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Radical Synthesis of Quinazolinone Natural Products

By

Tobias Stein


A Doctoral Thesis

Submitted in fulfilment of the requirements for the award of

PhD at Loughborough University

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For Babcia, Dziadek and Joan who will sadly never read this and Masood who perhaps one day might.

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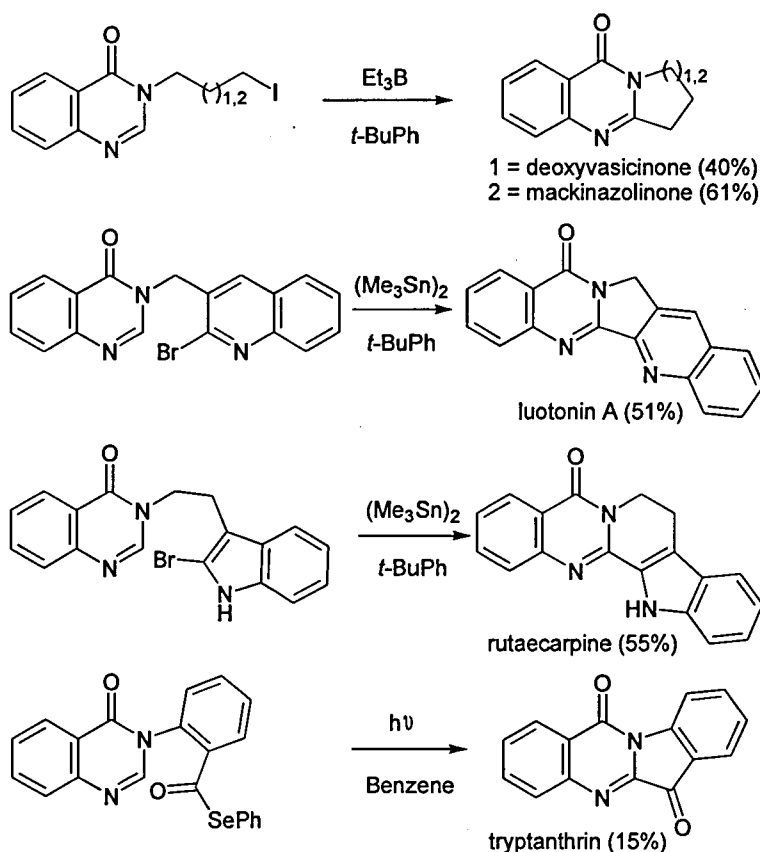
Plus thanks to the support of the girls who put up with me at various points over the years at university and all the other people who's names I should have put in, sorry!

“Follow those dreams as far as possible and try to do that thing that really interests you and you feel is worthwhile”

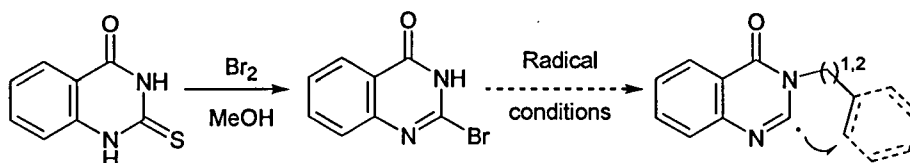
Fred Sanger the only two-time winner of the Noble Prize for chemistry (1958 and 1980)

Abstract

Investigations into radical and palladium (0) cyclisations onto the C-2 position of the 3*H*-quinazolin-4-one moiety have been made. This has led to the syntheses of a number of biologically active quinazolinone natural products using alkyl, heteroaryl and acyl radical cyclisations. The reactions proceeded *via* a homolytic aromatic substitution mechanism. As such, fully rearomatised products were recovered.



A C-2 radical 3*H*-quinazolin-4-one building block was also prepared. This turned out to have only limited synthetic applications. Radical cyclisations onto aryl groups were carried out using this building block.



Keywords

Radical, cyclisation, 3*H*-quinazolin-4-one, deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine, tryptanthrin

Abbreviations

Å	ångström
Ac.	Acetyl
ABCN	1,1'-azobis-(cyclohexanecarbonitrile)
AIBN	azobisisobutyronitrile
AMBN	2,2'-azobis-(methylbutyronitrile)
aq.	aqueous
Ar	aryl
atm.	Atmospheres
ATP	adenosine triphosphate
b	broad
BDE	bond disassociation energy
bp	boiling point
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
Bn	benzyl
BEB	(2-bromoethyl)benzene
°C	Celsius
cat.	catalytic
CoA	coenzyme A
coe	cyclooctene
COX	cyclooxygenase
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
DAH _P	<i>D</i> -arabino-heptulosonic acid 7-phosphate
DIAD	diisopropyl azodicarboxylate
dba	dibenzylidene acetone
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<i>dig.</i>	digonal
DMAP	4-(dimethylamino)pyridine

DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	diphenylphosphinoferrocene
EDG	electron donating group
E4P	erythrose 4-phosphate
EPSP	3-enolpyruvylshikimic acid 3-phosphate
equiv.	equivalent
Et	ethyl
EWG	electron withdrawing group
GC	gas chromatography
h	hour(s)
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correlation
HPLC	high performance liquid chromatography
IBX	iodoxybenzoic acid
IR	infra-red
J	Joules
k	kilo
k_{Cyc}	rate of cyclisation
k_{H}	rate of H-abstraction
LDA	lithium diisopropylamide
lit.	literature
m	multiplet
Me	methyl
min	minute(s)
mol	moles
mp	melting point
Ms	mesyl
MS	mass spectrum
<i>N</i>	Molar
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	<i>N</i> -bromosuccinimide

NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
<i>o</i>	ortho
OATB	organic ammonium tribromide species
<i>p</i>	para
P	phosphate
Pd	palladium
PEPA	phosphoenol pyruvate
Ph	phenyl
Phe	phenylalanine
PPA	polyphosphoric acid
ppm	parts per million
pr	propyl
q	quartet
rt	room temperature
s	singlet
SEM	2-(trimethylsilyl)-ethoxymethyl
S _H 2	substitution, homolytic, second order
SM	starting material
S _N 2	substitution, nucleophilic, second order
S _N Ar	substitution, nucleophilic, aromatic
subst.	substituted
t	triplet
TBDMS	tertiary-butyldimethylsilyl
TBDMSCl	tertiary-butyldimethylsilylchloride
TBAF	tertiary-butylammoniumfluoride
THF	tetrahydrofuran
Tf	triflate
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidide
TMS	trimethylsilyl

Tol	toluoyl
Tos	tosyl
<i>trig.</i>	Trigonal
Trp	tryptophan
Tyr	tyrosine
TTMSS	tris(trimethylsilyl)silane
UV	ultra violet
W	Watt
X	leaving group

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Chapter 1. Introduction

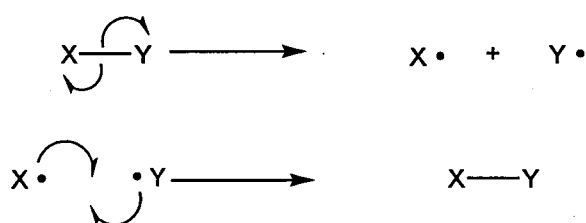
The research described in this thesis involves the use free radicals as reactive intermediates in the synthesis of 3*H*-quinazolin-4-one natural products. Therefore, the following introduction will include a review of free radical chemistry in organic syntheses, followed by a description of quinazolinone natural products, drugs, biosynthesis and organic syntheses of this moiety.

1.1 Free radicals

Radicals are usually defined as atoms or compounds containing an unpaired electron. Hence by definition radical species contain an odd number of electrons (e.g. $\text{H}\cdot$ and $\text{Br}\cdot$ contain 1 and 7 electrons in their outer valence shell respectively). This single unpaired electron is denoted by a dot. They are usually very unstable and highly reactive intermediates. This is due to their strong desire to pair with another electron to form a 2-electron covalent bond or lone pair.

However, not all radicals are highly reactive and $\text{NO}\cdot$ or O_2 are good examples of naturally occurring non-reactive radicals. Molecular oxygen is best thought of as a diradical, containing two unpaired radicals and is usually considered as $\cdot\text{O}-\text{O}\cdot$. Being a diradical O_2 contains 12 valence electrons i.e. an even number of electrons unlike the earlier definition.

Radicals can be formed by the homolysis or homolytic cleavage of a chemical bond. The bonding electrons are divided evenly and represented by single headed arrows (scheme 1).



Scheme 1. Radical formation and combination.

As radicals are inherently neutral, they do not suffer from solvent effects that are observed in ionic reactions. It is this inherent neutrality that gives radicals a major advantage over ionic intermediates, as a result high functional group tolerance is often observed. A radical can become charged though if reduced by an electron source to an anion, or loss of an electron producing an oxidised cation. Being uncharged radicals don't have surrounding solvent shells. The exception to this is radical anions and cations that have counter ions.

1.2 Radical stability

The formation of a radical is dependant on its thermodynamic stability. This can be empirically considered as its bond dissociation energy (BDE), i.e. the energy required for homolysis of the bond. An understanding of the BDE is crucial in organic synthesis in predicting a radical reactions outcome. The lower the BDE value the more easily the bond is cleaved. Some BDE values are given (table 1).

Table 1. Bond dissociation energy values.¹

Bond type	H—H	H—F	H—Cl	H—Br	H—I	H—OH
BDE (kJ mol ⁻¹)	435	565	431	364	297	498

Although radicals are considered electronically neutral, they can still be thought of as electron deficient. As a result, they are generally stabilized by electron donating substituents. This means they display the same trend in stability as carbocations (figure 1).

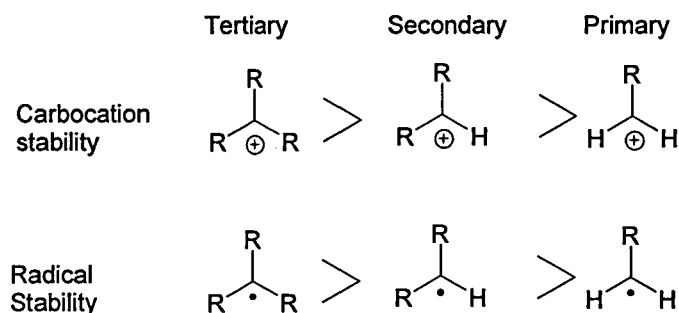


Figure 1. Stability of carbocations and radicals.

1.3 Radical polarity

The polarity of a radical is different to that of an ion. For an ion an EDG would aid the formation of an electrophilic centre and an EWG would aid the formation of a nucleophilic centre (figure 2). For radicals both electron withdrawing and donating groups can be used to stabilize the radical. The substituents then play a vital role in influencing the polarity of the radical. Electron donating groups cause the radical to be nucleophilic in nature **1**, whereas an EWG creates an electrophilic radical **2**. This reversal of reactivity can be described by the term *umpolung*.

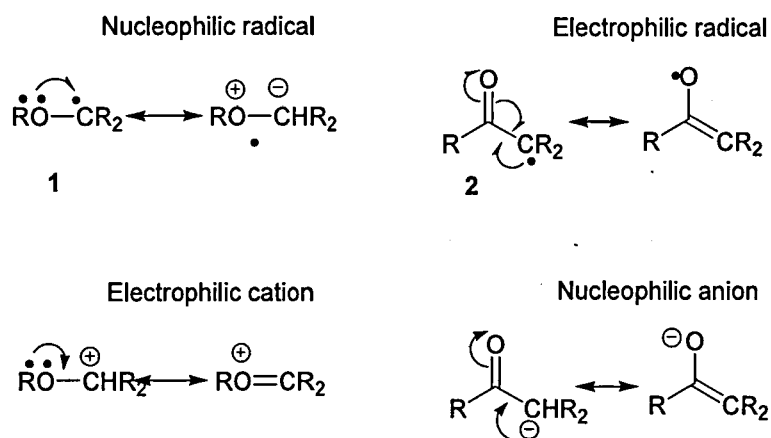
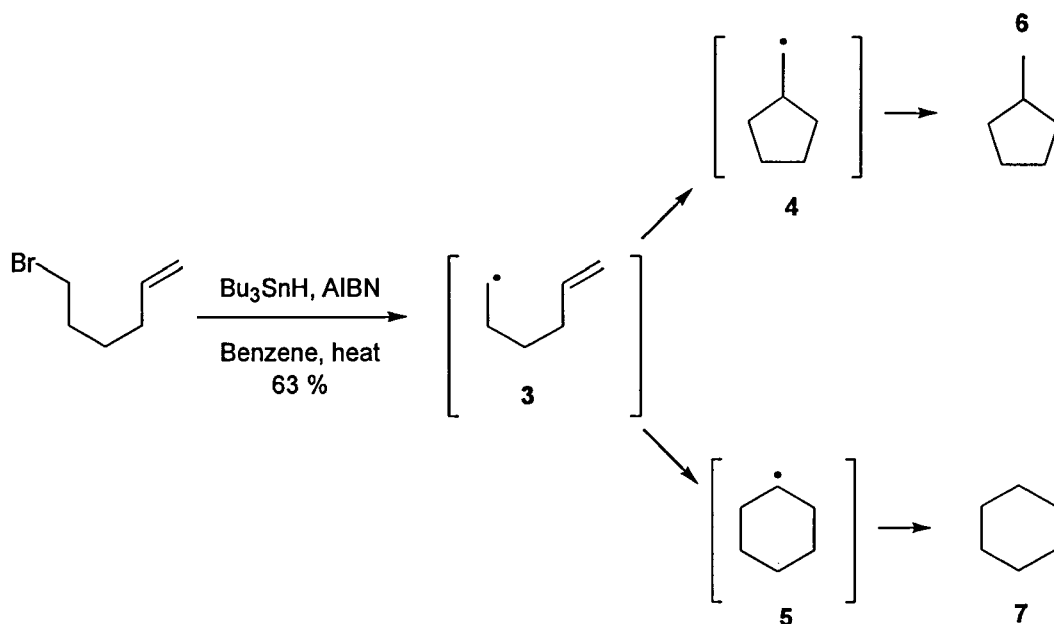


Figure 2. Comparison of polarity of radicals and ions.

1.4 Regioselectivity of intramolecular radical cyclisations

The reaction of a hex-5-en-1-yl radical **3** has two regio possibilities for cyclisation (scheme 2).¹ However it is the 5-*exo-trig* cyclised product **6** which predominates over the 6-*endo-trig* cyclised product **7**. The 6-*endo-trig* cyclisation is the thermodynamic product, because the secondary intermediate radical **5** is more stable than the primary intermediate radical **4** (which forms the 5-*exo-trig* product).



Scheme 2. Relative product ratios from hex-5-en-1-yl radical 5-*exo*: 6-*endo* (49:1).

This appears to be a contradiction. We know that the 5-*exo* cyclisation is the major reaction product. The explanation for this lies in the more favoured transition state of the 5-*exo* radical. This transition state is described as the 'Beckwith model' (figure 3).²



Figure 3. Favoured 5-*exo* chair like transition state 'Beckwith model'.

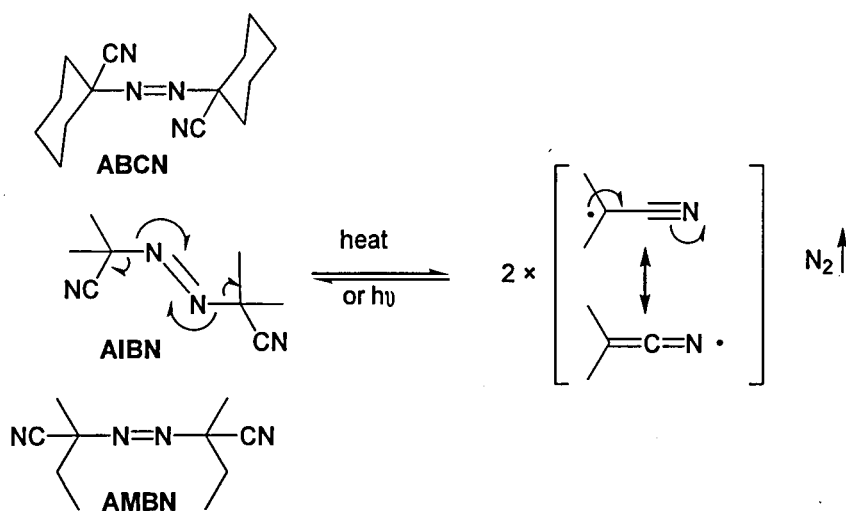
This mode of cyclisation is observed for many other related systems. Baldwin's rules can be used to predict the size of ring formation.³ Cyclisations onto alkynes are often slower than those onto alkenes. If a heteroatom is placed into the carbon chain this can greatly affect the regio selectivity. For example if nitrogen is inserted in the cyclising chain then the bond angle C—N—C becomes smaller (107.8 °) compared to the tetrahedral C—C—C angle (109 °). The C—N carbon bond length is also shorter (1.47 Å) than the C—C bond length (1.52 Å). As a result the radical is closer to the internal carbon providing an even better overlap in the 5-*exo* transition state and higher yield of the 5-*exo* product.

1.5 Tin Hydrides and azo initiators

There are a great variety of the reagents that are used in radical reactions. Commonly group 14 organometallic hydride reagents (often tin hydrides) are used in conjunction with azo initiators. The most common radical reagent is tributyltin hydride. This reagent readily facilitates either inter or intra-molecular radical reactions. Aryl and alkyl radicals are commonly generated from halides, selenides or sulphides. To minimize any undesired termination steps, low concentrations of radicals are used. This can be achieved by addition of Bu₃SnH with a syringe pump, for example.

As stated, initiation is commonly carried out using azo compounds such as AIBN (scheme 3). Usually 5-10% initiator is required. There are examples where high concentrations of initiator must be used, and these are discussed later. AIBN can be thermally cleaved and has a half life of 1 h at 81 °C.¹ This half life drops to 30 min in refluxing toluene (110 °C). The rate of forming the isobutyronitrile radical is much slower than rates of other radical propagation steps in the chain reaction. The isobutyronitrile radical abstracts hydrogen from Bu₃SnH. This

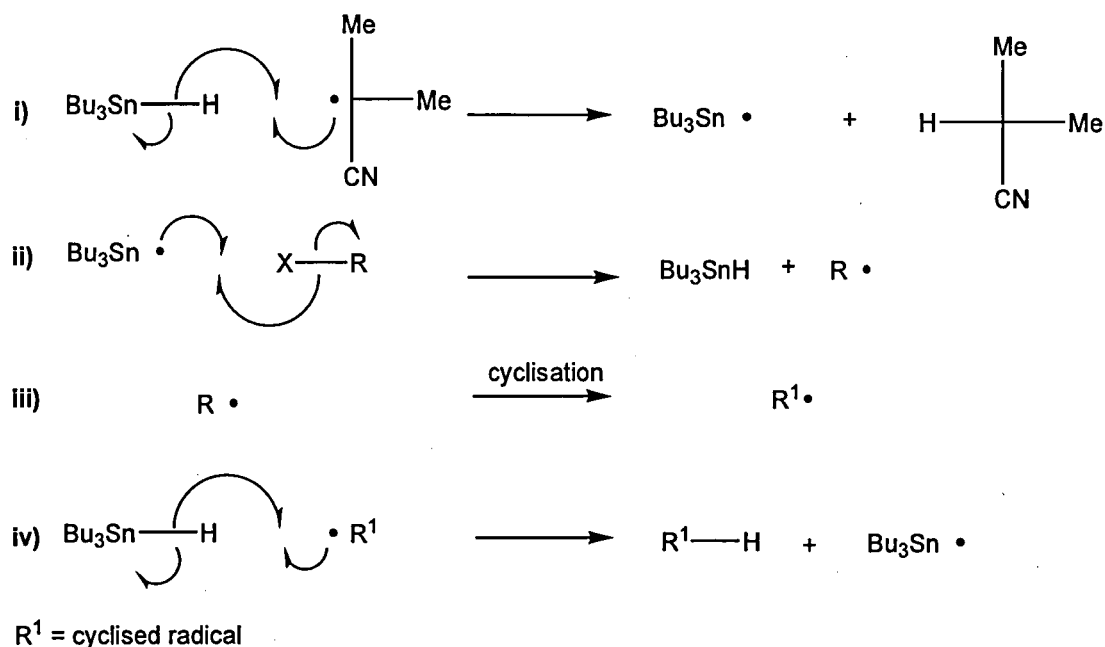
is a strongly favoured reaction as a strong C—H bond is formed at the expense of a weak Sn—H bond.



Scheme 3. Initiation of azo compounds and their resonance stability.

Importantly, the isobutyronitrile radical is tertiary and resonance stabilized. This decreases its expected reactivity. As a result, the abstraction of the hydrogen occurs solely from the Bu_3SnH and not any other organic compounds in the reaction containing stronger C—H bonds. This gives a good functional group tolerance, compared with many other ionic reaction processes.

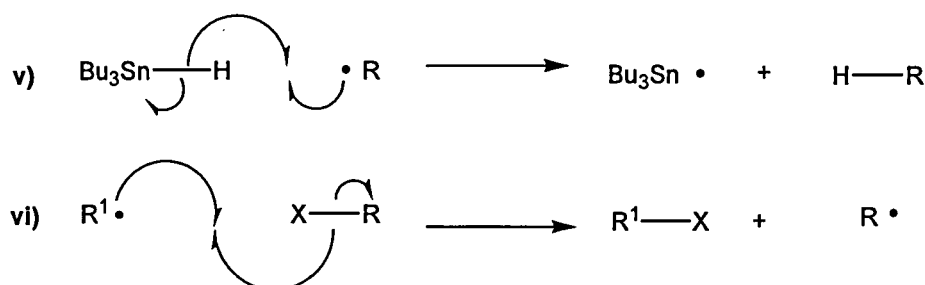
The newly formed tributyltin radical can react with alkyl or aryl halides (except fluorides), selenides and sulphides. Formation of a strong tributyltin halide bond over a weaker carbon halide makes this reaction a highly favoured reaction (scheme 4). Depending on the leaving group on the carbon the rate of abstraction can vary widely. Stronger bond strengths in aryl and vinyl halides, means chlorides are rarely used as precursors.



Scheme 4. Chain reaction sequence of isobutyronitrile radical and Bu_3SnH .

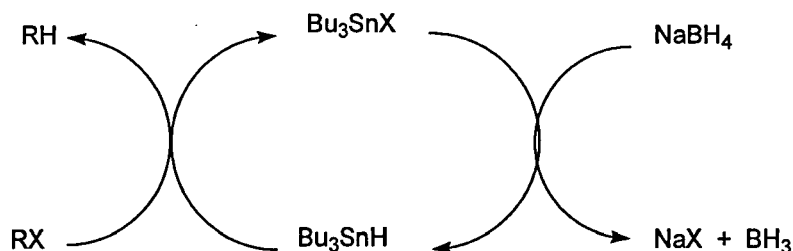
Unwanted side reactions may occur, for instance, with terminal alkynes, $\text{Bu}_3\text{Sn}\cdot$ addition is commonly observed and can disrupt the chain reaction.

Step v) is known as reduction and can be minimized by using low concentrations of Bu_3SnH (scheme 5). In the case of intramolecular reactions this is less of a problem. Here entropy will favour a unimolecular reaction over a bimolecular one with the Bu_3SnH . In practical terms the concentration of Bu_3SnH in the reaction can be kept low by slow addition using a syringe pump over several hours. At first glance step vi) looks like a problem, as we do not want to reform a carbon halogen bond. However, the reaction of $R\cdot$ with a halide causes no problem. This is because a further reaction with $\text{Bu}_3\text{Sn}\cdot$ will lead to the initial starting radical being reformed. Organohalide products are rarely isolated when using Bu_3SnH .



Scheme 5. Undesired propagation reactions.

There are some major drawbacks to using Bu_3SnH . Breakdown products can be very difficult to separate from the reaction. There are ways of avoiding stoichiometric amounts of Bu_3SnH . Using a reducing agent such as NaBH_4 (scheme 6) means Bu_3SnH can be used catalytically. This readily reduces the tin-halogen bond to a tin-hydrogen bond. However this isn't always a viable option if sensitive functional groups are present in the reaction. Corey and Suggs first described this reaction in 1975. They found that Bu_3SnH (10 mol%) and stoichiometric amounts of NaBH_4 were suitable to dehalogenate bromides and iodides in good yield.⁴



Scheme 6. Regeneration of Bu_3SnH using NaBH_4 .

1.6 Trialkylboranes as radical initiators

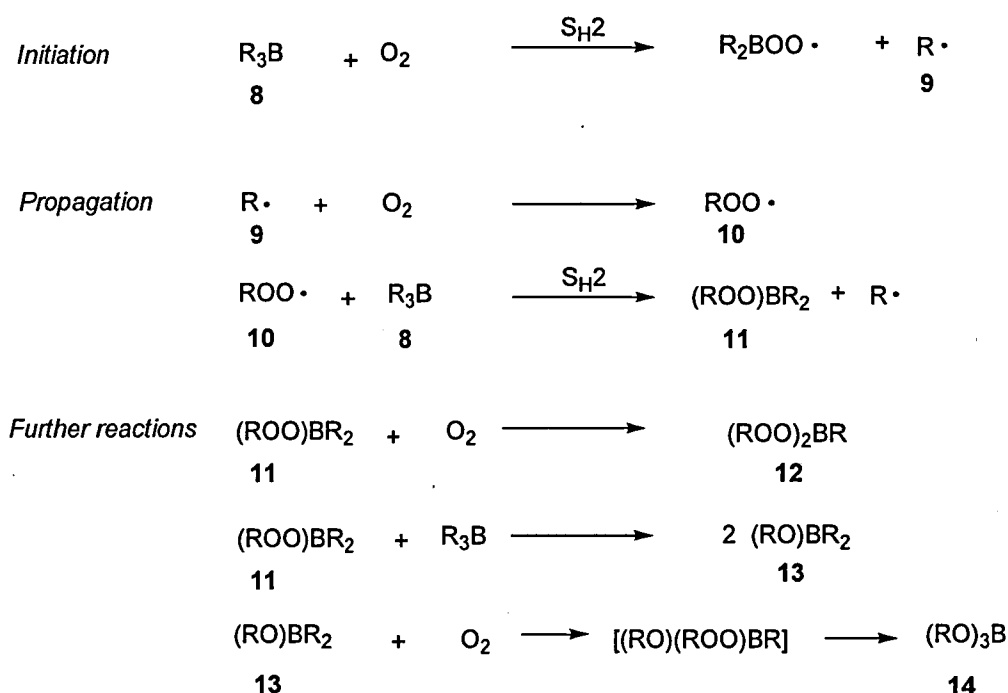
Azo compounds such as AIBN, ABCN and AMBN have proved to be very popular free radical initiators for a long time. However, the use of organoborane species has been pioneered by Brown.⁵ They pioneered the use of organoborane species in radical mediated reactions. Brown later went on to win the Nobel Prize in 1979 for his work on organoborane reagents in organic synthesis.

Trialkylborane species are now very popular initiating reagents as they easily undergo bimolecular homolytic substitution at the boron atom by oxygen.⁶ The alkyl radical can be displaced by a range of radicals such as peroxy or thiyl radicals.⁶ They are thermodynamically favoured due to the high bond strengths of the newly formed B—X bond (table 2).

Table 2. Relative BDE for various borane species.

Compound	Bond	BDE (kJ/mol)
Et ₃ B	B—C	344
(EtO) ₃ B	B—O	519
[(CH ₃) ₂ N] ₃ B	B—N	422
(Et ₃ S) ₃ B	B—S	377

One of the most common organoborane reagents used in radical chemistry is triethylborane, which readily undergoes auto-oxidation in air.⁶ Renaud has proposed a mechanism of this auto-oxidation. Alkyl radical **9** is liberated after a homolytic substitution reaction between triplet oxygen and triethylborane **8** (scheme 7). The alkyl radical **9** is then believed to react with oxygen to form a peroxy radical **10**. This radical can undergo a S_H2 reaction producing a monoperoxyborane species **11** (the rate constant for this reaction has been recorded) can also occur. The monoperoxyborane **11** species can then react with oxygen to produce the diperoxyborane species **12**, which is believed to be inert to oxygen. Alternatively, a reaction can take place where the monoperoxyborane species **11** reacts with Et₃B yielding a dialkyl borinate species **13** which can undergo a further reaction with oxygen to yield the trialkyl borate species **14**.



Scheme 7. Proposed mechanism for auto-oxidation of trialkylborane species.

Trialkylborane reagents have a number of advantages over azo-initiators such as AIBN. For instance, reactions can be carried out at low temperatures (down to -78°C). This allows enantioselective reactions to be carried out. Residual AIBN can make purification difficult, this is not so using trialkylborane species.

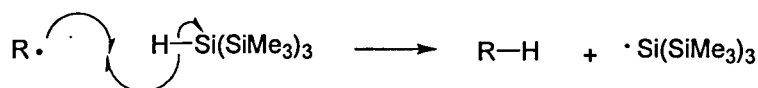
1.7 Silicon and Germanium hydrides

Due to the toxicity problems and purification problems of R_3SnH an attractive alternative is to use tri-organosilicon hydrides instead. Like tri-organotin hydrides the $\text{R}_3\text{Si}\cdot$ radical will react in the same fashion with organohalides, selenides and sulphides at similar rates. The $\text{Si}-\text{H}$ bond is 65 kJ mol^{-1} stronger than the $\text{Sn}-\text{H}$ bond. As a result their reaction with alkyl radicals is slower. This can be overcome in two separate ways.

The first involves the addition of a catalytic amount of alkyl thiol to the reaction. Alkyl radicals can more easily abstract hydrogen from the thiol.⁷ This results in a stronger carbon hydrogen bond over a weaker sulfur hydrogen bond. The silicon hydrogen bond is similar in strength to the thiol hydrogen bond. This means that it is not the BDE here that is playing the crucial role. It is by looking at polarities that we can gain insight into how the reaction proceeds. The hydrogen of the thiol can be thought of as electron poor due to the electronegative sulfur. As a result a nucleophilic alkyl radical will rapidly extract this hydrogen. The hydrogen in the $\text{Si}-\text{H}$ can be thought of as electron rich because electropositive nature of silicon. This means the electrophilic thiyl radical will look to abstract the hydrogen from the $\text{Si}-\text{H}$. This reaction proceeds despite not being an exothermic one. The silyl radical can then undergo halogen abstraction forming a strong silicon halide bond.

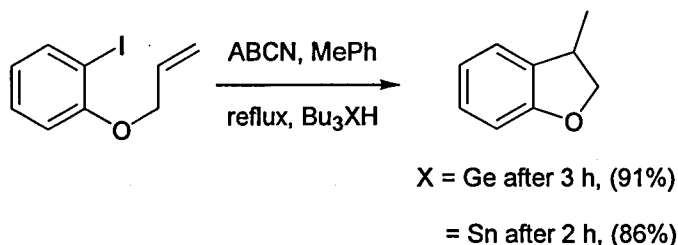
Secondly, the silicon hydride bond can be weakened by the addition of bulky substituents. This forms a more hindered and stable silyl radical. The most common reagent of this type is tris-(trimethylsilyl)silane (TTMSS) and is often used over Bu_3SnH (scheme 8).

The slower rate of hydrogen abstraction of $\text{Si}-\text{H}$ compared to the $\text{Sn}-\text{H}$ can help lower amounts of reduced product in a reaction. Silicon by products are easier to remove than their tin counter parts during purification. As with tri-organotin hydrides, the addition of a reducing agent like NaBH_4 can be used. This allows silicon hydrides to be used catalytically.



Scheme 8. TTMSS initiation of silyl radical.

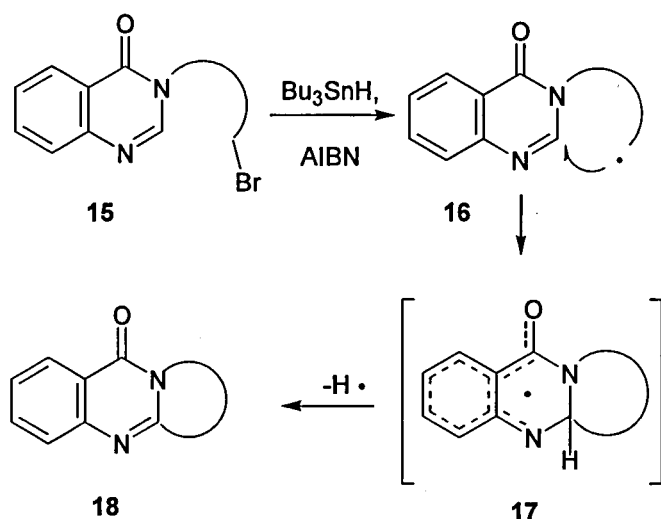
Another reagent of much interest is tributylgermanium hydride.⁸ Like silicon hydrides they have lower toxicity than tin hydrides, ease of work up and good stability. Tributylgermanium hydride has recently been used to generate radicals from iodides, bromides, activated chlorides and phenyl selenides. Bowman has shown similar yields of cyclised product can be obtained using Bu_3GeH as compared with Bu_3SnH (scheme 9).⁸ Initial studies indicate as with tin and silicon, the use of NaBH_4 enables catalytic amount of the Bu_3GeH to be used. The rate of hydrogen abstraction from the germanium is 20 times slower than Bu_3SnH . As with silicon hydrides, polarity reversal catalysis using thiols can also be use.



Scheme 9. Comparison between Bu_3GeH and Bu_3SnH .

1.8 Intramolecular homolytic oxidative radical cyclisations

Our work is concerned with studying intramolecular radical cyclisation reactions onto the quinazolinone moiety **16** (scheme 10) from halide precursors such as **15**. Importantly, we hope to achieve rearomatisation of the quinazolinone radical intermediate **17**, in the presence of reagents such as Bu_3SnH . These reaction conditions are reductive, yet we are aiming for rearomatisation. This would involve oxidation to form quinazolinone **18**.



Scheme 10. Desired rearomatised quinazolinone products using $\text{Bu}_3\text{SnH/AIBN}$.

However, Bu_3SnH mediated radical cyclisations of arenes and heteroarenes can produce rearomatised products in good yield. The mechanism of such reactions can be described as intramolecular homolytic aromatic substitution. Reactions like these proceed with the initial $\text{Bu}_3\text{Sn}\cdot$ producing the $\text{R}\cdot$ radical, which then adds onto an aromatic ring. This yields an intermediate substituted cyclohexadienyl radical **19** (figure 4). It has been widely debated the exact mechanism that leads to fully aromatic products **21**. Bowman *et al.* has extensively investigated this mechanism.⁹ There have been many possible explanations such as disproportionation of **19** or hydrogen-atom transfer by the Bu_3SnH producing rearomatised **21**. Some have argued the reaction may go *via* a dihydro compound such as **20**, which becomes oxidised on work up. However, dihydro compound **20** does not readily oxidize in air.¹⁰

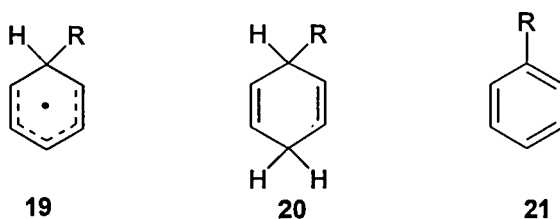
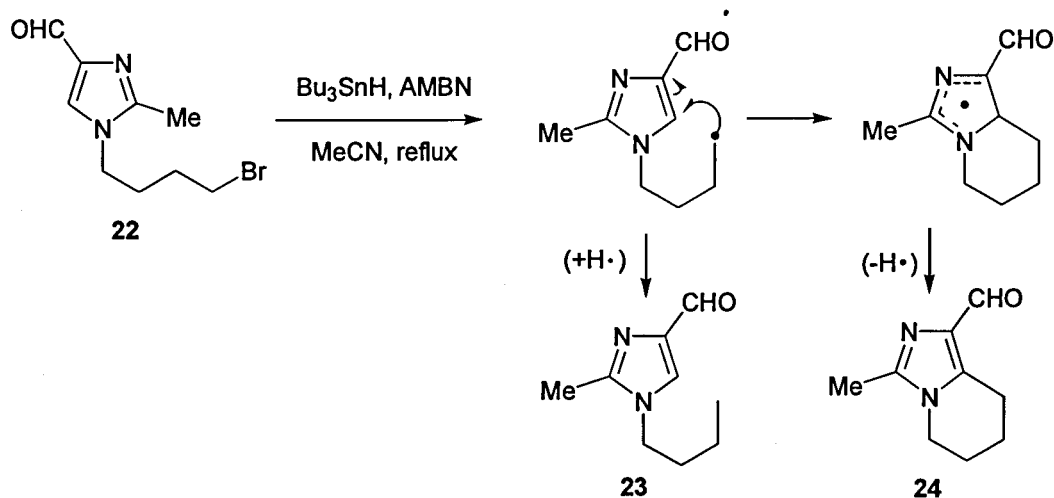


Figure 4. Key structures in rearomatisation arguments.

One fact is common to many of the reported examples of intramolecular homolytic aromatic substitution is the need for stoichiometric amounts of the radical initiator. Bowman *et al.* have carried out detailed work in this field and correlated reaction products of imidazole **22** to

amounts of initiator used (scheme 11).⁹ The use of ^1H NMR spectroscopy with an internal standard revealed a clear relationship between the ratio of AMBN added and the amount of cyclised product (e.g. AMBN: 1.0 equiv, cyclised **23** [92%], reduced **24** [0%]; 0.5 equiv, cyclised **23** [43 %], reduced **24** [53%]; 0.25 equiv, cyclised **23** [8%], reduced **24** [9 %]). This suggests along with work carried out by Curran *et al.* that it is the initiator that acts as the oxidizing agent in these reactions.¹¹ However the exact mechanism is still unknown.

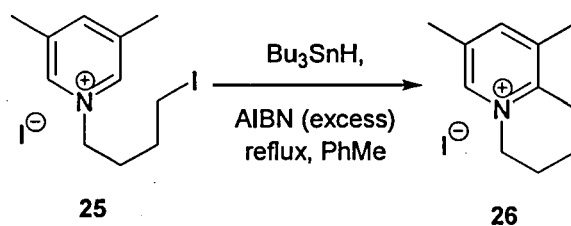


Scheme 11. Synthesis of bicyclic imidazole **22**.

1.9 Heterocyclic synthesis *via* intramolecular radical cyclisations

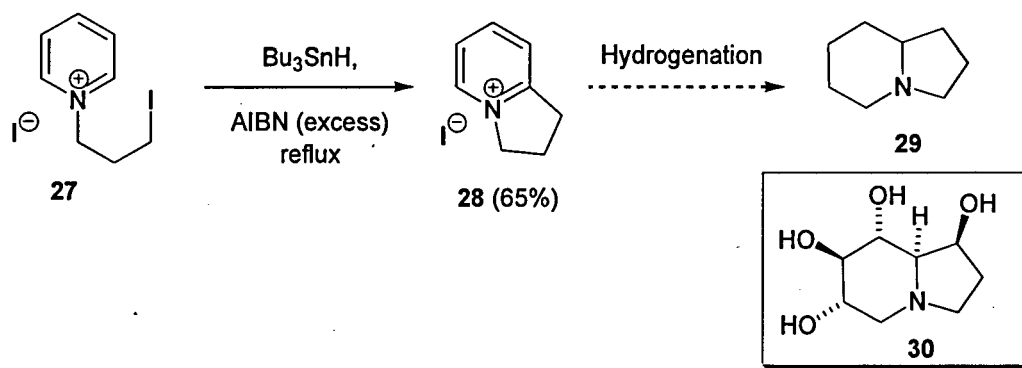
There is a rich history of radical cyclisations being employed in the synthesis of a wide range of heterocycles. Some noteworthy examples will now be discussed in relation to various heterocyclic systems. A wide ranging type of radical reagents will be shown. Some of these can be described as nucleophilic aromatic homolytic substitutions radical reactions.

The chemistry of pyridines has been studied for over a hundred years and examples of intermolecular oxidative radical substitution reactions have been reported by Minisci.¹² Murphy *et al.* has reported an intramolecular radical substitution reactions of pyridinium rings (scheme 12).¹³ Murphy reached [6,6]-bicyclic rearomatised pyridinium **26** from the simple alkylated pyridinium salt **25**. He noted the need for excess initiator to reach rearomatised pyridinium **26**.



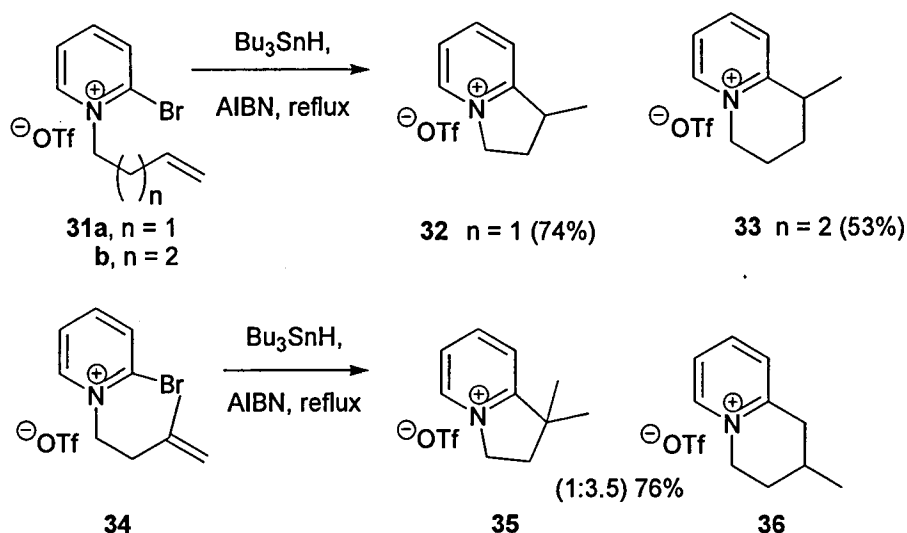
Scheme 12. Murphy's radical cyclisations onto pyridinium salts.

This reaction was extended to formation of a [6,5]-bicyclic system **28** from pyridinium salt **27** (scheme 13). On hydrogenation of the [6,5]-bicyclic system **28**, the indolizidine backbone **29** is formed. This is an important backbone for anti-viral drugs such as castanospermine **30**.¹³ Analogous [6,7]-bicyclic ring systems were also formed by Murphy.¹³



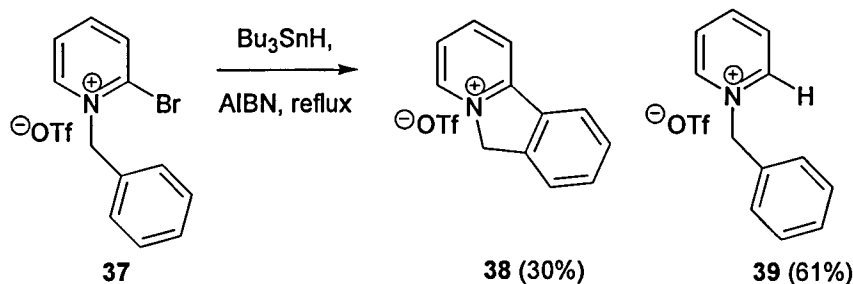
Scheme 13. Synthesis of bicyclic core of castanospermine.

Jones *et al.* has carried out work using pyridine centred radicals from 2-bromo-*N*-alkyl pyridinium salts **31** and **34** (scheme 14).¹⁴ Pyridinium salts **31a** and **31b** gave rise to 5-*exo-trig* cyclisation, to give [6,5]-bicycle **32** and 6-*exo-trig* cyclisation to give [6,6]-bicycle **33** products. These cyclisations again allowed easy access to indolizine and quinolizidine skeletons with subsequent hydrogenation.¹⁴ When steric bulk was added to the alkene **34**, a mixture of 5-*exo-trig* product **35** and 6-*endo-trig* product **36** and were obtained.¹⁴



Scheme 14. Radical cyclisations of 2-bromopyridinium salts.

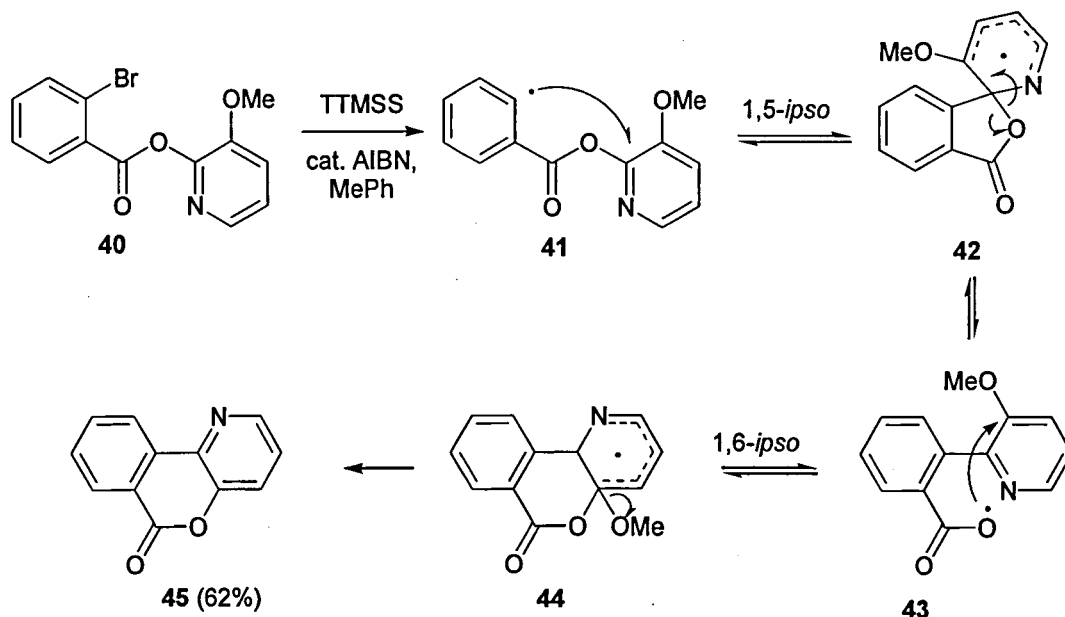
Cyclisation of pyridinium radical **37** onto an aromatic ring proceeded in moderate yield (scheme 15). This reaction produced the fully rearomatised benzene ring **38** and reduced product **39**. Jones could not successfully extend this work to include cyclisations onto alkynes.¹⁴



Scheme 15. 5-Membered radical cyclisation onto benzene.

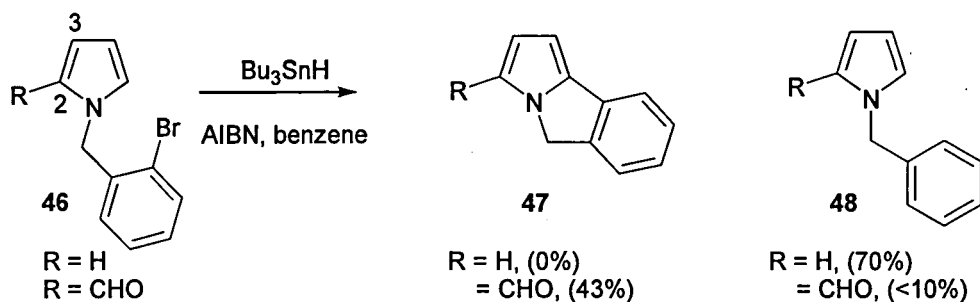
An unusual radical double *ipso* substitution reaction on pyridine has been used by Zhang and Pugh in the synthesis of azacoumarins **45** from bromoaryl benzoate pyridine precursor **40** (scheme 16).¹⁵ The mechanism proposes an initial 1,5 *ipso* attack of the aryl radical **41** at the 2-position of the pyridine. This is followed by the opening of the lactone **42** to form the acyl oxy radical **43**. This acyl oxy radical then undergoes a 1,6 *ipso* attack displacing the methoxy group on the pyridine ring to form the tricycle **45**. The displacement of the methoxy group was found to be crucial in reaching the azacoumarin core. Further studies on unsubstituted

methoxy pyridines predominantly revealed reduced products, and a substantial fall in yields of azacoumarins.



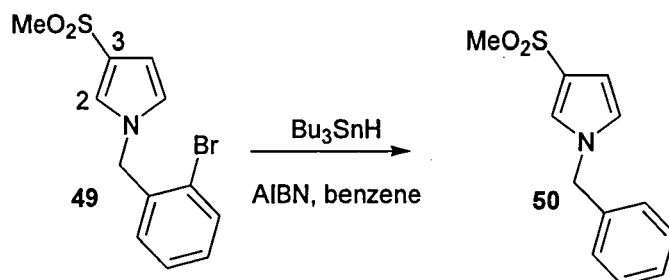
Scheme 16. Zhang and Pugh's unusual radical double *ipso* substitution reaction on pyridine.

Radical cyclisations of pyrroles have also been extensively investigated. De La Cruz *et al.* showed that aryl radicals cyclise onto pyrroles 46 (scheme 17).¹⁶ The pyrrole nucleus requires activation with an electron withdrawing group (aldehydes or sulfones) without which cyclised pyrrole 47 was not observed and only the reduction product 48 isolated.



Scheme 17. Aryl radical cyclisations onto pyrroles.

Likewise it was found that by moving the EWG on the pyrrole ring to C-3 49 no cyclisation occurred only reduction to pyrrole 50 (scheme 18). This demonstrates how finely balanced radical cyclisations can be. De La Cruz also postulates the mechanism of oxidative radical cyclisation is likely to be that proposed by Bowman.⁹



Scheme 18. Failed radical cyclisation onto pyrrole.

The cyclisation of aryl radicals onto pyrroles has been further investigated by Jones *et al.*¹⁷ It was the interest in synthesis of the potent gastric ATPase inhibitor **51** that led to this work (figure 5).

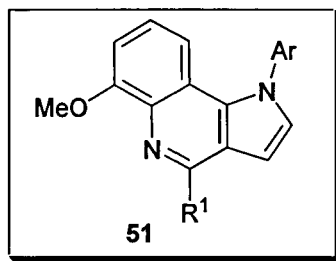
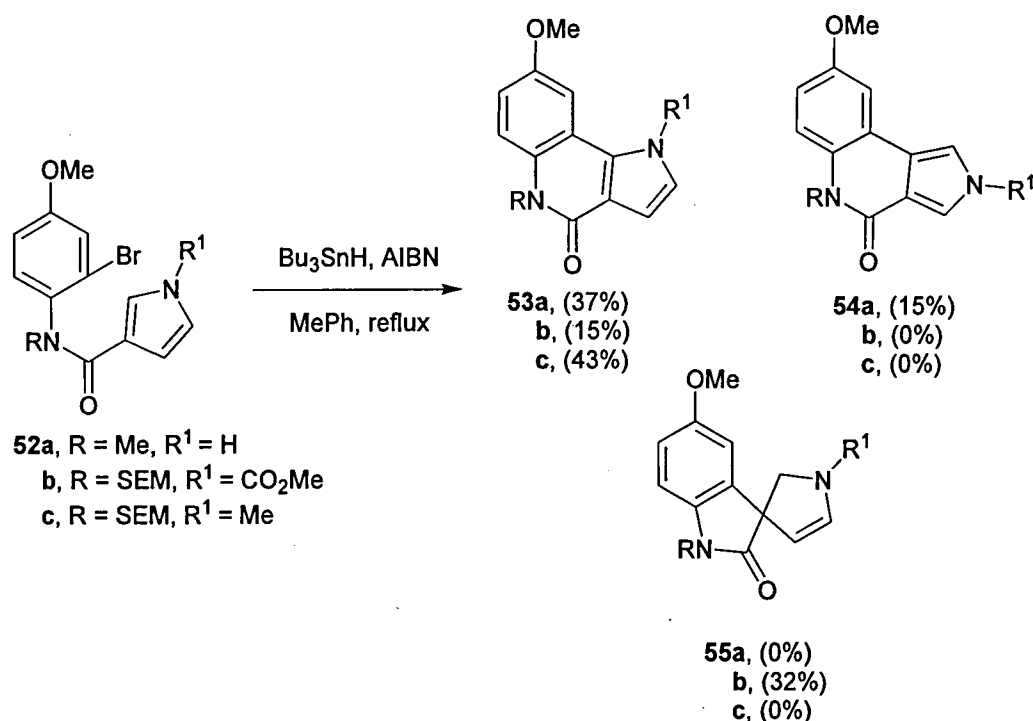


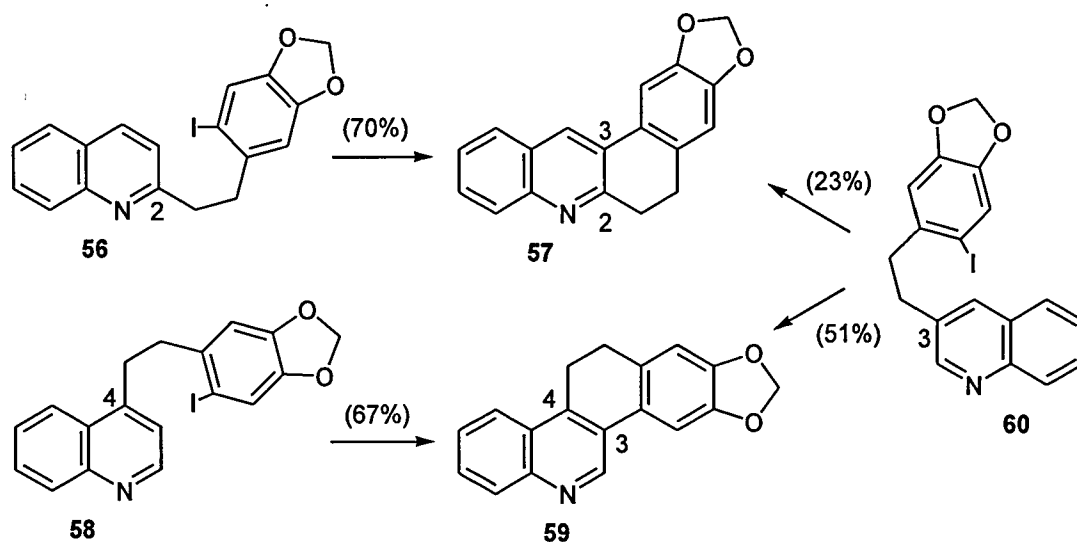
Figure 5. Pyrrole containing gastric inhibitor.

The regiochemistry of aryl radical cyclisations onto pyrrole rings proved interesting (scheme 19).¹⁷ The two nitrogen protecting groups R and R¹ proved to be very influential to reaction products. When the pyrrole nitrogen was unprotected (R¹ = H) **52a**, a mixture of pyrroloquinoline regioisomers **53a** and **54a** from a 6-*endo* cyclisation were isolated. When R¹ was electron withdrawing, as in ester **52b**, a spiropyrrolidinylloxindole product **55b** (the result of a 5-*exo* reduction radical cyclisation) and the 6-*endo* product **53b** were observed. When the pyrrole was protected with an EDG, as in methyl **52c** only one regioisomer product **53c** was recovered.



Scheme 19. Jone's regioselective radical cyclisations onto pyrroles.

Bicyclic heterocycles such as quinolines have provided interesting results to radical chemists over the years. Harrowven *et al.* has investigated radical cyclisations onto the C-2, C-3 and C-4 of quinolines (scheme 20).¹⁸ Radical cyclisation of the 2-substituted quinoline **56** resulted in selective cyclisation onto the C-3 position, forming pentacycle **57** in good yield. With 4-substituted quinoline **58** the sole reaction product was cyclisation onto C-3, resulting in pentacycle **59**. The cyclisation of 3-substituted quinoline **60** in contrast produced a mixture of cyclisation onto C-4 and C-2, resulting in pentacycles **57** and **59**. In all cases fully rearomatised products were observed. This work also highlights how radical methodology can be used to create large polycyclic heterocyclic compounds.



Scheme 20. Harrowven's quinoline radical cyclisations using $\text{Bu}_3\text{SnH/AIBN}$.

Quinoline centred radicals have also been studied. Formal synthesis of the natural product target camptothecin **61** (figure 6) has been completed by Bennasar *et al.* using a quinoline radical.¹⁹

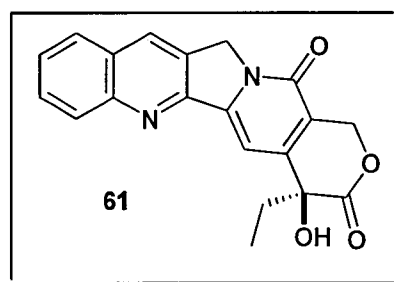
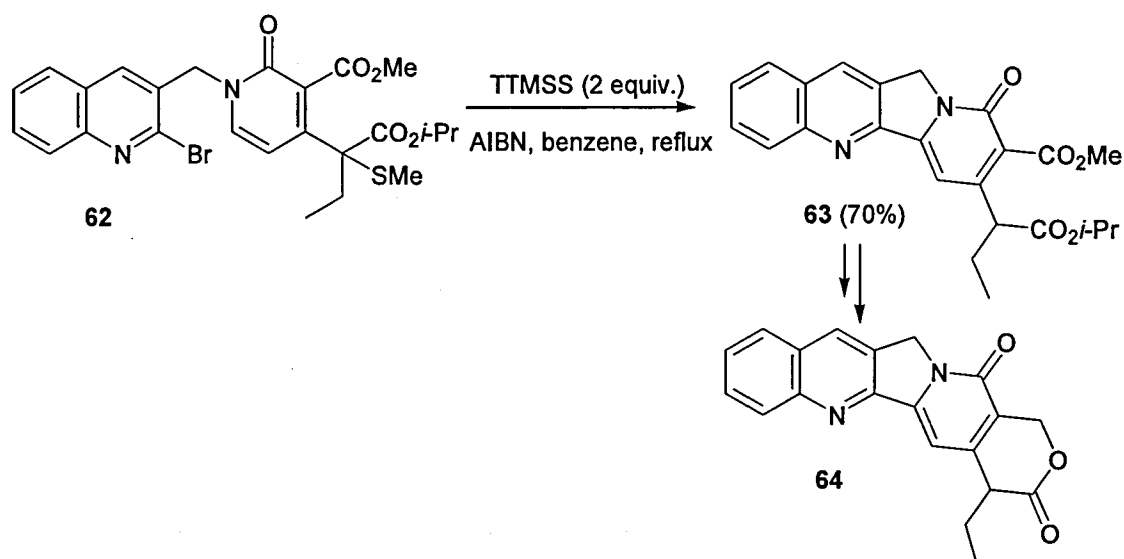


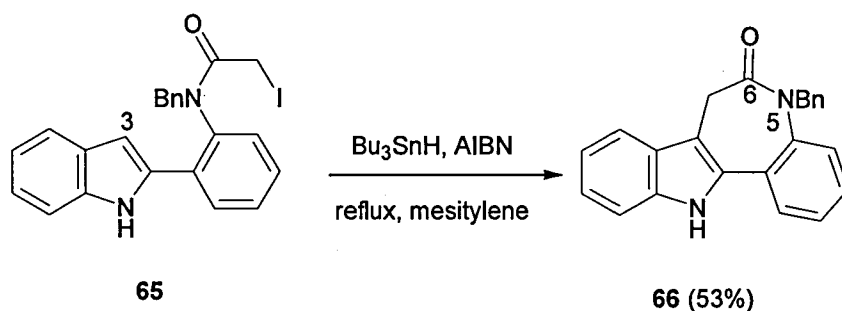
Figure 6. Important anticancer drug camptothecin.

This simple approach allowed access to the analogue of camptothecin, 20-deoxycamptothecin **64** (scheme 21). The key step involved generation of a C-2 quinoline radical from **62** followed by a *5-exo-trig* intramolecular radical cyclisation forming tetracyclic quinoline pyridone **63**. Use of TTMSS and AIBN brought about radical arylation and desulfurisation in high yield.



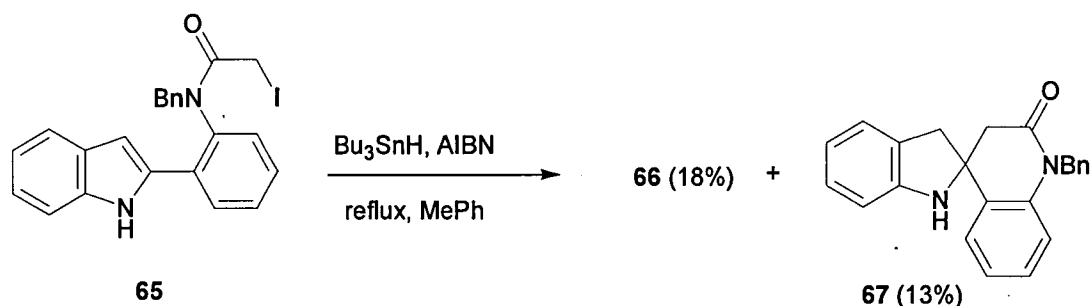
Scheme 21. Cyclisation of quinoline radicals in natural product synthesis.

One of the most common heterocyclic systems to be investigated by radical chemists are indoles. With so many natural products containing the indole core this is not surprising. Bremner and Sengpracha have utilised an iodoacetamide based radical in the synthesis of paullone type natural product **66** which is a potent cyclin dependant kinase inhibitors (scheme 22).²⁰ These natural products are traditionally made using a nitrogen carbon bond forming reaction between C-6 and N-5. Bremner's route involved employing a radical cyclisation onto the C-3 carbon of indole core **65**.²⁰ The desired paullone product **66** was produced in high yield (53%) using mesitylene as a solvent (high boiling).



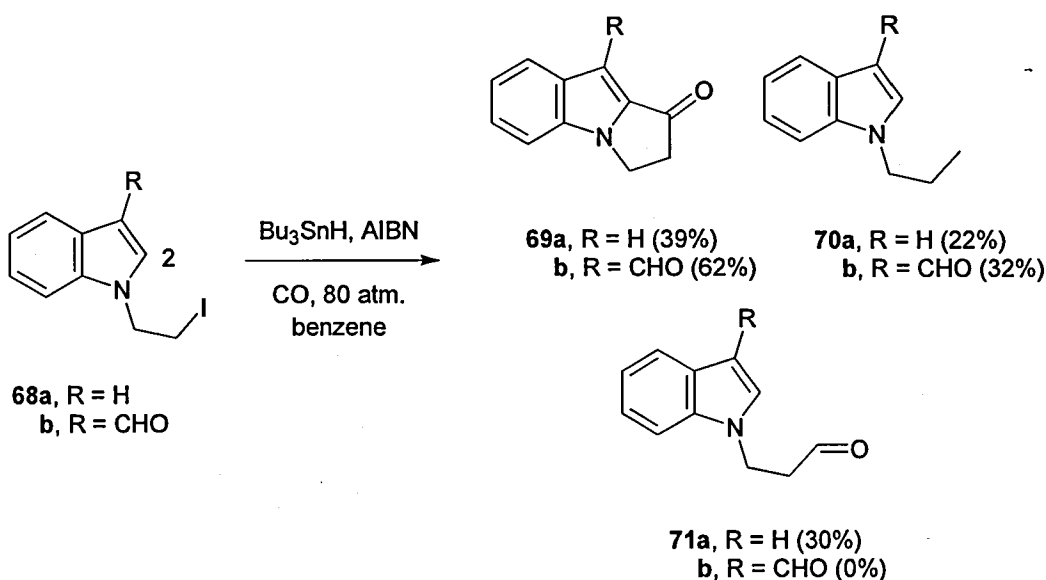
Scheme 22. Bremner and Sengpracha's indole cyclisations.

When using toluene a mixture of cyclised **66** and spiro compound **67** were retrieved from the reaction (scheme 23). The formation of the spiro type indole **67** products is not unique in radical cyclisations onto indoles. Further examples will be shown later.



Scheme 23. Spiro cyclic indole product in toluene.

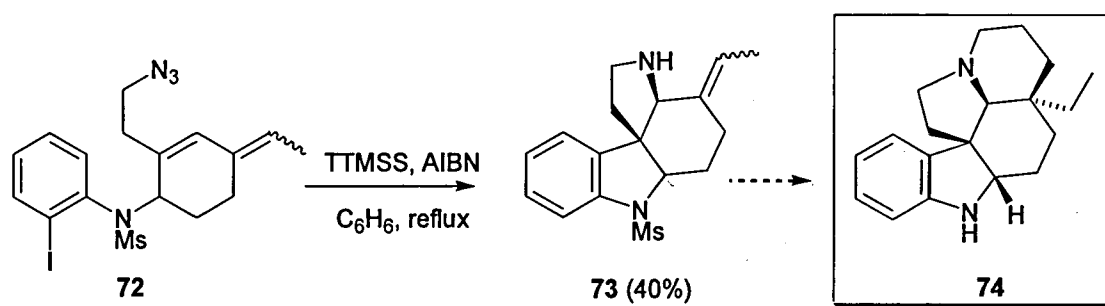
Miranda *et al.* have used a tandem carbonylation/radical cyclisation onto an indole core (scheme 24).²¹ By treating indole 68a under the radical conditions and 80 atmospheres of CO pressure, Miranda successfully generated an acyl radical. Cyclisation of the acyl radical onto the C-2 position of the indole core 69a was then observed, along with reduction and carbon monoxide trapped product 71. Addition of an aldehyde at the C-3 position of indole 68b increased the yield of cyclised indole 69b along with only reduced product 70. In this respect the work shares similarities with De La Cruz's pyrrole cyclisations previously discussed (scheme 17 and 18). The two reduced products 70a and 70b were also isolated along with alkyl carbonylated indole 71.



Scheme 24. Miranda's tandem carbonylation/radical cyclisation onto indole.

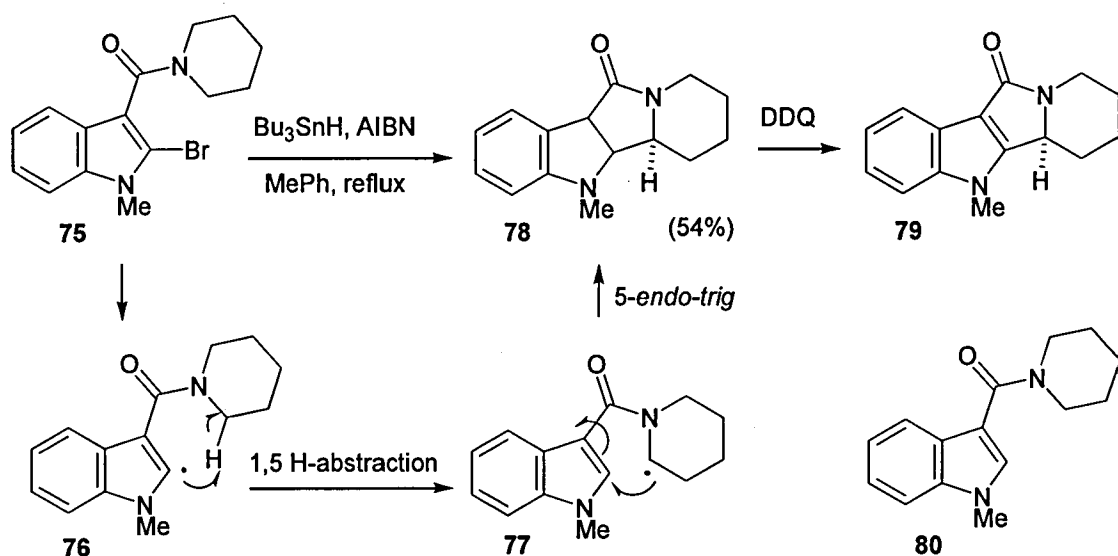
Although not nucleophilic homolytic aromatic substitution reactions, the next two examples are applicable in this general discussion through their use of radical indole synthesis. The first

example by Murphy employs a radical synthesis of indole core in the formal synthesis of pentacyclic (\pm)-aspidospermidine **74** (scheme 25).²² The aryl radical precursor **72** underwent a 5-*exo* radical cyclisation onto the near by alkene. This was followed by another 5-*exo* cyclisation onto the azide, with the elimination of nitrogen gas. The resulting aminyl radical picks up a hydrogen atom to yield tetracycle **73**. Minor elaboration then lead to a formal synthesis of (\pm)-aspidospermidine **74**.



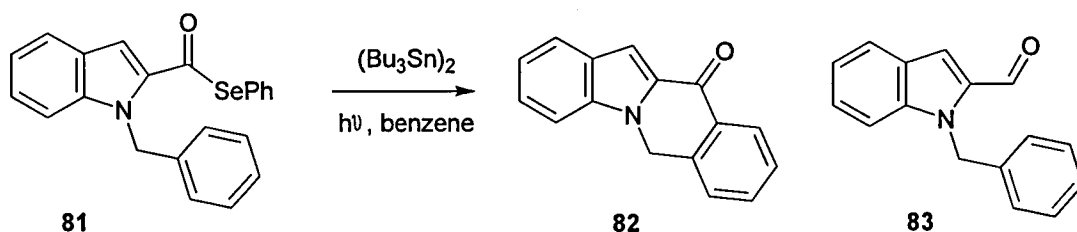
Scheme 25. Key tandem radical cyclisation reaction leading to (\pm)-aspidospermidine.

Generation of an indol-2-yl radical is of great interest and has been described many times in the literature.²³ Gribble *et al.* has successfully used an indol-2-yl radical to generate hexahydropyrrolo[3,4-*b*]indole **79** (scheme 26).²⁴ The bromination of the C-2 carbon of indole precursor **75** was achieved using the Bergman methodology for *N*-carboxy-indoles.²⁵ The radical cyclisation proceeds *via* a 1,5 H-abstraction of the indol-2-yl radical **76** to create the α -amidoyl radical **77** which then undergoes a 5-*endo-trig* cyclisation onto the indole double bond to form **78**. Reintroduction of the double bond in indole **78** was carried out using DDQ to form the fully aromatic indole **79**. The reduced indole product **80** was also obtained (42%).



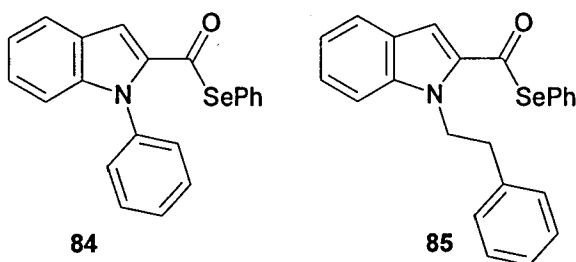
Scheme 26. 1,5 Radical translocation followed by 5-*endo-trig* cyclisation to the indole C-2 position.

Bennasar has extended the interest of this work by examining the behaviour of 2-indolylacyl radicals onto aromatic rings (scheme 27).²⁶ The 2-indolylacyl radical was generated from the corresponding seleno esters **81**. Crich has reported the use of seleno esters in radical chemistry before.²⁷ The 2-indolylacyl radical doesn't undergo decarbonylation. This is because of stabilization provided by the indole core. Cyclisations of the 2-indolylacyl radical was limited to the formation of the 6-membered ring product **82**. Use of Bu_3SnH gave rise to only reduced product **83** (90%). By using $(\text{Bu}_3\text{Sn})_2$ (0.2 mol%) the yield of indole tetracycle **82** was increased (40%), although reduced product **83** (10%) and starting material (25%) were also recovered. The desired tetracycle **82** was formed as the sole reaction product (65%) after increasing the amount of $(\text{Bu}_3\text{Sn})_2$ in the reaction to 2.2 mol equivalent % with respect to starting material.



Scheme 27. 2-Indolylacyl radical cyclisation to form indole tetracycle.

Despite considerable effort by Bennasar, the work could not be extended to form 5 or 7-membered tetracycles from the precursors **84** and **85** (scheme 28). There was no apparent reason for these failures.²⁷



Scheme 28. Failed cyclised starting materials.

An example of a spirocyclic heterocycle has already been shown by Bremner and Sengpracha's indole cyclisations forming the spirocycle **67** as an unwanted side product (scheme 23).²⁰ These spirocyclic indole cores constitute a wide range of natural products. One such is mytraginine pseudoindoxyl **86** (figure 7).

