Design and Synthesis of a Novel Series of Chiral Auxiliaries

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To my family.

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Abstract

The need for asymmetric synthesis has been outlined and methods for generating asymmetry discussed. The chemistry of the well known 2,2'-disubstituted-1,1'-binaphthyl system was reviewed and a novel chiral auxiliary has been designed around this system. Modifications were implemented to introduce originality into the system and hopefully increase stereoselectivity. These included an increase in steric bulk and the introduction of different co-ordinating functionalities.

A quick and efficient synthesis of a series of novel biphenanthryl compounds has been developed in four steps from commercially available starting material. Resolution was effected at an early stage in the synthesis. The resolution was confirmed by X-ray crystallography and circular dichroism. The absolute configuration of the series has also been assigned.

Investigations into the possible synthesis of a BINAP analogue, the chiral modification of lithium aluminium hydride, use as a chiral auxiliary and the possible synthesis of a chiral dihydropyridine reagent are also discussed.

Contents

Abbreviations

1. Introduction

Abbreviations

AcOH	acetic acid
b	broad
BINAL-H	binaphthol modified $LiAlH_4$
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Binaphthol	2,2'-dihydroxy-1,1'-binaphthyl
Biphenanthrol	10,10'-dihydroxy-9,9'-biphenanthryl
b.p.	boiling point
Bu	butyl
CD	circular dichroism
CIPE	complex induced proximity effect
Config.	configuration
d	doublet
2D	two dimensional
DABCO	1,4-diazabicyclo[2,2,2]octane
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
d.e.	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,3-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
DQF-COSY	double quantum filtered correlated spectroscopy
e.e.	enantiomeric excess

EI	electron impact
Et	ethyl
EtOH	ethanol
FAB	fast atom bombardment
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LDA	lithium diisopropylamide
lit.	literature value
m	multiplet
Me	methyl
MOP	2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
MOP-phen	biphenanthryl analogue of MOP
m.p.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
NADH	nicotinamide adenine dinucleotide
Ph	phenyl
ppm	parts per million
R	alkyl
ROESY	rotating frame Overhauser spectroscopy
s	singlet
S-AMP	(S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
t	triplet
Tbf	tetrabenzo[a,c,g,i]fluorene
Tbfmoc	tetrabenzo[a,c,g,i]fluorenyl-17-methoxycarbonyl
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride

THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	tetramethylsilane
TMSBr	bromotrimethylsilane
X	heteroatom

1. Introduction

1.1. Asymmetric Synthesis

The synthesis of new organic molecules and the improved synthesis of existing ones will always be a major task for the organic chemist. These molecules play an important part in modern life, not least in the area of pharmaceuticals, agrochemicals and other materials which possess useful biological activity. This activity arises through interaction with biomolecules such as enzymes and receptors which are chiral and are present as single enantiomers as they have been synthesised from enantiopure building blocks such as amino acids or carbohydrates. If the organic molecule itself is chiral then the two enantiomers are likely to interact differently with the biomolecule. Thus the enantiomers will probably possess different levels and/or types of activity. Using a racemate of a biologically active compound can be equivalent to using two different compounds.

It is rare for enantiomers to have the same biological activity. In general, one enantiomer is responsible for the biological activity. The other enantiomer, at best, will have no activity but more often than not inhibits the desired effect or exhibits adverse side effects. The most dramatic example is the case of thalidomide, the R-enantiomer is a good sedative but the S-enantiomer exhibits profound teratogenic activity.[1] Pharmacological studies on racemates also leads to unsound and misleading data. To combat this, there are more and more stringent guidelines in many countries for the registration of racemic clinical drugs. Furthermore, regulatory scrutiny has also turned on the agrochemical industry. Production of chiral agrochemicals as a single enantiomer is desirable so as to reduce the environmental impact of the compound.

The problem of synthesising enantiopure compounds can be solved in many ways. Resolution of racemates is the classical solution and is still the main method for industrial scale synthesis. However resolution is often expensive as a suitable resolving agent must be employed and the unwanted enantiomer disposed of (or racemised and recycled). Alternatively, enantiopure starting material may be employed, but this requires that such a molecule is available which possesses the desired absolute configuration and that a convenient and practical route be can developed.

The ideal solution to the problem is asymmetric synthesis. This involves the enantioselective conversion of a prochiral substrate to an optically active product by reaction with a chiral appendage. From an economic viewpoint the chiral appendage (or auxiliary) should be present in catalytic amount. An array of synthetic methods would then be available to the organic chemist to carry out the desired transformation with control of the relative and absolute stereochemistry.

In order to achieve asymmetric synthesis, at least one component of the reaction must be chiral and non racemic. In general, any feature of the reacting system leading to diastereotopic transition states and not enantiotopic transition states could lead to the formation of one diastereoisomer or enantiomer. This follows as the diastereotopic transition states need not be of equal energy. The reaction will then proceed through the lower energy transition state to give an excess of one enantiomer. For a schematic representation see Figure 1.

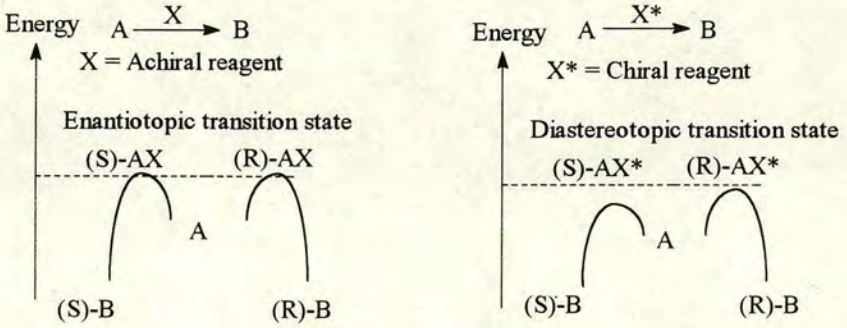

Figure 1. Diastereotopic Versus Enantiotopic Transition States.

Components that may be manipulated include the use of a chiral substrate, reagent, solvent or catalyst. In reality chiral solvents are not much used due to the expense of obtaining sufficient quantities of the solvent and the unpredictable and low levels of stereoselectivity. In principle, the use of a chiral reagent is an excellent approach. Unfortunately, the currently available reagents for this approach often lack the generality and level of stereospecificity required. Stoichiometric amounts are often needed and the reagents are expensive. Enantiomeric enrichment may be difficult due to the formation of the product as a mixture of enantiomers.

One of the most attractive methods for asymmetric synthesis involves the use of a chiral catalyst. For a schematic representation see Figure 2. A small amount of catalyst produces stoichiometric amounts of enantiomerically enriched product. Significant advances have been made in this area in the last few years in academia and in industry. Both enzymes (nature's catalysts) and synthetic catalysts have been used to produce chiral compounds on a large scale economically and with good stereoselectivity.

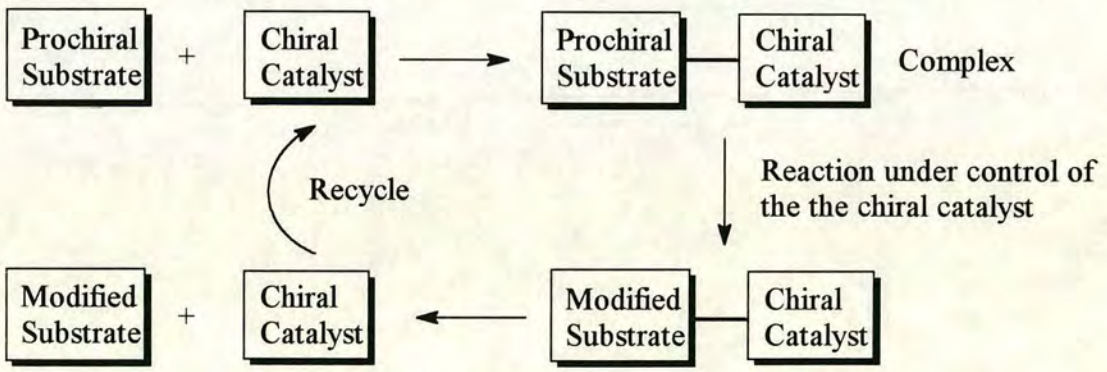

Figure 2. Asymmetric Catalysis Cycle.

Another general approach to asymmetric synthesis involves the use of a chiral auxiliary. The overall strategy is shown in Figure 3 and has clear similarities with the asymmetric catalysis cycle shown in Figure 2. In this approach, the prochiral substrate is attached to a chiral group or auxiliary prior to reaction. The products then become diastereotopic and one should be formed in excess. The major

diastereoisomer can then be isolated and the chiral auxiliary removed to give the chiral product. Stoichiometric amounts of the auxiliary are needed, but it can be recycled.

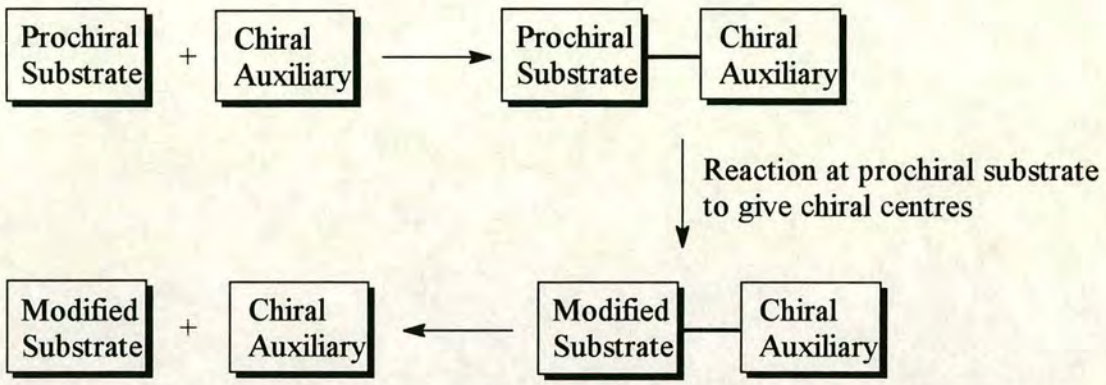

Figure 3. Asymmetric Synthesis Using A Chiral Auxiliary.

Chiral auxiliaries can be used in two ways. Firstly they can be used directly as described in Figure 3. Alternatively they can be attached to a transition metal to produce a chiral catalyst and used as described in Figure 2. Such an auxiliary must be enantiomerically pure, cheap and easy to obtain in sufficient quantity. Control of the stereochemistry of the reaction must be high and predictable and the auxiliary easily separated from the product and recovered. Furthermore, for the auxiliary to be used directly as described in Figure 3, the auxiliary must be easily attached to the substrate and removed without loss of optical purity. It is also advantageous if the major diastereoisomer can be easily purified. At present there are relatively few auxiliaries which meet all these demands.

One of the most successful class of auxiliaries to have been used are the 2,2'-bisubstituted-1,1'-binaphthyls (**1**) (Figure 4), which have shown excellent discriminating properties. It has been almost universally observed that auxiliaries with a C_2 symmetry element direct the stereochemical outcome of a reaction with higher control than those auxiliaries which lack symmetry. This is due to the presence of the C_2 symmetry axis which can serve the important role of dramatically reducing the number of possible competing diastereotopic transition states.[2]

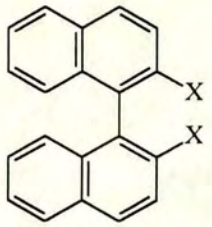

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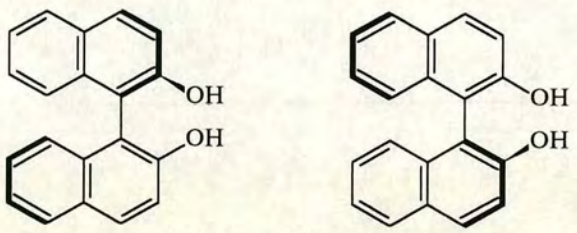
Figure 4. 2,2'-Bisubstituted-1,1'-binaphthyl.

1.2. 2,2'-Dihydroxy-1,1'-binaphthyl

When X equals hydroxyl in Figure 4 the resulting compound is called 2,2'-dihydroxy-1,1'-binaphthyl or binaphthol (**2**) (Figure 5). This is an axially disymmetric, bifunctional molecule and is an ideal chiral ligand. It is conformationally mobile and can accommodate a wide variety of transition metals and transition states through rotation about the C_1-$C_{1'}$ axis and the C-O bonds without introducing significant strain.[3]



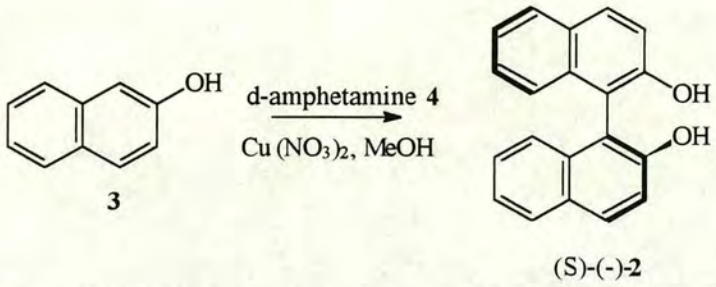
(R)-(+)-**2** (S)-(-)-**2**

Figure 5. (R)- and (S)-2,2'-Dihydroxy-1,1'-binaphthyl.

1.2.1. Synthesis of Binaphthol

Binaphthol (**2**) is normally prepared by the oxidative coupling of 2-napthol (**3**) with ferric chloride[4] or manganese tris(acetylacetonate)[5] to give racemic binaphthol (**2**) which can then be resolved by various methods. A stereoselective synthesis has also been reported using a chiral copper-amine complex in 85% yield and with up to 95% optical purity[6] (Figure 6). The chiral amine, (S)-(+)-α-methylbenzeneethanamine (**4**)

(d-amphetamine) is recovered with no loss of optical purity. However d-amphetamine is a controlled substance and so can not be used on a large scale in most laboratories.



3 (S)-(-)-2

Figure 6. Stereoselective Synthesis of Binaphthol.

1.2.2. Resolution of Binaphthol

There are various reported practical resolutions of binapthol (**2**). These include the enzymatic hydrolysis of the diester of binaphthol (**2**),[7] resolution of the cyclic phosphate of binaphthol (**2**)[8,9] and inclusion complexes with suitable compounds.[10,11] Until recently, the most attractive method for the resolution of both enantiomers of binaphthol (**2**) seems to be the formation of an inclusion complex with (R,R)-1,2-cyclohexanediamine,[10] but commercially available (R,R)-1,2-cyclohexanediamine is expensive. Other resolving reagents such as (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 inclusion complexes with binaphthol (**2**) but they must be synthesised from tartaric acid and are difficult to remove.[11] Toda *et. al.* have recently reported that N-benzylcinchonidium chloride (**5**) (Figure 7) readily forms an inclusion complex with one enantiomer of binaphthol (**2**).[12] This resolution has been optimised by Cai *et. al.* by changing the nature and volume of the solvent used for the resolution.[13] The resolution is outlined in Figure 8. Thus both enantiomers of binaphthol (**2**) can be easily obtained in greater than 95% yield and with greater than 99% optical purity.

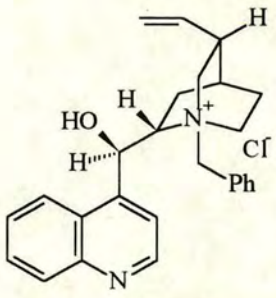


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Figure 7. N-Benzylcinchonidium Chloride.

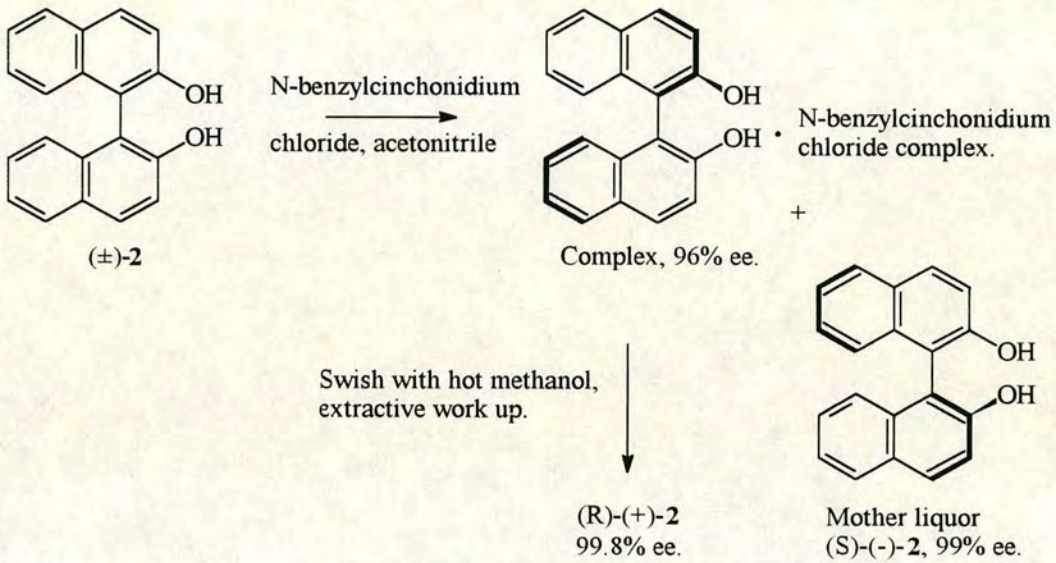
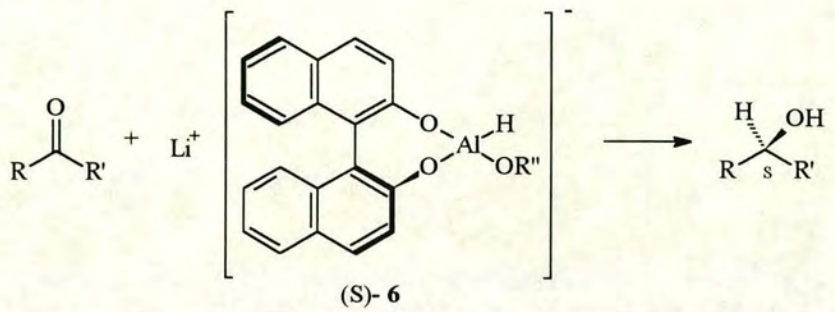


Figure 8. Resolution of Binaphthol.

1.2.3. Enantioselective Reduction of Prochiral Ketones

Outstandingly high enantioselectivities have been reported for the reduction of prochiral ketones using a binaphthol (**2**) modified lithium aluminium hydride reagent (**6**)[3,14,15] (BINAL-H) (**6**). This complex is shown in Figure 9. BINAL-H (**6**) is prepared *in situ* from lithium aluminium hydride, optically pure binaphthol (**2**) and a simple alcohol (R"OH). The simple alcohol is usually ethanol for high enantioselectivities. (R)-BINAL-H (**6**) yields (R)-alcohols, while (S)-BINAL-H (**6**) yields (S)-alcohols. This hydride reagent has been efficiently employed for the asymmetric reduction of a wide variety of unsaturated carbonyl compounds such as aryl, alkenyl and alkynyl ketones.[15] For some representative examples see Table 1.

However, BINAL-H reagents (**6**) are not capable of reducing prochiral dialkyl ketones in high optical yield.[14]



(S)- **6**

Figure 9. BINAL-H Reduction of a Prochiral Ketone.

R	*R'*	*Binaphthol Config.*	*% Yield*	*% e.e.*	*Config. of product*
Ph	Me	R	61	95	R
Ph	Et	S	61	98	S
$PhCH_2$	Me	S	/	13	S
CH≡C	nC_5H_{11}	S	71	84	S
(E)-nC_4H_9CH=CH	nC_5H_{11}	R	91	91	R

Table 1. Reduction of Selected Prochiral Ketones by BINAL-H.

The stereochemical result of the reduction has been rationalised by a mechanism involving a six membered, chelating transition state (Figure 10). Using acetophenone as a model substrate, it was presumed that the transition state (**7**) was favoured over (**8**). This was due to the unfavourable interaction of the larger phenyl group with the binaphthyl system in (**8**), resulting in the formation of the alcohol with the desired R configuration.[3]

It has also been proposed that electronic factors must be taken into account when discussing the enantioselectivity. This view has been supported by the fact that a high

level of enantioselectivity can only be achieved with prochiral compounds containing sp or sp^2 hybridised carbons.[14]

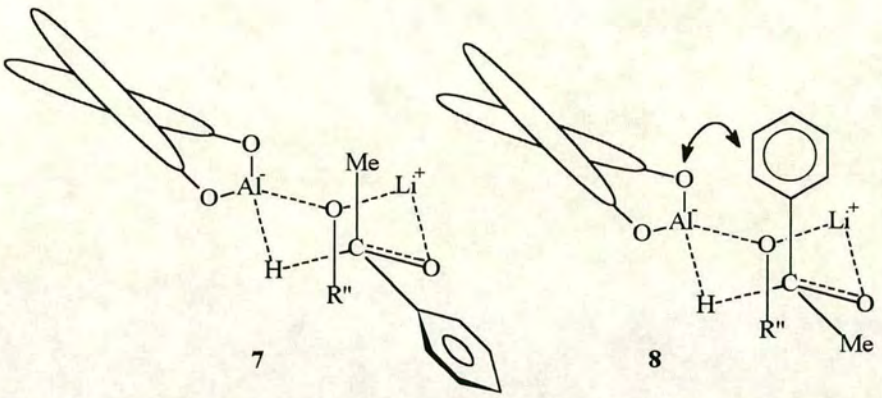


Figure 10. Possible Transition States for the Reduction of Acetophenone.

1.2.4. Chiral Organotitanium Complexes

Chiral organotitanium complexes have been prepared using binaphthol (**2**) as the chiral modifier and have been used as catalysts for various reactions. Three types of complex have been synthesised (**9**),[16] (**10**),[17,18] and (**11**)[18] (Figure 11).

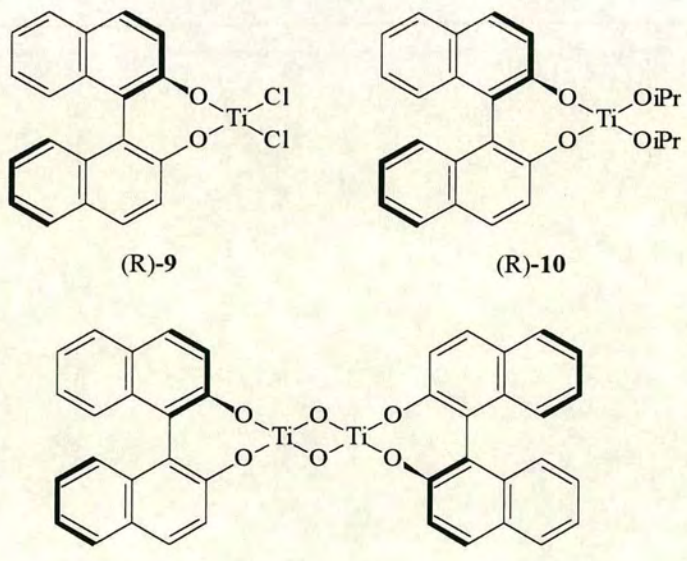


Figure 11. Organotitanium Complexes.

Complexes (**9**) and (**10**) are prepared *in situ*, while complex (**11**) is a second generation complex. That is, it is formed by the complete hydrolysis of complex (**10**), followed by the azeotropic removal of 2-propanol.[18] The resulting complex is a moisture tolerable enantioselective catalyst. Similar treatment of complex (**9**) also results in the formation of (**11**).[19]

These types of complex have been used to catalyse the glyoxylate-ene reaction with high enantioselectivity.[16] For example, complex (**11**) catalyses the ene reaction between α-methylstyrene (**12**) and methyl glyoxylate (**13**) in 98% e.e.[19] (Figure 12).

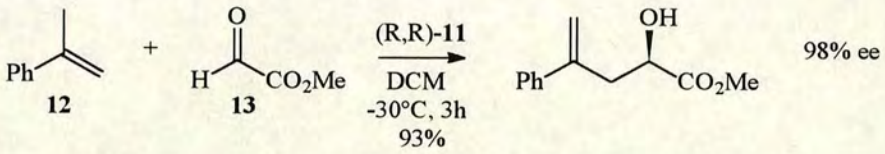


Figure 12. An Asymmetric Glyoxylate-Ene Reaction.

Similar C-C bond forming reactions have also been carried out. These include the Mukaiyama aldol reaction of ketone silyl enol ethers with glyoxylate esters.[20] Ene type products are formed with control of the absolute and relative stereochemistry. For example, the reaction between the trimethylsilyl enol ether of 3-pentanone (**14**) and methylglyoxylate (**13**) in the presence of 5% (R)-**9** proceeds in 58% yield to give (**15**) after careful work up. Hydrolysis of (**15**) gave the β-hydroxyketone (**16**) as the sole stereoisomer (Figure 13).

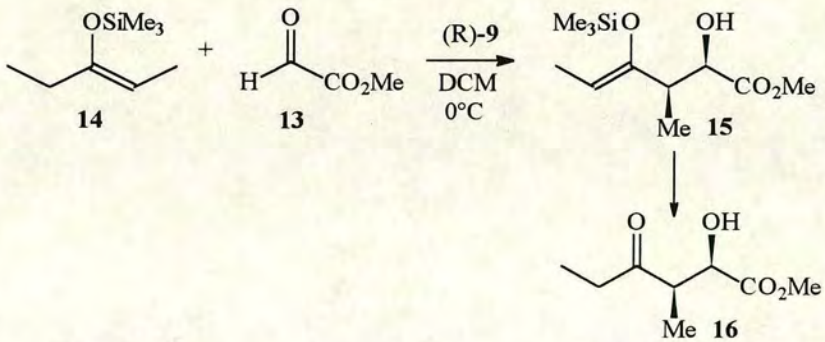


Figure 13. An Asymmetric Mukaiyama Aldol Reaction.

Another process successfully undertaken asymmetrically is the Diels-Alder cycloaddition.[21] Molecular sieve free (R)-**9** gives good endo-selectivity and enantioselectivity in the hetero Diels-Alder cycloaddition of glyoxylates and dienes. For example, methyl gyloxylate (**13**) reacts with 1-methoxy-1,3-butadiene (**17**) in 56% yield (Figure 14).

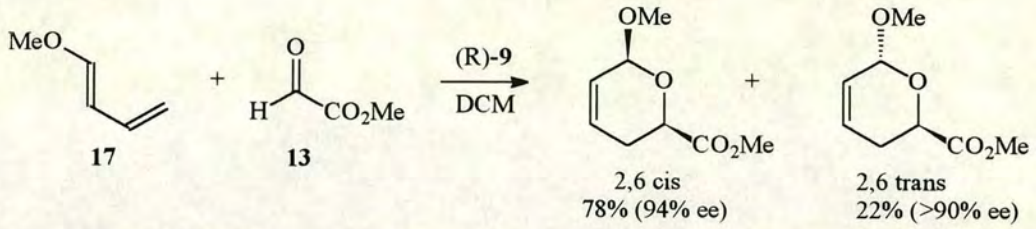


Figure 14. An Asymmetric Diels-Alder Cycloaddition.

The synthesis of homo-allylic alcohols is also catalysed by organotitanium complexes of this type. Both complexes (**9**) and (**10**) have been used successfully to catalyse the reaction between aldehydes and allyl stannanes in good yield and with good enantioselectivity.[17,22] For example, (R)-**10** catalyses the reaction between benzaldehyde (**18**) and allyltributyltin (**19**) in 88% yield and with 99% e.e. (Figure 15). It should be noted that in this reaction that diisopropoxytitanium dichloride alone gives no reaction[22] and that complex (**11**) is not as effective[17] under the same conditions. The same reaction has also been catalysed by a chiral silver complex with (S)-binaphthol (**2**) as the chiral ligand, again with good yield (88%) and enantioselectivity (96% e.e.) to give the (S)-alcohol.[23]

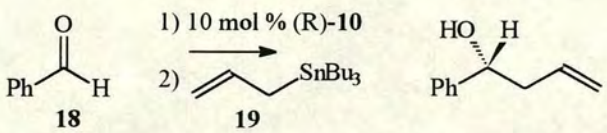


Figure 15. Aymmetric Synthesis of a Homo-Allylic Alcohol.

1.2.5. Binaphthol as a Chiral Auxiliary

Until recently, little investigation into the potential use of binaphthol (**2**) as a chiral auxiliary has been undertaken. Tanaka *et. al.* have studied in detail the alkylation of the enolate generated from binaphthyl phenylacetate (**20**).[24] The ester was easily prepared by the condensation of phenylacetic acid and binaphthol (**2**) in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide. The alkylation was carried out using lithium diisopropylamide as the base and THF/HMPA as the solvent system giving (**21**) with good diastereoselectivity. The diastereoselectivity increases with the bulkiness of the alkylating agent (up to 92% d.e. for isobutyl iodide). Acidic or basic hydrolysis gave the corresponding acid (**22**) with no loss of optical purity (Figure 16).

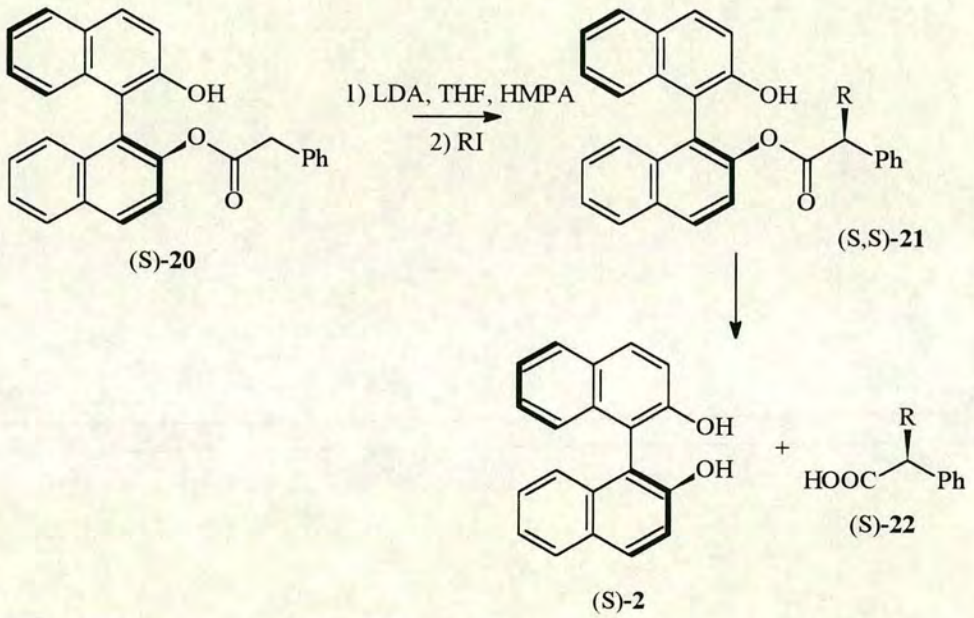
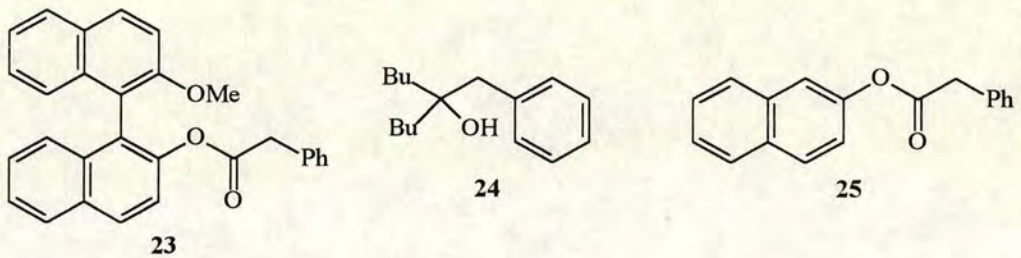


Figure 16. Alkylation of (S)-Binaphthyl Phenylacetate.

Although good diastereoselectivity was observed for bulky alkylating agents, poor selectivity was observed for small alkylating agents. In particular, an increase in the diastereoselectivity for methylation was important since 2-arylpropionic acids constitute an important class of non-steroidal anti-inflammatory drugs. Switching the base from lithium diisopropylamide to n-butyllithium achieved this. An increase in diastereoselectivity from 72% to 92% was obtained for this methylation.

This was a surprising result as n-butyllithium is normally too nucleophilic a base to generate enolates from esters. This surprising reactivity was due to a complex induced proximity effect (CIPE) involving the phenolic hydroxyl group as a directing element. When racemic ester (**23**), which possesses a methoxy group was used, a mixture of diastereoisomers was obtained in lower yield than before, along with about 20% of (**24**), arising from nucleophilic attack of n-butyllithium on the ester carbonyl group. This suggests that the hydroxyl group plays a crucial role in the successful generation of the enolate. When naphthyl ester (**25**), which lacks the upper naphthyl ring of binaphthol (**2**), was alkylated in the presence of 1 equivalent of 2-naphthol (**3**) (THF, 2 equivalents of n-butyllithium), a 23% yield of (**24**) was formed confirming the necessity of an intramolecular hydroxyl group.



23 **24** **25**

Figure 17. Structures of (23), (24), and (25).

Trapping experiments on enolates derived from binaphthyl esters have shown the predominant formation of the (E)-enolate. The amount of (E)-enolate increases slightly with the use of n-butyllithium as the base instead of lithium diisopropylamide. Using esters with substituents other than a hydroxyl group at the $C_{2'}$ position, for example (**23**), there was no great difference in the E:Z ratio of the enolates formed. This indicates that the hydroxyl group plays a crucial role in the predominant formation of the (E)-enolate in THF under kinetic control.

Figure 18 illustrates the plausible transition states leading to (E)- and (Z)-enolates, (**26**) and (**27**) from binaphthyl ester (**20**). In transition state (**28**), the CIPE of the phenolate provides a resident site for the second molecule of n-butyllithium which will abstract the pro-S hydrogen to give the (E)-enolate. The alternative transition state

(**29**) suffers from considerable steric repulsion. The nucleophilic carbon of the (E)-enolate is more open on the si-face than the re-face which is hindered by the attached naphthyl ring. Thus electrophilic attack takes place preferentially from the si-face of the (E)-enolate to give the observed (S,S) isomer (**21**).

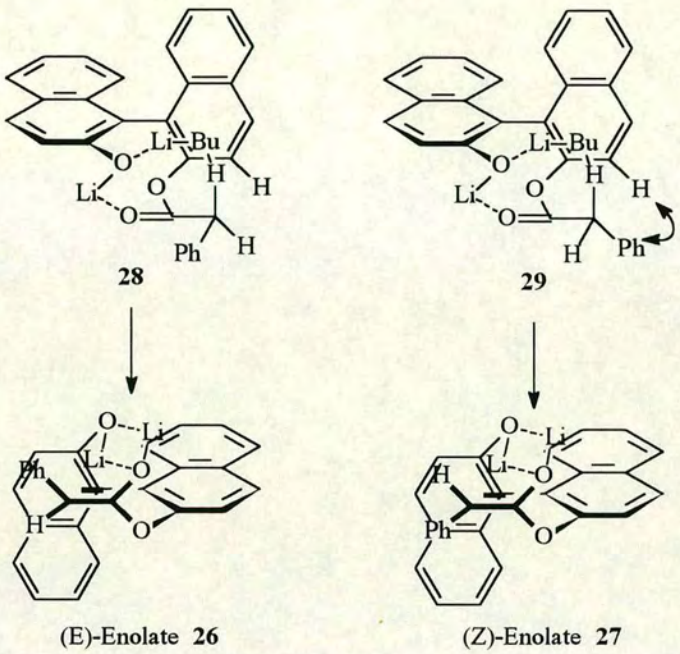


Figure 18. Plausible Transition States 28 and 19 leading to E and Z Enolates Respectively.

This methodology has been used to synthesise (S)-(+)-naproxen (**30**) and (S)-(+)-suprofen (**31**) (Figure 19) which are part of an important class of nonsteroidal anti-inflammatory drugs.

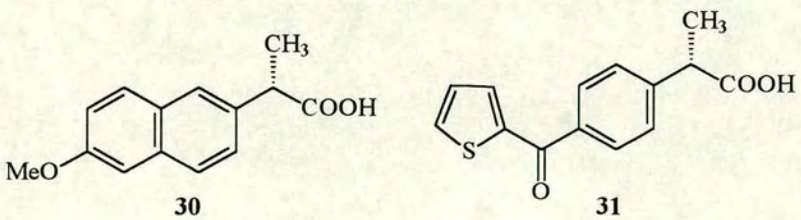


Figure 19. (S)-Naproxen and (S)-Suprofen.

Binaphthyl esters of α,β unsaturated carboxylic acids are also alkylated at the α position with accompanying double bond migration using lithium diisopropylamide in THF/HMPA. No alkylated product was observed without HMPA, probably due to internal proton return. This was confirmed by the isolation of the rearranged product in 67% yield. High diastereoselectivity was observed (9:1) regardless of the alkylating agent used. The alkylation of binaphthyl crotonate (**32**) is outlined in Figure 20.

