SYNTHESIS OF NOVEL SURFACTANTS
AND THEIR
USE IN ASYMMETRIC CATALYSIS.

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A thesis submitted in partial fulfilment of the requirement
for the degree Of Doctor Of Philosophy.

University College London

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Declaration: I, Prakashanand Caumul, hereby state that the following is entirely my own work and has not been submitted for any other degree or examination.

Prakashanand Caumul
July 2002.
ABSTRACT

Micelles can affect the rate, stereo-, regio- and enantioselectivity of organic reactions.\(^1,2,3\) This project investigates the synthesis and use of several novel surfactants as micellar catalysts in aqueous and organic media. Previous work within the group has involved the synthesis of surfactants derived from \((1S,2R)\)-norephedrine giving particularly good yields and selectivities in the diethyl zinc addition reactions.\(^4\)

This thesis is comprised of seven chapters. Initially **chapter one** reviews the background literature covering:

(i) The properties and applications of surfactants.
(ii) Previous literature on the addition of diethyl zinc to a range of aldehydes using various chiral catalysts.
(iii) Literature on the use of organic reactions in aqueous media.

**Chapter two** describes the synthesis of surfactants derived from different analogues: \(S\)-tyrosine, \(S\)-proline, oxazolo pyridinone, and the alkaloids hydroquinidine and cinchonine. The Critical Micelle Concentration (CMC) and Reverse Critical Micelle Concentration (RCMC) analysis of these surfactants are outlined in **chapter three** using dye solubilisation techniques.

**Chapters four to six** describe the use of these surfactants as catalysts for a number of asymmetric reactions including **diethylzinc reactions** with various aldehydes.

Then use of the catalysts in **Michael addition reactions** are presented. These reactions are carried out in water. In particular, the reaction between diethyl malonate and cyclopentenone is studied. In addition the use of an \(\alpha\)-substituted cyclopentenone is described and the reaction selectivities rationalised.

**The Baylis-Hillman reactions** are also investigated in water using a range of activated alkenes and aldehydes and the selectivities and yields obtained are presented and rationalised. Improved yields were achieved when using acidified water.

In the **final chapter**, the experimental section, all experimental procedures are given together with full compound characterisation.
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Abbreviations.

α - optical rotation.
Acac - acetylacetonato ion.
AIBN - azobisisobutyronitrile.
ATM - atmosphere of pressure.
BINAP - 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl.
BINOL - 1,1'-bi-2-naphthol.
BMS - borane-dimethyl sulfide.
br - broad.
Bu - butyl.
cal - calories.
CMC - Critical Micelle Concentration.
CTAB - Hexadecyltrimethyl ammonium bromide.
DABCO - 1,4-Diazabicyclo [2.2.2] octane.
DAIB - di-methylamino isoborneol.
DBU - 1,8-Diazabicyclo [5.4.0] undec-7-ene.
DCM - dichloromethane.
DMAP - 4-dimethylaminopyridine.
DMF - dimethylformamide.
DMSO - dimethylsulfoxide.
DPMPM - diphenyl (1-methylpyrrolidin-2-yl) methanol.
EDCI - 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide.
ε,e - enantiomeric excess.
EI - electron ionisation.
ES - electrospray.
ESR - Electron-spin resonance.
Et - CH2CH3.
EVK - ethyl vinyl ketone.
EWG - Electron withdrawing group.
FAB - fast atom bombardment.
ΔH - Enthalpy change.
HPLC - high-performance liquid chromatography.
Hz - Hertz.
IR - infra red.
J - Joules.
KDC - potassium dodecanoate micelles.
K - Kelvin.
LASC - Lewis acid-surfactant-combine catalyst.
m - mass.
M - Molar.
M - Molecular mass ion.
m.pt - melting point.
MVK - methyl vinyl ketone.
NMR - Nuclear magnetic resonance.
o - ortho.
p - para.
Ph - phenyl.
PMPM - phenyl (1-methylpyrrolidin-2-yl) methanol.
PNPM - phenyl (1-neopentylpyrrolidin-2-yl) methanol.
ppm - parts per million.
Pr - CH(CH3)2.
PTC - phase transfer catalysis.
RCMC - Reverse Critical Micelle conc.
rt - room temperature.
τc - rotational correlation time.
TCNQ - 7,7,8,8 tetracyanoquinodimethane.
Tert (t) - tertiary.
Tf - Triflic (Trifluoromethanesulfonic).
THF - tetrahydrofuran.
THP - tetrahydropyranyl.
TMS - trimethyl silyl.
s - strong.
SAMP - (S)-1-Amino-2-(methoxymethyl) pyrrolidine.
SDS - Sodium dodecyl sulfate.
STDS - scandium tris (dodecyl sulfate).
UV - Ultra Violet.
v - wavenumber.
vis - visible light.
w - weak.
z - charge.
1. Introduction.

The introduction is divided into 3 sections. The first covers an overview of surfactants, reviewing their aggregation to generate micelles as well as their properties and applications. The second section reviews background literature to the addition of dialkyl zinCs to a range of aldehydes in the presence of various chiral catalysts. The final section deals with organic reactions in aqueous media, reviewing in particular Diels-Alder, Michael additions, Baylis-Hillman reactions and phase-transfer reactions.

1.1 Surfactants (Surface Active Agents).

Surfactants are surface active compounds which are present in many consumer products ranging from soaps, detergents and cosmetics to cooking oil. By definition, surfactants are molecules which contain polar head groups linked to non-polar tails comprised of a long hydrophobic hydrocarbon chain. The hydrocarbon chain normally contains between 8-18 methylene groups (Figure 1.1.1).^5

![Representation of a surfactant monomer.](image)

Surfactants can be classified into four groups.^6 Their classification depends on the nature of their polar heads e.g anionic, cationic, non-ionic and zwitterionic (surfactants that have both a positive and negative polar head group), and examples of each are given in Table 1.1.1.^7
<table>
<thead>
<tr>
<th>Surfactant type</th>
<th>Example</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anionic</td>
<td>Sodium dodecyl sulfate (SDS)</td>
<td>CH$_3$(CH$<em>2$)$</em>{11}$SO$_4^-$Na$^+$</td>
</tr>
<tr>
<td>Cationic</td>
<td>Hexadecyltrimethyl ammonium bromide (CTAB)</td>
<td>CH$_3$(CH$<em>2$)$</em>{16}$N(CH$_3$)$_3^+$Br$^-$</td>
</tr>
<tr>
<td>Non-ionic</td>
<td>Polyethylene oxide</td>
<td>CH$_3$(CH$<em>2$)$</em>{11}$(OCH$_2$CH$_2$)$_6$OH</td>
</tr>
<tr>
<td>Zwitterionic</td>
<td>Dodecyl betaine</td>
<td>C$<em>{12}$H$</em>{25}$N$^+$((CH$_3$)$_2$CH$_2$)COO$^-$</td>
</tr>
</tbody>
</table>

Table 1.1.1 Classification and types of surfactants present.

Synthetic anionic surfactants are widely used in washing up liquids, shampoos and bath foam. Non-ionic surfactants are present in many household cleaners and washing powders. Cationic surfactants are used in fabric softeners and hair conditioners. The properties of these surfactants include detergency, foaming, wetting and micellisation.

Surfactants also have important biological functions. For example, the moist membrane in the air sac (the alveolus) in the lungs secretes a natural surfactant which is responsible for preventing the lungs from collapsing. In the absence of this surfactant, the water molecules would be attracted too strongly to the membrane forcing the entire lungs to collapse.

Another example includes bile salts such as 1 which are secreted into the intestinal tract where they function as powerful surfactants assisting mechanistically in the digestion of dietary lipids and the absorption of fat-soluble vitamins.

![Sodium Cholate (a bile salt).](image)

1.1.1 Formation of Micelles.

Since surfactants contain both a hydrophilic head group and a hydrophobic hydrocarbon tail, they can have limited solubility in many solvents.
As a result it has been observed that in most phase systems, e.g. oil/water, surfactant monolayers are formed at the interface. At low concentrations of surfactant in any solvent, it is found that they exist as monomers which adsorb onto the interface between two phases. The polar head group positions itself in the more polar phase and the non-polar hydrocarbon chain is immersed in the least polar phase.

As the concentration of a surfactant increases in a solvent, more of the surfactant molecules adsorb onto the surface until the interface is covered with one monolayer of surfactant (Figure 1.1.2). At this point, the surfactant begins to aggregate to form micelles. The concentration at which micelles begin to form is known as the critical micelle concentration (CMC). This aggregate formation is a dynamic process since the monomer and micelles are in dynamic equilibrium with each other.

![Figure 1.1.2. Adsorption of surfactants at the interface (1 monolayer).](image)

The concentration of micelles ($C_M$) can be calculated as proposed by Fendler et al using the following equation:

$$C_M = (C_D - CMC) \frac{N}{N}$$

$C_M = Critical\ Micelle\ Concentration$

$C_D = monomer\ concentration$

$N = aggregate\ number$
The value of $N$ can be determined by methods such as light scattering.\textsuperscript{11} Micelles made up of non-ionic surfactant molecules may cluster together in clumps of 1000 or more \textit{i.e.} $N \geq 1000$. However, for species with an ionic polar head group, the aggregation number ($N$) is low since there is an electrostatic repulsion between the neighbouring head groups ($N = 10-100$).

Investigations into the thermodynamics of micelle formation have shown that the enthalpy of formation in an aqueous system is positive \textit{i.e.} this is an endothermic process with $\Delta H \approx 1-2$ kJ mol$^{-1}$ of surfactant.\textsuperscript{12} The entropy change was also observed to be positive (+140 J K$^{-1}$mol$^{-1}$) even though the molecules cluster together at this point. This indicated that there must be a contribution to the entropy from the solvent which becomes less ordered once surfactant molecules started to aggregate. This may be due to the formation of a much larger solvent cage than the cage formed when each individual surfactant monomer is present.\textsuperscript{12} The increase in energy when the hydrophobic groups cluster together leads to \textbf{hydrophobic interactions} which tend to stabilise the hydrophobic groups in the micelle.

Micelles are formed due to the repulsion of the neighbouring head group, Van-der-waals attractions between the aliphatic hydrocarbon chains, and hydrogen bonding between the adjacent head groups.\textsuperscript{13}

\subsection*{1.1.2 Structure of micelles.}

Many investigations have been carried out to determine the structure of micelles.\textsuperscript{14} Light scattering, $^1$H NMR, $^{13}$C NMR, ESR, $^{19}$F NMR, X-ray diffraction and emission spectroscopy are some of the techniques that have been used. These studies showed that surfactant monomers aggregate in such a way that the hydrocarbon tail points into the core of the micelle with the polar head group pointing outwards into the aqueous solution. This aggregation shields the hydrophobic, hydrocarbon chains from water.

The most generally accepted model of a micelle is the one proposed by Hartley in 1936 (Figure 1.1.3).\textsuperscript{15} Whilst this can be considered to be a simplistic
representation, it is a useful means of visualisation of how a micelle may look in aqueous media. Hartley suggested that micelles consist of 3 regions:-

(i) The micellar core which is made up of hydrocarbon chains (normally 8-10 carbon units). This layer eliminates hydrocarbon-water interactions since the tail is hydrophobic and the layer has a size of between 10-28 Å. The outer core contains the first four methylene groups. This core also contains a few water molecules and this region is called the **palisade layer** or the **mantle**. The inner core contains the rest of the alkyl chains. These are packed closely together since they are held together by van der Waals forces.

(ii) The Stern layer contains the polar head groups which interact with the aqueous exterior and forms a spherical surface charge. Counterions which are tightly bound are also present in this layer which is only up to a few Å deep.

(iii) The Gouy-Chapman layer contains the remaining counterions which are diffused in the aqueous solution and is of several hundred Å in depth.

---

![Hartley model of a micelle](image)

**Fig. 1.1.3** Hartley model of a micelle.
Hartley's representation made the assumption that the hydrocarbon chains adopt a *trans* orientation. However this is not possible since there is insufficient space in the centre of the micelle to accommodate the hydrocarbon chains suggesting the chains fold and coil.

The Hartley model most likely reflects the spherical aggregates formed at a few percent above the CMC. Above this concentration, the micellar structure appears to change from spherical to an elongated, larger rod-like shape (Figure 1.1.4).[^18][^19]

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The Hartley model most likely reflects the spherical aggregates formed at a few percent above the CMC. Above this concentration, the micellar structure appears to change from spherical to an elongated, larger rod-like shape (Figure 1.1.4).[^18][^19]

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From the Hartley model, the volume of the micelle was calculated to be approximately twice the volume of the Stern layer. X-ray studies also showed a relationship between the micellar volume $V$ (Å$^3$), the aggregation number $n$, and the number of carbons in the hydrocarbon chain $n_c$:

$$V = n \left(27.4 + 26.9 n_c\right)$$

where 27.4 and 26.9 are measured constants.$^{14}$ Also according to the Hartley model, the presence of water in the micellar core is excluded due to the hydrophobic nature of that region.

In 1981 Dill and Flory modified the Hartley representation and proposed "the lattice model" which contains methylene chains in both $cis$ and $trans$ orientations where the alkyl chains can fold up on themselves to varying degrees (Figure 1.1.6).$^{20}$

![Fig. 1.1.6 Dill and Flory lattice model (1981)](image)

The Hartley model was also questioned by Menger.$^{21}$ Unlike Dill and Flory, Menger proposed that micelles were like "porous clusters" containing a large amount of water within the aggregates (Figure 1.1.7). However solubilisaton studies have indicated that this is incorrect.$^{22}$
Other models that have been used to elaborate the Hartley model, include the "fjord" model which is similar to Menger's micelle, in that it allows water molecules to penetrate into the micellar core. The "reef" model has also been studied, which was put forward by Stigter, where water is allowed to penetrate the first few methylene groups of the hydrophobic chain but not into the micellar core.

The formation and breakdown of a micelle is a dynamic process as mentioned above, with a half-life of approximately $10^{-7}$ seconds. This is governed by a balance between the hydrophobic attractions of the hydrocarbon chain and the repulsive forces of the polar head group. Since there is a rapid formation and breakdown of micelles in aqueous media, it is reasonable to assume that some water molecules could be found in the micellar interior, providing some credibility for Menger's proposal.

Reverse micelles can also be formed in apolar solvents where the hydrophilic head group aggregates to form the micellar core and the hydrophobic hydrocarbon chains are directed towards the apolar solvent (Figure 1.1.8). These micelles are ideal for water entrappment which can take place in the micellar core. They can also catalyse reactions by solubilising polar substrates, which then move towards the polar head group region. Reaction selectivities can occur as a result of preorientation and concentration effects.
1.1.3 Factors that affect the CMC.

There are several factors which affect the CMC. These include:

(i) Size of the head group.

It has been reported that as the size of the head group increases, the CMC also increases due to repulsion between the head groups. In addition strongly ionised polar groups such as SDS were found to give rise to a higher CMC whilst increasing the size of the counterion reduces the CMC.

(ii) Length of the hydrocarbon chain.

When the length of a hydrophobic alkyl chain of a surfactant is increased, micelle formation is favoured due to increased attractive Van-der-Waals forces. However, it has been found that above a chain length of C18 the CMC normally remains constant. The reason for this has been attributed to coiling and folding of the hydrocarbon chain. This is demonstrated by considering the anionic sodium alkyl sulphates where an increase in the hydrocarbon chain length from n=8 to n=18 decreases the CMC by a factor of 600. The
introduction of chain branching and the presence of double bonds also increases
the CMC compared to a linear alkyl series.\textsuperscript{32}

(iii) Temperature of surfactant solution.

The temperature of a solution will also effect the CMC which usually
increases as the temperature rises. Interestingly, surfactants acquire a rapid
increase in their solubility above a certain temperature called the \textbf{Krafft point}
(Graph 1.1.1).

![Graph 1.1.1: Effect of surfactant solubility on temperature in region of
Krafft point.]

Other factors which affect CMCs include the use of additives.\textsuperscript{31} An
example is the addition of sodium salts to an ionic surfactant solution which
reduces the repulsion between charged head groups. For example when 0.3 M
NaCl was added to solutions of SDS (sodium dodecyl sulphate), the CMC was
reduced by a factor of 10.\textsuperscript{31}

The addition of organic molecules to micellar solutions can also affect the
CMC, for example it has been observed that the addition of sugars can enhance
the hydrogen-bonded water structures which in turn decreases the CMC.\textsuperscript{7, 33}
1.1.4 Properties of micelles.

The formation of micelles above the CMC level can alter the physico-chemical properties of surfactants. These properties include solubilisation, turbidity, conductivity and osmotic pressure.

a) Surface tension.

Above the CMC region, the micellar aggregates are not as effective at reducing surface tension compared to when they were in the form of the monomer. This results in a reduction in surfactant viscosity and soaping abilities since micelles do not reduce the surface tension of water as well as single monomers. This reduces its detergency properties.

b) Osmotic pressure.

This depends on the number of surfactant molecules present. The osmotic pressure increases as the surfactant concentration increases. Above the CMC, the rate of change in pressure is lower due to aggregation of surfactant molecules into larger particles.

c) Turbidity.

An increase in turbidity is observed above the CMC, suggesting that larger particles are formed. This effect causes an increase in light scattering.

The CMC for a particular surfactant can be determined by plotting a graph of a physical property of the surfactant solution as a function of surfactant concentration (Graph 1.1.2). Examples of the physical property measurements used, are surface tension and conductance. The concentration at which a change in the gradient of the graph occurs is normally where the CMC is.
Micelles can also produce a number of effects which can influence organic reactions.\textsuperscript{16} The two main effects are concentration and medium effects.\textsuperscript{16,35}

**Concentration** effects occur when reactants solubilise within a micelle, due to both hydrophobic and electrostatic interactions. This effect can alter the reactivity of the substrate and the reactive ion.\textsuperscript{13,17,28}

**Medium** effects consist of mainly cage, preorientation, microviscosity, polarity and charge effects.

The cage effect is when the micelle traps the reactants within the interior of the micelle sufficiently long for the reaction to occur.\textsuperscript{35,36}

**Preorientation** effects occur when the micelle is able to solubilise a substrate with a specific orientation. This effect can control the regio and stereospecificity of reactions.\textsuperscript{16,37}

**Microviscosity** effects lead to a decrease in the translational and rotational freedom of the substrate within the micelle which results in an alteration of their reactivity. This occurs since there is a higher viscosity within the micelle than outside.\textsuperscript{16,38}

**Charge effects** involve the charged head groups in the Stern layer stabilising charged, partially charged or radical intermediates by hydrogen bonding, or a co-ordination or complexation between the head groups which can
align the surfactant molecules in such a way as to produce a favourable reaction environment.\textsuperscript{29,39}

Finally, polarity effects occur when the exterior of the micelle is more polar than the interior. Hence by changing the charged species present in the Stern layer, the micellar reactivity can be altered.\textsuperscript{16,35}

1.1.5 Techniques used to Determine CMC.

Many techniques such as X-ray diffraction, NMR and ESR have been used to determine the CMC of surfactants.\textsuperscript{40} However, two techniques which are regularly used are electrical conductivity and dye solubilisation.\textsuperscript{34,40}

(i) Electrical conductivity.

Upon the formation of micelles, the electrical conductivity is affected in several ways. When molecules aggregate above the CMC, the net viscous drag is reduced which in turn increases the conductivity. Also, upon the migration of surfactant ions, it has been found that the unattached counterions have a lower retarding influence compared to when they aggregate, and where the retarding influence is increased, the conductivity is reduced.

Furthermore, the counterions present may become part of the micelle. This reduces the number of counterions available for transporting charge, which results in the lowering of the net charge of the micelle and a reduced conductivity.

The two later effects outweigh the first and molar conductivity normally decreases with increasing surfactant concentration above the CMC.

(ii) Dye solubilisation.

This method has been commonly used to determine aqueous CMCs\textsuperscript{34,41-44} and has been found to be a useful tool in providing an initial indication of the CMC surfactant range. A known amount of an organic dye is solubilised into solution containing increasing concentrations of surfactant. The change in absorption (at $\lambda_{\text{max}}$ which is the wavelength at which maximum absorbance was observed) is plotted against surfactant concentration. Upon comparing the change
in absorption to surfactant concentration and graphically presenting this data, the resulting curve is normally sigmoidal in shape. The concentrations at which the absorbance maxima intersects, corresponds to the initial and final aggregation between the surfactant and the dye. The final aggregation is assumed to be the “CMC” range which represents a mixed micellar aggregate made up of the surfactant and the dye.

The changes in the UV spectrum upon micellar formation has been attributed to conjugate shifts of the organic dye as a result of strong electrostatic interactions when the dye is solubilised within the micelle. Dutta and Bhat showed that the different canonical forms of methyl orange (2) gave distinct UV spectra in solution when interacting with CTAB.44a, 44b Their findings can be represented in Figure 1.1.9. The two resonance forms 2a and 2b have a delocalised \( \pi \) electron system. In an apolar media, solutions would exhibit \( \lambda_{\text{max}} \) at 360 nm corresponding to the left handed resonance form which is preferred to the right handed canonical form which predominates in a polar media (\( \lambda_{\text{max}} \) at 460 nm).44a, 44b Below the CMC, 2b was found to exist preferentially in probably the more thermally stable trans isomer. At this point the methyl orange exhibited a \( \lambda_{\text{max}} \) at 460 nm which decreased in intensity as the concentration of CTAB was increased leading to an increase in intensity of \( \lambda_{\text{max}} \) at 360 nm.44a, 44b At and above the CMC, 2a can penetrate within the micelle existing in its less polar singly charged form. The change in electron delocalisation resulting in reduced conjugation explains the change in the UV absorption.44a, 44b It is postulated that a conformational change of the bound dye could also be partially responsible for the UV absorption change. However this has recently been ruled out on the basis of resonance Raman spectroscopy which showed that the dye retains its trans configuration when interacting with surfactants.44c
It is worth noting however that Reeves used kinetic studies to indicate some of the shortcomings of the dye solubilisation technique.\textsuperscript{44d} It was observed that the use of organic dyes affect the micellar structure and CMC to some extent. It was found that dye-surfactant interactions below the CMC led to the formation of dye aggregates, dye-surfactant salts or complexes which would affect the CMC.\textsuperscript{44d}

The presence of "submicelles" and "premicelles" below the CMC have been reported when surfactants have interacted with dyes. Interactions of anionic dyes with cationic surfactants have led to the formation of mixed micelles of varying composition structure and stability.\textsuperscript{44d}

These problems can be overcome when determining the CMC of novel surfactants, by testing the organic dyes on known surfactants whose CMC values have already been established before being tested on novel surfactants of interest.

\textit{p-Methyl red} and cresyl violet acetate are other commonly used dyes suitable for determining the CMC of surfactants.\textsuperscript{34,41}

Dye solubilisation methods to determine RCMCs have also been reported.\textsuperscript{45,46} These include iodine solubilisation which was initially investigated by Ross and Olivier.\textsuperscript{46} During solubilisation, iodine is in equilibrium with the charged iodonium ion as shown below:

\[ 2I_2 \rightleftharpoons I_3^- + I^+ \]

The iodonium ions are not stabilised below the RCMC in apolar solvent, however above the RCMC, the iodonium ion passes into the polar core of the
reversed micelle and is stabilised by the cationic head groups. This shift in equilibrium is observed by a change in the absorption of the solvated species present ($I_2$ absorbs at 500 nm whereas $I_3/I^+$ absorbs at 400 nm).

### 1.1.6 Nature of the interior of micelles.

Reports have indicated that the interior of micelles are liquid like in character. Studies using cetyl trimethylammonium bromide (CTAB) have found the same molecular motion as benzene in its liquid crystal phase.\(^{47}\) (Note that at the liquid crystal phase, the substance flows like a liquid but has some order in its molecular arrangement. This occurs at the point at which certain solids melt and some aspects of arrangement order of the molecule is retained giving a new liquid crystal phase).\(^{47a}\) Since micelles and liquid crystals begin to form at roughly the same temperature, it was concluded that the micellar interior was liquid like. This was confirmed by Schintzky who has studied the microviscosity of the liquid-like interior.\(^{48}\) He measured the fluorescence depolarisation of 2-methyl anthracene in a number of micellar solutions which included dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide (CTAB) and octadecyldimethylbenzyl ammonium bromide at 27 °C, and found that the ratio of microviscosity of the interior micelles to be 50:38 water:decane. He concluded that the micellar interior did have a liquid like property, but was not as fluid as hydrocarbons of a similar chain length. This argument has been supported by reports using NMR spectroscopy to indicate that the hydrocarbon tails are mobile, but slightly more restricted than the bulk solution.\(^{49,50}\) Menger also substantiated this argument when he used \(^{13}\)C NMR spin-lattice relaxation times to establish the microviscosity of \(\omega\)-phenyldecanoate.\(^{49,50}\)

Li et al. used an ESR spin-label method to study the physical state of CTAB by measuring the changes in the rotational correlation time ($\tau_c$), using a nitroxide labelled fatty acid probe (5-doxylo stearic acid) in several different surfactant concentrations.\(^{51}\) A change in $\tau_c$ was observed above the CMC of CTAB when the probe was solubilised in the surfactant. These results indicated that the micellar hydrocarbon core acquired a similar microviscosity to
hexadecane at -22 °C and 40 °C, indicating that the micelle interior was considered to be fluid-like in nature.  

1.1.7 Micellar Catalysts. 

Reports on the use of surfactants and micelles have shown that reaction pathways, routes and rates of certain reactions can be altered when reactions are performed in micellar media. A few of these reactions will be reviewed in the next sections. 

The advantage of using aqueous micellar media in which to perform organic transformations are that surfactants are relatively inexpensive, they can be recycled and reactions can be carried out in aqueous solutions. The two main properties that make micelles ideal catalysts are their ability to solubilise hydrophobic organic substrates into a micellar structure and the nature of the counterions present. Counterions are very important in micellar catalysis since reactive ions can either be repelled or attracted by the electrical charge on the polar head of the micelle resulting in either catalysis or inhibition of the reaction.

Hydrocarbon chain lengths and the size and nature of the head group are all important factors in micellar catalysts. It has been found that the more hydrophobic a surfactant is, the better its catalytic properties are.

Micellar catalysis can effect the reaction yields, regio-, stereo- and enantioselectivity of reactions. 

Enhancement of reaction yields/rates. 

Several investigations have been carried out into the use of micellar catalysis to enhance reaction rates. An example is the use of micellar catalysts in Diels-Alder reactions. Extensive work in this area has been covered by Breslow, Saur, Diego-Castro and co-workers (see section 1.3). The effects of CTAB as catalyst in the Diels-Alder reaction between cyclopentadiene and 3 is shown in Figure 1.1.10. In the absence of CTAB, the reaction does not proceed even when heating the reaction at reflux for 30 hours. In the presence of CTAB, compound 4, is generated at room temperature after 3 hours.
Micellar effects on regioselectivity, enantioselectivity and stereoselectivity.

Micellar catalysts have been found to affect regioselectivities in several photochemical reactions,\textsuperscript{16} for example the irradiation of 2-substituted naphthalenes. The \textit{cis}-dimer was the major product in micellar media such as SDS, whereas the \textit{trans}-dimer was predominant in conventional organic solvents. This is most likely due to the orientation of the substrates within a micelle where hydrophilic groups (R\textsubscript{1} and R\textsubscript{2}) are directed towards the micellar water interface (Figure 1.1.11).\textsuperscript{37,59}
A related example includes the dimerisation of 3-decylcyclopentenones in potassium dodecanoate micelles (KDC) where a reversal in the regiochemistry occurred compared to when an organic medium was used (Figure 1.1.12).\textsuperscript{16, 60} The product distribution was attributed to the orientation of the monomers with their carbonyl oxygen at the micellar interface.

\[ R = \text{CH}_3(\text{CH}_2)_9 \]
\[ \text{KDC} = \text{CH}_3(\text{CH}_2)_6\text{COO}^-\text{K}^+ \]

**Fig. 1.1.12 Effects of micellar KDC on 3-decylcyclo pentenone reaction.\textsuperscript{16, 60}**

Regioselectivities have also been observed in the chlorination of phenol using sodium dodecyl sulphate (SDS) and \textit{t}-butyl hypochlorite (\textit{t}-BuOCl) where enhanced ortho selectivity was observed compared to when no surfactant was used. Suckling indicated that NMR studies revealed the orientation of phenol in SDS was with the ortho position in a more polar environment, whilst the para position was protected by the hydrophobic alkyl chains of the SDS surfactant (Figure 1.1.13).\textsuperscript{61}
Zhang et al has recently used (-)-(1S,2R)-ephedrine derived surfactants 8 and 9 as catalysts in the enantioselective synthesis of oxiranes from dimethylsulfonium methyliede and aromatic aldehydes and ketones using dichloromethane:aqueous NaOH (50:50) as solvent.\(^{62}\) (Figure 1.1.14). When surfactant 9 was used, higher enantioselectivities were achieved than with 8 containing the shorter chain. However, when using both surfactants 8 and 9 in the enantioselective alkylation of ethyl 2-phthalimidoacetate where the surfactants behaved as reverse micelles the shorter chain analogue 8 led to higher enantioselectivities than the longer chained surfactant 9.\(^{63}\)

\[
\begin{align*}
\text{Fig. 1.1.14} \quad 62
\end{align*}
\]
1.1.8 Gemini surfactants.

This decade has seen the discovery of a new family of surfactants. Gemini surfactant is the name assigned to a group of amphiphiles containing in sequence, a long hydrocarbon chain, an ionic group, a spacer, a second ionic group and another hydrocarbon tail (Figure 1.1.15).\(^4\)

The presence of the spacer inhibits intramolecular chain/chain association preventing micellisation from occurring and an example is shown below (see 10).

The aggregation of the geminis were investigated using light scattering and surface tension analysis which indicated the formation of small micelles. It was observed that the longer chained geminis self-coil or form submicellar aggregates when initially exposed self-assembling into micelles. Normally for geminis containing two long chains of between 16-20 carbons, a higher CMC is observed compared to the shorter chained analogues.
1.2 Dialkyl Zinc Additions to Aldehydes.

The addition of dialkyl zinc to aldehydes in the presence of a chiral catalyst is an extremely direct method of generating secondary alcohols in high optical purities (Scheme 1.2.1). Several reviews have described the various types of catalysts used together with the selectivities achieved. Most of them have been based on amino alcohols, diols, diamines and their derivatives. More recently however chiral catalysts derived from pyridyl alcohols, BINOL, and chiral aprotic ligands such as chiral norephedrine-amino thioacetates have been reported.

\[ \text{R}_2\text{Zn, hexane} \rightarrow \text{OH} \]

Scheme 1.2.1 Addition of Dialkyl zinc to an aldehyde.

1.2.1 Mechanism of Dialkyl/zinc additions

The reaction mechanism has been a subject of extensive discussion and several researchers have carried out mechanistic investigations to determine the catalytic intermediates involved. Kitamura et al, postulated that the reaction produces a dinuclear zinc species containing the chiral catalyst, the liganded aldehydes and three alkyl groups. He postulated that when using β-amino alcohols as the chiral catalyst, they coordinate with the dialkyl zinc to form a chiral alkyl zinc alkoxide complex (Scheme 1.2.2). The relative stabilities of this complex then determines the enantioselective outcome. Initially coordination between the nitrogen and oxygen atoms of a β-amino alcohol and zinc occurs (A). The β-amino alcohol enables the dialkyl zinc to acquire its bent form (C) to allow stereochemical control. Noyori and co-workers confirmed the formation of dimer (A) using \(^1\)H NMR studies and single crystal X-ray analysis. The dynamic exchange of intermediates (B) and (C) were proven by NMR and mass spectroscopy analysis. The dimeric structure can then be spontaneously
broken by the addition of more dialkylzinc to produce adduct (D) (Scheme 1.2.2).\(^{68}\)

However, Noyori proposed an alternative route indicating that complexation of the aldehyde to give (G) could also rupture the structure before the production of adduct (D) (Scheme 1.2.3).\(^{68}\)
The pre-catalytic structures (C) and (G) can be regenerated by the breakdown of (E) upon the addition of diethylzinc or benzaldehyde to produce the stable tetramer (H) which can then be hydrolysed to give the chiral alcohol (F) (Scheme 1.2.4).[^68]

![Scheme 1.2.4][68]

Other alternative intermediates to (D) have been postulated by Schleyer, Houk and co-workers[^71] and by Corey and Hannon[^72]. Schleyer, Houk et al, used ab-initio molecular orbital calculations on the vapour-phase addition of dimeric methyllithium to formaldehyde. They postulated the formation of a folded bicycle transition structure (I) which features a tri-coodinate structure of the migrating ethyl group.[^71] However Corey and Hannon proposed an alternative coordination complex (J), for the reaction between trimethylaluminium and propiophenone containing a six-centre coordination.[^72]

![I][68]

![J][68]

In general, initial reactions between dialkyl zinc and benzaldehyde in the absence of catalysts show no reaction occurring below and at room temperature. However it was observed that the reaction proceeds at higher temperatures albeit extremely slowly.[^66] Preliminary trials using dialkylzinc for
the catalytic asymmetric alkylation of benzaldehyde were carried out in the presence of Pd \( \text{II} \) or Co\( \text{III} \) together with \((1R)\)-camphorquinone oxime. The reaction was accelerated to produce the ethylation product with 40-60% e.e.\(^7\)

Since then a variety of different chiral catalysts, most notably the \(\beta\)-amino alcohols have been tested on these reactions. This review summarises a few classes of chiral catalysts that have been used.

1.2.2 Choice of catalyst- \(\beta\)-amino alcohols.

In 1984, Oguni and Omi reported that several \(\beta\)-amino alcohols could catalyse the alkylation of benzaldehyde.\(^7\) For example the use of \(S\)-leucinol (2 mol\% \%) as catalyst in toluene at room temperature gave the resulting secondary alcohol in 96\% yield and 49\% e.e (\(R\)-isomer). In 1986 Noyori then reported that higher enantioselectivities could be achieved using a tertiary \(\beta\)-amino alcohol, \((-\)\)-3-exo-(di methylamino) isoborneol \([(\text{\})\text{-DAIB}] (11)\) with yields up to 97\% were generated with 98\% e.e to the \(S\)-isomer.\(^7\) When 12 was used to catalyse the alkylation of benzaldehyde, yields of 95\% selective for the \(R\)-isomer were achieved.\(^6\)

In an attempt to facilitate recovery and recycling of the chiral catalyst, Fréchet immobilised DAIB onto polystyrene supports. However, the reaction rate was decreased although a high yield of 91\% and 92\% e.e was observed.\(^6\)

\[ \text{(-)-DAIB} \]

\[ \text{(-)-DAIB} \]

\((-\)\)-DAIB (11) was used to catalyse the alkylation of heptanal to generate \(S\)-nonan-3-ol (13) in 81\% yield and 61\% e.e. Studies revealed that when using 11 on the enantioselective addition of organometallic reagents to aliphatic
aldehydes lower selectivities were observed than when aromatic aldehydes were used, possibly due to the stereoelectronic effects of the aryl group.$^6^7$

Another tertiary β-amino alcohol, reported by Soai et al is the catalyst $(1S, 2R)$-(-)-2-$(N,N$-dibutylamino)-1-phenyl propan-1-ol (15).$^7^7$ When this was used in the reaction between 3-methyl butanal and diethylzinc in hexane at 0 °C, the $(S)$-alcohol was generated with an e.e. of 93%. Other aliphatic aldehydes for example heptanal and nonanal were also alkylated enantioselectively in high e.e values (up to 95%). These reactions used room temperature conditions. Soai suggested that the dibutylamino moiety was an essential feature of the catalyst structure for high enantioselectivities to be achieved with aliphatic aldehydes. This catalyst was also found to be effective with aldehydes possessing phenyl groups e.g benzaldehyde where an e.e. of 90% was obtained.$^7^7$

Various β-secondary amino alcohols have also been used. For example, alcohols derived from $S$-tyrosine (16) were used to catalyse the addition of diethylzinc to both aromatic and aliphatic aldehydes to produce $(S)$-alcohols in 81-97% e.e.$^7^8$ However when the tertiary dibutylamino alcohol 17 was used, the enantioselectivities observed were reversed.$^7^8$ This showed that the use of secondary amino alcohols can be very different to the effect of the corresponding tertiary alcohol.
1.2.3 Choice of catalyst- heterocyclic amino alcohols.

The use of heterocyclic amino alcohols (chiral pyrrolidinylmethanols) derived from S-proline have also been reported as catalysts. Using 2-5 mol%, optically active secondary alcohols (R and S enantiomers) were formed in 100% e.e. For example (+)-DPMPM (18) (tertiary amino alcohol) was able to catalyse the reaction of aryl, α,β-unsaturated, and aliphatic aldehydes to give (S)-alcohols in high e.e.\(^{59,79}\)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{OH} \\
\text{Me} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{OH} \\
\end{align*}
\]

(+) -DPMPM

An example is the reaction between \(p\)-chlorobenzaldehyde (19) and diethyl zinc using 18 as catalyst. The secondary alcohol 20 was generated in up to 98% e.e selective to the \(S\)-isomer and 100% yield (Scheme 1.2.6).

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{Et}_2\text{Zn} & \quad \text{hexane} \\
\text{Cl} & \quad \text{OH} \\
\text{Cl} & \quad \text{OH} \\
\end{align*}
\]

Scheme 1.2.6 Use of (+)-DPMPM on \(p\)-chlorobenzaldehyde reaction.

It was also observed that when using bulky substituents, the formation of the \(R\)-alcohol was favoured. selectivity. For example the use of (-)-erythro-
phenyl(1-neopentylpyrrolidin-2-yl) methanol [(−)-erythro-PNPM], was found to afford the (R) alcohol in high e.e (up to 100%) (Scheme 1.2.7).

\[
\begin{align*}
\text{OH} & \quad \text{Et}_2\text{Zn} \\
\text{hexane} & \quad \text{Cl} \\
19 & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
& \quad \text{Cl}
\end{align*}
\]

\[\text{up to 100% e.e } \quad \text{R-isomer}\]

\[\text{Scheme 1.2.7}\]

1.2.4 Choice of catalyst- Alkaloids (Quinine and Quinidine).

Various alkaloids have also been used in the dialkyl zinc additions. \(^{69,80,81}\) Depending on the choice of alkaloids used, it was possible to obtain either enantiomer of the required secondary alcohol, e.g quinidine (23) was selective for the (S)-isomer and quinine (22) was selective for the (R)-isomer. \(^{69,80,81}\) Smaardijk and Wynley observed this trend when carrying out the diethylzinc addition to 2-ethoxy benzaldehyde. A selectivity of 92% for the R-isomer with a yield of above 90% was produced when using 22. Converting the OH substituent in quinine to OEt, resulted in a reduction in selectivity to 14% e.e. Using compound 23 generated the S-isomer in high e.e's. \(^{69,80,81}\)
1.2.5 Choice of catalyst- Amino thiols.

Anderson et al. has also synthesised a range of chiral amino thiol ligands such as (24), giving good chemical yields ranging between 81-87% with e.e values of between 70-74 % for the R-isomer using a range of aromatic aldehydes (Ph, o-CH₃OC₆H₄, p-MeOC₆H₄, p-MeC₆H₄, p-ClC₆H₄).³²

By analogy to Kang’s work,³³ Anderson postulated a reason for the R-selectivity. This is shown in Figure 1.2.1. He rationalised that transition structure A was favoured over B since the transition B structure undergoes a 1,3 interaction between diethylzinc and the iso-propyl group which is sterically hindered causing the transition state B to be destabilised. Hence the R-isomer going via transition A is more favourable.
1.2.6 Choice of catalyst- Chiral salt catalysts.

The use of catalytic salts have been shown to affect the reaction selectivity in dialkyl zinc additions. For example the use of lithium salts of DPMPM increased the e.e values of the S-alcohols generated to 100%. This was attributed to the lithium cations which have a stronger hard acid character than zinc and can more easily co-ordinate with the oxygen atom of the approaching aldehyde, controlling the steric course of the reaction.

The use of chiral quaternary ammonium salts such as 25 have also been reported. These catalysts were found to affect the selectivity of product formation depending on the degree of solvation to the ammonium cation (Table 1.2.1). The addition of lithium alkoxide increased the reaction yield to 100%, although no rise in reaction selectivity was observed.
Table 1.2.1 Enantioselectivity of product using chiral quaternary ammonium salt.\textsuperscript{84}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>t days</th>
<th>Condition</th>
<th>Yield</th>
<th>E.e %</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>3</td>
<td>at room temp.</td>
<td>90</td>
<td>74</td>
<td>(S)</td>
</tr>
<tr>
<td>Hexane</td>
<td>6</td>
<td>at 0\degree C</td>
<td>55</td>
<td>61</td>
<td>(S)</td>
</tr>
<tr>
<td>Hexane</td>
<td>3</td>
<td>at room temp. +Li+</td>
<td>100</td>
<td>68</td>
<td>(S)</td>
</tr>
<tr>
<td>DMF</td>
<td>2</td>
<td>at room temp.</td>
<td>71</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>DMSO</td>
<td>3</td>
<td>at room temp.</td>
<td>71</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

More recent reports include the use of a recyclable benzyloxyalkyl norephedrine salt (26) as a catalyst for the addition of diethylzinc to aromatic aldehydes.\textsuperscript{4} Hailes and Madden found that initial experiments using aromatic aldehydes showed enantioselectivities of up to 82% e.e with selection for the S-isomer which was in accordance with previous results using (1S,2R)-norephedrine analogues.\textsuperscript{76, 85} When the free amine was used, it led to a low 9% yield with a selectivity of 65% e.e (for S-isomer).\textsuperscript{4} It was postulated that reverse micelle formation occurs when salts are present which enhances the reaction. It was also found that use of the quaternary salt (27) of the catalytic isomer yielded product in only 15% yield with an e.e. of 6% for the R-isomer.\textsuperscript{4}
1.2.7 Effects of temperature on diethyl zinc additions to aldehydes.

Investigations were carried out to assess the effects of temperature on the dialkyl zinc addition. Initial studies showed that when using aminoalcohols, temperature changes had little effect. For example an e.e. of 83% was obtained with Chirald [(2S,3R)-(+)4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol] at room temperature which was only raised by 4% at -10 °C. When using (-)-N-methylephedrine, an increase in e.e. of only 6% was observed in lowering the temperature to -10 °C. These amino alcohols only led to the (R)-configuration of the product. However reports using prolinol and more recently benzyloxyalkyl norephedrine salts (26) produced higher yields and enantioselectivities when the temperature of the reaction was increased. For example Hailes and Madden observed selectivities of 62% e.e and yields of 95% at 70 °C for the addition of diethylzinc to benzaldehyde compared to room temperature where a low reaction yield of 35% and 44% e.e was observed. When using alkaloids for example quinidine (23) as catalyst, the best e.e (73%) was obtained at elevated temperatures using a short reaction time (15 minutes).