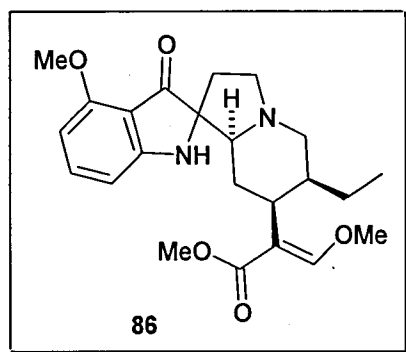
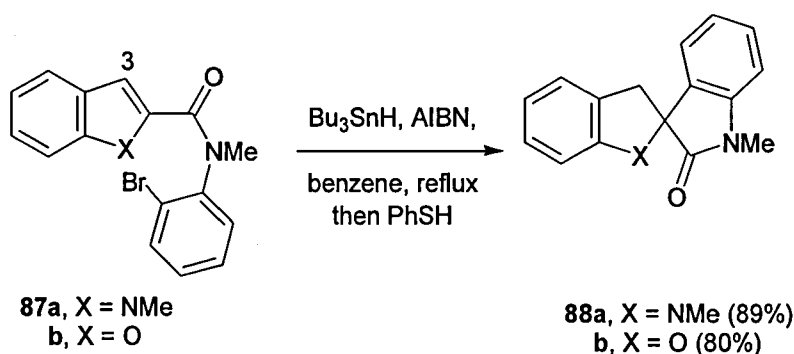


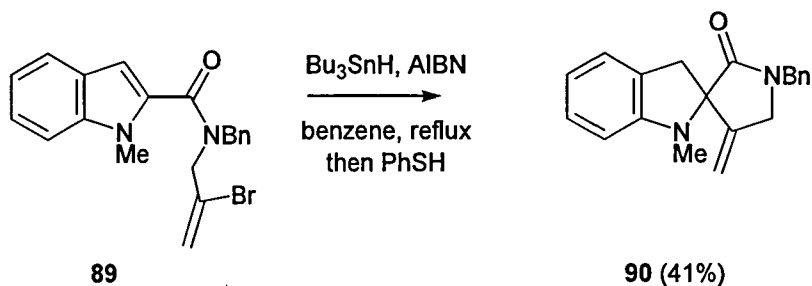
Figure 7. Spirocyclic indole natural product.

Baldwin *et al.* recently investigated radical dearomatisation of indoles and benzofurans to access these heterospirocyclic cores in high yield (scheme 29).²⁸ When indole **87a** and benzofuran **87b** were treated with Bu_3SnH , the resulting aryl radicals formed the desired *ipso*-type spirocyclic indole product **88a** and benzofuran **88b** in good yield.



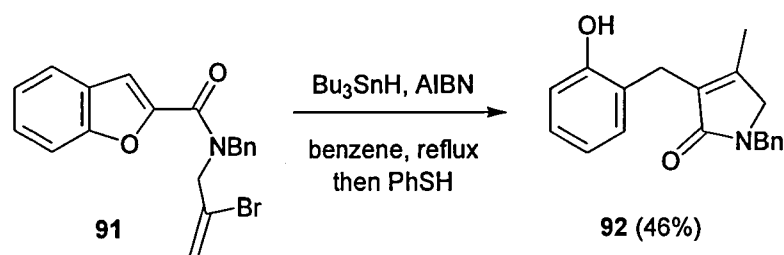
Scheme 29. Aryl radical *ipso 5-exo-trig* cyclisation to reach spirocyclic cores.

Formation of a stable intermediate benzylic radical on the indole and benzofuran C-3 aided formation of the desired products. Baldwin then investigated cyclisation of vinyl groups onto these systems, an unexpected result appeared. The cyclisation of the indole **89** proceeded well although the spirocyclic indole **90** was formed in lower yield than previous aryl analogue **88a** (scheme 30).²⁸



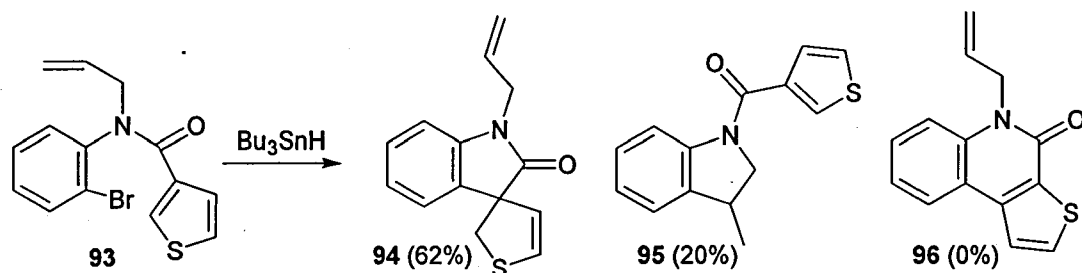
Scheme 30. Vinyl radical *ipso 5-exo-trig* cyclisation onto indoles and benzofuran.

Cyclisation of the benzofuran **91** yielded the unexpected phenol **92** (scheme 31).²⁸ A mechanism for this product **92** was proposed involving a fragmentation of the spirocyclic intermediate forming a stable phenoxy radical. The authors attribute the difference in the reaction pathways of indole **89** and benzofuran **91** to the extra lone pair stability provided by the nitrogen in indole.



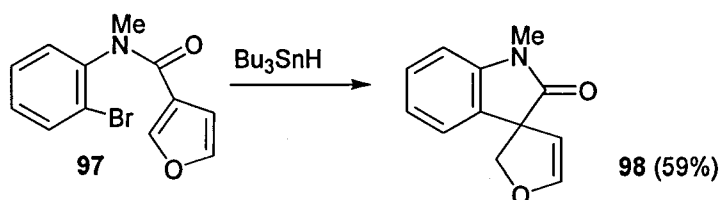
Scheme 31. Unexpected phenol product from radical cyclisation.

Examples of radical cyclisations onto sulphur containing heterocycles have also been carried out. For instance Ganguly *et al.* compared radical cyclisations onto thiophenes, carboxamides, furans and indoles to obtain a range of products.²⁹ Aryl radical cyclisation onto thiophene and alkene substituted **93** resulted in the spiro thiophene reduced product **94** (62%) and the 5-*exo-trig* product **95** onto the alkene (20%) (scheme 32). This indicated that addition of the radical to the vinyl group or thiophene proceeded well, but possible rearrangement to fused aromatic compound **96** was unfavourable.



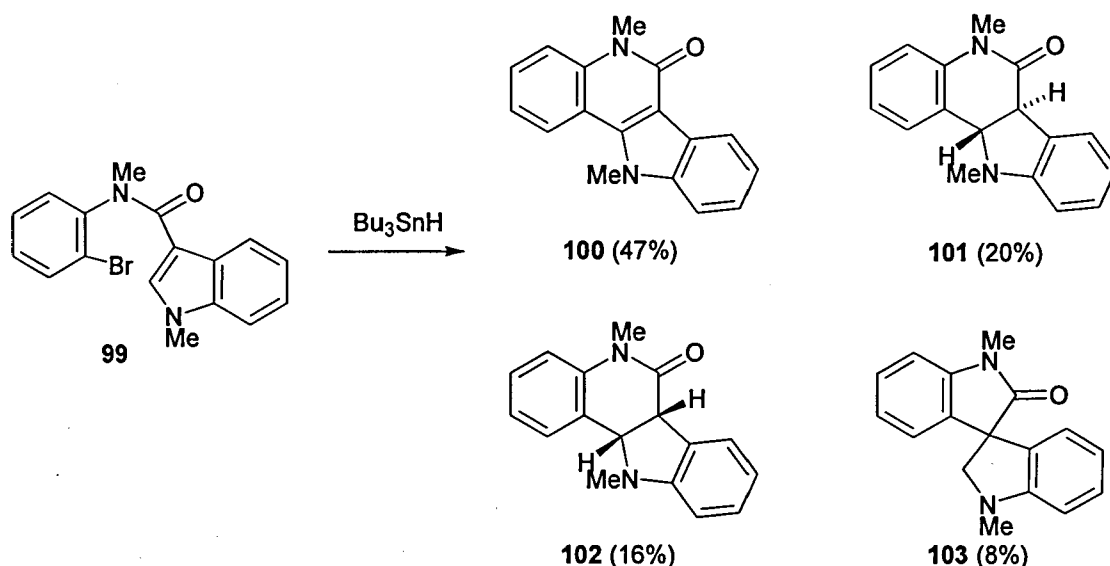
Scheme 32. Aryl radical cyclisation onto alkene and thiophene.

In the case of cyclisation onto the carboxyamide furan **97** only the spiro reduced furan compound **98** was obtained (scheme 33). The spiro furan is formed in similar yield to the previous thiophene cyclisation **94**, even though there is no competing pendant alkene for the radical to cyclise onto.²⁹



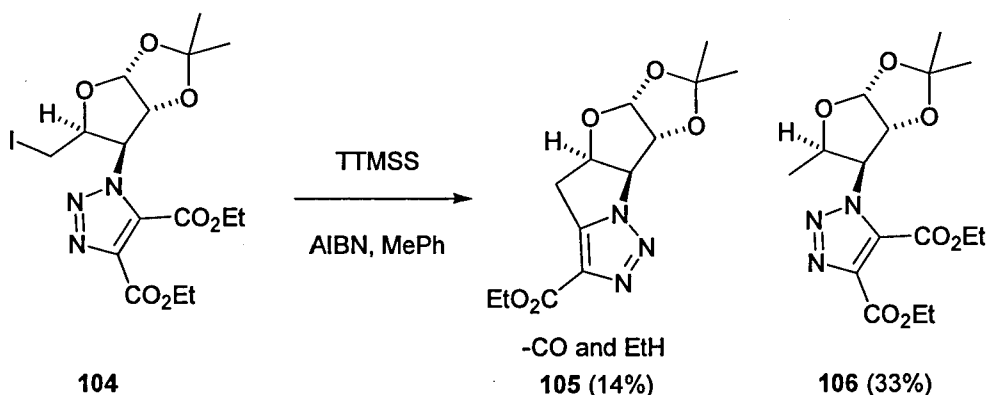
Scheme 33. Aryl radical cyclisation onto furan.

These results contrast with cyclisations carried out onto indole **99** (scheme 34).²⁹ Here the major product was the fused tetracycle compound **100** (47%). Minor products from this reaction included the cyclised reduced products **101** (20%) and **102** (16%) as well as the spiro compound **103** (8%).



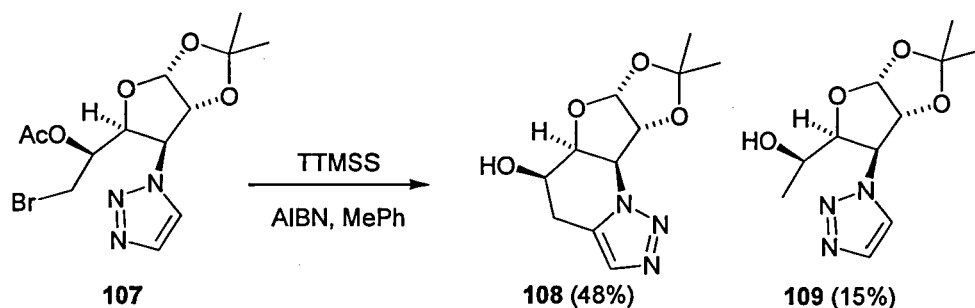
Scheme 34. Aryl radical cyclisation onto indole.

Heterocycles containing three heteroatoms have also been the subject of investigations by radical chemists. Marco-Contelles *et al.* have made sugar templates using 5-*exo-trig* radical cyclisations onto the triazole **104** (scheme 35).³⁰ The 5-*exo-trig* cyclisation of the triazole **104** was only feasible with the activation of the triazole with an ester group, yielding the cyclized triazole **105** and the reduced triazole **106**.



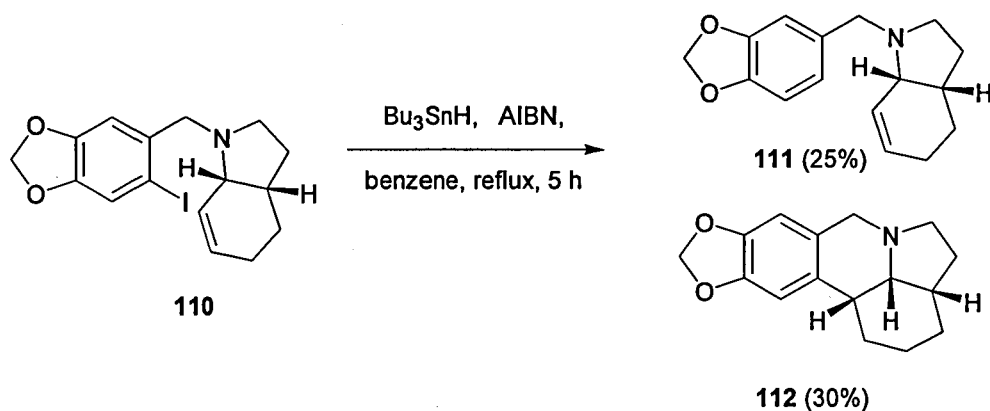
Scheme 35. 5-Membered ring radical cyclisations onto triazole.

In the case of 6-*exo-trig* cyclisation of the triazole **107** no activation was required (scheme 36). 6-*Exo-trig* cyclisation was found to be more favourable than 5-*exo-trig* ones. Here higher yields of the cyclised triazole **108** were recovered over the reduced triazole **109** (the yields for this reaction were based on hydrolysis of the AcO group).



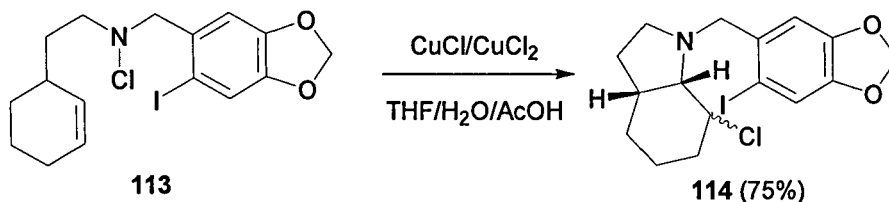
Scheme 36. 6-Membered ring radical cyclisation onto triazole.

Chemists have often turned to radical methodology when other synthetic methods have failed, without the need to alter precursors. When a key Heck reaction of the aryl iodide **110** could only be carried out in poor yield, Cossy *et al.* quickly altered their strategy towards (\pm)- γ -lycorane by using radical methodology (scheme 37).³¹ Although the final 6-*exo-trig* radical cyclisation was achieved in only a modest yield to (\pm)- γ -lycorane template **112** (30%) it was higher than previous palladium Heck conditions. Reduced compound **111** was also recovered from the reaction.



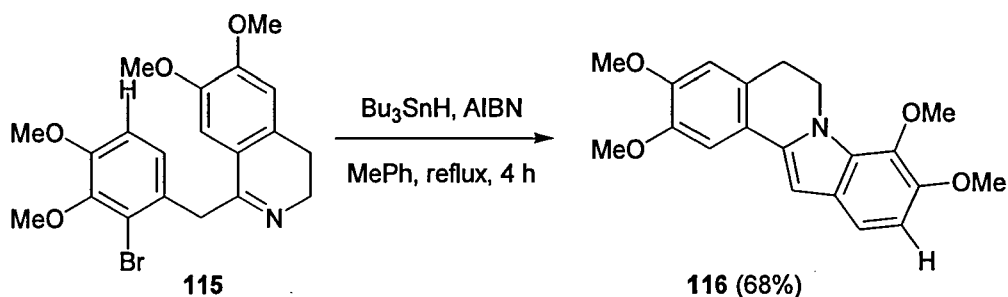
Scheme 37. Synthesis of (\pm)- γ -lycorane using an unplanned radical cyclisation.

Formation of a radical on a heteroatom can be very advantageous in organic synthesis. In the synthesis of (±)- γ -lycorane Cossy also used a 5-*exo-trig* aminyl radical cyclisation to form the octahydro indole **114** from aminyl chloride **113** in the syntheses (scheme 38).



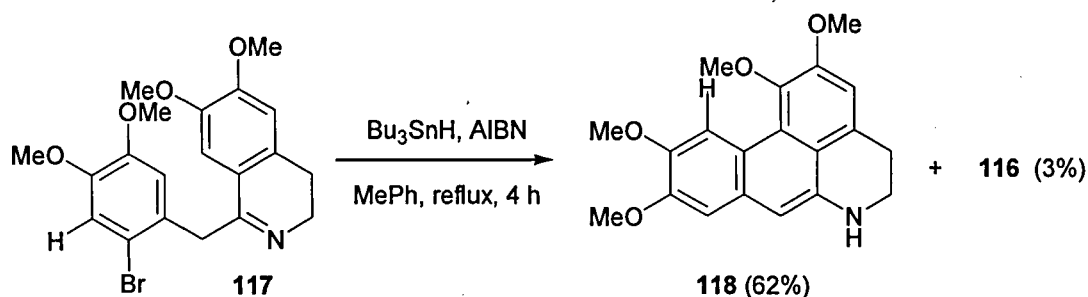
Scheme 38. Aminyl radical cyclisation.

Steric bulk can play an important role in the formation of products under radical cyclisations (shown in Jones work scheme 14).¹⁴ Orito *et al.* have shown how a favourable 6-*endo* cyclisation can be made to undergo the less favourable 5-*endo* radical cyclisation (scheme 39) by the use of steric bulk.³² With 3,4-dihydroisoquinoline **115** the effect of two neighbouring methoxy groups resulted in just one product 5,6-dihydroindolo[2,1-*a*]-isoquinoline **116**.



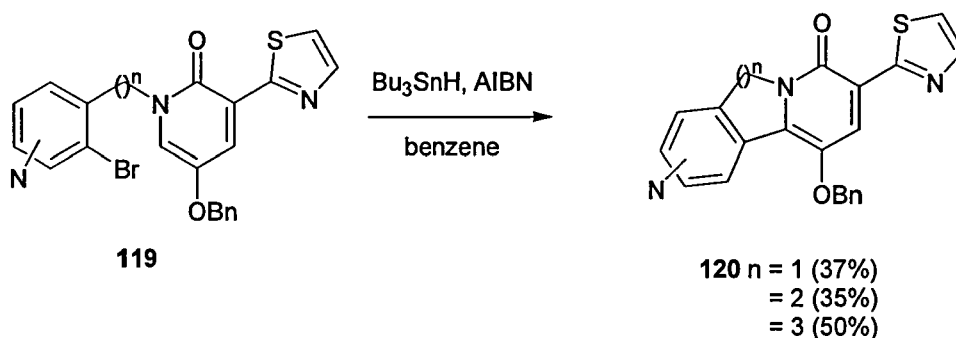
Scheme 39. Use of steric bulk to form the unfavoured 5-*endo* product.

By removal of one of these methoxy groups **117** two products were achieved, the fully rearomatised 6a,7-dehydroaporphine **118** resulted *via* a 6-*endo* cyclisation and a small amount of 5,6-dihydroindolo[2,1-*a*]-isoquinoline **116** was obtained (scheme 40).³² Examples of such unfavoured 5-*endo* radical cyclisations onto nitrogen atoms of a CN double bond have been reported before, although rare.³³



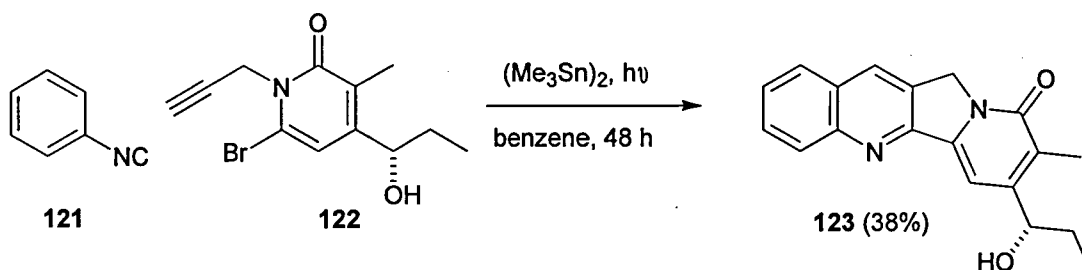
Scheme 40. Removal of steric bulk to give two radical cyclisation products.

Heterocycles containing 7-membered rings have also been formed by radical cyclisation reactions. Nadin *et al.* have shown 5, 6 and 7-membered ring formation of tricyclic pyridones (scheme 41).³⁴ The yields of tricyclic **120** appeared to be remarkably independent of ring size. Unfortunately this work could not be carried out using the alkyl radical analogues of **119**. This could be attributed to the greater drive to rearomatise by aryl radicals.



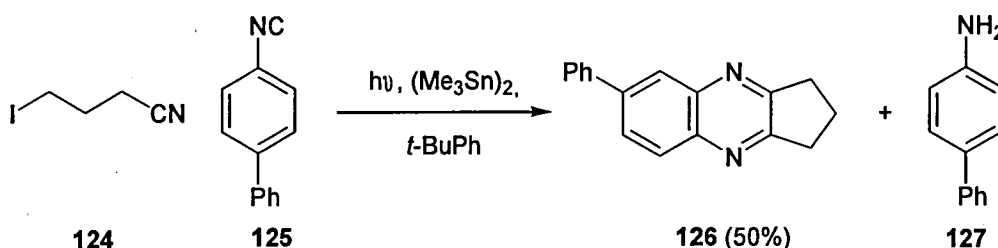
Scheme 41. 5-,6- and 7-membered ring formation.

The ability to form several bonds in one step has attracted synthetic chemists to cascade reactions for a long time. There are numerous examples where cascade reactions have been carried out using radical cyclisations. One such example is the synthesis of the natural product (*S*)-mappicine **123** (scheme 42) by Curran *et al.* The key radical reaction involved a [4+1] cascade reaction of isonitrile **121** and bromo pyridone **122**.³⁵ This is a rare example in radical cascade chemistry, as the initial step is inter-molecular. The addition onto the isonitrile has been utilized by Curran for several other notable natural product syntheses including the anticancer agent camptothecin.³⁵ Interestingly, when the reaction was carried out using a ketone (in place of the hydroxy group) on bromopyridone **122** the reaction yield was lower.



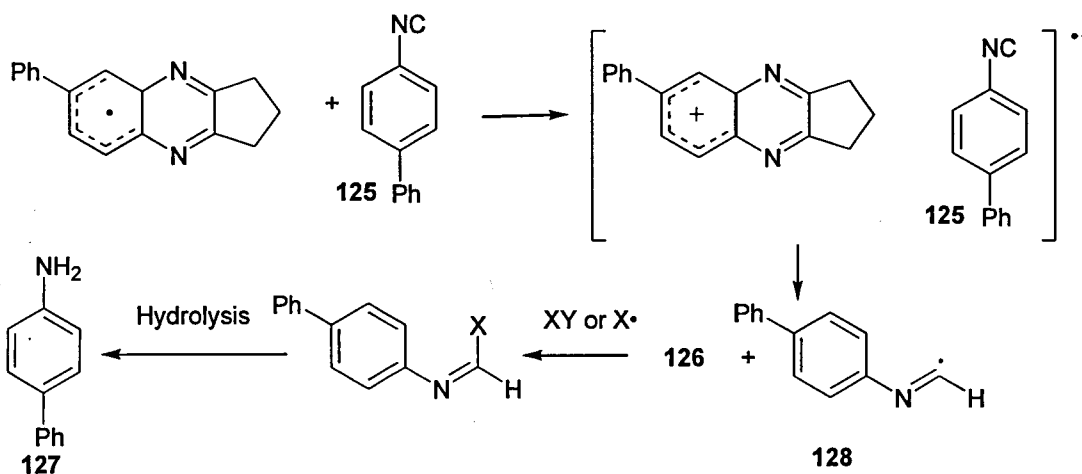
Scheme 42. Curran's synthesis of (*S*)-mappicine.

Nanni *et al.* have carried out the synthesis of cyclopentaquinoxaline **126** using a radical cascade reaction (scheme 43).³⁶ Alkyl iodide **124** and biphenyl isocyanides **125** were found to cyclise using $(\text{Me}_3\text{Sn})_2$ to form cyclopentaquinoxaline **126**. The associated amine **127** was also isolated from the reaction.



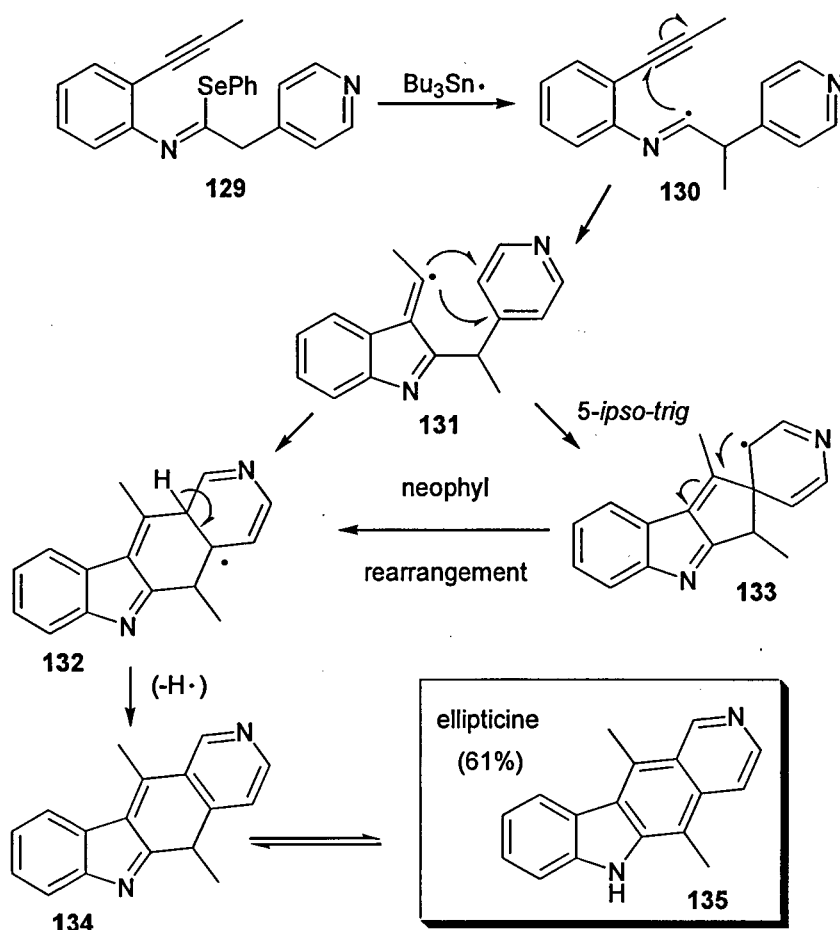
Scheme 43. Nanni's cyclopentaquinoxaline formation.

The formation of amine **127** is not obvious. It is postulated that intermediate imidoyl radical **128** (arising from electron then proton transfer) picks up a radical species and then hydrolyses to the amine **127** (scheme 44).³⁶



Scheme 44. Possible mechanism of amine formation.

Bowman *et al.* has also used a radical cascade reaction in the total synthesis of ellipticine **135** (scheme 45).³⁷ The key radical intermediate was the imidoyl radical **130**. This was generated from the imidoyl selenide **129**, which is stable and easy to handle. The imidoyl radical firstly undergoes a 5-*exo-dig* cyclisation to form the alkenyl radical **131**. This radical may then proceed either by a 5-*ipso-trig* cyclisation to form spiro intermediate **133** followed by neophyl rearrangement reaction or a 6-*endo-trig* cyclisation to form intermediate **132**. Both routes lead to the tetracycle intermediate **134**. On tautomerism this leads to ellipticine **135**. The mechanism of H-abstraction has previously been discussed (section 1.8).



Scheme 45. Radical cascade synthesis of ellipticine.

1.10 Introduction to quinazolines and quinazolinones

We are interested in developing and testing radical methodology to form 2,3-cyclised-3*H*-quinazolin-4-ones **18** (figure 8). 3*H*-Quinazolin-4-ones **136** comprise of a 3*H*-pyrimidin-4-one (A) ring and fully aromatic benzene (B) ring. It closely relates to quinazoline **137**, which also appear in many natural products and pharmaceutical drugs substitution. While it can be said that the A ring of a quinazoline is fully aromatic, the same cannot be said of 3*H*-quinazolin-4-ones. During the course of our studies we have found few examples of radical methodology being employed in the synthesis of quinazolines or quinazolinones. We therefore feel our investigations are timely. Syntheses of quinazolines and quinazolinones have recently been reviewed by Guiry.³⁸

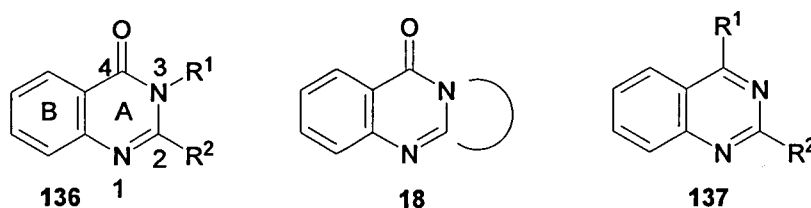


Figure 8. 3*H*-Quinazolin-4-ones and quinazoline structures.

Both 3*H*-quinazolin-4-ones and quinazolines have shown a vast array of biological activity over the years.³⁹ The 2,3-disubstituted-3*H*-quinazolin-4-one skeleton therefore, has become particular interest, and provides a rich source of synthetic targets. Herein, we concentrate on the chemistry of quinazolines and quinazolinones.

The 3*H*-quinazolin-4-one moiety has been extensively used as a drug like scaffold in medicinal chemistry and is therefore, considered ‘privileged’.³⁹ The term ‘privileged’ was first coined by Evans *et al.* in 1988 and was defined as “a single molecular framework able to provide ligands for diverse receptors”.⁴⁰

The rich variety of quinazoline drugs stem from the countless natural products that contain the quinazoline moiety. The chemistry of recently isolated naturally occurring quinazolinones has been reviewed by Mhaske and Argade.⁴¹ One of the earliest isolated quinazoline natural products was vasicine **138**. It was first isolated by Hooper in 1888, from *Adhatoda vasica* (an Indian plant) and the seeds of *Pegnum harmala*. It is unsaturated at the C-4 position of the quinazoline (figure 9).⁴² Febrifugine **139** (first fully characterised by Koepfli *et al.*) was one of the first 3*H*-quinazolin-4-ones to be isolated.⁴³ Contained within the powdered root of

Dichroa febrifuga, which had a long history of being used in Chinese medicines such as Ch'ang Shan. Febrifugine and was shown to possess anti-malarial properties.⁴³

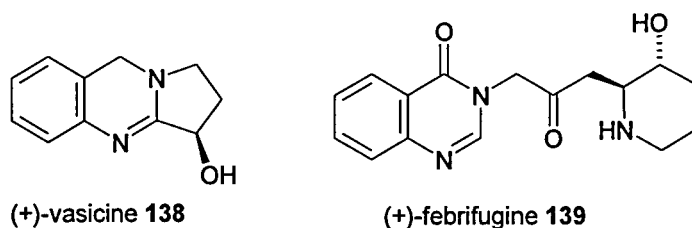


Figure 9. Early quinazoline and quinazolinone natural products.

A large amount of structural diversity is seen in quinazoline natural products, dictoquinazol B 140 (figure 10), for instance, contains the unusual *N*-formyl substituents at the N-1 position, and the rare 1,2,3,4-tetrahydroquinazoline moiety.⁴⁴ The continual discovery of new quinazolinones is highlighted by discovery in 2005 of complex plant metabolite lapatins A 141.⁴⁵

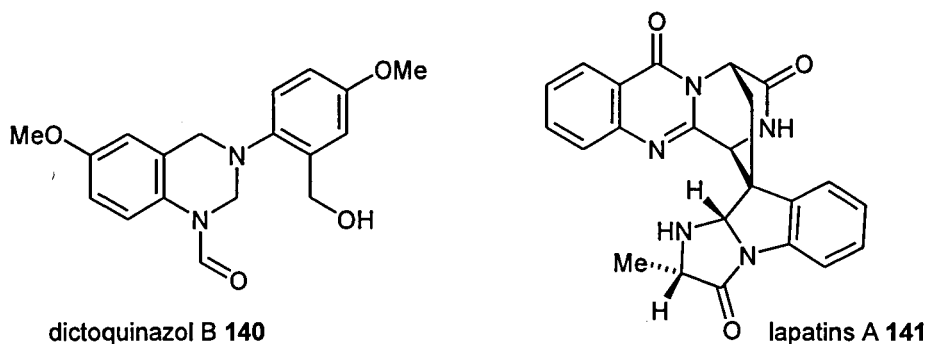


Figure 10. Unusual quinazoline and quinazolinone natural products.

Indeed, some structures are so complex they have yet to be fully synthesized. Hinckdentine A 142, is such a structure. Synthetic routes to hinckdentine A have been reviewed by McWhorter Jr (figure 11).⁴⁶ One of the most powerful and famous non-protein neurotoxins in the world, tetrodotoxin 143, is worth mentioning here. It is famous for being found in the ovaries of the Japanese puffer fish *Sphoerides rubripes* and *S. phyreus* as well as the Californian salamander *Taricha torosa*.⁴⁷ Stripped of its hydroxy and ether bridges it is a fully saturated 2-amino substituted quinazoline.

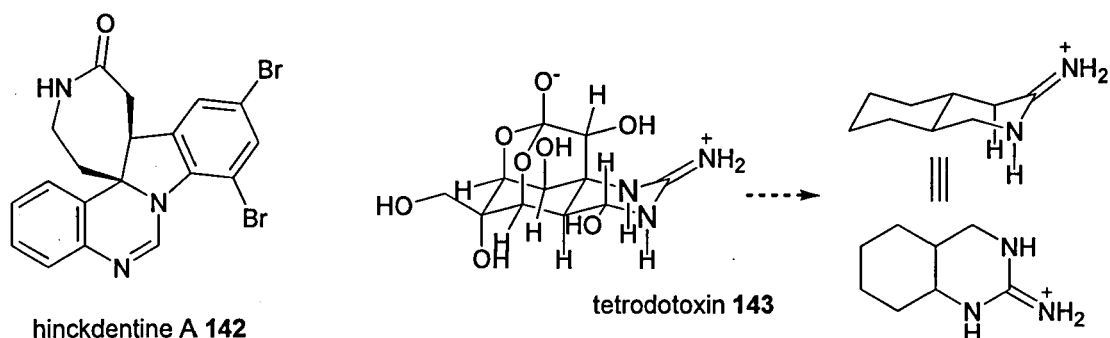


Figure 11. Other natural products containing the quinazolinone and quinazoline skeleton.

The total synthesis of *3H*-quinazolin-4-one natural products luotonin A **144**, rutaecarpine **145**, tryptanthrin **146**, deoxyvasicinone **147** and mackinazolinone **148** and will be discussed in more detail later in this thesis (figure 12).

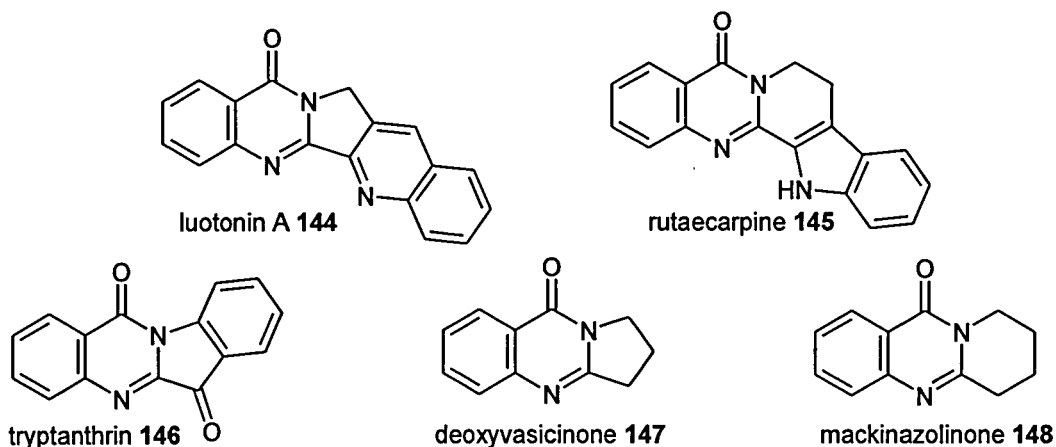


Figure 12. *3H*-quinazolin-4-one natural product targets.

So far, only natural products have been discussed. There are also a myriad of pharmaceutical drugs available and in clinical trials containing the *3H*-quinazolin-4-one core skeleton (figure 13). Raltitrexed **149** (Tomudex®), is substituted at the C-2 and C-6 (on the B ring), and is marketed as a colorectal cancer treatment.⁴⁸ Ispinesib **150**, is substituted at C-2 and N-3, and is currently in nine different phase two clinical trials for various cancers.⁴⁹

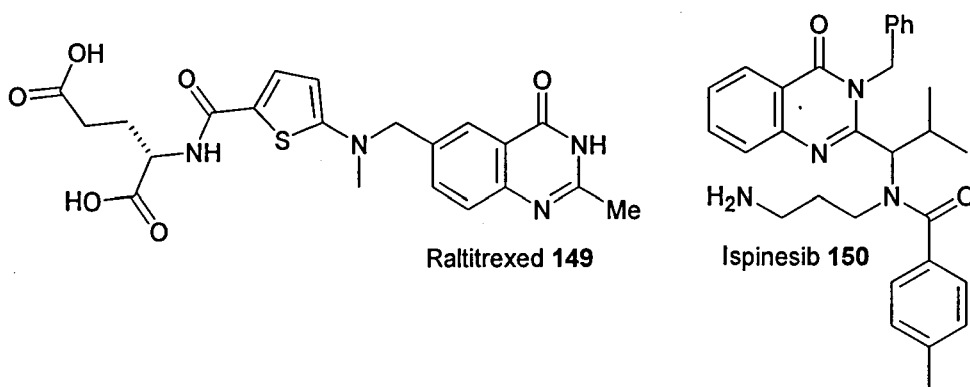


Figure 13. Quinazolin-4-one containing drugs.

Di-keto quinazolines such as Kentanserin 151 (figure 14), have found applications as selective serotonin receptor antagonist.⁵⁰ Quinazolinones such as Quinethazone 152, are used as diuretics and contains the thiazide functional group at C-6 (on the B ring).⁵¹

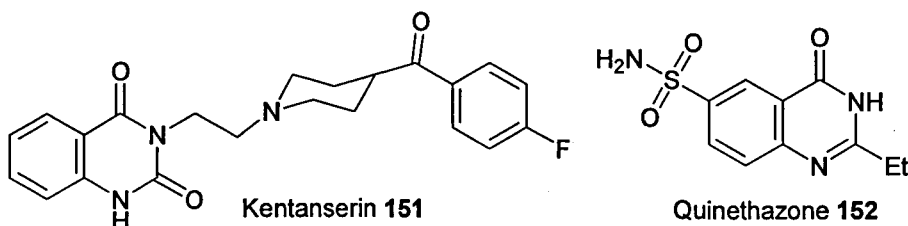


Figure 14. More quinazolinone and quinazoline drugs of interest.

The drug Tempostatin™ 153 (figure 15), is in phase II clinical trials for bladder, liver and others cancers.⁵² Tempostatin™ 153 bears a remarkable structural similarity with febrifugine 139 (figure 9). The side arm of febrifugine has been moved from the N-3 position to the C-2 position in Tempostatin™. The generic drug methaqualone 154 (Revonal®) has been available since the 1960's as a sedative.⁵³ Its biological activity should not be surprising given its structural similarities to barbiturates which, are largely pyrimidinone in structure.

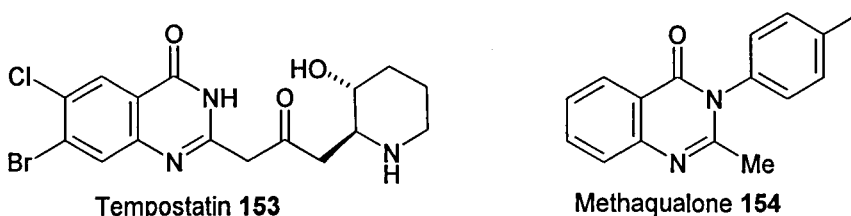


Figure 15. Other quinazolinone containing drugs.

Another common functional group found attached to quinazolines is the amino group. Prazosin **155** (figure 16), which is used to lower high blood pressure, is a di-amino substituted quinazoline.⁵⁴ Gefitinib **156**, which is a new class of lung cancer treatment drugs and is only a mono-amino substituted quinazoline.⁵⁵

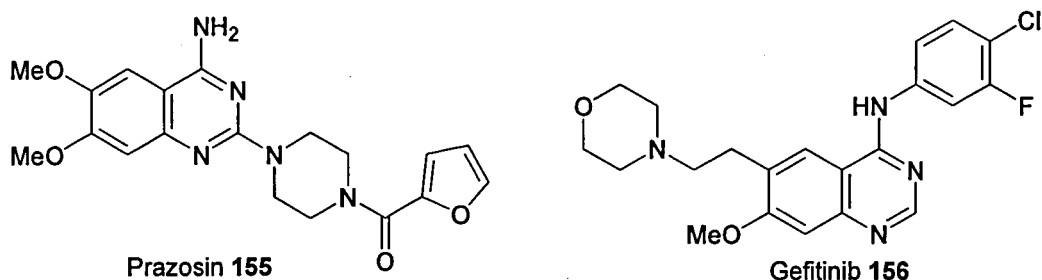


Figure 16. 4-Amino substituted quinazoline drugs.

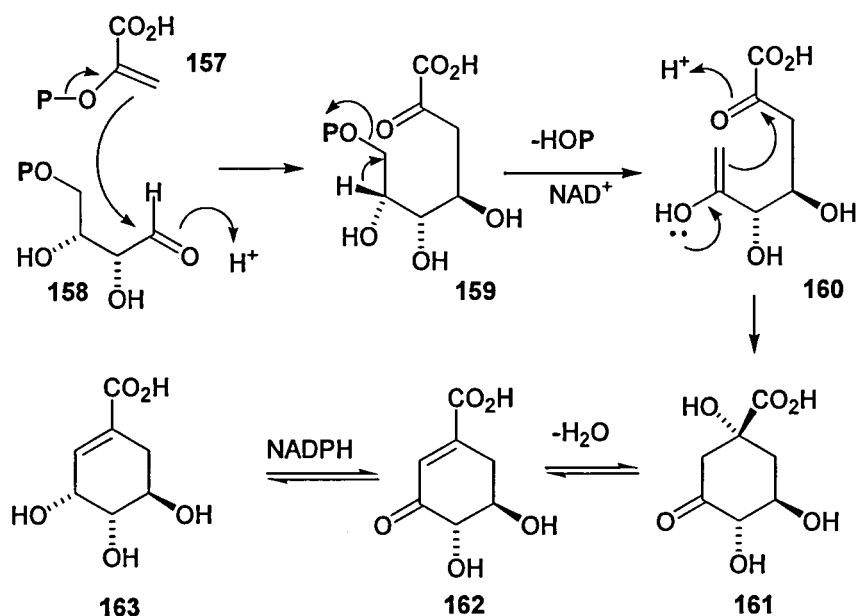
It is the vast collection of drugs and natural products that has caught our imagination. We want further expand the interest within the field of 3*H*-quinazolin-4-ones by carrying out further investigations into the field.

1.11 Biosynthesis of quinazolines and quinazolinones

Natural products containing the quinazolin-4-one moiety are most likely all derived from the amino acid anthranilic acid, which is a product of the shikimic acid pathway. This pathway also provides routes to other amino acids and heterocyclic compounds. Solely microorganisms and plants carry it out.⁵⁶ Thus it is no surprise that the amino acids derived from this sequence are considered essential to humans. There are very few studies reported for the biosynthesis of quinazolinones natural products. As mentioned those that do exist all derive from anthranilic acid, whose biosynthesis will now be discussed.

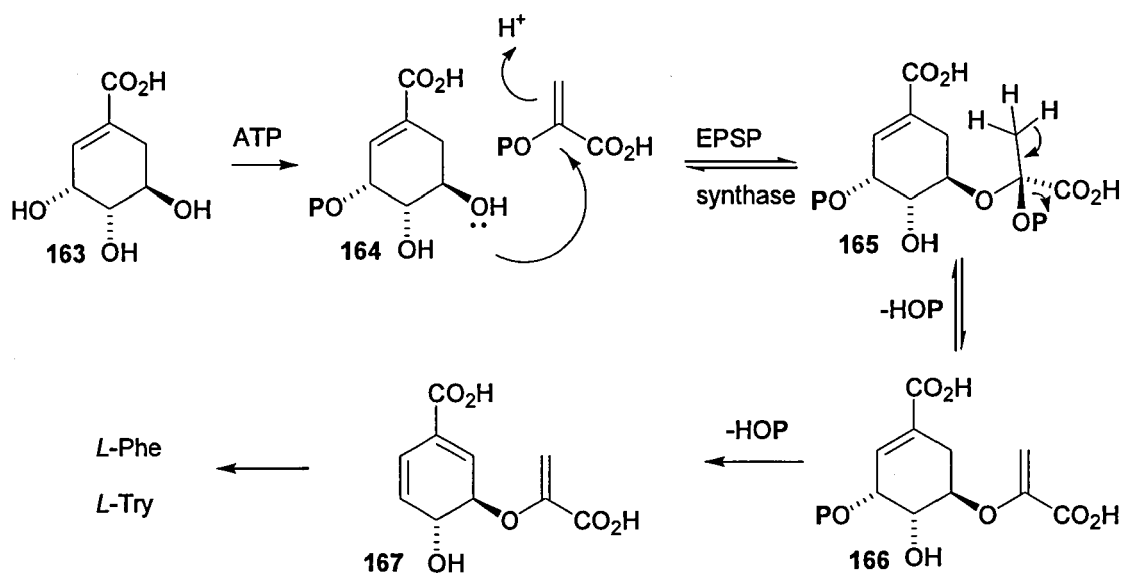
The shikimic acid pathway begins with the coupling of phosphoenol pyruvate **157** (PEPA) and D-erythrose 4-phosphate **158** (E4P) producing the seven carbon compound D-*arabino*-heptulosonic acid 7-phosphate **159** (DAHP) (scheme 46).⁵⁷ Although at first glance this reaction appears to be an aldol type condensation, the enzyme catalysed mechanism is known to be more complex. The first carbocyclic structure 3-dehydroquinic acid **161** is formed after elimination of the phosphoric acid from DAHP, yielding intermediate **160** which then undergoes an intramolecular aldol type reaction to form 3-dehydroquinic acid **161**. Again, this mechanism is more complex than stated. It is known NAD⁺ plays a key role in the oxidation of the central hydroxyl group. A single enzyme controls all these changes. Dehydration of 3-

dehydroquinic acid **161** leads to 3-dehydroshikimic acid **162**, which is then reduced leading to shikimic acid **163**.



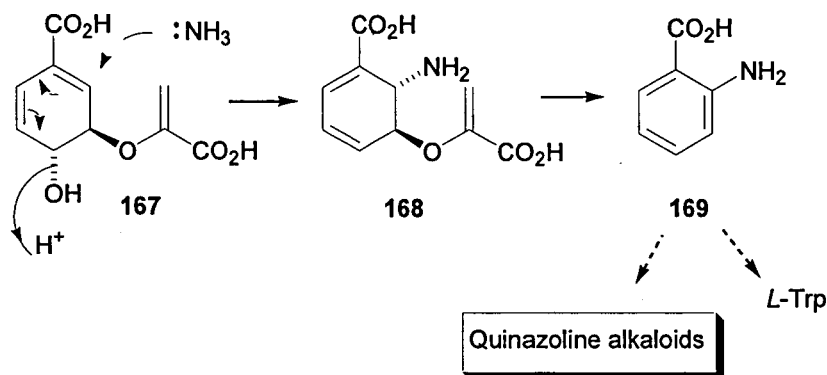
Scheme 46. Biosynthesis of shikimic acid.

A key intermediate from the shikimic acid pathway is chorismic acid **167** (scheme 47).⁵⁷ When shikimic acid **163** is phosphorylated by ATP **164**, it then reacts with PEPA *via* an addition reaction forming intermediate **165**. This is followed by a 1,2-elimination reaction of phosphoric acid yielding 3-enolpyruvylshikimic acid 3-phosphate (EPSP) **166**. The enzyme EPSP synthase, catalyses this reaction. 1,4-Elimination of phosphoric acid of EPSP then leads to chorismic acid **167**. Chorismic acid can then be further transformed to a number of amino acids such as *L*-phenylalanine and *L*-tyrosine..



Scheme 47. Biosynthesis to chorismic acid.

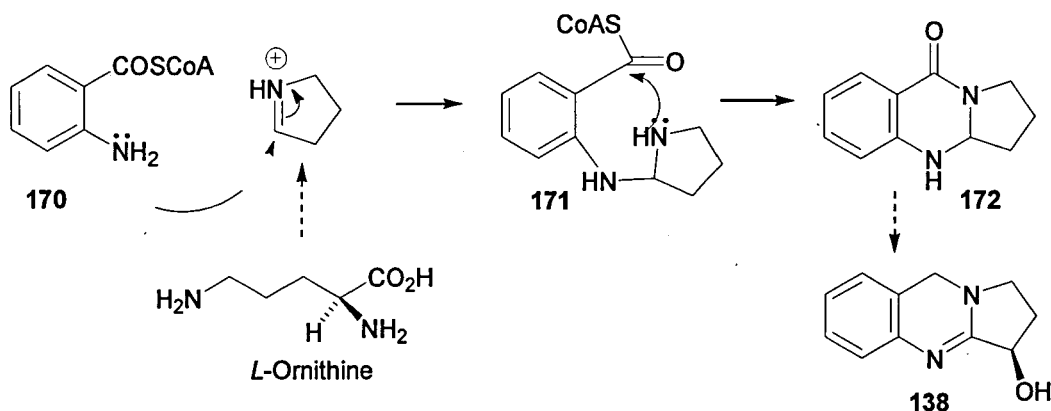
When glutamine acts to aminate at the C-2 position of chorismic acid, 167, 2-amino-2-deoxy-isochorismic acid 168 is formed (scheme 48).⁵⁷ Elimination then leads to the formation of anthranilic acid 169. This is the key intermediate to the formation of quinazolinone natural products, the amino acid *L*-tryptophan and other related indole alkaloids.



Scheme 48. Final biosynthesis steps to anthranilic acid.

The exact biosynthesis of quinazoline alkaloids varies and not many have been studied in great detail. The proposed biosynthesis of the bronchodilator vasicine 138 (already shown in figure 9) is shown (scheme 49).⁵⁶ The anthranilate nitrogen of anthraniloyl-CoA 170 undergoes nucleophilic attack of the pyrrolinium cation derived from *L*-ornithine which is

followed by amide formation 171 to form tricycle 172. Vasicine 138 is found in the *Peganum harmala* plant and this proposed biosynthesis is specific to this species only.⁵⁶



Scheme 49. Biosynthesis of vasicine.

Yamazaki *et al.* has reported a possible biosynthesis of rutaecarpine 145 (already shown in figure 12) and its analogue evodiamine 174 (scheme 50).⁵⁸ Using feeding experiments with radio-labelled ¹⁴C-tryptophan, sodium ¹⁴C-formate (or methionine) and anthranilic acid, Yamazaki showed all three units to be fully incorporated into the *Evodia rutaecarpa* plant. The 3,4-dihydro- β -carboline intermediate 173 has not been proven. Yamazaki showed that position 13-*b* of both rutaecarpine and evodiamine come from the incorporation of formate or methionine. Incorporation of this unit into evodiamine was slower than for rutaecarpine 145 and so the suggestion is that evodiamine 174 is not formed as result of *N*-methylation of rutaecarpine.

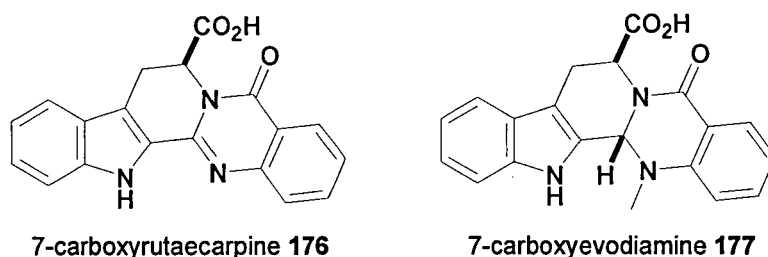
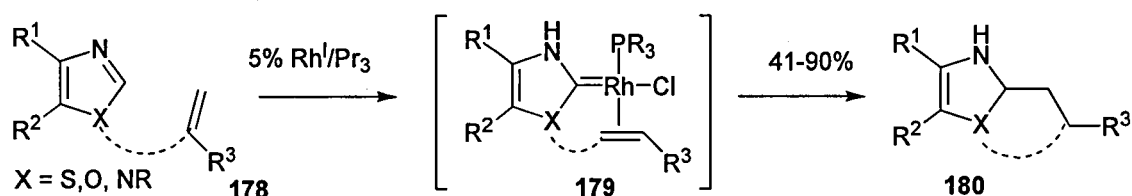


Figure 17. Other isolated rutaecarpine and evodiamine analogues.

1.12 Synthetic developments in quinazoline and quinazolinone chemistry

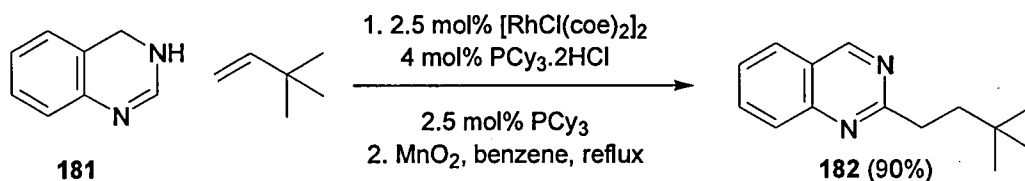
There is an expanding interest in quinazolines and quinazolinones and thus, new synthetic methodology is growing rapidly in this field. Some of these novel approaches to quinazoline and quinazolinone synthesis are now discussed.

Bergman *et al.* recently demonstrated a novel rhodium(I) catalysed route involving unactivated alkene additions to 3,4-dihydroquinazolines (scheme 52).⁶⁰ Both inter and intramolecular couplings from similar heterocycles **178** had been previously carried out by the group. It was proposed that the reaction proceeds *via* a catalytic-substrate, complexed with the aromatic heterocycle **179**. This could occur through rhodium acting as a *N*-heterocyclic carbene ligand. Once the alkene is complexed to the Rh, heterocyclic coupling to the alkene **180** can occur.



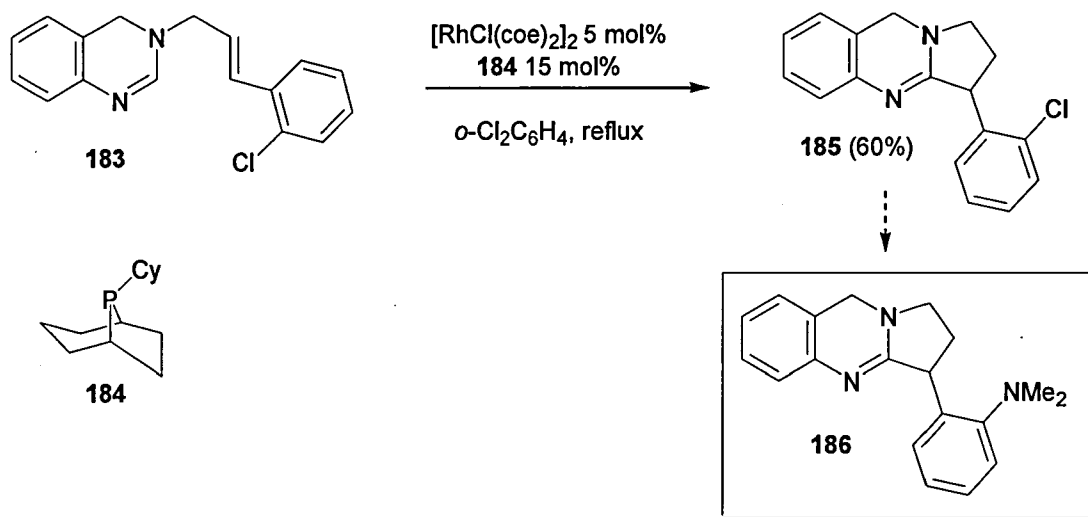
Scheme 52. Rhodium(I) catalysis route to quinazolines.

By coupling the 3,4-dihydroquinazoline **181** with a range of alkenes, quinazoline products like **182** were formed in good yield (scheme 53). An oxidative workup using MnO_2 was required.



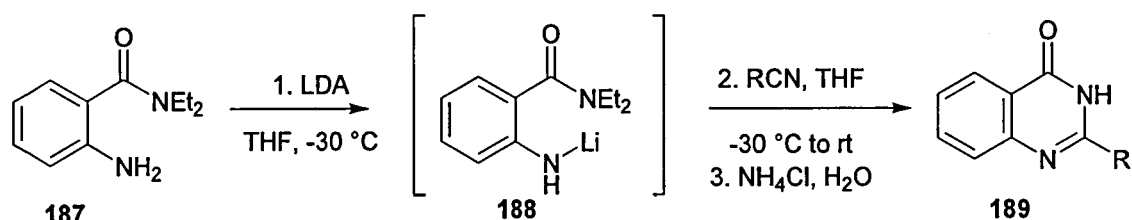
Scheme 53. Alkene coupling onto quinazoline using rhodium.

The intramolecular reaction of quinazoline **183** underwent Rh(I) cyclisation to tricyclic quinazoline **185** in good yield (scheme 54). Further elaboration of this product then lead to the natural product vasicoline **186**.



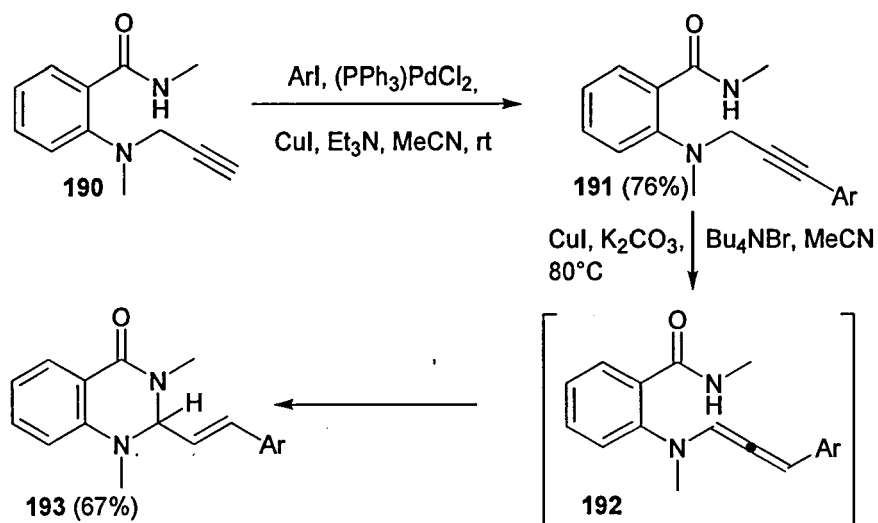
Scheme 54. Intramolecular alkene coupling to vasicoline.

Couture *et al.* have used nitriles and lithiated 2-aminobenzamides to form 2-aryl and 2-alkylquinazolin-4-ones **189** (scheme 55).⁶¹ It was shown that anthranilamide **187** forms the lithium 2-(diethylaminocarbonyl)anilide **188** species which reacts rapidly with the appropriate nitrile. Even for alkyl nitriles containing an acidic α -proton, conversion was good. One may have expected that an acidic α -proton could undergo a reaction with the lithium intermediate. Couture demonstrated a large range of alkyl and aryl nitriles were compatible with this reaction and so allows a very simple route to 2-aryl and 2-alkylquinazolin-4-ones **189**.



Scheme 55. Use of lithiated 2-aminobenzamides in quinazolinone synthesis.

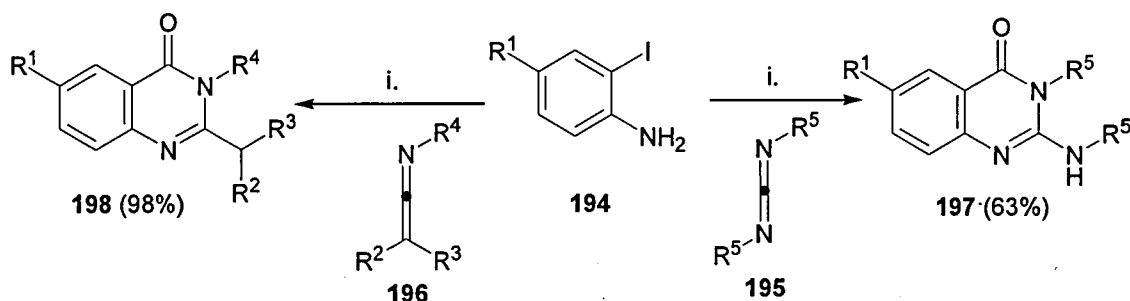
Kundu and Chaudhuri have developed a very mild method using copper catalysis in synthesis of C-2 substituted quinazolinones (scheme 56).⁶² The terminal alkyne **190** was initially reacted with aryl iodides under Sonogashira-Hagihara conditions to yield the alkyne **191**. The substituted alkyne **191** then underwent a highly regio and stereo selective reaction in the presence of CuI, K_2CO_3 and $n\text{-Bu}_4\text{NBr}$ in acetonitrile to yield the quinazolinone **193**. *E*-Stereochemistry was observed at the vinylic group. The proposed CuI mechanism suggests the alkyne **191** can rearrange to form the allene **192**. Attack by the amide nitrogen then leads to ring closure.



Scheme 56. Palladium/copper catalysed cyclisation quinazolinone synthesis.

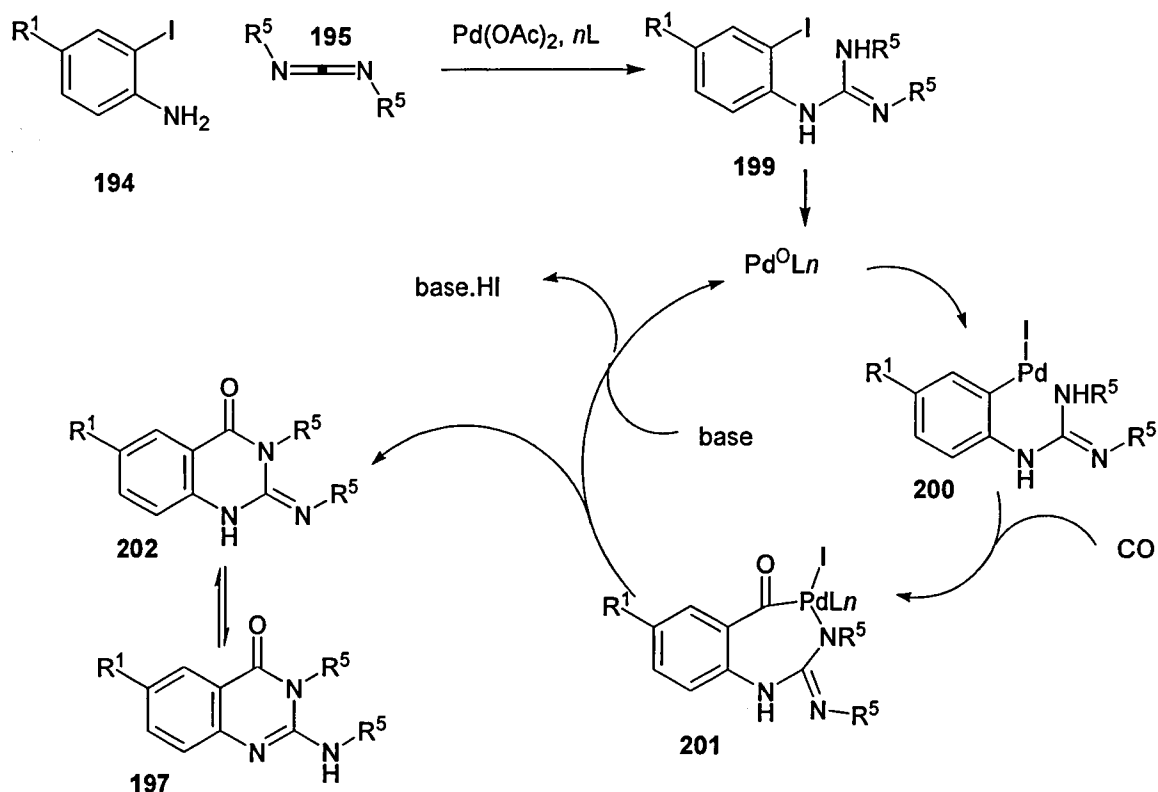
Larksarp and Alper have developed a Pd system for the carbonylation of the *o*-iodoanilines **194** (scheme 57).⁶³ Under an atmosphere of CO, the carbodiimide **195** and the ketenimine **196** were found to react with *o*-iodoanilines to form either the 2-amino quinazolinones **197** or the 2-alkyl quinazolinones **198**. The reaction tolerated hydroxy and nitrile groups on the *o*-

iodoaniline **194** (R^1), but not electron donating groups. There was found to be some sensitivity issues regarding the substitution of carbodiimide **195** ketenimine **196**.



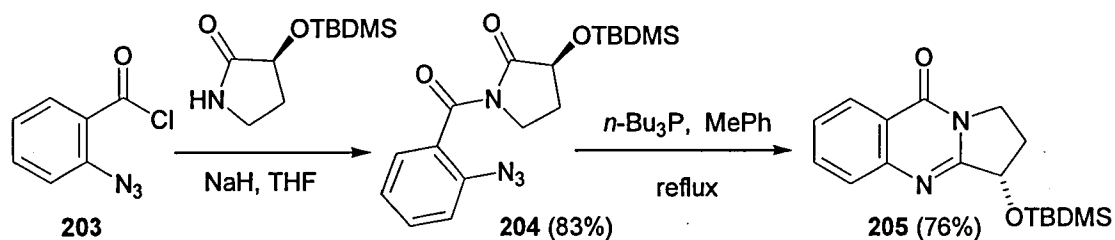
Scheme 57. Palladium catalysed cyclocarbonylation to quinazolinones; i) CO, Pd(OAc)₂, dppf, THF, K₂CO₃, 100 °C.

A mechanism was proposed for the reaction of the carbodiimide **195** and can easily be considered analogous for the ketenimine **196** (scheme 58).⁶³ Initially the *o*-iodoaniline **194** and the carbodiimide **195** form the guanidine intermediate **199**. Analogously in the case of the reaction with ketenimine **196** one of two amidine intermediates can be formed. Oxidative addition of Pd(0) to the C-I bond gives the intermediate palladium complex **200**. Insertion of carbon monoxide and coordination of NHPH could give rise to the palladium carbocycle **202**. This could be followed by reductive elimination forming the 2-imine quinazolinone **202**, which could rearrange to the more stable 2-amino quinazolinone **197**.



Scheme 58. Proposed catalytic cycle for Pd(0) formation of quinazolinones.

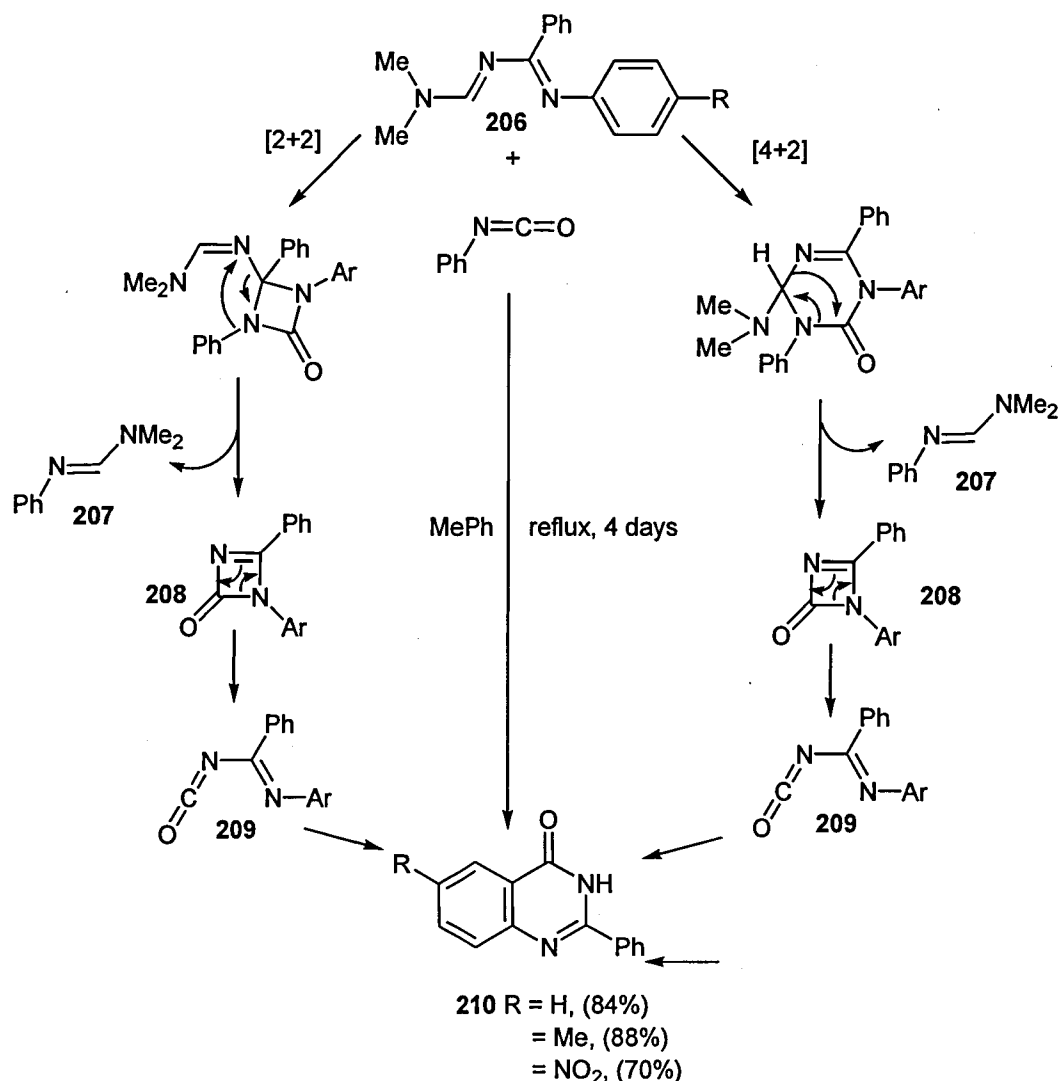
The intramolecular aza-Staudinger-Wittig reaction has lent itself well to heterocyclic synthesis.⁶⁴ Eguchi *et al.* have increased the scope of this reaction by applying it in quinazolinone synthesis (scheme 59).⁶⁵ From condensation of *o*-azidobenzoyl chloride **203** with a lactam, Eguchi formed the key azide intermediate **204**. The intramolecular aza-Staudinger-Wittig reaction was carried out using tri-*n*-butylphosphine. The silyl protected *l*-vasicinone quinazolinone **205** was obtained in excellent yield.



Scheme 59. Aza-Staudinger-Wittig route to *l*-vasicinone quinazolinone.