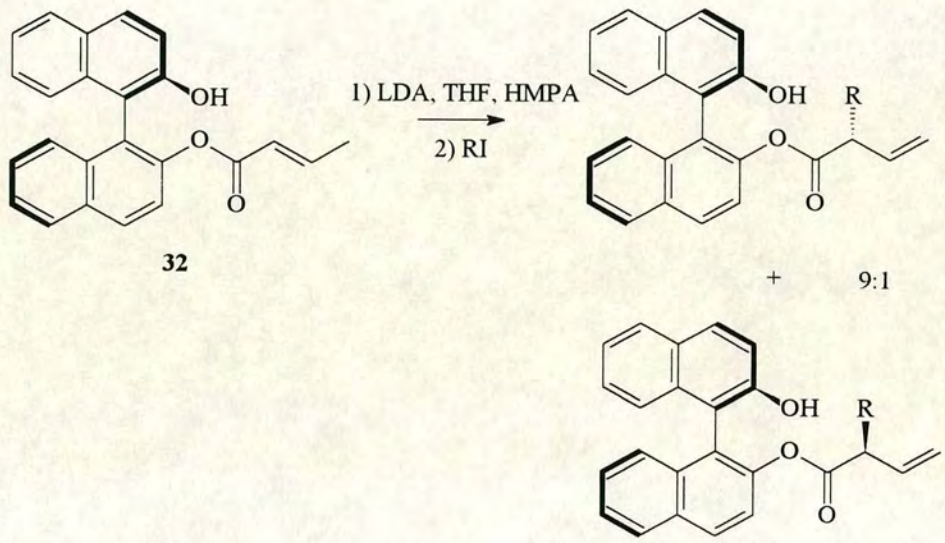
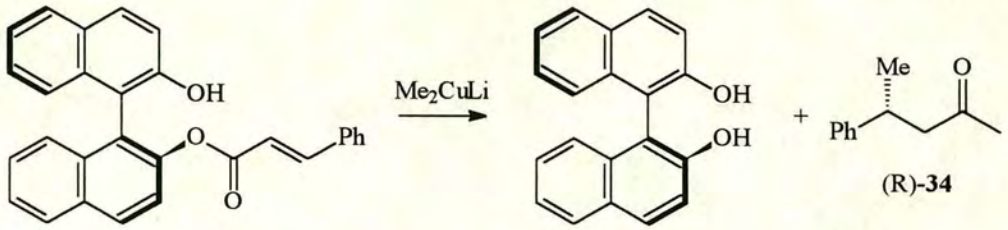


Figure 20. Alkylation of Binaphthyl Crotonate.

Organometallic reagents undergo a 1,4 addition onto binaphthyl esters of α,β unsaturated carboxylic acids followed by a 1,2 addition to the carbonyl group. For example, the reaction between (S)-**33** and lithium dimethylcuprate gives (R)-4-phenyl-2-pentanone (**34**) and proceeds in 84% yield and with 87% enantioselectivity (Figure 21). This transformation constitutes a new one pot synthesis of optically active β-substituted ketones in good yield and enantioselectivity.

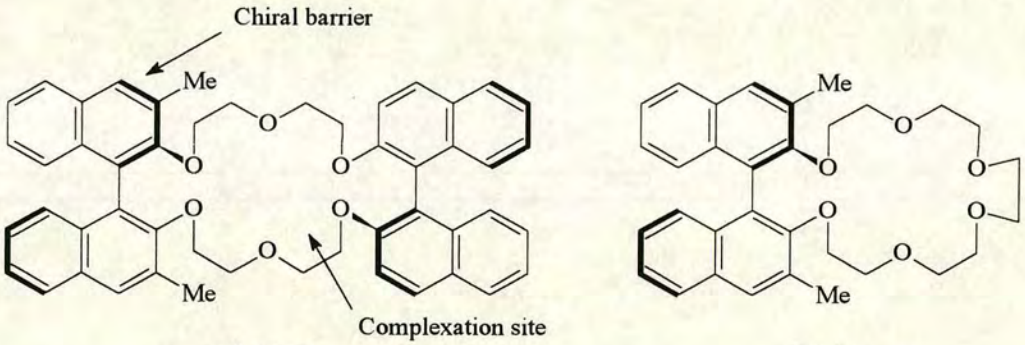


(S)-**33** (S)-**2** (R)-**34**

Figure 21. Successive 1,4 and 1,2 Addition of Lithium Dimethylcuprate to (S)-33.

1.2.6. Crown Ethers

Many crown ethers containing the binaphthyl moiety have been synthesised.[25] The binaphthyl moiety is chiral and the aryl rings are potential chiral barriers that should impart chiral recognition on the crown ether toward appropriate guest compounds. Additionally substituents on the binaphthyl ring can be manipulated so as to increase the chiral barrier, increase solubility or to bond the crown ether to a solid support.[26]



(R,R)-**35** (R)-**36**

Figure 22. Binaphthyl Containing Crown Ethers.

High chiral recognition by optically active hosts such as (R,R)-**35** (Figure 22) has been observed in the complexation of salts of primary amine racemates. Substances such as α-phenylethylamine, amino esters and amino acids have been studied as guests in distribution experiments between an aqueous layer of lithium hexafluorophosphate and a chloroform layer containing the optically pure host. The hosts are insoluble in the aqueous layer and the guest salts are insoluble in the organic layer in the absence

of the host. When present, the host selectively complexes, lipophilises and draws into the organic layer one guest enantiomer more than the other. After equilibrium, the layers are separated and the optical purity determined. In this approach to resolution, (R,R)-**35** is the most generally successful host developed thus far.[27]

Complexes of crown ethers, (**35**) and (**36**) and the potassium bases, potassium amide or potassium tert-butoxide, catalyse asymmetric Michael addition reactions to give products with 60-99% e.e..[28] For example, the reaction between methyl-1-oxo-2-indanecarboxylate (**37**) and methyl vinyl ketone (**38**) in the presence of (S,S)-**35** and potassium tert-butoxide gives the corresponding Michael adduct (**39**) in 48% yield and with 99% e.e. (Figure 23).

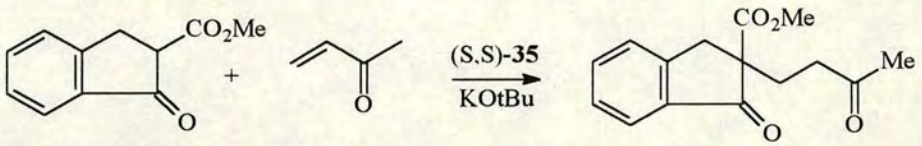


Figure 23. An Asymmetric Michael Addition Reaction.

1.3. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

When, in Figure 1, X = diphenylphosphino the resulting compound is called 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl[29] or BINAP (**40**) (Figure 24). Since its introduction in the early 1980s BINAP has become one of the most successful chiral ligands for catalytic asymmetric synthesis.[30]

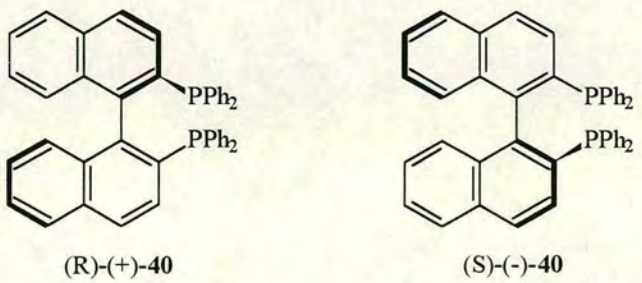


Figure 24. (R)- and (S)-Bis(diphenylphosphino)-1,1'-binaphthyl.

BINAP is a fully arylated, symmetrical chiral C_2 diphosphine ligand. Its full aromaticity imparts a higher stability than found for aliphatic phosphines. This also gives a greater steric influence, provides polarisability and enhances the Lewis acidity of the metal complex. BINAP (**40**) is a conformationally flexible molecule and so can accommodate a wide variety of transition metals by rotation about the C_1-$C_{1'}$ pivot and C_2 or $C_{2'}$-P bonds without a serious increase in torsional strain. The chirality which was originally due to the binaphthyl skeleton is then passed on to the other transition metal co-ordination sites through phosphorus-metal interaction.

1.3.1 Synthesis of BINAP

The first reliable synthesis of BINAP (**40**) was reported in 1980,[29] with the development of a more convenient route in 1984.[31] This involved the resolution of the racemic diphosphine oxide (**41**) by camphorsulfonic acid or 2,3-O-dibenzoyl tartaric acid followed by reduction with trichlorosilane[32,33] (Figure 25).

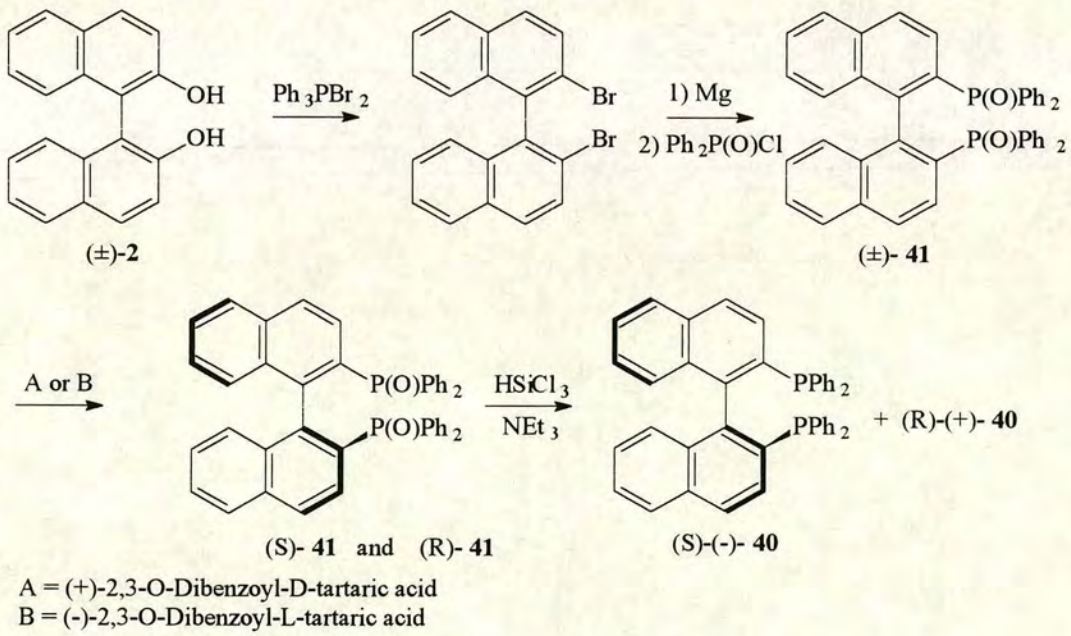


Figure 25. Synthesis of BINAP (Number 1).

This route is too inefficient for the synthesis of large quantities of BINAP (**40**). The high temperature bromination reaction (240-320°C) proceeds with the evolution of hot hydrogen bromide gas and the resolution is carried out at a late stage in the synthesis. These drawbacks make the chemistry dangerous and troublesome to carry out on a very large scale.

Cai *et. al.* have developed a simple practical synthesis of BINAP (**40**)[34] starting from binaphthol (**2**) which has been resolved using N-benzylcinchonidium chloride (**5**) (Figure 8). Each enantiomer is converted to its triflate (**42**) which is then converted directly into optically active BINAP (**40**). This is achieved using a novel nickel catalysed diphenylphosphine coupling reaction (Figure 26). As a result of this methodology BINAP (**40**) is now readily available in a simple resolution and a two step synthesis from binaphthol (**2**) in 70% overall yield, greatly improving its availability and synthetic utility.

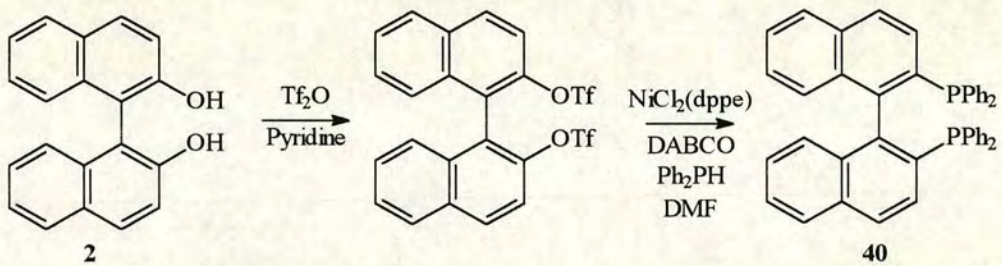


Figure 26. Synthesis of BINAP (Number 2).

BINAP (**40**) is normally used in conjunction with rhodium and ruthenium. Some common complexes are shown in Figure 27. The scope of rhodium catalysed reactions are limited. On the other hand BINAP-ruthenium chemistry has unprecedented broad utility,[30,35] especially the ruthenium dicarboxylate complexes (**42**).

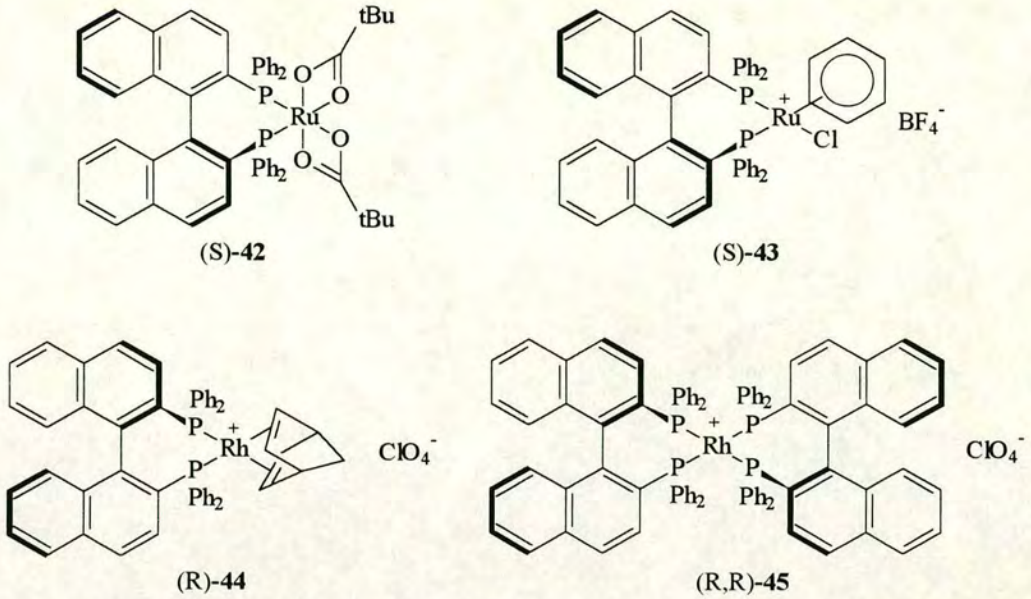


Figure 27. Common BINAP-Metal Complexes.

1.3.2. Asymmetric Hydrogenation of Olefins

Homogeneous asymmetric hydrogenation of olefins using a chiral phosphine-rhodium complex was first carried out in 1968.[36,37] This has been developed to include BINAP (**40**) as one of the possible chiral phosphine ligands.

BINAP-ruthenium complexes of type (**42**) hydrogenate prochiral α,β- or β,γ-unsaturated carboxylic acids to give optically active saturated carboxylic acids in 85-97% e.e.[38] (Figure 28). The reactive intermediates are thought to be chelate complexes in which the carboxylate and the olefinic double bond co-ordinate to a ruthenium metal centre. The sense and extent of the asymmetric induction are highly dependent on the substitution pattern and the reaction conditions. (S)-Naproxen (**30**) is obtainable in 97% e.e. by hydrogenation.

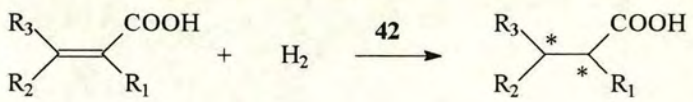


Figure 28. Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Acids.

Neutral functionalities also exert a directing effect through heteroatom co-ordination to the ruthenium. Enamide (**46**) is hydrogenated enantioselectively to an amide in the presence of a (R)-BINAP-ruthenium complex in 79-92% e.e..[39] With a (R)-BINAP-rhodium complex the same enamide (**46**) is hydrogenated to give the opposite enantiomer in 92-100% e.e.[31] even though the stereochemistry of the BINAP ligand is the same (Figure 29). Here the amide group is directing the reactivity and the selectivity.

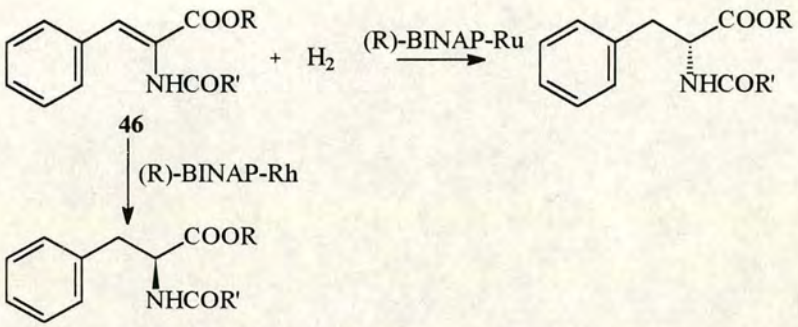


Figure 29. Asymmetric Hydrogenation of an Enamide.

BINAP-ruthenium complexes of type (**42**) catalyse the highly enantioselective hydrogenation of N-acyl-(Z)-1-alkylidene-1,2,3,4-tetrahydroisoquinolines (**47**) as depicted in Figure 30.[40] (R)-BINAP complexes give the (R)-isomers in 59-100% e.e. while the (S)-BINAP complexes give the opposite configuration and proceed with lower enantioselectivity. This enantioselective hydrogenation forms the basis of a general synthesis of the isoquinoline alkaloids. This hydrogenation, followed by a Grewe type annulation is a new route to optically active morphine (**48**) (Figure 31) and its analogues.

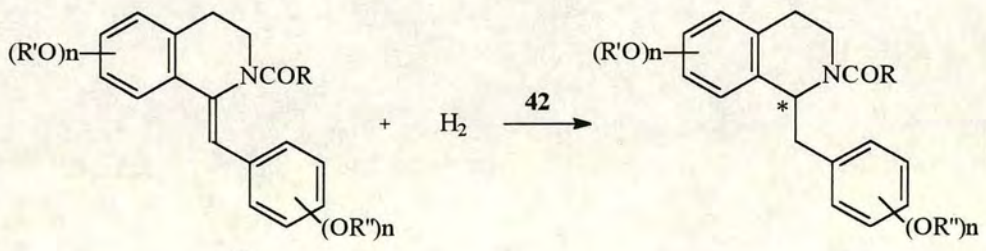


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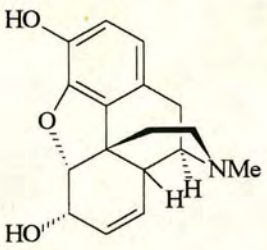
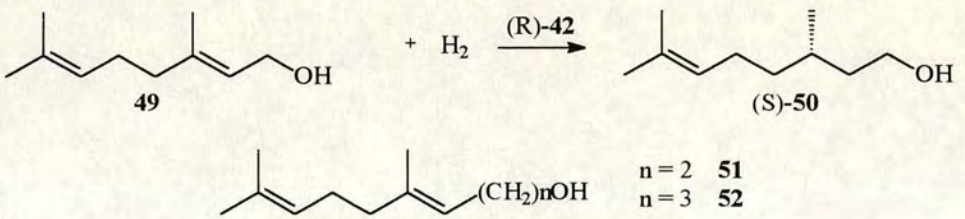
Figure 30. Asymmetric Hydrogenation of N-Acyl-(Z)-1-alkylidene-1,2,3,4-tetrahydroisoquinolines.



48

Figure 31. Morphine.

Allylic alcohols are another class of substrates that can be hydrogenated enantioselectively.[41] One example is the enantioselective hydrogenation of geraniol (**49**) to (S)-citronellol (**50**) in 96-99% e.e. (Figure 32). Either isomer is obtainable by changing the olefin geometry or the BINAP chirality. Homogeraniol (**51**) is also hydrogenated with high enantioselectivity while the bis-homologue (**52**) is inert to the hydrogenation.



49 **(S)-50**

Figure 32. Asymmetric Hydrogenation of Geraniol.

In the presence of a ruthenium-(R)-BINAP complex of type (**42**), the allylic alcohol (**53**), with the chiral azetidinone moiety at C_2 is hydrogenated enantioselectively to give (**54**) and (**55**) in a 99.9:0.1 ratio[42] (Figure 33). This when compared to the (S)-BINAP complex which gives (**54**) and (**55**) in a 28:72 ratio shows that the high diastereoselectvity is due to the efficiency of the chirality transfer from the (R)-BINAP complex to the olefinic face (catalyst control) and also the influence of the nearby chiral azetidinone backbone (substrate control) The diastereoselective hydrogenation of this system provides a powerful tool for the creation of the 1β-methyl structure of the carbapenems.

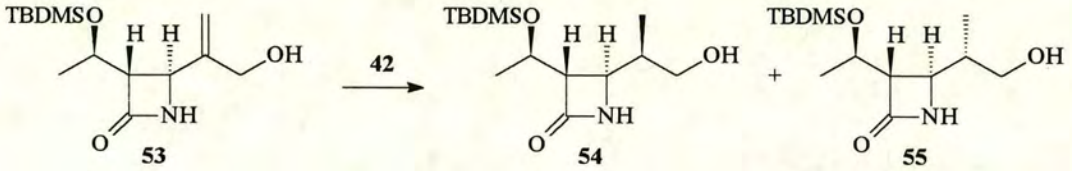


Figure 33. Asymmetric Hydrogenation of a Chiral Allylic Alcohol.

1.3.3. Asymmetric Hydrogenation of Ketones

Homogeneous asymmetric hydrogenation using ruthenium-BINAP complexes can be extended to ketones.[43] A general scheme is given in Figure 34. In general halogen containing complexes (**43**) are better than the dicarboxylate complexes (**42**). A wide range of ketonic substrates can be hydrogenated and functionalities acting as directing groups include dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, thiocarbonyl, (dialkylamino)carbonyl and carboxyl. Neighbouring halogen atoms affect the rate and the stereochemical outcome of the reaction.

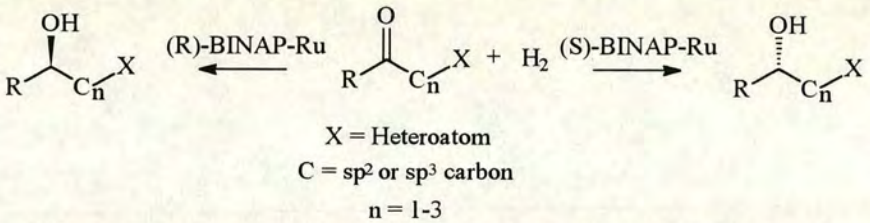


Figure 34. Asymmetric Hydrogenation of Prochiral Ketones.

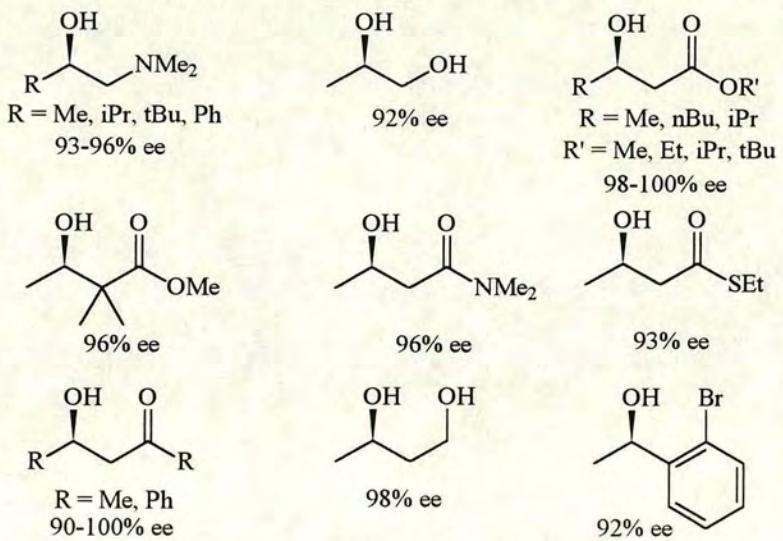
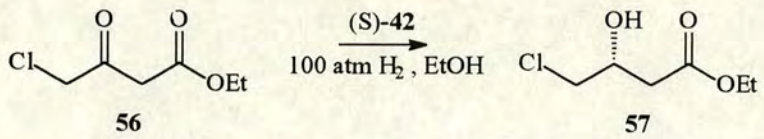


Figure 35. Examples of Products.

Examples of products formed are given in Figure 35. Thus a wide variety of ketonic substrates are hydrogenated in either asymmetric orientation with nearly 100% yield and up to 100% e.e..

The generality of Figure 34 suggests that the stereodifferentation is mainly due to the co-ordination of the carbonyl oxygen and the heteroatom X to a ruthenium atom giving a five to seven membered ring prior to hydrogen transfer. Thus in a bifunctional keto substrate only moderate stereoselectivities should be obtained due to the competing effects of 2 heteroatoms in the same molecule. For example, the γ-chloro-β-keto ester (**56**) is hydrogenated in the presence of a ruthenium-(S)-BINAP complex (S-**42**) under standard conditions to give (**57**) in less than 70% e.e. (Figure 36). Suprisingly, the same hydrogenation, when carried out at 100°C is complete within five minutes and proceeds with 97% e.e..[44]



56 **57**

Temperature	*Time*	*% e.e.*
Room Temperature	10-40 h.	<70
100°C	5 min.	97

Figure 36. Hydrogenation of a γ-Chloro-β-keto Ester.

Stereogenic centres installed in the ketonic substrate cause unique asymmetric induction. For example pentane-2,4-dione (**58**), a symmetrical β-diketone, undergoes asymmetric hydrogenation with a ruthenium-BINAP complex as a catalyst.[43,45] This yields the (R,R)-diol (**59**) and the meso-diol (**60**) in a 99:1 ratio. The reaction proceeds via the (R)-hydroxy ketone (**61**) which is formed in 98.5% e.e.. The (S)-hydroxy ketone is mostly removed by conversion to the meso-diol (**60**) (Figure 37).

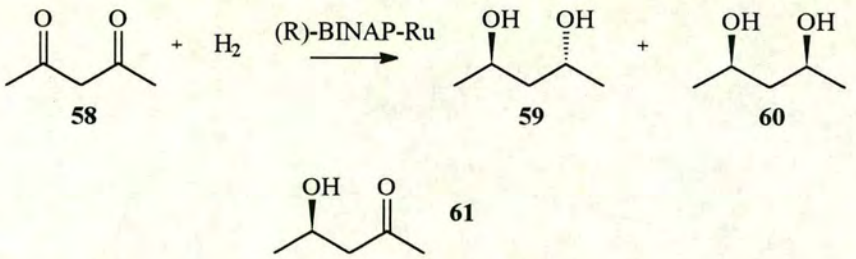


Figure 37. Asymmetric Hydrogenation of Pentane-2,4-dione.

1.3.4. Enantioselective Allylic Hydrogen Shift

Enantioselective allylic hydrogen shift is possible when catalysed by cationic rhodium-BINAP complexes. One example is the asymmetric isomerisation of N,N-diethylnerylamine (**62**) or N,N-diethylgeranylamine (**63**) to give citronellal-(E)-enamine (**64**) in 95% e.e.[46] (Figure 38). This process is now working on a 7 ton scale and is a key step in the production of (-)-menthol (**65**) (Figure 39).

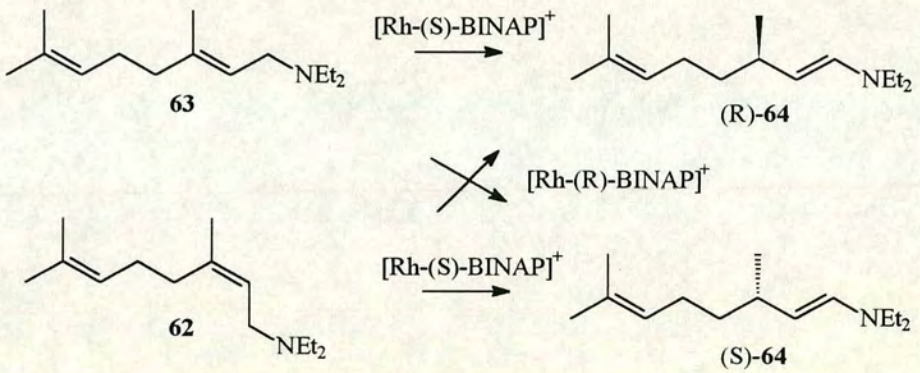


Figure 38. Enantioselective Allylic Hydrogen Shift.

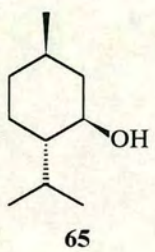


Figure 39. Menthol.

The isomerisation of allylic amines is believed to occur by a nitrogen triggered mechanism[47] (Figure 40). The cationic rhodium-BINAP complex differentiates efficiently the enantiotopic C_1 hydrogens of the allylamine through interaction with the adjacent nitrogen atom. The initial complex (**67**) is generated by ligand exchange between the substrate and the bis-solvent complex (**66**). The square planar complex (**67**) then undergoes a four centred hydride elimination to give a transient iminium rhodium hydride complex (**68**). Hydride delivery from the rhodium to C_3 of the ligand gives the η^3-enamine complex (**69**) which serves as the chain carrier in the actual catalytic cycle and has an aza allyl structure. Liberation of the enamine product from (**70**) is followed by immediate hydride elimination to give (**68**) and thus the catalytic cycle is finished.

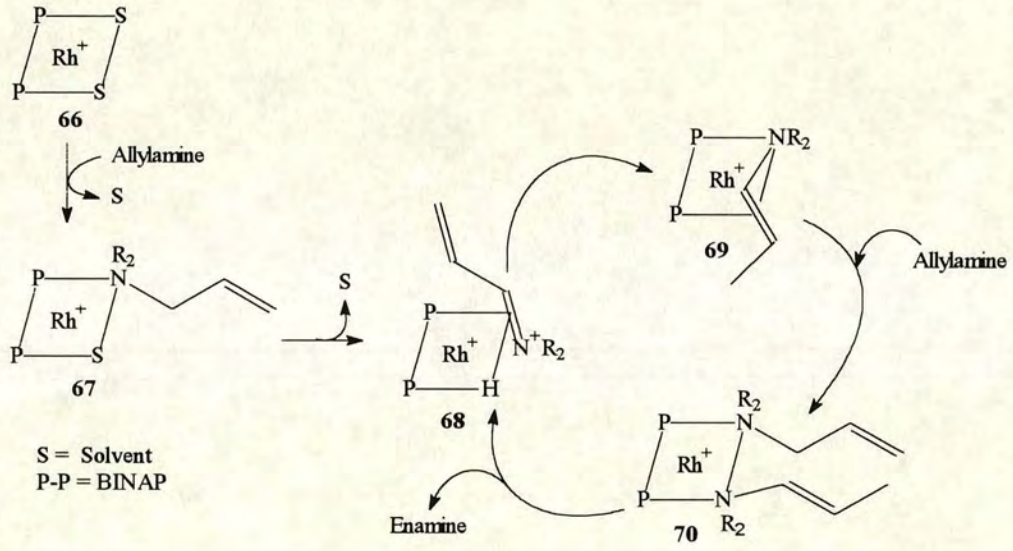
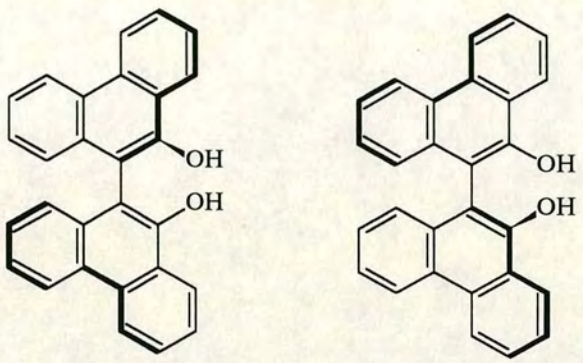


Figure 40. Mechanism for the Isomerisation of Allylic Amines.

1.4. The 9,9'-Biphenanthryl Moiety

A related system to the binaphthyl system is the biphenanthryl system. A C_2 axis of symmetry is also present in the molecule and so the system is chiral. The most researched biphenanthryl compound is 10,10'-dihydroxy-9,9'-biphenanthryl (biphenanthrol) (**71**), the dibenzo derivative of binaphthol (**2**) (Figure 41).

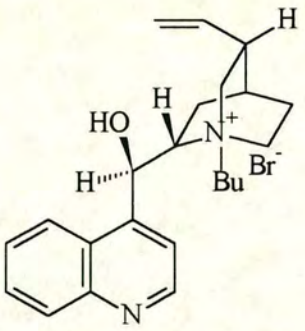


(R)-(+)-**71** (S)-(-)-**71**

Figure 41. (R)- and (S)-10,10'-Dihydroxy-9,9'-biphenanthryl.

1.4.1. Synthesis and Resolution of Biphenanthrol

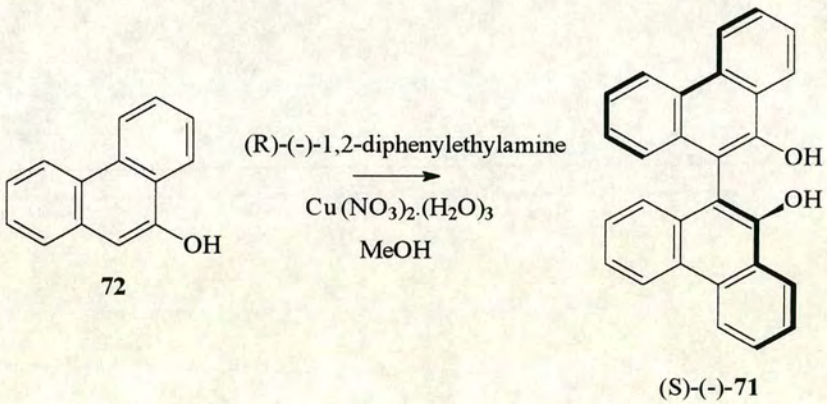
Racemic biphenanthrol (**71**) is usually prepared by the oxidative coupling of 9-phenanthrol (**72**) in the presence of manganese tris(acetylacetonate).[48] Various resolutions have been reported in the literature including chiral HPLC[48] and the formation of inclusion complexes with tartaric acid derivatives.[11,49] Resolution has also been achieved using N-alkylcinchonidium halides[50] however it was noted that N-benzylcinchonidium chloride (**5**) which so efficiently resolved binaphthol (**2**) would not form an inclusion complex with (±)-biphenanthrol (**71**). In contrast, the resolution was achieved with N-butylcinchonidium bromide (**73**) (Figure 42).



73

Figure 42. N-Butylcinchonidium Bromide.

Optically active biphenanthrol (**71**) can be prepared directly from 9-phenanthrol (**72**). This is achieved by carrying out the oxidative coupling in the presence of (R)-(-)-1,2-diphenylethylamine-copper (II) complex[51] in 86% yield and 98% optical purity (Figure 43). The reaction, however, is limited to small scale due to problems in obtaining the resolved amine.



72 (S)-(-)-**71**

Figure 43. Asymmetric Synthesis of Biphenanthrol.

The 9,9'-biphenanthryl system has received less attention in the literature than the related 1,1'-binaphthyl system. Correspondingly the uses of this system are not so wide-spread. Research into the possible uses of this system has been centred on 10,10'-dihydroxy-9,9'-biphenanthryl (**71**) and has been carried out in three main areas.

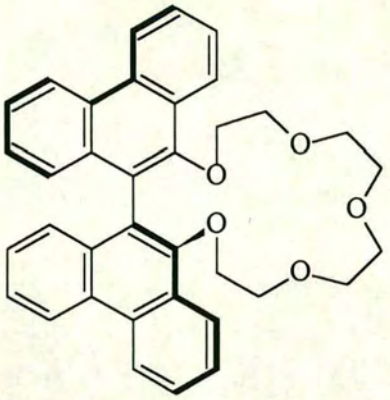
1.4.2. Complex Formation

The first of these areas is the use of biphenanthrol (**71**) to resolve compounds by the formation of inclusion compounds. Host-guest complexes form between optically active biphenanthrol (**71**) and various organic compounds. If the chiral recognition between the biphenanthrol (**71**) and the guest compound occurs efficiently, the guest compound will be resolved.[52] For example, the resolution of propionic and butyric acid derivatives has been reported. These compounds do not form complexes with optically active binaphthol (**2**).[53] Binaphthol (**2**), however, efficiently resolves sulfoxides,[54] selenoxides,[55] phosphine oxides[56] and phosphinates[56] through complex formation. Contrarily, these compounds are not resolved with biphenanthrol (**71**), though complexation occurs. Thus biphenanthrol (**71**) only recognises chirality on carbon and binaphthol (**2**) on heteroatoms.

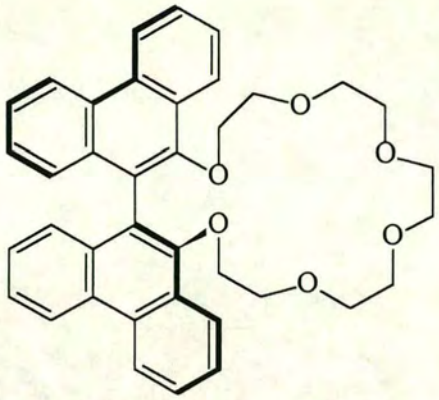
Crystal structure studies on these types of complex have shown that hydrogen bonds form between the polarised hetero-atom group and the hydroxyl group of binaphthol (**2**). Thus the components get close enough to recognise each other. In the case of biphenanthrol (**71**), the relatively larger phenanthrol rings surround the guest molecule more efficiently than the naphthol group of binaphthol (**2**), This "surrounding" makes it easier to accommodate the guest molecule in the crystal lattice of the complex.[53]

1.4.3. Crown Ethers

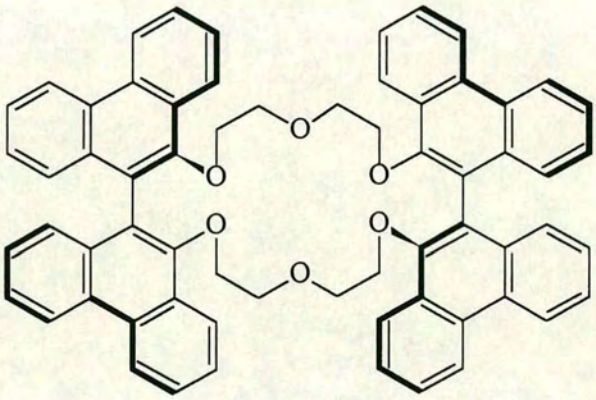
As with binaphthol (**2**), biphenanthrol (**71**) has been incorporated into crown ethers.[57,48] Of the binaphthyl crown ethers, (R,R)-**35** was one of the most enantioselective in resolution experiments. Methyl (±)-phenylglycinate was obtained in 90% optical purity by differential transport using this crown ether.[58]



(S)-(-)-**74**



(S)-(-)-**75**



(R,R)-(-)-**76**

Figure 44. Biphenanthrol Containing Crown Ethers.

