Studies of Intramolecular aziridination using 3-acetoxyaminoquinazolinones

A thesis submitted to the Faculty of Science in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Leicester

by

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Experimental

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Statement

The accompanying thesis submitted for the degree of Doctor of Philosophy entitled “Studies of Intramolecular aziridination using 3-acetoxyaminoquinazolinones” is based on work conducted by the author in the Department of Chemistry of the University of Leicester in the period October 1997 to January 2001.

All the work in this Thesis is original unless otherwise acknowledged by references. None of this work has been submitted for any other degree.

Signed..................................................Date..................................
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Abbreviations

Bicarbonate = saturated sodium hydrogen carbonate aqueous solution
BOC = $\tau$-butoxycarbonyl
DCM = dichloromethane
EA = ethyl acetate
eq. = molar equivalents
Ether = diethyl ether
HMDS = hexamethyldisilazane
HRMS = high resolution mass spectrometry
LDA = lead diacetate
LTA = lead (IV) acetate
mp. = melting point
NMO = $N$-methyl morpholine $N$-oxide
PE = light petroleum 60-80 °C
TFA = trifluoroacetic acid
TPAP = tetra-n-propylammonium perruthenate
Ts = Tosyl
Throughout this thesis

= Q^1

= Q^2

= Q^3

= Q^4

= Q^5

= Q^6

= Q^7

= Q^8

= Q^9

= Q^{10}

= Q^{11}

= Q^{12}

= Q^{13}

= Q^{14}

= Q^{15}

= Q^{16}
STUDIES OF INTRAMOLECULAR AZIRIDINATION USING 3-ACETOXYAMINOQUINAZOLINONES
Richard Draycott

Abstract

A general strategy was devised for the conversion of α,β-unsaturated acids into α- or β-amino acid enantiomers via intramolecular aziridination of the acid double bond as the key step.

The initial step involved tethering of the acid as its acid chloride to the ω-hydroxy group of a 2-(ω-hydroxyalkyl)-3-amino-quinazolin-4(3H)-one (QNH$_2$ compounds). Although competitive O- and N-acylation was observed in acylation reactions using 2-(1-hydroxyethyl)-3-aminoquinazolin-4(3H)-one as a model compound, all other QNH$_2$ compounds examined underwent highly chemoselective O-acylation.

Cinnamoylation of a series of 2-(ω-hydroxyalkyl) QNH$_2$ compounds (alkyl = n-propyl, n-butyl or n-pentyl) followed by intramolecular aziridination via the corresponding QNHOAc intermediates was carried out to identify the optimum length for the tether. In the presence of hexamethyldisilazane, the best yield (95%) was obtained with 6 atoms in the tether using 2-(4-hydroxybut-1-yl)-3-aminoquinazolin-4(3H)-one. In the presence of trifluoroacetic acid good yields of the corresponding ring-opened aziridine (benzylic) alcohols were obtained with the 2-(4-hydroxypropyl)- and 2-(5-hydroxypentyl)-3-aminoquinazolin-4(3H)-ones.

To examine the diastereoselectivity in the 6-atom tethered intramolecular aziridination, three racemic 2-(4-hydroxy-2-oxa-1-substituted butyl)-QNH$_2$ compounds were prepared bearing a phenyl, isopropyl, or methyl as the 1-substituent. Intramolecular aziridination of the O-cinnamoyl, O-tiglyl or O-3,3-dimethylacryloyl esters in the phenyl-substituted cases gave in each case, a single aziridine diastereoisomer in high yield.

Synthesis of the (R)-methyl-substituted QNH$_2$ compound 185 above was accomplished in five steps starting from (S)-α-bromopropionic acid and benzyloxyethanol without the need for chromatography; its enantiopurity was confirmed by $^1$H-NMR spectroscopy after derivatisation with (R)-myrtenal.

O-Cinnamoylation of QNH$_2$ 185 followed by intramolecular aziridination and then treatment with samarium diiodide brought about reductive C-N aziridine ring-cleavage at the lactone-linked position. The resulting lactone has been converted by another in the laboratory to (R)-3-amino-3-phenyl propionic acid methyl ester of high enantiopurity confirming the viability of the strategy above.
Chapter 1
General Introduction
**Introduction**

1.1 Aziridines: structure and bonding

It is the similar strain energy in aziridine 1 (113 kJmol\(^{-1}\)) to that in oxirane (114 kJmol\(^{-1}\)) which makes both liable to ring opening. In both cases the presence of the heteroatom facilitates ring-opening by comparison with cyclopropane\(^1\) which has a similar strain energy (115 kJmol\(^{-1}\)).

![Figure 1](image)

Aziridine rings accommodate their formal 60° internal bond angles, which are considerably smaller than the natural angle 109° 28' between sp\(^3\)-hybridised bonds, by a change in the hybridisation of the ring atoms. Inclusion of increased p-orbital character in the bonds forming the ring results in maximum orbital overlap outside the axes joining the nuclei of the ring atoms – so called banana bonds (Scheme 1). As a consequence the exocyclic bonds have more s-character and the angles between them are widened allowing nucleophiles attacking these ring carbons easier access. The enhanced s character of the C-H bonds can be quantified by NMR spectroscopy from the \(^{13}\)C-H coupling constant values. Methane with 25% s character (sp\(^3\)-hybridisation) has a \(^{13}\)C-H coupling constant of 125 Hz;\(^2\) the value for aziridine 1 is 166 Hz, suggesting ~ 32% s-character.\(^3\)

The increased % s-character also in the orbital containing the nitrogen lone pair results in aziridines (pKa 8.04)\(^4\) being less basic than e.g. diethylamine (pKa 10.7)\(^5\) because in effect the lone pair is held closer to the nucleus. The increased % s-character also has a significant effect on the barrier to \(\beta\)-inversion (see later).
1.2 Aziridines: History

Although epoxides are used widely in industry on the tonne scale, aziridines are little used by comparison, in spite of the fact that their discovery dates back to 1888. In spite of Meyer’s original pessimism as to the possible existence of aziridines, Gabriel succeeded in synthesising aziridine 1, from base treatment of 2-bromoethylamine in 1888 but erroneously assumed the reaction (Scheme 2) product was vinylamine 2. The correct formulation was made by Marckwald over a decade later after analysis of the properties of the product. This intramolecular displacement of a leaving group on a α-carbon by a β-nitrogen has become a general method of preparing aziridines and is now known as the Gabriel-Marckwald synthesis.
The work described in this thesis was directed towards the synthesis of aziridines as single stereoisomers and a brief review of important methods for accomplishing this end is given here.

1.3 Synthesis of aziridines from readily available enantiopure starting materials

Preparation of enantiopure aziridines is often achieved by utilising natural amino acids as starting materials to provide the 1,2-amino alcohols or their derivatives, required for Gabriel-Marckwald type synthesis. In some cases the required 1,2-amino alcohols are readily available. The three methods illustrated below are high yielding reactions on a multigram scale (Schemes 3a-c), however the use of LiAlH₄ restricts the use of these procedures in industry.

\[
\text{DMAP} = \text{N,N-Dimethyl-4-aminopyridine} \\
\text{DTPP} = \text{Diethoxytriphenyl phosphorane}
\]

Scheme 3
In the reduction of the amino acid to the alcohol (e.g. Scheme 3b) there may be difficulty in isolating the intermediate amino alcohol 3 owing to the formation of water-soluble metal complexes. D.Craig et al (Scheme 3c) avoided this problem by N-protecting the free amine in the first step, then reducing the carboxylic acid group in the second step, to provide enantiopure N-tosyl aziridine in high yield.\textsuperscript{15}

1.4 Synthesis from carbohydrates

The synthesis of aziridines from readily available sugar derivatives is another useful method which takes advantage of the latter’s enantiopurity,\textsuperscript{16-19} although only one sugar enantiomer is usually readily available. The following example shows how a readily available epoxide can be converted to a \textit{spiro}-aziridine\textsuperscript{20} (Scheme 4).

Another preparation (Scheme 5) utilises the easily available sugar D-ribose 4 to prepare the corresponding enantiopure aziridine-2-lactone isomer 5.\textsuperscript{19}
1.5 Catalytic enantioselective alkene aziridination

By utilising [N-(toluene-p-sulphonyl)imino]phenyliodinane (PhI=NTs), Jacobsen and Evans have established a highly enantioselective method of aziridinating alkenes. These reactions involve the use of low-valent metal complexes with enantiopure ligands. Jacobsen employs an enantiopure 1,2-diiminocyclohexane complexed copper catalyst (Scheme 6a). Evans employs a 4,4-disubstituted bis-oxazoline-complexed copper catalyst (Scheme 6b).  

\[ \text{Conditions: a) SOCl}_2, \text{NEt}_3, \text{THF}, 0 \, ^\circ\text{C}; \text{b) NaN}_3, \text{DMF}, 155 \, ^\circ\text{C}; \text{c) TsCl, pyridine; d) 4N HCl, dioxane, 100 \, ^\circ\text{C}; e) ^1\text{Bu(CH}_3)_2\text{SiSO}_2\text{CF}_3, \text{lutidine, DCM}; f) \text{Ph}_3\text{P, THF, 2h. then 2N NaOH, 80 }^\circ\text{C}; g) \text{Ac}_2\text{O, pyridine, 0 }^\circ\text{C}; h) \text{TBAF, THF, 0 to 25 }^\circ\text{C}; i) \text{TPAP, NMO, CH}_3\text{CN, mol. sieves, room temperature.} \]

Scheme 5
It is unfortunate that these nitrenoid mediated reactions are non-stereospecific and the configuration of a cis-alkene is not retained in the product; consequently only trans-alkenes or cyclic cis-alkenes can be used. In addition, only N-tosyl aziridines can be prepared, the deprotection of which is difficult\textsuperscript{22-23} with or without aziridine ring-opening.

1.6 Preparation of aziridines from epoxides

It was the discovery of enantioselective epoxidation of allylic alcohols in the early 1980s by Sharpless \textit{et al.}\textsuperscript{24-25} which led to an upsurge in the use of enantiopure epoxide products as relay compounds in stereoselective synthesis. The availability of these epoxides led to the development of methods for their conversion into enantiopure aziridines (Scheme 7).

The epoxides can be prepared via Sharpless epoxidation of the E-allylic alcohol followed by oxidation of the alcohol to acid. By varying the tartrate enantiomer used in the Sharpless epoxidation both stereoisomers of the aziridine are accessible.

Scheme 7 shows how trans-aziridine-2,3-dicarboxylic acid ester 6 and its N-tosyl analogue 7 can be prepared by utilising the enantioselective formation of epoxide 8 prepared through Sharpless epoxidation.\textsuperscript{26-27} The epoxide is ring opened by S$_N$2 inversion to give the aziridino alcohol 9.

The routes in Scheme 7, the first involving the Staudinger reaction,\textsuperscript{28} and the second an intramolecular Mitsunobu reaction,\textsuperscript{29} give aziridine 6 and 7 respectively with inversion at the chiral centre bearing the alcohol group in each case.
Toshimitsu and co-workers have developed a strategy by which a terminal epoxide enantiomer is converted into its analogous aziridine with overall retention of configuration at the chiral centre and no loss of enantiopurity (Scheme 8). The reaction proceeds with anchimeric assistance of the aryl thio group, hence a double inversion at the chiral centre.
1.7 Use of nitrenes in aziridination of alkenes

The reactivity of nitrenes is much affected by their electron configuration. A singlet nitrene reacts with a configured alkene stereospecifically in a one-step concerted mechanism to produce an aziridine in which the configuration of the alkene is retained in the product.

A few nitrenes are known to have singlet ground states. However, where the ground state is the triplet, two of the outermost electrons are not paired up as in the singlet state and the nitrene behaves like a diradical, reacting non-stereospecifically via a non-concerted two-step mechanism and giving a mixture of cis- and trans-substituted aziridines e.g. from a cis-alkenes (Scheme 9). Unfortunately, in many cases, the rate of singlet to triplet conversion is similar to the rate of aziridination and at low concentrations of alkene, even when the nitrene is generated solely in the singlet state, there can be decay to the triplet nitrene leading to loss of stereospecificity in the reaction.

The extent of singlet to triplet conversion is minimised using the alkene as the solvent in Scheme 9 and leads to formation of the cis-aziridine. However, decay of the nitrene
to its triplet ground state when the alkene is diluted using an inert solvent leads to both \textit{cis} 10 and \textit{trans} 11 isomers as products.

A further complication with higher energy nitrenes is that insertion into C-H bonds (especially allylic C-H bonds) may accompany aziridination. Few highly diastereoselective nitrene additions have been reported.

\section*{1.8 Aziridination of alkenes using 3-acetoxyaminoquinazolinones}

A general method for the aziridination of alkenes was discovered by Rees \textit{et al} in 1967.\textsuperscript{35} The method involved oxidative addition of \textit{N}-aminoheterocycles, e.g. 3-aminoquinazolinones\textsuperscript{36} 12 or \textit{N}-aminophthalimide 13 to alkenes mediated by lead tetra-acetate (LTA).

\begin{center}
\begin{tikzpicture}
\node[draw] (12) {\includegraphics[width=1cm]{12.png}};
\node[draw, right=1cm of 12] (13) {\includegraphics[width=1cm]{13.png}};
\node[below=0.5cm of 12] {12 = QNH$_2$};
\node[below=0.5cm of 13] {13 = PNH$_2$};
\end{tikzpicture}
\end{center}

For many years, LTA-mediated oxidative addition reactions of these \textit{N}-aminoheterocycles to alkenes\textsuperscript{37} were thought to proceed \textit{via} nitrene intermediates, although nitrenes were never spectroscopically detected. The oxidation of e.g. \textit{N}-aminophthalimide 13 with LTA was believed to produce the \textit{N}-nitrene 14 whose singlet state was stabilised by resonance at least to some degree, resulting in stereospecific addition to alkenes (Scheme 10).
The $N$-nitrene intermediate 14 is produced by a number of independent routes shown in Scheme 11. These include thermolysis of 7-azabenzenorbornadiene 15, aziridinobenzofurans 16, and sulphimide 17.\textsuperscript{38,39} This chemistry supported the assignment of structure 14 as the reactive intermediate in LTA oxidation. Similarly $N$-(quinazolinoyl) ylide 18 acts as a precursor for the $N$-nitrene 19 which can be trapped with alkenes;\textsuperscript{40} a similar nitrene intermediate was believed to be produced by LTA oxidation of 3-aminoquinazolinones.
In the 1980s, NMR spectroscopic observations by Grimshire\textsuperscript{42} on the reaction in Scheme 12, and the results of experiments subsequently performed by Kelly\textsuperscript{45b}, confirmed that the structure of the aziridinating species produced from the reaction of 3-aminoquinazolinones with LTA was the 3-acetoxyaminoquinazolinone 21 (Scheme 12).

![Scheme 12](image)

Thus 3-aminoquinazolinone 20 containing an alkene tethered to the 2-position of the quinazolinone (Q) group was shown to react with LTA at \(-20^\circ C\) to give an intermediate 21, stable at this temperature, in which the double bond was still present from NMR spectroscopy at this temperature. At \(0^\circ C\), reaction of this intermediate occurred intramolecularly to give the aziridine.\textsuperscript{41}

![Scheme 13](image)
Reaction of 3-amino-2-ethylquinazolinone 22 with LTA at −20 °C gave the analogous Q'NHOAc 23. \(^1\)H and \(^{13}\)C-NMR spectra of this intermediate 23 at −30 °C after removal of acetic acid produced in the acetoxylation revealed the presence of the N-acetoxy group. The additional carbonyl group was further identified by infrared spectral IR analysis from its C=O stretching frequency at 1768 cm\(^{-1}\) at −30 °C. The increase in the rate of disappearance of 23 and formation of aziridine 24 with increased alkene concentration was consistent with 23 being the actual aziridinating species.\(^{42}\)

The presence of an intermediate formed from N-aminophthalimide and LTA, stable at −40 °C, which aziridinated subsequently added alkenes, suggested that a similar N-acetoxylated species 25 was produced in this case also (Scheme 14).

1.9 Mechanism and diastereoselectivity of aziridination using 3-acetoxyaminoquinazolinones (QNHOAc)

Aziridination of a range of alkenes is possible using QNHOAc 26\(^{42}\) and the reaction may be regarded as the nitrogen analogue of the peroxyacid epoxidation of alkenes\(^{43}\) (Scheme 15). Aziridination of electron-available alkenes e.g. but-2-ene or styrene via QNHOAc 26 and epoxidation via RCO\(_3\)H\(^{44}\) probably follow similar mechanisms\(^{42}\) (the Bartlett mechanism for epoxidation) and both reactions are stereospecific (see below).
The epoxidation and aziridination of cyclohexen-3-ol in Scheme 16 are both observed to occur with \( \text{syn}-\)stereoselectivity\(^{45} \) which is good evidence for a mechanistic similarity. However, whereas cyclohexen-4-ol is also aziridinated highly \( \text{syn} \)-selectively with QNHOAc 26,\(^{46} \) epoxidation of this homoallylic alcohol with peroxyacids is hardly \( \text{syn} \)-selective at all.

A study of the reaction rates confirmed that the hydroxy group of cyclohexen-3-ol exerts an accelerating effect and H.B. Henbest \textit{et al} \(^{45} \) hypothesised that H-bonding between the allylic alcohol and the (non-transferred) acetoxy oxygen of the peroxyacid was responsible as shown in Scheme 16.
1.10 Use of hexamethyldisilazane (HMDS) in aziridinations

One mole equivalent of acetic acid is produced when N-aminoheterocycles are acetoxylated with LTA, with a further equivalent released when the acetoxy group of the QNHOAc reacts with the olefin. Acetic acid accelerates the decomposition of QNHOAc and hence is an important factor in determining the yield of aziridine obtained when the rate of aziridination of alkenes is slow. This accelerated decomposition mediated by acetic acid is believed to arise from protonation of N-1 or the carbonyl group of the quinazolinone ring and produces the corresponding 3H-quinazolinone 27 (Scheme 17). By using a scavenging agent during the aziridination to remove the acetic acid, the lifetime of the QNHOAc intermediate can therefore be increased and the yield of aziridine increased correspondingly. Hexamethyldisilazane has been shown to perform this scavenging function very well.47-48

1.11 The stereospecific nature of the aziridination

As previously mentioned, in epoxidation of alkenes with peroxyacids and aziridination using Q\textsuperscript{1}NHOAc 23 the configuration of the alkene is retained in the 3-membered ring product as a result of a concerted syn-addition to the double bond in each case. For example, trans-but-2-ene is aziridinated with Q\textsuperscript{1}NHOAc 23 to give only the aziridine in which the methyl groups are trans-disposed and likewise cis-but-2-ene gives only the cis-substituted aziridine (Scheme 18).
1.12 Ambiphilic aziridination using QNHOAc

3-Acetoxyaminoquinazolinones (e.g. 23) and N-acetoxyaminophthalimide were found to be efficient aziridinating agents that reacted stereospecifically as above with both electron available alkenes (such as aryl alkenes, 1,3-dienes and alkynes) and also with electron deficient alkenes (such as α,β-unsaturated esters) in good yield i.e. they showed ambiphilic behaviour. Peroxyacids do not react efficiently with electron-deficient alkenes.

\[ \textbf{Scheme 18} \]

\[ \textbf{Scheme 19} \]
1.13 N-inversion in N(Q)-aziridines

In order to invert at nitrogen, the aziridine must pass through an energy barrier where the nitrogen adopts a planar sp$^2$ hybrid geometry (Scheme 20).

![Scheme 20](image)

The effect of utilising increased p-character for the aziridine ring bonds (see earlier) is to raise the barrier to inversion at the aziridine ring nitrogen relative to an acyclic amine since in the transition state a pure p-orbital must be made available for the N-lone pair. Alternatively the increased barrier can be accounted for by recognising the necessity for constraining one aziridine ring bond angle to (formally) 109° in the ground state (sp$^3$) but 120° in the transition state (sp$^2$).

Changing the type of N-substituent of an aziridine can also affect the barrier to inversion. An acyl group lowers the inversion barrier by delocalising the nitrogen lone pair in the planar transition state. However a σ-electron withdrawing substituent on nitrogen will raise the barrier to inversion because the nitrogen responds by supplying more p-orbital character to the N-substituent via the σ-bond making a pure p-orbital less available for the inversion transition state.

When R=Q Scheme 20, exchange between the N-invertomers is slow on the NMR timescale (but fast on the real timescale at room temperature). When the substituents R$^1$ and R$^2$ on the aziridine are of comparable size, both aziridine N-invertomers (diastereoisomers) are present and recognisable from their different signals in the NMR spectrum of the mixture.
1.14 N-Inversion in QNHOAc

At -20 °C, the NMR spectrum of QNHOAc 28 (bearing CHMeBu as a chiral 2-substituent) shows the presence of a 4:1 ratio of diastereoisomers with the pyramidal exocyclic nitrogen as the second chiral element. Inversion at this nitrogen is slow on the NMR timescale but on the timescale for aziridination of alkenes, inversion is believed to be fast.

![Chemical Structure](image)

28 = QNHOAc

1.15 N-N bond rotamers

Acylation at the amine group of 3-aminoquinazolinones produces mono- or di-3-acylaminoquinazolinones (MAQs or DAQs). An important feature of DAQ stereostructure is that the barrier to rotation around the N-N bond is sufficient for it to become a chiral axis when the two N-acyl groups are different. Thus a DAQ which has two chiral elements (a chiral centre and a chiral axis in the case of 29) can exist as diastereoisomers. The barrier for the interconversion of one of these diastereoisomers into the other (ΔG° = 121 kJ mol⁻¹) in DAQ 29 has been measured experimentally and is consistent with rotation around the N-N bond.
The same chiral elements are also present in MAQ 30 and signals from the two diastereoisomers are present in its $^1$H-NMR spectrum. However, the $N-N$ bond in MAQs is not a stereostable chiral element at room temperature i.e. the barrier to $N-N$ bond rotation is not sufficient to maintain the chiral axis at room temperature.

$^1$H NMR analysis of MAQ 31 prepared from the corresponding enantiopure 3-aminoquinazolinone also has two chiral elements, a chiral centre substituent on the quinazolinone and a chiral $N-N$ axis; MAQ 31 also shows the presence of two diastereoisomers in its NMR spectrum.$^{56}$

1.16 Diastereoselectivity in aziridination of alkenes by QNHOAc; endo diastereoselectivity

The barrier to $N$-inversion in $N$-phthalimido aziridines is sufficient to allow $N$-invertomers to be distinguishable by their respective signals in their $^1$H-NMR spectra (see section 1.35). By carrying out the aziridination of styrene and methyl acrylate at low temperature and by monitoring the solution by $^1$H-NMR in each cell it was shown that only the cis-invertomers are produced initially on reaction with the $N$-acetoxyaminophthalimide intermediate (Scheme 21).$^{57}$ $N$-Inversion of these kinetically first-formed products occurs readily above 0 °C to give only the thermodynamically favoured trans-aziridine with the styrene-derived aziridine 32, and a 5:1 ratio of trans : cis in the methyl acrylate-derived case 33. In the kinetically formed cis-aziridine 32a, the bulky phenyl group clashes sterically with the phthalimide group, which favours complete conversion to the trans-invertomer 32b on thermal equilibration.$^{51}$ In the
aziridine from methyl acrylate, the corresponding repulsion is not so large, so a mixture of cis and trans-aziridines results at equilibrium.

This complete occasional diastereoselectivity\(^{58}\) illustrated in Scheme 21 is also believed to be present in aziridinations using \(N\)-acetoxyaminoquinazolinones \(26\). Since the barrier to \(N\)-inversion in the latter are lower, however, the rates of aziridination and aziridine \(N\)-inversion are comparable which make it difficult or impossible to show that the cis-aziridine is exclusively the first-formed product by the method successful in Scheme 21. In a small number of cases using QNHOAc \(26\) (see Scheme 30) the barrier to \(N\)-inversion is sufficiently raised that the kinetically formed product can be identified as the less stable cis-\(N\)-inverteromer as expected.

### 1.17 Mechanism and transition state geometry of aziridination using QNHOAc.

Scheme 22 depicts the suggested mechanism and transition state geometry for aziridination of methyl acrylate with QNHOAc. The preference for initial formation of the less stable aziridine \(N\)-inverteromer in the case of methyl acrylate (Scheme 21) is thought to result from a favourable attractive secondary interaction (endo overlap) between the carbonyl oxygen of the ester and the electrophilic carbonyl carbon of the quinazolinone in the aziridination transition state (an interaction which disappears when both bonds to the aziridine are fully formed) with the planes of the quinazolinone and ester almost parallel. This effect outweighs the unfavourable steric effects in the
transition state geometry from cis-disposed Q and ester groups. In this transition state geometry (Scheme 22), the secondary interaction is considered to activate the alkene towards Michael-type addition\(^5^9\) by the exocyclic nitrogen QVHOAc and the overlap increases the nucleophilicity of this nitrogen; it is only geometrically possible if the ester adopts an s-cis conformation.

This s-cis ester conformation has been shown to be mandatory by the response of \(\alpha\)-methylene-\(\delta\)-butyrolactone 34 and \(\gamma\)-butyrolactone 35 to attempted aziridination by oxidative addition of N-aminophthalimide. Compound 34 is compelled to adopt an s-cis conformation and is aziridinated efficiently by the intermediate N-acetoxyaminophthalimide via a TS\(^a\) analogous to that in Scheme 22. However when the double bond is trans-disposed to the carbonyl C=O bond as in 35, the secondary overlap (analogous to that in 36b) is geometrically impossible and no aziridination occurs.\(^4^2\)

Although the aziridination in Scheme 22 is considered to be concerted it is not synchronous. In Scheme 22, N-C\(\beta\) bond formation runs ahead of C\(\alpha\)-N bond formation
with SN 2-type displacement of the acetoxy group from the nitrogen. Thus in the reaction, the exocyclic nitrogen behaves primarily as a nucleophile in the initial Michael-type addition.

\[ \text{Scheme 23} \]

The transition state for aziridination of electron-available alkenes with QNHOAc is believed to be that shown in Scheme 23 and also leads to the cis-aziridine as is found experimentally.\(^6^0\) Endo-overlap is the result of a similar electronic interaction between the \(\pi\)-electron system of the phenyl ring with that of the Q carbonyl.\(^6^1\) The exocyclic nitrogen, however behaves primarily as an electrophile and \(C_\beta-N\) bond formation is believed to run slightly ahead of the \(N-C_\alpha\) bond formation so that cleavage of the \(N\)-acetoxy bond is underway before reaction of the QNHOAc nitrogen lone pair with \(C_\alpha\) of the alkene i.e. as in Scheme 21 the reaction is concerted but not synchronous. SN2 displacement of the acetoxy group is again taking place but the configuration at the exocyclic nitrogen is opposite in Schemes 22 and 23.

Whereas endo-overlap of ester and quinazolinone appears to be mandatory for successful aziridination of acrylates (Scheme 22), endo-overlap of phenyl and quinazolinones although preferred, is not a necessity for successful aziridination of styrenoid double bonds (see later).
1.18 Origin of the diastereoselectivity of aziridination with 2-R*(chiral group)-3-acetoxyaminoquinazolinones (Q*NOAc)

In the transition states (Schemes 22 and 23) for aziridination reactions using Q*NOAc, the position of a chiral group at the 2-position can result in chirality induction and the preferred formation of one diastereoisomer of the aziridine over the other. By representing large, medium and small groups at the 2-position by the letters L, M and S, and assuming the alkene has a high preference for approach from the side opposite the L group, two transition states (Scheme 24) are conceivable, each of which leads to a different diastereoisomer of the product aziridine.

![Scheme 24: Diastereoselectivity determined by the site selectivity of L, M and S groups in the transition state of aziridination](image-url)
The diastereoselectivity of this generalised reaction is dependent on whether the groups M and S have specific site preferences in the transition state for the aziridination. These site preferences of M and S will depend not only on their bulk, but also on electrostatic and stereoelectronic effects present in the transition state for the aziridination. If the site preferences are sufficiently large, the chiral 2-substituent will control the face of the alkene attacked and hence the configuration of the created chiral centre. In other words the aziridination can be achieved highly diastereoselectively.

1.19 Chelation-controlled diastereoselective aziridination using Q\textsuperscript{3}NHOAc (38)

Q\textsuperscript{3}NHOAc 28 with L=Bu\textsuperscript{i}, M=Me and S=H in Scheme 24 aziridinates both methyl acrylate and styrene with poor diastereoselectivity.\textsuperscript{53} For both diastereoisomers of the product to be produced in almost equal proportions, clearly the site selectivities of H and Me are not sufficient despite their difference in size (assuming transition states resembling A and B in Scheme 24).

If there was no possibility of rotation around the bond between the Q and chiral group at the 2-position the sites occupied by each group on the chiral centre would be fixed and the face of attack of the alkene would be more easily predictable. One possible way of at least hindering this rotation is by utilising chelation control between N-1 of the quinazolinone ring and a hydroxy substituent at the chiral centre; titanium (IV) \( \text{t-butoxide} \) \([\text{Ti(OBu})_4]\) has been shown to serve this purpose. The titanium mixed alkoxide formed, \textit{in situ}, locks the orientation of the chiral centre in one conformation as shown (Scheme 25), so fixing the orientation of the \textit{tert}-butyl and hydrogen groups. Thus attack of the alkene is directed on to the face distal to the \textit{t}-butyl and, together with an \textit{endo}-orientation of the alkene, gives rise to one diastereoisomer of the aziridine.
It has been shown that the aziridination reactions of styrene, indene, or butadiene using Q$^3$NHOAc 38 in the absence of Ti(OBu$^t$)$_4$ are hardly diastereoselective. However, in the presence of titanium (IV) $t$-butoxide, in every case a single diastereoisomer is formed as shown by NMR spectroscopic examination of the respective crude reaction mixture.$^{62}$

### 1.20 Aziridinations using QNHOAc-TFA: effect on yield and diastereoselectivity.

The above example$^{65}$ demonstrates that in aziridinations using QNHOAc compounds, an increased yield can be achieved by adding TFA (3 eq.), to the reaction mixture. It seems likely that at high concentration of TFA, the rate of decomposition of QNHOAc (c.f. Scheme 17) may be retarded.
It is possible that not only is the rate of aziridination increased in the presence of TFA but also the rate of decomposition of QNHOAc (c.f. Scheme 17) is decreased, possibly by attack of the acetoxy carbonyl oxygen on the C=NH+ of the Q group. Both effects would raise the yield of aziridine.

Scheme 27

Aziridination of methyl acrylate\textsuperscript{55} by racemic Q\textsuperscript{2}NHOAc 39\textsuperscript{46} in the absence of TFA gives 40 as a 2.4:1 ratio of diastereoisomers; in the presence of TFA a 1:8.7 ratio is observed at room temperature which is improved to 1:20 at -50 °C (Scheme 26). Thus the presence of TFA in this aziridination reaction leads to both inversion in the sense of diastereoselectivity and enhancement in the diastereoisomer ratio\textsuperscript{55,64} both of which were accounted for by a change in transition state geometry.
These reactions show a noticeable effect in the yield and diastereoisomer ratio only after three equivalents of TFA have been added to the aziridination reaction mixture. TFA is believed to protonate at \((Q)N-1\) and to bring about a change in the transition state geometry.\(^{66}\) In the absence of TFA the overlap is between the \((Q)C=O\) and the ester \(C=O\) shown in 41 (c.f. Scheme 22); in its presence the overlap is between the \((Q)C=NH^+\) and the ester \(C=O\) as shown in 42\(^{67}\) with the \((Q)C=O\) oxygen also likely to be protonated. The transition state of 42 (side view) for the reaction in the presence of TFA illustrates the particular sites for the substituents at the C-2 chiral centre and the increased diastereoselectivity arises from the augmented site preferences for these substituents due to their proximity to the alkene ester group in a tighter transition state.

1.21 Aziridine ring-opening and Q-N bond reductive cleavage

Aziridine chemistry is dominated by ring-opening reactions because of the release of strain energy contained within the ring and because the larger external ring bond angle allows easier ingress of nucleophiles (Fig. 1). Those reactions involving cleavage of a C-N ring bond may occur by two different mechanisms, depending on the nature of the \(N\)-substituent.\(^{68}\)

Non-activated aziridines bear an electron donating group or proton at the ring nitrogen and typically undergo electrophilic ring opening: protonation, quaternisation or formation of a Lewis acid adduct with the weakly basic ring nitrogen occurs prior to ring-opening, generating partial positive charge on the ring carbon and activating the aziridine for nucleophilic (usually \(S^2\)-type) attack. Thus ring-opening occurs on treatment of the butadiene-derived aziridine 43 with hydrochloric acid with inversion of configuration (Scheme 28).
Activated aziridines bear an electron-withdrawing group on the ring nitrogen and typically undergo direct nucleophilic ring-opening. Typically nucleophilic attack occurs preferentially at the less sterically hindered ring carbon with inversion of configuration ($S_N2$) and the non-basic ring nitrogen is capable of stabilising the negative charge which develops on it when the C-N bond is broken by the nucleophile. Subsequent protonation occurs after the substitution has occurred. In scheme 29 (a) nucleophilic attack by the small negatively charged nucleophile is directed to the methyl bearing carbon (as shown) by a repulsive interaction with the carboxylate anion. Wittig reagents have also been used in ring-opening reactions as in (b). Aziridines bearing a quinazolinone at the ring nitrogen have been shown to undergo ring-opening by nucleophiles without the necessity of preliminary protonation on the ring nitrogen (see Scheme 32) through experiments on the reaction rate. Thus, $N(Q)$-substituted aziridines may be regarded at activated or non-activated depending on the ring-opening conditions.
1.22 Using the Q group to control aspects of aziridine ring-opening

One of the major goals in the study of QNHOAc-derived aziridines has been to find ways of converting single enantiopure diastereoisomers, prepared as in e.g. Scheme 25, into useful chirs - functionalised small molecules containing one or two chiral centres useful as starting materials for stereoselective synthesis. A sub-goal has been to find ways of using the Q-group to control or influence aspects of the aziridine ring-opening.

It is unfortunate that the barrier to \(N\)-inversion in these \(N(Q)\)-aziridines is not in general sufficient to allow separation of the kinetically formed \(cis-N\)-invertomers (see section 1.35 earlier) since, where unusually \(cis\)- and \(trans\)-\(N\)-invertomers can be separated, the stereochemistry of their ring-opening reactions is different as illustrated in Scheme 30.
Protonation of the trans-N-invertomer 44 produces a stabilised ('fully developed') carbocation intermediate that leads to both the trans- and cis- ring-opened products 45 and 46 respectively. The cis-N-invertomer 47 however produces only trans 45; the configuration of 45 was confirmed by its re-conversion to the aziridine by treatment with base whereas none of the aziridine was recovered from the same base treatment of 46. It is clear that the Q-
3-group is in some way responsible for the change in stereochemistry in ring-opening of cis- and trans-N-invertomers of the aziridine.
The above example (Scheme 31) from work by W.T. Gattrell demonstrates a way in which the Q group can be used to change the regiosense of ring opening. Employing sodium iodide in the presence of samarium (III) and acetic acid, the aziridine 48 is nucleophilically ring-opened at the ester-substituted carbon. However aziridine 49, prepared by hydrolysing the ester to an acid and lactonising it with the OH substituent on the substituted Q-2 position of the quinazolinone, is attacked by iodide at the methylene carbon.72
Cleavage of the Q-N bond in the ring-opened aziridine can be effected in good yield by samarium diiodide. Scheme 32 illustrates the conversion of aziridine 50 into both enantiomers of the Q-free chiron 51 by reactions which include a nucleophilic ring opening of the 3-membered ring by azide without prior protonation of the ring nitrogen i.e. the Q group activates the ring for attack in this case. Samarium (II) iodide is an expensive reagent that becomes oxidised during the course of the reaction; magnesium has been shown to reduce the samarium in situ from Sm(III) back to Sm(II), thus allowing less than molar quantities to be employed.

Scheme 33
Raney nickel or sodium in liquid ammonia also cleave $N\cdot N$ bonds effectively; recent work has shown it is possible to cleave the $N\cdot Q$ bond with lithium in liquid ammonia without affecting the aziridine ring (Scheme 33). Other methods of aziridine ring-opening with C-C bond cleavage and the formation of 1,3-dipoles are possible but will not be discussed here.

1.23 Synthesis of $\alpha$-amino acids as single enantiomers

Proteins are essential to life and are found in enzymes in hormones and as participants in ion transport and the immune defence system. These complex molecules are made from $\alpha$-amino acids and these proteinogenic $\alpha$-amino acids are used industrially in many thousands of tonnes every year principally in food additives; they are also cheap enantiopure starting materials for laboratory synthetic work. There is also a demand for unnatural amino acids in enantiopure form. There are two general approaches to preparing these unnatural enantiopure $\alpha$-amino acids; one is to prepare a racemic mixture and subsequently resolve it into its enantiomers. Alternatively a single enantiomer of the required $\alpha$-amino acid can be prepared by stereoselective synthesis.

1.24 Amino acid synthesis by the resolution of racemates

The traditional approach to the resolution of racemates is to derivatise with an optically active reagent, separate the diastereoisomers, and then liberate the single enantiomer from its derivative. An alternative approach is to use enzymes to derivatise one enantiomer of the racemic $\alpha$-amino acid. Aminoacylases (proteases) are enzymes capable of hydrolysing CO-NH (peptide) bonds. If a racemic mixture of $N$-acylated amino acid is mixed with the appropriate aminoacylase, deacetylation of e.g. the L-$\alpha$-amino acid derivative occurs preferentially (Scheme 34). The separation of the acylated and non-acylated amino acids can be accomplished by standard means.
In the following example (Scheme 35) L-α-amino-ε-caprolactam hydrolase was used to selectively hydrolyse L-α-amino-ε-caprolactam in a racemic mixture. Unreacted D-lactam can be converted into the racemic mixture by adding the enzyme D-α-amino-ε-caprolactam racemase (Scheme 35).

