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SOME ASPECTS OF THE CHEMISTRY OF CYCLIC AMINOL ETHERS

by

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A Doctoral Thesis

Submitted in partial fulfilment of the requirements
for the award of

Doctor of Philosophy

at Loughborough University

July 2001

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ACKNOWLEDGEMENTS

Cheers then!

I would like to thank the numerous people who have helped me throughout my time at Loughborough. If I've forgotten anyone- sorry!

I would first like to thank my supervisors, Prof. Phil Page and Prof. Harry Heaney for their excellent support, guidance and enthusiasm throughout the course of these studies. I would like to thank the technical services at Loughborough, including Dr. Tim Smith, John Kershaw and Alistair Daley as well as Loughborough University for funding this research.

I would like to thank my family for all their support throughout my studies.

In addition, I would like to say a big thank you to the many people who have made my time in Loughborough so enjoyable including, Rob "Gripped" Baird, Kev "Brick Majors" Batchelor, "Stunt" Dave Rutherford, Abu "Alright boss/rod/todge etc" Taher, Emma "Howayyy!!" Mann, Serge "Noir" Reigner, Martin "No-ba-con" Button, Chris "The peacock" Northfield, Anthony "Fletch" Fletcher, "Nasty" Nigel Bainbridge, Colin "Canary yellow!" Bridge, "Waspy" Jon Boxhall, Maria Goula, Mark Grafton and everyone else who I've had the dubious honour of knowing over the last 3 years. I've come to regard you as people I.....met.

I would like to thank Pete Breed, Jon Boxhall and Adela Sánchez Pelegrí for their excellent proof reading skills.

Last but not least I would like to thank Adela Sánchez Pelegrí for all her support and encouragement she has given me during this work and especially during my never ending writing up period.

Abbreviations used in the text

Å	angstrom
Ac	acetyl
AcCl	acetyl chloride
AcOH	acetic acid
Ac ₂ O	acetic anhydride
aq.	aqueous
Ar	aromatic
atm.	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
b.p.	boiling point
ⁿ Bu	<i>n</i> -butyl
^t Bu	<i>t</i> -butyl
°C	degrees Celsius
cat.	catalytic
CI	chemical ionization
cm ⁻¹	wave number
conc.	concentration
CSA	camphor sulfonic acid
d.e.	diastereomeric excess
DIAZALD	<i>N</i> -methyl- <i>N</i> -nitroso- <i>p</i> -toluenesulfonamide
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DDP	di- <i>tert</i> -butyl <i>N,N</i> -diethylphosphoramidite
DEAD	diethylazodicarboxylate
δ	chemical shift
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine

DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
eq.	equivalents
EI	electron impact
Et	ethyl
EVE	ethylvinylether
FAB	fast atom bombardment
g	grams
h	hour(s)
HPLC	high performance liquid chromatography
IPA	isopropylalcohol
iPr	isopropyl
IR	infra red
M	molar
mCPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MEK	methyl ethyl ketone
MeOTf	methyl trifluoromethanesulfonate
min.	minute(s)
mg	milligram(s)
mL	millilitre(s)
mmol	millimole(s)
MOMCl	methoxymethyl chloride
m.p.	melting point
m/z	mass to charge ratio
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate

Pd/C	palladium on carbon
Ph	phenyl
ppm	parts per million
psi	pounds per square inch
quant.	quantitative
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography
u.v.	ultra violet
v.t.	variable temperature

Abstract

This thesis has been divided into three main sections. The first chapter contains a review of calixarene chemistry, in particular that relating to calix[4]resorcinarenes. Results and discussion are compiled in chapters two through seven and experimental details are provided in chapter eight.

Chapters two and three contain results and discussion relating to the novel synthesis of the first example of an enantiomerically pure axially chiral resorcinarene derivative. Chapter two outlines the key step in the reaction sequence, that being the tetramethylation of diastereomerically pure tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine)calix[4]resorcinarene derivatives. Chapter three describes the subsequent synthetic sequence developed to fragment 3,4-dihydro-2*H*-1,3-benzoxazines with a view to removing the α -methylbenzylamine chiral auxiliary, which was used to set up the observed axial chirality of the resorcinarene. The sequence incorporates a novel modified Eschweiler-Clarke reaction whereby refluxing the required tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine)calix[4]resorcinarene derivative in aqueous formic acid resulted in reductive ring opening, furnishing the *N*-methylated analogue.

Chapter four describes work on functionalising the 'lower rim' of resorcinarene macrocycles with a view to forming derivatives with a pendant functional group that could be manipulated further to support the newly formed axially chiral resorcinarene derivatives onto solid supports.

Chapter five contains preliminary investigations into the use of axially chiral resorcinarene derivatives as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde.

Chapter six contains results of investigations into the mechanism of the 'Retro-Mannich' reaction, whereby an amine exchange reaction is observed when refluxing a dihydro-1,3-benzoxazine or Mannich base in a high boiling amine such as morpholine. Evidence has been provided that the reaction proceeds *via* an o-quinone methide intermediate.

Chapter seven describes investigations into the generality of the modified Eschweiler-Clarke reductive ring opening methodology whereby refluxing a formic acid solution of a cyclic aminol ether results in the formation of *N,N*-dialkyl derivatives *via* reductive ring opening. It was found that the procedure was general for compounds without substituents at the two position. A second reaction protocol was developed for compounds with substituents at the two position, utilising a combination of sodium cyanoborohydride and chlorotrimethylsilane in acetonitrile to furnish the desired *N,N*-dialkyl derivatives in excellent yield.

Finally, chapter eight contains full experimental details for the synthetic studies carried out in the preceding chapters.

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Chapter 1

1.0 Introduction

Calixarenes are a family of cyclic oligomers prepared by an acid catalysed condensation reaction between a variety of phenols and aldehydes. The name calixarene derives from the fact that their shape resembles a Greek vase known as a *calix crater*. For the purposes of this introduction, only resorcinol derived cyclic tetramers will be considered except for pertinent examples of other calixarenes. A comprehensive account of the discovery and characterisation of these interesting families of compounds has been written by Gutsche.¹

1.1 Calixarenes and Calix[4]resorcinarenes

In general, the family of compounds known as calixarenes can be separated into two distinct categories, those derived from phenols and formaldehyde and those derived from resorcinol and aldehydes.

The reaction of a *p*-substituted phenol with formaldehyde can, depending on the reaction conditions used, form a cyclic oligomer with four, six or eight phenolic units per macrocycle. These compounds are known as calix[X]arenes where X can be four, six, eight etc. The use of *p*-*tert*-butylphenol leads to a configurationally locked compound that has been extensively studied and derivatised.²

Calix[4]resorcinarenes are the product of the reaction between resorcinol and an aldehyde (or derivatives thereof). They are also cyclic oligomers, characterised by having, in the vast majority of cases, four resorcinol units linked by four aliphatic or aromatic chains. There are also isolated examples of calix[5]resorcinarenes¹⁰ and calix[6]resorcinarenes,¹⁰ synthesised from resorcinol and formaldehyde, but calix[4]resorcinarenes are by far the most common and have been studied

extensively.³ Some authors name them resorcinarenes, the nomenclature which will be used throughout this thesis.

1.2 Synthesis of Resorcinarenes

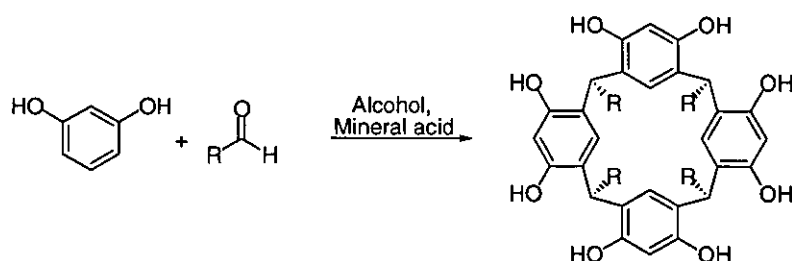
Resorcinarenes are cyclic tetramers formed by an acid catalysed condensation reaction between resorcinol and an aliphatic or aromatic aldehyde. In the majority of cases, mineral acids are used, although there is literature precedent for the use of Lewis acids.⁷⁻⁹ In all cases, excellent yields of the tetrameric products are isolated, without the need for high dilution or templating effects.

1.2.1 Mineral Acid Catalysed Resorcinol-Aldehyde Condensations

In general, the acid catalysed condensation reactions take place between equimolar amounts of resorcinol and an aldehyde in a mixture of ethanol and concentrated hydrochloric acid. The reaction mixtures are heated under reflux for several hours and after cooling, the desired oligomer often crystallises from the reaction mixture, although in some cases water is needed to precipitate the desired product. A wide variety of aldehydes can be used, ranging from straight chain aliphatic aldehydes such as hexanal and dodecanal, substituted aromatic aldehydes and 'masked' aldehyde precursors such as 2,3-dihydrofuran. There are several limitations. Very sterically crowded aldehydes such as 2,4,6-trimethylbenzaldehyde do not form resorcinarenes readily, possibly due to disruption of phenolic hydrogen bonding. In addition, aldehydes with functionalities close to the reactive centres do not give a good yield of the desired macrocycle.

Much work in terms of preparation and characterisation of these compounds has been carried out by the groups of Högberg⁴ and Cram.⁵ In simple terms, the fourfold condensation reaction can be represented as shown in **Equation 1**. Bearing in mind the vast numbers of macrocycles, oligomers and polymers that could be formed in the

reaction, the isolation of one product as one stereoisomer is remarkable.



Equation 1

1.2.2 Stereochemical Implications

In theory, resorcinarenes can exist in many stereoisomeric forms. Högberg and others proposed these could be defined as a combination of three basic stereochemical elements:

- (i) The conformation of the macrocyclic ring, whereby the resorcinarene may take up one of five extreme symmetrical arrangements, as shown in **Figure 1**.

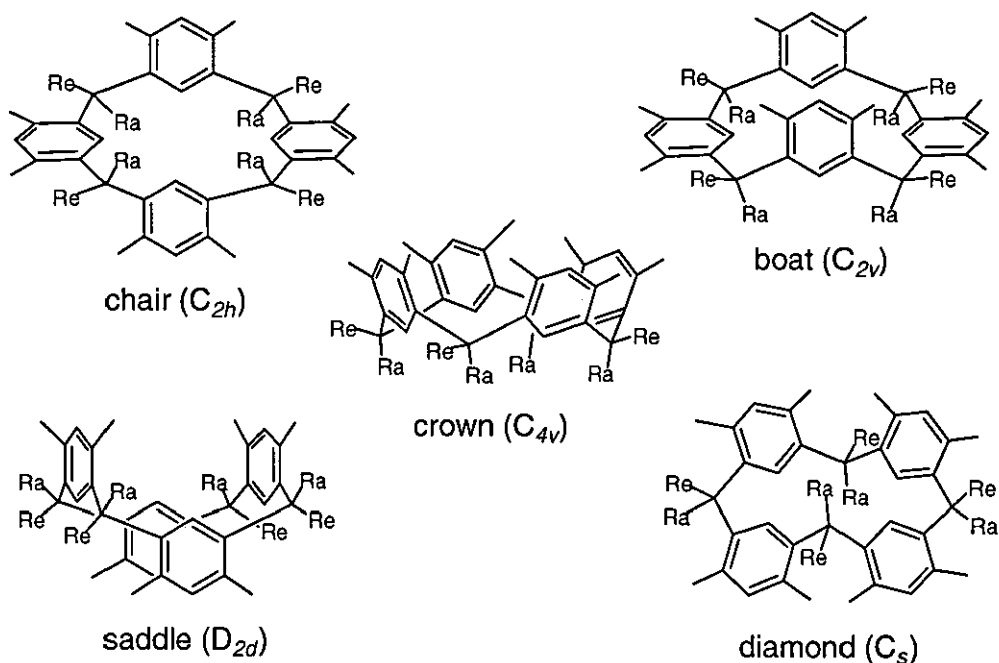


Figure 1

These conformations have been assigned the following names: the crown (C_{4v}), boat (C_{2v}), chair (C_{2v}), diamond (C_s) and saddle (D_{2d}).

- (ii) The relative configuration of the groups at the methylene linkers, giving the all-cis (rccc), cis-cis-trans (rcct), cis-trans-trans (rctt) and trans-cis-trans (rtct) arrangements, as shown in **Figure 2**.

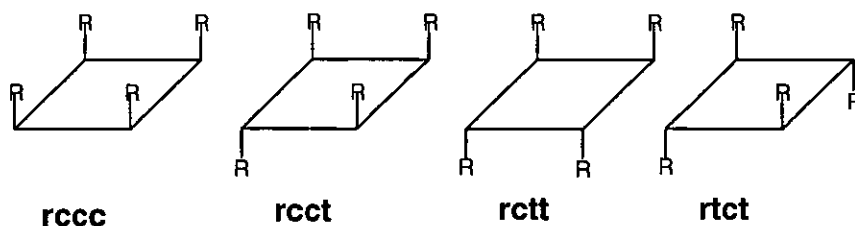


Figure 2

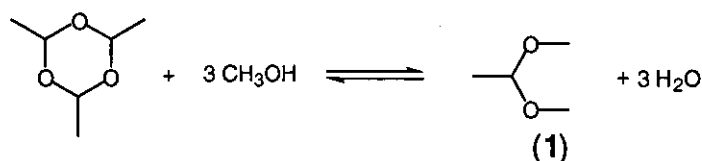
- (iii) The individual configurations of the substituents at the methylene linkers where in conformations of the macrocycle with C symmetry, the groups may be axial or equatorial.

Combinations of these stereochemical elements give rise to a large number of possible stereoisomers, of which only four have been detected experimentally.

Studying the acid catalysed condensation reaction between resorcinol and benzaldehyde, in refluxing ethanolic hydrochloric acid, Högberg and co-workers^{4b} isolated two distinct stereoisomers whose relative amounts varied over time. The initially formed product was found to be the 'chair' isomer, and reached a maximum after one hour and soon decreased. The final product observed after *ca.* twenty four hours was the less soluble 'boat' isomer, indicating that the formation of the 'chair' isomer was reversible under the reaction conditions. This was confirmed by taking the initially formed 'chair' isomer and treating it under similar reaction conditions to generate the thermodynamically preferred 'boat'.

Molecular modelling calculations showed that the 'chair' isomer is statistically twice as likely to form as the corresponding 'boat' isomer and consequently it is the kinetic product. The condensation reaction is reversible indicated by the conversion of the chair isomer to the boat isomer and also its isomerisation. (It presumably occurs *via* a 'protodealkylation' process with scission of the methine-aryl C-C bonds, facilitated by the hydroxy groups in the ortho and para positions). Recombination then follows to give the thermodynamically more stable 'boat' isomer. Differences in the stereochemical structures of the two isomers indicate that two C-C bonds are cleaved before recombination takes place. The differences in the solubility of the two products also plays a part in driving the reaction to form the 'boat' isomer

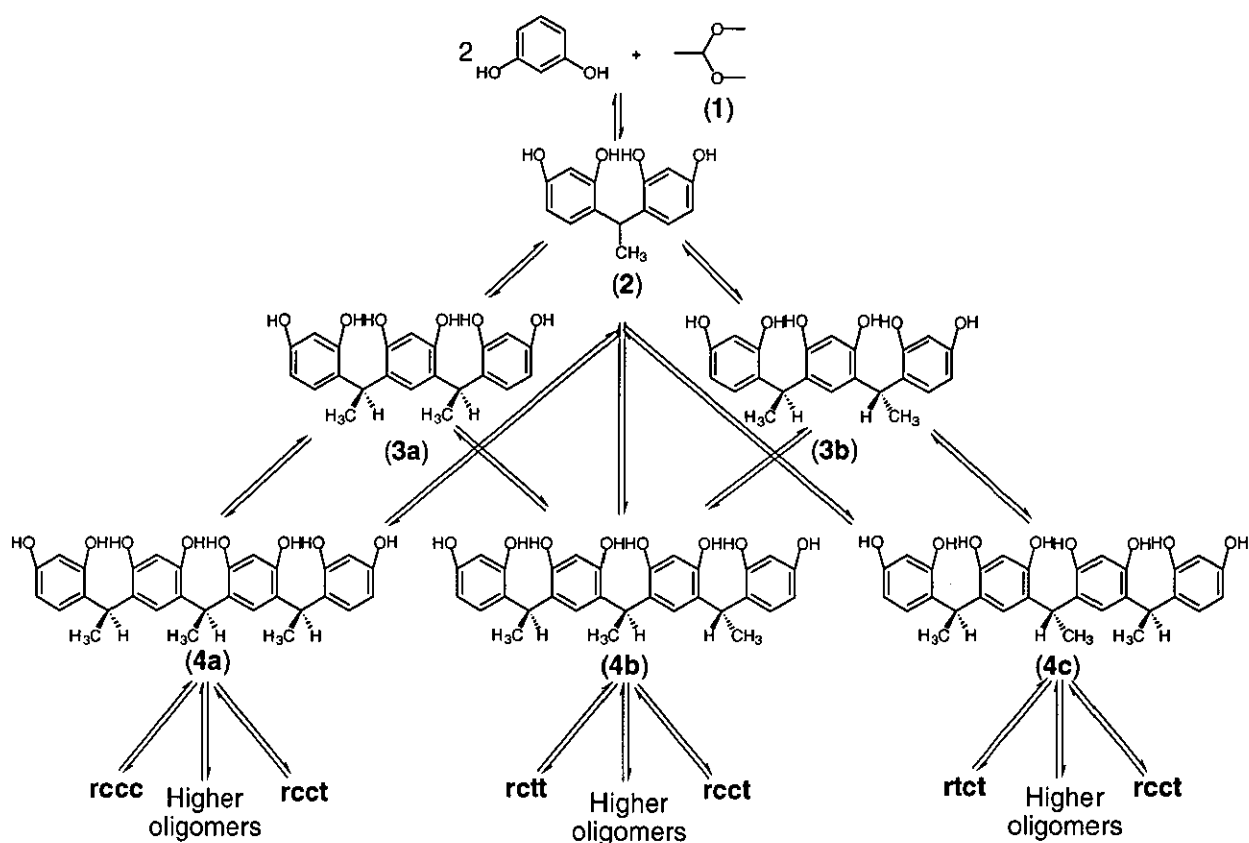
The mechanism of this macrocycle generation reaction has been studied in some depth by the groups of Weinelt and Schneider.⁶ By following the acid catalysed condensation reaction by high field ¹H NMR spectroscopy they were able to follow the formation and degradation of a range of oligomers and rings. They were able to deduce that the electrophilic species attacking resorcinol in methanol was not the aldehyde but the corresponding dimethyl acetal (1) which is rapidly formed, as depicted in **Equation 2**.



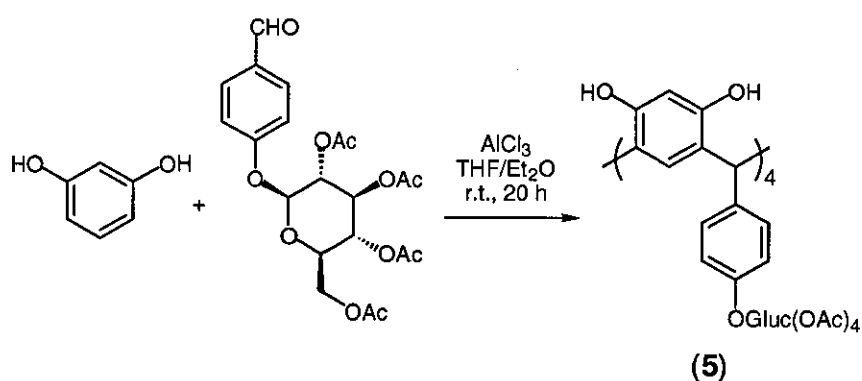
Equation 2

The mechanism of formation is shown in **Scheme 1**. Reaction of the dimethyl acetal (1) with two resorcinol units gave the first observable intermediate (2). Sequential coupling of this species with more resorcinol units gave the observed trimers (3a) and (3b) and tetramers (4a), (4b) and (4c) as well as higher oligomers, which are present as unidentified multicomponents in concentrations of up to 45% at intermediate reaction times. During the course of the reaction, these higher homologues reverted

back to the tetramers (4) since the condensation is reversible under the reaction conditions. The tetramers (4) were not observed in the reaction mixture as they rapidly cyclised to the desired resorcinarenes. This fast cyclisation is related to their conformation, which, according to molecular mechanics calculations, is folded rather than linear as a consequence of the ability to form stronger hydrogen bonds between phenolic hydroxyl groups of adjacent resorcinol units in the folded structure. It was also observed that all intermediates showed resorcinol and not methoxymethyl units at the terminal positions which is consistent with the fast reaction of these species under the reaction conditions.

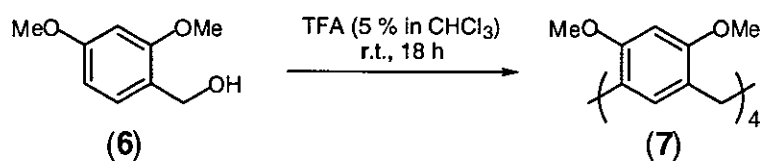


The following conclusions were therefore reported for the formation of the macrocyclic products: (i) Cyclisation of the tetramers (4) is as fast as chain propagation; (ii) The macrocyclic products act as a thermodynamic sink for the reaction; (iii) The higher



Equation 4

The unsubstituted resorcinarene (**7**) was isolated in excellent yield upon treatment of 2,4-dimethoxybenzyl alcohol (**6**) with TFA. The compound was conformationally flexible due to the lack of substitution at the C position and as a result, only one stereoisomer was observed,⁹ as shown in **Equation 5**. This product is not available from the conventional mineral acid catalysed reaction between resorcinol and formaldehyde as this gives polymer as the major product.

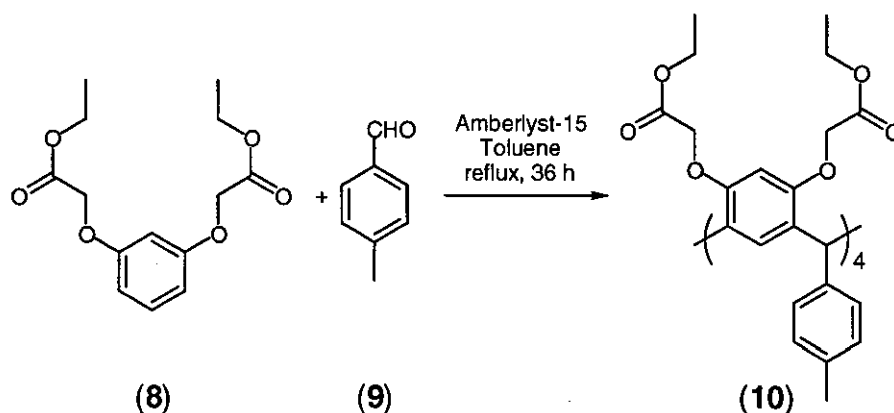


Equation 5

Lanthanide triflates have been shown to act as efficient catalysts for resorcinarene formation. For example, Ytterbium(III)triflate effectively catalyses the reaction between resorcinol and a range of aliphatic aldehydes in refluxing ethanol, to give the desired resorcinarenes exclusively as the rccc stereoisomer, in excellent yields. In the case of the condensation between resorcinol and benzaldehyde under the same reaction conditions, a 7:10 ratio of kinetic to thermodynamic diastereomers was isolated, which under prolonged reaction times gave completely the thermodynamic product. This is consistent with the observations of Högberg and others for the

Brønsted acid catalysis pathway, but not consistent with Lewis acid catalysis. This was explained by the liberation of triflic acid during the course of the reaction which slowly isomerised the initial kinetic product to the thermodynamically more stable product.¹⁰

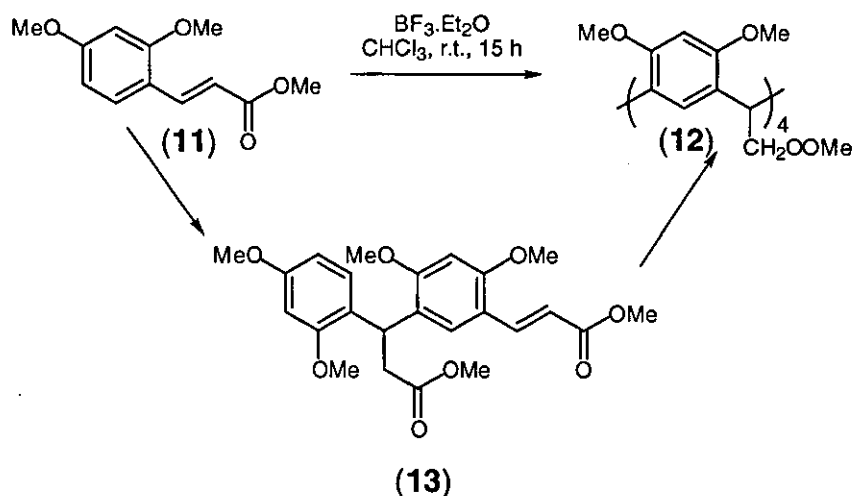
Heterogeneous catalysis has been employed *via* the use of cation exchange resins, *i.e.* Amberlyst-15. This catalysed the reaction between equimolar amounts of diethyl benzene-1,3-diylldioxydiacetate (**8**) and *p*-methylbenzaldehyde (**9**) in refluxing toluene to furnish the *rcct* stereoisomer as the octaacetate (**10**) in low yield,¹¹ as shown in **Equation 6**.



Equation 6.

Another general route to obtain resorcinarenes employs the Lewis acid condensation of 2,4-dimethoxycinnamates (**11**) using ethereal boron trifluoride.¹² A range of 2,4-dimethoxycinnamates, with a variety of ester functionalities, was treated with ethereal boron trifluoride to furnish the desired resorcinarenes (**12**), generally as a mixture of the boat isomer (*rcct*), diamond (*rcct*) and saddle (with the substituents in an all *cis* arrangement). Chiral derivatives have also been synthesised by employing the mixed anhydrides of cinnamic acid and L- or D-valine under the same reaction conditions, again furnishing the desired resorcinarenes as a mixture of stereoisomers. The isolation of the intermediate product (**13**), shown in **Scheme 2**, indicated that

stepwise growth may occur (monomer \rightarrow dimer \rightarrow trimer \rightarrow tetramer) followed by cyclisation, or alternatively *via* the cyclo-oligomerization of dimer (13).



Scheme 2

1.2.4 Synthesis of Calix[5]resorcinarene and Calix[6]resorcinarene

Konishi and co-workers¹³ have succeeded in isolating small quantities of calix[5]resorcinarene and calix[6]resorcinarene from the base catalysed reactions of 2-alkylresorcinols with formaldehyde or the acid catalysed reaction of 2-alkylresorcinols with formaldehyde diethyl acetal. The reaction of 2-propylresorcinol and formaldehyde diethyl acetal, catalysed by concentrated hydrochloric acid in ethanol, was followed by both ¹H NMR and HPLC analysis. The reaction mixture was shown to go through a number of distinct phases. After fifteen minutes a decrease of 2-propylresorcinol was observed, replaced by a series of linear oligomers. After thirty minutes the reaction mixture was shown to be made up of a mixture of three cyclic oligomers, the major one being calix[6]resorcinarene. After two hours, the major product was observed to be calix[4]resorcinarene with small amounts of both calix[5]resorcinarene and calix[6]resorcinarene present. After six hours, the reaction mixture was predominately calix[4]resorcinarene.

Further studies showed that upon resubjecting calix[6]resorcinarene to the reaction conditions, resulted in isomerisation to calix[4]resorcinarene, whereas treatment of calix[5]resorcinarene gave initially both calix[6]resorcinarene and calix[4]resorcinarene, giving finally calix[4]resorcinarene only. These reactions showed that the 'protodealkylation' reaction postulated by Högberg⁴ was indeed one of the most probable reaction pathways occurring in the synthesis of resorcinarenes *i.e.* higher oligomers and cyclic oligomers continually forming and degrading with the final product being the thermodynamically most stable calix[4]resorcinarene.

1.3 Molecular Recognition Phenomena Exhibited by Unsubstituted Calix[4]resorcinarenes.

By virtue of their well-defined upper and lower 'rims', the all cis C_{4v} crown stereoisomer, as shown in **Figure 3**, is well set up to act as a host in a variety of host-guest complexation studies, along with the potential for further functionalisation to enhance these complexation properties.

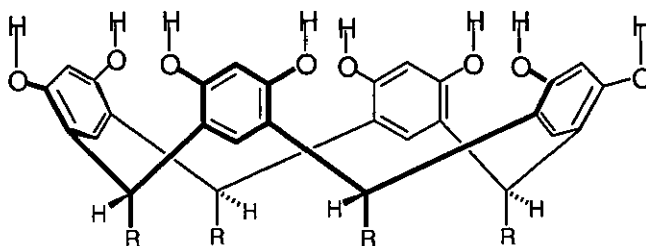


Figure 3.

The resorcinarene can be envisaged as a tetradentate host, having four independent binding sites, each composed of a pair of hydrogen-bonded OH groups on adjacent benzene rings, as shown in **Figure 4**.

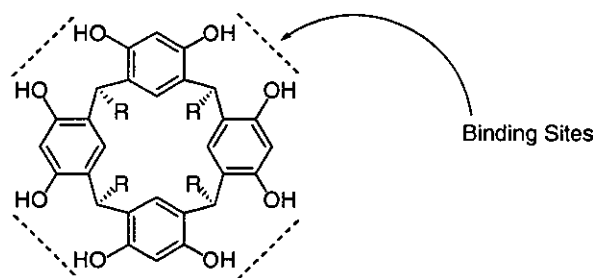


Figure 4

1.3.1 Binding with Small Polar Organic Molecules

These hosts have been shown to bind with a range of small polar organic molecules. A large amount of work in this area has been carried out by Aoyama and co-workers, especially on the complexation between resorcinarenes and polyols such as chiral glycols, steroidal polyols and sugars.¹⁴ The most interesting examples of this effect are observed when selectivity between guests is exhibited.

1.3.2 Complexation with D-ribose

D-Ribose is an aldopentose that can exist in two pyranose and two furanose forms, as shown in **Figure 5**, and is insoluble in carbon tetrachloride.

When an aqueous solution of D-ribose and a solution of β -undecylcalix[4]resorcinarene in carbon tetrachloride were stirred together, a 1:1 host guest complex between the resorcinarene and D-ribose was formed and extracted into the organic layer. Spectroscopic analysis showed the D-ribose was extracted *exclusively* in the α -pyranose form.¹⁵

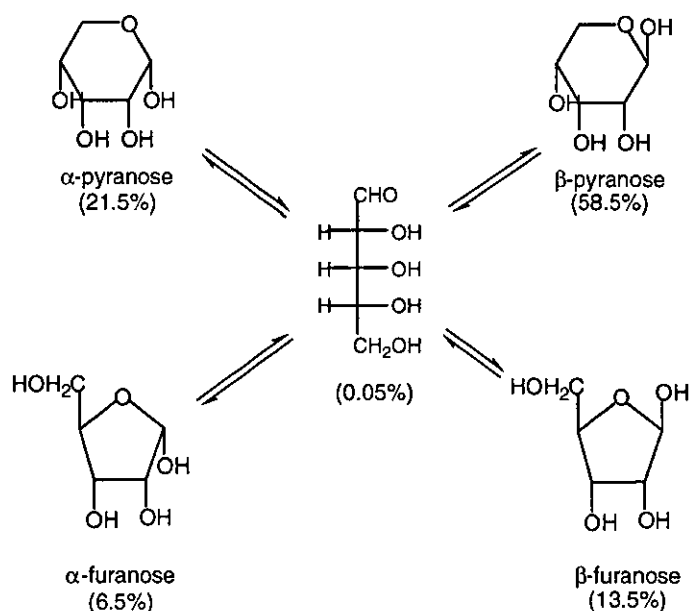


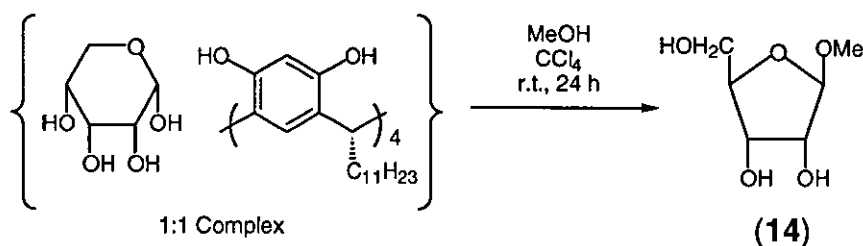
Figure 5

A similar result was observed with a mixture of D-fructose and D-glucose, with D-fructose being complexed readily and D-glucose showing almost no affinity to the host. A number of factors have been identified that are crucial for efficient complexation of sugars and cyclic polyols:¹⁶ (i) A *cis* relationship between hydroxyl groups at C-3 and C-4 is crucial for efficient complexation. (ii) The hydroxyl group at C-2 does not partake in binding and should be *cis* to the hydroxyl groups at C-3 and C-4 or otherwise absent as it leads to unfavourable exposure to the apoar media. (iii) The substituent at C-5 should be as hydrophobic as possible as this group determines the strength of the complexation. In addition, the CH- π interaction between host and guest plays an important part in the efficiency of the complexation, contributing up to 1.4 kcal/mol.¹⁷

1.3.3 Stereoselective Glycosidation of Ribose.

This selective complexation of the α -pyranose anomer with resorcinarenes has been exploited to effect stereoselective glycosidation of ribose to yield exclusively methyl- β -

ribofuranoside (**14**).¹⁸ Stirring a carbon tetrachloride solution of the resorcinarene:ribose complex and a ten fold excess of methanol for twenty four hours resulted in a quantitative conversion to methyl- β -ribofuranoside. Prolonged exposure resulted in isomerisation to all four possible glycosides, and using a larger excess of methanol resulted in no reaction, due to competitive complexation of methanol, as shown in **Equation 7**.



Equation 7

Another example of selectivity in resorcinarene host/guest complexation involves the discrimination between a variety of dicarboxylic acids,¹⁹ as shown in **Figure 6**.

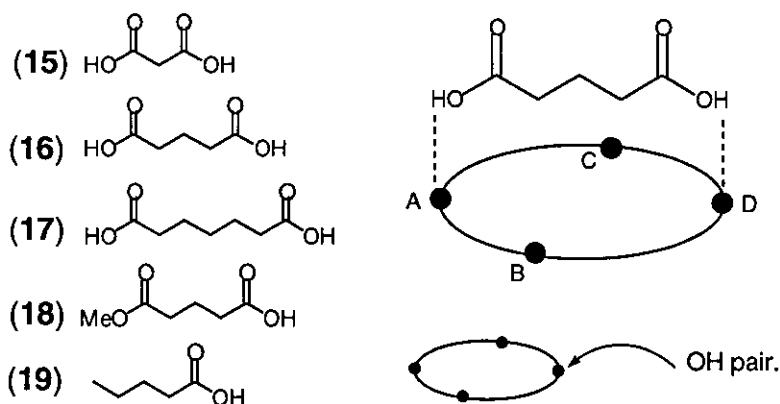


Figure 6

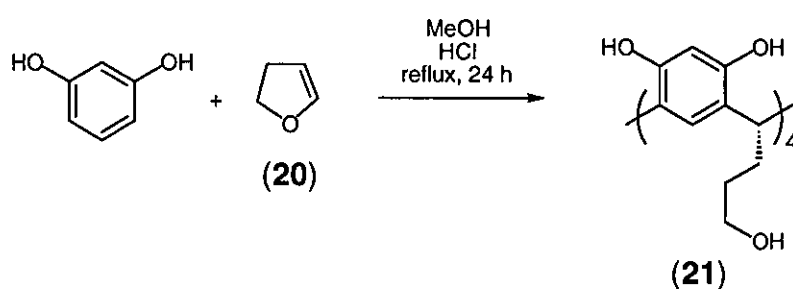
Glutaric acid (**16**) is slightly soluble in carbon tetrachloride, but is readily solubilised in the presence of *C*-undecylcalix[4]resorcinarene, forming a 1:1 complex. No complexation was observed between the resorcinarene and dimethyl glutarate or

between glutaric acid and the octaacetate derivative of the resorcinarene. Likewise, running the experiment in hydrogen bond breaking solvents such as acetone resulted in no complexation. Further evidence for a two point hydrogen bonding effect was supplied by the fact that valeric acid (**19**), glutaric acid monomethylester (**18**), pimelic acid (**17**) and malonic acid (**15**) had substantially lower binding affinities than that for glutaric acid. This suggests that glutaric acid has the optimum length chain for a two point hydrogen bonding interaction to occur.

1.4 Lower Rim Functionalisations

Along with the upper rim, the lower rim of resorcinarenes provides ample scope for further elaboration, either by varying the aldehyde component used in the resorcinarene forming condensation reaction, or by subsequent functional group manipulation. These transformations may be carried out with a view to creating 'handles' for isolation on solid supports or to create additional binding sites for molecular complexation.

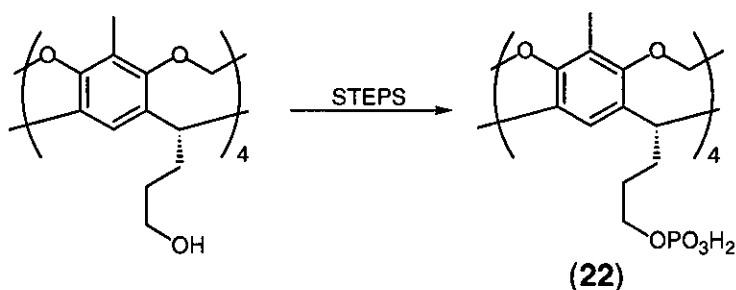
It has been shown that by reacting 2,3-dihydrofuran (**20**) with resorcinol under mineral acid catalysis the corresponding resorcinarene with four propanol chains (**21**) is formed in excellent yield,^{5,20} as shown in **Equation 8**.



Equation 8.

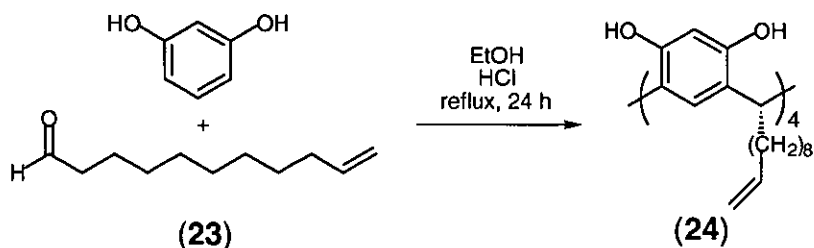
Compounds of this type have been used as precursors in the synthesis of water

soluble resorcinarene derivatives.²⁰ Phosphorylation of the hydroxyl groups with DDP followed by oxidation with hydrogen peroxide afforded the *tert*-butyl-protected phosphate derivative. Removal of the *tert*-butyl groups with TFA afforded the phosphate footed derivative (**22**), as shown in **Equation 9**.



Equation 9.

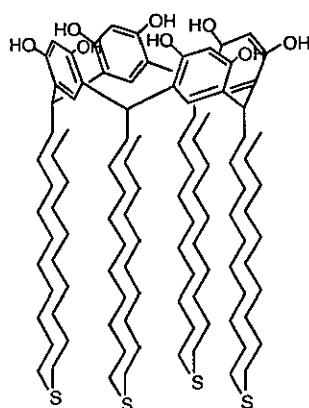
Treating 10-undecanal (**23**) with resorcinol in ethanolic hydrochloric acid under the standard reaction conditions gave the resorcinarene (**24**), exclusively as the *rccc* stereoisomer in 22% yield, as shown in **Equation 10**.²¹



Equation 10.

These compounds have been used as precursors to a range of other resorcinarenes. Treatment with thioacetic acid under UV irradiation followed by alkaline hydrolysis gave the corresponding resorcinarene with four thiol residues, which formed self assembled monolayers on the surface of gold.²² In a similar manner, addition of 1-decanethiol to the parent tetraalkene *via* an anti-Markovnikov addition with 9-BBN in THF at 0 °C, formed the tetrasulfide (**25**), which also formed self assembled

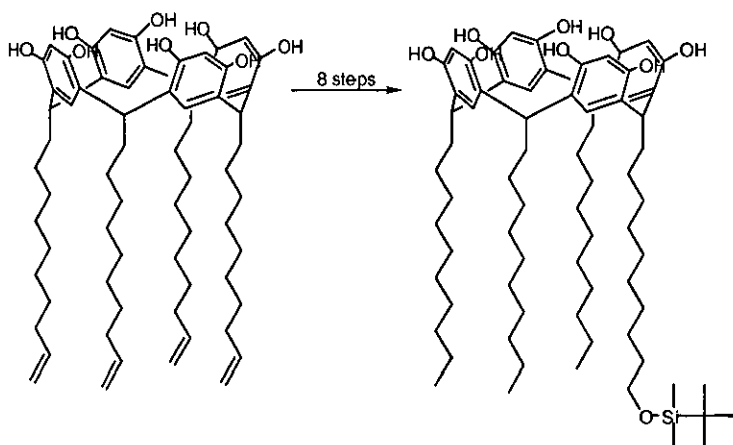
monolayers on gold, as shown in **Figure 7**.²³



(25)

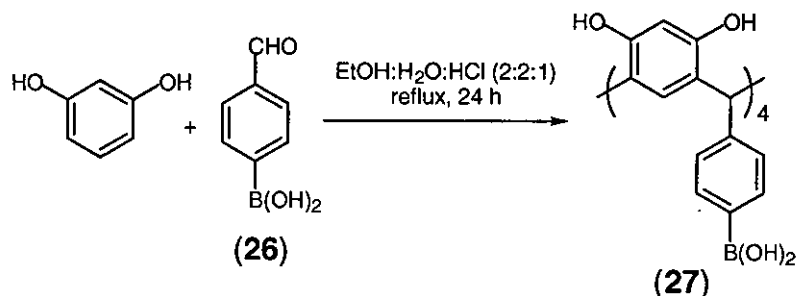
Figure 7.

The tetraalkene parent alkene has been utilised as a precursor for the selective derivatisation of the lower rim. It was shown that it is possible to selectively epoxidise one of the alkene residues using mCPBA to obtain the monoepoxide, albeit in low yield.²⁴ This useful functional group could then be manipulated further to give a range of interesting mono-functionalised resorcinarene derivatives, as shown in **Equation 11**.



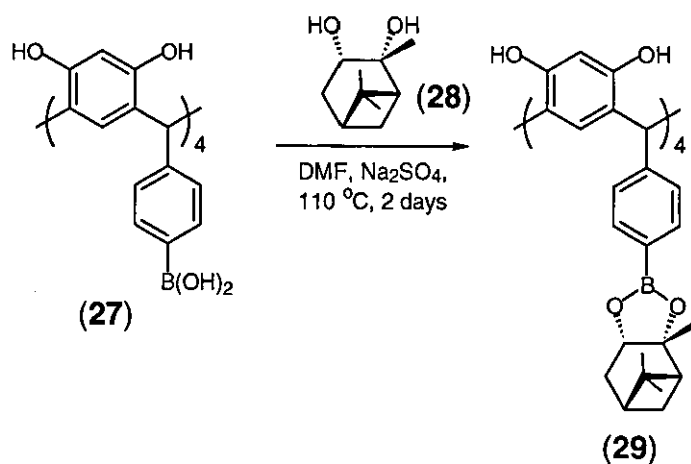
Equation 11

Another useful family of lower rim functionalised resorcinarene derivatives are those with boronic acid moieties present such as (27). Treating resorcinol with (4-formylphenyl)boronic acid (26) under the standard mineral acid catalysed reaction conditions gave the corresponding tetraboronic acid substituted resorcinarene (27) in almost quantitative yield as a 3:2 mixture of rccc (crown, C_{4v} symmetry) and rcctt (chair, C_{2h} symmetry) stereoisomers, which were easily separable by fractional crystallisation, as shown in **Equation 12**.



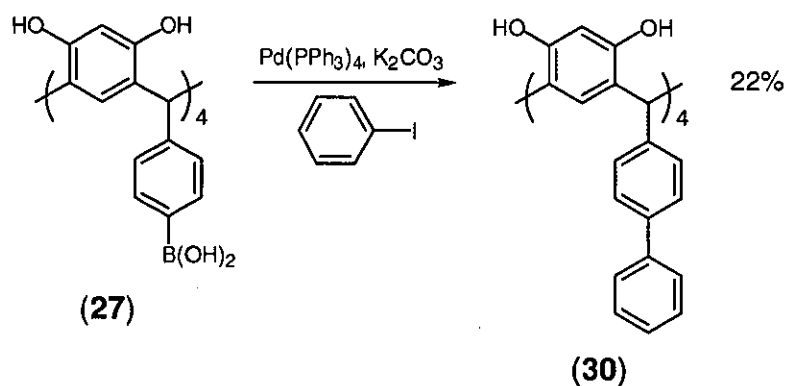
Equation 12

Boronic acid (27) could be converted to the corresponding boronate ester by reaction with (1*R*, 2*R*, 3*S*, 5*R*)-(-)-pinanediol (28), in the presence of Na_2SO_4 , in DMF in moderate yield. The resorcinarene derivative (29), shown in **Equation 13**, represented the first example of a resorcinarene with a chiral appendage on the lower rim.²⁵



Equation 13

The boronic acid functionalised resorcinarene derivatives (**27**) have also been shown to undergo Suzuki cross coupling reactions to furnish resorcinarenes with deepened polyaromatic lower cavities such as (**30**), as shown in **Equation 14**.²⁶

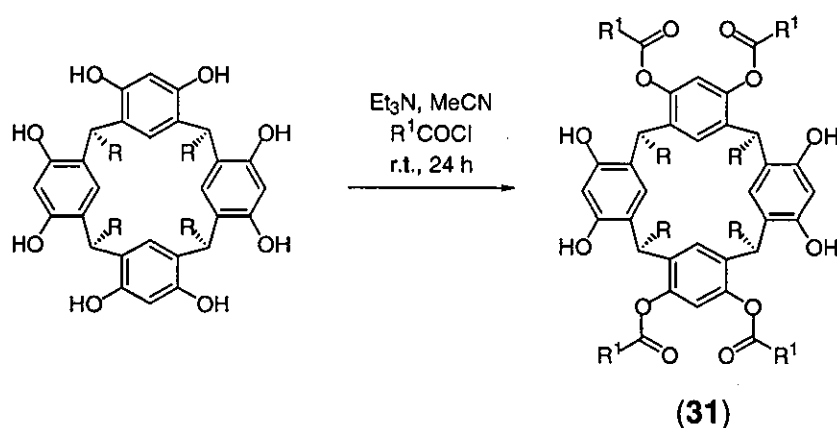


Equation 14

1.5 Upper Rim Functionalisations

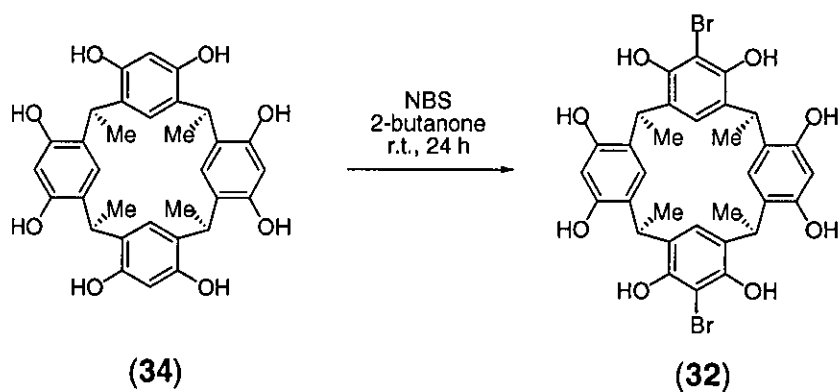
By virtue of the well defined upper and lower rims of the C_{4v} symmetric thermodynamic products, resorcinarenes are well set up for further functionalisation. A number of groups have attempted to effect regioselective functionalisations to partially derivatise just a number of the reactive sites on the upper rim, with a view to breaking the C_{4v} planes of symmetry. This can generate new and interesting intermediates with different symmetry elements.

Böhmer and co-workers²⁷ have successfully tetraacylated a series of resorcinarenes by selectively acylating the hydroxyl groups of two distal resorcinol rings. The distally tetraacylated resorcinarenes (**31**) were isolated in poor to moderate yield, as shown in **Equation 15**.



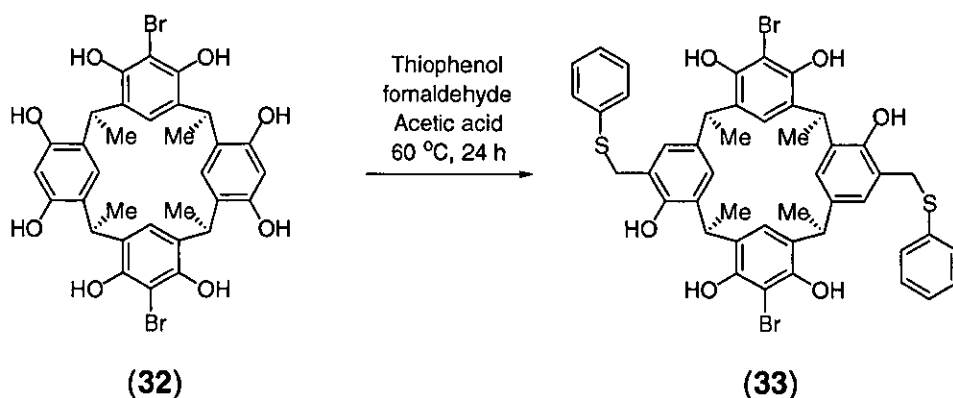
Equation 15

The selectivity is strongly dependent upon the reaction conditions and the acylating agent and is thought in part to be a result of a complex between triethylamine and the resorcinarene reacting with the acid chloride. The remaining unfunctionalised resorcinol rings can then be derivatised further, for example *via* bromination using NBS. A similar procedure for the regioselective distal-dibromination of resorcinarenes has been developed by Konishi and co-workers.²⁸ Employing two equivalents of NBS in a concentrated solution of *C*-methylcalix[4]resorcinarene (**34**) in 2-butanone, the distally substituted dibromo derivative (**32**) was isolated by recrystallisation in moderate yield, as shown in **Equation 16**.



Equation 16

The authors suggested that the regioselectivity was due to an electronic effect from the first bromine being transferred through an intramolecular hydrogen bond to the neighbouring resorcinol unit, thus deactivating it in comparison to the distal resorcinol group. These distally brominated resorcinarene derivatives (**32**) have been further functionalised with thiomethyl groups. The use of formaldehyde and thiols such as thiophenol gave resorcinarenes with distal thioether moieties, such as (**33**), shown in Equation 17.



Equation 17

Using α,ω -dithiols created bridged 'basket' type molecules containing a thioether linkage between the two opposite resorcinol units, such as those depicted in Figure 8.²⁹

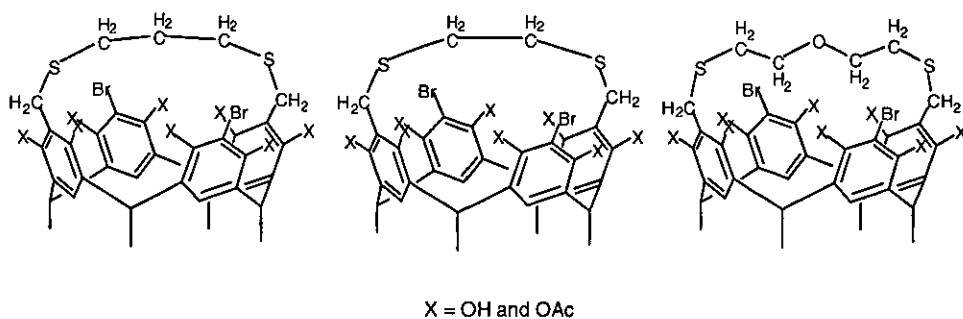
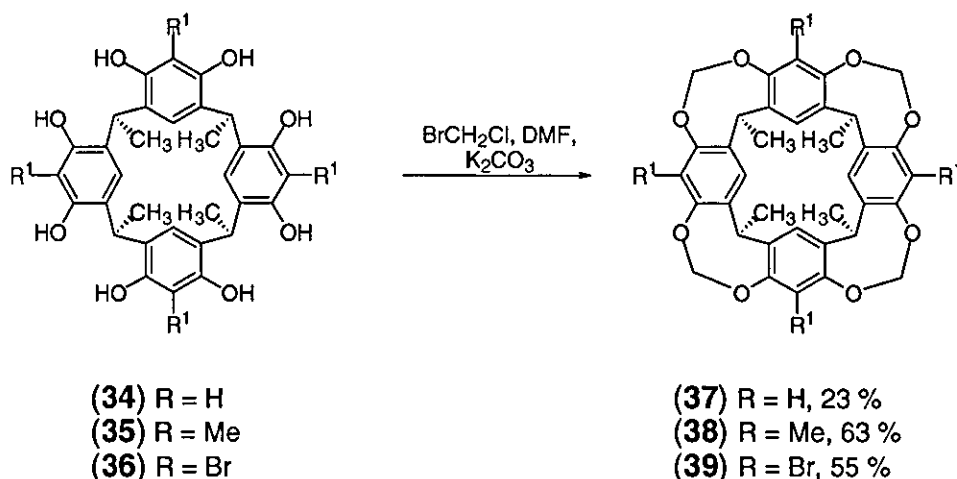


Figure 8

One of the most common types of functionalisation on the upper rim of rccc stereoisomers is the covalent linking of neighbouring phenolic groups. A wide range of linking groups have been used and these compounds have the advantage of having a more rigid structure with a permanent cavity. These compounds have become known as cavitands.

Cram and co-workers³⁰ found that by treating the all cis rccc stereoisomers (34), (35) and (36), with CH_2ClBr in DMSO in the presence of potassium carbonate, the tetra-bridged compounds (37), (38), and (39) were obtained in poor to good yield, as shown in **Equation 18**.

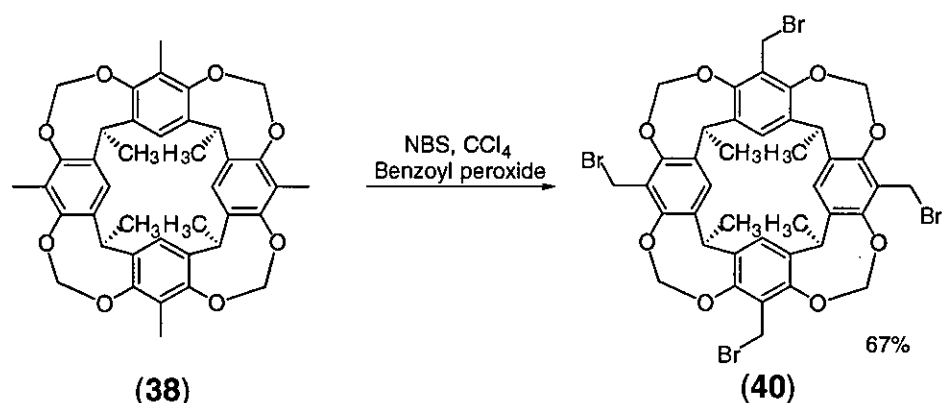


Equation 18

Studies showed that higher yields were obtained using resorcinarenes with $\text{R} = \text{CH}_3$ (35) or Br (36) (easily obtained by reaction of the resorcinarene with NBS in 2-butanone) than with $\text{R} = \text{H}$ (34).

Related to this, using NBS, the tetra bridged compound (38) has been shown to undergo exclusive free radical bromination, in good yield at the 2-methylresorcinol position with no attack at the Ar-CHR-Ar position. This gave the tetra-brominated resorcinarene (40),³¹ as shown in **Equation 19**. This preferred reactivity at the

formally less reactive primary, benzylic position can be explained by geometric constraints inhibiting resonance stabilisation, therefore inducing a reversal of selectivity.



Equation 19

1.6 Carcerands

Resorcinarenes such as (40) are important precursors to families of supramolecular compounds known as carcerands and hemicarcerands. When two cavitands are linked *via* their upper rims by covalent bonds, a carcerand is formed. These enforced cavities are large enough to imprison smaller organic molecules. The imprisoned molecule acts as a template for the formation of the carcerand and is crucial for the success of formation. The cavity also shows molecular recognition properties as formation in a 1:1 mixture of solvents results in just one of the two possible carcerands. The carcerand (41) shown in **Figure 9**,³² is rugby ball shaped and has two openings, one at each end between the four methyl groups, approximately 2.5 Å in diameter. Water is the largest molecule that can pass through the openings without bond breakage occurring.

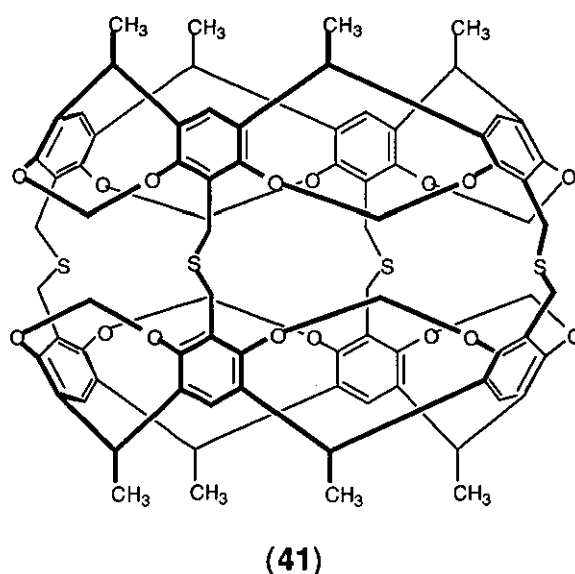
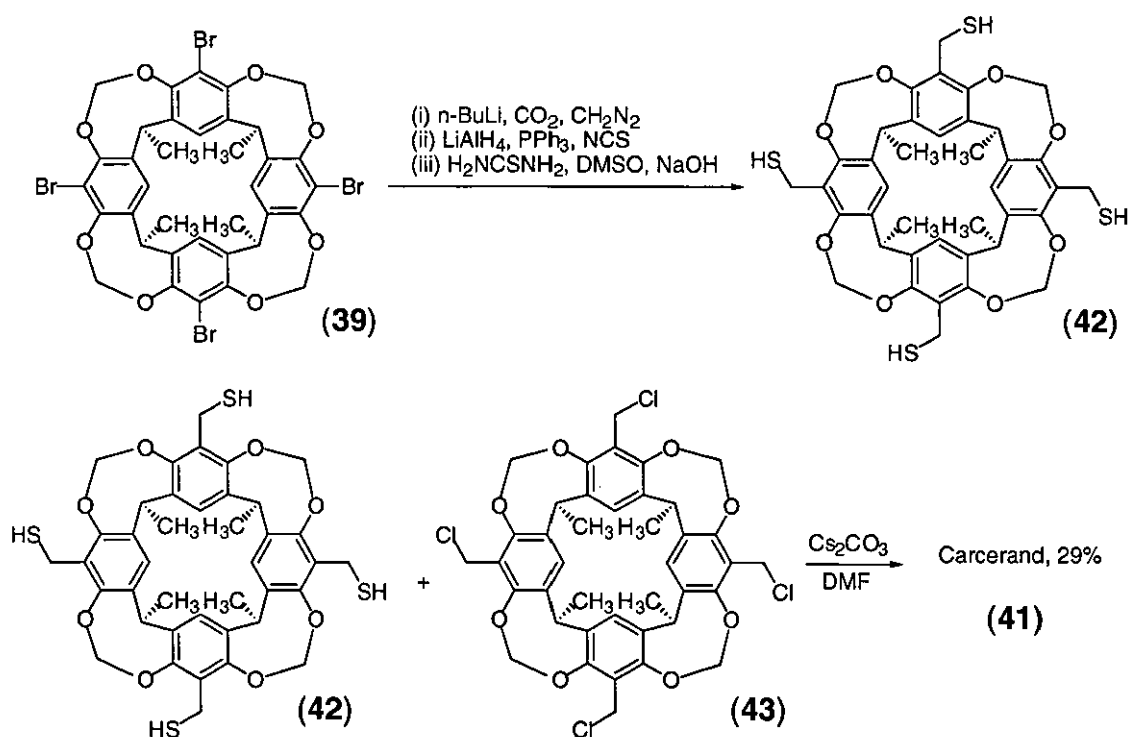


Figure 9

The synthesis, shown in **Scheme 3**, is relatively straightforward. Metalation of the tetrabromide (**40**) with $n\text{-BuLi}$ followed by quenching with carbon dioxide gave the tetraacid, which upon treatment with diazomethane gave the corresponding tetraester. Reduction with lithium aluminium hydride gave the corresponding tetraol, which was then chlorinated with NCS . Finally, thiolation with thiourea in DMSO furnished the tetrathiol precursor (**42**). Coupling of this substrate with the tetra(chloromethyl) compound (**43**) in the presence of caesium carbonate in DMF gave the desired carcerand (**41**) in 29% yield as an insoluble white powder. Analysis by elemental analysis and FAB m.s. showed amounts of Cs^+ present. Recently, other groups³³ have shown that other guests can be incorporated, e.g. benzene and tetrahydrofuran, when the carcerand synthesis is carried out in a mixture of a solvent that is too large to enter the carcerand and small amounts of the potential guest molecule.



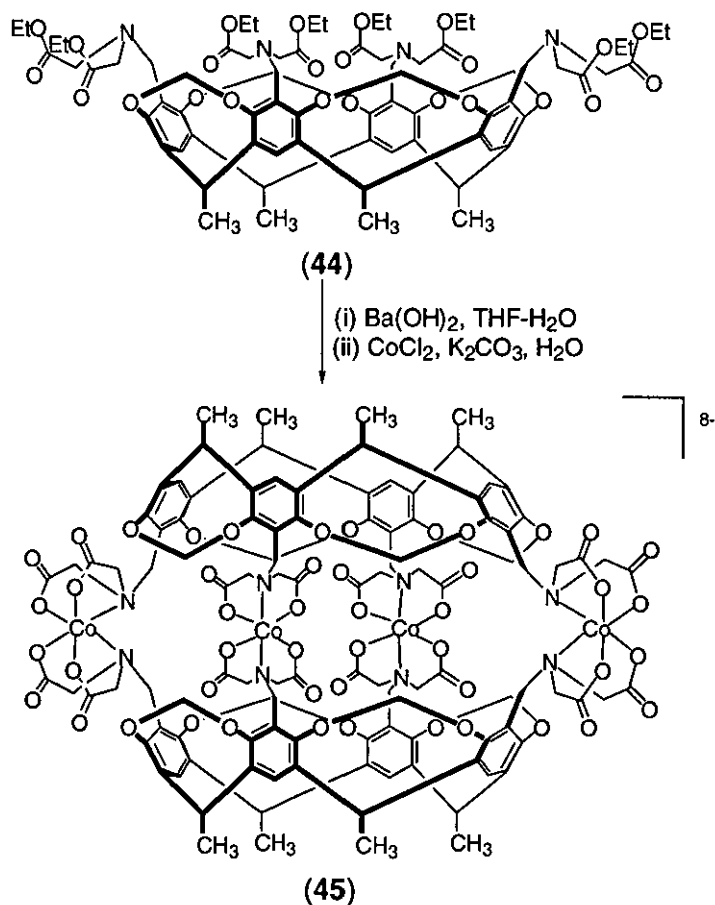
Scheme 3

1.6.1 Hemicarcerands

It has been shown that it is not possible to exchange the guest in a carcerand, once it has been incarcerated. However, it has been demonstrated to be possible *via* the synthesis of another class of compounds known as hemicarcerands. These differ from carcerands in that they have a stable cavity that cannot collapse even when it is empty. Larger spacers enable smaller molecules to pass in and out of the cavity, thus, the incarcerated guest does not have to be present at the synthesis stage. Molecules that have undergone inclusion include noble gases and also larger molecules such as cyclophanes. There are two general types, those with large spacers that allow passage of molecules in or out, or those with one spacer missing that acts as a door in and out of the cavity. Hemicarcerands are able to protect small reactive molecules from reactions with other species because of their small entrance.³⁴

1.7 Organometallic Complexes of Calixarenes

Calix[4]arene and resorcinarene derivatives have been used as ligands to form a wide range of organometallic complexes. An example using a resorcinarene derivative as a molecular scaffold is shown in **Scheme 4**. Hydrolysis of the four diethyl iminodiacetate groups of the resorcinarene (**44**) using barium hydroxide, followed by treatment with cobalt (II) chloride in the presence of potassium carbonate (pH ~ 6), gave the resorcinarene based cage molecule (**45**).³⁵



Scheme 4

The complex (**45**) consists of two resorcinarene molecules held together with four cobalt (II) ions. The diameter of the enclosed cavity is approximately 10 Å and is large

enough to accommodate small molecules including acetone, benzene, dioxane and dichloromethane. Calix[4]arenes with two distal diphenylphosphane centres have been shown to form organometallic complexes with silver (I), platinum (II), palladium (II) and ruthenium (II) species. In all cases the organometallic fragment sits inside the calix[4]arene cavity.³⁶ The use of calix[4]arenes and resorcinarenes as ligands in transition metal chemistry can be found in a review by Matt and co-workers.³⁷

1.8 Synthesis of Chiral Derivatives

Calixarenes and resorcinarenes, by virtue of their well-defined upper and lower rims, are well set up for further functionalisation, with a view to producing chiral derivatives. One can envisage two methods for achieving this aim. The first and simplest consists of derivatising the molecule by attaching chiral substituents at either the upper or lower rim of the macrocycle. Obviously, if enantiomerically pure reagents are used and the reaction proceeds without racemisation, then large amounts of enantiomerically pure material can be generated quickly and easily. The second and slightly more complicated method involves the synthesis of so called inherently chiral derivatives, whereby the stereochemistry of the molecule is a direct consequence of its shape. In these cases the stereochemistry is not due to the presence of a chiral subunit but depends rather on the absence of a plane of symmetry or inversion centre in the molecule as a whole. It can be envisaged that breaking a bond in the macrocyclic structure would lead to an achiral linear molecule with no inherent stereochemical elements. A large amount of work has been carried out on the synthesis of chirally derivatised calix[4]arenes, a review of which can be found in 'Inherently Chiral Calixarenes' by Böhmer and co-workers.³⁸ The derivatisation of resorcinarenes has received less attention, some examples of which will now be described.

