The Generation of Chiral Centres at Heterogeneous Surfaces

by

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Summary

Prochiral substrates may undergo enantioselective hydrogenation when a chirally modified metal catalyst is used. This involves the chemisorption of a chiral source, natural or synthetic, which creates a chiral environment on which the substrate may be reduced.

Historically, prochiral β-ketoesters and α-ketoesters (notably ethyl pyruvate) in conjunction with a cinchona modified platinum surface has led to the most efficient system known,[16] furnishing products with enantiomeric excesses as high as 95%.[18]

The original purpose of this work was to examine the possibility of obtaining a modifier which is effective across a range of substrates. However, these preliminary studies strongly suggest that the substrate and modifier must be thought of as a matched pair. It is now widely accepted that the substrate and modifier interact *via* a diastereomeric intermediate at which juncture chirality is conferred.[34]

Hydrogenation of prochiral alkenes using modified heterogeneous catalysis has yet to lead to significant induction.[20] As part of this speculative project, two alkenes of specific industrial interest were selected and prepared. A variety of modifiers were then synthesised, many of which were axially chiral. Such molecules are often particularly efficient with regard to the transmission of chirality. Preparation of molecules with 'conventional' C-centred chirality was also undertaken. Resolution of several potential modifiers was achieved using a variety of methods including fractional crystallisation of diastereomers and enantioselective enzymic hydrolysis of a target compound derivative.

Certain structural attributes are believed to be necessary in order to facilitate induction. Therefore, these characteristics were incorporated by design into the molecules under consideration. It is important that the modifier is able to adsorb onto the metal surface by way of a polar grouping or an aromatic moiety. In addition, a pendant polar grouping is now considered to be essential. This enables the formation of a transient hydrogen bond, which acts as a 'conduit' for enantioselectivity.

This thesis describes the search for an efficient substrate-modifier complementary pair and contributes to the overall understanding of the concepts involved in the generation of chiral centres at heterogeneous surfaces.

Acknowledgements

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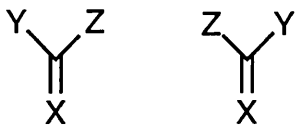
Abbreviations, symbols and definitions

Ac	Acetate
BOC	*tert*-Butyloxycarbonyl
COD	Cyclooctadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DOPA	3,4-Dihydroxyphenylalanine
e.e.	enantiomeric excess
E. I.	Electron impact (mass spectroscopy)
EtOAc	Ethyl acetate
FAB	Fast atom bombardment (mass spectroscopy)
FMOC	9-Fluorenylmethyl carbamate
g.c.	Gas chromatography
HMPA	Hexamethylphosphoramide
h.p.l.c.	High performance (pressure) liquid chromatography
MEM	Methoxyethoxymethyl
MMA	Methyl methacrylate
o/n	Overnight
r.p.	Reversed phase
TA	Tartaric acid
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

$$\text{Enantiomeric excess (\%)} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

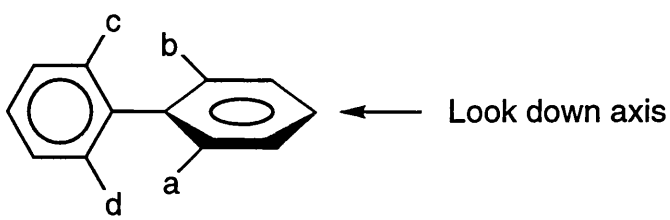
Re and *Si*

Attack by an achiral reagent at a non-symmetrical trigonal molecule entails enantiomeric transition states. Conversely, attack by a chiral reagent leads to diastereomeric transition states. Enantiotopic and diastereotopic faces are named using sequence priority rules [X>Y>Z].



re face *si* face

Labelling of axially chiral molecules



Establish the sequence of priority from a through b, then c and d.

Clockwise rotation = *R*
Anti-clockwise rotation = *S*

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Introduction

1 THE SOURCE OF CHIRALITY

The origin of natural chirality is unknown. With few exceptions, replicating organisms are based on (*S*)-amino acids and (*R*)-sugars (though not all natural products are optically pure, *e.g.* citronellal, 80%). Paradoxically, there is no evidence to suggest that life forms based on these isomers are in some way superior or preferable to those derived from (*R*)-amino acids and (*S*)-sugars. It is therefore logical to conclude that the primordial soup was racemic and somehow a bias was introduced.[1]

A saturated solution of a racemic compound may crystallise either as an inseparable mixture or as a conglomerate. The latter outcome is a much less common occurrence in which an equal quantity of each isomer crystallises in an optically pure form (*e.g.* the (*S*)-DOPA intermediate[2] shown in Fig. 1).

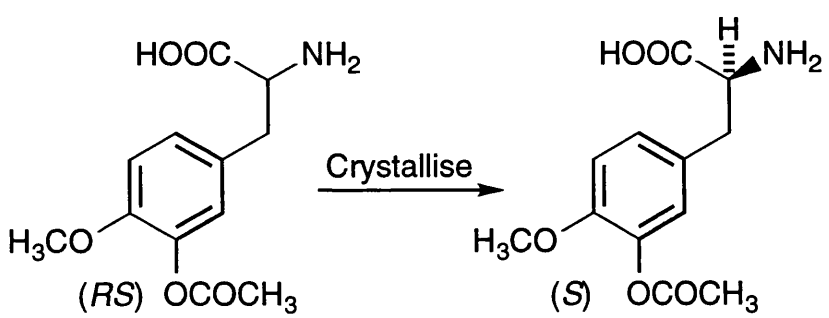


Fig. 1

In even fewer cases, the morphology of the conglomerate is distinct and it was this that led Pasteur to physically distinguish between crystals of sodium ammonium tartrate in 1848. In both cases, less than 50% of the total material can be isolated as a single enantiomer. However, there are some examples of total spontaneous resolution. While crystallisation of one enantiomer continues, the remaining enantiomer equilibrates with the

first, and ultimately the entire racemate will crystallise as one enantiomer (Fig. 2).

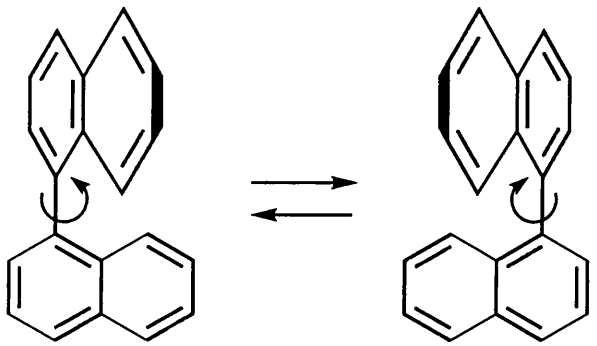


Fig. 2 Enantiomers of 1,1'-binaphthyl

The hindered rotation about the sigma bond allows two enantiomeric forms to exist, though they have very short half lives. A statistical study[3] of this process proved that the nucleation of the enantiomers was a random process, *i.e.*, either enantiomer may predominate in any one experiment.

It follows that biological receptors in living organisms will recognise and respond selectively to chiral molecules. The field of synthetic chiral chemistry is dependent on the chiral pool[4] as a source of enantiomerically pure materials. It has been noted that most of the effective chiral agents described in recent literature are totally synthetic, though a majority of these are derived directly or indirectly from natural sources. Techniques for resolution of racemates are comprised mainly from the following methods-

(a) Fractional crystallisation of diastereomeric salts (classical resolution).
(b) Separation of covalently bonded diastereomers by means of chromatography, distillation or fractional crystallisation.
(c) Enzymatic resolution (kinetic).
(d) Asymmetric homogeneous catalysis.
(e) Asymmetric heterogeneous catalysis.

1.1 Introduction

The application of a heterogeneous system in an industrial process is particularly advantageous for several reasons. Ease of handling and workup (filtration) together with the potential for recycling the active component are two such factors. Clearly, an *enantioselective* heterogeneous catalyst would be of great synthetic utility.

Hydrogenation of prochiral[5] substrates using the untreated metal catalysts nickel, palladium or platinum naturally lead to racemic products. However, the chemisorption of a monolayer of an organic optically pure 'modifier' may induce chirality in certain substrates.[6]

1.2 Aims

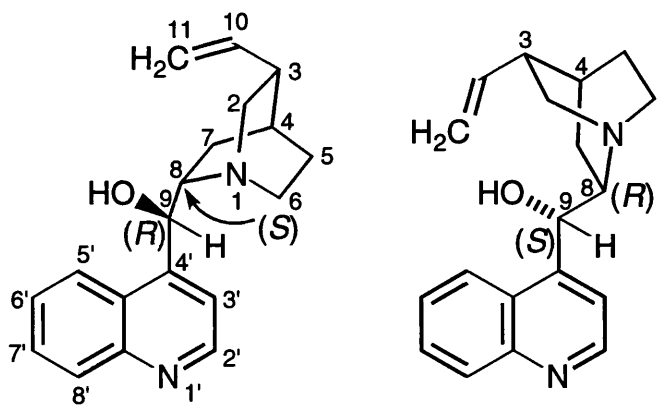
The remit of this project, as a whole, initially involved the examination of the adsorption characteristics of selected chiral molecules on Pt, Pd or Ni surfaces on carbon and alumina supports. This work was conducted in collaboration with Prof. P. B. Wells of Hull University and Prof. G. Webb of Glasgow University. A number of prochiral substrates were chosen and synthesised with the hope of devising a unique enantioselective heterogeneous catalytic system. This thesis makes a comparative examination of the field of heterogeneous and homogeneous catalysis and describes the asymmetric synthesis of a range of potential modifiers.

2 HETEROGENEOUS CATALYSIS

2.1 History

In 1932 Schwab[7] used cleaved quartz surfaces to support a metal dispersion thus creating the first recognised enantioselective heterogeneous catalyst. However, chirality in quartz is not homogeneous, but a product of crystal strain. These catalysts did indeed induce chirality but not surprisingly the optical yields were very low (<1% e.e.).

Some years later, Lipkin and Stewart[8] furthered this concept independently* by conducting hydrogenations using unsupported active metals. Two systems were studied: Raney nickel in conjunction with d-glucose and platinum dioxide in the presence of a naturally occurring cinchona alkaloid - molecules with four stereocentres, $C_{3,4,8,9}$ (Fig. 3).



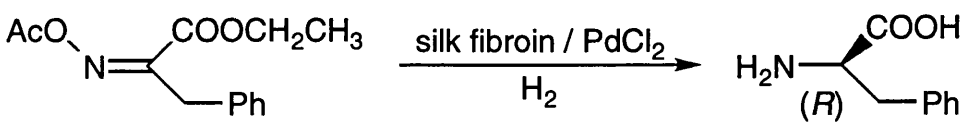
Cinchonidine Fig. 3 Cinchonine

The stereochemistries of cinchonidine and cinchonine are very similar. The stereocentres at C_3 (*R*) and C_4 (*S*) are identical in both compounds and each is of the *erythro* configuration with respect to their C_8, C_9 systems.[9]

* They make no mention of Schwab's work in their communications, and were almost certainly unaware of his contribution (the original paper was not published in a mainstream journal).

These experiments concentrated on the reduction of the carbon-carbon double bond in β-methylcinnamic acid yielding products with a very modest optical yield (8-10% e.e.). The conditions have since been modified and optimised. It is paradoxical that there have been many attempts[10] to diversify from those systems cited above, yet they remain the most successful to date.

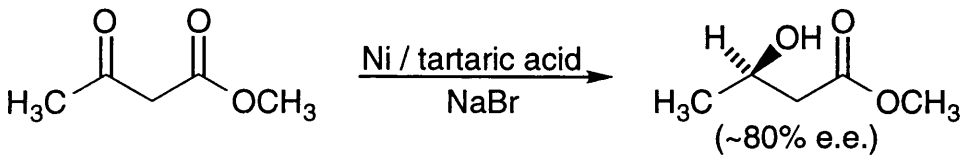
The natural biopolymer fibroin was used as a chiral support by Akabori[11] on which he achieved the reduction of the C=N bond in ethyl-α-acetoximinophenylpropionate by Pd with a small (and irreproducible[12]) chiral induction of ~10% e.e.



This "back to front" strategy (using metal dispersion) is historically unsuccessful, and has not been seriously pursued (though it should be recognised that using inductive heterogeneous catalysis to target the prochiral C=N bond has *never* realised products with an appreciable optical purity).

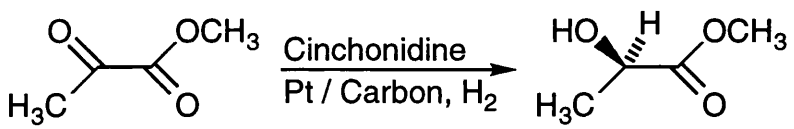
Isoda[13] re-examined the potential of modified Raney nickel, and successfully reduced the C=O bond (24% e.e.) using camphor as the chiral source. Amino acid modification gave a lower induction with the C=O group, but it was claimed that it reduced the C=C bond (substrate unknown) in up to 50% e.e. Some years later (1963) a Japanese group[14,15] announced the utility of NaBr / tartaric acid (TA) modified Raney nickel. With hindsight, methyl acetoacetate (MAA) was a fortuitous choice of

substrate since this catalyst is only effective over a specific range of compounds.



Methyl (*R*)-3-hydroxybutyrate

Many papers were published in the intervening years but none was able to advance the known science. The rediscovery of the cinchona modified platinum catalysts was communicated in 1978 and publicised through a series of papers in Japanese by Orito[16] in 1979.

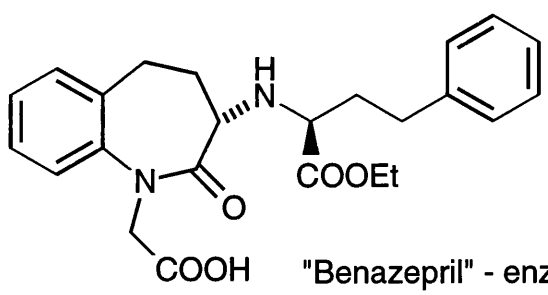


Methyl (*R*)-(+)-lactate

An 87% e.e. of methyl (*R*)-(+)-lactate was initially recorded, though optimisation by Wells *et al.*[17] and Blaser *et al.*[18] increased this to 95% (ethyl pyruvate and Pt / Al_2O_3 support).

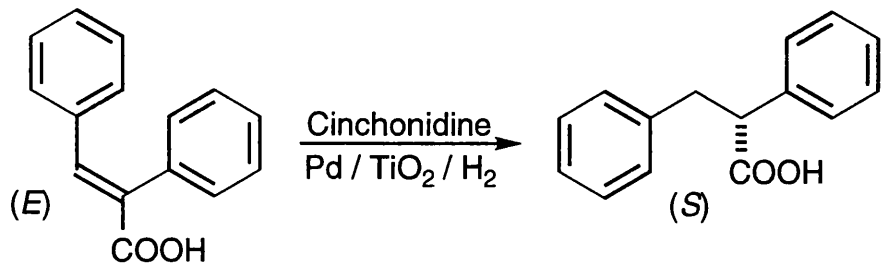
In a reprise of his original work, Izumi[19] refined the Ni / NaBr, tartrate system and was able to reduce methyl acetoacetate with an optical yield of 88.6%. This and similar combinations utilising nickel are still the subject of many research papers.

Enantioselective reduction of the prochiral C=C bond is notoriously difficult. By inference from several authors, doubt has been cast on the highest original claim of 50% e.e. for an unsaturated substrate (and is provisionally discounted). A recent paper[20] describes the most



"Benazepril" - enzyme inhibitor

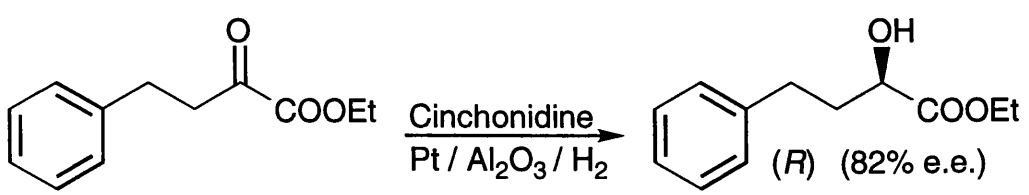
discriminating conditions to date. The C=C bond in (*E*)-α-phenylcinnamic acid was reduced giving an enantiomeric excess of 44%.



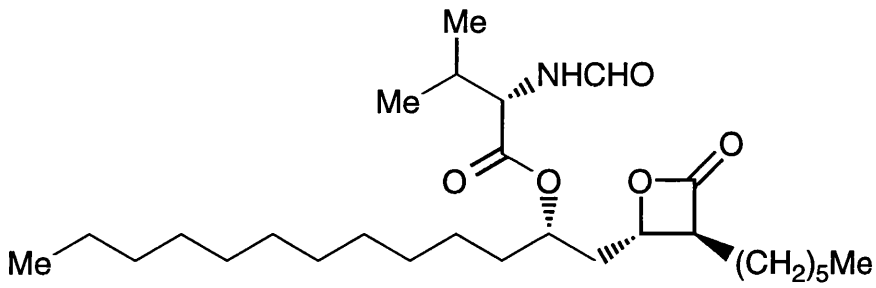
The usual reaction rate increase was observed (resulting from an increased concentration of substrate at the metal surface), and the exact physical conditions were found to have a critical bearing on the induction.

2.2 Commercial applications

Heterogeneous catalysts are very sensitive to their physical environment and are intolerant of specification change. This is a major drawback and rigorous quality control is necessary to sustain a reproducible process. Currently, there are very few commercial applications, but there are several potential intermediates that *could* be manufactured using this methodology. For example, the preparation of the intermediate required in the synthesis of Benazepril:[21]

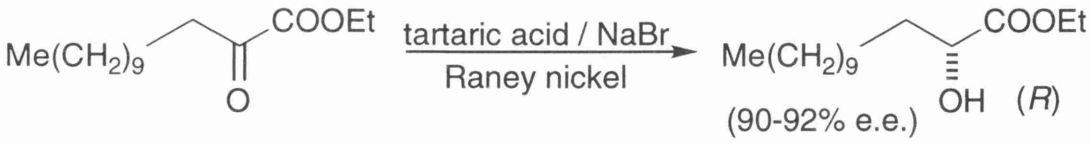


Since Benazepril is diastereomeric, there is a high probability that the diastereomeric excess could be raised quite considerably. Hoffmann-



"Tetrahydrolipstatin" - enzyme inhibitor

LaRoche synthesised the intermediate shown below in the preparation of Tetrahydrolipstatin.[22]



2.3 Topography

Various spectroscopic techniques have indicated that the topography of a heterogeneous catalyst is irregular and of a non-uniform structure. Furthermore, this complex situation is exacerbated in some experiments by the change of morphology when acidic reactants etch the metal surface. There is a method which purports to quantify the active sites by using the single turnover procedure.[23] This involves running stoichiometric reactions on the catalyst and analysing the results by 'in-line' gas chromatography. That is, only one product molecule will be derived from one active site. The ratio of the products is indicative of the type of site available and the relative number of these sites can be determined. But what is the nature of these sites? Augustine[24] states that there are thirteen types of atoms present within the structure of a face centred cubic metal crystallite (and embedded atoms are of a twelve-coordinate status). All of these are classified under four labels which are represented (Fig. 4) and defined below.

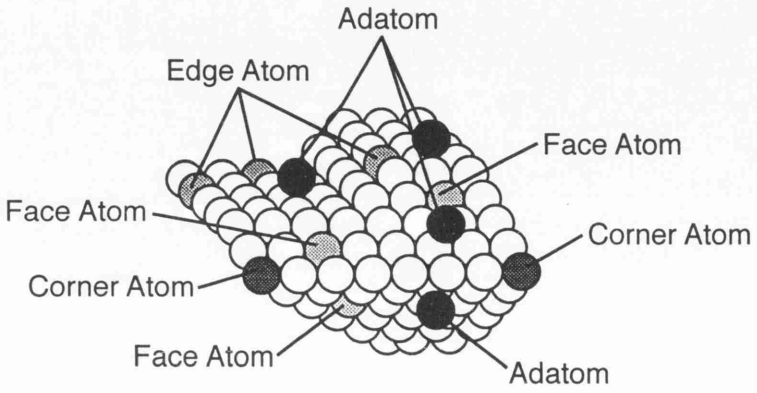


Fig. 4

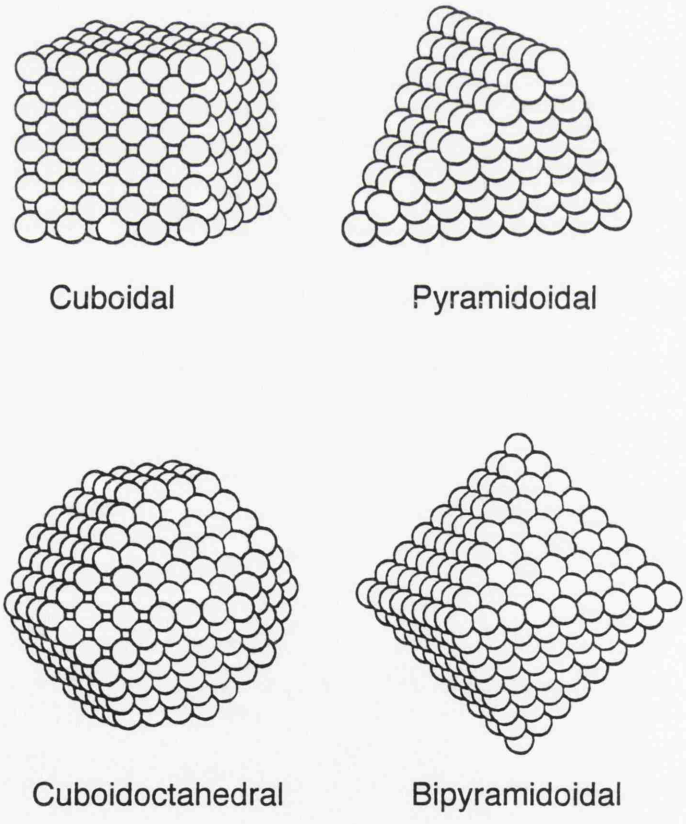

Cuboidal
Pyramidoidal
Cuboidoctahedral
Bipyramidoidal

Fig. 5

There have been numerous publications regarding the variety of adsorption and reaction centres; the combination of these data is represented comprehensively by Somorjai.[25] These conclusions are:

1) **Face atom** ensembles (terraces) promote the hydrogenolysis or rearrangements of alkanes but are unreactive to alkene hydrogenation.
2) **Corner atoms** are active two-step saturation and dehydrogenation sites.
3) **Adatoms** are the most prolific single atom reaction centres.
4) **Edge atoms** are known alkene isomerisation sites.

The four most common crystal shapes are 'cuboidal', 'pyramidoidal', 'cuboidoctahedral' and 'bipyramidoidal' (see opposite, Fig. 5) and each is capable of adopting an assortment of possible crystal packing configurations (Fig. 6).

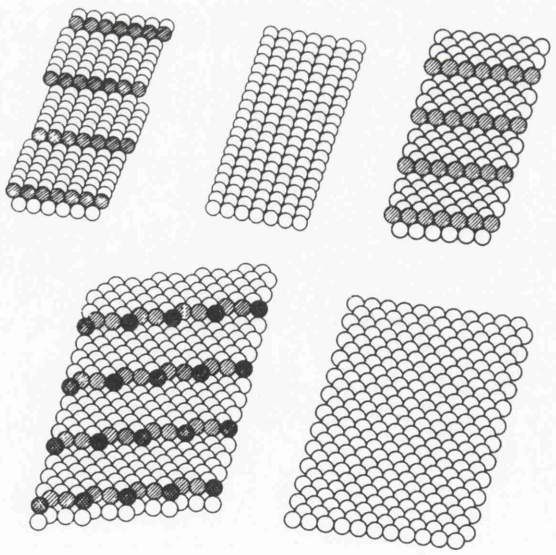


Fig. 6 Idealised atomic structures for Pt surfaces

2.4 C=C Adsorption characteristics

The mode of adsorption of alkenes is very difficult to ascertain. There are numerous permutations which are radically influenced by the type of metal surface, support, temperature, solvent, olefinic structure and isomerisation possibilities. This lists the primary variables but is an over-simplified representation. Using infrared spectroscopy and various electron probing techniques, a number of surface adsorption modes (represented by ethene) are known to occur. The species identified to date are depicted below (Fig. 7).

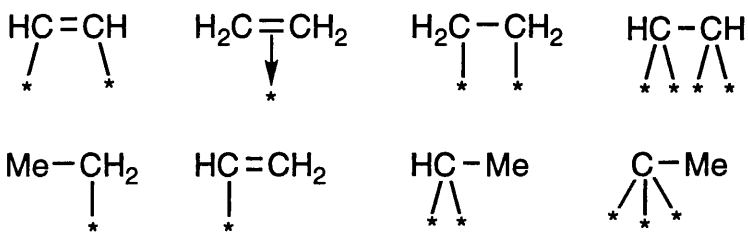


Fig. 7

In the absence of hydrogen ethene is adsorbed dissociatively, and hydrogen is desorbed. Whereas in the presence of pressurised hydrogen, associative adsorption occurs.[26] This is due to surface saturation with hydrogen which precludes certain adsorption modes and of course promotes the hydrogenation mechanism.

2.5 Effective Heterogeneous Systems

2.5.1 Platinum modified with cinchonidine

The chemisorption of cinchonidine alters the topography (but not the morphology) of the catalytic metal surface, such that the hydrogenation of a prochiral substrate, methyl or ethyl pyruvate, proceeds with high enantioselectivity. Three different mechanistic theories have been put forward:

1. Wells and co-workers have postulated[6,17] that the quinoline moiety in cinchonidine is chemisorbed flatly on the metal surface (terrace) *via* the π-electron system (though "the influence of the lone pair of electrons on the N atom probably induces a degree of tilt"). [For this complex to be stable, there must be π-electron donation into an empty d-orbital of the metal and an appreciable back-donation of electrons into a non-bonding orbital of the aromatic system.[27]]

The model proposed relies on the ordered adsorption of a non-closepacked array of cinchonidine molecules which obscures the surface atoms in a series of L-shapes. This leaves an exposed area on which the substrate can be hydrogenated. There is thought to be a facial / antifacial discrimination (steric) mechanism operating at the active sites. In its half-hydrogenated state the substrate is held in one orientation dictated by the proximity of the quinuclidine N-atom. In addition, the hydrogen bonded intermediate is responsible for the enhanced reaction rate and exerts a stabilising influence (Fig. 8). It is due to this transient interaction that chirality is conferred.

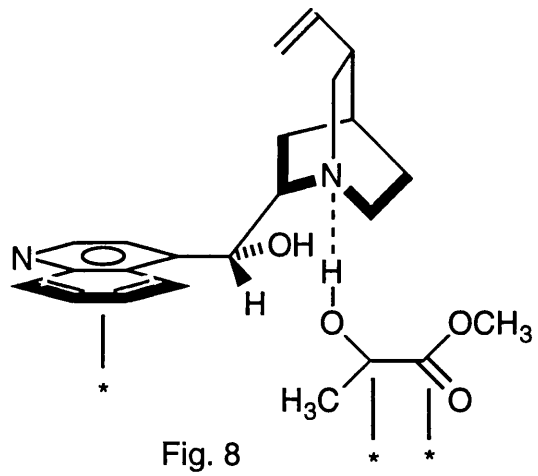


Fig. 8

This interpretation was recently severely criticised in an open Letter[28].

Latterly, Wells has conducted a deuterium exchange experiment[29] which lends credibility to this hypothesis (see below) but he points out that pyridine has been shown[30] to adsorb at an angle of 74° ± 10° at 300 K. In addition, the adsorption orientation of certain diphenols were shown to be concentration dependent[31] (flat at 10^{-4}M, π-bonded; upright at 10^{-3}M, di-σ-bonded). Whether parallels can be drawn is not an easy question to answer.

10,11-Dihydrocinchonidine was dissolved in C_2H_5OD and subjected to a pressurised deuterium atmosphere in the presence of 6.3% Pt on silica. The pattern of exchange was determined by ^1H NMR (45% conversion) and is most informative (Table 1).

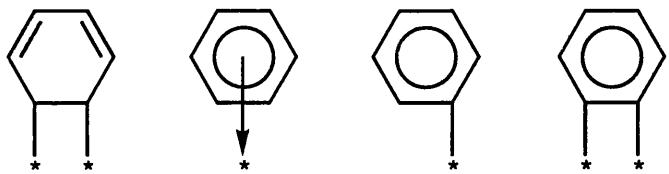
Atom Position:	2'	3'	5'	6'	7'	8'	9
Deuterium exchange (%)	94	49	22	51	31	85	31

Table 1

The ratio of exchange is not proof that all the quinoline rings lie (almost) flat, but since there was considerable exchange of the carbinyl proton at C_9, it suggests some degree of π-bonding.

It is widely accepted[32] that benzene can exist in several surface species (Fig 9).

Possible aromatic surface adsorption forms:

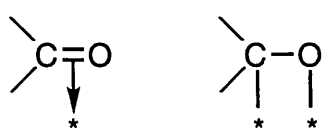


Associative Fig. 9 Dissociative

Intuitively, one would assume that these forms are indicative of those encountered with the quinoline ring system, but if there is a distinct difference between pyridine and quinoline adsorption, then no firm conclusions can be drawn.

2. Augustine *et al.*[33] also dispute the "template theory". They point out that ethanol is in excess and would be expected to hydrogen bond preferentially with the N-atom in quinuclidine ring. There is also speculation that the rate enhancement is due to a change in the adsorption characteristics of the substrate keto group* caused directly by modifier interaction. Two possible (1:1) interactions are presented, one in which the quinoline ring is in a vertical position (A) and the second suggests that it is horizontally adsorbed (B) (Fig. 10).

* This presumably includes the specific adsorption site since there are only two (theoretical) transitory adsorption states.



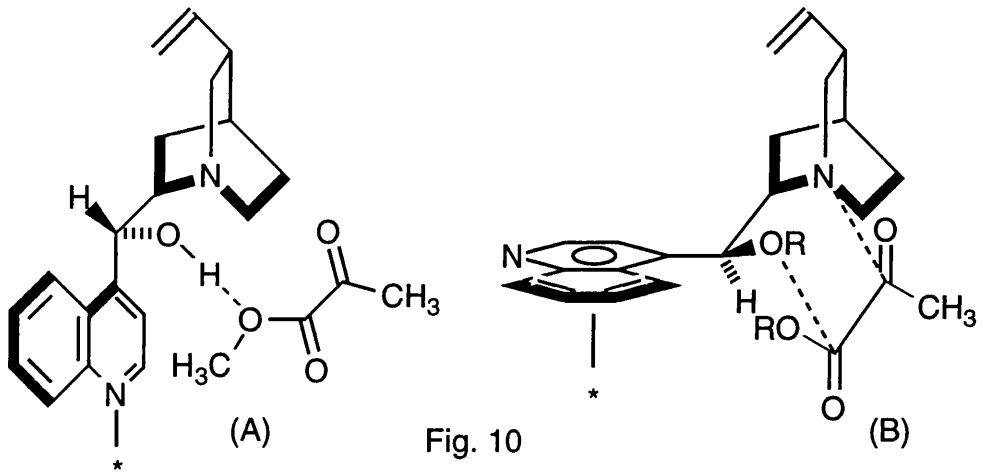


Fig. 10

(A) Quinoline edge adsorption in conjunction with a corner active site.

(B) Quinoline face adsorption adjacent to an adatom active site.

It is possible that both modes of adsorption are involved, one of which (B) accounts for the phenomena of (*S*)-lactate formation at low concentrations (as mentioned above: the concentration can have a profound influence).

3. The third mechanism is presented by O. Schwalm and A. Baiker[34]. Their model is based on computer generated data, but the physical parameters were derived from evidence that was experimentally obtained. They concur with Wells *et al.* that there is a hydrogen bond between the quinuclidine nitrogen and the half-hydrogenation state of methyl pyruvate, but they suggest it is formed *via* the alternate intermediary and protonated cinchonidine (Fig. 11). Steric hindrance of the (*S*)-producing intermediate is said to suppress its formation.

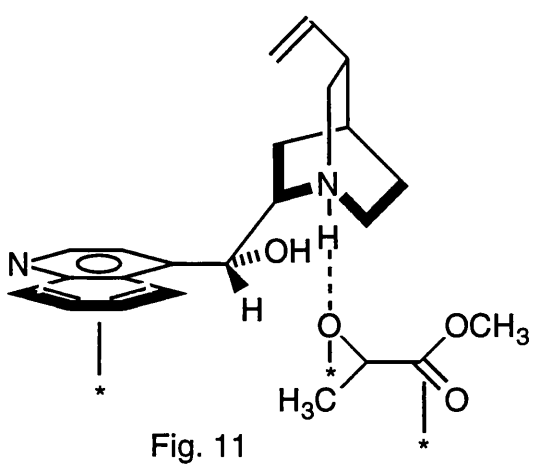


Fig. 11

4. There is a fourth suggestion outlined recently by Margitfalvi.[28] He has yet to publish the details in full but reports that he has considered the possibility of the quinoline moiety providing a specific shielding effect *via* π-π overlapping between the aromatic ring and the conjugated π-bonds of the α-keto esters.

Spectroscopic studies prove that cinchonidine is protonated in acetic acid and, astonishingly, in ethanol[35] after the aerobic pre-treatment of the catalyst. Indeed, the highest recorded induction[18] was achieved using 10,11-dihydro-O-methylcinchonidine in acetic acid on ethyl pyruvate. [What may or may not be important is that the protonated conformation of cinchonidine is subtly different from the parent molecule[36,37]]. The ethene double bond in cinchonidine is usually assumed to be hydrogenated *in situ*, and subsequently desorbed. This is of course a hindrance to reaction progress and so many researchers pre-hydrogenate it.

2.5.1.1 Solvent effects

The selection of the solvent chosen and its relative polarity is often based on its ability to dissolve the substrate being hydrogenated. But this variable has a considerable influence on the reaction outcome and should be selected carefully. It is of interest that cinchonidine-N-oxide has been detected[38] in ethanolic solutions in the presence of Pt / Al_2O_3 (although this is almost certainly reduced to the parent alkaloid under hydrogenation conditions). Intriguingly, no reaction occurs at all under strictly anaerobic conditions[39]. The destructive adsorption of ethanol leads to active 'H' which hydrogenates the ethene moiety in cinchonidine and poisons the catalyst with linear and bridge-bonded carbon monoxide (Fig. 12).

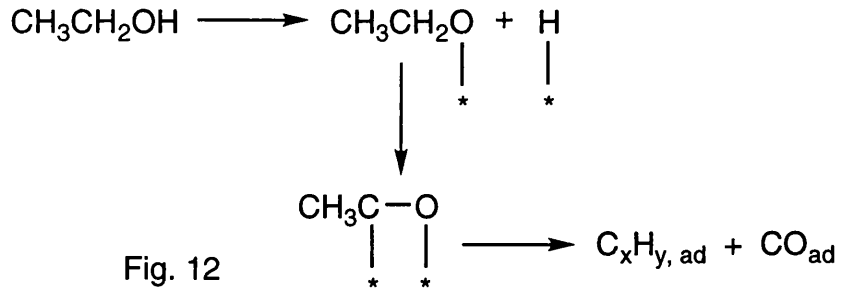


Fig. 12

Superficially, it does seem that an acidic environment increases selectivity. Basic conditions undoubtedly impede the reaction and reduce the induction markedly. Yet, when an aprotic neutral solvent like toluene is used there is still a very high induction (87% e.e.) and the reaction rate is almost as high as that observed with acetic acid.

2.5.1.2 Comparative analysis

Of the models presented, all are flawed. The "template model" relies on ordered adsorption on a very disordered metal surface.* It also contradicts the kinetic data[40] that indicates the existence of a 1:1 interaction.

* Prof. Wells has since made it clear[41] that he was under no illusion as to the morphology of the active phase, but concedes that there is no ordered adsorption of cinchonidine[42] and he now favours the 1:1 interaction hypothesis.

Augustine's model is dependent on the participation of the oxygen atom in cinchonidine forming a six-membered ring transition state with the substrate. But enantio-differentiation still occurs (22% e.e.) when the OH group is replaced with hydrogen[43] (but the O-atom is probably beneficial). If the adatoms were minimised by heat pre-treatment of the catalyst

(annealing) then one would expect a decrease in enantioselectivity in accord with this theory. In fact it has been reported[16] to increase the selectivity.

By the authors' own admission the computer modelled theory lacks sophistication. Interaction with the metal surface is not catered for and certain assumptions have been made, most notably the adsorption mode of the modifier (which is still unknown).

2.5.2 Nickel modified primarily with tartaric acid

The use of (*R*,*R*)-tartaric acid (TA) as a modifier on a nickel surface invariably alters the morphology due to etching. This of course introduces an extra element of unpredictability, and optical yield and reaction rates are often irreproducible. However, the best results have been achieved with β-ketoesters, and most notably with methyl acetoacetate (MAA).

There is apparently more tolerance towards substrates than with the cinchona system as demonstrated by Osawa[44] (Table 2) using [(*R*,*R*)-TA / NaBr / Raney Ni][45] at 60 °C.

Substrate	O.Y. (% e.e.)	Configuration
3-Methyl-2-butanone	85	(*S*)
2-Hexanone	80	(*S*)
2-Octanone	80	(*S*)
2-Decanone	76	(*S*)

Table 2

Complete TA coverage of all the active sites is difficult to achieve, which is unfortunate since unmodified surface sites yield a racemic product. When NaBr is introduced as co-modifier there is generally an increase in optical yield. It is widely accepted that the Br^- ion acts as a poison of bare nickel sites, and is a beneficial regulator of the adsorbed modifier concentration.[19] In addition, it may complex with any residual aluminium atoms which are known to inhibit enantio-differentiation. Therefore, in theory at least, only the enantio-differentiating interaction can occur.

2.5.2.1 Physical conditions

There are conflicting reports[44,53] regarding the optimum pH of the TA modifier solution, though the maximum adsorption corresponds to the isoelectric point (pH 5.1).[46] [The system is surprisingly pH tolerant.] This also holds true for alternative modifiers such as alanine (pH 6.0)[47] and mandelic acid (pH 2.9).[12] In the case of TA, the pH of the solution increases during the modification process, indicating that dissociative adsorption is taking place. TA's effectiveness as an induction agent falls off rapidly at pH <3 (almost total protonation) and at values of pH >9.0, after which point the dianion predominates (which precludes the formation of the required nickel tartrate complex). The solvent used is of some importance, medium polar organic solvents giving good results, whilst water has a deleterious effect on the enantioselectivity. The influence of the pH differs according to the modifier used. The following example[48] stands out as an example of when to expect the unexpected: (*S*)-mandelic acid modified Ni reduced MAA to give the (*S*) product at pH 2.4 but the (*R*) product at pH 5.0.

The optical yield obtained is moderately temperature (modification and hydrogenation) dependent. An exception was found when (*S*)-glutamic acid was used to modify Ni above and below 80 °C. When applied to the substrate MAA, the 'cold' catalyst yielded (*R*)-methyl 3-hydroxybutyrate and the 'hot' catalyst yielded the (*S*) enantiomer in excess.[49] This has led to the suggestion that "there may be two kinds of differentiating sites functioning in opposite directions of enantio-differentiation on the catalyst surface" - Y. Izumi, Japan.

Heat pre-treatment conditions the surface, yields slightly larger crystallites (the particle size distribution is quantifiable) and possibly removes amorphous areas. Since leaching is inevitable, the sizes of post-modified

metal particles are likely to change - experiments indicate[50] that larger metal particles give the best results.

The transition state involved in the TA / MAA reaction has yet to be established, but the most popular representation is shown below (Fig. 13).

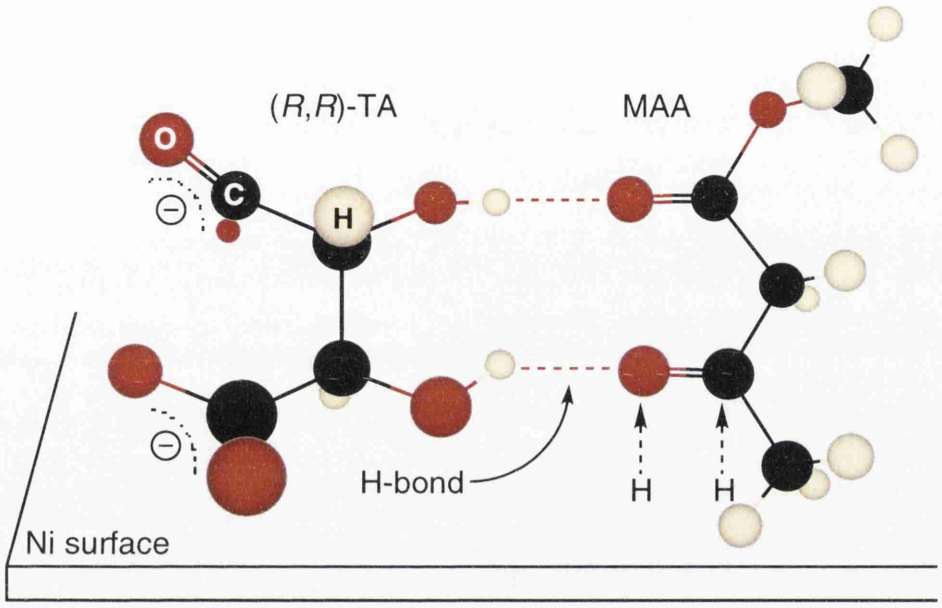


Fig. 13

It is interesting that (*S*)-malic acid compares poorly with TA in this reaction (and is generally an inferior modifier[51]), thus lending support to the doubly-bonded adduct.

2.6 Surface species

There is another aspect to the surface interactions, which was postulated in a Japanese journal[52] and one still considered seriously. It may be that H-atoms are stacked in multilayers on the metal surface, the upper layers being physically adsorbed. Each layer is polarised and thus hydrogenation can take place at a point distant from the metal surface. This may also explain the influence that the hydrogen pressure has on the

optical yield - theoretically it should be independent of pressure. An alternative hypothesis involves the delivery of atomic hydrogen to the half-hydrogenated substrate *via* a spillover* mechanism.[53]

All of the work described above relates to the hydrogenation of the prochiral C=O bond. Bartók *et al.*[54] studied the enantioselective hydrogenation of (*E*) and (*Z*)-α-phenylcinnamic acid using Raney nickel supported on silica, modified with (*R*,*R*)-tartaric acid. The physical conditions were altered in a series of experiments but the highest optical yield obtained was 17%. This class of substrate continues to be neglected mainly because of continued poor results and the successful domination of the area by homogeneous catalysis.

* Spillover has yet to be taken into account. It involves the transport of a sorbed or formed material to a surface phase that is in contact with the original adsorbing or activating surface. Therefore, by surface diffusion, monatomic hydrogen can migrate from one metal atom to another and onto the supporting phase[55] (Fig. 14). Since chemisorption on the original surface is exothermic, a small activation energy may be required to initiate diffusion. This also implies that bonds with the adsorbing surfaces are broken and new bonds are formed with the accepting medium. It is also surmised that a metal atom can migrate over the support. This phenomenon is reversible and presently is not well understood. A recent review[56] summarises what is currently known.

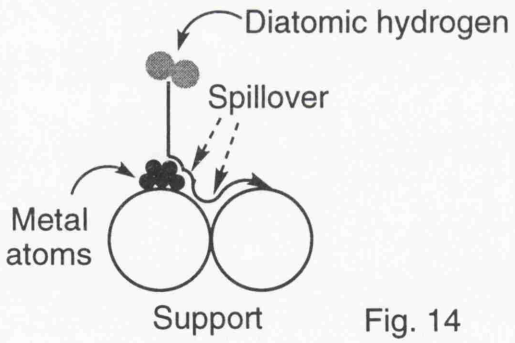
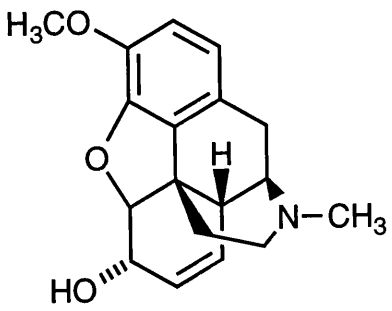


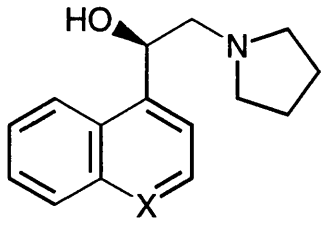
Fig. 14



Codeine

2.7 Recent developments

A considerable increase in reaction rate was noted[57,58] when butane-2,3-dione was hydrogenated using cinchonidine and (in a separate experiment) codeine modified Pt, though the optical yield recorded was very low. The potential for modifiers similar to that of cinchonidine has also been recognised by a Swiss group[59] who have demonstrated the utility of cinchona mimics (Fig. 15).



X=CH, N

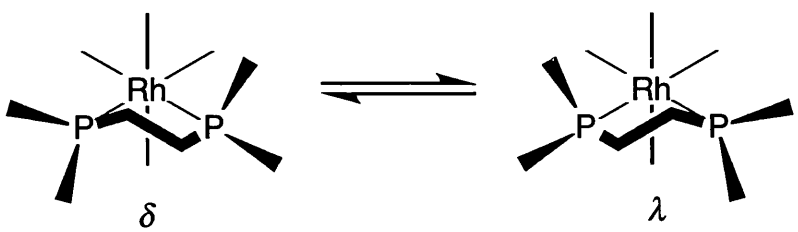
Fig. 15

The naphthalene based modifier used with ethyl pyruvate yielded a product of 75% e.e. Where X=N the modifier gave an inferior result, suggesting that the N-atom in the quinoline ring is not necessary. It further indicates that the aromatic π-system is involved in adsorption rather than the N-atom lone pair. Similarly, (*S*)-1-(1-naphthyl)ethylamine has been demonstated[60] to induce up to 82% e.e. in ethyl pyruvate *via* a diastereoselective reductive amination though the expense of this reagent would probably preclude its general implementation.

3 HOMOGENEOUS CATALYSIS

Homogeneous catalysis is a relatively recent development. Wilkinson[61] synthesised tris(triphenylphosphine)rhodium chloride, $[RhCl(PPh_3)_3]$ and demonstrated its use as a soluble hydrogenation catalyst for unhindered olefins. References cited within his research paper indicate that this was not the first homogeneous catalyst prepared, but one which delivered unparalleled reaction rates - comparable only with heterogeneous catalysts.

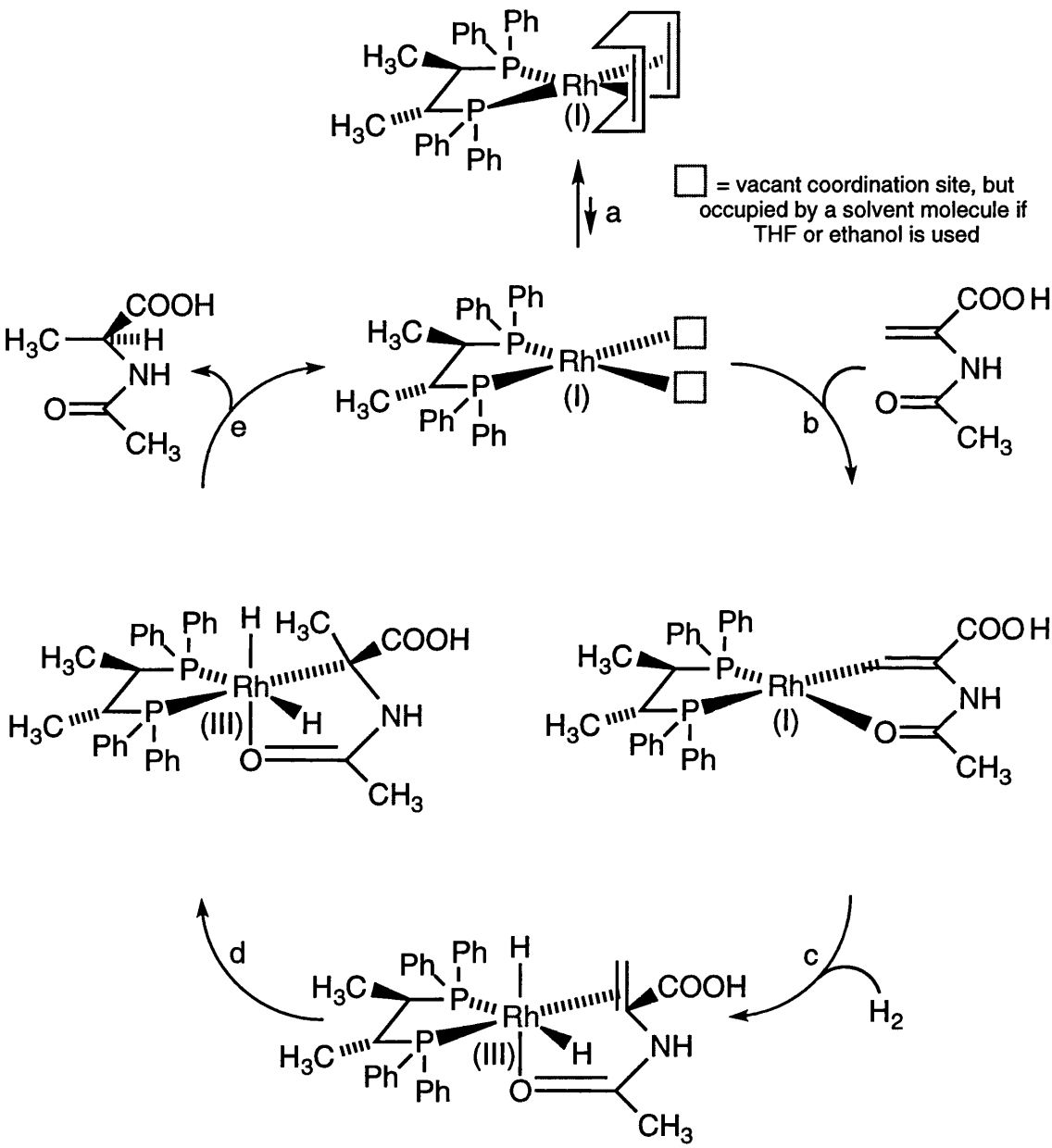
The breakthrough was recognised by Knowles[62] and Horner[63] who substituted the optically active phosphine ligands, (*R*)-(-)- and (*S*)-(+)-methyl-*n*-propylphenylphosphine respectively, and achieved asymmetric hydrogenation of the prochiral precursors α-phenylacrylic acid (15% e.e.) and α-ethylstyrene (8% e.e.). Knowles made a direct substitution of the ligand used in Wilkinson's catalyst whereas Horner was more innovative: *two* mole equivalents of the single enantiomer were combined *in situ* with $[Rh\text{-}(1,5\text{-hexadieneCl}]_2$. It was a natural progression to link the enantiomers to form a symmetrical diastereomer and preform the square planar rhodium chelate (Fig. 16).