1.2.8 Enantioselective 1,2-addition of dialkyl zins to α,β-unsaturated aldehydes.

The enantioselective 1,2-addition of dialkylzincs to α,β-unsaturated aldehydes producing optically active allyl alcohols have been studied. Various optically active allyl alcohols were obtained in high ee’s. An example is
indicated in Scheme 1.2.8. Using (-)-DAIB (18) as catalyst, resulted in the formation of 29 in 81% yield and a high selectivity of 96% to the R-isomer. More recently work has progressed in carrying out catalytic enantioselective conjugate additions of diethylzinc to α,β-unsaturated ketones (Scheme 1.2.9).

Feringa used a mixture of Ni (acac)₂ and (-)-DAIB (18) for the conjugate addition of diethylzinc to chalcone (28) to give e.e's ranging from between 51-81%. However, in 2001, Shadakshai and Nayak synthesised a chiral Ni (II) complex prepared from Ni (acac)₂ and N-trityl aziridine-2-(S)-diphenyl methanol (31) catalysing the reaction shown in Scheme 1.2.9 and giving good yields with e.es of up to 93%.
1.2.9 Effects of supports, polymer/surfactant based heterogeneous chiral catalysts on diethylzinc reactions.

The use of polymer-supported chiral catalysts have attracted increasing interest since such compounds are recyclable, easy to handle and produced good yields for various reactions. An example of the successful use of polymer-solid supports include polymer-bound chiral amines to catalyse the enantioselective addition of diethylzinc to aldehydes by Fréchet and Soai. However reports have indicated that to date, the catalytic activity and enantioselectivity of polymer catalysts are lower than the corresponding monomers. This can be explained by considering the steric hindrance of the polymer matrix restricting the freedom and mobility of the catalytic site.

Itsuno et al has used cross-linked polystyrene resins containing chiral primary amino alcohol moieties bound to ether linkages in the enantiomeric catalytic alkylation of aldehydes. The reaction of 32 with benzaldehyde to form Schiff bases helped catalyse the addition of diethylzinc to benzaldehyde leading to the production of optically active secondary alcohols having enantiomeric purities of up to 99% (Scheme 1.2.10). The enantioselective addition of dialkylzinc to aldehydes using norephedrine derivatives attached to polystyrene as catalysts yielded moderate e.e’s (56%) using aliphatic aldehydes. One of the reasons was believed to be due to the severe limitations of freedom and mobility of the reactive site of the polymer catalyst due to the nitrogen atom of norephedrine being directly attached to the benzyl group of the polystyrene resin.

One of the ways this was overcome, was to attach a methylene spacer to the polymer chiral catalyst. This enabled the production of an optically active secondary alcohol with e.e. values ranging from between 87-92%. The presence of a methylene spacer was assumed to lead to greater freedom of the active site and also greater distance between the catalytic site and the polystyrene resin. When N-butyl norephedrine was supported on a polystyrene resin with a 6-methylene spacer the enantiomeric excesses of the secondary alcohol formed was enhanced further leading to the highest enantioselectivity observed on a polymer catalyst.
In recent years, a wide range of other chiral catalysts derived from different families of compounds have been synthesised and tested on the diethyl zinc reactions. These include compounds derived from camphor, BINOL and pyridyl alcohols such as 35, giving moderate to high yields and selectivities. More recently however, chiral aprotic ligands such as chiral norephedrine-derived amino thioacetate were successfully used in the enantioselective reactions. Other novel chiral amino thioacetates derived from L-proline and L-cysteine have been used giving yields as high as 98% and selectivities of up to 97% in the reaction between diethyl zinc and a range of aldehydes. The addition of additives have been shown to further enhance reaction yields. More recently transition metal complexes such as Ti(OCHMe2)4 have been used to enhance this.
To conclude, the addition of dialkyl zins to aldehydes is a powerful synthetic tool. It has been widely explored and continues to be an active area of research.
1.3 Organic Reactions in Aqueous Media.

The use of aqueous media in organic chemistry provides a cleaner, safer and cheaper alternative to the more traditional methods of accomplishing many organic reactions. Increasing pressure by the government and the public has been put upon the chemical industry to reduce the use of volatile organic solvents. As a result, in more recent years, an increasing number of reports describing water-based reactions have been published.\textsuperscript{56, 57, 98, 99}

One of the first reactions using water as an organic reaction medium was studied by Diels and Alder in the early 1930s.\textsuperscript{100} However its potential use as a solvent for cycloaddition reactions was highlighted more recently in the 1980s, when Breslow reported that using water as solvent accelerated Diels-Alder reactions.\textsuperscript{101} Since then, several other organic reactions in aqueous media have been studied. These include Claisen rearrangements, aldolisations, Michael additions and the Baylis-Hillman reaction as well as a broad range of organometallic reactions.\textsuperscript{98, 102}

This section will cover the use of aqueous media for three major reactions; the Diels-Alder reaction (since extensive work in this area used water as solvent), Michael additions and Baylis-Hillman type reactions. A brief section reviewing phase-transfer reactions will also be presented.\textsuperscript{56, 57, 98, 99, 102}

1.3.1 Diels-Alder reactions.

One of the first Diels-Alder reactions in water was reported by Diels and Alder involving a pericyclic cyclocondensation.\textsuperscript{100} Then Woodward and Bauer in 1948 reported Diels-Alder reactions using aqueous maleic acid as a dienophile.\textsuperscript{103} In the 1980's Breslow initially investigated the cycloaddition reaction between water-soluble cyclopentadiene and buten-2-one (Scheme 1.3.1).\textsuperscript{101} A rate acceleration of over 700 fold in water was reported compared to when the organic solvent 2,2,4-trimethyl pentane was used.
Scheme 1.3.1 Diels-Alder reaction between cyclopentadiene and butenone in water.

Breslow and later Lubineau rationalised the rate enhancement. It was suggested that in water, the hydrophobic interactions between the organic substrates forces them to aggregate thus driving the reaction. Another explanation was that the high surface tension of water (72 dynes/cm) and large cohesive energy of water (550 Cal/ml or 22,000 atm) induces a reduction in the surface area of contact between hydrophobic reactants and water molecules. This high cohesive energy forces the reactants together.

Breslow also described the use of various additives such as salting-in and salting-out agents to influence the rate of the Diels-Alder reaction outlined in Scheme 1.3.1. Salting-out agents, by definition, increase the hydrophobic effect by decreasing the solubility of the apolar molecules in water. In the presence of 4.86 M LiCl (a salting-out agent), the reaction shown in Scheme 1.3.1 was increased by 2.5 fold compared to water alone. Conversely, salting-in agents such as guanidinium chloride led to a small drop in the reaction rate compared to water.

Other additives which have been used to accelerate the Diels-Alder reaction between cyclopentadiene and buten-2-one include the use of β-cyclodextrin or the covalent attachment of sugar moieties as shown in Scheme 1.3.2. The effect of cyclodextrins are generally favourable provided that the cavity size is compatible with the size of the reactant. For example when using the 7-glycoside unit β-cyclodextrin the cycloaddition was accelerated since it has a large hydrophobic cavity which promotes complexation of the hydrophobic reactants. The 6-unit analogue α-cyclodextrin on the other hand,
slows down the cycloaddition due to its smaller hydrophobic cavity size which prevents both substrate complexation.\textsuperscript{105,106}

When using glucose and saccharose, a greater acceleration was observed compared to using a saturated $\beta$-cyclodextrin. Glucose was found to have a similar rate effect as when lithium chloride was added. The reasons for the acceleration could be due to an increase in the hydrophobic effect when adding carbohydrate solutions to the reaction mixture.\textsuperscript{105,106}

\begin{center}
\textbf{Scheme 1.3.2} Diels-Alder reaction between glucosyldiene and butenone in water.
\end{center}

The use of metal derived Lewis acids such as Ti(Me$_5$Cp)$_2$(H$_2$O)$_2$$^{2+}$ or Sc(OTf)$_3$ have been used to successfully catalyse various Diels-Alder reactions in high yields and selectivities in water.\textsuperscript{109,110} For example the reaction shown in Scheme 1.3.3 generated the endo-isomer exclusively in 93\% yield.\textsuperscript{98}

\begin{center}
\textbf{Scheme 1.3.3}
\end{center}

Grieco \textit{et al.} in 1983 examined the intermolecular Diels-Alder reaction shown in Scheme 1.3.4.\textsuperscript{111} When performing the reaction using toluene as solvent this led to low yields. However, in water yields improved from 46\% to
85%. Using the acid rather than the ethyl ester, resulted in a 10 fold rate acceleration in water and when using the sodium salt of the acid, the reaction was accelerated further. Grieco concluded that the reason behind the acceleration was due to the diene molecules aggregating in a "micellar" manner and solubilising the dienophile.\textsuperscript{98,111}

\[ \text{Scheme 1.3.4} \]

Some investigations have been carried out using aqueous micellar media for Diels-Alder reactions.\textsuperscript{56,57,58,112} Breslow studied the reaction between cyclopentadiene and methylacrylate (Scheme 1.3.5) in the presence of either sodium dodecyl sulphate (SDS) or cetyltrimethylammonium bromide (CTAB).\textsuperscript{112} He concluded that these detergents had little effect compared to water on the product ratios \( N/X \) (\textit{endo}/\textit{exo}). He also observed that using SDS gave rise to only slight rate enhancements when used in dioxane compared to SDS in water for methyl and \( n \)-butyl acrylate reactions with cyclopentadiene.

\[ \text{Scheme 1.3.5} \]
However Saur observed that the use of CTAB did enhance the reaction rate as well as giving different selectivities.\textsuperscript{55} Saur's observation were confirmed by Singh using different substrates who had observed that the use of micellar solutions led to the reactions occurring faster at ambient temperatures (3 hours at 30 °C) giving better product yields, 68% and 86% for 39 and 40 respectively (Scheme 1.3.6), compared to using the conventional Diels-Alder reaction conditions, toluene as solvent and heating at reflux for 10-12 hours (50% and 0% respectively).\textsuperscript{58}

Diego-Castro and Hailes have also investigated the effect of aqueous surfactant solutions on Diels-Alder reactions using a range of acrylates from methyl to nonyl.\textsuperscript{56} Using methyl acrylate, the selectivities in water corresponded to exactly what Breslow had reported.\textsuperscript{112} However using CTAB led to a higher endo/exo ratio. This was attributed to the high concentrations above the CMC at which SDS and CTAB were used (2.4 and 770) in Breslow's work. This demonstrated that careful selection of the surfactant concentration can effect the product selectivity. At longer reaction times it was observed that the $N/X$ values decreased due to the more stable thermodynamic exo product predominating. Experiments using nonyl acrylate showed virtually no increase in the product yield when using water and surfactant solutions. It was postulated that this was due to the tendency for nonyl acrylate to self aggregate and produce a non-micellar aggregate.\textsuperscript{56}

They also investigated the effects of pH.\textsuperscript{56} It was observed that both the yield and selectivity was affected, depending on the pH of the solution. For
example, using CTAB gave the highest yield and $N/X$ ratio at high and lower acidity since at low pH, the acrylate is readily protonated and forms a mixed micelle. At high pH, counterion effects may influence the aggregate shape or polarise cyclopentadiene which in turn could influence the yields and selectivities.

Finally surfactants derived from S-leucine (41) and phenylalanine (42) were also used in the reaction between nonyl acrylate and cyclopentadiene $^{57,113}$ (Scheme 1.3.7):

![Scheme 1.3.7](image)

An e.e of 10% was observed when using 41. The $R$ enantiomer of the endo isomer was preferentially formed. A slight rise in the e.e value was observed when the surfactant concentration was increased (up to 15% e.e.). Performing the reaction at pH 3 resulted in a change in the enantioselectivity to 13%, although the yield of cycloadduct was low. The addition of LiCl was observed to enhance the yield and e.e. possibly due to an increase in concentration of the chloride counterion which can cause a shrinkage in the Stern-layer leading to a concentration of reactants which results in greater pre-orientation and enhanced yields (75%) and (15% e.e).$^{57}$ This can be compared to
the use of other additives such as cyclodextrins which were reported to lead to enantioselectivities of up to 21 %.\textsuperscript{114}

When using $42$ enantioselectivities of up to 13 % e.e were observed in the $exo$ adduct only. When the bromide counterion was present, the enantiomeric excess went up to 18% e.e. NMR experiments revealed that in $42$, the phenyl ring was directed into the micellar core, while the isopropyl group in $41$ was directed outwards from the micellar core. Surface tension measurements revealed that the head group area of $42$ was smaller than $41$. This suggested that the conformation of the surfactant head group influenced the positioning or orientation of substrates within the micelle during the reaction.\textsuperscript{57,113}

Other catalysts that have been used to enhance the Diels-Alder reaction, have included the use of cinchona bases in water, which was originally reported by Kagan in 1989.\textsuperscript{115,116,117} For example, the reaction between anthrone and $N$-methyl maleimide in the presence of a catalytic amount of quinidine (23) (Scheme 1.3.8) gave the cycloadduct 43 in 35% e.e at room temperature. However, repeating the reaction at -50 °C saw a rise in enantioselectivity to 61% e.e. When using dihydroquinidine $O$-4-chlorobenzoate as catalyst, racemic products were observed, highlighting the importance of using the free hydroxy group.

\begin{center}
\textbf{Scheme 1.3.8}
\end{center}
Other ways of accelerating Diels-Alder reactions have included using microwaves and ultrasounds. These methods have been used in several water-promoted reactions.\textsuperscript{118,119,120}

1.3.2 Michael Reactions

One of the key important carbon-carbon bond forming reactions is the Michael addition. Scheme 1.3.9 represents a Michael reaction involving nucleophilic attack by an enolate ion at the $\beta$-carbon of an unsaturated carbonyl compound (Michael "acceptor") followed by protonation of the resulting enolate.

Traditionally, these reactions have been performed using strong bases such as hydroxides and alkali metal alkoxides.\textsuperscript{121,122}

Most Michael reactions reported so far have been performed using organic solvents and have generated products in good yields and selectivities. The use of chiral catalysts have been reported. These include chiral metal complexes such as $(R)$-styrene oxide / benzylamine aluminium-lithium complex (44)\textsuperscript{123} or chiral amines such as SAMP (45).\textsuperscript{124}
The use of water as solvent for Michael-type additions has been relatively limited. However, it has been reported that various uncatalysed Michael reactions have proceeded well under neutral conditions only when using water as solvent, for example, the reaction between nitromethane with buten-2-one (Scheme 1.3.10). A huge acceleration was observed when going from a non-polar organic solvent to water.

The mixture of nitromethane and buten-2-one was unreactive under neat conditions and when using solvents such as dichloromethane, toluene and tetrahydrofuran. The use of catalysts and bases were required for the reaction to proceed. However when using methanol, the desired products were obtained without a catalyst or a base, albeit at a slower reaction rate. It was postulated that hydrophobic effects may play a part in this rate enhancement and the use of additives were used to confirm this.

\[
\text{CH}_3\text{NO}_2 + \text{CH}_2=\text{C}(=\text{O})\text{CH}_3 \xrightarrow{\text{H}_2\text{O}} \text{CH}_2\text{NO}_2\text{CH}_2\text{C}(=\text{O})\text{CH}_3 + \text{CH}_2\text{NO}_2\text{CH}_2\text{C}(=\text{O})\text{CH}_3
\]

\[\text{Without base} \quad 40^\circ\text{C}, 32\text{ hr} \quad \text{Quant.} \]

\[4 : 1\]

Scheme 1.3.10

Other Michael reactions which have been carried out in water include the addition of 1-trimethylsilyloxyhexene to methyl vinyl ketone. The 1,2-
addition pathway normally competes with the 1,4-conjugate addition. However in water, only 17% of 1,2-aldol was generated.

The reaction between alkyl halides and α-enones and α-enals have been reported to proceed well in the presence of zinc-copper in aqueous media.\textsuperscript{127,128} The use of sonication accelerated the reaction, leading to the production of the 1,4 adduct in moderate to high yields (45%) as shown in Scheme 1.3.11.

\[ \text{Bu, Zn-Cu} \]
\[ \text{EtOH-H}_2\text{O, (9:1)} \]
\[ \text{Ultrasound} \]
\[ 3\text{hr, 45\%} \]

\textbf{Scheme 1.3.11}

Several reports have demonstrated the use of Lewis acid-catalysed Michael additions enabling the reaction to proceed under milder conditions and thus reducing a number of undesirable side products in the process.\textsuperscript{99} Michael reactions involving β-ketoesters reacting with enones were "catalysed" by Ytterbium triflate (Yb(OTf))\textsubscript{3}.\textsuperscript{129,130} However, the reaction was reported to be very slow and needed a period of between three to five days for completion. In 2001 Mori and co-workers reported the use of scandium tris (dodecyl sulfate) (STDS) and scandium trisdodecanesulfonate in the addition reaction between benzyl 2-oxocyclopentane carboxylate (47) and methyl vinyl ketone in water (Scheme 1.3.11).\textsuperscript{99} These Lewis acid-surfactant-combined catalysts (LASC) were believed to have formed stable "colloidal dispersion systems" with the organic substrates in water. These catalysts have also been used successfully for Lewis acid catalysed aldol reactions.

The reaction proceeded very slowly in the presence of scandium, ytterbium and copper triflates, but when using STDS, the reaction was accelerated (Scheme 1.3.12). Interestingly lower yields were observed when using STDS in apolar solvents such as dichloromethane (57%) compared to using water as solvent.
1.3.3 Baylis-Hillman Reaction.

The Baylis-Hillman reaction is a carbon-carbon bond forming reaction which involves the coupling of activated alkenes with carbon electrophiles containing electron-deficient sp² carbon atoms under the influence of a suitable catalyst, normally a tertiary amine (Scheme 1.3.13).

\[
\begin{align*}
\text{Catalyst} & \quad X \quad \text{EWG} \\
\text{R} & \quad \text{R'} \\
\text{R'} & \quad \text{XH} \\
\text{EWG} & \quad \text{EWG}
\end{align*}
\]

\( X = \text{O}, \text{NR}_2 \)

EWG = electron withdrawing group.

The catalytic cycle for the Baylis-Hillman reaction between methyl acrylate and benzaldehyde using a tertiary amine catalyst A (Scheme 1.3.14). The rate determining step has been determined to be that between the aldehyde D with the ammonium enolate C.
Previous reports have reported the use of DABCO (49) and DBU (50) as basic catalysts which have generated products in 70-90% yields.\textsuperscript{131,132} In order to form optically active Baylis-Hillman adducts, a variety of chiral catalysts have been tested which have included (S)-BINAP and quinidine (51).\textsuperscript{133,134} giving products in low selectivities.

An alternative method for generating optically active Baylis-Hillman adducts has been to use solvents such as (+)-ethyl lactate, although only low selectivities were observed (3 % e.e.).\textsuperscript{135}
Several Lewis acids have also been used to help accelerate the Baylis-Hillman reactions including TiCl$_4$, BF$_3$-Et$_2$O, ZnCl$_2$, Et$_2$AlCl normally performed in organic polar solvents such as THF, acetonitrile, DMF as well as apolar solvents such as dichloromethane.$^{136,137}$

Interestingly, in 1994, Augé and co-workers reported the coupling between acrylonitrile and benzaldehyde using DABCO (49) and that the reaction was accelerated in water (Scheme 1.3.15) giving 50 in 90-98% yield at room temperature in 7-8 hours.$^{102}$ Since it has been reported that this reaction can be accelerated using salting-in/salting-out agents,$^{101}$ the reaction was repeated using various salts. When using 4M LiI or NaI, the reaction rate was enhanced further (92-93% in only 2-3 hrs). Surprisingly, the use of LiCl (a salting-out agent) was also found to decrease the rate of the reaction (24 hrs, 82%).$^{102}$

An acceleration rate in water was observed using other aldehydes with acrylonitrile. Acetaldehyde, furaldehyde and butanal gave adducts in good yields within 2 hours at 0 °C.$^{102}$

\[
\text{PhCHO} + \underset{\text{DABCO}}{\text{CN}} \xrightarrow{\text{rt, 7-8 hrs}} \text{PhCH} = \text{CHCN}
\]

**Scheme 1.3.15**

In 2000, Basavaiah et al. reported the use of trimethylamine in performing the Baylis-Hillman reaction between various alkyl acrylates and aldehydes such as 2-pyridinecarboxaldehyde, 4-nitrobenzaldehyde, 2-furaldehyde and paraformaldehyde (Scheme 1.3.16).$^{138}$ High yields of up to 74%, were observed in 4 hours. Analogous reactions using benzaldehyde and 4-chloro benzaldehyde were found to be extremely slow under these conditions.

\[
\text{ArCHO} + \underset{\text{aq. NMe$_3$}}{\text{COOR}} \xrightarrow{60\,^\circ\text{C}, 4-5\,\text{hrs}} \text{ArCH} = \text{CHCOOR}
\]

**Scheme 1.3.16**

\[\text{Ar} = \text{Pyrid-2-yl, 4-nitrophenyl, fur-2-yl}\]
\[\text{R} = \text{Me, Et, n-Bu}\]
Hill and Isaac have studied the effects of pressure on the Baylis-Hillman reaction. They observed that the $\alpha$-hydroxethylolation of acrylonitrile using DABCO (Scheme 1.3.17) proceeded in 4-5 days under standard pressure to produce the desired product in good yields. However, when the reaction was kept at 2-5 K bar pressure, the reaction went to completion in 5 minutes.

\[
\begin{align*}
&\text{OH} \\
&\text{CH}_3\text{CHO} + \text{MeCHO} \quad \text{4-5 days} \quad \text{DABCO} \\
&\text{CN} \quad \text{2-5 K bar} \quad \text{5 min} \\
&\text{OH} \\
\end{align*}
\]

Scheme 1.3.17

The effects of using temperature and ultrasound on the DABCO-catalysed $\alpha$-hydroxyalkylation of methyl acrylate was studied by Roos and Ramersadh. They observed that a rate increase took place if gentle warming of the reaction mixture (43 °C) was carried out rather than refluxing the reaction which normally produced polymer side products. The use of sonication was also observed to lead to rate acceleration.

Microwave irradiation has also been reported to provide considerable rate enhancement in the Baylis-Hillman reaction between aldehydes and activated olefins. For example under standard conditions, acrylamides are inert substances for Baylis-Hillman reactions. However, when acrylamide was reacted with 3,4,5-trimethoxy benzaldehyde (51) to give the corresponding adduct 52, a 40% yield using microwave irradiation was observed (Scheme 1.3.18).

\[
\begin{align*}
&\text{HO} \quad \text{25 min, microwave} \\
&\text{2CH}_3\text{O} + \text{CHO} \\
&\text{CN} \quad \text{CH}_3\text{O} + \text{NI}_2 \\
&\text{CN} \quad \text{CH}_3\text{O} + \text{CH}_3\text{O} \\
&\text{OH} \\
\end{align*}
\]

Scheme 1.3.18
1.3.4 **Phase-Transfer Catalysis (PTC).**

Phase-transfer catalysis (PTC) involves the use of a catalyst in a reaction which is carried out in different phases. The catalyst extracts one of the reactants, most commonly an anion, across the interface into the other phase so that the reaction can proceed. These catalysts exist as salts (*e.g.* tetraalkylammonium salts) or agents that complex inorganic cations. The catalyst cation is not consumed in the reaction, although a possible anion exchange does occur.

Many catalysts have been reported and chiral catalysts include the quaternary ammonium salts 53 and 54, where \( R, R^2, R^3 \) are aliphatic and aromatic substituents.\(^{145}\)

Among the quaternary ammonium salt catalysts, cinchonium derivatives have been shown to be very efficient.\(^{146}\) The enantioselective alkylation reaction under biphasic conditions was one of the first examples of chiral PTC. For example the following reaction shown in Scheme 1.3.19 led to high yields and selectivities.\(^{145}\)
PTC have also been used in Michael reactions. Towards the end of this Ph.D., Perrard and co-workers reported the use of 9-anthracenyl methyl-substituted quininium chloride (56) to mediate the addition of the dimethyl malonate anion to a cyclopentenone derivative in the enantioselective synthesis of methyl-dihydrojasmonates (Scheme 1.3.20). The key enantioselective step in the synthesis involved using asymmetric solid-liquid phase transfer catalysis in solvent free conditions. Selectivities up to 90% e.e were achieved together with high yields (91%) at -20 °C, although at higher temperatures, a drop in e.e was observed (31-48% e.e).
Other Michael addition reactions using solvent-free and liquid-liquid PTC conditions have included work by Diez-Barra et al. on the addition of enolates to methyl vinyl ketone. An example is the reaction shown in Scheme 1.3.21. The solvent free technique was found to normally afford higher yields, whereas the liquid-liquid phase procedure, although being less efficient, led to enantioselective reactions.

\[
\text{Catalyst} \quad \text{Base} \quad \text{PTC conditions} \quad \text{Yield}
\]

\begin{itemize}
  \item \(N\)-benzyl, \(N\)-methyl ephedrinium bromide
  \item \(N\)-(4-trifluoromethyl-benzyl) cinchonium bromide
\end{itemize}

\text{PTC has been used in several other asymmetric reactions which have included aldol condensation, olefination and Darzen reactions. In recent years, Lygo and co-workers have reported several reactions including the use of PTC on stereospecific epoxide formation (Scheme 1.3.22). The \(O\)-benzyl derivatives of the cinchona alkaloids together with sodium hypochlorite gave high stereocontrol and products with selectivities of between 69-89% e.e (Scheme 1.3.22).}
In summary, the use of water as solvent in organic reactions have been found to be very effective in enhancing reaction rates. Increasing number of reports continue to involve using this solvent, especially in phase-transfer based reactions leading to high yields and enantioselectivity.
Results and Discussion.

Chapter 2 Surfactant Synthesis.

As discussed in chapter one, the use of micellar environments in which to perform organic transformation, can alter the rate and regioselectivity of certain reactions within an aqueous phase. The application of aqueous micellar systems in reactions have become increasingly important since there is a need for the development of environmentally clean media and methodologies for use in organic synthesis. Surfactants have the ability to solubilise substrates in water, extending the potential of using this as a solvent. In addition, surfactants can be recycled, and the use of chiral micellar media also holds significant potential.

Previously work within the Hailes group has involved the synthesis of several solid supported and solution surfactants such as 26 which was synthesised from norephedrine, incorporating the benzyloxy group at one end of the alkyl chain. Its catalytic activities were compared to the corresponding amine 58 prepared by Watanabe and Soai.

![Chemical structures of compounds 26 and 58](image)

Compound 26 was used in diethyl zinc additions to afford products in high chemical yield and enantiomeric purity. This can be compared to when using the free amine where a reversed yield and temperature dependency was observed. With this in mind, our initial aim was to synthesise compounds with extra hydrogen-bonding capacity or structural rigidity such as 59, 60, and 61.
At the end of the results and discussion section, all the surfactants mentioned in those sections are listed.

2.1 **Surfactants derived from S-tyrosine.**

Several compounds derived from S-tyrosine were prepared initially incorporating lipophilic moieties on the N-atoms and leaving the phenolic and terminal alcohol as potential H-bonding sites. Initially the synthesis of 66 was sought incorporating a butyl chain since previous reports have indicated this can lead to enhanced yields and selectivity (Scheme 2.1).

![Scheme 2.1](image)

The synthetic route utilised after initial investigations is outlined in Scheme 2.2.
Whilst the reduction of amino acids to amino alcohols directly is not unprecedented using tyrosine, the conversion of the carboxylic acid into an ester functionality was carried out to increase the ease and yield of conversion. The methyl ester was readily formed from \( \text{S-tyrosine and thionyl chloride in methanol to give 62, the hydrochloride salt in 94\% yield.} \)

Introduction of the mono \( N \)-butyl group was explored via amide formation and subsequent reduction to avoid polyalkylation. We initially investigated the addition of butyryl chloride with the aim of selectively generating the corresponding amide rather than reaction at the phenolic moiety. However, using 1 equivalent of triethylamine and butyryl chloride, two compounds, 63 and 64, were formed which were readily isolated by flash chromatography. The mono acylated product 63 was formed in only 8\% yield and 64 was generated in 15\% yield. This is not surprising since the \( pK_a \) of \( R-NH_3^+ \) is approximately 10.67 compared to the phenolic \( \text{OH} \) which is about 10.19 indicating the ease in the production of 64.\(^{152}\)

\[ \text{i) SOCl}_2 \text{ in MeOH at 0 °C; ii) C}_2H}_2COCl and Et}_3N \text{ in THF at 70 °C; iii) LiAlH}_4 \text{ in THF, reflux 18 hours; iv) THF/Borane, reflux 18 hours.} \]
Attempts were made to improve the yield and selectivity to form more of 63 by increasing the reaction temperature to 20 °C and 40 °C as well as increasing the equivalents of triethylamine since the starting material 62 was a salt. However little change in the conversion yield was observed (Scheme 2.3). Addition of the acylation catalyst, 4-dimethylaminopyridine (DMAP) and increasing the quantity of butyryl chloride up to 2 equivalents also had little effect on the yields. Since only a small percentage of starting material was converted to acylation products, this suggested that generation of the free amine in situ was incomplete, therefore 4 equivalents of triethylamine were used. The reaction was also carried out at reflux (67 °C) for 3 hours. This yielded only one product which was purified on basic alumina to remove any traces of butanoic acid. Recrystallisation gave the di-butyryl compound 64 in 75% yield. Since reduction of the butyrate material 64 was required, it was not problematical that a second butyryl chain was present and therefore formation of 63 selectively was not explored further.

**Scheme 2.3**

Dibutyryl tyrosine methyl ester (64) was then reduced using lithium aluminium hydride in THF using a temperature range of between 40 °C and 60 °C for 24 hours followed by an acidified work up. The $^1$H NMR spectrum of the material generated was difficult to interpret due to the coalescence of key signals, however analysis by mass spectrometry indicated the presence of a compound of $m/z$ 238 which was consistent with the desired product 65. The
reaction temperature was then increased to reflux (67 °C) to generate crude 65 in 90% yield (Scheme 2.2). This material was then carried through to the next step. The amide 65 was readily reduced using THF/borane at reflux to give the crude free amine in 81% yield. The amine was stirred in 4M hydrochloric acid in dioxane to yield the hydrochloride salt which was purified by recrystallisation to give 66 in 67% yield.

Attempts were also made to generate the butyl amine 66 directly from the butyryl methyl ester (64) using larger equivalents of lithium aluminium hydride, however only 12% of 66 was isolated directly (Scheme 2.4). In addition the reduction of amide 64 to amine 66 was also explored using a stepwise procedure with 2 equivalents of lithium aluminium hydride followed by another 2 equivalents of the same reducing agent, but no amine was generated, instead 65 was isolated.

HPLC analysis was carried out on the free amine of compound 66 to verify that its absolute configuration was maintained throughout the synthesis. The synthesis of DL-N-butyl tyrosinol (racemic form of 66) was therefore carried out using the same procedure as indicated above. HPLC analysis of both 66 and its racemic form showed that the chiral centre was maintained. This was confirmed by the optical rotations of DL-N-butyl tyrosinol, [α]₀ = +10.4 ° (c 0.5, in methanol at 25 °C), and its corresponding starting material S-tyrosine methylester hydrochloride [α]₀ = +72.0 ° (c 3 in pyridine at 25 °C), which acquired the same direction of rotation.
The next crucial step was to attach long aliphatic chains to the amine intermediate 66 in order to generate the target surfactants 68, 70, 72. (Scheme 2.5). Surfactants of different carbon chain lengths, 12, 16 and 18 were synthesised in order to study how varying the aliphatic chain lengths can effect the reaction yields and enantioselectivity in organic as well as aqueous media. Chain lengths of 12, 16 and 18-carbons were selected to favour micellar aggregation.

The butyl salt 66 was reacted with 1-iodododecane and potassium carbonate. The resulting crude product was purified by flash-chromatography to give 67 in 28% yield (Scheme 2.4). In order to generate a charged head group, 67 was converted into the hydrochloride salt (68) by stirring with HCl in dioxane. A yield of 90% was obtained. Attempts to increase the alkylation yield by increasing the equivalents of potassium carbonate to 1.2 and 1.5 was unsuccessful since side products were produced which were difficult to separate from the monosubstituted compound 68.

The synthesis of the C\textsubscript{16} and C\textsubscript{18} tyrosine derived surfactants, 70 and 72 were then carried out using the same procedure (scheme 2.5). Compound 69 was prepared using 1-iodohexadecane and the butyl salt 66, giving 89% yield of the desired compound. Its HCl salt 70 was subsequently prepared giving a 92%
yield. Compound 71 was also prepared using the same procedure giving a yield of 87%. The corresponding hydrochloride salt 72 was obtained in 82%.

Scheme 2.5

The quaternisation of 67 was carried out using 3 equivalents of methyl iodide. Surfactant 73 was obtained as an oil in 91% yield after purification via flash chromatography (scheme 2.6).
Counterion exchange from iodide to hydroxide was carried out using an anion exchange resin (dowex OH⁻ resin). This gave 74 in 95% yield (scheme 2.7). Elemental analysis confirmed that no iodide remained.

Since Hailes and Madden had found that the use of a benzyloxy dodecyl chain led to good reaction yields and selectivities for the diethyl zinc reaction and assisted in recycling of the catalyst, we decided to also introduce a benzyloxy dodecyl chain.

The synthetic route for compounds 75 to 77 described by Soai and Watanabe was adopted to generate 78, 80 and their corresponding hydrochloride salts 79 and 81 (Scheme 2.8).
Using Soai’s procedure dodecan-1,12-diol was reacted with NaH and then benzyl chloride was added. Due to the poor solubility of dodecan-1,12-diol in DMF at 0 °C, the reaction mixture was heated to 60 °C until the diol had completely dissolved, then cooled to 0 °C prior to the addition of sodium hydride, followed by benzyl chloride. Interestingly only starting material was recovered. The reaction was repeated in DMF at 0 °C without raising the temperature to 60 °C and 2 products were formed; the monobenzylated product 75 in 33% yield together with the dibenzylated material in 18% yield. Using DMF at a higher temperature resulted in no product forming. Various attempts to improve the yield of the monobenzylated diol (75) are summarised in Table 2.1. The use of benzylbromide rather than benzylchioride led to a slight increase in yield (34%) (Scheme 2.8). Attempts were made to improve this further by varying the equivalents of base and halide together with the reaction temperature, but little enhancement in yield was observed. In addition, changing the reaction solvent from DMF to THF gave no alkylation products at all, presumably due to anion insolubility.
The monobenzylated material 75 was carried through to the next stage. The conversion of the alcohol 75 to the chloride 76 was readily achieved using thionyl dichloride and pyridine. The product was isolated in 85% and the purity was sufficiently high that it was carried on directly to the next step without further purification (Scheme 2.8).

Attempts were made to obtain the iodo compound 77 from the chloride 76 using NaI. When heating the reaction at reflux for 12 hours, only 40% of the chloride was converted into the iodide. The reaction was repeated but this time increasing the time scale of the reaction to 48 hours. After work-up, 77 was isolated in 94% yield. Analysis of the $^1$H NMR spectrum indicated that the iodide had been produced exclusively with no remaining chloride present. The 1-Benzzyloxy-12-iodododecane chain 77 was attached to the previously synthesised tyrosine butyl intermediate 66 in acetonitrile using potassium carbonate as base (Scheme 2.8). The reaction mixture was heated at reflux for 22 hours and two products were generated, compounds 78 (10%) and 80 (24%) which were separated using flash chromatography. Compounds 78 and 80 were stirred individually in excess 4M hydrochloric acid in dioxane to generate the hydrochloride salts 79 and 81 as before and a 90 and 92% conversion to the salt was obtained respectively.

<table>
<thead>
<tr>
<th>X</th>
<th>Solvent</th>
<th>Dodecan-1,12 diol</th>
<th>NaH</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>DMF</td>
<td>1.0eq</td>
<td>0.9</td>
<td>Starting material</td>
</tr>
<tr>
<td>Br</td>
<td>DMF</td>
<td>1.0</td>
<td>1.1</td>
<td>34% mono + starting material</td>
</tr>
<tr>
<td>Cl</td>
<td>DMF</td>
<td>1.0</td>
<td>1.1</td>
<td>30% mono + starting material</td>
</tr>
<tr>
<td>Cl</td>
<td>DMF</td>
<td>1.0</td>
<td>0.6</td>
<td>24% mono + starting material</td>
</tr>
<tr>
<td>Br</td>
<td>DMF</td>
<td>1.0</td>
<td>0.6</td>
<td>22% mono + starting material</td>
</tr>
<tr>
<td>Cl</td>
<td>THF</td>
<td>1.0</td>
<td>1.1</td>
<td>No reaction</td>
</tr>
<tr>
<td>Br</td>
<td>THF</td>
<td>1.0</td>
<td>1.1</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 2.1
The use of 1.5 equivalents of potassium carbonate could also deprotonate the phenol to allow attachment of another benzyloxyl chain. Hence in future work, the use of more equivalents of potassium carbonate should lead to the selective formation of 80.

2.2 **Surfactant synthesis derived from an Oxazolo Pyridinone (82).**

In an attempt to investigate the effects of using surfactants containing structurally rigid head groups as catalysts in aqueous and organic media, surface active compounds derived from \( [1S-(1\alpha, 2\beta, 8\alpha\beta)](+)-\text{hexahydro-2 (hydroxymethyl)-8\alpha methyl-1-phenyl-5H-oxazolo(2,1)} \) pyridin 5-one (82) were synthesised.

Initially the synthesis of surfactant analogues 82a and 82b were sought (Scheme 2.9).

![Scheme 2.9](image)

Conversion of the amide 82 to the amine 82c was investigated using LiAlH₄ in THF (Scheme 2.10). The reaction was heated at 50 °C for 18 hours and several products were formed which were difficult to isolate using flash chromatography. The reaction was repeated at a higher temperature. Unfortunately, none of the bicyclic compound 82c was isolated.
The synthetic route investigated was then carried out as shown in Scheme 2.11.

(i) 1M THF/Borane (3 eq.), 22 hrs, reflux, (ii) 1-iodohexadecane, K₂CO₃, acetonitrile, reflux 22 hours; (iii) Me₂O²BF₄, (1.2 eq.), dichloromethane, 25 °C, 48 hrs; (iv) 1-iodohexadecane, DMF/NaH (1 eq.), 60 °C, (v) 1M THF/Borane 2 eq. reflux, 18 hrs, (vi) Me₂O²BF₄, (1.2 eq.), dichloromethane, 25 °C, 48 hrs.
THF-Borane (H₃B-THF) and borane-dimethyl sulfide BMS (H₃B.SMe₂) have been reported to successfully reduce amides to the corresponding amines. The reduction of 82 was then repeated using THF-Borane to give the ring opened amine 83 in 68% yield (Scheme 2.11).

Attempts were made to alter the reaction conditions to avoid ring opening. Despite monitoring the reaction, 83 was the only product generated. The use of fewer equivalents of THF-Borane yielded mainly starting material. Regardless, 83 was then used as a scaffold to generate surface active compounds with a large ring containing head group.

Initially, quaternisation was explored using 1-iodohexadecane. Compound 84 was formed in 41% yield. Furthermore, the formation of 87 was explored by the reaction of 83 with 1-hexadecyl iodide (Scheme 2.12) under basic conditions where etherification at the primary position was envisaged to be more favourable.

![Scheme 2.12](image)

Interestingly, two products 87 and 87b were formed. From NMR spectroscopy analysis it was observed that compound 87 was produced in 19%, however attempts to isolate the two products via flash-chromatography using various solvent systems were unsuccessful.
An alternative route was explored involving the addition of the hexadecyl chain to the starting pyridinone 82 (Scheme 2.11). This resulted in the formation of the ether 86 in 41% yield. However, no improvement in this reaction yield could be achieved. The borane reduction was carried out as before and gave the ring-opened amine 87 in 93% yield. The salt formation of 87 to give 88 was then readily achieved using 4M HCl/dioxane (Scheme 2.11) and the resulting product was purified by recrystallisation to give 88 in an isolated yield of 92%.

Attempts were also made to quatemise compound 87 using methyl iodide. The reaction was carried out in a sealed tube (Scheme 2.13). Mass spectroscopy and $^1$H NMR spectroscopy indicated that a small amount of 89b was formed ($m/z$ 488) with predominantly starting material remaining. The reaction was repeated with more equivalents of methyl iodide, heating the reaction to reflux. However full quaternisation was still not observed.

In an attempt to overcome this problem, a stronger methylating agent, in the form of trimethyloxonium tetrafluoroborate (Meerwein salt) was used. This methylating agent has been extensively used in $O$-methylations.
The use of trimethyloxonium tetrafluoroborate led to the formation of 89 in 82% yield after purification via flash-chromatography (Scheme 2.11). Analysis of the NMR spectra and mass spectroscopy confirmed the presence of compound 89 (m/z 488).

Quaternisation of the open piperidine ring 83 was also carried out to assess the effect of the lipipholic salt 89 vs salt 85. Accordingly, trimethyloxonium tetrafluoroborate and compound 83 were stirred in dichloromethane to give 85 in 81% yield.

2.3 Surfactant Synthesis derived from S-Proline.

An S-proline derived surfactant was also synthesised. The synthetic route used is shown in Scheme 2.14.

\[
\begin{align*}
\text{(i) } & \text{37% formaldehyde,} \\
\text{88% formic acid} \\
\text{H}_2\text{O, KOH workup} \\
\text{(ii) } & \text{CH}_3(\text{CH}_2)_{13}\text{Br (1 eq.)} \\
\text{acetonitrile, 90 °C} \\
\end{align*}
\]

Scheme 2.14

S-Proline was reduced to S-prolinol (90) using sodium borohydride in THF in 55% yield. Monomethylation was carried out using formaldehyde and formic acid to give 90b in its crude form.
This was treated with hexadecyl bromide and acetonitrile in a sealed tube at 90 °C. After reaction workup and recrystallisation, compound 91 was generated in 79% yield.

2.4 Synthesis of Surfactants Derived from (+)-Cinchonine.

Alkaloids including (+)-cinchonine and \( N \)-alkylated derivatives have been used in for example phase transfer reactions to enhance reaction yields and selectivities.\(^{145,146,147}\) The use of cinchonine derived surfactants would enable us to utilise a rigid surfactant head group which could influence reaction selectivities. The synthetic route used to synthesise surface active compounds derived from (+)-cinchonine is given in Scheme 2.15.\(^{155}\) (+)-Cinchonine was reacted with 1-bromohexadecane in the presence of sodium hydride and DMF to yield 92 in 50% yield after purification by flash-chromatography. The hydrochloride salt 93 was then readily formed using 4M HCl and 92 in 88% yield.

![Scheme 2.15](image)

Quaternised salts of 92 were also prepared using methyl iodide in a sealed tube (Scheme 2.16). We noted that at room temperature 94 was selectively generated in 85% yield. However, the addition of methyl iodide, using a raised reaction temperature and more equivalents of alkylating reaction generated surfactant 95 in 90% yield.
In order to assess the effects of using more hindered quaternary salts, quaternisations using benzylic groups were also carried out. The ether 92 was reacted with benzyl bromide to give 96 in 82% yield after purification by flash column-chromatography (Scheme 2.17). Again by raising the reaction temperature, 97 was prepared in 90% yield.
2.5 The Synthesis and Polymerisation of Surfactant monomers.