Hetero Diels Alder approaches to quinazolinones have been carried out by Croce *et al.* (scheme 60).⁶⁶ The yields of 2-substituted quinazolinones such as **210** were good for a range

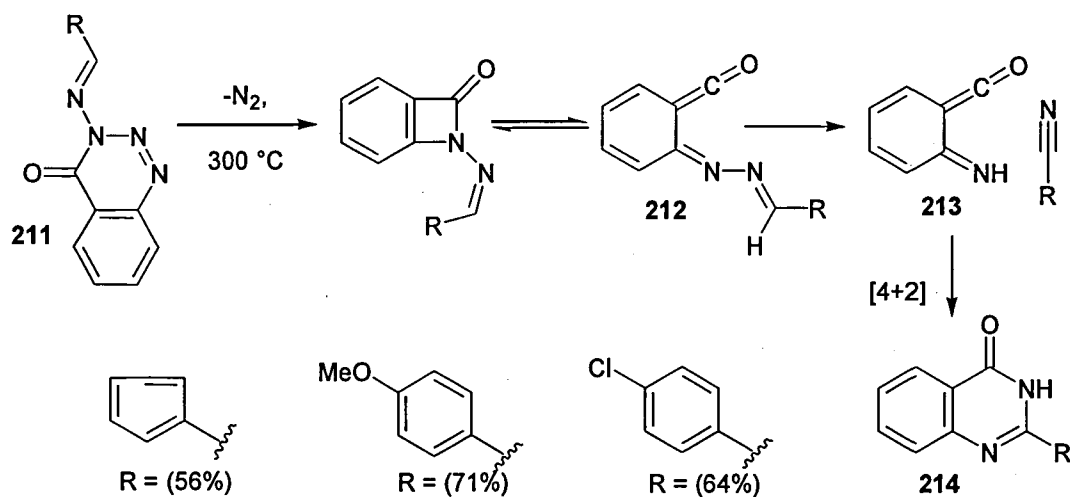
of the dienes **206**. The presence of the electron rich dimethyl amino group on the diene **206** was crucial in facilitating the elimination of the *N,N*-dimethylformamidine **207** as a side product by destabilizing the cycloaddition adduct. The authors recognised the mechanism of this reaction could proceed *via* an initial [2+2] cycloaddition instead of the [4+2] routes. Either route can go through a 4-membered ring diazidinone **208** which could open up to the imidoisocyanates **209**. These are well known to thermally cyclise to form quinazolinones.



Scheme 60. Diels Alder approach to quinazolinone products.

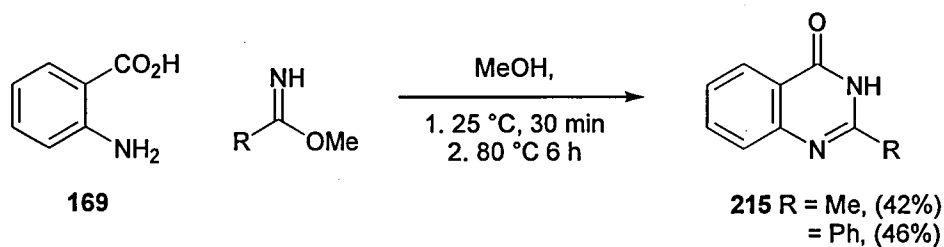
Simple thermolysis of the benzotriazin-4-ones **211** has been used by Smalley *et al.* in the synthesis of the 2-arylquinazolinones **214** (scheme 61).⁶⁷ During the thermolysis of benzotriazin-4-ones loss of nitrogen is observed followed by a 1,3-hydrogen shift in the intermediate **212** with the loss of aryl cyanide. The aryl cyanide then participates in a [4+2]

cycloaddition of the imino ketene **213**. The reaction tolerated a wide range of substituted aryl substituents in good yield.



Scheme 61. [4+2] Cycloaddition route to quinazolinones from benzotriazin-4-ones.

A number of synthetic strategies to quinazolinone can be started from anthranilic acid **169**. Much of this work was started in the 1960's by Reid *et al.*⁶⁸ Continuation of this work has been carried out by Guiry *et al.* who successfully reacted a range of alkyl and aryl imidates with anthranilic acid to form the 2-substituted quinazolinones **215** in good yield (scheme 62).⁶⁹ The imidates were prepared by reacting nitriles with gaseous HCl in MeOH. These imidate salts were then neutralized by an equivalent of base. Although not high yielding this route allows access to rapid synthesis of simple quinazolinone from cheap starting materials.



Scheme 62. Imidate condensation with anthranilic acid to form quinazolinones.

1.13 Conclusion

This introduction has covered a variety of chemistry. An overview into radical reactions and the types of reagents commonly used have been shown. This has been followed by a review of some notable radical cyclisations to form heterocycles, some of which can be described as aromatic homolytic substitution reaction. A summary of common quinazoline and quinazolinone natural products and drugs has been followed by a discussion of the biosynthesis of some of these natural products. Finally time has been taken to demonstrate some of the other approaches chemists have used to quinazolinone and quinazoline synthesis.

1.14 Project Objective

Heterocyclic syntheses have been of great interest for many years to organic chemists. Many different heterocyclic systems are seen within natural product compounds isolated from plants and animal species. The pharmaceutical industries rely on seeking inspiration from such natural products to develop new drug candidates. Some heterocyclic systems are considered “privileged” because of their ability to bind to many types of receptor sites in the human body. One such “privileged” heterocyclic structure is the 3*H*-quinazolin-4-one system. There are a great number of natural products that contain this moiety. To date there are only sporadic reports of free radical chemistry being employed as a synthetic tool in the syntheses of such natural products.

The aim was to develop a new synthetic methodology to apply to the syntheses of our chosen quinazolinone natural product targets. We have attempted and completed the synthesis of a number of biologically active 3*H*-quinazolin-4-one targets *via* radical chemistry. The feasibility of radical cyclisation onto the C-2 position of the quinazolinone template was tested, and used as the basis for this work. Determination of mechanisms of these radical reactions has been carried out. Where possible non-tin radical reagents were used to avoid the toxicity and purification issues surrounding tin reagents.

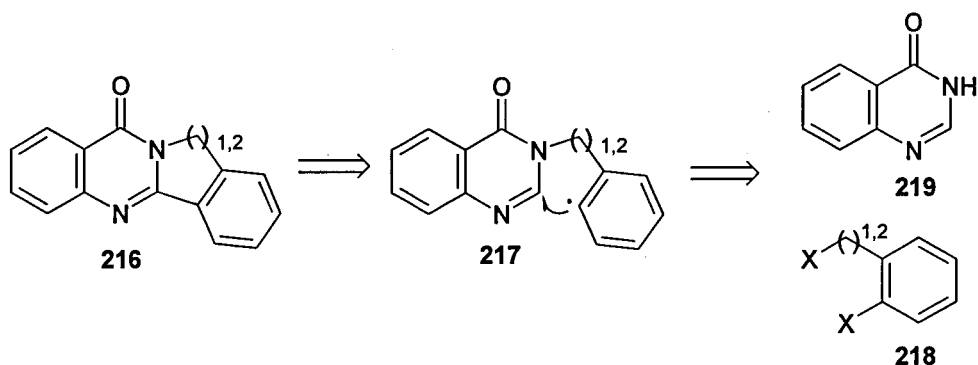
Pharmaceutical companies are particularly interested in heterocyclic building blocks, as they can apply combinatorial chemical methods to access new compound libraries. We were keen to make use of a C-2 indole radical building block of which there are reports in the literature. We also felt preparation of a C-2 radical quinazolinone building block would be of much interest. At our initial outset, there were no reports in the literature of C-2 radical quinazolinone building blocks. We hoped this work would open a new door to the syntheses of many quinazolinone natural products using radical or palladium chemistry.

Chapter 2. Aryl and Alkyl radical cyclisations onto 3*H*-quinazolin-4-one

In this chapter work describing investigations of aryl radical cyclisations onto the 3*H*-quinazolinone moiety are presented. This will be followed by a discussion of alkyl radical cyclisations carried out which led to the synthesis of the two quinazolinone natural products deoxyvasicinone and mackinazolinone. A brief introduction to each natural product is given. Unsuccessful cyclisations of organometallic species onto the 3*H*-quinazolin-4-one template are also shown.

2.1 Aryl radical cyclisations onto 3*H*-quinazolin-4-one

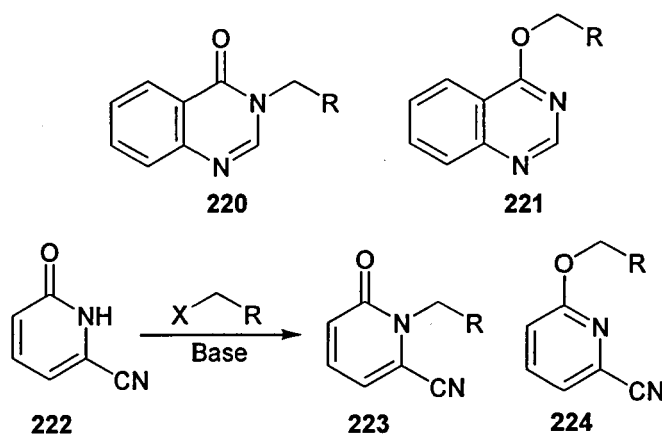
Before undertaking the synthesis of the quinazolin-4-one derived natural products, investigation of simple aryl radical cyclisations onto the C-2 position of 3*H*-quinazolin-4-one was carried out. It was hoped to rapidly access quinazolinone tetracycles **216** (scheme 63). The first aim was to learn more about the reactivity of aryl radicals **217** towards the commercially available 3*H*-quinazolin-4-one **219**. The required aryl building blocks **218** had been prepared previously.⁷⁰ A number of examples using these building blocks in aryl radical cyclisations are detailed in the introduction. This work has now been extended.



Scheme 63. Retrosynthesis of quinazolinones **216** using aryl radical cyclisations.

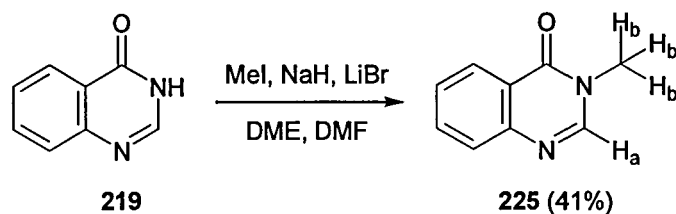
The first concern was to avoid the competition between *O*- and *N*-alkylation and to develop a methodology to obtain selective alkylation onto the *N*-3 position of the 3*H*-quinazolin-4-one **219** to yield quinazolinone **220** and not quinazolinone **221**.

Alkylation on *N*-1 is possible but there are few reports indicating that this regioisomer is favourable. Previous work has shown that alkylations of pyridinone **222** yielded *O*-substituted pyridinones **224** and *N*-substituted pyridinones **223** (scheme 64).⁷¹ It was unclear whether this problem would be encountered for the alkylation of 3*H*-quinazolin-4-one **219**.



Scheme 64. Pyridinone alkylation problems.

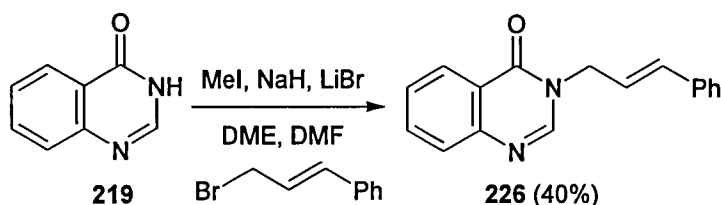
Alkylation of quinazolinones has been carried out in one-pot using lithium bromide, dry ethylene glycol dimethyl ether and NaH in DMF.⁷² Reports in the literature suggest that under these conditions, lithium can chelate to the oxygen atom, hence directing the alkylation towards *N*-3.⁷² The ethylene glycol dimethyl ether can bind to the lithium, increasing the steric hindrance, which should favour the alkylation onto *N*-3. Using these conditions, methylation of 3*H*-quinazolin-4-one **219** (scheme 65) gave 3-methyl-3*H*-quinazolin-4-one **225**. Yields for 3*H*-quinazolin-4-one alkylation reported in the literature are rarely greater than 60%.



Scheme 65.

Difficulties were encountered in distinguishing whether alkylation had taken place on the nitrogen or the oxygen atom using standard NMR spectroscopic techniques. In theory, the IR spectrum of the final product should have shown the disappearance of the NH bond in the wavelength range of $\approx 3000\text{ cm}^{-1}$. However, the NH and OH bond wavelengths in the IR spectrum of the starting material were close, and therefore it was not distinguishable which heteroatom was alkylated in the product. A NOE NMR spectroscopic experiment was carried out. The three hydrogen atoms (H_b) on the methyl group of quinazolinone **225** were irradiated and a slight change in intensity was noticed for the signal of the hydrogen atom on the C-2 position (H_a) of 3-methyl-3*H*-quinazolin-4-one **225** suggesting that the product was alkylated at *N*-3.

The alkylation reaction using cinnamyl bromide was carried out and quinazolinone **226** was obtained (scheme 66). A similar ^1H NMR spectroscopic experiment was carried out to prove the structure. The alkylation of *N*-1 can be ruled out. Previous work has shown that if alkylation occurs on *N*-1 there is a strong NOE correlation between the CH_2 hydrogen atoms and the hydrogen atom at C-8 **227** (figure 18).⁷³ Analysis of the NOE spectra of quinazolinones **225** and **226** showed no such correlation. The synthesis of quinazolinone **227** was undertaken by an alternative route involving ring synthesis to rule out the formation of side reaction products from the radical cascade approach to luotonin A (scheme 93).



Scheme 66.

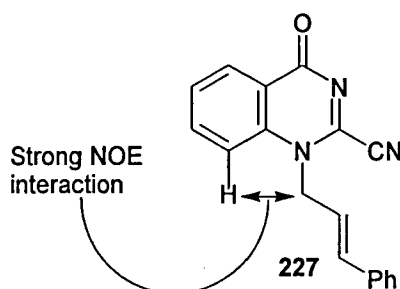
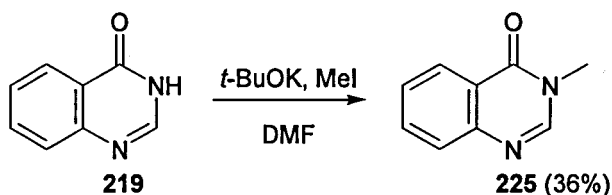


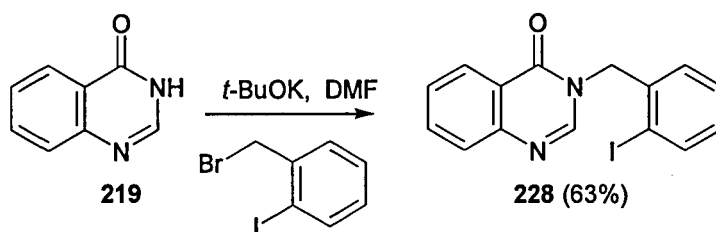
Figure 18.

The use of *t*-BuOK as a base was reported to give selective alkylation onto *N*-3 of 3*H*-quinazolin-4-one **219**.⁷⁴ This procedure did not require any additional reagents such as LiBr. The alkylation was carried out using methyl iodide and 3-methyl-3*H*-quinazolin-4-one, **225** was obtained in good yield (scheme 67). The *O*-alkylated product was also isolated in a low yield (less than 5%). As a result, it was chosen to use the latter method instead of the previously described lithium bromide reaction.



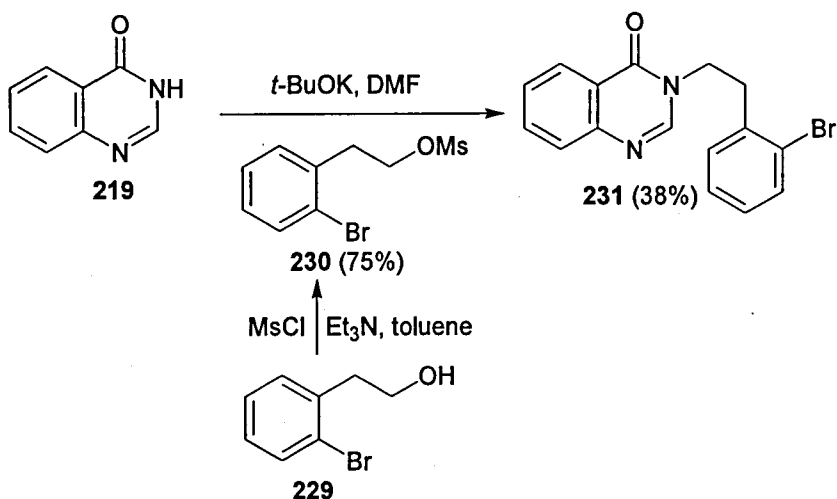
Scheme 67.

Attention was then turned to the synthesis of the first aryl radical precursors (scheme 68). Alkylation of 3*H*-quinazolin-4-one **219** using 2-iodobenzyl bromide proceeded in good yield giving the desired quinazolinone **228**.



Scheme 68. Synthesis of the aryl radical precursor.

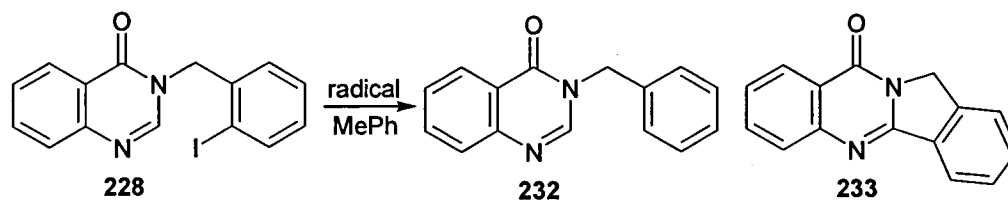
In order to prepare the six-membered ring precursor **231**, 2-(2-bromophenyl)ethanol **229** was converted to the mesylate **230** (scheme 69). However, alkylation of the quinazolinone **219** using the mesylate **230** did not proceed in as high a yield as the synthesis of the quinazolinone **228**.



Scheme 69.

The initial radical investigations began with the quinazolinone **228**. The radical cyclisations were investigated using Bu_3SnH and a range of initiators (table 3). No traces of the desired five-membered cyclised quinazolinone **233** were observed and the only product isolated was the reduced quinazolinone **232**.

Table 3. Radical reactions of quinazolinone **228** with Bu_3SnH .

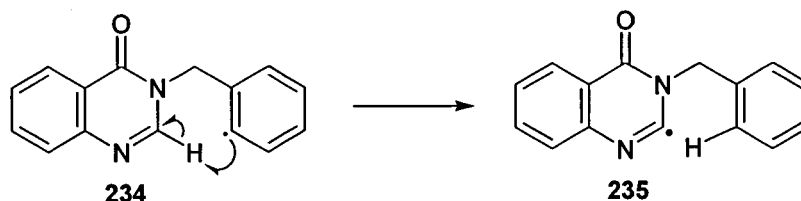


Initiator (equiv.)	Radical reagent (equiv.)	Reflux	Product
Et_3B (0.1)	Bu_3SnH (fast) (2.0)	No	232 (96%)
Et_3B (0.1)	Bu_3SnH (slow) (2.0)	No	232 (30%)
AIBN (2.0)	Bu_3SnH (slow) (2.0)	Yes	232 (45%)

Initially, triethylborane was chosen as the initiator. The advantages of triethylborane over AIBN have already been described previously.⁶ When triethylborane is used, the solvent was purged for 30 min with nitrogen to remove any traces of oxygen. Once the triethylborane is added, a needle was placed through the septum on the flask and atmospheric oxygen allowed to re-enter. It is not known how quickly the

triethylborane is consumed in these reactions. This depends on the rate of diffusion of oxygen through the needle into the vessel. In an attempt to slow down the rate of the ethyl radical generation from triethylborane, cotton wool was placed in the needle head. During the course of the work, additional triethylborane was added to radical reactions at different time intervals. The reaction mixtures were purged for 30 min with nitrogen before additional triethylborane was added, to remove unwanted oxygen which had re-entered the reaction vessel.

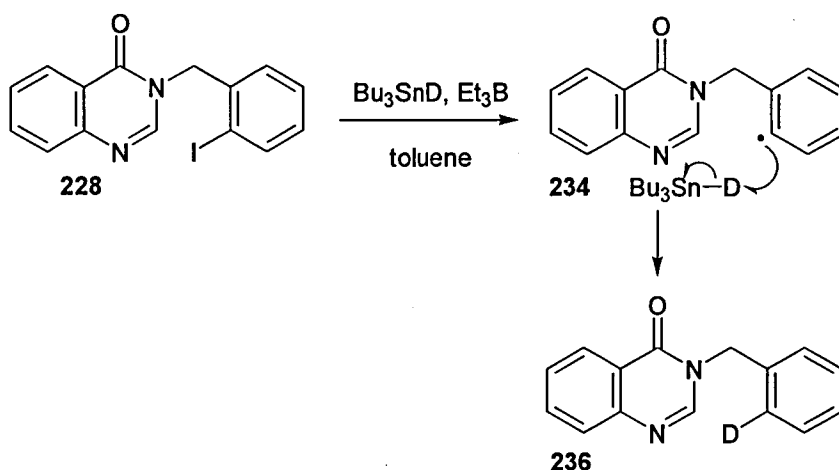
These results show that the rate of H-abstraction (k_H) by the intermediate aryl radical from Bu_3SnH is faster than the rate of cyclisation (k_{Cyc}). Hydrogen atom is most likely extracted from Bu_3SnH , however a possible explanation for the lack of cyclisation was that a 1,5-hydrogen shift could be occurring in radical **234** (scheme 70). If a 1,5-hydrogen shift had taken place, to form the radical **235** this radical could then have abstracted a hydrogen atom from Bu_3SnH or another molecule within the reaction mixture.



Scheme 70. Possible 1,5-H abstraction.

In order to determine whether this 1,5-hydrogen shift was taking place, a simple experiment was devised. The quinazolinone **228** was treated with Bu_3SnD in place of Bu_3SnH (scheme 71). The ^1H NMR spectrum showed that the hydrogen atom on the C-2 position of the quinazolinone **228** was still present on the reduced product (as were the CH_2 protons). It therefore appeared as though the intermediate radical **234** had abstracted a deuterium atom from Bu_3SnD . We hoped that the ^{13}C NMR spectrum of the quinazolinone **236** would indicate a triplet for the carbon bearing the deuterium atom. However, even after increasing the number of scans for the ^{13}C NMR analysis, this triplet was not detected. Mass spectral analysis confirmed the formation of the quinazolinone **236**. The major benzyl ion produced had an increased mass of 92,

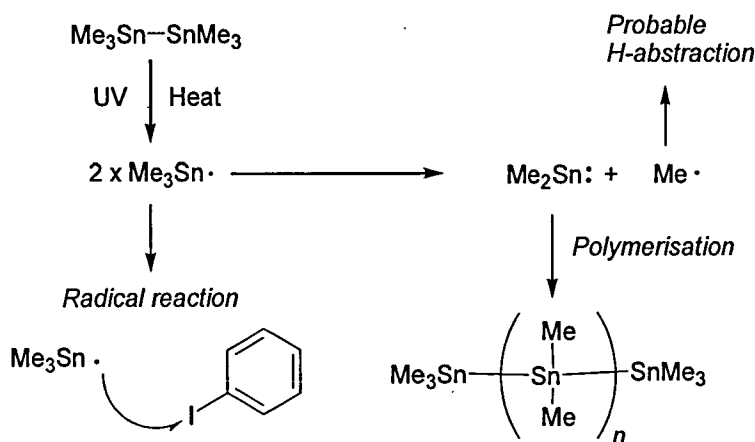
indicating a deuterium atom replacing a hydrogen atom on this fragment. This experiment eliminated the possibility of a 1,5-hydrogen shift (scheme 70).



Scheme 71.

Once it had been established that $k_{\text{H}} \gg k_{\text{Cyc}}$, it was chosen to use reagents where the rate of hydrogen abstraction would be lower than that for Bu_3SnH . The first reagent used was TTMSS, which is a poorer H-donor than Bu_3SnH . Again, triethylborane was used as the initiator. However, only the reduced quinazolinone **232** (35%) was isolated, although GC-MS did reveal a trace amount of a compound with a molecular ion corresponding to the cyclised product.

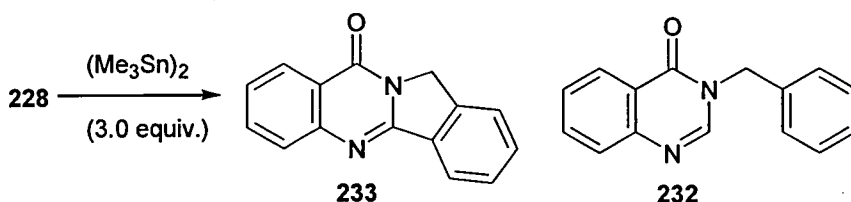
To minimise the opportunity for the intermediate phenyl radical to abstract a hydrogen atom, it was decided to use hexamethylditin $[(\text{Me}_3\text{Sn})_2]$. The proposed mechanism of this reagent is shown below (scheme 72). Homolysis of the tin-tin bond is caused by heat and light irradiation, leading to the formation of $\text{Me}_3\text{Sn}\cdot$ radicals, which can then go on to carry out the desired radical reaction. Alternatively, it can break down to form a stanylene and $\text{Me}\cdot$ radical. In reactions where homolytic aromatic substitution takes place, $\text{Me}\cdot$ radicals have been suggested to facilitate the hydrogen abstraction step.⁷⁵ The dimethyl tin polymer is often seen as a sticky yellow residue on the inside of the reaction vessel.



Scheme 72. Mechanism of $(\text{Me}_3\text{Sn})_2$ homolysis.

The reaction between the quinazolinone **228** and $(\text{Me}_3\text{Sn})_2$ showed only one spot by TLC (table 4) but GC-MS analysis of the crude reaction mixture showed the reduced and cyclised product in a ratio of ca. 4:1. A closer inspection of the ^1H NMR spectra also revealed that quinazolinones **233** and **232** were present. The two compounds could not be separated using column chromatography (attempts were made using silica and alumina gel as absorbent). However, having already obtained a clean ^1H NMR spectrum of the reduced compound, calculation for the reactions yields could be carried out.

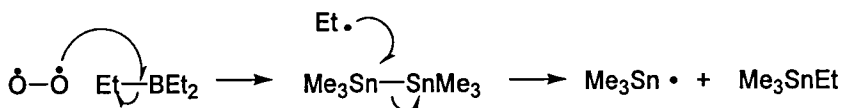
Table 4. Radical reaction between 3-(2-iodobenzyl)-3*H*-quinazolin-4-one **228** and $(\text{Me}_3\text{Sn})_2$.



Initiator	Reflux	Solvent	Product
hν	Yes	<i>t</i> -Butylbenzene	233 (18%) 232 (65%)
Et_3B	No	<i>t</i> -Butylbenzene	Trace 233

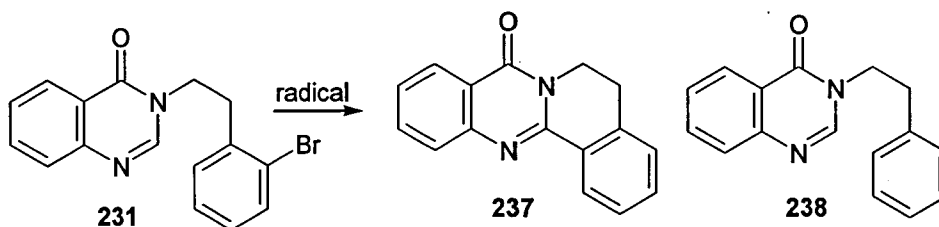
It is not known whether Et_3B can be used to initiate the $(\text{Me}_3\text{Sn})_2$ reaction. The bond dissociation constants for Sn-Sn bonds are similar to those of Sn-Et. It seemed valuable to test whether triethylborane could be used to initiate the homolysis of the

Sn-Sn bond. So far, there is no mention in the literature of triethylborane and $(\text{Me}_3\text{Sn})_2$ being used together (scheme 73). A ^1H NMR spectrum of the reaction using Et_3B and $(\text{Me}_3\text{Sn})_2$ showed possible cyclised product **233** but in a trace amount. A reaction was also attempted using only triethylborane, with no $(\text{Me}_3\text{Sn})_2$, heat or light irradiation. This resulted in only starting material being recovered which, was expected, due to the high bond strength of the aryl-halide bond.



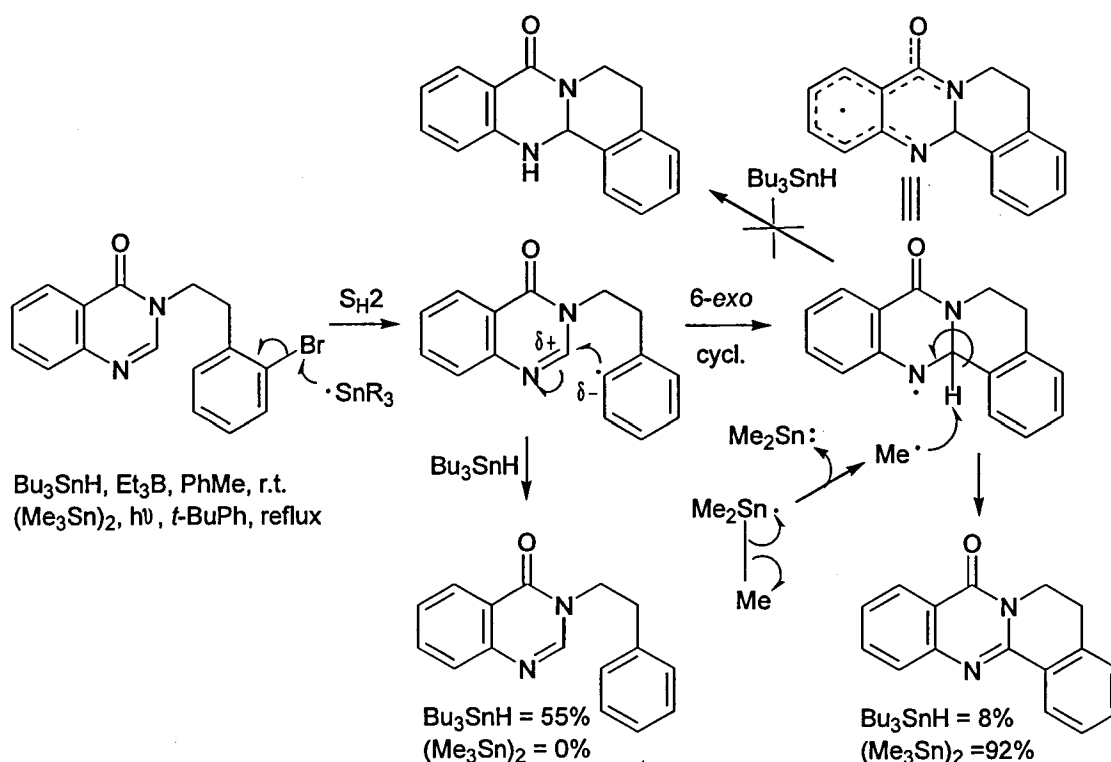
Scheme 73. Possible mechanism for the formation of the radical $\text{Me}_3\text{Sn}\cdot$.

Having obtained some cyclised product, attention was turned to the radical cyclisation of the quinazolinone **231** (scheme 74). From the initial studies it was shown that H-abstraction of intermediate aryl radical was favoured. Therefore, the cyclisation using $(\text{Me}_3\text{Sn})_2$ was attempted first. An excellent yield of cyclised quinazolinone **237** was obtained with none of the reduced quinazolinone **238**. The reaction was also carried out using fast $\text{Bu}_3\text{SnH}/\text{Et}_3\text{B}$ conditions, which gave the cyclised quinazolinone **237** (8%) and the reduced quinazolinone **238** (50%). It was surprising that the quinazolinone **237** was obtained using these conditions. The increased yield and ease of cyclisation here can be attributed to ring strain. The amount of ring strain for the five-membered ring is higher than the six-membered ring. This is highlighted by the ability of the quinazolinone **231** to cyclise using Bu_3SnH .



Scheme 74. i, $(\text{Me}_3\text{Sn})_2$, *t*-butylbenzene heated under reflux and $h\nu$; cyclised **237** (92%) and reduced **238** (0%); ii, $\text{Bu}_3\text{SnH}/\text{Et}_3\text{B}$ and toluene; cyclised **237** (8%) and reduced **238** (50%).

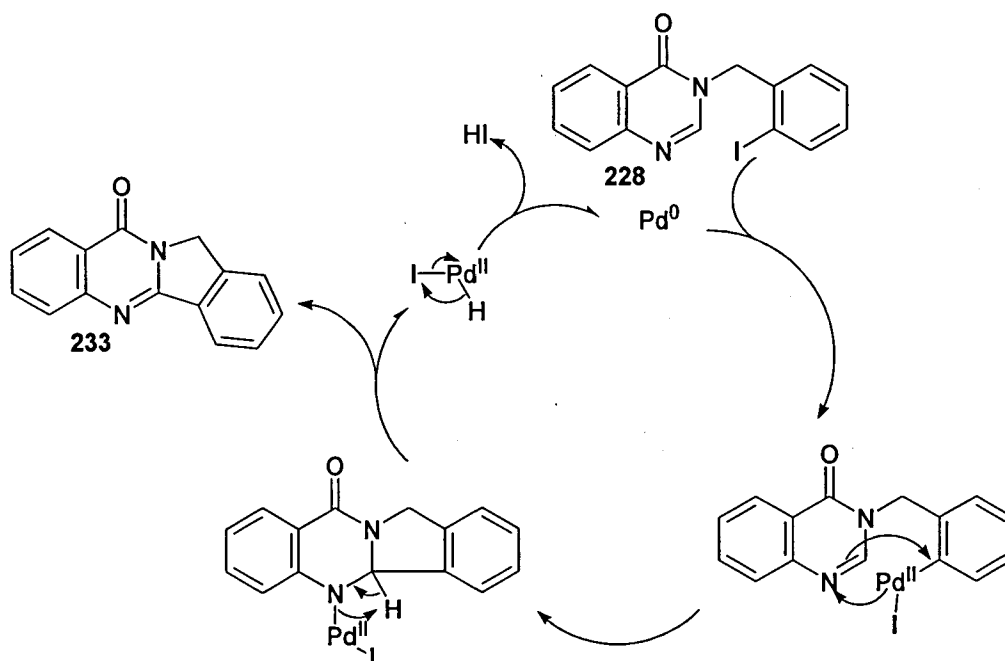
The mechanism for this reaction is shown (scheme 75). Phenyl radicals are slightly nucleophilic and attack the electron deficient carbon of the imine. The reaction can be regarded as a 6-*exo* radical cyclisation onto an imine leading to an aminyl radical. A disproportionation reaction does not occur. The yield of cyclisation product was high when using $(\text{Me}_3\text{Sn})_2$. The stability of the π -radical means the unpaired electron is delocalised over a large part of the molecule. Other species that could abstract the hydrogen include $\text{Me}_3\text{SnOO}\cdot$ ($\text{Me}_3\text{Sn}\cdot + \text{O}_2$ always present in trace quantities). The strong drive for rearomatisation leads to the high yield of cyclisation using $(\text{Me}_3\text{Sn})_2$.



Scheme 75. Mechanism of 6-*exo* aryl radical cyclisation onto 3*H*-quinazolin-4-one.

2.2 Palladium cyclisations onto 3*H*-quinazolin-4-one

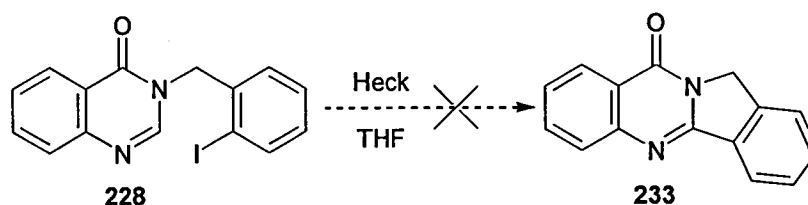
Palladium(0) catalysed cyclisations on quinazolinone **228** should also be possible. A Heck type reaction could be used to form the desired cyclised tetracycle **233** (scheme 76).



Scheme 76. Proposed Heck reaction on 3-(2-iodobenzyl)-3*H*-quinazolin-4-one **228**.

There are only a few examples of Heck reactions onto imines reported in the literature.⁷⁶ Therefore, it was considered an investigation would be novel. Harayama has shown that Cy_3P is an excellent ligand for Heck reactions onto quinazolinones.⁷⁴ Despite trying a variety of conditions the tetracycle **233** could not be observed or isolated. In every attempt the starting material was recovered (table 5).

Table 5. Attempted Pd(0) cyclisations

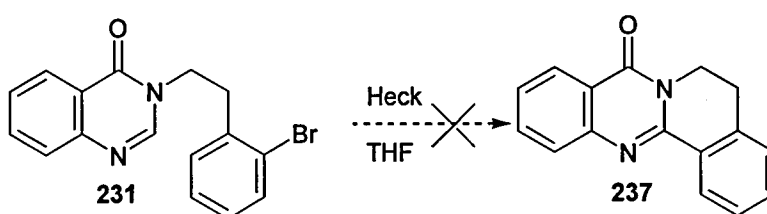


Pd source	Ligand	Base (2.0 equiv.)	Reflux
$\text{Pd}(\text{OAc})_2$ (5%)	PPh_3 (10%)	KOAc	Yes
$\text{Pd}(\text{OAc})_2$ (5%)	<i>n</i> - Bu_3P (10%)	KOAc	Yes
$\text{Pd}(\text{OAc})_2$ (5%)	PCy_3 (10%)	KOAc	Yes
$\text{Pd}(\text{OAc})_2$ (5%)	PCy_3 (10%)	K_2CO_3	Sealed tube
$\text{Pd}(\text{PPh}_3)_4$ (5%)	ZnBr_2 (as Lewis acid)	K_2CO_3	10 min*

* The reaction was carried out in a microwave reactor.

With no success in forming a five-membered ring, focus was turned to the quinazolinone **231** (table 6). The Cy₃P ligand is extremely air sensitive and a ³¹P NMR spectrum of the ligand revealed that it was about 20% oxidised. The amount of Cy₃P added was increased from 10% to 15%. Different bases, solvents, Pd sources and ligands were all investigated. These extensive investigations only lead to starting material being recovered and the tetracycle **233** was not isolated which was dissappointing.

Table 6. Attempted Heck reactions of quinazolinone **231**.



Pd source	Ligand	Base (2.0 equiv.)	Reflux
Pd(OAc) ₂ (5%)	PCy ₃ (10%)	KOAc	Yes
Pd(OAc) ₂ (5%)	PCy ₃ (15%)	KOAc	Yes
Pd(OAc) ₂ (5%) *	PCy ₃ (15%)	KOAc	60 °C
Pd(OAc) ₂ (5%)	PCy ₃ (15%)	K ₂ CO ₃	Yes
Pd(PPh ₃) ₄ (5%)	Dppe (10%)	KOAc	Yes
Pd(PPh ₃) ₄ (5%)	None	KOAc	Yes
Pd(OAc) ₂ (5%)	PCy ₃ (10%)	K ₂ CO ₃	Sealed tube

*The reaction was carried out in DMF as solvent.

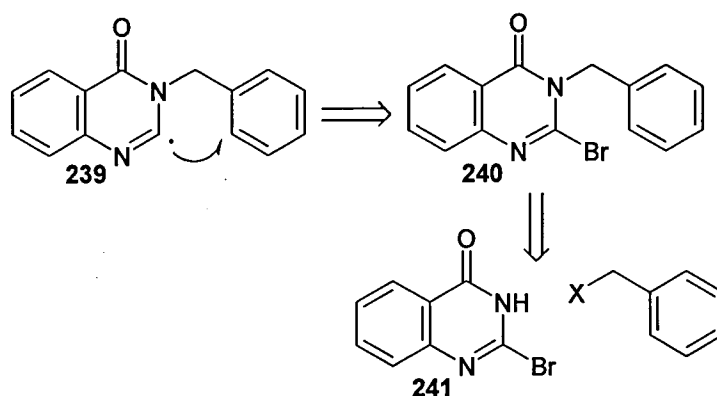
As only starting material was recovered, it suggested to us that the insertion of Pd(0) into the carbon-halide bond was not happening and that the Pd(0) may coordinate to the N-1 of the quinazolin-4-one to form a carbene type complex. This may compete with the initial oxidative insertion into the carbon-halide bond. To test this hypothesis, a reaction was carried out using stoichiometric amounts of quinazolinone **231** and Pd(PPh₃)₄ in deuterated DMF. A blank ¹H NMR spectrum of the catalyst enabled us to determine where the phenyl proton signal of the catalyst came in the ¹H NMR spectrum. No additional ligands had to be added as Pd(PPh₃)₄ is a source of Pd(0). The reaction was heated, and ¹H NMR spectra were taken of the crude reaction mixture at regular intervals. It was hoped to see shifting of signals to indicate Pd(0)

insertion into the carbon-halide bond or nitrogen coordination. However, no change in any signals was observed and therefore it could not be explained why cyclisation was not occurring using Pd(0).

It was decided to end these Pd investigations in order to follow the initial radical work. However the area is still open to more investigation and further catalysts, ligands, bases and solvents could be tested.

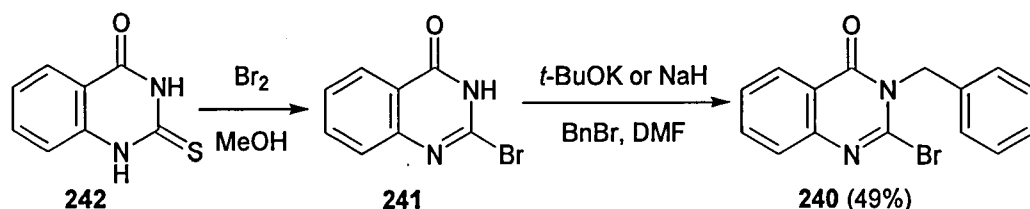
2.3 Radical cyclisations from 3*H*-quinazolin-4-one onto aryl groups

Having carried out radical cyclisations onto the quinazolinone moiety, it was decided to determine if the quinazolinone radical **239** could be cyclised onto aryl groups (scheme 77). The aim was to form a radical at the C-2 position of the 2-bromo substituted quinazolin-4-one **240**. First, a synthesis of the 2-bromo-3*H*-quinazolin-4-one **241** building block needed to be developed.



Scheme 77. Retrosynthesis of radical cyclisation using a radical precursor from the 3*H*-quinazolin-4-one.

A synthesis of the 2-bromo-3*H*-quinazolin-4-one building block **241** was developed involving treating the 2-mercapto-3*H*-quinazolin-4-one **242** with bromine. A detailed discussion of this building block, its uses and most importantly its limitations is reported in chapter 5. Firstly, the alkylation onto the *N*-3 position using benzyl bromide to yield the quinazolinone **240** was carried out (scheme 78). Only very limited *O*-alkylation was observed when *t*-BuOK or NaH were used and the *N*-alkylated quinazolinone **240** predominated.

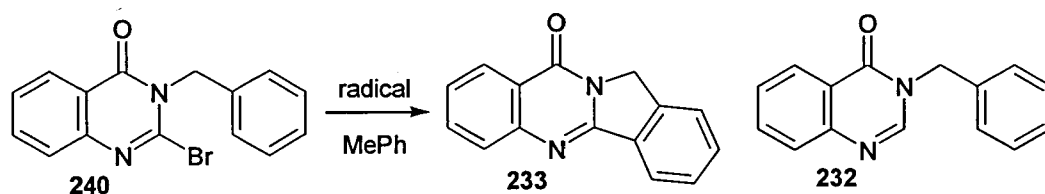


Scheme 78.

As already described, cyclised and reduced products were obtained from attempts to carry out 5-membered ring cyclisation onto the quinazolinone. The highest yield of cyclisation onto quinazolinone to form a five-membered ring was 18% alongside the reduced quinazolinone (65%). It was felt that a comparison of yields obtained *via* both radical methodologies would be interesting.

Initially the radical reaction was carried out using slow addition of $\text{Bu}_3\text{SnH}/\text{Et}_3\text{B}$ (table 7). As previously observed, only the reduced quinazolinone **232** was isolated. Slow addition of $\text{Bu}_3\text{GeH}/\text{Et}_3\text{B}$ was then attempted. The rate of hydrogen abstraction from Bu_3GeH is about twenty times slower than from Bu_3SnH . Again, only the reduced quinazolinone **232** was obtained. The use of $(\text{Me}_3\text{Sn})_2$ yielded an inseparable mixture of the cyclised quinazolinone **233** (27%) and the reduced quinazolinone **232** (41%). The overall recovery of the two products is similar to the recovery obtained from the cyclisation of **228**.

Table 7. Radical cyclisations of quinazolinone **240**.

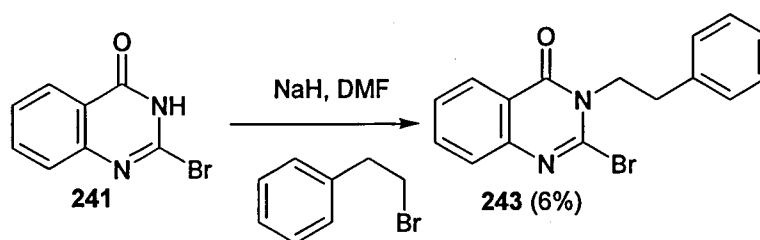


Radical reagent (equiv.)	Initiator (equiv.)	Product
Bu_3SnH (2.2)	Et_3B (20)	232 (62%)
Bu_3GeH (2.2)	Et_3B (20)	232 (47%)
$(\text{Me}_3\text{Sn})_2$ (3.0) *	$h\nu$ and Δ	233 (27%) 232 (41%)

* The reaction was carried out using *t*-BuPh as solvent.

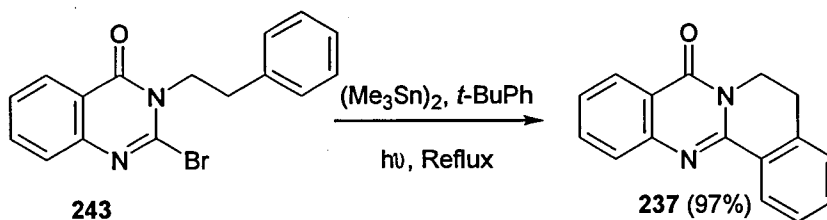
It was concluded that as before $k_H \gg k_{Cyc}$ and that sources of accessible hydrogen needed to be removed. An investigation of Pd chemistry with the precursor was not carried out given previous failures.

Attention was turned to the synthesis of the six-membered ring precursor **243** (scheme 79). Alkylation of 2-bromo-3*H*-quinazolin-4-one **241** with (2-bromoethyl)benzene gave the quinazolinone **243** in very low yield. An extensive discussion concerning the attempts to improve the yield of quinazolinone **243** is given in chapter 5.



Scheme 79. Synthesis of quinazolinone radical precursor.

Although only a limited amount of the quinazolinone **243** was obtained, the radical reaction was attempted (scheme 80). From previous experience, it was chosen to carry out the radical cyclisation using $(Me_3Sn)_2$. The reaction gave the cyclised quinazolinone **237** in a excellent yield. Other radical conditions or possible Pd(0) catalysed cyclisations could have been attempted but were precluded by the difficulties in preparing the precursor **243**.

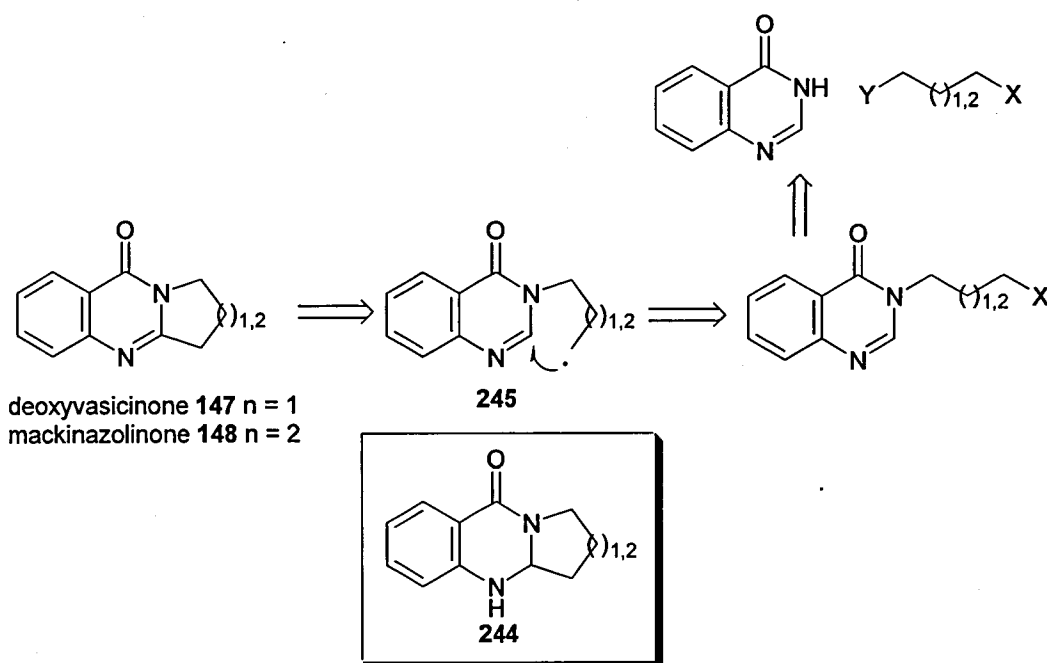


Scheme 80.

In this section, the competition between H-abstraction and aryl radical cyclisation onto the 3*H*-quinazolin-4-one has been observed. Cyclisation was favoured when using the reagent $(Me_3Sn)_2$ and reduction when Bu_3SnH was used.

2.4 Alkyl radical cyclisations onto 3*H*-quinazolin-4-one

The synthesis of deoxyvasicinone **147** and mackinazolinone **148** were attempted using an alkyl radical cyclisation onto the 3*H*-quinazolin-4-one template (scheme 81). The aim was to carry out alkyl radical cyclisations using the methodology described in the previous section for aryl radicals. It was not known whether, unlike the previous aryl radical cyclisations, any cyclised reduced quinazolinone **244** would also be recovered from these reactions.



Scheme 81. Planned retrosynthesis of deoxyvasicinone and mackinazolinone.

2.5 Introduction to deoxyvasicinone and mackinazolinone

Although neither compound has shown great biological activity, they are interesting synthetic targets. Deoxyvasicinone **147** is found in the seeds of the *Peganum harmala* plant and has been used as an antiseptic in Iraq (figure 19). Careful studies of the plant showed that the antimicrobial behaviour is predominantly due to the compound harmine **246** which is more potent than the deoxyvasicinone **147**, and is also found in the same plant.⁷⁷ However, deoxyvasicinone **147** is also of interest as it can be used as a precursor to vasicinone **247** which is a bronchodilator.⁷⁸

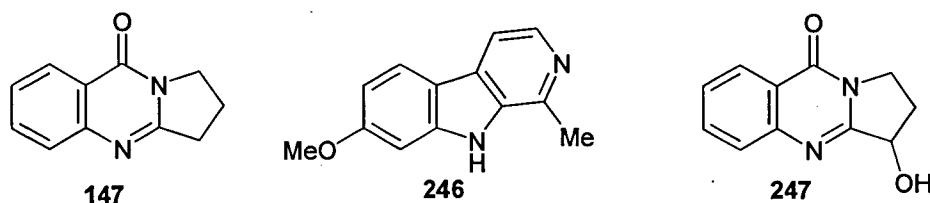
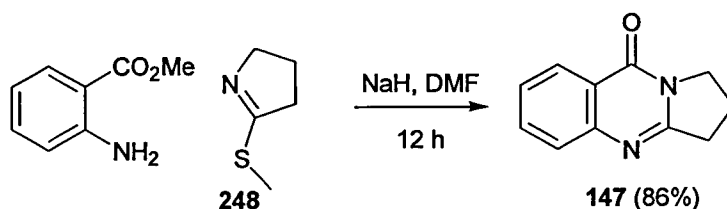


Figure 19. Deoxyvasicinone and closely related natural products.

There are many syntheses of deoxyvasicinone 147 in the literature.⁷⁹ Hamid *et al.* have used an intramolecular aza displacement of a methylthio group as the key synthetic step (scheme 82).⁷⁹ The spontaneous cyclodehydration of methyl anthranilamide and 5-methylsulfanyl-3,4-dihydro-2*H*-pyrrole 248 was shown to work in high yield, and utilised for a number of other closely related syntheses.



Scheme 82. Rapid synthesis of deoxyvasicinone by Hamid *et al.*

The other target, mackinazolinone 148, was first isolated by Johns and Lamberton from the *Mackinlaya* species of plants which are found in highlands of New Guinea.⁸⁰ A closely related quinazoline, 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazoline 249, was also isolated from the same plant (figure 20). This natural quinazoline and mackinazolinone are both closely related in structure to vasicine 138. The biosynthesis of vasicine has already been described. It could easily be envisaged that the biosynthesis of mackinazolinone is very similar to that of vasicine. The major difference would be the condensation of anthranilic acid with lysine instead of ornithine. Mackinazolinone 148 has been shown to possess a broad range of pharmacological activities.⁸¹

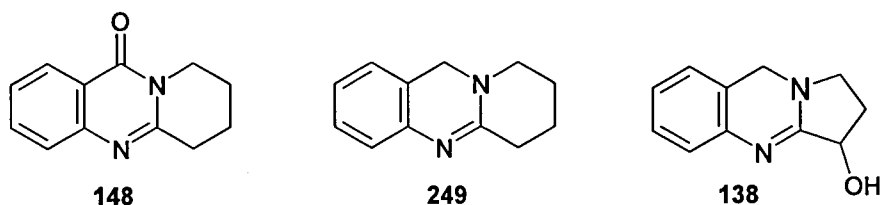
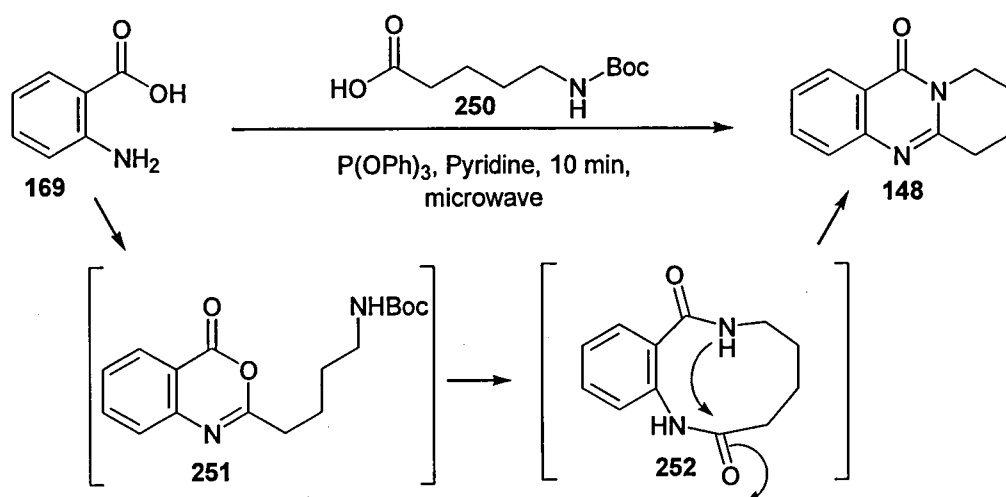


Figure 20. Vasicine and related alkaloids.

A number of syntheses of deoxyvasicinone **147** have been modified to access mackinazolinone **148**. One such example has been carried out by Liu *et al.* using a microwave-assisted, three-component domino reaction (scheme 83).⁸² The one-pot process is carried with anthranilic acid **169**, the protected amino acid **250**, triphenyl phosphite and pyridine. Liu proposed an initial intermediate Boc-benzoxazinone **251**. Deprotection and ring expansion would give the diamide intermediate **252**. Upon ring closure mackinazolinone **148** would be formed.

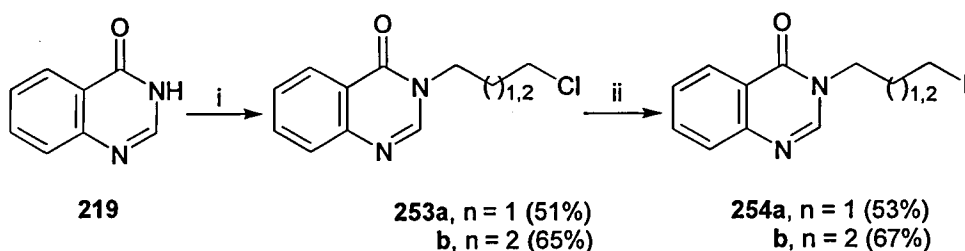


Scheme 83. Three-component microwave-assisted synthesis of mackinazolinone.

2.6 Radical synthesis of deoxyvasicinone and mackinazolinone

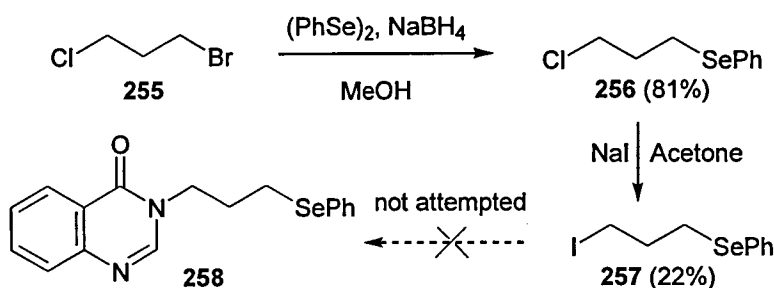
The first step of the synthesis of deoxyvasicinone and mackinazolinone was the alkylation of 3*H*-quinazolin-4-one **219**. In the aryl radical investigations *t*-BuOK was used to minimise the *O*-alkylation. Here NaH was used and no *O*-alkylation was observed (scheme 84). The alkylated quinazolinones **253a** and **253b** were treated under Finkelstein conditions to convert them to the iodoquinazolinones **254a** and

254b. Unusually the yields for both Finkelstein reactions were low whereas the reaction is normally quantitative. Part of the products were lost during the workup of the reaction, this accounts for the good but not quantitative yields.



Scheme 84. i. a) 1-Chloro-3-iodopropane, NaH, DMF; b) 1-Chloro-4-iodobutane, NaH, DMF; ii. NaI, acetone, reflux.

There was concern about the stability of the alkyl iodoquinazolinones **254a** and **254b**. For this reason, the synthesis of the alkyl phenylselenanide **256** was carried out (scheme 85). The carbon-selenium bond is polarisable and can break under homolytic conditions but is stable to S_N1 and S_N2 reactions. The alkyl bromide **255** was converted to the phenylselenanide **256** in good yield. This was followed by a Finkelstein reaction yielding the iodophenylselenanide **257**. Attempted alkylation of the 3H-quinazolin-4-one **219** was not carried out using the iodophenylselenanide **257** because the alkyl iodides **254a** and **254b** proved to be stable.

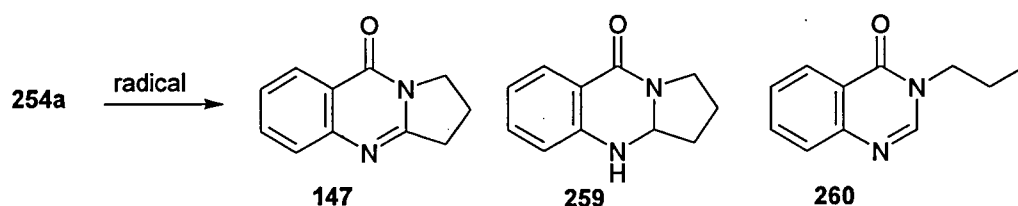


Scheme 85.

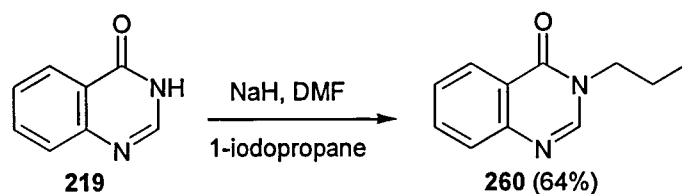
The first reaction investigated was between quinazolinone **254a** and $(Me_3Sn)_2$ to synthesise deoxyvasicinone (table 8). This reaction yielded three products, deoxyvasicinone **147**, the cyclised reduced quinazolinone **259** and the reduced

quinazolinone **260** in moderate yields. It was reasoned that triethylborane could be used to form the alkyl radical without the need for other radical propagating reagents. The reaction was repeated using just triethylborane and increased yields were observed. Triethylborane is known to generate radicals from alkyl iodides.⁶ Unsurprisingly, when quinazolinone **254a** was reacted with Bu₃SnH only the reduced quinazolinone **260** was obtained. As seen above, this showed that $k_H \gg k_{Cyc}$, and that the formation of a five-membered ring is not favoured in the case of alkyl and aryl radicals. It was proposed that the reduced cyclised quinazolinone **259** was obtained because the drive for rearomatisation is not as great as in the case of the aryl radical cyclisations. The source of the reducing hydrogen is not clear, possibly a small amount of disproportionation is occurring.

Table 8. Radical cyclisations to form deoxyvasicinone and other products

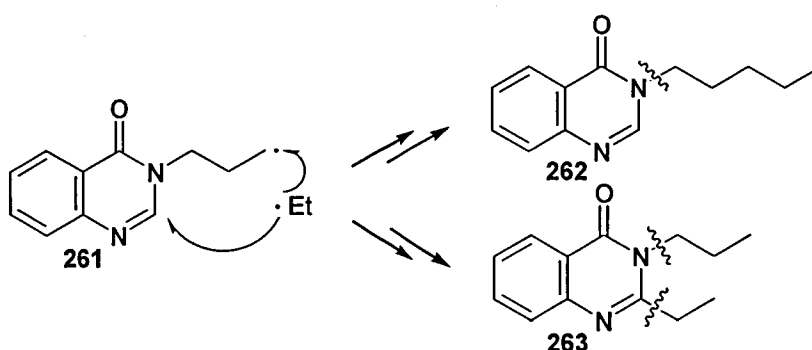
			
Radical reagent	Initiator	Solvent	Product
(Me ₃ Sn) ₂	hν and Δ	<i>t</i> -BuPh	147 (20%) 259 (12%) 260 (6%)
Et ₃ B	O ₂	<i>t</i> -BuPh	147 (40%) 259 (10%) 260 (30%)
Bu ₃ SnH	Et ₃ B	MePh	260 (78%)

To help with characterisation, the reduced quinazolinone **260** was prepared using a different route, *via* the alkylation of 3*H*-quinazolin-4-one **219** using 1-iodopropane (scheme 86).



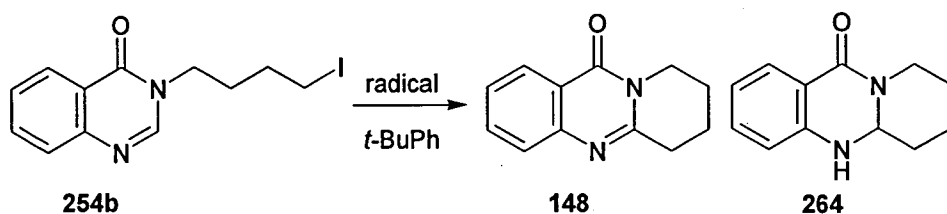
Scheme 86.

A sample of the crude reaction mixture for the triethylborane reaction (2nd entry, table 8) was analysed by GC-MS. The analysis revealed two other minor products which appeared to result from the addition of ethyl radical onto the propyl chain and onto 3 propyl quinazolinone **261** (scheme 87). Both compounds have relative molecular masses of 216. The fragmentation pattern of one product had a large ion of m/z 145, due to the loss of pentane chain from quinazolinone **262**. The other product had two major ions of m/z 187 (loss of ethyl) and m/z 173 (loss of propyl) from quinazolinone **263**. However, these are only postulated structures which could not be further characterised. The reaction provides extra evidence that hydrogen abstraction is carried out by ethyl radical.



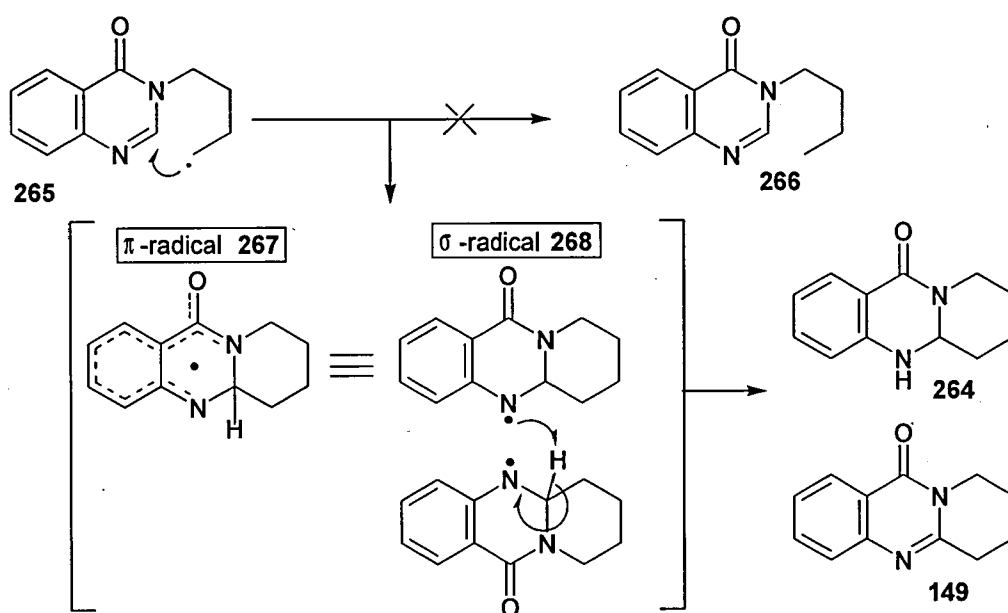
Scheme 87. Possible by-products in the reactions with Et_3B .

Attention was turned to the radical cyclisation of the quinazolinone **254b** to form mackinazolinone **148**. The radical reaction was carried out using only Et_3B because these conditions had proved successful in the deoxyvasicinone synthesis. Mackinazolinone **148** was formed in an excellent yield (61%) under these conditions (scheme 88). It was surprising to find the only other isolatable product to be the cyclised reduced quinazolinone **264**. The reaction was also carried out using $(\text{Me}_3\text{Sn})_2$ and again the same two products were isolated but in lower yields. These results are in stark contrast to the previous cyclisation of deoxyvasicinone where three products were isolated. The higher yields observed for mackinazolinone **148** and the cyclised reduced quinazolinone **264** show the preferential formation of six-membered rings over five-membered rings. The same trend was observed when studying aryl radical cyclisations.



Scheme 88. i. Et_3B ; mackinazolinone **148** (61%) and cyclised **264** (17%); ii. $(\text{Me}_3\text{Sn})_2$, $h\nu$, reflux; mackinazolinone **148** (30%) and cyclised **264** (23%).

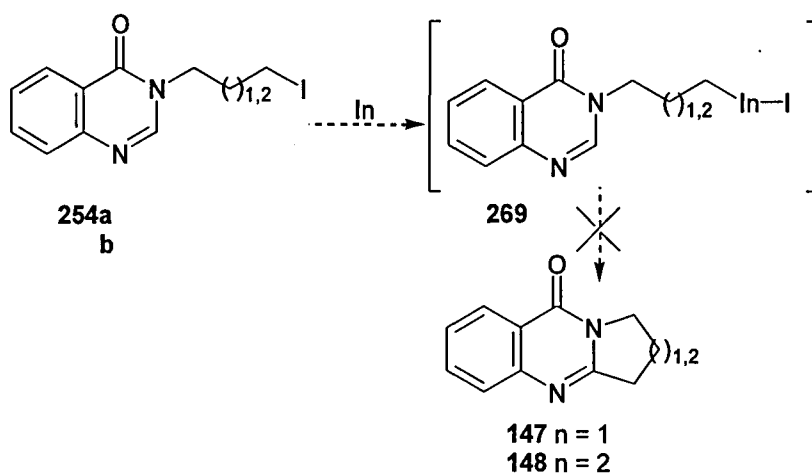
It was proposed that the formation of the cyclised reduced quinazolinone **264** arises *via* a disproportionation reaction. In the case of the reaction using $(\text{Me}_3\text{Sn})_2$ the two quinazolinone products **148** and **264** are formed in similar yield which suggests a disproportionation reaction (scheme 89). The reduced quinazolinone **266** was not obtained, indicating that cyclisation is highly favourable. The formation of reduced cyclised product was not observed in any other cyclisation reactions. The extra conjugation given by products with aryl and heteroaryl radicals may be important.



Scheme 89. Putative disproportionation mechanism.

2.7 Investigations into indium-mediated cyclisations onto 3*H*-quinazolin-4-one

With the iodoquinazolinones **254a** and **254b** in hand, organometallic reactions using these substrates were investigated. Heck reactions could not be carried out due to the presence of β -hydrogen atoms. However, we were curious to see if a reaction induced by indium would lead to Barbier type reactions on these substrates. Indium is relatively non-toxic and can also be used under aqueous conditions.⁸³ It was hoped that indium would insert into the carbon iodine bond **269** and possibly cyclise onto the quinazolin-4-one (scheme 90). Indium powder was added to both the quinazolinones **254a** and **254b**. These reactions were carried out using a mixture of water and DMF or THF to get the quinazolin-4-one into solution. Reactions were also undertaken with gentle heating. However, only trace quantities of possible cyclised compound could be seen in the ^1H NMR spectra and could never be isolated. As this was not the main focus of the work, no other organometallic investigations were carried out on alkyl halides.



Scheme 90. Attempted indium mediated cyclisations.

2.8 Conclusion

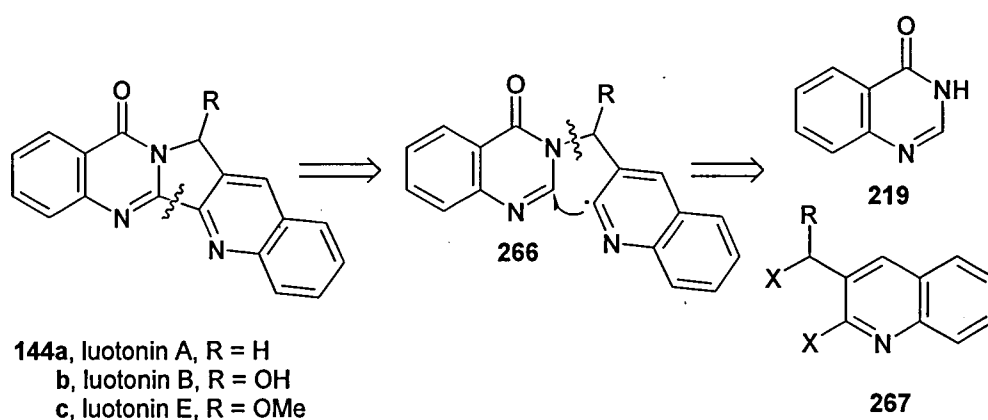
In this chapter, it has been shown the strong competition between hydrogen abstraction and cyclisation of aryl and alkyl radicals onto the C-2 position of the quinazolinone. The syntheses of deoxyvasicinone and mackinazolinone have been achieved. Attempts at using organometallic cyclisation chemistry proved unsuccessful.

Chapter 3. Heterocyclic radical cyclisations onto 3*H*-quinazolin-4-one

Having successfully carried out aryl and alkyl radical cyclisations onto 3*H*-quinazolin-4-one, focus was turned to heteroarene radical cyclisations. Many examples of heteroarene radical cyclisation are known and have been reviewed in chapter 1. The aim was to extend this work to the field of 3*H*-quinazolin-4-one chemistry.

3.1 Introduction to luotonin A

Heterocyclic radical cyclisations onto the 3*H*-quinazolin-4-one moiety were investigated with the aim of natural product synthesis. One of the synthetic targets was the recently discovered pyrroloquinazolinequinoline alkaloids luotonins **144a** A, B and E (scheme 91). These natural products have been isolated from *Peganum nigellastrum*, a Chinese medicinal plant that has been used in the treatment of rheumatism, inflammation and abscesses.⁸⁴ They have proved to be popular targets for synthetic chemists, and, at the time of writing twelve syntheses in six years of luotonin A have been reported.⁸⁵ It was envisaged a possible synthesis of the luotonin A by radical cyclisation of the quinoline radical **266** onto the C-2 position of a quinazolinone core. This could be achieved from the synthesis of the quinoline building block **267** and 3*H*-quinazolin-4-one **219**.



Scheme 91. Retrosynthesis of the luotonins.