The crown ethers **(74)**, **(75)** and **(76)**, shown in Figure 44, containing the biphenanthryl moiety have been synthesised and their selectivity for various salts demonstrated by differential transport.[48,57] See Table 2 for a summary of the results. From these results it can be seen that **(74)** and **(75)** exhibit the opposite enantioselectivity to **(76)**, and that the selectivity is higher. **(74)** and **(75)** have high selectivity for 1,2-diphenylethylamine.

Host	*Guest*	*Transport %*	*Config.*	*Optical Purity %*
74	a	1.4	R	21
74	b	3.1	S	88
74	c	3.5	S	49
75	a	2.8	R	24
75	b	3.8	S	78
75	c	2.5	S	45
76	a	2.6	S	19
76	b	3.2	R	23
76	c	3.2	R	21

Table 2. Selectivity of Various Biphenanthryl Containing Crown Ethers.

a) Methyl (±)-phenylglycinate.HCl.

b) (±)-1,2-diphenylethylamine.HCl.

c) (±)-1-phenylethylamine.HCl.

1.4.4. Enanioselective Reduction of Prochiral Ketones

The final reported use of biphenanthrol (**71**) is for the chiral modification of lithium aluminium hydride[51] (Figure 45). Like binaphthol (**2**), biphenanthrol (**71**) has been used successfully to modify lithium aluminium hydride for the enantioselective reduction of a variety of prochiral ketones. See Table 3 for some examples.

The chiral hydride reagent exhibits good enantiomeric face selectivity for compounds having a phenyl group directly attached to the carbonyl centre. Rather low enantioselectivities are obtained with aliphatic ketones. This mirrors the results observed for BINAL-H (**6**).

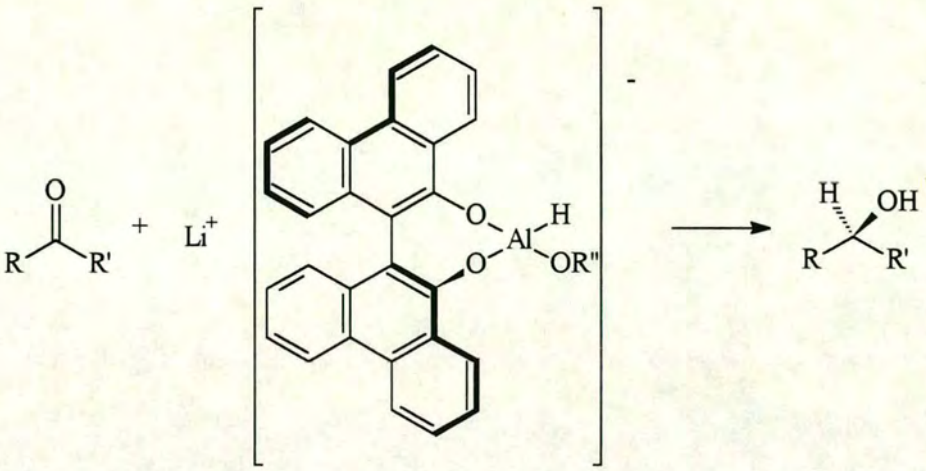


Figure 45. (S)-Biphenanthrol Modified Lithium Aluminium Hydride.

R	*R'*	*% Yield*	*% e.e.*	*Config. of product*
Ph	D	74	87	S
Ph	Me	75	97	S
Ph	Et	78	98	S
CH_2Ph	Me	76	33	S
Bu	Me	73	21	S

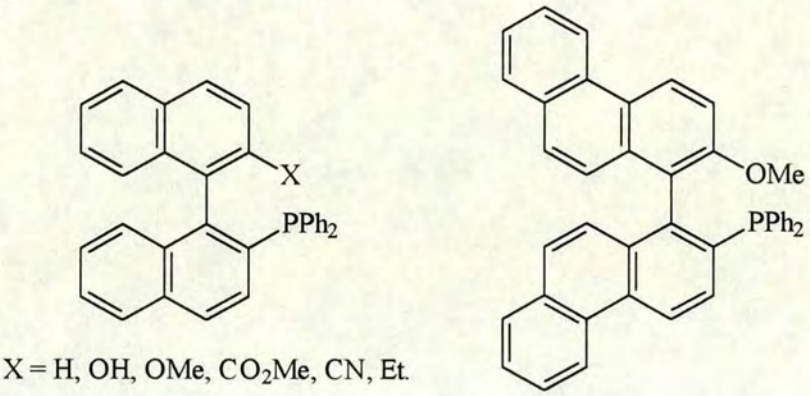
Table 3. Reduction of Selected Prochiral Ketones by (S)-Biphenanthrol Modified Lithium Aluminium Hydride.

1.5. Unsymmetrically Substituted Binaphthyls

The uses of symmetrically substituted biaryl compounds have been well documented, for example binaphthol (**2**) and biphenanthrol (**40**). Many organic transformations have been carried out asymmetrically using these biaryl molecules as chiral auxiliaries, for example reduction, hydrogenation, isomerisation and other reactions discussed earlier. However, unsymmetrically substituted biaryl compounds remain less well documented, though some have been prepared and their use in enantioselective reactions described.

1.5.1. Biaryl Monophosphines

One class of these unsymmetrically substituted biaryls are the biaryl monophosphines. Asymmetric transformations catalysed by transition metal complexes containing optically active phosphine ligands has attracted much attention. Most ligands developed thus far have been biphosphines. Some reactions, however, can not be catalysed by these types of biphosphine-metal complexes due to low catalytic activity and/or low selectivity. Chiral monodentate phosphine ligands have been developed to hopefully overcome these problems.



X = H, OH, OMe, CO_2Me, CN, Et.

77 **78**

Figure 46. Biaryl Monophosphines.

The binaphthyl skeleton has been chosen by Hayashi *et. al.* for the formation of such monodentate phosphine ligands.[59] One example is 2-(diphenylphosphino)-2'-alkoxy-1,1'-binaphthyl (MOP) (**77**) (Figure 46). These compounds are synthesised from the ditriflate of binaphthol (**2**) which is phosphorylated to give the monophosphine oxide (**79**) using a palladium catalyst. The remaining triflate group is then hydrolysed in basic conditions and the resulting hydroxyl group alkylated with an alkyl halide. Reduction of the phosphine oxide with trichlorosilane and triethylamine yields the corresponding phosphine (**77**). Alkyl substituents have also been introduced at the 2' position by a nickel catalysed reaction on (**79**). The synthetic procedure is outlined in Figure 47. A biphenanthryl analogue (MOP-phen) (**78**) has also been synthesised[60] (Figure 46).

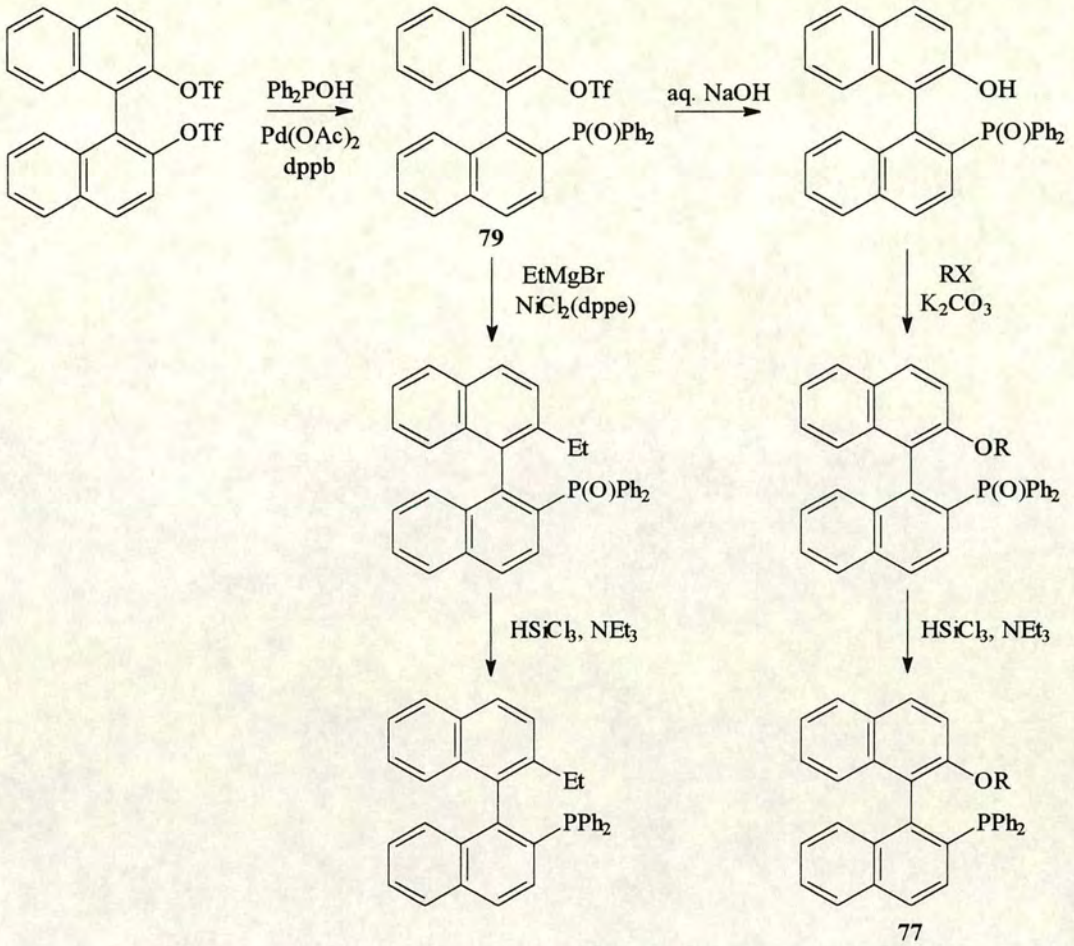


Figure 47. Synthesis of Binaphthyl Monophosphines.

Molecules of this type (**77**) and (**78**) have been complexed with palladium to enantioselectively catalyse various reactions.[60,61,62] One of these is the asymmetric synthesis of 2-alcohols (**80**) *via* the hydrosilylation of 1-alkenes (**81**).[61] The catalyst system for this reaction is a palladium complex with (S)-(-)-2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl ((S)-(-)-MOP-OMe). The reaction proceeds in good yield (90-100%) and with high enantioselectivity (94-97%) (Figure 48). The asymmetric hydrosilylation of styrenes (ArCH=CHR) with trichlorosilane in the presence of a palladium-(S)-(-)-2-(diphenylphosphino)-1,1'-binaphthyl ((S)-(-)-MOP-H) complex has also been reported. After oxidation, benzylic alcohols are formed with up to 96% e.e..[63]

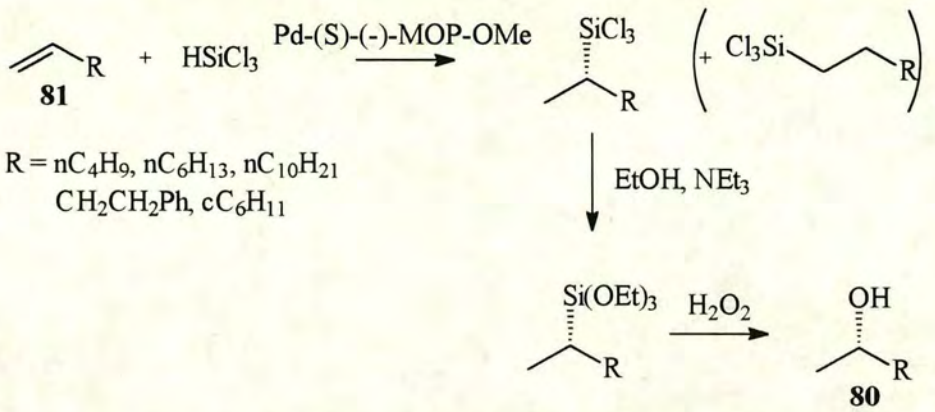


Figure 48. Asymmetric Synthesis of 2-Alcohols.

1.5.2. 2-Amino-2'-hydroxy-1,1'-binaphthyl

Another unsymmetrically substituted biaryl compound to have been synthesised and used successfully in asymmetric synthesis is 2-amino-2'-hydroxy-1,1'-binaphthyl (**82**) (Figure 49). The synthesis of this molecule has been recently reported by Kocovsky.[64] This proceeds in a single step *via* the oxidative coupling of 2-naphthol (**3**) and 2-naphthylamine in the presence of copper-(II)-chloride and a chiral amine, d-amphetamine (**4**). The reaction yields about 40% of each enantiomer, both with 46% e.e.. Two successive fractional recrystallisations from benzene yields optically pure (**82**).

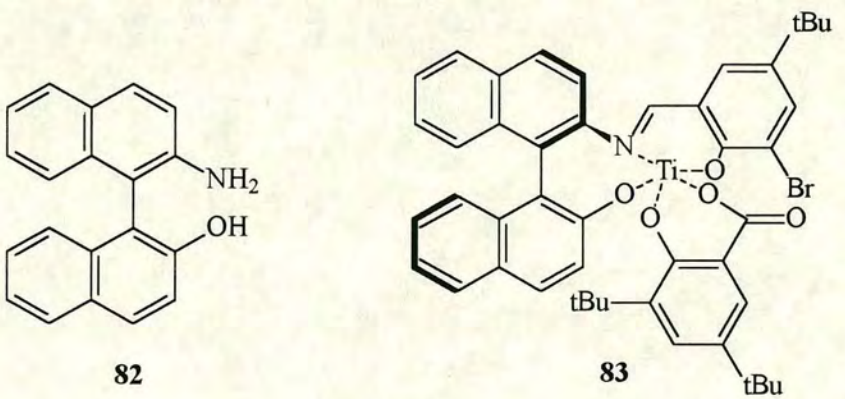


Figure 49. 2-Amino-2'-hydroxy-1,1'-binaphthyl and it's Titanium Complex.

This unsymmetrically substituted binaphthyl moiety (**82**) has been subsequently incorporated into a titanium complex (**83**) (Figure 49) to give an asymmetric catalyst for aldol reactions.[65,66] Condensation of (**82**) with 3-bromo-5-tert-butylsalicylaldehyde affords a Schiff base. This is then treated with titanium tetraisopropoxide and 3,5-di-tert-butylsalicylic acid to give (**83**) after the removal of the solvent *in vacuo*.

This complex has been used to catalyse the Mukaiyama aldol reaction of methyl and ethyl acetate derived silyl enolates (**84**) with aldehydes. The silylated aldol products are isolated in excellent yield and enantioselectivity. The catalyst system is general in its scope, affording excellent levels of enantioinduction for both aliphatic and aromatic aldehydes.

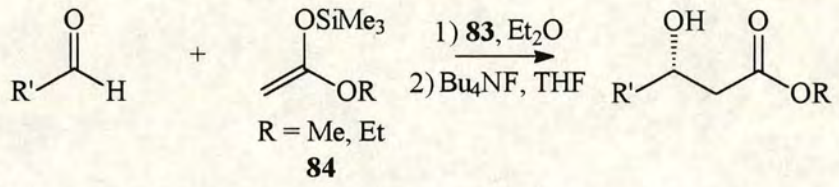
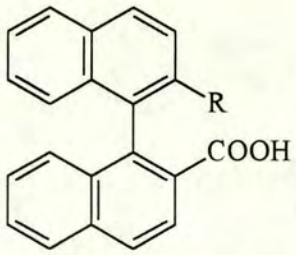


Figure 50. Asymmetric Mukaiyama Aldol Reaction.

1.5.3. 1,1'-Binaphthyl-Carboxylic Acids

Another class of unsymmetrically substituted biaryl compounds to have been used are the 1,1'-binaphthyl-2-carboxylic acids (**85**) (Figure 51). The presence of a carboxylic acid functionality is desirable for use as a chiral derivatising agent for the discrimination of enantiomeric alcohols and amines by HPLC and/or ^{1}H NMR[67] and for transformation into other functionalities.[68]



R = H, Me, OMe

85

Figure 51. 1,1'-Binaphthyl-2-Carboxylic Acids.

Various syntheses of these molecules have been reported. Meyers[69] and Cram[70] have reported a nucleophilic substitution of the 2-oxazoline-activated 1-alkoxynaphthylene by a naphthyl Grignard or lithium reagent to give 2-(1,1'-binaphthyl-2-yl)oxazolines which are latent binaphthyl-2-carboxylic acids. Alternatively, Miyano has reported a three stage synthesis from 2-methyl-1,1'-binaphthyls involving a bromination by N-bromosuccinimide to give a benzylic bromide which is treated with the sodium salt of 2-nitropropane to give an aldehyde. Oxidation by potassium permanganate yields the carboxylic acid.[68] Miyano has also reported a palladium catalysed carbonylation of a binaphthyl triflate to yield the carboxylic acid.[71]

1.6. Project Aims

The development of new auxiliaries is an important issue for organic chemists. As outlined earlier, they are an essential tool for asymmetric synthesis. Of these, one of the most extensively studied areas is that of axially dissymmetric biaryl compounds and in particular, symmetrically substituted binaphthyls. Some work has also been carried out in other areas, namely that of the biphenanthryl system and unsymmetrically substituted binaphthyl systems. These areas have been discussed in detail earlier.

The aim of this project was to develop a novel chiral auxiliary system. An effective synthesis and resolution of the system should be obtained and the potential use of the

compounds as chiral auxiliaries demonstrated. The starting point for the design of the new system was binaphthyl as this has been one of the most successful auxiliary systems to have been designed. However, there are many patents in this area and so it was desirable to develop a novel system. Two modifications have been made to the binaphthyl system to create a novel series of axially dissymmetric biaryl compounds. The modifications are shown in Figure 52.

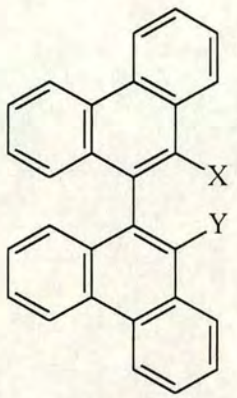


Figure 52. Target System.

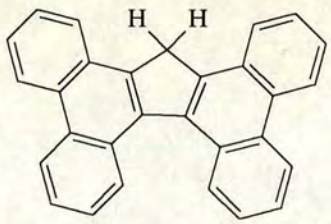
The first of these modifications is the addition of two extra aromatic rings. This increases the steric bulk of the system and hopefully the asymmetric induction imparted to a reaction. Replacement of the binaphthyl system with the biphenanthryl system has been found to be beneficial in certain areas, for example, the modification of lithium aluminium hydride and for the resolution of certain compounds as described in Section 1.4..

The second modification that has been made is introduction of different functionalities X and Y. In binaphthol (**2**) and BINAP (**40**) X and Y were the same. In this system, X and Y are different and so there are now different co-ordinating groups in the same molecule. The advantages of such a modification were demonstrated in Section 1.5.2.. It should also be possible to manipulate one functional group, while leaving the other intact.

2. Results and Discussion

2.1. Access to the System

As outlined earlier in Section 1.6., the aim of the project was to synthesise a series of unsymmetrically substituted biphenanthryls. An appropriate starting point for this aim was tetrabenzo[a,c,g,i]fluorene (Tbf) (**86**), a highly aromatic compound containing the biphenanthryl moiety (Figure 53). Tbf has been developed by Ramage to aid peptide and protein purification.[72] This has been achieved by exploiting two important features of the Tbf system. Firstly, it's strong fluorescent properties and secondly, it's affinity for porous graphitised carbon (PGC) and reverse phase HPLC supports.

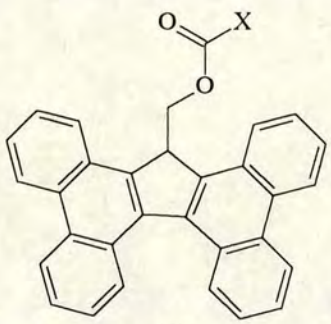


86

Figure 53. Tetrabenzo[a,c,g,i]fluorene.

Merrifield's revolutionary solid phase synthesis of peptides is based on the sequential addition of N^{α}-protected amino acids to an insoluble polymeric support.[73] This has greatly simplified peptide and protein synthesis, and in particular eliminated the need for purification of intermediates. However, one of the main obstacles in the stepwise chemical synthesis of peptides is the difficulty in purification of the final product due to the accumulation of truncated peptides on the resin. Truncated peptides are formed when the coupling of an amino acid fails to go to completion. The N^{α}-termini of these truncations are routinely capped with acetic anhydride to ensure that they play no further part in the synthesis.

Ramage *et al.*[72] have developed a base-labile N^{α}-protecting group, tetrabenzo[a,c,g,i]fluorenyl-17-methoxycarbonyl (Tbfmoc) (**87**) (Figure 54), for the affinity purification of peptides and proteins on PGC. Tetrabenzo[a,c,g,i]fluorenyl-17-methyl chloroformate is reacted with the N-terminus of the resin bound peptide. The Tbfmoc peptides are then cleaved from the resin and the solution of the crude mixture added to PGC. The PGC is washed and the acylated truncated peptide impurities removed. Deprotection of the Tbfmoc group and release of the purified peptide is then effected. Purification of the crude product by gel filtration or HPLC can be monitored by ultra violet absorbance of the Tbfmoc group at 364nm.



87

Figure 54. Tetrabenzo[a,c,g,i]fluorenyl-17-methoxycarbonyl.

The parent Tbf system can be synthesised in three steps[74] (Figure 55). The Grignard reagent derived from two equivalents of 9-bromophenanthrene was generated in anhydrous THF. One equivalent of methyl formate was added, resulting in the formation of bis-(phenanthryl-9-yl)methanol (**88**) in 42% yield. A cyclisation reaction occurred on the addition of TFA to a DCM suspension of the alcohol (**88**). The highly fluorescent Tbf was obtained in 96% yield.

Wahl[74] noticed that the cyclised product showed subtle differences in it's ^{1}H NMR to that expected for Tbf (**86**). A more complex splitting pattern was obtained than would be normally expected for a symmetrically substituted structure such as (**86**). Additionally, only one proton signal at δ 5.42 ppm was observed, whereas Tbf (**86**)

would require two. Slight differences were also observed in the ultra violet spectrum of the compound and the published spectrum.[75]

Based on the ^{1}H NMR data and analysis of the reaction mechanism, the initially formed product was the unsymmetrical 8b-H-tetrabenzo[a,c,g,i]fluorene (8b-H-Tbf) (**89**). Base treatment of 8b-H-Tbf (**89**) results in isomerisation to give 17-tetrabenzo[a,c,g,i]fluorene (**86**).

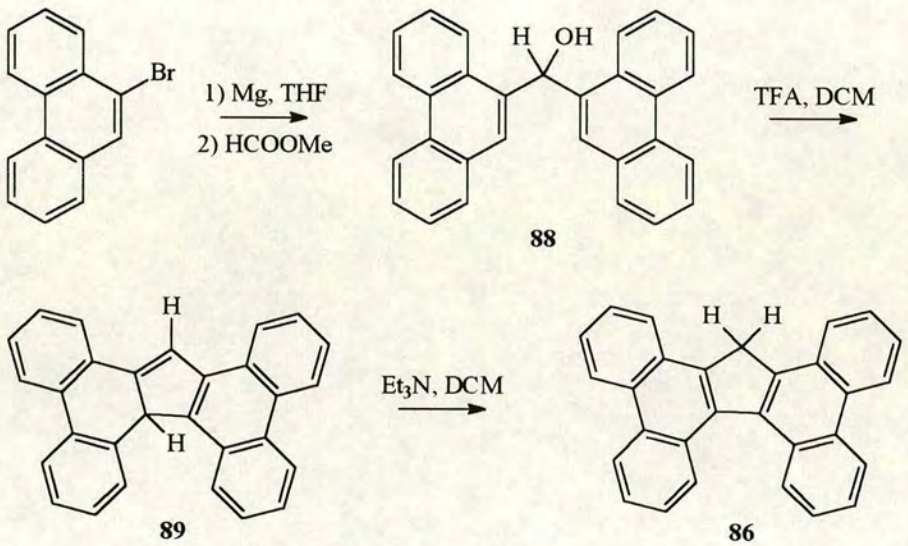


Figure 55. Synthesis of 17-Tetrabenzo[a,c,g,i]fluorene.

The unsymmetrical derivative 8b-H-Tbf (**89**) was the ideal candidate for transformation into unsymmetrical substituted biphenanthryl compounds. Many ways can be envisaged to cleave the central five membered ring of (**89**) to give such compounds. Here, only one of these possibilities has been selected: ozonolysis. Ozone gas was bubbled through a suspension of (**89**) in dry THF at -78°C. The resulting ozonide (**90**) was very stable and was isolated in 70% yield after trituration with ether (Figure 56). The stability of the ozonide was probably due to the presence of the large aromatic system.

The ozonide was stirred in THF and reduced using zinc and acetic acid to give (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) in 72% yield after

recrystallisation from DCM. Further reduction of the phenolic-aldehyde (**91**) with lithium aluminium hydride resulted in the formation of (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) in 95% yield after trituration with ether (Figure 56).

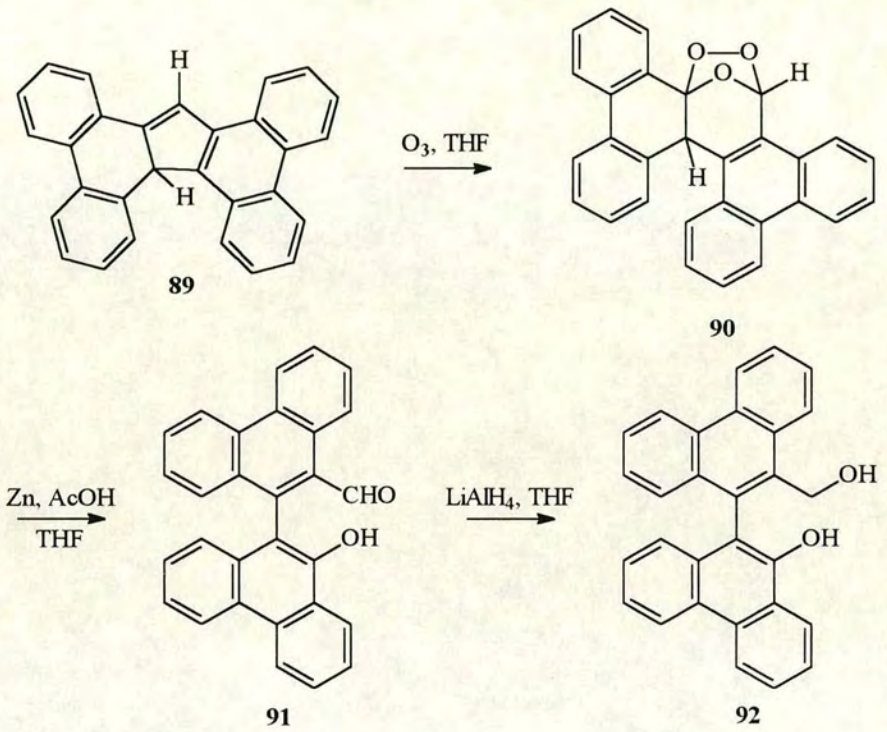
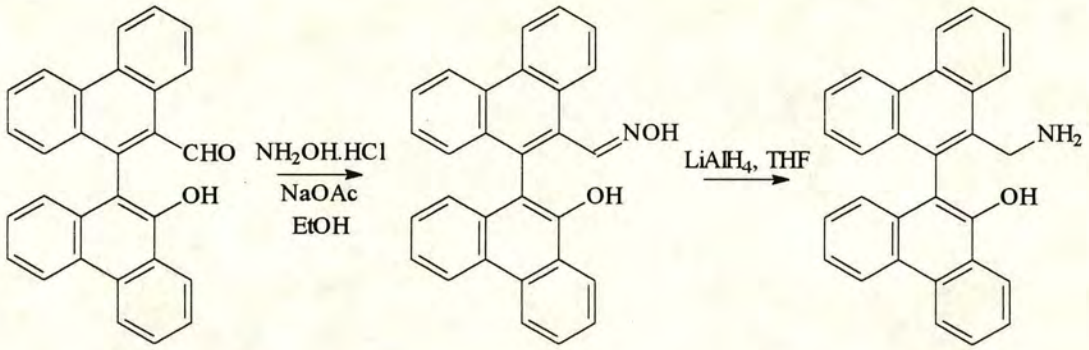


Figure 56. Synthesis of (±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl.

Alternatively, the phenolic-aldehyde (**91**) can be treated with hydroxylamine.hydrochloride to give (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde oxime (**93**) in 64% yield. Reduction of this oxime (**93**) with lithium aluminium hydride gave (±)-10-(aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (**94**) in 91% yield (Figure 57).



91 93 94

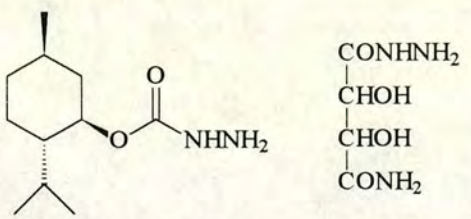
Figure 57. Synthesis of (±)-10-(Aminomethyl)-10'-hydroxy-9,9'-biphenanthryl.

2.2. Resolution of the System

A route into unsymmetrically substituted biphenanthryl compounds was thus obtained, which made it possible to synthesise a series of compounds which include a phenolic-aldehyde (**91**), a hydroxy-phenol (**92**), an oxime (**93**) and an amino-phenol (**94**). These compounds were formed as racemates and suitable resolution methodology was now investigated. The earliest point in the synthesis to effect the resolution was the phenolic-aldehyde (**91**). Resolution at this point would allow the isolation of all the members of the series as single enantiomers.

Many optically active hydrazines and semicarbazides have been investigated in the search for a reagent which could resolve aldehydes and ketones by the formation of diastereomeric hydrazones or semicarbazones. Only two compounds have proven themselves to be generally useful.[76] One is l-menthyl-N-aminocarbamate (l-menthylhydrazide) (**95**) (Figure 58) described by Woodward *et. al.*.[77] It is a commercially available, stable, crystalline compound which readily forms well defined crystalline derivatives with most carbonyl compounds. These derivatives, called menthylhydrazones, are usually decomposed to the optically active carbonyl compound by acid hydrolysis.

The second important reagent is tartramidic acid hydrazide (tartramazide) (**96**) (Figure 58) first described by Nerdel *et al.*.[78] Tartramazide is not commercially available but can be synthesised in two steps from (+)-tartaric acid. It's derivatives with carbonyl compounds are called tartramazones and can be readily hydrolysed with acid to yield optically active aldehyde or ketone.

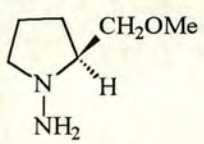


95 **96**

Figure 58. Resolving Agents for Carbonyl Compounds.

A resolution of the phenolic-aldehyde (**91**) using l-menthylhydrazide (**95**) was attempted. No recrystallisation occurred using the literature procedure involving ethanol. The diastereomeric l-menthylhydrazones were isolated and different solvents investigated. However, decomposition occurred before any diastereoselective recrystallisation could be achieved.

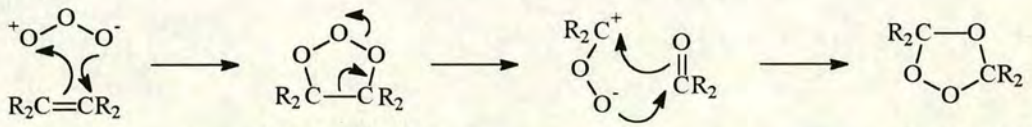
Enders *et al.* have reported the use chiral hydrazones in asymmetric synthesis. These can be used to prepare α-chiral aldehydes[79] and chiral α-substituted ketones.[80] The chiral hydrazide used to direct these reactions is (S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (S-AMP) (**97**) (Figure 59). S-AMP (**97**) also forms crystalline hydrazones with aldehydes and ketones and is commercially available. The resulting hydrazones can be regenerated to an aldehyde or ketone by hydrolysis of the methiodide of the hydrazone[81] or by ozonolysis. The ozone cleavage permits recovery of the chiral hydrazide after reduction of the resulting N-nitroso compound.[80]



97

Figure 59. (S)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine.

At this point it is worth mentioning the differences in mechanism between the two ozonolysis reactions that have been discussed. The first ozonolysis of 8b-H-Tbf (**89**) to produce the stable ozonide (**90**) is that of a classical carbon-carbon double bond. The basic mechanism for this reaction is outlined in Figure 60.[82] In the first step of the mechanism, a 1,3 dipolar addition of ozone to the substrate gives the initial ozonide or molozonide (**98**). However the molozonide (**98**) is highly unstable and cleaves to give an aldehyde or ketone and a zwitterion. This zwitterion then recombines with the aldehyde or ketone, again in a 1,3 dipolar addition, to give the more stable ozonide (**99**).



Molozonide **98** Ozonide **99**

Figure 60. Ozonolysis of a Carbon-Carbon Double Bond.

The second ozonolysis to have been mentioned is that of a carbon-nitrogen double bond. The proposed mechanism for this reaction varies from that outlined in Figure 60. Erickson *et al.* [83] have investigated the mechanism using dimethylhydrazones of various ketones and aldehydes, for example acetophenone. Several observations were made about the ozonolysis which indicated a different mechanistic pathway. It was noted that two moles of ozone were required per mole of hydrazone. The products from the ozonolysis were isolated and relative rate experiments carried out. The data obtained indicated that the initial attack of the ozone on the carbon-nitrogen double bond is electrophilic and may be strongly assisted by an electron donating group on the nitrogen. The final hypothesis for the mechanism is outlined in Figure 61 and is consistent with all the data reported by Erickson.

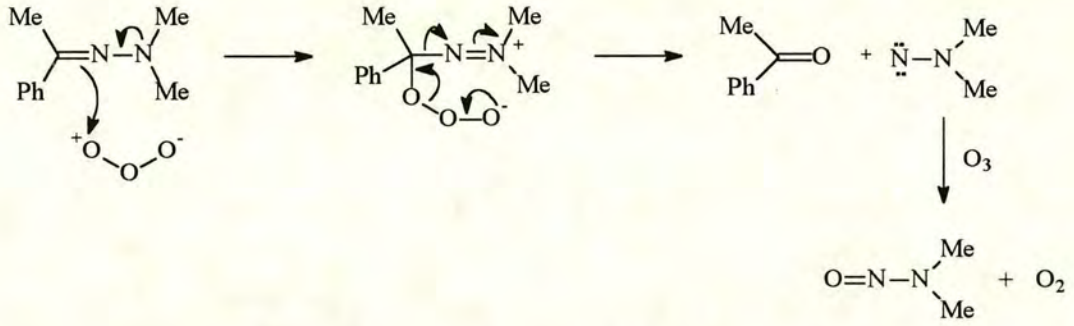


Figure 61. Ozonolysis of a Carbon-Nitrogen Double Bond.

The resolution of the phenolic-aldehyde (**91**) using S-AMP (**97**) was attempted. A diastereomeric mixture of S-AMP hydrazones (**100**) (Figure 62) was obtained after two hours. The two diastereoisomers were distinguishable by tlc, and so were separated by a combination of wet flash chromatography and recrystallisation. The resolution was confirmed using ^{1}H NMR. The resonances for the hydroxyl protons of the phenol came in an uncrowded region of the spectrum and were separated by 0.27 ppm. Approximately 70-80% of each diastereoisomer could be isolated in this way. Any unresolved diasteroisomers were put to one side and used in the next resolution.

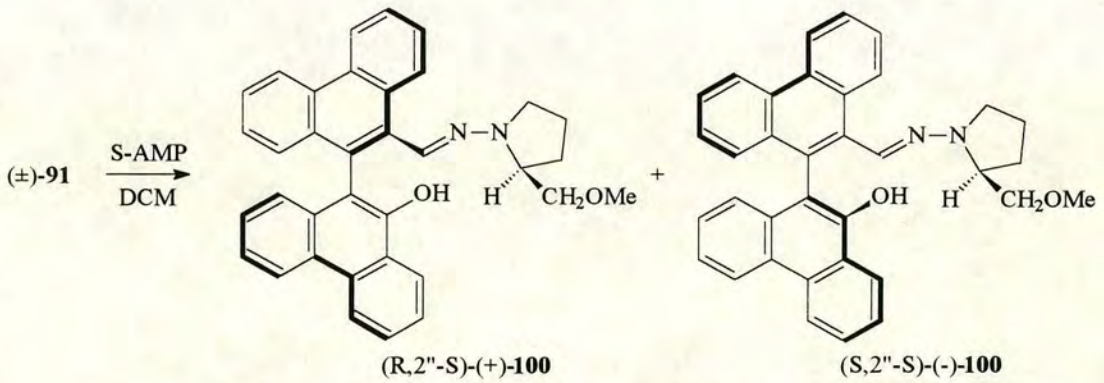
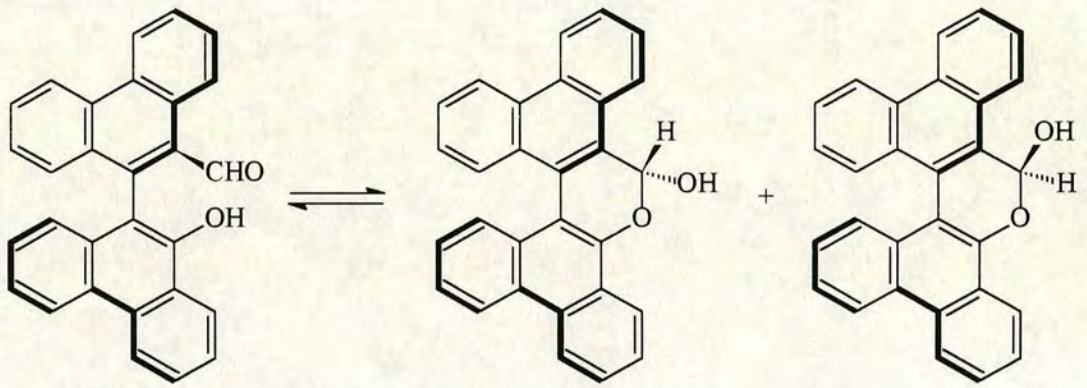


Figure 62. Synthesis of the S-AMP Hydrazones.