Preliminary studies, on the synthesis and polymerisation of surfactant monomers were carried out. In aqueous based reaction systems, the use of alkaloid based surfactants lead to the highest enantioselective inductions, hence these were selected as suitable monomers. Two polymerisable moieties were used, terminal alkene groups and acrylates. So the synthesis of 99 and 113 were investigated. The polymerisation of such compounds should generate materials with a large surface area and head group rigidity and when used as catalysts lead to higher reaction selectivities.

![Chemical structures](image)

2.5.1 Attempted polymerisation of surfactant containing a terminal alkene.

The synthesis of 99 was carried out as shown in the pathway carried out in Scheme 2.18. 11-Bromo-1-undecene was reacted with hydroquinidine and sodium hydride to give the corresponding etherified material 98 in 55% yield (Scheme 2.18). Quaternisation was achieved using methyl iodide to yield 88% of 99 after purification by flash chromatography.
Attempts were made to polymerise 99 using a procedure reported by Leydet et al. (Scheme 2.19). Leydet polymerised a range of unsaturated anionic surfactants whose polar head was derived from amino acids such as L-alanine, L-proline and L-threonine. These surfactants were polymerised in micellar solutions using γ-radiation.

Following Leydets procedure a 0.1 M solution of 99 was prepared in an ethanol/water (50:50) mixture. Whilst Leydet had used water alone at a concentration of 0.1 M, in our case insoluble material remained, so the solvent used was adjusted. γ-Radiation (Cs-source) was used and 99 was irradiated for 2 weeks using 662 KeV photon gamma-rays. Unfortunately, the formation of no polymerised material was observed. The unquaternised compound 98 was also treated using the same procedure but unfortunately, once again no polymerisation resulted. It is possible that an alternative γ-radiation source (higher than 662 KeV) is required although this is unclear from Leydet’s work.
2.5.2 Polymerisation of Surfactants containing an acrylate chain.

The synthesis of a monomer bearing an acrylate group was also explored. A 12-carbon linker was used between the acrylate groups and hydroquinidine and the synthetic route which has been previously carried out by Porter et al. was explored and is shown in Scheme 2.20.\(\text{157}\) The mono-bromination of dodecandiol using 1 equivalent of carbon tetrabromide and triphenylphosphine was investigated but interestingly yielded only 5\% of the desired product 100 (Scheme 2.20). Using further equivalents of the diol only increased the yield to 9\%. An alternative bromination route using HBr was used as reported by Michael Chong et al.\(\text{158}\) Compound 100 was formed in 84\% yield.

Attachment of the acrylate group was achieved using acryloyl chloride with triethylamine as base to give 89\% of 12-bromo dodecyl acrylate (101). Compound 101 was subsequently reacted with hydroquinidine using the etherification conditions previously used, to yield a mixture of 110 (12\%) and the acrylated compound (112) (42\% yield) (Scheme 2.20). This reaction was explored using an alternative solvent (THF) and different reaction temperatures, however none of the desired compound (112) was isolated. When repeating the reaction in DMF but also using lower reaction temperatures (0 °C and 40 °C), 110 and 112 were produced in identical yields to that shown in Scheme 2.20, however removal of the acrylate group was still observed.

With the aim of generating a more active electrophile, the bromo acrylate was converted into the corresponding iodide using sodium iodide in acetone (Scheme 2.20) in 90\% yield. The etherification reaction was repeated using hydroquinidine with 102 (Scheme 2.20), initially using NaH and in DMF at 80 °C. However none of the desired material was isolated. Again, the use of alternative solvents and reaction temperatures had no effect.
An alternative synthetic route was envisaged involving the protection of the diol and a late stage attachment of the acrylate as shown in Scheme 2.21. A trityl group was initially used and mono protection of the diol (105) was achieved in 62% yield.

The bromination of 105 using triphenylphosphine and carbon tetrabromide gave 106 in 40% yield. The coupling of 106 to hydroquinidine using sodium hydride and DMF gave compound 109 in only 8% yield, and a similar yield was observed using THF. Again, conversion to the iodide was explored and 107 was formed from 106 in 92%. The reaction of compound 107 with hydroquinidine using the reaction condition developed, surprisingly gave 109 in only 9% (Scheme 2.21). Modification of the reaction conditions such as solvents and base gave no further improvements.
The use of a trityl protected alkyl chain with an alternative non-halide leaving group was explored to assess whether a successful ether synthesis in reasonable yield could be established. The mesylate 108 was therefore synthesised as shown in Scheme 2.22. Compound 105 was mesylated using methane sulfonyl chloride and triethylamine in 58% yield. The reaction of 108 with hydroquinidine using 1.1 equivalents of sodium hydride in DMF gave 109 in 19% yield. The yield was increased to 32% when using 3 equivalents of sodium hydride suggesting that the deprotonation of hydroquinidine was more readily obtained under these conditions. By performing the reaction in THF at 70 °C using 1.5 equivalents of sodium hydride, a slightly higher yield of 34% was achieved and no further enhancements in yield were observed. Compound 109 was subsequently deprotected using 1M hydrochloric acid in 50:50 dichloromethane:methanol to give 110 in 86% yield (Scheme 2.22).

The next step involved attachment of the acrylate moiety. Initially acryloyl chloride was reacted with 110 in the presence of triethylamine at 40 °C (Scheme 2.22) following a similar procedure described by Porter et al.\textsuperscript{157} However, none of the desired product 112 was obtained. The reaction was repeated at lower temperatures (0-30 °C), but again none of the acrylate ester was isolated. Alternative ester coupling conditions using EDCI and DMAP (Scheme
2.22) yielded 18% of 112. Attempts were then made to quaternise 112 using excess methyl iodide in dichloromethane at 25 °C, however compound 113 was extremely difficult to isolate despite the indication of a 73% conversion yield from 1H NMR spectrometry analysis.

Scheme 2.2.2.
In an attempt to overcome the problem with the purity of 113, quaternisation was carried out prior to acrylate attachment. Compound 110 was quaternised using methyl iodide, however purification of the resulting compound 111 by flash chromatography proved to be problematical. The coupling reaction between crude 111 and acrylic acid using EDCI was also explored but was not successful, possibly due to the presence of impurities (Scheme 2.23).
Since the ether synthesis of the trityl protected surfactant 109 only led to yields of up to 34% (Scheme 2.22), it was envisaged that an alternative less bulky protecting group might enhance the yield. Accordingly, 3,4-dihydro-2H-pyran was used to mono protect the OH moiety in the diol to produce a tetrahydropyryanyl (THP) ether (103) in 60% yield (Scheme 2.24). The mesylation of 103 was carried out as before to give 104 as a colourless oil in 64%. Unfortunately the coupling of 104 to hydroquinidine was unsuccessful. Thin layer chromatography analysis indicated the presence of multiple spots and it was not possible to isolate individual reaction products.

At this stage, the polymerisation of 112 and 113 (obtained as a crude mixture) was performed using a procedure described by Boutevin et al.\textsuperscript{159} Using a catalytic amount of AIBN as initiator and 112 the reaction was heated for 18 hours at 80 °C (Scheme 2.25). After purification by flash chromatography, an oil
was isolated which contained a mixture of polymers and polymer fragments ranging between 1155-1988 according to mass spectroscopy analysis which corresponded to the addition of approximately 2 to 3 units. $^1$H NMR spectrometry analysis showed the presence of multiple peaks between 0.81-1.94 and no acrylate signals.

Repeating this reaction using surfactant 113 also resulted in the production of an oil which according to mass spectrometry was made up of polymer fragments of up to $m/z$ 913 (Scheme 2.26). The low $m/z$ maybe attributed to multiple charges in the polymers prepared.
All of the solution and “polymer” surfactants synthesised in this chapter were used as catalysts in both aqueous and organic media for a range of reactions which include the diethyl zinc (chapter 4), Michael addition (chapter 5) and Baylis-Hillman reactions (chapter 6).
Chapter 3  Determination of Critical Micelle Concentrations and Reverse Critical Micelle Concentrations.

A range of surfactants were tested for their aggregation ability in aqueous and organic media using dye solubilisation techniques. Although this technique is well established, there are many shortcomings which have been highlighted by Mukerjee and co-workers. (Also see section 1.1.5). One of the major problems is the accuracy of the technique since the dye may induce the formation of "mixed micelles" where an aggregation between the dye and surfactant occurs which can affect the CMC and RCMC values. Also the presence of the dye can alter the micellar structure of the surfactant during aggregation.

Since our intention was to use these surfactants in the presence of reaction substrates, we rationalised that the interaction of dye molecules and surfactant was a realistic approach in providing us with an indication of the surfactant CMC and RCMC range. Another criteria was the ease and rapidity of this technique (see section 1.1.5 on how to determine the surfactant CMC using dye solubilisation techniques).

Surfactants 70, 93 and 94 were selected since they were the most successful catalysts in the diethyl zinc, Michael addition and Baylis-Hillman reactions (see relevant chapters). Surfactants 68, 69 and 72 were also tested to see how varying the chain length or using a non ionic head group influences the CMC and RCMC compared to compound 70. The validity of this technique was verified by using a suitable dye on a known surfactant whose CMC value was established prior to the dye being used on our synthesised surfactants.

3.1  Determination of Critical Micelle Concentration in water.

A suitable dye was required for CMC surfactant analysis. Initially the CMC of a well characterised cationic surfactant, hexadecyltrimethylammonium
bromide (CTAB) (115a) was analysed using the dye methyl orange (115b) which has been used within the group to indicate an initial aggregation point (Scheme 3.1).\textsuperscript{41,162}

\[
\begin{align*}
\text{115a} & \quad \text{115b} \\
\text{Br}^- & \quad \uparrow \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
360 \text{ nm} & \quad 460 \text{ nm}
\end{align*}
\]

Scheme 3.1

A serial dilution was carried out and the UV absorption for each of these solutions were measured. A colour change from orange to yellow was observed as the surfactant concentration was increased (see section 1.1.5 for explanation). The change in the absorption maxima at \(\lambda_{\text{max}}\) 360 nm (yellow unpolarised canonical) and \(\lambda_{\text{max}}\) 460 nm (orange polarised canonical) were monitored. At a certain concentration at which the surfactant no longer exists as monomers and starts to aggregate, methyl orange interacts with the surfactant and exists in its less polar canonical form. As the surfactant concentration is further increased, the absorbance at 360 nm increases at the expense of the absorbance at 460 nm. The results are shown below in Graph 3.1.1.
The point at which the absorbance maxima at 360 nm and 460 nm intersected, occurred at a concentration of 0.028 mM of CTAB and this point was taken to correspond to an initial aggregation between the dye and micelle.\textsuperscript{31,162}

Since it is established that the CMC of CTAB is at 0.92 mM,\textsuperscript{41} a mixed micellar aggregation well below the CMC had occurred. The use of an alternative dye was therefore sought to give a clearer indication of not only an initial aggregation between dye and surfactant but of micellar formation. \textit{p}-Methyl Red (115e) has previously been used to establish the CMC of cationic surfactants on aqueous systems.\textsuperscript{41} The two canonical forms are given below and the absorbance measured over a range of concentrations is shown in Graph 3.1.2.
The UV absorption maxima at 380 nm (yellow unpolarised canonical) and 460 nm (pink polarised canonical) were monitored. From Graph 3.1.2 two crossover points were observed. The first intersection at 0.19 mM is possibly the point where an initial aggregation between the dye and the surfactant occurred. The second intersection at 0.92 mM represented the aggregation of the CTAB surfactant as it begins to micellise which is in agreement with literature values of the CMC.\(^1\) In view of the clear data points, this method was repeated with the synthesised surfactants whose CMC values were required. The absorbance versus concentration for compounds 68, 69, 70 and 72 was determined. This is shown on Graphs 3.1.3 to 3.1.6.

For surfactant 70 (Figure 3.1.3) an initial aggregation between the micelle and \(p\)-methyl red at \(6 \times 10^{-2}\) mM was obtained. The final aggregation at \(1.50 \times 10^{-1}\) mM corresponded to an approximate CMC of surfactant 70. The CMC of the free amine, 69 was observed to be lower (\(9 \times 10^{-2}\) mM) (Figure 3.14) in comparison to 70. This may be attributed to the repulsion between the cationic head groups in the Gouy-Chapman layer in surfactant 70 which does not favour micellar formation as much as surfactant 69 where a non ionic head group is present. As a result surfactant 70 would require an increased concentration of surfactant monomers for micellisation to occur in comparison to surfactant 69.

When using surfactant 72 (Graph 3.1.6) where the length of the alkyl chain is extended to C-18, a reduction in the CMC was observed (\(1.2 \times 10^{-1}\) mM).
This demonstrated that increasing the length of the hydrophobic surfactant chain tended to favour micellar formation due to increased attractive Van der Waals forces between the hydrocarbon chains. Conversely the shorter chained C-12 surfactant 68 acquired a higher CMC value of $2.1 \times 10^{-1}$ mM (Graph 3.1.5).

![Chemical Structure](image1)

![Graph 3.1.3](image2)

![Graph 3.1.4](image3)

![Graph 3.1.5](image4)

![Graph 3.1.6](image5)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Initial aggregation (mM)</th>
<th>CMC (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>$6 \times 10^{-2}$</td>
<td>$1.5 \times 10^{-1}$</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>$3 \times 10^{-2}$</td>
<td>$9 \times 10^{-2}$</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>$6 \times 10^{-2}$</td>
<td>$2.1 \times 10^{-1}$</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>$6 \times 10^{-2}$</td>
<td>$1.2 \times 10^{-1}$</td>
</tr>
</tbody>
</table>

Table 3.1.1
Higher CMC values were obtained for surfactants 93 ($2.38 \times 10^{-1}$ mM) and 94 ($2.57 \times 10^{-1}$ mM) in comparison to the tyrosine derived surfactants (Figure 3.17 and Figure 3.18). This may be due to the large size of the head groups which would repel each other, preventing micellisation from occurring. This effect is enhanced further since the head groups are charged.\textsuperscript{30,31}

![Chemical structures of 93 and 94](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Initial aggregation (mM)</th>
<th>CMC (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>$1.2 \times 10^{-1}$</td>
<td>$2.38 \times 10^{-1}$</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>$1.2 \times 10^{-1}$</td>
<td>$2.57 \times 10^{-1}$</td>
</tr>
</tbody>
</table>

Table 3.1.2

### 3.2 Determination of Reverse Critical Micelle Concentration in Organic Media.

When surfactants are dissolved in organic media they can generate reverse micelles. In view of this, a dye solubilisation technique using iodine as
described by Ross and Oliver was initially investigated to determine the reverse-critical micelle concentration RCMC of the relevant surfactants.

A range of surfactants were mixed in toluene (the surfactants were insufficiently soluble in hexane which was the solvent used to carry out most of the diethyl zinc analysis). Initially, different concentrations of surfactant and dye were used to establish the optimum conditions needed to determine the surfactant RCMC. These concentrations ranged from 0.3 mM to 0.1 M for surfactant 70 and 5 mg/litre and 5 mg/100 ml of iodine in toluene. The UV absorption maxima at 400 nm and 500 nm were monitored (see Section 1.1). It was observed that above 0.3 mM of surfactant 70, the absorption peak became swamped by surfactant absorption. However the optimal conditions required to carry out the RCMC analysis was using 0.3 mM of surfactant and 5 mg/100 ml of iodine. As shown in Graph 3.2.1 a change of absorption in two regions, 0.09 mM and 0.18 mM was observed. However, to verify which of the two concentrations was the RCMC, a different method was selected and these results compared to the results obtained using I$_2$/toluene solvent.

In 1973, Muto and Meguro made successful use of TCNQ (7,7,8,8-tetracyanoquinodimethane) (115d), a well-known strong electron acceptor.
Characteristic absorption spectra were observed, particularly at 750 nm and 850 nm where the maxima was found. Muto postulated that this was due to the formation of TCNQ anion radicals by a charge transfer mechanism from the surfactant to TCNQ. The surfactant head groups, concentrated in the inverted micelle can interact with TCNQ and produce an ionic charge transfer complex. The resulting TCNQ anion radical can then be solubilised inside the inverted micelle.\textsuperscript{163}

The reliability of using TCNQ to determine RCMC was confirmed by measuring the RCMC of sodium dioctyl sulfosuccinate (Aerosol OT) (\textbf{115e}) in carbon tetrachloride which has had the CMC determined by several methods (Graph 3.2.2).\textsuperscript{163}

As shown in Graph 3.2.2, the sudden increase in absorbance indicated that the RCMC of Aerosol OT was at $6.9 \times 10^{-1}$ mM. This surfactant was also analysed using I\textsubscript{2} in carbon tetrachloride as proposed in the literature (Graph 3.2.3).\textsuperscript{163} The RCMC value of Aerosol OT in this case was found to be $2.3 \times 10^{-1}$ mM. These values were in accordance with the literature, $0.6$ mM/lit. and $0.3$ mM/lit. respectively.\textsuperscript{163} This confirmed both the reliability of TCNQ, but also indicated how the use of different solvents can effect CMC value determined.
The RCMC of surfactant 70 was verified using TCNQ (Graph 3.2.4). A range of between 0.18 mM and 0.21 mM was observed in good agreement with the slightly higher value determined from using I\textsubscript{2}/toluene. It was therefore deduced that the RCMC of surfactant 70 was approximately 0.18 mM.

The techniques using I\textsubscript{2}/toluene and TCNQ were straightforward and were repeated with surfactant 72 containing the extended C-18 chain (Graph 3.2.5 and Graph 3.26). A reduction in the RCMC was observed (0.12mM) compared to compound 70. Conversely when using the shorter C-12 chained surfactant 68, a larger RCMC range of between 0.21-0.24 mM was obtained (Graph 3.2.7 and Graph 3.2.8). The non-ionic surfactant 69 was found to have a slightly lower RCMC of approximately 0.15-0.18 mM compared to its cationic counterpart 70 (0.18 mM) (Graph 3.2.9 and 3.2.10). This could be due to the disfavourable charge repulsion of the polar head group of surfactant 70 which
would increase its RCMC value, though the difference is relatively small (i.e. steric major effects).

\[
\begin{align*}
\text{HO-} & \quad \text{OH} \\
\text{H} & \quad \text{CF} \quad n = 11, \quad 68 \\
\text{N} & \quad \text{H} \quad n = 15, \quad 70 \\
\text{N} & \quad \text{H} \quad n = 17, \quad 72 \\
\text{HO'} & \quad n = 17, \quad 72
\end{align*}
\]

Graph 3.2.5

Graph 3.2.6

Graph 3.2.7

Graph 3.2.8
The RCMC of the cinchonine based surfactants 93 (Graphs 3.2.11 and 3.2.12) and 94 (Graphs 3.2.13 and 3.2.14) were found to be 0.25 mM and 0.30-0.35 mM respectively. These values were larger than the RCMC values obtained for the tyrosine based surfactants reflecting the effects of larger head groups.
In general the RCMC of all the tested surfactants followed a similar trend to that of their CMC values obtained in aqueous media. Hence factors such as the size of the polar head groups and varying chain length can affect CMC and RCMC of these compounds as confirmed in the literature.\textsuperscript{30, 31}
Chapter 4  Dialkyl Zinc Additions to Aldehydes.

4.1 Diethyl Zinc addition to Benzaldehyde using S-Tyrosine Derived Surfactants.

As previously mentioned in Section 1.2, a variety of catalysts particularly the β-amino alcohols have been successfully used in diethyl zinc addition reactions.65,66,67 More recently, compound 26 synthesised by Hailes and Madden was found to be an efficient recoverable catalyst for the addition of diethylzinc to aromatic aldehydes generating selectivities in up to 82% e.e.4

\[
\begin{align*}
\text{CH}_3 & \quad \text{Ph} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{HO'} & \quad \text{C}_6\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{n} = 11, & \quad 68 \\
\text{n} = 15, & \quad 70 \\
\text{n} = 17, & \quad 72
\end{align*}
\]

In order to investigate the effects of using catalysts similar to 26 but possessing extra hydrogen bonding capacity, the tyrosine analogues 68, 70 and 72, containing N-aliphatic chains were used. Surfactants 79 and 81 (whose phenolic OH moiety is blocked) containing the benzyloxy chain were also tested to make a direct comparison with the norephedrine derived surfactant 26.4

The addition of diethyl zinc to benzaldehyde was studied initially using 70, 79 and 81. The results are summarised in Table 4.1.1. The reactions were performed at 2 different temperatures and the desired secondary alcohol 116 was isolated and purified by flash chromatography.

The use of the tyrosine derived compounds 70, 79 and 81 preferentially generated R-phenyl propan-1-ol (116) (entries 1-7). This was contrary to the results obtained when using 26 where the S-isomer was preferentially formed (entries 8-9).4 The absolute configuration of the alcohol was confirmed by chiral
HPLC analysis as well as optical rotation \([\alpha]_D^{20} = +15^\circ \text{ c 1.25, CHCl}_3\) for entry 3 with 52% e.e).

As previously described, the use of different reaction temperatures can have an effect on reaction selectivities and yields and this appears to be very dependent on the catalyst used.\(^4\)\(^6\) We observed that when using 70, higher yields and selectivities were observed at room temperature compared to when increasing the reaction temperature to 70 °C. Interestingly using 79 and 81 where a benzyloxy dodecyl chain was used, a drop in reaction selectivity was observed at room temperature compared to 70. Increasing the reaction temperature to 70 °C resulted in minimal selectivity change and a drop in reaction yield in the case of 81. These results were in contrast to that previously observed within the group when using 26 where a higher yield and selectivity was achieved at 70 °C.\(^4\)\(^,\)\(^1\)\(^0\)

The lower reaction yields and selectivities for 79 and 81 maybe accounted for by considering their reduced solubility in hexane in comparison to 70. The bulkiness of the benzyloxy group will have a tendency to inhibit micellar formation and as a result effect its solubility in hexane, thus reducing its influence on the alkylation reaction. In the case of compound 81, since the phenolic OH is blocked by the addition of another benzyloxy group in that position, this can reduce the diethyl zinc complexation sites, thus reducing the catalytic effect on the reaction.

![Scheme 4.1.1](image-url)
Table 4.1.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (mM)</th>
<th>Surfactant</th>
<th>Time/temp. (hr°C)</th>
<th>Yield %</th>
<th>E.e % *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.31</td>
<td>70</td>
<td>6/70</td>
<td>87</td>
<td>20(R)</td>
</tr>
<tr>
<td>2</td>
<td>5.36</td>
<td>70</td>
<td>48/70</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>5.28</td>
<td>70</td>
<td>48/25</td>
<td>95</td>
<td>52(R)</td>
</tr>
<tr>
<td>4</td>
<td>5.37</td>
<td>79</td>
<td>6/70</td>
<td>69</td>
<td>2(R)</td>
</tr>
<tr>
<td>5</td>
<td>5.35</td>
<td>79</td>
<td>48/25</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>5.32</td>
<td>81</td>
<td>6/70</td>
<td>43</td>
<td>14(R)</td>
</tr>
<tr>
<td>7</td>
<td>5.35</td>
<td>81</td>
<td>48/25</td>
<td>62</td>
<td>11(R)</td>
</tr>
<tr>
<td>8</td>
<td>5.36</td>
<td>26</td>
<td>6/70</td>
<td>95</td>
<td>62(S)</td>
</tr>
<tr>
<td>9</td>
<td>5.30</td>
<td>26</td>
<td>48/25</td>
<td>35</td>
<td>44(S)</td>
</tr>
</tbody>
</table>

* Enantiomeric excess were determined using chiral cell OD column, 254nm detection wavelength, 2% iso-propanol, flow rate 1.0 ml/ min. 12.0 min (R), 17.0 min (S).

For the reactions carried out at 25 °C with compounds 70, 79 and 81 the conformation in the transition state adopted, is that which favours the R-isomer of 116. This is in contrast to compound 26 where the S-isomer was favoured.

For surfactant 70, a favourable surfactant aggregation was postulated where the polar head groups of the surfactant together with the reaction substrates would be found at the centre of this aggregate forming the micellar core. The surfactants and reaction substrates could aggregate by zinc coordination as shown in Figure 4.1.1 The alkyl chains are orientated into the organic solvent in a reverse micelle type manner. In representation A, the benzaldehyde substrate lies below surfactant 70. The top face is therefore blocked allowing the diethyl zinc to attack the benzaldehyde from below the plane. The aldehyde is positioned so that favourable \( \pi \)-stacking between the aromatic rings of benzaldehyde and the phenolic ring from 70 occurs, giving the preferred R-isomer. In comparison, representation B shows the benzaldehyde
substrate lying beneath surfactant 70, with the aromatic rings away from each other giving the less favourable $S$-isomer.

In comparison to the results obtained using surfactants 79 and 81 containing the benzyloxy chains, since good yields but low reaction enantioselectivities were observed, it can be assumed that diethyl zinc coordination with the phenolic OH is responsible for reaction selectivity and that diethyl zinc coordination between the nitrogen and OH moiety of the $\beta$-amino alcohol may be responsible for affecting the reaction yield.

![Diagram of reaction selectivity](https://via.placeholder.com/150)

**Figure 4.1.1**

Since a high yield in just 6 hours was observed when increasing the reaction temperature to 70 °C (Table 4.1.1, entry 8), we investigated the effect of a longer reaction time to assess the influence on reaction selectivity on compound 70. Interestingly a drop in reaction yield (42%) and no selectivity was
observed (Table 4.1.1, entry 2). Subjecting compound 70 to high temperatures for long periods may have caused partial degradation causing the above effect to take place.

In order to verify the recyclability of 70, this compound was recovered and re-used in the diethyl zinc addition reaction with benzaldehyde. Recovery was not as straightforward as envisaged since after the reaction workup and purification via flash chromatography a lower yield of 84% was obtained as well as a drop in the reaction selectivity to 20% e.e ($R$-isomer, Table 4.1.2). However when comparing these results to entry 3 (Table 4.2) where the corresponding free amine 69 was used, a selectivity to 19% e.e ($R$-isomer) was observed. This suggested that recovered 70 may have contained some free amine in addition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time/temp (hrr°C)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>48/25</td>
<td>95</td>
<td>52 ($R$)</td>
</tr>
<tr>
<td>2</td>
<td>70 recycled</td>
<td>48/25</td>
<td>84</td>
<td>20 ($R$)</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>48/25</td>
<td>70</td>
<td>19 ($R$)</td>
</tr>
</tbody>
</table>

Table 4.1.2

We wished to investigate more fully whether the catalyst was most effective as an HCl salt or free amine, so amine 69 was also used in the diethyl zinc reaction at different temperatures (Table 4.1.3). A reduction in both the yield and selectivity was observed. This clearly indicated that in the presence of the cationic amine, the diethyl zinc reaction is enhanced. Previous reports using amino alcohols have suggested that higher selectivities and yields can be obtained at lower temperatures, however when using 69, a drop in yield and no selectivity was achieved below 0 °C.86 This trend was also observed with the HCl salt 70, where a drop in selectivity to 26% e.e was noted.
To explain the importance of the amine functionality in forming the reaction intermediate used to drive this reaction, we prepared quaternary salts 73 and 74 containing different counterions, iodide and hydroxide respectively. A significant drop in reaction yield and selectivity was observed (Table 4.1.4). However compound 73 led to a slightly higher yield and selectivity of the 1-phenyl propanol (116) than 74 (Table 4.1.4). The yield and selectivity difference could be attributed to the solubility of both 73 and 74 in hexane since it was observed that 73 was slightly more soluble than 74. Also a change in the anion may alter the surfactant aggregation with its reacting substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Conc. (mM)</th>
<th>Time/ temp. (hr/ °C)</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>5.32</td>
<td>48/25</td>
<td>58</td>
<td>26 (R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48/0</td>
<td>95</td>
<td>52 (R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6/70</td>
<td>87</td>
<td>20 (R)</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>5.31</td>
<td>48/25</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48/0</td>
<td>70</td>
<td>19 (R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6/70</td>
<td>62</td>
<td>20 (R)</td>
</tr>
</tbody>
</table>

Table 4.1.3

The effect of using different solvent systems were also investigated using 70. The results are summarised in Table 4.1.5. A change in both the yields and selectivities of 70 were observed when varying the solvent system, however the use of hexane still led to the best set of reaction data. A suitable rationale is the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactants</th>
<th>Time/ temp. hr/ °C</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>48/25</td>
<td>42</td>
<td>8 (R)</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>48/25</td>
<td>36</td>
<td>4 (R)</td>
</tr>
</tbody>
</table>

Table 4.1.4
change in the reverse micellar aggregates formed in different solvents. The micellar aggregation of 70 in hexane (shown in Figure 4.1.1) could produce a more thermodynamically stable reaction intermediate leading to the required product 116 in high yields. Different reverse micelles may exist in other solvents adopting a preferential conformation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Conc. (mM)</th>
<th>Solvent</th>
<th>Time / temp. hr/°C</th>
<th>Yield (%)</th>
<th>(E.e) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>5.31</td>
<td>Toluene</td>
<td>48 / 25</td>
<td>51</td>
<td>38 (R)</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>5.37</td>
<td>DCM</td>
<td>48 / 25</td>
<td>32</td>
<td>18 (R)</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>5.34</td>
<td>Cyclohexane / hexane</td>
<td>48 / 25</td>
<td>88</td>
<td>46 (R)</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>5.29</td>
<td>Hexane</td>
<td>48 / 25</td>
<td>95</td>
<td>52 (R)</td>
</tr>
</tbody>
</table>

Table 4.1.5

The effects of varying the amount of catalyst 70 on the diethyl zinc reaction was also investigated. Since the RCMC of 70 was approximately 0.18 mM as determined from dye solubilisation methods (see chapter 3), this suggested that reverse micellar aggregates at this concentration were present. With this in mind, selected reactions using 70, before, at and after the RCMC range were carried out. The results are summarised in Graph 4.1.1.

Below the RCMC level, a very low yield of 116 was obtained. At the RCMC level, 14% of 116 was isolated and a sudden increase in the reaction yield and selectivity well above the RCMC was observed. It is possible that below or at the RCMC level, the diethyl zinc may co-ordinate with compound 70 to produce unstable di-nuclear or tri-nuclear transition state complexes. Above the RCMC level, there is enough of compound 70 to co-ordinate with diethyl zinc to produce a stable tetra-nuclear transition state, which in turn would generate the intermediate shown in Figure 4.1.1.
Since it was observed that when using 70 containing the aliphatic C-16 chain, the best yields and selectivities were observed, we decided to investigate the effects of varying the surfactant chain lengths. The alkyl tyrosine surfactants of chain lengths 12 (compound 68), 16 (compound 70) and 18 (compound 72) were all synthesised and used in the benzaldehyde reaction with diethyl zinc. The results are given in Table 4.1.6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time/ temp. (hr/°C)</th>
<th>yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12-chain (68)</td>
<td>48 / 25</td>
<td>64</td>
<td>20 (R)</td>
</tr>
<tr>
<td>2</td>
<td>16-chain (70)</td>
<td>48 / 25</td>
<td>95</td>
<td>52 (R)</td>
</tr>
<tr>
<td>3</td>
<td>18-chain (72)</td>
<td>48 / 25</td>
<td>91</td>
<td>69 (R)</td>
</tr>
</tbody>
</table>

Table 4.1.6

Increasing the chain length clearly resulted in both an increase in yield and selectivity. This is probably due to favourable reverse micellar aggregation as the aliphatic surfactant chain length is increased due to increased hydrophobic interactions between the surfactant chains by Van-der Waals forces.\textsuperscript{30,31} This was confirmed by the RCMC values obtained by dye solubilisation techniques (chapter 3) (Table 4.1.7).
Table 4.1.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>RCMC (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>0.21-0.24</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>≈ 0.18</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>≈ 0.12</td>
</tr>
</tbody>
</table>

It has been previously suggested within the group that during the diethyl zinc addition reaction, a co-ordination occurs between the surfactant and Zn$^{2+}$ as shown in Scheme 4.1.2.$^{150}$

Scheme 4.1.2

In order to verify this and to further investigate the possible reaction intermediate, 2 mol% of zinc chloride was added to assess its effect on the reaction (Table 4.1.7). The zinc chloride and diethyl zinc were pre-mixed before addition onto the aldehyde-surfactant mixture. It was observed however that the addition of zinc chloride produced a drop in both the yield and selectivity of these reactions. This could be due to the ZnCl$_2$ possibly disrupting the surfactant aggregation rather than helping to chelate the surfactant and diethyl zinc. However it is also possible that the ZnCl$_2$ is competing with Et$_2$Zn as shown in
Scheme 4.1.3 producing a stable EtZnCl complex which may not as readily add to benzaldehyde to produce the desired compound 116. This perhaps accounts for the drop in reaction yield and selectivity (Table 4.1.8).

![Scheme 4.1.3](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time / temp.</th>
<th>yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>hr / °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70</td>
<td>48 /25</td>
<td>95</td>
<td>52 (R)</td>
</tr>
<tr>
<td>2</td>
<td>70 + ZnCl₂</td>
<td>48/25</td>
<td>10</td>
<td>14 (R)</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>48/25</td>
<td>70</td>
<td>19 (R)</td>
</tr>
<tr>
<td>4</td>
<td>69 + ZnCl₂</td>
<td>48/25</td>
<td>15</td>
<td>20 (R)</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>48 /25</td>
<td>91</td>
<td>69 (R)</td>
</tr>
<tr>
<td>6</td>
<td>72 + ZnCl₂</td>
<td>48 /25</td>
<td>8</td>
<td>18 (R)</td>
</tr>
</tbody>
</table>

Table 4.1.8

4.2 Diethyl Zinc Addition to Benzaldehyde using Piperidine and Alkaloid Derived Surfactants.

Several of the other surfactants synthesised 84, 85, 87, 88 and 89 were employed in the diethyl zinc addition to benzaldehyde. The results are summarised in Table 4.2.1. Overall the piperidine derived compounds 84, 85, 87, 88 and 89 produced 116 in lower yields and selectivities compared to when tyrosine analogues were used. This could be due to the bulkiness of the piperidine ring which would hinder reverse micellar formation. Interestingly, the
use of compound 88 not only resulted in a higher yield than with its corresponding free-amine 87 but was also selective for a different enantiomer of product. When using the quaternised salt 89 a large reduction in the reaction yield was observed in comparison to the HCl salt 88. A further reduction in reaction yield and no selectivity was observed in the absence of the aliphatic chain 85 since no reverse micellar aggregates would be present. Compound 91 derived from S-prolinol led to the formation of 1-phenyl propanol (116) in a disappointing yield of 22% with 12% e.e (R-isomer). Surprisingly, despite being relatively hindered, compound 94 derived from (+)-cinchonine gave a high yield of 116 (82%) compared to the piperidine derivatives. However only selectivities up to 13% e.e were obtained. The free amine 92 and HCl salt 93 were also used. Again, it was observed that the HCl salt 93 gave the best yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time / temp. (hr/°C)</th>
<th>Yield (%)</th>
<th>Ee (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>48 / 25</td>
<td>34</td>
<td>10 (S)</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>48 / 25</td>
<td>61</td>
<td>6 (R)</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
<td>48 / 25</td>
<td>28</td>
<td>6 (R)</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>48 / 25</td>
<td>68</td>
<td>9 (R)</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>48 / 25</td>
<td>18</td>
<td>1 (R)</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>48 / 25</td>
<td>82</td>
<td>3 (R)</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>48 / 25</td>
<td>22</td>
<td>12 (R)</td>
</tr>
<tr>
<td>8</td>
<td>94</td>
<td>48 / 25</td>
<td>82</td>
<td>3 (R)</td>
</tr>
<tr>
<td>9</td>
<td>92</td>
<td>48 / 25</td>
<td>80</td>
<td>10 (R)</td>
</tr>
<tr>
<td>10</td>
<td>93</td>
<td>48 / 25</td>
<td>88</td>
<td>13 (R)</td>
</tr>
</tbody>
</table>

Table 4.2.1

*Enantiomeric excess were determined using chiral cell OD column, 254 nm detection wavelength, 2% iso-propanol, flow rate 1.0 ml/min. 12.0 min (R), 17.0 min (S).

A possible reaction intermediate was postulated. This is shown in Figure 4.2.1. The zinc complex could involve a chelation between the nitrogen moiety of the bridged ring, the O substituent in the surfactant and the diethyl zinc as
represented in Figure 4.2.1. In representation A, the benzaldehyde substrate lies below surfactant 93. The top face of benzaldehyde is therefore blocked. This enables the diethyl zinc to attack from below the plane. The aldehyde is approaching towards the fused aromatic ring of compound 93 in the direction shown in Figure 4.2.1, generating the unfavoured $S$-isomer. In representation B, the benzaldehyde substrates lies below compound 93, but is now possibly approaching from behind the bridged nitrogen ring of surfactant 93 as shown. Attack from below the plane will in this case generate the favourable $R$-isomer of 1-phenyl propanol (116).

Attempts to improve the selectivity of 93 by varying the reaction temperature were unsuccessful and the optimal conditions were obtained at room temperature together with a low selectivity of 13% e.e.
In order to highlight the importance of the nitrogen complexation when using the cinchonine derived surfactants in the diethyl zinc addition of benzaldehyde, a range of mono and di-cationic cinchonine surfactants were tested. The results are summarised in Table 4.2.3. The di-cationic surfactants 95 and 97 where both surfactant nitrogen centres were blocked led to slightly lower yields than their mono-cationic counterparts 94 and 96, where one of the nitrogen centres is available for co-ordination with diethyl zinc. However, despite blocking both nitrogen centres in compounds 95 and 97, reasonably high yields of product 116 were still produced. This suggests that the reaction intermediate involves coordination of the reacting substrates and the oxygen moiety of the surfactant or alternatively dequaternisation of the cinchonine surfactants may occur in situ. Using hindered benzylic quaternary salts resulted in lower reaction yields than the methylated salts. In both cases no reaction selectivity was obtained. These data suggest that coordination onto the oxygen moiety of these cinchonine surfactants may be responsible catalytically, to help generate the reaction yield. Coordination onto the nitrogen moiety may be responsible for enantiomeric control. One explanation for the low selectivity values obtained using these compounds could be their high rigidity, not allowing them to form reverse micellar complexes.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time/temp (hr/°C)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>48/25</td>
<td>75</td>
<td>2 (R)</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>48/25</td>
<td>82</td>
<td>3 (R)</td>
</tr>
<tr>
<td>3</td>
<td>97</td>
<td>48/25</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>48/25</td>
<td>58</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.2.3**

The diethyl zinc addition of benzaldehyde was tested with our synthesised polymers 114 and 115, in the hope that its large surface area and head group rigidity could give us high selectivities. Unfortunately, no yield of 116 was obtained (Table 4.2.4). Surfactant 99 whose attempted polymer synthesis was unsuccessful, was also tested. The secondary alcohol 116 was produced in only 18% and no selectivity was observed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Time/Temp (hr/°C)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hexane</td>
<td>115</td>
<td>48/25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Hexane</td>
<td>114</td>
<td>48/25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Hexane</td>
<td>99</td>
<td>48/25</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.2.4**

### 4.3 Diethyl zinc addition to Other aromatic aldehydes.

The tyrosine derived lipophilic salt 70, and the cinchonine derived surfactants 92, 93 and 94 were used in diethyl zinc additions with a range of aldehydes. 4-n-Hexyloxy benzaldehyde was initially synthesised since previous studies indicated that highest enantioselectivities were observed with 26, (entry 3 Table 4.3.1).^4,150^
4-Hydroxy benzaldehyde was deprotonated using sodium hydride in DMF. Addition of bromohexane and heating the reaction at 80 °C for 3 hours generated 4-n-hexyloxy benzaldehyde (118) in 22% yield (Scheme 4.3.1). This aldehyde was then reacted with diethyl zinc using our selected surfactants as catalysts and their results are shown in Table 4.3.1. Lower reaction yields were obtained using both surfactants 70 and 94 compared to when benzaldehyde was used. A variation in the reaction temperature also failed to improve the reaction yield. Since the best yields was obtained at room temperature, the cinchonine analogues 92 and 93 were used under these conditions and yields of up to 45% were achieved.
<table>
<thead>
<tr>
<th>Entry</th>
<th>surfactant</th>
<th>Time/ temp. (hr/°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>48/0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>48/25</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>6/70</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>48/0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>48/25</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>6/70</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>48/25</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>48/25</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>48/25</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 4.3.1 * denotes selectivity determined by chiral HPLC using a chiralcel OD column.

Attempts were made to determine the selectivity for the formation of 1-(4'-hexyloxyphenyl)-propanol (119) from these reactions. Chiral HPLC analysis indicated the presence of only one peak. Since it was uncertain whether there were two peaks superimposed on top of each other or just one genuine peak was present, the flow rate and retention times were varied. However only one peak was still observed. Previous use of this column to separate the isomers had been successful and it was thought that the chiral HPLC column (now 6 to 7 years old) had poorer resolution. The optical rotation of 119 (entry 1, table 4.3.1), using surfactant 70 at room temperature was found to be high ([α]$_{20}^c$ = -35.5 ° c 1.25, toluene), though 119 has not been reported in the literature. A Mosher’s ester of 119 was prepared to determine the enantiomeric composition of the alcohol (scheme 4.3.3) by reacting α-methoxy-α-trifluoromethyl phenyl acetyl chloride 119a with the alcohol 119. This coupling yielded the Mosher’s ester 120 in 48% yield (crude). δ$^{19}$F NMR analysis indicated that the ratio of the signals at -71.79 (corresponding to the R-isomer of 119) and -72.08 (corresponding to the S-isomer) were in a 1:1 ratio. It was deduced therefore that in this case 119 was
probably racemic. The configuration assigned to these signals are based on similar results obtained by Seebach et al. who has prepared a Mosher’s ester of 1-phenyl propanol (116).\textsuperscript{164}

![Scheme 4.3.3](image)

The use of catalysts 70 and 93 using 4-methoxy benzaldehyde in the diethyl zinc reaction resulted in a significantly higher yield for the formation of 1-(4-methoxyphenyl)-propan-1-ol (117) when using 70 (60%) compared to surfactant 93 (8%). The results are shown in Table 4.3.2. In both cases low selectivities were obtained where the use of 93 resulted in a small reversal in enantioselectivity compared to 70.

One possible explanation for the low enantioselectivities could be that when using compound 70, unfavourable charge stacking occurs between the methoxy based aromatic aldehydes and the phenolic ring of the tyrosine surfactant, since both aromatic rings are electron rich making the intermediate indicated in Figure 4.1.1 less favourable. When using compound 93, it is possible that the OMe moiety of the aldehyde competes with the O-moiety of the surfactant to coordinate with the diethyl zinc in the reaction. This may account for the lower yield and selectivity.

![Scheme 4.3.4](image)
This, in combination with the results obtained when using 4-n-hexyloxy benzaldehyde (118) suggested that the incorporation of an electron donating group to the aromatic ring of the aldehyde resulted in lower yields and selectivities and this was contrary to the results observed when using the norephedrine derived materials. In compound 70, the electron rich aromatic ring and the presence of electron rich aromatic aldehydes may reduce potential charge stacking in the complexes formed. In view of this the use of an aromatic aldehyde with a 4-chloro group was investigated, however no 1-(4-chlorophenyl)-propan-1-ol was formed in the reaction.

