Synthesis of atropisomeric 2,2'-disubstituted-3,3'-quinazolin-4,4'-diones and their application in asymmetric synthesis.

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A Thesis Submitted for the Degree of Doctor of Philosophy

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Dedicated to my "BLA BLA BLA"

"A Journey of 10000 miles begins with a single step."

-- Lao Tzu.

Abstract.

This thesis reports all the efforts made in the synthesis of 2,2'-disubstituted-3,3'-quinazolin-4,4'-ones (BiQ), a new class of atropisomeric molecules derived from the 4-quinazolinone scaffold, and their potential application as chiral auxiliaries in asymmetric synthesis.

Chapter **1** provides first an overview of axial chirality and atropisomerism and then it reports a review of asymmetric reactions such as Diels-Alder, 1,3-dipolar cycloaddition, epoxydation and cyclopropanation, which have been used in literature as a model for the development of new chiral auxiliaries and chiral ligands.

Chapter **2** describes first the synthesis of a series of 2-substituted benzoxazinones and 3-amino-2-substitute-quinazolinones units. Then the successful synthesis of racemic symmetrical and unsymmetrical 2,2'-disubstituted-3,3'-quinazolin-4,4'-ones (BiQ) by condensation of benzoxazinones and aminoquinazolinones units is presented.

Chapter **3** presents the design and synthesis of chiral non racemic unsymmetrical and symmetrical biquinazolinones. Once chirality has been introduced *via* the functionalization of 3-aminoquinazolinone with non-racemic amino acids, the corresponding unsymmetrical biquinazolines were produced using the same methodology previously adopted for the racemic unsymmetrical biquinazolinones.

Chapter **4** highlights the unexpected synthesis of 4-isopropyl-3-oxo-1,9a,10-triazaanthracen-9-ones. Full characterization of this new heterocyclic compound is herein reported together with the development of an efficient methodology (good to high yield, no chromatographic purification) for the synthesis of other members of this novel class of compounds.

Chapter **5** first presents all the attempts performed for the functionalization of symmetrical 2, 2'-methyl- and 2,2'-ethyl-biquinazolinones *via* carbanionic chemistry. Lithiation of 2,2'-dimethyl-3,3'-biquinazolinone, and further reaction with aromatic

aldehydes led to the corresponding styryl derivates. These compounds were used as a prochiral starting materials in diastereoselective reactions like epoxydation, Diels-Alder, 1,3-dipolar cycloaddition and cyclopropanations in order to assess the efficiency of the biquinazolinones as chiral auxiliaries.

Acknowledgements.

Firstly, I would like to thank my supervisor Dr. Mike Coogan for all his support and encouragement throughout my work at Cardiff University. It was his enthusiasm and excitement for chemistry has made my Ph.D. studies so enjoyable. I would also like to thank Dr. Sarah Oakley, for his huge effort in the revision of my thesis. Without her help the completion of this thesis wouldn't be possible.

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There are many others who have helped my Cardiff life, too many to mention but to you all I extend my gratitude.

Table of contents.

Abbreviations.

°	degree
°C	degree centigrade
Ac	acetyl
Alk	alkyl
APCI	atmospheric pressure chemical ionisation
Ar	aromatic
atm	atmosphere(s)
BINAL-H	2,2'-dihydroxy-1,1'-binaphthyl-lithium aluminum hydride
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BIPHEMP.	6,6'-dimethylbiphenyl-2,2'-bis(diphenylphosphino)-1,1'-biphenyl
BiQ	biquinazolinones
Bn	benzyl
br	broad
Bu	butyl
Bz	benzoyl
c	concentration
cat.	catalyst
CDs	circular dichroism
column chromatography	flash column chromatography
cycload.	cycloaddition
d	doublet
de	diastereosimeric excess
DET	diethyltartrate
DMF	dimethylformamide
DNA	deoxyribonucleic acid
E	Energy
ee	enantiomeric excess
eq	equivalent

ERG	electron releasing groups
ES	electrospray
Et	ethyl
ether	diethyl ether
EWG	electron withdrawing group
FMO	frontier molecular orbital
g	gram
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso*
IR	infra red
LDA	lithiumdiisopropylamide
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
m/z	mass-to-charge ratio
*m*CPBA	meta chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl ether
MHz	megahertz
min	minute(s)
ml	milliliter
mmol	millimole(s)
mol	mole(s)
mp	melting point
n	normal
NLO	non-linear optics
NMR	nuclear magnetic resonance
p	*para*

pag.	page
PG	protecting group
Ph	phenyl
ppm	parts per million
Pr	propyl
p-TSA	*para*-toluene sulfonic acid
q	quartet
quant.	quantitative
r.f.	Retardation Factor
RT	room temperature
s	singlet
sec	secondary
t	time
t	tertiary
t	triplet
$t_{1/2}$	half-life time
TBAF	*tetra*-butyl ammonium fluoride
TBAHS	tetrabutylammonium bisulfate
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilylchloride
Temp.	Temperature
tert	tertiary
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	trisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylendiamine
TMS	trimethylsilyl
Ts	tosyl
TS	transition state
z	charge

Chapter 1: Introduction.

1.1 Aim of the thesis.

Axially chiral molecules have been used in the past as chiral auxiliaries and as ligands for metal catalyzed reactions. These kinds of molecules occupy a relevant place in the field of synthetic chemistry and also in fundamental research. This thesis is concerned with the development of the basic chemistry[1] of a new class of axially chiral (atropisomeric) 3,3'-bisquinazoline-4,4'-diones.

In principle, three main areas will be addressed:

1. The synthesis of a range of symmetrical and unsymmetrical biquinazolinones (BiQ) bearing several substituents in the 2,2' positions and studies on their atropisomeric behaviour (if present).
2. The synthesis of biquinazolinones containing prochiral unsaturation or other groups applicable to asymmetric synthesis.
3. The optimisation of diastereoselectivity in reactions of prochiral groups on this scaffold; investigation of the scope and limitations of the reactions, which can be applied to these systems without compromising the integrity of the scaffold or its homochirality.

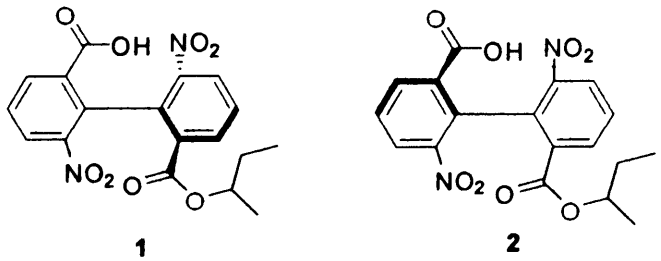
The first point is based on further development of the preliminary studies conducted by Coogan on the synthesis of symmetrical biquinazolinones.[1] Applications of this strategy toward the synthesis of unsymmetrical substituted biquinazolinones will be investigated, with particular attention to the synthesis of BiQ bearing chiral groups. In the second part, once a route to these molecules has been established, their application to substrate controlled asymmetric induction of a range of 2,2'-substituted BiQs will be investigated.
In this context the biquinazolinone scaffold will be investigated as a potential chiral auxiliary in a series of diastereoselective reactions which will include, among others, Diels-Alder cycloaddition, epoxidation and cyclopropanation. Although all these

reactions have been thoroughly investigated they will provide us with a good starting point for the confirmation of the utility of this new class of molecules as chiral auxiliary. In fact successful diastereoselective epoxidation on unsaturated biquinazolinones have been obtained previously in our group.[1] In the following introduction a panoramic of the general description of atropisomers, their synthesis and applications will be presented. Successively a description of the general features of the asymmetric reactions used as a model for the study of the chiral ativity of the biquinazolinones will be presented.

1.2 Axial chirality and atropisomerism.

Pasteur, while investigating chiral compounds, proposed the concept that the optical activity of some substances was due to enantiomorphism of the molecular configuration.[2] After Pasteur, Van't Hoff and Le Bell showed that the optical activity in all known chiral compounds at that time could be correlated with the presence of an asymmetric carbon atom in the molecule.[3]

Subsequently, several scientists have discovered that a molecule could be chiral without the presence of an asymmetric carbon (or another atom like sulphur). A special class is formed by molecules in which the rotation around a single bond is slow (or even blocked) because the steric interaction between the *ortho* groups is big enough to make the planar conformation an energy maximum, therefore two non-planar, axially chiral enantiomeric forms can exist. Moreover, if inversion through the planar conformation is slow enough, they may, under suitable circumstances, be isolated (resolved), like the *ortho*-substituted biphenyls **1** and **2** in Figure 1-1.



1 **2**

Figure 1-1.

This type of enantiomerism was first discovered by Christie and Kenner[4] with the resolution of 6,6'-dinitro-2,2'-diphenic acid and it was called later "atropisomerism" (from the Greek *a* meaning not, and *tropos* meaning turn).[5] Atropisomerism is a form of rotational isomerism where the conformers can be isolated. Oki arbitrarily defined the conditions for the existence of atropisomerism as one where two isomers can be isolated and have a half-life time ($t_{1/2}$) of at least 1000 s.[6] However, this value does not define the required free energy barrier, which depends on the temperature: usually this should be in the range of 70-90 kJ·mol^{-1}. Conceptually, one might want to think of a hindered biphenyl as being constituted of two orthogonal biphenyl rings: the condition that the *ortho* substituents must be different serves to eliminate the plane of symmetry that would otherwise exist in that conformation. In fact, in solution the two rings are neither coplanar nor orthogonal in the lowest energy conformation. The tendency to non-planarity imposed by the steric hindrance of the substituents is opposed by the π-electron overlap, which produces maximum stabilization when the rings are coplanar. The result in biphenyls is a compromise with the interplanar angle varying between 42° and 90°.[7]

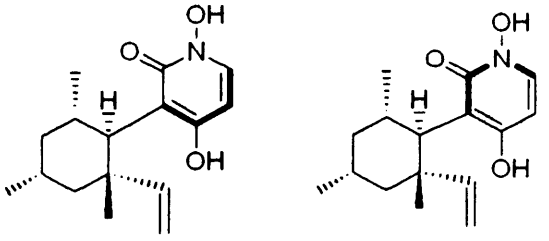
1.3 Classification of atropisomers.

Since the first discovery of axially chiral molecules, atropisomerism has been observed in a large number of chemical entities and so a suitable classification should be made.

Atropisomers are often broken down into several classes, based on the type of hybridisation of the atom involved in the hindered rotation or by the type of bonds around which the rotation is blocked (e.g. C-C, C-N, N-N). The first common class is the sp^2-sp^2 family. This group is exemplified by biaryls that are either tri- or tetra-*ortho* substituted. Perhaps the best known examples of this class are the binaphthyl ligands, which are commonly knows as 1,1'-bi-2-naphthol (BINOL) and are widely used in asymmetric synthesis and catalysis (see 1.8.1).

The sp^2-sp^3 class is found in some natural products, for example, cordypyridone A **3** and its atropisomer **4**, which are diastereoisomers and only interconvert upon

extended heating (Figure1-2).[8] Other examples are represented by aromatic molecules with bulky di-*tert*-butyl alcohol groups like the alcohols **5** and **6** in Figure 1-3.[9]



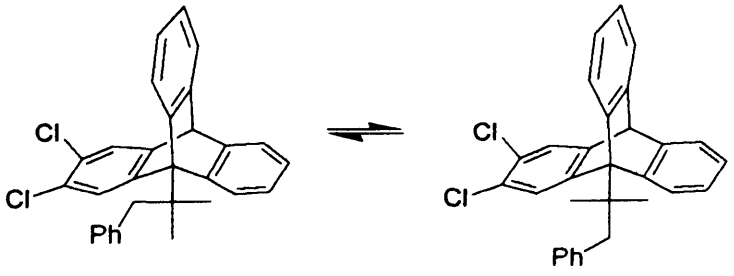
3 **4**

Figure 1-2.

5 **6**

Figure 1-3.

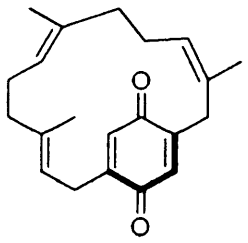
Atropisomerism about sp^3-sp^3 bonds usually only occurs in non-natural systems especially designed to hinder rotation. The framework within which atropisomerism of this type has been found is in the system derived from triptycene systems **7** and **8**, extensively studied by Oki and co-workers (Figure 1-4).[10]



7 **8**

Figure 1-4.

The last class of atropisomers is that created not by hindered rotation about a particular bond but rather by hindered rotation through the centre of a macrocycle or by conformational stability of a macrocycle.[11,12] This is clearly demonstrated by the byciclo benzoquinone **9** in Figure 1-5.

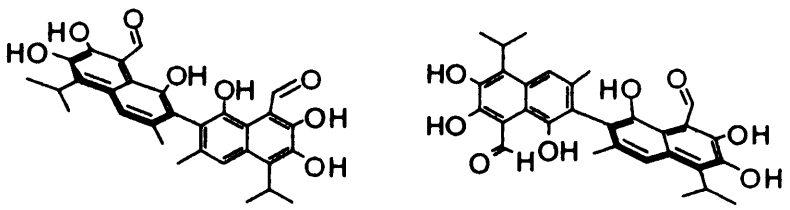


9

Figure 1-5.

1.4 Atropisomers in nature.

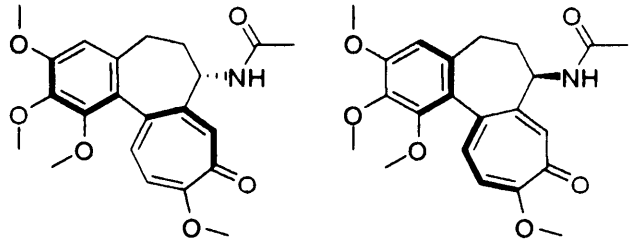
During the last ten years the importance of axially chiral molecules has become more relevant in the field of natural product synthesis. This is because of its widespread occurrence in nature and because substantially different bioactivities of atropisomers are sometimes shown. A classicl example is the dimeric bis-naphthalene natural product Gossypol **10** and **11** (Figure 1-6), isolated from the seed of cotton plants (various *Gossypium* species).[13] The interest in Gossypol derives from its activity as a contraceptive in male humans.[14] It has been shown to effect the maturation and motility of sperm and it inactivates the enzymes required for the sperm to fertilize the ova. The usefulness of racemic gossypol as an adjuvant in post-operative bladder cancer has also been demonstrated[15] and tumour regression has been observed in advanced cancer patients with gliomas.[16] Gossypol exists as two atropisomers due to restricted rotation about the biaryl bond and the contraceptive effect appears to be associated with the (-)-isomer **10**, while toxic effects (cardiac toxicity in cattle) appear to be associated with the (+) isomer **11**.



(-)-gossypol **10** (+)-gossypol **11**

Figure 1-6.

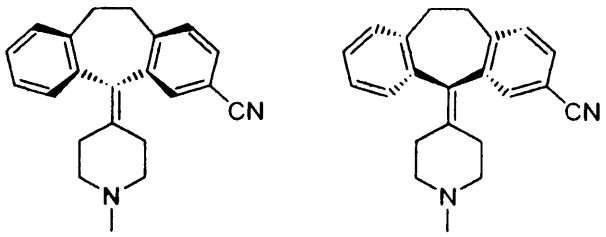
Other atropisomeric natural product are a series of alkaloids called colchicide **12** and isocolchicide **13** which are able to bind to tubulin ((-)-colchicine).[17] This leads to disruption of the microtubule assembly and thus is becoming an important tool in cancer research (Figure 1-7).



12 **13**

Figure 1-7.

The importance of the configuration of the chiral axis in biologically activity is demonstrated by the two isomeric 3-cyanocyproheptadine compounds **14** and **15,** which have been synthesized and resolved into enantiomeric atropisomers.[18] Whereas compound **14** was shown to be a potent antipsychotic agent, its corresponding atropisomeric enantiomer **15** was virtually inactive.



14 15

Figure 1-8.

1.5 Synthesis of Atropisomers.

1.5.1 Resolution based approach.

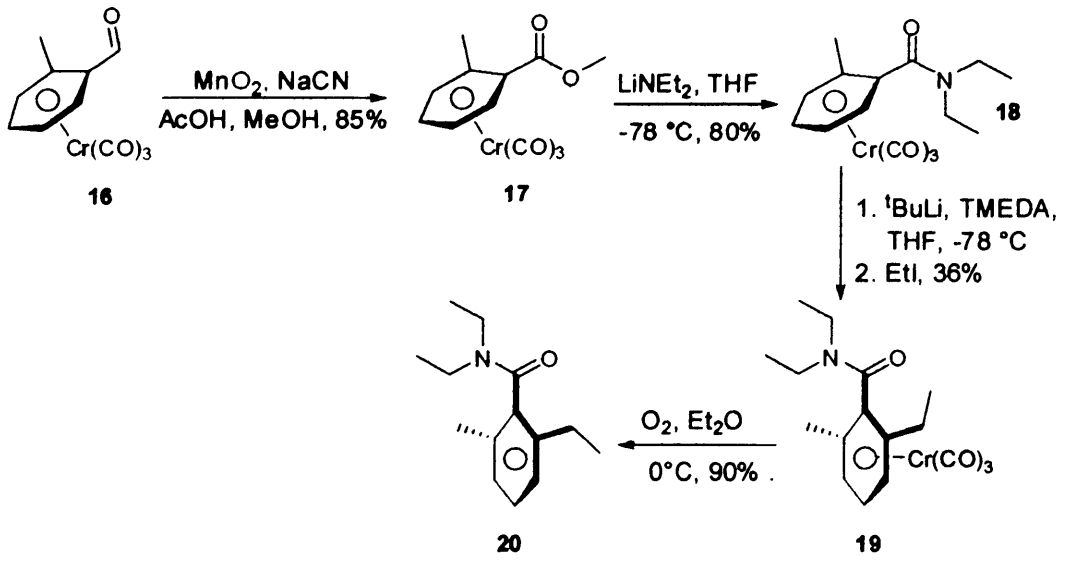
Normally, atropisomers are synthesised in their racemic form and then resolved as single enantiomer. Although resolution is usually not considered the best option in asymmetric synthesis, because it is difficult to control the setting of the stereocentre, resolution is often successful when other methods are not.

Non-biaryl atropisomers of P,O-ligands possessing an *N,N*-dialky-1,1-naphthamide have been synthesized *via* an efficient chemical resolution process.[19] Walsh and co-workers[20] report the kinetic resolution of some atropisomeric aromatic amides (and naphthamide) bearing an olefin moiety on the *ortho*-position by application of Sharpless asymmetric hydroxylation. Chromatographic separation of some racemic arylamides 2,6-disubstituted to optically active axial aromatic carboxamides has been achieved by using high performance liquid chromatography (HPLC) on chiral stationary phase.[21] Racemic synthesis followed by resolution is the method often employed for the synthesis of atropisomerically pure natural products. An example of the application of this strategy is the synthesis of anicistrocladidine carried out by Morris.[22]

1.5.2 Approaches based on asymmetric synthesis.

Asymmetric deprotonation of *N,N*-dialkyl-1-naphthamindes with a combination of *n*-butyllithium/(-)-sparteine followed by quenching with alkyl halides to give the axially

chiral *N,N*-dialkyl-2-alkyl-1-naphthamindes has been reported by Beak,[23] although the optical purity of the axial chiral carboxamides obtain by this method is moderate. An interesting protocol for the synthesis of axially chiral benzamides and anilides by the utilization of planar chiral (arene) chromium complexes has been proposed by Uemura (Scheme 1-1).[24]



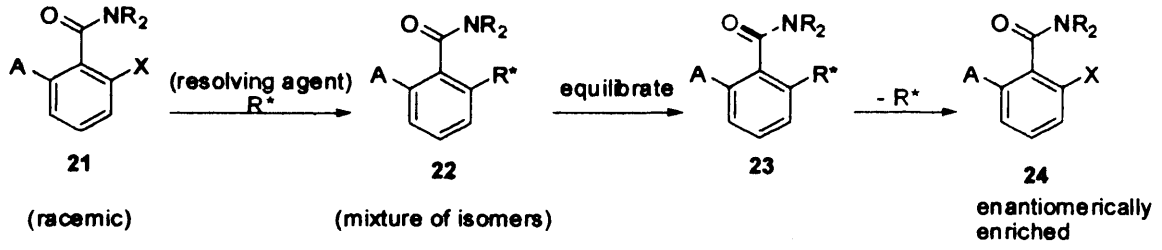
Scheme 1-1.

1.5.3 Approaches based on thermodynamic equilibration.

One distinct difference between atropisomeric chiral centers versus chiral carbons is that the former can be equilibrated thermally, whereas the latter must be equilibrated chemically, i.e. by making/breaking chemical bonds. This creates the advantageous circumstance in molecules possessing both types of chiral centers of being able to selectively equilibrate either the atropisomeric chiral centre or the chiral carbon to give the thermodynamically more stable diastereoisomer. This approach has been used in several cases in atropisomeric natural product synthesis.[25, 26, 27]

In the field of atropisomeric aromatic amides, Clayden and co-workers showed that it is possible to synthesize these compounds by using a thermodynamic approach together with some chiral auxiliaries. In one case, the strategy involved the reaction of racemic naphthamide with enantiomerically pure proline in order to obtain a

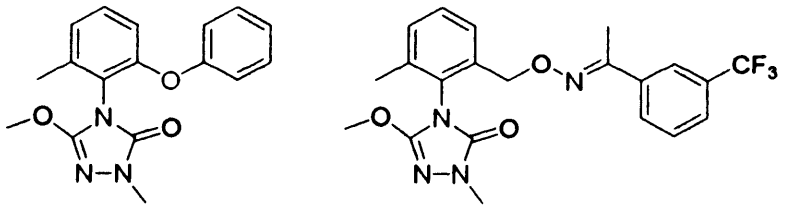
mixture of diastereoisomers which were then equilibrated to a single diastereoisomer. [28] The resolving agent was finally removed, leaving an enantiomerically enriched starting material (Scheme 1-2). Dynamic resolution under thermodynamic control has also been applied, by Clayden, in a series of *N,N*-dialkyl-2-formyl-1-naphthamides using ephedrine and pseudo ephedrine as chiral auxiliaries.[29]



Scheme 1-2.

1.6 C-N atropisomers.

Atropisomerism is not only confined to the familiar biaryls as hindered rotation about a variety of C–O and C–N bonds gives rise to the potential for stereoisomerism. Atropisomers different from biaryls have been described only rarely, with examples including *N*-aryl pyrroles,[32,30] and murrastifoline-F.[31] Takashi and co-workers[32] have synthesized and applied C-(aryl)-N(amine) bond atropisomeric amines to transition-metal catalysed asymmetric reactions such as palladium-catalyzed allylic alkylation. Other examples of C-N atropisomers are compounds derived from triazolone, important because of their capacity to bind at the ubihydroquinone, cytocrome-c oxidoreductase site[33] and for their activity as fungicides.[34] *N*-(2,6-disubstituted) phenyl triazolone **25** (Figure 1-9) and the commercial azoxystrobin,[35] **26** are important for their respiration inhibition action.[46] It is interesting to note that aryl triazolones and related respiration inhibitors without an *ortho* group are inactive. C-N atropisomerism is also present in carbohydrate imidazolidines as reported by the Babiano group.[36]



25 26

Figure 1-9.

1.7 N-N atropisomers and aminoquinazolinones.

Compounds like di-, tri- and tetra-substituted hydrazine show higher barriers to rotation around the N-N bond compared to other single bonds.[37] This is probably because of the repulsion between the lone pairs on the nitrogen when the molecule is close to a planar conformation.[38]

Compounds like 1,2-dibenzoyl-1,2-dipropanoylhydrazine **27** (Figure 1-10), display an ABX_3 system in their proton nuclear magnetic resonance (^{1}H-NMR) spectrum for the methylene groups demonstrating slow rotation around the N-N bond at least on the NMR timescale.[39] Variable temperature ^{1}H-NMR experiments on **27** were performed in order to establish whether the barrier of rotation is due to steric repulsion between the oxygen atoms in the carbonyl groups or simply by the repulsion of the lone pairs on the nitrogen. The results obtained (free energy barrier of 82-84 kJ·mol^{-1}) were in good agreement with theoretical results.[40] The conclusion is that the rotation barrier is due to the steric reasons rather then electronic factors (in the absence of steric repulsion the barrier is around 80 kJ·mol^{-1}.

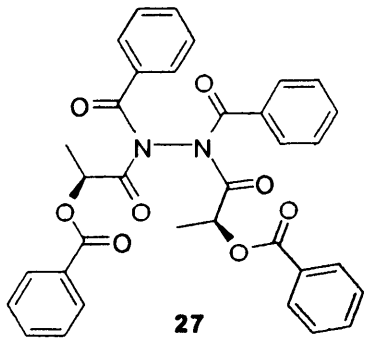


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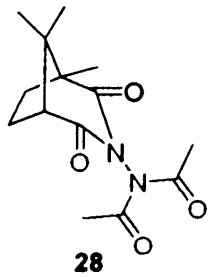
Figure 1-10.

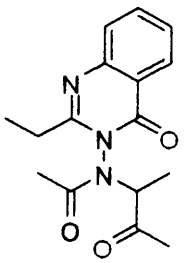
More interesting however, are systems in which the N-N motif is incorporated within more complex molecules. Verma and Prasad[41] have shown that the amide **28** (Figure 1-11) has a barrier to rotation about the N-N bond in excess of 97 $kJ \cdot mol^{-1}$, confirmed by the fact that no coalescence of the acetyl methyl signal was observed in the ^1H-NMR spectrum at 150 °C.



28

Figure 1-11.

Atkinson has also demonstrated that the barrier to N-N bond rotation in *N*-acyl-*N*-alkyl-4(3H)-quinazolinones is big enough to allow the separation of diastereoisomers when other chiral elements were present in the molecule. Thus, the keto amide **29** has been separated into two diastereoisomers which did not interconvert on heating at temperature close to 200 °C (Figure 1-12).[42]



29

Figure 1-12.

Further studies in the Atkinson group demonstrated that the N-N bond in 3-amino quinazolinones N-substituted with two different acyl groups is a chiral axis at room temperature.[43] In this case, the molecule comprises of two orthogonal planes, one containing the quinazolinone ring and the other the imide groups, with the N-N bond

as a chiral axis.The most favourable conformation in this type of molecule is where one of the imide carbonyl groups is *cis* and the other is *trans* with respect to the quinazolinone ring. When the N-acyl groups in the diacylamino quinazolinones **30** are identical (Figure 1-13), the ^{1}H-NMR spectrum shows some broadening of the acetyl methyl peak due to slow interconversion between the *exo/endo* and *endo/exo* conformations. Eventually, at -85 °C, signals from the two acetyl methyl groups are separated into two singlets of equal intensity. At this temperature, the methylene protons in the ethyl groups also become non-equivalent because of the presence of the N-N chiral axis. Interconversion of the two diastereoisomers, by rotation around the N-N bond, was found to be slow at room temperature and only takes place on heating in toluene at 100 °C for more then 1 hour.[43]

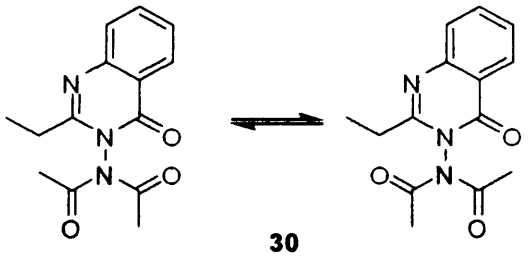


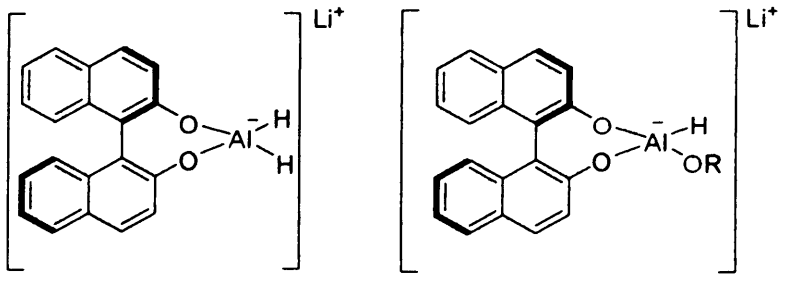
Figure 1-13.

3-(Diacylamino)-4(3H)-quinazolinones have found useful applications as chemoselective and enantioselective acylating agents from primary amines, meanwhile other acetoxyamino quinazolinones have been employed in aziridination of double bonds with excellent results.[44] On this basis, it is possible to design several atropisomers by only changing the substituents on the exocyclic nitrogen and test their applicability in organic synthesis.

1.8 Application of atropisomers.

1.8.1 Chiral ligands.

Asymmetric synthesis has become a major focal point of synthetic chemistry in the past two decades and today is probably the most important field of organic synthesis, especially because the pharmaceutical industry requires the synthesis of new and more efficient drugs against many diseases. An important tool for the introduction of a chiral centre to a molecule is asymmetric catalysis. This is commonly achieved through organometallic and coordination chemistry by employing chiral ligands, in particular, axially chiral phosphorus-based ligands. Among a wide variety of asymmetric reactions, enantioselective reduction of prochiral carbonyl compounds is one of the most extensively studied transformations.[45] A standard method to this stems from the use of metal hydride complexes bearing chiral alkoxy or amino ligands. In this area several reagents have been developed, in particular by modification of lithium aluminium hydride. The first generation of this catalyst is 2,2'-dihydroxy-1,1'-binaphthyl-lithium aluminum hydride (R)-BINAL-H **31** (prepared by mixing $LiAlH_4$ and an equimolar amount of enantiomerically pure 1,1'-bi-2-naphthol (BINOL) in tetrahydrofurane (THF), gave a very poor enantiomeric excess (2%) in the reduction of prochiral acetophenone. Replacement of either hydrogen by an ethoxy group produces a single aluminium hydride reagent with excellent enantiomeric excesses being obtained in the reduction of prochiral alkyl phenyl ketones with three equivalents of "modified" BINAL-H **32** (Figure 1-4).[46,47,48]



(R)- BINAL-H

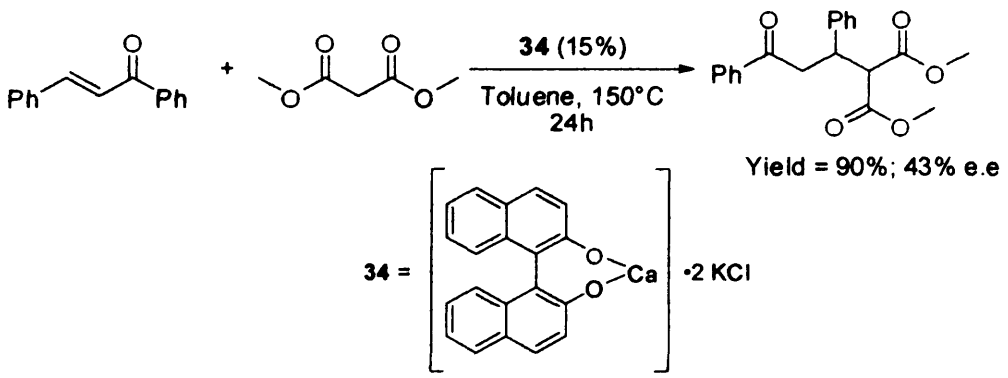
31

Modified (R)- BINAL-H

32

Figure 1-14.

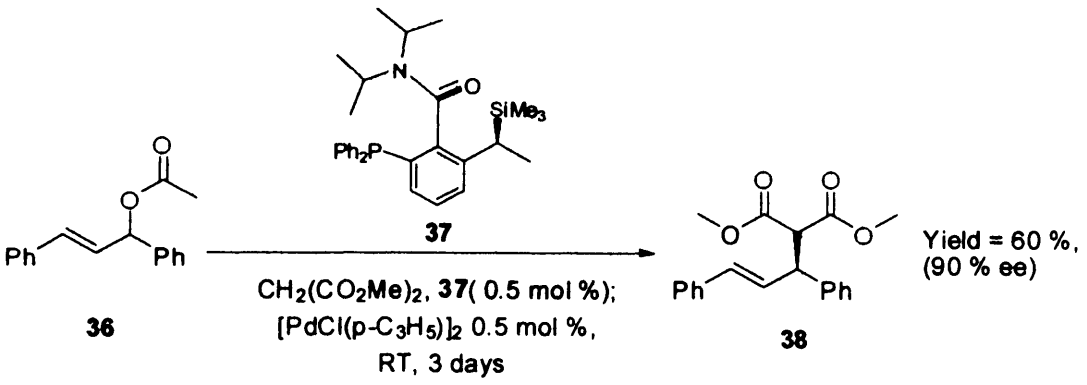
Systems based on BINOL have been successfully employed in other important transformations such as the epoxidation of olefins,[49] oxidation of sulphides,[50,51] Diels-Alder reactions[52,53] and catalytic asymmetric Michael additions (Scheme 1-3).[54] Following the success of BINOL as a ligand in asymmetric synthesis, new ligands have been developed by changing the donor atom in the molecule. Typical example of this strategy is represented by 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (BINAP).[55]



Scheme 1-3.

Today, the design and synthesis of chiral phosphine ligands plays a central role in the development of highly enantioselective transition metal catalyzed asymmetric reactions. In fact, subtle changes in conformational, steric, and electronic properties of the chiral ligands can often lead to dramatic variations in reactivity and enantioselectivity. For atropisomeric diphosphines, for example, a small variation in the dihedral angle of the ligands can have a significant impact on the reactivity and selectivity of reactions.[56, 57, 58]

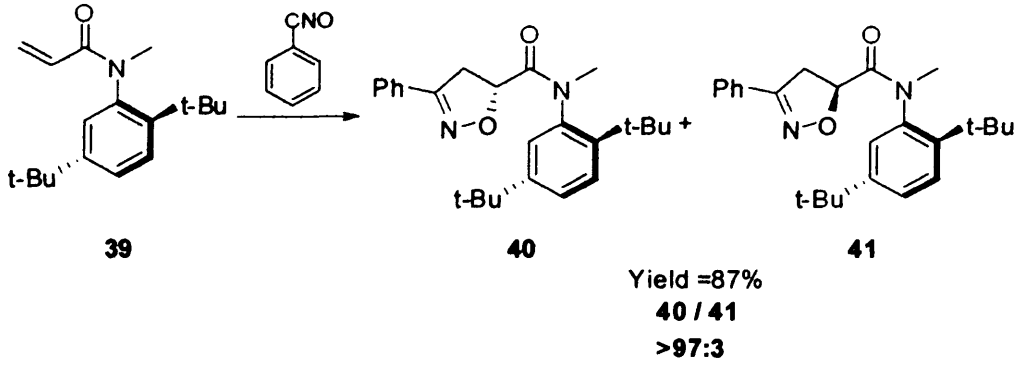
Although atropisomeric biaryl phosphines have been used effectively as chiral ligands, for many asymmetric reactions, the design of new non biaryl atropisomeric chiral ligands had been extensively developed as well in the last few years. The angled aromatic rings serve as a useful scaffold for the attachment of metal coordinating heteroatoms and the complex formed with transition metals is one of the most useful tools in modern organic asymmetric synthesis. On this basis, an atropisomeric amide chiral ligand **37** has been proposed by Clayden in the asymmetric allylic substitution (Scheme 1-4).[59,60]



Scheme 1-4.

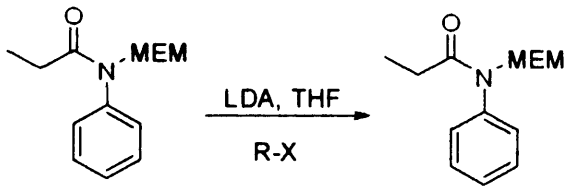
1.8.2 Chiral auxiliaries.

Despite the recent advances in chiral reagents and asymmetric catalysis, chiral auxiliaries remain the most well-developed, effective and reliable approach for asymmetric organic synthesis. In 1994, Curran and his co-workers published a paper about the powerful stereo-directing potential of certain types of axially twisted amides.[61] One of the applications of these systems was the cycloaddition reaction of a vinyl anilide with nitrile-oxide to give almost exclusively one diastereoisomer (Scheme 1-5).



Scheme 1-5.

Following the same strategy, Simpkins applied a racemic atropisomeric amide system to enolate chemistry, obtaining good yields and selectivity as indicated in Scheme 1-6 and Table 1-1.[62]



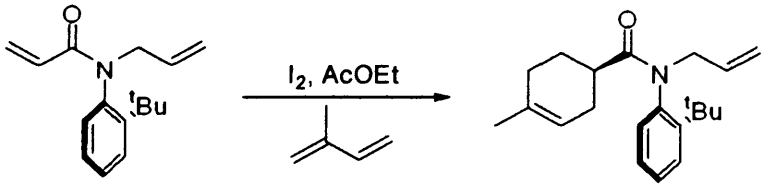
42 43

Scheme 1-6.

R-X	Yield (%)	d.e.
$PhCH_2Br$	83	25:1
EtI	89	15:1
$PhSSO_2Ph$	84	> 25:1

Table 1-1.

Enantiomerically enriched atropisomeric amides, like **44**, were also prepared by Taguchi and co-workers *via* manipulation of (S)-O-acetyl lactic acid and employed in the iodine-activated Diels Alder cycloaddition to generate **45**.[63]

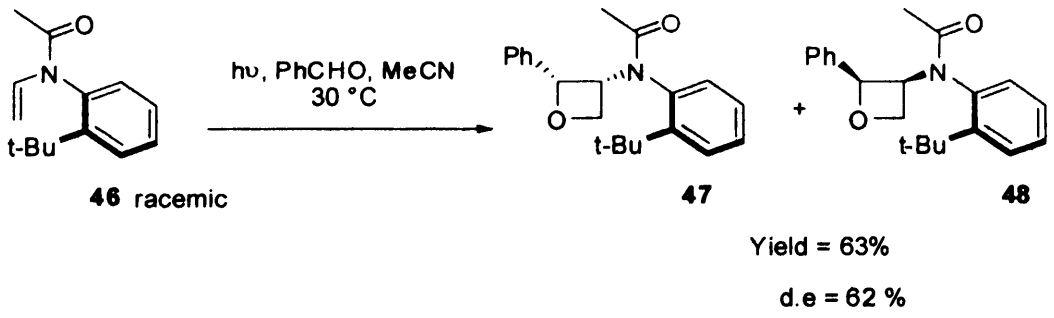


44 **45**

Figure 1-15.

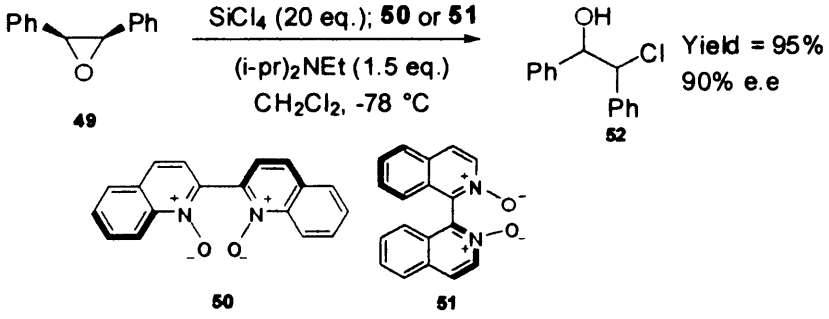
Axially chiral anilides similar to **44** have also found applications in asymmetric iodolactonization and asymmetric carbonyl addition reaction of alkyllithium reagents.[64]

A photochemical reaction has also been investigated and an example is showed in Scheme 1-7; the photocycloaddition of an axially chiral enamide with benzaldehyde affording the *trans*- oxetanes with moderate diastereoselectivity.[65]



Scheme 1-7.

Finally, some reactions are catalyzed by axially chiral compounds, as for example the enantioselective ring opening of *meso*-epoxide in the presence of tetrachlorosilane (Scheme 1-8).[66] Nucleophilic catalysts for the asymmetric acylation (resolution) of *sec*-alcohols have also been developed (Figure 1-16).[67]



Scheme 1-8.

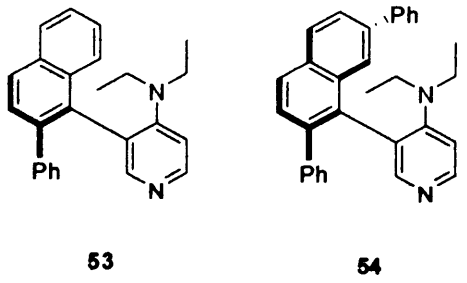
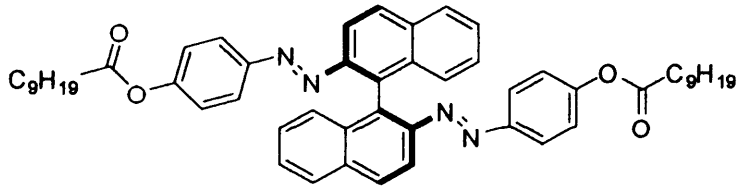


Figure 1-16.

1.9 *"Non synthetic" applications of atropisomers.*

As well as the most common application of atropisomers (chiral ligands, chiral auxiliaries), there are other applications of this kind of molecule in several sectors of chemistry and technology. For example nanotechnology, molecular machines and molecular switches are subjects of continuous interest. Chiral molecular switches seem particularly attractive because they undergo reversible transformations connected to changes in the chiral response of the system under the influence of external factors. A typical example is the isomerization of an azo group when irradiated with light of the right frequency. Photochemically driven chiral switches seem promising for several technological applications. [68] Because axially chiral binaphthyl shows strong exciton Circular Dichroism (CDs) and has large helical twisting power (which expresses the ability of a chiral solute to twist a nematic phase), they are suitable to be used in controlling the phase behaviour of liquid crystals. An example of this kind of molecule is the diazo-derivative of (R)-,2,2'-diamino-1,1'-binaphthyl **55** synthesized by Gottarelli (Figure 1-17).[69]



55

Figure 1-17.

Non-linear optics (NLO) has been recognized for several years as a field with important potential applications in optoelectronic devices, with much research having been devoted to the identification of suitable materials. An important class of these materials is represented by noncentrosymmetric polymers obtained by polymerization of suitable chiral monomers as for example 1,1'-binaphthyl. The important properties of these polymers are the formation of helical arrangements, which make them suitable for the formation of Langmuir-Blodget films with good NLO efficiency.[70]

Chirality is an important phenomenon in many chemical and biological processes, playing a key role in the assembly of supramolecular structures and also recognition between biomolecules. The development of deoxyribonucleic acid (DNA) binding agents as nano probes of the structure of nucleic acid has gained considerable importance. Between several fluorescence molecules able to bind to DNA, a special mention here must be given to atropisomeric luminescent viologens of the general structure indicated in Figure 1-18, of which enantiomer **56** has more affinity for DNA than **57**.[71]

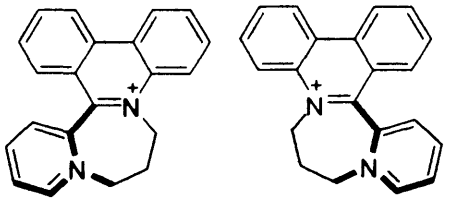


Figure 1-18.

In the field of colloidal chemistry, an important sector of chemistry, there are examples of axially chiral molecules that show amphiphilic properties. The molecule represented in Figure 1-19 is an example of an axially chiral amphiphilic molecule used by Bai,[72] in the study of assembly behaviour.[73]

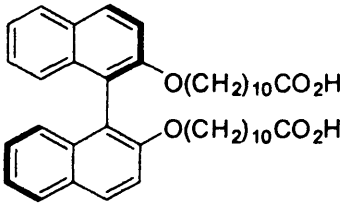


Figure 1-19.

Molecules possessing a chiral axis can in principle form liquid crystals, which, due to their special physical properties have been extensively studied over the last few years. Materials exhibiting a chiral smectic C-phase are of particular interest because of their ferroelectric properties and their use for displays and light shutter devices. Some examples of these molecules are indicated in Figure 1-20.[74]

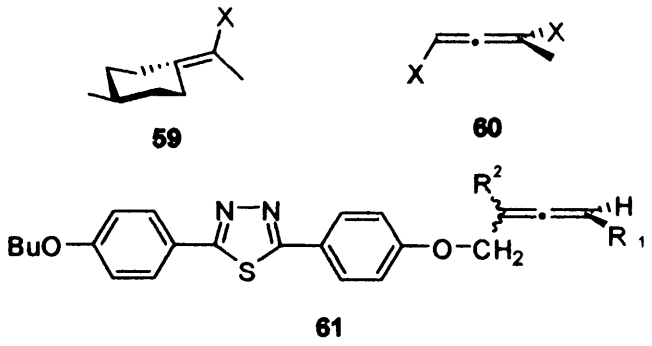


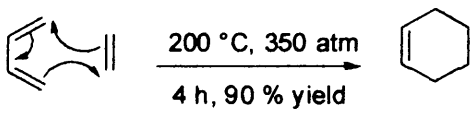
Figure 1-20.

1.10 Asymmetric organic transformations.

In the previous sections the use of atropisomeric molecules as chiral auxiliaries has been presented. As the final target of this thesis is to demonstrate the potential utility of atropisomeric biquinazolinone as chiral auxiliary on asymmetric reactions, in the next sections a general description of some diastereoselective reactions in which axially chiral auxiliaries could find potential applications will be described.

1.10.1 Diels-Alder reaction.

The Diels-Alder cycloaddition[75] involves the reaction between a diene and an alkene, (called the dienophile) with the formation of a cyclic product with rearrangement of the double bonds. The simplest example is the reaction between butadiene and ethylene to form cyclohexene (Scheme 1-9).



62 **63** **64**

Scheme 1-9.

Mechanistically, the reaction occurs in one step with a concerted mechanism. This conclusion is consistent with a number of experimental observations: (a) The *cis* or *trans* configuration of the dienophile is fully conserved in the configuration of the

cycloadduct, which proves that there is no intermediate involved with a lifetime long enough to allow rotation around a C-C bond. (b) The Hammett ρ-values, which can be considered as a measure of the development of charge in the activation process, are much smaller than those obtained for reactions known to proceed through charged intermediates. (c) Solvent effects on the Diels-Alder reaction are usually small or modest, excluding the involvement of charged intermediates in the rate determining step.

One peculiarity of the Diels-Alder reaction is that the diene is required to be in the s-*cis* conformation in order for the Diels-Alder reaction to work, (if the conjugated double bond is rigidly fixed in the s-*trans* configuration, the respective diene does not undergo a Diels-Alder reaction).

The reaction is often indicated as [4+2] -π-electron cycloaddition from the number of electrons involved in the transformation. The simplest Diels-Alder reactions require very harsh conditions which should be avoided in the synthesis of complex molecules. Dienophiles substituted with electron withdrawing groups (EWG) and/or a diene substituted with electron releasing groups (ERG) (Figure 1-21) in general react faster, at lower temperatures and at atmospheric pressure giving good yields.

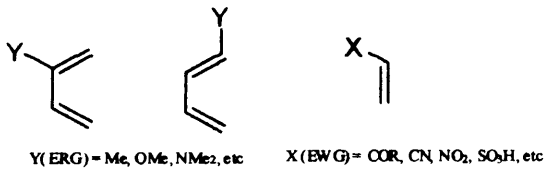


Figure 1-21.

1.10.2 Rate of Diels Alder reactions.

Cycloadditions are normally very slow reactions and for synthetic purposes this is a drawback. According to the Frontier Molecular Orbital (FMO) theory, developed during a study of the role of orbital symmetry in pericyclic reactions by Woodward and Hoffmann[76] and, independently, by Fukui,[77] the reaction between the diene and dienophile is controlled by highest occupied molecular orbital (HOMO) - lowest unoccupied molecular orbital (LUMO) interactions. In "normal" cycloadditions the principal interaction is between the HOMO of the diene and the LUMO of the

dienophile. This interaction is responsible of the rate of the cycloaddition: if the gap between the two frontier orbitals is small the reaction is fast because of the lower activation energy. Clearly the substituents on the molecules can change the relative energies of the molecular orbitals involved in the interaction and then change the rate of the reaction.[78,79]

ERGs increase the energy of the HOMO and the LUMO, while EWGs lower the energy of both.[80] In a situation like that shown in Figure 1-22 (a), there is a small energy-separation for the HOMO of the diene and the LUMO of the alkene, therefore the rate of the reaction will be controlled by that interaction and will be faster with respect to the one illustrated in Figure 1-22 (b) in which both the HOMO-LUMO and LUMO/HOMO have the same importance (normally, two medium-sized interactions are not as effective at lowering the transition state energy as a strong and a weak one).The situation depicted in Figure 1-22 (c) is called Inverse-Elecron-demand. In this case the most important interaction is between the higher energy HOMO of the dienophile which interacts with a low energy LUMO of the diene. In this case, a faster reaction is generally observed.

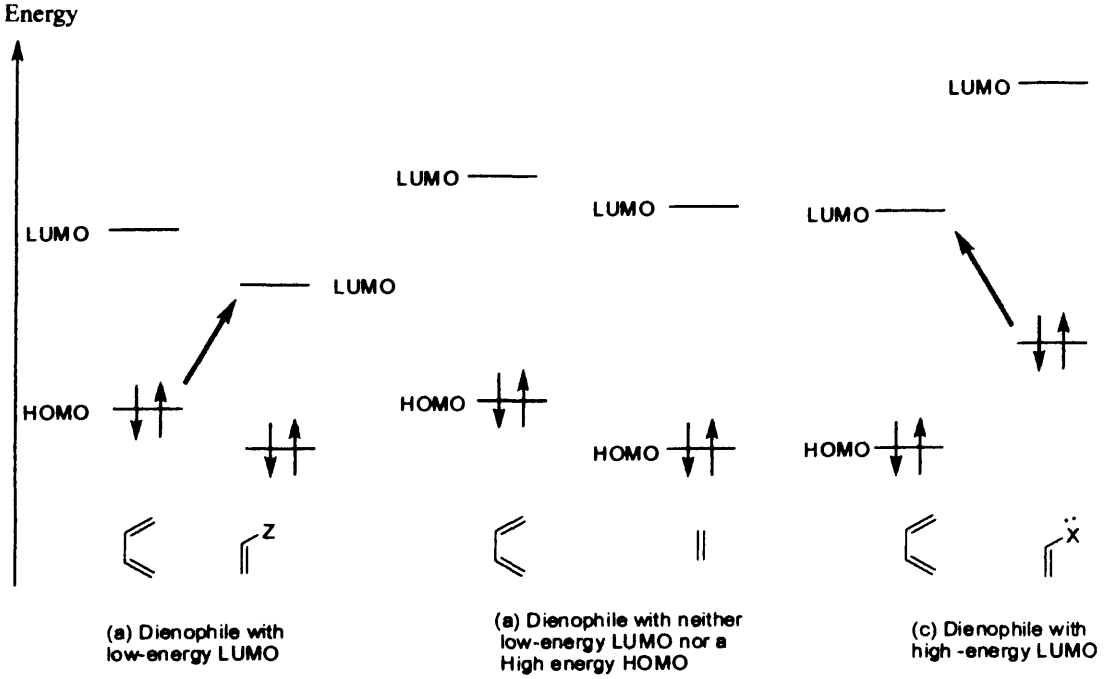


Figure 1-22.

1.10.3 Lewis-acid catalysis of Diels-Alder reactions.

A much larger rate acceleration can be achieved using a Lewis acidic catalyst such as $AlCl_3$, BF_3, $ZnCl_2$ or $TiCl_4$. Normally these catalysts coordinate at the Lewis base centre in the dienophile, lowering the energy of the orbitals of the dienophile. The key feature in rate enhancement is the lowering in energy of the LUMO which make the E_{LUMO} *dienophile* – E_{HOMO} *diene* small and hence lead to an increase in the rate of reaction.[81,82,83] In organic solvents, accelerations of the order of 10^4 to 10^6 times, accompanied by a considerable increase in selectivity, can be achieved as demonstrated by Yates and Heaton.[84] Under Lewis acid catalysis, the selectivity can be optimized as indicated by the work of Sauer and Kredel in 1966,[85] who demonstrated that the percentage of *endo* isomer passed from 82% without a catalyst to 98% when the reaction was carried out in the presence of $AlCl_3 \cdot OEt_2$. Regioselectivity[86] and diastereofacial selectivity[87] have also been increased in the presence of a Lewis acid. Again, as in the case of the rate acceleration, the enhanced selectivity could be explained with the aid of FMO theory. Coordination of the Lewis acid causes a redistribution of the electron density in the dienophile and in doing so, changes the site of reaction with the diene. The effects of Lewis acids on selectivity can be understood by considering the change in the molecular orbital of acrolein when "coordinated" with a proton (Figure 1-23).[82]

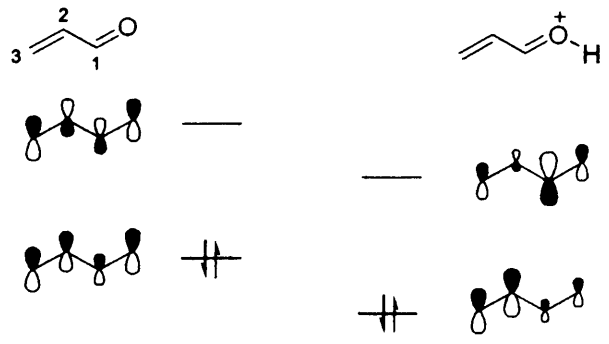


Figure 1-23.

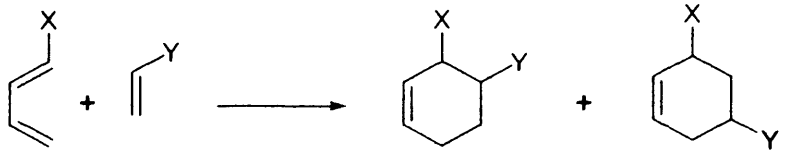
From the model in Figure 1-23 it appears that regioselectivity is enhanced because of the increased polarisation of the molecular orbital between carbon 1 and 2,

meanwhile the exo/endo selectivity is a result of an increased secondary orbital interaction that can be attributed to the increased orbital coefficient in the carbonyl part of the molecule.[88, 89]

Finally, catalysis by Brønsted acids,[90] Brønsted bases[91] and radicals[92] has found application in some special Diels-Alder reactions.

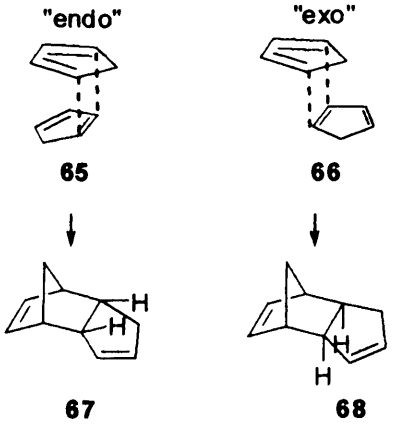
1.10.4 Stereochemistry of Diels Alder reactions.

When dienes or dienophiles are substituted as in Scheme 1-10, two different regioisomers that differ only in the relative orientation of the two substituents are possible.



Scheme 1-10.

Other than regioselectivity, Diels-Alder reactions can give two different stereoisomers, depending on which side of the diene is attacked by the dienophile. Without a catalyst the less stable *endo* adduct is formed preferentially (Alder *endo rule)*. Scheme 1-11 represents the two patterns for the formation of the two adducts.



Scheme 1-11.

Frontier molecular orbital theory also explains this anomalous behaviour with secondary bonding interactions that are present in the *endo* transition state (TS) and absent in the *exo* TS as indicated, for the dimerization of the cyclopentadiene in Figure 1-24.

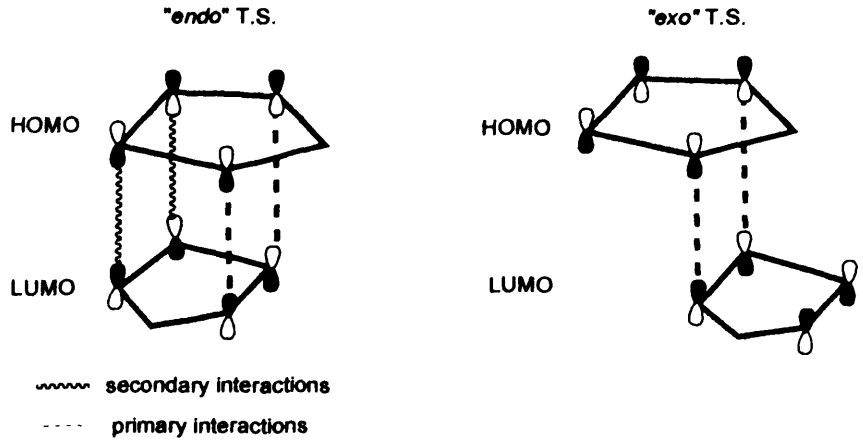
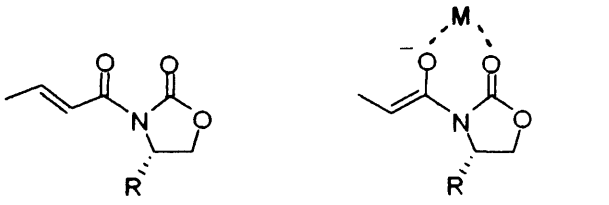


Figure 1-24.

1.10.5 Asymmetric Diels-Alder.

An exciting field of asymmetric organic synthesis is occupied by the asymmetric Diels-Alder reaction which has received great interest from a vast number of research groups who design chiral dienes, dienophiles and also Lewis acid catalysts and excellent diastereo- or enantio-selectivities have been achieved in each of these areas. An interesting aspect of this topic has been developed by Evans.[93] Compounds like α,β-unsaturated-N-acyloxazolidinones **69**, resembling enolate **70** [94] derived from the same scaffold, could in fact give Diels-Alder adducts with high stereoselectivity both alone or with the aid of a Lewis acid (Figure 1-25). In compound **70** the geometry of the enolate is defined by chelation with the metal ion which controls the rotational degrees of freedom in the substrate making the double bond prochiral. Compound **71,** in which the α,β-unsaturated carbonyl moiety exists principally in the s-*cis* conformation, is more stable than the s-*trans* conformation because of the severe steric interaction existing between the double bond and the oxazolidinone ring shown in conformation **72.** This leads to diastereofacial selectivity in the cycloaddition with cyclopentadiene (Scheme 1-12).

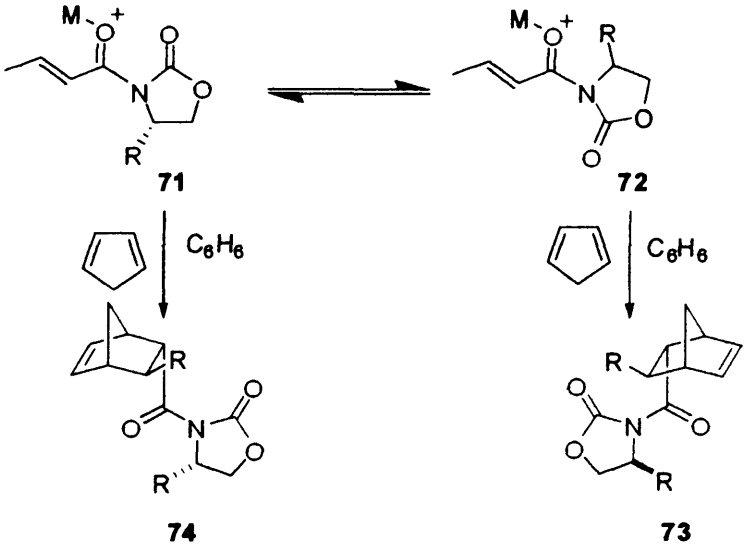


69 **70**

"Evans Dienophile" "Evans enolate"

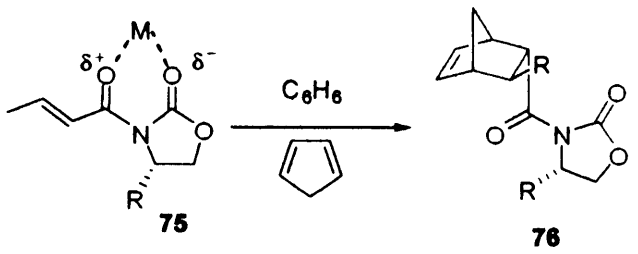
Figure 1-25.

