

The Design and Synthesis of a Novel Series of Chiral Catalysts

Richard Grant

A thesis submitted for the
degree of Doctor of Philosophy

Edinburgh University

June 2001



This thesis is submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy in the University of Edinburgh. Unless otherwise stated the work described is original and has not been previously submitted in whole or in part for any other degree at this or any other university.

Richard Grant
Edinburgh University, 2001

To my family and friends.

Acknowledgements

I would like to thank Professor R. Ramage FRS for the provision of research facilities and for his constant support and encouragement throughout the course of this work.

I wish to thank AstraZeneca (Grangemouth) for the provision of funds. In particular, I would like to thank Dr R. Jones for his support and encouragement.

I also thank the technical staff at the University of Edinburgh for their rapid and efficient work. Special thanks are due to Dr D.Reed and John Millar for the NMR studies.

I thank Lynne Crawford for her service as proof reader.

Finally, I really need to thank the following people for making my time here so enjoyable and unforgettable: Ramage Group Members '97-2000 (especially Carolyn and Ruairidh), Dale, Iain, Lynne, Ken and Johnstone, Katie, Wee Robbie, and all the lads from the Championship Winning Chemsoc Football Team.

Abstract

Design and Synthesis of a Novel Series of Chiral Catalysts

The last twenty years have witnessed a great increase in the discovery and development of chiral reagents for application in asymmetric synthesis. The aim of this project was to develop a novel series of chiral ligands from inexpensive materials, and to assess their potential as chiral catalysts in asymmetric synthesis. This was to be achieved through the exploitation of the chirality of the biphenanthryl system.

A pre-existing route into such asymmetrically substituted biphenanthryl systems was optimised to give quantities of racemic 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde. Resolution of this racemate was achieved through the formation of a diastereoisomeric hydrazone with S-AMP.

Chirally pure 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde was used as the starting point for the generation of a series of chiral catalysts. Four bi-dentate biphenanthryl ligands were developed and applied in asymmetric synthesis. A chiral hydrazone, oxime and *tert*-amine were applied in the asymmetric addition of diethylzinc to aldehydes. A primary amine was synthesised and applied in the enantioselective borane reduction of pro-chiral ketones. Chiral GC analysis of the modified substrates from these reactions was carried out by Avecia.

Finally, attempts were made to modify the chiral biphenanthryl moiety towards the synthesis of a chiral dihydropyridine reagent. This system was hoped to mimic the co-enzyme NADH.

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Abbreviations

Ac	acetyl
Ac₂O	acetic anhydride
AcOH	acetic acid
b	broad
BH₃.Me₂S	borane-methyl sulfide complex
BINAL-H	binaphthyl analogue of LiAlH ₄
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1-bi-2-naphthol
Binaphthol	1,1-bi-2-naphthol
Biphenanthrol	10,10'-dihydroxy-9,9'-biphenanthryl
BOC	<i>tert</i> -butoxycarbonyl
Bn	benzyl
b.p.	boiling point
Bu	butyl
CE	cholesterol esterase
d	doublet
2D	two dimensional
DBNE	(1S,2R)- <i>N,N</i> -di- <i>n</i> -butylnorephedrine
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
d.e.	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact
Et	ethyl
EtOAc	ethyl acetate

EtOH	ethanol
FAB	fast atom bombardment
FTIR	Fourier transform infra-red
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
Hz	hertz
LDA	lithium diisopropylamide
LiAlH₄	lithium aluminium hydride
lit.	literature value
<i>m</i>	<i>meta</i>
m	multiplet
Me	methyl
MeI	methyl iodide
MeOH	methanol
MOP	2-(diphenylphosphino)-2'-alkoxy-1,1'-binaphthyl
MOP-phen	biphenanthryl analogue of MOP
m.p.	melting point
MS	mass spectrometry
MTB	methyl <i>tert</i> -butyl ether
MW	molecular weight
<i>n</i>	normal
NaOAc	sodium acetate
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
NADH	nicotinamide adenine dinucleotide
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Pearlmans catalyst	palladium hydroxide on carbon
PEG	polyethylene glycol
Ph	phenyl
ppm	parts per million
q	quartet (NMR)

R	alkyl
R_F	retention factor
s	singlet (NMR)
S-AMP	(S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
<i>t</i>	tertiary
t	triplet (NMR)
TBAH	tetra- <i>n</i> -butylammonium hydroxide
Tbf	tetrabenz[a,c,g,i]fluorene
Temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
X	heteroatom

1. Introduction

1.1. Asymmetric Synthesis

Louis Pasteur's theory of molecular asymmetry, presented in a paper before the Paris Academy of Sciences in 1848, revealed a remarkable discovery – that enantiomers of tartaric acid behave differently towards plane polarised light¹. Pasteur had discovered that, though enantiomers have identical physical and chemical properties, they behave differently in chiral environments. There are 20 naturally occurring translational amino acids which are all (but one) enantiomeric, but predominantly one enantiomer is found in natural samples. In the course of synthesising natural products chemists have had to acknowledge the fact that enantiopurity is related to biological properties. These differences in how enantiomers interact within organisms are potentially enormous, with possibly devastating consequences. A wide range of biological and physical functions result from precise molecular recognition that involves strict matching of chirality. In living systems, enzymes, receptors and other binding sites interact with enantiomers in decisively different manners, with different levels and/or types of activity.

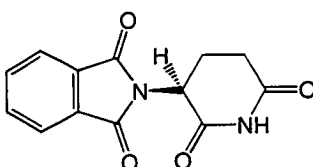


Figure 1.1: (+)-Thalidomide

Between 1958 and 1962 the sedative thalidomide (**Figure 1.1**) was prescribed to pregnant women as a racemic mixture. Unknown at the time the lesser sedating (-)-enantiomer was responsible for teratogenic side effects². It has been estimated that in the former West Germany alone, 10,000 children were born with deformities. Only 5,000 of these survived; the others died from other malformations.

The chiral drug propranolol (**Figure 1.2**) was introduced in the 1960's as a beta-blocker in the treatment of heart disease³. However, it is only the (-)-enantiomer which has this property; the (+)-enantiomer acting as a contraceptive.

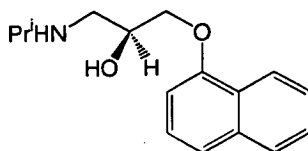


Figure 1.2: (+)-*propranolol*

(L)-3,4-Dihydroxyphenylalanine (L-DOPA) is used in the treatment of Parkinson's disease⁴; a neurological disorder characterised by tremor, rigidity, and disturbances of posture. L-DOPA is a chiral prodrug, which can pass through the blood-brain barrier, after which it is converted to the active achiral drug dopamine by the enzyme dopa decarboxylase (**Figure 1.3**). Dopamine itself cannot be administered as it cannot pass through this blood-brain barrier, whilst the enzyme dopa decarboxylase is stereoselective and reacts only with the (-)-enantiomer of L-DOPA. As a result DOPA must be delivered as the pure (-)-enantiomer to avoid a dangerous build up of the (+)-enantiomer in the body.

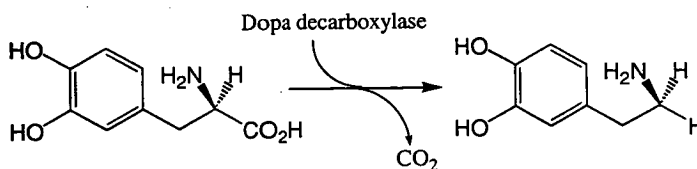


Figure 1.3: *L-Dopa mechanism of action*

Such examples have resulted in an increased awareness for pharmaceutical companies to synthesise chirally pure material, with the realisation that pharmacological studies on racemates can lead to unsound and

misleading data. Adequate information must be provided to establish the safety and effectiveness of any new drug. The US Food and Drug Administration prohibits the marketing of racemates and requires investigation into the pharmacological effect of a chiral drug and background information on each enantiomer.

Many of the more complicated organic molecules in the pharmaceutical industry possess chirality, and often only one enantiomer will be the desired product from a synthesis. Thus control of stereochemistry and the design of new strategies for asymmetric synthesis have become increasingly important.

To save both material and time it is desirable to find ways of producing one enantiomer rather than a racemate that must undergo subsequent chiral resolution. One approach to solving this problem is to introduce specific chirality to the substrate through the use of a chiral reagent.

In synthesis, where the generation of chirally pure material is desired, a reaction proceeds *via* a diastereomeric transition state. There will be two possible products from the reaction but the transition state of one is more favourable than the other. Whilst enantiomeric transition states must be of equal energy, diastereomeric transition states need not be and the reaction proceeds through the lower energy transition state to give an excess of one diastereoisomer (Figure 1.4).

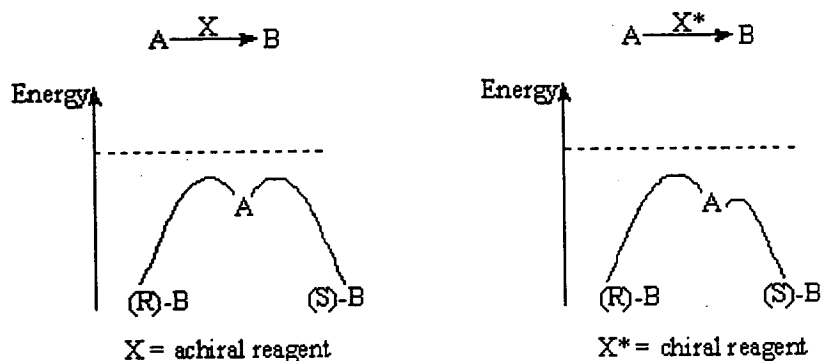


Figure 1.4: *Enantiomeric vs. diastereomeric transition states*⁵

Stereoselectivity is possible only *via* diastereomeric transition states. Where the starting material is chiral and one diastereoisomer is formed preferentially to the other, synthesis is diastereoselective. Where the starting material is achiral and the preferential formation of one enantiomer is desired, the reaction requires a chiral reagent, intrinsically or as a result of chelation, solvation, etc., in order to generate the diastereomeric transition state. Such a synthesis is enantioselective.

In this enantioselective reaction, the chiral reagent (or chiral catalyst) would temporarily attach itself to an achiral substrate. As the reaction proceeds, a new stereocentre is established in what is essentially a diastereomeric relationship to that in the catalyst.

There are some important consequences from the products of such a reaction being enantiomeric rather than diastereomeric. If recrystallisation is the only effective means of purification, an enantiomeric excess of 90% represents the lower level from which it is possible to obtain pure material with acceptable loss. The catalysed reaction must proceed more rapidly than any competing uncatalysed reactions, and the product must be released from co-ordination to the reagent under reaction conditions. The chiral catalyst would ideally produce modified chiral compounds on a large scale with good stereospecificity, and with only a small amount of catalyst. The chiral catalyst should be chirally pure and unchanged itself at the end of the reaction, ready for recycling (**Figure 1.5**).

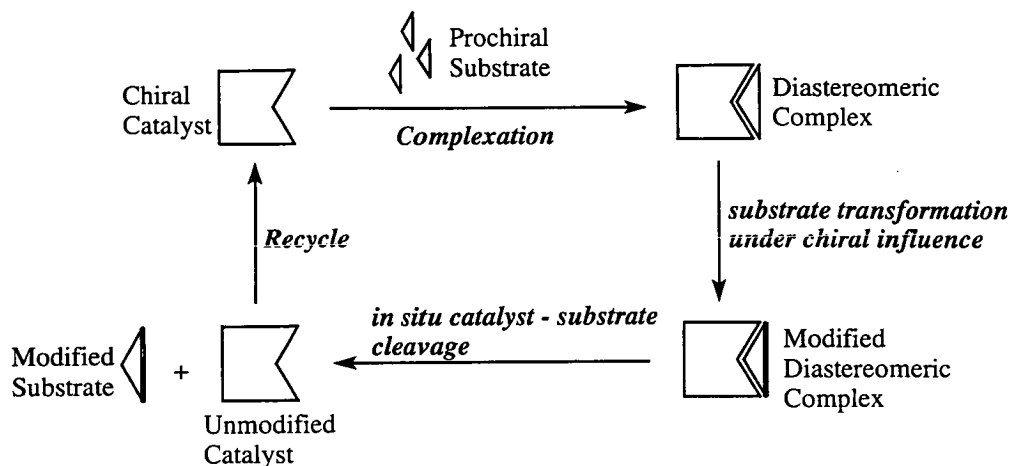


Figure 1.5: *The chiral catalyst*

A related chiral reagent to the chiral catalyst is the chiral auxiliary. The chiral auxiliary is typically used in stoichiometric amounts to the achiral substrate, though it, too, should ideally be recyclable. The typical usage of such a chiral auxiliary involves coordination to the substrate before the reaction and, isolation/removal after the reaction to yield pure chiral product (**Figure 1.6**).

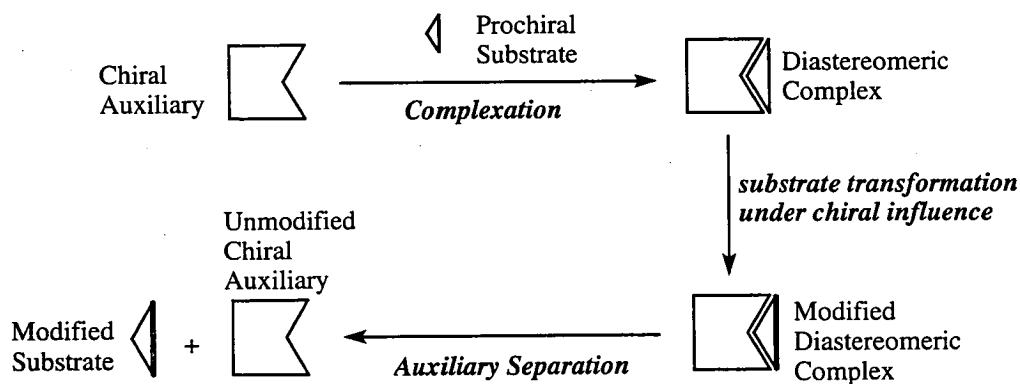


Figure 1.6: *The chiral auxiliary*

The Chiral Auxiliary

In 1981, Evans⁶ showed how chiral 2-oxazolidones could be used as recyclable chiral auxiliaries, for carboxylic acids in highly enantioselective aldol condensations *via* the boron enolates (**Figure 1.7**). These oxazolidones were derived from either (S)-valinol or (1S,2R)-norephedrine, and undergo highly enantio-selective enolisation with dibutylboryl trifluoromethanesulfonate to form the (Z)-enolates (Z:E $\geq$ 100). Condensation of these enolates with aldehydes gives aldol *erythro*-adducts, which readily hydrolyse without racemisation of either centre to the corresponding carboxylic acid.

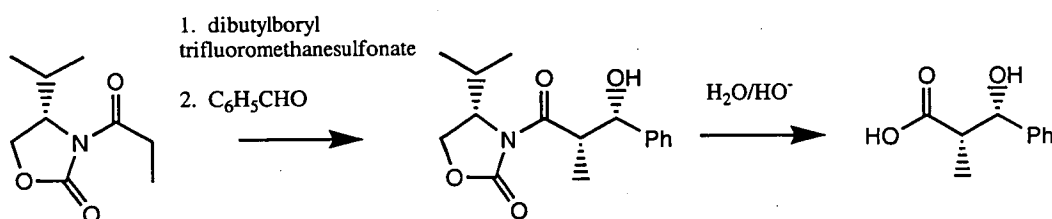


Figure 1.7: *Erythro*-selective chiral aldol condensations *via* boron enolates

The enantioselective reduction of prochiral ketones is one of the most extensively studied areas in asymmetric reactions⁷. By the early 1980's there were a number of methods available, utilising complex metal hydride reagents bearing chiral alkoxy or amino ligands⁸. Many of these reagents were comprised of modified lithium aluminium hydride (LiAlH_4) with derivatives of materials from the chiral pool, materials such as sugars⁹, amino alcohols¹⁰ and alkaloids¹¹. In the reduction of prochiral ketones these modified LiAlH_4 systems failed to obtain high levels of enantioselectivity, a failing ascribed to the *in situ* creation of plural reactive species¹². For example, the complexation of LiAlH_4 with 2 equivalents of the chiral alcohol R^*OH would introduce a chiral environment to the hydride reagent through the formation of $\text{LiAlH}_2(\text{OR}^*)_2$. The resultant hydride reagent now bears two chemically identical hydrides. Unfortunately, the aluminium hydride undergoes disproportionation, with the generation of mixtures of $\text{LiAl}(\text{OR}^*)_4$, $\text{LiAlH}_n(\text{OR}^*)_{4-n}$ ($n = 1-3$), and the achiral

LiAlH_4 . To add further complication there are a number of conformations available to each of the chiral ligands, the overall effect being a lack of enantioselectivity in the reduction by the metal hydride reducing reagent. The minimisation of the number of reactive species through the creation of a single, highly reactive hydride, which possesses chiral recognition, is crucial for the attainment of high enantioselection in this reduction.

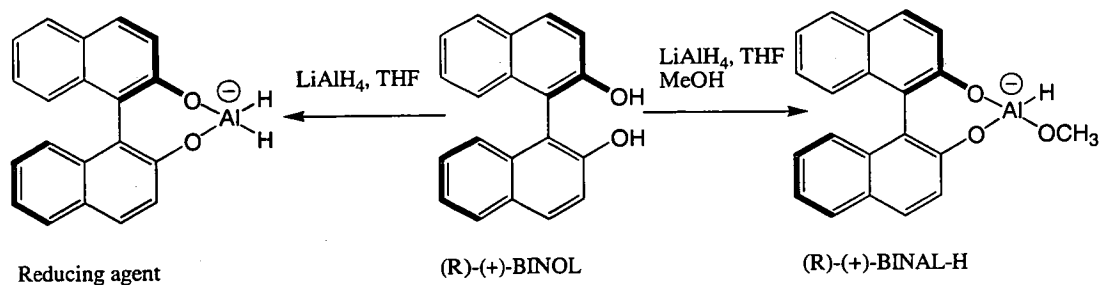


Figure 1.8: Preparation of *(R)*-(+)-BINAL-H from *(R)*-(+)-BINOL

A potential solution to this was the utilisation of bifunctional ligands such as diols, diamines and amino alcohols¹³. Initial investigation into the asymmetric reduction of acetophenone by BINOL-modified LiAlH_4 produced disappointing results, with only 2% ee¹⁴ (**Figure 1.8**). This was attributed to undesired disproportionation of the chiral aluminium hydride, as witnessed in the initial chiral reducing reagents. The hydrogens of the BINOL-modified LiAlH_4 are homotopic and so replacement of either by an achiral $\text{R}'\text{O}$ moiety produces an identical, single aluminium hydride reagent (BINAL-H). In the reduction of prochiral unsaturated ketones, *(R)*-BINAL-H produces alcohol enriched in the *(R)*-enantiomer whilst the reaction with *(S)*-BINAL-H gives alcohol enriched in the *(S)*-enantiomer (**Figure 1.9**).

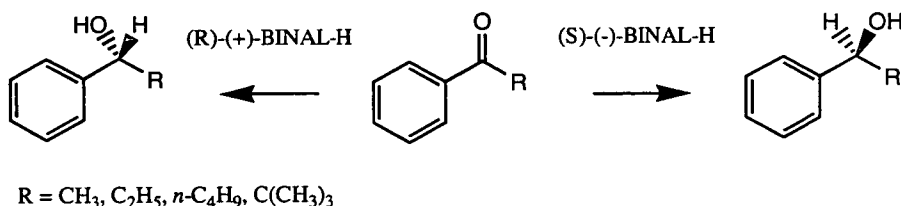


Figure 1.9: *Reduction of prochiral alkyl phenyl ketones by (R)-and (S)-BINAL-H*

Investigation into the application of the BINOL system as a chiral auxiliary in diastereoselective alkylation¹⁵, and later aldol and conjugate additions¹⁶, has been carried out recently by Fuji and his co-workers, with good to excellent chiral induction from the chiral biaryl system. Synthesis of the binaphthyl monoester from chirally pure (R)-BINOL and phenylacetic acids, and subsequent treatment with base followed by alkyl iodide generated the α -alkylated phenylacetic acids in high yield and optical purity (**Figure 1.10**).

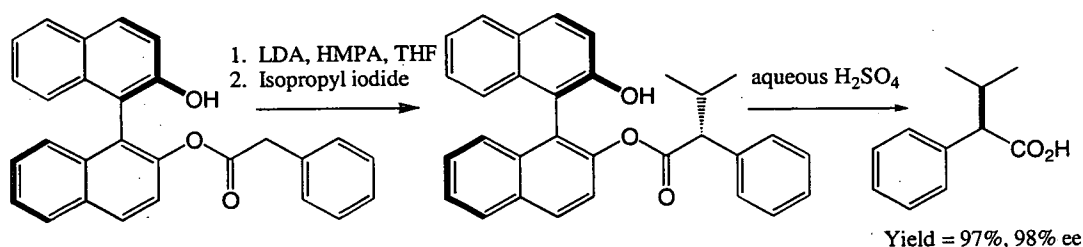


Figure 1.10: *Asymmetric alkylation of arylacetic acid with (R)-(+)-BINOL*

In the above system, the second phenol group of the BINOL system is free and unprotected. It is likely this can contribute to the stabilisation of the anion generated from treatment of the BINOL ester with LDA, through complexation to the lithium salt. However, methyl protection of the free phenolic hydroxyl group was found to greatly hinder the enantioselectivity of the alkylation, affording no preferential alkylation in the diastereoisomer formed. Molecular modelling studies by Fuji *et al.* showed that the above BINOL monoester with methyl protection of the free phenol allows more freedom of rotation around the ester C-O bond than the previous unprotected

moiety through a decreased repulsion between the enolate oxygen and the oxygen of the hydroxyl group. The free phenol creates a structural rigidity in the transition state without which the enantioselectivity in the alkylation is lost.

Further work with these systems includes the asymmetric alkylation of α,β -unsaturated carboxylic acids as investigated through similar formation of the appropriate binaphthyl monoesters¹⁷. Alkylation was found to occur at the α -position with a synchronous migration of the double bond to the β,γ -position with high diastereoselectivity (**Figure 1.11**).

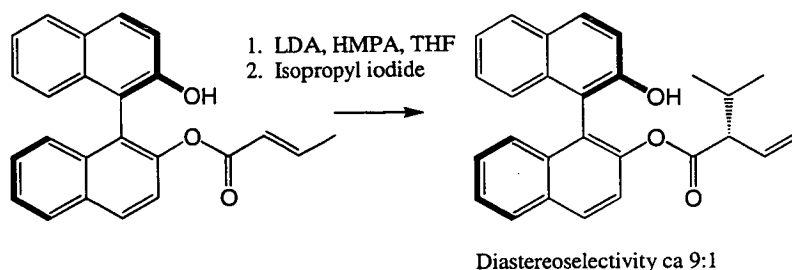


Figure 1.11: *Diastereoselective alkylation of binaphthyl esters of α,β -unsaturated carboxylic acids.*

Related studies by Fuji *et al.* emphasised the benefit of C_2 -symmetric chiral ligands for application in asymmetric synthesis. (R)-or (S)-binaphthol was converted to the corresponding cinnamate with one equivalent of cinnamoyl chloride to undergo asymmetric Michael addition with lithium dialkyl cuprates to give optically active bis-alkylated compounds¹⁸ (**Figure 1.12**). Again the unprotected phenolic hydroxy of the binaphthyl ring proved indispensable, with the conjugate addition of lithium dimethylcuprate in 20-92% chemical yield and 60-87% ee. It is of note that the binaphthols in the systems described above are recovered without loss of optical purity.

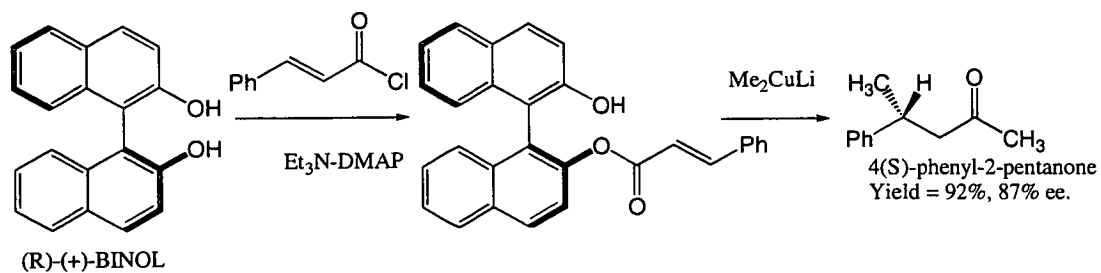


Figure 1.12: *Successive 1,4- and 1,2-addition of lithium dimethylcuprate to chiral binaphthyl ester*

This methodology allows for the practical synthesis of common as well as uncommon α -amino acid derivatives with predicted stereochemistry. In 1996, Fuji and his co-workers published the results from alkylations of chiral glycine derivatives that possessed the (S)-enantiomer of binaphthol as a chiral auxiliary, producing D- α -amino acids¹⁹.

The Chiral Catalyst

Tsutomu Katsuki and Barry Sharpless made one of the earliest and most useful discoveries in the field of asymmetric synthesis in 1980 through their discovery of a system for the asymmetric epoxidation of allylic alcohols²⁰. The problem of the regio- and enantioselective oxidation of the olefin bearing the allylic hydroxyl group in geraniol had been investigated with minimal success for a number of years²¹. The necessary components in this system were (+) or (-)-diethyl tartrate, titanium tetrakisopropoxide, and *tert*-butyl hydroperoxide. Upon use of a given tartrate enantiomer the system delivers the epoxide oxygen from the same enantioface regardless of the substitution pattern (**Figure 1.13**). The *Sharpless Epoxidation* is found to be highly enantioselective with a wide variety of allylic alcohol substrates, with yields between 70 and 87%, and optical purities in excess of 90% ee.

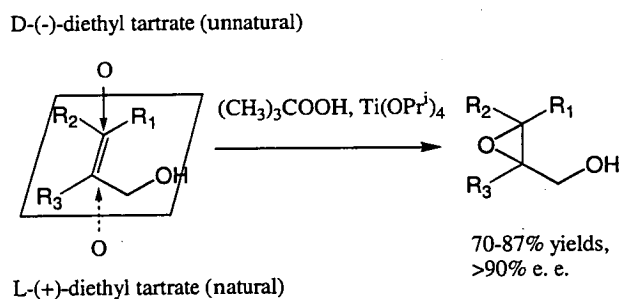


Figure 1.13: *Sharpless asymmetric epoxidation of allylic alcohols*

In 1990, a new method for achieving asymmetric olefin epoxidation was described by Eric Jacobsen²² after his successful introduction of enantioselectivity to existing salen ligand catalysts. These complexes constituted the most enantioselective, non-enzymatic olefin epoxidation catalysts reported thus far in which asymmetric induction resulted solely from nonbonded interactions. Jacobsen has since made several improvements to the original technology, including a much simplified synthesis of the chiral salen-based Mn(III) epoxidation catalyst and employing commercial bleach as the stoichiometric oxidant²³. In solutions buffered by commercial bleach, these

chiral Mn(III) salen complexes catalyse the enantioselective epoxidation of simple olefins in yields of up to 87%, optical purity 82% ee, and *cis/trans* 15/1 (**Figure 1.14**). The Jacobsen epoxidation offers good isolated yields of epoxides with inexpensive reagents under mild conditions, and a simple work-up protocol.

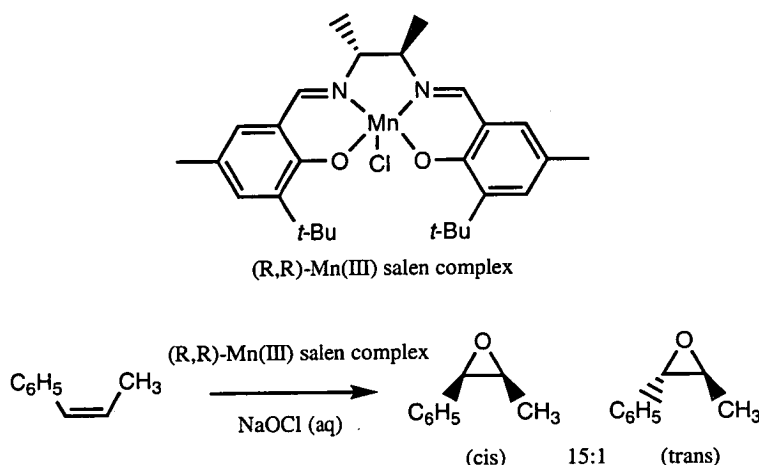


Figure 1.14: *Asymmetric olefin epoxidation with sodium hypochlorite catalysed by chiral Mn(III) salen complexes*

The range of reactions in which the Jacobsen catalysts have been applied has grown to include asymmetric alkene aziridination²⁴, enantioselective addition of hydrogen cyanide to imines²⁵ and asymmetric hetero-Diels-Alder reactions²⁶. This has been achieved through the continued development of the chiral salen ligands, and the range of metals the ligands are coordinated to, such as copper, aluminium and chromium.

Both Corey and Evans have investigated chiral bis (oxazoline) complexes for use in asymmetric synthesis. Corey found that chiral Fe(II) bis(oxazoline) complexes functioned as promising chiral Lewis acids in the catalysis of the Diels-Alder reaction of unsubstituted acrylimides²⁷.

Evans exploited the potential of this C_2 -symmetric ligand through complexation to copper. These bis(oxazoline)copper complexes proved to be excellent catalysts for enantioselective olefin cyclopropanation²⁸ and aziridination²⁹. These copper complexes were successfully applied again to the Diels-Alder reaction³⁰, obtaining selectivity's competitive with the best values reported for catalysed Diel-Alder reactions between cyclopentadiene and unsubstituted and β -substituted acrylimides (**Figure 1.15**). It was found that the reaction enantioselectivity is strongly dependent upon the nature of the bis(oxazoline) ligand substituent R. Low enantioselectivity was exhibited with the phenyl-substituted ligand, with a dramatic enhancement in *endo* enantioselection when the *tert*-butyl-derived bis(oxazoline) was employed. The application of this system has been further extended to include the enantioselective carbonyl-ene reactions with both glyoxylate and pyruvate esters³¹. The α -hydroxy ester products from this reaction offer versatile synthons in organic chemistry, this carbon-carbon bond forming process a topic of ongoing interest.

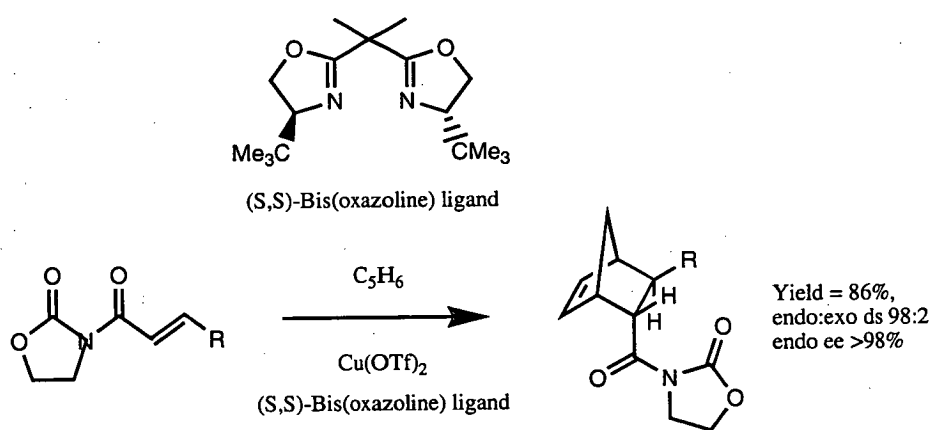


Figure 1.15: *Bis(oxazoline)copper(I) complex as a chiral catalyst for the enantioselective Diels-Alder reaction*

In 1987, Corey described a new method for the catalytic enantioselective reduction of ketones to chiral secondary alcohols³². This method involves the use of borane as the stoichiometric reagent and a chiral oxazaborolidine as the chiral catalyst. In contrast to earlier air and moisture sensitive oxazaborolidines³³ developed for use in this reaction, *B*-methylated oxazaborolidines can be stored in closed containers at room temperature and weighed or transferred in air (**Figure 1.16**). Both enantiomers of the chiral ligand 2-(diphenylhydroxymethyl)pyrrolidine (DPP) are available from (*S*)- and (*R*)-proline, though the expense of the (*R*)-proline has led to an alternative synthesis from the inexpensive pyroglutamic acid. The oxazaborolidine has proven to provide excellent enantioselectivities, easy recoverability of the chiral catalyst predecessor and near quantitative yields.

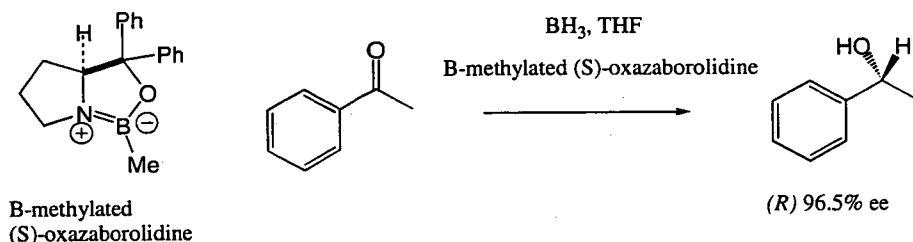


Figure 1.16: The enantioselective reduction of ketones catalysed by chiral *B*-methylated oxazaborolidine

Two research groups published the results from the first successful exploitations of the chirality of the binaphthalene system in catalysis in 1977. Robert Grubbs and Robert DeVries³⁴ used optically pure BINOL to generate a diphosphinite rhodium complex, which reduced unsaturated esters with 6 to 76% optical purity (**Figure 1.17(a)**). At the same time Kumada *et al.*³⁵ synthesised (*S*)-(-)-2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl (NAPHOS) and through complexation to Ni and Rh, investigated its usefulness in asymmetric hydrogenation, hydrosilylation and Grignard cross-coupling (**Figure 1.17(b)**). The optical purity of the substrates from these reactions was low.

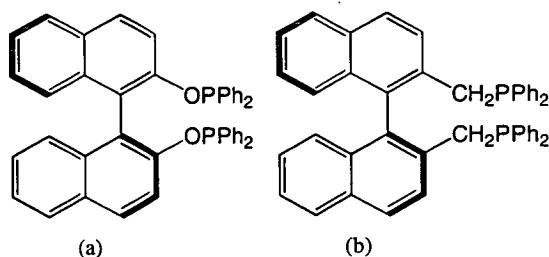


Figure 1.16: *Grubb's chiral diphosphonite rhodium complex and Kumada's NAPHOS chiral bidentate phosphine ligand*

It was not until 1980 that the first results of the bis(triaryl)phosphine ligand, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) by Noyori and his co-workers were published³⁶. BINAP was synthesised racemically from BINOL, the optical resolution of both BINAP enantiomers achieved by diastereoselective crystallisation of a chiral Pd(II) complex. Rh(I) complexed with BINAP was found to asymmetrically hydrogenate α -(acylamino)acrylic acid derivatives in high yield and high optical purity (84-100%). Since Noyori's methodology made both (R)-(+)- and (S)-(-)-BINAP ligands accessible, both enantiomers of the hydrogenation product can be obtained by choosing the appropriate chirality of the chiral ligand (**Figure 1.18**).

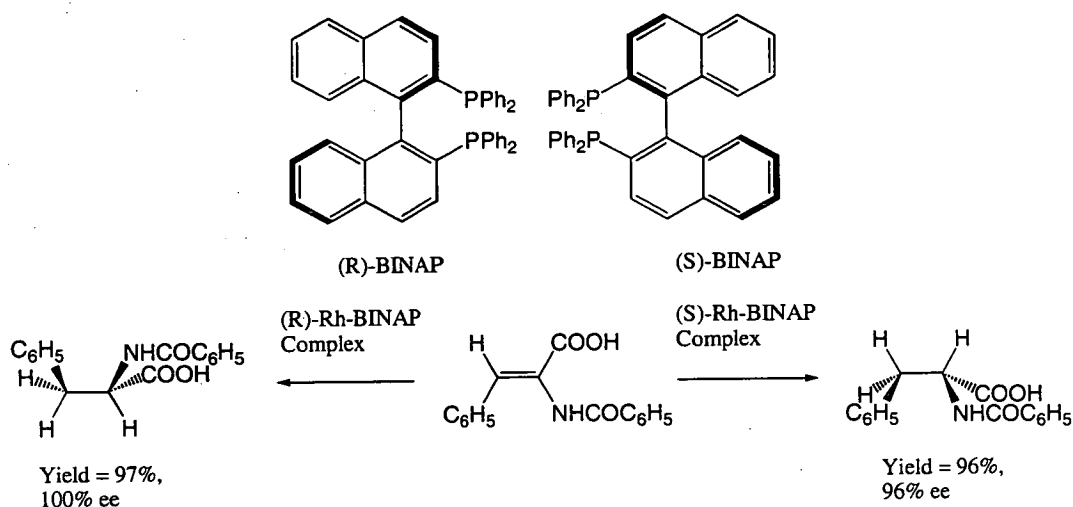


Figure 1.18: *Rh(I)-BINAP Complex asymmetric hydrogenation of an α -(acylamino)acrylic acid*

Noyori's rhodium-BINAP complex, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl(cyclo-octa-1,5-diene)rhodium perchlorate, was applied in the isomerisation of *N,N*-diethylnerylamine-(*E*)-enamine and *N,N*-diethylgeranylamine to produce optically active *N,N*-diethylcitronellal-(*E*)-enamine³⁷. Previous attempts at catalysing this isomerisation with a chiral cobalt catalyst had yielded product with optical yield and chemoselectivity too low to be of practical use. The rhodium-BINAP complex achieved this isomerisation in extremely high enantioselectivity (93%ee) and high catalytic rate (100% conversion) (**Figure 1.19**). The optical purity of the synthetic (*R*)-citronellal is far superior to that of the natural product, ca. 80%. This transformation, working on a 9-ton scale, represented the worlds largest industrial application of asymmetric catalysis in the early 1990's, allowing production of (-)-menthol and other terpenic substances totalling ca. 1500 tons per year³⁸.

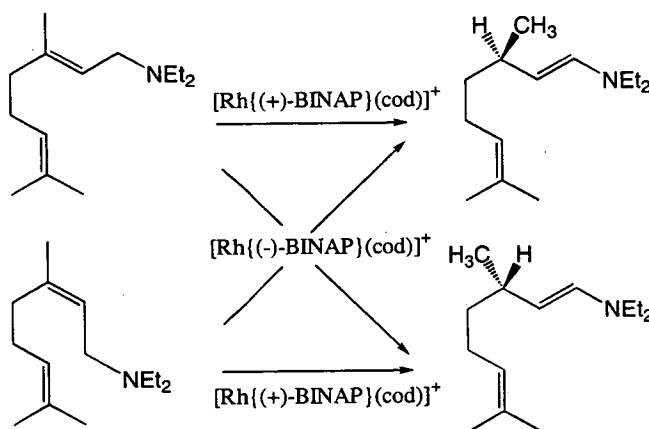


Figure 1.19: Cationic rhodium(I) complex-catalysed asymmetric isomerisation of allylamines to optically active enamines.

1-Benzylated tetrahydroisoquinolines, as well as possessing important physiological properties, also serve as key intermediates in the synthesis of a variety of isoquinoline alkaloids. Previous methods adopted towards synthesising such compounds were intricate and difficult, an example being the elegant asymmetric synthesis reported by Meyers³⁹. 1-Alkyl 1,2,3,4-

tetrahydroisoquinoline with 1*S* configuration was synthesised by Meyers through the diastereoselective alkylation of 1-lithiated 1,2,3,4-tetrahydroisoquinoline containing an amino acid derived *N*-imino function, followed by removal of the chiral auxiliary (**Figure 1.20**).

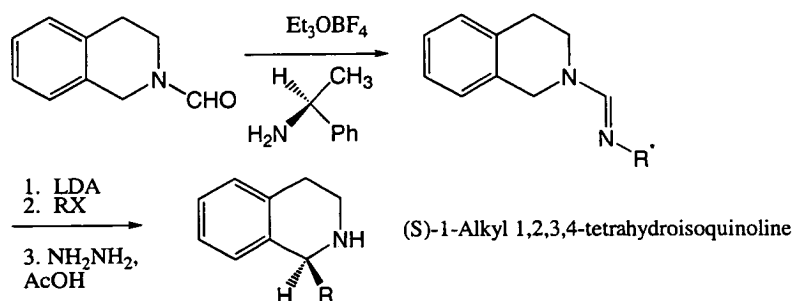


Figure 1.20: *Synthesis of (S)-1-alkyl 1,2,3,4-tetrahydroisoquinolines*

Catalytic hydrogenation of the dehydro precursors offered a simpler solution, achieved with extremely high enantioselectivity and near quantitative conversion from the enamide, through application of a hexacoordinate ruthenium complex bearing the chiral (S)- and (R)-BINAP ligand⁴⁰ (**Figure 1.21**).

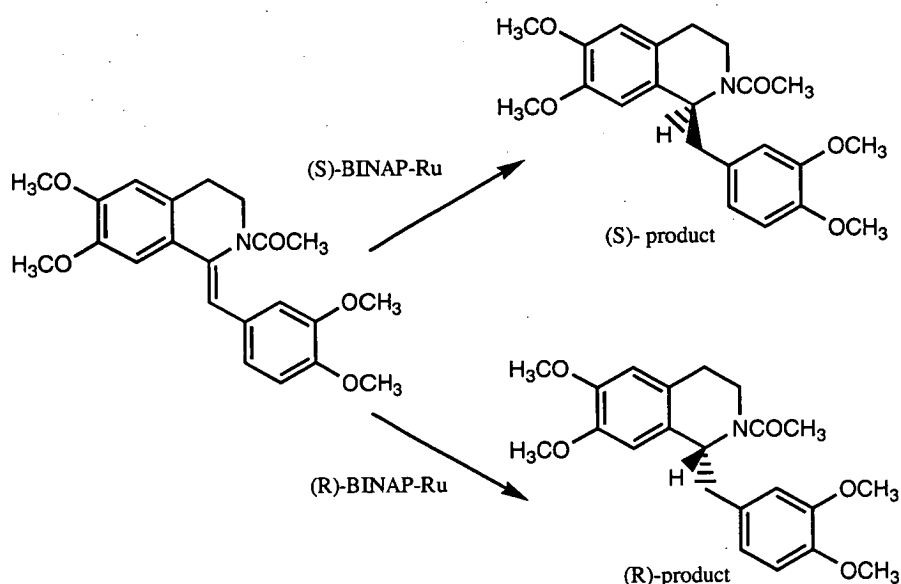


Figure 1.21: *Asymmetric synthesis of isoquinoline alkaloids by hydrogenation, catalysed by chiral (R)- and (S)-BINAP Ru complex*

This development realised a general asymmetric synthesis of isoquinoline alkaloids including morphine, benzomorphans, and morphinans such as the antitussive dextromethorphan⁴¹ (**Figure 1.22**).