The chiral conformations of a saturated five-membered chelate

Fig. 16

Possible mechanism for the hydrogenation of 2-acetamidoacrylic acid catalysed by [Rh((*S,S*)-chirophos) (COD)]ClO_4



(a) The COD ligand dissociates.

(b) Solvent molecules replaced by a molecule of 2-acetamidoacrylic acid.

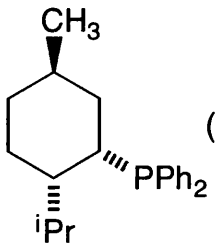
(c) Oxidative addition of hydrogen.

(d) One hydrogen atom moves from the metal atom to the double bond.

(e) Reductive elimination, the acetylated amino acid dissociates.

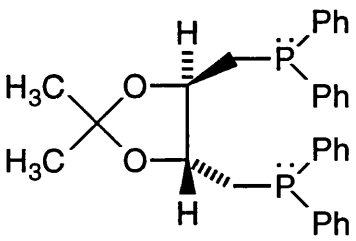
Scheme 1

A series of diastereomeric phosphines followed, initially with asymmetric phosphorus centres, then later with carbon-centred chirality adjacent to achiral phosphorus atoms, of which "NMDPP" was the first example.[64]

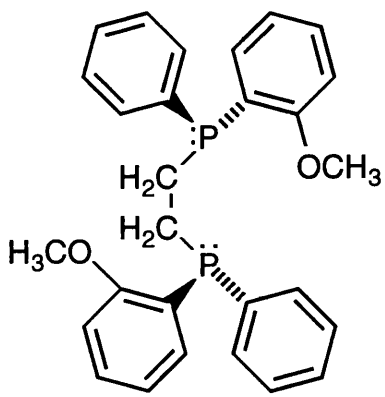


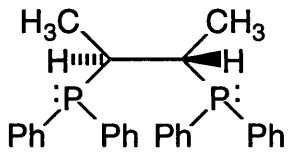
(*S,S*)-"NMDPP"

This development was closely followed by the introduction[65] of "DIOP". Significant advances in ligand design were made by Knowles[66] with a derivative christened "diPAMP" and Bosnich[67] who synthesised "chiraphos" (Fig.17).



(*R,R*)-DIOP





(*S,S*)-chiraphos

Fig. 17 (*R,R*)-diPAMP

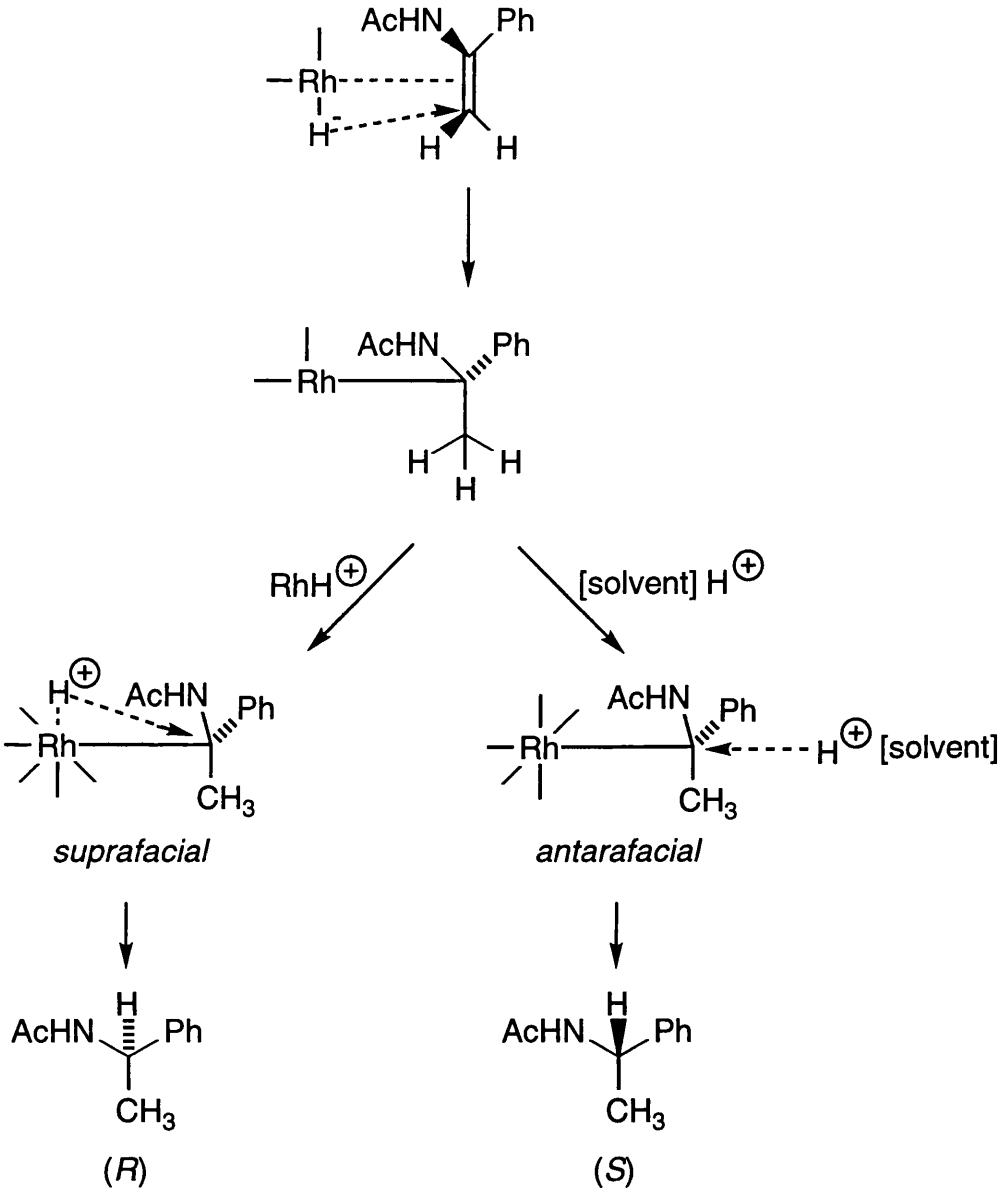
Clearly, the transient active species in all cases relies on the displacement of one or more of the ligands (Scheme 1). Invariably the 1,5-cyclooctadiene dissociates in favour of monatomic hydrogen, though the octahedral structure is in equilibrium with the substrate, solvent, hydrogen and product.

The choice of solvent has a profound effect in nearly all of the published reactions. For example, complexes which utilise the ligand chiraphos in conjunction with a series of α-*N*-acetyl / acylaminoacrylic acids are clearly influenced by solvent effects (up to ±15% e.e.), and when DIOP is used with the substrate 1-acetamido-1-phenyl-1-propene there are very notable differences (Table 3).

Complex	Solvent	e.e. (%)	Config.
Rh_2Cl_2(COD)DIOP	Ethanol	42.5	(*R*)
Rh_2Cl_2(COD)DIOP	Benzene	44	(*S*)
[Rh(COD)DIOP]$^+ClO_4^-$	Ethanol	38.5	(*R*)
[Rh(COD)DIOP]$^+ClO_4^-$	Benzene	68	(*R*)

Table 3

In the case of the neutral complex a switch in the sense of discrimination is observed. It has been suggested[68] that this effect is the result of H^+ delivery from opposite sides of the chelated intermediate. That is, the mechanistic pathway is solvent dependent. In benzene, the hydrogen atom responsible for hydrogenolysis is initially bound to the rhodium atom and is delivered to the reaction site from the same side as the hydrogen adding to the double bond. This is termed *suprafacial* addition. Protonated polar solvents attack from the opposite side of the complex giving rise to *antarafacial* addition, subsequently inducing rhodium carbon bond cleavage (Scheme 2).



Scheme 2

With a cationic catalyst there is an enhanced chiral recognition in a non-polar environment. This is surprising since benzene does not promote the dissociation of the labile ligand but it does essentially eliminate unwanted isomerisation.

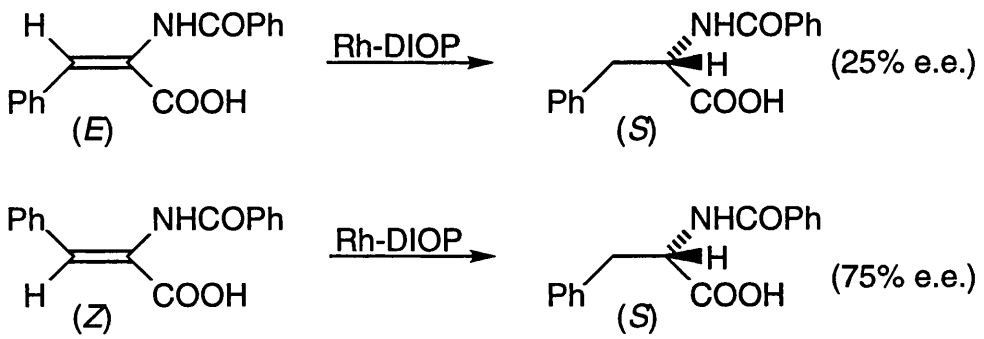
A study[69] was conducted to determine the extent of isomerisation during the rhodium catalysed hydrogenation of (*E*)-α-benzamidocinnamic

acid using various ligands. Results obtained using two of the ligands are shown (Table 4).

	% isomerisation		
	THF	Ethanol	Benzene
(*R,R*)-DIOP	20	33	0
(*R,R*)-diPAMP	0	6	0

Table 4

With regards to the type of substrates cited, the (*Z*) isomers afforded a larger enantiomeric excess and increased reaction rates, *e.g.*:



There is a preferential attack of hydrogen at the prochiral *Re-Si* face[70] when DIOP is utilised but this is reversed if the trifluoroacetyl group is substituted for the benzoyl substituent. This has been attributed to steric and / or electronic effects, but the substrate can adopt an infinite number of rotameric conformations in the transitionary stage leading to varying degrees of diastereotopic interaction.

The mechanism for detrimental isomerism can be postulated in several ways depending on whether a specific atom or the π-bond is associated with the metal surface. Carbon atom adsorption could lead to a single bonded intermediate which is able to rotate and eliminate (RhH).

The pathway which has gained most support is the π-allyl mechanism[71] (Fig. 18).

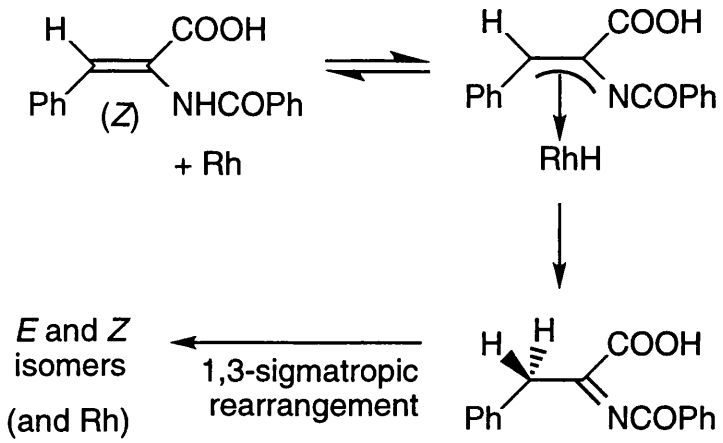


Fig. 18

The substrate (α-acyl/alkylaminoacylic acids) probably forms a bidentate low-energy complex in the transition state, evidence for which was provided by Christopfel.[72] Itaconic acid hydrogenated in the presence of $[Rh(COD)DIPAMP]^+BF_4^-$ afforded (*R*)-methylsuccinic acid with an enantiomeric excess of 77% in very dilute solutions (2 mM) but only 38% e.e. in 400 mM solution (Fig. 19). In the more concentrated solution, intermolecular hydrogen bonding effectively competes against the necessary chelate formation. It has been shown[73] that itaconic acid does indeed exist as a polymer (continual intermolecular hydrogen bonding *via* the acid moiety) in the crystal and is monomeric in very dilute solutions.

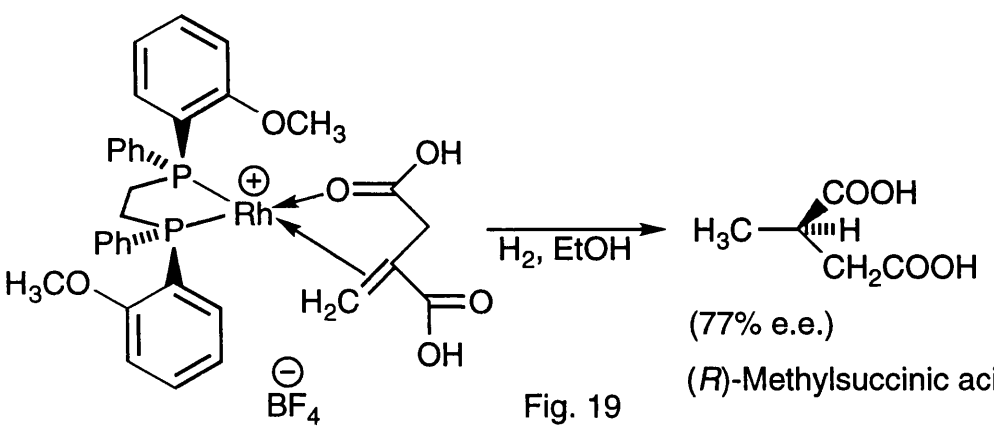
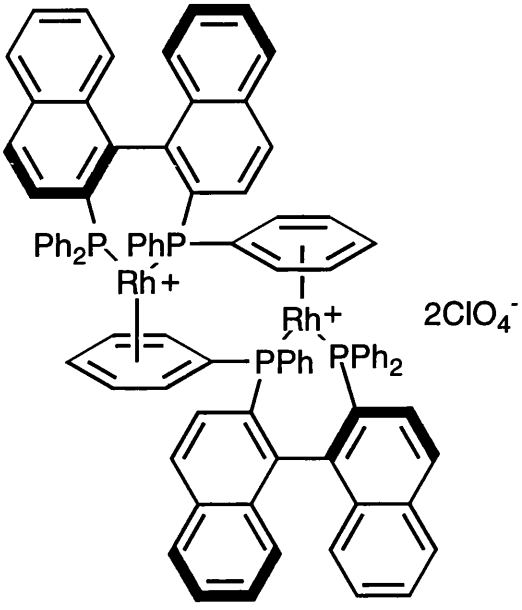
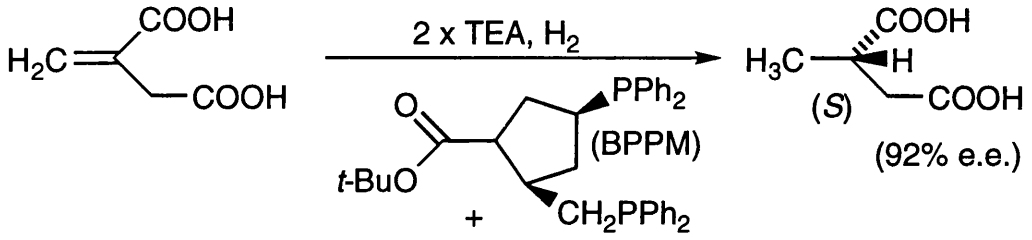


Fig. 19



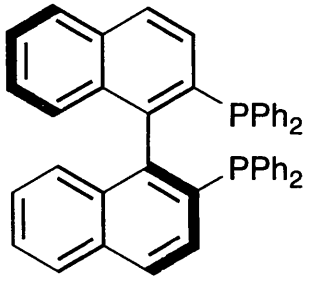
(*S*)-Rh-BINAP complex

A possible refinement when utilising diacid substrates involves the addition of two mole equivalents of triethylamine (TEA). Using a rhodium complex in conjunction with a previously reported[74] ligand (BPPM), Ojima[75] conducted the hydrogenation of itaconic acid in the presence of TEA. This was found to exert a considerable (favourable) influence on the chiral induction.



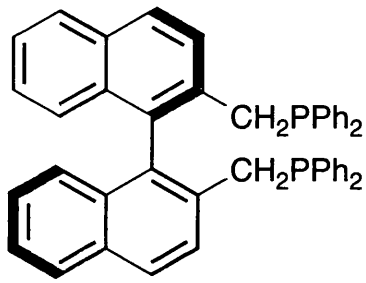
An accepted explanation is that the dianion is generated, and this species is more strongly attracted to the central rhodium atom in the coordination sphere. That is, the resulting shift in the equilibrium balance has a kinetic effect on the reaction outcome.

Binaphthalene ligands were a major breakthrough in this field. The most prolific of which was introduced by Noyori[76] in 1980. BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] was quickly recognised as having commercial potential and has since been the catalyst of choice in many synthetic procedures.

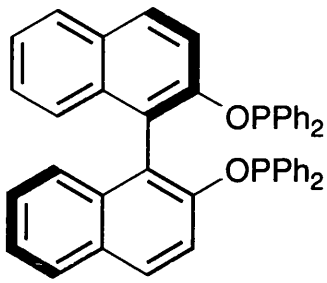


(*S*)-BINAP

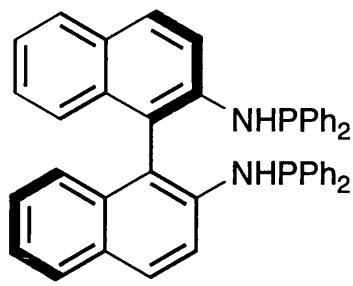
Yet, this was not an instant and isolated discovery. In fact the basic concept and groundwork was *not* instigated by Noyori at all. A Japanese group[77] published work using "NAPHOS" and Grubbs[78] independently reported results using an analogue (hereby termed "BDPOB") in 1977. This series was completed by Miyano[79] who synthesised the most proficient ligand of the three (BDPAB), obtaining a maximum optical yield of 95% with a sterically hindered acrylic acid derivative.



(*R*)-NAPHOS



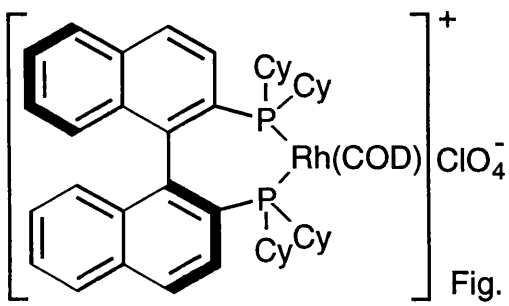
(*R*)-BDPOB



(*R*)-BDPAB

Noyori realised that the chirality was 'diluted' in the NAPHOS ligand due to the flexibility in the structure. Removing the CH_2 'spacers' and subsequently complexing the BINAP ligand with rhodium and norbornadiene yielded a catalyst with a rigid conformation. The whole structure is twisted in such a way that the chirality is transmitted throughout the molecular framework and conferred *via* the donor atoms.

An alternative to BINAP are two analogues which have been reported[80] to possess similar specificity (Fig. 20).



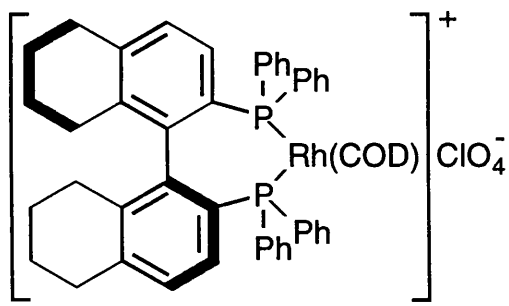
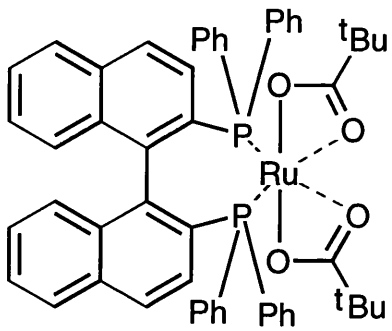


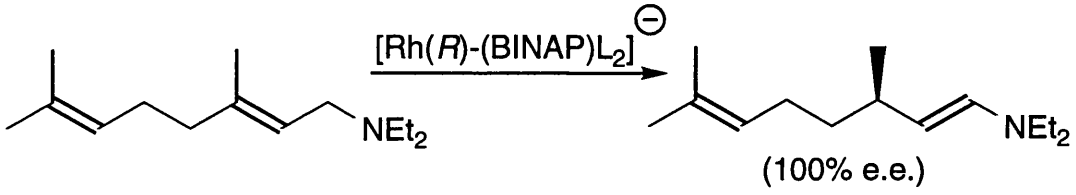
Fig. 20



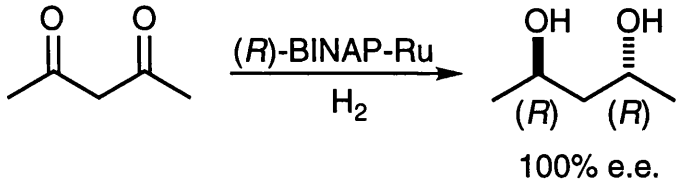
(*S*)-Ru(II)-BINAP complex

As expected, there is an attenuation of induction in certain applications, but an improvement of activity over BINAP with regards to certain aliphatic ketones.[81]

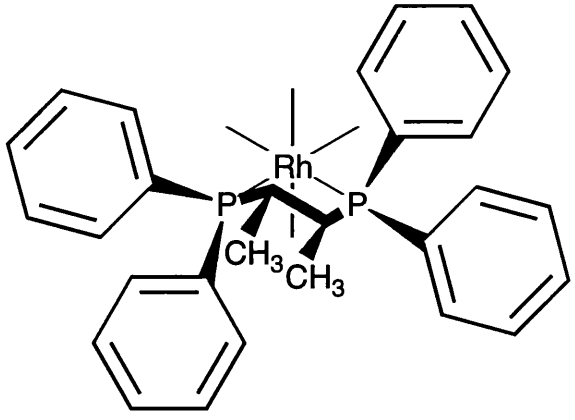
The Rh-BINAP complex is easily the most stereoselective catalyst of its class (optical yields >90% are common), and is receptive to a wide range of prochiral substrates. Of the many applications (too numerous to list) its ability to propagate an enantioselective allylic hydrogen shift[82] is of significance, since this not easily achieved by other methods.



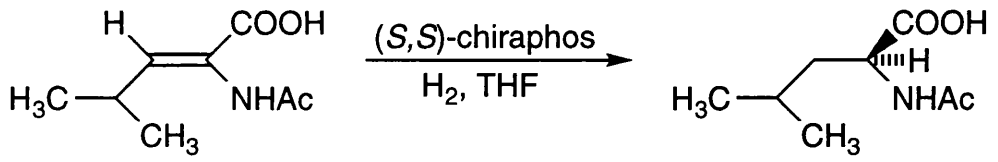
Ruthenium has a distinctly different reactivity. When substituted for rhodium, Ru-BINAP complexes[83] catalyse the reduction of α,β and β,γ-unsaturated carboxylic acids. Furthermore, at considerably elevated pressure and temperature, prochiral β-ketoesters and β-diketones[84] are hydrogenated with high to total selectivity, *e.g.*:



Homogeneous catalysts have considerable tolerance with regards to the type of substrate with which they are compatible. They are often effective across a whole class of prochiral precursors but more often than not a specific match between ligand, metal and substrate yield the most striking results.



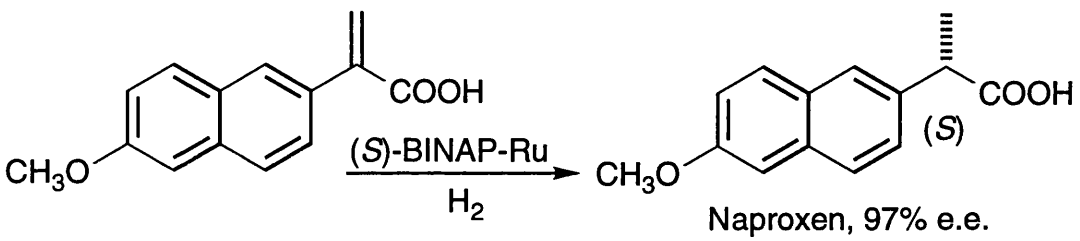
The preferred δ-conformation of the (*S,S*)-chiraphos chelate (structure determined by X-ray crystallography).



β-Isopropyl-α-acetamidoacrylic acid

(*S*)-*N*-Acetylleucine
(100% e.e.)

A commercial application for the Ru-BINAP catalyst has been found in its ability to reduce 2-(6'-methoxy-2'-naphthyl)acrylic acid to the anti-inflammatory agent Naproxen.[85]



Naproxen, 97% e.e.

A disadvantage of the BINAP series is that they are very soluble in the solvent medium, extremely air sensitive, and are therefore unrecoverable. Recently, a major advance has been announced. The derived homogeneous catalyst [Ru(BINAP-4SO_3Na) dissolved in a pseudo-aqueous phase*, was encapsulated as a thin film within a porous glass support[86] thus conferring long term stability. This reuseable "heterogeneous homogenous" catalyst has demonstrable potential and has been used successfully to catalyse the formation of Naproxen in 96% optical yield.

* Ethylene glycol was used as the 'aqueous phase' because it is immiscible with most organic solvents. And although it is described as an immobilised catalyst, the ethylene glycol is not covalently bonded but is physically trapped within porous beads.

There is no consistency amongst the many papers with regards to the physical parameters, notably the pressure of H_2 applied. Clearly, trends are easily recognised, but the complexity of the many interactions make it impossible to predict the reaction outcome, though retrospective analysis can make sense of the hydrogenation products which do not conform to expectations.

Summarised comparison of homogeneous with modified heterogeneous catalysts

Homogeneous Catalyst	Heterogeneous Catalyst
Reaction at metal core	Metal supplies 'H' to adduct
Complex is sterically crowded	Only the adduct leading to (*S*)-product is sterically crowded
Ligands direct the ultimate orientation	Electrostatic attraction
Catalyst is not recoverable	Catalyst is recoverable
Outer structure not important	Outer structure is important

There is a surprising aspect to both fields in that after decades of intense interest, there is still only a limited understanding of the mechanisms involved. This assertion is exemplified by the many reactions which do not conform with theoretical expectations.

4 BINAPHTHALENE CHEMISTRY

The rotation about the σ-bond of 1,1'-binaphthalene derivatives is restricted such that two axially chiral enantiomers may be isolated.[87] Steric hindrance of the substituents at the 8,8'-positions and to a lesser extent the 2,2'-positions are responsible for the prevention of free rotation. Therefore, it is very surprising that the 2,2'-derivatives are extremely resistant to thermal racemisation, yet many 8,8'-disubstituted compounds are not. An explanation[88] for this discrepancy, published in the early sixties, proposed that resolved binaphthalene molecules can rotate (if the substituents are small) by way of a 'racemoid' (one-step) or 'mesoid' (multistage) intermediate (Fig. 21) thus destroying chirality.

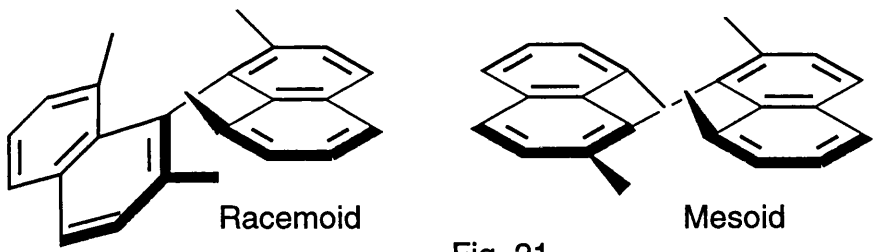
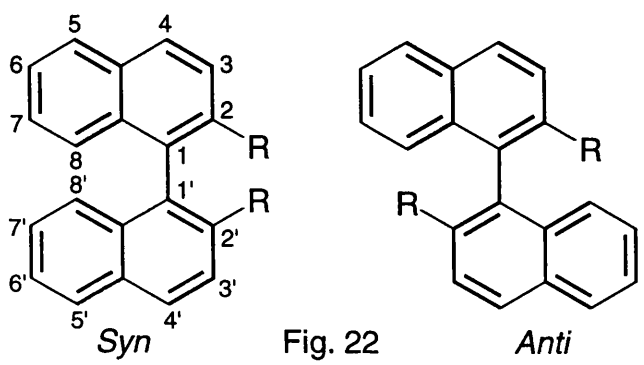


Fig. 21

Both of these transitionary structures invoke an *anti* mechanism. This pathway has gained universal acceptance in preference to *syn* rotation, since computer calculations suggest that the steric resistance is lower[89,90,91] (Fig. 22).



Syn Fig. 22 *Anti*

These studies corroborate the viability of the mesoid intermediate but favour a more complex chain of events. It seems likely that the *peri* effect[92] is a contributory factor and that subsequent ring deformation reduces the repulsive non-bonded interactions leading to an increase in optical lability. However, a recent paper[93] attacks previous assumptions and asserts that the *anti* process does not occur exclusively. The authors present evidence indicating that certain 2,2'-disubstituted binaphthalenes (*e.g.* 2,2'-dibromo-1,1'-binaphthyl) are able to racemise *via* multi-stage *syn* rotation.

Whichever process is invoked, the aromatic rings experience considerable distortion during the transition stages. The (computational) calculations[94] suggest that the deformation energy ($kcalmol^{-1}$) required for a 5-20° deviation from the plane is within theoretical limits, but accounts for two thirds of the activation energy required.[93] Indeed, it is a common misconception that aromatic systems are inflexible.[95] For example, naphthalene may bend (and stretch) at the 9,10 interface and/or the 1,4 and 5,8 axes (Fig. 23).[94]

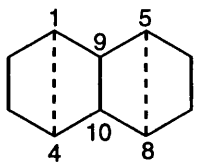
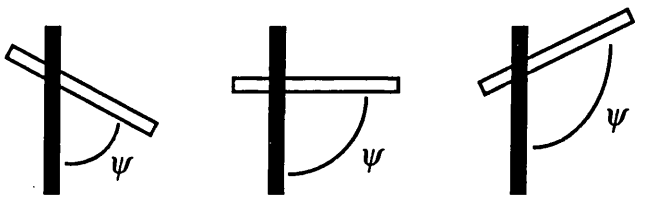


Fig. 23

There are two crystalline forms of 1,1'-binaphthyl: the *trans* or 'A' form that melts at 159 °C, has a dihedral angle of 103.1° and is chiral; and the racemic *cis* or 'B' form that melts at 145 °C, has a dihedral angle of 68.6° and is the less stable conformation. In the 'A' and 'B' forms the two six-membered rings comprising the naphthalene moiety are distorted by 1.7 and 1.0° respectively (with reference to planarity). The most astounding aspect of the structural geometry of 1,1'-binaphthyl is revealed by X-ray powder analyses.[96] In both forms, every bond length and angle in the naphthalene ring system is different, and consequently it exists as a

bisected polygon. The racemic compound has a greater density and must therefore possess the most efficient crystal packing in the solid state.

Clearly, the position and bulk of the substituents determine the conformation that it adopts. Molecules with a dihedral angle (ψ) less than 90° are described as having a 'cisoid' conformation, those with an angle between 90° and 180° are labelled 'transoid'. Should the helicity lead to perpendicular naphthalene rings, then a plane of symmetry would render the molecule racemic (Fig. 24 - (*R*) configurations).



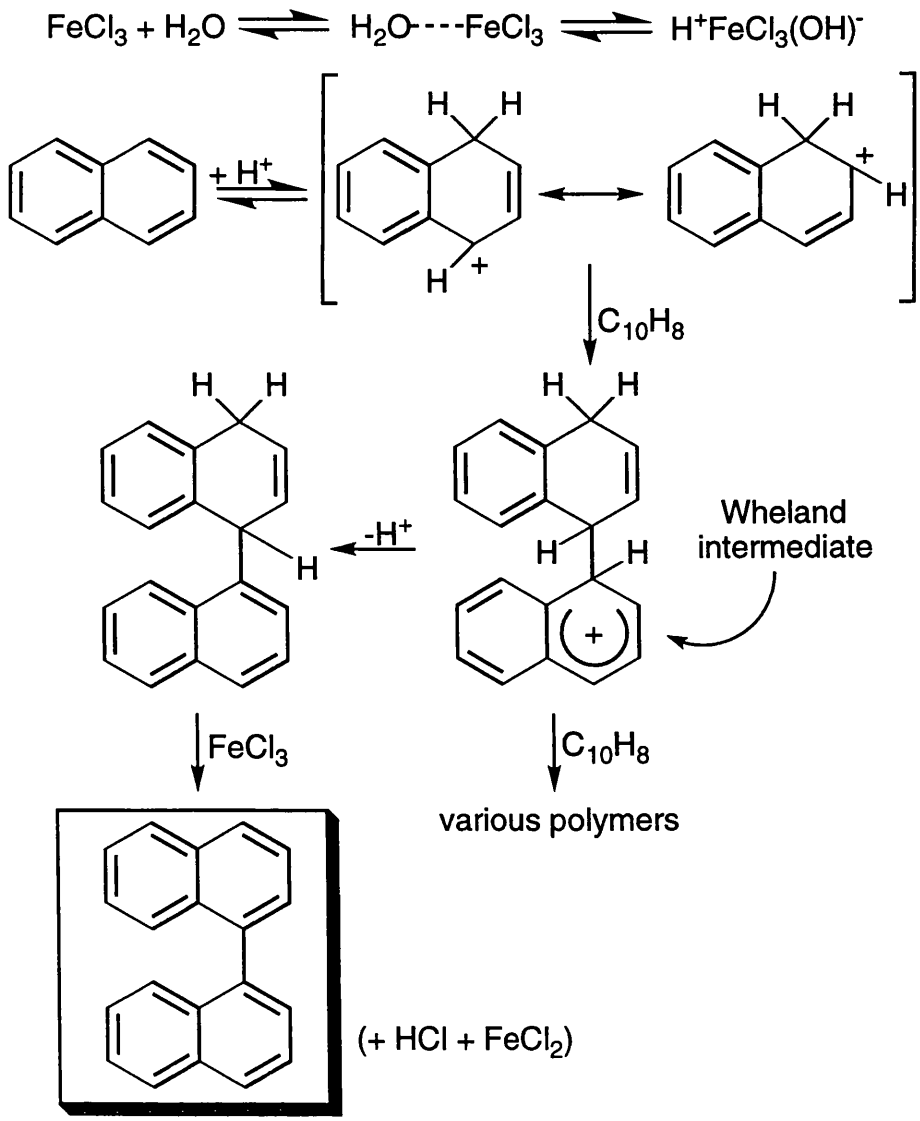
$0° < \psi < 90°$ $\psi = 90°$ $90° < \psi < 180°$

Fig. 24

One would assume that the dihedral angle could easily be adjusted by design. As it transpires, it is not that straightforward. The ψ-angle can indeed be altered by varying the substituents,[97] but the exact angle and conformation can only be established by experimentation (trial and error). For example, *N*,*N'*-dimethyl-[1,1'-binaphthalene]-2,2'-diamine has a minimum-energy transoid conformation with a ψ-angle of ~95° whilst *N*,*N*,*N'*,*N'*-tetramethyl-[1,1'-binaphthalene]-2,2'-diamine adopts a cisoid conformation with a ψ-angle of 71.2°.[98] Armed with this evidence, it seems likely that many binaphthalene compounds <u>are</u> able to exist as two independently stable conformers, a possibility that Smith *et al.*[99] speculate upon.

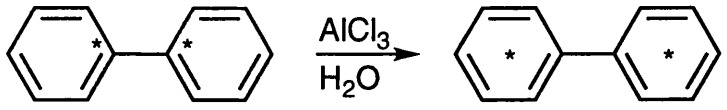
4.1 Synthesis

Chemists discovered 1,1'-binaphthalene derivatives in the middle of the 19th century. Since then, numerous methods of preparation have been published. The original Fittig procedure[100] was displaced in favour of a more versatile synthesis involving the oxidative coupling of naphthalene using ferric chloride.[101] It was later demonstrated that water is an essential co-catalyst and a large excess inhibits polymeric by-products.[102] With ferric chloride hydrate as the active species the cationic mechanism shown below was proposed by Kovacic[103] (Scheme 3) in 1965.



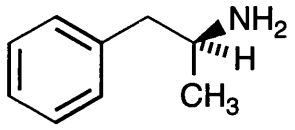
Scheme 3

Other Lewis acids such as molybdenum pentachloride[104] and aluminium chloride-cupric chloride[105] catalyse the dimerisation of naphthalene, but they both promote the isomerisation of the 1,1'-binaphthyl initially formed, yielding a mixture of 1,1', 1,2'- and 2,2'-binaphthyl in a ratio determined by the conditions employed. Wynberg[106] provided evidence supporting the postulated mechanism by way of a ^{14}C labelling experiment, effectively demonstrating that aluminium chloride promotes the intramolecular rearrangement of σ-bonded aromatic systems.

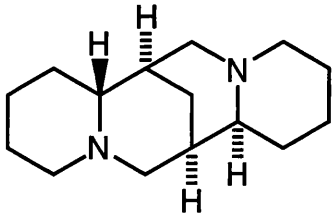


The oxidative coupling of activated systems, notably naphthols, is achieved under much milder conditions using manganic tris(acetylacetonate),[107] vanadium oxytrichloride[108] or copper(II) salts in conjunction with any aromatic or aliphatic amine.[109] It is interesting that β-naphthol cannot be dimerised by uncomplexed Cu(II) (though the disodium salt can be) but β-naphthylamine can, presumably because it is able to coordinate to Cu in its own right. Surprisingly, the three mechanisms are thought to be distinctly different. The V-catalysed reaction probably proceeds *via* a vanadium-centred polarised transition state involving two phenoxide residues, whilst the Mn catalyst is believed to promote the dimerisation of an aryloxy radical species.

The use of chiral amines with Cu(II) catalysts was a natural progression, which was followed up by Wynberg and Feringa.[110] It seems unjust that their efforts were not rewarded since they laid the groundwork for Brussee *et al.*,[111] who later refined the system and successfully obtained high stereoselectivity. These workers established that separation may be

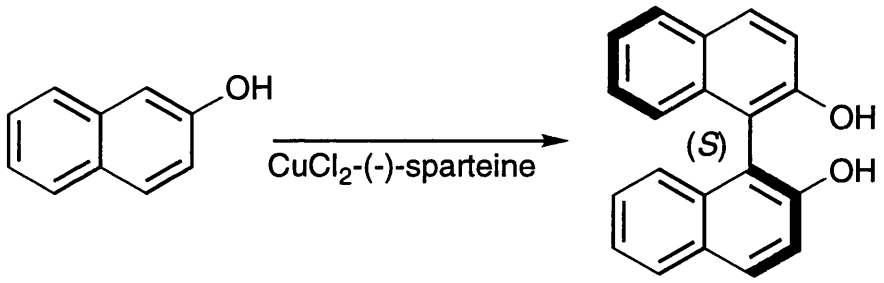


(*S*)-Amphetamine



(-)-Sparteine

achieved by the simultaneous oxidative dimerisation of β-naphthol and precipitation of a copper(II)-[(*S*)-amphetamine]-(*S*)-binaphthol complex followed by racemisation of the remaining (*R*)-binaphthol. This afforded a quantitative yield of a product with an enantiomeric excess of 95%. The choice of chiral amine not only affects the reaction outcome but has a decisive influence over the mechanistic pathway. The diamine (-)-sparteine is a particularly effective participant in these reactions.[112] Asymmetric coupling of β-naphthol (the best substrate match with the complex) yields a product of high optical purity.



(100% e.e.)

Interpretation of the stereodifferentiating step is controversial as there is a lack of supporting evidence. It has been postulated[113] that the intermediate sparteine/binaphthol complex can have a tetrahedral or square-planar Cu centre. The tetrahedral species would lead to an (*R*)-product, but formation of (*S*)-binaphthol is favoured, and so it is assumed that a square planar Cu(II) adduct (Fig 25) confers chirality.

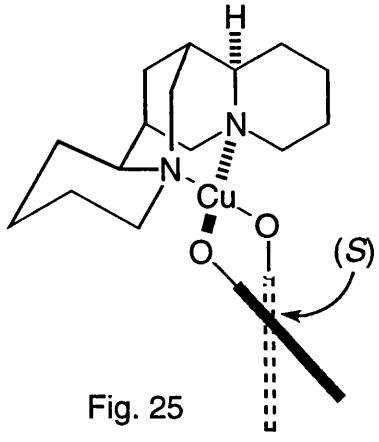
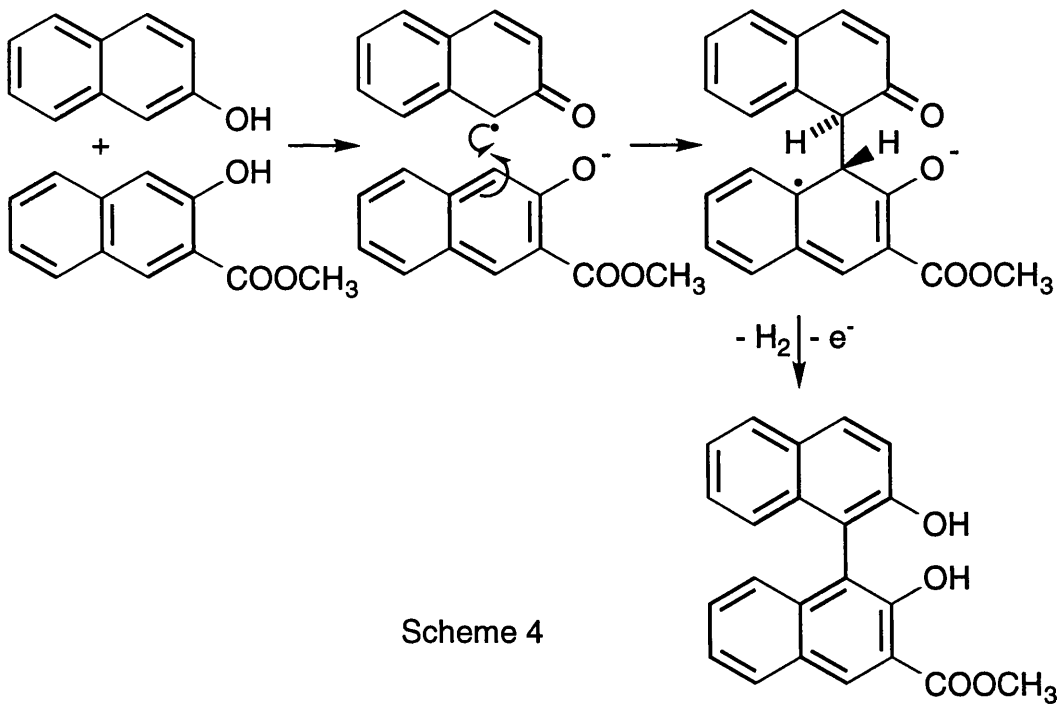


Fig. 25

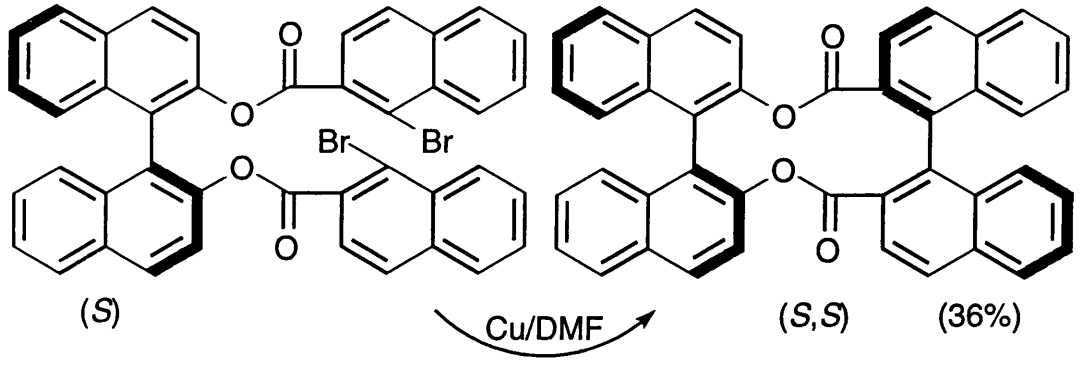
Cross-coupling of β-naphthol derivatives was demonstrated by Hovorka,[114,115] and Smrčina *et al.*[116] who were able to couple β-naphthol and β-naphthylamine using a Cu(II)/amine combination. Their attempts at asymmetric cross-coupling were only partially successful (low optical yields). The widely accepted view is that a radical recombination mechanism is in operation with the Cu catalysed systems, though this has been disputed as over-simplistic.[117] Indeed, it seems likely that the operating mechanism is influenced by reactant concentration and may follow a homolytic, heterolytic or radical insertion pathway. Furthermore, one or more of these processes could operate simultaneously. An alternative pathway,[118] specific to cross-coupling reactions is depicted below (Scheme 4).



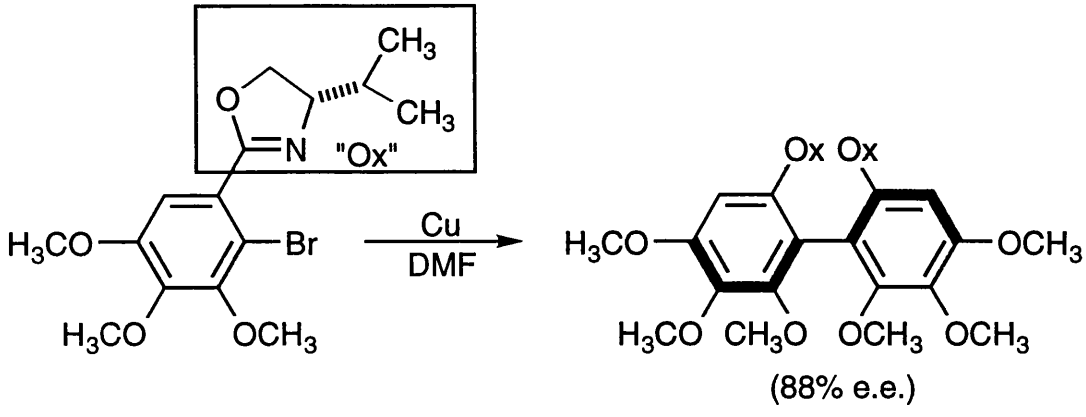
Scheme 4

Utilisation of the Ullmann reaction[119] facilitates the synthesis of a wide range of binaphthalene derivatives, but certain groups such as OH and NH_2 inhibit coupling, and others cause it to fail completely. This is due to the electron enrichment of the aromatic ring system thus reducing its

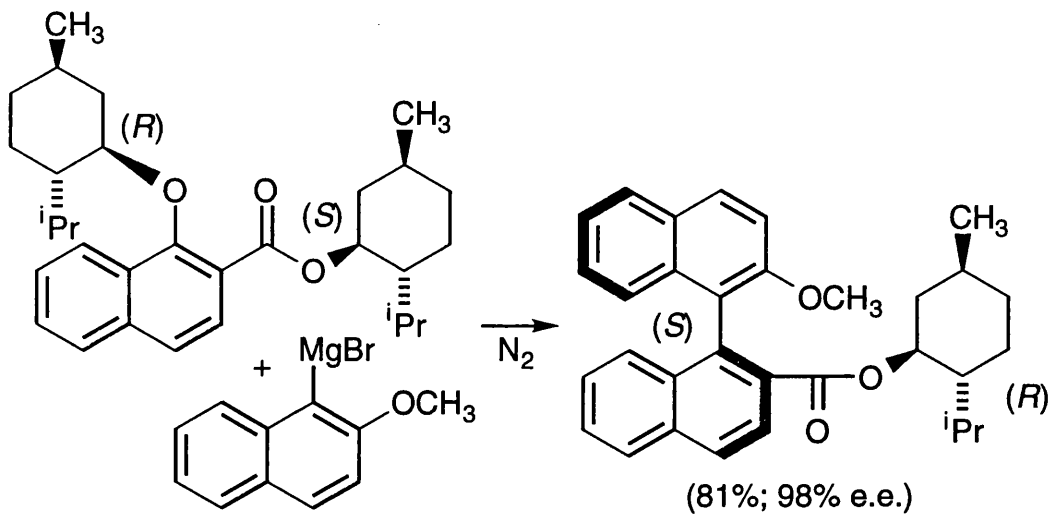
susceptibility to nucleophilic attack and / or the cause of side reactions. There is only one example[120] in the literature of a totally diastereoselective intramolecular Ullmann coupling reaction. The induction source is essentially a chiral auxiliary, since $LiAlH_4$ is subsequently used to reductively cleave the ester to furnish the two enantiomerically pure components.



The use of a chiral oxazoline as a transmission source in a intermolecular 'Ullmann' has shown great potential.[121,122] Laterally, the experimenters chose to synthesise biaryls, though the methodology could undoubtedly be extrapolated to include binaphthalenes. The mechanism is not known, but it is suspected that ArCu is formed (not literally, but represented by 'ArCu') which reacts with the parent molecule (ArBr) thus yielding the dimeric product.



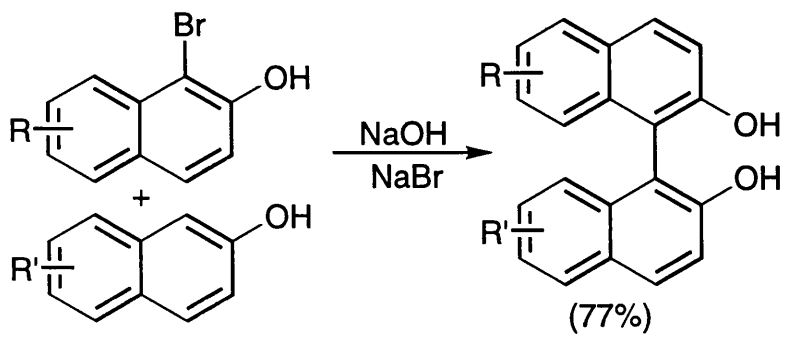
An analogous procedure[123] to that illustrated above involves another nucleophilic substitution reaction in which the enantio-discriminating menthyl moiety is displaced.



(81%; 98% e.e.)

It seems that the ester function activates the 1-position thereby rendering it susceptible to attack by the Grignard reagent. The way in which chirality is conferred is yet to be determined, but early indications suggest it is steric in origin. A variation of this strategy was accomplished by a Japanese group[124] who were able to induce e.e.'s of up to 95% during the coupling of a functionalised Grignard reagent and a halogenated naphthalene in the presence of a chiral nickel-ferrocene based catalyst.

The rediscovery[125] of a procedure first reported by Hinsberg[126] may be of synthetic utility in preparing binaphthalenes with a substitution pattern that is otherwise difficult to achieve.



(77%)

There are several by-products formed but these are easily removed. Once again, the proposed mechanism is unique to this reaction, and invokes an ion pairing interaction driven by H-bonding (Fig. 26).