The biological activity of the luotonins is of particular interest and has recently been explored further by Hecht and coworkers.⁸⁶ It was noted that luotonin A **145a** exhibits reasonable potency as a topoisomerase I poison by stabilising the enzyme linked DNA, with the same selectivity as the anticancer drug camptothecin **61** (figure 21).⁸⁷

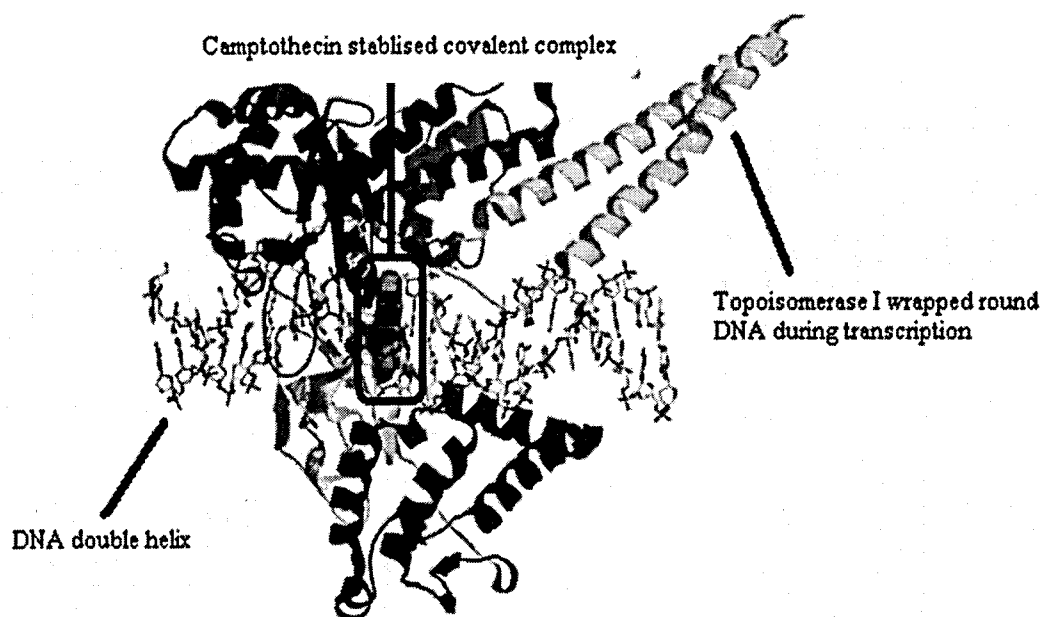


Figure 21. Camptothecin acting as topoisomerase I poison

The stereochemistry in the lactone E-ring for camptothecin is critical in its role to form a topoisomerase I-DNA covalent binary complex (figure 22). Hecht showed that removal of the hydroxyl group from the lactone E-ring (compound **268**) resulted in complete loss of covalent binary complex stabilisation. Notably, luotonin A **145a** has a very different E-ring to camptothecin **61**. The other major difference between the two compounds is that luotonin A **145a** contains an additional nitrogen in the D-ring at position C-14. Hecht has shown that removal of this extra nitrogen at N-14 leads to complete loss of activity for analogue **269**.

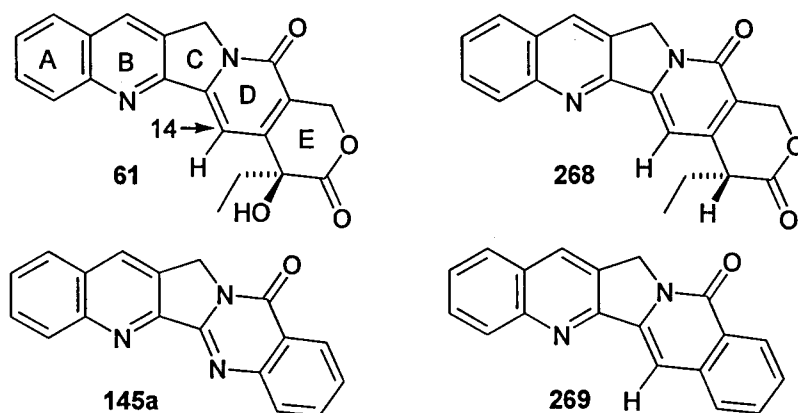
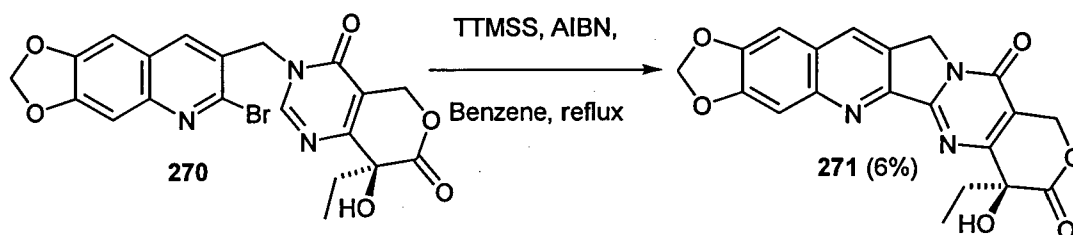


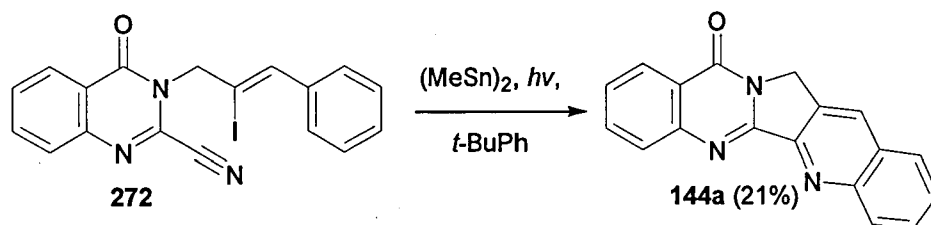
Figure 22. Luotonin A, camptothecin and analogues.

Hecht has now reported the synthesis of 10,11-methylenedioxy-14-azacampotothecin **271**, which incorporates the extra nitrogen in the D-ring of luotonin A into camptothecin (scheme 92).⁸⁸ The compound represents another important step to the development of camptothecin analogues in anti cancer treatment. Hecht employed a radical cyclisation in the synthesis from the quinoline **270** but in poor yield. The aim was to develop improved radical methodology for the synthesis of luotonin A.



Scheme 92.

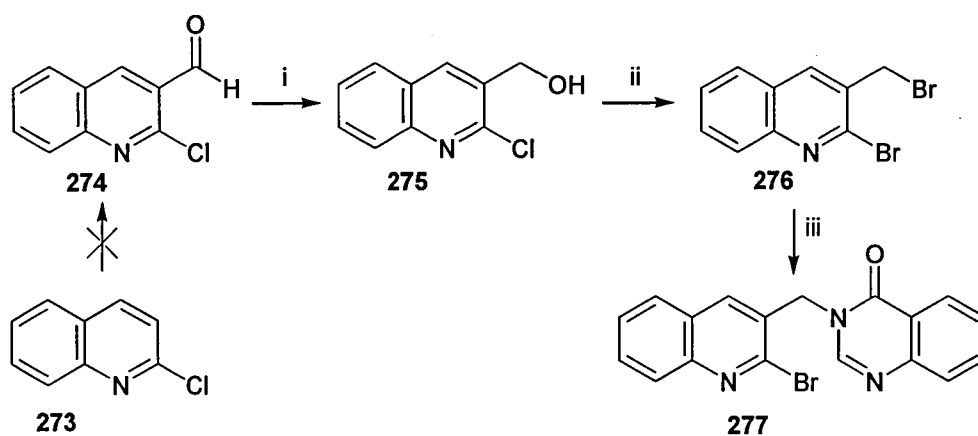
There have been a number of syntheses of luotonin A to date. The Bowman group has previously used a radical cascade reaction *via* an iminyl radical in the synthesis of luotonin A (scheme 93).⁷³ The reaction proceeds *via* an initial 5-*exo-dig* cyclisation of a vinyl radical formed from the substituted quinazolinone **272**. The resulting intermediate iminyl radical, then undergoes a 6-*endo* or 5-*exo* (followed by neophyl rearrangement) yielding luotonin A **144a** in a 21% yield. The radical reaction was carried out using $(\text{Me}_3\text{Sn})_2$ to overcome H-abstraction which led to unwanted side products.



Scheme 93. Bowman's previous synthesis of luotonin A.

3.2 Radical synthesis of luotonin A

The synthesis of the radical precursor for luotonin A is shown in scheme 94. Attempts to formylate 2-chloroquinoline **273** at C-3 failed (scheme 94). It was hoped that deprotonation with LDA at the C-3 on the quinoline **273** would access the aldehyde **274** using DMF as the formylating agent. However, after several attempts this was abandoned as only starting material was recovered. Instead, aldehyde **274** was purchased from Sigma-Aldrich. Literature methodology by Harayama was followed to reach quinazolinone **277**.⁷⁴ Reduction of the aldehyde **274** to the alcohol **275**, was followed by bromination and deoxybromination leading to the quinoline **276** in good yield. The dibromoquinoline **276** was used to alkylate 3*H*-quinazolin-4-one yielding the desired radical precursor **276**.

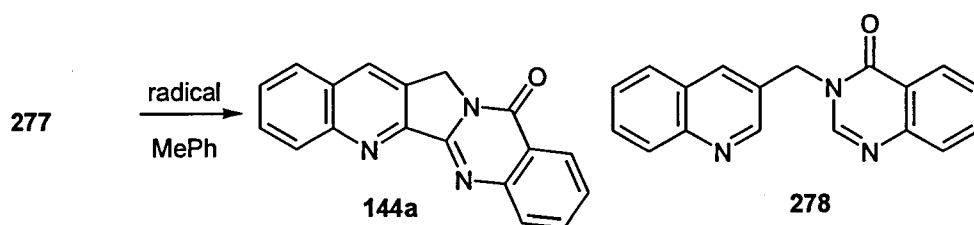


Scheme 94. i. NaBH₄, EtOH (75%); ii. PBr₃, THF (55%); iii. *t*-BuOK, 3*H*-quinazolin-4-one, DMF (65%).

Studies were considered to optimise the dibromination step. Following the reaction by TLC, an initial spot was seen for the rapid deoxybromination of the alcohol **275**. However, it took twenty-four hours before the nucleophilic aromatic substitution of the chlorine atom had taken place, yielding the dibromoquinazoline **276**.

The results of cyclisation studies are shown in table 9. Initial attempts at the radical cyclisations of the quinazolinone **277** were carried out using $(\text{Me}_3\text{Sn})_2$. As discussed previously this was to minimise the possibility of H-abstraction by the intermediate quinol-2-yl radical. Luotonin A **144a** was produced in good yield on the first attempt with only a small amount of the reduced quinazolinone **278**.

Table 9. Radical synthesis of luotonin A.



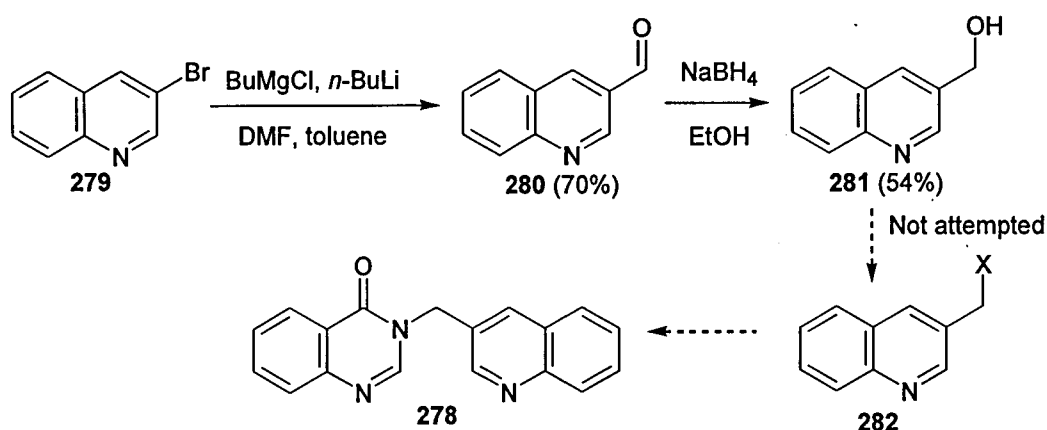
Radical reagent (equiv.)	Initiator (equiv.)	Product
$(\text{Me}_3\text{Sn})_2$ (3.0) *	$h\nu$ and Δ	144a (51%) 278 (15%)
Bu_3SnH fast (2.5)	Et_3B (20)	278 (53%)
Bu_3SnH slow (2.5)	Et_3B (20)	144a (14%) 278 (32%)
Bu_3GeH slow (2.5)	Et_3B (20)	144a (18%) 278 (11%)

* The reaction was carried out in *t*-BuPh

As expected, fast addition of Bu_3SnH (all added in one portion at the beginning of the reaction) yielded only the reduced quinazolinone **278**. However, when slow addition of Bu_3SnH (with a syringe pump) was used a small amount of luotonin A **144a** was also formed. This was the first time a five-membered ring cyclisation was carried out onto the quinazolinone using Bu_3SnH . The conclusion can be drawn that the cyclisation of the quinoline radical is more favoured than the aryl or alkyl radicals previously investigated. Slow addition of Bu_3GeH produced a mixture of both the reduced quinazolinone **278** and the cyclised luotonin A **144a**. This slight increase in yield of luotonin A using Bu_3GeH can be attributed to the stronger bond between

germanium-hydrogen compared to the tin-hydrogen bond, which means H-abstraction is less favourable when using Bu_3GeH .

From earlier investigations, there was concern that the separation of luotonin A **144a** and reduced quinazolinone **278** may be difficult. Separation of products had been a major problem in the formation of five-membered rings from aryl radicals. Therefore, the synthesis of the reduced quinazolinone **278** was attempted by an alternative route (scheme 95). The conversion of the commercially available 3-bromoquinoline **279** to the quinoline-3-carbaldehyde **280** worked well using DMF as a formylating agent utilising a literature procedure by Doumachel *et al.*⁸⁹ The authors proposed that the reaction proceeded *via* a tri-quinoyl co-ordinate magnesium ion to explain why only one third of an equivalent of BuMgCl is needed in the reaction. Reduction to the 3-hydroxymethylquinoline **281** proceeded smoothly. The aim was to convert the 3-hydroxymethylquinoline **281** to a suitable leaving group **282** and alkylate onto 3*H*-quinazolin-4-one to yield quinazolinone **278** unambiguously. However, this route was not further pursued after finding luotonin A **144a** and quinazolinone **278** were separable by careful column chromatography.



Scheme 95.

3.3 Introduction to rutaecarpine

The next target synthesis was the indoloquinazolinone natural product rutaecarpine **145** (figure 23). This natural product can be considered a quinazolinone or indole alkaloid and its biosynthesis from tryptophan and anthranilic acid has been discussed.⁵⁸

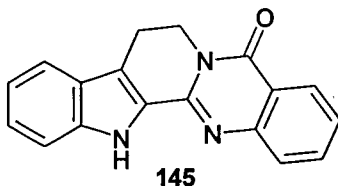
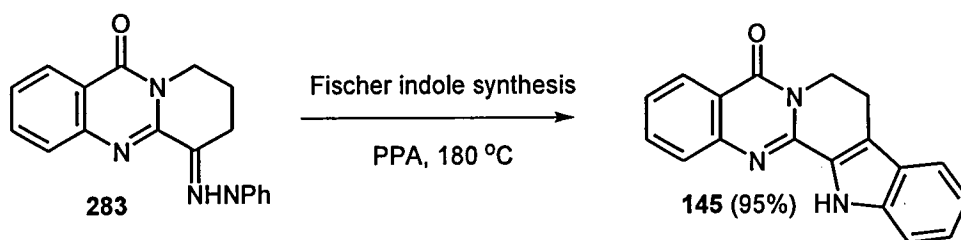


Figure 23.

Rutaecarpine **145** was first isolated in 1915.⁹⁰ Ashina *et al.* reported the first synthesis another decade later.⁹¹ Rutaecarpine is isolated from the plants *Evodia*, *Horita*, *Zanthoxylum*, *Euxylophorea* and *Phellodendron* which are all members of the *Rutaceae* family.⁹² The dried fruit of *Evodia rutaecarpa* has been used in traditional Chinese herbal medicines such as Wu-Chu-Yu and Shih-Hu.⁹³ These medicines have been used to treat a number of medical conditions such as headaches, dysentery, cholera, worm infections and postpartum disturbances. Recent literature has also shown that rutaecarpine displays strong inhibitory activity against cyclooxygenase (COX-2) and suppression of platelet plug formation in mesenteric venules and increased Ca^{+} concentration in endothelial cells.^{94,95}

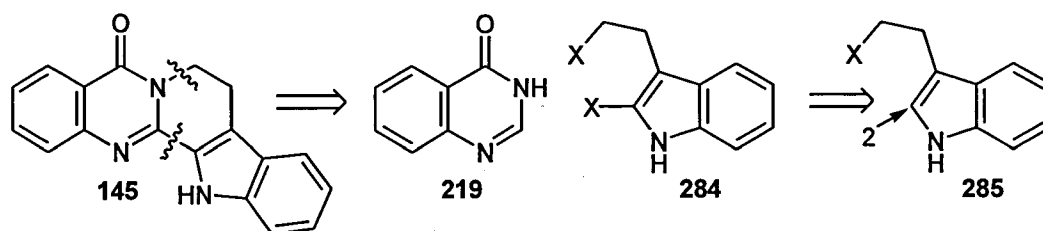
There have been a number of different synthetic approaches to rutaecarpine. Recently Chavan *et. al.* have carried a total synthesis using the Fischer indole reaction (scheme 96).⁹² Although several steps were required to reach the indole precursor **283**, the Fischer indole cyclisation using PPA afforded rutaecarpine **145** in excellent yield.



Scheme 96. Rutaecarpine synthesis using a Fischer indole reaction.

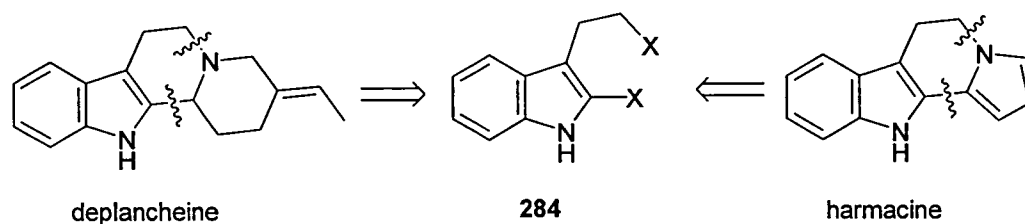
3.4 Radical synthesis of rutaecarpine

The key to the synthetic strategy to rutaecarpine **145** was to prepare the indole building block **284** which could be used to alkylate 3*H*-quinazolin-4-one **219** (scheme 97). It was considered that insertion of the required functionality at the C-2 position of indole **285** would be facile.



Scheme 97. Retrosynthesis of rutaecarpine.

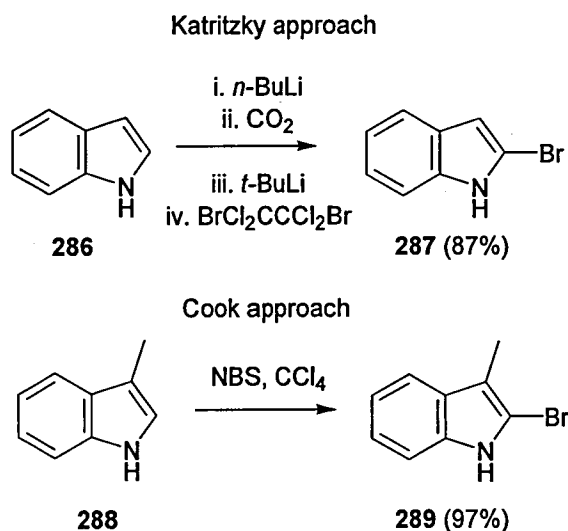
The aim was to develop a synthesis of the indole building block **284** which would provide radical routes to other indole natural products, e.g. as shown in scheme 98.



Scheme 98.

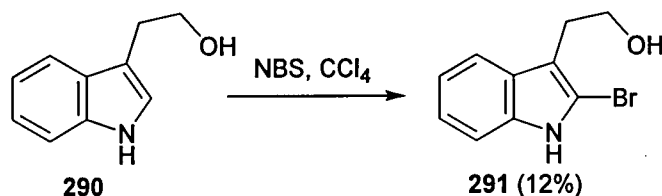
There are two methods for C-2 halogenation of indole reported in the literature (scheme 99). Katritzky has shown that C-2 substitution of 1*H*-indole **286** can be

carried out using carbon dioxide as a temporary protecting group for nitrogen.⁹⁶ Bergman and Venemalm elaborated this method to make 2-bromo-1*H*-indole **287**.²⁵ Cook *et al.* have described a second method of C-2 halogenation, where NBS in CCl₄ is used to carry bromination of 3-methyl-1*H*-indole **288** to 2-bromo-3-methyl-1*H*-indole **289** at C-2.⁹⁷ The latter method requires the C-3 position to be blocked, or bromination is directed onto C-3. The major problem for both these procedures is the instability of 2-haloindoles. Bergman and Venemalm noted the curious stability trend of 2-iodoindole > 2-chloroindole > 2-bromoindole.²⁵ However, Jones who has carried out studies with 2-bromoindoles has shown that once pure, the stability of C-2 bromoindoles increases greatly.⁹⁸



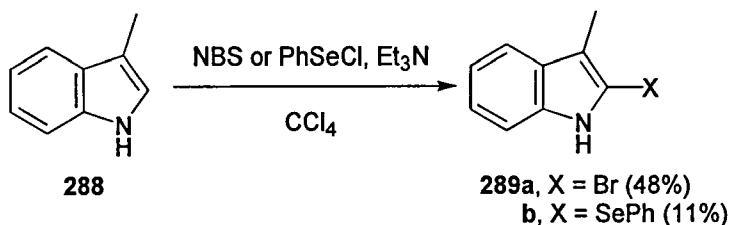
Scheme 99. C-2 Bromination of indole.

It was chosen to use the NBS reaction which appeared experimentally simpler than the Katritzky method. Initially, the commercially available indole, tryptophol **290** was treated with NBS to form 2-(2-bromo-1*H*-indol-3-yl)ethanol **291** in low yield (scheme 100). This compound appeared quite stable in air once purified.



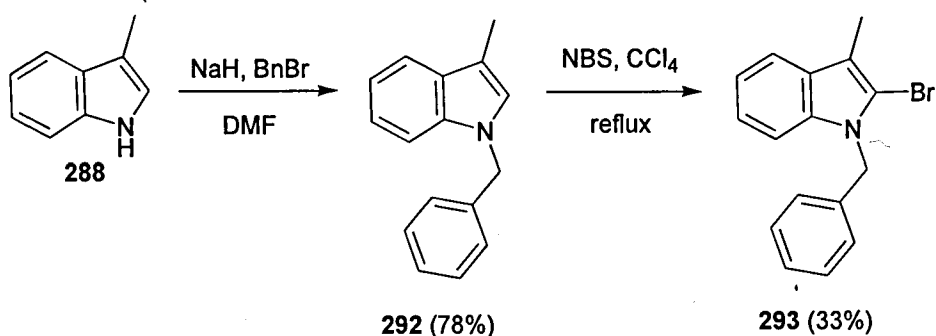
Scheme 100.

This chemistry obviously needed more investigation to optimise reaction conditions and yields. Therefore, initially a number of studies were carried out on 3-methyl-1*H*-indole **288** (scheme 101). 3-Methyl-1*H*-indole **288** was converted to 2-bromo-3-methyl-1*H*-indole **289a** and 2-(phenylselanyl)-3-methyl-1*H*-indole **289b**. Once pure both compounds proved stable. An attempt to replace NBS with NIS to form the 2-iodo-3-methyl-indole failed. The use of 2-(phenylselanyl)-3-methyl-1*H*-indole **289b** was considered for radical reactions. However, there is no precedent in the literature of the homolysis of a sp²C-SePh bond in radical reactions.



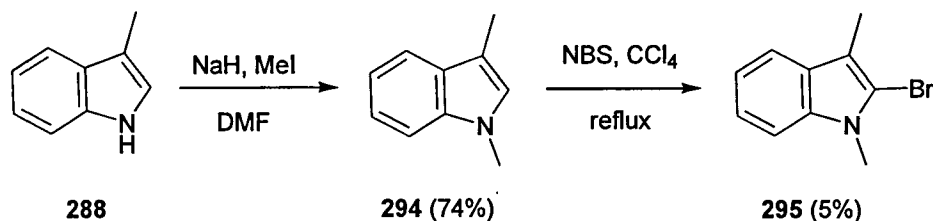
Scheme 101.

It was thought that protection of the nitrogen indole might increase reaction yields for bromination. Therefore, the benzyl protected indole **292** was prepared in excellent yield from the 3-methyl-1*H*-indole **288** (scheme 102). However, once brominated indole **293** appeared very unstable in air.



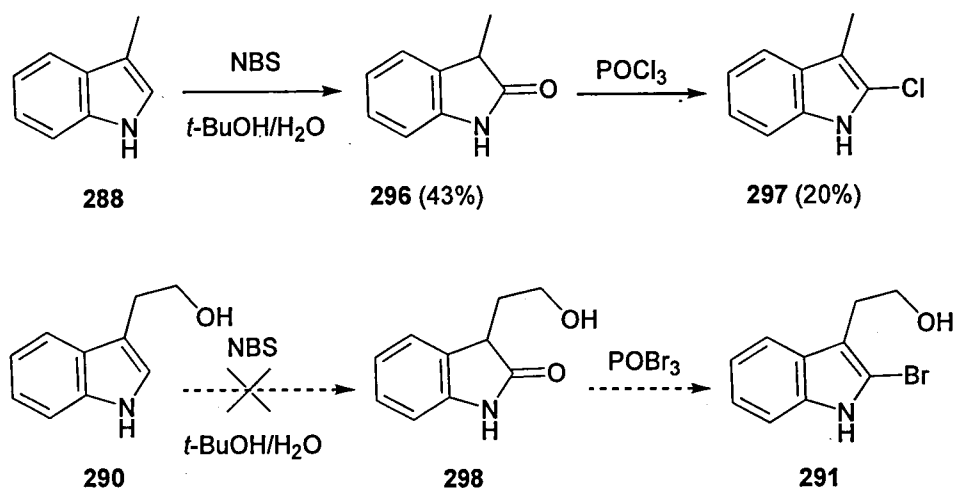
Scheme 102.

A less bulky protecting group on the nitrogen might make a difference to the stability of the C-2 brominated indole. Therefore 1,3-dimethyl-1*H*-indole 294 was synthesised (scheme 103). Treatment of this compound with NBS gave a very poor yield of 2-bromo-1,3-dimethyl-1*H*-indole 295, which also proved very unstable in air. An attempt to insert phenylselenide at C-2 using PhSeCl and 1,3-dimethyl-1*H*-indole 294 failed. Only (PhSe)₂ and starting material were recovered from this procedure.



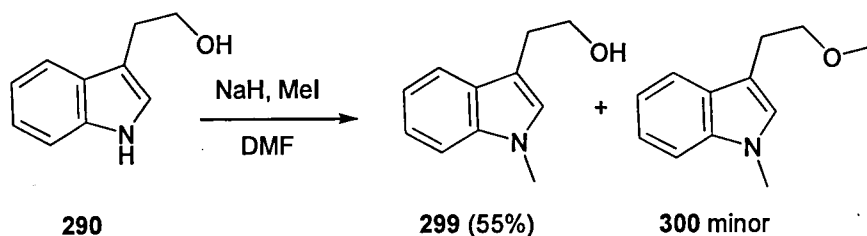
Scheme 103.

At this point, considering the results obtained, another pathway was investigated and the synthesis of C-2 oxindole was attempted that could then be halogenated (scheme 104). A literature procedure was used to prepare 3-methyl-1,3-dihydroindol-2-one 296 from 3-methyl-1*H*-indole 288.⁹⁹ Subsequent chlorination to 2-chloro-3-methyl-1*H*-indole 297 was carried out using POCl₃ in poor yield. When the same pathway was tried using tryptophol 290, the oxindole 298 was not obtained. With poor results obtained, this route was abandoned.



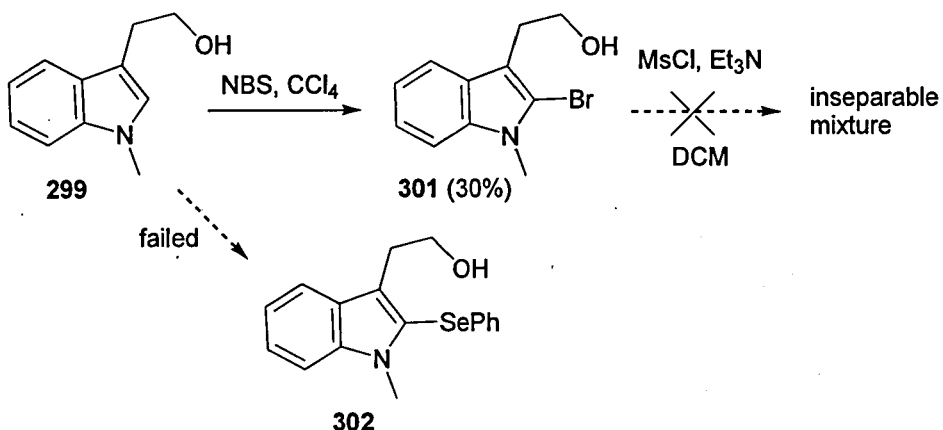
Scheme 104.

The next direction followed was to use the precursor tryptophol 290, and try different methods of nitrogen protection and subsequent bromination. Methyl protection of the nitrogen was carried out to yield the 2-(1-methyl-1-*H*-indol-3-yl)ethanol 299 (scheme 105). A range of bases were used to deprotonate the nitrogen. Although KOH and NaOH were used, NaH proved to be the highest yielding. Minor amounts of the dimethylated indole 300 were also recovered.



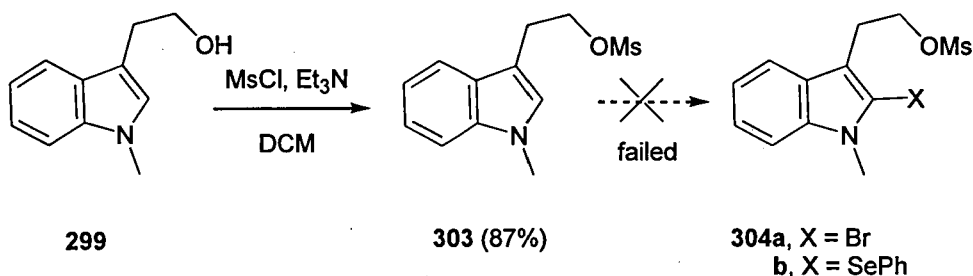
Scheme 105.

The methylated indole 299 was successfully brominated using NBS to yield the bromoindole 301 (scheme 106). The yield of the bromoindole 301 was low but the compound appeared quite stable in air. Attempts at mesylation of this compound resulted in inseparable mixtures of unidentified products. Attempts to form the phenylselenide indole 302 using PhSeCl and *N*-(phenylselenanyl)phthalimide also failed.



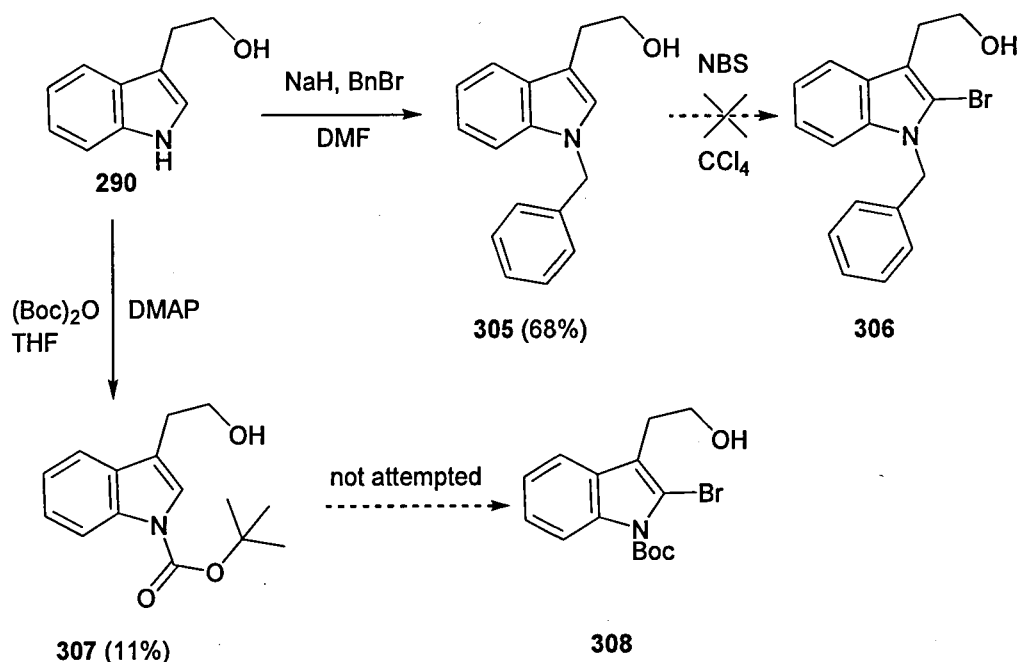
Scheme 106.

After the failure to convert the pendant alcohol of the bromoindole **301** to the mesylate, studies were carried out to see if the alcohol could be converted to a mesylate prior to bromination (scheme 107). The *N*-methyl tryptophol **299** was converted to the mesylate **303** in high yield. However, reactions with NBS and PhSeCl failed to produce either the bromoindole **304a** or the selanylindole **304b**.



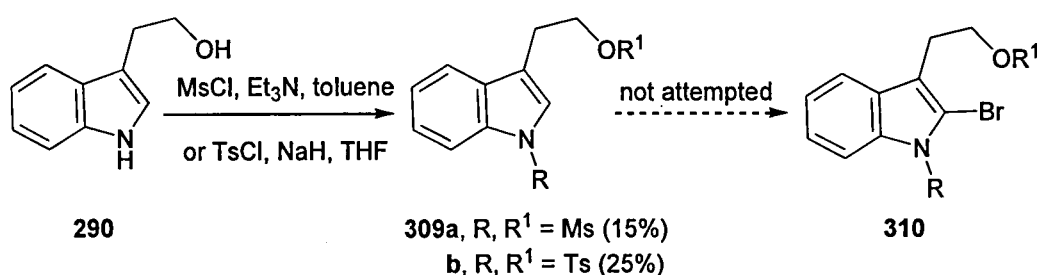
Scheme 107.

With little success using *N*-methyl tryptophol the *N*-benzylated tryptophol **305**, was prepared in good yield (scheme 108). However, no bromination of this compound could be achieved using NBS and bromotryptophol **306** was not obtained. When protection of the nitrogen atom of tryptophol **290** using (Boc)₂O was attempted, the Boc indole **307** was obtained in a poor yield, which precluded this route being explored further.



Scheme 108.

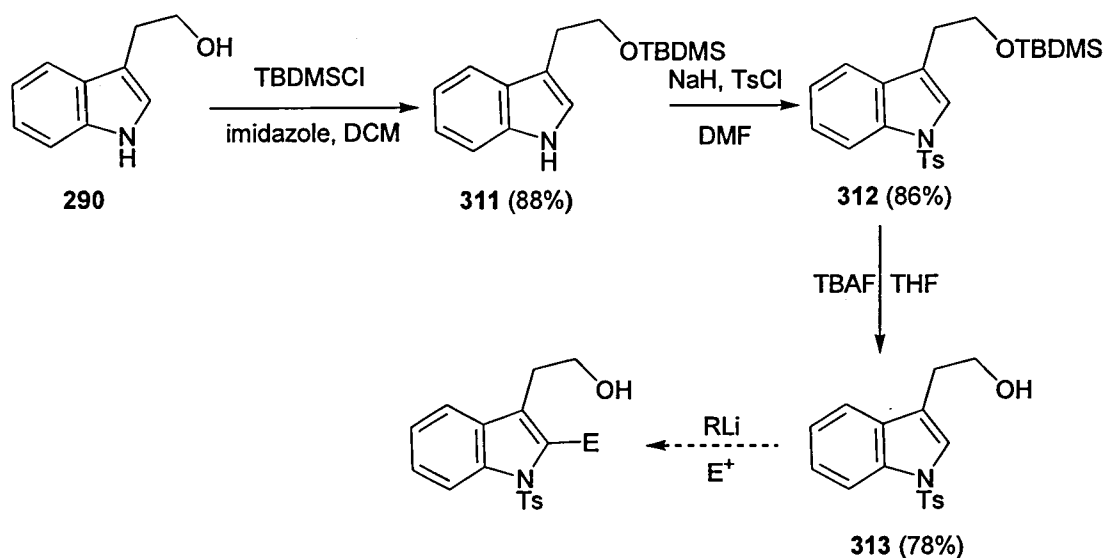
So far the studies had involved carrying out one synthetic transformation at a time. An attempt to protect the indole nitrogen and form a leaving group on the alcohol in one step was made. Both the di-tosyl indole **309a** and di-mesyl indole **309b** were isolated in low yield from tryptophol **290** (scheme 109) and as a result, no bromination was attempted with either compound to synthesise indole **310**.



Scheme 109.

All attempts to brominate indole or tryptophol had involved using NBS. However, lithium bases can also be used to trap bromine and other electrophiles (e.g. the Katritzky method).⁹⁶ The aim was to use indole **313** to trap electrophiles at C-2 (scheme 110). Firstly tryptophol **290** was protected with TBDMS to yield the

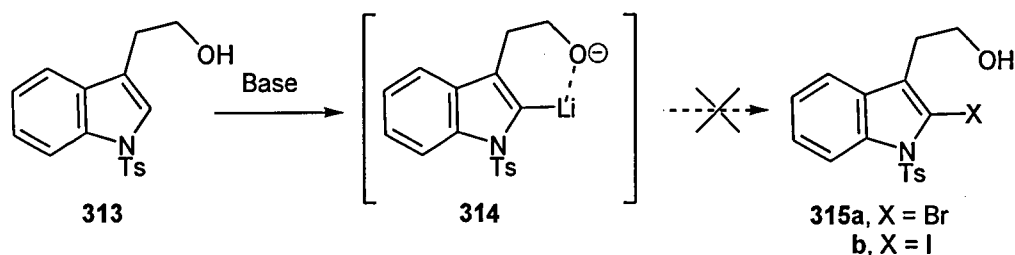
silylindole **311**. The nitrogen was then tosyl protected to form the indole **312**, and subsequent deprotection of the alcohol was carried out with TBAF yielding the indole **313**.



Scheme 110. Stepwise protection and deprotection of tryptophol.

Insertion of iodine and bromine at the C-2 position of indole **313** was attempted using various bases according to a literature procedure (table 10).¹⁰⁰ The halogenated products **315a** and **315b** were not obtained, and only starting material was recovered. In all cases, at least two equivalents of base were used to ensure the dianion was formed. We considered that this dianion may help facilitate chelation with the indole lithium intermediate **314** to enable electrophiles to be trapped.

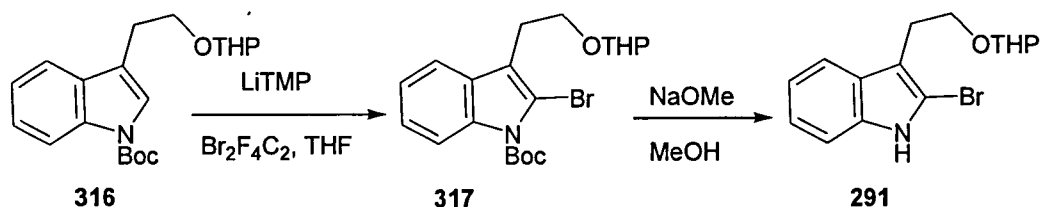
Table 10 Attempted conditions for halogenation of indole at the C-2 position.



Base (equiv.)	Halogen source (equiv.)	Solvent
LDA (4.4)	I ₂ (2.0)	MTBE
<i>t</i> -BuLi (4.0)	NIS (4.6)	MTBE
<i>t</i> -BuLi (8.0)	NIS (4.0)	MTBE
<i>n</i> -BuLi (4.6) refluxed	I ₂ (8.0)	MTBE
<i>t</i> -BuLi (4.4)	1,2-dibromoethane (4.4)	THF

Literature procedures using iodine were carried out on substrate **313**.¹⁰⁰ However, these reactions failed. The reaction with 1,2-dibromoethane was unsuccessful. 1,2-Dibromotetrafluoroethane had been used in the literature and clearly contains a more reactive source of bromine, possibly explaining the failed attempts.⁹⁸ No commercial source of 1,2-dibromotetrafluoroethane could be located. An excess of base with the NIS reaction was also used without success.

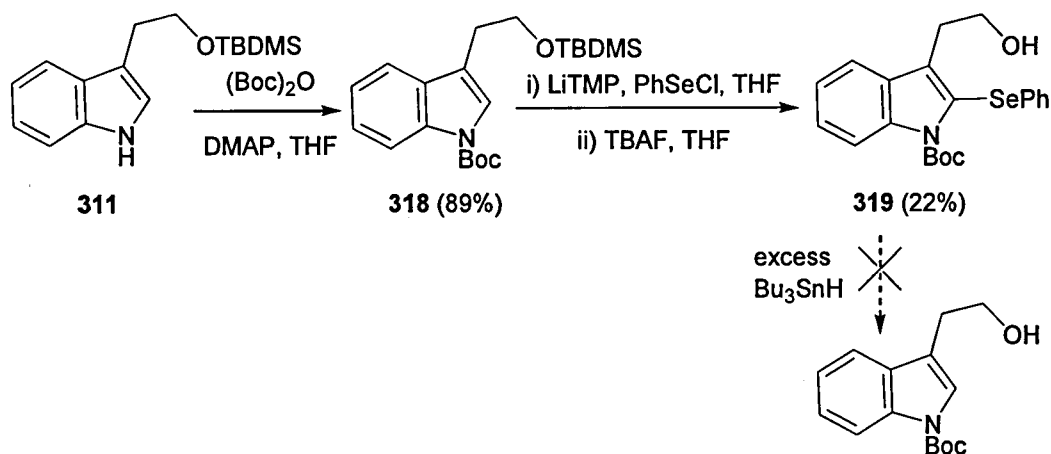
A literature procedure of Smith *et al.* had successfully used lithium tetramethylpiperidide (LiTMP) to deprotonate protected indole **316** (scheme 111).⁹¹ It was interesting to note that Smith reported that bromoindole **291** was very unstable.



Scheme 111. Smith's deprotonation using LiTMP.

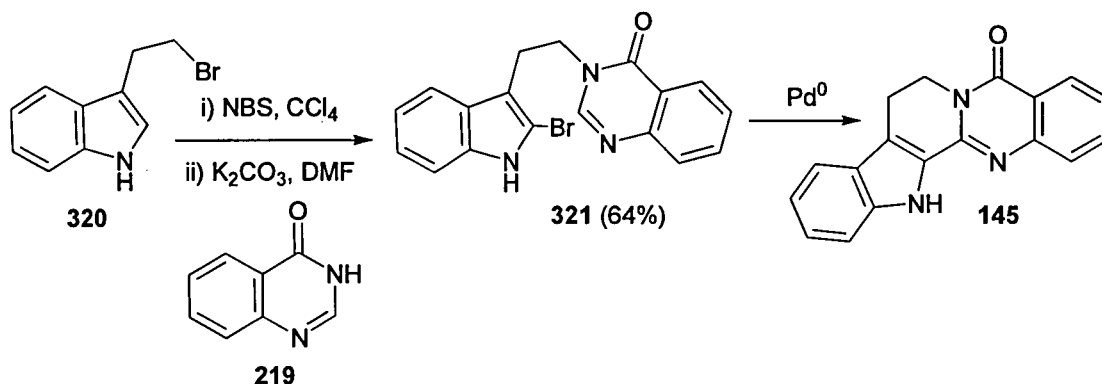
It was chosen to use the protected alcohol **311** and convert it to the *N*-Boc protected indole **318**, this was carried out in excellent yield (scheme 112). This compound was

then treated with LiTMP and phenylselanyl chloride to form the C-2 phenylselanide indole. Without further purification, the (phenylselanyl)indole was deprotected with TBAF *in situ* to yield (phenylselanyl)indole **319**. An attempt to remove the phenylselanide group with Bu_3SnH failed which indicated that the $\text{sp}^2\text{C-Se}$ bond was too strong to undergo abstraction. The bromo analogue of indole **319** could not be prepared as the reagent $\text{Br}_2\text{F}_4\text{C}_2$ could not be acquired.



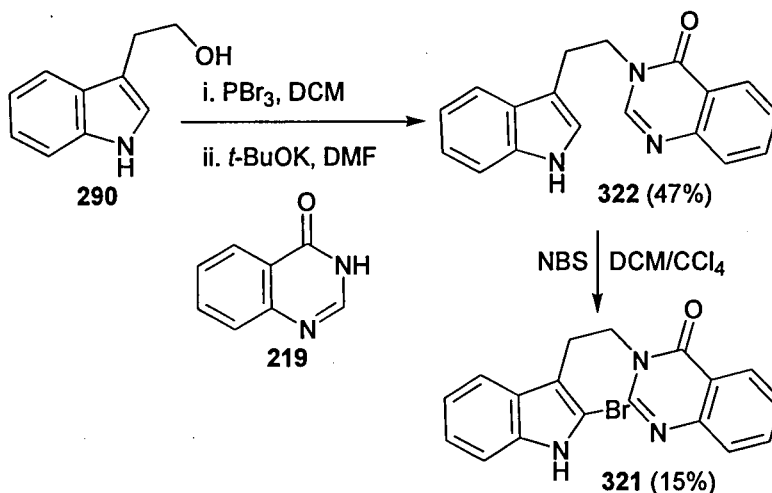
Scheme 112. Use of LiTMP as a base

At this point, Harayama *et al.* reported a Pd catalysed synthesis of rutaecarpine **145** which contained the required radical precursor **321** that was desired (scheme 113).¹⁰² Attempts to repeat Harayama's procedure proved unsuccessful. Harayama reacted 3-(2-bromoethyl)-1*H*-indole with NBS and alkylated the crude C-2 bromo indole product with 3*H*-quinazolin-4-one **219**. Realising that other groups may exploit the potential radical reaction of this precursor, Harayama's reaction sequence was further developed.



Scheme 113. Harayama's Pd catalysed synthesis of rutaecarpine

The indole **320** was added onto the quinazolinone by alkylation and then the C-2 bromination was carried out. In effect, it was hoped to use the quinazolinone as a protecting group for the ethyl arm of tryptophol **322** (scheme 114). Conversion of tryptophol **290** to the 3-(2-bromoethyl)-1H-indole **320** worked well, and was followed by alkylation to yield the indoloquinazolinone **322**. The alkylated product **322** was treated with NBS and the bromoindoloquinazolinone **321** was formed after 15 min, albeit it in poor yield.

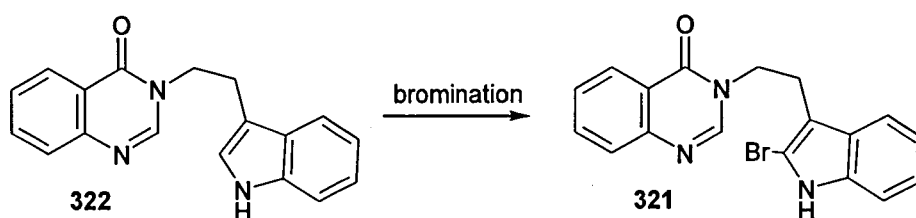


Scheme 114.

Encouraged by this result a careful study was carried out to optimise the NBS reaction (table 11). A longer reaction time gave an increased yield of bromoindoloquinazolinone **321**. Other products from side reactions that were showing

up on TLC were minimised by carrying out the reaction out 0 °C which slightly increased the yield. An attempt to carry out the reaction at -78 °C proved unsuccessful. In this reaction 1.0 equivalent of NBS was initially added and after 40 min a very faint new spot appeared on the TLC plate, so an additional 1.0 equivalent was added. However, this gave a completely inseparable mixture of products and bromoindoloquinazolinone **321** could not be isolated from this reaction mixture. The reaction appeared to be almost instantaneous at room temperature as shown when the reaction was halted after just one minute. Therefore, half an equivalent of NBS was used so that side reactions would be minimised. However, this made no real impact on the reaction yield. Optimum reaction conditions were found to be a reaction time of 30 min at 0 °C with exactly 1.0 equivalent of NBS. The NBS was recrystallised from hot water prior to use. The side reactions may be due to lack of protection of the indole NH. Unlike earlier 2-bromoindoles, the bromoindoloquinazolinone **321** was stable in air.

Table 11. Synthesis of the bromoindoloquinazolinone **321**.



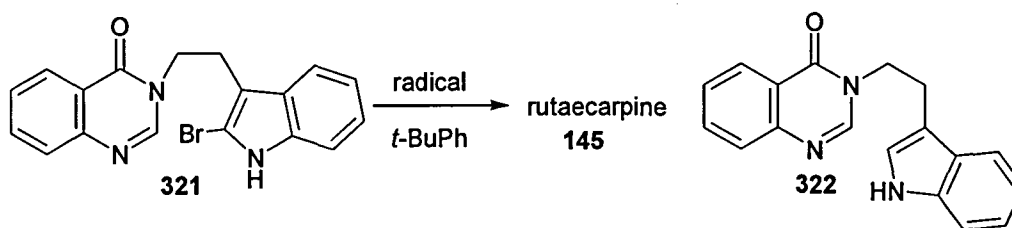
NBS (equiv.)	Solvent	Time (min)	Temperature	Yield
1.0	CCl ₄ /DCM (1:1)	15	rt	15%
1.2	DCM	30	rt	27%
1.2	DCM	25	0 °C	34%
2.0*	DCM	40	-78 °C	decomposition
1.2	DCM	1	rt	15%
0.5	DCM	30	0 °C	5%
1.0	DCM	30	0 °C	39%

* A second equivalent was added after 40 min.

NBS was stirred with one equivalent of 3*H*-quinazolin-4-one for one week in DCM and revealed no new reaction products. Therefore, side reactions observed in table 11 are not due to the reaction between NBS and the quinazolinone moiety.

Having obtained the bromoindoloquinazolinone **321** in acceptable yield, the radical cyclisations were investigated. The first attempt at radical cyclisation was carried out using $(\text{Me}_3\text{Sn})_2$ (table 12). Rutaecarpine **145** was produced as the sole product in good yield after 6 h. Increasing the reaction time lead to a mixture of inseparable products. The reaction was carried out using slow addition of Bu_3SnH which produced rutaecarpine **145** and reduced quinazolinone **322**. Earlier six-membered aryl radical cyclisations had shown that Bu_3SnH could be used to form cyclised products and therefore the formation of rutaecarpine from the slow Bu_3SnH reaction was not unexpected. Due to time constraints no further radical reactions were attempted.

Table 12. Radical synthesis of rutaecarpine



Radical reagent (equiv.)	Initiator (equiv.)	Time	Product
$(\text{Me}_3\text{Sn})_2$ (3.0)	$h\nu$ and Δ	6 h	145 (55%)
$(\text{Me}_3\text{Sn})_2$ (3.0)	$h\nu$ and Δ	24 h	Unidentifiable
Bu_3SnH (2.4) *	Et_3B (46)	12 h	145 (15%) 322 (57%)

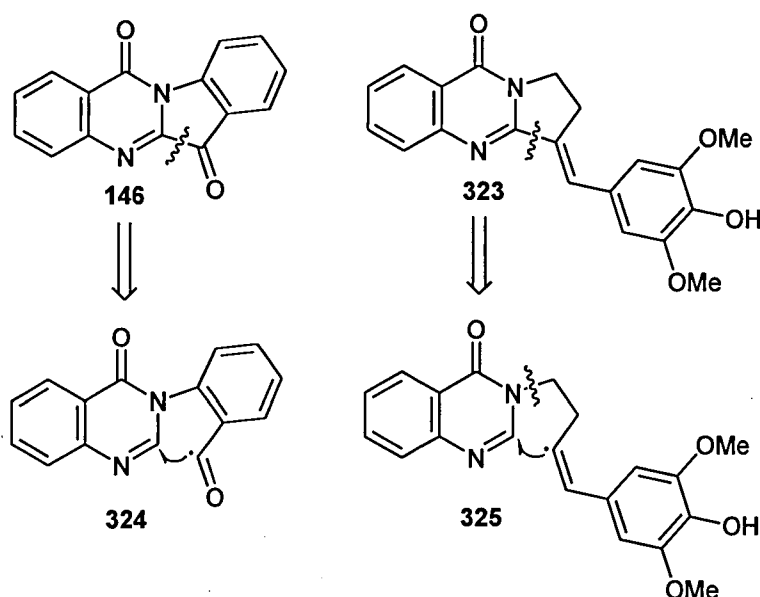
* The reaction was carried out in toluene.

3.5 Conclusions

In this chapter there has been a discussion of the syntheses of important natural products luotonin A and rutaecarpine. A brief introduction to each target has also been given along with previous syntheses and important biological effects. Luotonin A was successfully prepared using a variety of radical reagents. The planned procedure for the synthesis of rutaecarpine is the first radical synthesis of this natural product. The syntheses show that cyclisation of heteroaryl radicals on the C-2 of the 3*H*-quinazolin-4-one provide a productive route to natural products. Considerable effort was made to prepare a C-2 halogenated indole building block. Unfortunately time did not permit us to fully exploit this building block in the synthesis of other indole alkaloids.

Chapter 4. Acyl and Alkenyl radical cyclisations onto 3*H*-quinazolin-4-one

Having carried out alkyl, aryl and heteroaryl radical cyclisations onto quinazolinones the focus turned to the radical synthesis of two different natural products, tryptanthrin **146** and isaindigotone **323** (scheme 115). Neither of these natural products have been prepared using radical chemistry. It was envisaged the synthesis of tryptanthrin **146** could be reached using the acyl radical **324** and isaindigotone *via* the alkenyl radical **325**.



Scheme 115. Retrosyntheses of tryptanthrin and isaindigotone.

4.1 Introduction to tryptanthrin

Tryptanthrin **146** has been shown to have a rich and varied biological activity.¹⁰² It is isolated from *Isatis tinctoria* commonly known as woad.¹⁰² For many years this plant has been used as a herbal remedy.¹⁰² A recent report attributed anti-inflammatory activity from the leaves of woad to tryptanthrin as the principle source of this effect.¹⁰² In particular the HPLC-based activity profiling of tryptanthrin highlighted cyclooxygenase-2 (COX-2) inhibition. Hamburger has studied in great detail the biological activity of tryptanthrin.¹⁰²

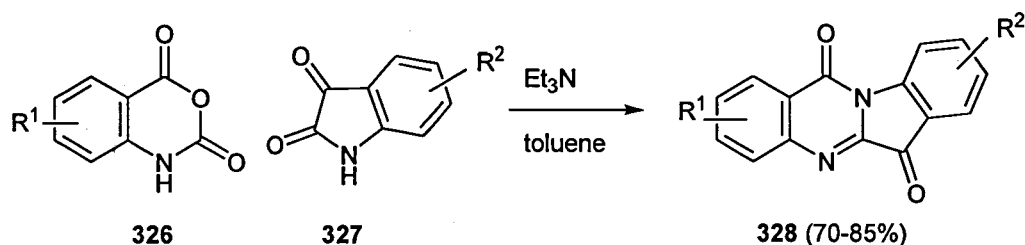
In vitro tests on tryptanthrin implicated that it has key enzymatic effects in eicosanoids. It has shown almost a hundred fold selectivity to COX-2 inhibition over

COX-1, by suppressing 6-ketoprostaglandin $F_{1\alpha}$ as well as inhibition of 5-lipoxygenase (*via* inhibition of leukotriene B_4). This makes it a rare example of a plant metabolite that shows dual effects on prostaglandin and leukotriene synthesis.¹⁰⁴

Tryptanthrin has also shown inhibition of interferon- γ and interleukin-2 I production of lymphocytes in response to Staphylococcal enterotoxin B. This means it has potential applications in control of food borne disease of the intestine.¹⁰⁵

Hamburger observed that tryptanthrin could be absorbed through the skin when handling the leaves of *Isatis tinctoria*. However, in solution the pure alkaloid could not be absorbed through the skin.¹⁰⁶ This is important to note for laboratory workers.

There are several syntheses of tryptanthrin in the literature. For example, Ajaykumur *et al.* have carried out a rapid synthesis of substituted tryptanthrin analogues **328** using the condensation of substituted isatoic anhydrides **326** and isatins **327** in boiling toluene with triethylamine (scheme 116). A library of analogues of tryptanthrin was prepared using this method.¹⁰⁷

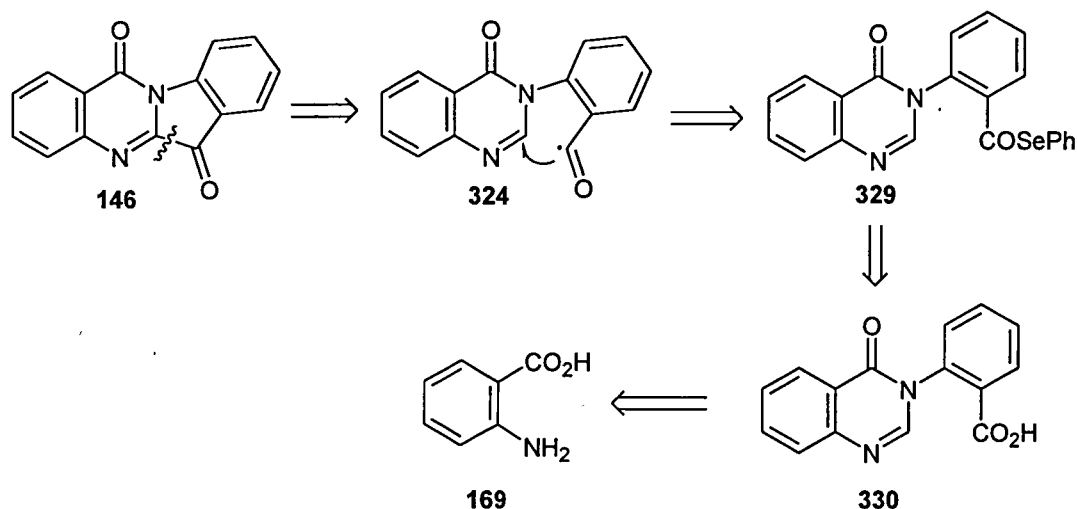


Scheme 116. Rapid access to substituted tryptanthrin analogues.

4.2 Radical synthesis of tryptanthrin

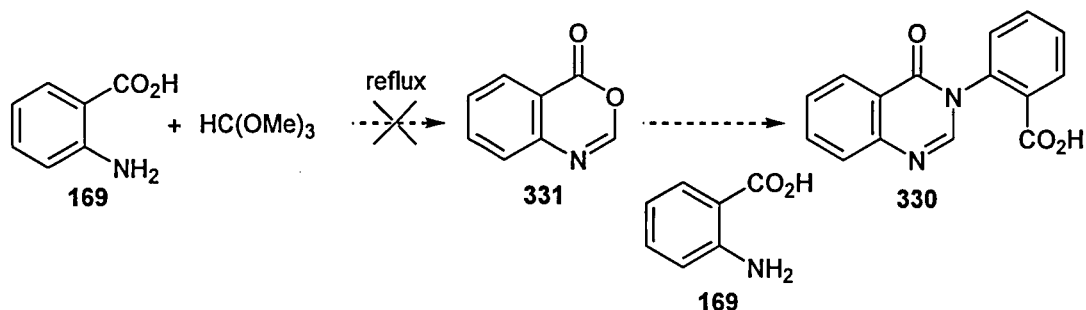
The planned synthesis involved acyl radical cyclisation onto C-2 of 3*H*-quinazolin-4-on (scheme 117). There was a reliance that the acyl radical would cyclise and not decarbonylate. It was envisaged that loss of CO from the acyl radical intermediate would not be a problem because of the strong sp^2 carbon bond. In the introduction, reports of reactions by Bennisar in which 2-acyl indolyl radicals were used in cyclisations without the loss of CO have been given (scheme 27).²⁶ There are no examples of 5-*exo/endo* acyl radical cyclisations onto heteroarenes in the literature to our knowledge.¹⁰⁸

Generation of the acyl radical **324** from the stable acyl selenide **329** was envisaged (scheme 117). Acyl selenides are easily formed from the respective carboxylic acids **330**. Unlike the other syntheses the required carboxylic acid **330** could not be prepared by *N*-3 alkylation. Therefore, it was planned to synthesise the acid **330** using condensation chemistry derived from anthranilic acid **169**.



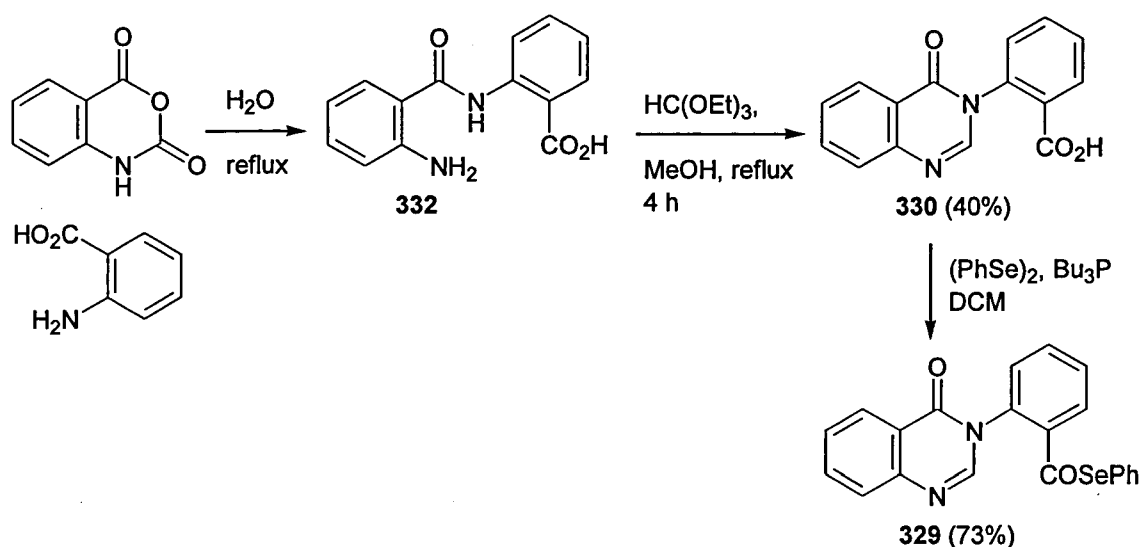
Scheme 117. Retrosynthesis of tryptanthrin using an acyl radical cyclisation.

The intermediate **331**, which has been reported by Khajavi *et al.* via the condensation of anthranilic acid and trimethyl orthoformate, looked a useful precursor (scheme 118).¹⁰⁹ Reaction between the intermediate **331** and anthranilic acid **169** should give the acid **330**. However, all attempts to make the intermediate **331** using the method reported by Khajavi failed and a new route was investigated to prepare the acid **330**.



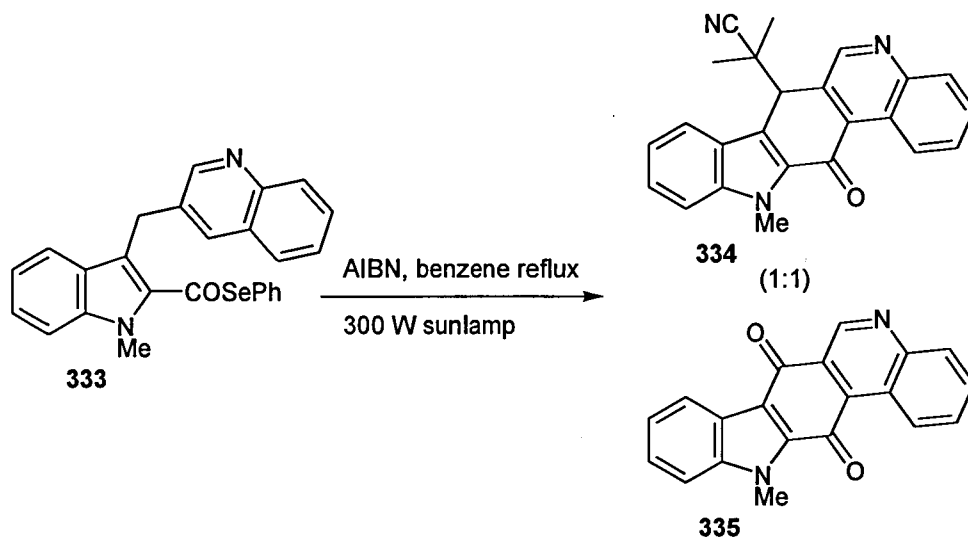
Scheme 118.

A literature method reported by John and Süss involving the condensation of isatoic anhydride with anthranilic acid to form the amide **332** was used instead (scheme 119).¹¹⁰ The amide **332** was reacted crude after workup with triethyl orthoformate to yield the acid **330**. An attempt to carry out the reaction neat in a one-pot procedure using isatoic anhydride, anthranilic acid and excess $\text{HC}(\text{OEt})_3$ resulted in a mixture of unidentifiable products. The acid **330** was readily converted to the acyl selenide **329** yielding the desired tryptanthrin radical precursor.



Scheme 119. Synthesis of tryptanthrin acyl radical precursor

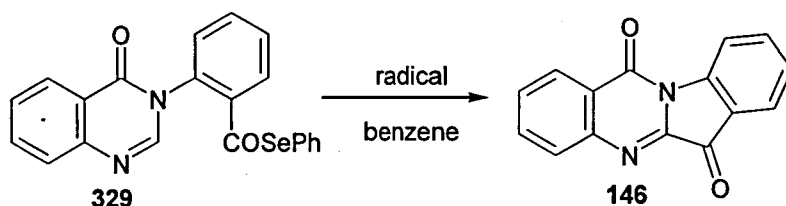
Bennasar has shown a number of unusual products arising from acyl selenide radical cyclisations onto heteroarenes.¹¹¹ For example the reaction of the 2-acylselenide **333** with AIBN and light irradiation produced the addition product **334** and the over oxidised product **335** (scheme 120). As previously stated, it was believed there are no examples of 5-*exo/endo* acyl radical cyclisations onto heteroarenes.



Scheme 120. Unusual acyl radical cyclisation products.

An initial attempt at radical cyclisation of the acyl selenide **329** was carried out using $(\text{Me}_3\text{Sn})_2$ in *t*-BuPh (table 13). After careful workup and purification a trace amount of tryptanthrin **146** was recovered along with an unidentified compound. When the reaction was carried out in benzene which has a lower boiling point, and with irradiation, no $\text{R}_3\text{Sn}^\bullet$ species was required to obtain tryptanthrin in a higher yield. The reaction mixture turned yellow before the boiling point had been reached. With this in mind, a third reaction was carried out at rt with just irradiation from a 300 W sunlamp. This resulted in the highest yield of tryptanthrin **146** (15%). The yields are poor, but as already mentioned no examples of this type of acyl radical cyclisation have been reported in the literature. An attempt to carry out a reaction using $h\nu/\text{AIBN}$ conditions as described by Bennasar lead to a mixture of unidentifiable products.¹¹¹ A final reaction was carried out in the absence of light irradiation, and the acyl selenide **329** was heated under reflux in benzene. Only starting material was recovered from this reaction, showing light irradiation was crucial to radical cyclisation.

Table 13. Radical cyclisation of **329** yielding tryptanthrin **146**.

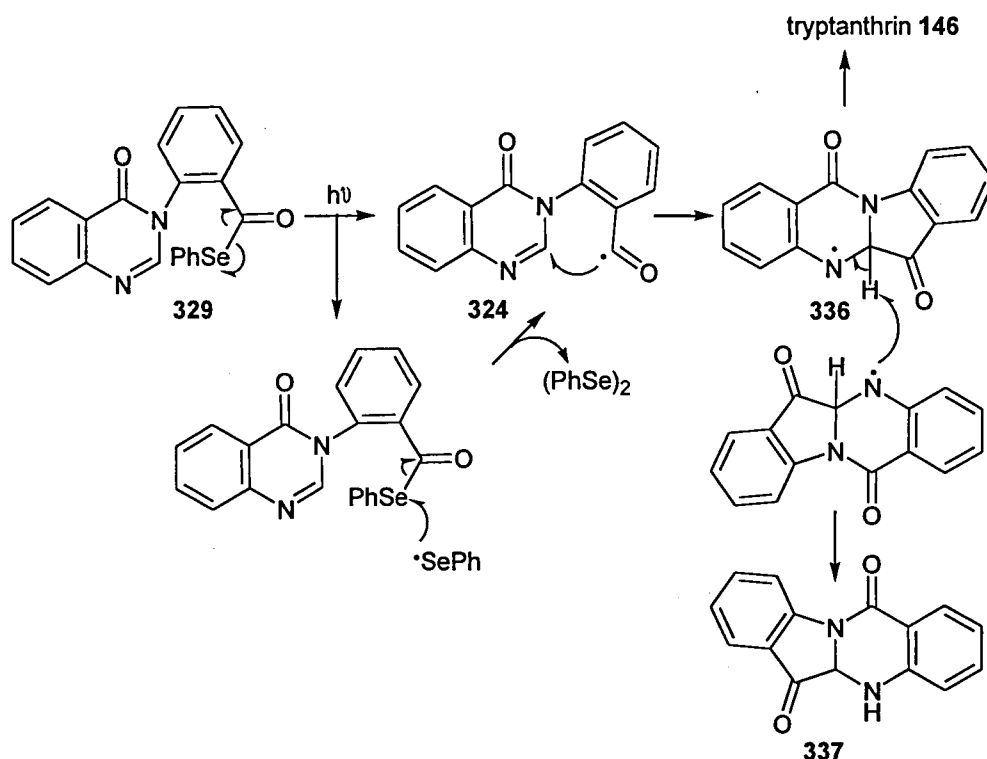


Reagent (equiv.)	Initiator	Time	Product
(Me ₃ Sn) ₂ (3.0) *	hν	4 h	Tryptanthrin 146 (3%) + unidentifiable
None	hν	10 h	Tryptanthrin 146 (13%) + unidentifiable
None **	hν	12 h	Tryptanthrin 146 (15%) + unidentifiable
None	No	24 h	SM
None	hν/AIBN	8 h	unidentifiable

* The reaction was carried out in *t*-BuPh.

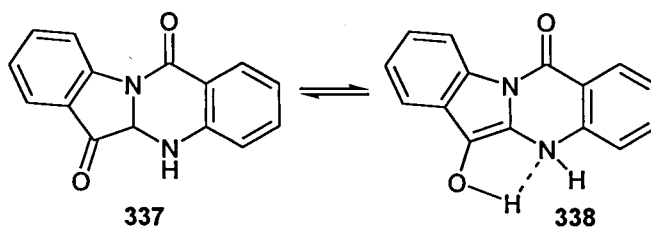
** The reaction was carried out at rt.

The mechanism of the formation of tryptanthrin in the absence of any radical reagent is unclear. The reaction rapidly turns to a yellow solution under light irradiation and the major isolated product is (PhSe)₂. No characteristic smell was detected, indicating the formation of phenylselanol is unlikely. A putative mechanism, involving initial homolysis of the Se-CO bond of the acyl selenide **329** is shown in scheme 121. The subsequent acyl radical **324** can cyclise and the phenylselanyl radical can propagate the reaction by forming diphenyl diselanide either by abstraction of PhSe from the acyl selenide or by dimerisation. The rearomatisation step yielding tryptanthrin **146** could arise from disproportionation of the σ-radical **336**. However, no products other than tryptanthrin and diphenyl diselanide were identified. The cyclised reduced quinazolinone **337** was not isolated.



Scheme 121. Putative radical mechanism for the synthesis of tryptanthrin.