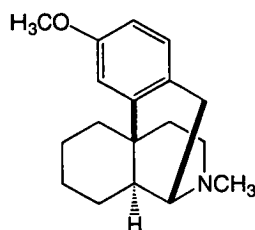


Figure 1.22: *The antitussive dextromethorphan*

Chiral BINAP-Ru catalysts have been applied to the stereoselective synthesis of other important pharmaceutical compounds. For example, (R)-BINAP-Ru(II) catalyses the hydrogenation of racemic methyl α -(benzamidomethyl)-acetoacetate to an intermediate for the synthesis of a chiral azetidinone⁴² (**Figure 1.23**). In 1990, the scale of the synthesis of this useful synthetic intermediate of carbapenem antibiotics was reported to be 120 tons per year.

Thus the BINAP chemistry is particularly powerful in the field of pharmaceuticals, agrochemicals, flavours, and fragrances. A diverse array of terpenes, amino acids, alkaloids, and other biologically significant compounds are accessible by homogenous asymmetric catalysis.

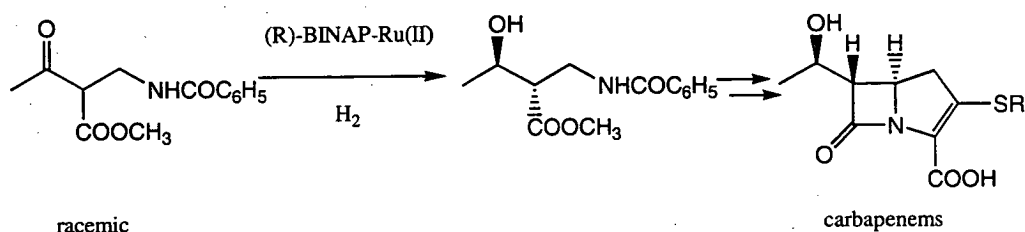


Figure 1.23: *(R)-BINAP-Ru(II) catalysed hydrogenation of racemic methyl α -(benzamidomethyl)-acetoacetate in the synthesis of a chiral azetidinone*

Application of the BINAP ligand in asymmetric synthesis has not wholly been restricted to Noyori and his research group. O'Donnell *et al.* used the chiral (+)-BINAP with $\text{Pd}(\text{OAc})_2$ to catalyse the enantioselective alkylation of Schiff base acetates with malonate types of stabilised carbon nucleophiles to give β -carboxyaspartic acid derivatives in high optical purity⁴³. The active catalyst is generated *in situ* using the palladium source $\text{Pd}(\text{OAc})_2$ and the bidentate BINAP ligand. A proposed model for the mechanism of palladium catalysis is presented below (Figure 1.24).

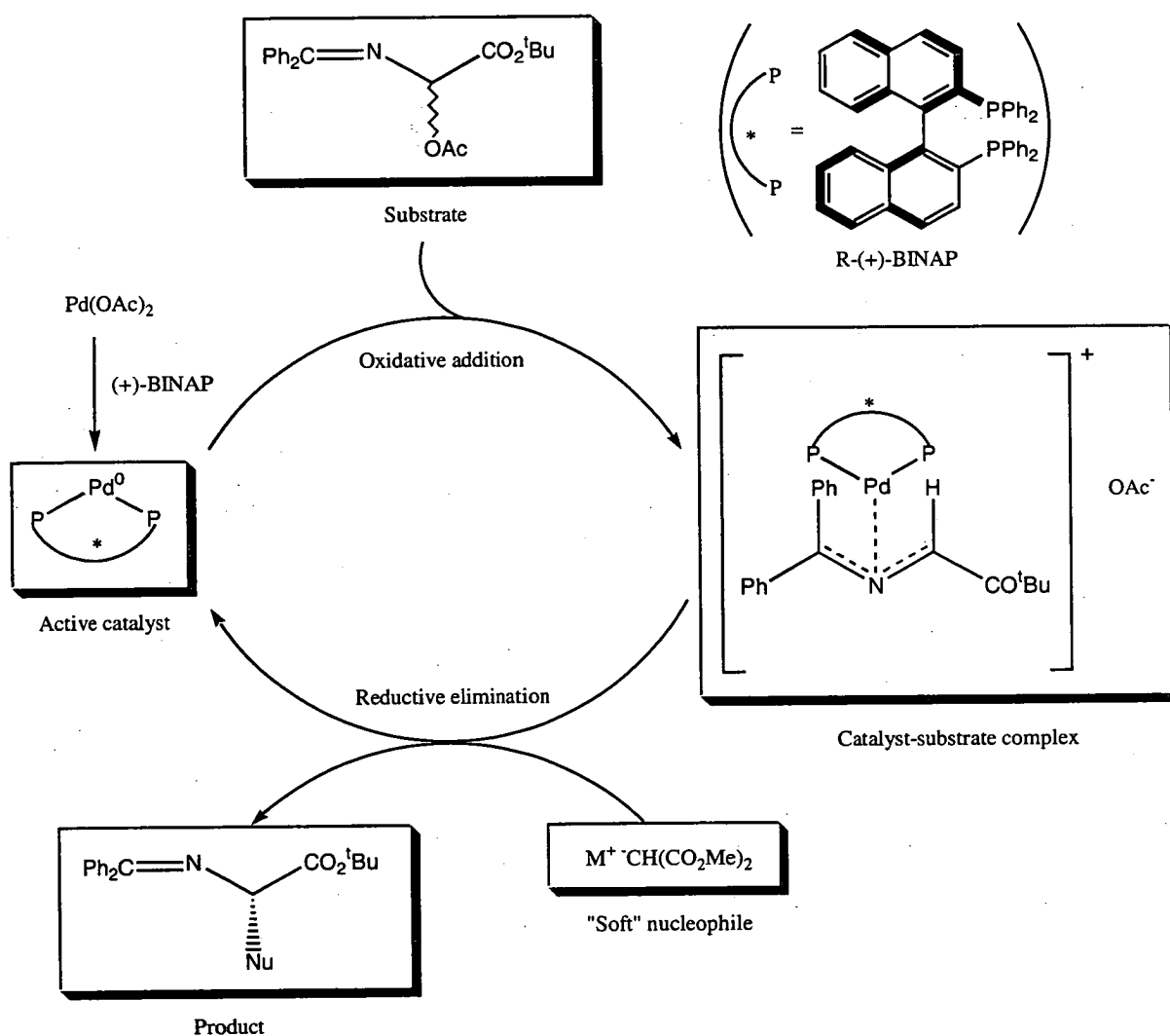


Figure 1.24: Catalytic enantioselective reaction of a glycine cation equivalent with malonate anion via palladium catalysis with $R\text{-(+)-BINAP}$

The imine product is recrystallised to enrich its optical purity and hydrolysed to give 1,1'-dimethyl 2-amino-2-carboxy-(*S*)-1,1-ethanedicarboxylate in 48% overall yield and 93.4% ee.

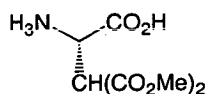


Figure 1.25: 1,1'-Dimethyl 2-amino-2-carboxy-(*S*)-1,1-ethanedicarboxylate

Other biaryl ligands have been devised and have proven successful in a range of important applications. Belokon *et al.*⁴⁴ investigated the potential of 2,2'-disubstituted-1,1'-binaphthyls as phase transfer catalysts with NaOH in the catalytic asymmetric synthesis of α -methyl substituted α -amino acids from alanine esters (**Figure 1.26**). The biaryls were used as chiral promoters, enantiopure 2-hydroxy-2'-amino-1,1'-binaphthyl (NOBIN) proving to be the most efficient asymmetric promoter of the alkylation of the Schiff's base of the alanine ester. The unsubstituted NOBIN gave optical purity of up to 68% ee, which could be increased substantially with crystallisation. It is believed the NOBIN is functioning as a chiral base and chelation of the NOBIN to the sodium ion provides a rigid structure in which the *si*-face of the carbanion is effectively shielded from electrophilic attack.

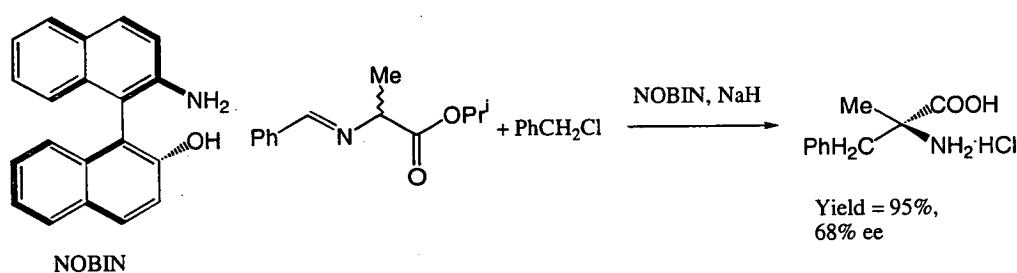


Figure 1.26: Synthesis of (*R*)- α -methylphenylalanine via asymmetric PTC
C-alkylation catalysed by NOBIN

Much attention has been turned recently towards the stereoselective alkylation of aldehydes by organometallic reagents, particularly by dialkylzincs⁴⁵. Until recently, a high degree of enantioselection in such reactions was only achieved using stoichiometric or even excess amounts of chiral auxiliary⁴⁶. Many ligands were found to accelerate the nucleophilic alkylation but did not differentiate enough between the catalysed and uncatalysed reaction rates to lead to a satisfactory asymmetric catalysis. The chiral ligand disclosed by Noyori in 1986 provided the first solution to this significant synthetic problem⁴⁷. Noyori's ligand for the activation of dialkylzinc was the camphor-derived sterically constrained, homochiral amino alcohol (-)-3-*exo*-(dimethylamino)isoborneol, or (DAIB) (**Figure 1.27**).

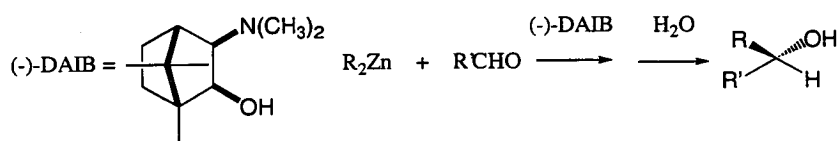


Figure 1.27: (-)-DAIB, and its catalysis of the addition of dialkylzincs to aldehydes

The typical procedure outlined for the reaction of dialkylzincs with aldehydes involves the use of 2mol% of the (-)-DAIB in toluene, which after aqueous work-up gives the corresponding secondary alcohol in high optical purity (up to 99% ee) and high chemical yield (80-98%). The presence of (+)-DAIB produces an alcohol enriched in the (R)-enantiomer whilst (-)-DAIB gives an alcohol enriched in the (S)-enantiomer, both displaying equally good enantioselectivities⁴⁸. This particular area of asymmetric synthesis has received much attention, and the developments in this particular area of asymmetric synthesis will be discussed in more depth in the following section.

1.2. The Enantioselective Addition of Diethylzinc to Aldehydes

The enantioselective addition of organometallics reagents to aldehydes to give optically active secondary alcohols is one of the most important and fundamental asymmetric reactions. Optically active secondary alcohols are components of many biologically active compounds and feature as synthetic intermediates for the introduction of functional groups such as halide, amine, ester, ether, etc⁴⁹. Two approaches to the generation of optically active secondary alcohols are the enantioselective alkylation of aldehydes and the enantioselective reduction of prochiral ketones. The former reaction achieves not only the formation of an optically active secondary alcohol but also allows a means of extending the skeleton of the alcohol through carbon-carbon bond formation (Figure 1.28).

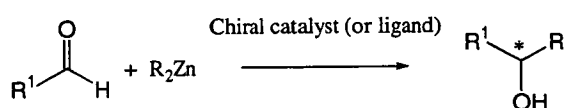


Figure 1.28: *Enantioselective addition of dialkylzinc to aldehyde.*

Diethylzinc was the first organometallic compound to be discovered⁵⁰. Until recently its addition to aldehydes has been utilised rarely in organic synthesis because the reaction is extremely slow. Clean nucleophilic addition of diethylzinc to benzaldehyde was achieved in the presence of β -amino alcohols derived from (*S*)-proline and (*S*)-leucine that accelerated the carbon-carbon-bond-forming reaction to afford 1-phenylpropanol⁵¹. The success of these systems in the catalysis of this reaction was attributed to a change in the geometry of the diethylzinc upon complexation to the amino alcohol.

This change in the behaviour of the diethylzinc upon complexation to the amino-alcohol may be explained from analysis of the geometry of the closely related system dimethylzinc⁵². Dimethylzinc has a 1.95Å bond length between the zinc and carbon atoms and does not add to aldehydes. Complexation to 1,3,5-trimethylhexahydro-1,3,5-triazine causes the coordination chemistry of the

zinc atom to change to the tetrahedral with a 145° carbon-zinc-carbon bond angle with an increase in the zinc and carbon bond length to $1.98\text{\AA}$ (**Figure 1.29**). The overall result is a decrease in the zinc and carbon bond energy and hence a direct increase in the nucleophilicity of the methyl group of the dimethylzinc.

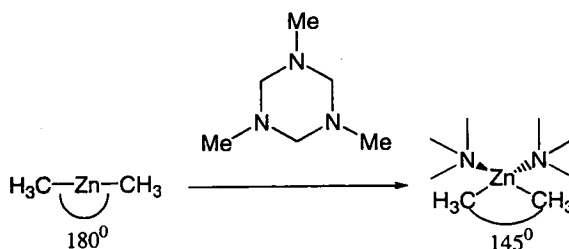


Figure 1.29: Structure of dimethylzinc and its adduct with 1,3,5-trimethylhexahydro-1,3,5-triazene.

In 1987 a number of attempts were made towards the design of effective systems for the catalysis of the asymmetric addition of diethylzinc to aromatic aldehydes with varying degrees of success. These systems included metal complexes of camphorquinone dioximes and chiral amino alcohols by Oguni and Omi which achieved moderate optical purity⁵³, and the highly enantioselective camphor-derived DAIB system developed by Noyori⁴⁷.

Chaloner and Prerera⁵⁴ reported diethylzinc to react enantioselectively with benzaldehyde derivatives in the presence of ephedrine to yield the secondary alcohol derivatives in optical yields of up to 80%. An advantage of the use of ephedrine as a chiral source in asymmetric synthesis is that both enantiomers are readily available (**Figure 1.30**).

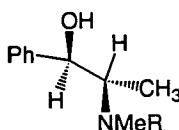


Figure 1.30: (1R,2S)-(-)-ephedrine.

By using the appropriate enantiomer of the catalyst, either enantiomer of the product can be synthesised in the same synthetic yield and the same enantioselectivity. *N*-Ethyl, *N*-propyl and *N*-methyl-1-ethyl ephedrine were synthesised from ephedrine. Investigation of these ephedrine derivatives in this reaction brought to light two notable trends. Firstly, both the hydroxyl and amino groups are essential to obtaining a good optical yield suggesting a chelated intermediate is responsible for the optical induction, and secondly the optical yield is increased with the size of the group substituted on nitrogen in the catalyst.

Published simultaneously were the results from Soai *at al.*⁵⁵ concerning the synthesis and investigation of the effectiveness of *C*-2-symmetric diamino alcohols derived from ephedrine as catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes. These diamino diols were generated from the coupling of two equivalents of ephedrine with 1,3-diiodopropane or oxalyl chloride (**Figure 1.31**). As catalysts they required lithiation by butyllithium to achieve high enantioselection with optical yields up to 85%.

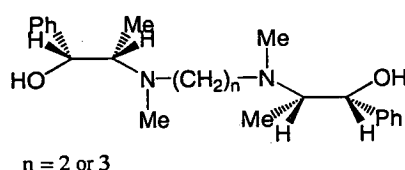


Figure 1.31: *C*-2-symmetric (1*R*,2*S*)-(-)-ephedrine derived diamino diol.

Most of the reported enantioselective additions of dialkylzincs to aldehydes involving the use of chiral catalysts have utilised aromatic aldehydes, which afford aromatic alcohols. The enantioselectivity of the addition of diethylzinc to aliphatic aldehydes is usually low to moderate. In 1991, Soai *at al.*⁵⁶ described the use of *N,N*-dialkylnorephedrines in the enantioselective addition of a range of dialkylzincs to aliphatic aldehydes in high yield and high optical purity (**Figure 1.32**). These chiral catalysts were easily derived from norephedrine, with both enantiomers of ephedrine available.

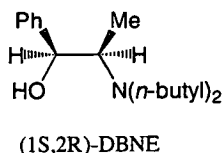


Figure 1.32: (1S,2R)-*N,N*-di-*n*-butylnorephedrine (DBNE).

From these studies it appeared that *N,N*-di-*n*-butylnorephedrine (DBNE) was the optimum catalyst, a catalyst widely regarded alongside DAIB as one of the most successful to date in this field.

The ephedrine and norephedrine systems have received much attention since the development of DBNE. In 1993, Jones and Heaton⁵⁷ created a chiral metallocyclic Lewis acid catalyst system derived from norephedrine (**Figure 1.33**). The key stereodirective element emanates from a tricarbonyl chromium group complexed to the aryl ring. This new family of enantioselective catalysts was found to mediate the addition of dialkylzincs to aldehydes with good to excellent enantioselectivity.

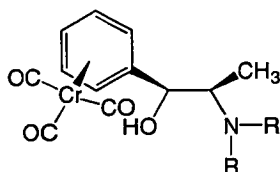


Figure 1.33: Norephedrine derived chiral tricarbonyl chromium (0) complex.

Further investigation into this area by Soai and Watanabe led to the incorporation of the DBNE system onto solid support⁵⁸. This medium has distinct advantages over solution phase chemistry in view of its ease of separation from the reaction mixture and the recyclable nature of the polymer-supported chiral catalyst. Soai attached *N*-butylnorephedrine to polystyrene resin *via* a six-methylene spacer, generating a recyclable catalyst for the enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes (**Figure 1.34**). The enantioselectivities were good to high, though as yet inferior to the results obtained in solution. Improved results were obtained through the

incorporation of a linker, increasing the freedom experienced by the catalyst on the solid phase.

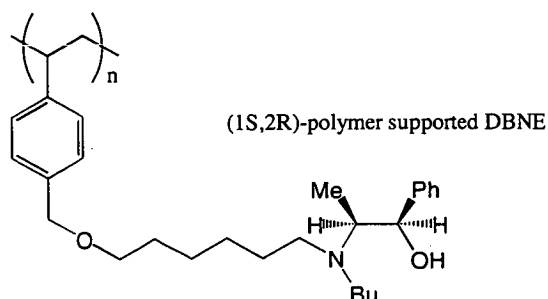


Figure 1.34: DBNE-based chiral polymer catalyst.

Within the last three years a variety of different chiral β -amino alcohols have been developed towards achieving asymmetric induction in the addition of dialkylzincs to aldehydes. Most of these systems have been derived from natural products from the chiral pool. Kragl and his co-workers used (*S*)-tyrosine as the basis for the synthesis of (*S*)-2-*N,N*-dibutylamino-3-butyl-1-[4-(4-phenylmethoxy)-phenyl]heptan-3-ol which catalysed the addition of diethylzinc to both aromatic and aliphatic aldehydes in optical yields up to 95% (**Figure 1.35**)⁵⁹.

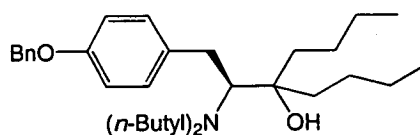


Figure 1.35: β -amino alcohol derived from (*S*)-tyrosine.

Cho *at al.*⁶⁰ exploited the chirality and functionality of D-mannitol to form chiral β -dialkylamino alcohols which catalysed the enantioselective addition of diethylzinc to relatively unhindered aliphatic aldehydes in high enantioselectivity with a range of 81-94% ee (**Figure 1.36(a)**).

(*S*)-Leucine provided the basis for Kawanami *at al.*⁶¹ to develop a new series of chiral β -amino alcohols through the addition of various Grignard reagents to the (*S*)-leucine ethyl ester and subsequent formation of a piperidine ring of the amine with 1,5-diiodopentane (**Figure 1.36(b)**).

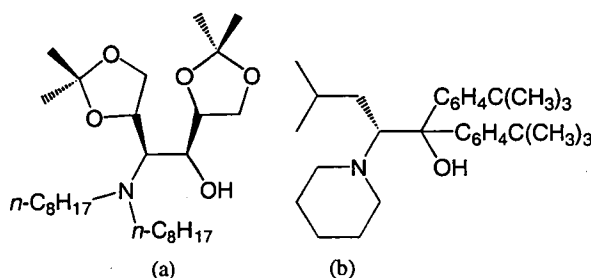


Figure 1.36: β -amino alcohols derived from (a) *D*-mannitol and (b) (*S*)-leucine.

These systems derived from (*S*)-leucine were found to be excellent catalysts in the enantioselective addition of diethylzinc to aromatic (up to 97% ee) and aliphatic (up to 95% ee) aldehydes.

Yanada and Ibuka⁶² have investigated derivatives of (*S*)-valinol for their potential as chiral catalysts in this asymmetric addition of diethylzinc to aldehydes (**Figure 1.37(a)**). The derivatives synthesised were C_2 -dimeric aminoalcohols, generated through highly diastereoselective coupling reactions of chiral imines from (*S*)-valinol with samarium iodide. These rigid and bulky C_2 -symmetric dimeric ligands catalysed the enantioselective addition of diethylzinc to benzaldehyde in up to 91% ee.

Fujita and his co-workers synthesised optically active 1,4-aminoalcohols from (+)-camphor and (-)-fenchone (**Figure 1.37(b)**). These ligands catalysed the enantioselective addition of diethylzinc to aromatic aldehydes in up to 95% ee and 62% respectively⁶³.

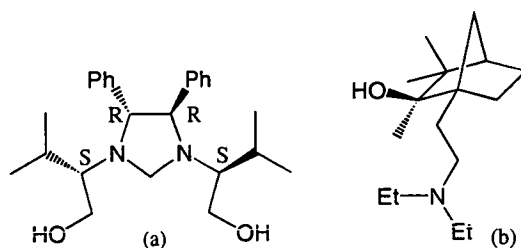


Figure 1.37: β -amino alcohols derived from (*S*)-valinol and (+)-camphor.

Chiral ligands for asymmetric catalysis have been derived generally from readily available natural products. As a result they belong to only a few structural types and in many cases do not allow significant optimisation of catalytic properties through structural modification. In the enantioselective addition of diethylzinc to benzaldehyde, Sardina and his co-workers recently investigated the influence of the substituents on the stereogenic centres of *N*-phenylfluorenyl β -amino alcohols (**Figure 1.38**)⁶⁴. These secondary amino alcohols were easily obtained through the reduction of α -amino ketones. The ketones were obtained from oxazolidinones, prepared in turn from the corresponding amino acids by *N*-phenylfluorenylation followed by reaction with aqueous formaldehyde. These studies indicated that the nature of the substituents in this series of β -amino alcohols has a profound influence in their ability to act as chiral catalysts. Ligands with bulky groups in the carbinol stereocentre and small groups α to the nitrogen atom displayed the best catalytic activity with respect to stereoselectivity.

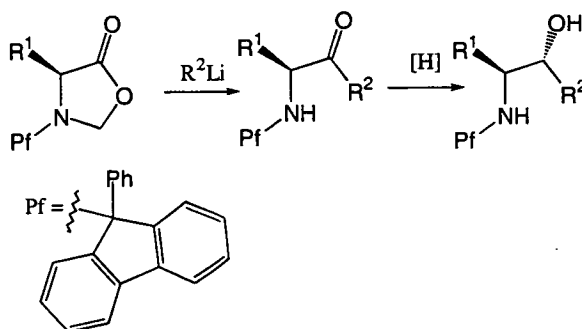


Figure 1.38: Synthesis of *N*-(9-phenylfluoren-9-yl) β -amino alcohols.

The Sharpless epoxidation (see p10) of cinnamyl alcohol followed by subsequent ring-opening with a secondary amine has been used by Pericàs and his co-workers to synthesise a family of enantiomerically pure (1R,2R)-1-(dialkylamino)-1-phenyl-3-(R-oxy)-2-propanols⁶⁵. Through the use of a variety of secondary amines in the regioselective ring opening and alkyl halides in the primary alcohol protection, a total of 19 different derivatives were synthesised (Figure 1.39).

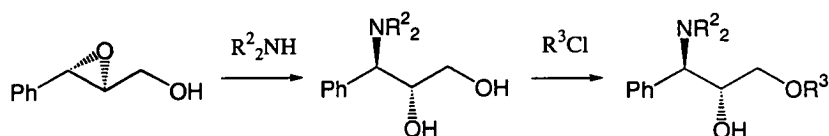


Figure 1.39: *Regioselective ring opening of epoxy alcohol by secondary amine and subsequent protection of primary alcohol.*

The advantage to this approach is that a large number of epoxy alcohols are readily available in enantiomerically pure form *via* the Sharpless epoxidation which can in principle be converted into amino diols with full control of all structural and stereochemical parameters. Initial investigations into this system have identified the steric bulk of the R-oxy group and the specification of the dialkylamino substituent as a nitrogen-containing six-membered ring as the key parameters for high catalytic activity and enantioselectivity. Two optimised ligands arising from this analysis allow the enantioselective addition of diethylzinc to aromatic aldehydes to be performed with ee's in the range 91-95% (Figure 1.40).

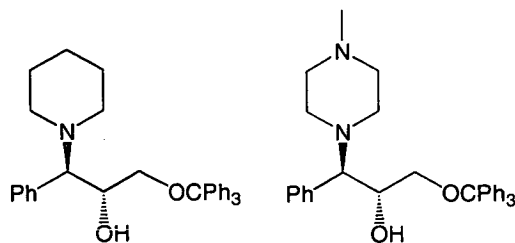


Figure 1.40: Optimised ligands derived from Sharpless epoxidation of cinnamoyl alcohol for the enantioselective addition of diethylzinc to aldehydes.

In 1996, the results from the first successful application of biaryl systems to this enantioselective process were published by Chan and his co-workers⁶⁶. Racemic generation of these ligands was achieved through Suzuki coupling to a new chiral biaryl pyridylphenol ligand (**Figure 1.41(a)**). Chromatographic separation of the (S)-(+)-camphorsulfonyl diastereoisomers and subsequent alkaline hydrolysis yielded enantiomerically pure ligands. However, these systems gave only moderate to good enantioselectivities in the addition of diethylzinc to a range of substituted aromatic aldehydes. Bringmann and Breuning⁶⁷ looked to combine the previously used N,O-functionality with the biaryl chirality by synthesising enantiopure 2-aminomethyl-1-(2'-hydroxyphenyl)naphthalene catalysts (**Figure 1.41(b)**).

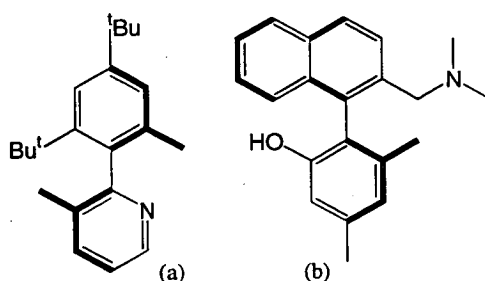


Figure 1.41: (a) Chiral pyridylphenol by Chan, and (b) chiral 2-aminomethyl-1-(2'-hydroxyphenyl)naphthalene by Bringmann and Breuning.

These *non* C₂-symmetric ligands were synthesised through intramolecular coupling, followed by dynamic kinetic resolution of the atropo-

enantiomeric mixture to generate enantiomerically pure biaryl material. In the addition of diethylzinc to aromatic aldehydes it was found the optical purity of the modified substrate increased with lengthening of the catalytic ligands *N*-alkyl chains. The optimum chain length was found to be four carbon atoms. Such a system catalysed the addition of diethylzinc to benzaldehyde in optical purity of 99%.

Chiral *N,O*-ferrocenyl ligands have also been adapted towards the enantioselective addition of diethylzinc to aldehydes⁶⁸. Hou *et al.* synthesised a novel 1,1'-disubstituted bidentate ferrocene ligand for application in this reaction (**Figure 1.42**). With the *N*- and the *O*-groups attached to the two different Cp rings of ferrocene, the addition of diethylzinc to a range of aromatic aldehydes was carried out in high chemical yield and with good *ee* values (up to 90.9%).

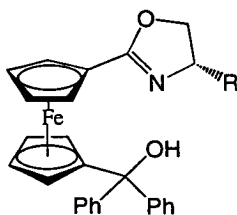


Figure 1.42: Chiral *N,O*-ferrocenyl ligand by Hou *et al.*

The studies described so far in this area of asymmetric synthesis have all involved the use of chiral alcohols or amines to catalyse the addition of diethylzinc to aldehydes. Excellent results have also been achieved using modified Lewis acids such as chiral titanate complexes⁶⁹. These catalytic systems involve the use of stoichiometric amounts of the Lewis acid and a catalytic amount of the chiral ligand, usually a sulphonamide. Zhang and his co-workers reported the use of a titanate complex with the tetradentate helical ligand ((1*R*,2*R*)-(+)-1,2-bis(3,5-dichloro-2-hydroxybenzenesulfonamido)-cyclohexane) which catalysed the addition of diethylzinc to a range of aromatic and aliphatic aldehydes in optical yields up to 99% (**Figure 1.43**)⁷⁰. The chiral

ligand not only provides a chiral environment but also an increase in the Lewis acidity of the catalyst, which results in a massive decrease in the reaction time.

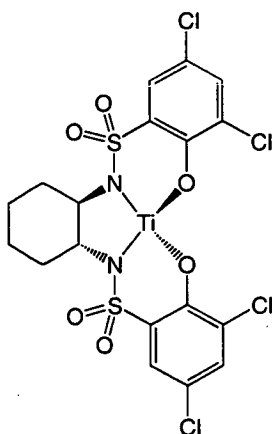


Figure 1.43: *Titanate complex with a chiral tetradentate ligand.*

1.3. Borane containing compounds for use in asymmetric reduction

Following the development by Yamamoto⁷¹ of acyloxyboranes as catalysts for asymmetric reductions and the success of oxazaborolidine catalysed reductions by Corey, Bakshi and Shabita (CBS reduction)³³, quite a number of different compounds containing borane have been investigated for use in this asymmetric reduction. At present chiral oxazaborolidines appear to be the most versatile catalysts of this kind, the CBS reduction having been successfully employed in the synthesis of important compound classes such as prostaglandins and amino acids⁷².

Alkoxy-amine-borane complexes derived from α -amino acids were investigated by Hirao *et al.*⁷³ for application in the asymmetric reduction of aromatic ketones. The complexes were formed *in situ* after treatment of the appropriate α -amino acid with $\text{BH}_3\cdot\text{THF}$ (Figure 1.44). The projected optical yields of the secondary alcohol products, based upon their optical rotations, were found to lie between 7 and 60%.

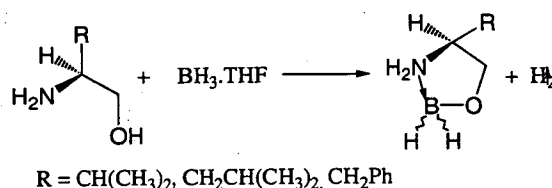


Figure 1.44: Alkoxy-amine-borane complexes formed with chiral amino-alcohols.

β -Amino alcohols prepared from L-cysteine and dimerised through a disulphide bond have been found to form chiral oxazaborolidines *in situ*⁷⁴ (Figure 1.45). These systems developed by Li and Xie possess two chiral centres, and are found to catalyse the enantioselective reduction of prochiral diketones in high enantiomeric excess.

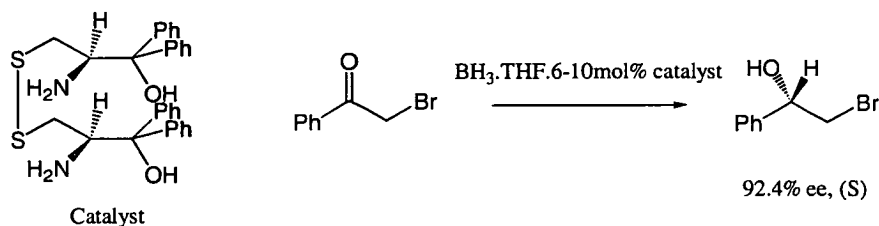


Figure 1.45: *Enantioselective reduction of prochiral ketone by bis-[(R,R)-5,5-diphenyl-1,3,2-oxazaborolidine methyl]disulphide from L-cysteine.*

Periasamay *at al.*⁷⁵ synthesised a range of chiral tertiary amines, amongst which was a binaphthalene based system (**Figure 1.46**). The borane source in these reductions was $\text{BF}_3 \cdot \text{OEt}_2$. In the reduction of acetophenone, the best results were obtained with the tertiary amine incorporating the binaphthalene system. The enantiomeric excess for this reduction was found to be 51.1% when the amine. BF_3 complex was used stoichiometrically, though optical purity of the reaction product fell sharply as the ketone-amine. BF_3 molar ratio was increased.

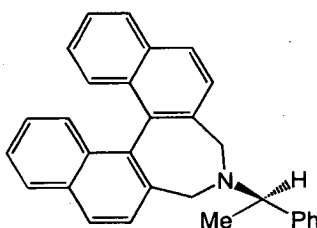


Figure 1.46: *(-)-7-(1-phenylethyl)-4,5-dihydro-3H-dinaphth[2,3-c;2',3'-e]azepine chiral tertiary amine.*

A recent publication by Chan and his co-workers describes the use of 1,3-amino alcohols derived from ketopininc alcohols in the catalytic reduction of prochiral ketones⁷⁶. Ketopininc acid can easily be derived from camphor, an easily obtainable and inexpensive chiral material. The oxazaborolidine was formed *in situ* with either $\text{BH}_3 \cdot \text{THF}$ or $\text{BH}_3 \cdot \text{Me}_2\text{S}$ and the chiral *exo*-1,3-amino alcohol (**Figure 1.47**). The optimum reaction conditions were found to be with $\text{BH}_3 \cdot \text{Me}_2\text{S}$ as the borane source and 20 mol% catalyst, relative to the substrate.

The enantiomeric excess of the reduction of acetophenone with these conditions was found to be 91%.

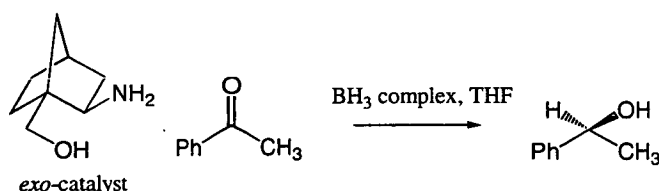


Figure 1.47: The *exo*-(1*S*,2*R*)-1-hydroxymethyl-2-amino-dimethyl bicyclo[2,2,1]heptane chiral ligand and application in the enantioselective reduction of prochiral ketones.

In an attempt to reduce the amount of catalyst required in these reductions and to provide a means of recovering the catalyst at the end of the reaction, a number of investigations have been made towards introducing these chiral borane complexes to polymer support⁷⁷. Some researchers have succeeded in preparing polymer supported CBS reduction catalysts, though good enantioselectivity was only possible when gel-type polymer supports with a very low degree of crosslinking (1-2%) were used⁷⁸. An increase in the degree of crosslinking creates diffusion limitations inside the polymer and therefore slows down the rate of the catalysed reaction. The result of this is that the direct, non-selective borane reduction becomes competitive, causing a marked decrease in the overall selectivity.

Schunicht *et al.*⁷⁹ recently achieved high enantioselectivities through the use of microgels as the solid support. Microgels offer the advantage of a very low solution viscosity. The catalysts were prepared through condensation of the microgel with (S)- α,α -diphenylprolinol (DPP) or (S)- α,α -diphenylalaninol (DPA), and employed in the enantioselective reduction of acetophenone in catalytic amount of 10 mol%. Enantioselectivities of 91 to 93% were achieved. Purification of the catalyst by membrane filtration allows the catalyst to be separated and recycled for at least three times, in addition to the first reduction, with no or only a slight decrease in the enantiomeric excess.

1.4. Novel Chiral NADH Mimic Systems

As new situations arise in asymmetric synthesis, there is always a need for either more reactive or more selective reagents. Homochiral boranes and metal hydrides for reduction have already been discussed in some depth, several of which are already in widespread use⁸⁰. There is a clear need for the development of new reagents that achieve high enantioselectivity where existing systems are unsuccessful, alongside a continued development of the existing technology.

In nature, enzyme mediated redox transformations are carried out both rapidly and stereoselectively. However, it would be difficult to artificially reproduce the entire enzyme, due to its size and complexity. A biomimetic system that reproduces this stereoselective reduction must therefore incorporate the key features of the enzyme that are responsible for its specific activity.

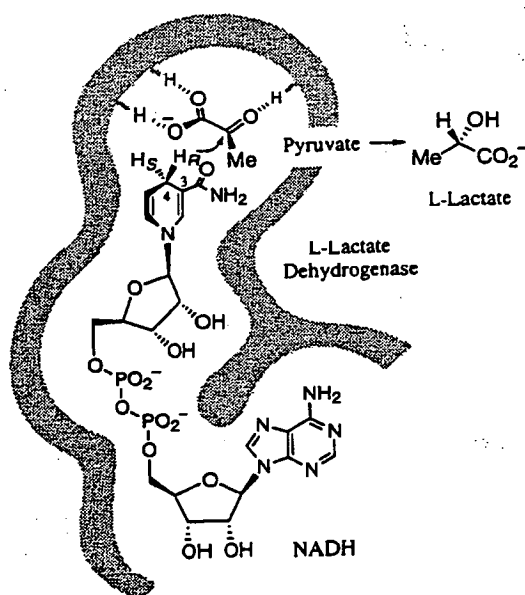


Figure 1.48: Schematic description of biological reduction with coenzyme NADH in L-lactate dehydrogenase.

Enzymes which carry out redox processes require coenzymes to act as reagents in the active site of the enzyme⁸¹. The coenzyme nicotinamide adenine dinucleotide (NADH) is a cofactor of the enzyme L-lactate dehydrogenase, and

functions as an enantioselective agent that reduces pyruvate to L-lactate during anaerobic glycolysis (**Figure 1.48**). The environment inside the active site of the dehydrogenase achieves the stereoselective transfer of one of the diastereotopic C-4 hydrogen atoms in the NADH to the achiral substrate through the activation and well-controlled orientation of both the substrate and NADH. Natural NADH contains a simple 1,4-dihydronicotinamide moiety as its recyclable redox centre, with prochiral unsubstituted hydrogens at its C-4 position⁸² (**Figure 1.49**). The biological reduction of the substrate in high enantioselectivity is achieved through the influence of the chiral environment provided by the enzyme. The orientation of the hydrogen removed from primary alcohols by liver dehydrogenase has been determined as *pro-R*.

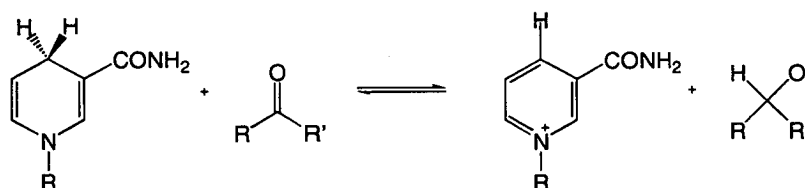


Figure 1.49: Reduction of a ketone using NADH as the reducing agent. *Enz* represents the dinucleotide moiety of NADH.

An effective biomimetic system must restrict the geometry of the transition state through control of the orientation and the direction of approach of the substrate to the 1,4-dihydropyridine ring. A number of strategies has been utilised towards this end. The first stereoselective reduction using this type of system was reported in 1975 by Ohno⁸³, utilising a prochiral 1,4-dihydropyridine possessing a chiral carboxamide at C-3 (**Figure 1.50**). In the presence of Mg^{2+} activated ketones such as ethyl benzoylformate and α,α,α -trifluoroacetophenone were reduced in optical purity up to 20%. The metal ion acts as a Lewis acid, polarising the carbonyl bond and is also responsible for the formation of a ternary complex where the metal ion is located between the dihydronicotinoyl group and the substrate in the transition state of the reduction. The low optical purity of the product is explained by the availability of both the hydrogen's at the C-4 position being accessible to the substrate.

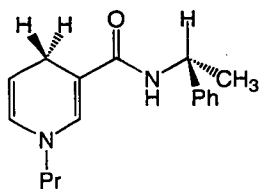


Figure 1.50: *1,4-Dihydropyridine derivative possessing chiral carboxamide at C-3 by Ohno.*

Modification of the chiral carboxamide by Inouye⁸⁴ to a (S)-prolinamide increased the reduction of ethyl benzoylformate to an enantiomeric excess of 83%. Upon discovery that these reductions proceeded in greatest yield with a 0.5 molar ratio of magnesium ions, Inouye coupled two such moieties within the same compound through a carbon bridge at N-1⁸⁵ (**Figure 1.51**). In the reduction of ethyl benzoylformate by these bis(NAH) derivatives with one equivalent of magnesium ions, an enantiomeric excess of 98% was obtained. This system, with only one equivalent of magnesium ions, cannot orientate the substrate through chelation.

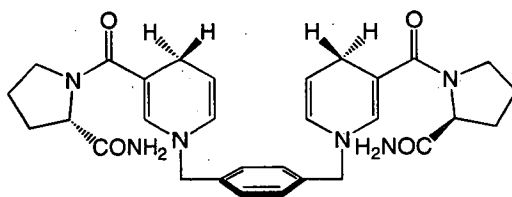


Figure 1.51: *Bis(NAH) derivative by Inouye.*

In the biological system, NADH binds to the enzyme such that only one face of the dihydronicotinoyl ring is exposed to the substrate for reduction. In the biomimetic model compound any feature that enhances the differences between the two C-4 hydrogens such that one hydrogen is more available for transfer, will influence the direction of substrate attack. Preliminary studies by Ohno⁸⁶ into this concept involved the stereoselective replacement one of the two C-4 hydrogen atoms with a methyl group (**Figure 1.52**).