4.4 Diethyl zinc addition to Aliphatic aldehydes.

The use of aliphatic aldehydes for the diethylzinc reaction was also explored with the reaction between hexanal and diethyl zinc (Scheme 4.4.1). The results are summarised in Table 4.4.1. The reaction was performed using three of the more successful surfactants, 70 and cinchonine salts 93 and 94. However, it was observed that the reaction only proceeded at room temperature albeit at very low yield (up to 7%) and very poor selectivities were obtained (from the low optical rotation value).
The use of further aliphatic aldehydes was investigated, 2-hexynal (122). Since 122 was not commercially available, 2-hexyn 1-ol was oxidised to the corresponding aldehyde (Scheme 4.4.2). Initial attempts involved the use of Fetizon’s reagent in toluene (silver carbonate in Celite). The reaction was heated at reflux for 18 hours. Unfortunately none of the desired aldehyde was obtained and instead an inseparable mixture of compounds were observed. The use of PCC in dichloromethane 0 °C also generated none of the aldehyde. The use of a procedure reported by Bandgar et al., using NaN₂-acetic anhydride under mild, solvent free conditions was explored but was again unsuccessful. Fortunately the use of manganese dioxide which is frequently used for the oxidation of benzylic and allylic alcohols successfully generated the aldehyde (122) in 93% yield.

Table 4.4.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time/ temp (hr / °C)</th>
<th>Yield (%)</th>
<th>[α]₂⁰° # c 1.50, CHCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>48 / 0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>48 / 25</td>
<td>6</td>
<td>+0.60°</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
<td>48 / 20</td>
<td>7</td>
<td>+0.67°</td>
</tr>
</tbody>
</table>

# (R)-3-Nonanol, [M]D⁰ = -11.6 (neat). * [M]D⁰ = a.M / I.c where α is the observed rotation, M is the molar mass in g mol⁻¹, I is the sample path length in decimeters and c is the concentration in grams per cm³.

Scheme 4.4.2
Compound 122 was subsequently reacted with diethyl zinc at 0 °C, 25 °C, and 70 °C using surfactants 70 and 93. Unfortunately only starting material was isolated.

To conclude two catalysts derived from tyrosine and cinchonine were found to give the best results for the diethyl zinc reactions. High yields and good selectivities were obtained using the aliphatic chained tyrosine surfactants in the reaction between benzaldehyde and diethyl zinc. This was in comparison to the results obtained using the surfactants containing the benzyloxy chains, since good yields but low reaction enantioselectivities were observed. It can therefore be assumed that diethyl zinc coordination with the phenolic OH is responsible for reaction selectivity and that diethyl zinc coordination between the nitrogen and OH moiety of the β-amino alcohol may be responsible for affecting the reaction yield.

When using the cinchonine derived surfactants, in general good yields but poor selectivities were obtained. These data suggest that coordination of diethyl zinc onto the oxygen moiety as indicated below may be responsible catalytically, to help generate the reaction yield. Coordination onto the nitrogen moiety may be responsible for enantiomeric control. Low selectivity values could be accounted for by the high rigidity of the cinchonine compounds, not allowing them to form reverse micellar complexes.

Low yields were obtained when using aliphatic aldehydes. When testing the O-ether based aromatic aldehydes with diethyl zinc, moderate yields but low selectivities were achieved. One possible explanation for the low enantioselectivities when using the tyrosine based compounds, is that unfavourable charge stacking occurs between the OMe based aromatic aldehydes and the phenolic ring of the tyrosine surfactant, since both aromatic rings are electron rich making the intermediate indicated in Figure 4.1.1 less favourable. When using the cinchonine compounds, the OMe moiety of the aldehyde possibly competes with the O-moiety of the surfactant to coordinate with the diethyl zinc in the reaction.
Important for enantioselectivity. Coordination important catalytically.

Important for enantiomeric control.
Chapter 5    Michael reactions.

5.1     Diethyl Malonate addition to Cyclopentenone.

Our research in this area was carried out primarily using water as a reaction solvent with the aim of investigating the efficacy of such reactions and monitoring the influence of micellar catalysis. As mentioned in Section 1.3, limited work on the use of water as a solvent for Michael-type reactions has been reported. Those that have been reported such as the reaction between nitromethane and buten-2-one (Scheme 1.3.9) have indicated a rate acceleration compared to similar reactions in organic media such as dichloromethane, toluene and tetrahydrofuran possibly due to hydrophobic effects where the reacting substrates aggregate in solution to reduce their hydrophobic interactions with water molecules.

Initial investigations within the group, focussed on the reaction between diethyl malonate and cyclopentenone where yields of up to 6% with very low selectivities of up to 5% e.e were achieved (Scheme 5.1.1). The reaction only proceeded using $N$-benzyl trimethylammonium hydroxide (Triton B) (123b), a mild base which was selected since its ampholitic nature should not significantly effect the micellar system and could be located in the Stern layer interacting with the reacting substrates. When Madden repeated the reaction using the norephedrine derived surfactant 26, 1% of 123 was generated with 5% e.e selective for the $S$-isomer (Table 5.1.1).
In view of this, we investigated the same reaction but using the salts 79 and 81 containing the benzyloxy chains. In each of these cases surfactant concentrations of 0.06 mM were used. The resulting product 123 was isolated via flash-chromatography and the product selectivity was monitored using chiral HPLC analysis (chiral cell OD column) and the results are summarised in Table 5.1.1.

All three tyrosine derived surfactant salts 70, 79 and 81 generated the product 123 in higher yields than the norephedrine derived compound 26 despite poor resulting selectivity. Yields of up to 15% were obtained (entry 3, Table 5.1.1).

In an attempt to increase the reaction yield of compound 123 using 70, its surfactant concentration was increased to 0.45 mM (5 mg) and 1.67 mM (20 mg). Increasing the amount of 70 to 0.45 mM, showed no improvement in reaction yield but showed some reaction selectivity for the S-isomer. Dramatically increasing the surfactant concentration to 1.67 mM, resulted in a drop in both yield and selectivity. This can be attributed to a different aggregate formation well above the CMC.\textsuperscript{12,18,19} The use of no surfactant in the presence of 2 mol\% Triton B produced compound 123 in negligible yield (2%), once again underlining the importance of compound 70 as catalyst. This result was also observed by Madden who used only 1\% base and half the reaction time.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction (time)/hr</th>
<th>medium</th>
<th>Base (mM)</th>
<th>Conc. (mM)</th>
<th>Surfactant mass (mg)</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>26</td>
<td>Triton B (2 mol%)</td>
<td>0.06</td>
<td>0.672</td>
<td>1</td>
<td>5 (S)</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>70</td>
<td>Triton B (2 mol%)</td>
<td>0.06</td>
<td>0.672</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>70</td>
<td>Triton B (2 mol%)</td>
<td>0.45</td>
<td>5</td>
<td>15</td>
<td>8 (S)</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>70</td>
<td>Triton B (2 mol%)</td>
<td>1.67</td>
<td>20</td>
<td>6</td>
<td>4 (S)</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>79</td>
<td>Triton B (2 mol%)</td>
<td>0.06</td>
<td>0.672</td>
<td>11</td>
<td>2 (S)</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>81</td>
<td>Triton B (2 mol%)</td>
<td>0.06</td>
<td>0.672</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>H₂O</td>
<td>Triton B (2 mol%)</td>
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<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>H₂O</td>
<td>Triton B (1 mol%)</td>
<td>0</td>
<td>0</td>
<td>&lt;1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 5.1.1

*Enantiomeric excess was determined using chiral cell OD column, 220 nm detection wavelength, 5% iso-propanol, flow rate 0.5 ml/min. 20.9 min (R), 22.3 min (S). Results obtained by J. Madden.*

Several other surfactants were employed in the Michael addition reaction between diethyl malonate and cyclopentenone using a concentration of 0.45 mM of surfactant and 2 mol% Triton B. The results are summarised in Table 5.1.2.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time /temp. (hr /°C)</th>
<th>Triton B % base</th>
<th>Yield (%)</th>
<th>E.e^* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>15</td>
<td>8 (S)</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>6</td>
<td>2 (S)</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>10</td>
<td>4 (S)</td>
</tr>
<tr>
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<td>89</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>5</td>
<td>6 (S)</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>4</td>
<td>2 (S)</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>4</td>
<td>10 (S)</td>
</tr>
<tr>
<td>7</td>
<td>87</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>7</td>
<td>5 (R)</td>
</tr>
<tr>
<td>8</td>
<td>88</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>9</td>
<td>6 (R)</td>
</tr>
<tr>
<td>9</td>
<td>95</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>34</td>
<td>11 (S)</td>
</tr>
<tr>
<td>10</td>
<td>91</td>
<td>48 /100</td>
<td>2 mol %</td>
<td>22</td>
<td>8 (S)</td>
</tr>
</tbody>
</table>

Table 5.1.2

^Enantiomeric excess was determined using chiral cell OD column, 220 nm detection wavelength, 5% iso-propanol, flow rate 0.5 ml/min. 20.9 min (R), 22.3 min (S).

Compound 70 was used to generate compound 123 in a higher yield and enantioselectivity compared to when using the free amine 69 or the quaternised salt 73. Interestingly, this was also the case in the reverse micellar applications.

A postulated reaction intermediate for the formation of 123 using surfactant 70 is shown in Figure 5.1.1. The cyclopentenone is probably orientated below the surfactant plane in a manner indicated in representations A and B and is held in position via hydrogen bonding as shown. The diethyl malonate is deprotonated using Triton B and is subsequently attracted towards the cationic surfactant head group in the Stern layer by charged attraction. In representation A, the top face of cyclopentenone is blocked by the surfactant. Attack by the Michael acceptor occurs from below the plane resulting in the formation of the S-isomer. However since the cyclopentenone molecule is small and mobile, its subsequent rotation 180° as shown in representation B would just as easily generate the R-isomer providing minimum steric hindrance. This observation can be reflected by the low selectivity observed in this reaction.
The importance of the phenolic OH in compound 70 to help coordinate with cyclopentenone, can be realised from the results obtained using compound 81 where the phenolic OH is blocked by the large benzyloxy moiety. This reduces the H-bonding sites required to coordinate with cyclopentenone, hence the possible reason for the poor yields (9%) and no selectivity obtained when using 81.

![Diagram](image)

**Figure 5.1.1**

The piperidine compounds 84, 85, 87 and 89 generated compound 123 in both relatively low yields and selectivities although compound 85 gave one of the better selectivities (10% e.e.) (Table 5.1.2). Surfactant 91 derived from S-proline produced 123 in a higher yield of 22% and an 8% selectivity for the S-isomer.
The use of the cinchonine derived compound 95, although being relatively hindered gave the best reaction yield (34%) and enantioselectivity (11% e.e. for the S-isomer).

It was envisaged that varying the amount of Triton B could increase the yield and may effect the enantioselectivity of the reaction. The results of these studies are shown in Table 5.1.3. An increase in the amount of base to 10 mol% led to an increase in the selectivity but a drop in the yield. Increasing the amount of Triton B up to 20 mol% resulted in increased yields, however above 20 mol%, a reduction in the yield and selectivity of 123 was seen due to the increasing formation of polymerised products. The highest yield was seen at 20 mol% but no selectivity was observed.

When adding lithium chloride (4.86 mM), a salting-out agent to the reaction, a further increase in yield for the formation of 123 was obtained. This could be due to the increased concentration of chloride counterions, which causes micellar shrinkage resulting in an increase in internal pressure forcing the reactants together and giving enhanced yields.¹⁶

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time / temp.</th>
<th>Triton B</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(hr / °C)</td>
<td>(mol. % base)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No surfactant</td>
<td>48 / 100</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>48 / 100</td>
<td>2</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>48 / 100</td>
<td>2 + LiCl</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4.86 mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>48 / 100</td>
<td>10</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>48 / 100</td>
<td>20</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>48 / 100</td>
<td>20 + LiCl</td>
<td>69</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4.86 mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>48 / 100</td>
<td>30</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>48 / 100</td>
<td>40</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>48 / 100</td>
<td>50</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>48 / 100</td>
<td>100</td>
<td>Polymerisation of product</td>
<td>Polymerisation of product</td>
</tr>
</tbody>
</table>

Table 5.1.3
Alternative bases were also used in the Michael addition reaction using the salt 70 as a catalyst. Both the use of sodium hydrogencarbonate and potassium carbonate produced 3-[bis(ethoxycarbonyl)methyl] cyclopentanone (123) in low yields. The higher yields when using Triton B could be partly attributed to its positioning together with diethyl malonate in the Stern layer.

The amount of Triton B used was also increased in the cyclopentenone-diethyl malonate reaction when using compound 95. The results are shown in Table 5.1.4 and followed a similar trend to that found when using compound 70 (Table 5.1.3), where high yields and low selectivity were observed when using 20 mol% Triton B and a reduction in reaction yield but selectivity increase when reducing the amount of Triton B to 10 mol%.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Time / temp. hr / °C</th>
<th>Base</th>
<th>Yield</th>
<th>E.e (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>48 / 100</td>
<td>NaHCO₃ 20 mol %</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>48 / 100</td>
<td>K₂CO₃ 20 mol %</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>48 / 100</td>
<td>Triton B 20 mol %</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
<td>48 / 100</td>
<td>Triton B 2 mol %</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>48 / 100</td>
<td>Triton B 10 mol %</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>95</td>
<td>48 / 100</td>
<td>Triton B 20 mol %</td>
<td>71</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 5.1.4

Since compound 95 led to the best selectivity for the reaction (Scheme 5.1.1) using lower amounts of Triton B, attempts to obtain the optimum yield and selectivity using this catalyst was performed. This was investigated by varying the temperature and quantity of surfactant present. The diethyl malonate-
cyclopentenone Michael reaction was found to be temperature dependent. Lowering the reaction temperature to 50 °C reduced both the yield and selectivity. Performing the reaction at room temperature resulted in no reaction taking place. When using an increased amount of 95 from 0.45 mM (5 mg) to 1.67 mM (20 mg), a drop in the reaction yield and selectivity was observed. This trend was similar to that observed when using compound 70. The best conditions to carry out these Michael reactions appeared to be to heat the reaction at reflux using 5 mg surfactant for 48 hours (Table 5.1.5).

The pH of the reaction was also monitored in each case. Over the course of the reaction the pH dropped from 9 to 7. Therefore the pH of 9 was maintained during the reaction by adding more Triton B intermittently. This resulted in a slight increase in reaction yield however no change in selectivity was observed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Malonate type</th>
<th>surfactant</th>
<th>Conc. (mM)</th>
<th>pH of R&lt;sup&gt;e&lt;/sup&gt; start-end</th>
<th>Temp. (°C)</th>
<th>Reaction time hr</th>
<th>Triton B (mol %)</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEM</td>
<td>95</td>
<td>0.45</td>
<td>9-7</td>
<td>20</td>
<td>18</td>
<td>10</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DEM</td>
<td>95</td>
<td>0.45</td>
<td>9-7</td>
<td>50</td>
<td>18</td>
<td>10</td>
<td>14</td>
<td>2(S)</td>
</tr>
<tr>
<td>3</td>
<td>DEM</td>
<td>95</td>
<td>0.45</td>
<td>9-7</td>
<td>70</td>
<td>48</td>
<td>10</td>
<td>18</td>
<td>4(S)</td>
</tr>
<tr>
<td>4</td>
<td>DEM</td>
<td>95</td>
<td>0.45</td>
<td>9-7</td>
<td>reflux</td>
<td>48</td>
<td>10</td>
<td>66</td>
<td>5(S)</td>
</tr>
<tr>
<td>5</td>
<td>DEM</td>
<td>95</td>
<td>0.45</td>
<td>reflux</td>
<td>reflux</td>
<td>48</td>
<td>10</td>
<td>75</td>
<td>5(S)</td>
</tr>
</tbody>
</table>

Table 5.1.5

The other cinchonine derived surfactants synthesised were also tested and the results are shown in Table 5.1.6. It was observed that out of the compounds tested (92 to 97), compound 93 produced compound 123 in the highest yield and selectivity. It is interesting to note that compound 93 produced the best results when 10 mol% Triton B was used. This is in comparison to when carrying out the reaction at 2 mol% Triton B where compound 95 gave the best yield and selectivity.
Attempts to increase the selectivity of entry 3 (Table 5.1.6) were investigated by lowering the amount of base to 2 mol% and adding lithium chloride (1.0 mM). Unfortunately, the use of LiCl had little effect (Table 5.1.7).

A postulated reaction intermediate is shown in Figure 5.1.2. The OH\(^-\) counterion from Triton B deprotonates the malonate which is subsequently drawn towards the cationic head group of the surfactant by electrostatic interaction. In representation A, cyclopentenone lies above the surfactant plane, enabling the malonate to attack from its \(\beta\)-face to give the preferential \(S\)-isomer. However like the postulation we envisaged when using 70 (Figure 5.1.1), since the cyclopentenone molecule is small and mobile, its subsequent rotation
180° would just as easily generate the $R$-isomer. Hence low enantiomeric excesses would be observed.

![Diagram](image)

**Figure 5.1.2**

Since the use of 70 which contained an aliphatic C-16 chain, gave us moderate yields and selectivities we decided to investigate the effects of varying the surfactant chain lengths. The results are shown in Table 5.1.8.

As expected, an increase in the yield and selectivity (albeit very low) was observed when increasing the chain lengths due to increased hydrophobic interactions between the alkyl chains producing a more stable micelle as the chain length is extended.
Attempts were made to synthesise a catalyst which also behaved as an internal base for the Michael reaction. Compound 74 was therefore synthesised and tested in the diethyl malonate reaction with cyclopentenone in the absence of any other base (Scheme 5.1.1). Since this compound had an OH\(^{-}\) counterion, it could behave as a base as well as a catalytic surfactant. The results are shown in Table 5.1.9. Using compound 74 produced 123 in a reasonable yield of 24% albeit with a low selectivity. Compounds 70 and 73 were used as controls and tested in the absence of base producing 123 in negligible yield. However, compound 73 surprisingly yielded some product. This was possibly due to the iodide ion deprotonating the malonate to enhance the Michael addition reaction. Hence we were able to successfully synthesise a catalytic base to drive the Michael reaction without using any other external bases.
The cyclopentenone-diethyl malonate Michael addition was tested with our synthesised polymers 114 and 115, in the hope that its large surface area and head group rigidity could give us high selectivities. Unfortunately, none of compound 123 was formed. Surfactant 99 whose attempted polymer synthesis was unsuccessful, was also tested. Compound 123 was produced in 4% with a small 2% selectivity for the S-isomer.

5.2 Dimethyl Malonate addition to 2-Pentyl-2-cyclopentan-1-one.

Having established the initial reaction parameters leading to good yields and with some enantioselectivity noted, we investigated the stereoselectivity of the reaction using a substituted cyclopentenone component to create a greater facial stereodifferentiation. 2-Pentyl-2-cyclopenten-1-one (125a) was used which is commercially available and conjugate additions lead to jasmonate precursors. In addition, during this work Perrard and co-workers reported the reaction using dimethyl malonate giving high e.e values up to 90% using cinchonidine, quinine and quinidine derived catalysts under solvent free conditions.

Scheme 5.2.1

Initial work (Scheme 5.2.1) made use of Triton B as base at 10 mol% in the presence of compound 70 and failed to produce any of the desired material 125. The amount of Triton B used was increased to 30, 50 and 100 mol% but unfortunately only starting material resulted. Other bases including potassium carbonate, sodium hydrogen carbonate, sodium hydroxide and potassium tert-
butoxide all failed to promote the reaction. The reactions were repeated using compounds 93 and 94 as catalysts but with no success.

A less bulky malonate was then used, dimethyl malonate. Compound 93 was also tested as the catalyst since it had produced better data for the cyclopentenone-diethyl malonate reactions (Scheme 5.1.1). The reaction was initially performed using 30 equivalents of dimethyl malonate and 1 equivalents of 125a since such molar ratios had been used in Perrard's work.\(^\text{147}\) The e.e values were determined by HPLC analysis and confirmed by optical rotation. The results are summarised in Table 5.2.1. Increasing the reaction temperature showed an increase in reaction yield to as high as 96%. The resulting product 125 was selective for the formation of the R-isomer giving e.e values of up to 27%.

![Scheme 5.2.2](image-url)
The reactions were then repeated using 1 equivalent of dimethyl malonate resulting in no change in the reaction yields or selectivities.

In an attempt to improve the yield and selectivity, the amount of surfactant used was varied and the results are summarised in Table 5.2.2. Using 100 mM of compound 93 generated compound 125 in 93% yield with a 30% e.e, selective to the $R$-isomer. The use of LiCl (salting out agent) led to a small enhancement in yield and selectivity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (10 mol %)</th>
<th>Temp/ time (°C/hr)</th>
<th>Catalyst Conc. (mM)</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃ (1)</td>
<td>20/48</td>
<td>93 (0.10)</td>
<td>LiCl 4.86 mM /H₂O</td>
<td>98</td>
<td>32 ($R$)</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃ (1)</td>
<td>20/48</td>
<td>93 (0.10)</td>
<td>H₂O</td>
<td>93</td>
<td>30 ($R$)</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃ (1)</td>
<td>20/48</td>
<td>93 (0.10)</td>
<td>H₂O</td>
<td>57</td>
<td>28 ($R$)</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃ (1)</td>
<td>20/48</td>
<td>93 (0.10)</td>
<td>H₂O</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5.2.2
The use of alternative bases were then investigated and the reaction was carried out at different reaction temperatures still using catalyst 93 (Scheme 5.2.2). When using Triton B at 10, 30, 50 and 100 mol%, surprisingly only starting material resulted. The use of other bases including sodium hydrogen carbonate (30 mol%), potassium carbonate, sodium hydroxide and potassium tert-butoxide (0 and 20 °C) also failed to promote the reaction.

Since K₂CO₃ seemed to be the only successful base in the promotion of the dimethyl malonate-pentyl enone reaction, the amount of base was varied to monitor its effect. The results are shown in Table 5.2.3. Increasing the amount of K₂CO₃ beyond 10 mol%, resulted in a drop in both reaction yield and selectivity. This can be attributed to the increased formation of several side products which were difficult to isolate via flash chromatography. The use of 10 mol% of K₂CO₃, led to the highest yield of Michael adduct with no traces of side products and the highest selectivity was observed (30% e.e). Increasing the reaction temperature above 20 °C, resulted in a large drop in reaction yield although the selectivity was maintained at 40 °C. This was attributed to the increased amount of polymerised products generated.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>mol %</th>
<th>Temp/time (°C/hr)</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>Ee (%) (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>5</td>
<td>20/48</td>
<td>H₂O</td>
<td>93</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃</td>
<td>10</td>
<td>20/48</td>
<td>H₂O</td>
<td>93</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>20</td>
<td>20/48</td>
<td>H₂O</td>
<td>93</td>
<td>82</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>30</td>
<td>20/48</td>
<td>H₂O</td>
<td>93</td>
<td>73</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>48</td>
<td>0</td>
<td>H₂O</td>
<td>93</td>
<td>90</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
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<td>20</td>
<td>H₂O</td>
<td>93</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃</td>
<td>48</td>
<td>40</td>
<td>H₂O</td>
<td>93</td>
<td>34</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 5.2.3

The reaction time for the dimethyl malonate-pentyl enone reaction (Scheme 5.2.2) was also monitored to assess how the yield and selectivity varies with time (Graph 5.2.1). A reaction time of 48 hours still lead the optimal yield and reaction selectivity with 93. Using these reaction conditions other selected
surfactants were tested on the dimethyl malonate-pentyl enone reaction (Scheme 5.2.1). The results are summarised in Table 5.2.4.

![Graph 5.2.1: Yield and selectivity effects with time using surfactant 93](image)

**Table 5.2.4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (10 mol %)</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>Ee (%) (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>20</td>
<td>48</td>
<td>H$_2$O</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>20</td>
<td>48</td>
<td>H$_2$O</td>
<td>93</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>20</td>
<td>48</td>
<td>H$_2$O</td>
<td>94</td>
<td>74</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$</td>
<td>20</td>
<td>48</td>
<td>H$_2$O</td>
<td>70</td>
<td>44</td>
<td>4</td>
</tr>
</tbody>
</table>

The use of both cinchonine derived surfactants 93 and 94 produced 125 in higher yields and selectivity than the tyrosine derived surfactant 70 although 94 was much less selective than 93.

A postulated reaction intermediate for the production of 125 using surfactant 93 is shown in Figure 5.2.1. In representation A, 2-pentyl-2-cyclopentenone sits on top of the surfactant plane in a manner shown, held in place by hydrogen bonding between the proton from the quaternised nitrogen in compound 93 and the carbonate base as indicated. This allows the dimethyl
malonate to attack it from the St-position. The aliphatic chain is positioned favourably in line with the surfactant alkyl chain producing the favoured R-isomer. In representation B, 180° rotation of 2-pentyl-2-cyclopentenone is shown such that its aliphatic chains are positioned away from the aliphatic chains of the surfactant producing the less favourable S-isomer.

![Diagram of malonate attack](image)

**Figure 5.2.1**

### 5.3 Variation in the type of malonate reactions used.

Other malonate substrates were also used in the cyclopentenone addition reaction using compounds 70 and 95 as catalysts and the results are summarised in Table 5.3.1. The cinchonine surfactant 95 generated products in generally better selectivities and yields compared to when using 70. A lower yield was obtained using dibenzyl malonate. This can be attributed to the hindered
structure of the malonate substrate in the reaction. Using the branched isopropyl malonate resulted in greater yields of product for both surfactants 70 and 95.

\[
\text{R} - \text{O} - \text{C} = \text{O} - \text{R} + \text{H}_2\text{O}, \text{Triton B reflux 48 hours.} \rightarrow \text{H}_2\text{O} \text{, Triton B reflux 48 hours.}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Malonate type</th>
<th>Surfactant</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅CH₂</td>
<td>70</td>
<td>Triton B (10 mol %)</td>
<td>H₂O</td>
<td>10</td>
<td>3 (S)</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅CH₂</td>
<td>95</td>
<td>Triton B (10 mol %)</td>
<td>H₂O</td>
<td>24</td>
<td>6 (S)</td>
</tr>
<tr>
<td>3</td>
<td>(CH₃)₂CH</td>
<td>70</td>
<td>Triton B (10 mol %)</td>
<td>H₂O</td>
<td>42</td>
<td>2 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₂CH</td>
<td>95</td>
<td>Triton B (10 mol %)</td>
<td>H₂O</td>
<td>60</td>
<td>1 (S)</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td>70</td>
<td>Triton B (10 mol %)</td>
<td>H₂O</td>
<td>23</td>
<td>5 (S)</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>95</td>
<td>Triton B (10 mol %)</td>
<td>H₂O</td>
<td>47</td>
<td>4 (S)</td>
</tr>
</tbody>
</table>

Table 5.3.1

It is interesting to note that a reversal of selectivity was observed in the reaction between cyclopentenone and the dialkyl malonates where the S-isomer was preferred albeit in low selectivities compared to when using 2-pentyl-2-cyclopentenone where the R-isomer was preferentially formed.

Since higher yields and selectivities were obtained using K₂CO₃ base in the reaction between 2-pentyl-2-cyclopentenone and dimethyl malonate, it can be envisaged that using K₂CO₃ instead of Triton B for the cyclopentenone-dimethyl malonate reactions in entries 5 and 6 (Table 5.3.1), may increase both their reaction yields and selectivities, although the use of K₂CO₃ was not found to be as successful a base as Triton B when reacting diethyl malonate with cyclopentenone. It can be concluded that Triton B works well as a base when reacting cyclopenten-2-one with the alkyl malonate substrates but not when reacting 2-pentyl-2-cyclopentenone where K₂CO₃ seems to be the preferred base.
5.4 Phase-transfer work.

5.4.1 Diethyl malonate reaction with cyclopentenone using phase-transfer catalysts.

Many asymmetric reactions have been carried out in bi-phasic systems leading to enantioselective reactions. With this in mind, surfactants 70 and 95 were used as catalysts in biphasic media comprising of toluene/water. Since surfactants are amphiphilic, they are likely to sit at the interface, where the reaction is likely to occur. The results obtained are shown in Table 5.4.1. It was observed with both surfactants 70 and 95 that increasing the amount of toluene in the reaction improved the yield considerably. However the use of bi-phasic systems resulted in lower selectivities. Surfactant 74 was tested in the cyclopentenone-diethyl malonate phase-transfer reaction, which can act as both a catalyst and base. It was observed that the toluene/water mix produced a better yield than when using just pure water. However no change in selectivity was observed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Malonate type</th>
<th>Surfactant</th>
<th>Base Triton B (mol %)</th>
<th>Solvent Toluene : H₂O</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEM</td>
<td>70</td>
<td>10 mol %</td>
<td>50 : 50</td>
<td>71</td>
<td>4 (S)</td>
</tr>
<tr>
<td>2</td>
<td>DEM</td>
<td>70</td>
<td>10 mol %</td>
<td>95 : 5</td>
<td>88</td>
<td>2 (S)</td>
</tr>
<tr>
<td>3</td>
<td>DEM</td>
<td>70</td>
<td>10 mol %</td>
<td>99 : 1</td>
<td>95</td>
<td>3 (S)</td>
</tr>
<tr>
<td></td>
<td>DEM</td>
<td>95</td>
<td>10 mol %</td>
<td>50 : 50</td>
<td>88</td>
<td>6 (S)</td>
</tr>
<tr>
<td>5</td>
<td>DEM</td>
<td>95</td>
<td>10 mol %</td>
<td>99 : 1</td>
<td>97</td>
<td>2 (S)</td>
</tr>
<tr>
<td>6</td>
<td>DEM</td>
<td>74</td>
<td>-</td>
<td>0 : 100</td>
<td>24</td>
<td>3 (S)</td>
</tr>
<tr>
<td>7</td>
<td>DEM</td>
<td>74</td>
<td>-</td>
<td>99 : 1</td>
<td>38</td>
<td>3 (S)</td>
</tr>
</tbody>
</table>

Table 5.4.1

Recent work using phase-transfer methods have involved using NaOH/toluene solvent and cinchonine derived catalysts. With this in mind, this
solvent mixture was used in the above diethyl malonate reaction using compound 93 as the catalyst. The results are shown in Table 5.4.2. A few drops of Triton B was added to the reaction mixture in an attempt to enhance the product selectivity. This was marginally achieved, however an increase in yield was obtained.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Malonate type</th>
<th>Surfactant</th>
<th>Base</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEM</td>
<td>93</td>
<td>1:2</td>
<td>71</td>
<td>6 (S)</td>
</tr>
<tr>
<td>2</td>
<td>DEM</td>
<td>93</td>
<td>1:2 and 2 drops 2 mol % triton B</td>
<td>94</td>
<td>8 (S)</td>
</tr>
</tbody>
</table>

Table 5.4.2

5.4.2 *Dimethyl malonate reaction with 2-Pentyl-2-cyclopentenone using phase-transfer catalysts.*

Compound 93 was used as a catalyst in two bi-phasic systems for the dimethyl malonate-pentyl enone reaction (Scheme 5.2.2 and Table 5.4.3). Although high yields were observed, a drop in the enantioselectivities was observed.

| Entry | Solvent | Base | Temp | Time (hr) | Catalyst | Yield (%) | Ee (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH 50 % sol. / toluene</td>
<td>-</td>
<td>20 °C</td>
<td>48</td>
<td>93</td>
<td>85</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>Toluene / H₂O (50:50)</td>
<td>K₂CO₃ 10 mol %</td>
<td>20 °C</td>
<td>48</td>
<td>93</td>
<td>94</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 5.4.3
5.4.3 Methyl vinyl ketone reaction with 2-phenyl cyclohexanone using phase-transfer catalysts.

In order to investigate the properties of our surfactants 70, 93, 94, 95, 96 and 97 as phase transfer catalysts, these compounds were used in a phase-transfer Michael reaction involving alternative reaction substrates. Diez-Barra et al have reported the reaction between 2-phenyl cyclohexanone and methyl vinyl ketone with cinchonine derived catalysts with enantiomeric excesses of up to 46% (monitored using optical rotation). Using similar reaction conditions described in the literature (aq NaOH and toluene), the reactions were performed with our surfactants as shown in Table 5.4.4, despite reasonable yields and low selectivities were observed. Interestingly, the reaction in NaOH solution alone generated the product 128 in slightly lower yields than when using a sodium hydroxide solution/toluene mix and in the absence of additional water (entry 8, Table 5.4.4).
Preliminary research on the use of ultrasound for the Michael reactions was investigated, since the use of ultrasound has been known to accelerate water-based reactions.\textsuperscript{119, 120} This method was tested on both the cyclopentenone-
diethyl malonate reactions (Scheme 5.1.1) as well as the dimethyl malonate-pentyl cyclopentenone reaction (Scheme 5.2.2) using in both cases surfactant 93 as catalyst. The results are shown in Table 5.5.1. A rise in the reaction yield was observed when using ultrasound. However, a drop in the reaction selectivity was obtained most likely due to breakdown of the reaction aggregate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp./Time</th>
<th>Condit.</th>
<th>Malon.</th>
<th>Enone</th>
<th>Product</th>
<th>Base</th>
<th>Yield (%)</th>
<th>Ee(%) (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>20/48</td>
<td>DEM</td>
<td>150</td>
<td>151</td>
<td>Triton B</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>20/48</td>
<td>Ultras.</td>
<td>DEM</td>
<td>150</td>
<td>151</td>
<td>Triton B</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
<td>20/48</td>
<td>-</td>
<td>DMM</td>
<td>155</td>
<td>157</td>
<td>K₂CO₃</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>20/48</td>
<td>Ultras.</td>
<td>DMM</td>
<td>155</td>
<td>157</td>
<td>K₂CO₃</td>
<td>98</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 5.5.1

To conclude, improved yields and low selectivity were observed between the dialkyl malonates and cyclopentenone selective to the S'-isomer. Introducing an aliphatic 5-carbon chain onto cyclopentenone improved the reaction yields and selectivities to above 30% e.e. However a reversal in selectivity was obtained. Using our surfactants particularly the cinchonine analogues as phase-transfer catalysts resulted in increased reaction yields but poor selectivities.
Chapter 6  Baylis-Hillman reactions.

As was mentioned in section 1.3.3, the Baylis-Hillman reaction has been reported in water. Those that have been reported have shown enhanced rate acceleration. Since DABCO (49) and DBU (50) have been successfully used, our initial investigations were carried out using these catalysts. Using benzaldehyde and methyl acrylate to produce 129, (Scheme 6.1) different concentrations of DABCO and DBU were used. The use of a range of solvents were explored and the results are summarised in Table 6.1. As observed by Aggarwal and Mereu et al, the use of DBU enhanced the production of 129 further compared to DABCO and the use of both water and THF resulted in similar product yields (Scheme 6.1).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Temp. (°C)</th>
<th>Catalyst</th>
<th>Equivalents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>48</td>
<td>25</td>
<td>50 (DBU)</td>
<td>0.2</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>48</td>
<td>25</td>
<td>50 (DBU)</td>
<td>0.2</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>72</td>
<td>25</td>
<td>49 (DABCO)</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>49 (DABCO)</td>
<td>0.2</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>72</td>
<td>25</td>
<td>49 (DABCO)</td>
<td>0.2</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 6.1

Previous reports on the use of cinchonine derived catalysts in Baylis-Hillman reactions have shown little success. However recent work by Hatakeyama and co-workers demonstrated that 1,1,1,3,3,3-hexafluoropropyl acrylate, reacting with a variety of aldehydes in the presence of a modified Cinchona base gave Baylis-Hillman products with yields as high as 58% and selectivities as high as 97% for the R-isomer (section 1.3.3). In view of this, we decided to utilise a mixture of DBU and our synthesised cinchonine surfactant (92) as amine catalysts in the benzaldehyde/methyl acrylate reaction. Different ratios of DBU:compound 92 were investigated (Table 6.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>Temp. (°C)</th>
<th>DBU:Cat. 92</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>48</td>
<td>25</td>
<td>25:75</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>48</td>
<td>25</td>
<td>50:50</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>48</td>
<td>25</td>
<td>75:25</td>
<td>78</td>
</tr>
</tbody>
</table>

*0.2 equivalents of catalytic mixture was used with respect to starting substrates.

Table 6.2

Upon increasing the relative quantity of 92, a decrease in reaction yield and negligible enantioselectivities were observed. In order to verify the effect of the
amine 92, the benzaldehyde/methyl acrylate reaction was repeated using 92 alone. In each case catalytic concentrations well above the CMC (when using water as solvent) and RCMC (when using THF as solvent) were used. The reaction was also carried out with another cinchonine derived surfactant 93 containing the HCl salt in order to make a direct comparison with the free amine 92 (Table 6.3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>Temp. (°C)</th>
<th>Catalyst</th>
<th>Conc. (mM)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>72</td>
<td>25</td>
<td>92</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>72</td>
<td>25</td>
<td>92</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>72</td>
<td>25</td>
<td>93</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>92</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>93</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>93 + LiCl (4.86 mM)</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>93</td>
<td>60</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 6.3

Upon increasing the concentration of compounds 92 and 93 increased quantities of 129 were formed. Interestingly the HCl salt 93, produced 129 in higher reaction yields than when using the free amine 92. This suggested that in water protonation of the nitrogen centre of the catalyst had a positive effect on the Baylis-Hillman reaction. The use of the salting out agent (LiCl) was explored and a rise in reaction yield was observed, unfortunately with negligible effect on selectivity.

The pH of the benzaldehyde/methyl acrylate reaction using 93 was monitored. A slight decrease in pH from 7 to 6 was noted throughout. In order to investigate the effect of pH on the reaction, it was further repeated at different pHs and the results are summarised in Table 6.4. Increasing the acidity of the solution (with HCl) led to further increases in yield. This can be explained by
considering the mechanism as shown in Figure 6.1 where increasing the reaction pH, helps to protonate the acrylate substrate. This can drive step 1 which in turn favours the formation of 129. The use of a 0 °C reaction led to a slight change in yield, but a very slight increase in reaction selectivity. Interestingly no reports have carried out Baylis-Hillman reactions under acidified conditions.

![Figure 6.1](image)

**Figure 6.1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Temp. (°C)</th>
<th>Catalyst</th>
<th>pH</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>93</td>
<td>6</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>93</td>
<td>3</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>72</td>
<td>25</td>
<td>93</td>
<td>1</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>72</td>
<td>0</td>
<td>93</td>
<td>6</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>72</td>
<td>0</td>
<td>93</td>
<td>1</td>
<td>47</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 6.4**

In the orientation indicated in representations A and B (Figure 6.2), the benzaldehyde is aligned below the surfactant plane 93. Lowering the pH of the reaction, protonates the acrylate which helps enhance the Baylis-Hillman reaction. The Re face of the benzaldehyde is attacked since the top face is
blocked by the surfactant moieties. The low selectivity may be due to poor stereo facial differentiation of the methyl acrylate as indicated in Figure 6.2.

![Representation A and Representation B]

**Figure 6.2.**

The reaction was also monitored over 120 hours, however after 72 hours no further increase in reaction yield were observed. The benzaldehyde/methyl acrylate reaction was then explored using a range of the quaternised cinchonine surfactants to investigate the importance of the available nitrogen centre in enhancing these reactions (Table 6.5). Quaternisation of the nitrogen centre on the bridged ring (94), resulted in a drop in reaction yield. A 15% yield was still obtained suggesting that in this case the nitrogen moiety in the aromatic ring of 94 may have coordinated with methyl acrylate in a similar way and adopted a similar mechanism indicated in Figures 6.1 and 6.2. The blocking of both nitrogen centres as shown with 95, resulted in no reaction taking place.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hrs)</th>
<th>Temp. (°C)</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>0</td>
<td>93</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>0</td>
<td>94</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>0</td>
<td>95</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6.5

The use of the tyrosine derived surfactant 69 and 70 led to the formation of 129 in only low yields (up to 8%) and with negligible selectivity. Repeating these reactions at 0 °C using the HCl salt 70 resulted in no change in yields.

The use of trimethylamine in the benzaldehyde/methyl acrylate Baylis-Hillman reaction has been previously investigated by Besavaiah et al, giving poor yields. We decided to repeat this reaction in water at acidic pH. With triethylamine, unfortunately no reaction was observed. However with trimethylamine as base, yields up to 6% were obtained.

The reaction between 2-nitrobenzaldehyde and methyl acrylate (Scheme 6.2), using a range of different catalysts were also investigated since with this more electron deficient aldehyde a more significant effect by other reaction parameters was envisaged. The results are shown in Table 6.6 and again no adduct was obtained when using triethylamine. However high yields were observed when using trimethylamine and DBU (50). The use of compound 93 gave the best yield of 54% which was similar to the benzaldehyde/methyl acrylate system (47% yield). No reaction selectivity was observed. The use of the tyrosine derived material 70, resulted in no product formation.

Scheme 6.2
The benzaldehyde/2-nitro benzaldehyde reactions with methyl acrylate were also carried out with our synthesised polymers 114 and 115 (Table 6.7). The reaction was initially carried out at 25 °C but no products were observed. When repeating the reactions at 0 °C, only low yields of up to 7% were observed. Surfactant 99 whose attempted polymer synthesis was unsuccessful, gave yields as high as 9%. When using these catalysts with the 2-nitrobenzaldehyde/methyl acrylate system, increased yields of up to 21% (compound 99) were observed.

![Scheme 6.3](image)

Table 6.6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Me₃N</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>DBU (50)</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hr)</th>
<th>Temp. (°C)</th>
<th>Catalyst</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>0</td>
<td>114</td>
<td>Ph</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>0</td>
<td>115</td>
<td>Ph</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>0</td>
<td>99</td>
<td>Ph</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>0</td>
<td>114</td>
<td>2-NO₂-C₆H₄</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>0</td>
<td>115</td>
<td>2-NO₂-C₆H₄</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>0</td>
<td>99</td>
<td>2-NO₂-C₆H₄</td>
<td>21</td>
</tr>
</tbody>
</table>
Other Baylis-Hillman reactions were investigated using alternative aldehydes (Table 6.8). The addition of electron donating substituents such as \( p \)-methoxy and \( p \)-hexyloxy benzaldehyde onto the aromatic ring of the aldehyde resulted in very low or negligible reaction yield presumably due to the more electron rich aldehyde moieties. The reaction between propanal and methyl acrylate was unsuccessful.

\[
\begin{align*}
\text{Scheme 6.4}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hr)</th>
<th>Temp. (°C)</th>
<th>R \text{ or } R'</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>0</td>
<td>Ph</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>0</td>
<td>( 2\text{-NO}_2\text{-C}_6\text{H}_4 )</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>0</td>
<td>( \text{CH}_3\text{O-C}_6\text{H}_4 )</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>25</td>
<td>( \text{CH}_3\text{O-C}_6\text{H}_4 )</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>25</td>
<td>( \text{CH}_3\text{O-C}_6\text{H}_4 )</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>0</td>
<td>( \text{CH}_3\text{CH}_2 )</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>0</td>
<td>( \text{CH}_3(\text{CH}_2)_5\text{O-C}_6\text{H}_4 )</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>25</td>
<td>( \text{CH}_3(\text{CH}_2)_5\text{O-C}_6\text{H}_4 )</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>120</td>
<td>0</td>
<td>( \text{CH}_3(\text{CH}_2)_5\text{O-C}_6\text{H}_4 )</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
<td>25</td>
<td>( \text{CH}_3(\text{CH}_2)_5\text{O-C}_6\text{H}_4 )</td>
<td>0</td>
</tr>
</tbody>
</table>

Since all the Baylis-Hillman reactions carried out up to this point failed to provide any reaction selectivity, preliminary attempts to enhance selectivity focussed on using a longer chained acrylate (pentyl acrylate) with benzaldehyde (Scheme 6.5) to enhance preorientation effects. The results are summarised in Table 6.9. Lower yields were observed compared to when methyl acrylate was used. Yields up to 34% were obtained when adding a salting out agent (LiCl,
4.86 mM) to the reaction and again the reaction was very temperature specific. The best yield was acquired when reacting 2-nitrobenzaldehyde with pentyl acrylate which resulted in a maximum yield of 36% but with no selectivity.