The phenolic-aldehydes, (R)-**91** and (S)-**91**, were regenerated using ozonolysis. Ozone gas was bubbled through a DCM solution of the S-AMP hydrazone (**100**) at -78°C. The resolved phenolic-aldehydes (**91**) were isolated in about 60% yield after wet flash chromatography. At this point it was noted that the optical rotations for

each enantiomer were not of equal value and of opposite sign as would normally be expected. Changing the concentration of the solution changed the optical rotation. This phenomenon was believed to be due to the formation of a hemi-acetal in solution (Figure 63). Indeed, the solution phase infra-red spectra of these enantiomers contained two OH stretches. One was for the phenolic hydroxyl group and the other was for the hemi-acetal hydroxyl group. The formation the hemi-acetal creates a new chiral centre in the molecule. Thus the two forms are now diastereomeric and not enantiomeric, and would not be expected to have equal and opposite values for their optical rotations.



(R)-**91**

Figure 63. Hemi-Acetal Formation.

On treatment of each of the two resolved phenolic-aldehydes (**91**) with lithium aluminium hydride both enantiomers of 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) were formed. As expected for enantiomerically pure compounds, these had equal and opposite values for their optical rotations. Similarly, treatment of each of the two phenolic-aldehydes (**91**) with hydroxylamine.hydrochloride gave optically pure 10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde oxime (**93**). Reduction of (**93**) using lithium aluminium hydride gave optically pure 10-(aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (**94**).

A second resolution of the system was also carried out to confirm the above resolution using S-AMP (**97**). This resolution was accomplished *via* the formation

and separation of diastereomeric esters of 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**). The diastereomeric esters were prepared using (R)- or (S)-2-phenylpropionic acid (**101**) in the presence of N,N-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).[84] The diastereoisomers were resolved by recrystallisation from ethyl acetate. The resolution was again monitored by ^{1}H NMR. The resonances for the methyl protons were separated by 0.05ppm and enabled the diastereoisomers to be distinguished.

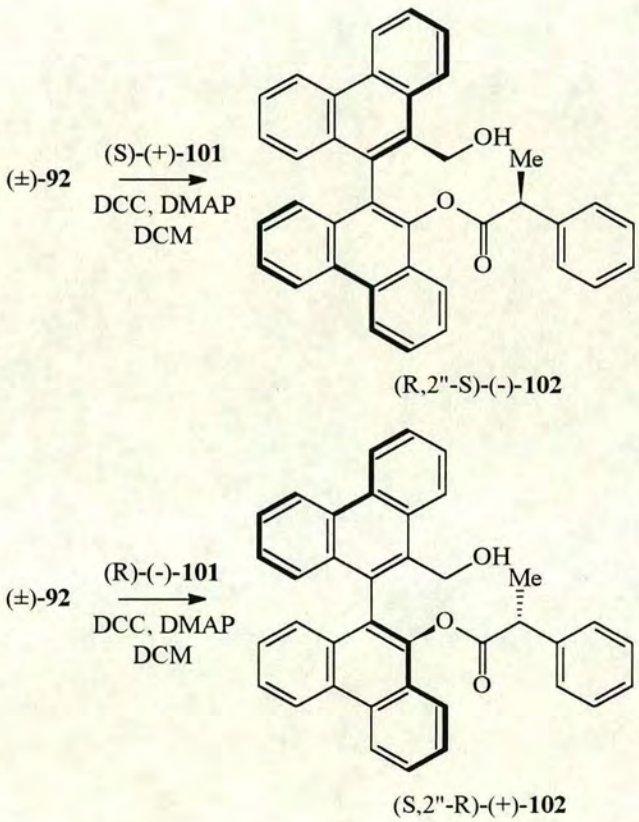


Figure 64. Synthesis of the Diastereomeric Esters.

Reduction of the ester using lithium aluminium hydride gave 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) in good yield. (S)-(+)-2-Phenylpropionic acid was used to obtain the (R)-(-)- isomer of the hydroxy-phenol (**92**) and (R)-(-)-2-phenylpropionic acid was used to obtain the (S)-(+)- isomer (Figure 64). The optical rotations obtained by this method for the resolution matched those obtained by the S-AMP (**97**) method.

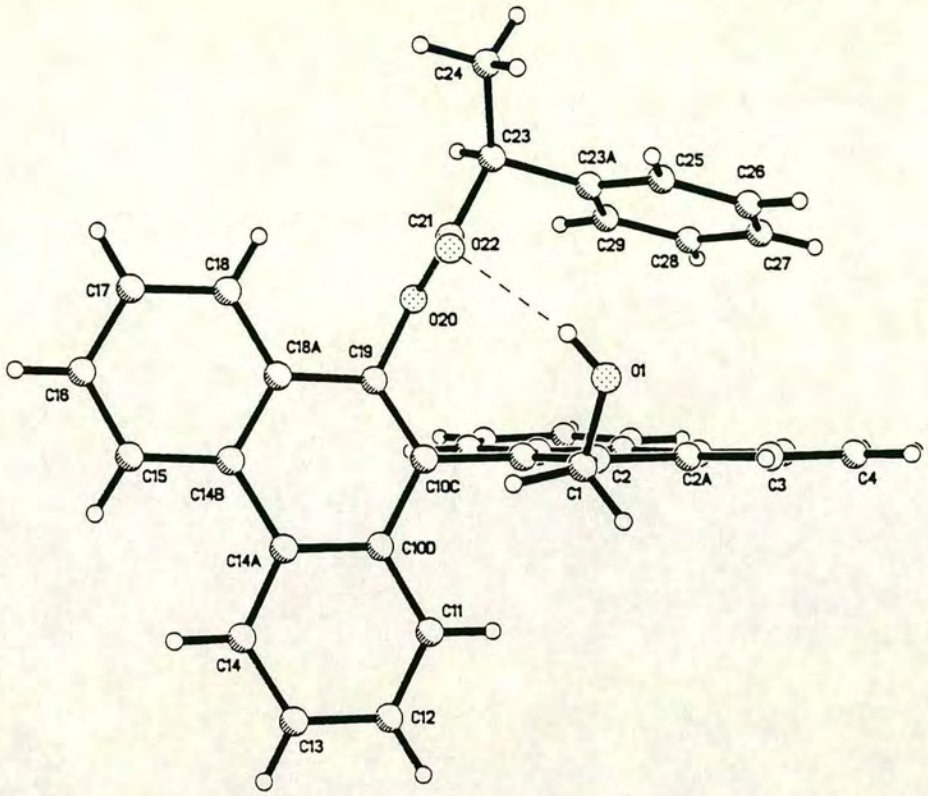


Figure 65. (R,2"-S)-(-)-10-(Hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (102).

A further confirmation of the resolution was obtained by X-ray crystallography. Crystals of (R,2"-S)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (**102**) were grown slowly in ethyl acetate and the crystal structure determined. The structure is given in Figure 65 and Table 4 (Appendix 1). From the crystal structure it was found that only one diastereoisomer was present and so the resolution had been successful. Other interesting features of this system were obvious from the structure. One was the presence of a hydrogen bond between the hydrogen of the hydroxyl group and the carbonyl oxygen. The second was a π-stacking interaction between the phenyl ring and the adjacent phenanthryl ring. The distance between the two rings was 3.599Å, which is of the same order of magnitude as found in graphite (3.35Å), and the angle between the plane of the two rings was 18.3°. From the crystal structure, using the IUPAC rules outlined below, it was also possible to assign the absolute configuration of the biphenanthryl moiety as (R).

The IUPAC has defined rules for the assignment of (R)- or (S)- to molecules which are chiral due to the presence of a chiral axis.[85] The structure is regarded as an elongated tetrahedron and viewed along the axis; it is immaterial from which end it is viewed. The nearer pair of ligands receives the first two positions in the order of preference as shown in Figure 66.

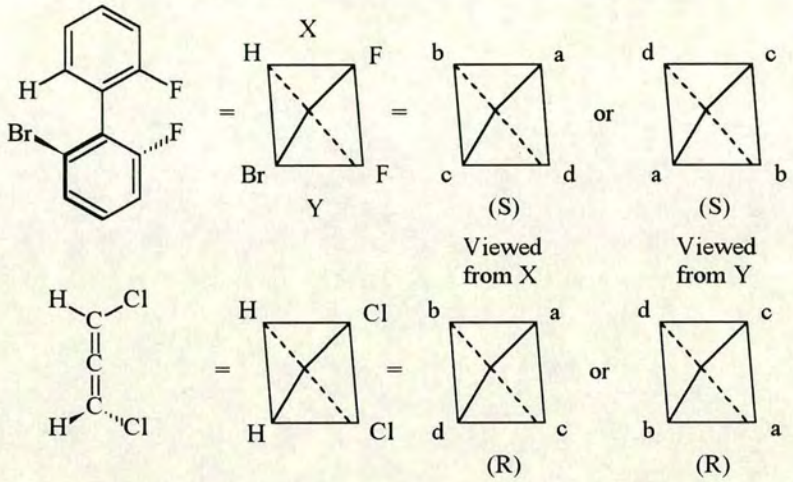


Figure 66. IUPAC Rules for the Assignment of Axial Chirality.

The circular dichroism (CD) spectra of the two enantiomers of hydroxy-phenol (**92**) were measured. Enantiomeric compounds give mirror image curves, for example, (R)- and (S)-binaphthol (**2**) (Appendix 2a). Mirror image curves were obtained for the two enantiomers of hydroxy-phenol (**92**) indicating that the resolution had indeed been effective (Appendix 2b).

An overall picture of the two resolution techniques is given in Figure 67. The absolute configurations have been assigned and the optical rotation values included.

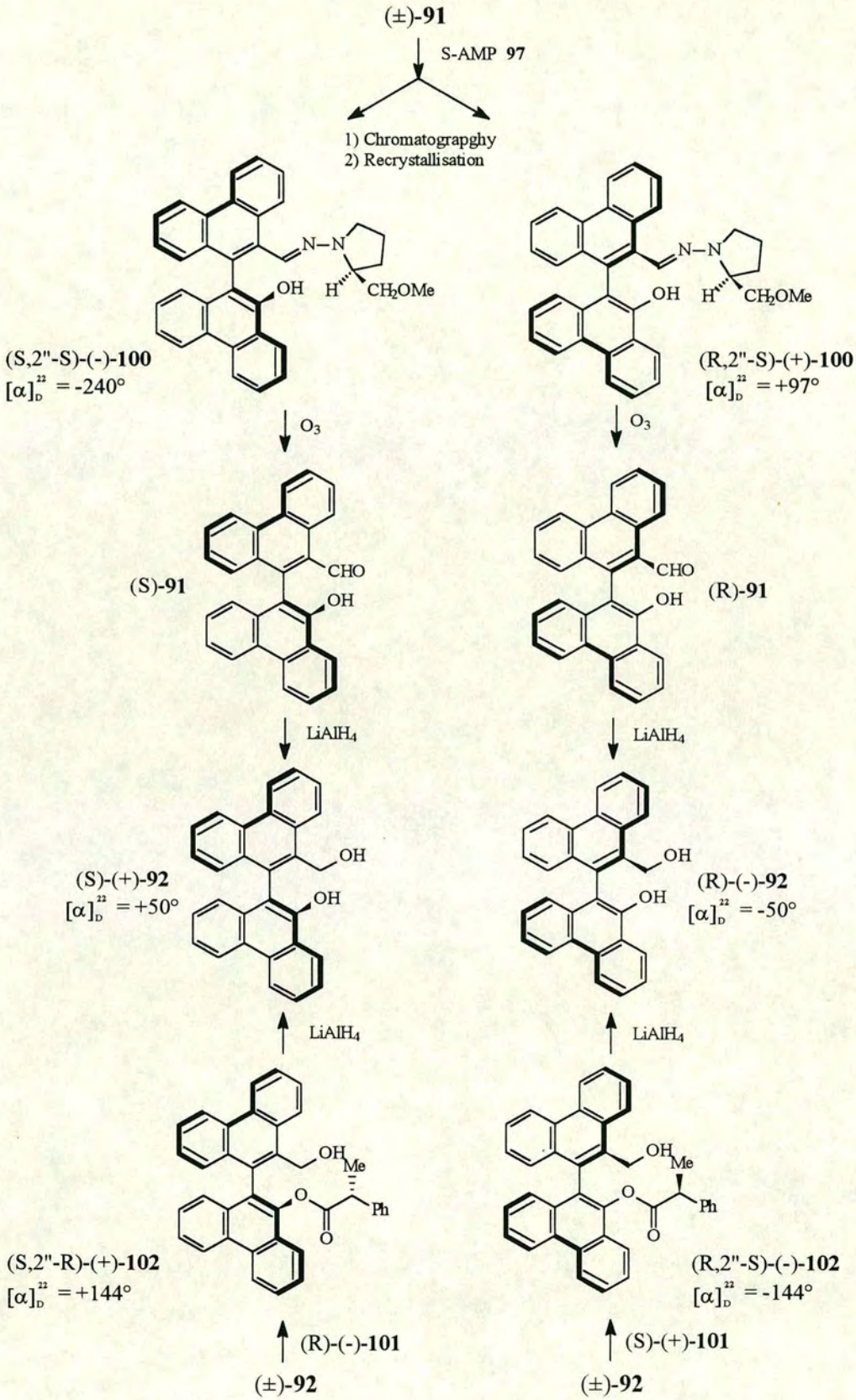


Figure 67. Summary of the Resolutions.

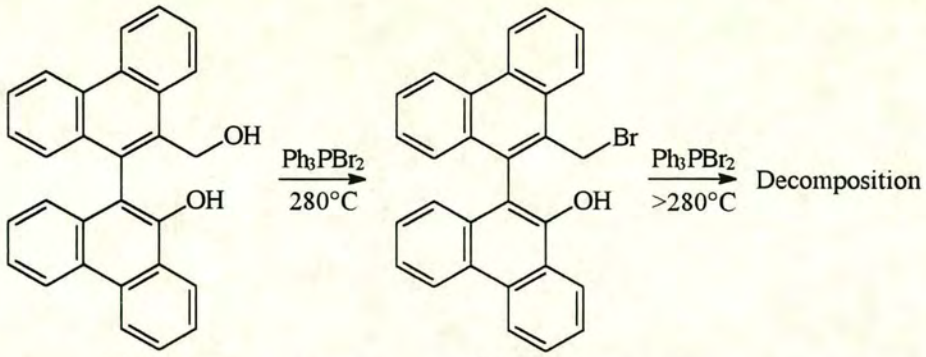
2.3. Investigation Into Uses of the System

In the previous Section, a route into unsymmetrically disubstituted biphenanthryl compounds was described. A series of compounds which includes a phenolic-aldehyde (**91**), a hydroxy-phenol (**92**), an oxime (**93**) and an amino-phenol (**94**) was synthesised. An effective resolution of the series was accomplished using S-AMP (**97**) as the resolving agent. It remained then to investigate the potential uses of these compounds.

2.3.1. An Analogue of BINAP

In Section 1.3. the importance of BINAP (**40**) as a chiral auxiliary for rhodium and ruthenium was discussed. The similarities of 10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) to binaphthol (**2**) make it an attractive proposition for conversion to an analogue of BINAP (**40**). Thus a novel enantioselective hydrogenation catalyst would be available, circumventing patents in this area.

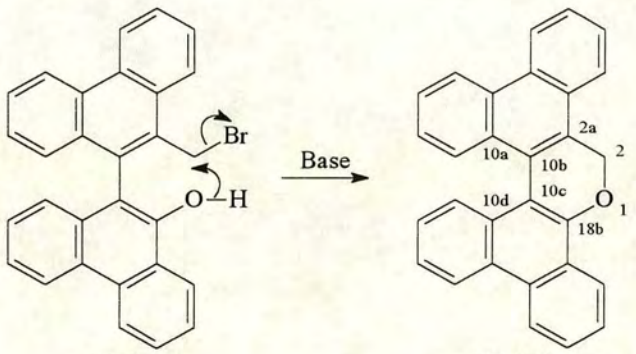
The synthesis of BINAP (**40**) developed by Noyori was investigated as a possible synthesis of the BINAP analogue.[31,32,33] This synthesis was outlined in Figure 25, in which the first step involved a high temperature bromination reaction using dibromotriphenylphosphorane. The temperature of the reaction between dibromotriphenylphosphorane and hydroxy-phenol (**92**) was raised slowly. At 230°C a homogeneous melt was observed. At 280°C, the reaction was stopped, the product analysed and found to (±)-10-(bromomethyl)-10'-hydroxy-9,9'-biphenanthryl (**103**). Only monobromination had occurred at the benzylic position. The reaction was repeated, and the temperature raised above 280°C. However, decomposition occurred to give a black tar and isolation of the desired product was not possible (Figure 68).



(±)-**92** (±)-**103**

Figure 68. High Temperature Bromination of 10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl.

The monobromo-phenol (**103**) could not be used in subsequent reactions to introduce the diphenylphosphine moiety due to its base sensitivity. A rapid S_N2 process occurred in base to give the exceptionally stable (±)-tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (**104**) (Figure 69), the structure of which was confirmed by x-ray crystallography (Table 5, Appendix 1) (Figure 70). The molecule is twisted about the central six membered ring. The key torsion angles are C_{18b}-O_1-C_2-C_{2a}: -53.4° and C_{10a}-C_{10b}-C_{10c}-C_{10d}: -37.9(4)°.



(±)-**103** (±)-**104**

Figure 69. Synthesis of (±)-Tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran.

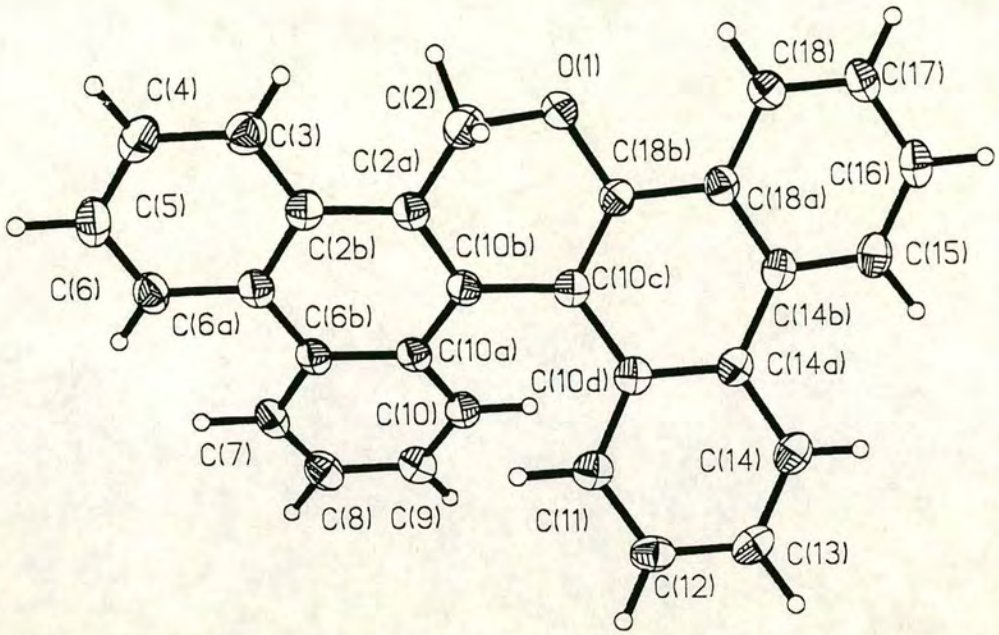
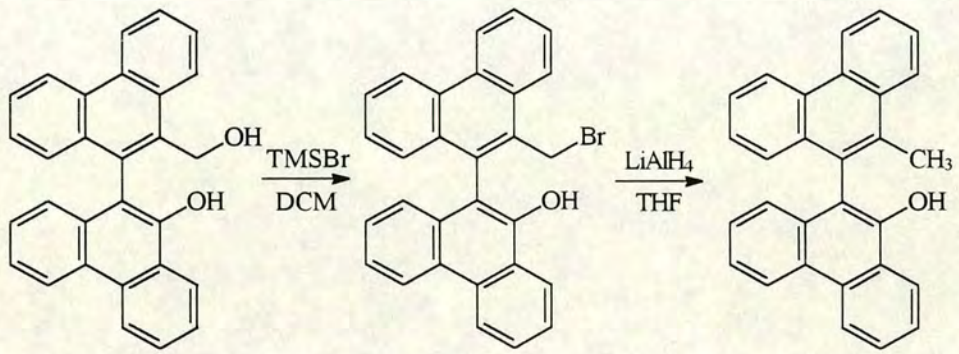


Figure 60. (±)-Tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (104).

A second approach to the formation of BINAP (**40**) involves the use of metal catalysed coupling reactions to introduce the diphenylphosphine moiety. Two methodologies have been developed using this approach, both of which involve the ditriflate of binaphthol (**2**). The first of these methodologies involves a nickel catalysed diphosphine coupling reaction to introduce both diphenylphosphine groups directly.[34] This method was outlined earlier in Figure 26. The second of these methodologies involves a palladium catalysed coupling of diphenylphosphine oxide, resulting in the formation of a monophosphine oxide.[59] This method was outlined in Figure 47.

The formation of the ditriflate of hydroxy-phenol (**92**) was not possible. This was again due to its sensitivity to the base required to form the triflate. The S_N2 process occurred in good yield to give (±)-tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (**104**).

These problems arose due to the functionality at the benzylic position. Thus, a possible solution to the problem would be to remove the functionality at the benzylic position. Subsequent phosphorylation at the phenolic position would yield a monophosphine oxide which also constitutes an important class of chiral molecule as outlined in Section 1.5.1.. A DCM solution of hydroxy-phenol (**92**) was treated with bromotrimethylsilane to give (±)-10-(bromomethyl)-10'-hydroxy-9,9'-biphenanthryl (**103**) in 61% yield.[86] Reduction of the benzylic bromide using lithium aluminium hydride gave (±)-10'-hydroxy-10-methyl-9,9'-biphenanthryl (**105**) in 84 % yield[87] (Figure 61).



(±)-**92** (±)-**103** (±)-**105**

Figure 61. Synthesis of (±)-10'-Hydroxy-10-methyl-9,9'-biphenanthryl.

With the methyl-phenol (**105**) in hand it was possible to synthesise the triflate. This was accomplished using trifluoromethanesulfonic anhydride and pyridine in DCM to give (±)-10-methyl-9,9'-biphenanthryl-10'-trifluoromethanesulfonate (**106**) in 67% yield.[59] However, neither of the metal catalysed coupling reactions were able to introduce the diphenylphosphine moiety using the conditions which are outlined in Figure 62. It is believed that the loss of reactivity in these reactions was due to the lack of a second functionality to co-ordinate to the metal centre catalysing the reaction. Thus, the reaction did not proceed.

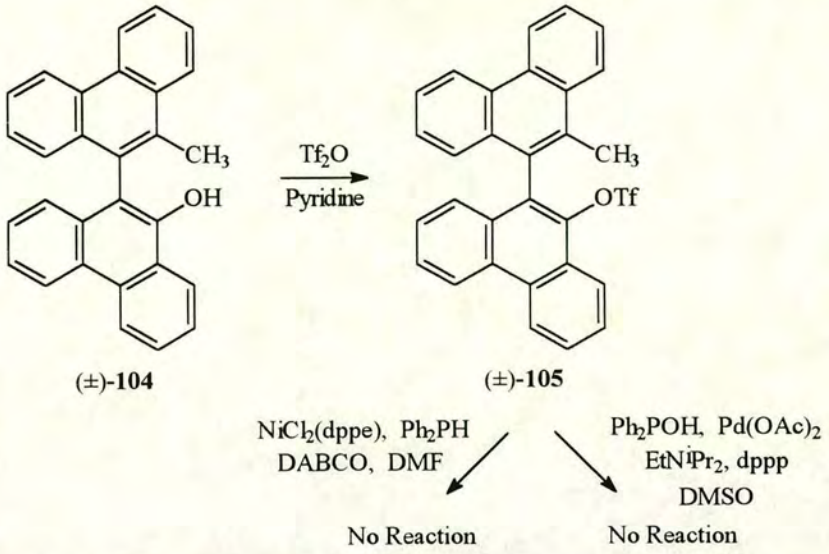


Figure 62. Attempted Phosphorylation Reactions.

2.3.2. Enantioselective Reduction of Prochiral Ketones

The possibility of using (±)-10'-hydroxy-10-(hydroxmethyl)-9,9'-biphenanthryl (**92**) as chiral modifier for lithium aluminium hydride was investigated. The use of binaphthol (**2**) and biphenanthrol (**71**) was described in Sections 1.2.3. and 1.4.2. respectively. (R)-(-)-10'-Hydroxy-10-(hydroxmethyl)-9,9'-biphenanthryl (**92**) was used, and the reduction of acetophenone and hexanone studied.

The modified lithium aluminium hydride reagent was prepared *in situ* at 0°C in THF from three equivalents of lithium aluminium hydride, three equivalents of ethanol and three equivalents of (R)-(-)-10'-hydroxy-10-(hydroxmethyl)-9,9'-biphenanthryl (**92**). The mixture was allowed to equilibrate for one hour at 0°C before being cooled to -78°C, at which point one equivalent of prochiral ketone (**107**) was added (Figure 63). After the work up, optically pure hydroxy-phenol (**92**) was recovered on trituration with ether. The product alcohol (**108**) was purified by Kugelrhor distillation.[51] The product alcohols (**108**) were converted to diastereomeric esters using (R)-(+)-α-methoxy-α-

(trifluoromethyl)phenylacetic acid (Mosher's acid). Thus the enantioselectivity of the reduction reaction could be measured using ^{19}F NMR.[88]

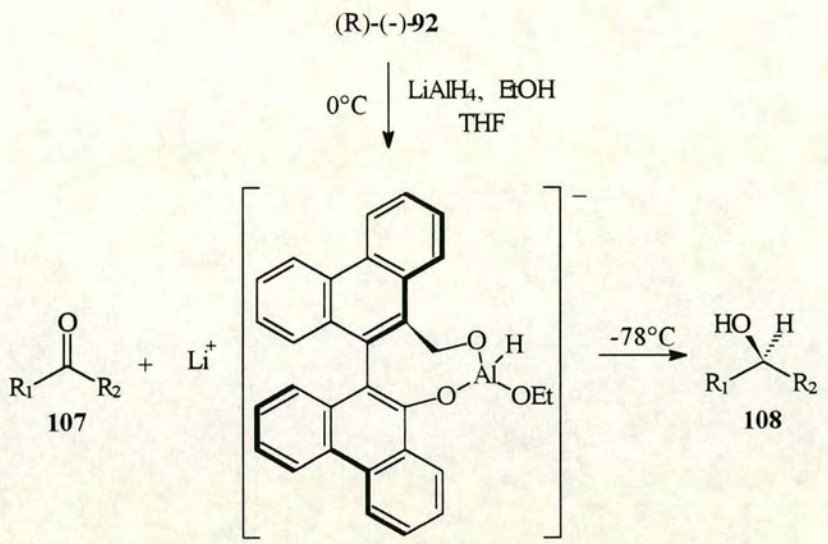


Figure 63. Enantioselective Reduction of Prochiral Ketones.

R_1	R_2	% e.e. (config.)	% e.e. (config.) A	% e.e. (config.) B
Ph	Me	35 (R)	97 (S)	95 (R)
Bu	Me	5 (R)	21 (S)	\

A = (S)-(-)-Biphenanthrol (**71**)[51]

B = (R)-(+)-Binaphthol (**2**)[3]

Table 6. Results for the Enantioselective Reduction of Selected Prochiral Ketones.

Table 6 contains the results for the reduction of acetophenone and hexanone. The results for biphenanthrol (**71**) and binaphthol (**2**) are also given for comparison. From these results it is obvious that there has been a drop in enantioselectivity for the reduction using the modified lithium aluminium hydride reagent derived from (**92**). This must be due to

the presence of the extra methylene carbon at C_{10} since biphenanthrol (**71**) gives good enantioselectivity. There are two possible explanations for the drop in enantioselectivity for the reduction. The first of these is the possible reduction of the steric strain in the six membered transition state outlined in Figure 10 due to the presence of the extra methylene carbon at C_{10}. The second problem with the use of hydroxy-phenol (**92**) as opposed to binaphthol (**2**) or biphenanthrol (**71**) can be understood when the chelating structures (**109-112**) are considered (Figure 64) where $R_1 \neq R_2$.

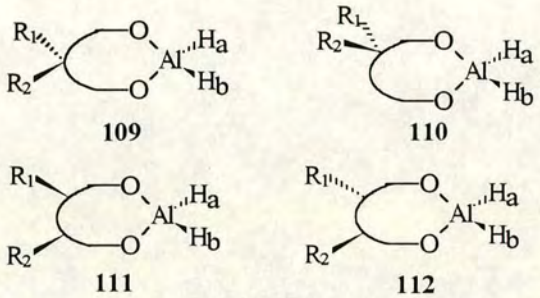


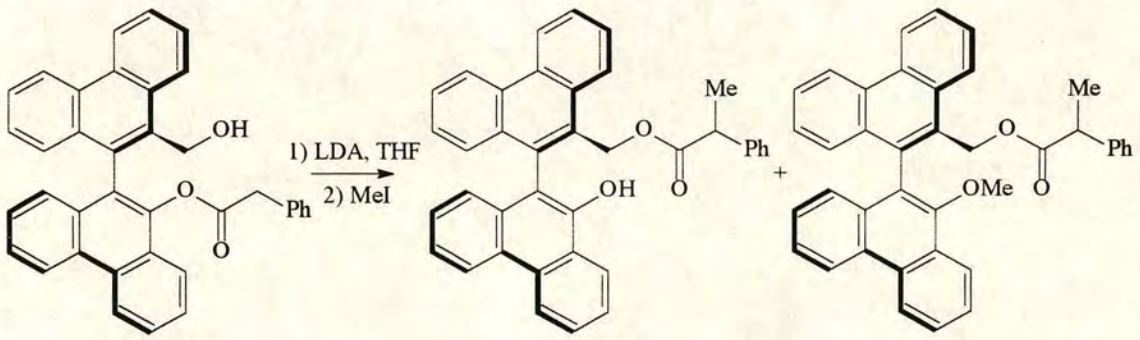
Figure 64. Chelating Structures 109-112.

H_a and H_b in such reagents are diastereotopic and behave differently in the enantioselective reduction. Only reagents of type (**112**), where $R_1=R_2$, which possess a modifying ligand with a C_2 axis, bear homotopic H_a and H_b and can thereby halve the kinds of active hydrogen attached to the aluminium. Binaphthol (**2**) and biphenanthrol (**71**) are the ideal chiral ligands in this respect. However, the use of hydroxy-phenol (**92**) means that H_a and H_b are no longer homotopic due to the extra methylene carbon and the stereoselectivity of the reduction using such a species would be lower due to the presence of more reactive species.[3]

2.3.3. As a Chiral Auxiliary

In Section 1.2.5. the use of binaphthol (**2**) as a chiral auxiliary to direct the stereoselective alkylation of phenylacetic acid esters (**20**) was discussed. A similar use for 10'-hydroxy-10-(hydroxymethyl)-biphenanthryl (**92**) was investigated.

The esterification of (R)-(-)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) was carried out using phenylacetic acid in the presence of DCC and DMAP to give (R)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**113**) in 72% yield.[84] The diastereoselective alkylation of this ester was attempted using lithium diisopropylamide as the base and methyl iodide as the alkylating agent (Figure 65).[24] Two problems were encountered in this reaction. The first was the migration of the ester grouping from the phenolic position to the benzylic position and the second was over-alkykation. Alkylation of the enolate occurred, but there was also over-alkylation at the phenol in some cases. Thus, two products were formed, a monoalkylated, migration product (**114**) and an over-alkylated, migration product (**115**). These were formed in a 1:1 ratio and were inseparable. The migration of the ester can be explained in terms of the formation of the more stable phenolic anion in base. The over alkylation is more difficult to explain as this phenomenon has never been reported for the binaphthol case.



(R)-(-)-**113** **114** **115**

Figure 65. Alkylation of (R)-(-)-10-(Hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate.

To study the effect of over-alkylation, two methyl ethers were prepared. The first of these was involved the introduction of the methyl ether at the benzylic position. This was achieved using methyl iodide and silver oxide[89] to give (R)-(-)-10-(methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**116**) in 23% yield and with good recovery of unreacted starting material (Figure 67). Crystals of this compound were obtained from ethyl acetate and the X-ray structure determined (Figure 66) (Table 7, Appendix 1). In the solid state the oxygen of the ether is orientated in the opposite direction to that of the oxygen of the ester, suggesting that there may be no stabilisation of the enolate during the alkylation reaction.

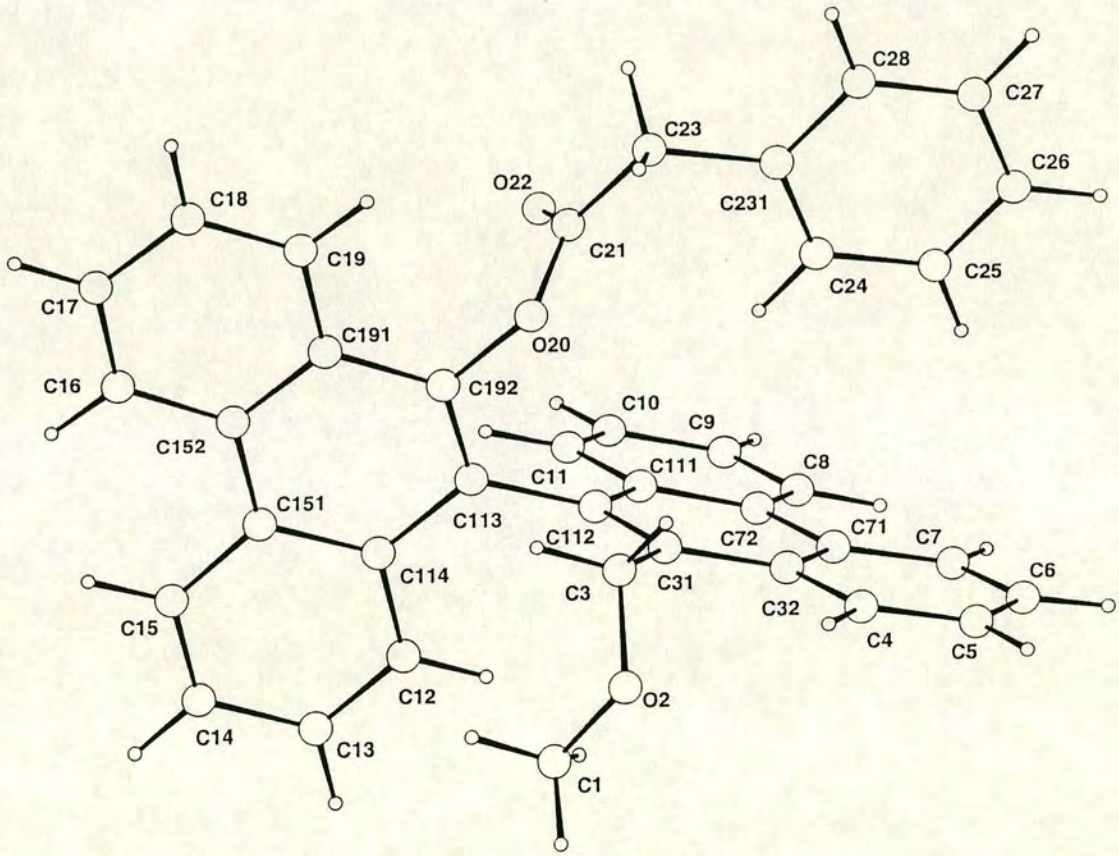
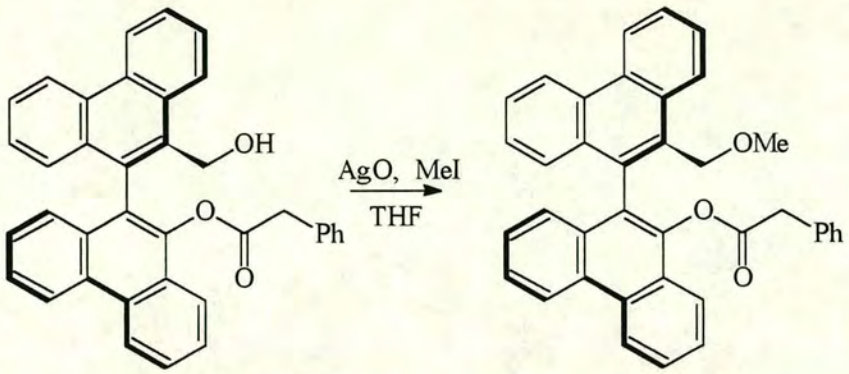


Figure 66. (R)-(-)-10-(Methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (116).