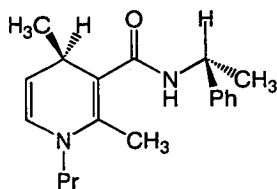


Figure 1.52: Dihydronicotinoyl compound prepared by Ohno with methyl groups at both C-2 and C-4.

The reduction of ethyl benzoylformate with this C-4 methyl substituted (R,R)-compound provided the (R)-mandelate in an enantiomeric excess of 98%, with a reaction time of two days at room temperature. Chiral reduction using the (S,R)-compound generated the (S)-mandelate in a 97% enantiomeric excess. It is evident that the chirality at C-4 and not the substituent at C-3 is responsible for the chirality transfer.

Vekemans⁸⁷ investigated similar C-4 methyl-substituted derivatives, with replacement of the chiral C-3 substituent by an achiral amide (**Figure 1.53**). The observed enantiomeric excess for the reduction of methyl benzoylformate at -25°C was 92%, with a reaction time of just five minutes. When the reaction was run at room temperature the optical purity of the modified substrate was found to fall significantly to 66%. Analysis of the results from these two C-4 substituted systems shows that the nature, if not the chirality, of the carboxamide side chain plays an important role in determining the stereochemical course and rate of reaction.

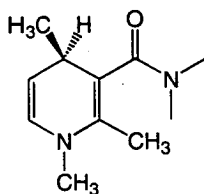


Figure 1.53: C-4 methyl substituted dihydronicotinoyl derivative by Vekemans, with achiral achiral C-3 substituent.

The strategy of stereoselectively replacing one of the hydrogens at the C-4 position has generated systems that reduce activated ketones in high optical purity and has also provided some understanding of the reaction mechanism. However, there exists an inherent flaw in their use as enantioselective reagents. The regioselective synthesis of a C-4 substituted dihydronicotinoyl is not trivial and when considering the development of a catalyst would make *in situ* regeneration very difficult to achieve⁸⁸. An alternative method for the blockage of the substrate to one of the C-4 diastereotopic hydrogens would be the further incorporation to the 1,4-dihydropyridine of an appropriately bulky chiral substituent. Davies⁸⁹ developed a series of 1,4-dihydropyridines possessing a chiral ferrocenyl auxiliary at C-3 with the intention of controlling substrate orientation, thus complementing the steric control exerted by a chiral carboxamide at C-5. Davies⁹⁰ further enhanced the steric control of the system by replacing the C-5 chiral carboxamide with a chiral hydroxycarboxamide moiety (Figure 1.54). The enantiomeric excess for the reduction of ethyl benzoylformate was found to be greater than 97%.

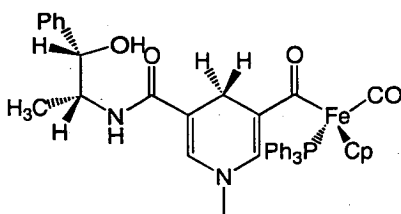


Figure 1.54: *Davies homochiral dihydronicotinoyl complex incorporating a sterically demanding chiral auxiliary at C-3 and a chiral hydroxycarboxamide moiety at C-5.*

A more recent development in this area is the development of a bridged 1,4-dihydropyridine system by Kanomata and Nakata⁹¹. The most successful of the systems discussed so far suffer from either a loss of chirality at the C-4 position during the course of the reaction or require significant modification of the dihydronicotinamide unit. Kanomata *et al.* incorporated an oligomethylene

bridge feigning an “enzyme wall” to regulate the stereoselective approach of pyruvate analogues to strictly mimic the stereoselective transfer of hydrogen in a recyclable artificial system. These bridged nicotines also incorporate either a primary carbamoyl group or an amide derived from (S)-valinol at the C-3 position (**figure 1.55**).

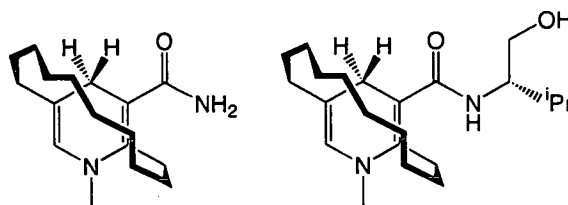


Figure 1.55: *Bridged nicotines incorporating primary carbamoyl group or (S)-valinol derived amide at C-3.*

These systems have been shown to reduce a range of pyruvate analogues in yields up to 81% and in enantiomeric excess between 88 and 99%. Highly stereoselective reduction of pyruvate analogues and usefulness for being recycled provides a compact chemical miniature comparable to the coenzyme NADH linked dehydrogenase.

1.5. Project Aims

The discovery and development of new chiral reagents in asymmetric synthesis is essential. One of the most extensively studied areas has been that of axially chiral biaryl systems. Some of these systems have been discussed in detail earlier, such as the BINAP and BINAL moieties devised by Noyori, Fuji's extensive application of BINOL as a chiral auxiliary, and Bringmann's *non-C₂*-symmetric chiral ligand for addition of diethylzinc to aldehydes. A related system to the binaphthalene system is the biphenanthrene system, though this has attracted considerably less attention. Initial investigations into the

applications of chirally pure 10,10'-dihydroxy-9,9'-biphenanthryl moieties by Yamamoto⁹² included complexation to LiAlH_4 to generate a chiral auxiliary for the asymmetric reduction of prochiral aromatic ketones (**Figure 1.56(a)**), and incorporation into crown ethers for use in chiral recognition⁹³ (**Figure 1.56(b)**).

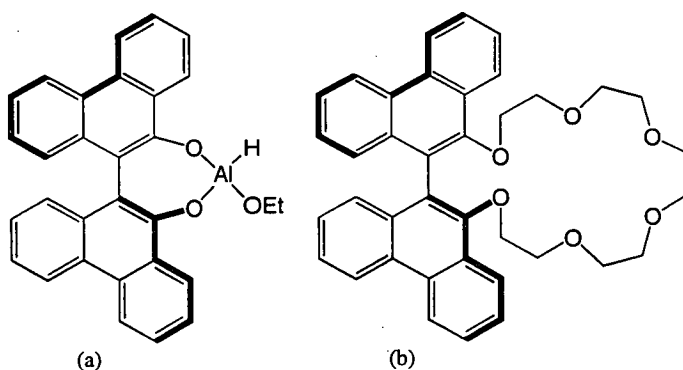


Figure 1.56: (a) *Asymmetric reductant* and (b) *crown ether, incorporating axially chiral biphenanthryl system.*

More recently, Hayashi⁹⁴ has used the chiral (R)-3-diphenylphosphino-3'-methoxy-4,4'-biphenanthryl ligand (**Figure 1.57**) with palladium to catalyse the reduction of allylic esters with formic acid in up to 92% ee.

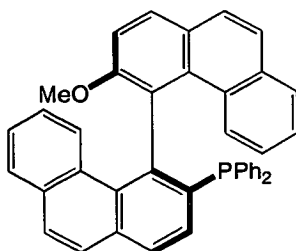


Figure 1.57: *Axially chiral monophosphine ligand for complexation to palladium.*

The aim of this project was to develop a novel series of chiral catalysts for use in asymmetric synthesis. A new chiral ligand must be sufficiently novel in order to be patented. Work done previously in this area by Professor Robert Ramage and Dr Louise Picken⁹⁵ in a previous collaboration with Zeneca has

realised a route to a novel asymmetrically substituted biaryl moiety (**Figure 1.58**). This system has two modifications that make it sufficiently different from the widely investigated binaphthelene compounds.

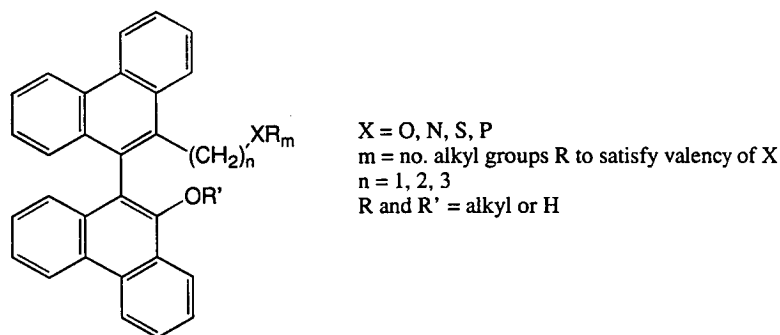


Figure 1.58: Parent biphenanthryl system with planned site of heteroatom introduction.

The first modification is the incorporation of an extra aromatic ring to each half of the biaryl system. It was hoped this extra bulk would amplify the axial chirality and result in an increase in the asymmetric induction imparted to the reaction.

The second modification is the presence of different functionality at the 10,10'-positions of the biphenanthrene moiety. The differences in the chemistry of these two functionalised positions provided a means of manipulating one functional group whilst leaving the other intact.

The overall aim of this was to generate a novel series of chirally pure biphenanthryl ligands possessing useful functionality for application in asymmetric synthesis. The enantioselective hydrogenation of olefins was to be achieved through the introduction of diphenylphosphine. The enantioselective addition of diethylzinc to aldehydes, the enantioselective reduction of prochiral ketones with borane, and lastly the generation of a new biomimetic for the reduction of prochiral ketones based upon the NADH dihydropyridyl system were to be achieved through the incorporation of mixed nitrogen and oxygen containing functional groups to the biphenanthryl moiety. The previously devised synthesis of these biphenanthryl compounds had first to be optimised,

and methods for efficient resolution of the biphenanthryl enantiomers investigated to generate chirally pure material for use in the synthesis of the above systems.

2. Results and Discussion

2.1. The Synthesis of Biphenanthryl Phenolic-Aldehyde

A number of direct approaches have been employed towards the synthesis of biaryl compounds. Symmetrical biaryl compounds can be synthesised using methodology such as the oxidative coupling of phenols using FeCl_3 ,⁹⁶ or the Ullmann reaction where two aryl halides are coupled using copper.⁹⁷ The generation of BINOL in high optical purity has been reported through a coupling reaction catalysed by a chiral copper-amine complex.⁹⁸ Mixed biaryl coupling can be achieved through $\text{Cr}(\text{CO})_3$ mediated nucleophilic aromatic substitution,⁹⁹ or through the palladium catalysed coupling of an aryl halide and a SnBu_3 aryl derivative as described by Stille.¹⁰⁰ In the palladium catalysed Suzuki coupling, the aryl tin derivative of the Stille coupling is replaced by a boronic acid aryl derivative.¹⁰¹ These approaches to the generation of biaryl compounds either involve complicated starting materials that are difficult to make, or are not applicable to the synthesis of asymmetrically substituted biphenanthryls.

Instead of this direct coupling approach to substituted biphenanthrenes, an indirect approach was devised. The parent compound and asymmetrical isomer of tetrabenzo[a,c,g,i]fluorene (Tbf) (**1**) is 8b-H-Tbf (**4**), and it is this moiety that has been found to be an excellent point of entry into the asymmetrically substituted biphenanthryls. Tbf was developed by Ramage to aid in peptide and protein purification, having strong fluorescent properties and an affinity for graphitised carbon (**Figure 2.1**).¹⁰²

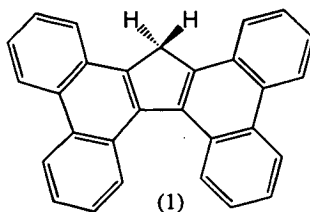


Figure 2.1: Tetrabenzo[a,c,g,i] fluorene.

The asymmetrical 8b-H-Tbf system can be synthesised in three steps from 9-bromophenanthrene (2) (Figure 2.2). Magnesium and 9-bromophenanthrene together generate a Grignard reagent, which with one half equivalent of methyl formate provides bis-(phenanthryl-9-yl)methanol (3). Cyclisation of this substituted methanol (3) can be achieved with TFA in DCM to give the 8b-H-Tbf moiety. Tbf for use in the peptide purification was obtained through isomerisation of the 8b-H-Tbf with base, typically triethylamine. The overall yield for the synthesis of the 8b-H-Tbf (4) was 48% from the 9-bromophenanthrene.

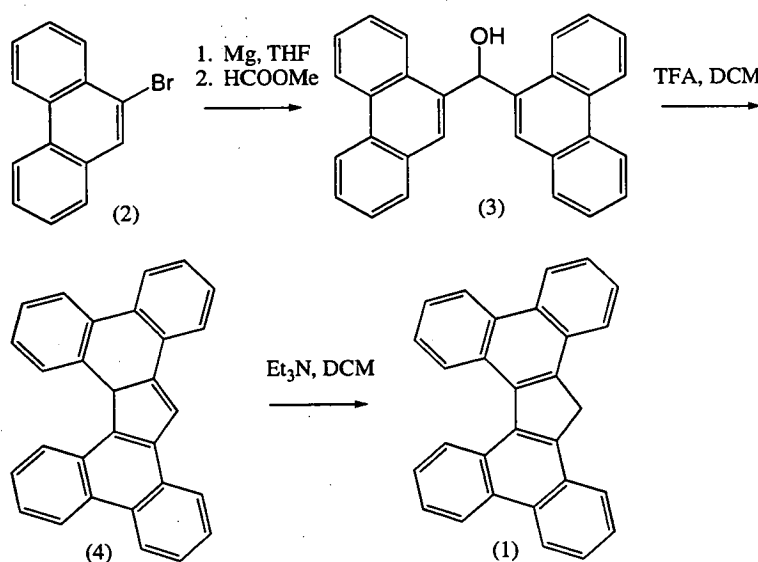


Figure 2.2: Synthesis of Tetrabenzo[a,c,g,i]fluorene.

The unsymmetrical derivative 8b-H-Tbf was the desired point of entry for the generation of unsymmetrical biphenanthryl compound, through the opening of the central five membered ring. The method originally explored for the breaking open of this system had involved cleavage of the central five membered ring by ozonolysis and subsequent reduction of the ozonide by zinc and glacial acetic acid.⁹⁵ Several modifications were made to the existing procedure due to problems encountered in reproducing this work. Firstly, the ozonolysis was inhibited by the presence of TFA from the earlier cyclisation

step, resulting in longer reaction times and a direct increase in the amount of undesired side-products generated in the ozonolysis. Removal of the TFA by weak base such as aqueous NaHCO_3 resulted in partial isomerisation of the 8b-H-Tbf to Tbf. These two isomers cannot be easily separated. Removal of the TFA from the 8b-H-tbf by aqueous wash and subsequent drying in a vacuum oven also converted the 8b-H-Tbf to the symmetrical Tbf. In an attempt to remove TFA and any Tbf impurity, 8b-H-Tbf was recrystallised from hot toluene. Analysis of the resulting brown crystalline precipitate revealed that a quantitative conversion of the asymmetrical 8b-H-Tbf to the symmetrical Tbf had occurred. From these discoveries it is clear that 8b-H-Tbf is not only base sensitive but heat sensitive too, undergoing a thermal rearrangement to Tbf.

The instability of the 8b-H-Tbf system and the system's preference for the symmetrical form may be partly understood by comparison and analysis of simple molecular modelling studies performed on both systems (**Figures 2.3, 2.4 and 2.5**).

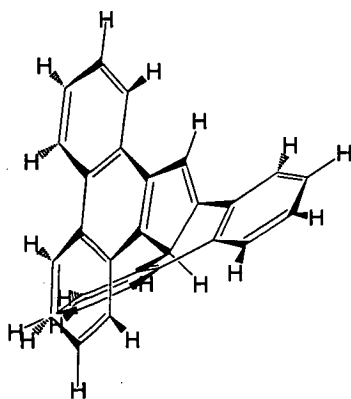


Figure 2.3: Molecular model of 8b-H-Tbf

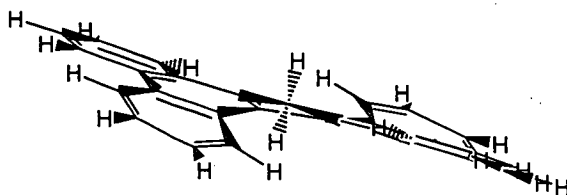


Figure 2.4: Molecular model of Tbf.

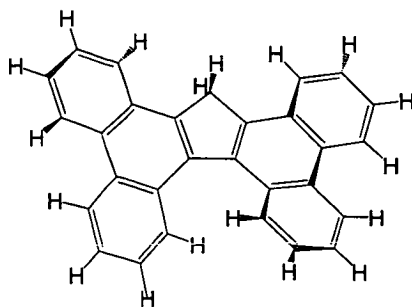


Figure 2.5: *Molecular model of Tbf.*

From these simple molecular models, 8b-H-Tbf appears to be twisted which would result in significant strain in the conjugated aromatic phenanthrene half containing the chiral saturated carbon. This unfavourable twisting out of plane is alleviated by the isomerisation to Tbf. Figures 5 and 6 show Tbf to have a much flatter and therefore more delocalised and less strained aromatic system. The transformation from a conformationally strained system to a flat, aromatic system explains the ease with which 8b-H-Tbf can be converted to Tbf.

The second problem encountered in the cleavage of the centre five membered ring by ozonolysis was that poor yields were obtained in the reduction of the ozonide with zinc and glacial acetic acid. Activating the zinc with 2M HCl prior to the reduction did not significantly improve the extent to which the reaction proceeded to completion. Dimethylsulfide was investigated as an alternative reducing agent with no reduction of the ozonide found to have occurred. Complete and efficient reduction of the ozonide was achieved through the addition of a small amount (1ml) of trifluoroacetic acid to the previously mentioned zinc and acetic acid reduction.

The ozonolysis of 8b-H-Tbf (**4**) was effected in dry THF at -78°C . The resulting ozonide (**5**) was stable and could be isolated as a white powder. This stability was believed to be due to the extensive conjugation in the large aromatic system. The ozonide was then easily reduced with zinc, glacial acetic acid and a small amount of TFA to racemic 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**), in an overall yield of 48% after crystallisation from

DCM (**Figure 2.6**). Reduction of the ($\pm$)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) to ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**7**) was achieved in 90% yield using LiAlH_4 .

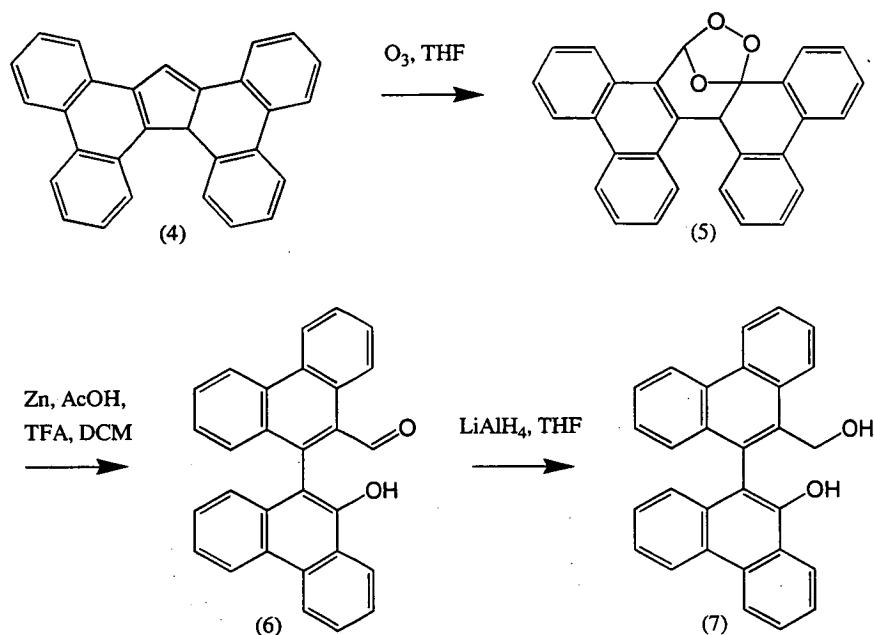


Figure 2.6: Synthesis of ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl.

2.2. The Resolution of the System

With the synthesis of the biphenanthryl phenolic aldehyde moiety having been optimised, providing quantities of ($\pm$)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) in good yield, an effective means of separating the enantiomers of this racemate had to be found. As a result of so much interest in the applications of the binaphthol system in asymmetric synthesis, there have been a number of different approaches to resolving racemic biaryl systems.

One of the most commonly used methods for achieving chiral resolution has been through the formation of inclusion complexes with suitable

compounds. Binaphthol has been resolved with (R,R)-1,2-cyclohexanediamine though this is still somewhat expensive.¹⁰³ (R,R)-(+)-2,3-Dimethoxy-*N,N,N',N'*-tetramethylsuccinamide and (R,R)-(+)-*N,N,N',N'*-tetramethyl-2,2'-dimethyl-1,3-dioxolane-*trans*-4,5-dicarboxamide also form suitable inclusion complexes with binaphthol though they are reportedly difficult to remove from the resolved material.¹⁰⁴ Toda *et al* reported that *N*-benzylcinchonidinium chloride readily formed an inclusion complex with one enantiomer of binaphthol.¹⁰⁵ Though *N*-benzylcinchonidinium chloride does not form an inclusion complex with (±)-biphenanthrol, the resolution has been achieved with *N*-butylcinchonidinium bromide (8) (Figure 2.7).¹⁰⁶

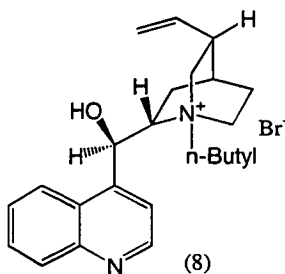


Figure 2.7: *N*-Butylcinchonidinium bromide.

N-Butylcinchonidinium bromide was prepared by refluxing cinchonidine with *n*-butyl bromide in acetone. The crystalline inclusion complex obtained with the biphenanthryl diol (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthrine (7) and *N*-butylcinchonidinium bromide was collected and examined, though it showed no sign of any optical purity and so had given rise to no chiral resolution of the biphenanthryl enantiomers.

In 1989, Roman Kazlauskas described the resolution of binaphthol through enantiospecific hydrolysis using the enzyme cholesterol esterase (CE).¹⁰⁷ A pancreatic enzyme, purified CE was expensive for synthetic use so a crude preparation was used instead (defatted, ground-up pancreas) which in turn was cheap and commercially available. Resolving biaryl diols using CE

was much simpler than any of the methods described previously and involves fewer manipulations. Kazlauskas reported the hydrolysis of binaphthol and spirobiindanol esters to be enantiospecific, the resolution of the binaphthol moiety achieved best through hydrolysis of the dipentanoate ester. This enantiospecific hydrolysis was catalysed by crude enzyme containing CE activity, and yielded each enantiomer in >60% of theoretical yield with $\geq 99\%$ enantiomeric purity (**Figure 2.8**).

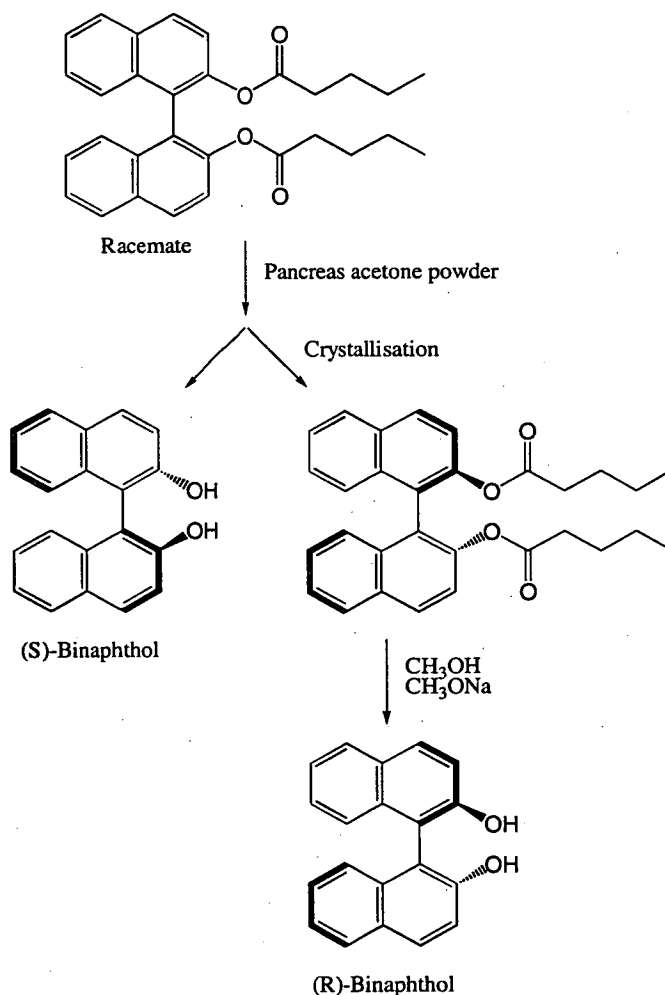


Figure 2.8: Resolution of binaphthol using cholesterol esterase.

Kazlauskas believed that the high enantiomeric purity of this resolution was due to the resolution involving two enzymic reactions: hydrolysis of the diester to the monoester, followed by hydrolysis of the monoester to the diol. In order

to investigate the compatibility of the asymmetrically substituted biphenanthryl system with CE, two diester moieties were prepared from the biphenanthryl diol ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryline (7). The diacetate derivative ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-acetate (9) was obtained in a yield of 79% from treatment of the biphenanthryl diol with acetic anhydride and a catalytic amount of DMAP in pyridine. The dipentanoate ester ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-pentanoate (10) was synthesised in 50% yield after reaction of the biphenanthryl diol with pentanoyl chloride (Figure 2.9).

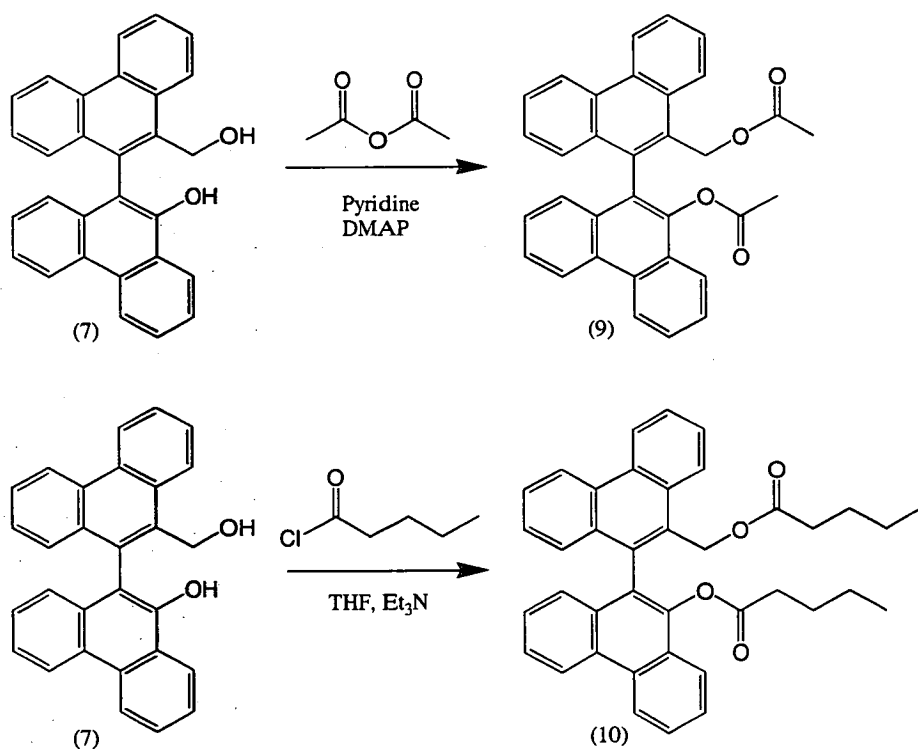


Figure 2.9: Synthesis of ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-acetate and ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-pentanoate.

The recommended procedure from the literature for the resolution of these types of systems was adhered to as closely as possible. The biaryl substrates were dissolved in an appropriate organic phase, whilst the enzyme

was buffered in an aqueous phase at pH 7.5 by a 0.1M phosphate buffer solution. To encourage interaction between the enzyme and substrate at the solvent frontier, sodium taurocholate from ox bile was added to generate an emulsion upon gentle stirring.

Unfortunately, it was found that neither of the biphenanthryl diesters dissolved in the recommended organic solvents of diethyl ether, toluene, or methyl isobutyl ketone. Other solvents were investigated to find one that would both dissolve the biphenanthryl diester and form an emulsion upon mixing with the aqueous phase and sodium taurocholate. The only solvent that satisfied the above criteria was benzene. The emulsions containing 1mmol of substrate were allowed to stir for three days, with the pH regularly checked and readjusted to pH 7.2 ± 0.2 with 1M NaOH solution. The reactions were followed by TLC though no sign of any reaction was witnessed. This was confirmed by analysis of the organics by ^1H NMR after their extraction from the emulsion with DCM.

A number of possible explanations existed for the failure of these reactions. The biphenanthryl diesters may be quite sterically congested at the proposed site of ester cleavage preventing enzymic action. To ease this potential congestion the selective removal the phenyl acetate of ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-acetate (**9**) was carried out using hydrogen peroxide in phosphate buffer at pH 10.5 (Figure 2.10).

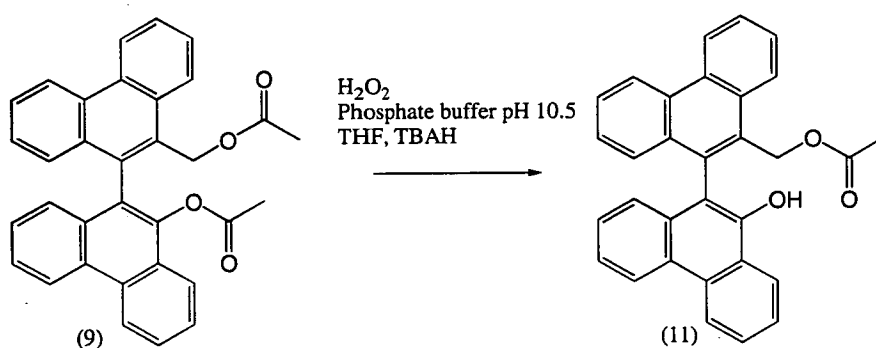


Figure 2.10: *Synthesis of ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-acetate.*

This biphenanthryl monoester substrate (**11**) was examined in the CE system as before, again using benzene as the organic solvent. Though a thick, cream emulsion formed there was no evidence of any CE activity, even after three days.

The possibility also existed that benzene, whilst forming an emulsion with the phosphate buffer and sodium taurocholate, was somehow inhibiting the activity of the enzyme. In order to assess the validity of this theory, a binaphthol test system was synthesised for use as the substrate in this CE catalysed enzymic hydrolysis. The binaphthol dipentanoate ester (**12**) was synthesised from binaphthol and pentanoyl chloride (**Figure 2.11**).

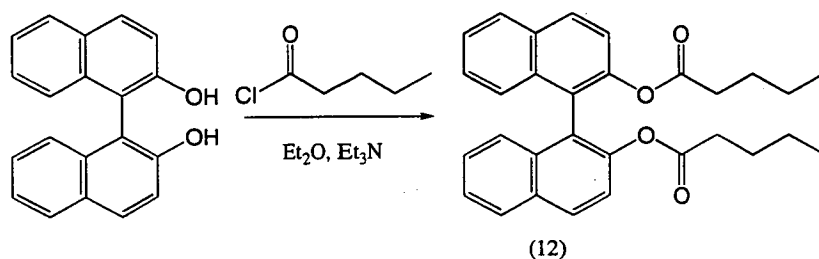


Figure 2.11: *Synthesis of dipentanoyl ester of binaphthol.*

Following the procedure described previously for this CE catalysed hydrolysis but using benzene as the organic solvent and 1mmol of binaphthol diester (**12**) as the substrate, the hydrolysis was run for three days, the pH checked at regular intervals and altered accordingly. The reaction was followed by TLC, which allowed the progress of the hydrolysis of the (S)-binaphthol diester to binaphthol to be followed easily. Analysis of the reaction products revealed the CE catalysed hydrolysis had proceeded to provide both (S)-binaphthol (**13**) and (R)-binaphthol dipentanoate ester (**14**) in good yield and optical purity (**Figure 2.12**).

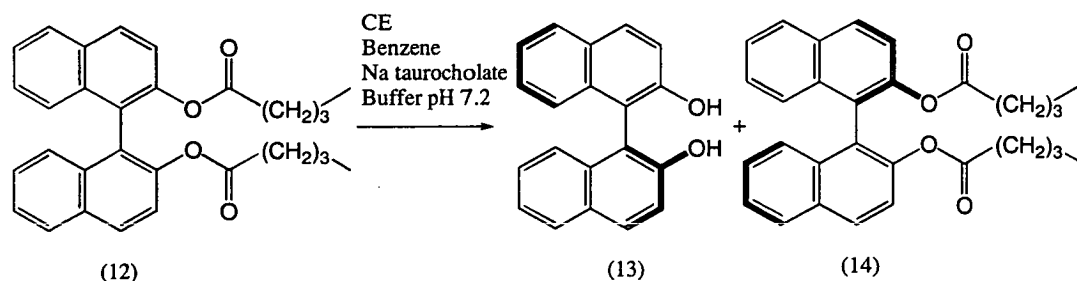


Figure 2.12: *CE catalysed hydrolysis of binaphthol diester.*

From these studies it was evident that benzene was a suitable solvent for CE catalysed ester hydrolysis, and that this biphenanthryl system is incompatible with the enzyme cholesterol esterase. The incompatibility of these biphenanthryl systems with CE may possibly be due to the extra steric bulk of the additional aromatic ring on each biaryl half compared to the binaphthyl system. It may also be a reflection on the sterical congestion imposed by the presence of the methylene unit of the benzyl position at the 'active site' of the substrate, close to where the enzyme must hydrolyse the ester.

Following the failure of the attempted enzymic resolution by CE, a commercially available lipase was tried instead. Lipases have been used successfully in the resolution of a broad range of primary and secondary alcohols through catalysing enantioselective esterification with vinyl acetate in *tert*-butyl methyl ether.¹⁰⁸ For example, racemic quantities of *cis*-1,2-dihydroxycycloalkanes, hydroxyvinylsilanes, and α -ketoalcohols have all been resolved in this way (Figure 2.13).¹⁰⁹

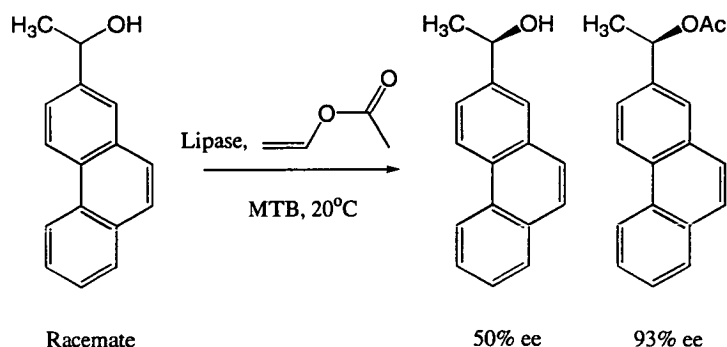


Figure 2.13: Lipase catalysed acylation of a secondary alcohol.

The experimental procedure to be followed was that utilised by Nicolosi *et al* in the resolution of a number of *cis*-hydroxydiols.¹¹⁰ The enzyme used is immobilised lipase from *Mucor miehei* (Lipozyme[®] TM). Lipase enzymes work at the forefront of the organic and aqueous phases and as a result do not require the presence of a buffered aqueous phase in order to operate. The organic solvent typically used for these biotransformations is *tert*-butyl methyl ether, though this is a poor solvent for the (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**7**) system. With enzymic action having shown to be greatly reduced in the presence of chlorinated solvents, *tert*-butyl methyl ketone and THF were tried instead. The suspensions of Lipozyme[®] TM, vinyl acetate and the racemic biphenanthryl diol in the organic solvent of choice were heated to 45°C and stirred at 300rpm overnight. There was no evidence of any enzymic action in either *tert*-butyl methyl ketone or THF.

Investigations into the resolution of these biphenanthryl systems by enzymic resolution discontinued after the failure of the CE and lipase enzymes and therefore an alternative means of achieving resolution of the biphenanthryl enantiomers were investigated.

Woodward *et al* reported L-menthyl *N*-aminocarbamate (**Figure 2.14**) as a stable, crystalline, optically active reagent which forms well-defined crystalline derivatives with a large number of carbonyl compounds of widely differing functionality.¹¹¹ Picken reported the resultant diastereoisomers of the

biphenanthryl phenolic-aldehyde (**6**) with these L-menthylhydrazines to be unstable, undergoing rapid decomposition.⁹⁵

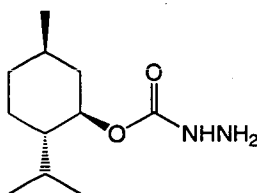


Figure 2.14: The resolving agent *L*-menthyl *N*-aminocarbamate.

In 1977, Enders *et al* described the use of the hydrazine (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (*S*-AMP) in forming chiral hydrazones with both α -chiral aldehydes and α -substituted ketones (**Figure 2.15**).¹¹² These chiral hydrazones were investigated in asymmetric alkylations *via* metalation with lithium diisopropylamide.

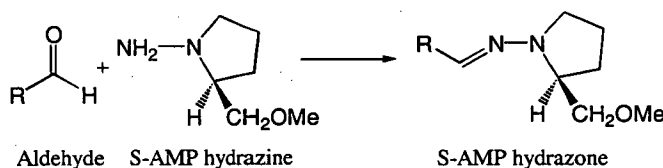


Figure 2.15: (*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (*S*-AMP).

Resolution of ($\pm$)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) was successfully achieved by Picken through the formation of the diastereotopic hydrazones with this *S*-AMP moiety (**Figure 2.16**).⁹⁵

The diastereomeric biphenanthryl hydrazones (**15**) and (**16**) were obtained after two hours stirring in DCM, and separated by wet flash chromatography. The two diastereoisomers were distinguishable by TLC, and after removal of organic solvent the purity of each diastereoisomer was determined through analysis by ¹H NMR. The (*S,S*)-diastereoisomer (**15**) has an *R_F* (DCM) value of 0.22 and its OCH₃ signal in the ¹H nmr is a distinct singlet at δ 3.21ppm. The slower running (*R,S*)-diastereoisomer (**16**) has an

R_F (DCM) value of 0.18 and its OCH_3 singlet in the ^1H NMR occurs at δ 3.28ppm. This difference in the values of the OCH_3 signals in the ^1H NMR made it simple and straightforward to determine the purity of the diastereomeric hydrazones obtained from the wet flash chromatography. The optical rotations of the two diastereoisomers are also markedly different. The (S,S) diastereoisomer has an optical rotation of $[\alpha]_D = -240^\circ$ and the (R,S) diastereoisomer has an optical rotation of $[\alpha]_D = +97^\circ$. Comparison of the optical rotations provides a further means of assessing the optical purity of the diastereoisomers. Approximately 70-80% of each diastereoisomer could be isolated in this way. Unresolved diastereoisomers were put to one side and used in the next resolution.

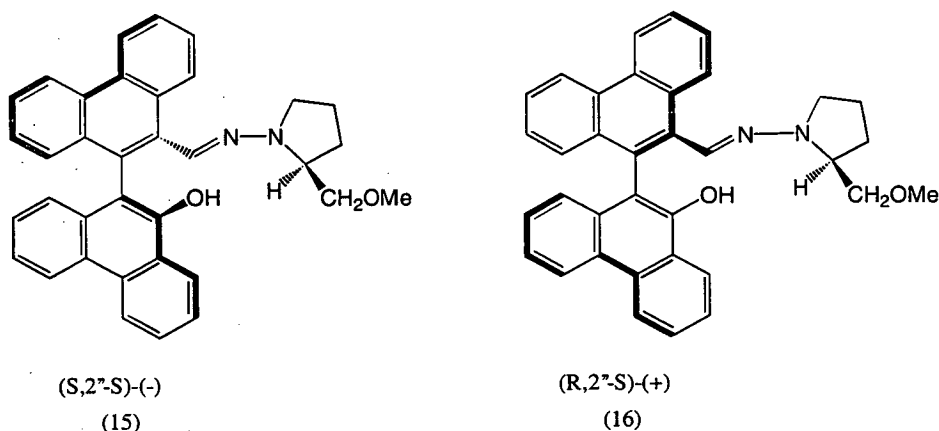


Figure 2.16: *S-AMP hydrazone diastereoisomers.*

Regeneration of chirally pure (S)- and (R)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) was achieved through ozonolysis of the appropriate diastereomerically pure hydrazone (**Figure 2.17**). Ozone gas was bubbled through a solution of the S-AMP hydrazone in dry THF, cooled to $-78^\circ C$, for five minutes. This ozonolysis proceeds much faster than the ozonolysis of the 8b-H-Tbf and requires no reducing agent to generate the aldehyde.

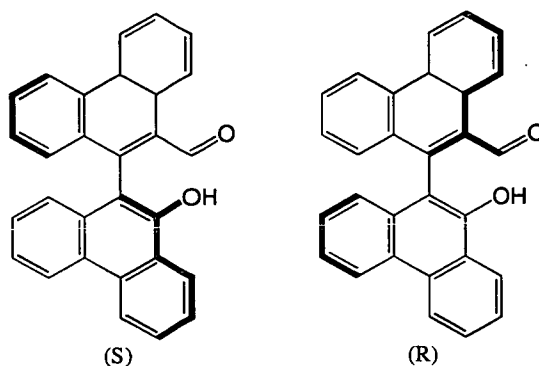


Figure 2.17: Resolved (*S*)- and (*R*)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde.

Mechanistic differences exist between the two ozonolysis reactions that have been discussed so far. The ozonolysis of 8b-H-Tbf produced a stable ozonide, following the mechanism of a classical ozonolysis of a carbon-carbon double bond.¹¹³ The first stage in this reaction involves a 1,3-dipolar addition of ozone to the substrate to give the initial ozonide or molozonide. This molozonide is highly unstable and cleaves *via* a retro 1,3-dipole addition to give a ketone and a zwitterion. In a second 1,3-dipole addition the zwitterion recombines with the ketone to give a more stable ozonide. This is the ozonide that was isolated and characterised (**Figure 2.18**).

