-propanol/methanol (different gradients, several isocratic runs)

  Results: always one peak, no separation.

4,6-Dimethoxy-3-(1,8-dimethoxy-3-methylnaphthalen-2-yl)-2-methylbenzonitrile (3.67)
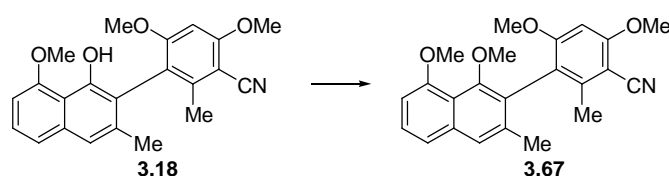
A solution of naphthol **3.18** (363 mg, 1.0 mmol) in dry *N,N*-dimethylformamide (7 mL) was added to a suspension of sodium hydride (60% in mineral oil, 80 mg, 2.0 mmol) in dry *N,N*-dimethylformamide (8 mL). The reaction was stirred for 1 h at r.t. resulting in a turbid red solution. Iodomethane (0.31 mL, 5.0 mmol) was added dropwise and the reaction stirred at r.t.

overnight. The reaction was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (*x* 4). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with dichloromethane, to give the title compound as a white solid (358 mg, 95%).

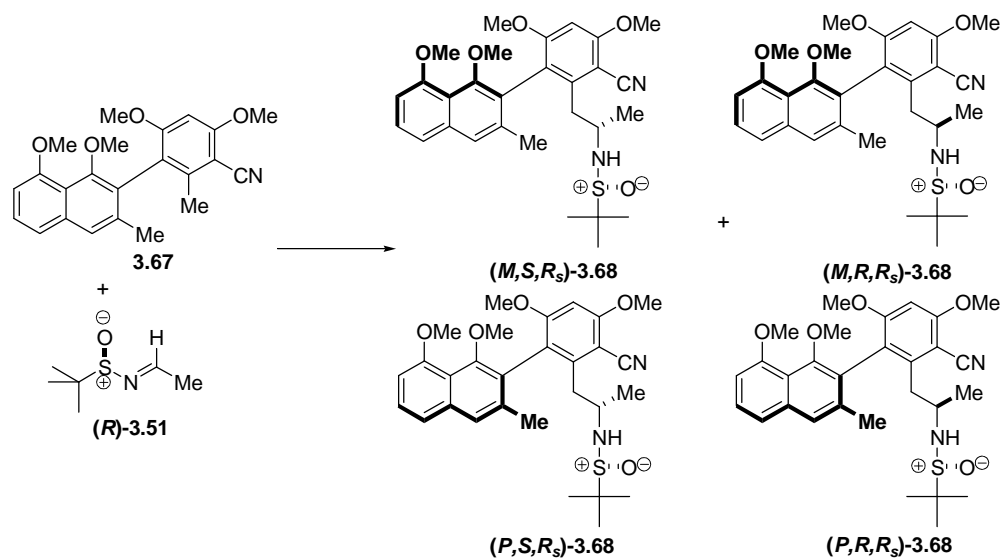**Mp**: 87-88 °C

IR (Neat): 2215 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 2.02 [s, 3H], 2.15 [s, 3H], 3.50, [s, 3H], 3.77 [s, 3H], 3.98 [s, 3H], 4.00, [s, 3H], 6.44 [s, 1H], 6.82 [dd, J = 3.0 Hz, J = 6.0 Hz, 1H], 7.33-7.39 [m, 2H], 7.49 [d, J = 0.9 Hz, 1H].

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.6, 19.9, 55.7, 55.9, 56.1, 61.4, 92.1, 94.7, 105.1, 116.7, 118.7, 119.8, 120.3, 124.2, 126.2, 127.5, 136.4, 137.0, 143.3, 153.7, 156.1, 161.4, 162.8.

LRMS (ES) 378 (100%).

HRMS: Calcd for C$_{23}$H$_{24}$NO$_4$ (MH$^+$) = 378.1705, found 378.1702.