(R)-(-)-**113** (R)-(-)-**116**

Figure 67. Synthesis of (R)-(-)-10-(methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate.

The second methyl ether to be prepared was at the phenolic position. This involved a migration of the ester group from the initial phenolic position. Lithium diisopropyl amide was used to achieve this in 66% yield to give (R)-(-)-10'-hydroxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (**117**). Alkylation using anhydrous potassium carbonate and methyl iodide gave (R)-(-)-10'-methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (**118**) (Figure 68). Again crystals of this compound were obtained from ethyl acetate and the structure solved by X-ray crystallography (Figure 69) (Table 8, Appendix 1). From the structure it was observed that in this case the oxygen of the methyl ether was orientated in the same direction to that of the oxygen of the ester. This suggested that there might be the possibility of stabilisation of the enolate through chelation during the alkylation reaction. Another interesting feature of this structure was the edge on interaction of the phenyl ring with the adjacent biphenanthryl ring stabilising the structure.

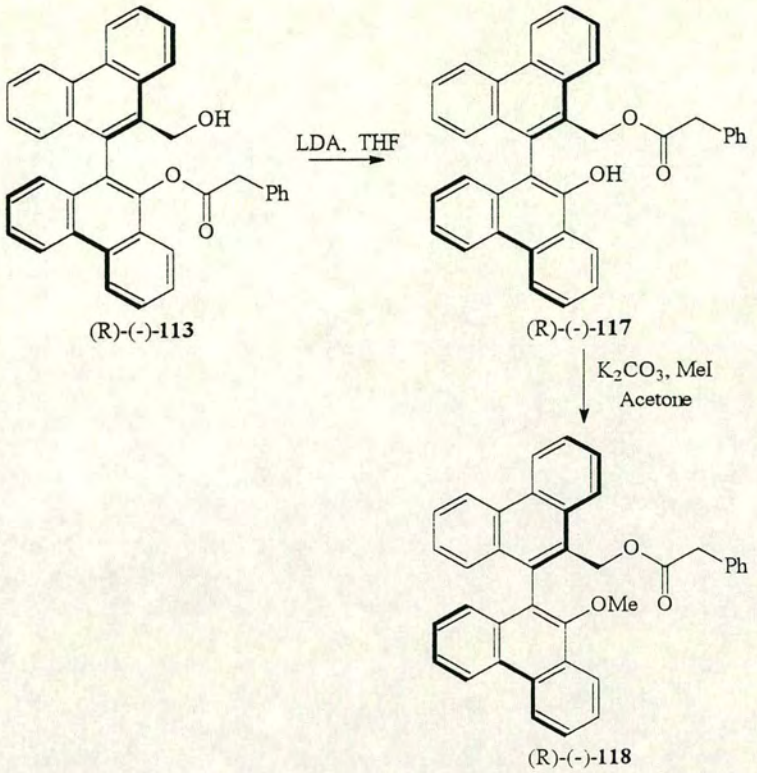


Figure 68. Synthesis of (R)-(-)-10'-Methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate.

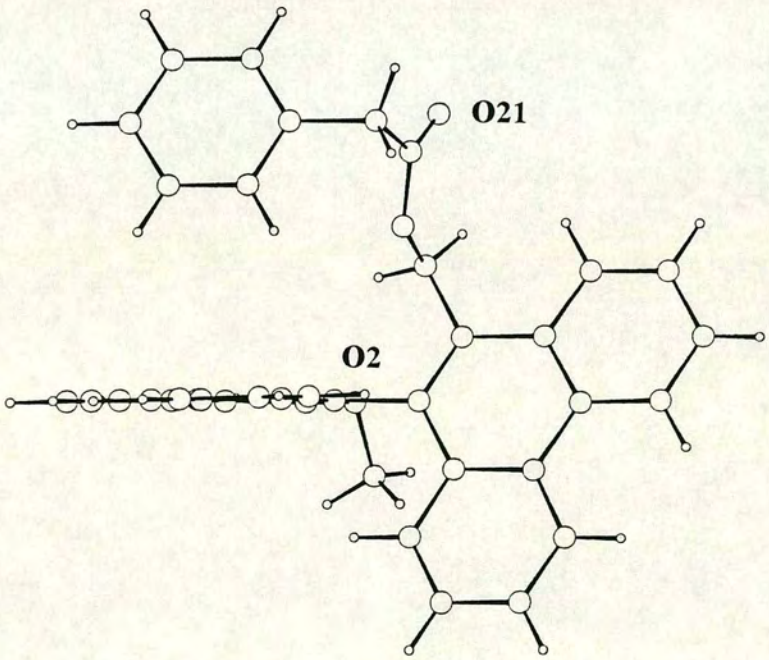


Figure 69. (R)-(-)-10'-Methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (118).

The alkylation reaction of (R)-(-)-10-(methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate **(116)** and (S)-(+)-10'-methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate **(118)** was investigated. Each was treated with one equivalent of lithium diisopropylamide in THF at -78°C followed by an excess of methyl iodide (Figure 70). After an aqueous work up and purification by wet flash chromatography, the diastereoselectivity of the reaction was measured by ^{1}H NMR. The resonances for the split methyl protons at about 1ppm were used to determine the diastereoselectivity. Approximately 1:1 ratios of diastereoisomers were obtained for both alkylation reactions. This mirrors the results observed for methyl ethers of binaphthol **(2)**.[24] Thus the oxygen atoms of the methyl ethers are not capable of chelating to the enolate and so direct the alkylation reaction.

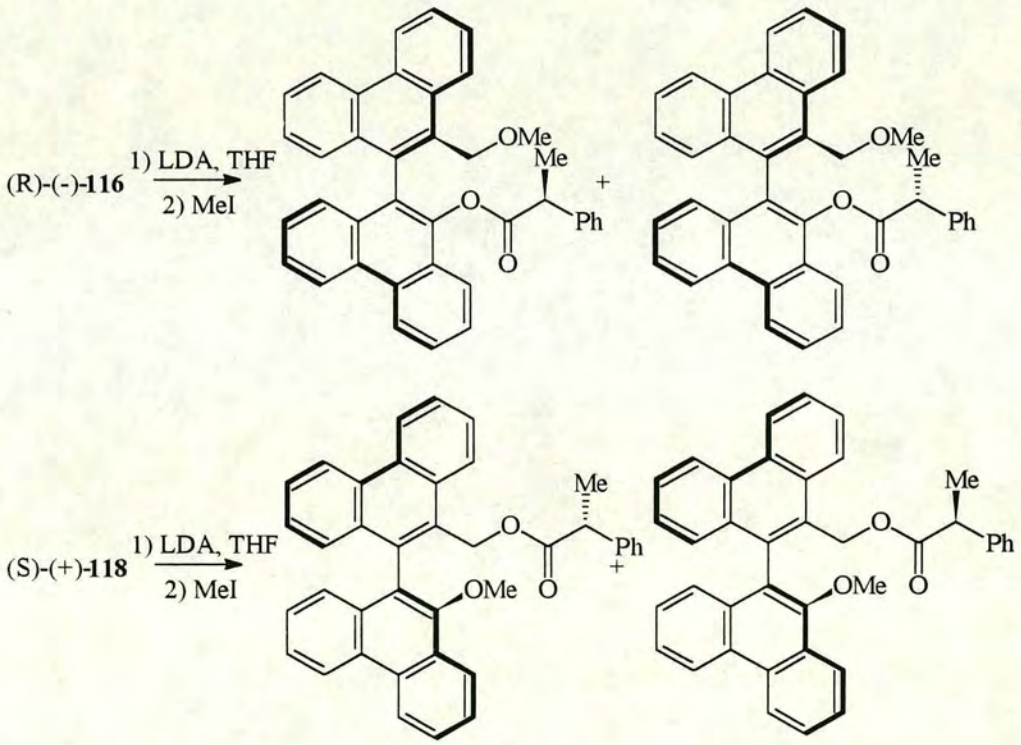
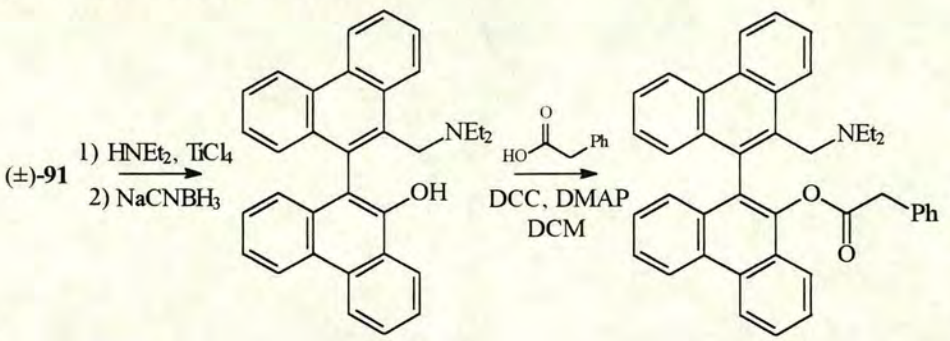


Figure 70. Attempted Diastereoselective Alkylations.

Thus, in the original alkylation of (R)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl **(113)** (Figure 65), if alkylation at the phenol occurred before alkylation at the enolate then chelation would not be possible. This would cause non-stereoselective alkylation of the enolate and the d.e. for the reaction would be lower.

A possible solution to these problems is the use of nitrogen based compounds instead of oxygen based ones. This would solve the both the problems of migration and over-alkylation. The nitrogen atom in the molecule would also co-ordinate to lithium forming a chelated transition state. Initial trials on the synthesis of such compounds was made using racemic material (Figure 71). Phenolic-aldehyde **(91)** was reacted with diethylamine to form an iminium salt which was reduced *in situ* with sodium cyanoborohydride to give (±)-10-(N,N-diethylaminomethylene)-10'-hydroxy-9,9'-biphenanthryl **(119)** in 91% yield.[90] Esterification of this tertiary amine was carried out, again using phenylacetic acid in the presence of DCC and DMAP. (±)-10-(N,N-Diethylaminomethylene)-9,9'-biphenanthryl 10'-phenylacetate **(120)** was formed in 52% yield after recrystallisation from ethyl acetate. Suitable crystals were again formed in ethyl acetate to allow the crystal structure to be determined (Figure 72) (Table 9, Appendix 1). From the crystal structure it was observed that one face of the ester grouping was blocked by the bulky (N,N-diethyl)amino grouping. This would hopefully be an advantage for the stereoselective alkylation reaction by directing the alkylation from one only face of the chelated enolate.



(±)-**119** (±)-**120**

Figure 71. Synthesis of (±)-10-(N,N-Diethylaminomethylene)-9,9'-biphenanthryl 10'-phenylacetate.

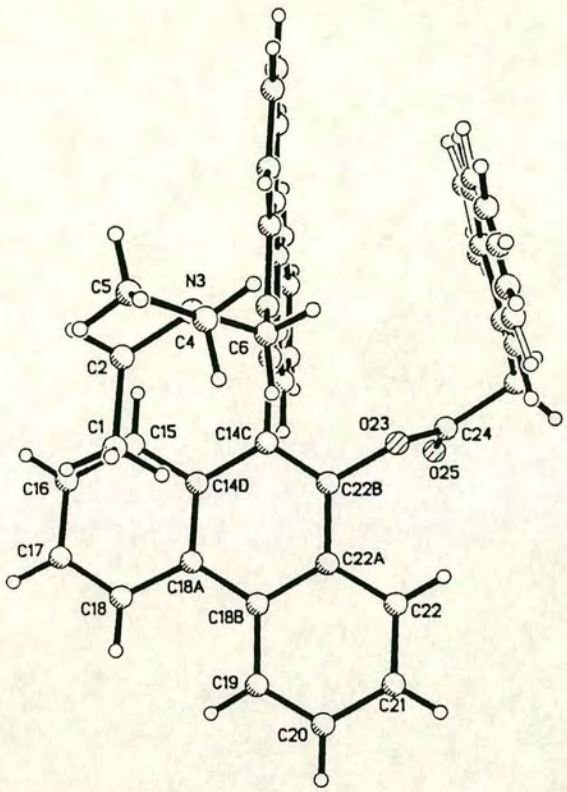


Figure 72. (±)-10-(N,N-Diethylaminomethylene)-9,9'-biphenanthryl 10'-phenylacetate (120).

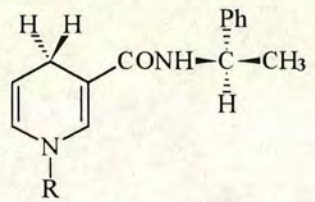
2.3.4. A Chiral Dihydropyridine

Chemists have long been envious of the remarkable rate acceleration and high regio- and stereoselectivities obtained under the mild conditions of enzyme catalysed reactions. Among the many enzymes playing important physiological roles *in vivo*, the pyridine nucleotide-dependent oxidoreductases have attracted organic chemists to attempt to simulate enzyme efficacy in simplified non-enzymatic systems. These enzymes are extremely important as they supply energy to all living cells through oxidation and reduction reactions. They effect a reversible and stereospecific transfer of hydrogen between coenzyme and substrate. The detailed mechanism of action of alcohol dehydrogenases that require nicotinamide adenine dinucleotide (NADH) as a co-factor

has been extensively studied. However, it is still not clear whether the hydrogen transfer arises from a one step hydride transfer or an electron transfer before a hydrogen radical transfer.

The stereospecificity of this system makes it very attractive to organic chemists. A number of studies have been made in the hope of shedding light on the *in vivo* hydrogen transfer. The potential for asymmetric reduction in organic synthesis using simplified NADH model compounds has also been investigated.

The first example of a non-enzymatic asymmetric reduction using optically active 1,4-dihydronicotinamide derivatives was reported in 1975.[91,92] 1,4-Dihydropyridines **(121)** (Figure 73) with (R)-α-methylbenzylamine at the 3-position were used as the chiral reductant. With these NAD derivatives, in the presence of magnesium perchlorate, methylbenzoyl formate and trifluoroacetophenone were reduced in 11-20% e.e..



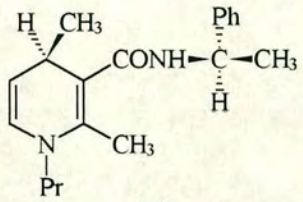
R = n-Propyl, Benzyl, 2,6-Dichlorobenzyl

121

Figure 73. A Chiral Dihydropyridine.

It has been known for some time that only one of the two diastereotopic hydrogens at the 4-position of the dihydropyridine nucleus in the natural coenzyme is transferred to and from substrates in the reactions catalysed by alcohol dehydrogenases.[93] Some exclusively use the (pro-R) hydrogen whereas others use only the (pro-S) hydrogen.

Chiral dihydropyridine reductant (**122**) (Figure 74) was examined and proved to be highly stereospecific in the reduction of various substrates (Table 10).[94] However, hydrogen transfer was attained at the expense of the chirality at C-4 of the dihydropyridine nucleus.



122

Figure 74. A More Enantioselective Chiral Dihydropyridine.

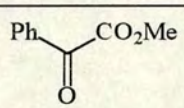
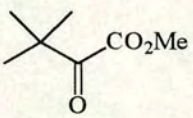
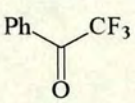
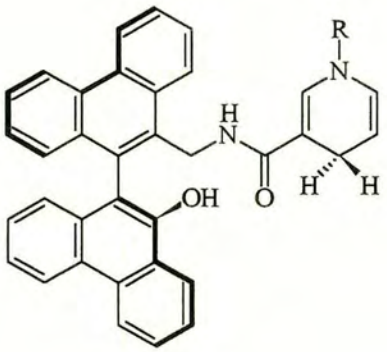
			Reduction products	
Substrate	***Config of (122)***	***% Conversion***	***% e.e.***	***Config.***
	R,R	100	97.6	R
"	S,R	100	96.5	S
"	S,R	100	94.7	S
	R,R	95	99	R
	R,R	60	70.3	R
"	S,R	56	70.3	S

Table 10. Enantioselective Reduction of Selected Substrates by (122).

A unique situation is found in the 4-methyl-substituted dihydronicotinamide system of (**122**). Access of the substrate is permitted only to the face bearing the sole hydrogen available for transfer. Thus, the substrate is forced to experience only one of the two

possible chiral environments, i.e. there is specific blockage of one face of the dihydropyridine.



123

Figure 75. Chiral Dihydropyridine Containing the Biphenanthryl Moiety

On the basis of this stereochemical concept, specific blockage of one face of the dihydropyridine intramolecularly would result in a greatly improved enantioselectivity for the reduction. A chiral dihydropryidine (**123**), based on the biphenanthryl moiety was designed (Figure 75).

Figure 76a. Model of the Chiral Dihydropyridine (123).

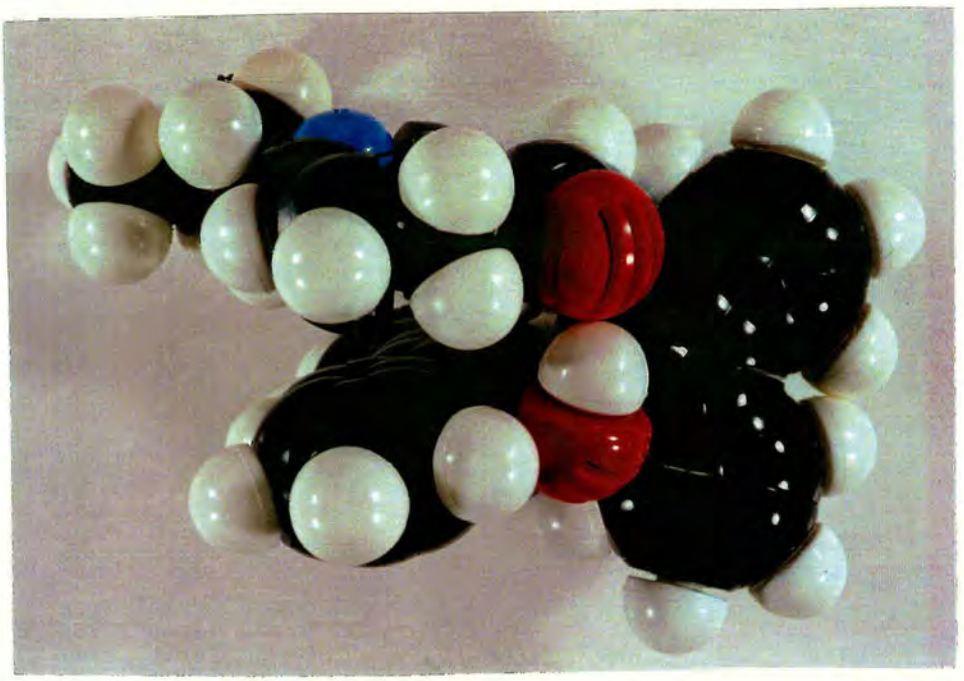
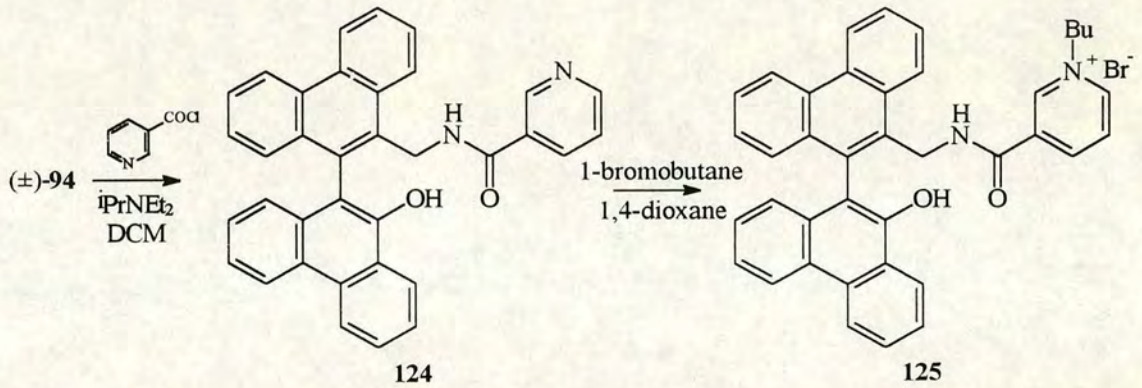


Figure 76b. Model of the Chiral Dihydropyridine (123).

Models (Figures 76a and 76b) of this compound have shown that one face of the dihydropyridine moiety is blocked by the biphenanthryl moiety. Thus the substrate will only have access to one face of the dihydropyridine. Only the hydrogen on this face of the molecule will be transferred and thus the reduction will be enantioselective. Models also suggested that the structure may be stabilised by a hydrogen bond between the hydrogen of the hydroxyl group and the carbonyl oxygen. It was also observed from the model that bulky groups in the prochiral substrate would point away from the adjacent biphenanthryl ring. Thus it would be possible to control the approach of the substrate to the 1,4-dihydropyridine. This system also has a major advantage over dihydropyridine **(122)**. On reduction, dihydropyridine **(122)** loses a chiral centre, thus only one cycle of reduction can occur. There is no loss of a chiral centre on reduction using dihydropyridine **(123)**. Thus the system can be recycled by the oxidation of a second alcohol, for example ethanol,[95] and only catalytic amounts of dihydropyridine **(123)** will be required.

Initial trials into the synthesis of such a system were again carried out on racemic material. (±)-10-(Aminomethyl)-10'-hydroxy-9,9'-biphenanthryl was reacted with the acid chloride of nicotinic acid in the presence of diisopropylethylamine. (±)-10-(Aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide (**124**) was formed in 60% yield after recrystallisation from DCM.[96] An attempt was made at the synthesis of the propyl bromide salt of this amide (**124**). However, the insolubility of the amide (**124**) and the relatively low boiling point of 1-bromopropane resulted in an unacceptably low yield of the salt even after 4 days at reflux.[96] Instead, the butyl bromide salt was prepared using the higher boiling 1-bromobutane and 1,4-dioxane as a solvent to increase the solubility of the amide (**124**). The butyl bromide salt of (±)-10-(aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide (**125**) was formed in 79% yield after reflux for only 24 hours (Figure 77).

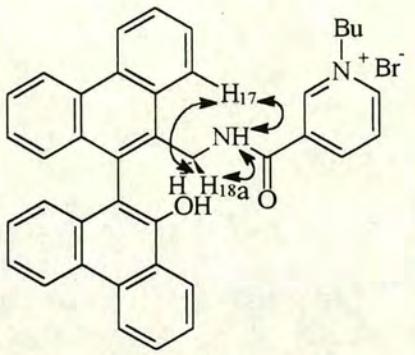


124 125

Figure 77. Synthesis of the Butyl Bromide Salt of (±)-10-(Aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide.

2D NMR studies were carried out on the butyl bromide salt of (±)-10-(aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide (**125**). 2D DQF-COSY and 2D ROESY experiments were performed which allowed the ^{1}H NMR to be assigned. The assignments are given in Appendix 3. The 2D ROESY experiment was used to show the through space interactions between the NH proton, H_{18a} and H_{17} on the adjacent

phenanthryl ring (Figure 78). These interactions agree with those observed for the proposed conformation of the reduced dihydropyridine (**123**) suggesting that this conformation is indeed correct.



125

Figure 78. Through Space Interactions of the Butyl Bromide Salt of (±)-10-(Aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide.

Attempts were made to reduce the butyl bromide salt (**125**) to the dihydropyridine (**123**), however, problems were encountered. Literature procedures for the reduction of pyridines to give 1,4-dihydropyridines involves the use of sodium dithionite and sodium bicarbonate[96] or sodium carbonate[97] under an argon atmosphere. The rapid appearance of a yellow colour using either set of reaction conditions suggested the reaction had occurred. Any attempt, however, to isolate the product of the reaction led to decomposition. The reduction was also attempted using sodium borohydride in methanol. Again there was yellow colouration, but it was not possible to isolate the product.

With the failure to accomplish the reaction chemically the process was studied electrochemically. The compound (**125**) was examined by means of cyclic voltammetry at a stationary platinum microdisk electrode in the aprotic solvent N,N-dimethylformamide (DMF). Figure 79 shows a typical voltammogram for this

compound, plainly exhibiting a chemically irreversible reduction, for which the forward cathodic peak potential is, in this case -1.28V *vs.* Ag/AgCl. Efforts to induce a degree of reversibility sufficient to observe a return anodic peak proved unsuccessful despite increasing the scan rates to $1000Vs^{-1}$ and lowering the temperature to 223K.

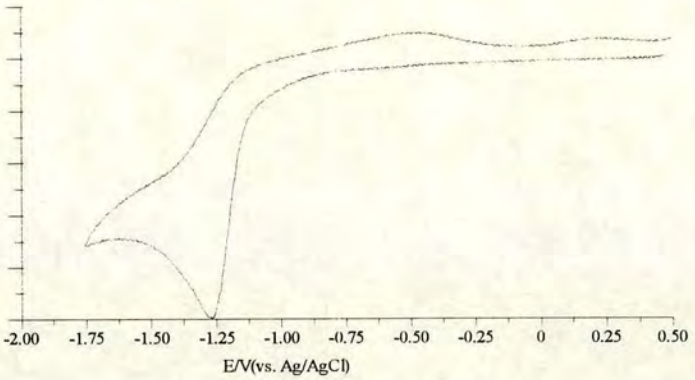


Figure 79. Cyclic Voltammogram of (125) in DMF/TBABF$_4$ 0.1M. Scan Rate = 100mVs^{-1}, Pt Disc Electrode.

From the cyclic voltammogram it was observed that the desired reduction had occurred to give the 1,4-dihydropyridine (**123**). On its formation, the 1,4-dihydropyridine (**123**) then underwent a rapid chemical process to give the 1,6-dihydropyridine. As the 1,4-dihydropyridine (**123**) was no longer present, it was not possible for the reverse oxidation process to occur and thus the return anodic peak was not observed.

The rapid formation of the 1,6-dihydropyridine was believed to be due to steric hindrance in the molecule. The two hydrogens at the 4- position of the pyridine ring in dihydropyridine (**123**) are sterically hindered by the adjacent phenanthryl ring. This steric hindrance is relieved by the formation of the 1,6-dihydropyridine. To overcome this problem it has been suggested that the inclusion of a second methylene carbon would further distance the pyridine ring from the biphenanthryl moiety while still retaining the desirable features outlined earlier for dihydropyridine (**123**). The structure of this dihydropyridine is given in Figure 80.

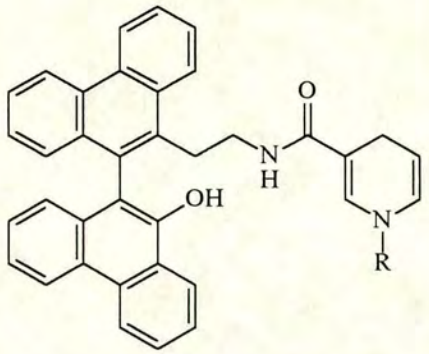


Figure 80. A More Attractive Dihydropyridine.

2.4. Conclusions and Future Work

A novel series of chiral organic compounds has been designed. The design of these compounds has been based around the highly successful binaphthyl moiety (**1**). Several modifications to the original system have been implemented to introduce originality to the system. These modifications include the addition of steric bulk and different co-ordinating functionalities. Another desirable benefit from these modifications would be an increase in stereoselectivity imparted to a reaction using these compounds as chiral auxiliaries.

A quick and efficient synthesis of these compounds was developed allowing access to unsymmetrically substituted biphenanthryl compounds in four steps from the commercially available 9-bromophenanthrene. A series of compounds have been synthesised. These include a phenolic-aldehyde (**91**), a hydroxy-phenol (**92**), an oxime (**93**) and an amino-phenol (**94**). Many other possibilities also exist including thiols and secondary amines.

Resolution of these compounds was obtained at the earliest possible point in the synthesis. This involved the formation and separation of diastereomeric hydrazones (**100**)

of the phenolic-aldehydes (**91**). The hydrazones (**100**) were converted to the phenolic-aldehyde (**91**) using ozonolysis. The resolving agent used was (S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (**97**). Resolution was confirmed by a second resolution involving the formation and separation of diastereomeric esters (**102**) of the hydroxy-phenol (**92**). The resolving agent used was (R)- or (S)-2-phenylpropionic acid (**101**). A crystal structure was obtained allowing the absolute configuration of the biphenanthryl moiety to be assigned.

Investigations into the possible uses of the system were carried out. The synthesis of a analogue of BINAP (**40**) was examined however problems were encountered due to the extra methylene carbon causing different reactivity at each functional group. Removal of the functionality at the benzylic position gave a compound which was unreactive in the phosphorylation reaction.

The chiral modification of lithium aluminium hydride was also examined. Lower enantioselectivities were obtained in comparison to the original binaphthol (**2**) or biphenanthrol (**71**). This was again believed to be due to the presence of the extra methylene carbon.

The use of hydroxy-phenol (**92**) as a chiral auxiliary to direct alkylation reactions was examined and problems were again encountered due to the extra methylene carbon. Ester migration and over-alkylation were observed. Methyl ether formation resulted in no stereoselectivity for the alkylation reaction. A nitrogen based reagent was proposed to overcome these problems.

A chiral dihydropyridine incorporating the biphenanthryl moiety was proposed and its synthesis investigated. The final step in the synthesis, reduction to yield the dihydropyridine, was not possible and a modified structure was proposed.

Thus, it is not possible to simply replace binaphthol (**2**) or biphenanthrol (**71**) with hydroxy-phenol (**92**). The extra methylene carbon in this compound caused vast differences in the chemistry of the system. This must be taken into account when designing future uses for the system.

Future work in this area involves the synthesis of other unsymmetrically substituted biphenanthryl compounds. Of particular interest is the synthesis of thiols and thioethers (Figure 81). This would allow the incorporation of a hard and a soft centre in the same molecule for co-ordination to metals.

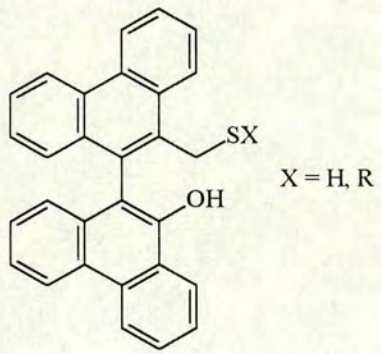


Figure 81. A Sulfur Containing Biphenanthryl.

Due to time constraints it has not been possible to fully investigate the chemistry of all the novel compounds and much work remains to be done in this area. The chemistry of the amino-phenol (**94**) is of particular interest and many uses can be envisaged for this compound. Also of interest are the tertiary amines (**119**), and their possible use to direct alkylation reactions.

3. Experimental

3.1. Notes

Chemicals were purchased from commercial sources such as Aldrich, Lancaster and Fluka and used without further purification. Melting points were determined in open capillaries using a Buchi 510 melting point apparatus. Optical rotations were measured on an AA1000 polarimeter (Optical Activity Limited) using a 1dm cell in the solvents indicated. Thin layer chromatography (tlc) was performed on aluminium sheets precoated with silica gel (Kieselgel 60 F254) in the solvent system indicated. Wet 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, methanolic sulfuric acid and ninhydrin. Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer in bromoform mull or DCM solution. Ultraviolet spectra were recorded on a Varian Cary 210 double beam spectrophotometer or on a Perkin Elmer Lamda 11 single beam spectrophotometer. CD spectra were recorded on a JASCO J600 spectropolarimeter in 1,4-dioxane. Fast atom bombardment mass spectra (FAB MS) were recorded on a Kratos MS50TC and electron impact mass spectra (EI MS) on a Kratos 902MS. Elemental analyses were carried out on a Perkin Elmer 2400 instrument. Proton NMR spectra were recorded on a AC 250 (250MHz) spectrometer in the solvent indicated relative to tetramethylsilane (TMS) as the internal standard. A Varian 600 Unity Plus Spectrometer was used to record NMR spectra at 600MHz. Carbon-13 NMR spectra were recorded on a AC250 (60MHz) instrument in the solvents indicated relative to TMS. Fluorine-19 NMR spectra were recorded on a AC 250 (235MHz) instrument relative to $CFCl_3$ as the external standard in the solvent indicated. X-ray structure determination was performed on a Stoe Stadi-4, four circle diffractometer equipped with an Oxford Cryosystem variable temperature device, graphite monochromated (Cu-K_α radiation, λ=1.54184Å). All solvents used were of analytical grade or were

distilled before use. The following were dried when required using the reagents indicated; dichloromethane (calcium hydride), diethyl ether (sodium wire), THF (sodium/benzophenone indicator).

3.2. Elemental Analysis on Tetrabenzo[a,c,g,i]fluorene Derivatives

Elemental analysis results on tetrabenzo[a,c,g,i]fluorine derivatives have generally been unsatisfactory. This has been attributed to the large number of quaternary carbons in the system. Increased oxygen concentrations and the addition of vanadium pentoxide have given improved combustion. Elemental analysis was also unsatisfactory for 2-hexanol due to its volatile nature.

3.3. Synthetic Procedures

Bis-(phenanthryl-9-yl)methanol (88).

A solution of 9-bromophenanthrene (100g, 39.0mmol) in dry THF (100ml) was slowly added to magnesium turnings (10g, 42.0mmol) 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, 19.4mmol) was added over a 20 minute period. After stirring for a further 2 hours at room temperature the mixture was poured onto ice/2N HCl (500ml). A white solid precipitated which was filtered off, washed with water (2 x 100ml) and ether (2x100ml) to give the *title compound* as a white solid (35g, 42%). **m.p.** 238-239°C, (lit.[74]238-239°C); **tlc** R_f (DCM) 0.49; **C.H.** Found C: 89.06%, H: 5.08%, $C_{29}H_{20}O$ Requires C: 90.06%, H: 5.08%; $\nu_{max.}$ ($CHBr_3$ mull) 3467 (-OH), 3078 (CH, aromatic), 1603, 1529 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 ($2885dm^3mol^{-1}l^{-1}$), 340 (3846), 299 (38942), 268 (77644)nm; **δH** (250 MHz, $CDCl_3$) 8.76 - 8.80 (m, 2H, aromatic), 8.68 - 8.73 (m, 2H, aromatic), 8.10 - 8.14 (m, 2H, aromatic), 7.80 (s, 1H, aromatic), 7.73 -7.76 (m, 2H, aromatic), 7.62 -7.70 (m, 4H, aromatic), 7.51 - 7.57 (m, 4H, aromatic) 7.31 (s, 1H, CHOH), 2.52 (s, 1H, OH) ppm; **δC** (60 MHz, $CDCl_3$) 136 24, 131.23, 130.81, 130.31, 129.99 (quaternary aromatic C), 120.00, 126.88, 126.64, 126.41, 125.10. 124.28, 123.19, 122.34 (aromatic CH), 69.73 (CHOH) ppm; **m/z** (FAB) 384 (M^+), 367 (M^+-OH); **HRMS** (FAB) Found: 384.15122, $C_{29}H_{20}O$ Requires 384.15142.

8b-H-Tetrabenzo[a,c,g,i]fluorene (89).

Bis-(phenanthryl-9-yl)methanol (**88**) (6.0g, 16mmol) was suspended in DCM (20ml) and trifluoroacetic acid (20ml) added. The reaction was monitored by the brief

appearance of a blue coloration. After stirring for 30 minutes the resulting yellow material was evaporated to dryness. Excess trifluoroacetic acid was removed by repeated evaporation of DCM (3x100ml). The resulting residue was triturated with ether to give the *title compound* as a yellow solid (5.5g, 96%). **m.p.** 280-282°C, (lit.[74]279-280°C); **tlc** R_f (DCM) 0.82; **C.H.** Found C: 95.45%, H: 5.09%, $C_{29}H_{18}$ Requires C: 95.05%, H: 4.95%; $\nu_{max.}$ ($CHBr_3$ mull) 3054 (CH, aromatic), 1606, 1562 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 374 (12593 $dm^3mol^{-1}cm^{-1}$), 358 (11111), 300 (34815), 254 (71111) nm; **δH** (360 MHz, $CDCl_3$) 8.81 - 8.77 (m, 2H, aromatic), 8.28 - 8.26 (m, 1H, aromatic), 8.09 - 8.11 (m, 1H, aromatic), 7.99 - 7.97 (m, 1H, aromatic), 7.85 -7.83 (m, 1H, aromatic), 7.74-7.72 (m, 1H aromatic) 7.71- 7.62 (m, 4H, aromatic),7.48 - 7.45 (m, 2H, aromatic),7.43 - 7.37 (m, 2H, aromatic),7.35 - 7.30 (m, 1H, aromatic), 7.13 -7.09 (m, 1H, aromatic), 5.41 (s, 1H CH) ppm; **m/z** (FAB) 366 (M^+); **HRMS** (FAB) Found 366.14193 $C_{29}H_{18}$ Requires 366.14085.

Ozonolysis of 8b-H-Tetrabenzo[a,c,g,i]fluorene (89).

A suspension of 8b-H-tetrabenzo[a,c,g,i]fluorene (**89**) (2.0g, 5.5mmol) was stirred in dry THF (100ml) at -78°C. Ozone gas (130V) was bubbled through the suspension at 1.8lmin^{-1} for 40 minutes to give an orange solution. Nitrogen was bubbled through to remove any unreacted ozone and the solvent removed *in vacuo*. Trituration with ether gave the *title compound* as a pale yellow solid (1.6g, 70%). **m.p.** decomp. at 177°C; **tlc** R_f (DCM) 0.76; $\nu_{max.}$ ($CHBr_3$ mull) 3067 (CH, aromatic), 1606 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 309 (11579$dm^3mol^{-1}cm^{-1}$), 295 (14737), 270 (35789), 259 (60000)nm; **δH** (250 MHz, $CDCl_3$) 8.76 - 8.80 (m, 2H, aromatic), 8.68 - 8.73 (m, 2H, aromatic), 8.08 - 8.04 (m, 1H, aromatic), 7.94 -7.90 (m, 2H, aromatic), 7.781 - 7.58 (m, 5H, aromatic), 7.53 -7.32 (m, 5H, aromatic), 7.08 - 7.02 (m, 1H, aromatic) 6,81 - 6.78 (m, 1H, aromatic), 5.49 (s, 1H, $C_{10}H$) ppm; **δC** (60 MHz, $CDCl_3$) 135.48, 134.58, 132.27, 130.55, 129.98, 129.81, 129.76, 128.16 (quaternary aromatic C), 130.85, 128.99, 128.35, 127.58, 127.30, 126.53, 126.44, 124.92,

124.19, 123.24, 123.12, 122.63, 122.06 (aromatic CH), 106.10 (quaternary C), 98.19 (CH) ppm; **m/z** (FAB) 415 (M^+); **HRMS** (FAB) Found: 415.13101, $C_{29}H_{20}O_3$ Requires 415.13342.