1.8.1 Examples of Asymmetric Resorcinarene Derivatives

Cram and co-workers,³⁹ in his work on the bridging of the four sets of proximate oxygens in resorcinarenes reported the synthesis of compound (46). It is inherently chiral, its dissymmetry being due to the inability of the aryls to ring invert and to the three types of substituents on the molecule, namely, OCH_2O , O,O -disubstituted quinoxaline and $\text{OH}\cdots\text{OH}$, as shown in **Figure 10**.

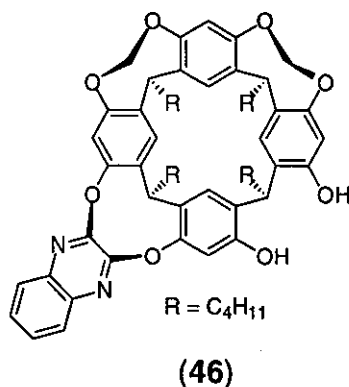
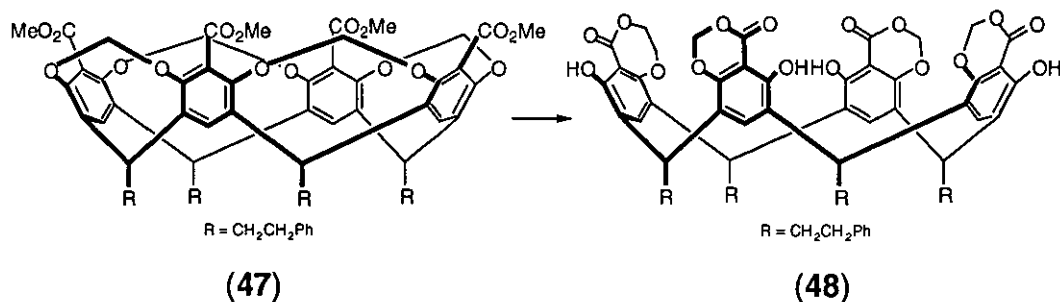


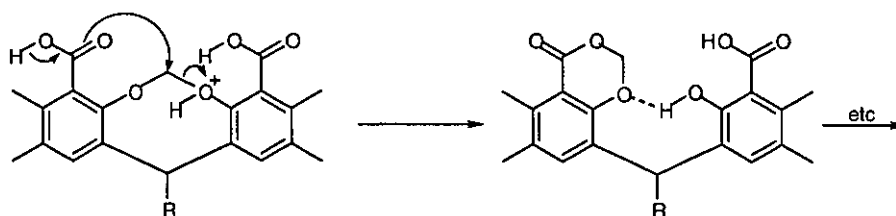
Figure 10

Another example of an inherently chiral non-racemic resorcinarene derivative also originated from the group of Cram.⁴⁰ During the synthesis of the hemicarcerand precursor (47), the tetralactone (48) was isolated in low yield, as shown in **Equation 20**.



Equation 20

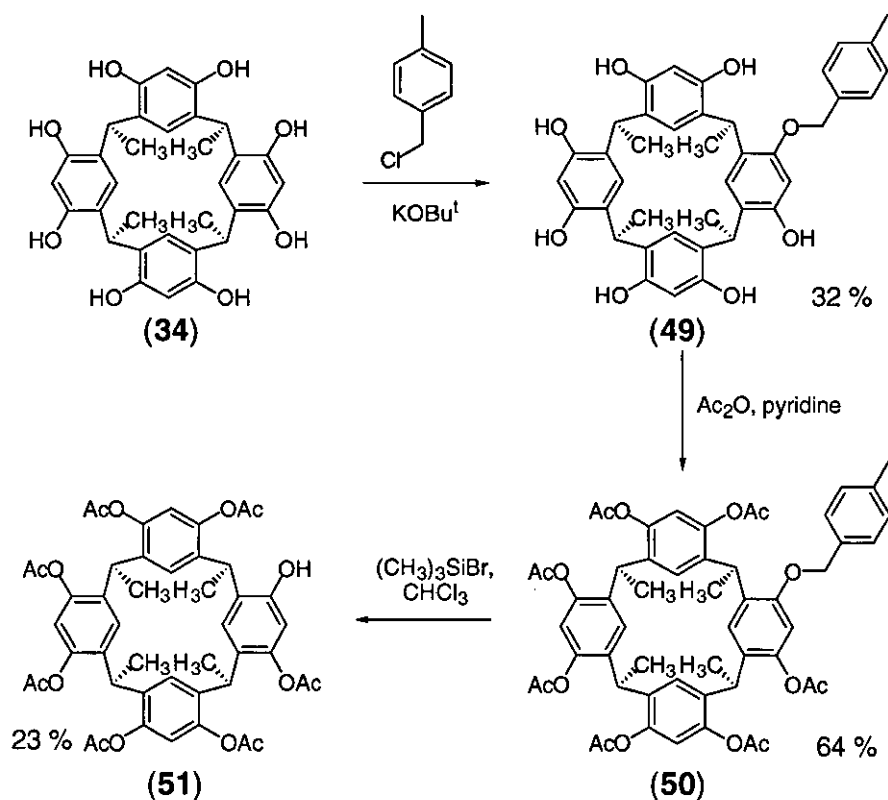
The base catalysed hydrolysis of the resorcinarene derivative (**47**) gave a salt solution, which after acidification, furnished the tetralactone derivative (**48**). The presumed mechanism by which this unusual rearrangement takes place is shown in **Scheme 5**.



Scheme 5

The carboxyl groups are in the ideal position to assist in the acid catalysed ring opening of the four eight membered rings which subsequently cyclise to form four six membered rings. Although it was not explicitly mentioned by the author, this is an example of an inherently chiral resorcinarene derivative by virtue of the chiral axis generated by the tetralactone around the upper rim of the macrocycle.

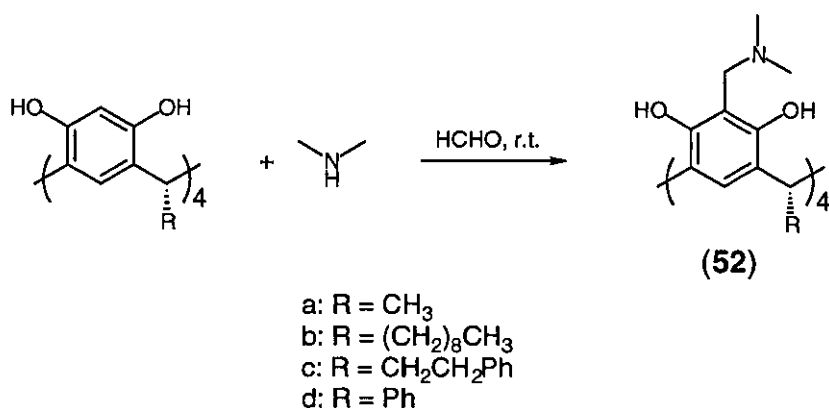
Another example of an inherently chiral resorcinarene derivative has been prepared by Konishi and co-workers and is shown in **Scheme 6**.⁴¹ Mono-*O*-benzylation of the resorcinarene (**34**) destroys the plane of symmetry of the molecule and generates a racemic mixture of the two possible enantiomers. Mono-*O*-benzylation was carried out with 4-methylbenzylchloride in DMF in the presence of potassium tertiary butoxide and the mono-*O*-benzylated product (**49**) was isolated by flash chromatography in moderate yield. Acylation using acetic anhydride in pyridine gave the acylated derivative (**50**) and finally, debenzylation using bromotrimethylsilane gave the inherently chiral monohydroxy derivative (**51**).



Scheme 6

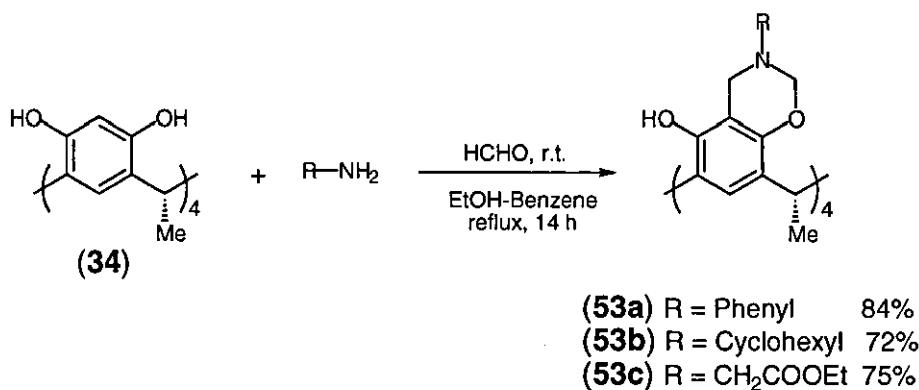
1.8.2 Aminomethylation Reactions

Matsushita⁴² first described the aminomethylation of resorcinarenes *via* a Mannich reaction between resorcinarenes, formaldehyde and a range of both primary and secondary amines. Reaction of the required resorcinarene with 37% aq. formaldehyde (5 eq.) and amine (5 eq.) in ethanol-benzene or ethanol-dichloromethane solution gave the desired aminomethylated compounds (**52**) in good yield, as shown in **Equation 21**. The aminomethylation procedure was applied to a variety of secondary amines with functional groups, including, morpholine, piperidine, 1-methylpiperazine, *N*-methylethanolamine and L and D proline, furnishing the desired compounds in good yields.



Equation 21

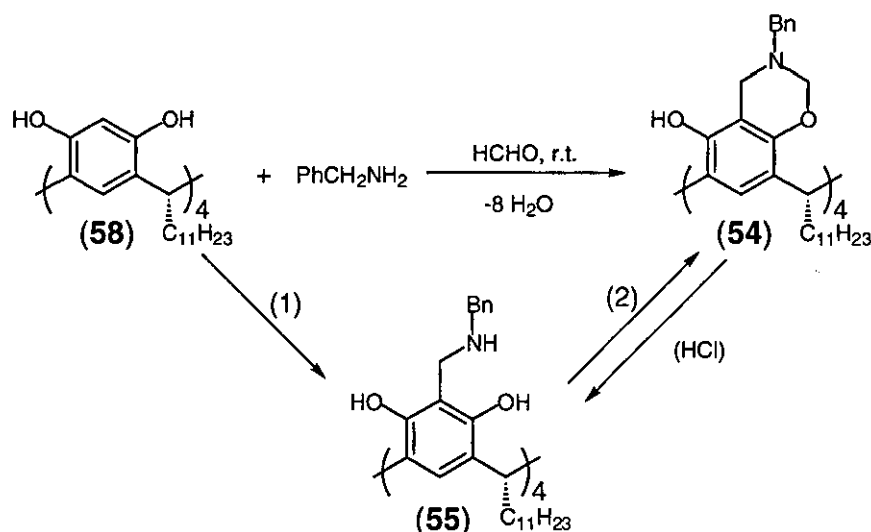
The reaction using primary amines was also examined. Reacting *C*-methylcalix[4]resorcinarene (**34**) with the required primary amine (5 eq.) and formaldehyde (10 eq.) under reflux, the desired tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) compounds were obtained in good yield, as shown in **Equation 22**.



Equation 22

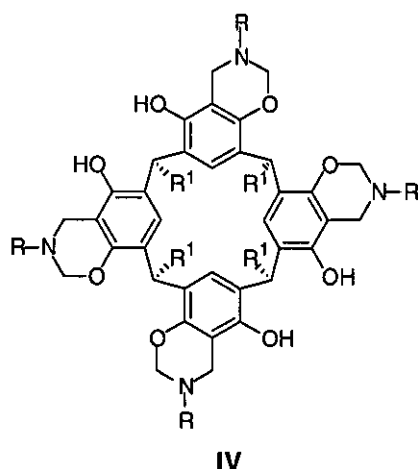
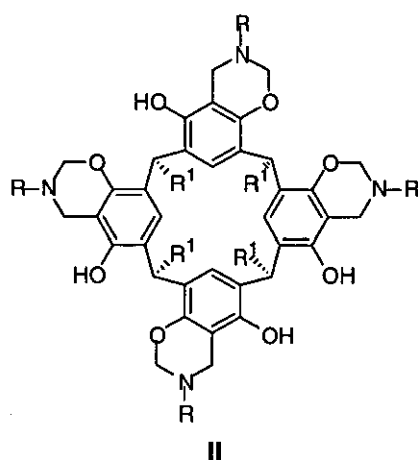
No comment was made by the author of the fact that these compounds are racemates of inherently axially chiral resorcinarene derivatives. Leigh and co-workers⁴³ carried out similar work soon afterwards and proved the structure of these compounds by X-ray crystallography. This work was expanded by Böhmer and co-workers.⁴⁴ He also formed the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) compound

(54) via the reaction of resorcinarenes with 4 eq. primary amine and 8 eq. of formaldehyde, as shown in **Scheme 7**.



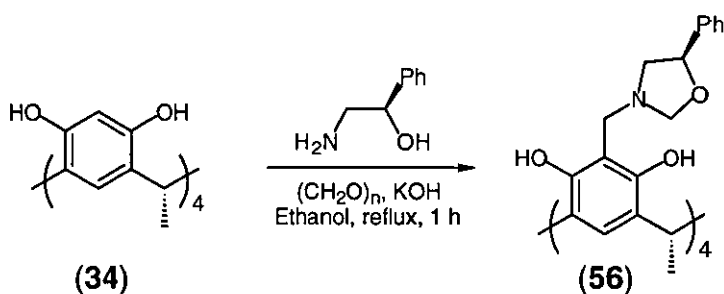
Scheme 7

Böhmer and co-workers observed that the ¹H NMR spectrum of (54) showed an AB quartet for both -CH₂- groups of the 3,4-dihydro-2H-1,3-benzoxazine, due to diastereotopic hydrogens. Since the starting materials are all achiral, the diastereotopicity must be due to the axial chirality of the newly formed tetrakis 2,3-benzoxazines. This can be explained if one considers the possible stereoisomers that can be formed from the reaction, as depicted in **Figure 11**.



C_4 -symmetrical regioisomer as the most stable product. This suggests that the second step in the oxazine ring formation reaction is reversible and this was shown to be correct by experiments utilising $(CD_2O)_n$. The reactions were repeated with a range of achiral primary amines. In each case, a racemic mixture of unidirectional tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) compounds was formed. Single crystal X-ray analysis confirmed the C_4 -symmetry. It was also shown that the four 3,4-dihydro-2*H*-1,3-benzoxazine rings can be hydrolysed under acidic conditions. Böhmer and co-workers⁴⁵ have successfully separated these compounds *via* chiral HPLC. The separation was very capricious and racemization was observed.

Iwanek and co-workers⁴⁶ repeated this work, but using chiral α -aminoalcohols in place of amines. Instead of obtaining the analogous 3,4-dihydro-2*H*-1,3-benzoxazine derivatives of (53) with a β -hydroxyalkyl group at nitrogen, a 1,3-oxazolidine derivative (56) was isolated in good yield, as shown in **Equation 23**.

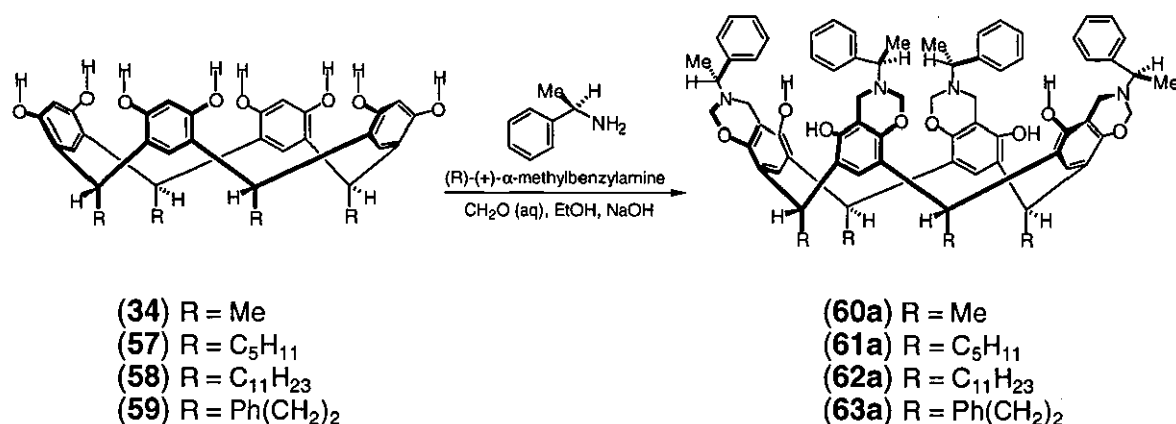


Equation 23

1.8.3 Regio and Diastereoselective Condensation Reactions Between Resorcinarenes, Primary amines and Formaldehyde

Repetition of these experiments using chiral primary amines were conducted by the Heaney^{47a}, Böhmer^{47b,d,e} and Iwanek^{47c} groups at approximately the same time. Heaney and co-workers found that when reacting *C*-pentylcalix[4]resorcinarene with (*R*)- α -methylbenzylamine and paraformaldehyde in ethanol in the presence of a

catalytic quantity of aqueous sodium hydroxide, the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) (**61a**) was formed in 79% yield [$\alpha_D=+118$], as shown in **Equation 24**. ^1H and ^{13}C NMR spectra indicated that the product was formed with very high diastereoselectivity.



Equation 24

The analogous product (**61b**) was obtained in a 74% yield using (*S*)- α -methylbenzylamine, had an [$\alpha_D=-116$] and both the ^1H and ^{13}C NMR data were identical to the product (**61a**). Since the chirality at the α -methylbenzylamine position is fixed it follows that the two products are unidirectional tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives with opposite axial chirality determined around the upper rim of the resorcinarene. Although the origin of this diastereoselectivity is not known with any certainty, it could be envisaged that it may involve the hydrogen bonding of one of the phenolic residues to the first formed 3,4-dihydro-2*H*-1,3-benzoxazine residue as well as steric gearing by the chiral auxiliary and so on around the upper rim leading to a chiral cone structure. The direction must be controlled by the stereochemistry of the starting primary amine as the products are clearly enantiomers. The products from the reactions are shown in **Figure 12**. The reaction of *C*-pentylicalixresorcinarene with (*R*)- α -methylbenzylamine gave a diastereomeric mixture of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives (**61a**) and (**61c**) with (**61a**) being the major diastereomer. Likewise, reacting *C*-

pentylcalixresorcinarene with (*S*)- α -methylbenzylamine gave a mixture of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**61b**) as the major diastereomer with a trace of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**61d**). The pairs of compounds (**61a**) and (**61b**) and (**61c**) and (**61d**) are therefore enantiomers of each other.

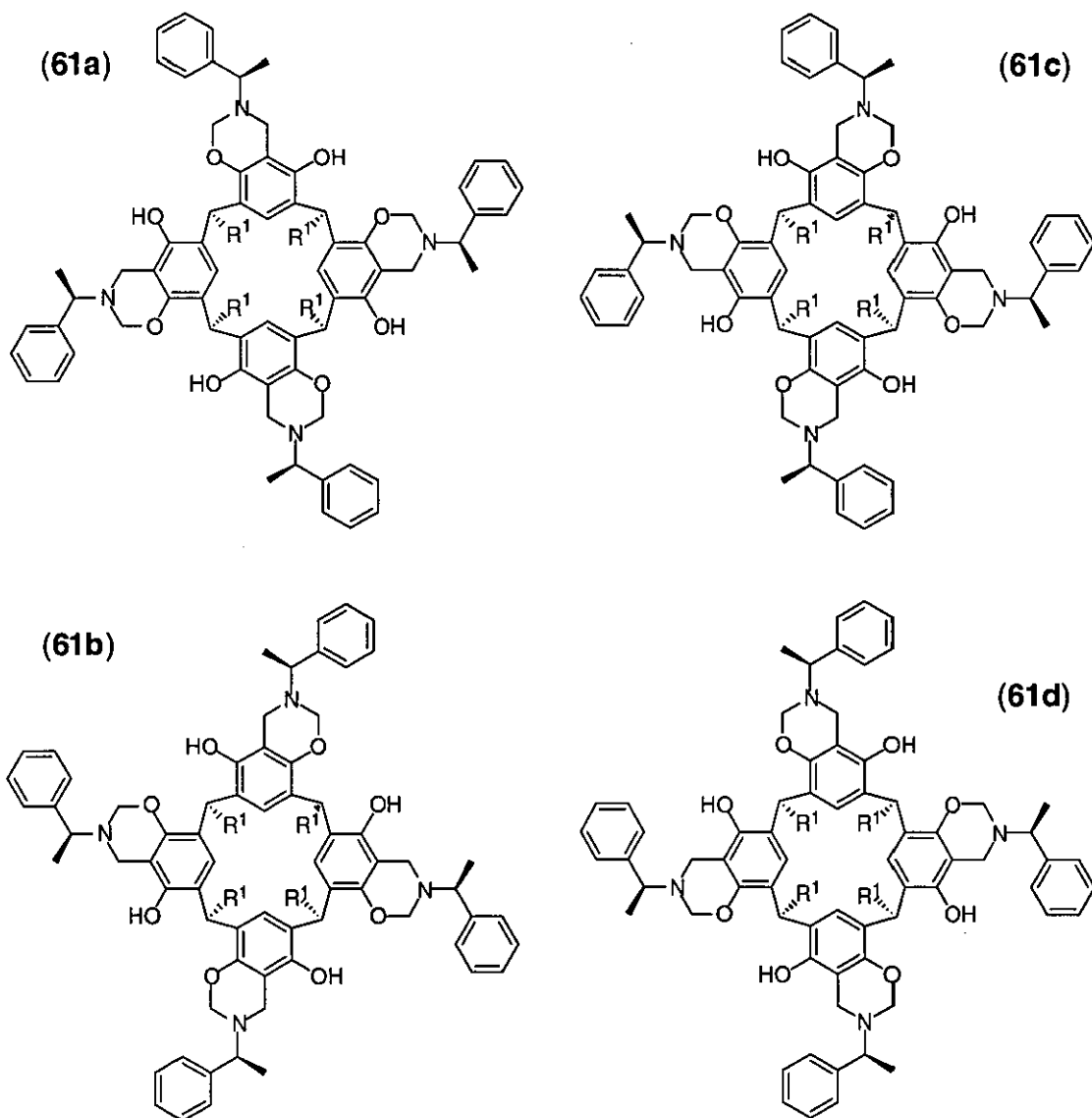


Figure 12 $R^1 = C_5H_{11}$

Analogous results were also obtained with resorcinarenes derived from ethanal,

dodecanal and dihydrocinnamaldehyde in reactions with both (*R*)-(+)- and (*S*)-(–)- α -methylbenzylamine. Böhmer also repeated the work, utilising (*S*)-(+)-cyclohexylethylamine and (*R*)-(+)-1-(1-naphthyl)ethylamine which gave similar results, but has recently retracted the claimed high diastereoselectivity.^{47e} A single crystal X-ray structure of (**61b**) was obtained and its axial chirality determined, as shown in **Figure 13**.

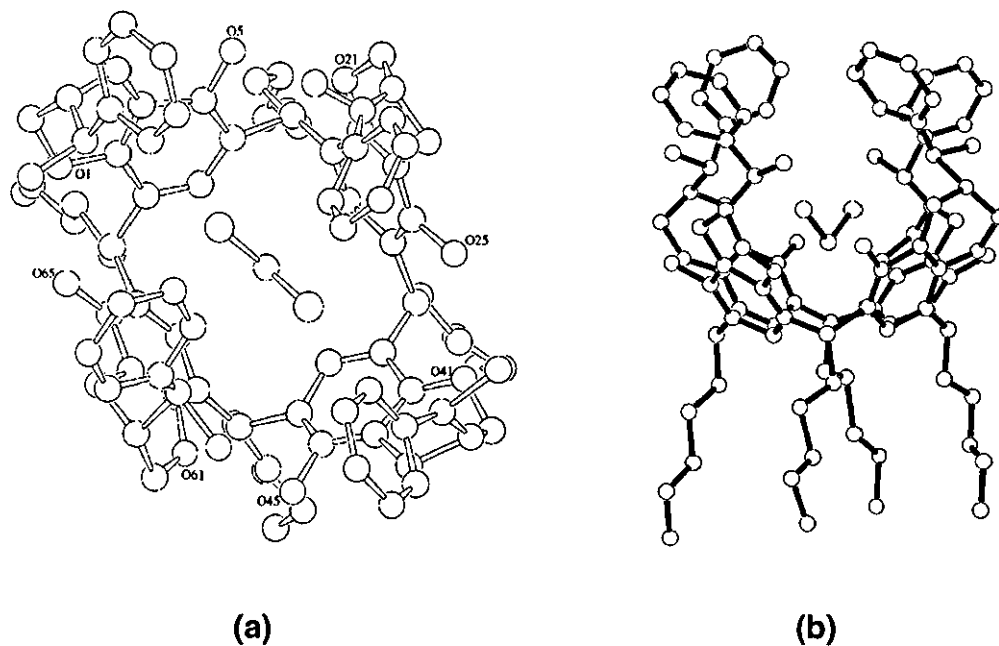


Figure 13

X-ray structure (a) From above showing the anticlockwise chirality and the oxygen atoms involved in hydrogen bonding. The crystal also incorporates a molecule of DCM. (b) From the side.

1.8.4 Acid Catalysed Diastereoisomerisation

It is known that 3,4-dihydro-2*H*-1,3-benzoxazines are unstable towards electrophiles and fragment to iminium salts which undergo Mannich reactions with, for example nucleophilic aromatic substrates such as furan and indole derivatives.⁴⁸ All three

research groups^{47a-c} showed that when the diastereomerically pure tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives were exposed to protic acids, diastereoisomerisation occurred with the compound forming a mixture of two diastereomers which equilibrated to a ratio of 2:1 after 48 h.

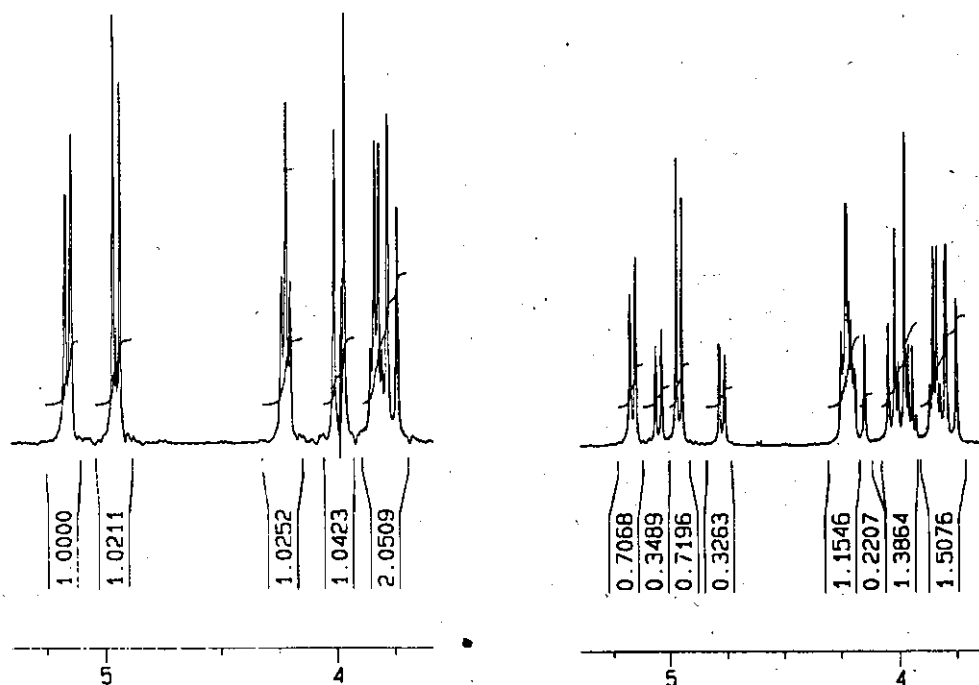
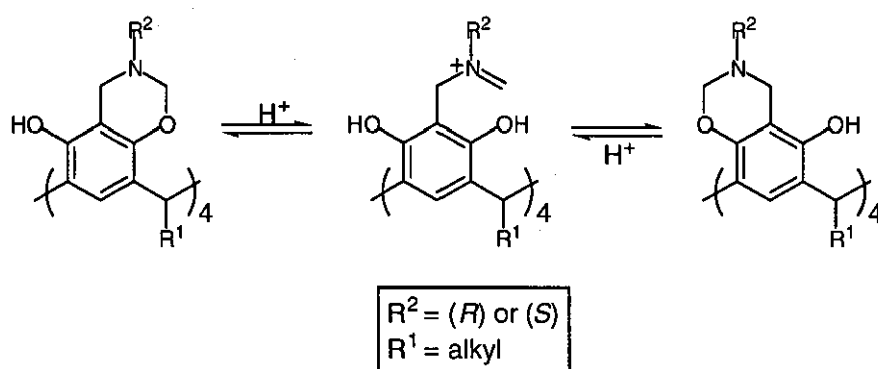


Figure 14

The ^1H NMR spectra reproduced in **Figure 14** shows compound (**61a**) in CDCl_3 on the left and the same sample after standing at room temperature for eight days on the right. The partial spectra on the right shows additional resonances of which the most diagnostically important is the A-B quartet, relating to the methylene group between the nitrogen and oxygen of the 3,4-dihydro-2*H*-1,3-benzoxazine. The mixture is made up of a 2.0:1 mixture of the initially formed derivative (**61a**) and its diastereomer (**61b**). These two products are in unequal energy wells, presumably because of different efficiencies of the gearing process. It was hypothesised that the other random mixtures obtained on acid catalysed ring opening and closing of the four 3,4-dihydro-2*H*-1,3-benzoxazine rings are at significantly higher energies because of

unfavourable hydrogen bonding and gearing and are therefore not observed.



Scheme 8

The mechanism of diastereoisomerisation is shown in **Scheme 8**. Protonation of the 3,4-dihydro-2*H*-1,3-benzoxazine occurs which then can fragment to form a transient iminium ion. This can then reclose in one of two directions by virtue of the second phenolic group. Obviously, derivatisation of the four 'free' hydroxyl groups would preclude diastereoisomerisation *via* this mechanism and therefore the axial chirality of the resorcinarene would effectively be 'locked'. Both Böhmer and Iwanek have reported in the literature the selective acylation of the four free phenolic groups. Iwanek^{47c} reported the formation of the tetraacetates of the pair of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazines) derived from *C*-methylcalix[4]resorcinarene and non-racemic α -methylbenzylamine by the reaction of acetic anhydride in the presence of triethylamine and 4-dimethylaminopyridine in chloroform at room temperature. Optical rotations appeared to show no diastereoisomerisation to have occurred and the compounds were fully characterised. Similarly, Böhmer^{47b} reported the tetraacylation of the corresponding tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derived from *C*-undecylcalix[4]resorcinarene and non-racemic α -methylbenzylamine with acetyl chloride and triethylamine in chloroform at room temperature although no experimental details were provided. These results have also been retracted by Böhmer.⁵⁴

1.9 Research Objectives.

The objectives at the start of this period of research were to functionalise the four free phenolic positions to prevent acid catalysed diastereoisomerisation *via* the acid catalysed pathway described in **Scheme 8**. The subsequent removal of the α -methylbenzyl group would leave the inherently axial chirality of the compounds as the only chiral element. The compounds would then be used in a range of asymmetric process to investigate their potential to act as chiral ligands. It was also of interest to attempt to synthesise resorcinarenes with inherent functionality on the lower rim of the macrocycle to enable the compounds to be isolated upon solid supports. Finally, any novel methodologies that resulted from this research would be investigated thoroughly.

Results and Discussion

Chapter 2

2.0 Synthesis and *O*-Functionalisation of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine)-calix[4]resorcinarene derivatives

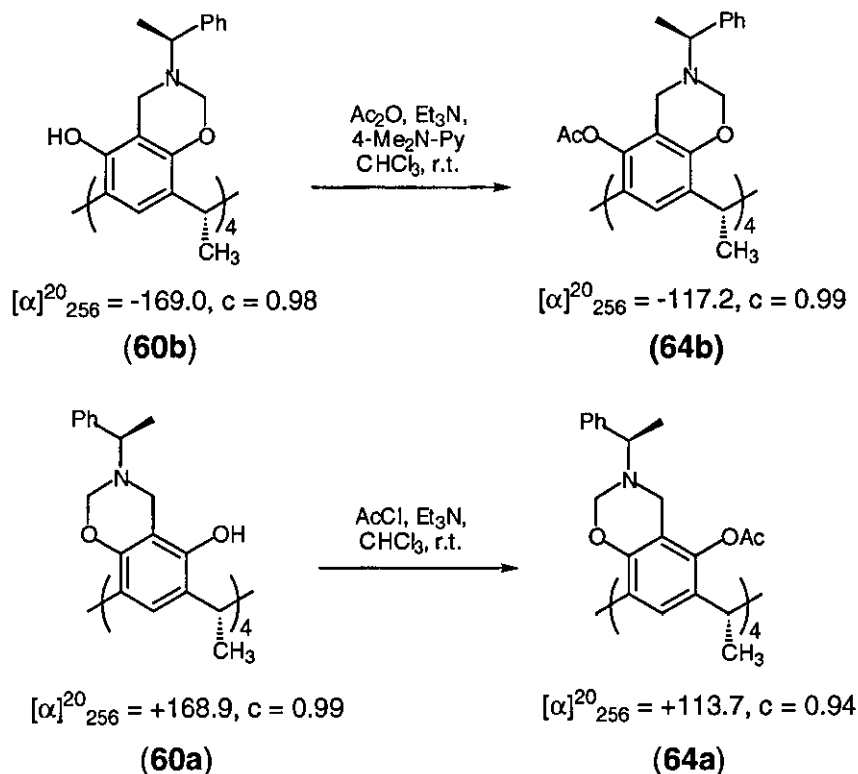
2.1 Introduction

This chapter contains results and discussion concerning work on the synthesis and subsequent derivatisation of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine)-calix[4]resorcinarene derivatives, with a view to imparting stability of the chiral axis towards diastereoisomerisation.

As has been shown, tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazines) formed from a Mannich reaction between chiral non-racemic primary amines, formaldehyde and calix[4]resorcinarenes are a novel family of inherently chiral molecules which undoubtedly have potential to act as hosts in a range of host-guest recognition phenomena.⁴²⁻⁴⁷ Unfortunately, studies by Heaney^{47a}, Böhmer^{47b,d} and Iwanek^{47c} have shown that the direction of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazines) around the upper rim of the calix[4]resorcinarene can be reversed and allows diastereoisomerisation in the presence of protic acids to form an unequal mixture of diastereomers, as shown in **Scheme 8**. Obviously, for this class of compounds to be exploited fully, this sensitivity to acids must be overcome. Derivatisation of the four free phenolic groups would preclude diastereoisomerisation *via* this mechanism as although the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazines) could undergo protonation and ring opening *via* iminium ion formation, ring closure could only occur in one direction, and therefore the directionality around the upper rim of the resorcinarene would effectively be 'locked'. The functionalisation of the phenolic groups would also provide the necessary dissymmetry between the two phenolic groups on each

resorcinol subunit, after fragmentation of the 3,4-dihydro-2*H*-1,3-benzoxazine heterocyclic rings.

The groups of both Böhmer^{47b} and Iwanek^{47c} have reported the selective acylation of the four free phenolic groups as shown in **Scheme 9**.



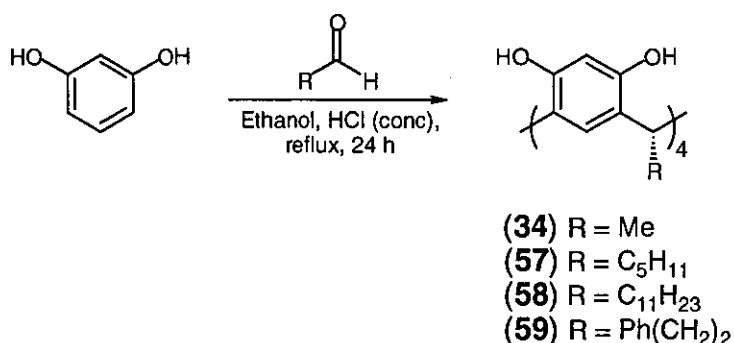
Scheme 9

Iwanek showed that the reaction of the resorcinarene derivative (**60b**) with acetic anhydride in the presence of triethylamine and 4-dimethylaminopyridine resulted in the formation of the tetraacetate derivative (**64b**) in good yield. Optical rotations appeared to show no diastereoisomerisation to have occurred and the compound was fully characterised. Similarly, Böhmer^{42b} reported the tetraacylation of the opposite diastereomer (**60a**) with acetyl chloride and triethylamine in chloroform at room temperature to furnish the tetraacetate derivative (**64a**), again in good yield, although no experimental details were provided. Heaney and co-workers were unable to

confirm these results.⁴⁸

2.2 Synthesis of Calix[4]resorcinarenes

A variety of *C*-substituted calix[4]resorcinarenes was synthesised from resorcinol and a range of aromatic and aliphatic aldehydes, according to known literature procedures,^{5,30} as shown in **Equation 25**. In general, the aldehyde was added slowly *via* a syringe pump to an ethanolic HCl solution of resorcinol at 0 °C and the resulting mixture heated at reflux for twenty four hours. Upon cooling in an ice bath, the desired all *cis* 'rccc' stereoisomer crystallised from the reaction mixture and could be easily recrystallised to high purity. In a number of cases, it was found to be necessary to add water in order precipitate the product. The compounds were all high melting solids whose relative solubilities in common organic solvents were related to the four alkyl or aryl groups derived from the aldehyde component. In general, the longer the aliphatic chain length, the more soluble the resorcinarene was in non-polar solvents, with all the examples being insoluble in aqueous solutions and sparingly soluble in alcoholic solvents. All examples agreed with literature spectroscopic data. The yields of these reactions are compiled in **Table 1**.



Equation 25

Entry	R	Product	Yield/%
a	Me	(34)	60
b	C ₅ H ₁₁	(57)	62
c	C ₁₁ H ₂₃	(58)	80
d	Ph(CH ₂) ₂	(59)	85

Table 1

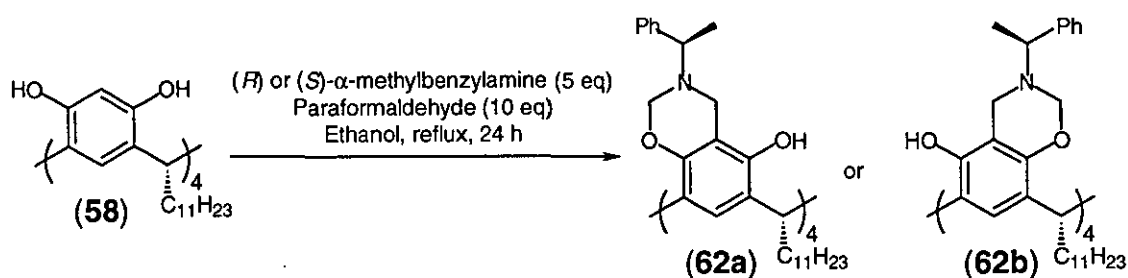
2.3 Synthesis of tetrakis-(3,4-Dihydro-2H-1,3-benzoxazine) Derivatives

With these materials in hand, work began on the synthesis of the corresponding tetrakis-(3,4-dihydro-2H-1,3-benzoxazine) derivatives. The general procedure developed in the group for the synthesis of these compounds involved the formation of an aqueous solution of formaldehyde derived from paraformaldehyde cracked with a catalytic amount of sodium hydroxide. The resulting aqueous solution was combined with the required non-racemic α -methylbenzylamine and resorcinarene in ethanol or a mixture of ethanol and toluene which was then heated under reflux for twenty four hours.^{47a,48} The solvent was removed under reduced pressure and the resulting solid washed with cold methanol to give the desired compound, generally in 50-80% yield. The crude product was routinely isolated with a d.e. > 90% and could be recrystallised to high levels of purity from dichloromethane-methanol mixtures.

Iwanek and co-workers^{47c} also used paraformaldehyde cracked with base as their formaldehyde source but kept the solution at room temperature for twenty four hours as opposed to reflux, postulating that a decrease in temperature resulted in an increase in diastereoselectivity. Böhmer^{47d} used a broadly similar method but eventually favoured the use of aqueous formaldehyde and a catalytic amount of glacial acetic acid, to achieve similar results.

Initially, the procedure of El Gihani was repeated, as described in **Equation 26**.⁴⁸

After combining *C*-undecylcalix[4]resorcinarene, (*R*) or (*S*)- α -methylbenzylamine and an aqueous solution of paraformaldehyde (cracked with a catalytic amount of sodium hydroxide) in ethanol, the mixture was heated at reflux for twenty four hours. After cooling in an ice bath, the resulting pink solid was collected by filtration and washed with a copious amount of cold methanol. ^1H NMR spectroscopy showed the product to have a d.e. > 90% and recrystallisation from a mixture of dichloromethane/methanol gave the desired compound with a d.e. > 99%, in good overall yield, as shown in **Table 2**. The physical and spectroscopic properties of both diastereomers agreed with those in the literature.^{47c,48}



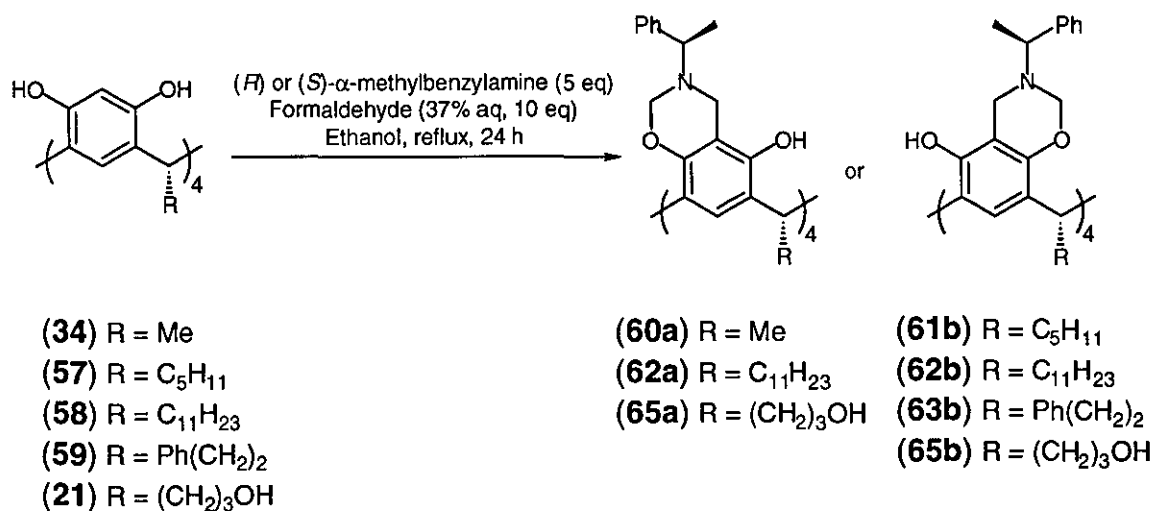
Equation 26

Entry	Product	Yield/%
a	(62a)	82
b	(62b)	76

Table 2

Although the crude compound was generally isolated in good yield, the d.e. varied, ranging between 80-90% (calculated from ^1H NMR spectra). It was thought that the amount of sodium hydroxide used to crack the paraformaldehyde maybe having an effect on the diastereoselectivity of the reaction. A series of reactions was run with varying amounts of sodium hydroxide and in all cases, the products obtained were comparable in both yield and diastereoselectivity. Therefore no correlation was

drawn. This finding was reinforced by the fact that aqueous formaldehyde (37% aqueous solution) could be used in place of the paraformaldehyde-sodium hydroxide mixture with no observed change in the yield or diastereoselectivity of the reaction as shown in **Table 3**. This became the method of choice and a selection of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives was synthesised, as shown in **Equation 27** and **Table 3**.



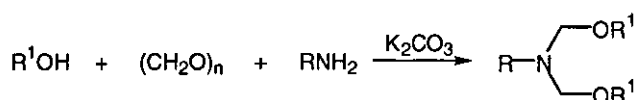
Equation 27

Entry	s.m.	α -methylbenzylamine	Product	Yield/%
a	(34)	(<i>R</i>)	(60a)	57
b	(57)	(<i>S</i>)	(61b)	76
c	(58)	(<i>R</i>)	(62a)	83
d	(58)	(<i>S</i>)	(62b)	77
e	(59)	(<i>S</i>)	(63b)	79
f	(21)	(<i>R</i>)	(65a)	53
g	(21)	(<i>S</i>)	(65b)	71

Table 3

2.3.1 The use of bis(Aminol ethers) as Iminium Ion Precursors

The use of bis(aminol ethers) as bis-iminium ion precursors has been reported in the literature for the formation of dihydro-1,3-benzoxazines.⁴⁹⁻⁵² Their synthesis is straight forward and involves the condensation of the required primary amine with paraformaldehyde and ethanol or methanol in the presence of potassium carbonate, as shown in **Equation 28**. Distillation furnishes the desired products, usually as stable colourless oils.



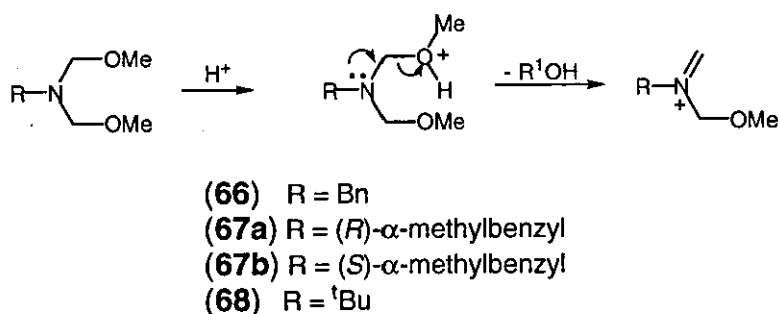
Equation 28

A range of bis(aminol ethers) were synthesised from a selection of primary amines according to a known literature procedure,⁵³ as shown in **Table 4**.

Result	Primary amine	Product	Yield/%
a	benzylamine	(66)	40
b	(<i>R</i>)- α -methylbenzylamine	(67a)	66
c	(<i>S</i>)- α -methylbenzylamine	(67b)	66
d	<i>tert</i> -butylamine	(68)	53

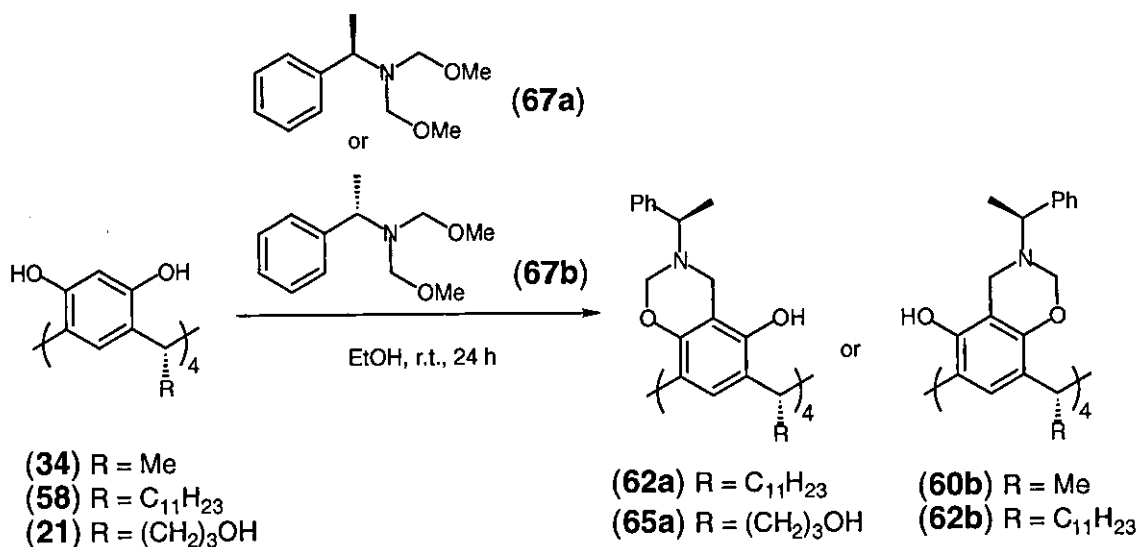
Table 4

The phenol activates the bis(aminol ether) *via* protonation of the oxygen, which subsequently fragments to the iminium ion *via* loss of ethanol or methanol, as depicted in **Scheme 10**.



Scheme 10

It was found that simply stirring a solution of the required bis(aminol ether) (67a) or (67b) with the required resorcinarene in methanol or ethanol for twenty four hours at room temperature resulted in the evolution of a white crystalline precipitate, which upon spectroscopic examination was found to be the required tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivative. Moreover, the product was formed in comparable yield and with comparable diastereoselectivity to that synthesised by the aqueous formaldehyde protocol described previously. The results of these reactions are described in **Equation 29** and **Table 5**.



Equation 29

Entry	s.m.	bis(aminol ether)	Product	Yield/%
a	(58)	(67a)	(62a)	83
b	(58)	(67b)	(62b)	76
c	(21)	(67a)	(65a)	65
d	(34)	(67b)	(60b)	74

Table 5

2.4 Origin of Diastereoselectivity

The origin of this highly diastereoselective tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) forming reaction has been the subject of some speculation. The formation of the four 3,4-dihydro-2*H*-1,3-benzoxazines proceeds in a highly regioselective manner resulting in a diastereomerically enriched product. As Böhmer observed,⁴⁴ the direction of formation of the benzoxazine residues around the upper rim has to be unidirectional to give the maximum number of intramolecular hydrogen bonds, thus leading to the thermodynamically favoured product. It has also been shown that in the presence of acid, the diastereomerically pure product undergoes diastereoisomerisation and equilibrates to a mixture of diastereomers, in a two to one ratio in favour of the initially formed diastereoisomer. It therefore follows that the two diastereomers are of unequal energy. This has been attributed^{47a} to a "steric gearing effect" of the α -methylbenzylamine chiral auxiliaries used. Indeed, X-ray crystal structure analysis shows the four benzene rings oriented in the same direction relative to each other, which has been attributed to a π - π stacking interaction.

It is the authors view that this π - π stacking interaction does indeed play a part in the observed diastereoselectivity of the reaction, although other factors may also come into play. Two further options are outlined below:

- (i) It is possible that the first 3,4-dihydro-2*H*-1,3-benzoxazine is formed in a regioselective manner and subsequently controls the regioselectivity of formation of the three remaining 3,4-dihydro-2*H*-1,3-benzoxazines.
- (ii) The four 3,4-dihydro-2*H*-1,3-benzoxazines are initially formed as a statistical mixture of possible regioisomers and, as the reaction is reversible under the reaction conditions, they diastereoisomerise to the thermodynamically most stable product which then preferentially crystallises from the reaction mixture.

As has been shown, temperature and the nature of the iminium ion precursor do not have any effect on the overall yield and diastereoselectivity of the reaction. In all cases, the reaction goes in 50-85% yield with an accompanying d.e. of approximately 90% for the crude material.

It was believed that option (ii) was more likely to be the pathway in which the diastereomerically pure material was formed, primarily due to visual observations of the reaction mixture during the course of the reaction. It was observed that the reaction mixture was not homogeneous throughout the course of the reaction but rather went through a number of distinct phases. After refluxing an ethanolic solution of the primary amine, aqueous formaldehyde and resorcinarene for thirty minutes, a very sticky red precipitate was generated which collected around the magnetic stirrer bar. As the reaction proceeded, this material was converted to a crystalline orange solid, more of which was formed when the reaction was cooled in an ice bath at the end of the reaction. It was proposed that this could be a sign that initially, a random mixture of regioisomers form which manifest themselves as the aforementioned sticky red precipitate. Due to the fact that the reaction is reversible, these initially formed regioisomers isomerise to the more thermodynamically stable mixture of diastereomers over time, one of which preferentially crystallises from the reaction mixture. Indeed, after filtration of the precipitated material ¹H NMR analysis of the filtrates showed a very complex mixture to be present.

To investigate this hypothesis a reaction was carried out in toluene, a solvent in which crucially, the reaction mixture remains homogeneous throughout the course of the reaction. After heating the reaction mixture under reflux for twenty four hours, the solvent was removed under reduced pressure and the residue analysed. ^1H NMR spectroscopy showed a mixture to be present made up of a roughly one to one mixture of the two diastereomers corresponding to the two directions possible around the upper rim, along with small amounts of other regioisomers. Adding ethanol to this oily residue and heating under reflux for a further twenty-four hours resulted in a crystalline product being produced which was effectively one diastereomer by ^1H NMR spectroscopy. Moreover, the filtrates showed a complex mixture to be present.

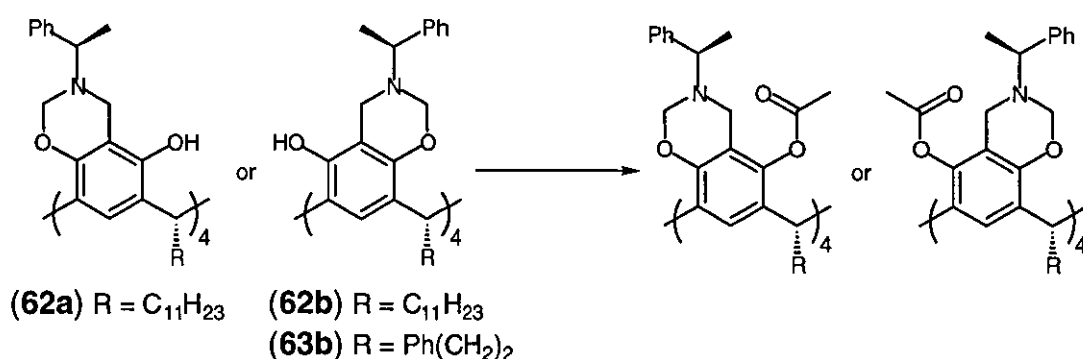
These results seem to suggest that hypothesis (ii) is more likely in that the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazines) initially form as a random mixture of regioisomers. Isomerisation under the reaction conditions eventually leads to the two thermodynamically more favoured diastereomers, one of which preferentially crystallises from the reaction mixture.

2.5 Functionalisation of the Four Free Phenolic Groups

With these materials in hand, work began on the functionalisation of the four free phenolic groups. As stated earlier, functionalisation would impart diastereomeric stability to these compounds. As the successful acylation of the four phenols had been reported in the literature,^{47b, 47c} repetition of these approaches was attempted. An earlier member of the Heaney group had also attempted to acylate the phenols using acetyl chloride or acetic anhydride in the presence of triethylamine and 4-DMAP under standard conditions but without success. Only extensive decomposition was observed.⁴⁸

2.5.1 O-Acylation

The acylation of a number of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) functionalised resorcinarene derivatives was attempted using both the conditions reported by Böhmer^{47b} and those of Iwanek,^{47c} as compiled in **Table 6**. In both cases, only a complex multi-component mixture was observed. Analysis by ¹H NMR showed decomposition of the dihydro-1,3-benzoxazines to have occurred. IR spectroscopy showed a carbonyl stretching band at approx 1760 cm⁻¹ indicating some reaction had occurred but no characterisation was attempted.



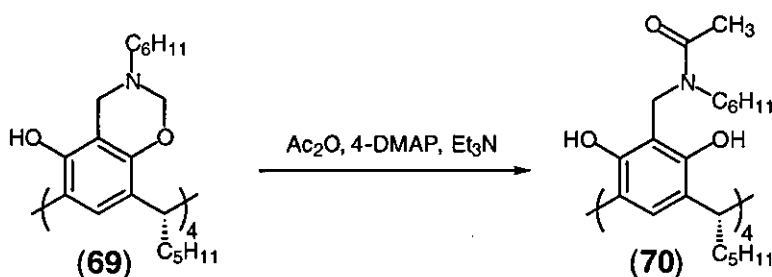
Equation 30

Entry	s.m.	Reaction conditions	Yield/%
a	(62a)	AcCl, 4-DMAP, Et ₃ N, DCM, r.t., 24 h	decomposition
b	(62b)	Ac ₂ O, 4-DMAP, Et ₃ N, DCM, r.t., 24 h	decomposition
c	(63b)	Ac ₂ O, 4-DMAP, Et ₃ N, DCM, r.t., 24 h	decomposition

Table 6

In a subsequent paper,⁵⁴ Böhmer reported on his attempts to acylate the phenolic groups, stating that both his own results, and those of Iwanek could not be repeated. Moreover, the only product he could isolate from the reaction of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**69**) with acetic anhydride was the tetraamide

(70) in poor yield, as shown in **Equation 31**.



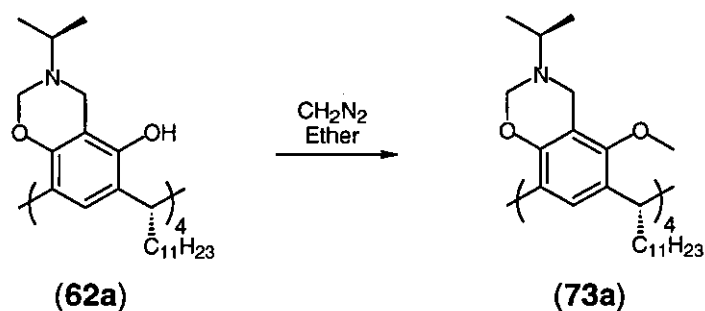
Equation 31

This result is in accordance with results for simple benzoxazines⁵⁵ in that the more nucleophilic nitrogen (in comparison to oxygen), is acylated, while formaldehyde is hydrolytically eliminated from the nitrogen/oxygen acetal.

2.5.2 O-Methylation

2.5.2.1 Use of Diazomethane

The use of diazomethane for the methylation of phenols is well known to be high yielding under mild conditions.⁵⁶ The small size of the reactive methanediazonium ion was thought to be ideal for our purposes as it was anticipated that the four residual phenolic groups would reside in a very sterically demanding environment. Therefore, an ethereal solution of diazomethane was added to an ethereal solution of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62a**). The reaction mixtures were stirred at room temperature for varying lengths of time, as shown in **Table 7**.



Equation 32

Entry	Conditions	Yield/%
a	r.t., 3 days	s.m.
b	r.t., 18 h	s.m.
c	r.t., varying times*	s.m.

* 6 solutions set up and analysed by ^1H NMR after 1, 2, 4, 8, 16 and 24 h.

Table 7

In all cases, analysis by ^1H NMR showed no methylation to have occurred, with starting material being recovered in almost quantitative yield. In addition, the starting material was recovered as a mixture of diastereomers due to the acetic acid used to decompose the excess diazomethane mediating acid catalysed diastereoisomerisation.

2.5.2.2 Application of Base/Methylating Agent Methodology

The acidity of the eight phenolic groups present in unsubstituted resorcinarenes has been studied in some depth.⁵⁷ It has been shown that the first four phenolic protons (one from each resorcinol subunit) are much more acidic than the last four. Potentiometric titrations have shown that the pK_a values of the first four phenolic

protons are two units lower than the pK_a of resorcinol. In contrast, the last four protons cannot be removed with sodium methoxide. The decreased acidity of the four remaining protons is attributed to the stability of the tetraphenolate due to the ideal arrangement of O-H-O interactions for delocalisation of the negative charges, as shown in **Figure 15**.

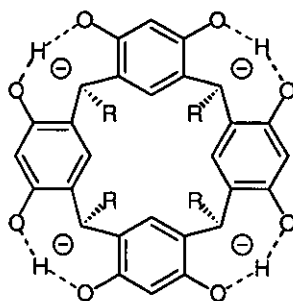
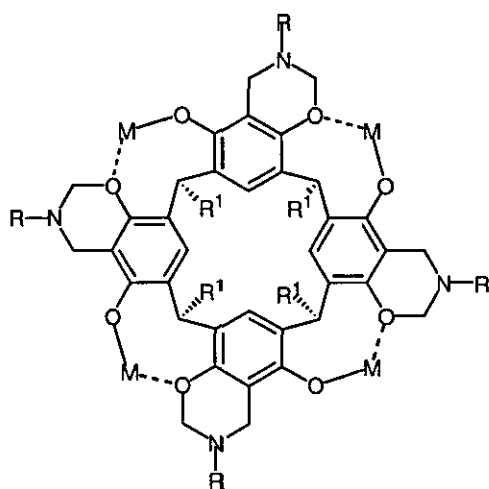


Figure 15

At this stage, it was not known whether the tetra-deprotonation and tetra-methylation of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives would proceed in a stepwise fashion or *via* a tetra-anionic species. In the first instance, the rapidly formed mono-anion would be methylated before the second phenol could be deprotonated, and so on. The alternative reaction pathway is *via* a tetra-anion that could initially form before all four methyl ethers are formed in the final step. The preferred reaction pathway merely depends on the energy and stability of this tetra-anion species. It was anticipated to be high in energy, although this could be reduced somewhat by the aforementioned charge delocalisation mediated by the four metal counter ions, as depicted in **Figure 16**



$M = \text{Li}^+ \text{ or } \text{Na}^+$

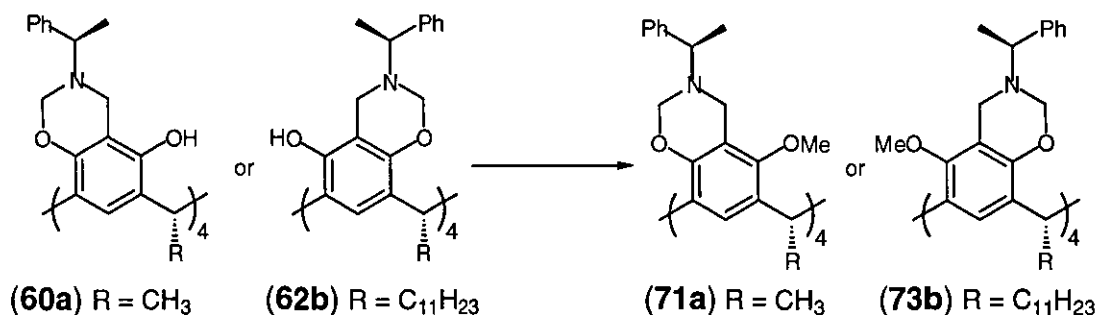
$R' = \text{C}_{11}\text{H}_{23}, \text{C}_5\text{H}_{11}, \text{CH}_3, \text{Ph}(\text{CH}_2)_2$

$R = (R)\text{-}\alpha\text{-methylbenzylamine or } (S)\text{-}\alpha\text{-methylbenzylamine}$

Figure 16

2.5.2.3 Use of Weak Bases

Literature precedents for the *O*-alkylation of the phenolic groups in calixarenes generally favour the use of a weak base such as caesium carbonate with the required alkyl iodide as the alkylating agent in acetone.⁵⁸ With this in mind, both potassium carbonate and potassium hydroxide were chosen as potential bases, accompanied by either methyl iodide or methyl-*p*-toluenesulfonate as the methylating agent. The results of these reactions are compiled in **Table 8**.



Equation 33

Entry	s.m.	Conditions	Yield/%
a	(60a)	K ₂ CO ₃ (4.4 eq), methyl- <i>p</i> -toluenesulfonate (4.4 eq), acetone, -78 °C to r.t., 24 h	s.m.
b	(60a)	K ₂ CO ₃ (4.4 eq), methyl- <i>p</i> -toluenesulfonate (4.4 eq), acetone, -78 °C to r.t., 20 days	s.m.
c	(62b)	K ₂ CO ₃ (10 eq), MeI (10 eq), acetone, reflux, 24 h	decomp
d	(62b)	KOH (10 eq), DMSO, MeI (4.0 eq), reflux, 12 h	decomp

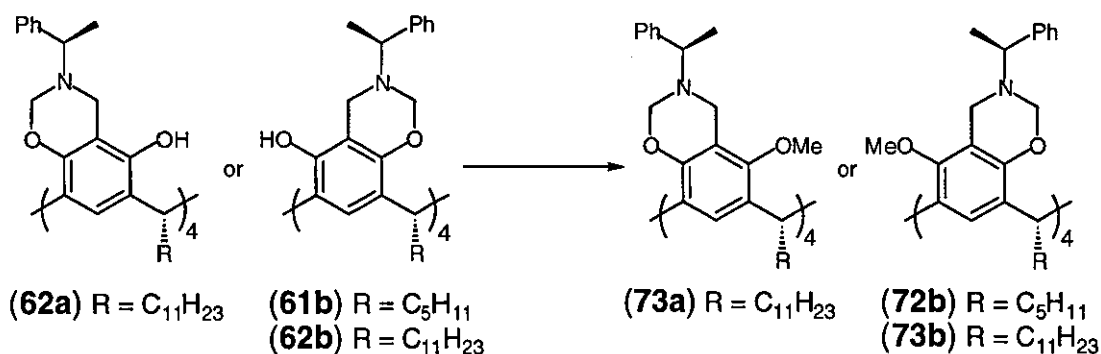
Table 8

Stirring a solution of the required resorcinarene in acetone at room temperature in the presence of anhydrous potassium carbonate and methyl-*p*-toluenesulfonate only resulted in unchanged starting material being re-isolated, even after prolonged reaction times. ¹H NMR analysis of the crude reaction mixtures failed to show any evidence for the formation of a methoxy resonance, which typically appear at approximately 3-3.5 ppm. In addition, IR spectroscopy showed evidence of OH bands still present. Upon refluxing an acetone solution of the resorcinarene in the presence of an excess of potassium carbonate and methyl iodide resulted in the isolation of a complex mixture. The same was true when the reaction was repeated with potassium hydroxide and methyl iodide in refluxing dimethylsulfoxide, again ¹H NMR spectroscopy showed a complex mixture present, with destruction of the benzoxazine rings evident. It was therefore envisaged that weak bases such as potassium carbonate and potassium hydroxide were unsuitable for deprotonation of these compounds. Attempting to force the reaction merely resulted in decomposition occurring.