Scheme 35

1.25 Amino acid synthesis by modification of available proteinogenic amino acids.

In principle, the selective chemical modification of the side chains of cheap and available proteinogenic amino acids offers an attractive access to unnatural L-α-amino acids.

Scheme 36

Scheme 36 shows how readily available L-glutamic acid can be chemically modified to make L-vinylglycine, a less common α-amino acid found in mushrooms. The first two steps of the synthesis use standard methodology in peptide synthesis to protect the amine and α-carboxylic acid functionalities. This leaves the side chain acid carboxylic exposed
and decarboxylation using LTA followed by deprotection gives the required L-vinyl glycine.80

1.26 Amino acid synthesis by enantioselective synthesis

Chirality induction is the use of an existing chiral centre in a molecule to control the configuration of a newly created chiral centre either in the same or in a different molecule. Usually the existing chiral centre is present in a single enantiopure form and thus the absolute configuration of the newly created centre is defined. The following examples demonstrate the enantioselective preparation of α-amino acids bearing one α-substituent making use of chiral auxiliaries.

Scheme 37 shows a completely stereoselective route to α-amino acids developed by Corey,81 which mimics the biological transamination process. Compound 52 is a transaminating agent that condenses with the methyl pyruvate to give an imine-lactone. The bulky alkyl group (CH₂O) hinders the top face of the molecule so that the reducing agent attacks preferentially from the bottom face. The α-amino acid moiety is cleaved from the transaminating agent to give D-alanine in >98% ee.
Another example of chirality induction being applied in stereoselective synthesis of α-amino acids is shown in Scheme 38. After preparing compound 53, the (chiral) substituent situated distal from the anion on the ring directs attack on the opposite face to provide the product in 70-90% ee depending on the nature of R.

1.27 Preparation of enantiopure α, α-disubstituted α-amino acids

α,α-Disubstituted α-amino acids are often effective enzyme inhibitors and also constitute a series of interesting building blocks for the synthesis of numerous bioactive peptides, potential therapeutic agents, and natural products. Their incorporation restricts the conformational freedom of molecules in which they are incorporated which makes them invaluable to the biological chemist investigating mechanisms of enzyme action and for probing the biologically active conformation within the molecules they are incorporated into. Two recent methods of preparing enantiopure α, α-disubstituted α-amino acids are given below; most available methods do not lend themselves to the preparation of these compounds.

The first example shows a catalytic enantioselective synthesis of an α, α-dialkyl-α-amino acid by phase-transfer alkylation. Alkylation of the achiral imine 54 in the
presence of a catalytic amount of 55 by benzyl bromide (as shown in Scheme 39) produces the α, α-dialkyl-α-amino acid ester 56 which can be easily hydrolysed in a subsequent step. The alkylation is almost completely enantioselective giving the R-configured product (98% ee) in a high isolated yield.$^85$

![Scheme 39](image)

In the example below$^82$ (Scheme 40), the chiral diol reacts with ethyl 2-methyl acetoacetate 57 producing a chiral acetal in 81% yield as a diastereoisomeric mixture at the methyl-substituted carbon. Subsequent alkylation at this centre produces the enol ether 58 in moderate yield.
Conditions: a) (S,S)-cyclohexane-1,2-diol (0.7 eq.), p-toluenesulfonic acid monohydrate (0.06 eq.), benzene, reflux 10 h.; b) LDA (5 eq.), nPr-I (5 eq.), THF-HMPA (5 eq.); c) BF₃·OEt₂ r.t.; d) NaN₃, CH₃SO₂OH, 5-6 h.

Scheme 40

The investigators explained the diastereoselection (d.e. >95%) in this step by consideration of a plausible Li-chelated intermediate. With the lithium atom tri-chelated (as shown in Fig. 2), the re-face of the C(2)-position might be shielded by the (S,S)-cyclohexa-1,2-diol moiety, and the electrophiles could exclusively attack the si-face of the enolate to afford (2S)-product 58.

Figure 2
The Schmidt rearrangement in step d proceeds with retention of configuration, the configuration of the quaternary carbon is retained to produce the \( R \)-configured product ester. The amino acid is easily prepared by hydrolysis of the amino acid ester.

It has been shown (Scheme 41) that \( N \)-(3,4-dihydro-4-oxo-3-yl)-substituted amino acid esters can be obtained directly by reaction of silyl ketene acetics with Q\(^{\text{NHOAc}}\) 60. A 3:1 ratio of diastereoisomers of \( N \)-(Q)-\( \alpha \)-aminoesters was produced and after separation of the major diastereoisomer, reductive cleavage of the quinazolinone gave the unnatural enantiopure \( \alpha,\alpha \)-disubstituted \( \alpha \)-amino acid ester (Scheme 41).\(^{86} \)

\[ \text{Scheme 41} \]

\[ \text{1.28 Tethers} \]

A tether in the present context is a chain of atoms connecting two reactants. A properly tailored tether can result in a greatly increased reaction rate with regiospecific and stereoselective formation of the product. Three important points may be considered when constructing the tether.

\[ \text{1.29 Tether length} \]

To ensure the benefits of intra- over an intermolecular reaction, the two interacting functional groups must be bound by a tether of an appropriate length. The most important factor when considering the tether length is that it must be long enough to accommodate the transition state geometry for the reaction. This means that in the solution in which the reaction is conducted, the two reactants are much more frequently brought together in a configuration conducive for reaction than had they not been linked by the tether. The
reaction rate is therefore increased primarily by the effect of the tether on $\Delta S^\#$, the entropy of activation.

Complete regioselectivity in a predictable sense is the consequences of limiting the tether length. Thus a 3- or 4- atom tether in the Diels Alder reaction with the diene linked at its terminal position can only give the fused product (Scheme 42). The analogous intermolecular reaction may be non-regioselective or completely regioselective in the opposite sense. With a longer tether, formation of the bridged product becomes competitive, and regiospecificity is lost.

![Scheme 42]

1.30 Fashionable and fissionable tether links

Clearly the tether must be fashioned from two reactants linked together using reactions chemospecific for formation of the tether. Although in some cases the tether is destined to become a required part of the target molecule (and is designed with this in mind) more often the tether serves its purpose in the intramolecular reaction step and must be either removed (a disposable tether$^87$) or transformed in a subsequent step such that it gives rise to, for example, the desired substituents of the product. Thus a desirable feature of the tether in either of these cases is that it should be *fissionable* - i.e. be cleavable in a controlled way, preferably under mild conditions not affecting the product formed from the intramolecular reaction step. Ideally the fissionable link must be robust enough to withstand the reaction conditions but chemospecifically cleaved under mild conditions after the intramolecular reaction has occurred. Single atoms e.g. O, S, Si, comprising the link have been used widely. The intramolecular Diels Alder reaction in Scheme 43 employs an ether linkage.$^{88}$
The ether linkage is introduced by nucleophilic displacement. Partial hydrolysis of the acetal followed by reaction with (EtO)$_2$P(O)CH$_2$CO$_2$Et (3 eq.) and NaH in THF (58%) produces the triene ether 61. Subsequent thermolysis at 170 °C for 18-22 h. afforded the cycloadducts 62a and 62b (40:60) in 86% yield.

In the general reaction scheme above, cleavage of the C-O bond in the intramolecular cyclisation product 63 (Scheme 44) can occur in two ways i.e. chemoselectivity cannot
be taken for granted. Cleavage may also require quite strong acid or Lewis acid. A useful attribute of a thioether linkage is its reductive cleavage to two C-H bonds (Scheme 45), with Raney nickel.

\[
\begin{align*}
\text{Ar} &= 4-^\text{TBuC}_6\text{H}_4 \\
\text{R-Ni} &\quad (99\%) \\
\text{Me, NHAr} &\quad \text{NHAr} \\
\text{OH} &\quad \text{OH} \\
\end{align*}
\]

Scheme 45

Tethers consisting of two oxygen or nitrogen atoms or N-O (O-O\textsuperscript{89}, N-N\textsuperscript{90}) are convenient fissionable groups and are broken under mild reductive conditions but formation of the bond between the heteroatoms may not be straightforward. (These bonds are more often found as fissionable bridges in cycloaddition products, see Scheme 45 above).

Other contiguous atom links are also widely used as a fissionable unit in intramolecular Diels Alder reactions\textsuperscript{91}, particularly O-Si and O-B (Scheme 46). Again formation is straightforward by reaction of a silyl or boronyl chloride with an alcohol.

\[
\begin{align*}
\text{R}^1 &\quad \text{R}^2 \\
\text{OH} &\quad \text{Cl} \\
\text{base} &\quad \text{OH} \\
\end{align*}
\]

Scheme 46
In the example in Scheme 47, Stork et al employ a Si-O containing tether for the diastereoselective radical-mediated C-C bond formation shown. The Si-O containing tether is formed in the initial step by reaction of the silyl chloride with the OH substituent on the heterocycle. Deselenylation using Bu3SnH and AIBN in benzene generates a radical that cyclises to give a cis ring fusion. In the last step the Si-O and Si-C bonds of the tether are cleaved by Bu4N+BF4⁻.

A disadvantage to using Si-O and B-O linkages is their hydrolytic instability. Purification of the tethered product before intramolecular reaction may be difficult by chromatographic means although cleavage in the product from intramolecular reaction is facile.
1.31 C=C and ester containing tethers

Unlike tethers containing single heteroatoms (O, S, Si) or two contiguous heteroatoms (O-Si, O-B) for which there are no or only very small geometrical preferences other than those arising from normal sp\(^3\) hybrid bond angles, functional groups which contain double bonds e.g. C=C or C=N or quasi-double bonds (e.g. esters and amides) clearly have a requirement for planarity which must be accommodated in the tether design. They may also have a configurational requirement i.e. normally the C=C must be used in the cis form, to avoid an excessive tether length (Scheme 48).

![Scheme 48: intramolecular reaction of a cis- or trans-alkene](image)

The ester is also in this category because there is a particularly high preference for the s-cis form over the s-trans. The s-cis conformer of methyl formate has been found to be more stable than the s-trans isomer by 3.85 kcal/mol\(^{92}\) and 4.75 kcal/mol\(^{93}\) in two separate calculations. The energy difference found in solution is about half as large (1.19 kcal/mol)\(^{94}\) as that obtained in the gas phase.\(^{95, 24-25}\) The preference in esters generally, for the s-cis conformation over the s-trans arises from overlap of the lone pair in a sp\(^2\) orbital on oxygen and \(\sigma^*\) (C=O) (Scheme 49) (an interaction resembling the anomeric effect present in glycosides). The s-cis conformation is also more stable because steric interactions are minimised.\(^{96}\) As with alkenes, reaction via the less stable s-trans conformation would be expected to be easier (Scheme 49).
The ester is a useful functional group in a tether and serves to link the two reactants, one present as an acid and the other as an alcohol and, after intramolecular reaction, allows easy hydrolytic cleavage or transesterification to give two chemo-differentiated functional groups in the product.

With a limited number of additional atoms in the tether besides the ester (3), intramolecular Diels Alder (IMDA) reaction is only possible from the s-trans conformation of the ester. Although the barrier for s-cis → s-trans interconversion is believed to be low, the required reaction temperature will be raised because of the necessity for reaction to take place via a conformation present in very small concentration.

A further factor which will raise the activation energy of these IMDA reactions with only one or even two methylene groups in the tether as well as the ester is that the planarity of the ester group cannot be maintained in the transition state for the $4\pi + 2\pi$ cycloaddition. The set of examples below (Scheme 50) illustrate the more severe reaction conditions and adverse effect on the yield that incorporation of any ester into the tether has relative to an amide or ketone.
<table>
<thead>
<tr>
<th>X</th>
<th>Conditions</th>
<th>Yield</th>
<th>ratio cis:trans</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂</td>
<td>0 °C / 1h.</td>
<td>78%</td>
<td>100 : 0</td>
<td>94</td>
</tr>
<tr>
<td>NMe</td>
<td>80 °C / 2h.</td>
<td>83%</td>
<td>8 : 1</td>
<td>95</td>
</tr>
<tr>
<td>NH</td>
<td>85 °C / 10h.</td>
<td>71%</td>
<td>7 : 1</td>
<td>95</td>
</tr>
<tr>
<td>O</td>
<td>210 °C / 5h.</td>
<td>42%</td>
<td>9 : 1</td>
<td>95</td>
</tr>
</tbody>
</table>

Scheme 50

High reaction temperatures can be detrimental to the outcome of ester-tethered IMDA reactions because competitive side-reactions such as syn-elimination can become important.¹⁰⁰

Scheme 51

The IMDA reaction below employs a substrate that makes use of an ester-containing tether,¹⁰¹ notice the requirement for the s-trans conformation of the ester in this example, and that the dienophile is additionally activated by its ester substituent.
The transition state geometry is sufficiently tight in Scheme 52 that the reaction is both completely diastereoselective and regiospecific; subsequent double bond reduction takes place exclusively from the exo face due to steric repulsion between the reagent and the erstwhile tether and ring-opening gives a product with four chiral centres. The selectivity inherent in this conversion is apparent when one considers how problematic synthesis of this product would be starting with the intermolecular Diels-Alder reaction shown.

Shea\textsuperscript{87} has reported IMDA reactions which contain 4 or 5 atoms in the tether in addition to the ester (which includes silicon) and which therefore can react \textit{via} the \textit{s-cis} conformation.\textsuperscript{99} (Scheme 53).
D. Craig and co-workers\textsuperscript{102} have demonstrated that diester-tethered trienes conformationally-restricted by including a trans-1,2-substituted cyclohexane in the tether undergo stereoselective intramolecular Diels Alder reactions. The success of this reaction is attributed to the presence of both esters in the tether of triene 64 in their preferred s-cis conformations and the \( \gamma \)-oxy-\( \alpha,\beta \)-unsaturated ester dienophile present in its preferred ‘outside’ conformation (Scheme 54).
The reaction above gave a 7:1 mixture of two tetrasubstituted cyclohexene adducts (65 and 66) in good yield with good levels of regio- and stereochemical control. The trans,cis-fused structure 65 assigned to the major product arises from an exo-transition state 67.

The stereostructural assignment of 65 was confirmed by X-ray analysis and hydrolysis experiments. The minor product though not fully characterized, was tentatively given the structure 66 being an endo-structure resulting from this reaction. The tether may easily be removed in good yield to release the cyclohexene derivative.

1.32 Incorporation of a chiral element into the tether

Incorporation of a chiral element (usually a chiral centre) into the tether can give rise to diastereoisomers when additional chiral centres are formed from two prochiral reactants e.g. in a cycloaddition reaction.
Scheme 55 shows the relationship between the transition states leading to the two alternative diastereoisomers of the product in an intramolecular Diels-Alder reaction. The reaction would be expected to proceed via the transition state 68b when \( R = \text{CO}_2\text{Me} \) because in the alternative diastereoisomeric transition state 68a there is a destabilising 1,3-type interaction between the \( \text{CO}_2\text{Me} \) on the dienophile and the methyl on the tether. Consequently, by a nice placement of the methyl on the tether, the cycloaddition has been rendered highly diastereoselective and were the chiral centre in the tether present in a single enantiopure form, the newly created chiral centres would be of a predictable absolute configuration.

In the cycloaddition in Scheme 55 the chair motif of the tether minimises angle and torsional strain and the greater stability of the chair-like conformation with its equatorially-located methyl substituent means that competitive reactions via transition states having alternative conformations for the tether are less likely. The usual preference for substituents to occupy equatorial rather than axial positions on a cyclohexane chair means that transition state 68b would be expected to be favoured over 68a even when \( R = \text{H} \) but the diastereoselectivity of the cycloaddition would certainly be expected to be more complete when \( R = \text{CO}_2\text{Me} \) because of the greater energy difference \( \Delta\Delta G^\circ \) between transition states 68a and 68b.
In general, diastereoselectivity is raised as the temperature of a reaction is reduced. Accordingly the diastereoselectivity of the reaction in Scheme 55 would be higher with R=CO₂Me if, as anticipated, the reaction temperature required was lowered. The ester activates the dienophile by reducing the energy of its LUMO level in the cycloaddition. The endo-overlap in the transition state would also be expected to lower the transition state energy (Alder’s endo-rule) by comparison with an analogous reaction when R=H. Thus, the presence of the ester raises the diastereoselectivity of the reaction in two ways.

To generalise: the diastereoselectivity in any reaction such as that in Scheme 55 will be maximised when a single conformation for the tether is preferred in the transition state and where there are clearly identifiable sites for the substituents on the inducing chiral centre in the tether. It follows that the tether must be of a nice length, ‘nice’ in this context meaning precise, i.e just long enough so that the tether is conformationally defined with all stereoelectronic and conformational factors accommodated. The tether must be sufficiently short to restrict severely the number of contending conformations for the tether in the transition state but not too short such that access to the preferred transition state geometry for the reaction is unduly raised in energy.

The inducing centre is expediently located on the tether because it will not usually be required in the target molecule and can be removed, along with the unwanted elements of the tether, after the intramolecular reaction (not easily the case in Scheme 55). It is also usually synthetically more convenient to install the chiral centre in the tether.

This discussion on tethered intramolecular reactions has focussed on the construction of stable, isolable tethered reactants but there is also a large important class of related reactions where the tether is formed and broken in situ. Thus epoxidation of cyclohexen-3-ols with peroxyacids commonly involve tethered reactions (see Scheme 16 earlier). Likewise in the Sharpless enantioselective epoxidation of allylic alcohols this tethering is present albeit in disguised form (Scheme 56). Here the titanium tartrate can be considered to be playing the role of a tether for the substrate (the allylic alcohol) and the reagent (the hydroperoxide), in which the binding of the reagent / substrate / product to the titanium tartrate catalyst is reversible i.e. the tether is continuously being made and broken as is required for the use of the catalyst in sub-molar quantity.
Many enzyme-catalysed reactions can be interpreted as involving a similar mechanism i.e. the substrate and the reagent are ‘tethered’ by the enzyme for reaction to occur.

1.33 Previous work on intramolecular aziridination of alkenes using QNHOAc compounds.

The work of Grimshire\textsuperscript{103} illustrates an alternative use to which tethered reactions can be put; to provide experimental evidence for the transition state (TS\textsuperscript{#}) geometry of a reaction. Grimshire studied the response to tether length of the selectivity between two alkenes contained in each branch of a bifurcated tether e.g. QNHOAc compounds \textbf{69a} and \textbf{70a}.

Yields of aziridines from intramolecular reactions with the tether-contained alkenes were almost quantitative but whereas the ratio of attack on the phenyl-substituted vs unsubstituted double bond in \textbf{69a} was 1.5:1, in \textbf{70a} it was 5.8:1. (In this work the reactive intermediates were supposed to be the corresponding nitrenes but are now known to be the corresponding 3-acetoxyaminoquinazolinones).
This change in selectivity was interpreted as a change from a highly asynchronous reaction involving build up of carbocation character at the alkene \( \beta \)-position 69b (R=Ph) in aziridination of QNHOAc 69a to a more synchronous concerted reaction 70b in aziridination using QNHOAc 70a. Thus concerted aziridination requires three carbons in the tether and, from examination of Dreiding models, this is consistent with approach of QNHOAc and alkene in almost parallel planes with the Q-N bond orthogonal to the C=C bond of the alkene (cf. Schemes 22 and 23).

The reaction shown in Scheme 58 also takes place in excellent yield presumably via the transition state shown, although endo-overlap of the Ph and Q in the transition state (cf Scheme 23) is geometrically impossible due to the short length of the tether. The complete diastereoselectivity observed can be rationalised by assuming that the non-reacting cinnamyl substituent prefers the equatorial-type position (shown) thereby avoiding adverse interaction with the N-HOAc.\(^{104}\)

![Scheme 58](image-url)
Chapter 2
Attempts to bring about chemoselective acylation of the $\omega$-hydroxyl group in 2-$(\omega$-hydroxyalkyl)-3-aminoquinazolinones
2.1 Aims of the work

Although there are a number of examples of high diastereoselectivity in intermolecular aziridinations using QNHOAc particularly using the method of Gattrell (see earlier), in most cases the diastereoselectivity is considerably reduced when the reacting alkene is di- or tri-substituted.\(^{62}\)

In the above aziridination of \(\alpha\)-methylstyrene, normal reaction conditions gave only a 5:1 diastereoisomeric ratio of aziridines. An increase in diastereoselectivity to 9:1 was obtained by stirring 38 with \(\text{Ti(OBu}^t\text{)}_4\) for 1h. at \(-20^\circ\text{C}\) before addition of the \(\alpha\)-methylstyrene, but only with a loss in yield.\(^{63}\)

The aim of this work was to take advantage of the high diastereoselectivity previously found in intramolecular aziridination of double bonds tethered to the 2-position of a 3-aminoquinazolinones (see above). By incorporating an ester as a fissionable group into the tether retrieval of the chiral centres created in the intramolecular aziridination would be facilitated.

By using an ester formed from an \(\alpha,\beta\)-unsaturated acid, a route to enantiopure substituted \(\alpha\)- or \(\beta\)-amino acids was envisaged (see below). It was anticipated that this strategy, if successful, would offer advantages over existing methods for formation of chirons from the products of intermolecular aziridination using QNHOAc compounds, described earlier.
The above Scheme summarises the general strategy envisaged for preparation of α- or β- amino acids as single enantiomers from (achiral) α,β-unsaturated acids. The starting 2-substituted 3-aminoquinazolinone, prepared in enantiopure form, would be chemoselectively O-acetylated with the corresponding acid chloride. N-Acetoxylation by lead tetra-acetate (LTA) and intramolecular aziridination by the resulting N-acetoxyamino functionality of the double bond of the α,β-unsaturated ester would be
required to provide the aziridine as a single diastereoisomer, the existing chiral centre in
the tether controlling the configuration of the two new chiral centres formed. Since the
aziridination is syn-stereospecific, the relative configuration of the two chiral centres is
defined by configuration of the double bond. The final steps require complete
stereoselective aziridine ring-opening in either regiosense, then retrieval of the newly
formed chiral centres in the α- or β-amino acid. Overall this Scheme involves the
addition of the elements NH₂ and Nu⁻ regio- and enantiospecifically across the double
bond. Synthesis in bulk of these chirons represents the final goal of this work.

2.2 Critical analysis of the strategy

The strategy in Scheme 60 offers a number of challenges that are identifiable.

i) The acylation must occur chemoselectively at the hydroxy group in the presence of
the amine group in QNH₂ in the first step. Since the Q group is known to be electron-
withdrawing (see Scheme 32), a reduction in nucleophilicity of this amine group is
anticipated; control over the chemoselectivity of the acylation reaction may be
accomplished by changing the reaction conditions or by modification of the substrate /
acylating agent.

ii) High diastereoselectivity in the aziridination requires a single conformation for the
tether and defined sites for R and H on its chiral centre in the transition state (TS#). To
maximise the diastereoselectivity, therefore, the tether needs to be kept to a nice length as
defined previously (see Introduction; Scheme 42) in which all the conformational
preferences in the tether and the preferred TS# geometry for the aziridination must be
accommodated. In particular enough atoms in the remainder of the tether will be required
to allow assumption of the planar s-cis conformation for the ester in the TS#.

iii) Intramolecular aziridination of electron-deficient double bonds such as that present
in QNHOAc always requires endo-overlap of the carbonyl group with the Q group (see
Introduction; Scheme 22) and so it is likely this overlap will also be necessary in the TS#
in this case.

iv) The siting of the chiral centre on the tether is an important consideration.
Intuitively, one would consider introduction of the inducing chiral centre as close as
possible to the site of reaction. It should be borne in mind, however, that it is the presence
of identifiable sites for R and H on the tether will dictate which diastereoface of the double bond is aziridinated in the TS#. With a defined conformation for the tether the chiral centre might well be located at a position more distant from the double bond.

v) The sense of regioselectivity for aziridine ring-opening may be controlled by whether this is carried out before or after lactone ring-opening. A previous study has shown that ring-opening in complementary senses can be achieved in analogous aziridine-lactones and the corresponding aziridine esters72 (see Scheme 31, Introduction). Mild methods for retrieval of the chiral centres will be necessary since epimerisation, particularly α- to the carbonyl group, will undermine any diastereoselectivity achieved in the aziridination.

2.3 The preferred conformation of the s-cis ester relative to the quinazolinone

The two TS#s in which the s-cis conformation of the ester and the orthogonal approach of C=C and N-Q bonds are both accommodated are illustrated in 71 and 72 but 71 is clearly preferred over 72 because a) the possibility of endo-overlap of the C=O of the ester with the C=N of the Q group is only possible in 71 (see Scheme 22) and b) the tether length in 71 is reduced by comparison with 72. In other words, with the tether a nice length, the mandatory endo-overlap of the ester C=O and Q may be present anyway as a consequence of a) above. However, in intermolecular aziridinations of α,β-unsaturated esters, endo-overlap of the ester C=O is believed to be with the Q C=O; only
in the presence of TFA when the QN-1 is protonated is overlap of the ester C=O and Q C=N preferred (see 42).

The conclusion, therefore, is that either the endo-overlap illustrated in 71 is adequate to permit nucleophilic attack of the (Q)NHOOAc on the β-position of the α,β-unsaturated ester (compare mechanism of aziridination in Scheme 22, Introduction) or the intramolecular aziridination must be carried out in the presence of TFA.

2.4 Attempts at chemoselective O-acylation using Q4NH2 76

This 3-aminoquinazolinone 76 was prepared as a model compound in order to determine whether selective O-acylation was possible in the presence of the 3-amino group.

\[
\text{(S)-lactic acid} \quad \xrightarrow{\text{AcCl}} \quad \text{73} \quad \xrightarrow{\text{SOCl}_2} \quad \text{74}
\]

The enantiopure 2-(1-hydroxyethyl)-substituted 3-aminoquinazolinone 76 was first prepared using the route in Scheme 61 by Williams,\textsuperscript{102} and subsequently developed by Coogan.\textsuperscript{105} The same procedure was used to prepare all the 3-aminoquinazolinones prepared in the course of the work described in this thesis, all of which were colourless crystalline solids. In this general procedure, the crude acid chloride, normally without purification, was added to methyl anthranilate (2.2 eq.) dissolved in ether. Precipitation of the thick methyl anthranilate hydrochloride required paddle-stirring of the mixture to
maintain homogeneity during this addition. $^1$H-NMR analysis identified the methyl $N$-alkanoyl anthranilate intermediate from four distinctive multiplets at $\delta$8.7, 8.1, 7.6 and 7.1 assigned to the aryl ring protons. Conversion of the $N$-alkanoyl anthranilate to the product QNH$_2$ with hydrazine was normally achieved by heating under reflux in ethanol for ~5h. but heating at higher temperatures (sealed tube) was necessary with bulkier alkanoyl groups. The $^1$H-NMR spectrum of the QNH$_2$ compounds have distinctive multiplets ($\delta$8.2, 7.7 and 7.5) assignable to their aryl ring protons. In the preparation in Scheme 61 the best overall yield by this author from lactic acid (which is only 85% pure, Aldrich) was 31% on a 50g scale (the acid chloride was distilled in this case).

Experiments in which Q$_4$NH$_2$ 76 was acylated with pent-4-enoyl chloride and with cinnamoyl chloride were initially studied.

a) **Using pent-4-enoyl chloride (1.3 eq.)**

![Scheme 62 with structures of MAQ$^2$, MAQ$^1$, and Q$^6$NH$_2$]
Acylation of Q^4NH_2 76 was carried out in pyridine using the title acid chloride (1.3 eq.) and the products were identified from the ¹H-NMR spectra following partial separation of the reaction mixture by column chromatography. Two fractions were obtained, the first a 4:1 mixture of the O-acylated product 79 (~40% yield) and the N,O-diacetylated compound 77 (~10% yield), the second fraction a 2:1 mixture of the N-acylated compound 78 (MAQ¹) (~12% yield) and starting material 76 (~24% yield). Further chromatography of the first fraction gave the O-acylated product 79 in 11% yield as a colourless crystalline solid.

Key spectroscopic data from the ¹H-NMR spectrum of compound 79 that supported its assigned structure were as follows; i) integration of the olefin and CH_2CH_2 protons in the pentenoyl group at δ 5.8, 5.0 and 2.4 relative to the CH_3CH protons at δ 1.60 and 6.22 indicated a monoacylation product, ii) although the NH_2 singlet overlaps the CH=CH_2 signal, its presence was betrayed by the 4H integration of this multiplet, iii) the absence of an NH singlet at low field and the lack of additional signals arising from the presence of N-N bond rotamers both of which are characteristic of 3-acylaminoquinazolinones (MAQs) such as 78 (see 1.15).

The identity of MAQ 78 as one of the products was confirmed when a pure sample was obtained (see below) and its ¹H-NMR spectrum compared with that of the second fraction obtained after chromatography above. Likewise a pure sample of the N,O-diacetylated product 77 was prepared as described below and its ¹H-NMR spectrum compared with that of the first fraction from the chromatography above.

b) Using excess pent-4-enoyl chloride

Acylation of Q^4NH_2 76 was carried out in pyridine and excess pent-4-enoyl chloride (2.2 eq.) and the N,O-diacetylated product 77 (~24%) separated by chromatography from unchanged starting material 76; no N- or O-acylated material were identified. As expected, two sets of signals (ratio 2.8:1) were visible in the NMR spectrum of this compound corresponding to the two N-N bond rotamers.
Key spectroscopic data from the $^1$H-NMR spectrum of compound 77 were:

i) the integration ratio of the signals for olefin and $CH_2CH_2$ protons at $\delta$ 5.84, 5.03 and 2.46 to the signals for the $CH_3CH$ protons at $\delta$ 1.60 and 6.10 is ~7:2 indicating diacylation had occurred, ii) an accurate mass determination agreed with incorporation of two acyl groups and iii) a pair of NH singlets (at $\delta$ 10.30 and 10.50) for the two rotamers and the absence of OH signal suggested acylation on both $O$ and $N$.

c) Conversion of MAQ 77 into MAQ 78: hydrolysis of the O-acyl group

Mild hydrolysis of MAQ$^2$ 77, prepared as described above by sodium hydroxide (5 eq.) in aqueous ethanol gave MAQ 78 after chromatography.

The $^1$H-NMR spectrum confirmed the presence of just one pentenoyl residue from the relative integration of the olefin and $CH_2CH_2$ protons at $\delta$ 5.88, 4.96 and 2.54 relative to both rotamer signals for the $CH_3CH$ protons at $\delta$ 1.50 and 4.70 was 7:4 indicating monoacylation.
d) Using trans-cinnamoyl chloride

\[
\begin{align*}
\text{Me} & \quad \text{N} & \quad \text{N} & \quad \text{O} & \quad \text{NH}_2 \\
\text{OH} & \quad \text{N} & \quad \text{N} & \quad \text{O} & \quad \text{NH}_2 \\
\text{Ph} & \quad \text{COCl} & \quad \text{pyr.} & \quad \text{Me} & \quad \text{N} & \quad \text{N} & \quad \text{O} & \quad \text{NH}_2 \\
\end{align*}
\]

Scheme 64

Acylation of \( Q^4 \text{NH}_2 \) 76 using cinnamoyl chloride (1.3 eq) was carried out in pyridine. After work up the crude reaction product was triturated with ethanol and the \( O \)-acylated product 80 (\( Q^5 \text{NH}_2 \)) was obtained as a colourless crystalline solid in 27% yield. Key spectroscopic data from the \( ^1\text{H}-\text{NMR} \) spectrum supporting structure 80 were: i) integration of the COCHCHPh (\( \delta 6.56 \)) and phenyl (\( \delta 7.5 \)) protons relative to CH\( _3 \) (\( \delta 1.78 \)) and CH\( _2 \text{CH} \) (\( \delta 6.46 \)) consistent with the presence of one cinnamoyl group, ii) the presence of the NH\( _2 \) singlet (at \( \delta 5.00 \)) and absence of the broad singlet for OH (at \( \delta 4.30 \) in 76) and iii) the downfield shift of the CHO(CO) proton from \( \delta 5.18 \) in QNH\( _2 \) 76 to \( \delta 6.46 \) in 80. The residue was believed to contain a mixture of starting material \( Q^4 \text{NH}_2 \) 76, \( N,O \)-diacylated and \( N \)-acylated products (Scheme 62) which was not further investigated.

2.5 Acylation of \( Q^4 \text{NH}_2 \): mechanism

\( Q^4 \text{NH}_2 \) 76 gave poor chemoselectivity in the attempted \( O \)-acylation reactions above producing the \( O \)-acylated, \( N \)-acylated and the \( N,O \)-diacylated product. Conceivably the acylation occurred more rapidly on oxygen, the rate of an initial \( N \)-acylation being much slower, but acyl group transfer to the nitrogen occurred followed by rapid \( O \)-acylation (Scheme 65). This mechanism may have explained the low yield of mono-\( N \)-acylated quinazolinone 82 isolated from chromatography of acylation reaction mixtures.
In a test to discover whether the \( O \)-acyl group was transferred to the nitrogen, the purified \( O \)-ester \( 83 \) (prepared as described below) was heated on a Kofler block over its melting point (152-153 °C) (Scheme 66).

The \( O \)-acetate \( 83 \) was recovered unchanged so transfer in the acylation reaction is unlikely. This \( O \)-acylated product \( 83 \) was also shown to be stable to flash silica during chromatography.
2.6 Reaction of Q\textsuperscript{4}NH\textsubscript{2} with acetic anhydride in the presence of TFA.

![Scheme 67](image)

Protonation of these 3-aminoquinazolinones is believed to occur on the Q-carbonyl oxygen or N-1 nitrogen or possibly both in preference to the 3-amino group.\textsuperscript{66} Protonation at either of these sites should adversely affect the base strength / nucleophilicity of the 3-amino group more than the hydroxyl group in Q\textsuperscript{4}NH\textsubscript{2} 76. Acylation of Q\textsuperscript{4}NH\textsubscript{2} 76 was therefore examined in dichloromethane containing TFA (3 eq.) with acetic anhydride (1.2 eq.) with the expectation that more selective O-acetylation would occur. The reaction mixture was an approx. 1:1 mixture of starting material 76 and the O-acylated compound 83.

Although this device for selective deactivation of the 3-amino group was not examined further for Q\textsuperscript{4}NH\textsubscript{2} 76, highly selective O-acylation of Q\textsuperscript{17}NH\textsubscript{2} 147 was accomplished using 3,3-dimethylacryloyl oxide chloride in TFA solution (see Chapter 4).

2.7 Using 2,6-di-\textit{tert}-butyl-4-methyl pyridine

Attempts to improve the chemoselectivity of Q\textsuperscript{4}NH\textsubscript{2} cinnamoylation by varying reaction time and/or temperature did not lead to any improvement in yield of O-acylated product. The actual acylating agent in reactions of acid chloride and pyridine is believed to be the N-acylpyridinium salt (shown acylating ROH in Scheme 68).
In 2,6-di-tert-butyl-4-methyl pyridine, the substitution adjacent to the pyridine nitrogen prevents pyridinium salt formation without reducing its basicity. The function of this base when substituted for pyridine in acylation reactions is therefore solely to remove the hydrogen chloride formed and since the reagent is now the less reactive acid chloride, the chemoselectivity for O-acylation might be increased.

Attempted cinnamoylation of QNH$_2$ 76 following the same procedure as before but replacing pyridine by 2,6-di-tert-butyl-4-methyl pyridine and comparison of the $^1$H-NMR spectrum of the crude product with those of authentic samples showed the presence of $\sim$2:1 mixture of $N,O$-diacylated product 81 (21% isolated yield) and starting material 76 (~10% isolated yield).

2.8 The insolubility of Q$^4$NH$_2$ 76

Q$^4$NH$_2$ 76 was found to be sparingly soluble in DCM. At least some of the $N,O$-diacylated products, therefore may have arisen because of the solubility of the $O$-acyl derivative and its greater exposure to the acylating agent. The solubility of Q$^4$NH$_2$ was somewhat higher in pyridine / dichloromethane mixtures but in this case also, large amounts of solvent were required for a homogenous solution than were desirable.
In an experiment (Scheme 69) where the Q\textsuperscript{4}NH\textsubscript{2} was almost all dissolved prior to addition of the cinnamoyl chloride (1.2 eq.), \textsuperscript{1}H-NMR analysis of the crude product mixture showed the presence of starting material and \textit{O}-acylated product (ratio 1:2). The \textit{O}-acylated product \textbf{80} was isolated by chromatography in 21\% yield and was identical to that isolated previously. Other QNH\textsubscript{2} compounds used subsequently were invariably more soluble than Q\textsuperscript{4}NH\textsubscript{2} in pyridine or pyridine / DCM.

The results from these experiments using Q\textsuperscript{4}NH\textsubscript{2} \textbf{76} as a model compound to examine the possibility of selective \textit{O}-acylation in the presence of the 3-amino group were not encouraging. Although selective \textit{O}-acylation did occur, the isolated yield of product was poor and \textit{N}- mono- or \textit{N},\textit{O}-di-acylation was often competitive. There also appeared to be significant and unexplained differences in chemoselectivity between cinnamoyl chloride and pentenoyl chloride. The fact that the alcohol in Q\textsuperscript{4}NH\textsubscript{2} is secondary may reduce its reactivity relative to the 3-amino group and so selective \textit{O}-acylation using the Q\textsuperscript{4}NH\textsubscript{2} compound \textbf{89} below was attempted.
2.9 O-Cinnamoylation of (R)-2-(1-hydroxymethyl)ethyl-3-aminoquinazolin-4(3H)-one 89

More selective O-acylation was anticipated for reaction of the less hindered primary hydroxyl group in the side-chain of 3-aminoquinazolinone 89. The previously unknown Q\textsuperscript{$\text{NH}_2$} 89 was prepared as a crystalline solid (overall 26% yield) with a specific rotation $[\alpha]_d^{20} = -16^\circ$ ($c=1, \text{CHCl}_3$) from the commercially available (R)-hydroxyl ester 84 (supplied courtesy of Roche) by the standard route shown in Scheme 70.