(±)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (91).

A suspension of the ozonide (**90**) (0.5g, 1.4mmol) in THF (25ml) was stirred at room temperature. A spatula of zinc powder followed by glacial acetic acid were added and the resulting mixture stirred for 20 minutes. The reaction was quenched by the addition of water (50ml). The mixture was extracted with DCM (3x30ml). The combined organics were washed with saturated $NaCO_3$ solution (3x30ml), water (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Recrystallisation from DCM gave the *title compound* as yellow crystals (0.35g,72%). **m.p.** 231-232°C; **tlc** R_f (DCM) 0.46; **C.H.** Found C: 87.10%,H: 4.69%, $C_{29}H_{18}O_2$ Requires C: 87.42%, H: 4.55%; $\nu_{max.}$ ($CHBr_3$ mull) 3484 (-OH), 3060 (CH, aromatic), 1672 (C=O stretch), 1593 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 354 (3889$dm^3mol^{-1}cm^{-1}$), 306 (14444), 286 (21111), 256 (63880)nm; **δH** (250 MHz, $CDCl_3$) 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 -7.30 (m, 2H, aromatic), 7.11 - 7.07 (m, 1H, aromatic) 5.18 (s, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 194.68 (C=O), 147.53 (phenolic C)140.69, 133.20, 132.46, 132.62, 130.93, 130.88, 130.04, 127.71, 126.34, 124.55 (quaternary aromatic C), 130.34, 128.44, 128.11, 128.04, 127.98, 127.81, 127.55, 126.95, 126.82, 125.58, 124.70, 123.10, 123.07, 122.72, 122.63 (aromatic CH) ppm; **m/z** (FAB) 399 (M^+), 382 (M^+-OH); **HRMS** (FAB) Found 398.13022, $C_{29}H_{18}O_2$ Requires 398.13068.

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (92).

Lithium aluminium hydride (0.29g, 7.4mmol) in dry THF (20ml) was stirred at room temperature under nitrogen. A solution of (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (3.0g, 7.4mmol) in dry THF (100ml) was added slowly and stirring continued for 30 minutes. The reaction was quenched by the careful addition of 2N HCl (20ml) and the pH adjusted to 1. The mixture was extracted with DCM (3x50ml) and the combined organics washed with water (50ml). Drying over $MgSO_4$, removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (2.9g, 95%) **m.p.** 155°C; **tlc** R_f (DCM) 0.21; **C.H.** Found C: 85.18%, H: 6.16%, $C_{29}H_{20}O_2$ Requires C: 86.98%, H: 5.03%; $\nu_{max.}$ ($CHBr_3$ mull) 3369 (-OH), 3073 (CH, aromatic),1620, 1596, 1492 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 359 ($2000dm^3mol^{-1}cm^{-1}$),342 (2000), 302 (15500), 278 (26500), 258 (77000)nm; **δH** (250 MHz, $CDCl_3$) 8.87 - 8.72 (m, 4H, aromatic), 8.42 - 8.36 (m, 2H, aromatic), 7.84 - 7.60 (m, 5H, aromatic), 7.54 -7.46 (m, 1H, aromatic), 7.38 -7.24 (m, 3H, aromatic), 7.09 - 7.04 (m, 1H, aromatic) 5.69 (s, 1H, -OH), 4.96 (d, 1H, J=11.9Hz), 4.76 (d, 1H, J=12.0Hz), 1.90 (s,1H, CH_2OH) ppm; **δC** (60 MHz, $CDCl_3$) 147.28 (phenolic C), 135.68, 132.13, 131.33, 131.14, 131,06, 130.82, 130.55, 130.09, 126.55, 125.13 (quaternary aromatic C), 127.50, 127.46, 127.44, 127.32, 127.28, 127.22, 126.71, 125.58, 125.30, 124.38, 123.04, 122.71, 122.68, 122.52, (aromatic CH) 113.91 (benzylic C), 60,68 (CH_2) ppm; **m/z** (FAB) 400 (M^+); **HRMS** (FAB) Found 400.14774, $C_{29}H_{20}O_2$ Requires 400.14633.

(±)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (93).

A suspension of (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (1.0g, 2.5mmol), hydroxylamine hydrochloride (2.0g, 28mmol) and sodium acetate (4.0g, 48mmol) in ethanol (50ml) was stirred at room temperature overnight. The reaction was quenched by the addition of water (50ml) and extracted with DCM (3x50ml). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo*.

Purification by wet flash chromatography (100% DCM) and recrystallisation from DCM gave the *title compound* as a white solid (67g, 64%). **m.p.** Decomp. at 178°C; **tlc** R_f (DCM) 0.19; **C.H.N.** Found C: 83.23%, H: 4.60%, N: 3.17%, $C_{29}H_{19}NO_2$ Requires C: 84.24%, H: 4.63%, N: 3.39%; $\nu_{max.}$ ($CHBr_3$ mull) 3523 (-OH), 3285 (N-OH), 3070 (CH, aromatic),1624, 1598, 1493 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 ($3540dm^3mol^{-1}l^{-1}$), 341 (4130), 301 (24189), 257 (101180)nm; **δH** (250 MHz, $CDCl_3$/DMSO) 10.46 (b, 1H, N-OH), 8.73 - 8.70 (m, 1H, aromatic), 8.58 - 8.39 (m, 4H, aromatic), 8.19 - 8.13 (m, 1H, aromatic), 7.93 (s, 1H, N=CH), 7.51 - 7.31 (m, 5H, aromatic), 7.25 -6.90 (m, 4H, aromatic), 6.74 - 6.71 (m, 1H, aromatic) ppm; **δC** (60 MHz, $CDCl_3$) 147.70 (CH=N), 147.32 (phenolic C), 133.01, 131.85, 130.52, 130.45, 129.98, 129.01, 128.22, 125.91, 121.83 (quaternary aromatic C), 127.01, 126.67, 126.41, 126.21, 126.16, 126.13, 126.07, 125.58, 125.22, 125.18, 124.43, 123.01, 122.58, 121.76, 121.71, 121.60 (aromatic CH) 112.45 (benzylic C) ppm; **m/z** (FAB) 414 (MH^+), 396 (MH^+-OH); **HRMS** (FAB) Found 414.15066, $C_{29}H_{19}NO_2$ Requires 414.14940.

(±)-10-(Aminomethyl)-10'-hydroxy-9,9'biphenanthryl (94).

Lithium aluminium hydride (33mg, 0.85mmol) in dry THF (5ml) was stirred at room temperature under nitrogen. A solution of (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (**93**) (0.35g, 0.85mmol) in dry THF (25ml) 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 2N NaOH (10ml) and the pH adjusted to 14. The mixture was extracted with DCM (3x30ml) and the combined organics washed with water (30ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a yellow solid. Purification by wet flash chromatography (2% MeOH/DCM) gave the *title compound* as a pale yellow solid (0.31g, 91%) **m.p.** 184-5°C; **tlc** R_f (5% MeOH/DCM) 0.52; **C.H.N.** Found C: 87.04%, H: 5.67%, N: 3.05%, $C_{29}H_{21}NO$ Requires C: 87.19%, H: 5.30%, N: 3.51%; $\nu_{max.}$ ($CHBr_3$ mull) 3517 (-OH), 3368 (NH_2) 3070 (CH, aromatic), 1603, 1582, 1492

(aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 359 (11947$dm^3mol^{-1}l^{-1}$), 341 (12831), 301 (64159), 262 (172124)nm; **δH** (250 MHz, $CDCl_3$) 8.90 - 8.86 (m, 1H, aromatic), 8.81 - 8.70 (m, 3H, aromatic), 8.57 - 8.53 (m, 1H, aromatic), 8.24 - 8.20 (m, 1H, aromatic), 7.80 - 7.66 (m, 4H, aromatic), 7.60 -7.54 (m, 1H, aromatic), 7.50 - 7.43 (m, 1H, aromatic), 7.27 -7.15 (m, 3H, aromatic), 7.03 - 7.00 (m, 1H, aromatic), 4.60 (d, 1H, J=12.1Hz), 3.96 (d, 1H, J=12.2Hz), 3.70 (b, 2H, NH_2) ppm; **δC** (60 MHz, $CDCl_3$) 149.61 (phenolic C), 134.60, 133.05, 132.61, 131.64, 131.29, 131.08, 130.36, 130.02, 128.74, 127.92 (quaternary aromatic C), 127.99, 127.26, 127.10, 126.94, 126.71, 126.55, 126.04, 124.02, 123.92, 123.57, 123.52, 122.48, 122.36, 122.36, 122.32 (aromatic CH) 117.35 (benzylic C), 65.75 (CH_2) ppm; **m/z** (FAB) 400 (MH^+); **HRMS** (FAB) Found 399.15972, $C_{29}H_{21}NO$ Requires 399.16231.

(S)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine Hydrazones of (±)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (100).

A suspension of (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (3.00g, 7.50mmol) in dry DCM (100ml) was stirred at 0°C. (S)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (**97**) (1.03g, 7.50mmol) was added and stirring continued for 2 hours at 0°C. Removal of the solvent *in vacuo* gave a yellow foam. The two diastereoisomers were separated by successive wet flash chromatography (100% DCM) and recrystallisation from ethyl acetate.

Diastereoisomer A: (1.49g, 78% of available diastereoisomer). **m.p.** 123-4°C; **tlc** R_f (DCM) 0.29; **C.H.N.** Found C: 82.14%, H: 5.87%, N: 5.17%, $C_{35}H_{31}N_2O_2$ Requires C: 82.33%, H: 5.92%, N: 5.49%; $\nu_{max.}$ ($CHBr_3$ mull) 3615 (-OH), 3070 (CH, aromatic), 2975 (CH, aliphatic), 1616, 1590, (aromatic rings), 1572 (C=N) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (14468$dm^3mol^{-1}l^{-1}$), 342 (161701), 298 (30638), 256 (117021) nm; **δH** (250 MHz, $CDCl_3$) 8.95 - 8.70 (m, 5H, aromatic), 8.53 - 8.49 (m, 1H, aromatic), 7.82 - 7.67 (m, 4H, aromatic), 7.62 -7.56 (m, 1H, aromatic),7.50 - 7.43 (m, 2H, aromatic), 7.30 -7.23 (m, 3H, aromatic), 7.11 - 7.07 (m, 1H, aromatic),6.32 (s, 1H, -

OH), 3.51 - 3.47 (m, 1H, N-CH), 3.44 - 3,28 (m, 2H, O-CH_2), 3.16 (s, 3H, -OMe), 3.08 - 3.01 and 2.62 - 2.16 (2xm, 2x1H, N-CH_2), 1.83 - 1.60 (m, 4H, 2xCH_2) ppm; **δC** (60 MHz, $CDCl_3$) 147.47 (phenolic C), 132.73, 132.50, 131.20, 130.97, 130.31, 130.08, 128.97, 127.45, 123.18 (quaternary aromatic C), 131.38 (HC=N), 127.12, 127.06, 126.91, 126.82, 126.41, 125.86, 123.95, 123.33, 122.77, 122.51, 122.39 (aromatic CH), 115.50 (benzylic C), 74.05 (O-CH_2), 62.80 (N-CH), 58.83 (O-Me), 48.83 (N-CH_2), 26.42 (CH_2), 21.95 (CH_2) ppm; **m/z** (FAB) 511 (MH^+); **HRMS** (FAB) Found 511.23857, $C_{35}H_{31}N_2O_2$ Requires 511.23855; $[\alpha]_D^{22}$=-240°, c=0.10, DCM.

Diastereoisomer B: (1.35g, 70% of available diastereoisomer) **m.p.** 192-4°C; **tlc** R_f (DCM) 0.20; **C.H.N.** Found C: 81.95%, H: 5.82%, N: 5.24%, $C_{35}H_{31}N_2O_2$ Requires C: 82.33%, H: 5.92%, N: 5.49%; $\nu_{max.}$ ($CHBr_3$ mull) 3616 (-OH), 3067 (CH, aromatic), 2928 (CH, aliphatic), 1588, (aromatic rings), 1570 (C=N) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (17347$dm^3mol^{-1}l^{-1}$), 342 (18878), 300 (40816), 256 (150570) nm; **δH** (250 MHz, $CDCl_3$) 8.97 - 8.93 (m, 1H, aromatic), 8.87 - 8.70 (m, 4H, aromatic), 8.48 - 8.44 (m, 1H, aromatic), 7.81 - 7.66 (m, 4H, aromatic), 7.63 -7.56 (m, 1H, aromatic),7.52 - 7.44 (m, 1H, aromatic), 7.37 (s, 1H, CH=N), 7.30 -7.24 (m, 3H, aromatic), 7.13 - 7.09 (m, 1H, aromatic),6.05 (s, 1H, -OH), 3.43 - 3.36 (m, 3H, N-CH and O-CH_2), 3.27 (s, 3H, -OMe), 3.04 - 2.99 and 2.44 - 2.40 (2xm, 2x1H, N-CH_2), 1.78 - 1.57 (m, 4H, 2xCH_2) ppm; **δC** (60 MHz, $CDCl_3$) 147.37 (phenolic C), 132.98, 132.32, 131.17, 131.06, 130.32, 130.08, 129.10, 125.87, 125.56, 123.95, 123.33 (quaternary aromatic C), 131.38 (HC=N), 127.45, 127.12, 127.08, 126.92, 126.89, 126.82, 126.44, 126.38, 125.77, 124.01, 123.18, 122.71, 122.53, 122.40 (aromatic CH), 114.97 (benzylic C), 74.01 (O-CH_2), 62.57 (N-CH), 58.98 (O-Me), 48.69 (N-CH_2), 26.21 (CH_2), 21.76 (CH_2) ppm; **m/z** (FAB) 511 (MH^+); **HRMS** (FAB) Found 511.23939, $C_{35}H_{31}N_2O_2$ Requires 511.23855; $[\alpha]_D^{22}$=+97°, c=0.10, DCM.

(S)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (91).

A suspension of (S,S"-2)-(-)-10'-hydroxy-9,9'-biphenanthryl-10-(methylideneamino)-2"-(methoxymethyl)pyrrolidine (**100**) (diastereoisomer A) (1.4g, 2.7mmol) was stirred in dry DCM (75ml) at -78°C. Ozone gas (130V) was bubbled through the solution at 1.4lmin^{-1} for 10 minutes to give a dark brown solution. Nitrogen was bubbled through to remove any unreacted ozone and the solvent removed *in vacuo.* Purification by wet flash chromatography (100% DCM) gave the *title compound* as a yellow foam (0.50g, 49%). **m.p.** 229-30°C; **tlc** R_f (DCM) 0.49; **C.H.** Found C: 87.53%, H: 4.88%, $C_{29}H_{18}O_2$ Requires C: 87.42%, H: 4.55%; $\nu_{max.}$ ($CHBr_3$ mull) 3536 (-OH), 3064 (CH, aromatic), 1676 (C=O stretch), 1597, 1491 (aromatic rings) cm^{-1}; ν_{max} (DCM solution) 3688 (OH of hemiacetal), 3536 (OH of phenol), 3080 (CH, aromatic),1685 (C=O stretch), 1601 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 372 (4382dm^{3}mol^{-1}l^1), 355 (7171), 256 (87251) nm; **δH** (250 MHz, $CDCl_3$) 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) 5.19 (s, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 194 90 (C=O), 147.80 (phenolic C)140.73, 133.18, 132.44, 132.61, 130.89, 130.85, 130.03, 127.88, 126.32 124.54 (quaternary aromatic C), 130.33, 128.43, 128.10, 128.01, 127.79, 127.54, 127.47, 126.94, 126.80, 125.57, 124.69, 123.09, 123.04, 122.71, 122.62 (aromatic CH), 110.59 (benzylic C) ppm; **m/z** (FAB) 398 (M^+), 381 (M^+-OH); **HRMS** (FAB) Found 398.13102, $C_{29}H_{18}O_2$ Requires 398.13068; $[\alpha]_D^{22}$=-78°, c=0.10, DCM, $[\alpha]_D^{22}$=-56°, c=1.0, DCM,

(S)-(+)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (92).

Lithium aluminium hydride (10mg, 0.25mmol) in dry THF (2ml) was stirred at room temperature under nitrogen. A solution of (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (0.10g, 0.25mmol) in dry THF (8ml) was added slowly and stirring continued for 30 minutes. The reaction was quenched by the careful addition

of 2N HCl (5ml) and the pH adjusted to 1. The mixture was extracted with DCM (3x10ml) and the combined organics washed with water (10ml). Drying over $MgSO_4$, removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (96mg, 95%) **m.p.** 164-5°C; **tlc** R_f (DCM) 0.18; **C.H.** Found C: 86.73%, H: 6.26%, $C_{29}H_{20}O_2$ Requires C: 86.98%, H: 5.03%; $\nu_{max.}$ ($CHBr_3$ mull) 3524 (-OH), 3071 (CH, aromatic), 1620, 1597, 1491 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (4464$dm^3mol^{-1}l^{-1}$), 341 (5357), 300 (35268), 159 (166071) nm; **δH** (250 MHz, $CDCl_3$) 8.88 - 8.73 (m, 4H, aromatic), 8.44 - 8.40 (m, 2H, aromatic), 7.83 - 7.62 (m, 5H, aromatic), 7.54 -7.47 (m, 1H, aromatic), 7.38 -7.25 (m, 3H, aromatic), 7.09 - 7.05 (m, 1H, aromatic), 5.61 (b, 1H, -OH), 4.98 (dd, 1H, J=11.8Hz and 4.0Hz), 4.78 (d, 1H, J=11.8Hz and 5.0Hz), 1.82 (b, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 147.27 (phenolic C), 135.69, 132.56, 131.32, 131.14, 131.05, 130.79, 130.53, 130.06, 126.53, 125.10 (quaternary aromatic C), 127.50, 127.47, 127.43, 127.33, 127.27, 127.22, 126.71, 125.56, 125.30, 124.39, 123.23, 123.05, 122.72, 122.68, 122.51, (aromatic CH) 113.90 (benzylic C), 60.69 (CH_2) ppm; **m/z** (FAB) 400 (M^+), 383(M^+-OH); **HRMS** (FAB) Found 400.14649, $C_{29}H_{20}O_2$ Requires 400.14633; $[\alpha]_D^{22}$=+50°, c=0.10, DCM.

(S,S"-2)-(-)-10'-Hydroxy-9,9'-biphenanthryl-10-(methylideneamino)-2"-(methoxymethyl)pyrrolidine (100).

A suspension of (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (50mg, 0.13mmol) in dry DCM (10ml) was stirred at 0°C. (S)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (**97**) (18mg, 0.14mmol) was added and stirring continued for 2 hours at 0°C. Removal of the solvent *in vacuo* gave a yellow foam. Purification by wet flash chromatography gave the *title compound* as a yellow foam (57mg, 89%). **m.p.** 253-5°C; **tlc** R_f (DCM) 0.22; **C.H.N.** Found C: 82.77%, H: 5.98%, N: 4.95%, $C_{35}H_{31}N_2O_2$ Requires C: 82.33%, H: 5.92%, N: 5.49%; $\nu_{max.}$ ($CHBr_3$ mull) 3517 (-OH), 3068 (CH, aromatic), 2973 (CH, aliphatic), 1618, 1597, 1489 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (14530$dm^3mol^{-1}l^{-1}$), 342 (16239), 298 (30769), 256 (117521)

nm; **δH** (250 MHz, $CDCl_3$) 8.92 - 8.68 (m, 5H, aromatic), 8.51 - 8.48 (m, 1H, aromatic), 7.81 - 7.66 (m, 4H, aromatic), 7.62 -7.55 (m, 1H, aromatic), 7.49 - 7.43 (m, 2H, aromatic), 7.28 -7.22 (m, 3H, aromatic), 7.09 - 7.05 (m, 1H, aromatic),6.29 (s, 1H, -OH), 3.49 - 3.46 (m, 1H, N-CH), 3.37 - 3.27 (m, 2H, O-CH_2), 3.15 (s, 3H, -OMe), 3.06 - 3.02 and 2.58 - 2.16 (2xm, 2x1H, N-CH_2), 1.80 - 1.56 (m, 4H, 2xCH_2) ppm; **δC** (60 MHz, $CDCl_3$) 147.48 (phenolic C), 132.74, 132.52, 131.20, 130.98, 130.32, 130.09, 128.97, 127.45, 123.18 (quaternary aromatic C), 131.38 (HC=N), 127.13, 127.07, 126.92, 126.85, 126.83, 126.45, 126.42, 125.88, 123.95, 123.34, 122.77, 122.51, 122.40 (aromatic CH), 115.50 (benzylic C), 74.05 (O-CH_2), 62.80 (N-CH), 58.83 (O-Me), 48.83 (N-CH_2), 26.41 (CH_2), 21.95 (CH_2) ppm; **m/z** (FAB) 511 (MH^+); **HRMS** (FAB) Found 511.24320, $C_{35}H_{31}N_2O_2$ Requires 511.23855; $[\alpha]_D^{22}$=-240°, c=0.10, DCM.

(S)-(-)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (93).

A suspension of (S)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (0.10g, 0.25mmol), hydroxylamine hydrochloride (0.20g, 3.0mmol) and sodium acetate (0.42g, 4.8mmol) in ethanol (20ml) 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 $MgSO_4$ and the solvent removed *in vacuo*. Purification by wet flash chromatography (100% DCM) and recrystallisation from DCM gave the *title compound* as a white solid (91mg, 88%). **m.p.** Decomp. at 158°C; **tlc** R_f (DCM) 0.17; **C.H.N.** Found C: 83.62%, H: 4.51%, N: 3.14%, $C_{29}H_{19}NO_2$ Requires C: 84.24%, H: 4.63%, N: 3.39%; $\nu_{max.}$ ($CHBr_3$ mull) 3526 (-OH), 3060 (CH, aromatic),1620, 1597, 1491 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (2390$dm^3mol^{-1}l^{-1}$), 341 (2789), 301 (18327), 259 (74502) nm; **δH** (250 MHz, $CDCl_3$/DMSO) 10.50 (b, 1H,N-OH), 8.78 - 8.74 (m, 1H, aromatic), 8.64 - 8.45 (m, 4H, aromatic), 8.25 - 8.18 (m, 1H, aromatic), 8.01 - 8.00 (m, 1H, aromatic), 7.57 - 7.37 (m, 5H, aromatic), 7.29 -6.95 (m, 5H, aromatic), 6.88 - 6.77 (m, 1H, aromatic) ppm; **δC** (60 MHz, $CDCl_3$/DMSO) 147.93 (C=N), 147.48 (phenolic C),

132.95, 132.06, 130.73, 130.27, 130.22, 129.30, 128.65, 126.75, 125.58, 125.51 (quaternary aromatic C), 127.25, 126.96, 126.65, 126.53, 126.47, 126.38, 126.34, 125.81, 125.39, 125.75, 123.27, 122.86, 122.08, 121.95, 121.84, (aromatic CH) 111.84 (benzylic C) ppm; **m/z** (FAB) 413 (M^+), 396 (M^+-OH); **HRMS** (FAB) Found 414.14390, $C_{29}H_{19}NO_2$ Requires 414.14940; $[\alpha]_D^{22}$=-30°, c=0.10, DCM.

(S)-(-)-10-(Aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (94).

Lithium aluminium hydride (14mg, 0.36mmol) in dry THF (5ml) was stirred at room temperature under nitrogen. A solution of (S)-(-)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (**93**) (0.15g, 0.36mmol) 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 2N NaOH (10ml) and the pH adjusted to 14. The mixture was extracted with DCM (3x15ml) and the combined organics washed with water (20ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a yellow solid. Purification by wet flash chromatography (2% MeOH/DCM) gave the *title compound* as a pale yellow solid (0.11g, 73%) **m.p.** 185-6°C; **tlc** R_f (2% MeOH/DCM) 0.34; **C.H.N.** Found C: 88.07%, H: 5.75%, N: 3.23%, $C_{29}H_{21}NO$ Requires C: 87.19%, H: 5.30%, N: 3.51%; $\nu_{max.}$ ($CHBr_3$ mull) 3515 (-OH), 3365 (NH_2) 3067 (CH, aromatic), 1582, 1489 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 360 (2147$dm^3mol^{-1}l^{-1}$), 343 (2147), 303 (15644), 259 (70859) nm; **δH** (250 MHz, $CDCl_3$) 8.83 - 8.62 (m, 4H, aromatic), 8.45 - 8.41 (m, 1H, aromatic), 8.16 - 8.12 (m, 1H, aromatic), 7.72 - 7.53 (m, 5H, aromatic), 7.49 -7.42 (m, 1H, aromatic), 7.26 -7.16 (m, 3H, aromatic), 6.98 - 6.94 (m, 1H, aromatic), 4.60 (b, 2H, NH_2), 4.48 (d, 1H, J=12.4Hz), 3.88 (d, 1H, J=12.6Hz) ppm; **δC** (60 MHz, $CDCl_3$) 149.19 (phenolic C), 133.19, 132.82, 131.43, 131.29, 130.96, 130.51, 129.81, 126.54 (quaternary aromatic C), 127.94, 127.34, 127.12, 126.97, 126.91, 126.79, 126.47, 125.83, 124.09, 123.73, 123.66, 123.41, 122.51, 122,40, 122.36 (aromatic CH) 116.65 (benzylic C), 40.67 (CH_2) ppm; **m/z** (FAB) 399 (M^+), 383

(M^+-OH); **HRMS** (FAB) Found 399.16077, $C_{29}H_{21}NO$ Requires 399.16231; $[\alpha]_D^{22}$=-140°, c=0.10, DCM.

(R)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (91).

A suspension of (R,S"-2)-(+)-10'-hydroxy-9,9'-biphenanthryl-10-(methylideneamino)-2"-(methoxymethyl)pyrrolidine (**100**) (diastereoisomer B) (1.0g, 2.0mmol) was stirred in dry DCM (50ml) at -78°C. Ozone gas (130V) was bubbled through the solution at 1.4lmin^{-1} for 7 minutes to give a dark brown solution. Nitrogen was bubbled through to remove any unreacted ozone and the solvent removed *in vacuo*. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a yellow foam (0.49g, 63%). **m.p.** 234-5°C; **tlc** R_f (DCM) 0.52; **C.H.** Found C: 87.15%, H: 4.50%, $C_{29}H_{18}O_2$ Requires C: 87.42%, H: 4.55%; $\nu_{max.}$ ($CHBr_3$ mull) 3536 (-OH), 3067 (CH, aromatic), 1679 (C=O stretch), 1598, 1491 (aromatic rings) cm^{-1}; $\nu_{max.}$ (DCM solution) 3683 (OH of hemiacetal), 3536 (OH of phenol), 3081 (CH, aromatic), 1685 (C=O stretch), 1600 (aromatic rings); $\lambda_{max.}$ (DCM) 372 (4636dm^{3}mol^{-1}l^{-1}), 355 (7285), 256 (80795) nm; **δH** (250 MHz, $CDCl_3$) 10.14 (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 -7.29 (m, 2H, aromatic), 7.11 - 7.07 (m, 1H, aromatic) 5.23 (s, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 194 73 (C=O), 147.83 (phenolic C)140.79, 133.17, 132.46, 132.61, 130.88, 130.85, 130.04, 128.01, 126.90, 126.32 (quaternary aromatic C), 130.32, 128.42, 128.09, 127.97, 127.79, 127.54, 127.48, 126.94, 126.79, 125.57, 124.69, 124,56, 123.10, 123.04, 122.72, 122.62 (aromatic CH) ppm; **m/z** (FAB) 399 (M^+), 382 (M^+-OH); **HRMS** (FAB) Found 398.13022, $C_{29}H_{18}O_2$ Requires 398.13068; $[\alpha]_D^{22}$=+48°, c=0.10, DCM, $[\alpha]_D^{22}$=+71°, c=1.0, DCM.

(R)-(-)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (92).

Lithium aluminium hydride (5.0mg, 0.13mmol) in dry THF (2ml) was stirred at room temperature under nitrogen. A solution of (R)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (50mg, 0.19mmol) in dry THF (8ml) was added slowly and stirring continued for 30 minutes. The reaction was quenched by the careful addition of 2N HCl (5ml) and the pH adjusted to 1. The mixture was extracted with DCM (3x5ml) and the combined organics washed with water (5ml). Drying over $MgSO_4$, removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (38mg, 77%) **m.p.** 163-4°C; **tlc**, R_f (DCM) 0.23; **C.H.** Found C: 85.04%, H: 6.20%, $C_{29}H_{20}O_2$ Requires C: 86.98%,H: 5.03%; $\nu_{max.}$ ($CHBr_3$ mull) 3230 (-OH), 3064 (CH, aromatic),1620, 1598, 1492 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 ($4444dm^3mol^{-1}l^{-1}$), 341 (5333), 300 (35111), 259 (144889) nm; **δH** (250 MHz, $CDCl_3$) 8.88 - 8.73 (m, 4H, aromatic), 8.44 - 8.40 (m, 2H, aromatic), 7.83 - 7.62 (m, 5H, aromatic), 7.54 -7.47 (m, 1H, aromatic), 7.39 -7.25 (m, 3H, aromatic), 7.09 - 7.05 (m, 1H, aromatic), 5.60 (b, 1H, -OH), 4.99 (d, 1H, J=11.8Hz), 4.78 (d, 1H, J=11.5Hz), 1.83 (b, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 147.27 (phenolic C), 135.70, 132.55, 131.32, 131.14, 131.05, 130.79, 130.53, 130.06, 126.54, 125.10 (quaternary aromatic C), 127.49, 127.47, 127.42, 127.33, 127.27, 127.22, 126.71, 125.56, 125.29, 124.39, 123.22, 123.05, 122.71, 122.68, 122.51, (aromatic CH) 113.90 (benzylic C), 60.70 (CH_2) ppm; **m/z** (FAB) 400 (M^+); **HRMS** (FAB) Found 400.14590, $C_{29}H_{20}O_2$ Requires 400.14633; $[\alpha]_D^{22}$=-50°, c=0.10, DCM.

(R,2"-S)-(+)-10'-Hydroxy-9,9'-biphenanthryl-10-(methylideneamino)-2"-(methoxymethyl)pyrrolidine (100).

A suspension of (R)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (50mg, 0.13mmol) in dry DCM (10ml) was stirred at 0°C. (S)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (**97**) (18mg, 0.14mmol) was added and stirring continued for 2 hours at 0°C. Removal of the solvent *in vacuo* gave a yellow foam. Purification

by wet flash chromatography gave the *title compound* as a yellow foam (42mg, 66%). **m.p.** 180-2°C; **tlc** R_f (DCM) 0.18; **C.H.N.** Found C: 82.75%, H: 5.92%, N: 4.89%, $C_{35}H_{31}N_2O_2$ Requires C: 82.33%, H: 5.92%, N: 5.49%; $\nu_{max.}$ ($CHBr_3$ mull) 3514 (-OH), 3068 (CH, aromatic), 2973 (CH, aliphatic), 1622, 1593, (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (175526$dm^3mol^{-1}l^{-1}$), 342 (19072), 298 (37113), 259 (152062) nm; **δH** (250 MHz, $CDCl_3$) 8.96 - 8.92 (m, 1H, aromatic), 8.86 - 8.70 (m, 4H, aromatic), 8.47 - 8.43 (m, 1H, aromatic), 7.81 - 7.65 (m, 4H, aromatic), 7.62 -7.56 (m, 1H, aromatic), 7.50 - 7.44 (m, 1H, aromatic), 7.36 (s, 1H, CH=N), 7.29 -7.23 (m, 3H, aromatic), 7.11 - 7.08 (m, 1H, aromatic),6.02 (s, 1H, -OH), 3.43 - 3.35 (m, 3H, N-CH and O-CH_2), 3.27 (s, 3H, -OMe), 3.04 - 2.99 and 2.43 - 2.39 (2xm, 2x1H, N-CH_2), 1.77 - 1.57 (m, 4H, 2xCH_2) ppm; **δC** (60 MHz, $CDCl_3$) 147.37 (phenolic C), 132.97, 132.32, 131.35, 131.18, 131.08, 130.33, 130.07, 129.09, 126.38, 125.56 125.87, 125.56 (quaternary aromatic C), 131.39 (HC=N), 127.45, 127.08, 126.90, 126.84, 126.45, 125.78, 124.01, 123.19, 122.72, 122.53, 122.41 (aromatic CH), 114.97 (benzylic C), 74.00 (O-CH_2), 62.59 (N-CH), 59.00 (O-Me), 48.70 (N-CH_2), 26.21 (CH_2), 21.79 (CH_2) ppm; **m/z** (FAB) 511 (MH^+); **HRMS** (FAB) Found 511.23939, $C_{35}H_{31}N_2O_2$ Requires 511.23855; $[\alpha]_D^{22}$=+97°, c=0.10, DCM.

(R)-(+)-10'-Hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (93).

A suspension of (R)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (0.10g, 0.25mmol), hydroxylamine hydrochloride (0.20g, 3.0mmol) and sodium acetate (0.42g, 4.8mmol) in ethanol (20ml) 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 $MgSO_4$ and the solvent removed *in vacuo*. Purification by wet flash chromatography (100% DCM) and recrystallisation from DCM gave the *title compound* as a white solid (63mg, 61%). **m.p.** Decomp. at 176°C; **tlc** R_f (DCM) 0.36; **C.H.N.** Found C: 84.47%, H: 4.65%, N: 2.83%, $C_{29}H_{19}NO_2$ Requires C: 84.24%, H: 4.63%, N: 3.39%; $\nu_{max.}$ ($CHBr_3$ mull) 3529 (-OH), 3067 (CH, aromatic),1620, 1596 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM)

358 (2479dm^{3}mol^{-1}l^{-1}), 341 (2893), 300 (19008), 258 (79339) nm; **δH** (250 MHz, $CDCl_3$) 8.89 - 8.71 (m, 4H, aromatic), 8.44 - 8.39 (m, 1H, aromatic), 7.92 - 7.63 (m, 5H, aromatic), 7.53 -7.25 (m, 5H, aromatic), 7.07 - 7.03 (m, 1H, aromatic), 5.42 and 5.90 (2xb, 2x0.5H, D_2O exchange, N-OH) ppm; **δC** (60 MHz, $CDCl_3$) 149.24 (C=N), 147.50 (phenolic C), 131.88, 131.52, 131.03, 130.97, 130.57, 130.49, 129.33, 127.80, 126.96, 126.70 (quaternary aromatic C), 128.19, 127.63, 127.56, 127.49, 127.54, 127.32, 127.20, 127.13, 126.60, 124.58, 123.25, 122.85, 122.74, 122.65, 122.51, (aromatic CH) 112.69 (benzylic C) ppm; **m/z** (FAB) 413 (M^+), 396 (M^+-OH); **HRMS** (FAB) Found 414.14949, $C_{29}H_{19}NO_2$ Requires 414.14940; $[\alpha]_D^{22}$=+30°, c=0.10, DCM.

(R)-(+)-10-(Aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (94).

Lithium aluminium hydride (5.0mg, 0.12mmol) in dry THF (2ml) was stirred at room temperature under nitrogen. A solution of (R)-(+)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde-oxime (**93**) (50mg, 0.12mmol) in dry THF (8ml) 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 2N NaOH (5ml) and the pH adjusted to 14. The mixture was extracted with DCM (3x5ml) and the combined organics washed with water (5ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a yellow solid. Purification by wet flash chromatography (2% MeOH/DCM) gave the *title compound* as a pale yellow solid (27mg, 56%) **m.p.** 184-5°C; **tlc** R_f (5% MeOH/DCM) 0.40; **C.H.N.** Found C: 87.71%, H: 5.67%, N: 2.86%, $C_{29}H_{21}NO$ Requires C: 87.19%, H: 5.30%, N: 3.51%; $\nu_{max.}$ ($CHBr_3$ mull) 3517 (-OH), 3367 (NH_2) 3068 (CH, aromatic), 1582 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 360 (3636dm^{3}mol^{-1}l^{-1}), 343 (3636), 303 (22101), 257 (95652) nm; **δH** (250 MHz, $CDCl_3$) 8.89 - 8.71 (m, 4H, aromatic), 8.54 - 8.50 (m, 1H, aromatic), 8.22 - 8.19 (m, 1H, aromatic), 7.79 - 7.66 (m, 4H, aromatic), 7.63 - 7.54 (m, 1H, aromatic), 7.50 - 7.43 (m, 1H, aromatic), 7.39 -7.17 (m, 3H, aromatic), 7.03 - 7.00 (m, 1H, aromatic), 4.58 (d, 1H, J=12.2Hz), 4.26 (b, 2H, NH_2), 3.94 (d,

1H, J=12.3Hz) ppm; **δC** (60 MHz, $CDCl_3$) 149.64 (phenolic C), 134.55, 133.03, 132.64, 131.63, 131.26, 131.05, 130.33, 130.00, 127.92, 126.51 (quaternary aromatic C), 127.99, 127.24, 127.07, 126.92, 126.69, 126.45, 126.02, 123.99, 123.92, 123.56, 123.49, 122.40, 122.35, 122.30 (aromatic CH) 117.32 (benzylic C), 41.22 (CH_2) ppm; **m/z** (FAB) 399 (M^+); **HRMS** (FAB) Found 399.16073, $C_{29}H_{21}NO$ Requires 399.16231; $[\alpha]_D^{22}$=+140°, c=0.10, DCM.