The establishment of a well-defined diastereofacial bias in unsaturated N-acyloxazolidinone **69** depends critically upon the ability to control the various degrees of freedom interconnecting chiral and prochiral centres as illustrated in Scheme 1-12.[95]



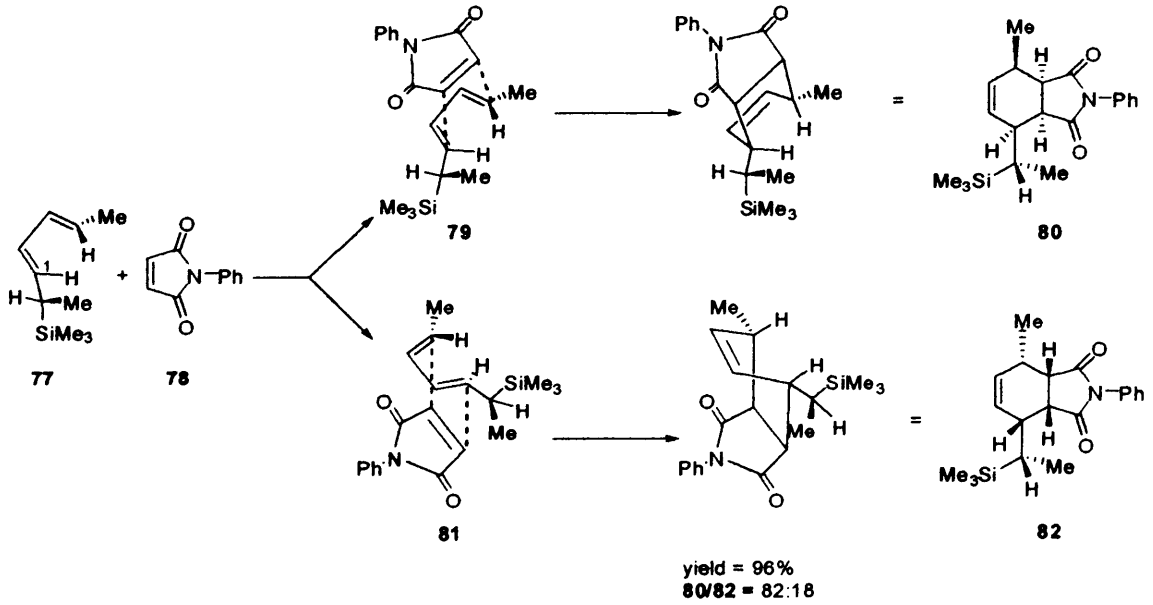
Scheme 1-12.

Improved diastereoselectivity can be obtained by bidentate chelation of the two carbonyl groups present in the oxazolidinone **75** by a Lewis acid promoter, i.e. an aluminium derivative which blocks the molecule in the conformation **75** as illustrated in Scheme 1-13.



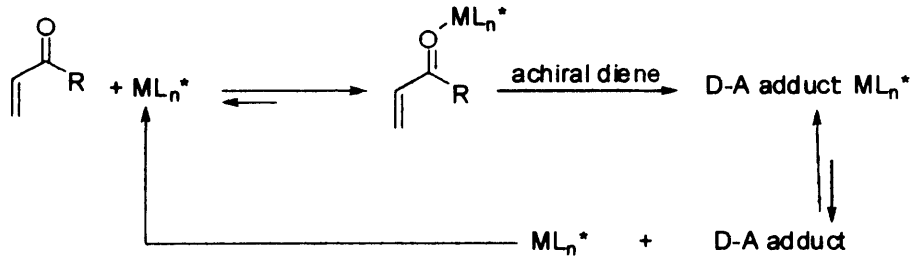
Scheme 1-13.

Other examples of Diels-Alder reactions in which the stereochemistry is influenced by the substrate is the case represented by the Diels-Alder reaction between diene **77**, bearing chiral substituents on C-1 that control the attack of the dienophile on maleimide **78** which takes place via two different transition states. In both of these transition states, the carbon-silicon bond is *anti* with respect to the developing C-C bond and the major diastereoisomer results from the transition state **79** in which the methyl group occupies the outside position and the hydrogen the inside position.[96] It is important to note that the chiral centre on the diene makes the two faces of the double bond diastereotopic and one of these is attacked preferentially.

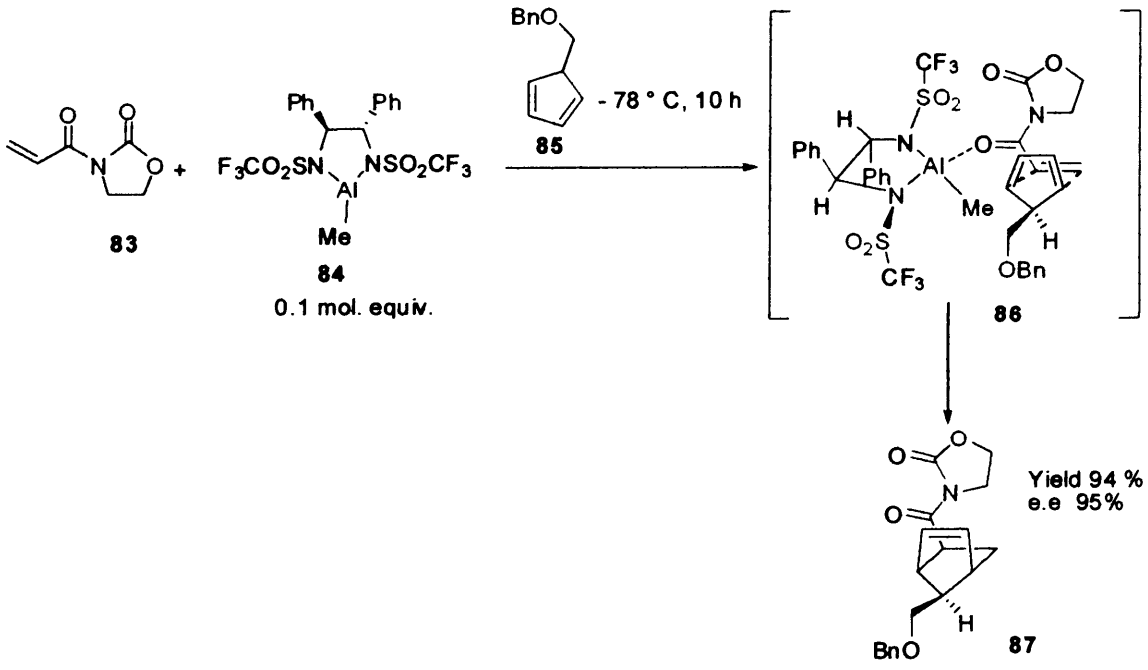


Scheme 1-14.

Diels-Alder reactions can be accomplished with α,β-unsaturated carbonyl compounds which are made chiral by complexation with chiral Lewis acids (Scheme 1-15). An application of this strategy has been provided by Corey. [97] The enantiopure imidoaluminium alkyl **84** was used as a chiral Lewis acid in the reaction between the cyclopentadiene derivate **85** and compound **83**. After complexation, the two faces of the double bond become diastereotopic, therefore, compound **85** can attack the double bond from the less hindered face leading to a Diels-Alder adduct in high enantiopurity (Scheme 1-16).



Scheme 1-15.



Scheme 1-16.

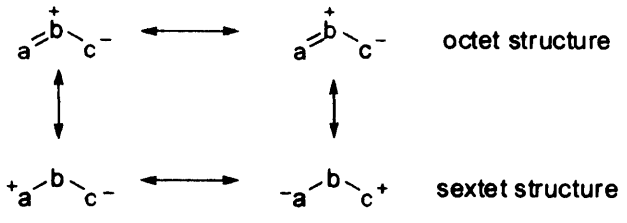
1.11 1,3 Dipolar cycloaddition.

After the Diels Alder reaction, the second most important cycloaddition reaction is probably the 1,3 dipolar cycloaddition, which is currently used in organic chemistry for the synthesis of molecules of fundamental importance for both academia and industry. The first example of a 1,3-dipolar reaction was from Buchner, who discovered that methyl diazoacetate reacts with α,β-unsaturated esters such as methyl acrylate to give pyrazole.[98]

A 1,3 dipolar molecule has a sequence of three atoms, **a-b-c**, of which **a** has a sextet of electrons in the outer shell and **c** an octet with at least one unshared pair. It follows that it is impossible to write resonance structures for these species without incorporating charges. 1,3 dipoles can be divided in two types: the allyl anion type and the propargyl/allenyl anion type as shown in Figure 1-26. The former is characterized by four electrons distributed in three parallel p_z orbitals perpendicular to the plane of the dipole and by its bent structure. In this case, the central atom is sp^2 hybridized and it is possible to draw two kinds of resonance forms in which the molecule has the complete octet, with two other structures in which only the terminal atoms of the dipole have an electron sextet. The allenyl/propargyl structure is characterised by a linear disposition of the atoms and by the fact that it has an extra π orbital located in an orthogonal plane.

A few example of 1,3 dipoles of both species are collected in Table 1-1.[99] These compounds are normally unstable and except for a few examples (nitrones and most azides) it is necessary to generate the dipole *in situ* from the parent compound.

Allyl anion type 1,3 dipole



Propargyl / allenyl anion type 1,3 dipole

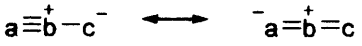


Figure 1-26: Structure of 1,3 dipoles

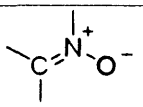
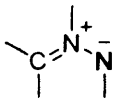
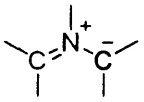
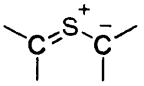
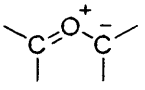
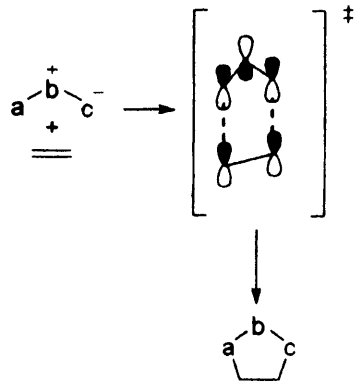
$A\equiv\overset{+}{B}-\overset{-}{C}$		$A=\overset{+}{B}-C^{-}$	
$N\equiv\overset{+}{N}-\overset{-}{N}-$	Azides		nitrones
$N\equiv\overset{+}{N}-\overset{-}{C}<$	Diazo compounds		Azomethine imides
$-C\equiv\overset{+}{N}-O^{-}$	Nitrile oxide		Azomethine ylides
$-C\equiv\overset{+}{N}-\overset{-}{N}-$	Nitrile imides		Thiocarbonyl ylides
$-C\equiv\overset{+}{N}-\overset{-}{C}<$	Nitrile ylides		Carbonyl ylides

Table 1-2.

Compounds which can react with 1,3-dipole are called dipolarophiles and they are characterised by the presence of unsaturated functional groups such as C≡C, C≡N, C=C, C=N, C=O and C=S. Because these molecules contain 2π electrons, the reaction with a 1,3-dipole is also classified as a $[{}_{\pi}4_s + {}_{\pi}2_s]$ reaction according to the Woodward and Hoffmann rules.[100] The notation implies that both molecules react suprafacially,

in the sense that the new bonds are formed on the same side of a π-bond, as indicated in Scheme 1-17.

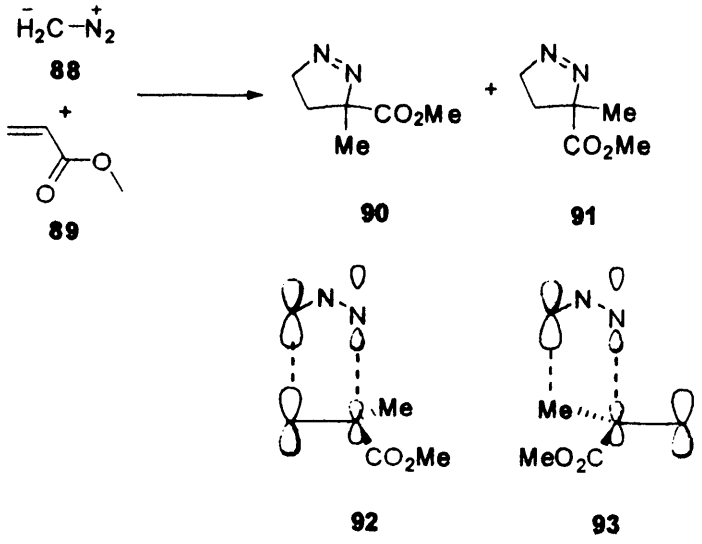


Scheme 1-17.

According to Sustman, 1,3-dipolar cycloadditions are classified in three types depending on which interactions between the FMO are important in the reaction: in so called type I the dominant interaction is $HOMO_{dipole}$-$LUMO_{alkene}$, in type II, because the FMOs have more or less the same energy, both HOMO-LUMO interactions are important and finally, in type III, the dominant interaction is $HOMO_{alkene}$ - $LUMO_{dipole}$.[101]

1.11.1 Selectivity in 1,3 Dipolar cycloadditions.

These reactions can, in theory, give a mixture of isomers but, fortunately, in practice this is not the case and most of such reactions have good regio- and stereo-selectivity. Electronic effects are most responsible for the observed selectivity, although steric interactions could change the fate of the reaction stereochemistry. The addition of diazomethane **88** to methyl acrylate **89** is taken as an example: in principle two regioisomers **90** and **91** are possible (Scheme 1-18), but because the interactions between the FMO in the transition state leading to compound **90** is much stronger than in **91** (due to the interaction between orbitals with the same coefficient), only regioisomer **90** is observed in the reaction.[80]

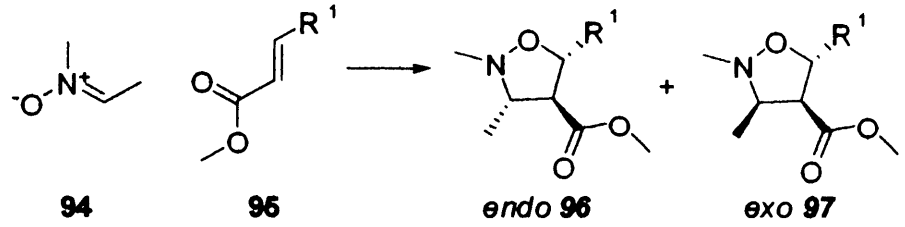


Scheme 1-18.

One interesting feature of the dipolar cycloaddition is that the stereochemistry of the dipolarophiles used as starting material is conserved in the cycloadduct. This means that a *trans* dipolarophile will retain its stereochemistry also in the cycloadduct. This constitutes evidence in favour of the concerted mechanism. Both reactivity and selectivity can always be improved or modified by changing the relative energies of the FMO and the molecular orbital coefficient of the reacting atoms of both the dipole and dipolarophile. Lewis acids are one of the most powerful instruments used by organic chemists for this purpose. In fact, coordination of a Lewis acid to a dipole or to a dipolarophile (α,β-unsaturated carbonyl compounds) changes, as in the case of the Diels-Alder reaction, both the energies and coefficients of the species present in the reaction.

1,3-dipolar cycloadditions are one of the most powerful tools for the stereospecific creation of chiral centres in organic molecules. The attack of the dipole on the double bond in the dipolarophiles is always stereospecifically *syn*, and the geometry of the substituents on the final product is identical to the one on the starting alkene. Furthermore, if the alkene itself contains a chiral centre (the same is valid if the dipole has a chiral centre on it), the approach toward one of the faces of the alkene is preferred leading to a diastereoselective reaction. When dipoles such as nitrones react with an alkene, diastereoisomers are formed and so called *endo/exo* diastereoselectivity is observed (Scheme 1-19).[102] Also, in this case, the *endo* isomer

is favoured because of the secondary bonding interaction in the corresponding transition state is more stable than the *exo* form.



Scheme 1-19.

1.11.2 Nitrones.

Because most dipoles are unstable they cannot be isolated as a pure compound and they must be generated *in situ* and then trapped with an appropriate alkene or dipolarophile. Nitrones receive a lot of attention in 1,3 dipolar cycloadditions because they are stable, often crystalline and isolable compounds. In asymmetric synthesis *via* dipolar reactions, nitrones are especially important because it is possible to generate at least three new chiral centres in the molecule. Furthermore, adducts such as isoxazolidines are important building blocks for organic synthesis because they can be transformed into β-aminoalcohols which are important building block for the synthesis of many natural products (Figure 1-27).

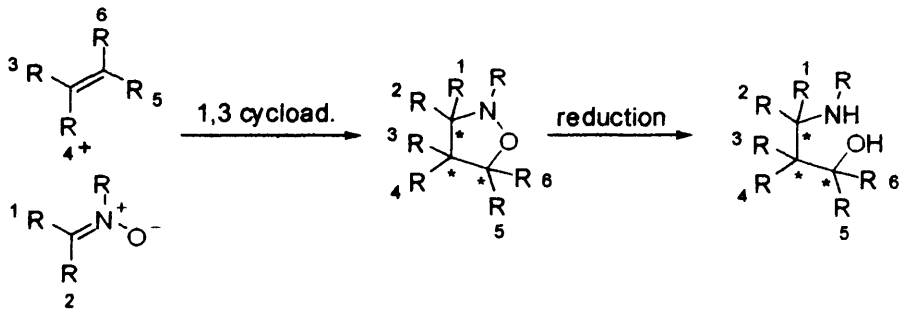
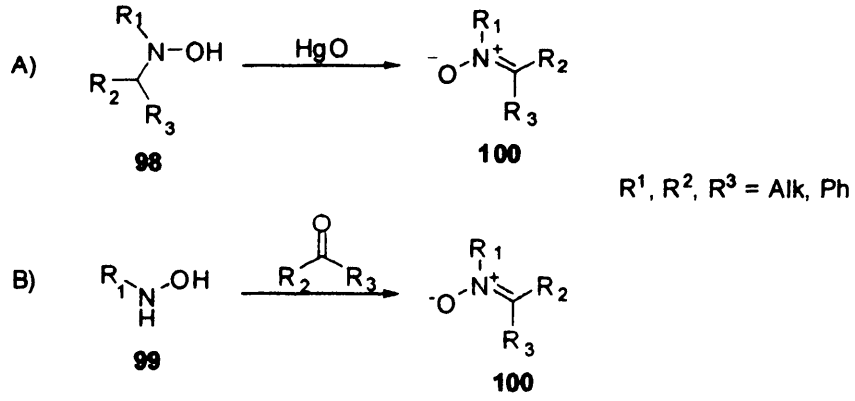


Figure 1-27.

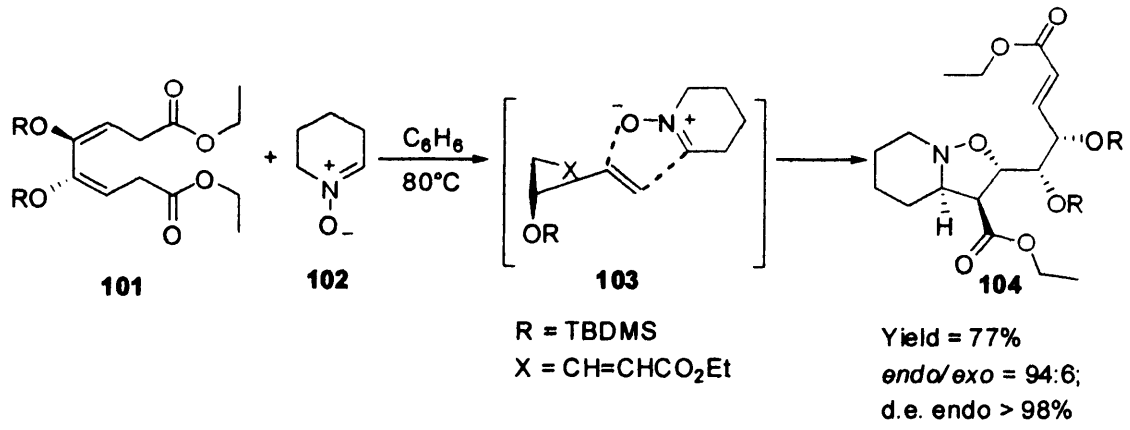
Nitrones **100** can be generated by two methods indicated in Scheme 1-20: oxidation of N,N di-substituted hydroxylamine **98** (path A) or by condensation of N-alkyl hydroxylamine **99** with carbonyl compounds (path B).



Scheme 1-20.

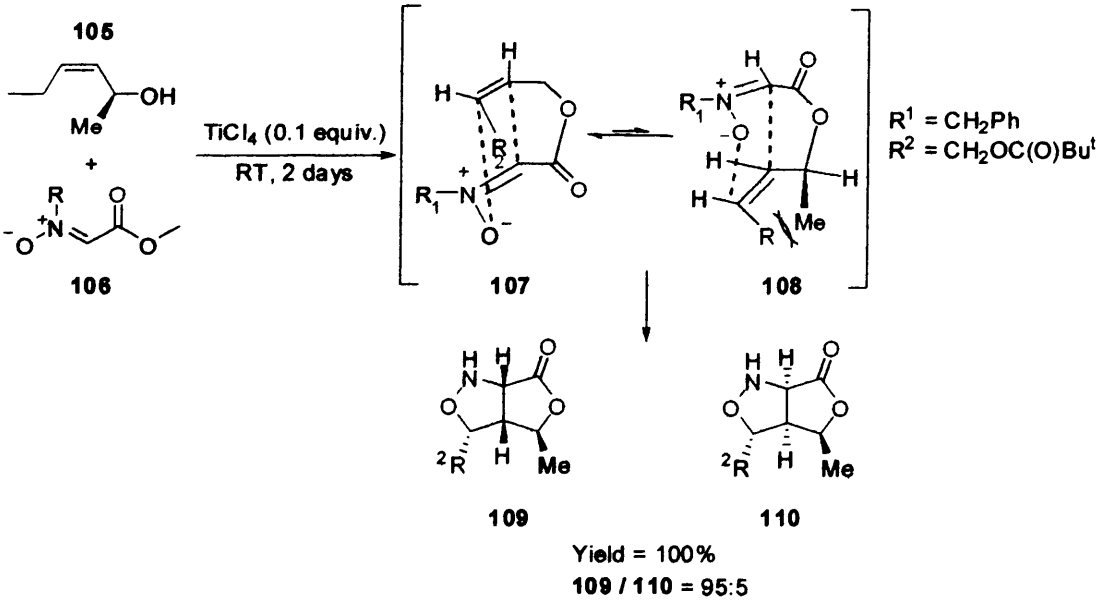
1.11.3 Asymmetric 1,3-dipolar cycloadditions.

Asymmetric 1,3-dipolar cycloadditions normally involve both a chiral dipole and/or a chiral alkene.[102, 103] However, since 1994, numerous catalytic enantioselective modifications of this reaction have been developed and reviewed.[104] Despite the great development of catalytic asymmetric hetero Diels-Alder reactions, metal-catalysed dipolar cycloaddition has received major attention only recently. One of the first examples to appear in the literature was Kanemasa[105] in 1992, in which the effect of several Lewis acids on the reaction between a nitrone and an α,β-unsaturated alkene was studied. It was shown that rate enhancement and an improvement of the *endo/ exo* ratio was possible with the aid of a Lewis acid, although stoichiometric amounts were necessary for good results. Saito and co-workers[106] have used C_2-symmetrical alkenes **101** derived from tartaric acid as controllers in discriminating the two faces of the dipole achieving excellent *endo/exo* diastereoselectivity as outlined in Scheme 1-21.



Scheme 1-21.

Diastereoselective intramolecular cycloadditions of nitrones are also useful for constructing nitrogen-containing cyclic structures as in the case of cycloaddition of nitrone **106** with chiral allylic alcohol **105** (Scheme 1-22). It is clear that the steric interaction (allylic 1,3-strain)[107] occurring between the methyl group and the ester moiety R_2 is responsible for the instability of the transition state **108** and of the shift of the equilibrium toward transition state **107** which leads to the major diastereoisomer **109** with excellent diastereoselectivity.



Scheme 1-22.

1.12 Epoxidation reactions.

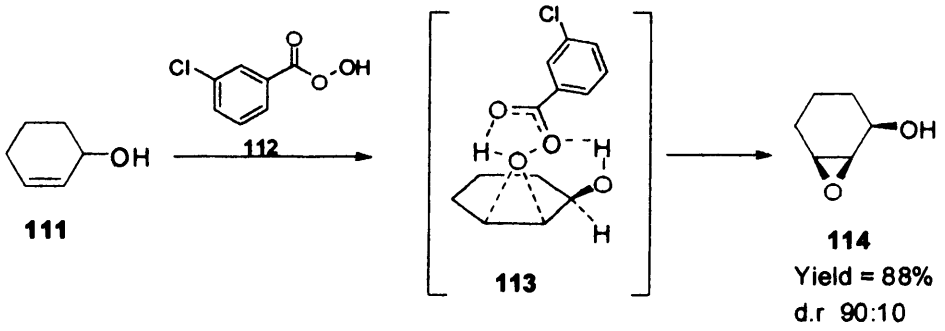
Epoxides or oxiranes are an important class of functional groups that are present in several natural products such as triptolide and epothilones which include epoxide units as essential structural moieties for their biological activity. Moreover, epoxides are believed to be the key intermediates in the biosynthesis of many natural products. They are also important building blocks in organic synthesis and so the development of efficient epoxidation methods continues to receive considerable attention.

Double bonds can be epoxidized with any of a number of peracids of which m-chloroperbenzoic acid has been the most often used. The reaction involves the one-step transfer of electrophilic oxygen from the peracid to olefins (Scheme 1-23). Because of the electrophilic nature of the reagent, substituents that increase electron density on the double bond increase the rate of the epoxidation, which is particularly fast for tetraalkyl olefins. Electron withdrawing substituents on the peracid act in the same direction, in fact trifluoroperacetic[108] acid and 3, 5-dinitroperoxybenzoic acid[109] are particularly reactive examples.

Scheme 1-23.

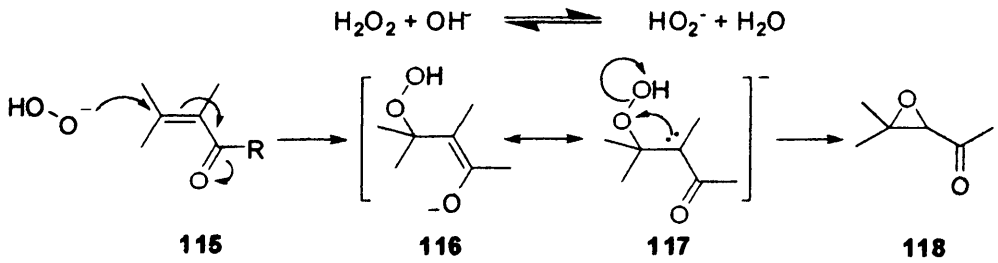
An important feature of this reaction is its stereospecificity, i.e. *trans* double bonds give *trans* epoxides and *cis* olefin *cis* epoxides. Further evidence for this mechanism is the second order kinetics and that the reaction readily takes place in non-polar solvents where formation of ions is inhibited.[110] In some cases the stereochemistry is modified by functional groups present in proximity to the double bond. A typical example is the epoxidation of allylic alcohols **111**. The epoxidation occurs on the same side of the hydroxyl group, probably because in the transition state **113** there is some coordination (by hydrogen bonding) between the peracid and the hydroxyl group which control the stereochemistry of the reaction (Scheme 1-24).[111] A

conjugated double bond reacts with the peracid but the reaction is slower in comparison to the corresponding olefins, because the conjugation makes the diene less nucleophilic. In fact, α,β-unsaturated ketones do not react with peracids although a few exceptions are known.[112]



Scheme 1-24.

Olefins deactivated towards peracid are epoxidized with hydrogen peroxide in alkaline media. An early attempt to epoxidize simple α,β-unsaturated aldehydes and ketones was reported by Weitz and Scheffer.[113] In these substrates, like for example **115** the olefinic double bond is activated by the carbonyl group towards nucleophilic addition (Michael-type mechanism) of the peroxy anion generated from hydrogen peroxide and alkaline hydroxide[114, 115] (Scheme 1-25).



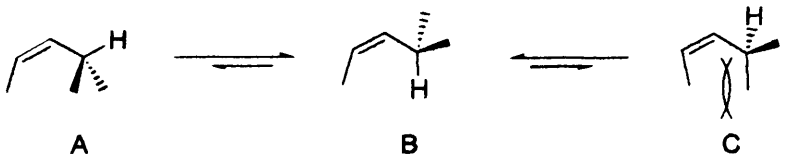
Scheme 1-25.

Epoxidation of α,β-unsaturated carboxylic acids are known,[116] and it is also possible to prepare oxiranes from α,β-unsaturated esters, amides, and sulfones employing t-BuOOH and an alkyllithium base in THF.[117] Finally, epoxides can be produced by

treatment of olefins with oxygen or alkyl peroxide in the presence of a transition-metal complex as a catalyst.[118]

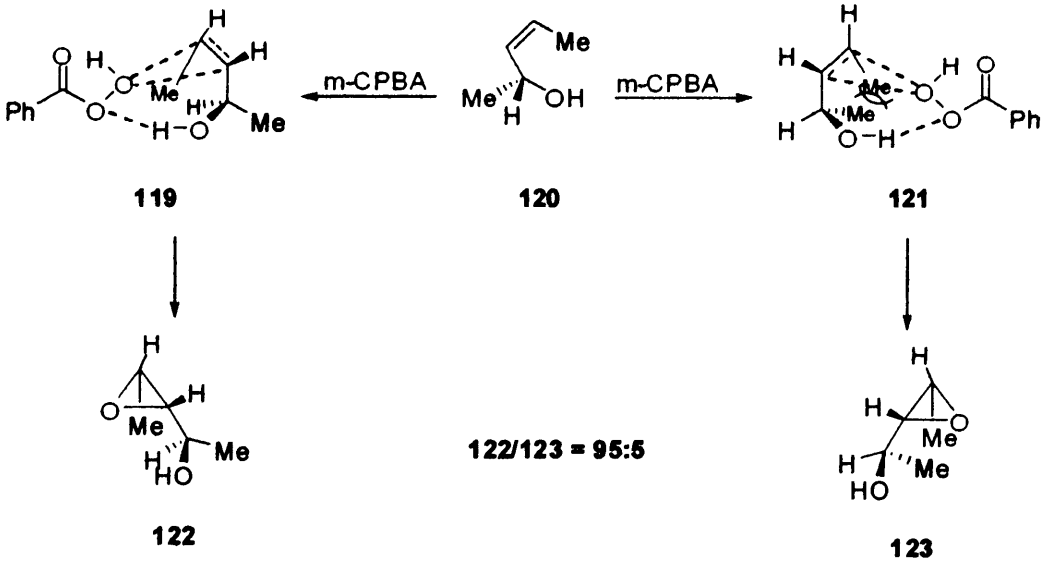
1.12.1 Asymmetric Epoxidation.

Epoxidation holds a venerable place in the history of asymmetric synthesis. Probably the most famous method is the one developed by Sharpless in the early 1980's for the epoxidation of allylic alcohols.[119] In order to achieve diastereoselectivity upon addition to a double bond present in an acyclic molecule, it is necessary to restrict the conformational freedom of the molecule. $A_{1,3}$-strain[120] is the steric strain associated with some substituted allyl systems. Minimization of $A_{1,3}$-strain can be an important factor in limiting the conformational freedom af an allyl system, thus increasing the likehood of diastereoselectivity in the attack on the double bond. In a Z-configured allyl system such as that in Scheme 1-20, conformation (B) is much preferred over (A) and (C), largely as a result of the diminished steric interaction between 1,3-methyl groups.



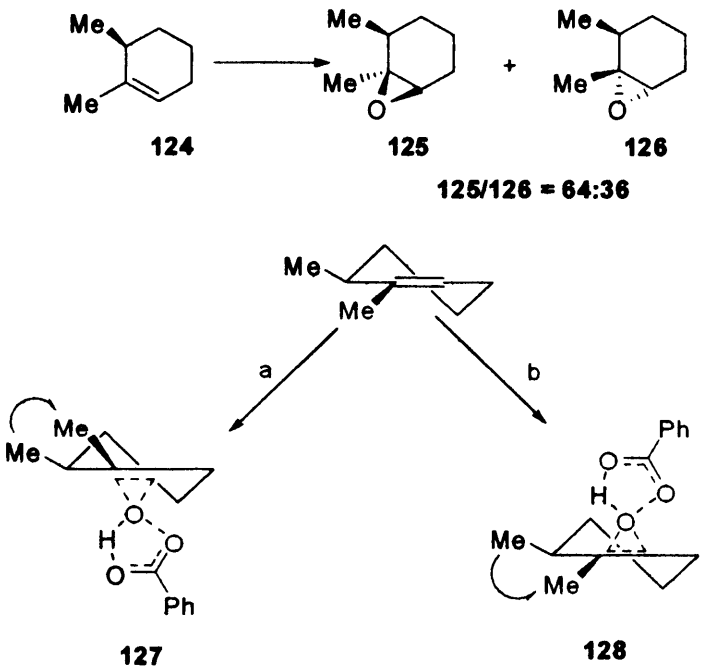
Scheme 1-26

An important feature of this concept is shown in the epoxidation of allylic alcohols **120** by means of *m*-chloroperbenzoic acid (*m*-CPBA) (Scheme 1-27).[121] Diastereoselectivity is higher because the steric interaction between the two methyl groups makes transition state **121** less stable than transition state **119** in which there is not such interaction. As a consequence the major diastereoisomer **122** is formed preferentially.



Scheme 1-27.

In cyclic compounds the conformational degrees of freedom are less than for their respective acyclic counterparts so control of the diastereoselectivity by steric interactions between the substrate and reagent should be more favourable. In the case of the epoxidation of 2,3-dimethyl cyclohexene **124**, the steric interaction between the two methyl groups in the transition state is responsible for the formation of one diastereoisomer over the other (Scheme 1-28). In the transition state **127**, the steric interaction between the two methyl groups increases as the hybridisation at the carbon changes from sp^2 to sp^3 during the reaction, disfavouring the formation of isomer **126**. Meanwhile, in the transition state **128**, the two methyl groups diminish their steric interaction, favouring the formation of diastereoisomer **125**. In this case, it was assumed that the 3-methyl group offers only a small steric impediment to the approach of the oxidant and the cyclohexene reacts when it is in its half-chair conformation with the methyl group in a pseudo–equatorial position.[122]

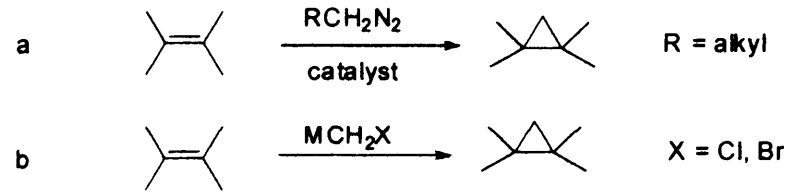


Scheme 1-28.

Other important methods for the asymmetric epoxidation of olefins, based on chiral ligands/metal peroxide systems have been developed by Jackson and co-workers.[123] Further, Ender and co-workers discovered that E-α,β-unsaturated ketones can be epoxidized in an asymmetric fashion using stoichiometric quantities of diethyl zinc and chiral alcohols under an oxygen atmosphere.[124]

1.13 Cyclopropanation reactions.

The smallest aliphatic ring existing in nature is a three-membered ring and is present in a wide range of natural products. Moreover, cyclopropanes have received a lot of attention as versatile synthetic intermediates for the synthesis of more functionalised cycloalkanes[125] and acyclic compounds.[126] From an academic point of view, this kind of compound is useful for testing particular bonding features.[127] Although there are several methods for the synthesis of cyclopropanes from olefins, two major systems have been developed: (a) decomposition of diazo compounds assisted by transition metal complexes, (b) reactions with metal-carbenoid species (Scheme 1-29).



Scheme 1-29.

1.13.1 Transition metal-catalyzed decomposition of diazoalkanes

Cyclopropanation by decomposition of diazocompounds (path a, Scheme 1-29), has been investigated by an extensive amount of research.[128] Several diazoalkanes have been used as synthetic tools for cyclopropanation and some examples are depicted in Figure 1-28.

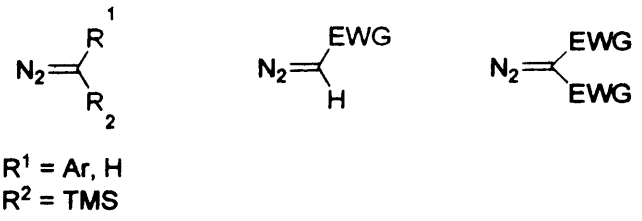
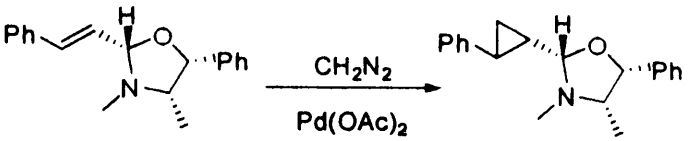


Figure 1-28.

The first and most studied diazoalkane used in cyclopropanation studies is diazomethane (CH_2N_2) together with the more stable and less dangerous counterparts ($TMSCHN_2$)[129] and ($PhCHN_2$).[130] In the literature, there are a huge number of examples of decomposition of diazomethane catalysed by metal salts[131] and from these it appears that the most active are palladium complexes, for example $Pd_2(dba)_3$.[132] Chiral auxiliaries have been used for the cyclopropanation of acyclic double bonds by diazomethane decomposition and shown to be very effective, as demonstrated in the cyclopropanation of cinnamaldehyde with diazomethane and palladium acetate (Scheme 1-30).[133]

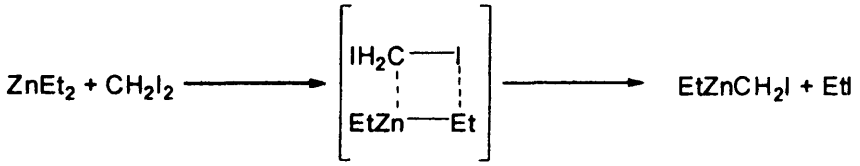


129 **130**

Scheme 1-30.

1.13.2 Halomethyl-metal-mediated cyclopropanation

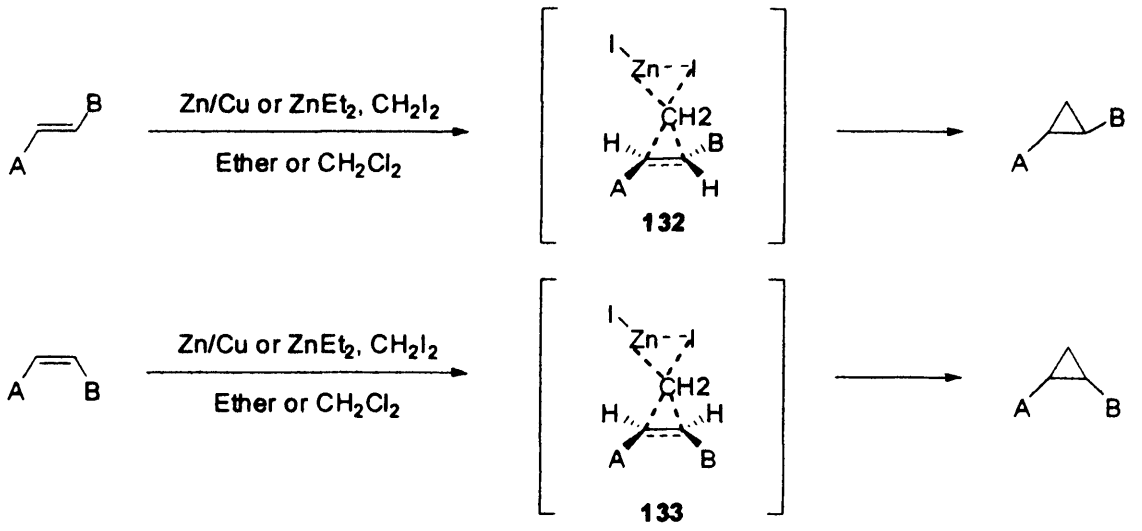
The observation by Emschwiller[134] in 1929 and by Simmons and Smith[135] 30 years later that iodomethyl zinc species are capable of stereospecifically transforming alkenes into cyclopropanes opened a new chapter in the book of synthetic organic chemistry. Following Simmons's and Smith's work, many other researchers developed cyclopropanating reagents. Wittig[136] for example, reported an alternative method for the synthesis of active species $IZnCH_2I$, meanwhile Furukawa[137] showed that similar active species could be prepared from $ZnEt_2$ and CH_2I_2. Denmark also discovered that $Zn(CH_2X)_2$ (X = Cl, I), prepared by reacting two equivalents of XCH_2I with one equivalent of $ZnEt_2$, was extremely reactive toward deactivated alkenes.[138, 139] According to the Furukawa protocol, the effective reagent is believed to be generated by a four-centre transition structure **131** resembling a methatesis reaction (Scheme 1-31).



131

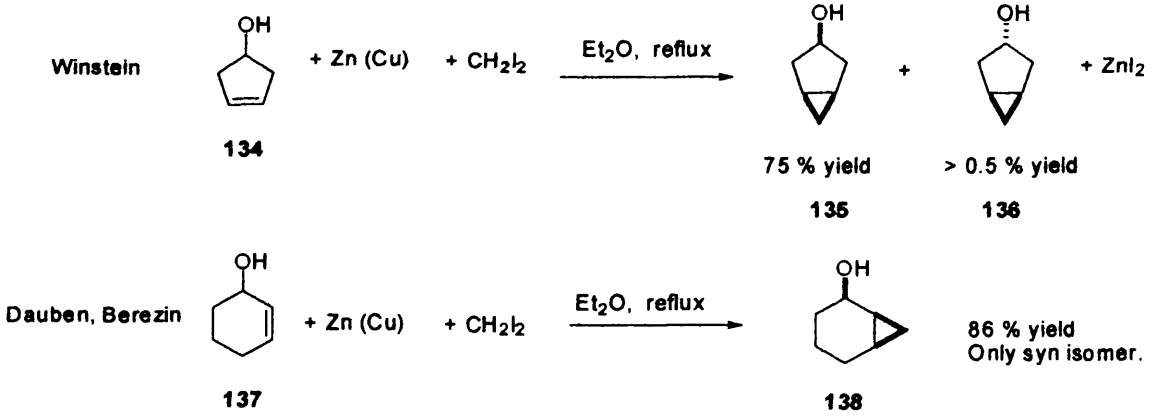
Scheme 1-31.

Mechanistically, the cyclopropanation reaction is a stereospecific, concerted, transfer of a methylene group from the organometallic reagent to a double bond (Scheme 1-32).[140]



Scheme 1-32.

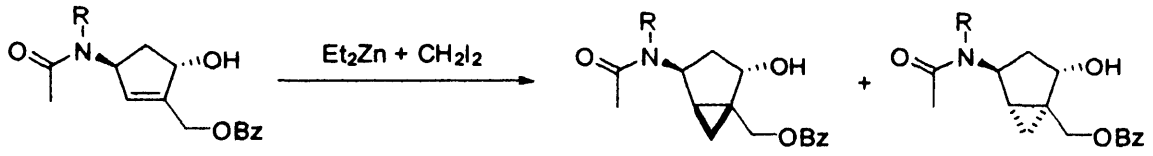
The stereoselective cyclopropanation of acyclic alkenes with a high degree of *syn* selectivity has been achieved when an alcoholic functional group is close to a double bond as reported by Winstein in 1959.[141] This was followed few years later, with more accurate studies, by Dauben and Berezin (Scheme 1-33).[142]



Scheme 1-33.

These results have been explained by coordination of the zinc carbenoid species with the oxygen atom in the transition state, which controls the stereochemistry of the methylene transfer, although there is strong debate over the real nature of this interaction. Carbenoid species can be coordinated not only by oxygen but also by

nitrogen atoms, achieving excellent *syn/anti* selectivity as reported by Russ (Scheme 1-34).[143]

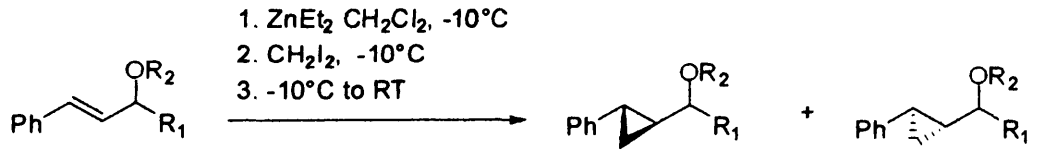


139 R = H
140 R = Bz

141 R = H; 100/0, 50 % yield
142 R = Bz; 0/100, 50 % yield

Scheme 1-34.

Diastereoselective cyclopropanation of allylic ethers employing Furukawa's reagent has been studied extensively by Charette, who evaluated the influence of the nature of the protecting group and of the substituents on the stereoselectivity of these reactions (Scheme 1-35).[144] Increasing the steric hindrance of R_1 led to an inversion of the *syn/anti* ratio (Table 1-3, entry 1-3). However, when the protecting group R_2 became larger the *syn* selectivity decreases dramatically. Comparison between entry 1 vs. 4 (Table 1-3) show that when methyl group is replaced by a benzyl (being R_1 fixed), the *syn* selectivity decrease from 39:61 to 10:90 in favour of *anty* diastereoisomer. Entries 2 vs. 5, and 3 vs. 6 confirm this tendency. The diastereoselectivity shown in Scheme 1-35, could not be rationalized by means of the $A_{1,3}$-strain alone, but it also strictly correlates to the size of the protecting group. This concept is better illustrated when benzyl ethers are replaced with more hindered silyl ether.[145]



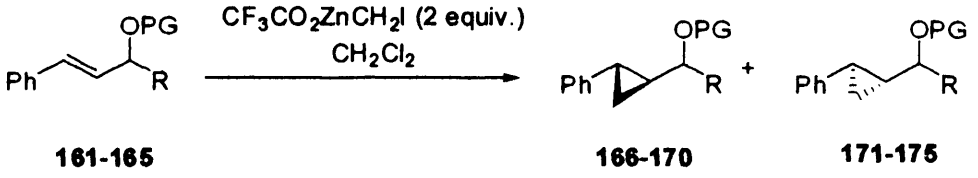
143-148 **149-154** **155-160**

Scheme 1-35.

Entry	Comp.	R^1	R^2	Yield	Products	*syn/anti ratio*
1	**143**	Me	Bn	94	**149/155**	10:90
2	**144**	Et	Bn	97	**150/156**	33:67
3	**145**	i-Pr	Bn	82	**151/157**	95:5
4	**146**	Me	Me	95	**152/158**	39:61
5	**147**	Et	Me	93	**153/159**	77:23
6	**148**	i-pr	Me	94	**154/160**	98:2

Table 1-3.

Scheme 1-36 and Table 1-4, clearly shows that excellent *anti* diastereoselectivity can be achieved protecting the alcohol with bulky silyl protecting groups. In this case the size of the substituents close to the oxygen is not important for the diastereoselectivity.



161-165 **166-170** **171-175**

PG = protecting group

Scheme 1-36.

Entry	Comp.	PG	R	Yield	Products	*syn/ant ratio*
1	**161**	TBDMS	Me	86	**166/171**	2:98
2	**162**	TBDMS	Me	87	**167/172**	1: >99
3	**163**	TIPS	Me	88	**168/173**	1: >99
4	**164**	TES	i-Pr	78	**169/174**	30:70
5	**165**	TBDMS	Et	85	**170/175**	3:97

Table 1-4.

The *anti* diastereoselectivity can be rationalized by saying that the transition state **176** is favoured over transition state **177** (Figure 1-29), assuming that the conformer with eclipsed C-O and C=C bonds is more highly populated when a bulky protecting group (e.g. a silyl group) is present on the alcohol as demonstrated by Gung.[146]

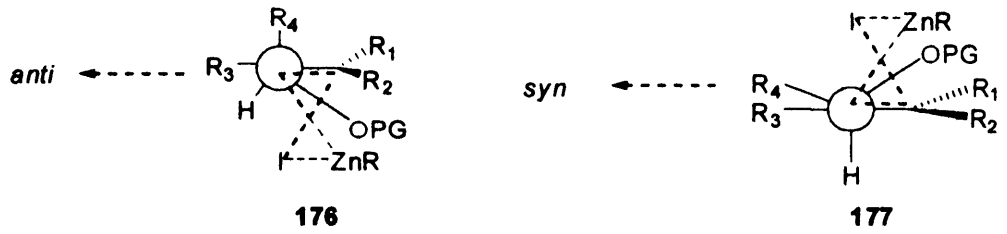
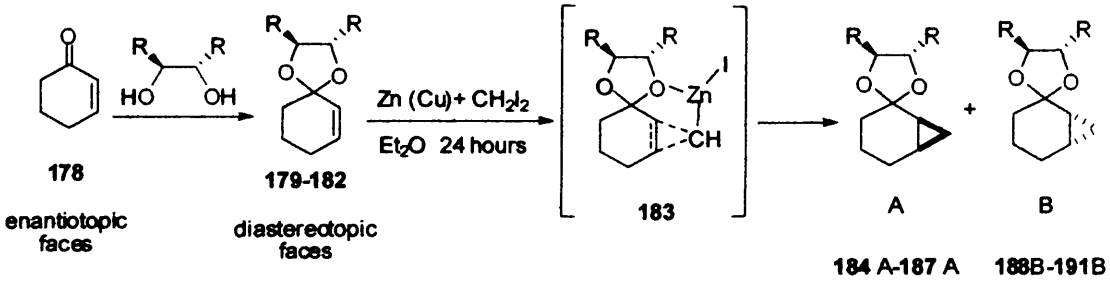


Figure 1-29.

1.13.3 Diastereoselective cyclopropanations.

The discovery of the directing power of oxygen and nitrogen on cyclopropanation reactions suggest that incorporation of these elements into chiral auxiliaries would improve diastereoselectivity.

One of the first uses of chiral auxiliaries in diastereoselective cyclopropanation was reported by Mash[147] who used cyclohexenone chiral ketals for the desymmetrisation of the two faces of the double bond (Scheme 1-37 and Table 1-5).



Scheme 1-37.

Entry	Ketal	R	Yield	Products	*syn/anti ratio*
1	**179**	CO_2CH_3	37	**184/188**	3:2
2	**180**	CH_2OH	50	**185/189**	1:2
3	**181**	CH_3	86	**186/190**	9:1
4	**182**	Ph	90	**187/191**	19:1

Table 1-5.

Other chiral auxiliaries employed successfully in cyclopropanation reactions are chiral allylic ethers, obtained principally by reaction of allylic alcohols with sugars,

those obtained by functionalization of α,β-unsaturated carbonyl compounds. Some examples of both types are represented in Table 1-6.

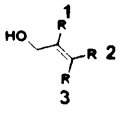
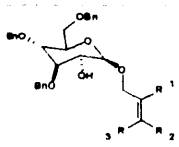
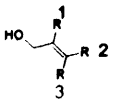
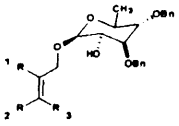
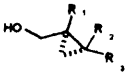
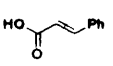
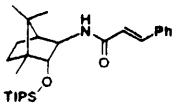
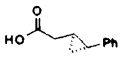
Class	Starting material	Chiral auxiliary	Conditions	Yield (%)	d.s. (%)	Product	Ref.
Allyl ether			Et_2Zn (10 eq.) CH_2I_2 (10 eq.) toluene	> 95	(>98)		148
Allyl ether			Et_2Zn (10 eq.) CH_2I_2 (10 eq.) toluene	> 95	(>98)		148
α,β-unsaturated carbonyl			Et_2Zn (3 eq.) CH_2I_2 (5 eq.) CH_2Cl_2, L-(+)-DET (0.5 eq.)	62	99		149

Table 1-6.

Summary.

Although a significant amount of research has been conducted within the area of atropisomers over the past few years, concerning with their applications in asymmetric synthesis, additional investigations are required to further advance this area. As discussed in this introduction there are several asymmetric reaction namely Diels-Alder, 1,3-dipolar cycloaddition, epoxydation and cyclopropanation, which have successfully been used as a model for the development of new chiral auxiliaries and chiral ligands. It was then reasonable to use these well known reactions as a starting point for testing the potential applications of the biquinazolinones as chiral auxiliary. Promising results have, in fact been obtained previously in our group in the diastereoselective epoxydation of unsaturated biquinazolinones. Optimization of these studies and application of the biquinazolinones scaffold to other asymmetric reactions seemed then a reasonable route to follow. Biquinazolinone scaffold could in principle exert strong secondary interactions by means of the nitrogen atoms, with molecules like dienes and and 1,3-dipoles which coupled with the stereochemistry around the chiral axis could lead to the achievement of high diastereoselectivity. Moreover coordination of carbenoids species by the nitrogens in the quinazolinone scaffold can be used to achieve good stereoselectivities in cyclopropanation reactions.

REFERENCES.

[1] a) M. P. Coogan, D. E. Hibbs, E. Smart, *J. Chem. Soc., Chem. Commun.*, 1999, 1991; b) M. P. Coogan and S. C. Passey, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2060; c) M. P. Coogan, unpublished work.

[2] L. Pasteur, *Lecture at the Societe' Chimique de France*, 20-01-1860.

[3] W. H.Perkin, W. J, Pope and O. Wallach, *J. Chem. Soc., 1909, **95**, 1789.*

[4] G.H. Christie, J. H. Kenner, *J. Chem. Soc.*, 1922, **121**, 614.

[5] R. Kunn, "Molekulare Asymmetrie", in Freudenberg K. ed., *Stereochemie*, Deutike, Leipzig, Germany, 1933, 803.

[6] M. Oki, *Top. Stereochem.*1983, **14**, 1.

[7] E.L Eliel, S. H.Wilen, *Stereochemistry of Organic Compounds*, 1994, Wiley.

[8] M. Isaka, M. Tanticharoen, P. Kongsaeree, Y. Thebtaranonth, *J. Org. Chem.* 2001, **66**, 4803.

[9] J.S. Lomas, J.E. Dubois, *J. Org. Chem.*, 1976, **41**, 3033.

[10] M. Oki, *The Stereochemistry of Rotational Isomers*, Springer, New York, 1993.

[11] X. Fu, M.B. Hossain, F.J. Schmitz, D. van der Helm, *J. Org. Chem.*, 1997, **62**, 3810.

[12] H.H Sun, C.J. Barrow, R. Cooper, *J. Nat. Prod.*, 1995, **58**, 1575.

[13] R. Adams, T.A Geissmann, J.D. Edwards, Gossypol, a pigment of cottonseeds, *Chem. Rev.*, 1990, **60**, 555.

[14] Y.W. Yu, *J. Ethnopharmacol.*, 1987, **20**, 65.

[15] L.S. Erukhimov, *Treatment of bladder tumours by gossypol and ionol in combination with surgical intervention*, Vopr. Onkol, 1966, **14**, 29.

[16] P.Bushnow, M. Reidberg, J.Winfield, S.Lemke, B. Himpler, T. Coyle, gossypol treatment in recurrent adult malign gliomas, *Proc. Ann. Meet. Am. Soc. Clin. Oncol.*, 1995, **14**, A282.

[17] U. Berg, H. Bladh, *Helv. Chim. Acta.*, 1999, **82**, 323.

[18] J.H.Rupald, T. Paulis, A. Janowsky, H.E. Smith, *J. Med. Chem.*,1989,**32**, 2261; D.C. Remy, K.E. Rittle, C.A. Huttle, P.S. Anderson, B. Arison, E. Enghehardt, R. Hirshmann, B.V. Clineschidt, V.J. Lotti, P.R. Bunting, R.J. Ballantine, N.L.Papp, L.Flataker, J.J.Witoslawski, *J. Med.Chem*, 1977, **270**, 30611.

[19] W.M. Dai, K.K.Y. Yeung, J.T. Liu, Y. Zhang and I.D. Williams, *Org. Lett.*, 2002, **9**, 1615.

[20] R.Rios, C.Jimeno, P.J. Carrol, P.J. Walsh, *J. Am. Chem. Soc.*2002, **124**, 10272.

[21] a)M.A. Cuyegkeng, A. Mannschreck, *Chem. Ber.*, 1987, **120**, 803; b) W.H. Pirkle, C.J. Welch and A.J. Zych, *J. Chromatogr.*, 1993, **648**, 101; c) Q. Cass, A. Degani, M.E. Tiritan, S.A. Matlin, D.P. Curran, A. Balog, *Chirality*, 1997, **9**, 109; d) K. Kondeo, H. Fukita, T. Suzuki, Y. Marakami, *Tetrahedron Lett.*, 1999, **40**, 5577.

[22] C.J. Bungard, J.C. Morris, *Org. Lett.*, 2002, **4**, 631.

[23] S. Thayumanavan, P. Beak, and D. P. Curran, *Tetrahedron Lett.*, 1996, **37**, 2899.

[24] H. Koide, M. Uemura, *Chem. Commun., 1998, 2483;* H. Koide, T. Hata and M. Uemura, *J. Org. Chem.*, 2002, **67**, 1929.

[25] D. Becker, L.R. Hughes, R.A. Raphael, *J. Chem. Soc., Perkin Trans. 1* 1977, 1674.

[26] D.L. Boger, S. Miyazaki, S.K. Kim, J.H. Wu, S.L. Castle, O. Loiseleur, Q. Jin, *J. Am. Chem. Soc.*,1999, **121**, 10004.

[27] D.A. Evans, M.R. Woods, W. Trotter, T.I. Richardson, J.C. Barrow, J.L. Katz, *Angew. Chem. Int. Ed.*, 1998, **37**, 2700.

[28] J. Clayden, L.W. Lai, *Angew. Chem. Int. Ed.*, 1999, **17**, 2556.

[29] J. Clayden, L.W.Lai, *Tetrahedron Lett.*, 2001, **42**, 3163.

[30] a)R. Adams, R.M. Joyce, *J. Am. Chem Soc.*, 1938, **60**, 1491; b) J. Vorkapic-Furac, M. Mintas, F. Kastaner, A. Mannschreck, *J. Heterocycl. Chem.*, 1992, **29**, 327.

[31] G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wholfarth, W. Lobin, *J. Am. Chem. Soc.*, 2001, **123**, 2703.

[32] M.Takashi, Y. Tanaka, T. Yabusaki, D. Okamura, M.Sakamoto, T. Fusjita, *Tetrahedron Asymmetry,* 2003, **14**, 2503.

[33] D. Jordan, R. Schwartz, M. Picolelli, Presonal Communication, Compound inhibiting this site have been reviewed: H. Sauter, W. Steglich, T. Anke, *Angew. Chem., Int. Ed.*, 999, **38**, 1328.