![Scheme 6.5](image)

**Scheme 6.5**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hrs)</th>
<th>Temp. (°C)</th>
<th>pH</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>25</td>
<td>1</td>
<td>49</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>25</td>
<td>1</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>25</td>
<td>6</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>25</td>
<td>1</td>
<td>Me₃N</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>25</td>
<td>1</td>
<td>93</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>25</td>
<td>6</td>
<td>93</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>25</td>
<td>1</td>
<td>93 + LiCl (4.86 mM)</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>40</td>
<td>1</td>
<td>93</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 6.9.**

The use of an alternative alkene, acrylonitrile and a range of aldehydes were also explored (Scheme 6.6, Table 6.10). Unlike when using the acrylates, Baylis-Hillman reactions involving acrylonitrile failed to work at 0 °C. Increasing the reaction temperature to 25 °C gave reaction yields up to 19% when using the electron deficient 2-nitrobenzaldehyde. Conversely, when using electron donating substituents on the aromatic aldehyde such as p-methoxy benzaldehyde and p-hexyloxy benzaldehyde, lower yields were observed. This trend was similar to that when using the acrylates in the Baylis-Hillman reaction. Repeating all these reactions above 25 °C resulted in no product formation.
Attempts were made to react propanal and acrylonitrile, however despite varying the reaction temperature no yield was observed. In all these cases, no reaction selectivity was obtained.

\[
\begin{align*}
\text{Catalyst} & \quad \text{H}_2\text{O, pH 1} \\
\text{Compound 93} &
\end{align*}
\]

\[\text{Scheme 6.6}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hr)</th>
<th>Temp. (°C)</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>0</td>
<td>Ph</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>25</td>
<td>Ph</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>25</td>
<td>CH\textsubscript{3}CH\textsubscript{2}</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>25</td>
<td>CH\textsubscript{3}O-C\textsubscript{6}H\textsubscript{4}</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>25</td>
<td>CH\textsubscript{3}(CH\textsubscript{2})\textsubscript{3}O-C\textsubscript{6}H\textsubscript{4}</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>25</td>
<td>2-NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 6.10.

To conclude, we have successfully shown that when using our surfactants (especially with compound 93) Baylis-Hillman reactions could proceed well in water. Using the electron withdrawing aldehyde, 2-nitro benzaldehyde with methyl acrylate resulted in the highest generated yield (54%) compared to when using electron donating aromatic aldehydes. Performing the reaction in acidified water was found to clearly enhance the Baylis-Hillman reaction. However, in all these reactions, low enantioselectivities were observed.
Summary

In summary, we have successfully synthesised and characterised a range of cationic and non-ionic surfactants derived from different starting materials, S-tyrosine, L-proline, oxazolo pyridinone, and the alkaloids hydroquinidine and cinchonine. These compounds were successfully employed as catalysts in a number of reactions in aqueous and organic media.

From our investigations and CMC/RCMC analysis, we showed micellisation to occur in both aqueous and organic media.

For the addition of diethyl zinc to a selection of aldehydes, compounds 70 and 72 derived from S-tyrosine incorporating the aliphatic chains, were the most successful. Compound 93 derived from cinchonine generated yields as high as 88% but with moderate selectivity (13% e.e). The use of compound 72 was found to be the most effective catalyst generating yields as high as 91% with an e.e of 69% selective for the R-isomer. Incorporating an electron donating group to the aromatic ring of the aldehyde resulted in lower yields and selectivities and this was contrary to the results observed when using the norephedrine derived material (26). The use of aliphatic aldehydes produced very low yields and poor selectivities when tested with compounds 70 and 93. From our results, clearly the head group size is important for reverse micellar formation. The synthesised alkaloids and the oxazolo pyridinone analogues have large head groups and did not seem to favour reverse micellar formation compared to the tyrosine analogues where better yields and selectivities were obtained. This can be confirmed from our CMC/RCMC analysis.

In aqueous media, the cinchonine derived surfactants particularly compounds 93 and 94 generally produced better yields in the Michael and Baylis-Hillman reactions than the surfactants derived from tyrosine.

For the Michael addition reaction between diethyl malonate and cyclopentenone, improved yields and low selectivities were observed. However the reaction selectivity was improved by the introduction of an aliphatic 5-carbon chain onto the cyclopentenone molecule to help effect the stereochemical outcome of these reactions. Enantiomeric excess of up to 30% were induced albeit with reversed selectivity.
Our synthesised cinchonine surfactants have proved to be particularly successful phase-transfer catalysts in a range of Michael type reactions enhancing yields. However, low enantioselectivities were observed.

Since limited work using Baylis-Hillman reactions in water has been published and the use of cinchonine derived catalysts have shown poor yields, it was surprising to find that our synthesised cinchonine surfactant generated better yields than the other surfactants tested in water. These yields were further enhanced under acidic conditions. Using activated electron withdrawing aldehydes in particular 2-nitro benzaldehyde reacting with methyl acrylate generated higher yields of 54% compared to using any of the electron donating aromatic aldehydes. Low enantioselectivities in all these reactions to date were achieved.

The possible synthesis of polymeric/dendrimeric surfactants resulted in low yields and selectivities being produced when tested on a number of reactions in aqueous and organic media.
Future work.

For the diethyl zinc/aromatic aldehyde reactions, a range of aliphatic dendrimeric surfactants derived from $S$-tyrosine should be synthesised to help enhance the reaction selectivity.

Since it was postulated that a reason for the low yield and selectivity of some of the surfactants synthesised for the diethyl zinc/aromatic aldehyde reaction may have been due to the poor solubility of these surfactants in hexane, dissolution of the relevant surfactants in deuterated hexane and $^1$H NMR studies may reveal whether a change of surfactant orientation is observed when changing the concentration and/or reaction temperature. We could also verify the solubility of these surfactants in hexane.

Further investigations on the Baylis-Hillman reaction and Michael addition reactions in aqueous media should be carried out, using other cinchonine solution based or solid support analogues to help enhance the reaction selectivity.

Since it was observed that the dynamic nature of aggregates provided problems in giving us reaction selectivity hence the use of fixed aggregates is required. So the synthesis of the dendrimeric polymers 114 and 115 need to be studied and tailored. Attempts must be made to polymerise compound 99 using a
stronger $\gamma$-radiation source than $^{137}\text{Cs}$ or alternative means such as using an initiator \textit{e.g.} azobisisobutyronitrile (AIBN). However, difficulties of using AIBN for the polymerisation of vinyl groups were reported, hence an alternative initiator may have to be used for example t-butyl $\alpha$-phenylperoxyacetate.\textsuperscript{169}

\[\text{AIBN} \quad \text{t-butyl $\alpha$-phenylperoxyacetate}\]
Summary of synthesised surfactants and catalysts tested in the diethyl zinc, Michael addition and Baylis-Hillman reactions.
7. Experimental

IR spectra were recorded on a Perkin Elmer Model 1600 series FTIR spectrometer. $^1$H and $^{13}$C NMR analysis was carried out using Bruker AMX 300 (300 MHz) and Bruker Avance 500 (500 MHz) machines. The chemical shift (δ) of each peak was assigned relative to tetramethylsilane (TMS), using the reference point δ TMS = 0 ppm.

Accurate mass spectra were performed on a VG 7070H spectrometer with a Finnigan Incos II data system at the London School of Pharmacy. Electrospray mass spectroscopy were recorded on a VG micromass 7070b, extended geometry or autospec Quattro LC instrument. Nominal FAB and EI mass spectra were performed using a VG ZAB SE double focusing machine at UCL. Melting point analysis was carried out using a Gallen-kemp melting point apparatus. The value was quoted uncorrected to the nearest °C.

UV/vis spectra were recorded on a Shimadzu UV-160A machine. Micro Analysis were performed by A. Stone and J. Maxwell at UCL. Flash-Chromatography was carried out using a 40-63 µm mesh silica (C60/C40 sorbsil). Analytical thin layer chromatography was performed on glass backed or aluminium backed normal phase silica gel plates (Merk Kiesel gel 60F$_{54}$). The plates were visualised with ultraviolet light (254nm), and/or using potassium permanganate stain [add Na$_2$CO$_3$ (62.5 g) in water (1.25 litres) to potassium permanganate (12.5 g) in water (1.25 litres)] or phosphomolybdic acid stain [PMA hydrate (12 g) and conc. H$_2$SO$_4$ (10 ml) in ethanol (250 ml)], vanillin stain [vanillin (2.4 g), conc. H$_2$SO$_4$ (2.5 ml), ethanol (100 ml)] or anisaldehyde stain [p-anisaldehyde (10 g) in ethanol- 99.7 % (500 ml), conc. H$_2$SO$_4$ (10 ml), glacial acetic acid (10 ml)].

HPLC analysis was carried out on a Gilson Model 805 S apparatus. The enantioselectivities were determined using a “DIACEL” chiralcel OD HPLC column at wavelengths 254 nm (for aromatic systems) and 222 nm or 226 nm (for non aromatic systems) using a Waters 486 tuneable absorbance detector and integrator.
Optical rotations were determined using an “optical activity automatic polarimeter”, model AA-10. The specific rotation values \([\alpha]\) were measured in degrees and were determined using the following equation:

\[
[\alpha]_D = \frac{100\alpha}{l.c}
\]

where \(\alpha\) is the observed rotation, \(l\) is the sample path length in decimeters and \(c\) is the concentration in grams per 100 ml of solution.\textsuperscript{70}

Chemicals and reagents were purchased from Sigma-Aldrich Co. Ltd, Lancaster and Acros-Fisher Scientific UK and were subsequently used without purification unless stated otherwise.

THF was freshly distilled over benzophenone and sodium under nitrogen prior to use. Diethyl ether was specially dried over sodium wire. Anhydrous dichloromethane was distilled from a solution of dichloromethane and calcium hydride. Toluene was distilled over calcium hydride. Acetonitrile and triethylamine were dried over anhydrous 4Å molecular sieves prior to use. Anhydrous DMF, hexane and cyclohexane were purchased from Sigma-Aldrich Co. Ltd and used without further purification. All other solvents used were of reagent grade.

All air and moisture sensitive reactions were carried out under an inert nitrogen atmosphere. All glassware were pre-dried in an oven (120 °C) prior to use.
7. Experimental.

7.1 S-Tyrosine methyl ester hydrochloride (62).\(^{167}\)

\[
\begin{align*}
\text{HO} & \\
\text{Cl} & \\
\text{C} & \\
\text{OCH}_3 & \\
\end{align*}
\]

S-Tyrosine (10.01 g, 50.0 mmol) was dissolved in dry methanol (200 ml). The solution was cooled to -5 °C and thionyl chloride (10.1 ml, 138 mmol) was slowly added. The temperature of the reaction mixture was maintained below 0 °C during the addition. The colourless solution was then stirred for 18 hours at room temperature. Excess methanol was removed in vacuo to give the crude product.

The material was purified by washing with methanol (3 x 50 ml) to give a white solid. This was recrystallised from ethyl acetate to yield the title compound as colourless crystals (12.23 g, 94%).

m.p. 190-192 °C (ethyl acetate; Lit. 192 °C).\(^{167}\)

\[\nu_{\text{max}}/\text{cm}^{-1} (\text{nujol}) \quad 3337 \text{m}, 2922 \text{br s}, 1741 \text{s}, 1613 \text{m}, 1591 \text{m}.
\]

\[
\begin{align*}
\delta_H & (300 \text{ MHz}; \text{D}_2\text{O}) \quad 3.13 (1\text{H}, \text{dd}, J 14.7 \text{ and } 7.4 \text{ Hz}, 3'-\text{H}), 3.33 (1\text{H}, \text{dd}, J 14.7 \text{ and } 5.7 \text{ Hz}, 3'-\text{H}), 3.69 (3\text{H}, \text{s}, \text{OCH}_3), 4.21 (1\text{H}, \text{dd}, J 7.4 \text{ and } 5.7 \text{ Hz}, 2'-\text{H}), \\
\delta_C & (75 \text{ MHz}; \text{D}_2\text{O}) \quad 37.61 (\text{C}-3), 56.37 \text{ and } 57.03 (\text{C}-2 \text{ and } \text{OCH}_3), 118.83, (2 \times \text{C}-3'), 128.25 (2 \times \text{C}-2'), 133.68 (\text{C}-1'), 158.09 (\text{C}-4'), 172.99 (\text{C}-1).
\end{align*}
\]

\[m/z (\text{ES}^+) \quad 196 (M^+\text{-Cl}, 100\%), 136 (M^+\text{-Cl}) -\text{COOCH}_3, 85), 119 (\text{C}_6\text{H}_5\text{CH}_2\text{NH}_3^+, 16);
\]

(Found: \(M^+-\text{Cl}, 196.0976. \text{C}_{10}\text{H}_{14}\text{O}_3\text{N} \text{ requires: } M^+\text{-Cl}, 196.0974);

[\alpha]_D = +72.0 \degree (c 3 \text{ in pyridine at } 25 \degree C), [\text{Lit. } +74.0 \degree (c 3 \text{ in pyridine at } 25 \degree C)].\(^{167}\)
7.2  *N*-Butyryl tyrosine methyl ester (63).

\[ \text{HO} \quad \overset{\text{1'}}{\text{N}} \quad \text{H} \quad \overset{\text{2''}}{\text{OCH}_3} \]

*S*-Tyrosine methyl ester hydrochloride (62) (3.01 g, 13.0 mmol) was dissolved in THF (100 ml) at 0 °C. Triethylamine (3.6 ml, 25.8 mmol) was added followed by butyryl chloride (1.35 ml, 13.0 mmol) over a 10 minute period. When the addition was complete, DMAP (1.04 g, 8.2 mmol) was added to the mixture and the reaction was stirred at 40 °C for 3 hours. The reaction mixture was quenched with water (100 ml) and the aqueous and organic layers separated. The aqueous layer was washed with ethyl acetate (4 x 100 ml) and the combined organic extracts were washed with sodium hydrogen carbonate (5%, 50 ml). After drying (sodium sulfate) the solvent was removed in *vacuo* and purified using flash chromatography (petroleum ether:ethyl acetate, 1:1) to yield the *title compound* as a pale cream solid (0.25 g, 8%). \( R_f 0.30 \) petroleum spirit:ethyl acetate, 1:1.

m.p. 115-116 °C (ethyl acetate).

\( \nu_{\text{max}}^{\text{nujol}}/ \text{ cm}^{-1} \) 3316m, 3252m, 1734s, 1655s, 1545m, 1513m.

\( \delta_\text{H} \) (300 MHz; CDCl3) 0.90 (3H, t, \( J 7.5 \text{ Hz} \), 4''-H), 1.63 (2H, m, 3''-H), 2.17 (2H, t, \( J 7.5 \text{ Hz} \), 2''-H), 2.94 (1H, dd, \( J 14.0 \text{ and } 5.9 \text{ Hz} \), 3'-H), 3.13 (1H, dd, \( J 14.0 \text{ and } 5.9 \text{ Hz} \), 3-H/H), 3.75 (3H, s, OCH3), 4.89 (1H, m, 2-H), 5.98 (1H, br s, N-H), 6.73 (2H, dd, \( J 8.9 \text{ and } 2.6 \text{ Hz} \), 2 x 3'-H), 6.96 (2H, dd, \( J 8.9 \text{ and } 2.6 \text{ Hz} \), 2 x 2''-H).
\[ \delta_C (125 \text{ MHz}; \text{CDCl}_3) 13.60 \text{ (C-4")}, 18.97 \text{ (C-3")}, 37.24 \text{ and } 38.97 \text{ (C-2" and C-3)}, 52.41 \text{ and } 53.08 \text{ (C-2 and OCH}_3\text{), } 115.53 \text{ (2 x C-3")}, 126.97 \text{ (2 x C-2")}, 130.21 \text{ (C-1")}, 155.47 \text{ (C-4")}, 172.41 \text{ and } 173.19 \text{ (C-1 and C-1")}. \]

\[ m/z (\text{ES}^+) 266 \text{ (M}', 100\%), 196 \text{ (M}' - \text{COCH}_2\text{CH}_2\text{CH}_3, 23). \]

(Found: \( M^+ \), 266.1385. \( \text{C}_{14}\text{H}_{20}\text{O}_4\text{N} \) requires: \( M^+ \), 266.1392); \( [\alpha]_D = +58.9^\circ \) (c 1.0 in methanol at 25 °C).

### 7.3 \( N \)-Butyryl \( O \)-butyryl tyrosine methyl ester (64).

\[ \text{S-Tyrosine methyl ester hydrochloride (62) (3.01 g, 13.0 mmol) was dissolved in THF (100 ml). Triethylamine (3.60 ml, 25.8 mmol) was added to the reaction mixture which was stirred for 30 minutes at room temperature. A further 2 equivalents of triethylamine (3.60 ml, 25.8 mmol) was added followed by 2 equivalents of butyryl chloride (2.70 ml, 26.0 mmol). When the addition was complete, DMAP (1.04 g, 8.2 mmol) was added to the mixture and the reaction was heated at reflux for 3 hours. The reaction mixture was quenched with water (100 ml) and the aqueous and organic layers separated. The aqueous layer was washed with ethyl acetate (4 x 100 ml) and the combined organic extracts were washed with sodium hydrogen carbonate (5%, 50 ml). The combined organic extracts were then dried over sodium sulfate, and the solvent was removed in vacuo to yield the crude product. The crude product was recrystallised from ethyl acetate to give a light brown solid of the desired product (3.24 g, 75%). } \]

\( R_f 0.48 \) petroleum spirit:ethyl acetate 1:1.

m.p. 73-74 °C (ethyl acetate).
\[ \nu_{\text{max}}(\text{nujol)/ cm}^{-1} \text{ 3330m, 2921br, 1745s, 1645s, 1548w, 1377s.} \]

\[ \delta_H (300 \text{ MHz; CDCl}_3) 0.93 (3H, t, J 7.3 \text{ Hz, 4''-H}), 0.99 (3H, t, J 7.4 \text{ Hz, 8''-H}) \]
\[ 1.60 (2H, m, 3''-H), 1.75 (2H, m, 7''-H), 2.17 (2H, t, J 7.2 \text{ Hz, 2''-H}), 2.53 (2H, t, J 7.4 \text{ Hz, 6''-H}), 3.06 (2H, m, 3-H), 3.71 (3H, s, OCH}_3), 4.90 (1H, m, 2-H), 5.87 (1H, d, J 7.7 \text{ Hz, N-H}), 6.97, (2H, dd, J 8.6 \text{ and 2.0 Hz, 3'-H, 5'-H}), 7.09 (2H, dd, J 8.6 \text{ and 2.0 Hz, 2'-H, 6'-H}). \]

\[ \delta_C (75 \text{ MHz; CDCl}_3) 14.05 (\text{C-4'' and C-8'' peaks superimposed}), 19.35 (\text{C-3'' and C-7'' peaks superimposed}), 36.63 \text{ and 37.72 (C-2'' and C-6''), 38.83 (C-3), 52.69 \text{ and 53.26 (C-2 and OCH}_3), 122.04 (\text{C-3' and C-5'}), 130.55 (\text{C-2' and C-6'}), 133.75 (\text{C-1'}), 150.29 (\text{C-4'}), 172.43 (\text{C-1''}), 172.88 (\text{C-5'' and C-1}). \]

\[ m/z (\text{ES}^+) 336 (M^+, 100\%), 266 (M^+- \text{COCH}_2\text{CH}_2\text{CH}_3, 99), 206 (\text{HOCH}_2\text{CH}_2\text{CHCOOCH}_3\text{NHCO(CH}_2)_2\text{CH}_3^+, 72) \]
\[ 179 (\text{C}_9\text{H}_3\text{CH}_2\text{CHCOOCH}_3\text{NH}^+, 27). \]

(Found: \( M^+ \), 336.1817. \( \text{C}_{18}\text{H}_{26}\text{O}_5\text{N} \) requires: \( M \), 336.1811); Anal. calc. for \( \text{C}_{18}\text{H}_{26}\text{O}_5\text{N} \): C, 64.48; H, 7.46; N, 4.18; found C, 64.24; H, 7.46; N, 4.17%.

\[ [\alpha]_D = +50.2^\circ (c 1.0, \text{ in chloroform at 25 }^\circ\text{C}). \]

7.4 **N-Butyryl tyrosinol (65).**

![Diagram of N-Butyryl tyrosinol (65)](65)

The reaction was carried out under anhydrous conditions. \( N \)-Butyryl \( O \)-butyryl tyrosine methyl ester (64) (5.21 g, 15.6 mmol), was stirred in THF (100 ml). Lithium aluminium hydride (1.60 g, 4.80 mmol) was added in small portions. The mixture was heated at reflux for 22 hours. To the mixture, water (1.0 ml), followed by sodium hydroxide (1.0 ml), and then a further aliquot of
water (1.0 ml) was added. The reaction mixture was then acidified with 2M HCl (100 ml). The aqueous layer was washed with ethyl acetate (3 x 50 ml) and the combined organic extracts were dried over sodium sulfate. The solvent was removed in vacuo to give the resulting product as a light brown, oil. The crude material was carried to the next step without further purification (3.32 g, 90%).

$\nu_{\text{max}}$ (nujol)/cm$^{-1}$: 3297 br, 2923 br, 1747 s, 1643 s, 1462 m, 1376 m, 1020 m.

$\delta_H$ (300 MHz; CDCl$_3$): 0.91 (3H, t, $J$ 7.1, 4''-H), 1.57 (2H, m, 3''-H), 2.06 (2H, t, $J$ 7.3 Hz, 2''-H), 2.78 (1H, dd, $J$ 11.5 and 7.3 Hz, 3-HH), 2.82 (1H, dd, $J$ 11.5 and 7.3 Hz, 3-HH), 3.05 (1H, m, 2-H), 3.60 (1H, dd, $J$ 11.0 and 5.8 Hz, 1-HH), 3.74 (1H, dd, $J$ 11.0 and 3.8 Hz, 1-HH), 5.68 (1H, br m, N-H), 6.79 (2H, d, $J$ 8.5 Hz, 2 x 3'-H), 7.08 (2H, d, $J$ 8.5 Hz, 2 x 2'-H).

$m/z$ (ES$^+$) 238 (MH$^+$, 100%), 220 ($M^+$ - OH, 75), 168 ($M^+$ - COCH$_2$CH$_2$CH$_3$, 32), 107 (HOCH$_2$CH$_2$OH, 5).

(Found: MH$^+$, 238.1436. C$_{13}$H$_{20}$O$_3$N requires: MH$^+$, 238.1443);

$[\alpha]_D = +11.8^\circ$ (c 0.025, in chloroform at 25 °C).

7.5  **N-Butyl tyrosinol hydrochloride (66).**

![Chemical Structure](image)

The reaction was carried out under anhydrous conditions. To a solution of the amide (65) (2.05 g, 8.65 mmol) in dry THF (100 ml), 1 M borane-THF solution was added dropwise (25.9 ml, 25.9 mmol) over 20 minutes. The reaction was heated at reflux for 18 hours before being quenched by the addition of 6M hydrochloric acid (2 ml). The solvent mixture was removed in vacuo and the residue dissolved in diethyl ether (60 ml), then made neutral by adding 1 M sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate.
The combined organic extracts were dried over sodium sulfate and the solvent removed in vacuo. The residue (1.56 g, 81%) was stirred with 4.0 M hydrogen chloride in dioxane to afford the product as its hydrochloride salt. The resulting solid was subsequently recrystallised from ethyl acetate to yield the title compound as a brown solid (1.50 g, 67%). Rf of free amine 0.05 - ethyl acetate:methanol, 19:1. m.p. 173-175 °C (ethyl acetate).

\[ \nu_{\text{max}} \text{(nujol)/cm}^{-1} = 3245, 2853, 1612, 1567, 1514, 1458, 1377. \]

\[ \delta_\text{H} \text{(CDCl}_3\text{)} \] 0.70 (3H, t, J 7.4 Hz, 4″-H), 1.22 (2H, m, 3″-H), 1.44 (2H, m, 2″-H), 2.72 (2H, m, 3-H$_2$), 2.92 (2H, m, 1″-H), 3.32 (1H, br s, 1-OH), 3.40 (2H, m, 2-H and 1-JH), 3.56 (1H, m, 1-HH), 6.71 (2H, d, J 8.5 Hz, 2 x 3″-H), 7.03 (2H, d, J 8.5 Hz, 2 x 2″-H).

\[ \delta_\text{C} \text{(CDCl}_3\text{)} \] 13.04 (C-4″), 19.52 (C-3″), 27.88 (C-2″), 32.84 (C-3), 45.02 (C-1″), 58.28 and 60.37 (C-1 and C-2), 116.11 (2 x C-3″), 127.63 (2 x C-2″), 131.00 (C-1′), 155.02 (C-4″).

\[ m/z \text{ (ES)}^{+} \] 224 (M$^+$-Cl, 100%) and 106 (HOC$_6$H$_4$CH$^+$, 59);
\[ m/z \text{ (EI)} \] 192 (M$^+$-Cl -CH$_2$OH, 16 %), 116 (M$^+$-Cl -HOC$_6$H$_4$CH$_2$, 100), 107 (HO C$_6$H$_4$CH$^+$, 19), 60 (CH$_2$NHCH$_2$OH$^+$, 23);
Salt (Found: M$^+$-Cl, 224.1647. C$_{13}$H$_{22}$O$_2$N requires: M-Cl, 224.1651).

\[ [\alpha]_D = +10.4 \, ^\circ \text{ (c 0.5, in methanol at 25 °C).} \]

7.6 (2S)-2-(N-butyl dodecylamino)-3-(4′-hydroxyphenyl)-propan-1-ol (67).

The reaction was carried out under anhydrous conditions. The amine salt (66) (0.51 g, 1.96 mmol), 1-bromododecane (0.47 ml, 1.95 mmol) and potassium
carbonate (0.27 g, 1.96 mmol) were stirred in acetonitrile (25 ml) and heated at reflux for 22 hours. Water (50 ml) was added to quench the reaction and the crude product was extracted using ethyl acetate (4 x 100 ml). The combined organic extracts were dried over sodium sulfate. The product was removed in vacuo and purified via flash-chromatography (dichloromethane:methanol, 19:1) yielding the title compound as a red oil. (0.22 g, 28%).

$\nu_{\text{max}}$ (neat)/ cm$^{-1}$ 3323m, 2924s, 2853s, 1613w, 1515m, 1465m, 1373w, 1235w.

$\delta_\text{H}$ (300 MHz; CDCl$_3$) 0.88 (6H, m, D-H and 12''-H), 1.19 (20H, m), 1.31 (4H, m), 2.19 (2H, m), 2.35 (2H, m), 2.51 (2H, m), 2.75 (1H, m, 2-H), 3.24 (2H, m, 1-H$_2$), 6.67 (2H, d, $J$ 8.5 Hz, 3'-H and 5'-H), 6.94 (2H, d, $J$ 8.5, 2'-H and 6'-H).

$\delta_\text{C}$ (75 MHz; CDCl$_3$) 12.98, 13.08, 19.54, 21.67, 26.40, 27.91, 28.33, 28.54, 28.63, 28.66, 29.94, 30.06, 30.91 (2 signals superimposed), 48.56 and 48.84 (C-A and C-1''), 59.07 and 62.90 (C-1 and C-2), 114.52 (C-3' and C-5''), 128.80 (C-2' and C-6''), 129.42 (C-1''), 153.63 (C-4'').

$m/z$ (FAB$^+$) 393 ($MH^+$, 100%), 360 [(($MH^+ \cdot \text{CH}_2\text{CH}_3$)$^+$, 11].

(Found: $M^+$, 392.3543. C$_{25}$H$_{46}$O$_2$N requires: $M$, 392.3529).

$[\alpha]_D^\circ = +14.2^\circ$ (c 0.05, in chloroform at 25°C).

### 7.7 (2S)-2-[N-butyl dodecylamino]-3-(4'-hydroxyphenyl)-propan-1-ol hydrochloride (68).

![Diagram of the molecule](68)

Compound (67) was treated with 1 equivalent of 4.0 M HCl in dioxane. The reaction mixture was washed with ethyl acetate (4 x 100 ml). The combined organic extracts were collected and the solvent removed in vacuo to yield the hydrochloride salt (68) as a brown oil (0.22 g, 90%).
δ_H salt (300 MHz; CDCl₃) 0.86 (6H, m, D-H and 12''-H), 1.19-1.74 (22H, m) 2.17-2.35 (4H, m), 2.51 (2H, m), 2.81 (1H, m, 2-H), 2.90-3.25 (3H, m, 1-H₂, and 1-OH), 6.65 (2H, 3'-H and 5'-H), 6.84 (2H, 2'-H and 6'-H).

[α]_D = +13.4 ° (c 0.05, in chloroform at 25 °C).

7.8 (2S)-2-[N-butyl hexadecylamino]-3-(4'-hydroxyphenyl)-propan 1-ol (69).

The reaction was carried out under anhydrous conditions. The amine salt (66) (1.05 g, 3.85 mmol), 1-iodohexadecane (1.36 g, 3.05 mmol) and potassium carbonate (0.73 g, 5.30 mmol) were stirred in acetonitrile (25 ml) and heated at reflux for 22 hours. Water (50 ml) was added, and the aqueous layer was washed with diethyl ether (3 x 50 ml). The combined organic layers were dried over sodium sulfate. The solvent was removed in vacuo leaving a brown oil. The crude oil was purified by flash chromatography (ethyl acetate:hexane, 1:1), to afford the free amine as a brown oil (1.53 g, 89%). R_f 0.73-of free amine (ethyl acetate and 5% methanol solution).

ν_max (neat)/ cm⁻¹ 3309m, 2924s, 1515s, 1464s, 1374m, 1028m.

δ_H (300 MHz; CDCl₃) 0.88 (6H, m, D-H and 16''-H), 1.19 (28H, m), 1.29 (4H, br m), 2.16 (2H, m), 2.35 (2H, m), 2.48 (2H, m), 2.76 (1H, m, 2-H), 3.18 (1H, br s, 1-OH), 3.29 (2H, m, 1-H₂), 6.89 (2H, d, J 8.3 Hz, 3'-H, 5'-H), 6.98 (2H, d, J 8.3 Hz, 2'-H, 6'-H).

δ_C (75 MHz; CDCl₃) 12.91, 13.12, 19.44, 21.69, 26.30, 26.47, 28.37, 28.47, 28.64, 28.68, 28.72, 29.17, 29.89, 30.23, 30.93 (4 signals superimposed), 49.02 and 49.23 (C-A and C-1''), 58.41 and 62.90 (C-1 and C-2), 114.71 (C-3' and C-5'), 128.80 (C-2' and C-6'), 128.95 (C-1'), 154.25 (C-4'').
m/z (ES^+) 448 (M^+ 100%), 298 (M^-HO-C_6H_4-CH_2, 59),
224 (M^-((CH_2)_{13}CH_3, 16).
[α]_D = +10.7 ° (c 0.05, in chloroform at 25 °C).

7.9  (2S)-2-[N-butyl hexadecylamino]-3-(4'-hydroxyphenyl)-propan 1-ol hydrochloride (70).

Compound (69) was treated with 1 equivalent of 4.0 M HCl in dioxane. The reaction mixture was washed with ethyl acetate (4 x 100 ml). The combined organic extracts were collected and the solvent removed in vacuo to give the hydrochloride salt (70) as a brown oil (1.52 g, 92%).

δ_H (300 MHz; CDCl_3) 0.57-0.98 (6H, br m, D-H and 16''-H), 1.19-1.54 (32H, m), 2.02 (2H, m), 2.68-3.27 (4H, m), 3.32 (1H, m, 2-H), 3.49-3.88 (1-H_2 and 1-OH), 6.76 (2H, br m, 3''-H, 5''-H), 7.02 (2H, br m, 2'-H, 6'-H).

(Found: MH^-Cl, 448.4158. C_{29}H_{55}O_2N requires: MH^-Cl, 448.4155);
[α]_D = +10.4 ° (c 0.05, in chloroform at 25 °C).

7.10  (2S)-2-[N-butyl octadecylamino]-3-(4'-hydroxyphenyl)-propan 1-ol (71).

(71)
The reaction was carried out under anhydrous conditions. The amine salt (66) (1.00 g, 3.85 mmol), 1-iodooctadecane (1.41 g, 3.78 mmol) and potassium carbonate (0.53 g, 3.84 mmol) were stirred in acetonitrile (25 ml) and heated at reflux for 22 hours. Water (50 ml) was added to quench the reaction and the crude product was extracted with ethyl acetate (4 x 100 ml). The combined organic layers were dried over sodium sulfate.

The solvent was removed in vacuo and purified via flash-chromatography [dichloromethane:methanol (19:1)] yielding the title compound as a red solid. (1.72 g, 87%).

m.p. 92-93 °C (ethyl acetate).

ν\text{max}(\text{CHCl}_3)/\text{cm}^{-1} 3321 \text{m}, 2924\text{s}, 2853\text{s}, 1613\text{w}, 1515\text{s}, 1464\text{s}, 1374\text{w}.

δ\text{H} (300 MHz; CDCl₃) 0.86 (6H, m, D-H and 18''-H), 1.19 (32H, m), 1.42 (4H, m), 2.20 (2H, m, 3-H₂), 2.39 (2H, m), 2.52 (2H, m), 2.78-2.83 (1H, m, 2-H), 3.30 (2H, m, 1-H₂), 4.09 (2H, br, 2 x OH), 6.67 (2H, d, J 8.6 Hz, 3'-H and 5'-H), 6.75 (2H, d, J 8.6, 2'-H and 6'-H).

δ\text{C} (75 MHz; CDCl₃) 12.98, 13.08, 20.92, 23.06, 27.79, 29.27, 29.74, 29.93, 30.03, 30.08, 31.42, 32.31 (9 signals superimposed), 50.01 and 50.30 (C-A and C-1''), 60.45 and 63.99 (C-1 and C-2), 115.90 (C-3' and C-5'), 130.24 (C-2' and C-6'), C-1' peak missing, 156.01 (C-4').

m/z (FAB⁺) 476 (M⁺, 42%).

7.11 (2S)-2-[\text{N-butyl octadecylamino}]-3-(4'-\text{hydroxyphenyl})-propan 1-ol hydrochloride (72).

Compound (71) was stirred in 4M hydrochloric acid/dioxane. The reaction mixture was washed with ethyl acetate (4 x 100 ml). The combined
organic extracts were collected and the solvent removed in vacuo to yield the hydrochloride salt (72) as a dark red oil (1.62 g, 82%).

δ<sub>H</sub> salt (300 MHz; CDCl<sub>3</sub>) 0.81 (6H, m, D-H and 18°-H), 1.19 (32H, m), 1.86 (4H, m), 3.16-3.60 (9H, m), 6.84 (4H, m, 3'-H, 5'H and 2'-H and 6'-H).

(Found: MH<sup>+</sup>-Cl 476.4461. C<sub>31</sub>H<sub>58</sub>O<sub>2</sub>N requires: MH<sup>+</sup>-Cl, 476.4468); [α]<sub>D</sub> = +9.4 ° (c 0.05, in chloroform at 25 °C).

7.12 (2S)-2-[N-butyl hexadecyl-N-methylammonium]-3-(4’-hydroxyphenyl]-propan 1-ol, iodide (73).

The free amine (69) (1.02 g, 2.23 mmol) and methyl iodide (0.50 ml, 8.03 mmol) were stirred together in acetonitrile and heated at reflux for 14 hours. After this time, the mixture was filtered through silica and the filtrate was washed with diethyl ether. The solvent was removed by distillation under atmospheric conditions to afford the title compound as a red oil (0.96 g, 91%).

ν<sub>max</sub> (neat)/ cm<sup>-1</sup> 3260n, 3019s, 2927s, 1515s, 1466s, 1246s, 1046m.

δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 0.83 (6H, m, D-H and 16°-H), 1.23 (28H, m), 1.61 (4H, m), 2.98-3.09 (5H, m, N<sup>-</sup>-CH<sub>3</sub> and 3-H<sub>2</sub>), 3.36 (2H, m), 3.61 (2H, m), 3.64 (2H, m, 2-H and 1-OH), 3.85 (2H, m, 1-H<sub>2</sub>), 6.79 (2H, m, 3’-H and 5’-H), 7.05 (2H, m, 2’-H and 6’-H).

δ<sub>C</sub> (75 MHz; CDCl<sub>3</sub>) 14.20, 14.47, 20.58, 23.05, 29.60, 29.73, 29.91, 29.96, 30.05, 30.10, 30.66, 32.94 (7 signals superimposed), 48.39 and 52.32 (C-A and C-1”), 61.21, 74.05, 116.45 (C-3’ and C-5’), 130.62 (C-2’ and C-6’), 131.01 (C-1’), 156.12 (C-4’).

m/z (FAB<sup>+</sup>) 462 (M<sup>+</sup>-I, 100%), 448 (M<sup>+</sup>-I)-CH<sub>3</sub>, 72).
Compound (73) (0.53 g, 0.90 mmol), was passed through a dawex-\text{-OH}
weakly basic anion column (25-50 mesh) which was pre-washed in methanol.
Compound (73) was dissolved in methanol prior to use and ran through the anion
exchange resin using methanol as the solvent. The product was removed in
\textit{vacuo} to yield the title compound as a light yellow oil (0.41 g, 95%).

$\nu_{\text{max}}$ (neat)/ cm$^{-1}$: 3418 m, 3018 s, 2926 w, 2400 s, 1515 s, 1423 s, 1217 s, 1046 m, 770 s.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$): 0.67 (6H, m, D-H and 16'-H), 1.19 (28H, m), 1.56 (4H, m), 2.82-2.88 (5H, m, N$^+$-CH$_3$ and 3-H$_2$), 3.28-3.39 (4H, m), 3.69 (3H, m, 2-H, 1-H), 6.74 (2H, m, 3'-H and 5'-H), 6.83 (2H, m, 2'-H and 6'-H).

$\delta_{\text{C}}$ (75 MHz; CDCl$_3$): 14.09, 20.17, 20.83, 23.05, 26.91, 29.74, 29.89, 29.95, 30.08, 30.11, 32.30 (signals superimposed), 47.87, 56.89, 116.64 (C-3' and C-5'), 130.25 (C-2' and C-6'), 130.81 (C-1'), 156.84 (C-4').

$\text{m/z}$ (FAB$^+$): 462 ($M^+\text{-OH}$, 100%), 448 ($M^+\text{-OH}$-CH$_3$, 36).

(Found: $M^+$-OH, 462.4301. C$_{30}$H$_{56}$O$_3$N requires: $M$-OH, 462.4311).

Anal. calc. for C$_{30}$H$_{57}$O$_3$N: C, 75.09; H, 11.98; N, 2.98; found C, 70.16; H, 11.53; N, 2.53 %; I, 0 %.

$[\alpha]_D = +7.8^\circ$ (c 0.05, in chloroform at 25 °C).
7.14 12-Benzyloxy dodecan-1-ol (75).4,93

To a cold solution of dodecan-1,12-diol (10.08 g, 49.5 mmol) in dry dimethylformamide (DMF) (60 ml), and sodium hydride (2.22 g, 54.4 mmol) was added at 0 °C followed by benzyl bromide (5.89 ml, 49.5 mmol). The reaction was heated at 60 °C for 2 hours and quenched with ice water (100 ml). The resulting white solid was filtered and the filtrate extracted with ethyl acetate (4 x 100ml). The organic layer was dried over magnesium sulfate and the solvent removed in vacuo. The residue was purified by flash chromatography (petroleum spirit 40-60 °C:ethyl acetate 10:1) to afford the title compound as a white solid (4.87 g, 33%) Rf 0.1, petroleum spirit 40-60 °C:ethyl acetate 10:1. m.p. 29-30 °C (diethyl ether).

\( \nu_{\text{max}}/\text{cm}^{-1} \) (nujol) 3356m, 3030w, 2923m, 1375m, 1103m.

\( \delta_{\text{H}} \) (300 MHz; CDCl\(_3\)) 1.20-1.50 (20H, m, 2-H to 11-H), 3.37 (2H, t, J 6.6 Hz, 12-H), 3.57 (2H, t, J 6.6 Hz, 1-H), 4.43 (2H, s, 1'-H), 7.26 (5H, m, 3'-H to 7'-H).

\( \delta_{\text{C}} \) (75 MHz; CDCl\(_3\)) 26.14, 26.60, 29.83, 29.88, 29.98, 30.18, 33.21 (C-2 to C-11, 3 signals superimposed), 63.51 (C-1), 70.94 (C-12), 73.26 (C-1'), 127.87 (C-5'), 128.03 (C-4' and C-6'), 128.74 (C-3' and C-7'), 139.15 (C-2').

m/z (ES \(^+\)) 293 (M\(^+\), 35%), 91 (C\(_5\)H\(_5\)CH\(_2\)^+\), 100).

(Found: M\(^+\), 293.2479 C\(_{19}\)H\(_{33}\)O\(_2\) requires: M, 293.2481);

7.15 1-Benzyl-12-chlorododecane (76).4,93

(76)
A mixture of the alcohol (75) (2.09 g, 6.83 mmol), thionyl dichloride (1.00 ml, 13.6 mmol) and pyridine (0.65 ml, 8.10 mmol) were heated at reflux for 2 hours. The reaction mixture was poured into crushed ice water (ca. 150 ml) and was extracted with ethyl acetate (4 x 100 ml). The combined extracts were dried over magnesium sulfate and the solvent removed in vacuo to afford the title compound as a pale yellow oil (1.90 g, 85%). R\_f 0.38 (petroleum spirit:ethyl acetate 19:1).

\( \nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3029w, 2927s, 2854s, 1456s, 1362m, 1103s.

\( \delta_H\) (300 MHz; CDCl\_3) 1.20-1.64 (20H, m, 2-H to 11-H), 3.39 (2H, t, \( J = 6.7\) Hz, 12-H), 3.45 (2H, t, \( J = 6.7\) Hz, 1-H), 4.43 (2H, s, 1'-H), 7.27 (5H, m, 3'-H to 7'-H).

\( \delta_C\) (75 MHz; CDCl\_3) 26.60, 27.30, 29.30, 29.86, 29.88, 29.92, 29.54, 30.18, 33.06 (C-2 to C-11) 1 signal superimposed, 45.61 (C-1), 70.94 (C-12), 73.26 (C-1'), 127.87 (C-5'), 128.02 (C-4' and C-6'), 128.75 (C-3' and C-7'), 139.12 (C-5').