(R,S)-(-)-10-(Hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (102).

To a solution of (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (1.0g, 2.5mmol), (S)-(+)-2-phenylpropionic acid (**101**) (0.35g, 2.5mmol) and a catalytic amount of DMAP in dry DCM (50ml) at 0°C was added N,N-dicyclohexycarbodiimide (0.52g, 2.5mmol). The resulting mixture was stirred at 0°C for 30 minutes and at room temperature for 2 hours. The precipitated dicyclohexylurea was filtered off and the filtrate washed with 0.5N HCl (20ml), saturated $NaHCO_3$ solution (20ml) and water (20ml). Drying over $MgSO_4$ followed by removal of the solvent *in vacuo* gave a white solid which was purified by wet flash chromatography (100% DCM). A single recrystallisation from ethyl acetate yielded the *title compound* as a single diastereoisomer (0.32g, 48% of available diastereoisomer) **m.p.** 254-6°C; **tlc** R_f (DCM) 0.44; **C.H.** Found C: 84.43%, H: 5.35%, $C_{38}H_{28}O_3$ Requires C: 85.69%, H: 5.30%; $\nu_{max.}$ ($CHBr_3$ mull) 3526 (-OH), 3064 (CH, aromatic), 1732 (C=O stretch), 1597, 1582, (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (3550$dm^3mol^{-1}l^{-1}$), 341 (4734), 302 (42604), 256 (178107) nm; **δH** (250 MHz, $CDCl_3$) 8.85 - 8.69 (m, 4H, aromatic), 8.47 - 8.43 (m, 1H, aromatic), 7.81 - 7.54 (m, 7H, aromatic), 7.38 -7.20 (m, 4H, aromatic), 6.85 -6.83 (m, 1H, aromatic), 6.65 (b, 4H, aromatic) 4.82 (d, 1H, J=12.4.Hz), 4.55 (d, 1H, J=12.8Hz), 3.62 (q, 1H, J=6.0Hz, -CH), 2.67 (b, 1H, -OH), 1.09 (d, 3H, J=7.2Hz, $-CH_3$) ppm; **δC** (60 MHz, $CDCl_3$) 143.24 (phenolic C), 137.71, 134.53, 131.98, 131.71, 130.88, 130.80, 130.47, 130.36, 129.01, 126.19, 126.01, (quaternary aromatic C), 127.98, 127.55,

127.45, 127.34, 126.85, 126.78, 126.68, 126.57, 126.51, 122.98, 122.83, 122.69, 122.35, 121.92 (aromatic CH), 61.01 (CH_2), 45.05 (CH), 17.14 (CH_3) ppm; **m/z** (FAB) 532 (M^+), 515 (M^+-OH); **HRMS** (FAB) Found 532.20140, $C_{38}H_{28}O_3$ Requires 532.20385; $[\alpha]_D^{22}$=-144°, c=0.10, DCM.

(R)-(-)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (92).

Lithium aluminium hydride (7.0mg, 0.19mmol) in dry THF (2ml) was stirred at room temperature under nitrogen. A solution of (R,S)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (**102**) (0.10g, 0.19mmol) in dry THF (8ml) was added slowly and stirring continued for 30 minutes. The reaction was quenched by the careful addition of 2N HCl (5ml) and the pH adjusted to 1. The mixture was extracted with DCM (3x5ml) and the combined organics washed with water (5ml). Drying over $MgSO_4$, removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (65mg, 87%) **m.p.** 155°C; **tlc** R_f (DCM) 0.28; **C.H.** Found C: 84.94%, H: 6.24%, $C_{29}H_{20}O_2$ Requires C: 86.98%, H: 5.03%; $\nu_{max.}$ ($CHBr_3$ mull) 3476 (-OH), 3070 (CH, aromatic),1624, 1606, 1492 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (4441$dm^3mol^{-1}l^{-1}$), 341 (5333), 300 (35111), 259 (144889) nm; **δH** (250 MHz, $CDCl_3$) 8.88 - 8.73 (m, 4H, aromatic), 8.44 - 8.41 (m, 2H, aromatic), 7.83 - 7.61 (m, 5H, aromatic), 7.54 -7.47 (m, 1H, aromatic), 7.39 -7.25 (m, 3H, aromatic), 7.09 - 7.06 (m, 1H, aromatic), 5.60 (b, 1H, -OH), 4.99 (d, 1H, J=11.8Hz), 4.79 (d, 1H, J=11.9Hz), 1.71 (b, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 147.27 (phenolic C), 135.70, 132.55, 131.32, 131.14, 131.05, 130.79, 130.53, 130.05, 126.54, 125.10 (quaternary aromatic C), 127.49, 127.47, 127.42, 127.33, 127.27, 127.22, 126.71, 125.56, 125.29, 124.39, 123.23, 123.05, 122.71, 122.68, 122.51, (aromatic CH) 113.90 (benzylic C), 60.70 (CH_2) ppm; **m/z** (FAB) 400 (M^+); **HRMS** (FAB) Found $C_{29}H_{20}O_2$ Requires 400.14633; $[\alpha]_D^{22}$=-50°, c=0.10, DCM.

(S,R)-(+)-10-(Hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (102).

To a solution of (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (0.30g, 0.75mmol), (R)-(-)-2-phenylpropionic acid (**101**) (0.10g, 0.75mmol) and a catalytic amount of DMAP in dry DCM (5ml) at 0°C was added N,N-dicyclohexycarbodiimide (0.14g, 0.75mmol). The resulting mixture was stirred at 0°C for 30 minutes and at room temperature for 2 hours. The precipitated dicyclohexylurea was filtered off and the filtrate washed with 0.5N HCl (10ml), saturated $NaHCO_3$ solution (10ml) and water (10ml). Drying over $MgSO_4$ followed by removal of the solvent *in vacuo* gave a white solid which was purified by wet flash chromatography (100% DCM). A single recrystallisation from ethyl acetate yielded the *title compound* as a single diastereoisomer (52mg, 26% of available diastereoisomer) **m.p.** 253-5°C; **tlc** R_f (DCM) 0.47; **C.H.** Found C: 85.11%, H: 5.29%, $C_{38}H_{28}O_3$ Requires C: 85.69%, H: 5.30%; $\nu_{max.}$ ($CHBr_3$ mull) 3532 (-OH), 3067 (CH, aromatic), 1733 (C=O stretch), 1601 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 359 (2212$dm^3mol^{-1}l^{-1}$), 341 (3540), 302 (35841), 259 (142920) nm; **δH** (250 MHz, $CDCl_3$) 8.85 - 8.69 (m, 4H, aromatic), 8.47 - 8.43 (m, 1H, aromatic), 7.82 - 7.56 (m, 7H, aromatic), 7.38 -7.20 (m, 4H, aromatic), 6.86 -6.82 (m, 1H, aromatic), 6.65 (b, 4H, aromatic) 4.82 (d, 1H, J=13.2.Hz), 4.55 (d, 1H, J=12.8Hz), 3.62 (q, 1H, J=7.3Hz, -CH), 2.67 (b, 1H, -OH), 1.09 (d, 3H, J=7.3Hz, $-CH_3$) ppm; **δC** (60 MHz, $CDCl_3$) 143.19 (phenolic C), 137.67, 134.43, 131.91, 131.29, 130.82, 130.73, 130.40, 130.30, 128.94, 126.13, 125.95, (quaternary aromatic C), 127.91, 127.49, 127.38, 127.28, 126.78, 126.72, 126.63, 126.58, 126.51, 126.44, 122.91, 122.77, 122.63, 122.29, 121.86 (aromatic CH), 60.93 (CH_2), 44.97 (CH), 17.08 (CH_3) ppm; **m/z** (FAB) 532 (M^+); **HRMS** (FAB) Found 532.20452, $C_{38}H_{28}O_3$ Requires 532.20315; $[\alpha]_D^{22}$=+144°, c=0.10, DCM.

(S)-(+)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (92).

Lithium aluminium hydride (4.7mg, 0.12mmol) in dry THF (2ml) was stirred at room temperature under nitrogen. A solution of (S,R)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (**102**) (65mg, 0.12mmol) in dry THF (8ml) was added slowly and stirring continued for 30 minutes. The reaction was quenched by the careful addition of 2N HCl (5ml) and the pH adjusted to 1. The mixture was extracted with DCM (3x5ml) and the combined organics washed with water (5ml). Drying over $MgSO_4$, removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (46mg, 94%) **m.p.** 164-5°C; **tlc** R_f (DCM) 0.23; **C.H.** Found C: 84.87%, H: 6.20%, $C_{29}H_{20}O_2$ Requires C: 86.98%, H: 5.03%; $\nu_{max.}$ ($CHBr_3$ mull) 3484 (-OH), 3088 (CH, aromatic),1619, 1593, 1492 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (5667$dm^3mol^{-1}l^{-1}$), 341 (6667), 301 (10700), 262 (125000) nm; **δH** (250 MHz, $CDCl_3$) 8.87 - 8.73 (m, 4H, aromatic), 8.44 - 8.40 (m, 2H, aromatic), 7.83 - 7.61 (m, 5H, aromatic), 7.53 -7.47 (m, 1H, aromatic), 7.38 -7.25 (m, 3H, aromatic), 7.09 - 7.05 (m, 1H, aromatic), 4.98 (d, 1H, J=11.8Hz), 4.77 (d, 1H, J=11.8Hz) ppm; **δC** (60 MHz, $CDCl_3$) 147.30 (phenolic C), 135.67, 132.58, 131.33, 131.13, 131.04, 130.82, 130.55, 130.11, 126.54, 125.12 (quaternary aromatic C), 127.48, 127.44, 127.30, 127.24, 127.20, 126.69, 125.57, 125.31, 124.37, 123.25, 123.03, 122.70, 122.65, 122.50, (aromatic CH) 113.96 (benzylic C), 60.66 (CH_2) ppm; **m/z** (FAB) 400 (M^+), 382 (M^+-OH); **HRMS** (FAB) Found 400.14436, $C_{29}H_{20}O_2$ Requires 400.14633; $[\alpha]_D^{22}$=+50°, c=0.10, DCM.

(±)-10-(Bromomethyl)-10'-hydroxy-9,9'-biphenanthryl (103) (Method A).

(±)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (0.50, 1.3mmol) and dibromotriphenylphosphorane (1.2g, 2.8mmol) were mechanically stirred under nitrogen. The temperature was raised slowly by the means of a graphite bath. At 230°C a homogeneous melt was observed. At 280°C the flask was allowed to cool to room temperature and the mixture solidified. Purification by wet flash

chromatography (100% DCM) gave the title compound as a pale orange solid (0.28g, 61%). **m.p.** 228°C; **tlc** R_f (DCM) 0.82; **C.H.** Found C: 76.01%, H: 4.20%, $C_{29}H_{19}BrO$ Requires C: 75.17%, H: 4.13%; $\nu_{max.}$ ($CHBr_3$ mull) 3521 (-OH), 3072 (CH, aromatic), 1622, 1598, 1492, (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 357 (2308$dm^3mol^{-1}cm^{-1}$),349 (3077), 306 (19231), 298 (21538), 274 (38462), 260 (84615)nm; **δH** (250 MHz, $CDCl_3$) 8.91 - 8.74 (m, 4H, aromatic), 8.50 - 8.46 (m, 1H, aromatic), 8.38 - 8.34 (m, 1H, aromatic), 7.86 - 7.65 (m, 5H, aromatic), 7.54 - 7.48 (m, 1H, aromatic), 7.40 -7.25 (m, 3H, aromatic), 7.07 - 7.03 (m, 1H, aromatic) 4.88 (d, 1H, J=10.3Hz), 4.71 (d, 1H, J=10.3Hz) ppm; **δC** (60 MHz, $CDCl_3$) 147.21 (phenolic C), 133.55, 131.84, 131.48, 131.25, 131.15, 130.75, 129.38, 126.58, 125.06 (quaternary aromatic C), 127.96, 127.65, 127.63, 127.59, 127.36, 127.26, 127.16, 126.71, 125.24, 124.42, 123.34, 123.20, 122.74, 122.64, 122.51 (aromatic CH) 112.65 (quaternary C), 29.78 (CH_2Br) ppm; **m/z** (FAB) 462, 464 (M^+); **HRMS** (FAB) Found 464.05147, $C_{29}H_{19}BrO$ Requires 464.06001.

Tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (104) (Method A).

A solution of (±)-10-(bromomethyl)-10'-hydroxy-9,9'-biphenanthryl (**103**) (0.40g, 0.86mmol) in THF (10ml) was stirred at room temperature. 1.0M Potassium hydroxide solution (1.7ml, 1.7mmol) was added dropwise. A permanent yellow colouration was observed and stirring continued for 1 hour. The mixture was diluted with water (20ml) and extracted with DCM (3x30ml). The combined organics were washed with 2N HCl (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Trituration with ether gave the *title compound* as a yellow solid (0.22g, 67%). **m.p.** 216-7°C; **tlc** R_f (DCM) 0.89; **C.H**, Found C: 90.56%, H: 5.00%, $C_{29}H_{20}O$ Requires C: 91.07%, H: 4.74%; $\nu_{max.}$ ($CHBr_3$ mull) 3056 (CH, aromatic), 1600, 1488 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 378 (14831$dm^3mol^{-1}l^{-1}$), 360 (16949), 301 (26271), 253 (79237) nm; **δH** (250 MHz, $CDCl_3$) 8.84 - 8.70 (m, 4H, aromatic), 8.49 - 8.46 (m, 1H, aromatic), 8.04 - 8.00 (m, 1H, aromatic), 7.78 - 7.53 (m, 8H, aromatic),7.39 - 7.30 (m, 2H, aromatic), 6.16 (d, 1H, J=13.2Hz), 5.21 (d, 1H,

J=13.1) ppm; δC (60 MHz, $CDCl_3$) 152.10 (phenolic C), 131.28, 130.66, 129.99, 128.25, 128.00, 127.09, 125.78 (quaternary aromatic C), 129.73, 128.17, 127.48, 127.42, 127.04, 126.66, 126.39, 126.21, 125.55, 125.37, 124.50, 123.21, 123.00, 122.74, 122.60, 122.31 (aromatic CH) 115.39 (benzylic C) ppm; **m/z** (FAB) 382 (M^+); **HRMS** (FAB) Found 382.13562, $C_{29}H_{18}O_1$ Requires 382.13577.

Attempted Preparation of (±)-10'-(Methyl)trifluoromethylsulphonate-9,9'-biphenanthryl-10-trifluoromethylsulphonate.
Tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (104) (Method B).

A solution of (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (0.50g, 1.3mmol) in dry 2,6-lutidine (10ml) was stirred under nitrogen at 0°C. Trifluoromethanesulphonic anhydride (1.8g, 6.3mmol) was added and stirring continued overnight at room temperature. The gradual appearance of a yellow colour was noted. The mixture was concentrated to dryness and diluted with DCM (30ml). Washing with 2N HCl (20ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a yellow residue. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a pale yellow solid (0.20 g, 48%).

(±)-10-(Bromomethyl)-10'-Hydroxy-9,9'-biphenanthryl (103) (Method B).

A solution of (±)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (1.0g, 2.5mmol) in dry DCM (50ml) was stirred under nitrogen at room temperature. Bromotrimethylsilane (1.5g, 10mmol) was added and the resulting mixture stirred overnight. The reaction was quenched by the addition of water (30ml), the organic layer separated and the aqueous layer washed with a further portion of DCM (30ml). The combined organics were dried over $MgSO_4$. Removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (0.71g, 61%).

(±)-10'-Hydroxy-10-methyl-9,9'-biphenanthryl (105).

Lithium aluminium hydride (52mg, 1.3mmol) in dry THF (10ml) was stirred at room temperature under nitrogen. A solution of (±)-10-(bromomethyl)-10'-hydroxy-9,9'-biphenanthryl (**103**) (0.62g, 1.3mmol) in dry THF (10ml) was added slowly and stirring continued for 30 minutes. The reaction was quenched by the careful addition of 2N HCl (10ml) and the pH adjusted to 1. The mixture was extracted with DCM (3x20ml) and the combined organics washed with water (30ml). Drying over $MgSO_4$, removal of the solvent *in vacuo* and trituration with ether gave the *title compound* as a white solid (0.43g, 84%) **m.p.** 249-251°C; **tlc** R_f (DCM) 0.77; **C.H.** Found C: 90.37%, H: 5.28%, $C_{29}H_{20}O$ Requires C: 90.60%, H: 5.25%; $\nu_{max.}$ ($CHBr_3$ mull) 3434 (-OH), 3065 (CH, aromatic), 1623, 1597, 1498 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 (2222$dm^3mol^{-1}cm^{-1}$),342 (2222), 300 (20000), 276 (37778), 258 (108333)nm; **δH** (250 MHz, $CDCl_3$) 8.90 - 8.75 (m, 4H, aromatic), 8.47 - 8.43 (m, 1H, aromatic), 8.27 - 8.24 (m, 1H, aromatic), 7.84 - 7.69 (m, 4H, aromatic),7.64 - 7.59 (m, 1H, aromatic), 7.55 -7.48 (m, 1H, aromatic), 7.40 -7.28 (m, 3H, aromatic), 7.16 - 7.12 (m, 1H, aromatic) 5.26 (s, 1H, -OH), 2.51 (s, 3H,-CH_3) ppm; **δC** (60 MHz, $CDCl_3$) 146.70 (phenolic C), 134.81, 132.24, 131.71, 131.29, 131.25, 130.03, 127.88, 124.90 (quaternary aromatic C), 127.24, 127.09, 126.66, 126.54, 126.47, 125.33, 123.08, 123.00, 122.63, 122.60, 122.53 (aromatic CH) 114.51 (benzylic C), 16.69 (CH_3) ppm; **m/z** (FAB) 384 (M^+); **HRMS** (FAB) Found 384.15354, $C_{29}H_{20}O_1$ Requires 384.15142.

(±)-10-Methyl-9,9'-biphenanthryl-10'-trifluoromethanesulphonate (106).

A solution of (±)-10'-hydroxy-10-methyl-9,9'-biphenanthryl (**105**) (0.50g, 1.3mmol) in dry DCM (20ml) was stirred under nitrogen at 0°C. Pyridine (0.15g, 2.0mmol) followed by trifluoromethanesulphonic anhydride (0.44g, 1.6mmol) were added and stirring continued overnight at room temperature. The gradual appearance of a yellow colour was noted. The mixture was concentrated to dryness and diluted with

DCM (30ml). Washing with 2N HCl (20ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a white solid (0.45g, 67%). **m.p.** 204-5°C; **tlc** R_f (DCM) 0.79; **C.H.** Found C: 70.79%, H: 3.80%, $C_{30}H_{19}F_3O_3S$ Requires C: 69.76%, H: 3.71%; $\nu_{max.}$ ($CHBr_3$ mull) 3072 (CH, aromatic), 1624, 1584 1489 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 301 (19355$dm^3mol^{-1}l^{-1}$), 255 (116129) nm; **δH** (250 MHz, $CDCl_3$) 8.90 - 8.77 (m, 4H, aromatic), 8.40 - 8.37 (m, 1H, aromatic), 8.24 - 8.20 (m, 1H, aromatic), 7.91 - 7.68 (m, 5H, aromatic),7.62 - 7.56 (m, 1H, aromatic), 7.41 -7.39 (m, 2H, aromatic), 7.36 - 7.29 (m, 1H, aromatic), 7.25 - 7.20 (m, 1H, aromatic) 2.44 (s, 3H,-CH_3) ppm; **δC** (60 MHz, $CDCl_3$) 142.48 (phenolic C), 133.74, 131.71, 131.13, 130.56, 129.73, 129.55, 129.51, 125.91 (quaternary aromatic C), 128.18, 128.02, 127.88, 127.95, 126.66, 126.52, 125.99, 125.13, 122.95, 122.92, 122.85, 122.70, 122.40 (aromatic CH) 113.53 (benzylic C), 17.62 (CH_3) ppm; **δF** (235MHz, $CDCl_3$) -73.98 (CF_3): **m/z** (FAB) 516 (M^+); **HRMS** (FAB) Found 516.10070, $C_{30}H_{19}F_3O_3S$ Requires 516.10070.

Attempted Palladium Catalysed Phosphorylation of (±)-10-Methyl-9,9'-biphenanthryl-10'-trifluoromethanesulphonate (106).

A solution of (±)-10-methyl-9,9'-biphenanthryl-10'-trifluoromethanesulphonate (**106**) (0.20g, 0.40mmol), diphenylphosphine oxide (0.16g, 0.80mmol), palladium acetate (4.5mg, 0.020mmol), 1,3-bis(piphenylphosphino)propane (8.2mg, 0.020mmol) and diisopropylethylamine (0.20g, 1.6mmol) in DMSO (20ml) was stirred overnight at 100°C under nitrogen. The resulting mixture was cooled and the solvent removed *in vacuo* to give a pale brown residue. This was taken up DCM (20ml), washed with water (20)ml, dried over $MgSO_4$ and the solvent removed *in vacuo* to give a pale yellow residue (0.18g). **tlc** R_f (DCM) = 0.71; **m/z** (FAB) 516 (M^+).

Attempted Nickel Catalysed Phosphoylation of (±)-10-Methyl-9,9'-biphenanthryl-10'-trifluoromethanesulphonate (106).

A solution of [bis(diphenylphosphino)ethane]nickel dichloride (20mg, 0.40mmol) in dry DMF (1ml) was stirred under nitrogen at room temperature, Diphenylphosphine (0.40ml, 2.3mmol) was added and the mixture heated at 100°C for 30 minutes. A solution of (±)-10-methyl-9,9'-biphenanthryl-10'-trifluoromethanesulphonate (**106**) (0.20g, 0.39mmol) and 1,4-diazabicyclo[2,2,2]octane (0.17g, 1.6mmol) in dry DMF (2ml) were added at once and the mixture stirred at 100°C for 24 hours to 4 days. Three additional portions of diphenylphosphine (0.40ml, 2.3mmol) were added 1,3 and 7 hours later. The mixture was cooled and the solvent removed *in vacuo* to give a yellow liquid. **m/z** (FAB) 516 (M^+).

Reduction of Acetophenone: 2-Phenethylalcohol.

A suspension of lithium aluminium hydride (1.0g, 2.5mmol) in dry THF (2ml) under nitrogen was stirred at room temperature. Ethanol (0.12g, 2.5mmol) was added with the evolution of hydrogen. The mixture was cooled to 0°C and a solution of (R)-(-)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (1.0g, 2.5mmol) in dry THF (15ml) was added slowly, again with the evolution of hydrogen. Stirring was continued at 0°C for 1 hour and then the mixture was cooled to -78°C. A solution of acetophenone (1.0g, 0.83mmol) in dry THF (5ml) was added slowly. Stirring was continued at -78°C for 1 hour and overnight at room temperature. The reaction was quenched by the addition of 2N HCl (10ml) and extracted with DCM (3x20ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to give a white oily solid. Trituration with ether (twice) gave quantitative recovery of (R)-(-)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) ($[\alpha]_D^{22}$=-50°, c=0.1, DCM). The mother liquors from the trituration were purified by Kugelrhor

distillation *in vacuo* to give 2-phenethylalcohol (69mg, 68%). **b.p.** 202-3°C (lit.[98] 204°C); **tlc** R_f (DCM) 0.30; **C.H.** Found C: 78.62%, H: 8.27%, $C_8H_{10}O$ Requires C: 78.65%,H: 8.25%; $\nu_{max.}$ (neat) 3354 (OH), 2972 (CH stretch), 1493, 1451 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 245 ($488dm^3mol^{-1}l^{-1}$), 226 (585) nm; **δH** (250 MHz, $CDCl_3$) 7.39 - 7.23 (m, 5H, Ph), 4.88 (q, 1H, J=6.4Hz, CH), 2.09 (b, 1H, D_2O exchangeable, OH), 1.49 (d, 3H, J=6.4Hz, CH_3), ppm; **δC** (60 MHz, $CDCl_3$) 145.65 (quaternary aromatic C), 128.33, 127.30, 125.23 (aromatic CH), 70.22 (CHOH), 25.00(CH_3) ppm; **m/z** (EI) 122(M^+); **HRMS** (EI) Found 122.07272, $C_8H_{10}O$ Requires 122.07317.

(R)-(+)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl Chloride.

A solution of (R)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (0.80g, 3.4mmol) in thionyl chloride (5ml) was heated at reflux for 24 hours and at room temperature for a further 36 hours. Excess thionyl chloride was removed *in vacuo* and the residue distilled *in vacuo* to give the *title compound* as a colourless oil (0.78g, 90%). **b.p.** 212-213°C (lit.[96] 213-4°C); $\nu_{max.}$ (neat) 2952 (CH stretch), 1790 (C=O).

Mosher Ester of 2-Phenethylalcohol.

A solution of (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (83mg, 0.33mmol) in dry carbon tetrachloride (5ml) was stirred at room temperature. 2-Phenethylalcohol (20mg, 0.16mmol) was added followed by dry pyridine (5 drops). The mixture was stirred overnight at room temperature before being concentrated to dryness. The resulting residue was diluted with ether (10ml), washed with 2N HCl (5ml), saturated $NaCO_3$ solution (5ml) and water (5ml). Drying over $MgSO_4$ and

removal of the solvent *in vacuo* gave a colourless oil. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a colourless oil (19mg, 35%). **δH** (250 MHz, $CDCl_3$) 7.68 - 7.22 (m, 10H, aromatic), 3.49 - 3.46 (m, 3H, OMe),1.65 - 1.56 (m, 3H, CH_3) ppm; **δC** (60 MHz, $CDCl_3$) 165.80 (C=O), 147.73 (quaternary aromatic C), 140.05 (quaternary aromatic C), 132.27 - 121.00 (aromatic CH), 74.88 (OMe), 55.51 (CH), 21.75 (CH_3) ppm; **δF** (235MHz, $CDCl_3$) -71.73 (intensity 18.25), -71.94 (intensity 8.70) ppm.

Reduction of 2-Hexanone: 2-Hexanol.

A suspension of lithium aluminium hydride (1.0g, 2.5mmol) in dry THF (2ml) under nitrogen was stirred at room temperature. Ethanol (0.12g, 2.5mmol) was added with the evolution of hydrogen. The mixture was cooled to 0°C and a solution of (R)-(-)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (1.0g, 2.5mmol) in dry THF (15ml) was added slowly, again with the evolution of hydrogen. Stirring was continued at 0°C for 1 hour and then the mixture was cooled to -78°C. A solution of 2-hexanone (83mg, 0.83mmol) in dry THF (5ml) was added slowly. Stirring was continued at -78°C for 1 hour and overnight at room temperature. The reaction was quenched by the addition of 2N HCl (10ml) and extracted with DCM (3x20ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to give a white oily solid. Trituration with ether (twice) gave quantitative recovery of (R)-(-)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl ($[\alpha]_D^{22}$=-50°, c=0.1, DCM). The mother liquors from the trituration were purified by Kugelrhor distillation to give 2-hexanol (75mg, 88%). **b.p.** 135-6°C (lit.[98] 136°C); **tlc** R_f (DCM) 0.24; **CH.** Found C: 66.60%, H: 12.68%, $C_6H_{14}O$ Requires C: 79.53%, H: 13.81%; $\nu_{max.}$ (neat) 3354 (OH), 2930 (CH stretch) cm^{-1}; **δH** (250 MHz, $CDCl_3$) 3.80 - 3.73 (m, 1H, CH), 1.59 (b, 1H, D_2O exchangeable, OH), 1.43 - 1.21 (m, 6H, 3xCH_2), 1.16 (d, 3H, J=6.2Hz, CH_3), 0.88 (t, 3H, J=6.4Hz, R-CH_3) ppm; **δC** (60 MHz, $CDCl_3$)

68.01 (CHOH), 38.90 (CH_2), 27.82 (CH_2), 23.32 (CH_3), 22.57 (CH_2), 13.93 (CH_3) ppm; **m/z** (FAB) 102(M^+); **HRMS** (FAB) Found 102.10477, $C_6H_{14}O$ Requires 102.10477.

Mosher Ester of 2-Hexanol.

A solution of (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (25mg, 0.10mmol) in dry carbon tetrachloride (1ml) was stirred at room temperature. 2-Hexanol (5mg, 0.050mmol) was added followed by dry pyridine (2 drops). The mixture was stirred overnight at room temperature before being concentrated to dryness. The resulting residue was diluted with ether (5ml), washed with 2N HCl (2ml), saturated $NaCO_3$ solution (2ml) and water (2ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a colourless oil. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a colourless oil (6mg, 38%). **δH** (250 MHz, $CDCl_3$) 7.53 - 7.33 (m, 5H, Ph), 5.16 - 5.09 (m, 1H, CH), 3.57 - 3.54 (m, 3H, OMe), 1.34 - 1.17 (m, 9H, 3xCH_2 and CH_3), 0.94 - 0.61 (m, 3H, CH_3) ppm; **δF** (235MHz, $CDCl_3$) -71.72 (intensity 16.78), -71.77 (intensity 15.08) ppm.

(R)-(-)-10-(Hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (113).

To a solution of (R)-(-)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (0.50, 1.3mmol), phenylacetic acid (0.16g, 1.2mmol) and a catalytic amount of DMAP in dry DCM (25ml) at 0°C was added N,N-dicyclohexycarbodiimide (0.26g, 1.2mmol). The resulting mixture was stirred at 0°C for 30 minutes and at room temperature for 2 hours. The precipitated dicyclohexylurea was filtered off and the filtrate washed with 0.5N HCl (20ml), saturated $NaHCO_3$ solution (20ml) and water (20ml). Drying over $MgSO_4$ followed by removal of the solvent *in vacuo* gave a white solid. Purification by wet flash chromatography (100% DCM) and trituration with ether gave the *title compound* as a white solid (0.47g, 72%) **m.p.** 242-3°C; **tlc**

R_f (DCM) 0.30; **C.H.** Found C: 86.02%, H: 5.11%, $C_{37}H_{26}O_3$ Requires C: 85.69%, H: 5.05%; $\nu_{max.}$ ($CHBr_3$ mull) 3394 (-OH), 3052 (CH, aromatic), 1750 (C=O stretch),1598, 1488 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 302 (20690$dm^3mol^{-1}l^{-1}$), 290 (20690), 257 (100000) nm; **δH** (250 MHz, $CDCl_3$) 8.86 - 8.76 (m, 4H, aromatic), 8.45 - 8.42 (m, 1H, aromatic), 7.83 - 7.60 (m, 7H, aromatic), 7.38 -7.32 (m, 3H, aromatic), 7.25 - 7.22 (m, 1H, aromatic), 6.92 -6.86 (m, 1H, aromatic), 6.75 - 6.69 (m, 2H, aromatic) 6.55 - 6.52 (m, 2H, aromatic), 4.81 (dd, 1H, J=12.7Hz and 9.9Hz), 4.55 (dd, 1H, J=12.7Hz and 3.9Hz), 3.43 (s, 2H, CH_2), 2.50 (b, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 143.46 (phenolic C), 131.93, 131.85, 131.38, 130.87, 138.80, 130.46, 130.42, 129.04, 126.25, 125.95(quaternary aromatic C), 128.29, 128.09, 127.60, 127.45, 127.33, 126.82, 126.77, 126.69, 126.58, 122.99, 122.84, 122.69, 122.37, 122.09 (aromatic CH), 61.02 (CH_2), 40.87 (CH_2) ppm; **m/z** (FAB) 518 (M^+), 501 (M^+-OH); **HRMS** (FAB) Found 518.18793, $C_{37}H_{26}O_3$ Requires 518.18819; $[\alpha]_D^{22}$=-178°, c=0.10, DCM.

Alkylation of (R)-(-)-10-(Hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (113).

A solution of lithium diisopropylamide (0.41ml of a 2.0M solution, 0.81mmol) in dry THF (1ml) under nitrogen was stirred at -78°C. A solution of (R)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**113**) (0.20g, 0.39mmol) in dry THF (4ml) was added slowly and the resulting yellow solution stirred at -78°C for 10 minutes. Methyl iodide (2.1g, 15mmol) was added and stirring continued for 4 hours at -78°C. Water (10ml) was added and the mixture warmed to room temperature. Extraction with DCM (3x10ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a pale yellow oil. Purification by wet flash chromatography (100% DCM) gave a white solid.(0.14g). **tlc** R_f (DCM) = 0.65; $\upsilon_{max.}$ ($CHBr_3$ mull) 3518 (-OH), 3054 (CH, aromatic), 1724 (C=O stretch), 1620, 1597, 1492 cm^{-1}; **δ(H)**, (250MHz, $CDCl_3$), 8.90 - 8.72 (m, aromatic), 8.48 - 8.36 (m, aromatic), 7.88 - 7.00

(m, aromatic), 5.58 - 5.48 (m, CH and OH), 5.26 - 5.16 (m, CH), 3.65 - 3.39 (m, CHPh and OMe), 1.38 - 1.34 (2xd, CH_3) ppm; **m/z** (FAB) 546 (M_1^+), 532 (M_2^+).

(R)-(-)-10-(Methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (116).

A suspension of (R)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**113**) (0.20g, 0.39mmol), methyl iodide (0.56g, 3.9mmol) and silver oxide (0.72g, 3.1mmol) in dry THF (10ml) was heated at 35-40°C for 48 hours. After 24 hours a second aliquot of methyl iodide (0.56g, 3.9mmol) was added. The mixture was then cooled, filtered through celite and the solvent removed *in vacuo*. Purification by wet flash chromatography (100% DCM) gave recovered starting material and the *title compound* as a white solid (48mg, 23%). **m.p.** 112-3°C; **tlc** R_f (DCM) 0.56; **C.H.** Found C: 85.14%, H: 5.28%, $C_{38}H_{28}O_3$ Requires C: 85.69%, H: 5.30%; $\nu_{max.}$ ($CHBr_3$ mull) 3063 (CH, aromatic), 1769 (C=O stretch), 1606, 1490 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 303 (30000$dm^3mol^{-1}l^{-1}$), 291 (30000), 258 (140667) nm; **δH** (250 MHz, $CDCl_3$) 8.86 - 8.73 (m, 4H, aromatic), 8.28 - 8.25 (m, 1H, aromatic), 7.81 - 7.57 (m, 7H, aromatic), 7.43 -7.30 (m, 4H, aromatic), 6.93 -6.87 (m, 1H, aromatic), 6.78 - 6.72 (m, 2H, aromatic) 6.57 - 6.54 (m, 2H, aromatic), 4.63 (d, 1H, J=11.2Hz), 4.35 (d, 1H, J=11.2Hz), 3.36 (s, 2H, CH_2), 2.98 (s, 3H, CH_3) ppm; **δC** (60 MHz, $CDCl_3$) 169.34 (C=O), 143.57 (phenolic C), 132.34, 132.08, 131.81, 131.34, 131.13, 130.84, 130.77, 130.61, 130.46, 128.93, 126.44, 126.17 (quaternary aromatic C), 128.43, 127.96, 127.62, 127.41, 127.16, 127.04, 126.82, 126.71, 126.14, 126.59, 126.32, 122.95, 122.68, 122.44, 122.35, 122.28 (aromatic CH), 70.33 (CH_2), 58.38 (CH_3), 40.73 (CH_2) ppm; **m/z** (FAB) 532 (M^+), 501 (M^+-OMe); **HRMS** (FAB) Found 532.20482, $C_{38}H_{28}O_3$ Requires 532.20385; $[\alpha]_D^{22}$=-90°, c=0.10, DCM.

Alkylation of (R)-(-)-10-(Methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (116).

A solution of lithium diisopropylamide (0.030ml of a 2.0M solution, 0.062mmol) in dry THF (1ml) was stirred under nitrogen at -78°C. A solution of (R)-(-)-10-(methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**116**) (30mg, 0.056mmol) in dry THF (2ml) was added slowly and the resulting yellow solution stirred at -78°C for 10 minutes. Methyl iodide (0.33g, 2.2mmol) was added and stirring continued for 4 hours at -78°C. Water (2ml) was added and the mixture warmed to room temperature. Extraction with DCM (3x10ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave a white solid (22mg). **tlc** R_f (DCM) 0.56; **δH** (250 MHz, $CDCl_3$) 8.88 - 8.72 (m, 4H, aromatic), 8.58 - 8.22 (m, 1H, aromatic), 7.83 - 7.58 (m, 7H, aromatic), 7.38 -7.24 (m, 7H, aromatic), 6.90 -6.54 (m, 2H, aromatic), 4.76 (d, 1H, J=11.0Hz), 4.60 (d, 1H, J=11.0Hz), 3.27 (intensity 42.00)and 3.09 (intensity 37.69) (2xs, 3H, Ome), 1.04 (intensity 37.94) and 1.01 (intensity 40.95) (2xs, 3H, CH_3) ppm; **m/z** (FAB) 546 (M^+).

(R)-(-)-10'-Hydroxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (117).