2.5.2.4 Use of Strong Bases

Both *n*-BuLi and sodium hydride have been utilised as bases in the alkylation of

phenols. The apparent unreactivity of weak inorganic bases in our systems implied the application of stronger bases may be more fruitful. Moreover, the proposed tetraphenolate intermediate may be stabilised *via* complexation of the small metal counter ion between the phenolate anion and the neighbouring benzoxazine ring oxygen in the resorcinarene as proposed in **Figure 16**. Initially it was decided to utilise a sequential approach by attempting a mono alkylation by using only one equivalent of base and alkylating agent. The results of these reactions are compiled in **Table 9**.



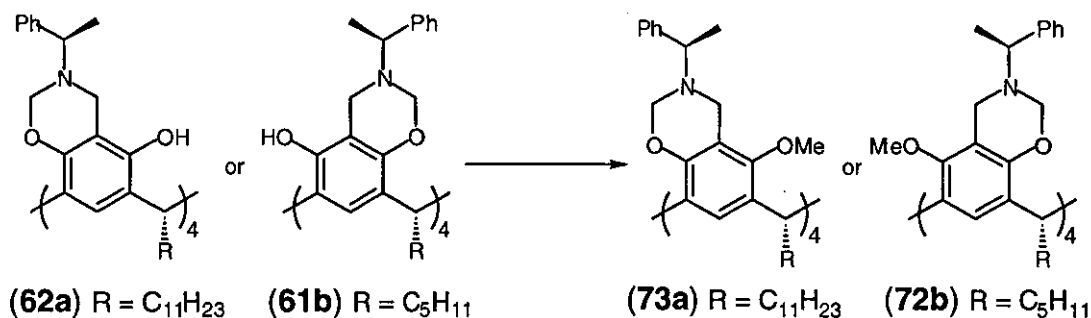
Equation 34

Entry	s.m.	Conditions	Yield/%
a	(61b)	NaH (1.0 eq), THF, dimethylsulfate (4.0 eq), $-78\text{ }^{\circ}\text{C}$ to r.t., 24 h	s.m.
b	(62a)	n-BuLi (1.5 eq), MeI (1.1 eq), Et_2O , $-78\text{ }^{\circ}\text{C}$, 12 h	s.m.
c	(62a)	n-BuLi (1.1 eq), MeI (1.1 eq), THF, $-78\text{ }^{\circ}\text{C}$, 12 h	s.m.
d	(62b)	n-BuLi (1.5 eq), MeI (10 eq), Et_2O , $0\text{ }^{\circ}\text{C}$, 12 h	s.m.
e	(61b)	n-BuLi (1.1 eq), Dimethyl sulfate (2.2 eq), THF, $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$, 12 h	s.m.

Table 9

In all cases, only unreacted starting material was isolated. ^1H NMR analysis of the

crude reaction mixtures failed to show any evidence for the formation of a methoxy resonance, which typically appears at approximately 3-3.5 ppm. In addition, IR spectroscopy showed evidence of OH bands still present. It was therefore decided to repeat the reactions using four equivalents of base and methylating agent in an attempt to force the reactions to completion. The reactions were first repeated using sodium hydride and then using *n*-butyl lithium. The results of these reactions are compiled in **Tables 10** and **11**



Equation 35

Entry	s.m.	Product	Conditions	Yield/%
a	(62a)	—	NaH (4.4 eq), THF, MeI (4.4 eq), -78 °C to r.t., 24 h	s.m.
b	(62a)	—	NaH (4 eq), DMSO, methyl- <i>p</i> -toluenesulfonate (4 eq), 100 °C, 12 h	decomp
c	(61b)	—	NaH (5.0 eq), THF, dimethylsulfate (5.0 eq), -78 °C to r.t., 24 h	decomp
d	(61b)	(72b)	NaH (4.4 eq), THF, methyltriflate (4.4 eq), -78 °C to r.t., 24 h	18

Table 10

Entry	s.m.	Product	Conditions	Yield/%
a	(61b)	(72b)	n-BuLi (4.4 eq), methyl triflate (4.4 eq), THF, -78 °C to r.t (MeOTf added at -78 °C), 1 h	54
b	(61b)	(72b)	n-BuLi (4.4 eq), methyl triflate (8.0 eq), THF, -78 °C to r.t (MeOTf added at 0 °C), 1 h	decomp
c	(62b)	(73b)	n-BuLi (4.4 eq), Dimethyl sulfate (4.4 eq), THF, -78°C to r.t., 1 h	36
d	(62b)	(73b)	n-BuLi (4.4 eq), Dimethyl sulfate (4.4 eq), THF, -78°C to r.t., 1 h	36
e	(63b)	(74b)	n-BuLi (4.4 eq), methyl triflate (4.0 eq), THF, -78 °C to r.t., 1 h	44
f	(62a)	(73a)	n-BuLi (4.0 eq), methyl triflate (4.0 eq), THF, -78 °C to r.t., 1 h	57
g	(62a)	(73a)	n-BuLi (4.0 eq), methyl triflate (4.0 eq), THF, -78 °C to r.t., (Quench at -78 °C), 1 h	65
h	(62a)	(73a)	n-BuLi (4.0 eq), methyl triflate (4.0 eq), THF, -78 °C (Quench at -78 °C), Mechanically stirred, 1 h	85
i	(62b)	(73b)	n-BuLi (4.0 eq), methyl triflate (4.0 eq), THF, -78 °C (Quench at -78 °C), Mechanically stirred, 1 h	87
j	(63a)	(74a)	n-BuLi (4.0 eq), methyl triflate (4.0 eq), THF, -78 °C (Quench at -78 °C), Mechanically stirred, 1 h	79

Table 11

It was found the reaction yield could be increased further by more efficient stirring of the reaction mixture. Vigorous overhead stirring along with increased dilution helped to keep the reaction mixture mobile, and consequently more efficient mixing of the

reactive methylating agent and the tetralithium salt resulted in higher yields. In addition, it was found that the more cost effective reagent dimethyl sulfate also functions as an effective methylating agent in this reaction, although at the expense of overall yield. In all cases, the tetrakis-(*O*-methylether) derivatives were isolated as viscous pale yellow oils, which stubbornly refused to crystallise. Following this methodology, this reaction could be carried out on up to a 20 g scale with yields of 85-90% becoming routine.

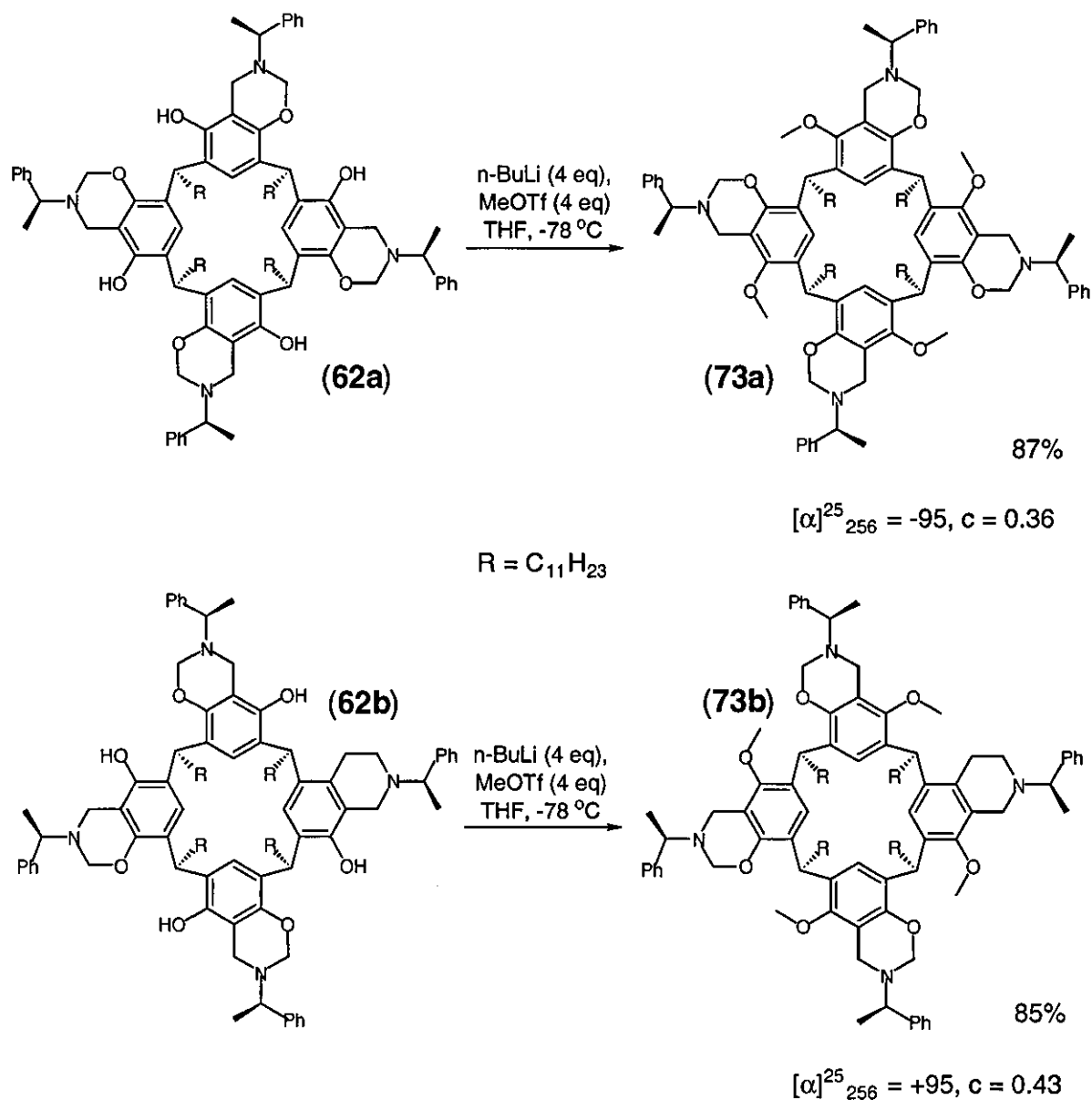
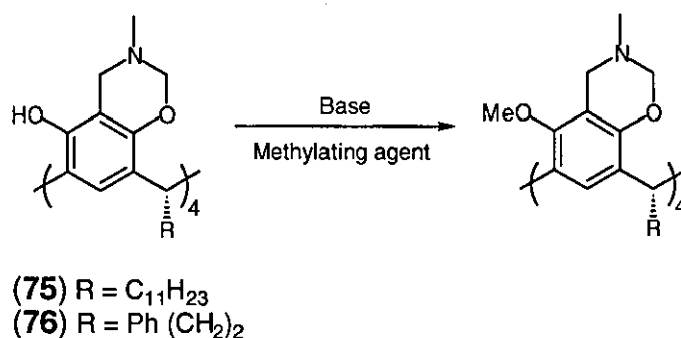


Figure 17

The pair of tetrakis-(*O*-methylether) derivatives derived from *C*-undecylcalix[4]resorcinarene, (**73a**) and (**73b**), were isolated and shown to have equal and opposite optical rotations, indicating no diastereoisomerisation had occurred during the reactions. This fact was confirmed when the pair were analysed by chiral HPLC which showed both compounds were enantiomerically and diastereomerically pure.

It is worth noting at this time that attempting to methylate the model substrates (**75**) and (**76**) under the same conditions only resulted in intractable oils being obtained that defied characterisation, as shown in **Equation 37**. Compounds (**75**) and (**76**) were obtained from a Mannich reaction of the parent resorcinarene with formaldehyde and methylamine. The methylation protocols attempted included our successful *n*-BuLi/methyl triflate methodology as well as a comprehensive range of other base and methylating agent combinations



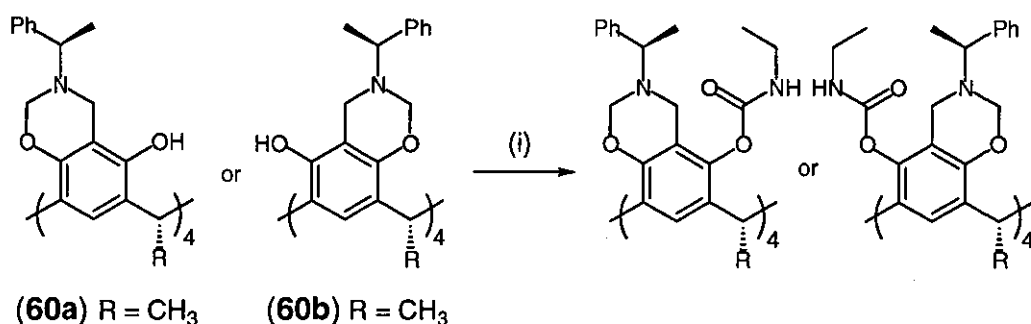
Equation 37

These results seem to suggest that the methylating agent initially reacts with the benzoxazine ring nitrogen, forming a quaternary ammonium salt, as opposed to the more hindered phenolate anion. It could be envisaged that the 3,4-dihydro-2*H*-1,3-benzoxazine ring could then undergo ring fragmentation to form an ortho quinone methide *via* the mechanism discussed in chapter 6. In the case of the diastereomerically pure series of compounds, however, the nitrogen is substituted

with a bulky α -methylbenzyl group and therefore the formation of a quaternary ammonium salt is less likely. The phenolate anion is therefore alkylated to give the desired product.

2.5.3 Carbamate formation

Isocyanates have been shown to undergo reactions with phenols to form carbamates very readily.⁵⁹ The resorcinarene derivatives were reacted with an excess of ethyl isocyanate in an attempt to form the corresponding tetrakis-carbamate derivative.



Equation 38 (i) EtNCO (10 eq), DCM, various times and temperatures, see table 12.

Entry	s.m.	Conditions	Yield/%
a	(60a)	−78 °C to r.t., 12 h	s.m.
b	(60a)	r.t., 12 h	s.m.
c	(60b)	r.t., 10 days	s.m.
d	(60b)	reflux, 24 h	decomp

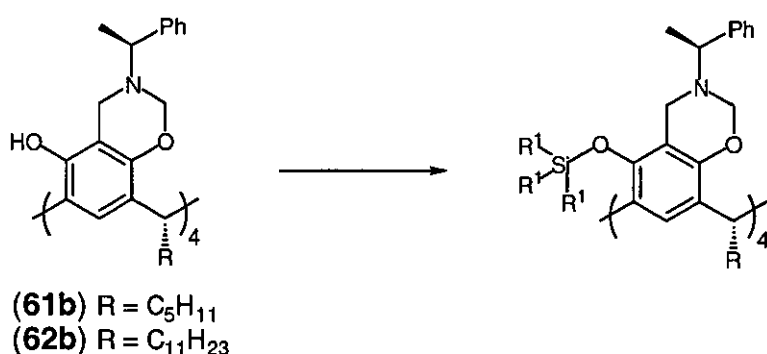
Table 12

As can be seen from **Table 12**, at room temperature no reaction occurred and only unreacted starting material was obtained, even after prolonged reaction times. Attempting to force the reaction to completion by carrying out the reaction in a

refluxing solution of dichloromethane only resulted in the decomposition of the substrate and the isolation of a complex mixture of products.

2.5.4 Miscellaneous O-Functionalisation Reactions

The use of oxophilic silicon protecting groups has been widely reported in the literature for the protection of both alcohols and phenols.⁶⁰ A mini study of conditions and reagents was applied to the resorcinarene derivatives **(61b)** and **(62b)**, the results of which are reported in **Table 13**.



Equation 39

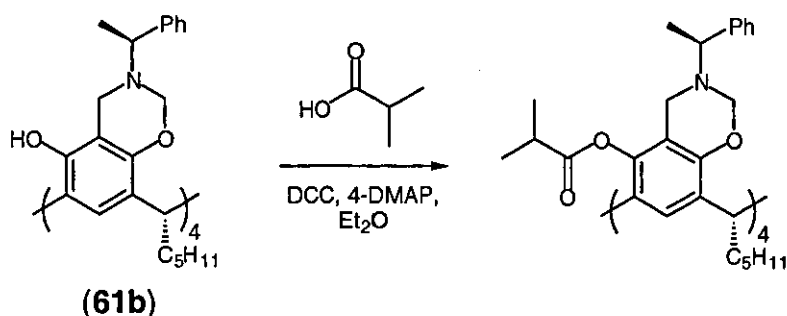
Entry	s.m.	Conditions	Yield/%
a	(62b)	n-BuLi (1 eq), TBDMSCI (1 eq), THF, -78 °C -r.t., 24 h	s.m.
b	(62b)	TBDMSCI (5 eq), Imidazole (10 eq), DMF, r.t., 24 h	decomp
c	(61b)	TMSOTf, (8 eq), Et ₃ N (8 eq), DCM, -40 °C -r.t., 24 h	s.m.

Table 13

The use of one equivalent of n-BuLi and one equivalent of TBDMSCI resulted in reisolation of starting materials, which is consistent with results observed in the methylation series. Treating the substrate with TBDMSCI with an excess of imidazole in DMF at room temperature resulted in decomposition of the substrate, whilst the use

of an excess of TMSOTf and triethylamine in dichloromethane resulted in reisolation of unchanged starting material.

Finally, a DCC coupling reaction between the resorcinarene and isobutyric acid was attempted, following the reaction by the generation of the urea derivative, as shown in **Equation 40**. Although quantities of the urea derivative were generated suggesting the reaction had proceeded ca. 65%, the ^1H NMR spectrum was very complex suggesting a number of different reaction pathways were competing with one another.



Equation 40

2.6 Conclusion

A range of inherently chiral non-racemic tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) functionalised calix[4]resorcinarenes derived from a series of *C*-functionalised calix[4]resorcinarenes and (*R*) and (*S*)- α -methylbenzylamine has been successfully synthesised following known procedures. In addition, new methodology has been developed employing enantiomerically pure bis(aminoethers). Strong evidence has been provided that the observed diastereoselectivity of the reaction is a result of the isomerisation of an initially formed statistical mixture of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) regioisomers to a mixture of the two more thermodynamically stable diastereoisomers, one of which preferentially crystallises from the reaction mixture. The first examples of acid stable variants *via* the tetramethylation of the four residual

phenolic groups of a range of inherently chiral non-racemic tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) calix[4]resorcinarene derivatives have been described. The best results were obtained when using *n*-butyl lithium and methyl triflate with the reactions proceeding in excellent yield. The resulting tetrakis-(*O*-methylether) derivatives are diastereomerically stable as the mechanism *via* which diastereoisomerisation could occur is now blocked. Both tetramethyl ethers derived from (*R*) and (*S*)- α -methylbenzylamine were synthesised from a range of different *C*-alkylcalix[4]resorcinarenes and were shown to have equal and opposite optical rotations. In addition, their non-racemic nature was proven by chiral HPLC, indicating the reaction occurred without diastereoisomerisation.

Chapter 3

3.0 Investigations into the Chemical Manipulation of Simple Benzoxazines.

3.1 Introduction

This chapter contains results and discussions regarding efforts towards the fragmentation of the newly formed tetrakis-(*O*-methylether) functionalised calix[4]resorcinarene derivatives, with a view to removing the α -methylbenzylamine moiety.

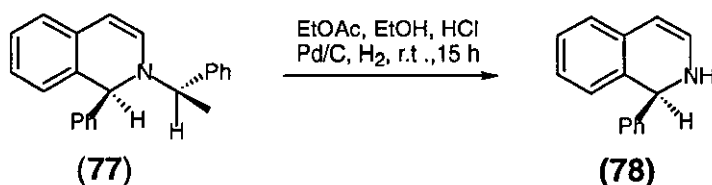
With the successful tetramethylation of the tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives accomplished, procedures for the removal of the α -methylbenzylamine chiral auxiliary were examined. This was desirable for two reasons:

- (i) Removal of the α -methylbenzylamine chiral centres would leave the axial chirality of the system as the only chiral element.
- (ii) The possible recovery of the non-racemic α -methylbenzylamine chiral auxiliary used to set up the helicity of these compounds would be economically desirable.

3.2 Attempted Hydrogenolysis of tetrakis-(*O*-methylether) Derivatives

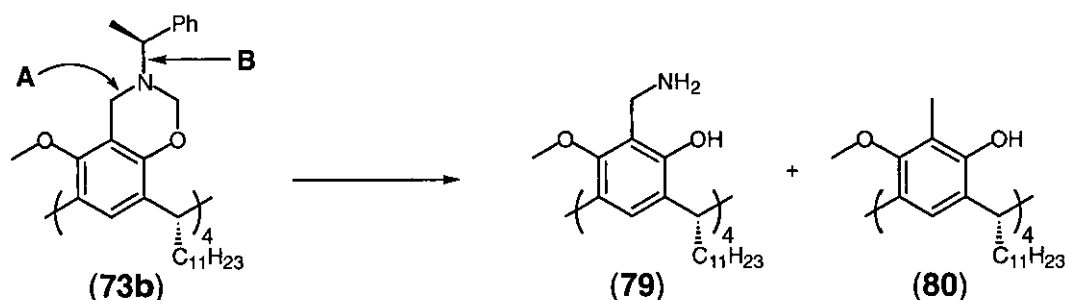
Examining the structure of the tetrakis-(*O*-methylether) functionalised calix[4]resorcinarene derivatives, it was obvious that one potential method of removing the α -methylbenzylamine group would be *via* the use of palladium catalysed hydrogenolysis. There is a vast number of examples of the cleavage of benzylic bonds *via* the action of hydrogen catalysed by palladium species.⁶¹ For example, hydrogenolysis of the 1,2-dihydroisoquinoline (**77**) using palladium on carbon in the

presence of hydrochloric acid gave exclusively the chiral substituted 1,2,3,4-tetrahydroisoquinoline in excellent yield, as shown in **Equation 41**.^{61a}



Equation 41

As can be seen if one examines the possible products of palladium catalysed hydrogenolysis of the tetrakis-(*O*-methylether)calix[4]resorcinarene derivative (62b), two possible products could theoretically be formed after hydrolysis of the initial product, as shown in **Equation 42**. This is by virtue of the two benzylic bonds **A** and **B** present in each 3,4-dihydro-2*H*-1,3-benzoxazine.

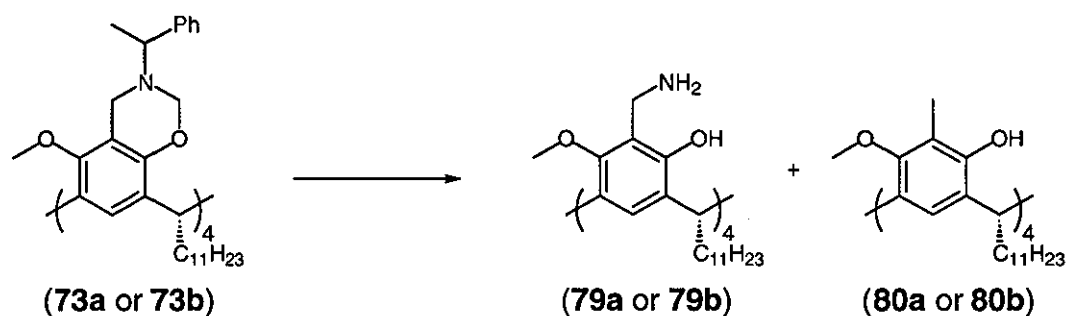


Equation 42

Cleavage of the benzylic bond (**A**) leads to compound (80), whereby recovery of the α -methylbenzylamine chiral auxiliary should be possible. This reaction pathway would result in the generation of a terminal methyl group on the resorcinarene. Alternatively, cleavage of the benzylic position (**B**) leads to compound (79) which results from destruction of the α -methylbenzylamine chiral centre but importantly is in possession of a functional group that could be manipulated further. (Both predicted pathways assume hydrolysis of the intermediate aminol ether). Of course, the reaction may

proceed down both reaction pathways, resulting in complex mixtures being formed.

Hydrogenolysis of compounds (**73a**) and (**73b**) was attempted using a range of conditions, the results of which are shown in **Table 14**.



Equation 43

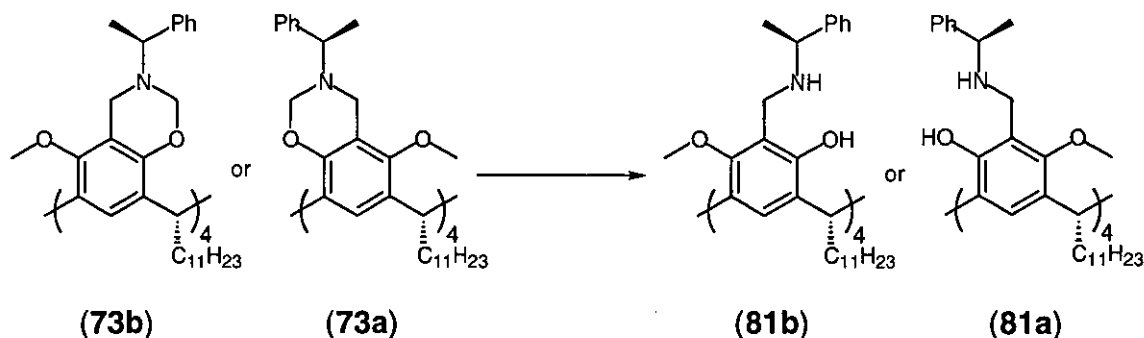
Entry	s.m.	Product	Conditions	Yield/%
a	(73a)	—	Pd/C, H ₂ (60 psi), THF, r.t., 24 h	no rxn
b	(73a)	(81a)	Pd/C, H ₂ (60 psi), THF, r.t., 24 h, HCl (conc) (4 eq)	Hydrolysed
c	(73b)	(81b)	Pd/C, H ₂ (balloon), Et ₂ O, r.t., 24 h, HCl (1M, Et ₂ O, 10 eq)	Hydrolysed
d	(73a)	(81a)	PdOH ₂ , H ₂ (balloon), EtOH/EtOAc, r.t., 24 h, HCl (2M, aq, 5 eq)	Hydrolysed

Table 14

Reacting a THF solution of the tetrakis-(*O*-methylether) functionalised calix[4]resorcinarene derivative (**73a**) with hydrogen (60mmHg) in the presence of a catalytic amount of palladium on carbon only resulted in the re-isolation of starting material. There is literature precedence for the addition of hydrochloric acid to hydrogenation reactions as a method of increasing the rate of reaction, possibly due

to the hydrochloride salt of the amine being a better leaving group.⁶²

Repetition of the reaction in the presence of both concentrated hydrochloric acid and an ethereal solution of hydrochloric acid, at atmospheric pressure and under high pressure did not result in any bond cleavage occurring. The only products isolated were the tetrakis-hydrolysed amino alcohol derivatives (**81a**) or (**81b**) (depending on whether (**73a**) or (**73b**) was used as the starting material). These products resulted from the hydrolysis of the 3,4-dihydro-2*H*-1,3-benzoxazine under the acidic reaction conditions. The structures of the products were confirmed by comparing their ¹H NMR spectra to that of fully characterised samples obtained from the independent hydrolysis of the tetrakis-(*O*-methylether) calix[4]resorcinarene derivatives (**73a**) and (**73b**), as shown in **Table 15**.



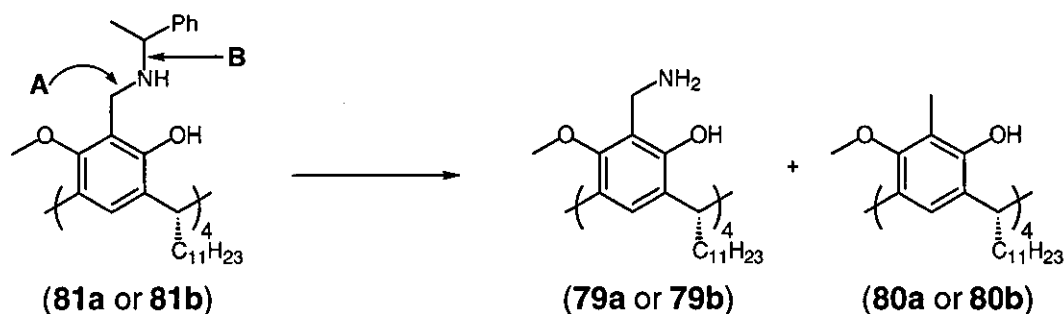
Equation 44

Entry	s.m	Product	Conditions	Yield/%
a	(73a)	(81a)	EtOH, HCl (conc, 5 eq), reflux, 3 h	87
b	(73b)	(81b)	EtOH, HCl (conc, 5 eq), reflux, 3 h	84

Table 15

The hydrolysed compounds (**81a**) and (**81b**) also have the two benzylic bonds **A** and **B** present as in the parent tetrakis-(*O*-methylether)calix[4]resorcinarene derivatives

(73a) and (73b). Dissolving these hydrolysed materials in a mixture of ethanol, ethyl acetate and hydrochloric acid and stirring the solution in the presence of palladium hydroxide under an atmosphere of hydrogen, again resulted in no hydrogenolysis taking place and merely the re-isolation of starting materials as shown in **Table 16**.



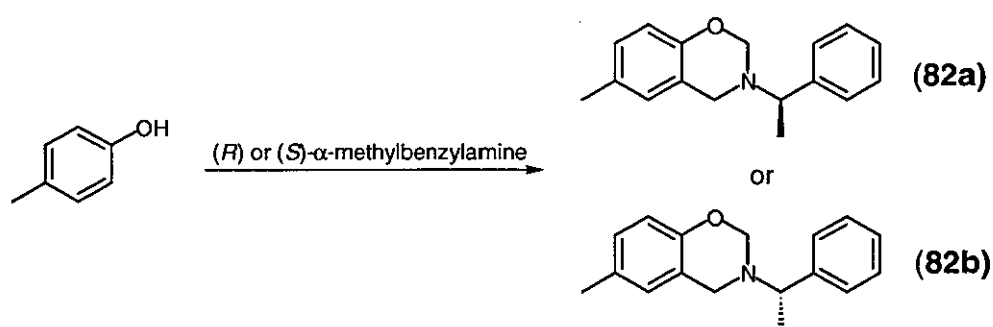
Equation 45

Entry	s.m.	Conditions	Yield/%
a	(81a)	Pd(OH) ₂ , H ₂ (balloon), EtOH/EtOAc, r.t., 24 h, HCl (2M, aq, 5 eq)	s.m.
b	(81b)	Pd(OH) ₂ , H ₂ (balloon), EtOH/EtOAc, r.t., 24 h, HCl (2M, aq, 5 eq)	s.m.

Table 16

These results indicate that both the parent tetrakis-(*O*-methylether)calix[4]resorcinarene derivatives (73a) and (73b) and their hydrolysed, ring opened counterparts (81a) and (81b) are unreactive to catalytic hydrogenolysis under a variety of conditions. As a consequence of this, other ways of fragmenting the 3,4-dihydro-2*H*-1,3-benzoxazine rings with a view to removing the chiral auxiliary were examined. As has already been shown, when subjecting resorcinarenes to chemical manipulation, each step in the synthesis must proceed in high yield to preclude the generation of complex mixtures. It was therefore decided to undertake a model study using a simple 3,4-dihydro-2*H*-1,3-benzoxazine.

3.3 Synthesis of Model Compound



Equation 46

6-Methyl-3-[1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine was synthesised in both enantiomeric forms, (82a) and (82b) respectively, via the procedures described in Table 17.⁶³

Entry	Amine	Product	Conditions	Yield/%
a	(<i>R</i>)	(82a)	Amine (1 eq), formaldehyde (37% aq, 2 eq), ethanol, reflux, 12 h	78
b	(<i>S</i>)	(82b)	Amine (1 eq), formaldehyde (37% aq, 2 eq), ethanol, reflux, 12 h	87
c	(<i>S</i>)	(82b)	Amine (1 eq), paraformaldehyde (2 eq), KOH (cat amount) ethanol, reflux, 12 h	83
d	(<i>S</i>)	(82b)	bis(aminoether) (1.2 eq), DCM, reflux, 12 h	88

Table 17

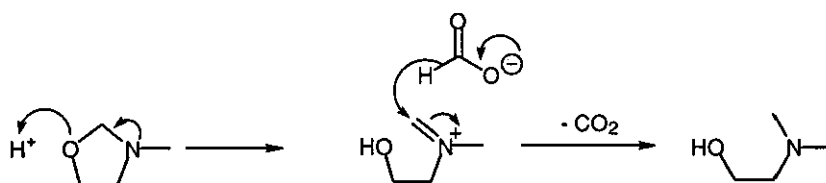
Both enantiomers were synthesised during the study and were isolated as stable pale yellow oils in each case. Both enantiomers had equal and opposite optical rotations and otherwise identical physical properties.

Due to the observed unreactivity of both the parent tetrakis-(*O*-methylether)calix[4]resorcinarene derivatives (**73a**) and (**73b**) and their hydrolysed, ring opened counterparts (**81a**) and (**81b**) to catalytic hydrogenolysis, another approach was envisaged.

3.3.1 Reductive Ring Opening of 3,4-Dihydro-2*H*-1,3-benzoxazines via a Modified Eschweiler-Clarke Ring Opening Reaction.

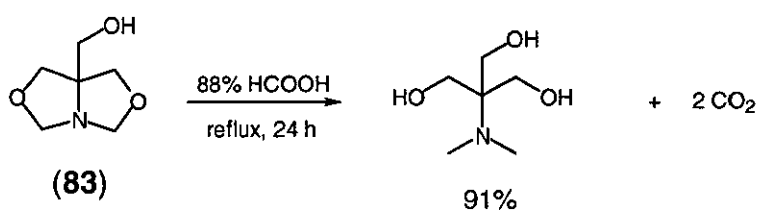
The reductive methylation of amines using formaldehyde and formic acid (the Eschweiler-Clarke reaction)⁶⁴ is usually a reliable method and proceeds by way of an aminol and an iminium ion that is reduced by formate ion. Formaldehyde and sodium dihydrogenphosphite has also been used.⁶⁵ The electrophile-induced reductive ring cleavage of cyclic aminol ethers can be thought of as proceeding in two stages. In the first stage interaction with an oxophilic electrophile generates an iminium ion, and in the second stage hydride ion effects the reduction. Aminol ethers in oxazolidines and 3,4-dihydro-2*H*-1,3-benzoxazines have been cleaved by reductive methods, including palladium on carbon,⁶⁶ alane generated *in situ* by the interaction of lithium aluminium hydride with aluminium chloride⁶⁷ and also by Grignard reagents.⁶⁸ Sodium cyanoborohydride has been used in the reductive amination of aldehydes and also in the reduction of some 2-methyleneoxazolidines.⁶⁹ Reductive cleavage of 2-aryloxazolidines by way of carbanion intermediates using metals such as potassium in THF has also been studied.⁷⁰

Since aminol ethers can give a range of iminium salts by interaction with a variety of electrophiles it was clear that formic acid could be used, in principle, both to generate a methyleneiminium ion and as the source of hydride ion in the reductive cleavage of cyclic alkoxymethyl-amines, as shown in **Scheme 11**.



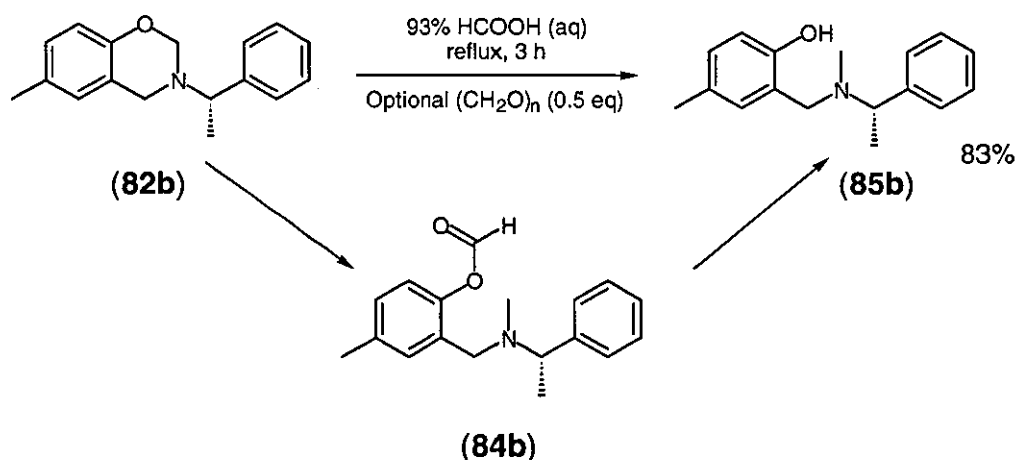
Scheme 11

However, the reductive ring opening of a cyclic aminol ether using formic acid has only received one brief mention, in the case of the bicyclic oxazolidine (**83**), as shown in **Equation 47**.⁷¹



Equation 47

Stirring a refluxing solution of 6-methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) in 96% aqueous formic acid resulted in clean conversion to 4-methyl-2-({methyl[(1*S*)-1-phenylethyl]amino}methyl) benzen-1-ol (**85b**), as shown in **Scheme 11**.



Scheme 12

Initially, the reaction mixture was concentrated under reduced pressure and partitioned between water and dichloromethane. After a conventional work up, examination of the crude material by ^1H NMR spectroscopy showed a mixture of two products to be present. The two unknown products were separated by careful flash column chromatography over silica gel and spectroscopic analysis showed one to be the desired material (85b) and the second to be the closely related formate ester (84b), as shown in **Scheme 12**.

^1H NMR spectroscopy showed different chemical shifts present for the important functional groups in the molecules, particularly the AB quartet corresponding to the methylene group and the *N*-methyl group as shown in **Figure 18**. In addition, ^{13}C NMR spectroscopy showed duplication of all the signals at slightly different chemical shifts in addition to a signal at 166 ppm that could be assigned to the C=O carbon of the phenolic ester.

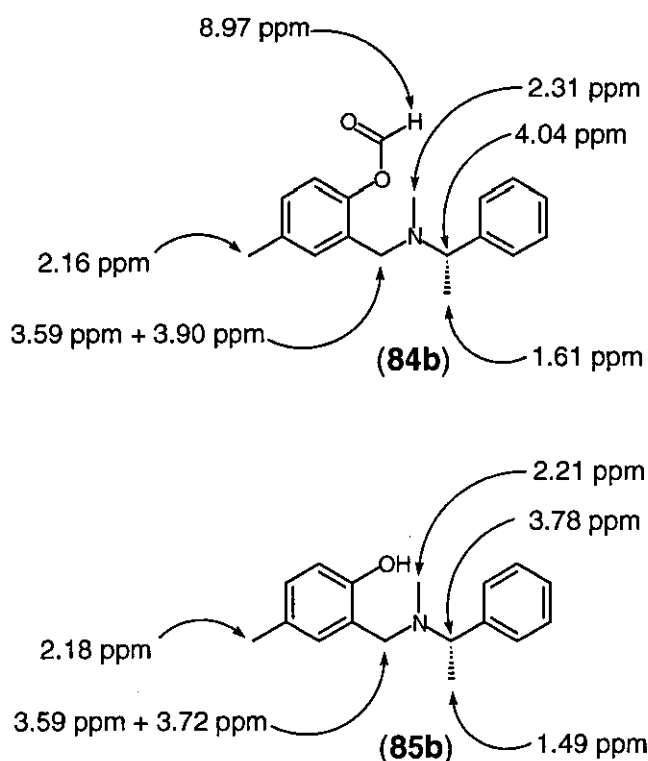


Figure 18

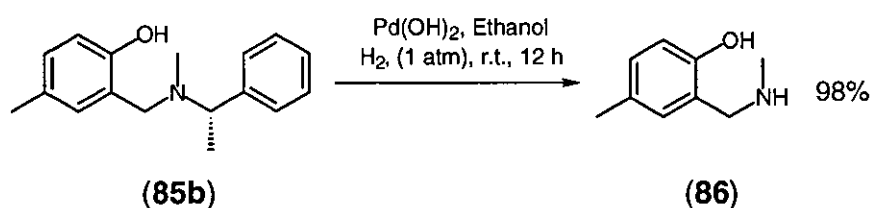
The formate ester (**84b**) was easily hydrolysed by treatment with either dilute aqueous sodium hydroxide or hydrochloric acid to furnish 4-methyl-2-((methyl[(1*S*)-1-phenylethyl]amino)methyl)benzen-1-ol (**85b**). The disappearance of the broad singlet at 8.97 ppm in the ^1H NMR spectrum accompanied this transformation. The reaction protocol was optimised to hydrolyse the material at the work up stage. Treatment of the crude reaction mixture with an ice cold solution of aqueous ammonia hydrolysed any formate ester present as well as neutralising the excess formic acid. Simply extracting into an organic solvent, drying over magnesium sulfate and concentrating under reduced pressure gave the crude product, which could be easily purified *via* flash chromatography to furnish the desired product in excellent yield. None of the corresponding secondary amino alcohol, produced *via* acid catalysed hydrolysis was observed, indicating that the reduction of the iminium ion provides the faster reaction pathway. In addition, running the reaction in the presence of paraformaldehyde under

standard Eschweiler-Clarke conditions showed no increase in the overall yield of the reaction.

The scope of this modified Eschweiler-Clarke reaction was investigated with a range of different cyclic aminol ethers and the results will be discussed in more detail in chapter 7. Meanwhile, with an efficient reaction protocol for the conversion of 3,4-dihydro-2*H*-1,3-benzoxazines to their ring opened *N*-methylated analogues in place, investigations into the further fragmentation of these compounds were initiated.

3.3.2 Removal of the α -Methylbenzylamine Moiety

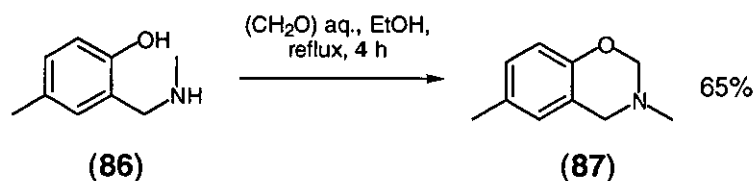
There is literature precedence for the use of palladium hydroxide as a potent hydrogenation catalyst, especially for the cleavage of benzyl groups in hindered compounds.^{61a}



Equation 48

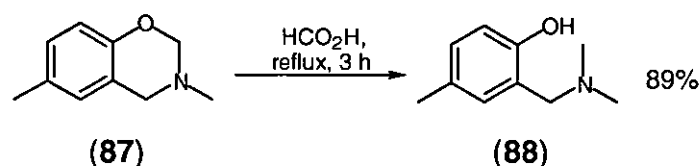
With this in mind, it was found that simply stirring a solution of the amino alcohol (85b) in ethanol, under an atmosphere of hydrogen in the presence of palladium hydroxide furnished 4-methyl-2-[(methylamino)methyl]benzen-1-ol (86) in almost quantitative yield, as shown in **Equation 48**. Indeed, it was found that cleavage of the amino alcohol (85b) was completely selective in that the α -methylbenzylamine bond was cleaved in preference to the phenolic benzyl bond. This reaction has the disadvantage in that the potentially valuable chiral starting material is destroyed, but the advantage that a pendant secondary amino functionality still remains.

Next, it was found that treating 4-methyl-2-[(methylamino)methyl]benzen-1-ol (**86**) with formaldehyde in refluxing ethanol furnished 3,6-dimethyl-3,4-dihydro-2*H*-1,5-benzoxazine (**87**) in good yield, as shown in **Equation 49**.



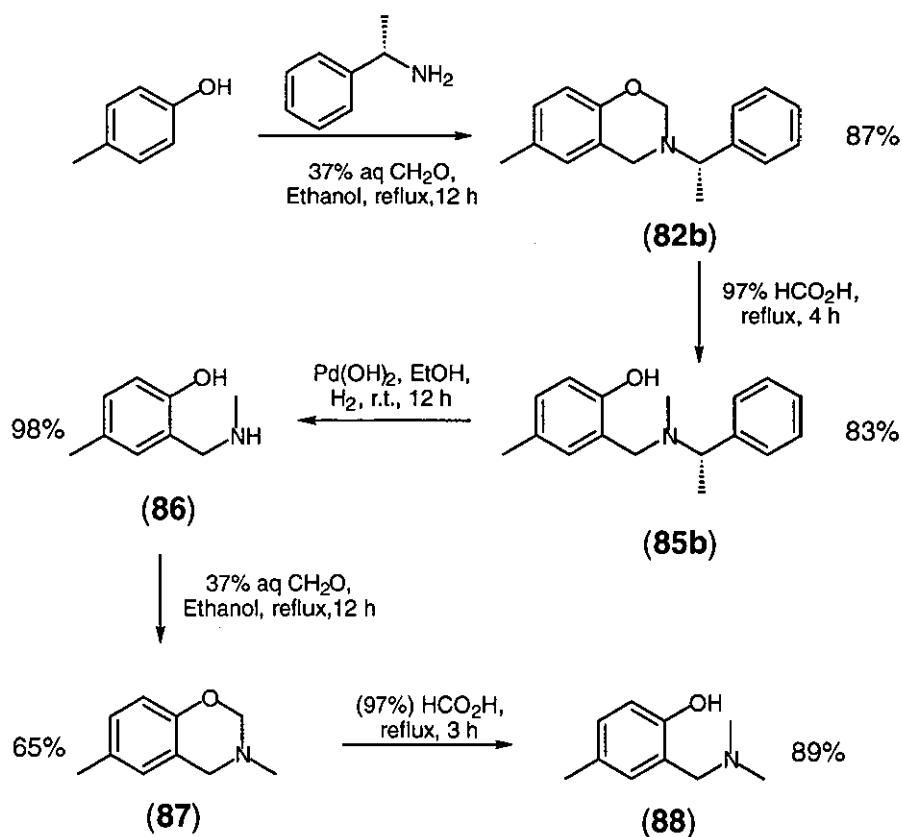
Equation 49

Finally, subjecting 3,6-dimethyl-3,4-dihydro-2*H*-1,5-benzoxazine (**87**) to a second modified Eschweiler-Clarke reductive ring opening reaction furnished 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) in excellent yield, as shown in **Equation 50**.



Equation 50

An efficient route for the conversion of 6-methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) to 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) has been developed which proceeds in good overall yield, as depicted in **Scheme 13**. The sequence incorporates two novel reductive ring opening steps based on modified Eschweiler-Clarke chemistry.

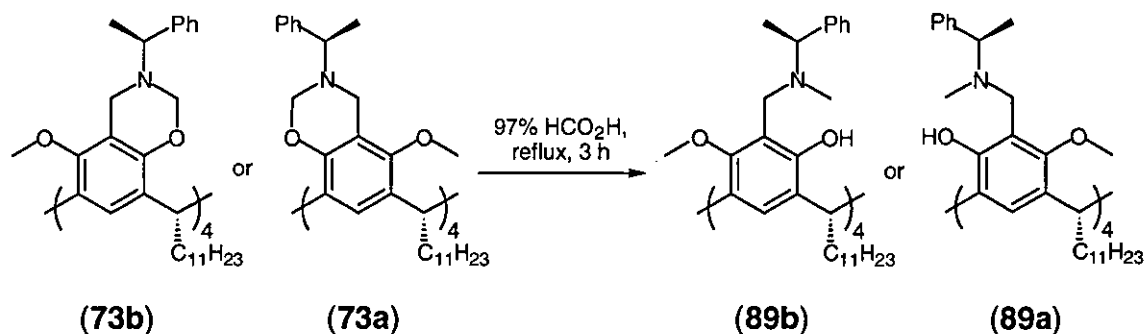


Scheme 13

3.4 Application to Resorcinarene Series

As has already been demonstrated with the tetramethylation step in the resorcinarene series, each step of the synthesis must proceed in high yield to ensure a high *overall* yield when applied to the resorcinarene substrates. With the success of the model studies, these criteria had been met and the chemistry was applied to the resorcinarene series of compounds.

Refluxing the resorcinarene derivatives **(73a)** and **(73b)** in formic acid under the modified Eschweiler-Clarke conditions resulted in isolation of the corresponding tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivatives **(89a)** and **(89b)** in excellent yield, as shown in **Equation 51**.



Equation 51

Again, the compounds were isolated as viscous golden oils which stubbornly refused to crystallise. The ¹H NMR spectrum of the product showed the disappearance of the AB quartet corresponding to the aminol ether methylene group accompanied by the appearance of an *N*-Me peak at 2.07 ppm. Again, the ¹H NMR spectrum was relatively simple suggesting the formation of the symmetrical tetrakis product and this was confirmed by high resolution mass spectrometry and combustion analysis.

It was found that DIBAL-H and LiAlH₄ were also both efficient reagents for this transformation. In both cases, it was assumed that aluminium acts as a Lewis acid, complexing onto the benzoxazine oxygen resulting in the formation of the transient iminium ion before delivering hydride ion. This alternative methodology has the advantage that the reaction can be run at a much lower temperature. After the usual work up and purification by column chromatography, the desired compound was obtained in comparable yield and with identical spectroscopic properties to that obtained *via* the formic acid methodology. The results of these reactions are compiled in **Table 18**.

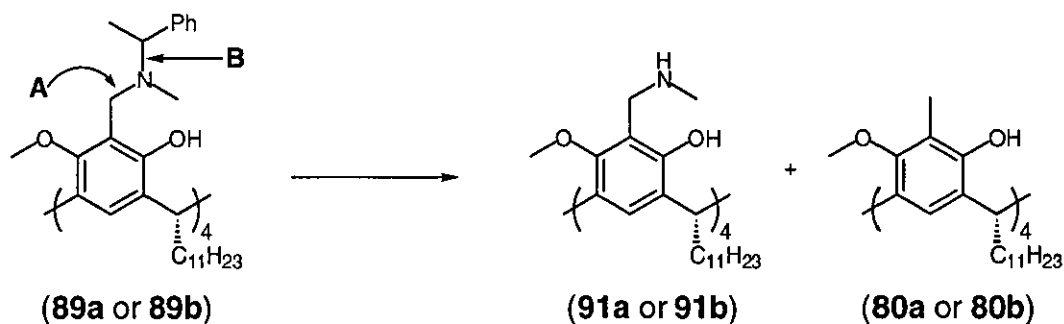
Entry	s.m.	Product	Conditions	Yield/%
a	(73a)	(89a)	97% HCO ₂ H	88
b	(73b)	(89b)	97% HCO ₂ H	86
c	(73b)	(89b)	97% HCO ₂ H + CH ₂ O (aq)	cplx
d	(73a)	(89a)	DIBAL-H (8 eq)	93
e	(73b)	(89b)	DIBAL-H (8 eq)	90
f	(73b)	(89b)	LiAlH ₄ (5 eq)	93

Table 18

Again, the pair of C₁₁H₂₃ enantiomers (89a) and (89b), produced by the formic acid protocol, were shown to have equal and opposite optical rotations. Their non-racemic nature was confirmed *via* analysis by chiral HPLC.

3.4.1 Hydrogenolysis of Reductively Ring Opened Resorcinarene Derivatives

As has already been shown, the attempted benzylic cleavage of both the parent tetrakis-(*O*-methylether)calix[4]resorcinarene derivatives (73a) and (73b) and their hydrolysed, ring opened counterparts (81a) and (81b) was unsuccessful. Therefore similar reactions on the corresponding *N*-methylated, ring opened derivatives (89a) and (89b) were attempted.



Equation 52

Again, there are two possible benzylic positions that could be cleaved, as shown in **Equation 52**. The results of these reactions are shown in **Table 19**. As can be seen, stirring an ethereal solution of the required resorcinarene in the presence of a catalytic amount of palladium hydroxide under an atmosphere of hydrogen only resulted in the re-isolation of unchanged starting material. The same result was observed under a high pressure atmosphere of hydrogen.

Entry	s.m.	Product	Conditions	Yield/%
a	(89a)	(91a)	Pd(OH) ₂ , Et ₂ O, H ₂ (balloon), 24 h	s.m.
b	(89a)	(91a)	Pd(OH) ₂ , Et ₂ O, H ₂ (50 psi), 24 h	s.m.
c	(89b)	(91b)	Pd(OH) ₂ , EtOH, EtOAc, HCl (2M, aq, 5 eq), H ₂ (balloon), 24 h	89
d	(89a)	(91a)	Pd(OH) ₂ , EtOH, EtOAc, HCl (2M, aq, 5 eq), H ₂ (balloon), 24 h	81

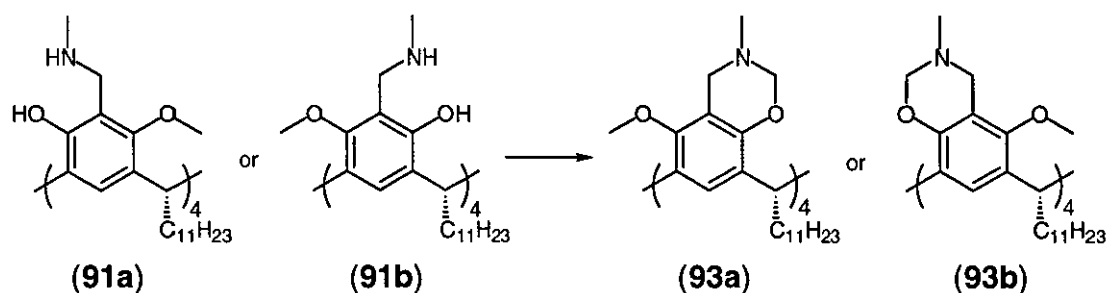
Table 19

The addition of acid to the reaction mixture resulted in a radical change in reactivity. Running the reaction in a mixture of ethanol, ethyl acetate and aqueous hydrochloric acid resulted exclusively in the formation of the tetrakis-(*N*-methyl) derivative (**91a**) or (**91b**) (according to the appropriate starting material used). The desired compound was formed in excellent yield, and resulted from cleavage of the benzylic bond **B**. None of the product resulting from the cleavage of bond **A** was observed. This is consistent with the reactivity of the model system.

°C and increasing the pressure to 45 psi resulted in the isolation of the desired product in 30% yield. Increasing the temperature and pressure still further resulted in a corresponding increase in yield. The hydrogenolysis products were routinely isolated >95% pure and no attempt at purification was made but they were instead reacted crude and purified at the next stage.

3.4.2 Formation of *N*-methyltetrakis(3,4-dihydro-2*H*-1,3-benzoxazine) calix[4]resorcinarene Derivatives

Following the protocol developed on the model system, it was shown that simply refluxing an ethanolic solution of the crude tetrakis-(*N*-methyl) derivative (**91a**) or (**91b**), in the presence of aqueous formaldehyde resulted in ring closure and formation of the corresponding tetrakis-(3-methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93a**) or (**93b**) in good yield. The results of these reactions are compiled in Table 21.



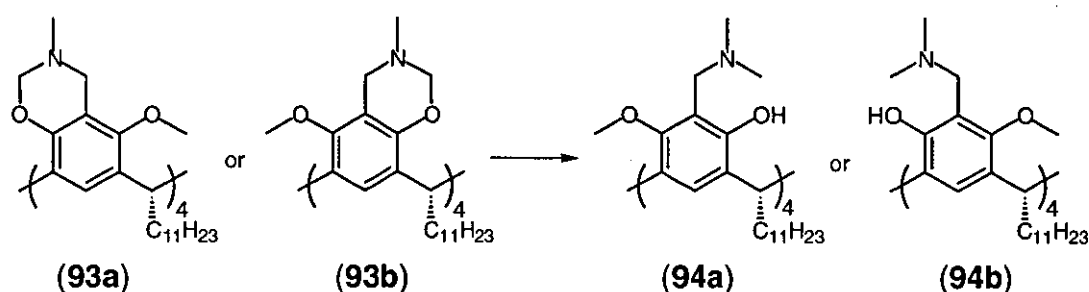
Equation 54

Entry	s.m.	Product	Conditions	Yield/%
a	(91a)	(93a)	CH ₂ O (37% aq, 5eq), EtOH, reflux, 4 h	66
b	(91b)	(93b)	CH ₂ O (37% aq, 5eq), EtOH, reflux, 4 h	79

Table 21

3.4.3 Second Modified Eschweiler Clarke Reductive Ring Opening Reaction

Finally, refluxing a formic acid solution of the required tetrakis-(3-methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93a**) or (**93b**) under our now standard conditions resulted in the isolation of the desired tetrakis-(2-[(dimethylamino)methyl]) derivatives (**94a**) or (**94b**) in excellent yield. Again, it was shown both DIBAL-H and LiAlH₄ could be used to perform this transformation, but obviously, due to the ease of handling, cost factors and practicality of using aqueous formic acid to effect this transformation, it was routinely used as the method of choice. The results of these reactions are compiled in **Table 22**.



Equation 55

Entry	s.m.	Product	Conditions	Yield/%
a	(93a)	(94a)	HCO ₂ H (37% aq), reflux, 4 h	90
b	(93b)	(94b)	HCO ₂ H (37% aq), reflux, 4 h	87
c	(93a)	(94a)	DIBAL-H (8 eq), Toluene, 0 °C, 3 h	77
d	(93b)	(94b)	DIBAL-H (8 eq), Toluene, 0 °C, 3 h	84
e	(93b)	(94b)	LiAlH ₄ (4.4 eq), THF, -78 °C - 0 °C, 30 min	54

Table 22

3.5 Conclusion

A short synthetic route (four steps) for the replacement of the four α -methylbenzylamine groups from diastereomerically stable tetrakis-(*O*-methylether)calix[4]resorcinarene derivatives (**62a**) and (**62b**), with four *N*, *N*-dimethylamino groups has been developed. The route was initially optimised on a model compound, 6-methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) and incorporates a novel transformation, namely using aqueous formic acid to effect reductive ring opening of 3,4-dihydro-2*H*-1,3-benzoxazine rings. Hydrogenolysis was shown to occur regioselectively on the resulting *N*-methylated compounds using a catalytic amount of palladium hydroxide under acidic reaction conditions. The route developed on the model system was successfully applied to the resorcinarene series of compounds. Both diastereoisomers derived from undecylcalix[4]resorcinarene were taken through the synthesis and were compared by optical rotations and chiral HPLC at convenient steps along the synthesis.⁷³

Chapter 4

4.0 Synthesis of Axially Chiral Non-racemic Resorcinarene Derivatives with Functionalised Lower Rims.

4.1 Introduction

This chapter contains results and discussion describing attempts to generate axially chiral non-racemic resorcinarenes with pendant functionalities on the lower rim. The aim of the work was to develop a method of supporting the newly developed enantiomerically pure resorcinarene derivatives onto solid phase supports. It was envisaged that these supported reagents may have the potential to act as chiral ligands in asymmetric processes or as stationary phases in chiral HPLC.

Because thermodynamic isomers of calix[4]resorcinarenes have an all cis 'rccc' structure, the well defined upper and lower 'rims' have been the target of some interesting functionalisation reactions. Work on the derivatisation of the upper rim has been reported in earlier chapters and attention now turned to functionalisation of the lower rim.

Varieties of resorcinarenes have been shown to form well defined monolayers when adsorbed onto the surface of gold. Moreover, resorcinarenes have been synthesised with useful terminal functionalities present that may be manipulated further to yield functional groups for immobilisation on polymeric resins. Indeed, there is literature precedence for the immobilisation of a calix[4]pyrrole onto a polymeric resin *via* an amide linkage.⁷⁴

The advantages of solid phase chemistry over conventional solution phase methodology have been extensively reported and include the following:⁷⁵

- (i) **Cleaner synthetic methods:** Cross-linked polymers are insoluble, non-volatile and most importantly environmentally friendly. In addition, toxic chemicals can be rendered inert and harmless through attachment to a polymeric support.
- (ii) **Potential for automated synthesis:** Polymer-supported chemistry lends itself to the development of automated techniques, such as high-throughput screens. For polymer supported catalysts, the possibility exists to develop both insoluble and soluble derivatives. Insoluble catalysts have the advantage that they can be removed by filtration, allowing for rapid recycling and re-use. With soluble polymers, the catalysis takes place in an homogeneous medium, which may be beneficial to a particular reaction, with the catalysts subsequently being rendered insoluble for re-isolation by precipitation.
- (iii) **Simplified product isolation and purification:** Following the completion of a reaction, the desired target and the insoluble polymer supported reagent can be separated simply by filtration.
- (iv) **Ready recovery of supported catalytic systems for reuse:** In the case of polymer-supported catalysts, this enables quantitative re-isolation for re-use, therefore increasing efficiency.

In addition, Pietraszkiewicz and co-workers have recently shown that calix[4]resorcinarenes can serve as an efficient and selective stationary phase for HPLC.⁷⁶ The lipophilic alkyl chains of C-undecylcalix[4]resorcinarene are strongly adsorbed on the modified silica gel RP-18, and this new stationary phase has been shown to separate uracil, thymine and cytosine in a relatively short period of time.

4.2 Synthesis of Resorcinarene Precursors

The initial objective of this work was to synthesise resorcinarenes with pendant functionalities present that could be used to enable the compounds to be isolated on polymeric supports. These groups may include, for example, carboxylic acids, phenols, alcohols, or esters in the terminal position of the four alkyl or aryl chains. A range of mono-functionalised aldehydes of the general structure shown in **Figure 19** was therefore required.

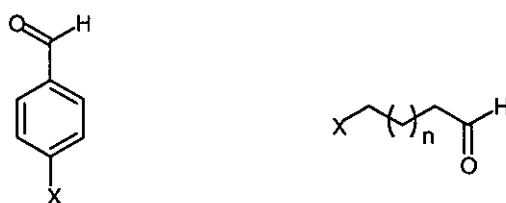
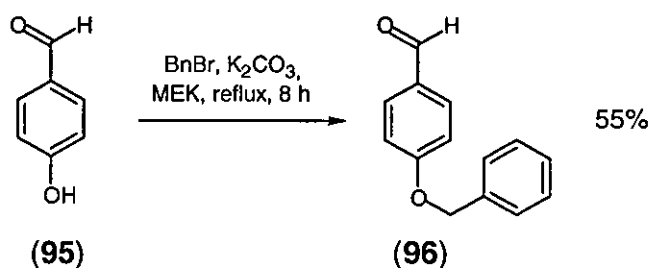


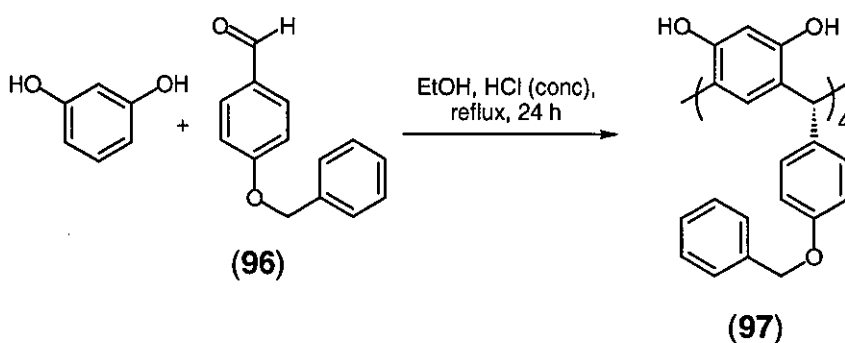
Figure 19

It was initially decided to explore the possibility of using 4-hydroxybenzaldehyde as a suitable starting material. Protection of the hydroxyl group was needed for the compound to be compatible with both the acid catalysed condensation with resorcinol and also the subsequent formation of the diastereomerically pure tetrakis(dihydro-1,3-benzoxazines). Protection as a benzyl ether seemed to be the obvious choice as removal could be effected under the hydrogenation conditions used to cleave the α -methylbenzyl group on the upper rim. Therefore, *O*-benzylation was accomplished as follows. Treatment of a solution of 4-hydroxybenzaldehyde (**95**) in methyl ethyl ketone with benzyl bromide in the presence of potassium carbonate, furnished, after chromatography 4-benzyloxybenzaldehyde (**96**) in moderate yield, as shown in **Equation 56**.



Equation 56

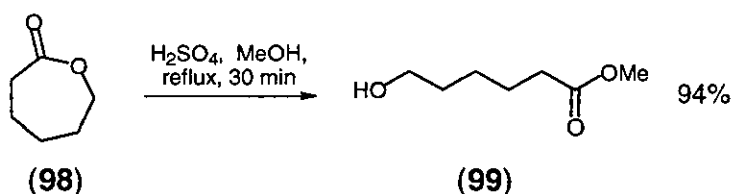
Stoichiometric amounts of 4-benzyloxybenzaldehyde (96) and resorcinol were reacted together in ethanolic hydrochloric acid under the standard conditions, as shown in **Equation 57**.



Equation 57

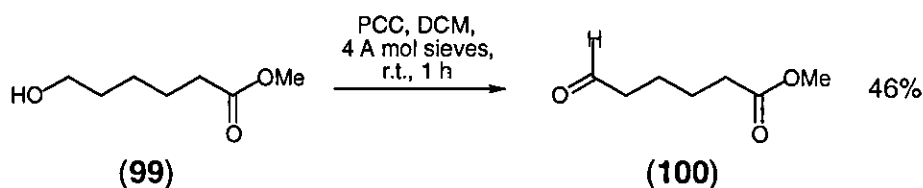
After twenty-four hours at reflux, the reaction mixture was cooled in an ice bath and the resulting beige crystalline solid was filtered and washed with copious amounts of cold ethanol. Unfortunately, the resulting material was insoluble in all common organic solvents and therefore defied characterisation. It was decided to not pursue the investigation of this material further. As has already been shown, alkyl functionalised resorcinarenes are generally more soluble in common organic solvents than their aryl cousins. It was therefore decided to attempt to synthesise a resorcinarene with a functionalised alkyl chain in place of an aryl group. Towards this aim, caprolactone (98) was successfully ring opened and esterified with methanol to furnish 6-hydroxyhexanoic acid methyl ester (99). Distillation gave the desired

compound as a colourless oil in excellent yield, as shown in **Equation 58**.⁷⁷



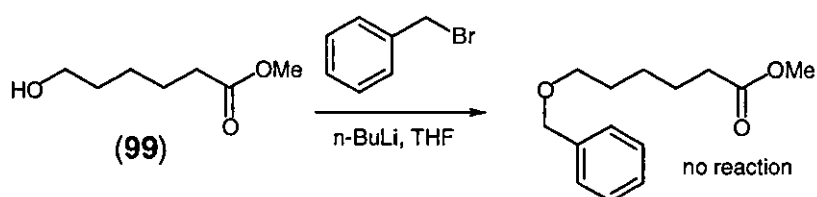
Equation 58

Oxidation of the alcohol to the corresponding aldehyde was accomplished with PCC to give methyl 6-oxohexanoate (**100**) in moderate yield, as shown in **Equation 59**.⁷⁸



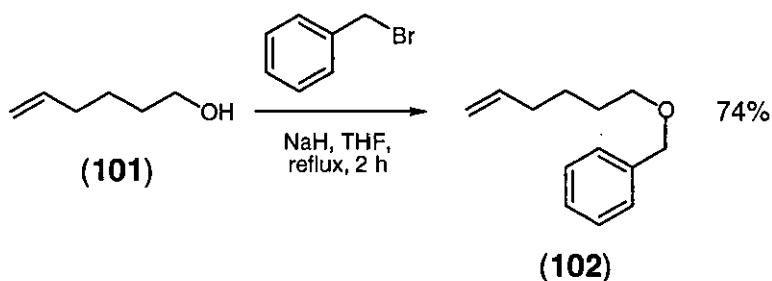
Equation 59

Reaction of stoichiometric amounts of methyl-6-oxohexanoate (**100**) with resorcinol in an ethanolic solution of hydrochloric acid under the standard reaction conditions resulted in the isolation of an intractable oil that defied characterisation. This may be due to the ester undergoing acid catalysed hydrolysis in addition to ester exchange, during the course of the reaction. With no resorcinarene being formed in the presence of a terminal ester, another approach was envisaged. It was anticipated that protection of 6-hydroxyhexanoic acid methyl ester (**99**) as a benzyl ether followed by reduction of the ester group to an aldehyde, would accomplish our target of producing an alkyl analogue of 4-benzyloxybenzaldehyde (**96**). Unfortunately, the attempted protection of 6-hydroxyhexanoic acid methyl ester (**99**) by treatment with benzyl bromide and *n*-BuLi resulted in no reaction and the isolation of unreacted benzyl bromide, as shown in **Equation 60**. This could possibly be due to the formed anion reacting with the ester, reforming caprolactone (**98**).