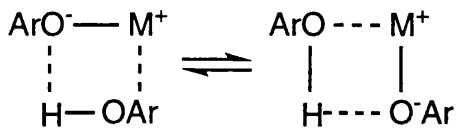
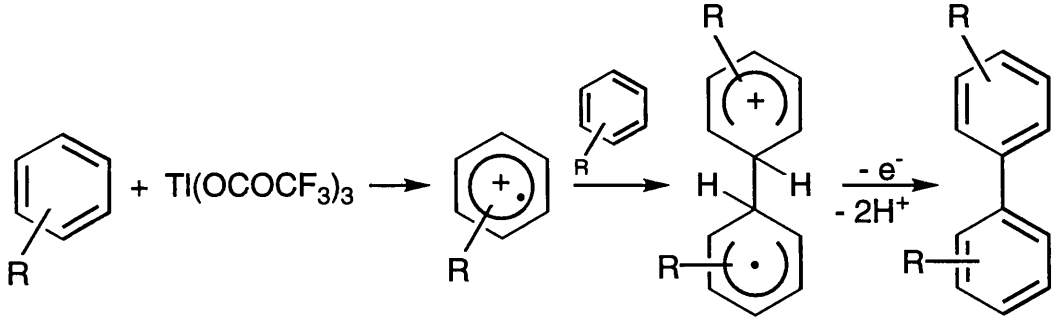


Fig. 26

Thallium(III) trifluoroacetate facilitates the intermolecular oxidative dehydrodimerisation of naphthalene derivatives.[127] The method is regioselective, and proceeds cleanly to give symmetrical binaphthyls in good yields. It is thought that the dimerisation occurs *via* a radical cation mechanism (Scheme 5), (*i.e.* essentially the same pathway as Fe(III) oxidation).



$$ArH + Tl(OCOCF_3)_3 \longrightarrow ArTl(OCOCF_3)_2 + CF_3COOH$$

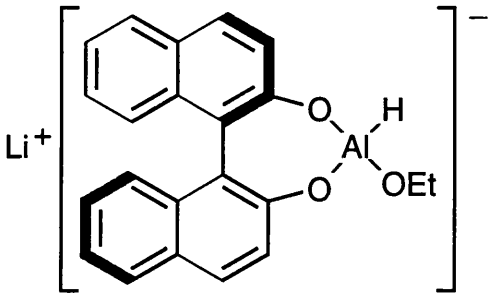
Scheme 5

Support for this hypothesis can be found in a recent study[128] of the radical intermediates using electron paramagnetic resonance spectroscopy. The presence of the monomeric and dimeric radical cation was confirmed.

As with previous methods, there are limitations. Electron donating substituents accelerate the reaction but powerful electron-withdrawing groups such as NO_2 cause it to fail completely.

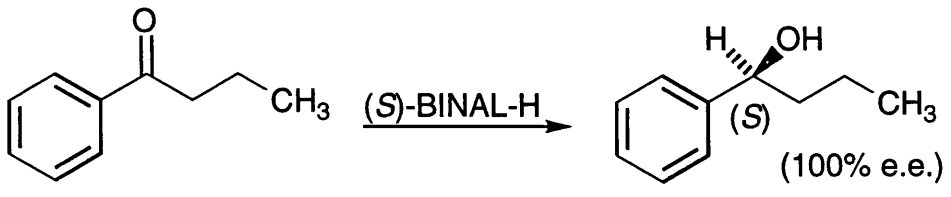
4.2 Uses of chiral binaphthalenes

Binaphthol is the basis for a chiral derivation of $LiAlH_4$, devised and introduced by Noyori *et al.*[129] in 1979 (Fig. 27). Infrared absorption data indicates that there are a variety of hydride species present; however, only one of these is believed to be responsible for asymmetric reduction. Evidence is ascribed to the linear relationship between the experimental temperature and the optical yield: induction becomes more efficient as the temperature decreases. This is probably due to an increasing kinetic bias, and may be visualised by the widening of the relative gap between the activation energy levels of the diastereomeric intermediates.

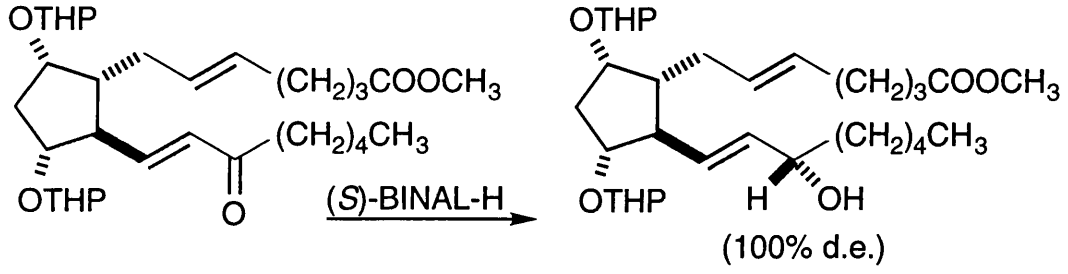


(*R*)-BINAL-H Fig. 27

The reagent (BINAL-H) is an effective reductant of the carbonyl group in a wide range of compounds, but very high optical yields are confined to a select group of well matched substrates.



It is, for example, of particular use in the synthesis of the prostaglandin intermediate cited below, an application[130] in which it is totally diastereo- and chemoselective.



Two 'chair' transition states (Fig. 28) are possible[131] since the binaphthoxy oxygens are diastereotopic. Structure (B) is thought to be less favourable since steric repulsion (R ≈ R' ≈ binaphthyl) has a destabilising effect.

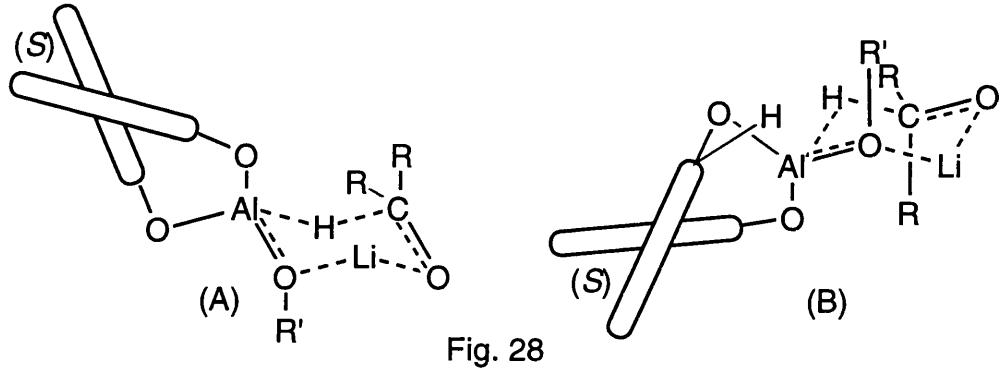


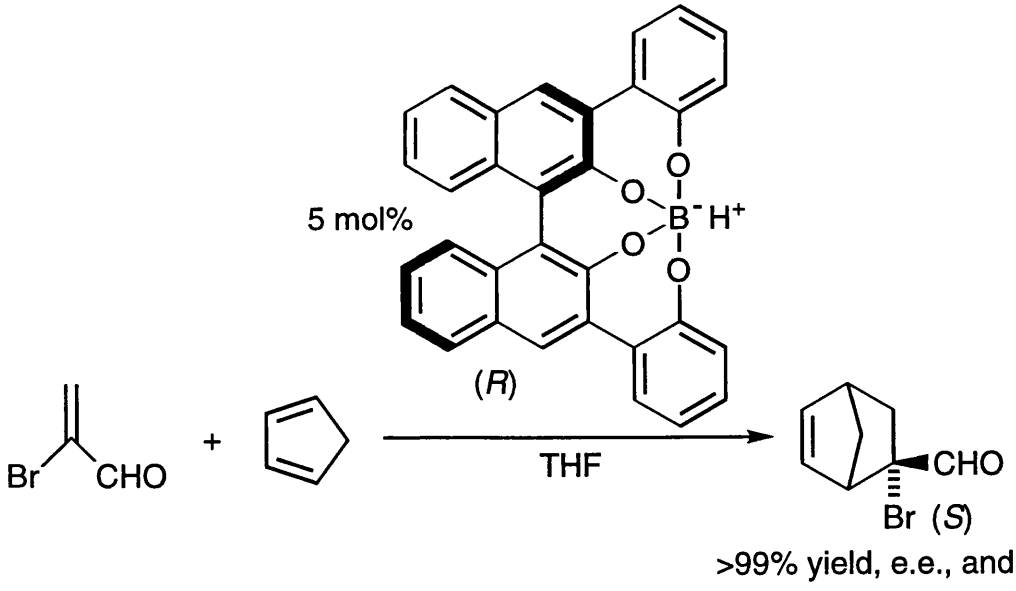
Fig. 28

The steric factor has a considerable bearing on the selectivity, though other physio-chemical parameters such as molecular flexibility, electron density at the carbonyl carbon, and electron contributions from substituents, all exert an influence on the outcome.

Varying degrees of chiral induction was achieved using auxiliaries similar to BINAL-H. Making a direct substitution of titanium for a lithium ion produced a reagent[132] capable of reducing aldehydes with e.e.'s of up to 88%. This does not represent the maximum attainable, but was the best substrate match at that time. The structure was later elaborated by Carreira *et al.*[133] who were able to perform enantioselective aldol additions to give hydroxy esters with e.e.'s as high as 97%. Significantly, only a catalytic quantity of the complex is required, in comparison to BINAL-H applications

for which three mole equivalents are used. Lanthanum[134] and zinc[135] based (BINOL) derivatives are known, but neither system offers an improvement in general enantioselectivity despite high optical yields being recorded.

Asymmetric induction of Diels-Alder reactions is possible using a chiral Lewis acid furnished from a boron based BINOL.[136] This original complex was utilised in stoichiometric quantities and gave enantioselectivity of greater than 98% with selected reactants. Refinement by Yamamoto and Ishihara[137] provided a catalyst that led almost exclusively to the *exo* products with consistently high optical yields.



>99% yield, e.e., and *exo*

4.3 Axially chiral macrocycles

In 1967 Pederson[138] published his introductory papers demonstrating the potential of "crown ethers" as complexing agents. Cram *et al.* initially derivatized the macrocycle by inserting a racemic binaphthyl moiety[139] as a constituent part of the ring. Incorporating two or three chiral binaphthalene[140] units ("chiral barriers") produced macrocyclic polyethers

with a cavity large enough to accept organic guest molecules, and which is capable of chiral recognition (Fig. 29).

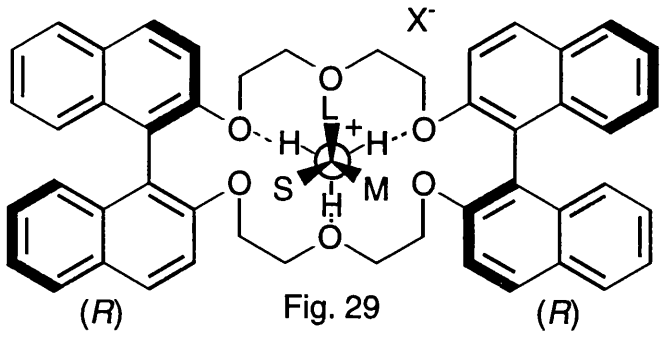


Fig. 29

The cavity is receptive to neutral compounds and salts, and complexes *via* three weak hydrogen bonds, though surprisingly it was found that the host:guest ratio is not always 1:1. The guest molecule is matched to the host by trial and error, *i.e.* a wide ranging screening program (molecular fine-tuning) was implemented.[141] The enantio-differentiating capability is almost total, especially in later refined systems.*e.g.*[142] There are around fifty research papers from Cram's group which comprehensively cover every facet of this niche area.

4.4 Sensors

Chiral sensor technology using chemical probes is an area of expanding interest. The chiral discrimination of a particular enantiomer (qualitative recognition) is made known by a visible colour change, facilitated by an attached azo dye moiety. The first macrocyclic sensors incorporating binaphthalenes (Fig. 30) as the chiral source were synthesised[143] using borrowed Cram methodology.[140]

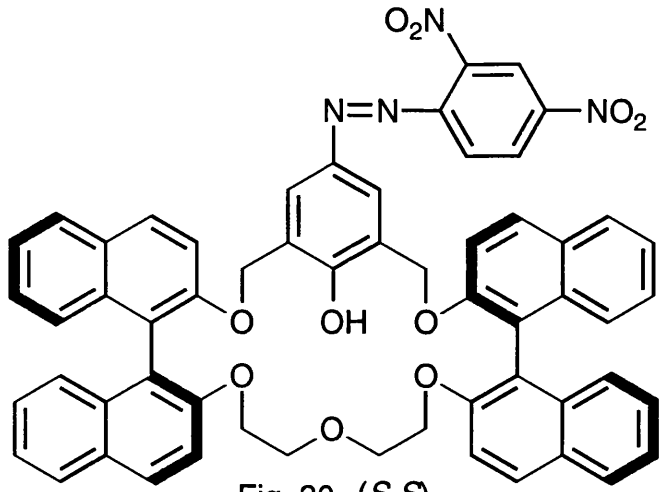
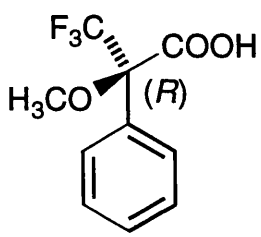


Fig. 30 (*S,S*)

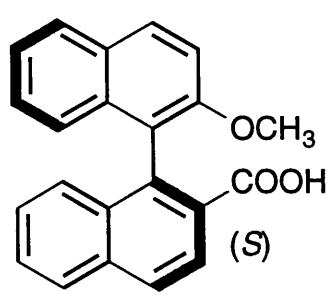
The reception of various amines yield complexes with differing light absorption characteristics, so the best results are obtained by matching the amine under test with a sensor that is 'tuned' to that molecule. As well as screening new potential sensor molecules, it is expected that their immobilisation will confer a quantitative capability of measuring enantiomeric excess.

4.5 Chiral derivatizing agents

Mosher's acid,[144] α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) is well known in this area. However, it is claimed[145,146] that 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (MBNC) is superior in facilitating the differentiation of enantiomeric alcohols and amines. Used in conjunction with $Eu(fod)_3$ the enantiomeric excess can be determined using ^1H NMR spectroscopy.



"MTPA"



"MBNC"

Similarly, MBNC used in the formation of diastereomeric amides and esters (*via* the acid chloride) discrimination can be achieved using high-performance liquid chromatography. Furthermore, the introduction of 500 MHz NMR spectroscopy has now made it possible to discriminate between the derived diastereomers by NMR without any additives.[147] The very latest derivatization agent has just been published,[148] and offers a promising method of assaying chiral carboxylic acids (Fig. 31).

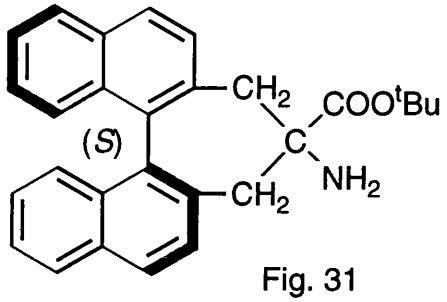


Fig. 31

The last few decades have seen an intense interest in axially chiral compounds, mainly because of their excellent (superior?) chiral induction properties. Most of the potential has already been exploited, but only a handful of compounds with a 5, 6 and 8 mono / di-substitution pattern have ever been made. Derivatives with multiple substituents are virtually unknown, so it seems that at the very least, there are academic possibilities yet to be addressed.

5 MACROCYCLES

5.1 Introduction

The field of macrocycles is exemplified by "crown" ethers. 18-Crown-6 is the best known, and is representative of the simpler rings. It is a neutral molecule and is puckered because of its size. Its utility lies in its innate ability to complex with the potassium cation, K^+ (Fig. 32). Unfolded, a cavity is created, in which the potassium ion just fits. The six oxygen atoms face inwards, thus creating a hydrophilic interior, and the CH_2 groups form the lipophilic exterior. There is therefore, a steric selectivity in favour of the potassium ion whose attraction is due to ion-dipole interactions between the oxygen lone pairs and the metal cation. The external lipophilic groups allow the complexed molecule to dissolve in low polarity solvents taking the anion with it. However the anion is shielded from the positive charge of the cation thus rendering it 'naked', and highly reactive.

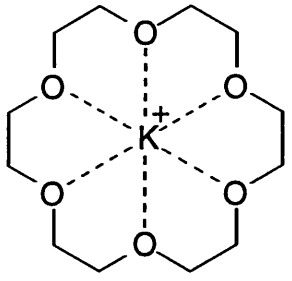


Fig. 32

By varying the cavity size, the ether can be designed to accommodate many other alkali and alkaline earth cations. Furthermore, the cation does not necessarily have to fit inside the cavity, but may be seated within the 'hollow' of one or other of the faces of the crown.

Alternative donor atoms such as sulphur, phosphorus or nitrogen (in any combination, with or without oxygen) may be substituted. In addition, there are a huge number of published examples in which the molecular framework has been altered to yield chiral or achiral molecules. Indeed,

the field of macrocycles is so vast, that to undertake a thorough review lies outside the scope of this thesis. Nevertheless, there are some excellent books which comprehensively cover the areas of crown ethers,[149] cryptands,[150] cyclophanes,[151] and catenanes.[152]

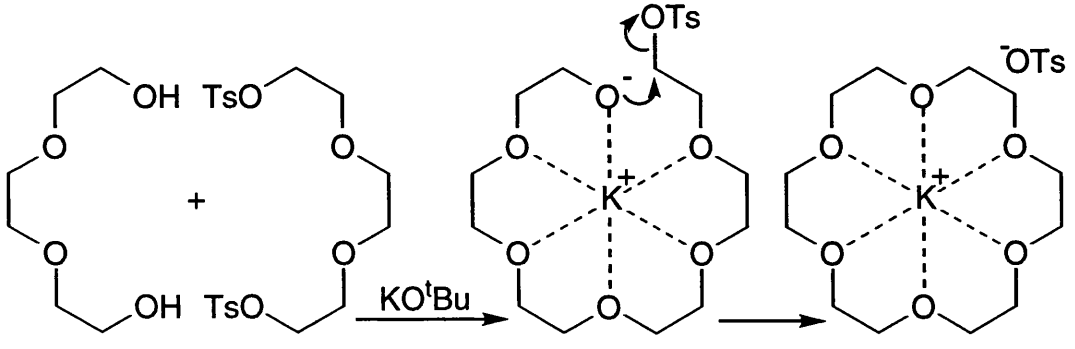
5.2 Synthesis

There are a number of recurring synthetic procedures used in the construction of the majority of macrocycles. The most popular method makes use of the Williamson[153] synthesis. There are a variety of permutations regarding the fragments used, but the actual mode of connection is common to all, illustrated by the preparation of 18-Crown-6.

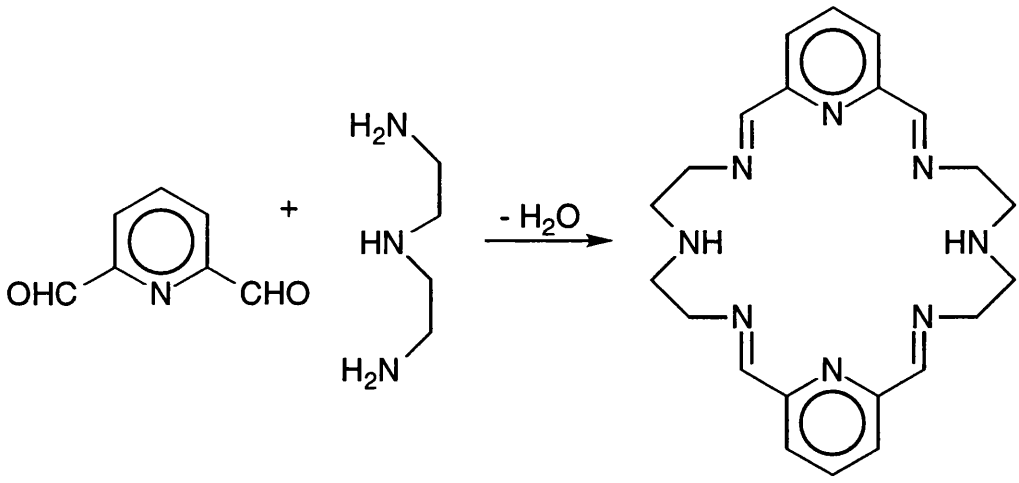
$$\begin{matrix} HOCH_2(CH_2OCH_2)_2CH_2OH \\ + \\ ClCH_2(CH_2OCH_2)_2CH_2Cl \end{matrix} \xrightarrow{KOH} \text{18-Crown-6}$$

The reaction is conducted under high dilution conditions in order to suppress polymeric by-products, and to simultaneously promote the process of intramolecular condensation.

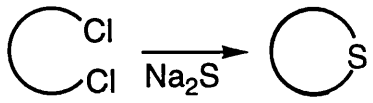
Two more methods of note are combined in the example below.[154] This involves the displacement of a leaving group, usually tosylate (Ts), and with this reaction the tosylate anion is retained as the counter ion. The macrocyclic unit is built up ("wrapped") around the metal cation, a procedure which has been named the "template effect".[155]



There are many other metal cations such as Ni, Ba and Cu which are able to take part in this type of reaction. A fourth synthetic possibility involves condensing two mole equivalents of a secondary triamine with two mole equivalents of a di-aldehyde[156] thus providing a route to many simple crown ethers. The resulting Schiff base may be reduced to the saturated macrocycle with $NaBH_4$.



The alternative use of a bridged hexamine leads to the formation of cryptands. Other useful reactions include the insertion of sulphur using sodium sulphide,[157] thus effecting ring closure.



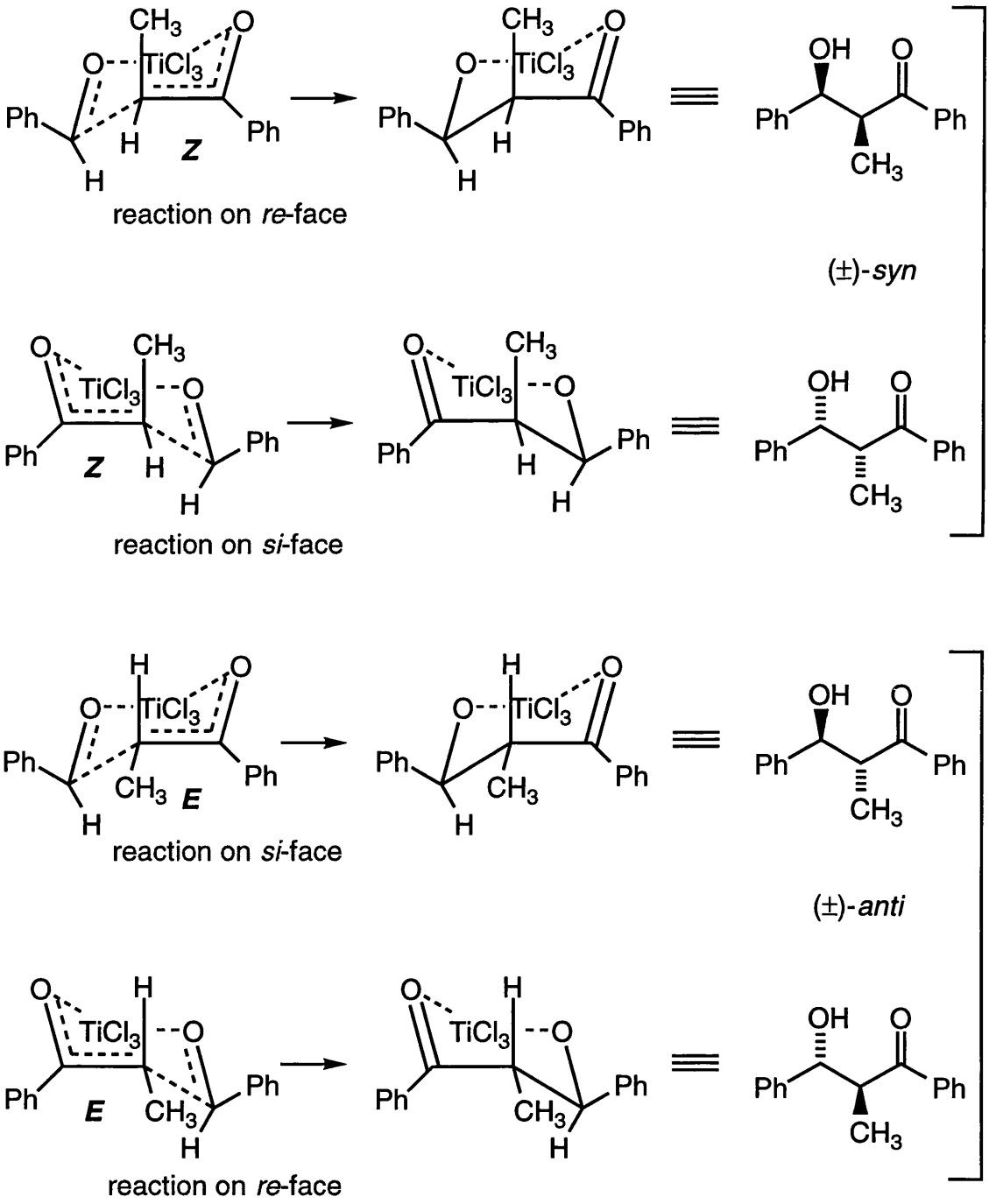
There is a procedure analogous to the Williamson reaction yet to be discussed, and is of particular relevance - an area studied intensively by Kellogg *et al.*

5.3 The "Caesium Effect"

Deprotonation of catechol and resorcinol using caesium carbonate[158] led to the dicaesium salt, which on reaction with alkyl dihalides gave high yields of cyclic ethers. The dipotassium salt was found to be an inferior reactant. The utility of caesium salts was simultaneously recognised by

RESULTS

The Enolate Geometry Of Aldol Products



Scheme 6

6 PROCHIRAL SUBSTRATES

6.1 α-Methylchalcone

As conjugated species, α,β-unsaturated ketones not only possess the properties expected of the individual functional groups, but in addition they participate in 'special' reactions specific to this combination. Thus, the two reactive centres may be considered as an integral functional group in its own right.

The substrate chosen for our initial studies was the (doubly) prochiral enone (*E*)-1,3-diphenyl-2-methyl-1-propanone (α-methyl chalcone). Possible synthetic approaches include Heck (palladium catalysed) chemistry,[168] Mukaiyama conditions,[169] or a simple base catalysed aldol reaction.[170] The method chosen was that of an aldol condensation *via* the transient titanium enolate with subsequent attack on the complexed benzaldehyde (Fig. 33).[171] The experimental conditions and reagents are, however, almost identical to those published[172] some years earlier. Treatment of propiophenone and benzaldehyde with titanium tetrachloride (followed by hydrolysis) yields the hydroxyketone (1) in a 94:6 *syn:anti* ratio (four stereoisomers - see Scheme 6 opposite).

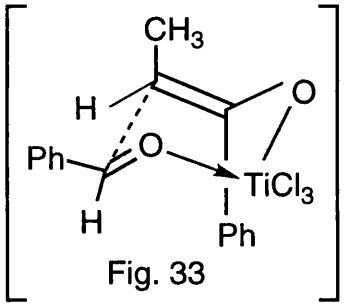
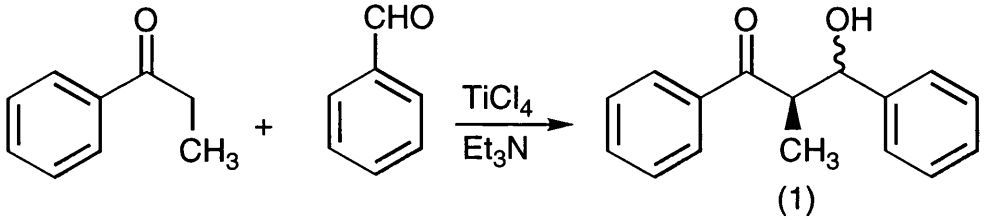
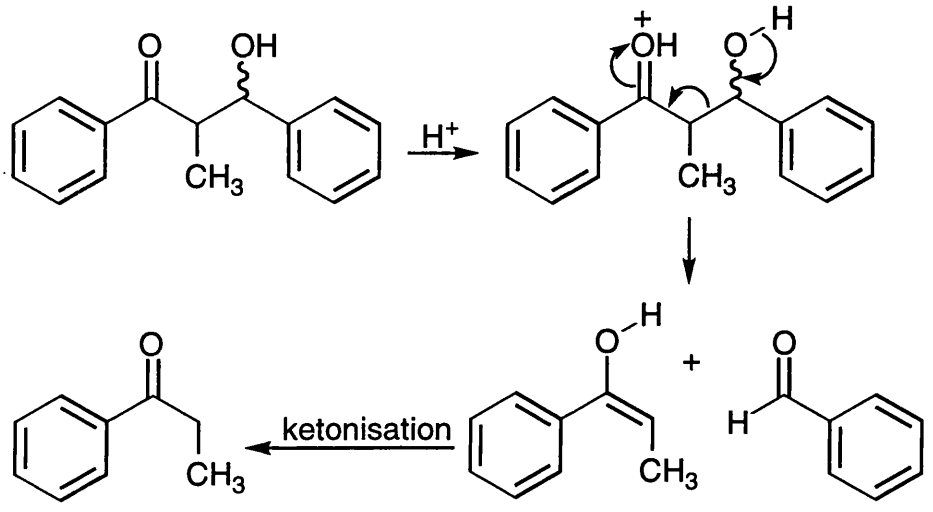


Fig. 33



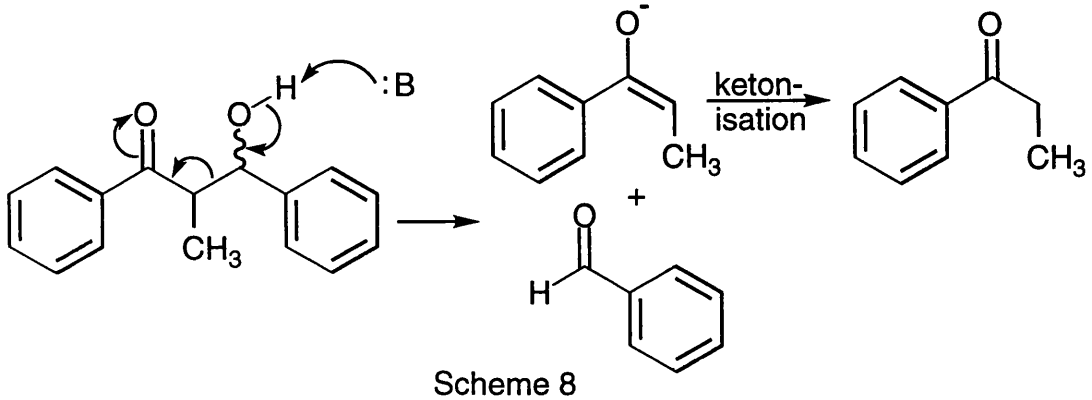
(1)

It is known that the deprotonation of propiophenone results in a predominance of the *Z*-enolate,[173] and thus, the *syn* isomers would be favoured in accordance with classical chair transition state theory.[174] Dehydration using *para*-toluenesulphonic acid (Dean & Stark apparatus) was only partially successful, a low yield of α-methylchalcone as an *E/Z* mixture (80:20) being obtained. As it transpired, the kinetically favoured outcome was that of a retro-aldol reaction (Scheme 7).



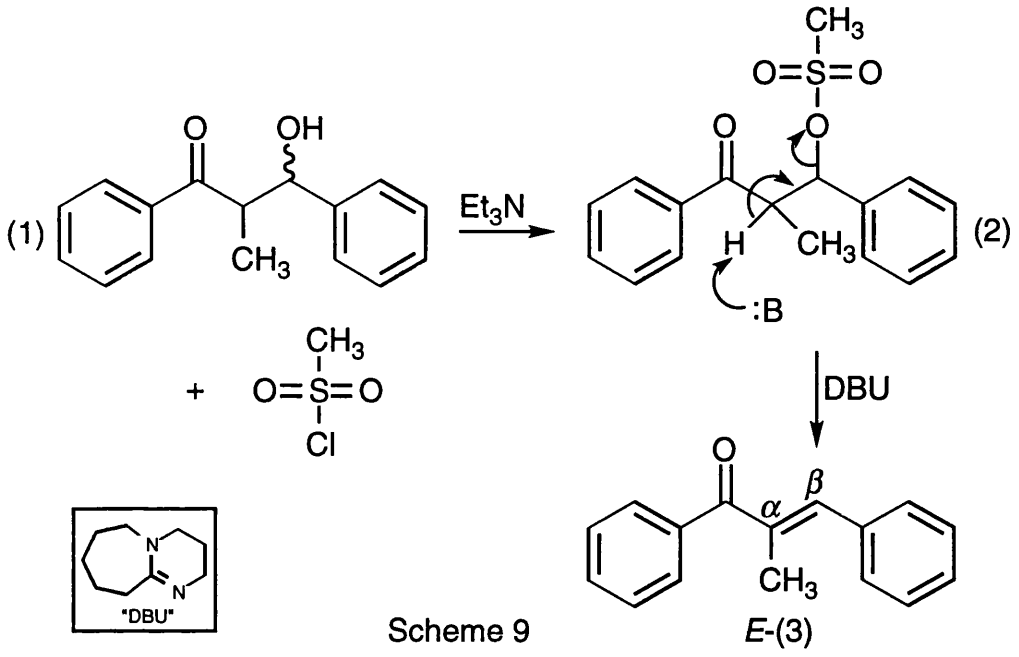
Scheme 7

Raising the pK_a of the acid catalyst had no beneficial effect. Similarly, substitution of a base catalyst also led to a retro-aldol reaction (Scheme 8). Mechanistically, it is proposed that the decomposition takes a comparable course, the presence of an acid invoking a pull of electrons whilst the base reaction involves a push of electrons.



Scheme 8

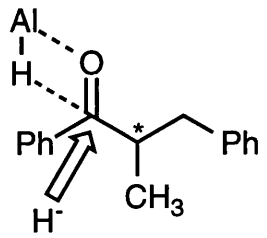
The problem was solved by blocking the reaction's capability of taking the retrograde pathway. Elimination of the mesylate group (a strong base was necessary) can only occur in the forward direction (Scheme 9).



Scheme 9 *E*-(3)

There was still a significant *Z*-isomer 'contamination'. Distillation of (3) at 155 °C, @0.55mm Hg did not alter the *E:Z* ratio, although admittedly at this temperature, isomerisation is quite possible. A German group[175] have isomerised this compound using trifluoroacetic acid at room temperature: after thirty-three days the thermodynamic equilibrium was reached, and the alkene was determined to have a 97:3 *E:Z* content. However, with our sample, multiple chromatographic separation was ultimately successful in achieving the isolation of the near-pure isomer. Assay was carried out using reverse phase h.p.l.c.: @99.7% *E*, 98.5% chemical purity.

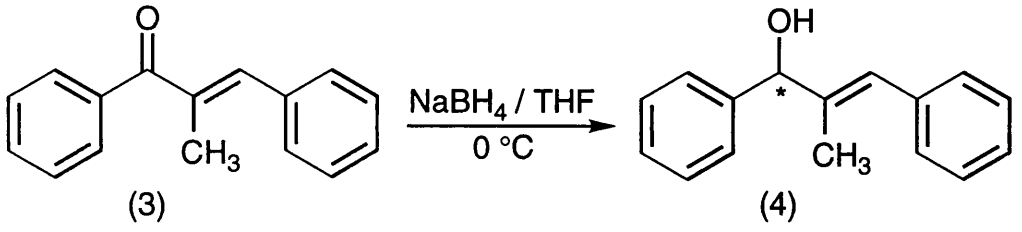
Hydrogenation of *E*-(3) is likely to generate one or more of three possible products. Therefore, samples of all these products were required for chromatographic comparison. Post-reduction analysis by g.c. assessed



"free" hydride delivery

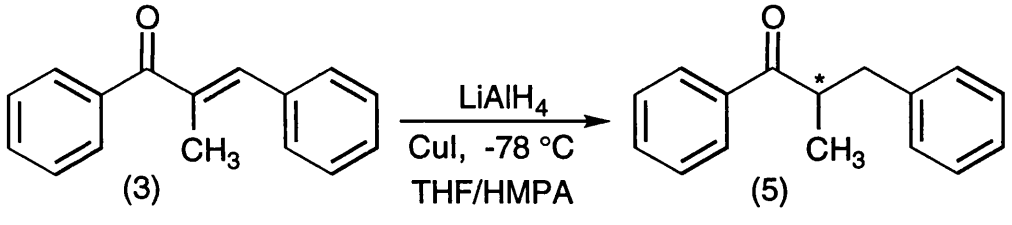
the qualitative and quantitative composition of the reaction mixture, and h.p.l.c. was used to determine the enantiomeric excess.

The carbonyl group of (3) was easily reduced to the alcohol (4).



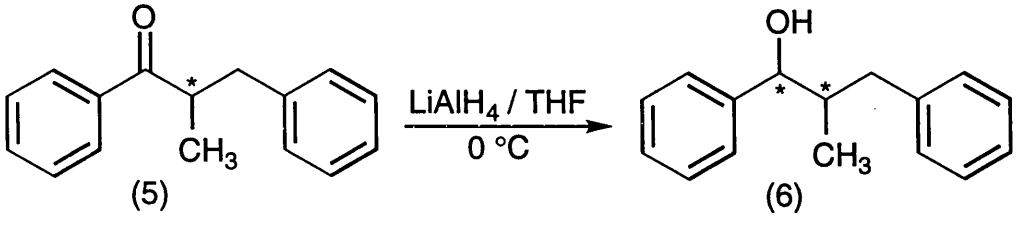
(3) (4)

The carbon-carbon double bond in enone (3) was selectively reduced to ketone (5) using a $LiAlH_4$/CuI mixture.[176] The CuI effectively operates as a catalyst, since only a 1-5 mol% is required, and although the mechanism has never been established, "$\overset{+}{Li}H\overset{-}{Cu}I$" is widely regarded as the active species.



(3) (5)

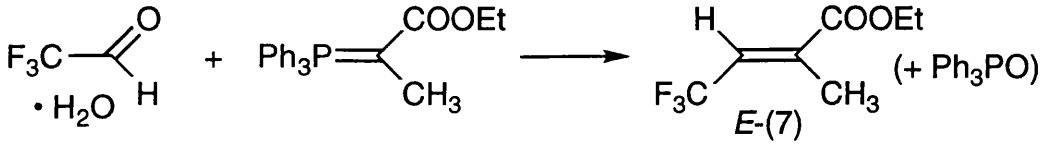
Further reduction of (5) yielded (6) as a 40:60 diastereomeric mixture.



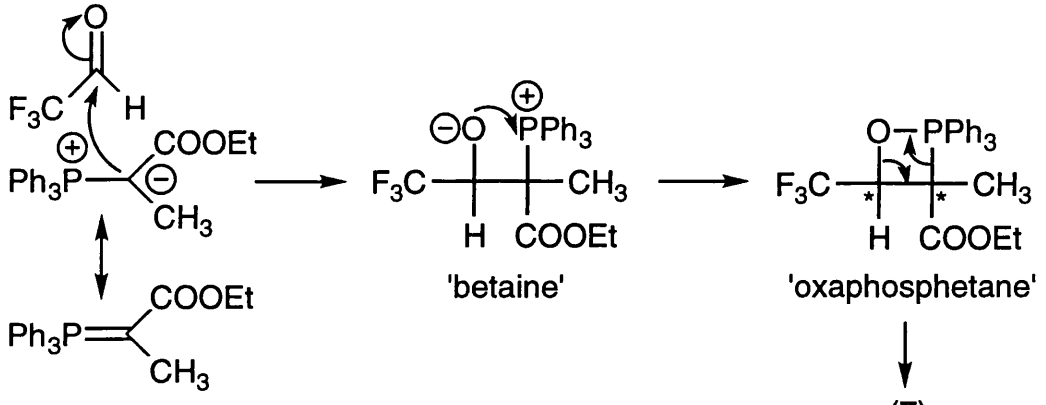
(5) (6)

6.2 *(E)*-Trifluoro-substituted butenes

The α,β-unsaturated ester *E*-(7) (a fluorinated analogue of ethyl tiglate) was synthesised by way of a Wittig reaction (no detectable *Z*-isomer formation).



As is common with low molecular weight fluorinated compounds, it is highly volatile: b.p. 131 °C @760mm. The proposed mechanism for this reaction (Scheme 10) includes the betaine intermediate for classical reasons, though its existence is in some doubt.[177]



Scheme 10

Electron-withdrawing groups such as COOEt are thought to preclude the formation of a betaine intermediate, though electron releasing groups (on C and P) do lead to stable betaines, some of which are isolable (Fig. 34). Since alkene (7) possesses stabilising groups and forms a diastereomeric intermediate, then the *E*-isomer is expected in accordance with historical observations.[178]

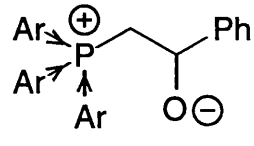
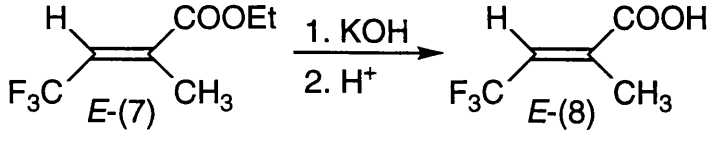
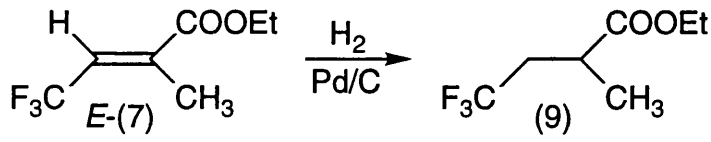


Fig. 34

Hydrolysis of (7) using NaOH was ineffective, but the substitution of KOH led to the exceptionally pungent acid *E*-(8).

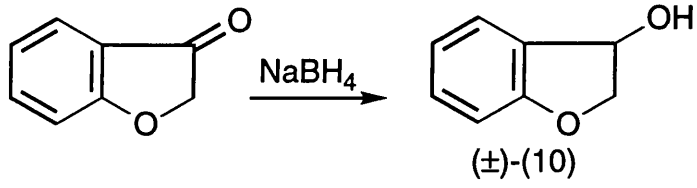


A sample of the product expected from a substrate/modifier hydrogenation experiment using (7) was prepared, and like the parent molecule, the saturated derivative (9) was also extremely volatile: b.p. 108 °C@760mm.

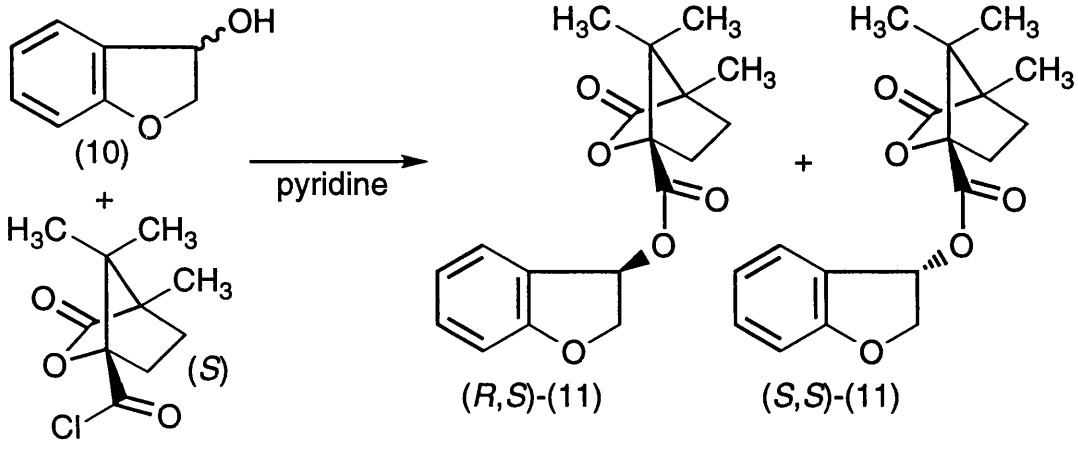


6.3 3-Coumarinol

A verifiable sample of (-)-(3*R*)-3-hydroxydihydrobenzofuran was required for comparison with chiral material obtained through induction. Commercial 3-coumaranone (Avocado Research Chemicals) was reduced with sodium borohydride to the hydroxybenzofuran (10).



Resolution of the alcohol (10) was accomplished through fractional crystallisation of the diastereomeric camphanic esters (11).[179]



Hydrolysis of (*R*,*S*)-(11) with aqueous KOH solution furnished a sample of (-)-(3*R*)-(10) with an enantiomeric excess of 88% (assay by g.c.).

7 MODIFIERS

7.1 Binaphthalene derivatives

Binaphthalene derivatives, and particularly 1,1'-binaphthalene-2,2'-diol, (binaphthol) make excellent chiral auxiliaries.*e.g.*[180,181] Most of these applications rely upon a diastereomeric interaction *via* a hydrogen or covalent bond. We were interested in determining the viability of steric induction without formal bonding. Resolution of binaphthol and its chemisorption (THF solution) on platinum, palladium and nickel surfaces should produce a helical chiral environment or 'chiral forest.' It is unknown as to whether the compound 'binds' to the metal surface through one or both oxygens but in view of the increase in acidity of the solution, it is assumed that the primary mode of adsorption is dissociative (Fig. 35).

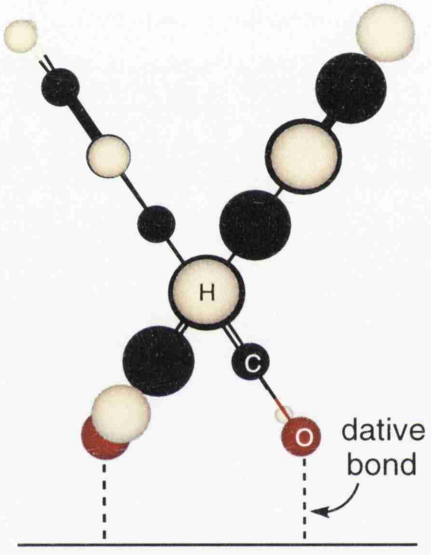


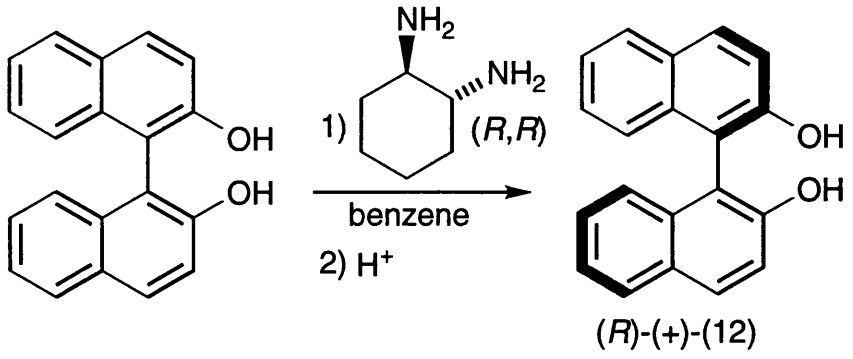
Fig. 35

However, deuteration in the presence of platinum results in the deuterium exchange of many of the ring hydrogen atoms.[182] Clearly, more than one adsorption mode is possible. This is unfortunate, since it introduces another degree of uncertainty in a system which is already complex.

Resolution of binaphthol was originally achieved[180] by fractional crystallisation of the diastereomeric salt formed from binaphthyl phosphoric acid and cinchonine. Other methods of note include the complexation of binaphthol with tartaric acid[183,184], and *N*-alkylcinchonidine halides[185], forming diastereomeric inclusion adducts; derivatisation using menthyl

chloroformate[186] to yield a covalently bonded menthyl ester (all of which are fractionally crystallised), and enzymic resolution[187] of the valeric ester of binaphthol.

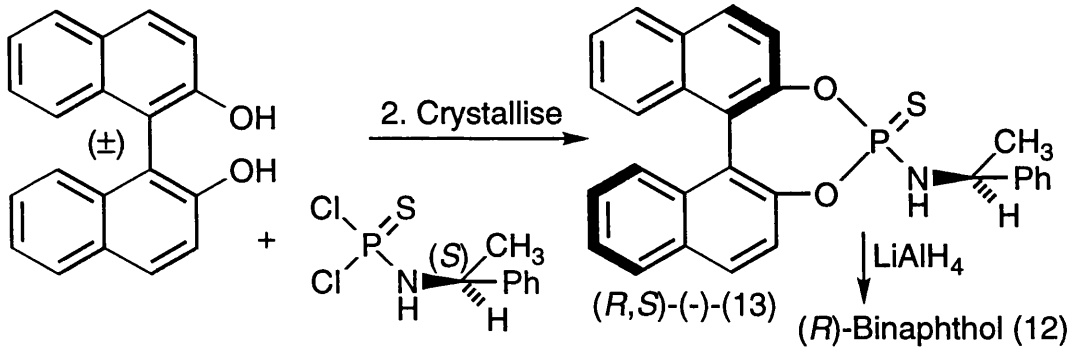
Small batches of (*R*)- and (*S*)-binaphthol (12) were prepared from (*R*,*R*)- and (*S*,*S*)-diaminocyclohexane as described by Kawashima and Hirayama.[188]



(*R*)-(+)-(12)

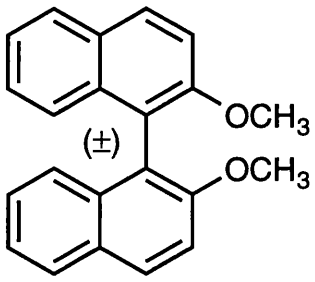
These authors stated that the diastereomeric salt was obtained in a 1:1:2 ratio, with two mole equivalents of benzene being occluded in the crystal lattice. Our salt was isolated in a 1:1:1 stoichiometric ratio as determined by ^{1}H NMR spectroscopy. The direct proportion of benzene in both examples is probably coincidence. The exact quantity retained is likely to be between 0 and 2 mole equivalents, and since no bonding is involved, the benzene content is rapidly diminished when the salt is heated above 80 °C.

A larger batch of (+)-binaphthol was prepared *via* thiophosphoro-amidate[189] (13) which was then reductively cleaved to give (+)-(12).