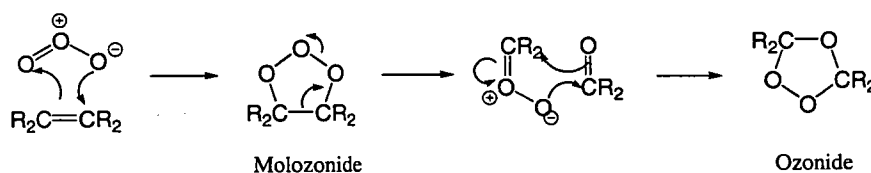


Figure 2.18: Ozonolysis of a carbon-carbon double bond, as proposed by Criegee.

The ozonolysis of the carbon nitrogen double bond, as witnessed in the cleavage of the S-AMP hydrazone, has been studied by Erickson *et al.*¹¹⁴ In these studies, it was discovered that two molar quantities of ozone were required per mole of hydrazone. It has been proposed that the initial attack of the ozone at the carbon nitrogen double bond is electrophilic, and may be

strongly assisted by an electron donating group on the nitrogen. A proposed mechanism for the cleavage of the S-AMP moiety has been devised that is consistent with the data reported by Erickson (**Figure 2.19**).

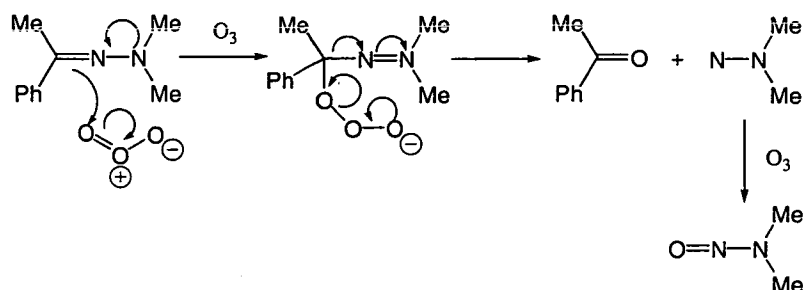


Figure 2.19: Ozonolysis of carbon-nitrogen bond.

The (S)-biphenanthryl phenolic aldehyde obtained from the ozonolysis of the (S,S)-hydrazone diastereoisomer was found to have an optical rotation of $[\alpha]_D = -56^\circ$, the optical rotation of the (R) enantiomer from the ozonolysis of the (R,S)-hydrazone diastereoisomer having the opposite optical rotation value of $[\alpha]_D = +71^\circ$.

Picken solved the absolute configuration of these biphenanthryl moieties by obtaining the crystallographic structures of the diastereomeric esters of racemic 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthrine (**7**) with a chiral carboxylic acid.⁹⁵ These phenolic esters were prepared using (R)- or (S)-2-phenylpropionic acid (**Figure 2.20**) in the presence of *N,N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).

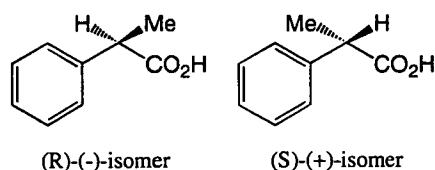


Figure 2.20: (R)- and (S)-2-phenylpropionic acid.

(S)-(+)-2-Phenylpropionic acid was used to obtain the (R)-(-)-isomer of the hydroxy phenol (**7**), and (R)-(-)-2-phenylpropionic acid used to obtain the (S)-(+)-isomer. Chirally pure biphenanthryl hydroxy phenol was regenerated through reduction of the appropriate diastereomeric ester with lithium aluminium hydride.

Thus the absolute configuration of the biphenanthryl diastereomeric esters could be assigned. This in itself did not in itself identify the absolute configuration of the diastereoisomers from the hydrazone resolution. The optical rotations of the (R)-and (S) biphenanthryl hydroxy phenols obtained when the phenylpropionic acid diastereomeric esters were cleaved with LiAlH_4 were measured. The enantiomerically pure biphenanthryl phenolic aldehydes obtained from ozonolysis of the diastereomeric hydrazones were similarly reduced with lithium aluminium hydride to chirally pure biphenanthryl hydroxy phenols. Measurement and comparison of the optical rotations of these two sets of biphenanthryl hydroxy phenols allowed the discovery of the absolute configuration of the biphenanthryl enantiomers from the hydrazone resolution to be deduced and assigned.

The absolute configuration of the diastereotopic esters was assigned according to the IUPAC rules. These rules guide the assignment of (R) and (S) to molecules that are chiral due to the presence of a chiral axis.¹¹⁵ The structure is regarded as an elongated tetrahedron and viewed along the axis, which end it is viewed from being immaterial. The nearer pair of ligands receives the first two positions in the order of preference shown (**Figure 2.21**).

The resolution using S-AMP required chemical manipulation in forming the hydrazone and in its removal by ozonolysis, which incurs a loss of material in each step. The separation of the enantiomers by wet flash chromatography, though a long and time consuming process, provides a means of removing impurities from the ozonolysis and unreacted phenolic aldehyde. The narrow separation between the hydrazone diastereoisomers compromises the yield of chirally pure material obtained. From 2g of crude racemic

hydrazone it is usual to obtain 0.7g of each hydrazone diastereoisomer, which after ozonolysis provides 0.4g chirally pure biphenanthryl phenolic aldehyde. This was the method chosen for the resolution of the biphenanthryl enantiomers.

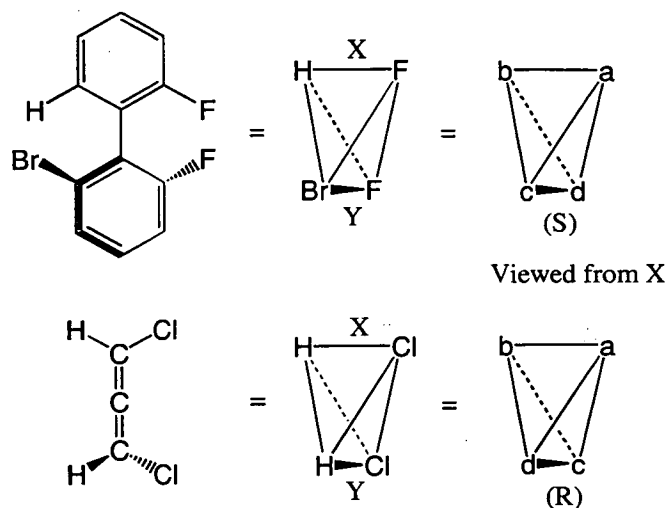


Figure 2.21: IUPAC rules for the assignment of axial chirality.

2.3. Development of Chiral Catalysts

With the synthesis of the biphenanthryl phenolic-aldehyde (**6**) optimised, interest turned to the introduction of heteroatoms and to increasing the length of the methylene chain to 2 or 3 carbons. The nucleophiles to be inserted included PPh_2^- , CN^- , and PhS^- . This required the modification of the aldehyde functionality to one more favourable to attack by these nucleophiles. The chosen target was the biphenanthryl alkyl bromide (**17**) (**Figure 2.22**).

The biphenanthryl diacetate (**9**) when refluxed with 30% HBr undergoes conversion to the alkyl bromide (**17**) at the benzyl position in moderate yield.

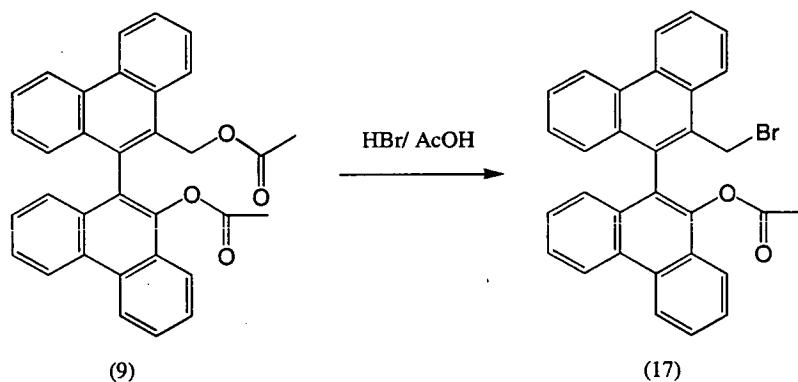
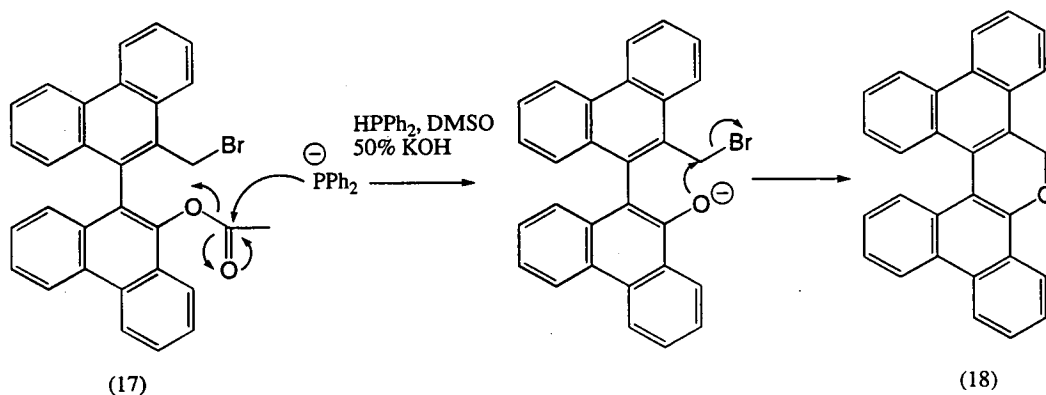


Figure 2.22: *Synthesis of ($\pm$)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate.*

A number of attempts were made to introduce the diphenylphosphine moiety without success. The initial conditions tried involved the generation of the diphenylphosphine anion from a diphenylphosphine and 50% KOH solution in DMSO.¹¹⁶ The biphenanthryl bromo-acetate (17) in DMSO was added to this solution at room temperature, with stirring continued for 1 hour. Upon reaction work-up it was discovered that there had been no introduction of the diphenylphosphine moiety. The phosphide nucleophile had instead caused the cleavage of the phenolic acetate, leaving the phenol free to subsequently attack the methyl bromide intramolecularly (**Figure 2.23**). The product from this reaction was the cyclic ether ($\pm$)-tetrabenzo[*a',c',g',i'*]-6H-dibenzo[*b,d*]pyran (18).



Alternative dipolar aprotic solvents such as DMF and dimethyl acetamide were used in place of the DMSO, though to the same effect. The solubility of the biphenanthryl bromo-acetate (**17**) in these solvents was poor, with the starting material left unreacted at the end of the reaction time. Different conditions were investigated. Using sodium dried THF as the solvent, the diphenylphosphine anion was generated using 2.5M BuLi at -78°C . The biphenanthryl bromo-acetate was added to this solution at this temperature and the reaction allowed to warm to room temperature. A quantitative conversion of the biphenanthryl bromo-acetate to the cyclic ether was obtained. Even with no base present it was found that diphenylphosphine caused cleavage of the acetate group with the cyclic ether appearing in increasing amounts over time.

It was clear that the acetate was more favourable to nucleophilic attack than the bromine. The *Finkelstein reaction* provided a means of converting the methylenebromide to a methyleneiodide.¹¹⁷ The replacement of the bromine by a better leaving group was carried out with the intention of inducing the diphenylphosphine anion to attack at the methyl position and not at the acetate. The reaction conditions for the *Finkelstein reaction* from the literature recommend acetone as the reaction solvent, taking advantage of the fact that sodium iodide and not the bromide, is soluble in acetone. These conditions were not suitable for the biphenanthryl system due to its low solubility in acetone. Instead, THF was used with an excess of sodium iodide and a crystal of iodine (**Figure 2.24**). A complete conversion to the biphenanthryl iodoacetate (**19**) was found to occur, though disappointingly the new biphenanthryl moiety proved to be inert to attack by the diphenylphosphine anion at the methyl iodide position. The diphenylphosphine anion was again generated from diphenylphosphine and BuLi in THF. No cyclised ether side product was recovered from the reaction.

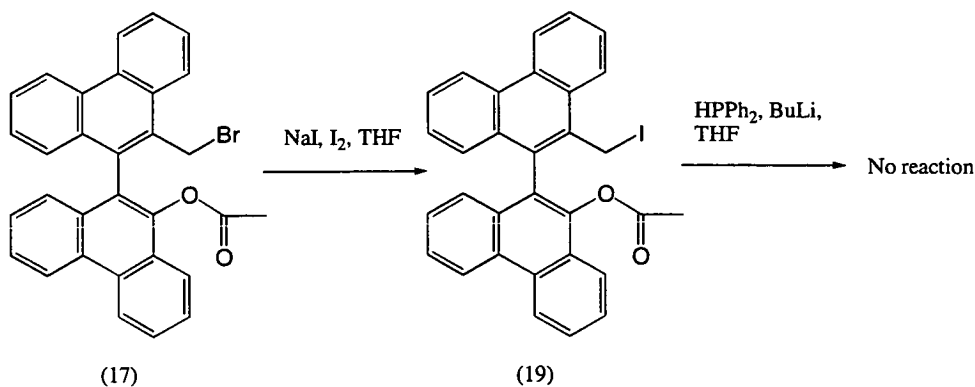


Figure 2.24: Synthesis of ($\pm$)-10'-Hydroxy-10-(iodomethyl)-9,9'-biphenanthryl.

A difficulty that arose in the introduction of the CN⁻ ion to the biphenanthryl bromo-acetate moiety was the differing solubilities of the biphenanthryl substrate and the CN⁻ anion.¹¹⁸ Whilst the biphenanthryl bromo-acetate is insoluble in water the CN⁻ ion is insoluble in organic solvents. Taking this into account, a 1:1 mixture of THF and DMSO was used with NaCN as the CN⁻ source. The reaction mixture was gradually heated over 4 hours to 85°C. The product from the reaction was identified after work-up as the biphenanthryl aldehyde (20) (Figure 2.25). The oxidation of primary halides to aldehydes is well documented and requires only DMSO. No reaction was found with replacement of the DMSO and THF mixture by benzene.

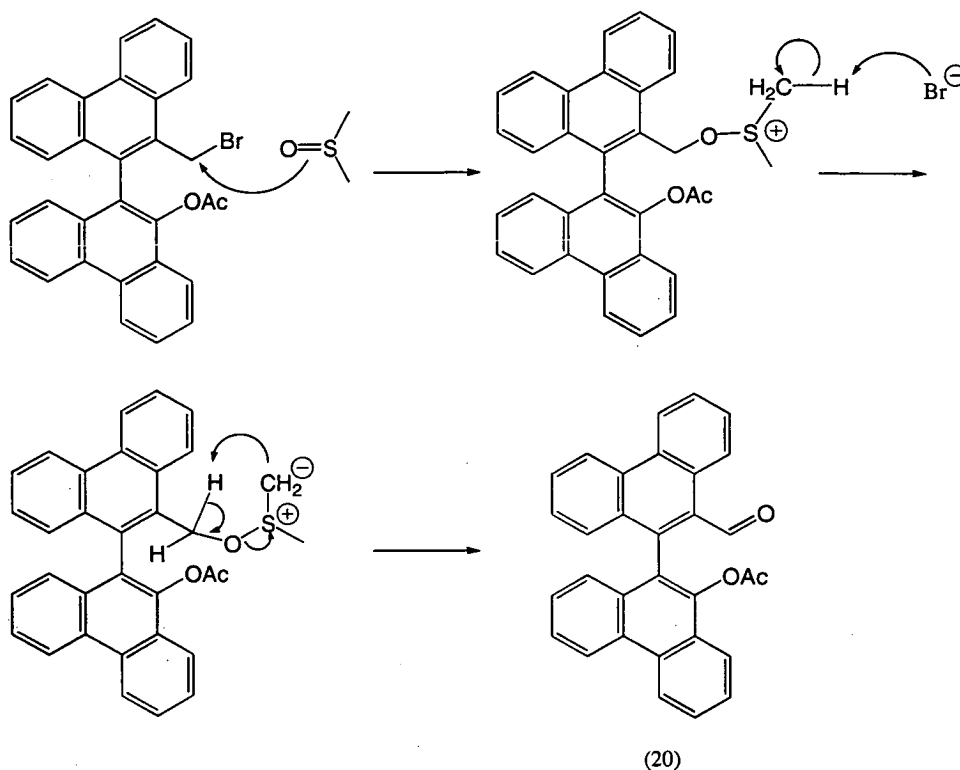


Figure 2.25: Oxidation of 10'-methoxy-10-(bromomethyl)-9,9'-biphenanthryl.

The last nucleophile for introduction into the biphenanthryl bromo-acetate moiety was the anion of thiophenol. The thiophenolate anion was generated through deprotonation of thiophenol with NaH in dry THF at 0°C.¹¹⁹ After addition of this suspension to the biphenanthryl bromo-acetate (17) in THF, the thioether product proved to be very difficult to purify. Removal of unreacted thiophenol by distillation and wet flash chromatography both proved unsuccessful. The removal of unreacted thiophenol was finally achieved through allowing it to evaporate to the atmosphere over time. Analysis of the product from this reaction showed that there not only had occurred successful creation of the thioether functionality, but that the acetate protecting group had been removed as well to leave the unprotected phenol (21) (Figure 2.26).

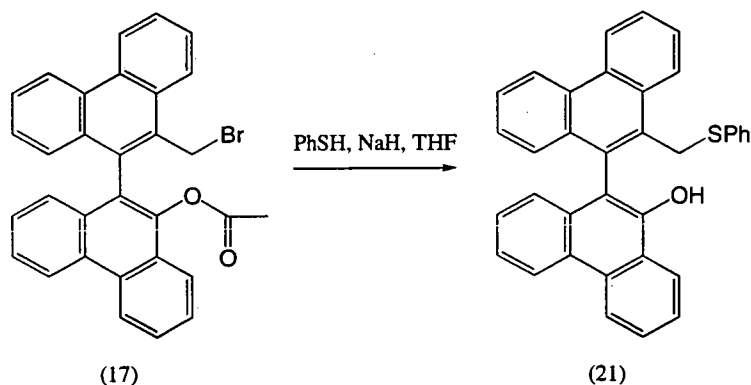


Figure 2.26: Synthesis of ($\pm$)-10'-hydroxy-10-(methyl)-9,9'-biphenanthryl-10-thiophenylether.

An oxime moiety was synthesised from a biphenanthryl phenolic aldehyde suspension in ethanol, with hydroxylamine hydrochloride and sodium acetate. Using chirally pure (R)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (6), the oxime (R)-(+)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (22) was made in moderate yield, $[\alpha]_D = -13^\circ$ (Figure 2.27). The swift colour change of the reaction from off-white to pale yellow indicated the successful formation of the oxime. The reaction yield was consistently between forty and fifty percent, a result unchanged by longer reaction times. Sonication to give a finer suspension similarly had no effect on the yield.

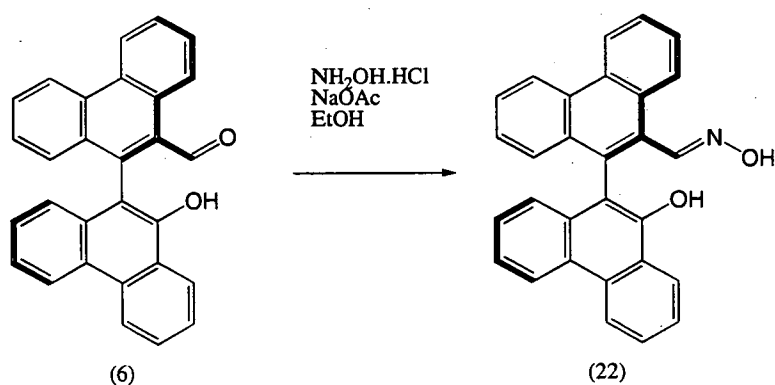


Figure 2.27: Synthesis of (R)-(+)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime.

Two methods were investigated towards the extension of the methylene chain at the C9-position of the biphenanthryl system using the ($\pm$)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) as the starting material.

The methylene chain can be extended by one carbon by the *Henry reaction*, which involves the condensation of nitromethane with an aldehyde to give a vinyl nitro derivative (**Figure 2.28**).

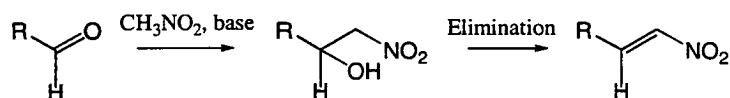


Figure 2.28: *The Henry reaction.*

A number of reactions were carried out using different conditions, though in all cases the nitromethane anion was generated through the removal of a α -hydrogen by potassium hydroxide. Following a procedure by Ramage *et al* the anion was generated in a mixture of THF, water and ethanol.¹²⁰ This was added to the biphenanthryl phenolic-aldehyde (**6**) dissolved in THF and stirring continued overnight. The reaction was re-run following the same reaction conditions, but with replacement of the THF by DMF. A third procedure was employed using only THF as the solvent, though with the crown ether 18-crown-6 added to complex the potassium of the potassium hydroxide.¹²¹ In all three reactions the formation of the nitromethane anion was visibly detectable after the addition of potassium hydroxide through the colour change from a clear to pale yellow solution. Further, in all cases the addition of the nitromethane anion to the biphenanthryl phenolic-aldehyde (**6**) resulted in the appearance of a deep red colouration which disappeared upon quenching with 2M HCl. From analysis by both TLC and ^1H NMR no reaction was found to have occurred.

A second approach to extending the methylene chain at the C9-position by one carbon was through the *Wittig reaction* with the phosphonium ylide of (methoxymethyl)-triphenylphosphonium-chloride (**Figure 2.29**).¹²²

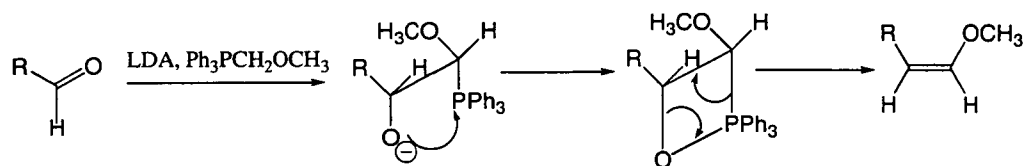


Figure 2.29: The *Wittig reaction* with (methoxymethyl)-triphenylphosphonium-chloride.

The phosphonium ylide was generated from (methoxymethyl)-triphenylphosphonium-chloride and freshly prepared lithium diisopropylamide (LDA). The organic solvent systems tried with this reaction included THF, DMF/THF, and DMSO/THF. The biphenanthryl phenolic-aldehyde (**6**) was added slowly to the phosphonium ylide at 0°C, at which time a deep red colouration appeared. This red colouration disappeared when the reaction was quenched, with no product detectable by either TLC or ¹H NMR. The unreacted starting material was recovered in good yield.

A possible explanation for the failure of these reactions could be that the biphenanthryl phenolic-aldehyde (**6**) undergoes cyclisation to form a hemi-acetal in the presence of base. This would occur through the deprotonation of the phenol and subsequent intramolecular attack by the phenolate anion at the carbonyl (**Figure 2.30**). The *Wittig* and *Henry reactions* were repeated with excess amounts of nucleophile to investigate the possibility that nucleophiles are merely being neutralised through deprotonation of the phenol of the biphenanthryl phenolic-aldehyde. With excess reagent and with the hemi-acetal in equilibrium with the phenolic aldehyde, some reaction should be seen to occur. The same results were obtained as described previously.

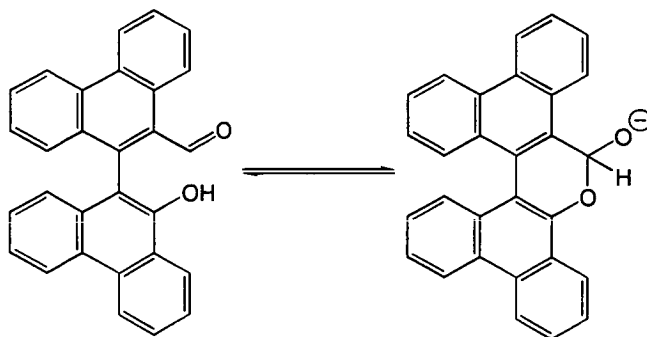


Figure 2.30: *Hemi-acetal formation.*

This red colouration was witnessed in the addition of potassium *tert*-butoxide in THF to a quantity of the biphenanthryl phenolic-aldehyde (**6**). The highly insoluble red precipitate obtained was isolated and analysed. From the IR there still appeared the aldehyde signal at 1680cm^{-1} and from ^1H NMR there still appeared the aldehyde signal at $\delta 10.15$ ppm. From these data it seems unlikely that the hemi-acetal is forming to any great extent, and even so, in such equilibrium there would be phenolic aldehyde present which could react with the nucleophiles. It is perhaps more likely that the deprotonated phenol is shielding the carbonyl from nucleophilic attack by either electrostatically repelling nucleophiles or by reducing the polarity of the carbonyl through hydrogen bonding.

The problems encountered in the modifying the functional group at the biphenanthryl C9 position were attributed to the generation of the phenolate anion at the C9' position. To achieve successful nucleophilic attack at this position a robust protecting group at the phenolic position was required. The methyl and benzyl ethers of the biphenanthryl phenolic-aldehyde were synthesised.

Biphenanthryl phenolic-aldehyde (**6**) with base gives the red phenolate anion discussed earlier. The addition of methyl iodide with stirring overnight generated the methyl ether ($\pm$)-10'-methoxy-9,9'-biphenanthryl-10-carboxaldehyde (**23**).¹²³ The reaction was complete following the colour change from red to yellow and the reaction yield was found to vary greatly

depending on the base used, the results of which are shown in the following table (Table 1).

BASE	SOLVENT	PRODUCT YIELD %
KOBu ^t	MeOH/THF	50
KOBu ^t	THF	70
KOBu ^t	THF	67
NaOMe	THF	0
KOH	THF	57
KOH	THF	83
NaH	THF	0

Table 1: Methyl protection results.

The base chosen for the methyl protection was KOBu^t. Enantiomerically pure (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) was methylated to give (S)-10'-methoxy-9,9'-biphenanthryl-10-carboxaldehyde (**23**) in 56% yield (Figure 2.31). The optical rotation of this biphenanthryl compound was $[\alpha]_D = +97^\circ$.

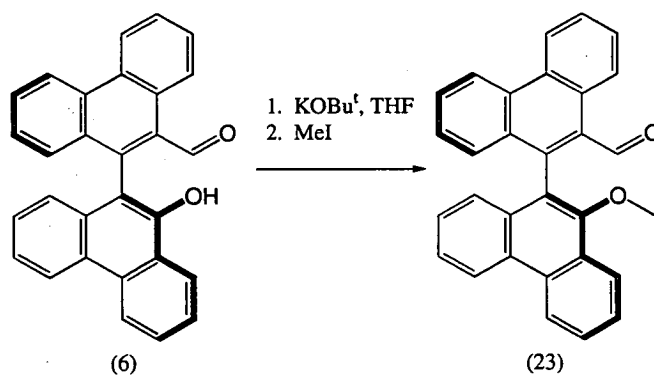


Figure 2.31: Synthesis of (S)-10'-methoxy-9,9'-biphenanthryl-10-carboxaldehyde.

The synthesis of the benzyl ether proved more problematic. Using the method described above, but replacing methyl iodide with benzyl bromide, reaction times were found to lie between three to five days, with low yields. Also, the benzylated reaction product proved impossible to separate from the biphenanthryl starting material by wet flash chromatography. Quantitative conversion of the biphenanthryl phenolic aldehyde (**6**) to the benzyl ether was achieved through the addition of one equivalent of *tert*-butylammonium iodide to the reaction mixture, with respect to the biphenanthryl substrate.¹²⁴ This ammonium salt converted the benzyl bromide to benzyl iodide *in situ*, which was much more susceptible to nucleophilic attack from the phenolate anion. Using the red to pale yellow colour change of the reaction as the indicator for the reactions completion, the reaction time was cut from five days to three hours. With sodium hydride as the base, (*S*)-10'-hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether (**24**) was synthesised in 78% yield, $[\alpha]_D = -7^\circ$ (Figure 2.32).

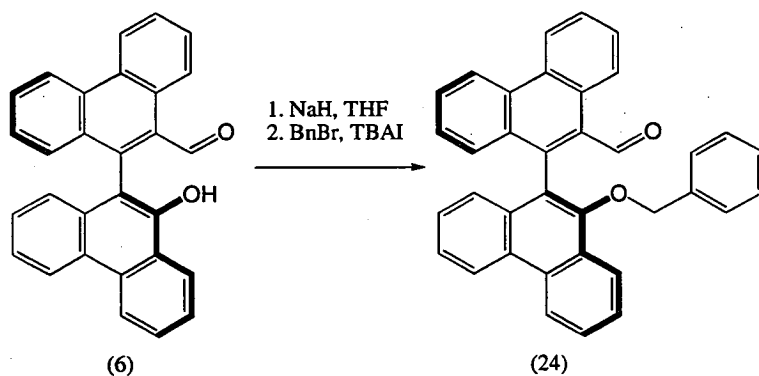


Figure 2.32: Synthesis of (*S*)-10'-hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether.

As an alternative to the resolution with S-AMP, the resolution of ($\pm$)-10'-hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether (**24**) was attempted through the formation of a diastereomeric urethane with S-(-)-(α -methylbenzyl)isocyanate. In the synthesis of L-(-)-prostaglandin E₂ by Fuchs *et al*, S-(-)-(α -methylbenzyl)isocyanate was used in the resolution of a racemic

sulphide alcohol through enantioselective crystallisation of the resultant diastereomeric urethanes from methanol (**Figure 2.33**).¹²⁵

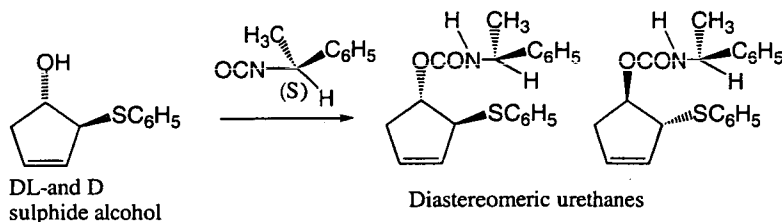


Figure 2.33: Resolution of chiral sulphide alcohol using *S*-(-)-(α -methylbenzyl)isocyanate.

Reduction of (*S*)-10'-hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether by diisobutylaluminium hydride gave ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-benzylether (**30**) in high yield. The biphenanthryl benzyl alcohol was dissolved in dry benzene and in the presence of *N,N*-dimethylethanolamine and *S*-(-)-(α -methylbenzyl)isocyanate at 80°C for 18h, gave the diastereoisomeric biphenanthryl urethane (**25**) in good yield (**Figure 2.34**).

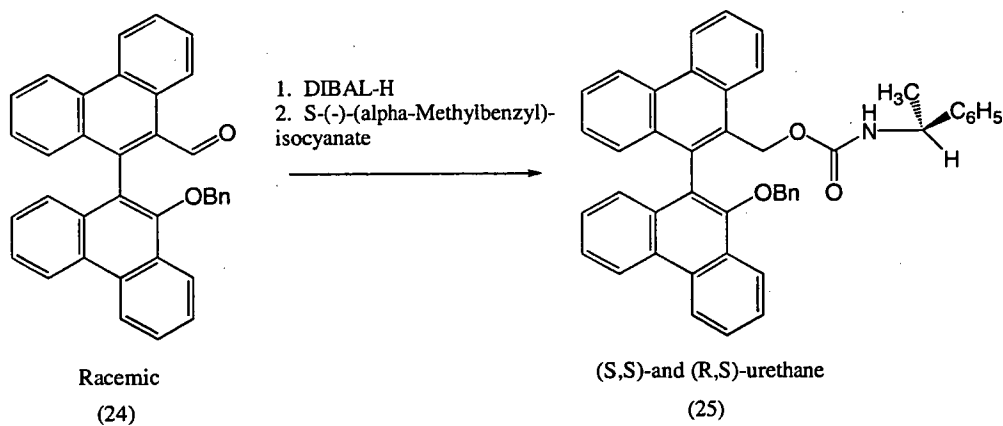


Figure 2.34: Synthesis of diastereomeric urethane.

These biphenanthryl urethanes proved insoluble in methanol, ethyl acetate, and diethyl ether, with no crystallisation achieved from DCM or

benzene. Separation of the diastereoisomers by wet flash chromatography was investigated, though a solvent system that would provide adequate separation of the diastereoisomers could not be found.

The deactivation of the phenol functionality through conversion to the methyl ether was hoped to provide a suitable moiety to which the nucleophile PPh_2^- could be introduced. ($\pm$)-10'-Methoxy-10-(bromomethyl)-9,9'-biphenanthryl (**28**) was synthesised using the same methodology as had been used to construct ($\pm$)-10'-hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate (**17**) (Figure 2.35).

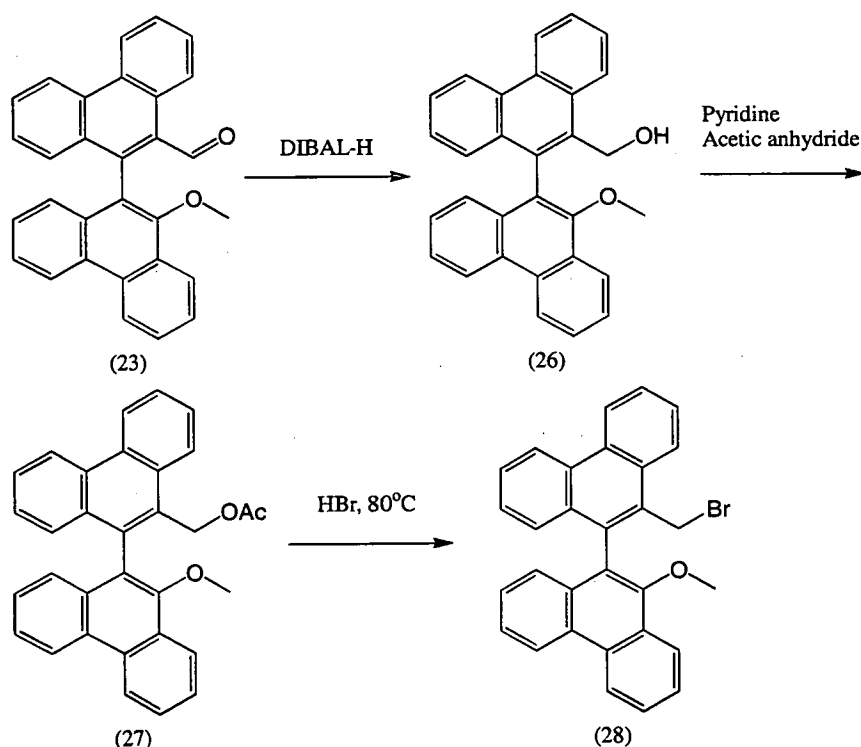


Figure 2.35: Synthesis of ($\pm$)-10'-methoxy-10-(bromomethyl)-9,9'-biphenanthryl

The biphenanthryl methoxy-aldehyde (**23**) provided the starting material for this short synthesis. Reduction with DIBAL-H in dry THF to the primary alcohol ($\pm$)-10'-methoxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**26**)

was achieved in high yield, with subsequent conversion to the acetate (**27**) in dry pyridine and acetic anhydride. ($\pm$)-10'-Methoxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-acetate (**27**) was converted to the biphenanthryl alkyl bromide (**28**) after refluxing for 1 hour in 30% hydrobromic acid.

The diphenylphosphine anion was generated from diphenylphosphine and butyl lithium in dry THF at -78°C . One equivalent of this PPh_2^- anion was added to a solution of 10'-methoxy-10-(bromomethyl)-9,9'-biphenanthryl (**28**) in dry THF. Analysis of the reaction product revealed that the desired $\text{S}_{\text{N}}2$ attack by the nucleophilic PPh_2^- at the biphenanthryl C9 methyl bromide position had not occurred. Instead, it appeared the nucleophile had directly attacked and cleaved the bromine, leaving a carbanion which converted to ($\pm$)-10'-hydroxy-10-(methyl)-9,9'-biphenanthryl-10'-methyl ether (**29**) in the aqueous acid work-up (Figure 2.36).

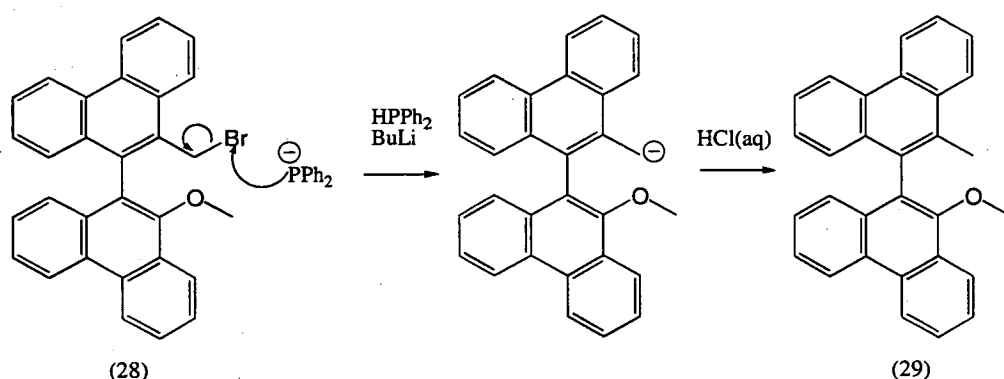


Figure 2.36: *Synthesis of ($\pm$)-10'-hydroxy-10-(methyl)-9,9'-biphenanthryl-10'-methyl ether.*

2.4. The Enantioselective Addition of Diethylzinc to Aldehydes

In the synthesis of chiral bidentate biphenanthryl ligands for application in the asymmetric addition of diethylzinc to aldehydes, it was necessary to synthesise chirally pure ligands with the previously discussed *N,O*-functionality. The chiral biphenanthryl oxime (**22**) and diastereomeric hydrazones (**15**) and (**16**) possess this functionality and were considered appropriate candidates for application in this reaction as chiral catalysts. Bringmann and Breuning found their tertiary amine biaryl derivative to catalyse the enantioselective addition of diethylzinc to aldehydes in high enantiomeric yields, and so a similar functionality was introduced to the biphenanthryl system.⁷⁶

(*S*)-10'-Hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10'-benzylether (**24**) was reduced with sodium borohydride in high yield to give the primary alcohol (*S*)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-benzylether (**30**). The primary alcohol was converted to the alkyl bromide using 1,2-dibromotetrachloroethane and triphenylphosphine in wet DCM. This reaction proceeded in high yield providing chirally pure (*S*)-10'-hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10-benzylether (**31**) in an overall yield of 60% from the biphenanthryl phenolic-aldehyde (**Figure 2.37**).

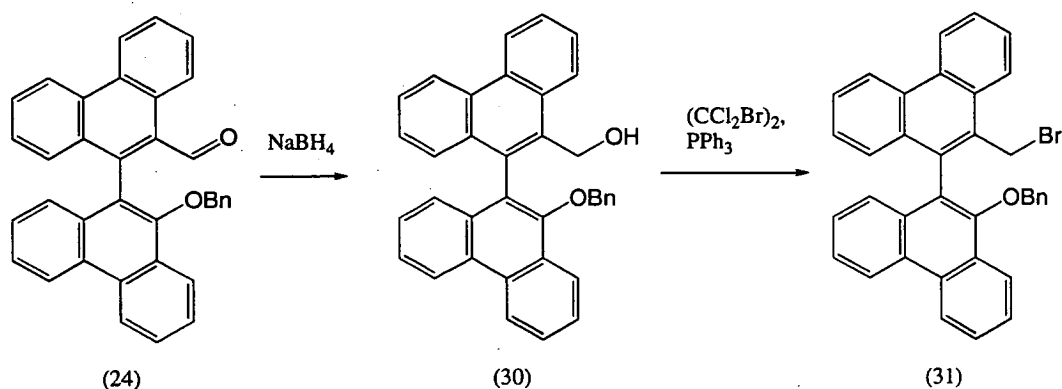


Figure 2.37: Synthesis of (*S*)-10'-hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-benzylether.

(S)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10-benzylether (31), dimethylamino hydrochloride and triethylamine were stirred at 0°C in dry DCM overnight. Dimethylamine (b.p. 7°C) was formed *in situ* which proved sufficiently reactive enough to generate the tertiary amine (S)- 10-(N,N-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl-10-benzylether (32) (Figure 2.38).

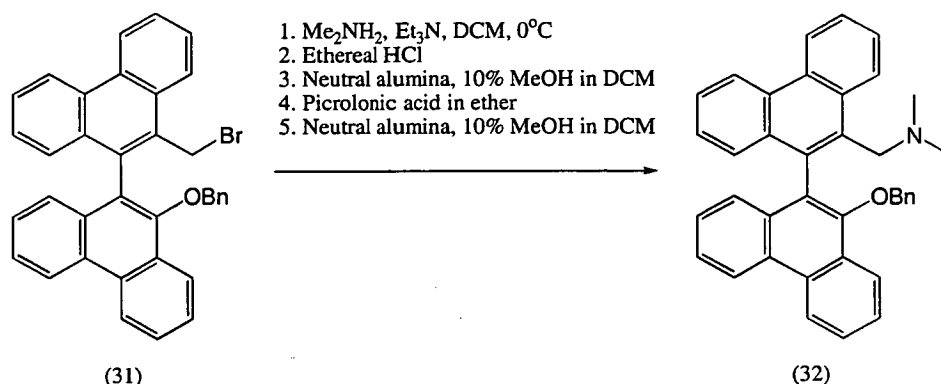


Figure 2.38: *Synthesis of (S)- 10-(N,N-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl-10-benzylether*

A number of methods were investigated towards purifying this tertiary amine. Purification by wet flash chromatography, even with polar solvent systems such as 10% methanol or 1% triethylamine in DCM resulted in the biphenanthryl product adsorbing to both silica and neutral alumina with very little recovery of product. Purification as the carbamate with di-*tert*-butyl dicarbonate (*t*-BOC₂O), or as a salt with *p*-toluenesulfonic acid proved problematic and ineffective. Attempts at crystallising the salts from DCM with a variety of co-solvents such as ethanol, methanol, ethyl acetate and hexane resulted only in the formation of oils. In the crystallisation of the amine with picric acid and picrolonic acid (Figure 2.39), the insolubility of the biphenanthryl moiety in ethanol meant the recommended procedure could not be adhered to¹²⁶.