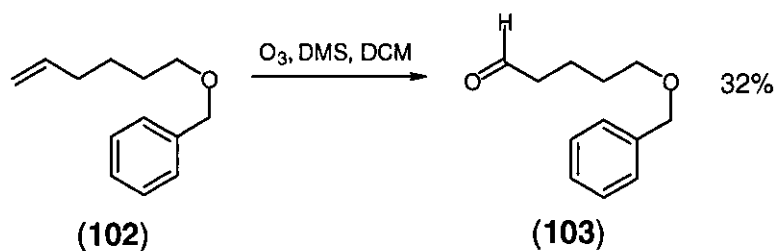
Equation 60

Due to the failures of the above reactions, an alternative strategy was investigated. Treatment of 5-hexen-1-ol (101) with benzyl bromide in the presence of sodium hydride in THF furnished 5-benzyloxyhex-1-ene (102) as a colourless oil in good yield, as shown in **Equation 61**.⁷⁹



Equation 61

Ozonolysis of 5-benzyloxyhex-1-ene (102) in the presence of dimethyl sulfide resulted in 5-benzyloxypentanal (103) being isolated in moderate yield, as shown in **Equation 62**.⁸⁰



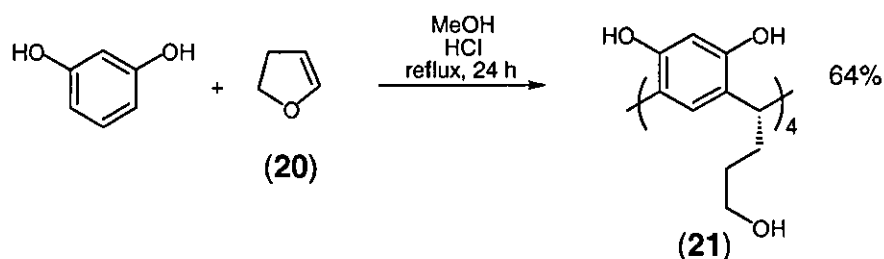
Equation 62

Once more, reaction of stoichiometric amounts of 5-benzyloxypentanal (103) with resorcinol in an ethanolic solution of hydrochloric acid under the standard reaction

conditions again resulted in the isolation of an intractable oil that defied characterisation.

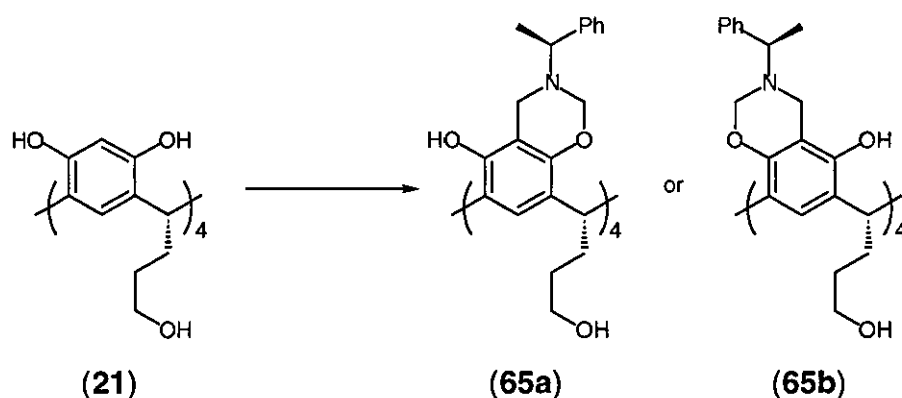
4.3 Synthesis and Functionalisation of C-3-Hydroxypropylcalix[4]-resorcinarene

At this stage, it was decided to take advantage of known chemistry to generate resorcinarenes with inherent functionality on the lower rim. It has been shown that by reacting 2,3-dihydrofuran (20) with resorcinol under mineral acid catalysis, the corresponding resorcinarene with four propanol chains (21) is formed in excellent yield as shown in **Equation 63**.⁵ Repetition of this work resulted in the desired compound being generated in good yield. The isolated compound agreed with known literature spectroscopic data.



Equation 63

Formation of the diastereomerically pure tetrakis(dihydro-1,3-benzoxazines) (65a) and (65b) occurred smoothly utilising the chemistry described in chapter one. Both diastereomers were synthesised and could be easily recrystallised to high levels of purity. The results of these reactions are compiled in **Table 23**.



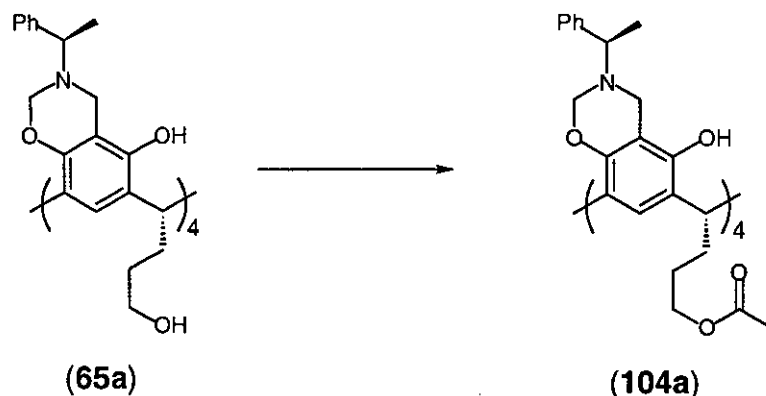
Equation 64

Entry	Product	Conditions	Yield/%
a	(65a)	(<i>R</i>)- α -methylbenzylamine (5 eq), CH ₂ O (37% aq, 10 eq), EtOH, reflux, 24 h.	53
b	(65b)	(<i>S</i>)- α -methylbenzylamine (5 eq), CH ₂ O (37% aq, 10 eq), EtOH, reflux, 24 h.	71
c	(65b)	bis(aminoether) (67b) (4.4 eq), EtOH, reflux, 24 h.	65

Table 23

4.3.1 Attempted Acylation of the Four Propanol Groups

As has been shown, the methylation of the four free phenolic groups precludes diastereoisomerisation *via* acid catalysed formation of transient iminium ions. Therefore, for this step to be carried out efficiently, the selective protection of the four propanolic groups must be carried out prior to this step. As we have shown in our attempts to derivatise the phenolic positions, the very nature of their sterically demanding location in the molecule makes them unreactive to a host of reaction protocols. It was therefore postulated that the four propanolic side chains should react preferentially. Once the propanolic positions were suitably derivatised we envisaged methylation of the phenolic groups would occur smoothly using known chemistry.⁷³



Equation 65

Initially it was hoped that the acetylation of the four alcohols would proceed easily. Treating the tetrakis(dihydro-1,3-benzoxazine) derivative (65a) with an excess of acetic anhydride according to the reaction conditions shown in **Table 24** only resulted in extensive decomposition of the tetrakis(dihydro-1,3-benzoxazines). This is consistent with the results obtained during the attempted acetylation of the four phenolic groups, described in chapter two.

Entry	Conditions	Yield/%
a	Ac ₂ O, pyridine, r.t., 12 h	Decomp
b	Ac ₂ O, pyridine, 4-DMAP, r.t., 12 h	Decomp

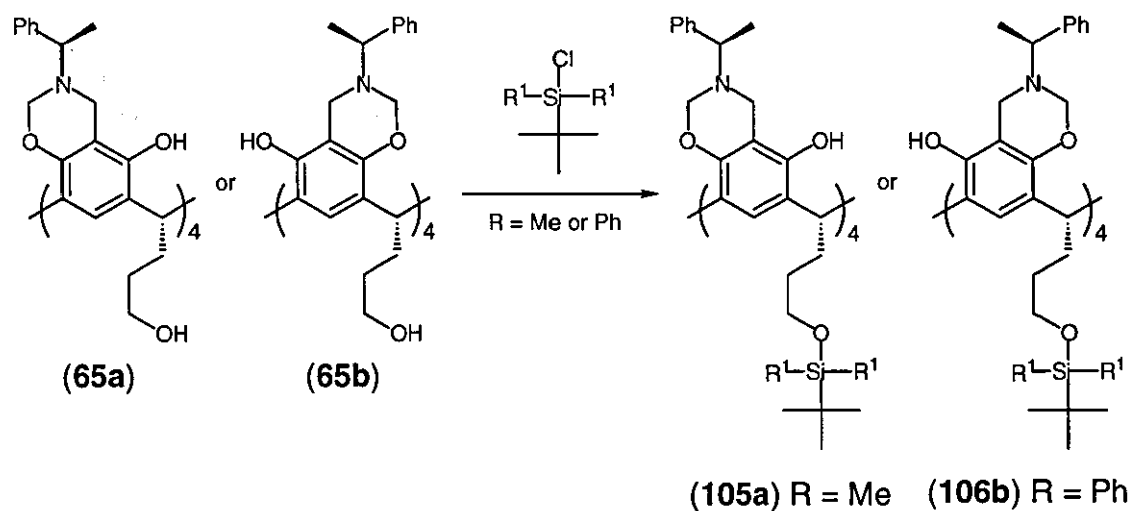
Table 24

4.3.2 Protection of the Propanol Groups using Silicon Reagents

After the failures of the attempted acetylations, attention turned to the use of silicon protecting groups, which have been extensively reported in the literature.⁶⁰ If the problem was indeed that the more nucleophilic nitrogen was being acylated preferentially, then it was envisaged the use of the more oxophilic silicon protecting groups should prove more fruitful. Reaction of the resorcinarene derivatives (65a) or

(65b) with a slight excess of *tert*-butyldimethylsilylchloride in pyridine proceeded smoothly at room temperature. Upon studying the ^1H NMR spectrum, it was evident a degree of diastereoisomerisation had occurred, evidently mediated by the hydrochloric acid that was liberated during the reaction. Recrystallisation of the crude product furnished the desired tetra-TBDMS ether in high purity, but the diastereoisomerisation explains the slightly lower yield of the reaction. This problem was overcome by adding an excess of triethylamine to the reaction mixture to neutralise any hydrochloric acid evolved in the reaction *via* the formation of triethylamine hydrochloride. Analysis of the crude product from this reaction showed no diastereoisomerisation to have occurred. Repeating the reaction with *tert*-butyldiphenylsilylchloride in place of *tert*-butyldimethylsilylchloride, only resulted in partial functionalisation of the resorcinarene, almost certainly due to the steric demands of placing four *tert*-butyldiphenylsilyl groups in close proximity to each other.

An attempt was also made to benzylate the four propanol groups with benzyl bromide and sodium hydride but this resulted in extensive decomposition. The results of all these reactions are compiled in **Table 25**.



Equation 66

Entry	s.m.	Product	Conditions	Yield/%
a	(65b)	(105b)	TBDMSCl (5 eq), pyridine, r.t., 1 h	61
b	(65b)	(105b)	TBDMSCl (5 eq), pyridine, Et ₃ N (10 eq), r.t., 3 h	86
c	(65b)	(105b)	TBDMSCl (5 eq), pyridine, Et ₃ N (10 eq), 0 °C, 3 h	80
d	(65a)	(106a)	TBDPSCI (5 eq), pyridine, Et ₃ N (10 eq), 0 °C, 3 h	Partial
e	(65a)	(106a)	TBDPSCI (5 eq), pyridine, Et ₃ N (10 eq), 4-DMAP (cat amount) 0 °C, 3 h	Partial
f	(65a)	(106a)	TBDPSCI (8 eq), imidazole (16 eq), Et ₃ N (8 eq), DMF, r.t., 12 h	Decomp
g	(65a)	—	NaH (10 eq), BnBr (5 eq), THF, 0 °C - r.t., 12 h	Decomp

Table 25

We observed no evidence for reaction at the more sterically demanding phenolic positions.

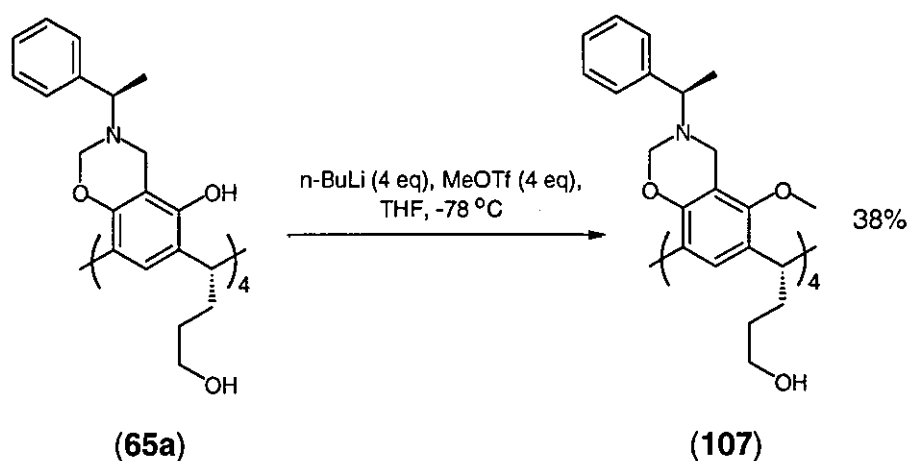
4.4 Methylation of the Phenolic Positions

With these materials in hand, work began on the methylation of the four residual phenolic positions. It was envisaged that following the standard conditions, (n-BuLi (4 eq), methyl triflate (4 eq) in THF at -78 °C) would furnish the desired compound. Desilylation of the propanol chains, either with TBAF or during the formic acid reductive ring opening step would furnish the four free alcohols ready for further manipulation.

Almost immediately, it was discovered that the tetra *tert*-butyldimethylsilyl protected derivative (105b) was insoluble in THF below room temperature and only sparingly soluble in diethyl ether below room temperature. As was found during the optimisation of the tetramethylation step, low temperature (-78 °C) is a prerequisite for good yield

in this step. We thought that the use of *tert*-butyldiphenylsilylchloride as the protecting group would improve the solubility of the tetra-protected compound at low temperature, but, as alluded to earlier, a complete reaction was not observed.

With these failures in mind it was decided to use the *unprotected* parent compound (**65a**) in the methylation step under our usual conditions. We postulated that the four phenolic groups may be deprotonated preferentially and form a stabilised tetra-anion. Indeed, running the reaction under the standard conditions furnished, after flash chromatography, the desired tetramethyl ether (**107**) in a reasonable yield as a white crystalline solid, as shown in **Equation 67**. It is felt that with optimisation this yield can be increased somewhat and this important intermediate can be carried through the sequence of reactions and eventually immobilised onto a solid support.



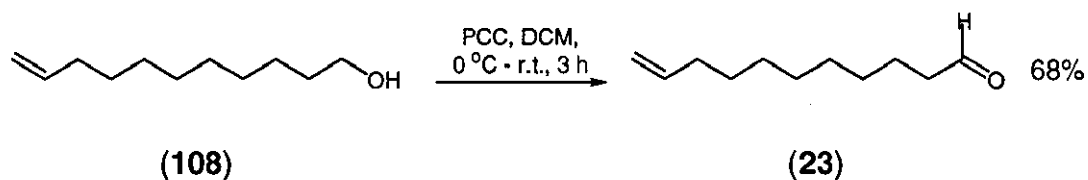
Equation 67

4.5 Synthesis and Functionalisation of C-Undecenylcalix[4]resorcinarene

Upon searching the literature, an example of a resorcinarene with four terminal alkene residues present was discovered.²¹ An alkene, of course, can be envisaged as a masked terminal alcohol (*via* anti-Markovnikov hydroboration), a terminal aldehyde (*via* reductive ozonolysis) or a terminal carboxylic acid (*via* oxidative ozonolysis).

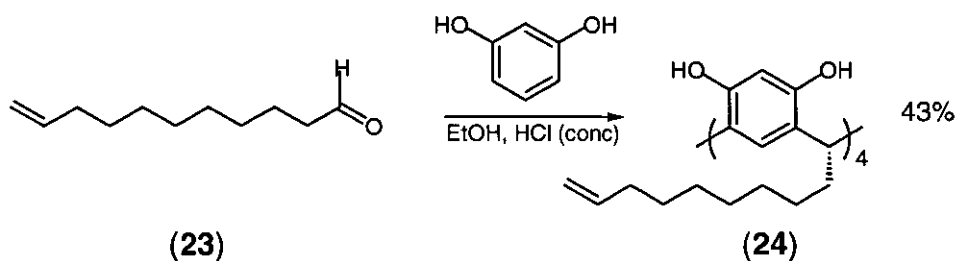
Therefore, the synthesis and application of *C*-decenylcalix[4]resorcinarene was subsequently investigated.

Oxidation of 10-undecen-1-ol (**108**) with PCC gave, after distillation, 10-undecenal (**23**) as a colourless, floral smelling oil in good yield, as shown in **Equation 68**.⁸¹



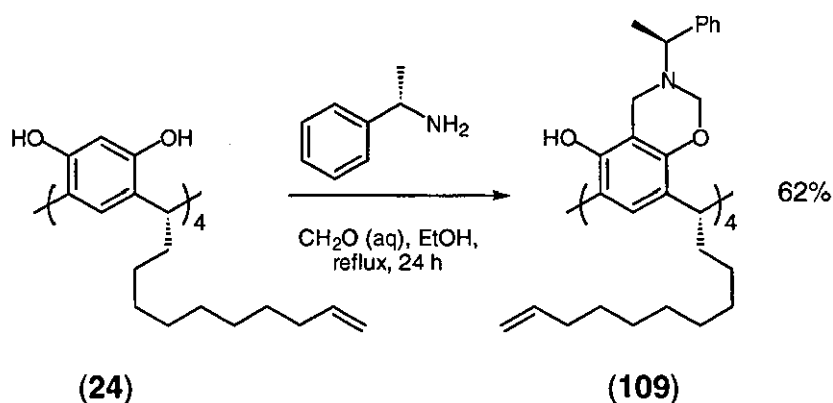
Equation 68

Reacting this aldehyde with a stoichiometric amount of resorcinol according to a literature procedure gave *C*-decenylcalix[4]resorcinarene (**24**) in low yield, but which agreed with known spectroscopic data, as shown in **Equation 69**.²¹



Equation 69

Reacting *C*-decenylcalix[4]resorcinarene (**24**) with (*S*)- α -methyl benzylamine and aqueous formaldehyde under standard conditions gave the corresponding tetrakis(dihydro-1,3-benzoxazine) derivative (**109**) in good yield, as shown in **Equation 70**.



Equation 70

4.6 Conclusion and Further work

Known chemistry has been applied to generate two novel inherently chiral non-racemic calix[4]resorcinarene derivatives with functionalised lower rims. These compounds have the potential to be manipulated further to enable them to be immobilised on solid supports.

Chapter 5

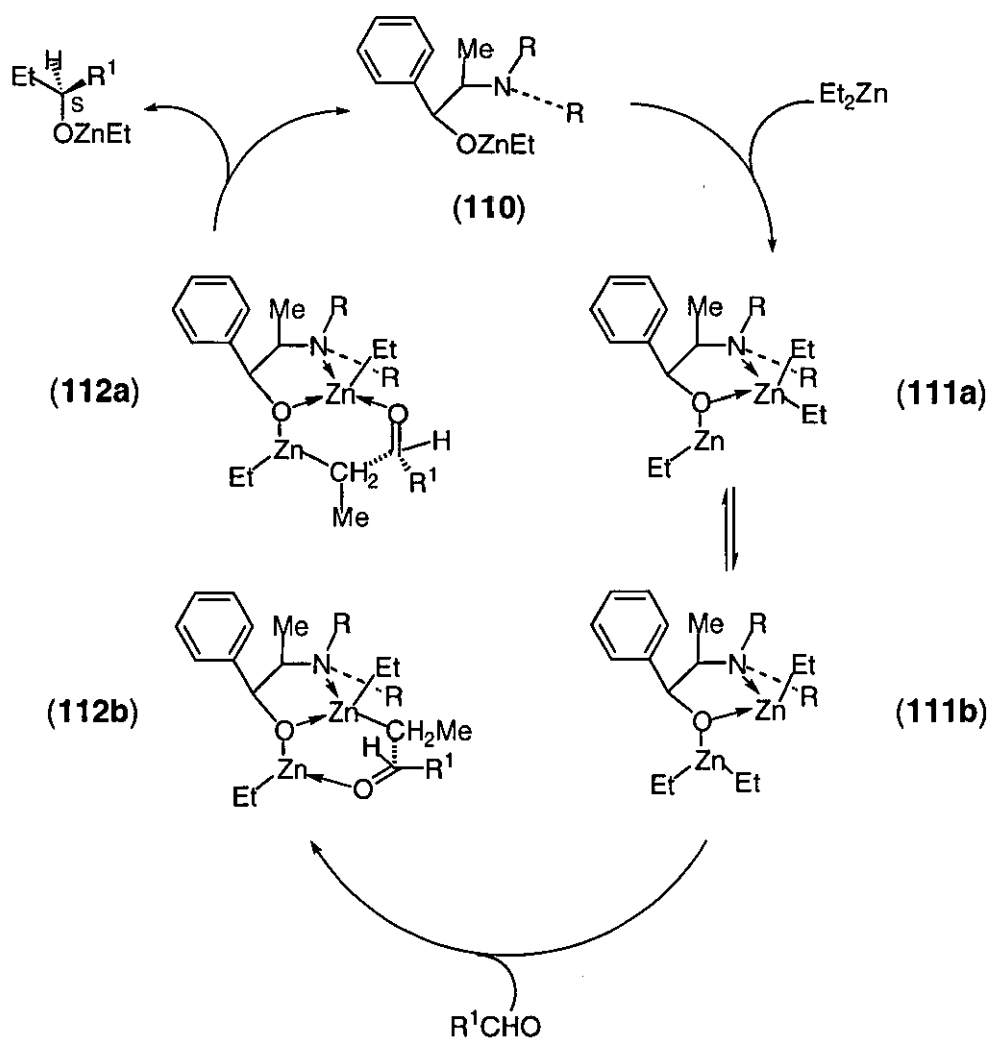
5.0 Investigations Into the Enantioselective Addition of Diethylzinc to Benzaldehyde using Inherently Chiral Resorcinarenes as Chiral Ligands

5.1 Introduction

A huge amount of work has been carried on the enantioselective addition of diethylzinc to aldehydes, especially using β -amino alcohols as chiral ligands.⁸² This chapter contains results and discussions on preliminary investigations into the applications of inherently chiral resorcinarene derivatives as chiral ligands. A range of resorcinarene derivatives was applied as ligands in the enantioselective addition of diethylzinc to benzaldehyde.

5.2 Catalytic Cycle

A proposed catalytic cycle for the addition of diethylzinc to aldehydes, catalysed by β -aminoalcohols such as ephedrine, is shown in **Scheme 14**.⁸³ Initially, the oxygen of the β -aminoalcohol ligand displaces one ethyl group of the diethylzinc, forming the zinc monalkoxide complex (**110**). Another molecule of diethylzinc complexes to (**110**) to form the complex(es) (**111a**) and (**111b**). The zinc atom is in the centre of a tetrahedral geometry and subsequently, the zinc-carbon bond length increases from 1.95-1.98 Å increasing the nucleophilicity of the ethyl moiety. The aldehyde subsequently forms a six-membered transition state (**112**) with the ethyl attacking from the *si* face. Therefore, bulky groups on nitrogen increase the enantioselectivity of the reaction by blocking one of the enantiotopic faces of the aldehyde



Scheme 14

5.3 Results and discussion

It was thought that the series of inherently chiral resorcinarenes may act as potential ligands in the asymmetric addition of diethylzinc to aldehydes, primarily due to their β -aminoalcohol structural motif, as depicted in **Figure 20**. It would also be intriguing to ascertain whether the inherently chiral resorcinarene (**94**), whose only chiral element is its inherent axis of chirality, would induce any enantioselectivity.

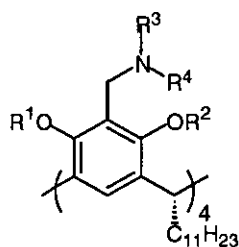
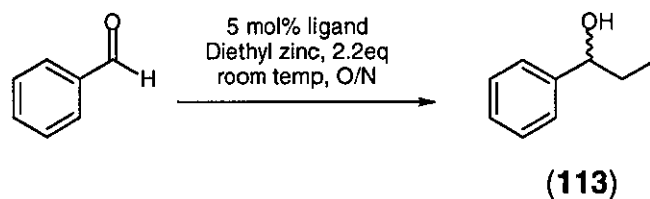


Figure 20

It was therefore decided to test some of the functionalised resorcinarenes in the catalytic asymmetric addition of diethylzinc to benzaldehyde, as depicted in **Equation 71**.⁸⁴



Equation 71

The reactions were carried out as follows. A catalytic amount of the required ligand was dissolved in toluene and cooled to 0 °C. Diethylzinc was then added followed by benzaldehyde. The reaction mixture was stirred for twenty four hours before being subjected to a conventional work-up. Purification by flash chromatography gave pure 1-phenyl-1-propanol (**113**) which was analysed by chiral HPLC to determine the enantiomeric excess of the reaction. The results of these reactions are compiled in **Table 26**. The ligands used are depicted in **Figure 21**.

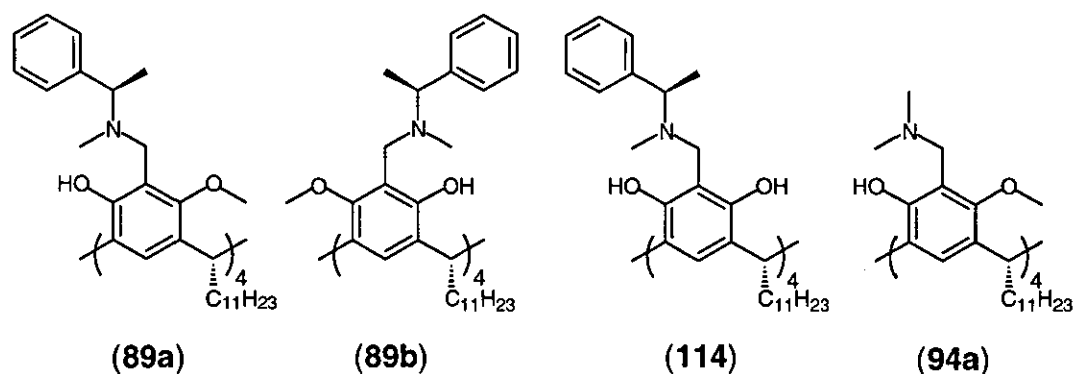


Figure 21

Entry	Ligand	R ^{1*}	R ^{2*}	R ^{3*}	R ^{4*}	Yield/%	e.e.	Config
a	(114)	H	H	(<i>R</i>)- α -methylbenzyl	Me	84	0	–
b	(89a)	H	Me	(<i>R</i>)- α -methylbenzyl	Me	80	56	(<i>S</i>)-(–)
c	(89b)	Me	H	(<i>S</i>)- α -methylbenzyl	Me	75	55	(<i>R</i>)-(+)
d	(94a)	H	Me	Me	Me	71	42	(<i>R</i>)-(+)

* Refers to Figure 19

Table 26

As can be seen from **Table 26**, ligands (**89a**) and (**89b**) gave 1-phenyl-1-propanol in good yield and more importantly, with moderate enantioselectivity. Ligand (**89a**) derived from (*R*)- α -methylbenzylamine gave 1-phenyl-1-propanol with 56% e.e in favour of the (*S*)-(–) enantiomer. Likewise, repeating the reaction with ligand (**89b**) derived from (*S*)- α -methylbenzylamine gave 1-phenyl-1-propanol with 55% e.e in favour of the (*R*)-(+) enantiomer. Running the reaction using ligand (**114**) gave a racemic mixture due to the rotation around the amine-carbon bond, as shown in **Figure 22**.

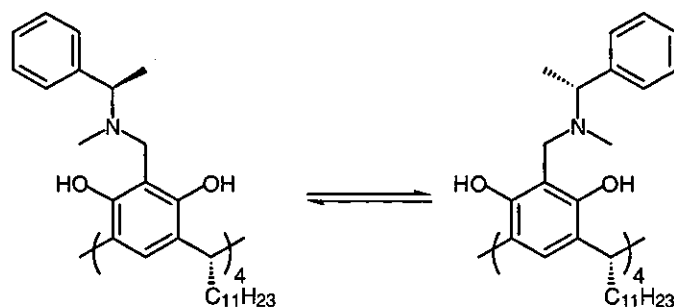
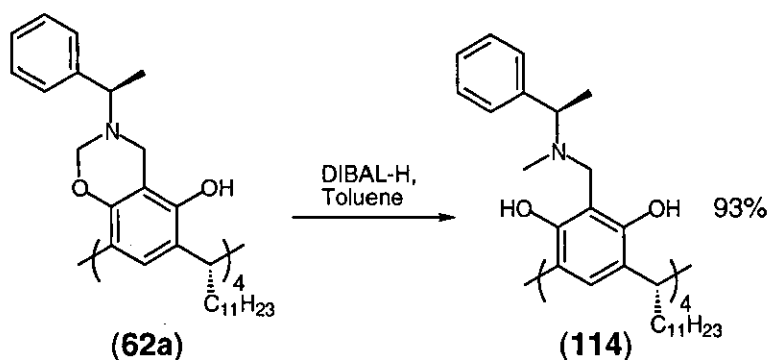


Figure 22

Perhaps the most interesting result was observed when using resorcinarene ligand (**94a**), a compound whose chirality is due only to its inherent axial chirality. Running the reaction under the same conditions gave 1-phenyl-1-propanol in comparable yield and with reasonable enantioselectivity, interestingly giving the opposite enantiomer as the major product to that obtained with the analogous ligand (**89a**)



Equation 72

The tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (**114**) was synthesised by the reductive ring opening of the tetrakis(dihydro-1,3-benzoxazine) calix[4]resorcinarene derivative (**62a**), as shown in **Equation 72**. This compound, with eight phenolic groups present, showed some interesting characteristics in its ^1H NMR spectra, which were related to the conformation the molecule adopts at room temperature. At room

temperature, the ^1H NMR spectrum of compound (110) was very broad with no discernible peaks present. However, upon warming, the spectrum sharpened considerably. The initial broadness of the spectrum was due to the fact that as there are two phenolic positions per resorcinol subunit (or eight per resorcinarene), the tertiary amine can form hydrogen bonds to either oxygen. Therefore, there is a large number of possible conformers that can be formed at room temperature. Warming the sample breaks the hydrogen bonds and consequently resolves the spectrum.

At the time this work was being carried out, Hunter and co-workers sent a sample of a chiral, non-racemic, distally-bridged resorcinarene (115) that they had synthesised, as shown in **Figure 23**. Using this compound in the same reaction gave 1-phenyl-1-propanol in good yield with an encouraging 26% e.e.

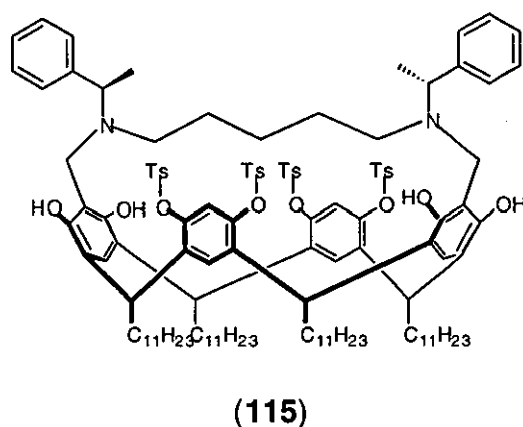


Figure 23

5.4 Conclusion and Further Work

A range of resorcinarene derivatives has been used as chiral ligands in the asymmetric addition of diethylzinc to benzaldehyde. The preliminary results were very encouraging with ligands **(89a)** and **(89b)** giving good enantioselectivities. More importantly, the axially chiral derivative **(94a)** gave good enantioselectivity proving the axial chiral derivatives have potential to act as an important new class of chiral molecules.⁸⁵

Chapter 6

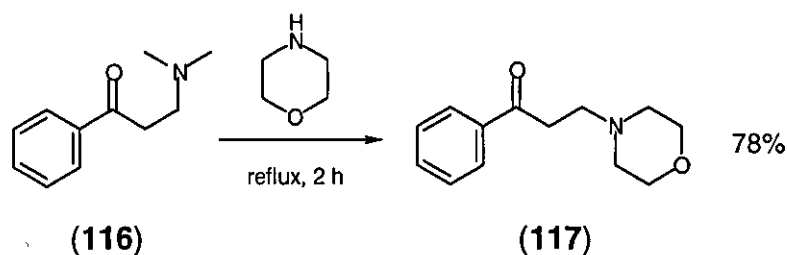
6.0 Investigation into the Mechanism of the 'Retro-Mannich' Reaction

6.1 Introduction

During the work on the generation of inherently chiral non-racemic calix[4]resorcinarene derivatives, a method was needed for the fragmentation of 3,4-dihydro-2*H*-1,3-benzoxazines with a view to removing the chiral amino group. It was noticed in the literature that there was a small number of reported examples of an amine exchange reaction occurring when a number of amines were heated in the presence of another high boiling amine.

6.2 Examples of the 'Retro-Mannich' Reaction

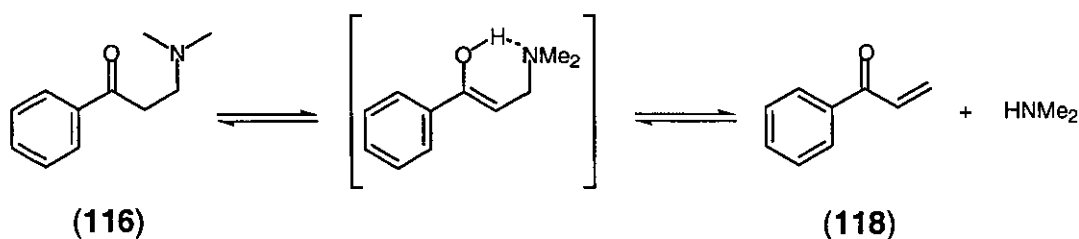
The first example originated from the lab of Brewster and co-workers.⁸⁶ It was found that when heating under reflux β -dimethylaminopropiophenone (**116**) in an excess of morpholine for two hours resulted in the isolation of β -morpholinopropiophenone (**117**) in good yield, as shown in **Equation 73**.



Equation 73

Repeating the reactions using either the hydrochloride salt or quaternary ammonium salt of β -dimethylaminopropiophenone again resulted in the isolation of β -morpholinopropiophenone in comparable yield. Interestingly, in both of these cases

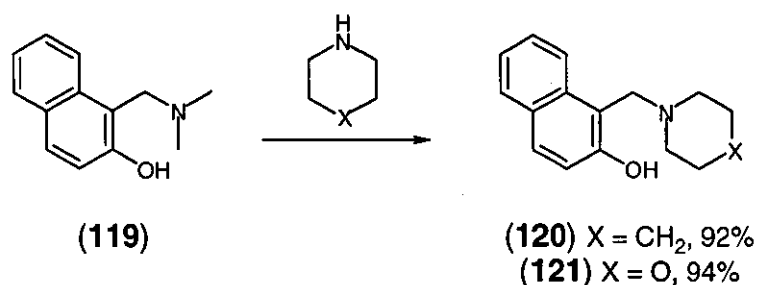
only a slight rate increase was observed suggesting the reaction was not occurring *via* a simple nucleophilic substitution reaction pathway but rather *via* some other mechanism. With this in mind, they postulated the reaction may be occurring *via* the α,β -unsaturated carbonyl compound (118), as depicted in **Scheme 15**.



Scheme 15

It was envisaged that morpholine underwent a formal Michael addition to the newly formed α,β -unsaturated carbonyl species (118).

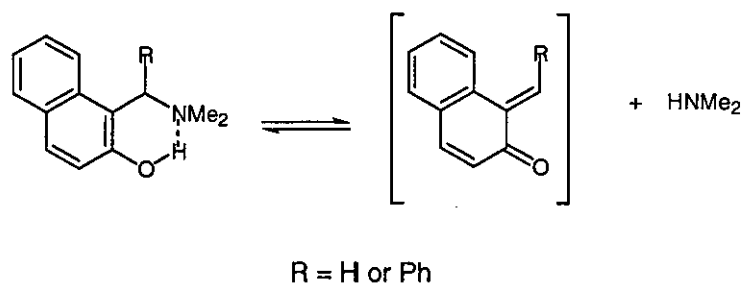
Similarly, heating a solution of α -dimethylaminomethyl- β -naphthol (119) in morpholine or piperidine under reflux resulted in the formation of the corresponding Mannich base in good yield. The morpholine or piperidine Mannich bases could be interconverted by simply heating under reflux in the appropriate solvent, as shown in **Equation 74**.



Equation 74

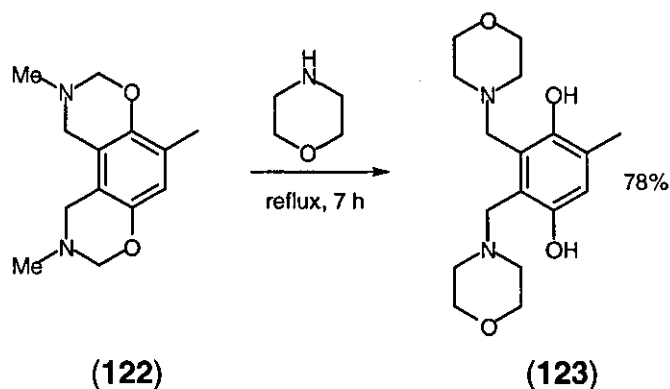
The related Betti bases formed from the condensation of β -naphthol with benzaldehyde and dimethylamine also reacted by amine exchange with morpholine

and piperidine. In both cases, the reactions were also postulated to proceed *via* a quinone methide, as shown in **Scheme 16**.



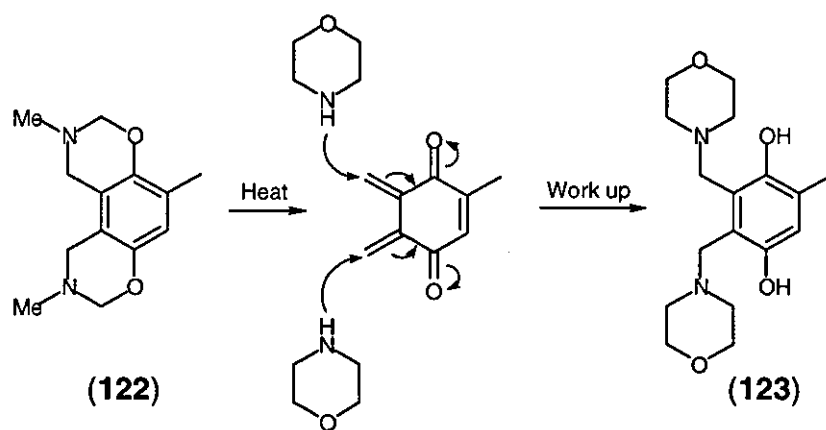
Scheme 16

A similar reaction has been shown to occur when repeating the reaction with 3,4-dihydro-2*H*-1,3-benzoxazines. Reynolds and co-workers⁵¹ showed that by refluxing 3,4-dihydro-2*H*-1,3-benzoxazines in an excess of morpholine, a reaction occurs whereby the heterocyclic ring undergoes ring fragmentation followed by capture of morpholine to give the morpholino analogue in good yield. This is exemplified in **Equation 75**.



Equation 75

Although a mechanism was not proposed, the reaction could also be envisaged as proceeding *via* a quinone methide, as shown in **Scheme 17**.

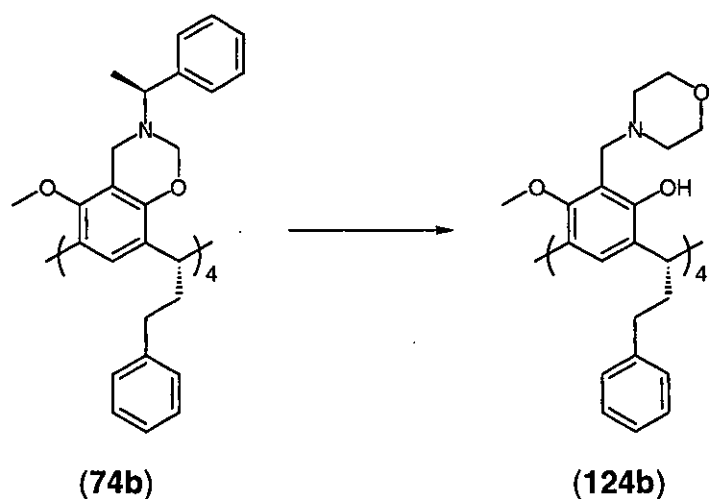


Scheme 17

It was envisaged that the application of this 'retro-Mannich' reaction would be useful in the context of the resorcinarene series of compounds. Not only would it achieve the aim of removing the α -methylbenzylamine chiral auxiliary, but it would also liberate the second phenolic hydroxyl group which has been shown is needed for efficient complexation of guest species.

6.3 Application to Resorcinarene Derivatives

Following the procedure of Reynolds,⁵¹ it was found that heating a solution of resorcinarene derivative (**74b**) in morpholine under reflux for fifteen hours resulted in the isolation of the tetramorpholino derivative (**124b**) in poor yield, as shown in **Table 27**.



Equation 76

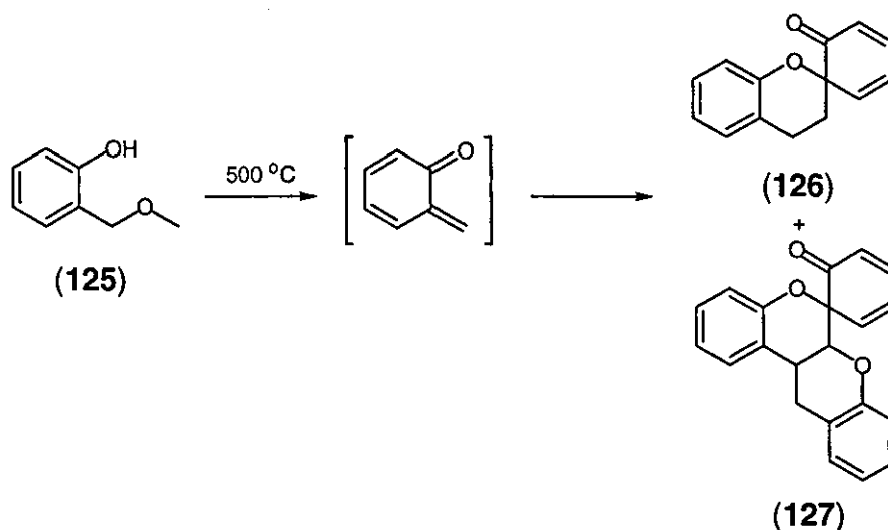
Entry	Conditions	Yield/%
a	Morpholine, reflux, 5 h	26
b	Morpholine, reflux, 15 h	33
c	Morpholine, Cu(OTf) ₂ (10 mol%), reflux, 5 h	33
d	Morpholine, Cu(OTf) ₂ (10 mol%), Toluene, reflux, 5 h	20
e	Morpholine, Cu(OTf) ₂ (10 mol%), DCM, reflux, 5 h	—
f	Morpholine, ZnCl ₂ (10 mol%), reflux, 5 h	26
g	Morpholine, BF ₃ ·Et ₂ O (10 mol%), reflux, 5 h	24
h	Morpholine, Zn(OTf) ₂ (10 mol%), reflux, 5 h	31

Table 27

The addition of Lewis acids to the reaction mixture did not have any effect on the yield of the reaction. The only prerequisite for the reaction to occur seemed to be high temperature.

6.4 Synthesis and Reactivity of Quinone Methides

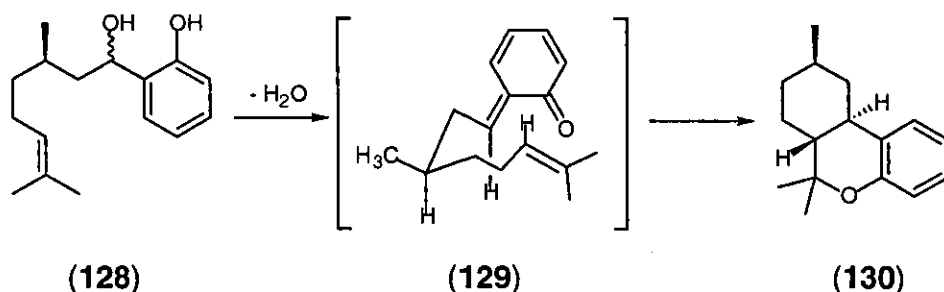
o- and *p*-Quinone methides are valuable intermediates in organic synthesis, for example, *o*-quinone methides have been used to carry out 'reverse electron demand' Diels-Alder [4+2] cycloadditions with electron rich alkenes to furnish chroman derivatives.⁸⁷ The mode of action of a number of important anti-cancer drugs as well as the biological toxicity of some chemicals have been ascribed to quinone methide chemistry.⁸⁸ A common method for the synthesis of *o*-quinone methides is *via* the thermolysis of precursor substrates. An example of this is from the group of Branden and co-workers.⁸⁹ Pyrolysis of *o*-methoxymethylphenol (**125**) resulted in the isolation of an impure sample of the *o*-quinone methide intermediate. Warming the sample above $-50\text{ }^{\circ}\text{C}$ resulted in the formation of some interesting dimeric (**126**) and trimeric (**127**) chroman fused ring systems, as shown in **Scheme 18**.



Scheme 18

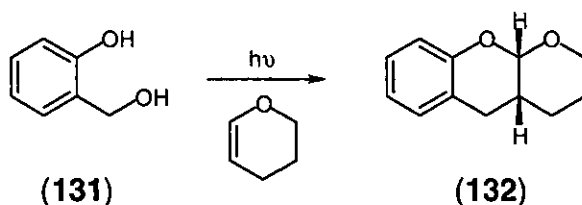
It has been found that *o*-hydroxy benzyl alcohols undergo thermal dehydration to furnish *o*-quinone methides at much lower temperatures. Talley⁹⁰ has described a stereospecific intramolecular Diels-Alder Reaction utilising this chemistry. Heating the hydroxy benzyl alcohol precursor (**128**), present as one to one mixture of

stereoisomers, at 180 °C resulted in the formation of the cycloadduct (**130**) as one diastereoisomer in excellent yield, as shown in **Scheme 19**. The pseudoequatorial conformation adopted by the C-9 methyl in the chair-like transition state of the intermediate *o*-quinone methide (**129**) accounts for the observed stereospecificity.



Scheme 19

It has been shown that *o*-quinone methides can be generated photochemically as well as thermally. Wan and co-workers⁹¹ have shown that irradiating an aqueous solution of 2-hydroxybenzyl alcohol (**131**) in the presence of dihydropyran gave the corresponding chroman adduct (**132**) in excellent yield as predominantly the *cis* diastereomer, as shown in **Equation 77**.

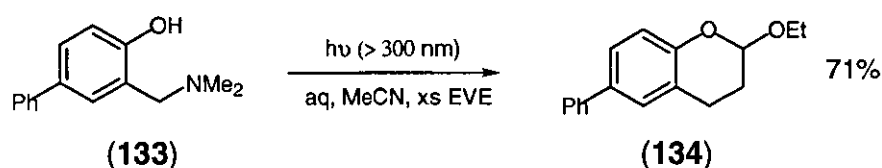


Equation 77

Ethyl vinyl ether and dihydrofuran have also been shown to trap quinone methide intermediates efficiently. The phenolic methyl ether analogues gave no reaction under the same conditions.

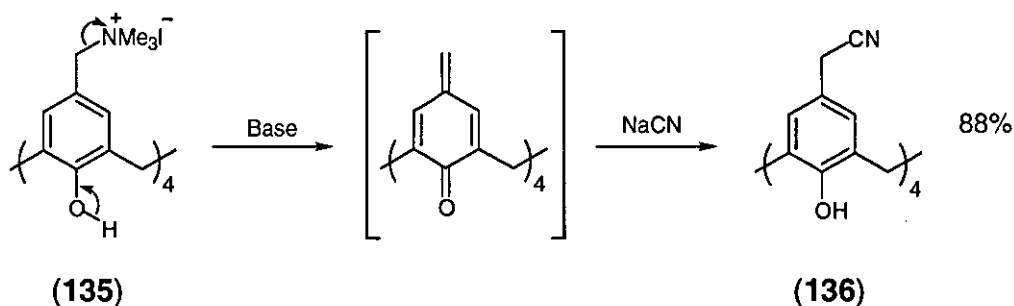
Saito and co-workers⁹² have shown that phenolic Mannich bases can undergo

fragmentation to form quinone methides under similar conditions. Photo-irradiation of a range of phenolic and naphtholic Mannich bases were carried out in acetonitrile using a high pressure mercury lamp through a pyrex filter. The quinone methides formed were trapped with a large excess of ethyl vinyl ether. Substitution of the dimethylamino group with hydroxyl or methoxy groups resulted in a dramatic loss of reactivity. This reaction is depicted in **Equation 78**.



Equation 78

o-Quinone methides have also been generated *via* chemical means. 2-Phenyl-4*H*-1,3,2-benzodioxaborin⁹³ and *o*-[1-(alkylthio)alkyl]phenols⁹⁴ have been shown to fragment to *o*-quinone methide intermediates in the presence of acids and Lewis acids respectively. In addition, disilylated *o*-hydroxy benzyl alcohols have been shown to fragment *via* treatment with caesium fluoride.⁹⁵ Base induced *p*-quinone methide formation has been exploited by Gutsche and co-workers⁹⁶ in the functionalisation of calixarenes. Treating the quaternary ammonium salt (135) with base in the presence of a suitable nucleophile furnished a range of derivatives, such as (136), in good to excellent yield, as shown in **Equation 79**.



Equation 79

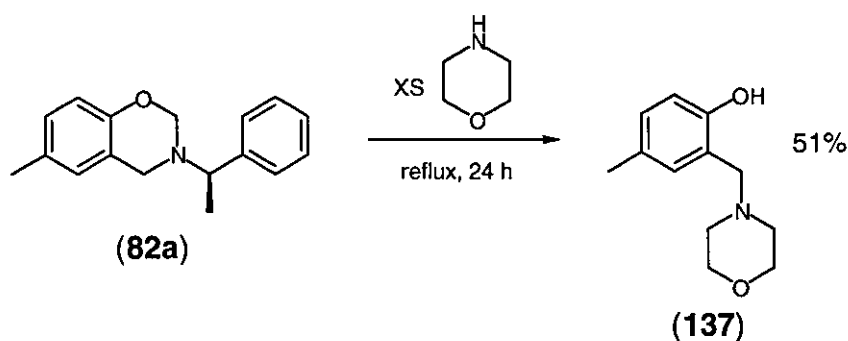
The fact that the reaction proceeds *via* a *para*-quinone methide was proven by the fact that when the phenol was protected as the *p*-bromobenzenesulfonate the corresponding quaternary ammonium salt did not react with sodium cyanide even after many hours.

6.5 Mechanistic Studies

With the mechanism of the reaction being by no means clear, an investigation into this interesting reaction was initiated, using a range of simple benzoxazines as model compounds.

6.5.1 Reactions using 6-Methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine and Derivatives

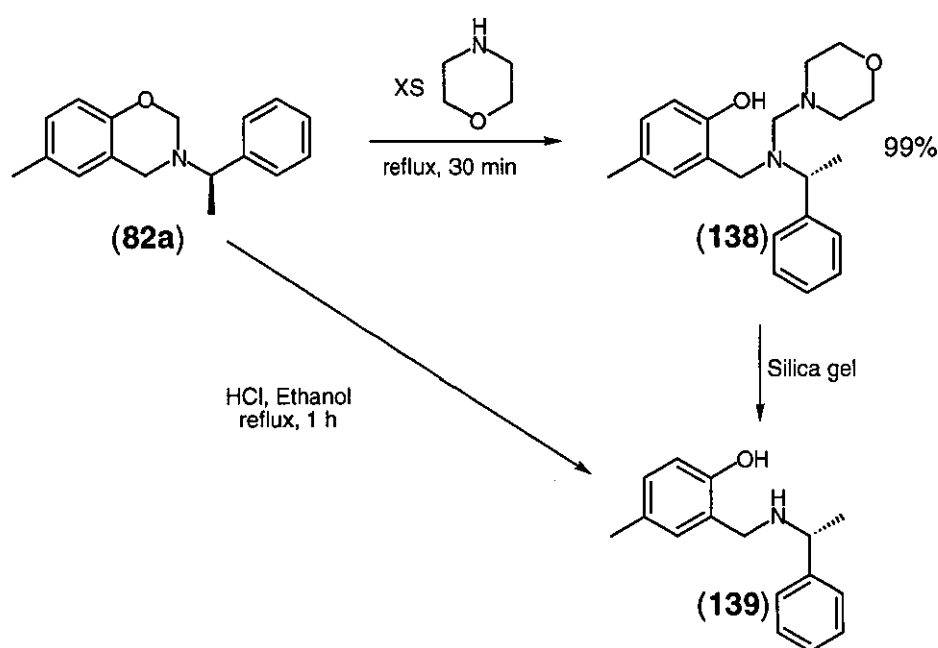
Initially, 6-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) was chosen as a model compound. Stirring a solution of (**82a**) in refluxing morpholine for twenty-four hours resulted in the isolation of 4-methyl-2-(morpholino)-benzen-1-ol (**137**) in average yield, after purification over silica gel, as shown in **Equation 80**.



Equation 80

It was decided to investigate whether it was possible to isolate any intermediates that may be forming during the course of the reaction. After stirring a refluxing solution of

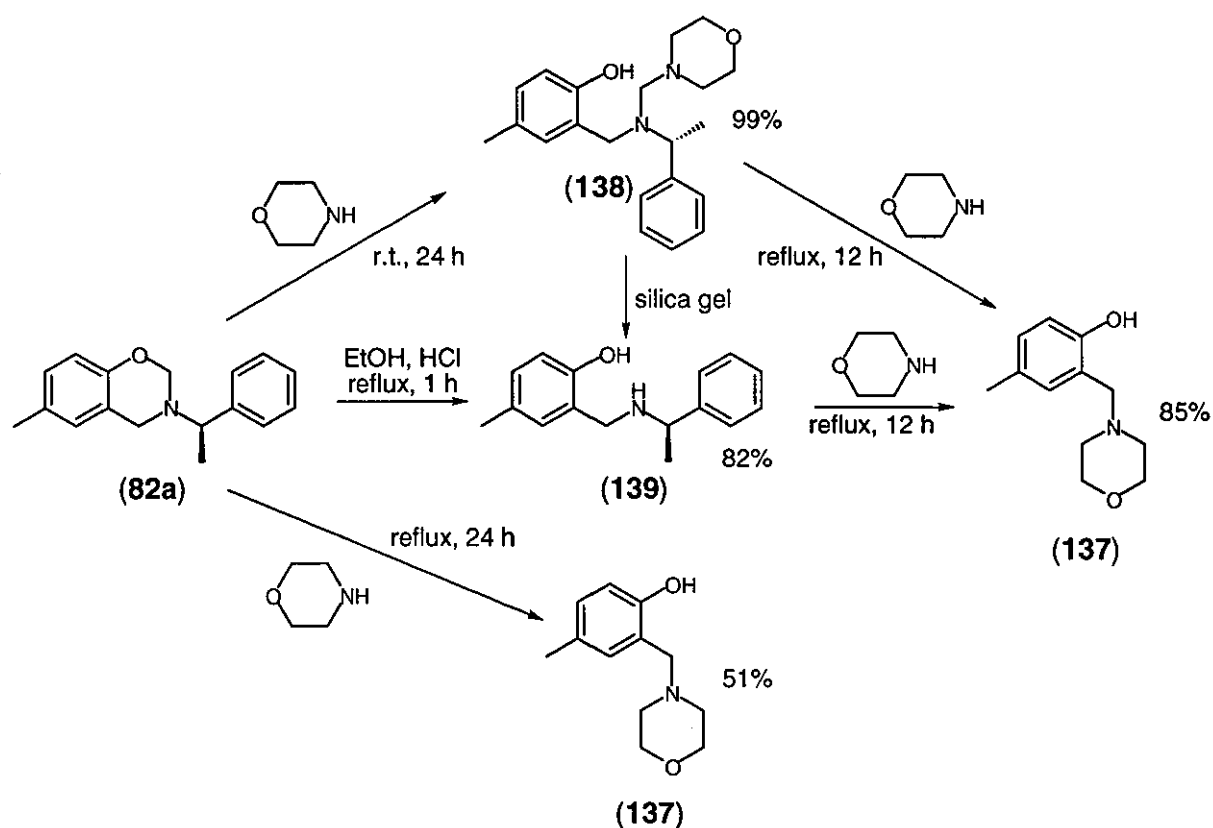
the 3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) in morpholine for thirty minutes, the unstable aminoral, 4-methyl-2-(((1,4-oxazinan-4-ylmethyl)((1*R*)-1-phenylethyl)amino)methyl)-benzen-1-ol (**138**), was isolated in almost quantitative yield. This material was isolated by careful removal of the excess morpholine under reduced pressure to furnish the aminoral as a colourless oil. It was shown to be unstable in the presence of silica gel, hydrolysing to the secondary amine very readily. This material was compared to an authentic sample of 4-methyl-2-(((1*R*)-1-phenylethyl)amino)methyl)benzen-1-ol (**139**), prepared by the hydrolysis of the 3,4-dihydro-2*H*-1,3-benzoxazine (**82a**). These reactions are shown in **Scheme 20**.



Scheme 20

The same aminoral was isolated in a similar manner after stirring a solution of 6-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) in morpholine for twenty four hours at room temperature. The aminoral was characterised by both ^1H and ^{13}C NMR spectroscopy along with infra-red spectroscopic analysis. The ^{13}C NMR spectrum showed four methylene groups to be present, which together with the other resonances confirmed the proposed structure.

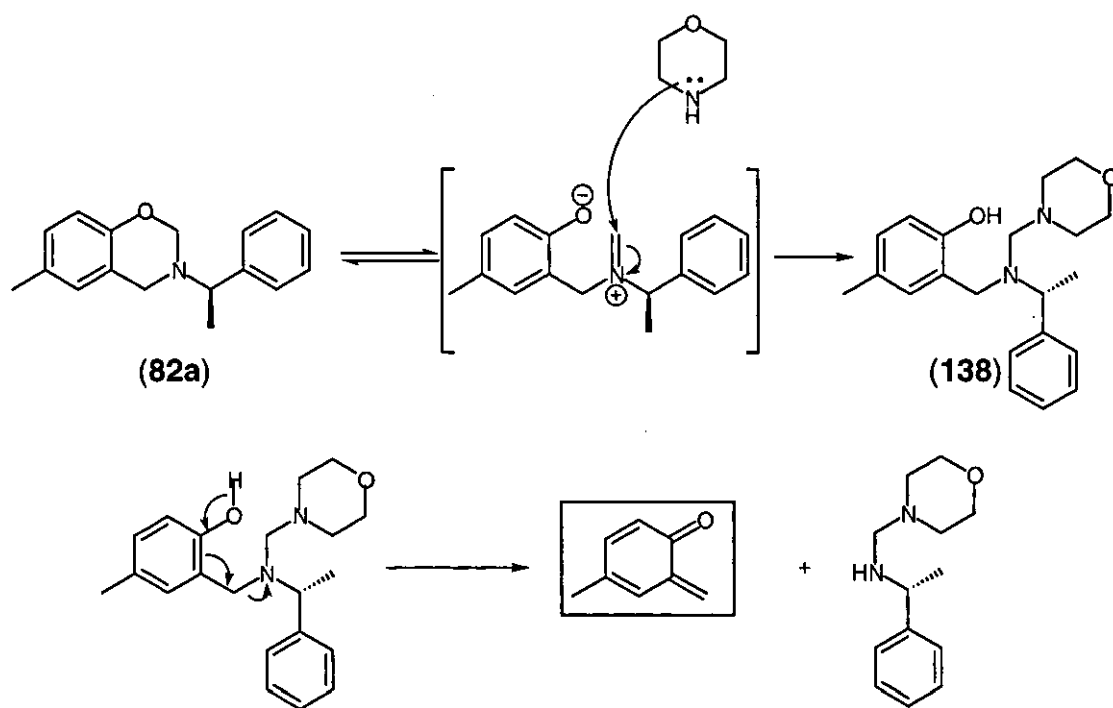
Taking the aminol (**138**) or the amino-alcohol (**139**) and stirring in morpholine under reflux for twelve hours again resulted in the retro-Mannich product (**137**) being isolated in good yield in both cases. These reactions are summarised in **Scheme 21**.



Scheme 21

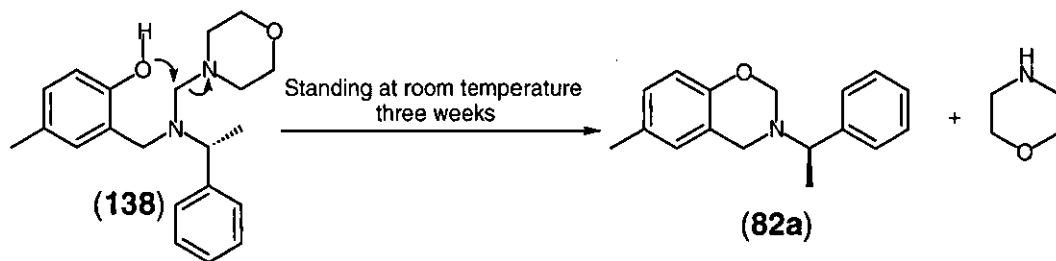
Scheme 22 shows a possible mechanism of formation of the observed aminorol (**138**). What is certain is that ring opening occurs to form an iminium ion that reacts with morpholine to furnish the aminorol. This ring opening may be mediated by trace amounts of protic acids in the morpholine. Indeed, Lambert and co-workers⁹⁷ have studied ring-chain tautomerism in 1,3-diaza and 1,3-oxaza heterocycles. Analysing a range of dioxolanes, oxazolidines and perhydrooxazines by ¹H NMR spectroscopy in neutral carbon tetrachloride showed just the ring form to be present. Running the ¹H NMR spectrum in trifluoroacetic acid meanwhile, showed between 10–20% of the ring

opened tautomer present. This percentage was shown to increase with temperature. Once the aminoral is formed, it may be favourable to undergo fragmentation to the quinone methide, or indeed, to hydrolyse to the secondary amino alcohol (**139**), which we have shown, also undergoes amine exchange to give the morpholino derivative.



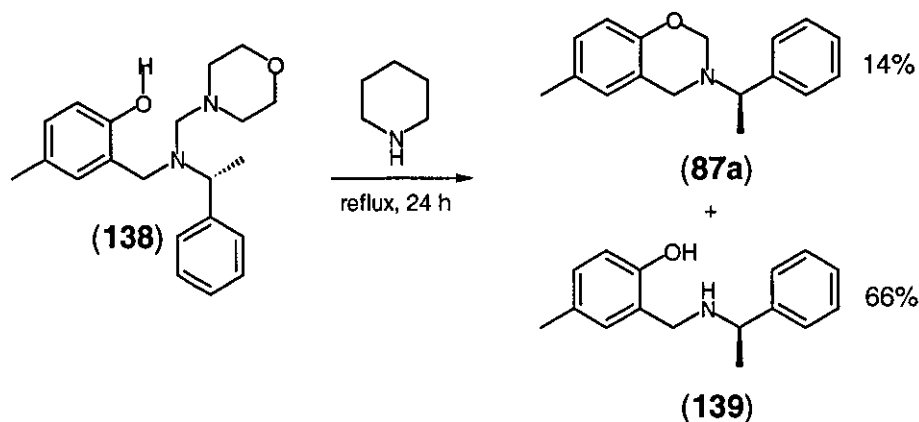
Scheme 22

Interestingly, upon leaving the aminoral (**138**) at room temperature for prolonged periods, the starting benzoxazine (**82a**) was reformed and morpholine evolved, as shown in **Equation 81**.



Equation 81

Repeating the reaction using the secondary amines piperidine and *t*-dibutylamine resulted in no reaction and the recovery of starting materials and indeed, refluxing the aminoral (**138**) in piperidine only resulted in reforming the starting benzoxazine (**87a**) and the hydrolysed secondary amino alcohol (**139**) as shown in **Equation 82**.