[34] R.J. Brown, P.P. Castro, D.M.T. Chan, J.P Daub, G.M. Koether, T.P. Selby, PCT Patent Application PubblicationWO98/23156.; T. Ohsumi, T. Hirose, K. Ujihara, R. Matsunga, Patent Application Pubblication WO96/38425.

[35] J.R. Godwin, V.M. Anthony, J.M. Clough, C.R. Godfrey, A.ICIA5504: *A Novel Broad Spectrum – Systemic B-Methoxy-acrylate Fungicide*, Brighton Crop Protection conference Pest and Diseases, 1992, **1**, 403.

[36] M. Avalos, R.Babiano, P. Cintas, F.J. Higes, J.L. Jimenez, J.C. Palacios and G. Silvero, *Tetrahedron Asymmetry,* 1999, **10**, 4071.

[37] Y. Shvo in "*The chemistry of the Hydrazo, Azo, and Azoxy Groups*", Ed. S. Patai Interscience, New York, 1972, part 2.

[38] a) M.J.S. Dewar and W.B. Jennings, *J. Am. Chem. Soc.*, 1969, **91**, 3655; b) M.J.S. Dewar and W.B. Jennings, *J. Am. Chem. Soc.*, 1973, **95**, 1562; c) R.S. Atkinson, B.D: Judkins and B. Patwardhan, *J. Chem. Soc., Perkin Trans.*, 2, 1979, 1490.

[39] M. P. Coogan, S.C. Passey, *J. Chem. Soc., Perkin Trans.2,* 2000, 2060.

[40] J. A. Platts, M. P. Coogan, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1075.

[41] S. M. Verma, R. Prasad, *J. Org. Chem.*, 1973, **38**, 1004.

[42] R.S. Atkinson, P.J. Edwards and G.A. Thomson, *J. Chem. Soc., Perkin Trans.*, 1994, 3209.

[43] R.S. Atkinson, E. Barker, P.J. Edwards and G.A. Thomson, *J. Chem. Soc., Perkin Trans.* 1, 1996, 1047.

[44] R.S.Atkinson, C. K. meads, *Tetrahedron*, 2002, **58**, 1415.

[45] L. Deloux, M. Srebnik, *Chem Rev.*, 1999, **93**, 763.

[46] R. Noyori, I. Tomino, M. Nishizawa, *J. Am. Chem Soc.*, 1979,**101**, 5843.

[47] R. Noyori, I. Tomino, Y. Tanimoto, *J. Am. Chem. Soc.*, 1979,**101**, 3129.

[48] R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.*, 1984,**106**, 6789.

[49] H. Kakei, T. Nemoto, T. Oshima, M. Shibasaki, *Angew. Chem., Int. Ed.*, 2004, **43**, 317.

[50] M.A. M. Capozzi, C. Cardellicchio, F. Naso, V. Rosito, *J. Org. Chem.*, 2002, **67**, 7289.

[51] M.A.M. Capozzi, C. Cardellicchio, G. Fracchiolla, F. Naso, P. Tortorella, *J. Am. Chem. Soc.*,1999, **121**, 4708.

[52] D. Seebach, A.K. Back, R. Imwinkelried, S. Roggio, A. Wonnacott, *Helv. Chim. Acta*, 1987, **70**, 954.

[53] G.E: Keck, D. Krishnamurthy, *Synth. Commun.*, 1996, **26**, 367.

[54] G. Kumaraswamy, M.N.V. Sastry, N. Jena, *Tetrahedron Lett.*, 2001, **42**, 8515.

[55] For a recent review: W.Tang, X. Zhang, *Chem. Rev.*, 2003, **103**, 3029.

[56] T. Saito, T. Yokozawa, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Cat.*, 2001, **343**, 264.

[57] C.P. Casey, G.T. Whiteker, M.G. Melville, L.M. Petrovich, J.A. Gavney, D.R. Powell, *J. Am. Chem. Soc.*, 1992, **114**, 5535.

[58] C.P. Casey, G.T. Whiteker, *Isr. J. Chem.*, 1990, **30**, 299.

[59] J. Clayden, P. Johnson, J.H. Pink, M.Helliwell, *J. Org. Chem.*, 2000, **65**, 7033.

[60] J. Clayden, L. W. Lai, M. Helliwell, *Tetrahedron: Asymmetry*, 2001 **12**, 695.

[61] D.P. Curran, H. Qi, S.J. Geib and N.C. Demello, *J. Am. Chem. Soc.*, 1994, **116**, 3131.

[62] A.D. Hughes, D. A. Price, and N. S. Simpkins, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1295.

[63] O. Kitagawa, H. Izawa, K. Sato, A. Dobashi, T. Taguchi and M. Shiro, *J. Org. Chem.*, 1998, **63**, 2634.

[64] O. Kitagawa, S.-I. Momose, Y. Fushimi, T. Taguchi, *Tetrahedron Lett.*, 1999, **40**, 8827.

[65] T. Bach, J. Schröder, and K. Harms, *Tetrahedron Lett.*, 1999, **40**, 9003.

[66] M. Nakajima, M. Saito, M. Uemura, and S. Hashimoto, *Tetrahedron Lett.*, 2002, **43**, 8827.

[67] A.C. Spivey, D.P. Leese, F. Zhu, S.G. Davey, and R.L. Jarvest, *Tetrahedron*, 2004, **60**, 4513.

[68] For a comprehensive review, see: *Chem. Rev.*, 2000, **100**, 1685; *Molecular Switches*, ed. B. Feringa, Wiley-VCH, Weinheim 2001.

[69] S. Pieraccini, S. Masiero, G.P. Spada, G. Gottarelli, *Chem. Commun.*, 2003, 593.

[70] S. Van Elschoct, T. Verbiest, M. Kauranen, L. Ma, H. Cheng, K. Y. Musick, L. Pu, A. Persoons, *Chem. Phys. Lett.*, 1999, **309**, 315.

[71] M. Barcena, G. Colmenarcjo, M.C. Gutierrez-Alonso, F. Montero, G. Orellana, *Biochem. Biophys. Res. Commun.*, 1995, **214**, 716.

[72] J. Lu, S.-Z. Kang, S.-L. Xu, Q. -D. Zeng, C. Wang, L.-J. Wan, C.-L. Bai, *Chem. Commun.*, 2003, 1498.

[73] K. Töllner, R. Popovitz-Biro, M. Lahav, and D. Milstein, *Science*, 1997, **287**, 2100.

[74] R. Lunkwitz, C. Tschierske, A. Langhoff, F. Gieselmann, P. Zugenmaier, *J. Mater. Chem.*, 1997, **7**, 1713.

[75] O. Diels, K Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98.

[76] R. B. Woodward, R. Hoffmann, *Angew. Chem.*, 1969, **81**, 797.

[77] K. Fukui, *Acc. Chem. Res.*, 1971, **4**, 57.

[78] G. Klopman, *J. Am. Chem. Soc.*, 1968, **90**, 223.

[79] L. Salem, *J. Am. Chem. Soc.*, 1968, **90**, 543 and 553.

[80] I. Fleming. *Frontiers Orbitals and Organic Chemical Reactions*, Wiley-Interscience, 1976.

[81] P. V. Alston, R. M. Ottenbrite, *J. Org. Chem.*, 1975, **40**, 1111.

[82] K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 4094.

[83] N. T. Anh and J. Seyden-Penne, *Tetrahedron*, 1973, **29**, 3259.

[84] P. Yates and P. Eaton, *J. Am. Chem. Soc.*, 1960, **82**, 4436.

[85] J. Sauer, J. Kredel, *Tetrahedron, Lett.*, 1966, **7**, 731.

[86] T. Inukai, T. Kojima, *J. Org. Chem.*, 1966, 31, 1121.

[87] a) H. M. Walbosky, L. Barush, *Tetrahedron*, 1963, **19**, 2333; b) L.M. Tolbert, M.B. Ali, *J. Am. Chem. Soc.*, 1984, **106**, 3806.

[88] J. Motoyoshiya, T. Kameda, M. Asari, M. Miyamoto, S. Narita, H. Aoyama, S. Hayashi, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1845.

[89] M. D. Rozeboom, I. Tegmo-Larsonn, K. N. Houk, *J. Org. Chem.*, 1981, **46**, 2338.

[90] S. Bischoff, F. Kasper, *J. Prakt. Chem.*, 1986, **328**, 449.

[91] O. Riant, H. Hagan, L. Ricard, *Tetrahedron*, 1994, **50**, 4543.

[92] D. J. Bellville, D. D. Wirt, N. L. Bauld, *J. Am. Chem. Soc.*, 1981, **103.**, 718.

[93] a) D. E. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* 1984, **106**, 4261; b) D. E. Evans, K. T. Chapman, J. Bisaha, *Tetrahedron Lett.*, 1984, **25 (37)**, 4071.

[94] D. E. Evans, *Aldrichim. Acta*, 1982, **15**, 23.

[95] D. E. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* 1988, **110**, 1238.

[96] I. Fleming, A. K. Sarkar, M. J. Doyle, P. R. Raithby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2023.

[97] a) E. J. Corey, R. Imwinkelreid, S. Pikul, and Y. B. Xiang, *J. Am. Chem. Soc.*, 1989, **111**, 5493; b) E. J. Corey, N. Imai, and S. Pikul, *Tetrahedron Lett.*, 1991, **32**, 7517.

[98] E. Buchner, M. Fritsch, A. Papendieck, H. Witter, *Liebig. Ann. Chem.*, 1983, **273**, 214.

[99] R. Huisgen in *1,3-Dipolar Cycloaddiction Chemistry;* A. Pawda Ed.; Wiley, New York, 1984; vol. 1

[100] R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry;* Verlag Chemie: Weinheim, 1970.

[101] a) R. Sustmann, *Tetrahedron, Lett.*, 1971, 2717; b) R. Sustmann, *Pure Appl. Chem.*, 1974, **40**, 569.

[102] K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863.

[103] M. Frederickson, *Tetrahedron*, 1997, **53**, 403.

[104] K. V. Gothelf and K. A. Jørgensen, *Chem. Commun.*, 2000, 1449.

[105] S. Kanemasa, T. Uemura, E. Wada, *Tetrahedron Lett.*, 1992, **33**, 7889.

[106] S. Saito, T. Ishikawa, and T. Moriwake, *Synlett*, 1994, 279.

[107] a) R. W. Hoffmann, *Chem. Rev.*, 1989,**89**, 1841; b) A. H. Hoeyda, D. A. Evans, G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307.

[108] Emmons, Pagano, *J. Am. Chem. Soc.*, 1955, **77**, 89.

[109] Rastetter, Richard, Lewis, *J. Org. Chem.*, 1978, **43**, 3163.

[110] Jerry March, *Advance Organic Chemistry*, Wiley Interscience, 1992, p.826 and references therein.

[111] H. B. Henbest, R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958, 1965.

[112] H. Hart, Verma, Wang *J. Org. Chem.*, 1973, **38**, 3418.

[113] E. Weitz and A Scheffer, *Ber.*, 1921, **54B**, 2327.

[114] Bunton, Minkoff *J. Chem. Soc.*, 1949, 665.

[115] Temple, *J. Org. Chem.*, 1970, **35**, 1275.

[116] O. Sakata, T. Kaneda, I. Ogawa, *Chem. Lett.*, 1989, 2053.

[117] Meth-Cohn, M. Moore, E. Taljaard, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2663.

[118] K. A. Jorgensen, *Chem. Rev.*, 1989, **89**, 431.

[119] R. A. Johnson, K. B. Sharpless, *Catalytic Asymmetric Synthesis;* I Ojima., Ed. VCH: New York 1993; Chapter 4.1.

[120] R. W Hoffman, *Chem. Rev.*, 1989, **89**, 1841.

[121] K. B. Sharpless, and T. R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63.

[122] a) P. M. Mc Murry, *Tetrahedron Lett.*, 1971, 1841; b) E. W. Garbish, *J. Am. Chem. Soc.*, 1965, **87**,2932.

[123] C. L. Elston, R. F. W. Jackson, S. J. F. MacDonald and P. J. Murray, *Angew. Chem., Int. Ed. Engl.*, 1999, **36**, 410.

[124] a) D. Eders, J. Zhu, and G. Raabe, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1725; b) D. Eders, J. Zhu, and L. Kramps, *Liebigs Ann.*, 1997, 1101.

[125] a) H. M. L. Davies, *Tetrahedron*, 1993, **49**, 5203; b) J. Mann, *Tetrahedron*, 1986, **42**, 4611.

[126] a) D. C. Nonhebel, *Chem. Soc. Rev.*, 1993, 347; b) H.N.C. Wong, M.–Y. Hon, C.-W. Tse, Y.–C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165.

[127] A. Deijere, *Angew. Chem. Int. Ed.*, 1979, **18**, 809; b) K. B. Wiberg, *Acc. Chem. Res.*, 1996, **29**, 229.

[128] a) H.M.L. Davies, E. Antoulinakis, *Org. React.*, 2001, **57**, 1; b) T. Rovis, D.A. Evans, *Progr. Inorg. Chem.*, 2001, **50**, 1; c) H.Nishiyama, *Enantiomer*, 1999, **4**, 569; d) M. P. Doyle, D. C. Forbes, *Chem. Rev.*, 1998, **98**,911.

[129] G. Maas, J. Seitz, *Tetrahedron, Lett.*, 2001, **42**, 6137.

[130] a) W. J. Seitz, M. M. Hossain, *Tetrahedron, Lett.*, 1994, **35**, 7561; b) V. K. Aggarwal, J. De Vicente, R. V. Bonnert, *Org. Lett.*, 2001, **3**, 2785.

[131] M. Putala, D. A. Lemenovskii, *Russ. Chem. Rev.*, 1994, **63**, 197. b) Y. Li, J.–S., Huang, Z.–Y. Zhou, C.–M. Che, *J. Am. Chem. Soc.*, 2001, **123**, 4843.

[132] A. Nakamura, T. Yoshida, M. Cowie, S. Otsuka, J. A. Ibers, *J. Am. Chem. Soc.*, 1977, **99**, 2108.

[133] a) H. Abadallah, R. Gree, R. Carrie *Tetrahedron Lett.*, 1982, **23**, 503; b) R. Carrie', *Heterocycles*, 1980, **14**, 1529.

[134] G. Emschwiller, *Compt. Rend.*, 1929, **188**, 1555.

[135] a) H. E. Simmons, R.D. Smith, *J. Am. Chem. Soc.*, 1959, **80**, 5323; b) H. E. Simmons, R.D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256.

[136] a) G. Wittig, F. Wingler, *Chem. Ber.*, 1964, **97**, 2146; b) G. Wittig, F. Wingler, F. Justus, *Liebig Ann. Chem.*, 1961, **650**, 18; c) G. Wittig, M. Jeutelat , *Liebig Ann. Chem.*, 1967, **702**, 24.

[137] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.*, 1966, **7**, 3353; b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* 1968, **24**, 53.

[138] S. E. Denmark, J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974.

[139] E. Piers, P. D. Coish, *Synthesis*, 1995, 47.

[140] a) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, C. M. Hoiness, *Org. React.*, 1973, **20**, 1; b) J. Furukawa, N. Kawabata, *Adv. Organomet. Chem.*, 1974, **12**, 83.

[141] S. Winstein, J. Sonnenberg, L.De Vries, *J. Am. Chem. Soc.*, 1959, **81**, 6523.

[142] W. G. Dauben, G. H. Berezin, *J. Am. Chem. Soc.*, 1963, **85**, 468.

[143] P. Russ, A. Ezzitouni, V. E. Marquez, *Tetrahedron Lett.*, 1997, **38**, 723.

[144] A. B. Charette, H. Lebel, A. Gagnon, *Tetrahedron*, 1999, **55**, 8845.

[145] A. B. Charette, M. –C. Lacasse, *Org. Lett.*, 2002, **2**, 3351.

[146] a) B. W. Gung, J. P. Melnick, M. A. Wolf, A. King, *J. Org. Chem.*, 1995, **60**, 1947; b) S. D. Khan, C. F. Pau, A. R. Chamberlin, W. J. Hehre, *J. Am. Chem. Soc.*, 1987, **109**, 650.

[147] E. A. Mash, K. A. Nelson, *J. Am. Chem. Soc.*, 1985, **107**, 8256.

[148] a) A. B.Charette, B.Co^te', J.-F.Marcoux, *J. Am. Chem. Soc.*, 1991, 113, 8166; b) A. B.Charette, B. J. Cote', *J. Am. Chem. Soc.*, 1995, 117, 12721.

[149] K.Tanaka, H.Uno, H.Osuga, H. Suzuki, *Tetrahedron: Asymmetry*, 1994, **5**, 1175.

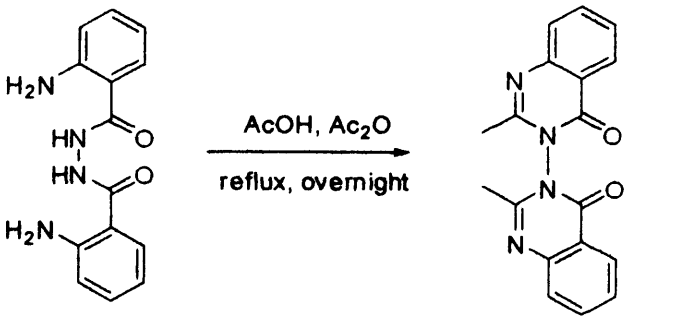
Chapter 2: Synthesis of racemic symmetrical and unsymmetrical bisquinazolinones.

2.1 Introduction.

As stated in Chapter 1, atropisomeric compounds are important in organic chemistry, especially in asymmetric synthesis and asymmetric catalysis. In this chapter the synthesis of symmetrical and unsymmetrical 2,2'-disubstituted-3,3'-biquinazolin-4,4'- diones, as a new class of atropisomeric compounds will be discussed. In 1992 Reddy and Bhavani reported the synthesis of a series of 2,2'-dialkyl-3,3'-biquinazolin-4,4'-diones as a new class of bis azaheterocycles, but in their paper there was no report of any atropisomerism around the *N-N* bond.[1] With the aim of investigating the presence of any evidence of atropisomerism in this class of heterocycles, different 2,2' disubstituted biquinazolinones have been re-synthesized and the results herein reported.

2.2 Synthesis of symmetrical biquinazolinones.

The synthesis of symmetrical 2,2'-dialkyl-3,3'-bisquinazoline-4,4'-diones, accomplished by a modification of the method of Reddy, was achieved by heating at reflux bisanthranoyl hydrazine **192**, previously prepared by the reaction between isatoic anhydride and hydrazine monohydrate, with an excess of carboxylic acid or anhydride.[1,2,3] The synthesis of 2,2'-dimethyl-3,3'-biquinazolin-4,4'-one **193** (in 80% yield) is reported in Scheme 2-1 as example of the method.

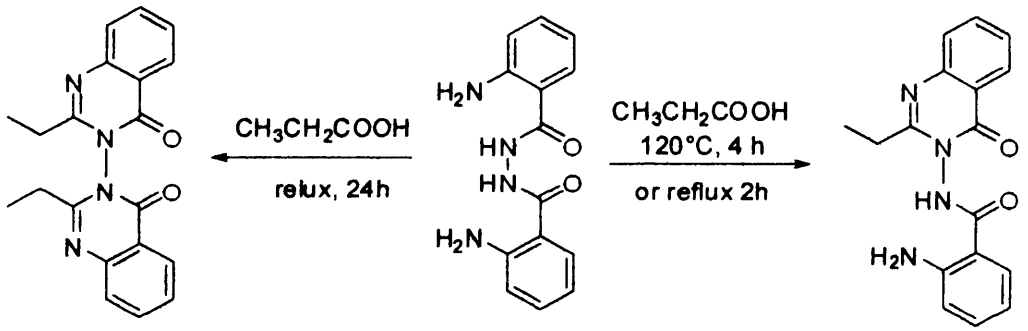


192 **193** Yield = 80%

Scheme 2-1.

This procedure has been applied to the synthesis of the corresponding ethyl derivative using propionic acid. Surprisingly, when compound **192** was heated for two hours, with an excess of propionic acid at 120°C, an unexpected compound, identified as compound **194** was obtained in place of the desired compound **195**. The ^{1}H-NMR analysis of **194** (broad singlet at 5.5 ppm relative to two hydrogens, assigned to NH_2 group) and the APCI mass spectrum at *m/z* 295.3 ($M+H^+$), were both consistent with 2-amino-N-(2-ethyl-4-oxoquinazolin-3(4H)-yl)-benzamide **194** in which only one heterocyclic ring was formed. Further investigations into the reaction conditions showed that prolonged reflux (24h) of bis-anthranoylhydrazine in propionic acid leads to a double cyclization affording the symmetrical biquinazolinone **195**, slightly contaminated with starting material, whereas reflux for only two hours yields, after crystallization, 2-amino-N-(2-ethyl-4-oxoquinazolin-3(4H)-yl)-benzamido **194** as the only product (Scheme 2-2).

From the ^{1}H-NMR analysis it appears that compound **195** is present in racemic form, as indicated by the presence of a complex multiplet at 2.8 ppm, assigned to the diastereotopic methylene group. This means that the *N-N* bond is a chiral axis, but the rotation around it is too fast at room temperature to separate the two isomers.



195 Yield = 75% **192** **194** Yield =65%

Scheme 2-2.

The unexpected synthesis of the 2-amino-*N*-(2-ethyl-4-oxoquinazolin-3(4*H*)-yl) benzamides **194** clearly opened a potential new route for the preparation of unsymmetrical biquinazolinones. In theory it is feasible to form a second ring with different substituents simply by refluxing the molecule with a different acid or anhydride.

2.3 Attempted synthesis of unsymmetrical biquinazolinones by reaction of 3-aminoquinazolinones and isatoic anhydride.

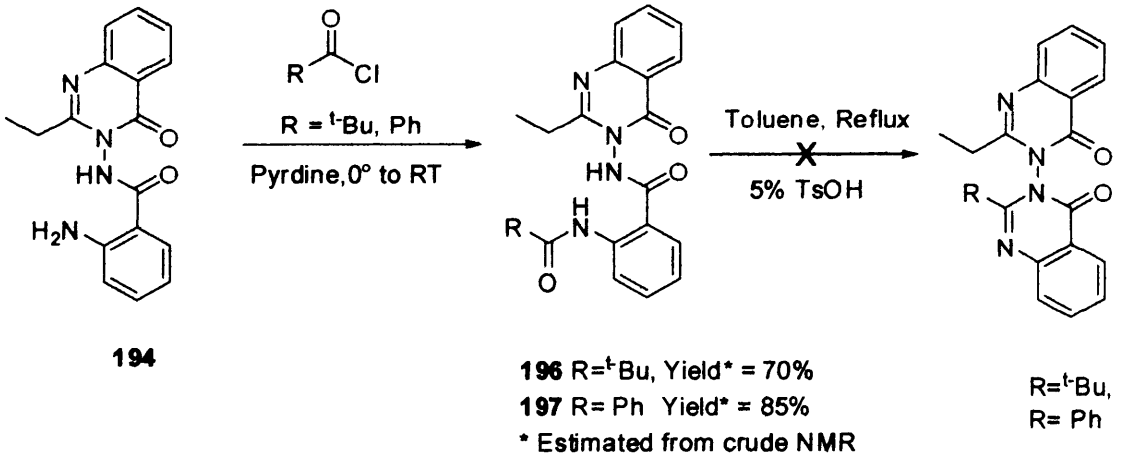
The interest in the synthesis of unsymmetrical biquinazolinones derives from the possibility of tuning the bulkiness of the substituents in order to evaluate the necessary steric requirements for the atropisomerism. It is possible, for example, to insert one reactive functional group in one side of the molecule and leave an unreactive alkyl chain on the other side and evaluate the selectivity in reactions of such molecules in terms of the steric hindrance of the unreactive group. Another advantage due to the presence of different groups onto the 2 and 2' positions is the possibility of evaluating the barrier of rotation around the *N-N* bond in terms of the dimensions of only one group, the other one being fixed. For this reason a rational synthesis of unsymmetrical biquinazolinones was devised.

Taking in account that atropisomerism is due to restricted rotation around a single bond, the introduction of a bulky group such as a *tert*-butyl or a phenyl group on the

second ring would be a reasonable starting point to investigate this molecular characteristic.

The first attempt at the synthesis of unsymmetrical biquinazolines was carried out by treatment of 2-amino-*N*-(2-ethyl-4-oxoquinazolin-3(4*H*)-yl) benzamide **194** with pivaloyl chloride in pyridine at 0 °C. Upon completion of the addition of acid chloride, the reaction mixture was warmed to room temperature and stirred for further two hours.

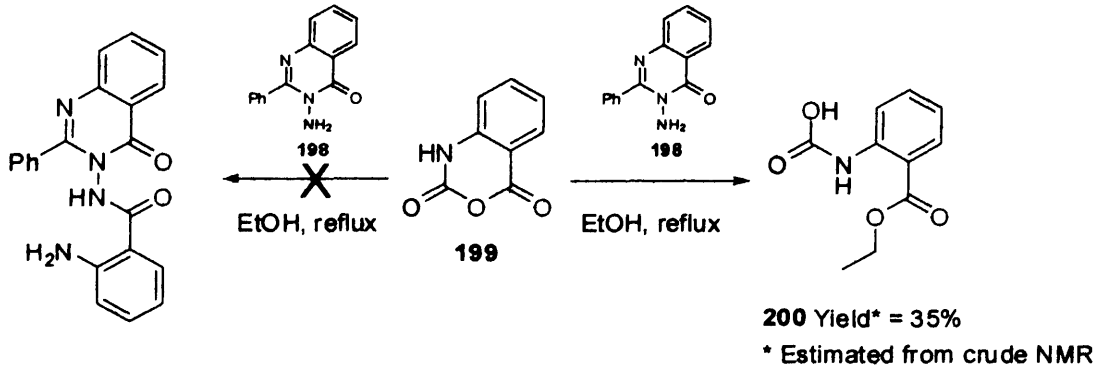
After evaporation of the solvent, the ^{1}H-NMR analysis of the residue showed the presence of the amide **196** as the only product. An attempt to cyclize *N*-(2-ethyl-4-oxoquinazolin-3(4*H*)-yl)-2-pivalamidobenzamide **196** was carried out by refluxing a toluene solution of **196** in the presence of a catalytic amount of *p*-toluene sulfonic acid under Dean and Stark conditions. Unfortunately, cyclization was not observed even after several days at reflux, probably because the bulkiness of the *tert*-butyl group. The same experiment, carried out on the crude benzoyl derivative **197**, unfortunately gave the same results (Scheme 2-3).



Scheme 2-3.

Due to this lack of success at the straightforward formation of compounds like **194** from bisanthranoyl hydrazine, it was decided to follow an alternative approach. A first attempt was to react isatoic anhydride with suitable 3-amino quinazolinones.

The reaction between 2-phenyl-3-aminoquinazolinone **198** (see pag. 62 for the synthesis of this compound) and isatoic anhydride **199,** carried out in refluxing ethanol, gave only compound **200** resulting from the nucleophilic attack of the solvent on the isatoic anhydride, along with unreacted **199**. In this case it appears evident that the solvent is much more nucleophilic than the amino group present on compound **199** (Scheme 2-4).



Scheme 2-4.

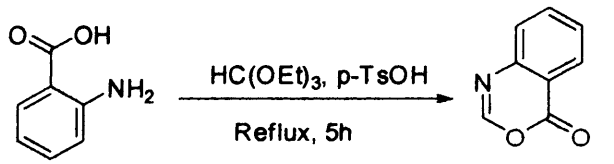
In order to avoid nucleophilic competition from the solvent, ethanol was replaced with toluene, hoping that its inertness and its relatively high boiling point would favour the attack of the amino group present on compound **198** to the carbonyl moiety of the isatoic anhydride **199.** Unfortunately no reaction was observed and only starting materials were recovered. In the light of all these disappointingly results so far obtained for the synthesis of unsymmetrical biquinazolinones a third route was devised.

2.4 Synthesis of unsymmetrical biquinazolinones by reaction of 3-aminoquinazolinones with benzoxazinones.

Synthesis of unsymmetrical *N,N'*-linked quinazolinones could potentially be achieved by condensation of 2-substituted-benz[1,3]oxazin-4-ones with 2-substituted-3-aminoquinazolinones. In the following sections the synthesis of these two halves and their final coupling will be discussed.

2.4.1 Synthesis of benzoxazinones.

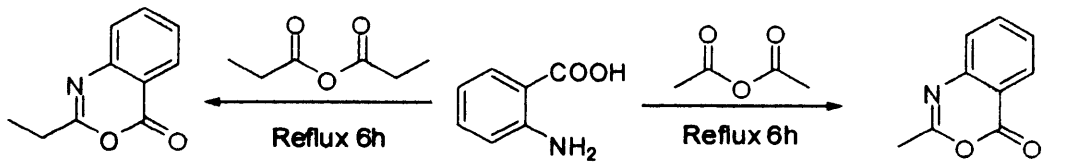
In order to investigate the viability of this synthesis of unsymmetrical biquinazolinones, a range of 2-substituted-4H-3,1-benzoxazin-4-one were prepared following literature procedures.[4] The 2-protio-derivative was synthesized by a modification of the literature method.[5] The first attempt was performed by simply refluxing anthranilic acid **201** with an excess of triethylorthoformate however after evaporation of the solvent only starting material was recovered (Scheme 2-5). Since the mechanism proposed in the literature showed that the reaction was initiated by the protonation of the one of the alkoxy groups of the orthoester, a catalytic amount of *p*-toluene sulfonic acid was added in order to promote the reaction and the mixture refluxed for five hours.[5] Evaporation of the solvent, followed by crystallization of the crude mixture from dry octane, afforded the benzoxazinones **202** in 89 % yields. The product is extremely moisture sensitive and must be stored under vacuum in a desiccator in order to prevent hydrolysis.



201 **202** Yield = 89%

Scheme 2-5.

The 2-methyl and 2-ethyl derivatives **203** and **204** were synthesized by refluxing anthranilic acid **201** with an excess of the corresponding anhydride (Scheme 2-6).[4] After evaporation of the excess anhydride the crude mixture was crystallized from dry ethyl acetate-petroleum ether mixture. The use of dry solvents for the crystallization is required, as they are extremely moisture sensitive. Rapid decomposition of these compounds occurs if they are not stored in a desiccator.

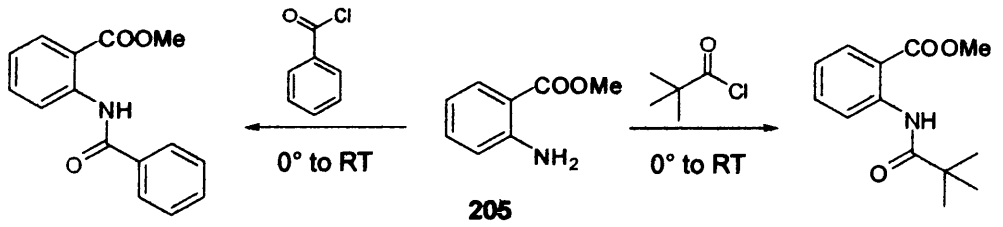


204 Yield = 62% **201** **203** Yield= 52%

Scheme 2-6.

2.4.2 Synthesis of 2-alkyl-3-aminoquinazolinones.

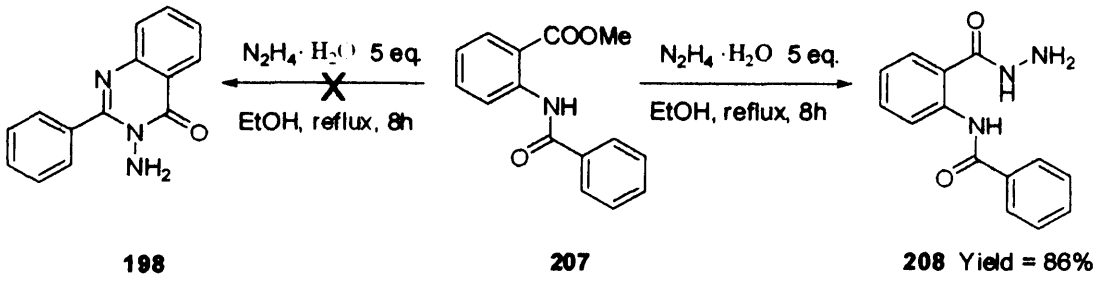
The 2-alkyl-3-aminoquinazolinones, partners of the benzoxazinones in the synthesis of biquinazolinones, were synthesized in three steps, starting from methyl anthranilate **205** following the well-known procedure developed by Atkinson's group.[6] Our initial effort was directed toward the synthesis of the intermediate amides **206** and **207.** This was achieved by stirring an ethereal solution of **205** with pivaloyl chloride or benzoyl chloride for the synthesis of **206** and **207** respectively, at 0° C for one hour and then warming the mixture at room temperature with further stirring for another hour. Filtration of the white precipitate and evaporation of the filtrate gave amide **206** in 92% yields and amide **207** in 84% yields, both after crystallization from ethanol (Scheme 2-7).



207 Yield 84% **205** **206** Yield 92%

Scheme 2-7.

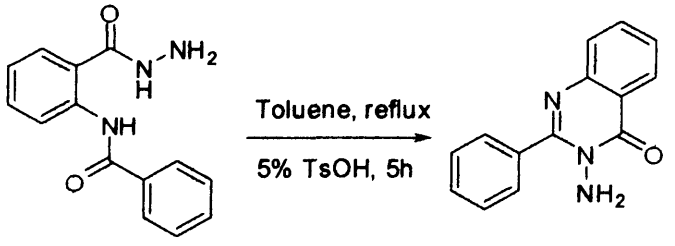
Although it has been reported that 2-phenyl-3-aminoquinazolinones **198** can be obtained from **207** and an ethanolic solution of hydrazine hydrate at reflux, in our hands we were only able to produce hydrazide **208** using these conditions (Scheme 2-8).[7]



198 **207** **208** Yield = 86%

Scheme 2-8.

It is reasonable to believe that, in this case, the temperature has an important role. Atkinson reported that aminoquinazolinones are the only product obtained when an ethanolic solution of anthranilate are heated in a degassed sealed tube at 140-150 °C however, when the temperature is decreased to 120 °C, the yield of quinazolinones is reduced to 24% and hydrazide are the main product.[8] The synthesis of 3-amino-2-phenyl-4-(3*H*)-quinazolinone **198** was achieved by refluxing a toluene solution of compound **208** in the presence of a catalytic amount of *p*-toluene sulfonic acid for five hours, upon cooling a white precipitate was collected and crystallized from ethanol, affording compound **198** in 80% yield (Scheme 2-9).

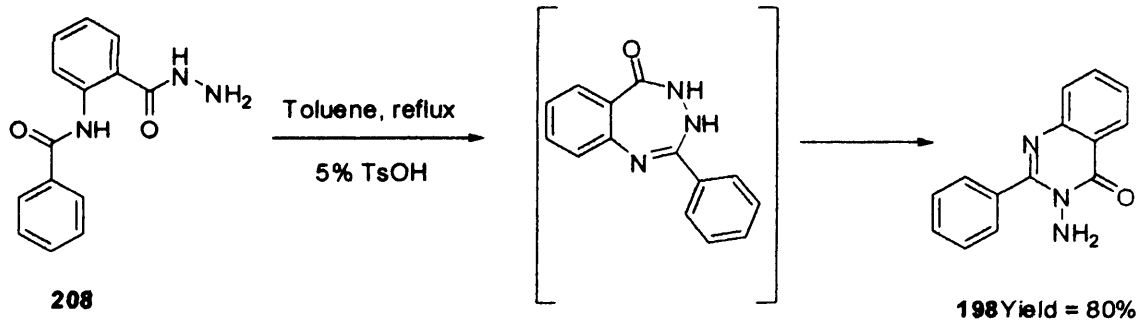


208 **198** Yield = 80%

Scheme 2-9.

It is known from literature, that under these cyclization conditions a possible side product that is, benzotriazepi-5-one can be formed.[9] The infrared spectrum of compound confirmed the absence of the triazepinone due to the absence of the bands at 3310 and 3200 cm^{-1} characteristic of the amide group. Literature data indicates that some benzotriazepinones undergo rearrangement into the respective 3-aminoquinazolinones when treated with *p*-toluene sulfonic acid.[9] It is reasonable to

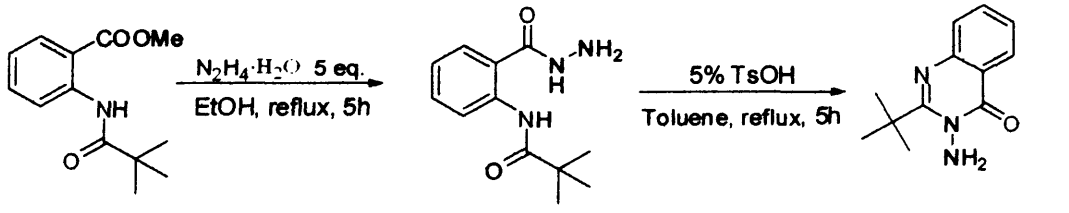
believe that if some triazepinone is formed, it is immediately converted into the corresponding quinazolinone as the conditions of the reaction are acidic (Scheme 2-10).



208 **198** Yield = 80%

Scheme 2-10.

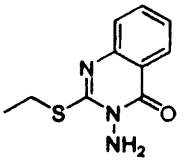
The synthesis of 3-amino-2-*tert*-butyl-quinazolin-4(3*H*)-one **210** was accomplished with the same methodology adopted for the preparation of compound **198** as outlined in Scheme 2-11.



206 **209** Yield = 93% **210** Yield = 80%

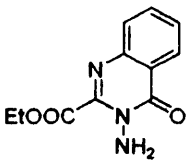
Scheme 2-11.

Other amino-quinazolinones bearing different functional groups, previously synthesized in our and in Atkinson laboratories were also used: 3-amino-2-ethylthio-4(3*H*)-quinazolinone **211**, 3-amino-2-ethoxycarbonyl-3H-quinazolin-4-one[10] **212**, 3-amino-2-(1-methyl-4-phenyl-but-3-enyl)-quinazolin-4-one[11] **213** and finally 3-amino-2-neopentyl-4(3*H*)-quinazolinone[11] **214** (Figure 2-1).



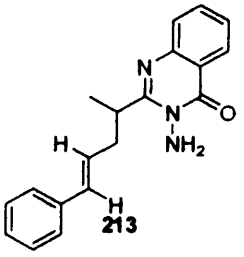
211

3-amino-2-(ethylthio)-4(3*H*)-quinazolinone



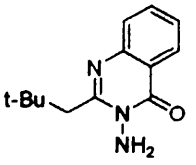
212

3-amino-2-(ethoxycarbonyl)-4(3*H*)-quinazolinone



213

(±)-2-(1-Methyl-4-phenyl)but-3-enyl-3-amino-4(3H)-quinazolinone



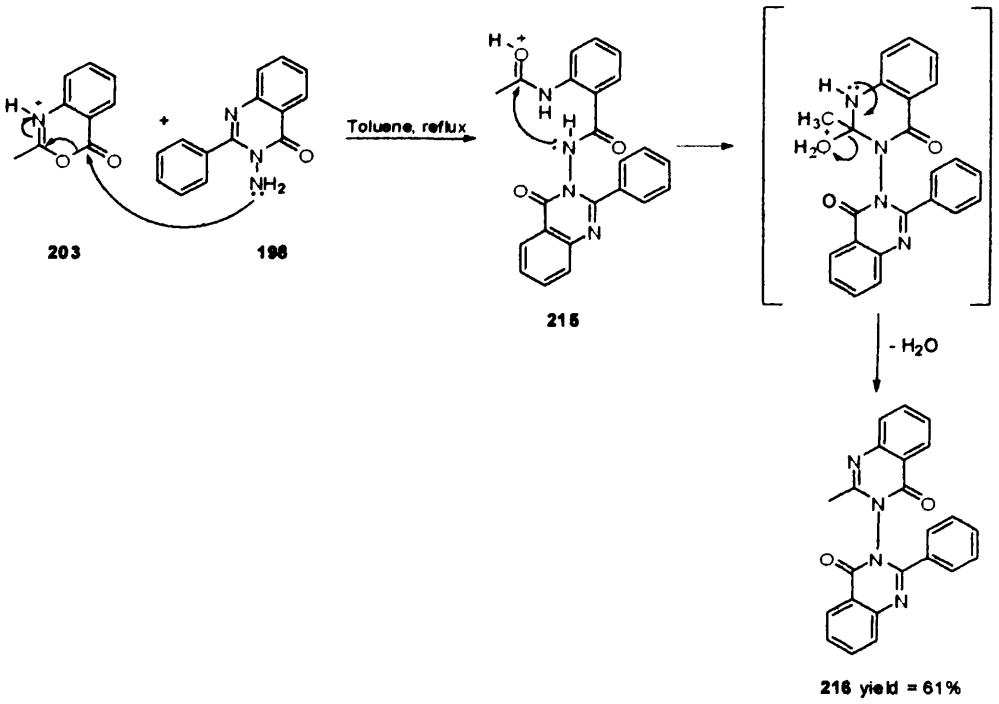
214

3-amino-2-neopentyl-4(3*H*)-quinazolinone

Figure 2-1.

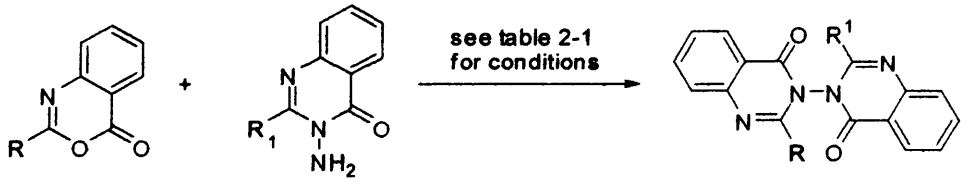
2.4.2 Synthesis of unsymmetrical biquinazolinones via condensation of benzoxazinones and aminoquinazolinones.

Once a series of different benzoxazinones and aminoquinazolinones had been synthesised, their condensation reactions were investigated in order to prepare 3,3'-bisquinazoline-4,4'-diones. In a typical procedure a mixture of 3-aminoquinazolinone and 3[*H*]benzoxazinone (generally 1.1 equivalents) was heated at reflux in toluene in presence of a catalytic amount of *p*-toluene sulfonic acid (usually 5% mol) in a flask equipped with a Dean-Stark trap for water removal. The use of a slight excess of 2-alkylbenzoxazinone was due to the hydrolytic instability of these molecules. It can be reasoned that, mechanistically, the reaction begins with the nucleophilic attack of the 3-aminoquinazolinones on the carbonyl group of the activated benzoxazinone ring with formation of the corresponding intermediate amide **215** as illustrated in the case of 2-phenyl-3-aminoquinazolinone **198** and 2-methyl-benzoxazinones **203** in Scheme 2-12. In the next step dehydration occurs by nucleophilic attack of the nitrogen on the protonated carbonyl of the second amide group with the formation of the second quinazolinone ring of the desired compound **216** (Scheme 2-12).



Scheme 2-12.

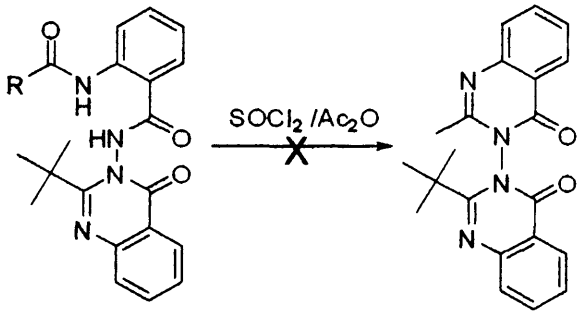
As indicated in Table 2-1, in almost every reaction the desired compound was obtained in moderate to good yield.



Entry	R	R^1	% cat	Time (h)	BiQ	Yield (%)
1	Me (**203**)	Ph (**198**)	5	6	**216**	61
2	Et (**204**)	Ph (**198**)	5	10	**217**	79
3	Et (**204**)	SEt (**211**)	5	10	**218**	44
4	Et (**204**)	COOEt (**212**)	8	24	**219**	51
5	H (**202**)	^{t}Bu (**210**)	8	8	**220**	38
6	H (**202**)	$CH(Me)CH_2CH{=}CHPh$ (**213**)	5	24	**221**	47
7	Me (**203**)	^{t}Bu (**210**)	5	48	-	-
8	Me (**203**)	^{t}Bu (**210**)	5	3 days	-	-
9	Et (**204**)	^{t}Bu (**210**)	5	3 days	-	-

Table 2-1.

From the data reported in Table 2-1 it appears that the steric bulk of the substituent plays an important role in this kind of reaction. In fact, when the 2-*tert*-butyl-3-aminoquinazolinone **210** is condensed with 2-alkyl-benzoxazinone (Table 2-1, entry 7-9), the reaction fails to give the desired 3,3'-biquinazoline-2,2'-diones. However, along with the starting material, the open amides **222** and **223** were detected by ^{1}H-NMR and also confirmed by mass spectrometry (APCI, $[M+H^+]$ = 379.4 and 393.4). Their presence suggests that the initial attack of the aminoquinazolinones to a carbonyl group of the benzoxazinone ring is not prevented by the steric encumbrance of the alkyl group, which becomes relevant only in the following step, when the two heterocyclic partners are forced into proximity to each other. Moreover, the low yields obtained when compound **202** was condensed with other bulky aminoquinazolinones **210** and **213** (Table 2-1, entries 5, 6) seem to confirm this suggestion. However, since relatively bulky groups are very important for the development of atropisomerism, the synthesis of *tert*-butyl biquinazolinones was attempted by using strong dehydrating conditions. With this aim, strong dehydrating agents like thionyl chloride or acetic anhydride were heated at reflux with the amides **222** and **223** but in both cases unreacted compounds, along with decomposition products were observed without any traces of the biquinazolinones (Scheme 2-13).

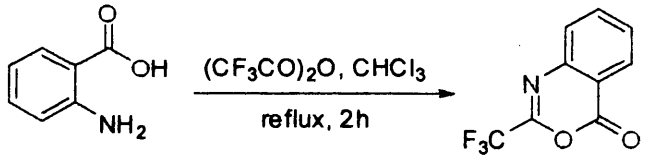


222 R= Me
223 R= Et

R = Me, Et

Scheme 2-13.

It has to be pointed out that the phenyl ring, although a relatively bulky substituent, seems to not affect the reaction, probably because it is able to assume a flat conformation, which still allows the ring closure in the second step of the cyclization. From the data in Table 2-1 it emerges also that the reaction is probably unaffected by electronic factors. The presence of an electron withdrawing substituent on the aminoquinazolinones, like the carboxyethyl group in compound **212** or an electron donating substituent like the thioethyl group in compound **211**, seems not have strong influence on the course of the reaction. When **211** and **212** were reacted with ethyl benzoxazinone **204** comparable, although not excellent, yields were obtained (Table 2-1, entries 3 and 4). In order to test this hypothesis it was decided to synthesize benzoxazinones and aminoquinazolinones bearing a powerful electron withdrawing group such as a trifluoromethyl group. Following a literature procedure, anthranilic acid **201** was treated with three molar excess of trifluoroacetic anhydride in refluxing chloroform for two hours.[12] Evaporation to dryness of the reaction provided 2-trifluoromethyl-4H-3,1-benzoxazin-4-one (**224**) as a white solid in 65 % yield (Scheme 2-14).



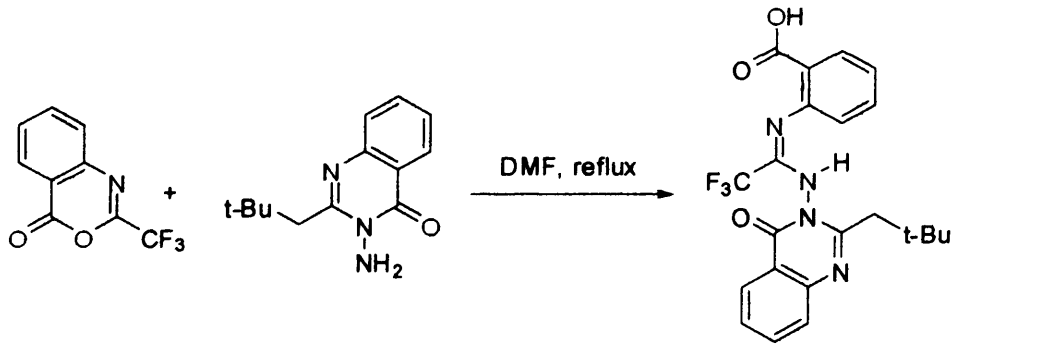
201 **224** Yield: 65 %

Scheme 2-14.

Unfortunately the reaction between 2-trifluoromethyl-4H-3,1-benzoxazin-4-one **224** and compound **214** in refluxing toluene in the presence of a catalytic amount of *p*-toluene sulfonic acid for two days yielded only the starting materials. This result appeared strange considering that compound **224**, among the other members of the series, was expected to be the most reactive toward nucleophilic attack. Moreover, the bulky *tert*-butyl group of compound **214** is remote from the reactive part of the molecule so it would not be expected to significantly interfere in the reaction.

When the reaction was repeated in dimethylformamide (DMF) at reflux in order to enhance the nucleophilicity of the amino group, only a small amount of **225**, together with unreacted starting materials, were detected by ^{1}H-NMR of the crude mixture. A

reasonable explanation of this result is that in the case of trifluoromethyl-4H-3,1-benzoxazin-4-one the nucleophilic attack of the amino group occurred onto the imine carbon of the benzoxazinone which is more prone to accept the incoming electrons from NH_2 than the carbonyl group, leading to the amide **225**. Presumably because the lone pair on the nitrogen is less available due to the strong electron withdrawing effect of the trifluoromethyl group and is therefore is unable to complete the cyclization (Scheme 2-15).



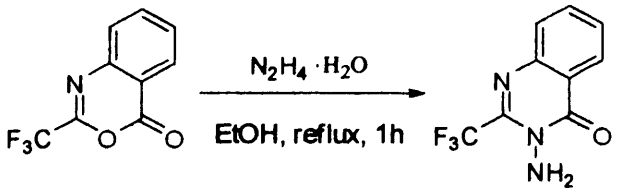
224 **214** **225** Yield* = 8%

* estimated from crude ^{1}H-NMR

Scheme 2-15.

Introduction of the trifluoromethyl group onto the biquinazolinone is, at least in theory, possible by means of 2-trifluoromethyl-3-aminoquinazolinones **226** and the desired 2-substituted benzoxazinones.

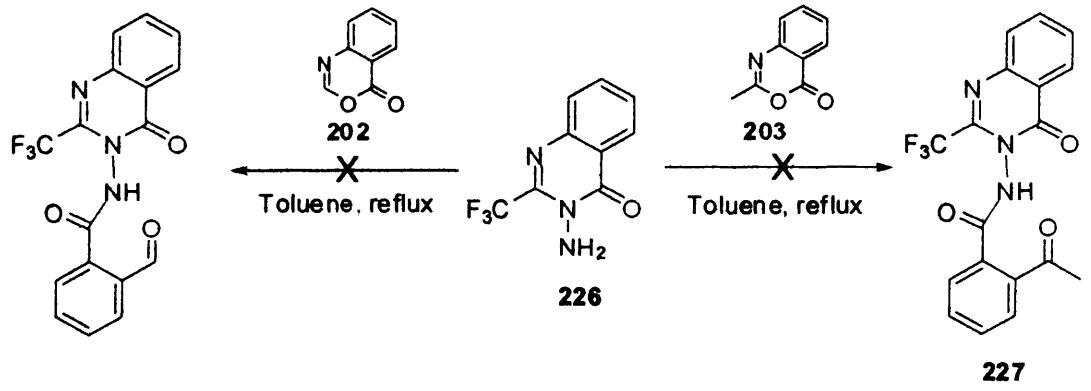
The synthesis of the 3-amino-2-trifluoromethyl-4-(3H)-quinazolinone (**226**) was accomplished simply by refluxing an ethanolic solution of **224** with one equivalent of hydrazine hydrate to yield the desired product **226** as a pale yellow crystals in 55% yield (Scheme 2-16).



224 **226** yield = 55%

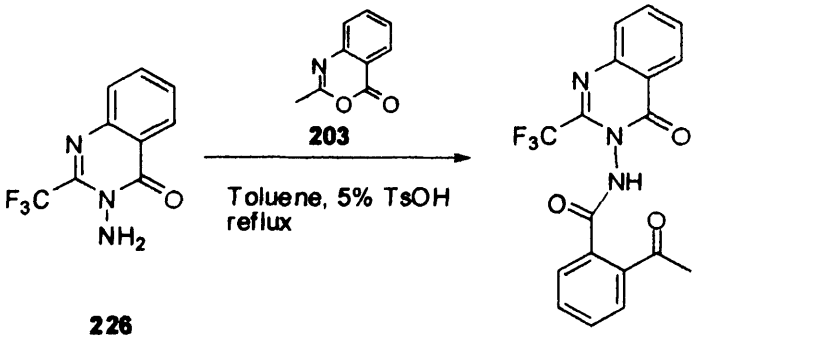
Scheme 2-16.

The condensation reaction between compound **226** and 2-methyl-4H-3,1-benzoxazin-4-one **203** which at least in theory should not have a big steric demand was attempted. In this case, again no reaction occurred and after two days at reflux in toluene without acid catalyst the starting material was recovered completely. The same result was obtained when **226** was reacted with **202** (Scheme 2-17).



Scheme 2-17.

Repeating the reaction between **226** and 2-methyl-benzoxazinone **203** in refluxing toluene with catalytic amount of *p*-toluenesulfonic acid gave only a small amount of amide **227** in about 5% yield (Scheme 2-18). In this case it seems reasonable to believe that the trifluoromethyl group dramatically decreases the nucleophilicity of the amino group of **226,** which is then unable to attack the carbonyl group in the benzoxazinone ring.



Scheme 2-18.

However it cannot be excluded that the steric bulk of the CF_3 group, is also involved. In fact a trifluoromethyl group is almost as large as an isopropyl group as a result of the van der Waals radii (F = 1.35 and H = 1.2 Å). Moreover the fluorine atoms in the trifluoromethyl group repel one another in a more pronounced way and give therefore rise to a large effective radius.[13,14] Hirst and co-workers have found that in the aromatic nucleophilic displacement of 2-trifluoromethyl- and 2-cyano-4-nitrofluoro-benzenes with piperidine and *n*-butyl-amine the CF_3 group bulkiness is responsible for the apparent diminished nucleophilicity of the piperidine compared with the linear primary amine ($k_{pip.}/k_{Bu}$ = 4.5 for 2-CN derivative and $k_{pip.}/k_{Bu}$ = 0.2 for 2-CF_3).[15] However in our case, the small amount of open amide formed when compound **226** is reacted with benzoxazinones **203** or **204** can be taken as an evidence of the predominance of the electronic effect rather then steric one. This is also supported by the fact that 3-amino-2-*tert*-butyl-quinazolinone **210**, in which the electronic effects are negligible, react with **203** leading to the corresponding biquinazolinone **220**.

Summary

In this chapter the synthesis of symmetrical and unsymmetrical biquinazolinones has been presented. Symmetrical biquinazolinones 2,2'-alkyl di-substituted were successfully synthesized, in racemic form from 1,2-bis-(2-aminobenzoyl)hydrazine **192** and carboxylic acids in one step and in good yields. The synthesis of unsymmetrical bis-azaheterocycles was unsuccessfully attempted by cyclization of amides derived from partial cyclization of **192** under several dehydrating conditions. Failure of this method force us to design an alternate synthesis, based on the condensation of 2-substituted 3-aminoquinazolinones and 3[H]benzoxazinones under Dean-Stark conditions. This method has been found to be of general applicability as a large range of functional groups can be incorporated into both starting materials and a wide range of biquinazolinones are then available. It is worthy of note that our method does not require tedious chromatographic purification, with only one or occasionally two crystallizations of the crude reaction mixture being necessary to obtain the pure compounds. Moreover we demonstrate that the reaction is tolerant of a range of heteroatoms and unsaturated functionality and in most cases electronic factors appear not to be important.

However it has to be mention that the synthesis of biquinazolinones failed when bulky substituent or powerful electron-withdrawing groups (such as trifluoromethyl) are present in the benzoxazinone or aminoquinazolinone. In these cases only small amount of open amides were obtained. Furthermore the entire attempts to complete the cyclization of these substrates failed under the conditions used successfully for the other members of the series.

The synthesis of biquinazolinones carrying bulky groups has to be accomplished following another route. One possible approach could be the functionalization of simple hydrocarbon chains (i.e. methyl, ethyl) which are easy to introduce into the biquinazolinone scaffold. This strategy will be discussed in Chapter 5.

In the future more studies towards the cyclization of open amides have to be done. Employment of solvent with higher boiling point, or more polar environment and more powerful dehydrating agent could be a reasonable suggestion for the accomplishment of the target.

REFERENCES.

[1] P. S. N Reddy, A. K. Bhavani, *Indian J. Chem., Sec. B*, 2502, **11**, 740.

[2] K. Nagahara, A. Takada, *Chem. Pharm. Bull.*, 1977, **25**, 2713.

[3] M.P. Coogan, D. E. Hibbs, E. Smart, *J. Chem. Soc., Chem. Commun.*, 1999, 1991; b) M.P. Coogan and S.C. Passey, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2060.

[4] D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, 1948, **14**, 967.

[5] M. S. Khajavi, N. M. Montazari, S. S. Sadat Hosseini, *J. Chem. Research (S)*, 1997, 286.

[6] R. S. Atkinson, M. J. Grimshire, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2407.

[7] A. Arques, P. Molina, A. Soler, *Synthesis*, 1980, 702.

[8] R. S. Atkinson, M. J. Grimshire, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2797.

[9] N. P. Peet, *Synthesis*, 1984, 1065.

[10] T. Gorge, D.V. Metha, and R. Tahilramani, *Ind. J. Chem.*, 1971, 755

[11] B.J. Kelly, Ph.D. Thesis, Leicester University, 1989.

[12] G. Hoffle, O. Hollitzer, and W. Steglich, *Angew. Chem., Int. Ed.*, 1972, **11**, 720.

[13] C. M. Timperley, W. E. White, *J. Fluorine Chem.*, 2003, **123**, 65.

[14] M. Schlosser, D. Michel, *Tetrahedron*, 1996, **52**, 99.

[15] R. E. Akpojivi, T. A. Emokpaea and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1994, 443.

Chapter 3: Synthesis of non-racemic unsymmetrical and symmetrical biquinazolinones.

3.1 Introduction.

The successful synthesis of a series of biquinazolinones, some of which are depicted in Figure 3-1 bearing different substituents in 2,2' positions were reported in Chapter Two. Unfortunately in all cases investigated, we were able to obtain only racemic structures, due to the low rotational barrier of rotation around the N-N bond.

R = Me, Et, Ph
R_1 = Me, Et, Ph
different combinations

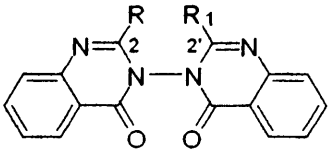


Figure 3-1.

The presence of diastereotopic methylene groups in the diethyl-biquinazolinones encouraged us to investigate the possibility to introduce into the biquinazolinone scaffold a non-racemic chiral center in one or both the 2 and 2' positions. The presence of such chiral element in the molecule would then allow the preparation, of a diastereomeric biquinazolinones (Figure 3-2). In this case it would be interesting evaluate the influence of the chiral center on the configuration of the chiral axis.