\( m/z\) (FAB\(^{+}\)) 309 (\( M^+\), 30%), 107 (\( M^+\)-C\(_{12}\)H\(_{24}\)Cl, 46), 91 (\( M^+\)-C\(_{12}\)H\(_{24}\)ClO, 100).

7.16 1-Benzylxylo-12-Iodododecane (77).

\[ \text{To a solution of sodium iodide (1.75 g, 11.65 mmol) in acetone (40 ml), a solution of the chloride (76) (1.90 g, 6.12 mmol) in acetone (10 ml) was added dropwise at room temperature. The reaction mixture was then heated at 70 °C for 48 hours. The solvent was removed in vacuo and the residue was extracted with diethyl ether (4 x 100 ml) and washed with aqueous sodium metabisulfite. The organic solvent was removed in vacuo to yield the title compound as a brown oil (2.35 g, 94%). R\_f 0.36 (using petroleum spirit:ethyl acetate 19:1).} \]
$\nu_{\text{max}}$/cm$^{-1}$ (neat) 3062w, 2924s, 2852s, 1456s, 1362m, 1204m, 1102s.

$\delta_H$ (300 MHz; CDCl$_3$) 1.19-1.72 (20H, m, 2-H to 11-H), 3.12 (2H, t, $J$ 6.8 Hz, 1-H), 3.39 (2H, t, $J$ 6.8 Hz, 12-H), 4.39 (2H, s, 1'-H), 7.26 (5H, m, 3'-H to 7'-H).

$\delta_C$ (75 MHz; CDCl$_3$) 7.79 (C-1), 29.82, 29.88, 29.93, 30.92, 33.98 (C-2 to C-11) 5 signals superimposed, 70.94 (C-12), 73.26 (C-1'), 127.87 (C-5'), 128.03 (C-4' and C-6'), 128.75 (C-3' and C-7'), 138.70 (C-2').

$m/z$ (FAB$^+$) 401 ($M^+$, 6%), 91 (C$_6$H$_5$CH$_2^+$, 100).

(Found: $M^+$, 402.1420. C$_{19}$H$_{31}$OI requires: $M$, 402.1436).

7.17 (2S)-2-[N-(12''-Benzyloxydodecyl)-N-butylamino]-3-(4''-hydroxyphenyl) propan 1-ol (78).

A mixture of the amine (66) (1.33 g, 5.99 mmol), iodide (77) (2.34 g, 5.82 mmol) and potassium carbonate (1.13 g, 8.19 mmol) were stirred in acetonitrile (5 ml) and heated at reflux for 22 hours. The reaction mixture was washed with water (50 ml) and then extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried over sodium sulfate. The solvent was removed in vacuo. The residue was purified by flash chromatography (petroleum spirit: ethyl acetate 4:1) to afford the title compound as a brown oil (0.30 g, 10%). $R_f$ 0.08-petroleum spirit:ethyl acetate 4:1.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 3247s, 2926s, 2856s, 1614m, 1516s, 1458s.

$\delta_H$ (300 MHz; CDCl$_3$) 0.80 (3H, t, $J$ 7.2 Hz, D-H), 1.19 - 1.52 (24H, m, B-H to C-H and 2''-H to 11''-H), 1.53 (2H, br, 1-OH and 4'-OH), 2.31 (2H, m, 3-H$_2$), 2.47 (4H, m, A-H, 1''-H), 3.18 (1H, m, 2-H), 3.22 (2H, m, 1-H), 3.37 (2H, t, $J$ 2.5 Hz, 12''-H), 4.44 (2H, s, 13''-H), 6.65 (2H, d, $J$ 8.4 Hz, 3'-H and 5'-H), 6.92 (2H, d, $J$ 8.4 Hz, 2'-H, 6'-H), 7.20 (5H, m, 15''-H to 19''-H).
δ_C (125 MHz; CDCl_3) 13.99 (C-D), 20.36, 25.94, 29.13, 29.22, 29.38, 29.46, 29.55, 29.64, 31.78, 32.60 (signals superimposed), 42.85, 52.74, 57.94 (C-1), 66.23 (C-2), 70.46 (C-12''), 72.75 (C-13''), 116.16, 127.55, 128.06, 129.41, 130.38, 138.46 (7 signals superimposed), 155.99 (C-14''), 158.36 (C-4').

m/z (FAB^+) 498 (M^+ , 28%), 390 (M^+ -HOC_6H_5CH_2O, 50), 107 (C_6H_5CH_2O^+, 77), 91 (C_6H_5CH_2^+, 100).

(Found: M^+ 498.3941. C_{32}H_{52}O_3N requires: M, 498.3947).

[α]_D = -2.3 ° (c 0.4, in chloroform at 25 °C).

7.18 (2S)-2-[N-(12'"'-Benzyloxydodecyl)-N-butylamino]-3-(4'-' hydroxyphenyl)propan-1-ol hydrochloride (79).

\[
\text{Compound (78) was stirred in 4M hydrochloric acid/dioxane. The reaction mixture was washed with ethyl acetate (4 x 100 ml) and the solvent removed in vacuo to yield the hydrochloride salt (79) as a brown oil (0.27 g, 90% conversion to the salt).}
\]

δ_H Salt (300MHz; CDCl_3) 0.91 (3H, m, D-H), 1.20-1.54 (24H, m, B-H to C-H and 2''-H to 11''-H), 1.69-1.97 (5H, m, 3-H_2, A-H, R_2NH^+), 2.43 (3H, 1''-H and 2-H), 3.39-3.57 (4H, m, 1-H and 12''-H), 4.43 (2H, s, 13''-H), 6.41 (4H, m), 7.26 (5H, m).

[α]_D = -2.8 ° (c 0.4, in chloroform at 25 °C).
7.19 (2S)-2-[N-(12''-Benzyloxidodecyl)-N-butylamino]-3-[4''-(18''-benzyloxidodecyl oxy)-phenyl propan 1-ol (80).

Compound (80) was synthesised according to the same procedure carried out for compound (78). The title compound was obtained from flash chromatography of the crude residue (using petroleum spirit 40-60 °C:ethyl acetate 10:1) as a brown oil, 0.70 g, 24%). Rf 0.28 using petroleum spirit 40-60 °C.

$\nu_{\text{max}}$ (neat)/ cm$^{-1}$ 2925s, 2854s, 1512s, 1460m, 1247m, 1102m.

$\delta$H (300 MHz; CDCl$_3$) 0.79 (3H, t, J 7.2 Hz, D-H), 1.19 - 1.69 (44H, m, B-H to C-H and 2''-H to 11''-H and 8'-H to 17'H), 2.32 (1H, s, OH), 2.48 (2H, m, 3-H$_2$), 2.78 (4H, m, A-H and 1''-H), 2.91 (1H, m, 2-H), 3.21 (2H, m, 1-H), 3.37 (4H, t, J 1.6 Hz, 12''-H and 18''-H), 3.82 (2H, t, J 6.6 Hz, 7'-H), 4.43 (4H, s, 13''-H and 19'-H), 6.71 (2H, d, J 8.5 Hz, 3'-H and 5'-H), 6.74 (2H, d, J 8.5 Hz, 2'-H, 6'-H), 7.26 (1OH, m, Ar).

$\delta$C (125 MHz; CDCl$_3$) 13.60 (C-D), 20.28, 25.68, 25.98, 26.13, 26.65, 26.98, 27.17, 29.01, 29.17, 29.33, 29.41, 29.51, 29.52, 29.63, 29.71, 30.78, 31.86, 32.74 (11 signals superimposed), 51.08 and 52.66 (C-A and C-1''), 58.66 and 62.99 (C-1 and C-2), 67.01 (C-12''), 68.08 (C-13''), 70.48 (C-18''), 72.80 (C-19''), 115.08, 126.83, 127.41, 127.56, 128.10, 128.28, 128.95, 129.46, 129.69, 130.12, 158.50, 130.27, 138.64.

$m/z$(FAB$^+$) 772 (M$^+$,12%), 390 [M$^+$(C$_6$H$_5$CH$_2$O)$_2$(CH$_2$)$_{12}$, 26], 107 (C$_6$H$_3$CH$_2$O$^+$, 37), 91 (C$_6$H$_5$CH$_2^+$, 100).

(Found: M$^+$, 772.6225. C$_{31}$H$_{82}$O$_4$N requires: M, 772.6244).

$[\alpha]_D$ = +6.3 ° (c 0.02, in chloroform at 25 °C).
7.20 \((2S)-2-[N-(12''-'-Benzyloxycododecyl)-N-butyamin]-3-[4''-(18''-benzyloxocododecyl oxy)-phenyl propan 1-ol hydrochloride (81).

\[
\text{(81)}
\]

Compound (80) was stirred in 4M hydrochloric acid/dioxane. The reaction mixture was washed with ethyl acetate (4 x 100 ml) and the solvent removed in vacuo to yield the hydrochloride salt (81) (0.64 g, 92% conversion to salt).

\[\delta_H \text{ Salt (300 MHz; CDCl}_3) \]

\[
0.92 (3H, m, D-H), 1.20-1.67 (44H, m, B-H to C-H, 2''-H to 11''-H and 8'-H to 17''-H), 1.68-2.01 (6H, m), 2.10 (1H, s, N/H), 2.94-2.99 (3H, m), 3.41 (4H, t, J 1.6 Hz, 12''-H and 18''-H), 3.72 (2H, m, 7'-H), 4.43 (4H, s, 13''-H and 19'-H), 6.78 (2H, m, 3'-H and 5'-H), 7.04 (2H, m, 2'-H and 6'-H), 7.26 (10H, m, Ar).

\[[\alpha]_D^0 = +5.8 ^\circ (c 0.02, \text{ in chloroform at } 25 ^\circC).]

7.21 \([1S-(1\alpha, 2\beta, 8\alpha\beta)]-(+)-Hexahydro-2-(hydroxymethyl)-8\alpha \text{ methyl-1-phenyl-5H-oxazolo(2,1) pyridin 5-one (82).}

\[
\text{(82)}
\]

Compound (82) is commercially available from Aldrich catalogue\textsuperscript{167} reference number:- 38,811-4.

m.p. 98-100 °C.\textsuperscript{167}

\(\nu_{\text{max}}/\text{cm}^{-1}\) (nujol) 3356s, 2924m, 2863m, 1622s.
δ_H (300 MHz; CDCl₃) 1.81 (3H, s, 9-H), 2.08-2.28 (2H, m, 7-H), 2.45 (2H, m, 8-H), 2.60-2.85 (2H, m, 6-H), 4.05 (2H, m, 3-H), 4.25 (1H, m, 2-H), 4.90 (1H, d, J 9.3 Hz, 1-H), 8.62 (5H, m, Ar).

δ_C (75 MHz; CDCl₃) 17.61 (C-7), 24.58 (C-9), 30.45 (C-6), 35.63 (C-8), 65.40 (C-3), 67.47 (C-2), 78.50 (C-1), 94.52 (C-8α), 127.18 (C-4'), 129.25 (C-3' and C-5'), 129.39 (C-2' and C-6'), 137.94 (C-1'), 171.53 (C-5).

m/z (APCI⁺) 262 (MH⁺ 100%).

[α]_D = +14 ° (c 1.0, in ethanol at 25 °C).

7.22 2-[(S)-2-Methyl-piperidin-1-yl]-1-phenyl-propane-1,3 diol (83).

Compound (82) (1.01 g, 3.87 mmol) was dissolved in THF (20 ml). THF-Borane (14 ml, 14.0 mmol) was added slowly at room temperature. The mixture was heated at reflux for 18 hours before being quenched with 6 M HCl (2 ml). The aqueous layer was basified using 6 M NaOH and the material extracted from the aqueous layer using ethyl acetate (3 x 100 ml). The organic layer was dried using sodium sulfate. The solvent was removed in vacuo and the residue recrystallised using ethyl acetate to afford the title compound as a colourless solid (0.66 g, 68%).

m.p. 148-150 °C (ethyl acetate).
ν_max/cm⁻¹ (nujol) 3390s, 2881s, 1459s, 1376s.

δ_H (300 MHz; CDCl₃) 1.13 (3H, d, J 6.6 Hz 9-H), 1.29-1.67 (4H, m, 6-H and 7-H), 2.38 (2H, m), 2.84-2.90 (1H, m), 2.99 (2H, m, 5-H), 3.09-3.13 (1H, m, 2-H), 3.42-3.48 (2H, m, 3-H), 4.24 (1H, d, J 9.6 Hz, 1-H), 7.31 (5H, m, Ar).
The reaction was carried out under anhydrous conditions. Compound (83) (0.25 g, 1.00 mmol), 1-iodohexadecane (0.35 g, 1.00 mmol) and potassium carbonate (0.14 g, 1.00 mmol) in acetonitrile (5 ml) were heated at reflux for 22 hours. Water (50 ml) was added, and the mixture was extracted with diethyl ether (3 x 50 ml). The combined organic layer was dried over sodium sulfate, and the solvent was removed in vacuo to yield the title compound as a yellow oil (0.20 g, 41%).

\[ \nu_{\text{max}} / \text{cm}^{-1} (\text{neat}) \quad 3393 \text{m}, 2923 \text{m}, 2852 \text{m}, 1461 \text{s}, 1373 \text{w}. \]

\( \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) 0.79 (3 \text{H, t, } J 6.3 \text{ Hz, 16''-H}), 1.12 (3 \text{H, d, } J 6.2 \text{ Hz, 9-H}), 1.18 (28 \text{H, m, 2''-H to 15''-H}), 1.63 (4 \text{H, m, 6-H and 7-H}), 2.39 (2 \text{H, m}), 2.95 \)
(1H, m), 3.07-3.14 (5H, m, 1"-H and 2-H and 5-H), 3.44-3.70 (2H, m, 3-H), 4.25 (1H, d, J 9.7 Hz, 1-H), 7.25 (5H, m, Ar).

$\delta_C$ (75 MHz; CDCl$_3$) 7.84 (C-16"), 14.55 (C-15"), 21.51, 23.11, 25.28, 27.27, 28.96, 29.78, 29.63, 30.09, 30.93, 32.34, 33.98, 36.91 (9 signals superimposed), 55.89, 59.71, 65.15, 70.05 (C-1), 127.60 (C-4'), 128.40 (C-3' and C-5'), 128.98 (C-2' and C-6').

$m/z$ (FAB$^+$) 474 (M$^+$-I, 3%), 250 [(M$^+$-I)-(CH$_2$)$_3$CH$_3$, 7].

(Found: $M^+$, 474.4330. C$_{31}$H$_{56}$O$_2$N requires: $M^+$, 474.4311).

$[\alpha]_D = +15^\circ$ (c 1.0, in ethanol at 25°C).

7.24 N-Methyl-2-(1-Hydroxy-3-hydroxymethyl-1-phenyl-ethyl) piperidinium tetrafluoroborate (85).

![Chemical Structure](image)

Compound (83) (0.51 g, 2.05 mmol) and trimethyloxonium tetrafluoroborate (0.36 g, 2.46 mmol) were dissolved in dichloromethane (25 ml). The reaction mixture was stirred under nitrogen for 62 hours. The solvent was evaporated under vacuo. The crude product was purified via flash chromatography, (dichloromethane : methanol, 19:1), to yield the title compound as a red oil (0.58 g, 81%).

$\nu_{\text{max}}$/cm$^{-1}$(neat) 3520w, 2949br, 1458s, 1396s, 1042s.

$\delta_H$ (300 MHz; CDCl$_3$) 1.45 (3H, d, J 6.4 Hz, 9-H), 1.51-1.96 (6H, m, 6-H, 7-H and 8-H), 3.20 (3H, s, N$^+$-CH$_3$), 3.21 (1H, m, 8$\alpha$-H), 3.35-3.52 (3H, m, 2-H and 5-H), 3.91 (2H, m, 3-H), 4.88 (1H, d, J 10.3 Hz, 1-H), 6.19 (1H, br, CH$_2$OH), 7.30 (5H, m, Ar).
\( \delta_c \) (75 MHz; CDCl\(_3\)) 20.57, 24.53, 25.99, 31.91, 35.22, 51.72, 61.29 (CH\(_3\)N\(^+\)), 63.38, 67.84, 70.51 (C-1), 129.06 (C-4'), 131.31 (C-3' and C-5'), 131.49 (C-2' and C-6'), 140.81 (C-1').

\( m/z \) (APCI\(^+\)) 264 \((M^+\cdotBF_4, 100\%)\), 250 \((M^+\cdotBF_4\cdotCH_3, 17)\).


\( \alpha \) = +6.4 ° (c 1.0, in ethanol at 25 °C).


The reaction was carried out under anhydrous conditions. Compound (82) (1.02 g, 3.91 mmol) and sodium hydride (60 % dispersion in mineral oil), (0.17 g, 4.19 mmol) were stirred together in dry DMF at 0 °C and hexadecyl iodide (1.35 g, 3.86 mmol) was then added. The reaction was stirred at 80 °C for 3 hours and quenched with ice-cold water. The product was extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried over sodium sulfate, then the solvent removed in \textit{vacuo}, to yield the title compound as a colourless oil (0.78 g, 41%).

\( \nu_{\text{max}}/\text{cm}^{-1} \) (nujol) 2924s, 2853s, 1652s, 1461s, 1395s, 1263w.

\( \delta_h \) (300 MHz; CDCl\(_3\)) 0.80 (3H, d, \( J 6.3 \) Hz, 16'-'H), 1.19 (28H, m, 2''-'H to 15''-'H), 1.53 (3H, s, 9-H), 1.73-2.43 (6H, m, 6-H, 7-H, 8-H), 3.40 (2H, m, 1''-'H), 3.58-3.80 (2H, m, 3-H), 3.98 (1H, m, 2-H), 5.21 (1H, d, \( J 7.9 \) Hz, 1- 'H), 7.28 (5H, m, Ar).

\( \delta_c \) (75 MHz; CDCl\(_3\)) 13.11 (C-16''), 16.22, 21.68, 22.85, 25.18, 27.93, 28.15, 28.45, 28.62, 28.69, 29.63, 30.92, 32.81, 34.57 (5 signals superimposed), 62.46,
67.45, 70.54 (C-2), 77.03 (C-1), 92.67 (C-8α), 113.06 (C-4'), 125.70 (C-3' and C-5'), 127.47 (C-2' and C-6'), 138.25 (C-1'), 168.09 (C-5).

\[ m/z (\text{FAB}^+) \] 486 (M^+, 51%).

(Found: M^+, 486.3952. C\textsubscript{31}H\textsubscript{52}O\textsubscript{3}N requires: M, 486.3947).

\[ \alpha \] = +9° (c 1.0, in ethanol at 25 °C).

7.26 2S-Hexadecyl oxy-2-(2-methyl-piperidin-1-yl)-1-phenyl-propan-1-ol (87).

Compound (86) (1.38 g, 2.85 mmol) was dissolved in THF (20 ml). THF-Borane (15 ml, 15.0 mmol) was added slowly at room temperature. The mixture was heated at reflux for 18 hours before being quenched with 6 M HCl (2 ml). The aqueous layer was made basic using 6 M NaOH and the material extracted from the aqueous layer using ethyl acetate (3 x 100 ml). The organic layer was dried using sodium sulfate. The solvent was removed in vacuo and the residue recrystallised using ethyl acetate to afford the title compound as a yellow oil (1.26 g, 93%).

\( v_{\text{max/cm}^{-1}} \) (nujol) 3322m, 2924s, 2853s, 1460s, 1412m.

\( \delta_{\text{H}} \) (300 MHz; CDCl\textsubscript{3}) 0.85 (3H, t, J 7.1 Hz, 16''-H), 1.07 (3H, d, J 6.1 Hz, 9-H), 1.18 (28H, m, 2''-H to 15''-H), 1.33-1.65 (4H, m, 6-H and 7-H), 2.33 (2H, m), 2.90-2.94 (3H, m), 3.08 (4H, m, 2-H and 5-H), 3.33 (2H, m, 3-H2), 4.13 (1H, d, J 7.0 Hz, 1-H), 7.21 (5H, m, Ar).

\( \delta_{\text{C}} \) (75MHz; CDCl\textsubscript{3}) 13.11 (C-16''), 21.68, 24.02, 25.16, 28.36, 28.66, 28.69, 30.92, 35.64 (10 signals superimposed), 44.94, 54.35, 61.70, 65.83, 68.10, 70.04 (C-1), 126.24 (C-4'), 126.57 (C-3' and C-5'), 127.20 (C-2' and C-6'), 141.96 (C-1').
\[ m/z \text{ (FAB}^+ \text{)} 474 (M^+ \text{, 36%}). \]

(Found: \( M^+ \text{, 474.4295}. \) \( C_{31}H_{56}O_2N \text{ requires: } M, 474.4311 \).

\( [\alpha]_D^\circ = +7^\circ \text{ (c 1.0, in ethanol at 25} \text{°C)}. \)

7.27 2S-Hexadecyl oxy-2-(2-methyl-piperidin-1-yl)-1-phenyl-propan-1-ol hydrochloride (88).

\[
\text{(88)}
\]

Compound (87) was stirred in 4M hydrochloric acid/dioxane. The reaction mixture was washed with ethyl acetate (4 x 100 ml) and the solvent removed in vacuo to yield the hydrochloride salt (88) as a white solid (1.22 g, 92% conversion to salt).

m.p 97-99 °C

\( \delta_H \text{ (300 MHz; CDCl}_3 \text{) 0.88 (3H, t, J 6.3 Hz, 16”-H), 1.26 (31H, m, 2”-H to 15”-H and 9-H), 1.60-1.97 (4H, m, 6-H and 7-H), 2.33 (2H, m), 3.32 (6H, m), 3.95 (2H, m, 3-H), 4.97 (1H, m, 1-H), 7.36 ( 5H, m, Ar).} \)

\( [\alpha]_D^\circ = +5^\circ \text{ (c 1.0, in ethanol at 25} \text{°C)}. \)

7.28 N-methyl, S-(3-Hexadecyl oxy methyl-1-hydroxy-1-phenyl-ethyl)-2-methyl-piperidinium tetrafluoroborate (89).

\[
\text{(89)}
\]
Compound (87) (0.75 g, 1.59 mmol) and trimethyloxonium tetrafluoroborate (0.29 g, 1.99 mmol) were dissolved in dichloromethane (25 ml). The reaction mixture was stirred under nitrogen for 62 hours. The solvent was evaporated under 
\textit{vacuo} to yield the title product as a red oil (0.75 g, 82%).

\[\nu_{\max}/\text{cm}^{-1} (\text{neat})\text{ }3130\text{s}, 2923\text{m}, 2849\text{m}, 1458\text{s}, 1396\text{m}, 1329\text{w}, 1042\text{m}.\]

\[\delta_{\text{H}} (300 \text{ MHz}; \text{CDCl}_3) 0.90 (3\text{H}, \text{t}, J 6.4 \text{ Hz}, 16''-\text{H}), 1.25 (28\text{H}, \text{m}, 2''-\text{H to 15''}-\text{H}) 1.53 (3\text{H}, \text{d}, J 6.4 \text{ Hz}, 9-\text{H}), 1.54 (2\text{H}, \text{m}), 2.05 (5\text{H}, \text{m}), 3.11-3.50 (7\text{H}, \text{m}), 3.85 (1\text{H}, \text{m}), 4.94 (1\text{H}, \text{d}, J 10.4 \text{ Hz}, 1-\text{H}), 7.26-7.41 (5\text{H}, \text{m}, \text{Ar}).\]

\[\delta_{\text{C}} (75 \text{ MHz}; \text{CDCl}_3) 14.54 (\text{C-16''}), 24.08, 26.54, 29.77, 29.98, 30.02, 30.07, 30.11, 32.33 (11 \text{ signals superimposed}), 49.78, 61.85 (\text{CH}_3-\text{N}^+), 64.53, 65.94, 68.86, 72.25 (\text{C-1}), 127.33 (\text{C-4'}), 129.49 (\text{C-3'} and \text{C-5'}), 129.68 (\text{C-2'} and \text{C-6'}), 138.92 (\text{C-1'}).\]

\[m/z (\text{APCI}^+) 488 (M^+\text{-BF}_4, 6\%), 474 (M^+\text{-BF}_4-\text{CH}_3, 100).\]

\[m/z (\text{FAB}^+) 488 (M^+\text{-BF}_4, 9\%), 474 (M^+\text{-BF}_4-\text{CH}_3, 82).\]

(Found: \(M^+\text{-BF}_4, 488.4479\). \(\text{C}_{32}\text{H}_{38}\text{O}_2\text{N}\) requires: \(M\text{-BF}_4, 488.4468\)).

\[\alpha_D = +2.5^\circ (c 1.0, \text{in ethanol at } 25^\circ\text{C}).\]

\textbf{7.29} \hspace{1em} (\textit{S})-\text{Prolinol (90)}\textsuperscript{167}

\[\begin{array}{c}
\text{H} \\
\text{N} \\
\text{2} \\
\text{OH} \\
\text{1} \\
\text{3} \\
\text{4} \\
\text{5}
\end{array}\]

(90)

The reaction was carried out under anhydrous conditions. Sodium borohydride (3.26 g, 0.09 mol) was stirred in THF (150 ml) at 0 °C. (\textit{S})-Proline (5.01 g, 43.58 mol) was cautiously added followed by iodine (11.57 g, 45.55 mmol) in THF. The reaction was heated to reflux for 18 hours. The mixture was then cooled to room temperature. Methanol was cautiously added until the solution was clear. The solution was mixed with 20 mol% potassium hydroxide solution (60 ml). The organic layer was extracted using dichloromethane (3 x 100 ml). The crude product was obtained in \textit{vacuo} and purified via flash-
chromatography (dichloromethane:methanol 20:1) to yield the title compound as a colourless oil (2.42 g, 55%).

$\nu_{\text{max/cm}^{-1}}$ (neat) 3294s, 2956s, 1458s, 1181w, 1053m.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 1.34-1.40 (1H, m, 3-$\text{H}$), 1.68-1.77 (3H, m, 3-$\text{H}$, 4-$\text{H}$), 2.16 (2H, m, 5-$\text{H}$), 2.84-2.92 (2H, m, 2-$\text{H}$, NH), 3.24-3.29 (2H, m, 1-$\text{H}$, 1-OH), 3.31-3.50 (1H, m, 1-$\text{H}$).

$\delta_{\text{C}}$ (75 MHz; CDCl$_3$) 26.47, 28.02, 46.80 (C-5) 59.76 (C-2), 65.19 (C-1).

$m/z$ (FAB$^+$) 102 ($\text{MH}^+$, 100%).

(Found: $\text{MH}^+$, 102.0912. C$_5$H$_{12}$ON requires: $\text{MH}$, 102.0919).

$[\alpha]_{D} = +28^\circ$ (c 1.6, in toluene at 25 $^\circ$C). Lit. $+30^\circ$ (c 1.6 toluene, 20 $^\circ$).

7.30 (S)-N-Hexadecyl-N-methylprolinol bromide (91).

![Chemical Structure](image)

Compound (90) (1.071 g, 0.011 mol) was stirred in 25 ml of water. Formaldehyde solution 37% (1.75 g, 1.62 ml, 0.022 mol), and formic acid solution 88% (2.07 g, 1.60 ml, 0.04 mol) were slowly added. The mixture was stirred at room temperature for 1 hour before being heated at reflux for 18 hours. The pH of the reaction was raised to 12 using potassium hydroxide and the mixture extracted with ether (3 x 50 ml). The combined organic layer was neutralised using dilute hydrochloric acid and dried over anhydrous sodium sulfate. The solvent was removed in vacuo. The resulting oil was dissolved in dichloromethane (20 ml) and 1-bromohexadecane (9.91 g, 0.03 mol) was added. The mixture was stirred in a sealed tube at 90 $^\circ$C for 18 hours before being cooled to room temperature. Anhydrous diethyl ether was added to the mixture to precipitate the product which was subsequently filtered and recrystallised from methanol to yield the title compound as colourless crystals (4.48 g, 79%).

m.p. 109-111 $^\circ$C (methanol).
\[ \nu_{\text{max/cm}^{-1}}(\text{CHCl}_3) \, 3411\text{m}, \, 2918\text{s}, \, 2850\text{m}, \, 1471\text{w}. \]

\[ \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) \, 0.65 \, (3\text{H}, \text{ t}, \delta 6.3 \text{ Hz, 22-H}), \, 1.03-1.12 \, (26\text{H}, \text{ m, 9-H to 21-H}), \, 1.51-1.82 \, (6\text{H, m, 3-H, 4-H, 8-H}), \, 2.94 \, (3\text{H, s, Me}), \, 3.14-3.34 \, (2\text{H, m, 7-H}), \, 3.49-3.74 \, (5\text{H, m, 1-H, 2-H, 5-H}), \, 3.69 \, (1\text{H, br s, 1-OH}). \]

\[ \delta_{\text{C}} (75 \text{ MHz; CDCl}_3) \, 14.46 \, (\text{C-22}), \, 20.38, \, 20.58, \, 23.04, \, 23.66, \, 24.41, \, 24.47, \, 24.78, \, 26.94, \, 27.07, \, 29.71, \, 29.88, \, 32.28, \, 43.88, \, 50.87, \, 56.42, \, 59.31, \, 59.42, \, 63.44, \, 65.15, \, 66.17, \, 76.61. \]

\[ m/z \, (\text{FAB}^+) \, 340 \, (M^+\cdot\text{Br, 100 \%}), \, 114 \, (M^+\cdot\text{Br})\cdot\text{H(CH}_2)_3\text{CH}_3, \, 18) \]

(Found: \( M^+\cdot\text{Br, 340.3579}. \, \text{C}_{22}\text{H}_{46}\text{ON requires: } M^\text{Br, 340.3579}). \]

\[ [\alpha]_D = +15^\circ \, (c \, 1.6, \, \text{in toluene at } 20^\circ\text{C}). \]

7.31 \((10S, 11R)-(\pm)-O\text{-hexadecyl cinchonine (92).}

The reaction was carried out under anhydrous conditions. To a suspension of \((\pm)-\text{cinchonine (1.06 g, 3.62 mmol) in dry DMF (25 ml) sodium hydride (60 \% wt in mineral oil 0.19 g, 4.86 mmol) was slowly added in small portions at 0 \, ^\circ\text{C}}. \]

The resulting solution was warmed to ambient temperature and stirred for 45 minutes. 1-Bromohexadecane (1.04 g, 3.40 mmol) was added in one portion and the solution heated at 60 \, ^\circ\text{C for 18 hours. The solution was diluted with dichloromethane (200 ml) and water (150 ml). The organic layer was removed and the aqueous layer extracted with further dichloromethane (2 x 100 ml). The organic layers were combined and washed with saturated lithium chloride solution (2 x 100 ml) to remove any excess DMF and dried over sodium sulfate. The solution was filtered and removed in \textit{vacuo} to afford the crude product. The
product was purified via column chromatography (dichloromethane:methanol, 40:1) to afford the title compound as a pale yellow oil (0.75 g, 50%).

$\nu_{\text{max/cm}^{-1}(\text{neat})} 3069\text{w}, 2924\text{s}, 2446\text{w}, 1636\text{w}, 1590\text{s}, 1508\text{w}.$

$\delta_{\text{H}} (300 \text{ MHz; CDCl}_3) 0.79 (3\text{H, t, } J = 6.3 \text{ Hz, 35-H}), 1.32 (28\text{H, m, 21-H to 34-H}), 1.32-1.92 (4\text{H, m}), 2.22-2.44 (2\text{H, m}), 2.72-3.16 (4\text{H, m, 15-H, 17-H}), 3.55 (3\text{H, m, 11-H, 20-H}), 5.04 (2\text{H, m, 19-H}), 5.26 (1\text{H, m, 10-H}), 5.97-6.08 (1\text{H, m, 18-H}), 7.41 (1\text{H, d, } J = 4.4 \text{ Hz, 2-H}), 7.51 (1\text{H, dd, } J = 7.6 \text{ Hz and 8.3 Hz, 7-H}), 7.65 (1\text{H, dd, } J = 7.6 \text{ Hz and 8.3 Hz, 6-H}), 8.08 (2\text{H, d, } J = 8.3 \text{ Hz, 5-H and 8-H}), 8.82 (1\text{H, d, } J = 4.4 \text{ Hz, 3-H}).$

$\delta_{\text{C}} (75 \text{ MHz; CDCl}_3) 14.54 (\text{C-35}), 21.69, 23.10, 26.73, 26.93, 28.71, 29.77, 29.87, 30.04, 30.09, 30.11, 30.46, 32.33 (6 \text{ signals superimposed}), 40.76, 50.57, 60.58, 70.18, 81.81, 114.78 (\text{C-18}), 118.75 (\text{C-19}), 123.31, 126.88, 126.96, 129.37, 130.86, 141.29, 147.27 (\text{C-4a}), 148.89 (\text{C-8a}), 150.54 (\text{C-3}).$

$m/z (\text{FAB}^+) 519 (M^+, 100\%).$

$[\alpha]_D = +120^\circ (c \ 0.5, \text{ in methanol at } 25^\circ \text{C}).$

7.32 (10S, 11R)-(+)-O-hexadecyl cinchonine hydrochloride (93).

The hydrochloride salt (93) was formed by stirring the amine (92) in 4 M HCl/dioxane for 10 minutes to yield the salt of the title compound (0.70 g, 88% conversion).

$\delta_{\text{H}} \text{ salt (300 MHz; CDCl}_3) 0.80 (3\text{H, t, } J = 6.3 \text{ Hz, 35-H}), 1.18 (28\text{H, m, 21-H to 34-H}), 1.33-2.07 (4\text{H, m, 12-H, 16-H}), 2.47-2.65 (2\text{H, m, 13-H, 14-H}), 3.21-3.57 (4\text{H, m, 15-H, and 17-H}), 3.70-3.97 (3\text{H, m, 11-H and 20-H}), 5.26 (2\text{H, m, 19-}
H), 5.94 (1H, m, 10-H), 6.83 (1H, m, 18-H), 8.01 (3H, m, 2-H, 6-H and 7-H), 8.72 (1H, m, 5-H), 9.05 (1H, m, 8-H), 9.19 (1H, m, 3-H).

(Found: $M\text{H}^+\text{Cl}$, 520.4381. C$_{35}$H$_{56}$ON$_2$ requires: $M\text{H-CI}$, 520.4393).

$[\alpha]_D$ = +117° (c 0.5, in methanol at 25 °C).

7.33) (10S, 11R)-(−)-N-methyl-O-hexadecyl cinchoninium iodide (94).

The reaction was carried out under anhydrous conditions. To O-hexadecyl cinchonine (92) (0.26 g, 0.5 mmol) in a round-bottom flask, iodomethane (0.03 ml, 0.5 mmol) was added. The mixture was stirred in 20 ml of anhydrous dichloromethane at 25 °C for 12 hours. The dichloromethane was removed in vacuo and the resulting red solid was purified by flash chromatography, dichloromethane : methanol (19:1) to yield the title product as a yellow solid (0.23 g, 85%).

m.p. 148-151 °C (methanol).

$\nu_{\text{max}}$ cm$^{-1}$ (CHCl$_3$) 2924s, 2853s, 1592w, 1465m.

$\delta$ (300 MHz; CDCl$_3$) 0.79 (3H, t, $J$ 5.9 Hz, 35-H), 1.18-1.36, (28H, m, 21-H to 34-H), 1.66 (2H, m), 1.95-1.96 (2H, m), 2.22 (1H, m), 2.90 (1H, m), 3.39-3.81 (7H, m, $\text{N}^+\text{-CH}_3$, 15-H and 17-H), 4.00-4.22 (2H, m, 20-H), 4.38 (1H, m, 11-H), 5.19 (3H, m, 10-H and 19-H), 5.77 (1H, m, 18-H), 7.44 (1H, m, 2-H), 7.69 (1H, m, 7-H), 7.76 (1H, m, 6-H), 8.06 (1H, d, $J$ 8.3 Hz, 5-H), 8.38 (1H, d, $J$ 8.3 Hz, 8-H), 8.80 (1H, m, 3-H).

$\delta$ (125 MHz; CDCl$_3$) 14.11 (C-35), 21.07, 22.67, 23.77, 26.35, 26.89, 29.34, 29.43, 29.55, 29.69, 29.94, 31.90, 37.53 (signals superimposed), 49.19, 60.03,
60.60, 66.37, 70.17, 118.02, 123.55, 129.31, 130.18, 130.40, 135.35, 139.69 (C-4a), 148.56 (C-8a), 149.58 (C-3).

$m/z$ (APCI$^+$) 533 ($M^+$/HI, 100%), 519 ($M^+$/I$^-$/CH$_3$, 35.

(Found: $M^+$/HI, 533.4490. $C_{36}H_{57}ON_2$ requires: $M^+$/HI, 533.4471).
Anal. calc. for $C_{36}H_{57}ON_2$: C, 65.36; H, 8.77; N, 4.58; found C, 64.99; H, 8.50; N, 4.13%.

$\alpha_\lambda = +110^\circ$ (c 0.5, in methanol at 25°C).

7.34) (10S, 11R)-(+)-$N,N'$-dimethyl-$O$-hexadecyl cinchoninium iodide (95).

The reaction was carried out under anhydrous conditions. To $O$-hexadecyl cinchonine (92) (0.95 g, 1.84 mmol) in a sealed tube, iodomethane (2.0 ml, 32.11 mmol) was added. The mixture was stirred in 20 ml of dichloromethane at 80°C for 3 hours before being cooled to room temperature. The dichloromethane was removed in vacuo and the resulting red solid was recrystallised from ether to yield the title compound as orange crystals (1.32 g, 90%).
m.p. 169-171°C (diethyl ether).

$\nu_{max}/cm^{-1}$ (CHCl$_3$) 2922s, 2852s, 1469w, 1108m, 1034w, 760m.

$\delta_{H}$ (300 MHz; CDCl$_3$) 0.81 (3H, t, $J$ 6.4 Hz, 35-H), 1.19, (28H, m, 21-H to 34-H), 1.66 (2H, m, 12-H), 1.88-2.04 (2H, m, 16-H), 2.14 (1H, m, 13-H), 2.78-2.80 (1H, m, 14-H), 3.45-3.50 (4H, m, 15-H and 17-H), 3.59 (3H, s, N$^-$-CH$_3$), 4.02-4.10 (2H, m, 20-H), 4.49 (1H, m, 11-H), 4.78 (3H, s, PhN$^-$-CH$_3$), 5.14-5.26 (3H, m,
The reaction was carried out under anhydrous conditions. To \( O \)-hexadecyl cinchonine (92) (0.31 g, 0.61 mmol), benzyl bromide (0.07 ml, 0.61 mmol) was added. The mixture was stirred in 20 ml of dichloromethane at 25 °C for 12 hours. Dichloromethane was removed in \textit{vacuo} and the resulting yellow solid was purified by flash chromatography, dichloromethane:methanol (19:1) to yield the title product as a yellow solid (0.30 g, 82%). Note that any residual benzyl bromide was removed using an on-line vacuum connected to an oil pump and a trap.

m.p. 191-193 °C (ethyl acetate).

\( \nu_{\text{max}}/\text{cm}^{-1}(\text{CHCl}_3) \): 2925s, 2854s, 1604m, 1534m, 1458m.

\( \delta_{\text{H}} \): (300 MHz; CDCl\(_3\)) 0.83 (3H, t, \( J = 7.0 \text{ Hz} \), 35-H), 1.19-1.49, (28H, m, 21-H to 34-H), 1.69 (4H, m, 12-H and 16-H), 2.23-2.42 (1H, m), 2.77 (1H, m), 3.36-3.62
(4H, m, 15-H and 17-H), 4.15-4.35 (3H, m, 11-H and 20-H), 4.74 (2H, m, 1'-H),
5.13-5.27 (3H, m, 10-H and 19-H), 5.82 (1H, m, 18-H), 7.44 (5H, m, 3'-H to 7'-H), 7.71 (2H, m, 2-H and 7-H), 7.76 (2H, m, 5-H and 6-H), 8.05 (1H, d, J 8.4 Hz, 8-H), 8.91 (1H, m, 3-H).

δC (125 MHz; CDCl₃) 14.08 (C-35), 22.64 (C-34), 26.60, 26.93, 27.19, 29.31,
29.43, 29.65, 29.92, 31.87, 37.59 (signals superimposed), 54.54, 55.98, 61.18,
61.97 71.29, 118.52 (C-18), 126.59, 127.70, 129.25, 129.39, 129.47, 129.57,
130.60, 130.85, 132.35, 133.97, 134.87, 136.45, 153.37.

m/z (APCI⁺) 609 (M⁺-Br, 100 %), 519 (MH⁺-Br)-CH₂Ph, 54).

[α]D = +104 ° (c 0.5, in methanol at 25 °C).

7.36 (10S, 11R)-(+)–N,N’-dibenzyl-O-hexadecyl cinchoninium bromide (97).

The reaction was carried out under anhydrous conditions. To O-
hexadecyl cinchonine (92) (0.80 g, 1.54 mmol) in a sealed tube, benzyl bromide
(2.20 ml, 18.5 mmol) was added. The mixture was stirred in 20 ml of
dichloromethane at 80 °C for 18 hours before being cooled to room temperature.
Dichloromethane was removed in vacuo and the resulting red residue was
purified using dichloromethane:methanol (19:1) to yield the title product as a red
oil (0.85 g, 79%). Note that any residual benzyl bromide was removed using an on-line vacuum connected to an oil pump and a trap.

\( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2930s, 2856s, 1619m, 1471m, 1433w, 1380w.

\( \delta_H \) (300 MHz; CDCl\(_3\)) 0.81 (3H, t, 5.9 Hz, 35-H), 1.19, (28H, m, 21-H to 34-H), 1.30-1.87 (4H, m, 12-H and 16-H), 2.21 (1H, m), 2.75 (1H, m), 3.29-3.59 (4H, m, 15-H and 17-H), 4.38-4.58 (7H, m, 1'-H, 8'-H, 11-H and 20-H), 5.09-5.28 (3H, m, 10-H and 19-H), 5.79-5.85 (1H, m, 18-H), 7.21-7.46 (10H, m, 3'-H to 7'-H and 10'-H to 14'-H), 7.77-7.82 (2H, m, 2-H and 7-H), 7.98-8.03 (2H, m, 5-H and 6-H), 8.39 (1H, m, 8-H), 9.46 (1H, m, 3-H).

\( \delta_C \) (125 MHz; CDCl\(_3\)) 14.00 (C-35), 22.30, 22.56, 22.69, 23.22, 24.20, 25.77, 26.08, 26.98, 28.98, 29.23, 29.51, 29.87 31.79, 37.53 (signals superimposed), 48.41, 54.44, 55.98, 59.83, 62.21, 65.57, 70.99, 118.35, 126.61, 128.72, 126.95, 127.38, 127.90, 129.27, 129.42, 130.71, 131.22, 132.44, 133.89, 134.93, 135.74, 149.48, 153.35 (C-3).

\( m/z \) (APCI\(^+\)) 700 (M\(^+\)-Br\(_2\), 30%), 610 (M\(^+\)-Br\(_2\)-PhCH\(_2\)), 100), 519 (M\(^+\)-(PhCH\(_2\))\(_2\), 58) (Found: M\(^+\)-Br\(_2\), 700.5346. C\(_{49}\)H\(_{68}\)ON\(_2\) requires: M\(^+\)-Br\(_2\), 700.5332).