Using the conditions given in Scheme 71, esterification of the hydroxy group in the now completely soluble 3-amino-quinazolinone 89 with cinnamoyl chloride took place selectively; $^1$H-NMR analysis of the crude reaction product suggested that the only other minor component present was the starting material. The O-cinnamoylated product 90 was isolated as an oil by chromatography in 87% yield with an integration of the CH$_3$CH doublet signal ($\delta$ 1.47) relative to the olefinic CHPh proton doublet ($\delta$ 6.35) of 3:1.
In this and in all other subsequent O-acylations reported there was a greater difference in polarity between the alcohol and the O-acylated product than between the O- and what was believed to be the N,O-diacylated product. Consequently separation by chromatography of the O-acylated product from starting material Q\textsuperscript{4}NH\textsubscript{2} was found to be easier than separation of the O-acylated from the N,O-diacylated product.

These experiments involving 3-aminoquinazolinone 89 established that Q\textsuperscript{4}NH\textsubscript{2} 76 was a poor model to test the feasibility of chemoselective O-acylation of an alcohol in the presence of the 3-amino group.

### 2.10 QNH\textsubscript{2} conversion to imines as a method for N-protection

The disappointing chemoselectivity obtained in reactions of Q\textsuperscript{4}NH\textsubscript{2} 76 with acylating agents lead us briefly to examine the possibility of selective N-protection of the 3-amino group, O-acylation and N-deprotection according to Scheme 72.

![Scheme 72](image)

In a model reaction the aryldiene derivative 91 of Q\textsuperscript{4}NH\textsubscript{2} 22 was prepared and then heated with N-aminophthalimide in the presence of toluene p-sulphonic acid to liberate the QNH\textsubscript{2} under mild conditions by N-amino-imine exchange. An authentic sample of crystalline derivative 92 was prepared for comparison purposes.
Reaction of 2,4-dimethoxybenzaldehyde with 3-amino-2-ethyl-quinazolinone 22 gave the arylidene imine 91 (63%), mp. 187-187.5 °C as colourless crystals. Reaction of the imine 91 with N-aminophthalimide gave a yellow solid in quantitative yield containing a ~1:3.4 ratio of 91:92. Imine 92 was isolated (48% yield) by chromatography as a solid mp. 174-175 °C. If an equilibrium is set up in this reaction between the two N-heterocyclic-arylidene imines and the two N-amino-heterocycles then heating imine 92 with QNH2 22 should lead to the same products.

Reaction of 3-aminoquinazolinone 22 and imine 92 gave a yellow solid in quantitative yield containing a ~1:3.7 ratio of 91 to 92 from 1H-NMR comparison with authentic samples. These experiments suggest that the 3-amino group in Q^1NH2 22, protected as the arylidene derivative as in 91 could be deprotected in large part by imine exchange using N-aminophthalimide but the Scheme 72 was not further pursued.
Chapter 3
Exploration of the relationship between tether length and reactivity in intramolecular aziridination
3.1 Introduction

Identifying the length for the tether that would accommodate the ester with its requirement for planarity and an s-cis conformation was important for success of the strategy in Chapter 2, Scheme 60. Because of the lack of thermal stability of the QNHOAc intermediate in Scheme 60, heating the reaction mixture to bring about reaction from the s-trans conformation as in analogous IMDA reactions (e.g. Scheme 50) was not an option.

\[ \text{LTA (1.1 eq.)} \quad \text{HMDS (2 eq.)} \quad \text{DCM} \]

\[ \text{Me} \quad \text{NHOAc} \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{O} \quad \text{Ph} \quad \text{Ph} \quad 93 = Q^5\text{NHOAc} \]

Scheme 75

3.2 A 3-atom tether

From inspection of models of the TS\(^h\), it seems highly unlikely that intramolecular aziridination in QNHOAc 93 would be successful. It is clear that a direct link between the (Q)2-position and the carbon \(\alpha\) to the ester oxygen is not possible if the Q and ester are contained in parallel planes and planarity at the (Q)2-position is maintained (95).
Even if rotation around the Q-N bond is permitted as in 96, the distance between the same two positions is greater than that of a single bond. It was no surprise, therefore, that lead tetra-acetate (LTA) oxidation of $Q^{5}\text{NH}_2\ 80$ which was available from the chemoselectivity studies described in Chapter 2 failed to give any aziridine-containing product from examination of the $^1\text{H}$-NMR spectrum of the crude reaction product. Although the expected $3H$-quinazolinone may have been present in the crude reaction product, it was not obtained pure after chromatography. It is noteworthy that lactone 94 is very likely stable enough to be isolated although it has not been prepared.

![Scheme 76](image)

Gattrell$^{106}$ has however prepared both diastereoisomers of the $t$-butyl analogue of lactone 94 by the route shown in Scheme 76. One of these lactones 49b was exceedingly unstable and decomposed on standing after a few hours but the other 49a was stable. Since the lactones are contained in 7-membered rings their $-\text{O-C}=\text{O}$ configurations must be $s$-trans (assuming they are planar).
3.3 A 4-atom tether

Inclusion of an additional atom in the tether as in the also previously prepared cinnamoyl ester 90 obviously will provide a greater opportunity for intramolecular aziridination to occur. From examination of models however, although a strained TS such as that in 97 may be possible with a twisted Q-N bond, the required *endo* overlap of the carbonyl oxygen is absent in this geometry; this secondary interaction is mandatory for the aziridination of such electron-poor alkenes.

Not surprisingly again, reaction of the purified ester 90 with LTA did not lead to any intramolecular aziridination product, but in this case the 3H-quinazolinone 98 was isolated by chromatography. Even with a 4-atom tether therefore, not all the necessary factors are present for successful intramolecular aziridination.
3.4 Preparation of 3-amino-2-(ω-alkenylcarbonyloxy)quinazolinones: tethers with 5, 6 and 7 atoms.

![Scheme 78](image)

To establish the nice length of the ester-containing tether that would lead to diastereoselective aziridination when incorporating a chiral centre (Scheme 60), a homologous series of non-chiral 2-(ω-hydroxyalkyl)-3-aminoquinazolinones 99 (with n = 3, 4 and 5) was prepared. Each was reacted with cinnamoyl chloride in the presence of pyridine (Scheme 78) and the optimum length of tether determined from the yield of product 101 from intramolecular aziridination of the O-cinnamoylated ester 100.
3.5 Preparation and acylation of 3-(o-hydroxyalkyl)-3-aminoquinazolinones

Identical procedures were used to produce 3-aminoquinazolines 107, 113 and 119 from lactones 102, 108 and 114. Reaction of the lactone 102 with an aqueous NaOH solution gave the sodium salt 103 which was O-acylated by acetyl chloride. $^1$H-NMR analysis of the crude product of the reaction showed that a ~1:1 mixture of O-acetate 104 and γ-butyrolactone 102 was present (Scheme 80) from the relative integration of the signals at δ 2.05 and δ 2.90. The low yield is attributed to the conversion under the acid conditions of 103 to the corresponding acid and thence to the lactone 102. In preparations of the analogous O-acetates 110 and 116 much less of the corresponding lactone was obtained presumably as a result of the slower rate of cyclisation of the corresponding hydroxy-acids.
Conversion of O-acetyl-acids to the crystalline \( \text{QNH}_2 \) compounds was accomplished in the usual way (Scheme 81).

Cinnamoyl chloride (1.1 eq) was added to \( \text{Q}^8\text{NH}_2\ 107 \) in DCM and pyridine at \(-40 \, ^\circ\text{C}\) with gradual warming to ambient temperature over 6 h. Recrystallisation provided the \( O\)-cinnamoyl-3-aminoquinazolinone \( 120 \) as a colourless solid in 47% yield, mp. 129-130 °C. As with \( O\)-cinnamoylation of \( \text{Q}^8\text{NH}_2\ 90 \), the acylation took place chemoselectively on the alcohol, the remaining material in the crude reaction mixture being unchanged \( \text{Q}^8\text{NH}_2\). \( O\)-Cinnamoylated \( \text{QNH}_2 \) compounds \( 121 \) and \( 122 \) were similarly obtained in crystalline form.

Scheme 81

Scheme 82
In early experiments before optimisation of reaction conditions (see above) treatment of \( \text{Q}^9\text{NH}_2 \) 107 with crotonyl chloride (1.2 eq.) in the presence of pyridine / DCM solution provided the crotonyl ester \( \text{Q}^{14}\text{NH}_2 \) 123 isolated after chromatography in 28% yield as a colourless oil together with \( N,O\)-diacylated product 124 and unchanged \( \text{Q}^9\text{NH}_2 \) 107 on further elution.

3.6 Intramolecular aziridination of 3-amino-2-(\( \omega \)-alkenylcarbonyloxy)quinazolinones 120, 121 and 122 in the presence of TFA (3 eq.)

Attempts to carry out intramolecular aziridinations using each of the title \( \text{QNH}_2 \) compounds were initially carried out in the presence of TFA because it was thought that protonation of the \( \text{(Q)N-1} \) was required for \textit{endo}-overlap of the ester \( \text{C}=\text{O} \) with the \( \text{(Q)} \) imine carbon (see 42). In practice, the \( \text{QNH}_2 \) compounds were converted to their respective \( \text{QNHOAc} \) derivatives at low temperature (-15 °C) and the cold solutions containing the latter were added to a solution of TFA in dichloromethane held at room temperature. Subsequently it was found that the yield was not significantly affected when the \( \text{QNH}_2 \) and LTA were added alternately and in small quantities to the TFA-dichloromethane solution, an experimentally more convenient procedure. The presence of TFA in intermolecular aziridination reactions has been previously shown to increase yields particularly using less reactive alkenes (Scheme 27). However, it was anticipated that the presence of the phenyl ring on the aziridine ring would make it liable to ring-opening by TFA as turned out to be the case.

![Scheme 83](image.png)
From reaction of ester 120 the crude product (81% yield) was identified as trifluoroacetate 125. Hydrolysis of this crude product by stirring overnight in dry ethanol gave the corresponding alcohol 126 in 78% yield based on ester 120. The stereostructure assigned to this alcohol is based on the assumption that the mechanism of aziridine ring-opening is effectively Sn2.

Reaction of the ester 121 under the same conditions gave trifluoroacetate 127 as an orange oil (87% yield). Hydrolysis by trituration with ethanol and crystallisation of the product from ethyl acetate gave the alcohol 128 in 32% yield based on ester 121. An X-ray structure determination (below) confirmed the structure of compound 128 showing that the 10-membered ring adopts a boat-like conformation for the (Q)C-(CH2)4O(C=O) segment but without the eclipsing or stem-prow interaction present in the cyclohexane boat conformation. The configurations at the two chiral centres confirm the Sn2-type ring-opening of the presumed aziridine intermediate.
Similarly, reaction of ester 122 gave the trifluoroacetate 129 as an oil in 86% yield. Again the trifluoroacetate was hydrolysed in quantitative yield on trituration with ethanol and the alcohol 130 isolated in 84% yield based on ester 122.

No conclusion should be drawn from the lower yield in the case of alcohol 128 by comparison with 126 and 130 because much of this alcohol remained behind after trituration with ethanol.
3.7 Intramolecular aziridination of 3-amino-2-(ω-alkenylcarbonyloxy)quinazolinones 120, 121 and 122 in the absence of TFA

Ring-opening of the presumably first formed aziridines in each of the three reactions above is facilitated by the stability of the incipient benzylic carbocation in the aziridine ring-opening. Although aziridine ester ring-opening does not invariably occur in the presence of TFA, it would be desirable to devise conditions for the aziridination that would allow isolation of the 3-membered ring intact so that alternative ways of ring-opening could be explored.

Accordingly oxidation of QNH$_2$ compounds 120, 121 and 122 in the absence of TFA was carried out. In these aziridination attempts two equivalents of acetic acid are produced which were removed by adding two equivalents of the acid scavenging agent hexamethyldisilazane (HMDS).

![Scheme 86]

Ester 120 and LTA (1.1 eq.) in separate DCM solutions were added slowly at the same rate to a stirred DCM solution of HMDS (2 eq.). After chromatography of the reaction product the aziridine 131 was isolated in 10% yield as a colourless solid, mp. 167-168 °C (from ethanol). Further elution provided the 3H-quinazolinone (Q$_9^9$H), as the major product. $^1$H-NMR analysis shows the characteristic aziridine ring protons of compound 131 at $\delta$ 4.81 and 3.80 with a coupling constant $J$ 5.6 Hz and the disappearance of the olefinic proton doublets of compound 120. The rigid conformation for the trimethylene unit was indicated by the structured multiplets for the proton signals within it.
Reaction of Q$^{13}$NH$_2$ 121 with LTA / HMDS under the same conditions gave aziridine 132 as a colourless solid in practically quantitative yield, mp. 161-162 °C (from ethanol). The same features were present in its $^1$H-NMR spectrum as for aziridine 131. One proton in the tetramethylene unit was significantly deshielded at $\delta$ 4.79, each of the other seven protons have a distinctly different chemical shifts over 4 ppm ($\delta$4.56 to 1.56). Examination of both the pseudo-boat and pseudo-chair conformation for the (Q)C-(CH$_2$)$_4$-O unit of aziridine 132 using models indicates that one methylene proton may point toward the carbonyl oxygen of the tether and the resulting anisotropic effect accounts for this downfield shift in the NMR spectrum. As before, $^1$H-NMR analysis shows the aziridine ring proton doublets of compound 132 are at higher field (at $\delta$ 4.56 and 3.68) than the olefinic proton doublets of compound 121 (at $\sim$δ 7.7 and 6.44) with a difference in J values as seen with compound 131.
Reaction of ester 122 by the same procedure and chromatography of the reaction product gave aziridine 133 in 7% yield as a colourless solid mp. 97-98 °C (from ethanol). Again, $^1$H-NMR analysis shows the aziridine ring proton doublets of compound 133 at $\delta$ 4.60 and 3.63 with a coupling constant $J$ 5.5 Hz.

The foregoing results show that there is a strong dependence of the yield of aziridine on the tether length in the reactions carried out in the absence of TFA. Examination of Dreiding models for the TS* 134 leading to aziridine 131 suggested that some eclipsing in the trimethylene unit may be responsible for the reduced yield. Replacement of the two carbons atoms bearing the eclipsing protons as in QNH$_2$ 135 might have lead to an improved yield in the intramolecular aziridination.

Normally, the amino group of methyl anthranilate is unreactive to esters or lactones, but it was found that the more reactive coumarone reacted on heating with methyl anthranilate giving the corresponding N-acylanthranilate in 43% yield. The derived QNH$_2$ compound 136 was obtained in the usual way as a crystalline solid but its $O$-acylation with $\alpha,\beta$-unsaturated acid chlorides was not further investigated because the use of 6-atom tethers proved to be more fruitful (see below).

From its $^1$H-NMR spectrum it is not clear whether aziridine 132 adopts a chair 137 or a boat motif 138 for the (Q)C-(CH$_2$)$_4$-O segment of its 10-membered ring and accordingly whether the TS* for its formation involves the chair 137 or boat 138 motif for what was the tether (see later).
An important prediction that can be made from examination of the TS$^\#$ for formation of aziridine 132, whether this is 137 or 138, is that a substituent R (Scheme 91) on the methylene group adjacent to the Q ring will have a large preference to be equatorial rather than axially disposed i.e. 139 rather than 140, assuming a chair motif as in 137 above.

The origin of this preference is the close approach of the R group in 140 to the ester function (R projects slightly towards the interior of the 10-membered ring). The importance of this preference for TS$^\#$ 139 over 140 is that high diastereoselectivity is predictable in the aziridination with the diastereoface indicated in 140 selectively attacked by NHOAc. There are, of course other positions on the tether where preferred sites for a substituent R can be identified (notably OCH$CH_2$) but substitution at the methylene indicated in 139 is attractive when the task of preparing this substituted QNH$_2$ compound in a single enantiomeric form is considered.
3.8 Intermolecular aziridination of alkenes using Q₅NHOAc 93

The advantages both in yield and diastereoselectivity available from intramolecular aziridination using Q¹¹NH₂ 121 are apparent by comparison with the intermolecular aziridination of ethyl cinnamate using Q₅NHOAc 93. Aziridine 142 was obtained in 14% yield as a 5:1 ratio of diastereoisomers. Aziridination of styrene under the same conditions gave aziridine 141 in 34% yield as a 7:1 ratio of diastereoisomers. These successful intermolecular aziridinations using Q₅NHOAc 93 support the previous conclusion that intramolecular aziridination in this compound is precluded by the inadequate length of the tether.

Summary

A series of non-chiral 2-(co-hydroxyalkyl)-3-aminoquinazolinones was prepared and esterified with cinnamoyl chloride to provide the esters with complete chemoselectivity. Intramolecular aziridination via the corresponding 3-acetoxyaminoquinazolinones occurs on reaction with LTA. The highest yield of aziridine was observed when the ester with the carboxyloxybutyl tether.
Chapter 4
Diastereoselectivity of intramolecular aziridination
4.1 Preparation of chiral but racemic 3-amino-2-(ω-alkenylcarbonyloxy)quinazolinones suitable for intramolecular aziridination

The foregoing Chapter suggested that further work on intramolecular aziridinations following the strategy in Scheme 60 using QNH$_2$ compounds with 6-atoms in the tether would be rewarding. This tether length gave far superior yields of aziridine in reactions carried out in the absence of TFA and examination of a TS$^\#$ models (139/140) suggested a means of achieving diastereoselectivity in the aziridination through 1,7-chirality induction.

To test the prediction that a substituent R on the methylene adjacent to the Q-ring would bring about high diastereoselectivity in the aziridination, required the synthesis of lactone 143 eventually in enantiopure form; conversion of lactone 143 into 145 would follow the route followed previously to Q$^{13}$NH$_2$ 121 (Schemes 79 and 82).

A literature search revealed few easy and direct methods for the preparation of enantiopure valerolactones 143. It occurred to us that replacement of the methylene in the tether adjacent to the chiral centre by oxygen would probably not affect the preferred TS$^\#$ geometry for aziridination but might well facilitate synthesis of the Q$^{13}$NH$_2$ compound 147 in enantiopure form (Scheme 93).
Thus, a direct route to $Q^{17}\text{NH}_2$ 147 might be by $O$-alkylation of $Q\text{NH}_2$ 149 with ethylene oxide or its equivalent. In a model reaction to test the feasibility of this route, $Q^{1}\text{NH}_2$ 76 (R=Me) was treated with sodium hydride and then with ethyl $\alpha$-bromoacetate but only unchanged starting $Q^{1}\text{NH}_2$ 76 was recovered (Scheme 95).

Exploration of an alternative route to 147 (R=Ph) started with an attempt to prepare the dioxanone 146 by the route shown in Scheme 96.\textsuperscript{107a}
Since mandelic acid 150 is available in enantiopure form, the lactone 146 would also be enantiopure if conditions for cyclisation of 151 could be found which would avoid epimerisation at the chiral centre. D-(-)-Mandelic acid and 2-bromoethanol (12 eq.) were heated under reflux in toluene with a catalytic amount of H₂SO₄ and the ester 151 was isolated by distillation as a pale orange solid in 82% yield. However attempts to cyclise 151 failed to produce the desired lactone 146 using a variety of conditions.

The chiral 3-aminoquinazolinone 147 was prepared from the sodium salt 154. An initial four-step route to 154 from benzaldehyde via 152, 153 and 146 (Scheme 97) was superseded by a direct route from α-bromophenylacetic acid; the eventual route to 3-aminoquinazolinone 147 is shown in Scheme 98.

\[ \text{Scheme 98} \]
a- Bromophenylacetic acid was added to a large excess of the sodium salt of ethylene glycol. Removal of the bulk of the ethylene glycol by distillation (4.3 x 10^{-1} \text{ mbar}, 55 \degree \text{C}) followed by trituration with dry acetone, afforded the solid sodium salt 154 in quantitative yield. Compound 154 was O-acylated by an excess of acetyl chloride (4 eq.) in quantitative yield. Following the same route to QNH_{2} compounds 107, 113 and 119, the sodium salt was converted into 3-aminoquinazolinone 147 which was obtained and purified by crystallization as a colourless solid (44% yield based on salt 154) (Scheme 98).

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{O} \\
\text{O} & \quad \text{NH}_2 & \quad \text{O} \\
\text{147} & \quad \text{acid chloride (1.1 eq.), pyr, DCM} & \quad \text{Ph} \quad \text{N} & \quad \text{O} \\
\text{O} & \quad \text{NH}_2R^2 & \quad \text{O} \\
\text{148} R^1= R^2= H, R^3= \text{Ph} & \quad 69\% \\
\text{158} R^2= H, R^1= R^3= \text{Me} & \quad 79\% \\
\text{159} R^1= H, R^2= R^3= \text{Me} & \quad 57\%
\end{align*}
\]

Scheme 99

Three different esters 148, 158 and 159 were prepared from 3-aminoquinazolinone 147 by O-acylation with the appropriate acid chloride and the corresponding esters obtained in the yields indicated (Scheme 99).

In work carried out by D.Hirst, 3,3-dimethylacryloyl chloride was added to the methyl analogue of compound 147 (i.e. Q^{22}NH_{2}) over 1.5 h. at 0 \degree \text{C} in the presence of 3 eq. TFA, and pyridine in chloroform. After stirring a further 1.5 h. at ambient temperature, the product was isolated in 86% yield.
Reaction of 3-aminoquinazolinone 147 with cinnamoyl chloride (4.1 eq.) in dichloromethane lead to triple acylation and $N,N,O$-tricinnamoyl-3-aminoquinazolinone 160 was isolated in 60% yield following chromatography. The formation of ester 160 is evident from the three COCH= signals in the $^1$H-NMR spectrum at $\delta$ 6.33, 6.58 and 6.95 each with the same coupling constant (16.1 Hz).

![Scheme 100](image)

Intermolecular aziridination of ethyl cinnamate with Q$^2$NH$_2$ 147, LTA and HMDS provided aziridine 161 in 60% yield following chromatography as a 1:1 mixture of diastereoisomers. A single diastereoisomer was isolated by crystallisation. Formation of the aziridine is evident from the aziridine ring proton doublets at $\delta$ 3.59 and 4.46 with a coupling constant $J$ 4.5 Hz in its $^1$H-NMR spectrum.
4.2 Reactions of 3-aminoquinazolinones 148, 158 and 159 with LTA in the presence of TFA

Each of the three esters 148, 158 and 159 was treated with LTA in the presence of TFA and the crude trifluoroacetates hydrolysed by stirring with ethanol. Isolation of the corresponding alcohols required chromatography in the case of 163 and 164. In each case only a single diastereoisomer of the product 162, 163 and 164 appeared to be present from examination of its NMR spectrum prior to chromatographic purification.

Compound 162 was treated with sodium ethoxide in ethanol to effect lactone ring opening but the only product recovered was 165 in high yield. Lactone ring opening was
evident in the $^1$H-NMR spectrum of the terminally hydroxy-containing QH 165 from the absence of a downfield shifted methylene group of the OCH$_2$CH$_2$OH moiety present in lactones 162, 166 and 167; N-N bond cleavage evident from the NH signal at $\delta$ 11.70. The mechanism of formation of this product was not investigated.

4.3 Intramolecular aziridination of 3-aminoquinazolinones 148, 158 and 159

![Scheme 102](image)

Intramolecular aziridination of the three esters 148, 158 and 159 was also carried out by treatment with LTA in the presence of HMDS instead of TFA. All of these aziridine products were obtained in high yield (92, 82 and 86% yields for the preparation of 167, 168 and 169) and in crystalline form. From $^1$H-NMR analysis the presence of the aziridine ring in 167 was identified from the coupling $J$ 5.9 of the two doublets at $\delta$ 4.40 and 3.70. The aziridinations of 158 and 159 were confirmed by $^1$H-NMR analysis from the loss of the amine group singlet at $\delta$ 5.20 and formation of the aziridine ring protons (at $\delta$ 3.42 for 169). In each of the three cases the aziridination appeared to be completely diastereoselective.

X-Ray structure determinations were carried out on aziridine 168 and the ring-opened alcohol 164. An interesting feature of both these structures is the presence of a boat motif in what was the tether in the 10-membered rings (see next page).
X-ray structure of 164

X-ray structure of 168
4.4 Synthesis of racemic 3-aminoquinazolinone (Q$^{21}$NH$_2$)

Although the redundant reactions above, using the phenyl-substituted tether were highly diastereoselective, the easy racemisation of α-bromophenylacetic acid meant that the route in Scheme 98 could not be applied to the synthesis of enantiopure Q$^{17}$NH$_2$ 147. Since α-bromoisopentanoic acid is available from valine in enantiopure form and since the isopropyl is comparable in size to the phenyl group we carried out the synthesis of Q$^{21}$NH$_2$ 175 as in Scheme 103 using racemic α-bromoacid 170 in the first instance.

![Diagram of the synthesis](image)

The 3-aminoquinazolinone 175 was obtained as a colourless solid (in 8% yield based on 171). N-acylanthranilhydrazide 176 was also produced in equal yield but not isolated, its production was the result of an insufficient reaction time. Although the yields in most of these steps were acceptable, the displacement of the bromine in α-bromoisopentanoic acid by the ethylene glycol anion gave the sodium salt 171 in low yield (11%) which was not unexpected, bearing in mind the hindered character of this bromide.
3-Aminoquinazolinone 175 was O-acylated completely chemoselectively with cinnamoyl chloride in 91% yield. Intramolecular aziridination to give 178 took place in quantitative yield without need for further purification of the product. With a single configuration at the chiral centre, the two diastereoisomers of aziridine 178 would be expected to have different conformations of the tether. Consequently, the two $^1$H-NMR spectra would show different chemical shift differences, particularly for $CH_2$Ph and $OCOCOCH_3$ protons. From the single set of signals in the $^1$H-NMR spectrum of the crude product, the aziridination was deemed to be completely diastereoselective.

4.5 Synthesis of racemic 3-aminoquinazolinone 185 ($Q^{32}$NH$_2$)

The high diastereoselectivity obtained in formation of aziridines 167, 168, 169 and ring-opened alcohol 164 suggested that similar high diastereoselectivity might be possible with substituents smaller than phenyl or isopropyl in the tether. An advantage in using e.g. a methyl group might be a higher yield in reaction of methyl $\alpha$-chloropropanoate 179 with the ethylene glycol anion. Another change in the reaction procedure would be to substitute ethylene glycol by a mono-$O$-protected ethylene glycol and hence to remove the necessity for the $O$-acylation step involving acetyl chloride (171 to 172). In practice an equivalent of 2-benzyloxyethanol was used instead of an excess of ethylene glycol. By changing the procedure in this way the necessity for distillation / trituration to remove
excess unreacted ethylene glycol was avoided along with the risk of epimerisation at the chiral centre. Ester 180 was prepared in 34% yield after purification by chromatography.

Scheme 105

After hydrolysis with sodium hydroxide, the acid obtained was converted via reaction of its sodium salt with oxalyl chloride into the acid chloride before reaction with methyl anthranilate in ether; N-acyl-anthranilate 183 was isolated by chromatography in high yield (81% yield based on compound 181). The 3-aminoquinazolinone 184 was prepared by reaction of 183 with hydrazine hydrate in ethanol and after stirring for 1 day with aqueous hydrobromic acid (48%) produced racemic 3-aminoquinazolinone Q^{23}NH_2 185 purified by crystallisation (in 39% yield based in 184) as a colourless solid, mp. 119-120 °C.

Scheme 106
3-Aminoquinazolinone 185 was O-acylated completely chemoselectively with cinnamoyl chloride but in only 16% yield after crystallisation mp. 114-115 °C (Scheme 106). Aziridine 187 was prepared by reaction of the QNH2 186 with LTA and HMDS (2 eq.) in almost quantitative yield as a colourless solid, mp. 184-185 °C. 1H-NMR analysis of the product before crystallisation showed a single set of signals confirming that even with the smaller methyl group as a substituent on the tether, aziridination is completely diastereoselective. The 1H-NMR spectrum of this aziridine in enantiopure form is discussed in Chapter 5.

4.6 Summary
A series of chiral but racemic QNH2 compounds were prepared having a 6 atom tether with an ether oxygen replacing the β-methylene thus facilitating incorporation of a Ph, Pr1 or methyl on the position α to the Q-2 position. In all three cases the aziridines were produced as single diastereoisomers from analysis by 1H-NMR of the crude reaction product.
Chapter 5
Exploitation of diastereoselectivity by retrieval of chiral centres (chirons) formed in the intramolecular aziridination
5.1 Preparation of 3-aminoquinazolinones in enantiopure form suitable for intramolecular aziridination

The above synthesis of (R)-3-aminoquinazolinone 185 from (S)-2-bromopropionic acid and ethylene glycol provided the N-acylanthranilate 192 in a meagre 3% overall yield. This route was much improved by the higher yielding synthesis in Scheme 108 which used benzyloxyethanol instead of ethylene glycol.
Conversion of the sodium salt 193 to the N-acylanthranilate 183 followed the method previously used for the racemic material (Scheme 105) except that debenzylation was more efficiently accomplished at this stage by palladium/hydrogen in acetic acid solution giving 194. After crystallisation, QNH₂ 185 was obtained with [α]₀ +65 (c=1.0, CHCl₃) and the overall yield was 37% based on the α-bromoacid 188 without the requirement for chromatography at any stage. This overall yield has since been raised to 62%, again without the requirement for chromatography by Mr D. Hirst in these laboratories.
5.2 Enantiopurity of 3-aminoquinazolinone (185): synthesis of imine (195)

To confirm the enantiopurity of the Q$^{23}$NH$_2$ 185 obtained above it was derivatised with (1R)-myrtenal. The NMR spectrum of the imine 195 produced was compared with that of the imine prepared from racemic Q$^{23}$NH$_2$ 185 (Scheme 105).

The signals from the imine diastereoisomers formed from the racemic material ($\delta$ 8.52 and 8.59 for the N=CH proton) showed clearly that QNH$_2$ 185 from Scheme 108 was enantiopure since only one of these signals was present in the product from the enantiopure material.

5.3 Intramolecular aziridination of the O-cinnamoyl ester of enantiopure 3-aminoquinazolinone 185
O-Cinnamoylation of enantiopure QNH$_2$ 185 was carried out as described previously. Although the yield of the ester was unchanged (at 16%) by direct crystallisation, it has been raised to 62% by Mr D. Hirst in these laboratories by using chromatography with the only other recovered product being unreacted starting material. Reaction of the Q$^{24}$NH$_2$ 186 with LTA and HMDS provided aziridine 187, again in quantitative yield with crystallisation as a colourless solid, mp. 184-185 °C but with a specific rotation $[\alpha]_D$ -144 (c=1, CHCl$_3$). The appearance of only one set of signals in the $^1$H-NMR spectrum of the crude product again suggested that only one diastereoisomer was present. Key signals in the $^1$H-NMR spectrum of aziridine 187 include aziridine proton doublets with a coupling constant $J$ 6.0 at $\delta$ 4.52 and 3.70.

Although the signals for the O-CH$_2$CH$_2$-O protons were second-order in CDCl$_3$ because of overlap of two of them, in C$_6$D$_6$ they were well-separated and each appeared as an eight line signal. The much deshielded proton at $\delta$ 4.45 was identified as either H$_a$ or H$_b$ by proton correlation with the $^{13}$C signal at $\delta$ 68.0. The assumption here is that of the two carbon signals for the methylene groups at $\delta$ 68.0 and 63.5, the lower field signal will be that affected by the acylated oxygen. Deshielding of H$_a$ by the neighbouring carbonyl oxygen is expected and assignments of H$_b$ - H$_a$ follow.

![Diagram of two possible conformational structures of aziridine 187](image-url)
The key to distinguishing between the chair in 196 and the boat motif in 197 in the 10-membered ring is the presence of two coupling constants of ~2 Hz and ~6 Hz for each of the OCH$_2$CH$_2$O protons in the product; examination of models indicates that there is in 196 a small distribution from a cyclohexanoid chair where equivalence of these J values (~3 Hz) would be expected. The distortion explains the difference in J values and the relevant Newman projections together with the angles giving rise to the observed J values and shown in Figure 3.

![Chair conformation](image1)

![Boat conformation](image2)

Figure 3

The boat form 197 cannot account *inter alia* for two coupling constants of ~2 Hz and ~6 Hz for all of the protons in the -OCH$_2$CH$_2$O- segment. The Karplus curve correlates the dihedral angle (between vicinally disposed protons) to coupling constant. The shaded band indicated on the example below illustrates the region where experimental values are found.
5.4 Reactions of aziridine 187

Having produced two chiral centres in aziridine 187 with defined configuration, their retrieval as components of useful α- or β-amino acids involves cleavage of the aziridine ring, the lactone and the N-Q bond though not necessarily in this order.

Aziridine 187 was ring-opened with complete regioselectivity by stirring for 1.5 h in dichloromethane containing one equivalent of TFA and the crude trifluoroacetate 198 (81% yield) hydrolysed by stirring with a solution of sodium carbonate in aqueous THF. Crystallisation provided the alcohol 199 as a colourless solid, mp. 181-182 °C (from ethanol), [α]D = +182.5° (c=1.0, CHCl3). 1H-NMR analysis of unpurified 199 showed that the reaction produced a single diastereoisomer.

In a second procedure, aziridine 187 was stirred for only 1 min. in aqueous THF containing three equivalents of TFA and after the same hydrolysis / work-up, provided
alcohol 199 as a 3:1 mixture of epimers by comparison of its $^1$H-NMR spectrum with that of the product 199 from the experiment above. It was also revealed that the product of the earlier experiment was the minor epimers present in the later experiments.

The lactone 199 was cleaved by ethanolation with sodium in ethanol. The product diol 200 was produced as a 2:1 mixture of diastereoisomers. Lactone ring-opening was evident in the $^1$H-NMR spectrum from the ethyl ester signals in the major diastereoisomer at $\delta$ 1.11 and 4.18 ($\delta$ 1.27 and 4.10 for the minor diastereoisomer).

Evidence in the $^1$H-NMR spectrum of 199 for the regioselectivity of aziridine ring-opening comes from the similarity in appearance of the signals from the OCH$_2$CH$_2$O protons in the 10-membered ring to that in the spectrum of aziridine 187. The appearance of these protons in the NMR spectrum of a product from ring-opening in a regiocomplementary sense, giving an 11-membered ring (see later), was quite different. Moreover ring-opening reactions carried out independently by I.S.T.Loche$^{72}$ involving a similar aziridine to 187 prepared from the intermolecular reaction of a QNH$_2$ and methyl cinnamate invariably occurred regiospecifically at the Ph substituted position.

5.5 Attempted Q-N bond reduction using Sml$_2$

The initial strategy was to cleave the lactone ring prior to N-N bond cleavage (Scheme 112); because of the lack of acidity of the proton on the aziridine ring adjacent to the ester group, no epimerisation was anticipated and in any case, the trans-configured aziridine is more stable.
Hydrolysis of the lactone ring in aziridine 187 with sodium carbonate in ethanol and $^1$H-NMR analysis of the crude reaction mixture showed the presence of two compounds in a 3:1 ratio. Separation of these two products was not accomplished by chromatography. Key signals in the spectrum included the ethoxy proton signals (at δ 4.00 and 1.00).

The minor product, which was possibly in equilibrium with aziridine 201 and hence not separated by chromatography was assigned the dihydroquinazolinone structure 202 and is distinguished by a distinctive highfield shift of one of the CH$_2$CH$_2$ protons at δ2.05. This proton is thought to be shielded by the aziridine ring (203) i.e. the stereostructure is 202a rather than 202b with interconversion with 201 being catalysed by acid (Scheme 113).
The aziridine mixture of 201 and 202 was ring-opened with complete regioselectivity by stirring for 3 h. in dichloromethane containing one equivalent of TFA and the trifluoroacetate 204 was isolated in 36% yield. Although 202 does not produce the ring-opened product 204 in one step on addition of TFA, the diether ring may be opened before or after aziridine ring-opening. Hydrolysis by stirring with a solution of sodium carbonate in aqueous THF produced 200 in quantitative yield as a single diastereoisomer by comparison of its $^1$H-NMR spectrum with that of the diastereoisomeric mixture 200 produced previously from 199 (Scheme 114).

Scheme 114

It has been previously shown that the N-N bond cleavage of several non-tethered N(Q)-aziridines could be achieved by reduction using samarium diiodide. This reduction was achieved albeit in low yield (6%) using the single diastereoisomer of 200 producing the $\alpha$-amino acid 220 obtained by Kieselgel chromatography (8 mg) lead to only superficial characterisation without polarimetry data.
The mechanism (Scheme 115) for this reduction was expected to proceed via initial donation of an electron into the Q carbonyl group followed by further electron donation and aromatisation by loss of the aziridinyl anion.

The mixture of 201 and 202 in THF containing Bu'OH was reduced by addition of SmI2 (0.1 M solution in THF). The product (Scheme 116) identified as the lactone 205 i.e. reductive ring-opening of the aziridine had occurred but was accompanied by reformation of the lactone! An identical product was obtained by direct reduction of aziridine 187 (see Scheme 118).
Aziridine ester reduction with SmI$_2$ has been previously explored by Molander$^{113}$ and a mechanism (Scheme 117) similar to that for $N$-$N$ bond cleavage in Scheme 115 is assumed to occur with the samarium firstly donating an electron into the carbonyl substituent of the aziridine followed by donation of a second electron onto the radical.
nitrogen; the resulting enolate system is quenched by protonation. Conceivably the reformation of the lactone 205 could take place via the samarium-coordinated intermediate in Scheme 116.

![Scheme 118](image)

Work by others in our group has shown that lactone 205 is converted into methyl 3-amino-3-phenylpropanoic acid 209 by lactone hydrolysis followed by further reduction with SmI₂ in the presence of β-dimethylamino ethanol (Scheme 118).
The configuration of 187 at the newly created chiral centres would be $R, S$ as indicated from our TS$^b$ model and the absolute configuration at the chiral centre in $\beta$-amino acid, therefore would be $(R)$. The purified material recovered had a specific rotation $[\alpha]_D^{20} +21$ $(c 0.46, \text{CHCl}_3)$ in accordance with the literature$^{110}$ value $[\alpha]_D^{20} +22.3$ $(c 1.99, \text{CHCl}_3)$ of a sample known to have the $R$-configuration.