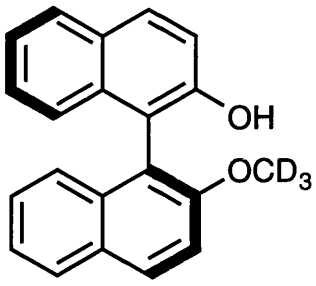


(*R*,*S*)-(-)-(13)

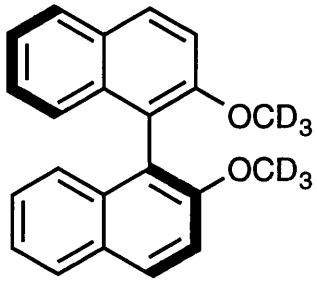
(*R*)-Binaphthol (12)



(14)



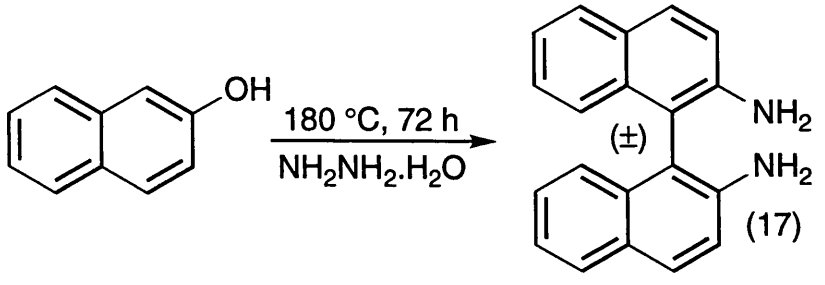
(*S*)-(15)



(*S*)-(16)

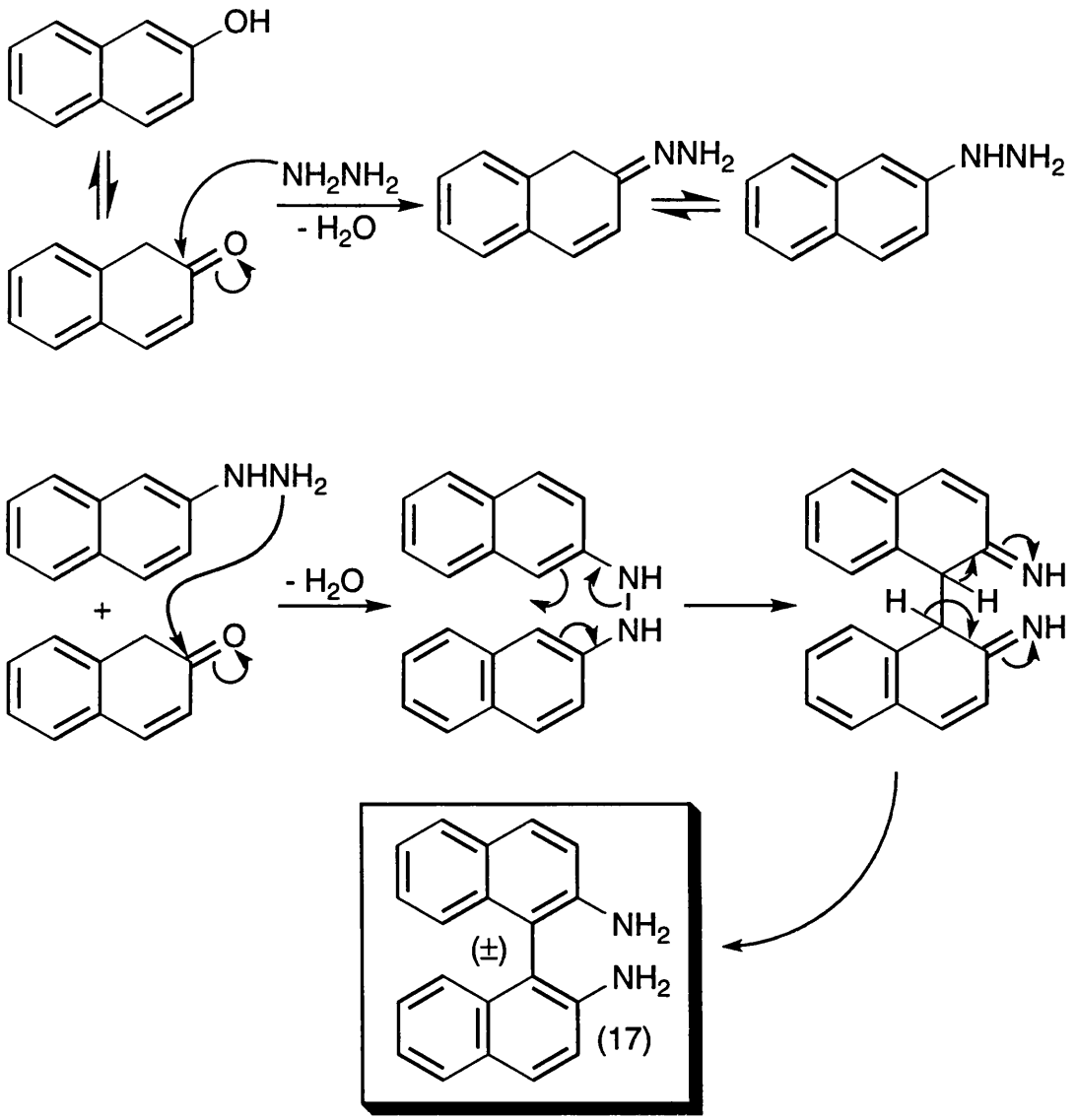
Dimethyl sulfate is the reagent of choice when undertaking O-alkylation.*e.g.*[190] However, treatment of binaphthol with dimethyl sulfate in the presence of an excess of KOH gave a reproducibly low yield of (±)-2,2'-dimethoxy-1,1'-binaphthalene (14) and a high yield of the undesired monoalkylated product. The phenolic hydrogens are easily removed to give the binaphthoxide dianion so it is not clear why the alkylation does not go to completion. On the other hand, deprotonation with NaH and alkylation with CH_3I furnished the dialkyl derivative in 72% yield. Treatment of (*S*)-binaphthol with deuterated dimethyl sulfate gave the monoalkyl compound (15) ($-OCD_3$) and the dialkyl material (16) $(-OCD_3)_2$ in equal amounts. This chiral derivative could have been obtained from the racemate by 'entrainment' as it is capable of spontaneous resolution.[191] As expected, compounds (14) and (16) do not adsorb on the metal surfaces under study, with the exception of Pd/C (though it is suspected that the support adsorbs the bulk of the material).

A sample of (±)-2,2'-diamino-1,1'-binaphthalene (DABN) was required. Heating β-naphthol and hydrazine hydrate[192] in a pressure bottle for three days gave a chemical cocktail from which DABN (17) was isolated in 45% yield (this represents the best result from many attempts).



It is necessary to use very pure β-naphthol in order to minimise the many side reactions that are possible (β-naphthylamine is a major by-product).

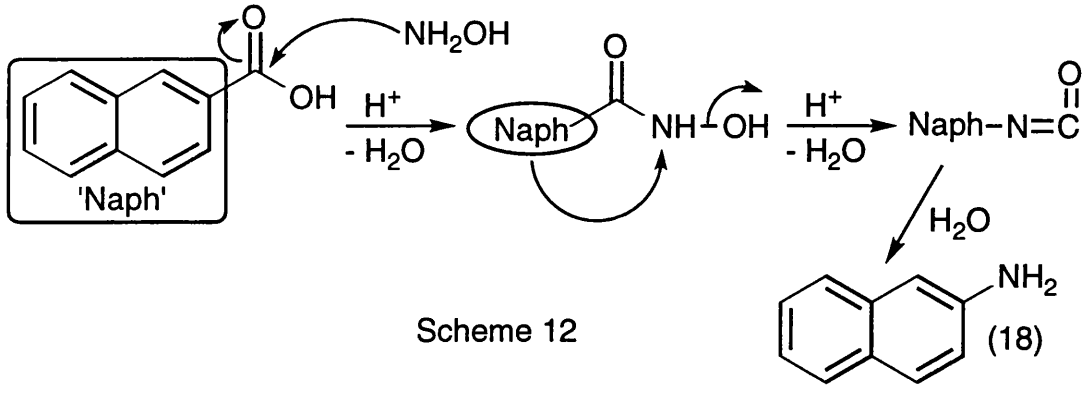
The predominant mechanism is believed to be that of an intramolecular bis-aza [3,3] sigmatropic Cope rearrangement (Scheme 11).



Scheme 11

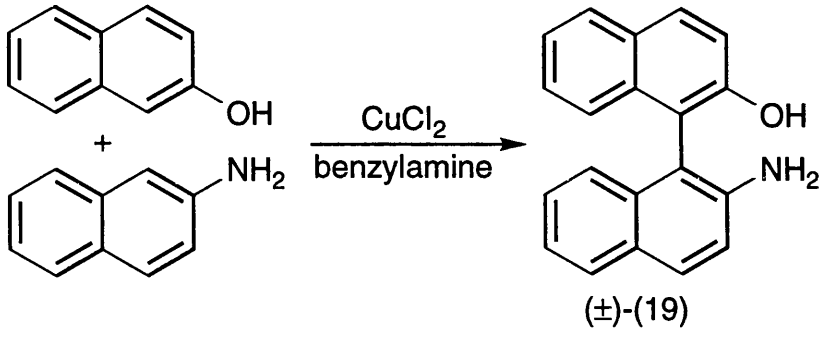
Subjecting β-naphthol to Bucherer[193] conditions (sodium hydrogen sulphite and ammonia solution) results in the overall replacement of the hydroxyl for an amino group. The yield is low, though the bisulphite adducts of β-naphthols are known to be less stable than α-naphthols.[194] In the event, β-naphthylamine was prepared using a variation of the Lossen rearrangement[195] (acid as opposed to base catalysis). β-Naphthoic acid on

treatment with hydroxylamine in the presence of hot phosphoric acid (dehydrating agent) led to the formation of β-naphthylamine (18) in good yield. The intermediate hydroxamic acid rearranges to the corresponding isocyanate which is hydrolysed with the loss of CO_2 (Scheme 12).



Scheme 12

Copper mediated cross-coupling of β-naphthylamine with β-naphthol[116] was conducted under anaerobic conditions. This is necessary because copper adducts have a propensity to complex with dioxygen (although aerobic oxidative coupling using a catalytic quantity of a CuCl-amine catalyst is known[196]). Despite these precautions only a small quantity of 'aminol' (19) was isolated.



Binaphthol adsorbed strongly on all the metals under study. The behaviour of chiral 2,2',7,7'-tetrahydroxy-1,1'-binaphthalene (22) was therefore of interest, especially in view of its spatially distinct hydroxyl groups (Fig. 36). Many of the synthetic problems regarding the derivatives

of this compound were addressed by Diederich *et al.*[197] and followed up by a Japanese group,[198] but optically pure (22) has never been reported.

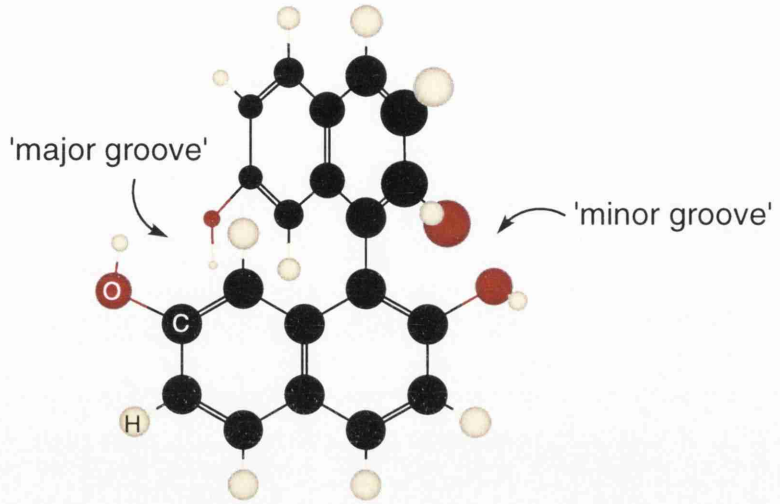
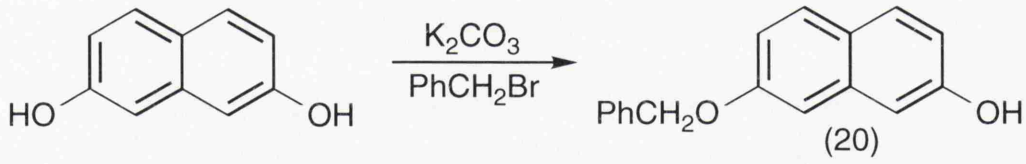


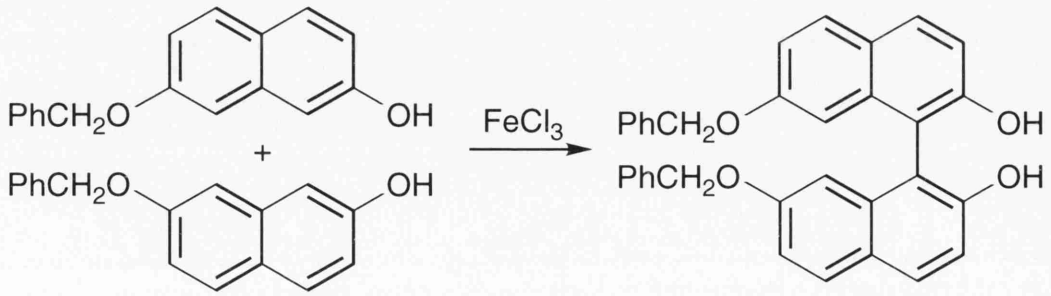
Fig. 36

Monoalkylation (O-'protection') was achieved, albeit inefficiently using benzyl bromide to afford compound (20) in 26% yield.



(20)

Oxidative coupling using $FeCl_3$ led to the binaphthalene (±)-(21).



(±)-(21)

Resolution of (21) was achieved by way of fractional crystallisation of its diastereomeric clathrate, formed with quinine. X-ray crystal structure analysis[199] has confirmed that interaction takes the form of a strong hydrogen bond between the quinuclidine nitrogen atom and one of the hydroxyl groups; and a weak hydrogen bond between the quinine hydroxyl group and the 'lower' benzylic oxygen atom (Fig. 37).

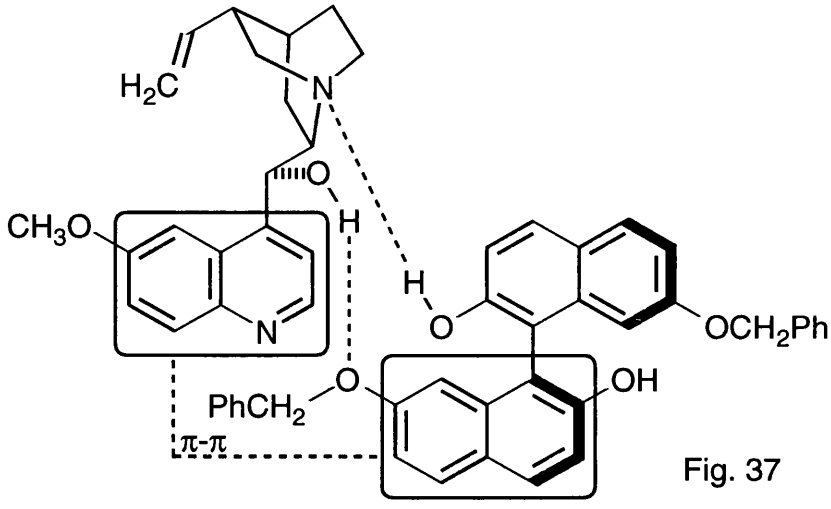
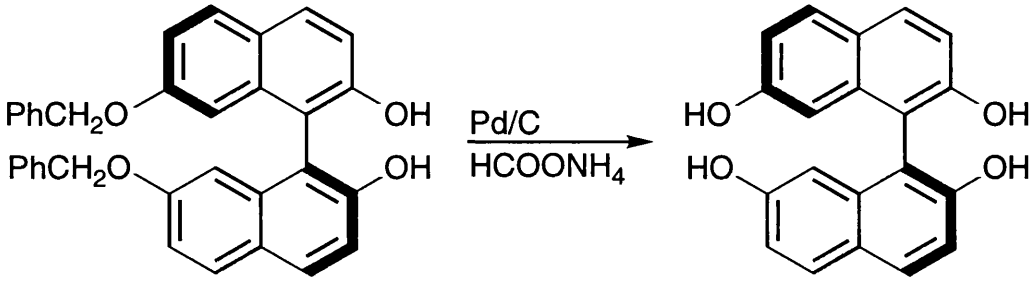


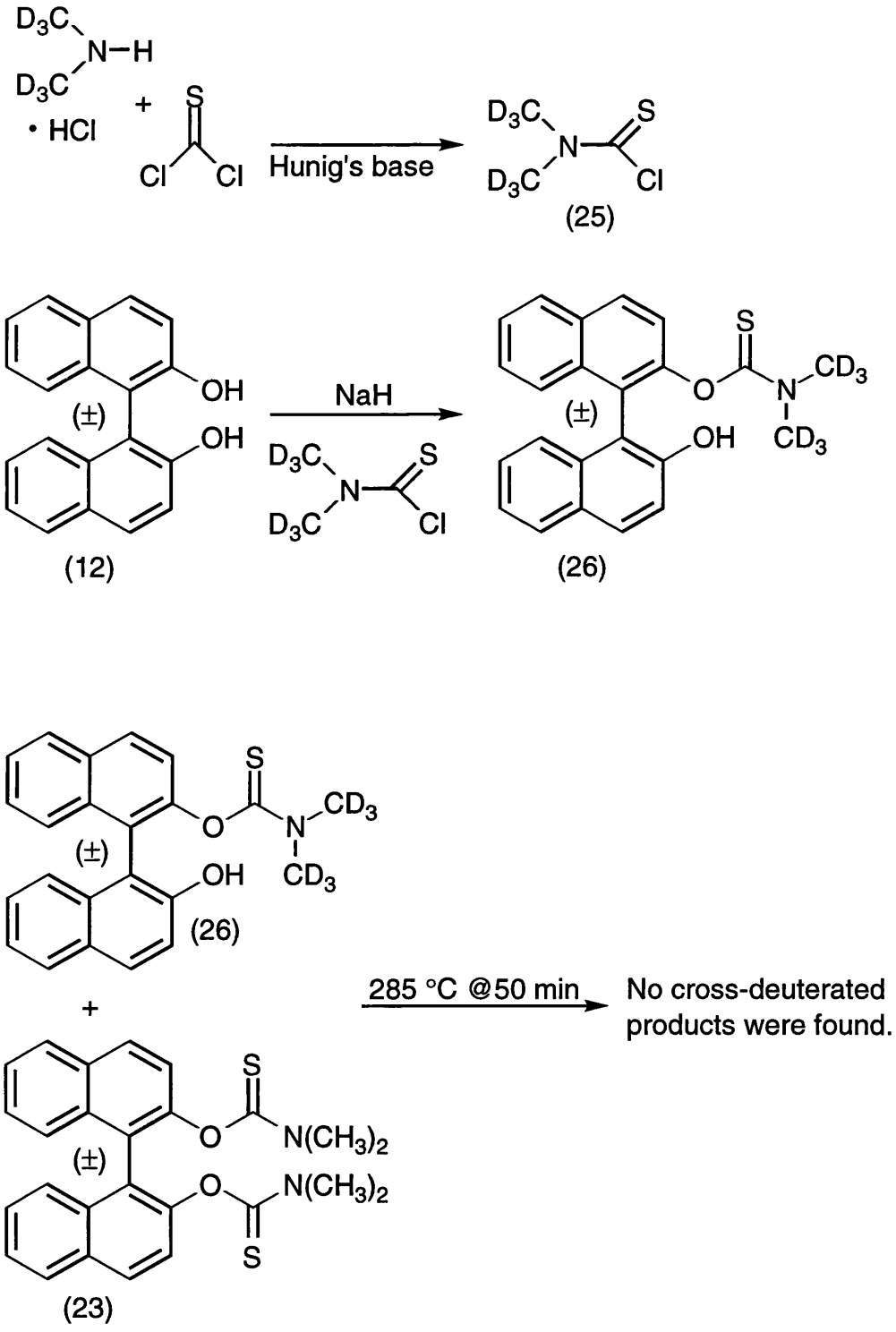
Fig. 37

Bond angles have been distorted for clarity. The 'lower' naphthalene ring adopts a π-stacking configuration which provides ideal bond orientations and atom proximities which enable hydrogen bonding to take place. Acidification led to enantiomerically pure (*S*)-(-)-(21) and deprotection by catalytic transfer hydrogenation[200] gave (*S*)-(-)-(22) with an overall yield of 2.6%.



(*S*)-(-)-(21) (*S*)-(-)-(22)

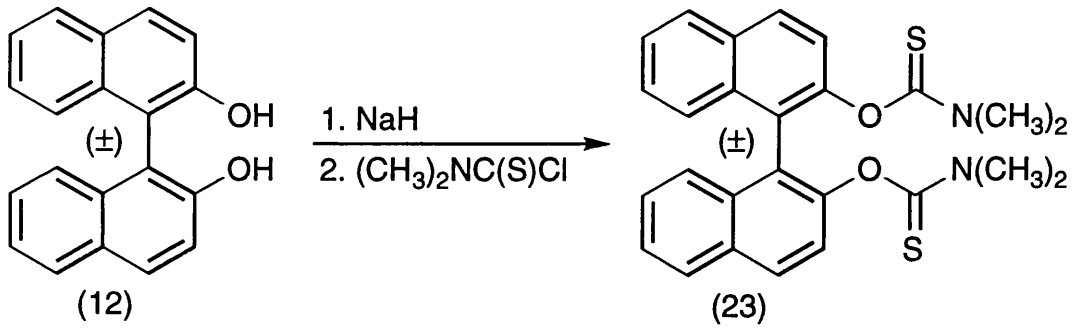
Confirmation of an intramolecular Newman-Kwart rearrangement



Scheme 13

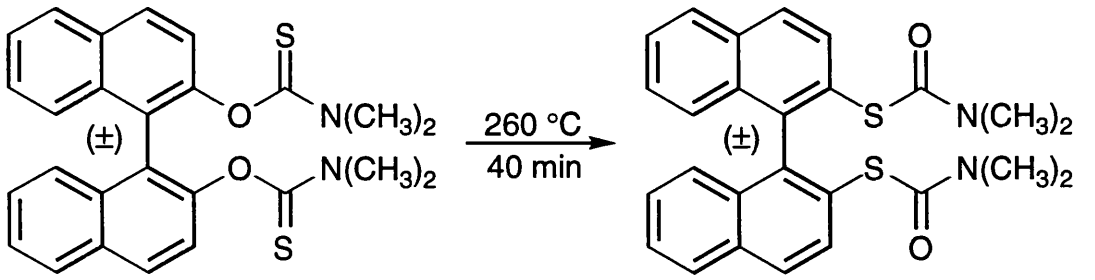
7.2 Binaphthalene derivatives with constituent sulphur atoms

With regard to reverse-templating experiments, substitution of sulphur for the oxygen atoms in binaphthol (12) was a logical path to take. The initial synthetic steps were published in a preliminary report[201] which were then elaborated upon by Modena *et al.*[202]



(12) (23)

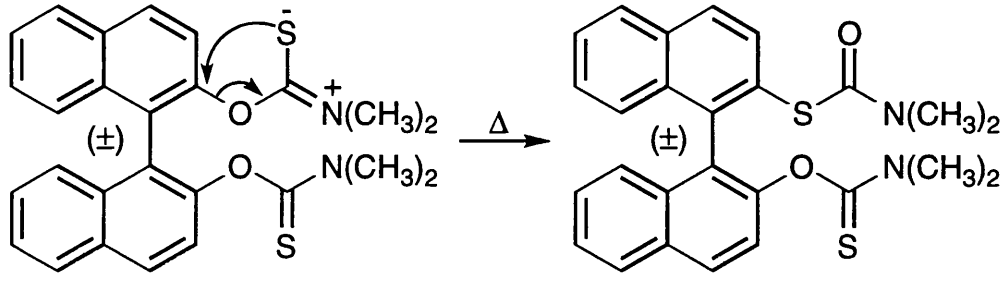
The second stage of this synthesis involved the thermal rearrangement of compound (23), a reaction which was discovered independently by Kwart[203] and Newman.[204]



(23) (24)

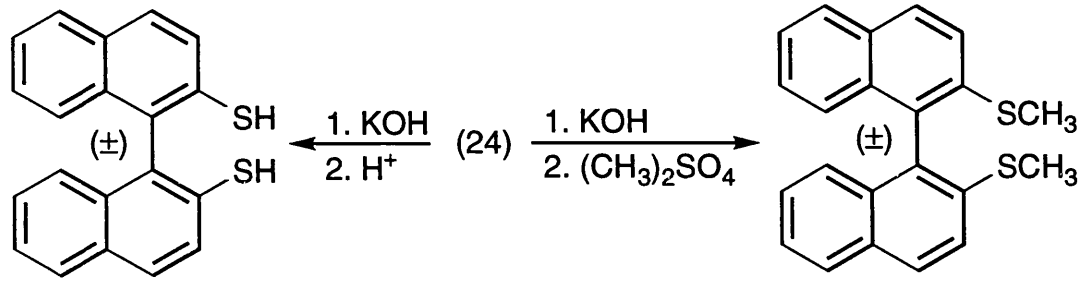
A deuterium labelling experiment confirmed that the reaction proceeds *via* a concerted intramolecular mechanism. Treatment of binaphthol (12) with an excess of the prepared reactant (25) and sodium hydride, furnished (26) in low yield. The desired disubstituted material was not found. Thermolysis of (26) in admixture with intermediate (23) resulted in no cross-deuteration - as determined by ^{1}H NMR and mass spectroscopy (Scheme 13).

The thermal rearrangement has been described as "erratic",[201] which is possibly due to conformational polymorphism.[99] In this critical step, if the temperature is lowered from the accepted standard 285 °C to 260 °C there is a much more consistent outcome. As a consequence of lowering the temperature, a small quantity of a known[214, 215] intermediary compound (27) was isolated and fully characterised. This observation suggests that the substituent chains rearrange sequentially.



(23) (27)

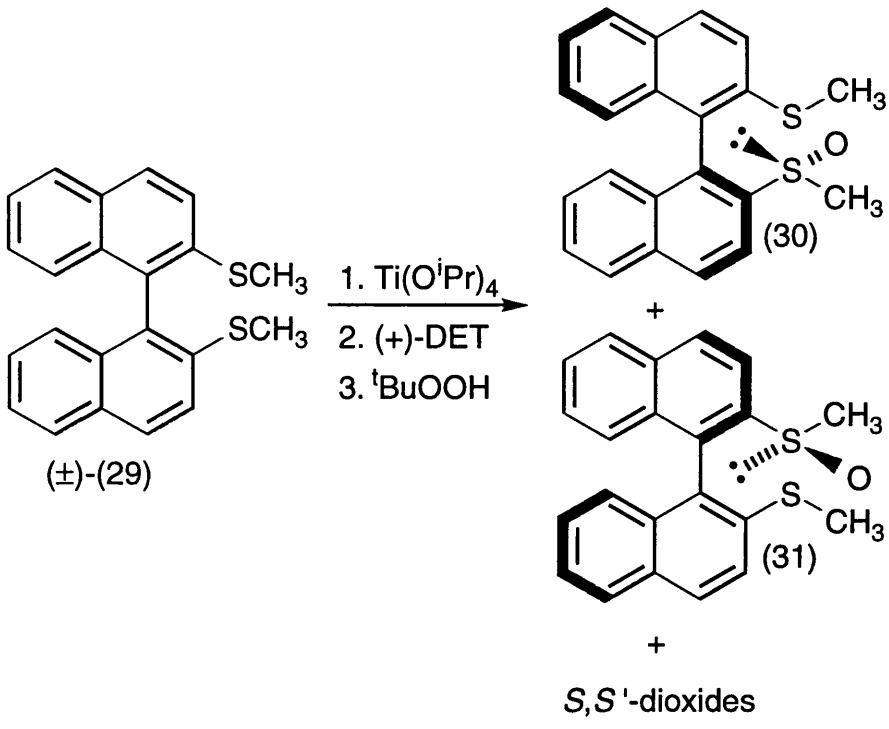
Hydrolysis of compound (24) gave the dithiol (28) but an analytically pure sample was never obtained. It is extremely retentive on SiO_2 and air oxidation partially transforms it into the dithiin. Hydrolysis, followed by *in situ* alkylation led to the bis-thioether (29).



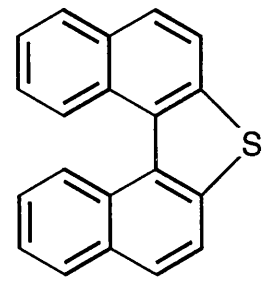
(28) (29)

Sharpless oxidation conditions[205] were used to generate the diastereomeric *S*-oxides (30) and (31) [and four *S,S'*-dioxides]. It was intended to resolve these compounds chromatographically [and ultimately

obtain a chiral sample of (28)], but unfortunately they were found to be inseparable - despite careful fractionation.

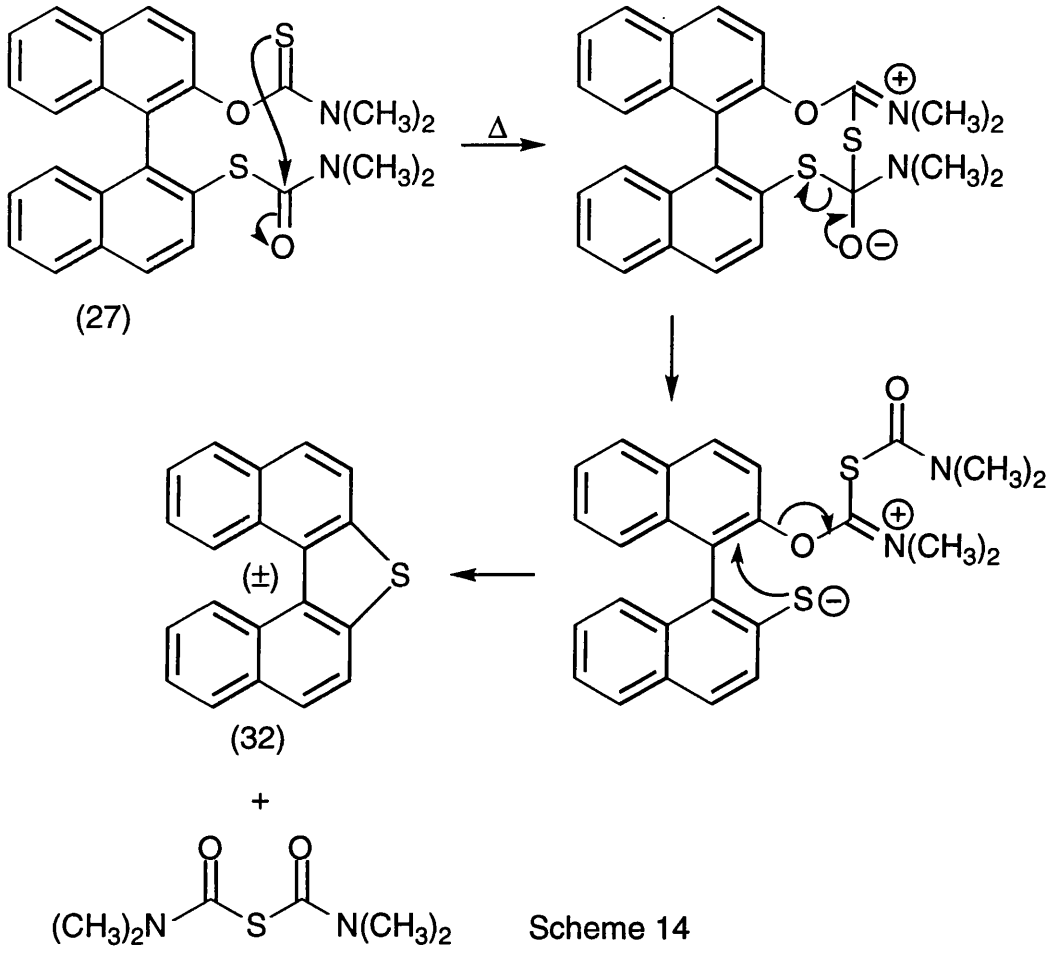


Remarkably, it is feasible to conduct the thermolysis of (*R*)-(23) without incurring a loss of optical integrity.[189] The synthesis was repeated, starting with ~10 g (*R*)-binaphthol. Thus, (*R*)-(23) was obtained with a comparable specification to that published. Thermolysis of (*R*)-(23) at 260 °C for 25 min gave only the intermediary (*R*)-(27), some of which was retained. Increasing the temperature to 285 °C @20 min afforded the target compound (*R*)-(24) [35%], (*R*)-(27) [32%] and thiophene (±)-(32) [10%]. The optical rotation of (*R*)-(24) was recorded as $[\alpha]_D$ +41.1 (*c* 1 in THF), [lit.: $[\alpha]_D$ +40.6 (*c* 1 in THF).[189] The point at which racemisation occurs is pivotal and takes place at a temperature of approximately 290 °C. In theory at least, it should be possible to isolate the thiophene in a optically pure form. However, this has never been achieved, presumably due to the high temperatures required for its formation.



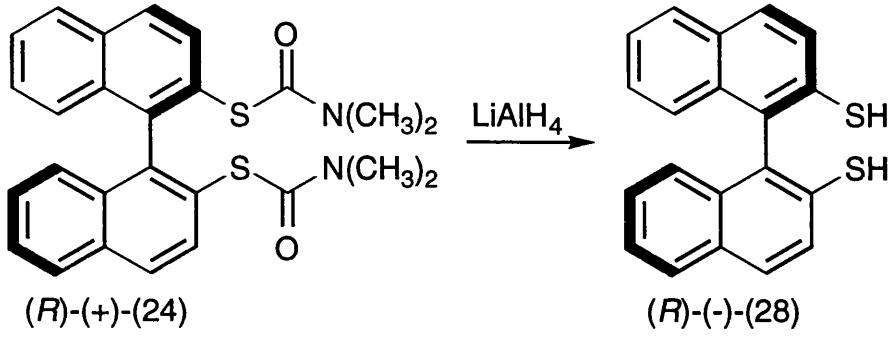
(±)-(32)

One might postulate that rearrangement of one branch of (23) and degradation of the intermediate compound (27) may lead to the thiophene by way of the mechanism depicted below (Scheme 14).



Scheme 14

Reduction of (*R*)-(+)-(24) using $LiAlH_4$ gave the desired dithiol (*R*)-(-)-(28).

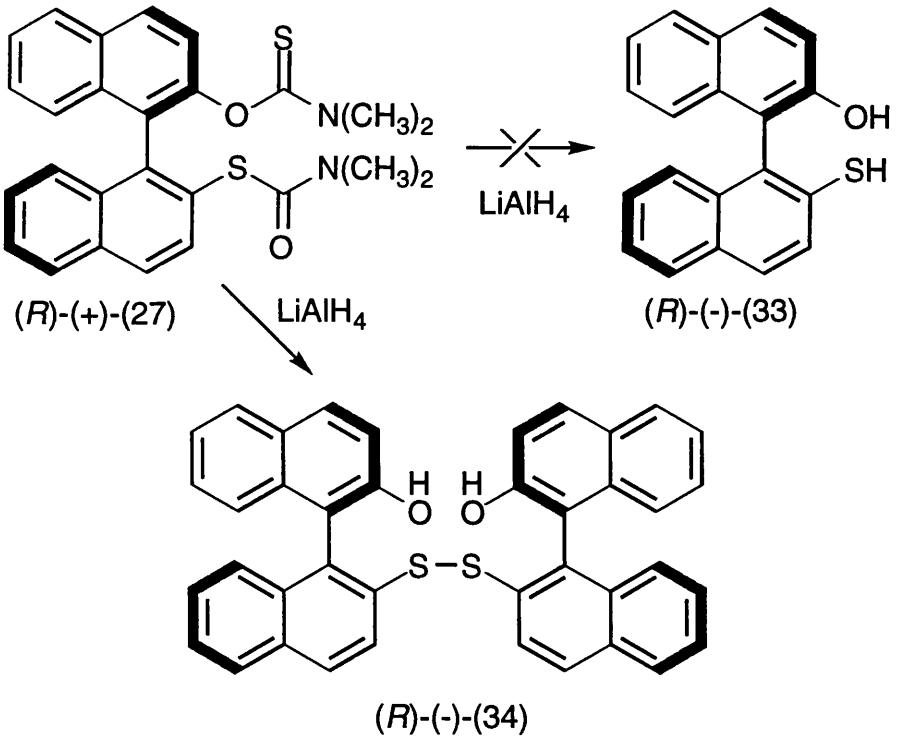


(*R*)-(+)-(24) (*R*)-(-)-(28)

Regrettably, as encountered with the racemic compound (28), a truly pure

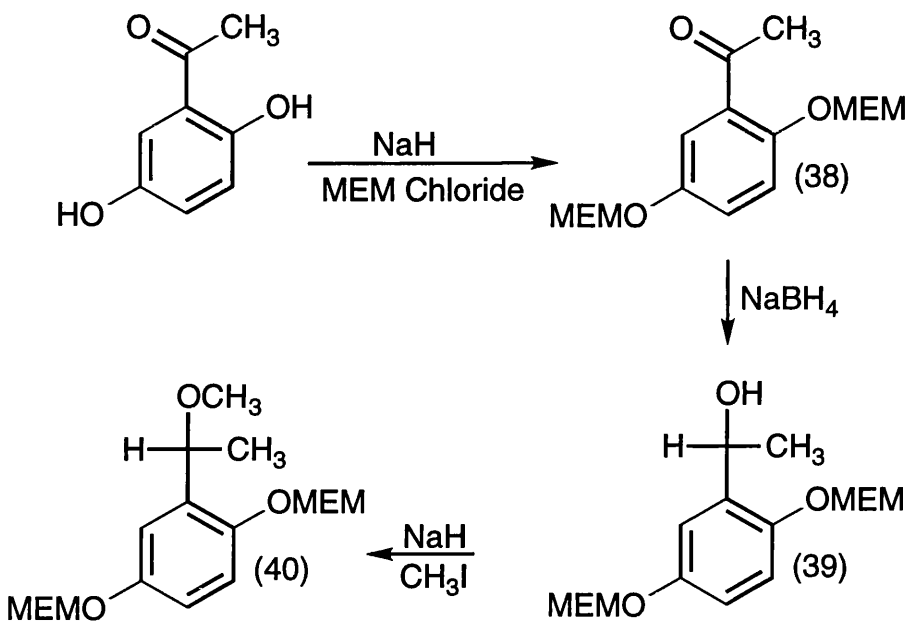
sample could not be obtained (and therefore the measured $[\alpha]_D$ value was unacceptably low). Superior methods of resolution have since been disclosed: resolution may be achieved by the selective enzyme hydrolysis[206] of a derivative or alternatively by the chromatographic separation of diastereomeric dithioacetals derived from *D*-glucose,[207] though the purification problem remains.

Reduction of (*R*)-27 was expected to give the 2-hydroxy, 2'-thiol (33), but only the disulphide (*R*)-(-)-(34) was isolated. This is surprising since a large excess of $LiAlH_4$ was used.

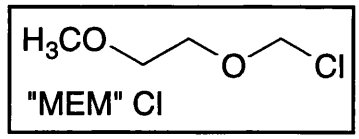


(*R*)-(-)-(34)

In the event, the concept of reverse-templating by deliberate poisoning of metal surfaces with sulphur containing compounds was superseded in favour of conventional modification techniques.

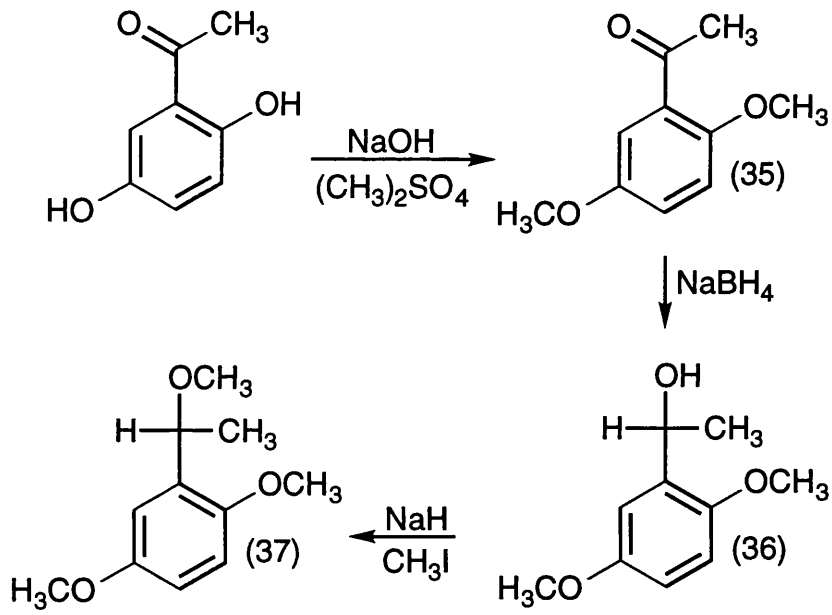

O
CH3
OH
HO
NaH
MEM Chloride
OMEM
(38)
MEMO
NaBH4
OCH3
H
CH3
OMEM
(40)
MEMO
NaH
CH3I
OH
H
CH3
OMEM
(39)
MEMO

Scheme 16


H3CO
O
Cl
"MEM" Cl

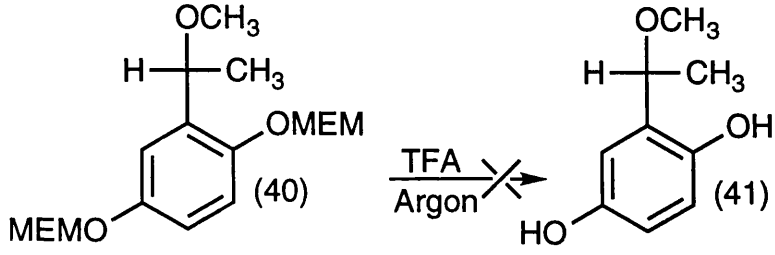
7.3 Hydroquinone derivatives

A variety of simple hydroxybenzenes was synthesised in an effort to establish which metal adsorption modes predominate. The molecules are empirical models, and actual modifiers would almost certainly require a CH_2 spacer group between the aromatic ring(s) and the enantiodirecting site. Standard synthetic steps furnished compounds (35), (36) and (37) (Scheme 15).



Scheme 15

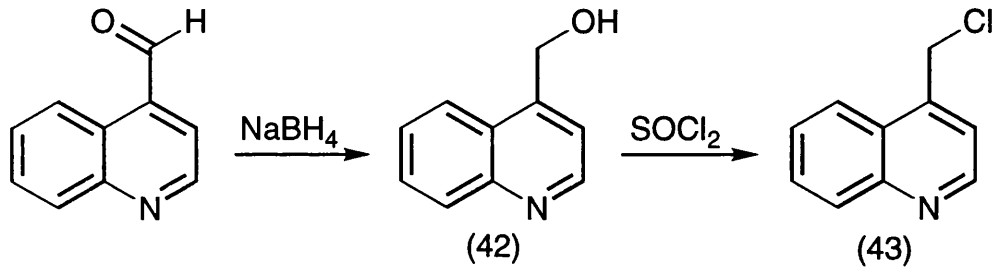
An analogous pathway was followed (Scheme 16 - opposite) in an attempt to secure a sample of the hydroquinone (41). Deprotection was achieved using trifluoroacetic acid, but efforts to recover the hydroquinone were unsuccessful. The product appeared to be polymeric, though it is not clear how this could have come about. The problem remains unresolved.



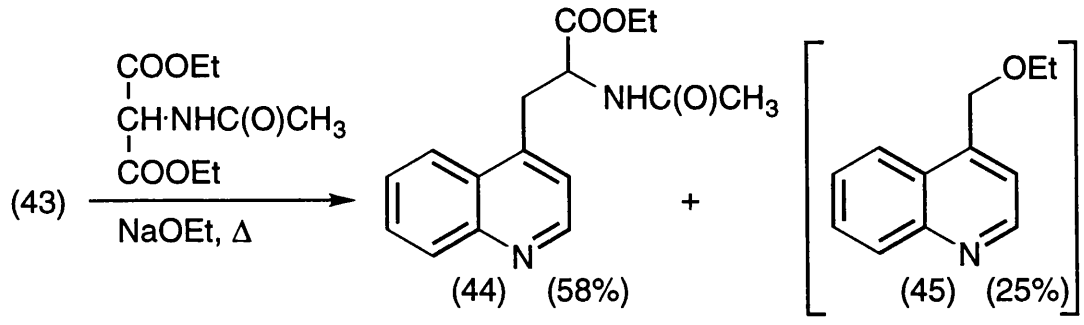
7.4 Phenylalaninol analogue

The commercially available (*S*)-alaninol was screened as a potential modifier. A very modest chiral induction was noted with some substrates, so a quinoline based analogue was synthesised.

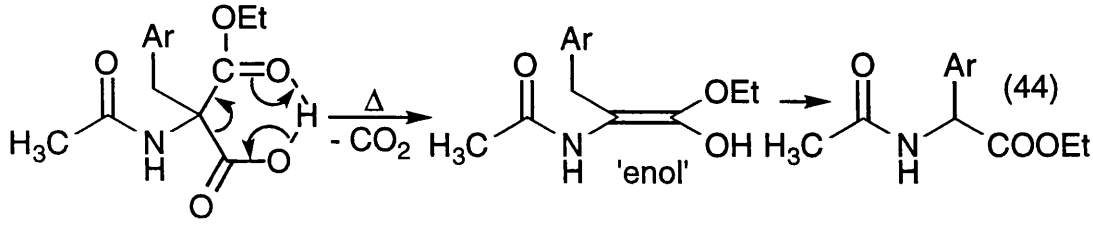
Reduction of quinoline-4-carboxaldehyde, followed by chlorination of alcohol (42) gave the chloromethyl compound (43).[208]



Deprotonation of diethyl acetamidomalonate and reaction with (43) led to the monoester (44) and a significant quantity of the (kinetic) by-product (45).

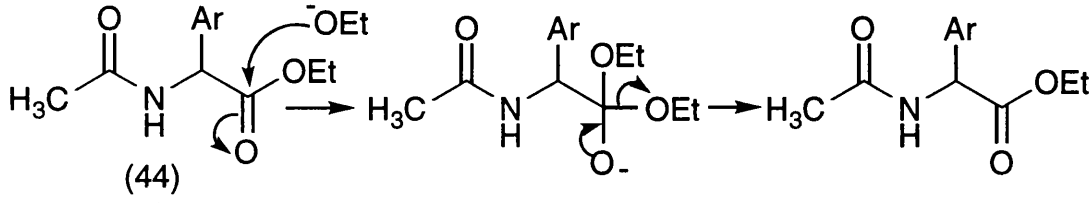


The diester which is initially formed, reacts progressively to give a β-ketoacid which spontaneously decarboxylates (Scheme 17).



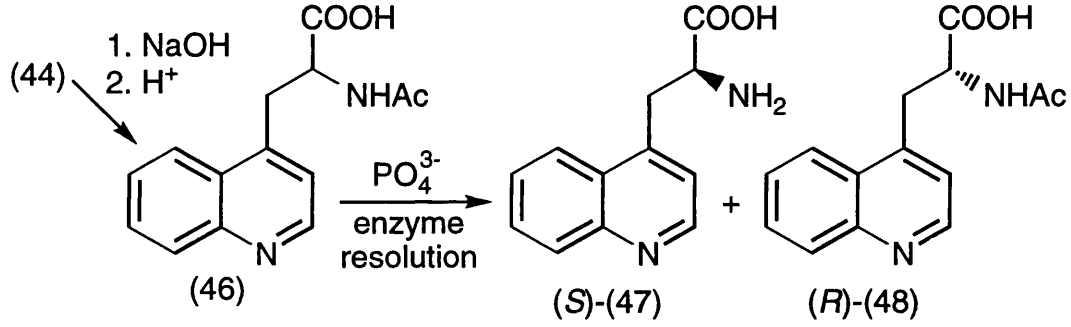
Scheme 17

The product (44) does not undergo any further discernible change, though it is actually reacting continuously in a pseudo-equilibrium fashion (Scheme 18).

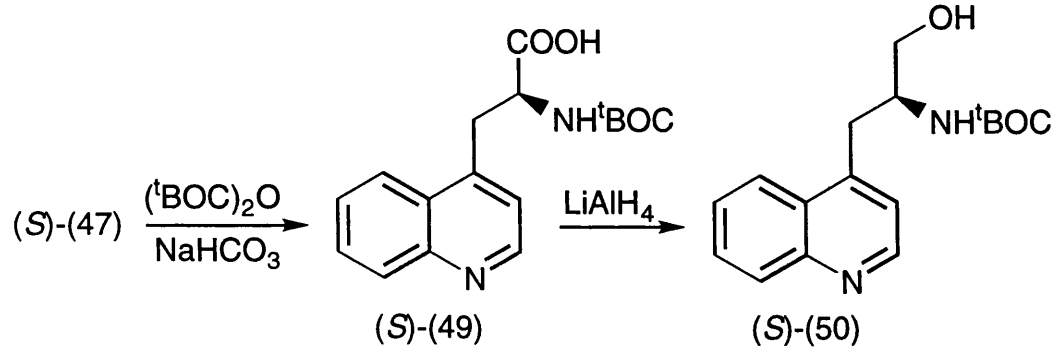


Scheme 18

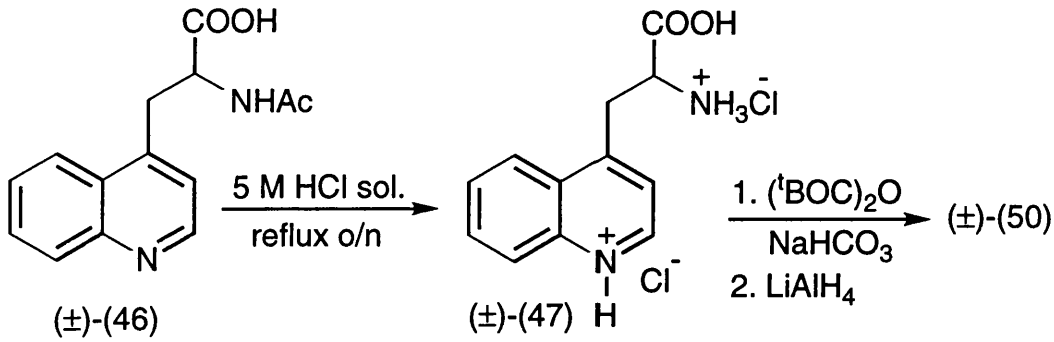
Following hydrolysis of ester (44), resolution of acetamide (46) was achieved enzymically using *Aspergillus* genus acylase.