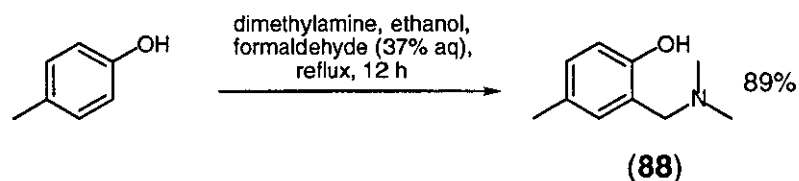


Equation 82

At this stage, it was decided to simplify matters by utilising a different precursor. As α -dimethylaminomethyl- β -naphthol had been shown by Brewster and co-workers⁸⁶ to undergo retro-Mannich exchange, it was decided to use an *N,N*-dimethylamino analogue of *para*-cresol namely 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol, (**88**).

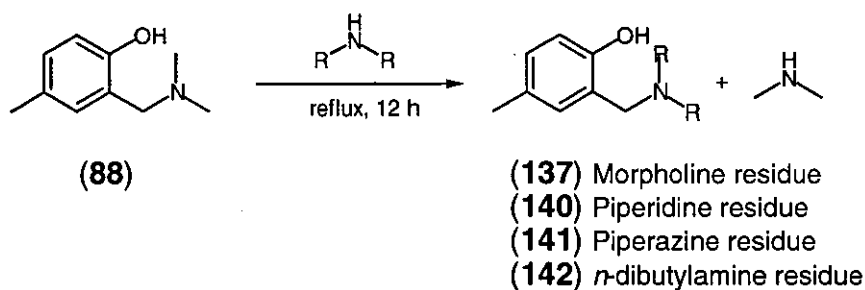
6.5.2 Reactions of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol and Derivatives

2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) was synthesised in excellent yield by the reaction of *para*-cresol with aqueous formaldehyde and dimethylamine in refluxing ethanol, as shown in **Equation 83**.



Equation 83

Compound **(88)** was heated under reflux in a variety of secondary amines for twelve hours as shown in **Equation 84**. The results of these reactions are compiled in **Table 28**.



Equation 84

Entry	Product	Amine	B.P.	Yield/%
a	(140)	Piperidine	106 °C	s.m.
b	(137)	Morpholine	129 °C	82
c	(141)	Piperazine	146 °C	58
d	(142)	<i>n</i> -dibutylamine	159 °C	78

Table 28

As can be seen from the above table, piperidine is unusual in that the all the other secondary amines undergo amine exchange to furnish the desired amino alcohols in reasonable to good yield. This may be explained if one examines the boiling points of

the secondary amines involved. Piperidine is the lowest boiling amine and consequently the reaction is run at 106 °C. This suggests that the reaction needs to be run at a temperature above 106 °C for the intermediate quinone methide to form.

It was thought that if the phenolic group was suitably functionalised, it would impede the generation of a quinone methide in the reaction. Indeed, work by Gutsche and co-workers⁹⁶ has shown that generation of a *para*-quinone methide was impeded when the phenol was protected as the *p*-bromobenzenesulfonate. Therefore it was envisaged that repeating the retro-Mannich reaction using a substrate with a suitably functionalised phenolic group should give evidence as to the mechanism of the reaction.

- (i) If only unreacted starting material was isolated then this suggests that the retro-Mannich reaction does proceed *via* a quinone methide and, as it cannot be formed in this case, the reaction does not proceed.
- (ii) If the retro-Mannich reaction is evident then this suggests the reaction is simply an S_N2 nucleophilic substitution.

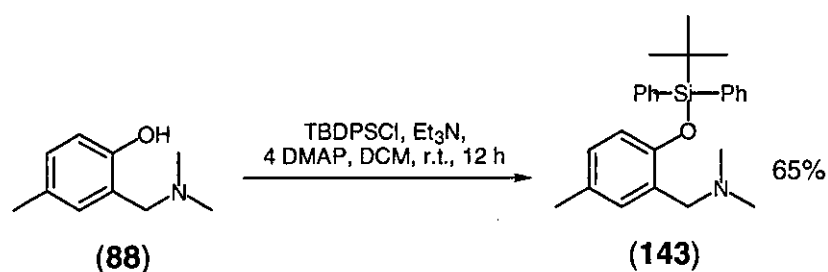
All initial attempts at derivatising the phenol group as a methyl ether failed. The results of these reactions are compiled in **Table 29**.

Entry	Reaction conditions	Yield/%
a	DMSO, KOH (1.5 eq), Dimethyl sulfate (1 eq), r.t., 2 h	Mixture
b	DMSO, KOH (1.5 eq), Dimethyl sulfate (1 eq), r.t., 2 h	Mixture
c	THF, n-BuLi (1.1 eq), Dimethyl sulfate (1 eq), -78 °C - r.t., 1 h	66% s.m. 34% quat
d	THF, n-BuLi (1.1 eq), MeOTf (1.1 eq), -78 °C - r.t., 1 h	Mixture
e	DMF, K ₂ CO ₃ (2.0 eq), MeI (1.0 eq), 100 °C, 3 h	Mixture
f	THF, TMSCH ₂ N ₂ (1.1 eq), MeOH, 0 °C - r.t., 4 h	Mixture
g	THF, TMSCH ₂ N ₂ (1.1 eq), MeOH, Hünigs base (1.1 eq), 0 °C - r.t., 4 h	Mixture
h	THF, NaH (1.1 eq), MOMCl (1.0 eq), 0 °C - r.t., 1 h	Mixture
i	DCM, DEAD (1.1 eq), PPh ₃ (1.1 eq), MeOH (1.1 eq), r.t., 12 h	s.m.

Table 29

The substrate was subjected to a wide variety of conditions and in all cases a complex mixture was isolated that defied characterisation. In the majority of cases, no starting material could be detected by TLC or NMR spectroscopy at the end of the reaction. In addition, ¹H NMR spectroscopy showed no characteristic methoxy resonance at three to four ppm in the crude reaction mixtures.

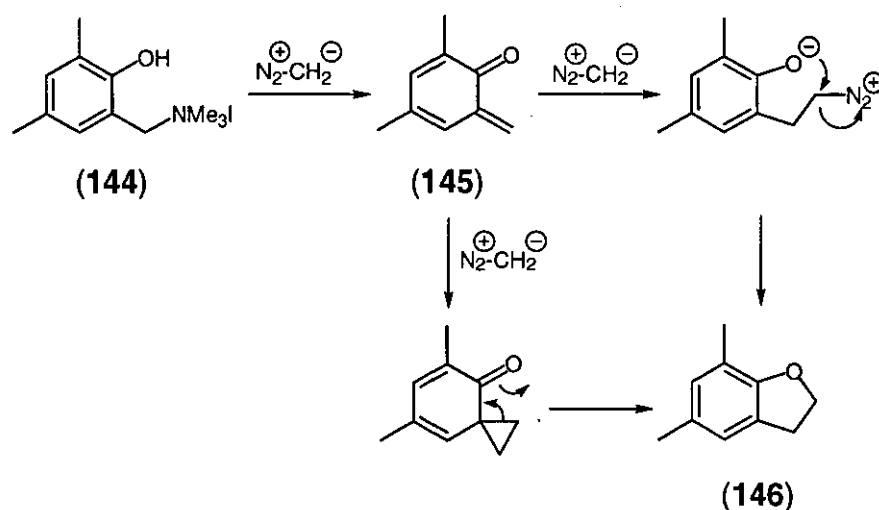
With these failures in mind, it was decided to attempt to derivatise the phenolic group with another protecting group. *tert*-Butyldiphenylsilyl group is a well known protecting group for a wide range of hydroxyl groups and is known to be base stable and moreover moderately acid stable also. Therefore, subjecting compound (**88**) to standard conditions furnished the corresponding TBDPS ether (**143**) in reasonable yield, as shown in **Equation 85**.



Equation 85

With the success of the TBDPS protection and the spectacular failure of the methylations, possible reasons as to why the alkylation of the phenolic group was so problematic were examined. Upon comparing the two reactions, the only major difference was the protecting group. The difference in the outcome of the reaction seemed to come down to the oxo and aza-philicity of the two electrophilic reagents. The silicon is very oxophilic and therefore very readily reacts with the phenolate anion. The reactivity of the methylating agents on the other hand is more ambiguous. They have a choice as to whether react with the phenolate anion or to react with the tertiary amine forming a quaternary ammonium salt. Evidence gained from our methylation experiments seems to suggest the latter to be occurring. Indeed, when using *n*-BuLi and dimethyl sulfate, only starting material and quaternary ammonium salt was isolated. It may be that the phenolate anion is too sterically hindered to be alkylated and the formation of the quaternary ammonium salt is the preferred reaction pathway.

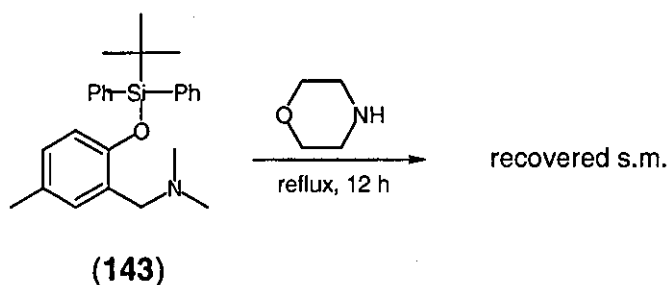
Bladé-Font and co-workers⁹⁸ have shown that quaternary ammonium salts like that which we have described above may form quinone methides very readily. Indeed, they have been shown to react with diazomethane to form dihydrobenzofurans (**146**) in reasonable yields under mild conditions, as shown in **Scheme 23**, where a quinone methide is postulated to be an intermediate.



Scheme 23

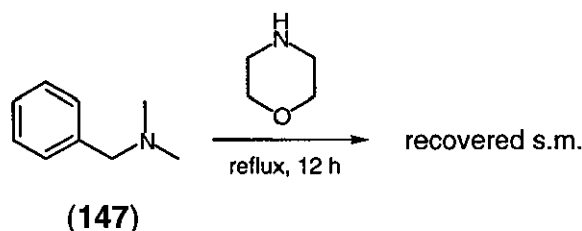
It seems reasonable to assume that the methylating agent in the reactions preferentially reacts with the tertiary amine forming a quaternary ammonium salt which, in the presence of the base, decomposes under the reaction conditions to form a quinone methide which then reacts on to form complicated mixtures. The possibilities of this reaction pathway will be discussed in due course.

Taking the TBDPS protected substrate **(143)** and heating under reflux in morpholine for twelve hours merely resulted in the re-isolation of starting material in 82% yield. No evidence of retro-Mannich amine exchange product was detected, as shown in **Equation 86**.



Equation 86

This strongly suggests the reaction proceeds *via* a quinone methide, unless the bulky TBDPS group is hindering an S_N2 reaction. This seems unlikely. Further evidence was provided by the fact that refluxing *N,N*-dimethylbenzylamine (**147**) in morpholine for twelve hours merely resulted in the re-isolation of starting materials, as shown in **Equation 87**.

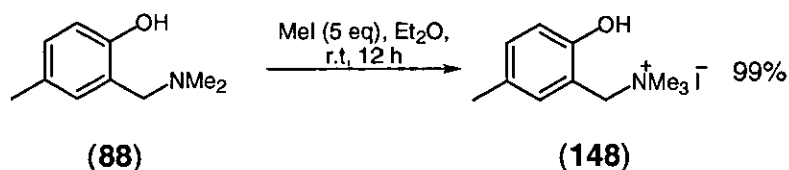


Equation 87

6.5.3 Investigations into Chemically Generated *o*-Quinone Methides

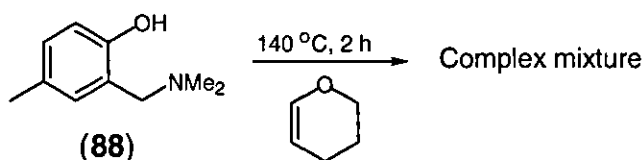
As described above, quinone methides have been generated by the action of base on quaternary ammonium salts of phenolic Mannich bases.⁹⁶ In addition, *o*-quinone methides have been trapped with a range of electron rich dieneophiles to furnish oxygenated heterocycles in excellent yield.^{91,92} These findings prompted an investigation into these possibilities, in particular, the possible chemical generation of *o*-quinone methides from phenolic Mannich bases⁹³⁻⁹⁵ and their derivatives, and also, the possibility of trapping *o*-quinone methide intermediates from the 'retro-Mannich' reaction *via* a [4+2] cycloaddition with a suitable dieneophile.

Treating 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) with methyl iodide in dry ether furnished the desired quaternary ammonium salt (**148**) in quantitative yield as a stable white solid, as shown in **Equation 88**.



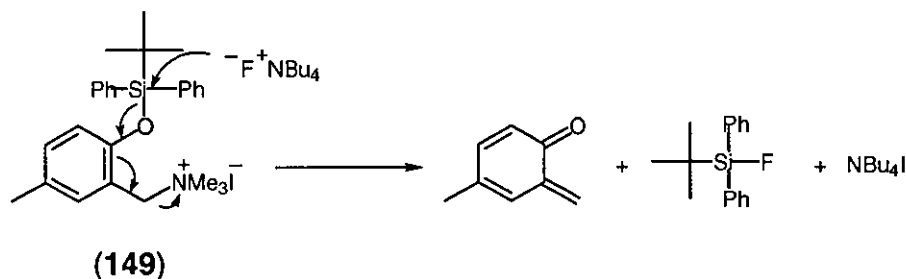
Equation 88

In the retro-Mannich reaction, it has been speculated that a temperature greater than 106 °C is needed to fragment 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol to the intermediate quinone methide before attack by the nucleophilic amine. To test this hypothesis 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) in 3,4-dihydropyran was heated at 140 °C, as shown in **Equation 89**. As the boiling point of 3,4-dihydropyran is only 86 °C, it necessitated the use of a sealed stainless steel bomb. The reaction was run twice, in the second case with an equivalent of Hünigs base present. After two hours at elevated temperature, only a complex mixture of products was observed in both cases. The mixtures defied characterisation with only seemingly polymeric products present.



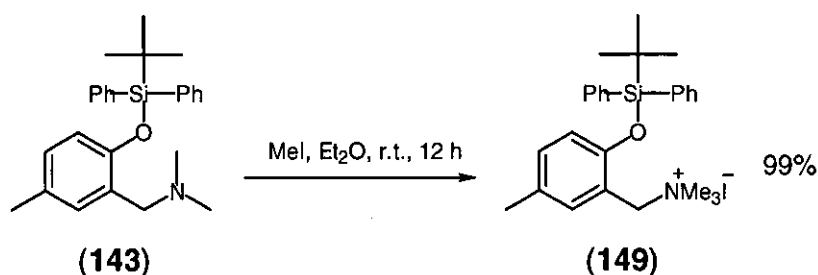
Equation 89

It was anticipated that treating the TBDPS ether protected quaternary ammonium salt of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**149**) with TBAF may induce fragmentation of the molecule and subsequently form a quinone methide *via* the mechanism shown in **Equation 90**.



Equation 90

The methiodide (149) was formed in near quantitative yield by treatment of the tertiary amine (143) with methyl iodide in diethyl ether at room temperature, as shown in Equation 91.



Equation 91

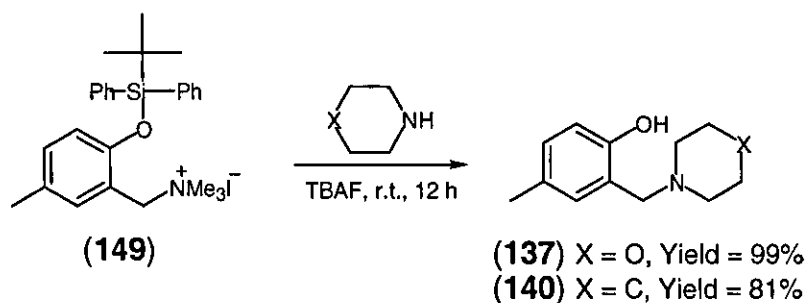
The TBDPS protected quaternary ammonium salt (149) was treated with TBAF under a range of conditions. The reactions were carried out in excess 3,4-dihydropyran as the trapping dienophile. These results are compiled in Table 30.

Entry	Conditions	Yield/%
a	3,4-dihydropyran, TBAF (1.1 eq), r.t., 12 h	Mixture
b	3,4-dihydropyran, TBAF (1.1 eq), r.t., 48 h	Mixture
c	3,4-dihydropyran, TBAF (1.1 eq), $-78\text{ }^{\circ}\text{C}$, 48 h	Mixture

Table 30

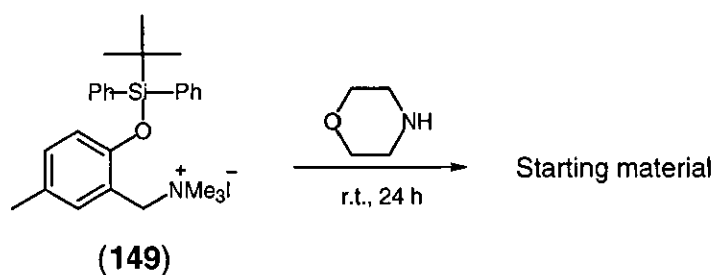
As can be seen from the above table, only a complex mixture was isolated in each case, although no starting material was detected.

Treatment of the TBDPS ether protected quaternary ammonium salt of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**149**) with TBAF in the presence of a suitable secondary amine gave the desired retro-Mannich product. However, it is ambiguous as to whether the reaction was proceeding *via* a quinone methide or just *via* an S_N2 substitution reaction, as shown in **Equation 92**.



Equation 92

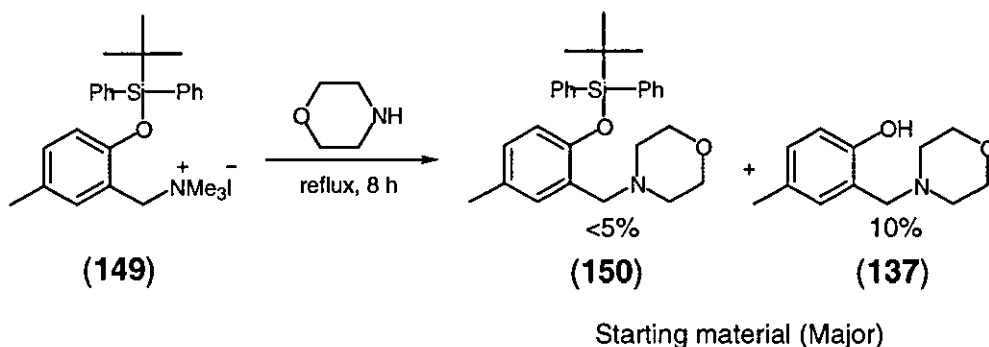
The reaction with morpholine was run once more but this time with the absence of TBAF. Stirring the mixture at room temperature for twenty-four hours only resulted in the re-isolation of starting materials, as shown in **Equation 93**.



Equation 93

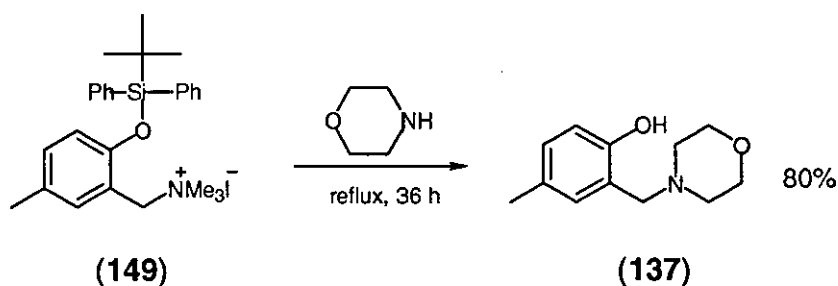
Upon refluxing the reaction mixture for eight hours, starting material (**149**) was again the major product isolated with small amounts of both the TBDPS protected retro-

Mannich product (**150**) and the unprotected derivative (**137**), as shown in **Equation 94**



Equation 94

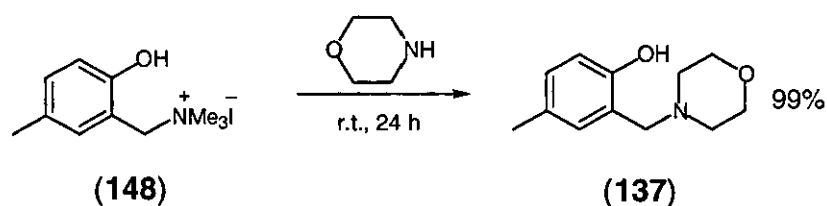
Repeating the reaction but refluxing for thirty-six hours resulted in the isolation of almost exclusively the deprotected retro-Mannich product (**137**), as shown in **Equation 95**.



Equation 95

It was deduced that the compound (**149**) did not undergo substitution, possibly due to similar reason to that provided by Gutsche.⁹⁶ It was thought that over time, the molecule underwent an internal deprotection mediated by the iodide anion of the quaternary ammonium salt (either inter or intramolecularly), thus giving the phenolate anion that can undergo the retro-Mannich reaction, presumably *via* a quinone methide. This was reinforced by the finding that stirring the quaternary ammonium salt of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**148**) in morpholine resulted in

the retro-Mannich product being formed in excellent yield, as shown in **Equation 96**.



Equation 96

6.6 Conclusion and Further Work

The retro-Mannich reaction has been studied in some depth and strong evidence has been found that the reaction proceeds by way of an *o*-quinone methide intermediate. Attempts to trap the *o*-quinone methide *via* [4+2] cycloadditions at elevated temperature failed.

An intermediate aminol (**138**) has been isolated which is believed to be a precursor to either the *o*-quinone methide or to the hydrolysed secondary amino-alcohol derivative (**139**), which has also been shown undergoes the retro-Mannich reaction.

Strong evidence has been presented that the thermal generation of *o*-quinone methide intermediates from phenolic Mannich bases requires high temperatures for the reaction to proceed. Further evidence was provided by the fact that repeating the reaction with *N,N*-dimethylbenzylamine in place of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) resulted in no reaction occurring.

Other groups have shown that quinone methides can be formed from quaternary ammonium salts of phenolic Mannich bases by treatment with base. It has been shown to be also true with our substrates, with the amine exchange reaction proceeding at room temperature simply by stirring the quaternary ammonium salt of

our phenolic Mannich base substrate (**148**) in morpholine. The blocking of the o-quinone methide formation in these examples was shown by the derivatisation of the phenolic group as the *tert*-butyldiphenylsilyl ether, with amine exchange not occurring even after heating for prolonged periods under reflux. Indeed an internal deprotection of the *tert*-butyldiphenylsilyl ether mediated by the iodine counter-ion of the quaternary ammonium salt was shown to have to occurred before exchange could take place.

Chapter 7

7.0 The Reductive Cleavage of Cyclic Aminol Ethers to Furnish *N,N*-Dialkylamino derivatives: Modifications to the Eschweiler-Clarke Procedures

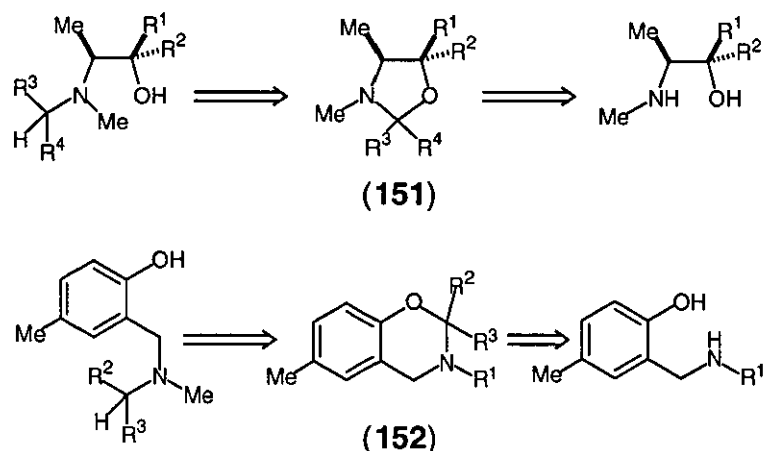
7.1 Introduction

This chapter contains results and discussions concerning work on the reductive cleavage of cyclic aminol ethers. It was found that a number of reducing agents could be used for the reductive cleavage of cyclic aminol ethers, to furnish *N*-methylated amino derivatives. These included lithium aluminium hydride and di-isobutylaluminium hydride, but the most interesting discovery was that it was possible to use a refluxing solution of aqueous formic acid to effect the transformation. These reactions are described in Chapter 3.

Aqueous formic acid was shown to reductively ring open both a series of model benzoxazine compounds as well as a range of axially chiral calix[4]resorcinarene derivatives. Bearing in mind the ease of handling and low cost factors involved with this novel reaction protocol, it was intriguing to ascertain whether this was indeed a general procedure. Other workers in the group needed to develop a method to synthesise a range of *N*- β -hydroxyethyl-, *N*- γ -hydroxypropyl-, and *o*-hydroxybenzyl-*N,N*-dialkylamines. The range of compounds required could in theory be produced from the reductive cleavage of 2,3-di-substituted-1,3-oxazolidines (**151**) and 2,3-disubstituted-3,4-dihydro-2H-1,3-benzoxazines (**152**), as shown in **Scheme 24**.

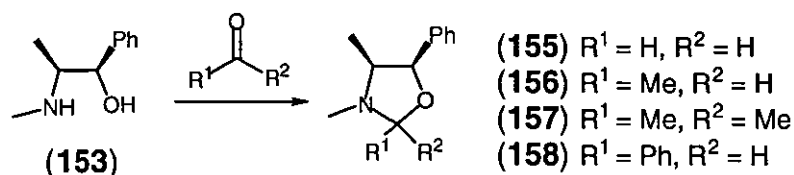
The chirality in the oxazolidines and oxazinanes could be provided, for example, by using commercially available starting materials. The use of pseudoephedrine as a chiral auxiliary has been reported in a number of recent publications⁹⁹ and the use of ephedrine continues to be reported.¹⁰⁰ In some cases, the conversion of those

compounds into their *N,N*-di-alkyl-analogues has been required in connection with the synthesis of compounds with potential pharmacological activity.



Scheme 24

7.2 Synthesis of 2,3-Di-substituted-1,3-Oxazolidines from Ephedrine and Pseudoephedrine

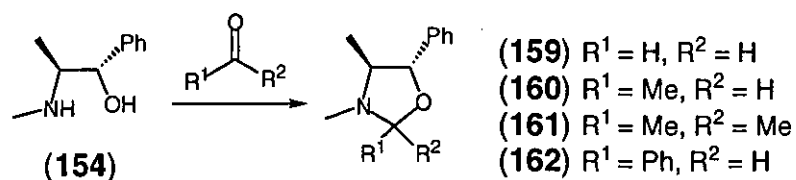


Equation 97

A range of oxazolidines was synthesised by condensations of ephedrine (153) and pseudoephedrine (154) with formaldehyde, acetaldehyde, acetone and benzaldehyde. The results are compiled in **Tables 31** and **32**.¹⁰¹

Entry	Product	R ¹	R ²	Conditions	Yield/%
a	(155)	H	H	(CH ₂ O) _n (1.1 eq), K ₂ CO ₃ (1.1 eq), benzene, reflux, 6 h	98
b	(156)	Me	H	CH ₃ CHO (1.1 eq), DCM, 4Å m.s., r.t., 12 h	92
c	(157)	Me	Me	Acetone (excess), CSA (cat), 4Å m.s., reflux, 3 days	64
d	(158)	Ph	H	PhCHO (1.1 eq), DCM, 4Å m.s., r.t., 3 days	98

Table 31



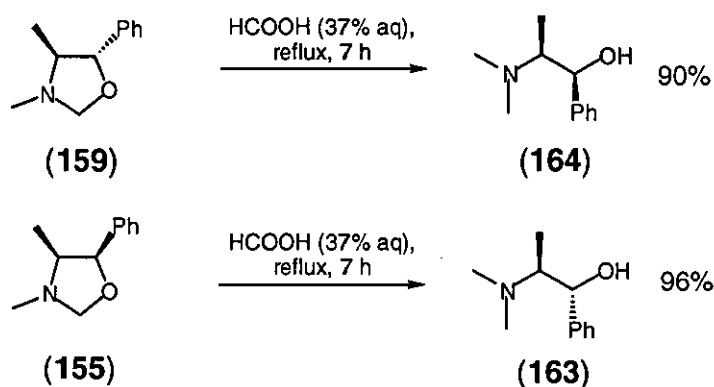
Equation 98

Entry	Product	R ¹	R ²	Conditions	Yield/%
a	(159)	H	H	(CH ₂ O) _n (1.1 eq), K ₂ CO ₃ (1.1 eq), benzene, reflux, 6 h	98
b	(160)	Me	H	CH ₃ CHO (excess), 4Å m.s., r.t., 12 h	83
c	(161)	Me	Me	Acetone (excess), CSA (cat), 4Å m.s., reflux, 4 days	99
d	(162)	Ph	H	PhCHO (1.1 eq), DCM, CSA (cat), 4Å m.s., r.t., 3 days	99

Table 32

7.2.1 Reductive Cleavage of 1,3-Oxazolidines

Heating a solution of (4*S*, 5*S*)-3,4-dimethyl-5-phenyloxazolidine (**159**) under reflux in 37% aqueous formic acid for seven hours gave *N*-methylpseudoephedrine (**164**) in excellent yield. A similar result was observed when using (4*S*, 5*R*)-3,4-dimethyl-5-phenyloxazolidine (**155**) to furnish *N*-methylephedrine (**163**), again in excellent yield, as shown in **Scheme 25**.¹⁰²



Scheme 25

Unfortunately, repeating the reaction with any of the substrates with substitution at the two position only resulted in complex mixtures being isolated with only very minor amounts of the desired *N*-alkylated material being isolated. ¹H NMR spectra of the crude reaction mixtures appeared to show alkene protons present, presumably formed *via* acid catalysed dehydration. This may be due to the more substituted transient iminium ion being less reactive. In other cases, only starting materials and ephedrine or pseudoephedrine was isolated indicating hydrolysis had occurred preferentially over reduction.

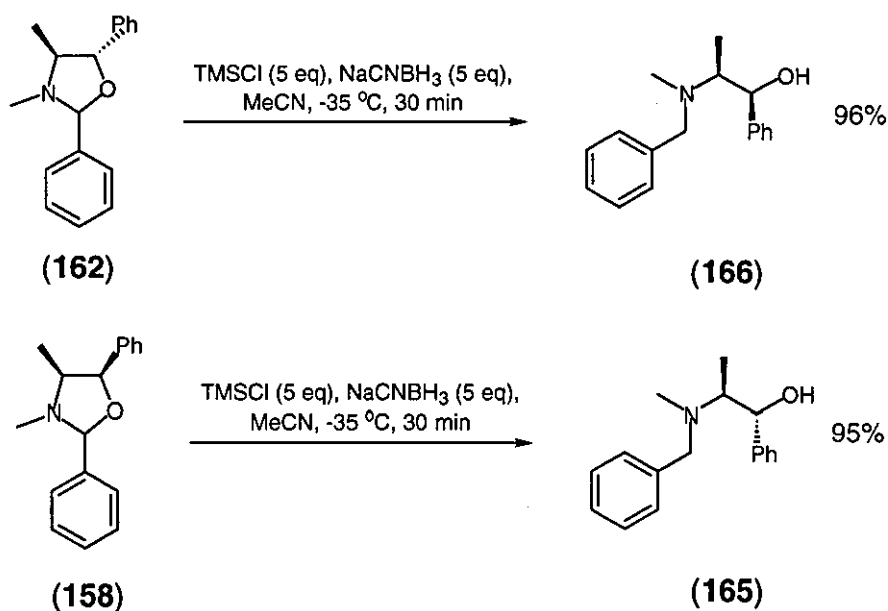
Due to the failure of the use of formic acid to effect reductive ring opening of substituted cyclic aminol-ethers, other reaction conditions were investigated

After studying a range of Lewis acid/reducing agent combinations, two reagent systems were developed that gave excellent results. It was found that treating the desired cyclic aminol ether with titanium tetraisopropoxide and sodium borohydride in DME at low temperature, gave the reductively ring opened *N*-alkylated product in almost quantitative yield. The second reaction protocol involved treating the cyclic aminol ether with chlorotrimethylsilane/sodium cyanoborohydride. Chlorotrimethylsilane, acting as an oxophilic Lewis acid ring opened the cyclic aminol ether, forming a trimethylsilyl ether and the desired iminium ion. Carrying out the reaction in acetonitrile stabilised the iminium ion, which was reduced in-situ with sodium cyanoborohydride. The reactions were typically run using an excess of trimethylsilylchloride and sodium cyanoborohydride and carrying out the reaction at low temperature helped to moderate the sometimes strongly exothermic reaction.

It was found that the reaction did not proceed in the absence of chlorotrimethylsilane and in addition, that trimethylsilane does not function both as a Lewis acid and a source of hydride ion, suggesting that the reactions are not initiated by the reduction of chlorotrimethylsilane by sodium cyanoborohydride.

Both methods gave excellent yields of the desired reductively ring opened product, although the chlorotrimethylsilane/sodium cyanoborohydride/acetonitrile reaction protocol was decided to be investigated further due to its ease of work up and economy of reagents.

Applying these conditions to (4*S*, 5*S*)-3,4-dimethyl-2,5-diphenyl-1,3-oxazolane (**162**) and (4*S*, 5*R*)-3,4-dimethyl-2,5-diphenyl-1,3-oxazolane (**158**) gave *N*-benzylpseudoephedrine (**166**) and *N*-benzylephedrine (**165**), both in excellent yield, as shown in **Scheme 26**.



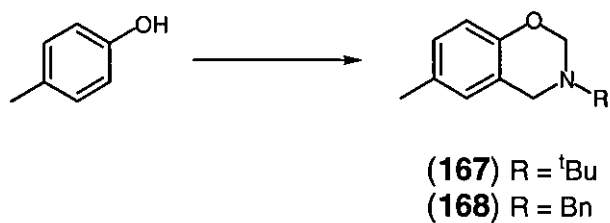
Scheme 26

7.3 Synthesis of other Cyclic Aminol Ethers

With the methodology in place for the efficient and mild reductive ring opening of substituted cyclic aminol ethers, a range of different substrates was synthesised for testing.

7.3.1 Synthesis of 3,4-Dihydro-2*H*-1,3-Benzoxazines and Derivatives

A number of simple 3,4-dihydro-2*H*-1,3-benzoxazines were synthesised from para-cresol, benzylamine and *t*-butylamine,⁶³ as shown in Table 33.

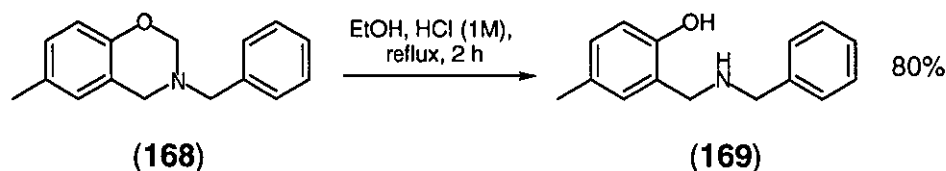


Equation 99

Entry	R ¹	Product	Conditions	Yield/%
a	Bu ^t	(167)	<i>tert</i> -Butylamine (1 eq), paraformaldehyde (2 eq), 1,4-dioxane, reflux, 3 h	65
b	Bn	(168)	Benzylamine (1 eq), CH ₂ O (37% aq, 2 eq), 1,4- dioxane, 0 °C - reflux, 3 h	62

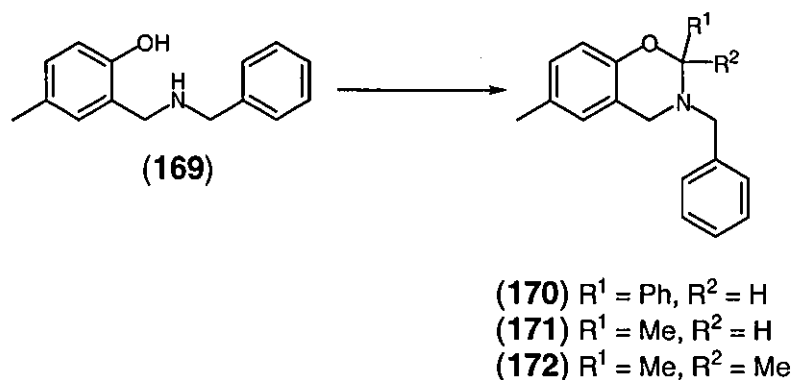
Table 33

Hydrolysis of 6-methyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (168) with ethanolic hydrochloric acid gave 4-methyl-2-[[[(phenylmethyl)amino]methyl]benzen-1-ol (169) in good yield, as shown in **Equation 100**.¹⁰³



Equation 100

Condensation of 4-methyl-2-[[[(phenylmethyl)amino]methyl]benzen-1-ol (169) with a variety of carbonyl compounds gave a range of 2-substituted 3,4-dihydro-2*H*-1,3-benzoxazines, the results of which are compiled in **Table 34**



Equation 101

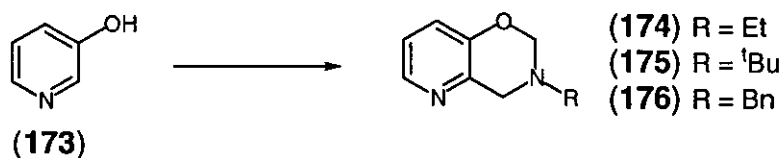
Entry	product	R ¹	R ²	Conditions	Yield/%
a	(170)	Ph	H	DCM, PhCHO (5 eq), CSA (cat), reflux, 12 h	74
b	(171)	Me	H	DCM, CH ₃ CHO (20 eq), 4 Å m.s., stand r.t., 12 h	95
c	(172)	Me	Me	Acetone, CSA (cat), 4 Å m.s., reflux, 12 h	73

Table 34

Condensation of 4-methyl-2[[(phenylmethyl)amino]methyl]benzen-1-ol (**169**) with acetone, benzaldehyde and acetaldehyde all proceeded smoothly, although in some cases a catalytic amount of (1*R*)-(-)-10-camphorsulfonic acid was needed.

7.3.2 Synthesis of Dihydro-1,3-oxazinoquinolines and Dihydro-1,3-pyridobenzoxazines

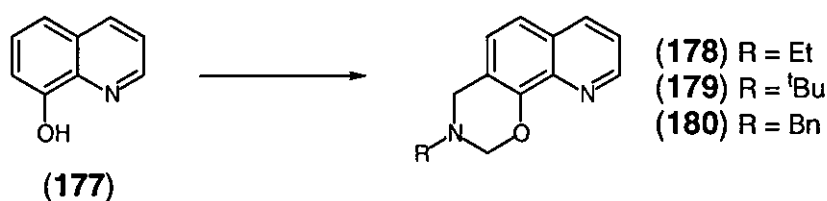
Pyridoxazines and pyrido[e]benzoxazines are structurally related compounds and are valuable precursors for the preparation of 2-dialkylaminomethyl-3-hydroxypyridines and 7-dialkylaminomethyl-8-hydroxyquinolines with two different alkyl groups. We noted that Mannich bases derived from 3-hydroxypyridine¹⁰⁴ and 8-hydroxyquinoline¹⁰⁵ have been prepared using secondary amines for potential use as pharmacologically active compounds. In addition, dihydro-1,3-oxazinoquinolines and dihydro-1,3-pyridobenzoxazines have been evaluated as potential antimalarial agents.¹⁰⁶ A range of pyridoxazines and pyrido[e]benzoxazines was synthesised from 3-hydroxypyridine and 8-hydroxyquinoline, using both literature procedures and slightly modifying our conventional methods. The results are compiled in **Tables 35 and 36**.



Equation 102

Entry	Product	R	Conditions	Yield/%
a	(174)	Et	Ethylamine (70% aq, 4 eq), CH ₂ O (37% aq, 12 eq), 1,4-dioxane, 90 °C, 12 h	15
b	(175)	^t Bu	<i>tert</i> -Butylamine (2 eq), CH ₂ O (37% aq, 6 eq), 1,4-dioxane, 90 °C, 12 h	81
c	(176)	Bn	Benzylamine (1 eq), (CH ₂ O) _n (2 eq), 1,4-dioxane, reflux, 3 h	76

Table 35



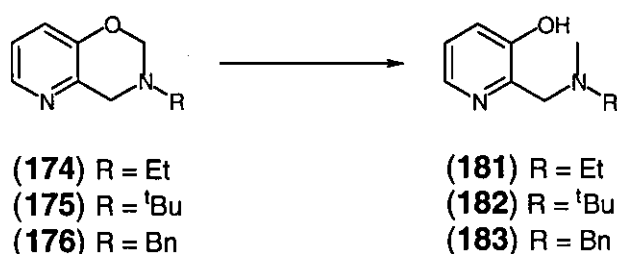
Equation 103

Entry	Product	R	Conditions	Yield/%
a	(178)	Et	Ethylamine (70% aq, 1.1 eq), (CH ₂ O) _n (2 eq), ethanol/benzene, reflux, 12 h	44
b	(179)	^t Bu	<i>tert</i> -Butylamine (1 eq), (CH ₂ O) _n (2 eq), 1,4-dioxane, reflux, 3 h	78
c	(180)	Bn	Benzylamine (1 eq), (CH ₂ O) _n (2 eq), ethanol/benzene, reflux, 12 h	19

Table 36

7.4 Reductive Cleavage of 3,4-Dihydro-2-H-1,3benzoxazines, 2,3-Disubstituted-3,4-dihydro-2-H-1,3-benzoxazines, Dihydro-1,3-pyridobenzoxazines and Dihydro-1,3-oxazinoquinolines

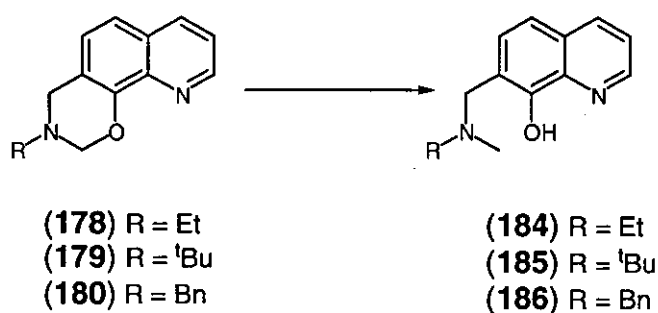
The range of prepared heterocycles was subjected to both the newly developed chlorotrimethylsilane/sodium cyanoborohydride methodology and the formic acid reaction protocol. The results are compiled in **Tables 37, 38 and 39**.



Equation 104

Entry	s.m.	Product	R	Conditions	% Yield
a	(175)	(182)	^t Bu	MeCN, TMSCl (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	90
b	(174)	(181)	Et	MeCN, TMSCl (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	88
c	(176)	(183)	Bn	MeCN, TMSCl (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	79
d	(175)	–	^t Bu	HCOOH (37% aq), reflux, 3 h	0
e	(174)	(181)	Et	HCOOH (37% aq), reflux, 3 h	40
f	(176)	(183)	Bn	HCOOH (37% aq), reflux, 3 h	74

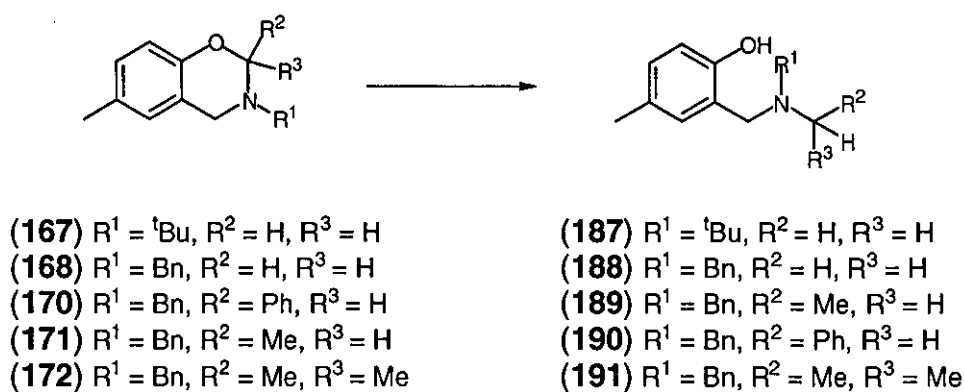
Table 37



Equation 105

Entry	s.m.	Product	R ¹	Conditions	Yield/%
a	(179)	(185)	^t Bu	MeCN, TMSCl (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	95
b	(178)	(184)	Et	MeCN, TMSCl (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	98
c	(180)	(186)	Bn	MeCN, TMSCl (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	95
d	(179)	–	^t Bu	HCOOH (37% aq), reflux, 3 h	0
e	(178)	(184)	Et	HCOOH (37% aq), reflux, 3 h	49
f	(180)	(186)	Bn	HCOOH (37% aq), reflux, 3 h	54

Table 38



Equation 106

Entry	s.m.	product	Conditions	Yield/%
a	(167)	(187)	MeCN, TMSCI (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	95
b	(168)	(188)	MeCN, TMSCI (2 eq), NaCNBH ₃ (2 eq), -35 °C – r.t., 15 min	96
c	(167)	(187)	HCOOH (37% aq), reflux, 3 h	0
d	(168)	(188)	HCOOH (37% aq), reflux, 3 h	78
e	(171)	(189)	MeCN, TMSCI (5 eq), NaCNBH ₃ (5 eq), -35 °C – r.t., 15 min	63
f	(170)	(190)	MeCN, TMSCI (5 eq), NaCNBH ₃ (5 eq), -35 °C – r.t., 15 min	99
g	(172)	(190)	MeCN, TMSCI (5 eq), NaCNBH ₃ (5 eq), -35 °C – r.t., 15 min	92

Table 39

As can be seen from **Tables 37, 38 and 39**, all substrates were reductively ring opened successfully using the chlorotrimethylsilane/sodiumcyanoborohydride reaction protocol, in the vast majority of cases giving the desired products in excellent yield. It should be noted that low temperatures were required to moderate the strongly exothermic reaction, particularly in the case of the dihydro-1,3-pyridobenzoxazine series of compounds, to avoid decomposition of the substrate.

The cyclic aminol ethers with no substitution at the two position were all heated under reflux in 37% aqueous formic acid and were generally found to give average to good yield of the desired products. In some cases, there was a tendency for the aminol ether to suffer hydrolysis although this was minimised by adding the substrate to a boiling solution of formic acid. *N-tert*-Butyl derivatives were exceptional in that they were not efficiently reduced and suffered extensive hydrolysis.

7.5 Conclusion

It has been shown that the modified Eschweiler-Clarke procedure for the reductive ring opening of cyclic aminol ethers is a general procedure and works well for substrates without substitution at the two position. The desired *N*-alkylated derivatives were isolated in good yields, except in the cases of the *N*-*tert*-butyl derivatives where hydrolysis of the aminol was the dominant reaction pathway.

An alternative reaction protocol involving the use of sodium cyanoborohydride and chlorotrimethylsilane has also been developed. This methodology has been shown to work well with a wide range of cyclic aminol ethers including those with substitution at the two position.¹⁰⁷ Soon after, Reddy and co-workers independently developed the same reaction methodology and employed it on similar substrates.¹⁰⁸

Chapter 8

8.0 GENERAL EXPERIMENTAL PROCEDURES

8.1 Purification of Reagents, Compounds and Solvents

Commercially available reagents were used as supplied, without further purification, unless otherwise stated. Air and moisture sensitive compounds were stored in a dessicator over self-indicating silica pellets, under an atmosphere of nitrogen.

Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh) and hand bellows to apply pressure to the column. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF₂₅₄. Plates were visualised under UV light (at 254 nm), staining with potassium permanganate solution followed by heating or by exposure to an ethanolic solution of phosphomolybdic acid, (acidified with concentrated sulfuric acid, followed by charring where appropriate).

Light petroleum refers to the fraction of petroleum ether which boils between 40 °C and 60 °C and was distilled from anhydrous CaCl₂ before use. Ethyl acetate and dichloromethane were distilled from anhydrous CaCl₂ and phosphorous pentoxide, respectively. Tetrahydrofuran was distilled from the sodium/benzophenone ketyl radical or lithium aluminium hydride before use. Methanol and ethanol were distilled from the corresponding magnesium alkoxide prior to use. Triethylamine and diisopropylethylamine were stored over potassium hydroxide pellets.

8.1.1 Preparation of Glassware

Highly air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 150 °C. These were allowed to cool in a desiccator

over self-indicating silica pellets, under a nitrogen atmosphere. All organometallic and air sensitive reactions were carried out under slight static positive pressure of nitrogen, and reagents and solvents were introduced using syringe or cannula techniques, through a septum cap.

8.1.2 Elemental Analyses and Melting Points

Microanalyses were performed on a Perkin Elmer Elemental Analyser 2400 CHN, and melting points were measured on a Electrothermal-IA 9100 apparatus and were uncorrected.

8.1.3 Infrared and Mass spectra (IR, MS)

Fourier transformed infrared absorption spectra were recorded on a Perkin Elmer Paragon 2001 instrument in the range $600\text{--}4000\text{ cm}^{-1}$. Solid samples were run as nujol mulls on sodium chloride discs or as thin films of their solution usually in dichloromethane. Liquid samples were run neat on sodium chloride discs.

High and low-resolution mass spectra were recorded on a Kratos MS80 or Jeol (JMX)SX102 instrument using electron impact (EI) or fast atom bombardment (FAB), ionisation techniques.

8.1.4 Nuclear Magnetic Resonance (NMR)

Proton nuclear magnetic resonance spectra were recorded using Bruker AC-250 and Bruker DPX-400 instruments operating at 250.13 and 400.13 MHz, respectively. The experiments were conducted in deuteriated solvents with tetramethylsilane as the internal standard. The following symbols have been adopted in the description of NMR spectra. J = coupling constant (Hz), Multiplicities were recorded as broad

signals (br), singlets (s), doublets (d), triplets (t), quartets (q), septets (s), doublets of doublets (dd), doublets of triplets (dt) and multiplets (m).

Carbon-13 nuclear magnetic resonance spectra were recorded on a Bruker AC250 and Bruker DPX-400, operating at 62.86 and 100.62 MHz, respectively. Normally, the ^{13}C NMR spectrum for each compound was recorded in the same deuteriated solvent as that used for the ^1H NMR spectrum, unless otherwise stated. Tetramethylsilane was used as the internal standard. DEPT, nOe and COSY analyses were recorded on the same instruments.

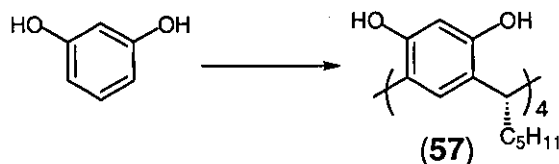
8.2 Experimental Chapter 2

C-Methylcalix[4]resorcinarene³⁰ (34)



Acetaldehyde (10.17 mL, 0.18 mol) was added dropwise to a solution of resorcinol (20.00 g, 0.18 mol) in a mixture of ethanol (95%, 90 mL) and hydrochloric acid (S.G. 1.12, 45 mL) at 15 °C. After the addition was complete, the reaction mixture was heated under reflux for 1 hour before being allowed to cool to room temperature where it was continued stirring for 3 days. After this time the resulting yellow precipitate was collected by filtration. The crude product was washed with water and recrystallised from acetonitrile to furnish C-methylcalix[4]resorcinarene (34) as a cream solid, 13.09 g, 60%: ¹H (250 MHz, CDCl₃) δ 1.28 (d, *J*=7.0 Hz, 12H, -CHCH₃), 4.44 (q, *J*=7.0 Hz, 4H, -CHCH₃), 6.14 (s, 4H, ArH), 6.76 (s, 4H, ArH), 8.54 (s, 8H, OH).

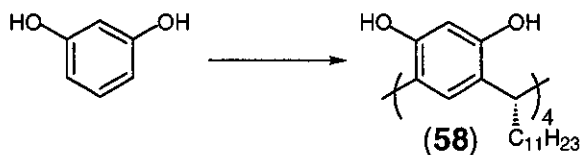
C-Pentylcalix[4]resorcinarene⁵ (57)



Hydrochloric acid (S.G. 1.12, 1.18 mL) was rapidly added to a solution of resorcinol (1.00 g, 9.1 mmol) and hexanal (1.08 mL, 9.1 mmol) in ethanol (95%, 7.25 mL) and the solution was stirred under reflux for 24 hours. After this time the reaction mixture was cooled in an ice bath and the resulting yellow precipitate was collected by filtration. The crude product was washed with a mixture of ethanol and water (1:1) and recrystallised from ethanol to furnish C-pentylcalix[4]resorcinarene (57) as a

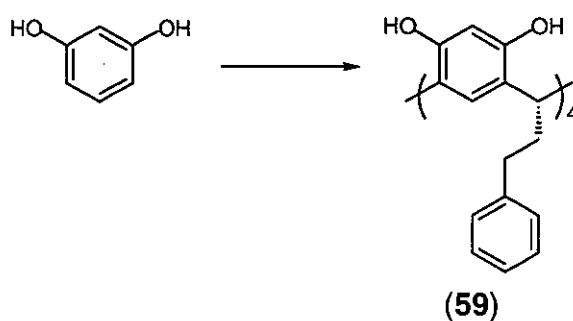
yellow solid, 1.08 g, 62%: ^1H (250 MHz, CDCl_3) δ 0.80 (t, $J=6.7$ Hz, 12H, $-\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.19 (m, 24H, $-\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.97 (m, 8H, $-\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 4.19 (t, $J=7.6$ Hz, 4H, $-\text{CHCH}_2-$), 6.17 (s, 4H, ArH), 7.11 (s, 4H, ArH).

C-Undecylcalix[4]resorcinarene⁵ (58)



Resorcinol (19.8 g, 0.18 mol) was dissolved in a mixture of ethanol (95%, 75 mL) and hydrochloric acid (S.G. 1.12, 25 mL) and cooled to 0 °C. Dodecanal (39.76 mL, 0.18 mol) was added dropwise over 2 hours and the resulting milky solution was allowed to come to room temperature before being heated under reflux for 24 hours. After this time, the reaction mixture was cooled in an ice bath and the resulting yellow precipitate was collected by filtration. The crude product was washed with acid methanol and recrystallised from methanol to furnish C-undecylcalix[4]resorcinarene (**58**) as a beige solid, 39.70 g, 80%: ^1H (250 MHz, CDCl_3) δ 0.85 (t, $J=6.9$ Hz, 12H, $-\text{CH}_2(\text{CH}_2)_9\text{CH}_3$), 1.26 (bm, 72H, $-\text{CH}_2(\text{CH}_2)_9\text{CH}_3$), 2.21 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9\text{CH}_3$), 4.29 (bt, 4H, $-\text{CHCH}_2-$), 6.11 (s, 4H, ArH), 7.21 (s, 4H, ArH).

C-Phenylethylcalix[4]resorcinarene⁵ (59)



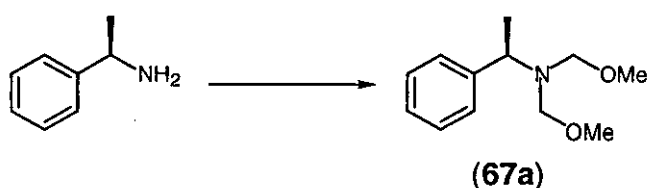
Resorcinol (2.00 g, 18.17 mmol) was dissolved in a mixture of ethanol (95%, 15 mL) and hydrochloric acid (S.G. 1.12, 3.64 mL) and cooled to 0 °C. Dihydrocinnamaldehyde (2.39 mL, 18.17 mmol) was added dropwise over 2 hours and the resulting solution was stirred at room temperature for 24 hours. After this time, the reaction mixture was heated under reflux for 24 hours before being cooled in an ice bath. Water was added and the resulting brown precipitate was collected by filtration. The crude product was washed with cold methanol and recrystallised from methanol to furnish C-phenylethylcalix[4]resorcinarene (**59**) as a beige solid, 3.50 g, 85%: ¹H (250 MHz, DMSO) δ 2.01 (bm, 16H, $-(CH_2)_2Ph$), 3.81 (bt, 4H, $-CH(CH_2)_2Ph$), 5.74 (s, 4H, ArH), 6.96 (s, 4H, ArH), 8.59 (s, 4H, ArH).

Formation of Bis(aminol ethers)

General procedure⁵³

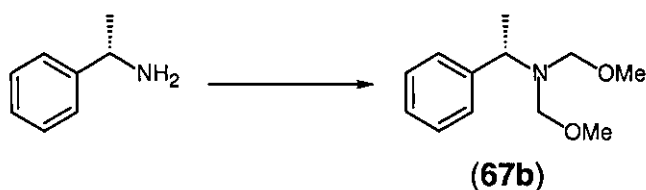
Paraformaldehyde (2.00 eq) was added to a stirred mixture of anhydrous primary amine (1.00 eq), ethanol or methanol (4.00 eq) and potassium carbonate (1.00 eq) at 0 °C. The mixture was then vigorously stirred for 2 days at room temperature. After this time the solid was collected *via* filtration and the filtrates concentrated under reduced pressure. The desired products were then purified by distillation and generally isolated as colourless oils. The following bis(aminol ethers) were synthesised by this method.

***N,N*-di[(Methoxy)methyl]-*N*-[(1*R*)-1-phenylethyl]amine⁷³ (67a)**



(*R*)- α -Methylbenzylamine (5.32 mL, 41.26 mmol), paraformaldehyde (2.47 g, 82.52 mmol), potassium carbonate (5.70 g, 41.26 mmol) and methanol (6.68 mL, 165.04 mmol) were reacted together as described in the general procedure. The residue was purified by Kugelrohr distillation to furnish *N,N*-di[(methoxy)methyl]-*N*-[(1*R*)-1-phenylethyl]amine (67a) as a colourless oil, 5.69 g, 66%: $[\alpha]_D +4.5$, $c=1.32$, CHCl_3 ; HRMS (EI): calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$ (M^+) 209.14158; Found 209.14120; ν_{max} (NEAT) 3509, 2924, 2808, 1492, 1453, 1382, 1068 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.54 (d, $J=6.7$ Hz, 3H, $-\text{CHCH}_3$), 3.08 (s, 6H, $2\times\text{OCH}_3$), 4.20 (d, $J_{AB}=9.8$ Hz, 2H, $2\times\text{CH}_A\text{H}_B^-$), 4.28 (d, $J_{AB}=9.8$ Hz, 2H, $2\times\text{CH}_A\text{H}_B^-$), 4.29 (q, 1H, CHCH_3), 7.26 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 20.30 (CH_3), 54.67 (CH), 57.69 (CH_3), 84.57 (CH_2), 126.63 (CH), 127.52 (CH), 128.27 (CH), 144.21 (C).

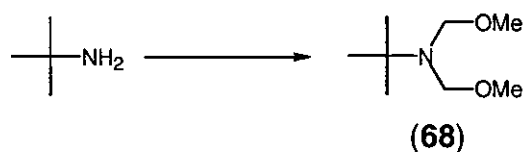
***N,N*-di[(Methoxy)methyl]-*N*-[(1*S*)-1-phenylethyl]amine⁷³ (67b)**



(*S*)- α -Methylbenzylamine (5.32 mL, 41.26 mmol), paraformaldehyde (2.47 g, 82.52 mmol), potassium carbonate (5.70 g, 41.26 mmol,) and methanol (6.68 mL, 165.04 mmol,) were reacted together as described in the general procedure. The residue was purified by Kugelrohr distillation to furnish *N,N*-di[(methoxy)methyl]-*N*-[(1*S*)-1-phenylethyl]amine (67b) as a colourless oil, 5.69 g, 66%: $[\alpha]_D -2.4$, $c=1.31$, CHCl_3 ; HRMS (EI): calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$ (M^+) 209.14158; Found 209.14140; ν_{max} (NEAT)

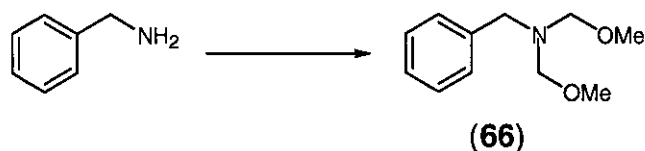
3508, 2978, 2925, 2876, 1492, 1452, 1068 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.46 (d, $J=6.9\text{Hz}$, 3H, $-\text{CHCH}_3$), 3.20 (s, 6H, $2\times\text{OCH}_3$), 4.20 (d, $J_{AB}=10.4\text{ Hz}$, 2H, $2\times\text{CH}_A\text{H}_B-$), 4.29 (d, $J_{AB}=10.4\text{ Hz}$, 2H, $2\times\text{CH}_A\text{H}_B-$), 4.29 (q, 1H, CHCH_3), 7.23-7.26 (5H, m, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 20.12 (CH_3), 54.75 (CH), 56.95 (CH_3), 84.65 (CH_2), 126.93 (CH), 127.53 (CH), 128.53 (CH), 144.22 (C)

***N,N*-di[(Methoxy)methyl]-*N*-*tert*-butylamine⁵³ (68)**



tert-Butylamine (7.18 mL, 68.36 mmol), paraformaldehyde (4.10 g, 136.72 mmol), potassium carbonate (9.44 g, 68.36 mmol) and methanol (11.00 mL, 2.73 mol) were reacted together as described in the general procedure. The residue was purified by Kugelrohr distillation to furnish *N,N*-di[(methoxy)methyl]-*N*-*tert*-butylamine (**68**) as a colourless oil, 5.73 g, 53%: ν_{max} (NEAT) 3508, 2975, 2912, 1466, 1364, 1064 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.22 (s, 9H, ^tBu), 3.19 (s, 6H, $2\times\text{OCH}_3$), 4.35 (s, 4H, $2\times\text{CH}_2-$); ^{13}C NMR (100 MHz, CDCl_3): δ 29.38 (CH_3), 53.84 (CH_3), 53.35 (C), 83.15 (CH_2).

***N,N*-di[(Methoxy)methyl]-*N*-benzylamine (66)**



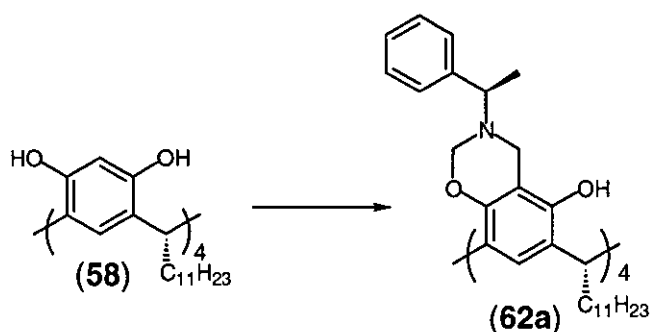
Benzylamine (30.58 mL, 0.279 mol), paraformaldehyde (16.78 g, 0.559 mol), potassium carbonate (38.56 g, 0.279 mol) and methanol (45.20 mL, 1.12 mol) were reacted together as described in the general procedure. The residue was purified by Kugelrohr distillation to furnish *N,N*-di[(methoxy)methyl]-*N*-benzylamine (**66**) as a

colourless oil, 22.00 g, 40%: HRMS (EI): (m/z) calcd for $C_{11}H_{17}NO_2$ (M^+) 195.12593; Found 195.12588; ν_{\max} (NEAT) 2981, 2879, 1453, 1383, 1070 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 3.25 (s, 6H, $2 \times OCH_3$), 4.01 (s, 2H, $-CH_2-$), 4.23 (s, 4H, $-NCH_2O-$), 7.25-7.53 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.69 (CH_2), 55.56 (CH_3), 85.84 (CH_2), 127.00 (CH), 128.34 (CH), 128.95 (CH), 138.89 (C).

Synthesis of tetrakis-(3,4-dihydro-2*H*-1,3-benzoxazine) derivatives

tetrakis-(3-[(1*R*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (62a)

48



Procedure A⁴⁸

A solution of (*R*)- α -methylbenzylamine (0.65 mL, 5.00 mmol) and *C*-undecylcalix[4]resorcinarene (**58**) (1.10 g, 1.0 mmol) in ethanol (99%, 100 mL) was stirred at room temperature. Aqueous sodium hydroxide (cat amount) and paraformaldehyde (0.30 g, 10.00 mmol) were dissolved in water (5 mL) and this solution was added to the reaction mixture. The reaction mixture was heated under reflux for 24 hours before being cooled to room temperature. The solvent was removed under reduced pressure to furnish the crude product as a pink solid. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62a**) as a white crystalline solid, 1.45 g, 82%: mp 75-79 °C; (lit⁴⁸ mp 74-76 °C); $[\alpha]_D^{25} +113$, $c=0.05$, $CHCl_3$; ν_{\max} (DCM evap) 3363, 2923, 2853, 1601, 1467, 1347, 885 cm^{-1} ; 1H NMR (400 MHz,

CDCl₃), δ 0.88 (t, $J=6.8$ Hz, 12H, -CHCH₂(CH₂)₉CH₃), 1.26-1.37 (m, 84H, -CHCH₂(CH₂)₉CH₃ + -CHCH₃), 2.13-2.20 (m, 8H, -CHCH₂(CH₂)₉CH₃), 3.73 (d, $J_{AB}=17.4$ Hz, 4H, -CH_AH_B-), 3.80 (q, $J=6.0$ Hz, 4H, -CHCH₃), 3.94 (d, $J_{AB}=17.4$ Hz, 4H, -CH_AH_B-), 4.19 (t, $J=7.6$ Hz, 4H, -CHCH₂(CH₂)₉CH₃), 4.92 (d, $J_{AB}=10.2$ Hz, 4H, -NCH_AH_BO-), 5.13 (d, $J_{AB}=10.2$ Hz, 4H, -NCH_AH_BO-), 6.93-7.24 (m, 24H, ArH), 7.66 (s, 4H, OH); ¹³C NMR (100MHz, CDCl₃) δ 14.56 (CH₃), 21.86 (CH₃), 23.13 (CH₂), 28.55 (CH₂), 29.85 (CH₂), 30.17 (CH₂), 30.22 (CH₂), 32.38 (CH₂), 33.09 (CH), 34.13 (CH₂), 44.96 (CH₂), 58.41 (CH), 81.31 (CH₂), 108.49 (C), 121.50 (CH), 124.00 (C), 124.71 (C), 127.43 (CH), 128.64 (CH), 144.93 (C), 149.11 (C), 149.98 (C).

3x(CH₂), 1x(CH) obscured by other signals.