5.6 Intramolecular aziridination using 3-amino-2-[(ω-cinnamylloxycarbonyl)alkyl]-quinazolinone

The procedure in Scheme 120 is an alternative means by which the two reactants, the QNH$_2$ and the double bond can be tethered to facilitate intramolecular aziridination. Here an $\omega$-carboxyalkyl 2-substituent on the QNH$_2$ is employed and esterified via reaction of its sodium salt with an allylic halide. Thus the ester in the product 210 is inverted by comparison with that in Scheme 60 and the strategy is complementary to the previous one in that the double bond of the allylic system is electron-available. Much the same analysis of the strategy in Scheme 60 applies to that for intramolecular aziridination via the QNH$\text{HOAc}$ derivative of QNH$_2$ 210 except that the requirement for endo-overlap of the ester C=O with the Q C=N is now absent.
Methyl N-adipoyl anthranilate 211 was prepared by reaction of adipoyl-poly dichloride with methyl anthranilate and the product cyclised in the presence of hydrazine hydrate. Addition of glacial acetic acid to the reaction mixture precipitated compound 212 as a crystalline solid and reaction with sodium hydride (1.3 eq.) gave the corresponding salt. Reaction of cinnamyl bromide (1.3 eq.) with this salt gave ester 213 which was purified by chromatography (21%).

Reaction of Q²⁻NH₂ 213 with LTA and HMDS and chromatography of the crude product gave aziridine 214 (11%) as a colourless crystalline solid mp. 204-205 °C; the only other product isolated was the 3H-quinazolinone 215 (11%). From analysis of the purified product the aziridine was identified inter alia from doublets assigned to the 3-membered ring protons at δ 4.65 and 3.55 with a coupling constant J 5.0.

The reason for the low yield of aziridine 214 is of interest because there do not appear to be any unfavourable eclipsing interactions in the preferred TS* from examination of models. Conceivably the conformation that the O-CH₂-C=C moiety must assume is not a favourable one.
Attempted intramolecular aziridination of 3-amino-(3-trans-cinnamyloxycarbonyl-propyl)quinazolin-4(3H)-one 216 in the presence of HMDS did not lead to any aziridine or aziridine-derived products. After chromatography of the crude product only unchanged Q25NH2 (7%) and 3-H quinazolinone 217, were isolated.

**Summary**

The strategy in Scheme 60 has been successfully implemented. Efficient synthesis of the QNH2 185 without the requirement for chromatography is noteworthy. Since ring-opening of aziridine 187 at the phenyl-substituted position has been accomplished, the synthesis of α-amino acid enantiomers should be straightforward.

Synthesis of a more substituted enantiopure amino acid stereoisomers from highly substituted α,β-unsaturated acids should be possible. Such products are not presently available via existing intermolecular aziridination methods.

**Acknowledgements**

The preparation of QNH2s 213 and 216 and their reaction products with LTA were first carried out by Mr D. Hook in these laboratories. The aziridine 214 was isolated in 5% yield by him.

Acknowledgement is also due to Mr D. J. Hirst who has increased the yields of products 185 and ester 186 following the route devised by the author and who converted the lactone into the β-amino ester 209. I thank both these students for their assistance.
Experimental
General Experimental
Proton and carbon-13 NMR spectra were recorded using a 250 MHz Bruker ARX 250 spectrometer ($^{13}$C spectra at 63MHz), a 300 MHz Bruker DPX 300 spectrometer or a 400 MHz Bruker DRX 400 spectrometer in CDCl$_3$ solution unless otherwise indicated. Infrared spectra of both solid and liquid samples were recorded as solutions in chloroform using a Perkin Elmer 298 spectrometer. Mass spectra were obtained using a Kratos “concept” 1H spectrometer. X-Ray structure determinations were carried out by Dr. J. Fawcett at the University of Leicester. Optical rotations were determined on a Perkin Elmer 341 polarimeter at 589nm.

Flash chromatography was carried out using silica gel C60 (35-70), or Kieselgel 60 (230-400 mesh) manufactured by Merck and Co. The eluting solvent used was typically a mixture of light petroleum 60-80 °C and ethyl acetate. Thin layer chromatography (TLC) analysis was conducted using 0.2 mm thick pre-coated silica on aluminium sheets, manufactured by Merck and Co. Melting point determinations were conducted using Reichert KOFLER Micro cooling/heating stage and values are uncorrected.

Solvents
Unless otherwise indicated solvents were removed by rotary evaporation at water pump pressure (~ 16mm Hg), then on standing under oil pump pressure (~ 2mm Hg) prior to compound characterisation. Drying of organic solutions carried out using magnesium sulphate except where otherwise indicated. Dry tetrahydrofuran (THF) was obtained by distillation from sodium metal in the presence of benzophenone. Dry dichloromethane (DCM) was obtained by distillation from calcium hydride. Diethyl ether (ether) was dried and distilled prior to use. All other organic solvents were dried by methods described by Perrin and Armarego.

Chemicals purchased
LTA was purchased (Lancaster) as a solid under acetic acid and was freed from residual acetic acid before use by filtration and subjecting to a water pump vacuum for ~20 min. Sodium hydride was routinely freed from mineral oil by washing with petroleum ether at least twice prior to use. (R)-methyl 3-hydroxy-2-methyl propionate was supplied by Roche; (S)-methyl 3-hydroxy-2-methyl propionate was purchased
from Aldrich. All other chemicals were purchased from either Aldrich, Lancaster or Avocado and used as received unless otherwise stated.

Physical data

Chemical shifts in all NMR spectra are expressed in ppm on the δ scale relative to trimethylsilane (TMS) as internal standard. The following abbreviations are used: s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet; dd-doublet of doublets; ddd-doublet of doublet of doublets; h-heptet; br-broad; struct-structured; Ar-aryl; azir-aziridine; Ph-phenyl; Q-quinazolinone; MA-Methyl anthranilate; J-coupling constant (Hz). Assignment of chemical shifts to $^{13}$C resonances were assisted by DEPT.

Mass spectra were determined in units of mass relative to charge (m/z) with fast atomic bombardment (FAB) ionisation. Except for the molecular ion MH$^+$, only peaks ≥20% of the base peak are given. IR spectra were measured in units of wavenumber (cm$^{-1}$) and the following abbreviations have been used: s-strong, m-medium and w-weak.

Optical rotation values are given in units of 10$^1$deg cm$^2$g$^{-1}$.
Preparation of (S)-3-amino-2-(1-hydroxy ethyl)quinazolin-4(3H)-one 76

3-Amino-2-(2-hydroxyethyl)quinazolin-4(3H)-one 76 was prepared using the procedure described by M.P. Coogan but with modifications as indicated below.

![Chemical structure](image)

\[ \text{76} = \text{Q}^\text{NH}_2 \]

**General procedure A for acetylation of hydroxyacids; acetylation of (S)-lactic acid.**

Acetyl chloride (64 cm\(^3\), 0.90 mol) was added dropwise and cautiously via a pressure equalising dropping funnel to rapidly stirred (S)-(+-)lactic acid (53.9 g, 0.60 mol) (Aldrich) cooled in an ice bath. The mixture was stirred for a further 2 h. before the unreacted acetyl chloride evaporated off under reduced pressure using a water pump. Further distillation of the residue afforded (S)-2-acetoxypropanoic acid as a clear oil, bp 134-164 °C / 33mm Hg (39.85 g, 50% overall yield) (not distilled by Coogan previously) \[ [\alpha]_D^{20} -44 (c 1.0, \text{CHCl}_3); \delta_H 1.54 (3H, d, J 7.2, \text{CHCH}_3), 2.25 (3H, s, \text{COCH}_3), 5.14 (1H, q, J 7.2, \text{CHCH}_3) \text{ and } 10.78 (1H, s br, \text{COOH}). \]

**General procedure B for preparing an acid chloride from an acid; 2-acetoxypropanoyl chloride**

Two drops of \( N, N \)-dimethylformamide (DMF) were added to the above 2-acetoxyacid (39.9 g, 0.30 mol) followed by thionyl chloride (61 cm\(^3\), 0.90 mol) dropwise with stirring. The solution was stirred at ambient temperature for 1 h., then for 1 h. at 40 °C under water pump pressure to remove unreacted thionyl chloride. Distillation of the residue afforded a fraction bp 64-70 °C / 33mm Hg of the acid chloride (38.64 g, 43% overall yield from lactic acid) as a clear oil (not distilled by Coogan).

\[ \delta_H 1.60 (3H, d, J 7.0, \text{CHCH}_3), 2.15 (3H, s, \text{COCH}_3) \text{ and } 5.19 (1H, q, J 7.0, \text{CHCH}_3). \]
General procedure C; preparation of methyl N-acylanthranilates; reaction of (S)-2-acetoxypropanoyl chloride with methyl anthranilate.

To a vigorously paddle-stirred solution of methyl anthranilate (39.55 cm³, 0.29 mol) in dry ether (800 cm³) in a 1 litre flask was added the above acid chloride (20 g, 0.13 mol) dropwise over 1 h. during which time a thick white precipitate of methyl anthranilate hydrochloride was formed. After stirring for a further 18 h. the solid was separated, washed well with ether and the combined ether filtrates washed successively with dilute HCl (2M, 5 x 40 cm³), bicarbonate (2 x 20 cm³), saturated brine (2 x 20 cm³), then dried with sodium sulphate and evaporated under water pump pressure to give the anthranilate as an oil (29 g, 37% overall yield from lactic acid); \([\alpha]_D^{20} -73\) (c 1.0, CHCl₃); (Found: C, 58.7; H, 5.6; N, 5.1. C₁₃H₁₅NO₅ requires C, 58.9; H, 5.7; N, 5.3%); (Found: MH⁺ 266.1028. C₁₃H₁₅NO₅ requires MH⁺, 266.1029); \(v_{\text{max}}/\text{cm}^{-1}\) 3230m, 1745s, 1680s, 1690s, 1605s, 1590s, 1530s, 1450s, 1435s and 1370s; \(\delta\) for numbering see below 1.58 (3H, d, J 6.9, CHCH₃), 2.31 (3H, s, COCH₃), 3.92 (3H, s, CO₂CH₃), 5.37 (1H, q, J 6.9, CHCH₃), 7.12 [1H, dd, J 7.5 and 7.5, H-5(Ar)], 7.58 [1H, dd, J 7.5 and 7.5, H-4 (Ar)], 8.06 [1H, d, J 7.5, H-6(Ar)], 8.73 [1H, d, J 7.5, H-3(Ar)] and 11.7 (1H, s br, NH); \(\delta_c\) 18.3 (CH₂CH), 21.3 (COCH₃), 52.7 (CO₂CH₃), 71.1 (CH₃CH), 115.9 [C-1(Ar)], 120.7, 123.4, 131.2, 135.0 [4 x CH(Ar)], 141.1 [C-2(Ar)] and 168.9, 170.1, 170.2 (3 x C=O); \(m/z\) 288 (MNa⁺ 53), 266 (MH⁺100) and 234 (MH⁺-Ac 56).
General procedure D; conversion of methyl N-acylanthranilates into 3-aminoquinazolinones. Preparation of (S)-3-amino-1-hydroxyethylquinazolin-4(3H)-one 76, Q^4NH_2.

The anthranilate (58.2 g, 0.22 mol) was dissolved in dry ethanol (300 cm³) containing hydrazine hydrate (81 cm³, 1.32 mol), the solution heated under reflux for 5 h. then left to stir overnight. After cooling, the bulk of the ethanol was evaporated under water pump pressure, water (100 cm³) added, and the resulting white solid separated, washed well with water, air dried and crystallised to give 3-aminoquinazolinone (Q^4NH_2) 76 as a colourless solid (38.0 g, 31% overall yield from lactic acid) mp. 118-120°C (from ethyl acetate).^63 (Found: MH^+ 206.0929. C_{10}H_{11}N_3O_2 requires MH^+, 206.0930); ν_max/cm⁻¹ 1680s, 1600s, 1470m and 1270m; δ_H for numbering see below 1.60 (3H, d, J 6.3, CHCH_3), 4.30 (1H, s br, CHO_H), 4.79 (2H, s, NH_2), 5.18 (1H, q, J 6.3, CHCH_3), 7.45 [1H, dd, J 6.6 and 6.6, H-6(Q)], 7.65 [2H, m, H-7, H-8(Q)] and 8.21 [1H, d, J 6.6, H-5(Q)]; δ_C 22.3 (CH_3), 65.6 (CHCH_3), 120.1 [CCO(Q)], 126.5, 126.9, 127.1, 134.2 [H-5, H-6, H-7,H-8(Q)], 146.1 [CN=C(Q)], 159.4 [C=N(Q)] and 162.0 [CO(Q)]; m/z 206(MH^+, 100) and 188 (MH^+-H_2O, 100).
General procedure E; esterification of 2-(1-hydroxyalkyl)- or 2-[1-(ω-hydroxyalkyl)alkyl]-3-aminoquinazolin-4(3H)-ones. Synthesis of (S)-3-amino-2-(1-cinnamoyloxyethyl)quinazolin-4(3H)-one (Q^5NH_2).

To a stirred solution of Q^4NH_2 76 (2.00 g, 9.75 mmol) in dry pyridine (8 cm^3) cooled in an ice bath at 0 °C was added cinnamoyl chloride (2.4 g, 12.97 mmol) dropwise and the solution stirred for 2 h. at 0 °C then for a further 2 h. at ambient temperature. The solution was treated with ice water, then extracted with dry DCM (30 cm^3) and the organic layer separated, washed with bicarbonate (2 x 60 cm^3) and dried with sodium sulphate. Following evaporation under reduced pressure, the yellow solid/oil obtained was crystallised to give the title cinnamoyl ester 80 (0.87 g, 26.6% yield) mp. 152-153 °C (from ethanol). (Found: MH^+ 335.1270. C_{19}H_{17}N_{3}O_{3} requires MH^+, 335.1270); ν_max/cm⁻¹ 1700s, 1680s, 1640s, 1600s and 1470s; δ_H 1.78 (3H, d, J 7.0, CHCH_3), 5.00 (2H, s, NH_2), 6.46 (1H, q, J 7.0, CHCH_3), 6.56 (1H, m, COCHCHPh), 7.45 [6H, m, 5 x CH(Ph), H-6(Q)J], 7.72 [3H, m, COCHCHPh, H-7, H-8(Q)J and 8.28 [1H, d, J 8.0, H-5(Q)]; δ_C 18.2 (CH_3), 68.0 (CHCH_3), 117.3 (CHCHPh), 120.5 [CCO(Q)], 125-135 (7 signals) [H-5, H-6, H-7, H-8(Q), 5 x CH(Ph)], 146.1 (CHPh), 146.7 [CN=C(Q)], 155.7 [C=N(Q)], 161.7 [s, CO(Q)] and 166.6 (COCH_2); m/z 336 (MH^+ 55). Further elution of the residue was believed to contain a mixture of QNH_2 76, N,O-diacylated product 81 and N-acylated product 82, each isolated in low yields which were not characterised..

The reaction was carried out as above with an additional 6cm^3 of dichloromethane, however there was no improvement in the chemoselectivity, the O-acylated product 80 was isolated in 21% yield by chromatography. The reaction was also repeated with
pyridine substituted by 2,6-di-tert-butyl-4-methylpyridine and produced the \(N,O\)-diacylated product 81 and starting material 76 in 21% and \(~10\%\) isolated yields following chromatography.

**General Procedure F for Intramolecular aziridination of 3-amino quinazolinones mediated by LTA: attempted intramolecular aziridination of \(Q^5\text{NH}_2\).**

\[
\begin{align*}
&\text{Me} \quad \text{NH} \quad \text{Ph} \\
&\text{LTA} \\
&\text{Ph} \\
&\text{O} \\
&\text{Me} \quad \text{N} \quad \text{CO} \\
&\text{NH}_2 \quad \text{Ph} \\
\rightarrow & \quad \text{LTA} \\
\rightarrow & \quad \text{No Aziridine}
\end{align*}
\]

\[
\begin{align*}
\text{80} &= Q^5\text{NH}_2 \\
\text{93} &= Q^5\text{NHOAc}
\end{align*}
\]

To a solution of powdered LTA (145 mg, 0.33 mmol) in dry DCM (2 cm\(^3\)) stirred at -20°C was added a solution of the \(Q^5\text{NH}_2\) 80 (100 mg, 0.30 mmol) in dry DCM (2 cm\(^3\)) dropwise over 10 min. The mixture was stirred for a further 3 min. then decanted from the sticky / oily lead di-acetate, the reaction flask rinsed with DCM (2 cm\(^3\)) and the combined cloudy organic extracts washed with bicarbonate (2 x 20 cm\(^3\)), then dried and evaporated under water pump pressure. TLC of the resulting mixture showed the presence of at least 3 components but chromatography (3:1 PE/EA) did not result in the isolation of any homogenous products. In the \(^1\text{H}-\text{NMR}\) spectrum of the crude reaction product, there were no signals assignable to aziridine ring protons.

**Aziridination of styrene by \(Q^5\text{NH}_2\).**
In a round bottomed flask equipped with a stirring bar and cooled to −10 °C in a lagged acetone-CO₂ bath, DCM (6 cm³) was added followed by powdered LTA (145 mg, 0.33 mmol). After stirring a few minutes, the LTA dissolved. Styrene (34 mg, 0.33 mmol) was added to the solution followed by dropwise addition over 15 min. of a solution of Q₅NH₂ 80 (100 mg, 0.30 mmol) in DCM (2 cm³), stirring throughout. After stirring for a further 5 min. the solution was decanted from the sticky LDA, the flask rinsed with further DCM (2 cm³) and the combined cloudy organic extracts washed with a solution of bicarbonate and worked up as described for general procedure F. Column chromatography of the crude product (114 mg) (eluting solvent 3:1 PE/EA), gave aziridine 141 (Rf 0.28) as an oil [44 mg, 34 % yield based on compound 80] as a 7:1 ratio of diastereoisomers from comparison of signals at δ 6.13 and 6.51 in the NMR spectrum (see below) (Found: MH⁺ 438.1817. C₂₇H₂₃N₃O₃ requires MH⁺ 438.1818); νₘₙₐₓ/cm⁻¹ 1670s, 1640s, 1600s; δH major diastereoisomer 1.60 (3H, d, J 6.6, CHCH₃), 2.97, 3.49, 4.15 (3H, 3 x m, NCH₂-CHPh), 6.13 (1H, q, J 6.6, CHCH₃), 6.59 (1H, m, =CHCO), 7.28-7.81 [14H, m, H-6,7,8(Q), 10x CH(Ph), =CHPh] and 8.21 [1H, m, H-5(Q)]; signals from the minor diastereoisomer are observable at δ 1.72 (1H, d, J 6.6, CHCH₃), 2.76, 3.68 and 4.47 (3H, m, NCH₂-CHPh), 6.51 (1H, q, J 6.6, CHCH₃) and 6.65 (1H, m, CHCO); δC major diastereoisomer 18.1 (CH₃), 43.8 [CH₂ (azir)], 48.3 (CHPh), 68.7 (CH₃CH), 117.8 (CHCO), 122.2 [CCO(Q)], 126.6-134.3 [4 x CH(Q), 10 x CH(Ph)], 134.7, 136.6 [2 x CH-C(Ph)], 146.1 (CHPh), 146.3 [CN=C(Q)], 156.0 [C=N(Q)], 160.2 [CO(Q)] and 167.1 (CO₂); m/z 438 (MH⁺ 100) and 85 (100); signals from the minor diastereoisomer are observable at 18.9 (CH₃), 42.5 [CH₂ (azir)], 44.3 (CHPh), 68.4 (CH₃CH).
General Procedure for intermolecular aziridination of alkenes by oxidative addition of 3-aminoquinazolinones to alkenes mediated by LTA.

Aziridination of methyl cinnamate by Q5NH2 – LTA.

Q5NH2 80 (100 mg, 0.30 mmol), LTA (145 mg, 0.33 mmol) and ethyl cinnamate (48 mg, 0.33 mmol) were reacted in dry DCM (1 cm3). Flash chromatography (5:2 PE/EA) gave unchanged ethyl cinnamate Rf 0.54 followed by aziridine 142 as an oil (Rf 0.28) [20 mg, 14 % yield based on compound 80] as a 5:1 ratio of diastereoisomers from comparison of signals at δ 4.72 and 4.98 in the NMR spectrum below. (Found: MH+ 510.2030. C10H11N3O2 requires MH+, 510.2029); νmax/cm⁻¹ 1730s, 1670s, 1640m and 1600m; δH major diastereoisomer 1.18 (3H, t, J 7.3, CH2CH3), 1.53 (1H, d, J 6.7, CHCH3), 3.82 [1H, d, J 4.8, CH (azir.)], 4.14 (2H, q, J 7.3, CH2CH3), 4.72 [1H, d, J 4.8, CH (azir.)], 6.12 (1H, q, J 6.7, CHCH3), 6.60 (1H, d, J ~16, CH=CHPh), 7.34-7.75 [13H, m, H-6,7,8(Q), 10 x CH(Ph)], 7.80 (1H, d, J ~16, CHPh) and 8.17 [1H, d, J 8.0, H-5(Q)]; signals from the minor diastereoisomer are observable at δ 1.12 (3H, t, J 7.3, CH2CH3), 1.82 (1H, d, J 6.4, CHCH3), 3.58 [1H, d, J 4.8, CH (azir.)], 4.14 (2H, q, J 7.3, CH2CH3), 4.98 [1H, d, J 4.8, CH (azir.)], 6.22 (1H, q, J 6.7, CHCH3), 6.58 (1H, d, J 16.1, CH=CHPh) and 8.22 [1H, d, J 8.0, H-5(Q)]; δC major diastereoisomer 14.2 and 18.0 (2 x CH3), 51.7 and 54.2 (CHPh and CHCO2Et), 62.4 (CO2CH2CH3), 67.8 (CH3CH), 117.7 (COCH=), 121.8 [CCO(Q)], 126.6-134.7 [4 x CH(Q), CN=C(Q), C-CO(Q), 10 x CH (Ph)], 146.2 (CHPh), 146.4 [CN=C(Q)], 154.0 [C=N(Q)], 160.2 [CO(Q)], 166.1 (CO2Et) and 166.9 (CO2); m/z 510 (MH+ 100) and 85 (54).
Synthesis of \( O,N \) di-pent-4-enoylated compound 77

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{N}
\end{align*}
\]

\( \text{77} \)

Q\(^4\)NH\(_2\) 76 (0.1 g, 0.48 mmol) was dissolved in dry pyridine (1 cm\(^3\)) and stirred in an ice bath at \( \sim 0^\circ \text{C} \). Pent-4-enoyl chloride (0.127 g, 1.07 mmol) was added dropwise over 10 min and the solution stirred for 30 min at 0 °C. Work up as described previously gave a yellow oil (72 mg). Chromatography (2:1 PE/EA) afforded the \( N,O \)-diacylated product 77 (~44 mg, 24%) \( \text{Rf} 0.48 \). An \(^1\text{H}-\text{NMR}\) spectrum of 77 established that it was a 2.8:1 mixture of N-N bond rotamers from signals at \( \delta 6.10 \) and \( \delta 6.22 \). (Found: MH\(^+\) 370.1767. C\(_{20}\)H\(_{23}\)N\(_3\)O\(_4\) requires MH\(^+\) \text{370.1767}); \( \delta \text{H major rotamer 1.60 (3H, d, J 6.4, CH\(_3\)), 2.46 (8H, m, CH\(_2\)CH\(_2\)), 5.03 (4H, m, CH=CH\(_2\)), 5.84 (2H, m, CH=CH\(_2\)), 6.22 (1H, q, J 6.4, CHCH\(_3\)), 7.45 [1H, m, H-6(Q)], 7.74 [2H, m, H-7, H-8 (Q)], 8.19 [1H, d, J 7.9, H-5(Q)] and 10.30 (s, NH); minor rotamer (observable signals) 1.60 (3H, d, J 6.4, CH\(_3\)), 6.10 (1H, q, J 6.4, CHCH\(_3\)), 10.0 (s, NH); \( \delta \text{C major rotamer 18.5 (CH\(_3\)), 29.0, 29.2 (CH\(_2\)CH\(_2\)), 33.6, 33.7 (CO-CH\(_2\)), 67.9 (CH\(_3\)CH), 116.4 (CH=CH\(_2\)), 127.4–135.3 [4 x CH(Q)], 136.8 (CH=CH\(_2\)), 147.0 [C-N=C(Q)], 156.3 [N=C-N(Q)], 160.3 [CO-N(Q)], 173.4 and 173.6 [NH-CO(Q) and O-CO(Q)]; minor rotamers not visible. m/z (%) 391.9 (MNa\(^+\) 100). Further elution with the same solvent mixture gave unchanged Q\(^4\)NH\(_2\) 76 (~28 mg, 39%) \( \text{Rf} 0.18 \).
Synthesis of mono-\(N\)-pent-4-enoylated compound 78

The \(N,O\)-dipent-4-enoylated product 77 isolated above (1.2 g, 3.25 mmol) was added to a rapidly stirred solution of ethanol (30 cm\(^3\)) and water (30 cm\(^3\)) before adding sodium hydroxide pellets (650mg, 16.24 mmol). The reaction mixture becomes homogenous after 15 min. but was stirred for 2 days. After the bulk of the ethanol was removed under reduced pressure the residue was extracted with DCM (2 x 30 cm\(^3\)), the organic layer separated, dried and evaporated to give a crude oil/solid product mixture. Chromatography (2:1 PE/EA) gave \(N\)-acylated product 78 (216 mg, 13\%) (R\(_f\) 0.08) as a \(\sim 1:1\) ratio of \(N\)-\(N\) rotamers. (Found: \(M^+\) 288.1348. \(\text{C}_{15}\text{H}_{17}\text{N}_{3}\text{O}_{3}\) requires \(M^+\), 288.1348); \(\nu_{\text{max}}/\text{cm}^{-1}\) 1690s, 1610s, 1470m and 1280m; \(\delta_{\text{H}}\) first rotamer 1.50 (3H, d, \(J\) 6.6, \(\text{CH}_3\)), 2.54 (4H, m, \(\text{CH}_2\text{CH}_2\)), 4.70 (1H, q, \(J\) 6.6, \(\text{CH}_3\text{CH}\)), 4.96 (2H, m, \(\text{CH}=\text{CH}_2\)), 5.88 (1H, m, \(\text{CH}=\text{CH}_2\)), 7.30-7.80 [3H, m, H-6, H-7, H-8(Q)], 8.12 [1H, d, \(J\) 8.0, H-5(Q)] and 8.79 (1H, s, \(\text{NH}\)); second rotamer (observable signals) 1.45 (3H, d, \(J\) 6.6, \(\text{CH}_3\)), 8.12 [1H, d, \(J\) 8.0, H-5(Q)] and 8.58 (1H, s, \(\text{NH}\)); \(\delta_{\text{C}}\) first rotamer 22.6 (\(\text{CH}_3\)), 29.1, 33.6 (\(\text{CH}_2\text{-CH}_2\)), 65.2 (\(\text{CH}_3\text{CH}\)), 116.5 (\(\text{CH}=\text{CH}_2\)), 120.8 [\(\text{CCO(Q)}\)], 127.2, 127.4, 135.3, 136.5 [4 x \(\text{CH(Q)}\)], 127.6 (\(\text{CH}=\text{CH}_2\)), 146.2 [\(\text{CN=C(Q)}\)], 159.8 [\(\text{C=N(Q)}\)], 160.7 [\(\text{CO(Q)}\)] and 173.8 (NCO); second rotamer 22.7 (\(\text{CH}_3\)), 29.2, 33.7 (\(\text{CH}_2\text{-CH}_2\)), 65.4 (\(\text{CH}_3\text{CH}\)), 116.3 (\(\text{CH}=\text{CH}_2\)), 121.0 [\(\text{CCO(Q)}\)], 127.3, 127.5, 135.6, 136.6 [4 x \(\text{CH(Q)}\)], 127.6 (\(\text{CH}=\text{CH}_2\)), 146.2 [\(\text{CN=C(Q)}\)], 160.0 [\(\text{C=N(Q)}\)], 160.7 [\(\text{CO(Q)}\)] and 173.7 (NCO); \(m/z\) (%) 288 (\(M^+\) 100).
Attempted $O$-pent-4-enoylation of $Q^4\text{NH}_2\ 76$

$Q^4\text{NH}_2\ 76$ (0.5 g, 2.44 mmol) in dry pyridine (5 cm$^3$) was reacted with pent-4-enoyl chloride (0.375 g, 3.17 mmol) as described in general procedure E except that the reaction was stirred for 30 min in an ice bath at 0 °C, then for 1 h. at ambient temperature. Following solvent evaporation, the residue was left overnight under vacuum (oil pump) and the resulting thick brown oil (698 mg) purified by column chromatography (1:1 PE/EA) to give a 4:1 mixture (368 mg) containing a ~1:1 ratio of N-N rotamers of $Q^6\text{NH}_2\ 79$ as a pale yellow oil (~278 mg, 40%) and $N,O$-diacylated product 77 (~90mg, 10%). The $N$,$O$-diacylated product 77 was assigned from comparison of the $^1$H NMR spectrum of the above mixture with the spectrum of an authentic sample. The $O$-acylated product was isolated on further chromatography using the same solvent mixture in 11% yield as pale yellow oil (Rf 0.41) $\delta_H$: 1.60 (3H, d, $J\ 6.4$, CH$_3$), 2.42 (4H, m, CH$_2$CH$_2$), 4.98 (4H, m, CH=CH$_2$, NH$_2$), 5.75 (1H, m, CH=CH$_2$), 6.22 (1H, q, $J\ 6.4$, CHCH$_3$), 7.36 [1H, m, H-6(Q)], 7.65 [2H, m, H-7, H-8(Q)] and 8.15 [1H, d, $J\ 7.9$, H-5(Q)]; $m/z$ 370 [MH$^+$ (8) 100] and 288 [MH$^+$ (7) 12].

Further elution of the crude product mixture with 2:1 PE/EA gave the $N$-acylated product 78 (~84 mg, 12%) and starting material $Q^4\text{NH}_2\ 76$ (~121 mg, 24%) as a white foam (Rf 0.08) from comparison with $^1$H NMR spectra of authentic samples (see above). The $N$-acylated product was analysed by IR and mass spectrometry: (Found: MH$^+$ 288.1348. C$_{15}$H$_{17}$N$_3$O$_3$ requires MH$^+$, 288.1348); $\nu$$_{\text{max}}$/cm$^{-1}$ 3300s, 2980m, 1700s, 1600s, 1510m and 1460m.
Reaction of the sodium salt of Q\(^{4}\)NH\(_{2}\) 76 with pent-4-enoyle chloride

A solution of Q\(^{4}\)NH\(_{2}\) 76 (0.5 g, 2.44 mmol) in dry THF (10 cm\(^3\)) was stirred at 40 °C, then cooled to 0 °C. Sodium hydride (0.088 g, 3.66 mmol) was added and the mixture stirred for 10 min, during which time H\(_{2}\) was evolved. After 10 min, pent-4-enoyle chloride (0.631 g, 5.36 mmol) was added with stirring which generated a vigorous reaction and the mixture then stirred for 1 h. After evaporation of solvent, the residue was dissolved in DCM (10 cm\(^3\)), the solution washed with water (2 x 5 cm\(^3\)), dried and evaporated to give the N,O-dipent-4-enoylated Q\(^{4}\)NH\(_{2}\) 79 as a yellow oil (0.5 g, 71%) as a mixture of rotamers (ratio 3:1) identical with that observed previously.
Synthesis of (R)-2-(1-hydroxymethyl)ethyl-3-aminoquinazolin-4(3H)-one

\[ \text{MeCO}_2\text{Me} \rightarrow \text{MeCO}_2\text{H} \rightarrow \text{MeCO}_2\text{H} \rightarrow \text{MeCOCl} \]

Hydrolysis of ester 84

Methyl (R)-(-)-3-hydroxy-2-methyl propionate 84 (1 g, 8.47 mmol) was heated under reflux in a solution of NaOH (1M, 8.5 cm³) in ethanol (5 cm³) for 5 h. The bulk of the ethanol was evaporated under reduced pressure, the residual solution extracted twice with ethyl acetate, the aqueous layer cooled in ice-water and acidified to ~pH 3 by adding concentrated hydrochloric acid dropwise. After extraction using ethyl acetate (2 x 10 cm³), the organic extracts were combined, dried and then evaporated to give (R)-(-)-3-hydroxy-2-methyl propionic acid 85 as a yellow oil (685 mg, 78%). \( \delta_H 1.20 \) (3H, d, \( J 7.2 \), \( CH_3 \)), 2.73 (1H, m, 6 lines, \( CHCH_3 \)), 3.74 (2H, m, \( J 6.3 \), \( CH_2OH \)) and 6.60 (1H, s br, \( OH \)).

Acetylation of hydroxy acid 85

Acid 85 (723 mg; 6.94 mmol) was reacted with acetyl chloride (0.99 cm³, 13.88 mmol) as described in general procedure A except that the solution was heated under reflux for four days. Evaporation under reduced pressure gave O-acetate 86 [982 mg, 97% yield from the compound 85] as a brown oil. \( \delta_H 1.25 \) (3H, d, \( J 7.2 \), \( CHCH_3 \)), 2.10 (3H, s, \( COCH_3 \)), 2.83 (1H, m, 6-lines, \( CHCH_3 \)), 4.20 (2H, m, \( CHCH_2 \)) and 6.60 (1H, s br, \( COOH \)).
Acid chloride 87

The crude O-acetylated acid 86 from the previous step (982 mg, 6.72 mmol) was reacted with thionyl chloride (0.59 cm³, 8.06 mmol) as in general procedure B except the reaction mixture was stirred at 50 °C for 2 days. Evaporation gave the product 87 (961 mg, 87%) as an orange oil. δH 1.34 (3H, d, J 7.2, CHCH₃), 2.08 (3H, s, COCH₃), 3.22 (1H, m, CHCH₃) and 4.28 (2H, d, J 7.2, CHCH₂).

Methyl N-acylanthranilate 88

A solution of the acid chloride prepared above 87 (961 mg, 5.84 mmol) in dry ether (4 cm³) was added to a solution of methyl anthranilate (1.74 cm³, 13.43 mmol) in dry ether (10 cm³) as described in general procedure C. The methyl N-acylanthranilate 88 was obtained as an oil (981 mg, 60% yield from acid chloride) following solvent evaporation without chromatography. (Found: MH⁺ 280.1185. C₁₄H₁₇NO₅ requires MH⁺ 280.1185); νmax/cm⁻¹ 3280m, 2960m, 1750s, 1680s, 1600s, 1530s and 1450s; δH 1.31 (3H, d, J 7.2, CH₃), 2.03 (3H, s, CH₃CO), 2.85 (1H, m, CH₃CH), 3.90 (3H, s, CO₂CH₃), 4.29 (2H, m, CH₃CHCH₂), 7.03 [1H, m, H-5 (Ar)], 7.50 [1H, m, H-4 (Ar)], 7.99 [1H, d, J 7.9, H-6 (Ar)], 8.70 [1H, d, J 8.5, H-3 (Ar)] and 11.22 (1H, s, NH); δC 14.6 (CH₃CH), 21.2 (CH₃CO), 42.7 (CHCH₃), 52.7 (OCH₃), 66.3 (CH₂CH), 115.4 [C-1 (Ar)], 120.9, 123.0, 131.2, 135.1 [ 4 x CH(Ar)], 141.8 [C-2 (Ar)] and 169.1, 171.2, 172.9 (COOCH₃, CONH, COCH₃); m/z (%) 280 (MH⁺ 100).

3-Aminoquinazolinone (QHN₂) 89

The 3-aminoquinazolinone QHN₂ 89 was prepared as in general procedure D, using a solution of the N-acylanthranilate 88 (1 g, 3.58 mmol) in ethanol (0.3 cm³) and hydrazine hydrate (0.54 cm³, 17.90 mmol). The product solidified to give 3-aminoquinazolinone (QHN₂) as a colourless solid [484 mg, 63% from 88] mp. 128-129°C (from ethanol); [α]D²⁰ −16 (c 1.0, CHCl₃); (Found: C, 60.1; H, 6.0; N, 19.1. C₁₁H₁₃N₃O₂ requires C, 60.3; H, 6.0; N, 19.2%); (Found: MH⁺ 220.1087. C₁₁H₁₃N₃O₂ requires MH⁺ 220.1086); νmax/cm⁻¹ 1690s, 1610m, 1590s, 1530s and 1450s; δH 1.38 (3H, d, J 6.9, CH₃), 3.77-4.06 (4H, m, CHCH₃, CHCH₂, OH), 4.96 (2H, s, NH₂), 7.43 [1H, dd, J 8.2 and 8.2, H-6(Q)], 7.68 [1H, d, J 8.2, H-8(Q)], 7.71 [1H, dd, J 8.2, 8.2, H-7(Q)] and 8.20 [1H, d, J 8.2, H-5(Q)]; δC 15.7 (CH₃CH), 38.2 (CHCH₃), 65.9 (CH₂OH), 120.4 [CCO(Q)], 126.8, 127.0, 127.5, 134.7 [ 4 x CH(Q)], 146.8 [CN=C(Q)], 161.3 [C=N(Q)] and 162.1 [CO(Q)]; m/z 220 (MH⁺ 100) and 202 (42).
Synthesis of (R)-3-amino-2-(1-cinnamoyloxymethyl)ethyl-quinazolin-4(3H)-one

Using a modification of general procedure E, cinnamoyl chloride (0.455 g, 2.74 mmol) was added dropwise over 10 min. to a solution of Q NH\textsubscript{2} \textsc{89} (500 mg, 2.28 mmol) and dry pyridine (5 cm\textsuperscript{3}) and the solution was stirred for a further 6 h. at ambient temperature. Purification of the residual oil (1.164 g) by chromatography (1:1 PE/EA) yielded the O-cinnamoyl-3-aminoquinazolinone Q NH\textsubscript{2} \textsc{90} as an oil (689 mg, 87%) R\textsubscript{f} 0.46. (Found: MH\textsuperscript{+} 350.1504. \textit{C}_{20}\text{H}_{19}\text{N}_{3}\text{O}_{3} requires MH\textsuperscript{+}, 350.1505); \nu_{\text{max}}/cm\textsuperscript{-1} 1710s, 1670s, 1630m, 1600m, and 1170s; \delta\textsubscript{H} 1.47 (3H, d, J 7.0, CH\textsubscript{3}), 4.15 (1H, q, J 7.0, CH\textsubscript{2}), 4.45-4.71 (2H, m, CH\textsubscript{2}), 4.95 (2H, s, NH\textsubscript{2}), 6.35 (1H, d, J 16.1, COCH\textsubscript{3}), 7.25-7.78 \{9H, m, CHPh, 5 x CH(Ph), H-6,7,8(Q)\} and 8.23 \{1H, m, H-5(Q)\}; \delta\textsubscript{C} 16.4 (CH\textsubscript{3}CH), 36.3 (CH\textsubscript{3}CH), 67.5 (CH\textsubscript{3}CH-CH\textsubscript{2}), 118.1 (COCH), 125.0 [CCO(Q)], 126.8-134.6 \{4 x CH(Q), CN=C, C-CO(Q), 5 x CH(Ph), C(Ph)\}, 145.6 (CHPh), 147.0 [CN=C(Q)], 158.0 [C=N(Q)], 158.6 (CO\textsubscript{2}) and 167.2 [CO(Q)]; m/z (%) 355 (MH\textsuperscript{+} 28) and 85 (100).