Alkylation of 3.67

A solution of *n*-BuLi in hexanes (0.82 mL, 2.2 M, 1.8 mmol) was added to a solution of dry diethylamine (0.19 mL, 1.8 mmol) in dry tetrahydrofuran (4 mL) at -78 °C and the solution allowed to warm to r.t. over 20 mins. The pale yellow solution was cooled to -78 °C and a solution of biaryl **3.67** (228 mg, 0.6 mmol) in dry tetrahydrofuran (4 mL) was added dropwise. The now deep red solution was stirred at -78 °C for 0.5 h. After this time sulfinimine **(*R*)-3.51**

(115 mg, 0.78 mmol) in dry tetrahydrofuran (2 mL) at -78 $^{\circ}$ C was added dropwise via cannula to give a brown solution. After stirring for 2 h at -78 $^{\circ}$C the reaction was quenched with saturated aqueous sodium bicarbonate solution (10 mL) and the mixture extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (MgSO$_4$). Removal of the solvent under reduced pressure gave a pink gum which was purified by flash chromatography on silica gel eluting with ethyl acetate to give **3.68** as a white solid (223 mg, 67%).

Mp:165-167 $^{\circ}$C.

**IR** (Nujol Mull): 3177, 2215, 1586, 1565 cm^{-1}.

^{1}H NMR (600 MHz, mixture of atropisomers, CDCl$_3$): δ 0.81 [s, 9H, major diastereoisomer], 0.92 [d, *J* = 6.0 Hz, 3H, minor diastereoisomer], 0.96 [s, 9H, minor diastereoisomer], 1.02 [d, *J* = 6.0 Hz, 3H, major diastereoisomer], 1.05 [s, 9H, major diastereoisomer], 1.09 [d, *J* = 6.0 Hz, 3H minor diastereoisomer], 1.12 [s, 9H, minor diastereoisomer], 1.16 [d, *J* = 6.0 Hz, 3H major diastereoisomer], 2.04 [s, 3H, major diastereoisomer], 2.06 [s, 3H, minor diastereoisomer], 2.08 [s, 3H, major diastereoisomer], 2.09 [s, 3H, minor diastereoisomer], 2.57-2.79 [m, 8H, all diastereoisomers], 2.85-3.15 [m, 8H, all diastereoisomers], 3.45-3.48 [m, 12 H, all diastereoisomers], 3.79-3.81 [m, 12 H, all diastereoisomers], 3.96-4.02 [m, 24 H, all diastereoisomers], 6.45-6.49 [m, 4H, all diastereoisomers], 6.82-6.84 [m, 4H, all diastereoisomers], 7.34-7.40 [m, 4H, all diastereoisomers], 7.49-7.54 [m, 4H, all diastereoisomers].

^{13}C NMR (150 MHz, mixture of atropisomers, CDCl$_3$): δ 20.0, 20.1, 21.1, 22.0, 22.3, 22.4, 22.7, 22.88, 22.95, 24.2, 25.17, 29.7, 40.9, 41.4, 42.0, 50.5, 50.7, 53.0, 54.5, 55.1, 55.2, 55.6, 55.97, 55.99, 56.0, 56.1, 56.2, 56.47, 56.52, 61.31, 61.37, 61.39, 92.6, 92.8, 93.0, 93.3, 96.3, 97.0, 105.0, 105.3, 105.8, 105.9, 116.9, 117.2, 117.6, 118.8, 119.1, 120.0, 120.31, 120.34, 120.4, 120.5, 124.57, 124.64, 124.7, 126.4, 126.5, 126.56, 126.62, 136.4, 136.5, 136.7, 137.1, 137.2, 137.3, 143.9, 144.1, 144.2, 144.8, 153.0, 153.5, 156.20, 156.24, 156.3, 161.56, 161.59, 161.7, 162.6, 162.8, 163.1.

ESI-MS 525 (100%).

HRMS: Calcd for C$_{29}$H$_{37}$N$_2$O$_5$S (MH$^+$) = 525.2418, found 525.2420.