Although the cyclised reduced quinazolinone **337** was not isolated, it may have been an unidentified reaction product. Its formation could be aided by the extra resonance stability from tautomer **338** which includes a weak hydrogen bonding interaction (scheme 122). It is stressed this is only a proposed mechanism based on observations from the reaction.

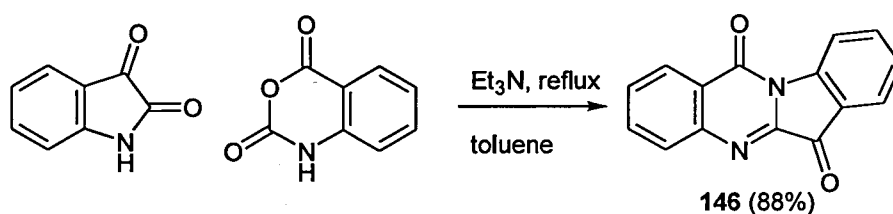


Scheme 122. Possible resonance stabilisation of dihydrotryptanthrin.

Although the yields of tryptanthrin **146** were low, the new protocol described gives a novel use of 5-*exo/endo* acyl radical cyclisation onto heteroarenes and a novel radical

synthesis of tryptanthrin. The reason for the success of the 5-*exo/endo* cyclisation may be explained by the 1-N to 2-C imine bond being localised, and not fully incorporated into the aromatic ring. This means the reaction could be envisaged as a 5-*exo* cyclisation onto an imine rather than 5-*exo/endo* cyclisation onto a heteroarene.

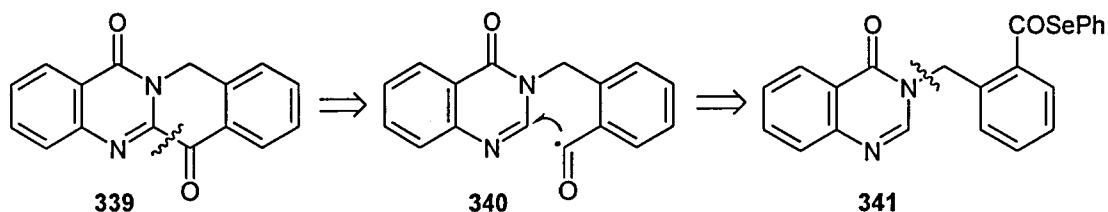
An authentic sample of tryptanthrin **146** was prepared using the method described by Ajaykumar *et al.* (scheme 123).¹⁰⁷ The ¹H and ¹³C NMR spectra were identical to the product of the radical syntheses of tryptanthrin. Mitscher *et al.* have shown NaH can be used instead of Et₃N, but this method failed to yield tryptanthrin in our hands.¹¹²



Scheme 123. Non radical synthesis of an authentic sample of tryptanthrin.

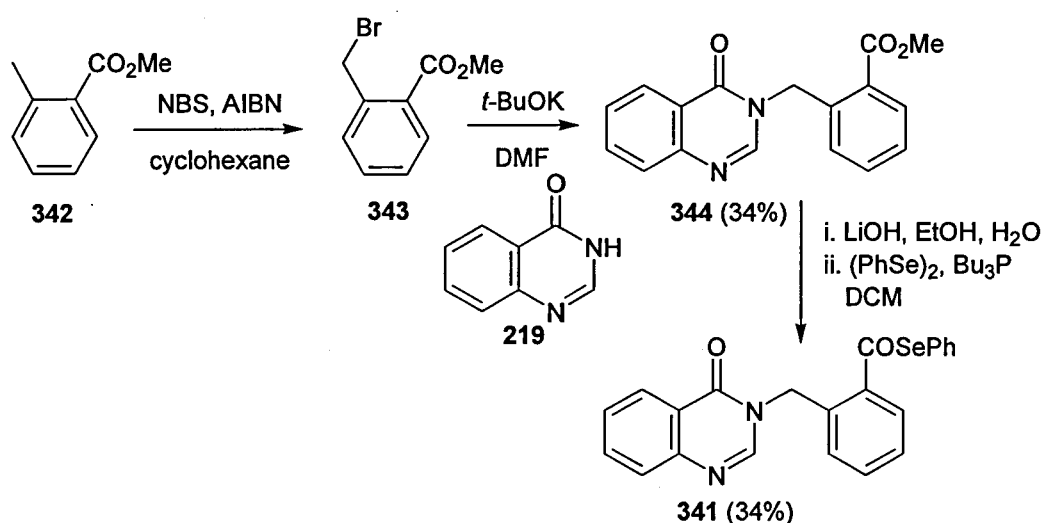
4.3 Radical synthesis of six-membered ring tryptanthrin analogue

The synthesis of the six-membered ring analogue **339** of tryptanthrin **146** was also investigated (scheme 124). The aim was to compare the 5-*exo* acyl radical cyclisation with the 6-*exo* acyl radical cyclisation of the intermediate **341**. From previous studies it was presumed that the cyclisation of the acyl radical **340** would be more favourable, and give the tetracyclic compound **339** in good yield. Numerous examples have already shown that 6-*exo* cyclisation is strongly favoured over 5-*exo/endo* cyclisation onto aromatic rings. Similarly to the previous tryptanthrin synthesis, it was planned to access the acyl radical from the acyl selenide **341**.



Scheme 124. Planned 6-*exo* acyl radical cyclisation.

The acyl selenide **341** proved harder to obtain than expected. Bromination of the *o*-methyl toluate **342** was carried using a literature procedure, but in poor yield (scheme 125).¹¹³ This reaction had previously been used and yielded the 2-(bromomethyl)toluate **343** was obtained in poor yield. Attempts at using a large excess of NBS had no effect, nor did carrying the reaction in the dark. Alkylation of 3*H*-quinazolin-4-one **219** using the 2-(bromomethyl)toluate **343** gave an overall disappointing yield of 34% of the quinazolinone ester **344**. Ester hydrolysis was carried out followed by formation of the acyl selenide using the same procedure for the previous tryptanthrin synthesis. The radical precursor acyl selenide **341** proved to be stable in air.

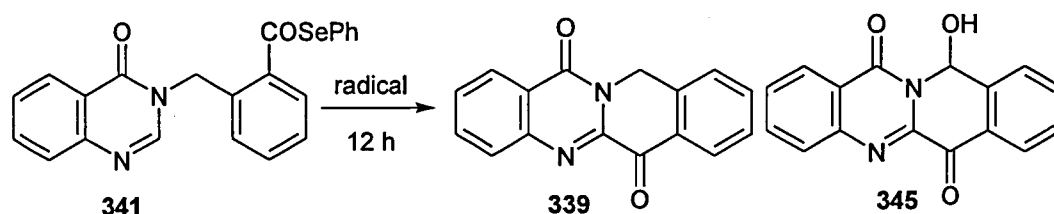


Scheme 125. Synthesis of the radical precursor **341**.

With the acyl selenide **341** in hand, various radical conditions were investigated to form the tetracycle **339**. It quickly became apparent that the formation of the tetracycle **339** was not favourable (table 14). The first attempt at cyclisation using (Me₃Sn)₂ produced a mixture of unidentifiable products. When this method was repeated, under a shortened reaction time, the unexpected hydroxytetracycle **345** was formed in moderate yield. Various other radical conditions were tried and resulted in starting material recovery or unidentifiable products. The other result of note occurred when the reaction was carried using only light irradiation. A ¹H NMR spectra of the

crude reaction mixture appeared to show a peak at 10 ppm, which may have corresponded to an aldehyde. However, the aldehyde was not isolated.

Table 14. Attempts at forming tetracycle 339.



Reagents (equiv.)*	Solvent	Reflux	Product
(Me ₃ Sn) ₂ (3.0)	Benzene	Yes	Unidentifiable
(Me ₃ Sn) ₂ (3.0) **	Benzene	Yes	345 (40%)
hν	MePh	No	Possible aldehyde
Et ₃ B (10.0)	DCM	No	SM
AIBN (3.0)	MePh	Yes	Unidentifiable
TTMSS (3.0) and Et ₃ B (10)	MePh	No	Unidentifiable

* The reaction time was 12 h.

** The reaction time was 3 h.

An X-ray crystal structure was obtained for the tetracycle **345** (figure 24). Until this point, the ¹H and ¹³C NMR spectra of this compound had been perplexing as identification of the formation of a hydroxyl group had not been envisaged.

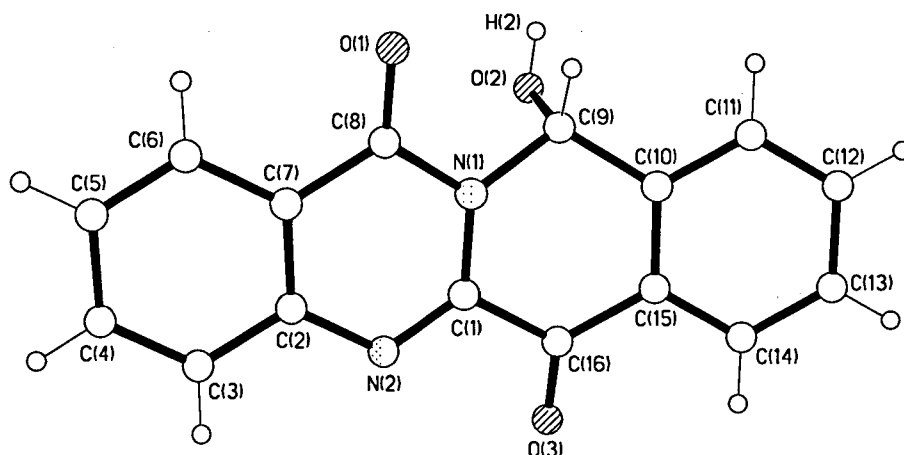
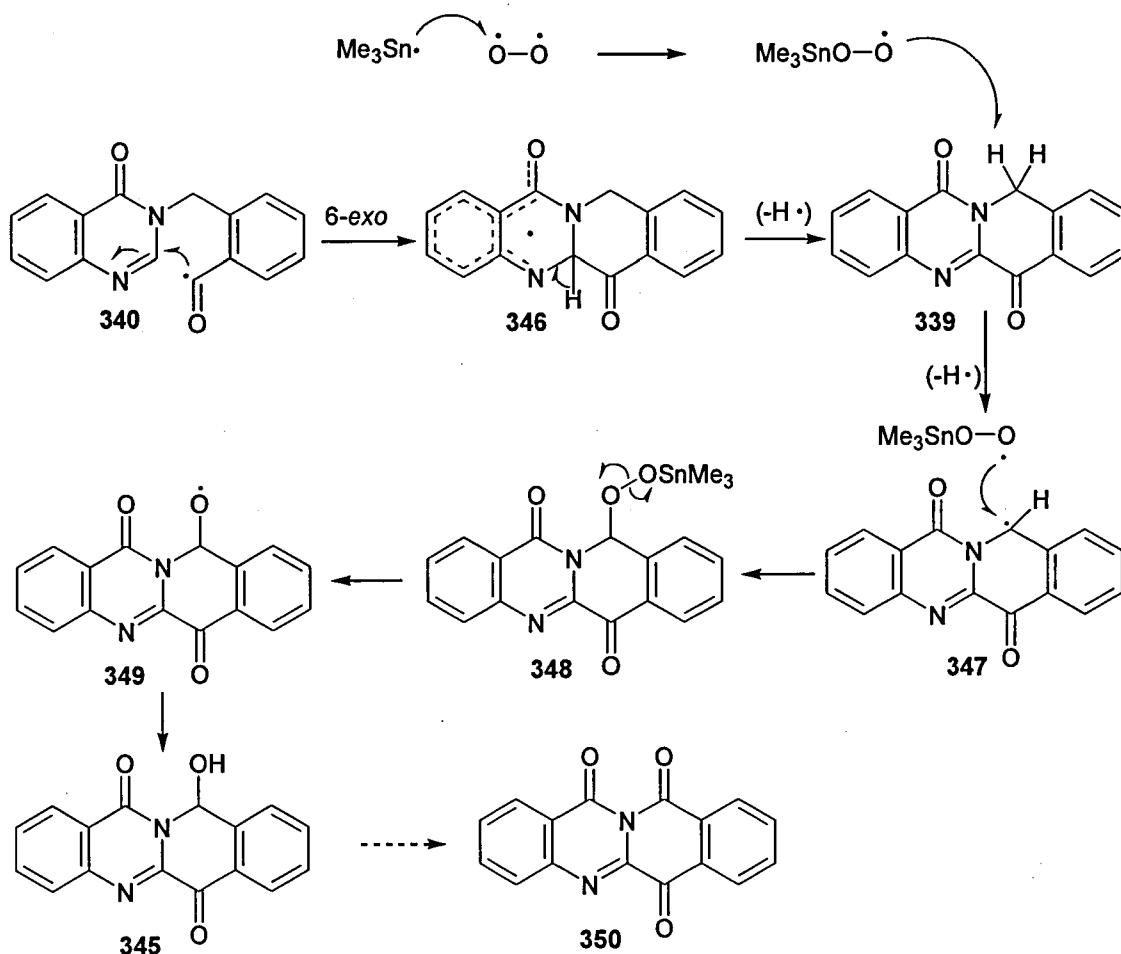


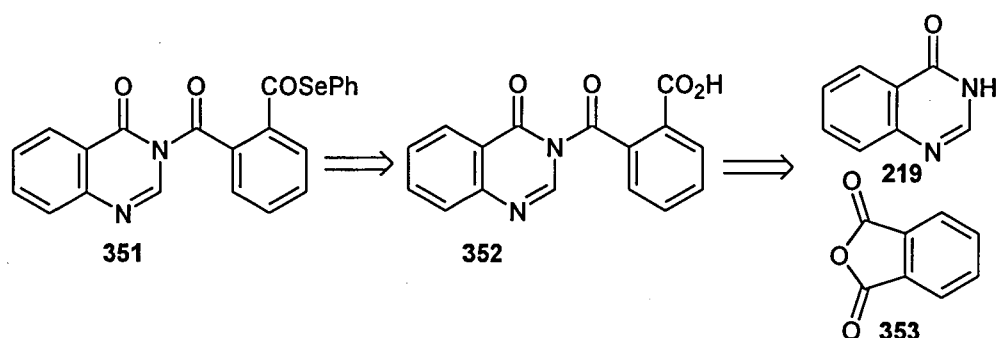
Figure 24. X-ray structure of hydroxytetracycle **345**.

A possible mechanism for the formation of the hydroxytetracycle **345** is shown in the scheme 126. Firstly, the acyl radical **340** undergoes a 6-*exo* cyclisation onto the quinazolinone. After rearomatisation of the π -intermediate **346** by loss of $\text{H}\cdot$ by some means (most likely $\text{Me}\cdot$ or $\text{MeOO}\cdot$) quinazolinone tetracycle **339** is produced. $\text{Me}_3\text{Sn}\cdot$ radicals can react rapidly with O_2 to form $\text{Me}_3\text{SnO}-\text{O}\cdot$ radicals which could then abstract one of the benzylic hydrogens, forming the benzylic stabilised radical **347**. Presumably the benzylic radical **347** has a sufficiently long lifetime to react further with $\text{Me}_3\text{SnO}-\text{O}\cdot$ and form the intermediate **348**. This could break down to leave the oxy radical intermediate **349**, which after H-abstraction forms the hydroxytetracycle **341**. It is surprising that the hydroxytetracycle **341** did not go on further to form the oxidised product **350**.



Scheme 126. Possible mechanism for formation of the hydroxytetracycle **345**.

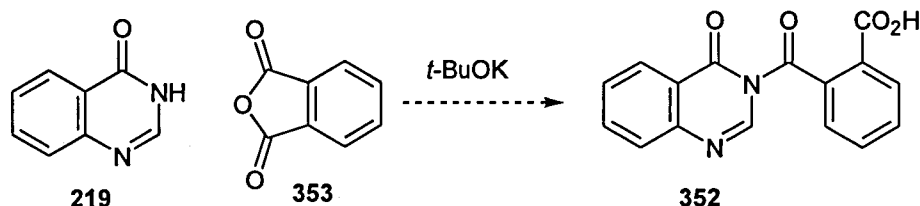
Whilst carrying out radical investigations of the acyl six-membered ring synthesis, simultaneous attempts to prepare the related acyl selenide precursor **351** were made (scheme 127). It was hoped that the acyl selenide precursor **351** might be easier to prepare and provide some interesting results given the apparent odd results previously obtained. It was considered that the acyl selenide analogue **351** would be easy to prepare from the acid **352** which in turn could be prepared by the reaction between 3*H*-quinazolin-4-one **219** and phthalic anhydride **353**.



Scheme 127. Planned route to new the acyl precursors **351**.

However, the reaction of 3*H*-quinazolin-4-one with phthalic anhydride proved unsuccessful under a variety of reaction conditions (table 15). It was clear that the 3-*N* quinazolinone anion **356** was being formed, because the colour of the reaction mixture turned yellow, however, no indication of the possible alkylation with phthalic anhydride **353** was seen in any crude ¹H NMR spectra.

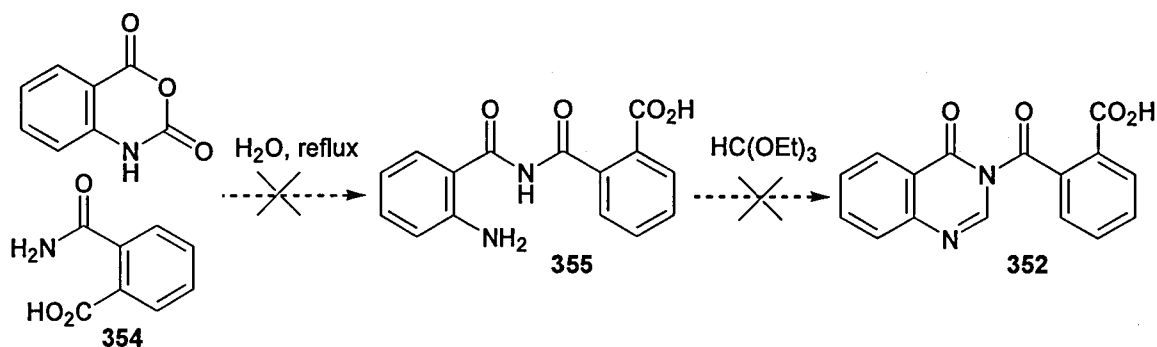
Table 15. Attempted synthesis of the acid **352**.



Solvent	Temperature	Product
DMF	rt	Unidentifiable
DMF	80 °C	Unidentifiable
THF	Reflux	Unidentifiable
DMF*	rt	Unidentifiable
DMF*	Reflux	Unidentifiable
MeCN*	Reflux	Unidentifiable

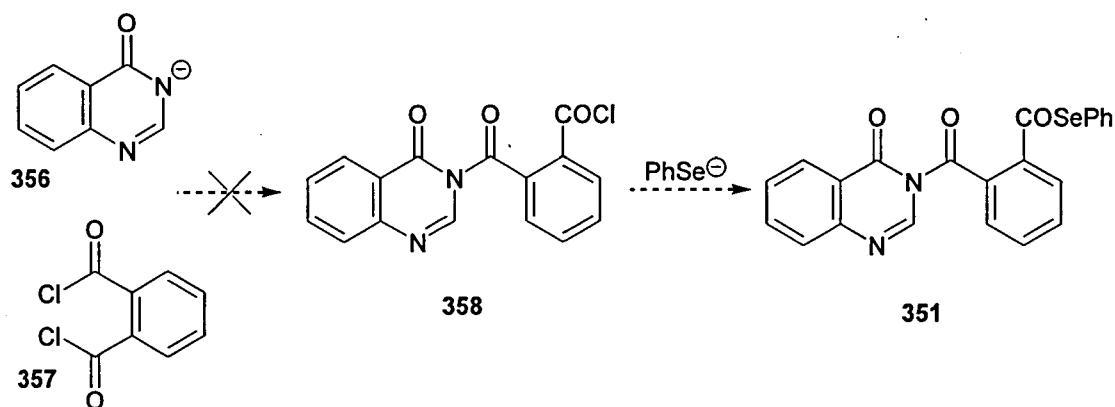
* A catalytic amount of DMAP added.

An attempt to prepare the acid **352** starting from anthranilamide **354** and isoatoic anhydride was undertaken (scheme 128). However, this route proved unsuccessful and the amide **355** was never isolated. An attempt to carry out this synthesis in one-pot also failed.



Scheme 128. Attempted synthesis of the acid **352**.

A final attempt to synthesise the acyl selenide **351** was made using phthaloyl dichloride **357** (scheme 129). It was hoped the 3-*N* quinazolinone anion **356** would react with phthaloyl dichloride **357**. The crude product **358** (if formed) of this reaction was reacted with PhSe^- , but no acyl selenide **351** was formed. Mixtures of unidentifiable products were obtained.

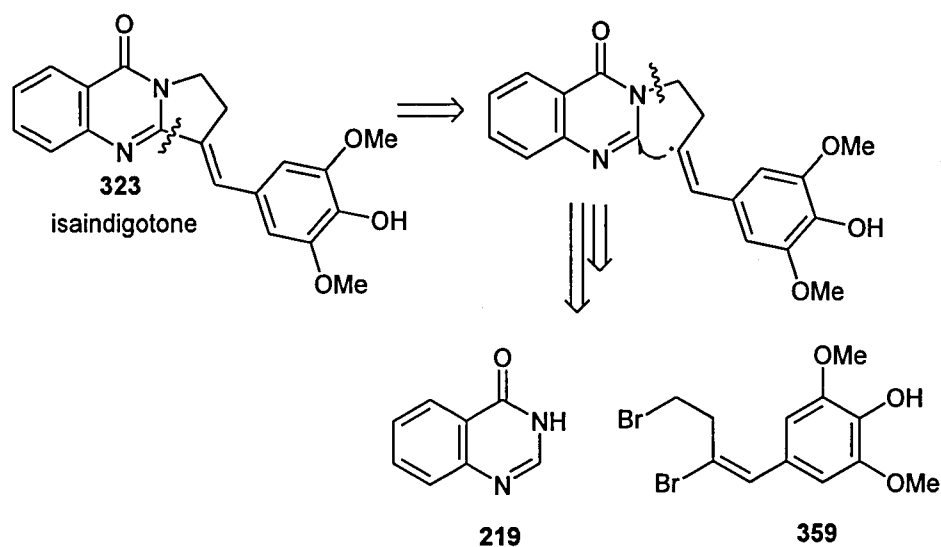


Scheme 129. Attempted synthesis of the acyl selenide **351**.

With attempts to form the acyl selenide **351** not proving profitable and failed attempts to form desired tetracycle **339** under radical condition, work was halted on acyl radical studies. The results from cyclisations of acyl radicals onto C-2 of 3H-quinazolin-4-one **219**, are unusual and in most part unexplained. Cyclisation of the five-membered ring to form tryptanthrin was observed, albeit in low yield. The six-membered ring acyl radical cyclisations results were disappointing, however, the unexpected hydroxytetracycle **345** was obtained in moderate yield.

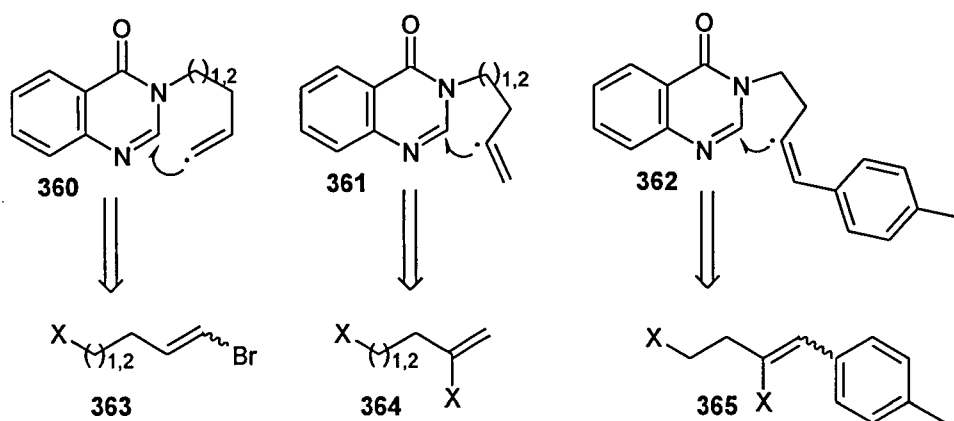
4.4 Investigations into alkenyl and vinyl radical cyclisations onto 3H-quinazolin-4-one

Having investigated aryl, alkyl and acyl radical cyclisations onto the 3H-quinazolinone moiety, attention was turned to the investigation of alkenyl radical cyclisations in the synthesis of natural product isaindigotone **323** (scheme 130). Only recently isolated, its biological activity is still under investigation.¹¹⁴ To date, there are very few syntheses of this quinazolinone natural product. The only notable synthesis was by Liu *et al.* using a one-pot microwave reaction already shown for the synthesis of mackinazolinone **148** (scheme 83).⁸² The planned synthesis of isaindigotone required alkylation of 3H-quinazolin-4-one with alkenyl radical precursor **359** side chain.



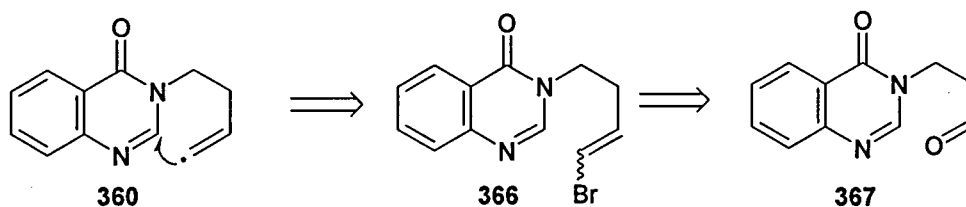
Scheme 130. Retrosynthesis of isaindigotone.

Alkenyl radical cyclisations onto the 3*H*-quinazolin-4-one template are unknown and therefore, it was decided to investigate a number of simpler systems before attempting the total synthesis of isaindigotone (scheme 131). The unhindered vinyl **360** and alkenyl **361** radicals were planned as the first experiments. This required the synthesis of substituted alkenes **363** and **364** for alkylation with 3*H*-quinazolin-4-one. The simpler alkenyl radical analogue of isaindigotone **362** was also planned from alkene **365** which did not contain the methoxy or hydroxy groups present on isaindigotone. There is a possibility these groups may hinder the radical cyclisation.



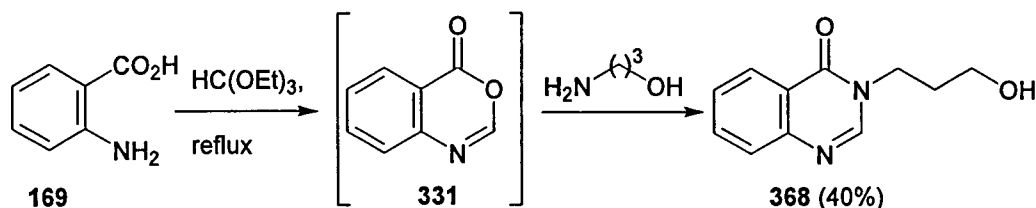
Scheme 131. Planned routes to vinyl and alkenyl radical cyclisations onto 3*H*-quinazolin-4-one

The initial investigation began with the study of the vinyl radical **360** (scheme 132). The planned retrosynthesis involved a Wittig reaction to make the key vinyl bromide **366**.¹¹⁵ The aldehyde **367** could be reached by either alkylation of 3*H*-quinazolin-4-one using 1-hydroxy-3-chloropropane and then oxidation or condensation chemistry of anthranilic acid, 1-amino-3-hydroxypropane and triethyl orthoformate.



Scheme 132. Retro synthesis of vinyl radical **366**.

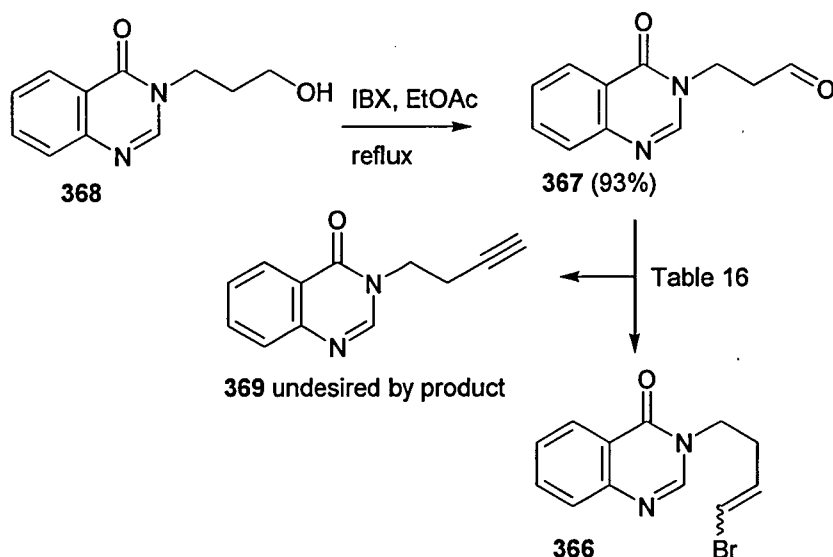
A condensation chemistry route with anthranilic acid was chosen (scheme 133). The reaction of anthranilic acid **169** and triethyl orthoformate was carried out followed by addition of 3-aminopropan-1-ol after the removal of excess triethyl orthoformate. The previous attempt to use the intermediate **331** reported by Khajavi *et al.* had been unsuccessful (scheme 118).¹⁰⁹ The overall yield of alcohol **368** was moderate. An attempt to adapt this procedure into a one-pot synthesis failed.



Scheme 133. Synthesis of the alcohol precursor **368**.

With the alcohol **368** in hand, oxidation was carried out to the aldehyde **367** using 2-iodoxybenzoic acid (IBX) in excellent yield (scheme 134). Kuroda and Masakatsu have reported Wittig reactions to form vinylbromides.¹¹⁵ The authors emphasized the

problem of the acetylene formation in the presence of an excess of base. The Wittig reaction with aldehyde **367** and bromomethylenetriphenylphosphorane was found to be problematic. Alkyne **369** was never isolated as a reaction side product. Eventually, the vinyl bromide **366** was formed in low yield (table 16).



Scheme 134. Synthesis of the vinyl bromide **366**.

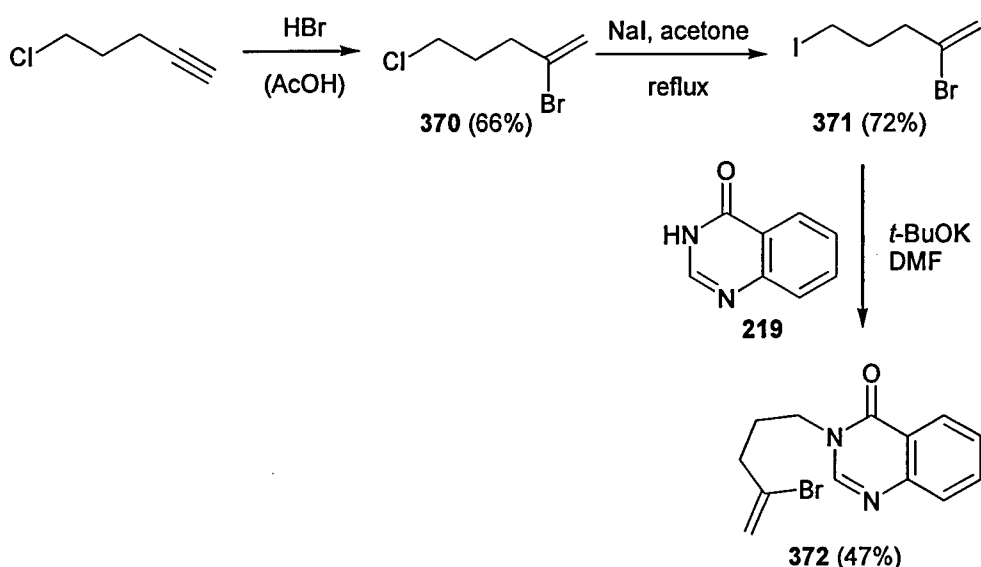
Table 16. Wittig reaction conditions (see scheme 134)

Base	Temperature	Solvent	Product
<i>t</i> -BuLi	-78 °C	THF	Unidentifiable
<i>n</i> -BuLi	-78 °C	THF	Unidentifiable
NaH	rt	DCM	Unidentifiable
<i>t</i> -BuOK	rt	DCM	Unidentifiable
<i>t</i> -BuOK	-78 °C	THF	366 (15%)

The radical reaction of vinyl bromide **366** using $(\text{Me}_3\text{Sn})_2$ resulted in a mixture of unidentifiable products. Given the poor yield of the Wittig reaction it was decided not to pursue this work any further. It was decided to concentrate on the synthesis of alkene radicals **360** and **361** which were more closely related to isaindigotone.

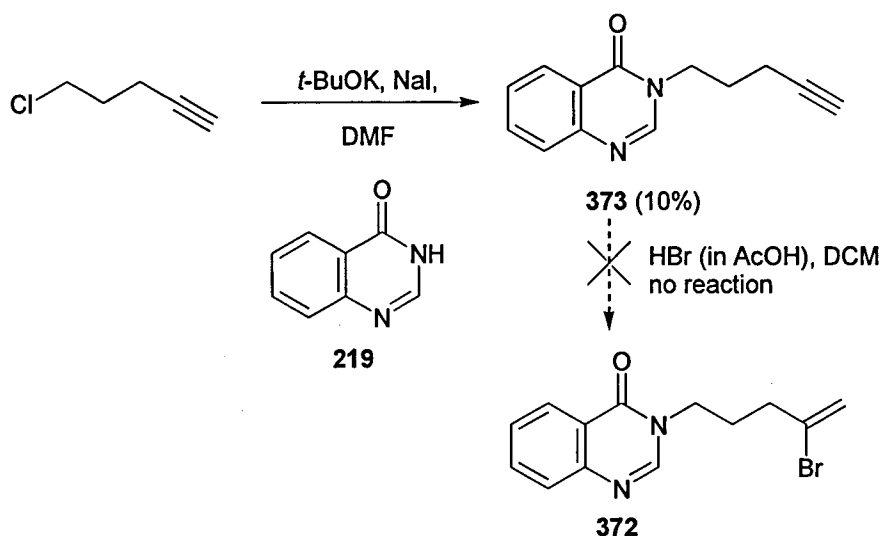
The synthesis of the bromoalkene quinazolinone **372** was the first target (scheme 135) which could undergo radical cyclisation to form a six-membered ring onto the 3*H*-quinazolin-4-one **219** moiety. The literature procedure of Köllner and Molander was

chosen for the bromination of alkynes using HBr in AcOH.¹¹⁶ Using Köllner and Molander's methodology, 5-chloro-1-pentyne was cleanly converted to the bromoalkene **370**. A Finkelstein reaction was carried out to form iodobromo alkene **371**. Alkylation onto the 3*H*-quinazolin-4-one **219** gave the desired bromoalkene quinazolinone **372**.



Scheme 135. Synthesis of the vinyl radical precursor **372**.

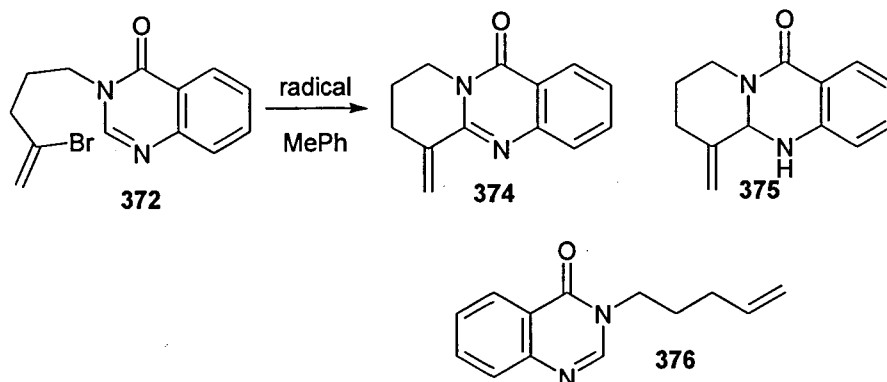
To reduce the number of synthetic step it was decided to by alkylate 3*H*-quinazolin-4-one **219** with 5-chloro-1-pentyne (scheme 136). However, the alkylation using 5-chloro-1-pentyne to produce the terminal alkyne **373** proceeded in a poor yield. It was disappointing when this alkyne was treated with HBr in DCM, no bromination took place, even after two days. Complete recovery of the starting material was observed. This result was most unexpected and given the poor yield of the alkylation reaction this particular route was not investigated further. It was decided to use the previous synthesis of bromoalkene quinazolinone **372** (scheme 129).



Scheme 136. Attempted synthesis of the bromoalkene quinazolinone **372**.

However, the radical reaction of the bromoalkene quinazolinone **372** did not prove straightforward. The initial attempts using $(\text{Me}_3\text{Sn})_2$ resulted in a mixture of starting material and unidentifiable products (table 17). The reaction was repeated using a fresh ampoule of $(\text{Me}_3\text{Sn})_2$, but the reaction failed again. Use of Bu_3SnH and Et_3B also failed. A GC-MS chromatogram of this reaction revealed three peaks. Two of the peaks on the chromatogram are likely to be the cyclised quinazolinone **374** and the reduced quinazolinone **376**. No clean ^1H NMR spectra could be obtained from this reaction. In the reaction using Bu_3SnH and AIBN, a ^1H NMR spectrum of the reduced quinazolinone **376** was obtained. However, the yield of this product was low (<5%). The reduced cyclised quinazolinone **375** was never identified in any of these reactions. The reduced quinazolinone **376** was prepared unambiguously *via* the reaction of 3H-quinazolin-4-one **219**, $t\text{-BuOK}$ and 5-bromopent-1-ene in DMF in good yield (44%) to help with characterisation.

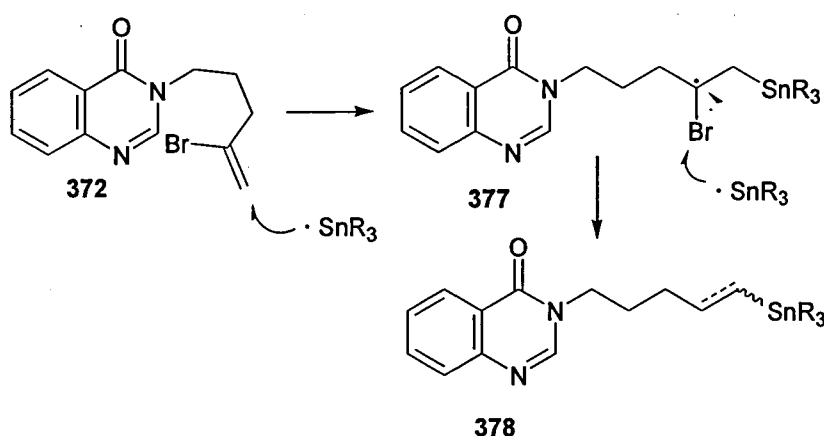
Table 17. Attempted radical reactions of the alkenylbromide **372**.



Radical reagent (equiv.)	Initiator (equiv.)	Reflux	Product
(Me ₃ Sn) ₂ (3.0)*	hν	Yes	SM + decomposition
Bu ₃ SnH (4.0)	Et ₃ B (10)	No	SM + decomposition
Bu ₃ SnH (2.0)	Et ₃ B (10)	No	SM + decomposition
Bu ₃ SnH (2.2)	AIBN (2.2)	Yes	376 (<5%) decomposition
TTMSS (3.0)	Et ₃ B (10)	No	SM + decomposition

*The reaction was carried out in *t*-BuPh.

An explanation for the failures may be explained by the potential addition of $\cdot\text{SnR}_3$ to the bromoalkene **372** (scheme 137). Quinazolinone radical intermediate **377** could react further to produce quinazolinone **378**. Quinazolinone **378** was not isolated, but its formation cannot be ruled out.

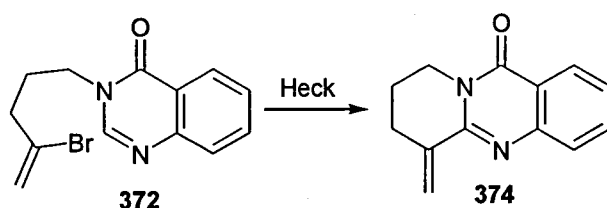


Scheme 137. Possible unwanted radical side reactions.

With the unexpected failure of the radical reaction and having a large quantity of the precursor to hand it was chosen to investigate some Pd-catalysed reactions (table 18).

These proved unsuccessful and were not pursued as new work was undertaken. There was disappointment that no Pd-catalysed reactions for bromoalkenes were observed. These results were similar to those observed in the case of arylbromides above.

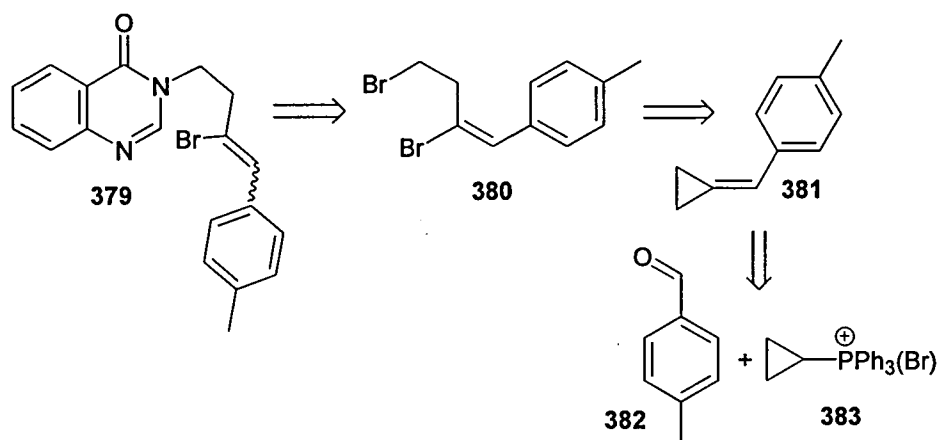
Table 18. Failed Heck conditions



Pd source	Ligand	Base	Solvent	Temperature
Pd ₂ (dba) ₃	PBu ₃	Cy ₂ NMe	Dioxane	Reflux
Pd ₂ (dba) ₃	PBu ₃	NEt ₃	Dioxane	Reflux
Pd(OAc) ₂	PPh ₃	<i>i</i> -Pr ₂ NEt	DMF	Reflux
Pd(OAc) ₂	PPh ₃	NEt ₃	neat	Reflux
Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	DMF	Reflux
Pd(PPh ₃) ₄	none	NEt ₃	MeCN	10 min*
Pd(PPh ₃) ₄	none	<i>i</i> -Pr ₂ NEt	THF	10 min *

*The reaction was carried out in a microwave reactor.

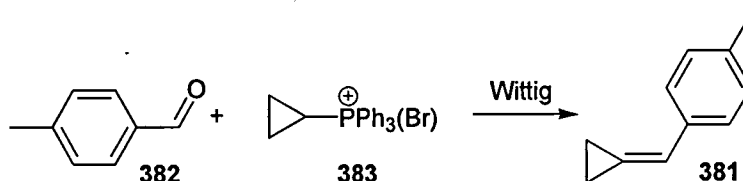
With both radical and Pd-catalysed cyclisations not proving successful for the bromoalkenequinazolinone **372**, it was decided to move onto the synthesis of the alkene **379** (scheme 138). It was hoped dibromo compound **380** could be accessed *via* the ring-opening of the cyclopropene **381** with CuBr₂ as shown by Brinker and Nordvik.¹¹⁷ The cyclopropene **381** should be synthesised from a Wittig reaction of 4-methylbenzaldehyde **382** and the commercially available cyclopropane Wittig reagent **383**.



Scheme 138. Retrosynthesis of the alkene radical precursor **379**.

After several attempts, the Wittig reaction was successfully carried out (table 19). The reaction worked best when the Wittig reagent, the base and the aldehyde were reacted in one-pot. This indicated the intermediate ylid has a short lifetime.

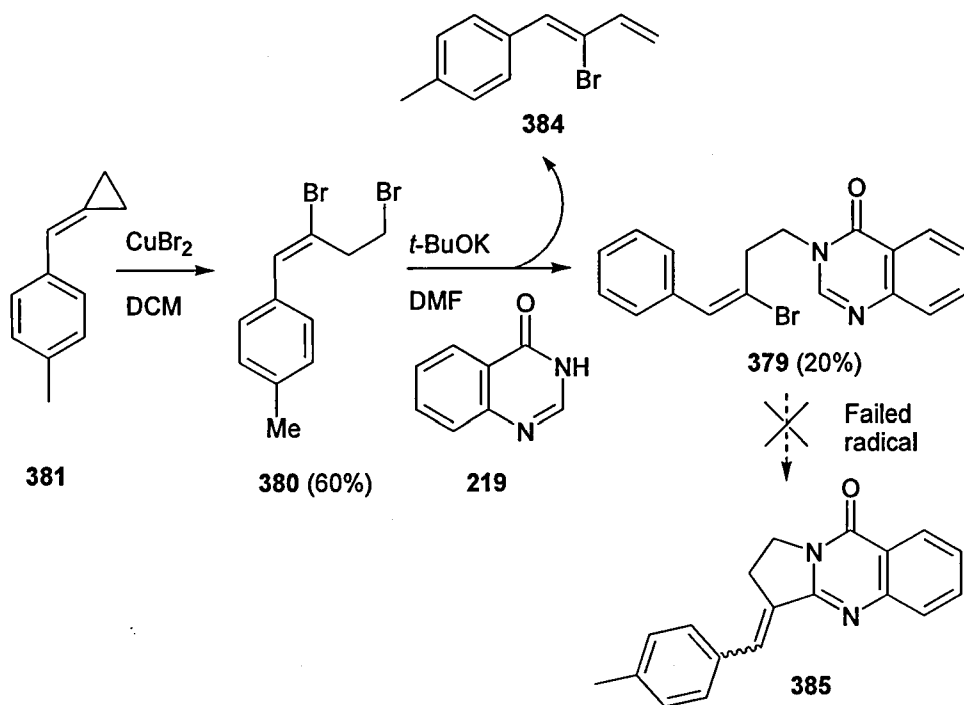
Table 19. Wittig synthesis of the cyclopropene **383**.



Base	Solvent	Time	Temperature	Product
NaH	THF	12 h	Reflux	SM
<i>n</i> -BuLi	THF	12 h	-78 °C → rt	Unidentifiable
NaH (slow)	THF (ultra dry)	4 h	Reflux	SM
NaH (slow)	THF +4Å sieves	12 h	Reflux	SM
<i>t</i> -BuOK	DCM	12 h	rt	381 (<5%)
<i>t</i> -BuOK	DCM	12 h	Reflux	381 (44%)

After successfully preparing the cyclopropene **381**, the ring-opening reaction was carried out using CuBr_2 to yield dibromide **380** (scheme 139). It wasn't envisaged that the alkylation of 3H-quinazolin-4-one **219** using the dibromide **380** would prove difficult not prove difficult. However, after several attempts, it was realised that the styrene **384** was the major reaction product and the yield of the alkylation

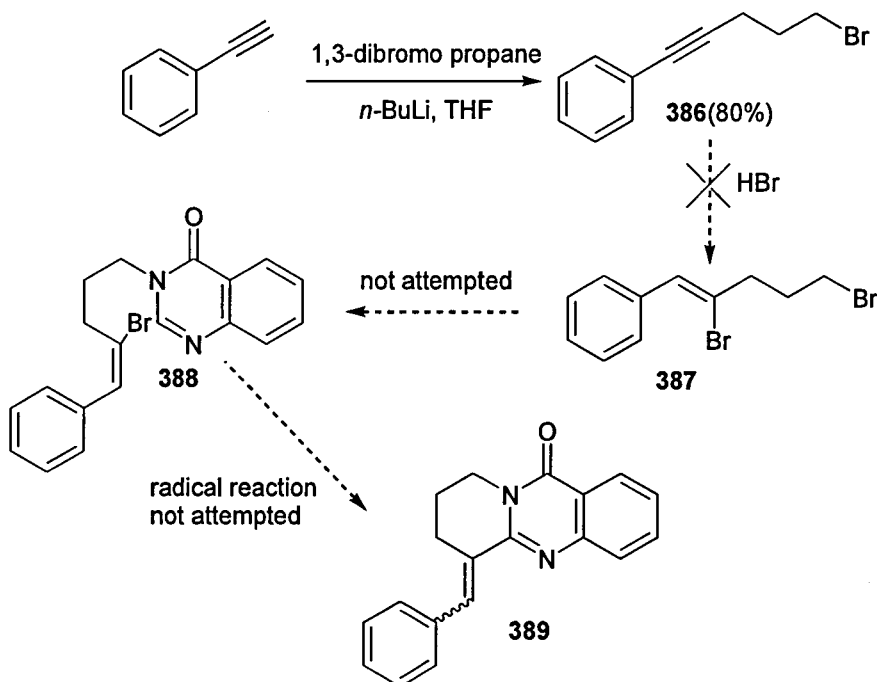
quinazolinone **379** was lower than expected. This is the first example of an attempted alkylation of 3*H*-quinazolin-4-one **219** where the elimination reaction competed with the S_N2 substitution. Finally a small amount of the alkylated product **379** was obtained which was reacted under radical conditions using $(Me_3Sn)_2$. It was disappointing that cyclisation did not occur and a number of unidentifiable products were recovered. The reaction was investigated twice more using Bu_3SnH/Et_3B and $Bu_3SnH/AIBN$ but this also resulted in number of unidentifiable products being produced. The cyclised product quinazolinone **385** was never obtained.



Scheme 139. Failed radical reactions of the hindered alkene.

A final alkene radical synthesis was attempted in which it was hoped to form a six-membered ring quinazolinone **389** using radical cyclisation using with the bromoalkene quinazolinone **388** similar to quinazolinone **385** (scheme 140). Key to this synthesis was the bromination of alkyne **386** which had been prepared *via* a literature procedure.¹¹⁸ However, bromination using HBr appeared to give a mixture of unidentified products. As a result, dibromide **387** was never obtained. Had time

permitted, further investigations of this route would have been pursued. It is believed that bromination of the alkyne could be achieved given more time.



Scheme 140.

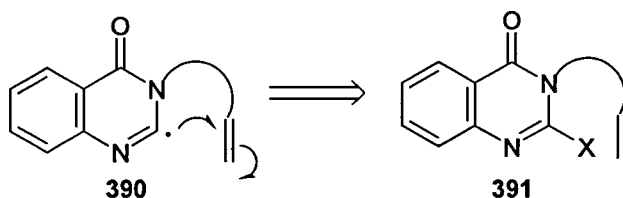
It was disappointing that alkenyl and vinyl radical cyclisations onto quinazolinones were not successful. It has been shown that these types of radical cyclisations onto quinazolinones are largely unfavourable. Had time permitted further attempts at radical cyclisations would have been carried out.

4.5 Conclusions

This chapter concludes the work in natural product synthesis using the radical cyclisation chemistry. A novel synthesis of tryptanthrin 146 has been shown and further discussion of acyl radical cyclisations. An unusual hydroxytetracycle 345 was identified in the six-membered ring radical cyclisation. The discussion and investigations of vinyl radical cyclisations onto 3*H*-quinazolin-4-ones has also been shown. This was not successful and no radical cyclisation products were obtained from these reactions. It had been hoped this would allow access to the natural product isaindigotone 323.

Chapter 5. Syntheses of 2-bromo-3*H*-quinazolin-4-one

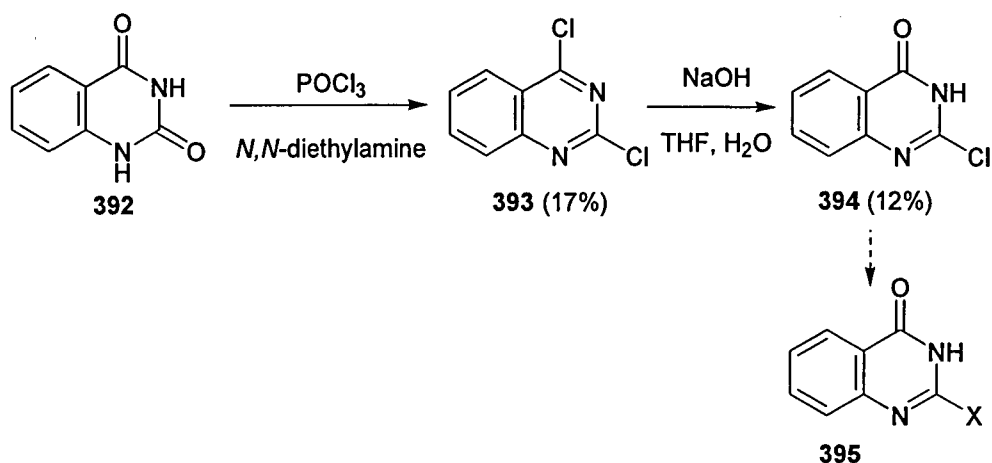
During the investigations of radical cyclisations, it was also considered whether it would be possible to form a radical on the C-2 position of the quinazolinone **390** (scheme 141). At the time no reports of the insertion of suitable functionality (e.g. bromine) have been described at this position on the 3*H*-quinazolin-4-one **391**. It was hoped that if it could be formed open up a new area of radical reactions.



Scheme 141. Proposed radical cyclisation from C-2 of 3*H*-quinazolin-4-one.

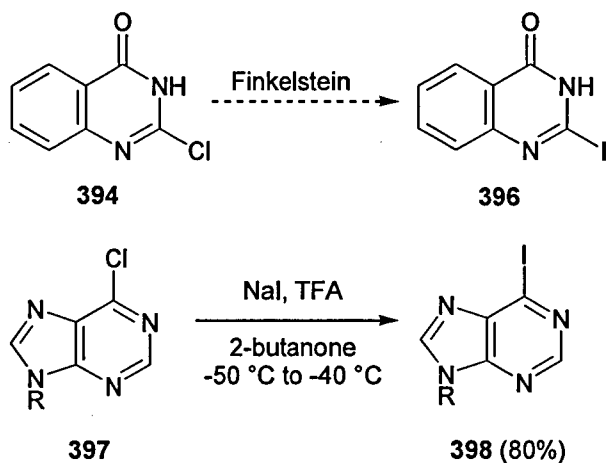
5.1 Investigation into the syntheses of a C-2 radical quinazolinone building block

2-Chloro-3*H*-quinazolin-4-one **394** is well reported in the literature and can be prepared from the 2,4-diketoquinazolinone **392** (scheme 142).¹¹⁹ It was hoped that a method could be developed to convert the chlorine of 2-chloro-3*H*-quinazolin-4-one **394** to a better radical leaving group as in quinazolinone **396**. 2-Chloro-3*H*-quinazolin-4-one **394** was prepared using a procedure by Hess. It was found the 2,4-diketoquinazolinone **392** and 2-chloro-3*H*-quinazolin-4-one **394** difficult to handle, both were insoluble in organic solvents, even in DMF. Hydrolysis of 2,4-dichloroquinazolinone **393** occurs solely at C-4. Confirmation of the 2-chloroquinazolinone **394** came from an IR spectral analysis, which clearly showed a secondary amide carbonyl peak at 1653 cm⁻¹.



Scheme 142. Synthesis of 2-chloroquinazolinone.

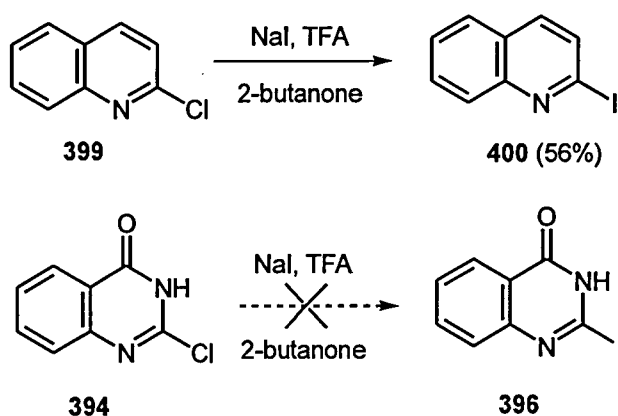
The question remained whether 2-chloro-3*H*-quinazolin-4-one **394** could be converted to the 2-iodo-3*H*-quinazolin-4-one **396** via a Finkelstein S_NAr type reaction (scheme 143). Normally Finkelstein reactions are limited to alkyl halides. However, Janeba *et al.* have shown *N*-heterocycles can also undergo these reactions in the presence of an acid such as TFA.¹²⁰ Janeba showed that 6-chloro purine **397** was converted to 6-iodopurine **398**.



Scheme 143.

Before attempting this reaction on 2-chloro-3*H*-quinazolin-4-one **394**, the simpler 2-chloroquinoline **399** substrate was tested first (scheme 144). The method appeared to

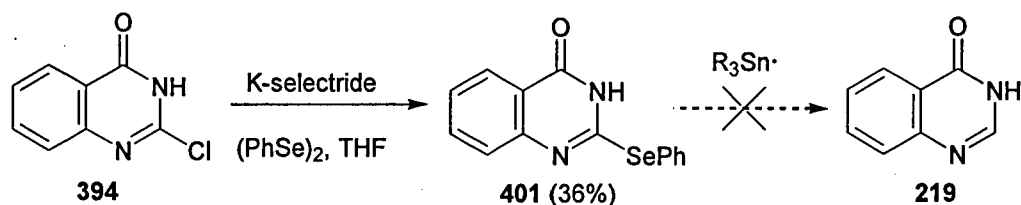
work well using NaI and TFA and 2-iodoquinoline **400** was formed in good yield. It was presumed the acid is required to protonate the quinoline to facilitate nucleophilic attack of the iodine. Janeba *et al.* reported that such reactions need to be carried out at low temperature to increase the lifetime of the intermediate.¹²⁰ However, it was found that the low temperature was not necessary and reached the highest yield of 2-iodoquinoline **400** at room temperature. Attempt to carry out the same reaction using 2-chloro-3*H*-quinazolin-4-one **394**, gave several unidentifiable products. It was clear that reaction was not compatible using the 2-chloroquinazolin-4-one **394** and no further attempts at preparing 2-iodo-3*H*-quinazolin-4-one **396** were made using this reaction.



Scheme 144.

Next, it was considered if the 2-chloro-3*H*-quinazolin-4-one **394** could be converted to the 2-(phenylselanyl)-3*H*-quinazolin-4-one **401** even though there was uncertainty whether this would be synthetically useful in radical chemistry (scheme 145). The results previous from the 3-(2-hydroxyethyl)-2-(phenylselanyl)-*N*Boc-indole **319** showed no reaction when treated under radical conditions (scheme 112). Nevertheless, it was decided to prepare the selenide which was carried out by the reaction of (PhSe)₂ and K-selectride in THF, which is a well known method of forming imidoyl selenides from their chloro analogues within the group.³⁷ Although the 2-(phenylselanyl)-3*H*-quinazolin-4-one **401** was made in reasonable yield, no reaction took place when treated under radical conditions using Bu₃SnH/Et₃B. The sp²C-Se bond is obviously too strong. There are no reports in the literature of cleaving

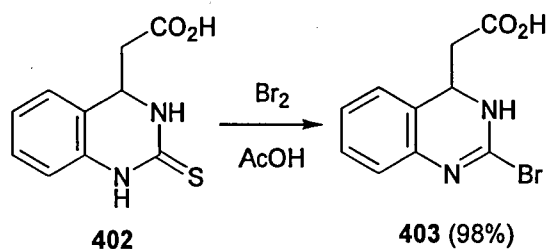
the Ph-Se bond in radical reactions so the result is not unusual. Given this result and that of the 3-(2-hydroxyethyl)-2-(phenylselanyl)-*N*Boc-indole **319**, this work was not continued. Given these disappointing results in attempting to make a suitable C-2 radical quinazolin-4-one precursor inspiration from the literature was sought.



Scheme 145. Unsuccessful radical reaction of 2-phenylselanyl-3*H*-quinazolin-4-one.

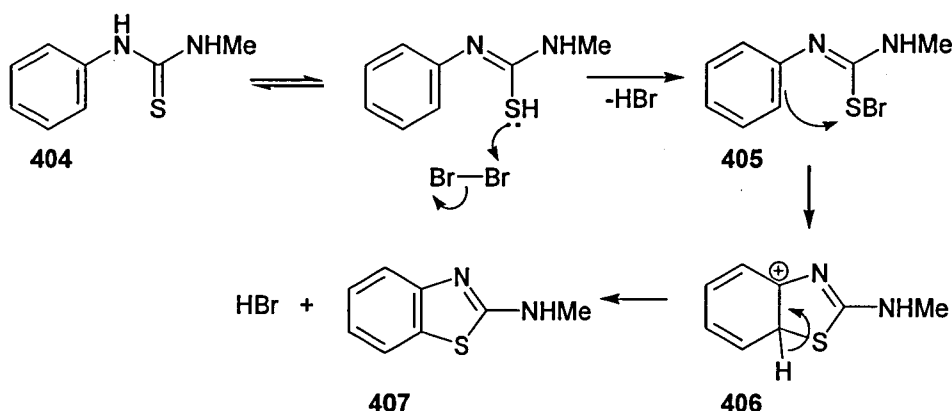
5.2 Introduction to bromination of thioamides and thioureas

A reaction by Hull and Swain caught our attention (scheme 146). The authors had reported the reaction of 1,2,3,4-tetrahydro-2-thioxoquinazolin-4-yl-acetic acid **402** with bromine in acetic acid, leading to 2-bromo-3,4-dihydroquinazolin-4-yl-acetic acid **403**.¹²¹ This immediately posed the question whether the same reaction could be carried out to provide a route to C-2 substituted quinazolin-4-one **395**. Hull and Swain gave no account of the possible mechanism. It was decided to look more closely in the literature to find out more about the reaction of thioureas and thioamides with bromine. The next few pages consist of an introduction covering the notable reactions of thioureas and thioamides with bromine or other brominating species. This short review is intended to provide an introduction into the work, which was carried out to form a 2-bromo-3*H*-quinazolin-4-one building block **241** (scheme 77).



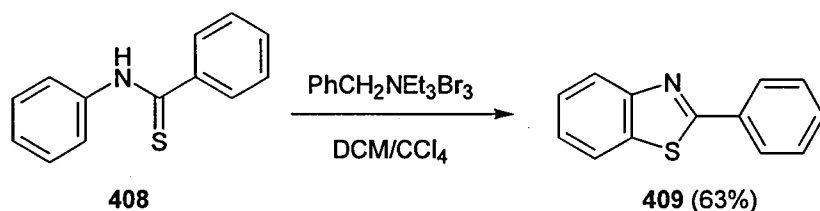
Scheme 146. Bromination of 1,2,3,4-tetrahydro-2-thioxoquinazolin-4-yl-acetic acid **402** by Hull and Swain.¹²¹

The reaction of thioamides and thioureas with bromine is not unprecedented in the literature. However, the reactions do not usually produce imido-yl-bromides as Hull and Swain had shown and more often result in cyclisation *via* a sulfanylbromide intermediate.¹²¹ A classic example of this is the Hegerschoff reaction to form benzothiazoles. Jordan *et al.* have used this reaction recently in the synthesis of various substituted benzothiazoles **407** (scheme 147).¹²² For example, the reaction between thiourea **404** and bromine forms intermediate sulfanylbromide **405**, which is followed by cyclisation and rearomatisation **406** to produce benzothiazole **407**.



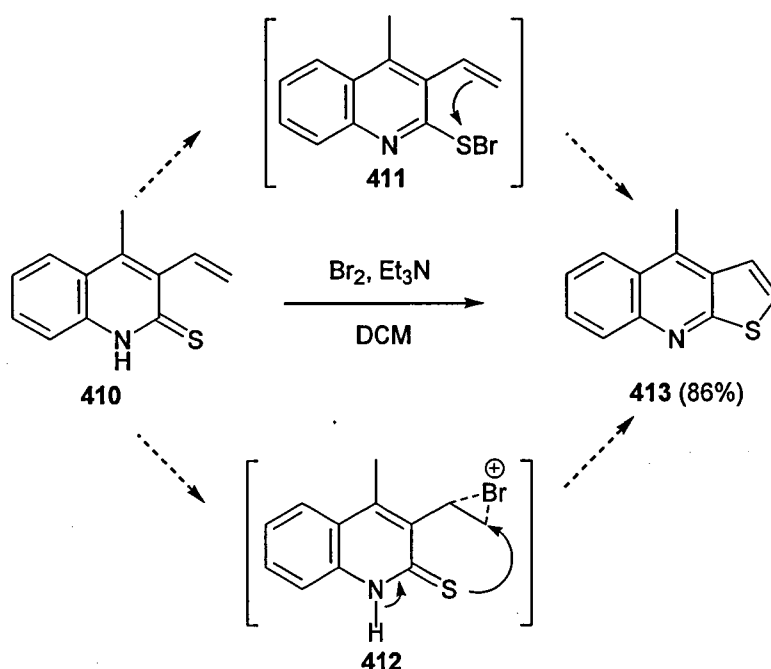
Scheme 147. The Hegerschoff synthesis of benzothiazole.

Similar reactions exist in the literature using thioamides. Moghaddam and Boeini have reported the cyclisation of thioamide **408** using organic ammonium tribromide species (OATB) to form benzothiazole **409** (scheme 148).¹²³ Organic ammonium tribromide species were used instead of bromine as they are usually solid and much easier to handle. Cyclisation presumably takes place *via* a similar mechanism as described in scheme 147.



Scheme 148. Oxidative cyclisation of thioamide using OATB.

The driving force for rearomatisation plays a major role in these reactions. Shanmugam *et al.* have shown a similar reaction for 2-thioquinoline **410** which cyclised to form tricyclic quinoline **413** (scheme 149).¹²⁴ However, the authors believe this reaction takes place *via* bromination of the alkene **412** rather than the double bond attacking sulfanylbromide **411**. None the less this reaction constitutes a possible example of bromine addition to a thioamide. The 5-*exo* cyclisation of the alkene onto the sulfanylbromide **411** appears more favoured than the 5-*endo* cyclisation of the thioamide **412** onto the alkene.



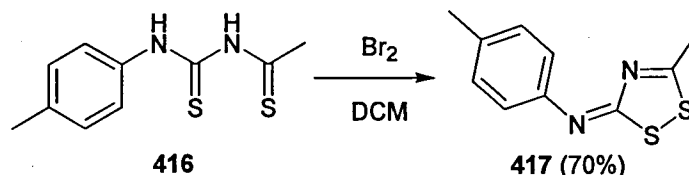
Scheme 149. Cyclisation of a thioquinoline using bromine.

The bromination of thioamides and thioureas has also been shown to give a wide range of different products. There are examples where bromination of thioamides has led to disulfides (scheme 150). Ali and McDermott have shown that the reaction of 2-thiopyridine **414** leads to formation of bis(2-pyridyl) disulfide **415**.¹²⁵ This is perhaps expected due to the strong aromatic nature of 2-thiopyridine. Other examples of disulfide formation of 2-thiobenzimidazole are also reported in the literature.¹²⁶



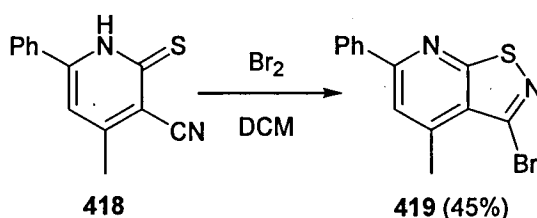
Scheme 150. Formation of disulfides.

A related reaction is the reaction between thioacyl urea compounds **416** and bromine to form dithiazoles **417** (scheme 151). Verma *et al.* has reported a number of these examples.¹²⁷ Ali and McDermott's reaction in scheme 145 proceeded *via* the sulfanylbromide being trapped by intermolecular sulfur addition,¹²⁵ whereas in the examples by Verma, intramolecular sulfur addition is seen.¹²⁷



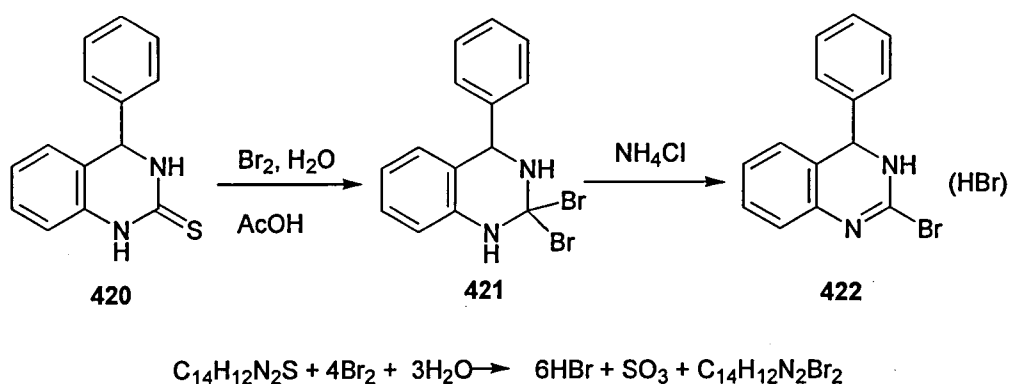
Scheme 151. Formation of a dithiazole using bromine.

Gewald *et al.* have shown that the sulfanylbromide intermediate can be trapped with nitriles (scheme 152).¹²⁸ However, nitrogen attack of the nitrile **418** is only facilitated by concomitant addition of bromide to the nitrile, this explains the presence of a bromine atom on cyclised product **419**. This is not the only example of nitrogen intercepting such intermediates. Bossio *et al.* have shown a similar example of nitrogen interception of sulfanylbromide intermediate using benzimidazoles.¹²⁹ The literature also contains examples of nitrogen attack from amidines and amides.^{130, 131}



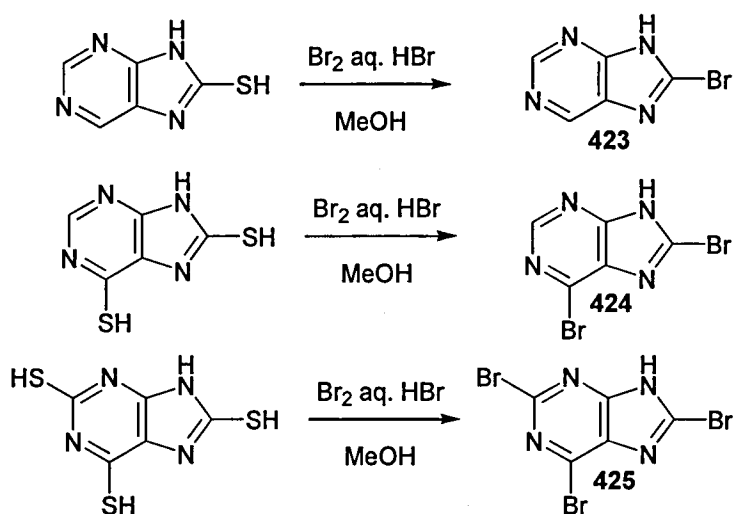
Scheme 152. Isonitrile cyclisation onto sulfur using bromine.

There are other examples in the literature where brominated products such as Hull and Swain's 2-bromo-3,4-dihydroquinazolin-yl-acetic acid **403** have been isolated. A very early example of a nearly identical reaction of 4-phenyl-3,4-dihydro-1*H*-quinazolin-2-thione **420** with bromine has been reported by Gabriel and Stelzner in 1896 (scheme 153).¹³² The reaction was carried out using bromine in acetic acid and water but no yield was given. The dibromo-intermediate **421** was reportedly isolated prior to formation of 2-bromo-4-phenyl-3,4-dihydroquinazoline **422**.