Further elution with the same solvent mixture gave unchanged starting material Q NH\textsubscript{2} \textsc{89} (99mg) (Rf 0.16)
Attempted intramolecular aziridination of Q₈NH₂ 90

![Diagram of chemical structures]

General Procedure H for intramolecular aziridination of 3-amino quinazolinones at ambient temperature by LTA in the presence of HMDS.

A 3-necked flask was equipped with two identical dropping funnels and a calcium chloride tube. One of the dropping funnels was charged with a solution of LTA (279 mg, 0.63 mmol) in dry DCM (2 cm³) and the other with a solution of Q₈NH₂ 90 (200 mg, 0.57 mmol) in dry DCM (2 cm³). The solutions in the two dropping funnels were each added dropwise at the same rate to a stirred solution of HMDS (185 mg, 1.14 mmol) in dry DCM (30 cm³) over 10 min. The mixture was left to stir for 3 min. then separated from the LDA, the LDA washed with DCM (5 cm³) and the combined organic solutions washed with bicarbonate (2 x 20 cm³), then dried and evaporated under water pump pressure. Chromatography of the product (218 mg) (2:1 PE/EA), gave (24 mg) (Rf 0.09) 3H-quinazolinone 98 as a solid as the only homogeneous product.

δ_H: 1.40 (3H, d, J 7.0, CH₃), 4.05 (1H, q, J 7.0, CH₂CH), 4.48 (2H, d, J 7.0, CH₂), 6.26 (1H, d, J 16.1, COCH), 7.20-7.70 [7H, m, H-6(Q), H-7(Q), 5 x CH (Ph)], 7.52 (1H, d, J 16.1, CHPh) and 8.22 [1H, d, J 8.2, H-5(Q)].
Synthesis of 3-amino-2(3-hydroxyalkyl)quinazolin-4(3H)-ones. Synthesis of Q^N\text{H}_2 107

General procedure I for ester / lactone hydrolysis with aqueous NaOH

γ-Butyrolactone 102 (30 g, 28.47 cm³, 0.35 mol) was added to an ice-cold 12.6M solution of NaOH (15.33 g, 0.38 mol) in water (30 cm³) and the mixture stirred for 5h at this temperature. Evaporation of the bulk of the water on a rotary evaporator gave the sodium salt 103 as a white solid (44 g) which was thoroughly dried in a desiccator in vacuo using an oil-pump for 2 days in the presence of dry P₂O₅ (replacing the P₂O₅ twice to ensure its dryness) and retained in a sealed sample tube before use.

General procedure J for acylation of sodium salt compound 103

The dry (powdered) sodium salt (46 g, 0.36 mol) prepared above was added portion-wise to acetyl chloride (99.3 cm³, 109.6 g, 1.46 mol) in an ice-cooled flask with exclusion of moisture. Sodium chloride immediately forms during the addition. After stirring at ambient temperature for 6 h, the solution was diluted with CHCl₃ (10 cm³), the solids separated and the solution evaporated on a water pump to give ~1:1 mixture (39.5 g) of O-acetate 104 and γ-butyrolactone 102 from comparison of signals in the \textsuperscript{1}H-NMR spectrum at δ 2.05 and δ 2.90 respectively; for O-acetate 104 δ\textsubscript{H} 1.44-1.68 (2H, m, CH₂), 2.05 (3H, s, COCH₃), 2.28-2.45 (2H, t, J 7.1, CH₂CO), 4.06 (2H, t, J 6.4, CH₂OCO) and 11.30 (1H, s br, CO₂H).
Synthesis of acid chloride 105

The acid chloride was prepared as in general procedure B from the mixture containing acid 104 prepared above (20 g, 0.14 mol), thionyl chloride (14.97 cm$^3$, 0.21 mol) and DMF (2 drops). Evaporation of the excess thionyl chloride under reduced pressure gave the acid chloride 105 [37.4 g, 59% yield based on compound 104] as an oil, which was used directly in reaction with methyl anthranilate below. $\delta_H$ 1.44 and 1.70 (2H, 2 x m, CHH), 2.04 (3H, s, COCH$_3$), 2.95 (2H, t, $J$ 7.1, CH$_2$CO) and 4.06 (3H, t, $J$ 6.4, CH$_2$OCO).

Synthesis of N-acylanthranilate 106 from the acid chloride 105

The anthranilate was prepared as in general procedure C, using a solution of the crude acid chloride from the previous reaction step (37.4 g, 0.21 mol) in dry ether (30 cm$^3$) and a solution of methyl anthranilate (71.9 g, 61.6 cm$^3$, 0.48 mol) in dry ether (400 cm$^3$). The methyl N-acylanthranilate 106 was obtained as an orange oil (41.4 g, 72%) and used without further purification in the next reaction step. (Found: $M_{H^+}$ 280.1185. C$_{14}$H$_{17}$NO$_5$ requires $M_{H^+}$ 280.1185); $\nu_{max}$/cm$^{-1}$ 3320m, 1730s, 1690s, 1590s, 1530s and 1450s; $\delta_H$ 1.48-1.70 (2H, m, CH$_2$CH$_2$O), 2.03 (3H, s, COCH$_3$), 2.47 (2H, t, $J$ 7.1, CH$_2$CO), 3.93 (3H, s, OCH$_3$), 4.16 (2H, t, $J$ 6.4, CH$_2$O), 7.05 [1H, ddd, $J$ 8.0, 7.3, 0.9, H-5 (Ar)], 7.52 [1H, ddd, $J$-8, 7.3, 1.4, H-4 (Ar)], 8.00 [1H, dd, $J$ 8.0, 1.4, H-6 (Ar)], 8.70 [1H, dd, $J$-8, 0.7, H-3 (Ar) and 11.10 (1H, s br, NH$\_2$); $\delta_C$ 21.1 (COCH$_3$), 24.7 (CH$_2$), 35.1 (COCH$_2$), 52.6 (CO$_2$CH$_3$), 63.8 (CH$_2$O), 115.1 [C-CO(Ar)], 120.6, 122.7, 131.1, 134.9 [4 x CH(Ar)], 141.8 [C-2 (Ar)], 169.0 [C-1 (Ar)] and 171.2 (CO$_2$CH$_3$, CO$_2$CH$_3$); $m/z$ (%) 301.8 (MNa$^+$ 100).
Synthesis of 3-aminoquinazolinone 107

Following general procedure D, a solution of the N-acylanthranilate 106 (41.4 g, 0.15 mol) in ethanol (80 cm³) containing hydrazine hydrate (26.2 cm³, 27 g, 0.89 mol) was heated under reflux for 4 h. then left to stir overnight at ambient temperature. After workup, the solid obtained was crystallised to give the 3-aminoquinazolinone 6NH₂ 107 as a colourless solid (19.46 g, 25% yield based on γ-butylrolactone) mp. 115-6 °C (from acetonitrile). (Found: C, 60.2; H, 5.9; N, 19.3. C₁₁H₁₃N₃O₂ requires C, 60.3; H, 6.0; N, 19.2%); (Found: MH⁺ 220.1086. C₁₁H₁₃N₃O₂ requires MH⁺, 220.1086); νₓ/ cm⁻¹ 3340w, 1670s, 1600s and 1470m; δH 2.12 (2H, m, CH₂CH₂CH₂), 3.22 (2H, t, J 7.1, CH₂Q), 3.40 (1H, s br, OH), 3.79 (2H, t, J 6.4, CH₂OH), 5.00 (2H, s, NH₂), 7.45 [1H, dd, J 7.8, H-6(Q)], 7.64 [1H, d, J 7.8, H-8(Q)], 7.71 [1H, dd, J 7.8, H-7(Q)] and 8.22 [1H, d, J 7.8, H-5(Q)]; δC 29.6 (CH₂CH₂CH₂), 32.0 (CH₂Q), 62.6 (CH₂OH), 120.2 [CCO(Q)], 126.9, 126.9, 127.2, 134.8 [4 x CH(Q)], 146.8 [CN=C(Q)], 158.6 [C=N(Q)] and 162.0 [C=O(Q)]; m/z (%) 220 (MH⁺ 100).
Synthesis of 3-amino-2-(3-cinnamoyloxypropyl)quinazolin-4(3H)-one 120

General procedure E was followed using a solution of Q\textsuperscript{9}NH\textsubscript{2} 107 (1 g, 4.56 mmol) in dry pyridine (4 cm\textsuperscript{3}) in a flame-dried flask at -40 °C and cinnamoyl chloride (0.911 g, 5.47 mmol) added dropwise over 10 min. and the solution was stirred for 2 h. at -40 °C, then for a further 2 h. at -20 °C, and finally for 2 h. at ambient temperature. Crystallisation of the solid obtained provided O-cinnamoyl-3-aminoquinazolinone 120 (Q\textsuperscript{10}NH\textsubscript{2}) as a colourless solid (748 mg, 47%) mp. 129-130 °C (from acetonitrile). (Found: C, 68.6; H, 5.5; N, 11.7. C\textsubscript{20}H\textsubscript{19}N\textsubscript{3}O\textsubscript{3} requires C, 68.8; H, 5.5; N, 12.0%); (Found: MH\textsuperscript{+} 350.1505. C\textsubscript{20}H\textsubscript{19}N\textsubscript{3}O\textsubscript{3} requires MH\textsuperscript{+} 350.1505); \nu\textsubscript{max}/cm\textsuperscript{-1} 1710s, 1680s, 1640s, 1600s and 1470m; \delta\textsubscript{H} 2.31 (2H, m, 5-lines), 3.19 [2H, t, J 7.4, CH\textsubscript{2}-Q], 4.40 (2H, t, J 6.2, CH\textsubscript{2}O), 4.86 (2H, s, NH\textsubscript{2}), 6.37 (1H, d, J 16.1, CHCHPh), 7.30-7.75 [8H, m, H-6,7 and 8 (Q), 5 x CH(Ph)], 7.65 (1H, d, J 16.1, CHCHPh) and 8.22 [1H, m, J 8.1, H-5(Q)]; \delta\textsubscript{C} 26.2, 31.3 (CH\textsubscript{2}CH\textsubscript{2}), 64.3 (CH\textsubscript{2}O), 118.3, 126.7, 126.8, 126.8, 127.6, 128.5, 128.6, 129.2, 130.7, 134.6, 145.3 [4 x CH(Q), 5 x CH(Ph), CH=CH, CCO(Q), CH(Ph)], 147.3 [CN=C(Q)], 157.5 [C=N(Q)], 162.3 [CO(Q)] and 167.3 (O-CO); m/z (%) 350 (MH\textsuperscript{+} ,100), 202 (90) and 131 (38). Evaporation of the filtrate after crystallisation of 120 above and chromatography of the residue over silica gave unchanged Q\textsuperscript{9}NH\textsubscript{2} (80mg) (Rf 0.06).
Intramolecular aziridination of Q\textsuperscript{10}NH\textsubscript{2} 120 in the presence of HMDS

The aziridine 131 was prepared as in general procedure H from Q\textsuperscript{10}NH\textsubscript{2} 120 (200 mg, 0.57 mmol), LTA (279 mg, 0.63 mmol) and HMDS (185 mg, 0.765 cm\textsuperscript{3}, 1.15 mmol) to give a yellow solid (230 mg). Chromatography (1:2 PE/EA) gave aziridine 131 (20 mg, 10%) Rf 0.33 as a colourless solid mp. 167-168 °C (from ethanol). ν\textsubscript{max}/cm\textsuperscript{-1} 1740s, 1680s, 1600s, 1470m, 1340m and 1170s; δ\textsubscript{H} 2.39 (1H, m, CHH), 2.60 (1H, m, CHH), 2.95 (1H, m, CHH), 3.58 (1H, m, CHH), 3.80 (1H, d, J 5.6, azir. CO-CH), 4.60 (2H, m, 2 x CHH), 4.81 (1H, d, J 5.6, azir. CHPh), 7.28-7.65 [8H, m, H-6, H-7, H-8(Q), 5 x CH(Ph)] and 8.14 [1H, d, J 8.0, H-5(Q)]; δ\textsubscript{C} 30.0, 30.5 (2 x CH\textsubscript{2}), 52.1 and 52.6 (CH-CH), 69.5 (CH\textsubscript{2}O), 121.7 [CCO(Q)], 126.9, 127.0, 127.1, 127.8, 128.5, 129.1, 134.5 [5 x CH(Ar), 4 x CH(Q)], 135.0 [C(Ph)], 146.0 [CN=C(Q)], 155.5 [C=N(Q)], 161.0 [CO(Q)] and 167.2 (CO\textsubscript{2}); Further elution with PE/EA 1:2 gave 3H-quinazolinone (Q\textsuperscript{7}H) (35 mg) Rf 0.76.
Intramolecular aziridination of $^{10}$NH$_2$ 120 in the presence of TFA

![Chemical structure](image.png)

General procedure K for the oxidative aziridination of a 3-aminoquinazolinone with LTA in the presence of TFA at ambient temperature: preparation of trifluoroacetate 125.

$^{10}$NH$_2$ 120 (400 mg, 1.15 mmol) was dissolved in DCM (6 cm$^3$) and powdered LTA (559 mg, 1.26 mmol) was dissolved in dry DCM (5 cm$^3$). Both these solutions were added dropwise and simultaneously using flame-dried syringes via a septum cap over 30 min. to a stirred solution of TFA (392 mg, 3.44 mmol) in dry DCM (5 cm$^3$) at ambient temperature. After addition the solution was decanted from the flask, the residual LDA was washed with DCM (10 cm$^3$) and the combined DCM extracts washed with bicarbonate (2 x 20 cm$^3$), and dried. The residual brown foam was identified as the trifluoroacetate 125 (427 mg, 81%); mp. 170-171 °C (from ethanol).

$\nu_{\text{max}}$/cm$^{-1}$ 1800s, 1760s, 1680s, 1595s, 1260s, 1170s and 1150s; $\delta_{\text{H}}$: 2.40 (1H, struct m, CH$_2$CHH/CH$_2$), 2.70 (2H, m, 2 x CH), 3.42 (1H, ddd, $J$ 14.0, 11.7, 3.4, CHH), 4.15 (1H, m, CHHO), 4.17 (1H, dd, $J$ 9.4, 1.4, NH-CH), 4.95 (1H, m, CHHO), 5.44 (1H, s, NH), 6.39 (1H, d, $J$ 9.4, CHOCOCF$_3$), 7.40-7.80 [8H, m, H-6, H-7, H-8 (Q), 5 x CH(Ph)] and 8.16 [1H, dd, $J$ 8.0, 1.14, H-5 (Q)]; $\delta_{\text{C}}$: 27.7, 29.2 (2 x CH$_2$), 63.8 (CH$_2$O), 63.9, 76.9 (CH-CH), 120.4 [COC(Q)], 126.9-131.2, 135.3 [4 x CH(Q), 5 x CH(Ph)], 132.4 [C(Ph)], 146.6 [CN=C(Q)], 160.9, 161.2 [CO(Q), C=N(Q)] and 170.5 (O-CO).
Methanolysis of trifluoroacetate 125

![Chemical structure of compound 126](image)

General procedure L for the hydrolysis of a trifluoroacetate group

The trifluoroacetate 125 (427 mg) stirred overnight in dry methanol (3 cm³) to give after evaporation the alcohol 126 (310 mg, 96%); δ_H 2.36 and 2.68 (3H, 2 x m, 3 x CH), 3.45 (1H, m, CH_H), 3.78 (1H, d, J 5.0, NH-CH), 4.03 (1H, m, OCH_H), 4.98 (1H, m, OCH_H), 5.35 (1H, d, J 5.0, CHPh), 5.77 (1H, s, NH), 7.23-7.80 [8H, m, H-6, H-7, H-8 (Q), 5 x CH(Ph)] and 8.20 [1H, d, J 8.0, H-5 (Q)]; δ_C 28.5 and 30.0 (2 x CH_2), 64.1 (CH_2_O), 67.1 and 73.3 (CH-CH), 120.4 [CCO(Q)], 126.9-135.2 [4 x CH(Q), 5 x CH(Ph)], 138.0 [C(Ph)], 147.6 [CN=C(Q)], 157.5 and 161.5 [CO(Q), C=N(Q)] and 173.5 (O-CO); m/z (%) 366 (MH⁺ 100).
Preparation of N-acylanthranilate 218 from coumaranone

A mixture of coumaranone (500 mg, 3.73 mmol) and methyl anthranilate (2 cm³, 7.46 mmol) were heated at 40 °C for 1 h. and then set aside overnight. After dissolving in DCM (10 cm³), the solution was washed successively with HCl (2M) (3 x 10 cm³), bicarbonate (2 x 10 cm³) then dried (MgSO₄) and evaporated to give a solid. Crystallisation gave N-acylanthranilate 218 as colourless crystals (455 mg, 43%) mp. 144-145 °C (from ethanol). (Found: C, 67.1; H, 5.3; N, 4.9. C₁₆H₁₅NO₄ requires C, 67.4; H, 5.3; N, 4.9 %); (Found: MH⁺ 286.1079. C₁₆H₁₅NO₄ requires MH⁺, 286.1079); νmax/cm⁻¹ 1700m, 1670m, 1590s, 1540s, 1450s, 1280s and 1260s; δH 3.70 (2H, s, CH₂), 3.89 (3H, s, OCH₃), 6.80 [1H, ddd, J 7.3, 7.3, 1.2, CH(Ar)], 6.91 [1H, dd, J 8.0, 0.9, CH (Ar)], 7.10-7.25 [3H, m, 2 x CH(Ar), H-5 (Ar)], 7.48 [1H, ddd, J 8.0, 7.1, 1.6, H-4 (Ar)], 7.96 [1H, dd, J 8.0, 1.6, H-6 (Ar)], 8.55 [1H, dd, J 8.5, 0.9, H-3 (Ar)] and 9.00 (1H, s br, NH); δC 43.5 (CH₂), 52.9 (OCH₃), 116.0 [C(Ar)], 121.7 [C(Ar)], 118.5, 121.0, 121.2, 123.9, 129.7, 131.1, 131.3, 135.1 [8 x CH(Ar)], 141.0 [C(Ar)], 156.5 {C(Ar)}, 169.2 (NH-CO) and 172.6 (CO₂CH₃); m/z (%) 307.7 (MNa⁺ 100).
Synthesis of 3-amino-2-(2-hydroxybenzyl)quinazolin-4(3H)-one

Following procedure D a solution of N-acylanthranilate 218 (400 mg, 1.40 mmol) in ethanol (5 cm³) containing hydrazine hydrate (262 cm³, 0.27 g, 8.41 mmol) was heated at reflux for 8 h. then left stirring at ambient temperature overnight. The bulk of the ethanol was evaporated under reduced pressure, water added, the solids obtained separated, washed well with water and dried. Crystallisation gave 3-aminoquinazolinone 136 as a colourless solid (19.46 g, 25%) mp. 115-6 °C (from acetonitrile). (Found: C, 67.4; H, 4.9; N, 15.7. C₁₅H₁₃N₃O₂ requires C, 67.4; H, 4.9; N, 15.7%); (Found: MH⁺ 268.1086. C₁₅H₁₃N₃O₂ requires MH⁺, 268.1086); νmax/cm⁻¹ 1680s, 1590m, 1470m and 1260s; δH 4.47 (2H, s, CH₂), 4.93 (2H, s, NH₂), 6.88 [1H, ddd, J 8.0, 7.6, 1.2, CH(Ar)], 6.97 [1H, dd, J 8.0, 0.9, CH(Ar)], 7.19 [1H, ddd, J 8.0, 7.6, 1.6, CH(Ar)], 7.35 [1H, dd, J 7.6, 1.6, CH(Ar)], 7.45 [1H, ddd, J 8.0, 7.1, 1.2, H-6(Q)], 7.65 [1H, dd, J 7.1, 1.2, H-8(Q)], 7.75 [1H, ddd, J 7.1, 7.1, 1.4, H-7(Q)], 8.19 [1H, dd, J 8.0, 1.2, H-5(Q)] and 9.84 (1H, s br, OH); δC 36.54 (CH₂), 118.7, 120.9, 127.1 127.4, 129.7, 131.3, 135.2 [4 x CH(Q), 4 x CH(Ar)], 122.1 and 126.8 [2 x C(Ar)] 120.3 [CCO(Q)], 157.3 [CN=C(Q)], 152.2 [C=N(Q)] and 161.3 [CO(Q)]; m/z (%) 268 (MH⁺ 100).
Synthesis of 3-amino-2-(δ-hydroxybutyl)quinazolin-4(3H)-one 113

Hydrolysis of δ-valerolactone
Compound 109 was prepared from δ-valerolactone 108 (10.5 g, 9.47 cm³, 0.10 mol) and NaOH (4.39 g, 0.12 mol) in water (10 cm³) as in general procedure I to produce the hygroscopic sodium salt 109 in quantitative yield (14.49 g), which was stored in vacuo over P₂O₅.

NMR (250 MHz, D₂O) δH 1.57 (4H, m, CH₂CH₂), 2.19 (2H, m, CH₂CO), 3.58 (2H, m, CH₄O) and 4.70 (1H, s br, OH).

Preparation of δ-acetoxypentanoic acid 110
General procedure J was used to react the dry (powdered) alcohol salt (14.49 g, 0.10 mol) with acetyl chloride (29.4 cm³, 0.41 mol) to give γ-acetoxypentanoic acid (24 g) which was used directly in the next step without separation from some reformed valerolactone.

δH 1.70 (4H, m, CH₂CH₂), 2.00 (3H, s, COCH₃), 2.30 (1H, m, CHHCO), 3.00 (1H, m, CHHCO), 4.00 (2H, m, CH₂O) and 11.04 (1H, s br, CO₂H);

Preparation of δ-acetoxypentanoyl chloride 111
To the crude δ-acetoxypentanoic acid 110 above (24 g, 0.15 mol) was added oxalyl chloride (8.5 cm³, 0.18 mol) and 3 drops DMF and the solution stirred at ambient
temperature overnight. Evaporation under reduced pressure gave the acid chloride as a brown oil (22 g), which was used directly in the next stage.

δH 1.73 (4H, m, CH₂CH₂), 2.08 (3H, s, COCH₃), 2.37 (1H, m, CHHCO), 2.98 (1H, m, CHHCO) and 4.10 (2H, m, CH₂O).

Synthesis of N-arylanthranilate 112
Following general procedure C the acid chloride 111 (11.8 g, 0.066 mol) and methyl anthranilate (5.88 cm³, 6.87 g, 0.16 mol) were reacted together. Chromatography (1:1 PE/EA) of the residue gave the N-acylanthranilate 112 as an oil Rf 0.40 [11.6 g, 38% yield based on 110].  

Synthesis of 3-aminoquinazolinone (Q₁₂NH₂) 113
Using general procedure D the N-acylanthranilate 112 (10.6 g, 0.036 mol) and hydrazine hydrate (6.75 cm³, 0.22 mol) were reacted together. Crystallisation of the product gave 3-aminoquinazolinone 113 as a colourless solid [5.04 g, 60% yield based on N-acylanthranilate 112]. mp. 132-133 °C (from ethanol-water); (Found: C, 61.4; H, 6.5; N, 17.4. C₁₂H₁₅N₃O₂ ½ C₂H₅OH requires C, 61.3; H, 6.8; N, 17.2%); (Found: MH⁺ 234.1242. C₁₂H₁₅N₃O₂ requires MH⁺, 234.1243); νmax/cm⁻¹ 1670s, 1660s, 1470m and 1470m; δH 1.77 (2H, m, CH₂), 1.99 (2H, m, CH₂), 2.25 (1H, s br, OH), 3.09 (2H, t, J 7.4, CH₂CO), 3.70 (2H, t, J 6.2, CH₂O), 4.88 (2H, s, NH₂), 7.45 [1H, dd, J 7.5, 7.8, H-6(Q)], 7.70 [2H, m, H-7, H-8(Q)] and 8.25 [1H, d, J 7.8, H-5(Q)]; δC 22.9, 32.4, 34.1 (3 x CH₂), 62.5 (CH₂OH), 120.4 [CCO(Q)], 126.8, 126.9, 127.4 and 134.8 [4 x CH(Q)], 150.5 [CN=C(Q)], 158.4 [C=N(Q)] and 162.2 [C=O(Q)]; m/z (%) 238 (MH⁺ 100).
Synthesis of 3-amino-2-(4-cinnamoyloxybutyl)quinazolin-4(3H)-one

Following procedure E, a solution of cinnamoyl chloride (0.357 mg, 2.14 mmol) in dry DCM (2 cm³) was added dropwise over 10 min. to a stirred solution of Q¹¹³NH₂ 113 (500 mg, 2.14 mmol) in dry DCM (2 cm³) and dry pyridine (3 cm³) in a flame-dried flask at ambient temperature, stirring continued for a further 10 min. The reaction was worked up as described in general procedure E to give 3-aminoquinazolinone 121 as a colourless solid (420 mg, 54%). mp. 113-114 °C (from ethanol); (Found: C, 68.4; H, 5.8; N, 11.0. C₂₁H₂₁N₃O₃ ¼ C₂H₅OH requires C, 68.9; H, 6.1; N, 11.2%); (Found: MH⁺ 364.1661. C₂₁H₂₁N₃O₃ requires MH⁺, 364.1661); νmax/cm⁻¹ 1710s, 1680s, 1670s, 1650m and 1600m; δH 1.94 (4H, m, 2 x CH₂), 3.09 [2H, t, J 7.3, CH₂(Q)], 4.29 (2H, t, J 6.2 CH₂O), 4.88 (2H, s, NH₂), 6.44 (1H, d, J 16.1, CHCHPh), 7.30-7.80 [9H, m, H-6, H-7, H-8(Q), 5 x CH(Ph), CHCHPh and 8.22 [1H, d, J 7.1, H-5(Q)]; δC 23.8, 28.8, 34.3 (3 x CH₂), 64.6 (1 x CH₂O), 118.5, 120.5, 126.7, 126.9, 127.6, 128.5, 129.3, 130.7, 134.7, 134.8, 145.2 [CH=CHPh, CCO(Q), 5 x CH(Ph), 4 x CH(Q), C(Ph)], 147.4 [CN=C(Q)], 158.1 [C=N(Q)], 162.3 [CO(Q)] and 167.4 (O-CO); m/z (%) 494 (28), 365 (24), 364 (MH⁺ 100), 216 (28) and 131 (28).
Intramolecular aziridination of Q\textsuperscript{13}NH\textsubscript{2} 121 in the presence of HMDS

General procedure H was followed using Q\textsuperscript{13}NH\textsubscript{2} 121 (90 mg, 0.25 mmol), LTA (134 mg, 0.27 mmol) and HMDS (0.116 cm\textsuperscript{3}, 0.50 mmol). The aziridine product was obtained as a colourless solid (88 mg, 98%) mp. 161-162 °C (from ethanol). (Found: MH\textsuperscript{+} 362.1505. C\textsubscript{21}H\textsubscript{19}N\textsubscript{3}O\textsubscript{3} requires MH\textsuperscript{+}, 362.1505); ν\textsubscript{max}/cm\textsuperscript{-1} 1740s, 1670s, 1590s, 1180s and 1020s; δ\textsubscript{H} : 1.56 (1H, m, CHH), 1.95 (1H, m, CHH), 2.20 (1H, m, CHH), 2.63 (1H, m, 7-lines, CHH), 2.88 (1H, ddd, J 16.3, 6.4, 2.5, CHH), 3.68 (1H, d, J 5.7, azir. CO-CH), 3.77 (1H, m, CHH), 4.05 (1H, m, CHH), 4.56 (1H, d, J 5.7, arir. CHPh), 4.79 (1H, dd, J 10.8, 5.1, CHH), 7.30-7.70 [8H, m, H-6, H-7, H-8(Q), 5 x CH(Ph)] and 8.22 [1H, d, J 7.8, H-5(Q)]; δ\textsubscript{C} 21.8, 24.3, 30.3 (3 x CH\textsubscript{2}), 52.3 and 54.2 (CH-CH), 68.9 (CH\textsubscript{2}O), 121.4 [CCO(Q)], 126.8, 126.9, 127.0, 127.7, 128.9, 129.0, 134.3 [5 x CH(Ar), 4 x CH(Q)], 134.9 [C(Ph)], 146.3 [CN=C(Q)], 155.2 [C=N(Q)], 160.7 [CO(Q)] and 165.5 (CO\textsubscript{2}); m/z (%) 362 (MH\textsuperscript{+} 100).
Intramolecular aziridination of Q\textsuperscript{13}NH\textsubscript{2} 121 in the presence of TFA

![Chemical structure of 127](image)

**General procedure** K was followed using Q\textsuperscript{13}NH\textsubscript{2} 121 (200 mg, 0.55 mmol), LTA (408 mg, 0.61 mmol) and TFA (0.18 cm\textsuperscript{3}, 1.65 mmol) to give trifluoroacetate 127 as an orange oil [227 mg, 87% yield based on compound 121]. \(\delta_H\) 1.75 (2H, m, \(\text{CH}_2\)), 1.98 (1H, m, \(\text{CH}\)), 2.40 (1H, m, \(\text{CH}\)), 2.70 (1H, m, \(\text{CH}\)), 3.85 (1H, m, \(\text{CH}\)), 4.43 - 4.58 (3H, m, \(\text{CH}_2\text{O}, \text{CHNH}\)), 5.08 (1H, s, \(\text{NH}\)), 6.30 (1H, d, \(J 9.4, \text{CHPh}\)), 7.30-7.80 [8H, m, H-6, H-7, H-8(Q), 5 x \(\text{CH(Ph)}\)] and 8.17 [1H, d, \(J 8.0, \text{H-5(Q)}\)].

**Methanolation of trifluoroacetate 127**

![Chemical structure of 128](image)

The trifluoroacetate 127 (227 mg, 0.48 mmol) was triturated with methanol (1 cm\textsuperscript{3}) and set aside overnight. Crystallisation of the resulting solid gave alcohol 128 [58 mg, 32% yield based on 127], mp. 187.5-188.5 °C (from ethyl acetate). (Found: C, 66.3; H, 5.6; N, 10.8. \(\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_4\) requires C, 66.5; H, 5.6; N, 11.1%). (Found: MH\textsuperscript+ 380.1611. \(\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_4\) requires \(\text{MH}^+\), 380.1610); \(\nu_{\max}/\text{cm}^{-1}\) 1740s, 1680s and 1595s; \(\delta_H\) 1.70 (2H, m, 2 x \(\text{CH}\)), 2.00 (1H, m, \(\text{CHH}\)), 2.45 (1H, m, \(\text{CHH}\)), 2.62 (1H, ddd, \(J\) 146.
15.4, -4.0, 4.5, (CHH), 3.04 (1H, s br, OH), 3.78 (1H, ddd, J 15.4, 11.7, -4.0, (CHH), 4.12 (1H, dd, J 7.4, 1.8, NH-CH), 4.30 (1H, dt, J 11.7, 4.5, (CHH), 4.48 (1H, m, CHH), 5.08 (1H, d, J 7.4, C(Ph)), 5.17 (1H, d, J 1.8, NH), 7.27-7.67 [8H, m, H-6, H-7, H-8(Ph)], and 8.12 [1H, dd, J 8.0, 1.2, H-5(Ph)]; δC 25.2, 25.7, 30.3 (3 x CH2), 67.0, 67.3, (CH-CHPh) 73.7 [CH2O], 122.0 [C(Ph)], 126.7, 127.1, 127.3, 127.6, 129.3, 129.6, 134.9 [4 x CH(Q), 5 x CH(Ph)], 138.9 [C(Ph)], 148.0 [CN=C(Q)], 159.8 [C=N(Q)], 162.5 [CO(Q)] and 170.2 (O-CO); m/z (%) 402 (MNa+ 22), 381 (22), 380 (MH+ 100).

Synthesis of 2-(4-crotonyloxybutyl)-3-aminoquinazolin-4(3H)-one

Following general procedure E, a solution of Q15NH2 113 (500 mg, 2.14 mmol) in dry DCM (50 cm³) and dry pyridine (338 mg, 4.29 mmol) was treated with crotonyl chloride (0.270 mg, 2.57 mmol) but the solution was heated under reflux for 1 h. then stirred at ambient temperature overnight. After work up the solid (488 mg) obtained was chromatographed (1:1 PE/EA), to give crotonyl ester Q14NH2 123 as a colourless oil (182 mg, 28%) Rf 0.39. (Found: MH+ 302.1505. C16H19N3O3 requires MH+, 302.1505); νmax/cm⁻¹ 1710s, 1670s, 1600s and 1190s; δH 1.90 (7H, m, CH2(CH2)2CH2, CH3), 3.08 [2H, t, J 7.5, CH2Q], 4.20 (2H, t, J 6.2, CH2O-CO), 4.90 (2H, s, NH2), 5.85 (1H, dq, J 15.5, 1.7, COCH), 6.96 (1H, dq, J 6.9, 15.5, C(PhCH3)), 7.42 [1H, dd, J 7.4, 7.4, H-6(Q)], 7.60-7.79 [2H, m, H-7(Q), H-8(Q)] and 8.22 [1H, d, J 7.4, H-5(Q)]; δC 18.3 (CH3), 23.8, 28.8, 34.3 (3 x CH2), 64.2 (CH2O), 120.4 [CO(Q)], 123.1 (COCH), 126.8, 126.9, 127.6, 134.7 [4 x CH(Q)], 145.1 (CHCH3), 147.5 [CN=C(Q)], 159.4 [C=N(Q)], 163.5 [CO(Q)] and 167.0 (CO2); m/z (%) 370 (20), 303 (20), 302 (MH+ 100) and 216 (30).
Further elution gave an oil (56 mg) Rf 0.24 identified as the N,O-diacylated product 124. (Found: MH+ 370.1766. C20H23N3O4 requires MH+, 370.1767); vmax/cm⁻¹: 1710s, 1660s, 1600s, 1470m and 1300m; δH 1.78 (3H, dd, J 6.9, 1.6, CH3), 1.80 (7H, m, CH2-CH2, CH3), 2.72 (2H, m, CH2), 4.08 (2H, m, CH2), 5.76 (1H, dq, J ~14, 1.6, COCH), 6.07 (1H, dq, J ~14, 1.4, COCH), 6.90 (1H, dq, J 13.8, 6.9, CHCH3), 6.96 (1H, dq, J 13.8, 6.9, CHCH3), 7.36 [1H, ddd, J 8.0, 7.5, 1.2, H-6(Q)], 7.64 [2H, m, H-7, H-8(Q)], 8.12 [1H, dd, J 8.0, 0.9, H-5(Q)] and 9.31 (1H, s, NH); observable signals from the minor rotamer 3.03 (2H, m, CH2), 4.35 (2H, m, CH2) and 9.26 (NH); δC 18.3, 18.4 (2 x CH3), 23.2, 28.6, 33.3 (3 x CH2), 64.2 (CH2O), 121.0, 122.0 (2 x COCH), 123.0 [CCO(Q)], 127.1, 127.2, 127.9, 135.3 [4 x CH(Q)], 144.7, 145.2 (2 x CHCH3), 147.5 [CN=C(Q)], 158.1 [C=N(Q)], 161.4 [CO(Q)] and 166.4, 167.1 (2 x CO2); m/z (%) 370 (MH+ 100).

Further elution gave a solid (163 mg) Rf 0.06 identified as the starting material 113 by comparison with the 1H-NMR spectrum of an authentic sample.
Synthesis of 3-amino-2-(ε-hydroxypentyl)quinazolin-4(3H)-one

Hydrolysis of ε-caprolactone

Compound 115 was prepared from ε-caprolactone 114 (11 g, 9.71 cm³, 0.076 mol) and a solution of NaOH (3.052 g, 0.084 mol) in water (10 cm³) as in general procedure I to give the hygroscopic sodium salt as a fine powder after drying, in quantitative yield (11.83 g). δH (D₂O) 1.48 (2H, m, CH₂), 1.66 (4H, m, 2 x CH₂), 2.32 (2H, t, J 7.5, CH₂), 3.74 (2H, t, J 6.5, CH₂) and 4.88 (1H, s, OH).