Procedure B

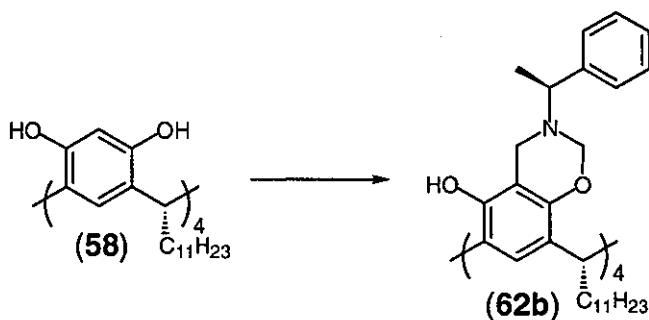
A solution of *C*-undecylcalix[4]resorcinarene (**58**) (5.00 g, 4.8 mmol) in ethanol (99%, 500 mL) was cooled to 0 °C. (*R*)- α -Methylbenzylamine (3.09 mL, 24.00 mmol) was added dropwise followed by aqueous formaldehyde (37% aq. solution, 3.89 mL, 48.00 mmol). The resulting pink solution was heated under reflux for 24 hours. After this time the reaction mixture was cooled in an ice bath and the resulting pale pink precipitate was collected by filtration and washed with cold methanol. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62a**) as a white crystalline solid, 6.68 g, 83%.

Procedure C

A solution of *C*-undecylcalix[4]resorcinarene (**58**) (1.10 g, 1.0 mmol) and *N,N*-di[(methoxy)methyl]-*N*-[(1*R*)-1-phenylethyl]amine (**67a**) (1.04 g, 5.00 mmol) in ethanol (100 mL) were heated under reflux for 24 hours. After this time the reaction mixture was cooled in an ice bath and the resulting pale pink precipitate was collected by filtration and washed with cold methanol. Recrystallisation from

dichloromethane/methanol gave the tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62a**) as a white crystalline solid, 1.47 g, 83%.

tetrakis-(3-[(1*S*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative⁴⁸
(**62b**)



Procedure A

(*S*)- α -Methylbenzylamine (0.32 mL, 2.50 mmol), *C*-undecylcalix[4]resorcinarene (**58**) (0.52 g, 0.5 mmol), aqueous sodium hydroxide (cat amount) and paraformaldehyde (0.15 g, 5.0 mmol) were combined in ethanol (99%, 50 mL) and reacted together according to procedure A. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62b**) as a white crystalline solid, 0.63 g, 76%; mp 74-76 °C; (lit⁴⁸ mp 74-76 °C); $[\alpha]_D^{25}$ -112, $c=0.05$, CHCl₃; ν_{\max} (DCM evap) 3375, 2924, 2853, 1598, 1468, 1347, 886 cm⁻¹; ¹H NMR (400 MHz, CDCl₃), δ 0.88 (t, $J=6.4$ Hz, 12H, -CHCH₂(CH₂)₉CH₃), 1.24-1.37 (m, 84H, -CHCH₂(CH₂)₉CH₃ + -CHCH₃), 2.13-2.20 (m, 8H, -CHCH₂(CH₂)₉CH₃), 3.76 (d, $J_{AB}=17.6$ Hz, 4H, -CH_AH_B-), 3.80 (q, $J=6.4$ Hz, 4H, -CHCH₃), 3.99 (d, $J_{AB}=17.6$ Hz, 4H, -CH_AH_B-), 4.19 (t, $J=7.6$ Hz, 4H, -CHCH₂(CH₂)₉CH₃), 4.92 (d, $J_{AB}=10.0$ Hz, 4H, -NCH_AH_BO-), 5.13 (d, $J_{AB}=10.0$ Hz, 4H, -NCH_AH_BO-), 6.90-7.21 (m, 24H, ArH), 7.67 (s, 4H, OH); ¹³C NMR (100MHz, CDCl₃) δ 14.15 (CH₃), 21.45 (CH₃), 22.17 (CH₂), 28.13 (CH₂), 29.42 (CH₂), 29.75 (CH₂), 29.79 (CH₂), 29.80 (CH₂), 31.96 (CH₂), 32.68 (CH), 33.72 (CH₂), 44.55 (CH₂), 58.03 (CH), 80.19 (CH₂), 108.91 (C), 121.10 (CH), 123.45 (C), 124.30 (C), 127.02 (CH), 128.22 (CH), 144.52 (C), 148.71 (C), 149.57 (C).

2x(CH₂), 1x(CH) obscured by other signals.

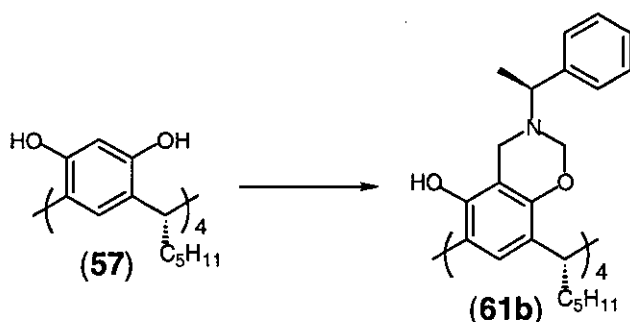
Procedure B

C-Undecylcalix[4]resorcinarene (**58**) (3.00 g, 2.88 mmol), (*S*)- α -methylbenzylamine (1.85 mL, 14.39 mmol) and aqueous formaldehyde (37% aq. solution, 2.33 mL, 28.80 mmol) were reacted together in ethanol (99%, 300 mL) according to procedure B. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62b**) as a white crystalline solid, 3.74 g, 77%.

Procedure C

A solution of *C*-undecylcalix[4]resorcinarene (**58**) (2.00 g, 1.92 mmol) and *N,N*-di[(methoxy)methyl]-*N*-[(1*S*)-1-phenylethyl]amine (2.00 g, 9.60 mmol) in ethanol (99%, 150 mL) was heated under reflux for 24 hours. After this time the reaction mixture was cooled in an ice bath and the resulting pale pink precipitate was collected by filtration and washed with cold methanol. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62b**) as a white crystalline solid, 2.45 g, 76%.

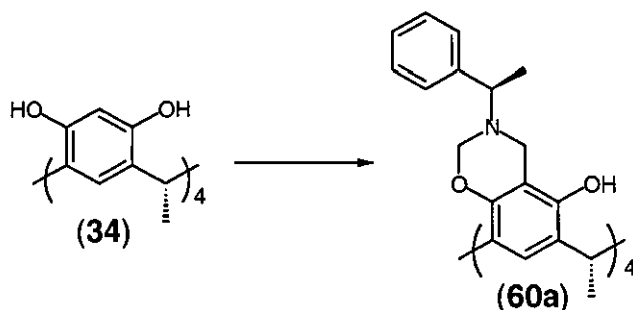
tetrakis-(3-[(1*S*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative⁴⁸ (61b)



(*S*)- α -Methylbenzylamine (8.38 mL, 65.00 mmol), *C*-pentylcalix[4]resorcinarene⁵ (**57**) (10.00 g, 13.00 mmol) and aqueous formaldehyde (37% solution, 10.31 mL, 0.13 mol) were reacted together in ethanol (99%, 500 mL) according to procedure B. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**61b**) as a white crystalline solid, 13.4 g, 76%: mass spectrum (FAB⁺) m/z 1350 (MH⁺); ν_{\max} (DCM evap) 3388, 2929, 1598, 1469, 1338, 883, 701 cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ 0.91 (t, $J=6.7$ Hz, 12H, -CHCH₂(CH₂)₃CH₃), 1.28 (d, $J=6.4$ Hz, -CHCH₃), 1.35 (m, 24H, -CHCH₂(CH₂)₃CH₃), 2.17 (m, 8H, -CHCH₂(CH₂)₃CH₃), 3.70 (d, $J_{AB}=17.5$ Hz, 4H, -CH_AH_B-), 3.81 (q, $J=6.4$ Hz, 4H, -CH₂CH₃), 3.98 (d, $J_{AB}=17.5$ Hz, 4H, -CH_AH_B-), 4.19 (t, $J=7.6$ Hz, 4H, -CH₂CH₂(CH₂)₃CH₃), 4.92 (d, $J_{AB}=10.3$ Hz, 4H, -NCH_AH_BO-), 5.14 (d, $J_{AB}=10.3$ Hz, 4H, -NCH_AH_BO-), 6.92-7.23 (m, 24H, ArH), 7.68 (s, 4H, OH). ¹³C NMR (100 MHz, CDCl₃): δ 14.15 (CH₃), 21.38 (CH₃), 22.66 (CH₂), 27.78 (CH₂), 31.93 (CH₂), 32.68 (CH), 33.62 (CH₂), 44.49 (CH₂), 57.93 (CH), 80.84 (CH₂), 108.84 (C), 120.97 (CH), 123.41 (C), 124.26 (C), 126.96, (CH), 128.16 (CH), 144.45 (C), 148.63 (C), 149.49 (C).

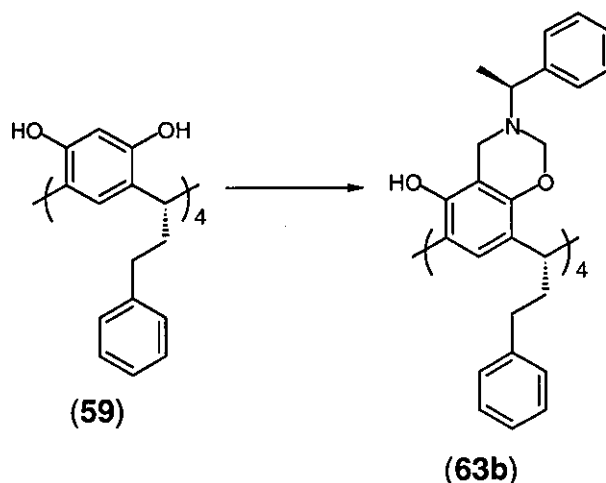
1x(CH) obscured by other signals.

tetrakis-(3-[(1*R*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative⁴⁸
(60a)



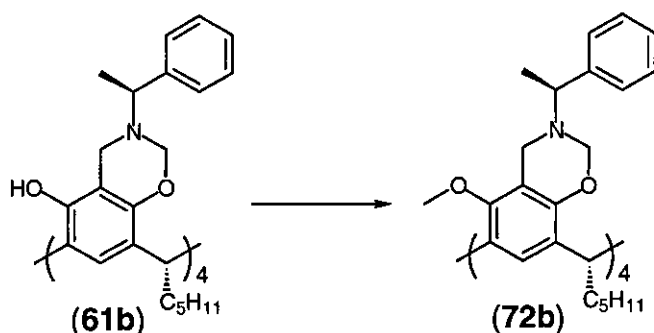
C-Methylcalix[4]resorcinarene (**34**) (1.00 g, 2.08 mmol), (*R*)- α -methylbenzylamine (1.34 mL, 10.40 mmol) and aqueous formaldehyde (37% aq. solution, 1.68 mL, 20.80 mmol) were reacted together in ethanol (200 mL) according to procedure B. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**60a**) as a white crystalline solid, 3.74 g, 77%: ¹H NMR (250 MHz, CDCl₃): δ 1.30 (d, $J=6.4$ Hz, 12H, -Ar₂CHCH₃), 1.74 (d, $J=7.4$ Hz, 12H, -CHCH₃), 3.74 (d, $J_{AB}=17.5$ Hz, 4H, -CH_AH_B-), 3.83 (q, $J=6.4$ Hz, 4H, -CHCH₃), 3.97 (d, $J_{AB}=17.5$ Hz, 4H, -CH_AH_B-), 4.48 (q, $J=7.4$ Hz, 4H, -CHCH₃), 4.92 (d, $J_{AB}=10.2$ Hz, 4H, -NCH_AH_BO-), 5.14 (d, $J_{AB}=10.2$ Hz, 4H, -NCH_AH_BO-), 6.92-7.26 (m, 24H, ArH), 7.75 (s, 4H, OH).

tetrakis-(3-[(1*S*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative⁴⁸
(63b)



C-Phenylethylcalix[4]resorcinarene (**59**) (0.904 g, 1.00 mmol), (*S*)- α -methylbenzylamine (0.61 g, 5.00 mmol) and aqueous formaldehyde (37% aq. solution, 0.811 mL, 10.00 mmol) were reacted together in ethanol (150 mL) according to procedure B. Recrystallisation from dichloromethane/methanol gave the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**63b**) as a white crystalline solid, 1.17 g, 79%: ν_{\max} (DCM evap) 3333, 2921, 1599, 1465, 1376, 1146, 879, 699 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3): δ 1.28 (d, $J=6.6$ Hz, 12H, $-\text{CHCH}_3$), 2.49-2.63 (m, 16H, $-\text{CH}(\text{CH}_2)_2\text{Ph}$), 3.78 (d, $J_{AB}=17.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.80 (q, 4H, $-\text{CHCH}_3$), 3.98 (d, $J_{AB}=17.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 4.27 (t, $J=7.4$ Hz, 4H, $-\text{CHCH}_2$), 4.92 (d, $J_{AB}=10.2$ Hz, 4H, $-\text{NCH}_A\text{H}_B\text{O}-$), 5.14 (d, $J_{AB}=10.2$ Hz, 4H, $-\text{NCH}_A\text{H}_B\text{O}-$), 6.92-7.24 (m, 44H, ArH), 7.66 (s, 4H, OH).

tetrakis-(*O*-Methylether) derivative (72b)



Procedure A

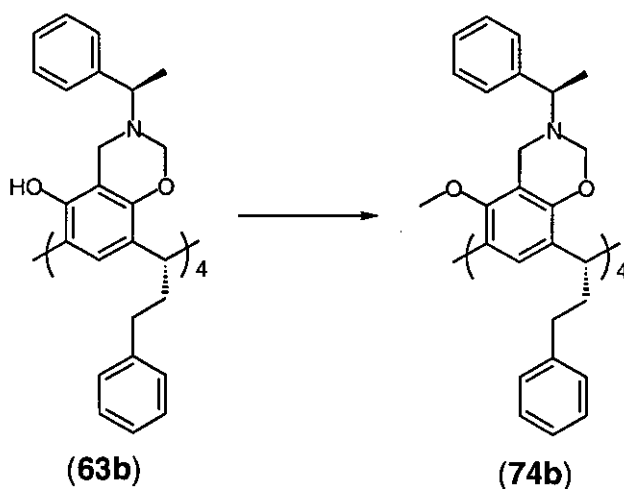
The tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**61b**) (1.00 g, 0.74 mmol) was dissolved in anhydrous THF (10 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (2.03 mL, 3.26 mmol) was added dropwise whilst the solution was vigorously stirred. The resulting gelatinous mixture was stirred for 15 min before methyl triflate (0.36 mL, 3.26 mmol) was added dropwise. Stirring was continued until the mixture reached room temperature. After this time the reaction was quenched by the addition of methanol (10 mL) and the solvent removed under reduced pressure. The resulting brown residue was dissolved in dichloromethane, washed with water and a saturated aqueous solution of sodium chloride and the organic solution separated. This solution was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to furnish the crude product as a pale brown foam. Purification by flash chromatography (silica gel, 40% ethyl acetate/light petroleum ($40\text{ }^{\circ}\text{C}$ - $60\text{ }^{\circ}\text{C}$)) furnished the tetrakis-(*O*-methylether) derivative (**72b**) as a colourless foam, 0.56 g, 54%: mp $82\text{--}83\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -131$, $c=1.05$, CHCl_3 ; mass spectrum (FAB⁺) m/z 1406 (MH^+); Anal. Calcd for $\text{C}_{92}\text{H}_{116}\text{N}_4\text{O}_8$: C, 78.59; H, 8.33; N, 3.98; Found C, 78.19; H, 8.17; N, 3.93. ν_{max} (DCM evap) 2927, 2857, 1590, 1468 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, $J = 6.4\text{ Hz}$, 12H, $-\text{CHCH}_2(\text{CH}_2)_3\text{CH}_3$), 1.32-1.38 (m, 24H, $-\text{CHCH}_2(\text{CH}_2)_3\text{CH}_3$), 1.37 (d, $J = 6.4\text{ Hz}$, 12H, $-\text{CHCH}_3$), 1.78-1.91 (m, 8H, $-\text{CHCH}_2(\text{CH}_2)_3\text{CH}_3$), 3.26 (s, 12H, $-\text{OCH}_3$), 3.68 (q, $J = 6.4\text{ Hz}$, 4H, $-\text{CHCH}_3$), 3.77 (d, $J = 16.8\text{ Hz}$, 4H, $-\text{CH}_A\text{H}_B-$),

4.14 (d, $J = 16.8$ Hz, 4H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 4.35 (t, $J = 7.4$ Hz, 4H, $-\text{CHCH}_2(\text{CH}_2)_3\text{CH}_3$), 4.51 (d, $J = 10.0$ Hz, 4H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 4.56 (d, $J = 10.0$ Hz, 4H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 6.66 (s, 4H, ArH), 7.15-7.10 (m, 20H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.23 (CH_3), 21.25 (CH_3), 22.69 (CH_2), 27.89 (CH_2), 32.21 (CH_2), 35.40 (CH_3), 35.77 (CH_2), 44.66 (CH_2), 57.29 (CH), 60.05 (CH), 79.55 (CH_2), 112.23 (C), 124.54 (CH), 127.30 (CH), 127.53 (CH), 127.85 (C), 128.39 (C), 128.81 (C), 144.12 (CH), 150.11 (CH), 153.58 (CH).

Procedure B

Sodium hydride (0.13 g, 3.26 mmol) was stirred in THF (2.00 mL) at -78°C . The tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**61b**) (1.00 g, 0.74 mmol) was dissolved in THF (5.00 mL) and added to the reaction vessel dropwise. The reaction mixture was stirred at -78°C for 45 min. After this time, methyl triflate (0.36 mL, 3.26 mmol) was added dropwise and the mixture continued stirring at -78°C for 1 hour. The reaction mixture was then warmed to room temperature and methanol (5 mL) added. The reaction mixture was concentrated under reduced pressure and the resulting yellow residue dissolved in DCM, washed with water and saturated aqueous solution of sodium chloride and the organic solution separated. This solution was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to furnish the crude product as a pale pink oil. Purification by flash chromatography (silica gel, 30%-50% ethyl acetate/light petroleum (40°C - 60°C)) furnished the tetrakis-(*O*-methylether) derivative (**72b**) as pale yellow crystalline solid, 0.186 mg, 18 %.

tetrakis-(*O*-Methylether) derivative (74b)

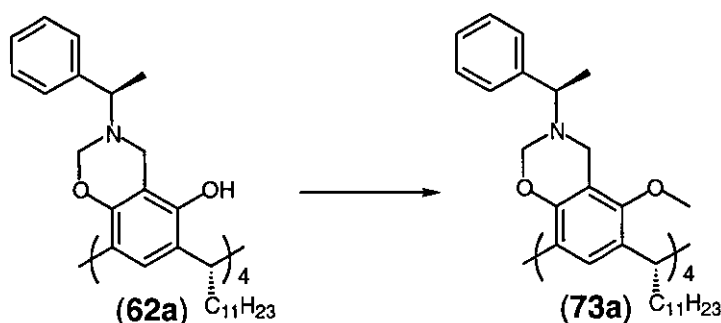


The tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**63b**) (10.00 g, 6.72 mmol) was dissolved in THF (200 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (10.76 mL, 26.92 mmol) was added dropwise whilst the solution was vigorously stirred. The resulting gelatinous mixture was stirred for 15 min before methyl triflate (3.04 mL, 26.92 mmol) was added dropwise. Stirring was continued at $-78\text{ }^{\circ}\text{C}$ for 30 min before being quenched by the addition of methanol. The reaction mixture was allowed to reach room temperature before the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane and washed with water, saturated aqueous solution of sodium chloride and the organic solution separated. This solution was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to furnish the crude product as a pale pink oil. Purification *via* flash chromatography (silica gel, 30-50% ethyl acetate/light petroleum ($40\text{ }^{\circ}\text{C}$ - $60\text{ }^{\circ}\text{C}$)) furnished the tetrakis-(*O*-methylether) derivative (**74b**) as pale yellow crystalline solid, 8.21 g, 79 %: mp= 116 - $119\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25}$ -117, $c=1.04$, CHCl_3 ; mass spectrum (FAB⁺) m/z 1542 (MH⁺); Anal. Calcd for $\text{C}_{104}\text{H}_{108}\text{N}_4\text{O}_8$: C, 80.99 ; H, 7.07 ; N, 3.63 ; Found C, 80.64 ; H, 6.95 ; N, 3.50; ν_{max} (DCM evap) 2936, 1589, 1470, 1453, 931 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.39 (d, $J = 7.0\text{ Hz}$, 12H, $-\text{CHCH}_3$), 2.11-2.31 (m, 8H, $-(\text{CH}_2)(\text{CH}_2)\text{C}_6\text{H}_5$), 2.68 (t, $J = 8.0\text{ Hz}$, 8H, $-(\text{CH}_2)(\text{CH}_2)\text{C}_6\text{H}_5$), 3.21 (s, 12H, -

OCH₃), 3.81 (q, $J = 7.0$ Hz, 4H, -CHCH₃), 3.87 (d, $J = 16.8$ Hz, 4H, -CH_AH_B-), 4.18 (d, $J = 16.8$ Hz, 4H, -CH_AH_B-), 4.52 (t, $J = 7.6$ Hz, 4H, -CHCH₂), 4.57 (d, $J = 10.0$ Hz, 4H, -CH_AH_B-), 4.63 (d, $J = 10.0$ Hz, 4H, -CH_AH_B-), 6.84 (s, 4H, ArH), 7.11-7.20 (m, 40H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 21.27 (CH₃), 34.57 (CH₂), 35.31 (CH₃), 37.64 (CH₂), 44.55 (CH₂), 57.21 (CH), 59.96 (CH), 79.62 (CH₂), 112.45 (C), 124.40 (CH), 125.51 (CH), 127.32 (CH), 127.52 (CH), 128.22 (CH), 128.41 (CH), 128.47 (CH), 128.54 (C), 142.70 (C), 144.03 (C), 150.33 (C), 153.83 (C).

1x(C) obscured by other signals.

tetrakis-(*O*-Methylether) derivative⁷³ (73a)

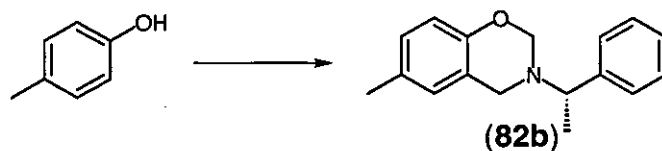


The tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62a**) (6.00 g, 3.57 mmol) was dissolved in dry THF (500 ml) and stirred at to -78 °C. *n*-BuLi (1.6M solution in hexane, 8.93 mL, 14.82 mmol) was added dropwise and the resulting gelatinous precipitate stirred at -78 °C for 30 min. Methyl triflate (1.61 mL, 14.28 mmol) was added dropwise and the reaction mixture stirred at -78 °C until a homogeneous solution was observed. After this time, the reaction mixture was quenched by the addition of water, and the mixture was allowed to reach room temperature. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with water and a saturated aqueous solution of sodium chloride. The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure to yield the crude product as a pale pink oil. Purification by flash chromatography (silica gel, 30% ethyl acetate/light petroleum (40

para-Cresol (10.00 g, 92.47 mmol), formaldehyde (22.18 mL, 273.43 mmol), (*R*)- α -methylbenzylamine (13.11 mL, 101.71 mmol) and ethanol (100 mL) were reacted together according to general procedure B. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish the 6-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) as a pale yellow oil, 18.4 g, 78%.

para-Cresol (1.50 g, 13.86 mmol) and bis aminol ether (3.15 g, 15.24 mmol) were dissolved in dichloromethane (30 mL) and reacted together according to general procedure C. The crude product was purified by flash chromatography (silica gel, 5% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 6-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) as a pale yellow oil, 2.91 g, 83%:

6-Methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine⁷³ (82b**)**



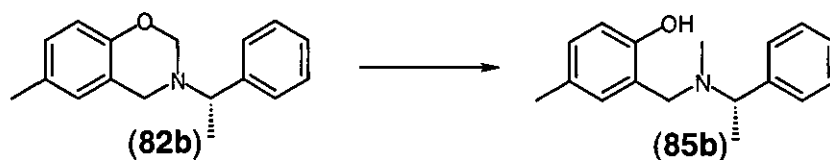
para-Cresol (10.00 g, 92.47 mmol), formaldehyde (22.18 mL, 273.43 mmol), (*S*)- α -methylbenzylamine (13.11 mL, 101.71 mmol) and ethanol (100 mL) were reacted together according to general procedure B. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 6-methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) as a pale yellow oil, 20.4 g, 87%; $[\alpha]_D^{25}$ -25, $c=2.29$, CHCl_3 ; HRMS (EI): (m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$ (M^+) 253.14666; Found: 253.14658; ν_{max} (NEAT) 2974, 1739, 1618; 1587, 1453 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.44 (d, $J=6.5$ Hz, 3H, $-\text{CHCH}_3$), 2.22 (s, 3H, ArCH_3), 3.71 (d, $J_{\text{AB}}=16.8$ Hz, 1H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 3.95 (q, $J=6.5$ Hz, 1H, $-\text{CHCH}_3$), 4.04 (d, $J_{\text{AB}}=16.8$ Hz, 1H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 4.80 (d, $J_{\text{AB}}=10.2$ Hz, 1H, $-\text{NCH}_\text{A}\text{H}_\text{B}\text{O}-$), 5.03 (dd, $J_{\text{AB}}=10.2$ Hz, $J=1.2$ Hz, 1H, $-\text{NCH}_\text{A}\text{H}_\text{B}\text{O}-$), 6.66 (d, $J=1.2$ Hz, 1H, ArH), 6.68 (d, $J=8.2$ Hz, 1H, ArH), 6.90 (dd, $J=8.2$ Hz, $J=2.2$ Hz, 1H, ArH), 7.25-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz,

CDCl_3): δ 20.57 (CH_3), 21.59 (CH_3), 48.72 (CH_2), 57.61 (CH), 80.03 (CH_2), 115.98 (CH), 120.12 (C), 127.20 (CH), 127.30 (CH), 127.83 (CH), 128.13 (CH), 128.50 (CH), 129.67 (C), 144.72 (C), 152.57 (C).

para-Cresol (0.50 g, 4.62 mmol) and *N,N*-di[(methoxy)methyl]-*N*-[(1*S*)-1-phenylethyl]amine (**67b**) (1.05 g, 5.08 mmol) were dissolved together in dichloromethane (20 mL) and reacted together according to general procedure C. The crude product was purified by flash chromatography (silica gel, 5% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 6-methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) as a pale yellow oil, 0.84 g, 88%.

para-Cresol (10.00 g, 92.47 mmol), paraformaldehyde (5.55 g, 184.95 mmol), potassium hydroxide (cat amount) and (*S*)- α -methylbenzylamine (11.92 mL, 92.47 mmol) were dissolved together in methanol (20 mL) and reacted together according to general procedure A. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 6-methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) as a pale yellow oil, 14.5 g, 62%.

4-Methyl-2-({methyl[(1*S*)-1-benzyl]amino)methyl}benzen-1-ol⁷³ (**85b**)



Procedure A

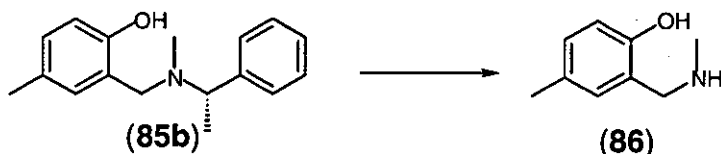
6-Methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) (1.00 g, 3.95 mmol) was dissolved in formic acid (10 mL) and the solution heated under reflux for 1 hour. After this time the solution was carefully poured into a dilute solution of aqueous ammonia and extracted with ethyl acetate. The organic solution was dried over

magnesium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel, 10% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 4-methyl-2-({methyl[(1*S*)-1-benzyl]amino}methyl)benzen-1-ol (**85b**) as a colourless oil, 0.70 g, 70%: HRMS (EI): (*m/z*) calcd for C₁₇H₂₁NO (*M*⁺) 255.16231; Found: 255.14682; *v*_{max} (NEAT) 3291, 2968, 1600, 1498, 1451, 1253 cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ 1.48 (d, *J*=6.9 Hz, 3H, -CHCH₃), 2.18 (s, 3H, ArCH₃), 2.22 (s, 3H, -NCH₃), 3.56 (d, *J*_{AB}=14.0 Hz, 1H, -CH_AH_B-), 3.70 (d, *J*_{AB}=14.0 Hz, 1H, -CH_AH_B-), 3.74 (q, *J*=6.9 Hz, 1H, -CHCH₃), 6.69 (m, 2H, ArH), 6.92 (dd, *J*=8.1 Hz, *J*=2.1 Hz, 1H, ArH), 7.25-7.39 (m, 5H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 17.19 (CH), 20.47 (CH₃), 37.19 (CH₃), 58.10 (CH₂), 62.57 (CH₃), 115.70 (CH), 121.67 (C), 127.60 (CH), 128.00 (CH), 128.03 (C), 128.49 (CH), 128.94 (CH), 129.01 (CH), 140.71 (C), 155.64 (C) ppm.

Procedure B

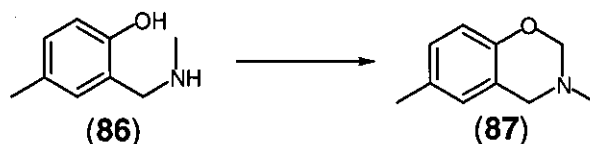
6-Methyl-3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82b**) (1.00 g, 3.95 mmol) was dissolved in formic acid (10 mL) and the solution stirred at room temperature. Paraformaldehyde (1.97 mmol, 60 mg) was added and the resulting solution heated under reflux for 1 hour. After this time the solution was carefully poured into a dilute solution of aqueous ammonia and extracted with ethyl acetate. The organic solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel, 10% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 4-methyl-2-({methyl[(1*S*)-1-benzyl]amino}methyl)benzen-1-ol (**85b**) as a colourless oil, 0.75 g, 76%.

4-Methyl-2-[(methylamino)methyl]benzen-1-ol⁷³ (86)



Palladium hydroxide on carbon (ca. 20% Pd, 50 mg) was added to a solution of 4-methyl-2-[(methyl[(1*S*)-1-benzyl]amino)methyl]benzen-1-ol (**85b**) (700 mg, 2.75 mmol) in ethanol (20 mL) and the mixture was stirred under a balloon of hydrogen for 10 hours. After this time the reaction mixture was filtered through celite and the filtrates concentrated under reduced pressure. The resulting residue was dissolved in hydrochloric acid (2 N) and washed with ethyl acetate. The aqueous solution was separated, basified with aqueous ammonia and extracted into ethyl acetate. The organic solution was separated, washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish 4-methyl-2-[(methylamino)methyl]benzen-1-ol (**86**) as a brown solid, 405 mg, 98%; mp 55-57 °C; HRMS (EI): (*m/z*) calcd for C₁₇H₂₁NO (*M*⁺) 151.09771; Found: 151.09796; ν_{max} (DCM evap) 2951, 1599, 1498, 1499, 1260, 1023, 816 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.22 (s, 3H, ArCH₃), 2.41 (s, 3H, -NHCH₃), 3.85 (s, 2H, -CH₂-), 6.69 (d, *J*=8.0 Hz, 1H, ArH), 6.76 (d, *J*=1.6 Hz, 1H, ArH), 6.92 (dd, *J*=8.0 Hz, *J*=2.0 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 20.41 (CH₃), 35.09 (CH₃), 54.53 (CH₂), 115.98 (CH), 121.95 (C), 128.30 (C), 129.43 (CH), 129.46 (CH), 156.34 (C).

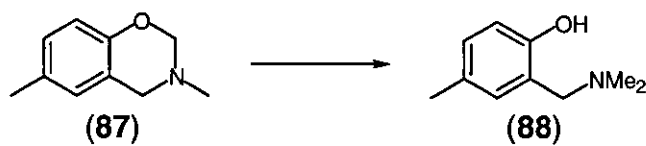
3,6-Dimethyl-3,4-dihydro-2*H*-1,3-benzoxazine⁷³ (87)



Formaldehyde (37% aqueous solution, 0.32 mL, 3.96 mmol) was added to a solution of 4-methyl-2-[(methylamino)methyl]benzen-1-ol (**86**) (0.50 g, 3.31 mmol,) in ethanol

(absolute, 10 mL) and the mixture heated under reflux for 2 hours. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue subjected to flash chromatography (silica gel, 10% ethyl acetate-light petroleum (40°C-60°C)) to furnish a colourless oil that slowly crystallised to give 3,6-dimethyl-3,4-dihydro-2*H*-1,3-benzoxazine (**87**) as a white crystalline solid, 0.35 g, 65%: mp 53-54 °C; HRMS (EI): (*m/z*) calcd for C₁₀H₁₃NO (*M*⁺) 163.09771; Found: 163.09742; ν_{max} (DCM evap) 2942, 1618, 1587, 1500, 1228, 936, 814 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.24 (s, 3H, ArCH₃), 2.58 (s, 3H, -NCH₃), 3.89 (s, 2H, -CH₂-), 4.74 (s, 2H, -NCH₂O-), 6.67 (d, *J*=8.4 Hz, 1H, ArH), 6.75 (m, 1H, ArH), 6.89 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 20.56 (CH₃), 39.75 (CH₃), 52.18 (CH₂), 83.71 (CH₂), 116.09 (CH), 119.50 (C), 127.88 (CH), 128.23 (CH), 129.74 (C), 151.47 (C).

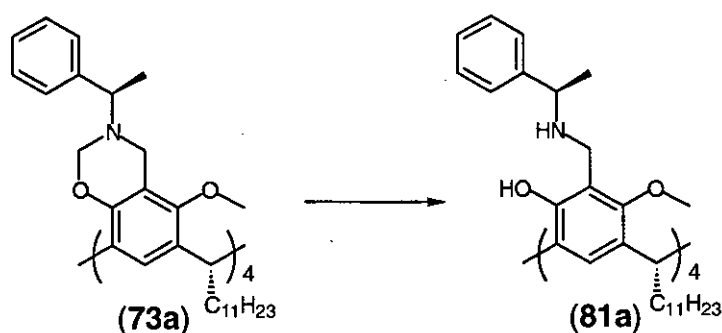
2-[(Dimethylamino)methyl]-4-methylphenol⁷³ (**88**)



3,6-Dimethyl-3,4-dihydro-2*H*-1,3-benzoxazine (**87**) (130 mg, 0.79 mmol) was dissolved in formic acid (2 mL) and the solution heated under reflux for 1 hour. After this time the solution was carefully poured into a dilute solution of aqueous ammonia and extracted with ethyl acetate. The organic solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel 50% ethyl acetate/light petroleum (40 °C-60 °C)) to furnish 2-[(dimethylamino)methyl]-4-methylphenol (**88**) as a colourless oil, 115 mg, 89%: HRMS (EI): (*m/z*) calcd for C₁₀H₁₅NO (*M*⁺) 165.11536; Found: 165.11531; ν_{max} (NEAT) 2951, 2826, 1600, 1500, 1261, 816 cm⁻¹; ¹H (400 MHz, CDCl₃): δ 2.23 (s, 3H, CH₃), 2.31 (s, 6H, -NCH₃), 3.58 (s, 2H, -CH₂), 6.71 (d, *J*=8.0 Hz, 1H, ArH), 6.76 (d, *J*=1.6 Hz, 1H, ArH), 6.94 (dd, *J*=8.0 Hz, *J*=1.6 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 20.45 (CH₃), 44.47 (CH₃), 62.78 (CH₂), 115.81 (CH),

121.55 (C), 127.59 (C), 128.92 (CH), 129.14 (CH), 155.62 (C).

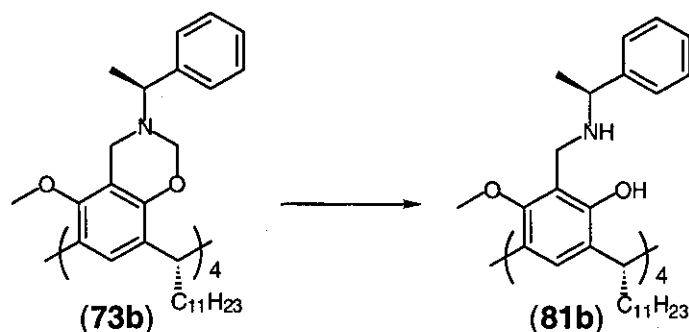
tetrakis-Hydrolysed derivative⁷³ (81a)



tetrakis-(O-Methylether) derivative (73a) (0.458 g, 0.264 mmol) was dissolved in ethanol (absolute, 5 mL) and stirred at room temperature. Hydrochloric acid (S.G 1.12, 0.132 mL, 1.32 mmol) was added and the mixture heated under reflux for 2 hours. After this time the reaction mixture was evaporated to dryness under reduced pressure and the residue partitioned between ethyl acetate and dilute ammonium hydroxide solution. The organic solution was washed with water and brine, separated, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to furnish the crude product as a pale yellow oil. Purification by flash chromatography (silica gel, 20% methanol/dichloromethane) gave the tetrakis-hydrolysed derivative (81a) as a pale yellow solid, 0.39 g, 87%: mp 122-123 °C; HRMS (FAB): (m/z) calcd for (M+2H⁺) 1695.2706; Found 1695.2698; ν_{\max} (DCM evap) 3312, 3196, 2923, 2852, 1594, 1459, 1092 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, $J=8.0$ Hz, 12H, -(CH₂)₉CH₃), 1.22-1.30 (m, 72H, -(CH₂)₉CH₃), 1.37 (d, $J=8.0$ Hz, 12H, -CHCH₃), 1.76-1.90 (m, 8H, -CH₂(CH₂)₉), 3.34 (s, 12H, OCH₃), 3.67 (d, $J_{AB}=12.0$ Hz, 4H, -CH_AH_B-), 3.84 (d, $J_{AB}=12.0$ Hz, 4H, -CH_AH_B-), 3.72 (q, $J=8.0$ Hz, 4H, -CHCH₃), 4.41 (t, $J=8.0$ Hz, 4H, -CHCH₂), 6.69 (s, 4H, ArH), 7.21-7.32 (m, 20H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 14.11 (CH₃), 22.69 (CH₂), 23.03 (CH₃), 28.57 (CH₂), 29.39 (CH₂), 29.73 (CH₂), 29.79 (CH₂), 29.83 (CH₂), 29.92 (CH₂), 30.16 (CH₂), 31.94 (CH₂), 35.71 (CH₂), 35.97 (CH₃), 43.91 (CH₂), 57.89 (CH), 61.41 (CH), 114.94 (C), 125.53 (CH), 126.51 (CH), 127.42 (CH), 127.93 (C), 128.00 (C), 128.69 (CH), 143.63 (C), 153.94

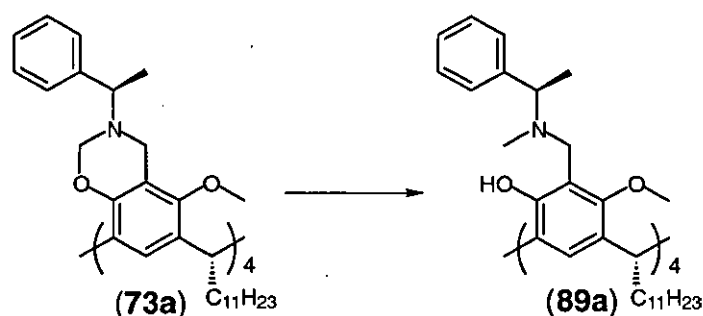
(C), 154.18 (C).

tetrakis-Hydrolysed derivative⁷³ (81b)



Pale yellow solid, 0.32 g, 84%: mp 120-125 °C; ν_{max} (DCM evap) 2923, 2853, 1594, 1458, 1101 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, $J=6.8$ Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.22-1.30 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.38 (d, $J=6.4$ Hz, 12H, $-\text{CHCH}_3$), 1.76-1.90 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9$), 3.35 (s, 12H, OCH_3), 3.67 (d, $J_{AB}=13.5$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.84 (d, $J_{AB}=13.5$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.72 (q, $J=6.4$ Hz, 4H, $-\text{CHCH}_3$), 4.45 (t, $J=7.2$ Hz, 4H, $-\text{CHCH}_2$), 6.71 (s, 4H, ArH), 7.21-7.32 (m, 20H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11 (CH_3), 22.69 (CH_2), 23.93 (CH_3), 28.55 (CH_2), 29.39 (CH_2), 29.72 (CH_2), 29.79 (CH_2), 29.82 (CH_2), 29.91 (CH_2), 30.14 (CH_2), 31.94 (CH_2), 35.72 (CH_2), 35.88 (CH_3), 43.83 (CH_2), 57.87 (CH), 61.45 (CH), 114.86 (C), 125.52 (CH), 126.55 (CH), 127.46 (CH), 127.99 (C), 128.43 (C), 128.71 (CH), 143.63 (C), 153.95 (C), 154.14 (C).

tetrakis-(*N*- α -Methylbenzyl,*N*-methyl) derivative⁷³ (89a)



Procedure A

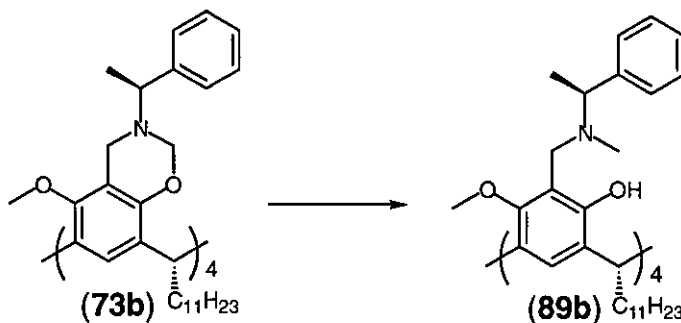
tetrakis-(*O*-methylether) derivative (73a) (1.54 g, 0.88 mmol) was dissolved in formic acid (96%, 15 mL) and heated under reflux for 3 hours. After this time the reaction mixture was concentrated to afford a pale yellow oil. Purification by flash chromatography (silica gel, 5% methanol/dichloromethane) furnished the tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (89a) as a pale yellow oil, 0.88 g, 65%: $[\alpha]_D^{25}$ -2.8, $c=0.268$, CHCl_3 ; mass spectrum (FAB⁺) m/z 1750 (MH^+); Anal. Calcd for $\text{C}_{116}\text{H}_{172}\text{N}_4\text{O}_8$: C, 78.82; H, 9.95; N, 3.14. Found C, 78.69; H, 9.95; N, 3.14; ν_{max} (DCM evap) 2924, 2853, 1595, cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, $J=8.0$ Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.21-1.30 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.41 (d, $J=4.0$ Hz, 12H, CHCH_3), 1.75-2.04 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9$), 2.07 (s, 12H, NCH_3), 3.31 (s, 12H, OCH_3), 3.55 (d, $J_{AB}=13.2$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.69 (q, 4H, CHCH_3), 3.73 (d, $J_{AB}=13.2$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 4.47 (t, $J=6.8$ Hz, 4H, CHCH_2), 6.68 (s, 4H, ArH), 7.25-7.30 (m, 20H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11 (CH_3), 15.98 (CH_3), 22.70 (CH_2), 28.41 (CH_2), 29.40 (CH_2), 29.73 (CH_2), 29.79 (CH_2), 29.84 (CH_2), 29.91 (CH_2), 30.14 (CH_2), 31.95 (CH_2), 35.93 (CH_3), 37.09 (CH_3), 51.15 (CH_2), 61.06 (CH), 62.18 (CH), 113.95 (C), 125.99 (CH), 127.75 (CH), 127.97 (C), 128.42 (CH), 128.42 (C), 128.71 (CH), 141.65 (C), 154.48 (C), 154.77 (C).

1x(CH_2) obscured by other signals.

Procedure B

tetrakis-(*O*-Methylether) derivative (**73a**) (1.00 g, 0.604 mmol) was dissolved in dry toluene (15 mL) and stirred at 0 °C. DIBAL-H (1.5M solution in toluene, 3.22 mL, 4.83 mmol) was added in one portion and the resulting solution was allowed to come to room temperature before being stirred for 3 hours. After this time the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium/sodium tartrate (10 mL), methanol (10 mL) and ethyl acetate (20 mL) and continued stirring for 12 hours. After this time the organic solution was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish the crude product as a pale yellow oil. Purification by flash chromatography (silica gel, 5% methanol/dichloromethane) furnished the tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (**89a**) as a pale yellow oil 0.92 g, 93%.

tetrakis-(*N*- α -Methylbenzyl,*N*-methyl) derivative⁷³ (**89b**)



Procedure A

tetrakis-(*O*-Methylether) derivative (**73b**) (1.54 g, 0.88 mmol) was dissolved in formic acid (96%, 15 mL) and heated under reflux for 3 hours. After this time the reaction mixture was concentrated to afford a pale yellow oil. Purification by flash chromatography (silica gel, 5% methanol/dichloromethane) furnished the tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (**89b**) as a pale yellow oil, 0.88 g, 88%: ν_{\max} (DCM evap) 2923, 2852, 1594, 1453 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, *J*

=8.0 Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.21-1.30 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.41 (d, $J=4.0$ Hz, 12H, CHCH_3), 1.75-2.04 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9$), 2.07 (s, 12H, NCH_3), 3.31 (s, 12H, OCH_3), 3.55 (d, $J_{AB}=13.2$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.73 (d, $J_{AB}=13.2$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.69 (q, 4H, CHCH_3), 4.48 (t, $J=6.8$ Hz, 4H, CHCH_2), 6.69 (s, 4H, ArH), 7.25-7.31 (20H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11 (CH_3), 15.92 (CH_3), 22.69 (CH_2), 28.41 (CH_2), 29.40 (CH_2), 29.72 (CH_2), 29.79 (CH_2), 29.83 (CH_2), 29.91 (CH_2), 30.14 (CH_2), 31.94 (CH_2), 35.93 (CH_3), 37.09 (CH_3), 51.12 (CH_2), 61.05 (CH), 62.15 (CH), 113.57 (C), 125.61 (CH), 127.38 (CH), 127.60 (C), 128.04 (CH), 128.04 (C), 128.33 (CH), 141.27 (C), 154.10 (C), 154.39 (C).

1x(CH_2) obscured by other signals.

Procedure B

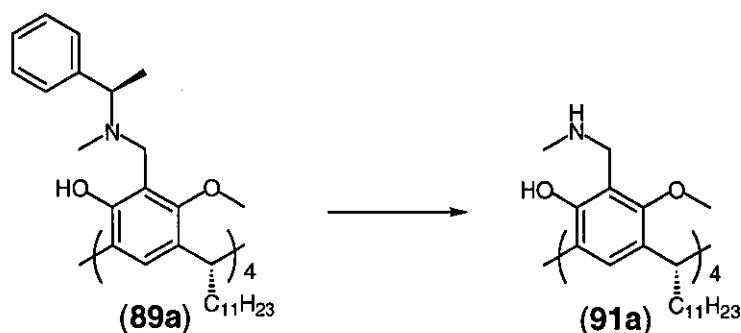
tetrakis-(*O*-Methylether) derivative (**73b**) (1.00 g, 0.604 mmol) was dissolved in dry toluene (15 mL) and stirred at 0 °C. DIBAL-H (1.5 M solution in toluene, 3.22 mL, 4.83 mmol) was added in one portion and the resulting solution was allowed to come to room temperature before being stirred for 3 hours. After this time the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium/sodium tartrate (10 mL), methanol (10 mL) and ethyl acetate (20 mL) and continued stirring for 12 hours. After this time the organic solution was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish a pale yellow oil. Purification by flash chromatography (silica gel, 5% methanol/dichloromethane) furnished the tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (**89b**) as a pale yellow oil, 0.91 g, 90%.

Procedure C

tetrakis-(*O*-Methylether) derivative (**73b**) (1.00 g, 0.604 mmol) was dissolved in THF (15 mL) and stirred at -78 °C. LiAlH_4 (183 mg, 4.83 mmol) was added in one portion and the resulting solution was allowed to come to room temperature before being

stirred for 3 hours. After this time the reaction mixture was quenched by the addition methanol (10 mL) and the solvents removed under reduced pressure. The resulting residue was partitioned between DCM. The organic solution was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish a pale yellow oil. Purification by flash chromatography (silica gel, 5% methanol/dichloromethane) furnished the tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (**89b**) as a pale yellow oil, 0.92 g, 93%.

tetrakis-(*N*-Methyl) derivative⁷³ (91a**)**

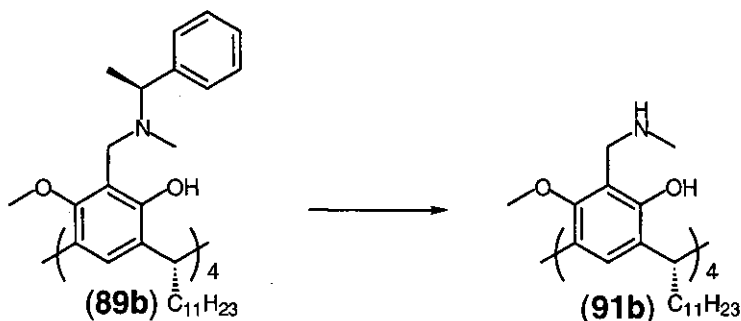


The tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (**89a**) (3.64 g, 2.079 mmol) was dissolved in a mixture of ethyl acetate (10 mL) and ethanol (100%, 10 mL). Hydrochloric acid (10.39 mmol, 2 M aq. solution) was added followed by palladium hydroxide on carbon (50 mg, 5 mol%) and the mixture was stirred at room temperature under a hydrogen filled balloon for 4 days or until the reaction was complete by TLC. After this time the reaction mixture was filtered, concentrated under reduced pressure, and the residue partitioned between dilute ammonium hydroxide solution and ethyl acetate. The organic layer was separated, washed with water and brine and dried over sodium sulfate. The solution was filtered and the solvent removed under reduced pressure, to afford the tetrakis-(*N*-methyl) derivative (**91a**) as a dark brown oil which was used without further purification, 2.07 g, 75%: ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, J = 6.8 Hz, 12H, -(CH₂)₉CH₃), 1.23-1.32 (m, 72H, -(CH₂)₉CH₃), 1.78-1.93 (m, 8H, -CH₂(CH₂)₉), 2.40 (s, 12H, NCH₃), 3.44 (s, 12H, OCH₃), 3.77 (d, J_{AB} = 13.6 Hz, 4H, -CH_AH_B-), 4.02 (d, J_{AB} = 13.6 Hz, 4H, -CH_AH_B-), 4.47 (t, J =

7.2 Hz, 4H, $-\text{CHCH}_2-$), 6.70 (s, 4H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.49 (CH_3), 23.08 (CH_2), 28.96 (CH_2), 29.77 (CH_2), 30.10 (CH_2), 30.16 (CH_2), 30.22 (CH_2), 30.28 (CH_2), 30.54 (CH_2), 32.32 (CH_2), 35.60 (CH_3), 36.13 (CH_2), 36.42 (CH_3), 48.26 (CH_2), 61.71 (CH), 114.68 (C), 126.02 (CH), 128.30 (C), 154.47 (C), 154.88 (C).

1x(C) obscured by other signals.

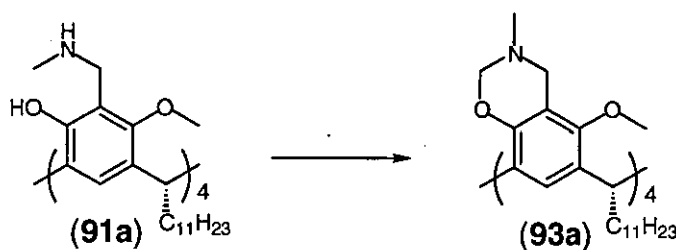
tetrakis-(*N*-Methyl) derivative⁷³ (91b)



The tetrakis-(*N*- α -methylbenzyl,*N*-methyl) derivative (89b) (3.64 g, 2.08 mmol) was dissolved in a mixture of ethyl acetate (10 mL) and ethanol (100%, 10 mL). Hydrochloric acid (10.39 mmol, 5 M aq. solution) was added followed by palladium hydroxide on carbon (50 mg, 5 mol%) and the mixture was stirred at room temperature under a hydrogen filled balloon for 4 days or until the reaction was complete by TLC. After this time the reaction mixture was filtered, concentrated under reduced pressure, and the residue partitioned between dilute ammonium hydroxide solution and ethyl acetate. The organic layer was separated, washed with water and brine and dried over sodium sulfate. The solution was filtered and the solvent removed under reduced pressure, to afford the tetrakis-(*N*-methyl) derivative (91b) as a dark brown oil which was used without further purification, 2.25 g, 80%: ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, $J = 6.8$ Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.22-1.31 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.77-1.93 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9$), 2.41 (s, 12H, NCH_3), 3.43 (s, 12H, OCH_3), 3.78 (d, $J_{AB} = 13.2$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.99 (d, $J_{AB} = 13.2$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 4.47 (t, $J = 7.2$ Hz, 4H, $-\text{CHCH}_2-$), 6.70 (s, 4H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11 (CH_3), 22.70 (CH_2), 28.60 (CH_2), 29.40 (CH_2), 29.73 (CH_2), 29.79 (CH_2), 29.85 (CH_2), 29.92

(CH₂), 30.17 (CH₂), 31.95 (CH₂), 35.31 (CH₃), 35.73 (CH₂), 36.10 (CH₃), 48.10 (CH₂), 61.32 (CH), 114.32 (C), 125.66 (CH), 127.88 (C), 127.93 (C), 154.09 (C), 154.53 (C).

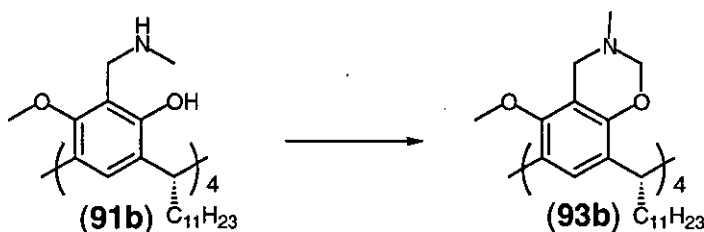
tetrakis-(3-Methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative⁷³ (93a)



The tetrakis-(*N*-methyl) derivative (**91a**) (210 mg, 0.157 mmol) was dissolved in absolute ethanol (2 mL) and the solution stirred at room temperature. Formaldehyde (37% aqueous solution, 0.063 mL, 0.787 mmol) was added and the mixture heated under reflux for 3 hours. After this time the reaction mixture was concentrated under reduced pressure and the residue partitioned between water and ethyl acetate. The organic solution was separated, dried over magnesium sulfate and the solvent removed under reduced pressure to afford the crude product as a pale yellow oil. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) furnished the tetrakis-(3-methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93a**) as a white crystalline solid, 189 mg, 87%; mp 57-60 °C; $[\alpha]_D^{25} +55$, $c=11.66$, CHCl₃; Anal. Calcd for C₈₈H₁₄₀N₄O₈: C, 76.47%; H, 10.21%; N, 4.05%; Found C, 76.54; H, 10.26; N, 3.97; ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, $J=6.8$ Hz, 12H, -(CH₂)₉CH₃), 1.23-1.29 (m, 72H, -(CH₂)₉CH₃), 1.75-1.85 (m, 8H, -CH₂(CH₂)₉), 2.45 (s, 12H, NCH₃), 3.42 (s, 12H, OCH₃), 3.80 (d, $J_{AB}=16.4$ Hz, 4H, -CH_AH_B-), 3.94 (d, $J_{AB}=16.4$ Hz, 4H, -CH_AH_B-), 4.44 (t, $J=7.6$ Hz, 4H, -CHCH₂-), 4.48 (d, $J_{AB}=9.6$ Hz, 4H, -NCH_AH_BO-), 4.67 (d, $J_{AB}=9.6$ Hz, 4H, -NCH_AH_BO-), 6.64 (s, 4H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 14.11 (CH₃), 23.07 (CH₂), 28.19 (CH₂), 29.77 (CH₂), 30.10 (CH₂), 30.13 (CH₂), 30.15 (CH₂), 30.24 (CH₂), 30.33 (CH₂), 32.31 (CH₂), 35.77 (CH₃), 35.96 (CH₂), 40.00 (CH₃), 49.10 (CH₂), 60.48 (CH), 83.39 (CH₂), 112.38 (C), 124.97 (CH), 128.14 (C), 129.33 (C), 149.56 (C), 154.02 (C); Analysis by chiral HPLC (Chiralcel OD column, 2%

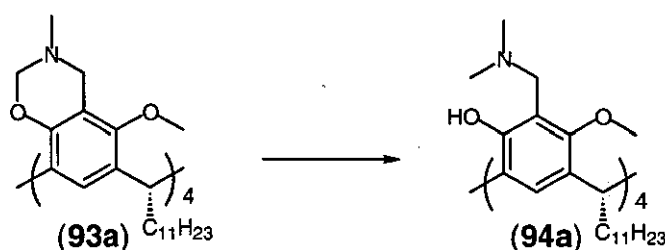
IPA/hexane) showed the product to be enantiomerically pure.

tetrakis-(3-Methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative⁷³ (93b)



The tetrakis-(*N*-methyl) derivative (**91b**) (2.12 g, 0.157 mmol) was dissolved in absolute ethanol (20 mL) and the solution stirred at room temperature. Formaldehyde (37% aqueous solution, 0.64 mL, 7.96 mmol) was added and the mixture heated under reflux for 12 hours. After this time the reaction mixture was concentrated under reduced pressure and the residue partitioned between water and ethyl acetate. The organic solution was separated, dried over magnesium sulfate and the solvent removed under reduced pressure to afford the tetrakis-(3-methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93b**) as a pale yellow oil. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) furnished the tetrakis-(3-methyl-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93b**) as a white crystalline solid, 2.21 g, 79%; mp 55-59 °C; $[\alpha]_D^{25}$ -54, $c=12.01$, CHCl_3 ; ν_{max} (DCM evap) 2924, 2852, 1467 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, $J=6.4$ Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.23-1.30 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.76-1.85 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9$), 2.45 (s, 12H, NCH_3), 3.42 (s, 12H, OCH_3), 3.80 (4H, d, $J_{AB}=16.4$ Hz, $-\text{CH}_A\text{H}_B-$), 3.94 (4H, d, $J_{AB}=16.4$ Hz, $-\text{CH}_A\text{H}_B-$), 4.44 (t, $J=7.6$ Hz, 4H, $-\text{CHCH}_2-$), 4.48 (4H, d, $J_{AB}=9.2$ Hz, $-\text{NCH}_A\text{H}_B\text{O}-$), 4.67 (4H, d, $J_{AB}=9.2$ Hz, $-\text{NCH}_A\text{H}_B\text{O}-$), 6.64 (s, 4H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11 (CH_3), 22.70 (CH_2), 28.19 (CH_2), 29.40 (CH_2), 29.73 (CH_2), 29.76 (CH_2), 29.79 (CH_2), 29.87 (CH_2), 29.96 (CH_2), 31.95 (CH_2), 35.41 (CH_3), 35.60 (CH_2), 39.64 (CH_3), 48.75 (CH_2), 60.12 (CH), 83.04 (CH_2), 112.03 (C), 124.62 (CH), 127.79 (C), 128.97 (C), 149.22 (C), 153.67 (C).

tetrakis-(2-[(Dimethylamino)methyl]) derivative⁷³ (**94a**)



Procedure A

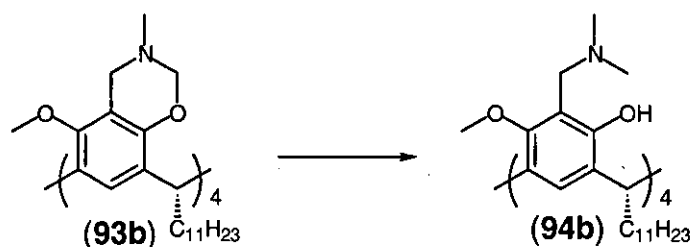
The *N*-methyl-tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93a**) (400 mg, 0.288 mmol) was dissolved in formic acid (5 mL, 96%) and heated under reflux for 3 hours or until the reaction was complete by TLC. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, 5% methanol/dichloromethane). Trituration of the combined fractions with methanol furnished the tetrakis-(2-[(dimethylamino)methyl]) derivative (**94a**) as a white solid, 360 mg, 90%; mp 87-89 °C; $[\alpha]_D^{25} +12$, $c=1.58$, CHCl_3 ; Anal. Calcd for $\text{C}_{88}\text{H}_{148}\text{N}_4\text{O}_8$: C, 76.03; H, 10.75; N, 4.03; Found C, 75.80; H, 10.60; N, 3.61. ν_{max} (DCM evap) 2925, 2781, 1595, 1459 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); d 0.86 (t, $J=6.4$ Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.22-1.30 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.77-1.92 (m, 8H, $-\text{CH}_2(\text{CH}_2)_9$), 2.23 (s, 24H, $\text{N}(\text{CH}_3)_2$), 3.42 (s, 12H, OCH_3), 3.52 (d, $J_{AB}=13.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.69 (d, $J_{AB}=13.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 4.49 (t, $J=6.8$ Hz, 4H, $-\text{CHCH}_2$), 6.73 (s, 4H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.46 (CH_3), 23.05 (CH_2), 28.87 (CH_2), 29.76 (CH_2), 30.08 (CH_2), 30.14 (CH_2), 30.22 (CH_2), 30.25 (CH_2), 30.49 (CH_2), 32.31 (CH_2), 36.27 (CH_3), 36.40 (CH_2), 44.68 (CH_3), 56.61 (CH_2), 61.45 (CH), 114.04 (C), 126.00 (CH), 127.91 (C), 128.34 (C), 154.48 (C), 154.71 (C).

Procedure B

N-Methyl-tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93a**) (0.50 g, 0.36 mmol) was dissolved in dry toluene (10 mL) and stirred at 0 °C. DIBAL-H (1.5 M

solution in toluene, 1.92 mL, 2.89 mmol) was added in one portion and the resulting solution was stirred for 3 hours at room temperature. After this time the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium/sodium tartrate (10 mL), methanol (10 mL) and ethyl acetate (20 mL) and continued stirring for 12 hours. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, 5% methanol/dichloromethane). Trituration of the combined fractions with methanol furnished the tetrakis-(2-[(dimethylamino)methyl]) derivative (**94a**) as a white solid, 387 mg, 77%.

tetrakis-(2-[(Dimethylamino)methyl]) derivative⁷³ (94b**)**



Procedure A

The *N*-methyl-tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93b**) (400 mg, 0.288 mmol) was dissolved in formic acid (5 mL, 96%) and heated under reflux for 3 hours or until the reaction was complete by TLC. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, 5% methanol/dichloromethane). Trituration of the combined fractions with methanol furnished the tetrakis-(2-[(dimethylamino)methyl]) derivative (**94b**) as a white solid, 361mg, 87%; mp 87-89 °C; $[\alpha]_D^{25}$ -12, $c=1.47$, CHCl_3 ; ν_{max} (DCM evap) 2925, 2782, 1595, 1459, 1354, 1091 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); δ 0.86 (t, $J=6.4$ Hz, 12H, $-(\text{CH}_2)_9\text{CH}_3$), 1.22-1.30 (m, 72H, $-(\text{CH}_2)_9\text{CH}_3$), 1.77-1.92 (m, 8H, $\text{CH}_2(\text{CH}_2)_9$), 2.23 (s, 24H, $\text{N}(\text{CH}_3)_2$), 3.42 (s, 12H, OCH_3), 3.52 (d, $J_{AB}=13.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.69 (d, $J_{AB}=13.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 4.48 (t, $J=7.2$ Hz, 4H,

-CHCH₂), 6.73 (s, 4H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 14.11 (CH₃), 22.70 (CH₂), 28.52 (CH₂), 29.40 (CH₂), 29.73 (CH₂), 29.78 (CH₂), 29.87 (CH₂), 29.89 (CH₂), 30.14 (CH₂), 31.95 (CH₂), 35.91 (CH₃), 36.07 (CH₂), 44.31 (CH₃), 56.25 (CH₂), 61.12 (CH), 113.61 (C), 125.73 (CH), 127.54 (C), 128.40 (C), 154.22 (C), 154.35 (C).

Procedure B

N-Methyl-tetrakis(3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**93b**) (250 mg, 0.18 mmol) was dissolved in dry toluene (5 mL) and stirred at 0 °C. DIBAL-H (1.5 M solution in toluene, 0.96 mL, 1.44 mmol) was added in one portion and the resulting solution was allowed to come to room temperature before being stirred for 3 hours. After this time the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium/sodium tartrate (5 mL), methanol (5 mL) and ethyl acetate (10 mL) and continued stirring for 12 hours. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, 5% methanol/dichloromethane). Trituration of the combined fractions with methanol furnished tetrakis-(2-[(dimethylamino)methyl]) derivative (**94b**) as a white solid, 210 mg, 84%.

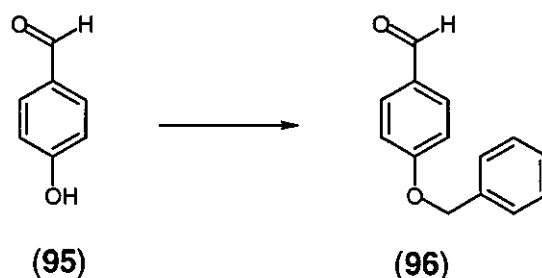
Procedure C

N-Methyl-tetrakis(3,4-dihydro-2-*H*-1,3-benzoxazine) derivative (**93b**) (200 mg, 0.145 mmol) was dissolved in THF (10 mL) and stirred at -78 °C. LiAlH₄ (24 mg, 0.636 mmol) was added in one portion and the resulting solution was allowed to come to room temperature before being stirred for 3 hours. After this time the reaction mixture was quenched by the addition methanol (10 mL) and the solvents removed under reduced pressure. The resulting residue was partitioned between DCM. The organic solution was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, 5% methanol/dichloromethane).