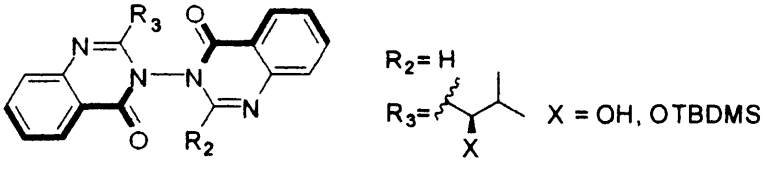


Figure 3-2.

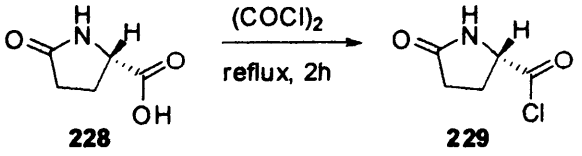
Because acid catalyzed condensation of benzoxazinones with amino quinazolinones has been demonstrated a valid synthetic methodology we reasoned that incorporating a chiral non racemic building block, such as an amino acid, into one or both

heterocyclic ring would be a suitable strategy for the synthesis of new chiral non racemic biquinazolinones. However as it is well known that benzoxazinones are relatively unstable and susceptible to hydrolysis, our attention was turned towards the synthesis of chiral 3-aminoquinazolinones, which may be handled with no special precautions.[1]

3.2 Synthesis of unsymmetrical biquinazolinones with a chiral center on the lateral chain.

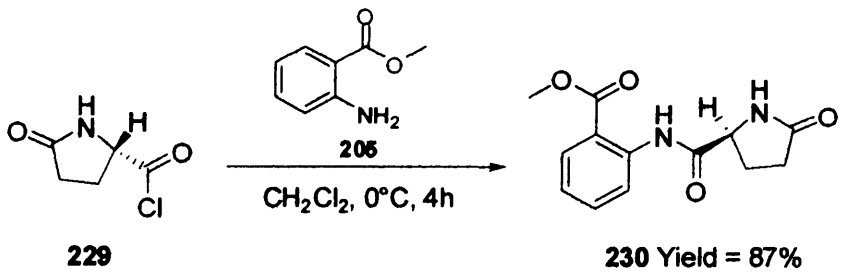
3.2.1 First attempts at the synthesis of chiral biquinazolinones.

In the first attempt (2*S*)-pyrrolidone-5-carboxylic acid (pyroglutamic acid **228**), which does not require protection of the nitrogen in the course of the synthesis, was chosen as chiral synthon for the preparation of the corresponding chiral 3-aminoquinazolinone **231**. Transformation of **228** to its more reactive acid chloride was accomplished in excellent yield by refluxing compound **228** in an excess of oxalyl chloride for three hours (Scheme 3-1). Unreacted oxalyl chloride was then removed under vacuum, affording **229**, obtained in 99% yield as pale yellow oil, which was then used without further purification in the next step.



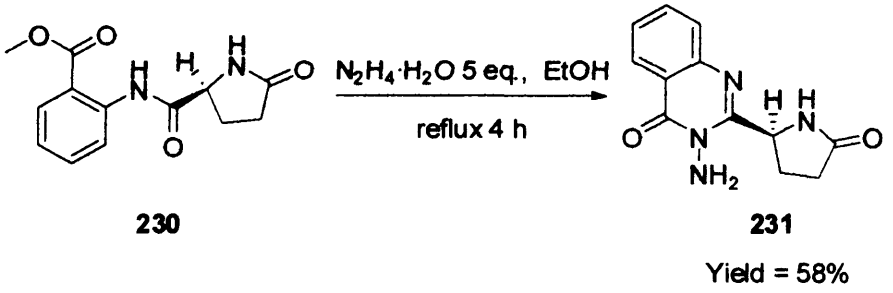
Scheme 3-1.

Upon treatment of a dichloromethane solution of the acid chloride **229** with methyl anthranilate **205**, a thick precipitate was formed, which was vigorously stirred overnight and then removed by filtration. The organic solvent was washed with 2M HCl, in order to eliminate unreacted methyl anthranilate, dried over $MgSO_4$ and the solvent evaporated affording amide **230** in 87% yield after crystallization from ethanol (Scheme 3-2).



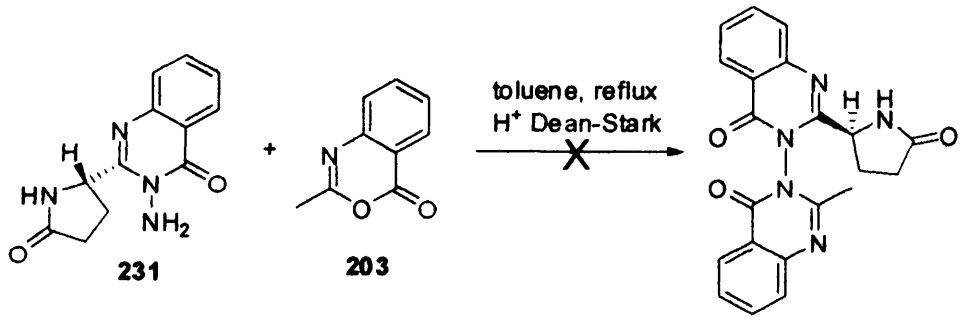
Scheme 3-2.

The successive reaction of **230** with an excess of hydrazine hydrate (5 equivalents) in refluxing ethanol afforded the corresponding chiral amino quinazolinones **231** in 58% yield. Purification of crude material was achieved by trituration of the solid with cold petroleum ether and further crystallization from ethanol (Scheme 3-3).



Scheme 3-3.

With our first non racemic chiral amino quinazolinone in hand its condensation with its benzoxazinone counterpart was attempted under the same protocol developed for the synthesis of non racemic biquinazolinones. Acid catalyzed condensation of **231** with 2-methyl-4*H*-3,1-benzoxazin-4-one **203**, was then carried out in refluxing toluene, under Dean-Stark condition. Unfortunately the ^{1}H-NMR analysis of the crude reaction mixture shows the presence of the starting materials, along with other unidentified products. The crude reaction mixture was also subjected to mass spectrometry analysis (APCI) which shows two major peaks, one belonging to the unreacted starting material, *m/z* 245 ($M+H^+$), and one at *m/z* 190 belonging to an unidentified substance (Scheme 3-4).

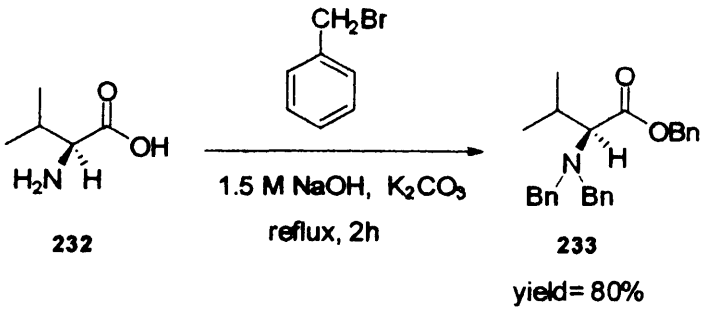


231 203

Scheme 3-4.

Condensation of **231** with 4*H*-3,1-benzoxazin-4-one **202**, was then attempted. In this case a complex mixture of products was recovered. ^{1}H-NMR and mass spectrometry analysis of the crude reaction mixture reveals the presence of several peaks which were impossible to assign to any feasible product of the reactions. Moreover the infrared spectrum of the crude mixture lacks of any N-H peaks (no peaks above 3000 cm^{-1} was observed) suggesting that decomposition of pyroglutamic moiety occurred during the condensation. In the first instance it was thought that steric congestion of the aminoquinazolinone **231** and methyl benzoxazinone **203** was the main cause of the reaction failure but the result obtained with less bulky benzoxazinone **202**, suggests that other factor have to be take into account.

It was then decide to replace the pyroglutamic acid with the commercially available (*S*)-valine (**232**). The bulky isopropyl group would not be directly attached to the quinazolinone ring and therefore should not affect the reaction course. However, in this case the nitrogen group needed to be protected before transforming the carboxylic acid into its acid chloride, in order to avoid side reactions during the further steps of the synthesis. The protected amino acid was prepared in 80% yield by a modification of literature method.[2] To a solution of **232**, 1.5M NaOH and K_2CO_3 in water, benzyl bromide was added and the resulting mixture was kept under reflux for two hours. Upon cooling to 0 °C, the solution was neutralized with 1M HCl and successively extracted with diethyl ether which was dried and evaporated. Compound **233** was collected in 80% after crystallization of the residue from ethanol (Scheme 3-5).



232 233

yield= 80%

Scheme 3-5.

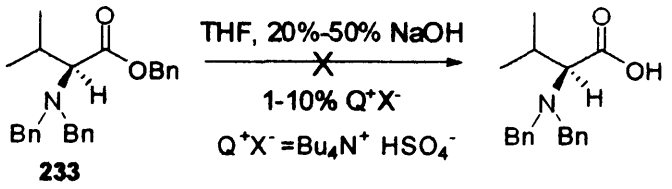
3.2.2 Attempted alkaline hydrolysis of (S)-benzyl 2-(dibenzylamino)-3-methylbutanoate.

A consequence of the protection of the amine in (S)-valine (**232**) was the transformation of the carboxylic acid into its corresponding benzyl ester **233.** This needed to be hydrolyzed back to the acid in order to be converted into the acid chloride. Several attempts carried out in order to hydrolyze the benzyl ester are discussed in this section.

A solution of the benzyl ester **233** in THF was treated with two equivalents of 2M NaOH for two days. No sign of reaction was observed and the starting ester was completely recovered. It was supposed that hydrolysis failed because of the poor solubility of the hydroxide ion in the organic phase, even though tetrahydrofuran is able to dissolve a small amount of water and, more importantly, inorganic ions. Unfortunately even with a more concentrated alkaline solution or a longer period of contact between the two phases, no sign of hydrolyzed product was observed and the starting ester **233** was the only material recovered.

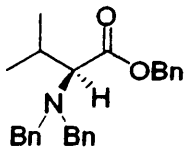
In order to overcome this solubility problem, a phase transfer catalyst was added to the reaction mixture. In a typical procedure, a solution of **233** in tetrahydrofuran was poured into a solution of 30% NaOH in the presence of 1% mol of tetrabutylammonium bisulfate (TBAHS) and stirred for one day at room temperature. Because no reaction occurred, the concentration of the hydroxide was increased to 50% and after that more TBAHS was added to reach a final concentration of 10% mol.. Unfortunately even after two days stirring at room temperature no hydrolysis

was observed (Scheme 3-6). Table 3-1 summarizes all the attempts to hydrolyze the benzyl ester **233** under alkaline conditions.



233

Scheme 3-6.

	Conditions	Yield (%)
	THF, NaOH 20%, RT, overnight	-
	THF, NaOH 50%, RT, 3 days	-
	NaOH 50%, RT, 2 days	-
	THF, NaOH 30%, 1% mol Q^+X^-	-
	THF, NaOH 50%, 5% mol Q^+X^-	-
	THF, NaOH 50%, 10% mol Q^+X^-	-

233

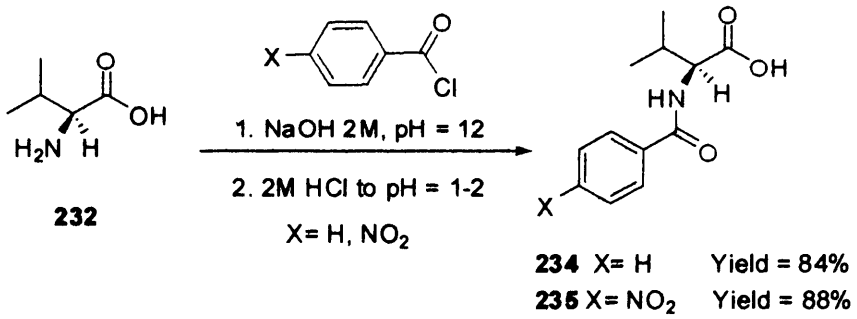
Table 3-1.

The failure to hydrolyze the benzyl ester forced us to find another way to protect the amino group without affecting the carboxylic moiety. A second method was benzoylation under Schotten-Baumann conditions which is the topic of the next section.

3.2.3 (S)-Valine protection by Schotten Baumann benzoylation.

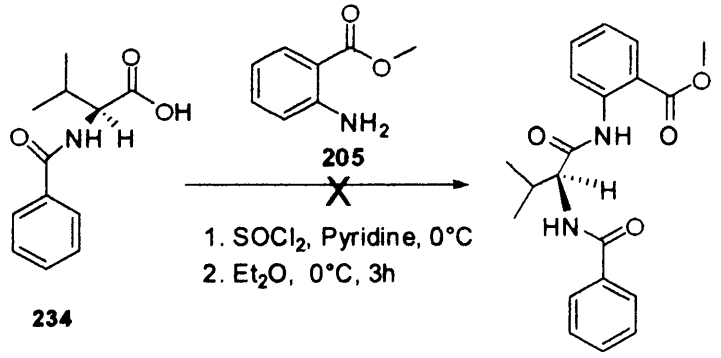
A rapid and convenient method of protecting the nitrogen in amino acids is its reaction with benzoyl chloride under Schotten-Baumann condition.[3] According to the typical procedure (*S*)-valine **232** was dissolved in 2M NaOH, followed by the dropwise addition of 1.2 equivalents of benzoyl chloride. The pH, continuously checked, was kept constantly alkaline (around pH 12) until completion of the reaction. Acidification to pH 1-2 with 2M HCl, gave a precipitate, which was collected by suction filtration. Purification of the product from benzoic acid was

achieved by dry distillation (Kugelrohr apparatus), obtaining **234** in 84% yield. Protection of the amino acid with the more reactive *p*-nitro benzoyl chloride was also performed and the resulting product **235** was easily purified by a simple crystallization from aqueous ethanol (Scheme 3-7).



Scheme 3-7.

N-benzoylated amino acid **234** was then converted into the corresponding acid chloride by treatment with an excess of thionyl chloride in the presence of a catalytic amount of pyridine at 0 °C in dry ether. The residue, obtained after removal of the solvent and the excess of chlorinating reagent, was immediately reacted, without any further purification, with methyl anthranilate **205**. Unfortunately, no evidence of amide formation was observed in the ^{1}H-NMR of the crude reaction mixture (Scheme 3-8).



Scheme 3-8.

Further studies of the reaction of **234** with thionyl chloride showed that the ^{1}H-NMR spectrum of the crude reaction mixture was inconsistent with formation of the acid chloride, which was also confirmed by mass spectrometry (EI, *m/z* 203 instead of the expected peak at *m/z* = 221). This suggested that formation of the oxazolinone by displacement of the chloride from the acetoxy group on the nitrogen had occurred instead of the expected acid chloride (Figure 3-3). No further investigations were conducted on this reaction.

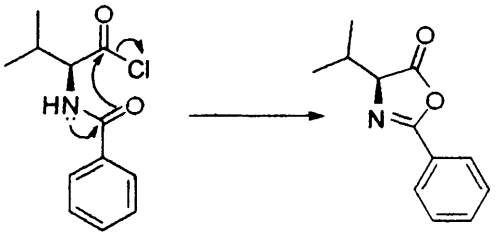


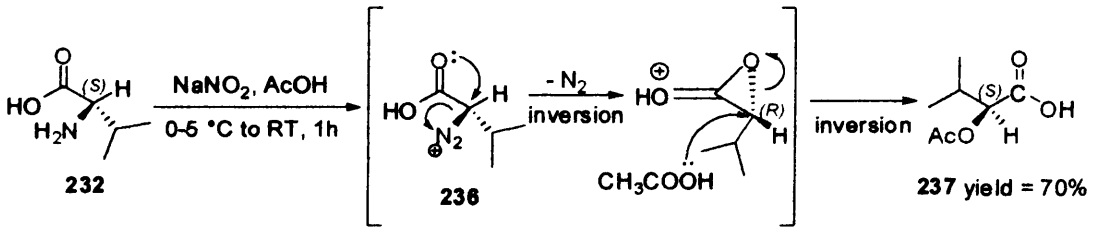
Figure 3-3.

3.2.4 Synthesis of chiral 3-aminoquinazolinones.

On the basis of all these disappointing results we turned our attention to a different method of the synthesis of 3-aminoquinazolinone bearing chiral group in the 2-position. The synthesis of chiral 3-aminoquinazolinones was accomplished using the Atkinson protocol[4] which in its first step involves the transformation of (*L*)-valine **232** into its acetoxy derivative by means of diazotization of the amino group in excess of acetic acid. In a representative procedure an excess of sodium nitrite was added in small portions to a suspension of (*L*)-valine **232,** in acetic acid (kept between 0°C and 5°C) over one hour in order to prevent any increase in the reaction temperature. Upon completion of the addition, the reaction mixture was stirred at room temperature for a further hour. The solvent was then evaporated under reduced pressure and the resulting solid re-dissolved in water and extracted repeatedly with diethyl ether. The organic layer was then dried and evaporated giving **237** as a pale yellow oil in 70% yield.

Mechanistically, the reaction starts with the transformation of the amino group into the corresponding diazonium salt **236** by action of the sodium nitrite. At this stage the

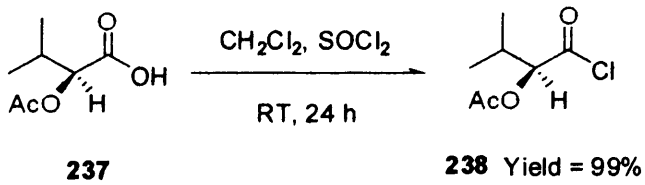
carboxylic group of the amino acid displaces dinitrogen, forming a cyclic intermediate with inversion of the configuration at the chiral centre. One molecule of acetic acid then attacks, (*via* a bimolecular nucleophilic displacement reaction), the carbon bearing the amino group to afford the acetoxy derivative **237** with the same configuration of the original amino acid (Scheme 3-9).[5,6]



Scheme 3-9.

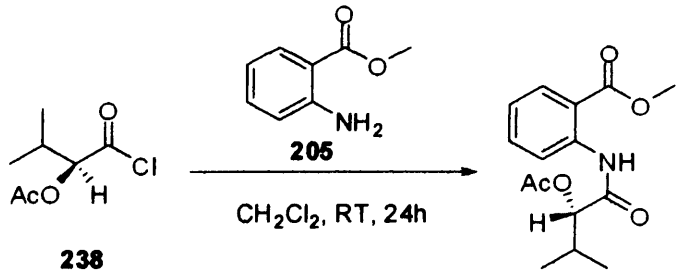
During the synthesis of **237** we found the temperature to be a key factor in the successful preparation of the compound. If the temperature was allowed to increase due to the exothermic course of the reaction, racemization occurred. However if the temperature was kept too low only poor yields were obtained. Therefore a temperature of between 0°C and 5°C was recognized to be the optimum for this reaction.

(*L*)-acetoxy valine **237** was then transformed into the corresponding acid chloride **238** in the usual manner by reaction with thionyl chloride in dichloromethane at room temperature. Unreacted thionyl chloride was removed together with solvent under reduced pressure and the acid chloride was then utilized in the next step without any further purification (Scheme 3-10).



Scheme 3-10.

The reaction of **238** with methyl anthranilate **205** was carried out by dropwise addition of methyl anthranilate to a dichloromethane solution of the acid chloride **238**. The thick precipitate that formed was stirred for 24 hours at room temperature and then removed by filtration. The organic solvent, washed with 2M HCl, in order to eliminate unreacted methyl anthranilate, was then dried over $MgSO_4$ and finally evaporated affording amide **239** in 88% yield.

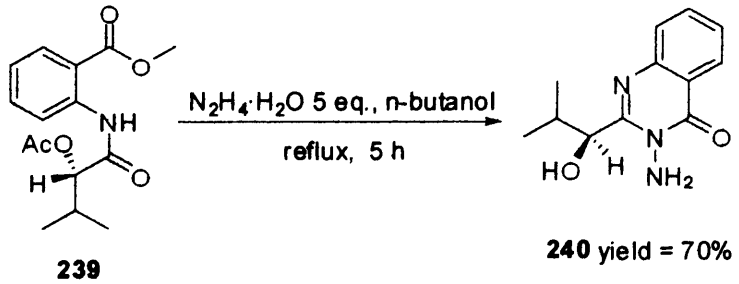


238

239 Yield = 88%

Scheme 3-11.

The final step of the synthesis was the formation of the quinazolinone ring by treatment of the anthranyl amide **239** with five equivalents of hydrazine in refluxing n-butanol for five hours. The crude material obtained, after evaporation of the solvent was dissolved in dichloromethane and washed with water in order to eliminate the excess of hydrazine. The solvent was dried over Mg_2SO_4 and then evaporated to afford pure amino quinazolinone **240** in 70% yield, after crystallization from ethanol (Scheme 3-12).

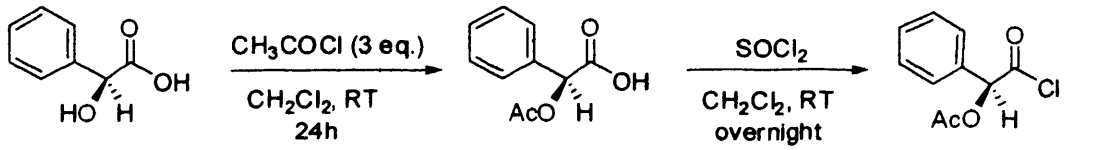


239

240 yield = 70%

Scheme 3-12.

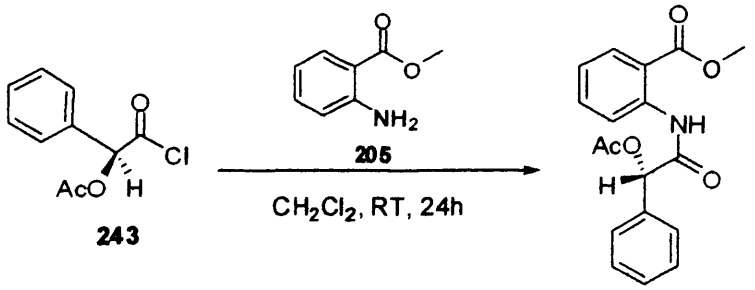
The same strategy was adopted for the synthesis of the 3-amino-2-hydroxyphenyl-4(3H)-quinazolinone **245**. The hydroxyl group of the commercially available mandelic acid **241** was protected by treatment with an excess of acetyl chloride in dichloromethane at room temperature. Evaporation of the solvent gave the acetoxy derivative **242** in 89% yield. It was then dissolved in dry dichloromethane and transformed quantitatively into the corresponding acid chloride **243** by treatment with an excess of thionyl chloride (Scheme 3-13).



241 **242** Yield = 89% **243** Yield = 99%

Scheme 3-13.

Compound **244** was then synthesised in 69% yield, from acid chloride **243** adopting the same methodology used for the parent compound **239** (Scheme 3-14).

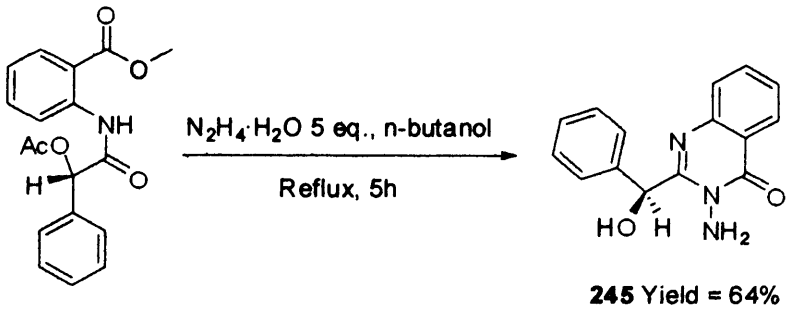


243

244 yield = 69%

Scheme 3-14.

Finally, 3-amino-2-[(S)-1-hydroxy-2-methylphenyl]-4(3H)-quinazolinone **245** was synthesized in 64% yield by reaction of **244** with hydrazine hydrate in n-butanol at reflux as outlined in Scheme 3-15.



244

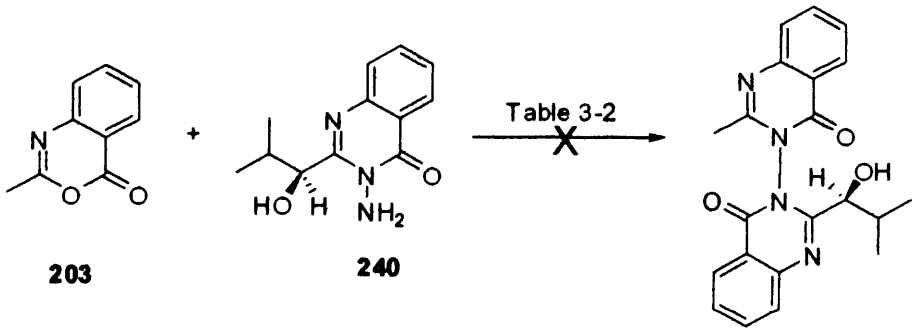
245 Yield = 64%

Scheme 3-15.

3.2.5 Synthesis of unsymmetrical chiral biquinazolinones.

The synthesis of the target chiral unsymmetrical biquinazolinone was achieved by condensation of the chiral derivatives **240** or **245** with different benzoxazinones that had been previously prepared (see section 2.4.1). This was achieved adopting the same protocol developed for the synthesis of the symmetrical biquinazolinones discussed in section 2.4.3.

As a first attempt, the derivative **240** was reacted with 2-methyl-4H-3,1-benzoxazin-4-one **203** in refluxing toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid for one day. However, no sign of the desired product was detected by ^{1}H-NMR spectroscopy carried out on deuterated chloroform solution of the crude mixture. Only starting material, together with a small amount of open amide were recovered (Scheme 3-16). Moreover when the reaction was performed in acetic acid, which provides a polar environment and act as a dehydrating agent, no evidence of the formation of the desired biquinazolinone was observed and only *N*-acetylated starting material was recovered (Table 3-2). The same results were obtained with ethyl benzoxazinones **204.**



203 240

Scheme 3-16.

Solvent	Time	Condition	Yield(%)
Toluene	2 days	Reflux, *p*-TsOH	-
Ac_2O	2 days	Reflux	-
CH_3CN	4 days	Reflux	-
AcOH	2 days	Reflux	-

Table 3-2.

A viable explanation for the lack of reactivity of **240** is the possibility for this compound to form aggregate by hydrogen bonding when in a solution state (Figure 3-4). Indeed, an infrared spectrum of a solution of aminoquinazolinone **240** in chloroform shows the presence of a broad peak above 3400 cm^{-1} due to hydrogen bonded O-H. Following this line of though, we reasoned that disrupting any hydrogen-bonded network would increase the reactivity of **240**. However, even when the reaction was carried on in more polar solvents such as DMF or acetonitrile, it was not possible to prevent the formation of these intra- and intermolecular hydrogen bonding from occurring as the expected product was not formed and only the starting materials were recovered.

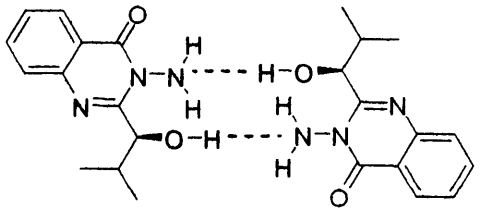
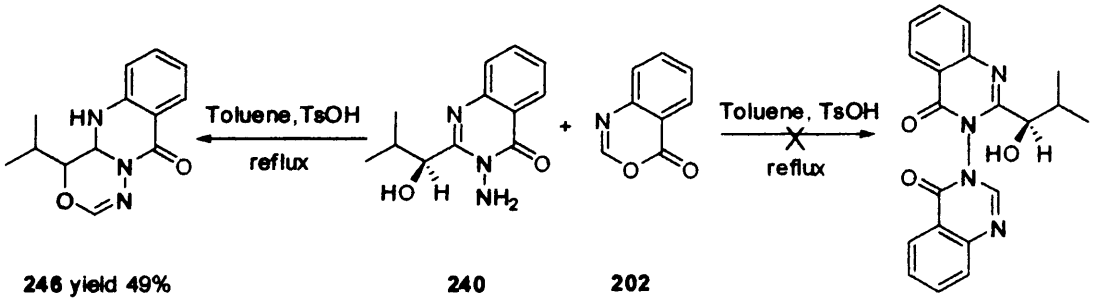


Figure 3-4.

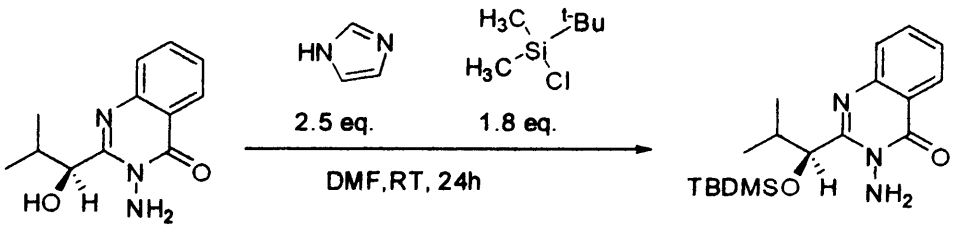
In order to investigate if steric encumbrance plays an important role in this kind of reaction compound **240** was reacted with the 4*H*-3,1-benzoxazin-4-one **202** in refluxing toluene in the presence of an acid catalyst. A highly crystalline compound was isolated by crystallization from methanol. Mass spectrometry (APCI, *m/z* 246, $M+H^+$) and X-ray crystallographic characterization revealed a new heterocyclic compound **246** formed in 49% yield (Scheme 3-17), instead of the expected biquinazolinone. The synthesis of other members of this previously unreported heterocyclic system will be described in Chapter four.



Scheme 3-17.

These results showed that the synthesis of chiral biquinazolinones *via* condensation of unprotected 3-amino-2-hydroxylalkyl-4(3H)-quinazolinones and benzoxazinones were difficult to achieve. Therefore it was then decided to protect the hydroxyl group in order to eliminate any possible hydrogen bonding interaction with other hydroxyl and amino groups. Several methods for protection of alcohol groups are reported in the literature but as organosilicon compounds show a great affinity for oxygen and a higher affinity for fluorine, (which provides a very selective deprotection pathway), the hydroxyl aminoquinazolinone was protected using a *tert*-butyldimethylsilylchloride (TBDMSCl), protocol. Furthermore, silyl ethers are stable to a wide range of reaction conditions including most oxidising agents. Following a procedure reported by the Atkinson,[7] 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]-4(3*H*)-quinazolinone **240** was dissolved in DMF together with 2.5 equivalents of imidazole and 1.8 equivalents of TBDMSCl and the resulting mixture was stirred at room temperature for two days. Compound **247** was obtained in 88% yield after crystallization from petroleum ether (Scheme 3-18). Imidazole is normally employed

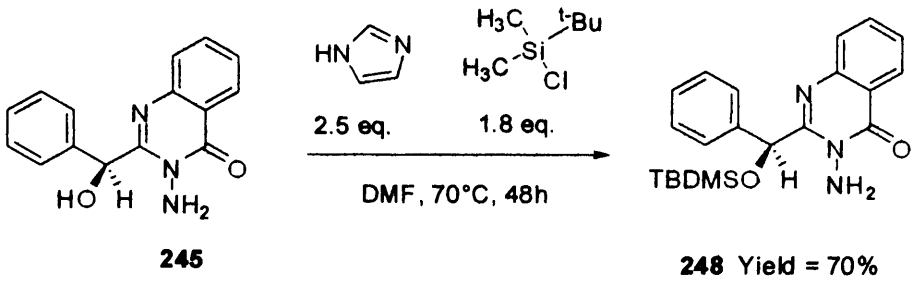
as a base to scavenge the formation of HCl during the reaction and as nucleophilic catalyst because, when the alcohol is sterically hindered or when the silicon is substituted with a bulky group as in the case of TBDMSCl, the silylation is too slow. Imidazole is also used because it is generally more nucleophilic than most alcohols and when protonated behaves as an excellent leaving group.



240 **247** Yield: 88%

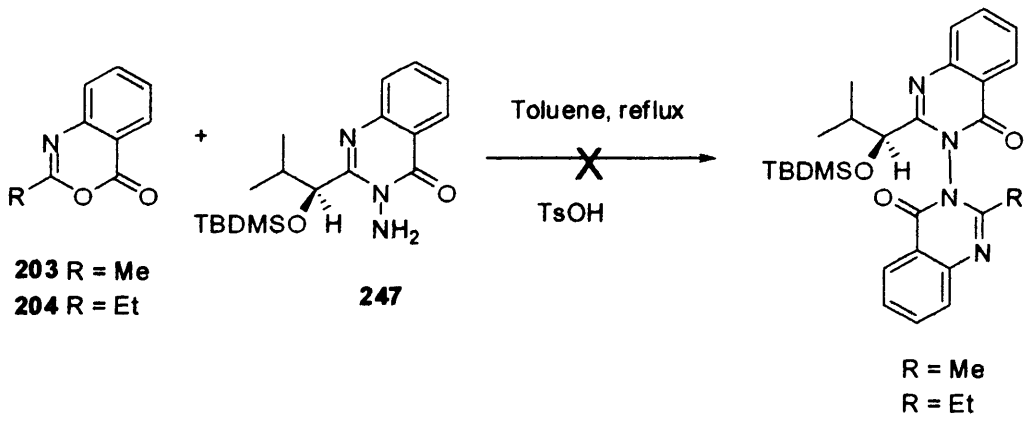
Scheme 3-18.

Attempts at protecting 3-amino-2-[(*S*)-1-hydroxy-2-methylphenyl]-4(3*H*)-quinazolinone **245** under the same condition lead to failure with only starting materials being were recovered. In the attempt to protect the alcohol the reaction time was then prolonged to two days, with the temperature set to be 30°C. Even under this condition the desired product was not observed. It was then decided to conduct the reaction at higher temperature. Compound **245** was reacted with imidazole and TBDMSCl in DMF at 70 °C overnight. Disappointingly also under this condition, only a small amount of silylated product was observed. Finally, protection of alcohol **245** was accomplished carrying out the reaction at 70°C for over two days. Compound **248** was recovered in 70% yields after crystallization from diethyl ether (Scheme 3-19).



Scheme 3-19.

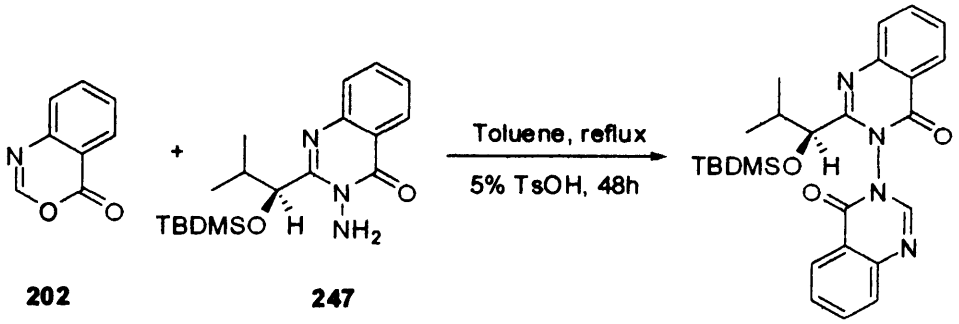
The reactions of aminoquinazolinone **247** with methyl and ethyl benzoxazinones **203** or **204** under the condition employed for the other series of biquinazolinones (toluene, acid catalyst, reflux), were not successful (Scheme 3-20). Even when the condensation was repeated under more drastic conditions (without solvent, simply melting two reactants together for one day), only unreacted starting materials were recovered.



Scheme 3-20.

Target biquinazolinone was finally obtained reacting amino quinazolinone **247** with 4*H*-3,1-benzoxazin-4-one (**202**) in toluene under reflux and in the presence of catalytic amount of *p*-toluenesulfonic acid. Compound **249** was recovered as a mixture of two diastereoisomers in 71 % yield (d.r. 60:40) after crystallization from petroleum ether (Scheme 3-21). Attempts to separate these diastereoisomers by several crystallizations (petrol ether) as well by flash chromatography failed.

Unfortunately, on a thin layer chromatographic (TLC) plate the two isomers showed the same retention factor even using different solvent systems.

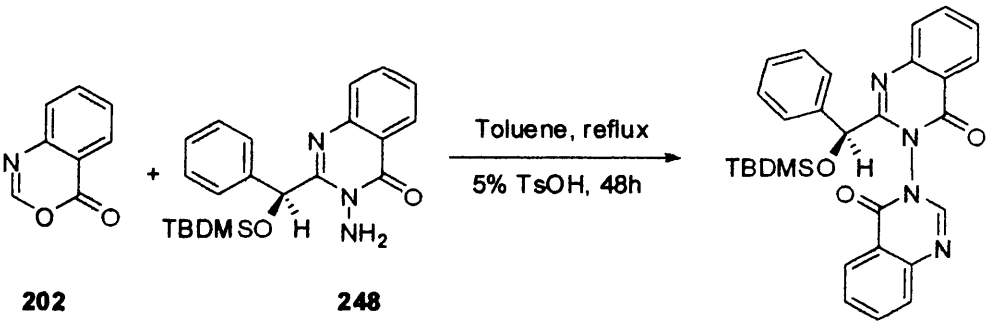


202 **247** **249**

Yield = 71%; d.r. = 60:40

Scheme 3-21.

Following the successful synthesis of an unsymmetrical biquinazolinone, the same reaction was carried out using 3-aminoquinazolinone **248** and 4*H*-3,1-benzoxazin-4-one **202**. 2-(1-*Tert*-butyldimethylsilyloxy-2-phenyl)-2'-H-biquinazolin-4,4'-dione **250** was obtained in 73% yield as a mixture of two diastereoisomers in 80:20 ratio (Scheme 3-22).



202 **248** **250**

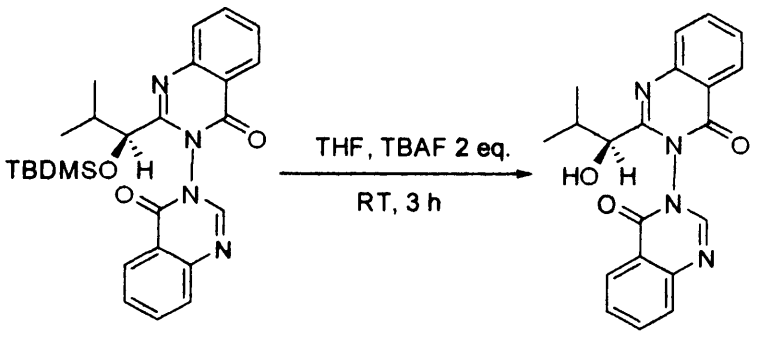
Yield = 73%; d.r. = 80:20

Scheme 3-22.

A first purification attempt was carried out by crystallization with petroleum ether giving a pure compound but with the diastereoisomeric ratio was unchanged.
Changing solvents from petrol ether to methanol and after three recrystallizations, the major diastereoisomers was obtained in 40% isolated yield. Unfortunately the same

approach failed in the case of the valine derivatives **249** with only a small improvement in the diastereoisomeric ratio (from 60:40 to 70:30) was obtained after four recrystallizations from methanol.

In order to utilize the hydroxyl group for further functionalization the silicon protecting group was removed following the method developed by Corey.[8] The protected alcohol **249** was dissolved in tetrahydrofuran and treated with 2 equivalents of *tetra*-butyl ammonium fluoride (TBAF) for three hours at room temperature. Again, after crystallization from methanol, the alcohol **251** was obtained in 80% yield as a mixture of two diastereoisomers in a 60:40 ratio (Scheme 3-23).



249 **251** Yield = 80% d.r. = 60:40

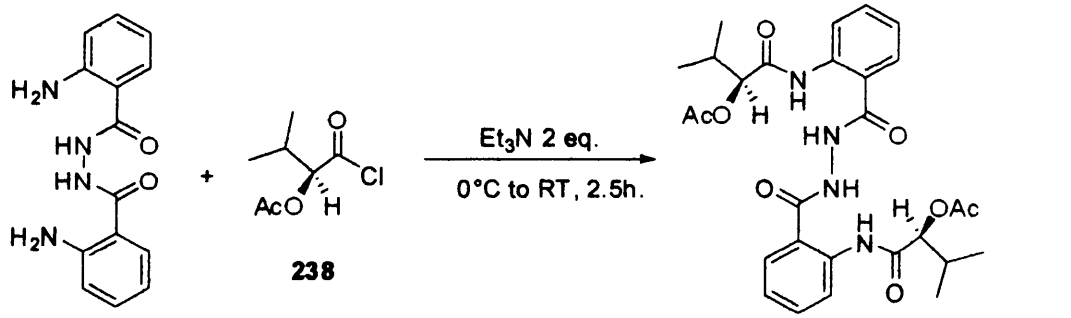
Scheme 3-23.

Once a working protocol had been developed for the synthesis of unsymmetrical non-racemic chiral biquinazolinones, we decided to direct our attention towards the synthesis of symmetrical chiral biquinazolinones. In principle if the role of chiral auxiliary is taken into account, symmetrical compounds appear also interesting because after removal of the auxiliary, two molecules of the desired product will be formed with a neat gain in the economy of the process. In the next section preparation of symmetrical chiral biquinazolinone is presented.

3.3 Synthesis of symmetric non-racemic biquinazolinones.

After the successful synthesis of unsymmetrical non racemic biquinazolinones the next target was the synthesis of symmetrical analogues, bearing a chiral group on the

lateral chain of the quinazolinone scaffold. The two step strategy for this synthesis was based on the conversion of bisanthranoyl hydrazine into the corresponding symmetric amide by treatment with the acid chloride, **238** and/or **243**, followed by amide cyclization under dehydrating conditions.[9] In a typical procedure, acid chloride **238** was added dropwise over 30 minutes to a solution of compound **192,** triethylamine (2 equivalents) in DMF cooled at 0°C. The mixture was kept at 0°C for 30 minutes and then stirred at room temperature for a further two hours (Scheme 3-24).

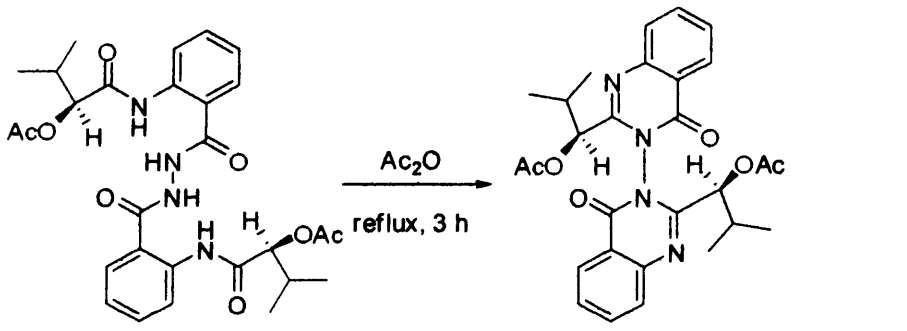


192 + **238** → **253** Yield* = 89%

* Estimated from ^{1}H-NMR of crude mixture

Scheme 3-24.

According to our previous experience, bulky amides require harsh conditions in order to form the biquinazolinones. Therefore ring closure of the amide **253** was attempted by refluxing it in a strong dehydrating agent such as acetic anhydride for a prolonged reaction time. Initially, six hours at reflux led to the formation of the symmetrical biquinazolinones **254** along with several impurities. Surprisingly however, after several attempts, we discovered that shorter reaction times (three hours) gave the cleanest product (Scheme 3-25).



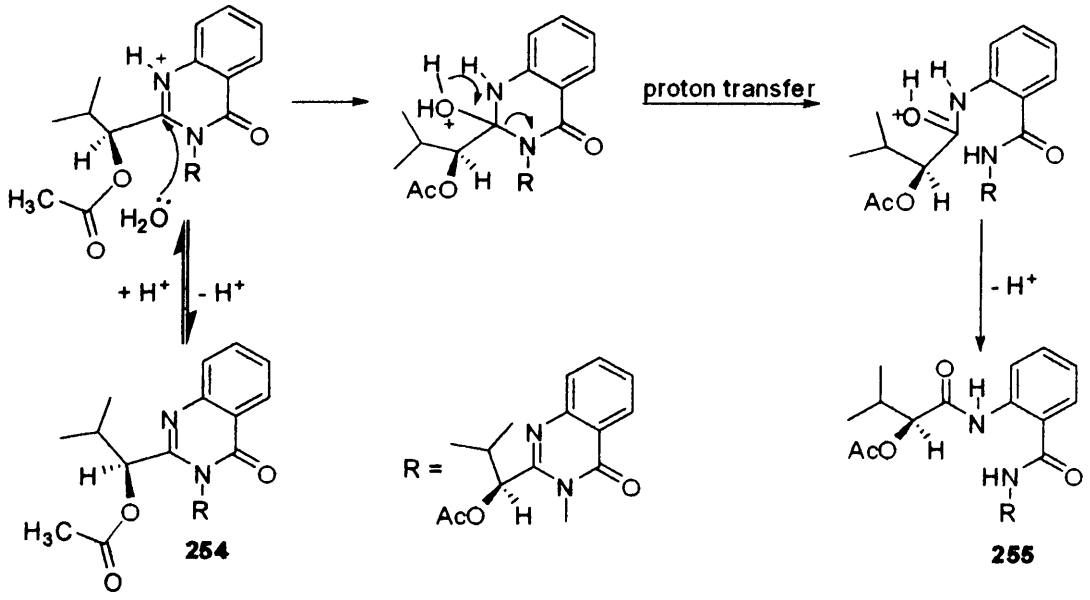
253 **254** Yield* = 45%

* Estimated from ^{1}H-NMR of crude mixture

Scheme 3-25.

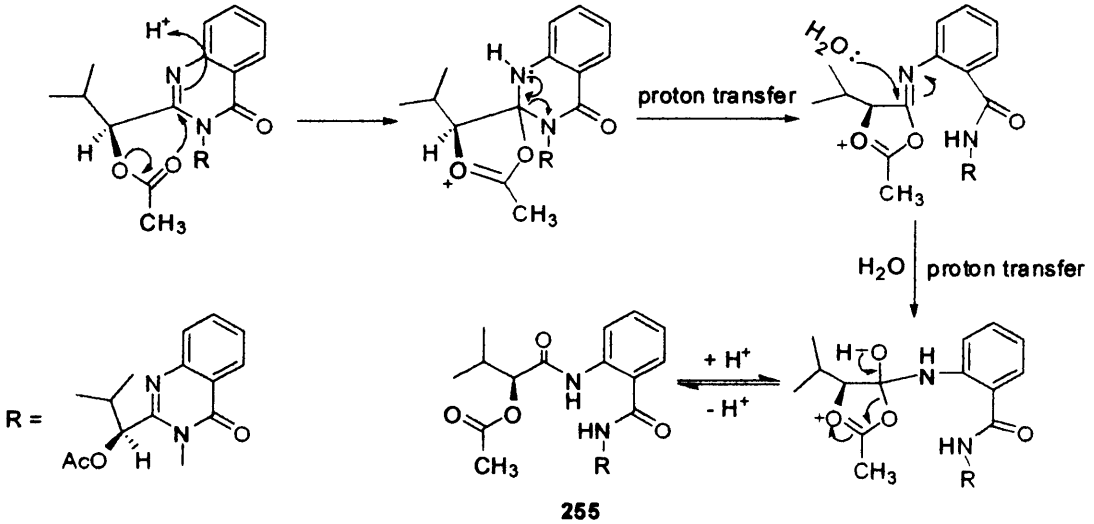
Trituration with both petroleum ether and diethyl ether of the crude mixture, failed to give pure biquinazolinone as well as any attempt at purification by dry distillation. Flash chromatography with silica gel and ethyl acetate/petroleum ether 2:1 as the eluent, enabled the purification of **254**, but unfortunately decomposition also occurred inside the column affording hydrolysed by products.

In the first instance, a possible explanation could be found in the hydrolysis of the quinazolinone ring catalyzed by the acidity of the silica gel itself or by some acidic impurities derived from acetic anhydride. In Scheme 3-26, a possible mechanism of decomposition is proposed. Water probably present in the solvent used for the chromatography can hydrolyse the protonated C=N bond, in the quinazolinone ring causing formation of the amide **255** (Scheme 3-26).



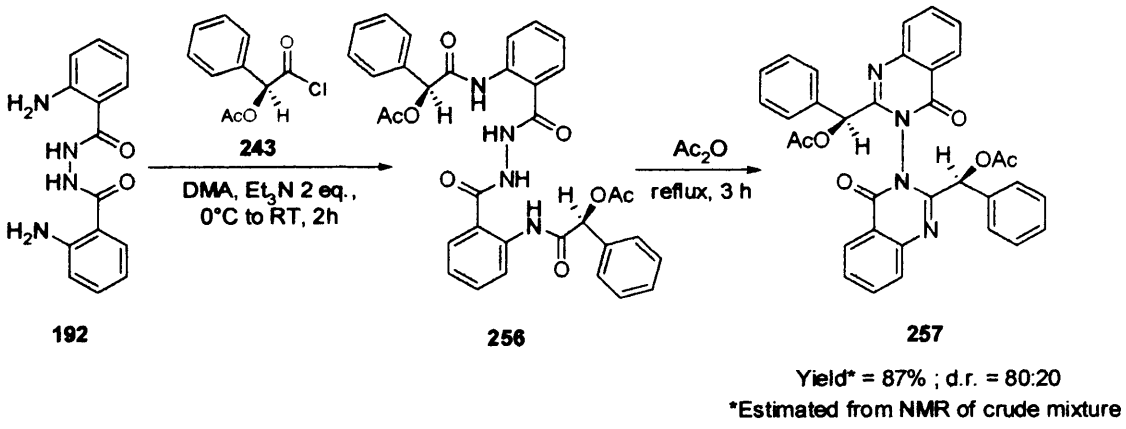
Scheme 3-26.

Another explanation accounting for this instability could found in the steric encumbrance of the lateral chain, which, forcing the quinazolinone ring into a "non planar" conformation with a partial loss of conjugation, which reduces the stability of the molecule. Finally another decomposition pathway is proposed in Scheme 3-27. The neighbouring acetate group α to the C=N bond can participate in the hydrolysis process, acting as a nucleophilic catalyst and favouring the hydrolysis of the imine bond.



Scheme 3-27.

An alternative synthesis of symmetrical non-racemic biquinazolinones was attempted with a different group, in order to investigate whether the steric bulkiness was responsible for the susceptibility of this compound to hydrolysis. The phenyl group was chosen due to its planarity as it may adopt a conformation in which the steric encumbrance is diminished and then the stability of symmetrical biquinazolinones should as a result improve. The synthesis was accomplished by the same strategy adopted in the synthesis of compound **254.** The acid chloride **243** was reacted with **192** and the resulting crude bis-amide **256** was immediately refluxed in acetic anhydride without purification. The symmetrical biquinazolinones **257** was obtained as a pair of diastereoisomers in 80:20 ratio in about 87% yield according to crude ^{1}H-NMR analysis (Scheme 3-28). However, once again, every attempt to purify **257** by column chromatography or by crystallization led to decomposition of the symmetrical biquinazolinone, which seems to be intrinsically unstable perhaps for the same reason, invoked for the instability of the valine derivate **254.**



Scheme 3-28.

Summary.

In this chapter the syntheses of a non-racemic unsymmetrical and symmetrical biquinazolinones have been presented. The application of the methodology developed for the preparations of the symmetrical series has been successfully applied to chiral one. Chirality has been introduced into the aminoquinazolinones scaffold *via* the functionalization of 3-aminoquinazolinone with non-racemic amino acids. Synthesis of this material was initially complicated by the difficulty encountering in transforming the *N*-protected amino acids into the corresponding acid chloride derivatives used to build the quinazolinone scaffold, forcing us a change in methodology. Transformation of the amino acids into the corresponding acetoxy derivatives eliminated these drawbacks and the target was successfully reached.

Unprotected 3-amino-2-hydroxylalkyl-4(3H)-quinazolinones failed to condense with benzoxazinones probably because of the formation of hydrogen bonded aggregates, diminishing the nucleophilicity of the amino group. As discussed in Chapter 2 the steric interactions constitute a limitation to this kind of reaction which, at least under the conditions employed, does not permit the introduction of any substituents bigger than a hydrogen atom. During the reaction between hydroxyalkyl amino quinazolinone and benzoxazinone a new compound with an anthracene-like structure was discovered. Further development in its synthesis will be the topic of the next chapter.

However when the hydroxyl group is protected with TBDMSCl and when 4*H*-3,1-benzoxazin-4-one **202** is used, a chiral unsymmetrical biquinazolinone is efficiently synthesized. Production of diastereomeric biquinazolinones constitutes an indication of the control of the chiral center over the formation of the chiral axis itself. In the case of compound **250** a few recrystallizations permit the separation of these diastereoisomers. However, in the case of compound **249,** the separation of the isomers was not possible either by crystallization or chromatography. In general, fairly good yields and the easy of purification by simple recrystallization of the crude mixture are the main advantages of this methodology.

Symmetrical chiral biquinazolinones were also successfully synthesized from the reaction between bisanthranoyl hydrazine, chiral acid chloride derivative and

successive cyclization of the chiral bis-amide in acetic anhydride. Unfortunately those molecules are unstable and tend to decompose back to the corresponding bis-amide. The reason for this is not yet clear and will be the subject of further investigations.

REFERENCES.

[1] D. T. Zentmyer, E. C. Wagner, *J. Org. Chem.*, 1948, **14**, 967.

[2] I. Baussanne, O. Schwardt, J. Royer, M. Pichon, B. Figadhe, A. Cave, *Tetrahedron Lett.*, 1997, **38**, 2259.

[3]a) C. Schotten, *Ber.*, 1884, **17**, 2544; b) E. Baumann, *Ber.*, 1886, **19**, 3218

[4] R. S. Atkinson, J.R. Malpass, K.L. Woodthorpe, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2407.

[5] T. Kolasa, M. J. Miller, *J. Org. Chem.*, 1987, **52**, 4978.

[6] E. Testa, B. J. R. Nicolaus, L. Mariani, G. Patgani, *Helv. Chim. Acta,* 1963, **46**, 766.

[7] A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D.R. Russell, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4413.

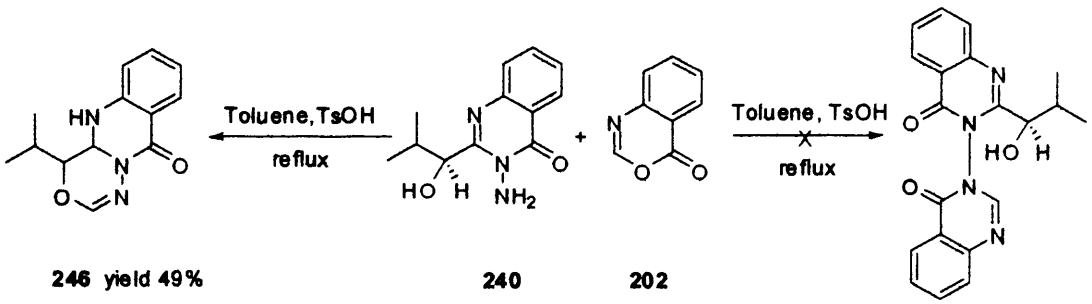
[8] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.*,1972, **23**, 6190.

[9] M. P. Coogan, S. Passey, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2060.

Chapter 4: Synthesis of 4-alkyl-3-oxo-1,9a,10 triazaanthracen-9-ones.

4.1 Introduction.

Previous work discussed in chapter three showed that attempts to synthesize unsymmetrical biquinazolines *via* condensation of chiral amino-quinazolinones and various benzoxazinones, led instead to a product characterized by the presence in the APCI mass spectrum, of a pseudomolecular peak at *m/z* 244. It was isolated in 49% yield when 3-aminoquinazolinones **240** was reacted with 4H-3,1-benzoxazin-4-one **202** in refluxing toluene and in presence of acid catalyst for 24 hours (Scheme 4-1). In this chapter a full characterization of this new compound, proposed route for its formation and the development of a general methodology for the synthesis of this new class of compounds namely, 4-alkyl-3-oxo-1,9a,10-triazaanthracen-9-ones will be discussed.



246 yield 49% **240** **202**

Scheme 4-1.

4.2 Characterization of 4-isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one 246.

In order to clarify the structure of the new compound **246**, a series of NMR studies were carried out. The ^{1}H-NMR spectrum in $CDCl_3$, showed a doublet of doublets at 8.2 ppm typical of a quinazolinone ring. The presence of a non-exchangeable singlet (after treatment with D_2O) at 7.2 ppm is consistent with a methine proton. From this

data and the ^{13}C-NMR chemical shift data (δ_C 126 ppm), this signal appears to belong to a heterocyclic system. Therefore it was possible to tentatively state that the 4-isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one was the right structure to assign to **246.** Due to the highly crystalline nature of this compound, it was possible to obtain single crystals suitable for X-ray diffraction studies.[1] Analysis disclosed the structure of **246** as 4-isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one **246**, thereby confirming the solution state findings (Figure 4-1).

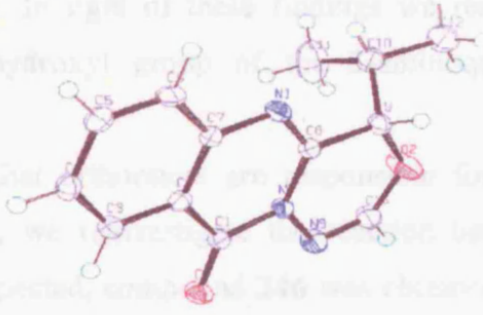


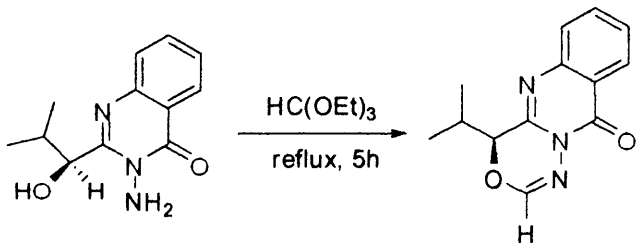
Figure 4-1.

Compound **246** crystallised in the non-chiral $P2_1/c$ space group, with the asymmetric unit being repeated through an improper rotation, not possible for a crystal containing homochiral material. This indicated that the chiral centre of the valine-derived substituent of the quinazolinone had racemised at some point during the reaction (confirmed by the zero optical rotation). This racemization was unexpected as such chiral carbons are usually stable under the reaction conditions involved in the cyclization. However subsequent work revealed that the starting material was itself racemic. As this was derived from L-valine it was interesting that racemization had occurred, as diazotization-substitution reactions usually involve classic double inversion and should therefore proceed with retention of configuration. A reinvestigation of the synthetic pathway to **241** allowed us to show that the diazotization step is particularly sensitive to heat. The temperature has to be kept between 0 °C and 5 °C in order to avoid racemization but also to maintain high yields as discussed in chapter three.

4.3 Proposed route to the formation of 4-isopropyl-3-oxo-1,9a,10- triazaanthracen-9-one 246.

Formation of this new heterocyclic system was presumably generated by the donation of a formyl group to the amino quinazolinones **240,** which then dehydrated to the corresponding product **246.** It seems unlikely that the benzoxazinone **202** could act as a formyl donor and in fact during synthesis one batch of benzoxazinone was contaminated with traces of triethylorthoformate, suggesting that the orthoester was competing with the benzoxazinone in the reaction with the hydroxyl group of the 3-aminoquinazolinone. In light of these findings we reasoned that the orthoformate reacted with the hydroxyl group of the 3-aminoquinazolinone leading to the formation of **246.**

In order to prove that orthoesters are responsible for the formation of this new heterocyclic system, we reinvestigate the reaction between **240** and neat triethyl orthoformate. As expected, compound **246** was obtained in 68% yield as depicted in Scheme 4-2.