Preparation of ε-acetoxyacid 116

The acylation was carried out using general procedure J from the dry (powdered) sodium salt 115 (11.83 g, 0.076 mol) and acetyl chloride (24 g, 22.02 cm³, 0.31 mol) to give ε-acetoxyhexanoic acid [12.57 g, 95% yield based on compound 115] as an oil which was used directly in the following step without separation from the small amount of ε-caprolactone reformed. νmax/cm⁻¹ 1720s, 1370m and 1250s; δH 1.40 (2H, m, CH₂), 1.65 (4H, m, 2 x CH₂), 2.05 (3H, s, COCH₃), 2.35 (2H, m, CH₂), 4.10 (2H, t, J 6.5, CH₂O) and 8.34 (1H, s br, CO₂H); m/z (%) 197 (MNa⁺ 38), 175 (MH⁺ 15) and 115 (lactone MH⁺ 100).

Acid chloride 117

The acid chloride 117 was prepared as in general procedure B from the ε-acetoxyhexanoic acid 116 above (12.57 g, 0.072 mol), thionyl chloride (10.53 cm³, 0.14 mol) and 3 drops DMF but the solution was stirred for 2 days at ambient
temperature. Evaporation gave the acid chloride as an oil [13.05 g, 93% yield based on compound 116] which was used directly in the following step.

δ_H: 1.44 (2H, m, CH_2), 1.72 (4H, m, CH_2), 2.00 (3H, s, CH_3), 2.90 (2H, t, J 6.5, CH_2), 4.04 (2H, t, J 6.5, CH_2).

**Preparation of N-acylanthranilate 118**

The anthranilate 118 was prepared as described in general procedure C from acid chloride 117 (13.09 g, 0.067 mol) and methyl anthranilate (10.196 g, 0.16 mol). Chromatography (1:1 PE/EA) of the residue gave the N-acylanthranilate 118 Rf 0.43 [12.1 g, 52% yield based on compound 115] as an oil which was used directly in the next step. (Found: MH⁺ 308.1498. C_{16}H_{21}NO_5 requires MH⁺, 308.1498); ν_max/cm⁻¹ 1730s, 1690s, 1590s, 1530s, 1450s and 1260s; δ_H 1.66 (2H, m, CH_2), 1.94 (4H, m, 2 x CH_2), 2.28 (3H, s, COCH_3), 2.66 (2H, t, J 7.6, CH_2CO), 4.19 (3H, s, OCH_3), 4.32 (2H, t, J 6.6, CH_2O), 7.30 [1H, dd, J 7.9, 7.9, H-5(Ar)], 7.75 [1H, dd, J 7.9, 7.9, H-4(Ar)], 8.23 [1H, d, J 7.9, H-6(Ar)], 8.94 [1H, d, J 7.9, H-3(Ar)]; δ_C 21.4 (COCH_3), 25.5, 26.0, 28.8, 38.8 (4 x CH_2), 52.7 (CO_2CH_3), 64.7 (CH_2O), 115.2 [C-1(Ar)], 120.7, 122.8, 131.2, 135.1 [4 x CH(Ar)], 142.0 [C-2(Ar)] and 169.2, 171.6, 172.2 (COCH_3, CO_2CH_3, NHCO); m/z (%) 422 (56), 330 (MNa⁺ 56) and 308 (MH⁺ 100).

**Synthesis of 3-aminooquinazolinone 119 from anthranilate 118**

The 3-aminooquinazolinone Q_{15}^{15}NH_2 119 was prepared as in general procedure D, using a solution of N-acylanthranilate 118 (12.1 g, 0.039 mol) in ethanol (30 cm³) and hydrazine hydrate (6.31 g, 6.13 cm³, 0.20 mol). The resulting solid gave 3-aminooquinazolinone Q_{15}^{15}NH_2 119 as a colourless solid [7.046 g, 72% yield based on compound 118], mp. 121-121.5 °C (from ethanol). (Found: MH⁺ 248.1399. C_{13}H_{17}N_3O_2 requires MH⁺, 248.1399); ν_max/cm⁻¹ 1670s, 1600s and 1470m; δ_H 1.50 - 2.05 (7H, m, CH_2(CH_2)_2CH_2O), 3.05 [2H, t, J 7.6, CH_2(Q)], 3.70 (2H, t, J 6.3, CH_2O), 4.90 (2H, s, NH_2), 7.44 [1H, ddd, J 8.0, 6.7, 1.4, H-6(Q)], 7.70 [2H, m, H-7, H-8(Q)] and 8.22 [1H, dd, J 8.0, 0.9, H-5(Q)]; δ_C 25.8, 26.7, 32.5, 34.6 (4 x CH_2), 62.9 (CH_2OH), 120.4 [CCO(Q)], 126.7, 126.9, 127.5, 134.7 [4 x CH(Q)], 147.3 [CN=C(Q)], 158.6 [C=N(Q)] and 162.3 [C=O(Q)]; m/z (%) 270 (MNa⁺ 100), 248 (MH⁺ 58).
Synthesis of 3-amino-2-(5-cinnamoyloxypentyl)quinazolin-4(3H)-one

A solution of cinnamoyl chloride (0.357 mg, 2.02 mmol) in dry DCM (2 cm$^3$) was added dropwise over 30 min to a stirred solution of $Q^{16}$NH$_2$ 119 (500 mg, 2.02 mmol) in dry pyridine (3 cm$^3$) at ambient temperature and the solution stirred for a further 10 min. Work up as described in general procedure E gave 3-aminquinazolinone 122, by crystallisation as a colourless solid (430 mg, 56%) mp 104-105 °C (from ethanol). (Found: C, 69.8; H, 6.0; N, 10.6. C$_{22}$H$_{23}$N$_3$O$_3$ ¼ C$_2$H$_5$OH requires C, 69.5; H, 6.4; N, 10.8%); (Found: MH$^+$ 378.1818. C$_{22}$H$_{23}$N$_3$O$_3$ requires MH$^+$, 378.1818); $\nu$ max/cm$^{-1}$ 1700s, 1680s, 1640s, 1600s, 1470m and 1310s; $\delta$ H 1.58 (2H, m, CH$_2$), 1.88 [4H, m, (CH$_2$)$_2$], 3.07 (2H, t, J 7.7, CH$_2$Q), 4.25 (2H, t, J 6.5, CH$_2$O), 4.88 (2H, s, NH$_2$), 6.42 (1H, d, J 15.8, COCH), 7.30-7.70 [9H, m, H-6, H-7, H-8(Q), 5 x CH(Ph), CHPh] and 8.21 [1H, d, J 7.8, H-5(Q)]; $\delta$ C: 26.1, 26.9, 28.9, 34.7 (4 x CH$_2$), 64.7 (CH$_2$O), 118.5 (COCH=), 120.4 [CCO(Q)], 126.7, 126.9, 127.6, 128.5, 129.3, 130.6, 134.6 [4 x CH(Q), 5 x CH(Ph)], 134.8 [C(Ph)], 145.1 (CHPh), 147.6 [CN=C(Q)], 158.4 [C=N(Q)], 162.5 [CO(Q)] and 167.5 (CO$_2$); m/z (%) 378 (MH$^+$ 100).
Intramolecular aziridination of Q^{16}NH_2 122 with LTA in the presence of HMDS

Using general procedure H, Q^{16}NH_2 122 (200 mg, 0.53 mmol), LTA (258 mg, 0.58 mmol) and HMDS (171 mg, 1.06 mmol) reacted to give a yellow solid (252 mg). Aziridine 133 (14 mg, 7%) (Rf 0.76) was isolated by chromatography (2:1 PE/EA) as a white solid mp. 97-98 °C (from ethanol); (Found: MH⁺ 376.1661. C_{22}H_{21}N_3O_3 requires MH⁺, 376.1661); ν max/cm⁻¹ 1740s, 1670s, 1590s and 1180s; δ_H 1.55 (3H, m, 3 x CH), 1.86 (2H, m, 2 x CH), 2.70 (2H, m, 2 x CH), 3.35 (1H, m, 1 x CH), 3.63 (1H, d, J 5.5, azir. CO-CH), 3.78 (1H, m, 1 x CH), 4.60 (1H, d, J 5.5, azir. CHPh), 4.72 (1H, m, 1 x CH), 7.25-7.55 [7H, m, H-6, H-8(Q), 5 x CH(Ph)], 7.60 [1H, ddd, J 8.0, 6.9, 1.4, H-7(Q)] and 8.15 [1H, dd, J 8.0, 1.4, H-5(Q)]; δ_C 24.7, 25.6, 30.2, 30.6 [(CH₂)₄], 53.2, 53.0 (CH-CHPh), 67.5 (CH₂O), 121.5 [CCO(Q)], 126.7, 126.9, 127.4, 127.8, 129.0, 129.1, 134.0 [4 x CH(Q), 5 x CH(Ph)], 135.0 [C(Ph)], 146.3 [CN=C(Q)], 154.6 [C=N(Q)], 160.7 [CO(Q)] and 165.5 (CO₂); m/z (%) 376 (MH⁺ 100).
Intramolecular aziridination of Q$^{16}$NH$_2$ 122 with LTA in the presence of TFA; hydrolysis to the corresponding alcohol.

Following general procedure K, Q$^{16}$NH$_2$ 122 (200 mg, 0.53 mmol), LTA (258 mg, 0.58 mmol) and TFA (181 mg, 0.12 cm$^3$, 1.59 mmol) gave the trifluoroacetate 129 which was hydrolysed in quantitative yield (general procedure L) to give alcohol 130 as an oil [176 mg, 84% yield based on 122].

$\delta$H 1.56 [4H, m, 2 x CH$_2$], 2.42 (1H, m, CHH), 2.70 (2H, m, 2 x CH), 3.41 (1H, ddd, J 14.1, 11.9, 2.8, CHH), 4.16 (2H, m, CHH, CHNH), 4.95 (1H, m, CHH), 5.40 (1H, d, J 1.6, NH), 6.40 (1H, d, J 9.4, CHPh), 7.40 [1H, ddd, J ~8, 7.5, 1.1, H-6(Q)], 7.61 [7H, m, H-7, H-8(Q), 5 x CH(Ph)], and 8.25 [1H, dd, J 8.0, 1.1, H-5(Q)]; m/z (%) 416 (MNa$^+$ 100), 394 (MH$^+$ 95), 150 (42), 102 (38).
Synthesis of the 2,4-dimethoxybenzylidene derivative of 3-amino-2-ethyl-quinazolin-4(3H)-one 91

3-Amino-2-ethyl-quinazolinone 22 (200 mg, 1.06 mmol) was dissolved in dry ethanol (4 cm³), 2,4-dimethoxybenzaldehyde (0.221 g, 1.27 mmol) added portionwise over 5 mins. followed by a few crystals of toluene p-sulphonic acid and the mixture heated under reflux for 2 h. Evaporation gave a yellow solid (359 mg) which crystallised to gave colourless crystals of imine 91 (225 mg, 63%), mp. 187-187.5 °C (from ethanol). (Found: C, 67.2, H, 5.6; N, 12.3. C₁₉H₁₉N₃O₃ requires C, 67.6; H, 5.7; N, 12.5 %); (Found: MH⁺ 338.1505. C₁₉H₁₉N₃O₃ requires MH⁺, 338.1505); ν_max/cm⁻¹ 1670m, 1600s, 1280m and 1210m; δ_H : 1.36 (3H, t, J 6.9, CH₂CH₃), 2.94 (2H, q, J 6.9, CH₂CH₃), 3.88 (6H, 2 x s, 2 x OCH₃), 6.47 [1H, s, 3-H (Ar)], 6.60 [1H, d, J 8.7, 5-H (Ar)], 7.46 [1H, m, H-6(Q)], 7.70 [2H, m, H-7(Q), H-8(Q)], 8.14 [1H, d, J 8.7, 6-H (Ar)], 8.29 [1H, d, J 8.0, H-5(Q)] and 9.11 (1H, s, NCH); δ_C : 11.0 (CH₂CH₃), 28.5 (CH₂CH₃), 55.6 (2 x OCH₃), 98.0, 106.1, 126.1 [3 x CH(Ar)], 114.2 [2 x C(Ar)], 121.6 [CCO(Q)], 127.1, 127.2, 128.8, 133.9 [4 x CH(Q)], 128.8 [C(Ar)], 146.8 [CN=C(Q)], 157.6 [C=N(Q)], 161.2 and 163.9 [CO(Q), CH=N]; m/z (%) 338 (MH⁺ 100).
Reaction of the benzylidene derivative 91 with N-aminophthalimide.

The imine 91 (208 mg, 0.62 mmol) and N-aminophthalimide (100 mg, 0.62 mmol) were dissolved in dry DCM (4 cm³) containing a few crystals of toluene p-sulphonic acid and the solution heated under reflux for 2 h. and then stirred at ambient temperature overnight. A yellow solid (191 mg) was obtained, ¹H-NMR analysis of the crude reaction mixture following solvent evaporation showed the ratio of imines 92 : 91 present was 3.4:1 from comparison of non-exchangeable ¹H-NMR signals at δ3.04 and 2.94. Imine 92 (44 mg, 48%), (Rf 0.70) was isolated by chromatography (1:1 PE/EA) as a yellow solid mp. 174-175 °C (from ethanol); (Found: C, 65.2; H, 4.5; N, 8.7. C_{17}H_{14}N_{2}O_{4} \frac{1}{4} C_{2}H_{5}OH requires C, 65.3; H, 4.9; N, 8.7%); (Found: MH⁺ 311.1032. C_{17}H_{14}N_{2}O_{4} requires MH⁺, 311.1032); v_{max}/\text{cm}^{-1} 1730s, 1600s, 1470m, 1320s, 1280s and 1210s; δ_H 3.87 (6H, s, OCH₃), 6.46 [1H, d, J 2.3, 3-H (Ar)], 6.55 [1H, dd, J 8.7, 2.3, 5-H (Ar)], 7.75 [2H, m, 2 x CH (phthal)], 7.89 [2H, m, 2 x CH (phthal)], 8.13 [1H, d, J 8.7, 6-H (Ar)] and 9.48 (1H, s, NCH); δ_C 55.9, 56.0 (2 x OCH₃), 98.4, 106.1, 123.9 and 129.0 [3 x CH (Ar), 2 x CH (phthal)], 115.5 [2 x COCH₃], 119.5 (2 x C(Ar), 130.9 [CCH=N], 134.7 [2 x CH (phthal)], 157.0 (CH=N), 161.1 and 162.0 [2 x C-CO (phthal)] and 164.6, 165.6 [2 x CO (phthal)]; m/z (%) 343 (M⁺+CH₃OH, 100).
Reaction of Q-NH$_2$ 22 with imine 92

3-Aminoquinazolinone 22 (100 mg, 0.53 mmol) and imine 92 (163 mg, 0.53 mmol) obtained from the reaction described above, were dissolved in dry DCM (2 cm$^3$) and a few crystals of p-toluene sulphonic acid added. After heating under reflux at 83 °C for 8 h. the solution was left to stir at ambient temperature overnight. After solvent evaporation a yellow solid (200 mg) was obtained containing a ~1:3.7 ratio of 91 to 92 from comparison of $^1$H-NMR signals of 91 and 92 at 89.11 and 89.48 respectively.
Synthesis of racemic 3-aminoquinazolinone 147

(i) via cyanoether 153

\[
\begin{align*}
\text{Ph} - \text{CHO} & \quad \rightarrow \quad \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{Me}_3\text{SiO} \\
\text{CN}
\end{array} \\
\text{Ph} & \quad \rightarrow \quad \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \\
\text{AcO} & \quad \rightarrow \quad \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \\
\text{AcO} & \quad \rightarrow \quad \begin{array}{c}
\text{HN} \\
\text{CO}_2\text{Me}
\end{array} \\
\text{Ph} & \quad \rightarrow \quad \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \\
\text{AcO} & \quad \rightarrow \quad \begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array}
\end{align*}
\]

Synthesis of dioxolane 152

A mixture of benzaldehyde (20 g, 189 mmol) and ethane-1,2-diol (12 g, 193 mmol) in benzene (250 cm\(^3\)), containing a catalytic quantity of toluene p-sulphonic acid (1.9 g, 10 mmol) was heated at reflux in a Dean-stark trap until water ceased to be evolved (6 h). Evaporation of solvent followed by distillation (83-89 °C; 0.55 mbar) gave dioxolane 152 as a colourless oil (19.7 g, 67%).

\[\delta_{1H} 4.02 (4\text{H, m, OCH}_2\text{CH}_2\text{O}), 5.80 (1\text{H, s, PhCH}), 7.37 \text{ and } 7.45 (5\text{H, 2 x m, Ph}).\]

Ring-opening of dioxolane 152 to give \(\alpha\)-cyanoether 153

Following the literature procedure\(^{107}\) trimethylsilylcyanide (3.88 g, 5.21 cm\(^3\), 0.039 mol) and ZnI\(_2\) (50 mg) were added to the dioxolane 152 (5.9 g, 0.039 mol) in dry ether (2 cm\(^3\)) under N\(_2\) and the solution stirred at room temperature for 30 min. Evaporation of the ether left a red liquid which was purified by distillation (83 °C; 0.55 mbar) to give \(\alpha\)-cyanoether 153 as a colourless oil [9.6 g, 97% yield based on compound 152].

\[\delta_{1H} 0.00 [9\text{H, s, Si(CH}_3)_3], 3.64 (4\text{H, m, OCH}_2\text{CH}_2\text{O }), 5.30 (1\text{H, s, PhCH}) \text{ and } 7.20 \text{ and } 7.40 [5\text{H, 2 x m, 5 x CH(Ph)}]; \delta_{13C} 0.0 [\text{Si(CH}_3)_3], 62.2 (\text{CH}_2\text{OSi}), 71.4 (\text{CH}_2\text{CH}_2\text{O}), 71.6 (\text{PhCH}), 117.8 [\text{C(Ph)}], 127.8, 129.4 [4 \times \text{CH(Ar)}], 130.2 [1 \times \text{CH(Ar)}] \text{ and } 134.0 (\text{CN}).\]
Cyclisation of cyanoether 153 to 1,4-dioxanone 146

The silyl ether 153 (9.62 g, 0.038 mol) and conc. HCl (32%, 8 cm³) were heated under reflux for 1 h. Toluene (30 cm³) was added and the solution heated under reflux with water separation (1.2 cm³ water obtained) for 12 h. After cooling and evaporation of toluene under reduced pressure, ether (20 cm³) was added, the solution washed with bicarbonate (20 cm³), dried and evaporated, then distilled (bp 145 °C/0.35 mm Hg) to give dioxanone 146 [2.31 g, 34% yield based on compound 153].

NMR δH 4.00, 4.58 (4H, m, CH₂CH₂), 5.38 (1H, s, C/Ph) and 7.40 (5H, m, Ph).

Ring opening of 1,4-dioxanone 146

Sodium salt 154 was prepared from dioxanone 146 (2.35 g, 0.013 mol) and a solution of NaOH (580 mg, 0.015 mol) in water (3 cm³) as in general procedure I to give the sodium salt 154 [2.50 g, 86% yield based on compound 146].

NMR (250 MHz, D₂O) δH 3.35 and 3.52 (4H, 2 × m, CH₂CH₂), 4.63 (1H, s, CPh) and 7.20 (5H, m, Ph); m/z (%) 241 (MNa⁺ 100); 219 (MH⁺ 42).

Alternative route to sodium salt 154

General procedure M for reaction of ethylene glycol with α-haloacids.

Mineral oil-freed sodium hydride (15 g) and an excess of ethylene glycol (100 cm³) were heated under nitrogen at 100 °C for 30 min. to form the sodium salt. The cooled solution stirred for a further 20 min. before α- bromophenylacetic acid (20 g, 0.093 mol) (Aldrich) was added portionwise to the stirred mixture at ambient temperature and then the solution heated at 100 °C for 2 h. before setting aside overnight. The solution was distilled (4.3 × 10⁻¹ mbar, 55 °C) to remove the bulk of the ethylene glycol. Trituration of the residue using dry acetone (2 × 8 cm³) removed more ethylene glycol and freed the acid sodium salt 154 as a paste which solidified on drying in a desiccator for 2 days over P₂O₅, to give a white solid (30.6 g); δH (d₆-DMSO) 3.66 (4H, m, CH₂CH₂), 4.92 (IH, s, CPh), 7.50 (5H, m, Ph); δC (D₂O) 60.4, 70.6
(CH₂CH₂), 82.1 (CHPh), 127.5, 127.9, 128.3 [5 x CH(Ph)], 139.2 [C(Ph)] and 173.4 (CO₂Na).

**Acylation of sodium salt 154**

The acylation was carried out using general procedure J from the dry (powdered) sodium salt 154 (2.488 g, 0.011 mol) and acetyl chloride (3.58 g, 3.24 cm³, 0.046 mol) to give α-(2-acetoxy)ethoxy phenyl acetic acid 155 as an orange oil (2.71 g, 99.7%) which was used directly in the next step.

NMR δH 2.08 (3H, s, COCH₃), 3.75-4.27 (4H, m, CH₂CH₂), 4.96 (1H, s, CHPh), 7.45 (5H, m, Ph) and 8.80 (1H, s br, CO₂H); m/z(%) 347 (50), 261 (MNa⁺ 100) and 87 (42).

**Synthesis of acid chloride 156**

Two drops of DMF were added to the crude acid 155 (2.71 g, 0.011 mol) followed by thionyl chloride (2.7 g, 1.66 cm³, 0.023 mol) dropwise with stirring and the solution was stirred at ambient temperature for 1 day. Evaporation gave the acid chloride 156 as an orange oil (2.9 g) which was used directly in the next step.

δH 2.09 (3H, s, COCH₃), 3.84 and 4.30 (4H, 2 x m, CH₂CH₂), 5.17 (1H, s, CHPh) and 7.40 [5H, m, 5 x CH(Ph)].
Synthesis of N-acyl-anthranilate 157

Following general procedure C, a solution of the above crude acid chloride 156 (2.9 g, 0.011 mol) in dry ether (20 cm³) was added to methyl anthranilate (4.21 g, 3.6 cm³, 0.026 mol) in dry ether (80 cm³). After work up N-acyl-anthranilate 157 [3.4 g, 80% yield based on compound 156] was obtained as a yellow oil and used without further purification in the next step; (Found: \( \text{MH}^+ \) 372.3879. \( \text{C}_{20}\text{H}_{21}\text{NO}_6 \) requires \( \text{MH}^+ \), 372.3879); \( \nu_{\max}/\text{cm}^{-1} \) 1740s and 1700s;

\( \delta_H \) 2.08 (3H, s, COCH₃), 3.81 (2H, m, CH₂), 3.96 (3H, s, CO₂CH₃), 4.38 (2H, m, CH₂), 4.95 (1H, s, CHPh), 7.09 [1H, dd, \( J \) 8.5, 8.0, H-5(Ar)], 7.35-7.52 [6H, m, H-4(Ar), 5 x CH(Ph)], 8.05 [1H, d, \( J \) 8.0, H-6(Ar)] and 8.71 [1H, d, \( J \) 8.5, H-3(Ar)]; \( \delta_C \) 21.3 (OCOCH₃), 52.7 (CO₂CH₃), 63.9, 68.2 (CH₂CH₂), 83.7 (CHPh), 116.3 [C-1(Ar)], 120.9, 123.3, 131.3, 134.8 [4 x CH(Ar)], 127.4-129.0 [5 x CH(Ph)], 137.3 [C(Ph)], 141.0 [C-2(Ar)], 168.5, 170.1 and 171.4 [NH-CO(Ar), O-COCH₃ and CO₂CH₃]; \( m/z \) (%) 372 (MH⁺ 100).

Synthesis of 3-aminoquinazolinone 147

Following general procedure D, using a solution of the N-acylanthranilate 157 (3.37 g, 9.07 mmol) and hydrazine hydrate (1.74 g, 1.7 cm³, 0.054 mol) were reacted together. Crystallisation gave the 3-aminoquinazolinone (QNH₂) 147 as a colourless solid [1.57 g, 56% yield based on compound 157] mp. 158-160°C (from ethanol).

(Found: \( \text{MH}^+ \) 312.1348. \( \text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3 \) requires \( \text{MH}^+ \), 312.1348); \( \nu_{\max}/\text{cm}^{-1} \) 3320m, 3270w, 1680s, 1610s and 1460m; \( \delta_H \) 3.68-3.70 (2H, m, CH₂), 3.89 (2H, m, CH₂), 4.70 (2H, s br, NH₂), 5.97 (1H, s, CHPh), 7.29-7.42 [6H, m, H-6(Q), 5 x CH(Ph)], 7.70 [2H, m, H-7, H-8(Q)] and 8.16 [1H, d, \( J \) 8.3, H-5(Q)]; \( \delta_C \) 62.1, 72.4 (CH₂CH₂), 79.8 (CHPh), 120.5 [C-CO(Q)], 126.9-134.9 [4 x CH(Q), 5 x CH(Ph)], 137.4 [C(Ph)], 146.6 [CN=C(Q)], 156.0 [C=N(Q)] and 161.7 [C=O(Q)]; \( m/z \) (%) 334 (MNa⁺ 30), 312 (MH⁺ 58), 250 (100) and 233 (70).
Synthesis of $O$-ester 148

To a stirred solution of $Q^{17}NH_2$ 147 (500 mg, 1.61 mmol) and dry pyridine (2 cm$^3$) in a flame-dried flask at ambient temperature was added a solution of cinnamoyl chloride (268 mg, 1.61 mmol) in dry DCM (1 cm$^3$) over 20 min and the solution stirred for a further 3 h. before work up following general procedure E. Column chromatography (1:1 PE/EA) of the orange oil (851 mg) gave the $O$-ester 148 as a yellow oil (489 mg, 69%); (Found: MH$^+$ 442.1767. C$_{26}$H$_{23}$N$_3$O$_4$ requires MH$^+$, 442.1767); $v_{max}$/cm$^{-1}$ 3320w, 1710s, 1680s, 1640s, 1590s, 1470m and 1450m; $\delta_H$ 3.96 (2H, m, $CH_2$), 4.48 (2H, m, $CH_2$), 5.15 (2H, s br, NH$_2$), 6.08 (1H, s, CHPh), 6.42 (1H, d, $J$ 16.1, COCH), 7.30-7.82 [9H, m, H-6, H-7, H-8(Q), 5 x CH(Ph), CHCHPh] and 8.25 (1H, d, $J$ 8.3, H-5(Q)); $\delta_C$ 64.0 and 68.5 (CH$_2$CH$_2$), 81.2 (CHPh), 118.0 (COCH=), 120.6 [C-CO(Q)], 126.7-137.2 [4 x CH(Q), 2 x CH(Ph)], 145.7 (=CHPh), 146.9 [CN=C(Q)], 154.5 [C=N(Q)], 161.5 [CO(Q)] and 167.2 (O-CO); $m/z$ (%) 464 (MNa$^+$ 100), 442 (MH$^+$ 70), 215 (38) and 131 (56).
**N,N,O-tricinnamoylation of 3-aminoquinazolinone 147**

3-Aminoquinazolinone 147 Q\(^1\)NH\(_2\) (758 mg, 2.43 mmol) was dissolved in dry pyridine (2 cm\(^3\)), cinnamoyl chloride (1.61 g, 10 mmol) in dry DCM (1 cm\(^3\)) added over 20 mins. and the solution stirred for 1.5 h. Work up as described in general procedure E gave a yellow foam which after chromatography (1:2 PE/EA) gave the **N,N,O-tricinnamoyl-3-aminoquinazolinone 160** (1 g, 60%) (R\(_f\) 0.41) as an oil.

(Found: M\(^+\) 702.2605. C\(_{44}\)H\(_{35}\)N\(_3\)O\(_6\) requires M\(^+\), 702.2604); \(\nu_{\text{max/cm}}\) 1710s, 1620s, 1580m and 1450m; \(\delta\)\(_H\) 3.93 (2H, m, CH\(_2\)), 4.36 (2H, m, CH\(_2\)), 5.60 (1H, s, CHPh), 6.33 (1H, d, J 16.1, COCH=), 6.58 (1H, br d, J 16.1, COCH=), 6.95 (1H, br d, J 16.1, COCH=), 7.09-7.90 [26H, 20 x CH(Ph), 3 x CH(Q), 3 x =CH(Ph)], 8.28 [1H, d, J 8.3, 5-H(Q)]; \(\delta\)\(_C\) 63.7, 69.3 (CH\(_2\)-CH\(_2\)), 83.3 (PhCH), 117.0, 118.2, 118.6 (3 x COCH=), 121.6 [C-CO(Q)], 127.5-134.6 [20 x CH(Ph), 4 x CH(Q)], 134.8, 135.9, 136.2 [4 x C(Ph)], 145.4, 146.8, 147.3 (3 x =CHPh), 146.9 [CN=C(Q)], 154.5 [C=N(Q)], 160.6 [CO(Q)] and 166.8, 167.0, 167.1 (3 x O-CO); m/z (%) 704 (15), 703 (55) and 702 (M\(^+\) 100).
Intramolecular aziridination of $^{18}$NH$_2$ 148 by LTA in the presence of TFA and subsequent hydrolysis of the trifluoroacetate.

Following general procedure K using $^{18}$NH$_2$ 148 (500 mg, 1.13 mmol), LTA (552 mg, 1.25 mmol) and TFA (416 mg, 0.28 cm$^3$, 3.40 mmol) gave the trifluoroacetate 166 (397 mg, 63%) as yellow oil without chromatography.

$\nu_{\text{max}}$/cm$^{-1}$ 1800s, 1760s, 1680s and 1600s; $\delta_1$H 3.78 (1H, m, CHH), 3.98 (2H, m, CHH, NH), 4.10 (1H, m, CHH), 4.40 (1H, dd, $J$ 8.7, 1.2, NHCH), 5.30 (1H, m, CHH), 5.68 (1H, s, CHPh), 6.22 [1H, d, $J$ 8.7, CH(OOCF$_3$)Ph], 7.20-7.55 [11H, m, H-6(Q), 10 x CH(Ph)], 7.77 [2H, m, H-7, H-8(Q)] and 8.18 [1H, d, $J$ 7.8, H-5(Q)]; $\delta_C$ 61.1 (COCHNH), 62.5, 65.5 (CH$_2$CH$_2$), 77.4, 86.4 (2 x CHPh), 121.8 [CCO(Q)], 125.9-130.7, 135.3 [10 x CH(Ph), 4 x CH(Q), COCF$_3$], 132.6 and 138.0 [2 x C(Ph)], 146.3 [CN=C(Q)], 156.5 [C=N(Q)], 162.6 [CO(Q)] and 170.3 (O-CO). An accurate mass determination carried out on a sample corresponded to that anticipated for the alcohol.

Found: MH$^+$ 458.1716. C$_{26}$H$_{25}$N$_3$O$_5$ requires MH$^+$, 458.1716; Found: m/z (%) 480 (MNa$^+$100), 102 (70).
Intramolecular aziridination of Q^{15}NH_2 148 with LTA in the presence of HMDS

Aziridine 167 was prepared as in general procedure H from Q^{18}NH_2 148 (100 mg), LTA (111 mg, 0.25 mmol) and HMDS (73 mg, 0.096 cm^3, 0.45 mmol) to give a yellow foam. Crystallisation gave the aziridine product as a colourless solid (92 mg, 92%) mp. 83-84 °C (from ethanol); Found: C, 70.4, H, 4.8; N, 8.9%; C_{20}H_{21}N_3O_4 \frac{1}{4}C_2H_5OH requires C, 70.6; H, 5.0; N, 9.3%; Found: MH^+ 440.1610. C_{20}H_{21}N_3O_4 requires \text{MH}^+ (440.1610); \nu_{\text{max/cm}^{-1}} 1760\text{w} and 1710\text{s}; \delta_{\text{H}} 3.70 (2\text{H, d on m, J 5.9, CHH, azir. CHCO}), 4.16 (1\text{H, ddd, J 2.3, 3.6, 11.6, CHH}), 4.25 (1\text{H, ddd, J 2.1, 3.6, 14.1 CHH}), 4.40 (1\text{H, d, J 5.9, azir. CHPh}), 5.13 (1\text{H, ddd, J 11.6, 8.5, 2.1, CHH}), 6.32 (1\text{H, s, PhCHQ}), 7.07-7.60 [13\text{H, m, H-6, H-7, H-8(Q), 10 x CH(Ph)}] and 8.0 [1\text{H, d, J 7.6, H-5(Q)}]; \delta_{\text{C}} 31.5 (\text{CHCO}_2), 52.9 (\text{azir. CHPh}), 54.0, 67.0, 68.2 (\text{PhCHQ, CH}_2\text{CH}_2), 122.1 [\text{CCO(Q)}], 126.6, 127.2, 127.3, 127.8, 128.6, 128.8, 133.9 [4 x CH(Q), 5 x CH(Ph)], 134.5, 138.0 [2 x C(Ph)], 146.8 [\text{CN=C(Q)}], 156.8 [C=N(Q)], 160.0 [\text{CO(Q)}] and 165.3 (\text{CO}_2); m/z (%) 494 (\text{MNa}^+ 100).

Proton NMR analysis of compound 167 was analysed in C_6D_6 using a 300 MHz spectrometer: \delta_{\text{H}} 3.42 (1\text{H, ddd, J 14.0, 6.7, 2.7, CHH}), 3.47 (1\text{H, ddd, J 11.5, 5.5, 2.7, CHH}), 3.53 (1\text{H, d, J 5.9, azir. CHCO}), 3.93 (1\text{H, ddd, J 14.0, 5.5, 2.6, CHH}), 4.78 (1\text{H, ddd, J 11.5, 6.7, 2.6, CHH}), 4.96 (1\text{H, d, J 5.8, azir. PhCHQ}), 6.30 (1\text{H, s, CHPh}), 6.92 [1\text{H, d, J 7.8, H-6(Q)}], 7.10-7.35 [7\text{H, m, H-7(Q), 6 x CH(Ph)}], 7.65 [4\text{H, m, 4 x CH(Ph)}], 7.96 [1\text{H, d, J 7.8, H-8(Q)}] and 8.37 [1\text{H, d, J 7.8, H-5(Q)}].
Intermolecular aziridination of ethyl cinnamate with Q$^{17}$NH$_2$

A solution of the 3-aminoquinazolinone Q$^{17}$NH$_2$ (200 mg, 0.64 mmol) in dry DCM (2 cm$^3$) was added slowly to a stirred solution of LTA (313 mg, 0.71 mmol) in dry DCM (2 cm$^3$) held at $-15$ °C. The cold QNHOAc solution obtained was filtered through a cotton wool plug, and whilst maintained at $-15$ °C and added portionwise over 10 min. to a second flask containing a stirred solution of HMDS (207 mg; 1.28 mmol) and ethyl cinnamate (341 mg, 0.71 mmol) in dry DCM (2 cm$^3$) kept at ambient temperature. After removal from the ice-bath the solution was filtered and worked up as described for general procedure H to give an orange oil (341 mg). Chromatography 1:1 PE/EA (material absorbed onto silica) gave the aziridine 161 (177 mg, 60%) $R_f$ 0.25 determined as an $\sim$1:1 mixture of diastereoisomers from $^1$H-NMR analysis. Crystallisation provided a single diastereoisomer of 161 as a colourless solid, mp 136-137 °C (from ethyl acetate). (Found: MH$^+$ 486.2029. C$_{28}$H$_{27}$N$_3$O$_5$ requires MH$^+$, 486.2029); $\nu$max/cm$^{-1}$ 1680s, 1600s, 1470m, 1340m, 1250m and 1190m; $\delta_H$ 1.13 (3H, J 6.8, CO$_2$CH$_2$CH$_3$), 3.59 [1H, d, J 4.5, CHCO$_2$Et (azir.)], 3.70, 3.87 (5H, 2 x m, OCH$_2$CH$_2$OH), 4.09 (2H, q, J 4.5, CH$_2$CH$_3$), 4.46 [1H, d, J 4.5, CHPhe (azir.)], 5.90 (1H, s, CHPhe), 7.28 [11H, m, 10 x CH(Ph), H-6(Q)], 7.75 [2H, m, H-7, H-8(Q)] and 8.15 [1H, d, J 8.0, H-5(Q)]; $\delta_C$ 14.1 (CH$_2$CH$_3$), 51.0, 54.4 (2 x azir. CH), 62.1, 62.5, 72.2 (3 x CH$_2$), 79.5 (CHPh), 121.7 (CCO), 126.7-136.6 [4 x CH(Q), 10 x CH(Ph)], 145.6 (CN=C), 154.1 (C=N), 160.4 (C=O) and 166.4 (O-CO); $m/z$ (%) 508 (MNa$^+$ 100), 486 (MH$^+$ 38); observable signals for the other diastereoisomer $\delta_H$ 4.53 [1H, d, J 4.5, CHPhe (azir.)], 5.75 (1H, s, CHPhe) and 8.36 [1H, d, J 8.0, H-5(Q)].
Attempted lactone ring-opening of compound 162

![Diagram of compounds 162 and 165]

To a solution of compound 162 (143 mg, 0.31 mmol) in dry ethanol (2 cm³) was added to a solution of sodium ethoxide (22 mg) in dried ethanol (0.353 cm³) and the mixture stirred for 3 h. After addition of further dry ethanol (10 cm³), the solution was acidified to pH 5 by adding hydrochloric acid solution (2M), the solution evaporated and redissolved in ether, dried (MgSO₄) and evaporated to give a colourless solid on standing identified as compound 165 in quantitative yield (95 mg) mp. 138.5–139.5 ºC. (Found: M H⁺ 297.1239. C₁₇H₁₆N₂O₃ requires M H⁺ 297.1239); νmax/cm⁻¹ 1660s, 1620m and 1270s; δH 3.80 (5H, m, CH₂CH₂OH), 5.50 (1H, s, CHPh), 7.34 [3H, m, 3 x CH(Ph)], 7.51 [1H, ddd, J 7.8, 7.8, 1.4, H-6(Q)], 7.70 [4H, m, H-7, H-8(Q), 2 x CH(Ph)], 8.43 [1H, d, J 7.8, H-5(Q)] and 11.70 (1H, s br, NH); δC 62.1, 71.5 (CH₂CH₂), 83.2 (CHPh) and 127.0, 127.3, 128.0, 128.2, 129.3, 135.4 [4 x CH(Q), 5 x CH(Ph)]; m/z (%) 319 (MNa⁺ 10), 297 (MH⁺ 90) and 235 (100).
Synthesis of O-ester 158

In a variation of general procedure E, a solution of E-2,3-dimethylacryloyl chloride (0.229 g, 1.93 mmol) in dry DCM (1 cm³) was added dropwise over 20 min. to a solution of 3-aminoquinazolinone 147 (500 mg, 1.61 mmol) in dry pyridine (2 cm³) at ambient temperature. After stirring for 3 h. ice was added followed by DCM (10 cm³) and the solution washed with bicarbonate solution (2 x 10 cm³), hydrochloric acid (2M) solution (2 x 10 cm³), dried and evaporated to give an orange oil. Chromatography (1:1 PE/EA) gave a yellow oil (Rf 0.50) which crystallised on standing (501 mg, 79%). (Found: MH⁺ 394.1767. C₂₂H₂₄N₃O₄ requires MH⁺ 394.1768); νmax/cm⁻¹ 1700s, 1680s, 1600s, 1470m, 1260s, 1140m and 1110m; δH 1.78 (3H, dq, J ~7.0, 0.9, CH₃), 1.80 (3H, dq, J 1.2, 0.9, CH₃), 3.93 (2H, ddd, J 5.5, 4.3, ~2.0, CHH-CH₂), 4.39 (2H, ddd, J ~5.0, 4.3, 2.1, CHH-CH₂), 5.14 (2H, s br, NH₂), 6.02 (1H, s, CHPh), 6.85 (1H, qq, J 7.0, 1.2, CHCH₃), 7.36-7.50 [6H, m, H-6(Q), 5 x CH(Ph)], 7.78 [2H, m, H-7, H-8(Q)] and 8.27 [1H, d, J 8.3, H-5(Q)]; δC 12.4, 14.8 (2 x CH₃), 60.8 (C=CH), 63.9, 68.6 (CH₂-CH₂), 81.5 (CHPh), 120.6 [C-CO(Q)], 126.8, 127.4, 128.3, 128.5, 128.9, 129.0, 134.5 [4 x CH(Q), 5 x CH(Ph)], 137.1 [C(Ph)], 138.2 (COC=), 146.9 [CN=C(Q)], 154.0 [C=N(Q)], 161.3 [CO(Q)] and 168.2 (CO₂); m/z (%) 394 (MH⁺ 100).