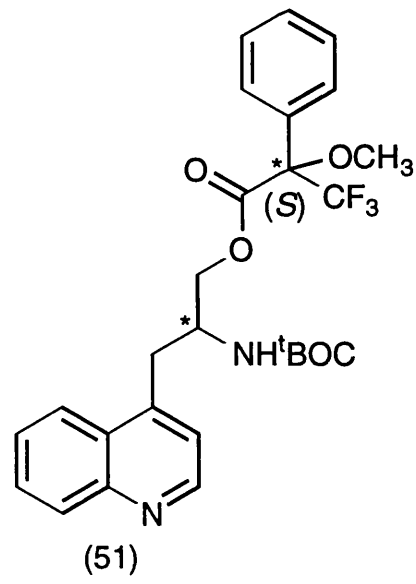
The e.e. of (*S*)-(47) was not established at this point because it was not analytically pure, and there was no easy method of purification (the optical purity determined by previous workers[209] was 99.5% e.e.). Protection of the amine group in (*S*)-(47) with the ^{t}BOC moiety gave acid (*S*)-(49) which was only slightly soluble in DMSO. Reduction by $LiAlH_4$ led to alcohol (*S*)-(50).



Attempting to reduce the acid (*S*)-(49) directly without first forming the methyl ester proved inferior, since the lithium salt precipitated during the reaction resulting in a yield of just 37%. A racemic sample of (50) was obtained from the simple steps outlined below.

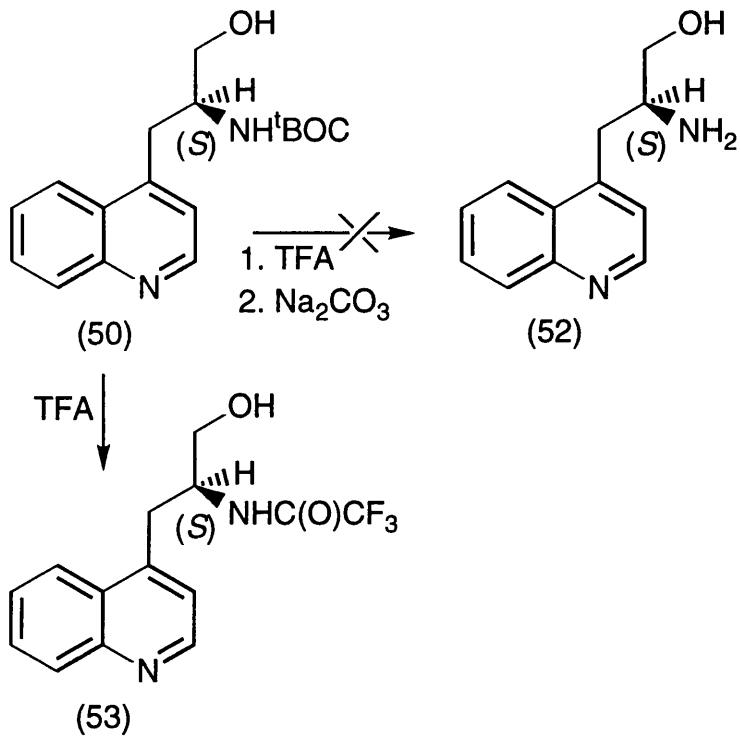


Mosher's ester derivative (51) was prepared from the racemic and chiral alcohols (50). Unfortunately, an attempt to establish the enantiomeric excess using 360 MHz ^{1}H and ^{19}F NMR was unsuccessful (5-600 MHz NMR spectrometer required). Furthermore, reverse phase h.p.l.c. was unable to provide a base line separation, thus negating an accurate assay.

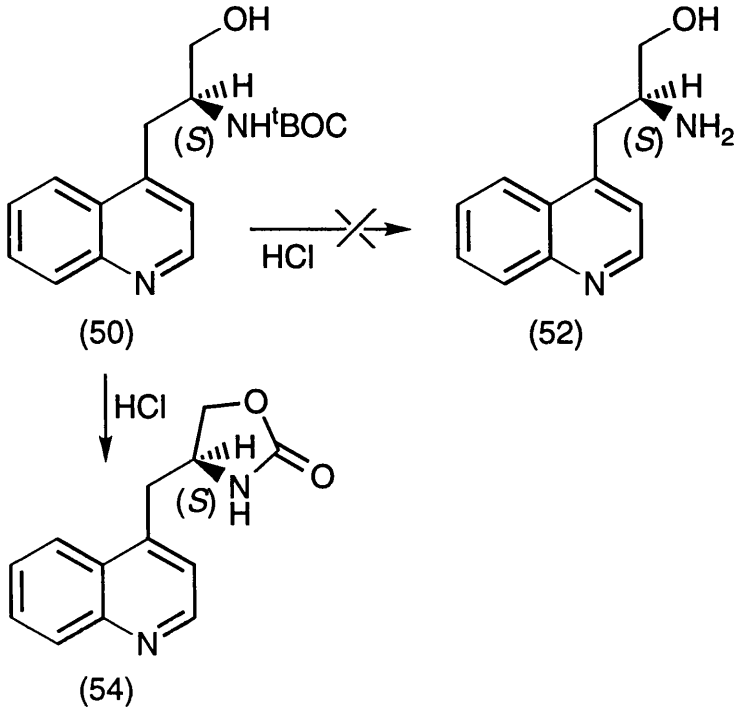


(51)

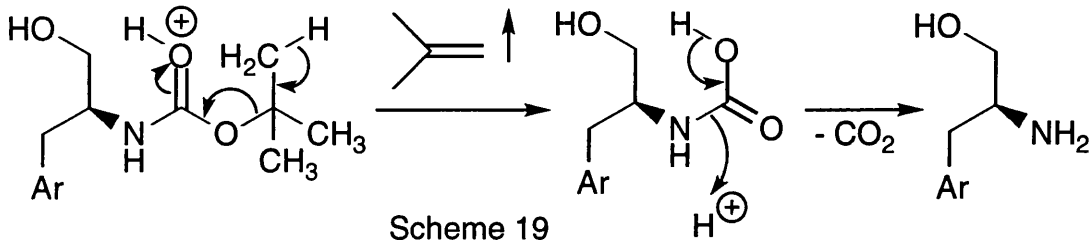
Deprotection of (*S*)-(50) using TFA did not give the expected free base (*S*)-(52), only the trifluoroacetamido derivative (*S*)-(53) being isolated.



Acetylation by TFA is a surprising result. This anomaly was confirmed by inference: phenylalaninol when stirred with cold TFA does indeed react, forming two unidentified derivatives. Substitution of aqueous HCl solution for TFA gave another undesirable product, characterisation of which suggests the formation of oxazolidone (54).

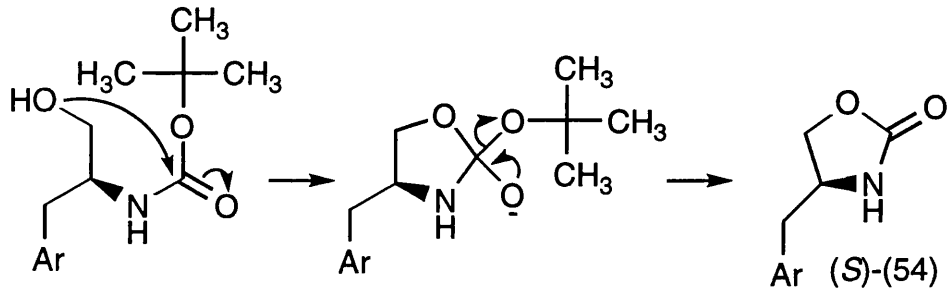


It seems that the reaction follows its conventional course (Scheme 19) in the presence of TFA, though the product undergoes further change.



Scheme 19

It is proposed that the alternative pathway predominates when aqueous HCl solution is used (Scheme 20).



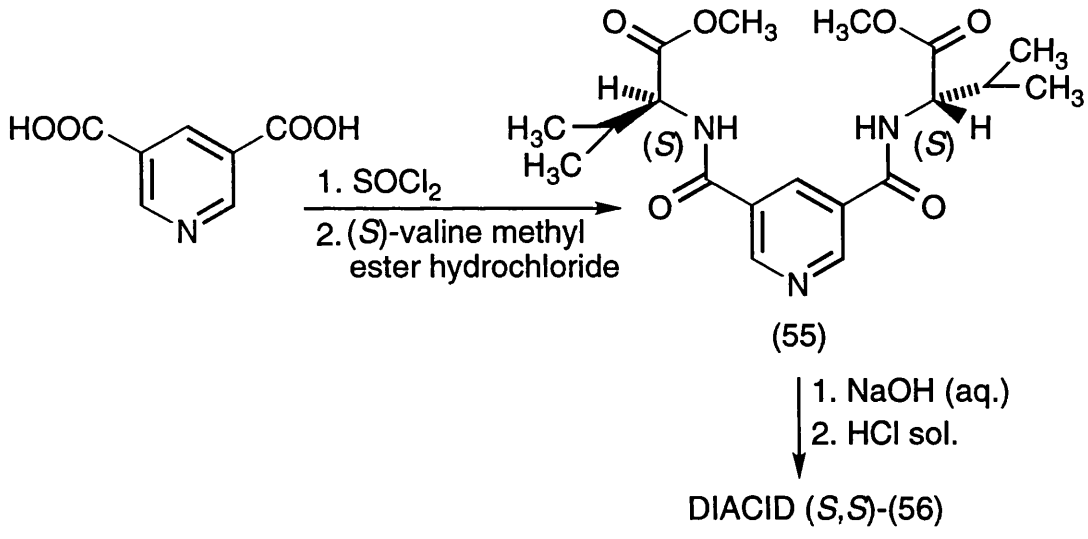
Scheme 20

In retrospect, ^{t}BOC was a poor choice of protecting group. FMOC would have been more appropriate since deprotection is brought about under basic conditions. In order to salvage the effort expended, deprotection using trimethylsilyl iodide[210] was attempted. This appears to have been successful, but the product is water soluble and so purification is difficult. This final stage awaits completion and confirmation by characterisation.

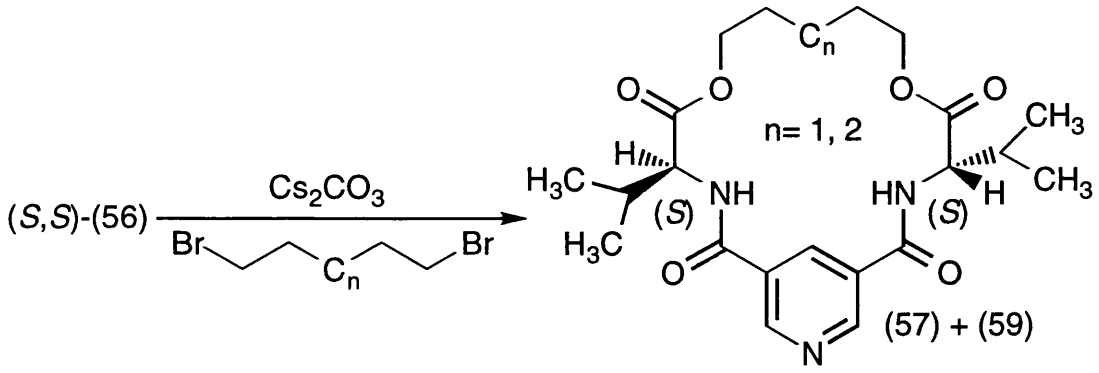
8 MACROCYCLES

The case for support specifies an investigation into the viability of macrocyclic modifiers. Of the many compounds that fall into this category, C_2 symmetric molecules were chosen, based on the synthetic studies of Kellogg.

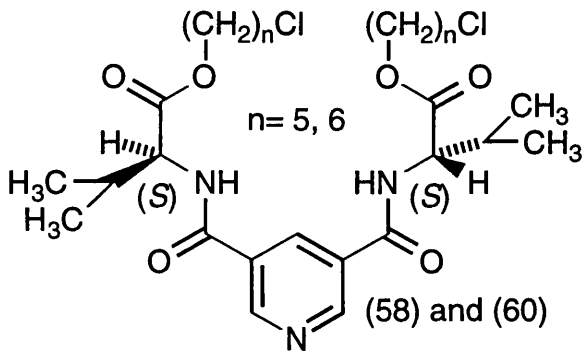
Two macrocycles of initial interest were previously prepared by Kellogg *et al.*[211] The commercially available pyridine-3,5-dicarboxylic acid (Aldrich) was converted to the diester (*S*,*S*)-(55) *via* the diacid chloride. The amino acid (*S*)-valine was chosen above all others as it was found to be amongst the least susceptible to epimerisation. Hydrolysis gave the diacid (*S*,*S*)-(56) [and NaCl] which was used 'as is' due to the difficulty in purifying a compound that is only soluble in water and DMSO.



Intramolecular bridging was achieved using the appropriate aliphatic dihalide by way of the dicaesium salt to yield macrocycles (*S*,*S*)-(57) and (*S*,*S*)-(59). Both compounds were formed under high dilution conditions in order to discourage intermolecular reaction. As expected with rings of these sizes, the yields are generally low and are often less than 20% (the longer the bridge, the lower the yield).



A small quantity of by-product was isolated from both reactions. These were identified as the bi-intermolecular reaction products (*S*,*S*)-(58) and (*S*,*S*)-(60), formed from the two molecules of the dihalide to form two long aliphatic chains.



It is interesting that a 'Finkelstein' halide exchange has taken place.

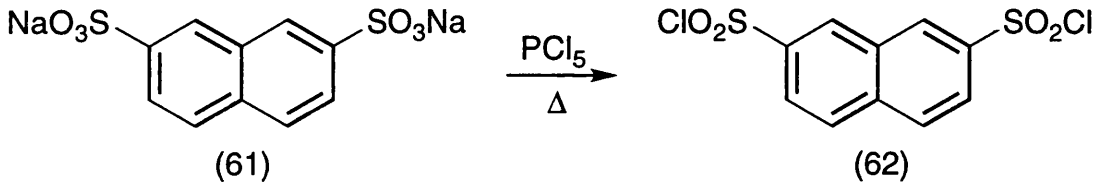
$$Ar\sim\!\!\sim CH_2Br + Cl^- \rightleftharpoons Ar\sim\!\!\sim CH_2Cl + Br^-$$

This exchange is likely to be the result of a thermodynamic equilibrium in which the less soluble salt precipitates.

It was intended to chelate these macrocycles with nickel(II) ions, but there was insufficient time to complete this part of the project.

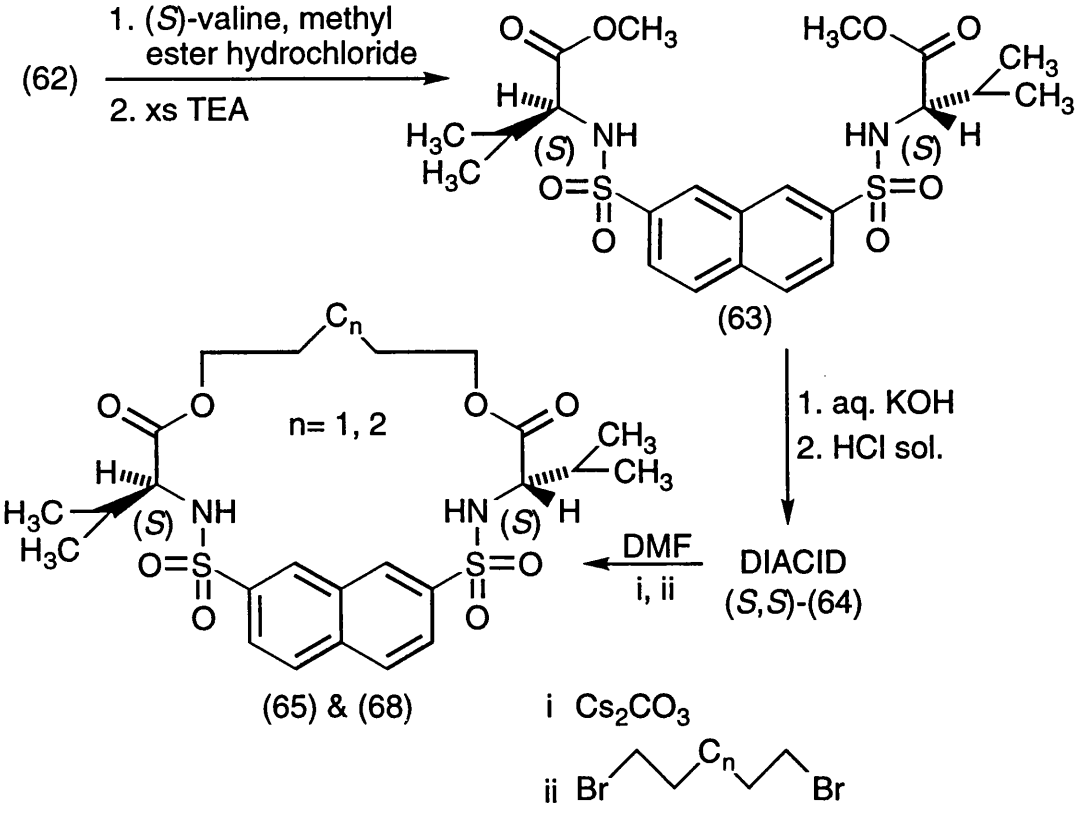
Analogues of the aforementioned macrocycles, but based on naphthalene, were successfully prepared from the naphthalene-2,7-disulfonic acid, disodium salt (61). The desired base compound,

naphthalene-2,7-dicarboxylic acid, was not commercially available and so the sulfonyl equivalent was a suitable isostere for this application. The disulfonyl chloride (62) was prepared by the 'neat' thermolysis of an admixture of (61) and phosphorus pentachloride.



(61) (62)

The synthetic pathway was very similar to the one used before:



The yields of macrocycles (*S*,*S*)-(65) and (*S*,*S*)-(68) were 24% and 7% respectively. This correlates with the yields obtained in the case of the pyridine analogues. On paper, it may appear that a longer carbon chain would be required to bridge the compound. This is almost certainly not the case. Such a molecule has a certain degree of flexibility and will twist (if

necessary) to allow the ring to form. It is unfortunate that all of the prepared macrocycles are amorphous since this precludes the use of X-ray crystallography in conformation elucidation.

To date, the role of caesium at the molecular level has yet to be established. As mentioned in the introduction it does seem likely that there is a dual interaction 'on' or close to one of the metal atom surfaces (Fig. 38).

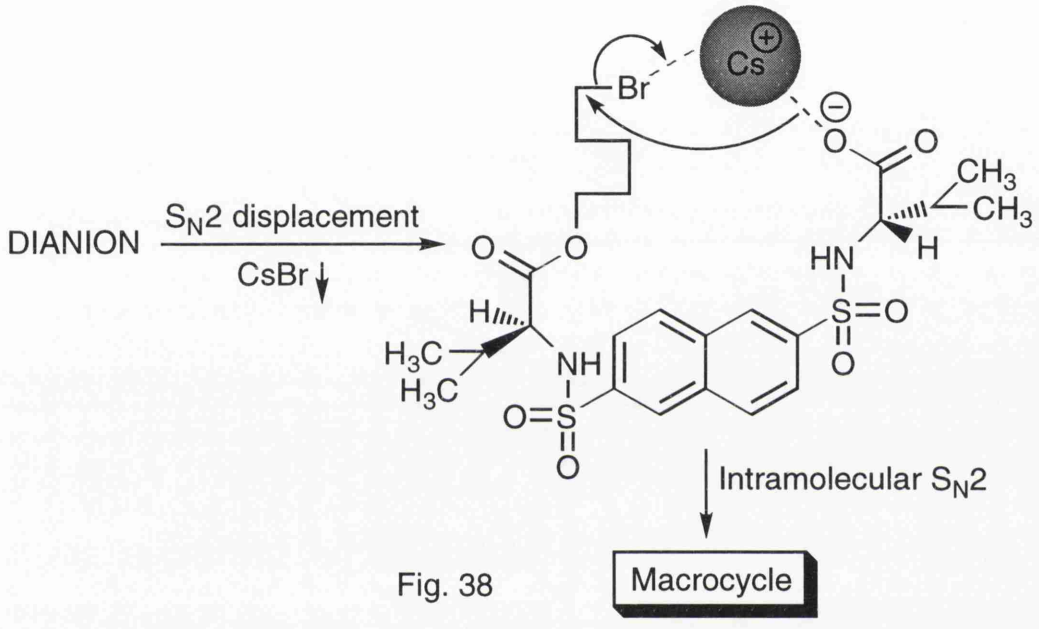
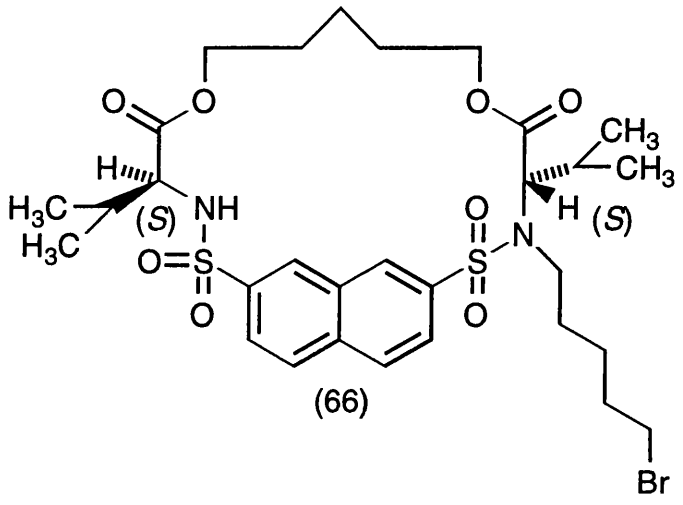


Fig. 38

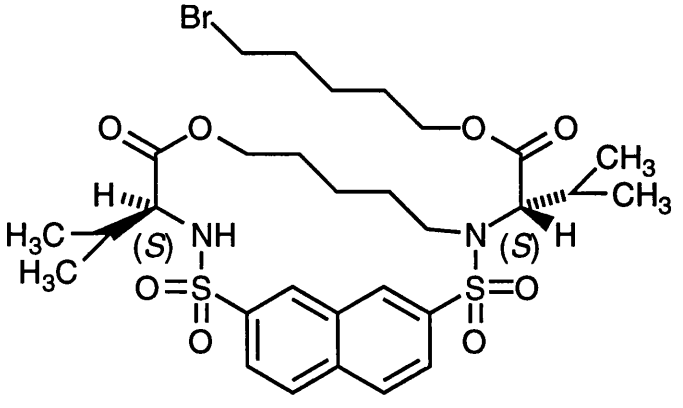
Two by-products were isolated from each of the reactions forming C_5 and C_6-bridged naphthalene based macrocycles. These were separated and examined. One of the by-products from the C_5 mixture was carefully purified and characterised. A definitive structure could not be assigned, but the molecule is believed to be (*S*,*S*)-(66) or (*S*,*S*)-(67). Normally, caesium carbonate would be too weak a base to deprotonate $ArSO_2NH$~~, but in the superior solvating conditions encountered with DMF, this side reaction must be possible albeit to a minor extent.

Alkylation at only one nitrogen site is presumably due to 'reagent starvation'. Nevertheless, the postulated structures are open to criticism. In

both cases, and notably with compound (*S*,*S*)-(66), one would expect a certain correlation of NMR data with macrocycle (*S*,*S*)-(65). However, there are (perceived) discrepancies. The structure (*S*,*S*)-(67) is intriguing; the protons at the central bridging carbon <u>are</u> strongly shielded, but the effect is less pronounced than anticipated (for a structure of this type).

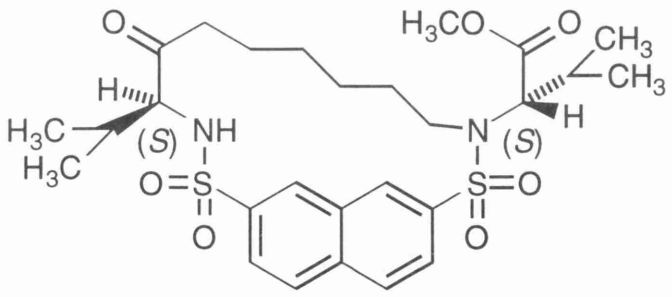


(66)



(67)

There were two by-products generated when forming the C_6-bridged macrocycle, one of which was purified and characterised (*S*,*S*)-(69). It is believed to be the analogous C_5 by-product which was not characterised (*i.e.* the opposite by-product from each reaction was identified).



(69)

The assignment of the structure above to by-product (*S*,*S*)-(69) is strongly supported by ^{1}H NMR data. The reason for this confidence is expanded upon in the following sub-section.

Within a uniform magnetic field, the circulation of electrons surrounding a nucleus induce an opposing secondary magnetic field. This effect is particularly applicable to aromatic rings (Fig. 39). With regards to naphthalene, the doughnut shaped field transforms to a figure of eight.

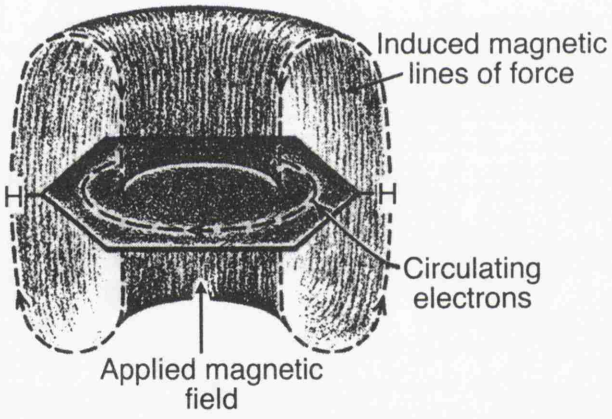


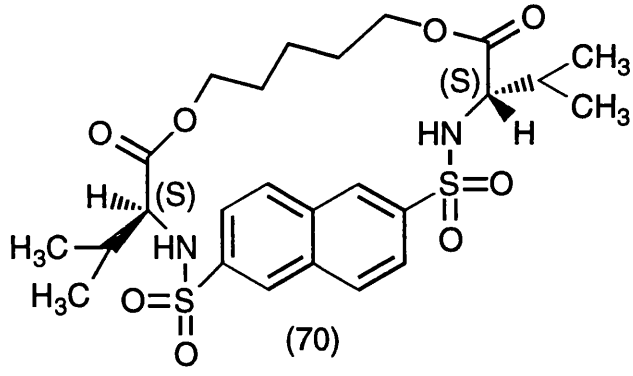
Fig. 39

Nuclei in a high electron density environment are subjected to a lower field strength relative to their neighbours. Protons in this situation are said to be 'shielded' and experience a chemical shift upfield. Disparate electron density may induce magnetic fields which are also 'polarised' and give rise to an anisotropic effect.

Therefore, protons held above or below the plane of a naphthalene ring would be significantly shielded. It is fascinating that in its ^{1}H NMR

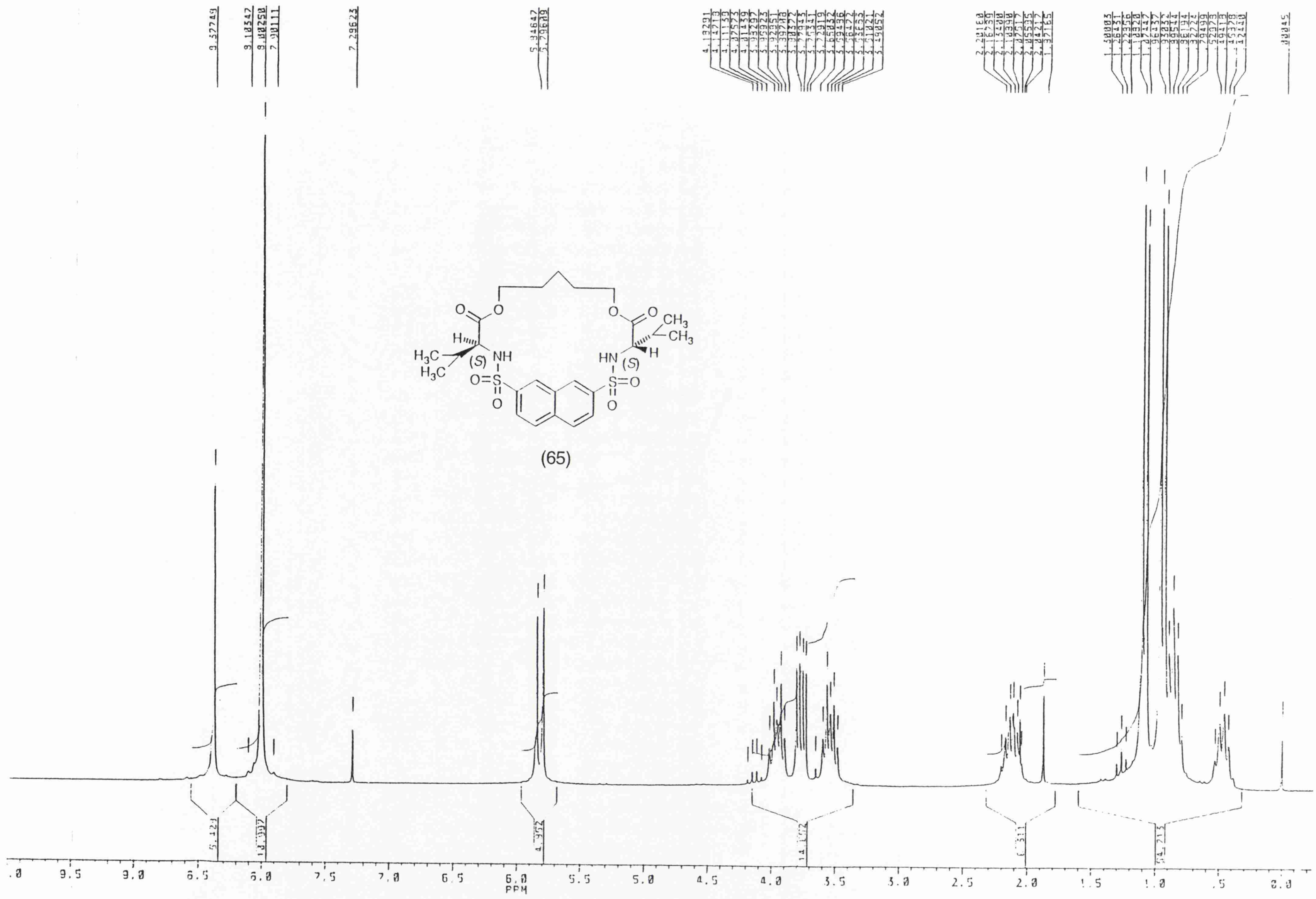
spectrum, the central C$\underline{H_2}$ in macrocycle (*S*,*S*)-(65) is indeed shifted to δ0.48 (see spectrum). Furthermore, every constituent proton in the 'bridge' is diastereotopic, and this results in a fairly complex spectrum. The same C$\underline{H_2}$ signal in pentane-1,5-diol has a chemical shift of δ1.5, so the anisotropic effect is quite pronounced. The intensity of shielding is dependent on substituent proximity to the aromatic plane, as exemplified by the cyclophane series of compounds.[212]

It seems logical that the shielding of the central C$\underline{H_2}$ in the 2,6-disubstituted equivalent of macrocycle (*S*,*S*)-(65) would be slightly more intense. Macrocycle (*S*,*S*)-(70) was synthesised as one of the target compounds in a undergraduate project. As expected, the chemical shift of the C$\underline{H_2}$ protons was recorded at δ0.39.



(70)

Support is lent to the postulated structure (*S*,*S*)-(69), since one of the protons has a chemical shift of δ0.23. If this structure has been correctly elucidated, then that suggested for (*S*,*S*)-(67) is in doubt. Clearly, a definitive assignment of the by-products cannot easily be made without X-ray diffraction data.



(65)

9 CONCLUSIONS

It is essential that modifiers confer chirality catalytically, and are otherwise passive. The adsorption orientation of these modifiers is concentration and temperature dependent. Catalyst preparation and hydrogen pressure are also important factors. It is apparent that the many variables are themselves subject to a certain degree of variance. Therefore, it would seem that the successful discovery of a match-pairing of substrate and modifier is more likely if the variables are minimised by way of standardisation.

Adsorption of the binaphthalene molecules on Pt, Pd and Ni surfaces is generally considered to (preferentially) occur *via* the lone pair(s) of the substituent atom(s) and not by way of the aromatic ring(s). However, the dimethoxybinaphthalene, for example, did not adsorb onto these metals but did adsorb onto the support. Indeed, this factor interfered with the data in some experiments and had to be taken into account. Thus, the complexities of each molecule must really be considered individually.

Adsorption of the prepared macrocycles in their unchelated form was successful in as much as they do adsorb. This is not a surprise, though - there are many substituent anchor points, not to mention the aromatic ring(s). It would therefore be necessary to sequentially 'mask' all of these potential 'anchors' in order to apply any kind of theoretical understanding of events. Chirality was not conferred upon the few test substrates, almost certainly due to a lack of interaction between the two molecules.

Adsorption of naphthalene on a metal surface results in the coverage of ten metal atoms.[213] It is surmised that the molecular canopy of a

molecule like cinchonidine would obscure even more of the surface area. Regrettably, it is this uncertainty of the metal topography and the resulting physical attributes of the treated catalyst which undermine efforts to rationalise (or understand) the nature of interaction.

Of the many compounds which were prepared and screened, none of these were able to match the outstanding qualities of the cinchona alkaloids in this application. However, a great deal of data has been generated, and it is hoped that the efforts ascribed above has laid down some of the groundwork for future projects in this exciting field of chemistry.

9.1 Future Work

A greater understanding of the surface and modifier-substrate interactions is essential. Since cinchona alkaloids can serve as efficient modifiers, it would be prudent to 'backtrack' and examine the interaction(s) between cinchonidine and methyl pyruvate by way of cinchona mimics.

The macrocycles require refinement. It is essential that a pendant arm be incorporated in order to interact with the substrate through hydrogen bonding. It is also necessary to chelate the molecule such that only one surface binding mode is possible.

A project of this sort relies on experimental feedback, thus speculating on the direction of a future synthesis program is not possible. However, through the work conducted so far, and as mentioned elsewhere, there are specific guidelines to which both modifier and substrate must conform.

EXPERIMENTAL

10.1 General methods

^1H NMR Spectra were recorded at 200 or 360 MHz on Bruker spectrometers (WP200SY and AM360 respectively). Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 50 MHz. Chemical shifts in the ^1H NMR spectra are reported in p.p.m. (δ) relative to the proton shift of tetramethylsilane (δ = 0) as an internal standard. Chemical shifts in the ^{13}C NMR spectra are relative to the central signal at 77.0 ppm ($CDCl_3$) or 39.7 (d_6-DMSO). Coupling constants (J) are quoted in Hertz. Signal description is reported using the following convention: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened.

Infrared spectra were recorded on a Perkin-Elmer P-1000 spectrometer.

Mass spectra were recorded using a VG/Kratos MS12 spectrometer for low resolution work and a VG/Kratos MS90S for accurate mass determination.

Optical rotations were measured on a AA-100 polarimeter (Optical Activity Limited).

Melting points were determined on a Kofler hot stage melting point apparatus, and are uncorrected.

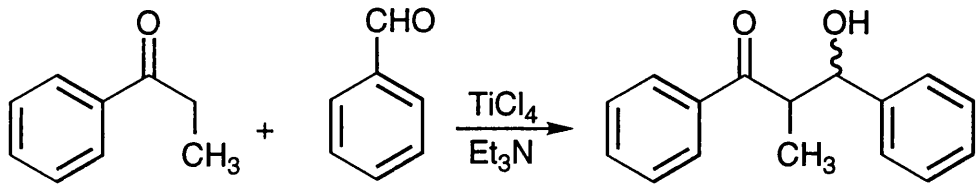
All chemical separations were achieved using positive pressure chromatography. The silica gel was supplied by Rhône-Poulenc: Sorbsil® C-60H (5% water).

Gas chromatography was undertaken using a Chrompack CP9000 instrument fitted with a flame ionisation detector, HP3395 integrator, and a chiral CP Cyclodex-B (β-cyclodextrin) fused silica WCOT 0.25 mm column [injection and detector temperature: 180 °C; 100 kPa column head pressure; programmed elution: 110 °C (10 mins.) to 140 °C at 1 °C min^{-1}].

H.p.l.c. was performed on a Spherisorb C8-SB5 r.p. column. Elution was achieved using 60% acetonitrile / 40% water (by volume).

10.2 Experimental procedures

3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one



(1)

C. R. Harrison, *Tetrahedron Lett.*, **28**, 4135.

Propiophenone (13.42 g, 0.1 mol) was added in one batch to a chilled solution of titanium tetrachloride (12.09 cm^3, 0.11 mol in dry DCM (350 cm^3). A solution of benzaldehyde (10.61 g, 0.1 mol) in dry DCM (100 cm^3) was carefully added, followed by the dropwise addition of a solution of triethylamine (11.64 g, 0.115 mol) in dry DCM (50 cm^3). The mixture was stirred for a further 3 h at 0 °C, and then poured into ice water and extracted with ether (2 x 750 cm^3). The combined extracts were washed with water until neutral, dried, and the solvent removed under reduced pressure. Purification by chromatography (20% ether/hexane) yielded the *title compound* (18.57 g, 77%) as an oil which subsequently crystallised; m.p. 71-71.5 °C. Several batches were prepared similarly.

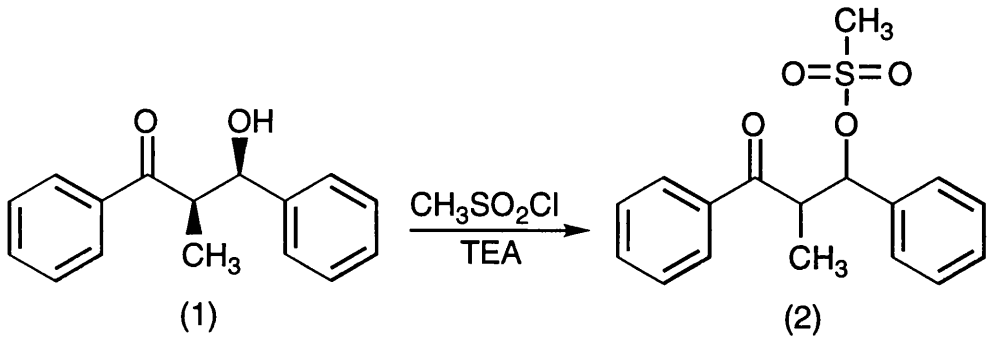
δ_H NMR ($CDCl_3$) 7.93 (2 H, m, aromatic H), 7.59-7.25 (8 H, m, aromatic H), 5.24 (1 H, d, *J* 3.1, CHOH), 3.70 (1 H, q of d, *J* 7.2 and 3.1, $CHCH_3$), 3.59 (1 H, br s, OH), 1.19 (3 H, d, *J* 7.2, CH_3).

Found: *m/z* 240 (M^+, 0.5%), 134 (31), 105 (87), 77 (100), 51 (54), 50 (25).

Found: C, 79.93; H, 6.56.

$C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71%.

3-(Methanesulfonyloxy)-2-methyl-1,3-diphenylpropan-1-one



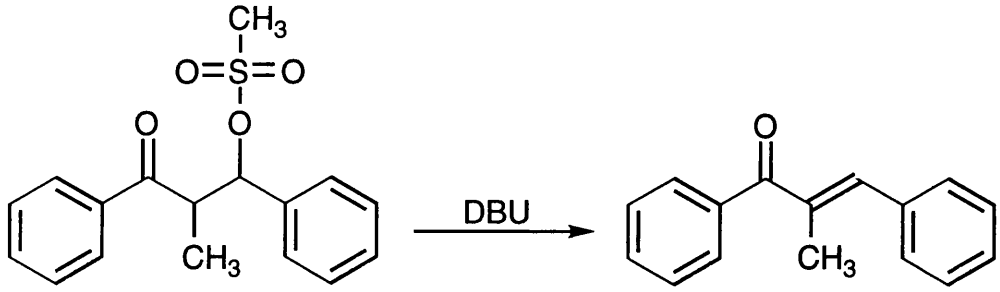
(1) (2)

The aldol product (1) (90.00 g, 0.375 mol), and methanesulfonyl chloride (51.48 g, 0.45 mol) were dissolved in dry DCM (1500 cm^3) and cooled to 0 °C under an argon atmosphere. An excess of triethylamine (49.27 g, 0.487 mol) was added dropwise over 1 h and the solution subsequently allowed to warm to room temperature. The organic phase was washed with HCl solution (0.1 mol dm^{-3}; 2 x 200 cm^3) and then water until neutral. The solvent was dried and removed *in vacuo* to leave a viscous residue. Purification on SiO_2, eluting with 50:50 hexane/$CHCl_3$, yielded the mesylate (2) (68.84 g, 58%) as an off-coloured oil.

δ_H NMR ($CDCl_3$) 7.77 (2 H, m, aromatic H), 7.56-7.26 (8 H, m, aromatic H), 5.89 (1 H, d, *J* 9.1, CHMes.), 4.13 (1 H, d of q, *J* 9.1 and 6.9, $CHCH_3$), 2.65 (3 H, s, CH_3S), 1.50 (3 H, d, *J* 6.9, CH_3).

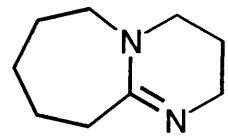
Found:*m/z* 222 (*M*-CH_3SO_2O, 7.0), 105 (99), 77 (100), 51 (56).

(*E*)-2-Methyl-1,3-diphenyl-2-propen-1-one



(2) (3)

The prepared mesylate (2) (68.78 g, 0.216 mol), dissolved in dry benzene (2000 cm^3), was treated with an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (49.33 g, 0.324 mol) and heated under reflux for 2 h. The cooled organic solution was washed with HCl solution (0.1 mol dm^{-3}; 2 x 300 cm^3) and water until neutral. The solvent was dried and removed under reduced pressure. Purification by chromatography (10% ether/hexane) afforded the *title compound* (24.69 g, 51%) as a viscous colourless oil.



"DBU"

δ_H NMR ($CDCl_3$) 7.75 (2 H, m, aromatic H), 7.54-7.35 (8 H, m, aromatic H), 7.18 (1 H, q, *J* 1.4, CH), 2.27 (3 H, d, *J* 1.4, CH_3).

Found: *m/z* 222 (M^+, 29%), 115 (52), 105 (55), 91 (35), 77 (100), 51 (63), 39 (25).

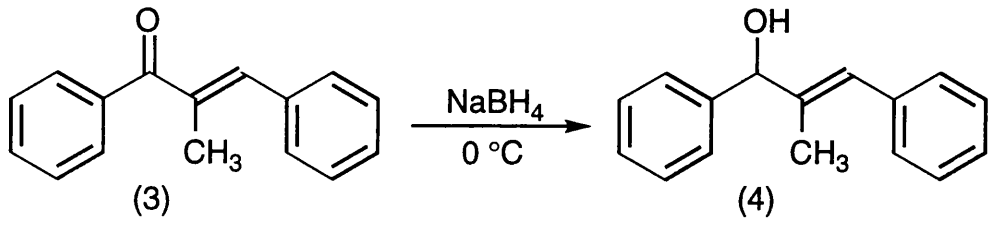
Found: M^+, 222.1038. $C_{16}H_{14}O$ requires *M* 222.1045.

Found:	C, 86.66; H, 6.49.
$C_{16}H_{14}O$ requires	C, 86.45; H, 6.35%.

E-isomer content was determined by reverse phase h.p.l.c.: @99.7%.

H.p.l.c. analysis was undertaken using a Spectra-Physics pump, a Spherisorb (5μm) C8-SB5 column (200 x 4.6 mm), and sample recognition was achieved using a UV detector. Isocratic elution was performed using a mobile phase of 60% acetonitrile / 40% water (by volume) with a flow rate of 1 cm^3 / min. All h.p.l.c. grade solvents were supplied by Rathburn Chemicals.

(*E*)-2-Methyl-1,3-diphenyl-2-propen-1-ol



(3) (4)

Compound (3) (1.00 g, 4.5 mmol) was dissolved in methanol (30 cm^3) and treated batchwise with a large excess of sodium borohydride (0.51 g, 13.5 mmol). The solvent was removed under reduced pressure and the residue was dissolved in water (50 cm^3), neutralised with citric acid solution and extracted with ether (2 x 20 cm^3). The combined extracts were dried and the solvent was removed *in vacuo*. Purification by chromatography, eluting with 10% ether/hexane, yielded the *title compound* (0.57 g, 56%) as a colourless oil.

δ_H NMR ($CDCl_3$) 7.48-7.16 (10 H, m, aromatic H), 6.78 (1 H, q, *J* 1.3, C=CH), 5.27 (1 H, br s, CHOH), 2.11 (1 H, br s, OH), 1.73 (3 H, d, *J* 1.3, CH_3).*

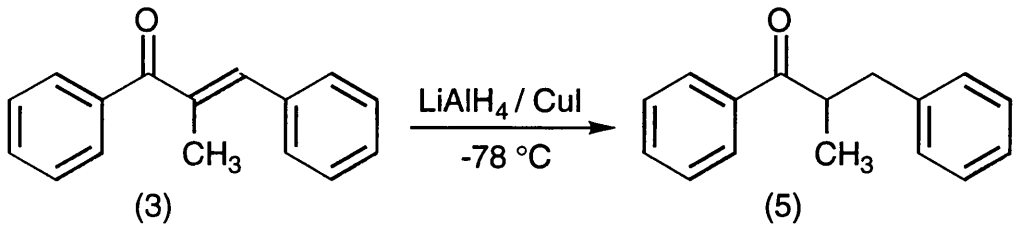
Found: *m/z* 224 (M^+, 15%), 115 (26), 105 (100), 91 (35), 77 (46).*

Found: C, 85.66; H, 7.21.

$C_{16}H_{16}O$ requires C, 85.68; H, 7.19%.

* These data are in agreement with that published by E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, 1970, **92**, 226.

2-Methyl-1,3-diphenylpropan-1-one



(3) (5)

$LiAlH_4$ (0.21 g, 5.53 mmol) was suspended in dry THF (20 cm^3) under an argon atmosphere, chilled to -78 °C, and treated with a solution of CuI (2.14 g, 11.24 mmol) in dry THF (5 cm^3) and HMPA (5 cm^3). The temperature was maintained and stirring continued for 30 min before the substrate (3) (2.50 g, 11.24 mmol) dissolved in THF (10 cm^3) was added dropwise. Stirring at -78 °C was continued for a further 1 h before quenching with saturated aqueous NH_4Cl solution. The mixture was allowed to attain room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ether (50 cm^3) and water (50 cm^3), neutralised with dilute citric acid solution, and filtered through Celite. The organic solution was separated and the aqueous layer extracted with ether (30 cm^3). The combined extracts were dried and the solvent removed *in vacuo*. Purification on SiO_2 eluting with 10% ether/hexane afforded *compound* (5) (0.39 g, 39% based on recovered starting material) as a colourless oil.

ν_{max} (film)/cm^{-1} 3062 (Ar-H), 2970 and 2932 (CH_2, CH_3), 1448 (CH_2, CH_3), 1682 (C=O), 740 and 700 (Ar-H, monosubstituted).

δ_H NMR ($CDCl_3$) 7.93 (2 H, m, aromatic H), 7.59-7.40 (3 H, m, aromatic H), 7.35-7.10 (5 H, m, aromatic H), 3.75 (1 H, m, CH), 3.17 (1 H, dd, *J* 13.7 and 6.2, H_AH_B), 2.69 (1 H, dd, *J* 13.7 and 7.9, H_AH_B), 1.20 (3 H, d, *J* 6.9, CH_3).

Found: *m/z* 224 (M^+, 16%), 105 (100), 91 (31), 77 (51).

Found: C, 85.53; H, 7.38.

$C_{16}H_{16}O$ requires C, 85.68; H, 7.19%.

2-Methyl-1,3-diphenylpropan-1-ol

(5) (6)

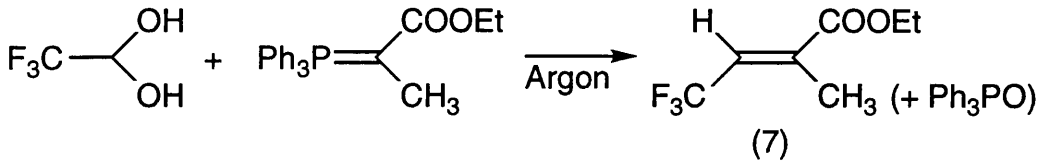
$LiAlH_4$ (12 mg, 0.32 mmol) suspended in dry ether (10 cm^3), was reacted with ketone (5) (175 mg, 0.78 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirring was continued for a further 30 min. Citric acid solution (aq.) (1 mol dm^{-3}; 10 cm^3) was added and the organic layer separated. The aqueous solution was extracted with ether (10 cm^3) , and the combined extracts washed with brine (5 cm^3), dried, and the solvent removed under reduced pressure. The resultant oil was subjected to column chromatography [20% ether/hexane as eluent] to give the *title compound* (100 mg, 57%) as a colourless oil [diastereomeric ratio after purification was 42:58].

δ_H NMR (360MHz; $CDCl_3$) 7.38-7.24 (14 H, m, aromatic H), 7.22-7.13 (6 H, m, aromatic H), 4.61 (1 H, d, *J* 5.0, CHOH), 4.50 (1 H, d, *J* 7.1, CHOH), 3.08 (1 H, dd, *J* 13.3 and 3.8, $CH_{A1}H_{B1}$), 2.79 (1 H, dd, *J* 13.3 and 5.8, $CH_{A2}H_{B2}$), 2.39 (1 H, dd, *J* 13.3 and 9.8, $CH_{A1}H_{B1}$) 2.38 (1 H, dd, *J* 13.3 and 9.1, $CH_{A2}H_{B2}$), 2.18-2.06 (2 H, m, 2 x $CHCH_3$), 1.91 (1 H, br s, OH), 1.83 (1 H, br s, OH), 0.86 (3 H, d, *J* 6.7, CH_3), 0.67 (3 H, d, *J* 6.8, CH_3).

Found: *m/z* 226 (M^+, 3%), 107 (100), 91 (50), 79 (52), 77 (33).

Found: M^+, 226.1362. $C_{16}H_{18}O$ requires *M* 226.1358.

Ethyl (*E*)-2-methyl-4,4,4-trifluoro-2-butenoate



(7)

Carboethoxyethylidene triphenylphosphorane (200 g, 0.552 mol) was dissolved in DCM (800 cm^3) and added dropwise to a stirred solution of trifluoroacetaldehyde hydrate (100 g, 0.862 mol) in THF (500 cm^3) at room temperature. After stirring overnight, the solvent was removed by fractional distillation. The occluded product was extracted from triphenylphosphine oxide using chilled hexane and again subjected to fractional distillation. The product was redistilled at atmospheric pressure to yield the *title compound* (74.40 g, 74%) as a mobile oil; b.p. 131 °C.