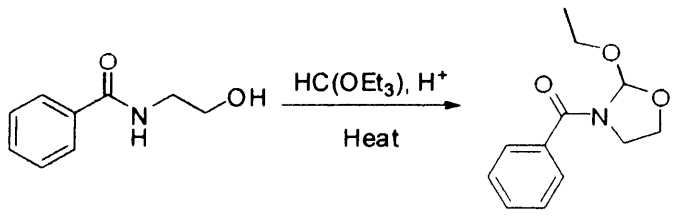


240 **246**

Yield = 68%

Scheme 4-2.

Support for these finding comes from the literature, revealing that 1,2- and 1,3-amino alcohols are readily converted, by reaction with orthoesters, into 2-oxazoline derivatives in reasonable yield[2] (Scheme 4-3).



Scheme 4-3.

Surprisingly no reports regarding the synthesis of azaanthracenone heterocyclic system or even of the bicyclic non-benzanullated analogues were found in the literature. Furthermore as routes to new heterocyclic systems are of interest, we decided to investigate the generality of this reaction through the reaction of several amino quinazolinones with different orthoesters.

4.4 Synthesis of 4-alkyl-3-oxo-1,9a,10-triazaanthracen-9-ones via hydroxyalkyl-aminoquinazolinones and ortoesters.

In an effort to prepare more examples of this new heterocyclic system, we found that it is possible to prepare oxatriazaanthracenones with several substituents in the 2-position simply by using different combinations of 3-amino-2-substituted-4(3H)-quinazolinones and orthoesters as indicated in Figure 4-2.

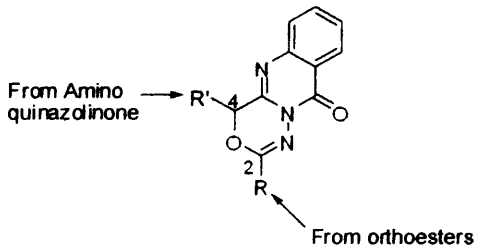
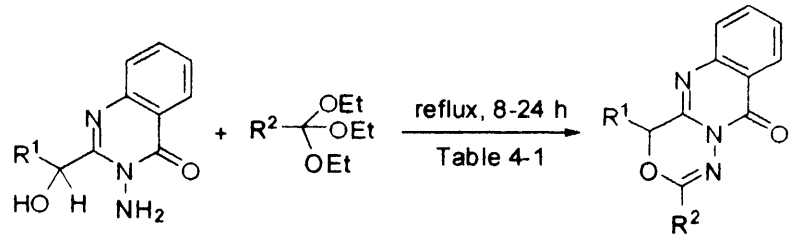


Figure 4-2.

A typical protocol for the synthesis of triazaanthracenones follows: amino quinazolinone is allowed to reflux in an excess of the orthoester for a period of time varying from 8 to 24 hours. When the reaction is complete (as determined by TLC) the reaction mixture is cooled to room temperature and the excess orthoester is

removed under reduced pressure. The solid residue is then crystallized from a suitable solvent, affording the desired triazaanthracenone in moderate to good yields (Scheme 4-4 and Table 4-1).



Scheme 4-4.

Entry	R^1	R^2	Time (hr)	Product	Yield %
1	^{i}Pr (±) **240**	H	5	(±) **246**	68
2	^{i}Pr (-) **240**	Me	24	(-) **258**	77
3	^{i}Pr (±) **240**	Et	36	(±) **259**	54
4	^{i}Pr (±) **240**	Ph	36	(±) **260**	60
5	Ph (+) **245**	H	24	(-) **261**	58
6	H **264**	H	24	**262**	85

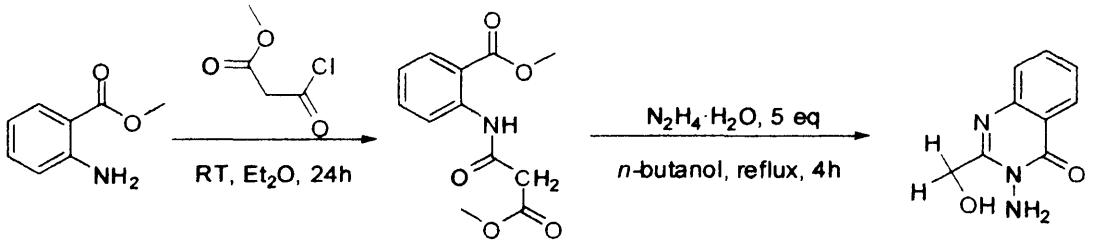
Table 4-1.

From the data in Table 4-1 it is possible to appreciate that the procedure adopted is very general and requires short reaction times and no special precautions such as dry solvents or an inert atmosphere. It is also worthy to note that samples of analytical purity are easily obtained, with good yields, from crude reaction mixture after only a couple of crystallizations.

Moreover, when enantiomerically pure aminoquinazolinone is used, the desired products **258** and **261** (Table 4.2, Entry 2 and 5) were obtained in enantiomerically pure form in 77% and 58% yields respectively, after crystallization of the crude mixtures.

In order to expand the series of oxatriazaanthracenones with no substituents in position 4, aminoquinazolinone **264** was also prepared following the method adopted by Atkinson and co-workers.[3] Commercially available acetoxyacetyl chloride was condensed with methyl anthranilate **205** in diethyl ether leading to the corresponding

amide **263** (84% yield after crystallization from ethanol). Treatment of **263** with five equivalents of hydrazine in refluxing *n*-butanol afforded 3-amino-2-hydroxymethyl-4(3H)-quinazolinone **264** in 78% after evaporation of the solvent and crystallization from ethanol (Scheme 4-5).



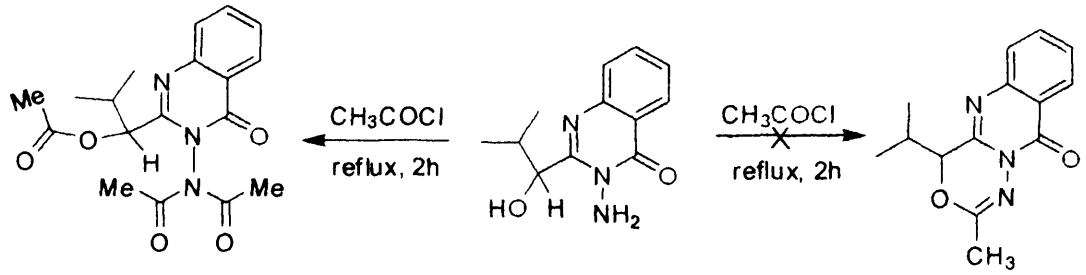
205 **263** Yield = 84% **264** Yield = 78%

Scheme 4-5.

4.5 Attempts at the synthesis of oxatriazaanthracenones via ordinary reagents.

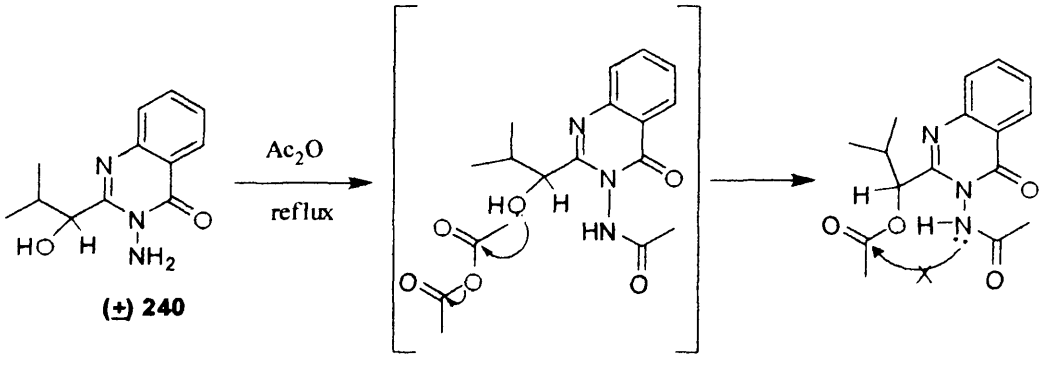
Once that the reaction between the unprotected hydroxyl amino quinazolinones and orthoester was confirmed to be of general application, we decided to investigate the possibility of synthesizing this new heterocyclic system *via* other reactions. The use of more common and more reactive reagents, for examples acid chlorides or anhydrides were investigated. Such reagents were expected to react in the same way as the orthoesters with the advantage of producing triazaanthrazen-9-ones with different substituents on the heterocyclic ring.

Unfortunately the treatment of **240** with acetyl chloride afforded, even after several days at reflux, the *N*-di-acylated and O-acylated compound **265** with only traces of oxatriazaanthracenone. Mass spectrometry, peak at *m/z* 360.1 (APCI, M+H) and ^{1}H-NMR analysis (three singlets at 2.52, 2.28 and 2.08 ppm, belonging to the three CH_3 groups of the O-acetyl and N-acetyl moieties) were consistent with the structure of compound **265** (Scheme 4-6).



Scheme 4-6.

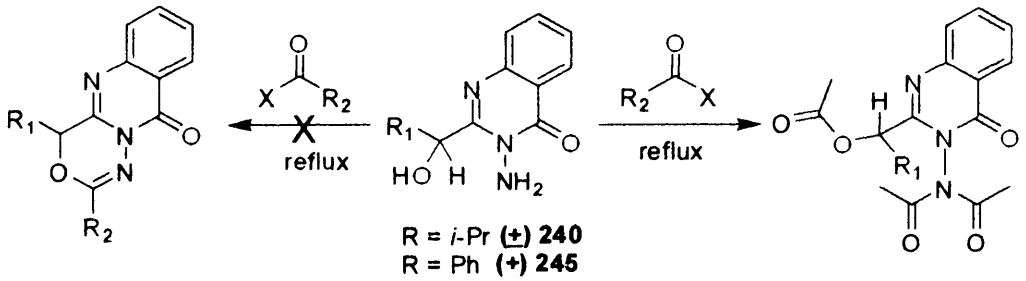
Atkinson reported that treatment of O-protected-3-amino quinazolinones with benzoyl chloride at room temperature caused the mono *N*-acylation of the "exo" amino group, whereas reflux of this product with an excess of acid chloride in dichloromethane lead to the diacyl-quinazolinone derivative.[4] In the same way, when amino quinazolinone (±) **240** was treated with acetic anhydride at reflux, acetylation on both oxygen, and nitrogen occurred. From these two attempts it appears evident that acetylation of the *exo* amino group on the aminoquinazolinone makes the nitrogen atom less nucleophilic and not able to attack the acetoxy group in the lateral chain causing cyclization to the oxatriazaanthracenone (Scheme 4-7).



Scheme 4-7.

Several experiments were also performed by refluxing the 2-hydroxyalkyl-3-aminoquinazolinone with other carboxylic acids derivatives (Scheme 4-8 and Table 4-2). In all the experiments the product of the reaction was the fully acetylated aminoquinazolinone, which was identified by ^{1}H-NMR analysis of the crude mixture,

but not isolated. When ethyl benzoate was used (Table 4-2, Entry 5), substantial decomposition was also observed. All the unsuccessful attempts are reported in Table 4-2

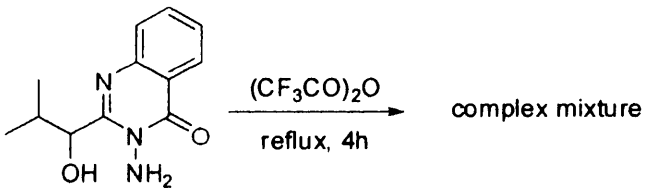


Scheme 4-8.

Entry	3-amino quinazolinones	Reagent		Time	Product
		R_2COX			
1	R = i-pr (±) **240**	R_2 = Me	X= Cl	24h	O, N -Acetylation
2	R = i-pr (±) **240**	R_2 = Me	X = OH	24h	O, N -Acetylation
3	R = i-pr (±) **240**	R_2 = Et	X = Cl	12h	O, N - Acetylation
4	R = i-pr (±) **240**	R_2 = Me	X= OC(O)Me	24h	O, N - Acetylation
5	R = i-pr (±) **240**	R_2 = Ph	X = OC(O)Et	24h	decomposition
6	R = Ph (+) **245**	R_2 = Me	X = OC(O)Me	24h	O, N - Acetylation
7	R = Ph (+) **245**	R_2 = Me	X = Cl	24h	O, N - Acetylation

Table 4-2.

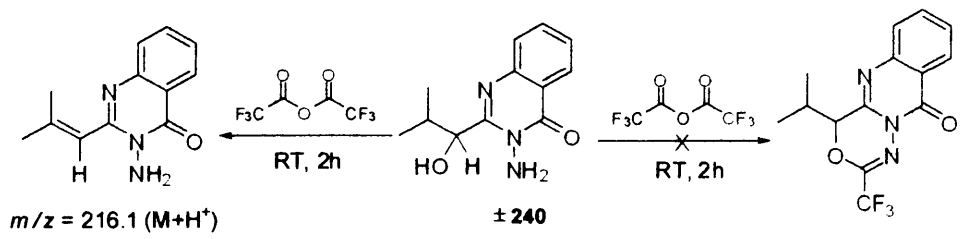
The reaction of aminoquinazolinones with trifluoroacetic anhydride was also attempted. Compound **240** was refluxed in neat trifluoroacetic anhydride for four hours. Upon cooling to room temperature the excess anhydride was evaporated under high vacuum affording a yellow-brown solid (Scheme 4-9). According to the ^{1}H-NMR spectrum of the crude reaction mixture a complex mixture of compounds was formed.



(±) 240

Scheme 4-9.

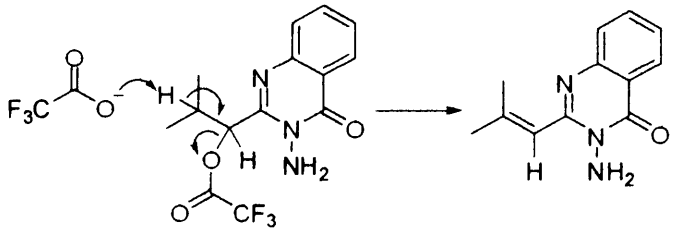
The same reaction was then repeated at room temperature and monitored by TLC. Addition of an excess of trifluoroacetic anhydride caused the immediate dissolution of amino quinazolinone **240**. TLC analysis revealed the formation of one product with R_f of 0.3 (ethyl acetate/Petrol ether 1/3). After one hour the spot with R_f 0.3 disappeared and another one with R_f of 0.5 appeared. After two hours at room temperature the excess of trifluoroacetic anhydride was evaporated and the white crystalline residue (not soluble in $CDCl_3$) was analyzed by ^{1}H-NMR spectroscopy (*d6*-DMSO). The spectrum revealed the presence of a typical aromatic pattern belonging to the quinazolinone ring (including the typical doublet of doublets at 8.2 ppm) and the presence of a singlet, relative to one hydrogen at 5.7 ppm suggesting the presence of a double bond. Mass spectrometry (APCI) of the crude mixture showed the presence of a peak at *m/z* 216 ($M+H^+$) belonging to the compound generated from the elimination of the oxygen from **240,** confirming the findings in the NMR spectrum (Scheme 4-10).



Scheme 4-10.

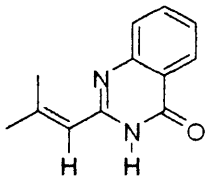
The infrared spectrum of the crude mixture also revealed the disappearance of the peaks belonging to the amino group (3294 and 3320 cm^{-1}) and the appearance of new signals at 1606 cm^{-1} belonging to the newly formed double bond.

It is reasonable to believe that the strong electron withdrawing effect of the trifluoroacetoxy group, a good leaving group, eliminated presumably according to the mechanism depicted in Scheme 4-11.



Scheme 4-11.

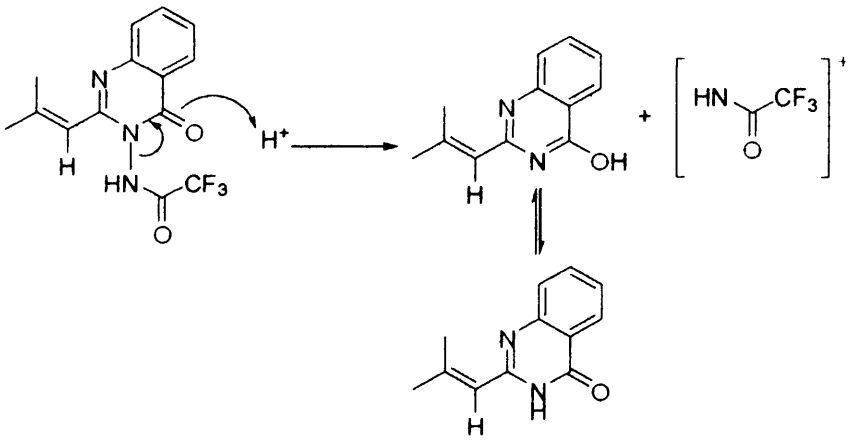
Interestingly the mass spectrum showed the presence of another peak at *m/z* 201 belonging to the quinazolinone derivative which has lost both oxygen and the *exo* amino group (Figure 4-3).



M+H = 201.10

Figure 4-3.

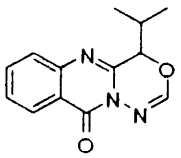
This result is in agreement with Atkinson who reported that 2-ethyl-3-acetoxy aminoquinazolinone undergoes partial decomposition to the corresponding 2-ethylquinazolin-4(3H)-one caused by the acetic acid co-produced during its formation from 3-aminoquinazolinone and lead tetraacetate.[4a] On this basis, a suggested decomposition pattern is shown in Scheme 4-12.



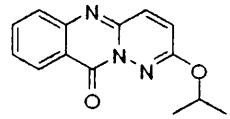
Scheme 4-12.

After these results, our attention turned back to the reactions of 3-amino-2-hydroxymethylquinazolin-4(3H)-one **264** with different orthoesters. It appears that it is possible to incorporate various alkyl chains in the 4-H-3-oxo-1,9a,10-triazaanthracen-9-one ring simply by varying the nature of the orthoester employed. Moreover the procedure does not require an inert atmosphere, or, more importantly chromatography, considered a tedious and solvent consuming procedure in the purification step, thereby greatly increasing the ease and praticality of this method.

Functionalization of 4-H-3-oxo-1,9a,10-triazaanthracen-9-ones can be obtained by changing the nature of the group present in the 3-amino-quinazolinones, in either the 2-position or in the aromatic ring, and also by varying the nature of the orthoester employed. This opens a new route for heterocyclic systems which are of importance in pharmaceutical industries. Moreover, in the literature, there are several examples of similar heterocyclic structures with very similar skeletons, which appear to play an important biological role. As outlined in Figure 4-4 some of these structures possess herbicidal activity while others have antitrichomonal activity.

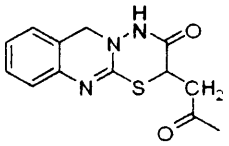


246



2-isopropoxy-10*H*-pyridazino[6,1-*b*]quinazolin-10-one
an herbicides

[1,3,4]thiadiazino[2,3-*b*]quinazolin-6(2*H*)-one



2-(2-oxopropyl)-4,6-dihydro-[1,3,4]thiadiazino[2,3-*b*]quinazolin-3(2*H*)-one
an antitrichomonal agent

Figure 4-4.

Summary.

In conclusion, this chapter demonstrates that 2-hydroxyalkyl-3-aminoquinazolinones can be easily transformed into a new heterocyclic system simply by refluxing in an excess of orthoester used as the solvent. This methodology provides oxatriazaanthracenones in good to high yields with no need for chromatographic purification, only crystallization of the crude solid obtained after evaporation of the solvent being necessary. The only limitation of this synthetic route is represented by the difficulty in isolating oxatriazaanthracen-9-ones bearing strong electron withdrawing groups (i.e. a trifluoromethyl group). Also, other ordinary reagents such as acid chlorides, anhydrides or esters are not able to afford the oxatriazaanthracenone ring when the amino quinazolinones is reacted at reflux temperature in an excess of the reagent. In all the case studied the only material recovered was the product resulting from the acylation of the exo amino group and oxygen. This material appears to be very hard to convert into the corresponding triazaanthracenone ring, at least under the condition so far investigated.

A future target would be the introduction of functional groups in the oxatriazaanthracen-9-ones ring other than simple alkyl chains in order to enlarge the number of structures available.

The use of trifluoroacetic anhydride produced a complex mixture of product including decomposition of the starting material under reflux. However, when the reaction was conducted at room temperature a mixture of various elimination products was observed. It seems reasonable to deduce that in order to obtain the 2-trifluoromethyl triazaanthracenones it will be necessary to carry out the reaction under milder conditions (lower temperature, inert solvent).

In future it would be interesting to explore other conditions (e.g. different solvents, the presence of a catalyst), that could lead to other members of this new heterocyclic family.

REFERENCES.

[1] Crystallographic data for **246**: $C_{13}H_{13}N_3O_2$, crystal system monoclinic; space group, P21/c; a = 9.891(5), b = 10.066(5), c = 11.732(c) Å; α= 90, β= 96.743(5), γ= 90°; Z = 4; T = 150 K; μ = 0.097 mm–1; l = 0.71069 Å (MoKα); F(000) 512; 3.85 < θ < 30.02; 8656 reflections, 3323 unique [R(int) = 0.0626]; R1 = 0.0584, wR2 = 0.1410 [I > 2σ (I)]; R1 = 0.0974, wR2 = 0.1609 (all data). CCDC reference numbers 259058.

[2] M. I. Butt, D.G. Neilson, K. M. Watson, Z. Ullah, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2328.

[3] A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D. R. Russell, *J. Chem. Soc., Perkin Trans.1*, 2000, 4413.

[4] A. G., Al-sehemi, R. S. Atkinson, J. Fewcett, *J. Chem. Soc., Perkin Trans. 1*, 2002, 257.

Chapter 5: Diastereoselective reactions of biquinazolinones.

5.1 Introduction.

The synthesis of symmetrical and unsymmetrical biquinazolinone has been described in Chapters Two and Three. In this chapter studies carried out on the biquinazolinones in order to assess their efficiency as chiral auxiliaries in asymmetric reactions will be presented.

Firstly, the modification of symmetric ethyl and methyl biquinazolinones, *via* alkyl lithium chemistry, will be addressed with the aim to elucidate if and how the *N-N* chiral axis has any influence on the stereochemistry of the product. Any evidence of control exerted by the *N-N* chiral axis on the formation of a new stereocenter would provide us with important information on the possibility of using these compounds as chiral auxiliaries (Figure 5-1).

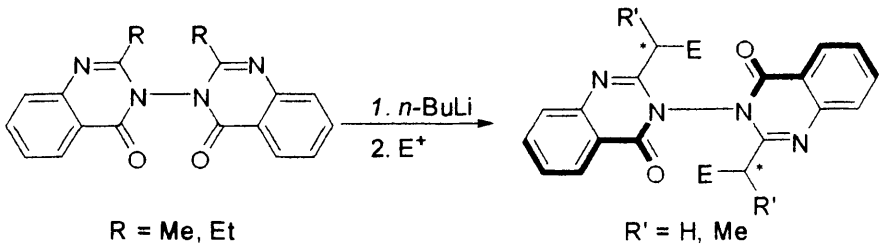


Figure 5-1.

Secondly, introduction of a prochiral double bond in the lateral chain will allow us to study the applications of this scaffold in several asymmetric reactions, such as Diels-Alder, 1,3 dipolar cycloaddition, epoxidation and cyclopropanation (Figure 5-2).

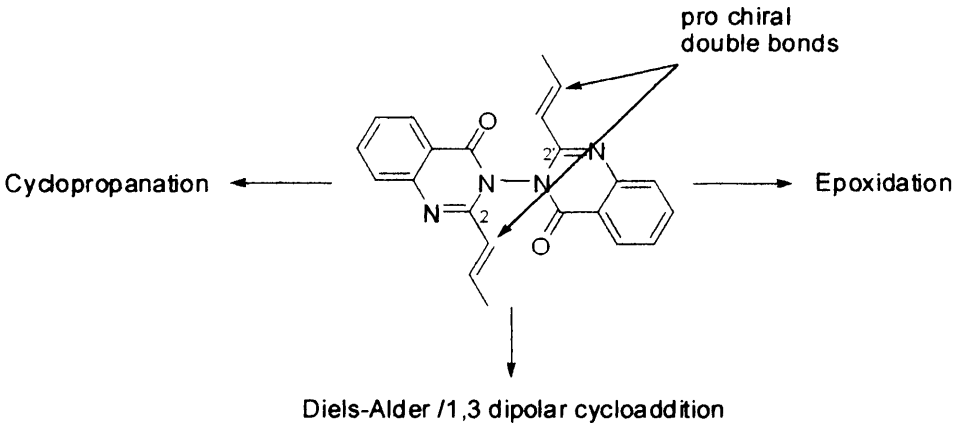


Figure 5-2.

5.2 Functionalization of 2,2'- diethyl-biquinazolinone.

5.2.1 Attempted lithiation of 2,2'-diethyl-biquinazolinone.

In order to introduce different substituents at positions 2 and 2', we decided to attempt the elaboration of the alkyl lateral chain of the biquinazolinone scaffolds by lateral metalation and further reaction with electrophiles (Figure 5-3).

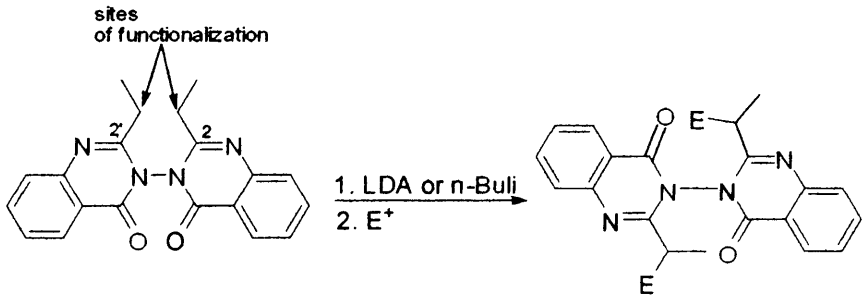
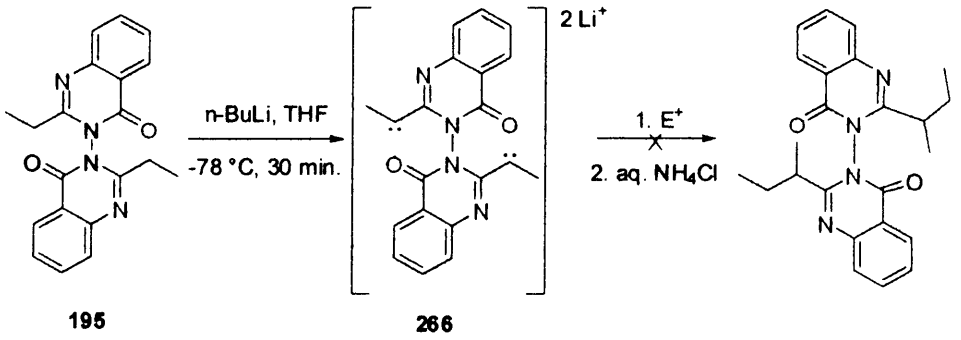


Figure 5-3.

Lithiation of biquinazolinone **195** was carried out by the use of *n*-butyl lithium in anhydrous THF at -78 °C under a nitrogen atmosphere. Addition of one equivalent of the organometallic base produced the monolithio product, which was then converted into the dilithio product on addition of a second equivalent of *n*-butyl lithium. Formation of the lithiated species **266** was evidenced by the appearance of a deep red

color upon the addition of the lithio-alkyl base in analogy to what is reported in the literature on lithiation of monomeric 2-substituted quinazolinones.[1,2] To the resulting solution (stirred for a further 60 minutes at -78 °C to ensure complete reaction), 2.2 equivalents of ethyl iodide were then added at -78 °C. Surprisingly, the ^{1}H NMR analysis of the crude reaction mixture revealed only the presence of the starting material without any evidence of the formation of the alkylation product (Scheme 5-1.



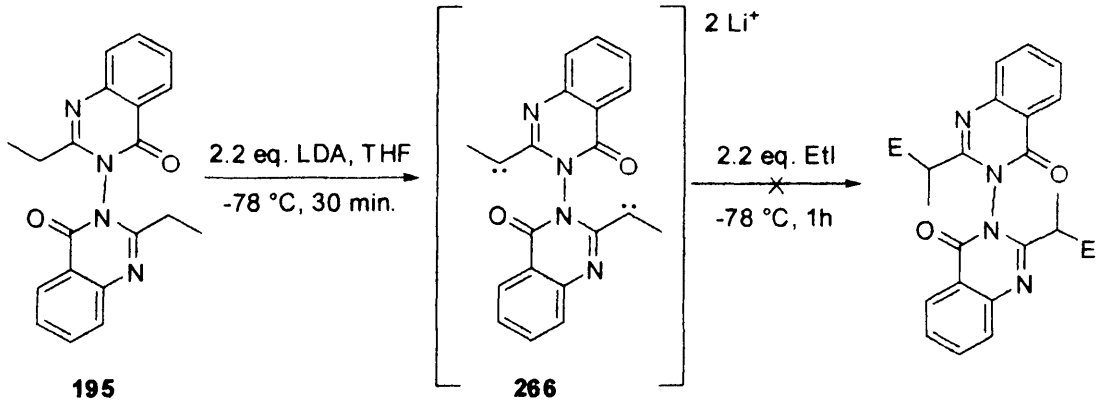
195 266

Scheme 5-1.

Further experiments were then carried out in order to investigate the reason of this lack of reactivity, but even using an excess of electrophile (up to five equivalents) or the addition of 2.5 equivalents of *n*-butyl lithium, could not afford the desired product. Reactions with **266** and other electrophiles such allyl bromide, methyl iodide or benzaldehyde also failed to give the corresponding products.

Searching the literature for work on lithiation of similar substrates, for example monomeric aminoquinazolinones, provided us with work that described the attempted lithiation of 2-ethyl, specifically and in general of 2-alkyl-3-amino-quinazolinones. The work showed that the reactions failed when *n*-butyl lithium was used, but has been successfully accomplished using lithium diisopropylamide (LDA). The lithiated species thus generated are reported to react with several electrophiles affording the corresponding product in good to excellent yields.[1,2] Unfortunately application of the same methodology to diethyl biquinazolinone failed to afford the desired product. Addition of LDA to a stirred solution of compound **195** in THF at -78 °C led to a dark red solution, suggesting that the formation of the dianion **266** had been achieved.

Disappointingly, the addition of 2.2 equivalents of ethyl iodide to the solution, kept at -78 °C for one hour, to ensure the complete formation of the dianion, failed to afford the desired dialkyl derivative even after a prolonged period of time (Scheme 5-2).



Scheme 5-2.

From the above observation it seem reasonable to believe that, at -78 °C the reaction between the lithium salt and alkyl iodide is slow and that a more reactive electrophile has to be used in order to accomplish the functionalization of the biquinazolinone. In this regard Wolfe and co-workers have reported that alkylation of the lithium derivative of 2-methyl-3-o-tolyl-4(3*H*)-quinazolinone **A** (obtained by metalation at 0 °C with LDA) with ethyl iodide, proceeds more slowly than methylation (with MeI) and results in isolation of the monoethyl derivative **C** (25%), diethyl derivative **D** (5%) and unreacted starting material (42%) (Figure 5-4).[3] According to Wolfe, the diethyl derivative **D** can result from proton-metal exchange between the lithiated tolyl-quinazolinone **B** and the monoalkylated product **C**, forming the side-chain lithio salt of the latter (**E**), which then undergoes alkylation with ethyl iodide to form the diethyl derivative **D**.[4] Similar dialkylation reactions were reported also when benzyl chloride end ethyl bromide were employed as electrophiles. Wolfe has also found that using more reactive halides, the rate of the initial alkylation of the lithium salt appears to be significantly faster than both the proton-metal exchange and the subsequent alkylation of the secondary lithio salt. It is noteworthy to point out that in this work, alkylation of the dianion derived from 2-methyl-4(3H)-quinazolinone and *n*-butyl lithium, with either ethyl bromide or benzyl chloride did not produce isolable

amounts of dialkylated product. Wolfe explained this result suggesting that a higher reactivity of this lithium salt with respect to the lithiated tolyl-quinazolinone **B**, allows initial alkylation to compete favorably with the proton-metal exchange and realkylation.

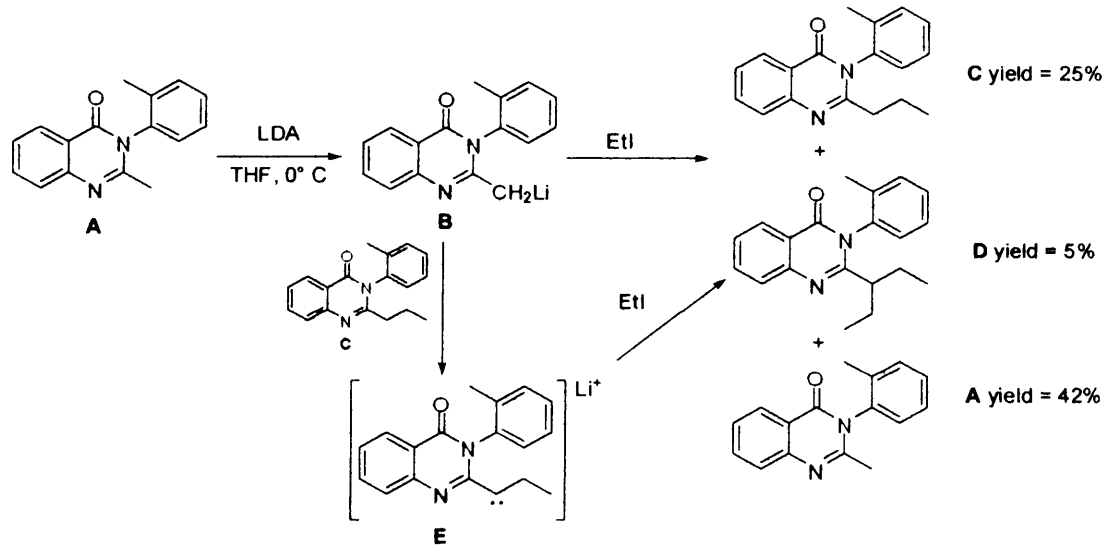
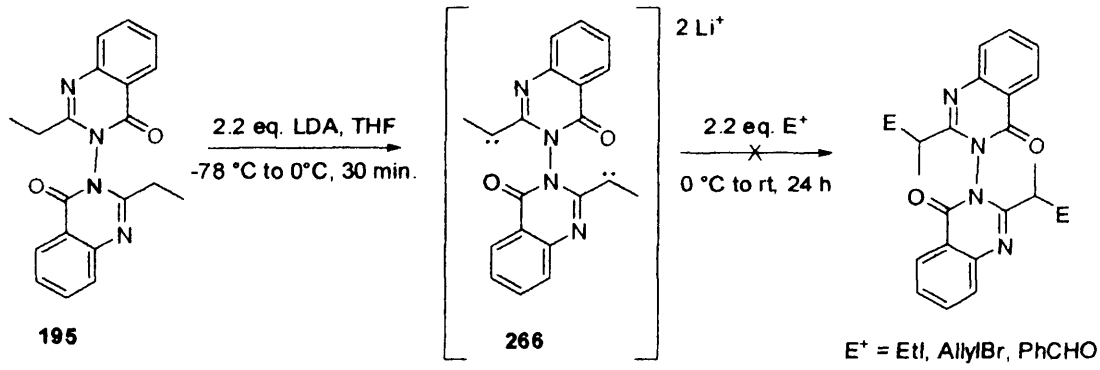


Figure 5-4.

Wolfe's results describing the apparent stability of the lithio salt of 2,3-disubstituted quinazolinone, inspired us attempt the alkylation of the diethyl biquinazolinone **195** at higher temperatures. The addition of 2.2 equivalents of LDA to a -78°C cooled solution of **195** generated a dark brown solution, which was stirred at -78°C for further 30 minutes and then allowed to warm to 0°C. At this point a solution of the electrophile was added dropwise into the dianion solution and the resulting mixture stirred for 24 hours at room temperature. Disappointingly, after acidic work-up, only starting material was recovered. Attempts at alkylating **195** with other electrophiles such as allyl bromide and benzaldehyde (3 to 5 equivalents) using an excess of LDA (2.2 to 3.0 equivalents), were all unsatisfactory and only starting material was detected by ^{1}H-NMR analysis of the reaction mixture (Scheme 5-3). All the results using either *n*-butyl lithium or LDA are reported in Table 5-1. From all these findings, it can be concluded that the dianion **266** has a very small tendency to react

with electrophiles even when the temperature is increased up to room temperature and the reaction time is prolonged.



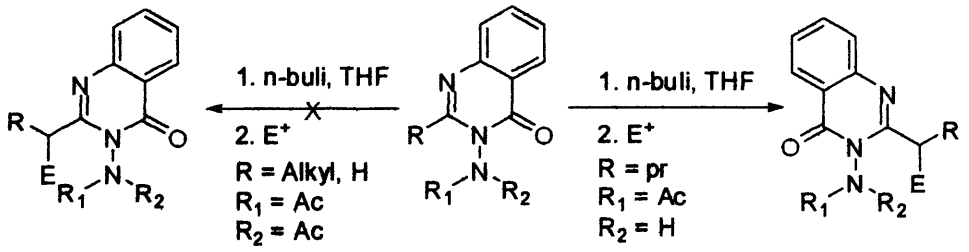
195 266

Scheme 5-3.

Starting Material	Organometallic Base (eq.)	Temp. (°C)	E^+ (eq.)	Time	Yield (%)
195	*n*-BuLi (2.2)	-78	EtI (2.2)	2h	-
195	*n*-BuLi (2.2)	-78	PhCHO (2.2)	2h	-
195	*n*-BuLi (2.2)	-78	AllylBr (2.2)	2h	-
195	LDA (2.2 to 3)	-78 to RT	PhCHO (3 to 5)	24h	-
195	LDA (2.2 to 3)	-78 to RT	AllylBr (3 to 5)	24h	-

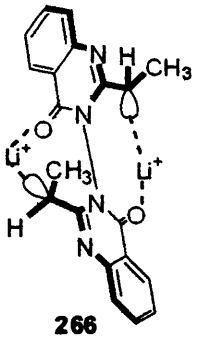
Table 5-1.

In spite of the fact that numerous examples of lithiation of quinazolinone rings have been reported, little is known about the reasons why in some cases certain organometallic reagents fail to give the corresponding metalated heterocycles while in other circumstances the same reagent gives good results. For example, no explanation was given for the fact that lithiation, with n-butyl lithium of 3-acetylamino-2-propyl-4(3H)-quinazolinone and its reaction with several electrophiles occurred smoothly, whereas under the same conditions, 3-(diacetylamino)-2-ethyl-quinazolinone, 3-(diacetylamino)-2(H)-quinazolinone or 3-amino-2-unsubstituted-4(3H)-quinazolinone failed to give the desired product (Scheme 5-4).[5,13]



Scheme 5-4.

Our hypothesis is that the lack of reactivity of the anion **266** towards alkylating agents is due to its stability and therefore it is only able to react with more reactive electrophiles. Its stability could be due to the steric encumbrance of the methyl group, which limits the availability of the electronic doublet to the electrophile. Furthermore coordination of the lithium atom between the carbonyl oxygen and the lone pair of the dianion locks the molecule in such a conformation that make any approach of the electrophile difficult (Figure 1).



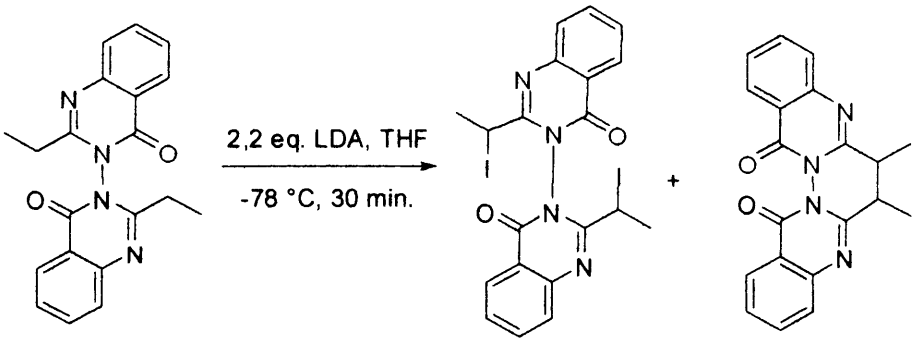
266

Figure 5-5.

Thus, stability and steric hindrance could be the most reasonable explanations as to why such a bulky anion as **266** is recalcitrant to react with these kinds of electrophiles. Due to the problems encountered in the alkylation of the diethyl biquinazolinones **195** we decided to attempt its functionalization with other electrophiles such as iodine and bromine, which is the topic of the next section.

5.2.2 *Iodination of 2,2'-diethyl-biquinazolinone.*

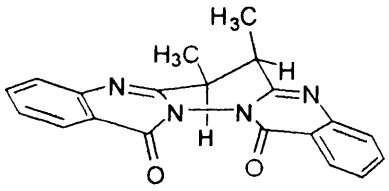
In order to overcome the lack of reactivity of **195** towards alkylating agents, it was then decided to trap the lithium salt **266** with other electrophiles for example iodine, hoping to be able to afford the desired product. When 2.2 equivalents of iodine were added to a solution of **266**, generated by the reaction of 2,2'-diethyl-biquinazolinone with 2.2 equivalents of LDA at -78 °C, a change of color from deep red to pale yellow occurred almost immediately. The reaction mixture was stirred for one hour at room temperature before being quenched with ammonium chloride. After work up, (dilution with DCM, water washing and drying) the solvent was evaporated leaving a solid residue which was analyzed by ^{1}H-NMR spectroscopy. The analysis revealed the presence of a small amount of the iodinated product **267** (in about 5% yield as judged from ^{1}H-NMR and a pseudomolecular peak at *m/z* 598.9 in the APCI mass spectrum of the crude reaction mixture) along with an unexpected compound.



Scheme 5-5.

Crystallization of the crude reaction mixture from methanol gave a brown compound **268** as a crystalline solid, which the APCI mass spectrum showed to have a pseudomolecular ion peak at *m/z* 344. The ^{1}H NMR spectrum was characterized by the presence of multiplets with very unusual coupling constant patterns, for an aliphatic alkyl chain: two sharp multiplets centered at 2.84 ppm and at 1.50 ppm and two overlapping doublets with a small coupling constant (J = 2.06 Hz) at 1.48 ppm.

The presence of these features in the ^{1}H-NMR spectrum suggested that this new compound may be formed by dimerization of the carbanion obtained by treatment of **195** with LDA. A further careful study of the coupling constants in ^{1}H-NMR spectrum indicated also that this new compound was present in a conformation resembling a cyclohexene with the hydrogen and the methyl group occupying alternating axial and equatorial positions in such a way as to avoid steric contact between the two methyl groups as suggested by Figure 5-6. The mass spectrometry analysis and ^{1}H-NMR analysis were both consistent with the structure shown in Figure 5-6.

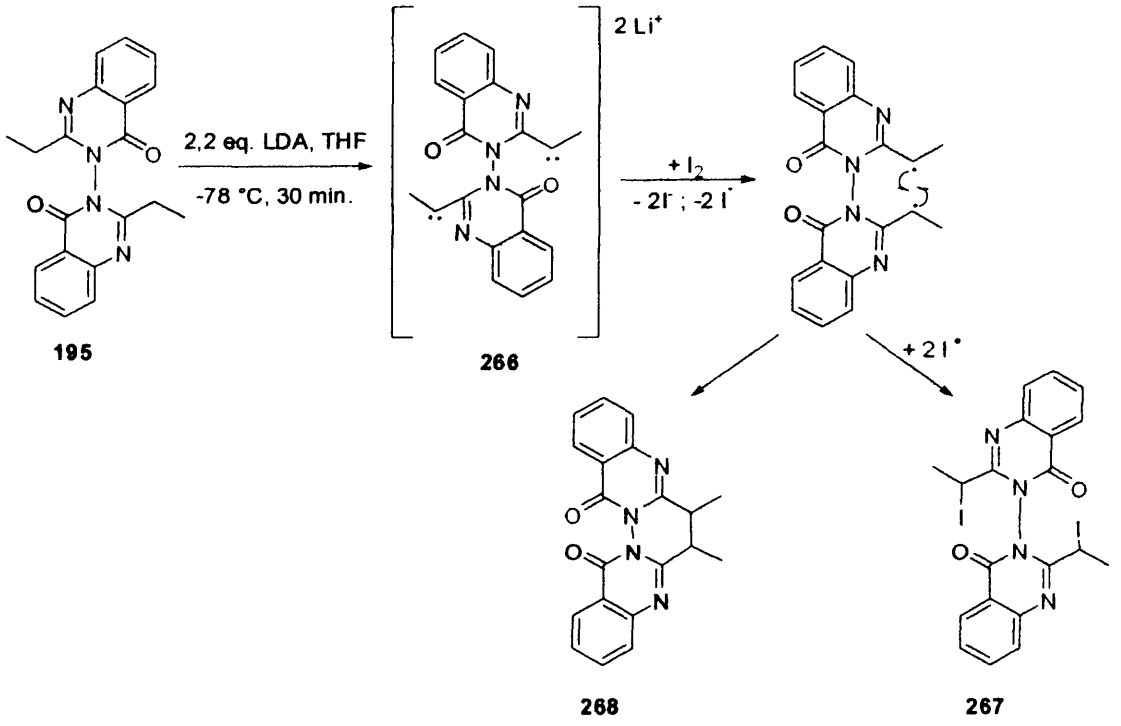


268

Figure 5-6.

Smith and co-workers reported similar behavior of the lithiated salt of 2-unsubstituted-3-acylamino-quinazolinone in its reaction with 2.2 equivalents of iodine, which led to the oxidative dimerization of this heterocycle.[1,2] Our result is also supported by the well documented tendency of electron rich carbanions to undergo oxidative dimerization when treated with oxidants like iodine or copper.[6,7,8] From a mechanistical point of view the reaction affording **268** may proceed *via* two different pathways: 1) a single electron transfer (S.E.T.) mechanism involving oxidation of the dianion by the iodine through a radical mechanism; 2) a nucleophilic intramolecular displacement of iodine by the carbanion.

According to the S.E.T. mechanism, iodine acting as an oxidizing agent, removes one electron from the dianionic **266,** forming a di-radical species which undergoes cyclization to compound **268**. This kind of mechanism is able to explain also the formation of small amount of iodinated compound **267**. Further, the di-radical species can react with an iodine radical forming two carbon halogen bonds as indicated in Scheme 5-6.



Scheme 5-6.

Evidence to support this mechanism is provided in studies by Fox and Renaud in which di-lithiated carboxylic acids treated with iodine are reported to undergo oxidative dimerization *via* the SET mechanism.[7] As shown in Figure 5-7, the dilithiated species **A** reacts with iodine by single electron transfer to give the anion **D**. This radical anion may react with iodine to give iodide **C**, which in turn can be displaced in a S_N2-type reaction by the dianion **A**, which is still present in solution. Alternatively the anion radical **D** can also give the dimer **B** by radical coupling, a route that Fox and Renaud show to be particularly important with sterically hindered anion radicals in which S_N2 reactivity is blocked. However the formation of iodide **C** by an ionic mechanism is not ruled out within this body of work.

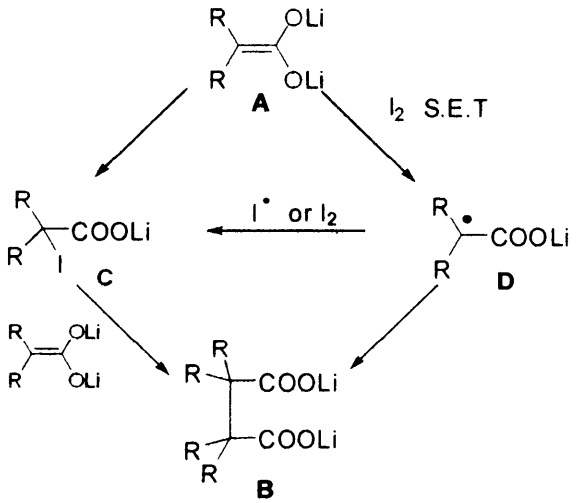
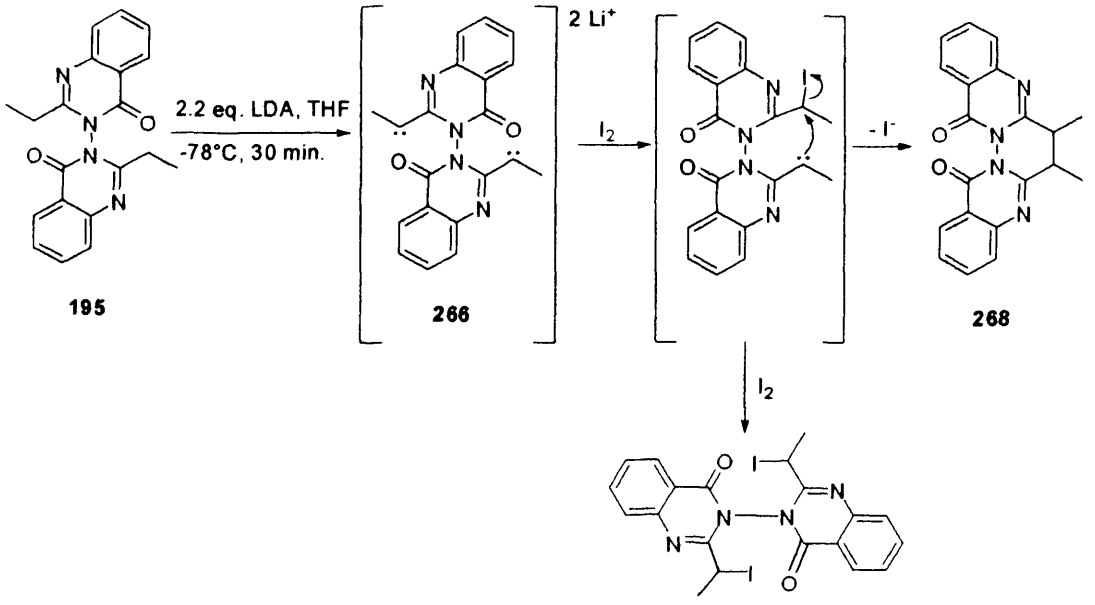


Figure 5-7.

Although the SET mechanism seems reasonable in the reaction between dianion **266** and iodine the complete exclusion of an S_N2 mechanism is not possible. Thus a mechanism for the formation of **268** *via* nucleophilic intramolecular displacement of iodine by the carbanion is proposed in Scheme 5-7. An initial iodination of one side of the biquinazolinone can occur, followed by subsequent displacement of the iodine atom in a S_N2 fashion to afford the dimer **268**. The presence of a small amount of the iodo derivative **267** in the crude ^{1}H-NMR mixture (quartet at 3.48 ppm, 1H assigned to the -CHI proton) also supports this second mechanistic hypothesis.



Scheme 5-7.

To support this second mechanism it is noteworthy to remember that the successful alkylation of ester enolates with α-haloesters and the ready formation of α-halo-esters by treatment of ester enolates with an equimolar quantity of halogens have also been reported.[9,10,11] In addition, Brocksom[12] and co-workers proposed a S_N2 mechanism for the iodine promoted dimerization of the enolate, generated by lithiation of ethyl succinate with LDA (Figure 5-8). The observation that quenching of the reaction mixture at -78°C gave only the α-iodo ester, was made by Brocksom as evidence for fast iodination of the enolate followed by slow alkylation.

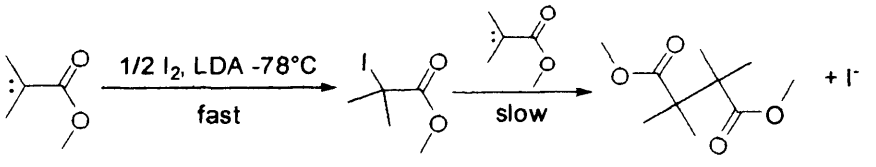


Figure 5-8.

The rapid discoloration of the solution of the dianion upon addition of iodine at -78°C is remarkably similar to the Brocksom data on α-halogenation of ester enolates. It

seems then reasonable to assume that, as in the case of the biquinazolinone, the anion **266** reacts fast with iodine forming the mono-iodo anion which is then transformed by a S_N2 mechanism into the dimer **288**. Reaction with a second iodine molecule appears then to be slow compared to the dimerization reaction. Based only on the literature data, it is not an easy task to decide which mechanism is operating in the formation of compound **288** from diethyl biquinazolinone and iodine in the presence of LDA. Of course, in order to discriminate between the two mechanisms, further studies have to be carried out. For example the influence of a radical scavenger (like TEMPO) or molecular oxygen on the course of the reaction would help to clarify the operating mechanism.

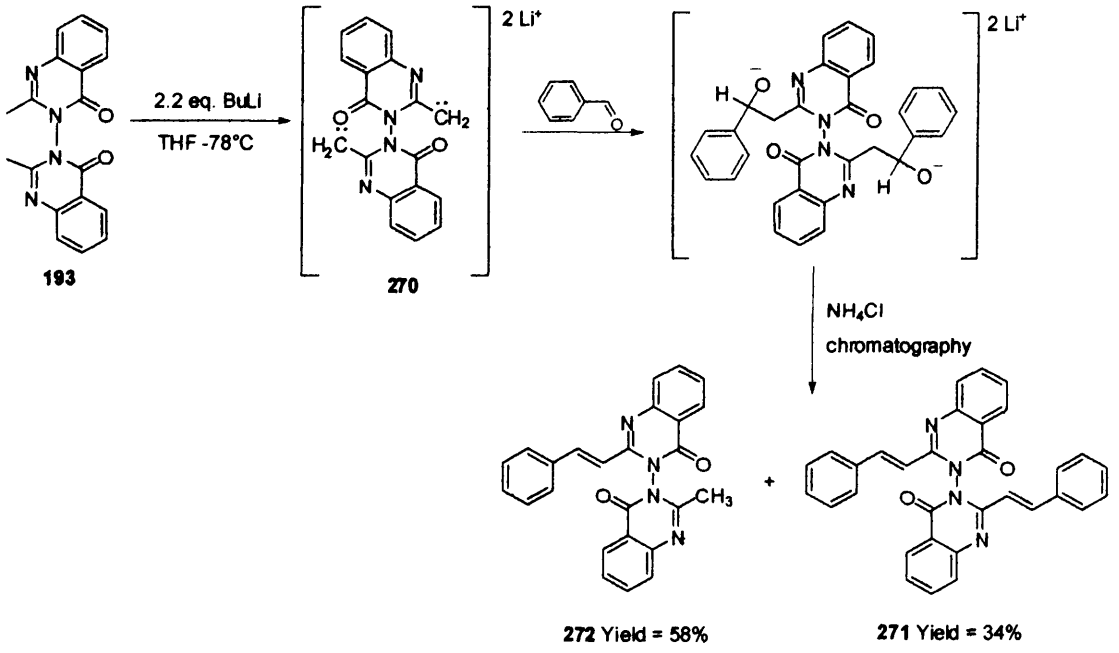
5.3 Functionalization of 2,2'-dimethyl-biquinazolinones.

Since it was quite difficult to obtain different 2-substituted biquinazolinones by functionalization of 2,2'-diethyl-biquinazolinone, it was decided to attempt the elaboration of 2-methyl-biquinazolinones *via* lithium chemistry. This route appeared to be promising in light of the reports by Smith and co-workers[13] who showed that lithiation and further elaboration of 3-amino-2-methyl-4(3H)-quinazolinone can be easily achieved with *n*-butyl lithium chemistry, and the successful results obtained by Wolfe *et al.*[3] in the functionalization of different 2,3 disubstituted quinazolinones using LDA as the lithiating agent.

5.3.1 Synthesis of styryl biquinazolinones.

In a typical procedure, 2,2'-dimethyl-3,3'biquinazolin-4,4'-one **193** was dissolved in dry THF under a nitrogen atmosphere and 2.2 equivalents of *n*-butyl lithium were added dropwise to the resulting solution at -78 °C. Over the course of the addition of *n*-butyl lithium the initial pale yellow solution turned into a deep red solution, also containing a red precipitate. This change of color was assumed to be due to the formation of the dianion **270**. Addition of 2.2 equivalents of an electrophile such as benzaldehyde at -78 °C, caused the disappearance of the red precipitate with

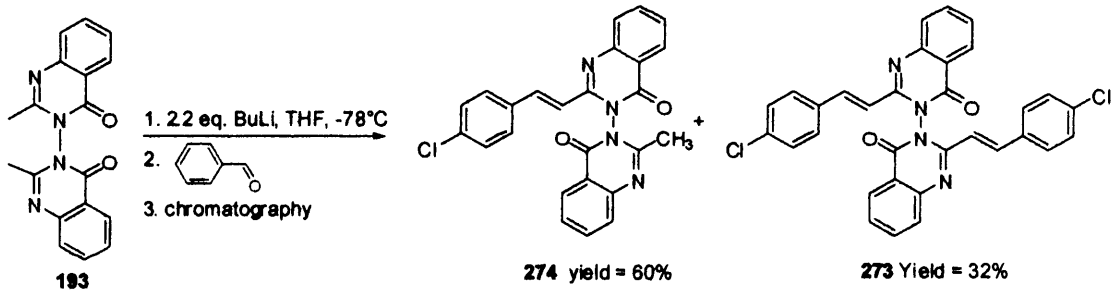
formation of a yellow solution which gave, after work, up a yellow crystalline powder (Scheme 5-8).



Scheme 5-8.

^{1}H-NMR analysis of the crude reaction mixture revealed the presence of two different compounds together with unreacted starting material. The spectrum, characterized by two sets of doublet at 6.42 and 8.05 ppm with coupling constants of 15.4 Hz, thereby being assigned to olefinic hydrogen atoms, confirms the presence of two different molecules with a styryl moiety in a *trans* configuration about the double bond. An extra singlet at 2.3 ppm, in addition to the one from the starting material (overlapping it), clearly suggests the presence of a mono styryl derivative such as **272**. Moreover, in accordance with the ^{1}H-NMR spectrum, the APCI mass spectrum of the crude mixture showed the presence of two pseudomolecular peaks, one at *m/z* 407 [M+1], consistent with **272**, and one at *m/z* 441 [M+1] that accounts for compound **271**, along with a peak corresponding to the starting material (*m/z* 319 [M+1]). The two compounds were easily separated and obtained in 34% (**271**) and 58% (**272**) isolated yields after separation by column chromatography on silica gel using ethyl acetate/ hexane 1:3 as eluent.