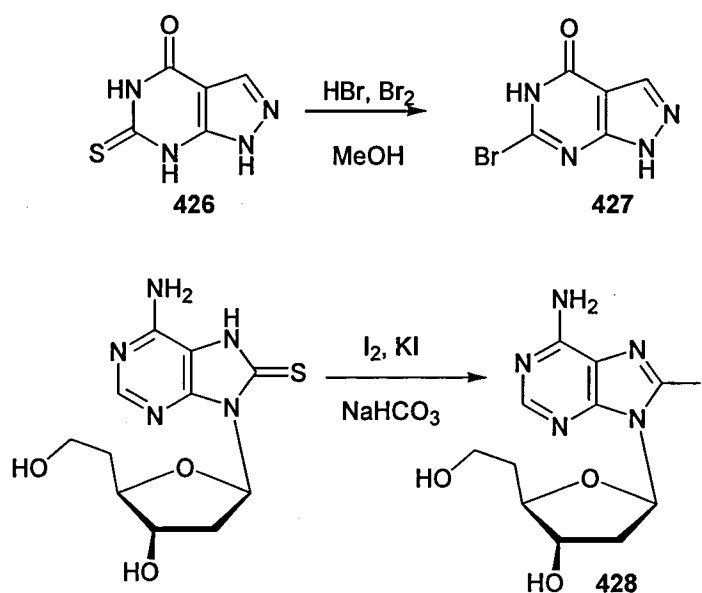
Scheme 153. Early reported bromination of thioquinazoline.

Robins *et al.* used the procedure for the preparation of mono-, di- and tri-substituted bromopurines **423**, **424** and **425** (scheme 154).¹³³ Robins postulated the mechanism involved an oxidised sulfur intermediate (sulfanyl bromide) being displaced by a bromide ion in solution.



Scheme 154. Bromination of purines

Robins *et al.* extended the same procedure for the conversion of thiopyrimidine 426 to the brominated analogue 427 (scheme 155).¹³⁴ They also showed that this protocol can be extended to form iodo compounds by treating thiopurines with iodine under basic conditions, e.g. 9-furanol-8-iodo-9*H*-purin-6-ylamine 428.¹³⁵

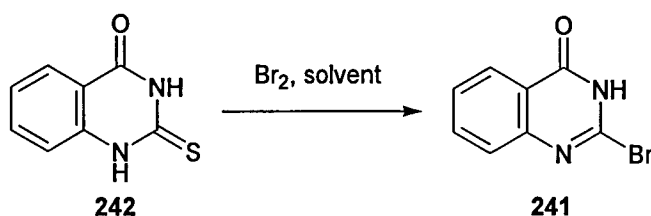


Scheme 155. Bromination of thiopyrimidine.

5.3 Reactions and bromination of 2-Mercapto-3*H*-quinazolin-4-one

Having carefully reviewed the literature, it was considered there was enough evidence that the synthesis of the 2-bromo-3*H*-quinazolinone **241** building block could be successfully made using this method. 2-Mercapto-3*H*-quinazolin-4-one **242** was commercially available, and to our delight, treatment with bromine formed the desired 2-bromoquinazolinone **241** (table 20). Characterisation by ^1H and ^{13}C NMR spectroscopy was inconclusive and mass spectral data was relied upon to verify the presence of a bromine atom. There was concern that the hydrobromide salt product may form, which could have affected subsequent alkylations at the *N*-3 position. At this stage the mechanism of the reaction was unclear. No smell of H_2S was detected indicating it was not formed in the reaction. The move away from acetic acid was made and found the yields were similar in ethanol.

Table 20. Optimisation for 2-bromo-3*H*-quinazolin-4-one synthesis.



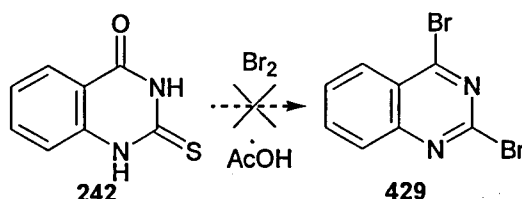
Br_2 (equiv.)	Time (min)	Solvent	Yield (%)
1.5	30	MeOH	24
1.5	10	AcOH	35
1.5	15	AcOH/ H_2O (5:1)	48
1.5	120	EtOH	50
3.0*	30	AcOH	35
3.0	180	AcOH	40
3.0**	30	AcOH	14
3.5	20	AcOH/ H_2O (5:1)	42
3.5	30	AcOH/ H_2O (5:1)	40
4.0	40	AcOH/ H_2O (5:1)	37

* Dried in a vacuum oven for 24 h over P_2O_5 (^1H NMR spectroscopy showed slight decomposition).

** Extracted into DCM and washed with $\text{Na}_2\text{S}_2\text{O}_3$ (^1H NMR spectroscopy showed evidence of some debromination).

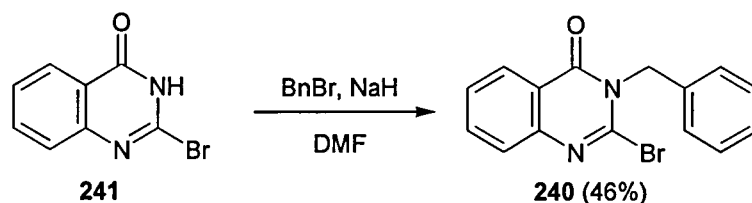
Due to the high polarity of the product, work ups and purification were extremely difficult. When the crude reaction was washed with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ a loss in product yield was observed. It was also found that a slight excess of bromine was required. The reactions were not homogenous and therefore monitoring by TLC was precluded.

A ^1H NMR spectrum showed that when the reaction was carried out in AcOH, an unknown intermediate appears in the spectra before the reaction goes to completion. This is not the case when the reaction is carried out in MeOH or EtOH. There is very little difference in the ^1H NMR spectra of the compounds. However, careful study of the ^1H NMR spectra of some of the reactions indicated a loss of NH peaks (about 13 ppm for **242** and 11 ppm for **241**). It is proposed that the loss of NH peaks could imply the formation of a 2,4-dibromoquinazoline **429** as the unknown intermediate. An attempt to determine if the 2,4-dibromoquinazolinone **429** could be made by treating 2-mercapto-3*H*-quinazolin-4-one **242** with an excess of Br_2 in AcOH was carried out (scheme 156). However, this failed and no further evidence could be found to identify the unknown intermediate of the reaction in AcOH.



Scheme 156. Attempt synthesis of 2,4-dibromoquinazoline.

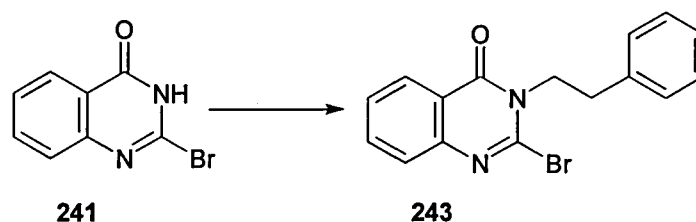
With the 2-bromo-3*H*-quinazolin-4-one **242** building block in hand, alkylation using benzyl bromide was carried out in good yield to give quinazolinone **241** (scheme 157). The radical reaction of quinazolinone **213** has already been described in chapter one, and is not the focus here.



Scheme 157.

However, the alkylation of 2-bromo-3*H*-quinazolin-4-one **241** with (2-bromoethyl)benzene proceeded extremely poorly. A number of different conditions were attempted and the yields are reported in table 21. Even when the reaction was attempted using the triflate derived from (2-hydroxyethyl)benzene, no alkylation was observed. It appeared to us that the ambident anion formed is not reactive enough.

Table 21. Alkylation conditions of (2-bromoethyl)benzene (BEB) in DMF.



Base (equiv.)	BEB (equiv.)	Deprotonation time	Reaction time	Temperature	Yield
NaH (1.5)	1.5	1 h	12 h	rt	3%
NaH (1.5)*	1.2	1 h	4 h	rt	6%
NaH (1.2)**	1.5	10 min	12 h	rt	<2%
NaH (1.5)	3.0	1 h	12 h	80 °C	<5%
<i>t</i> -BuOK (1.5)	1.5	3 h	12 h	120 °C	<5%
CS ₂ CO ₃ (1.5)	1.5	1 h	12 h	120 °C	<5%
CS ₂ CO ₃ (1.5)	5.0	1 h	48 h	120 °C	<5%

* NaI (20.0 equiv.) was added at the beginning of the reaction.

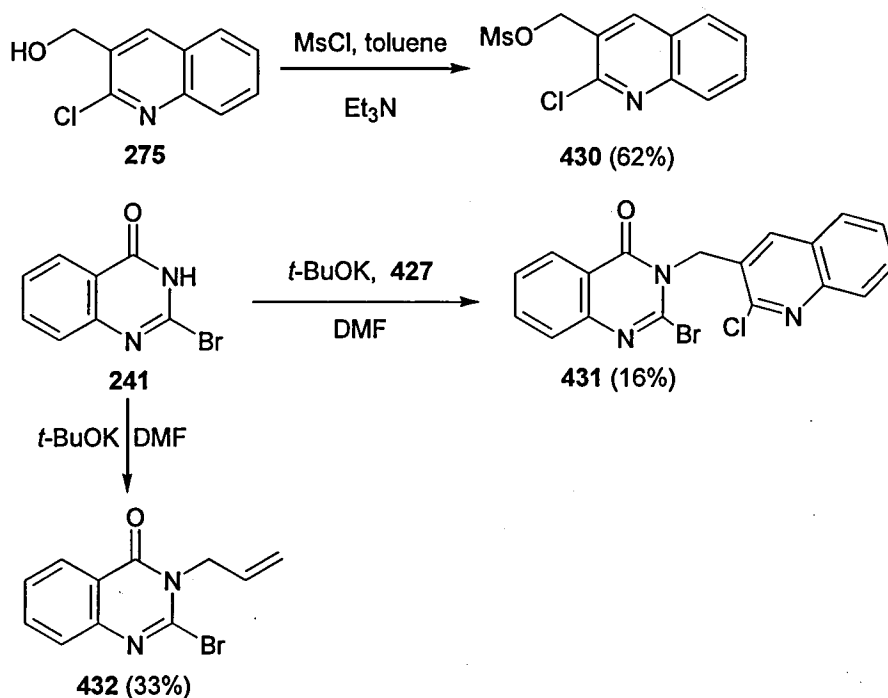
** NaI (5.0 equiv.) was added at the beginning of the reaction.

2-Bromo-3*H*-quinazolin-4-one **241** is insoluble in Et₂O, MeCN, toluene, DCM and THF which left no other obvious highly polar solvents to use other than DMF. CS₂CO₃ has been shown to be a good base for deactivated amine alkylations, but in

this case made no improvement.¹³⁶ However, it was noted that *O*-alkylation appeared to increase when Cs₂CO₃ was used. Molecular sieves were added to the (2-bromoethyl)benzene to ensure its dryness. A fresh new bottle of anhydrous DMF also had no effect. Increased yield was not observed when NaI was added to see if a Finkelstein type reaction could be carried. Attempts to carry out the reaction at a higher temperature had little effect.

An attempt to carry out the reaction under Mitsunobu conditions using DIAD, PPh₃, quinazolinone **219** and 2-(2-bromophenyl)ethanol was made, but that produced a complex mixture of inseparable products. Comins *et al.* have extensively investigated this reaction with respect to oxygen and nitrogen alkylation of 2-pyridones.¹³⁷

Attention was turned to studying the alkylation with active bromides instead (scheme 158). At this point, the mesylquinoline **430** was made from the previously prepared quinoline **275**. It was hoped this might open a new route to luotonin A. However, the alkylation of quinoline **430** with 2-bromo-3*H*-quinazolin-4-one **241** occurred in such poor yield that no radical reactions were attempted with the quinazolinone **431**. Alkylation of 2-bromo-3*H*-quinazolin-4-one **241** was successfully carried out using allyl bromide to give quinazolinone **432**.



Scheme 158. Successful alkylations of 2-bromoquinazolin-4-one

Attempts to alkylate 2-bromo-3*H*-quinazolin-4-one **241** using methyl bromoacetate **433** which we hoped would be sufficiently active were not successful (figure 25) and no alkylation was observed. Three other alkylation reactions were attempted using propargyl bromide **434**, bromopropyl benzene **435** and 3-(2-bromoethyl)indole **320**. All failed to give any 3-*N* alkylated product. At the completion of the studies, Curran reported the successful alkylation of 2-bromo-3*H*-quinazolin-4-one **241** with propargyl halides.¹³⁸

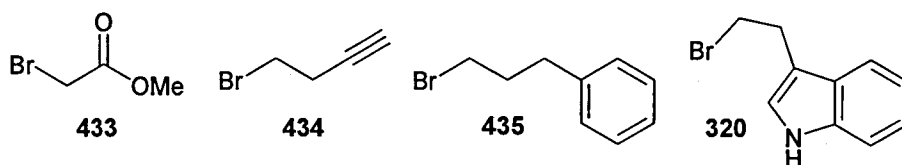


Figure 25.

In summary, the electron withdrawing effect (-I) of the bromine, the aromatic imine and amide in **436** are deactivating the anion, making it unreactive towards electrophiles (figure 26). It is not believed that the steric bulk of the bromine plays a role.

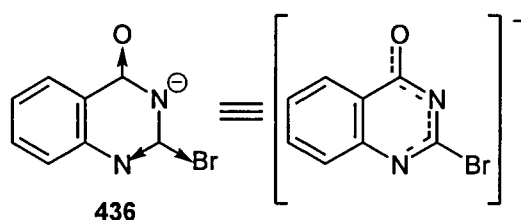
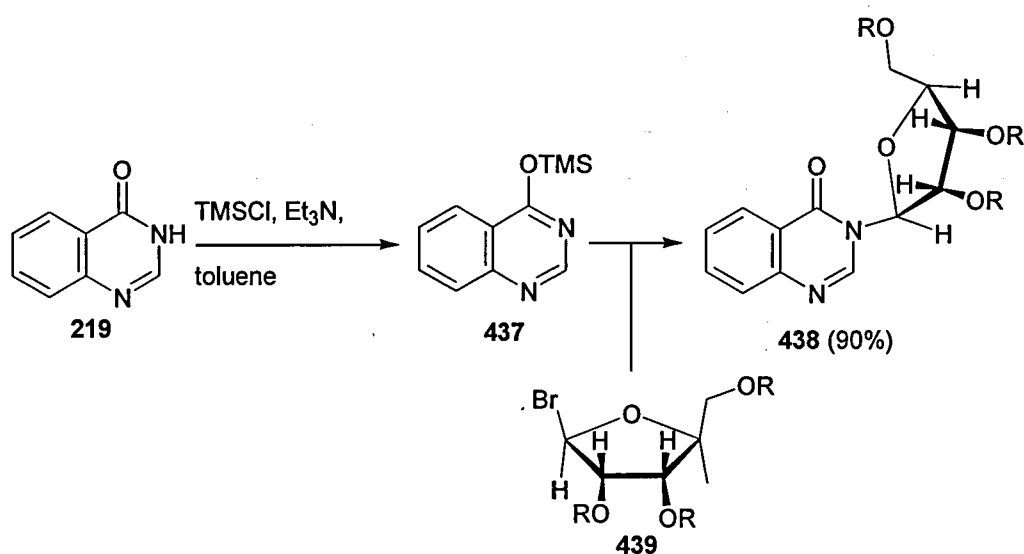


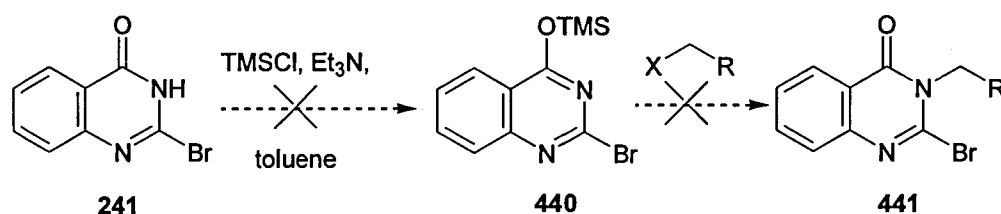
Figure 26. Ambident anion of 2-bromo-3*H*-quinazolin-4-one.

At this point, consideration of overcoming the problem encountered in the alkylation reaction was sought. We investigated a method developed by Robins and Stout for the alkylation of 3*H*-quinazolin-4-one **219** (scheme 159) using a TMS protected quinazolin-4-one **437**.¹³⁹ This was shown to react rapidly with the activated bromofuranose **439** to yield the alkylated quinazolinone **438**.



Scheme 159.

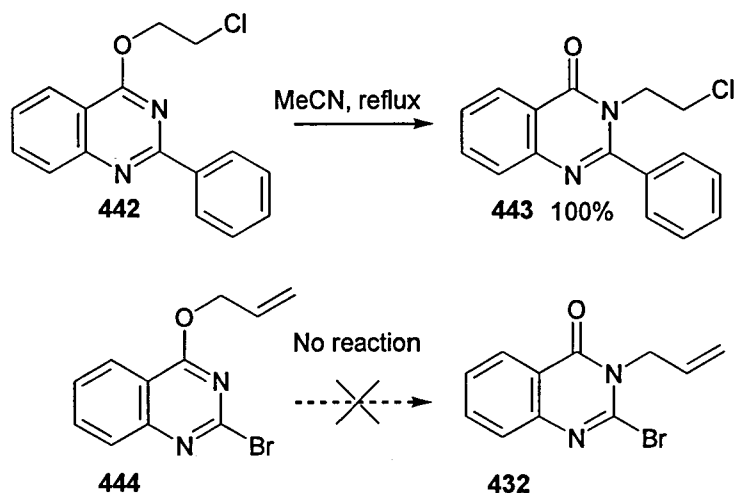
It was hoped to form 3-*N*-alkylated 2-bromo-3*H*-quinazolin-4-ones **441** from the 2-bromo-3*H*-quinazolin-4-one **241** building block using this method (scheme 160). There was uncertainty whether the TMS protected intermediate **440** would be reactive enough towards unactivated alkyl halides. Several unsuccessful attempts were made to carry out this reaction.



Scheme 160.

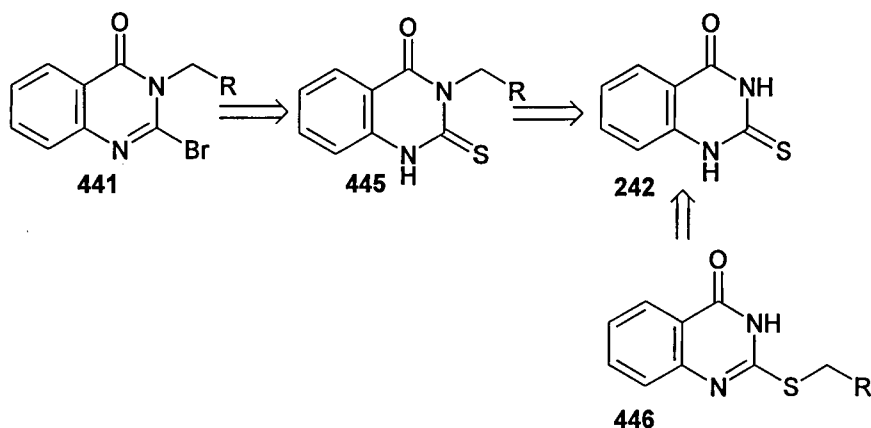
Preparation of the same TMS quinazolinone **437** that Robins and Stout had reported was unsuccessful (scheme 159). A range of conditions were employed without success. It was decided this work should be put to one side to concentrate on more profitable research.

A Chapman rearrangement as described by Chern *et al.* could be applied to quinazolin-4-one chemistry was considered next (scheme 161).¹⁴⁰ Chern has described a 1,3-shift from oxygen of the quinazolinone **442** to the nitrogen of the quinazolinone **443** of alkyl halides in excellent yield. Aryl, allyl and alkyl groups have all been shown to undergo this migration. A small amount of *O*-alkylated quinazolinone **444** had been recovered from previous alkylation experiments, and so the reaction the solution of quinazolinone **444** in MeCN overnight was heated overnight under reflux. However, no reaction was observed. An attempt to carry out the same reaction under microwave conditions also failed to yield quinazolinone **432**.



Scheme 161. Chapman rearrangement and failed attempt.

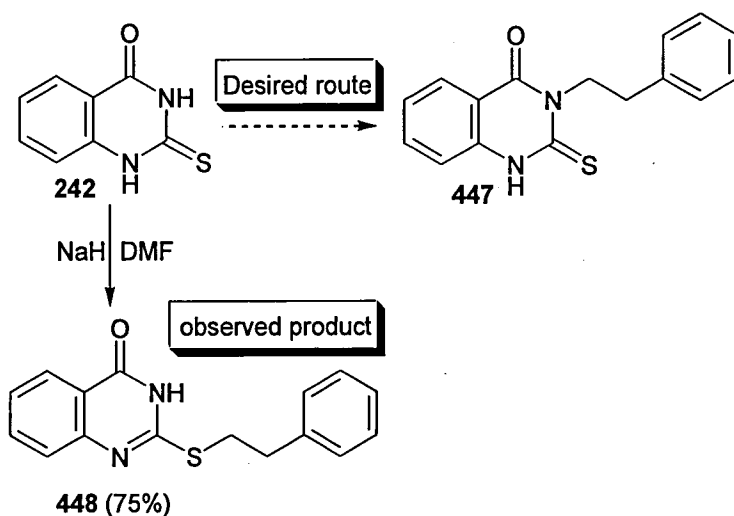
At this point, the reaction order was considered. It was not known if the alkylation of the nitrogen could be carried out first, before bromination to yield 3-*N* alkylated bromoquinazolinone 441 (scheme 162). The obvious problem with this route is that alkylation of 2-mercaptoquinazolinone 242 would most likely give undesired quinazolinone 446 rather than quinazolinone 445.



Scheme 162. Planned retrosynthesis of alkylated bromoquinazolinone.

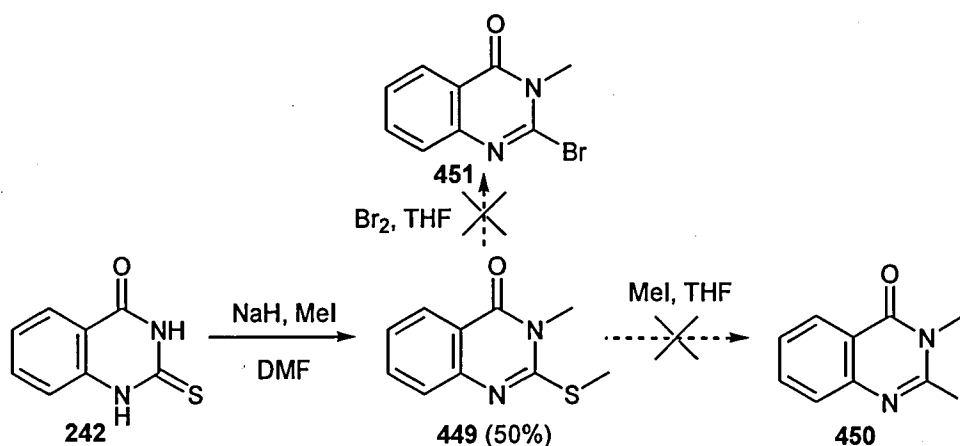
It was reasoned that the dianion of 2-mercaptoquinazolin-4-one (N^{\ominus} and S^{\ominus}), might preferentially alkylate on the nitrogen (scheme 163). This was reasoned as the nitrogen anion would be less stable than the sulfur anion thus reacting faster to yield

quinazolinone **447**. However, when this hypothesis was tested by treating 2-mercaptoquinazolinone **242** with 2 equivalents of base, only the sulfur alkylated product **448** was observed.



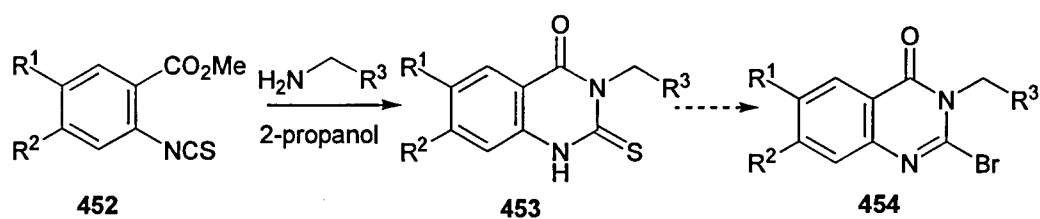
Scheme 163.

However, undeterred further investigations were made. It was not known whether the alkylated sulfur quinazolinone could be displaced at the C-2 position using bromine. This was tested by treating 3-methyl-2-methylsulfanyl-3*H*-quinazolin-4-one **449** with bromine (scheme 164). However, only starting material was recovered from this reaction. The reaction was repeated using MeI, but again this failed to facilitate a S_NAr reaction. Bromo- or iodo-quinazolinone **451** or **450** were not obtained.



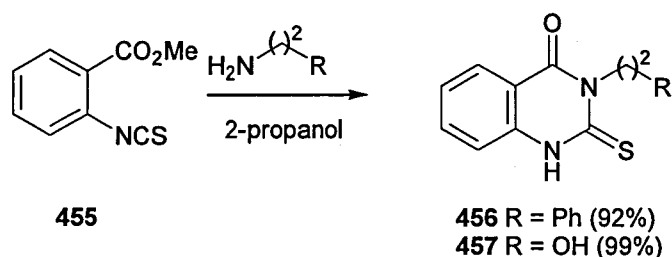
Scheme 164.

The next method investigated was to introduce the *N*-alkyl substituents during the ring synthesis and convert the thio group to the 2-bromoquinazolin-4-one (scheme 165). Drushlyak *et al.* have shown that 2-(methoxycarbonyl)phenyl isothiocyanate **452** reacts rapidly with amines to form *N*-alkylated 2-thioquinazolin-4-ones **453**.¹⁴¹ This looked promising and should allow access to quinazolinone **454**.



Scheme 165.

Two of the desired mercaptoquinazolinones **456** and **457** were prepared in excellent yields from a commercially available isothiocyanate **455** (scheme 166). A crystal structure of the quinazolinone **456** was obtained to prove the structure (figure 27).



Scheme 166.

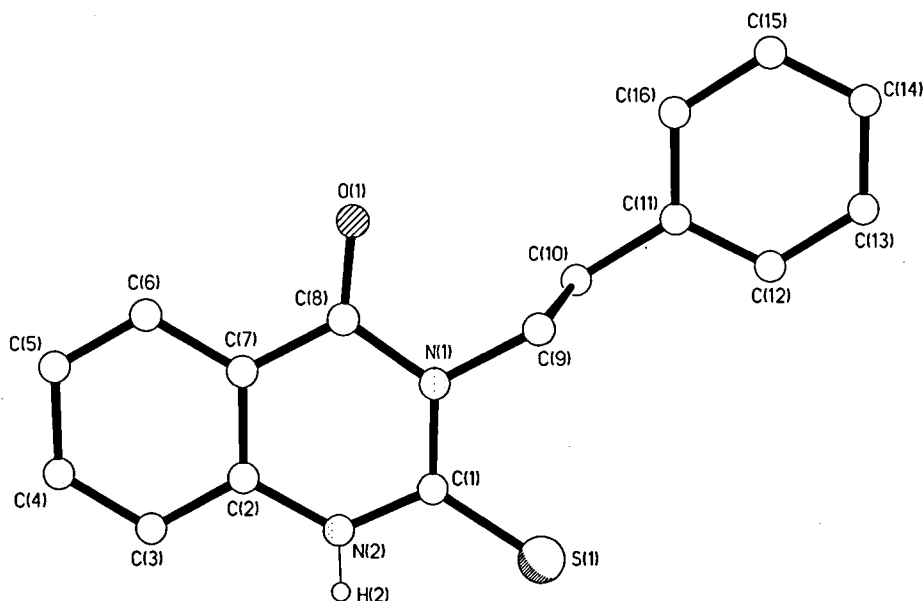
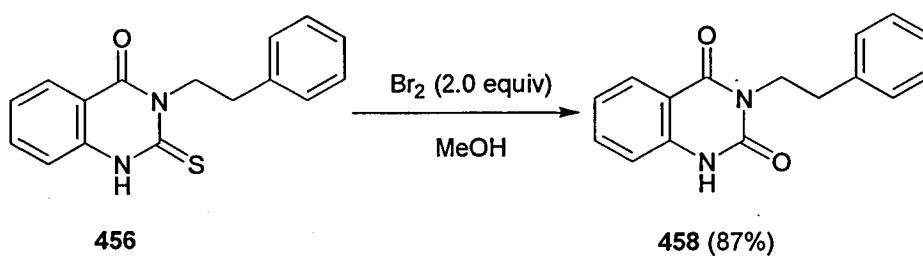


Figure 27. X-ray structure of quinazolinone **456**.

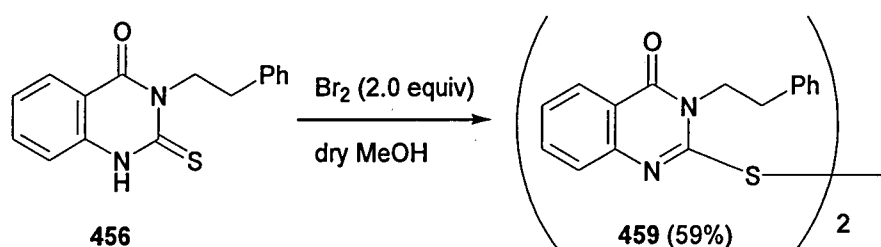
Investigations were then carried out to brominate at the C-2 position of the 2-thioquinazolinones **456** and **457**. When 2-thioquinazolinone **456** was treated with bromine (2.0 equivalents) in MeOH, only one product was obtained (scheme 167). The ^1H NMR spectrum of the reaction showed the presence of a broad NH peak at 10.42 ppm (confirmed by a D_2O shake). The ^1H NMR spectrum was clearly different to that of the starting material. The mass spectrum revealed that the product was the 3-(2-phenylethyl)-1*H*-quinazoline-2,4-dione **458**. This product is likely to have arisen by attack of water present in the MeOH on the sulfanylbromide intermediate.



Scheme 167.

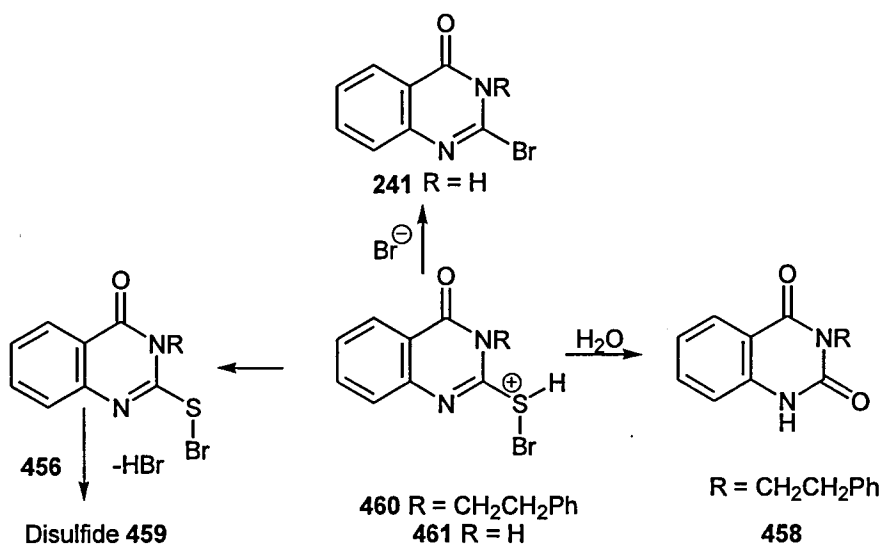
When the 3-(2-hydroxyethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **457** was treated with bromine in MeOH a mixture of unidentifiable products were obtained. It is believed that the pendant hydroxyl group is interfering in the reaction.

The reaction under anhydrous conditions between 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **456** and bromine gave a new product (scheme 168). The ¹H NMR spectra revealed no NH peaks, suggesting the formation of the 2-bromo product. However, the mass spectrum showed no bromine isotope patterns and indicated that the dimer **459** had been formed.



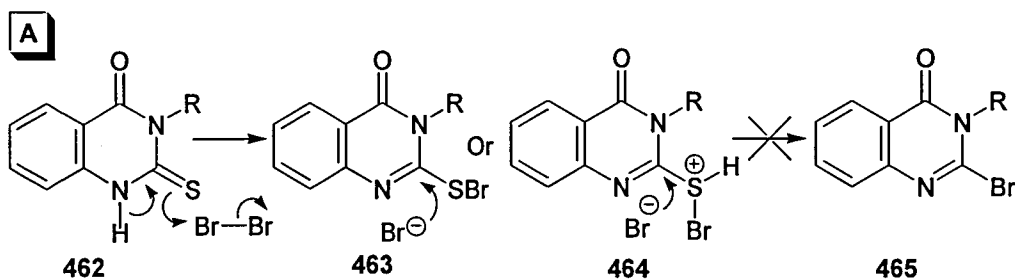
Scheme 168. Unexpected disulfide formation using bromine

The disulfide formation can be rationalised by reaction between a second thioquinazolinone molecule **456** and the sulfanylbromide intermediate **460** (scheme 169). It is now known that this sulfanylbromide intermediate **460** is also susceptible to attack by water to form 3-(2-phenylethyl)-1*H*-quinazoline-2,4-dione **458**. It is now clear that bromo substitution of this sulfanylbromide intermediate **461** can only occur when 3-*N* is unsubstituted.



Scheme 169. Proposed routes to the quinazolin-4-one products.

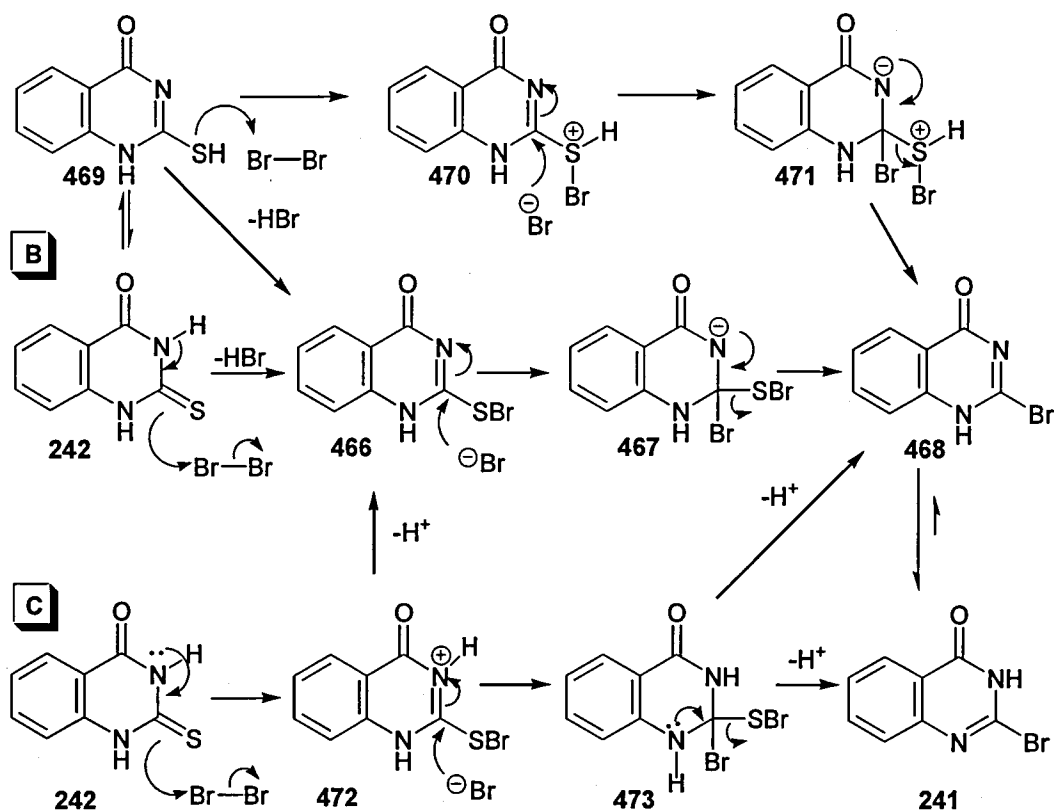
Initially, it was considered that the NH at the 3-*N* position was not important in the mechanism for the bromination of 2-mercapto-3*H*-quinazolin-4-one **242**. However, observations show that bromination does not occur with 3-*N*-alkylated 2-thioquinazolin-4-ones **462** to yield the desired 2-bromoquinazolin-4-one **465** (scheme 170). This indicates that the 3-NH is involved in the mechanism, hence it is unlikely that intermediates **463** and **464** of route A would be obtained. The 3-NH is more acidic than the 1-NH and it could be predicted to be preferentially abstracted in the bromination/ $\text{S}_{\text{N}}\text{Ar}$ reaction shown, therefore it is proposed route A is unlikely for the mechanism.



Scheme 170.

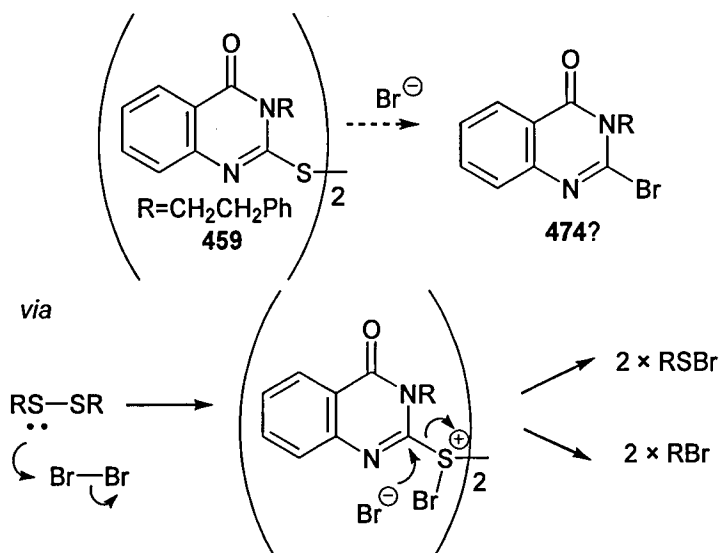
An alternative route B could also be proposed by loss of H^+ from **242** to form intermediate **466** should be rapid because the 3-NH is acidic (scheme 171). The alternative is that tautomerism to the thio-imine **469** is required prior to attack by bromine to form **470**. This would be followed by S_NAr attack by a bromide ion followed by loss of HSBBr on **467** and **471** to yield product **468**, which would rapidly tautomerise to 2-bromo-3*H*-quinazolin-4-one **241**.

Alternatively route C, which takes into account the lone pair electrons of 3-N **242** could occur. This is followed by attack of a bromide ion on intermediate **472**. It could be envisaged that the lone pair of the 1-N of intermediate **473** becomes involved. Loss of HSBBr from intermediate **473** should yield 3*H*-quinazolin-4-one **241**. Route C should work out equally well whether the 3-N substituents are hydrogen or R as only the lone pair is involved, hence route C is ruled out. It is postulated that the loss of the 3-NH is crucial to the bromination mechanism. If this loss of a proton is crucial in the mechanism then 3-N alkylated starting material **458** will yield other products as observed. The conclusion therefore is that this synthetic method of alkylation followed by bromination will not provide a route to the required 2-bromo-3*H*-quinazolin-4-ones **465**.



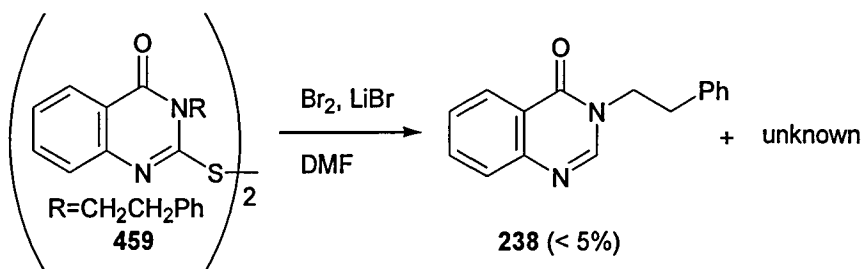
Scheme 171. Possible bromination mechanisms of 3H-quinazolin-4-one

Consideration for the synthetic use of the disulfide **459** was given (scheme 172). There was an interest to see how this might react in the presence of an excess of bromine and whether this may lead to the bromo analogues **474**. The conversion of disulfides to sulfanyl halides is well known.¹⁴²



Scheme 172. Possible use of 2-thioquinazolin-4-one disulfide.

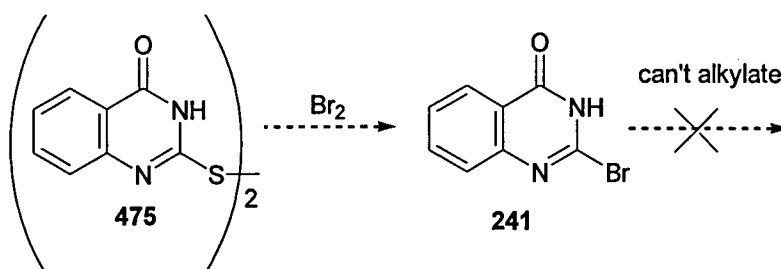
When quinazolin-4-one disulfide **459** was treated with an excess of bromine, TLC showed two products (scheme 173). Lithium bromide was added to ensure the excess of bromide ions in the reaction. Of the two products only one could be fully identified as unsubstituted C-2 quinazolin-4-one **238** in a very low yield. The mechanism of this dethionation to yield quinazolin-4-one product **238** is unclear. Even after repeating the reaction the other product could not be identified. However, both were obtained in low yields and the route did not look promising. A reaction was also carried out stirring disulfide **459** and Br₂ in MeOH, but no new products were observed after 24 h.



Scheme 173.

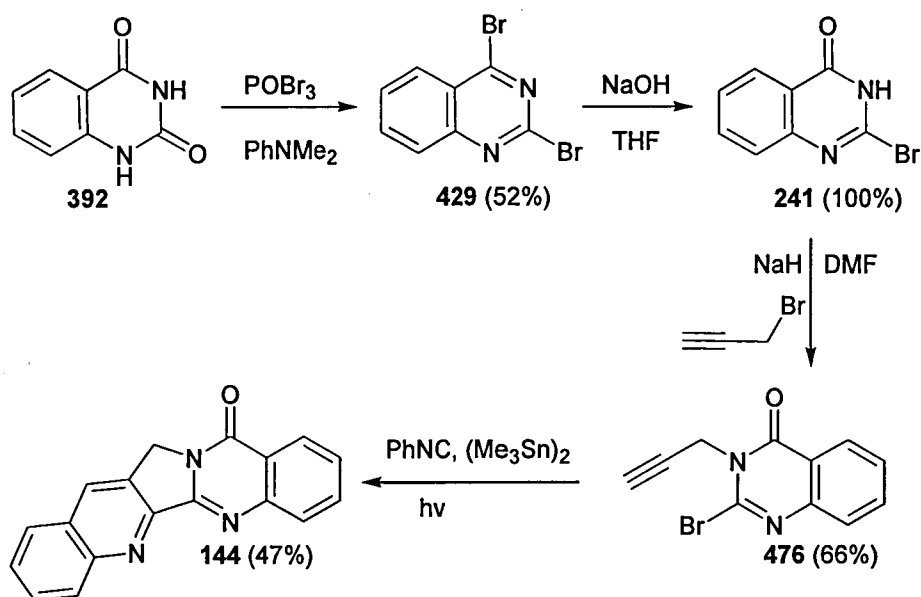
Although this route was unsuccessful the reaction of an unsubstituted disulfide **475** at the 3-N position was given, and how it may react if treated with bromine (scheme 174). However, had bromination occurred, the problem of the low reactivity of 2-

bromo-3*H*-quinazolin-4-one **241** would still have needed overcoming. As a result termination of the disulfide work was decided. Up to here the investigations in the bromination reactions of 2-mercapto-3*H*-quinazolin-4-one were thorough, but, at this point it was decided to concentrate on returning to the natural product syntheses.



Scheme 174.

In the course of this study a report of radical reactions at C-2 of quinazolinone was published in the literature. Curran *et al.* has recently carried out a cascade radical annulation reaction using a C-2 quinazolinone radical (scheme 175).¹³⁸ Curran describe the synthesis of 2,4-dibromo-3*H*-quinazoline **429** from 2,4-diketoquinazolinone **392** in good yield. This idea had been considered, but then abandoned after the fairly unsuccessful attempts at making the 2,4-dichloro-3*H*-quinazolin-4-one **393**. Curran reported no problems in the propgarylation of 2-bromo-3*H*-quinazolin-4-one **241** to radical precursor **476**. This had been unsuccessful in our hands.



Scheme 175.

Although disappointed that the 2-bromoquinazolinone **241** could not be fully exploited in natural product syntheses ourselves, we were pleased to see it being explored by other chemists and that these results showed the potential of cyclisation onto arenes.

5.4 Conclusions

This chapter has given a detailed account of attempts to prepare a C-2 radical of 3*H*-quinazolin-4-one. Various methods were attempted. The most successful of which was the bromination of 2-mercapto-3*H*-quinazolin-4-one. However, great difficulty in attempting to carry out alkylations at the 3-*N* position was encountered. Attempts at carrying out the bromination once substituents have been added at 3-*N* failed. It has been shown that unexpected products lead us to help propose a mechanism for the bromination of 3-mercapto-3*H*-quinazolin-4-one.

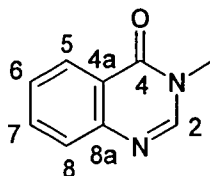
Chapter 6. Experimental

6.1 General experimental

Commercial dry solvents were used in all reactions except light petroleum and ethyl acetate that were distilled from CaCl_2 and dichloromethane that was distilled over CaH_2 . Light petroleum refers to the bp 40-60 °C fractions. All reactions were carried out under an atmosphere of nitrogen unless stated otherwise. Sodium hydride was obtained as 60% dispersion in oil. A 2.5 M solution of *n*-butyllithium in hexane was used in all stated cases. A 1.0 M solution of Et_3B in hexane was used in all cases. A 1.0 M solution of *t*-BuLi in THF was used in all cases. A solution of 1 M TBAF in THF was used in all cases. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 MHz). ^1H (250 MHz) were also carried out on a Bruker AC-250 spectrometer. Samples were run as solutions of CDCl_3 with TMS as the internal standard for ^1H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a Jeol JMS-SX102 quadrupole high resolution mass spectrometer or carried out by the EPSRC MS Service at University of Wales, Swansea. GCMS was carried out on Fisons 8000 series GCMS using a 15 m x 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F₂₅₄), and TLC using alumina as absorbent was carried out with aluminium backed plates coated with neutral aluminium oxide (Merck 150 F₂₅₄, Type T). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified. Column chromatography using alumina was carried out with Aldrich aluminium oxide, activated neutral, Brockmann 1, STD Grade, 150 mesh size. Prep-TLC was carried out using aluminium oxide (Merck 60 PF₂₅₄, Type E).

6.2 Experimental for Chapter 2

3-Methyl-3*H*-quinazolin-4-one



225

Method A using sodium hydride and lithium bromide

Sodium hydride (0.40 g, 10.0 mmol) was added to 3*H*-quinazolin-4-one (0.73 g, 5.0 mmol) at 0 °C in dry DMF (5 cm³) and dry ethylene glycol dimethyl ether (10 cm³) and stirred for 40 min. Lithium bromide (0.87 g, 10.0 mmol) was added and the reaction mixture stirred for another 15 min. Methyl iodide (1.25 cm³, 20.0 mmol) was added with stirring for another 3 h. The reaction mixture was quenched by dropwise addition of H₂O (5 cm³). The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (1:1) as eluent yielding 3-methyl-3*H*-quinazolin-4-one as yellow crystals (0.33 g, 2.0 mmol, 41%), mp 103-104 °C (lit.¹⁴³ 104-105 °C); (Found: MH⁺, 161.0708. C₉H₉N₂O requires 161.0708); ν_{\max} (thin film)/cm⁻¹ 3377, 2923, 1664, 1612, 1340, and 779; δ_{H} 3.59 (3 H, s, CH₃), 7.45 (1 H, dd, *J* 8.2 7.2, 6-H), 7.72-7.63 (2 H, m, ArH), 8.04 (1 H, s, 2-H) and 8.25 (1 H, d, *J* 8.0, 5-H); δ_{C} 33.91 (CH₃), 121.73 (4a-C), 126.24 (8-C), 127.03 (6-C), 127.22 (5-C), 133.92 (7-C), 146.78 (2-C), 148.06 (8a-C) and 161.27 (4-C); NMR spectral assignments were confirmed by NOESY, COSY and ¹H-¹³C correlation NMR techniques; *m/z*(Electrospray) 161 (M⁺, 34%), 160 (100), 132 (36), 119 (30), 97 (35), 83 (40), 71 (47), 69 (59), 57 (65) and 43 (85).

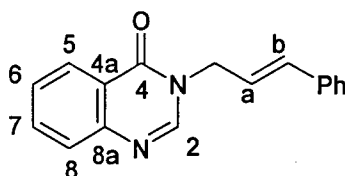
Method B using potassium *t*-butoxide

Potassium *t*-butoxide (0.50 g, 4.5 mmol) was added to 3*H*-quinazolin-4-one (0.44 g, 3.0 mmol) in dry DMF (20 cm³) and stirred for 1 h. Methyl iodide (0.43 cm³, 5.0 mmol) was added and the reaction mixture stirred for a further 10 h. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and evaporated to dryness under reduced pressure. The crude product was

purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) yielding 3-methyl-3*H*-quinazolin-4-one as yellow crystals (0.17 g, 1.1 mmol, 37%).

The data were consistent to the literature.¹⁴³

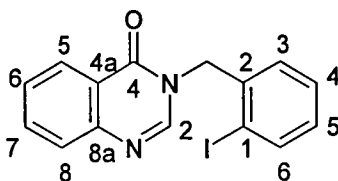
3-(3-Phenylallyl)-3*H*-quinazolin-4-one⁷³



226

Sodium hydride (0.39 g, 10.0 mmol) was added at 0 °C to 3*H*-quinazolin-4-one (0.73 g, 5.0 mmol) in dry DMF (5 cm³) and dry ethylene glycol dimethyl ether (10 cm³) and stirred for 1 h. Lithium bromide (0.86 g, 10.0 mmol) was added and the reaction mixture stirred for a further 15 min. Cinnamyl bromide (3.9 g, 20.0 mmol) was added and the reaction mixture stirred for an additional 2 h. The reaction mixture was quenched by dropwise addition of H₂O (5 cm³). The reaction mixture was extracted into DCM (50 cm³) and washed with H₂O (5 × 50 cm³) and with brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent to yield 3-(3-phenylallyl)-3*H*-quinazolin-4-one as yellow crystals (0.51 g, 2.0 mmol, 40%); mp 115–116 °C (lit.⁷³ 115–116 °C); (Found: MH⁺, 263.1182. C₁₇H₁₅N₂O requires 263.1179); ν_{\max} (thin film)/cm⁻¹ 3423, 1670, 1652, 1608, 1558, 1473 and 773; δ_{H} 4.79 (2 H, dd, *J* 6.4, 1.4, CH₂), 6.34 (1 H, dt, *J* 15.8, 6.4, propenyl-2-H), 6.66 (1 H, dt, *J* 15.8, 1.4, propenyl-CH₆), 7.23–7.38 (5 H, m, ArH), 7.53, (1 H, ddd, *J* 8.0, 8.0, 1.0, 6-H), 7.73 (1 H, ddd, *J* 8.0, 8.0, 1.0, 7-H), 8.11 (1 H, s, 2-H), 7.76 (1 H, dd, *J* 8.0, 1.0, 8-H) and 8.34 (1 H, dd, *J* 8.0, 1.0, 5-H); δ_{C} 48.15 (CH₂), 122.16 (4a-C), 122.77 (propenyl 2-C), 126.50 (phenyl-2,6 or 3,5), 126.82 (5-C), 127.41 (6-C), 127.54 (7-C), 128.30 (phenyl-4-C), 128.68 (phenyl-2,6 or 3,5-C), 134.35 and 134.50 (propenyl-3-C and 8-C), 135.75 (phenyl-1-C), 146.19 (2-C), 148.11 (8a-C) and 160.95 (O=C); NMR spectral assignments were confirmed by NOESY, COSY and ¹H-¹³C correlation NMR techniques; *m/z*(Electrospray) 263 (M⁺, 21 %), 147 (42), 121 (100), 79 (87) and 74 (26).

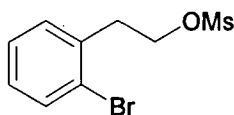
3-(2-Iodobenzyl)-3*H*-quinazolin-4-one



228

Potassium *t*-butoxide (1.35 g, 12.0 mmol) was added to 3-*H*-quinazolin-4-one (1.17 g, 8.0 mmol) in dry DMF (50 cm³) and stirred for 1 h. 2-Iodobenzyl bromide (2.96 g, 10.0 mmol) was added to the reaction mixture and stirred for a further 16 h. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding 3-(2-iodobenzyl)-3*H*-quinazolin-4-one as yellow crystals (1.82 g, 5.03 mmol, 63%); mp 94-95 °C; (Found: M⁺, 362.9987. C₁₅H₁₁IN₂O requires 362.9989); ν_{\max} (thin film)/cm⁻¹ 3055, 1689, 1469, 1230, 962 and 734; δ_{H} 5.71 (2 H, s, CH₂), 6.93 (1 H, ddd, *J* 7.9, 7.4, 1.6, 4-PhH), 7.09 (1 H, dd, *J* 7.9, 1.6, 3-PhH), 7.22 (1 H, ddd, *J* 7.4, 7.2, 1.6, 5-PhH), 7.45 (1 H, ddd, *J* 8.0, 6.2, 1.7, 6-H), 7.75-7.64 (2 H, m, 7,8-H), 7.81 (1 H, dd, *J* 7.2, 1.6, 6-PhH), 8.11 (1 H, s, 2-H) and 8.26 (1 H, dd, *J* 8.0, 1.6, 5-H); δ_{C} 54.90 (CH₂), 98.60 (1-Ph), 122.14 (4a-C), 126.95 (5-C), 127.48 (6-C), 127.63 (8-C), 128.88 (5-Ph), 129.10 (3-Ph), 129.94 (4-Ph), 134.46 (7-C), 137.74 (8a-C), 139.92 (6-Ph), 146.44 (2-C), 148.03 (2-Ph) and 161.11 (4-C); *m/z*(EI) 252 (M⁺, 98%), 129 (43), 107 (41), 90 (100), 89 (77), 76 (51), 63 (58), 50 (42) and 40 (85).

2-(2-Bromophenyl)ethyl methanesulfonate⁷⁰



230

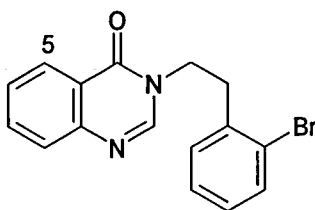
Methanesulfonyl chloride (2.38 cm³, 30.7 mmol) was slowly added to 2-(2-bromophenyl)ethanol (4.74 g, 25.6 mmol) in dry DCM (50 cm³) followed by addition of triethyl amine (5.34 cm³, 38.4 mmol) at 0 °C and stirred for 48 h. The crude reaction mixture was washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 2-(2-bromophenyl)ethyl methanesulfonate as an orange oil (4.91 g, 18.66 mmol, 75%); ν_{\max} (neat)/cm⁻¹ 3057, 3024,

2939, 1594, 1568, 1473, 1442, 1038 and 858; δ_{H} 2.87 (3 H, s, CH₃), 3.20 (2 H, t, J 6.9, CH₂), 4.43 (2 H, t, J 6.9, OCH₂), 7.17-7.09 (1 H, m, ArH), 7.29-7.26 (2 H, m, ArH) and 7.57 (1 H, d, J 7.7, ArH).

The data were consistent to the literature.⁷⁰

The product was used without further characterisation.

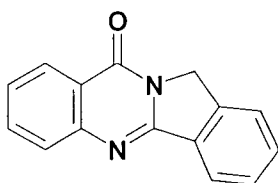
3-[2-(Bromophenyl)ethyl]-3*H*-quinazolin-4-one



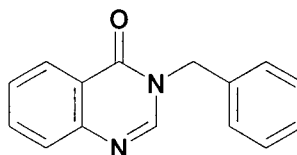
231

Potassium *t*-butoxide (2.61 g, 23.3 mmol) was added to 3-*H*-quinazolin-4-one (2.27 g, 15.5 mmol) in dry DMF (150 cm³) and stirred for 1 h. 2-(2-Bromophenyl)ethyl methanesulfonate (4.90 g, 18.6 mmol) was added to the reaction mixture and stirred for a further 48 h. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent yielding 3-[2-(bromophenyl)ethyl]-3-*H*-quinazolin-4-one as colourless crystals (1.93 g, 5.9 mmol, 38%); 119-120 °C; (Found: MH⁺, 329.0290. C₁₆H₁₄⁷⁹BrN₂O requires 329.0284); ν_{max} (thin film)/ cm⁻¹ 3423, 1972, 1609, 1470, 1069, 1027 and 773; δ_{H} 3.25 (2 H, t, J 7.0, CH₂), 4.25 (2 H, t, J 7.0, NCH₂), 7.22-7.07 (3 H, m, ArH), 7.58-7.48, (2 H, m, ArH), 7.78- 7.64 (3 H, m, ArH) and 8.34 (1 H, dd, J 8.3, 1.5, 5-H); δ_{C} 35.35 (CH₂), 46.73 (NCH₂), 122.02 (PhC), 124.45 (ArC), 126.61 (ArH), 127.24 (ArH), 127.49 (ArH), 127.94 (ArH), 128.94 (ArH), 131.36 (ArH), 133.14 (ArH), 134.21 (ArH), 136.73 (ArC), 146.36 (ArH), 148.10 (PhC) and 161.13 (ArC); m/z (Electrospray) 330 (M⁺, 98%), 328 (97), 251 (49), 249 (56) and 52 (14).

Radical cyclisation of 3-(2-iodobenzyl)-3*H*-quinazolin-4-one



233



232

Method A - Bu₃SnH (fast) and Et₃B as initiator

A solution of Bu₃SnH (0.76 g, 2.6 mmol) and 3-(2-iodobenzyl)-3*H*-quinazolin-4-one (0.44 g, 1.2 mmol) in dry toluene (40 cm³) was deoxygenated under nitrogen and stirred for 1 h. Triethylborane (3.6 cm³, 3.6 mmol) was added *via* a needle through a septum; the needle was left open to allow air (oxygen) to enter the reaction and the mixture stirred for 1 h. More triethylborane (3.6 cm³, 3.6 mmol) was added and the reaction mixture stirred for a further 10 h. Dilute hydrochloric acid was added to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum to remove tributyltin residues. The aqueous layer was basified with sodium hydroxide to pH 14 and extracted with DCM. The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding the reduced product 3-benzyl-3*H*-quinazolin-4-one 232 as colourless crystals (0.27 g, 1.2 mmol, 96%); mp 116-117 °C (lit.¹⁴⁴ 117-118 °C); ν_{max} (thin film)/cm⁻¹ 3419, 1675, 1609, 1559, 1473, 1369, 1332, 1161, 1026, 773, 709, 694 and 645; δ_{H} 5.08 (2 H, s, CH₂), 7.24-7.23 (5 H, m), 7.48 (1 H, ddd, *J* 8.2 6.3 1.8, 6-H), 7.74-7.68 (2 H, m, 7,8-H), 8.11 (1 H, s, 2-H) and 8.32 (1 H, dd, *J* 8.2 2.0, 5-H); δ_{C} 49.6 (CH₂), 122.2 (4a-C), 126.9 (5-H), 127.4 (6-H), 127.5 (8-H), 128.0 (CH), 128.3 (CH), 129.0 (CH), 134.3 (7-H), 135.8 (C), 146.4 (2-H), 148.0 (8a-C) and 161.1 (4-C).

The data were consistent to the literature.¹⁴⁴

Method B - TTMSS (fast) reaction using Et₃B as initiator

The procedure for method A was repeated using TTMSS in place of Bu₃SnH to yield 3-benzyl-3*H*-quinazolin-4-one 232 (35%).

Method C - Bu₃SnH (slow) reaction using Et₃B as initiator

The general procedure for method A was repeated except that Bu₃SnH was added by a syringe pump over 6 h to give 3-benzyl-3*H*-quinazolin-4-one 232 (30%).

Method D - Bu_3SnH (slow) reaction using AIBN as initiator

The general procedure for method C was repeated except that AIBN (0.25 molar equiv.) was used as initiator and the reaction was heated under reflux for 6 h to yield 3-benzyl-3*H*-quinazolin-4-one **232** (45%).

Method E - Photolysis with hexamethylditin

A solution of 3-(2-iodobenzyl)-3*H*-quinazolin-4-one (0.36 g, 1.0 mmol) and $(\text{Me}_3\text{Sn})_2$ (0.99 g, 3.0 mmol) in *t*-butylbenzene (20 cm³) in a two-necked pyrex flask (5 x 1 cm and 25 cm high, wall thickness = 1 mm), was purged with nitrogen for 30 min. The mixture was irradiated with a combined 300 W sunlamp at 150 °C for 10 h. The reaction mixture was cooled to room temperature, diluted with MeOH and evaporated under reduced pressure to a small volume. The residue was purified using column chromatography using silica gel as absorbent with light petroleum as eluent to remove the *t*-butylbenzene. A precipitate of polymeric dimethyltin was produced. The product was eluted with ethyl acetate and dilute hydrochloric acid was added to extract the protonated quinazalone products into the aqueous layer. The aqueous layer was washed with light petroleum to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM. The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) yielding 3-benzyl-3*H*-quinazolin-4-one **232** (65%) and cyclised 12*H*-isoindolo[1,2-*b*]quinazolin-10-one **233** (18%) as an inseparable colourless crystals. ¹H NMR spectroscopy was used to calculate the yield of the two products. 12*H*-Isoindolo[1,2-*b*]quinazolin-10-one **233** was identified in the mixture and therefore not fully characterised. δ_{H} 5.19 (2 H, s, CH_2), 7.28-7.35 (3 H, m), 7.51 (1 H, ddd, J 8.0, 8.0, 1.6, 7-H), 7.81 (1 H, ddd, J 8.0, 8.0, 1.6, 8-H), 7.85 (1 H, dd, 8.0, 1.6, 6-H), 8.21 (1 H, d, J 7.2, 4-H) and 8.41 (1 H, dd, J 8.0, 1.6, 9-H); δ_{C} 49.6 (CH_2), 120.6 (ArC), 123.4 (ArH), 123.5 (ArH), 126.4 (ArH), 126.4 (ArH), 127.3 (ArH), 128.8 (ArH), 132.3 (ArH), 132.6 (ArC), 134.2 (ArH), 139.6 (ArC), 149.4 (ArC), 154.9 (ArC) and 160.5 (ArC).

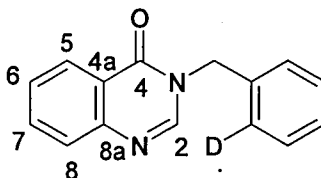
The data were consistent to the literature.¹⁴⁵

GC-MS analysis confirmed only two products to be in a rough ratio 4:1 of the reduced produced and cyclised product:

12*H*-isoindolo-[1,2-*b*]-quinazolin-10-one **233**; R_T 22.8 min, m/z 234 (M^+ , 100%), 205 (24) and 77 (20).

3-Benzyl-3*H*-quinazolin-4-one **232**; R_T 24.5 min, m/z 236 (M^+ , 51%), 130, (37), 91 (100) and 65 (27).

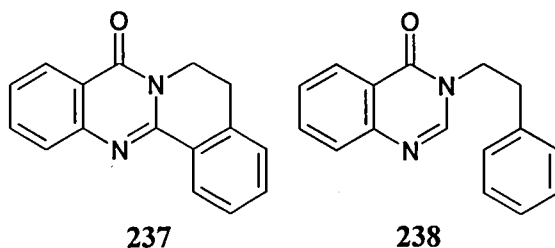
3-(2-Deuterio)benzyl-3*H*-quinazolin-4-one



236

Tributyltin deuteride (0.54 cm³, 2.0 mmol) and triethylborane (0.20 cm³, 0.2 mmol) were added to 3-(2-iodobenzyl)-3*H*-quinazolin-4-one (0.36 g, 1.0 mmol) in dry toluene (40 cm³) with an air bleed into the round bottom flask through a needle for 12 h. Dilute hydrochloric acid was added to the reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove tributyltin residues. The aqueous layer was basified with sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding the reduced product 3-(2-deuterio)benzyl-3*H*-quinazolin-4-one as colourless crystals (0.10 g, 0.4 mmol, 41%); mp 100–101 °C; (Found: MH^+ , 238.1084. C₁₅H₁₂DN₂O requires 238.1085); ν_{max} (thin film)/cm⁻¹ 3421, 2359, 1670, 1610, 1471, 1396, 1153 and 773; δ_H 5.21 (2 H, s, CH₂), 7.38–7.29 (4 H, m, PhH), 7.52 (1 H, ddd, J 8.0, 6.7, 1.4, 6-H), 7.71 (1 H, dd, J 8.2, 1.4 ArH), 7.77 (1 H, ddd, J 8.2, 6.7, 1.4, 7-H) 8.12 (1 H, s, 2-H) and 8.34 (1 H, dd, J 8.0, 1.4, 5-H); δ_C 49.66 (CH₂), 104.09 (PhCD), 122.24 (4a-C), 126.91 (5-C), 127.39 (6-C), 127.55 (ArH), 128.03 (ArH), 128.34 (ArH), 128.94 (ArH), 129.05 (ArH), 134.32 (ArH), 135.66 (PhC), 146.32 (5-C), 148.07 (8a-C) and 161.10 (4a-C); m/z (Electrospray) 238 (M^+ , 50%), 235 (21), 130 (33), 92 (100), 91 (75), 65 (21) and 51 (23); Anal. Calcd for C₁₅H₁₁DN₂O. C, 75.93; H, 5.52; N, 11.81. Found: C, 75.69; H, 5.20; N, 11.64.

Radical cyclisation of 3-[2-(bromophenyl)ethyl]-3*H*-quinazolin-4-one



Method A - Photolysis with hexamethylditin

The reaction mixture of 3-[2-(bromophenyl)ethyl]-3*H*-quinazolin-4-one (0.32 g, 1.0 mmol) and (Me₃Sn)₂ (0.99 g, 3.0 mmol) in *t*-butylbenzene (20 cm³) was purged with nitrogen for 30 min, and left to reflux whilst irradiating with a 300 W sunlamp at 150 °C for 10 h. The reaction mixture was cooled and dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one **237** as colourless crystals (0.22 g, 0.92 mmol, 92%); mp 195-197 °C (lit.¹⁴⁶ 196 °C); (Found: MH⁺, 249.1025. C₁₆H₁₃N₂O requires 249.1022); ν_{max} (thin film)/cm⁻¹ 3421, 1682, 1590, 1556, 1471, 1150, 762 and 692; δ_{H} 3.06 (2 H, t, *J* 6.4, CH₂), 4.35 (2 H, t, *J* 6.4, NCH₂), 7.22-7.13 (1 H, m, ArH), 7.43-7.37 (3 H, m, ArH), 7.71-7.69 (2 H, m, ArH), 8.25 (1 H, d, *J* 7.6, ArH) and 8.43-8.40 (1 H, m, ArH); δ_{C} 27.39 (CH₂), 39.54 (NCH₂), 120.70 (ArC), 126.48 (ArH), 126.82 (ArH), 127.40 (ArH), 127.56 (2 × ArH), 127.96 (ArH), 129.48 (ArC), 131.66 (ArH), 134.18 (ArH), 137.02 (ArC), 147.73 (ArCN), 149.29 (ArCN₂) and 161.63 (CO); *m/z*(Electrospray) 249 (M⁺, 17%), 247 (100), 128 (20), 116 (46), 104 (30), 90 (34), 89 (62), 77 (85), 76 (97), 63 (53) and 39 (54).

The data were consistent to the literature.¹⁴⁶

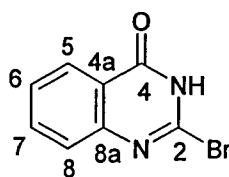
Method B - Bu₃SnH (fast) and Et₃B

Triethylborane (0.20 cm³, 0.20 mmol) and Bu₃SnH (0.54 cm³, 2.0 mmol) were added to 3-[2-(bromophenyl)ethyl]-3*H*-quinazolin-4-one (0.32 g, 1.0 mmol) in dry toluene (40 cm³) and stirred for 1 h with an air bleed into the round bottom flask through a needle. More triethylborane (0.20 cm³, 0.2 mmol) was added and the reaction left to stir for a further 10 h. Dilute hydrochloric acid was added to the reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light

petroleum ($3 \times 50 \text{ cm}^3$) to remove tributyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and with DCM ($3 \times 50 \text{ cm}^3$). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure yielding a mixture of reduced product 3-[2-(phenyl)ethyl]-3*H*-quinazolin-4-one **237** and 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one as **238** inseparable colourless crystals.

^1H NMR spectral analysis used to calculate yield of cyclised 5,6-dihydro-isoquino[1,2-*b*]quinazolin-8-one **237** (8%) and reduced product 3-[2-(phenyl)ethyl]-3*H*-quinazolin-4-one **238** (50%).

2-Bromo-3*H*-quinazolin-4-one

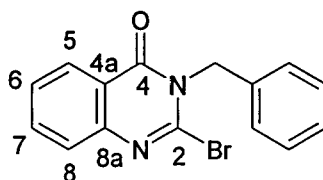


241

Bromine (0.76 cm^3 , 15.0 mmol) was slowly added to a solution of 2-mercapto-3*H*-quinazolin-4-one (0.89 g, 5.0 mmol) in EtOH (20 cm^3) and stirred for 2 h. The crude reaction product was filtered and triturated with EtOH and DCM. The solid was dried under reduced pressure yielding 2-bromo-3*H*-quinazolin-4-one as colourless crystals (0.55 g, 2.46 mmol, 50%); mp $134\text{--}136^\circ\text{C}$; (Found: M^+ , 223.9585. $\text{C}_8\text{H}_5^{79}\text{BrN}_2\text{O}$ requires 223.9585); ν_{max} (thin film)/ cm^{-1} 2959, 2722, 2579, 1714, 1628, 1565, 1536, 1465, 1376, 1288, 1255, 1181, 1068, 755, 721 and 511; δ_{H} (CD_3) $_2\text{SO}$ 7.20–7.16 (2 H, m, 6,8-H), 7.64 (1 H, ddd, J 8.6, 7.0, 1.5, 7-H) and 7.89 (1 H, dd, J 8.6, 1.5, 5-H); δ_{C} (CD_3) $_2\text{SO}$ 114.27 (4a-C), 115.28 (6/8-C), 122.30 (6/8-C), 126.90 (5-C), 134.95 (7-C), 140.81 (8a-C), 150.25 (2-C) and 162.80 (4-ArC); m/z (EI) 226 (M^+ , 51%), 224 (52), 145 (100), 90 (46), 82 (26) and 80 (27).

The data were consistent to the literature.¹³⁸

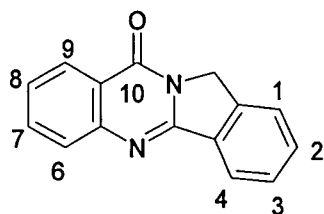
3-Benzyl-2-bromo-3*H*-quinazolin-4-one



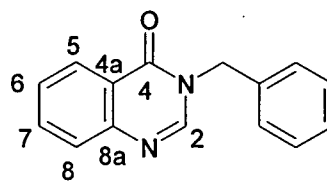
240

Sodium hydride (0.13 g, 3.2 mmol) was added to a solution of 2-bromo-3*H*-quinazolin-4-one (0.49 g, 2.1 mmol) in DMF (10 cm³) and stirred for 1 h. Benzyl bromide (0.5 cm³, 4.2 mmol) was added and the reaction was stirred for a further 3 h. The reaction mixture was quenched with H₂O (5 cm³). The crude reaction mixture was extracted into Et₂O and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (6:1) as eluent to yield 3-benzyl-2-bromo-3*H*-quinazolin-4-one as colourless crystals (0.31 g, 0.97 mmol, 46%); mp 109–111 °C; (Found: MH⁺, 315.0128. C₁₅H₁₂⁷⁹BrN₂O requires 315.0128.); ν_{\max} (thin film)/cm⁻¹ 3457, 3064, 1653, 1558, 1494, 1430, 1339, 1234, 1134, 1074, 1023, 901 and 819; δ_{H} 5.56 (2 H, s CH₂), 7.29–7.37 (5 H, m, Ph-H), 7.52 (1 H, ddd, *J* 8.2, 8.0, 2.0, 7-H), 7.66 (1 H, dd, *J* 8.0, 1.2, 8-H), 7.79 (1 H, ddd, *J* 8.2, 8.0, 1.2, 6-H) and 8.27 (1 H, dd, *J* 8.0, 2.0, 5-H); δ_{C} 51.76 (CH₂), 120.55 (4a-C), 126.88 (6/8-C), 127.49 (2 × Ph-H), 127.56 (6/8-C), 127.73 (5-C), 127.94 (7-C), 127.77 (2 × Ph-H), 135.12 (Ph-H), 135.36 (Ph-C), 136.20 (8a-C), 147.19 (2-C) and 161.65 (4-C); *m/z*(Electrospray) 316 (M⁺, 15%), 314 (16), 235 (75), 144 (39), 129 (22) and 91 (100).