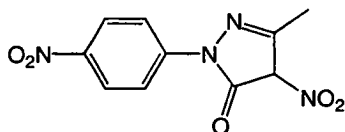


Figure 2.39: *Picrolonic acid.*

Initial purification was achieved through the formation of the hydrochloride salt through sonication and triturating the biphenanthryl tertiary amine (**32**) in ethereal HCl. This ethereal HCl was prepared from the passage through ether of the HCl gas emitted from the addition of concentrated HCl to concentrated H₂SO₄. A white precipitate was obtained from the trituration which could easily be filtered. Analysis of this salt showed that it was the desired product, but insufficiently pure. The amine was recovered through the passage of the salt through a neutral alumina plug with 10% methanol in DCM. The solvent was removed *in vacuo* and the biphenanthryl tertiary amine (**32**) again sonicated in ether but this time in the presence of excess picrolonic acid. After alternately sonicating and triturating the mixture for one hour, a yellow precipitate had formed which could be filtered and washed with ice cold ethanol to give the picrolonic acid derivative. The amine was stored as this picrolonic acid salt until it was required for use, at which time it was passed through an alumina plug with 10% methanol in DCM to give (S)- 10-(*N,N*-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl-10-benzylether (**32**) in good yield and purity.

Cleavage of the benzyl protecting group of the biphenanthryl tertiary amine (**32**) was achieved using two sets of conditions. The benzyl ether was initially cleaved using 2 equivalents of boron trichloride (BCl₃) in dry DCM at 0°C.⁷⁶ The BCl₃ was purchased as a 1M solution in hexanes. Though the procedure was relatively straightforward and proceeded in high yield, the reproducibility of the results varied considerably. It was found that once the BCl₃ solution had been opened, its reactivity fell sharply. This decrease in reactivity was such that after two reactions, no benzyl ether cleavage was

detectable in the reaction product by ^1H NMR. Due to the difficulty involved in the purification of this biphenanthryl tertiary amine, the benzyl ether cleavage had to be near quantitative.

Benzyl cleavage was achieved instead by catalytic hydrogenation in the presence of *Pearlman's Catalyst* (palladium hydroxide on carbon). The hydrogenation was performed in ethyl acetate at room temperature and atmospheric pressure for two hours. Analysis of the crude product by ^1H NMR detected no remaining benzyl functionality. Purification of the hydrogenation product (S)- 10-(*N,N*-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl (**33**) as the picronic acid salt was achieved through the procedure described previously (**Figure 2.40**).

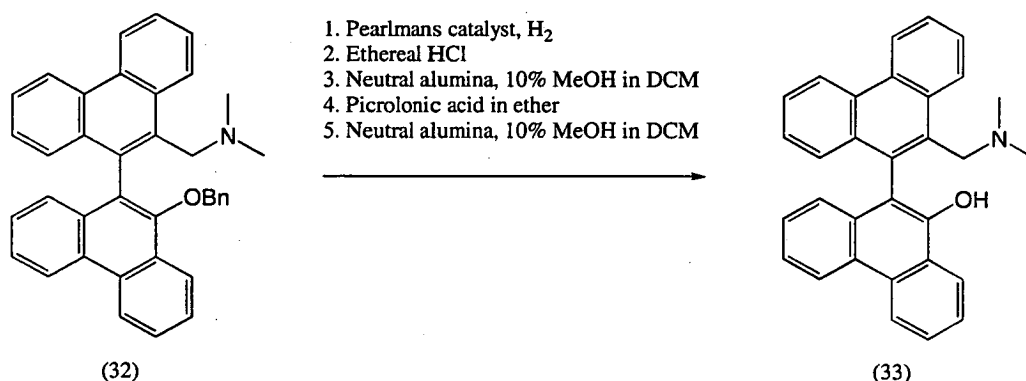


Figure 2.40: Synthesis of (S)- 10-(*N,N*-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl.

Three biphenanthryl catalysts were thus synthesised with both nitrogen and oxygen containing functional groups for use in the asymmetric addition of diethylzinc to aldehydes. The biphenanthryl hydrazones (**15**) and (**16**) are diastereomeric, and so the (S,S)-and (R,S)-diastereoisomers were tested in this reaction, along with the (R)-oxime (**22**) and the (S)-tertiary amine (**33**). Each of these systems was chirally pure, with the phenol position unprotected. As a control in these experiments the widely investigated and highly effective catalyst (1R,2S)-(-)-ephedrine (**Figure 2.41**), was also employed.⁵⁴ The

efficiency and enantiomeric success of the ephedrine system in this reaction was used to bring to attention any faults in methodology.

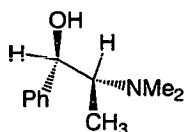


Figure 2.41: (1*R*,2*S*)-(-)-ephedrine.

The aldehydes benzaldehyde and anisaldehyde were chosen as the substrates in these reactions (**Figure 2.42**). Both are aromatic and are commonly employed in these types of studies, allowing a comparison of these biphenanthryl systems to previously published results.

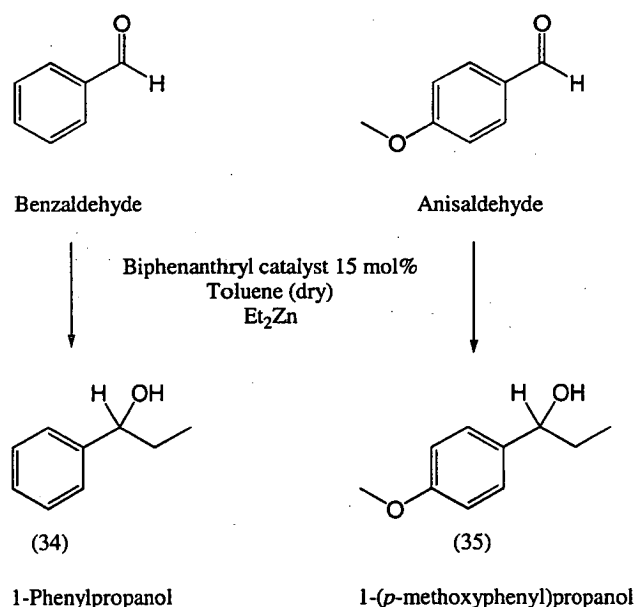


Figure 2.42: Asymmetric synthesis of 1-phenylpropanol and 1(*p*-methoxyphenyl)propanol.

The reaction procedures described by Bringmann were adopted and followed as closely as possible.⁷⁶ This procedure is described in detail in the experimental section. Much care was taken to keep the reaction as dry as

possible. Glassware was successively flame dried under vacuum and flushed with dry argon.. Both the argon and nitrogen were passed through concentrated sulphuric acid, silica gel and finally sodium hydroxide pellets to ensure the removal of any moisture. Fresh toluene was dried over sodium wire immediately before each set of reactions were run. The catalysts were employed at 15 mol% with respect to the substrate and the reactions quenched after 24 hours. The results obtained from the enantioselective synthesis of 1-phenylpropanol (**34**) and 1-(*p*-methoxyphenyl)propanol (**35**) are shown in Table 2.

CATALYST	REACTION PRODUCT	$[\alpha]_D$	% EE	YIELD
(S,S)-hydrazone	1-phenylpropanol	+2.5	12% (R)	81
(S,S)-hydrazone	1-(<i>p</i> -methoxyphenyl)propanol	+4.9	14% (R)	65
(R,S)-hydrazone	1-phenylpropanol	-4.8	17% (S)	75
(R,S)-hydrazone	1-(<i>p</i> -methoxyphenyl)propanol	-7.4	11% (S)	82
(1R,2S)-(-)-ephedrine	1-phenylpropanol	+38.9	38% (R)	55
(1R,2S)-(-)-ephedrine	1-(<i>p</i> -methoxyphenyl)propanol	+17.3	58% (R)	87
(R)-oxime	1-phenylpropanol	-5.7	*	65
(R)-oxime	1-(<i>p</i> -methoxyphenyl)propanol	-6.3	*	76
(R)-3° amine	1-phenylpropanol	-5.0	*	63
(R)-3° amine	1-(<i>p</i> -methoxyphenyl)propanol	-6.7	*	45

Table 2: Results from asymmetric addition of diethylzinc to benzaldehyde and anisaldehyde.

* Note: the %EE for these samples was not obtainable due to the delay in Avecia running the necessary chiral analysis. This delay resulted in the degradation of the submitted samples.

Initial attempts at running these reactions with the biphenanthryl hydrazone and oxime under a nitrogen atmosphere proved unsuccessful, prompting a change to argon. From this it became clear that these reactions are very moisture sensitive.

In analysing the results from these experiments, the low enantiomeric excess found in all of these reactions at first indicates that these biphenanthryl systems are poor chiral catalysts for the addition of diethylzinc to aldehydes. The hydrazone reactions were repeated several times with comparable results obtained to those shown. In the initial attempts at running these reactions it was found that prior to quenching the reactions the syringe needles supplying the inert atmosphere over the reactions were blocked. Care was taken to keep these needles free from blockage in future. However, this may have hindered the success of the reactions due to the nature of the gas passing overhead. Instead of having a still atmosphere of inert gas over the reaction, the argon was slowly passed over the system. However, over a period of twenty-four hours, a sensitive reaction run on such a small scale may be exposed to appreciable levels of moisture through such a set up.

In similar studies performed by Zeneca with the ephedrine catalyst (1S,2R)-DBNE it was reported that vigorous exclusion of air and moisture was required in these reactions since diethylzinc is readily hydrolysed in the presence of moisture. It was found that continuous purging introduced sufficient moisture to cause this hydrolysis and that a static blanket of inert gas was required. The scale of the reaction was larger also, employing 0.6 mmol of catalyst, though the experimental procedure was otherwise identical. The excellent results obtained from the investigation of this reaction by Zeneca with (1S,2R)-DBNE in comparison to the results obtained here support the suspicion that there exists a fault in the reaction set-up. Even taking this into account however, the results obtained with ephedrine they are still appreciably higher than the results obtained with the biphenanthryl catalysts. A true appraisal of the potential of these biphenanthryl systems can only be made upon repetition of these reactions on a larger scale under a static blanket of inert gas. The results obtained are promising and perhaps give an indication of

the potential of these systems in the asymmetric addition of diethylzinc to aromatic aldehydes.

The enantiomeric excess for each sample was determined by chiral gas chromatography by Dr John Blacker. In order to perform these chromatographic experiments, racemic samples of both 1-phenylpropanol (**34**) and 1-(*p*-methoxyphenyl)propanol (**35**) had to be prepared. Both were prepared through reaction of the respective aldehyde with the Grignard reagent ethyl magnesium bromide, prepared from ethyl bromide and magnesium (**Figure 2.43**).

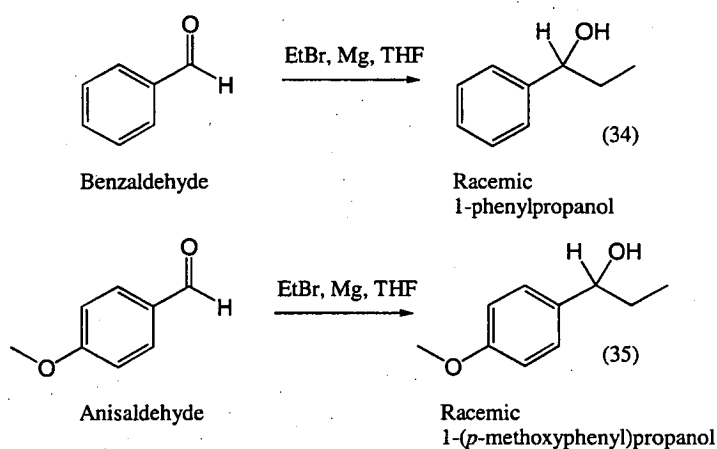


Figure 2.43: *Synthesis of racemic 1-phenylpropanol and 1-(*p*-methoxyphenyl)propanol.*

Care must be taken in the purification of these secondary alcohols. After final purification by bulb-to-bulb distillation it was found that if the samples were not kept refrigerated and in darkness they coupled to form diastereomeric ethers (**36**). The formation of these ethers from 1-(*p*-methoxyphenyl)propanol is immediately detectable by the strong, sweet smell of aniseed (**Figure 2.44**).

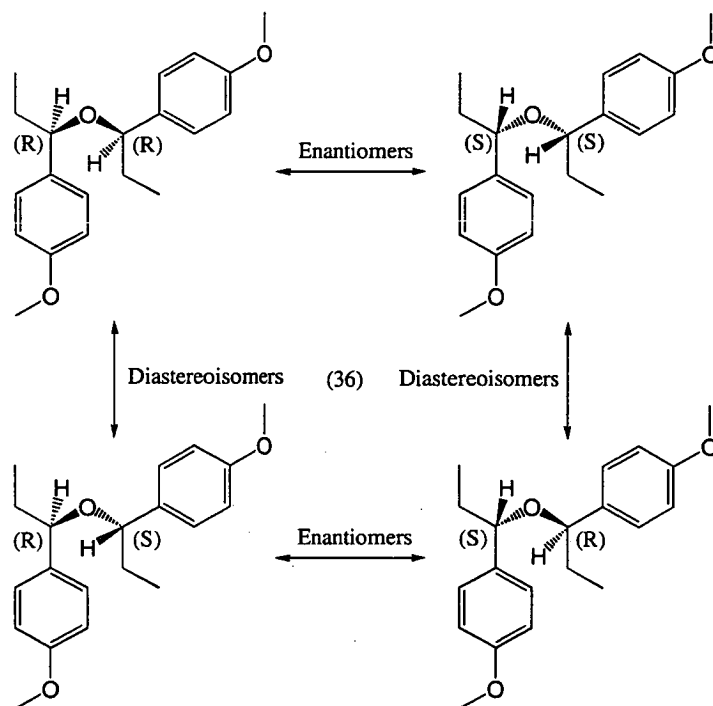


Figure 2.44: *Bis-[1-(4-methoxy-phenyl)-propyl]-ether diastereoisomers.*

The structure elucidation of these ether linked dimers of 1-(*p*-methoxyphenyl)propanol (**36**) was aided through analysis by NMR. The ^1H NMR contains two pairs of signals for each signal found in the ^1H NMR of the secondary alcohol 1-(*p*-methoxyphenyl)propanol. This is due to the presence of equal amounts of the two diastereoisomers. The ether coupling at the C1 position explains the absence in the ^1H NMR of the broad peak at 2.0–2.5 ppm from the OH group. It was hoped a long distance heteronuclear coupling experiment (HMQC) would show some coupling across the ether bond, though no such correlation was found.

2.5. The Enantioselective Reduction of Prochiral Ketones

In the enantioselective reduction of prochiral ketones to chiral alcohols through borane complexation, chiral bidentate catalysts possessing phenolic and primary amine functionality have been found to produce the best results. Such bidentate functionality was introduced to the biphenanthryl system for investigation into its potential as a chiral catalyst in this reaction.

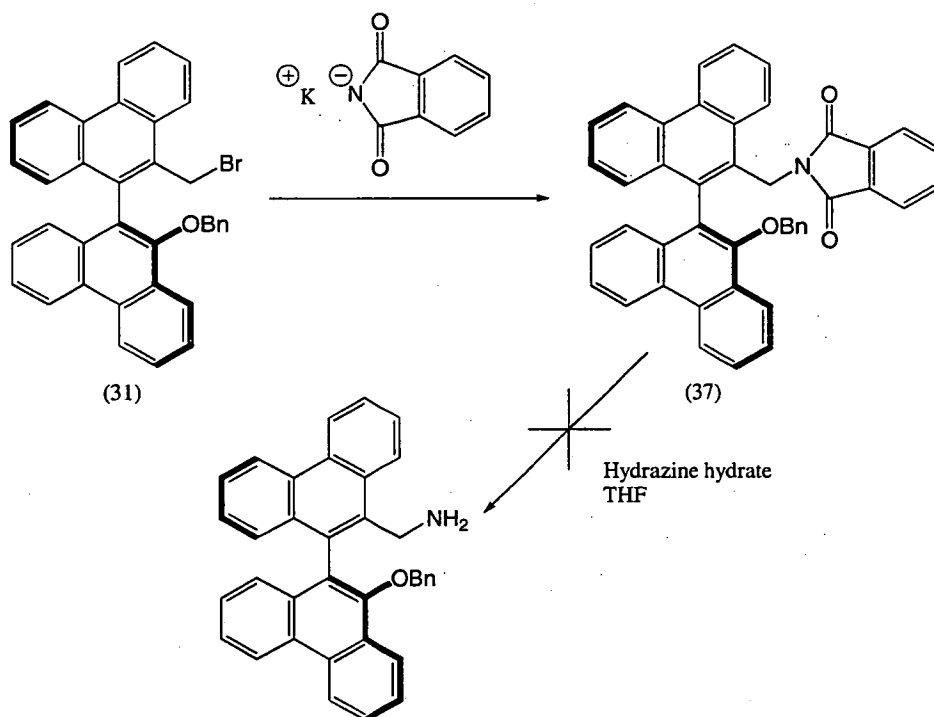


Figure 2.45: *Gabriel synthesis.*

The *Gabriel synthesis* provides a means of synthesising primary amines from halides.¹²⁷ (±)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10-benzyl-ether (31) and potassium phthalimide refluxed in THF give the alkylphthalimide (±)-10'-hydroxy-10-(methylphthalimide)-9,9'-biphenanthryl-10'-benzylether (37) in moderate yield. Conversion to the primary amine was to be achieved through hydrolysis with hydrazine hydrate in alcohol (**Figure 2.45**). The insolubility of the biphenanthryl moiety in this medium meant that

an alternative solvent had to be found. Hydrolysis in THF and 10% ethanol in THF produced crude product from which the biphenanthryl primary amine could not be purified. The *Gabriel synthesis* approach to synthesising a biphenanthryl primary amine was thus abandoned.

An alternative synthesis of the biphenanthryl primary amine was adopted. The chiral biphenanthryl oxime (**22**) was refluxed with LiAlH_4 in dry THF for 30 minutes to give the reduced primary amine (*S*)-(-)-10-(aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (**38**) (**Figure 2.46**). Efforts to purify this amine by wet flash chromatography with 10% methanol in DCM resulted in a complete loss of material. The purification procedure adopted for the purification of the biphenanthryl tertiary amine (**33**) proved more successful, though the yield of pure material obtained was low. The poor quality of the ^1H NMR spectra of the crude product indicates that this low yield was as much a consequence of the reduction as the purification procedure.

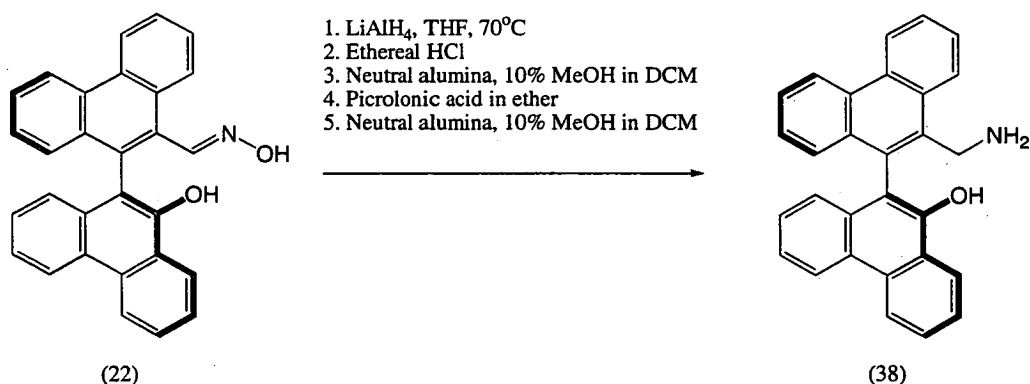


Figure 2.46: Synthesis of (*S*)-(-)-10-(aminomethyl)-10'-hydroxy-9,9'-biphenanthryl.

Despite the low yields obtained in the reduction of the oxime, enough chirally pure biphenanthryl primary amine (**38**) was obtained for application in the enantioselective reduction of acetophenone. The catalyst was employed at 10 mol% with respect to the substrate. The catalyst, together with

stoichiometric amounts of the borane source $\text{BH}_3\cdot\text{Me}_2\text{S}$, were stirred at 0°C in dry THF for two hours to allow the formation of an oxazaborolidine complex.⁷⁴

The reduction of the acetophenone to *sec*-phenylethyl alcohol (**39**) was achieved in moderate yield, and the optical activity of the product was disappointingly low (**Figure 2.47**).

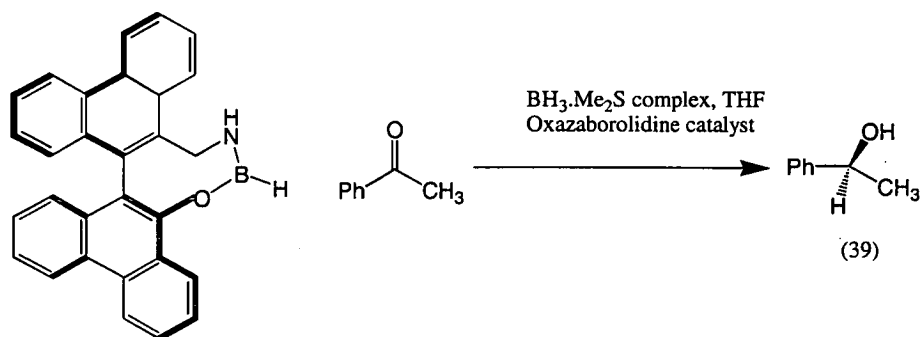


Figure 2.47: *Biphenanthryl oxazaborolidine catalyst and enantioselective reduction of acetophenone.*

The enantiomeric excess of the *sec*-phenylethyl alcohol was determined by chiral gas chromatography. In order to perform the chromatographic experiment, racemic *sec*-phenylethyl alcohol had to be prepared. The reduction of acetophenone by DIBAL-H was achieved in good yield. The results from the analysis of the reaction product by chiral gas chromatography are shown below (**Table 3**).

CATALYST	REACTION PRODUCT	$[\alpha]_D$	EE	YIELD
Oxazaborolidine	<i>sec</i> -phenylethyl alcohol	$+4^\circ$	*	62%

Table 3: *Results from enantioselective reduction of acetophenone.*

* Note: the %EE for these samples was not obtainable due to the delay in AVECIA running the necessary chiral analysis. This delay resulted in the degradation of the submitted samples.

The results from this enantioselective reduction are disappointing, with both the yield and enantiopurity lower than expected. The small scale of this reaction would have increased its sensitivity to moisture, which may account for both the moderate yield and poor optical purity of the product. Another possible explanation for this may have been inactivity of the borane source.

2.6. Synthesis of an NADH Mimic System

Previous attempts to incorporate the biphenanthryl biaryl system into an NADH mimic system have proved unsuccessful. It was believed the coupling of the chiral biphenanthryl system and 1,4-dihydropyridine, through an amide linkage at the C3 position of the pyridine, would create a reagent capable of reducing ketones enantioselectively. In such a system, the bulky biphenanthryl moiety and the amide carbonyl would be responsible for the correct orientation of the substrate. With no chiral centre at the C4 position of the pyridine ring, the system would suffer no compromise to its chirality after reducing the ketone. It would thus have the capacity for reduction back to the chiral 1,4-dihydropyridine reducing agent with no loss of chirality. Picken synthesised this compound from racemic biphenanthryl primary amine and the acid chloride of nicotinic acid (**Figure 2.48**).

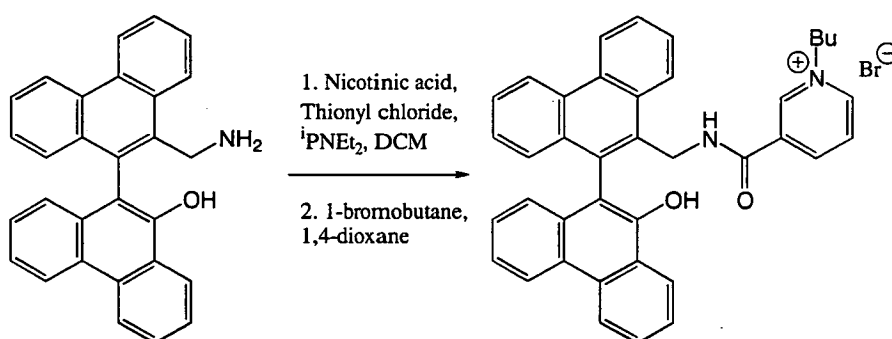


Figure 2.48: Synthesis of the butyl bromide salt of (±)-(aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide, by Picken⁹⁵

However, reduction of the pyridine to the 1,4-dihydropyridine proved difficult. Studies with cyclic voltammetry indicated that the 1,4-dihydropyridine was being formed initially, but was then undergoing a rapid isomerisation to give the corresponding 1,6-dihydropyridine. This instability was attributed to sterical hinderance from the biphenanthryl system. To investigate this proposal it was intended to synthesise this same compound but with an extended methylene chain between the biaryl and nicotinic acid fragments (**Figure 2.49**).

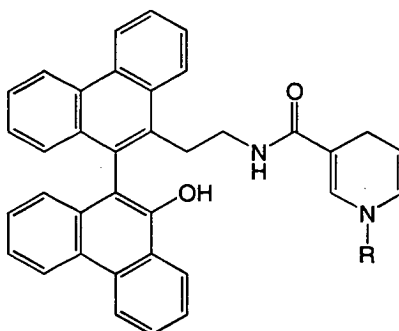


Figure 2.49: A less hindered dihydropyridine system.

Two approaches were investigated towards the extension of the methylene chain at the C9 position of the biphenanthryl moiety, using the methyl and benzyl ether protected compounds after the difficulties experienced earlier with the unprotected biphenanthryl phenolic-aldehyde.

The *Horner-Emmons reaction*, using the phosphonate stabilised anion of triethyl phosphonoacetate, offered several advantages over the previously attempted *Wittig reaction*. Stabilised phosphonate anions are more reactive than the corresponding phosphoranes, often reacting with ketones and aldehydes that are inert to phosphoranes. The by-product is a phosphate ester and is soluble in water, thus rendering simple purification.

The phosphonate stabilised anion was generated through addition of the base sodium hexamethyldisilazane to triethylphosphino acetate in dry THF. Chirally pure biphenanthryl aldehyde was added and the reaction stirred overnight, generating the biphenanthryl α,β -unsaturated ester (**40**) in high yield (**Figure 2.50**). From analysis of the ¹H NMR, the geometry of the double bond

appears to be *trans*, with a vicinal coupling constant of 16 Hz. It was hoped that through hydrogenation of the double bond and subsequent conversion of the ester to the amide would provide a system capable of undergoing the Hofmann rearrangement to give an isocyanate. The hydrolysis of this isocyanate would yield the desired biphenanthryl primary amine with a two-carbon methylene chain.

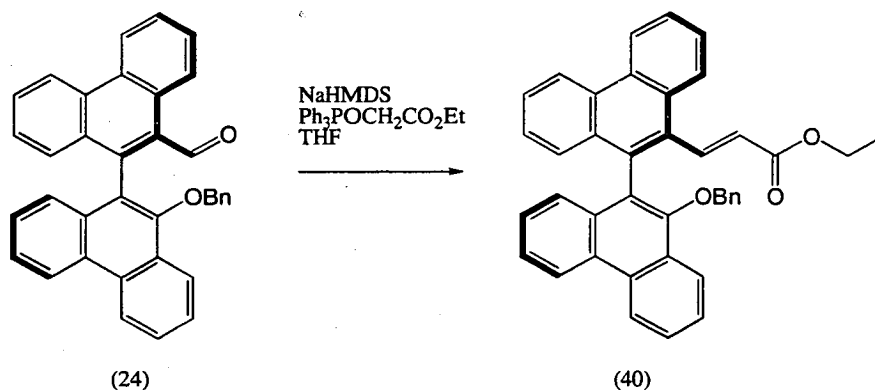


Figure 2.50: Synthesis of (*R*)-biphenanthryl α,β -unsaturated ester.

The homogenous catalyst chlorotris(triphenylphosphine)rhodium(I), also known as *Wilkinson's catalyst* was known to catalyse the hydrogenation of olefinic compounds without disturbing such groups as esters or ethers present in the same molecule. This level of selectivity was required, due to the presence of a benzyl group susceptible to hydrogenation. The hydrogenation was carried out in benzene at 60°C and 60 psi following the procedure described by Harmon *et al.* No hydrogenation was found to have occurred after 6 hours. The *Wilkinson's catalyst* has reputedly failed to hydrogenate sterically hindered systems such as 1-menthyl- α -phenylcinnamate, and this may explain why it failed catalyse the hydrogenation of the bulky biphenanthryl α,β -unsaturated ester (40).

Due to the ineffectiveness of the *Wilkinson catalyst* in this reaction, the hydrogenation of the double bond was attempted with 10% palladium on carbon. It was hoped that in ethyl acetate at atmospheric pressure and at room

temperature, a hydrogenation time of only ten minutes would prove sufficient to reduce the double bond of the biphenanthryl α,β -unsaturated ester (**40**) without affecting the benzyl ether or the ester. After ten minutes hydrogenation, analysis of the reaction mixture showed some reaction to have occurred. However, after a further 10 minutes hydrogenation analysis by TLC showed several reaction products to have formed, all relatively close to the starting material. Attempts to both purify unreacted starting material and to identify the reaction products by wet flash chromatography were unsuccessful and this line of synthesis was discontinued.

The *Henry reaction* was investigated with the methyl protected biphenanthryl phenolic-aldehyde (**23**) as the substrate. A number of conditions were initially tried using racemic material, with varying levels of success. Following a procedure described by Andrew and Raphael the biphenanthryl aldehyde was heated in THF with nitromethane, potassium *tert*-butoxide and 18-crown-6¹²⁸. A number of products were generated from which it was impossible to separate any biphenanthryl vinyl nitro product (**41**). Generation of the nitromethane anion in DMF with KOBu^t before the addition of the biphenanthryl aldehyde in THF, provided the product in yields of 5-46%. High yields were reported in the literature through the use of ultrasound with nitromethane, ammonium acetate and acetic acid at room temperature¹²⁹. Solubility difficulties with the biphenanthryl aldehyde in this mixture required the addition of THF. Overnight sonication produced the biphenanthryl compound (**41**) in yields of up to 40%. These reaction conditions were unsatisfactory in that the yields were inconsistent and often irreproducible.

A different set of conditions was employed in the synthesis of the chirally pure biphenanthryl compound (**41**). The biphenanthryl aldehyde (S)-10'-methoxy-9,9'-biphenanthryl-10-carboxaldehyde (**23**) was dissolved in nitromethane with heating by a heat gun and stirred for 2 hours after the addition of triethylamine. The *Henry reaction* proceeds via nucleophilic attack of the nitromethane anion at the aldehyde carbonyl followed by elimination to

compound (41). These conditions generate a mixture of unreacted starting material, compound (41) and the uneliminated precursor to compound (41). The uneliminated precursor was transformed to the vinyl nitro compound (41) by stirring in acetic anhydride with a catalytic amount of DMAP (Figure 2.51).

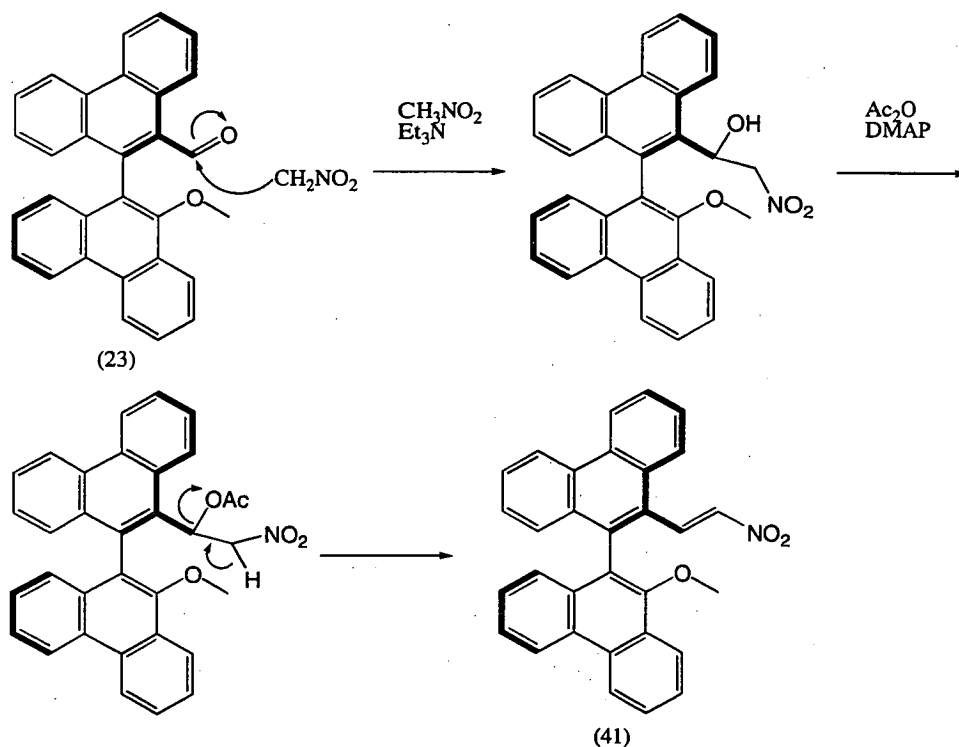


Figure 2.51: *Synthesis of biphenanthryl vinyl nitro compound.*

The separation of the biphenanthryl compound (41) from unreacted biphenanthryl aldehyde compound (23) proved impossible by wet flash chromatography. TLC studies could not find a suitable solvent system to separate the biphenanthryl moieties. The crude mixture was reduced with DIBAL-H in dry THF. This reduction converted the aldehyde to the primary alcohol (26), which possesses a very low R_F value in DCM, and compound (41) to the saturated nitro compound (42) through reduction of the double bond. This reduced biphenanthryl nitro compound had a very similar R_F value to the compound (41) and was easily separable from the primary alcohol (26) by wet flash chromatography (Figure 2.52). These reductions proceeded quantitatively with no other products formed.

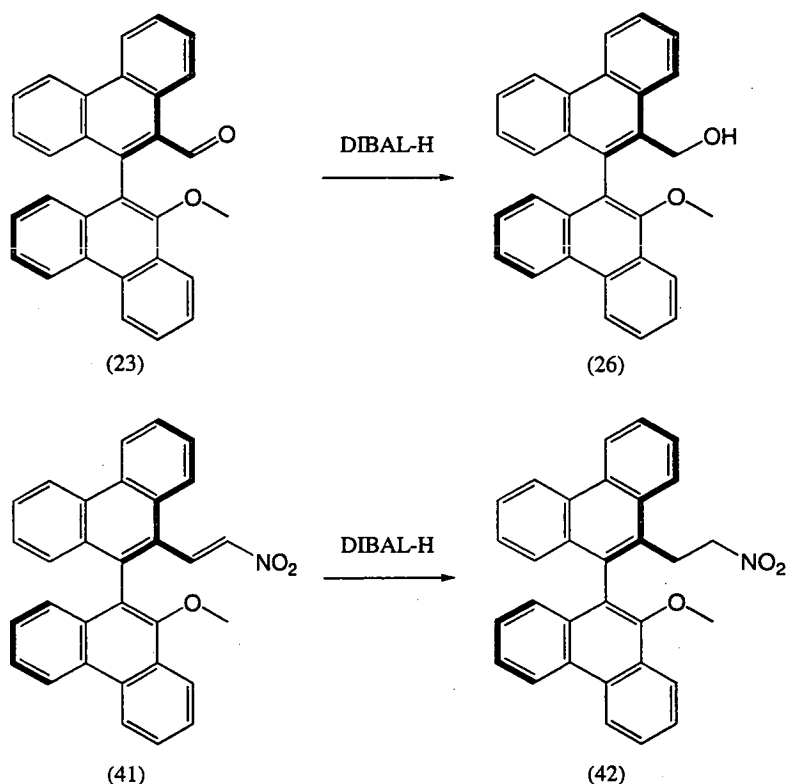


Figure 2.52: *DIBAL-H reduction of biphenanthryl aldehyde and biphenanthryl vinyl nitro compounds.*

Reduction of the biphenanthryl nitro compound (42) to the primary amine (S)-(-)-10-(aminoethyl)-10'-9,9'-biphenanthryl (43) was achieved using sodium borohydride with a catalytic amount of 10% palladium on charcoal.¹³⁰ The procedure adopted previously for the purification of biphenanthryl amines was adopted. The final yield of product obtained was 70% (**Figure 2.53**).

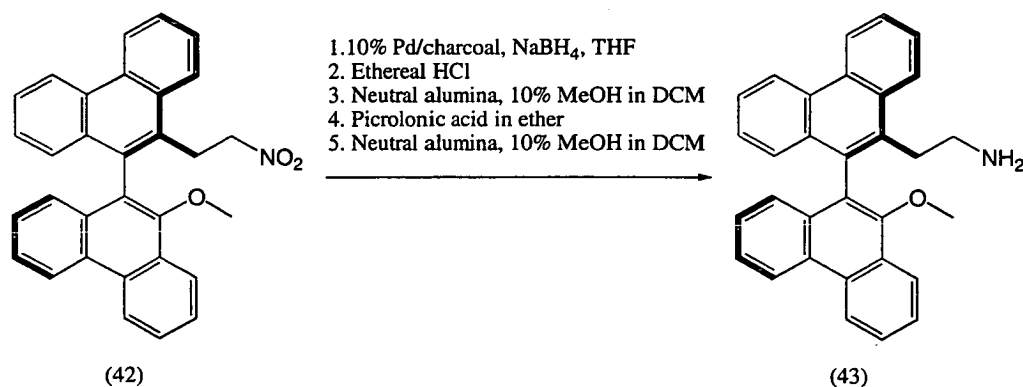


Figure 2.53: *Synthesis of (S)-(-)-10-(aminoethyl)-10'-9,9'-biphenanthryl.*

The synthesis of the biphenanthryl primary amine, with two carbons in the methylene chain at the C9 position of the biphenanthryl system was thus achieved. More material was required to couple it to the acid chloride of nicotinic acid for investigation as a chiral reducing agent, though unfortunately time did not permit further investigation into the development of this NADH mimic.

2.7. Conclusions and Future work

In summary, a number of novel, chirally pure biphenanthryl systems have been synthesised and applied in such reactions as the enantioselective addition of diethylzinc to aromatic aldehydes, and the enantioselective reduction of prochiral ketones. The results from these investigations have been disappointing, though further investigation is required before the biphenanthryl system is dismissed as a useful chiral reagent in asymmetric synthesis.

The modified procedure for the synthesis of the biphenanthryl phenolic-aldehyde is cheap and proceeds in good yield. The resolution method currently used, whilst utilising an expensive chiral hydrazine and being time consuming, provides chiral material in good yield and optical purity. The process could quite conceivably be automated and run overnight, and the hydrazine can be

regenerated from the *N*-nitroso compound by reduction after the ozonolysis of the hydrazone.

With a simple and effective synthesis of chirally pure asymmetrically substituted biphenanthryl compounds devised and optimised, it remains only to more fully investigate their potential in asymmetric synthesis. In conclusion, the work included in this thesis has taken steps towards assessing this potential, but further investigation is required before a full assessment can be made.

3. Experimental

3.1. Notes

Chemicals were purchased from the Aldrich Chemical Company, Fisher (Acros) Scientific UK, and Rathburn Chemicals. The purity was checked by means of melting point and/or proton NMR. Liquids were distilled before use and the boiling point checked. The following solvents were dried when required using the reagents indicated; dichloromethane (calcium hydride), THF (sodium/benzophenone indicator) and pyridine (phosphorus pentachloride).

Melting points were determined in open capillaries using a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer in bromoform mull or DCM solution. Ultraviolet spectra were recorded on a Perkin Elmer Lambda 11 single beam spectrometer. Fast atom bombardment mass spectra (FAB MS) were recorded on a Kratos MS50TC. Elemental analyses were carried out on a Perkin Elmer 2400 instrument, by Tim Calder.

Analytical thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Kieselgel 60 F₂₅₄) in the solvent system indicated. Flash chromatography was performed using silica gel 60 (230-400 mesh). Compounds were visualised using suitable combinations of ultra violet absorption at 254 and 365nm, iodine vapour and ammonium molybdenate.

Proton nuclear magnetic resonance spectra for routine use were performed on a Varian Gemini 200 (200MHz) spectrometer. Higher field spectra for characterisations were performed on Brücker AC250 (250MHz) spectrometer. Deuterated solvents were used as indicated and samples contained no external reference.

Carbon and two dimensional nuclear magnetic resonance spectra were run on a Brücker AC250 or DPX360 spectrometers. Carbon spectra were run at 62MHz, ^1H - ^1H COSY, TOCSY and NOESY at 250MHz or 360MHz and ^1H - ^{13}C at 360MHz and 91MHz. Deuterated solvents were used as indicated and samples contained no external reference.

Optical rotations were measured using a A1000 polarimeter (Optical Activity Ltd) using a 10.0cm cell in the solvents indicated in the text. Dr John Blacker of Avecia Process Technology carried out chiral analysis and enantiomeric excess determination. This analysis was performed on a chiral GC with a CPSilDex CB modified at 10 PSI hydrogen.

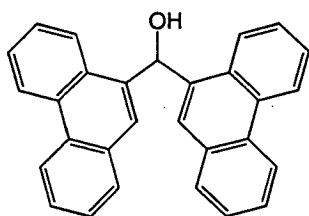
3.2. Elemental analysis on tetrabenzo[a,c,g,i]fluorene derivatives

Elemental analysis results on tetrabenzo[a,c,g,i]fluorene derivatives have generally been unsatisfactory over a period of ten years. This has been attributed to the large number of quaternary carbons in the system. Increased oxygen concentrations have been necessary to improve combustion.

3.3. Synthetic Procedures

Bis-(phenanthr-9-yl)methanol (3).

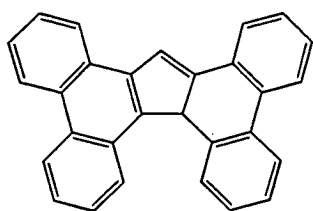
This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ A solution of 9-bromophenanthrene (2) (50g, 195mmol) in dry THF (100ml) was slowly added to magnesium turnings (5g, 206mmol) under an atmosphere of nitrogen. A crystal of iodine was added to initiate the exothermic reaction. After 2 hours stirring at room temperature a thick green jelly formed and methyl formate (8.60ml, 9.7mmol) was added over a 20-minute period. After stirring for a further 2 hours at room temperature the mixture was poured into ice/2M HCl (500ml) and precipitation of the product induced by the addition of diethyl ether (50ml). A white solid precipitated which was filtered, washed with water (2x100ml) and ether (2x100ml) to give the *title compound* as a white solid (34.5g, 90mmol, 92%).