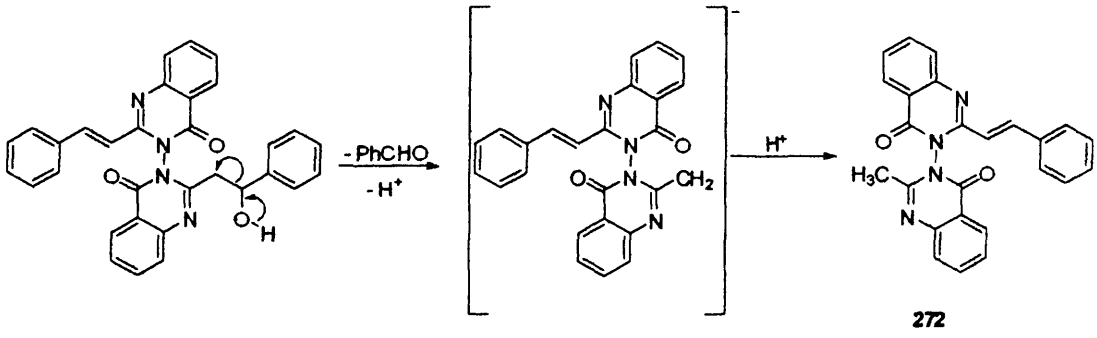
Reactions using p-chloro benzaldehyde as the electrophile, also gave a mixture of mono and di- styryl derivatives **274** and **273** in 60% and 32% yield respectively, along with a small amount of unreacted starting material (Scheme 5-9). Isolation of the two compounds was achieved by repeated crystallization (up to 7-8 crystallizations) although a quicker separation was obtained with column chromatography (silica gel, ethyl acetate/ hexane 1:3).



Scheme 5-9.

An unusual feature of the reaction between the lithiated species **270** and benzaldehyde is the lack of the hydroxyl derivative. With both benzaldehyde and *p*-chloro-benzaldehyde no sign of the hydroxylate compound was observed in the crude solid obtained after work up. It seems clear that this compound undergoes immediate dehydration during the acidic work up. It is worthy to note that Wolfe and co-workers[3] reported that 2-methyl-3-substituted quinazolinones, when treated with LDA and benzaldehyde, led to the corresponding alcohol derivative in good yields with only small amounts of styryl derivatives seen. This alcohol was successfully transformed into the corresponding styryl derivative by treatment with LiOH in a THF-water mixture. Wolfe attributes the tendency of the alcohol to undergo dehydration from the severe steric repulsion between the 3-substituent (o-tolyl) and the bulky 2-(2-hydroxy-2-phenylethyl) substituent. It appears then that the steric hindrance of the biquinazolinone moiety is responsible for the immediate dehydration of the hydroxyl derivative generated in the reaction of the anion **270** with benzaldehyde. It is interesting to note that in the Wolfe and Rathman[3] studies, 2-methyl-quinazolinone bearing a less bulky group in the 3 position with respect to the o-tolyl moiety gave the corresponding carbinol derivative in good yields and without any sign of spontaneous dehydration, which occurred only under acid hydrolytic

conditions. Moreover, the lithio salt of 3-(o-tolyl)-2-methyl-quinazolinone failed to undergo condensation with benzophenone. The persistence of the red color typical of the lithio anion throughout reaction periods up to 24 hours was taken as indicative of the fact that steric hindrance constitutes an obstacle to the formation of the new carbon-carbon bond. On the basis of the last observation pointed out in Wolfe's work, it appears that the steric hindrance of biquinazolinone could be responsible for the presence of a mono-styryl derivative and the starting material. Another possibility to take into account, in order to explain the formation of the mono-styryl derivatives **272** and **274** (plus starting material), is the operation of a retro-aldol mechanism, which was invoked to explain the observed isolation of great amount of starting material after the reaction of lithiated 2-methyl-3-o-tolyl-4(3H)-quinazolinone (methaqualone) with benzaldehydes. Wolfe proposed that the tendency of the alcohol product to undergo facile retro-aldol condensation appears to arise from severe steric repulsion between the 3-o-tolyl group and the bulky substituent in the 2 position. These interactions were evident in the ^{1}H-NMR spectrum of methaqualone with the presence of two signals for different methyl groups caused by restricted rotation around the C-N bond. On this bases a retro-aldol mechanism can be proposed for the formation of mono-styryl derivative **272** in the 2,2'-dimethyl-biquinazolinone series (Scheme 5-10).



Scheme 5-10.

In summary, it seems generally possible to obtain functionalized biquinazolinones *via* lithiation chemistry, that is, deprotonation of the activated alkyl chain in the 2 and 2' positions and subsequent reaction with electrophiles. While this is quite easy to

accomplish with the methyl derivative, it appears more difficult to do it when an ethyl group or longer alkyl chains are present in the biquinazolinone lateral chain. More detailed studies are required in order to optimize the yields (in the case of the methyl derivative) and to widen the range of electrophiles that are available for use in the case of the ethyl derivative.

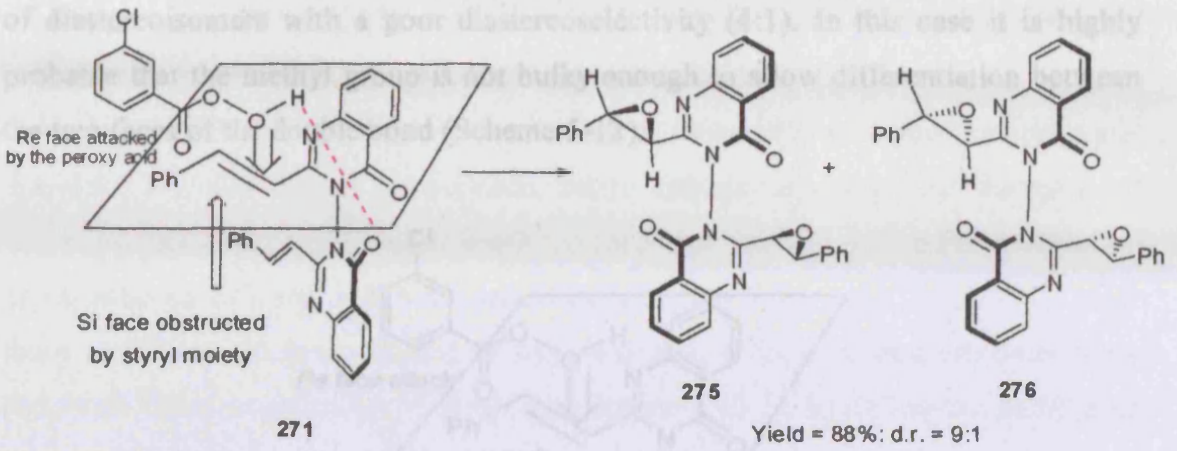
5.4 Epoxidation reactions.

One of the easiest ways to test for efficiency of asymmetric induction by the chiral axes of biquinazolinones is to epoxidize of the styryl double bond. From a vast choice of oxidizing agents, commonly employed in epoxidation reactions, the 3-chloroperbenzoic acid (*m*-CPBA) was used, which has been extensively and successfully employed in these kinds of reactions.

5.4.1 Synthesis of 2,2'-Bis-(3-phenyl-oxiranyl)-3,3'-biquinazolin-4,4'-one

In a typical procedure the di-styryl derivative **271** was dissolved in dichloromethane and *m*-CPBA then added portion-wise over a period of 30 minutes. The resulting mixture was then stirred at room temperature for one day, affording after crystallization, the pure epoxide derivatives in 88% yield.

From the ^{1}H-NMR spectrum of the crude reaction mixture, two major isomers were detected in a 9:1 ratio, confirming the high diastereoselectivity. Traces of the third diastereoisomer were just detectable in the ^{1}H-NMR spectrum. A possible explanation of the high diastereoselectivity observed is proposed in Scheme 5-11. The oxidant coordinates to the carbonyl group of the quinazolinone ring by hydrogen bonding in such a way that the oxygen can be delivered only on the top face (*Re* face) of the double bond. Moreover the rotation around the single bond between the alkene and the quinazolinone ring (-CH=CH-CH=N) seems to be hindered by the second styryl moiety and thus the *Re* face of the alkene remains the more "exposed face" to the peroxy acid and hence more easily epoxidised.



Scheme 5-11.

Conformational analysis was carried out on the di-styryl derivative **271** and the more stable conformer generated by MM calculations [14] is illustrated in Figure 5-9. Examination of this molecular model reveals that rotation around the single bond between the alkene and the quinazolinone ring is unlikely as an interaction between the phenyl group and the other quinazolinone ring appears unavoidable. It is then probable that *m*-CPBA approaches the double bond from the *Re* face, which is virtually free from any steric interaction.

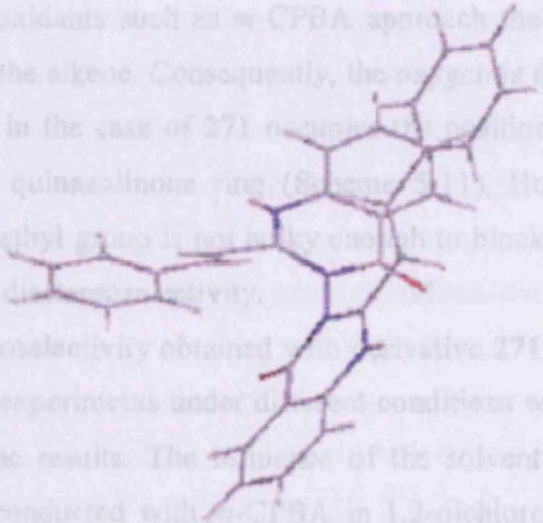
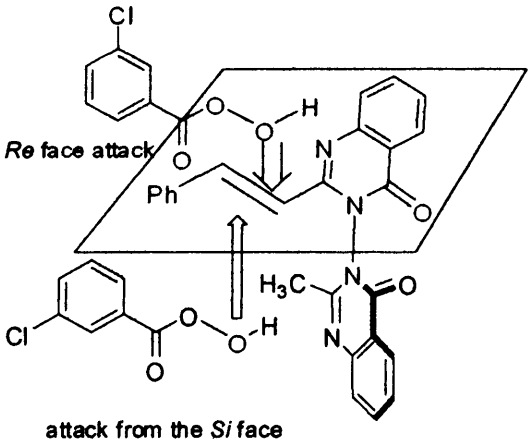


Figure 5-9.

To support this theory it is noteworthy that the epoxidation of the mono-styryl derivative **272** in DCM at room temperature with *m*-CPBA as oxidant gave a mixture

of diastereoisomers with a poor diastereoselectivity (4:1). In this case it is highly probable that the methyl group is not bulky enough to allow differentiation between the two faces of the double bond (Scheme 5-12).



attack from the *Si* face
less favoured but still possible

272

Scheme 5-12.

In addition, the steric hindrance of the bulky oxidant can be important in the determining of which face of the double bond is more susceptible to attack by the oxidant. In general, oxidants such as *m*-CPBA approach the double bond from the less hindered face of the alkene. Consequently, the oxygen is delivered to the top face of the alkene, which in the case of **271** occupies the position opposite to the styryl moiety on the other quinazolinone ring (Scheme 5-11). However, in the case of derivative **272,** the methyl group is not bulky enough to block one face of the alkene leading to poor facial diastereoselectivity.

Although the diastereoselectivity obtained with derivative **271** under these conditions was good, additional experiments under different conditions were performed in order to further improve the results. The influence of the solvent was first investigated Epoxidation of **271** conducted with *m*-CPBA in 1,2-dichloroethane gave a slightly better diastereoselectivity with a diastereomeric ratio of 10:1 and almost the same yield. Attempts in toluene and acetonitrile were unsuccessful, presumably because the

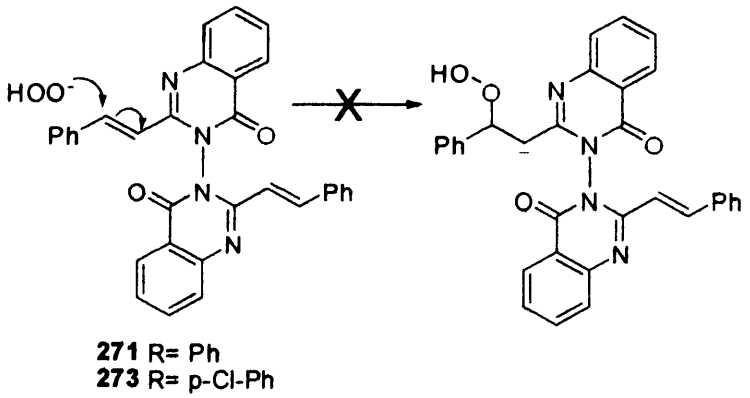
styryl derivatives **271** and **272** were insoluble in these solvents. Even with an increase in temperature up to 50°C, no epoxidation was observed.

Because diastereoselectivity is a characteristic of kinetically controlled reactions and therefore is a function of temperature, better diastereoselectivity can be obtained when epoxidation is performed at lower temperatures. For this reason the epoxidation of compounds **271** and **272** were performed with *m*-CPBA in DCM at 0°C. Under these conditions no improvement in the yield and in the diastereoselectivity were observed. Other experiments at lower temperature (-10 °C in an ice-salt bath) gave the epoxides with the same yield and comparable diastereoselectivity.

In summary the di-styryl derivative **271** shows good diastereoselectivity in epoxidation reactions while under the same conditions the mono-styryl derivative **272** gave less satisfactory diasteroselectivities, presumably due to the lack of sufficient steric bulk.

5.4.2 Attempted alkaline epoxidation.

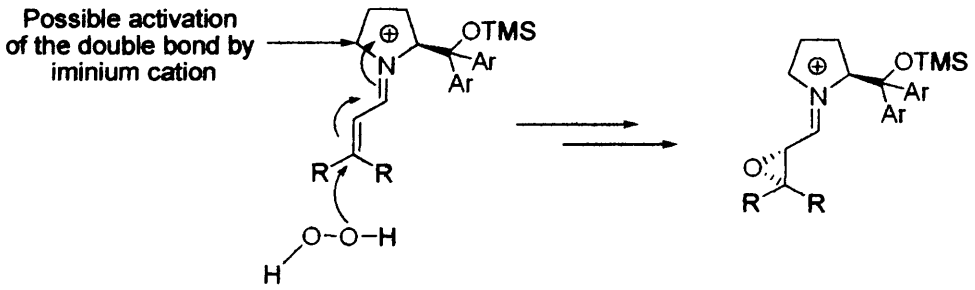
Zwanenburg[15] reported that treatment of an electron poor styryl derivative with hydrogen peroxide under basic conditions in acetone produces the corresponding epoxide in good yield. Due to the insolubility of derivatives **271** and **273** in acetone the epoxidation was performed with a modification of the previous methodology. A mixture of THF/acetone (3:1) was used as a solvent in place of neat acetone. Hydrogen peroxide and 2M sodium hydroxide were added and the resulting mixture stirred at 45°C-50°C for eight hours. Unfortunately no sign of the formation of the epoxide was detected in the ^{1}H-NMR spectrum of the crude reaction mixture and only unreacted styryl derivatives **271** or **273** were recovered. Increasing the amount of hydrogen peroxide employed as well as the reaction temperature was also unsuccessful. Mechanistically, the alkaline epoxidation normally proceeds by nucleophilic attack (in a Michael addition type) of the HOO^- to the "activated" double bond as for example the styryl double bond and is finished by a ring closure of the Michael adduct with the elimination of HO^-.



271 R= Ph
273 R= p-Cl-Ph

Scheme 5-13.

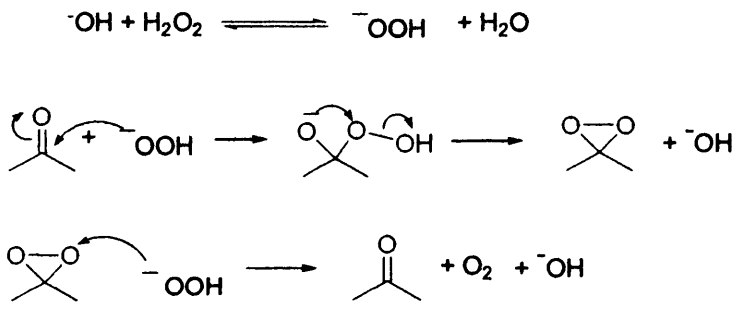
Under alkaline epoxidation conditions the double bond of either **271** or **273** seems to be unreactive towards the hydrogen peroxide ion. One possible explanation is that the quinazolinone ring is not sufficiently electron withdrawing to activate the double bond towards the attack of the hydro peroxide ion. To support this theory the results obtained by Jorgensen and coworkers[16] established that α,β-unsaturated carbonyl are efficiently epoxidised by hydrogen peroxide under alkaline conditions in the presence of a catalytic amount of chiral amine as shown in Scheme 5-14.



Scheme 5-14.

The driving force in the Jorgensen epoxidation is the formation of the iminium cation which makes the double bond more reactive towards the nucleophile. On this basis it is possible to suggest that the olefinic bond in both compounds **271** and **273** is not sufficiently activated in regard to attack of the hydroperoxy species necessary for the epoxidation

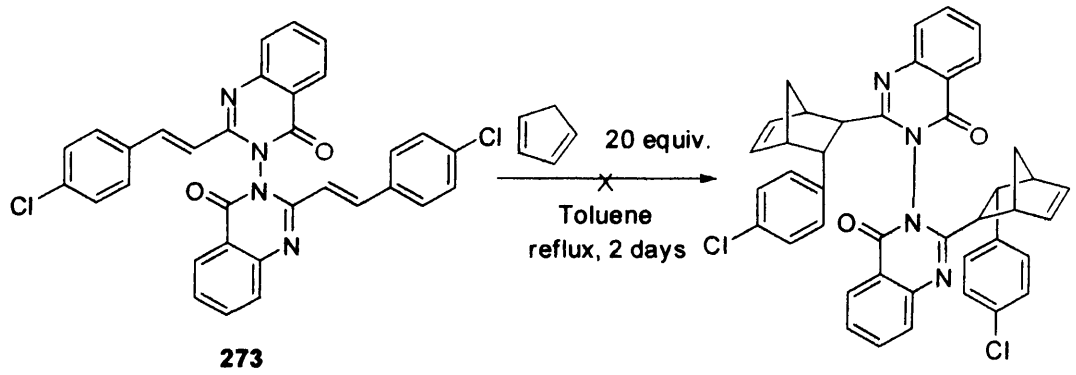
It is also possible that in the conditions employed in the reaction, part of the hydrogen peroxide present in the reaction medium, reacts with the acetone forming dimethyl dioxirane which, in the basic environment, immediately decomposes thereby removing any species able to epoxidize the double bond (Scheme 5-15).[17]



Scheme 5-15.

5.5 Diels- Alder reactions.

Following on from the positive asymmetric induction by the chiral axis on the diasteroselective epoxidation of the prochiral double bond in the styryl quinazolinone, the study of the stereochemical outcome of the reaction between the prochiral double bond in compound **273** and a suitable diene namely cyclopentadiene, was carried out. The first attempt to prepare the cycloadduct was conducted by refluxing the di-styryl derivative **273** with a large excess (20 equivalents) of freshly prepared cyclopentadiene in toluene. After one day at reflux, the solvent was evaporated and the resulting oil was treated with petrol ether in order to eliminate the unreacted dicyclopentadiene, affording a brown powder (Table 5-2, entry 1). ^{1}H-NMR analysis of the crude material obtained showed no sign of the desired cycloadduct.



273

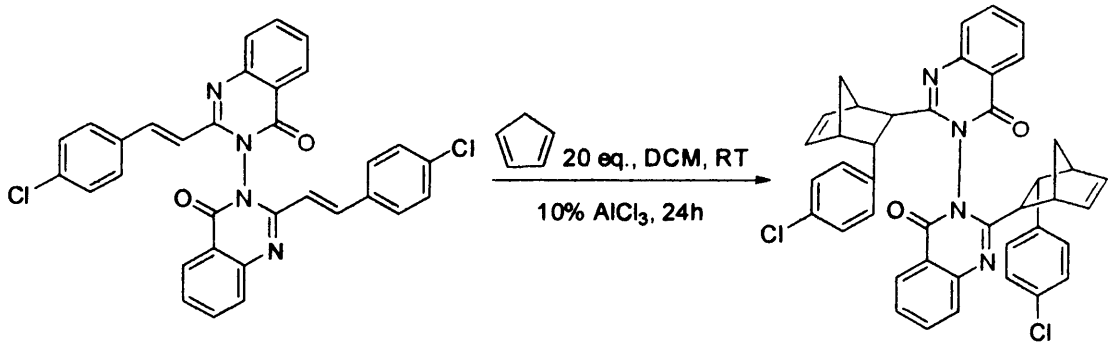
Scheme 5-16.

Along with dicyclopentadiene and the unreacted styryl derivative **273** (identified by the =C-H peaks at 8.10 and 6.48 ppm) a large broad peak at high field in the spectrum was also present. This peak probably belongs to polymeric compound, which might derive from the partial polymerization of compound **273**. The same reaction conducted at room temperature with compound **273** required higher dilution (20 ml for 100 mg of compound **273**), in order to ensure complete solubilization. Unfortunately, even under these conditions no sign of the Diels-Alder adducts was observed with only dimerization of cyclopentadiene occurring (Table 5-2, entry 2).

It is clear from the above results that the cycloaddition is reluctant to proceed without catalysis. Therefore, the cycloaddition was carried out in the presence of a Lewis acid, which has proved to be an excellent catalyst for the Diels-Alder cycloaddition.[18] Reaction of the di-styryl derivative **273** with cyclopentadiene was carried out at 25 °C in the presence of 10% $AlCl_3$ in toluene but was unsuccessful. Unfortunately, increasing the temperature up to 55 °C (at which temperature complete dissolution of all of the reagents occurred), failed to generate the expected cycloadduct and led only to cyclopentadiene dimerization (Table 5-2, entry 3). The negative results obtained with toluene prompted us to attempt the cycloaddition in a different solvent.

The reaction was thus repeated in DCM. In a typical procedure a solution of styryl derivative **273**, a 20-fold excess of cyclopentadiene and the Lewis acid, (10% mol $AlCl_3$ with respect to the styryl derivative) in DCM, were stirred at room temperature for one day. The solvent was then removed under reduced pressure giving a crude product. This time the ^{1}H-NMR spectrum of the crude mixture showed that two

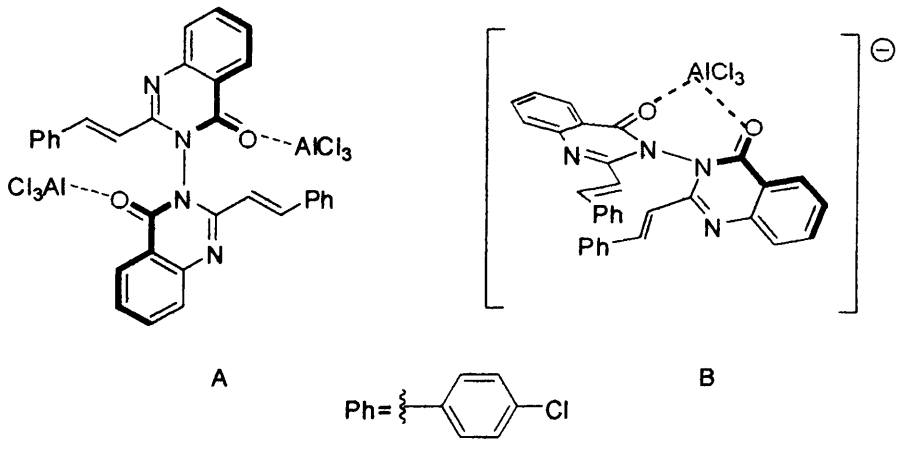
Diels-Alder adducts (**277a** and **277b**), had been formed in 80% overall yield with a diastereoisomeric ratio of 70:30 (Table 5-2, entry 4).



273 **277 a-b**
Yield = 80%
d.r = 70:30

Scheme 5-17.

From the above results it appears that the Lewis acid plays an important role in the course of the reaction by increasing the reaction rate presumably by coordination to the carbonyl group of the quinazolinone rings lowering the energy of both the HOMO and LUMO and making it in to a better dienophile. Although it is not possible to say where effectively the coordination occurs either on the imine or the carbonyl, it seems a likely hypothesis that coordination of $AlCl_3$ occurs on the carbonyl oxygen on the quinazolinone ring as indicated in Scheme 5-18.

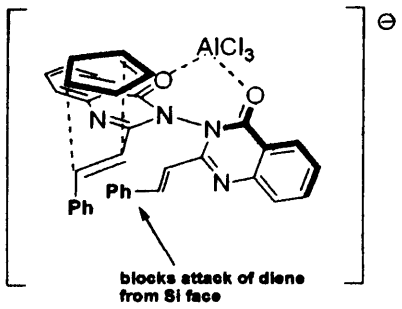


A B

Ph= Cl

Scheme 5-18.

It appears that in both cases the rate of the reaction is increased but in case A the coordination mode cannot explain the selectivity, for case B however, it could be reasoned that coordination locks the molecule in a conformation in which one face of the double bond is less crowded so the diene prefers to react from the less hindered *Re* face of the double bond (Scheme 5-19).



Scheme 5-19.

In principle, analysis of the coupling constant pattern of the bridgehead protons should be useful for the determination of the *exo/endo* stereochemistry in the Diels-Alder cycloadducts. The different dihedral angles formed between H_1 and H_6 in *endo* or *exo* cycloadducts have to lead to diverse theoretical *J* values (Figure 5-10).

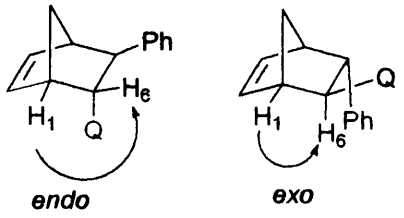


Figure 5-10.

Unfortunately in our case the signals belonging to the bridgehead protons appeared as two broad singlets making impossible to use them as a stereochemical probe.

It is clear that in the future the availability of a crystal structure of one of those products could disclose without any doubt the stereochemistry of the cycloadducts obtained. Attempts to reduce the amount of Lewis acid failed to give the Diels-Alder

adducts in good yield. When the reaction was carried out in DCM in the presence of only 1% of $AlCl_3$ after two days of reaction at room temperature, only 10% of the product was observed in the ^{1}H-NMR spectrum of the crude reaction mixture (Table 5-2, entry 5). In order to test the influence of the acid catalyst on the selectivity of the Diels-Alder reaction, copper triflate ($CuOTf_2$) was employed instead of $AlCl_3$. Under the conditions adopted for the $AlCl_3$ reaction (10% $CuOTf_2$, DCM, room temperature, 24 hours) a slight increase in the yield was observed with no improvement in the stereoselectivity, which was the same as that observed in the aluminum catalyzed cycloaddition (judging from integration of ^{1}H-NMR spectrum of the crude mixture).
It is well known that selectivity can be enhanced when the reaction is carried out at low temperatures, but in this case when the Diels-Alder was carried out at 0 °C in DCM for 12 hours, in the presence of either 10% $AlCl_3$ or 10% $Cu(OTf_2)$, no sign of the cycloadduct was observed and only starting material was recovered with the cyclopentadiene dimer. The Table 5-2 summarizes all the data obtained for the Diels-Alder reactions performed.

Entry	Comp.	[diene]	Cat. (%)	Solvent	Temp. (°C)	Yield (%)	*endo:exo*
1	273	20 eq.	-	toluene	reflux	-	-
2	273	20 eq.	-	toluene	RT	-	-
3	273	20 eq.	$AlCl_3$ (10)	toluene	RT to 55°C	-	-
4	273	20 eq.	$AlCl_3$ (10)	DCM	RT	80	70:30
5	273	20 eq.	$AlCl_3$ (1)	DCM	RT	10	70:30
6	273	20 eq.	Cu $(OTf)_2$ (10)	DCM	RT	85	70:30
7	273	20 eq.	Cu $(OTf)_2$ (10)	toluene	RT	-	-
8	273	20 eq.	$AlCl_3$ (10)	DCM	0 °C		
9	273	20 eq.	Cu $(OTf)_2$ (10)	DCM	0 °C	-	-

Table 5-2.

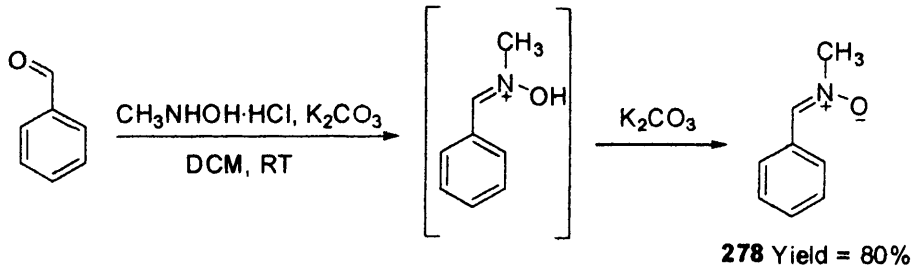
The data reported in Table 5-2 shows that the solvent, the concentration of Lewis acid catalyst and the temperature are important factors for the formation of the Diels Alder cycloadduct.
Results from this preliminary investigation show that the chiral axis of the biquinazolinone is able to influence the stereochemical outcome of the Diels-Alder cycloaddition. Further investigations are necessary in order to improve the yields and

the diastereoselectivity of these reactions. Determination of the configuration of the cycloadduct by means of X-ray crystallography would be necessary in order to have a clearer picture of the reaction outcome. Moreover, a better screening of solvent systems, temperature, and Lewis acid catalysts would be a necessary step to accomplish the development of a new family of chiral auxiliaries.

5.6 1,3-Dipolar cycloadditions.

In order to further evaluate the influence of the chiral axis of the biquinazolinones on asymmetric induction in the reactions of the biquinazolinone lateral chain, the 1,3 dipolar cycloaddition between the styryl derivatives **271** and *C*-phenyl-*N*-methyl nitrones **278** was also investigated.

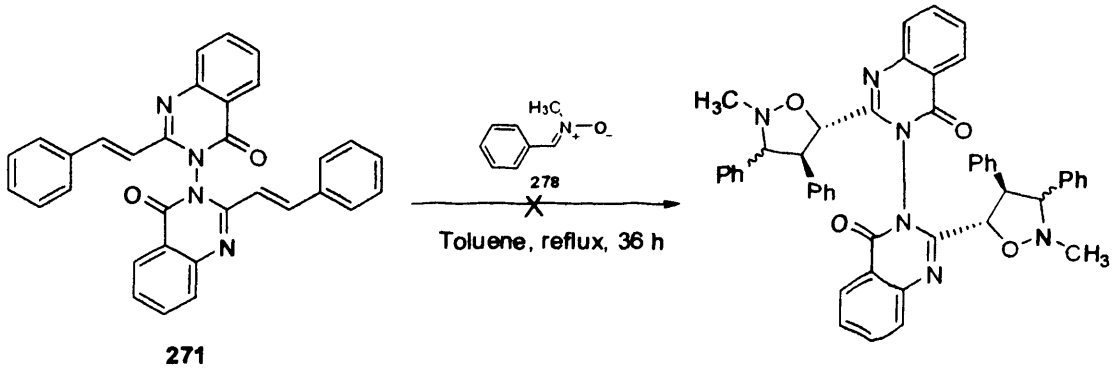
The straightforward synthesis of nitrone **278** was accomplished following a modification of the original procedure developed by Torsell. [19] A solution of benzaldehyde in DCM was treated with commercially available *N*-methyl hydroxylamine chloridrate in the presence of an excess of potassium carbonate (3 eq.). Free methyl-hydroxylamine, generated *in situ* with potassium carbonate, condensed with benzaldehyde, giving the corresponding hydroxyl-imine derivative, which in turn was deprotonated by excess base to afford crude **278.** Pure nitrone **278** was finally obtained by crystallization from petroleum ether in 80% yield as a white crystalline solid (Scheme 5-20).



Scheme 5-20.

With nitrone **278** in hand, attempts to produce the isoxazolidine derivatives by reaction with the styryl derivative **271** were then undertaken. Both reagents were

dissolved in deuterated chloroform in a NMR tube and left at room temperature. The reaction was followed by ^{1}H-NMR over a period of three weeks with no observable reaction. Analogous results were obtained using toluene as a solvent but in this case the failure of the reaction could be due to the poor solubility of the styryl derivative **271** at room temperature in this solvent. After these unencouraging preliminary results, the attempted cycloaddition was carried out in toluene under reflux, but after one day under these conditions no sign of the desired product was observed by TLC or in the ^{1}H-NMR spectrum of the crude reaction mixture (Scheme 5-21).



271

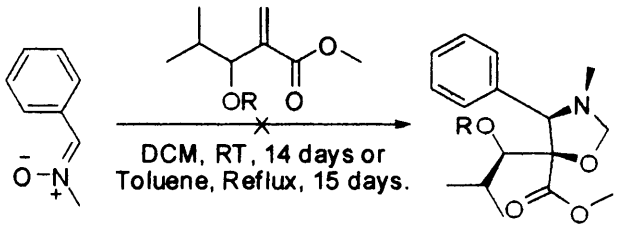
Scheme 5-21.

Screening of the literature revealed that 1,3-dipolar cycloadditions in toluene or DCM require prolonged reflux times (from several hours to several days). Fisera[20] reported that chiral nitrones undergo dipolar cycloaddition to Baylis-Hillman adducts in DCM after fourteen days at room temperature or after seven days in refluxing DCM (88 % and 92 % yield respectively). Unfortunately even with prolonged reaction times the styryl biquinazolinone **271** and nitrone **278** failed to give the desired cycloadduct.

Considering our previous experience of the Diels-Alder reaction we decided to attempt the same cycloaddition in the presence of a Lewis acid. Among the wide variety of Lewis acids available, a "mild" acid (compared to $AlCl_3$ for example) such as zinc bromide was chosen. This acid had been used successfully by Merino[21] in the cycloaddition of *N*-benzyl nitrone with alkenes. Unfortunately when compound **271** was reacted with **278** in the presence of 5% zinc bromide in DCM no reaction occurred and only starting materials were recovered. Moreover, no sign of the

cycloadduct was observed when the reaction was attempted in refluxing toluene for three days. Increasing the concentration of zinc bromide from 5% up to 10 % gave no results either.

All these results are in agreement with the results reported by Hameter[22] who found that the attempted 1,3-dipolar cycloaddition of C-phenyl-N-methyl nitrone with electron poor alkene failed to give the desired cycloadduct under harsh conditions such as 15 days at reflux in toluene as indicated in Scheme 5-22.



Scheme 5-22.

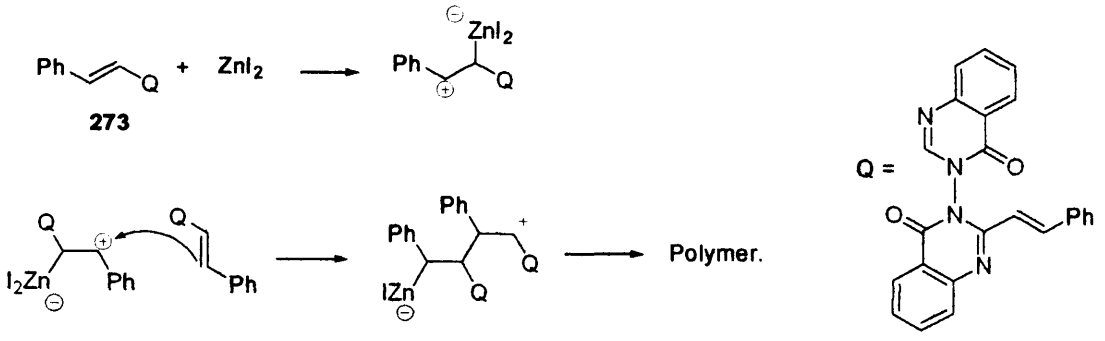
Probably in our case, the lack of reactivity observed in the conditions showed above was due to large steric demand from both the starting materials. This is in accordance with the fact previously observed that the synthesis of crowded biquinazolinones is quite sensitive to the steric bulk of the reagents involved in the reaction. As suggested by other authors, performing the cycloaddition under high pressure could be helpful in the successful preparation of the 1,3 dipolar cycloadducts.[23] Further it would be interesting to investigate the effect that stronger Lewis acids may have on the rate of the cycloaddition between nitrones and styryl biquinazolinones.

5.7 Cyclopropanation reactions.

The study of the cyclopropanation reaction of the double bond present on the lateral chain of the biquinazolinones so far synthesized was also undertaken. Among the various methods for the cyclopropanation of olefins presented in the literature, the method originally proposed by Simmons and Smith,[24] and developed by Furukawa,[25] based on the use of a CH_2I_2 / $ZnEt_2$ mixture was chosen. Following Furukawa's, procedure the styryl derivative **273** was dissolved in dry and degassed DCM and the

resulting solution was cooled to 0°C under a stream of nitrogen. After 10 minutes, one equivalent of diethyl zinc was added followed by the addition of two equivalent of CH_2I_2. The resulting mixture was stirred at 0 °C for a further 30 minutes then allowed to reach room temperature and stirred for a further 30 minutes. Unfortunately, only the unreacted styryl derivative **273** was recovered from the reaction mixture after work up. Repeating the reaction by prolonging the stirring at room temperature for more then one day was also unsuccessful and no sign of the cyclopropane derivative was observed in the ^{1}H NMR of the crude mixture.

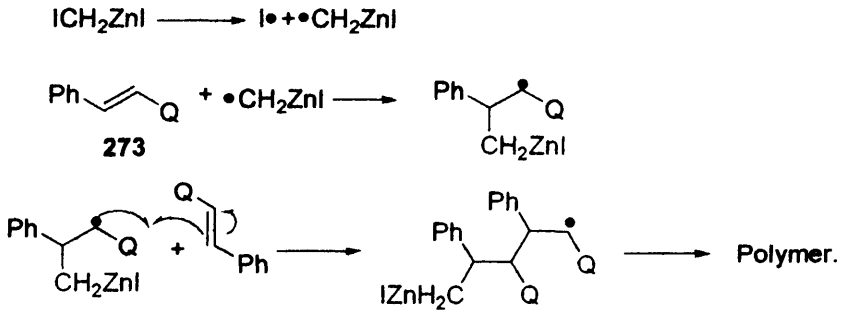
Considering that maybe the concentration of the active species was too low for the reaction to occur, the number of equivalents of both reagents was increased, maintaining the same ratio as before (Et_2Zn / CH_2I_2 1:2). Under these conditions the disappearance of the signals due to the olefinic protons was observed, but also the appearance of a broad peak in the aromatic region in the ^{1}H-NMR spectrum of the crude reaction mixture was observed. The presence of this broad signal could be due to a partial polymerization of the styryl part of the biquinazolinone, catalyzed by the strong Lewis acid ZnI_2 (Scheme 5-21).



Scheme 5-23.

Confirmation for this hypothesis was found in the original work by Simmons and Smith[26] in which they reported that yields in the cyclopropanation of styrene are sometimes low because of polymerization side reactions. It is also possible to suggest that polymerization could proceed by a radical mechanism due to homolytic dissociation of the ICH_2ZnI as proposed in Scheme 5-24.

A similar mechanism has been proposed also by Simmons and Smith[26] in their paper on cyclopropanations.



Scheme 5-24.

Also present in the ^{1}H-NMR spectrum was a broad multiplet in the aliphatic region between 0.8 and 1.5 ppm, which is the typical position for the hydrogen of the cyclopropane ring.[27] This suggested the presence of a cyclopropane ring. In order to remove the polymer the crude mixture was filtered through a pad of silica gel using diethyl ether as a solvent. However, the ^{1}H-NMR spectrum of the solid, obtained after evaporation, only showed very small amounts of cyclopropane suggesting that probably all the material was the polymeric species. No sign of the peaks typical of cyclopropane were detected in the filtrate even after elution with different solvents.

More studies on the cyclopropanation reaction are necessary as it is not immediately apparent that substrates such as **273** can not be transformed in to the corresponding cyclopropane. From these preliminary results it seems that the double bond in the styryl biquinazolinone is not prone to undergo cyclopropanation. Because of the electrophilic nature of the carbenoid reagent, it is reasonable to believe that the alkene is deactivated towards this kind of reagent by the *p*-chlorophenyl ring and by the quinazolinone ring both being electron withdrawing. It would be interesting to test the cyclopropanation on the styryl derivative with aldehydes bearing electron donating substituents (for example *p*-methoxy benzaldehyde and analogues) in order to test if electronic effects have some influence on the cyclopropanation. In light of this, alternative cyclopropanation reactions could be used in order to form the cycloalkane. A valid alternative could be the Michael-initiated ring closure method which involves the conjugated addition of nucleophiles like, for example, sulfonium salt,[28,29] or

phosphonites [30] to an electrophilic alkene to produce an enolate, which then subsequently undergoes an intramolecular ring closure. Styryl biquinazolinones with electron withdrawing groups in the aromatic ring would be a good candidate for this kind of reaction.

5.8 Other diastereoselective reactions of biquinazolinones.

The synthesis of a biquinazolinone bearing an alcoholic group (compound **251**), discussed in Chapter Three (see section 3.2.5), was carried out in order to provide a precursor compound to investigate any potential stereoinduction by the chiral axis of the biquinazolinone.

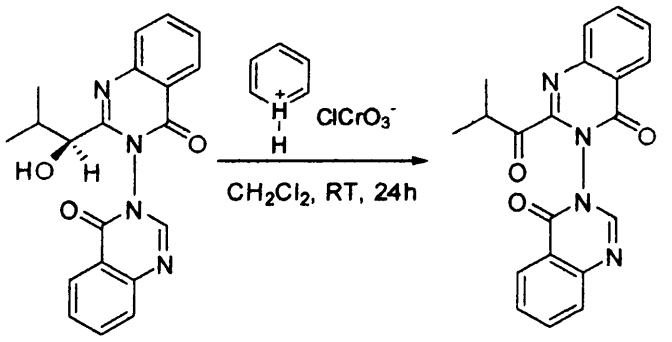
When a chiral alcohol is oxidized to the corresponding ketone, the chiral center is eliminated, and a prochiral material created. Therefore, oxidation of alcohol **251** to the corresponding ketone **279** was envisaged as a good strategy to afford a prochiral intermediate suitable for further diastereoselective synthesis of new quinazolinones scaffolds.

Because asymmetric reactions of carbonyl compounds, (i.e. asymmetric reduction, aldol condensation, and many others), have been extensively investigated in the past, we were in the position to use some of these reactions to test the stereoinduction of the chiral axis of the biquinazolinone on the asymmetric reaction of a prochiral carbonyl group.

5.8.1 Synthesis of 1-oxo-2-methylpropyl-2'-H-3,3'-biquinazoline-4,4'-dione 279.

The synthesis of 1-oxo-2-methylpropyl-2'-H-3,3'-biquinazoline-4,4'-dione **279** was easily accomplished following the method published by Corey and co-workers in 1975.[31] A solution of **251** in DCM was treated with 1.5 equivalents of solid pyridinium chlorochromate and the resulting black mixture was stirred at room temperature for one day. The mixture was then diluted with diethyl ether, decanted from the black precipitate and the combined organic phases were filtered through a plug of Celite in order to eliminate the metal residues. Evaporation at reduced

pressure gave a pale brown solid which, after crystallization from methanol gave the ketone **279** in 87% yield (Scheme 5-25.). The proposed structure for compound **279** is supported by the presence of two carbonyl bands at 1693 cm^{-1} (quinazolinone C=O) and 1714 cm^{-1} (the carbonyl group in the lateral chain), by mass spectrometry (APCI, *m/z* 361.1, $M+H^+$) and by ^{1}H-NMR with the characteristic disappearance of the doublet at 4.89 ppm belonging to the CHOH in the starting material.



251 **279** Yield = 87%

Scheme 5-25.

5.8.2 Attempted reduction of 1-oxo-2-methylpropyl-2'-H-3,3'-biquinazoline-4,4'-dione 279.

The ketone **279** can be simply reduced back to the alcohol **251** in order to verify whether any diastereoselectivity can be achieved by the chiral axis of the biquinazolinone scaffold. However the stereochemistry of the chiral axis could in principle shield one face of the ketone and permit the delivery of the hydride to the other face of the double bond as illustrated in Figure 5-11.

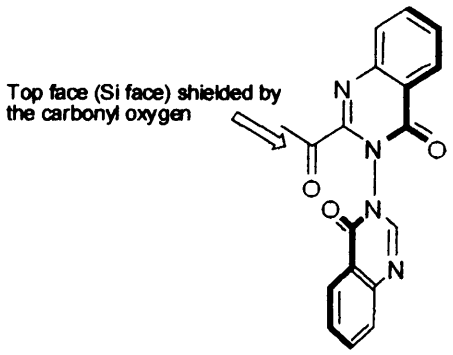
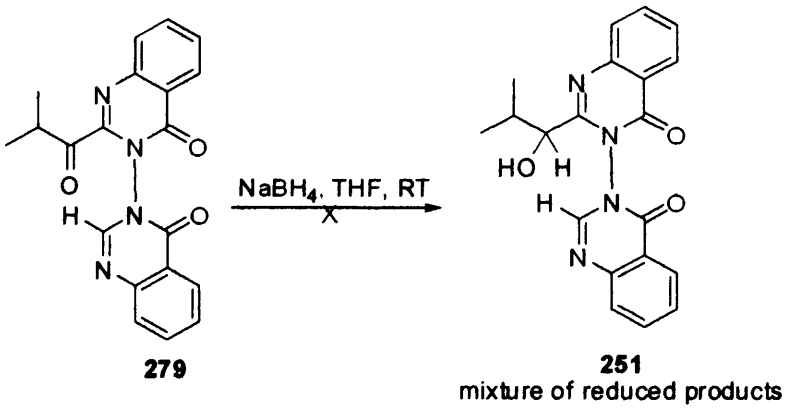


Figure 5-11.

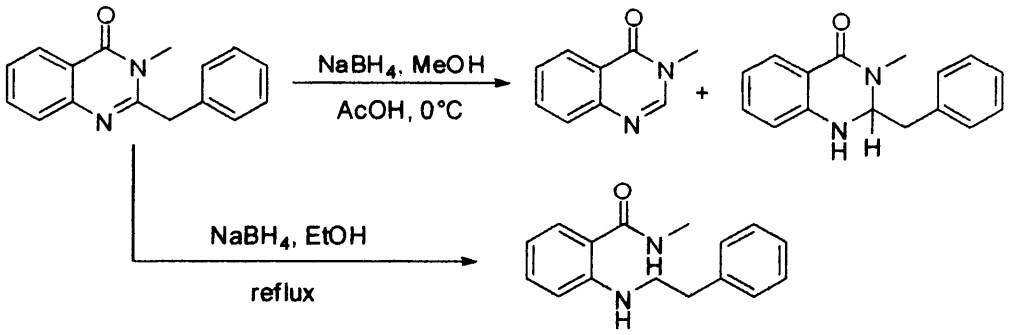
Reduction of a ketone is normally accomplished by the addition of a hydride ion provided by compounds like $LiAlH_4$ or $NaBH_4$. The alkoxide ion formed, after subsequent protonation by an acid added in the work up step, produces the corresponding alcohol. One potential problem in the reduction of ketone **279** arises from the presence of the C=N moiety, which it also susceptible to reduction. For this reason the reaction was first attempted using the less reactive $NaBH_4$.

In a standard procedure ketone **279** was dissolved in ethanol and then the metal hydride added portion wise, following the reaction by TLC. Due to the poor solubility of compound **279** in ethanol, the reduction of the ketone did not occur and only starting material was recovered. The reaction was then attempted in THF as the ketone **279** is entirely soluble in this solvent. In spite of the poor solubility of $NaBH_4$ in THF, the reaction proceded rapidly as evidenced by the disappearance of the starting material (by TLC) after one minute following addition of the reducing agent. The solid mass obtained after work up was then analyzed by ^{1}H-NMR spectroscopy. Quite disappointingly, the spectrum showed the presence of a rather complex mixture of products. The presence of a peak around 4.78 ppm suggested that reduction of C=N group had probably occurred.



Scheme 5-26.

The presence of other products in the reaction mixture was also consistent with some literature reports, which showed that some quinazolinone derivatives undergo decomposition to the corresponding open amide when treated with reducing agents as outlined in Scheme 5-27.

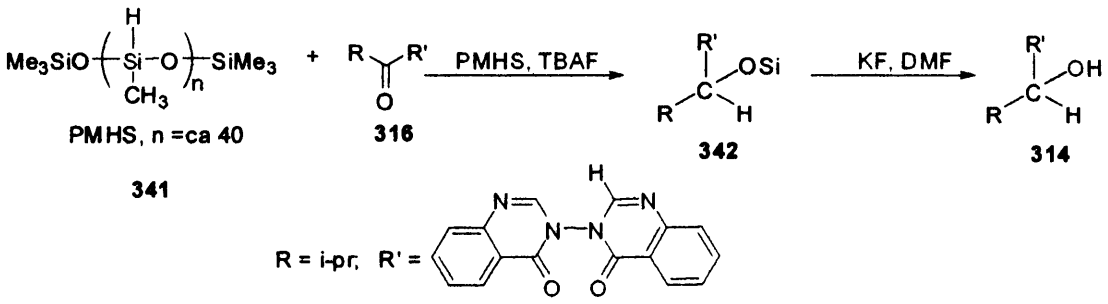


Scheme 5-27.

In order to control the reaction outcome, a different solvent system was used. However, when the reaction was carried out in a 50:50 mixture of THF/ ethanol (a solvent in which ketone **279** is only partially soluble), no reaction was observed and unreacted starting material was recovered. Further attempts with different ratios of the two solvents gave similar poor results, with only starting ketone recovered in all cases. At this point due to the difficulties encountered in controlling the reaction conditions, no further attempts at reduction with $NaBH_4$ were carried out.

5.8.3 Attempted reductions of ketone 279 with polymethyl hydrosiloxane (PMHS).

An alternative method for the reduction of compound **279** was suggested by by Lawrence group in the Cardiff Chemistry Department, who developed a reduction reaction based on polymethylhydrosiloxane (PMHS) and a tin derivative as a catalyst.[32] In the literature there are several other similar reactions which use different siloxane activators and after screening several of those methods, the procedure proposed by Kobayashi[33] was followed. In this paper, several aldehydes and ketones were reduced to the corresponding alcohols by using a combination of polymethylhydrosiloxane $\{Me_3SiO\text{-}[(CH_3)\ HSiO]_nSiMe_3\}$ and TBAF. In a typical procedure compound **279** was dissolved in THF together with one equivalent of TBAF and to the resulting solution, 1.5 equivalent of PMHS were added at 0 °C. The mixture was stirred for a further 20 minutes at 0°C and then the solvent removed *in vacuo*. The residue was dissolved in a 1:1 mixture of ethyl ether and acetone and then KF was added to the solution (Scheme 5-28). The resulting mixture was stirred for 30 minute at room temperature and filtered through a pad of Celite® (with ether as solvent). Unfortunately the ^{1}H-NMR spectrum of the crude mixture revealed that no reduction had occurred and only peaks belonging to the polysiloxane were visible along with peaks belonging to the unreacted starting material. In the original paper the evolution of gas (hydrogen) was observed after the addition of the silane to the reaction mixture. Because no evolution of hydrogen was observed in the reaction of compound **279** with PMHS it can be concluded that the first step failed. Increasing the amount of silane (up to four equivalents of H were used) failed to give the corresponding silyl ether.



Scheme 5-28.

From the synthesis of the unsymmetrical biquinazolinones (described in Chapter Two), this kind of molecule is sensitive to steric effects. It is then reasonable to believe that the bulky PMHS is too sterically demanding and its reaction with **279** is unfeasible. Therefore the use of other less bulky silanes in order to establish if steric effects were the real problem in this reaction would be reasonable. According to Corriu,[34] bulky ketones such as 4-*tert*-butyl cyclohexanone are only partially reduced and without selectivity by PMHS or diethoxymethylsilane in the presence of excess KF in DMF.

Summary.

In this chapter the functionalization of symmetrical ethyl and methyl biquinazolinones has been presented. While the elaboration of diethyl biquinazolinone **195** has proved to be difficult *via* deprotonation by an organometallic base and further reaction with electrophiles, the same procedure allowed us to synthesize and functionalize compound **193**.

With diethyl biquinazolinone **195**, it was only possible to react the corresponding anion with iodine leading to the formation of the dimer **268** due to the oxidative dimerization of dianion **266**. Reaction with other electrophiles, failed to give the corresponding products. The reason for this poor reactivity was explained by the stability of the dianion, which was therefore reluctant to react with electrophiles. The reason for this is not yet clear but it is possible that it comes from steric hindrance of the lone pair on the anion and by internal coordination of the lithium counterion between the two halves of the biquinazolinones.

The methyl derivative **193** appears to be more reactive in comparison to the diethyl derivative, and its treatment with an organometallic base followed by addition of benzaldehyde led to the formation of the corresponding styryl derivatives. The partial formation of the mono-styryl product and the absence of the hydroxyl derivative led us to think that a retro-aldol mechanism, forced by the steric hindrance of the molecule, was operating. These substrates have been valuable materials for the studies on the stereo-induction of the chiral axis on asymmetric reaction of the prochiral double bond of compounds **271** and **273**. Epoxidation of compound **271** with *m*-CPBA led to the corresponding epoxides whit good diastereoselectivity and in good yield. The attempted alkaline epoxidation failed to produce the corresponding epoxy-biquinazolinones presumably because the quinazolinone ring is not electron-withdrawing enough to activate the double bond toward nucleophilic attack from the hydroperoxide ion.

The Diels-Alder reaction between **273** and cyclopentadiene in the presence of a catalytic amount (10%) of $AlCl_3$ gave the corresponding cycloadduct in moderate yield and moderate diastereoselectivity.

Unfortunately, 1,3-dipolar cycloaddition and cyclopropanation of compounds **273** and **271** failed to give the corresponding products under the screening of various reaction conditions. In the case of the 1,3-dipolar cycloaddition attempts, unreacted starting material was always recovered even after several days of reaction. In the case of cyclopropanation partial polymerization of the styryl derivative **273** occurred under the Simmons-Smith protocol.

Finally, we tried to test the ability of the biquinazolinone scaffold to induce asymmetry by the oxidation of compound **251** to the corresponding ketone **279** and then reducing it back to the alcohol with sodium borohydride or PMHS/TBAF. In the first case we were only able gave an inseparable mixture of reduced products, meanwhile in the latter unreacted starting materials were recovered.

Further investigation is necessary in order to elucidate the reason for these failures and, in the case of those which gave positive results, to improve the stereochemical outcome and yields.

REFERENCES.

[1] K. Smith, G. A. El-Hiti, M. F. Abdel-Megeed, M. A. Abdo, *Collect. Czech. Chem. Commun.*, 1999, **64**, 515.

[2] G. A. El-Hiti, M. F. Abdel-Megeed, M. A. Abdo, *Synthesis*, 2004, 2121.

[3] T. L. Rathman, M. C. Sleevi, M. E. Krafft, J. F. Wolfe, *J. Org. Chem.*, 1980, **45**, 2169.

[4] T. P. Murray, J. V. Hai, D. E. Portlock, J. F. Wolfe, *J. Org. Chem.*, 1974, **39**, 595.

[5] G. A. El-Hiti, *Heterocycles*, 2000, **57**, 327.

[6] T.J. Brocksom, N Petragnani, R. Rodrigues, H La Scala Teixeira, *Synthesis*, 1975, 396.

[7] P. Renaud and M. A. Fox, *J. Org. Chem.*, 1988, **53**, 3745.

[8] J. L Belletire and D. F. Fry, *J. Org. Chem.*, 1987, **52**, 2549.

[9] B. E. Hudson, C. R. Hausers, *J. Am. Chem. Soc.*, 1941, **63**, 3156.

[10] W.G. Kofron, C.R. Hausers, *J. Org. Chem.*, 1970, **35**, 2085.

[11] R. N. McDonald, R. R. Reitz, *Chem. Commun.*, 1971, 90.

[12] T. J. Brocksom, N. Petragnani, R. Rodrigues, H. La Scale Teixeira, *Synthesis*, **1975**, 396.

[13] K. Smith, G. A. El-Hiti, M. F. Abdel-Megeed, M. A. Abdo, *J. Org. Chem.*, 1996, **61**, 656.

[14] Performed with Chem 3D Ultra 9.0.

[15] B. Zwanenburg, J. Ter Wiel, *Tetrahedron Lett.*, 1970, **12**, 935.

[16] M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964.

[17] W. Adam, R. Curci, J. O. Edwards, *Acc.Chem. Res.*, 1989, **22**, 205.

[18] a) P. Yates, P. Eaton, *J. Am. Chem. Soc.*,1960, **82**, 4436; b) C. K. N. Houk, R. W. Strozier, *J. Am. Chem. Soc.*, 1973, **12**, 4094.

[19] K. Torsell, O. Zeuthen, *Acta Chem. Scand., Sect. B*, 1978, **B32**, 118.

[20] B. Dugavic, L., Fisera, C. Hametner, M. K. Cyuransky, and N. Pronayova, *Monatshefte für Chemie*, 2004, **135**, 685.

[21] P. Merino, T. Tejero, M. Laguma, E. Cerrada, A. Moreno, J. A. Lopez, *Org. Biomol. Chem.*, 2003, **1**, 2336.

[22] B. Dugovic, L.Fišera, C. Hametner, N. Prónayová, *Arkivoc*, 2003, **14**, 162-169.

[23] a) I. Blanáriková, L. Fišera, Z. Kopaničáková, P. Salanski, J. Jurczak, and C.Hametnerc, *Arkivoc*, 2003, **14**, 162-169; b) F. Cardona, P. Salanski, M. Chmielewski, S.Valencia, A. Goti, A. Brandi, *Synlett*, **1998**,1444.

[24] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.*, 1958, **80**, 5323.

[25] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron, Lett.*, 1966, **7**, 3353; b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron*, 1968, **24**, 53.

[26] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256.

[27] a) A.B. Charette, H. Juteau, H. Lebel, C. Molinaro, *J. Am. Chem. Soc.*, 1998, **120**, 11943; b) J.-F. Fournier, S. Mathieu and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 13140.

[28] F. Krollpfeiffer, H. Hartmann, *Chem. Ber.*, 1950, **83**, 90.

[29] a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 867; b) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.

[30] D. Caine, *Tetrahedron*, 2001, **57**, 2643.

[31] E. J. Corey and J. W. Suggs, *Tetrahedron, Lett.*, 1975, **31**, 3127.

[32] N.J. Lawrence, M.D Drew, S.M. Bushell, *J. Chem. Soc., Perkin Trans.* 1, 1999, 3381.

[33] Y. Kobayashi, E. Takahisa, M. Nakano, K. Watani, *Tetrahedron*, 1997, **53**, 1627.

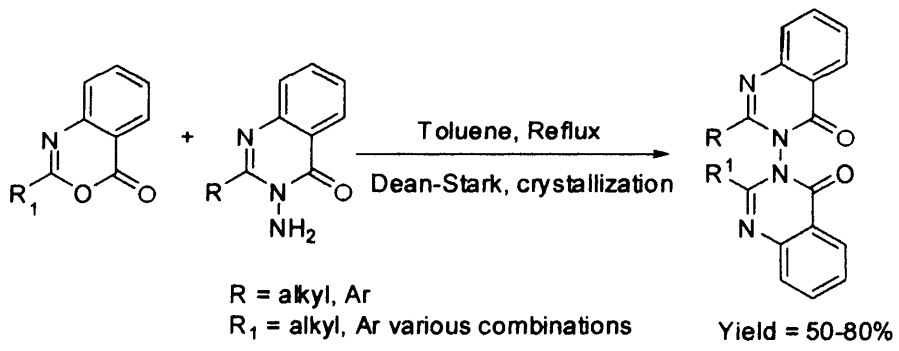
[34] a)C. Chuit, R. J. P. Corriu, R. Perz, C. Reye', C. Chuit, R. J. P. Corriu, R. Perz, C. Reye', *Synthesis*, 1982, 981; b) R. J. P. Corriu, R. Perz, C. Reye', *Tetrahedron*, 1983, **39**, 999.