Further elution provided compound Q¹⁴NH₂ 147 (129 mg) as an oil Rf 0.07.
Intramolecular aziridination of Q\textsuperscript{19}NH\textsubscript{2} 158 with LTA and TFA and subsequent hydrolysis

Following general procedure K, Q\textsuperscript{19}NH\textsubscript{2} 158 (100 mg, 0.25 mmol), LTA (124 mg, 0.28 mmol) and TFA (0.059 cm\textsuperscript{3}, 0.76 mmol) were reacted together and gave an oil (82 mg). Chromatography (3:1 PE/EA) followed by chromatography using Kieselgel (4:1 PE/EA) provided the trifluoroacetate which was hydrolysed in the presence of EtOH using procedure K to give a white solid identified as the alcohol 163 (11 mg, 11%) mp. 174-175 °C.

$\nu_{\text{max/ cm}^{-1}}$ 1740s, 1680s, 1590s, 1470m, 1280s, 1180s and 1100s; $\delta_H$ 1.73 (3H, d, $J$ 6.0, $\text{CH}_3$), 1.84 (3H, s, $\text{CH}_3$), 3.64 (1H, $q$, $J$ 6.0, $\text{CHCH}_3$), 3.80, 4.16 and 5.10 (4H, m, $\text{CH}_2\text{CH}_2$), 6.16 (1H, s, $\text{CHPh}$), 7.21-7.73 [8H, m, 5 x $\text{CH(Ph)}$, H-6, H-7, H-8(Q)] and 8.19 [1H, d, $J$ 7.8, H-5(Q)]; $\delta_C$ 13.0 and 14.3 (2 x $\text{CH}_3$), 52.7 ($\text{CHCH}_3$), 56.8 ($\text{COCCH}_3$), 65.7 and 68.2 ($\text{CH}_2\text{-CH}_2$), 77.1 ($\text{CHPh}$), 121.7 [$\text{C-CO(Q)}$], 126.8, 126.9, 127.3, 128.1, 128.9, 129.0 and 134.1 [4 x $\text{CH(Q)}$, 5 x $\text{CH(Ph)}$], 139.1 [$\text{C(Ph)}$], 146.1 [$\text{CN=C(Q)}$], 153.7 [$\text{C=N(Q)}$], 160.6 [$\text{CO(Q)}$] and 167.7 ($\text{CO}_2$).
Synthesis of 3-aminoquinazolinone ester 159

Q\textsuperscript{20}NH\textsubscript{2} compound 159 was prepared via a route similar to general procedure E. To a solution of Q\textsuperscript{17}NH\textsubscript{2} 147 (500 mg, 1.61 mmol) dissolved in dry pyridine (2 cm\textsuperscript{3}) was added 3,3-dimethylacryloyl chloride (0.229 g, 1.93 mmol) in dry DCM (1 cm\textsuperscript{3}) over 20 min. at ambient temperature. After stirring for a further 15 min. ice was added followed by DCM (10 cm\textsuperscript{3}). The solution was washed with bicarbonate (2 x 10 cm\textsuperscript{3}), hydrochloric acid solution (2M, 2 x 10 cm\textsuperscript{3}), dried and evaporated. Chromatography (1:1 PE/EA) of the residue gave the ester 159 as an oil (358 mg, 57%) R\textsubscript{f} 0.54 which partially crystallised on standing. (Found: MH\textsuperscript{+} 394.1767. C\textsubscript{22}H\textsubscript{23}N\textsubscript{3} requires MH\textsuperscript{+} 394.1767); \nu_{max}/cm\textsuperscript{-1} 1670s, 1600s, 1450s, 1230s and 1150s; \delta_{H} 1.88 (3H, d, J 1.2, CH\textsubscript{3}CCH\textsubscript{3}), 2.10 (3H, d, J 1.2, CH\textsubscript{3}CCH\textsubscript{3}), 3.90 (2H, t, J 4.81, 2 x CH\textsubscript{2}), 4.36 (2H, m, 2 x CH\textsubscript{2}OCO), 5.20 (2H, s br, NH\textsubscript{2}), 5.65 [1H, qq, J 1.2, CH\textsubscript{2}CH(CH\textsubscript{3})\textsubscript{2}], 6.05 (1H, s, CH/Ph), 7.23-7.80 [8H, m, 3 x CH(Q), 5 x CH(Ph)] and 8.09 [1H, d, J 8.3, H-5(Q)]; \delta_{C} : 20.6 and 27.8 (2 x CH\textsubscript{3}), 62.9 and 68.7 (CH\textsubscript{2}CH\textsubscript{2}), 81.4 (PhCH), 115.8 (CO-CH), 120.5 [C-CO(Q)], 126.8, 127.5, 128.2, 128.4, 128.9, 129.0 and 134.6 [4 x CH (Q), 5 x CH (Ph)], 136.9 [C(Ph)], 146.5 [CN=C(Q)], 154.5 [C=N(Q)], 158.3 (Me\textsubscript{2}C=), 161.3 [CO(Q)] and 166.7 (CO\textsubscript{2}); m/z (%) 394 (MH\textsuperscript{+} 100).

Further elution provided compound Q\textsuperscript{17}NH\textsubscript{2} 147 as an oil (146 mg) R\textsubscript{f} 0.08.
Intramolecular aziridination of Q^{17}NH_2 159 with LTA in the presence of TFA and subsequent hydrolysis of the product

Following general procedure K, Q^{20}NH_2 159 (70 mg, 0.18 mmol), LTA (87 mg, 0.20 mmol) and TFA (77 mg, 0.052 cm^3, 0.53 mmol) reacted together to produce an oil (92 mg), which partially solidified on standing. Chromatography (1:1 PE/EA) gave the alcohol 164 as a crystalline solid (56 mg 77%) mp. 209-210 °C (from ethanol).

(Found: MH^+ 410.1716. C_{22}H_{23}N_3O_5 requires MH^+ 410.1715); \nu_{\text{max/cm}^{-1}} 1670s, 1590s, 1460m and 1130s; \delta_H 1.38 (6H, s, 2 x CH_3), 3.70 (2H, s on dd, J \sim 11, 4.1, NH, C/H/CH_2), 4.03 (1H, ddd, J 11.0, 11.0, \sim 4.0, C/H/CH_2), 4.11 (1H, dd, 11.0, 4.1, C/H/CH_2), 4.93 (1H, s, CO-CH), 5.32 (1H, ddd, J 11.0, 11.0, 4.1, 1 x CHH-CH_2), 5.72 (1H, s, CHPh), 7.20-7.43 [5H, m, 5 x CH(Ph)], 7.56 [1H, m, H-6(Q)], 7.85 [2H, m, H-7(Q), H-8(Q)] and 8.25 [1H, d, J 7.8, H-5(Q)]; \delta_C : 24.1 and 28.4 (2 x CH_3), 61.6 and 66.5 (CH_2-CH_2), 68.1 (CHPh), 71.5 [CH-C(CH_3)_2], 86.6 (CH-NH), 122.1 [C-CO(Q)], 126.1-135.3 [4 x CH(Q), 5 x CH(Ph)], 137.9 [C(Ph)], 146.7 [CN=C(Q)], 156.9 [C=N(Q)], 163.5 [CO(Q)] and 171.7 (CO_2); m/z (%) 432 (MNa^+ 12) and 410 (MH^+ 100).
Synthesis of aziridine 169

Following general procedure H, Q\textsuperscript{20}NH\textsubscript{2} 159 (126 mg, 0.32 mmol), LTA (156 mg, 0.35 mmol) and HMDS (0.135 cm\textsuperscript{3}, 0.104 g, 0.64 mmol) gave a yellow/orange solid (122 mg) which gave a colourless crystalline solid (108 g, 86\%) mp. 177-178 °C (from ethanol). (Found: MH\textsuperscript{+} 392.1610. C\textsubscript{22}H\textsubscript{21}N\textsubscript{3}O\textsubscript{4} requires MH\textsuperscript{+}, 392.1610); \nu_{\text{max}}/\text{cm}^{-1} 1750\text{m} and 1720\text{s}; \delta\textsubscript{H} 1.55 (3H, s, CH\textsubscript{3}), 1.78 (3H, s, CH\textsubscript{3}), 3.42 (1H, s, CO-CH\textsubscript{2}), 3.87, 4.18 and 5.20 (4H, 3 x m, CH\textsubscript{2}CH\textsubscript{2}), 6.10 (1H, s, CHPh), 7.20-7.76 [8H, m, H-6, H-7, H-8(Q), 5 x CH(Ph)], 8.15 [1H, dd, J 7.8, 1.4, H-5(Q)]; \delta\textsubscript{C} : 16.4 and 26.5 (2 x CH\textsubscript{3})), 53.0 [C(CH\textsubscript{3})\textsubscript{2}], 54.1 (COCH), 67.3 and 68.0 (CH\textsubscript{2}CH\textsubscript{2}), 78.1 CH(Ph), 121.4 [CCO(Q)], 126.5-139.2 [4 x CH(Q), 5 x CH(Ph)], 146.4 [CN=C(Q)], 154.8 [C=N(Q)], 161.2 [C=O(Q)] and 166.9 (O-CO); m/z (%) 498 (32), 446 (M\textsuperscript{+}MeOH 100) and 414 (MNa\textsuperscript{+} 32).
Synthesis of 3-aminoquinazolinone (Q^{21}NH_{2})

Preparing the alcohol-acid 171
Following general procedure M, sodium hydride (2.92 g, 0.073 mol), ethylene glycol (15 cm³) and α-bromoisobutyric acid (3.3 g, 0.018 mol) were reacted to give the sodium salt of the acid 171 as a colourless solid (327 mg, 11%). A sample of the salt was acidified to pH 3 with concentrated hydrochloric acid solution to give the corresponding acid characterised below:

δH 1.27 (6H, 2 x d, J 7.0, 2 x CH₃), 2.40 [1H, m, CH(CH₃)₂], 4.18 (1H, d, J 7.0, CHPr) and 8.45 (1H, s br, CO₂H); δC 20.1 and 20.5 (2 x CH₃), 32.5 [CH(CH₃)₂], 54.4 (CHPr) and 175.5 (CO₂H).

Acylation of alcohol-acid 171
Acetyl chloride (23 cm³, 0.032 mol) was added dropwise to compound 171 (5.25 g, 0.032 mol), cooled in an ice bath. The mixture was stirred overnight, chloroform (10 cm³) was added and the acetyl chloride was evaporated off under reduced pressure. Sodium chloride produced in the reaction was filtered off and the filtrate evaporated to give acid 172 as an oil (4.179 g, 63%).
Preparation of acid chloride 173

Acid 172 prepared above (4.179 g, 0.020 mol), thionyl chloride (4.5 cm³, 0.061 mol) and 2 drops DMF were stirred together for 1 day at ambient temperature. Evaporation under reduced pressure gave the acid chloride as an oil, (2.579g, 57%) which was used directly in the following step.

Synthesis of N-acyl anthranilate 174

Following general procedure C, the acid chloride 173 (2.6 g, 0.012 mol) and methyl anthranilate (4 g, 3.5cm³, 0.027 mol) were reacted together to produce an oil. Chromatography (1:1 PE/EA) of this oil gave the N-acylanthranilate 174 (1.848 g, 47%) Rf 0.35 (3:1 PE /EA). (Found: MH⁺ 338.1604. C₁₇H₂₃NO₇ requires MH⁺ 338.1604); v_max/cm⁻¹ 1740s, 1690m, 1590m, 1530s, 1450s and 1270s; δ_H 0.88 (3H, d, J 6.9, CH₃), 0.97 (3H, d, J 6.9, CH₃), 1.93 (3H, s, COCH₃), 2.10 [1H, m, CH(CH₃)₂], 3.60 (1H, d, J 4.4, CHPr₁), 3.56-3.70 (2H, m, CHH-CH₂), 3.83 (3H, s, CO₂CH₃), 4.26 (2H, m, CH₂CH₂), 6.98 [1H, dd, J 8.5, 7.7, H-5(Ar)], 7.45 [1H, dd, J 8.0, 7.7, H-4(Ar)], 7.94 [1H, dd, J 8.0, 1.6, H-3(Ar)] and 8.70 [1H, d, J 8.5, H-6(Ar)]; δ_C 19.5 and 21.2 (2 x CH₃), 32.5 [CH(CH₃)₂], 52.7 (CO₂CH₃), 64.0 and 70.3 (CH₂CH₂), 87.6 (CHPr₁), 116.1 [C-CO(Ar)], 120.8, 123.2, 131.3 and 134.9 [4 x CH(Ar)], 141.0 [CNH(Ar)] and 172.0, 172.2 and 172.2 (3 x CO); m/z (%) 338 (MH⁺ 100).
Synthesis of 3-aminoquinazolinone 175 from N-acyl anthranilate 174

Following general procedure D, the N-acylanthranilate 174 (1.848 g, 5.48 mmol) and hydrazine hydrate (1.05 g, 1.02 cm³, 0.033 mol) were reacted together to give the 3-aminoquinazolinone Q²¹NH₂ 175 and N-acylanthranilhydrazide 176 in ~1:1 ratio. Chromatography (1:2 PE/EA) isolated the 3-aminoquinazolinone Q¹⁸NH₂ 175 as a yellow solid (756 mg, 50%) Rf 0.59. (Found: MH⁺ 278.1505. C₁₄H₁₉N₃O₃ requires MH⁺ 278.1504); ʋmax/cm⁻¹ 3310m, 1730s, 1660s, 1590s, 1470s and 1260s; δH 0.80 (3H, d, J 6.7, CH₃), 1.15 (3H, d, J 6.7, CH₃), 2.31 [1H, m (8-lines), J 6.7, CH(CH₃)₃], 3.50-3.88 (4H, m, 2 x CH₂), 4.67 (1H, d, J 3.4, CHPr), 5.24 (2H, s br, NH₂), 7.48 [1H, ddd, J 8.0, 7.1, 1.6, H-6(Q)], 7.73 [2H, m, H-7, H-8(Q)] and 8.21 [1H, d, J 8.0, H-5(Q)]; δC 18.0 (CH₃), 19.7 (CH₃), 31.7 (CH(CH₃)₃), 62.0 (CH₂), 72.5 (CH₂), 84.7 (CHPr), 120.3 (CCO), 127-128 [3 x CH(Q)], 134.8 [CH(Q)], 146.5 (C=C), 156.3 (C=N) and 161.7 (C=O); m/z (%) 300 (MNa⁺ 100), 278 (MH⁺ 45), 216 (40).

Further elution with the same solvent mixture gave 3-aminoquinazolinone solid 219 (120 mg) Rf 0.35.
Synthesis of 3-aminoquinazolinone ester Q$^{22}$NH$_2$ 177

To a solution of 3-aminoquinazolinone Q$^{21}$NH$_2$ 175 (76 mg, 0.27 mmol) in dry DCM (0.2 cm$^3$) and dry pyridine (0.4 cm$^3$) in a flame-dried flask at ambient temperature was added a solution of cinnamoyl chloride (55 mg, 0.33 mmol) in dry DCM (0.4 cm$^3$) dropwise over 10 min. and the solution stirred for a further 10 min. Work up as described in general procedure E gave a yellow foam (102 mg, 91%) identified as Q$^{22}$NH$_2$ 177. (Found: M$^+$ 408.1923. C$_{23}$H$_{25}$N$_3$O$_4$ requires M$^+$ 408.1923); ν$_{max}$/cm$^{-1}$ 1705s, 1670s, 1630s, 1590s and 1300m; δ$_H$ 0.89, 1.15 (6H, d, J 6.9, 2 x CH$_3$), 2.75 [1H, m, CH(CH$_3$)$_2$], 3.82 and 4.37 (4H, 2 x m, CH$_2$CH$_2$), 4.40 (1H, d, J 4.4, CHPr$_1$), 5.46 (2H, s, NH$_2$), 6.32 (1H, d, J 16.1, CO-CH), 7.31-7.80 [9H, m, 5 x CH(Ph), H-6, H-7, H-8(Q), CHPh] and 8.23 [1H, d, J 8.0, H-5(Q)]; δ$_C$ 19.3 and 19.5 (2 x CH$_3$), 30.6 [CH(CH$_3$)$_2$], 63.9 and 68.8 (CH$_2$-CH$_2$), 88.2 (CHPr$_1$), 117.6 (CO-CH), 120.3 [CCO(Q)], 126.7, 127.3, 128.1, 128.6, 129.2, 130.8 and 134.4 [5 x CH(Ph), 4 x CH(Q)], 134.6 [C-CH(Ph)], 145.8 (CHPh), 146.6 [CN=C(Q)], 154.1 [N=C(Q)], 160.9 [C=O(Q)] and 167.1 (CO$_2$); m/z (%) 408 (M$^+$ 100).
Synthesis of aziridine 178

Following general procedure H, Q$^{22}$NH$_2$ 177 (99 mg), LTA (118 mg, 0.27 mmol) and HMDS (78 mg, 0.49 mmol) were reacted together to give aziridine 178 as an oil in quantitative yield (110 mg). (Found: MH$^+$ 406.1767. C$_{23}$H$_{23}$N$_3$O$_4$ requires MH$^+$ 406.1767); ν$_{max}$/cm$^{-1}$, 1750s, 1690s and 1590s; δ$_H$ 0.72 (3H, d, J 7.0, CH$_3$), 1.10 (3H, d, J 6.4, CH$_3$), 2.12 [1H, m, CH(CH$_3$)$_2$], 3.56 [1H, d, J 5.9, CH (azir)], 3.75 and 3.98 (3H, 2 x m, 3 x O-CH), 4.37 [1H, d, J 5.6, CH (azir)], 4.86 (2H, d, J 8.8, CHPr$^i$ superimposed on m, CHH-CH$_2$), 7.16-7.46 [6H, m, H-6(Q), 5 x CH(Ph)], 7.60 [2H, m, H-7, H-8(Q)] and 8.10 [1H, dd, J 8.2 and 1.2, H-5(Q)]; δ$_C$ 15.8 and 17.8 (2 x CH$_3$), 35.4 [CH(CH$_3$)$_2$], 50.5 and 51.8 [CH-CH(azir)], 64.9 and 66.7 (CH$_2$-CH$_2$), 79.8 (CHPr$^i$), 119.3 (C CO), 124.7, 125.1, 125.3, 125.6, 126.7, 126.8 and 132.1 [5 x CH(Ph), 4 x CH(Q)], 132.4 [C(Ph)], 143.9 [CN=C(Q)], 153.0 [N=C(Q)], 157.7 [C=O(Q)] and 163.5 (CO$_2$); m/z (%) 406 (MH$^+$ 100).
Synthesis of (±) 3-amino 2-[1”-(2”-hydroxy)ethoxy]ethylquinazoline-4(3H)-one 185

Preparation of ester 180

2-Benzylxethanol (1 g, 6.60 mmol) and racemic methyl 2-chloropropionate 179 (0.89 g, 7.26 mmol) were dissolved in THF (7 cm$^3$). To this solution, NaH (0.39 g, 9.90 mmol) was added portionwise over 20 min. and the mixture stirred at ambient temperature for 1 day. The solvent was evaporated under reduced pressure, ethyl acetate (10 cm$^3$) and water (10 cm$^3$) added, the residue and the aqueous layer made just acid with hydrochloric acid solution (2M). After shaking the ethyl acetate layer was separated and dried. Solvent evaporation under reduced pressure gave a yellow oil (1.7 g) and purification by chromatography (1:1 PE/EA) gave ester 180 as an oil (593 mg, 34%) Rf 0.30.

Hydrolysis of ester 180

A solution of NaOH (1.2 g, 0.030 mol) in water (3 cm$^3$) was added to the ester 180 (600 mg, 2.52 mmol), and the solution was heated under reflux for 12 h. The cooled solution was extracted with ethyl acetate (10 cm$^3$) and the bulk of the water removed on a rotary evaporator to give the sodium salt 181 which was thoroughly dried in a desiccator in vacuo using an oil-pump for 2 days in the presence of dry P$_2$O$_5$ (replacing the P$_2$O$_5$ twice to ensure its dryness) and retained in a sealed sample tube. (538 mg, 95%) Acid treatment of a sample provided the corresponding acid as a yellow oil characterised below. $\nu$$_{max}$/cm$^{-1}$ 3400m, 1750s, 1735s; $\delta$$_H$ 1.48 (3H, d, $J$ 6.9, $CH_3$), 3.68-3.86 (4H, m, $CH_2CH_2$), 4.07 (1H, q, $J$ 6.9, $CHCH_3$), 4.61 (2H, s, $CH_2$Ph) and 7.36 [5H, m, 5 x $CH$(Ph)]; $\delta$$_C$ 18.8 ($CH_3$), 69.5, 70.1 and 73.8 (3 x $CH_2$), 75.8 ($CHCH_3$), 128.3, 128.9 and 130.1 [5 x $CH$(Ph)], 137.9 [$CH_2C$(Ph)] and 176.8 (C=O).
Synthesis of the acid chloride 182

The sodium salt 181 (5.62 g, 0.025 mol) was dissolved in dry benzene (40 cm³) containing dry pyridine (10 drops) in a flame-dried flask under N₂. After cooling the solution using an ice bath, oxalyl chloride (6.55 cm³, 0.075 mol) was added over 10 min. via syringe and the mixture stirred for ~2 h. at room temperature, then evaporated to give the product 182 as a solid / oil mixture which was used directly below (5.3 g, 87%). δH 1.45 (3H, d, J 6.9, CH₃), 3.70 (4H, m, CH₂CH₂), 4.09 (1H, q, J 6.9, CHCH₃), 4.58 (2H, s, CH₂Ph) and 7.30 [5H, m, 5 x CH(Ph)]; δC 18.8 (CH₃), 69.5, 70.1 and 73.8 (3 x CH₂), 75.8 (CHCH₃), 128.3, 128.9 and 130.1 [5 x CH(Ph)], 137.9 [C(Ph)] and 176.8 (C=O);

m/z (%) 511 (60), 247 (MNa⁺ 65), 225 (MH⁺ 100) and 91 (65).

Synthesis of N-acylanthranilate 183 from the acid chloride 182

Following general procedure C, the acid chloride 182 (5.3 g, 0.022 mol) and methyl anthranilate (6.5 cm³, 0.050 mol) were reacted together and the oily product chromatographed (6:1 PE/EA) to give the N-acylanthranilate 183 (6.6 g, 85%) Rᶠ 0.48. (Found: MH⁺ 358.1654. C₂₀H₂₃NO₅ requires MH⁺, 358.1655); νmax/cm⁻¹ 3280m, 1700s, 1590s and 1520s; δH 1.50 (3H, d, J 6.7, CH₃), 3.80 (3H, s, CO₂CH₃), 3.80 (4H, m, CH₂CH₂), 4.10 (1H, q, J 6.7, CHCH₃), 4.58 (2H, s, CH₂Ph), 7.05 [1H, dd, J 8.5, ~7, H-5(Ar)], 7.30 [5H, m, 5 x CH(Ph)], 7.52 [1H, dd, J 7.1, 8.5, H-4(Ar)], 8.00 [1H, d, J 8.5, H-3(Ar)], 8.81 [1H, d, J 8.5, H-6(Ar)] and 11.80 (1H, s br, NH); δC 19.2 (CH₃), 51.7 (CO₂CH₃), 70.0 and 70.3 (CH₂CH₂), 73.6 (CH₂Ph), 78.4 (CHCH₃), 116.1 [C-CO(Ar)], 120.7, 123.1, 131.3 and 134.7 [4 x CH(Ar)], 127.7-129.2 [5 x CH(Ph)], 138.7 [C(Ph)], 141.1 [C-NH(Ar)], 168.2 [NH-CO(Ar)] and 173.1 (CO₂CH₃); m/z (%) 452 (28), 380 (MNa⁺ 100) and 370 (60).
3-Aminoquinazolinone 184

The 3-aminoquinazolinone 184 was prepared as described in general procedure D using the N-acylanthranilate 183 (300 mg, 0.84 mmol) and hydrazine hydrate (0.183 cm³, 5.04 mmol) in ethanol (2 cm³). The crude product 3-aminoquinazolinone 184 was obtained as a colourless solid [244 mg, 86% from 183], mp. 85-86 °C (from ethanol). (Found: C, 67.1, H, 6.2; N, 12.0%; C₁₉H₂₁N₃O₃ requires C, 67.2; H, 6.2; N, 12.4%); (Found: MH⁺ 340.1661, C₁₉H₂₁N₃O₃ requires MH⁺ 340.1661); νmax/cm⁻¹ 1680s, 1600s, 1470m, 1250m and 1100s; δ_H 1.70 (3H, d, J 6.7, CH₃), 3.72 (4H, m, CH₂CH₂), 4.50 (2H, s, CH₂Ph), 4.98 (1H, q, J 6.7, CHCH₃), 5.75 (2H, s br, NH₂), 7.30 [5H, m, 5 × CH(Ph)], 7.48 [1H, m, H-6(Q)], 7.73 [2H, m, H-7, H-8(Q)] and 8.27 [1H, d, J 7.8, H-5(Q)]; δ_C 16.9 (CHCH₃), 69.2 and 69.8 (OCH₂CH₂), 73.8 (CH₂Ph), 76.7 (CHCH₃), 120.6 (CCO), 126.8, 127.2, 128.1, 128.3 and 128.9 [3 × CH(Q), 5 × CH(Ph)], 134.2 [CH(Q)], 138.1 [C(Ph)], 146.7 (CN=C), 154.2 (C=N) and 160.5 (C=O); m/z (%) 340 (MH⁺ 100).

Debenzylation of QNH₂ 184 to give 3-aminoquinazolinone 185

The 3-aminoquinazolinone (244 mg, 0.72 mmol) and conc. hydrobromic acid (1 cm³, 48%) were stirred together at room temperature. After 1 h. the reaction mixture became homogenous and stirring was continued for 2 days. Ethyl acetate (10 cm³) was added and the solution washed with bicarbonate (4 × 20 cm³), the organic layer dried, and evaporated. Crystallisation gave the racemic 3-aminoquinazolinone Q²³NH₂ 185 [70 mg, 39% yield based on compound 184] as a colourless solid mp. 119-120 °C (from ethyl acetate) [α]D = 0 (c 1, CHCl₃). (Found: C, 57.8, H, 6.0; N, 16.4%, requires C₁₂H₁₅N₃O₃ ¾ C₂H₅OH C, 57.8; H, 6.0; N, 16.2%); (Found: MH⁺ 250.1192. C₁₂H₁₅N₃O₃ requires MH⁺ 250.1192); νmax/cm⁻¹ 1670s, 1600s, 1470m, 1250m and 1110s; δ_H 1.65 (3H, d, J 6.4, CH₃), 3.66 and 3.85 (4H, m, CH₂CH₂), 4.20 (1H, s br, OH), 5.09 (1H, q, J 6.4, CHCH₃), 5.32 (2H, s br, NH₂), 7.50 [1H, ddd, J 8.2, ~8, 2.8, H-6(Q)], 7.70 [2H, m, H-7, H-8(Q)] and 8.13 [1H, d, J 7.8, H-5(Q)]; δ_C 18.9 (CH₃CH), 62.2 and 71.6 (CH₂CH₂), 74.8 (CH₃CH), 121.0 [CCO(Q)], 126.9, 127.5, 127.9 and 134.8 [4 × CH(Q)], 146.6 [CN=C(Q)], 156.8 [C=N(Q)] and 162.0 [CO(Q)]; m/z (%) 272 (MNa⁺ 100) and 250 (MH⁺ 64).
(i) Synthesis of (S)-3-amino-2-[1’-(2”-hydroxy)ethoxy]ethylquinazolin-4(3H)-one from (S)-2-bromopropionic acid and ethylene glycol.

![Chemical structures]

**Preparation of sodium salt 189**
Sodium hydride (4.53 g, 0.081 mol) and ethylene glycol (3.52 g, 0.040 mol) were heated under nitrogen in THF (20 cm³) at 100 °C to form the sodium salt. The cooled solution containing suspended sodium salt was stirred at ambient temperature and (S)-2-bromopropionic acid (8.7 g, 0.040 mol) added dropwise over 5 min. then the stirred solution was heated at 50 °C overnight. Evaporation of the solution (at 100 °C and 1.72 mm Hg) and removal of remaining ethylene glycol on trituration with acetone gave sodium salt 189 as a thick white paste (10 g) which was stored *in vacuo* until used in the next step.

**Acylation of compound 189**
Using general procedure J, the dry (powdered) sodium salt 189 (10.0 g, 0.046 mol), acetyl chloride (19.43 cm³, 0.137 mol) and dry pyridine (7.2 g, 0.046 mol) gave acid 190 as an oil (3 g) which was used directly in the next step.

**Preparation of acid chloride 191**
The crude acid 190 from the previous step (3 g, 0.017 mol) was reacted with thionyl chloride (2.43 g, 1.49 cm³, 0.020 mol) as in general procedure B. Evaporation under
reduced pressure gave the product as an oil 191 (3 g) which was used directly in the next experiment.

**Preparation of methyl N-acylanthranilate 192**

A solution of the acid chloride 191 (3.0 g, 0.015 mol) from the previous reaction step in dry ether (20 cm³) was added to a solution of methyl anthranilate (4.6 cm³, 0.035 mol) in dry ether (80 cm³) as described in general procedure C. Evaporation of solvent and chromatography (1:1 PE/EA) of the residual oil (2.80 g) gave methyl N-acylanthranilate 192 [571 mg, 3% yield based on compound 188] Rf 0.38 \([\alpha]_D = +118^\circ \ (c=1.0, \text{CHCl}_3)\); δH 1.52 (3H, d, J 6.7, CH₃), 2.10 (3H, s, COCH₃), 3.85, 4.38 (4H, 2 x m, CH₂CH₂), 3.93 (3H, s, CO₂CH₃), 4.06 (1H, q, J 6.7, CHCH₃), 7.14 [1H, ddd, J 8.5, 8.0, 0.9, H-5(Ar)], 7.56 [1H, ddd, J 8.5, 8.0, 1.4, H-4(Ar)], 8.05 [1H, d, J 8.0, 1.4, H-6(Ar)] and 8.75 [1H, d, J 8.0, 0.9, H-3(Ar)].

**3-Aminoquinazolinone 185**

A solution of the N-acylanthranilate 192 (571 mg, 1.85 mmol) and hydrazine hydrate (356 mg, 0.35 cm³, 0.011 mol) in ethanol (1 cm³) were reacted together using general procedure D. The resulting oil (319 mg) was purified by chromatography (PE/EA 1:3) to give the product Q²³NH₂ [225 mg, 49% yield based on compound 192] Rf 0.17 \([\alpha]_D = +65^\circ \ (c=1.0, \text{CHCl}_3)\) otherwise identical to that isolated previously.
(ii) Synthesis of (S)-3-amino-2-[1’-(2”-hydroxy)ethoxy]ethylquinazolin-4(3H)-one from (S)-2-bromopropionic acid and 2-benzyloxyethanol.

Preparation of acid 193

Mineral oil-freed sodium hydride (2.61 g, 0.047 mol) was added to a solution of 2-benzyloxyethanol (4.97 g, 4.6 cm³, 0.023 mol) in THF (20 cm³), the mixture was heated under reflux for 20 min. under nitrogen then cooled in an ice bath. (S)-2-Bromopropionic acid (5 g, 0.023 mol) was added dropwise over 35 min. to the cold stirred solution in an ice bath and then the reaction mixture stirred at 50 °C overnight. After cooling, water (20 cm³) was added cautiously followed by ethyl acetate (10 cm³), the organic layer separated, dried and evaporated to retrieve unreacted 2-benzyloxyethanol. The aqueous layer was acidified to pH 3 and then re-extracted into ethyl acetate (30 cm³) the ethyl acetate layer separated, washed with water, dried and evaporated to give the acid as an oil (5.62 g, 77% yield) [α]D = +14° (c=1.0, CHCl₃) otherwise identical to that isolated previously. (Found: MH⁺ 225.1127. C₁₂H₁₆O₄ requires MH⁺ 225.1127; m/z (%) 225 (MH⁺ 100) and 247 (MNa⁺ 68).
Conversions of acid 193 into acid chloride 182 and 182 into N-acylanthranilate 183 $[\alpha]_D +36^\circ$ (c=1.0, CHCl$_3$) were carried out as described previously for racemic compounds.

**Hydrogenation of compound 183 using palladium-charcoal**

The N-acylanthranilate 183 prepared above (500 mg, 1.40 mmol) dissolved in acetic acid (1 cm$^3$) was hydrogenated using Pd/C (30 mg) for 4 h. The catalyst was separated washed well with DCM and then combined, the solutions washed with bicarbonate (2 x 20 cm$^3$) dried with sodium sulphate and evaporated under water pump pressure to give the anthranilate 194 (353 mg; 94%). Rf 0.23 $[\alpha]_D = +29^\circ$ (c=1.0, CHCl$_3$);

(Found: MH$^+$ 268.1185. C$_{13}$H$_7$NO$_5$ requires MH$^+$, 268.1185); $\nu$$_{max}$/cm$^{-1}$ 3570s, 3280s, 1700s, 1590s and 1520s; $\delta$$_H$: 1.45 (3H, d, $J$ 6.6, CH$_3$), 3.58-3.78 (4H, m, CH$_2$CH$_2$), 3.89 (3H, s, CO$_2$CH$_3$), 4.00 (1H, q, $J$ 6.6, CHCH$_3$), 7.04 [1H, dd, $J$ 7.1, 7.1, H-5(Ar)], 7.49 [1H, dd, $J$ 7.1, 7.1, H-4(Ar)], 7.96 [1H, d, $J$ 7.1, H-6(Ar)] , 8.70 [1H, d, $J$ 7.1, H-3(Ar)] and 11.98 (1H, s br, NH); $\delta$$_C$: 16.7 (CH$_3$), 51.5 (CO$_2$CH$_3$), 61.1, 70.7 (CH$_2$CH$_2$), 76.3 (CHCH$_3$), 114.3 [C-CO(Ar)], 119.1, 121.8, 130.0, 133.9 [4 x CH(Ar), 139.9 [C-2(Ar)], 167.8 [NH-CO] and 170.9 (CO$_2$CH$_3$); $m/z$ (%) 290 (MNa$^+$ 100) and 152 (72).