R_f (DCM) = 0.49; **m.p.** 238-240°C (lit.⁹⁵ 238-239°C); **C.H.** Found C: 88.17%, H: 5.36%, $C_{29}H_{20}O$ Requires C: 90.63, H: 5.21; **FTIR** ν_{max}/cm^{-1} (CHBr_3 mull) 3453 (OH), 3064 (aromatic CH), 1607 (aromatic rings); λ_{max}/nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 354 (2434), 299 (21472), 287 (19018), 278 (25767), 256 (107362); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 8.80-8.79 (d, $J = 1.3\text{Hz}$, 1H, aromatic), 8.77-8.76 (d, $J = 1.2\text{Hz}$, 1H, aromatic), 8.71 (d, $J = 0.5\text{Hz}$, 1H, aromatic), 8.68 (d, $J = 0.6\text{Hz}$, 1H, aromatic), 8.13-8.13 (d, $J = 1\text{Hz}$, 1H, aromatic), 8.10-8.10 (d, $J = 1\text{Hz}$, 1H, aromatic), 7.81 (s, 2H, aromatic), 7.76-7.72 (m, 2H, aromatic), 7.70-7.62 (m, 4H, aromatic), 7.57-7.51 (m, 4H, aromatic), 7.31-7.30 (d, $J = 3.2\text{Hz}$, 1H, CHOH), 2.56-2.54 (d, $J = 4.5\text{Hz}$, 1H, OH); **$^{13}\text{C}\{^1\text{H}\}$ nmr** (63MHz, CDCl_3 , δ/ppm) 136.24, 131.23, 130.80, 130.30, 129.99 (quaternary aromatic C), 130.00, 126.89, 126.64, 126.39, 126.10, 124.28, 123.18, 122.33 (aromatic CH), 69.71 (CHOH); **m/z** (FAB) 384 (M^+), 367 ($\text{M}-\text{OH}^+$); **HRMS** (FAB) Found: 384.15128, $C_{29}H_{20}O$ Requires 384.15142.

8b-H-Tetrabenzo[a,c,g,i]fluorene (4).

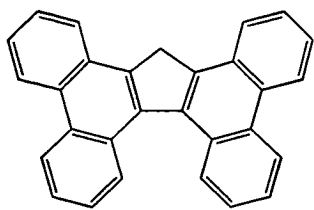
This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ Bis-(phenanthr-9-yl)methanol (**3**) (13.5g, 35.16mmol) was suspended in DCM (40ml) and trifluoroacetic acid (20ml) added, resulting in the brief appearance of a blue colouration. After stirring for 1 hour the resulting yellow suspension was filtered and washed successively with diethyl ether (3x150ml) to remove trifluoroacetic acid. Careful removal of organic solvent *in vacuo* at room temperature gave the *title compound* as a yellow solid (5.5g, 15mmol, 84%).



R_f (DCM) = 0.82; **m.p.** 280-282°C (lit.⁹⁵ 279-280°C); **C.H.** Found C: 95.58%, H: 5.12%, C₂₉H₁₈ Requires C: 95.08, H: 4.92; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3062 (aromatic CH), 1608, 1506 (aromatic rings); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 374 (12500), 301 (33456), 288.21 (34559), 262 (63235), 254 (66544); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.82-8.76 (m, 2H, aromatic), 8.27-8.24 (m, 1H, aromatic), 8.12-8.06 (m, 1H, aromatic), 7.98-7.86 (m, 1H, aromatic), 7.83-7.82 (m, 1H, aromatic), 7.74-7.72 (m, 1H, aromatic), 7.74-7.61 (m, 4H, aromatic), 7.50-7.40 (4H, m, aromatic), 7.37-7.30 (m, 1H, aromatic), 7.16-7.07 (m, 1H, aromatic), 5.40 (s, 1H, CH); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 148.40, 140.00 (quaternary aromatic C), 129.40, 128.25, 127.20, 126.95, 126.63, 126.21, 126.03, 125.85, 125.62, 125.07, 124.60, 124.23, 123.57, 123.26, 121.23 (aromatic CH), 53.30 (CH); **m/z** (FAB) 367 (M)⁺; **HRMS** (FAB) Found: 366.14085, C₂₉H₁₈ Requires 366.14049.

Tetrabenzo[a,c,g,i]fluorene (**1**).

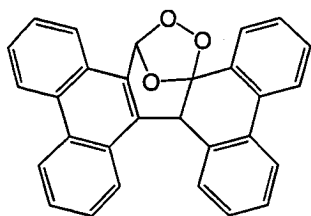
8b-H-tetrabenzo[a,c,g,i]fluorene (**4**) (4g, 10.9mmol) in toluene (200ml) was refluxed for 2 hours and allowed to stand at room temperature overnight. The resultant light brown tetrabenzo[a,c,g,i]fluorene crystals were filtered, collected and dried in a vacuum oven to provide pure *title compound* (4g, 10.9mmol, 100%).



R_f (DCM) = 0.95; **m.p.** >230°C; **C.H.** Found C: 93.40%, H: 5.24%, $C_{29}H_{18}$ Requires C: 95.08, H: 4.92; **FTIR** ν_{max}/cm^{-1} (DCM) 3022 (CH, aromatic), 1643 (aromatic rings); λ_{max}/nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 377 (17 841), 364 (18756), 300 (41628), 288 (35224), 277 (33394), 261 (65416), 253 (70000); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 8.83-8.69 (m, 6H, aromatic), 8.23-8.19 (m, 2H, aromatic), 7.74-7.59 (m, 8H, aromatic), 4.64 (s, 2H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 139.96, 137.40, 131.17, 130.03, 129.42, 128.21 (quaternary aromatic C), 127.17, 126.97, 126.02, 125.60, 125.05, 124.21, 123.54, 123.23 (aromatic CH), 36.20 (CH_2); **m/z** (FAB) 367 (MH^+), 366 (M^+); **HRMS** (FAB) Found 367.14862, $C_{29}H_{19}$ Requires 367.14868.

Ozonolysis of 8b-H-tetrabenzo[a,c,g,i]fluorene (5).

This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ A suspension of 8b-H-tetrabenzo[a,c,g,i]fluorene (**4**) (0.5g, 1.36mmol) was stirred in dry THF (100ml) at -78°C. Ozone gas (130V) was bubbled through the suspension at 1.81min^{-1} for 40 minutes to give a yellow solution. As the solution warmed to room temperature nitrogen was bubbled through to remove any unreacted ozone, and the solvent removed *in vacuo*. Triturating with ether gave the *title compound* as a pale yellow solid (1.6g, 3.9mmol, 70%).



R_f (DCM) = 0.76; **m.p.** decomposes at 177°C; **C.H.** Found C: 83.94%, H: 4.50%, $C_{29}H_{18}O_3$ Requires C: 84.05, H: 4.37; **FTIR** ν_{max}/cm^{-1} (DCM) 3070 (CH, aromatic), 1610 (aromatic rings), 1425 (alkane CH); λ_{max}/nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 354 (2143), 308 (12143), 329 (714), 308 (12143), 259 (66423); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 8.84-8.74 (m, 2H, aromatic), 8.10-8.03 (m, 1H, aromatic), 8.00-7.90 (m, 2H, aromatic), 7.81-7.59

(5H, m, aromatic), 7.58-7.29 (m, 5H, aromatic), 7.09-6.97 (m, 1H, aromatic), 6.82-6.78 (m, 1H, aromatic), 5.49 (s, 1H, CH); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 135.49, 134.60, 132.29, 130.51, 130.00, 129.81, 129.76, 128.17 (quaternary aromatic C), 130.83, 128.98, 128.33, 127.56, 127.30, 126.90, 126.52, 126.41, 124.17, 123.23, 123.11, 122.62, 122.04 (aromatic CH), 106.08 (quaternary C), 98.18 (CH); m/z (FAB), 415 (M) $^+$, 414 (M-H) $^+$; HRMS (FAB) Found: 415.13342, $\text{C}_{29}\text{H}_{19}\text{O}_3$ Requires 415.13415.

($\pm$)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (6).

Method 1.

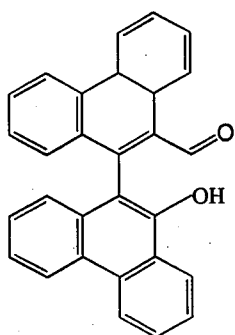
This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ A suspension of the ozonide of 8b-H-tetrabenzo[a,c,g,i]fluorene (**5**) (0.1g, 0.24mmol) in THF (13ml) was stirred at room temperature. Excess amount of activated zinc powder followed by glacial acetic acid (5ml) and trifluoroacetic acid (1ml) was added and the resulting mixture stirred for 1 hour. The reaction was quenched by the addition of water (50ml) and filtered. Saturated KOH solution was then added until the appearance of a deep red colouration, and the solution then brought back to the previous yellow colouration by careful addition of 2M HCl. The organics were extracted with DCM (3x30ml), washed with saturated NaHCO_3 solution (2x50ml), water (2x50ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Crystallisation from DCM gave the *title compound* as yellow crystals (63mg, 0.16mmol, 65%).

Method 2.

The synthesis of ($\pm$)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) from 8b-H-tetrabenzo[a,c,g,i]fluorene (**4**):

A suspension of 8b-H-tetrabenzo[a,c,g,i]fluorene (**4**) (4g, 10.9mmol) was stirred in dry THF (200ml) at -78°C . Ozone gas (130V) was bubbled through the suspension at 1.81min^{-1} for 1 hour to give a yellow solution. As the solution

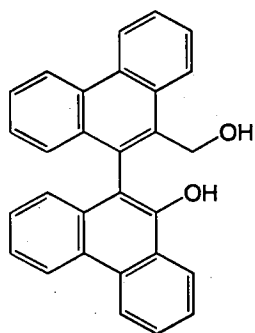
warmed to room temperature, nitrogen was bubbled through to remove any unreacted ozone. An excess of activated zinc powder (3 spatulas) followed by by glacial acetic acid (30ml) and trifluoroacetic acid (1ml) were added and the resulting mixture stirred for 1 hour. The reaction was quenched by the addition of water (50ml) and filtered. Saturated KOH solution was then added until the appearance of a deep red colouration, and the solution then brought back to the previous yellow colouration by careful addition of 2M HCl. The organics were extracted with DCM (3x50ml), washed with saturated NaHCO₃ solution (2x100ml), water (2x100ml), dried (Na₂SO₄) and the solvent removed *in vacuo*. Recrystallisation from DCM gave the *title compound* as yellow crystals (2.14g, 5.38mmol, 50%).



R_f (DCM) = 0.46; **m.p.** 230-232°C (lit.⁹⁵ 231-232°C); **C.H.** Found C: 72.86%, H: 4.52%, C₂₉H₁₈O Requires C: 82.01, H: 5.63; **FTIR** $\nu_{\text{max.}}$ cm^{-1} (CHBr₃ mull) 3531 (OH), 3017 (CH, aromatic), 1680 (C=O stretch), 1595 (aromatic rings); $\lambda_{\text{max.}}$ nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 374 (3500), 354 (5500), 329 (9000), 258 (76500); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 10.15 (s, 1H, CHO), 9.35-9.30 (m, 1H, aromatic), 8.87-8.73 (m, 4H, aromatic), 8.43-8.39 (m, 1H, aromatic), 7.87-7.66 (m, 5H, aromatic), 7.58-7.49 (m, 2H, aromatic), 7.43-7.30 (m, 2H, aromatic), 7.11-7.07 (m, 1H, aromatic), 5.29-5.27 (b, 1H, -OH); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 194.72 (CHO), 147.86, 140.82, 133.18, 132.47, 132.61, 130.89, 130.86, 130.07, 128.83, 127.70, 126.32, 124.59 (quaternary aromatic C), 130.32, 128.43, 128.09, 128.04, 127.96, 127.79, 127.54, 127.50, 126.94, 126.81, 125.57, 125.51, 124.68, 123.11, 123.04, 122.71 (aromatic CH); **m/z** 398 (M)⁺, 381 (M-OH)⁺; **HRMS** (FAB) Found: 398.13068, C₂₉H₁₈O Requires 398.13033.

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthrine (7).

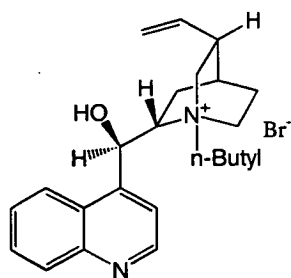
This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ Lithium aluminium hydride (0.5g, 12.5mmol) in dry THF (5ml) was stirred at 0°C under nitrogen. A solution of (±)-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (1g, 2.51mmol) in dry THF (50ml) was added slowly and stirring continued for 1 hour. The reaction was quenched by the careful addition of saturated aqueous Rochelle salt solution and filtered. The organics were extracted with DCM (3x30ml) and the combined organics washed with water (30ml). Drying over MgSO₄, removal of the solvent *in vacuo* and purification by wet flash chromatography (DCM) gave the *title compound* as a white solid (0.9g, 2.3mmol, 90%).



R_f (DCM) = 0.18; **m.p.** 164-165°C (lit.⁹⁵ 155°C); **C.H.** Found C: 84.48, H: 6.10, C₂₉H₂₀O₂ Requires C: 87.00, H: 5.00; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr₃ mull) 3390 (OH), 3018 (aromatic CH), 1597 (aromatic rings); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 377 (2000), 358 (6000), 341 (4667), 301 (32667), 258 (161333); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.87-8.73 (m, 4H, aromatic), 8.44-8.40 (dd, 2H, aromatic), 7.83-7.61 (m, 5H, aromatic), 7.53-7.47 (m, 1H, aromatic), 7.38-7.25 (m, 3H, aromatic), 7.08-7.05 (m, 1H, aromatic), 5.78-5.29 (d, J = 12Hz, 1H, CH₂), 5.01-4.96 (d, J = 12Hz, 1H, CH₂), 4.80-4.75 (d, J = 12Hz, 1H, OH); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 147.32, 135.70, 132.59, 131.32, 131.11, 131.03, 130.83, 130.57, 130.14 (quaternary aromatic C), 127.46, 127.43, 127.28, 127.25, 127.20, 126.69, 126.52, 125.61, 125.30, 125.18, 124.35, 123.24, 123.02, 122.69, 122.65, 122.50 (aromatic CH), 60.69 (CH₂); **m/z** (FAB) 400 (M)⁺, 383 (M-OH)⁺; **HRMS** (FAB) Found 400.14633, C₂₉H₂₀O₂ Requires 400.14533.

N-Benzylcinchonidinium bromide (8).

This compound was synthesised by an adaptation of the procedure described by Tanaka.¹⁰⁶ Cinchonidine (5g, 17mmol) and 1-bromobutane (3.65ml, 34mmol) were refluxed together in acetone (150ml) for 70 hours. The reaction was cooled and the precipitate collected by filtration. The precipitate was recrystallised from water as a white solid (2.41g, 33%, 5.59mmol).



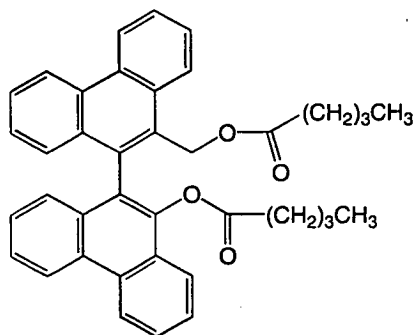
m.p. 229°C (lit.¹⁰⁶ 232-234°C); **C.H.N.** Found C: 63.26%, H: 7.22%, N: 6.29%, $C_{23}H_{31}N_2OBr$ Requires C: 64.04, H: 7.19, N: 6.50; **FTIR** ν_{max}/cm^{-1} (DCM) 3156 (OH), 2946 (CH), 1636 (C=C); λ_{max}/nm (DCM $\epsilon/dm^3mol^{-1}l^{-1}$) 317 (4923), 309 (4615), 233 (24308);

^1H nmr (250MHz, $CDCl_3$, δ/ppm) 8.69-8.67 (d, $J = 4.5Hz$, 1H, aromatic), 8.02-7.98 (dd, $J = 1Hz$ and $8.4Hz$, 1H, aromatic), 7.91-7.87 (d, $J = 8.4Hz$, 1H, aromatic), 7.59-7.53 (m, 2H, aromatic), 7.29-7.22 (m, 1H, aromatic), 5.71-4.82 (m, 4H, $CH=CH_2$ and $CHOH$), 3.52-3.50 (m, 1H, alkyl CH), 3.03-2.94 (m, 2H, alkyl), 2.62-2.54 (m, 2H, alkyl), 2.20 (broad s, 1H, OH), 1.76-1.75 (m, 3H, alkyl), 1.45-1.37 (m, 2H, alkyl); **$^{13}C\{^1H\}$ nmr** (63MHz, $CDCl_3$, δ/ppm) 149.67, 147.77, 125.40 (quaternary aromatic C), 149.79, 141.54, 129.82, 128.84, 126.42, 122.78 (aromatic CH), 71.32, 60.16, 39.68, 27.71 (alkyl CH), 56.72, 43.03, 27.33, 21.05 (alkyl CH_2); **m/z** (FAB) 351 (M^+); **HRMS** (FAB) Found 351.24360, $C_{23}H_{31}N_2O$ Requires 351.24369; $[\alpha]_D^{25} = -73.6^\circ C$ ($c = 1.4$ in MeOH).

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-pentanoate (9).

Pentanoyl chloride (0.6ml, 5mmol) was added over 15min to a suspension of 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryline (7) (1g, 2.5mmol) in dry THF (10ml) containing triethylamine (0.7ml, 5mmol). Stirring was continued for an additional hour, and the organics were extracted with DCM (2x50ml).

The combined organics were washed with satd. sodium bicarbonatesolution (2x50ml) and water (2x50ml). Drying over MgSO₄, removal of the solvent *in vacuo* and purification by flash chromatography (50/50 DCM/hexane) gave the *title compound* as a white solid (0.7g, 1.2mmol, 50%).



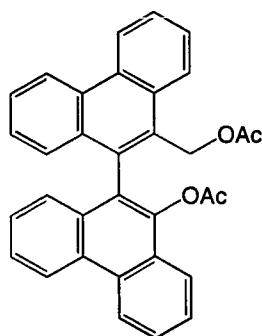
R_f (DCM) = 0.44; **m.p.** 145°C; **C.H.** Found C: 81.97%, H: 6.54%, C₃₉H₃₆O₄ Requires C: 82.39, H: 6.34; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (CHBr₃ mull) 3018 (aromatic CH), 1754 (aryl ester), 1722 (alkyl ester); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 374 (7952), 354 (9058), 258

(114736); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.88-8.81 (m, 4H, aromatic), 8.11-8.08 (m, 1H, aromatic), 7.88-7.85 (m, 1H, aromatic), 7.82-7.60 (m, 6H, aromatic), 7.42-7.31 (m, 4H, aromatic), 5.48-5.43 (d, J = 12Hz, 1H, CH₂), 5.21-5.16 (d, J = 12Hz, 1H, CH₂), 1.47-1.10 (m, 2H, CH₂), 1.27 (s, 6H, CH₃), 0.97-0.87 (m, 2H, CH₂), 0.83-0.77 (t, 4H, CH₂), 0.77-0.52 (m, 2H, CH₂), 0.35-0.29 (t, 2H, CH₂); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 173.28, 171.33 (carbonyl C), 143.84, 133.40, 131.72, 131.45, 130.67, 130.63, 130.52, 129.63, 129.03, 128.00 (quaternary aromatic C), 127.48, 127.26, 127.22, 127.15, 127.04, 126.86, 126.52, 126.35, 125.65, 125.14, 122.99, 122.93, 122.69, 122.47, 122.23 (aromatic CH), 62.06 (CH₂), 33.78, 33.54, 26.75, 26.54, 22.04, 21.53 (CH₂), 13.53, 13.06 (CH₃); **m/z** (FAB) 568 (M)⁺, 467 (M-CO₂(CH₂)₃CH₃)⁺, 383 (M-(CO₂(CH₂)₃CH₃)₂)⁺; **HRMS** (FAB) Found 568.26136, C₃₉H₃₆O₄ Requires 568.26320.

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-acetate (10).

10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (7) (0.5g, 1.25mmol), acetic anhydride (10ml), dry pyridine (10ml) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were stirred overnight at room temperature under nitrogen. Heptane (30ml) was added and the resulting mixture

concentrated. Acetic acid and pyridine were removed by successive evaporation of heptane to give an off-white solid. Purification by wet flash chromatography (DCM) gave the *title compound* as an off-white solid (0.46g, 9.5mmol, 79%).



R_f (DCM) = 0.30; mp 218 - 220°C; C.H. Found C: 79.06, H: 5.38, $C_{33}H_{24}O_4$ Requires C: 81.82, H: 4.96; FTIR ν_{max}/cm^{-1} (CHBr₃ mull) 3064 (aromatic CH stretch), 1760 (aryl ester), 1731 (alkyl ester); λ_{max}/nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 354 (7000), 272 (184000), 259 (182000); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 8.78-8.91 (m, 4H, aromatic), 8.12-8.17 (m, 1H, aromatic), 7.59-7.92 (m, 7H, aromatic), 7.31-7.42 (m, 4H, aromatic), 5.46-5.39 (d, $J = 12\text{Hz}$, 1H, CH_2), 5.28-5.22 (d, $J = 12\text{Hz}$, 1H, CH_2), 1.87 (s, 3H, CH_3), 1.82 (s, 3H, CH_3); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 170.47, 168.59 (carbonyl C), 143.84, 133.42, 131.65, 131.45, 130.67, 130.56, 130.44, 129.40, 125.60 (quaternary aromatic C), 127.90, 127.52, 127.31, 127.17, 126.91, 126.85, 126.60, 126.22, 125.21, 123.00, 122.71, 122.50, 122.32 (aromatic CH), 62.23 (CH_2), 20.53, 20.08 (CH_3); m/z (FAB) 484 (M^+); HRMS (FAB) Found 484.16742, $C_{33}H_{24}O_4$ Requires 484.16746.

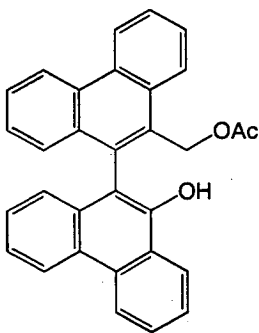
Cholesterol esterase ester hydrolysis.

General Procedure:

The ester substrate (1mmol) was dissolved in ether (5ml) and stirred with 0.1M phosphate buffer pH 7.5 (5ml). Sodium taurocholate (30mg) was added to form an emulsion. Bovine pancreas acetone powder (0.28g) was added with stirring. The pH of the aqueous phase was measured several times a day and readjusted to $\text{pH } 7.2 \pm 0.2$ with 1M NaOH solution. The reaction was left to stir for three days, at the end of which time the substrate extracted into DCM (2x50ml), dried over MgSO_4 , concentrated *in vacuo* and purified by flash chromatography (50:50 DCM:hexane). The sample was then subjected to analysis.

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-acetate (11).

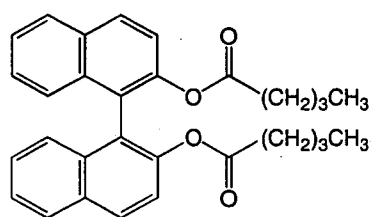
10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-acetate (**10**) (50mg, 0.1mmol) was dissolved in THF (5ml). 1M $\text{KH}(\text{PO}_4)^-$ buffer pH 10.5 (2ml) was added along with a catalytic amount of tetrabutylammonium hydroxide and H_2O_2 (60 μl @ 100vol.). The reaction was followed by tlc and after one hour was quenched by addition of satd. NH_4Cl solution (30ml). The organics were extracted with DCM (3x30ml), combined and washed with water (2x30ml) and dried (MgSO_4). Removal of the solvent *in vacuo* and purification by flash chromatography (50/50 DCM/hexane) gave the *title compound* as a white solid (22mg, 0.05mmol, 48%).



R_f (DCM) = 0.50; **m.p.** 262-264 °C; **C.H.** Found C: 80.92, H: 5.06, $\text{C}_{31}\text{H}_{22}\text{O}_3$ Requires C: 80.92, H: 5.06; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr_3 mull) 3600, 3512 (OH), 3019, 2969 (aromatic CH stretch), 1732 (alkyl ester), 1594 (aromatic rings); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 357 (1894), 340 (1894), 301 (12629), 258 (61880); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 8.91-8.71 (m, 4H, aromatic), 8.46 (dd, 1H, aromatic), 8.43 (dd, 1H, aromatic), 7.85-7.64 (m, 5H, aromatic), 7.52-7.24 (m, 4H, aromatic), 7.05-7.01 (dd, $J = 1\text{Hz}$ and 12Hz , 1H, aromatic), 5.54-5.50 (d, $J = 12\text{Hz}$, 1H, CH_2), 5.23-5.18 (d, $J = 12\text{Hz}$, 1H, CH_2), 1.91 (s, 3H, CH_3); **$^{13}\text{C}\{^1\text{H}\}$ nmr** (63MHz, CDCl_3 , δ/ppm) 170.67 (carbonyl C), 147.39, 132.42, 131.50, 131.46, 131.24, 231.05, 130.73, 130.36 (quaternary aromatic C), 127.84, 127.46, 127.42, 127.38, 126.99, 126.64, 126.51, 125.33, 125.08, 124.28, 123.20, 122.65, 122.55 (aromatic CH), 62.42 (CH_2), 20.60 (CH_3); **m/z** (FAB) 442 (M^+), 398 ($\text{M}-\text{CH}_3\text{O/H}^+$); **HRMS** (FAB) Found 442.15689, $\text{C}_{31}\text{H}_{22}\text{O}_3$ Requires 442.15680.

1,1'-Bi-2-naphthol dipentanoate diester (12)

This compound was synthesised by an adaptation of the procedure described by Kazlauskas.¹⁰⁷ Valeryl chloride (0.6ml, 5mmol) was added slowly to a suspension of binaphthol (2g, 7.0mmol) in dry THF (10ml) containing triethylamine (1ml, 7.1mmol). Stirring was continued for an additional hour, and the organics were extracted with DCM (2x50ml). The combined organics were washed with satd. sodium bicarbonate solution (2x50ml) and water (50ml). Drying over MgSO₄, removal of the solvent *in vacuo* and purification by flash chromatography (50/50 DCM/hexane) gave the *title compound* as a white solid (2.3g, 5.1mmol, 72.4%).

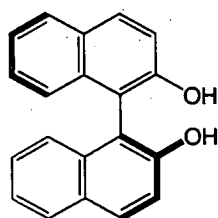


R_f (DCM) = 0.63; **m.p.** 58-60°C (lit.¹⁰⁷ 55-60°C); **C.H.** Found C: 78.71%, H: 6.73%, C₃₀H₃₀O₄ Requires C: 79.30, H: 6.61; **FTIR** ν_{max} /cm⁻¹ (CHBr₃ mull) 1742 (ester); λ_{max} /nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 320 (24242), 290 (160606), 283 (163636); **¹H nmr** (250MHz, CDCl₃, δ /ppm) 8.00-7.97 (d, J = 9Hz, 2H, aromatic), 7.93-7.90 (d, J = 8Hz, 2H, aromatic), 7.48-7.40 (m, 4H, aromatic), 7.33-7.22 (m, 4H, aromatic), 2.12-2.06 (dt, J = 1Hz and 7.5Hz, 4H, CO₂CH₂) 1.16-1.03 (m, 4H, CH₂), 0.97-0.84 (m, 4H, CH₂), 0.66-0.60 (t, J = 7Hz, 6H, CH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ /ppm) 171.79 (carbonyl C), 146.67, 133.23, 131.41, 123.45 (quaternary aromatic C), 129.25, 127.78, 126.55, 126.05, 125.51, 121.80 (aromatic CH), 33.63 (CH₂), 26.40 (CH₂), 21.60 (CH₂), 13.40 (CH₃); **m/z** (FAB) 455 (M)⁺, 370 (M-CO(CH₂)₃CH₃)⁺, 286 (M-(CO(CH₂)₃CH₃)₂)⁺; **HRMS** (FAB) Found 455.22230, C₃₀H₃₀O₄ Requires 455.22223.

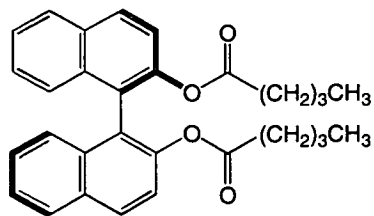
Resolution of Binaphthol

(S)-Binaphthol (13) and (R)-1,1'-bi-2-naphthol dipentanoate diester (14).

This compound was synthesised by an adaptation of the procedure described by Kazlauskas.¹⁰⁷ 1,1'-bi-2-naphthol dipentanoate diester (12) (2g, 4.4mmol) in diethylether (6ml) was added to 0.1M pH 7.5 phosphate buffer solution (10ml) containing sodium taurocholate (5g of crude material from ox bile, Sigma) with stirring, to form an emulsion. Bovine pancreas acetone powder (0.6g) was added and the reaction stirred for three days. The pH of the aqueous phase was measured several times a day and readjusted to pH 7.2 ± 0.2 with 1M sodium hydroxide solution as required. The modified substrate was extracted into DCM (2x50ml), passed through a celite filter, and washed with water (50ml). The organics were dried over MgSO_4 and the solvent removed *in vacuo*. Purification by flash chromatography (50:50 DCM:hexane) gave the *title compound* as a white powder (0.4g, 1.4mmol, 32%). (R)-1,1'-bi-2-naphthol dipentanoate diester which had not undergone hydrolysis was similarly purified as a white powder (1.2g,)



R_f (DCM) = 0.17; **m.p.** 212-214°C (lit.¹⁰⁷ 214-217°C); **C.H.** Found C: 82.67%, H: 5.20%, $\text{C}_{20}\text{H}_{14}\text{O}_2$ Requires C: 83.92, H: 4.90; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3531 (OH), 1598 (aromatic rings); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 333 (3269), 319 (2043), 289 (3677), 278 (4056), 231 (42900); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 7.96-7.93 (d, $J = 9\text{Hz}$, 2H, aromatic), 7.89-7.86 (d, $J = 9\text{Hz}$, 2H, aromatic), 7.40-7.27 (m, 6H, aromatic), 7.16-7.13 (m, 2H, aromatic), 5.09 (broad s, 2H, OH); **$^{13}\text{C}\{^1\text{H}\}$ nmr** (63MHz, CDCl_3 , δ/ppm) 152.59, 133.27, 129.29, 110.72 (quaternary aromatic C), 131.26, 128.26, 127.34, 124.07, 123.90, 117.62 (aromatic CH); **m/z** (FAB) 287 ($\text{M}+\text{H}$)⁺, 286 (M)⁺; **HRMS** (FAB) Found 286.10752, $\text{C}_{20}\text{H}_{15}\text{O}_2$ Requires 287.10720; $[\alpha]_{\text{D}}^{25}(\text{deg}) = -27.4^\circ$, $c = 0.4$, THF.



R_f (DCM) = 0.63; **m.p.** 54-57°C (lit. 55-60°C); **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (CHBr₃ mull) 1747 (ester); **¹H nmr** (250MHz, CDCl₃, δ /ppm) 8.01-7.97 (d, J = 9Hz, 2H, aromatic), 7.94-7.90 (d, J = 8Hz, 2H, aromatic), 7.49-7.40 (m, 4H, aromatic), 7.30-7.26

(m, 4H, aromatic), 2.13-2.06 (t, J = 7Hz, 4H, CO₂CH₂), 1.16-1.05 (m, 4H, CH₂), 0.96-0.85 (m, 4H, CH₂), 0.67-0.63 (t, J = 7Hz, 6H, CH₃); **m/z** (FAB) 455 (M)⁺, 370 (M-CO(CH₂)₃CH₃)⁺, 286 (M-(CO(CH₂)₃CH₃)₂)⁺; $[\alpha]_D^{25}(\text{deg})$ = +17°, c = 0.4, THF.

LypozymeTM catalysed esterification.

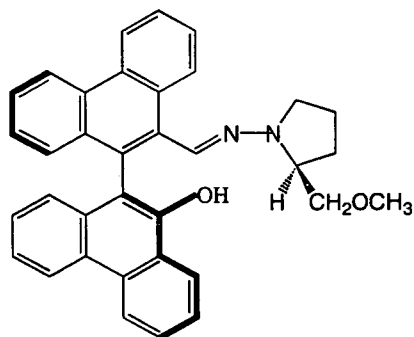
General Procedure:

The enzyme (1g) at and vinyl acetate (2ml) were added to a 50mM solution of the biphenanthryl diol ($\pm$)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryline (**7**) in the appropriate organic solvent (100ml). The suspension was stirred at 300rpm and heated to 45°C and the reaction monitored by TLC. After 24 hours the substrate was extracted into DCM (2x50ml), dried over MgSO₄, concentrated *in vacuo* and purified by flash chromatography (50:50 DCM:hexane). The sample was then subjected to analysis by TLC and ¹H NMR.

(S,S''-2)-(-)-10'-Hydroxy-9,9'-biphenanthryl-10-(methylideneamino)-2''-(methoxymethyl)pyrrolidine (**16**)

This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ A suspension of racemic 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (2.22g, 5.58mmol) in dry DCM (10ml) was stirred at 0°C. (S)-(-)-Amino-2-(methoxymethyl)pyrrolidine (0.81ml, 6.14mmol) was added and stirring continued for 2 hours at 0°C. Removal of the solvent *in vacuo* and

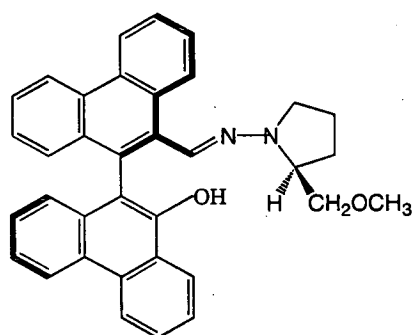
initial purification of the two resultant diastereoisomers by wet flash chromatography (chloroform) gave intensely coloured yellow foam (1.97g, 3.86mmol, 69.17%). Separation of the diastereoisomers by wet flash chromatography (DCM) gave pure *title compound* a pale yellow solid (0.50g, 0.98mmol, 35%).



R_f (DCM) = 0.22; **m.p.** 252-255° (lit.⁹⁵ 253-255°C); **C.H.N.** Found C: 73.34, H: 4.46, N: 3.87, C₃₅H₃₀N₂O₂ Requires C: 82.35, H: 5.88, N: 5.49; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3680 (OH), 3014 (CH, aromatic), 1520, 1475 (aromatic rings); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 359 (15330), 343 (23188), 257 (160869); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 9.05 (m, 1H, aromatic), 8.91-8.89 (m, 1H, aromatic), 8.86-8.76 (m, 3H, aromatic), 8.58-8.56 (m, 1H, aromatic), 7.85-7.74 (m, 4H, aromatic), 7.66-7.61 (m, 1H, aromatic), 7.54-7.49 (m, 2H, aromatic), 7.37-7.29 (m, 3H, aromatic), 7.17-6.40 (m, 1H, aromatic), 6.40 (s, 1H, OH), 3.56-3.50 (m, 1H, NCH), 3.42-3.38 (m, 1H, OCH₂), 3.23-3.18 (m, 1H, OCH₂), 3.21 (s, 3H, OCH₃), 3.11-3.06 (m, 1H, NCH₂), 2.66-2.59 (m, 1H, NCH₂), 1.87-1.68 (m, 4H, 2CH₂); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 148.10, 133.36, 133.13, 131.81, 131.58, 130.92, 130.71, 129.60, 128.23, 128.06, 127.72, 116.09 (aromatic quaternary C), 131.99, 127.69, 127.64, 127.52, 127.47, 127.42, 127.05, 127.03, 126.47, 124.56, 123.95, 123.37, 123.12, 123.01 (aromatic CH), 74.64 (OCH₂), 63.36 (NCH), 59.40 (OCH₃), 49.41 (NCH₂), 27.01 (CH₂), 22.52 (CH₂); **m/z** (FAB) 511 (M⁺); **HRMS** (FAB) Found 511.23866, C₃₅H₃₁N₂O₂ Requires 511.23855; $[\alpha]_D^{25}(\text{deg})$ = -240°, c = 0.4, DCM.

(R,2''-S)-(+)-10'-Hydroxy-9,9'-biphenanthryl-10-(methyldeneamino)-2''-(methoxymethyl)pyrrolidine (17).

This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ A suspension of racemic 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (2.22g, 5.58mmol) in dry DCM (10ml) was stirred at 0°C. (S)-(-)-Amino-2-(methoxymethyl)pyrrolidine (0.81ml, 6.14mmol) was added and stirring continued for 2 hours at 0°C. Removal of the solvent *in vacuo* and initial purification of the two resultant diastereoisomers by wet flash chromatography (chloroform) gave intensely coloured yellow foam (1.97g, 3.86mmol, 69.17%). Separation of the diastereoisomers by wet flash chromatography (DCM) gave pure *title compound* as a pale yellow solid (0.58g, 1.14mmol, 41%).



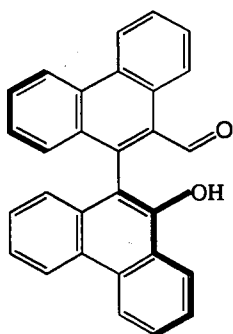
R_f (DCM) = 0.18; **m.p.** 180-182° (lit.⁹⁵ 180-182°C); **C.H.N.** Found C: 80.63, H: 5.35, N: 4.49, C₃₅H₃₀N₂O₂ Requires C: 82.35, H: 5.88, N: 5.49; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3529 (OH), 3022 (CH, aromatic), 1495, 1450 (aromatic rings); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 329 (10220), 257 (84823); **¹H nmr** (250MHz,

CDCl₃, δ/ppm) 8.99-8.96 (m, 1H, aromatic), 8.86-8.84 (m, 1H, aromatic), 8.81-8.71 (m, 3H, aromatic), 8.50-8.47 (m, 1H, aromatic), 7.80-7.68 (m, 4H, aromatic), 7.61-7.56 (m, 1H, aromatic), 7.50-7.44 (m, 1H, aromatic), 7.39 (s, 1H, CH=N), 7.34-7.24 (m, 3H, aromatic), 7.15-7.10 (m, 1H, aromatic), 6.15 (s, 1H, OH), 3.43-3.37 (m, 3H, NCH and CH₂O), 3.28 (s, 3H, OCH₃), 3.05-2.99 (m, 1H, NCH₂), 2.45-2.39 (m, 1H, NCH₂), 1.78-1.56 (m, 4H, 2xCH₂); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 148.02, 133.58, 132.95, 131.79, 131.66, 130.93, 130.69, 129.77, 126.99, 126.20, 115.57 (quaternary aromatic C), 132.00, 131.97, 128.07, 127.73, 127.68, 127.54, 127.49, 127.42, 127.05, 126.37, 124.62, 123.80, 123.32, 123.13, 123.01 (aromatic CH), 74.62 (CH₂O), 63.16 (NCH), 59.56 (OCH₃), 49.29 (NCH₂), 26.82 (CH₂), 22.36 (CH₂); **m/z** (FAB) 511 (M⁺);

HRMS (FAB) Found 511.23850, $C_{35}H_{31}N_2O_2$ Requires 511.23855; $[\alpha]^{25}_D(\text{deg}) = +97^\circ$, $c = 0.4$, DCM.

(S)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (6).

This compound was synthesised following the procedure described by Louise Picken.⁹⁵ A suspension of (S,S''-2)-(-)-10'hydroxy-9,9'biphenanthryl-10-(methylideneamine)-2''-(methoxymethyl)pyrrolidine (**16**) (0.77, 1.51mmol) was stirred in dry THF (75ml) at -78°C . Ozone gas was bubbled through the solution at 1.41min^{-1} for 5 minutes. As the solution warmed to room temperature nitrogen was bubbled through to remove any unreacted ozone and the solvent removed *in vacuo*. Purification by wet flash chromatography (chloroform) gave the *title compound* as yellow foam (0.38g, 0.95mmol, 62.91%).

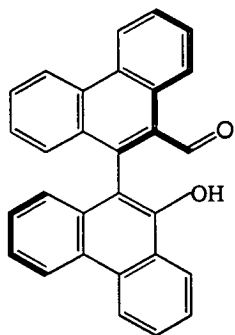


R_f (DCM) = 0.48; **m.p.** $227-230^\circ\text{C}$ (lit.⁹⁵ $229-230^\circ\text{C}$); **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr_3 mull) 3536 (OH), 3064 (CH, aromatic), 1676 (C=O stretch), 1597 (aromatic rings); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 10.15 (s, 1H, CHO), 9.35-9.31 (m, 1H, aromatic), 8.88-8.73 (m, 4H, aromatic), 8.43-8.39 (m, 1H, aromatic), 7.87-7.69 (m, 5H, aromatic), 7.58-7.49 (m, 2H, aromatic), 7.44-7.22 (m, 2H, aromatic), 7.11-7.08 (m, 1H, aromatic), 5.28 (b, 1H, -OH); **m/z** 398 (M^+), 381 ($\text{M}-\text{OH}^+$); **HRMS** (FAB) Found: 398.13102, $\text{C}_{29}\text{H}_{18}\text{O}$ Requires 398.13068; $[\alpha]^{25}_D(\text{deg}) = -56^\circ$, $c = 0.4$, DCM.

(R)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (6).

This compound was synthesised following the procedure described by Louise Picken.⁹⁵ A suspension of (R,2''-S)-(+)-10'hydroxy-9,9'biphenanthryl-10-

(methylideneamine)-2''-(methoxymethyl)pyrrolidine (**17**) (1.18g, 2.31mmol) was stirred in dry THF (75ml) at -78°C. Ozone gas was bubbled through the solution at 1.41min⁻¹ for 5 minutes. As the solution warmed to room temperature nitrogen was bubbled through to remove any unreacted ozone and the solvent removed *in vacuo*. Purification by wet flash chromatography (chloroform) gave the *title compound* as yellow foam (0.63g, 1.58mmol, 68%).