Chapter 6: Conclusions.

The work herein stands as an independent investigation into the synthesis of axially chiral 2,2'-disubstituted biquinazolinones towards their potential applications as chiral auxiliaries in asymmetric synthesis.

Previous work within the group had shown that biquinazolinones with various substituents on the 2,2' position exist as atropisomers due to the hindered rotation around the *N-N* bond. These earlier studies proved to be possible, depending on the nature of the substituent in the lateral chain, to isolate the single atropisomer and clearly revealed that the chiral axis is able to exert asymmetric induction in some transformation occurring in their lateral chain itself.[1]

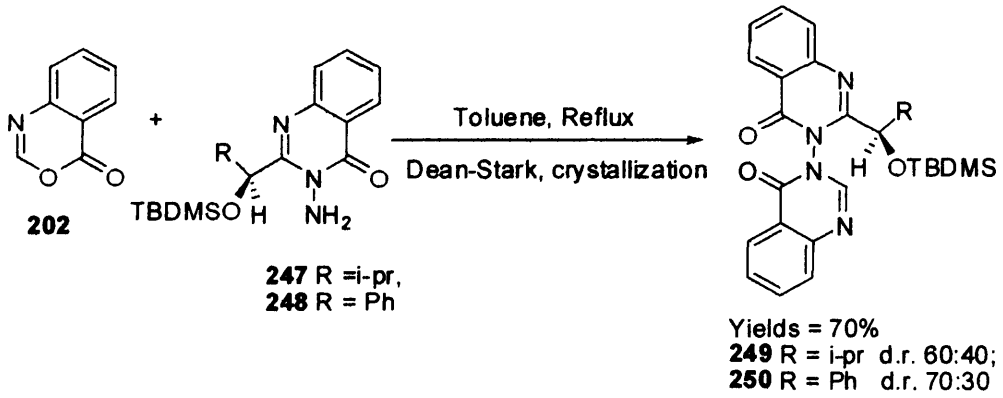
These interesting features coupled together with the high crystalline nature of these compounds, which allows their purification by simple crystallization, pushed us to start the actual research program directed at first toward the optimization of the synthesis of these substrates and then toward the exploration of their possible applications. We prepared simple 2,2-dialkyl-biquinazolinones in high yields by treating bisanthranoyl hydrazine **192** with different carboxylic acids or anhydrides. We also developed a new methodology, which allows a further functionalization of these structures. Unsymmetrical biquinazolinones were easily prepared by condensation of 3-amino-2-substituted-4(3H)-quinazolinones with 2-substituted-4H-3,1-benzoxazin-4-ones under Dean-Stark conditions in an inert solvent such as toluene. A key point of this protocol is the easy purification of the biquinazolinones obtained without the needed of tedious chromatographic separations, which very often characterize the organic synthesis.



Scheme 6-1.

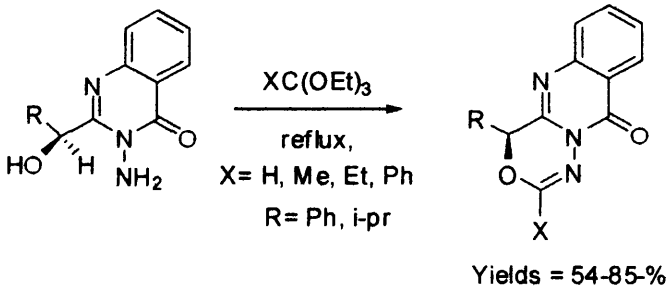
However this methodology has a drawback that comes out from the difficulty to prepare biquinazolinones bearing bulky groups in their lateral chains. Thus all the reactions employing 3-amino-2-tert-butyl-(3H)-quinazolin-4-one (**210**) and 2-methyl (**203**) or 2-ethyl-4H-3,1-benzoxazin-4-one (**204**) as counterpart failed to give the corresponding biquinazolinones, leading only to the intermediate open amides. These compounds appeared to be somewhat difficult to cyclize, and when harsh conditions were employed decomposition occurred. Only the reaction between 23-amino-2-tert-butyl-(3H)-quinazolin-4-one (**210**) and 2H-benzoxazinone (**202**) gave the corresponding product. In the future new strategies need to be investigated in order to introduce bulky groups into the biquinazolinone scaffold. Bulky groups are important because would allow us to prepare enantiomerically pure atropisomers thanks to the increased barrier to rotation around *N-N* bond.

We have also demonstrated that by this protocol it was possible to introduce into the biquinazolinone scaffold substituents bearing non racemic chiral centers, using amino acids as chiral synthons. The amino acids were converted by diazotization in acetic acid into the corresponding acetoxy derivatives, which were coupled with the methyl anthranilate and finally cyclised to the corresponding 3-amino-2-hydroxyalkyl-4(3H)-quinazolinone. Unfortunately the reaction of these substrates with benzoxazinones failed. The reason of this unreactivity is not completely clear at the moment, although association of the starting material by hydrogen bonding due to the hydroxy group could be the cause of this failure. After protection of the hydroxy group the preparations of diastereomeric biquinazolinones was successfully accomplished with good diastereoselectivity. We also proved that by fractional crystallization it was possible to increase the diastereoisomeric ratio and in the best case, as for biquinazolinone **250** the complete separation of the diastereoisomers was easily achieved.



Scheme 6-2.

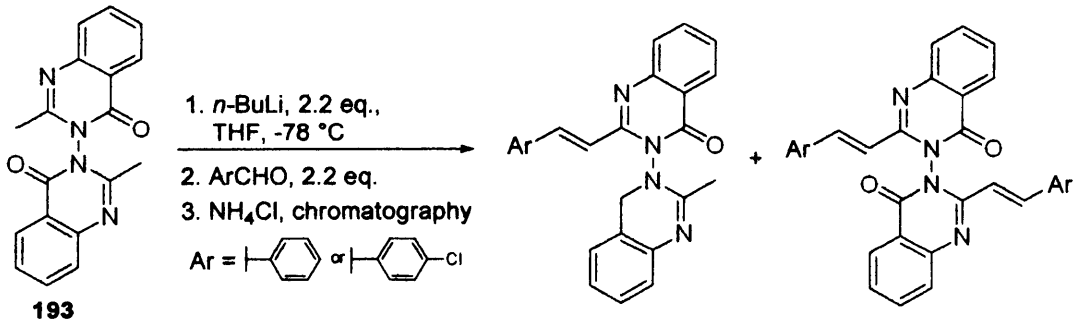
The work directed to the synthesis of chiral biquinazolinones turned at some point to a formation of an oxatriazaanthracenone system as an unexpected product. Once its structure was disclosed and the reasons of its formation were elucidated, we were able to improve a new efficient methodology for the synthesis of this new class of heterocyclic system. This methodology, based on the refluxing of 2-hydroxyalkyl-3-aminoquinazolinones in an excess of orthoester, allowed us to introduce several different substituents in various positions of the ring simply changing the nature of the groups on the orthoester or on the starting aminoquinazolinones. This opened a new route for heterocyclic systems of great interest because their potential biological activity.



Scheme 6-3.

One of the aims of this project was to establish a reliable methodology for the synthesis of axially chiral biquinazolinone. With this in mind, and encouraged by literature findings, we envisioned the possibility to increase the range of simple substituents which can be incorporated into the biquinazolinones by functionalization

of symmetrical 2,2'-dialkyl biquinazolinone *via* organometallic chemistry. This methodology gave positive results only when 2,2'-dimethyl-biquinazolinone derivative **193** was metalated with butyl lithium and the metal salt thus formed reacted with different aldehydes affording the corresponding styryl derivative (Scheme 6-4).



193

Scheme 6-4.

On the contrary metalation of diethyl derivative **195** has proved to be more difficult to accomplish and it was only possible with LDA but not with butyl lithium. The corresponding metal salt failed to react with a range of electrophiles and only the starting material was recovered except when iodine was used as a reagent. In the latter case the product generated by oxidative coupling of the metal salt **266** was observed. We proposed that the lack of reactivity of the biquinazolinone metal salts could be caused by steric effects rather then electronic ones.

Preliminary studies on the applications of the biquinazolinone scaffold to diasteroselective reactions have been performed with a good degree of success.

Epoxidation of styryl biquinazolinones **271** with *m*-CPBA has been accomplished obtaining a good degree of diastereoselectivity, which proved that the chiral axis is able to induce asymmetry. Similarly the cycloaddition of the styryl biquinazolinones **273** with cyclopentadiene has been accomplished with a good stereoselectivity and moderate yields. A future goal would be then prove the stereochemistry of the two cycloadducts obtained by X-ray diffraction studies in order to gain a better knowledge of the stereochemical outcome of the reaction. All these data would help to improve the design of newly biquinazolinone scaffolds. These promising

achievements were accompanied by other less satisfactory results. Cyclopropanation of compounds **273**, carried out through the Simmons-Smith conditions failed to give the desired cyclopropanes, leading instead to a partial polymerization of the styryl moiety of compound **273**. Moreover any attempt to carry out a 1,3-dipolar cycloaddition on analogue substrate, namely compound **271** return only the unreacted starting material (Figure 6-1).

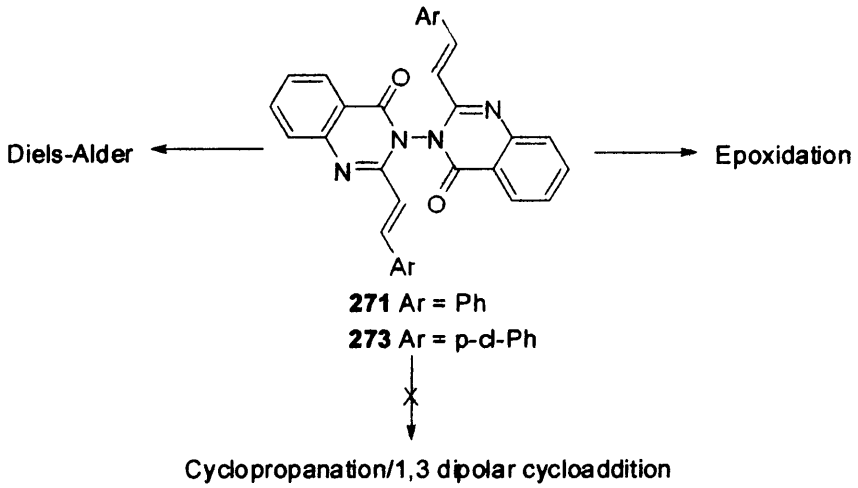


Figure 6-1.

In conclusion we established an excellent methodology for the synthesis of a new family of atropisomeric heterocycles based on the quinazolinone scaffold. The method aloud the synthesis of various biquinazolinones bearing different groups in their lateral chain and more importantly doesn't require chromatography for the purification of the products thanks to high crystalline nature of the biquinazolinones.

Future Work.

Although we obtained some promising results more work has to be done in order to better understand the biquinazolinone chemistry. The methodology developed in this thesis has the drawback of being sensitive to the steric bulkiness of the starting materials and this means that the method has to be optimized in order to circumvent this problem.

Introduction of such bulky groups could be done by modification of simple alkyl substituents in the biquinazolinone scaffold. Preliminary investigations showed that modification of 2,2'-dialkyl biquinazolinones is feasible *via* lateral metalation and further reactions with electrophiles. Improvement of the results obtained with this strategy, and better understanding of the behavior of the metalated biquinazolinones toward electrophiles has to be carried out in future works.

Diastereoselective reactions on unsaturated biquinazolinones have proved that in some cases the chiral axis is able to exert stereo-control on the stereochemistry of the products (epoxidation and Diels-Alder). Notwithstanding further studies on these reactions finalized to improve the results obtained have to be accomplished. For example, improvement of the diastereoselectivity, understanding the influence of the Lewis acid catalyst on the yields and the stereochemical outcoming of the Diels-Alder adducts will all be future targets.

Finally the search for mild cleavage procedure of the newly formed chiral moiety from the biquinazolinone scaffold to give the free chiral compound (epoxide and Diels-Alder adducts) and bisanthranoyl hydrazine **192,** which can be recovered and recycled, will be the goal to reach in the near future in order to establish the biquinazolinone scaffold as a chiral auxiliary in the wide panorama of asymmetric organic synthesis.

REFERENCES.

[1] M. Coogan, D. E. Hibbs, E. Smart, *J. Chem. Soc., Chem. Commun.*, 1999, 1991; M. Coogan, S. Passey, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2530.

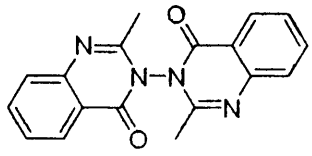
Chapter 7: Experimental section.

7.1 General methods.

All melting points were determined upon a Kofler hot stage melting point apparatus. All infrared spectra were recorded on a Perkin-Elmer 1600 series spectrometer, as Nujol mull or as thin film. NMR spectra were recorded on a Bruker DPX 400 MHz at 400 MHz (proton) and 100 MHz (carbon), or an APX 250 at 250 MHz and 75 MHz respectively. The following abbreviations are used throughout; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, *etc.* All *J* values are quoted in Hz. Chemical shift ($\delta_{H \text{ and }} \delta_C$) are reported in parts per million (ppm) from tetramethylsilane using deuterochloroform as solvent unless otherwise notified. Mass spectra were recorded on a VG Fisons Platform II or at EPSRC National Mass Spectrometry Service in Swansea (HRMS). Elemental analyses were performed by Warwick Analytical Services (University of Warwick). All reactions using air and/or moisture sensitive reagents were performed in an oven dried apparatus, under nitrogen atmosphere. Solvents and reagents were purified according to procedures outlined in "purification of Laboratory Chemicals" by D.D. Perrin and W.L.F. Armarengo. Petrol refers to light petroleum ether; b.p. 40-60 °C, ether refers to diethyl ether. Unless otherwise stated butyl lithium refers to *n*-butyl lithium, in all cases this was the commercially available solution in hexane (2.5M). Column chromatography was performed using Matrix silica gel 60 (particle size 37-70μ).

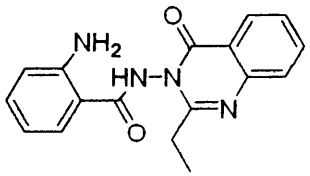
7.2 Experimental related to Chapter 2.

7.2.1 2,2'-Dimethyl-3,3'-biquinazolin-4,4'-one (193).



Bisanthranoyl hydrazine **192** (10 g, 34 mmol) is refluxed in acetyl anhydride (100 ml) for 24 hours. The reaction mixture is cooled at 0° C with an ice bath and the resulted precipitate is filtered off and crystallised from ethanol. The filtrate is reduced to half volume and the solid obtained filtered of and crystallised from ethanol. The two crops were crystallised again from ethanol to obtain pure **193**[1] (8.65g, 80% yield); m.p. 176 °C, (Lit.[1] 175 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.20 (2H, dd, J = 7.9 and 1.5 Hz, 5-H, 5'-H), 7.77 (2H, ddd, J = 8.3, 7.9 and 1.5 Hz, 7-H, 7'-H), 7.70 (2H, dd, J = 7.9 and 1.2 Hz, 8-H, 8'-H), 7.46 (2H, ddd, J = 8.3, 7.9 and 1.2 Hz, 6-H, 6'H,), 2.34 (6H, s, 2x $-CH_3$).

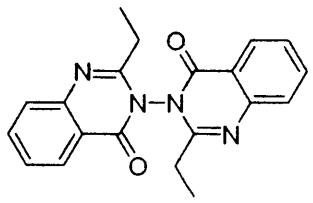
7.2.2 Amino-N-[2-ethyl-4-oxo-3(4H)-quinazolinyl]benzamide (194).



Bisanthranoyl hydrazine **192** (10 g, 34 mmol) is refluxed in propionic acid (100 ml) for 2 hours. The reaction mixture is cooled at 0° C with an ice bath and the resulted precipitate is filtered off and crystallised from ethanol. The filtrate is reduced to half volume and the solid obtained filtered of and crystallised from ethanol. The two crops were crystallised again from ethanol to obtain pure **194** (6.8g, 65% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 11.26 (1H, br, NH), 8.12 (1H, d, J = 7.94 Hz, 5-H), 7.88 (1H, t, J = 7.65 Hz, Ar), 7.74 (1H, d, J = 8.0 Ar), 7.71 (1H, d, J = 8.1, Ar), 7.57 (1H,

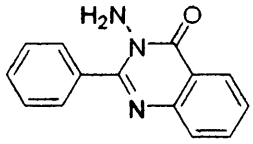
t, J = 8.2 Hz, Ar), 7.28 (1H, J =7.9 Hz, Ar), 6.80 (1H, d, J = 8.2 Hz, Ar), 6.63 (1H, d, J =7.5, Ar), 6.61 (2H, br, $-NH_2$), 2.83 (1H, m, $-CH_{2A}$), 2.70 (1H, m, CH_{2B}), 1.25 (3H, t, J = 7.3 Hz, $-CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 165.0, 160.1, 156.0, 150.0, 147.2, 134.0, 132.9, 128.0, 127.9, 126.7, 126.5, 120.0, 118.0, 117.8, 116.0, 25.4, 9.8; ν_{max} (nujol)/cm^{-1} 3510, 3410, 3370, 3280, 1680, 1640, 1398, 1330; *m/z* (APCI) (%) 309.1 (100) [M + H$^+$]; $C_{17}H_{16}N_4O_2$ requires: C 69.61; H 5.15; N 14.33 (%), found: C 69.58; H 5.20; N 14.48 (%).

7.2.3 2,2'-Diethyl-3,3'-biquinazolin-4,4'-one (195).



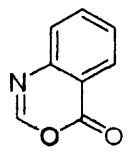
Bisanthranoyl hydrazine **192** (10 g, 34 mmol) is refluxed in propionic acid (100 ml) for 24 hours. The reaction mixture is cooled at 0° C with an ice bath and the resulted precipitate is filtered off and crystallised from ethanol. The filtrate is reduced to half volume and the solid obtained filtered of and crystallised from ethanol. The two crops were crystallised again from ethanol to obtain pure **195**[1] (8.83g, 75% yield); m.p. 222 °C, (Lit.[1] 225 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.13 (2H, dd, J = 8.1 and 1.7 Hz, 5-H, 5'-H), 7.70 (2H, ddd, J = 8.1, 7.4 and 1.7 Hz, 7-H, 7'-H), 7.67 (2H, dd, J = 8.1 and 1.3 Hz, 8-H, 8'-H), 7.49 (2H, ddd, J = 8.1, 7.4 and 1.3 Hz, 6-H, 6'-H), 2.54 (4H, m, 2x $-CH_2$), 1.22 (6H, t, J = 7.3 Hz, 2x $-CH_3$).

7.2.4 3-Amino-2-phenyl-4-(3H)-quinazolinone (198).



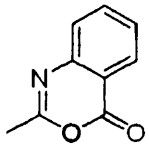
A solution of **208** (21.5 g, 83.8 mmol) and *p*-toluene sulfonic acid (2.1 g, 4.19 mmol, 5%) in toluene (220 ml) was refluxed for five hours. Then, the mixture was cooled to room temperature and the solvent removed under vacuum. The residue obtained was crystallized from ethanol affording **198** (15.84 g, 80% yield); m.p. 104 °C (Lit.[2] 102 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.31 (1H, d, J = 8.4 Hz, 5-H), 7.78 (4H, m, Ar), 7.51 (4H, m, Ar), 5.0 (2H, br, $-NH_2$).

7.2.5 4H-3,1-Benzoxazin-4-one (202).



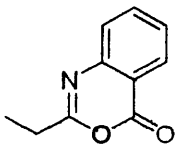
Following the method of S. Khajavi,[3] a oven dried two necks round bottom flask equipped with a condenser, connected to a calcium chloride valve, was charged with anthranilic acid (**201**) (2 g, 14.6 mmol) and triethylorthoformate (21.5 g, 24.1 ml, 10 eq.) and then heated at reflux for five hours. Then, the mixture was cooled at room temperature and the excess of orthoformate was removed under vacuum affording a brown solid, which was crystallized from dry octane affording **202** as white needles (1.9 g, 89% yield); m.p. 42 °C (Lit.[4] 43-44 °C); ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 8.04 (5H, m, 2-CH and Ar); ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ_C 159.4, 149.7, 146.0, 137.6, 129.2, 128.6, 126.9, 119.8.

7.2.6 2-Methyl-4H-3,1-benzoxazin-4-one (203).



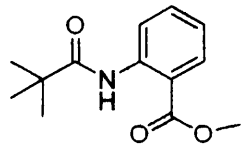
In an oven dried round bottomed flask, anthranilic acid (**201**) (48 g, 353 mmol) and acetic anhydride (100 ml) were refluxed for six hours. The mixture was allowed to reach room temperature overnight. Acetic anhydride was removed under reduced pressure and the residue crystallized from dry ethyl acetate affording **203** as a pale yellow crystals. (29.5 g 52% yield); m.p. 83 °C (Lit.[4] 80-81 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.84 (4H, m, Ar), 2.40 (3H, s, $-CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 160.7, 159.0, 147.0, 136.8, 127.9, 127.50, 125.0, 116.9, 22.0.

7.2.7 2-Ethyl-4H-3,1-benzoxazin-4-one (204).



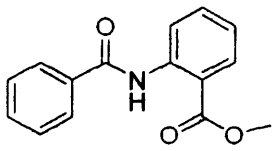
In an oven dried round bottomed flask anthranilic acid (**201**) (50 g, 373 mmol) and propionic anhydride (150 ml) were refluxed for six hours, the mixture was allowed to reach room temperature overnight. The crystals were filtered and crystallized from dry ethyl acetate affording **204** as yellow needles. (40.8 g, 62% yield); m.p. 85 °C (Lit.[4] 85-86 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.79 (4H, m, Ar), 2.75 (2H, q, J = 7.2 Hz, $-CH_2$), 1.35 (3H, t, J = 7.2 Hz, $-CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 164.1, 159.0, 146.4, 136.8, 127.49, 128.4, 125.9, 116.9, 27.8, 10.8.

7.2.8 Methyl-2-(pivalamido)benzoate (206).



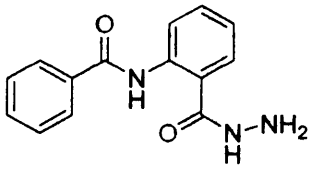
In a round bottom flask methyl anthranilate (**205**) (23.4 g, 158 mmol, 20 ml) was dissolved in diethyl ether (90 ml), pivaloyl chloride (9.3 g, 77.4 mmol, 9.5 ml) was added dropwise, and the mixture was stirred at 0 °C for one hour. After that period, the white solid was filtered off, washed with diethyl ether. The combined organic layer were washed with diluted 2M hydrochloric acid (3 x 30 ml), brine (1 x 50 ml) dried over magnesium sulphate and evaporated under reduced pressure affording **206** as brown crystals (16.8 g, 92% yield); m.p. 145 °C (Lit.[5] 46-47 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.21 (1H, s br, -NH), 8.91 (1H, dd, J = 8.2 and 0.9 Hz, 6-H), 8.82 (3H, m, Ar), 3.79 (3H, s, $-OCH_3$), 1.25 (9H, s, $-C(CH_3)_3$).

7.2.9 Methyl 2-(benzamido)benzoate (207).



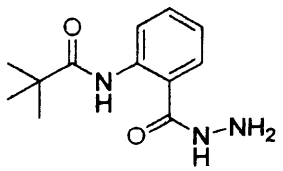
In a round bottomed flask, methyl anthranilate (**205**) (23.4 g, 158 mmol, 20 ml) was dissolved in diethyl ether (90 ml), then benzoyl chloride (9.8 g, 69 mmol, 8.2 ml) was added dropwise and the resulting mixture was stirred at 0 °C for one hour. After that period, the white solid was filtered off and washed with diethyl ether. The combined organic phases were washed with diluted 2M hydrochloric acid (3 x 30 ml), brine (1 x 50 ml) dried over magnesium sulphate and evaporated under reduced pressure affording **207** as a white solid (15 g, 84% yield); m.p. 95 °C (Lit.[6] 93-96 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.04 (1H, s br, -NH), 8.95 (1H, dd, J= 8.6 and 0.7 Hz, 6-H), 8.97 (3H, m, Ar), 7.55 (4H, m, Ar), 7.13 (1H, dd, J = 7.6 and 1.3 Hz, Ar), 3.85 (3H, s, $-CH_3$); *m/z* (APCI) (%) 256.0 (100) [M + H^+].

7.2.10 2-Benzoylaminobenzoic hydrazide (208).



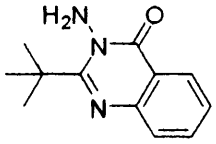
A solution of **207** (15 g, 58.76 mmol) and hydrazine monohydrate (14.70 g, 293.8 mmol, 14.2 ml, 5 eq) in ethanol (100 ml) was refluxed for eight hours. The resulting mixture was then cooled to room temperature and the solid product obtained was collected by filtration. Crystallization of the solid from ethanol gave the hydrazide **208** as colourless crystals (12.8 g, 86% yield); m.p. 184 °C, (Lit.[7] 83-185 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.9 (1H, s br, -NH), 9.29 (1H, s br,-N<u>H</u>NH$_2$), 8.66 (1H, d, J = 7.8 Hz, 6-H), 7.90 (2H, m, Ar), 7.55 (1H, m, Ar), 7.4 (4H, m, Ar), 6.98 (1H, t, J = 7.8 Hz, Ar), 4.02 (2H, s br, -NHN<u>H$_2$</u>); *m/z* (APCI) (%) 256.1 (100) [M + H$^+$].

7.2.11 2-(Pivalamido)benzoic hydrazide (209).



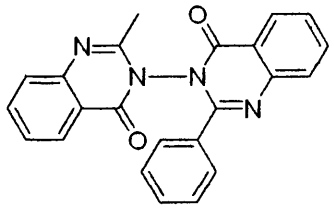
To a solution of **206** (20 g, 85 mmol), in ethanol (220 ml), was added hydrazine monohydrate (21.3 g, 425 mmol, 20.6 ml, 5 eq.) and the mixture refluxed for five hours. After that period, the mixture was cooled to room temperature and the white solid formed was filtered off and the solid obtained was crystallized from ethanol affording **209**[8] (18.6 g, 93% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.0 (1H, s br, -NH), 8.60 (1H, dd J = 7.6 and 0.7 Hz, 6-H), 7.4 (3H, m, -N<u>H</u>NH$_2$, Ar), 6.98 (1H, ddd, J = 8.7, 7.6 and 0.7 Hz, Ar), 4.1 (2H, s br, -NH$_2$), 1.28 (9H, s, -C(CH$_3$)$_3$); ν_{max}(nujol)/cm^{-1} 2915, 2362, 1662, 1584, 1522, 1463, 1377, 1332, 1164, 939; *m/z* (APCI) (%) 236.1 (100) [M + H$^+$].

7.2.12 3-Amino-2-tert-butyl-(3H)-quinazolin-4-one (210).



A solution of **209** (21.5 g, 89.3 mmol) and *p*-toluene sulfonic acid (2.23 g, 4.46 mmol, 5%) in toluene (220 ml) was refluxed for five hours. After that period, the mixture was cooled to room temperature and the solvent removed under vacuum. The residue obtained was crystallized from ethanol affording **210**[8] (15.5 g, 80% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.29 (1H, d, J = 8.4 Hz, 5-H), 7.76 (2H, m, Ar), 7.4 (1H, m, Ar), 5.2 (2H, s br, $-NH_2$), 1.32 (9H, s, $-C(CH_3)_3$); ν_{max} (nujol)/cm^{-1} 3300, 3202, 1650, 1563, 1300, 1070, 769, 69; *m/z* (APCI) (%) 218 (100).

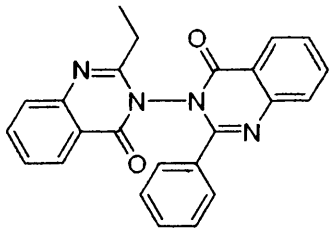
7.2.13 2-Phenyl-2'-methyl-3,3'-bisquinazolinyl-4,4'-one (216).



A mixture of **203** (0.63 g, 4.2 mmol), **198** (1 g, 4.26 mmol), and *p*-toluene sulfonic acid (0.05 g, 0.21 mmol, 5%) was heated at reflux in toluene for six hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was crystallised from ethanol to give **216** as white crystals (0.955 g, 62% yield); mp 162 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.29 (1H, dd, J = 8.0 and 0.9 Hz, 5-H), 8.14 (1H, dd, J = 8.0 and 1.4 Hz, 5'-H), 7.82 (2H, m, 8-H and 8'-H), 7.69 (1H, ddd, J = 8.0, 7.8 and 1.2 Hz, 7'-H), 7.52 (5H, m, Ar), 7.39 (1H, ddd, J = 8.0, 7.0 and 1.2 Hz, 7'-H), 7.28 (2H, m, 6-H and 6'-H), 2.32 (3H, s, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.8, 159.4, 154.9, 153.6, 147.2, 146.9, 136.2, 135.8, 132.7, 131.3, 129.0, 128.8, 128.4, 128.1, 128.0, 127.8, 127.7, 127.6, 121.4, 120.1, 22.0; ν_{max} (nujol)/cm^{-1} 1692, 1599, 1566,

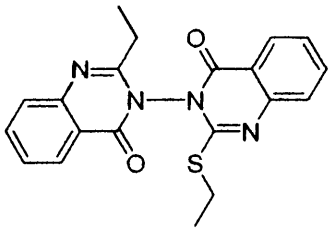
1378, 1324, 1268, 776, 698; *m/z* (APCI) (%) 381.1 (100) [M + H^+]; $C_{23}H_{16}N_4O_2$ requires: C 72.62; H 4.24; N 14.73 (%), found: C 72.50; H 4.24; N 14.50 (%).

7.2.14 2-Ethyl-2'-phenyl-3,3'-biquinazolinyl-4,4-one (217).



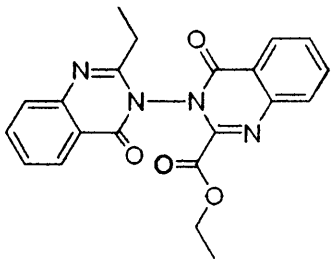
A mixture of **204** (3 g, 17.1 mmol), **198** (3 g, 12.6 mmol) and *p*-toluene sulfonic acid (0.147 g, 0.85 mmol, 5%) was heated at reflux in toluene for ten hours. After cooling, the toluene was evaporated in vacuo and the solid obtained was triturated with diethyl ether to give a pale yellow solid which was then crystallised from ethanol to give **217** as white crystals (3.90 g, 79% yield); m.p 94 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, dd J = 8.0 and 1.3 Hz, 5-H), 8.15 (1H, dd J = 7.9 and 1.3 Hz, 5'-H), 7.83 (2H, m, 8-H and 8'-H), 7.68 (1H, ddd, J = 8.0, 7.0 and 1.3 Hz, 7-H), 7.54 (5H, m, Ar), 7.38 (1H, ddd, J = 8.0, 7.1 and 0.9 Hz, 7'-H), 7.25 (2H, m, 6-H and 6'-H), 2.50 (2H, q, J = 7.3 Hz, -CH_2), 1.21 (3H, t, J = 7.3 Hz, -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 160.0, 159.5, 156.5, 155.1, 147.0, 136.1, 135,7, 135.3, 132.7, 131.9, 131.2, 129.0, 128.7, 128.4, 128.0, 128.0, 127.8, 127.5, 121.5, 120.9, 26.6, 10.3; ν_{max} (nujol)/cm^{-1} 1686, 1591, 1464, 1377, 1331, 1274, 1116, 909, 873, 764, 695; *m/z* (APCI)(%) 395.1 (100) [M+H^+]; $C_{24}H_{18}N_4O_2$ requires: C 73.08; H 4.60; N 14.20 (%), found C 73.01; H 4.62; N 14.12 (%).

7.2.15 2-Ethyl-2'-thioethyl-3,3'-bisquinazolinyl-4,4-dione (218).



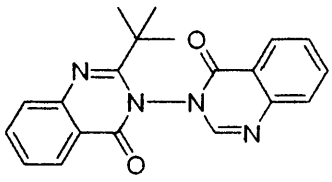
A mixture of **204** (0.63 g, 3.57 mmol), 3-amino-2-thioethyl-3*H*-quinazolin-4-one (**211**) (0.71 g, 3.58 mmol) and *p*-toluene sulfonic acid (0.03 g, 0.18 mmol, 5%) was heated at reflux in toluene for ten hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was triturated with diethyl ether to give a pale yellow solid which was then crystallised from DCM–light petroleum ether to give **218** as white crystals (0.60 g, 44% yield); mp 173 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.22 (1H, dd, J = 7.8 and 1.3 Hz, 5-H), 8.17 (1H, dd, J = 7.9 and 1.3 Hz, 5'-H), 7.75 (3H, m, 7-H, 7'-H and 8-H), 7.61 (1H, d, J = 7.9 Hz, 8'-H), 7.44 (2H, m, 6-H and 6'-H), 3.15 (2H, m, $-SCH_2$), 2.54 (2H, m, $-CH_2$), 1.28 (6H, m, $-CH_2\underline{CH_3}$ and $-SCH_2\underline{CH_3}$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 158.8, 158.5, 156.6, 156.3, 147.4, 146.82, 135.6, 135.4, 127.8, 127.7, 127.5, 127.1, 126.8, 126.4, 121.0, 119.7, 26.3, 25.8, 13.7, 9.9; ν_{max}(nujol)/cm^{-1} 1674, 1633, 1609, 1578; *m/z* (APCI)(%) 379.1 (100) [M+ H$^+$]; $C_{20}H_{18}N_4O_2S$ requires: C 63.46; H 4.79; N 14.82 (%), found: C 63.16; H 4.73; N 14.58 (%).

7.2.16 2-Ethyl-2'-ethoxycarbonyl-3,3'-bisquinazolinyl-4,4'-dione (219).



A mixture of **204** (1.35 g, 7.85 mmol), 3-amino-2-ethoxycarbonyl-3*H*-quinazolin-4-one (**212**) (1.22 g, 5.2 mmol) and *p*-toluenesulfonic acid (0.07 g, 0.39 mmol, 8%) was heated at reflux in toluene for 24 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was triturated with diethyl ether to give a pale yellow solid, which was then crystallised from DCM–light petroleum ether to give **219** as white crystals (1.04 g, 51% yield); mp 175 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, dd, J = 7.9 and 1.0 Hz, 5-H), 8.15 (1H, dd, J = 7.6 and 1.1 Hz, 5'-H), 7.89 (2H, m, 8-H and 8'-H), 7.76 (2H, m, 7-H and 7'-H), 7.60 (1H, ddd, J = 7.9, 7.2 and 1.0 Hz, 6-H), 7.42 (1H, ddd, J = 7.6, 7.1 and 1.1 Hz, 6'-H), 4.24 (1H, dq, J = 11.2 and 7.0 Hz, $-CO_2C\underline{H}_{2a}$), 4.19 (1H, dq J = 11.2 and 7.0 Hz, $-CO_2C\underline{H}_{2b}$), 2.77 (1H, dq, J = 17.2 and 7.2 Hz, $-N{=}C{-}C\underline{H}_{2a}$), 2.58 (1H, dq, J = 17.2 and 7.2 Hz, $-N{=}C{-}C\underline{H}_{2b}$), 1.31 (3H, t, J = 7.0 Hz, $-CO_2CH_2C\underline{H}_3$), 1.13 (3H, t, J = 7.2 Hz, $-N{=}C{-}CH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 174.1, 158.16, 157.62, 155.90, 145.82, 144.45, 143.43, 134.87, 134.32, 128.47, 128.15, 126.86, 126.73, 126.20, 125.96, 121.42, 119.56, 62.64, 24.95, 12.65, 8.74; ν_{max} (nujol)/ cm^{-1} 1738, 1709, 1686, 1601; *m/z* (APCI) (%) 391.1 (100) [M + H$^+$]; $C_{21}H_{18}N_4O_4$ requires: C 64.61; H 4.65; N 14.35 (%), found: C 64.54; H 4.64; N 14.29 (%).

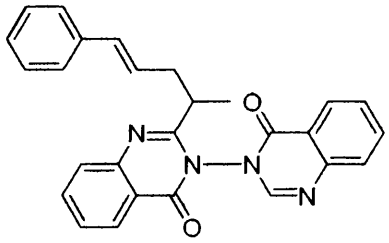
7.2.17 2-tert-Butyl-2'-H-3,3-bisquinazolinyl-4,4-dione (220).



A mixture of **202** (1.02 g, 7 mmol), **210** (1 g, 4.6 mmol) and *p*-toluenesulfonic acid (0.07 g, 0.35 mmol, 8%) was heated at reflux with a Dean–Stark apparatus in toluene for eight hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained crystallised from ethanol to give **220** as pale brown crystals (0.64 g, 38% yield); m.p. 225 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.28 (1H, dd, J = 8.0 and 1.3 Hz, 5-H), 8.19 (1H, dd J = 7.7 and 1.1 Hz, 5'-H), 7.80 (1H, s, 2'-H), 7.75 (4H, m, 7-H, 8-H, 7'-H, 8'-H), 7.52 (1H, ddd J = 8.0, 6.7 and 1.1 Hz, 6-H), 7.44 (1H, ddd, J = 7.7,

6.1 and 1.3 Hz, 6'-H), 1.3 (9H, s, -C(CH_3)$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.63, 159.06, 158.83, 146.74, 146.09, 145.21, 134.49, 134.40, 127.33, 127.10, 127.09, 126.64, 126.48, 126.20, 121.52, 119.42, 38.71, 28.84; ν_{max}(nujol)/cm^{-1} 1692, 1594; *m/z* (APCI)(%) 347.1 (100) [M + H^+]; $C_{20}H_{18}N_4O_2$ requires: C 69.35; H 5.24; N 16.17 (%); found: C 68.95; H 5.24; N 15.95 (%).

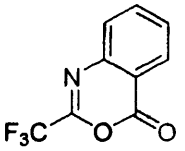
7.2.18 (+)(-)-2-(1-Methyl-4-phenyl-but-3-enyl)-3,3'-bisquinazoline-4,4'-one (221). (Prepared as a 1:1 mixture of diastereoisomers and not separated).



A mixture of **202** (0.76 g, 5.160 mmol), (+)(−) 3-amino-2-(1-methyl-4-phenyl-but-3-enyl)quinazolin-4- one (**213**) (1.05 g, 3.44 mmol) and *p*-toluenesulfonic acid (0.026 g, 0.13 mmol, 5%) in toluene(10 ml) was heated at reflux for 24 hours. After cooling, the solvent was evaporated *in vacuo* and the solid obtained was crystallised from toluene– light petroleum ether to give **221** as pale yellow crystals (0.70 g, 47% yield); m.p. 144 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) (1 : 1 mixture of isomers referred to as A and B, many signals overlapped assigned as m): ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.28 (1H, d, J = 7.4 Hz, 5-H_A), 8.26 (1H, d, J = 7.4 Hz, 5-H_B), 8.20 (1H, d, J = 7.5 Hz, 5'-H_A), 8.16 (1H, d , J = 7.5 Hz, 5'-H_B), 7.95 (1H, s, 2-H_A), 7.74 (8H, m, Ar), 7.70 (1H, s, 2'-H_B), 7.50 (4H, m, Ar), 7.14 (10H, m, Ar), 6.34 (1H, d, J = 11.2 Hz, PhC$\underline{H}_A$=CH), 6.30 (1H, d, J = 11.2 Hz, PhC$\underline{H}_B$=CH), 6.02 (2H, m, =C$\underline{H}$C$\underline{H}_2$), 2.84 (1H, m, -C$\underline{H}_A$CH_3), 2.69 (3H, m, -C$\underline{H}_B$CH_3 and –CH_{2A}), 2.48 (2H, m, -CH_{2B}), 1.32 (3H, d, J = 6.4 Hz, -CH_{3A}), 1.28 (3H, d, J = 6.4 Hz, -CH_{3B}); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.4, 159.3, 159.2, 159.1, 158.5, 158.4, 147.2, 147.1, 146.62, 146.60 145.71, 145.5, 137.1, 136.4, 135.34, 135.32, 132.9, 132.2, 128.7, 128.4, 128.2, 128.1, 128.0, 127.99, 127.94, 127.6, 127.5, 127.37, 127.32, 127.3, 127.1, 127.0, 126.8, 125.9, 125.8, 125.7, 125.0, 122.0, 120.5, 120.4, 40.5, 38.9, 37.0, 35.6, 28.2, 21.7,

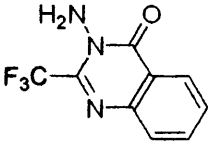
20.6, 18.6, 18.5; ν_{max}(nujol)/cm^{-1} 2920, 1693, 1603, 1568, 1462, 1377, 1266, 768, 741, 692; *m/z* (EI) (%) 434.5 (38)(M+) 211 (82); HRMS $C_{27}H_{22}N_4O_2$ requires: 435.1816, found 435.1815.

7.2.19 2-Trifluoromethyl-4H-3,1-benzoxazin-4-one (224).



To a stirred suspension of anthranilic acid (**201**) (2 g, 14.5 mmol) in chloroform (20 ml), was added dropwise trifluoroacetic anhydride (9.2 g, 43.8 mmol, 6 ml).
The resulting mixture was heated at reflux for two hours then evaporated to dryness and the residue crystallized from light petroleum ether to yield **224** as colourless solid (2.03 g, 65% yield); m.p. 50 °C (Lit.[9] 51-52.°C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.5 (1H, d, J = 8.3 Hz, 5-H), 7.7 (3H, m, Ar).

7.2.20 3-Amino-2-trifluoromethyl-(3H)-quinazolin-4-one (226).

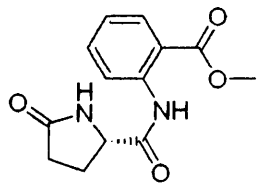


The benzoxazinone **224** (1.9 g, 9.1 mmol) was dissolved in ethanol (12 ml), hydrazine monohydrate (0.45g, 9.1 mmol, 0.44 ml) added directly and the mixture stirred for one hour at reflux. The resulting solid product was dissolved in ethyl acetate (50 ml) the solution washed with 2M hydrochloric acid (3 x 50 ml), saturated aqueous sodium hydrogen carbonate (3 x 50 ml) and brine (2 x 50 ml), dried over sodium sulphate and evaporated to give **226** as white crystals after crystallization from methanol (1.2 g, 55% yield); m.p. 150 °C (Lit.[10] 150 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.3 (1H, d, J = 8.7, 5-H), 7.5 (3H, m, Ar), 5.3 (2H, s br, -NH_2); *m/z*

(APCI) (%) 230 [M+H$^+$] (100), (Lit.[10] *m/z* (EI) (%) 229 (M+) (97), 200 (66), 180 (39)).

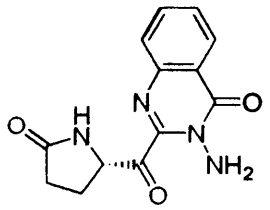
7.3 Experimental procedures related to Chapter 3.

7.3.1 (S)-Methyl-2-(5-oxopyrrolidine-2-carboxamido)benzoate. (230)



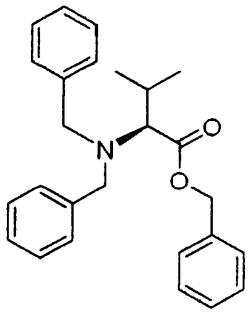
Following the method of J. Royer,[11] (S)-(-)-2-pyrrolidone-5-carboxylic acid (**228**) (5 g, 38.5 mmol) and oxalyl chloride (47.7 g, 33 ml), were heated at reflux for two hours, then the excess of oxalyl chloride removed under reduced pressure and the 5-oxopyrrolidine-2-carbonyl chloride (**229**) (5.2 g, 99% yield) used in the next step without further purification. **229** (5 g, 31 mmol), was dissolved in DCM and the resulting solution cooled at 0 °C, methyl anthranilate (**205**) (10.30 g, 8.8 ml, 68 mmol) was added dropwise. The thick suspension was stirred at 0 °C for four hours. The white precipitate was filtered and washed with fresh DCM, the combined organics layer washed with 2M hydrochloric acid (3 x 40 ml), sodium hydrogen carbonate (2 x 40 ml) and brine (40 ml) and finally dried over magnesium sulphate and evaporated under reduced pressure. The solid residue was crystallized from ethanol affording **230** as a white solid (7.9 g, 88 % yield); m.p.133 °C (Lit.[12] m.p. 131-132 °C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 11.2 (1H, s br, -NH), 8.65 (1H, d, J = 9 Hz, 6-H), 7.95 (1H, dd, J = 9 and 2 Hz, 3-H), 7.40 (3H, m, 4-H, 5-H and -CH_2N<u>H</u>), 4.34 (1H, m, NHC<u>H</u>CO), 3.78 (3H, s, -CH_3), 2.45 (4H, m, -C<u>H$_2$</u>C<u>H$_2$</u>); ν_{max}(nujol)/cm^{-1} 3435, 3270, 1699, 1609, 1592, 1530, 1452, 1438, 1408; $[\alpha]^{25}_D$ = -32.12° (c = 1.2, $CHCl_3$).

7.3.2 *(2S)-3-Amino-2-(5-oxopyrrolidinyl-2-carbonyl)-4(3H)-quinazolinone. (231)*



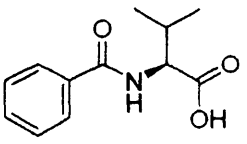
230 (7.85 g, 32 mmol) was dissolved in ethanol (60 ml) and to the resulting solution hydrazine monohydrated (5.33 ml, 5.53 g, 110 mmol) were added and the mixture heated at reflux for four hours. The oil obtained after removal the solvent was triturated with cold diethyl ether to obtain a pale yellow solid that was then crystallized from methanol affording **231** as pale yellow crystals (4.88 g, 58% yield); m.p 212 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.16 (1H, d, J = 8.0 Hz, 5-H), 7.80 (1H, ddd, J = 8.1, 7.0 and 1.0 Hz, 7-H), 7.60 (1H, d, J = 8.1 Hz, 8-H), 7.40 (1 H, ddd, J = 8.0, 7.0 and 1.0 Hz, 6-H), 6.95 (1H, s br, -NH), 5.22 (1H, m, NHC<u>H</u>CO), 4.82 (2H, s br, $-NH_2$), 2.5 (4H, m, $-C\underline{H_2}-C\underline{H_2}$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 178.7, 169.8, 162.3, 155.6, 146.5, 134.6, 127.8, 127.2, 126.5, 120.4, 55.0, 29.7, 25.2; ν_{max} (nujol)/cm^{-1} 3424, 3370, 1702, 1688, 1590, 1120; *m/z* (APCI) (%) 273 (100) [M+H$^+$]; 273.1 (15); HRMS $C_{13}H_{12}N_4O_3$ requires: 273.0909, found: 273.0958; $[\alpha]^{25}_D$ = - 28.2° (c =1, DMSO).

7.3.3 *(S)-Benzyl-2-(N, N-dibenzylamino)-3-methylbutanoate (233).*



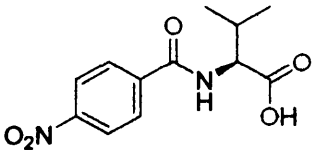
To a solution of sodium hydroxide (6.3 g, 113 mmol) and potassium carbonate (14.5 g, 105 mmol) in water (100 ml), was added (S)-(+)-valine (**232**) (6.3 g, 53.6 mmol). Benzyl bromide (19.2 ml, 162 mmol) was then added dropwise and the mixture heated at reflux for two hours before cooling in ice bath. The mixture was acidified with 2M hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The organic layer was dried with magnesium sulphate and evaporated under reduced pressure to give **233** as white crystals after crystallization from ethanol (16 g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.24 (15H, m, Ar), 5.15 (1H, d, J = 12.3 Hz, -OC$\underline{H}_{2a}$Ph), 5.14 (1H, d, J = 12.2 Hz, -OC$\underline{H}_{2b}$OPh), 3.97 (2H, d, J = 14.0 Hz, -NC$\underline{H}_2$Ph), 3.40 (2H, d, J = 14.1 Hz, -NC$\underline{H}_2$Ph), 3.40 (1H, -CHN), 2.15 (1H, m, -C$\underline{H}$(CH_3)$_2$), 0.98 (3H, d, J = 6.3 Hz, -CH_3), 0.70 (3H, d, J = 6.3 Hz, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 140.5, 130.1, 127.0, 128.0, 127.7, 68.0, 66.6, 54.1, 26.1, 20.4, 16.8; $[\alpha]^{25}_D$ = -56.2° (c =1.5, $CHCl_3$).

7.3.4 (S)-2-benzoylamino-3-methylbutanoic acid (234).



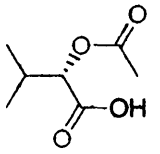
A suspension of (S)-(+)-valine (**232**) in 2M sodium hydroxide (6.8 g, 58 mmol) was stirred with benzoyl chloride (18 g, 128 mmol, 14.8 ml) for 30 min. some from times to time sodium hydroxide was added in order to keep the mixture alkaline. When all the benzoyl chloride was consumed, the mixture was acidified with 2M hydrochloric acid until pH 1-2 and the product, precipitated from the solution, was collected by filtration and washed with cold water and then crystallized form aqueous ethanol. The residue of benzoic acid was removed by kugerholl distillation affording **234** (12.8 g, 84% yield). m.p.113 °C (Lit.[13] m.p. 113-114 °C); ^{1}H-NMR (400 MHz, CD_3OD): δ_H 7.83 (2H, d, J = 7.4 Hz, Ar), 10.5 (1H, s br, -NH), 7.50 (3H, m, Ar), 4.39 (1H, d, J = 6.2 Hz, C$\underline{H}$NHCO), 2.24 (1H, m, -C$\underline{H}$(CH_3)$_2$), 1.04 (6H, d, J = 6.8 Hz, -CH(C$\underline{H}_3$)$_2$); $[\alpha]_D^{25}$ = +20, (c = 4.9, ethanol), Lit.[10] $[\alpha]^{25}_D$ = + 22°, (c = 4.9, EtOH).

7.3.5 (S)- 2-(4-nitrobenzoylamino)-3-methylbutanoic acid (235).



A suspension of (S)-(+)-valine (**232**) in 2M sodium hydroxide (6.8 g, 58 mmol) was stirred with *p*-nitrobenzoyl bromide (21.39 g, 128 mmol, 14.8 ml) for 30 min. some from times to time sodium hydroxide was added in order to keep the mixture alkaline. When all the *p*-nitrobenzoyl bromide was consumed, the mixture was acidified with 2M hydrochloric acid until pH 1-2 and the product, precipitated from the solution, was collected by filtration and washed with cold water and then crystallized form aqueous ethanol. The residue of *p*-nitro benzoic acid was removed by kugerholl distillation affording **235** (13.7 g, 88% yield). m.p.225 °C (Lit.[14] m.p. 227-228 °C); ^{1}H-NMR (400 MHz, CD_3OD): δ_H 8.34 (1H, d, J = 4.5 -NH), 8.28 (2H, d, J = 10 Hz, Ar), 8.05 (2H, d, J = 10 Hz, Ar), 4.56 (1H, d, J = 4.5, -NHC<u>H</u>CO), 2.27 (1H, m, -C<u>H</u>$(CH_3)_2$), 1.09 (6H, d, <u>J</u> = 6.5 -CH(C<u>H</u>$_3)_2$); $[\alpha]^{25}_D$ = -135° (c =1.0, CH_3OH).

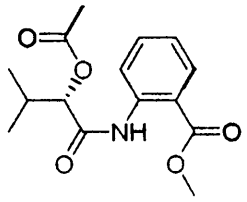
7.3.6 (2S)-2-Acetoxy-3-methylbutanoic acid (237).



Following the procedure of Kolasa[15] to a stirred suspension of (S)-(+)-valine (**232**) (4 g, 34 mmol) in acetic acid (160 ml) was added portion wise and with stirring over one hour sodium nitrite (9.4 g, 136 mmol). During the addition, the reaction vessel was cooled in a water bath, which was kept between 0 °C and 5 °C by the intermittent addition of ice, not being allowed to exceed these limits. After the addition was complete, the bath was removed and the mixture allowed attaining ambient temperature while it was stirred for a further one hour. The acetic acid was then removed under vacuum, the residue dissolved in warm water (30 ml), extracted with

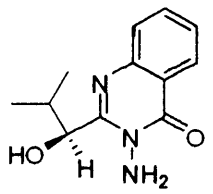
ether (3 × 30 ml), washed with brine (30 ml), dried on magnesium sulphate and evaporated to give **237** (3.79 g, 70% yield) as a pale oil which was used in subsequent steps without further purification ^{1}H-NMR (400 MHz $CDCl_3$): δ_H 10.0 (1H, s br, -COOH), 4.9 (1H, d, J = 6.1 Hz, -C<u>H</u>COOH), 2.30 (1H, m, -C<u>H</u>$(CH_3)_2$), 2.15 (3H, s, -$COCH_3$), 1.06 (3H, d, J = 6.6 Hz, -CH(C<u>H</u>$_3)_2$), 1.11 (3H, d, J = 6.6 Hz, -CH(C<u>H</u>$_3)_2$); $[\alpha]^{25}_D$ = -19.6° (c= 1, $CHCl_3$).[15]

7.3.7 Methyl-(S)-N-(2-acetoxy-3-methylpropanoyl) anthranilate (239).



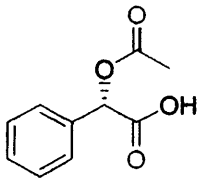
237 (14.5 g, 84 mmol), was converted into its acid chloride **238** by dissolving it in DCM (50 ml), dried over silica gel, adding two drops of DMF and then thionyl chloride (14 ml, 198 mmol), dropwise. The mixture was stirred for 24 hours and then DCM and unreacted thionyl chloride were removed under reduced pressure to give the acid chloride (15.84g, 99% yield) which was immediately dissolved in DCM (200 ml). To the resulting solution was added methyl anthranilate (**205**) (23.8 g, 157.7 mmol, 20.4 ml) and the thick white precipitate was stirred at room temperature for 24 hours, the white solid was filtered, washed with DCM (4 x 20 ml) and the combined filtrates washed with 2M hydrochloric acid (7 x 40 ml), saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulphate and evaporated under reduced pressure to give **239** as a green yellow oil (15.0 g, 88% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 10.9 (1H, s br, -NH), 8.70 (1H, dd, J = 8.5 and 1.0 Hz, 3-H), 8.0 (1H, dd, J = 8.2 and 1.5 Hz, 6-H), 7.50 (1H, ddd, J = 8.5, 7.0 and 1.5 Hz, 4-H), 7.0 (1H, ddd, J = 8.2, 7.0 and 1.0 Hz, 5-H), 5.10 (1H, d, J = 4.1 Hz, -C<u>H</u>O$COCH_3$), 3.70 (3H, s, -OCH_3), 2.30 (1H, m, -C<u>H</u>$(CH_3)_2$), 2.20 (3H, s, -COC<u>H</u>$_3$), 0.90 (3H, d, J = 5.6 Hz, -CH(C<u>H</u>$_3)_2$), 1.01 (3H, d, J = 5.6 Hz, -CH(C<u>H</u>$_3)_2$);[16] $[\alpha]^{25}_D$ = -125.6° (c = 1.2, $CHCl_3$).

7.3.8 3-Amino-2-[(S)-1-hydroxy-2-methylpropyl]-4(3H)-quinazolinone[16] (240).



239 (11.9 g, 40.7 mmol) was dissolved in *n*-butanol (75 ml) and heated at reflux with hydrazine (9.6 ml, 5 eq.) for five hours. After cooling, the bulk of the solvent was removed under vacuum, the residue dissolved in DCM washed with water (4 x 30 ml), dried on magnesium sulphate and evaporated under reduced pressure to give pale yellow oil, which was solidified on standing overnight. The solid was then crystallized from ethanol affording **240** as white crystals (6.64 g, 70% yield); m.p. 139 °C (Lit.[16] 138-140 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.12 (1H, d, J = 8.1 Hz, 5-H), 7.55 (1H, dd, J = 8.1 and 1.1 Hz, 8-H), 7.5 (1H, ddd, J = 8.1, 7.1 and 1.1 Hz, 7-H), 7.4 (1H, ddd, J = 8.1, 7.1 and 1.1 Hz, 6-H), 4.89 (1H, d, J = 4.2 Hz, C<u>H</u>OH), 4.75 (2H, s br, $-NH_2$), 2.3 (1H, m, $-C\underline{H}(CH_3)_2$, 1.1 (3H, d, J = 7.1 Hz, $-CH(C\underline{H}_3)_2$), 0.80 (3H, d, J = 7.1 Hz, $-CH(C\underline{H}_3)_2$); *m/z* (APCI) (%) 235.1 (100) [M + H^+], $[\alpha]^{25}_D$ = -20° (c = 1.2, $CHCl_3$), Lit.[16] $[\alpha]^{25}_D$ = -24° (c 1.2, $CHCl_3$).

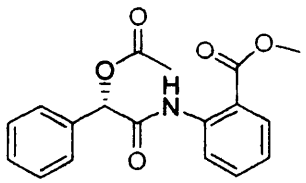
7.3.9 (S)-2-acetoxy-phenyl acetic acid (242).



(S)-(+)-α-hydroxyphenyl acetic acid (**241**) (2 g, 13.1 mmol) was dissolved in DCM (20 ml) and acetyl chloride (2.8 ml, 3 eq.) added with stirring. After setting aside overnight the solvent and unreacted acetyl chloride were removed under reduce pressure to leave (S)-2-acetoxy-phenyl acetic acid (**242**) as a white solid (2.45 g, 89% yield); m.p. 98 °C (Lit.[17] 97-99 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.05 (1H, s, br -

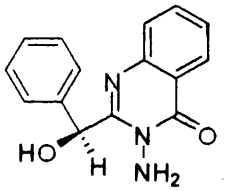
OH), 7.28 (5H, m, Ar), 5.87 (1H, s, -CHOCOCH$_3$), 2.08 (3H, s, -CH$_3$); $[\alpha]_D^{25}$ = +150° (c= 2.0, 95% EtOH), Lit.[17] $[\alpha]_D^{25}$ = +153° (c = 2.04, 95% EtOH).

7.3.10 (S)-2-{[(acetoxy)(phenyl)acetyl]amino}benzoate (244).