Trituration of the combined fractions with methanol furnished tetrakis-(2-[(dimethylamino)methyl]) derivative (**94b**) as a white solid, 108 mg, 54%:

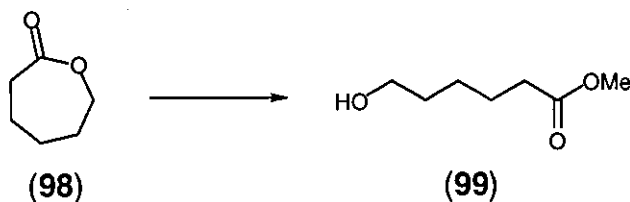
8.4 Experimental for Chapter 4

4-Benzyloxybenzaldehyde (96)



4-Hydroxybenzaldehyde (95) (12.20 g, 0.10 mol), benzyl chloride (12.60 mL, 0.11 mol), potassium carbonate (30.5 g) and methyl ethyl ketone (65 mL) were combined and stirred at reflux for 8 hours. After this time the reaction mixture was cooled, poured into a dilute aqueous solution of potassium hydroxide and extracted into ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish the crude product as a brown solid. Recrystallisation from methanol gave 4-benzyloxybenzaldehyde (96) as a beige crystalline solid, 11.5 g, 55%: mp 72-73 °C, ν_{\max} (DCM evap) 3365, 2829, 2745, 1686, 1603 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); δ 5.14 (s, 2H, $-\text{CH}_2-$), 7.06-7.08 (m, 2H, 2xArH), 7.38-7.43 (m, 5H, 5xArH), 7.82 (m, 2H, 2xArH), 9.87 (s, 1H, CHO); ^{13}C NMR (100 MHz, CDCl_3); δ 70.27 (CH_2), 115.15 (CH), 127.47 (CH), 128.32 (CH), 128.73 (CH), 130.15 (C), 131.98 (CH), 135.96 (C), 163.73 (C), 190.73 (CHO).

Methyl 6-hydroxyhexanoate⁷⁷ (99)



Caprolactone (98) (20 g, 0.175 mol) was stirred in methanol (50 mL) at room

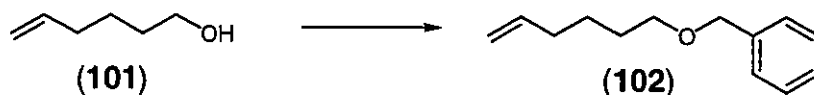
temperature. Sulfuric acid (conc, 0.1 mL) was added dropwise and the resulting mixture heated to reflux and stirred for 30 minutes. After this time the reaction mixture was concentrated and the residue partitioned between water and dichloromethane. The organic solution was separated, washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Purification *via* flash chromatography (silica gel, 5% ethyl acetate/light petroleum (40 °C-60 °C)) furnished methyl 6-hydroxyhexanoate (**99**) as a colourless oil, 23.05 g, 94%: ν_{\max} (NEAT) 3422, 2940, 2864, 1735 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3); δ 1.35-1.45 (m, 2H, $-\text{CH}_2-$), 1.53-1.72 (m, 4H, $-\text{CH}_2-$), 2.29-2.36 (m, 2H, $-\text{CH}_2-$), 3.61-3.66 (t, $J=6.6$ Hz, 2H, $-\text{CH}_2-$), 3.67 (s, 3H, $-\text{CH}_3$).

Methyl 6-oxohexanoate⁷⁸ (**100**)



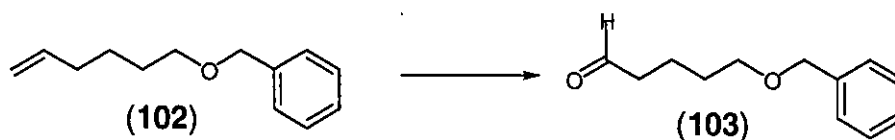
To a mixture of PCC (36.80 g, 0.171 mol) and 4Å molecular sieves (20 g) in dichloromethane (100 mL) at room temperature was added methyl 6-hydroxyhexanoate (**99**) (10 g, 68.4 mmol) slowly and the mixture was stirred for 1 hour. After this time, diethylether was added and the reaction mixture filtered through celite. The filtrates were concentrated under reduced pressure to furnish the crude product as a brown oil. Purification by Kugelrohr distillation gave methyl 6-oxohexanoate (**100**) as a colourless oil, 4.01 g, 46%: ν_{\max} (NEAT) 3435, 1734, 1638 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3); δ 1.64-1.69 (m, 4H, 2x- CH_2-), 2.32-2.38 (m, 2H, $-\text{CH}_2-$), 2.45-2.48 (m, 2H, $-\text{CH}_2-$), 3.67 (s, 3H, OCH_3), 9.77 (t, $J=1.63$ Hz, 1H, CHO).

6-(Benzyloxy)hex-1-ene (102)



To a suspension of sodium hydride (0.22 g, 5.49 mmol) in dry THF (50 mL) was added 5-hexen-1-ol (**101**) (0.50 g, 4.99 mmol) and the mixture heated at reflux for 30 minutes. Benzyl bromide (0.59 mL, 4.99 mmol) was added in one portion and the reaction mixture continued at reflux for 2 hours. After this time the reaction mixture was allowed to cool to room temperature and then partitioned between ether and water. The organic solution was separated and washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish a yellow oil. Purification by flash chromatography (silica gel, 5% ethyl acetate/light petroleum (40 °C-60 °C)) yielded 6-(benzyloxy)hex-1-ene (**102**) as a colourless oil, 0.69 g, 74%: ^1H NMR (250 MHz, CDCl_3); δ 1.43-1.52 (m, 2H, $-\text{CH}_2-$), 1.58-1.69 (m, 2H, $-\text{CH}_2-$), 2.02-2.11 (m, 2H, $-\text{CH}_2-$), 3.47 (t, $J=6.4$ Hz, 2H, $-\text{CH}_2-$), 4.50 (s, 2H, $-\text{CH}_2-$), 4.91-5.04 (m, 2H, $\text{CH}_2=\text{CH}$), 5.72-5.86 (m, 1H, $\text{CH}_2=\text{CH}$), 7.24-7.34 (m, 5H, ArH); ^{13}C NMR (66 MHz, CDCl_3); δ 25.44 (CH_2), 29.171 (CH_2), 33.52 (CH_2), 70.18 (CH_2), 72.81 (CH_2), 114.46 (CH_2), 127.44 (CH), 127.56 (CH), 128.29 (CH), 138.58 (C), 138.72 (alkene CH).

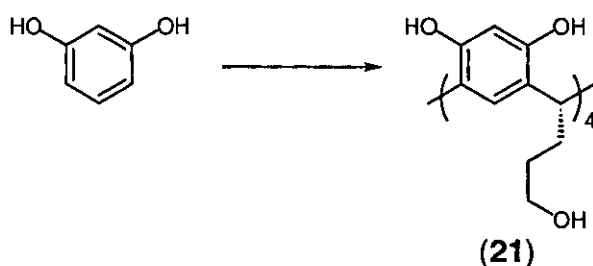
5-(Benzyloxy)pentanal⁸⁰ (103)



6-(Benzyloxy)hex-1-ene (**102**) (9.50 g, 49.90 mmol) was dissolved in dichloromethane (500 mL) and the solution was cooled to -78°C . Ozone was bubbled through the reaction mixture until the solution turned pale blue. After this time, nitrogen was bubbled through the mixture until the solution turned colourless. DMS was gradually

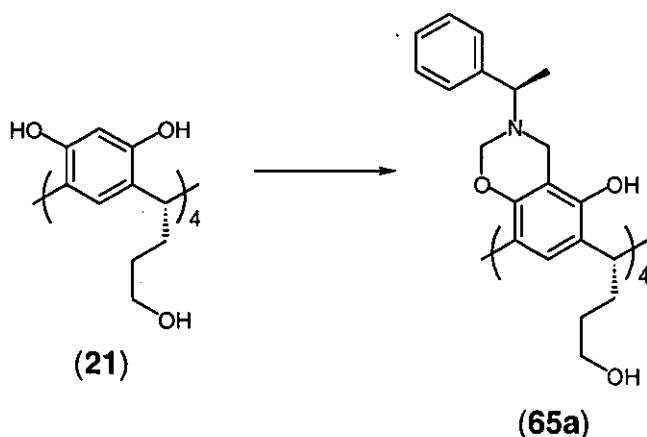
added to the reaction vessel and the solution was allowed to come to room temperature and stirred overnight. After this time, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, 10% ethyl acetate/light petroleum (40 °C-60 °C)) yielding 5-(benzyloxy)pentanal (**103**) as a colourless oil, 3.01 g, 32 %: ^1H NMR (250 MHz, CDCl_3); δ 1.62-1.77 (m, 4H, 2x- CH_2 -), 2.42 (dt, $J=6.5$ Hz, $J=2.0$ Hz 2H, - CH_2 -), 3.47 (t, $J=6.5$ Hz, 2H, - CH_2 -), 4.49 (s, 2H, - CH_2 -), 7.25-7.35 (m, 5H, ArH), 9.75 (t, $J=2.0$ Hz, 1H, - CHO); ^{13}C NMR (66 MHz, CDCl_3); δ 18.88 (CH_2), 29.07 (CH_2), 43.51 (CH_2), 69.67 (CH_2), 72.87 (CH_2), 127.50 (CH), 127.56 (CH), 128.38 (CH), 138.38 (C), 202.45 (CHO).

C-Hydroxypropylcalix[4]resorcinarene⁵ (**21**)



2,3-Dihydrofuran (6.08 mL, 80.6 mmol) was slowly added to a solution of resorcinol (8.87 g, 80.6 mmol) and hydrochloric acid (12 N, 15.2 mL) in methanol (60 mL), and the resulting mixture was stirred 16 hours under an atmosphere of nitrogen. After this time the reaction mixture was heated to 50 °C and stirred for 5 days. The resulting precipitate was then collected by filtration, washed with water and dried. The crude product was then suspended in THF, sonicated and filtered to give C-hydroxypropylcalix[4]resorcinarene (**21**) as a crystalline white solid, 8.68 g, 64%: ^1H NMR (400 MHz, DMSO); δ 1.34 (sept, $J=6.6$ Hz, 8H, - CH_2 -), 2.11 (q, $J=7.4$ Hz, 8H, - CH_2 -), 3.43 (q, $J=6.6$ Hz, 4H - CH_2OH -), 4.21 (q, $J=7.4$ Hz, 4H, - CH -), 4.33 (q, $J=5.2$ Hz, 4H, - CH_2OH), 6.16 (s, 4H, ArH), 7.24 (s, 4H, ArH), 8.91 (s, 8H, ArOH); ^{13}C NMR (100 MHz, CDCl_3); δ 30.43 (CH_2), 31.54 (CH_2), 33.09 (CH), 61.09 (CH_2), 102.66 (CH), 123.56 (C), 125.34 (CH), 151.97 (C).

tetrakis-(3-[(1*R*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (65a)



Procedure A

A suspension of *C*-hydroxypropylcalix[4]resorcinarene (**21**) (10.00 g, 14.86 mmol) in ethanol (absolute, 200 mL) was stirred at room temperature. Formaldehyde (37% aqueous solution, 12.01 mL, 0.148 mol) was added followed by (*R*)- α -methylbenzylamine (9.57 mL, 74.29 mmol) and the mixture heated to reflux and stirred at this temperature for 18 hours. After this time the solution was cooled in an ice bath and the resulting precipitate was collected *via* filtration and washed with copious amounts of cold methanol. Recrystallisation from dichloromethane/methanol furnished the tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**65a**) as a white crystalline solid, 10.45 g, 56%: mp 165–170 °C (decomp); $[\alpha]_D^{25} +117$, $c=1.10$, CHCl_3 ; mass spectrum (FAB⁺) m/z 1302 (MH^+); ν_{max} (NUJOL mull) 3342, 1601, 1347 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); δ 1.28 (d, $J=6.4\text{ Hz}$, 12H, CHCH_3), 1.52 (m, 8H, $-\text{CH}_2-$), 2.32–2.47 (m, 8H, $-\text{CH}_2-$), 3.63–3.75 (m, 8H, $-\text{CH}_2-$), 3.74 (d, $J_{\text{AB}}=17.6\text{ Hz}$, 4H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 3.95 (d, $J_{\text{AB}}=17.6\text{ Hz}$, 4H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 3.81 (q, $J=6.4\text{ Hz}$, 4H, $-\text{CHCH}_3$), 4.22 (t, $J=8.0\text{ Hz}$, 4H, $-\text{CHCH}_2$), 4.92 (d, $J_{\text{AB}}=10.4\text{ Hz}$, 4H, $-\text{NCH}_\text{A}\text{H}_\text{B}\text{O}-$), 5.13 (d, $J_{\text{AB}}=10.4\text{ Hz}$, 4H, $-\text{NCH}_\text{A}\text{H}_\text{B}\text{O}-$), 6.94–7.24 (m, 24H, ArH), 7.34 (s, 4H, OH), 7.66 (s, 4H, ArOH); ^{13}C NMR (100 MHz, CDCl_3); δ 21.44 (CH_3), 30.40 (CH_2), 31.59 (CH_2), 33.27 (CH), 44.57 (CH_2), 58.06 (CH), 62.08 (CH_2), 80.96 (CH_2), 108.97 (C), 121.64 (CH), 123.46 (C), 124.16 (C), 127.02 (CH), 128.25 (CH), 144.53 (C), 148.72 (C),

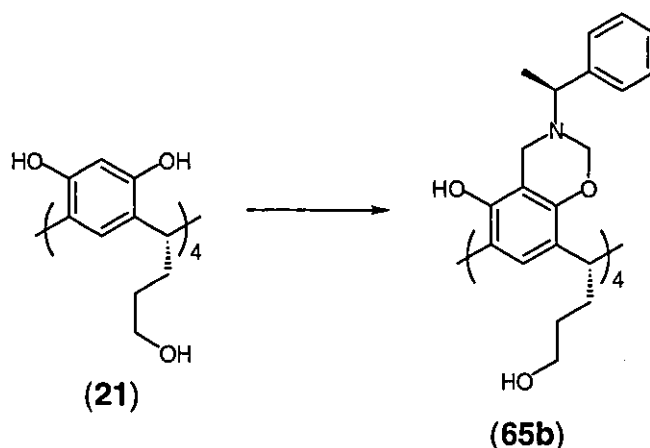
149.59 (C).

1x(CH) obscured by other signals.

Procedure B.

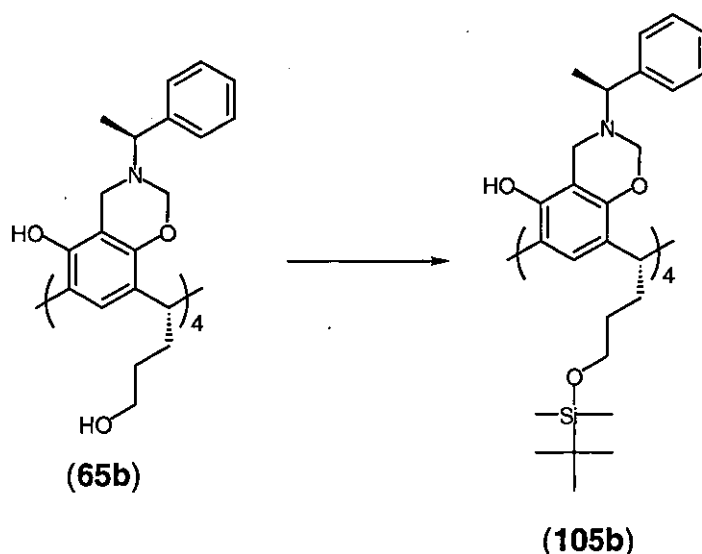
To a solution of *C*-hydroxypropylcalix[4]resorcinarene (**21**) (7.31 g, 10.86 mmol) in ethanol (absolute, 150 mL) was added bis(aminol ether) (10 g, 47.78 mmol) in one portion. The mixture was heated and stirred at reflux for 17 hours. After this time the solution was cooled in an ice bath and the resulting precipitate was collected by filtration and washed with copious amounts of cold methanol. Recrystallisation from dichloromethane/methanol furnished the tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**65a**) as a white crystalline solid (8.78g, 65%)

tetrakis-(3-[(1*S*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (65b)



C-Hydroxypropylcalix[4]resorcinarene (**21**) (10 g, 14.85 mmol), formaldehyde (37% aqueous solution, 12.01 mL, 0.148 mol) and (*S*)- α -methylbenzylamine (9.57 mL, 74.29 mmol) were reacted together in ethanol (200 mL) according to procedure A to give the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**65b**) as a white crystalline solid, 13.3 g, 71%; mp 171-176 °C (decomp); Anal. Calcd for C₈₀H₉₂N₄O₁₂: C, 73.82; H, 7.13; N, 4.30; Found C, 73.18; H, 7.05; N, 4.23.

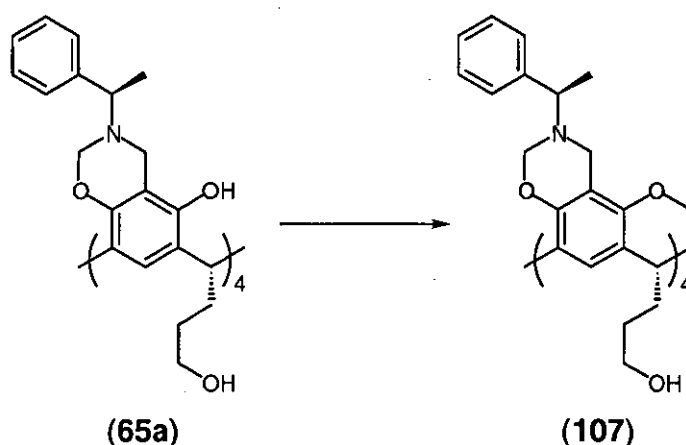
tetrakis-(*tert*-Butyldimethylsilylether) derivative (105b)



tetrakis-(3-[(1*S*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**65b**) (10 g, 7.97 mmol) was dissolved in a mixture of pyridine (50 ml) and triethylamine (9.89 mL, 70.97 mmol) the solution cooled to 0 °C. TBDMSCl (6.01 g, 39.87 mmol) was added portionwise and the mixture allowed to come to room temperature before being stirred for 3 hours. After this time the solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was separated and washed with more water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield an off white solid. Recrystallisation from methanol-dichloromethane furnished the tetrakis-(*tert*-butyldimethylsilylether) derivative (**105b**) as a white solid, 10.94 g, 80%: mp 110-112 °C; $[\alpha]_D^{25}$ -94, $c=1.06$, CHCl_3 ; mass spectrum (FAB^+) m/z 1758 (MH^+); Anal. Calcd for $\text{C}_{104}\text{H}_{148}\text{N}_4\text{O}_{12}\text{Si}_4$: C, 71.02; H, 8.49; N, 3.18; Found C, 70.96; H, 8.48; N, 3.15; ν_{max} (DCM evap) 3360, 2928, 2856, 1600, 1469, 1255, 1098 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); δ 0.00 (s, 24H, $(\text{CH}_3)_2^t\text{BuSi}$), 0.86 (s, 36H, ^tBu), 1.22 (d, $J=8.0$ Hz, 12H, CHCH_3), 1.46 (m, 8H, $-\text{CH}_2-$), 2.15 (m, 8H, $-\text{CH}_2-$), 3.59 (t, $J=6.4$ Hz, 8H, $-\text{CH}_2\text{OTBDMS}-$), 3.64 (d, $J_{AB}=17.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.88 (d, $J_{AB}=17.6$ Hz, 4H, $-\text{CH}_A\text{H}_B-$), 3.74 (q, $J=6.4$ Hz, 4H, $-\text{CHCH}_3$), 4.86 (d, $J_{AB}=12.0$ Hz, 4H, $-\text{NCH}_A\text{H}_B\text{O}-$), 5.00

(d, $J_{AB}=12.0$ Hz, 4H, $-\text{NCH}_A\text{H}_B\text{O}-$), 6.87-7.18 (m, 24H, ArH), 7.57 (s, 4H, ArOH) ppm;
 ^{13}C NMR (100 MHz, CDCl_3); δ -5.21 (CH_3), 18.43 (C), 21.45 (CH_3), 26.07 (CH_3), 29.80 (CH_2), 31.07 (CH_2), 32.20 (CH), 44.55 (CH_2), 58.07 (CH), 62.88 (CH_2), 80.97 (CH_2), 109.07 (C), 121.02 (CH), 123.32 (C), 124.03 (C), 127.01 (CH), 127.04 (CH), 128.22 (CH), 144.53 (C), 148.78 (C), 149.69 (C).

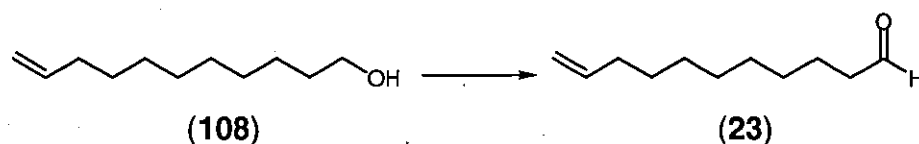
tetrakis-(*O*-Methylether) derivative (107)



To a solution of tetrakis-(3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**65a**) (0.50 g, 0.398 mmol) in dry THF (50 mL) at -78°C was added *n*-BuLi (1.6 M solution in hexanes, 1.00 mL, 1.59 mmol) dropwise and the resulting mixture was stirred for 15 min. After this time methyl triflate (0.18 mL, 1.59 mmol) was added dropwise and the solution stirred for 30 min, before the reaction mixture was quenched by the addition of water. The reaction was allowed to come to room temperature before being concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate and water and the organic solution separated, washed with more water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) furnished the tetrakis-(*O*-methylether) derivative (**107**) as a white solid, 200 mg, 38%; mp 160°C (decomp); $[\alpha]_D^{25}+125$, $c=1$, CHCl_3 ; mass spectrum (FAB $^+$) m/z 1358 (MH^+), 1380 (MNa^+); ν_{max}

(DCM evap) 3361, 2938, 2869, 1590, 1470, 1454 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); δ 1.37 (t, $J=6.4$ Hz, 12H, CHCH_3), 1.59-1.67 (m, 8H, $-\text{CH}_2-$), 1.82-2.04 (m, 8H, $-\text{CH}_2-$), 3.26 (s, 12H, OCH_3), 3.65 (t, $J=6.4$ Hz, 8H, $-\text{CH}_2-$), 3.77 (q, $J=6.4$ Hz, 4H, $-\text{CHCH}_3$), 3.82 (4H, d, $J_{AB}=16.8$ Hz, $-\text{CH}_A\text{H}_B-$), 4.13 (4H, d, $J_{AB}=16.8$ Hz, $-\text{CH}_A\text{H}_B-$), 4.45 (t, $J=7.6$ Hz, 4H, $-\text{CHCH}_2$), 4.60 (4H, d, $J_{AB}=10.0$ Hz, $-\text{NCH}_A\text{H}_B\text{O}-$), 4.66 (4H, d, $J_{AB}=10.0$ Hz, $-\text{NCH}_A\text{H}_B\text{O}-$), 6.76 (s, 4H, ArH), 7.24-7.29 (m, 20H, ArH), 7.66 (4H, s, OH); ^{13}C NMR (100 MHz, CDCl_3); δ 21.25 (CH_3), 31.53 (CH_2), 31.94 (CH_2), 35.33 (CH_3), 44.62 (CH_2), 57.40 (CH), 60.10 (CH), 63.00 (CH_2), 79.64 (CH_2), 112.53 (C), 124.49 (CH), 127.37 (CH), 127.46 (CH), 127.78 (C), 128.37 (C), 128.44 (CH), 143.97 (C), 150.22 (C), 153.63 (C).

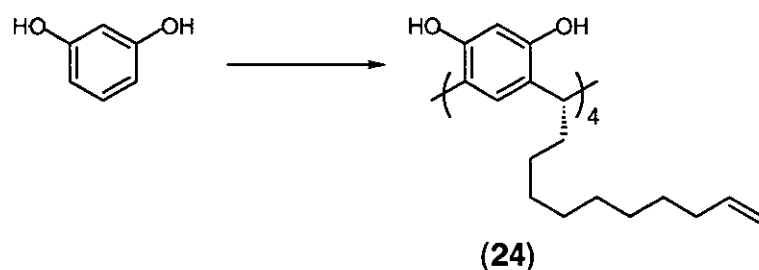
Undec-10-enal⁸¹ (23)



To a mixture of PCC (31.47 g, 0.146 mol) and 4Å molecular sieves (50 g) in dichloromethane (150 mL) at 0 °C was added alcohol 10-undecen-1-ol (**108**) (10 g, 68.4 mmol) in one portion. The mixture was allowed to come to room temperature and stirred for 1 hour. After this time, diethyl ether was added and the reaction mixture filtered through celite. The filtrates were concentrated under reduced pressure to furnish the crude product as a brown oil. Purification by flash column chromatography (silica gel, 4% ethyl acetate/light petroleum (40 °C-60 °C)) furnished undec-10-enal (**23**) as a colourless oil, 6.72 g, 68%: HRMS (EI) calcd for $\text{C}_{11}\text{H}_{20}\text{O}$ (M^+) 167.14359; Found 167.14367; ν_{max} (NEAT) 3432, 2926, 1727 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); δ 1.30-1.37 (m, 10H, 5x- CH_2 -), 1.61-1.65 (m, 2H, $-\text{CH}_2-$), 2.01-2.05 (m, 2H, $-\text{CH}_2-$), 2.40-2.44 (m, 2H, $-\text{CH}_2-$), 4.91-5.01 (m, 2H, $-\text{CH}_2\text{CH}-$), 5.76-5.84 (m, 1H, $-\text{CH}_2\text{CH}-$), 9.76 (s, 1H, CHO); ^{13}C NMR (100 MHz, CDCl_3); δ 22.08 (CH_2), 28.89 (CH_2),

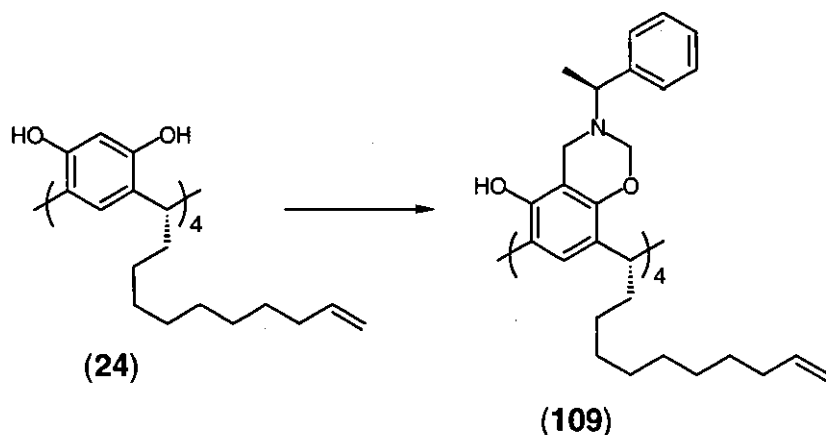
29.04 (CH₂), 29.15 (CH₂), 29.26 (CH₂), 29.30 (CH₂), 33.78 (CH₂), 43.92 (CH₂), 114.18 (CH₂), 139.15 (CH), 202.92 (CHO).

C-Decenylcalix[4]resorcinarene²³ (24)



Hydrochloric acid (12 N, 13.31 ml) was added dropwise to a solution of resorcinol (9.16 g, 83.19 mmol) and 10-undecenal (14.00 g, 83.19 mmol) in ethanol (absolute, 80 mL) at 0 °C. The mixture was stirred at 60 °C for 16 hours before being poured into de-ionised water (300 mL). The resulting red precipitate was collected by filtration and washed with hot water. Recrystallisation from acetonitrile furnished C-decenylcalix[4]resorcinarene (24) as a yellow solid, 8.56 g, 43%: mass spectrum (FAB⁺) *m/z* 1040/1 (M⁺), 1063/4 (M+Na⁺) ¹H (400 MHz, CDCl₃) 1.28 (m, 48H, -(CH₂)₆-), 2.04 (m, 8H, -(CH₂)CH=CH_AH_B), 2.20 (bm, 8H, -(CH₂)₂-), 4.28 (bt, 4H, RCHAr₂), 4.91 (dd, *J*_A=10.0 Hz, *J*_A=0.8 Hz, 4H, RCH=CH_AH_B), 5.00 (dd, *J*_A=17.2 Hz, *J*_A=1.6 Hz, 4H, RCH=CH_AH_B), 5.75-5.86 (m, 4H, RCH=CH_AH_B), 6.12 (s, 4H, ArH), 7.21 (s, 4H, ArH), 9.63 (m, 8H, ArOH).

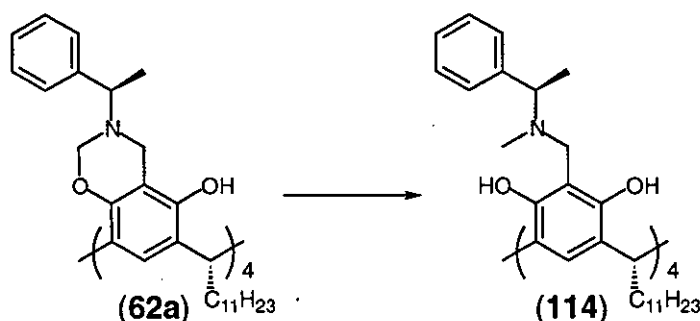
tetrakis-(3-[(1*S*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (109)



A solution of *C*-decenylcalix[4]resorcinarene (**24**) (5.28 mmol, 5.00 g) in ethanol (absolute, 100 mL) was cooled to 0 °C. Formaldehyde (37% aqueous solution, 52.80 mmol, 4.28 mL) and (*S*)- α -methylbenzylamine (26.43 mmol, 3.40 mL) were both added in one portion sequentially before the mixture was heated to reflux and stirred for 20 hours. After this time the mixture was cooled in an ice bath and the resulting precipitate collected. Recrystallisation from methanol-dichloromethane furnished the tetrakis-(3-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**109**) as a yellow crystalline solid (5.2 g, 61%) mp=69-75°C; mass spectrum (FAB⁺) m/z 1623 (MH⁺); $[\alpha]_D^{25}$ -95, $c=1.21$, CHCl₃; ν_{\max} 3362, 2925, 2853, 1639, 1600, 1469 cm⁻¹; ¹H NMR (400 MHz, CDCl₃); δ 1.26-1.39 (m, 48H, -(CH₂)₆CH=CH₂), 2.03 (q, $J=6.8$ Hz), 8H, -CH₂-), 2.18 (m, 8H, -CH₂-), 3.72 (d, $J_{AB}=17.6$ Hz, 4H, -CH_AH_B-), 3.80 (q, $J=6.4$ Hz, 4H, -CHCH₃), 3.95 (d, $J_{AB}=17.6$ Hz, 4H, -CH_AH_B-), 4.19 (t, $J=6.4$ Hz, 4H, -CHCH₂-), 4.91-5.01 (m, 12H, -(CH₂)₆CH=CH₂+NCH_AH_BO-), 5.12 (d, $J_{AB}=10.0$ Hz, 4H, -NCH_AH_BO-), 5.82 (m, 4H, -(CH₂)₆CH=CH₂), 6.94-7.25 (m, 24H, ArH), 7.65 (s, 4H, ArOH); ¹³C NMR (100 MHz, CDCl₃); δ 21.42 (CH₃), 28.10 (CH₂), 29.01 (CH₂), 29.18 (CH₂), 29.60 (CH₂), 29.70 (CH₂), 32.67 (CH), 33.72 (CH₂), 33.84 (CH₂), 44.56 (CH₂), 58.07 (CH), 80.96 (CH₂), 108.96 (C), 114.17 (CH₂), 121.10 (CH₂), 123.45 (C), 124.30 (C), 127.04, (CH), 128.22 (CH), 139.16 (CH), 144.51 (C), 148.74 (C), 149.59 (C). 1x(CH), 1x(CH₂) obscured by other signals.

8.5 Experimental for Chapter 5

tetrakis-(*N*- α -Methylbenzyl,*N*-methyl) derivative (114)



Procedure A

tetrakis-(3-[(1*R*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (62a) (1.00 g, 0.604 mmol) was dissolved in anhydrous toluene (15 mL) and stirred at 0 °C. DIBAL-H (1.5 M solution in toluene, 3.22 mL, 4.83 mmol) was added in one portion and the resulting solution was allowed to come to room temperature before being stirred for 3 hours. After this time the reaction mixture was quenched by the addition of a saturated aqueous solution of potassium/sodium tartrate (10 mL), methanol (10 mL) and ethyl acetate (20 mL) and continued stirring for 12 hours. After this time the organic solution was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish the title compound as an orange crystalline solid, 0.92 g, 93%; mp 84-88 °C; $[\alpha]_D^{25} +12$, $c=1.59$, CHCl₃; mass spectrum (FAB⁺) m/z 1694/5 (MH⁺); Anal. Calcd for C₁₁₂H₁₆₄N₄O₈: C, 79.37; H, 9.77; N, 3.30; Found: C, 79.29; H, 9.66; N, 3.20; ν_{\max} (DCM evap) 3282, 2923, 2852, 1609, 1463, 1304, 701 cm⁻¹; ¹H NMR (400 MHz, C₆D₆ v.t. at 70 °C): δ 0.91 (t, $J=8.0$ Hz, 12H, -(CH₂)₇CH₃), 1.16 (d, $J=4$ Hz, 12H, -CHCH₃), 1.38 (m, 56H, -(CH₂)₇CH₃), 1.49-1.64 (m, 16H, -(CH₂)₂(CH₂)₇), 1.87 (s, 12H, NCH₃), 2.54 (m, 8H, -CH₂-), 3.47 (q, $J=8.0$ Hz, 4H, -CHCH₃), 3.79 (d, $J_{AB}=16.1$ Hz, 4H, -CH_AH_B-), 3.88 (d, $J_{AB}=16.1$ Hz, 4H, -CH_AH_B-), 4.85 (t, $J=8.0$ Hz, 4H, -CHCH₂), 6.96-7.16 (m,

24H, ArH), 7.65 (s, 4H, OH); ^{13}C NMR (100 MHz, C_6D_6 , v.t. at 70 °C); δ 14.11 (CH_3), 16.71 (CH_3), 23.00 (CH_2), 28.92 (CH_2), 29.76 (CH_2), 30.09 (CH_2), 30.14 (CH_2), 30.20 (CH_2), 30.25 (CH_2), 30.29 (CH_2), 32.34 (CH_2), 34.30 (CH_3), 34.76 (CH_2), 37.39 (CH), 52.80 (CH_2), 62.74 (CH), 109.06 (C), 122.77 (CH), 127.66 (CH), 128.42 (CH), 128.60 (CH), 141.20 (C);

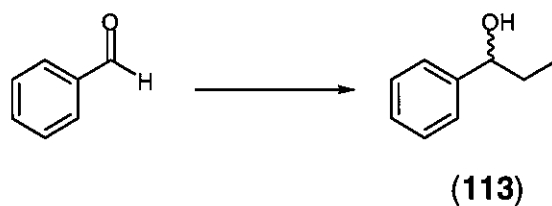
2x(C) obscured by C_6D_6 .

Procedure B

tetrakis-(3-[(1*R*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine) derivative (**62a**) (1.00 g, 0.604 mmol) was dissolved in formic acid (96%, 20 mL) and stirred at reflux for 4 hours. After this time the reaction mixture was poured into an ice cold solution aqueous ammonia solution (5 M, excess) and extracted into dichloromethane. The organic solution was separated, washed with water and brine solution and dried over magnesium sulfate. The mixture was filtered and the filtrates were concentrated under reduced pressure to furnish the title compound as a pale orange solid, 0.84 g, 84%.

General Procedure for the Enantioselective Addition of Diethylzinc to Benzaldehyde.

1-Phenyl-1-propanol⁸⁴ (**113**)

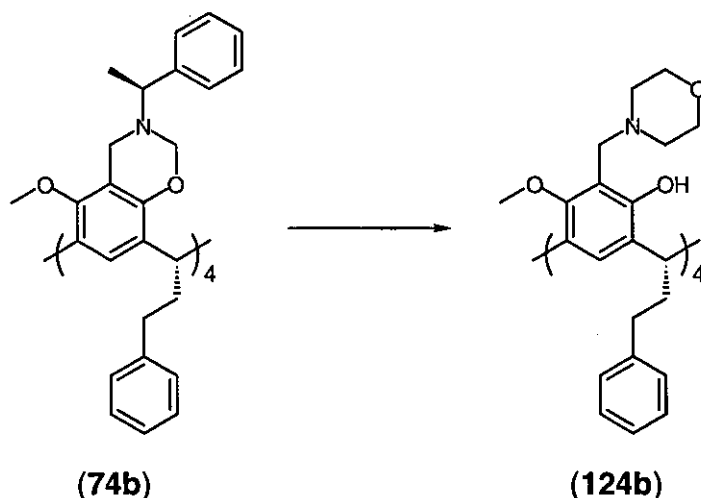


The required ligand (5 mol%, 0.05 mmol) was dissolved in toluene (1 mL) and stirred at room temperature under an atmosphere of nitrogen. Diethylzinc (2.2 mmol) was

added slowly to the reaction vessel and the resulting yellow solution cooled to 0 °C. Benzaldehyde (1 mmol) was added dropwise and the solution was allowed to come to room temperature before being stirred for 12 hours. After this time the reaction mixture was partitioned between aqueous hydrochloric acid (2 N) and diethyl ether. The organic layer was separated, dried over sodium sulfate, filtered and concentrated to furnish the crude product as a yellow oil. Purification by flash chromatography (silica gel, 20% ethyl acetate-light petroleum (40 °C-60 °C)) gave 1-phenyl-1-propanol as a colourless oil. HRMS (EI):calcd for $C_9H_{12}O$ (M^+) 136.08881; Found 136.08860; IR (NEAT) 3374 cm^{-1} . The enantioselectivity of the reaction was subsequently determined by chiral HPLC (Chiralcel OD, eluent = 98:2 Hexane/IPA, flow rate 0.5 mL/min)

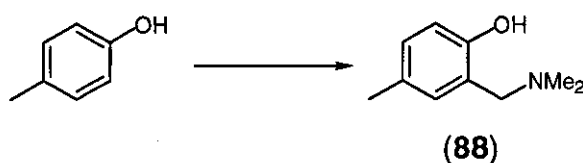
8.5 Experimental for Chapter 6

tetra(Morpholino) derivative (124b)



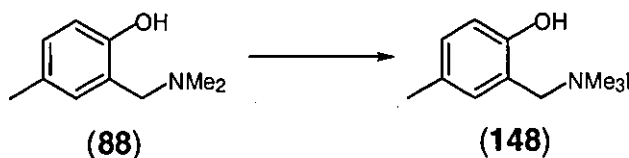
The tetrakis-(O-methylether) derivative (**74b**) (1.00 g, 0.65 mmol) was dissolved in morpholine (10 mL) and the mixture was heated under reflux for 5 hours. After this time, the morpholine was removed by distillation and the residue subjected to flash chromatography (silica gel, 2% methanol/dichloromethane) to isolate the tetra(morpholino) derivative (**124b**) as a cream solid, 0.23 g, 26%; mp=146-148 °C; $[\alpha]_D^{25} +10$, $c=0.55$, CHCl_3 ; mass spectrum (FAB⁺) m/z 1357.7466 (MH⁺), 1356.7407 (M⁺); Anal. Calcd for $\text{C}_{104}\text{H}_{108}\text{N}_4\text{O}_8$: C, 80.99; H, 7.07; N, 3.63; Found C, 80.64; H, 6.95; N, 3.50: ν_{max} (DCM evap) 3423, 2933, 2852, 2361, 1455, 1117 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 2.04-2.35 (m, 8H, $-\text{CH}_2-$), 2.47-2.77 (m, 24H, $-\text{CH}_2-$), 3.43 (s, 12H, OCH_3), 3.61-3.77 (m, 24H, $-\text{CH}_2-$), 4.61 (t, $J=7.4$ Hz 4H, $-\text{CHCH}_2$), 6.86 (s, 4H, ArH), 7.05-7.25 (m, 20H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 34.62 (CH_2), 35.61 (CH_3), 38.01 (CH_2), 52.83 (CH_2), 55.26 (CH_2), 61.09 (CH), 66.77 (CH_2), 112.66 (C), 125.47 (CH), 125.70 (CH), 127.37 (C), 128.08 (C), 128.19 (CH), 128.42 (CH), 142.78 (C), 154.14 (C), 154.83 (C).

2-[(Dimethylamino)methyl]-4-methylbenzen-1-ol (88)



Dimethylamine (40% aqueous solution, 11.49 mL, 0.102 mol) was added dropwise to a solution of formaldehyde (37% aqueous solution, 8.27 mL, 0.102 mol) in ethanol (absolute, 100 ml) at 0 °C. The mixture was stirred for 1 hour before para-cresol (11.03 g, 0.102 mol) was added in one portion. The resulting solution was heated to reflux and stirred for 12 hours. After this time the reaction mixture was cooled to room temperature before being concentrated under reduced pressure. The residue was subjected to flash chromatography (silica gel 50% ethyl acetate/light petroleum (40 °C-60 °C)) to furnish the title compound as a pale yellow oil, 10.32 g, 67%: HRMS (EI): (*m/z*) calcd for C₁₇H₁₉NO (*M*⁺) 165.11536; Found: 165.11531; ν_{max} (NEAT) 2951, 2826, 1600, 1500, 1261, 816 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3H, ArCH₃), 2.31 (s, 6H, N(CH₃)₂), 3.58 (s, 2H, -CH₂-), 6.71 (d, *J*=8.0 Hz, 1H, ArH), 6.76 (d, *J*=1.6 Hz, 1H, ArH), 6.94 (d, *J*=8.0 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 20.45 (CH₃), 44.47 (CH₃), 62.78 (CH₂), 115.81 (CH), 121.55 (C), 127.59 (C), 128.92 (CH), 129.14 (CH), 155.62 (C).

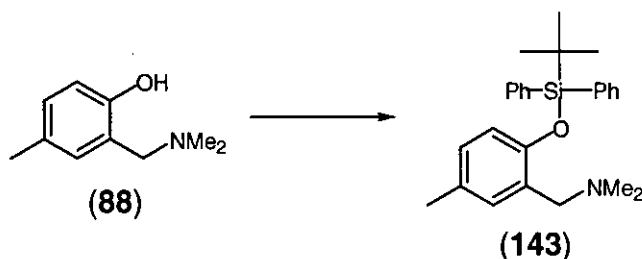
Quaternary ammonium salt (148)



Methyl iodide (9.42 mL, 151.31 mmol) was added in one portion to a solution of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (88) (5.00 g, 30.25 mmol) in diethyl ether (40 mL) and the mixture stirred for 24 hours. After this time the evolved precipitate was collected by filtration, washed with excess diethyl ether and dried at

the pump, to furnish the quaternary ammonium salt (**148**) as a colourless solid, 9.29 g, 99%: mp 168–169 °C; HRMS (FAB): (m/z) calcd for $C_{11}H_{18}NO$ ($M-I^+$) 180.13884; Found: 180.13843; Anal. Calcd for $C_{11}H_{18}NOI$: C, 43.00%; H, 5.91%; N, 4.55%. Found C, 42.84%; H, 5.87%; N, 4.41; ν_{\max} (Nujol) 3267, 1615, 1377, 1263 cm^{-1} ; 1H NMR (400 MHz, DMSO): δ 2.24 (s, 3H, $ArCH_3$), 3.05 (s, 6H, $N(CH_3)_3$), 4.42 (s, 2H, $-CH_2-$), 6.88 (d, $J=8.2$ Hz, 1H, ArH), 7.15–7.17 (dd, $J=8.2$ Hz, $J=2.0$ Hz, 1H, ArH), 7.19 (d, $J=1.6$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO): δ 19.86 (CH_3), 51.94 (CH_3), 63.05 (CH_2), 114.18 (C), 115.87 (CH), 127.75 (C), 132.42 (CH), 134.61 (CH), 154.88 (C).

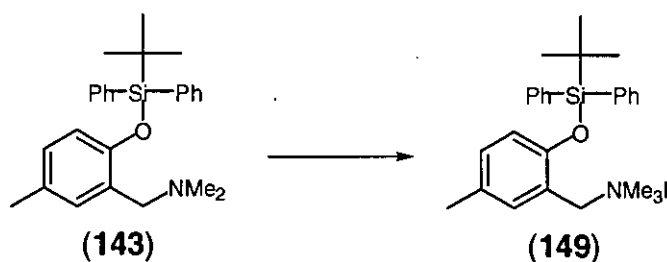
***N,N*-Dimethyl-(2-[[1-(1,1-dimethylethyl)-1,1-diphenylsilyl]oxy]-5-methylphenyl)methanamine (**143**)**



TBDPSCI (8.65 mL, 33.28 mmol) was added dropwise to a solution of 2-[(dimethylamino)methyl]-4-methylbenzen-1-ol (5.00 g 30.26 mmol), triethylamine (6.32 mL, 45.39 mmol) and 4-DMAP (5.00 mg) in dichloromethane (100 mL) at room temperature. The mixture was stirred for 12 hours before being concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel 10% methanol/dichloromethane) to furnish a colourless oil that slowly crystallised. Recrystallisation from acetonitrile gave *N,N*-dimethyl-(2-[[1-(1,1-dimethylethyl)-1,1-diphenylsilyl]oxy]-5-methylphenyl)methanamine (**143**) as a white solid, 8.00 g, 65%; HRMS (EI): (m/z) calcd. for $C_{26}H_{33}NOSi$ (M^+) 403.23314; Found 403.23331; Anal. Calcd. for $C_{26}H_{33}NOSi$: C, 77.36%; H, 8.25%; N, 3.47%; Found C, 77.27%; H, 8.17%; N, 3.32%; ν_{\max} (DCM evap) 3871, 2932, 1499, 1427, 1259 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 9H, tBu), 2.19 (s, 3H, $ArCH_3$), 2.33 (s, 6H, $N(CH_3)_3$), 3.62 (s, 2H, -

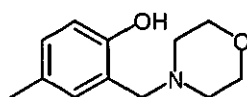
CH₂-), 6.31 (d, $J=8.4$ Hz, 1H, ArH), 6.52 (dd, $J=8.4$ Hz, $J=2.0$ Hz, 1H, ArH), 7.16 (d, $J=2.0$ Hz, 1H, ArH), 7.32 (6H, m, ArH), 7.71-7.73 (4H, m, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 19.57 (CH₃), 20.50 (C), 26.65 (CH₃), 45.64 (CH₃), 57.77 (CH₂), 118.57 (CH), 127.14 (CH), 127.81 (CH), 128.29 (C), 129.79 (CH), 129.95 (C), 131.19 (CH), 132.96 (C), 135.45 (CH), 151.40 (C).

Quaternary ammonium salt (149)



Methyl iodide (4.62 mL, 74.30 mmol) was added in one portion to a solution of *N,N*-dimethyl-2-(2-(1-(1,1-dimethylethyl)-1,1-diphenylsilyl)oxy-methylphenyl)-5-methylphenylmethanamine (**143**) (6.00 g, 14.86 mmol) in diethyl ether (60 mL) and the mixture stirred for 24 hours. After this time the evolved precipitate was collected by filtration, washed with excess diethyl ether and dried at the pump, to furnish the desired product as a colourless solid, 8.10 g, 99%: mp 185 °C (decomp); HRMS (EI): (m/z) calcd for C₁₁H₁₈NOSi (M-I⁺) 418.25662; Found 418.25662; Anal. Calcd for C₂₇H₃₆NOSi: C, 59.03; H, 6.68; N, 2.49; Found: C, 59.43; H, 6.66; N, 2.39; ν_{\max} (DCM evap) 2924, 1500, 1465, 1262 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.11 (s, 9H, ^{*t*}Bu), 2.24 (s, 3H, ArCH₃), 3.15 (s, 9H, N(CH₃)₃), 4.94 (s, 2H, -CH₂-), 6.51 (d, $J=8.6$ Hz, 1H, ArH), 6.85 (dd, $J=8.6$ Hz, $J=2.0$ Hz, 1H, ArH), 7.37-7.65 (11H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 19.53 (CH₃), 20.37 (C), 27.01 (CH₃), 53.04 (CH₃), 64.53 (CH₂), 116.90 (C), 119.96 (CH), 128.18 (CH), 128.27 (CH), 130.58 (CH), 131.40 (C), 131.72 (C), 132.95 (CH), 135.13 (CH), 153.01 (C).

4-Methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**)



(**137**)

Procedure A

2-[(Dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) (0.50 g, 3.03 mmol) was dissolved in morpholine (7 mL) and stirred at reflux for 12 hours. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 4-methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**) as a colourless oil, 0.52 g, 82%: HRMS (EI): (m/z) calcd for $C_{12}H_{17}NO_2$ (M^+) 207.12593; Found 207.12605; ν_{\max} (NEAT) 2924, 2852, 1599, 1499, 1119 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H, $ArCH_3$), 2.55 (bm, 4H, 2x- CH_2 -), 3.66 (s, 2H, $-CH_2-$), 3.73 (t, $J=4.0$ Hz, 4H, 2x- CH_2 -), 6.71 (d, $J=8.0$ Hz, 1H, ArH), 6.78 (d, $J=4.0$ Hz, 1H, ArH), 6.96 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.97 (CH_2), 61.91 (CH_2), 66.83 (CH_2), 115.86 (CH), 120.37 (C), 128.39 (C), 129.37 (CH), 129.40 (CH), 155.12 (C).

Procedure B

6-Methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) (253 mg, 1.00 mmol) was dissolved in morpholine (5 mL) and stirred at reflux for 12 hours. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 4-methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**) as a colourless oil, 106 mg, 51%.

Procedure C

4-Methyl-2-((methyl[(1*S*)-1-benzyl]amino)methyl)benzen-1-ol (**85b**) (241 mg, 1 mmol) was dissolved in morpholine (5 mL) and stirred at reflux for 12 hours. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 4-methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**) as a colourless oil, 176 mg, 85%.

Procedure D

Quaternary ammonium salt (**149**) (545 mg, 1.00 mmol) was dissolved in morpholine (1.0 mL) and stirred at room temperature. TBAF (1M sol in THF, 1.10 mL, 1.10 mmol) was added in one portion and the mixture stirred overnight at room temperature. After this time, the reaction mixture was concentrated under reduced pressure and the resulting residue subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 4-methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**) as a colourless oil, 191 mg, 100%.

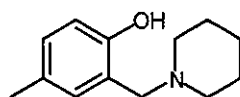
Procedure E

Quaternary ammonium salt (**149**) (545 mg, 1.00 mmol) was dissolved in morpholine (5 mL) and stirred at reflux for 36 hours. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 4-methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**) as a colourless oil, 152 mg, 85%.

Procedure F

Quaternary ammonium salt (**148**) (307 mg, 1.00 mmol) was dissolved in morpholine (5 mL) and stirred at room temperature for 24 hrs. After this time, the reaction mixture was concentrated under reduced pressure and the resulting residue subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 4-methyl-2-(1,4-oxazinan-4-ylmethyl)benzene-1-ol (**137**) as a colourless oil, 152 mg, 85%.

2-(Hexahydropyridin-1-ylmethyl)-4-methyl-benzene-1-ol (**140**)



(**140**)

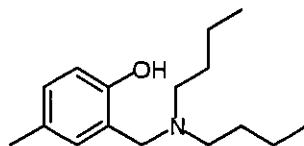
Procedure A

2-[(Dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) (0.165 g, 1.00 mmol) was dissolved in piperidine (3 mL) and stirred at reflux for 12 hours. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 2-(hexahydropyridin-1-ylmethyl)-4-methyl-benzene-1-ol (**140**) as a pale yellow oil, 0.52 g, 82%: ^1H NMR (400 MHz, CDCl_3 v.t. at 55 °C): δ 1.45 (q, $J=6.0$ Hz, 2H, CH_3), 1.58 (q, $J=6.0$ Hz, 4H, 2x- CH_2 -), 2.21 (s, 3H, CH_3), 2.46 (bt, $J=4.8$ Hz, 4H, 2x- CH_2 -), 3.59 (s, 2H, - CH_2 -), 6.67 (d, $J=8.2$ Hz, 1H, ArH), 6.71 (bd, 1H, ArH), 6.90 (bdd, $J=8.2$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 20.44 (CH_3), 24.03 (CH_2), 25.87 (CH_2), 53.90 (CH_2), 62.71 (CH_2), 115.70 (CH), 121.33 (C), 127.86 (C), 128.88 (CH), 129.00 (CH), 155.66 (C).

Procedure B

Quaternary ammonium salt (**149**) (545 mg, 1.00 mmol) was dissolved in piperidine (1.00 mL) and stirred at room temperature. TBAF (1M sol in THF, 1.10 mL, 1.10 mmol) was added in one portion and the mixture stirred overnight at room temperature. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 20% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 2-(hexahydropyridin-1-ylmethyl)-4-methyl-benzene-1-ol (**140**) as a colourless oil, 166 mg, 81%.

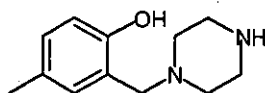
2-[(Dibutylamino)methyl]-4-methylbenzen-1-ol (**142**)



(**142**)

2-[(Dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) (0.33 g, 2.00 mmol) was dissolved in *n*-dibutylamine (2.00 mL) and stirred at 140 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and the dibutylamine was removed by distillation. The resulting residue was subjected to flash chromatography (silica gel, 10% ethyl acetate/light petroleum (40 °C-60 °C)) to isolate 2-[(dibutylamino)methyl]-4-methylbenzen-1-ol (**142**) as a pale yellow oil, 0.39 g, 78%: HRMS (EI): (*m/z*) calcd for C₁₆H₂₇NO (M⁺) 249.20925; Found 249.20961; ν_{\max} (NEAT) 2957, 1600, 1499, 1467, 1257 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J*=7.6 Hz, 6H, -CH₂CH₃), 1.25 (m, 4H, 2x-CH₂-), 1.47 (m, 4H, 2x-CH₂-), 2.23 (s, 3H, ArCH₃), 2.47 (m, 4H, 2x-CH₂-), 3.69 (s, 2H, -CH₂-), 6.68 (d, *J*=8.2 Hz, 1H, ArH), 6.75 (d, *J*=1.4 Hz, 1H, ArH), 6.93 (dd, *J*=8.2 Hz, *J*=1.4 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 13.97 (CH₃), 20.48 (CH₃), 20.60 (CH₂), 28.49 (CH₂), 53.20 (CH₂), 58.27 (CH₂), 115.70 (CH), 121.98 (C), 127.81 (C), 128.85 (CH), 128.90 (CH), 155.78 (C).

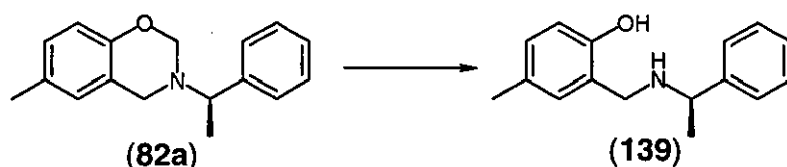
2-(Hexahydropyrazin-1-ylmethyl)-4-methylbenzen-1-ol (141)



(141)

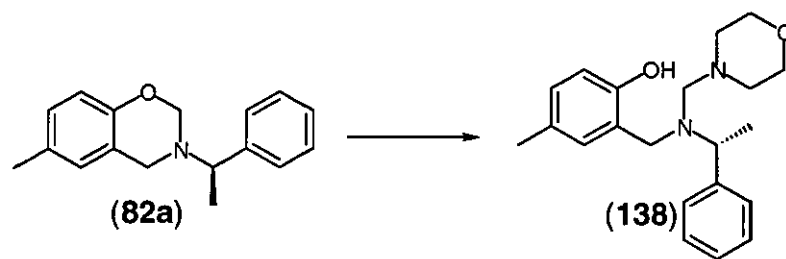
2-[(Dimethylamino)methyl]-4-methylbenzen-1-ol (**88**) (0.330 g, 2.00 mmol) and piperazine (5.00 g, 58.04 mmol) were melted together and then heated at 140 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and partitioned between water and dichloromethane. The organic solution was separated, washed with more water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 30%-50% methanol/dichloromethane) to isolate 2-(hexahydropyrazin-1-ylmethyl)-4-methylbenzen-1-ol (**141**) as a colourless oil that slowly crystallised, 0.24 g, 58%: mp 105-107 °C; HRMS (EI): (m/z) calcd for $C_{16}H_{27}NO$ (M^+) 206.14191; Found 206.14161; ν_{\max} (DCM evap) 3267, 2822, 1631, 1499, 1467, 1249 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3): δ 2.23 (s, 3H, ArCH_3), 2.49 (bt, 2x 4H, $-\text{CH}_2-$), 2.87 (t, $J=4.8$ Hz, 4H, 2x- CH_2-), 3.61 (s, 2H, $-\text{CH}_2-$), 6.67 (d, $J=8.2$ Hz, 1H, ArH), 6.75 (bd, 1H, ArH), 6.91 (dd, $J=8.2$ Hz, $J=1.8$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 20.76 (CH_3), 46.32 (CH_2), 54.05 (CH_2), 62.34 (CH_2), 116.06 (CH), 121.12 (C), 128.43 (C), 129.46 (CH), 129.55 (CH), 155.62 (C).

4-Methyl-2-([[(1*R*)-1-phenylethyl]amino]methyl)benzen-1-ol



Hydrochloric acid (5 M, 15.78 mL, 78.94 mmol) was added to a solution of 6-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) (10.00 g, 39.47 mmol) in ethanol (99%, 100 mL), and the mixture was heated at reflux for 2 hours. After this time the solvent was removed under reduced pressure and the residue taken up in water. The aqueous solution was washed with ethyl acetate before being basified with dilute ammonia solution and re-extracted with ethyl acetate. The organic solution was dried and the solvent removed under reduced pressure to furnish 4-methyl-2-([[(1*R*)-1-phenylethyl]amino]methyl)benzen-1-ol (**139**) as a pale brown oil, 7.8 g, 82%: $[\alpha]_D^{25} + 57.6$. ($c = 1.00$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$ (M^+) 241.14666; Found 241.14694; ν_{max} (NEAT) 3289, 2967, 1599, 1498, 1252, 700 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 1.44 (d, $J=7.5$ Hz, 3H, $-\text{CH}_3$), 2.21 (s, 3H, $-\text{CH}_3$), 3.62 (d, $J_{AB}=14.2$ Hz, 1H, $-\text{CH}_A\text{H}_B-$), 3.76 (d, $J_{AB}=14.2$ Hz, 1H, $-\text{CH}_A\text{H}_B-$), 3.73 (q, $J=7.5$ Hz, $-\text{CHCH}_3$), 6.69 (d, 1H, ArH), 6.73 (d, $J=8.0$ Hz, 1H, ArH), 6.94 (dd, $J=8.0$ Hz, 1H, ArH), 7.25-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.20 (CH_3), 23.38 (CH_3), 50.36 (CH_2), 57.24 (CH), 116.12 (CH), 122.42 (C), 126.50 (CH), 127.54 (CH), 128.10 (C), 128.80 (CH), 128.88 (CH), 129.07 (CH), 143.46 (C), 155.77 (C)

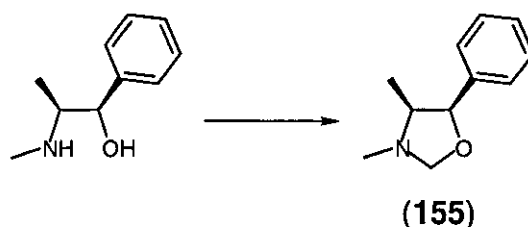
4-Methyl-2-(((1,4-oxazinan-4-ylmethyl)((1*R*)-1-phenylethyl)amino)methyl)benzen-1-ol (138)



6-Methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine (**82a**) (253 mg, 1.00 mmol) was dissolved in morpholine (5.00 mL) and stirred at reflux for 30 min. After this time, the reaction mixture was cooled to room temperature and the excess morpholine removed by Kugelrohr distillation to furnish 4-methyl-2-(((1,4-oxazinan-4-ylmethyl)((1*R*)-1-phenylethyl)amino)methyl)benzen-1-ol (**138**) as an unstable colourless oil, 319 mg, 99%. ν_{\max} (NEAT) 2960, 2852, 1599, 1499, 1452, 1116, 867 cm^{-1} ; ^{13}C NMR (100 MHz, CDCl_3) δ 20.42 (CH_3), 23.29 (CH_3), 50.39 (CH_2), 52.05 (CH_2), 57.28 (CH), 67.06 (CH_2), 81.71 (CH_2), 116.13 (CH), 121.43 (C), 126.50 (CH), 127.55 (CH), 128.12 (C), 128.81 (CH), 128.88 (CH), 129.09 (CH), 143.48 (C), 155.78 (C).

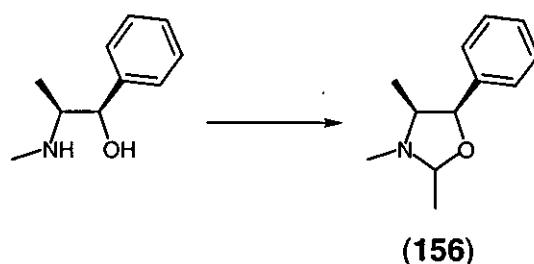
8.6 Experimental for Chapter 7

(4*S*, 5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidine^{101b} (155)



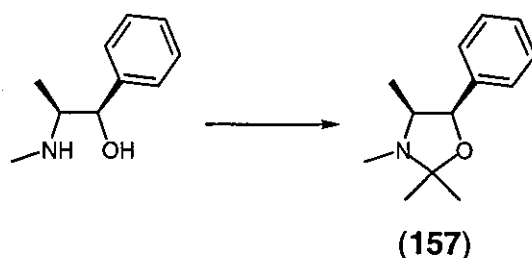
(1*R*, 2*S*)-(-)-Ephedrine (2.00 g, 12.10 mmol), paraformaldehyde (0.39 g, 13.31 mmol), potassium carbonate (1.83 g, 13.31 mmol) and benzene (20 mL) were combined and heated at reflux for 6 hours. After this time, the reaction mixture was filtered and the solid washed with diethyl ether. The organic solutions were combined and concentrated under reduced pressure to furnish a pale yellow oil. This residue was distilled by Kugelrohr distillation to furnish the (4*S*, 5*R*)-3,4-dimethyl-5-phenyl-1,3-oxazolidine (155) as a colourless oil, 1.95 g, 98%: $[\alpha]_D^{25} +19.3$ ($c = 1.14$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{11}\text{H}_{15}\text{NO}$ (M^+) 177.11536; Found: 178.12323 ($M+H^+$); ν_{max} (NEAT) 2786, 1455, 1064 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.67 (d, $J = 6.6$ Hz, 3H, CH_3), 2.38 (s, 3H, NCH_3), 2.88 (quintet, $J = 6.6$ Hz, 1H, $-\text{CHCH}_3$), 4.08 (d, $J = 3.2$ Hz, 1H, $-\text{NCH}_A\text{H}_B\text{O}-$), 4.88 (d, $J = 3.2$ Hz, 1H, $-\text{NCH}_A\text{H}_B\text{O}-$), 5.10 (d, $J = 7.2$ Hz, 1H, ArCH), 7.24-7.32 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.31 (CH_3), 37.81 (CH_3), 63.49 (CH), 81.49 (CH), 88.24 (CH_2), 126.92 (CH), 127.37 (CH), 127.98 (CH), 139.87 (C).

(4*S*, 5*R*)-2,3,4-Trimethyl-5-phenyl-1,3-oxazolidine^{101c} (156)



(1*R*, 2*S*)-(-)-Ephedrine (2.00 g, 12.10 mmol), acetaldehyde (0.74 mL, 13.31 mmol), dichloromethane (10 mL) and 4 Å mol sieves were combined and stirred at room temperature for 12 hours. After this time, the reaction mixture was filtered, concentrated under reduced pressure to furnish a pale yellow oil. The resulting residue was distilled by Kugelrohr distillation to give (4*S*, 5*R*)-2,3,4-trimethyl-5-phenyl-1,3-oxazolidine (156) as a pale yellow oil, 2.12 g, 92%; b.p. 130 °C at 1mmHg; $[\alpha]_D^{25} +46.6$ ($c = 1.81$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$ (M^+) 191.13101; Found: 191.13082; ν_{max} (NEAT) 2779, 1457, 1068, 699 cm^{-1} . ^1H NMR (250 MHz, CDCl_3) δ 0.67 (d, $J = 6.5$ Hz, 3H, CH_3), 1.47 (d, $J = 5.0$ Hz, 3H, $-\text{CHCH}_3$), 2.25 (s, 3H, NCH_3), 2.77 (dq, $J = 6.5$ Hz, $J = 7.8$ Hz, 1H, $-\text{CHCH}_3$), 3.94 (q, $J = 5.0$ Hz, 1H, $-\text{CHCH}_3$), 4.99 (d, $J = 8.1$ Hz, 1H, ArCH_2), 7.22-7.32 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 15.14 (CH_3), 19.39 (CH_3), 36.49 (CH_3), 64.65 (CH), 82.33 (CH), 94.33 (CH), 128.16 (CH), 128.29 (CH), 128.44 (CH), 140.48 (C).