A solution of lithium diisopropylamide (0.20ml of a 2.0M solution, 0.39mmol), in dry THF (1ml) at -78°C was stirred under nitrogen. A solution of (R)-(-)-10-(hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**113**) (0.20g, 0.39mmol) in dry THF (10ml) was added slowly. The resulting yellow solution was stirred for 10 minutes at -78°C before water (10ml) was added. The mixture was extracted with DCM (3x10ml) and the combined organics washed with water (20ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a white foam (0.13g, 66%). **m.p.** 122-3°C; **tlc** R_f (DCM) 0.64; **C.H.** Found C: 85.61%, H: 4.86%, $C_{37}H_{26}O_3$ Requires C: 85.69%, H: 5.05%; $\nu_{max.}$ ($CHBr_3$ mull) 3541 (-OH), 3077

(CH, aromatic), 1723 (C=O stretch), 1623, 1599, 1492 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 ($1036dm^3mol^{-1}l^{-1}$), 341 (1554), 301 (22798), 259 (116580) nm; **δH** (250 MHz, $CDCl_3$) 8.90 - 8.72 (m, 4H, aromatic), 8.46 - 8.42 (m, 1H ,aromatic), 8.09 - 8.06 (m, 1H, aromatic), 7.84 - 7.64 (m, 5H, aromatic), 7.53 - 7.46 (m, 1H, aromatic), 7.42 -7.18 (m, 6H, aromatic), 7.11 -7.03 (m, 3H, aromatic), 5.55 (d, 1H, J=12.0Hz), 5.50 (s, 1H, -OH), 5.24 (d, 1H, J=12.0Hz), 3.48 (s, 2H, CH_2) ppm; **δC** (60 MHz, $CDCl_3$) 171.11(C=O), 141.37 (phenolic C), 133.47, 132.44, 132.36, 131.46, 131.40, 131.27, 131.00, 130.70, 130.31, 126.50, 125.03 (quaternary aromatic C),129.08, 128.36, 127.86, 127.53, 127.49, 127.32, 127.05, 126.89, 126.62, 125.32, 125.14, 124.28, 123.26, 123.11, 122.66, 122.56 (aromatic CH), 113.04 (benzylic C), 62.70 (CH_2), 41.02 (CH_2) ppm; **m/z** (FAB) 518 (M^+); **HRMS** (FAB) Found 518.19175, $C_{37}H_{26}O_3$ expect 518.18819; $[\alpha]_D^{22}$=-68°, c=0.10, DCM.

(R)-(-)-10'-Methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (118).

A suspension of (R)-(-)-10'-hydroxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (**117**) (0.19g, 0.37mmol) anhydrous potassium carbonate (45mg, 0.37mmol) and methyl iodide (0.53g, 3.7mmol) in dry acetone (10ml) was stirred overnight at 35°C. The mixture was filtered and the solid washed with dry acetone (20ml). The filtrate was concentrated to dryness and redissolved in DCM (20ml). Washing with 2N HCl (10ml), water (10ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a white solid (0.16g, 80%). **m.p.** 219-220°C; **tlc** R_f (DCM) 0.64; **C.H.** Found C: 85.13%, H: 5.45%, $C_{38}H_{28}O_3$ Requires C: 85.69%, H: 5.30%; $\nu_{max.}$ ($CHBr_3$ mull) 3070 (CH, aromatic), 1718 (C=O stretch), 1592, 1490 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 303 ($24155dm^3mol^{-1}l^{-1}$), 291 (27536), 259 (120290) nm; **δH** (250 MHz, $CDCl_3$) 8.91 - 8.75 (m, 4H, aromatic), 8.29 - 8.25 (m, 1H ,aromatic), 8.06 - 8.02 (m, 1H, aromatic), 7.83 - 7.54 (m, 6H, aromatic), 7.43 -7.16 (m, 7H, aromatic), 7.08 -7.03 (m, 2H, aromatic), 5.44 (d, 1H, J=12.1Hz), 5.36 (d, 1H, J=12.1Hz), 3.48 (s, 3H, CH_3), 3.41 (s, 2H, CH_2) ppm; **δC** (60 MHz, $CDCl_3$) 171.06 (C=O), 151.96

(phenolic C), 134.84, 133.61, 132.49, 132.01, 131.32, 130.79, 130.65, 130.59, 128.91, 128.36, 128.10, 123.70 (quaternary aromatic C), 129.06, 128.28, 127.84, 127.50, 127.28, 127.24, 127.06, 126.92, 126.87, 126.80, 126.77, 127.57, 125.67, 125.14, 123.32, 123.00, 122.94, 122.55 (aromatic CH), 62.85 (CH_2), 60.98 (CH_2), 41.03 (CH_3) ppm; **m/z** (FAB) 532 (M^+); **HRMS** (FAB) Found 532.20483, $C_{38}H_{28}O_3$ expect 532.20385; $[\alpha]_D^{22}$=-93°, c=0.10, DCM.

(S)-(+)-10-(Hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (113).

To a solution of (S)-(+)-10'-hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (**92**) (0.46, 1.1mmol), phenylacetic acid (0.20g, 1.5mmol) and a catalytic amount of DMAP in dry DCM (20ml) at 0°C was added N,N-dicyclohexycarbodiimide (0.31g, 1.5mmol). The resulting mixture was stirred at 0°C for 30 minutes and at room temperature for 2 hours. The precipitated dicyclohexylurea was filtered off and the filtrate washed with 0.5N HCl (20ml), saturated $NaHCO_3$ solution (20ml) and water (20ml). Drying over $MgSO_4$ followed by removal of the solvent *in vacuo* gave a white solid. Purification by wet flash chromatography (100% DCM) and trituration with ether gave the *title compound* as a white solid (0.41g, 68%) **m.p.** 239-40°C; **tlc** R_f (DCM) 0.30; **C.H.** Found C: 86.19%, H: 5.22%, $C_{37}H_{26}O_3$ Requires C: 85.69%, H: 5.05%; $\nu_{max.}$ ($CHBr_3$ mull) 3430 (-OH), 3064 (CH, aromatic), 1748 (C=O stretch), 1629, 1600, 1490 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 302 (25325$dm^3mol^{-1}l^{-1}$), 289 (25325), 257 (1123378) nm; **δH** (250 MHz, $CDCl_3$) 8.86 - 8.75 (m, 4H, aromatic), 8.45 - 8.42 (m, 1H, aromatic), 7.83 - 7.60 (m, 7H, aromatic), 7.38 - 7.32 (m, 3H, aromatic), 7.25 - 7.21 (m, 1H, aromatic), 6.91 - 6.85 (m, 1H, aromatic), 6.74 - 6.68 (m, 2H, aromatic) 6.54 - 6.50 (m, 2H, aromatic), 4.81 (d, 1H, J=12.8Hz), 4.54 (d, 1H, J=12.7), 3.42 (s, 2H, CH_2), 1.61 (b, 1H, -OH) ppm; **δC** (60 MHz, $CDCl_3$) 143.47 (phenolic C), 134.52, 131.93, 131.86, 131.39, 130.88, 130.81, 130.45, 129.91, 129.06, 125.96 (quaternary aromatic C), 128.29, 128.10, 127.61, 127.47, 127.35, 126.79, 126.70, 126.59, 123.01, 122.85, 122.70, 122.38, 122.09 (aromatic CH), 61.03 (CH_2), 40.89 (CH_2) ppm; **m/z** (FAB) 518(M^+), 501(M^+-OH); **HRMS**

(FAB) Found 518.18664, $C_{37}H_{26}O_3$ Requires 518.18819; $[\alpha]_D^{22}$=+175°, c=0.10, DCM.

(S)-(+)-10'-Hydroxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (117).

A solution of lithium diisopropylamide (0.42 ml of a 2.0M solution, 0.85mmol), in dry THF (2ml) at -78°C was stirred under nitrogen. A solution of (S)-(+)-10-(hydroxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (**113**) (0.40g, 0.78 mmol) in dry THF (15ml) was added slowly. The resulting yellow solution was stirred for 10 minutes at -78°C before water (10ml) was added. The mixture was extracted with DCM (3x10ml) and the combined organics washed with water (20ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a white foam (0.24g, 60%). **m.p.** 124-5°C; **tlc** R_f (DCM) 0.64; **C.H.** Found C: 85.48%, H: 4.96%, $C_{37}H_{26}O_3$ Requires C: 85.69%, H: 5.05%; $\nu_{max.}$ ($CHBr_3$ mull) 3625 (-OH), 3063 (CH, aromatic), 1726 (C=O stretch), 1616, 1596, 1492 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 ($3627 dm^3 mol^{-1} l^{-1}$), 341 (4145), 301 (30052), 259 (140415) nm; **δH** (250 MHz, $CDCl_3$) 8.90 - 8.72 (m, 4H, aromatic), 8.46 - 8.42 (m, 1H ,aromatic), 8.09 - 8.06 (m, 1H, aromatic), 7.84 - 7.64 (m, 5H, aromatic), 7.53 - 7.47 (m, 1H, aromatic), 7.42 - 7.18 (m, 6H, aromatic), 7.12 - 7.03 (m, 3H, aromatic), 5.55 (d, 1H, J=12.0Hz), 5.51 (s, 1H, -OH), 5.24 (d, 1H, J=12.0Hz), 3.48 (s, 2H, CH_2) ppm; **δC** (60 MHz, $CDCl_3$) 171.11 (C=O), 147.38 (phenolic C), 133.46, 132.45, 132.36, 131.47, 131.40, 131.27, 131.00, 130.71, 130.32, 126.51, 125.03 (quaternary aromatic C), 129.08, 28.36, 127.86, 127.53, 127.49, 127.44, 127.39, 127.32, 127.05, 126.89, 126.62, 125.32, 125.14, 124.28, 123.26, 123.11, 122.66, 122.56 (aromatic CH), 113.04 (benzylic C), 62.79 (CH_2), 41.02 (CH_2) ppm; **m/z** (FAB) 518 (M^+); **HRMS** (FAB) Found 518.18954, $C_{37}H_{26}O_3$ expect 518.18819; $[\alpha]_D^{22}$=+74°, c=0.10, DCM.

(S)-(+)-10'-Methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (118).

A suspension of (S)-(+)-10'-hydroxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (**117**) (0.20 g, 0.39mmol) anhydrous potassium carbonate (60mg, 0.43mmol) and methyl iodide (0.56g, 3.9mmol) in dry acetone (10ml) was stirred overnight at 35°C. The mixture was filtered and the solid washed with dry acetone (20ml). The filtrate was concentrated to dryness and redissolved in DCM (20ml). Washing with 2N HCl (10ml), water (10ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave the *title compound* as a white solid (0.18g, 88%). **m.p.** 222-3°C; **tlc** R_f (DCM) 0.64; **C.H.** Found C: 86.19%, H: 5.32%, $C_{38}H_{28}O_3$ Requires C: 85.69%, H: 5.30%; $\nu_{max.}$ ($CHBr_3$ mull) 3056 (CH, aromatic), 1716 (C=O stretch), 1589, 1489 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 303 (28723$dm^3mol^{-1}l^{-1}$), 256 (134574) nm; **δH** (250 MHz, $CDCl_3$) 8.91 - 8.75 (m, 4H, aromatic), 8.28 - 8.24 (m, 1H ,aromatic), 8.05 - 8.01 (m, 1H, aromatic), 7.82 - 7.54 (m, 6H, aromatic), 7.43 - 7.16 (m, 7H, aromatic), 7.08 - 7.02 (m, 2H, aromatic), 5.43 (d, 1H, J=12.0Hz), 5.36 (d, 1H, J=12.1Hz), 3.48 (s, 3H, CH_3), 3.41 (s, 2H, CH_2) ppm; **δC** (60 MHz, $CDCl_3$) 171.09 (C=O), 151.95 (phenolic C), 134.84, 133.59, 132.48, 132.01, 131.31, 130.70, 130.65, 130.58, 128.89, 128.08, 127.49, 123.70 (quaternary aromatic C), 129.07, 128.29, 127.83, 127.29, 127.24, 127.07, 126.93, 126.87, 126.80, 126.77, 126.56, 125.68, 125.14, 123.32, 123.00, 122.94, 122.55 (aromatic CH), 62.86 (CH_2), 61.00 (CH_2), 41.01 (CH_3) ppm; **m/z** (FAB) 532 (M^+); **HRMS** (FAB) Found 532.20200, $C_{38}H_{28}O_3$ expect 532.20385; $[\alpha]_D^{22}$=+94°, c=0.10, DCM.

Alkylation of (S)-(+)-10'-Methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (118).

A solution of lithium diisopropylamide (0.080ml of a 2.0M solution, 0.16mmol) in dry THF (1ml) was stirred under nitrogen at -78°C. A solution of (S)-(+)-10'-methoxy-9,9'-biphenanthryl-10-(methyl)phenylacetate (**118**) (75mg, 0.14mmol) in dry THF

(4ml) was added slowly and the resulting yellow solution stirred at -78°C for 10 minutes. Methyl iodide (0.81g, 5.6mmol) was added and stirring continued for 4 hours at -78°C. Water (4ml) was added and the mixture warmed to room temperature. Extraction with DCM (3x10ml), drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a white residue. Purification by wet flash chromatography (100% DCM) gave a white solid (68mg, 88%). **tlc** R_f (DCM) 0.64; **δH** (250MHz, $CDCl_3$) 8.90 - 8.74 (m 4H, aromatic), 8.32 - 8.23 (m, 1H, aromatic), 7.93 - 7.88 (m, 1H, aromatic), 7.83 - 7.53 (m, 6H, aromatic), 7.42 - 7.18 (m, 7H, aromatic), 7.14 - 7.09 (m, 2H, aromatic), 5.45 - 5.29 (m, 2H, CH_2Ar), 3.59 - 3.49 (m, 1H, CH), 3.52 (intensity 37.99) and 3.41 (intensity 43.29) (2xs, 3H, OMe), 1.38 (intensity 22.99) and 1.29 (intensity 24.36) (2xd, 3H, CH_3, J=7.2 and 7.2 Hz respectively) ppm; **ms** (FAB) 546 (M^+).

(±)-10-(N,N-Diethylaminomethylene)-10'-hydroxy-9,9'-biphenanthryl (119).

To a suspension of (±)-10'-hydroxy-9,9'-biphenanthryl-10-carboxaldehyde (**91**) (0.50g, 1.3mmol) in dry DCM (20ml) was added titanium tetrachloride (3.8ml of a 1M solution in DCM, 3.8mmol) followed by diethylamine (0.92g, 13mmol). The resulting dark red solution was stirred for 5 minutes under nitrogen before adding sodium cyanoborohydride (0.23g, 3.7mmol) followed by 5N HCl/MeOH (3ml). The mixture was stirred for 1 hour before being diluted with water (10ml). The organic layer was separated and the aqueous layer washed with DCM (2x20ml). The combined organics dried over $MgSO_4$ and the solvent removed *in vacuo* to give a yellow residue. Purification by wet flash chromatography (100% DCM, 2% MeOH/DCM) gave the *title compound* as a yellow foam (0.52g, 91%). **m.p.** 224-5°C; **tlc** R_f (DCM) 0.11; **C.H.N.** Found C: 81.88%, H: 6.06%, N: 3.19%, $C_{33}H_{29}NO$ Requires C: 87.00%, H: 6.42%, N: 3.07%; $\nu_{max.}$ ($CHBr_3$ mull) 3526 (-OH), 3068 (CH, aromatic), 1586, 1487 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 361 (2283$dm^3mol^{-1}l^{-1}$), 344 (2740), 305 (21005), 293 (23288), 259 (96804) nm; **δH** (250 MHz, $CDCl_3$) 8.90 - 8.69 (m, 4H, aromatic), 8.58 - 8.54 (m, 1H ,aromatic), 8.34 - 8.27 (m, 1H,

aromatic), 7.82 - 7.13 (m, 10H, aromatic), 6.81 - 6.77 (m, 1H, aromatic), 4.40(d, 1H, J=12.7Hz), 3.95 (d, 1H, J=12.9Hz), 2.78 - 2.50 (m, 4H ,2xCH_2), 0.87 (t, 3H, J=7.2Hz, CH_3) ppm; **δC** (60 MHz, $CDCl_3$) 150.87 (phenolic C), 136.80, 133.06, 131.73, 131.47, 131.35, 130.57, 130.48, 127.49, 127.39, 127.25 (quaternary aromatic C), 127.96, 127.06, 126.99, 126.61, 126.50, 126.44, 123,.36, 125.43, 124.27, 124.08, 123.67, 123.37, 122.48, 122.27, 122.25 (aromatic CH), 117.86 (benzylic C), 52.30 (CH_2), 45.44 (2xCH_2), 9.39 (2xCH_3) ppm; **m/z** (FAB) 456 (MH^+); **HRMS** (FAB) Found 456.23268, $C_{33}H_{30}NO$ expect 456.23274.

(±)-10-(N,N-Diethylaminomethylene)-9,9'-biphenanthryl 10'-phenylacetate (120).

A solution of phenylacetic acid (66mg, 0.48mmol) in thionyl chloride was heated at reflux for 1 hour. Excess thionyl chloride was removed *in vacuo* and the residue dissolved in dry DCM (1ml). This was added slowly to a solution of (±)-10-(N,N-diethylaminomethylene)-10'-hydroxy-9,9'-biphenanthryl (**119**) (0.20g, 0.44mmol) and diethylamine (48mg, 0.44mmol) in dry DCM (20ml) at 0°C. The mixture was stirred overnight. The mixture was then washed with 2N HCl (10ml), 1N $NaHCO_3$ (10ml) and water (10ml). Drying over $MgSO_4$ and removal of the solvent *in vacuo* gave a yellow residue. Purification by wet flash chromatography (100% DCM, 5% MeOH) and recrystallisation from ethyl acetate gave the *title compound* as white crystals (0.13g, 52%).**m.p.** 138-9°C; **tlc** R_f (DCM) 0.18; **C.H.N.** Found C: 85.22%, H: 5.96%, N: 2.03%, $C_{41}H_{35}NO_2$ Requires C: 85.83%, H: 6.15%, N: 2.44%; $\nu_{max.}$ ($CHBr_3$ mull) 3068 (CH, aromatic), 2968 (CH, aliphatic), 1625, 1597, 1489 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 302 (17703), 258 (87081) nm; **δH** (250 MHz, $CDCl_3$) 8.85 - 8.73 (m, 5H, aromatic), 7.77 - 7.58 (m, 7H, aromatic), 7.39 - 7.25 (m, 4H, aromatic), 6.94 - 6.91 (m, 1H, aromatic), 6.84 - 6.75 (m, 2H, aromatic), 6.58 - 6.55 (m, 2H, aromatic), 3.60 (b, 2H, CH_2Ph), 3.45 (d, 1H, J=14.8Hz), 3.35 (d, 1H, J=14.8Hz), 2.27 (b, 2H ,N-CH_2), 2.11 (b, 2H, N-CH_2), 0.62 (t, 3H, J=6.9Hz, CH_3) ppm; **δC** (60MHz, $CDCl_3$) 168.84 (C=O), 143.58 (phenolic C), 132.23, 131.21,

130.58, 128.96, 127.69, 127.14 (quaternary aromatic C), 128.38, 128.25, 128.05, 126.68, 126.50, 126.19, 122.96, 122.63, 122.44, 122.37, 122.01 (aromatic CH), 53.42 ($ArCH_2$), 45.99 ($2xNCH_2$), 40.90 (CH_2Ph), 11.04 ($2xCH_3$); **m/z** (FAB) 574 (M^+); **HRMS** (FAB) Found 574.27705, $C_{41}H_{35}NO_2$ expect 574.27460.

(±)-10-(Aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide (124).

A suspension of nicotinic acid (86mg, 0.70mmol) in thionyl chloride (2ml) was heated at reflux for 1 hour. Excess thionyl chloride was removed *in vacuo*. The residue was dissolved in dry DCM (1ml) and slowly added to a solution (±)-10-(aminomethyl)-10'-hydroxy-9,9'-biphenanthryl (**94**) (0.28g, 0.70mmol) and diisopropylethylamine (90mg, 0.70mmol) in dry DCM (10ml) at 0°C. The mixture was warmed slowly to room temperature and stirred for 4 hours. The mixture was then poured onto ice/water (20ml), rendered alkaline with 2N NaOH and extracted with DCM (3x20ml). The combined organic extracts were washed with 2N NaOH (20ml), water (20ml), and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a yellow/brown residue. Purification by wet flash chromatography (5% MeOH/DCM) and recrystallisation from DCM gave the *title compound* as a white solid (0.21g, 60%). **m.p.** 296-8°C; **tlc** R_f (5% MeOH/DCM) 0.22; **C.H.N.** Found C: 80.27%, H: 5.02%, H: 5.03%, $C_{35}H_{24}N_2O_2$ Requires C: 83.15%, H: 4.98%, N: 5.54%; $\nu_{max.}$ ($CHBr_3$ mull) 3463 (-OH), 3357 (NH stretch) 3071 (CH, aromatic), 1621 (C=O stretch), 1594 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 358 ($2274 dm^3 mol^{-1} l^{-1}$), 341 (2809), 302 (23596), 259 (119101) nm; **δH** (250 MHz, $CDCl_3$/DMSO) 8.65 (b, 1H, aromatic), 8.52 - 8.29 (m, 4H, aromatic), 8.05 - 7.76 (m, 5H, aromatic), 7.39 - 7.25 (m, 7H, aromatic), 7.08 - 7.02 (m, 1H, aromatic), 6.96 -6.95 (m, 2H, aromatic), 6.89 -6.83 (m, 3H, aromatic), 6.64 - 6.61 (m, 1H, aromatic), 4.81 (dd, 1H, J=13.9Hz and 5.9Hz), 4.00 (d, 1H, J=13.1Hz) ppm; **δC** (60 MHz, $CDCl_3$/DMSO) 163.47 (C=O), 149.10 ($C_{2''}H$), 148.07 ($C_{6''}H$), 146.90 ($C_{4''}H$), 146.00 ($C_{3''}$), 137.32 ($C_{5''}H$), 132.91 (phenolic C), 132.54, 132.51, 131.21, 131.06, 130.59, 130.54, 130.48, 126.13, 125.86 (quaternary aromatic C), 127.26, 127.16, 127.06, 127.02, 126.87, 126.26,

125.06, 124.81, 123.86, 123.25, 122.73, 122.37, 123.24, 122.14 (aromatic CH) 113.32 (benzylic C), 40.28 (CH_2) ppm; **m/z** (FAB) 504 (M^+); **HRMS** (FAB) Found 505.19263, $C_{35}H_{25}N_2O_2$ Requires 505.19160.

N-Butyl Bromide Salt of (±)-10-(Aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide (125).

A suspension of (±)-10-(aminomethylene)-10'-hydroxy-9,9'-biphenanthryl-nicotinamide (124) (0.15g, 0.30mmol), in 1-bromobutane (3ml) and 1,4-dioxane (15ml) was heated at 107°C for 24 hours. The mixture was cooled to room temperature, the resulting precipitate filtered off and washed with ether (2x20ml) to give the *title compound* as a white solid (0.15g, 79%). **m.p.** 211-2°C; **tlc** R_f (5% MeOH/DCM) 0.00; **C.H.N.** Found C: 71.26%, H: 5.25%, N: 4.00%, $C_{39}H_{33}BrN_2O_2$ Requires C: 73.01%, H: 5.18%, N: 2.19%; $\nu_{max.}$ ($CHBr_3$ mull) 3171 (CH, aromatic), 1655 (C=O stretch), 1598, 1491 (aromatic rings) cm^{-1}; $\lambda_{max.}$ (DCM) 359 ($6897 dm^3 mol^{-1} l^{-1}$), 342 (7882), 300 (30542), 278 (52217), 258 (129557) nm; **δH** (250 MHz, $CDCl_3$/DMSO) 9.16 - 9.07 (m, 3H, aromatic), 9.04 - 9.00 (m, 1H, aromatic), 8.94 - 8.92 (m, 3H, aromatic), 8.89 - 8.74 (m, 1H, aromatic), 8.55 - 8.52 (m, 1H, aromatic), 8.38 - 8.29 (m, 1H, aromatic), 8.19 - 8.13 (m, 1H, aromatic), 7.89 - 7.67 (m, 1H, aromatic), 7.42 - 7.31 (m, 2H, aromatic), 7.23 - 7.16 (m, 2H, aromatic), 7.06 - 7.03 (m, 1H, aromatic), 4.86 (dd, 1H, J=14.0Hz and 4.6Hz), 4.71 (dd, 1H, J=14.0Hz and 2.6Hz), 4.57 (t, 2H, N^+-CH_2), 1,91 - 1.74 (m, 2H, CH_2), 1.40 - 1.22 (m, 2H, CH_2), 0.90 (t, 3H, CH_3) ppm; **δC** (60 MHz, $CDCl_3$/DMSO) 160.67 (C=O), 147.95 ($C_{2"}H$), 146.32 ($C_{6"}H$), 144.28 ($C_{4"}H$), 142.95 ($C_{5"}H$), 141.93 ($C_{3"}$), 133.43 (phenolic C), 133.25 132.78, 131.80, 131.22, 131.15, 130.99, 130.66, 130.61, 126.18, 125.95 (quaternary aromatic C), 127.70, 127.55, 127.37, 127.29, 127.00, 126.82, 125.45, 125.26, 123.95, 123.66, 123.26, 123.16, 123.00 (aromatic CH) 114.12 (benzylic C),66.47 (Ar-CH_2), 60.98 (N^+-CH_2), 32.73 (CH_2), 18.88 (CH_2), 13.47 (CH_3) ppm; **m/z** (FAB) 561 (M^+); **HRMS** (FAB) Found 561.25586, $C_{39}H_{33}N_2O_2$ Requires 561.25420.

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Appendix 1

Crystallographic Data

Molecular formula	$C_{38}H_{28}O_3$
Formula weight	532.60
Crystal dimensions (mm^3)	0.51x0.39x0.19
Crystal system	Orthorhombic
Cell dimensions a (Å)	9.1564(5)
Cell dimensions b (Å)	9.3817(6)
Cell dimensions c (Å)	31.268(2)
Cell dimensions α (°)	90
Cell dimensions β (°)	90
Cell dimensions γ (°)	90
Density $_{calc.}$ (g/cm^3)	1.317
Z	4

Table 4. (R,2"-S)-(-)-10-(Hydroxymethyl)-9,9'-biphenanthryl-10'-(2"-phenyl)propionate (102).

Molecular formula	$C_{29}H_{18}O$
Formula weight	382.13
Crystal dimensions (mm^3)	0.80x0.80x0.30
Crystal system	monoclinic
Cell dimensions a (Å)	19.607(15)
Cell dimensions b (Å)	5.079(5)
Cell dimensions c (Å)	29.157(16)
Cell dimensions α (°)	90
Cell dimensions β (°)	114.84
Cell dimensions γ (°)	90
Density $_{calc.}$ (g/cm^3)	1.39
Z	4

Table 5. (±)-Tetrabenzo[a',c',g',i']-6H-dibenzo[b,d]pyran (104).

Molecular formula	$C_{38}H_{28}O_3$
Formula weight	532.64
Crystal dimensions (mm^3)	0.70x0.16x0.12
Crystal system	orthorhombic
Cell dimensions a (Å)	9.2897(15)
Cell dimensions b (Å)	10.275(2)
Cell dimensions c (Å)	27.604(6)
Cell dimensions α (°)	90
Cell dimensions β (°)	90
Cell dimensions γ (°)	90
Density $_{calc.}$ (g/cm^3)	1.34
Z	4

Table 7. (R)-(-)-10-(Methoxymethyl)-9,9'-biphenanthryl 10'-phenylacetate (116).

Molecular formula	$C_{38}H_{28}O_3$
Formula weight	532.64
Crystal dimensions (mm^3)	0.70x0.16x0.12
Crystal system	triclinic
Cell dimensions a (Å)	9.205(4)
Cell dimensions b (Å)	9.3804)
Cell dimensions c (Å)	10.006(5)
Cell dimensions α (°)	91.74(2)
Cell dimensions β (°)	115.00(2)
Cell dimensions γ (°)	117.61(1)
Density $_{calc.}$ (g/cm^3)	1.33
Z	1

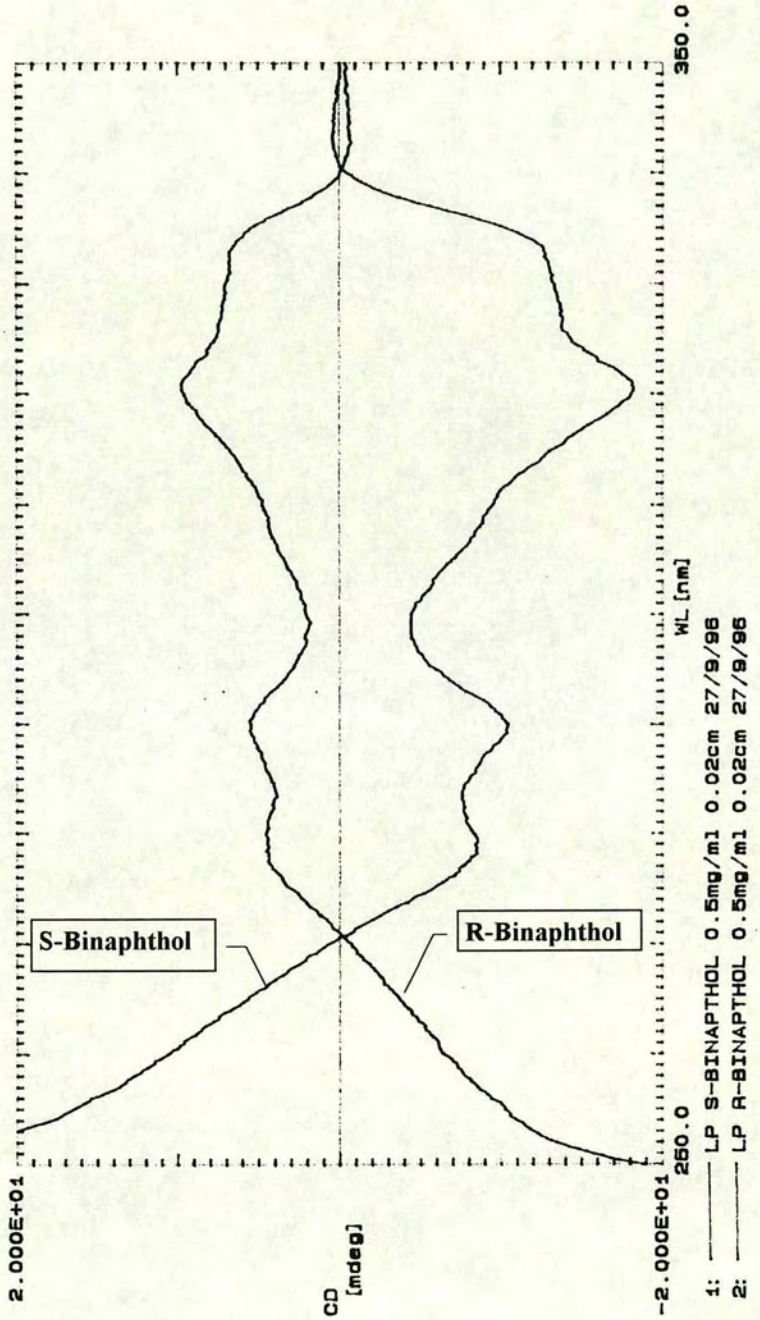
Table 8. (R)-(-)-10'-Methoxy-9,9'-biphenanthryl 10-(methyl)phenylacetate (118).

Molecular formula	$C_{41}H_{35}O_2$
Formula weight	573.70
Crystal dimensions (mm^3)	0.54x0.39x0.19
Crystal system	Monoclinic
Cell dimensions a (Å)	10.4133(8)
Cell dimensions b (Å)	16.7204(13)
Cell dimensions c (Å)	17.906(2)
Cell dimensions α (°)	90
Cell dimensions β (°)	98.409(6)
Cell dimensions γ (°)	90
Density $_{calc.}$ (g/cm^3)	1.236
Z	4

Table 9. (±)-10-((N,N-Diethylamino)methyl)-9,9'-biphenanthryl 10'-phenylacetate (120).

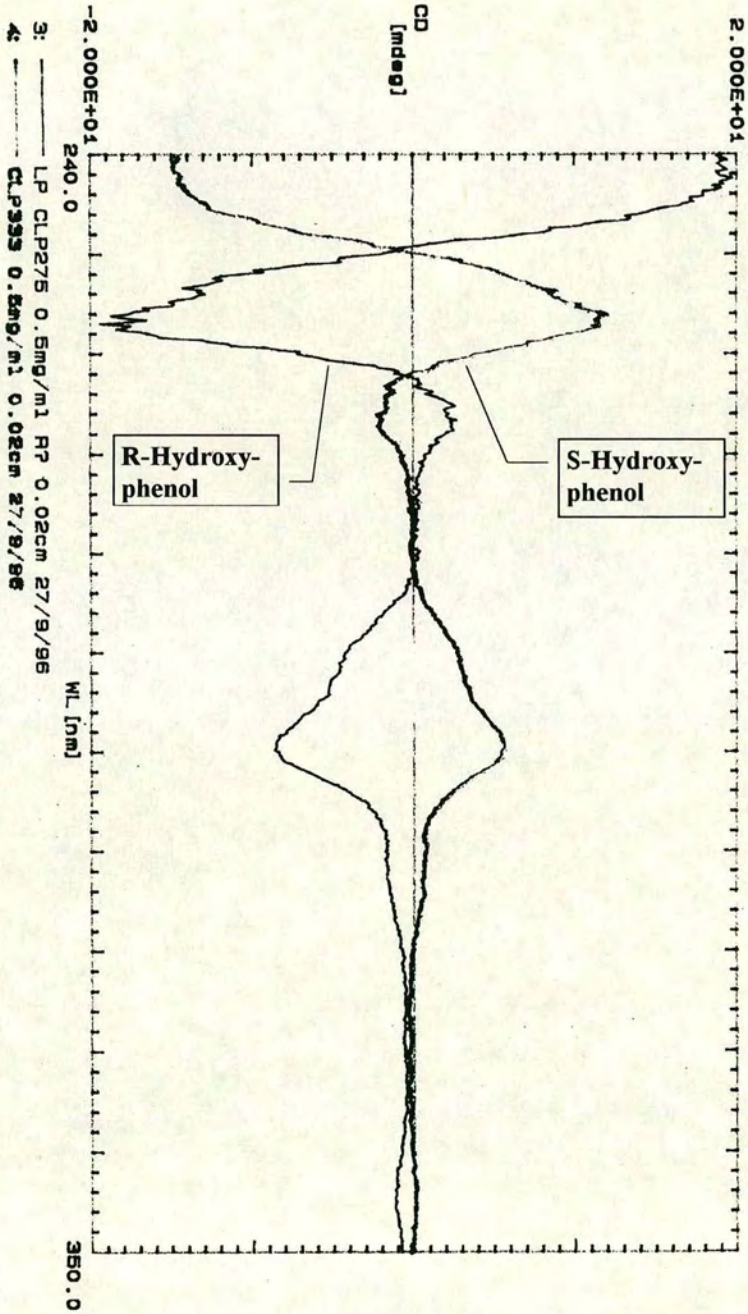
Appendix 2a

Circular Dichroism Spectra of (R)- and (S)-Binaphthol (2)



Appendix 2b

Circular Dichroism Spectra for (R)- and (S)-10'-Hydroxy-10-(hydroxymethyl)-9,9'-biphenanthryl (92)



Appendix 3

NMR Data for (±)-10'-Hydroxy-9,9'-biphenanthryl-10-(aminomethyl)(N"-butyl)nicotinamide Bromide (125)

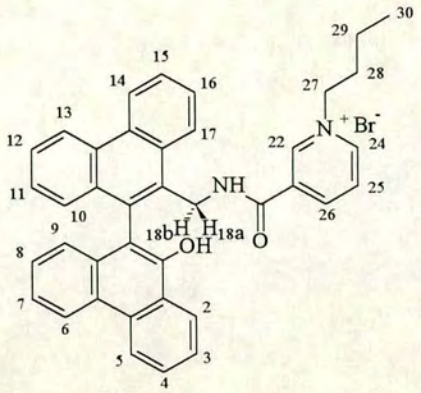


Table 11. ^{1}*H NMR Data. (1D and 2D DQF-COSY).*

H	*ppm*	*m*	*J(Hz)*
H_{22}	8.64	s	/
H_{24}	8.56	d	5.68 (J_{24-25})
H_{14}	8.25	d	8.79 (J_{14-15})
H_{13}	8.18	d	8.78 ($_{13-12}$)
NH	8.14	b	/
H_5	8.08	d	8.31 (J_{4-5})
H_6,H_{26}	8.00-7.97	m	/
OH	7.82	b	/
H_4	7.67-7.66	m	/
H_{17}	7.53	d	8.30 (J_{17-16})
H_{25}	7.43-7.41	m	/
H_{15}orH_{16}	7.12-7.09	m	/
H_3,H_{15} or H_{16}	7.06-7.02	m	/
H_{12},H_2	6.98-6.92	m	/
H_7,H_{11}	6.69-6.65	m	/
H_{10}	6.58	d	8.30 (J_{10-11})
H_8	6.50	m	/
H_9	6.32	d	8.30 (J_{9-8})
H_{18a}	4.32	dd	4.88 (J_{18a-NH}), 14.16 ($J_{18a-18b}$)
H_{27}	3.95	t	7.32 (J_{27-28})
H_{18b}	3.88	d	14.16 ($J_{18b-18a}$)
H_{28}	1.20	tt	7.33 (J_{28-27}), 7.81 (J_{28-29})
H_{29}	0.64	tq	7.33 (J_{29-30}), 7.81 (J_{29-28})
H_{30}	0.25	t	7.33 (J_{30-29})

^{1}***H NMR (2D-ROESY):*** 7.53ppm (NH, H_{18a}).

Courses Attended

Departmental Colloquia, University of Edinburgh, various speakers, 1993-1996..

Organic Research Seminars, University of Edinburgh, various speakers, 1993-1996.

Royal Society of Chemistry, Perkin Division, Scottish Meeting, various speakers, Aberdeen 1993, St. Andrews 1994, Glasgow 1995.

"Medicinal Chemistry", Prof. R. Baker and colleagues, Merck Sharp and Dohme, University of Edinburgh, 1994-1996.

NMR Spectroscopy, Drs I. Sadler & P Barlow, University of Edinburgh, 1996.

SCI Graduate Symposium Novel Organic Chemistry, various speakers, Heriot Watt 1994, St. Andrews 1996.

24th European Peptide Symposium, various speakers, Edinburgh, 1996.