(*S*)-3,4-Dihydro-6,8-dimethoxy-5-(1,8-dimethoxy-3-methylnaphthalen-2-yl)-1,3-dimethyl-isoquinoline (3.63)
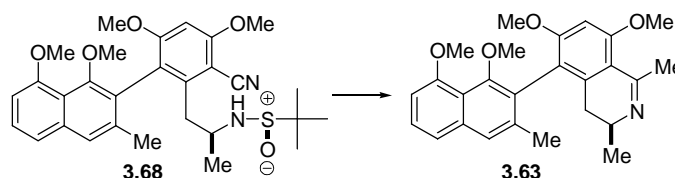
A solution of methyllithium in diethyl ether (1.4 mL, 1 M, 1.4 mmol) was added to a solution of sulfinamide **3.68** (141 mg, 0.27 mmol) in dry tetrahydrofuran (4 mL) at -78 °C. The resulting deep red solution was allowed to warm to r.t. over 1 h. Hydrochloric acid (2 M, 10 mL) was added and the reaction mixture stirred vigorously for 2 h. After this time the yellow solution was brought to a pH of 10 with 10% aqueous sodium hydroxide and extracted with ethyl acetate (*x* 4). The organic extracts were combined and washed with water, saturated brine solution and dried (Na$_2$SO$_4$). Removal of the solvent under reduced pressure gave a brown smear, which was purified by flash chromatography on reverse phase silica gel eluting with methanol to give the title compound as a white solid (43 mg, 37%) as a 63:37 mixture of atropisomers from integration of the methyl signals at 2.01 and 2.03.

Mp: 84-86 °C

IR (Neat): 2727, 1613, 1584, 1567 cm^{-1}.

^{1}H NMR (300 MHz, mixture of atropisomers (relative ratio 63:37), CDCl$_3$): δ 0.86-0.89 [m, 2H], 1.18 [d, *J* = 6.9 Hz, 3H,], 1.24 [d, *J* = 6.9 Hz, 3H,], 1.85-1.90 [m, 2H], 2.01 [s, 3H], 2.03 [s, 3H], 2.31-2.38 [m, 3H], 2.50 [s, 3H], 2.61 [s, 3H], 3.02-3.18 [m, 1H], 3.29-3.38 [m, 1H], 3.49 [s, 3H], 3.53 [s, 3H], 3.76 [s, 3H], 3.77 [s, 3H], 3.96 [s, 3H], 3.97 [s, 3H], 3.98 [s, 3H], 6.48 [s, 2H], 6.81-6.83 [m, 2H], 7.31-7.39 [m, 4H], 7.49 [s, 1H], 7.50 [s, 1H].

^{13}C NMR (150 MHz, mixture of atropisomers, CDCl$_3$): δ 20.08, 20.13, 20.17, 21.4, 22.3, 22..7, 27.4, 29.3, 29.7, 31.9, 32.4, 50.7, 51.5, 55.38, 55.44, 55.45, 55.49, 55.9, 56.0, 56.16, 56.18, 61.3, 61.5, 61.7, 93.18, 93.24, 93.35, 104.9, 105.1, 105.2, 113.8, 117.0, 117.5, 118.9, 120.3, 120.31, 123.9, 124.0, 126.1, 127.9, 136.5, 136.92, 136.94, 137.0, 140.6, 141.2, 153.6, 154.4, 156.18, 156.20.

ESI-MS 442 (100%).

HRMS: Calculated for C$_{26}$H$_{30}$NO$_4$ (MH$^+$) 420.2175, found 420.2169.

5.4   References

(1)   Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923

(2)   Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry, Second Edition*; Blackie Academic & Professional, 1995.

(3)   Suffert, J. *J. Org. Chem.* **1989**, 509.

(4)   Linderman, R. J.; Jaber, M.; Griedel, B. D. *J. Org. Chem.* **1994**, 6499.

(5)   Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877.

(6)   Borchardt, R. T.; Sinhababu, A. K. *J. Org. Chem.* **1981**, *46* 5021.

(7)   Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2773.

(8)   Bungard, C. J.; Morris, J. C. *J. Org. Chem.* **2002**, *67* 2361.

(9)   Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 2068.

(10)   Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, 3901.

(11)   Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 7559.

(12)   Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269.

(13)   Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.