Radical cyclisation of 3-benzyl-2-bromo-3*H*-quinazolin-4-one



233



232

Method A - Bu₃SnH (slow) and Et₃B

Tributyltin hydride (0.59 cm³, 2.2 mmol) in toluene (10 cm³) was added over 6 h to a solution of triethylborane (10 cm³, 10.0 mmol) and 3-benzyl-2-bromo-3*H*-quinazolin-4-one (0.31 g, 1.0 mmol) in dry toluene (40 cm³) with an air bleed into the round bottom flask through a

needle. More triethylborane (10 cm³, 10.0 mmol) was added and the reaction left to stir for a further 5 h. Dilute hydrochloric acid was added to the reaction to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove tributyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) yielding the reduced product 3-benzyl-3*H*-quinazolin-4-one **232** as colourless crystals (0.15 g, 0.62 mmol, 62%).

The data were consistent to previous synthesis and literature.¹⁴⁴

Method B - Bu₃GeH (slow) and Et₃B

Tributylgermanium hydride (0.53 g, 2.2 mmol) in toluene (10 cm³) was added over 6 h to a solution of triethylborane (10 cm³, 10 mmol) and 3-benzyl-2-bromo-3*H*-quinazolin-4-one (0.31 g, 1.0 mmol) in dry toluene (40 cm³) with an air bleed into the round bottom flask through a needle. Additional triethylborane (10 cm³, 10 mmol) was added to the reaction mixture after 3 h. Dilute hydrochloric acid was added to the reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove tributylgermanium residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding 3-benzyl-3*H*-quinazolin-4-one **232** (0.11 g, 0.47 mmol, 47%).

Method C – Photolysis with hexamethylditin

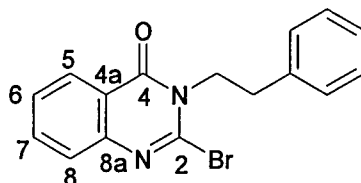
The reaction mixture between 3-benzyl-2-bromo-3*H*-quinazolin-4-one (0.30 g, 0.95 mmol) and (Me₃Sn)₂ (0.93 g, 2.85 mmol) in *t*-butylbenzene (20 cm³) was purged with nitrogen for 30 min, refluxed and irradiated with 300 W sunlamp for 10 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. ¹H NMR spectroscopy revealed a mixture of cyclised 12*H*-isoindolo-[1,2-*b*]-quinazolin-10-one **233**

(27%) and reduced product 3-benzyl-3*H*-quinazolin-4-one **232** (41%) as inseparable colourless crystals.

The amounts of products were determined using ^1H NMR spectroscopy.

The data were consistent to the previous synthesis and literature.¹⁴⁴

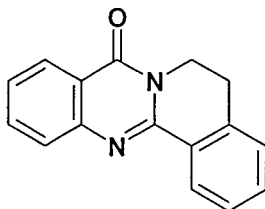
2-Bromo-3-phenylethyl-3*H*-quinazolin-4-one



243

Sodium hydride (0.14 g, 3.6 mmol) and sodium iodide (2.2 g, 15.0 mmol) were added to 2-bromo-3-*H*-quinazolin-4-one (0.53 g, 3.0 mmol) in dry DMF (20 cm³) and stirred for 1 h. 2-Bromoethylbenzene (0.82 cm³, 6.0 mmol) was added to the reaction mixture and stirred for a further 12 h. The reaction mixture was extracted into EtOAc and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc as eluent (10:1) yielding 2-bromo-3-phenylethyl-3*H*-quinazolin-4-one as colourless crystals (0.06 g, 0.18 mmol, 6%); mp 109-110 °C; (Found: M^+ , 328.0206. C₁₆H₁₃⁷⁹BrN₂O requires 328.0206.); ν_{max} (thin film)/cm⁻¹ 3060, 2930, 2359, 1866, 1714, 1655, 1621, 1604, 1493, 1452, 1405, 1072, 1028, 938 and 908; δ_{H} 2.99 (2 H, t, J 7.6, CH₂), 4.37 (2 H, t, J 7.6, NCH₂), 7.26-7.15 (5 H, m, ArH), 7.34-7.30 (1 H, m, 6-H), 7.49 (1 H, d, J 7.6, 8-H), 7.67-7.63 (1 H, m, 7-H) and 8.20 (1 H, d, J 7.6, 5-H); δ_{C} 33.98 (CH₂), 42.25 (NCH₂), 114.55 (4a-C), 114.88 (ArH), 123.12 (8-C), 126.39 (6-C), 128.27 (5-C), 128.42 (2 × ArH), 128.93 (2 × ArH), 134.85 (7-C), 138.54 (ArC), 138.75 (ArC), 151.17 (2-C) and 162.28 (4-C); m/z (EI) 330 (M^+ , 26%), 328 (25%), 145 (25%), 130 (33%), 104 (100%), 90 (95%), 65 (30%) and 39 (40%).

Radical cyclisation of 2-bromo-3-phenylethyl-3*H*-quinazolin-4-one



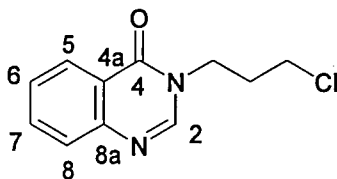
237

Method A – Photolysis and hexamethylditin

The reaction mixture of 2-bromo-3-phenylethyl-3*H*-quinazolin-4-one (28 mg, 0.085 mmol) and (Me₃Sn)₂ (82 mg, 0.25 mmol) in *t*-butylbenzene (20 cm³) was purged with nitrogen for 30 min, refluxed and irradiated with a 300 W sunlamp for 24 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one **237** as colourless crystals (0.02 g, 0.082 mmol, 97%).

The data were consistent to the previous synthesis and literature.¹⁴⁶

3-(3-Chloropropyl)-3*H*-quinazolin-4-one



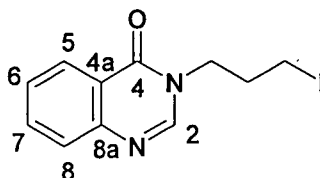
253a

Sodium hydride (1.78 g, 44.6 mmol) was added at 0 °C to 3*H*-quinazolin-4-one (6.50 g, 44.6 mmol) in dry DMF (50 cm³), warmed to 60 °C and stirred for 1 h. 1-Chloro-3-iodopropane (4.0 cm³, 37.2 mmol) was added and stirred for a further 12 h. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding 3-(3-chloropropyl)-3*H*-quinazolin-4-one as colourless crystals (5.06 g, 22.8 mmol, 51%); mp 97-99 °C (lit.¹⁴⁷ 98-100 °C); (Found: MH⁺,

223.0635. $C_{11}H_{12}^{35}ClN_2O$ requires 223.0633.); ν_{\max} (thin film)/ cm^{-1} 3439, 1659, 1613, 1469, 1366, 774 and 696; δ_H 2.34-2.28 (2 H, m, CH_2), 3.60 (2 H, t, J 9.9, $ClCH_2$), 4.19 (2 H, t, J 10.4, NCH_2), 7.51 (1 H, ddd, J 8.1, 6.4, 1.5, 6-H), 7.81-7.69 (2 H, m, 7,8-H), 8.11 (1 H, s, 2-H) and 8.30 (1 H, dd, J 8.1, 1.5, 5-H); δ_C 31.02 (CH_2), 41.58 ($ClCH_2$), 44.49 (NCH_2), 122.00 (4a-C), 126.57 (5-C), 127.42 (6-C), 127.49 (8-C), 134.38 (7-C), 146.61 (2-C), 148.05 (8a-C) and 161.15 (3-C); m/z (Electrospray) 225 (M^+ , 23%), 223 (79%), 187 (46), 160 (48), 129 (36), 77 (41), 63 (29), 49 (39) and 41 (100); Anal. Calcd for $C_{11}H_{11}N_2ClO$. C, 59.33; H, 4.98; N, 12.58. Found: C, 58.98; H, 4.98; N, 12.31.

The data were consistent to the literature.¹⁴⁷

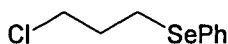
3-(3-Iodopropyl)-3*H*-quinazolin-4-one



254a

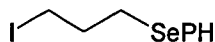
3-(3-Chloropropyl)-3*H*-quinazolin-4-one (4.43 g, 20.0 mmol) and sodium iodide (14.9 g, 100.0 mmol) were added to dry acetone (50 cm^3) and stirred under reflux for 12 h in the dark. The precipitated sodium chloride was removed by filtration on a celite bed and the solvent removed under reduced pressure. The solid residue was triturated with diethyl ether and the solution filtered a second time. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford 3-(3-iodopropyl)-3*H*-quinazolin-4-one propane as colourless crystals (3.35 g, 10.6 mmol, 53%); mp 119-121 $^{\circ}C$ (lit.¹⁴⁷ 120-122 $^{\circ}C$); (Found: MH^+ , 314.9990. $C_{11}H_{12}IN_2O$ requires 314.9989.); ν_{\max} (thin film)/ cm^{-1} 3421, 1667, 1614, 1470, 1364, 1118, 775 and 698; δ_H 2.37-2.30 (2 H, m CH_2), 3.20 (2 H, t, J 6.4, ICH_2), 4.13 (2 H, t, J 6.8, NCH_2), 7.52-7.48 (1 H, m, 6-H), 7.74-7.68 (2 H, m, 7,8-H), 8.13 (1 H, s, 2-H) and 8.27 (1 H, dd, J 8.0, 1.6, 5-H); δ_C 2.31 (ICH_2), 31.91 (CH_2), 47.42 (NCH_2), 121.94 (4a-C), 126.22 (5-C), 126.52 (6-C), 126.70 (8-C), 134.31 (7-C), 146.52 (2-C), 147.98 (8a-C), 161.03 (3-C); m/z (Electrospray) 187 (M^+ , 37%), 127 (35), 76 (28) and 41 (100).

The data were consistent to the literature.¹⁴⁷

1-Chloro-3-(phenylselanyl) propane¹⁴⁸**256**

Diphenyl diselanide (4.67 g, 15.0 mmol) was dissolved in methanol (250 cm³) at rt. Sodium borohydride (1.41 g, 37.5 mmol) was added slowly to the stirred solution at 0 °C. Hydrogen gas was allowed to escape through a needle. After 30 min, 3-bromo-1-chloropropane (2.97 cm³, 30.0 mmol) was added dropwise and the mixture was stirred for 12 h. The reaction mixture was extracted into Et₂O and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 1-chloro-3-(phenylselanyl)propane as a yellow oil (5.67 g, 24.2 mmol, 81%); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 2952, 1576, 1476, 1436, 1261, 1021, 734 and 690; δ_{H} 2.09-1.98 (2 H, m, CH₂), 2.96 (2 H, t, *J* 7.0, PhSeCH₂), 3.56 (2 H, t, *J* 6.2, ClCH₂), 7.23-7.17 (3 H, m, ArH) and 7.44-7.42 (2 H, m, ArH); δ_{C} 24.64 (CH₂), 32.56 (PhSeCH₂), 44.46 (ClCH₂), 127.17 (ArH), 129.32 (2 × ArH), 129.74 (ArC) and 132.87 (2 × ArH).

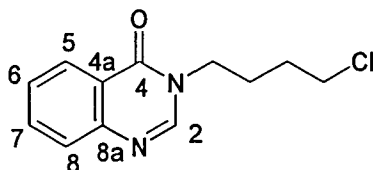
The data were consistent to the literature.¹⁴⁸

1-Iodo-3-(phenylselanyl)propane¹⁴⁸**257**

1-Chloro-3-(phenylselanyl)propane (3.50 g, 15 mmol) and sodium iodide (22.50 g, 150 mmol) were added to dry acetone (100 cm³) and stirred under reflux for 18 h in the dark. The precipitated sodium chloride was removed by filtration on a celite bed and triturated with diethyl ether. The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 1-iodo-3-(phenylselanyl)propane as a yellow oil (1.08 g, 3.4 mmol, 22%); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 1577, 1476, 1436, 1201, 1021, 732 and 689; δ_{H} 2.10-1.99 (2 H, m, CH₂), 2.87 (2 H, t, *J* 7.0, PhSeCH₂), 3.16 (2 H, t, *J* 6.7, ICH₂), 7.24-7.19 (3 H, m, ArH) and 7.49-7.24 (2 H, m, ArH); δ_{C} 6.36 (ICH₂), 28.56 (PhSeCH₂), 33.34 (CH₂), 126.99 (ArH), 129.17 (2 × ArH), 130.02 (ArC) and 132.77 (2 × ArH).

The data were consistent to the literature.¹⁴⁸

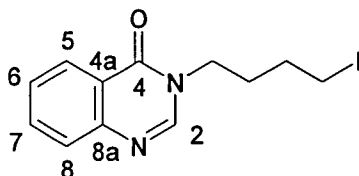
3-(4-Chlorobutyl)-3*H*-quinazolin-4-one



253b

Sodium hydride (0.19 g, 4.8 mmol) was added at 0 °C to 3*H*-quinazolin-4-one (0.70 g, 4.8 mmol) in dry DMF (50 cm³) and warmed to 60 °C and stirred for 1 h. 1-Chloro-4-iodobutane (0.49 cm³, 4.0 mmol) was added and the reaction stirred for a further 12 h. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (3:1) as eluent yielding 3-(4-chlorobutyl)-3*H*-quinazolin-4-one as colourless crystals (0.61 g, 2.6 mmol, 65%); mp 74-76 °C; (Found: MH⁺, 237.0792. C₁₂H₁₄³⁵ClN₂O requires 237.0789.); ν_{\max} (thin film)/cm⁻¹ 3446, 2953, 1662, 1609, 1471, 1367, 908, 875, 769 and 696; δ_{H} 1.86-1.89 (2 H, m, CH₂CH₂Cl), 2.05-1.97 (2 H, m, NCH₂CH₂), 3.61 (2 H, t, *J* 6.5, CH₂Cl), 4.06 (2 H, t, *J* 7.6, NCH₂), 7.52 (1 H, m, 6-H), 7.77-7.12 (2 H, m, 7,8-H), 8.05 (1 H, s, 2-H) and 8.32-8.30 (1 H, m, 5-H); δ_{C} 26.89 (NCH₂CH₂), 29.47 (CH₂CH₂Cl), 44.16 (NCH₂), 46.10 (CH₂Cl), 122.06 (4a-C), 126.67 (5-CH), 127.34 (6-C), 127.46 (8-C), 134.26 (7-C), 146.30 (2-C), 148.06 (8a-C) and 161.06 (4-C); *m/z*(Electrospray) 238 (M⁺, 7%), 236 (50%), 201 (29), 146 (39), 77 (28), 63 (25), 55 (42), 49 (74); Anal. Calcd for C₁₂H₁₃N₂OCl. C, 60.89; H, 5.54; N, 11.84. Found: C, 60.76; H, 5.44; N, 12.00.

3-(4-Iodobutyl)-3*H*-quinazolin-4-one

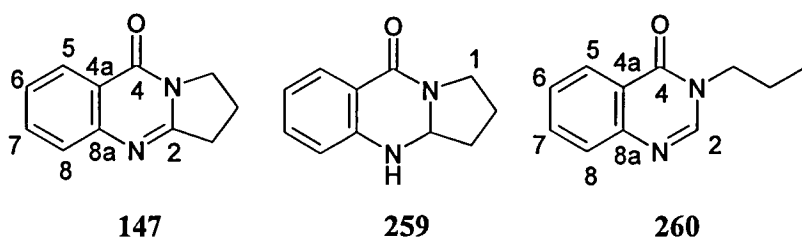


254b

3-(3-Chlorobutyl)-3*H*-quinazolin-4-one (0.37 g, 1.6 mmol) and sodium iodide (2.25 g, 15.0 mmol) were added to dry acetone (50 cm³) and stirred under reflux for 12 h in the dark. The precipitated sodium chloride was removed by filtration on a celite bed and the solution evaporated to dryness. The solid residue was triturated with diethyl ether and the solution filtered a second time. The organic layer was dried over MgSO₄ and the solvent removed

under reduced pressure to afford 3-(4-iodobutyl)-3*H*-quinazolin-4-one as colourless crystals (0.34 g, 1.1 mmol, 67%); mp 79-80 °C; (Found: M^+ , 329.0253. $C_{12}H_{13}IN_2O$ requires 329.0254.); ν_{\max} (thin film)/ cm^{-1} 3424, 2949, 1656, 1614, 1471, 1372, 1172, 1111, 888, 769 and 697; δ_H 1.89-1.91 (4 H, m, CH_2CH_2), 3.24 (2 H, t, J 6.4, CH_2I), 4.04 (2 H, t, J 6.8, NCH_2), 7.51 (1 H, ddd, J 8.2, 6.8, 1.2, 6-H), 7.78-7.70 (2 H, m, 7,8-H), 8.06 (1 H, s, 2-H) and 8.32-8.29 (1 H, dd, J 8.2, 1.0, 5-H); δ_C 5.21 (CH_2I), 30.25 (CH_2), 30.38 (CH_2), 45.71 (NCH_2), 122.05 (4a-C), 126.67 (5-C), 127.35 (6-C), 127.58 (8-C), 134.26 (7-C), 146.29 (2-C), 148.05 (8a-C) and 161.02 (4-C); m/z (EI) 201 (M^+ , 43%), 141 (27), 90 (100), 76 (53), 62 (41) and 50 (30).

Radical cyclisation of 3-(3-iodopropyl)-3*H*-quinazolin-4-one



Method A – Photolysis and hexamethylditin

The reaction mixture of 3-(3-iodopropyl)-3*H*-quinazolin-4-one (0.31 g, 1.0 mmol) and $(Me_3Sn)_2$ (0.96 g, 3.0 mmol) in *t*-butylbenzene (20 cm^3) was purged with nitrogen for 30 min, refluxed and irradiated with a 300 W sunlamp for 24 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 \times 50 cm^3) to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with EtOAc (5 \times 50 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure and purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding:

147 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one as colourless crystals (0.04 g, 0.2 mmol, 20%); mp 190-192 °C (lit.¹⁴⁹ 196-198 °C); ν_{\max} (thin film)/ cm^{-1} 3418, 2355, 1651, 1621, 1470, 1385, 1285, 775, 695 and 667; δ_H 2.35-2.23 (2 H, m, CH_2), 3.18 (2 H, t, J 8.2, CH_2), 4.21 (2 H, t, J 7.4, NCH_2), 7.47-7.62 (1 H, m, 6-H), 7.76-7.62 (2 H, m, 7,8-H) and 8.28 (1 H, dd, J 7.8,

1.5, 5-H); δ_c 19.52 (CH₂), 32.51 (CH₂), 46.51 (NCH₂), 120.45 (4a-C), 126.25 (5-C), 126.38 (6-C), 126.76 (8-C), 134.19 (7-C), 149.07 (8a-C), 159.47 (2-C) and 161.01 (4-C).

The data were consistent to the literature.¹⁴⁹

259 2,3,3a,4-Tetrahydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one as colourless crystals (0.02 g, 0.12 mmol, 12%); mp 187-188 °C (lit.¹⁵⁰ 184-185 °C); ν_{\max} (thin film)/cm⁻¹ 3421, 1633, 1503, 1470, 1434, 1337, 1151, 752 and 695; δ_H 2.32-2.29 (2 H, m, CH₂), 3.19 (1 H, t, *J* 8.0, 1-H), 3.75-3.67 (2 H, m, CHCH₂), 4.21 (1 H, t, *J* 7.2, 1-H), 5.03 (1 H, t, *J* 7.2, CH), 6.69 (1 H, d, *J* 8.1, 8-H), 6.92-6.88 (1 H, m, 6-H), 7.27-7.24 (1 H, m, 7-H) and 7.90 (1 H, dd, *J* 7.7, 1.5, 5-H); δ_c 21.73 (CH₂), 33.22 (CHCH₂), 44.29 (NCH₂), 69.86 (CH), 114.88 (5-C), 118.39 (4a-C), 119.95 (6-C), 126.78 (8-C), 132.92 (7-C), 147.31 (8a-C) and 162.22 (4-C).

The data were consistent to the literature.¹⁵⁰

260 3-Propyl-3*H*-quinazolin-4-one as colourless crystals (0.01 g, 0.06 mmol, 6%); mp 99-100 °C (lit.¹⁵¹ 96-98 °C); δ_H 1.01 (3 H, t, *J* 7.6, CH₃), 1.89-1.79 (2 H, m, CH₂), 3.98 (2 H, t, *J* 8.4, NCH₂), 7.49-7.26 (1 H, m, 5-H), 7.76-7.71 (2 H, m, 7,8-H), 8.04 (1 H, s, 2-H) and 8.33-8.31 (1 H, m, 5-H); δ_c 11.14 (CH₃), 22.66 (CH₂), 48.61 (NCH₂), 122.19 (4a-C), 126.71 (5-C), 126.82 (6-C), 127.23 (8-C), 134.16 (7-C), 146.12 (2-C), 148.12 (8a-C) and 161.10 (4-C).

The data were consistent to the literature.¹⁵¹

Method B - Et₃B only

The reaction mixture of 3-(3-iodopropyl)-3*H*-quinazolin-4-one (0.31 g, 1.0 mmol) and triethylborane (4 cm³, 4.0 mmol) in *t*-butylbenzene (20 cm³) was stirred for 10 h with an air bleed into the round bottom flask through a needle. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³). The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding 2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one **147** (40%), 2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one **259** (10%) and 3-propyl-3*H*-quinazolin-4-one **260** (30%).

The data were consistent with the previous synthesis.^{149, 150, 151}

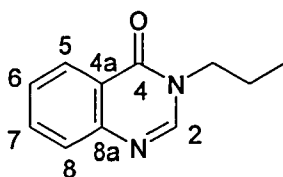
The yields were calculated from ¹H NMR spectral calculations.

Method C – Bu₃SnH (fast) and Et₃B

Tributyltin hydride (0.54 cm³, 2.0 mmol) and triethylborane (0.20 cm³, 0.20 mmol) were added to 3-(3-iodopropyl)-3*H*-quinazolin-4-one (0.31 g, 1.0 mmol) in dry toluene (40 cm³) and stirred for 1 h with an air bleed into the round bottom flask through a needle. More triethylborane (0.20 cm³, 0.2 mmol) was added and the reaction stirred for a further 10 h. Dilute hydrochloric acid was added to the reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove tributyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and evaporated to dryness under reduced pressure yielding 3-propyl-3*H*-quinazolin-4-one **260** (78%).

The data were consistent to the previous synthesis.

3-Propyl-3*H*-quinazolin-4-one

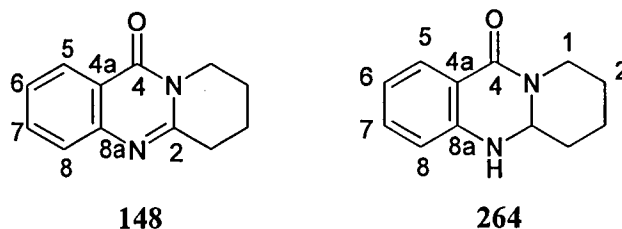


260

Sodium hydride (0.29 g, 7.2 mmol) was added at 0 °C to 3*H*-quinazolin-4-one (0.87 g, 6.0 mmol) in dry DMF (50 cm³), warmed to 60 °C and stirred for 1 h. 1-Iodopropane (1.75 cm³, 18.0 mmol) was added and stirred for a further 2 h. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding 3-propyl-3*H*-quinazolin-4-one as colourless crystals (0.72 g, 3.8 mmol, 64%); mp 93-95 °C (lit.¹⁵¹ 96-98 °C); ν_{\max} (thin film)/cm⁻¹ 3416, 2963, 2875, 2462, 1674, 1611, 1473, 1376, 1324, 1091, 899, 767, 695, 610 and 552; δ_{H} 0.99 (3 H, t, *J* 7.4, CH₃), 1.88-1.79 (2 H, m, CH₂), 3.97 (2 H, t, *J* 7.2, NCH₂), 7.48 (1 H, ddd, *J* 8.1, 6.8, 1.5, 6-H), 7.75-7.67 (2 H, m, 7,8-H), 8.06 (1 H, s, 2-H) and 8.30 (1 H, dd, *J* 8.1, 1.5, 5-H); δ_{C} 11.02 (CH₃), 22.20 (CH₂), 48.38 (NCH₂), 122.03 (4a-C), 126.48 (5-C), 126.62 (6-C), 126.81 (8-C), 133.65 (7-C), 146.60 (2-C), 148.00 (8a-C) and 160.84 (4-C); Anal. Calcd for C₁₁H₁₂NO. C, 70.19; H, 6.43; N, 14.88. Found: C, 69.91; H, 6.43; N, 14.78.

The data were consistent to previous synthesis and the literature.¹⁵¹

Radical cyclisation of 3-(4-iodobutyl)-3*H*-quinazolin-4-one



Method A – photolysis with hexamethylditin

The reaction mixture of 3-(4-iodobutyl)-3*H*-quinazolin-4-one (0.32 g, 1.0 mmol) and (Me₃Sn)₂ (0.96 g, 3.0 mmol) in *t*-butylbenzene (20 cm³) was purged with nitrogen for 30 min, refluxed and irradiated with a 300 W sunlamp for 10 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure and purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding:

148 6,7,8,9-Tetrahydropyrido[2,1-*b*]quinazolin-11-one as colourless crystals (0.06 g, 0.3 mmol, 30%); mp 94-95 °C (lit.¹⁸⁰ 96-97 °C); (Found: MH⁺, 201.1020. C₁₂H₁₃N₂O requires 201.1022.); ν_{\max} (thin film)/cm⁻¹ 3423, 2948, 2110, 1655, 1614, 1565, 1477, 1173, 1102, 990, 870, 771 and 583; δ_{H} 2.18-1.91 (4 H, m, CH₂CH₂), 3.00 (2 H, t, *J* 6.6, NCCH₂), 4.09 (2 H, t, *J* 6.3, NCH₂), 7.44-7.40 (1 H, m, 6-H), 7.59 (1 H, dd, *J* 8.3, 0.5, 8-H), 7.73-7.69 (1 H, m, 7-H) and 8.26 (1 H, dd, *J* 8.0, 1.5, 5-H); δ_{C} 19.33 (CH₂), 22.10 (CH₂), 31.93 (CH₂), 42.32 (CH₂), 120.40 (4a-C), 126.06 (5-C), 126.37 (6-C), 126.61 (8-C), 134.15 (7-C), 147.39 (8a-C), 154.86 (2-C) and 162.17 (4-C); *m/z*(Electrospray) 200 (M⁺, 50%), 199 (40), 90 (33), 76 (34), 63 (33), 50 (34), 41 (90) and 39 (100).

The data were consistent to the literature.¹⁸⁰

264 5,5a,6,7,8,9-Hexahydropyrido[2,1-*b*]quinazolin-11-one as colourless crystals (0.05 g, 0.23 mmol, 23%); mp 128-130 °C (lit.¹⁵² 134 °C); (Found: MH⁺, 203.1180. C₁₂H₁₅N₂O requires 203.1179.); ν_{\max} (thin film)/cm⁻¹ 3398, 3058, 2938, 2224, 1632, 1518, 1416, 1218, 1153, 1026, 754 and 692; δ_{H} 1.52-1.49 (2 H, m, 2-H), 1.91-1.75 (4 H, m, CH₂), 2.66-2.59 (1 H, m, 1-H), 4.25 (1 H, m, NH), 4.64-4.59 (1 H, m, 1-H), 4.78 (1 H, dd, *J* 10.2, 3.1, CH), 6.57

(1 H, d, J 7.1, 8-H), 6.79 (1 H, ddd, J 7.8, 2.9, 1.0, 6-H), 7.25 (1 H, m, 7-H) and 7.90 (1 H, dd, J 7.8, 1.6, 5-H); δ_c 22.30 (CH₂), 24.16 (CH₂), 33.43 (CH₂), 41.99 (CH₂), 68.51 (CH), 113.70 (8-C), 115.18 (4a-C), 118.81 (6-C), 128.71 (5-C), 133.41 (7-C), 145.89 (8a-C) and 164.32 (4-C); m/z (Electrospray) 201 (M⁺, 30%), 146 (42), 119 (48), 92 (42), 55 (79) and 41 (100).

The data were consistent to the literature.¹⁵²

Method B - Et₃B only

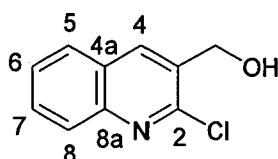
3-(4-Iodobutyl)-3*H*-quinazolin-4-one (0.32 g, 1.0 mmol) and triethylborane (4 cm³, 4.0 mmol) in *t*-butylbenzene (20 cm³) were stirred for 10 h with an air bleed into the round bottom flask through a needle. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³). The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding 6,7,8,9-tetrahydropyrido[2,1-*b*]quinoxalin-11-one **148** (61%) and 5,5a,6,7,8,9-hexahydropyrido[2,1-*b*]quinazolin-11-one **264** (23%).

The data were consistent to the previous synthesis.^{80, 152}

The yields were calculated from ¹H NMR spectral calculations

6.4 Experimental for Chapter 3

2-Chloro-3-(hydroxymethyl)quinoline¹⁵³



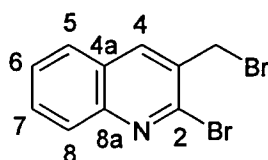
275

Sodium borohydride (0.18 g, 4.8 mmol) was added to a stirred solution of 3-carboxaldehyde-2-chloroquinoline (0.76 g, 4.0 mmol) in EtOH (50 cm³) at 0 °C and left stirring for 2 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 2-chloro-3-(hydroxymethyl)quinoline as colourless crystals (0.58, 3.0 mmol, 75 %); mp 151-152 °C (lit.¹⁵³ 149 °C); (Found: MH⁺, 194.0368. C₁₀H₉³⁵ClNO requires 194.0367.); ν_{\max} (thin film)/cm⁻¹ 3410, 1256, 1201, 1187, 1016, 942, 896, 778, 756 and

670; δ_{H} 4.94 (2 H, d, J 3.0, CH_2), 7.57 (1 H, ddd, J 8.3, 6.8, 1.3, 6-H), 7.73 (1 H, ddd, J 8.1, 6.8, 1.5, 7-H), 7.85 (1 H, dd, J 8.3, 1.5, 5-H), 8.03 (1 H, dd, J 8.1, 1.3, 8-H) and 8.30 (1 H, s, 4-ArH); δ_{C} 62.05 (CH_2), 127.25 (6-C), 127.38 (4a-C), 127.59 (5-C), 128.24 (8-C), 130.29 (7-C), 132.24 (3-C), 136.25 (4-C), 146.94 (8a-C) and 149.07 (2-C); m/z (Electrospray) 195 (M^+ , 15%), 193 (38), 163 (42), 156 (38), 140 (30), 130 (42), 129 (45), 128 (100), 75 (36), 63 (44), 62 (88), 50 (53) and 39 (59); Anal. Calcd for $\text{C}_{10}\text{H}_7\text{NClO}$. C, 62.03; H, 4.16; N, 7.23. Found: C, 61.92; H, 4.16; N, 7.23.

The data were consistent to the literature.¹⁵³

2-Bromo-3-(bromomethyl)quinoline¹⁰²

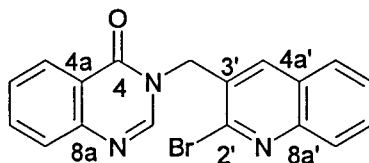


276

Phosphorous tribromide (1.5 cm^3 , 16.0 mmol) was added to a stirred solution of 2-chloro-3-(hydroxymethyl)quinoline (0.77 g, 4.0 mmol) in THF (20 cm^3) at 0 °C and stirred for a further 24 h. The crude reaction mixture was extracted into DCM and washed with H_2O (3 \times 50 cm^3) and brine (50 cm^3). The organic layer was dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (10:1) as eluent to yield 2-bromo-3-(bromomethyl)quinoline as colourless crystals (0.66 g, 2.2 mmol, 55%); mp 137-138 °C (lit.¹⁰² 139-140 °C); ν_{max} (thin film)/ cm^{-1} 1559, 1490, 1430, 1399, 1249, 1210, 1131, 1022, 968, 920, 858, 776, 757, 695, 594 and 474; δ_{H} 4.74 (2 H, s, CH_2), 7.60 (1 H, ddd, J 8.0, 6.8, 2.0, 6-H), 7.76 (1 H, ddd, J 8.6, 6.8, 1.7, 7-H), 7.82 (1 H, dd, J 8.0, 1.7, 5-H), 8.05 (1 H, dd, J 8.6, 2.0, 8-H) and 8.23 (1 H, s, 4-H); δ_{C} 28.98 (CH_2), 127.25 (4a-C), 127.55 (5-C), 127.64 (6-C), 128.47 (8-C), 131.12 (7-C), 131.45 (3-C), 138.66 (4-C), 143.10 (2-C) and 147.94 (8a-C).

The data were consistent to the literature.¹⁰²

3-[(2-Bromoquinolin-3-yl)methyl]-3*H*-quinazolin-4-one¹⁰²

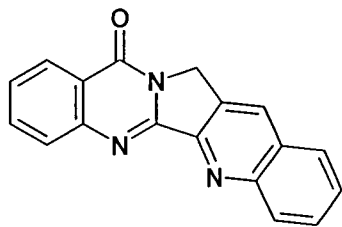


277

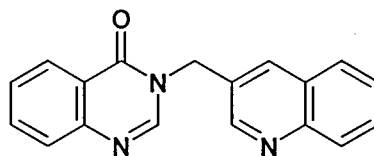
Potassium *t*-butoxide (0.14 g, 1.28 mmol) was added to a solution of 3*H*-quinazolin-4-one (0.17 g, 1.16 mmol) in DMF (20 cm³) and stirred 1 h. 2-Bromo-3-(bromomethyl)-quinoline (0.42 g, 1.4 mmol) was added and stirred for a further 12 h. The crude reaction mixture was extracted into Et₂O and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (1:1) as eluent to yield 3-[(2-bromoquinolin-3-yl)methyl]-3*H*-quinazolin-4-one as colourless crystals (0.279 g, 0.76 mmol, 65%); mp 200-202 °C (lit.¹⁰² 201-203 °C); ν_{\max} (thin film)/cm⁻¹ 3424, 1664, 1470, 1359, 1318, 1220, 1164, 960, 858, 774, 693 and 494; δ_{H} 5.42 (2 H, s, CH₂), 7.59-7.53 (2 H, m, ArH), 7.83-7.16 (4 H, m, ArH), 8.04-7.99 (1 H, m, ArH), 8.05 (1 H, s, ArH), 8.34-8.30 (1 H, m, ArH) and 8.35 (1 H, s, ArH); δ_{C} 49.53 (CH₂), 122.07 (4a-C), 126.84 (ArH), 127.04 (4a'-C), 127.67 (ArH), 127.72 (ArH), 127.78 (ArH), 127.83 (ArH), 128.31 (ArH), 128.73 (3'-C), 131.03 (ArH), 134.69 (ArH), 138.29 (ArH), 142.02 (2'-C), 146.52 (ArH), 147.91 (8a'-C), 148.02 (8a-C) and 161.21 (4-C).

The data were consistent to the literature.¹⁰²

Radical cyclisation of 3-[(2-bromoquinolin-3-yl)methyl]-3*H*-quinazolin-4-one



144a



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Method A – Photolysis with hexamethylditin

The reaction mixture between 3-[(2-bromo-quinolin-3-yl)methyl]-3*H*-quinazolin-4-one (0.16 g, 0.43 mmol) and (Me₃Sn)₂ (0.42 g, 1.29 mmol) in *t*-butylbenzene (20 cm³) was refluxed and irradiated with UV lamp for 24 h. Dilute hydrochloric acid was added to the cooled reaction

mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum ($3 \times 50 \text{ cm}^3$) to remove trimethyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14 and extracted with DCM ($3 \times 50 \text{ cm}^3$). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (1:1) as eluent yielding:

144a Luotonin A as colourless crystals (62 mg, 0.22 mmol, 51%); ν_{max} (thin film)/ cm^{-1} 3430, 2100, 1640, 1551, 1466, 1438, 1337, 741 and 691; δ_{H} 5.35 (2 H, s, CH_2), 7.59 (1 H, t, J 8.2, ArH), 7.69 (1 H, t, J 8.2, ArH), 7.88-7.82 (2 H, m, ArH), 7.95 (1 H, d, J 8.2, ArH), 8.21 (1 H, d, J 8.2, ArH) and 8.49-8.42 (3 H, m, ArH); δ_{C} 47.33 (CH_2), 121.32 (ArC), 126.46 (ArH), 127.47 (ArH), 127.98 (ArH), 128.55 (ArH), 128.78 (ArH), 129.42 (ArC), 130.72 (ArH), 130.74 (ArC), 131.59 (ArH), 134.62 ($2 \times$ ArH), 149.37 (ArC), 149.45 (ArC), 151.19 (ArC), 152.57 (ArC) and 160.69 (ArC).

The data were consistent to the literature.⁷³

278 3-[(Quinolin-3-yl)methyl]-3*H*-quinazolin-4-one as colourless crystals (19 mg, 0.07 mmol, 15%): mp 252-253 °C; (Found: MH^+ , 288.1131. $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}$ requires 288.1130.); ν_{max} (thin film)/ cm^{-1} 3420, 2357, 2107, 1646, 1558, 1450, 1361, 1332, 510 and 454; δ_{H} 5.39 (2 H, s, CH_2), 7.58-7.53 (2 H, m, ArH), 7.81-7.70 (4 H, m, ArH), 8.10 (1 H, dd, J 8.9, 0.4, ArH), 8.17 (1 H, d, J 1.8, ArH), 8.35-8.32 (1 H, m, ArH) and 8.99 (1 H, d, J 1.8, ArH); δ_{C} 47.73 (CH_2), 122.14 (ArC), 126.89 (ArH), 127.28 (ArH), 127.66 ($2 \times$ ArH), 127.86 (ArH), 128.60 ($2 \times$ ArC), 129.29 (ArH), 130.04 (ArH), 134.59 (ArH), 135.41 (ArH), 145.90 (ArH), 147.88 (ArC), 148.02 (ArC), 150.11 (ArH) and 161.07 (ArC); m/z (Electrospray) 287 (M^+ , 47%), 270 (45), 142 (100), 115 (68) and 89 (20).

Method B - Bu_3SnH (fast) and Et_3B

Tributyltin hydride (0.049 cm^3 , 0.17 mmol) was added to a solution of triethylborane (10 cm^3 , 10 mmol) and 3-[(2-bromo-quinolin-3-yl)methyl]-3*H*-quinazolin-4-one (0.025 g, 0.068 mmol) in dry toluene (40 cm^3) with an air bleed into the round bottom flask through a needle and stirred 5 h. Triethylborane (10 cm^3 , 10 mmol) was added and the reaction mixture stirred for a further 5 h. Dilute hydrochloric acid was added to the reaction mixture to extract the

protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum ($3 \times 50 \text{ cm}^3$) to remove tributyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with DCM ($3 \times 50 \text{ cm}^3$). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure yielding 3-[(quinolin-3-yl)methyl]-3*H*-quinazolin-4-one **278** (10.3 mg, 0.036 mmol, 53%).

The data were consistent to the previous synthesis.

Method C - Bu_3SnH (slow) and Et_3B

Tributyltin hydride (0.034 cm^3 , 0.14 mmol) was added to a solution of triethylborane (10 cm^3 , 10 mmol) and 3-[(2-bromoquinolin-3-yl)methyl]-4(3*H*)-quinazolinone (0.02 g, 0.055 mmol) in dry toluene (40 cm^3) via a syringe pump over 5 h. The round bottom flask had a needle to bleed air through. After 3 h, triethylborane (10 cm^3 , 10 mmol) was added and stirred for a further 3 h. Dilute hydrochloric acid was added to the reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum ($3 \times 50 \text{ cm}^3$) to remove tributyltin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with DCM ($3 \times 50 \text{ cm}^3$). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure yielding luotonin A **144a** (22 mg, 0.0076 mmol, 14%) and [(3-quinolin-3-yl)methyl]-3*H*-quinazolin-4-one **278** (50 mg, 0.174 mmol, 32%).

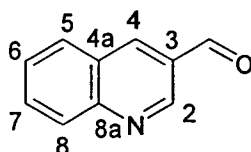
The data were consistent to the previous synthesis and literature.⁷³

Method D - Bu_3GeH (slow) and Et_3B

Tributylgermanium hydride (0.034 cm^3 , 0.14 mmol) was added to a solution of triethylborane (10 cm^3 , 10 mmol) and 3-[(2-bromoquinolin-3-yl)methyl]-3*H*-quinazolin-4-one (0.02 g, 0.055 mmol) in dry toluene (40 cm^3) over 5 h via a syringe pump, with an air bleed into the round bottom flask through a needle and stirred. After 3 h, triethylborane (10 cm^3 , 10 mmol) was added and stirred for a further 3 h. Dilute hydrochloric acid was added to the reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum ($3 \times 50 \text{ cm}^3$) to remove tributylgermanium residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with DCM ($3 \times 50 \text{ cm}^3$). The combined organic layers were dried over MgSO_4 and

the solvent removed under reduced pressure yielding luotonin A **144a** (28 mg, 0.0098 mmol, 18%) and [(3-quinolin-3-yl)methyl]-3*H*-quinazolin-4-one **278** (17 mg, 0.0059 mmol, 11%). The data were consistent to the previous synthesis.⁷³

Quinoline-3-carbaldehyde⁸⁹

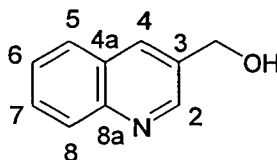


280

Butylmagnesium chloride (1.25 cm³, 2.5 mmol) and *n*-butyllithium (2.0 cm³, 5.0 mmol) were stirred in toluene (10 cm³) at -10 °C for 1 h. 3-Bromoquinoline (0.91 cm³, 6.7 mmol) was added slowly at -10 °C and stirred for 2.5 h. DMF (0.51 cm³, 6.7 mmol) was added at -10 °C and stirred for a further 12 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (9:1) as eluent yielding quinoline-3-carbaldehyde as a yellow oil (0.73 g, 4.7 mmol, 70%); ν_{\max} (thin film)/cm⁻¹ 3052, 2983, 2252, 1732, 1699, 1617, 1497, 1423, 1373, 1264 and 908; δ_{H} 7.62 (1 H, ddd, *J* 8.4, 7.0, 1.0, 6-H), 7.84 (1 H, ddd, *J* 8.4, 7.0, 1.4, 7-H), 7.92 (1 H, dd, *J* 8.4, 1.4, 5-H), 8.14 (1 H, dd, *J* 8.4, 1.0, 8-H), 8.54 (1 H, d, *J* 2.0, 4-H), 9.31 (1 H, d, *J* 2.0, 2-H) and 10.19 (1 H, s, OCH); δ_{C} 126.82 (3-C), 127.71 (6-C), 128.41 (4a-C), 129.18 (7-C), 129.52 (5-C), 132.48 (8-C), 139.99 (4-C), 148.81 (2-C), 150.33 (8a-C) and 190.62 (CO).

The data were consistent to the literature.⁸⁹

3-Hydroxymethylquinoline



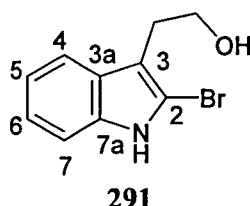
281

Sodium borohydride (0.55 g, 14.0 mmol) was added to a stirred solution of quinoline-3-carbaldehyde (0.57 g, 3.4 mmol) in EtOH (50 cm³) at 0 °C and left stirring for 2 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (3 × 50 cm³) and brine (50

cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) yielding 3-hydroxymethylquinoline as a colourless oil (0.32 g, 2.0 mmol, 54%); mp 80-81 °C (lit.¹⁵⁴ 81-83 °C); ν_{\max} (thin film)/cm⁻¹ 3420, 2862, 1652, 1576, 1456, 1328, 1126, 1058, 886, 786, 667 and 472; δ_{H} 4.8 (2 H, s, CH₂), 7.43 (1 H, ddd, *J*, 8.0, 7.0, 1.2, 6-H), 7.58 (1 H, ddd, *J* 8.6, 7.0, 1.4, 7-H), 7.64 (1 H, dd, *J* 8.0, 1.4, 5-H), 7.96 (1 H, dd, *J* 8.6, 1.2, 8-H), 8.02 (1 H, d, *J* 1.6, 4-H) and 8.72 (1 H, d, *J* 1.6, 2-H); δ_{C} 62.12 (CH₂), 126.87 (6-C), 127.75 (7-C), 127.88 (4a-C), 128.35 (5-C), 129.40 (8-C), 133.98 (4-C), 134.29 (3-C), 146.80 (8a-C) and 149.84 (2-C).

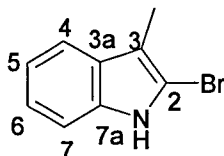
The data were consistent to the literature.¹⁵⁴

2-(2-Bromo-1*H*-indol-3-yl)ethanol



N-Bromosuccinimide (0.52 g, 4.0 mmol) was added to tryptophol (0.32 g, 2.0 mmol) in carbon tetrachloride (20 cm³) and heated under reflux for 5 h. After cooling to room temperature the succinimide was filtered off. The organic solution was dried over MgSO₄ and the solvent removed under reduced pressure. The crystalline solid was purified by column chromatography using alumina as absorbent with light petroleum/EtOAc (6:1) yielding 2-(2-bromo-1*H*-indol-3-yl)ethanol as yellow crystals (55 mg, 0.3 mmol, 12%); mp 88.5-89.5 °C; (Found: *M*⁺, 238.9945. C₁₀H₁₀⁷⁹BrNO requires 238.9946.); ν_{\max} (thin film)/cm⁻¹ 3625, 2039, 1817, 1784, 1699 and 580; δ_{H} 3.26-3.30 (2 H, t, *J* 6.5, CH₂), 3.57-3.61 (2 H, t, *J* 6.5, CH₂OH), 7.41-7.11 (3 H, m, ArH), 7.50 (1 H, d, *J* 7.0 ArH) and 8.03 (1 H, brs, NH); δ_{C} 27.81 (CH₂), 30.35 (CH₂OH), 107.82 (3-C), 109.56 (7-C), 111.98 (2-C), 116.89 (6-C), 119.31 (4-C), 121.51 (5-C), 126.18 (3a-C) and 134.91 (7a-C); *m/z*(EI) 225 (*M*⁺, 79%), 223 (81), 208 (22), 144 (100), 130 (61), 115 (60), 89 (24), 77 (23) and 63 (21). The compound was unstable in air.

2-Bromo-3-methyl-1*H*-indole¹⁵⁵

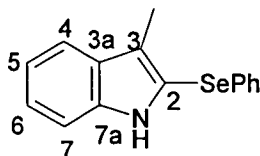


289a

A solution of *N*-bromosuccinimide (1.56 g, 12.0 mmol) and 3-methyl-1*H*-indole (1.31 g, 10.0 mmol) in dry carbon tetrachloride (50 cm³) was refluxed for 2 h. The reaction mixture was cooled to rt before being filtered through a celite bed and washed with carbon tetrachloride (3 × 20 cm³). The solvent was removed under reduced pressure, and the crude product purified using column chromatography with neutral alumina as absorbent with light petroleum/EtOAc (6:1) as eluent yielding 2-bromo-3-methyl-1*H*-indole as colourless crystals (0.86 g, 4.8 mmol, 48%); mp 93-94 °C (lit.¹⁵⁵ 94-95 °C); (Found: M^+ , 208.9840. C₉H₈⁷⁹BrN requires 208.9840.); δ_H 2.27 (3 H, s, CH₃), 7.11-7.21 (3 H, m, ArH), 7.46-7.48 (1 H, m, ArH) and 7.82 (1 H, brs, NH); δ_C 9.66 (CH₃), 107.92 (3-C), 110.28 (7-C), 111.37 (2-C), 118.20 (4-C), 119.34 (6-C), 121.60 (5-C), 128.00 (3a-C) and 135.94 (7a-C); m/z (EI) 211 (M^+ , 58 %), 209 (53), 210 (65), 147 (100), 130 (90), 129 (49) and 119 (65).

The data were consistent with the literature.¹⁵⁵

3-Methyl-2-(phenylselanyl)-1*H*-indole



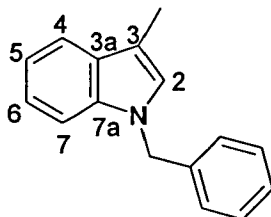
289b

3-Methyl-1*H*-indole (0.66 g, 5.0 mmol) and phenylselanyl chloride (1.05 g, 5.5 mmol) were placed in a round bottom flask containing dry carbon tetrachloride (50 cm³) and triethylamine (0.68 cm³, 5.0 mmol) was added dropwise. The solution was heated under reflux for 4 h. The reaction mixture was cooled, filtered through a celite bed and washed with carbon tetrachloride (3 × 20 cm³). The organic layer was dried using MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography

using neutral alumina as absorbent with light petroleum/EtOAc (8:1) as eluent yielding 3-methyl-2-(phenylselanyl)-1*H*-indole as yellow crystals (0.15 g, 0.5 mmol, 11%), mp 77.6-77.8 °C; (Found: M^+ , 287.0215. $C_{15}H_{13}N^{80}Se$ requires 287.0213.); $\nu_{max}(\text{thin film})/\text{cm}^{-1}$ 3452, 3053, 1477, 1261, 896 and 706; δ_H 2.49 (3 H, s, CH_3), 7.21-7.32 (8 H, m, ArH), 7.66-7.70 (1 H, m, ArH) and 8.12 (1 H, brs, NH); δ_C 10.49 (CH_3), 110.55 (7-C), 118.18 (3-C), 119.39 (4-C), 119.61 (6-C), 120.62 (2-C), 123.22 (5-C), 126.44 ($2 \times$ ArH), 127.82 (ArC), 129.92 (ArH), 129.34 ($2 \times$ ArH), 132.30 (3a-C) and 137.64 (7a-C); $m/z(\text{EI})$ 287 (M^+ , 51 %), 285 (26), 207 (100) and 206 (48).

The data were consistent with the literature.¹⁵⁶

1-Benzyl-3-methyl-1*H*-indole¹⁵⁷

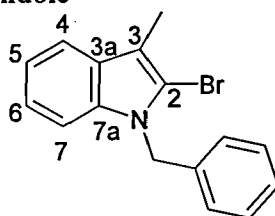


292

A solution of 3-methylindole (0.66 g, 5.0 mmol) in dry DMF (15 cm^3) was added to sodium hydride (0.24 g, 6.0 mmol) in dry DMF (50 cm^3) and stirred for 1.5 h. Benzyl bromide (2.97 ml, 25.0 mmol) was added and stirred the reaction stirred for a further 1 h. The reaction mixture was quenched with distilled water (5 cm^3). The reaction mixture was extracted into Et_2O (50 cm^3) and washed with distilled water ($5 \times 50 \text{ cm}^3$) and brine (50 cm^3) to remove the DMF. The crude product was dried with MgSO_4 and the solvent removed under reduced pressure before being purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (10:1) as eluent yielding 1-benzyl-3-methyl-1*H*-indole as colourless crystals (0.86 g, 3.9 mmol, 78%); mp 66-67 °C (lit.¹⁵⁷ 65-66 °C); $\nu_{max}(\text{thin film})/\text{cm}^{-1}$ 3057, 1717, 1640, 1396, 1089 and 739; δ_H 2.85 (3 H, s, CH_3), 5.48 (2 H, s, CH_2), 6.76 (1 H, s, 2-H) and 7.01-7.49 (9 H, m, ArH); δ_C 9.76 (CH_3), 49.82 (CH_2), 109.56 (7-C), 110.93 (3-C), 118.88 (6-C), 119.13 (4-C), 121.71 (5-C), 125.93 (2-C), 126.89 ($2 \times$ ArH), 127.56 (ArH), 128.79 ($2 \times$ ArH), 129.01 (3a-C), 136.73 (ArC) and 138.39 (7a-C).

The data were consistent with the literature.¹⁵⁷

1-Benzyl-2-bromo-3-methyl-1*H*-indole

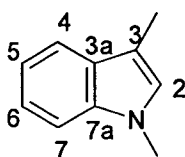


293

A solution of 1-benzyl-3-methyl-1*H*-indole (0.44 g, 2.0 mmol) and *N*-bromosuccinimide (0.31 g, 2.4 mmol) in dry carbon tetrachloride (50 cm³) was heated under reflux in the dark for 3. The reaction mixture was cooled and filtered through a celite bed and washed with carbon tetrachloride (3 × 20 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum as eluent in the dark yielding 1-benzyl-2-bromo-3-methyl-1*H*-indole as a colourless oil (0.20 g, 0.7 mmol, 33%); ν_{\max} (thin film)/cm⁻¹ 3059, 2901, 1599, 1473, 778 and 657; δ_{H} 2.15 (3 H, s, CH₃), 5.14 (2 H, s, CH₂) 6.88-6.91 (2 H, m, ArH) and 7.06-7.52 (7 H, m, ArH); δ_{C} 10.14 (CH₃), 48.41 (CH₂), 112.62 (7-C), 113.16 (3-C), 115.85 (2-C), 119.72 (4-C), 123.06 (6-C), 126.38 (2 × ArH), 126.98 (3a-C), 127.68 (ArH), 128.86 (5-C), 128.89 (2 × ArH), 136.88 (ArC) and 137.66 (7a-C). Compound was unstable in air and no further characterisation could be carried out.

The data were consistent with the literature.¹⁵⁸

1,3-Dimethyl-1*H*-indole¹⁵⁹



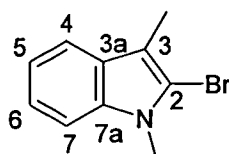
294

3-Methyl-1*H*-indole (1.87 g, 14.3 mmol) was added to sodium hydride (0.69 g, 17.1 mmol) in dry DMF (50 cm³) and stirred for 1 h. Methyl iodide was added slowly over 1 h and the mixture was left stirring for a further 2 h. The reaction mixture was quenched with distilled water (5 cm³). The reaction mixture was extracted into Et₂O (50 cm³) and washed with distilled water (5 × 50 cm³) and brine (50 cm³) to remove the DMF. The organic layer was dried using MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel absorbent with light petroleum as eluent to afford 1,3-dimethyl-1*H*-indole as colourless crystals (1.54 g, 10.6 mmol, 74%); mp 139-

140 °C (lit.¹⁵⁹ 142 °C); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$ 3055, 2918, 1618, 1473 and 740; δ_{H} 2.56 (3 H, s, CH₃), 3.84 (3 H, s, NCH₃), 6.96 (1 H, s, 2-H), 7.49-7.59 (2 H, m, ArH) and 7.78-7.93 (2 H, m, ArH); δ_{C} 9.89 (CH₃), 32.59 (NCH₃), 109.33 (7-C), 110.27 (3-C), 118.83 (6-C), 119.08 (4-C), 121.71 (5-C), 126.85 (2-C), 128.99 (3a-C) and 137.30 (7a-C).

The data were consistent with the literature.¹⁵⁹

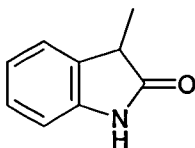
2-Bromo-1,3-dimethyl-1*H*-indole



295

N-Bromosuccinimide (0.52 g, 4.0 mmol) was added to a solution of 1,3-dimethyl-1*H*-indole (0.29 g, 2.0 mmol) in dry carbon tetrachloride (20 cm³) and refluxed in the dark for 2 h. The reaction mixture was cooled, filtered through a celite bed and washed with carbon tetrachloride (3 × 20 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified using column chromatography using silica gel as absorbent with light petroleum as eluent to yield 2-bromo-1,3-dimethyl-1*H*-indole as a colourless oil (less than 5%); δ_{H} 2.25 (3 H, s, CH₃), 3.67 (3 H, s, NCH₃) and 6.91-7.63 (4 H, m, ArH); δ_{C} 9.86 (CH₃), 31.66 (NCH₃), 112.12 (7-C), 113.90 (4-C), 115.40 (3-C), 116.86 (2-C), 119.86 (6-C), 122.51 (5-C), 126.25 (3a-C) and 137.33 (7a-C). Compound was unstable in air and no further characterisation could be carried out.

3-Methyl-1,3-dihydroindol-2-one⁹⁹



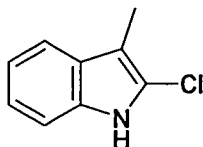
296

N-Bromosuccinimide (2.60 g, 20 mmol) was added to a solution of 3-methyl-1*H*-indole (2.64 g, 20 mmol) in *t*-BuOH/H₂O (155 cm³ 10:1) and stirred for 1 h. The reaction mixture was extracted into Et₂O and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using alumina as absorbent with light

petroleum/EtOAc (5:1) as eluent yielding 3-methyl-1,3-dihydroindol-2-one as colourless crystals (1.29 g, 8.6 mmol, 43%); mp 120-122 °C; (lit.⁹⁹ 122-124 °C); (Found: MH⁺, 148.0755. C₉H₁₀NO requires 148.0757.); ν_{\max} (thin film)/cm⁻¹ 3216, 2972, 2873, 1731, 1624, 1470, 1331, 1223, 1174 and 749; δ_{H} 1.51 (3 H, d, *J* 6.4, CH₃), 3.48 (1 H, q, *J* 6.4, CH), 6.93 (1 H, d, *J* 7.4, ArH), 7.02 (1 H, t, *J* 7.4, ArH), 7.32-7.17 (2 H, m, ArH) and 9.57 (1 H, brs, NH); δ_{C} 15.11 (CH₃), 41.28 (CH), 109.94 (ArH), 121.81 (ArH), 123.02 (ArH), 127.89 (ArH), 128.54 (ArC), 141.43 (ArC) and 181.99 (ArC); *m/z*(Electrospray) 147 (M⁺, 58%), 119 (64), 118 (75), 91 (50), 63 (46), 52 (52), 51 (68) and 50 (44).

The data were consistent to the literature.⁹⁹

2-Chloro-3-methyl-1*H*-indole

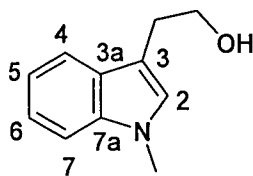


297

3-Methyl-1,3-dihydroindol-2-one (0.29 g, 2.0 mmol) were heated under reflux in phosphorous oxychloride (0.8 cm³, 1.2 mmol) under for 10 min. The solution was poured onto an ice and saturated sodium carbonate solution. The reaction mixture was extracted into DCM and washed and with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (12:1) as eluent yielding 2-chloro-3-methyl-1*H*-indole as colourless crystals (0.06 g, 0.4 mmol, 20%); mp 124 °C (lit.¹⁶⁰ 125 °C); ν_{\max} (thin film)/cm⁻¹ 3209, 2974, 1730, 1620, 1469, 1333, 1223, 1104, 752, 666, 540 and 493; δ_{H} 2.24 (3 H, s, CH₃), 7.21-7.11 (3 H, m, ArH) and 7.46 (1 H, d, *J* 7.5, ArH); δ_{C} 8.32 (CH₃), 107.95 (ArC), 110.35 (ArH), 118.32 (ArH), 119.94 (ArH), 120.60 (ArC), 122.22 (ArH), 128.32 (ArC) and 134.40 (ArC).

The data were consistent with the literature.¹⁶⁰

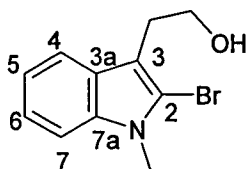
2-(1-Methyl-1*H*-indol-3-yl)ethanol



299

Sodium hydride (1.37 g, 34.2 mmol) was added to a solution of tryptophol (5.0 g, 31.1 mmol) in dry DMF (50 cm³) and stirred for 30 min. Methyl iodide (2.3 cm³, 37.3 mmol) was added to the solution and stirred for 3 h. The reaction mixture was quenched by dropwise addition of H₂O (5 cm³). The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude reaction mixture was purified using column chromatography with silica gel as absorbent with light petroleum/EtOAc (2:1) yielding 2-(1-methyl-1*H*-indol-3-yl)ethanol as a yellow oil (2.98 g, 17.0 mmol, 55%); (Found: *M*⁺, 175.0999. C₁₁H₁₃NO requires 175.0997.); *v*_{max}(thin film)/cm⁻¹ 3388, 2947, 1656, 1620, 1444 and 1328; *δ*_H 3.01 (2 H, t, *J* 6.7, CH₂), 3.36 (3 H, s, CH₃), 3.64 (2 H, t, *J* 6.7, CH₂OH), 6.84 (1 H, s, 2-H), 7.24-7.06 (3 H, m, ArH) and 7.58 (1 H, d, *J* 6.9, ArH); *δ*_C 28.52 (CH₂), 32.32 (CH₃), 62.60 (CH₂OH), 109.50 (7-C), 110.73 (3-C), 118.50 (6-C), 119.10 (4-C), 121.63 (5-C), 126.74 (2-C), 127.85 (3a-C) and 137.00 (7a-C); *m/z*(EI) 175 (*M*⁺, 11%), 144 (100), 129 (4), 115 (6), 103 (5) 102 (6) and 77 (7).

2-Bromo-3-(2-hydroxyethyl)-1-methyl-1*H*-indole

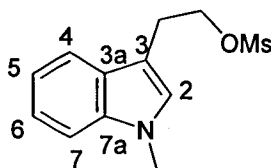


301

A solution of *N*-bromosuccinimide (5.20 g, 40.0 mmol) and 2-(1-methyl-1*H*-indol-3-yl)-ethanol (0.70 g, 4.0 mmol) in dry carbon tetrachloride (20 cm³) was heated under reflux for 1 h. The reaction mixture was cooled, filtered and washed with carbon tetrachloride (3 × 15 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (10:1) as eluent yielding 2-bromo-3-(2-hydroxyethyl)-

1-methyl-1*H*-indole as a colourless oil (0.30 g, 1.2 mmol, 30%); (Found M^+ , 256.0155. $C_{11}H_{12}^{81}BrNO$ requires 256.0155.); ν_{max} (thin film)/ cm^{-1} 3427, 1724, 1612, 1471, 1373 and 750; δ_H 2.96-2.75 (2 H, m, CH_2), 3.23 (3 H, s, CH_3), 3.40-3.26 (2 H, m, $HOCH_2$), 6.87 (1 H, d, J 7.7, 4-H), 7.14 (1 H, t, J 7.7, 6-H) and 7.41- 7.34 (2 H, m, ArH); δ_C 26.27 (CH_2), 26.89 (CH_3), 41.93 ($HOCH_2$) 109.14 (7-C), 109.14 (2-C), 123.95 (4-C), 124.56 (6-C), 128.79 (3-C), 130.67 (5-C), 142.30 (3a-C) and 173.28 (7a-C); m/z (CI) 256 (M^+ , 3%), 254 (80), 252 (82), 173 (100), 172 (93), 158 (85), 144 (90), 130 (96), 115 (55), 89 (43) and 77 (51).

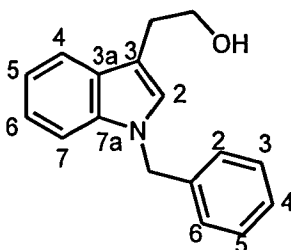
Methanesulfonic acid 2-(1-methyl-1*H*-indol-3-yl)ethyl ester



303

Methanesulfonyl chloride (0.19 cm^3 , 2.4 mmol) was added to a solution of 2-(1-methyl-1*H*-indol-3-yl)ethanol (0.35 g, 2.0 mmol) in dry DCM (50 cm^3) over 30 min. Triethylamine (0.41 cm^3 , 3.0 mmol) was added and the reaction stirred for a further 18 h. The reaction mixture was washed with H_2O (3 \times 50 cm^3) and brine (50 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure yielding methanesulfonic acid 2-(1-methyl-1*H*-indol-3-yl)ethyl ester as a colourless oil (0.44 g, 1.7 mmol, 87%); δ_H 2.75 (3 H, s, SO_2CH_3), 3.13 (2 H, t, J 7.0, CH_2), 3.63 (3 H, s, NCH_3), 4.35 (2 H, t, J 7.0, $MsOCH_2$), 6.86 (1 H, s, 2-H), 7.26-7.06 (3 H, m, ArH) and 7.54 (1 H, d, J 7.7, ArH); δ_C 25.47 (CH_2), 32.49 (SO_2CH_3), 37.16 (NCH_3), 70.37 ($MsOCH_2$), 108.82 (3-C), 109.62 (7-C), 118.46 (6-C), 119.10 (4-C), 121.92 (5-C), 127.62 (2-C), 127.68 (3a-C) and 137.05 (7a-C).

1-Benzyl-3-(2-hydroxyethyl)-1*H*-indole



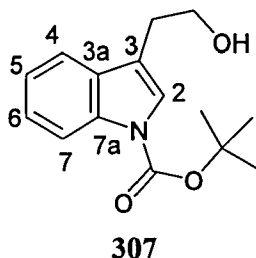
305

Sodium hydride (0.19 g, 4.8 mmol) was added to a solution of tryptophol (0.64 g, 4.0 mmol) in dry DMF (20 cm^3) at 0 $^{\circ}C$ and stirred 40 min at rt. Benzyl bromide (0.57 cm^3 , 4.8 mmol)

was added and the reaction mixture stirred for a further 3 h. The crude reaction was quenched by dropwise addition of H₂O (5 cm³). The mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent to yield 1-benzyl-3-(2-hydroxyethyl)-1*H*-indole as a yellow oil (0.68 g, 2.7 mmol, 68%); (Found: M⁺, 251.1311. C₁₇H₁₇NO requires 251.1310.); δ_H 3.02 (2 H, t, *J* 6.5, CH₂), 3.90 (2 H, t, *J* 6.5, OCH₂), 5.26 (2 H, s, BnCH₂), 7.00 (1 H, s, 2-H), 7.23-7.08 (8 H, m, ArH) and 7.83 (1 H, d, *J* 8.2, ArH); δ_C 26.03 (CH₂), 49.98 (BnCH₂), 62.85 (HOCH₂), 110.01 (7-C), 111.78 (3-C), 119.23 (6-C), 119.31 (4-C), 122.10 (5-C), 126.78 (Ph 4-C), 127.01 (Ph 3,5-C), 127.71 (2-C), 128.20 (3a-C), 128.94 (Ph 2,6-C), 136.96 (Ph 1-C) and 137.94 (7a-C); *m/z*(EI) 251 (M⁺, 44%), 220 (93), 130 (28), 97 (21), 91 (100) and 57 (21).

The data were consistent to the literature.¹⁶¹

3-(2-Hydroxyethyl)-1*H*-indole-1-carboxylic acid *t*-butyl ester

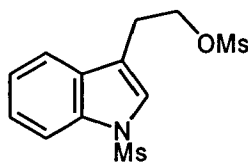


Triethylamine (0.56 cm³, 4.0 mmol) was added to a solution of tryptophol (0.32 g, 2.0 mmol) in dry THF (20 cm³) with stirring. DMAP (0.02 g, 0.2 mmol) was added and the reaction stirred for a further 15 min. Di-*t*-butyl dicarbonate (0.44 g, 2.0 mmol) in dry THF (10 cm³) was added slowly over 12 h using a syringe pump. The reaction mixture was washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (10:1) as eluent to yield 3-(2-hydroxyethyl)-1*H*-indole-1-carboxylic acid *t*-butyl ester as a yellow oil (0.06 g, 0.2 mmol, 11%); ν_{max}(thin film)/cm⁻¹ 3687, 3384, 3064, 1733, 1683, 1456, 1255, 1161 and 792; δ_H 1.48 (9 H, s, *t*-BuH), 3.14 (2 H, t, *J* 7.8, CH₂), 4.37 (2 H, t, *J* 7.8, HOCH₂), 7.00 (1 H, s, 2-H), 7.12 (1 H, t, *J* 8.0, ArH), 7.19 (1 H, t, *J* 8.0, ArH), 7.35 (1 H, d, *J* 8.0, ArH) and 7.63 (1 H, d, *J* 8.0, ArH); δ_C 24.91 (CH₂), 27.82 (3 × CH₃), 66.94 (HOCH₂), 82.01 (CMe₃), 111.17 (7-C),

111.53 (3-C), 118.77 (4-C), 119.47 (6-C), 122.11 (5-C), 122.23 (2-C), 127.41 (3a-C), 136.19 (7a-C) and 153.62 (C=O).

The data were consistent to the literature.¹⁶²

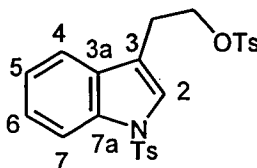
Methanesulfonic acid 2-[1-(methanesulfonyl)-1*H*-indol-3-yl]ethyl ester



309a

Methanesulfonyl chloride (3.26 cm³, 33.2 mmol) was added slowly at 0 °C to a solution of tryptophol (3.34 g, 16.6 mmol) and triethylamine (8.9 cm³, 64.0 mmol) in dry toluene (50 cm³). The reaction mixture was stirred for 12 h and extracted into EtOAc and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (5:1) as eluent yielding methanesulfonic acid 2-[1-(methanesulfonyl)-1*H*-indol-3-yl]ethyl ester as yellow crystals (0.74 g, 2.45 mmol, 15%); mp 98-99 °C; (Found: MNH₄⁺, 335.0733. C₁₂H₁₉N₂O₅S₂ requires 335.0730.); ν_{\max} (thin film)/cm⁻¹ 3111, 3022, 2932, 1606, 1448, 1351, 1281, 1167, 1121, 959, 909, 781, 748 and 589; δ_{H} 2.90 (3 H, s, NMsCH₃), 3.03 (3 H, s, OMsCH₃), 3.12 (2 H, t, *J* 6.8, CH₂), 4.45 (2 H, t, *J* 6.8, OMsCH₃), 7.35-7.25 (3 H, m, ArH), 7.57 (1 H, d, *J* 7.6, ArH) and 7.86 (1 H, d, *J* 8.0, ArH); δ_{C} 25.00 (CH₂), 37.15 (OMsCH₃), 40.49 (NMsCH₃), 70.49 (OCH₂), 113.20 (ArH), 117.31 (ArC), 118.39 (ArH), 123.18 (ArH), 123.71 (ArH), 125.17 (ArH), 130.43 (ArC) and 136.25 (ArC); *m/z*(Electrospray) 317 (M⁺, 36%), 221 (0), 208 (32), 142 (100), 130 (78), 115 (60), 101 (48), 79 (80) and (62).