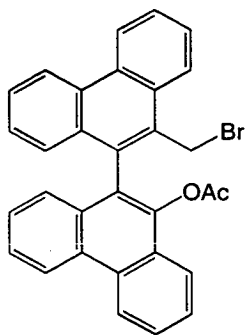


R_f (DCM) = 0.50; **m.p.** 232-235°C (lit.⁹⁵ 234-235°C); **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr₃ mull) 3536 (OH), 3067 (CH, aromatic), 1679 (C=O stretch), 1598 (aromatic rings); **¹H nmr** (250MHz, CDCl₃, δ /ppm) 10.15 (s, 1H, CHO), 9.34-9.30 (m, 1H, aromatic), 8.87-8.73 (m, 4H, aromatic), 8.43-8.39 (m, 1H, aromatic), 7.86-7.69 (m, 5H, aromatic), 7.58-7.49 (m, 2H, aromatic), 7.43-7.24 (m, 2H, aromatic), 7.11-7.07 (m, 1H, aromatic), 5.23 (b, 1H, -OH); **m/z** 398 (M)⁺, 381 (M-OH)⁺; **HRMS** (FAB) Found: 398.13022, C₂₉H₁₈O Requires 398.13068; $[\alpha]_{\text{D}}$ = +71°, c = 0.4, DCM.

(±)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate (17**).**

To 30% hydrobromic acid (2ml) was added 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl di-acetate (**10**) (100mg, 0.21mmol), and refluxed with stirring at 80°C for 1 hour. After this time the reaction was quenched by the careful addition of water (10ml). The organics were extracted with a 50:50 THF:DCM mixture (2x30ml), washed with water (2x20ml) and dried (MgSO₄). Removal of the solvent *in vacuo* and purification by wet flash chromatography (DCM) gave the *title compound* as a light brown solid (76mg, 0.15mmol, 73%).

R_f (DCM) = 0.78; **m.p.** 262-264°C; **C.H.** Found C: 72.96, H: 4.37, C₃₁H₂₁O₂Br Requires C: 73.66, H: 4.16; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr₃ mull) 3064 (aromatic CH stretch), 1762 (aryl ester); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 377 (12120), 354 (12120), 258 (141400); **¹H nmr** (250MHz, CDCl₃, δ /ppm) 8.90-

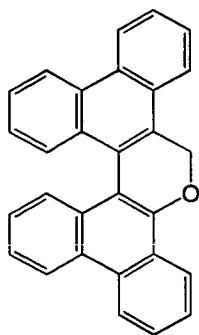


8.76 (m, 4H, aromatic), 8.39-8.35 (m, 1H, aromatic), 7.91-7.61 (m, 7H, aromatic), 7.41-7.32 (m, 4H, aromatic), 4.84-4.80 (d, $J = 11\text{Hz}$, 1H, CH_2), 4.77-4.73 (d, $J = 11\text{Hz}$, 1H, CH_2), 1.80 (s, 3H, CH_3); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 168.90 (carbonyl C), 143.70, 132.29, 131.57, 130.95, 130.81, 130.72, 130.58, 129.43, 129.15, 128.04, 126.22, 125.74 (quaternary aromatic C), 130.50, 127.86, 127.66, 127.45, 127.25, 127.17, 127.18, 126.99, 126.93, 125.47, 123.06, 122.63, 122.49, 122.37 (aromatic CH), 30.00 (CH_2), 20.16 (CH_3); m/z (FAB) 504 (M) $^+$; **HRMS** (FAB) Found 504.07135, $\text{C}_{31}\text{H}_{21}\text{O}_2^{79}\text{Br}$ Requires 504.42404. Found 506.07188, $\text{C}_{31}\text{H}_{21}\text{O}_2^{81}\text{Br}$ Requires 506.42199.

(±)-Tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (18).

To dry THF (15ml) under a nitrogen atmosphere was added diphenyl phosphine (30 μl , 0.17mmol) and the solution cooled to -78°C . 2.5M Butyllithium in hexanes (88 μl , 0.22mmol) was added and the solution allowed to warm to room temperature with stirring over a 30 min period. (±)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate (100mg, 0.20mmol) in dry THF (5ml) was added slowly and the reaction allowed to continue for 1 hour before being quenched by the careful addition of 2M HCl (10ml). The organics were extracted with DCM (2x20ml), the combined organics washed with water (2x20ml) and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification by wet flash chromatography gave the *title compound* as a yellow solid (74mg, 0.19mmol, 97%).

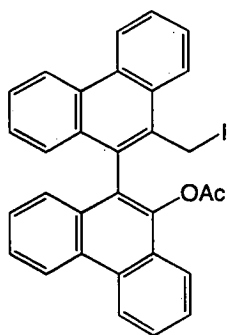
R_f (DCM) = 0.90; **m.p.** 190-191 $^\circ\text{C}$; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3012 (CH); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 8.84-8.69 (m, 4H, aromatic), 8.50-8.46 (m, 1H, aromatic), 8.03-8.00 (m, 1H, aromatic), 7.98-7.53 (m, 8H, aromatic), 7.39-7.31 (m, 2H, aromatic), 6.18-6.13 (d, $J = 13.3\text{Hz}$, 1H, CH_2), 5.24-5.18 (d, $J = 13.3\text{Hz}$, 1H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 152.07, 131.25, 130.63,



129.96, 129.71, 128.21, 127.97, 125.74, 115.36 (quaternary aromatic C), 128.14, 127.45, 127.40, 127.01, 126.64, 126.35, 126.18, 125.53, 124.48, 123.17, 122.98, 122.71, 122.58, 122.29 (aromatic CH), 66.98 (CH₂O); **m/z** (EI) 382 (M)⁺, 352 (M-CH₂O)⁺; **HRMS** (FAB) Found 382.13575, C₂₉H₁₈O Requires 382.13577.

(±)-10'-Hydroxy-10-(iodomethyl)-9,9'-biphenanthryl-10'-acetate (19).

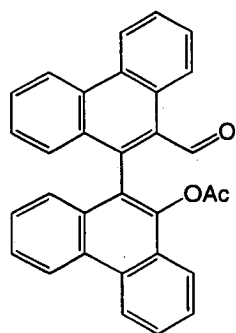
To a suspension of (±)-10'-hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate (**17**) (100mg, 0.20mmol) in dry THF (10ml) was added excess sodium iodide (300mg, 2mmol) and a crystal of iodine. The suspension was stirred overnight at room temperature, quenched with water (20ml), the organics extracted with DCM (2x30ml) and the combined organics washed with a saturated sodium thiosulphate solution (20ml). Removal of solvent *in vacuo* and purification by wet flash chromatography (DCM) gave the *title compound* as a white solid (76mg, 0.14mmol, .69%)



R_f (DCM) = 0.80; **m.p.** 140-142°C; **C.H.** Found C: 67.11%, H: 4.23%, C₃₁H₂₁O₂I Requires C: 67.39, H: 3.80; **FTIR** ν_{max} /cm⁻¹ (DCM) 3054 (aromatic CH stretch), 1767 (aryl ester); λ_{max} /nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 302 (30667), 257 (122053); **¹H nmr** (250MHz, CDCl₃, δ /ppm) 8.89-8.74 (m, 4H, aromatic), 8.34-8.31 (m, 1H aromatic), 7.90-7.60 (m, 7H, aromatic), 7.41-7.27 (m, 4H, aromatic), 4.71 (s, 2H, CH₂I), 1.81 (CH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ /ppm) 168.80 (C=O), 143.58, 131.55, 131.41, 131.04, 130.88, 130.13, 126.30, 125.96 (quaternary aromatic C), 129.28, 127.90, 127.76, 127.63, 127.21, 127.04, 126.91, 126.59, 125.63, 123.06, 122.98, 122.69, 122.51, 122.41 (aromatic CH), 29.58 (CH₂I), 20.21 (CH₃); **m/z** (FAB) 553 (M)⁺, 425 (M-I)⁺; **HRMS** (FAB) Found 553.06635, C₃₁H₂₁O₂I Requires 553.06646.

(±)-10'-Hydroxyacetate-9,9'-biphenanthryl-10-carboxaldehyde (20).**(±)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate (17)**

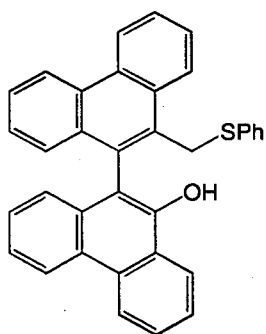
(100mg, 0.2mmol) was dissolved with heating in a 1:1 mixture of dry THF and dry DMSO (5ml) with stirring under nitrogen. To this solution was added a suspension of cuprous cyanide (17mg, 0.19mmol) in dry DMSO (3ml). The reaction mixture was stirred without external heating for 1 hour, heated to 40°C for 1 hour, and finally heated at 85°C for 2 hours. After cooling, the mixture was diluted with water and the organics extracted with DCM. The organics were washed with water (3x30ml), the combined organics dried over Na₂SO₄, and the solvent removed *in vacuo* to give the product as a light brown solid. Purification by wet flash chromatography (DCM) gave the *title compound* as a white solid (35mg, 0.08mmol, 40%).



R_f (DCM) = 0.30; **m.p.** 228-232°C; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 1735 (aryl ester), 1682 (aromatic aldehyde); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 375 (15860), 301 (41887), 288 (43107), 280 (46360), 260 (76453), 255 (80250); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 10.12 (s, 1H, CHO), 9.44-9.40 (m, 1H, aromatic), 8.87-8.79 (m, 4H, aromatic), 7.92-7.63 (m, 7H, aromatic), 7.53-7.49 (dd, J = 1Hz and 8Hz, 1H, aromatic), 7.42-7.34 (m, 2H, aromatic), 1.83 (s, 3H, CH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 194.64 (CHO), 168.75 (carbonyl C), 144.44, 142.34, 132.50, 131.85, 131.60, 130.54, 129.89, 128.83, 128.81, 127.91, 125.95, 123.76 (quaternary aromatic C), 129.82, 128.17, 127.98, 127.69, 127.63, 127.51, 127.17, 126.98, 123.05, 122.88, 122.63, 122.46 (aromatic CH), 20.08 (CH₃); **m/z** (FAB) 440 (M)⁺, 397 (M-CH₃CO)⁺; **HRMS** (FAB) Found 440.49764, C₃₁H₂₀O₃ Requires 440.49721.

(±)-10'-Hydroxy-10-(methyl)-9,9'-biphenanthryl-10-thiophenylether (21).

10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate (**17**) (0.1g, 0.2mmol) was dissolved in dry THF (5ml) under nitrogen and cooled to 0°C with stirring. Separately, a suspension of sodium hydride (88mg, 2.4mmol) in dry THF (5ml) at 0°C under nitrogen was treated with thiophenol (0.23ml, 2.2mmol) with stirring for 30 minutes. A portion of this freshly prepared sodium thiophenoxide suspension (0.7ml, 0.24mmol, 1.2 eq.) was added by syringe slowly to the 10'-hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10'-acetate solution. The reaction was subsequently warmed to room temperature and stirred for a further 4 hours. After this time the reaction mixture was treated with water, passed through a celite pad and the organics extracted with DCM (2x50ml). The combined organics were washed with satd. potassium carbonate solution (2x30ml), dried (MgSO₄) and purified by wet flash chromatography (hexane then DCM) to give the *title compound* as an off-white solid (30mg, 0.6mmol, 31%).

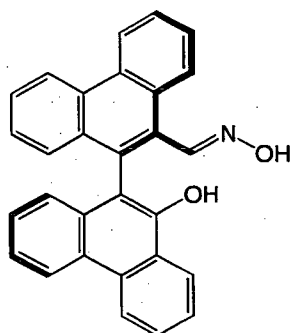


R_f (DCM) = 0.78; **m.p.** 124-127°C; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3507 (OH), 3023 (aromatic CH stretch), 1579 (aromatic rings); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 358 (820), 341 (1 639), 329 (2 459), 295 (16 393), 259 (75410); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.93-8.92 (m, 1H, aromatic), 8.89-8.80 (m, 1H, aromatic), 8.77-8.74 (m, 1H, aromatic), 8.49-8.36 (m, 1H, aromatic), 7.87-7.63 (m, 4H, aromatic), 7.56-7.44 (m, 4H, aromatic), 7.42-7.21 (m, 5H, aromatic), 7.17-6.95 (m, 4H, aromatic), 5.53 (s, 1H, OH), 4.66-4.62 (d, $J = 11.5\text{Hz}$, 1H, CH₂), 4.35-4.30 (d, $J = 11.5\text{Hz}$, 1H, CH₂); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 147.39, 136.86, 136.28, 134.07, 132.09, 131.33, 131.11, 131.05, 130.64, 129.85, 125.18, 113.83 (quaternary aromatic C), 130.24, 130.13, 128.92, 128.57, 127.37, 127.33, 127.14, 127.07, 127.00, 126.60, 126.53, 126.44, 125.75, 125.36, 124.28, 123.36, 123.12, 122.64, 122.56, 122.41 (aromatic CH), 36.00 (CH₂S); **m/z** (FAB) 492

(M)⁺, 383 (M-SPH)⁺; HRMS (FAB) Found 492.15479, C₃₅H₂₄OS Requires 492.15479.

(S)-(-)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (22).

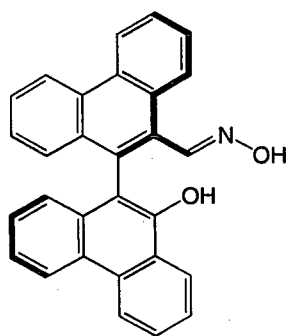
This compound was synthesised following the procedure described by Louise Picken.⁹⁵ A suspension of (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (271mg, 0.70mmol), hydroxylamine hydrochloride (0.7g, 10mmol) and sodium acetate (1.54g, 1.9mmol) in ethanol (30ml) was stirred at room temperature for 30 minutes. The reaction was quenched by the addition of water (20ml) and extracted with DCM (2x25ml). The combined organics were dried over Na₂SO₄ and the solvent removed *in vacuo*. Purification by wet flash chromatography (chloroform) gave the *title compound* as a white solid (130mg, 0.31mmol, 44%).



R_f (DCM) = 0.36; m.p. Decomp. at 176°C; C.H.N. Found C: 82.84%, H: 4.83%, N: 2.96%, C₂₉H₁₉NO₂ Requires C: 84.26, H: 4.60, N: 3.39; FTIR $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3569 (OH), 3006 (aromatic CH); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 384 (1033), 359 (3098), 341 (4130), 302 (19101), 259 (79502); ¹H nmr (250MHz, DMSO, δ/ppm) 11.16 (s, 1H, OH), 9.13-9.10 (d, J = 8Hz, 1H, aromatic), 8.99-8.76 (m, 4H, aromatic), 8.48-8.45 (dd, J = 1Hz and 8Hz, 1H, aromatic), 8.12 (s, 1H, CH=N), 7.91-7.66 (m, 5H, aromatic), 7.49-7.09 (m, 4H, aromatic), 6.96-6.94 (d, J = 8Hz, 1H, aromatic); ¹³C{¹H} nmr (63MHz, DMSO, δ/ppm) 149.08 (CH=N), 145.93, 135.31, 133.42, 132.07, 131.95, 131.51, 131.43, 131.33, 130.34, 129.17, 126.88, 123.33 (quaternary aromatic C), 128.51, 128.37, 128.29, 128.22, 127.98, 127.81, 127.64, 127.55, 127.43, 127.26, 125.69, 124.76, 124.05, 123.75, 123.65, 123.33 (aromatic CH); m/z (FAB) 414 (M+H)⁺, 413 (M)⁺, 396 (M-OH)⁺; HRMS (FAB) Found 414.14937, C₂₉H₂₀NO₂ Requires 414.14940; $[\alpha]_D^{25}(\text{deg}) = +10^\circ$, c = 0.4, DCM.

(R)-(+)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (22).

This compound was synthesised following the procedure described by Louise Picken.⁹⁵ A suspension of (R)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (400mg, 1.0mmol), hydroxylamine hydrochloride (1.0g, 14mmol) and sodium acetate (2.2g, 27mmol) in ethanol (80ml) was stirred at room temperature for 20 minutes. The reaction was quenched by the addition of water (20ml) and extracted with DCM (2x25ml). The combined organics were dried over Na₂SO₄ and the solvent removed *in vacuo*. Purification by wet flash chromatography (chloroform) gave the *title compound* as a white solid (130mg, 0.31mmol, 31%).

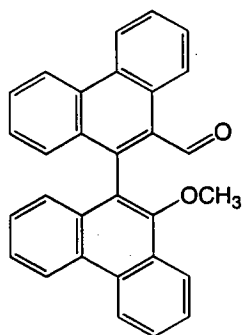


R_f (DCM) = 0.36; **m.p.** Decomp. at 176°C; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3529 (OH), 3067 (aromatic CH); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 359 (3098), 341 (2893), 300 (19008), 258 (79339); **¹H nmr** (250MHz, DMSO, δ/ppm) 11.14 (s, 1H, OH), 9.11-9.07 (d, J = 8Hz, 1H, aromatic), 8.96-8.76 (m, 4H, aromatic), 8.46-8.42 (dd, J = 1.5Hz and 7Hz, 1H, aromatic), 8.10 (s, 1H, CH=N), 7.79-7.62 (m, 5H, aromatic), 7.45-7.21 (m, 4H, aromatic), 6.94-6.90 (d, J = 7.5Hz, 1H, aromatic); **m/z** (FAB) 413 (M)⁺, 396 (M-OH)⁺; **HRMS** (FAB) Found 414.14949, C₂₉H₂₀NO₂ Requires 414.14940; $[\alpha]_{\text{D}}^{25}(\text{deg}) = -13^\circ$, c = 0.4, DCM.

(±)-10'-Methoxy-9,9'-biphenanthryl-10-carboxaldehyde (23).

Potassium *tert*-butoxide (1.2 equivalents, 0.134g, 1.2mmol) was added to 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (400mg, 1mmol) in dry THF (10ml) under nitrogen at room temperature with stirring. A red colouration indicated the successful formation of the phenolate anion. Stirring was continued for a further 30 min before the addition of methyl iodide (0.1ml,

1.58mmol), and the reaction was left stirring overnight. A change from the red colouration to a cream colour indicated the reaction's completion. The mixture was acidified with 2M HCl (30ml), the organics extracted with DCM (2x50ml), washed with water (2x50ml) and dried (Na_2SO_4). Solvent removal *in vacuo* and purification by wet flash chromatography (hexane then chloroform) gave the *title compound* as a yellow solid (230mg, 0.56mmol, 56%).

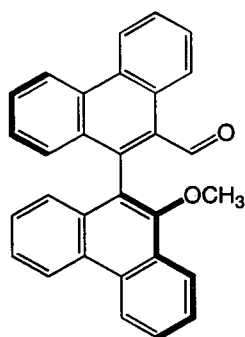


R_f (DCM) = 0.48; **m.p.** 260-263°C; **C.H.** Found C: 87.77%, H: 5.11%, $\text{C}_{30}\text{H}_{21}\text{O}_2$ Requires C: 87.38, H: 4.85; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr_3 mull) 3018 (aromatic CH), 1684 (α,β -unsatd. aldehyde), 1423 (aromatic rings); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 10.21 (s, 1H, CHO), 9.43-9.39 (m, 1H, aromatic), 8.88-8.77 (m, 4H, aromatic), 8.30-8.27 (dd, $J = 1\text{Hz}$ and 7.5Hz , 1H, aromatic), 7.84-7.72 (m, 5H, aromatic), 7.63-7.57 (dt, $J = 1.4$ and 7Hz , 1H, aromatic), 7.53-7.50 (dd, $J = 1\text{Hz}$ and 7.3Hz , 1H, aromatic), 7.40-7.32 (m, 2H, aromatic), 7.24-7.21 (dd, $J = 1\text{Hz}$ and 7.8Hz , 1H, aromatic), 3.54 (s, 3H, aromatic); **$^{13}\text{C}\{^1\text{H}\}$ nmr** (63MHz, CDCl_3 , δ/ppm) 195.08 (CHO), 132.71, 132.42, 132.14, 130.81, 130.51, 121.89 (quaternary aromatic C), 129.67, 128.18, 127.96, 127.70, 127.50, 127.41, 127.17, 126.79, 126.05 (aromatic CH), 61.17 (CH_3); **m/z** (FAB) 413 ($\text{M}+\text{H}^+$), 412(M^+); **HRMS** (FAB) Found 413.15423, $\text{C}_{30}\text{H}_{21}\text{O}_2$ Requires 413.15416.

(S)-10'-Methoxy-9,9'-biphenanthryl-10-carboxaldehyde (23).

Potassium *tert*-butoxide (1.2 equivalents, 0.134g, 1.2mmol) was added to (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (400mg, 1mmol) in dry THF (10ml) under nitrogen at room temperature with stirring. A red colouration indicated the successful formation of the phenolate anion. Stirring was continued for a further 30 minutes before the addition of methyl iodide (0.1ml, 1.58mmol), and the reaction left stirring overnight. A change from the red

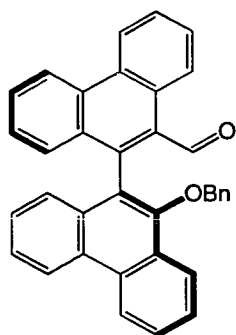
colouration to a cream colour indicated the reaction's completion. The mixture was acidified with 2M HCl (30ml), the organics extracted with DCM (2x50ml), washed with water (2x50ml) and dried (Na_2SO_4). Removal of solvent *in vacuo* and purification by wet flash chromatography (hexane then chloroform) gave the *title compound* as a yellow solid (230mg, 0.56mmol, 56%).



R_f (DCM) = 0.48; m.p. 255-257°C; FTIR ν_{max} , cm^{-1} (CHBr_3 mull) 3018 (aromatic CH), 1684 (α,β -unsatd. aldehyde), 1423 (aromatic rings); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 10.22 (s, 1H, CHO), 9.45-9.40 (m, 1H, aromatic), 8.89-8.76 (m, 4H, aromatic), 8.32-8.27 (m, 1H, aromatic), 7.86-7.74 (m, 5H, aromatic), 7.72-7.49 (m, 2H, aromatic), 7.41-7.31 (m, 2H, aromatic), 7.25-7.20 (m, 1H, aromatic), 3.55 (s, 3H, aromatic); m/z (FAB) 413 ($\text{M}+\text{H}$) $^+$, 412(M) $^+$; HRMS (FAB) Found 413.15378, $\text{C}_{30}\text{H}_{21}\text{O}_2$ Requires 413.15416; $[\alpha]_D = +64^\circ$, $c = 0.4$, DCM.

(S)-10'-Hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether (24).

Sodium hydride (52mg, 1.3mmol, 60% in oil) was added to (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (0.378g, 0.95mmol) in dry THF (5ml) at room temperature under nitrogen with stirring. The appearance of a deep red colouration indicates the successful formation of the phenolate anion. Stirring was continued for a further 30 minutes before the addition of tetrabutylammonium iodide (0.4g, 1.1mmol) and benzyl bromide (0.23ml, 1.9mmol). The mixture was left stirring overnight after which time the reaction colour had changed from deep red to pale yellow. The reaction was quenched by the addition of water (50ml), the organics extracted with DCM (2x50ml) and the combined organics dried over Na_2SO_4 . Removal of the solvent *in vacuo* and purification by wet flash chromatography gave (DCM) the *title compound* as a yellow solid (0.362g, 0.74mmol, 78%).

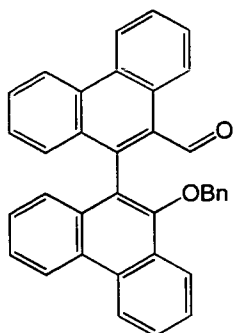


Rf (DCM) = 0.90; **m.p.** 199-201°C; **C.H.** Found C: 84.99%, H: 4.53%, $C_{36}H_{24}O_2$ Requires C: 88.52, H: 4.92; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (CHBr_3 mull) 3019 (aromatic CH), 2887 (-O-CH₃), 1680 ($\alpha\beta,\gamma\delta$ -unsatd. aldehyde); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 305 (24457), 257 (109239); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 10.25 (s, 1H, CHO), 9.41-9.37 (m, 1H, aromatic), 8.88-8.79 (m, 4H, aromatic), 8.34-8.30 (dd, $J = 1.5\text{Hz}$ and 8Hz, 1H, aromatic), 7.85-7.56 (m, 7H, aromatic), 7.41-7.25 (m, 3H, aromatic), 7.10-6.97 (m, 3H, aromatic), 6.82-6.79 (m, 2H, aromatic), 4.84-4.79 (d, $J=11\text{Hz}$, 1H, OCH₂), 4.65-4.60 (d, $J = 11\text{Hz}$, 1H, OCH₂); **$^{13}\text{C}\{^1\text{H}\}$ nmr** (63MHz, CDCl_3 , δ/ppm) 194.97 (CHO), 151.94, 143.52, 136.41, 132.68, 132.50, 132.08, 130.80, 130.45, 129.15, 128.27, 122.84, 122.22 (quaternary aromatic C), 129.59, 128.10, 128.05, 127.94, 127.73, 127.65, 127.54, 127.41, 127.20, 127.17, 127.04, 126.90, 126.78, 126.10, 123.49, 122.96, 122.69, 122.44 (aromatic CH), 75.28 (OCH₂); **m/z** (FAB) 488 (M^+), 397 ($\text{M}-\text{CH}_2\text{Ph}^+$); **HRMS** (FAB) Found 488.17772, $C_{36}H_{24}O_2$ Requires 488.17763; $[\alpha]^{25}_{\text{D}}(\text{deg}) = -7^\circ$, $c = 0.4$, DCM.

(±)-10'-Hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether (24).

Sodium hydride (110mg, 2.6mmol, 60% in oil) was added to (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**6**) (1.0g, 2.5mmol) in dry THF (10ml) at room temperature under nitrogen with stirring. The appearance of a deep red colouration indicates the successful formation of the phenolate anion. Stirring was continued for a further 30 minutes before the addition of tetrabutylammonium iodide (0.5g, 2.5mmol) and benzyl bromide (0.4ml, 3.4mmol). The mixture was left stirring overnight after which time the reaction colour had changed from deep red to pale yellow. The reaction was quenched by the addition of water (50ml), the organics extracted with DCM (2x50ml) and the combined organics dried over Na_2SO_4 . Removal of the solvent *in vacuo* and

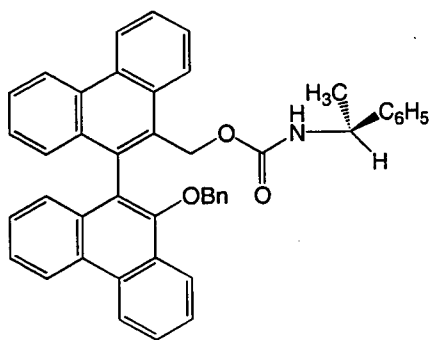
purification by wet flash chromatography (chloroform) gave the *title compound* as a yellow solid (0.9g, 1.8mmol, 76%).



R_f (DCM) = 0.90; **m.p.** 198-200°C; **FTIR** $\nu_{\text{max.}}$ cm^{-1} (CHBr₃ mull) 3015 (aromatic CH), 1678 ($\alpha\beta,\gamma\delta$ -unsatd. aldehyde); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 10.13 (s, 1H, CHO), 9.30-9.25 (m, 1H, aromatic), 8.78-8.67 (m, 4H, aromatic), 8.23-8.19 (d, J = 8Hz, 1H, aromatic), 7.75-7.45 (m, 7H, aromatic), 7.31-15 (m, 3H, aromatic), 6.97-6.86 (m, 3H, aromatic), 6.72-6.68 (m, 2H, aromatic), 4.73-4.68 (d, J=11Hz, 1H, OCH₂), 4.54-4.49 (d, J = 11Hz, 1H, OCH₂); **m/z** (FAB) 488 (M)⁺, 397 (M-CH₂Ph)⁺.

Diastereomeric biphenanthryl urethanes (25).

A solution of ($\pm$)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-benzylether (**30**) (80mg, 0.16mmol) and *N,N*-dimethylethanolamine (30 μ l, 1wt%) in dry benzene (5ml) under a nitrogen atmosphere was treated dropwise with (S)-(-)- α -methylbenzylisocyanate (43 μ l, 0.30mmol) with stirring. The solution was heated at 80°C for 18h. The crude product was concentrated and the residue purified by wet flash chromatography (DCM) to to give the *title compound* as a white solid (70mg, 0.11mmol, 70%).

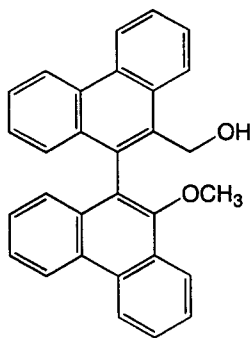


R_f (DCM) = 0.38; **m.p.** 129-132°C; **FTIR** $\nu_{\text{max.}}$ cm^{-1} (DCM) 3023 (aromatic CH), 1714 (C=O); **$\lambda_{\text{max.}}$ nm** (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 304 (19110), 293 (19906), 258 (93958), 229 (39016); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.89-8.76 (m, 4H, aromatic), 8.32-8.28 (m, 1H, aromatic), 8.19-8.16 (d, J = 6.7Hz, 1H, aromatic), 7.81-7.55 (m, 6H, aromatic), 7.47-7.43 (m, 1H, aromatic), 7.37-6.95 (m, 11H, aromatic), 6.81-6.74 (m, 2H, aromatic), 5.45-5.28 (m, 2H, OCH₂),

4.75-4.58 (m, 2H, OCH₂), 1.75 (broad s, 1H, NH), 1.28 (d, J = 12.5Hz, 3H, CH₃), 0.92-0.84 (m, 1H, CH); ¹³C{¹H} nmr (63MHz, CDCl₃, δ/ppm) 206.90 (C=O), 155.19, 151.19, 151.14, 143.28, 143.19, 136.97, 134.32, 132.64, 131.91, 130.71, 130.62, 129.83, 124.21 (quaternary aromatic C), 128.52, 128.33, 128.15, 127.88, 127.41, 127.28, 127.07, 126.98, 126.89, 126.74, 125.65, 125.60, 125.37, 123.44, 122.88, 122.51 (aromatic CH), 74.98 (OCH₂Ph), 62.79 (CH₂OCO), 50.26 (NCH), 22.28 (CH₃); m/z (FAB) 637 (M)⁺, 473 (M-CO₂NHCH(CH₃)Ph)⁺; HRMS (FAB) Found 637.26169, C₄₅H₃₅NO₃ Requires 637.26358.

(±)-10'-Methoxy-10-(hydroxymethyl)-9,9'-biphenanthryl (26).

(±)-10'-Methoxy-9,9'-biphenanthryl-10-carboxaldehyde (**23**) (100mg, 0.24mmol) was dissolved in dry THF (5ml) under nitrogen and cooled to 0°C. To this solution was slowly added 1.2eq. diisobutylaluminium hydride (DIBAL-H, 1M soln. in toluene) (0.48ml, 0.48mmol) and stirring continued for 1 hour. The reaction was quenched by the careful addition of saturated Rochelle salt solution and filtered. The organics were extracted with DCM (3x30ml) and the combined organics washed with water (30ml). Drying over Na₂SO₄, removal of the solvent *in vacuo* and purification by wet flash chromatography (DCM) gave the *title compound* as a white solid (92mg, 0.22mmol, 93%).

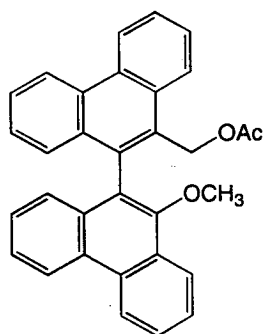


R_f (DCM) = 0.25; m.p. 218-220°C; C.H. Found C: 82.8%, H: 5.17%, C₃₀H₂₂O₂ Requires C: 86.96, H: 5.31; FTIR ν_{max}/ cm⁻¹ (CHBr₃ mull) 3365 (OH), 3018 (aromatic CH); λ_{max}/ nm (DCM ε/dm³mol⁻¹l⁻¹) 352 (592), 336 (1183), 364 (21302), 293 (21893), 258 (100000); ¹H nmr (250MHz, CDCl₃, δ/ppm) 8.94-8.80 (m, 4H, aromatic), 8.62-8.58(m, 1H, aromatic), 8.41-8.37 (m, 1H, aromatic), 7.86-7.75 (m, 4H, aromatic), 7.69-7.59 (m, 2H, aromatic), 7.43-7.25 (m, 4H, aromatic), 5.17-5.09 (t, J = 11Hz, 1H, CH₂OH), 4.72-4.68 (d, J = 12Hz, 1H,

CH_2OH), 3.49 (s, 3H, OCH_3), 3.22-3.20 (d, $J = 6\text{Hz}$, 1H, OH); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 151.91, 134.46, 132.29, 131.76, 131.50, 131.40, 130.80, 130.76, 130.53, 128.12, 125.31 (quaternary aromatic C), 127.77, 127.36, 127.32, 127.18, 127.01, 126.97, 126.79, 126.64, 125.92, 125.70, 123.14, 122.86, 122.80, 122.60, 122.57 (aromatic CH), 61.18 (CH_2OH), 61.07 (OCH_3); m/z (FAB) 415 ($\text{M}+\text{H}$) $^+$, 414 (M) $^+$, 397 ($\text{M}-\text{OH}$) $^+$; HRMS (FAB) Found 414.16198, $\text{C}_{30}\text{H}_{22}\text{O}_2$ Requires 414.16140.

($\pm$)-10'-Methoxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-acetate (27).

($\pm$)-10'-Methoxy-10-(hydroxymethyl)-9,9'-biphenanthryl (26) (500mg, 1.21mmol) in dry pyridine (5ml) and distilled acetic anhydride (5ml) was stirred overnight under nitrogen at room temperature. Heptane (30ml) was added and the resulting mixture concentrated. The acetic anhydride and pyridine were removed by successive evaporation with heptane. Purification by wet flash chromatography (hexane then DCM) gave the *title compound* as a pale yellow solid (271mg, 0.57mmol, 47%).



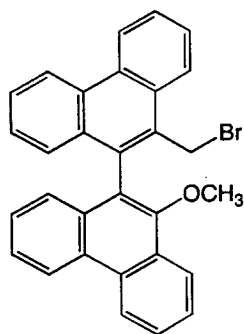
R_f (DCM) = 0.57; **m.p.** 220-223°C; **C.H.** Found C: 82.66%, H: 5.24%, $\text{C}_{32}\text{H}_{24}\text{O}_3$ Requires C: 84.21, H: 5.26; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (CHBr_3 mull) 3017 (aromatic CH), 1731 (alkyl ester); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 353 (1000), 336 (2000), 303 (31000), 292 (33000), 258 (160000), 229 (70000); ^1H nmr (250MHz, CDCl_3 ,

δ/ppm) 8.92-8.75 (m, 4H, aromatic), 8.31-8.28 (dd, $J = 1.7\text{Hz}$ and 7.2Hz , 1H, aromatic), 8.16-8.12 (dd, $J = 2\text{Hz}$ and 7.2Hz , 1H, aromatic), 7.82-7.54 (m, 6H, aromatic), 7.44-7.22 (m, 4H, aromatic), 5.44-5.37 (d, $J = 12\text{Hz}$, CH_2O), 5.39-5.32 (d, $J = 12\text{Hz}$, CH_2O), 3.54 (s, 3H, OCH_3), 1.84 (s, 3H, acetyl CH_3); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 170.63 ($\text{C}=\text{O}$), 151.91, 134.82, 132.43, 131.99, 131.30, 130.75, 130.67, 130.60, 128.92, 128.07, 127.48, 123.76 (quaternary aromatic C), 127.80, 127.27, 127.22, 127.12, 126.92, 126.88,

126.78, 126.74, 126.60, 125.67, 125.03, 123.28, 123.06, 122.94, 122.53 (aromatic CH), 61.03 (OCH₃), 20.55 (CH₃C=O); **m/z** (FAB) 457 (M+H)⁺, 456 (M)⁺, 397 (M-CO₂CH₃)⁺; **HRMS** (FAB) Found 456.17256, C₃₂H₂₄O₃ Requires 456.17254.

(±)-10'-Methoxy-10-(bromomethyl)-9,9'-biphenanthryl (28).

To 30% hydrobromic acid (3ml) was added (±)-10'-methoxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-acetate (**27**) (200mg, 0.44mmol), and refluxed with stirring at 80°C for 1 hour. After this time the reaction was quenched by the careful addition of water (10ml). The organics were extracted with a 50:50 THF:DCM mixture (2x30ml), washed with water (2x20ml) and dried (MgSO₄). Removal of the solvent *in vacuo* and purification by wet flash chromatography (DCM) gave the *title compound* as a white solid (90mg, 0.19mmol, 43%).

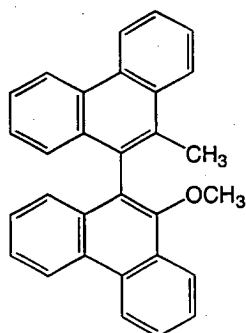


R_f (DCM) = 0.95; **m.p.** 250-255°C; **C.H.** Found C: 75.37%, H: 4.67%, C₃₀H₂₁OBr Requires C: 75.47, H: 4.40; **FTIR** ν_{max} / cm^{-1} (CHBr₃ mull) 3013 (aromatic CH), 1253 (C-O-C stretch); λ_{max} / nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 329 (1190), 303 (7143), 259 (33333); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.92-8.77 (m, 4H, aromatic), 8.43-8.32 (m, 2H, aromatic), 7.85-7.72 (m, 4H, aromatic), 7.68-7.57 (m, 2H, aromatic), 7.41-7.20 (m, 4H, aromatic), 4.92-4.88 (d, J = 10.5Hz, 1H, CH₂Br), 4.82-4.81 (d, J = 10.4Hz, 1H, CH₂Br), 3.53 (s, 3H, OCH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 151.70, 133.58, 132.08, 131.86, 131.45, 130.89, 130.67, 130.63, 129.64, 128.13, 127.57 (quaternary aromatic C), 127.95, 127.38, 127.25, 126.98, 126.95, 125.85, 125.38, 123.59, 123.39, 123.08, 122.95, 122.62, 122.48 (aromatic CH), 61.04 (OCH₃), 30.05 (CH₂Br); **m/z** (FAB) 478 (M⁸¹Br)⁺, 476 (M⁷⁹Br)⁺, 397 (M- Br)⁺; **HRMS** (FAB) Found 478.06240,

$C_{30}H_{21}O^{81}Br$ Requires 478.07566. Found 476.07627, $C_{30}H_{21}O^{79}Br$ Requires 476.07758.

(±)-10'-Hydroxy-10-(methyl)-9,9'-biphenanthryl-10'-methyl ether (29).

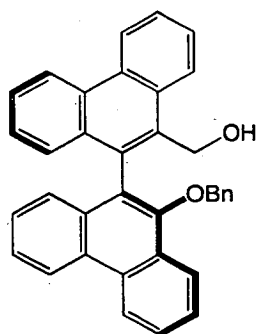
To dry THF (15ml) under a nitrogen atmosphere was added diphenyl phosphine (30 μ l, 0.17mmol) and the solution cooled to -78°C. 2.5M Butyl lithium in hexanes (88 μ l, 0.22mmol) was added and the solution allowed to warm to room temperature with stirring over a 30 minute period. (±)-10'-Methoxy-10-(bromomethyl)-9,9'-biphenanthryl (**28**) (80mg, 0.17mmol) in dry THF (5ml) was added slowly and the reaction allowed to continue for 1 hour before being quenched by the careful addition of 2M HCl (10ml). The organics were extracted with DCM (2x20ml), the combined organics washed with water (2x20ml) and dried over Na_2SO_4 . Removal of the solvent *in vacuo* and purification by wet flash chromatography (chloroform) gave the *title compound* as a white solid (52mg, 0.13mmol, 78%).



Rf (DCM) = 0.90; **m.p.** 211-213°C; **C.H.N.** Found C: 83.72%, H: 5.60%, $C_{30}H_{22}O$ Requires C: 90.45, H: 5.53; **FTIR** ν_{max}/cm^{-1} (DCM) 3017 (aromatic CH); λ_{max}/nm (DCM $\epsilon/dm^3mol^{-1}l^{-1}$) 353 (2000), 337 (2000), 329 (2000), 303 (31000), 291 (31000), 257 (147000); **^1H nmr** (250MHz, DMSO, δ/ppm) 8.90-8.75 (m, 4H, aromatic), 8.39-8.20 (m, 2H, aromatic), 8.11-7.68 (m, 4H, aromatic), 7.66-7.53 (m, 2H, aromatic), 7.34-7.17 (m, 4H, aromatic), 3.51 (s, 3H, OCH₃), 2.46 (s, 3H, CH₃); **$^{13}C\{^1H\}$ nmr** (63MHz, DMSO, δ/ppm) 151.64, 132.43, 131.97, 131.91, 131.85, 131.73, 131.44, 131.09, 130.62, 130.28, 129.64, 129.48 (quaternary aromatic C), 128.12, 127.36, 127.24, 126.79, 126.41, 126.35, 125.83, 125.75, 125.52, 125.38, 125.08, 123.24, 123.07, 122.83, 122.53, 122.41 (aromatic CH), 60.65 (OCH₃), 17.34 (CH₃); **m/z** (FAB) 398 (M)⁺, 367 (M-OCH₃)⁺; **HRMS** (FAB) Found 398.16708, $C_{30}H_{22}O$ Requires 398.16707.

(S)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-benzylether (30).

(S)-10'-Hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether (24) (478mg, 0.98mmol) was dissolved in dry THF (5ml) under nitrogen with stirring. To this solution was added 2 eq. sodium borohydride (78mg, 2mmol) and the reaction stirred for a further 1 hour. The reaction was quenched by the addition of satd. Rochelle salt soln. and filtered through Celite. The organics were extracted with DCM (2x50ml), washed with water (2x50ml) and dried over Na₂SO₄. Removal of the solvent *in vacuo* and purification by wet flash chromatography gave the *title compound* as a white solid (435mg, 0.89mmol, 89%).