\([\alpha]_D = +87^\circ \) (c 0.50, in methanol at 25 °C).

7.37 \((10S, 11R)-(+)-O-Undecen-30-yl\) hydroquinidine (98).

\[
\begin{align*}
29 & \quad 28 & \quad 27 & \quad 26 & \quad 25 & \quad 24 & \quad 23 & \quad 22 & \quad 21 & \quad 20 & \quad 19 & \quad 18 & \quad 17 & \quad 16 & \quad 15 & \quad 14 & \quad 13 & \quad 12 & \quad 11 & \quad 10 & \quad 9 & \quad 8 & \quad 7 & \quad 6 & \quad 5 & \quad 4a & \quad 3 & \quad 2 & \quad 1
\end{align*}
\]

(98)

The reaction was carried out under anhydrous conditions. To a suspension of hydroquinidine (1.07 g, 3.28 mmol), in dry DMF (20 ml), sodium
hydride (60% wt in mineral oil) (0.13 g, 3.29 mmol), was slowly added in small portions at 0 °C. The resulting solution was warmed to ambient temperature and allowed to stir for 45 minutes. 11-Bromo-1-undecene (0.74 g, 3.33 mmol) was added and the solution heated at 80 °C for 18 hours.

The solution was diluted with dichloromethane (200 ml) and water (150 ml). The organic layer was removed and the aqueous layer extracted with dichloromethane (2 x 100 ml). The organic layers were combined and washed with saturated lithium chloride solution (2 x 100 ml) to remove any excess DMF. The organic layer was dried over sodium sulfate which was filtered and removed in vacuo to afford the crude product. The product was purified using column flash chromatography, dichloromethane : methanol (19:1), to afford the title compound as a light brown oil (0.86 g, 55%).

\( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2924s, 1636m, 1590s, 1508w, 1460m, 1057s.

\( \delta_H \) (300 MHz; CDCl\(_3\)) 0.90 (3H, t, J 7.3 Hz, 19-H), 1.22-1.35 (12H, m, 23-H to 27-H, 18-H), 1.54-1.72 (8H, m, 21-H, 22-H, 12-H and 16-H), 1.72 (2H, m, 28-H), 2.22-2.44 (2H, m, 13-H and 14-H), 3.18-3.41 (4H, m, 15-H, 17-H), 3.58-3.61 (3H, m, 11-H and 20-H), 4.05 (3H, s, OCH\(_3\)), 4.83-4.94 (3H, m, 10-H and 30-H), 5.67-5.78 (1H, m, 29-H), 7.30-7.39 (1H, m, 2-H), 7.51 (1H, dd, J 7.6 Hz and 8.1 Hz, 6-H), 7.65 (1H, dd, J 7.6 Hz and 8.1 Hz, 5-H), 8.08 (2H, d, J 9.2 Hz, 8-H), 8.67 (1H, m, 3-H).

\( \delta_C \) (75 MHz; CDCl\(_3\)) 10.53 (C-19), 17.51 (C-18), 23.23, 23.60, 24.50, 25.32, 27.90, 28.09, 28.45, 29.07, 32.77, 34.44 (3 signals superimposed), 48.24, 48.87, 56.62, 58.76, 68.80, 99.90, 114.78 (C-29), 117.00 (C-30), 122.10, 125.92, 130.75, 138.15, 140.78, 143.73, 146.05 (C-3), 157.99 (C-7).

\( m/z \) (APCI\(^+\)) 478 (MH\(^+\), 100 %).

(Found: MH\(^+\), 479.3662. C\(_{31}\)H\(_{47}\)O\(_2\)N\(_2\) requires: MH\(^+\), 479.3638).

\([\alpha]_D = +131^\circ \) (c 0.5, in methanol at 25 °C).
The reaction was carried out under anhydrous conditions. To O-Undecen-1'-yl hydroquinidine (98) (0.24 g, 0.51 mmol), iodomethane (0.20 ml, 3.21 mmol.) was added. The mixture was stirred in 20 ml of dichloromethane at 25 °C for 12 hours. The dichloromethane was removed in vacuo and the resulting orange oil was purified by flash chromatography, dichloromethane:methanol (19:1) to yield the title product as an orange oil (0.28 g, 88%).

$\nu_{\text{max/cm}^{-1}}$(neat) 2924s, 1619s, 1471m, 1433w, 1380w, 1272m.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 0.91 (3H, t, $J$ 4.0 Hz, 19-H), 1.22-1.33 (12H, m, 23-H to 27-H, 18-H), 1.50-1.70 (8H, m, 21-H, 22-H, 12-H and 16-H), 1.97 (2H, m, 28-H), 2.20 (1H, m), 2.97 (1H, m), 3.25-3.38 (4H, m, 15-H and 17-H), 3.54-3.75 (3H, m, 11-H, 20-H), 4.15 (3H, s, OCH$_3$), 4.73 (3H, s, N$^+$-CH$_3$), 4.84-4.95 (3H, m, 10-H and 30-H), 5.70-5.79 (1H, m, 29-H), 7.72-7.76 (1H, m, 2-H), 7.85 (1H, m, 6-H), 8.00 (1H, m, 5-H), 8.25 (1H, m, 8-H), 9.56 (1H, m, 3-H).

$\delta_{\text{C}}$ (75 MHz; CDCl$_3$) 11.93 (C-19), 25.03 (C-19), 25.70, 26.64, 29.29, 29.46, 29.80, 29.85, 30.38, 34.14 (signals superimposed), 47.45, 49.91, 50.85, 53.80, 60.37, 71.16, 104.32, 113.47, 114.52, 121.33, 130.35, 135.06, 139.52, 146.09, 161.01 (C-7).

$m/z$ (APCI$^+$) 493 ($M^+-I$, 100 %), 479 ($MH^+-I$)-CH$_3$, 100.

(Found: $M^+$, 493.3810. C$_{32}$H$_{49}$O$_4$N$_2$ requires: $M^+$, 493.3794).

$[\alpha]_D^\circ = +101 \, ^\circ$ (c 0.5, in methanol at 25 °C).
7.39 12-Bromo-dodecan-1-ol (100).\(^{158}\)

![Chemical structure of 12-Bromo-dodecan-1-ol (100)](image)

To Dodecan-1,12-diol (1.07 g, 5.31 mmol) in toluene (20 ml), hydrogen bromide (48 % aq. solution) (0.65 ml, 5.74 mmol) was added and the mixture was heated at reflux for 72 hours. The organic layer was diluted with ether and washed with sodium hydroxide solution (1M) and saturated brine. The organic layer was removed under **vacuo** and purified by flash chromatography to yield the title compound as a waxy white solid (1.12 g, 84%).

\[
\text{m.pt } 34-36 \degree C \text{ (ether)}.
\]

\[
\nu_{\text{max/cm}^{-1}}(\text{CHCl}_3): 3348 \text{s, } 2937 \text{s, } 2852 \text{s, } 1461 \text{m}.
\]

\[
\delta_H (300 \text{ MHz; CDCl}_3): 1.29 \text{ (16H, m, 3-H to 10-H)}, 1.58 \text{ (2H, m, 11-H)}, 1.82 \text{ (2H, m, 2-H)}, 3.31 \text{ (2H, t, } J \text{ 6.6 Hz, 12-H)}, 3.55 \text{ (2H, t, } J \text{ 6.6 Hz, 1-H}).
\]

\[
\delta_C (75 \text{ MHz; CDCl}_3): 26.14, 28.56, 29.14, 29.80, 29.89, 29.90, 29.96, 30.08, 33.23 \text{ (C-2 to C-11, 1 signal superimposed)}, 34.37 \text{ (C-12)}, 63.49 \text{ (C-1)}.
\]

\[
m/z (\text{EI}^+) \text{ 265 (MH}^+, 1\%).
\]

(Found: $\text{MH}^+$, 265.1180. $\text{C}_{12}\text{H}_{26}\text{OBr}$ requires: $\text{MH}^+$, 265.1167).

7.40 12-Bromo dodecyl acrylate (101).\(^{157}\)

![Chemical structure of 12-Bromo dodecyl acrylate (101)](image)

The reaction was carried out under anhydrous conditions. Acryloyl chloride (0.31 ml, 3.82 mmol) was slowly added to 12-bromododecanol (100) (0.85 g, 3.20 mmol) in dichloromethane (30 ml) at 0 °C. Triethylamine (0.54 ml,
3.87 mmol) was then added dropwise and the reaction stirred overnight at room temperature. The dichloromethane was removed in vacuo and the resulting oil purified by flash chromatography (dichloromethane:hexane, 1:1) to yield the title compound as a colourless oil (0.91 g, 89%).

$\nu_{\text{max}}\text{cm}^{-1}(\text{neat})$ 2923s, 2853s, 1732s, 1461m, 1408s, 1296s.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 1.21-1.32 (16H, m, 3-H to 10-H), 1.54-1.59 (2H, m, 11-H), 1.61-1.77 (2H, m, 2-H), 3.30-3.34 (2H, t, $J$ 6.8 Hz, 12-H), 4.05-4.09 (2H, t, $J$ 6.7 Hz, 1-H), 5.70-5.74 (1H, dd, $J$ 10.3 Hz, 1.7 Hz, H$_b$), 5.99-6.08 (1H, dd, $J$ 17.3 Hz, 10.3 Hz, H$_a$), 6.28-6.34 (1H, dd, $J$ 17.3 Hz, 1.7 Hz, H$_a$).

$\delta_{\text{C}}$ (75 MHz; CDCl$_3$) 21.69, 24.92, 26.09, 27.18, 27.64, 28.23, 28.71, 29.04, 30.93, 32.82, 44.02, 63.63 (C-1), 126.15 (C-2'), 129.24 (C-1'), 165.18 (C=O).

$\text{m/z}$ (EI$^+$) 319 ($\text{MH}^+$, 100%).

(Found: $\text{MH}^+$, 319.1255. C$_{15}$H$_{28}$O$_2$Br requires: $\text{MH}^+$, 319.1273).

### 7.41 12-Iodododecyl acrylate (102)$^{157}$

![Structure of 12-Iodododecyl Acrylate (102)](image)

To a solution of sodium iodide (2.36 g, 15.76 mmol) in acetone (30 ml), a solution of 12-bromododecyl acrylate (101) (0.50 g, 1.58 mmol) in acetone (10 ml) was added dropwise at room temperature. The reaction mixture was then heated at reflux for 48 hours. The solvent was removed in vacuo and the residue was extracted with diethyl ether (4 x 100 ml) and washed with aqueous sodium hydrogen sulfite. The organic solvent was removed in vacuo to yield the title compound as a brown oil (0.52 g, 90%).

$\nu_{\text{max}}\text{cm}^{-1}(\text{neat})$ 2928s, 2855s, 1720s, 1636m, 1459m, 1410s.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 1.21-1.29 (16H, m, 3-H to 10-H), 1.36-1.51 (2H, m, 11-H), 1.64-1.80 (2H, m, 2-H), 3.09-3.13 (2H, t, $J$ 7.0 Hz, 12-H), 4.04 (2H, t, $J$ 6.7 Hz,
\[1-H), 5.73 (1H, dd, J 10.9 Hz, 1.3 Hz, H_b), 6.04 (1H, dd, J 17.3 Hz, 10.9 Hz, H_c),
6.29-6.35 (1H, dd, J 17.3 Hz, 1.3 Hz, H_a).
\]
\[\delta_C (75 \text{ MHz; CDCl}_3) 7.53 (C-12), 26.30, 28.90, 29.01, 29.60, 29.76, 29.85,
30.18, 33.96, 39.10 (C-2 to C-11, 1 signal superimposed), 65.06 (C-1), 129.08
(C-2’), 130.68 (C-1’), 166.65 (C=O).
\]
\[m/z (E^+) 367 (M^+^+, 1\%).
\]
(Found: \(M^+\), 367.1122. \(C_{15}H_{28}O_2\) requires: \(M^+\), 367.1134).

**7.42 1-(Tetrahydro-pyran-2'-yl oxy)-dodecan-12-ol (103).**

\[\text{(103)}\]

The reaction was carried out under anhydrous conditions. To a solution
of dodecan-1,12-diol (5.01 g, 24.8 mmol) in dichloromethane (100 ml), a
solution of 3,4-dihydro-2H-pyran (1.88 g, 22.3 mmol) in dichloromethane was
added dropwise at room temperature. \(p\)-Toluene sulphonic acid monohydrate
(0.26 g, 1.37 mmol) was added to the mixture and the reaction was stirred at
room temperature for 18 hours. The reaction was quenched with water (100 ml)
and the aqueous and organic layers separated. The aqueous layer was washed
with dichloromethane (4 x 100 ml). The combined organic extracts were
removed in \(\text{vacuo}\). The crude product was purified by flash chromatography-
dichloromethane : hexane (1:1) to yield the title product as a colourless oil (3.83
g, 60%).

\[\nu_{\text{max/cm}^{-1}(\text{neat}) 3422\text{m}, 2925\text{s}, 1458\text{m}, 1351\text{m}.}
\]
\[\delta_H (300 \text{ MHz; CDCl}_3) 1.20-1.36 (16H, m, 3-H to 10-H), 1.50-1.54 (10H, m, 2-H,
11-H and 4’-H to 6’-H), 3.27-3.80 (4H, m, 3’-H and 12-H), 3.56 (2H, t, \(J 6.6 \text{ Hz,}
1-H), 4.49-4.52 (1H, m 1’-H).
\]
\[\delta_C (75 \text{ MHz; CDCl}_3) 20.05, 25.90, 26.12, 26.61, 29.79, 29.83, 29.93, 30.13,
31.17, 33.19 (3 signals superimposed), 62.68 (C-3’), 63.38 (C-12), 68.07 (C-1),
99.21 (C-1’).\]
\[ m/z \text{ (FAB)} = 285 (M^+ - H, 8\%), 85 \text{ ((CH}_2)_8\text{CHO})^+, 100. \]

(Found: \(M^+ + Na, 309.2420\). \(C_{17}H_{34}O_3Na\) requires: \(M^+ + Na, 309.2406\)).

7.43 Methane sulfonic acid 1-(tetrahydro-pyran-2'-yl oxy)-dodecyl ester (104).

\[
\text{(104)}
\]

The reaction was carried out under anhydrous conditions. 1-(Tetrahydro-pyran-2'-yl oxy)-dodecan-12-ol (103) (1.00 g, 3.50 mmol), was dissolved in dichloromethane (20 ml) at 0 °C. Methane sulfonyl chloride (0.82 ml, 10.6 mmol) was added dropwise to the mixture followed by triethylamine (1.46 ml, 10.47 mmol) in 10 minute intervals keeping the temperature at 0 °C . The reaction was stirred for 18 hours at room temperature. The mixture was washed with water. The organic layer was collected and the aqueous layer was washed with further aliquots of dichloromethane (3 x 100 ml). The organic layer was extracted and removed under \textit{vacuo}. The resulting crude oil was purified by flash chromatography-dichloromethane : hexane \(1:1\) to yield \textit{the title compound} as a colourless oil (0.82 g, 64%).

\(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3055m, 2929s, 1737m, 1358m, 1266s, 1175s.

\(\delta_H\) (300 MHz; CDCl\(_3\)) 1.21 (16H, m, 3-H to 10-H), 1.45-1.77 (10H, m, 2-H, 11-H, 4'-H to 6'-H), 2.93 (3H, s, OSO\(_2\)CH\(_3\)), 3.27-3.80 (4H, m, 3'-H and 12-H), 4.15 (2H, t, \(J \) 6.6 Hz, 1-H), 4.50 (1H, m 1'-H).

\(\delta_C\) (75 MHz; CDCl\(_3\)) 29.09, 25.79, 25.91, 26.61, 29.39, 29.52, 29.76, 29.84, 31.19, 37.77 (3 peaks superimposed), 53.77 (OSO\(_2\)CH\(_3\)), 62.72 (C-3'), 68.06 (C-12), 70.53 (C-1), 99.24 (C-1').

\[ m/z \text{ (APCI}^+) = 387 (M^+ - Na, 11\%). \]

(Found: \(M^+ + Na, 387.2168\). \(C_{18}H_{36}O_4SNa\) requires: \(M^+ + Na, 387.2181\)).
7.44 1-Trityloxy-dodecan-12-ol (105).

![Chemical structure diagram](image)

The reaction was carried out under anhydrous conditions. Dodecan-1,12-diol (10.13 g, 0.05 mmol) was dissolved in dichloromethane (150 ml) followed by triethylamine (10 ml, 0.07 mol). The mixture was stirred for 10 minutes before trityl chloride (16.89 g, 0.03 mmol) was added to the mixture.

When the addition was complete, DMAP (0.61 g, 0.005 mol) was added and the reaction was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (100 ml) and the aqueous and organic layers separated. The aqueous layer was washed with dichloromethane (4 x 100 ml) and the combined organic extracts were washed with sodium hydrogen carbonate (5%, 50 ml). The organic layer was removed under vacuo. The crude product was purified by flash chromatography, dichloromethane:hexane (1:1) to yield the title product as a colourless oil (6.92 g, 62%).

\[ \nu_{\text{max/cm}^{-1}}(\text{neat}) \quad 3395\text{m}, 2926\text{s}, 2854\text{s}, 1602\text{m}, 1490\text{m}, 1449\text{m}, 1071\text{s}. \]

<table>
<thead>
<tr>
<th>Chemical Shifts</th>
<th>Assignments</th>
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<tbody>
<tr>
<td>( \delta \text{H} )</td>
<td>(300 MHz; CDC\textsubscript{3}) 1.18-1.29 (16H, m, 3-H to 10-H), 1.44-1.58 (4H, m, 2H and 11-H), 2.97 (2H, t, ( J = 6.6 \text{ Hz} ), 12-H), 3.56 (2H, t, ( J = 6.3 \text{ Hz} ), 1-H), 7.12-7.48 (15H, m, 3 Ar).</td>
</tr>
<tr>
<td>( \delta \text{C} )</td>
<td>(75 MHz; CDC\textsubscript{3}) 26.14, 26.67, 29.82, 29.91, 29.96, 30.46, 33.22 (C-2 to C-11) peaks superimposed, 63.50 (C-12), 64.09 (C-1), 86.67 (C-1'), 127.17 (3 x [C-3' and C-7']), 128.05 (3 x [C-5']), 129.11 (3 x [C-4' and C-6']), 144.97 (3 x C-2').</td>
</tr>
</tbody>
</table>

\[ m/z \text{ (EI\textsuperscript{+})} \quad 444 (M\textsuperscript{+}, 2%), 367 (M\textsuperscript{+}-Ph, 18), 243 (Ph\textsubscript{3}C\textsuperscript{+}, 100), 202 (MH\textsuperscript{+}-PH\textsubscript{3}C, 1) \]

(Found: \( M\textsuperscript{+} + Na \), 467.2910. C\textsubscript{31}H\textsubscript{40}O\textsubscript{2}Na requires: \( M\textsuperscript{+} + Na \), 467.2926).
7.45 1-Trityloxy-12-bromododecane (106).

![Chemical Structure](Image)

(106)

1-Trityloxy-dodecan-12-ol (105) (1.88 g, 4.23 mmol) was dissolved in dichloromethane and stirred at 0 °C. Carbon tetrabromide (1.44 g, 4.35 mmol) in dichloromethane was slowly added followed by triphenyl phosphine (1.09 g, 4.14 mmol) in 10 minute intervals. The reaction was stirred at room temperature for 18 hours and quenched with water. The aqueous and organic layers were separated. The aqueous layer was washed with dichloromethane (4 x 100 ml) and the combined organic extracts were washed with sodium hydrogen carbonate (5%, 50 ml). The organic layer was concentrated under vacuo. The crude product was purified by flash chromatography (dichloromethane solution) to yield the title product as a yellow oil (0.86 g, 40%).

$\nu_{\text{max}}/\text{cm}^{-1}$(neat) 2928s, 2855s, 1650m, 1490m, 1450m, 1382w.

$\delta_{H}$ (300 MHz; CDC$_3$) 1.15 (16H, m, 3-H to 10-H), 1.50-1.78 (2H, m, 2-H and 11-H), 2.96 (2H, t, $J$ 6.6 Hz, 12-H), 3.29 (2H, t, $J$ 5.6 Hz, 1-H), 7.09-7.35 (15H, m, 3 Ar).

$\delta_{C}$ (75 MHz; CDC$_3$) 25.24, 27.15, 27.73, 28.37, 28.48, 28.51, 28.56, 29.03, 31.81, 32.93, 62.65 (C-1), 85.25 (C-1''), 125.74 (3 x [C-3' and C-7'']), 127.41 (3 x [C-5'']), 127.68 (3 x [C-4' to C-6'']), 143.53 (3 x C-2').

$m/z$ (EI$^+$) 508 ($M^+$, 5%), 243 (Ph$_3$C$^+$, 100).
7.46 1-Trityloxy-12-iodododecane (107).

![Chemical Structure](image)

To a solution of sodium iodide (1.01 g, 6.75 mmol) in acetone (30 ml), a solution of 1-trityloxy-12-bromododecane (106) (0.50 g, 0.99 mmol) in acetone (10 ml) was added dropwise at room temperature. The reaction mixture was then heated at reflux for 48 hours. The solvent was removed in vacuo and the residue was extracted with diethyl ether (4 x 100 ml) and washed with aqueous sodium hydrogen sulfite. The organic solvent was removed in vacuo to yield the title compound as a brown oil (0.51 g, 92%).

$\nu_{\text{max}}$/cm$^{-1}$(neat) 2927s, 2855s, 1490s, 1450s, 1362m, 1087m, 733s.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 1.17 (16H, m, 3-H to 10-H), 1.48-1.56 (2H, m, 11-H), 1.58-1.66 (2H, m, 2-H), 2.97 (2H, $J$ 6.6 Hz, 12-H), 3.10 (2H, $t$, $J$ 5.5 Hz, 1-H), 7.11-7.23 (15H, m, 3 Ar).

$\delta_{\text{C}}$ (75 MHz; CDCl$_3$) 7.59 (C-12), 26.68, 28.93, 29.78, 29.81, 29.91, 29.99, 30.47, 30.90, 30.91, 33.99, 64.10 (C-1), 86.70 (C-1'), 127.17 (3 x [C-3' and C-7']), 128.05 (3 x [C-5']), 129.13 (3 x [C-4' and C-6']), 144.99 (3 x C-2').

$m/z$ (EI$^+$) 554 ($M^+$, 27%), 477 ($M^+$-Ph, 37), 243 (Ph$_3$C$,^+$, 100).

(Found: $M^+$, 554.2026. C$_{31}$H$_{39}$OI requires: $M^+$, 554.2046).
The reaction was carried out under anhydrous conditions. 1-Trityloxydodecan-12-ol (6.01 g, 13.53 mmol) (105) was dissolved in dichloromethane (20 ml) at 0 °C. Methane sulfonyl chloride (3.0 ml, 38.76 mmol) was added dropwise to the mixture. Triethylamine (10 ml, 71.75 mmol) was slowly added after 10 minutes while the reaction was maintained at 0 °C. The reaction was stirred for 18 hours at room temperature. The mixture was washed with water. The organic layer was collected and the aqueous layers were washed with further aliquots of dichloromethane (3 x 100 ml). The organic layer was extracted and removed under vacuo. The resulting crude oil was purified by flash chromatography-dichloromethane:hexane (1:1) to yield the title compound as a colourless oil (4.12 g, 58%).

$\nu_{\text{max}}$/cm$^{-1}$ (neat) 3055w, 2929w, 1712m, 1650w, 1545w, 1490m, 1358m.

$\delta$H (300 MHz; CDCl$_3$) 1.18 (16H, m, 3-H to 10-H), 1.49-1.71 (2H, m, 2-H and 11-H), 2.89 (3H, s, SO$_2$CH$_3$), 2.97 (2H, t, $J$ 6.6 Hz, 12-H), 4.13 (2H, t, $J$ 6.6 Hz, 1-H), 7.11-7.38 (15H, m, 3 Ar).

$\delta$C (75 MHz; CDCl$_3$) 14.48, 23.03, 25.82, 26.67, 29.42, 29.55, 29.80, 30.46, 31.97, 37.77, 64.09, 70.54 (C-1), 86.70 (C-1’), 127.17 (3 x [C-3’ and C-7’]), 128.33 (3 x [C-5’]), 129.12 (3 x [C-4’ and C-6’]), 144.99 (3 x C-2’).

$\text{m/z}$ (APCI$^+$) 545 ($M^+ + Na$, 27%), 279 ($M^+ - $Ph$_3$C, 0.5), 243 ($$Ph$_3$C$, 100).

(Found: $M^+ + Na$, 545.2720. C$_{32}$H$_{42}$O$_4$SNa requires: $M^+ + Na$, 545.2702).
The reaction was carried out under anhydrous conditions. To a suspension of hydroquinidine (0.50 g, 1.54 mmol) in THF (100 ml), sodium hydride (60% wt in mineral oil) (0.09 g, 2.32 mmol), was slowly added in small portions at 0 °C. The resulting solution was warmed to ambient temperature and allowed to stir for 45 minutes. Methane sulfonic acid 1-trityloxy-dodecyl ester (108) (0.81 g, 1.54 mmol) was added and the solution heated at 80 °C for 18 hours.

The solution was diluted with dichloromethane (200 ml) and water (150 ml). The organic layer was removed and the aqueous layer extracted with dichloromethane (2 x 100 ml). The organic layer was dried over sodium sulfate which was filtered and removed in vacuo to afford the crude product. The product was purified via column chromatography (dichloromethane:methanol, 19:1) to afford the title compound as a light brown oil (0.40 g, 34%).

\( \nu_{\text{max}}/\text{cm}^{-1}(\text{neat}) \) 2928s, 2855m, 1679m, 1620m, 1508m, 1452m, 1228m, 1072m.

\( \delta_H (300 \text{ MHz}; \text{CDCl}_3) \) 0.86 (3H, t, J 7.3 Hz, 19-H), 1.18 (18H, m, 3'-H to 10'-H and 18-H), 1.49-1.84 (8H, m, 2'-H, 11'-H, 12-H, 16-H), 2.16-2.31 (1H, m), 2.97 (2H, t, J 6.6 Hz, 11'-H), 3.14-3.19 (5H, m), 3.56 (2H, t, J 6.5 Hz, 12'-H), 3.86-3.96 (2H, m, 10-H and 11-H), 4.03 (3H, s, OCH\(_3\)), 6.96-7.38 (18H, m, 3 Ar, 2-H, 5-H, 6-H), 7.94-7.97 (1H, d, J 9.2 Hz, 8-H), 8.67-8.68 (1H, m, 3-H).

\( \delta_C (75 \text{ MHz}; \text{CDCl}_3) \) 12.11 (C-19), 25.24 (C-18), 26.27, 26.68, 26.77, 29.89, 29.91, 29.99, 30.47, 30.51, 36.66 (some peaks superimposed), 50.03, 50.70, 57.18, 60.16, 64.10, 70.19, 101.43, 118.63, 122.95, 127.15, 127.28 (3 x [C-15']
and C-19'], 128.04, 128.13 (3 x [C-17'], 129.11 (3 x [C-16' to C-18'], 132.17, 147.64.

m/z (APCI⁺) 754 (MH⁺, 100%), 243 (Ph₂C⁺, 17).
(Found: M⁺, 753.5006, C₅₁H₅₅O₃N₂ requires: M⁺, 753.4995).
[α]D = +122 ° (c 0.5 in methanol, 25°C).

7.49 (10S, 11R)-(++)-O-12'-Hydroxydodecyl hydroquinidine (110).

(10S, 11R)-(++)-O-12'-Trityloxydodecyl hydroquinidine (109) (0.11 g, 0.14 mmol) was dissolved in a dichloromethane:methanol (50:50) mixture. 1M Hydrochloric acid (1.0 ml, 1.0 mmol) was added dropwise over a 10 minute period, and stirred for 1 hour. 1M Sodium hydrogen carbonate was added until the pH of the mixture went neutral. The solution was diluted with dichloromethane (200 ml) and water (150 ml). The organic layer was removed and the aqueous layer extracted with dichloromethane (2 x 100 ml). The organic layer was dried over sodium sulfate which was filtered and removed in vacuo to afford the crude product. The product was purified via column chromatography (dichloromethane:methanol, 19:1) to afford the title compound as a colourless oil (0.06 g, 86%).

υ_max/cm⁻¹ (neat) 3419m, 2925s, 2853m, 1650m, 1511m, 1458s.
δ_H (300 MHz; CDCl₃) 0.83 (3H, t, J 7.0 Hz, 19-H), 1.20-1.30 (18H, m, 3'-H to 10'-H and 18-H), 1.30-1.62 (6H, m, 11'-H, 12-H, 16-H), 2.82-3.29 (10H, m), 3.58 (2H, t, J 6.6 Hz, 12'-H), 3.87 (3H, s, OCH₃), 7.14-7.45 (6H, m, 2-H, 5-H and 6-H), 7.93-7.98 (1H, m, 8-H), 8.64-8.72 (1H, m, 3-H).
\(\delta_C\) (125 MHz; CDCl\(_3\)) 11.65 (C-19), 18.64 (C-18), 24.51, 24.87, 25.53, 26.22, 29.56, 29.64, 30.00, 35.89 (6 signals superimposed), 49.38, 50.21, 55.88, 59.81, 63.64, 67.92, 86.19, 118.54, 121.69, 126.71, 127.61, 131.44, 143.86, 144.49, 147.27 (C-3), 157.93 (C-7).

\(m/z\) (APCI\(^+\)) 511 (\(MH^+\), 100 %).

(Found: \(MH^+\), 511.3886. \(C_{32}H_{51}O_3N_2\) requires: \(MH^+\), 511.3900).

\([\alpha]_D^\circ = +115^\circ\) (c 0.5 in methanol, 25°C).

7.50 (10S,11R)-(+)\(-N\)-Methyl-\(O\)-12'-hydroxydodecyl hydroquinidinium iodide (111).

![Structure of (111)](image_url)

The reaction was carried out under anhydrous conditions. To (10S, 11R)-(+)\(-O\)-12'-Hydroxydodecyl hydroquinidine (110) (0.06 g, 0.12 mmol), iodomethane (0.20 ml, 3.21 mmol) was added. The mixture was stirred in 20 ml of dichloromethane at 25°C for 12 hours. The dichloromethane was removed in vacuo. The resulting crude oil consisted mainly of the product, however attempts to purify the compound proved to be very difficult. Compound (111) was subsequently characterised in its crude form as an orange oil (0.04 g, 65%).

\(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3418 m, 2925 m, 1650 m, 1590 w, 1510 m, 1458 m, 1058 m, 823 m, 751 m, 693 m, 564 m, 461 m, \(\delta_H\) (300 MHz; CDCl\(_3\)) 0.89 (3H, t, \(J\) 7.2 Hz, 19-H), 1.21-1.36 (18H, m, 3'-H to 10'-H, 18-H), 1.47-1.76 (6H, m, 11'-H, 12-H and 16-H), 1.93-1.97 (2H, m, 13-H, 14-H), 3.48-3.56 (6H, m, 11-H, 1'-H and \(N^+\)-CH\(_3\)), 3.91-4.08 (10H, m, 10-H, 15-H, 17-H, 12'-H and OCH\(_3\)), 7.31-7.65 (3H, m, 2-H, 5-H, 6-H), 7.99-8.02 (1H, m, 8-H), 8.82-8.84 (1H, m, 3-H).
m/z (APCI⁺) 526 (MH⁺-I, 100%).
(Found: M⁺-I, 525.4078. C_{33}H_{55}O_{3}N_{2} requires: M⁺-I, 525.4056).
[α]_D = +102 ° (c 0.5, in methanol at 25 °C).

7.51 (10S, 11R)-(+-O-(12'-Acryloyloxy dodecyl) hydroquinidine (112).

Method A

The reaction was carried out under anhydrous conditions. To a suspension of hydroquinidine (1.03 g, 3.15 mmol) in dry DMF (20 ml), sodium hydride (60% wt in mineral oil) (0.08 g, 3.46 mmol) was slowly added in small portions at 0 °C. The resulting solution was warmed to ambient temperature and allowed to stir for 45 minutes. 12-Bromo dodecyl acrylate (101) (1.01 g, 3.19 mmol) was added and the solution heated at 80 °C for 18 hours.

The solution was diluted with dichloromethane (200 ml) and water (150 ml). The organic layer was removed and the aqueous layer extracted with dichloromethane (2 x 100 ml). The organic layer was combined and washed with saturated lithium chloride solution (2 x 100 ml) to remove any excess DMF. The organic layer was dried over sodium sulfate which was filtered and removed in vacuo to afford the crude product. The product was purified via column chromatography (dichloromethane:methanol, 19:1) to afford the title compound as a colourless oil (0.21 g, 12%).
Method B

The reaction was carried out under anhydrous conditions. (10S, 11R)-(+)-O-12'-Hydroxydodecyl hydroquinidine (110) (0.33 g, 0.65 mmol) was dissolved in dichloromethane at room temperature. Acrylic acid (0.04 g, 0.65 mmol) followed by EDCI (0.12 g, 0.65 mmol) and DMAP (0.008 g, 0.06 mmol) were added slowly. The mixture was stirred for 18 hours at 25 °C before being quenched by water. The crude product was extracted from the aqueous layer using dichloromethane (3 x 100 ml). The combined organic layer was removed under vacuo to afford the crude product which was purified by flash chromatography (dichloromethane:methanol, 19:1) to afford the title compound as a colourless oil (0.32 g, 18%).

νmax/cm⁻¹(neat) 2958s, 2840s, 1679m, 1576m, 1514s, 1460s, 1427s.

δH (300 MHz; CDCl₃) 0.89 (3H, t, J 7.3 Hz, 19-H), 1.21-1.45 (18H, m, 3'-H to 10'-H, 18-H), 1.45-1.75 (6H, m, 11'-H, 12-H, 13-H, 14-H, 16-H), 2.46-2.56 (2H, m), 3.19-3.41 (6H, m), 3.54-3.59 (2H, t, J 6.6 Hz, 1'-H), 3.89-4.10 (6H, m, 12'-H, OCH₃, 10-H), 5.71-5.75 (1H, dd, J 10.4 Hz and 1.1 Hz, Hₜ), 6.00-6.10 (1H, dd, J 15.8 Hz and 10.4 Hz, Hₜ), 6.23-6.34 (1H, dd, J 15.8 and 1.1 Hz, Hₜ), 7.20-7.39 (2H, m, 2-H, 6-H), 7.55 (1H, m, 5-H), 7.92-7.97 (1H, m, 8-H), 8.64-8.69 (1H, m, 3-H).

δC (125 MHz; CDCl₃) 11.89 (C-19), 18.82 (C-18), 24.96, 25.88, 26.69, 29.46, 29.59, 29.78, 29.92, 30.44, 33.20, 35.82 (3 signals superimposed), 49.59, 50.24, 57.76, 60.11, 63.25, 64.99, 70.21, 101.20, 118.37, 123.47, 125.78, 127.28, 129.05, 130.67, 132.09, 139.54, 142.14, 147.38 (C-3), 159.40 (C-7), 166.67 (C=O).

m/z (APCI⁺) 565 (MH⁺, 100%).


[α]D = +110 ° (c 0.5, in methanol at 25 °C).
7.52 (10S,11R)-(+)–N-Methyl-O-12’–acyloyloxy dodecyl hydroquinidinium iodide (113).

To (10S,11R)-(+)–O-Acryloyloxy dodecyl hydroquinidine (112) (0.20 g, 0.35 mmol), iodomethane (0.20 ml, 3.21 mmol) was added. The mixture was stirred in 20 ml of dichloromethane at 25 °C for 12 hours under nitrogen. The solvent mixture was removed in vacuo. The resulting crude oil was difficult to isolate and was subsequently carried on to the next step without further purification (0.15 g, 73%).

$\nu_{\text{max}}/\text{cm}^{-1}(\text{neat})$ 2958m, 2840m, 1678s, 1576s, 1514s, 1460s, 1252s, 1109s, 1025s.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 0.76-0.81 (3H, m, 19-H), 1.19 (18H, m, 3’-H to 10’-H, 18-H), 1.51-1.59 (4H, m), 1.91-2.10 (4H, m), 2.48-2.57 (2H, m), 2.95-3.33 (8H, m), 3.56-3.74 (6H, m, 12’-H, OCH$_3$, 10-H), 5.60-5.83 (1H, m, H$_b$), 6.00-6.09 (1H, m, H$_c$), 6.21-6.40 (1H, m, H$_a$), 7.14-7.38 (2H, m, 5-H, 6-H), 7.35-7.38 (1H, m, 8-H), 7.98-8.00 (1H, m, 3-H).

$m/z$ (APCI$^+$) 580 (MH$^+$-I, 5%).

$[\alpha]_D = +105^\circ$ (c 0.5, in methanol at 25 °C).
Polymerisation of (10S)-(+)\textendash O\textendash 12\textendash Acryloyloxy dodecyl hydroquinidine (114).

(10S, 11R)-(+)\textendash O\textendash 12\textendash Acryloyloxy dodecyl hydroquinidine (112) (0.31 g, 0.56 mmol) was dissolved in acetonitrile (30 ml) and placed in a sealed tube. AIBN initiator (0.01 g, 0.06 mmol) was added to the mixture and heated at 80 °C for 18 hours. The resulting solution was cooled and removed in vacuo. The resulting red oil was purified by flash chromatography using pure methanol (R_f 0.1 in methanol) to leave a mixture of polymers and polymer fragments (0.25 g).

δ_H (300 MHz; CDCl_3) 0.81-1.94 (multiple peaks observed), 7.12-7.36 (trace presence of aromatic signals).

m/z (APCI\textsuperscript{+}) multiple polymers ranging between 1155-1988.
7.54 Polymerisation of (10S)-(+-)-N-Methyl-O-12'-acryloyloxy dodecyl hydroquinidinium iodide (115).

(10S,11R)-(+-)-N-Methyl-O-12'-acryloyloxy dodecyl hydroquinidinium iodide (113) (0.15 g, 0.26 mmol) was dissolved in acetonitrile (30 ml) and placed in a sealed tube. AIBN initiator (0.01 g, 0.06 mmol) was added to the mixture and heated at 80 °C for 18 hours. The resulting solution was cooled and removed in vacuo. The resulting red oil was purified by flash chromatography using pure methanol (Rf 0.50 in methanol) to leave a mixture of polymers and polymer fragments (0.10 g).

δH (300 MHz, CDCl3) 1.19-1.93 (multiple peaks observed), 7.22-7.47 (trace presence of aromatic signals).

m/z (APCI⁺) multiple polymers up to 913.
7.55 1-phenylpropan-1-ol (55).

\[
\begin{array}{c}
\text{OH} \\
\text{3} \\
\text{2} \\
\text{1} \\
\text{4'} \\
\text{5'} \\
\text{6'} \\
\end{array}
\]

The reaction was carried out under anhydrous conditions. Surfactant (70) (28.6 mg, 0.06 mmol) was dissolved in dry hexane (12 ml) and stirred at 0 °C prior to the addition of reagent grade redistilled benzaldehyde (0.12 ml, 1.18 mmol). The mixture was stirred for a further 10 minutes before the dropwise addition of diethyl zinc (1.0 M in hexane; 2.55 ml, 2.55 mmol). The reaction was stirred for a further 48 hours at 25 °C. The reaction was quenched by the addition of 1.5 M hydrochloric acid (10 ml). The organic layer was separated and the aqueous layer was extracted using diethyl ether (2 x 15 ml) and dried over sodium sulfate. The product was removed in vacuo and the resulting oil purified via flash chromatography (hexane : diethyl ether, 2:1) to yield the title product as a clear oil (0.151 g, 95%).

\[\begin{align*}
\nu_{\text{max/cm}^{-1}(\text{neat})} &= 3386\text{m}, 2963\text{m}, 1453\text{m}, 1261\text{w}, 1092\text{m}. \\
\delta_{\text{H}} (300 \text{ MHz; CDCl}_3) &= 0.83 (3\text{H, t, } J = 7.4 \text{ Hz, } 3\text{-H}), 1.71 (3\text{H, m, } 2\text{-H and OH}), 4.53 (1\text{H, t, } J = 6.7 \text{ Hz, } 1\text{-H}), 7.26 (5\text{H, m, } 2'\text{-H to } 6'\text{-H}). \\
\delta_{\text{C}} (75 \text{ MHz; CDCl}_3) &= 10.57 (\text{C-3}), 32.30 (\text{C-2}), 76.44 (\text{C-1}), 126.37 (\text{C-4'}), 127.92 (\text{C-3' and C-5'}), 128.82 (\text{C-2' and C-6'}), 144.97 (\text{C-1'}). \\
m/z (\text{APCI}^+) &= 135 (M^+\text{-H, } 19\%), 119 (M^+\text{-OH, } 35). \\
(\text{Found: } MH^+, 137.0955. \text{ C}_9\text{H}_{13}\text{O requires: } MH^+, 137.0966). \\
\end{align*}\]

Chiral HPLC: a chiral cell OD column was used, solvent - 2% iso-propanol in hexane, 1.0 ml/min, retention time R-isomer 9.5 min, S-isomer 14.2 min. Waters 486 absorbance detector was used, set at wavelength 254 nm.
7.56 1-(4'-Methoxyphenyl)-propan-1-ol (117).

\[
\begin{align*}
\text{MeO} & \quad \text{hexane} \quad \text{surfactant} \\
\text{surfactant} & \quad \text{48 hr, 25 °C} \\
\text{MeO} & \quad \text{2-H, 2-H} \\
\end{align*}
\]

The reaction was carried out under anhydrous conditions. Surfactant (70) (28.6 mg, 0.06 mmol) was dissolved in dry hexane (12 ml) and stirred at 0 °C prior to the addition of \( p \)-anisaldehyde (0.14 ml, 1.15 mmol). The mixture was stirred for a further 10 minutes before the dropwise addition of diethyl zinc (1.0 M in hexane; 2.55 ml, 2.55 mmol). The reaction was stirred for a further 48 hours at 25 °C. The reaction was quenched by the addition of 1.5 M hydrochloric acid (10 ml). The organic layer was separated and the aqueous layer was extracted using diethyl ether (2 x 15 ml) and dried over sodium sulfate. The product was removed in vacuo and the resulting oil purified via flash chromatography (dichloromethane:methanol, 40:1) to yield the title product as a clear oil together with traces of 1-(4'-methoxyphenyl) alcohol (0.19 g, 60%).

\( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3379s, 3029s, 2934s, 1708w, 1604w, 1456s, 1331m, 1201m, 1045w.

\( \delta_{\text{H}} \) (300 MHz; CDC\( _{3} \)) 0.83 (3H, t, \( J \) 7.4 Hz, 3-H), 1.77 (2H, m, 2-H), 3.68 (3H, s, OCH\( _{3} \)), 4.49 ( 1H, t, \( J \) 6.6 Hz, 1-H), 6.84 (2H, d, \( J \) 9.7 Hz, Ph), 7.24 (2H, d, \( J \) 9.7 Hz, Ph).