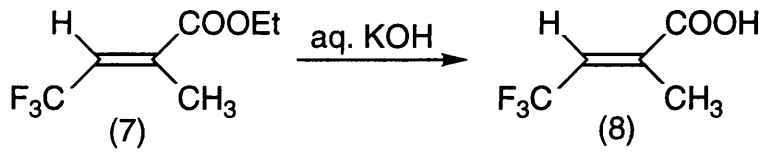
ν_{max} (film)/cm^{-1} 2988, 1730, 1668, 998.

δ_H NMR ($CDCl_3$) 6.68 (1 H, m, C<u>H</u>), 4.27 (2 H, q, *J* 7.1, C<u>H</u>$_2$), 2.08 (3 H, m, C<u>H</u>$_3$), 1.33 (3 H, t, *J* 7.1, C<u>H</u>$_3$CH$_2$).

δ_C NMR ($CDCl_3$) 165.5 (<u>C</u>=O), 139.8 (*J* 5.3, C=<u>C</u>COOH), 125.4 (q, *J* 34.8, <u>C</u>H), 122.8 (q, *J* 270.9, <u>C</u>F$_3$), 61.4 (<u>C</u>H$_2$), 13.3 (<u>C</u>H$_3$), 12.7 (CH$_2$<u>C</u>H$_3$).

Found:*m/z* 137 (*M*-OEt, 100), 114 (33), 113 (88), 109 (78), 89 (48), 45 (29), 39 (40).

(*E*)-2-Methyl-4,4,4-trifluoro-2-butenoic acid



(7) (8)

The prepared ester (7), (73.77 g, 0.405 mol) was taken up in chilled ethanol (400 cm^3) and a cold aqueous solution of KOH (400 cm^3; 5 mol dm^{-3}) was added. The solution was allowed to attain room temperature and stirring was continued overnight. The solution was concentrated under reduced pressure, brine (500 cm^3) was added and the solution was extracted with ether (2 x 100 cm^3). These organic extracts were discarded. The aqueous solution was acidified with HCl solution (4 mol dm^{-3}) and re-extracted with ether (3 x 150 cm^3). The combined organic extracts were washed with brine (50 cm^3), dried, and the solvent removed *in vacuo.* Fractional distillation yielded acid (8) (45.77 g, 73%) as a pungent mobile oil; b.p. 116-118 °C/115 mmHg which subsequently crystallised. Trituration with chilled hexane gave colourless crystals; m.p. 35-36 °C.

ν_{max} (KBr disc)/cm^{-1} 3432, 1718, 998.

δ_H NMR ($CDCl_3$) 12.27 (1 H, br s, COO<u>H</u>), 6.81 (1 H, m, C<u>H</u>), 2.11 (3 H, m, C<u>H</u>$_3$).

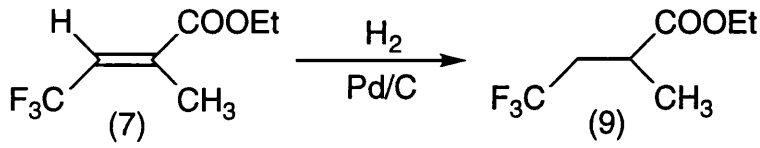
δ_C NMR ($CDCl_3$) 172.2 (<u>C</u>=O), 138.8 (*J* 5.0, C=<u>C</u>COOH), 128.4 (q, *J* 35.2, <u>C</u>H), 122.6 (q, *J* 271.4, <u>C</u>F$_3$), 13.0 (<u>C</u>H$_3$).

Found: *m/z* 154 (M^+, 1.2%), 114 (47), 89 (38), 86 (55), 64 (25), 59 (25), 45 (31), 39 (100), 32 (36).

Found: C, 38.90; H, 3.36.

$C_5H_5F_3O_2$ requires C, 38.97; H, 3.27%.

Ethyl 2-methyl-4,4,4-trifluorobutanoate

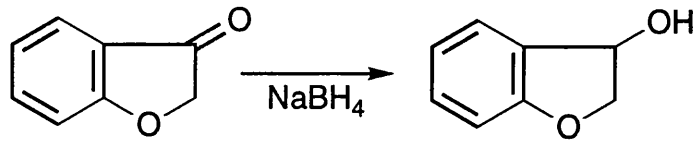


10% Pd/C Catalyst (1 g) was suspended in a solution of α,β-unsaturated ester (7) (5.00 g) in methanol (150 cm^3). Hydrogenation was achieved within 1 h at room temperature using a Parr hydrogenation apparatus at 40 psi. Fractional distillation yielded *compound* (9) (0.5 g, 10%) as a volatile oil; b.p. 108 °C/760 mmHg [most of the product co-distilled with methanol].

δ_H NMR ($CDCl_3$) 4.73 (2 H, m, $CF_3C\underline{H}_2$), 4.17 (2 H, q, *J* 7.1, $CH_3C\underline{H}_2$), 2.25-2.0 (1 H, m, C<u>H</u>), 1.29 (3 H, d, *J* 7.1, $C\underline{H}_3CH$), 1.27 (3 H, t, *J* 7.1, $C\underline{H}_3CH_2$).

Found: *m/z* 184 (M^+, 4.9%), 32 (100), 31 (33).

(±)-3-Hydroxy-2,3-dihydrobenzofuran



(±)-(10)

3-Coumaranone (5.00 g, 37.3 mmol), slurried in methanol (100 cm^3) at 0 °C, was treated batchwise with an excess of $NaBH_4$ (7.05 g, 186.4 mmol). The mixture was stirred for a further hour and allowed to attain room temperature. The solvent was removed under reduced pressure and the residue partitioned between EtOAc (200 cm^3) and citric acid solution (1 mol dm^{-3}, 50 cm^3). The organic layer was separated, washed with brine (50 cm^3), dried and the solvent removed *in vacuo*. The oil remaining was purified by chromatography, eluting with 50:50 ether/hexane to yield the pure product (4.51 g, 89%) as a colourless oil.

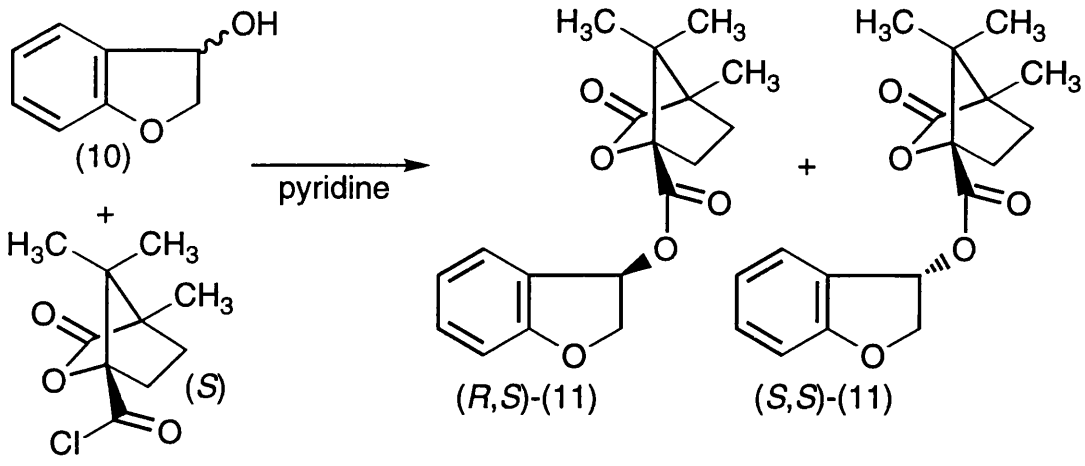
δ_H NMR ($CDCl_3$) 7.42 (1 H, 'd' [ddd], *J* 7.5 [*ortho*], aromatic H), 7.27 (1 H, 't' [ddd], aromatic H), 6.93 (2 H, 'd' [ddd], *J* 7.5 [*ortho*], and 't' [ddd], aromatic H), 5.33 (1 H, br m [ddd], CH), 4.49 (1 H, dd, *J* 10.7 and 6.3, CH_AH_B), 4.38 (1 H, dd, *J* 10.7 and 2.7 CH_AH_B), 2.07 (1 H, br s, OH).

Found: *m/z* 136 (M^+, 100%), 135 (27), 119 (61), 107 (25), 105 (35), 94 (27), 91 (89), 90 (30), 79 (39), 77 (81), 65 (30), 63 (34), 51 (50), 50 (32), 39 (43).

Found: C, 70.75; H, 5.92.

$C_8H_8O_2$ requires C, 70.58; H, 5.92%.

Camphanate ester of 3-hydroxy-2,3-dihydrobenzofuran



D. R. Boyd, N. D. Sharma, R. B. Boyle, J. F. Malone, J. Chima, and H. Dalton, *Tetrahedron: Asymmetry*, 1993, **4**, 1307.

Racemic 3-hydroxy-2,3-dihydrobenzofuran (2.72 g, 20 mmol), was treated at room temperature with (-)-(1*S*)-camphanic chloride (4.98 g, 23 mmol) in dry pyridine (40 cm^3). Stirring was continued for 15 min after which time the solvent was removed under reduced pressure. The organic residue was extracted with EtOAc (250 cm^3), washed with water (2 x 50 cm^3), dried, and the solvent removed *in vacuo*. Chromatography on SiO_2 using 50:50 ether/hexane yielded the pure diastereomeric mixture as a silvery white solid. Fractional recrystallisation from ether/hexane and finally ether [d.e. monitored by NMR] yielded a crystalline solid (1.45 g, 46%); m.p. 96 °C; $[\alpha]_D$ -98.1 (*c* 1.25 in $CHCl_3$), [lit.: $[\alpha]_D$ -109 (*c* 1.25 in $CHCl_3$)], enriched in diastereomer (*R*,*S*)-(11) [d.e. 88%; absolute optical purity was not required in these circumstances].

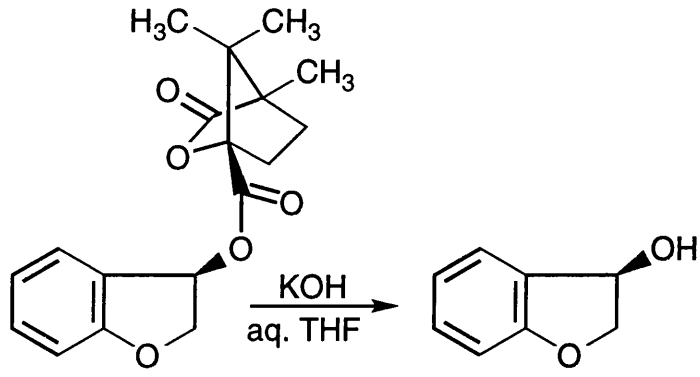
δ_H NMR ($CDCl_3$) 7.47 (1 H, 'd' [ddd], aromatic H), 7.32 (1 H, 't' [ddd], aromatic H), 6.95 (2 H, 'd' [ddd] and 't' [ddd], aromatic H), 6.41 (1 H, 2 x d, *J* 6.2 and 2.5, CH), 4.66 (1 H, dd, *J* 11.6 and 6.2, CH_AH_B) 4.56 (1 H, dd, *J* 11.6 and 2.5, CH_AH_B), 2.47-2.33 (1 H, m, CH_2), 2.09-1.82 (2 H, m, CH_2), 1.73-1.63 (1 H, m, CH_2), 1.09 (3 H, s, CH_3), 0.93 (3 H, s, CH_3), 0.90 (3 H, s, CH_3).

Found: *m/z* 316 (M^+, 4%), 139 (27), 119 (74), 118 (100), 109 (39), 91 (55), 90 (58), 89 (55), 83 (47), 67 (28), 63 (43), 55 (52), 43 (33), 41 (82), 39 (62).

Found: C, 68.49; H, 6.27.

$C_{18}H_{20}O_5$ requires C, 68.30; H, 6.37%.

(3*R*)-(-)-3-Hydroxydihydrobenzofuran



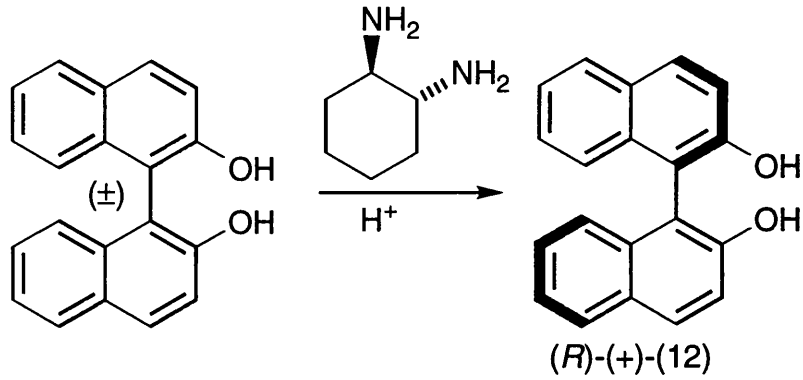
(*R*,*S*)-(11) (-)-(3*R*)-(10)

D. R. Boyd, N. D. Sharma, R. B. Boyle, J. F. Malone, J. Chima, and H. Dalton, *Tetrahedron: Asymmetry*, 1993, **4**, 1307.

Diastereomer (-)-(11) (500 mg, 1.58 mmol) was hydrolysed by heating under reflux for 3 h in aqueous THF (2 cm^3 H_2O in 40 cm^3 THF) containing potassium hydroxide (380 mg, 6.77 mmol). On cooling, the volatiles were removed under reduced pressure. The residue was acidified with HCl solution (1 mol dm^{-3}; 50 cm^3) and extracted with ether (2 x 25 cm^3). The combined extracts were washed with water until neutral, dried and the solvent removed *in vacuo*. Chromatography, eluting with 50:50 ether/hexane yielded the pure product (3*R*)-(10) as an oil which subsequently solidified (67 mg, 31%); m.p. 54 °C, [lit.: 57-58 °C]; $[\alpha]_D$ -59.1 (*c* 0.63 in $CHCl_3$), [lit.: $[\alpha]_D$ -67 (*c* 0.63 in $CHCl_3$). The enantiopurity was determined by gas chromatography to be 88% e.e. [retention times of 28.4 and 28.7 minutes were recorded for the two enantiomers].

The spectroscopic data were identical to that of the racemic compound.

(*R*)-(+)-1,1'-Bi-2-naphthol



M. Kawashima and A. Hirayama, *Chem. Lett.*, 1990, 2299.

Racemic 1,1'-bi-2-naphthol (12.55 g, 43.8 mmol) was suspended in benzene (200 cm^3) and heated to 60 °C. A warm solution of (1*R*,2*R*)-(-)-diaminocyclohexane (5.00 g, 43.8 mmol) in benzene (100 cm^3) was prepared and mixed with the binaphthol slurry. The combined solutions clarified, and on cooling, a micro-crystalline clathrate precipitated [1:1:1 binaphthol:diamine:benzene, by ^1H NMR]. Two further crystallisations yielded the pure diastereomeric salt (8.70 g).

The prepared diastereomer was slurried in methanol (60 cm^3) and cooled to 0 °C. Chilled HCl solution (1 mol dm^{-3}; 40 cm^3) was added, the solution clarified, and the resolved binaphthol precipitated. Dilution with water (20 cm^3) induced further crystallisation (4.59 g, 37% [73%]); m.p. 208-209 °C, [literature: m.p. 208-210 °C]; $[\alpha]_D$ +34.5 (*c* 1.00 in THF), [literature: $[\alpha]_D$ +34.5 (*c* 1.00 in THF)].*

* There have been many differing literature values reported, ranging from ~ +33 to +36. This is probably because the optical rotation is influenced by the water content of the THF solution.

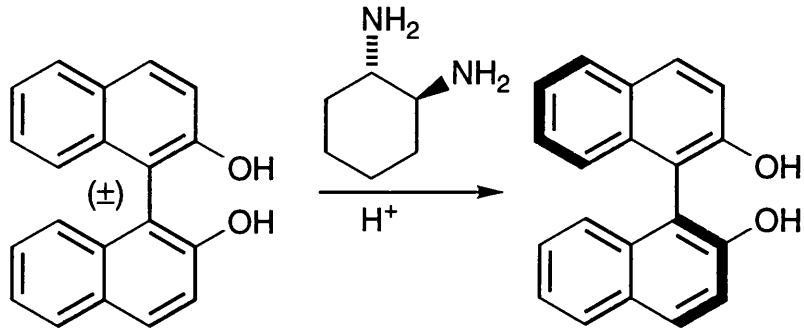
δ_H NMR ($CDCl_3$) 7.92 (2 H, d, *J* 9.0, aromatic H), 7.86 (2 H, dd, *J* 6.8 and 1.1, aromatic H), 7.39-7.10 (8 H, m, aromatic H), 5.02 (2 H, br s, OH).

Found: *m/z* 286 (M^+, 100%), 257 (27), 239 (25).

Found: C, 83.94; H, 4.98.

$C_{20}H_{14}O_2$ requires C, 83.90; H, 4.93%.

(*S*)-(-)-1,1'-Bi-2-naphthol



(*S*)-(-)-(12)

M. Kawashima and A. Hirayama, *Chem. Lett.*, 1990, 2299.

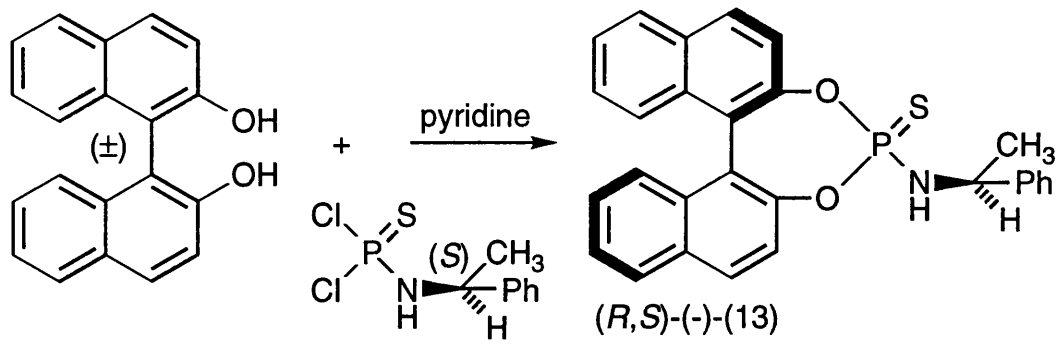
The scale and procedure described for the isolation of the (*R*) enantiomer was repeated for the (*S*) isomer using (1*S*,2*S*)-(+)-diaminocyclohexane. Yield: (4.81 g, 38% [76%]); m.p. 206-208 °C, [literature: m.p. 208-210 °C]; $[\alpha]_D$ -34.5 (*c* 1.00 in THF), [literature: $[\alpha]_D$ -34.5 (*c* 1.00 in THF).

The ^1H NMR spectrum and other data were identical to that obtained for the (*R*) isomer.

Found: *m/z* 286 (M^+, 100%), 239 (30).

Found:	C, 83.89; H, 4.85.
$C_{20}H_{14}O_2$ requires	C, 83.90; H, 4.93%.

(*R*)-1,1'-Binaphthyl-2,2'-diyl-*N*-((*S*)-α-methylbenzyl)-thiophosphoroamidate



(*R,S*)-(-)-(13)

D. Fabbri, G. Delogu, and O. De Lucchi, *J. Org. Chem.*, 1993, **58**, 1748.

(*S*)-α-Methylbenzylamine (19.95 g, 164.6 mmol), dissolved in pyridine (120 cm^3) was added dropwise under argon to a chilled solution of thiophosphoryl chloride (27.95 g, 165.0 mmol) in pyridine (180 cm^3). The solution was stirred at 0 °C for 2 h and then allowed to warm to room temperature. Racemic 1,1'-bi-2-naphthol (44.88 g, 156.7 mmol) was added and the mixture heated under reflux for 6 h. On cooling, the solution was made slightly acidic using H_2SO_4 solution (10%) and a large volume of water (3000 cm^3) was added. The aqueous solution was extracted with DCM (3 x 500 cm^3) and the combined extracts were washed with brine. The solution was dried and then concentrated under reduced pressure. The product was purified by chromatography, eluting with $CHCl_3$, to yield the two diastereomers (51.27 g, 70%) as a white solid.

The diastereomeric mixture was dissolved in $CHCl_3$ (750 cm^3) and absolute ethanol (350 cm^3) was added. The volume of solvent was reduced *in vacuo* to ~250 cm^3. The mixture was chilled and the insoluble diastereomer collected by filtration (16.52 g, 32%); $[\alpha]_D$ -356 (*c* 1.7 in $CHCl_3$), [literature: $[\alpha]_D$ -309 (*c* 1.7 in $CHCl_3$)].

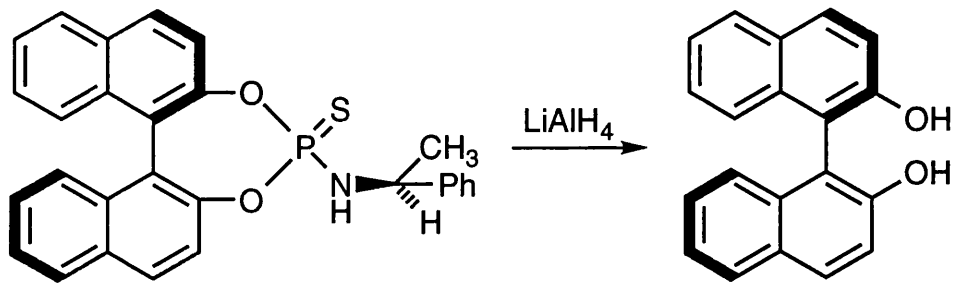
δ_H NMR ($CDCl_3$) 8.02 (1 H, d, *J* 8.8, aromatic H), 7.92 (2 H, m, aromatic H), 7.79 (1 H, d, *J* 8.8, aromatic H), 7.58 (1 H, dd, *J* 8.8 [*ortho*] and 1.2 [*meta*], aromatic H), 7.51-7.29 (11 H, m, aromatic H), 6.66 (1 H, dd, *J* 8.8 [*ortho*] and 1.0 [*meta*], aromatic H), 4.83 (1 H, m, CH), 3.52 (1 H, dd, NH), 1.52 (3 H, d, *J* 7.0, CH_3).

Found: *m/z* 467 (M^+, 41%), 434 (53), 348 (40), 315 (100), 284 (27), 268 (54), 239 (30), 120 (93), 105 (39).

Found: C, 71.87; H, 4.62; N, 2.89.

$C_{28}H_{22}NO_2PS$ requires C, 71.93; H, 4.74; N, 3.00%.

(*R*)-(+)-1,1'-Bi-2-naphthol



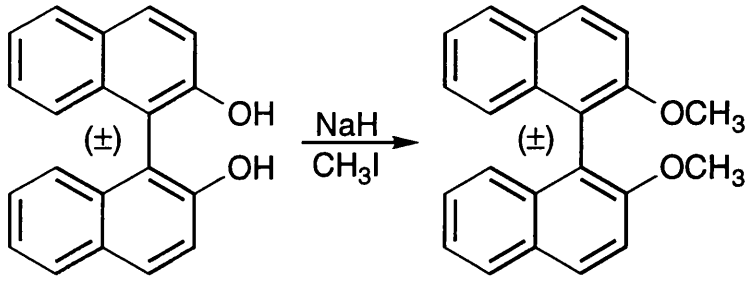
(*R,S*)-(-)-(13) (*R*)-(+)-(12)

D. Fabbri, G. Delogu, and O. De Lucchi, *J. Org. Chem.*, 1993, **58**, 1748.

A solution of (*R,S*)-(13) (16.05 g, 34.3 mmol) in dry THF was treated with $LiAlH_4$ (2.96 g, 78.0 mmol) under argon. The solution was chilled and the excess $LiAlH_4$ destroyed by the dropwise addition of water. The solvent was removed under reduced pressure, and the residue was acidified with dilute HCl sol. (1 mol dm^{-3}; 250 cm^3). The aqueous solution was extracted with $CHCl_3$ (2 x 75 cm^3) and the combined extracts were washed with water. The solution was dried and concentrated *in vacuo*. The product was purified by chromatography, eluting with $CHCl_3$, to yield binaphthol (*R*)-(12) as a crystalline solid (7.50 g, 76%); $[\alpha]_D$ +35.4 (*c* 1.00 in THF).

The ^1H NMR spectrum and other data were identical to that obtained from the sample prepared by the previous method.

(±)-2,2'-Dimethoxy-1,1'-binaphthalene



(14)

1,1'-Bi-2-naphthol (5.72 g, 20 mmol) was dissolved in dry THF (100 cm^3) under an atmosphere of argon. The solution was cooled to 0 °C and treated batchwise with hexane-washed NaH (1.76 g, 60%, 44 mmol). Once H_2 evolution had ceased, a tenfold excess of CH_3I (56.8 g, 400 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue shaken in DCM (100 cm^3) and water (100 cm^3). The layers were separated and the aqueous layer extracted with DCM (20 cm^3). The combined extracts were washed with water until neutral, dried, and the solvent removed *in vacuo*. Chromatography of the residue on silica gel using DCM-hexane (50:50) afforded *compound* (14) (4.53 g, 72%) as a white crystalline solid (EtOAc); m.p. 197-198 °C, [lit.: m.p. 198-202 °C].*

* G. Gottarelli and G. P. Spada, *J. Org. Chem.*, 1991, **56**, 2096.

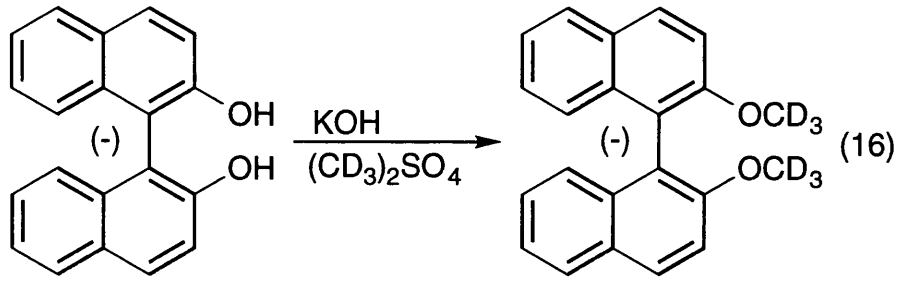
δ_H NMR ($CDCl_3$) 7.96 (2 H, d, *J* 9.0, aromatic H), 7.85 (2 H, 'd', aromatic H), 7.44 (2 H, d, *J* 9.0, aromatic H), 7.31 (2 H, ddd, aromatic H), 7.18 (2 H, ddd, aromatic H), 7.09 (2 H, 'd', aromatic H), 3.74 (6 H, s, OCH_3).

Found: *m/z* 314 (M^+, 100%), 268 (72), 239 (44), 226 (25), 119 (30), 32 (26).

Found: C, 84.07; H, 5.68.

$C_{22}H_{18}O_2$ requires C, 84.05; H, 5.77%.

(-)-2,2'-Dimethoxy(d_6)-1,1'-binaphthalene



(16)

+ monoalkylated product, (15)

(-)-1,1'-Bi-2-naphthol (1.00 g, 3.5 mmol) was dissolved in dry THF (45 cm^3) and methanol (5 cm^3) under an atmosphere of argon. The solution was treated with KOH (1.18 g, 21.0 mmol) and heated under reflux for 3 h. Once cooled, the prepared dianion was reacted with dimethyl-d_6 sulfate (0.95 g, 7 mmol) at room temperature. The solvent was removed under reduced pressure and the crude product was extracted with DCM (50 cm^3). The organic solution was washed with water until neutral, dried, and the solvent removed *in vacuo*. Chromatography, eluting with 30% hexane/$CHCl_3$, led to the isolation of unreacted dihydroxy (~300 mg), monoalkylated (340 mg, 32%) and dialkylated (310 mg, 28%) binaphthalene.

(-)-2-Hydroxy-2'-methoxy(d_3)-1,1'-binaphthalene (15):

δ_H NMR ($CDCl_3$) 8.06 (1 H, d, *J* 9.0, aromatic H), 7.88 (3 H, 't', aromatic H), 7.48 (1 H, d, *J* 9.0, aromatic H), 7.41-7.15 (6 H, m, aromatic H), 7.04 (1 H, 'd', aromatic H), 4.92 (1 H, s, OH).

Found: *m/z* 303 (M^+, 100%), 304 (26), 119 (25).

Found: M^+, 303.1329. $C_{21}H_{13}D_3O_2$ requires *M* 303.1338.

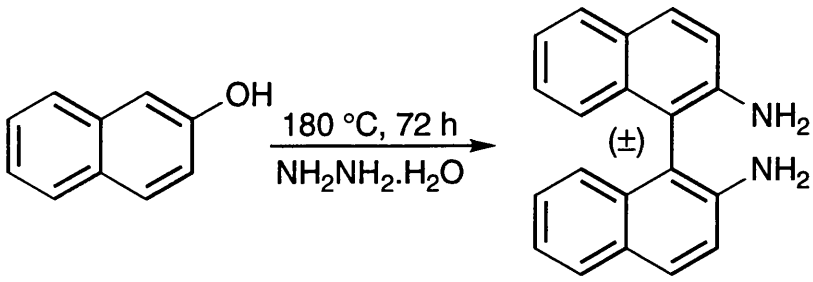
(-)-2,2'-Dimethoxy(d_6)-1,1'-binaphthalene (16):

δ_H NMR ($CDCl_3$) the NMR spectrum is similar to the non-deuterated compound (14) but there is of course no signal for OCD_3.

Found: *m/z* 320 (M^+, 100%), 268 (54), 119 (25).

Found: M^+, 320.1674. $C_{22}H_{12}D_6O_2$ requires *M* 320.1684.

(±)-2,2'-Diamino-1,1'-binaphthalene



(17)

K. J. Brown, M. S. Berry, and J. R. Murdoch, *J. Org. Chem.*, 1985, **50**, 4345.

β-Naphthol (80.04 g, 0.555 mol), and hydrazine monohydrate (18.06 g, 0.361 mol) were mixed in a Carius tube which was subsequently evacuated and sealed. The reaction was conducted at 180 °C and this temperature was maintained for 3 days. The crude product was extracted with $CHCl_3$ (1000 cm^3), washed with water (200 cm^3), dried, and the solvent removed *in vacuo*. The residue was subjected to chromatography using 2% MeOH/$CHCl_3$ as eluent which gave an off-coloured oil. Trituration with chilled ethanol and crystallisation of the solid obtained (ethanol), yielded white needles (35.37 g, 45%); m.p. 193-194 °C, [lit.: m.p. 193.2-194.5 °C].

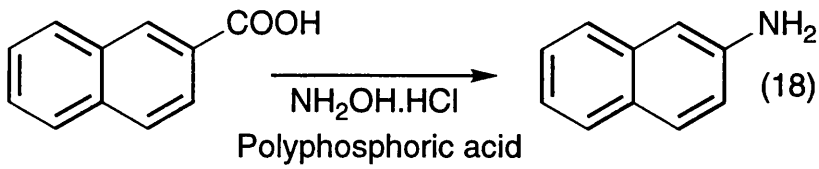
δ_H NMR ($CDCl_3$) 7.82 (4 H, m, aromatic H), 7.30-7.07 (8 H, m, aromatic H), 3.68 (4 H, br s, NH_2).

Found: *m/z* 284 (M^+, 100%), 267 (31).

Found: C, 84.48; H, 5.67; N, 9.85.

$C_{20}H_{16}N_2$ requires C, 84.48; H, 5.79; N, 9.81%.

β-Naphthylamine



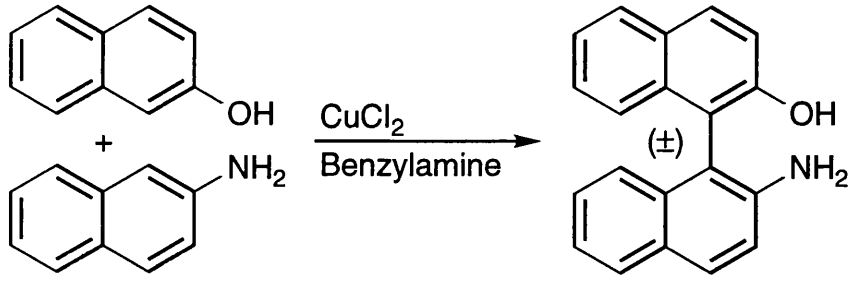
(18)

H. R. Snyder, C. T. Elston, and D. B. Kellom,

J. Am. Chem. Soc., 1953, **75**, 2014.

Hydroxylamine hydrochloride (6.80 g, 97.86 mmol) and β-naphthoic acid (16.00 g, 92.93 mmol) were mixed with polyphosphoric acid (~200 g) and heated slowly up to 160 °C over 1.5 h. Mechanical stirring was used to 'whip out' the CO_2 produced and reduce frothing. The cooled mixture was poured onto ice and filtered through Celite to remove insoluble by-products. The solution was neutralised with chilled aqueous KOH solution (10 mol dm^{-3}) and the precipitated brown product (7.59 g, 57%) was filtered and washed; m.p. 109-110 °C, [lit.: m.p. 107-109 °C]. The material was used without further purification.

(±)-2-Amino-2'-hydroxy-1,1'-binaphthalene



(19)

M. Smrčina, M. Lorenc, V. Hanuš, and P. Kočovský, *Synlett*, 1991, 231.

A solution of $CuCl_2.2H_2O$ (22.59 g, 132.51 mmol) in methanol (400 cm^3) through which argon was passed, was treated with benzylamine (56.80 g, 530.05 mmol) dissolved in methanol (400 cm^3). After a short delay, a solution of β-naphthylamine (7.59 g, 53.01 mmol) and β-naphthol (7.64 g, 52.99 mmol) in methanol (200 cm^3) was added. The reaction mixture was then stirred overnight at room temperature under an argon atmosphere. A brown solid was filtered, but found to contain no product. The filtrate was evaporated under reduced pressure and the residue basified with ammonia solution. This was extracted with EtOAc (2 x 200 cm^3), washed with water (50 cm^3), dried, and the solvent removed *in vacuo*. Chromatography, eluting with $CHCl_3$ yielded a very small quantity (~100 mg) of the pure 'aminol' (19); m.p. 241 °C, [lit.: m.p. 239-241 °C].

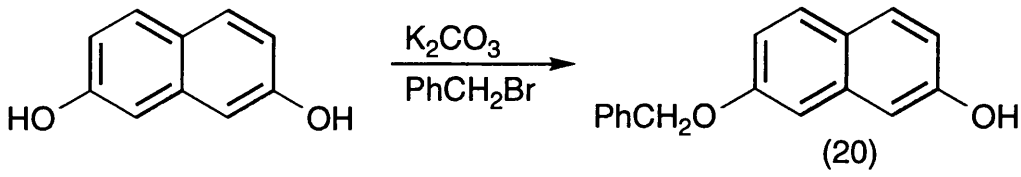
δ_H NMR ($CDCl_3$) 7.95-7.78 (4 H, m, aromatic H), 7.40-7.13 (7 H, m, aromatic H), 7.06 (1 H, m, aromatic H), 5.13 (1 H, br s, OH), 1.60 (2 H, br s NH_2).

Found: *m/z* 285 (M^+, 100%), 268 (26).

Found: C, 84.22; H, 5.38; N, 4.83.

$C_{20}H_{15}NO$ requires C, 84.18; H, 5.30; N, 4.91%.

2-Benzyloxy-7-hydroxynaphthalene



(20)

T. Horiuchi, T. Ohta, M. Stephan, and H. Takaya,

Tetrahedron: Asymmetry, 1994, **5**, 325.

2,7-Dihydroxynaphthalene (24.02 g, 150 mmol) in dry DMF (280 cm^3) was treated with solid anhydrous K_2CO_3 (15.54 g, 112.6 mmol). Benzyl bromide (26.94 g, 157.6 mmol) was dissolved in dry DMF (120 cm^3) and added dropwise. The mixture was warmed to 35 °C and stirred overnight. The solvent was removed under reduced pressure, the residue was acidified with HCl solution (1 mol dm^{-3}; 1200 cm^3) and extracted with EtOAc (2 x 400 cm^3). The combined extracts were washed with brine (200 cm^3), dried and the solvent removed *in vacuo*. Trituration with chilled $CHCl_3$ facilitated the crystallisation of the disubstituted by-product. This was removed by filtration and discarded. The mother liquor was purified on SiO_2 eluting with 50:50 EtOAc/hexane, which was repeated using 30:70 EtOAc/hexane to yield a viscous colourless oil (9.64 g, 26%).

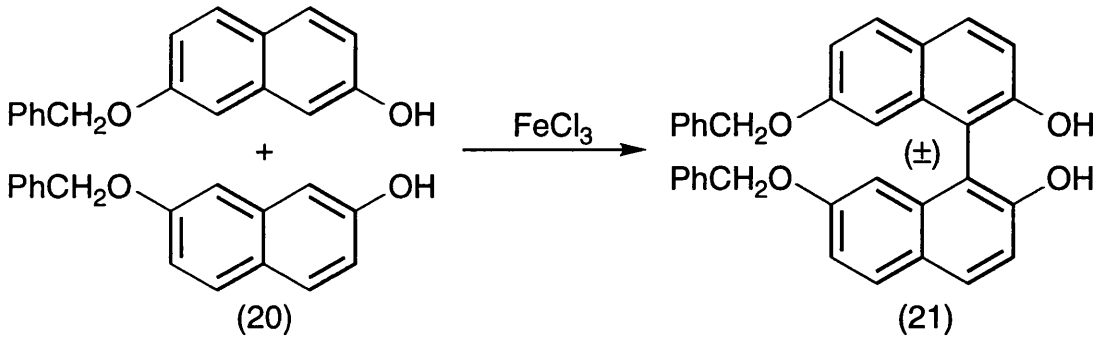
δ_H NMR ($CDCl_3$) 8.85 (1 H, v br s, O<u>H</u>), 7.64 (1 H, d, *J* 3.5, aromatic <u>H</u>), 7.59 (1 H, d, *J* 3.5, aromatic <u>H</u>), 7.40 (5 H, m, aromatic <u>H</u>), 7.02 (4 H, m, aromatic <u>H</u>), 5.13 (2 H, s, C<u>H_2</u>).

Found: *m/z* 250 (M^+, 29%), 91 (100).

Found: C, 81.32; H, 5.50.

$C_{17}H_{14}O_2$ requires C, 81.58; H, 5.64%.

(±)-7,7'-Dibenzyloxy-bis(2,2'-hydroxy)-1,1'-binaphthalene



(20) (21)

T. Horiuchi, T. Ohta, M. Stephan, and H. Takaya,

Tetrahedron: Asymmetry, 1994, **5**, 325.

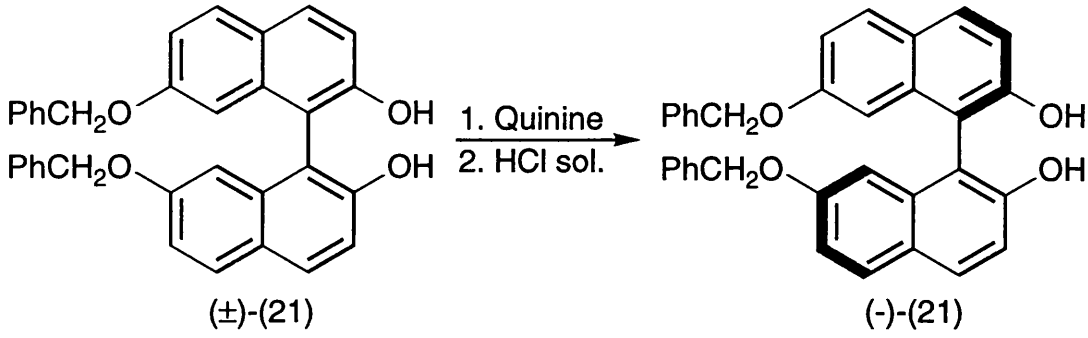
The prepared compound (20) (7.80 g, 31.2 mmol) was oxidatively dimerised using ferric chloride hexahydrate (25.27 g, 93.5 mmol). The reagents were dissolved in acetonitrile (100 cm^3) and water (200 cm^3) and heated under reflux for 1 h. The solvents were removed under reduced pressure and the residue partitioned between EtOAc (600cm^3) and water (200cm^3). The organic layer was separated and washed with water (2 x 200cm^3), dried and the solvent removed *in vacuo*. Purification by chromatography, eluting with 30:70 EtOAc/hexane, yielded the *title compound* (3.70 g, 48%) as a colourless oil.

δ_H NMR ($CDCl_3$) 7.83 (2 H, d, *J* 8.9, aromatic H), 7.76 (2 H, d, *J* 8.9, aromatic H), 7.23-7.05 (14 H, m, aromatic H), 6.47 (2 H, d, *J* 2.4, aromatic H), 4.77 (2 H, s, OH), 4.71 (2 H, d, *J* 11.8, CH_AH_B), 4.70 (2 H, d, *J* 11.8, CH_AH_B).

Found: *m/z* 498 (M^+, 18.7%), 91 (100).

Found: M^+, 498.1807. $C_{34}H_{26}O_4$ requires *M* 498.1831.

(*R*)-(-)-7,7'-Dibenzyloxy-2,2'-dihydroxy-1,1'-binaphthalene



(±)-(21) (-)-(21)

T. Horiuchi, T. Ohta, M. Stephan, and H. Takaya,

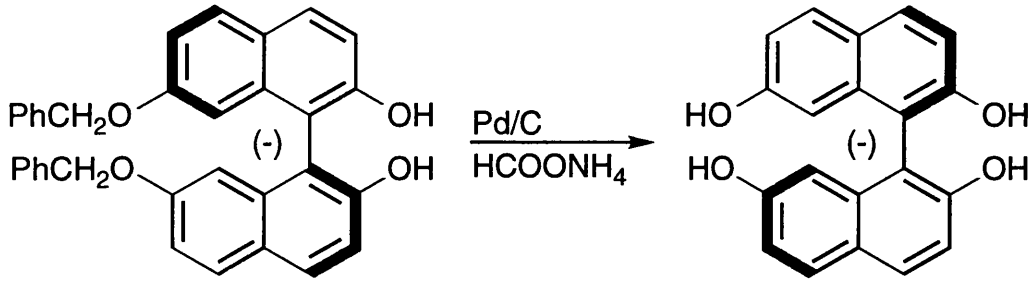
Tetrahedron: Asymmetry, 1994, **5**, 325.

Binaphthalene derivative (±)-(21) (3.60 g, 75.9 mmol) dissolved in ethanol (15 cm^3) was mixed with a prepared solution of quinine (2.467 g, 75.9 mmol) in ethanol (15 cm^3). This solution was allowed to stand at room temperature for 48 h. The clathrate precipitated and was collected by filtration. A further two crystallisations from ethanol yielded the pure diastereomer as a white solid (0.93 g, 26% [52%]); m.p. 190-191 °C, [lit.: 186-187 °C]; $[\alpha]_D$ -160.4 (*c* 0.52 in $CHCl_3$), [lit.: $[\alpha]_D$ -163 (*c* 0.52 in $CHCl_3$)].

The pure diastereomeric intermediate was slurried in EtOAc (100 cm^3) and shaken with HCl solution (1 mol dm^{-3}; 100 cm^3). The organic solution was washed with water (30 cm^3), dried and the solvent removed under reduced pressure to give a near quantitative yield of an off-coloured oil (0.55 g).

The spectroscopic data were identical to that of the racemic compound.

(*R*)-(-)-2,2',7,7'-Tetrahydroxy-1,1'-binaphthalene



(21) (22)

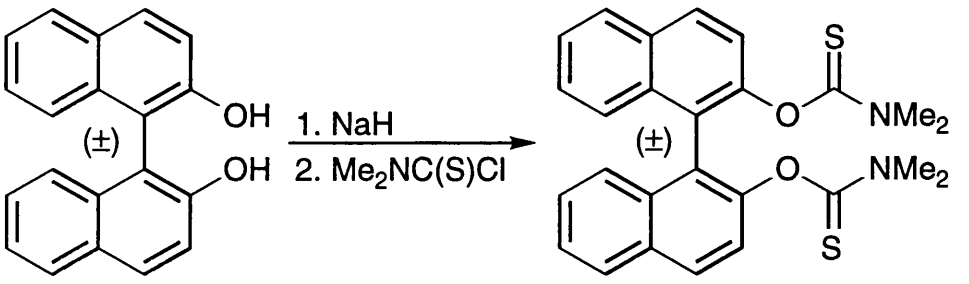
Hydrogenation of compound (-)-(21) (0.55 g, 1.1 mmol) was achieved using $HCOONH_4$ (0.69 g, 11 mmol) and Pd/C (~1 g) in methanol (20 cm^3). The mixture was heated under reflux for 1 h, cooled and the unwanted suspension removed by filtration. The filtrate was concentrated under reduced pressure and the residue purified by chromatography, eluting with $CHCl_3$. Trituration in cyclohexane yielded the *title compound* (0.30 g, 85 %) as a brown amorphous solid; m.p. indiscernible; $[\alpha]_D$ -56.9 (*c* 1.00 in THF).

δ_H NMR ($CDCl_3$) 8.02 (2 H, br s, O<u>H</u>), 7.76 (2 H, d, *J* 8.8, aromatic <u>H</u>), 7.70 (2 H, d, *J* 8.7, aromatic <u>H</u>), 7.12 (2 H, d, *J* 8.8, aromatic <u>H</u>), 6.96 (2 H, dd, *J* 8.7 and 2.4, aromatic <u>H</u>), 6.39 (2 H, br s, O<u>H</u>), 6.37 (2 H, d, *J* 2.4, aromatic <u>H</u>).

Found: *m/z* 318 (M^+, 100%), 300 (41), 113 (25).

Found: M^+, 318.0886. $C_{20}H_{14}O_4$ requires *M* 318.0892.

[1,1'-Binaphthalene]-2,2'-diyl-O,O-bis(*N,N*-dimethylthiocarbamate)



(12) (23)

F. Di Furia, G. Licini, G. Modena, and G. Valle,

Bull. Soc. Chim. Fr., 1990, **127**, 734.

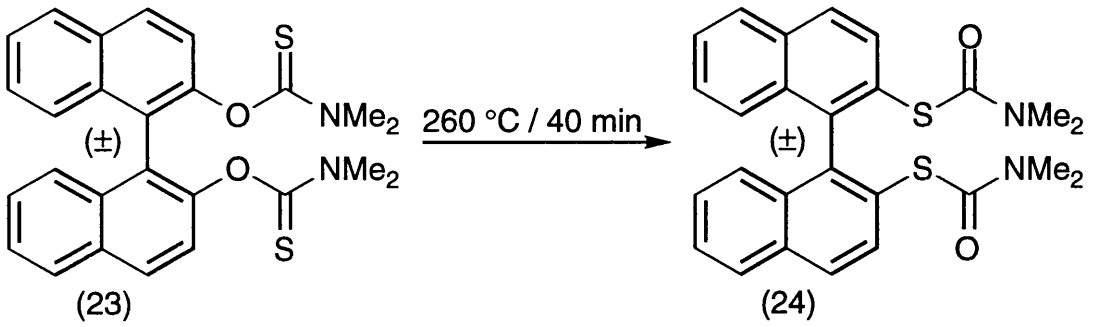
A solution of (±)-1,1'-bi-2-naphthol (19.70 g, 68.8 mmol) in dry DMF (300 cm^3), at 0 °C and under argon, was treated with hexane-washed NaH (6.05 g [60% oil dispersion], 151.3 mmol) over a period of 1 h. Stirring was continued for 2 h, then *N,N*-dimethylthiocarbamoyl chloride (18.69 g, 151.2 mmol) was added and the solution warmed to 85 °C for 1 h. On cooling, the mixture was poured into KOH solution (0.2 mol dm^{-3}; 3000 cm^3) whereupon a white solid precipitated. This was collected by filtration and dissolved in DCM (1000 cm^3). The organic solution was washed with KOH solution (0.1 mol dm^{-3}, 200 cm^3), then water (2 x 200 cm^3), dried, and the solvent removed *in vacuo*. *Compound* (23) was obtained from toluene/heptane as dense white crystals (21.75 g, 69%); m.p. 209-210 °C [literature: m.p. 208-209.5 °C]. Several batches were similarly prepared.

δ_H NMR (360 MHz; $CDCl_3$) 7.97 (2 H, d, *J* 8.9, aromatic H), 7.90 (2 H, dd, *J* 8.5 [*ortho*], 1.3 [*meta*], aromatic H), 7.62 (2 H, d, *J* 8.9 [*ortho*], aromatic H), 7.46 (2 H, d, *J* 6.9 [*ortho*], aromatic H), 7.44 (2 H, ddd, *J* 1.3 [*meta*], {*ortho's* indiscernible}, aromatic H), 7.30 (2 H, ddd, *J* 8.5 [*ortho*], 6.9 [*ortho*] and 1.3 [*meta*], aromatic H), 3.08 (6 H, s, CH_3), 2.52 (6 H, s, CH_3).

Found: *m/z* 460 (M^+, 3.5%), 284 (27), 88 (100), 72 (48).

Found:	C, 67.89; H, 5.08; N, 5.94.
$C_{26}H_{24}N_2O_2S_2$ requires	C, 67.80; H, 5.25; N, 6.08%.

(±)-[1,1'-Binaphthalene]-2,2'-diyl-S,S-bis(*N,N*-dimethylcarbamate)



(23) (24)

M. S. Newman and H. A. Karnes, *J. Org. Chem.*, 1966, **31**, 3980.

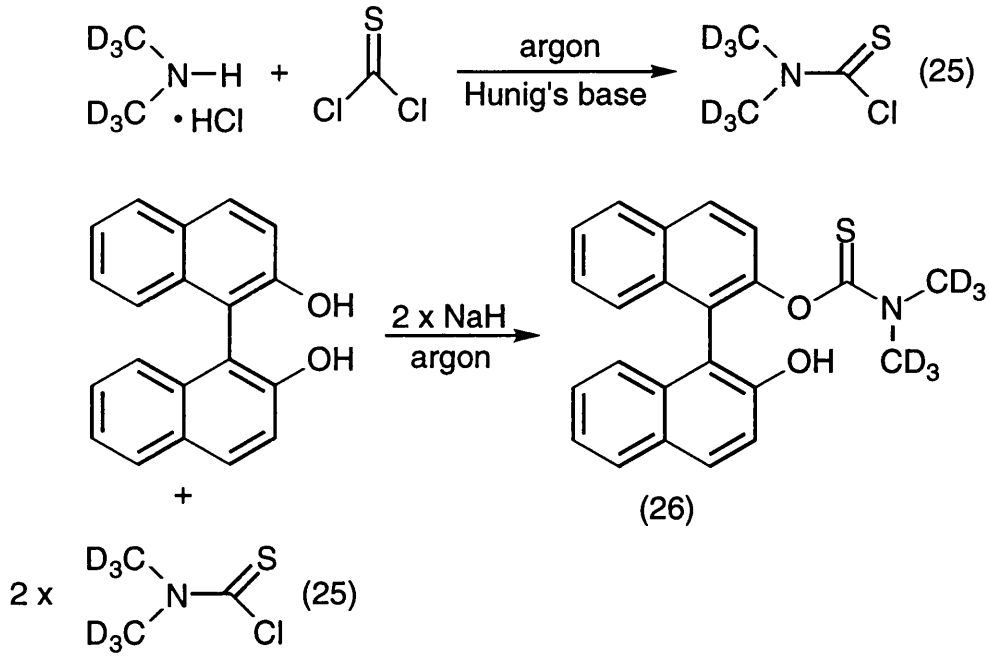
The prepared thioester (23) (20.53 g, 44.6 mmol) was placed in a thin-walled flask and immersed into a Wood's metal bath preheated to 260 °C for 40 min. The glass obtained was dissolved in $CHCl_3$, and purified by chromatography using $CHCl_3$ as eluent to yield the *title compound* (15.16 g, 74%) as a white solid; m.p. 247 °C [literature: m.p. 247-249 °C].