242 (14.5 g, 75 mmol), was converted into its acid chloride by dissolving it in DCM (50 ml), dried over silica gel, adding two drops of DMF and then thionyl chloride (10.5 ml, 149 mmol), dropwise. The mixture was stirred overnight and then DCM and unreacted thionyl chloride were removed under reduced pressure to give the acid chloride **243**. To a solution of **243** in DCM (50 ml) was added methyl anthranilate (**205**) (20 ml, 23.4 g, 0.15 mol) dropwise and the thick white precipitate was stirred at room temperature for 24 hours, the white solid was filtered, washed with DCM and the combined filtrates washed with 2M hydrochloric acid (3 × 100 ml), saturated aqueous sodium hydrogen carbonate solution (2 × 50 ml), brine (100 ml) dried on magnesium sulphate and evaporated to dryness. Crystallisation of the residue from light petroleum ether gave **244** as white crystals (11.3 g, 69% yield); m.p. 91°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.85 (1H, s br, -NH), 8.63 (1H, d, J = 8.0 Hz, 6-H), 7.99 (1H, dd, J = 8.0 and 1.5 Hz, 3-H), 7.50 (3H, m, Ar and 4-H), 7.30 (3H, m, Ar), 7.05 (1H, dd, J = 8.0 and 7.1 Hz, 5-H), 6.33 (1H, s, -CHPh), 3.88 (3H, s, -OCH$_3$), 2.23 (3H, s, -OCOCH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 169.9, 168.9, 167.9, 141.1, 135.8, 135.0, 131.2, 129.3, 127.8, 126.3, 123.5, 120.8, 115.9, 76.3, 52.7, 21.3; ν_{max} (nujol)/cm^{-1} 3263, 1751, 1701, 1662; *m/z* (APCI)(%) 328.1 (100)[M+H$^+$] 117(58) 107(13); $C_{18}H_{17}NO_5$ requires: C 66.05; H 5.23; N 4.28 (%), found: C 66.25; H 5.28; N 4.34 (%); $[\alpha]_D^{25}$ = +88° (c= 1.0, 95% EtOH),

7.3.11 3-Amino-2-[(S)-hydroxyphenylmethyl]-4(3H)-quinazolinone (245).

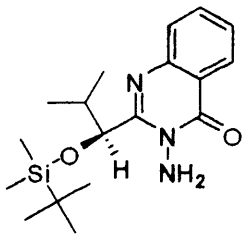


To a solution of **244** (2.36 g, 7 mmol) in *n*-butanol (20 ml) was added hydrazine monohydrate (2 ml, 2.06 g, 5.7 eq) and the resulting solution heated at reflux for five hours. The reaction mixture was concentrated under reduced pressure and the residue crystallised from ethanol to give **245** as colourless crystals (1.19 g, 64% yield); m.p. 139 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.19 (1H, d, J = 8.0 Hz, 5-H), 7.78 (2H, m, Ar), 7.48 (1H, m, Ar), 7.37 (5H, m, Ar), 6.01 (1H, d, J = 5.5 Hz, -CHOH), 5.22 (1H, d, J = 5.5 Hz, OH, exchanges D_2O), 4.46 (2H, s br, -NH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 169.9, 160.7, 156.0, 144.7, 139.0,133.7, 127.8, 127.4, 126.5, 126.2, 125.7, 119.1, 70.3; ν_{max}(nujol)/cm^{-1} 3357, 3101, 1673, 1588; *m/z* (APCI)(%) 269.1 (100)[M + H$^+$] 250.0 (77), 233.1 (11), 106.8 (42); $C_{15}H_{13}N_3O_2$ requires: C 62.40; H 4.90; N 15.72 (%), found: C 61.96; H 4.55; N 15.77 (%); $[\alpha]^{25}_D$ = +10° (c = 1.2, $CHCl_3$).

7.3.12 4-Isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one (246).

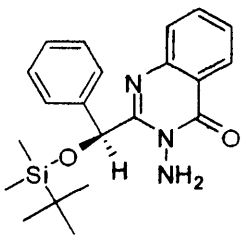
See pag. 188.

7.3.13 (S)-3-Amino-2-(1-tert-butyldimethylsilyloxy-2-methylpropyl)-4(3H)-quinazolinone[16] (247).



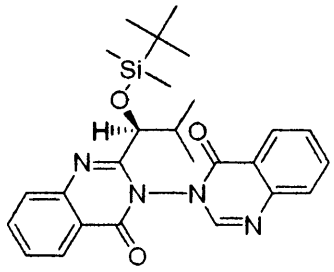
Following the procedure of Atkinson,[16] **240** (3 g, 12.8 mmol), was dissolved in *N, N*-dimethylformamide (7 ml), then *tert*-butyldimethylsilyl chloride (3.7 g, 24.5 mmol), imidazole (2.2 g, 32 mmol) were added and the solution stirred at room temperature for 24 hours. Light petroleum ether (20 ml) was then added to the mixture and the solution washed with water, dried and evaporated under reduced pressure. Crystallization from petroleum ether of the white residue gave **247** as white needles. (3.98 g, 88% yield); m.p. 125 °C (Lit.[16] 126-128 °C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.35 (1H, dd, J = 8.2 and 1.1 Hz, 5-H), 7.86 (1H, dd, J = 8.2 and 1.5 Hz, 8-H), 7.82 (1H, ddd, J = 8.2, 7.1 and 1.1 Hz, 7-H), 7.55 (1H, ddd, J = 8.2, 7.1 and 1.5 Hz, 6-H), 5.80 (2H, s, $-NH_2$), 4.63 (1H, d, J = 6.6 Hz, -CHOSi), 2.81 (1H, m, $-C\underline{H}(CH_3)_2$), 1.12 (3H, d, J = 6.6 Hz, $-CH(C\underline{H}_3)_2$), 0.95 (9H, s, $SiC(C\underline{H}_3)_3$), 0.92 (3H, d, J = 6.6 Hz, $-CH(C\underline{H}_3)_2$), 0.13 (3H, s, $-SiCH_3$), -0.05 (3H, s, $-SiCH_3$); *m/z* (APCI) (%) 348.00 (100%) [M + H$^+$], 348.21 (17%); $[\alpha]^{25}_D$ = -90° (c 1.3, $CHCl_3$), Lit.[16] $[\alpha]^{25}_D$ = -95° (c 1.3 $CHCl_3$).

7.3.14 (S)-3-amino-2-(1-tert-butyldimethylsilyloxy-2-phenyl)-quinazolin-4(3H)-one (248).



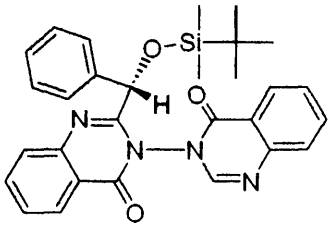
By a modification of the procedure of Atkinson,[16] **245**, (1.0 g, 3.74 mmol) was dissolved in *N, N*-dimethylformamide (3 ml), *tert*-butyldimethylsilyl chloride (1.0 g, 6.73 mmol), imidazole (0.63 g, 9.35 mmol) were added and the solution stirred at 70 °C for 48 hours. Diethyl ether was then added to the mixture (20 ml) and the solution washed with water, dried and evaporated under reduced pressure. Crystallization of the white residue from diethyl ether gave **248** as white needles. (0.98 g, 70% yield). ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 8.18 (1H, d, J = 8.5 Hz, 5-H), 7.70 (2H, m, Ar), 7.41 (3H, m, Ar), 7.28 (3H, m, Ar), 6.15 (1H, s, -C<u>H</u>OSi), 5.42 (2H, s br, -NH_2), 0.90 (9H, s,-C(C<u>H</u>$_3$)$_3$), 0.10 (6H, s, -Si(C<u>H</u>$_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 166.0, 160.3, 154.0, 146.6, 138.9, 134.0, 128.3, 127.9, 126.9, 126.5, 126.2, 120.0, 76.5, 33.2, 25.8, -4.8, -5.0; ν_{max} (nujol)/cm^{-1} 3335, 3303, 1675, 1596, 1421, 1264; *m/z* (APCI)(%) 383.2 (100) [M + H$^+$]; HRMS for $C_{21}H_{27}N_3O_2Si$ requires: 383.1951, found: 383.1949; $[\alpha]^{25}_D$ = -46° (c = 1.2, $CHCl_3$).

7.3.15 (S)-1-tert-butyldimethylsilyloxy-2-methylpropyl)-2'-H-biquinazolin-4,4'-one (249).



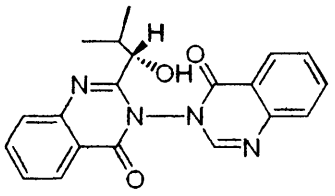
247 (1.0 g, 2.89 mmol) and **202** (0.51 g, 3.44 mmol) were dissolved in toluene and *p*-toluenesulphonic acid is added (0.025 g, 0.444 mmol, 5%). The mixture is refluxed for 48 hours. After cooling the solvent was removed under reduced pressure and the dark brown residue was crystallized from light petroleum ether affording **249** as white crystals as a mixture of diastereoisomers (ratio 60/40 referred to as A and B, many signals overlap) (0.98 g, 71 % yield). R_f= 0.3 (hexane: ethyl acetate, 3:1) m.p. 147 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.3 (2H, d, J = 7.9 Hz, 5-H), 8.2 (2H, d, J = 8.1 Hz, 5'-H), 7.93 (1H, s, 2'-H_A), 7.88 (1H, s, 2'-H_B), 7.80 (8H, m, Ar), 7.53 (4H, m, Ar), 4.36 (1H, d, J = 8.5 Hz, -C$\underline{H}_A$OSi), 4.24 (1H, d, J = 8.5 Hz -C$\underline{H}_B$OSi), 1.68 (2H, m, -C$\underline{H}$(CH_3)$_2$), 0.9 (18H, s, -SiC(C$\underline{H}_3$)$_3$), 0.8 (12H, m, -CH(C$\underline{H}_3$)$_2$), 0.53 (6H, s, -$SiCH_3$), 0.01 (6H, s, -$SiCH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.8, 159.4, 158.9 158.3, 155.2, 154.7, 147.5, 147.2, 147.1, 135.6, 135.3, 128.3, 128.1, 128.0, 127.9, 127.8, 122.2, 121.1, 120.8, 79.9, 33.1, 26.7, 19.3, 18.5, -4.1, -5.1; ν_{max} (nujol)/cm^{-1} 2924, 1699, 1603, 1463, 1377, 1291, 1260; *m/z* (APCI) (%) 477.2 (100) [M + H$^+$]; $C_{26}H_{32}N_4O_3Si$ requires: C 65.52; H 6.77; N 11.75 (%), found: C 65.40; H 6.77; 11.77 (%). $[\alpha]^{25}_D$ = -13.2° (c= 1.2, $CHCl_3$).

7.3.16 2-(1-tert-butyldimethylsilyloxy-2-phenyl)-2'-H-biquinazolin-4,4'-dione (250).



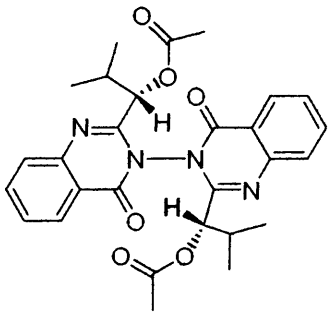
248 (0.10 g, 0.262 mmol) and **202** (0.059 g, 0.393 mmol), were dissolved in toluene (3 ml) and and *p*-toluenesulphonic acid is added (0.002 g, 0.013 mmol, 5%). The mixture is refluxed for 48 hours. After cooling the solvent was removed under reduced pressure and the dark brown residue, a mixture of diastereoisomers (ratio 80/20) (0.098 g, 73 % yield) was crystallized three times from methanol affording **250** (major diastereoisomer) as white crystals (0.053g, 40% yield); m. p. 195° C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.15 (1H, d, J = 7.9 Hz, 5-H), 7.70 (3H, m, Ar and 2'-H), 7.57 (3H, m, Ar), 7.40 (2H, m, Ar), 7.23 (2H, m, Ar), 6.93 (1H, d, J = 7.8 Hz, 8'-H), 6.79 (2H, m, Ar), 5.85 (1H, s, C<u>H</u>OSi), 0.83 (9H, s, -SiC$(CH_3)_3$), 0.54 (3H, s, -$SiCH_3$), 0.01 (3H, s, -$SiCH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 159.7, 157.0, 154.3, 146.8, 146.2, 145.9, 137.0, 135.5, 134.8, 128.9, 128.3, 127.8, 127.6, 127.6, 127.5, 127.4, 126.1, 124.7, 122.1, 121.3, 77.8, 25.9, 18.5, -4.8, -5.2; ν_{max}(nujol)/cm^{-1} 2930, 1690, 1598, 1456, 1368, 1299, 1260, 1421, 1264; *m/z* (APCI) (%) 512 (100) [M+H$^+$]; HRMS for $C_{29}H_{30}N_4O_3Si$ requires: 511.2160, found: 511.2163; $[\alpha]^{25}_D$ = +3.8° (c = 1.2, $CHCl_3$).

7.3.17 [(2S)- 2-methylpropyl)-2'-H-biquinazolin-4, 4'-one (251).



249 (0.5 g, 1.04 mmol), dissolved in THF (10 ml) was treated with *tetra*-butyl ammonium fluoride (TBAF, 0.543g, 2.08 mmol) and the resulting mixture stirred at room temperature for three hours. Evaporation of the solvent and crystallization from methanol afforded the alcohol **251** as a mixture of two diastereoisomers (60:40 ratio, referred to as A and B, many signals overlapped) (0.304 g, 80% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.28 (2H, d, J = 7.5 Hz, 5-H), 8.20 (2H, d, J = 8.1 Hz, 5'-H), 7.89 (1H, s, 2'-H_A), 7.85 (1H, s, 2'-H_B), 7.80 (8H, m, Ar), 7.53 (4H, m, 7'-H and Ar), 4.45 (1H, d, J = 8.5 Hz, -C$\underline{H}_A$OH), 4.35 (1H, d, J = 8.5 Hz -C$\underline{H}_B$OH), 1.68 (2H, m, -C$\underline{H}$(CH$_3$)$_2$), 1.01 (12H, m, -CH(C$\underline{H}_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 160.3, 159.2, 157.9 158.1, 155.0, 153.7, 146.5, 145.2, 144.1, 134.6, 133.3, 128.5, 127.9, 127.6, 127.3, 127.1, 122.0, 121.7, 121.5, 80.2, 32.9, 19.5; ν_{max} (nujol)/cm^{-1} 2950, 1690, 1610, 1474, 1300; *m/z* (APCI) (%) 363.1 (100) [M + H$^+$]; $C_{20}H_{18}N_4O_3$ requires: C 66.29; H 5.01; N 15.46 (%), found: C 66.08; H 4.98; 15.02 (%).; $[\alpha]^{25}_D$ = +31.1° (c 1.2, $CHCl_3$).

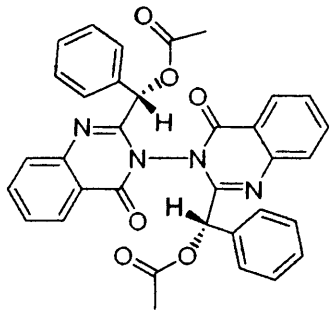
7.3.18 2,2'-[2-methyl-1-acetoxymethylpropyl]-biquinazolin-4,4'-one (254).



A stirred solution of 1,2-dianthraniloylhydrazide **192** (1.38 g, 5.09 mmol) in dry *N,N*-dimethylacetamide (10 ml) was treated with triethylamine (1.04 g, 10.1 mmol, 1.45 ml) then cooled at 0 °C before the dropwise addition of (2S)-2-acetoxy-3-methylbutanoic chloride (**238**) (1.82 g, 10.1 mmol) dissolved in tiny amount of dichlorometane over 15 minutes. The solution was allowed to warm to room temperature over further two hours and then diluted with ethyl acetate (300 ml), washed with 2M hydrochloric acid (3 x 50 ml) and with aqueous saturated sodium hydrogen carbonate (2 x 50 ml). The organic layer was then dried over magnesium

sulphate and evaporated to give 1,2 bis amide **253** which was not isolated but heated at reflux in neat acetic anhydride (100 ml) for two hours, the solvent evaporated affording **254** as a brown oil (1.2 g, 45% yield estimated by ^{1}H-NMR of crude mixture). Flash chromatography (ethyl acetate : hexane 1:3) afforded **254** as a transparent oil (r.f = 0.32) along with decomposition products. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.08 (2H, dd, J = 7.8 and 1.4 Hz, 5-H, 5'-H), 7.72 (2H, ddd, J = 8.8, 7.8 and 1.5 Hz, 7-H, 7'-H), 7.51 (2H, d, J = 7.8 Hz, 8-H, 8'-H), 7.46 (2H, ddd, J = 8.8, 7.8 and 1.5 Hz, 6-H, 6'-H), 5.13 (2H, d, J = 5.9 Hz, 2x C<u>H</u>OCOCH$_3$), 2.35 (2H, m, 2x -C<u>H</u>(CH$_3$)$_2$), 2.12 (6H, s, 2x -COCH$_3$), 0.98 (12H, d, J = 6.6 Hz, 2x -CH(C<u>H</u>$_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.3, 169.5, 158.2, 157.8, 144.6, 135.9, 127.9, 127.7, 127.6, 75.7, 29.7, 19.8, 17.9, 16.4; ν_{max} (nujol)/cm^{-1} 1758, 1649, 1608, 1466, 1390, 1226, 774, 734, 690; *m/z* (APCI)(%) 519 (100) [M+H$^+$] (20) 160 (100).

7.3.19 2,2'-[2-Phenyl-1-acetoxymethylpropyl] biquinazolin-4,4'-one (257).

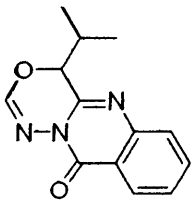


A stirred solution of 1,2-dianthraniloylhydrazide (**192**) (2.06g, 7.65 mmol) in dry *N,N*-dimethylacetamide (10 ml) was treated with triethylamine (2.20 ml, 1.58g, 15.3 mmol) then cooled at 0 °C before the dropwise addition of (S)-2-acetoxy-phenyl acetyl chloride (**243**) (3.25 g, 15.3 mmol) dissolved in tiny amount of DCM over 15 minutes. The solution was allowed to attain room temperature over further two hours and then diluted with ethyl acetate (300 ml), washed with 2M hydrochloric acid (3 x 50 ml), aqueous saturated sodium hydrogen carbonate (2 x 50 ml). The organic layer was then dried over magnesium sulphate and evaporated to give 1,2 bis amide **256** which was not isolated but heated at reflux in neat acetic anhydride (100 ml) for two hours, the solvent evaporated affording **257** as a mixture of diastereoisomers (ratio

80:20, referred to as A and B, many signals overlapped) (3.9g, 87% yield, from ^{1}H-NMR of crude mixture) as a brown oil which decompose on standing. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.14 (2H, dd, J = 7.8 and 1.4 Hz, 5-H, 5'-H), 7.85 (2H, ddd, J = 8.7, 7.8 and 1.6 Hz, 7-H, 7'-H), 7.51 (2H, d J = 7.8 Hz, 8-H, 8'-H), 7.4 (2H, ddd, J = 8.7, 7.8 and 1.6 Hz, 6-H, 6'-H), 7.37 (2H, m, Ar), 7.28 (8H, m, Ar), 5.16 (1H, d, J = 5.8 Hz, CH_AOCOCH_3), 5.06 (1H, d, J = 5.8 Hz, CH_BOCOCH_3), 2.10 (6H, s, 2x -$COCH_3$).

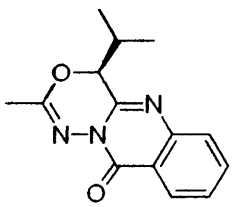
7.4 Experimental procedures related to Chapter 4.

7.4.1 4-Isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one (246).



A solution of (±) **240** (0.354 g, 1.5 mmol) in triethyl orthoformate (8 ml) was heated at reflux for five hours. After that period the mixture was allowed to reach room temperature, and then the solvent was removed under reduced pressure. The red residue was crystallised from ethanol to give **246** as white crystals (0.248 g, 68%); mp 230 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, dd, J = 8.1 and 1.3 Hz, 8-H), 7.70 (1H, dd, J = 8.1 and 7.0 Hz, 7-H), 7.60 (1H, d, J = 7.7 Hz, 5-H), 7.50 (1H, dd, J = 7.7 and 7.0 Hz, 6-H), 7.24 (1H, s, 2-H), 4.95 (1H, d, J = 4.2 Hz, 4-CH), 2.55 (1H, m,-C<u>H</u>$(CH_3)_2$), 1.05 (3H, d, J = 6.9 Hz, -CH(C<u>H</u>$_3)_2$), 0.95 (3H, d, J = 6.98 Hz, -CH(C<u>H</u>$_3)_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 155.4, 145.0, 144.9, 143.3, 133.6, 126.8, 126.5, 126.4, 121.2, 77.6, 31.9, 17.5, 15.3; ν_{max}(nujol)/cm^{-1} 1699, 1654, 1598, 1463; *m/z* (APCI) (%) 244.1 (100) [M + H$^+$]; $C_{13}H_{13}N_3O_2$, HRMS requires: 244.1081, found: 244.1084; $C_{13}H_{13}N_3O_2$, requires: C 64.12; H 5.39; N 17.27, (%) found: C 63.83; H 5.38; N 17.12 (%).

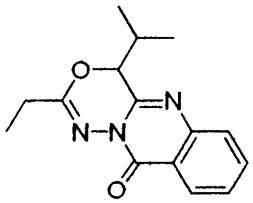
7.4.2 (S)-4-Isopropyl-2-methyl-3-oxo-1,9a,10-triazaanthracen-9-one (258).



A solution of (-) **240** (0.20 g, 0.85 mmol) in triethyl orthoacetate (3 ml) was heated at reflux for 24 hours. After that period the mixture was allowed to reach room

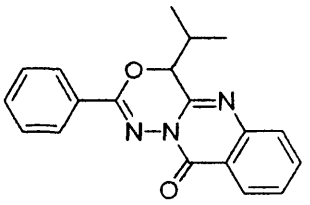
temperature and then the solvent was removed under reduced pressure. The residue was crystallised from ethyl acetate–light petroleum ether to give **258** as white crystals (0.17 g, 77% yield); m.p. 147 °C; ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 8.30 (1H, dd, J = 8.1 and 1.2 Hz, 8-H), 7.68 (1H, ddd, J = 8.1, 7.0 and 1.0 Hz, 7-H), 7.60 (1H, dd, J = 8.1 and 1.0 Hz, 5-H), 7.50 (1H, ddd, J = 8.1, 7.0 and 1.2 Hz, 6-H), 4.90 (1H, d, J = 4.8 Hz, 4-CH), 2.48 (1H, m,-C<u>H</u>$(CH_3)_2$), 2.21 (3H, s, -N=CHC<u>H</u>$_3$), 1.05 (3H, d, J = 6.9 Hz, -CH(C<u>H</u>$_3)_2$), 0.95 (3H, d, J = 6.8 Hz, -CH(C<u>H</u>$_3)_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 155.5, 145.1, 143.2, 133.4, 126.7, 126.2, 126.1, 125.5, 121.7, 78.0, 31.7, 18.1, 17.6, 15.5; ν_{max} (nujol)/cm^{-1} 1688, 1654, 1606, 1248, 1028; *m/z* (EI)(%) 257.2 (18) [M^+], 174.1 (80), 119.1 (60); $C_{14}H_{15}N_3O_2$, requires: C 65.4; H 5.9; N 16.3, (%) found: C 65.1; H 5.9; N 16.1 (%); $[\alpha]^{25}_D$ = -51.5° (c= 1, $CHCl_3$).

7.4.3 4-Isopropyl-2-ethyl-3-oxo-1,9a,10-triazaanthracen-9-ones (259).



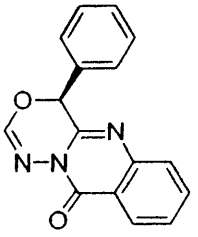
A solution of (±) **240** (0.37 g, 1.60 mmol) in triethyl orthopropionate (2 ml) was heated at reflux for 36 hours. The excess of orthoester was then removed by vacuum distillation and the brown residue crystallised from ethyl acetate–petroleum ether to give **259** as white crystals (0.23 g, 54% yield); mp 82°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, dd, J = 8.4 and 1.0 Hz, 8-H) 7.68 (1H, dd, J = 8.4 and 7.0 Hz, 7-H), 7.58 (1H, d, J = 8.1 Hz, 5-H), 7.42 (1H, ddd, J = 8.1, 7.0 and 1.0 Hz 6-H), 4.90 (1H, d, J = 4.6 Hz, 4-CH), 2.51 (2H, q, J = 7.6 Hz, -C<u>H$_2$</u>CH$_3$), 2.44 (1H, m, -C<u>H</u>$(CH_3)_2$), 1.24 (3H, t, J = 7.6 Hz, CH_2C<u>H$_3$</u>), 1.06 (3H, d, J = 6.9 Hz, -CH(C<u>H</u>$_3)_2$), 0.97 (3H, d, J = 6.9 Hz, -CH(C<u>H</u>$_3)_2$); ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ_C 159.6, 156.5, 146.1, 144.3, 134.3, 127.6, 127.2, 127.1, 122.2, 88.3, 32.7, 26.6, 18.6, 16.5, 10.4; ν_{max} (nujol)/cm^{-1} 1692, 1654, 1377, 1328, 1149, 1090, 1062; *m/z* (APCI)(%) 272.1 (100), [M + H^+]; $C_{15}H_{17}N_3O_2$ requires: C 66.40; H 6.32; N 15.49 (%), found: C 66.21; H 6.32; N 15.40 (%).

7.4.4 4-Isopropyl-2-phenyl-3-oxo-1,9a,10-triazaanthracen-9-one (260).



A solution of (±) **240** (0.400 g, 1.70 mmol) in triethyl orthobenzoate (3 ml) was heated at reflux for 36 hours. The excess of orthoester was then removed by vacuum distillation and the brown residue was crystallised from diethyl ether to give **260** as pale brown crystals m.p. 240 °C (0.32 g, 60% yield); ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 8.38 (1H, dd, J = 8.0 Hz, 1.2 Hz, 8-H), 8.12 (1H, dd, J = 8.0 Hz, 1.6, 7-H), 7.66 (2H, m, 5-H and 6-H), 7.45 (5H, m, Ar), 5.06 (1H, d, J = 5.2 Hz, 4-CH), 2.55 (1H, m, -C<u>H</u>$(CH_3)_2$), 1.20 (3H, d, J = 6.9 Hz, -CH(C<u>H</u>$_3)_2$), 1.05 (3H, d, J = 6.9 Hz, -CH(C<u>H</u>$_3)_2$); ^{13}C-NMR (62.5 MHz, CDCl3): δ_C 157.0, 154.2, 146.3, 145.2, 134.8, 132.6, 129.6, 128.9, 128.2, 128.0, 127.7, 127.6, 122.6, 79.9, 32.7, 19.3, 17.2; ν_{max} (nujol)/cm^{-1} 1696, 1605, 1465, 1362, 1318, 1176; *m/z* (APCI)(%) 320.1 (100) [M+ H$^+$]; HRMS $C_{19}H_{17}N_3O_2$ requires: 320.1394, found: 320.1389.

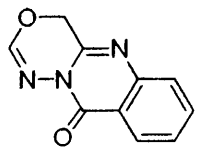
7.4.5 (S)-4-Phenyl-3-oxo-1, 9a, 10-triazaanthracen-9-one (261).



A solution of (+) **245** (0.5 g, 1.92 mmol) in triethyl orthoformate (3 ml) was heated at reflux for 24 hours. After that period the mixture was allowed to reach room temperature and then the solvent was removed under reduced pressure. The residue was crystallised from DCM/methanol to give **261** as pale orange crystals; mp 228 °C (0.307 g, 58% yield); ^{1}H-NMR (250 MHz, $CDCl_3$): δ_H 8.35 (1H, dd, J = 8.2 and 1.2

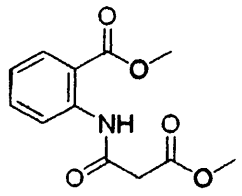
Hz, 8-H), 7.70 (1H, ddd, J = 8.2 and 7.0 Hz, 1.2, 7-H), 7.60 (1H, d, J = 8.2 Hz, 5-H), 7.48 (1H, ddd, J = 8.2, 7.0 and 1.2 Hz, 6-H), 7.35 (5H, m, Ar), 7.28 (1H, s, 2-H), 6.15 (1H, s, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 155.4, 145.1, 144.5, 142.7, 134.3, 133.7, 128.9, 128.2, 126.8, 126.7, 126.6, 125.9, 121.4, 74.2; ν_{max}(nujol)/cm^{-1}, 1708, 1648, 1600, 1463, 1368, 1172; *m/z* (APCI) (%) 278.0 (100) [M + H$^+$]; HRMS $C_{16}H_{11}N_3O_2$ requires: 278.0924, found: 278.0926; $[\alpha]^{25}_D$ = -127° (*c*= 1, CH_2Cl_2).

7.4.6 3-Oxo-1, 9a,10-triazaanthracen-9-one (262).



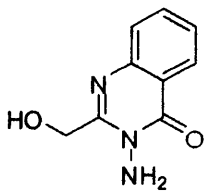
A solution of **264** (0.51 g, 2.66 mmol) in triethyl orthoformate (6 ml) was heated at reflux for 24 hours. After that period the mixture was allowed to reach room temperature and then the solvent was removed under reduced pressure. The residue was crystallised from methanol to give **262** as pale yellow crystals; m.p. 200 °C; (0.46 g, 85% yield); ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 8.30 (1H, dd, J = 8.3 Hz, 1.2 Hz, 8-H), 7.70 (1H, ddd, J = 8.3, 7.0 and 1.2 Hz, 7-H), 7.60 (1H, d, J = 7.7 Hz, 5-H), 7.46 (1H, ddd, J = 7.7, 7.0 and 1.2 Hz, 6-H), 7.24 (1H, s, 2-H), 5.05 (2H, s, -CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 156.6, 146.4, 146.3, 142.1, 135.2, 128.2, 128.0, 127.6, 123.0, 63.4; ν_{max}(nujol)/cm^{-1} 1703, 1649, 1605,1360; *m/z* (APCI)(%) 202.1 (100) [M + H$^+$]; $C_{10}H_7N_3O_2$ requires: C 59.70; H 3.51; N 20.89 (%), found: C 59.55; H 3.51; N 20.77 (%).

7.4.7 Methyl 2-(3-methoxy-3-oxopropanamido) benzoate (263).



In a round bottomed flask, methyl anthranilate (**205**) (23.4 g, 158 mmol, 20 ml) was dissolved in diethyl ether (90 ml), then acetoxyacetyl chloride (9.42 g, 69 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for one hour and then allowed to reach room temperature. After that the white solid was filtered off and washed with diethyl ether. The combined organic phases were washed with diluted 2M hydrochloric acid (3 x 30 ml), brine (1 x 50 ml) dried over magnesium sulphate and evaporated under reduced pressure affording **263** (14.6 g, 84% yield); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 11.64 (1H, s, -NH), 8.30 (1H, d, J = 7.8 Hz, 6-H), 7.72 (2H, m, Ar), 7.28 (1H, m, Ar), 3.88 (3H, s, $-CO_2C\underline{H}_3$), 3.71 (3H, s, $-CH_2CO_2C\underline{H}_3$), 3.44 (2H, s, $-CH_2$).[18]

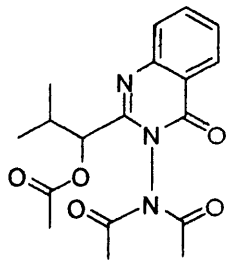
7.4.8 3-Amino-2-hydroxymethyl-4(3H)-quinazolinone (264).



263 (14.6 g, 57.9 mmol) was dissolved in *n*-butanol (85 ml) and heated at reflux with hydrazine (13.8 ml, 5 eq.) for four hours. After cooling, the bulk of the solvent was removed under vacuum, the residue dissolved in DCM washed with water (4x 35 ml), dried on magnesium sulphate and evaporated under reduced pressure to give pale yellow oil, which was solidified on standing overnight. The solid was then crystallized from ethanol affording **264** (8.62 g, 78% yield); ^{1}H-NMR (400 MHz,

CDCl3): δ_H 8.15 (1H, d, J = 7.9 Hz, 5-H), 7.4 (3H, m, Ar), 4.90 (2H, s br, -NH_2), 4.56 (2H, s, -CH_2), 3.07 (1H, s, -OH).[19]

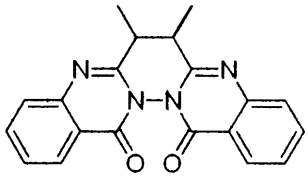
7.4.9 3-N-acetylacetamido-2-(1-acetoxy-2-methylpropyl)-quinazolin-4(3H)-one (265).



(±) **240** (0.5g, 2.14 mmol) is refluxed in acetyl chloride for two hours, then the solvent is evaporated and the crude is crystallized from ethanol to obtain **265** (0.67 g, 87% yield); ^{1}H-NMR (400MHz, $CDCl_3$): δ_H 8.22 (1H, d, J = 7.8 Hz, 5-H), 7.77 (2H, m, Ar), 7.49 (1H, dd, J = 7.8 Hz, Ar), 5.37 (1H, d, J = 6.6 Hz, C<u>H</u>O), 2.51 (3H, s, $OCOCH_3$), 2.40 (1H, m, -C<u>H</u>($C\underline{H}_3$)$_2$), 2.28 (3H, s, -NCOC<u>H</u>$_3$), 2.1 (3H, s, -NCOC<u>H</u>$_3$), 0.9 (6H, m, -CH($C\underline{H}_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 175.1, 174.3, 170.2, 160.6, 157.8, 147.0, 133.1, 127.3, 127.0, 126.9, 120.8, 78.6, 25.4, 21.0, 21.23 20.98, 18.8, 19.1; *m/z* (APCI)(%) 360.15 (100) [M + H^+]; ν_{max} (nujol)/cm^{-1}1764, 1740, 1710, 1680, 1608; HRMS for $C_{18}H_{21}N_3O_5$ requires: 360.1481, found: 360.1484.

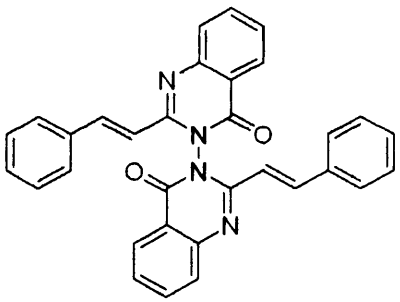
7.5 Experimental procedures related to Chapter 5.

7.5.1 6,7-dimethyl-6,7-dihydro-5,8,13a,13b-tetraaza-pentaphene-13,14-dione (268).



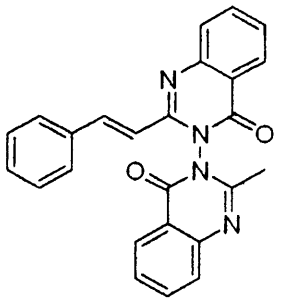
To a cooled (-78 °C, dry ice/acetone), stirred solution of 2,2'-diethyl-3,3'-biquinazoline-4,4'-dione **195** (0.3 g, 0.82 mmol) in dry THF (6 ml) was added 2.2 equivalent of 2.0 M LDA solution in hexane, (0.90 ml, 1.81 mmol). Formation of dianion was observed as a deep red solution. The resulting mixture was stirred at –78 °C for additional 15 min after which iodine (0.46g, 1.81 mmol, 2.2 eq.) was added and the resulting mixture was then stirred at -78°C for additional 30 min then allowed to warm to room temperature, diluted with DCM, and quenched with aqueous saturated ammonium chloride (15 ml). The organic layer was washed with water (2 x 20 ml), dried on magnesium sulphate and evaporate to obtain **268** as a yellow-white solid after crystallization from methanol (0.107g, 38%); m.p. 226 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.20 (2H, dd, J = 7.5 and 1.0 Hz, 1-H, 12-H), 7.76 (4H, m, 10-H, 9-H, 3-H, 4-H), 7.45 (2H, m, 11-H, 2-H), 2.75 (2H, m, 6-H, 7-H), 1.54 (6H, m, 2x -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 154.6, 153.2, 144.8, 133.8, 126.5, 126.3, 120.6, 38.3, 11.8; ν_{max} (nujol)/cm^{-1} 2940, 1694, 1604, 1267, 768, 740, 694; (APCI) (100) 345.1 [M + H$^+$], 173 (80); HRMS for $C_{20}H_{16}N_4O_2$ requires: 345.1273, found: 345.1278.

7.5.2 2,2'-Bis-styryl-3,3'-bisquinazoline-4,4'-dione (271)



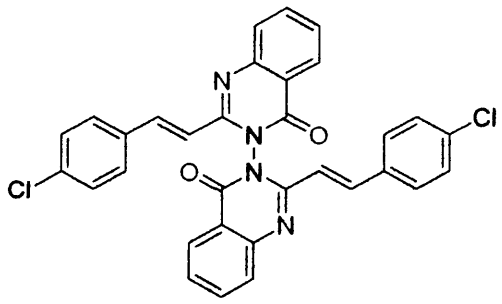
To a cooled (-78 °C, dry ice/acetone), stirred solution of 2,2'-dimethyl-3,3'-biquinazoline-4,4'-dione **193** (0.2 g, 0.60 mmol) in dry THF (6 ml) was added 2.5 M butyl lithium solution in hexane (0.57 ml, 1.44 mmol). Formation of dianion was observed as a deep red solution along with a red precipitate. The resulting mixture was stirred at –78 °C for additional 15 min after which benzaldehyde (0.140 g, 0.135 ml, 1.32 mmol, 2.2 eq) was added as a THF solution. The mixture was stirred for further 30 min at –78 °C, then allowed to reach room temperature and stirred for further 60 min., diluted with DCM (30 ml), and quenched with aqueous saturated ammonium chloride (10 ml). Organic layer was then washed with water (2 x 10 ml), dried over sodium sulphate and evaporated to dryness. Chromatography on silica gel and ethyl acetate/hexane 1:3 afforded **271** as yellow crystals (0.108 g, 34 % yield); R_f = 0.29 (hexane : ethyl acetate, 3:1); m.p. 210 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.2 (2H, dd, J = 7.9 and 0.7 Hz, 5-H, 5'-H), 8.1 (2H, d, J = 15.3 Hz, 2x C<u>H</u>=CHPh), 7.81 (4H, m, 7-H, 8-H, 7'-H, 8'-H), 7.42 (2H, m, Ar), 7.28 (4H, dd, J = 8.5 and 1.8 Hz, Ar), 7.20 (6H, dd, J = 8.5 and 1.8 Hz, Ar), 6.45 (2H, d, J = 15.4 Hz, 2x CH=C<u>H</u>Ph); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.4, 151.7, 147.6, 143.9, 136.1, 135.0, 130.7, 129.2, 128.6, 128.4, 128.2, 127.6, 121.2, 115.3; ν_{max} (nujol)/cm^{-1} 1697, 1548, 1469, 1334; *m/z* APCI (%) 495.17 (100) [M + H$^+$]; HRMS for $C_{32}H_{22}N_4O_2$ requires: 495.1743, found: 495.1749. Further elution with the same solvents afforded:

2-Styryl-2'-methyl-3,3'-biquinazoline-4,4'-dione (272).



272 is obtained as yellow crystals, (0.146 g, 58% yield); R_f = 0.22 (hexane : ethyl acetate, 3:1); m.p. 207°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.2 (2H, d, J = 7.9 Hz, 5-H, 5'-H), 8.1 (1H, d, J = 15.4 Hz, C<u>H</u>=CHPh), 7.8 (3H, m, Ar), 7.48 (1H, m, Ar), 7.46 (2H, m, Ar), 7.25 (2H, m, Ar), 7.20 (3H, m, Ar), 6.45 (1H, d, J = 15.4 Hz, CH=C<u>H</u>Ph), 2.40 (3H, s, -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 157.9, 152.7, 149.7, 146.2, 145.8, 142.6, 134.6, 133.5, 129.4, 127.8, 127.1, 126.9, 126.7, 126.6, 126.5, 126.4, 126.2, 119.8, 119.7, 113.5, 20.3; ν_{max} (nujol)/cm^{-1} 1694, 1551, 1465; *m/z* (APCI) (%) 407.1 (40) [M + H$^+$]; $C_{25}H_{18}N_4O_2$ requires: C 73.88; H 4.46; N 13.78 (%), found. C 73.61; H 4.46; N 13.70 (%).

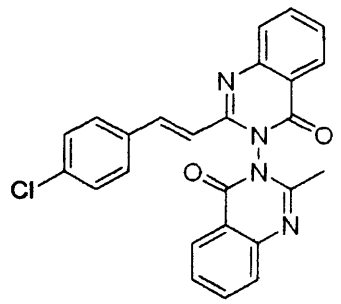
7.5.3 2,2'-Bis-(p-Chlorostyryl)-3,3'-biquinazolin-4,4'-one (273).



To a cooled (-78 °C, dry ice/acetone), stirred solution of 2,2'-dimethyl-3,3'-biquinazoline-4,4'-dione **193** (0.2 g, 0.60 mmol) in dry THF (6 ml) was added 2.5 M butyl lithium solution in hexane (0.57 ml of, 1.44 mmol). The resulting mixture was stirred at –78 °C for additional 15 min after which *p*-chloro-benzaldehyde (0.19 g,

1.32 mmol, 2.2 eq.,) was added as solid. The mixture was stirred for 30 min at –78 °C, allowed to reach room temperature and stirred for a further 60 min., diluted with DCM 30 ml, and quenched with aqueous saturated ammonium chloride (10 ml). The organic layer was then washed with water (2 x 10 ml), dried over sodium sulphate and evaporated to dryness. Chromatography on silica gel using like eluents ethyl acetate/hexane 1:3 afforded **273** as yellow crystals (0.109 g, 32% yield); R_f= 0.3 (hexane: ethyl acetate, 3:1); m.p. 270 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.22 (2H, d, J = 8.4 Hz, 5-H, 5'-H), 8.11 (2H, d, J = 15.4 Hz, 2x C<u>H</u>=CHPh), 7.80 (4H, m, Ar), 7.55 (2H, m, Ar), 7.24 (4H, d, J = 8.5 Hz, Ar), 7.18 (4H, d, J = 8.4 Hz, Ar), 6.48 (2H, d, J = 15.4 Hz, 2x -CH=C<u>H</u>Ph); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 158.0, 150.0, 146.1, 141.0, 135.2, 134.7, 132.0, 128.3, 128.1, 127.0, 126.8, 126.4, 119.7, 114.3; ν_{max} (nujol)/cm^{-1} 1701, 1550, 1467; *m/z* (APCI) (%) 563.1 (5) [M + H$^+$] 281.1 (50), 90 (100); HRMS for $C_{32}H_{20}Cl_2N_4O_2$ requires: 563.0963, found: 563.0950. Further elution with the same solvent afforded:

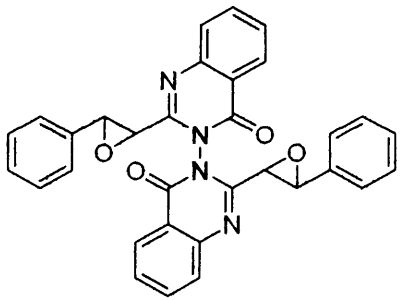
2-(p-Chlorostyryl)-2'-methyl-3,3'-biquinazoline-4,4'-dione (274).



274 (0.324g, 60% yield); m.p. 216 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.23 (2H, d, J = 7.9 Hz, 5H, 5'-H), 8.13 (1H, d, J = 15.3 Hz, -C<u>H</u>=CHPh), 7.80 (3H, m, Ar), 7.70 (1H, d, J = 7.9 Hz, Ar), 7.52 (2H, m, Ar), 7.46 (2H, d, J = 8.4 Hz, Ar), 7.25 (2H, m, Ar), 6.45 (1H, d, J = 15.3 Hz, -CH=C<u>H</u>Ph), 2.36 (3H, s, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.3, 159.2, 154.2, 150.9, 147.5, 147.1, 142.6, 136.7, 136.2, 136.1, 133.4, 129.7, 129.6, 128.4, 128.1, 128.0, 127.9, 127.8, 121.2, 121.1, 115.4, 21.6; ν_{max} (thin film)/cm^{-1} 1702, 1626, 1573, 1467, 1404, 1399, 1221, 1091, 769, 692; *m/z*

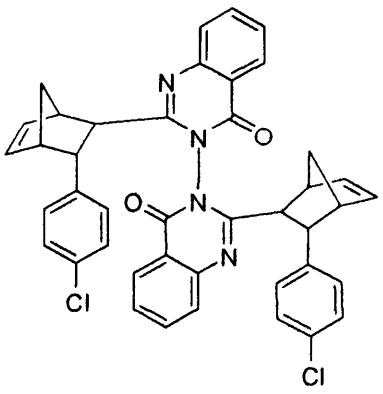
(APCI)(%) 441.1 (100) [M+H$^+$]; HRMS $C_{25}H_{17}ClN_4O_2$ requires: 441.1040, found: 441.1030.

7.5.4 2,2'-Bis-(3-phenyl-oxiranyl)-3,3'-biquinazolin-4,4'-one (275 and 276).



To a solution of **271** (200 mg, 0.40 mmol) in DCM was added MCPA (0.44g, 1.62 mmol, 4eq) and the resulting mixture stirred at room temperature for 24 hours. After this period the mixture was washed with aqueous saturated sodium thiosulfate (2 x 10 ml), water (2 x 10 ml), dried over magnesium sulphate and evaporated. The epoxides **275** and **276** were obtained after crystallization from ethanol as a mixture of two diastereoisomers (9:1 ratio referred to as A and B, many signals overlap) (184 mg, 88% yield); m.p. 260 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.2 (2H, d, J = 8.4 Hz, 5-H, 5'-H), 7.78 (4H, m, 7-H, 8-H, 7'-H, 8'-H), 7.47 (2H, m, 6-H, 6'-H), 7.12 (10H, m, Ar), 4.32 (1H, d, J = 1.72 Hz, 10-H_B), 4.27 (1H, d, J = 1.75 Hz, 10-H_A), 3.68 (1H, d, J = 1.75 Hz, 9-H_A), 3.61 (1H, d, J = 1.75 Hz, 9-H_B); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 157.9, 157.8, 149.4, 149.3, 145.3, 145.2, 134.8, 133.2, 132.6, 129.2, 128.7, 127.8, 127.6, 127.5, 127.4, 127.2, 127.1, 126.5, 124.7, 124.6, 58.8, 58.8, 56.5, 56.3; ν_{max}(nujol)/cm^{-1} 2922, 1713, 1600, 1458; *m/z* (APCI) 527.1 (100) [M+H$^+$], 409 (20); HRMS for $C_{32}H_{22}N_4O_4$ requires: 527.1641, found: 527.1608; $C_{32}H_{22}N_4O_4$ requires: C 72.99; H 4.21; N 10.64 (%), found C 72.80; H 4.23; N 10.63 (%).

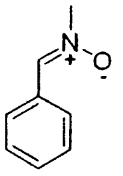
7.5.5 2,2'-Bis-[3-(p-chloro-phenyl)-bicyclo[2.2.1]hept-5-en-2-yl]-[3,3']biquinazolinyl-4,4'-dione (277-A and 277-B).



To a stirred solution at room temperature of **273** (0.10g, 0.19 mmol), in DCM (2 ml) was added cyclopentadiene (0.25g, 3.72 mmol, 0.3 ml, 20 eq,) and aluminium chloride (2.48 mg, 10% mol). The mixture was stirred for additional 24 hours at room temperature then the solvent was evaporated, and the waxy solid obtained was washed with light petroleum ether giving a brown powder containing a mixture 70/30 of **277a** and **277b** which was purified by column chromatography using ethyl acetate/ *n*-hexane affording compound **277a** as white powder (59 mg, 45% yield); m.p. 270 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.18 (2H, dd, J = 8.0 and 1.2 Hz, 5-H, 5'-H), 7.78 (2H, dd, J = 8.0 and 1.2 Hz, 7-H, 7'-H), 7.62 (2H, d, J = 8.0 Hz, 8-H, 8'-H), 7.43 (2H, m, 6-H, 6'-H), 6.92 (4H, d, J = 8.4 Hz, Ar), 6.78 (4H, d, J = 8.4 Hz, Ar), 6.22 (2H, dd, J = 5.4 and 3.1 Hz, 12-H, 12'-H), 6.03 (2H, dd, J = 5.5 and 2.7 Hz, 11-H, 11'-H), 3.59 (2H, d, J = 4.4 Hz, 14-H, 14'-H), 3.05 (2H, dd, J = 4.9 and 3.4 Hz, 9-H, 9'-H), 2.96 (2H, s br, 13-H, 13'-H), 2.66 (2H, s br, 10-H, 10'-H), 1.47 (2H, d, J = 8.6 Hz, 15-H_a, 15'-H_a), 1.21 (2H, d, J = 8.8 Hz, 15-H_b, 15'-H_b); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.5, 155.4, 145.1, 140.9, 136.5, 134.1, 133.5, 130.7, 127.3, 127.2, 127.0, 126.3, 126.2, 119.7, 49.5, 47.9, 47.3, 46.5, 45.7; ν_{max}(nujol)/cm^{-1} 2960, 1691, 1596, 1463; *m/z* (APCI) 695.2 (100) [M + H$^+$]; HRMS for $C_{42}H_{32}Cl_2N_4O_2$ requires: 695.1902, found: 695.1900; further elution with the same solvent afforded **277b** (37 mg, 28%); m.p. 283 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.19 (2H, dd, J = 8.0 and 1.2 Hz 5-H, 5'-H), 7.72 (2H, m, 7-H, 7'-H), 7.63 (2H, d, J = 8.0 Hz, 8-H, 8'-H), 7.46 (2H, m, 6-H, 6'-H), 6.89 (4H, d, J = 8.4 Hz, Ar), 6.71 (4H, d, J = 8.4 Hz, Ar), 6.33

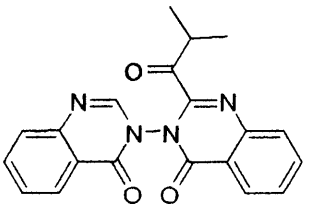
(2H, dd, J = 5.4 and 3.1 Hz, 11-H, 11'-H), 6.21 (2H, dd, J = 5.45 and 2.7 Hz, 12-H, 12'-H), 3.37 (2H, d, J = 4.7 Hz, 14-H, 14'-H), 3.23 (2H, dd, J = 5.1 and 3.2 Hz, 9-H, 9'-H), 3.15 (2H, s br, 13-H, 13'-H), 2.72 (2H, s br, 10-H, 10'-H) 1.61 (2H, d, J = 8.4 Hz, 15-H_a, 15'-H_a), 1.43 (2H, d, J = 8.9 Hz, 15-H_b, 15'-H_b); ν_{max}/cm^{-1} (Nujol) 2958, 1698, 1580, 1461; *m/z* (APCI) 695.2 (100) ($M+H^+$); HRMS for $C_{42}H_{32}Cl_2N_4O_2$ requires: 695.1902, found: 695.1905.

7.5.6 N-benzylidenemethanamine oxide (278).



A solution of benzaldehyde (1g, 9.6mmol) in DCM (15 ml) was treated with *N*-methyl hydroxylamine chloridrate (0.86g, 1.1 mmol) in presence of an excess of potassium carbonate (3.97g, 3 eq.). The mixture was stirred at room temperature for 24 hours. The inorganic was then filtered off and the solvent evaporated in *vacuo* giving a crystalline solid. Pure nitrone **278** was finally obtained by crystallization from petroleum ether (1.03g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.81 (2H, m, Ar), 7.35 (3H, m, Ar), 7.31 (1H, s, C<u>H</u>=N), 3.82 (3H, s, -CH_3).[20]

7.5.7 2-[2-methyl-1-oxopropyl]-2'H—biquinazolin-4,4'-one (279).



Following a procedure developed by Corey[21]. to a solution of **240** (0.065 g, 0.179 mmol) in DCM (4 ml) was added pyridinium chlorochromate (0.77 g, 0.71 mmol, 4 eq) and the resulting dark brown solution was stirred overnight. The solution was

diluted with diethyl ether (15 ml), the solvent decanted and the brown residue was treated with diethyl ether (3 x 5 ml) and the combined organic layer were filtered over Florisil® (or Celite) and evaporated to dryness. The resulting residue was crystallized from methanol affording **279** as white crystals (0.20 g, 87 % yield); m.p. 266 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.32 (1H, d, J = 8.4 Hz, 5-H), 8.2 (1H, d, J = 7.9 Hz, 5'-H), 8.05 (1H, s, 2'-H), 7.82 (5H, m, Ar), 7.61 (1H, m, Ar), 3.91 (1H, m, -C<u>H</u>$(CH_3)_2$), 1.08 (3H, d, J = 6.8 Hz, -CH(C<u>H</u>$_3$)), 1.07 (3H, d, J = 6.8 Hz, -CH(C<u>H</u>$_3$)); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 198.4, 158.1, 157.3, 146.3, 145.1, 144.1, 134.8, 134.3, 128.7, 128.2, 127.3, 126.8, 126.2, 121.6, 121.4, 35.5, 17.8, 16.2; ν_{max} (nujol)/cm^{-1} 1714, 1693, 1606, 1451, 1373, 1262; *m/z* (APCI)(%), 361(100) [M+H$^+$], 298(60), 71(58); HRMS for $C_{20}H_{16}N_4O_3$ requires: 361.1295, found: 361.1290; $[\alpha]^{25}_D$ = -8.0° (c = 1, $CHCl_3$).

REFERENCES.

[1] a) P. S. N. Reddy, A. K Bhavani, *Indian J. Chem.*, Sect. B 1992, 31B, 740; b) K. Nagahara, A. Takada, *Chem. Pharm. Bull.*, 1977, **25**, 2713.

[2] A. Tiwary, V. Singh, A. Bajpai, G. Shukla, S. Singh, A. Mishra, *Eur. J. Med. Chem.*, 2007, **42**, 1234.

[3] M. Khajavi, N. Montazari, S. Sadat-Hosseini, *J. Chem. Res.(S)*, 1997, 286.

[4] D. Zentmyer, E. Wagner, *J. Org. Chem.*, 1949, **14**, 967.

[5] L. Legrand, *Bul. Soc. Chim. Fr.*, 1960, 337.

[6] J. Williams, A. Salvadori, *J. Chem. Soc., Perkin Trans. 2*, 1972, 883.

[7] D. Harrison, A. Smith, *J. Chem. Soc.*, 1961, 4827.

[8] A. Itai, S. Muto, T. Inoue, Y. Urade, U. S. Patent NO.: US 200610229324 A1, Oct. 12 ,2006.

[9] G. Hoffle, O. Hollitzer, W. Steglich, *Angew. Chem., Int. Ed.*, 1972, **11**, 720.

[10] R. Atkinson, M. Coogan, and C. Cornell, *J. Chem. Soc., Perkin Trans. 1*, 1995, 157

[11] I. Boussamme, O. Schwardt, M. Pichon, B. Figadere, J. Royer, A. Cave', *Tetrahedron Lett.*, 1997, **38**, 2259.

[12] H. Matsamura, H. Hashizume, A. Matsushita, M. Eigyo, *Eur. Pat. Appl.* (1990), 39 pp CODEN: EPXXDW EP 353778 A2 19900207.

[13] B. Dean, M. Mijovic, J. Walker, *J. Chem. Soc.*, 1961, 3394.

[14] P. Karrer, C. Christoffel, *Helv. Chim. Acta*, 1944, 27, 622.

[15] T. Kolasa, M. Miller, *J. Org. Chem.*, 1987, **52**, 4978.

[16] A. Al-Sehemi, R. Atkinson, J. Fawcett, D. Russell, *J. Chem. Soc., Perkin Trans.1*, 2000, 4413.

[17] E. T. Kaiser, F. W. Carson, *J. Am. Chem. Soc.*, 1964, **86**, 2922.

[18] A. Folkes, S. D. Brown, L. E. Canne, J. Chan, E. Engelhardt, S. Epshteyn, R. Faint, J. Golec, A. Hanel, P. Kearney, J. W. Leahy, M. Mac, D. Matthews, M. P. Prisbylla, J. Sanderson, R. J. Simon, Z. Tesfai, N. Vicker, S. Wang, R. R. Webbb and P. Charltona, *Biorg. Med. Chem. Lett.*, 2002, **12**, 1063.

[19] M. Uskovic, J. Iacobelli; V. Toome, W. Wenner, *J. Org. Chem.*, 1964, **29**, 582.

[20] E. Tyrrell, J. Allen, K. Jones, R. Beauchet, *Synthesis*, 2005, **14**, 2393

[21] E. J. Corey, J. William Suggs, *Tetrahedron Lett.*, 1975, **31**, 2647.

APPENDIX.

Crystallographic data for compound 246.

$C_{13}H_{13}N_3O_2$, crystal system monoclinic; space group, $P2_1/c$; a = 9.891(5), b = 10.066(5), c = 11.732(c) Å; a = 90, β= 96.743(5), γ = 90°; Z = 4; T = 150 K; μ = 0.097 mm^{-1}; l = 0.71069 Å (MoK a); F(000) 512; 3.85 <θ< 30.02; 8656 reflections, 3323 unique [R(int) = 0.0626]; $R1$ = 0.0584, w$R2$ = 0.1410 [$I > 2\sigma(I)$]; $R1$ = 0.0974, w$R2$ = 0.1609 (all data). CCDC reference numbers 259058.

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and is
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H12A C12 H12B 109.5 . . ?
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H12B C12 H12C 109.5 . . ?
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C1 C2 C3 C4 -178.75(14) . . . . ?
C2 C3 C4 C5 -0.4(2) . . . . ?
C3 C4 C5 C6 -0.4(3) . . . . ?
C4 C5 C6 C7 1.0(3) . . . . ?
C5 C6 C7 N1 -179.27(15) . . . . ?
C5 C6 C7 C2 -0.7(2) . . . . ?
C3 C2 C7 N1 178.41(15) . . . . ?
C1 C2 C7 N1 -2.2(2) . . . . ?
C3 C2 C7 C6 -0.1(2) . . . . ?
C1 C2 C7 C6 179.30(14) . . . . ?
N1 C8 C9 O2 -178.40(15) . . . . ?
N2 C8 C9 O2 3.1(2) . . . . ?
N1 C8 C9 C10 -53.8(2) . . . . ?
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N2 C8 C9 C10 127.74(16) . . . . ?
O2 C9 C10 C11 64.96(19) . . . . ?
C8 C9 C10 C11 -62.0(2) . . . . ?
O2 C9 C10 C12 -59.73(18) . . . . ?
C8 C9 C10 C12 173.36(14) . . . . ?
N2 C8 N1 C7 1.5(2) . . . . ?
C9 C8 N1 C7 -176.84(14) . . . . ?
C6 C7 N1 C8 179.79(15) . . . . ?
C2 C7 N1 C8 1.3(2) . . . . ?
N1 C8 N2 C1 -3.4(2) . . . . ?
C9 C8 N2 C1 174.92(14) . . . . ?
N1 C8 N2 N3 176.08(14) . . . . ?
C9 C8 N2 N3 -5.6(2) . . . . ?
O1 C1 N2 C8 -177.95(14) . . . . ?
C2 C1 N2 C8 2.2(2) . . . . ?
O1 C1 N2 N3 2.5(2) . . . . ?
C2 C1 N2 N3 -177.30(13) . . . . ?
O2 C13 N3 N2 1.8(3) . . . . ?
C8 N2 N3 C13 3.3(2) . . . . ?
C1 N2 N3 C13 -177.17(15) . . . . ?
N3 C13 O2 C9 -4.0(3) . . . . ?
C8 C9 O2 C13 1.2(2) . . . . ?
C10 C9 O2 C13 -125.96(18) . . . . ?
 diffrn measured fraction theta max 0.981
_diffrn_reflns_theta_full        30.02
 diffrn measured fraction theta full 0.981
_refine_diff_density_max         0.333
 refine diff density min         -0.316
 refine diff density rms         0.063
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