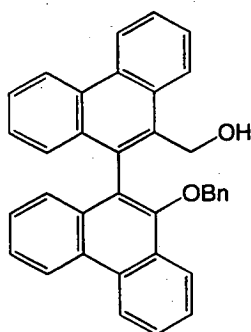


R_f (DCM) = 0.23; **m.p.** 168-171°C; **C.H.** Found C: 83.80%, H: 5.63%, C₃₆H₂₆O₂ Requires C: 88.16, H: 5.31; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (CHBr₃ mull) 3487 (OH), 3019 (aromatic CH); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 305 (18478), 293 (19022), 258 (85870); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.95-8.85 (m, 4H, aromatic), 8.58-8.54 (dd, J = 1.5Hz and 8Hz, 1H, aromatic), 8.42-8.39 (dd, J = 1.3Hz and 8Hz, 1H, aromatic), 7.88-7.76 (m, 4H, aromatic), 7.70-7.64 (m, 2H, aromatic), 7.46-7.30 (m, 4H, aromatic), 7.18-7.13 (m, 1H, aromatic), 7.09-7.00 (m, 2H, aromatic), 6.81-6.79 (m, 2H, aromatic), 5.14-5.11 (dd, 1H, J = 11Hz and 12Hz, 1H, CH₂OH), 4.82-4.49 (d, J = 10.4Hz, 1H, OCH₂Ph), 4.71-4.68 (d, J = 12Hz, 1H, CH₂OH), 3.08-3.05 (d, J = 10Hz, 1H, OH); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 151.79, 136.46, 135.39, 132.98, 132.37, 132.09, 131.50, 131.34, 131.26, 128.86, 128.28 (quaternary aromatic C), 128.75, 128.56, 128.52, 128.47, 128.04, 127.79, 127.70, 127.65, 127.43, 127.34, 126.65, 126.53, 123.97, 123.49, 123.37, 123.34, 123.25 (aromatic CH), 76.34 (OCH₂Ph), 61.93 (CH₂OH); **m/z** (FAB) 490 (M)⁺, 382 (M-OH)⁺; **HRMS** (FAB) Found 490.19331, C₃₆H₂₆O₂ Requires 490.19328; $[\alpha]_D^{25}(\text{deg}) = +71^\circ$, c = 0.4, DCM.

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-benzylether (30).

(±)-10'-Hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzylether (24) (130mg, 0.3mmol) was dissolved in dry THF (5ml) under nitrogen with stirring. To this solution was added 2eq. diisobutylaluminium hydride (DIBAL-H, 1M soln. in toluene) (0.55ml, 5.5mmol) and the reaction stirred for a further 1 hour. The reaction was quenched by the addition of satd. Rochelle salt soln. then filtered through Celite. The organics were extracted with DCM (2x50ml), washed with water (2x50ml) and dried over Na₂SO₄. Removal of the solvent *in vacuo* and purification by wet flash chromatography (chloroform) gave the *title compound* as a white solid (80mg, 0.16mmol, 62%).

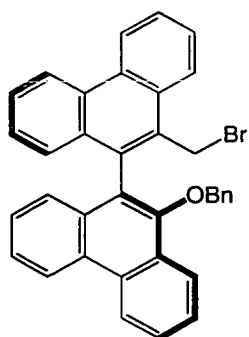
R_f (DCM) = 0.23; **m.p.** 168-171°C;; **FTIR** ν_{max} / cm^{-1} (CHBr₃ mull) 3451 (OH), 3019 (aromatic CH); **¹H nmr** (250MHz, CDCl₃, δ /ppm) 8.82-8.70 (m, 4H, aromatic), 8.44-8.39 (d, J = 9.5Hz 1H, aromatic), 8.28-8.24 (d, J = 7Hz, 1H, aromatic), 7.76-7.50 (m, 6H, aromatic), 7.32-7.15 (m, 4H, aromatic), 7.02-6.89 (m, 3H, aromatic), 6.67-6.63 (m, 2H, aromatic), 5.02-4.90 (dd, 1H, J = 11Hz and 12Hz, 1H, CH₂OH), 4.69-4.67 (d, J = 10.5Hz, 1H, OCH₂Ph), 4.56-4.50 (d, J = 12Hz, 1H, CH₂OH), 4.27-4.22 (d, J = 10.2Hz, 1H, OCH₂Ph), 2.93-2.88 (d, J = 10Hz, 1H, OH); **m/z** (FAB) 490 (M)⁺, 382 (M-OH)⁺.



(S)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10-benzylether (31).

To (S)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl-10-benzylether (30) (381mg, 0.78mmol) in wet DCM (10ml) were added triphenylphosphine (419mg, 1.60mmol) and 1,2-dibromotetrachloroethane (518mg, 1.60mmol). The reaction was stirred for 1 hour at room temperature and the solvent removed

in vacuo. The product was purified by wet flash chromatography (chloroform) to give the *title compound* as a white solid (381mg, 0.69mmol, 86%).

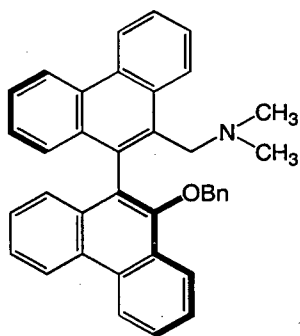


R_f (DCM) = 0.85; **m.p.** 195-198°C; **C.H.N.** Found C: 76.94%, H: 3.81%, C₃₆H₂₅OBr Requires C: 78.12, H: 4.52; **FTIR** ν_{max} / cm^{-1} (CHBr₃ mull) 3014 (aromatic CH), 1520 (aromatic rings); λ_{max} / nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 384 (1010), 354 (2020), 329 (5051), 297 (26263), 260 (109090); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.90-8.77 (m, 4H, aromatic), 8.41-8.35 (m, 2H, aromatic), 7.85-7.58 (m, 6H, aromatic), 7.46-7.25 (m, 4H, aromatic), 7.13-7.00 (m, 3H, aromatic), 6.84-6.81 (d, J = 6.5Hz, 1H, aromatic), 4.88 (s, 2H, CH₂Br), 4.83-4.79 (d, J = 11Hz, 1H, OCH₂Ph), 4.59-4.55 (d, J = 11Hz, 1H, OCH₂Ph); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 150.95, 136.84, 133.43, 132.01, 131.94, 131.42, 130.97, 130.86, 130.68, 129.60, 128.19, 127.98, 123.94 (quaternary aromatic C), 127.92, 127.21, 127.12, 126.96, 125.91, 125.36, 123.52, 123.04, 122.91, 122.64, 122.51 (aromatic CH), 74.99 (OCH₂Ph), 30.10 (CH₂Br); **m/z** (FAB) 554 (M⁸¹Br)⁺, 552 (M⁷⁹Br)⁺, 473 (M-Br)⁺; **HRMS** (FAB) Found 554.10838, C₃₀H₂₁O⁸¹Br Requires 554.10696; $[\alpha]_{\text{D}}^{25}(\text{deg}) = +31^\circ$, c = 0.4, DCM.

(S)-10-(N,N-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl-10-benzylether (32).

Dimethylamine hydrochloride (228mg, 2.76mmol) and triethylamine (0.38ml, 2.76mmol) were dissolved in dry DCM (2ml) and cooled to 0°C under an atmosphere of nitrogen. (S)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10-benzylether (**31**) (381mg, 0.69mmol) was similarly dissolved in dry DCM (10ml) and cooled to 0°C under an atmosphere of nitrogen and this solution transferred into the flask containing the dimethylamine with stirring. The reaction was kept at 0°C for one hour before warming to room temperature and then left stirring overnight. The reaction was quenched by the addition of

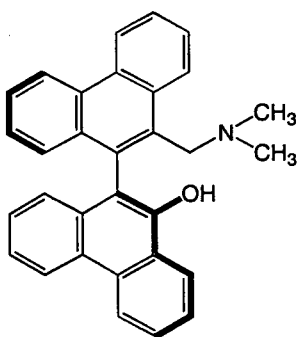
satd. potassium carbonate solution (10ml), the organics extracted with DCM (2x20ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. Added to this crude product was a saturated solution of picrolonic acid in diethyl ether (5ml) and the resultant suspension agitated on a sonic bath for 30 minutes. The resultant pale brown precipitate was filtered and subsequently washed with water (10ml) and ethanol (10ml), both chilled to 0°C . The product was thus purified as the picrolonic acid salt, with passage through a neutral alumina plug (10% methanol in DCM) and removal of solvent *in vacuo* giving the *title compound* as a brown solid (150mg, 0.3mmol, 43%).



m.p. 180-185°C; **C.H.N.** Found C: 73.52%, H: 5.23%, N: 1.90 $\text{C}_{38}\text{H}_{32}\text{NOCl}$ Requires C:82.38, H:5.78, N: 2.53; **FTIR** $\nu_{\text{max.}}$ cm^{-1} (CHBr_3 mull) 3040 (aromatic CH), 1599 (aromatic rings); $\lambda_{\text{max.}}$ nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 260 (49412), 295 (8235), 306 (8235); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 8.89-8.71 (m, 5H, aromatic), 8.37-8.33 (dd, $J = 1.3\text{Hz}$ and 9Hz , 1H, aromatic), 7.84-7.67 (m, 4H, aromatic), 7.63-7.41 (m, 2H, aromatic), 7.41-7.29 (m, 4H, aromatic), 7.24-6.97 (m, 3H, aromatic), 6.79-6.73 (m, 2H, aromatic), 4.75-4.70 (d, $J = 10.5\text{Hz}$, 1H, OCH_2Ph), 4.35-4.30 (d, $J = 10.5\text{Hz}$, 1H, OCH_2Ph), 4.06-4.00 (d, $J = 13\text{Hz}$, 1H, CH_2N), 3.58-3.52 (d, $J = 13\text{Hz}$, 1H, CH_2N); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 150.67, 136.70, 135.63, 132.01, 131.56, 131.28, 130.77, 130.19, 128.58, 125.83, 124.23 (quaternary aromatic C), 129.56, 128.87, 128.30, 128.22, 128.12, 128.05, 127.50, 127.26, 127.08, 126.67, 126.47, 125.07, 123.21, 123.10, 122.99, 122.87 (aromatic CH); 75.57 (OCH_2Ph), 56.16 (CH_2N); **m/z** (FAB) 518 (M^+), 473 ($\text{M}-\text{NH}(\text{CH}_3)_2^+$); **HRMS** (FAB) Found 518.24732, $\text{C}_{36}\text{H}_{32}\text{NO}$ Requires 518.24839; $[\alpha]_D^{25}(\text{deg}) = -49^\circ$, $c = 0.4$, DCM.

(S)- 10-(*N,N*-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl (33).

Wet palladium hydroxide on carbon (Pd 20%, 0.1g) was added to a solution of (S)- 10-(*N,N*-dimethylaminomethyl)-10'-hydroxy-9,9'-biphenanthryl-10-benzylether (32) (130mg, 0.25mmol) in ethyl acetate (50ml). The dark suspension was transferred to the high-pressure hydrogenation apparatus, and the reduction conducted at room temperature and 15psi pressure for two hours. The suspension was passed through a celite pad with DCM to remove the catalyst, and the solvent removed *in vacuo*. Added to this crude product was a saturated solution of picrolonic acid in diethyl ether (5ml) and the resultant suspension agitated on a sonic bath for 30 minutes. The resultant pale brown precipitate was filtered and subsequently washed with water (10ml) and ethanol (10ml), both chilled to 0°C. The product was thus purified as the picrolonic acid salt, with passage through a neutral alumina plug (10% methanol in DCM) and removal of solvent *in vacuo* giving the *title compound* as a brown solid (42mg, 0.10mmol, 40%).

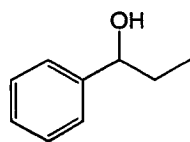


m.p. 210-212°C; **C.H.N.** Found C: 80.74%, H: 4.03%, N: 1.50 C₃₁H₂₅NO Requires C: 87.12, H: 5.85, N: 1.50; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3153 (OH); **$\lambda_{\max}/\text{nm}$** (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 360 (5338), 344 (4804), 303 (20283), 293 (21350), 259 (85934), 228 (41099); **^1H nmr** (250MHz, CDCl₃, δ/ppm) 8.90-8.87 (dd, $J = 2\text{Hz}$ and 6.4Hz , 1H, aromatic), 8.80-8.63 (m, 4H, aromatic), 8.39-8.35 (dd, $J = 2.5\text{Hz}$ and 7Hz , 1H, aromatic), 7.79-7.67 (m, 4H, aromatic), 7.66-7.53 (m, 1H, aromatic), 7.45-7.38 (m, 1H, aromatic), 7.35-7.09 (m, 3H, aromatic), 6.80-6.76 (dd, 1Hz and 8Hz , 1H, aromatic), 6.15 (d, $J = 13\text{Hz}$, N-H), 5.25-5.20 (d, $J = 13\text{Hz}$, N-H), 4.24-4.19 (d, $J = 12.5\text{Hz}$, 1H, CH₂N), 3.89-3.84 (d, $J = 12.5\text{Hz}$, 1H, CH₂N), 2.29 (s, 6H, 2xCH₃); **$^{13}\text{C}\{^1\text{H}\}$ nmr** (63MHz, CDCl₃, δ/ppm) 151.09, 136.09, 133.27, 131.96, 131.75, 131.43, 131.24, 130.53, 130.40, 128.86, 127.42, 118.62 (quaternary aromatic C), 128.09, 126.97, 126.89, 126.76, 126.61, 126.50,

126.39, 126.32, 125.79, 124.41, 124.09, 123.64, 123.34, 123.00, 122.39, 122.24 (aromatic CH), 57.15 (CH₂N), 44.54 (NCH₃); **m/z** (FAB) 428 (M+H)⁺, 427 (M)⁺, 382 (M-NH(CH₃)₂)⁺; **HRMS** (FAB) Found 428.20137, C₃₁H₂₆NO Requires 428.20144; [α]_D²⁵(deg) = -65°, c = 0.4, DCM.

(±)-1-Phenylpropanol (34).

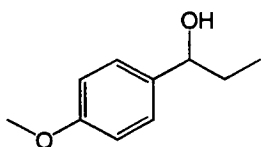
To a dry three necked flask equipped with condenser and pressure equilibrated dropping funnel under an atmosphere of nitrogen, was added magnesium turnings (1.2g, 50mmol), a crystal of iodine and dry THF (50ml). A small amount of ethyl bromide (0.34ml, 4.5mmol) was added and the reaction slowly warmed to 40°C, the heating process paused when the exotherm was observed. The remaining ethyl bromide (3.1ml, 41mmol) was added and the reaction refluxed at 100°C for 1 hour. After this time benzaldehyde (5ml, 45mmol) was added and stirring continued for a further hour at room temperature. The mixture was poured into ice/2M HCl (100ml) and the organics extracted with DCM (3x50ml). The combined organics were washed with water (2x100ml), dried over Na₂SO₄ and the solvent removed *in vacuo*. Purification by vacuum distillation (107-110°C/18mm Hg) to give the *title compound* as a clear liquid.



R_f (DCM) = 0.20; **b.p.** 107-110°C/18mm Hg (lit.¹³¹ 217-221°C); **FTIR** ν_{max} / cm⁻¹ (DCM) 3377 (OH), 3024 (aromatic CH), 2876 (CH); λ_{max} / nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 258 (732), 252 (732); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 7.33-7.27 (m, 5H, aromatic), 4.59-4.53 (t, J = 6.3Hz, 1H, CH), 2.15-2.02 (broad s, 1H, OH), 1.78-1.71 (m, 2H, CH₂), 0.92-0.87 (t, J = 7.4Hz, 3H, CH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 144.45 (quaternary aromatic C), 128.19, 125.80 (aromatic *o*- and *m*-CH), 127.27 (aromatic *p*-CH), 75.78 (CH), 31.70 (CH₂), 9.97 (CH₃); **m/z** (EI) 136 (M)⁺, 117 (M-CH₂CH₃)⁺, 77 (M-CH(OH)CH₂CH₃)⁺; **HRMS** (EI) Found 136.08875, C₉H₁₂O Requires 136.08882.

(±)-1-(*p*-Methoxyphenyl)propanol (35).

To a dry three necked flask equipped with condenser and pressure equilibrated dropping funnel under an atmosphere of nitrogen, was added magnesium turnings (1.2g, 50mmol), a crystal of iodine and dry THF (50ml). A small amount of ethyl bromide (0.34ml, 4.5mmol) was added and the reaction slowly warmed to 40°C, the heating process paused when the exotherm was observed. The remaining ethyl bromide (3.1ml, 41mmol) was added and the reaction refluxed at 100°C for 1 hour. After this time *p*-anisaldehyde (5.5ml, 45mmol) was added and stirring continued for a further hour at room temperature. The mixture was poured into ice/2M HCl (100ml) and the organics extracted with DCM (3x50ml). The combined organics were washed with water (2x100ml), dried over Na₂SO₄ and the solvent removed *in vacuo*. Purification by vacuum distillation (124-127°C/20mm Hg) to give the *title compound* as a clear liquid.



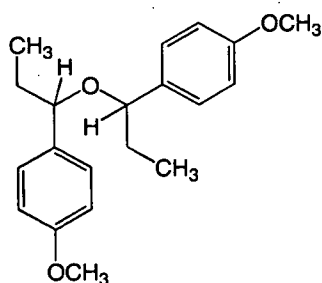
R_f (DCM) = 0.25; **b.p.** 124-127°C/20mm Hg (lit.¹³¹ 252-256°C); **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3381 (OH), 2960 (aromatic CH); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 328 (223), 283 (1337); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 7.25-7.21 (dd, *J* = 0.5Hz and 9Hz, 2H, aromatic), 6.87-6.83 (d, *J* = 9Hz, 2H, aromatic), 4.52-4.47 (t, *J* = 6.7Hz, 1H, CH), 2.21 (broad s, 1H, OH), 1.85-1.63 (m, 2H, CH₂), 0.90-0.84 (t, *J* = 7.5Hz, 3H, CH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 158.72, 136.61 (quaternary aromatic C), 127.03, 113.52 (aromatic CH), 75.38 (CH), 55.05 (OCH₃), 31.57 (CH₂), 10.03 (CH₃); **m/z** (EI) 166 (M)⁺, 151 (M-CH₃)⁺, 107 (M-CH(OH)CH₂CH₃)⁺; **HRMS** (EI) Found 166.09930, C₁₀H₁₄O₂ Requires 166.09938.

General procedure for enantioselective addition of diethylzinc to aldehydes catalysed by chiral catalysts.

15 mol% of the catalyst (0.050M in toluene) were treated with 2.00 equivalents of diethylzinc (1.00M in *n*-hexane) at room temperature. After 30 min of stirring the reaction mixture was adjusted to 0°C and 1.00 equivalent of the aldehyde (1.00mmol) added. Stirring was continued for 24h, the reaction mixture was hydrolysed slowly with 2M HCl (3ml), filtered through a Celite pad and extracted with DCM (3x20ml). After drying over MgSO₄, the solvent was removed *in vacuo*. The crude product was purified first by wet flash chromatography (DCM) and then was bulb-to-bulb distilled. The product was identified by of b.p., ¹H NMR, and mass spectrometry. Optical purity was established by optical rotation and ee's determined by HPLC on chiral phase [CPSilDex CB modified at 10 psi hydrogen]. The absolute configurations were based on the sign of their known optical rotations.

Bis-[1-(4-methoxyphenyl)-propyl]-ether (36).

(±)-1-(*p*-Methoxyphenyl)propanol (35) left for over 24 hours in acidic medium resulted in the formation of the ether bis-[1-(4-methoxy-phenyl)-propyl]-ether, identifiable by a strong aniseed odour. Purification by vacuum distillation (154-158°C/1mm Hg) gave the *title compound* as a clear liquid.

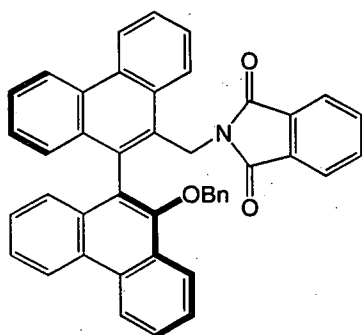


R_f (DCM) = 0.75; **b.p.** 154-158°C/1mm Hg; **λ_{max}/nm** (DCM ε/dm³mol⁻¹l⁻¹) 283 (2800), 276 (3300); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 7.20-7.18 (d, J = 8.5Hz, 2H, aromatic), 7.14-7.11 (d, J = 8.5Hz, 2H, aromatic), 6.93-6.90 (d, J = 8.7Hz, aromatic), 6.82-6.79 (d, J = 8.7Hz, 2H, aromatic), 4.26-4.23 (t, J = 6Hz, 1H, CH), 3.94-3.90 (t, J = 7Hz, 1H, CH), 3.86 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 2.14-1.56 (m, 4H, 2xCH₂), 0.89-0.85 (t, J = 7.4Hz, 3H, CH₃), 0.82-0.78 (t, J = 7.4Hz, 3H, CH₃);

$^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 160.42, 159.76 (quaternary aromatic *p*-C), 136.92, 136.63 (quaternary aromatic C), 128.69, 128.35 (aromatic *o*-CH), 113.97, 113.72 (aromatic *m*-CH), 80.40, 79.60 (CH), 55.62 (*p*- OCH_3), 31.70, 30.01 (CH_2), 10.93, 10.28 (CH_3); **m/z** (EI) 314 (M^+), 217 ($\text{M}-\text{C}_6\text{H}_4\text{OCH}_3$) $^+$; **HRMS** (EI) Found 314.18819, $\text{C}_{20}\text{H}_{26}\text{O}_3$ Requires 314.18819.

(S)-10'-Hydroxy-10-(methylphthalimide)-9,9'-biphenanthryl-10'-benzylether (37).

(S)-10'-Hydroxy-10-(bromomethyl)-9,9'-biphenanthryl-10-benzylether (31) (100mg, 0.18mmol) in THF (20ml) was refluxed with potassium phthalimide (67mg, 0.36mmol) for 2 hours. The solvent was removed *in vacuo* and the product purified by wet flash chromatography (DCM) to give the *title compound* as a white solid (40mg, 0.60mmol, 36%).



R_f (DCM) = 0.65.; **m.p.** 192-196°C; **C.H.N.** Found C: 83.99%, H: 5.54%, N: 1.84%, $\text{C}_{44}\text{H}_{29}\text{NO}_3$ Requires C: 85.30, H: 4.68, N: 2.26; **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3017 (aromatic CH), 2888 (CH stretch), 1707 (imide stretch); **$\lambda_{\text{max}}/\text{nm}$** (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$); ^1H nmr (250MHz,

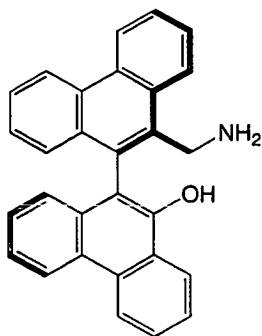
DMSO, δ/ppm) 8.90-8.74 (m, 3H, aromatic), 8.55-8.46 (m, 2H, aromatic), 8.34-8.13 (m, 1H, aromatic), 7.81-7.55 (m, 6H, aromatic), 7.42-7.18 (m, 7H, aromatic), 7.12-6.92 (m, 5H, aromatic), 6.75-6.70 (m, 2H, aromatic), 5.22-5.21 (d, $J = 2\text{Hz}$, 2H, CH_2N), 4.75-4.58 (m, 1H, OCH_2Ph), 4.34-4.26 (m, 1H, OCH_2Ph); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, **DMSO**, δ/ppm) 166.93, 151.15, 136.76, 133.24, 132.08, 131.87, 131.50, 130.45 (quaternary aromatic C), 128.46, 128.16, 127.87, 127.57, 127.45, 127.32, 127.20, 126.72, 126.54, 126.06, 125.93, 125.33, 125.15, 124.45, 123.32, 123.04, 122.89, 122.76, 122.63, 122.29 (aromatic CH), 75.01 (OCH_2Ph), 37.07 (CH_2N); **m/z** (FAB) 619 (M^+), 529 ($\text{M}-\text{CH}_2\text{Ph}$) $^+$, 473

(M-phthalimide)⁺; **HRMS** (FAB) Found 619.21421, C₄₄H₂₉NO₃ Requires 619.21474; [α]_D = -24°, c = 0.4, DCM.

(S)-(-)-10-(Aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (38).

This compound was synthesised by an adaptation of the procedure described by Louise Picken.⁹⁵ Lithium aluminium hydride (16mg, 0.41mmol) in dry THF (5ml) was stirred at room temperature under nitrogen. A solution of (S)-(-)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (**22**) (143mg, 0.35mmol) in dry THF (20ml) was added slowly and stirring continued for 30 minutes with heating at reflux. The mixture was cooled to room temperature, the reaction quenched by the careful addition of 2M NaOH (50ml) and the pH adjusted to 14. The mixture was extracted with DCM (50ml) and the combined organics washed with water (2x30ml). Drying over Na₂SO₄ and removal of the solvent *in vacuo* gave a yellow solid. Initial purification was achieved through the formation of the HCl salt. The HCl salt was formed through the addition of ethereal HCl (30ml) which with agitation formed a pale yellow salt which could be filtered. Passage of this salt through a neutral alumina plug (10% methanol in DCM) and removal of solvent *in vacuo* gave the *title compound* as an off-white solid. Further purification was achieved through the formation of the picrolonic acid salt. This was formed through the addition to this crude product of a saturated solution of picrolonic acid in diethyl ether (5ml) and the resultant suspension agitated on a sonic bath for 30 minutes. The resultant precipitate was filtered and subsequently washed with water (10ml) and ethanol (10ml), both chilled to 0°C. The product was thus purified as the picrolonic acid salt, with passage through a neutral alumina plug (10% methanol in DCM) and removal of solvent *in vacuo* giving the *title compound* as a pale yellow solid (42mg, 0.1mmol, 29%).

m.p. 183-185°C (lit.⁹⁵ 185-186°C); **FTIR** $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3515 (-OH), 3067 (aromatic CH); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 329 (6111), 302 (15267), 258

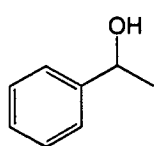


-27°, $c = 0.4$, DCM.

(74809); ^1H nmr (250MHz, DMSO, δ/ppm) 8.94-8.65 (m, 3H, aromatic), 8.60-8.20 (m, 3H, aromatic), 8.15-7.70 (m, 4H, aromatic), 7.64-7.17 (m, 5H, aromatic), 7.14-6.84 (m, 1H, aromatic), 4.65-4.62 (d, $J = 12\text{Hz}$, 1H, CH_2N), 4.03-3.99 (d, $J = 12\text{Hz}$, 1H, CH_2N); m/z (FAB) 400 ($\text{M}+\text{H}$)⁺, 399 (M)⁺, 383 ($\text{M}-\text{OH}$)⁺; HRMS (FAB) Found 400.17014, $\text{C}_{29}\text{H}_{22}\text{NO}$ Requires 400.17012; $[\alpha]_{\text{D}}^{25}(\text{deg}) =$

(±)-1-Phenylethanol (39).

Acetophenone (0.12ml, 1mmol) was added to dry THF (5ml) under nitrogen and cooled to 0°C. To this solution was slowly added 1.2eq. diisobutylaluminium hydride (DIBAL-H, 1M soln. in toluene) (2ml, 2mmol) and stirring continued for 1 hour. The reaction was quenched by the careful addition of saturated Rochelle salt solution and filtered. The organics were extracted with DCM (3x30ml) and the combined organics washed with water (30ml). Drying over Na_2SO_4 , removal of the solvent *in vacuo* and purification by bulb-to-bulb distillation (95-100°C/18mm Hg) gave the *title compound* as a colourless liquid.



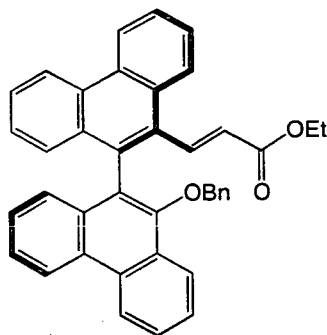
Rf (DCM) = 0.25; b.p. 95-100°C/18mm Hg (lit.¹³¹ 100°C/18mm Hg); FTIR $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3377 (OH), 3024 (aromatic CH), 2876 (CH); $\lambda_{\text{max}}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 238 (11881), 241 (7921), 253 (11881), 258 (14851), 264 (10891); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 7.38-7.25 (m, 5H, aromatic), 4.86-4.78 (q, $J = 6.5\text{Hz}$, 1H, CHOH), 3.18 (broad s, 1H, OH), 1.47-1.45 (d, $J = 6.5\text{Hz}$, 2H, CH_3); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 145.62 (quaternary aromatic C), 128.10, 125.16 (aromatic *o*- and *m*-CH), 127.01 (aromatic *p*-CH), 69.83 (CH), 24.84 (CH_3); m/z (EI) 122 (M)⁺, 107 ($\text{M}-\text{CH}_3$)⁺; HRMS (EI) Found 122.07309, $\text{C}_8\text{H}_{10}\text{O}$ Requires 122.07317.

General procedure for the catalytic reduction of prochiral ketones

Under a nitrogen atmosphere, 20mg of catalyst in dry THF (2ml) was added to 0.25ml a 2M $\text{BH}_3\cdot\text{Me}_2\text{S}$ solution (0.25ml, 0.5mmol) at 0°C . The reaction mixture was stirred for 3 hours at ambient temperature to form an oxazaborolidine catalyst and then was warmed to 50°C . A solution of acetophenaone (0.5mmol) in 2ml dry THF was added dropwise over 1 hour at the same temperature. Stirring was continued for a further 1 hour, after which time the reaction mixture was cooled to 0°C and was quenched with 2M HCl solution (1ml). Ethyl acetate (5ml) was added to extract the product and the organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified first by wet flash chromatography (DCM) and then was bulb-to-bulb distilled. The product was identified by of b.p., ^1H NMR, and mass spectrometry. Optical purity was established by optical rotation and ee's determined by HPLC on chiral phase [CPSilDex CB modified at 10 PSI hydrogen]. The absolute configurations were based on the sign of their known optical rotations.

(S)-Biphenanthryl α,β -unsaturated ethyl ester (40).

To triethylphosphino acetate (380 μl , 2.35mmol) in dry THF (10ml), under a nitrogen atmosphere, was added carefully 1.0M sodium hexamethyldisilazane in THF (2.35ml, 2.35mmol) and the resultant solution stirred for 1 hour. A solution of (S)-10'-hydroxy-10-(carboxaldehyde)-9,9'-biphenanthryl-10-benzyl ether (**24**) (458mg, 0.94mmol) in dry THF (10ml) was added to the phosphonium ylid and the mixture stirred overnight. The reaction was quenched by the addition of water (10ml) and the organics extracted with DCM (2x20ml), combined and dried over Na_2SO_4 . Removal of the solvent *in vacuo* and purification by wet flash chromatography gave the *title compound* as a white solid (400mg, 0.73mmol, 78%).

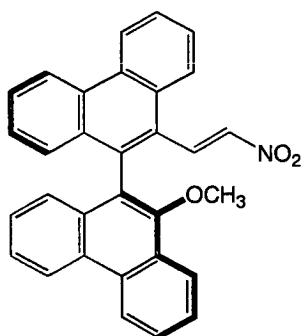


R_f (DCM) = 0.85; **m.p.** 185-187°C; **C.H.** Found C: 85.61%, H: 5.51%, C₃₉H₂₈O₃ Requires C: 86.03, H: 5.15; **FTIR** ν_{max} / cm^{-1} (DCM) 3022 (aromatic CH), 1715 (aryl ester); λ_{max} / nm (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$) 258 (160200), 238 (100392); **¹H nmr** (250MHz, CDCl₃, δ/ppm) 8.97-8.82 (m, 4H, aromatic), 8.39-8.37 (dd, J = 1Hz and 8Hz, 1H, aromatic), 8.32-8.30 (dd, J = 1Hz and 8Hz, 1Hm aromatic), 8.05-8.00 (d, J = 16Hz, 1H, *trans* CH=CHCO), 7.86-7.79 (m, 2H, aromatic), 7.77-7.62 (m, 4H, aromatic), 7.51-7.48 (dd, J = 1Hz and 8Hz, 1H, aromatic), 7.44-7.34 (m, 3H, aromatic), 7.16-7.04 (m, 3H, aromatic), 6.87-6.85 (m, 2H, aromatic), 6.16-6.12 (d, J = 16Hz, *trans* CH=CHCO), 4.87-4.84 (d, J = 11Hz, OCH₂Ph), 4.62-4.59 (d, J = 11Hz, OCH₂Ph), 3.59 (s, 3H, OCH₃); **¹³C{¹H} nmr** (63MHz, CDCl₃, δ/ppm) 167.01 (C=O), 151.67, 137.56, 132.97, 132.88, 132.55, 132.52, 132.05, 131.09, 130.96, 130.53, 128.68, 128.63, 125.18 (quaternary aromatic C), 143.49 (CH=CHCO), 128.46, 128.28, 127.95, 127.78, 127.70, 127.67, 127.54, 127.48, 127.39, 127.17, 126.86, 126.26, 124.14, 123.50, 123.45, 123.29, 123.18 (aromatic CH), 125.27 (CH=CHCO), 75.46 (OCH₂Ph), 51.86 (OCH₃); **m/z** (FAB) 544 (M+H)⁺, 512 (M-OCH₃)⁺, 484 (M-CO₂CH₃)⁺, 452 (M-OCH₂Ph)⁺; **HRMS** (FAB) Found 545.21158, C₃₉H₂₈O₃ Requires 545.31170; $[\alpha]_D^{25}(\text{deg}) = -13^\circ$, c = 0.4, DCM.

(S)-10'-Methoxy-9,9'-biphenanthryl-10-(2-nitroethene) (41).

(S)-10'-Methoxy-9,9'-biphenanthryl-10-carboxaldehyde (**23**) (200mg, 0.48mmol) was dissolved in nitromethane (5ml) with heating and stirred in a closed system under nitrogen. Triethylamine (1ml) was added and stirring continued overnight at room temperature. Solvent was removed *in vacuo* to give yellow foam. Acetic anhydride and a catalytic amount of DMAP were added and the solution was stirred for two hours to generate a bright yellow solution. Unreacted acetic anhydride was removed *in vacuo* and the mixture of unreacted biphenanthryl aldehyde compound and biphenanthryl vinyl nitro

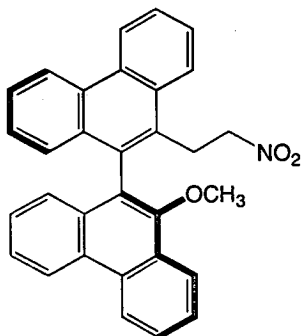
compound was purified by wet flash chromatography (DCM) to give the crude *title compound* as yellow foam.



R_f (DCM) = 0.77; FTIR $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3020 (aromatic CH), 1681 (CHO), 1519, 1342 (vinyl nitro); m/z (FAB) 456 ($M+H$)⁺, 425 ($M-OCH_3$)⁺, 410 ($M-NO_2$)⁺.

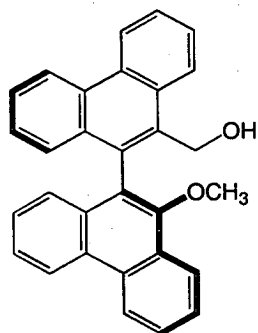
(S)-10'-Methoxy-9,9'-biphenanthryl-10-(2-nitroethane) (26)

Crude biphenanthryl vinyl nitro (**41**) (200mg, 0.49mmol) was added to dry THF (5ml) under nitrogen and cooled to 0°C. To this solution was slowly added 1.2eq. diisobutylaluminium hydride (DIBAL-H, 1M soln. in toluene) (0.5ml, 0.6mmol) and stirring continued for 30 minutes. The reaction was quenched by the careful addition of saturated Rochelle salt solution (10ml) and filtered. The organics were extracted with DCM (3x30ml) and the combined organics washed with water (30ml). Drying over Na_2SO_4 , removal of the solvent *in vacuo* and purification wet flash chromatography (DCM) gave the *title compound* as a pale yellow solid (20mg). The biphenanthryl aldehyde present in the crude starting material was reduced to the primary alcohol (**26**) and was obtained from the above purification in good yield (100mg).



R_f (DCM) = 0.75; **m.p.** 204-207°C; FTIR $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3042 (aromatic CH), 1554, 1380 (NO_2); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 353 (1714), 336 (2286), 304 (20000), 292 (21714), 258 (93714); ^1H nmr (250MHz, $CDCl_3$, δ/ppm) 8.93-8.77 (m, 4H, aromatic), 8.31-8.20 (m, 2H, aromatic), 7.84-7.70 (m,

4H, aromatic), 7.68-7.56 (m, 2H, aromatic), 7.33-7.25 (m, 3H, aromatic), 7.12-7.08 (dd, $J = 1\text{Hz}$ and 8Hz , 1H, aromatic), 4.87-4.77 (m, 1H, CH), 4.56-4.44 (m, 1H, CH), 3.80-3.67 (m, 1H, CH), 3.52-3.40 (m, 1H, CH), 3.44 (s, 3H, OCH_3); $^{13}\text{C}\{^1\text{H}\}$ nmr (63MHz, CDCl_3 , δ/ppm) 151.88, 133.29, 132.03, 131.74, 130.79, 130.26, 130.08, 129.43, 128.36, 124.56 (quaternary aromatic C), 127.63, 127.57, 127.47, 127.16, 127.09, 126.88, 126.75, 126.23, 125.98, 124.00, 123.52, 123.29, 123.01, 122.81, 122.59 (aromatic CH), 73.61 (CH_2NO_2), 60.90 (OCH_3), 28.99 (CH_2); m/z (FAB) 457 (M^+), 411 ($\text{M}-\text{NO}_2$) $^+$; HRMS (FAB) Found 457.16775, $\text{C}_{31}\text{H}_{23}\text{NO}_3$ Requires 457.16779; $[\alpha]_D^{25}(\text{deg}) = +27^\circ$, $c = 0.4$, DCM.

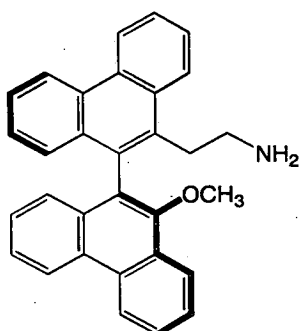


R_f (DCM) = 0.25; **m.p.** 220-222°C; FTIR $\nu_{\text{max}}/\text{cm}^{-1}$ (DCM) 3342 (OH), 3065 (aromatic CH); ^1H nmr (250MHz, CDCl_3 , δ/ppm) 8.95-8.81 (m, 4H, aromatic), 8.66-8.59(m, 1H, aromatic), 8.42-8.38 (m, 1H, aromatic), 7.87-7.78 (m, 4H, aromatic), 7.76-7.59 (m, 2H, aromatic), 7.44-7.26 (m, 4H, aromatic), 5.19-5.08 (t, $J = 11\text{Hz}$, 1H, CH_2OH), 4.74-4.69 (d, $J = 11\text{Hz}$, 1H, CH_2OH), 3.50 (s, 3H, OCH_3), 3.17-3.13 (d, $J = 8\text{Hz}$, 1H, OH); m/z (FAB) 414 (M^+), 397 ($\text{M}-\text{OH}$) $^+$; $[\alpha]_D^{25}(\text{deg}) = -34^\circ$, ($c = 0.4$, DCM).

(S)-(-)-10-(Aminoethyl)-10'-methoxy-9,9'-biphenanthryl (43).

In a three-necked flask equipped with reflux condenser the biphenanthryl nitro compound (42) (15mg, 0.03mmol) was dissolved in dry THF (20ml) with stirring. The solution was cooled in an ice bath to 0°C and 10% palladium-on-carbon (0.1g) was added. NaBH_4 (10mg, 0.25mmol) was added, the ice bath removed, and stirring continued at room temperature for 1 hour. Excess NaBH_4 was decomposed with 2M HCl and the reaction slurry passed through Celite, washed through with DCM (50ml) and then water (10ml). The organics were extracted with DCM (2x50ml) and the combined organics were dried over Na_2SO_4 . Removal of the solvent *in vacuo* gave the crude *title compound* as a

white solid. Initial purification of the amine was achieved through the formation of the HCl salt. The HCl salt was formed through the addition of ethereal HCl (30ml) which with agitation formed an off-white salt that could be filtered. Passage of this salt through a neutral alumina plug (10% methanol in DCM) and removal of solvent *in vacuo* gave the *title compound* as a pale yellow solid. Further purification was achieved through the formation of the picrolonic acid salt. To this pale yellow solid was added a saturated solution of picrolonic acid in diethyl ether (5ml), and the resultant suspension agitated on a sonic bath for 30 minutes. The resultant precipitate was filtered and subsequently washed with water (10ml) and ethanol (10ml), both chilled to 0°C. The product was thus purified as the picrolonic acid salt, with passage through a neutral alumina plug (10% methanol in DCM) and removal of solvent *in vacuo* giving the *title compound* as a pale yellow solid (10mg, 0.02mmol, 70%).



m.p. 150-154°C; **FTIR** $\nu_{\max}/\text{cm}^{-1}$ (DCM) 3120 (NH_3^+); $\lambda_{\max}/\text{nm}$ (DCM $\epsilon/\text{dm}^3\text{mol}^{-1}\text{l}^{-1}$) 304 (12390), 258 (66080); **^1H nmr** (250MHz, CDCl_3 , δ/ppm) 8.97-8.68 (m, 4H, aromatic), 8.48-8.25 (m, 2H, aromatic), 7.87-7.76 (m, 4H, aromatic), 7.74-7.61 (m, 2H, aromatic), 7.38-7.32 (m, 2H, aromatic), 7.16-7.13 (dd, $J = 1\text{Hz}$ and 8Hz , 1H, aromatic), 7.02-7.02 (d, $J = 0.5\text{Hz}$, 1H, aromatic), 4.91-4.82 (m, 1H, CH_2), 4.58-4.50 (m, 1H, CH_2), 3.82-3.72 (m, 1H, aromatic), 3.54-3.46 (m, 1H, aromatic), 3.49 (s, 3H, OCH_3); **m/z** (FAB) 428 ($\text{M}+\text{H}$) $^+$, 411 ($\text{M}-\text{NH}_3$) $^+$; **HRMS** (FAB) Found 428.20140, $\text{C}_{31}\text{H}_{26}\text{NO}$ Requires 428.20144; $[\alpha]_D^{25}(\text{deg}) = +12^\circ$, $c = 0.4$, DCM.

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