δ_H NMR ($CDCl_3$) 7.97 (2 H, d, *J* 8.6 [*ortho*], aromatic H), 7.90 (2 H, d *J* 8.1 [*ortho*], aromatic H), 7.79 (2 H, d, *J* 8.6 [*ortho*], aromatic H), 7.45 (2 H, m, aromatic H), 7.22 (2 H, m, aromatic H), 7.08 (2 H, d, *J* 8.1, aromatic H).

Found: *m/z* 460 (M^+, 3.4%), 284 (33), 72 (100).

Found:	C, 67.52; H, 5.23; N, 5.91.
$C_{26}H_{24}N_2O_2S_2$ requires	C, 67.80; H, 5.25; N, 6.08%.

Deuterium labelling experiment



d_6-Dimethylamine (0.90 g, 10.3 mmol) was dissolved in dry DCM (20 cm^3) and diisopropylethylamine (3.98 g, 30.8 mmol) was added. This solution was chilled and added dropwise under argon to a solution of thiophosgene (1.18 g, 10.3 mmol) in DCM (10 cm^3) at 0 °C. The mixture was allowed to attain room temperature, and the solvent was removed under reduced pressure. The residue was redissolved in dry DMF (10 cm^3).

A solution of binaphthol (1.47 g, 5.15 mmol) in dry DMF was treated with sodium hydride (0.76 g, 12.3 mmol) under argon. The previously prepared d_6-labelled solution was added, and an analogous procedure to that above (page 130) was followed. Chromatography (50:50

$CHCl_3$/Hexane) yielded the (unexpected) monosubstituted *compound* (25) as a solid (115 mg, 6%).

Thermolysis of a 50:50 mixture of compounds (23) and (26) resulted in products expected from an intramolecular process. No cross-deuterated products were isolated.

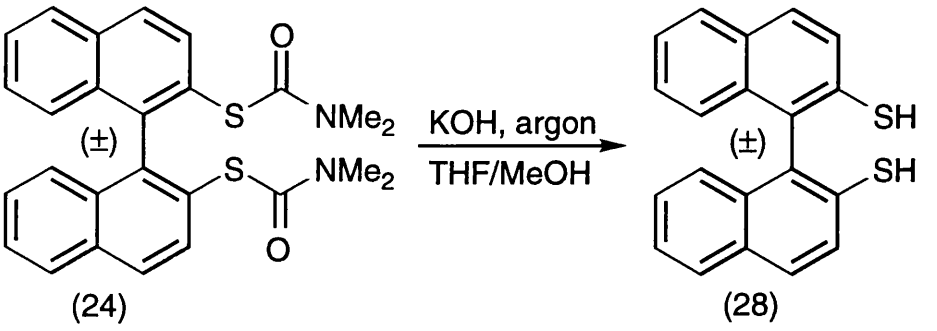
δ_H NMR ($CDCl_3$) 8.09-7.82 (4 H, m, aromatic H), 7.51-7.14 (8 H, m, aromatic H), 5.82 (1 H, s, OH).

Found: *m/z* 379 (M^+, 44%), 284 (27), 94 (100), 78 (75).

Found: C, 72.65; H, 3.21; N, 3.50.

$C_{23}H_{13}D_6NO_2S$ requires C, 72.79; H, 3.45; N, 3.69%.

(±)-[1,1'-Binaphthalene]-2,2'-dithiol



(24) (28)

F. Di Furia, G. Licini, G. Modena, and G. Valle,

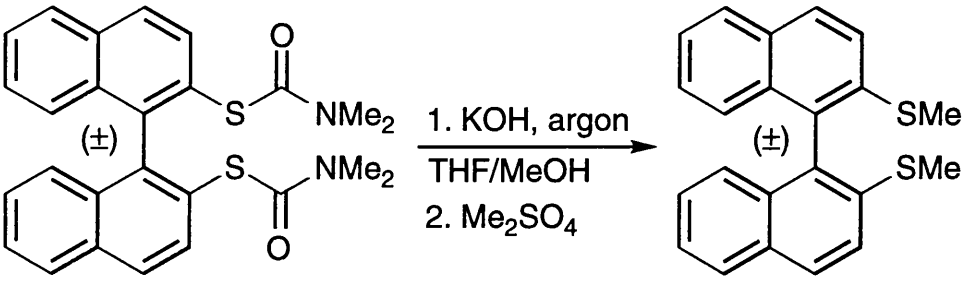
Bull. Soc. Chim. Fr., 1990, **127**, 734.

Thioamide (24) (15.16g, 32.9 mmol), dissolved in dry methanol (150 cm^3) and dry THF (150 cm^3), was treated with KOH pellets (14.77 g, 263.2 mmol) and heated under reflux for 5 h. The mixture was cooled, and the solvent removed under reduced pressure. The residue was acidified with HCl solution (1 mol dm^{-3}; 600 cm^3) and extracted with DCM (2 x 200 cm^3). The combined extracts were washed with water (2 x 50 cm^3), dried, and the solvent removed *in vacuo* to yield *compound* (28) (9.27 g, 88%) as a yellow oil. Trituration of some of the oil with ether precipitated a white solid; m.p. 151 °C, [lit.: 152-153 °C].

δ_H NMR ($CDCl_3$) 7.88 (4 H, 2 x d, aromatic H), 7.57 (2 H, d *J* 8.6 [*ortho*], aromatic H), 7.40 (2 H, ddd, aromatic H), 7.27 (2 H, ddd, aromatic H), 7.00 (2 H, d, aromatic H), 3.26 (2 H, s, SH).

Found: *m/z* 318 (M^+, 67%), 286 (25), 285 (100), 284 (75), 283 (65), 282 (82), 142 (26), 141 (67), 126 (26).

Bis(2,2'-methylthio)-1,1'-binaphthalene



(24) (29)

F. Di Furia, G. Licini, G. Modena, and G. Valle,

Bull. Soc. Chim. Fr., 1990, **127**, 734.

Thioamide (24) (32.06g, 69.6 mmol), dissolved in dry methanol (60 cm^3) and dry THF (540 cm^3) was treated with KOH pellets (14.77 g, 263.2 mmol) and heated under reflux for 8 h in an argon atmosphere. The mixture was cooled, and dimethyl sulfate (14.56 cm^3, 153.9 mmol) was added dropwise at room temperature. Stirring was continued overnight. The solvent was removed under reduced pressure, and the residue dissolved in DCM (800 cm^3). The organic solution was washed with NaOH solution (1 mol dm^{-3}; 2 x 100 cm^3), water (2 x 100 cm^3), dried, and the solvent removed *in vacuo*. Purification on SiO_2 eluting with 15% $CHCl_3$/hexane afforded the *title compound* (11.76 g, 49%) as a white solid; m.p. 189 °C [literature: m.p. 185-186 °C].

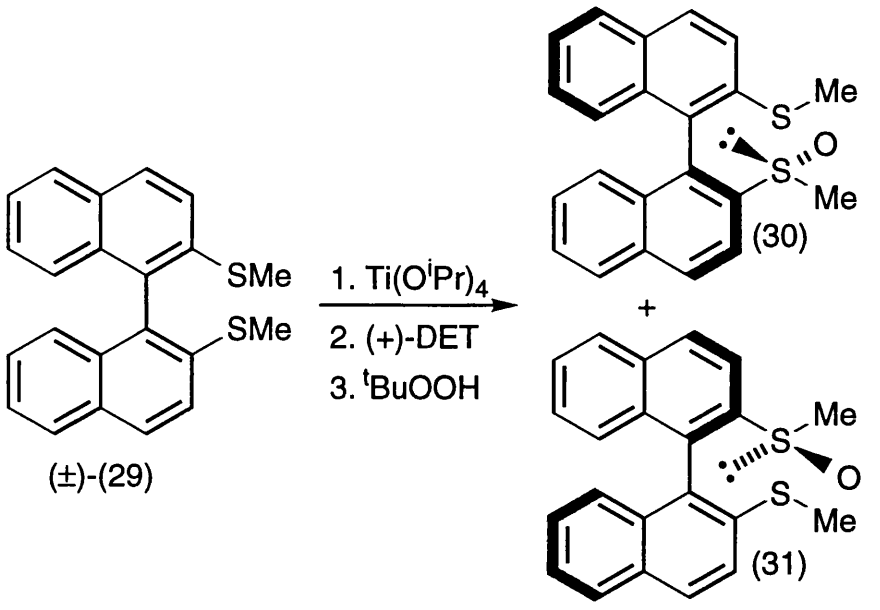
δ_H NMR ($CDCl_3$) 7.98 (2 H, 'd', *J* 8.7 [*ortho*], aromatic H), 7.88 (2 H, 'd' *J* 8.0 [*ortho*], aromatic H), 7.58 (2 H, d, *J* 8.8, aromatic H), 7.39 (2 H, m, aromatic H), 7.22 (2 H, m, aromatic H), 7.00 (2 H, 'd', *J* 8.0 [*ortho*], aromatic H), 2.42 (6 H, s, CH_3).

Found: *m/z* 346 (M^+, 40%), 299 (63), 284 (100), 283 (72), 282 (77), 141 (45).

Found: C, 75.41; H, 5.24.

$C_{22}H_{18}S_2$ requires C, 76.26; H, 5.24%.

(±)-2-(Methylsulfinyl)-2'-(methylthio)-1,1'-binaphthalene



F. Di Furia, G. Licini, G. Modena, and G. Valle,

Bull. Soc. Chim. Fr., 1990, **127**, 734.

Titanium (IV) isopropoxide (2.5 cm^3, 8.5 mmol) dissolved in dry DCM (40 cm^3) and (+)-diethyl tartrate (7.02 g, 34 mmol) dissolved in dry DCM (40 cm^3) were mixed at room temperature and stirred vigorously for 10 min. The homogeneous solution was cooled to -20 °C and treated with *t*-butyl hydroperoxide (2.4 cm^3, 80% in di-*t*-butylperoxide, 17 mmol). The mixture was stirred for 5 min before the thioether (29) (11.76 g 33.9 mmol) dissolved in dry DCM (150 cm^3) was added. Stirring was continued at -20 °C for 6 h and the mixture was placed in a freezer overnight. The reaction mixture was quenched with water and warmed to room temperature. It was then diluted with DCM (600 cm^3) and washed with aqueous sodium metabisulfite solution (10%; 100 cm^3), aqueous NaOH solution (5%; 100 cm^3) and finally brine until neutral. Chromatography

using $CHCl_3$ with an increasing proportion of methanol separated the products (~6 g) from recovered thioether (7.67 g, 65%).

Trituration of the crude product with EtOAc facilitated the isolation of the *S,S* '-dioxide by-products (1.80 g) [a mixture of four compounds, two of which are enantiomers]. The mother liquor was further purified by chromatography, eluting with 30% hexane/EtOAc to yield the diastereomers (30) and (31) as a foam (2.60 g, 61%). Attempts to separate the diastereomeric components by chromatography were unsuccessful.

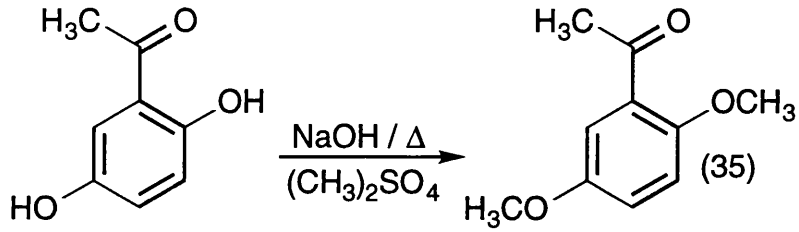
δ_H NMR ($CDCl_3$) Diastereomeric mixture: aromatic protons are too complex to assign: 8.33-6.78 (24 H, m, aromatic H).

δ_H NMR Diastereomer (30): 2.45 (3 H, s, CH_3SO), 2.27 (3 H, s, CH_3S).

δ_H NMR Diastereomer (31): 2.71 (3 H, s, CH_3SO), 2.43 (3 H, s, CH_3S).

Found: *m/z* 362 (M^+, 1.5%), 299 (96), 284 (100), 283 (59), 282 (55), 141 (46).

2,5-Dimethoxyacetophenone



(35)

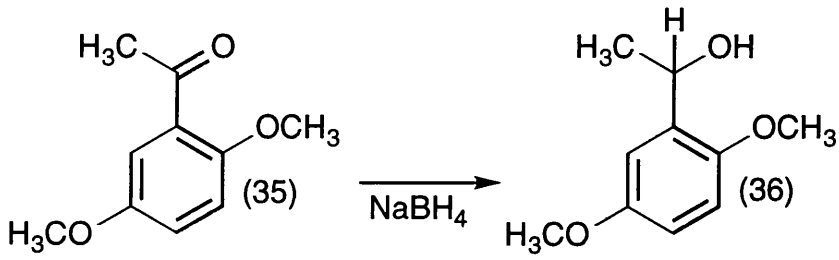
2,5-Dihydroxyacetophenone (4.56 g, 30 mmol) was dissolved in absolute ethanol (100 cm^3) and treated with solid NaOH (4.20 g, 105 mmol) at room temperature. Dimethyl sulfate (9.46 g, 75 mmol) was added in one batch and the mixture was heated under reflux for 3 hours. The solvent was removed under reduced pressure and the residue partitioned between EtOAc (200 cm^3) and water (50 cm^3). The organic layer was washed with water until neutral, dried and the solvent removed *in vacuo*. Purification on SiO_2, eluting with 50:50 ether/hexane, yielded the *title compound* (3.24 g, 60%) as a colourless oil and the monoalkylated by-product as a yellow solid (0.60 g, 12%).

δ_H NMR ($CDCl_3$) 7.29 (1 H, d, *J* 3.2 [*meta*], aromatic H), 7.04 (1 H, dd, *J* 9.0 [*ortho*], and 3.2 [*meta*], aromatic H), 6.91 (1 H, d, *J* 9.0, [*ortho*], aromatic H), 3.87 (3 H, s, OCH_3 [*meta*]), 3.79 (3 H, s, OCH_3 [*ortho*]), 2.62 (3 H, s, $COCH_3$).

Found: *m/z* 180 (M^+, 55%), 165 (100), 107 (26).

Found: M^+, 180.0783. $C_{10}H_{12}O_3$ requires *M* 180.0787.

(±)-1-(2',5'-Dimethoxyphenyl)-1-ethanol



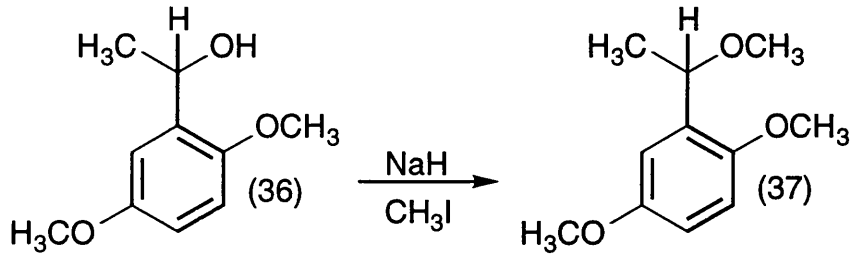
2,5-Dimethoxyacetophenone (3.20 g, 17.76 mmol) was taken up in methanol (50 cm^3) and treated with $NaBH_4$ (3.35 g, 88.55 mmol) batchwise at 0 °C over a period of 1 h. The solvent was removed under reduced pressure and the residue was suspended in aqueous HCl solution (1 mol dm^{-3}; 60 cm^3). The product was extracted with ether (2 x 20 cm^3), washed with brine (20 cm^3), dried, and the solvent removed *in vacuo*. Purification by chromatography eluting with 30% ether/hexane yielded the *title compound* (2.79 g, 86%) as a colourless viscous oil.

δ_H NMR (C_6D_6) 7.19 (1 H, d, *J* 3.1 [*meta*], aromatic H), 6.70 (1 H, dd, *J* 8.8 [*ortho*] and 3.1 [*meta*], aromatic H), 6.44 (1 H, d, *J* 8.8, [*ortho*], aromatic H), 5.15 (1 H, d of q, *J* 6.5 and 4.8, CH), 3.39 (3 H, s, OCH_3), 3.24 (3 H, s, OCH_3), 1.94 (1 H, d, *J* 4.8, OH), 1.49 (3 H, d, *J* 6.5, CH_3).

Found: *m/z* 182 (M^+, 72%), 167 (93), 139 (100), 137 (39), 124 (37), 43 (38).

Found: M^+, 182.0946. $C_{10}H_{14}O_3$ requires *M* 182.0949.

(±)-2,5-Dimethoxy-1-(α-methoxy-α-methyl)benzene



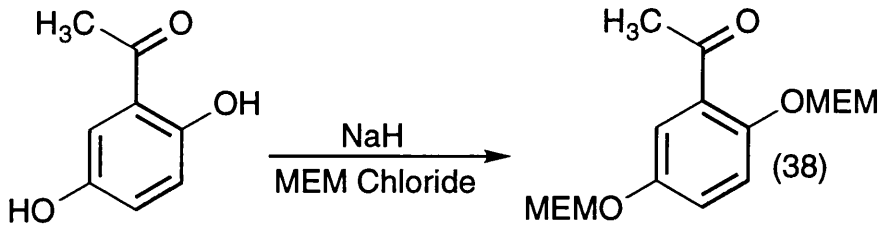
The prepared alcohol (36) (1.75 g, 9.6 mmol) was dissolved in dry THF (30 cm^3) and petrol-washed NaH (0.58 g, 60% oil dispersion, 14.4 mmol) was added batchwise at 0 °C under argon. After a short duration, the salt was treated with CH_3I (13.63 g, 96 mmol) and stirring was continued overnight at room temperature. The solvent was removed under reduced pressure and the residue was quenched with water. The product was extracted with ether (2 x 20 cm^3), washed with water (10 cm^3), dried, and the solvent removed *in vacuo*. Purification by chromatography, eluting with 30% ether/hexane, yielded *compound* (37) as an oil (1.52 g, 81%).

δ_H NMR (C_6D_6) 7.34 (1 H, d, *J* 3.1 [*meta*], aromatic H), 6.75 (1 H, dd, *J* 8.8 [*ortho*], and 3.1 [*meta*], aromatic H), 6.52 (1 H, d, *J* 8.8, aromatic H), 4.92 (1 H, q, *J* 6.4, CH), 3.41 (3 H, s, OCH_3), 3.34 (3 H, s, OCH_3), 3.18 (3 H, s, OCH_3), 1.53 (3 H, d, *J* 6.4, CH_3).

Found: *m/z* 196 (M^+, 28%), 181 (100), 165 (25), 151 (32), 45 (71).

Found: M^+, 196.1100. $C_{11}H_{16}O_3$ requires *M* 196.1101.

2,5-Bis(2-methoxyethoxymethoxy)acetophenone



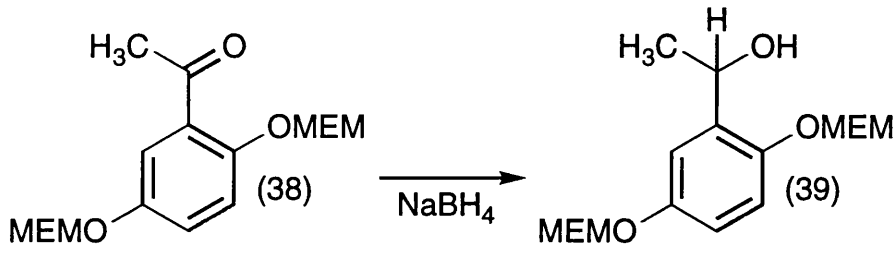
2,5-Dihydroxyacetophenone (7.00 g, 46 mmol) was slurried in dry THF (75 cm^3) and deprotonated with NaH (4.24 g, 60% oil dispersion, 106 mmol) at 0 °C under argon. An excess of MEM chloride (12.55 g, 101 mmol) dissolved in dry THF (25 cm^3) was added dropwise *via* syringe over 15 min. The mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was quenched with water (200 cm^3) and extracted with ether (2 x 40 cm^3), dried, and the solvent was removed *in vacuo*. Purification on SiO_2 [40->90% ether/hexane] gave the monosubstituted derivative (3.30 g) as a yellow oil, and the *title compound* (7.47 g, 49%) as a colourless oil.

ν_{max} (film)/cm^{-1} 2927 (CH_3 and CH_2), 1677 (C=O).

δ_H NMR ($CDCl_3$) 7.37 (1 H, m, aromatic H), 7.17 (2 H, m, aromatic H), 5.32 (2 H, s, OCH_2O), 5.22 (2 H, s, OCH_2O), 3.87-3.80 (4 H, m, OCH_2), 3.60-3.54 (4 H, m, CH_3OCH_2), 3.39 (3 H, s, OCH_3), 3.38 (3 H, s, OCH_3), 2.62 (3 H, s, CH_3).

Found: *m/z* 328 (M^+, 3.7%), 89 (70), 59 (100).

(±)-2,5-Bis(2-methoxyethoxymethoxy)phenethyl alcohol



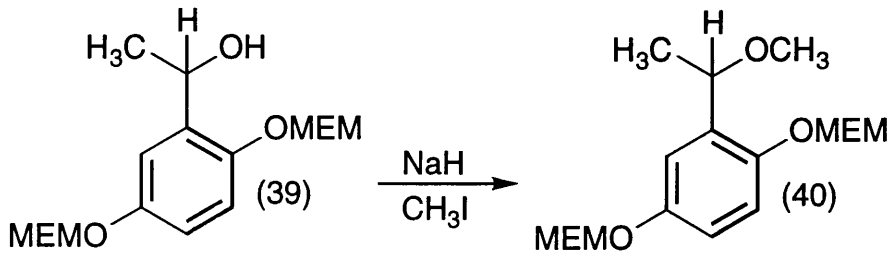
The protected compound (38) (3.94 g, 12 mmol) was taken up in methanol (40 cm^3) and treated with a large excess of $NaBH_4$ (2.27 g, 60 mmol) at 0 °C over 10 min. The solvent was removed under reduced pressure and the residue was neutralised with dilute HCl solution (1 mol dm^{-3}). Water was added (60 cm^3) and the product was extracted with ether (2 x 20 cm^3). The organic solution was dried and the solvent was removed *in vacuo*. Purification by chromatography eluting with 80% ether in hexane --> ether gave the *title compound* (3.21 g, 81%) as a colourless oil.

ν_{max} (film)/cm^{-1} 3440 (OH), 2928 (CH_3 and CH_2).

δ_H NMR ($CDCl_3$) 7.10 (1 H, d, *J* 2.9 [*meta*], aromatic H), 7.04 (1 H, d, *J* 8.9 [*ortho*], aromatic H), 6.90 (1 H, dd, *J* 8.9 [*ortho*] and 2.9 [*meta*], aromatic H), 5.26 (2 H, s, OCH_2O), 5.20 (2 H, s, OCH_2O), 5.11 (1 H, br q, *J* 6.5, CH), 3.84-3.80 (4 H, m, OCH_2), 3.58-3.54 (4 H, m, CH_3OCH_2), 3.372 (3 H, s, OCH_3), 3.368 (3 H, s, OCH_3), 2.83 (1 H, br s, OH), 1.47 (3 H, d, *J* 6.5, CH_3).

Found: *m/z* 330 (M^+, 1.2%), 89 (73), 59 (100).

(±)-2,5-Bis(2-methoxyethoxymethoxy)-α-methoxy-α-methyltoluene

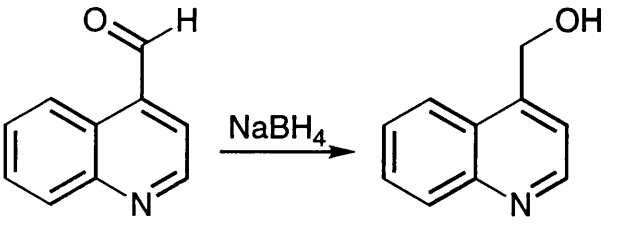


The protected hydroquinone (39) (3.21 g, 9.72 mmol) was dissolved in dry THF and deprotonated with petrol-washed NaH (0.51 g, 60% oil dispersion, 12.8 mmol). A large excess of CH_3I (14.2 g, 100 mmol) was added in one aliquot and the mixture was warmed to 40 °C for 2 h. The excess NaH was destroyed with aqueous ethanol and the volatiles were removed under reduced pressure. Purification on SiO_2 [60% EtOAc/hexane] yielded (40) as a colourless oil (2.57 g, 77%).

δ_H NMR ($CDCl_3$) 7.08 (1 H, d, *J* 3.0 [*meta*], aromatic H), 7.06 (1 H, d, *J* 8.9 [*ortho*], aromatic H), 6.91 (1 H, dd, *J* 8.9 [*ortho*] and 3.0 [*meta*], aromatic H), 5.24 (2 H, s, OCH_2O), 5.22 (2 H, s, OCH_2O), 4.70 (1 H, q, *J* 6.4, CH), 3.86-3.80 (4 H, m, OCH_2), 3.60-3.55 (4 H, m, CH_3OCH_2), 3.39 (3 H, s, OCH_3), 3.38 (3 H, s, OCH_3), 3.26 (3 H, s, OCH_3), 1.37 (3 H, d, *J* 6.4, CH_3).

Found: *m/z* 344 (M^+, 2.1%), 89 (100), 59 (88).

4-α-Hydroxymethylquinoline



(42)

S. R. Ramadas and M. V. Krishna, *Curr. Sci.*, 1981, **50**, 120.

Quinoline-4-carboxaldehyde (20 g, 127.25 mmol) was dissolved in methanol (100 cm^3) and chilled to 0 °C. Sodium borohydride powder (24.07 g, 636.25 mmol) was added batchwise over 15 min. On warming to room temperature, the solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ (1000 cm^3), washed with water (2 x 200 cm^3), the organic solution dried, and concentrated *in vacuo*. The crude product was subjected to chromatography using EtOAc as eluent and the solid obtained was crystallised from benzene to furnish *compound* (42) (15.63 g, 77%) as a white solid; m.p. 96-97 °C, [lit.: 96-97 °C].

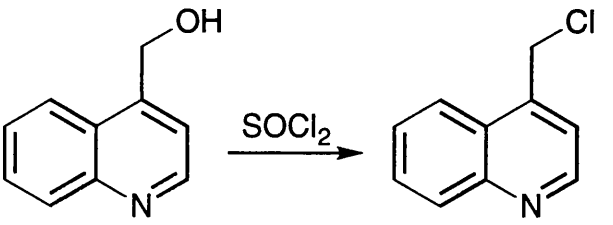
δ_H NMR (360 MHz; $CDCl_3$) 8.84 (1 H, d, *J* 4.4, aromatic N-C<u>H</u>-), 8.12 (1 H, ddd, *J* 8.5 [*ortho*], aromatic <u>H</u>), 7.96 (1 H, ddd, *J* 8.5 [*ortho*], aromatic <u>H</u>), 7.72 (1 H, ddd, *J* 7.0 [*ortho*] and 1.4 [*meta*], aromatic <u>H</u>), 7.57 (1 H, ddd, *J* 7.0 [*ortho*] and 1.4 [*meta*], aromatic <u>H</u>), 7.55 (1 H, d, *J* 4.4, aromatic =N-CH=C<u>H</u>-), 5.24 (2 H, d, *J* 0.8, C<u>H_2</u>), 3.16 (1 H, br s, O<u>H</u>).

Found: *m/z* 159 (M^+, 23%), 130 (100), 77, (27), 75 (30), 51 (30).

Found: C, 75.21; H, 5.77; N, 8.66.

$C_{10}H_9NO$ requires C, 75.45; H, 5.70; N, 8.80%.

4-α-Chloromethylquinoline



(42) (43)

S. R. Ramadas and M. V. Krishna, *Curr. Sci.*, 1981, **50**, 120.

Alcohol (42) (15.50 g, 97.4 mmol), was slurried in sodium dried diethyl ether (300 cm^3) and cooled to 0 °C. A large excess of thionyl chloride (30 cm^3, 411.3 mmol) dissolved in dry ether (100 cm^3) was added dropwise (rapidly) with cooling. The mixture was allowed to warm to room temperature and then stirred overnight. The volatiles were distilled off under reduced pressure, and the residue basified with concentrated ammonia solution. The crude product was extracted with ether (2 x 500 cm^3) and the combined extracts washed with water (100 cm^3), dried, and evaporated to dryness. Chromatography on silica gel with 20% hexane/EtOAc as eluent yielded the unstable* *compound* (43) (7.63 g, 44%) as a white solid; m.p. 56-57 °C, [lit.: 55-57 °C].

* It has a shelf life of a few weeks only.

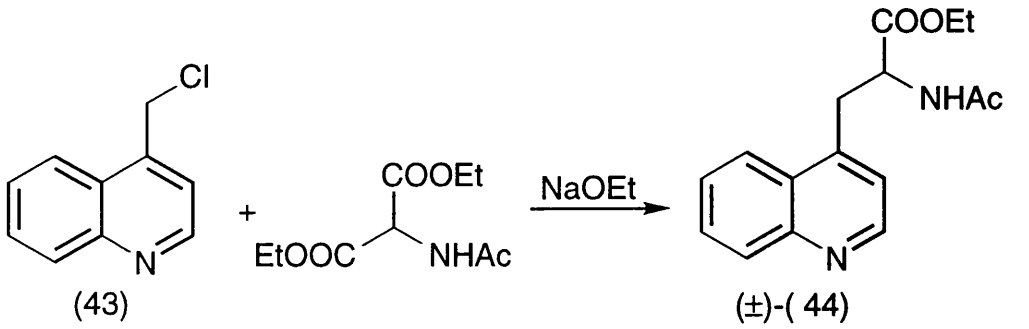
δ_H NMR ($CDCl_3$) 8.92 (1 H, d, *J* 4.4, aromatic =N-C<u>H</u>-), 8.17 (1 H, 'd' [ddd], aromatic <u>H</u>), 8.11 (1 H, 'd' [ddd], aromatic <u>H</u>), 7.78 (1 H, 't' [ddd], aromatic <u>H</u>), 7.65 (1 H, 't' [ddd], aromatic <u>H</u>), 7.47 (1 H, d, *J* 4.4, aromatic =N-CH=C<u>H</u>-), 5.02 (2 H, s, C<u>H_2</u>).

Found: *m/z* 177 (M^+, [$^{35}Cl/^{35}Cl$], 57%), 179 ($M^+ + 2$, [$^{35}Cl/^{37}Cl$], 18), 143 (25), 142 (100), 115 (61).

Found: C, 67.61; H, 4.61; N, 7.87.

$C_{10}H_8ClN$ requires C, 67.62; H, 4.54; N, 7.89%.

4-(1-Ethoxycarbonyl-1-acetamido)quinoline



Diethyl acetamidomalonate (9.33 g, 42.95 mmol) was deprotonated at room temperature using sodium ethoxide solution, prepared from sodium metal (1.18 g, 51.33 mmol) in anhydrous ethanol (125 cm^3).

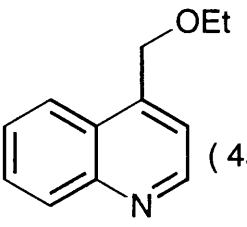
Chloride (43) (7.63 g, 42.95 mmol) was taken up in anhydrous ethanol (25 cm^3) and added to the prepared carbanion. The mixture was brought to reflux which was maintained overnight. The solvent was removed *in vacuo* and the residue partitioned between water (200 cm^3) and EtOAc (200 cm^3). The aqueous layer was discarded and the organic layer was washed with water (100 cm^3), dried, and the solvent evaporated under reduced pressure. Purification on silica gel eluting with 50:50 EtOAc/hexane -> EtOAc -> 5% methanol/EtOAc yielded two products. The more polar *title compound* was triturated with cyclohexane and isolated as a colourless solid (7.13 g, 58%); m.p. 148-149 °C.

δ_H NMR (360MHz; $CDCl_3$) 8.82 (1 H, d, *J* 4.4, aromatic =N-C<u>H</u>-), 8.13 (2 H, m, [ddd], aromatic <u>H</u>), 7.74 (1 H, 't' [ddd], *J* 7.0 [*ortho*] and 1.3 [*meta*], aromatic <u>H</u>), 7.60 (1 H, 't' [ddd], *J* 7.0 [*ortho*] and 1.3 [*meta*], aromatic <u>H</u>), 7.18 (1 H, d, *J* 4.4, aromatic =N-CH=C<u>H</u>-), 6.08 (1 H, br d, *J* 7.2, N<u>H</u>), 5.03 (1 H, 2 x dd, *J* 14.0 and 7.2, C<u>H</u>), 4.07 (2 H, m [2 x dq], *J* 7.1, C<u>H_2</u>CH_3), 3.60 (2 H, dd, *J* 7.2 and 14.0, Ar.C<u>H_2</u>), 1.98 (3 H, s, C(O)C<u>H_3</u>), 1.10 (3 H, t, *J* 7.1, CH_2C<u>H_3</u>).

Found: *m/z* 286 (M^+, 8%), 154 (62), 143 (78), 115 (31), 43 (100).

Found:	C, 67.01; H, 6.42; N, 9.66.
$C_{16}H_{18}N_2O_3$ requires	C, 67.12; H, 6.34; N, 9.78%.

The by-product, 4-ethoxymethylquinoline, (45) was isolated as a colourless oil (1.98 g, 25%).



(45)

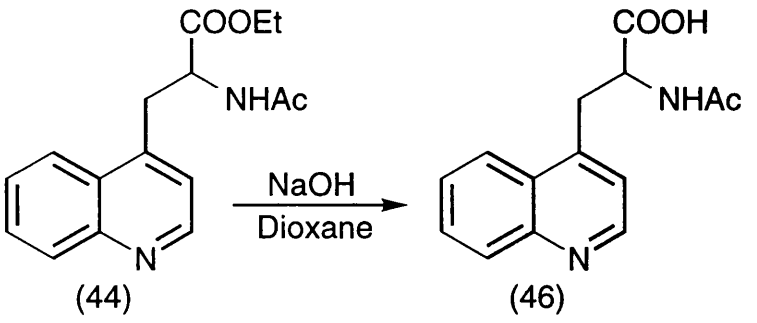
δ_H NMR ($CDCl_3$) 8.90 (1 H, d, *J* 4.4, aromatic =N-C<u>H</u>-), 8.14 (1 H, 'd', [ddd], aromatic <u>H</u>), 7.99 (1 H, 'd' [ddd], *J* 7.6 [*ortho*] and 1.3 [*meta*], aromatic <u>H</u>), 7.72 (1 H, 't' [ddd], *J* 7.6 [*ortho*] and 1.3 [*meta*], aromatic <u>H</u>), 7.57 (1 H, 't' [ddd] *J* 7.6 [*ortho*] and 1.3 [*meta*], aromatic <u>H</u>), 7.49 (1 H, d, *J* 4.4, aromatic =N-CH=C<u>H</u>-), 4.99 (2 H, s, Ar.C<u>H_2</u>), 3.68 (2 H, q, *J* 7.0, C<u>H_2</u>CH_3), 1.32 (3 H, t, *J* 7.0, CH_2<u>C</u>H_3).

Found: *m/z* 187 (M^+, 21%), 143 (100), 142 (30), 130 (51), 115 (38).

Found: C, 76.61; H, 7.18; N, 7.52.

$C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%.

(*S*)-*N*-Acetyl-(4-quinolyl)alanine



(44) (46)

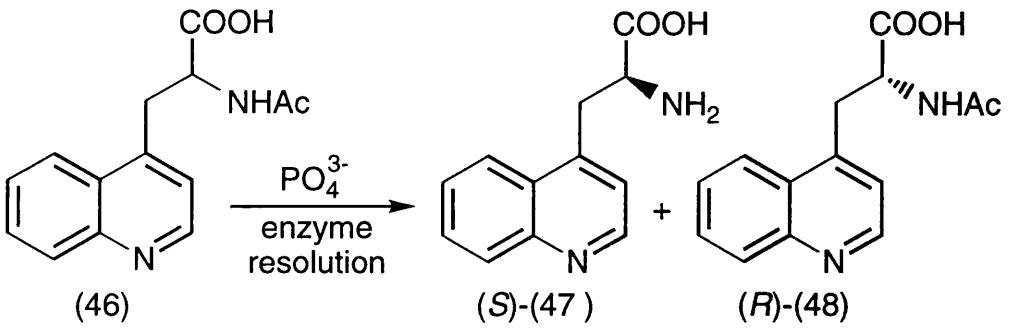
Ester (44) (7.10 g, 24.8 mmol) was slurried in dioxane (70 cm^3) and NaOH solution (4 mol dm^{-3}; 10 cm^3) was added. The solution was then stirred for 3 h at room temperature. The volatiles were removed under reduced pressure and the residue was dissolved in water (200 cm^3). The solution was neutralised using HCl solution (6 mol dm^{-3}) whereupon the product precipitated. The white solid was filtered and washed well with water to yield acid (46) (5.73 g, 90%); m.p. 272-273 °C.

δ_H NMR (CD_6SO) 8.81 (1 H, d, *J* 4.4, aromatic H), 8.39 (1 H, d, *J* 8.1, NH), 8.18 (1 H, d, *J* 7.6, aromatic H), 8.04 (1 H, 'd' [ddd], *J* 7.6 [*ortho*], aromatic H), 7.78 (1 H, 't' [ddd], *J* 7.6 [*ortho*] and 1.3 [*meta*], aromatic H), 7.67 (1 H, 't' [ddd], *J* 7.6 [*ortho*] and 1.3 [*meta*], aromatic H), 7.38 (1 H, d, *J* 4.4, aromatic H), 3.61 (1 H, m, CH), 3.45 (1 H, dd, *J* 14.2 and 4.7, H_AH_B), 3.30 (1 H, dd, *J* 14.2 and 4.4, H_AH_B), 1.75 (3 H, s, CH_3).

δ_C NMR (CD_6SO and HCl) 172.2 (C=O), 170.6 (C=O), 157.9 (=C<), 143.7 (-CH<), 137.4 (=C<), 135.1 (-CH<), 130.5 (-CH<), 128.2 (=C<), 125.7 (-CH<), 123.5 (-CH<), 121.6 (-CH<), 52.5 (CH), 34.5 (CH_2), 22.6 (CH_3).

Found: *m/z* 258 (M^+, 18%), 199 (43), 154 (85), 143 (100), 142 (40), 115 (45), 43 (93).

(*S*)-3-(4-Quinolyl)alanine



P. Daumas *et al.*, *Int. J. Peptide Protein Res.*, 1991, **38**, 218.

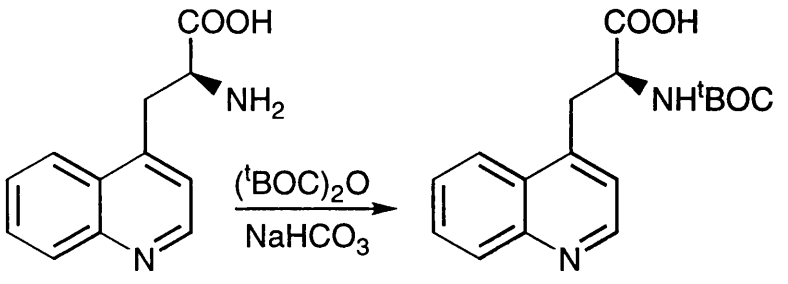
The acetylated amino acid (5.50 g, 21.3 mmol) was dissolved in phosphate buffer (75 mmol dm^{-3}; 100 cm^3, pH 6.8) [Sigma] and the pH was adjusted to pH 7.2 by the addition of NaOH solution (2 mol dm^{-3}, 11 cm^3). After stirring at 37 °C for 0.5 h, *Aspergillus* genus acylase (500 mg, 30,000 units g^{-1}) [TCI, Tokyo]. Stirring was continued for 24 h at a temperature of 37 °C. Another portion of acylase (500 mg) was added and stirring was continued for a further 24 h. (*S*)-3-(4-Quinolyl)alanine (47) precipitated and was collected by filtration (quantitative yield). It is slightly water soluble at pH 7, and so was washed with a very small volume of water. The acetylated enantiomer (48), (*R*)-*N*-acetyl(4-quinolyl)alanine remained in the mother liquor.

δ_H NMR (CD_6SO and DCl) 9.33 (1 H, d, *J* 5.6, aromatic H), 8.62 (1 H, 'd' [ddd], *J* 8.4 [*ortho*], aromatic H), 8.52 (1 H, 'd' [ddd], *J* 8.4 [*ortho*], aromatic H), 8.26 (1 H, 't' [ddd], aromatic H), 8.22 (1 H, d, *J* 5.6, aromatic H), 8.08 (1 H, 't' [ddd], aromatic H), 4.44 (1 H, 't', *J* 7.2, CH), 4.01 (2 H, br d, *J* 7.2, CH_2).

Found: *m/z* 216 (M^+, 1.0%), 143 (100).

Found: M^+, 216.0913. $C_{12}H_{12}N_2O_2$ requires *M* 216.0899.

(*S*)-*N*-*tert*-Butoxycarbonyl(4-quinolyl)alanine



(*S*)-(47) (*S*)-(49)

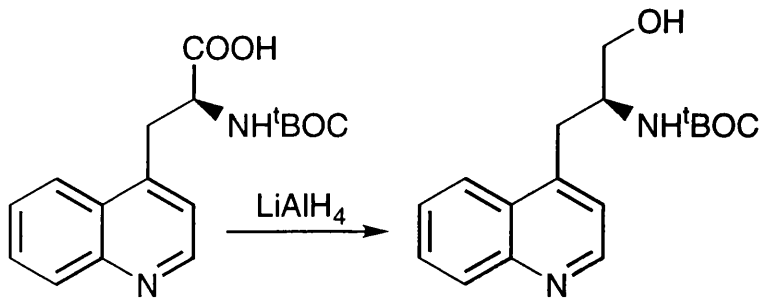
The amino acid (47) (2.30 g, 10.6 mmol) was slurried in dioxane (67 cm^3) and water (33 cm^3). An excess of di-*tert*-butyl dicarbonate (5.78 g, 26.5 mmol) and sodium hydrogen carbonate (6.30 g, 75 mmol) was added. The reaction mixture was heated to 60 °C for 1 h. The volatiles were removed under reduced pressure and the residue taken up in water (30 cm^3). When neutralised with HCl solution (0.5 mol dm^{-3}), the product (49), (2.25 g, 56%) precipitated as a white solid.

δ_H NMR (CD_6SO) 8.80 (1 H, d, *J* 4.4, aromatic H), 8.18 (1 H, 'd' [ddd], aromatic H), 8.03 (1 H, 'd' [ddd], aromatic H), 7.77 (1 H, 't' [ddd], aromatic H), 7.70 (1 H, 't' [ddd], aromatic H), 7.41 (1 H, d, *J* 4.4, aromatic H), 7.22 (1 H, br d, NH), 4.24 (1 H, 2 x dd, CH), 3.62 (1 H, dd, CH_ACH_B), 3.23 (1 H, dd, CH_ACH_B), 1.27 (9 H, s, $(CH_3)_3$).

Found: *m/z* 316 (M^+, 1.1%), 199 (27), 143 (88), 142 (40), 115 (33), 57 (100), 41 (38).

Found: M^+, 316.1450. $C_{17}H_{20}N_2O_4$ requires *M* 316.1423.

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-quinolyl)propanol



(*S*)-(49) (*S*)-(50)

A slurry of the protected amino acid (49), (2.25 g, 7.11 mmol) and $LiAlH_4$ (0.5 g, 13.18 mmol) in dry THF (100 cm^3) was heated under reflux for 2 h. The solution was cooled and the excess $LiAlH_4$ quenched with water. The solvent was removed under reduced pressure and the crude product was neutralised with HCl solution (0.5 mol dm^{-3}). The aqueous solution was extracted with EtOAc (2 x 50 cm^3), the combined extracts dried, and the solvent removed *in vacuo*. Purification on SiO_2 eluting with 3% MeOH/EtOAc yielded the *title compound* (0.8 g, 37%) as a yellow crystalline solid; m.p. 143-144 °C; $[\alpha]_D$ -53.3 (*c* 1.00 in $CHCl_3$).

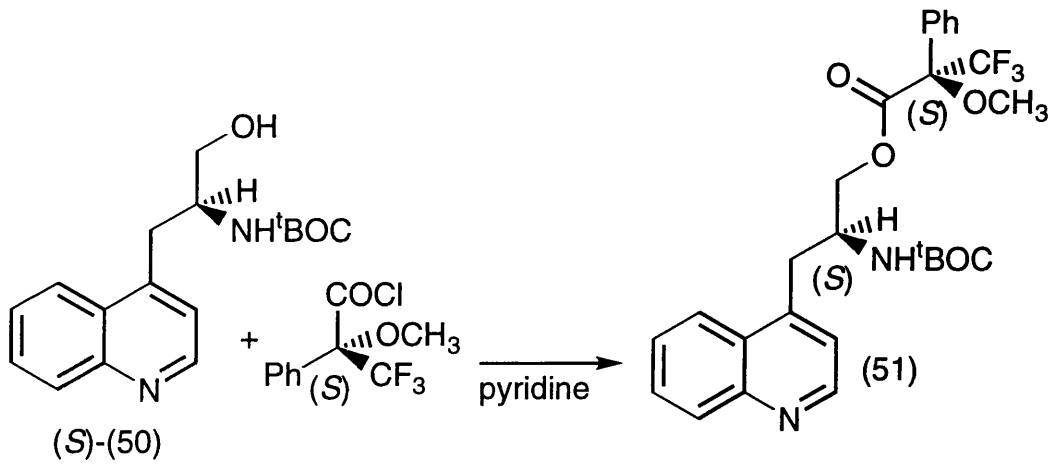
δ_H NMR ($CDCl_3$) 8.79 (1 H, d, *J* 4.4, aromatic H), 8.23 (1 H, br 'd' [ddd], aromatic H), 8.11 (1 H, 'd' [ddd], aromatic H), 7.72 (1 H, 't' [ddd], aromatic H), 7.60 (1 H, 't' [ddd], aromatic H), 7.30 (1 H, d, *J* 4.4, aromatic H), 5.02 (1 H, br d, NH), 4.06 (1 H, m CH), 3.64 (2 H, 2 x dd, $ArCH_2$), 3.35 (2 H, br m, CH_2OH), 1.41 (10 H, br s, OH and $(CH_3)_3$).

Found: *m/z* 302 (M^+, 0.2%), 143 (100), 57 (52).

Found: *m/z* (FAB) 303 (MH^+, 100%).

Found:	C, 67.27; H, 7.35; N, 9.14.
$C_{17}H_{22}N_2O_3$ requires	C, 67.53; H, 7.33; N, 9.26%.

Mosher's ester derivative of compound (*S*)-(50)



Compound (50) (20 mg, 0.066 mmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (22 mg, 0.087 mmol) were mixed in dry pyridine (5 cm^3) and stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc (100 cm^3). The organic extract was washed with Na_2CO_3 solution (2 x 20 cm^3), and brine until neutral. The solution was dried, and the solvent removed *in vacuo*. ^{19}F and ^1H NMR experiments were conducted on the crude product.

δ_H NMR (360MHz; $CDCl_3$) 8.78 (1 H, d, *J* 4.4, aromatic H), 8.12 (1 H, 'd' [ddd], *J* 8.5 [*ortho*], aromatic H), 8.06 (1 H, 'd' [ddd], *J* 8.5 [ortho], aromatic H), 7.73 (1 H, 't' [ddd], aromatic H), 7.56 (3 H, 't' [ddd] and m, aromatic H), 7.46 (3 H, m, aromatic H), 7.11 (1 H, d, *J* 4.4, aromatic H), 4.62 (1 H, br d, NH), 4.44 (1 H, dd, OCH_AH_B), 4.31 (1 H, m, CH), 4.19 (1 H, dd, OCH_AH_B), 3.57 (3 H, 's' [m], OCH_3), 3.34 (1 H, dd, $ArCH_AH_B$), 3.12 (1 H, dd, $ArCH_AH_B$), 1.39 (9 H, s, $(CH_3)_3$).

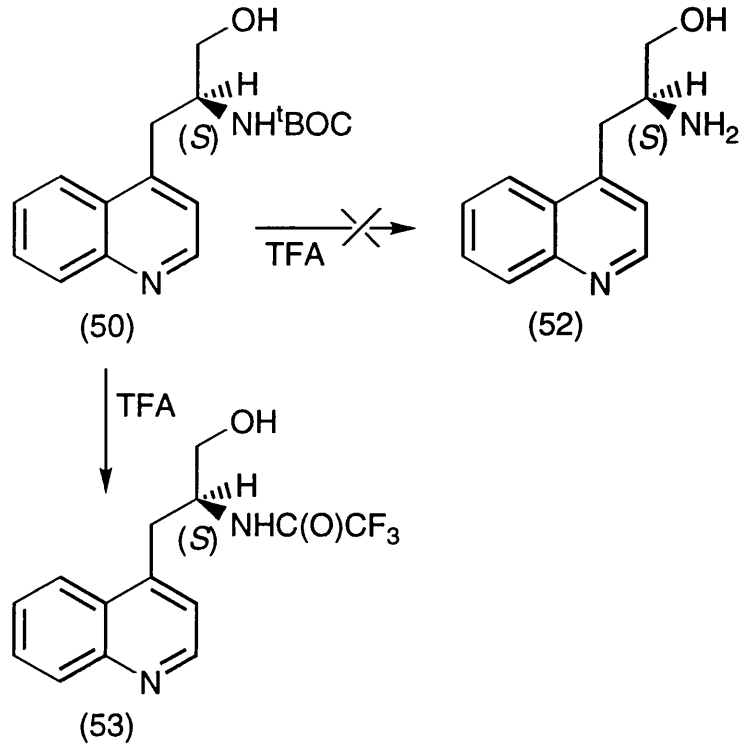
δ_F NMR (188MHz; $CDCl_3$) -71.6 (CF_3).

Found: *m/z* (FAB) 519 (MH^+, 100%).

UV λ_{max} 205, 226 and 288nm.