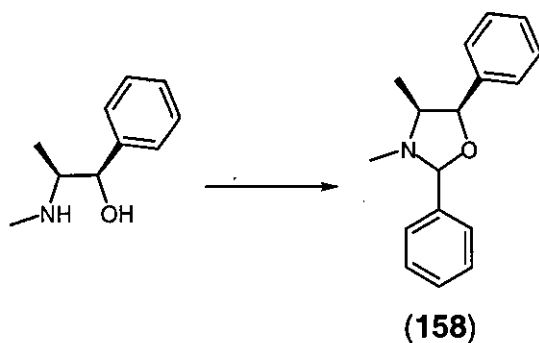
(4*S*, 5*R*)-2,2,3,4-Tetramethyl-5-phenyl-1,3-oxazolidine^{101c} (157)



(1*R*, 2*S*)-(-)-Ephedrine (1.00 g, 6.05 mmol), acetone (10 mL), (1*R*)-(-)-10-camphorsulfonic acid (50 mg) and 4 Å mol sieves were combined and stirred at reflux

for 3 days. After this time, the reaction mixture was cooled to room temperature, filtered and the filtrates concentrated under reduced pressure to furnish a pale yellow oil. Purification by Kugelrohr distillation gave a colourless oil that slowly crystallised to give (4*S*, 5*R*)-2,2,3,4-tetramethyl-5-phenyl-1,3-oxazolidine (**157**) as a colourless crystalline solid, 0.65 g, 64%; $[\alpha]_D +56.8$ ($c = 1.00$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$ (M^+) 205.14666; Found: 205.14704; Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$: C, 76.05; H, 9.35; N, 6.82. Found: C, 74.85; H, 9.13; N, 6.81; ν_{max} (DCM) 2973, 1602, 1702, 1456, 1223 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.63 (d, $J = 4.0$ Hz, 3H, CH_3), 1.22 (s, 3H, $-\text{CH}_3$), 1.51 (s, 3H, $-\text{CH}_3$), 2.26 (s, 3H, $-\text{NCH}_3$), 3.14 (dq, $J = 6.5$ Hz, $J = 8.1$ Hz, 1H, $-\text{CHCH}_3$), 5.03 (d, $J = 5.0$ Hz, 1H, $-\text{ArCHCHCH}_3-$), 7.23-7.32 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 15.47 (CH_3), 18.30 (CH_3), 26.66 (CH_3), 33.54 (CH_3), 60.53 (CH), 80.82 (CH), 95.12 (C), 127.38 (CH), 127.65 (CH), 127.82 (CH), 140.42 (C);

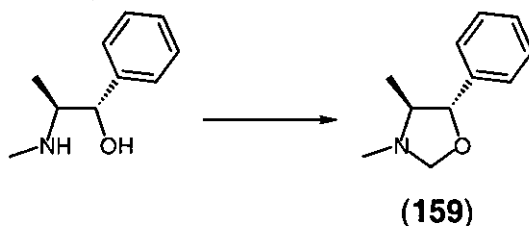
(4*S*, 5*R*)-3,4-Dimethyl-2,5-diphenyl-1,3-oxazolidine^{101d} (158**)**



(1*R*, 2*S*)-(-)-Ephedrine (2.00 g, 12.10 mmol), benzaldehyde (1.35 mL, 13.31 mmol), dichloromethane (20 mL) and 4 Å mol sieves were combined and stirred at room temperature for 3 days. After this time, the reaction mixture was filtered and the filtrates concentrated under reduced pressure to furnish a pale yellow oil that slowly crystallised. The resulting brown solid was recrystallised from ethanol to furnish (4*S*, 5*R*)-3,4-dimethyl-2,5-diphenyl-1,3-oxazolidine (**158**) as a colourless crystalline solid, 3.00 g, 98%; mp 71 °C; (lit^{101d} mp 86 °C); $[\alpha]_D -55.07$ ($c = 1.30$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$ (M^+) 253.14666; Found: 253.14658; Anal. Calcd for

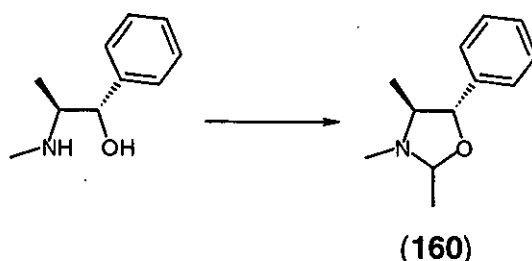
$C_{17}H_{19}NO$: C, 80.59; H, 7.57; N, 5.53. Found: C, 80.52; H, 7.50; N, 5.45. ν_{\max} (DCM) 2973, 1702, 1457, 1018, 752 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, $J = 6.6$ Hz, 3H, CH_3) 2.18 (s, 3H, NCH_3), 2.99 (dq, $J = 6.6$ Hz, $J = 8.4$ Hz, 1H, $-CHCH_3$), 4.69 (s, 1H, $-NCHAr$), 5.13 (d, $J = 8.4$ Hz, 1H, $-ArCHCHCH_3$), 7.31-7.66 (m, 10H, ArH).

(4*S*, 5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidine^{101c} (159)



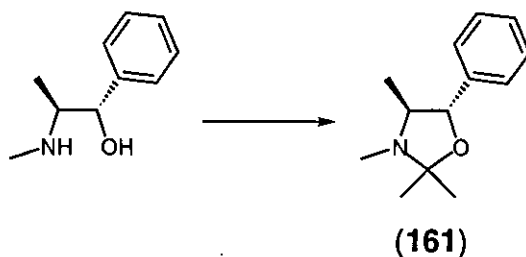
(1*S*, 2*S*)-(+)-Pseudoephedrine (2.00 g, 12.10 mmol), paraformaldehyde (0.39 g, 13.31 mmol), potassium carbonate (1.83 g, 13.31 mmol) and benzene (20 mL) were combined and heated at reflux for 6 hours. After this time, the reaction mixture was filtered and the solid washed with diethyl ether. The organic solutions were combined and concentrated under reduced pressure to furnish a pale yellow oil. This residue was distilled by Kugelrohr distillation to furnish (4*S*, 5*R*)-3,4-dimethyl-5-phenyl-1,3-oxazolidine (**159**) as a colourless oil, 1.84 g, 93%; $[\alpha]_D +44.6$ ($c = 1.05$, $CHCl_3$); HRMS (EI): (m/z) calcd for $C_{11}H_{15}NO$ (M^+) 177.11536; Found: 177.11518; ν_{\max} (NEAT) 2970, 2874, 2786, 1454, 1230, 1051 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, $J = 6.4$ Hz, 3H, CH_3) 2.39 (s, 3H, NCH_3), 2.46 (dq, $J = 6.4$ Hz, $J = 4.4$ Hz, 1H, $-CHCH_3$), 4.31 (d, $J = 3.2$ Hz, 1H, $-NCH_AH_BO-$), 4.48 (d, $J = 8.1$ Hz, 1H, $ArCH-$), 4.77 (d, $J = 3.2$ Hz, 1H, $-NCH_AH_BO-$), 7.26-7.31 (m, 5H, ArH).

(4*S*, 5*S*)-2,3,4-Trimethyl-5-phenyl-1,3-oxazolidine^{101c} (160)



(1*R*, 2*S*)-(+)-Pseudoephedrine (1.00 g, 6.05 mmol), acetaldehyde (6.76 mL, 121.00 mmol) and 4 Å mol sieves were combined and allowed to stand at room temperature for 12 hours. After this time, the reaction mixture was filtered, concentrated under reduced pressure to furnish (4*S*, 5*S*)-2,3,4-trimethyl-5-phenyl-1,3-oxazolidine (**160**) as a pale yellow oil, 0.96 g, 83%: $[\alpha]_D^{25} +21.4$ ($c = 1.10$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$ (M^+) 191.13101; Found: 190.12353 ($M-H^+$); ν_{max} (NEAT) 2973, 1454, 1228, 1077 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.15 (d, $J = 6.3$ Hz, 3H, CH_3), 1.39 (d, $J = 5.0$ Hz, 3H, $-\text{CHCH}_3$), 2.28 (3H, s, NCH_3), 2.31-2.41 (m, 1H, $-\text{CHCH}_3$), 4.24 (q, $J = 5.0$ Hz, 1H, $-\text{CHCH}_3$), 4.53 (d, $J = 8.7$ Hz, 1H, ArCH), 7.26-7.33 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.41 (CH_3), 19.75 (CH_3), 35.73 (CH_3), 69.14 (CH), 85.21 (CH), 94.71 (CH), 126.60 (CH), 127.85 (CH), 128.39 (CH), 140.68 (C).

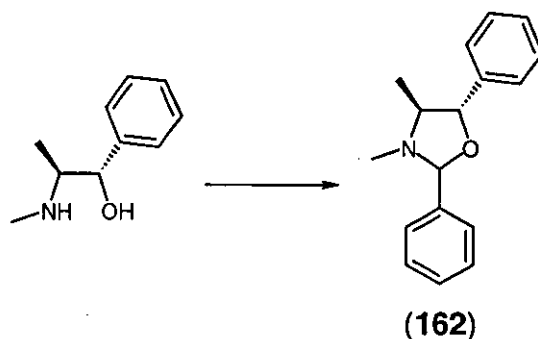
(4*S*, 5*S*)-2,2,3,4-Tetramethyl-5-phenyl-1,3-oxazolidine^{101c} (161)



(1*R*, 2*S*)-(+)-Pseudoephedrine (1.00 g, 6.05 mmol) was dissolved in acetone (60 mL). (1*R*)-(-)-10-camphorsulfonic acid (50 mg) and 4 Å mol sieves were added and the mixture left to stand at room temperature for 4 days. After this time, the reaction

mixture was filtered and the filtrates concentrated under reduced pressure to furnish a pale yellow oil. Purification by Kugelrohr distillation gave (4*S*, 5*S*)-2,2,3,4-tetramethyl-5-phenyl-1,3-oxazolidine (**161**) as a colourless oil, 1.27 g, 99%: $[\alpha]_D +42.33$ ($c = 1.71$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{13}\text{H}_{19}\text{NO}$ (M^+) 205.14666; Found: 205.14666; ν_{max} (NEAT) 2973, 1604, 1375, 1042, 754 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.09 (d, $J = 6.0$ Hz, 3H, CH_3), 1.33 (s, 3H, $-\text{CH}_3$), 1.42 (s, 3H, $-\text{CH}_3$), 2.29 (s, 3H, $-\text{NCH}_3$), 2.55 (dq, $J = 6.0$ Hz, $J = 8.7$ Hz, 1H, $-\text{CHCH}_3$), 4.45 (d, $J = 8.7$ Hz, 1H, $-\text{ArCHCHCH}_3$), 7.25–7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.57 (CH_3), 21.63 (CH_3), 27.71 (CH_3), 32.83 (CH_3), 65.16 (CH), 84.97 (CH), 95.32 (C), 126.70 (CH), 127.82 (CH), 128.31 (CH), 139.99 (C).

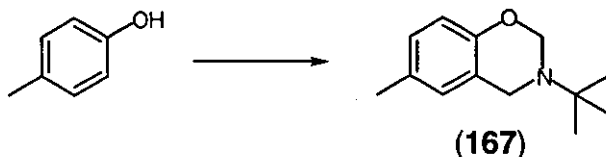
(4*S*, 5*S*)-3,4-Dimethyl-2,5-diphenyl-1,3-oxazolidine^{101d} (162**)**



(1*R*, 2*S*)-(+)-Pseudoephedrine (1.00 g, 6.05 mmol), benzaldehyde (12.29 mL, 121.00 mmol), dichloromethane (20 mL), (1*R*)-(-)-10-camphorsulfonic acid (50 mg) and 4 Å mol sieves were combined and stirred at room temperature for 3 days. After this time, the reaction mixture was filtered and the filtrates concentrated under reduced pressure to furnish a pale yellow oil that slowly crystallised. The resulting brown solid was recrystallised from ethanol to furnish (4*S*, 5*S*)-3,4-dimethyl-2,5-diphenyl-1,3-oxazolidine (**162**) as a colourless crystalline solid, 1.53 g, 99%: $[\alpha]_D +50.51^\circ$ ($c = 1.37$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$ (M^+) 253.14666; Found: 253.14622; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}$: C, 80.59; H, 7.57; N, 5.53. Found: C, 80.41; H, 7.48; N, 5.41; IR (DCM) 1632, 1452, 1376, 1018, 1036 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.24

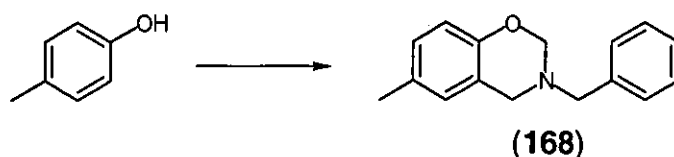
(d, $J = 6.2$ Hz, 3H, CH_3) 2.21 (s, 3H, NCH_3), 2.55 (dq, $J = 6.2$ Hz, $J = 8.8$ Hz, 1H, $-\text{CHCH}_3$), 4.77 (d, $J = 8.8$ Hz, 1H, $-\text{NCHAr}$), 4.96 (s, 1H, $-\text{ArCH}$), 7.25-7.57 (m, 10H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.37 (CH_3), 35.18 (CH_3), 68.84 (CH), 86.55 (CH), 99.63 (CH), 126.70 (CH), 127.92 (CH), 128.05 (CH), 128.37 (CH), 128.39 (CH), 129.06 (CH), 139.52 (C), 140.47 (C).

6-Methyl-3-(*tert*-butyl)-3,4-dihydro-2*H*-1,3-benzoxazine (167)



para-Cresol (1.00 g, 9.25 mmol) and *N,N*-di[(methoxy)methyl]-*N-tert*-butylamine (68) (1.74 g, 11.09 mmol) were reacted together in dichloromethane (10 mL) according to general procedure 3. The residue was subjected to flash chromatography (silica gel, 20% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 6-methyl-3-(*tert*-butyl)-3,4-dihydro-2*H*-1,3-benzoxazine (167) as a pale yellow oil, 1.00g, 53%: HRMS (EI): (m/z) calcd for $\text{C}_{13}\text{H}_{19}\text{NO}$ (M^+) 205.14675; Found: 205.14675; ν_{max} (NEAT) 2971, 2877, 1503, 1304, 1132, 901 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.19 (s, 9H, *t*Bu), 2.24 (s, 3H, ArCH_3), 4.07 (s, 2H, $-\text{CH}_2-$), 4.95 (s, 2H, $-\text{NCH}_2\text{O}-$), 6.63 (d, $J=8.0$ Hz, 1H, ArH), 6.78 (d, 1H, ArH), 7.26 (m, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 20.59 (CH_3), 28.29 (CH_3), 45.26 (CH_2), 79.07 (CH_2), 116.41 (CH), 122.91 (C), 126.82 (CH), 127.71 (CH), 129.48 (C), 152.93 (C).

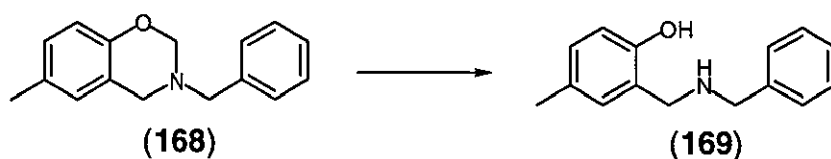
6-Methyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine¹⁰³ (168)



para-Cresol (3.00 g, 27.74 mmol) and *N,N*-di[(methoxy)methyl]-*N*-benzylamine (66)

(6.50 g, 33.29 mmol) were reacted together in ethanol (50 mL) according to general procedure 3. The residue was subjected to flash chromatography (silica gel, 10% ethyl acetate-light petroleum (40 °C-60 °C)) to furnish 6-methyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (**168**) as a colourless crystalline solid, 4.87 g, 73%: mp 73-74 °C; (lit mp¹⁰³ 70-71°C); HRMS (EI): (m/z) calcd for C₁₆H₁₇NO (M⁺) 239.13101; Found M⁺: 239.13080; Anal. Calcd for C₁₆H₁₇NO: C, 80.30; H, 7.10; N, 5.85. Found: C, 80.42; H, 7.08; N, 5.80; ν_{\max} (DCM evap) 2924, 1879, 1501, 1456, 1377, 1321, 1216, 1114, 939 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.23 (s, 3H, CH₃), 3.90 (s, 2H, -CH₂-), 3.91 (s, 2H, -CH₂-), 4.82 (s, 2H, -CH₂-), 6.70-7.33 (m, 8H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 21.05 (CH₃), 50.11 (CH₂), 56.00 (CH₂), 82.64 (CH₂), 116.63 (CH), 120.11 (C), 127.78 (CH), 128.41 (CH), 128.74 (CH), 128.88 (CH), 129.40 (CH), 130.25 (C), 138.75 (C), 152.35 (C).

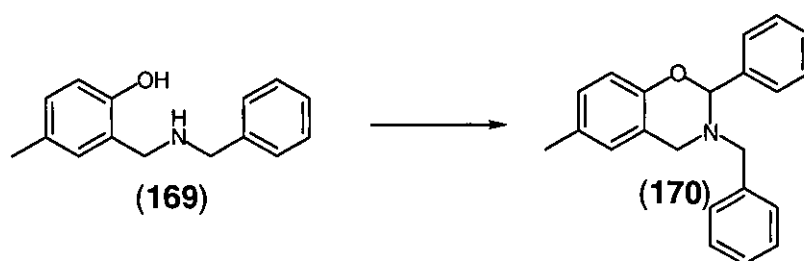
4-Methyl-2-[[[(phenylmethyl)amino]methyl]benzen-1-ol]¹⁰³ (**169**)



Hydrochloric acid (1M, 25.06 mL, 25.06 mmol) was added to a solution of 6-methyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (3.00 g, 12.53 mmol) in ethanol (99%, 20 mL) and the mixture was stirred at reflux for 2 hours. After this time the solvent was removed under reduced pressure and the residue taken up in water. The aqueous was washed with ethyl acetate before being basified with dilute aqueous ammonia and re-extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification by flash chromatography (silica gel, 30% ethyl acetate-light petroleum (40 °C-60 °C)) furnished 4-methyl-2-[[[(phenylmethyl)amino]methyl]benzen-1-ol (**169**) as a pale yellow oil, 2.27 g, 80%: HRMS (EI): (m/z) calcd for C₁₅H₁₇NO (M⁺) 227.13101; Found M⁺: 239.13137; ν_{\max}

(NEAT) 3314, 3027, 2916, 1879, 1735, 1498, 1252 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.24 (s, 3H, Me), 3.81 (s, 2H, $-\text{CH}_2-$), 3.97 (s, 2H, $-\text{CH}_2-$), 6.74-6.98 (m, 3H, ArH), 7.24-7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.20 (CH_3), 51.97 (CH_2), 52.66 (CH_2), 116.17 (CH), 121.94 (C), 127.55 (CH), 128.15 (C), 128.35 (CH), 128.69 (CH), 129.05 (CH), 129.20 (CH), 138.48 (C), 152.78 (C).

6-Methyl-2-phenyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (170)

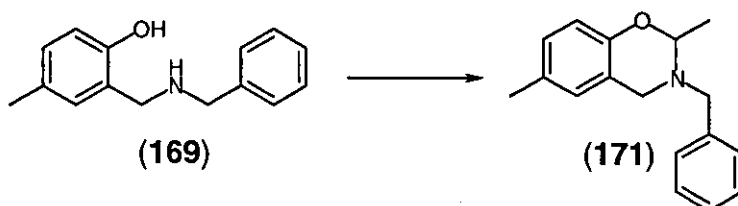


Benzaldehyde (2.23 mL, 21.97 mmol), (1*R*)-(-)-10-camphorsulfonic acid (50 mg) and 4 Å mol sieves were added to a solution of 4-methyl-2-[[[(phenylmethyl)amino]methyl]benzen-1-ol (**169**) (1.00 g, 4.39 mmol) in dichloromethane (20 mL). and the resulting mixture was heated at reflux overnight. After this time, the reaction mixture was filtered, evaporated under reduced pressure and the excess benzaldehyde removed by distillation. The resulting pale yellow oil slowly crystallised to furnish a white solid. Recrystallisation from ethanol gave 6-methyl-2-phenyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (**170**) as a white solid, 1.02 g, 74%; mp 101-102 °C; HRMS (EI): (m/z) calcd for $\text{C}_{22}\text{H}_{21}\text{NO}$ (M^+) 315.16231; Found: 315.16262; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.38; H, 6.52; N, 4.35; ν_{max} (DCM evap) 3441, 1498, 1219 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.23 (s, 3H, CH_3) 3.75-3.87 (m, 4H, 2 x CH_2), 5.95 (s, 1H, CH), 6.67 (d, $J = 1.2$ Hz, 1H, ArH), 6.88 (d, $J = 8.5$ Hz, 1H, ArH), 6.97 (d, $J = 8.5$ Hz, 1H, ArH), 7.22-7.37 (m, 8H, ArH), 7.62-7.64 (m, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 21.03 (CH_3), 47.26 (CH_2), 53.82 (CH_2), 90.73 (CH), 116.67 (CH), 119.85 (C), 127.08 (CH), 127.53 (CH), 128.31 (CH), 128.44 (CH), 128.78 (CH), 128.79 (CH), 129.07

(CH), 130.20 (C), 139.38 (C), 139.66 (C) 151.76 (C).

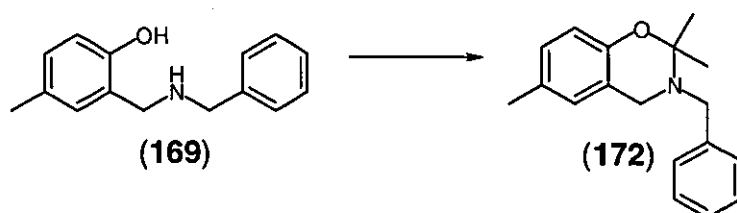
1x(C) obscured by other signals.

2,6-Dimethyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (171)



Acetaldehyde (4.91 mL, 87.90 mmol) and 4 Å mol sieves (1.00 g) were added to a solution of 4-methyl-2-(((phenylmethyl)amino)methyl)benzen-1-ol (**169**) (1.00 g, 4.39 mmol) in dichloromethane (20 mL), and the resulting mixture was allowed to stand at room temperature overnight. After this time, the molecular sieves were removed by filtration and the dichloromethane and excess acetaldehyde removed under reduced pressure, furnishing 2,6-dimethyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (**171**) as a pale orange oil, 1.05 g, 95%: HRMS (EI): (m/z) calcd. for $C_{17}H_{19}NO$ (M^+) 253.14666; Found: 253.14682; ν_{\max} (neat) 2988, 2916, 2860, 1499, 1139, 864 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 1.52-1.54 (d, $J = 6.2$ Hz, 3H, CHCH_3), 2.24 (s, 3H, $-\text{CH}_3$), 3.62-3.67 (d, $J = 14.0$ Hz, 1H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 3.86 (s, 2H, $-\text{CH}_2-$), 3.94-3.99 (d, $J = 14.0$ Hz, 1H, $-\text{CH}_\text{A}\text{H}_\text{B}-$), 5.03-5.29 (q, $J = 6.2$ Hz, 1H, CHCH_3), 6.68-6.72 (m, 2H, ArH), 6.92-6.96 (m, 1H, ArH), 7.23-7.27 (m, 5H, ArH); ^{13}C NMR (100MHz, CDCl_3) δ 19.06 (CH_3), 20.59, (CH_3), 47.77 (CH_2), 52.36 (CH_2), 87.39 (CH), 116.21 (CH), 118.70 (C), 127.05 (CH), 127.97 (CH), 128.31 (CH), 128.36 (CH), 128.66 (CH), 129.52 (C), 139.08 (C), 151.51 (C).

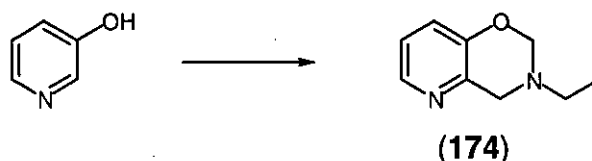
2,2,6-Trimethyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (172)



(1*R*)-(-)-10-Camphorsulfonic acid (50 mg) and 4 Å mol sieves were added to a solution of 4-methyl-2-[(phenylmethyl)amino]benzen-1-ol (**169**) (1.10 g, 4.83 mmol) in acetone (60.00 mL), and the resulting mixture was heated at gentle reflux overnight. After this time, the reaction mixture was filtered and evaporated under reduced pressure to furnish 2,2,6-trimethyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (**172**) as a pale yellow oil, 0.94 g, 73%: HRMS (EI): (*m/z*) calcd for C₁₈H₂₁NO (*M*⁺) 267.16231; Found: 267.16185; ν_{max} (DCM evap) 3422, 2992, 1498, 1111 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.59 (s, 6H, 2xCH₃) 2.23 (s, 3H, CH₃) 3.78 (s, 2H, -CH₂-), 6.69-6.72 (m, 2H, ArH), 6.93 (dd, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H, ArH), 7.24-7.32 (m, 5H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 20.58 (CH₃), 26.01 (CH₃), 46.26 (CH₂), 52.34 (CH₂), 90.21 (C), 116.55 (CH), 118.29 (C), 126.84 (CH), 127.77 (CH), 128.32 (CH), 128.36 (CH), 129.13 (C), 139.98 (C), 151.07 (C) 208.65 (CH).

1x(CH) obscured by other signals.

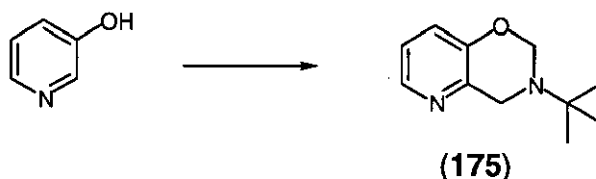
3-Ethyl-3,4-dihydro-2H-pyrido[2,3-*e*][1,3]oxazine (174)



Ethylamine (70% (aq) solution, 4.06 mL, 63.09 mmol) was added dropwise to a solution of formaldehyde (37% (aq) solution, 15.00 mL, 0.189 mol) in 1,4-dioxane (15.00 mL) at 0 °C. The solution was then warmed to room temperature and 5-hydroxypyridine (1.50 g, 15.77 mmol) was added in one portion and the resulting

solution was stirred at 90 °C for 12 hours. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic solution was separated, washed with more water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 10% methanol/dichloromethane) to furnish 3-ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**174**) as a brown oil, 0.78 g, 15%: HRMS (EI): (*m/z*) calcd for C₉H₁₂N₂O (M⁺) 164.09496; Found: 164.09501; ν_{max} (NEAT) 3396, 2971, 1575, 1450, 1232, 917 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.18 (t, *J* = 7.2 Hz, 3H, -CH₂CH₃), 2.82 (q, 2H, *J* = 7.2 Hz, 2H, -CH₂CH₃), 4.11 (s, 2H, -CH₂-), 4.90 (s, 2H, -CH₂-), 7.02-7.09 (m, 2H, ArH), 8.11-8.12 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 13.33 (CH₃), 45.95 (CH₂), 52.52 (CH₂), 82.15 (CH₂), 122.95 (CH), 123.25 (CH), 141.74 (CH), 141.96 (C), 151.35 (C).

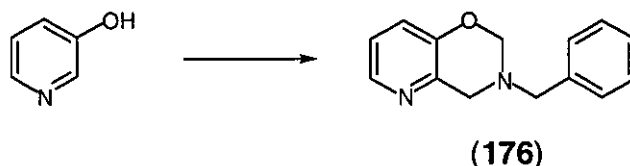
3-*t*-Butyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**175**)



tert-Butylamine (4.42 mL, 42.06 mmol) and formaldehyde (37% (aq) solution, 10.24 mL, 0.126 mol) were dissolved in 1,4-dioxane (20 mL) and the solution was stirred at 50 °C for 1 hour. 5-Hydroxypyridine (2.00 g, 21.03 mmol) was then added in one portion and the resulting solution was stirred at 90 °C for 12 hours. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic solution was separated, washed with more water, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by Kugelrohr distillation to furnish 3-*t*-butyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**175**) as a brown oil, 3.27 g, 81%: b.p. = 230 °C at 1mmHg; HRMS (EI): (*m/z*) calcd for

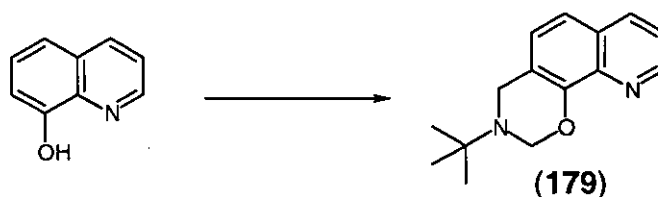
$C_{11}H_{16}N_2O$ (M^+) 192.12026; Found: 192.12671; ν_{\max} (NEAT) 3385, 2971, 1576, 1498, 1458, 1233, 904 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.89 (s, 9H, ^tBu), 4.22 (s, 2H, $-\text{CH}_2-$), 5.01 (s, 2H, $-\text{CH}_2-$), 7.02-7.03 (m, 2H, ArH), 8.08-8.09 (m, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 28.29 (CH_3), 48.13 (CH_2), 54.50 (C), 79.43 (CH_2), 122.51 (CH), 123.49 (CH), 141.35 (CH), 144.55 (C), 152.08 (C).

3-Benzyl-3,4-dihydro-2H-pyrido[2,3-e][1,3]oxazine (176)



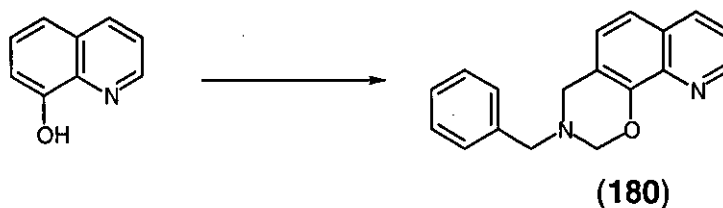
Paraformaldehyde (0.95 g, 31.54 mmol) and benzylamine (1.72 mL, 15.77 mmol) were dissolved in 1,4-dioxane (15 mL) and the mixture stirred at 50 °C for 40 minutes. After this time, 5-hydroxypyridine (1.5 g, 15.77 mmol) was added in one portion and the resulting solution heated to reflux and stirred for 12 hours. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography (silica gel, 10% methanol/dichloromethane) to furnish 3-benzyl-3,4-dihydro-2H-pyrido[2,3-e][1,3]oxazine (176) as a brown oil, 2.72 g, 76%; HRMS (EI): (m/z) calcd for $C_{14}H_{14}N_2O$ (M^+) 226.11013; Found: 226.11061; ν_{\max} (NEAT) 3061, 3026, 2890, 2846, 1574, 1450, 1229, 921 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.93 (s, 2H, $-\text{CH}_2-$), 4.11 (s, 2H, $-\text{CH}_2-$), 4.87 (s, 2H, $-\text{CH}_2-$), 7.10-7.35 (m, 7H, ArH), 8.13-8.14 (m, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 55.65 (CH_2), 55.98 (CH_2), 82.07 (CH_2), 123.03 (CH), 123.39 (CH), 127.55 (CH), 128.51 (CH), 129.01 (CH), 137.63 (C), 141.75 (C), 141.96 (CH), 151.30 (C).

3-(*t*-Butyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (179)



Paraformaldehyde (0.82 g, 27.56 mmol) and *t*-butylamine (1.72 mL, 13.78 mmol) were dissolved in 1,4-dioxane (15 mL) and the mixture stirred at 50 °C for 1 hour. After this time, 8-hydroxyquinoline (2.00 g, 13.78 mmol,) was added in one portion and the resulting solution heated to reflux and stirred for 3 hours. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane and water. The organic solution was separated, washed with more water and brine, dried over magnesium sulfate, filtered and the filtrates concentrated under reduced pressure to give a green residue. Trituration with light petroleum (40 °C-60 °C) furnished 3-(*t*-butyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (179) as a green solid, 2.62 g, 78%: HRMS (EI): (*m/z*) calcd for C₁₅H₁₈N₂O (*M*⁺) 242.14191; Found: 242.14237; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (s, 9H, *t*Bu), 4.28 (s, 2H, -CH₂-), 5.28 (s, 2H, -CH₂-), 7.15-7.36 (m, 3H, ArH), 8.05-8.07 (m, 1H, ArH), 8.88-8.89 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 28.40 (CH₃), 45.41 (CH₂), 54.71 (C), 80.02 (CH₂), 118.69 (CH), 121.02 (CH), 121.35 (C), 125.25 (CH), 127.79 (C), 135.84 (CH), 139.82 (C), 149.35 (CH), 150.85 (C).

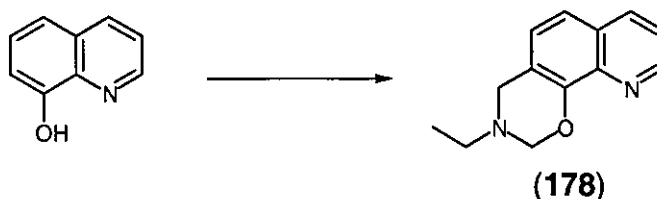
3-(Benzyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline¹⁰⁶ (180)



Benzylamine (3.76 mL, 34.45 mmol), paraformaldehyde (2.32 g, 77.51 mmol) and

400 mL of 50% benzene/ethanol were heated under reflux for 2 hours. To this was slowly added a solution of 8-hydroxyquinoline (5.00 g, 34.45 mmol) in benzene (20 mL). The resulting mixture was heated under reflux for 9 hours. After this time, the solution was cooled and concentrated under reduced pressure to afford a yellow/green oil. The oil was treated with decolourising carbon and then triturated with 30% ethyl acetate/light petroleum (40 °C-60 °C) to give a green solid. Recrystallisation from absolute ethanol/water furnished 3-(benzyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**180**) as a green solid, 1.81 g, 19%: m.p.=99-101 °C (lit¹⁰⁶ mp 104-105 °C); HRMS (EI): (m/z) calcd for C₁₈H₁₆N₂O (M⁺) 276.12626; Found: 276.12626; ¹H NMR (400 MHz, CDCl₃) δ 4.02 (s, 2H, -CH₂-), 4.12 (s, 2H, -CH₂-), 5.20 (s, 2H, -CH₂-), 7.09 (d, *J* = 8.0 Hz, 1H, ArH), 7.26-7.41 (m, 7H, ArH), 8.08 (m, 1H, ArH), 8.92 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 46.57 (CH₂), 55.92 (CH₂), 83.48 (CH₂), 117.85 (C), 119.06 (CH), 121.23 (CH), 126.20 (CH), 127.41 (CH), 128.17 (C), 128.46 (CH), 128.96 (CH), 135.94 (CH), 138.18 (C), 139.43 (C), 149.49 (CH), 149.58 (C).

3-(Ethyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**178**)



8-Hydroxyquinoline (5.00 g, 34.45 mmol), ethylamine (70% (aq) solution, 2.65 mL, 41.34 mmol), paraformaldehyde (2.32 g, 77.51 mmol) and 400 mL of a 50% solution of benzene-ethanol were reacted together according to the procedure described above. 3-(Ethyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**178**) was isolated as a green oil, 1.67 g, 44%: HRMS (EI): (m/z) calcd for C₁₃H₁₄N₂O (M⁺) 214.11061; Found: 214.11074; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (t, *J* = 7.2 Hz, 3H, -CH₂CH₃), 2.86 (q, *J* = 7.2 Hz, 2H, -CH₂CH₃), 4.17 (s, 2H, -CH₂-), 5.18 (s, 2H, -CH₂-), 7.13-7.40 (m, 3H,

ArH), 8.06-8.10 (m, 1H, ArH), 8.88 (m, 1H, ArH).

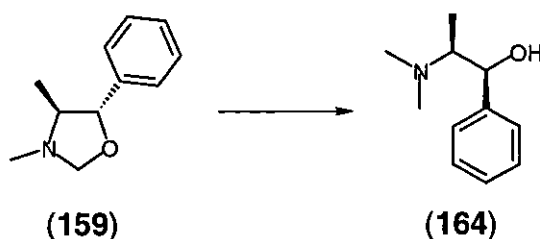
General procedure A. Reductive cleavage using chlorotrimethylsilane and sodium cyanoborohydride.

A solution of the required cyclic aminol ether (1.0 eq) in dry acetonitrile was cooled to $-35\text{ }^{\circ}\text{C}$, under an atmosphere of nitrogen. Sodium cyanoborohydride (5 or 2 eq) was added in one portion followed by chlorotrimethylsilane (5 or 2 eq) over 5 minutes. The reaction mixture was stirred for 30 minutes before being quenched with aqueous potassium carbonate solution. The reaction mixture was allowed to come to room temperature and stirred for 1 hour before being evaporated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic layer was separated, washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to furnish the desired product generally analytically pure, although purification could be carried out *via* flash chromatography if required.

General procedure B. Reductive cleavage using formic acid.

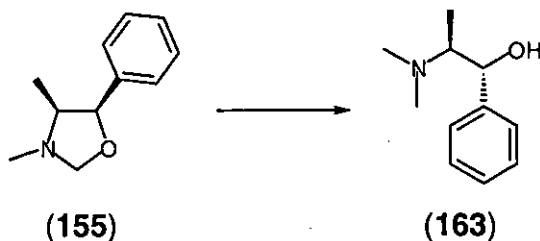
A solution of the required cyclic aminol ether (1.0 eq) was dissolved in formic acid (96%, 5%w/v) and stirred at reflux until the reaction had gone to completion. After this time, the reaction mixture was allowed to cool to room temperature before being poured into an ice cold aqueous solution of ammonia and extracted into ethyl acetate. The organic solution was separated, dried over magnesium sulfate and concentrated under reduced pressure to give the desired product generally analytically pure, although purification could be carried out by flash chromatography if required.

***N*-Methylpseudoephedrine (164)**



(4*S*, 5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolan-2-one (**159**) (1.00 g, 5.64 mmol) and formic acid (20 mL) were reacted together according to the general procedure (B). After work up, *N*-methylpseudoephedrine (**164**) was isolated as a colourless oil, 0.91 g, 90%: $[\alpha]_D^{25} +53.1$ ($c = 1.47$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{11}\text{H}_{17}\text{NO}$ (M^+) 179.13101; Found: ($M-H^+$) 178.12345; ν_{max} (DCM evap) 3355, 2972, 1452, 1039, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.71 (d, $J = 6.8\text{Hz}$, $-\text{CHCH}_3$), 2.31 (s, 6H, $-\text{N}(\text{CH}_3)_2$), 2.57-2.61 (m, 1H, $-\text{CHCH}_3$), 4.18 (d, $J = 10.0\text{Hz}$, 1H, $-\text{CH}-$), 7.26-7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 6.39 (CH_3), 39.88 (CH_3), 65.91 (CH), 74.92 (CH), 126.96 (CH), 127.37 (CH), 127.69 (CH), 142.05 (C).

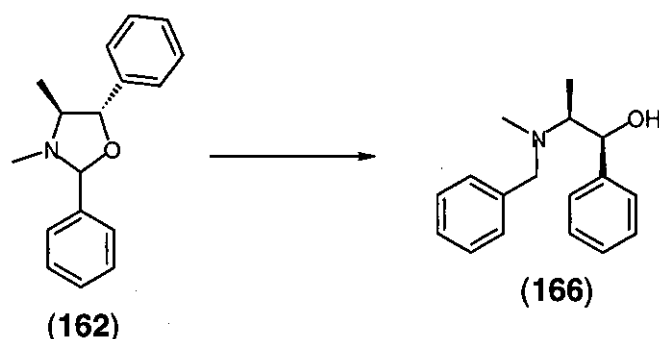
***N*-Methylephedrine (163)**



(4*S*, 5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolan-2-one (**155**) (1.00 g, 5.64 mmol) and formic acid (20 mL) were reacted together according to the general procedure (B). After work up, *N*-methylephedrine (**163**) was isolated as a colourless crystalline solid, 0.95 g, 96%: $[\alpha]_D^{25} +0.64$ ($c = 1.24$, CHCl_3); Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}$: C, 64.35; H, 9.58; N, 7.81. Found: C, 72.79; H, 9.38; N, 7.59; ν_{max} (DCM evap) 3082, 2708, 1366, 1134, 989, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.82 (d, $J = 6.8\text{Hz}$, $-\text{CHCH}_3$), 2.35 (s, 6H, $-\text{N}(\text{CH}_3)_2$), 2.57-2.61 (m, 1H, $-\text{CHCH}_3$), 4.18 (d, $J = 10.0\text{Hz}$, 1H, $-\text{CH}-$), 7.26-7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 6.39 (CH_3), 39.88 (CH_3), 65.91 (CH), 74.92 (CH), 126.96 (CH), 127.37 (CH), 127.69 (CH), 142.05 (C).

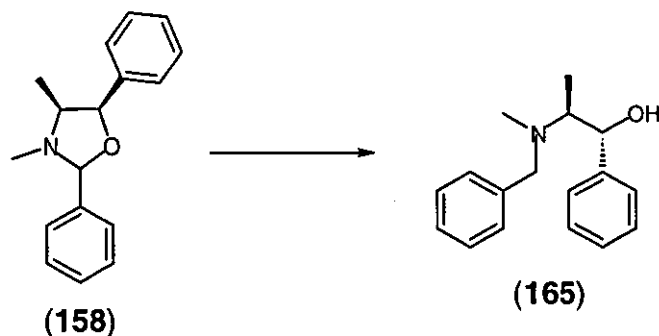
-N(CH₃)₂), 2.54-2.55 (dq, $J = 6.8$ Hz, $J = 3.6$ Hz, 1H, -CHCH₃), 3.92 (bs, 1H, OH), 4.95 (d, $J = 5.6$ Hz, 1H, CH), 7.21-7.33 (m, 5H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 9.87 (CH₃), 42.96 (CH₃), 65.53 (CH), 72.26 (CH), 125.92 (CH), 126.82 (CH), 128.02 (CH), 142.31 (C).

***N*-Benzylpseudoephedrine (166)**



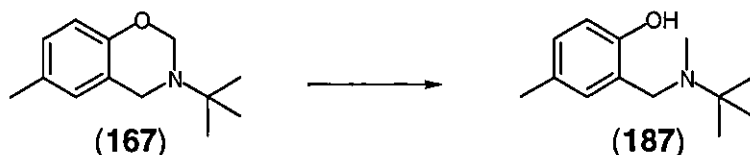
(4*S*, 5*S*)-3,4-Dimethyl-2,5-diphenyl-1,3-oxazolidine (**162**) (253 mg, 1.00 mmol), chlorotrimethylsilane (0.63 mL, 5.00 mmol) and sodium cyanoborohydride (0.31 g, 5.00 mmol) were reacted together in acetonitrile (10 mL) according to the general procedure A. The resulting crude material was purified by flash chromatography (silica gel, 10% methanol/dichloromethane) furnishing *N*-benzylpseudoephedrine (**166**) as a pale yellow oil, 245mg, 96%; [α]_D +114.9 ($c = 1.64$, CHCl₃); HRMS (EI): (m/z) calcd for C₁₇H₂₁NO (M^+) 255.16231; Found: 255.16154; ν_{\max} (NEAT) 3365, 2970, 1493, 1451, 1026, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.80 (d, $J = 4.0$ Hz, -CHCH₃), 2.23 (s, 3H, -NCH₃), 2.73-2.77 (m, 1H, -CHCH₃), 3.49 (d, $J = 13.2$ Hz, 1H, ArCH_AH_B-), 3.74 (d, $J = 13.2$ Hz, 1H, ArCH_AH_B-), 4.31 (d, $J = 8.0$ Hz, 1H, CH), 7.25-7.37 (m, 10H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 7.32 (CH₃), 35.72 (CH₃), 58.31 (CH₂), 64.87 (CH), 74.83 (CH), 127.32 (CH), 127.39 (CH), 127.71 (CH), 128.22 (CH), 128.49 (CH), 128.95 (CH), 138.68 (C), 142.00 (C).

N-Benzylephedrine (165)



(4*S*, 5*R*)-3,4-Dimethyl-2,5-diphenyl-1,3-oxazoline (**158**) (253 mg, 1.00 mmol), chlorotrimethylsilane (0.63 mL, 5.00 mmol) and sodium cyanoborohydride (0.31 g, 5.00 mmol) were reacted together in acetonitrile (10 mL) according to the general procedure A. The resulting crude material was purified by flash chromatography (silica gel, 10% methanol/dichloromethane) furnishing *N*-benzylephedrine (**165**) as a pale yellow oil, 242 mg, 95%; $[\alpha]_D^{25}$ -34.01 ($c = 1.47$, CHCl_3); HRMS (EI): (m/z) calcd for $\text{C}_{17}\text{H}_{21}\text{NO}$ (M^+) 255.16231; Found: 255.16215; ν_{max} (NEAT) 3385, 1637, 1493, 1451, 1026, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.99 (d, $J = 8.0$ Hz, $-\text{CHCH}_3$), 2.20 (s, 3H, $-\text{NCH}_3$), 2.93 (dq, $J = 4.8$ Hz, $J = 6.8$ Hz, 1H, $-\text{CHCH}_3$), 3.59 (d, $J = 13.6$ Hz, 1H, ArCH_AH_B), 3.64 (d, $J = 13.6$ Hz, 1H, ArCH_AH_B), 4.90 (d, $J = 8.0$ Hz, 1H, CH), 7.22-7.33 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 9.89 (CH_3), 36.68 (CH_3), 59.21 (CH_2), 63.47 (CH), 73.65 (CH), 126.59 (CH), 126.99 (CH), 127.02 (CH), 128.03 (CH), 128.33 (CH), 128.71 (CH), 139.37 (C), 142.47 (C).

2-[(1,1-Dimethylethyl)(methyl)amino]methyl-4-methylbenzen-1-ol (**187**)



6-Methyl-3-(*tert*-butyl)-3,4-dihydro-2*H*-1,3-benzoxazine (**167**) (205 mg, 1.00 mmol), chlorotrimethylsilane (0.254 mL, 2.00 mmol) and sodium cyanoborohydride (125 mg,

2.00 mmol) were reacted together in acetonitrile (5.00 mL) according to general procedure A to furnish the crude product as an off white solid. Recrystallisation from ethanol/water gave 2-[[[(1,1-dimethylethyl)(methyl)amino]methyl]-4-methylbenzen-1-ol (**187**) as a white crystalline solid, 197 mg, 95%; mp = 65-67 °C; HRMS (EI): (m/z) calcd for C₁₃H₁₉NO (M⁺) 205.14666; Found: 205.14608; Anal. Calcd for C₁₈H₁₉NO: C, 75.31; H, 10.23; N, 6.75. Found: C, 75.05; H, 10.18; N, 6.59; ν_{\max} (DCM EVAP) 2962, 1596, 1499, 1367, 1263, 1230 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.20 (s, 9H, 'Bu), 2.22 (s, 3H, -CH₃), 2.23 (s, 3H, -CH₃), 3.75 (bs, 2H, -CH₂-), 6.67 (d, *J* = 8.2 Hz, 1H, ArH), 6.74 (d, *J* = 1.6 Hz, 1H, ArH), 6.92 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 20.47 (CH₃), 25.79 (CH₃), 34.45 (CH₃), 54.40 (C), 54.78 (CH₂), 115.78 (CH), 122.02 (C), 127.74 (C), 128.55 (CH), 128.85 (CH), 155.98 (C).

2-[[[(Phenylmethyl)(methyl)amino]methyl]-4-methylbenzen-1-ol (**188**)



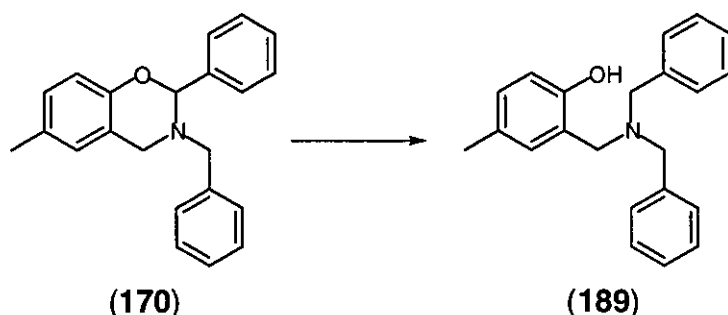
6-Methyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (**168**) (239 mg, 1.00 mmol), chlorotrimethylsilane (0.254 mL, 2.00 mmol) and sodium cyanoborohydride (125 mg, 2.00 mmol) were reacted together in acetonitrile (5.00 mL) according to general procedure A to furnish the crude product as a yellow solid. Recrystallisation from ethanol/water gave 2-[[[(phenylmethyl)(methyl)amino]methyl]-4-methylbenzen-1-ol (**188**) as a pale yellow solid, 231 mg, 96%; mp = 62-66 °C; HRMS (EI): (m/z) calcd for C₁₆H₁₉NO (M⁺) 241.14666; Found: 241.14682; ν_{\max} (DCM EVAP) 3063, 1503, 1495, 1262, 1015, 819 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.21 (s, 3H, -CH₃), 2.24 (s, 3H, -CH₃), 3.57 (s, 2H, -CH₂-), 3.69 (s, 2H, -CH₂-), 6.75 (d, *J* = 8.2 Hz, 1H, ArH), 6.79 (d, *J* = 1.6 Hz, 1H, ArH), 6.96 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 2H, ArH), 7.27-7.34 (5H, m, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 20.46 (CH₃), 41.25 (CH₃), 60.99 (CH₂), 61.48 (CH₂), 115.81 (CH), 121.58 (C), 127.61 (CH), 128.12 (C), 128.55 (CH), 129.09 (CH), 129.16

(CH), 129.32 (CH), 136.98 (C), 155.42 (C).

Procedure B

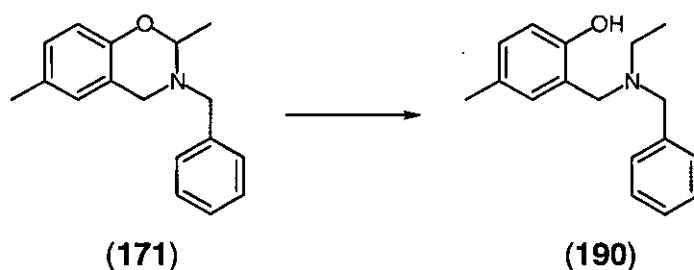
6-Methyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (**168**) (239 mg, 1.00 mmol), and formic acid (20 mL) were reacted together according to the general procedure (B). After work up 2-[[di(phenylmethyl)amino]methyl]-4-methylbenzen-1-ol (**188**) was isolated as a pale yellow solid, 188 mg, 78%.

2-[[Di(phenylmethyl)amino]methyl]-4-methylbenzen-1-ol (**189**)



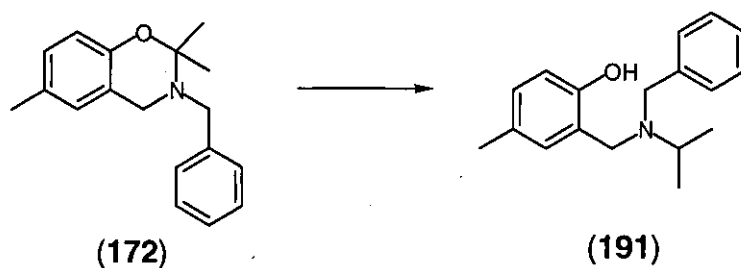
6-Methyl-2-phenyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (**170**) (315 mg, 1.00 mmol), chlorotrimethylsilane (0.634 mL, 5.00 mmol) and sodium cyanoborohydride (313 mg, 5.00 mmol) were reacted together in acetonitrile (10 mL) according to general procedure A, to furnish 2-[[di(phenylmethyl)amino]methyl]-4-methylbenzen-1-ol (**189**) as a yellow oil that slowly crystallised to yield a colourless solid, 316 mg, 99%; mp 105-107 °C; HRMS (EI): (*m/z*) calcd for C₂₂H₂₃NO (*M*⁺) 317.179963; Found: 317.17978; Anal. Calcd for C₂₂H₂₃NO: C, 83.24; H, 7.32; N, 4.40. Found: C, 83.31; H, 7.30; N, 4.42; ν_{\max} (DCM evap) 3026, 1599, 1496, 1253, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.22 (s, 3H, CH₃), 3.59 (s, 4H, 2x-CH₂-), 3.68 (s, 2H, -CH₂-), 6.73 (d, *J* = 8.0 Hz, 1H, ArH), 6.79 (d, *J* = 1.4 Hz, 1H, ArH), 6.96 (dd, *J* = 1.4 Hz, *J* = 8.0 Hz, 1H, ArH), 7.22-7.37 (m, 10H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 20.51 (CH₃), 56.95 (CH₂), 57.90 (CH₂), 115.85 (CH), 121.68 (C), 127.68 (CH), 128.33 (C), 128.65 (CH), 129.21 (CH), 129.53 (CH), 129.61 (CH), 136.90 (C), 155.09 (C).

2-[[Ethyl(phenylmethyl)amino]methyl]-4-methylbenzen-1-ol (190)



2,6-Dimethyl-3-(phenylmethyl)-3,4-dihydro-2H-1,3-benzoxazine (**171**) (253 mg, 1.00 mmol), chlorotrimethylsilane (0.634 mL, 5.00 mmol) and sodium cyanoborohydride (513 mg, 3.00 mmol) were reacted together in acetonitrile (10 mL) according to general procedure A to furnish the crude product as a yellow oil. Purification by flash chromatography (silica gel, 10% ethyl acetate/light petroleum (40 °C-60 °C)) gave 2-[[ethyl(phenylmethyl)amino]methyl]-4-methylbenzen-1-ol (**190**) as a yellow oil, 162 mg, 63%: HRMS (EI): (*m/z*) calcd for $C_{17}H_{21}NO$ (M^+) 255.16231; Found: 255.16227; ν_{\max} (NEAT) 2971, 1600, 1498, 1257 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.11 (t, $J = 8.0$ Hz, 3H, $-\text{CH}_2\text{CH}_3$), 2.23 (s, 3H, CH_3), 2.56 (q, $J = 8.0$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 3.61 (s, 2H, $-\text{CH}_2-$), 3.71 (s, 2H, $-\text{CH}_2-$), 6.73 (d, $J = 8.1$ Hz, 1H, ArH), 6.78 (d, $J = 2.0$ Hz, 1H, ArH), 6.95 (dd, $J = 8.1$ Hz, $J = 2.0$ Hz, 1H, ArH), 7.22-7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 11.00 (CH_3), 20.46 (CH_3), 46.48 (CH_2), 56.92 (CH_2), 57.55 (CH_2), 115.79 (CH), 121.72 (C), 127.50 (CH), 128.05 (C), 128.53 (CH), 129.02 (CH), 129.18 (CH), 129.42 (CH), 137.11 (C), 155.48 (C).

4-Methyl-2-[[[1-methylethyl](phenylmethyl)amino]methyl]benzen-1-ol (191)



2,2,6-Trimethyl-3-(phenylmethyl)-3,4-dihydro-2*H*-1,3-benzoxazine (**172**) (267 mg, 1.00 mmol), chlorotrimethylsilane (0.634 mL, 5.00 mmol) and sodium cyanoborohydride (313 mg, 5.00 mmol) were reacted together in acetonitrile (10 mL) according to general procedure A to furnish 4-methyl-2-[[*(1-methylethyl)*(phenylmethyl)amino]methyl]benzen-1-ol (**191**) as a colourless oil that slowly crystallised to give a colourless solid, 247 mg, 92%: HRMS (EI): (*m/z*) calcd for C₁₈H₂₈NO (*M*⁺) 269.17996; Found: 269.18006; ν_{\max} (NEAT) 2978, 2360, 1496, 1259 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.11 (d, *J* = 6.8 Hz, 6H, -CH(CH₃)₂), 2.22 (s, 3H, CH₃), 3.08 (sept, *J* = 6.8 Hz, 1H, -CH(CH₃)₂), 3.58 (s, 2H, -CH₂-), 3.74 (s, 2H, -CH₂-), 6.69 (d, *J* = 8.2 Hz, 1H, ArH), 6.79 (d, *J* = 1.8 Hz, 1H, ArH), 6.92 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H, ArH), 7.21-7.34 (m, 5H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 17.32 (CH₃), 20.88 (CH₃), 48.83 (CH), 52.70 (CH₂), 53.94 (CH₂), 116.15 (CH), 121.88 (C), 127.99 (CH), 128.60 (C), 129.08 (CH), 129.49 (CH), 129.78 (CH), 129.85 (CH), 138.02 (C), 155.81 (C).

2-[[Methyl(phenylmethyl)amino]methyl]pyridin-3-ol (**183**)



Procedure A

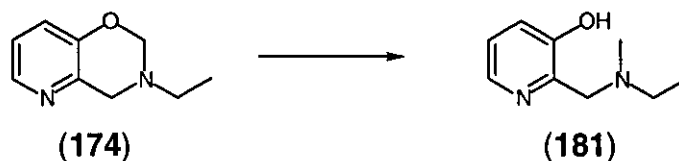
3-Benzyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**176**) (226 mg, 1.00 mmol), chlorotrimethylsilane (0.254 mL, 2.00 mmol) and sodium cyanoborohydride (125 mg, 2.00 mmol) were reacted together in acetonitrile (5.00 mL) according to general procedure A to furnish 2-[[methyl(phenylmethyl)amino]methyl]pyridin-3-ol (**183**) as a yellow oil. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) gave 2-[[methyl(phenylmethyl)amino]methyl]pyridin-3-ol (**183**) as a pale yellow oil, 180 mg, 79%: HRMS (EI): (*m/z*) calcd for C₁₄H₁₈N₂O (*M*⁺)

228.12626; Found: 228.12600; ν_{\max} (NEAT) 3029, 2848, 1576, 1447, 1272, 1015, 747 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.30 (s, 3H, $-\text{NCH}_3$), 3.65 (s, 2H, $-\text{CH}_2-$), 3.97 (s, 2H, $-\text{CH}_2-$), 7.10-7.11 (m, 2H, ArH), 7.11-7.38 (m, 5H, ArH), 8.01-8.02 (m, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 41.62 (CH_3), 61.80 (CH_2), 63.09 (CH_2), 122.94 (CH), 123.62 (CH), 128.70 (CH), 128.96 (CH), 129.42 (CH), 136.43 (C), 140.00 (CH), 142.96 (C), 154.37 (C).

Procedure B

3-Benzyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**176**) (500 mg, 2.21 mmol), and formic acid (10 mL) were reacted together according to the general procedure (B). After work up 2-[[methyl(phenylmethyl)amino]methyl]pyridin-3-ol (**183**) was isolated as a pale yellow solid, 373 mg, 74%.

2-[[Ethyl(methyl)amino]methyl]pyridin-3-ol (**181**)



Procedure A

3-Ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**174**) (164 mg, 1.00 mmol), chlorotrimethylsilane (0.254 mL, 2.00 mmol) and sodium cyanoborohydride (125 mg, 2.00 mmol) were reacted together in acetonitrile (5.00 mL) according to general procedure A to furnish the crude product as a yellow oil. Purification by flash chromatography (silica gel, 20% methanol/dichloromethane) gave 2-[[ethyl(methyl)amino]methyl]pyridin-3-ol (**181**) as a pale yellow oil, 146 mg, 88%: HRMS (EI): (m/z) calcd for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}$ (M^+) 166.11061; Found: 166.11066; ν_{\max} (NEAT) 2973, 1578, 1448, 1272, 802 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (t, $J = 7.2$ Hz,

3H, -CH₂CH₃), 2.35 (s, 3H, -NCH₃), 2.59 (q, *J* = 7.2 Hz, 2H, -CH₂CH₃), 3.91 (s, 2H, -CH₂-), 7.08-7.09 (m, 2H, ArH), 7.97-7.99 (m, 1H, ArH), 10.00 (bs, 1H, OH); ¹³C NMR (100 MHz, CDCl₃) δ 11.94 (CH₃), 41.15 (CH₃), 51.05 (CH₂), 62.99 (CH₂), 122.92 (CH), 123.49 (CH), 139.63 (CH), 143.00 (C), 154.77 (C).

Procedure B

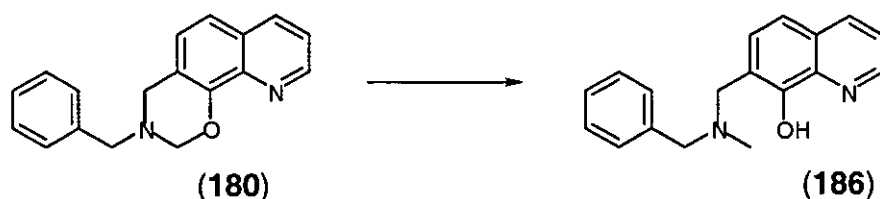
3-Ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**174**) (164 mg, 1.00 mmol), and formic acid (5.00 mL) were reacted together according to the general procedure (B). After work up, 2-[[ethyl(methyl)amino]methyl]pyridin-3-ol (**181**) was isolated as a pale yellow oil, 66 mg, 40%.

2-[[[(1,1-Dimethylethyl)(methyl)amino]methyl]pyridin-3-ol (**182**)



3-*t*-Butyl-3,4-dihydro-2*H*-pyrido[2,3-*e*][1,3]oxazine (**175**) (178 mg, 1.00 mmol), chlorotrimethylsilane (0.634 mL, 5.00 mmol) and sodium cyanoborohydride (313 mg, 5.00 mmol) were reacted together in acetonitrile (10 mL) according to general procedure A to furnish the crude product as a yellow oil. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) gave 2-[[[(1,1-dimethylethyl)(methyl)amino]methyl]pyridin-3-ol (**182**) as a pale brown oil, 162 mg, 90%; HRMS (EI): (*m/z*) calcd for C₁₁H₁₈N₂O (*M*⁺) 194.14191; Found: 194.14166; *v*_{max} (NEAT) 2973, 1577, 1448, 1234, 802 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, v.t. at 50 °C) δ 1.22 (s, 9H, ^{*t*}Bu), 2.31 (s, 3H, -NCH₃), 4.00 (s, 2H, -CH₂-), 7.01-7.02 (m, 2H, ArH), 7.95-7.96 (m, 1H, ArH), 8.90 (bs, 1H, OH); ¹³C NMR (100 MHz, CDCl₃, v.t. at 50 °C) δ 25.99 (CH₃), 35.65 (CH₃), 55.37 (C), 57.50 (CH₂), 123.12 (CH), 123.38 (CH), 139.61 (CH), 143.87 (C), 155.46 (C).

7-[[Methyl(phenylmethyl)amino]methyl]quinolin-8-ol (**186**)

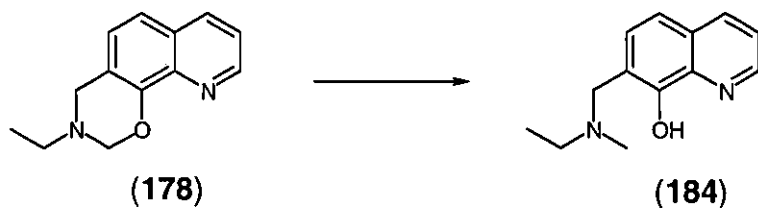


3-(Benzyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**180**) (276 mg, 1.00 mmol), chlorotrimethylsilane (0.254 mL, 2.00 mmol) and sodium cyanoborohydride (125 mg, 2.00 mmol) were reacted together in acetonitrile (5.00 mL) according to general procedure A to furnish 7-[[methyl(phenylmethyl)amino]methyl]quinolin-8-ol (**186**) as a yellow oil, 264 mg, 95%: ^1H NMR (400 MHz, CDCl_3) δ 2.29 (s, 3H, $-\text{NCH}_3$), 3.68 (s, 2H, $-\text{CH}_2-$), 3.92 (s, 2H, $-\text{CH}_2-$), 7.25-7.39 (m, 8H, ArH), 8.05 (dd, $J = 8.4$ Hz, $J = 1.6$ Hz, 1H, ArH), 8.86 (dd, $J = 4.0$ Hz, $J = 1.6$ Hz, 1H, ArH).

Procedure B

3-(Benzyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**180**) (276 mg, 1.00 mmol), and formic acid (5 mL) were reacted together according to the general procedure (B). After work up 7-[[methyl(phenylmethyl)amino]methyl]quinolin-8-ol (**186**) was isolated as a pale yellow solid, 150 mg, 54%.

7-[[Ethyl(methyl)amino]methyl]quinolin-8-ol (**184**)



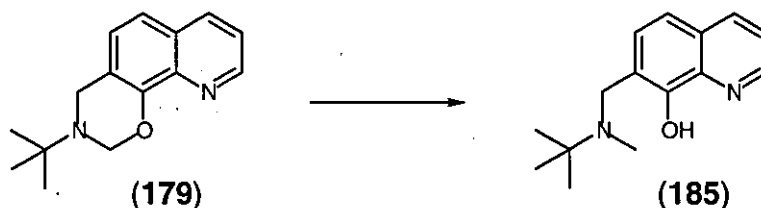
3-(Ethyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**178**) (331 mg, 1.54 mmol), chlorotrimethylsilane (0.392 mL, 3.09 mmol) and sodium cyanoborohydride (0.193

mg, 3.09 mmol) were reacted together in acetonitrile (10 mL) according to general procedure A to furnish 7-[[ethyl(methyl)amino]methyl]quinolin-8-ol (**184**) as a yellow oil, 327 mg, 98%: ^1H NMR (250 MHz, CDCl_3) δ 1.19 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$), 2.37 (s, 3H, $-\text{NCH}_3$), 2.63 (d, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 3.89 (s, 2H, $-\text{CH}_2-$), 7.17-7.38 (m, 3H, ArH), 8.08 (dd, $J = 8.3$ Hz, $J = 2.7$ Hz, 1H, ArH), 8.86 (dd, $J = 4.0$ Hz, $J = 1.7$ Hz, 1H, ArH);

Procedure B

3-(Ethyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**178**) (214 mg, 1.00 mmol), and formic acid (5 mL) were reacted together according to the general procedure (B). After work up 7-[[ethyl(methyl)amino]methyl]quinolin-8-ol (**184**) was isolated as a pale yellow solid, 106 mg, 49%.

7-[[1,1-Dimethylethyl)(methyl)amino]methyl]quinolin-8-ol (**185**)



3-(*t*-Butyl)-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**179**) (230 mg, 0.95 mmol), chlorotrimethylsilane (0.24 mL, 1.89 mmol) and sodium cyanoborohydride (0.119 mg, 1.89 mmol) were reacted together in acetonitrile (10 mL) according to general procedure A to furnish 7-[[1,1-dimethylethyl)(methyl)amino]methyl]quinolin-8-ol (**185**) as a yellow oil, 235 mg, 95%: ^1H NMR (250 MHz, CDCl_3) δ 1.26 (s, 9H, ^tBu), 2.32 (s, 3H, $-\text{NCH}_3$), 3.98 (s, 2H, $-\text{CH}_2-$), 7.12-7.34 (m, 3H, ArH), 8.01 (m, 1H, ArH), 8.83 (m, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ 25.84 (CH_3), 34.85 (CH_3), 54.43 (CH_2), 55.03 (C), 116.83 (CH), 118.51 (C), 120.86 (CH), 127.06 (CH), 128.32 (C), 135.57 (CH), 139.66 (C), 148.82 (CH), 154.41 (C).

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