**Preparing 3-aminoquinazolinone 185 from anthranilate 194**

The Q$_{23}$NH$_2$ 185 was prepared as described in general procedure D using the N-acylanthranilate 194 (1.969 g, 7.37 mmol) and hydrazine hydrate (1.42 cm$^3$, 0.044 mol). Crystallisation from ethyl acetate gave the 3-aminoquinazolinone 185 (1.27 g, 69%) as a colourless solid mp. 119-120 °C (from ethanol-water) $[\alpha]_D +65^\circ$ (c=1.0, CHCl$_3$) identical with that isolated previously.
Synthesis of 3-aminoquinazolinone (Q²⁴NH₂) 186

To a solution of the Q²³NH₂ 185 (820 mg, 3.29 mmol) in dry DCM (2 cm³) and dry pyridine (4 cm³) was added a solution of cinnamoyl chloride (656 mg, 3.95 mmol) in dry DCM (4 cm³) dropwise over 10 min. at 0 °C and the solution stirred for a further 2 h. Following work up as in general procedure E crystallisation of the product gave 3-aminoquinazolinone 186 as a pale-yellow solid (194 mg, 16%) mp. 114-115 °C (from ethanol). (Found; C, 66.2; H, 5.6; N, 10.5. C₁₂H₁₅N₃O₂ ½ C₂H₅OH requires C, 66.1; H, 5.8; N, 10.8%); (Found: MH⁺ 380.1611. C₂₁H₂₁N₅O₄ requires MH⁺, 380.1610; vmax/cm⁻¹ 1680s, 1640s and 1605m; δH 1.65 (3H, d, J 6.7, CH₃), 3.78 and 4.30 (4H, 2 x m, CH₂CH₂), 5.00 (1H, q, J 6.7, CHCH₃), 5.50 (2H, s, NH₂), 6.31 (1H, d, J 16.1, COCH=), 7.20-7.70 [8H, m, H-6, H-7, H-8(Q), 5 x CH(Ph)], 7.65 (1H, d, J 16.1, CPh) and 8.15 [1H, d, J 8.3, H-5(Q)]; δC 15.8 (CH₃), 62.6, 66.1 (CH₂CH₂), 74.9 (CHCH₃), 111.6 (COC=), 119.2 [C(CO(Q))], 125.4-133.0 [5 x CH(Ph), 4 x CH(Q)], 133.2 [C(Ph)], 144.6 (CHPh), 145.3 (CN=C), 152.9 (C=N), 159.6 (C=O) and 165.7 (O-CO); m/z (%) 402 (MNa⁺ 88) and 380 (MH⁺ 100).
Synthesis of aziridine 187

Following general procedure H Q^{24}NH₂ 186 (34 mg, 0.090 mmol), LTA (44 mg, 0.099 mmol) and HMDS (29 mg, 0.038 cm³, 0.18 mmol) gave a colourless solid. Crystallisation gave aziridine 187 as a colourless solid in quantitative yield (37 mg) mp. 184-185 °C (from ethanol); [α]D -144 (c=1, CHCl₃); (Found: MH⁺ 378.1454. C₂₁H₁₀N₃O₄ requires MH⁺ 378.1454); ν₁ max/cm⁻¹ 1750 s, 1680 s, 1590 s and 1180 s; δₜ 1.60 (3H, d, J 6.0, CH₃), 3.70 (1H, d, J 6.0, azir. H), 3.78, 4.09, 5.07 (4H, 3 x m, CH₂CH₃), 4.52 (1H, d, J 6.0, azir. H), 5.48 (1H, q, J 6.0, CHCH₃), 7.30-7.60 [6H, m, H-6(Q), 5 x CH(Ph)], 7.73 [2H, m, H-7, H-8(Q)] and 8.24 [1H, d, J 8.0, H-5(Q)]; δₜ 21.4 (CH₃), 52.9, 54.0 [2 x CH (azir.)]; 65.7, 68.4 (CH₂CH₂), 72.4 (CHCH₃), 122.0 [CCO(Q)], 127.0-129.1 [5 x CH(Ph), 3 x CH(Q)], 134.4 [CH(Q)], 134.7 [C(Ph)], 146.2 (CN=C), 154.9 (C=N), 160.4 (C=O) and 165.7 (O-CO); m/z (%) 410 (44), 400 (MNa⁺ 42) and 378 (MH⁺ 100).

Proton NMR analysis of compound 187 was analysed in C₆D₆ using a 300 MHz spectrometer: δₜ 1.51 (3H, d, J 6.0, CH₃), 3.13 (1H, ddd, J 14.1, 5.6, 2.9, CHH), 3.23 (1H, d, J 5.8, azir. CHCO₂), 3.38 (1H, ddd, J 11.5, 6.8, 2.9, CHH), 3.70 (1H, ddd, J 14.1, 6.8, 2.5, CHH), 4.46 (1H, ddd, J 11.5, 5.6, 2.5, CHH), 4.81 (1H, d, J 5.8, azir. CHPh), 5.45 (1H, q, J 6.0, CHPh), 6.92 [1H, d, J 7.8, H-6(Q)], 7.15 [4H, m, H-7(Q), 3 x CH(Ph)], 7.46 [2H, m, 2 x CH(Ph)], 7.70 [1H, d, J 7.8, H-8(Q)] and 8.38 [1H, d, J 7.8, H-5(Q)].
Attempted synthesis of compound 199

![Chemical Structure](image)

General procedure N for aziridine ring opening using TFA

A solution of undried TFA\(^1\) (10 mg) and DCM (5 cm\(^3\)) was added dropwise to a solution of the aziridine 187 (11 mg, 0.029 mmol) in DCM (5 cm\(^3\)). The solution was stirred overnight then washed successively with bicarbonate and brine, dried and evaporated to give alcohol 199 as a colourless foam and as a 3:1 mixture of epimers in quantitative yield (11 mg).

(Found: C, 63.5; H, 5.4; N, 10.0. C\(_{12}H_{15}N_3O_2\) \(1/4\) C\(_2\)H\(_5\)OH requires C, 63.5; H, 5.6; N, 10.3%); \(\nu_{max}/cm^{-1}\) 1750s, 1660s, 1600s; (major epimer) \(\delta_H\) 1.48 (3H, d, \(J\ 6.7\), CH\(_3\)), 3.92 (2H, m, 2 x CHH), 3.98 (1H, dd, \(J\ 9.8\), 2.3, CHNH), 4.27 (2H, m, 2 x CHH), 4.58 (1H, dd, \(J\ 9.8\), 4.1, CHPh), 5.37 (1H, q, \(J\ 6.7\), CHCH\(_3\)), 5.94 (1H, d, \(J\ 4.1\), OH), 6.35 (1H, d, \(J\ 2.3\), NH), 7.20-7.30 [5H, m, 5 x CH(Ph)], 7.58 [1H, m, H-6(Q)], 7.80-7.92 [2H, m, H-7,8(Q)] and 8.35 [1H, dd, \(J\ 7.9\), 0.9, H-5(Q)]; for minor epimer (observable signals) : \(\delta_H\) 1.77 (3H, d, \(J\ 7.0\), CH\(_3\)), 3.45-3.80 (2H, m, 2 x CHH), 4.68 (1H, q, \(J\ 7.0\), CHCH\(_3\)) and 6.15 (1H, s, NH).

\(^1\) The epimerisation in this reaction is thought to be a result of adventitious water in the TFA.
A solution of the aziridine 187 (346 mg, 0.92 mmol) in dry DCM (2 cm³) containing distilled and dried TFA (104 mg, 0.0070 cm³, 0.92 mmol) was monitored by TLC (1:1 PE/EA) and after 1.5 h. showed compound 187 Rf 0.41 and product 198 Rf 0.69 in a ~1:1 ratio. After addition of further TFA (104 mg, 0.92 mmol) in DCM (10 cm³) the mixture was stirred for an additional 2 h. and then worked up as described in general procedure N to give trifluoroacetate 198 as a white foam (367 mg, 81%). νmax/cm⁻¹ 1790s, 1750s, 1670s, 1590s and 1460m; δH 1.68 (3H, d, J 6.9, CH₃), 3.72 (1H, m, CHH-CH₂), 3.99 (2H, m, 2 x CH), 4.47 (1H, dd, J 9.2, 1.4, CHNH), 4.58 (1H, q, J 6.9, CH₂), 4.83 (1H, d, J 1.4, NH), 6.46 (1H, d, J 9.2, CHPh), 7.40-7.80 [8H, m, 5 x CH(Ph), 3 x CH(Q)] and 8.21 [1H, dd, J 8.0, 1.2, H-5(Q)]; δC 19.1 (CH₃), 61.7 (CHNII), 62.5, 65.6 (CH₂-CH₂), 77.5 (CHCH₃), 83.5 (CHPh), 121.4 [CCO(Q)], 127.1-129.5 [5 x CH(Ph), 4 x CH(Q)], 138.6 [C(Ph)], 146.4 [CN=C(Q)], 156.7 [C=N(Q)], 162.6 [CO(Q)] and 170.1 (O-CO).
Hydrolysis of trifluoroacetate 198

To the crude trifluoroacetate (174 mg, 0.35 mmol) in THF (2 cm³) was added sodium carbonate (100 mg) and deionised water (2 cm³). The reaction mixture was stirred 3 h. to give alcohol 199 as a single diastereoisomer a colourless solid (118 mg, 84%), mp. 181-182 °C (from ethanol), [α]D = +182.5° (c=1.0, CHCl3). (Found: MH⁺ 396.1560. C21H21N3O5 requires MH⁺ 396.1559); νmax/cm⁻¹ 1740s, 1670s, 1610m and 1590m; δH 1.69 (3H, d, J 7.0, CH₃), 3.53 (1H, dt, J ~11.4, 4.1, CHH-CH₂), 3.65 (1H, dd, J 9.8, CHPh), 4.58 (1H, q, J 7.0, CHCH₃), 5.06 (1H, dt, J 11.4, 4.1, CHH-CH₂), 5.38 (2H, s on d, J 4.3, NH, OH), 7.15-7.80 [8H, m, 3 x CH(Q), 5 x CH(Ph)] and 8.21 [1H, dd, J 8.0, 1.4, H-5(Q)]. δC : 18.9 (CH₃), 62.2, 66.6 (CH₂CH₂), 65.6 (CHNH), 73.9 (CHCH₃), 82.8 (CHPh), 121.3 [CCO(Q)], 126.3, 126.8, 127.6, 127.8, 128.1, 128.5, 134.8 [5 x CH(Ph), 4 x CH(Q)], 139.6 [C(Ph)], 146.4 [CN=C(Q)], 156.7 [C=N(Q)], 162.5 [CO(Q)] and 173.2 (O-CO); m/z (%) 396 (MH⁺ 100).
Ethanolysis of aziridine lactone 187

The aziridine 187 (1.85 g, 4.90 mmol) was dissolved in dry EtOH (18 cm³) in a flame dried flask under nitrogen, sodium carbonate (1.9 g) added to the solution and the reaction mixture was stirred overnight; TLC (1:1 PE/EA) showed disappearance of the starting material and appearance of product. After evaporation of the bulk of the ethanol, the residue was extracted into DCM, dried and evaporated to give a colourless foam which was purified by chromatography (1:1 PE/EA) to give a 3:1 mixture of the alcohol 201 (516 mg, 24%) as a single diastereoisomer and its cyclised dihydroquinazolinone isomer 202 (201 mg) (both Rf 0.13). Data for compound 201:

(Found: MH⁺ 424.1873, C₂₃H₂₅N₃O₅ requires MH⁺ 424.1872); νmax/cm⁻¹ 1730s, 1670s and 1600s; δH 1.00 (3H, m, CH₂CH₂), 1.60 (3H, d, J 6.4, CHCH₃), 3.50 [1H, d, J 4.8, CHCO (azir)], 3.55 (1H, m, CHH-CH₂), 3.80 (2H, m, 2 x CHH), 4.00 (2H, m, CH₃-CH₂), 4.10 (1H, m, CHH-CH₂), 4.70 [1H, d, J 4.8, CHPh (azir)], 4.80 (1H, q, J 6.4, CHCH₃), 7.20-7.40 [6H, m, H-6(Q), 5 x CH(Ph)], 7.60 [2H, m, H-7(Q), H-8(Q)] and 8.20 [1H, d, J 8.1, H-5(Q)]; δC 13.7 (CH₃CH₂), 19.8 (CH₃CH), 50.3, 53.2 [2 x CH (azir)], 61.7, 62.4, 71.0 (CH₂-CH₂, CH₃-CH₂), 72.7 (CH₃CH), 121.4 [CCO(Q)], 126.5, 127.0, 127.1, 127.2, 129.0, 129.2, 134.2 [5 x CH(Ph), 4 x CH(Q)], 134.3 [CH-C(Ph)], 145.4 [CN=C(Q)], 155.9 [C=N(Q)], 159.6 [CO(Q)] and 165.8 (CO₂Et); m/z (%) 446 (MNa⁺ 38) and 424 (MH⁺ 100).

For compound 202 (observable signals):

δH 1.30 (3H, t, J 7.1, CH₃CH₂), 1.52 (3H, d, J 6.4, CHCH₃), 2.05 (1H, m, CHH), 3.11 (1H, m, CHH), 3.40 (1H, m, CHH), 4.32 (1H, q, J 6.4, CH₃CH), 4.48 (2H, q, J 7.1, CH₃CH₂) and 8.22 [1H, d, J 8.0, H-5(Q)].
Ethanolysis of lactone 199

Sodium metal (0.007 g, 0.29 mmol) was added to a solution of alcohol 199 (3:1 epimeric mixture prepared previously) (94 mg, 0.24 mmol) in ethanol (1.5 cm$^3$). The mixture was stirred for 2.5 h., and the solvent evaporated to give a yellow foam (45 mg), which was purified by chromatography (1:1 PE/EA) to give a foam (17 mg, 16%) identified as compound 200 as a 2:1 mixture of diastereoisomers.

(Found: MH$^+$ 442.1978. C$_{23}$H$_{27}$N$_3$O$_6$ requires MH$^+$ 442.1978); $\nu_{\text{max}}$/cm$^{-1}$ 3300m, 1730s, 1680s and 1600s; $\delta_H$ (major diastereoisomer): 1.11 (3H, t, $J$ 7.1, CH$_3$CH$_2$), 1.39 (3H, d, $J$ 6.4, CH$_3$CH), 3.26, 3.40, 3.75 (6H, 3 x m, CH$_2$CH$_2$, OH, CHNH), 4.18 (2H, q, $J$ 7.1, CH$_2$CH$_3$), 4.54 (1H, q, $J$ 6.4, CHCH$_3$), 5.07 (1H, d, $J$ 5.5, CHP), 5.92 (1H, d, $J$ 6.8, NH), 7.25-7.58 [6H, m, 5 x CH(Ph), H-6(Q)], 7.73 [2H, m, H-7 and H-8(Q)], 8.17 [1H, d, $J$ 7.8, H-5(Q)]; $\delta_C$ 14.3 (CH$_3$CH$_2$), 20.3 (CH$_3$CH), 62.1, 71.0 and 71.7 (CH$_2$CH$_2$, CH$_2$CH$_3$), 70.0, 73.1, 73.9 (CHPh, CHNH and CH$_3$CH), 121.0 [COC(Q)], 126.9-135.6 [5 x CH(Ph), 4 x CH(Q)], 139.8 [CPh], 146.5 [CN=C(Q)], 159.3 [C=N(Q)], 162.6 [CO(Q)] and 171.4 (O-CO); $\delta_H$ (minor diastereoisomer, observable signals) 1.27 (3H, t, $J$ 7.1, CH$_3$CH$_2$), 1.46 (3H, d, $J$ 6.4, CH$_3$CH), 4.10 (2H, q, $J$ 7.1, CH$_2$CH$_3$), 4.80 (1H, q, $J$ 6.4, CHCH$_3$), 6.09 (1H, d, $J$ 6.8, NH); m/z (%) 464 (MNa$^+$ 100) and 442 (MH$^+$ 70).
Ring opening of aziridine 201 with TFA

Following general procedure N, the mixture of compounds 201 and 202 obtained previously (516 mg, 1.22 mmol), TFA (139 mg, 0.094 cm³) in DCM (5 cm³) was stirred for 3 h. Chromatography of the oil obtained (636 mg) (1:2 PE/EA) gave trifluoroacetate 204 Rf 0.39 (235 mg; 36%) as a yellow foam.

ν_max/cm⁻¹ 3300m, 1790m, 1730s, 1680s and 1600s; δ_H 0.87 (3H, t, J 7.1, CH₂CH₃), 1.36 (3H, d, J 6.4, CH₃), 3.40 and 3.65 (4H, m, CH₂-CH₂), 4.06 (2H, q, J 7.1, CH₂-CH₂), 4.17 (1H, m, CHNH), 4.74 (1H, q, J 6.4, CHCH₃), 4.98 (1H, d, J 6.8, NH), 6.00 (1H, d, J 9.4, CHPh), 7.18-7.42 [6H, m, 5 x CH(Ph), H-6(Q)], 7.65 [2H, m, H-7, H-8(Q)] and 8.09 [1H, d, J 7.8, H-5(Q)].
Hydrolysis of trifluoroacetate 204

![Chemical Structure](image)

The foregoing trifluoroacetate 204 (40 mg, 0.074 mmol) in THF (1 cm$^3$) was hydrolysed with sodium carbonate (50 mg), by stirring the mixture overnight. Following solvent evaporation, chromatography (1:1 PE/EA) of the product gave alcohol 200 as an oil Rf 0.38 in quantitative yield (33 mg). (Found: MH$^+$ 442.1978. C$_{23}$H$_{27}$N$_3$O$_6$ requires MH$^+$ 442.1978); $\nu_{\text{max}}$ cm$^{-1}$ 3300m, 1730s, 1680s, 1600s, 1470m and 1375m; $\delta_{\text{H}}$ 0.87 (3H, t, $J$ 7.1, $CH_3$CH$_2$), 1.38 (3H, d, $J$ 6.4, $CH_3$CH), 3.39 and 3.62 (6H, 2 x m, $CH_2$CH$_2$, OH, $CH$NH), 3.95 (2H, q, $J$ 7.1, $CH_2$CH$_3$), 4.72 (1H, q, $J$ 6.4, $CH_3$CH), 5.00 (1H, dd, $J$ 5.5, 3.0, $C$Ph) 6.04 (1H, d, $J$ 6.8, NH), 7.22-7.43 [6H, m, 5 x $CH$(Ph), H-6(Q)], 7.65 [2H, m, H-7, H-8(Q)] and 8.09 [1H, d, $J$ 7.8, H-5(Q)]; $m/z$(%) 464 (MNa$^+$ 100) and 442 (MH$^+$ 80)
General Procedure O for N-N bond reduction using samarium(II) iodide

A two-necked round bottom flask fitted with a 3-way tap and a septum cap was flame dried, flushed with argon and N(Q)-amino alcohol 200 (266 mg, 0.60 mmol) dissolved in THF (3 cm³) added via a syringe followed by tert-butanol (8 cm³) in THF (8 cm³). The solution stirred 1 min. under argon before samarium (II) iodide (0.1M solution in THF) was added dropwise until the dark blue colour of samarium (II) persisted (~23 cm³). Addition of ethyl acetate (75 cm³) to the reaction mixture immediately after the SmI₂ addition followed by washing of the organic layer with bicarbonate solution (75 cm³) and then drying and evaporation of the solvent gave the crude product as a yellow oil (216 mg). Column chromatography (2:1 PE/EA) gave amino acid ester 220 R f 0.53 containing minor impurities. Subsequent kieselgel chromatography (1:3 PE/EA) gave a pure sample of 220 (8 mg, 6%) R f 0.38.

Further elution with the same solvent mixture provided compound 208 (12mg) R f 0.31 (1:3 PE/EA); (Found: M⁺ 235.1083. C₁₂H₁₄N₂O₃ requires M⁺ 235.1083); νmax/cm⁻¹ 1650s and 1130s; δH: 1.65 (3H, d, J 6.4, CH₃), 3.66 and 3.91 (4H, 2 x m, CH₂CH₂), 4.60 (1H, q, J 6.4, CHCH₃), 7.31 [1H, dd, J 8.2, 7.8, H-6(Q)], 7.50-7.74 [1H, m, H-7, 8(Q)], 8.34 [1H, d, J 7.8, H-5(Q)] and 10.30 (1H, s br, NH); δC 20.4 (CH₃CH), 62.0 and 71.7 (CH₂-CH₂), 76.5 (CH₃CH), 121.5 [CCO(Q)], 127.0, 127.4,
127.6, 135.3 [4 x CH(Q)], 149.3 [CN=C(Q)], 157.5 [C=N(Q)] and 164.30 [CO(Q)];
m/z (%) 173 (100), 257 (MNa+ 100) and 235 (MH+ 78).

Attempted N-N bond reduction of aziridine 201/202

Following general procedure O the mixture of aziridines 201 and 202 isolated
previously (200 mg, 0.47 mmol) was reduced in 1BuOH (6 cm³) and THF (6 cm³) with
the solution of Sml₂ (50 cm³). (Because insufficient Sml₂ solution was available not
enough was added to result in a permanent blue colouration). Work up gave an oil
(203 mg) which solidified on titration with ethanol. Recrystallisation gave 205 (82
mg; 46%) mp. 182-183 °C (from ethanol). (Found: MH+ 380.1610. C₂₁H₂₂N₃O₄
requires MH⁺ 380.1611); νmax/cm⁻¹ 1730s, 1680s and 1600s; δH 1.40 (3H, d, J 6.4,
CH₃CH), 2.54 (1H, dd, J 14.2, ~3.5, CHHCO₂), 2.89 (1H, dd, J 14.2, 9.2, CHHCO₂),
3.91 (1H, m, CHHO), 4.17 (1H, m, CHHO), 4.36 (2H, m (3-lines), 2 x OCH), 4.88
(1H, ddd, J 9.2, ~3.5, ~2.3, CHPh), 5.20 (1H, d, J 2.3, NH), 5.88 (1H, q, J 6.4,
CHCH₃), 7.38 [6H, m, 5 x CH(Ph), H-6(Q)], 7.70 [1H, ddd, J 8.3, ~8.3, ~1.5, H-
7(Q)], 7.79 [1H, dd, J 8.3, 0.7, H-8(Q)] and 8.24 [1H, dd, J 8.0, ~1.5, H-5(Q)]; δC
21.8 (CH₃CH₂), 41.7 and 66.0, 62.8 and 66.2 (CH₂CH₂, CHPh, CH₂CO), 72.1
(CHCH₃), 121.5 [CCO(Q)], 126.9, 127.2, 127.5, 128.2, 128.9, 129.3, 135.0 [5 x
CH(Ph), 4 x CH(Q)], 140.7 [C(Ph)], 147.4 [CN=C(Q)], 159.9 [C=N(Q)], 162.5
[CO(Q)] and 171.2 (O-CO); m/z (%) 380 (MH⁺ 84), 402 (MNa⁺ 100).
Enantiopurity of 3-aminoquinazolinone 185: synthesis of imine 195

3-Aminoquinazolinone Q\textsuperscript{23}NH\textsubscript{2} 185 previously isolated (20 mg, 0.080 mmol) [\(\alpha\)]\textsubscript{D} 65 was dissolved in dry ethanol (1 cm\textsuperscript{3}) with (1R)-(+) myrtenal (12 mg, 0.012 cm\textsuperscript{3}, 0.080 mmol) and the solution heated under reflux under nitrogen for 1 day, monitoring the disappearance of the starting material by TLC. Chromatography (1:1 PE/EA) gave a clear oil identified as the imine 195 (27 mg, 88%) \(R_f\) 0.66. (Found: \(M^+\) 382.2131. \(C_{22}H_{27}N_3O_3\) requires \(M^+\) 382.2131); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3300s, 1730s, 1670s, 1600s, 1460m and 1370m; \(\delta_H\) 0.90, 1.45 [6H, 2 x s, 2 x CH\textsubscript{3} (myr)], 1.30 [2H, m, C=CH-CH\textsubscript{2} (myr)], 1.52 (3H, d, \(J\) 6.4, \(CH\textsubscript{3}\)), 2.20 [1H, m, CH-CH\textsubscript{2} (myr)], 2.58 [2H, m, CH\textsubscript{2} (myr)], 3.10 [1H, t, \(J\) 5.6, \(CH=\text{C(CH}_3)\text{)}\textsubscript{2} (myr)], 3.61 and 3.83 (4H, 2 x m, \(CH\textsubscript{2}CH\text{OH})\), 4.38 (1H, s br, \(OH\)), 4.89 (1H, q, \(J\) 6.4, \(C\text{H}_3\text{CH})\), 6.42 (1H, m, C=CH), 7.50 [1H, m, H-6(Q)], 7.75 [2H, m, H-7, H-8(Q)] and 8.27 [1H, d, \(J\) 8.0, H-5(Q)], 8.52 (1H, s, N=CH); \(\delta_C\) 20.0 and 21.4 [(\(CH\textsubscript{3})\text{)}\text{2} myr], 26.4 (CH\textsubscript{3}CH), 31.4, 33.5 [2 x CH\textsubscript{2} (myr)], 38.2 [\(C(CH\text{)}\text{)}\text{2} myr], 40.0, 41.0 [2 x CH (myr)], 62.2, 72.0 (CH\textsubscript{2}-CH\text{2}), 73.8 (CH\textsubscript{2}CH), 121.9 [C\text{CO(Q)}], 127.4, 127.5, 127.6, 134.9 [4 x CH(Q)], 141.9 [CH=CHR (myr)], 145.7 [=C=\(N\) (myr)], 146.1 [CN=\(C\)\text{)}\text{2}], 157.2 [C=\(N\)\text{)}\text{2}], 159.0 [N=CH] and 167.9 [CO(Q)]; \textit{m/z} (%) 382 (\(M^+\) 100).

The above procedure was reported using racemic Q\textsuperscript{23}NH\textsubscript{2} 185. For the product, (1:1 ratio of diastereoisomers) there were identifiable different signals from those above at 0.91 [3H, s, \(CH\textsubscript{3}\) (myr)], and 8.59 (1H, s, N=CH).
Preparation of 3-amino-2-(4-carboxybutyl)quinazolin-4(3H)-one Q\textsuperscript{25}NH\textsubscript{2} 212

A solution of the \( N \)-acylanthranilate 211 kindly supplied by Mr D. F. Hook, (41.4 g, 0.15 mol) in ethanol (80 cm\(^3\)) and hydrazine hydrate (26.2 cm\(^3\), 27 g, 0.89 mol) was heated at reflux for 3 h. The solution was left 12 h. at ambient temperature then filtered from the precipitated hydrazine salt (38 g, 90\%). After dissolving the salt in water, neutralisation using glacial acetic acid to pH 4 gave the 3-aminoquinazolinone Q\textsuperscript{25}NH\textsubscript{2} 212 as a colourless solid; further crystalline product was obtained from the aqueous filtrate on setting aside at 5 °C overnight (giving in total 32.9 g, 85\%) mp. 134-135 °C. (Found: C, 59.7, H, 5.8; N, 16.0. C\textsubscript{13}H\textsubscript{15}N\textsubscript{2}O\textsubscript{5} requires C, 59.8; H, 5.8; N, 16.1\%); (Found: MH\textsuperscript{+} 262.1192, C\textsubscript{13}H\textsubscript{15}N\textsubscript{3}O\textsubscript{3} requires MH\textsuperscript{+} 262.1192); \( \nu_{\text{max}}/\text{cm}^{-1} \): 1670s, 1600s; \( \delta_{\text{H}} \) (DMSO, 250MHz): 1.75-1.93 (4H, m, 2 x CH\textsubscript{2}), 2.40 (2H, t, \( J \) 7.3, CH\textsubscript{2}), 3.08 (2H, t, \( J \) 7.1, CH\textsubscript{2}), 5.82 (2H, s, NH\textsubscript{2}), 7.58 [1H, dd, \( J \) 7.8, ~8, H-6(Q)], 7.75 [1H, d, \( J \) 8.1, H-8(Q)], 7.90 [1H, dd, \( J \) 8.1, ~8, H-7(Q)] and 8.23 [1H, d, \( J \) 7.8, H-5(Q)]; \( m/z \) (%) 262 (MH\textsuperscript{+} 100) and 284 (MNa\textsuperscript{+} 33).
Preparation of 3-amino-(3-trans-cinnamyloxycarbonylbutyl)quinazolin-4(3H)-one $Q^{26}NH_2$ 213

3-Aminoquinazolinone $Q^{25}NH_2$ 212 (1.637 g, 6.27 mmol) was dissolved in anhydrous DMF (20 cm$^3$) under a nitrogen atmosphere. Sodium hydride (326 mg, 8.14 mmol) was added to the vigorously stirred solution, precipitating an insoluble sodium salt. After a further 30 min. the solution was heated to 100 °C to dissolve the salt then the solution cooled to 80 °C before adding cinnamyl bromide (1.6 g, 8.14 mmol) in one portion. After cooling, water (250 cm$^3$) was added and the solution extracted with DCM (2 x 100 cm$^3$). The organic layer was washed with water (2 x 250 cm$^3$) then saturated brine solution (250 cm$^3$) before being dried. Removal of solvent under reduced pressure afforded an oil (~2 g). Purification of the crude product by flash chromatography (1:1 PE/EA) provided the title 3-aminoquinazolinone 213 (Rf 0.33) as a solid (500 mg, 21%); mp. 116-117 °C (from ethanol). (Found: MH$^+$ 378.1818. C$_{22}$H$_{24}$N$_3$O$_3$ requires MH$^+$ 378.1818); $\nu_{max}$/cm$^{-1}$ 1730s, 1670s, 1600s; $\delta_H$ 1.87 (4H, m, $CH_2CH_2$), 2.45 (2H, t, $J$ 7.1, $CH_2$), 3.03 (2H, t, $J$ 7.1, $CH_2$), 4.70 (2H, dd, $J$ 6.4, 1.2, $CH_2CH$), 4.80 (2H, s, $NH_2$), 6.26 (1H, dt, $J$ 15.8, 6.4, $CH_2CH=CH$), 6.60 (1H, d, $J$ 15.8, $CH_2CH=CHPh$), 7.32 [5H, m, 5 x CH(Ph)], 7.42 [1H, ddd, $J$ 8.3, 6.9, 1.4, H-6(Q)], 7.63 [1H, dd, $J$ 8.3, 1.4, H-8(Q)], 7.70 [1H, ddd, $J$ 8.3, 6.9, 1.4, H-7(Q)] and 8.22 [1H, dd, $J$ 8.1, 1.4, H-5(Q)]; $\delta_C$ 25.0, 26.7, 34.4, 34.4 (4 x CH$_2$), 65.4 (CH$_2$O), 120.1 [CCO(Q)], 123.6, 126.7, 126.9, 127.0, 127.6, 128.5, 129.0, 134.6 [$CH=CH$, 4 x CH(Q), 5 x CH(Ph)], 136.6 [C(Ph)], 146.9 [CN=C(Q)], 158.1 [C=N(Q)], 163.0 [C=O(Q)] and 173.6 (CO$_2$); m/z (%) 378 (MH$^+$ 33) and 117 (100).
Preparation of aziridine 214

The aziridine 214 was prepared following general procedure H from Q^{26}NH$_2$ 213 (100 mg, 0.26 mmol), LTA (129 mg, 0.29 mmol) and HMDS (95 mg, 0.13 cm$^3$, 0.53 mmol) to give a yellow solid (72 mg). Aziridine 214 (11 mg, 11%) was isolated by chromatography (1:1 PE/EA containing 2% Et$_3$N) as a colourless solid mp. 204-205 °C (from ethyl acetate).

(Found: M H$^+$ 376.1661, C$_{22}$H$_{21}$N$_3$O$_3$ requires M H$^+$ 376.1662); $\nu_{max}$/cm$^{-1}$ 1730 s, 1710 s, 1670 s and 1600 s; $\delta_H$ 1.78 [2H, m, 2 x CH], 2.35 [1H, m, CH], 2.43 [1H, dd, J 14.6, 12.2, 2.1, CHH], 2.65 [1H, ddd, J 14.6, 6.5, 1.7, CHH], 2.77 [1H, m, CH], 2.87 [1H, m, CH], 3.40 [1H, ddd, J 18.4, 13.3, 3.1, CHH], 3.55 [2H, ddd, J 10.8, ~5, 2.8, CH$_2$CH (azir.)], 3.69 [1H, dd, J 12.3, 10.8, OCHH], 4.65 [1H, d, J 5.0, CHPh (azir.)], 5.00 [1H, dd, J 12.3, 2.8, OCHH], 7.42 [5H, m, 5 x CH(Ph)], 7.54 [1H, dd, J 7.8, ~7.8, H-6(Q)], 7.64 [1H, d, J 8.3, H-8(Q)], 7.73 [1H, ddd, J 8.3, 7.8, 1.4, H-7(Q)], 8.23 [1H, dd, J 7.8, 1.4, H-5(Q)]; $\delta_C$ 21.3, 24.5, 30.7 and 35.1 (4 x CH$_2$), 48.3, 51.1 [CH-CH (azir)], 63.5 (CH$_2$O), 121.8 [CCO(Q)], 126.7, 127.0, 127.4, 127.8, 128.8, 129.0, 134.2 [4 x CH(Q), 5 x CH(Ph)], 135.8 [C(Ph)], 146.5 [CN=C(Q)], 156.3 [C=N(Q)], 161.8 [CO(Q)] and 173.5 (CO$_2$); m/z (%) 376 (MH$^+$100).
Attempted intramolecular oxidative aziridination of 3-amino-(3-trans-cinnamyloxy carbonyl-propyl)quinazolin-4(3H)-one Q$^{27}$NH$_2$ 216 in the presence of HMDS

Compound 216 was kindly supplied by Mr D. F. Hook. The aziridination following general procedure H with Q$^{27}$NH$_2$ 216 (233 mg, 0.64 mmol), LTA (313 mg, 0.71 mmol) and HMDS (0.271 cm$^3$, 1.28 mmol) gave a yellow solid / oil (291.5 mg). Chromatography (1:1 PE/EA) gave unchanged Q$^{27}$NH$_2$ (26 mg) followed by 3-H quinazolinone 217 (16 mg, 7%) as a solid Rf 0.50: no other homogeneous products were obtained.

(Found: MH$^+$ 349.1552, C$_{21}$H$_{20}$N$_2$O$_3$ requires MH$^+$ 349.1552); $\nu_{\text{max}}$/cm$^{-1}$ 1730s, 1680s and 1620s; $\delta_{\text{H}}$ 2.28 (2H, m, CH$_2$), 2.55 (2H, t, J 7.1, CH$_2$), 2.88 (2H, t, J 7.3, CH$_2$), 4.71 (2H, d, J 6.4, CH$_2$CH), 6.20 (1H, dt, J 16.2, 6.4, CH$_2$CH), 6.60 (1H, d, J 16.2, CHCHPh), 7.25 [6H, m, 5 x CH(Ph), H-6(Q)], 7.72 [2H, m, H-7, H-8(Q)] and 8.30 [1H, d, J 8.3, H-5(Q)]; $\delta_{\text{C}}$ : 22.7, 33.7 and 35.1 (3 x CH$_2$), 65.6 (CH$_2$O), 121.0 [CCO(Q)], 123.4, 126.7, 127.0, 127.7, 128.5, 129.0, 134.7, 135.2 [CH=CH, 4 x CH(Q), 5 x CH(Ph)], 136.5 [C(Ph)], 149.7 [CN=C(Q)], 156.0 [C=N(Q)], 164.2 [CO(Q)] and 173.2 (CO$_2$); m/z (%) 349 (MH$^+$100).
Appendix
Crystal structure data for alcohol 128
Table 1. Crystal data and structure refinement for 128.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>1007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C21 H21 N3 O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>379.41</td>
</tr>
<tr>
<td>Temperature</td>
<td>180(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>10.4796(12) Å</td>
</tr>
<tr>
<td>b</td>
<td>11.7176(14) Å</td>
</tr>
<tr>
<td>c</td>
<td>15.2209(18) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>1862.5(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.353 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.095 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>800</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.27 x 0.22 x 0.15 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.20 to 26.50°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-12&lt;=h&lt;=13, -14&lt;=k&lt;=14, -13&lt;=l&lt;=18</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>10740</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3832 [R(int) = 0.0367]</td>
</tr>
<tr>
<td>Completeness to theta = 26.50°</td>
<td>99.4 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
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</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0632, wR2 = 0.0911</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.210 and -0.164 e.Å⁻³</td>
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Crystal structure data for aziridine 168
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<tbody>
<tr>
<td>Empirical formula</td>
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<tr>
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<tr>
<td>Temperature</td>
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<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 15.1623(12) Å, ( \alpha = 90^\circ )</td>
</tr>
<tr>
<td></td>
<td>b = 9.6950(8) Å, ( \beta = 117.4660(10)^\circ )</td>
</tr>
<tr>
<td></td>
<td>c = 14.2622(11) Å, ( \gamma = 90^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>1860.2(3) Å³</td>
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<td>Z</td>
<td>4</td>
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<tr>
<td>Density (calculated)</td>
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<tr>
<td>F(000)</td>
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<td>Crystal size</td>
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</tr>
<tr>
<td>Theta range for data collection</td>
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</tr>
<tr>
<td>Index ranges</td>
<td>-19&lt;=h&lt;=19, -12&lt;=k&lt;=12, -17&lt;=l&lt;=18</td>
</tr>
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<td>Independent reflections</td>
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<tr>
<td>Completeness to theta = 27.00°</td>
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<tr>
<td>Absorption correction</td>
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<td>Refinement method</td>
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<td>Data / restraints / parameters</td>
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<td>Largest diff. peak and hole</td>
<td>0.238 and -0.162 e.Å⁻³</td>
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Crystal structure data for alcohol 164
### Table 1. Crystal data and structure refinement for 164.

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<tr>
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<td>Temperature</td>
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</tr>
<tr>
<td>Wavelength</td>
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<tr>
<td>Crystal system</td>
<td>Triclinic</td>
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<td>Space group</td>
<td>P-1</td>
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<tr>
<td>Unit cell dimensions</td>
<td>a = 9.9886(8) Å</td>
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<tr>
<td></td>
<td>b = 10.9796(9) Å</td>
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<td></td>
<td>c = 11.4998(9) Å</td>
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<td></td>
<td>α = 74.0120(10)°</td>
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<td></td>
<td>β = 88.7810(10)°</td>
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<tr>
<td></td>
<td>γ = 69.1960(10)°</td>
</tr>
<tr>
<td>Volume</td>
<td>1129.24(16) Å</td>
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<tr>
<td>Z</td>
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<tr>
<td>Density (calculated)</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
<td>484</td>
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<tr>
<td>Crystal size</td>
<td>0.08 x 0.18 x 0.30 mm³</td>
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<tr>
<td>Theta range for data collection</td>
<td>1.85 to 26.00°</td>
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<tr>
<td>Index ranges</td>
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<td>Independent reflections</td>
<td>4417 [R(int) = 0.0209]</td>
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<td>Absorption correction</td>
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<td>Refinement method</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.354 and -0.169 e.Å⁻³</td>
</tr>
</tbody>
</table>
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