(*S*)-*N*-Trifluoroacetyl-(4-quinolyl)alaninol

[Attempted preparation of (*S*)-quinoline-4-alaninol]



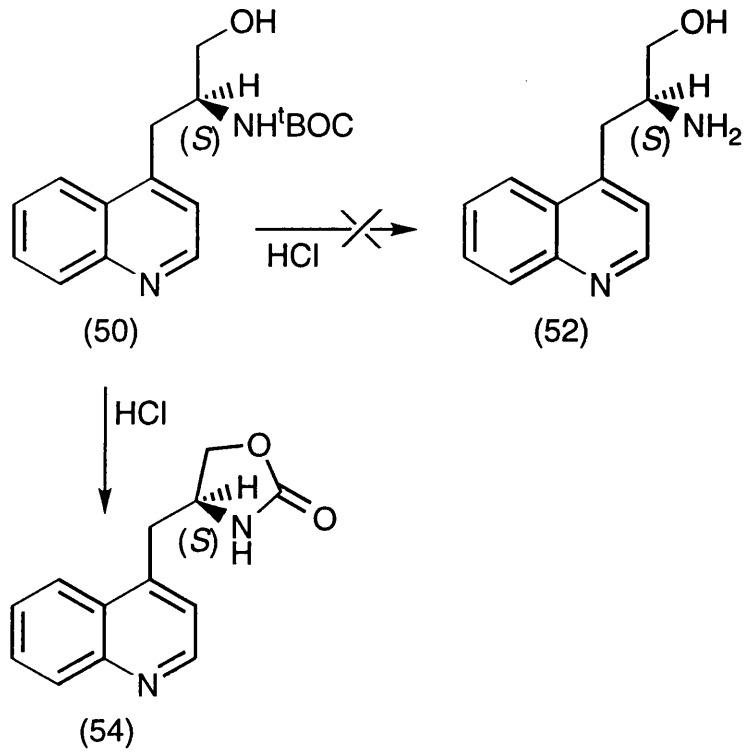
Intermediate (50) (50 mg, 0.165 mmol) was taken up in dry DCM (20 cm^3) under argon and cooled to 0 °C. A large excess of TFA (188 mg, 1.65 mmol) was added and the stirred solution was allowed to attain room temperature. The volatiles were removed under reduced pressure and the residue partitioned between DCM (50 cm^3) and Na_2CO_3 solution (1 mol dm^{-3}, 20 cm^3). The organic solution was washed with Na_2CO_3 solution (1 mol dm^{-3}, 10 cm^3) and brine until neutral. The solvent was dried and removed *in vacuo*. Chromatography on reverse phase SiO_2 eluting with 80% MeOH/H_2O yielded the unexpected product (53) (16 mg, 33%) as a solid.

δ_H NMR ($CDCl_3$) 8.80 (1 H, d, *J* 4.4, aromatic H), 8.40 (1 H, d, *J* 8.2, aromatic H), 8.10 (1 H, d, *J* 8.2, aromatic H), 7.69 (2 H, m, aromatic H), 7.36 (1 H, d, *J* 4.4, aromatic H), 7.32 (1 H, d, *J* 4.5 NH), 4.28 (1 H, m, CH), 3.68-3.31 (4 H, m, CH_2Ar, CH_2OH), 2.68 (1 H, br s, OH).

Found: *m/z* 298 (M^+, 10%), 154 (31), 143 (100).

(*S*)-4-(4'-Quinolinylmethyl)-oxazolidin-2-one

(Attempted preparation of (*S*)-quinoline-4-alaninol)



(50) (52) (54)

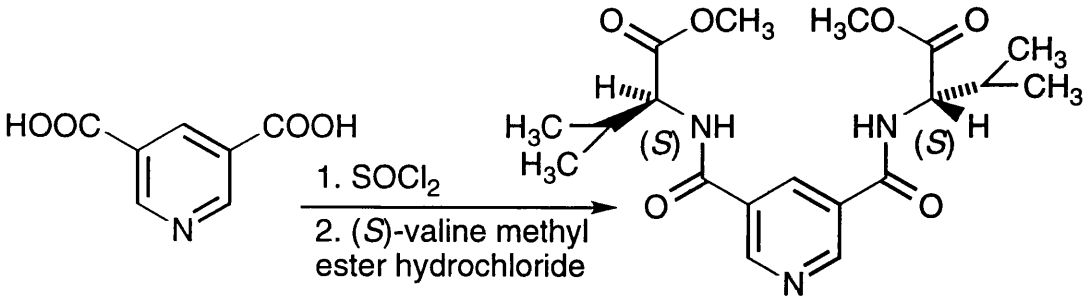
Intermediate (50) (50 mg, 0.165 mmol) was taken up in EtOAc (20 cm^3) and treated with HCl solution (10 cm^3; 3 mol dm^{-3}). The mixture was then stirred vigorously for 2 h at room temperature. Once basified with Na_2CO_3 solution (1 mol dm^{-3}), the organic layer was isolated, dried and the solvent removed under reduced pressure. The residue was examined using NMR and mass spectroscopy. Again, the desired product was not obtained, and it is suggested that the product is oxazolidone (54).

δ_H NMR ($CDCl_3$) 8.53 (1 H, d, *J* 4.4, aromatic H), 7.97 (2 H, m, aromatic H), 7.60 (2 H, m, aromatic H), 7.14 (2 H, coincidental d, aromatic H; NH), 4.49 and 4.20 (2 H, m, CH_2Ar), 4.33 (1 H, m, CH), 3.32 (2 H, m, CH_2O).

δ_C NMR ($CDCl_3$) 159.4 (C=O), 149.6 (=CH-), 147.9 (=C<), 142.1 (=C<), 129.9 (=CH-), 129.5 (=CH-), 127.0 (=CH- and =C<?), 122.9 (=CH-), 121.7 (=CH-), 69.6 (CH_2Ar), 52.5 (CH), 37.6 (CH_2).

Found: *m/z* 228 (M^+, 2%), 143 (100).

N,N'-Bis[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]-3,5-bis(aminocarbonyl)pyridine



(55)

R. M. Kellogg *et al.*, *J. Am. Chem. Soc.*, 1985, **107**, 3981.

Pyridine-3,5-dicarboxylic acid (20.72 g, 0.124 mol) suspended in sodium dried benzene (400 cm^3) with a large excess of thionyl chloride (50 cm^3, 0.685 mol) was treated with dry DMF (0.5 cm^3). The mixture was heated under reflux in an argon atmosphere for 3 h after which time the solution had clarified. The volatiles were removed *in vacuo* and the residue was taken up in DCM (200 cm^3).

(*S*)-(+)-Valine methyl ester hydrochloride (41.57 g, 0.248 mol) was dissolved in aqueous KOH solution (2 mol dm^{-3}; 125 cm^3) and cooled to 5 °C. To this vigorously stirring solution was added simultaneously, with continued cooling, the prepared diacid chloride solution and aqueous KOH solution (4 mol dm^{-3}; 200 cm^3). On warming to room temperature the organic layer was separated and the aqueous solution extracted with DCM (2 x 100 cm^3). The combined organic extracts were washed with water until neutral, dried, and the solvent removed *in vacuo*. The crude diester (55) was crystallised from ethyl acetate/hexane to yield a crystalline solid (28.13 g, 58%); m.p. 153-153.5 °C; $[\alpha]_D$ +27.8 (*c* 1.0 in EtOAc).

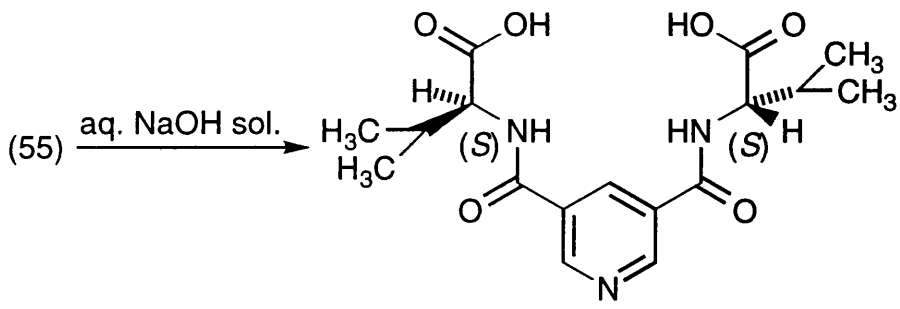
δ_H NMR ($CDCl_3$) 9.13 (2 H, m, aromatic H), 8.48 (4 H, m, aromatic H), 6.97 (2 H, br d, *J* 8.4, NH), 4.79 (2 H, dd, *J* 8.6 and 5.1, CH.CH(CH_3)$_2$), 3.80 (6 H, s, COOCH_3), 2.30 (2 H, m, CH_3.CH.CH_3), 1.03 (6 H, d, *J* 6.8, CH_3.CH.CH_3), 1.01 (6 H, d, *J* 6.8, CH_3.CH.CH_3).

Found: *m/z* 393 (M^+, 1.6%), 334 (70), 280 (35), 274 (36), 263 (100), 133 (45), 105 (64), 77 (47), 72 (25).

Found: C, 58.04; H, 7.13; N, 10.84.

$C_{19}H_{27}N_3O_6$ requires C, 58.00; H, 6.92; N, 10.68%.

N,N'-Bis[(1*S*)-1-carboxy-2-methylpropyl]-3,5-bis(aminocarbonyl)pyridine



(56)

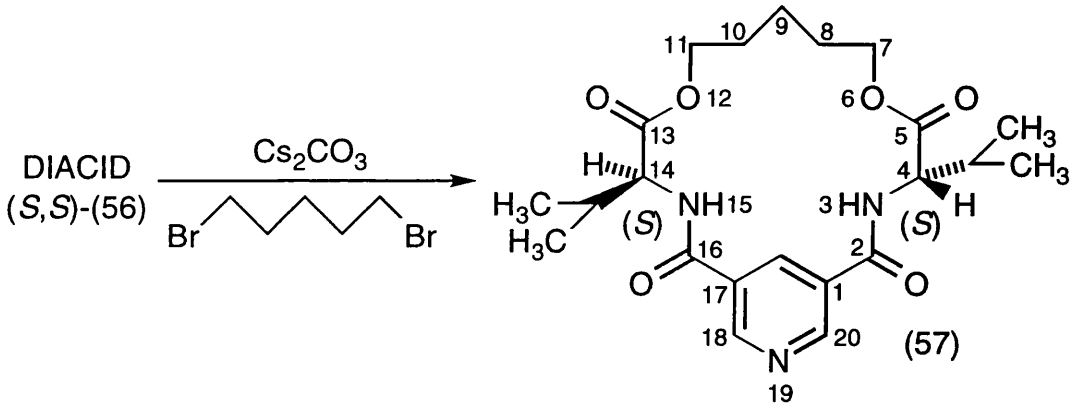
R. M. Kellogg *et al.*, *J. Am. Chem. Soc.*, 1985, **107**, 3981.

Diester (55) (30.83 g, 78.36 mmol) was taken up in methanol (800 cm^3) and NaOH solution (4 mol dm^{-3}; 800 cm^3) was added. The solution was stirred at room temperature overnight. After acidifying to pH 6 with HCl solution (1 mol dm^{-3}), the volatiles were removed *in vacuo*. The diacid (56) was dried in a vacuum oven to give a quantitative yield of the crude solid.

δ_H NMR (DMSO) 9.09 (2 H, m, aromatic H), 8.66 (3 H, m, aromatic H and NH), 4.28 (2 H, dd, *J* 8.1 and 6.2, CH.CH(CH_3)$_2$), 2.22 (2 H, m, CH_3.CH.CH_3), 0.95 (12 H, 2 x d, *J* 6.8, CH_3.CH.CH_3 and CH_3.CH.CH_3).

δ_C NMR (DMSO) 173.3 (C=O), 164.2 (C=O), 150.3 (=CH-), 133.8 (=CH-), 129.2 (=C<), 59.0 (CH.CH(CH_3)$_2$), 29.7 (CH_3.CH.CH_3), 19.2 (CH_3.CH.CH_3), 18.3 (CH_3.CH.CH_3).

(4*S*,14*S*)-4,14-Bis(1-methylethyl)-6,12-dioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetraone



R. M. Kellogg *et al.*, *J. Am. Chem. Soc.*, 1985, **107**, 3981.

Diacid (56) (3.3 g, 9.03 mmol) was dissolved in methanol (90 cm^3) and deprotonated with Cs_2CO_3 (2.85 g, 8.75 mmol). Once CO_2 evolution had ceased, dry DMF (200 cm^3) was added and the solvent removed at reduced pressure using a powerful vacuum pump (taking care that the water bath temperature was <50 °C).

1,5-Dibromopentane (2.08 g, 9.03 mmol) was dissolved in dry DMF (500 cm^3) and combined with the prepared dicesium salt. Stirring was continued for 48 h at 48 °C. The solvent was removed *in vacuo* and the residue taken up in EtOAc (400 cm^3). The extract was washed with water (2 x 100 cm^3), the solvent dried and the solution concentrated. The residue was purified by column chromatography eluting with 50:50 EtOAc/DCM to yield the *title compound* and a by-product. The macrocycle was triturated with ether and obtained as an a amorphous solid (220 mg, 5.6%); m.p. 244 °C, [lit.: 246.6 °C]; $[\alpha]_D$ -163.8 (*c* 0.5 in DMF), [lit.: $[\alpha]_D$ -162.0 (*c* 0.5 in DMF)]. A yield of 26% was obtained from an optimised experiment, which was conducted on a larger scale.

δ_H NMR ($CDCl_3$) 8.34 (2 H, br s, aromatic H), 7.79 (2 H, br d, *J* 9.6, NH), 7.61 (1 H, br s, aromatic H), 4.81 (2 H, dd, *J* 9.6 and 4.8, CH.CH(CH_3)$_2$), 4.39 (2 H, m, OC$H_A H_B$), 4.17 (2 H, m, OC$H_A H_B$), 2.31 (2 H, m, CH_3.CH.CH_3), 1.76 (6 H, br s, $CH_2CH_2CH_2$), 0.93 (12 H, 2 x d, CH_3.CH.CH_3).

δ_C NMR ($CDCl_3$) 170.2 (C=O), 166.0 (C=O), 150.4 (=CH-), 131.6 (=CH-), 129.1 (=C<), 65.7 (OCH_2), 58.2 (CH.CH(CH_3)$_2$), 31.8 (CH_3.CH.CH_3), 29.1 (OCH_2CH_2), 24.7 ((CH_2)$_2$$CH_2$), 19.0 ($CH_3$.CH.$CH_3$), 17.7 ($CH_3$.CH.$CH_3$).

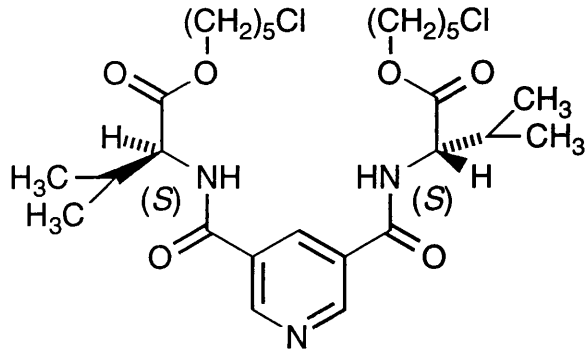
Found: *m/z* 433 (M^+, 8%), 346 (-2CO_2, 45), 274 (27), 176 (48), 105 (100), 77 (57), 72 (75), 55 (25), 43 (25), 41 (52).

Found: M^+, 433.2226. $C_{22}H_{31}N_3O_6$ requires *M* 433.2213.

Found: C, 60.73; H, 7.29; N, 9.64.

$C_{22}H_{31}N_3O_6$ requires C, 60.96; H, 7.21; N, 9.69%.

The by-product (58), *N*,*N*′-bis[(1*S*)-14-chloropentamethylene-2-methylpropyl]-3-bis(aminocarbonyl)pyridine was obtained as a crystalline solid (105 mg, 2%); m.p. 90-90.5 °C.



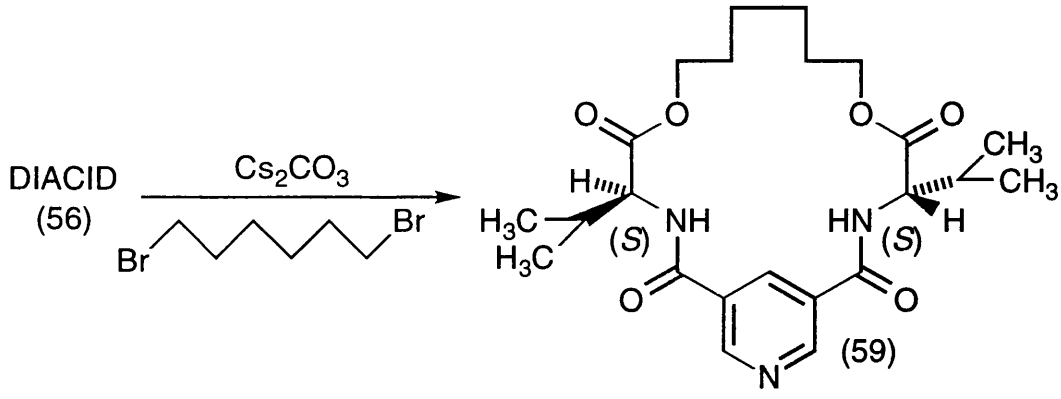
(58)

δ_H NMR ($CDCl_3$) 9.16 (2 H, m, aromatic H), 8.50 (1 H, m, aromatic H), 6.84 (2 H, d, *J* 8.5, NH), 4.79 (2 H, dd, *J* 8.5 and 4.8, CH.CH$(CH_3)_2$), 4.21 (4 H, t, *J* 6.5, OCH_2), 3.56 (4 H, t, *J* 6.5, CH_2Cl), 2.31 (2 H, m, $CH_3.CH.CH_3$), 1.76 (8 H, m, OCH_2CH_2 and CH_2CH_2Cl), 1.56 (4 H, m, $CH_2(CH_2)_2Cl$), 1.04 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 1.01 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$).

δ_C NMR ($CDCl_3$) 172.0 (C=O), 164.8 (C=O), 150.8 (=CH-), 133.7 (=CH-), 129.4 (=C<), 65.2 (OCH_2), 57.7 (CH.$CH(CH_3)_2$), 44.6 (CH_2Cl), 31.9 (OCH_2CH_2), 31.3 ($CH_3.CH.CH_3$), 27.7 (CH_2CH_2Cl), 23.1 ($O(CH_2)_2CH_2(CH_2)_2Cl$), 19.0 ($CH_3.CH.CH_3$), 17.9 ($CH_3.CH.CH_3$).

Found: *m/z* (FAB) 574 (MH^+, [$^{35}Cl/^{35}Cl$], 100%), 576 (MH^+ + 2, [$^{35}Cl/^{37}Cl$], 69), 578 (MH^+ + 4, [$^{37}Cl/^{37}Cl$], 14).

(4*S*,15*S*)-4,15-Bis(1-methylethyl)-6,13-dioxa-3,16,20-triazabicyclo[16.3.1]docosa-1(22),18,20-triene-2,5,14,17-tetraone



R. M. Kellogg *et al.*, *J. Am. Chem. Soc.*, 1985, **107**, 3981.

Diacid (56) (3.3 g, 9.03 mmol) was dissolved in methanol (90 cm^3) and deprotonated with Cs_2CO_3 (2.85 g, 8.75 mmol). Once CO_2 evolution had ceased, dry DMF (200 cm^3) was added and the solvent removed at reduced pressure using a powerful vacuum pump (taking care that the water bath temperature was <50 °C).

1,6-Dibromohexane (2.08 g, 9.03 mmol) was dissolved in dry DMF (500 cm^3) and combined with the prepared dicesium salt. Stirring was continued for 120 h at 48 °C. The solvent was removed *in vacuo* and the residue taken up in EtOAc (400 cm^3). The extract was washed with water (2 x 100 cm^3), the solvent dried and the solution concentrated. The residue was purified by column chromatography eluting with 50:50 EtOAc/DCM to give two components. Further purification on SiO_2 using 3% MeOH dissolved in $CHCl_3$ yielded the *title compound* (1.04 g, 12.9%) as an amorphous solid; m.p. 230 °C, [lit.: 236.5 °C]; $[\alpha]_D$ -123 (*c* 0.5 in DMF) and a by-product (60) (0.90 g, 8%).

δ_H NMR ($CDCl_3$) 9.15 (2 H, d, *J* 2.0, aromatic H), 8.23 (1 H, t, *J* 2.1, aromatic H), 6.65 (2 H, d, *J* 8.9, NH), 4.64 (2 H, dd, *J* 9.0 and 5.6, CH.$CH(CH_3)_2$), 4.34 (2 H, m, OCH_AH_B), 4.00 (2 H, m, OCH_AH_B), 2.34 (2 H, m, $CH_3.CH.CH_3$), 1.61 (4 H, m, OCH_2CH_2), 1.35 (4 H, m, $O(CH_2)_2CH_2$), 1.08 (6 H, d, *J* 8.8, $CH_3.CH.CH_3$), 1.04 (6 H, d, *J* 8.8, $CH_3.CH.CH_3$).

δ_C NMR ($CDCl_3$) 170.2 (C=O), 165.8 (C=O), 150.8 (=CH-), 132.4 (=CH-), 130.1 (=C<), 64.9 (OCH_2), 59.2 (CH.$CH(CH_3)_2$), 30.4 ($CH_3.CH.CH_3$), 28.8 (OCH_2CH_2), 26.1 ($O(CH_2)_2CH_2$), 19.2 ($CH_3.CH.CH_3$), 18.2 ($CH_3.CH.CH_3$).

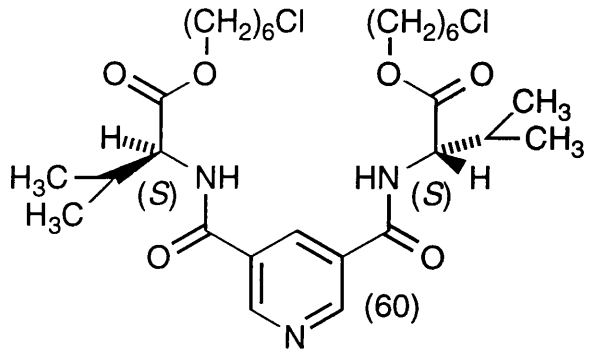
Found: *m/z* 447 (M^+, 15%), 360 (71), 332 (26), 274 (37), 176 (59), 105 (92), 77 (43), 72 (100), 55 (45), 41 (29).

Found: M^+, 447.2377. $C_{23}H_{33}N_3O_6$ requires *M* 447.2369.

Found: C, 61.55; H, 7.40; N, 9.33.

$C_{23}H_{33}N_3O_6$ requires C, 61.73; H, 7.43; N, 9.39%.

N,N'-Bis[(1*S*)-15-chlorohexamethylene-2-methylpropyl]-3,-bis(aminocarbonyl)pyridine



δ_H NMR ($CDCl_3$) 9.17 (2 H, m, aromatic H), 8.51 (1 H, m, aromatic H), 6.83 (2 H, d, *J* 8.6, NH), 4.79 (2 H, dd, *J* 8.6 and 4.8, CH.CH$(CH_3)_2$), 4.20 (4 H, t, *J* 6.6, OCH_2), 3.54 (4 H, t, *J* 6.6, CH_2Cl), 2.30 (2 H, m, $CH_3.CH.CH_3$), 1.74 (8 H, m, OCH_2CH_2 and CH_2CH_2Cl), 1.45 (8 H, m, $O(CH_2)_2CH_2$ and $CH_2(CH_2)_2Cl$) 1.04 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 1.01 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$).

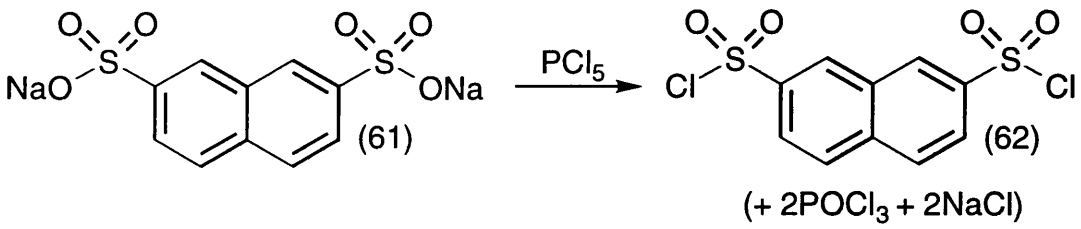
δ_C NMR ($CDCl_3$) 172.0 (C=O), 164.8 (C=O), 150.7 (=CH-), 133.7 (=CH-), 129.4 (=C<), 65.4 (OCH_2), 57.7 (CH.$CH(CH_3)_2$), 44.8 (CH_2Cl), 32.2 (OCH_2CH_2), 31.3 ($CH_3.CH.CH_3$), 28.3 (CH_2CH_2Cl), 26.3 ($OCH_2CH_2CH_2$), 25.1 ($CH_2CH_2CH_2Cl$), 19.0 ($CH_3.CH.CH_3$), 17.9 ($CH_3.CH.CH_3$).

Found: *m/z* (FAB) 602 (MH^+, [$^{35}Cl/^{35}Cl$], 100%), 604 (MH^+ + 2, [$^{35}Cl/^{37}Cl$], 71), 606 (MH^+ + 4, [$^{37}Cl/^{37}Cl$], 15).

Found: C, 57.62; H, 7.75; N, 6.69.

$C_{29}H_{45}Cl_2N_3O_6$ requires C, 57.80; H, 7.53; N, 6.97%.

Naphthalene-2,7-disulfonyl chloride



Org. Synth., Coll. Vol. IV, 1967, 693.

Naphthalene-2,7-disulfonic acid disodium salt [Tokyo Kasei Organic Chemicals, UK distributor: Fluorochem Limited] (66.45 g, 0.2 mol) was shaken with ground phosphorus pentachloride (104.12 g, 0.5 mol) [HCl gas was vented]. The resulting mixture was heated to 110 °C and this temperature maintained for 1.5 h. Occasional manual stirring was necessary. The large volume of HCl gas produced was removed by a constant stream of dry argon. On cooling, the residual phosphorus oxychloride was carefully destroyed with chilled water (500 cm^3). The residue was extracted with $CHCl_3$ (1500 cm^3), washed with water (2 x 300 cm^3), dried, and the solvent removed *in vacuo* to leave the crude sulfonyl chloride (56.22 g, 86%) as an off-white solid.

ν_{max} (film)/cm^{-1} 1384 and 1176.

δ_H NMR ($CDCl_3$) 8.82 (2 H, s, aromatic H), 8.26 (4 H, m, aromatic H).

δ_C NMR ($CDCl_3$) 143.4 (=C-SO_2), 137.9 (=C<), 130.7 (=CH-), 130.4 (=C<), 130.3 (=CH-), 125.6 (=CH-).

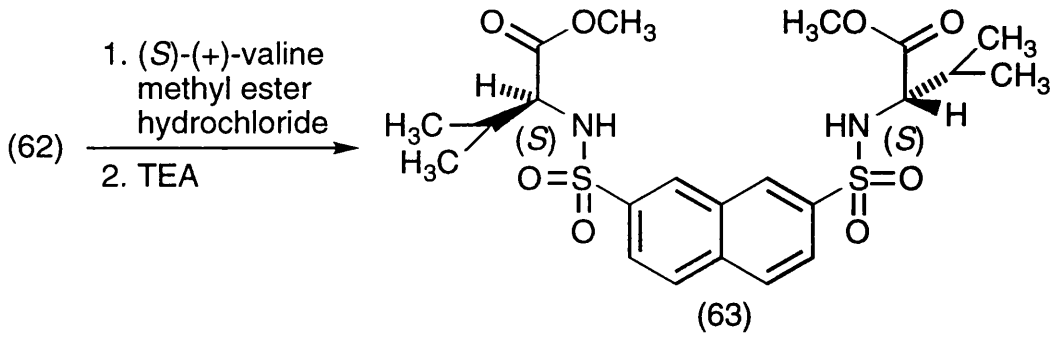
Found: *m/z* 323 (MH^+, [$^{35}Cl/^{35}Cl$], 22%), 325 (MH^+ + 2, [$^{35}Cl/^{37}Cl$], 17), 327 (MH^+ + 4, [$^{37}Cl/^{37}Cl$], 4).

Found: M^+, 323.9072. $C_{10}H_6(^{35}Cl)_2O_4S_2$ requires *M* 323.9085.

Found: M^+, 325.9052. $C_{10}H_6(^{35}Cl)(^{37}Cl)O_4S_2$ requires *M* 325.9055.

Found: M^+, 327.9007. $C_{10}H_6(^{37}Cl)_2O_4S_2$ requires *M* 327.9026.

N,N'-Bis[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]-2,7-bis(aminosulfonyl)naphthalene



(63)

The prepared compound (62) (25.00 g, 76.9 mmol) was taken up in DCM (500 cm^3) and (*S*)-(+)-valine methyl ester hydrochloride (21.00 g, 125.3 mmol) was added. A large excess of triethylamine (60 cm^3) in DCM (140 cm^3) was added dropwise with cooling. On warming to room temperature the solution was washed with water (2 x 150 cm^3), dried, and the solvent removed *in vacuo*. Chromatography using 50:50 EtOAc/hexane as eluent yielded ester (63) (29.25 g, 91%) as a viscous oil.

ν_{max} (film)/cm^{-1} 3281, 2968, 1740, 1393, 1163 and 1141.

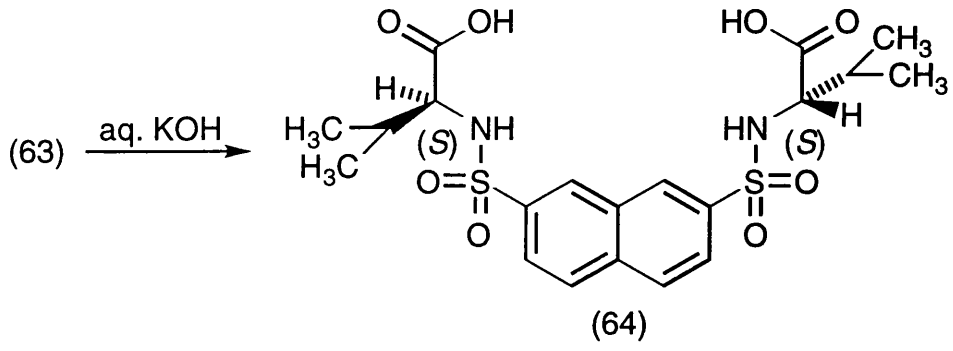
δ_H NMR ($CDCl_3$) 8.46 (2 H, m, aromatic H), 7.98 (4 H, m, aromatic H), 5.28 (2 H, d, *J* 10.2, NH), 3.84 (2 H, dd, *J* 10.2 and 5.1, CH.$CH(CH_3)_2$), 3.30 (6 H, s, $COOCH_3$), 2.05 (2 H, m, $CH_3.CH.CH_3$), 0.97 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.88 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$).

δ_C NMR ($CDCl_3$) 171.7 (C=O), 138.4 (=C<), 135.8 (=C<), 130.8 (=C<), 129.3 (=CH-), 129.2 (=CH-), 125.2 (=CH-), 61.2 (CH.$CH(CH_3)_2$), 52.2 ($COOCH_3$), 31.4 ($CH_3.CH.CH_3$), 18.9 ($CH_3.CH.CH_3$), 17.4 ($CH_3.CH.CH_3$).

Found: *m/z* 514 (M^+, 3%), 455 (65), 395 (32), 261 (33), 190 (25), 127 (29), 126 (100), 43 (31).

Found: M^+, 514.1421. $C_{22}H_{30}N_2O_8S_2$ requires *M* 514.1443.

N,*N*′-Bis[(1*S*)-1-carboxy-2-methylpropyl]-2,7-bis(aminosulfonyl)naphthalene



(64)

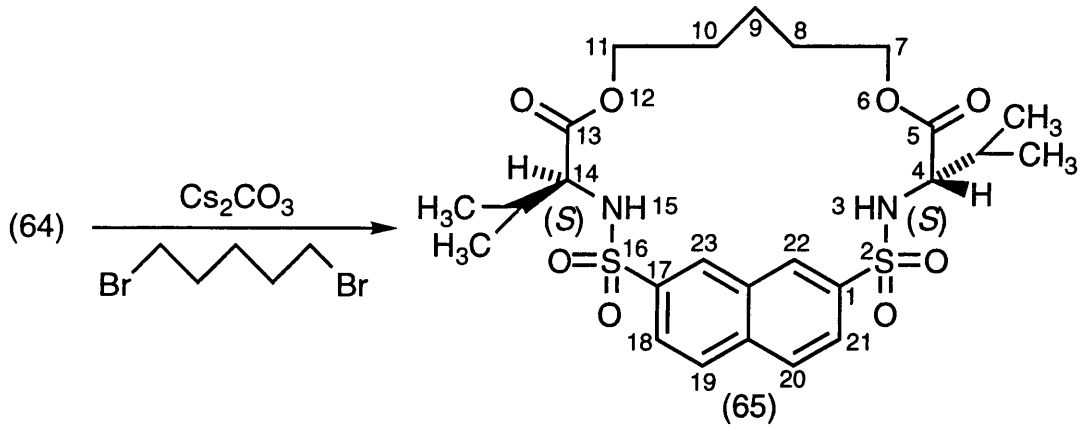
Diester (63) (29.20 g, 56.7 mmol) was treated with aqueous KOH solution (1 mol dm^{-3}; 800 cm^3). After stirring at room temperature for 48 h the solution was acidified with citric acid solution, and saturated with NaCl. The crude diacid was extracted with EtOAc (3 x 200 cm^3), dried, and the solvent removed *in vacuo*. The residue was purified by chromatography using 50:50 ether/hexane -> 100% ether to yield *compound* (64) (16.4 g, 60%) as a glass.

δ_H NMR ($CDCl_3$) 8.40 (2 H, m, aromatic H), 8.00 (4 H, m, aromatic H), 6.38 (2 H, br s, COOH), 5.45 (2 H, d, *J* 10.6, NH), 3.8 (2 H, dd, *J* 10.6 and 5.5, CH.CH(CH_3)$_2$), 2.03 (2 H, m, CH_3.CH.CH_3), 1.00 (6 H, d, *J* 6.7, CH_3.CH.CH_3), 0.92 (6 H, d, *J* 6.9, CH_3.CH.CH_3).

δ_C NMR ($CDCl_3$) 174.4 (C=O), 138.2 (=C<), 135.8 (=C<), 130.7 (=C<), 129.4 (=CH-), 129.1 (=CH-), 125.1 (=CH-), 61.0 (CH.CH(CH_3)$_2$), 31.1 (CH_3.CH.CH_3), 18.9 (CH_3.CH.CH_3), 17.1 (CH_3.CH.CH_3).

Found:*m/z* 441 (*M*-CO_2, 31), 395 (-CO_2, 43), 261 (28), 126 (100), 72 (94), 43 (36).

C-5 Bridged naphthalene based macrocycle



Diacid (64) (4.40 g, 9.04 mmol) was dissolved in methanol (150 cm^3) and deprotonated with Cs_2CO_3 (2.95 g, 9.04 mmol). Once CO_2 evolution had ceased, dry DMF (250 cm^3) was added and the solvents (and water) were removed *in vacuo*.

1,5-Dibromopentane (2.08 g, 9.04 mmol) was dissolved in dry DMF (1000 cm^3) and combined with the prepared dicesium salt. Stirring was continued for 72 h at 45 °C. The solvent was removed *in vacuo* and the residue taken up in EtOAc (400 cm^3). The extract was washed with water (2 x 100 cm^3), the solvent dried and the solution concentrated. The residue was purified by column chromatography eluting with 50:50 EtOAc/hexane to yield a viscous oil. On trituration with EtOAc the *title compound* (1.19 g, 23.7%) was isolated as an amorphous solid; m.p. 181 °C; $[\alpha]_D$ -44.4 (*c* 0.5 in DMF).

δ_H NMR ($CDCl_3$) 8.38 (2 H, m, aromatic H), 8.00 (4 H, m, aromatic H), 5.82 (2 H, d, *J* 10.1, NH), 3.96 (2 H, m, OCH_AH_B), 3.77 (2 H, dd, *J* 10.1 and 4.9, $CH.CH(CH_3)_2$), 3.55 (2 H, m, OCH_AH_B), 2.12 (2 H, m, $CH_3.CH.CH_3$), 1.09 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.95 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.86 (4 H, m, OCH_2CH_2), 0.48 (2 H, m, $(CH_2)_2CH_2$).

^{1}H NMR Decoupling Experiment:

Irradiation at 0.86 results in the collapse of the multiplets at 3.96 and 3.55 to two doublets: 3.96 (2 H, d, *J* 10.85, OCH_AH_B), 3.55 (2 H, d, *J* 10.80, OCH_AH_B).

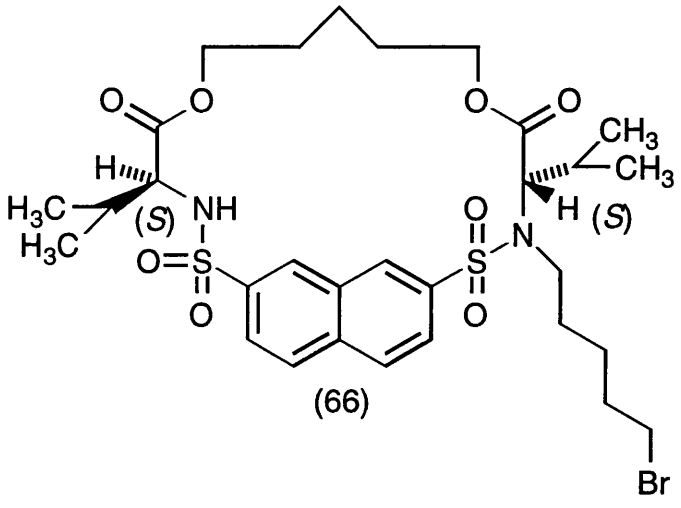
δ_C NMR ($CDCl_3$) 171.2 (C=O), 139.0 (=C<), 136.0 (=C<), 131.1 (=C<), 129.5 (=CH-), 129.2 (=CH-), 125.4 (=CH-), 64.8 (OCH_2), 61.2 ($CH.CH(CH_3)_2$), 31.9 ($CH_3.CH.CH_3$), 27.2 (OCH_2CH_2), 23.7 ($(CH_2)_2CH_2$), 19.1 ($CH_3.CH.CH_3$), 17.3 ($CH_3.CH.CH_3$).

Found:*m/z* 554 (M^+, 8%), 467 (48), 395 (32), 261 (38), 126 (100), 72 (58), 43 (27), 41 (35).

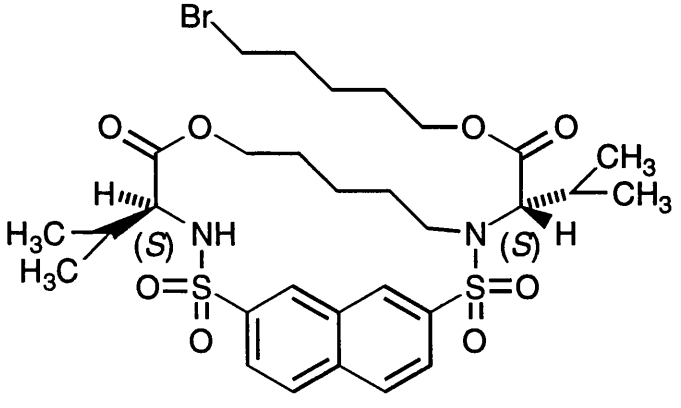
Found: C, 54.28; H, 6.22; N, 5.06.

$C_{25}H_{34}N_2O_8S_2$ requires C, 54.13; H, 6.18; N, 5.05%.

The EtOAc wash from the experiment above was evaporated and subjected to further chromatography eluting with 40:60 EtOAc/hexane to yield by-product (66) or (67) (120 mg) as a foam.



(66)

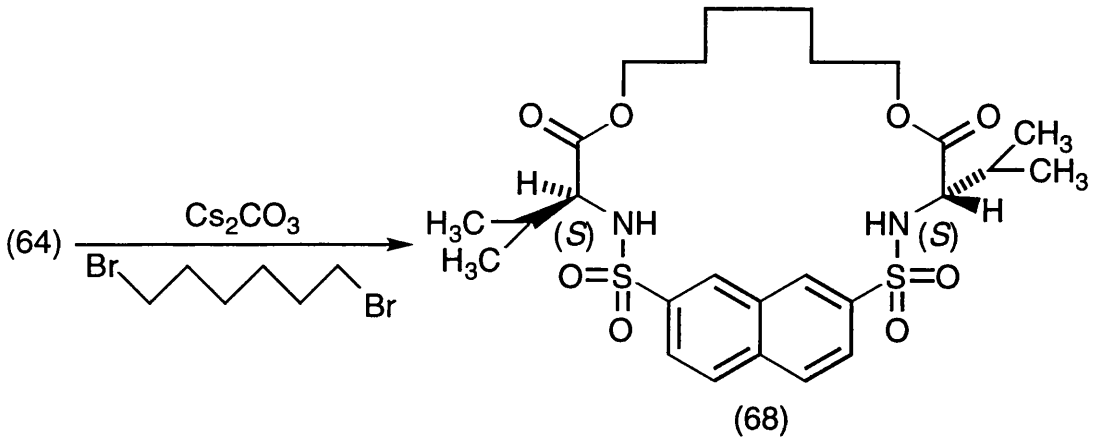


(67)

δ_H NMR ($CDCl_3$) 8.51 (1 H, 's', aromatic H), 8.46 (1 H, 's', aromatic H), 8.01 (4 H, m, aromatic H), 5.34 (1 H, d, *J* 10.1, NH), 4.03 (1 H, d, *J* 10.7, NCH), 4.00 (1 H, m, OCH_AH_B), 3.81 (1 H, dd, *J* 10.1 and 5.0, NHCH), 3.72-3.23 (7 H, m, OCH_AH_B, OCH_2, NCH_2, $BrCH_2$), 2.30-1.40 (6 H, m, CH_3CHCH_3 and CH_3CHCH_3, 2 x CH_2), 1.52 (2 H, m, CH_2), 1.18 (3 H, d, *J* 6.6, CH_3CHCH_3 [1]), 1.08 (3 H, d, *J* 7.2, CH_3CHCH_3 [2]), 0.94 (6 H, 2 x d, CH_3CHCH_3 [1] and CH_3CHCH_3 [2]), 0.91 (2 H, m, CH_2), 0.72 (2 H, m, CH_2), 0.55 (2 H, m, CH_2).

δ_C NMR ($CDCl_3$) 170.9 (C=O), 169.8 (C=O), 139.5 (=CH<), 138.7 (=C<), 135.8 (=C<), 131.0 (=C<), 129.1 (-CH<), 129.0 (-CH<), 126.3 (-CH<), 125.7 (-CH<), 66.1 (CH), 64.0 (CH_2), 63.8 (CH_2), 61.1 (CH), 46.2 (CH_2), 33.6 (CH_2), 32.1 (CH_2), 31.6 (CH_3CHCH_3), 30.5 (CH_2), 28.7 (CH_3CHCH_3), 27.2 (CH_2), 26.7 (CH_2), 25.6 (CH_2), 20.9 (CH_2), 19.5 (CH_3CHCH_3[1]), 19.45 (CH_3CHCH_3[2]), 19.1 (CH_3CHCH_3[1]), 17.2 (CH_3CHCH_3[2]).

C-6 Bridged naphthalene based macrocycle



(68)

Diacid (64) (4.95 g, 10.17 mmol) was dissolved in methanol (150 cm^3) and deprotonated with Cs_2CO_3 (3.31 g,10.17 mmol). Once CO_2 evolution had ceased, dry DMF (250 cm^3) was added and the solvents (and water) were removed *in vacuo*.

1,6-Dibromohexane (2.48 g, 10.17 mmol) was dissolved in dry DMF (1000 cm^3) and combined with the prepared dicesium salt. Stirring was continued for 72 h at 45 °C. The solvent was removed *in vacuo* and the residue taken up in EtOAc (400 cm^3). The extract was washed with water (2 x 100 cm^3), the solvent dried and the solution concentrated. The residue was purified by column chromatography eluting with 50:50 EtOAc/hexane to yield a viscous oil. On trituration with ether the *title compound* (420 mg, 7%) was isolated as an amorphous solid; m.p. 198 °C; $[\alpha]_D$ -45 (*c* 0.5 in DMF)

The ether wash was evaporated and subjected to further chromatography eluting with 40:60 EtOAc/hexane to yield by-product (69) (380 mg) as a foam.

δ_H NMR ($CDCl_3$) 8.56 (2 H, m, aromatic H), 7.95 (4 H, m, aromatic H), 5.40 (2 H, d, *J* 10.1, NH), 3.97 (2 H, m, OCH_AH_B), 3.88 (2 H, dd, *J* 10.0 and 5.0, $CH.CH(CH_3)_2$), 3.63 (2 H, m, OCH_AH_B), 2.11 (2 H, m, $CH_3.CH.CH_3$), 1.08 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.95 (6 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.94 (4 H, m, OCH_2CH_2), 0.57 (4 H, m, $(CH_2)_2CH_2$).

^1H NMR Decoupling Experiment:

Irradiation at 0.94 results in the collapse of the multiplets at 3.96 and 3.61 to two doublets: 3.97 (2 H, d, *J* 10.7, OCH_AH_B), 3.63 (2 H, d, *J* 10.7, OCH_AH_B).

δ_C NMR ($CDCl_3$) 171.2 (C=O), 139.0 (=C<), 136.0 (=C<), 131.1 (=C<), 129.5 (=CH-), 129.2 (=CH-), 125.4 (=CH-), 64.8 (OCH_2), 61.2 ($CH.CH(CH_3)_2$), 31.9 ($CH_3.CH.CH_3$), 27.2 (OCH_2CH_2), 23.7 ($(CH_2)_2CH_2$), 19.1 ($CH_3.CH.CH_3$), 17.3 ($CH_3.CH.CH_3$).

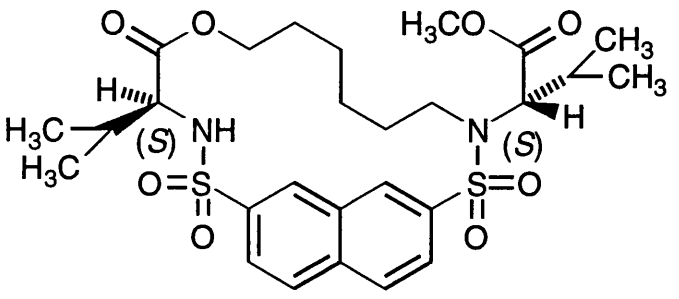
Found: *m/z* 568 (M^+, 7%), 481 (55), 395 (34), 261 (51), 190 (25), 126 (100), 72 (50), 55 (41), 43 (32), 41 (30).

Found: M^+, 568.1901. $C_{25}H_{34}N_2O_8S_2$ requires *M* 568.1913.

Found: C, 54.90; H, 6.43; N, 4.90.

$C_{25}H_{34}N_2O_8S_2$ requires C, 54.91; H, 6.38; N, 4.93%.

The by-product (69) was identified primarily from NMR irradiation experiments.



(-)-(69)

δ_H NMR (360MHz; $CDCl_3$) 8.53 (1 H, 's', aromatic H), 8.40 (1 H, 's', aromatic H), 8.04 (4 H, m, aromatic H), 5.25 (1 H, d, *J* 10.5, NH), 4.50 (1 H, d, *J* 11.0, NCH.$CH(CH_3)_2$), 4.01 (1 H, m, OCH_AH_B), 3.87 (1 H, dd, *J* 10.5 and 4.5, NHCH.$CH(CH_3)_2$), 3.67 (3 H, s, $COOCH_3$) 3.63 (1 H, m, NCH_AH_B), 3.31 (1 H, m, OCH_AH_B), 3.13 (1 H, m, NCH_AH_B), 2.24 (1 H, m, $(CH_3)_2CH.CHCOOCH_3$), 2.10 (1 H, m, $CH_3.CH.CH_3$), 1.41 (1 H, m, $NCH_2CH_AH_B$), 1.19 (1 H, m, $NCH_2CH_AH_B$, ?), 1.12 (3 H, d, *J* 6.8, $(CH_3CHCH_3)CHCOOCH_3$), 1.09 (3 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.98 (3 H, d, *J* 6.8, $(CH_3CHCH_3)CHCOOCH_3$), 0.90 (3 H, d, *J* 6.8, $CH_3.CH.CH_3$), 0.80 (1 H, m, $NCH_2CH_2CH_AH_B$, ?), 0.71 (2 H, m, $OCH_2CH_AH_B$ and $OCH_2CH_2CH_AH_B$, ?), 0.62 (2 H, m, $OCH_2CH_AH_B$ and $OCH_2CH_2CH_AH_B$, ?), 0.23 (1 H, m, $N(CH_2)_2CH_AH_B$).

^{1}H NMR Decoupling Experiments:

Irradiation at 4.50 results in the collapse of the multiplet at 2.24 to a septet.

Irradiation at 2.24 results in the collapse of the doublets at 1.12 and 0.98 to singlets.

Irradiation at 3.13 has an effect on the multiplet at 3.63.

Irradiation at 3.31 has an effect on the multiplet at 4.01.

Irradiation at 1.41 has an effect on the multiplets at 3.13, 3.63 and 0.80.

Irradiation at 0.23 has an effect on the multiplets at 0.62, 0.71 and 0.80.

δ_C NMR ($CDCl_3$) 170.9 (<u>C</u>=O and <u>C</u>OOCH$_3$), 141.8 (=<u>C</u><), 138.4 (=<u>C</u><), 135.7 (=<u>C</u><), 130.5 (=<u>C</u><), 129.6 (-<u>C</u>H<), 129.1 (-<u>C</u>H<), 128.6 (-<u>C</u>H<), 128.2 (-<u>C</u>H<), 125.7 (-<u>C</u>H<), 66.5 (<u>C</u>H), 65.0 (O<u>C</u>H$_2$), 60.8 (<u>C</u>H), 51.6 (COO<u>C</u>H$_3$), 44.7 (N<u>C</u>H$_2$), 31.4 (CH$_3$.<u>C</u>H.CH$_3$), 28.0 (<u>C</u>H$_2$), 27.4 (CH$_3$.<u>C</u>H.CH$_3$), 26.9 (<u>C</u>H$_2$), 25.4 (<u>C</u>H$_2$), 25.1 (<u>C</u>H$_2$), 19.2 (<u>C</u>H$_3$.CH.CH$_3$ and CH$_3$.CH.<u>C</u>H$_3$), 19.0 (CH$_3$.CH.<u>C</u>H$_3$), 16.9 (<u>C</u>H$_3$.CH.CH$_3$).

Found: *m/z* (FAB) 583 (MH^+, 100%).

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