\( \delta_{\text{C}} \) (75 MHz; CDC\( _{3} \)) 9.16 (C-3), 30.78 (C-2), 54.29 (OCH\( _{3} \)), 74.66 (C-1), 112.82, 113.00 (C-3' and C-5'), 126.19, 127.62 (C-2' and C-6'), 135.80 (C-1'), 158.06, 158.28 (C-4').

\( m/z \) (EI') 167\( (M^+) \), 109 (\( MH^+\)-C\(_{3}\)H\(_{2}\)O, 12), 107 (\( M^+\)-C\(_{3}\)H\(_{2}\)O, 100).

(Found: \( M^+\), 167.1064. C\(_{10}\)H\(_{14}\)O\(_{2}\) requires: \( M^+\), 167.1072).
Chiral HPLC: a chiral cell OD column was used, solvent- 2.5% iso-propanol in hexane, 1.0 ml/min, retention time R-isomer 17.5 min, S-isomer 18.9 min. Waters 486 absorbance detector was used, set at wavelength 254 nm.

7.57 4-n-Hexyloxy benzaldehyde (118).\textsuperscript{167}

\begin{center}
\includegraphics[width=0.5\textwidth]{118.png}
\end{center}

The reaction was carried out under anhydrous conditions. 4-hydroxy benzaldehyde (1.21 g, 9.90 mmol) and sodium hydride (60% dispersion in mineral oil) (0.48 g, 12.1 mmol) were stirred together in dry DMF at room temperature before gradual addition of bromohexane (1.50 ml, 10.70 mmol). The mixture was heated to 80°C for 3 hours. The mixture was poured into ice and the product extracted with ethyl acetate (3 x 100 ml) and the combined organic extracts washed with water (3 x 50 ml). The organic extracts were dried with sodium sulfate and the solvent removed in vacuo. The crude oil was purified by flash-chromatography, petroleum spirit:ethyl acetate (9:1) to afford the title product as a clear oil (0.45 g, 22%).

\begin{align*}
\nu_{\text{max}}/\text{cm}^{-1} (\text{neat}) & : 2928s, 2734m, 1696m, 1603s, 1468m, 1253m, 1159m. \\
\delta_{\text{H}} (300 \text{ MHz; } \text{CDCl}_3) & : 0.82 (3\text{H, m, 10-H}), 1.19-1.72 (8\text{H, m, 6-H to 9-H}), 3.97 (2\text{H, t, } J 6.5 \text{ Hz, 5-H}), 6.94 (2\text{H, d, } J 8.7 \text{ Hz, 3-H}), 7.74 (2\text{H, d, } J 8.7 \text{ Hz, 2-H}), 9.85 (1\text{H, s, CHO}). \\
\delta_{\text{C}} (75 \text{ MHz; } \text{CDCl}_3) & : 14.35 (\text{C-10}), 22.94 (\text{C-9}), 26.01 (\text{C-8}), 29.42 (\text{C-7}), 31.89 (\text{C-6}), 68.84 (\text{C-5}), 114.61 \text{ and } 115.16 (\text{C-3}), 130.22 (\text{C-2}), 132.35 (\text{C-1}), 164.68 (\text{C-4}), 190.80 (\text{C=O}). \\
m/z (\text{FAB}) & : 207 (M^+, 100\%), 123 (M^+ - C_6H_{13}, 34). \\
\text{(Found: } M^+, 207.1390. C_{13}H_{15}O_2 \text{ requires: } M, 207.1385). 
\end{align*}
7.58 1-(4'-n Hexyloxyphenyl)-propan-1-ol (119).

The reaction was carried out under anhydrous conditions. Surfactant (70) (25.3 mg, 0.050 mmol) was dissolved in dry hexane (12 ml) and stirred at 0 °C prior to the addition of 4-n-hexyloxy benzaldehyde (0.15 ml, 1.13 mmol). The mixture was stirred for a further 10 minutes before the dropwise addition of diethyl zinc (1.0 M in hexane; 2.55 ml, 2.55 mmol). The reaction was stirred for 48 hours at 25 °C. The reaction was quenched by the addition of 1.5 M hydrochloric acid (10 ml). The organic layer was separated and the aqueous layer was extracted using diethyl ether (2 x 15 ml) and dried over sodium sulfate. The product was removed in vacuo and the resulting oil purified via flash chromatography, petroleum spirit (60 °C - 80 °C):ethyl acetate (2:1), to yield the title product as a clear oil (0.114 g, 42%).

$\nu_{\text{max}}$/cm$^{-1}$(neat) 3406br, 2961m, 1612w, 1512w.

$\delta_{H}$ (300 MHz; CDCl$_3$) 0.83 (6H, m, 3-H and 10-H), 1.18-1.73 (10H, m, (CH)$_2$ and 2-H), 3.89 (2H, t, $J$ 6.6 Hz, OCH$_2$(CH)$_2$(CH)$_3$), 4.55 (2H, m, 1-H and 1-OH), 6.84 (2H, d, $J$ 8.7 Hz, 2 x 2'-H), 7.19 (2H, d, $J$ 8.7 Hz, 2 x 3'-H),

$\delta_{C}$ (75 MHz; CDCl$_3$) 13.02, 21.58, 24.69, 28.20, 30.56 (4 signals superimposed), 67.04 (C-5'), 75.57 (C-1), 113.53 (C-6'), 127.62 (C-2'), 131.83 (C-1'), 157.78 (C-4').

$m/z$ (APCI$^+$) 236 ($M^+$, 1%), 207 ($M^+$-C$_2$H$_5$, 15).

(Found: $M^+$, 236.1778. C$_{15}$H$_{24}$O$_2$ requires: $M$, 236.1776).
The reaction was carried out under anhydrous conditions. 1-(4-n-hexyloxyphenyl)-propan-1-ol (119) (0.08 g, 0.32 mmol) was dissolved in dichloromethane. (R)-(−)-α-Methoxy-α-(trifluoromethyl) phenyl acetyl chloride (0.11 g, 0.43 mmol) was added to the mixture followed by pyridine (0.08 ml, 0.99 mmol). The mixture was stirred for 18 hours. Water (1 ml) and ether (10 ml) were added to quench the reaction. The organic and aqueous layers were separated and the organic phase was washed with 1 M hydrochloric acid (10 ml) and saturated sodium hydrogen carbonate. The organic phase was dried using sodium sulfate and the solvent was filtered and removed under vacuo to yield the title compound as a colourless oil (0.07 g, 48%).

\[ \delta^1H (300 MHz; CDCl_3) 0.72-0.86 (6H, m, 1'-H and 13'-H), 1.16-1.97 (10H, m, 2'-H and 9'-H to 12'-H), 3.36-3.50 (5H, m, OCH_3 and 8'-H), 3.84-4.04 (1H, m, 5'-H), 5.68-5.77 (1H, m, 2-H), 7.05-7.50 (9H, m, 2 x 5'-H, 2 x 6'-H and Ar). \]

\[ \delta^{19}F (282 MHz; CDCl_3) -71.79, -72.08 \text{ (isomers)} \]

**7.60 Octan 3-ol (121).**

\[ \text{hexane surfactant} \]

\[ \text{surfactant} \]

\[ \text{48 hr, 25 °C} \]

(121)
The reaction was carried out under anhydrous conditions. Surfactant (70) (25.2 mg, 0.034 mmol) was dissolved in dry hexane (12 ml) and stirred at 0 °C prior to the addition of hexanal (0.14 ml, 1.18 mmol). The mixture was stirred for a further 10 minutes before the dropwise addition of diethyl zinc (1.0 M in hexane; 2.55 ml, 2.55 mmol). The reaction was stirred for 48 hours at 25 °C. The reaction was quenched with 1.5 M hydrochloric acid (10 ml). The organic layer was separated, and the aqueous layer was extracted using diethyl ether (2 x 15 ml) and dried over sodium sulfate. The product was removed in vacuo and the resulting oil purified via flash chromatography, (hexane : diethyl ether, 2:1) to yield the title product as an oil (9 mg, 6%).

\[ \text{v}_{\text{max/cm}^{-1}}(\text{neat}) = 3356 \text{s}, 2925 \text{s}, 1459 \text{m}. \]

\[ \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) = 0.88-0.97 (6\text{H, m, 1-H and 8-H}), 1.30-1.49 (11\text{H, m, 2-H, 4-H, 5-H, 6-H, 7-H, OH}), 3.77 (1\text{H, m, 3-H}). \]

\[ \delta_{\text{C}} (75 \text{ MHz; CDCl}_3) = 10.27 (\text{C-8}), 14.44 (\text{C-1}), 23.05 (\text{C-7}), 25.74 (\text{C-2}), 30.51 (\text{C-6}), 32.33 (\text{C-4}), 37.30 (\text{C-2}), 73.70 (\text{C-3}). \]

\[ m/z (\text{FAB}^+) = 131 (\text{MH}^+, 3\%). \]

7.61 Hexyn-2-al (122).

The reaction was carried out under anhydrous conditions. Hexyn-2-ol (2.00 g, 0.02 mol) was stirred in dichloromethane (20 ml), prior to the addition of manganese oxide (10.01 g, 0.12 mol). The mixture was stirred for 72 hours. The manganese oxide was filtered and hexyn-2-al (122) was distilled from the reaction mixture at 55 °C under vacuum (20 mm Hg) to generate the title compound (1.82 g, 93%).

\[ \text{v}_{\text{max/cm}^{-1}}(\text{neat}) = 2969 \text{s}, 2238 \text{s}, 1686 \text{s}. \]
δ_H (300 MHz; CDCl_3) 0.96 (3H, t, J 7.3 Hz, 6-H), 1.53 (2H, m, 5-H), 2.28 (2H, t, J 7.3 Hz, 4-H), 9.43 (1H, s, 1-H).
δ_C (75 MHz; CDCl_3) 13.76 (C-6), 21.39 (C-5), 53.77 (C-4), 82.19 (C-2), 99.42 (C-3), 177.49 (C-1).

m/z (FAB') 95 (M⁺-H, 100%), 12 (C₃H₇⁺, 43).

7.62 3-[Bis(ethoxycarbonyl)methyl] cyclopentanone (123).

\[
\begin{align*}
\text{\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}_2\text{OH} + \text{Cyclopentenone}} & \xrightarrow{\text{H}_2\text{O, Triton B reflux 48 hours.}} \\
\text{O} & \text{O} & \text{O}
\end{align*}
\]

Diethyl malonate (0.38 ml, 2.50 mmol), cyclopentenone (0.25 ml, 2.50 mmol) and aqueous 4.0 M Triton B (0.12 ml, 0.50 mmol) were stirred together with surfactant (70) (0.06 mM) in distilled water (25 ml) and heated at reflux for 48 hours. After this time, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by flash chromatography (petroleum spirit 40-60:ethyl acetate, 2:1) to afford the desired product as a colourless oil (0.082 g, 14%).

ν max/cm⁻¹ (nujol) 2882s, 1736s, 1463w, 1372w.
δ_H (300 MHz; CDCl_3) 1.24 (6H, m, 9-H), 1.59-2.00 (2H, m, 4-H), 2.17-2.40 (4H, m, 2-H and 5-H), 2.78 (1H, m, 3-H), 3.25 (1H, d, J 9.4 Hz, 6-H), 4.10 (4H, m, 8-H).
δ_C (75 MHz; CDCl_3) 14.48, 27.91, 36.73, 38.63, and 43.33 (C-2), 56.94 (C-6), 62.05 (2 x C-8), 168.48 and 168.56 (2 x C-7), 218 (C-1).

m/z (FAB') 243 (M⁺, 19%), 161 (M⁺-COCH₂CH₂CHCH₂, 100).

Chiral HPLC: a chiral cell OD column was used, solvent- 5% iso-propanol in hexane, 1.0 ml/min, retention time R-isomer 20.9 min, S-isomer 22.3 min. Waters 486 absorbance detector was used, set at wavelength 222 nm.
7.63  3-[Bis(methoxycarbonyl)methyl] cyclopentanone (124).

\[
\begin{align*}
\text{H}_2\text{O}, \text{Triton B} & \text{ reflux 48 hours.} \\
\end{align*}
\]

Dimethyl malonate (0.29 ml, 2.50 mmol), cyclopentenone (0.25 ml, 2.50 mmol) and aqueous 4.0 M Triton B (0.60 ml, 0.25 mmol) were stirred together with surfactant (70) (0.06 mM) in distilled water (25 ml) and heated at reflux for 48 hours. After this time, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried over sodium sulphate and the solvent removed in \textit{vacuo}. The crude product was purified by flash chromatography (petroleum spirit 40-60:ethyl acetate, 1:1) to afford the desired product as an oil (0.12 g, 23%).

\[
\begin{align*}
\text{v}_{\text{max/cm}^{-1}(\text{neat})} & : 3006w, 2959s, 1752s, 1439m, 1150m. \\
\delta_{\text{H}} & (300 \text{ MHz; CDCl}_3) 1.55 (2\text{H, m, 4-H}), 1.61-2.40 (4\text{H, m, 2-H and 5-H}), 2.78 (1\text{H, m, 3-H}), 3.30 (1\text{H, d, J 9.4 Hz, 6-H}), 3.71 (6\text{H, d, J 6.8 Hz, 8-H}). \\
\delta_{\text{C}} & (125 \text{ MHz; CDCl}_3) 27.46, 36.37, 38.17, 42.86, 52.65 (\text{C-6}), 56.07 (2 \text{ x C-8}), 168.43 \text{ and } 168.51 (2 \text{ x C-7}), 216.97 (\text{C-1}). \\
m/\text{z} \text{ (FAB^+)} & 215 (\text{MH}^+, 18\%), 133 (\text{M}^+-\text{COCH}_2\text{CH}_2\text{CHCH}_2, 81). \\
\text{(Found: M}^+\text{+Na, 237.0751. C}_{10}\text{H}_{14}\text{O}_3\text{Na requires: M}^+\text{+Na, 237.0739).}
\end{align*}
\]

Chiral HPLC: a chiral cell OD column was used, solvent- 5% iso-propanol in hexane, 1.0 ml/min, retention time \textit{R}-isomer 19.1 min, \textit{S}-isomer 20.4 min. Waters 486 absorbance detector was used, set at wavelength 222 nm.
7.64 3-[Bis(methoxycarbonyl)methyl]-2-pentyl-2-cyclopentan-1-one (125).

Dimethyl malonate (0.29 ml, 2.50 mmol), 2-pentyl-2-cyclopent-1-one (0.42 ml, 2.54 mmol), and potassium carbonate (0.34 g, 2.47 mmol) were stirred together with surfactant 93 (0.08 g, 0.15 mmol) in distilled water (25 ml) at room temperature for 48 hours. The reaction mixture was extracted with diethyl ether (3 x 20 ml). The organic layer was washed with aqueous hydrochloric acid (0.1 M) (2 x 5 ml), 5 ml of water and brine (2 x 5 ml). The combined organic extracts were dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by flash chromatography (dichloromethane:hexane, 2:1) to afford the desired product as a colourless oil (0.65 g, 90%).

$\nu_{\text{max}}$ cm$^{-1}$ (neat) 2957w, 2254m, 1736s, 1711s, 1459w, 1263m, 1224m, 910s

$\delta$H (300 MHz; CDCl$_3$) 0.82 (3H, t, $J$ 3.0 Hz, 5'-H), 1.14-1.41 (9H, m, 2-H to 4'-H), 1.98-2.57 (4H, m, 4-H and 5-H), 2.58-2.60 (1H, m, 3-H), 3.43 (1H, d, $J$ 7.3 Hz, 6-H), 3.65 (6H, s, 8-H).

$\delta$C (125 MHz; CDCl$_3$) 14.33, 22.71, 25.18, 26.99, 28.86, 32.10, 36.66, 41.46, 52.42, 52.79, 54.90, 168.77 and 169.11 (2 x C-7), 218.70 (C-1).

$m/z$ (FAB$^+$) 283 ($M^+$, 20%)


Chiral HPLC: a chiral cell OD column was used, solvent- 1% iso-propanol in hexane, 0.55 ml/min, retention times 25.98 and 27.23 min. Waters 486 absorbance detector was used, set at wavelength 222 nm.
**7.65 3-[Bis(isopropylxoycarbonyl)methyl] cyclopentanone (126).**

\[
\text{Diisopropyl malonate (0.48 ml, 2.50 mmol), cyclopentenone (0.25 ml, 2.50 mmol) and aqueous 4.0 M Triton B (0.60 ml, 0.25 mmol) were stirred together with surfactant (70) (0.06 mM) in distilled water (25 ml) and heated at reflux for 48 hours. After this time, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by flash chromatography (petroleum spirit 40-60:ethyl acetate 1:1), to afford the desired product as a colourless oil (0.28 g, 42%).}
\]

\[
\nu_{\text{max}}/\text{cm}^{-1} (\text{neat}) 2884 \text{m}, \ 2940 \text{w}, \ 1723 \text{s}, \ 1470 \text{m}, \ 1374 \text{w}.
\]

\[
\delta_{\text{H}} (300 \text{ MHz; CDCl}_3) \ 1.19 (12\text{H, m, 9-H}), \ 1.59-1.90 (2\text{H, m, 4-H}), \ 1.94-2.47 (4\text{H, m, 2-H and 5-H}), \ 2.75-2.80 (1\text{H, m, 3-H}), \ 3.21 (1\text{H, d, } J_9 \text{ 9.3 Hz, 6-H}), \ 4.99 (2\text{H, m, 8-H}).
\]

\[
\delta_{\text{C}} (75 \text{ MHz; CDCl}_3) 21.91, 27.83, 36.57, 38.53, 43.24, 57.35 (\text{C-6}), 69.53 (2 \times \text{C-8}), 167.96 \text{ and } 168.04 (2 \times \text{C-7}), 218 (\text{C-1}).
\]

\[
m/z (\text{FAB}^+) 271 (M^+ , 37\%), 189 (M^+ -\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3, 39), 83 (\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}^+ , 100).
\]

(Found: \(M^+ , 271.1537. \text{C}_{14}\text{H}_{23}\text{O}_5 \text{ requires: } M^+, 271.1545).\)

Chiral HPLC: a chiral cell OD column was used, solvent-3 % iso-propanol in hexane, 1.0 ml/min, retention time \(R\)-isomer 12.9 min, \(S\)-isomer 14.4 min.

Waters 486 absorbance detector was used, set at wavelength 222 nm.
7.66 3-[Bis(benzyloxy carbonyl) methyl] cyclopentanone (127).

Dibenzyl malonate (0.62 ml, 2.50 mmol), cyclopentenone (0.25 ml, 2.50 mmol) and aqueous 4.0 M Triton B (0.60 ml, 0.25 mmol) were stirred together with surfactant (70) (0.06 mM) in distilled water (25 ml) and heated at reflux for 48 hours. After this time, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by flash chromatography (petroleum spirit 40-60:ethyl acetate, 1:1) to afford the desired product as a colourless oil (0.09 g, 10%).

$\nu_{\text{max/cm}^{-1}}$(neat) 3034s, 2953w, 1760s, 1499s, 1456s, 1437w

$\delta_H$ (300 MHz; CDCl$_3$) 1.27 (2H, m, 4-H), 1.88 to 2.16 (4H, m, 2-H and 5-H), 2.76-2.79 (1H, m, 3-H), 3.38 (1H, d, $J_{1.10}$ Hz, 6-H), 5.08 (4H, m, 8-H), 7.23 (10H, m, Ph).

$\delta_C$ (75 MHz; CDCl$_3$) 28.33, 37.28, 39.08, 43.70, 57.36 (C-6), 68.30 (2 x C-8), 129.20, 129.46, 129.54, 135.90 and 135.96 (2 x C-1'), 168.72 and 168.64 (2 x C-7), 218 (C-1).

$m/z$ (FAB$^+$) 367 ($M^+$, 7 %), 285 ($MH^+$-CH$_2$CH$_2$COCH$_2$CH, 1).

(Found: $MH^+$, 367.1540. C$_{22}$H$_{23}$O$_5$ requires: $MH^+$, 367.1545).

Chiral HPLC: a chiral cell OD column was used, solvent- 5 % iso-propanol in hexane, 1.0 ml/min, retention time R-isomer 22.7 min, S-isomer 24.2 min. Waters 486 absorbance detector was used, set at wavelength 254 nm.
7.67 2-phenyl-2-(2-oxobutyl) cyclohexanone (128).

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{NaOH (50 %) / Toluene} & \quad \text{Ph} \\
\text{Surfactant (70) (0.04 g, 0.09 mmol) and 50 % aqueous sodium hydroxide} & \quad \text{Ph} \\
(3.75 ml) were added to a solution of the corresponding Michael donor (2-phenyl} & \quad \text{Ph} \\
cyclohexanone) (0.26 g, 1.50 mmol) in 11 ml of toluene. The mixture was stirred} & \quad \text{Ph} \\
at 20 ^\circ C and a solution of the Michael acceptor (methyl vinyl ketone) (0.12 ml,} & \quad \text{Ph} \\
1.50 mmol) in 4 ml of toluene was added dropwise over 30 minutes. The} & \quad \text{Ph} \\
reaction was stirred for 24 hours. The organic layer was separated and washed} & \quad \text{Ph} \\
with 10 ml of 1M HCl. The toluene layer was dried over magnesium sulfate,} & \quad \text{Ph} \\
filtered and the solvent removed in \textit{vacuo}. The crude product was purified by} & \quad \text{Ph} \\
flash chromatography (pure dichloromethane) to yield the \textit{title compound} as a} & \quad \text{Ph} \\
colourless oil (0.20 g, 55%).
\end{align*}
\]

\[\nu_{\text{max}}/\text{cm}^{-1} (\text{neat}) \quad 2930s, 2857w, 1698s, 1500m, 1449m, 1311w, 1125m.\]
\[\delta_\text{H} (300 \text{ MHz; CDCl}_3) \quad 1.18-2.60 (12H, m, 3'-H, 4'-H, 3-H to 6-H), 1.92 (3H, s,} & \quad \text{Ph} \\
1'-H), \quad 7.04-7.31 (5H, m, Ph).\]
\[\delta_\text{C} (75 \text{ MHz; CDCl}_3) \quad 28.69 (C-3'), 30.06 (C-4'), 34.44, 36.49, 39.29 (C-3), 40.59} & \quad \text{Ph} \\
(C-6), \quad 53.78, 57.25, 127.31, 127.385, 129.34 (\text{Ph}), 140.76 (\text{Ipso-Ph}), 208.97 (C-2')} & \quad \text{Ph} \\
213.67 (C-1).\]

\[m/z (\text{FAB}^+) \quad 245 (MH^+, 16%), \quad 175 (MH^+-\text{CH}_3\text{COCH}_2\text{CH}_3, 11).\]
(Found: \(MH^+, 245.1535. \quad \text{C}_{16}\text{H}_{21}\text{O}_2 \text{requires: } MH^+, 245.1542).\]

Chiral HPLC: a chiral cell OD column was used, solvent- 2 % iso-propanol in hexane, 0.50 ml/min, retention time \(R\)-isomer 26.5 min, \(S\)-isomer 28.1 min.
Waters 486 absorbance detector was used, set at wavelength 254 nm.
Surfactant (93) (0.63 g, 1.14 mmol) was stirred in acidified water (pH 1) at 0 °C. Benzaldehyde (0.12 ml, 1.18 mmol) and methyl acrylate (0.24 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo.

The crude oil was purified by flash chromatography (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.11 g, 47%).

$\nu_{\text{max}}/\text{cm}^{-1}\text{(neat)}$ 3447br, 3056s, 1712s, 1633w, 1441w.

$\delta_{H}$ (300 MHz; CDCl$_3$) 2.89 (1H, d, $J$ 5.6 Hz, OH), 3.66 (3H, s, OCH$_3$), 5.50 (1H, d, $J$ 8.3 Hz, 1-H), 5.75 (1H, br s, $=\text{CH}_2$), 6.26 (1H, br s, $=\text{CH}_2$), 7.19-7.33 (5H, m, Ph).

$\delta_{C}$ (75 MHz; CDCl$_3$) 52.30 (OCH$_3$), 73.73 (C-1), 126.48 (2 x C-2'), 126.96 (2 x C-3'), 128.92 (C-4'), 128.82 (C-2a), 141.67 (C-1'), 142.43 (C-2), 166.40 (C-3).

$m/z$ (Ei$^+$) 192 ($M^+$, 93%).

(Found: $M^+$, 193.0858. C$_{11}$H$_{13}$O$_3$ requires: $M^+$, 193.0865).

$[\alpha]_D = +5.0^\circ$ (c 0.5 in methanol, 25 °C).
7.69 2-[1-Hydroxy-1'-{(4'-methoxyphenyl)-methyl]-acrylic acid methyl ester (130).

\[ \text{HO} \quad \text{O} \]

\[(130)\]

Surfactant (93) (0.61 g, 1.10 mmol) was stirred in acidified water (pH 1) at 0 °C. \( p \)-anisaldehyde (0.15 ml, 1.18 mmol) and methyl acrylate (0.24 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in \textit{vacuo}. The crude oil was purified by flash chromatography, (hexane:ethyl acetate 6:1), to afford the \textit{title compound} as a clear oil (0.03 g, 10%).

\( \nu_{\text{max}}/\text{cm}^{-1} (\text{neat}) \) 3416m, 2926m, 2854m, 1713m, 1612m, 1513m, 1442m.

\( \delta_H \) (300 MHz; \( \text{CDCl}_3 \)) 2.52 (1H, d, \( J 5.6 \text{ Hz, OH} \)), 3.65 (3H, s,\( \text{CO}_2\text{CH}_3 \)), 3.73 (3H, s, \( \text{CH}_3\text{O-Ph} \)), 5.13 (1H, d, \( J 5.3 \text{ Hz, 1-H} \)), 5.77 (1H, s, =\( \text{CHH} \)), 6.22 (1H, s, =\( \text{CHH} \)), 6.80 (2H, m, 2 x 2'-H), 7.22 (2H, m, 2 x 3'-H).

\( \delta_C \) (75 MHz; \( \text{CDCl}_3 \)) 50.90 and 54.26 (2 x \( \text{OCH}_3 \)) 71.86 (C-1), 112.85 (2 x C-3'), 124.64 (C-2a), 128.14 (2 x C-2'), 132.14, 142.41 (C-1'), 159.11 (C-4').

\( m/z \) (EI\(^+\)) 222 (\( M^+ \), 37%).

(Found: \( M^+ + \text{Na} \), 245.0800, \( \text{C}_{12}\text{H}_{14}\text{O}_{3}\text{Na} \), requires: \( M^+ + \text{Na} \), 245.0790).

\([\alpha]_D = +6.0^\circ \) (c 0.5 in methanol, 25 °C).
Surfactant (93) (0.66 g, 1.18 mmol) was stirred in acidified water (pH 1) at 0 °C. 2-Nitrobenzaldehyde (0.18 g, 1.19 mmol) and methyl acrylate (0.24 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography, (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.15 g, 54%).

\[ \text{\( V_{\text{max/cm}}\)} \neat = 3590\text{br}, 3056\text{s}, 2956\text{w}, 1710\text{s}, 1528\text{s}, 1441\text{m}, 1356\text{m}. \]

\[ \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) \ 3.64 \ (3\text{H, s, OCH}_3), \ 5.64 \ (1\text{H, s, 1-H}), \ 6.12 \ (1\text{H, s, C/H}), \ 6.37 \ (1\text{H, s, C/H}), \ 7.35-7.41 \ (1\text{H, m, 3'-H}), \ 7.53-7.58 \ (1\text{H, m, 4'-H}), \ 7.66-7.69 \ (1\text{H, m, 6'-H}), \ 7.84-7.87 \ (1\text{H, m, 5'-H}). \]

\[ \delta_{\text{C}} (75 \text{ MHz; CDCl}_3) \ 51.13 \ (\text{OCH}_3), \ 66.65, \ 123.55 \ (\text{C-3'}), \ 125.41 \ (\text{C-4'}), \ 127.68 \ (\text{C-6'}) \text{ and } 127.91, \ 132.41 \ (\text{C-2}), \ 135.15 \ (\text{C-5'}), \ 139.88 \ (\text{C-1'}), \ 165.42 \ (\text{C-3}). \]

\[ m/z \text{ (ESP}^+ \text{) 260 (} M^+ + \text{Na, 16%).} \]

(Found: \( MH^+ \), 238.0726. \( C_{11}H_{12}O_5N_\text{ requires: } MH^+, 238.0715). \]

\[ \gamma_{\text{D}} = +8.0^\circ \text{ (c 0.5 in methanol, 25°C).} \]
Surfactant (93) (0.65 g, 1.17 mmol) was stirred in acidified water (pH 1) at 0 °C. 4-Hexyloxy benzaldehyde (118) (0.24 g, 1.17 mmol) and methyl acrylate (0.24 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 120 hours then diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography, (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.03 g, 9%).

$\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3565m, 3052s, 2986w, 1712m, 1650w, 1421m, 1266s.

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 0.83 (3H, t, $J$ 6.7 Hz, 12'-H), 1.16-1.74 (8H, m, 11'-H, 10'-H, 9'-H, 8'-H), 2.74 (1H, d, $J$ 5.4 Hz, OH), 3.65 (3H, s, OCH$_3$), 3.87 (2H, t, $J$ 6.6 Hz, 7'-H), 5.45 (1H, d, $J$ 5.2 Hz, 1-H), 5.77 (1H, s, = CHH), 6.25 (1H, s, = CHH), 6.81 (2H, d, $J$ 9.1 Hz, 2 x 2'-H), 7.20 (2H, d, $J$ 8.4 Hz, 2 x 3'-H).

$\delta_{\text{C}}$ (75 MHz; CDCl$_3$) 13.00 (C-12'), 21.58 (C-11'), 24.71 (C-10'), 28.23 (C-9'), 30.57 (C-8'), 50.89 (OCH$_3$), 67.02 (C-7'), 71.87 (C-1), 113.42 (C-2a), 124.59, 126.82.

$m/z$ (EI$^+$) 292 ($M^+$, 47%).

(Found: $M^+$, 292.1664. C$_{17}$H$_{24}$O$_4$, requires: $M^+$, 292.1675).

$[\alpha]_{D} = +6.0^\circ$ (c 0.5 in methanol, 25 °C).
7.72 Pentyl acrylate (133).

\[
\begin{align*}
\text{H}_6 & 2 \quad \text{O} \\
\text{H}_b & 1
\end{align*}
\]

(133)

The reaction was carried out under anhydrous conditions. Thionyl chloride (5.00 ml, 69.3 mmol) was added dropwise to a stirred solution of acrylic acid (4.76 ml, 69.3 mmol) and stirred for 1 hour at 25 °C. Pentan-1-ol (8.30 ml, 76.3 mmol) in dichloromethane (25 ml) was added slowly followed by DMAP (1.01 g, 8.2 mmol) in dichloromethane (10 ml). The mixture was then heated at reflux for 18 hours. The reaction mixture was washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the combined organic extracts were dried over sodium sulfate. The solvent was filtered and removed in vacuo to give a brown oil which was heated at reflux for 48 hours in dichloromethane (100 ml) with triethylamine (5 ml, 35.9 mmol). The solvent was removed in vacuo and the product was purified through a pad of silica using petroleum spirit (30-40 °C) to give the title compound as a yellow oil (5.91 g, 60%).

\[\nu_{\text{max/cm}^{-1}}(\text{neat})\text{ } 2957s, 1724s, 1636m, 1471m, 1410m, 1194m, 1057m.\]

\[\delta_{\text{H}}(300 \text{ MHz; } \text{CDCl}_3)\text{ } 0.84 \text{ (3H, t, } J 7.0 \text{ Hz, } 8-\text{H}), 1.27 \text{ (4H, m, 6-H, 7-H), 1.55 (2H, m, 5-H), 4.08 (2H, t, } J 6.7 \text{ Hz, 4-H), 5.75 (1H, d, } J 10.4 \text{ Hz, } H_b), 6.05 \text{ (1H, dd, } J 17.3 \text{ and 10.4 Hz, } H_a).\]

\[\delta_{\text{C}}(75 \text{ MHz; } \text{CDCl}_3)\text{ } 14.34 \text{ (C-8), 22.83 (C-7), 28.44 (C-6), 32.87 (C-5), 65.02 (C-4), 129.07 (C-1), 130.61 (C-2), 166.63 (C-3).}\]

\[m/z \text{ (FAB}^+\text{) } 165 \text{ (M}^+\text{Na, 28%).}\]

(Found: \(M^+\text{Na, } 165.0880.\) \(C_9H_{14}O_2Na\) requires: \(M^+\text{Na, } 165.0891).\)
7.73 2-(1-Hydroxy-1'-phenylmethyl)-acrylic acid pentyl ester (134).

Surfactant (93) (0.64 g, 1.19 mmol) was stirred in acidified water (pH 1) at 0 °C. Benzaldehyde (0.12 ml, 1.18 mmol) and pentyl acrylate (133), (0.37 g, 2.61 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography, (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.06 g, 22%).

\[ v_{\text{max/cm}^{-1}}(\text{neat}) = 3592\text{br, 3055s, 2986m, 1712s, 1421m, 1362m, 1266s}. \]

\[ \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) = 0.81 \text{ (3H, t, J 6.8 Hz, 8-H), 1.14-1.58 \ (6H, m, 5-H, 6-H, 7-H), 2.92 \ (1H, d, J 5.8 Hz, OH), 4.08 \ (2H, t, J 6.9 Hz, 4-H), 5.48-5.50 \ (1H, d, J 5.7 Hz, 1-H), 5.74 \ (1H, s, = CH), 6.27 \ (1H, s, = CH), 7.19-7.33 \ (5H, m, Ph).} \]

\[ \delta_{\text{C}} (75 \text{ MHz; CDCl}_3) = 14.29 \text{ (C-8), 22.65 \ (C-7), 28.41 \ (C-6), 28.57 \ (C-5), 65.49 \ (C-4), 73.84 \ (C-1), 126.32 \ (2 \times \ C-2'), 126.95 \ (2 \times \ C-3'), 128.20 \ (2 \times \ C-4'), 128.81 \ (C-2a), 142.11 \ (C-2), 166.45 \ (C-4).} \]

\[ m/z (\text{EI}^+) = 248 (M^+, 21\%). \]

(Found: \( M^+ + \text{Na}, 271.1301, C_{15}H_{20}O_3\text{Na}, \) requires: \( M^+ + \text{Na}, 271.1310)\).

\[ [\alpha]_D = +11.0^\circ \ (c 0.5 \text{ in methanol, 25 °C}). \]
7.74 2-[1-Hydroxy-1'-(2'-nitrophenyl)-methyl]-acrylic acid pentyl ester (135).

Surfactant (93) (0.65 g, 1.18 mmol) was stirred in acidified water (pH 1) at 0 °C. 2-Nitrobenzaldehyde (0.18 g, 1.19 mmol) and pentyl acrylate (0.37 g, 2.63 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.12 g, 34%).

ν_max/cm^-1 (neat) 3590m, 3055s, 2986m, 1712s, 1528s, 1420m, 1354m, 1266s.

δ_H (300 MHz; CDCl_3) 0.80 (3H, t, J 6.9 Hz, 8-H), 1.13-1.26 (4H, m, 6-H, 7-H), 1.52 (2H, m, 5-H), 3.32 (1H, d, J 4.8 Hz, OH), 4.03 (2H, m, 4-H), 5.69 (1H, s, =CH_H), 6.10 (1H, d, J 4.7 Hz, 1-H), 6.32 (1H, s, =CH_H), 7.19-7.42 (1H, m, 3'-H), 7.55-7.57 (1H, m, 4'-H), 7.65-7.67 (1H, d, J 7.8 Hz, 6'-H), 7.86-7.89 (1H, d, J 8.1 Hz, 5'-H).

δ_C (75 MHz; CDCl_3) 14.27 (C-8), 22.63 (C-7), 28.52 (C-6), 65.72 (C-4), 68.24 (C-1), 124.99 (C-2a), 126.75 (C-3'), 129.09 (C-6'), 133.85 (C-4'), 135.21 (C-5'), 141.15 (C-2), 166.41 (C-3).

m/z (El^-) 292 (M^+ - H, 10%).

(Found: MH^+, 294.1328, C_{15}H_{20}O_{5}N, requires: MH^+, 294.1341).

[α]_D = +4.0° (c 0.5 in methanol, 25 °C).
7.75 2-(1-Hydroxy-1'-phenylmethyl)-acrylonitrile (136). 

Surfactant (93) (0.63 g, 1.14 mmol) was stirred in acidified water (pH 1) at 0 °C. Benzaldehyde (0.12 ml, 1.18 mmol) and acrylonitrile (0.18 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.03 g, 14%).

$\nu_{\text{max}}/\text{cm}^{-1}(\text{neat})$ 3445br, 2361m, 2230m, 1710m, 1620w, 1455w, 1365w, 1267w, 1226w, 1087w, 1054m.

$\delta_{H}$ (300 MHz; CDCl$_3$) 2.97 (1H, d, $J$ 4.0 Hz, OH), 5.51 (1H, m, 1-H), 6.25 (1H, s, =CHH), 6.46 (1H, s, =CH/Ph), 7.62 (5H, m, Ph).

$\delta_{C}$ (75 MHz; CDCl$_3$) 68.28 (C-1), 117.34 (C-3), 126.70 (2 x C-2'), 126.95 (2 x C-3'), 129.34 (C-2a), 130.23, 139.64.

$m/z$ (EI$^+$) 159 ($M^+$, 23%).

(Found: $M^+$+Na, 182.0590. C$_{10}$H$_7$NO$_2$Na, requires: $M^+$+Na, 182.0582).

$[\alpha]_D = +7.0^\circ$ (c 0.5 in methanol, 25 °C).
Surfactant (93) (0.63 g, 1.14 mmol) was stirred in acidified water (pH 1) at 0 °C. 2-Nitrobenzaldehyde (0.18 g, 1.19 mmol) and acrylonitrile (0.18 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase was extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.05 g, 19%).

\[
\text{v}_{\text{max}}/\text{cm}^{-1} (\text{neat}) = 3444 \text{br}, 3056 \text{m}, 2987 \text{s}, 1711 \text{s}, 1528 \text{s}, 1420 \text{m}, 1352 \text{s}, 1266 \text{s}.
\]

\[
\delta^\text{H} (300 \text{MHz; CDCl}_3) = 3.25 (1\text{H}, \text{br, OH}), 6.09 (1\text{H, m, 1-H}), 6.21 (1\text{H, s, } = \text{CH})11, 6.24 (1\text{H, s, } = \text{CH}), 7.61-7.66 (1\text{H, m, 3'-H}), 7.79-7.85 (1\text{H, m, 4'-H}), 7.92-7.95 (1\text{H, d, J 7.9 Hz, 6'-H}), 8.11-8.13 (1\text{H, d, J 8.1 Hz, 5'-H}).
\]

\[
\delta^\text{C} (75 \text{MHz; CDCl}_3) = 69.64 (\text{C-1}), 116.88 (\text{C-3}), 124.65 (\text{C-3'}), 125.52 (\text{C-4'}), 129.55 (\text{C-2a, C-6'}), 132.44 (\text{C-1'}), 134.65 (\text{C-5'}), 147.21 (\text{C-2}).
\]

\[
m/\text{z (FAB)}^+ = 227 (M^{+} + \text{Na}, 70 \%).
\]

(Found: \(M^{+} + \text{Na}, 227.0448\). \(\text{C}_{10}\text{H}_{8}\text{O}_{3}\text{Na}\), requires: \(M^{+} + \text{Na}, 227.0433\)).

\([\alpha]_{D} = +10^\circ (c 0.5 \text{ in methanol, 25 °C}).\)
2-[[1-Hydroxy-1'- (4'-methoxyphenyl)- methyl]-acrylonitrile (138).

![Structure of 2-[[1-Hydroxy-1'- (4'-methoxyphenyl)- methyl]-acrylonitrile (138).](image)

Surfactant (93) (0.61 g, 1.10 mmol) was stirred in acidified water (pH 1) at 0 °C. p-Anisaldehyde (0.15 ml, 1.18 mmol) and acrylonitrile (0.18 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 72 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.02 g, 9%).

ν max/cm⁻¹ (neat) 3591 br, 3055 s, 2986 s, 1712 m, 1650 m, 1514 m, 1420 m, 1286 s.

δ H (300 MHz; CDCl₃) 2.33 (1H, br, OH), 3.84 (3H, s, OCH₃), 5.31 (1H, m, 1-H), 6.05 (1H, s, =CH), 6.12 (1H, s, =CHH), 7.01-7.04 (1H, d, J 8.8 Hz, 2 x 2'-H), 7.28-7.32 (1H, d, J 8.8 Hz, 2 x 3'-H).

δ C (75 MHz; CDCl₃) 55.73 (OCH₃), 74.28 (C-1), 114.80 (C-3'), 117.38 (C-3), 126.85 (C-2'), 129.34, 129.68 (C-2a), 137.80 (C-1' or C-2), 160.56 (C-4').

m/z (EI⁺) 189 (M⁺, 25%).

(Found: M⁺, 189.0776, C₁₁H₁₁O₂N, requires: M⁺, 189.0790).

[α]D = +4.0° (c 0.5 in methanol, 25 °C).
Surfactant (93) (0.65 g, 1.17 mmol) was stirred in acidified water (pH 1) at 0 °C. 4-(4'-Hexyloxy)-benzaldehyde (118) (0.24 g, 1.17 mmol) and acrylonitrile (0.18 ml, 2.66 mmol) were then added. The reaction was stirred at 0 °C for 120 hours and diluted with ethyl acetate (50 ml). The reaction mixture was washed with water (100 ml) and the organic phase were extracted using ethyl acetate (4 x 100 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (hexane:ethyl acetate, 6:1) to afford the title compound as a clear oil (0.02 g, 5%).

$\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3566br, 1712m, 1651m, 1542w, 1513m, 1458m, 1266s.

$\delta_H$ (300 MHz; CDCl$_3$) 0.83 (3H, t, J 7.0 Hz, 12'-H), 1.24-1.49 (8H, m, 8'-H to 11'-H), 2.19 (1H, m, OH), 3.89 (2H, t, J 6.6 Hz, 7'-H), 5.20 (1H, m, 1-H), 5.95 (1H, s, =CHH), 6.04 (1H, s, =CHH), 6.82-6.93 (2H, m, 2 x 2'-H), 7.19-7.21 (2H, m, 2 x 3'-H).

$\delta_C$ (75 MHz; CDCl$_3$) 14.36 (C-12'), 22.96 (C-11'), 226.07 (C-10'), 29.57 (C-9'), 31.94 (C-8'), 68.54 (C-7'), 74.33 (C-1), 115.36 (C-3), 128.30 (2 x C-2'), 129.63 (2 x C-3'), 131.53.

$m/z$ (El$^+$) 259 ($M^+$, 20%).

(Found: $M^+$+Na, 282.1458. C$_{16}$H$_{21}$O$_2$Na, requires: $M^+$+Na, 282.1470).

$[\alpha]_D = +3.0^\circ$ (c 0.5 in methanol, 25 °C).
8. References.


150. J. Madden, H. C. Hailes, unpublished results.


167. Aldrich Catalogue.