1-Tosyl-3-(2-tosyloxyethyl)-3*H*-indole

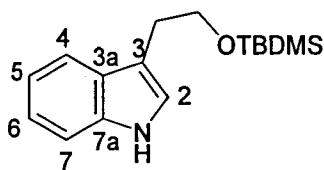


309b

Sodium hydride (0.40 g, 10.0 mmol) was added to tryptophol (0.60 g, 4.0 mmol) in dry THF (20 cm³) and stirred for 40 min. Tosyl chloride (1.67 g, 8.8 mmol) was added at 0 °C and stirred for 2 h. The crude reaction mixture was quenched with H₂O (5 cm³). The crude

reaction mixture was extracted into DCM and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent to yield 1-tosyl-3-(2-tosyloxyethyl)-3*H*-indole a yellow oil (0.45 g, 1.0 mmol, 25%); (Found: M⁺, 469.1009. C₂₄H₂₃NO₅S₂ requires 469.1001.); ν_{\max} (thin film)/cm⁻¹ 3055, 2923, 1596, 1495, 1269, 1020, 813 and 704; δ_{H} 2.30 (3 H, s, TsCH₃), 2.37 (3 H, s, TsCH₃), 3.00 (2 H, t, *J* 6.6, CH₂), 4.24 (2 H, t, *J* 6.6, OCH₂), 7.32-7.13 (8 H, m, ArH), 7.57-7.54 (2 H, m, TsH), 7.75-7.72 (2 H, m, TsH) and 7.94-7.92 (1 H, m, ArH); δ_{C} 21.52 (TsCH₃), 21.60 (TsCH₃), 24.88 (CH₂), 68.75 (OCH₂), 113.67 (7-C), 117.18 (3-C), 119.05 (4-C), 123.13 (6-C), 124.09 (2-C), 124.74 (5-C), 126.78 (2 × TsH), 127.62 (2 × TsH-C), 129.70 (2 × TsH), 129.92 (2 × TsH), 130.17 (3a-C), 132.49 (3-C), 135.03 (TsC), 135.17 (TsC), 144.80 (2 × TsC); *m/z*(EI) 297 (M⁺, 39%), 155 (49), 142 (80), 129 (26), 115 (50), 91 (100) and 65 (39).

3-[2-(*t*-Butyl-dimethylsilyloxy)ethyl]-1*H*-indole¹⁶³



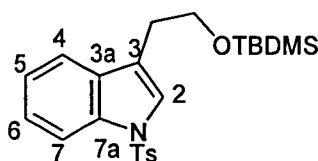
311

Imidazole (0.93 g, 13.6 mmol) was added to a solution of tryptophol (1.0 g, 6.2 mmol) in THF (50 cm³) with stirring at cooled to 0 °C. TBDMSCl (1.02 g, 6.8 mmol) was added and stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (20 cm³) and washed with H₂O (5 × 50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by flash sinter chromatography using silica gel as absorbent with light petroleum/EtOAc (3:1) as eluent to yield 3-[2-(*t*-butyl-dimethylsilyloxy)ethyl]-1*H*-indole as a yellow oil (1.67 g, 6.1 mmol, 88%); (Found: MH⁺, 276.1778. C₁₆H₂₆NOSi requires 276.1778.); ν_{\max} (thin film)/cm⁻¹ 3398, 3195, 2850, 1712, 1328, and 723; δ_{H} 0.42 (6 H, s, 2 × CH₃), 1.29 (9 H, s, 3 × CH₃), 3.46 (2 H, t, *J* 7.3, CH₂), 4.24 (2 H, t, *J* 7.3, SiOCH₂), 7.13 (1 H, s, 2-H), 7.50-7.42 (3 H, m, ArH), 7.94 (1 H, d, *J* 7.8, ArH) and 8.54 (1 H, brs, NH); δ_{C} -4.95 (2 × CH₃), 21.84 (3 × *t*-Bu), 26.36 (3 × CH₃), 31.53 (CH₂), 64.35 (SiOCH₂), 111.83 (7-C), 112.66 (3-C), 118.74 (6-C), 119.07 (4-C), 122.22 (5-C), 122.70 (2-

C), 129.71 (3a-C) and 136.57 (7a-C); m/z (Electrospray) 276 (M^+ , 46 %), 179 (23), 162 (100) and 144 (24).

The data were consistent with the literature.¹⁶³

3-[2-(*t*-Butyldimethylsilanoxy)ethyl]-1-tosyl-1*H*-indole¹⁶⁴

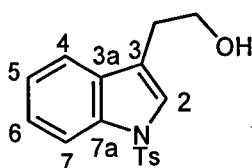


312

Sodium hydride (1.20 g, 30.0 mmol) was added to 3-[2-(*t*-butyl-dimethylsilyloxy)ethyl]-1*H*-indole (5.50 g, 20.0 mmol) in dry DMF (75 cm³) and stirred for 1 h. Tosyl chloride (4.57 g, 24.0 mmol) was added at 0 °C and stirred for 24 h. The crude reaction was quenched with H₂O (5 cm³). The crude reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (15:1) to yield 3-[2-(*t*-butyldimethylsilanoxy)ethyl]-1-tosyl-1*H*-indole as yellow crystals (7.35 g, 17.13 mmol, 86%); mp 99-101 °C; (Found: MNH_4^+ , 447.2136. C₂₃H₃₅N₂O₃SSi requires 447.2132.); ν_{max} (thin film)/cm⁻¹ 2925, 1448, 1371, 1174, 1095, 812 and 669; δ_H 0.01 (6 H, s, 2 × SiMe), 0.90 (9 H, s, *t*-Bu), 2.31 (3 H, s, TsMe), 2.88 (2 H, t, J 7.2, CH₂), 3.88 (2 H, t, J 7.2, OCH₂), 7.35-7.19 (4 H, m, ArH), 7.43 (1 H, s, 2-H), 7.52-7.48 (1 H, m, ArH), 7.76 (2 H, d, J 8.4, 2 × TsH) and 7.99 (1 H, m, ArH); δ_C -5.34 (2 × SiMe), 18.30 (q-*t*-Bu), 21.51 (TsMe), 25.96 (3 × *t*-Bu), 28.61 (CH₂), 62.63 (OCH₂), 113.68 (ArH), 119.60 (ArH), 120.16 (ArC), 112.97 (ArH), 123.55 (ArH), 124.55 (ArH), 127.04 (2 × TsArH), 129.81 (2 × TsArH), 131.28 (ArC), 135.16 (ArC), 135.50 (ArC) and 144.70 (ArC); m/z (Electrospray) 447 (M^+ , 100%), 298 (18), 276 (22) and 144 (14).

The data were consistent with the literature.¹⁶⁴

3-(2-Hydroxyethyl)-1-tosyl-3*H*-indole¹⁶⁵

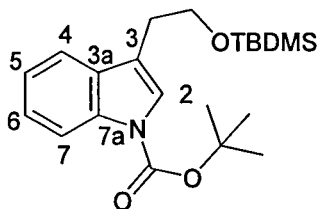


313

TBAF (21.40 cm³, 21.4 mmol) was added to 3-[2-(*t*-butyldimethylsilanoxy)ethyl]-1-tosyl-1*H*-indole (6.12 g, 14.3 mmol) in THF (50 cm³) and stirred for 24 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent to yield 3-(2-hydroxyethyl)-1-tosyl-3*H*-indole as yellow crystals (3.34 g, 11.1 mmol, 78%); mp 66-67 °C; (Found: MNH₄⁺, 333.1269. C₁₇H₂₁N₂O₃S requires 333.1267.); ν_{\max} (thin film)/cm⁻¹ 3568, 1647, 1446, 1172, 860 and 570; δ_{H} 2.32 (3 H, s, CH₃), 2.92 (2 H, t, *J* 6.4, CH₂), 3.87 (2 H, t, *J* 6.4, OCH₂), 7.26-7.19 (4 H, m, ArH), 7.32 (1 H, s, 2-H), 7.43 (1 H, m, ArH), 7.75 (2 H, d, *J* 8.4, ArH) and 7.90 (1 H, d, *J* 8.4, ArH); δ_{C} 21.54 (CH₃), 28.42 (CH₂), 61.84 (OCH₂), 113.80 (7-C), 119.33 (3-C), 119.46 (6-C), 123.13 (4-c), 123.76 (5-c), 124.81 (2-C), 126.79 (2,6 TsH), 129.86 (3,5 TsH), 130.87 (7a-C), 135.30 (3a-C), 135.33 (1-TsC) and 144.86 (4-TsC); *m/z*(Electrospray) 155 (M⁺, 33%), 130 (60), 91 (100), 77 (25), 65 (30), 44 (41) and 40 (11).

The data were consistent with the literature.¹⁶⁵

3-[2-(*t*-Butyl-dimethylsilanyloxy)-ethyl]indole-1-carboxylic acid *tert* butyl ester

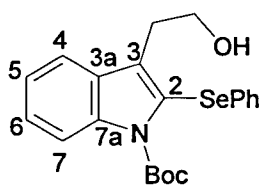


318

3-[2-(*t*-Butyl-dimethylsilanyloxyethyl)-1*H*-indole (1.66 g, 6.05 mmol) was dissolved in dry THF (20 cm³). Triethyl amine (1.66 cm³, 12.1 mmol), DMAP (0.036 g, 0.3 mmol) and di-*t*-butyl dicarbonate (1.44 g, 6.6 mmol) were added and stirred for 12 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The

crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent to yield 3-[2-(*t*-butyldimethylsilyloxy)-ethyl]indole-1-carboxylic acid *t*-butyl ester as a yellow oil (2.0 g, 5.4 mmol, 8 %); (Found: MH^+ , 376.2304. $C_{21}H_{34}NO_3Si$ requires 376.2302.); ν_{max} (thin film)/ cm^{-1} 3050, 2979, 2855, 1718, 1609, 1471, 166, 1369, 1163, 1090, 919, 838, 706 and 665; δ_H 0.01 (6 H, s, $2 \times SiMe$), 0.86 (9 H, s, $SiC-t-Bu$), 1.62 (9 H, s, $OC-t-Bu$), 2.88 (2 H, t, J 6.8, CH_2), 3.86 (2 H, t, J 6.8, OCH_2), 7.19 (1 H, dd, J 7.8, 6.8, 5-H) 7.27 (1 H, dd, J 6.8, 6.0, 6-H), 7.41 (1 H, s, 2-H) 7.49 (1 H, d, J 7.8, 4-H) and 8.12 (1 H, d, J 6.0, 7-H); δ_C -5.29 ($2 \times Me$), 21.06 ($Si-t-BuC$), 26.15 ($3 \times Si-t-Bu$), 27.84 ($3 \times O-t-Bu$), 28.59 (CH_2), 62.89 (OCH_2), 83.21 ($O-t-BuC$), 115.25 (7-C), 117.25 (3-C), 122.35 (5-C), 123.36 (2-C), 124.23 (6-C), 130.88 (4-C), 135.45 (3a-C), 149.80 (7a-C) and 171.08 (CO); m/z (Electrospray) 262 (M^+ , 22%), 218 (64), 216 (20), 144 (26), 130 (30), 75 (28), 73 (32), 57 (100) and 41 (54).

3-(2-Hydroxyethyl)-2-(phenylselanyl)-indole-1-carboxylic acid *tert* butyl ester

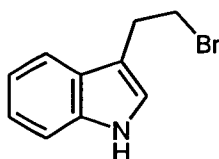


319

n-Butyllithium (0.66 cm^3 , 1.65 mmol) was added to 2,2,6,6-tetramethylpiperidine (0.28 cm^3 , 1.65 mmol) at $-78^\circ C$ and stirred for 30 min in dry THF (20 cm^3). 3-[2-(*t*-Butyldimethylsilyloxy)-ethyl]indole-1-carboxylic acid *tert* butyl ester (0.56 g, 1.5 mmol) was added and stirred for 40 min. Phenylselanyl chloride (0.34 g, 1.8 mmol) was added and stirred for a further 12 at rt. The crude reaction mixture was extracted into EtOAc and washed with H_2O ($3 \times 50\text{ cm}^3$) and brine (50 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was added to a solution of TBAF in (15 cm^3 , 15 mmol) in THF (20 cm^3) and stirred for 24 h. The crude reaction was extracted into EtOAc and washed with H_2O ($3 \times 50\text{ cm}^3$) and brine (50 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent to yield 3-(2-hydroxy-ethyl)-2-phenylselanyl-indole-1-carboxylic acid *t*-butyl ester as yellow crystals (0.14 g, 0.34 mmol, 22%); mp $93-94^\circ C$ (Found: MH^+ , 418.0919. $C_{21}H_{24}NO_3^{80}Se$ requires 418.0916.); ν_{max} (thin film)/ cm^{-1} 3363, 3050, 2987, 1727, 1576, 1476, 1444, 1399, 1354, 1250, 1156, 1101, 1067 and 998; δ_H 2.17 (9 H, s, *t*-Bu), 3.04 (2 H, t, J 6.8,

CH₂), 3.72 (2 H, t, *J* 6.8, OCH₂), 7.16-7.14 (3 H, m, ArH), 7.27-7.24 (3 H, m, ArH), 7.36-7.28 (1 H, m, ArH) 7.59-7.57 (2 H, m, ArH) and 8.14 (1 H, d, *J* 8.0, 1.5, ArH); δ_c 28.00 (3 \times *t*-Bu), 29.85 (CH₂), 62.47 (OCH₂), 84.58 (*t*-BuC), 115.48 (7-C), 119.18 (ArH), 121.55 (3-C), 122.77 (ArH), 126.07 (ArH), 128.74 (2-C), 128.87 (2 \times ArH), 129.16 (ArH), 129.43 (2 \times ArH), 129.47 (ArC), 133.92 (3a-C), 138.09 (7a-C) and 149.88 (CO); *m/z*(Electrospray) 417 (M⁺, 28%), 415 (14), 363 (21), 361 (100), 359 (53) and 358 (21).

3-(2-Bromoethyl)-1*H*-indole¹⁶⁶

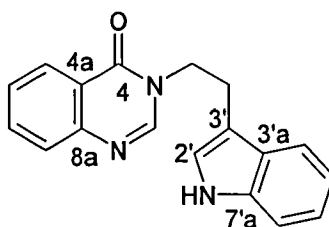


320

Phosphorous tribromide (1.2 cm³, 11.0 mmol) was added slowly at 0 °C to a solution of tryptophol (1.78 g, 11.0 mmol) in dry DCM (10 cm³) and stirred for 2 h. The crude reaction mixture was quenched with H₂O (5 cm³) and extracted into EtOAc and washed with H₂O (3 \times 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (9:1) as eluent to yield 3-(2-bromoethyl)-1*H*-indole as yellow crystals (1.40 g, 6.2 mmol, 56%); mp 96-97 °C (lit.¹⁶⁶ 97-98 °C); ν_{\max} (thin film)/cm⁻¹ 3412, 3053, 2919, 2480, 1620, 1455, 1264, 1008, 744 and 564; δ_H 3.33 (2 H, t, *J* 7.4, CH₂), 3.63 (2 H, t, *J* 7.4, BrCH₂), 7.05 (1 H, s, 2-ArH), 7.13 (1 H, ddd, *J* 7.0, 6.6, 1.3, ArH), 7.20 (1 H, ddd, *J* 7.9, 7.0, 1.5, ArH), 7.35 (1 H, dd, *J* 6.6, 1.5, ArH) and 7.58 (1 H, dd, *J* 7.9, 1.3, ArH); δ_c 29.32 (CH₂), 32.90 (BrCH₂), 111.29 (ArH), 113.47 (ArC), 118.46 (ArH), 119.57 (ArH), 122.21 (ArH), 122.25 (ArH), 126.93 (ArC) and 136.14 (ArC).

The data were consistent to the literature.¹⁶⁶

3-[2-(1*H*-Indol-3-yl)ethyl]-3*H*-quinazolin-4-one

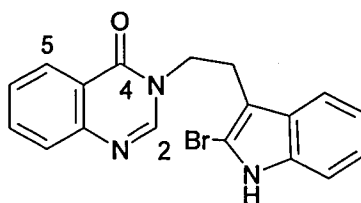


322

Potassium *t*-butoxide (0.14 g, 1.28 mmol) was added to a solution of 3*H*-quinazolin-4-one (2.24 g, 15.4 mmol) in DMF (20 cm³) and stirred for 1 h. 3-(2-Bromoethyl)-1*H*-indole (4.13 g, 18.4 mmol) was added and the reaction stirred for a further 12 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent to yield 3-[2-(1*H*-indol-3-yl)ethyl]-3*H*-quinazolin-4-one as colourless crystals (1.72 g, 5.9 mmol, 39%); (Found: MH⁺, 290.1291. C₁₈H₁₆N₃O requires 290.1288.); mp 170-171 °C (lit.¹⁰² 173-174 °C); ν_{\max} (thin film)/cm⁻¹ 3441, 2099, 1650, 1643, 1530, 1474, 1376, 1021, 996, 642 and 631; δ_{H} 3.28 (2 H, t, *J* 7.0, CH₂), 4.31 (2 H, t, *J* 7.0, NCH₂), 6.86 (1 H, d, *J* 2.0, 2'-H), 7.14 (1 H, ddd, *J* 8.0, 6.8, 0.8, ArH), 7.21 (1 H, ddd, *J* 8.0, 6.8, 0.8, ArH), 7.37-7.35 (1 H, m, ArH), 7.54-7.50 (2 H, m, ArH), 7.67-7.63 (2 H, m, ArH), 7.76-7.772 (1 H, m, ArH) and 8.38-8.35 (1 H, m, ArH); δ_{C} 24.96 (CH₂), 47.55 (NCH₂), 111.37 (4a-ArC), 111.52 (ArH), 118.42 (ArH), 119.81 (ArH), 122.14 (3'-ArC), 122.44 (ArH), 122.77 (2'a-ArH), 126.67 (ArH), 126.83 (3'a-ArC), 127.14 (ArH), 127.41 (ArH), 134.16 (ArH), 136.47 (7'a-ArC), 146.74 (ArH), 148.19 (8a-ArC) and 161.14 (4-ArC); *m/z*(Electrospray) 143 (M⁺, 100%), 129 (58), 115 (13), 102 (14) and 77 (27).

The data were consistent to the literature.¹⁰²

3-[2-(2-Bromoindol-3-yl)ethyl]-3*H*-quinazolin-4-one

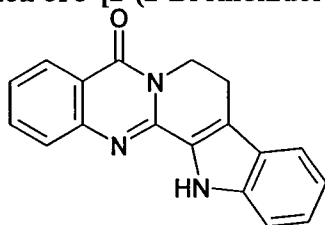


321

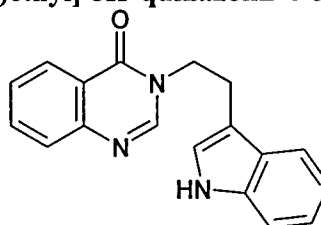
N-Bromosuccinimide (0.12 g, 0.65 mmol) was added to a solution of 3-[2-(1*H*-indol-3-yl)ethyl]-3*H*-quinazolin-4-one (0.19 g, 0.65 mmol) at 0°C in DCM and stirred for 30 min. The crude reaction mixture was extracted into EtOAc and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent to yield 3-[2-(2-bromoindol-3-yl)ethyl]-3*H*-quinazolin-4-one as yellow crystals (0.09 g, 0.24 mmol, 38%); mp 198-200 °C; (Found: MH⁺, 368.0395. C₁₈H₁₅⁷⁹BrN₃O requires 368.0393.); ν_{\max} (thin film)/cm⁻¹ 3407, 2358, 1651, 1611, 1471, 1446, 1376, 1157 and 742; δ_{H} 3.23 (2 H, t, *J* 6.4, CH₂), 4.27 (2 H, t, *J* 6.4, NCH₂), 7.06 (1 H, ddd, *J* 8.0, 6.8, 0.8, ArH), 7.15-7.10 (1 H, m, ArH), 7.19 (1 H, d, *J* 8.8, ArH), 7.39 (1 H, s, 2-H), 7.53-7.51 (2 H, m, ArH), 7.64 (1 H, dd, *J* 9.2, 0.8, ArH), 7.73 (1 H, ddd, *J* 8.4, 6.8, 1.2, ArH), 8.37 (1 H, dd, *J* 8.0, 1.6, 5-H) and 8.98 (1 H, brs, NH); δ_{C} 24.13 (CH₂), 46.82 (NCH₂), 109.69 (ArC), 110.83 (ArC), 110.85 (ArH), 117.58 (ArH), 120.43 (ArH), 122.10 (ArC), 122.69 (ArH), 126.65 (ArH), 127.14 (ArC), 127.18 (ArH), 127.24 (ArH), 134.19 (ArH), 136.21 (ArC), 146.56 (ArH), 147.95 (ArC) and 161.36 (4-ArC); *m/z*(Electrospray) 369 (M⁺, 5%), 367 (5), 288 (21), 221 (100), 208 (36), 147 (22), 129 (74), 115 (28), 102 (54), 90 (20) and 77 (61).

The data were consistent to the literature.¹⁰²

Radical cyclisation of 3-[2-(2-Bromoindol-3-yl)ethyl]-3*H*-quinazolin-4-one



145



322

Method A - Bu₃SnH (slow) and Et₃B

3-[2-(2-Bromoindol-3-yl)ethyl]-3*H*-quinazolin-4-one (0.094 g, 0.26 mmol) was added to toluene (20 cm³) which had been degassed with nitrogen for 30 min. Triethylborane (3 cm³,

3.0 mmol) was added and Bu_3SnH (0.18 g, 0.64 cm^3) in toluene (10 cm^3) was added over 12 h. At 3 h intervals the solution was purged with nitrogen for 30 min and triethylborane (3 cm^3 , 3.0 mmol) was added. The reaction mixture was washed through a sinter containing silica absorbent with light petroleum (100 cm^3). The sinter was flushed with EtOAc (200 cm^3). The filtrate was dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified initially by a column chromatography using silica absorbent with light petroleum/EtOAc (4:1) as eluent yielding:

145 Rutaecarpine as colourless crystals (11 mg, 0.038 mmol, 15%); (Found: MH^+ , 288.1131. $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}$ requires 288.1132.); ν_{max} (thin film)/ cm^{-1} 3338, 2923, 2359, 1851, 1753, 1659, 1592, 1468, 1326, 1228, 1140, 796, 726 and 667; δ_{H} 3.24 (2 H, t, J 8.0, CH_2), 4.59 (2 H, t, J 8.0, NCH_2), 7.19 (1 H, d, J 8.0, ArH), 7.35 (1 H, d, J 8.0, ArH), 7.47-7.41 (2 H, m, 2-H and ArH), 7.67-7.63 (2 H, m, 4-H and ArH), 7.73 (1 H, t, J 8.0, 3-H), 8.38 (1 H, d, J 8.0, 1-H) and 9.10 (1 H, brs, NH); δ_{C} 20.72 (CH_2), 39.22 (NCH_2), 112.05 (2-C), 118.29 (ArC), 120.12 (ArH), 120.66 (ArH), 125.61 (ArH), 126.20 (ArH), 126.69 (4-C), 127.23 (7-C), 128.22 (ArC), 129.04 (ArC), 134.32 (3-C), 138.22 (ArC), 144.82 (ArC), 147.53 (ArC), 159.72 (ArC) and 169.26 (ArC); m/z (Electrospray) 286 (M^+ , 100%), 155 (27), 140 (24), 128 (38), 115 (25), 102 (37), 91 (28), 77 (54), 63 (37) and 51 (34).

The data were consistent to the literature.¹⁰²

322 3-[2-(1*H*-Indol-3-yl)ethyl]-3*H*-quinazolin-4-one as colourless crystals (0.42 g, 0.15 mmol, 57%).

The data were consistent to the previous synthesis and literature.¹⁰²

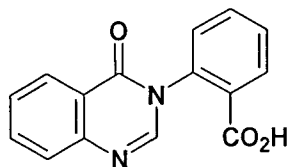
Method B – Photolysis with hexamethylditin

The reaction between 3-[2-(2-bromoindol-3-yl)ethyl]-3*H*-quinazolin-4-one (0.52 g, 1.41 mmol) and $(\text{Me}_3\text{Sn})_2$ (1.39 g, 4.25 mmol) in *t*-butylbenzene (20 cm^3) was purged for 30 min with nitrogen, refluxed and irradiated with a 300 W sunlamp for 6 h. The reaction mixture was washed through a sinter containing silica absorbent with petrol (100 cm^3). The sinter was flushed with EtOAc (200 cm^3). The filtrate was dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica absorbent with light petroleum/EtOAc (4:1) yielding the sole product rutaecarpine **145** (0.22 g, 0.77 mmol, 55%).

The data were consistent with the previous synthesis and literature.¹⁰²

6.4 Experimental for Chapter 4

2-(4-Oxo-4*H*-quinazolin-3-yl)benzoic acid methyl ester¹¹⁰

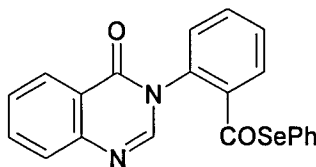


330

Isatoic anhydride (7.5 g, 45.9 mmol) and anthranilic acid (6.9 g, 50.4 mmol) were heated under reflux in water for 12 h. The reaction mixture was cooled over ice water. The precipitate was collected by filtration, washed with EtOAc and dried. The yellow precipitate was refluxed with triethyl orthoformate (17 cm³, 108 mmol) in MeOH (50 cm³) for 4 h. The reaction mixture was cooled and the precipitate collected by filtration and dried yielding 2-(4-oxo-4*H*-quinazolin-3-yl)benzoic acid methyl ester as colourless crystals (4.85 g, 18.2 mmol, 40%); mp 281-283 (lit.¹¹⁰ 282-284 °C); (Found: MH⁺, 267.0764. C₁₅H₁₁N₂O₃ requires 267.0764.); ν_{\max} (thin film)/cm⁻¹ 3405, 1873, 1785, 1762, 1690, 1657, 1639, 1629, 789 and 669; δ_{H} (CD₃)₂SO 7.62-7.57 (2 H, m, ArH), 7.69-7.66 (1 H, m, ArH), 7.83-7.74 (2 H, m, ArH), 7.91-7.87 (1 H, m, ArH), 8.09 (1 H, d, *J* 9.2, ArH), 8.17 (1 H, d, *J* 9.2, ArH) and 8.33 (1 H, s, 2-H); δ_{C} (CD₃)₂SO 121.85 (4a-C), 126.33 (ArH), 127.25 (ArH), 127.28 (ArH), 129.13 (ArC), 129.56 (ArH), 129.76 (ArH), 131.08 (ArH), 133.41 (ArH), 134.64 (ArH), 137.12 (ArC), 147.14 (2-C), 147.93 (8a-C), 160.29 (4-C) and 165.86 (CO₂H); *m/z*(Electrospray) 266 (M⁺, 30%), 221 (100), 145 (22), 119 (24), 102 (29), 90 (37), 76 (35) and 65 (30).

The data were consistent to the literature.¹¹⁰

2-(4-Oxo-4*H*-quinazolin-3-yl)selenobenzoic acid *Se*-methyl ester

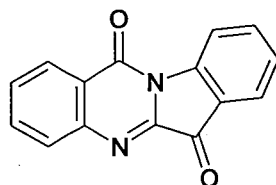


329

Tributyl phosphine (2.5 cm³, 10.4 mmol) was slowly added to diphenyl diselanide (2.47 g, 7.9 mmol) in dry DCM and left to stir for 15 min. 2-(4-Oxo-4*H*-quinazolin-3-yl)benzoic acid methyl ester (1.40 g, 5.2 mmol) was added and stirred for 12 h until no solid was visible. The crude reaction mixture was extracted into DCM and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced

pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) the yellow solid was recrystallised from hot EtOH yielding 2-(4-oxo-4*H*-quinazolin-3-yl)selenobenzoic acid *Se*-methyl ester as yellow crystals (1.55 g, 3.8 mmol, 73%); mp 234-236 °C; (Found: MH^+ , 407.0289. $C_{21}H_{15}N_2O_2^{80}Se$ requires 407.0293.); ν_{max} (thin film)/ cm^{-1} 3165, 2831, 2063, 1798, 1519, 1367, 1118, 960 and 915; δ_H 7.36-7.30 (3 H, m, ArH), 7.42 (1 H, dd, J 9.2, 1.6, ArH), 7.55-7.45 (3 H, m, ArH), 7.70-7.66 (1 H, m, ArH), 7.81-7.72 (3 H, m, ArH), 8.02 (1 H, s, 2-H), 8.14 (1 H, dd, J 9.2, 1.6, ArH) and 8.34-8.32 (1 H, m, ArH); δ_C 122.34 (ArC), 125.91 (ArC), 127.14 (5-C), 127.58 (6-C), 127.71 (ArH), 129.25 (ArH), 129.44 (2 \times ArH), 129.74 (ArH), 129.85 (ArH), 130.11 (ArH), 133.64 (ArC), 133.72 (ArH), 134.65 (ArH), 136.02 (2 \times ArH), 136.91 (ArC), 145.62 (2-C), 147.99 (ArC), 160.71 (4-C) and 192.72 (CO); m/z (Electrospray) 407 (M^+ , 100%), 251 (39), 235 (55) and 223 (46).

Radical cyclisation of 2-(4-oxo-4*H*-quinazolin-3-yl)selenobenzoic acid *Se*-methyl ester



146

Method A - Photolysis with reflux (benzene)

2-(4-Oxo-4*H*-quinazolin-3-yl)selenobenzoic acid *Se*-methyl ester (240 mg, 0.59 mmol) was refluxed in benzene (20 cm^3) for 10 h and irradiated with a 300 W sunlamp. The solvent was removed under vacuum and the crude reaction product was purified by column chromatography using silica gel as absorbent and light petroleum/EtOAc (2:1) as eluent yielding tryptanthrin 146 as yellow crystals (20 mg, 0.07 mmol, 13%); mp 213-214 °C (lit.¹⁰⁷ 215-217 °C); (Found: MH^+ , 249.0659. $C_{15}H_9N_2O_2$ requires 249.0660.); δ_H 7.43 (1 H, t, J 8.0, ArH), 7.68 (1 H, t, J 8.0, ArH), 7.79 (1 H, t, J 8.0, ArH), 7.86 (1 H, t, J 8.0, ArH), 7.92 (1 H, d, J 8.0, ArH), 8.04 (1 H, d, J 8.0, ArH), 8.44 (1 H, d, J 8.0, ArH) and 8.64 (1 H, d, J 8.0, ArH); δ_C 117.98 (ArH), 121.96 (ArC), 123.76 (ArC), 125.40 (ArH), 127.20 (ArH), 127.56 (ArH), 130.24 (ArH), 130.74 (ArH), 135.13 (ArH), 138.27 (ArH), 146.36 (ArC), 146.66 (ArC), 158.11 (ArC) and 171.13 (2 \times ArH); m/z (Electrospray) 248 (M^+ , 51%), 220 (22), 130 (28), 102 (54), 90 (100), 76 (81), 63 (55) and 50 (74).

The data were consistent to the literature.¹⁰⁷

Method B – Photolysis only

2-(4-Oxo-4*H*-quinazolin-3-yl)selenobenzoic acid *Se*-methyl ester (240 mg, 0.59 mmol) in benzene (20 cm³) was irradiated with a 300 W sunlamp for 30 min. The solvent was removed under reduced pressure and the crude reaction product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding tryptanthrin **146** (23 mg, 0.081 mmol, 15%).

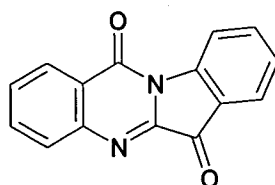
The data were consistent with the previous synthesis and literature.¹⁰⁷

Method C- Photolysis with hexamethylditin

The reaction mixture of 2-(4-oxo-4*H*-quinazolin-3-yl)selenobenzoic acid *Se*-methyl ester (290 mg, 0.72 mmol) and (Me₃Sn)₂ (700 mg, 2.15 mmol) in *tert*-butylbenzene (20 cm³) was refluxed and irradiated with a 300 W sunlamp for 4 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolone products into the aqueous layer. The aqueous layer was washed with light petroleum (3 × 50 cm³) to remove tin residues. The aqueous layer was basified with a solution of sodium hydroxide to pH 14. The basic solution was extracted with DCM (3 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure and purified by column chromatography using silica gel as absorbent and light petroleum/EtOAc (2:1) yielding tryptanthrin **146** (5 mg, 0.02 mmol, 3%).

The data were consistent with the previous synthesis and literature.¹⁰⁷

Tryptanthrin¹⁰⁷



146

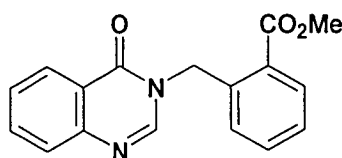
Non-radical synthesis

Isatin (0.88 g, 6.0 mmol), isatoic anhydride (0.97 g, 6.0 mmol) and triethyl amine (0.97 cm³, 7.0 mmol) were refluxed in toluene for 12 h under Dean Stark conditions. The crude reaction mixture was extracted into DCM and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding tryptanthrin as yellow crystals (1.32 g, 5.3 mmol,

88%); mp 213-214 °C (lit.⁹⁷ 215-217 °C); (Found: MH^+ , 249.0659. $C_{15}H_9N_2O_2$ requires 249.0660.); δ_H 7.43 (1 H, t, J 8.0, ArH), 7.68 (1 H, t, J 8.0, ArH), 7.79 (1 H, t, J 8.0, ArH), 7.86 (1 H, t, J 8.0, ArH), 7.92 (1 H, d, J 8.0, ArH), 8.04 (1 H, d, J 8.0, ArH), 8.44 (1 H, d, J 8.0, ArH) and 8.64 (1 H, d, J 8.0, ArH); δ_C 117.98 (ArH), 121.96 (ArC), 123.76 (ArC), 125.40 (ArH), 127.20 (ArH), 127.56 (ArH), 130.24 (ArH), 130.74 (ArH), 135.13 (ArH), 138.27 (ArH), 146.36 (ArC), 146.66 (ArC), 158.11 (ArC) and 171.13 ($2 \times$ ArC); m/z (EI) 248 (M^+ , 51%), 220 (22), 130 (28), 102 (54), 90 (100), 76 (81), 63 (55) and 50 (74).

Data were consistent with the previous synthesis and literature.¹⁰⁷

2-[(4-Oxo-4H-quinazolin-3-yl)methyl]benzoic methyl ester

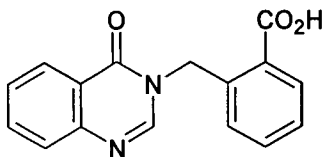


344

N-Bromosuccinimide (19.0 g, 107.1 mmol), methyl *o*-toluate (7.5 g, 50 mmol) and AIBN (1.16 g, 7.1 mmol) were heated under reflux in cyclohexane in the dark for 5 h. The reaction mixture was cooled to 0 °C and filtered. The filtrate was extracted into DCM, washed with H_2O ($3 \times 50\text{ cm}^3$) and brine (50 cm^3). The organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The crude residue was added to a solution of 3*H*-quinazolin-4-one (7.3 g, 50 mmol) and potassium *t*-butoxide (7.3 g, 65 mmol) in DMF (50 cm^3) for 40 min. The reaction mixture was stirred for 12 h, extracted into DCM, washed with H_2O ($5 \times 50\text{ cm}^3$) and brine (50 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent yielding 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl ester as a colourless oil (4.98 g, 16.6 mmol, 34%); (Found: MH^+ , 295.1077. $C_{17}H_{15}N_2O_3$ requires 295.1077.); ν_{max} (thin film)/ cm^{-1} 3541, 3417, 1715, 1681, 1563, 1367, 1322, 1079, 968 and 774; δ_H 3.88 (3 H, s, OMe), 5.62 (2 H, s, CH_2), 7.31-7.22 (2 H, m, ArH), 7.44-7.41 (2 H, m, ArH) 7.70-7.69 (2 H, m, ArH), 7.97 (1 H, dd, J 7.8, 1.4, ArH) and 8.28-8.23 (2 H, m, ArH); δ_C 47.86 (CH_2), 52.41 (Me), 122.20 (4a-C), 126.91 (ArH), 127.33 (ArH), 127.54 (ArH), 128.03 (ArH), 128.59 (ArC), 129.06 (ArH), 131.31 (ArH), 132.96 (ArH), 134.36 (ArH), 137.36 (ArC), 147.14 (ArH), 148.12 (8a-C),

161.36 (4-C) and 167.37 (CO₂Me); *m/z*(Electrospray) 421 (M⁺, 4%), 262 (53), 132 (80), 118 (30), 102 (60), 91 (100), 77 (58), 63 (33) and 50 (23).

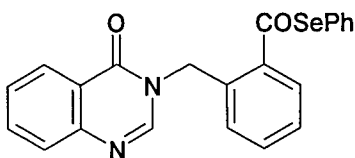
2-[(4-Oxo-4*H*-quinazolin-3-yl)methyl]-benzoic acid



2-[(4-Oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl ester (1.93 g, 6.14 mmol) and LiOH (1 M, 200 cm³) were stirred in EtOH/H₂O (100 cm³, 10:1) for 18 h. The reaction mixture was acidified with HCl and extracted with EtOAc (3 × 50 cm³). The organic layers were combined and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl acid as a colourless oil (1.26 g, 4.16 mmol, 68%); (Found: MH⁺, 281.0918. C₁₆H₁₃N₂O₃ requires 281.0921.); *v*_{max}(thin film)/cm⁻¹ 3160, 2825, 2059, 1801, 1511, 1380, 1111, 930 and 904; *δ*_H 5.58 (2 H, s, CH₂), 6.96 (1 H, d, *J* 8.0, ArH), 7.41-7.39 (1 H, m, ArH), 7.50-7.49 (1 H, m, ArH), 7.58 (1 H, ddd, *J* 8.0, 6.8, 1.0, ArH), 7.74 (1 H, dd, *J* 8.2, 1.0, ArH), 7.88 (1 H, ddd, *J* 8.2, 6.8, 1.2, ArH), 7.97 (1 H, dd, *J* 8.0, 1.2, ArH), 8.16 (1 H, d, *J* 8.0 ArH) and 8.51 (1 H, s, ArH); *m/z*(Electrospray) 262 (M⁺, 31%), 146 (35), 132 (86), 118 (38), 104 (47), 90 (58), 77 (100), 63 (28), 51 (32) and 43 (53).

The acid was converted to the acyl selenide without further characterisation

2-[(4-Oxo-4*H*-quinazolin-3-yl)methyl]seleno benzoic acid *Se*-methyl ester

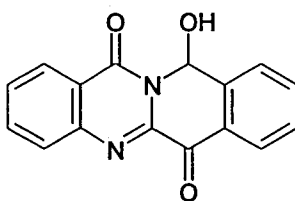


341

Tributyl phosphine (0.51 cm³, 1.3 mmol) was slowly added to diphenyl diselanide (480 mg, 1.5 mmol) in dry DCM and left to stir for 15 min. 2-[(4-Oxo-4*H*-quinazolin-3-yl)methyl]benzoic acid (310 mg, 1.0 mmol) was added and stirred for 12 h until no precipitate was visible. The crude reaction mixture was extracted into DCM and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using

silica gel as absorbent with light petroleum/EtOAc (2:1) yielding 2-(4-oxo-4*H*-quinazolin-3-ylmethyl)-seleno benzoic acid *Se*-methyl ester as colourless crystals (310 mg, 0.71 mmol, 68%); mp 314-316 °C; (Found: MH^+ , 421.0450. $C_{22}H_{17}N_2O_2^{80}Se$ requires 421.0451.); ν_{max} (thin film)/ cm^{-1} 3361, 1911, 1659, 1589, 1542, 1392, 1336, 1188, 801, 760 and 722; δ_H 5.43 (2 H, s, CH_2), 7.37-7.35 (1 H, m, ArH), 7.53-7.45 (6 H, m, ArH), 7.61-7.59 (2 H, m, ArH), 7.79-7.73 (2 H, m, ArH), 8.04 (1 H, dd, J 7.6, 1.3, ArH), 8.13 (1 H, s, 2-H) and 8.33-8.30 (1 H, m, ArH); δ_C 47.24 (CH_2), 122.14 (4a-C), 126.29 (ArC), 126.91 (ArH), 127.41 (ArH), 127.52 (ArH), 128.53 (ArH), 129.43 (ArH), 129.59 (2 \times ArH), 129.62 (ArH), 129.74 (ArH), 133.21 (ArH), 133.60 (ArC), 134.45 (ArH), 136.23 (2 \times ArH), 137.65 (ArC), 147.03 (ArH), 147.99 (8a-C), 161.29 (4-C) and 196.73 (CO); m/z (Electrospray) 263 (M^+ , 60%), 156 (45), 129 (100), 102 (43), 89 (46), 77 (60), 63 (23) and 51 (33).

Radical cyclisation of 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]seleno benzoic acid *Se*-methyl ester



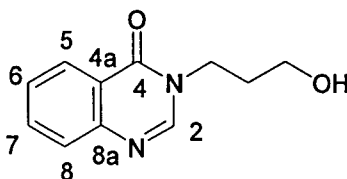
345

The reaction mixture between 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]seleno benzoic acid *Se*-methyl ester (0.044 g, 0.1 mmol) and $(Me_3Sn)_2$ (0.099 g, 0.3 mmol) in benzene (20 cm^3) were heated under reflux and irradiated with a sunlamp lamp for 3 h. The benzene was removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent and recrystallised from $CDCl_3$ yielding 11-hydroxy-11*H*-isoquinolino[3,2-*b*]quinazolin-6,13-dione **345** as colourless crystals (11 mg, 0.04 mmol, 39%); mp 164-165 °C; (Found: MH^+ , 279.0768. $C_{16}H_{11}N_2O_3$ requires 279.0764.); ν_{max} (thin film)/ cm^{-1} 3421, 2919, 2360, 1699, 1683, 1653, 1559, 1461, 1260, 1100, 936, 910, 728 and 667; δ_H 5.29 (1 H, d, J 4.6, OH), 7.21 (1 H, d, J 4.6, CH), 7.69-7.65 (2 H, m, ArH), 7.80 (1 H, d, J 8.0, ArH), 7.93-7.84 (2 H, m, ArH), 8.10 (1 H, d, J 8.0, ArH), 8.32 (1 H, dd, J 7.6, 1.2, ArH) and 8.39 (1 H, dd, J 8.0, 1.2, ArH); δ_C 75.48 (CH), 121.89 (ArC), 126.70 (ArH), 128.03 (ArH), 128.71 (ArH), 129.20 (ArC), 129.57 (ArH), 130.01 (ArH), 130.35 (ArH), 135.58 (ArH), 135.68 (ArH), 137.01 (ArC), 142.61 (ArC),

146.74 (ArC), 162.74 (ArC) and 176.58 (ArC); m/z (Electrospray) 278 (M^+ , 50%), 262 (43), 249 (40), 221 (26), 135 (38), 119 (36), 105 (100), 91 (45), 84 (60), 77 (68) and 51 (69).

The structure was confirmed by X-ray crystallography (see appendix).

3-(2-Hydroxypropyl)-3*H*-quinazolin-4-one¹⁶⁷

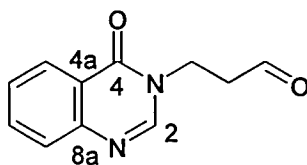


368

Anthranilic acid (11.3 g, 82.0 mmol) and triethyl orthoformate (273 cm³, 1650 mmol) were refluxed for 24 h. The excess triethyl orthoformate was removed under vacuum. 3-Aminopropan-1-ol (50 cm³) was added to the slurry and the reaction mixture stirred for 48 h. The excess 3-aminopropan-1-ol was removed under vacuum yielding 3-(2-hydroxypropyl)-3*H*-quinazolin-4-one as brown crystals (6.53 g, 32.0 mmol, 40%); mp 148-49 °C (lit.¹⁶⁷ 150-152 °C); ν_{\max} (thin film)/cm⁻¹ 3400, 1652, 1475, 1379, 1325, 1160, 1060 and 775; δ_H 2.76-2.00 (2 H, m, CH₂), 3.65 (2 H, t, J 6.2, NCH₂), 4.21 (2 H, t, J 6.2, OCH₂), 7.52 (1 H, ddd, J 8.0, 6.8, 1.2, 6-H), 7.72 (1 H, dd, J 8.2, 1.2, 8-H), 7.77 (1 H, ddd, J 8.2, 6.8, 1.4, 7-H), 8.14 (1 H, s, 2-H) and 8.30 (1 H, dd, J 8.0, 1.4, 5-H); δ_C 31.85 (CH₂), 43.51 (CH₂), 58.06 (NCH₂), 121.78 (4a-C), 126.67 (5-C), 127.35 (8-C), 127.46 (6-C), 134.44 (7-C), 146.83 (2-C), 148.05 (8a-C) and 161.81 (4-C).

The data were consistent to the literature.¹⁶⁷

3-(4-Oxo-4*H*-quinazolin-3-yl)propionaldehyde

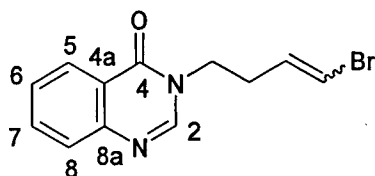


367

3-(2-Hydroxypropyl)-3*H*-quinazolin-4-one (0.40 g, 2.0 mmol) and 2-iodoxy benzoic acid (1.68 g, 6.0 mmol) were refluxed in EtOAc (50 cm³) for 4 h. The reaction mixture was filtered and the filtrate was washed with brine (20 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 3-(4-oxo-4*H*-quinazolin-3-

yl)propionaldehyde as a yellow oil (370 mg, 1.86 mmol, 93%); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$ 3341, 2837, 2248, 1668, 1564, 1472, 1384, 1263, 1066, 962 and 880; δ_{H} 3.11 (2 H, m, CH_2), 4.26 (2 H, t, J 6.0 NCH₂), 7.48-7.46 (1 H, m, ArH), 7.72-7.69 (2 H, m, ArH), 8.23-8.22 (1 H, m, 5-H), 8.29 (1 H, s, 2-H) and 9.78 (1 H, s, OCH); δ_{C} 42.15 (CH_2), 43.44 (NCH₂), 122.59 (4a-C), 12.38 (ArH), 127.27 (ArH), 127.32 (ArH), 134.35 (ArH), 147.38 (ArH), 147.79 (8a-C), 161.22 (4-C) and 199.20 (CO). Compound was unstable in air and no further characterisation could be carried out.

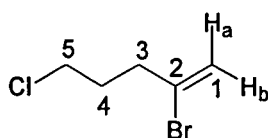
3-(4-Bromobut-3-enyl)-3H-quinazolin-4-one



366

Bromomethylenetriphenylphosphorane (1.97 g, 4.5 mmol) was stirred with potassium *t*-butoxide (500 mg, 4.5 mmol) at $-78\text{ }^{\circ}\text{C}$ in THF for 15 min. 3-(4-Oxo-4H-quinazolin-3-yl)propionaldehyde (0.83 g, 4.10 mmol) was added and stirred for 12 h at rt. The crude reaction mixture was extracted into DCM and washed with H_2O ($3 \times 50\text{ cm}^3$) and brine (50 cm^3). The organic layer was dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) yielding 3-(4-bromobut-3-enyl)-3H-quinazolin-4-one as a yellow oil (170 mg, 0.61 mmol, 15%); (Found: MH^+ , 279.0130. $\text{C}_{12}\text{H}_{12}^{79}\text{BrN}_2\text{O}$ requires 279.0128.); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$ 3508, 3076, 1668, 1608, 1472, 1373, 1261, 1152, 1048, 878, 775 and 700; δ_{H} 2.76-2.56 (2 H, m, CH_2), 4.12 (2 H, t, J 8.0, NCH₂), 6.22-6.13 (1 H, m, CH), 6.33 (1 H, d, J 9.2, BrCH), 7.53-7.48 (1 H, m, 6-H), 7.78-7.70 (2 H, m, 7,8-H), 8.08 (1 H, s, 2-H) and 8.29-8.20 (1 H, m, 5-H); δ_{C} 29.41 (CH_2), 45.01 (NCH₂), 111.97 (BrCH), 121.94 (4a-C), 126.61 (5-C), 127.35 (ArH), 127.38 (6-H), 129.65 (CH), 134.36 (ArH), 146.49 (2-C), 147.81 (8a-C) and 160.95 (4-C); $m/z(\text{Electrospray})$ 279 (M^+ , 13%), 277 (13), 199 (62), 159 (28), 145 (75), 129 (60), 102 (47), 76 (48), 50 (50) and 40 (100).

2-Bromo-5-chloropent-1-ene¹¹⁶

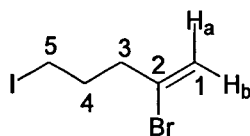


370

HBr (33% in AcOH) (30.0 cm³, 160 mmol) was added dropwise using a syringe pump, over 1 h at 0 °C to a neat solution of 5-chloro-1-pentyne (14.0 cm³, 133 mmol). The reaction mixture was stirred at rt for 24 h. DCM (100 cm³) and water (100 cm³) were added and the reaction mixture basified with sodium bicarbonate (Na₂CO₃) to pH 8. The organic phase was washed with dilute Na₂CO₃ solution (50 cm³) and water (3 × 50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was distilled under reduced pressure and temperature yielding 2-bromo-5-chloropent-1-ene as a yellow oil (16.0 g, 87.3 mmol, 66%); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$ 3416, 2925, 1436, 1179, 1121, 896, 749 and 694; δ_{H} 2.07-2.00 (2 H, m, 4-H), 2.61 (2 H, t, *J* 7.8, 3-H), 3.57 (2 H, t, *J* 6.3, 5-H), 5.31 (1 H, d, *J* 1.7, H_a) and 5.66 (1 H, dt, *J* 1.7, 1.1, H_b); δ_{C} 30.35 (4-C), 38.31 (3-C), 43.34 (5-C), 118.08 (1-C) and 132.46 (2-C).

The data were consistent to the literature.¹¹⁶

2-Bromo-5-iodopent-1-ene¹⁶⁸

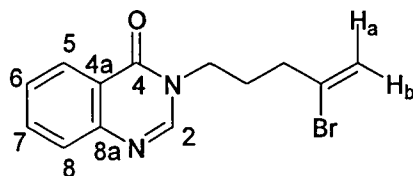


371

Sodium iodide (107.0 g, 714 mmol) and 2-bromo-5-chloropent-1-ene (16.0 g, 87 mmol) were refluxed in dry acetone (300 cm³) for 20 h. The reaction mixture was extracted into DCM (100 cm³) and washed with water (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 2-bromo-5-iodopent-1-ene as a yellow oil (17.3 g, 62.8 mmol, 72%); (Found: *M*⁺, 273.8849. C₅H₈⁷⁹BrI requires 273.8848.); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$ 3413, 2920, 1456, 1230, 1125, 896, 888, 845, 749 and 684; δ_{H} 2.09-2.05 (2 H, m, 4-H), 2.58-2.54 (2 H, m, 3-H), 3.22-3.18 (2 H, m, 5-H), 5.47 (1 H, d, *J* 1.7, H_a) and 5.68 (1 H, dt, *J* 1.7, 1.1, H_b); δ_{C} 5.37 (5-C), 31.06 (4-C), 41.06 (3-C), 118.34 (1-C) and 135.76 (2-C); *m/z*(EI) 276 (*M*⁺, 20%), 374 (21), 148 (43), 126 (20), 67 (100), 64 (21) and 41 (65).

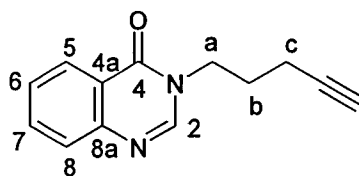
The data were consistent to the literature.¹⁶⁸

3-(4-Bromopent-4-enyl)-3*H*-quinazolin-4-one



Potassium *t*-butoxide (5.40 g, 48.30 mmol) was added to a solution of 3*H*-quinazolin-4-one (48.3 g, 7.05 mmol) in DMF (100 cm³) and stirred for 1 h. 2-Bromo-5-iodopent-1-ene (17.26 g, 62.80 mmol) was added and stirred for a further 12 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (3:1) as eluent to yield 3-(4-bromopent-4-enyl)-3*H*-quinazoline-4-one as colourless crystals (6.65 g, 22.7 mmol, 47%); mp 157-158 °C; (Found: MH⁺, 293.0285. C₁₃H₁₄⁷⁹BrN₂O requires 293.0284.); ν_{\max} (thin film)/cm⁻¹ 3498, 2945, 1673, 1608, 1562, 1471, 1372, 1321, 1291, 1180, 1118 and 883; δ_{H} 2.19-2.12 (2 H, m, CH₂), 2.56-2.48 (2 H, m, BrCCH₂), 4.09-4.00 (2 H, m, NCH₂), 5.49 (1 H, d, *J* 1.7, H_a), 5.69-5.68 (1 H, dt, *J* 1.7, 1.1, H_b), 7.54-7.49 (1 H, m, 6-H), 7.79-7.70 (2 H, m, 7 and 8-H), 8.04 (1-H, s, 2-H) and 8.32-8.30 (1 H, m, 5-H); δ_{C} 27.65 (CH₂), 38.21 (BrCCH₂), 46.24 (NCH₂), 118.09 (CH_aH_b), 122.07 (4a-C), 126.67 (5-C), 127.38 (6-C), 127.47 (ArH), 132.52 (8a-C), 134.29 (ArH), 146.43 (2-C), 148.06 (BrC) and 161.10 (4-C); *m/z*(Electrospray) 295 (M⁺, 11%), 293 (10), 213 (100), 147 (32), 129 (40), 102 (33), 77 (36), 67 (72) and 53 (35).

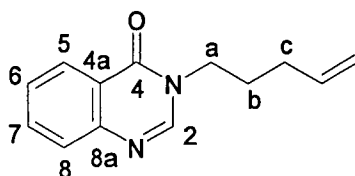
3-(Pent-4-ynyl)-3*H*-quinazolin-4-one



Potassium *t*-butoxide (3.17 g, 33.3 mmol) was added to a solution of 3*H*-quinazolin-4-one (4.50 g, 31.0 mmol) in DMF (100 cm³) and the reaction mixture stirred for 1 h at 60 °C. 5-Chloropent-1-yne (3.40 cm³, 32.25 mmol) and sodium iodide (4.7 g, 30.60 mmol) were added and stirred for 20 h at rt. The crude reaction mixture was extracted into EtOAc and washed with H₂O (5 × 100 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column

chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent to yield 3-(pent-4-ynyl)-3*H*-quinazolin-4-one as colourless crystals (0.64 g, 3.00 mmol, 10%); mp 127-128 °C; (Found: MH^+ , 213.1023. $C_{13}H_{13}N_2O$ requires 213.1022.); ν_{max} (thin film)/ cm^{-1} 2963, 2923, 1617, 1614, 1472, 1367, 1324, 1156, 775 and 634; δ_H 2.08-2.01 (2 H, m, *b*-CH₂), 2.16 (1 H, s, CH), 2.32-2.27 (2-H, m, *c*-CH₂), 4.14 (2 H, t, *J* 6.8, NCH₂), 7.45 (1 H, ddd, *J* 8.0, 7.0, 1.2, 6-H), 7.64 (1 H, dd, *J* 8.0, 1.2, 8-H), 7.70 (1 H, ddd, *J* 8.0, 7.0, 1.4, 7-H), 8.04 (1 H, s, 2-C) and 8.24 (1 H, dd, *J* 8.0, 1.4, 5-H); δ_C 15.60 (*b*-CH₂), 27.19 (*a*-CH₂), 45.87 (NCH₂), 70.19 (CH), 82.32 (C), 122.14 (4a-C), 126.65 (5-C), 127.34 (6-C), 127.50 (8-C), 134.28 (7-C), 146.70 (2-C), 148.15 (8a-C) and 161.18 (4-C); *m/z*(Electrospray) 169 (M^+ , 36%), 159 (100), 146 (35), 129 (28) and 50 (35); Anal. Calcd for $C_{13}H_{12}N_2O$. C, 73.56; H, 5.70; N, 13.20. Found: C, 73.33; H, 5.68; N, 13.12.

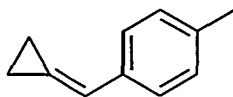
3-(Pent-4-enyl)-3*H*-quinazolin-4-one



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Potassium *t*-butoxide (0.82 g, 7.4 mmol) was added to a solution of 3*H*-quinazolin-4-one (0.98 g, 6.7 mmol) in DMF (100 cm³) and stirred for 1 h. 5-Bromopent-1-ene (1.20 cm³, 8.05 mmol) was added and stirred for 20 h. The crude reaction was extracted into EtOAc and washed with H₂O (5 × 100 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (4:1) as eluent to yield 3-(pent-4-enyl)-3*H*-quinazolin-4-one as colourless crystals (0.63 g, 3.0 mmol, 44%); mp 134-135 °C; (Found: MH^+ , 215.1179. $C_{13}H_{15}N_2O$ requires 215.1179.); ν_{max} (thin film)/ cm^{-1} 3415, 3069, 2866, 1666, 1613, 1474, 1175, 1112, 1003 and 918; δ_H 1.95-1.88 (2 H, m, C₆H₂), 2.18-2.13 (2 H, m, C₆H₂), 4.03-3.99 (2 H, m, NCH₂), 5.11-5.02 (2 H, m, CH₂), 5.82-5.76 (1 H, m, CH), 7.49 (1 H, ddd, *J* 8.1, 5.4, 1.4, 6-H), 7.76-7.68 (2 H, m, 7+8-H), 8.04 (1 H, s, 2-H) and 8.30 (1 H, dd, *J* 8.1, 1.4, 5-H); δ_C 28.07 (C_b), 30.51 (C_c), 46.39 (C_a), 115.90 (CH₂), 122.08 (4a-C), 126.55 (5-C), 126.94 (6-C), 127.14 (ArH), 134.06 (ArH), 136.83 (CH), 146.59 (2-C), 148.05 (8a-C) and 160.96 (4-C); *m/z*(Electrospray) 160 (M^+ , 38%), 147 (28), 68 (29), 55 (36) and 40 (100).

4-(Cyclopropylidenemethyl)toluene¹¹⁷

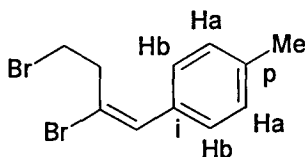


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A solution of cyclopropyltriphenylphosphonium bromide (10.20 g, 26.60 mmol), *p*-toluylaldehyde (3.03 cm³, 26.6 mmol) and potassium *t*-butoxide (6.25 g, 55.86 mmol) in DCM (100 cm³) were refluxed for 48 h. The reaction mixture was cooled and the DCM removed under reduced pressure. The crude mixture was partially dissolved in MeOH (200 cm³), NaBH₄ (3.01 g, 79.8 mmol) was added and the reaction mixture stirred for a further 12 h to reduce the remaining aldehyde. The MeOH was removed under reduced pressure and the crude slurry was extracted with DCM (100 cm³). The DCM solution was washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified with column chromatography using silica gel as absorbent with light petroleum as eluent yielding 4-(cyclopropylidenemethyl)toluene as a colourless oil (1.53 g, 11.6 mmol, 44%); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$ 3044, 2973, 1784, 1512, 1456, 1408, 1109, 1043, 973, 930, 832, 754 and 512; δ_{H} 1.16-1.23 (2 H, m, CH₂), 1.40-1.47 (2 H, m, CH₂), 2.20 (3 H, s, CH₃), 6.55 (1 H, t, *J* 1.6, CH), 7.17 (2 H, d, *J* 8.0, ArH) and 7.46 (2 H, d, *J* 8.0, ArH); δ_{C} 0.00 (CH₂), 3.63 (CH₂), 20.56 (Me), 117.59 (CH), 122.54 (C), 126.02 (2 × ArH), 129.20 (2 × ArH), 135.02 (ArC) and 135.86 (ArC).

The data were consistent to the literature.¹¹⁷

(*E*)-4-(2,4-Dibromobut-1-enyl)toluene¹¹⁷



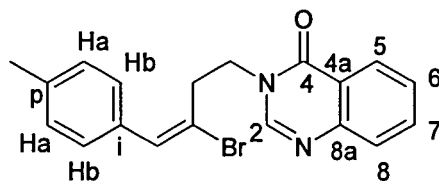
380

The reaction between 4-(cyclopropylidenemethyl)toluene (1.31 g, 9.9 mmol) and copper (II) bromide (4.42 g, 18.8 mmol) was heated under reflux in MeCN (50 cm³) for 14 h. The reaction mixture was cooled and washed with sat. NH₄Cl and extracted light petroleum (4 × 50 cm³). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure yielding (*E*)-4-(2,4-dibromobut-1-enyl)toluene as a colourless oil (1.80 g, 5.9 mmol, 60%); (Found: M^+ , 301.9299. C₁₁H₁₂⁷⁹Br₂ requires 301.9300.); $\nu_{\max}(\text{thin film})/\text{cm}^{-1}$

2919, 1511, 1417, 1257, 1212, 1147, 1008, 912, 865, 802 and 709; δ_{H} 2.33 (3 H, s, Me), 3.08 (2 H, t, J 6.9, CH_2), 3.62 (2 H, t, J 6.9, BrCH_2), 6.80 (1 H, s, CH), 7.16 (2 H, d, J 8.0, H_a) and 7.49 (2 H, d, J 8.0, H_b); δ_{C} 21.33 (Me), 30.58 (BrCH_2), 46.03 (CH_2), 121.98 (BrC), 128.84 ($2 \times \text{H}_b$), 128.86 ($2 \times \text{H}_a$), 130.52 (CH), 132.51 (p -C) and 137.99 (i -C); m/z (EI) 306 (M^+ , 15%), 304 (27), 302 (14), 210 (14), 142 (31), 129 (100), 115 (70), 93 (41), 63 (30) and 51 (39).

The data were consistent to the literature.¹¹⁷

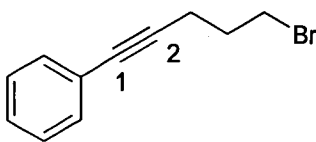
(*E*)-3-(3-Bromo-4-*p*-toluylbut-3-enyl)-3*H*-quinazoline-4-one



379

Potassium *t*-butoxide (0.57 g, 4.67 mmol) was added to a solution of 3*H*-quinazolin-4-one (0.68 g, 4.67 mmol) in DMF (100 cm^3) and stirred for 1 h. (*E*)-4-(2,4-Dibromobut-1-enyl)toluene (1.70 g, 5.60 mmol) was added and stirred for a further 12 h. The crude reaction mixture was extracted into EtOAc and washed with H_2O ($5 \times 50 \text{ cm}^3$) and brine (50 cm^3). The organic layer was dried over MgSO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (3:1) as eluent to yield (*E*)-3-(3-bromo-4-*p*-toluylbut-3-enyl)-3*H*-quinazoline-4-one as colourless crystals (0.05 g, 0.13 mmol, 20%); mp 201–202 $^\circ\text{C}$; (Found: MH^+ , 369.0595. $\text{C}_{19}\text{H}_{18}^{79}\text{BrN}_2\text{O}$ requires 369.0597.); ν_{max} (thin film)/ cm^{-1} 3021, 2918, 1716, 1675, 1609, 1507, 1472, 1373, 1321, 1259, 1154, 909, 805, 774, 698, 537 and 452; δ_{H} 2.31 (3 H, s, Me), 3.10 (2 H, t, J 6.4, CH_2), 4.31 (2 H, t, J 6.4, NCH_2), 6.63 (1 H, s, CH), 7.10 (2 H, d, J 8.0, H_a), 7.29 (2 H, d, J 8.0, H_b), 7.51 (1 H, ddd, J 8.2, 6.8, 1.2, 6-H), 7.69 (1 H, dd, J 8.2, 1.2, 8-H), 7.75 (1 H, ddd, J 8.2, 6.8, 1.4, 7-H), 8.04 (1 H, s, 2-H) and 8.32 (1 H, dd, J 8.2, 1.4, 5-H); δ_{C} 21.31 (Me), 42.02 (CH_2), 45.63 (NCH_2), 121.00 (C), 121.97 (C), 126.59 (5-C), 127.31 (6-C), 127.61 (8-C), 128.67 ($2 \times \text{ArH}$), 128.85 ($2 \times \text{ArH}$), 131.60 (CH), 132.30 (p -C), 134.33 (7-C), 138.07 (i -C), 146.73 (2-C), 148.17 (8a-C) and 161.15 (4-C); m/z (Electrospray) 371 (M^+ , 4%), 369 (4), 289 (75), 143 (79), 128 (100), 115 (54), 102 (33), 77 (46) and (51).

5-Bromo-1-phenylpent-1-yn¹¹⁸



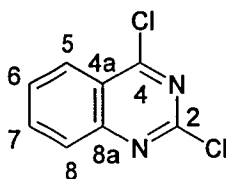
386

Phenylacetylene (0.69 cm³, 6.3 mmol) was slowly added to *n*-butyllithium (2 cm³, 5 mmol) in THF. The reaction was refluxed for 1 h until no gas evolution. The reaction mixture was cooled to rt and 1,3-dibromopropane (0.76 cm³, 7.5 mmol) was added and refluxed for 12 h. After cooling to rt the crude reaction was quenched with water (2 cm³). The crude reaction mixture was extracted into EtOAc and washed with H₂O (3 × 100 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure yielding 5-bromo-1-phenylpent-1-yne as a colourless oil (1.11 g, 5.0 mmol, 80%); ν_{\max} (thin film)/cm⁻¹ 2929, 2858, 1489, 1441, 1246, 1069, 1033, 998, 913 and 775; δ_{H} 2.14 (2 H, sep, *J* 6.6, CH₂) 2.61 (2 H, t, *J* 6.6, CH₂), 3.58 (2 H, t, *J* 6.6, CH₂Br), 7.35-7.32 (3 H, m, ArH) and 7.51-7.48 (2 H, m, ArH); δ_{C} 18.15 (CH₂), 32.19 (CH₂Br), 34.86 (CH₂), 81.63 (1-C), 87.94 (2-C), 123.55 (ArC), 127.82 (ArH), 128.26 (2 × ArH) and 131.77 (2 × ArH).

The data were consistent to the literature.¹¹⁸

6.5 Experimental for Chapter 5

2,4-Dichloroquinazoline¹¹⁹



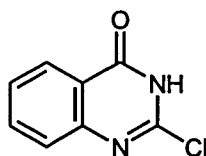
393

Phosphorous oxychloride (14.3 cm³, 154 mmol) was added to a solution of benzoyleneurea (5.0 g, 30.8 mmol) in *N,N*-dimethylaniline (1.8 cm³, 15.0 mmol) and refluxed for 4 h. The reaction mixture was cooled and carefully quenched with chilled water. The reaction mixture was extracted into DCM and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with EtOAc/light petroleum (3:1) as eluent yielding 2,4-dichloroquinazoline as colourless crystals (1.04 g, 5.3 mmol, 17%); mp 115-116 °C (lit.¹¹⁹ 116-118 °C); ν_{\max} (thin film)/cm⁻¹ 3290, 2901,

1340, 1245, 1109, 1097, 956 and 779; δ_{H} (CD_3)₂SO 7.71 (1 H, ddd, J 8.8, 7.1, 1.2, 7-H), 7.88 (1 H, dd, J 8.3, 1.2, 5-H), 8.00 (1 H, ddd, J 8.3, 7.1, 1.2, 6-H) and 8.15 (1 H, dd, J 8.8, 1.2, 8-H); δ_{C} (CD_3)₂SO 121.13 (4a-C), 125.42 (5-C), 129.11 (8-C), 130.78 (6-C), 134.54 (7-C), 148.90 (8a-C), 162.01 (4-C) and 164.58 (2-C).

The data were consistent to the literature.¹¹⁹

2-Chloro-3*H*-quinazolin-4-one¹¹⁹

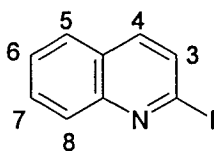


394

To a stirred solution of 2,4-dichloroquinazoline (5.0 g, 25.4 mmol) in THF (50 cm³) was added 1 *N* NaOH (127 cm³, 127 mmol) and the reaction mixture was stirred for 6 h. The organic solvent was removed under reduced pressure and the solid triturated with H₂O. The precipitate was recrystallised from hot EtOH to afford 2-chloro-3*H*-quinazolin-4-one as colourless crystals (0.58 g, 3.2 mmol, 12%); mp 210-211 °C (lit.¹¹⁹ 214-218 °C); ν_{max} (thin film)/cm⁻¹ 3410, 1699, 1653, 1601, 1582, 1523, 1399, 1124, 958, 762, 734, 659, 620 and 542; δ_{H} (CD_3)₂SO 7.73 (1 H, ddd, J 8.6, 7.0, 1.2, 6-H), 7.78 8.15 (1 H, dd, J 8.6, 1.2, 8-H) 8.00 (1 H, ddd, J 8.2, 7.0, 1.2, 7-H) and 8.24 (1 H, dd, J 8.2, 1.2, 5-H); δ_{C} (CD_3)₂SO 119.37 (4a-C), 123.42 (5-C), 128.78 (8-C), 128.80 (6-C), 134.40 (7-C), 146.81 (8a-C), 153.56 (2-C) and 164.78 (4-C).

The data were consistent to the literature.¹¹⁹

2-Iodoquinoline



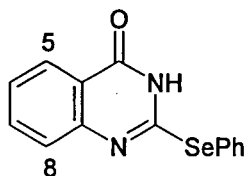
400

Trifluoroacetic acid (1.53 cm³, 20 mmol) was added to a solution of 2-chloroquinoline (0.65 g, 4 mmol) and sodium iodide (11 g, 80 mmol) in 2-butanone (20 cm³) and stirred for 48 h. The crude reaction mixture was extracted into DCM and washed with H₂O (3 × 50 cm³) and brine

(50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (8:1) yielding 2-iodoquinoline as red crystals (0.57 g, 2.22 mmol, 56%); mp 49-50 °C (lit.⁸⁹ 51-53 °C); ν_{\max} (thin film)/cm⁻¹ 1577, 1557, 1491, 1415, 1282, 1122, 1073, 934, 829, 815, 772 and 764; δ_{H} 7.52 (1 H, ddd, *J* 8.0, 7.2, 1.2, 6-H), 7.77-7.65 (4 H, m, ArH) and 8.00 (1 H, dd, *J* 8.0, 1.2, 8-H); δ_{C} 119.09 (2-C), 127.10 (4a-C), 127.26 (6-C), 127.96 (5-C), 128.52 (8-C), 130.44 (3-C), 131.97 (7-C), 137.32 (4-C) and 149.35 (8a-C).

The data were consistent to the literature.⁸⁹

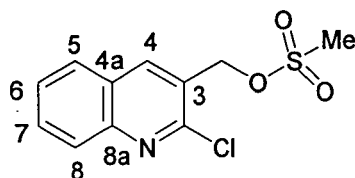
2-Phenylselanyl-3*H*-quinazolin-4-one



401

K-selectride in 1 *N* THF (1.1 cm³, 1.1 mmol) was added to diphenylselanide (0.16 g, 0.5 mmol) in dry THF (20 cm³) and stirred for 10 min. 2-Chloro-3*H*-quinazolin-4-one (0.22 g, 1.0 mmol) was added and the mixture was stirred for 12 h. The solvent was removed under reduced pressure. The crude product was triturated hot petrol yielding 2-phenylselanyl-3*H*-quinazolin-4-one as colourless crystals (12 mg, 0.36 mmol, 36%); mp 120-121 °C; (Found: MH⁺, 303.0031. C₁₄H₁₁N₂O⁸⁰Se requires 303.0028.); ν_{\max} (thin film)/cm⁻¹ 3644, 2357, 1694, 1573, 1557, 1465, 1337, 1304, 1168, 940 and 870; δ_{H} 7.29 (1 H, dd, *J* 8.0, 1.1, 8-H), 7.49-7.41 (4 H, m, ArH), 7.73-7.68 (3 H, m, ArH) and 8.04 (1 H, dd, *J* 7.6, 0.8, 5-H); δ_{C} 120.42 (ArC), 125.87 (ArH), 125.99 (ArH), 126.06 (ArC), 127.84 (ArH), 129.02 (ArH), 129.31 (ArH), 129.49 (ArH), 129.94 (ArC), 130.72 (ArH), 134.33 (ArH), 135.79 (ArH), 148.51 (ArC) and 161.80 (ArC); *m/z*(Electrospray) 302 (M⁺, 18%), 300 (8) 145 (51), 117 (26), 90 (100), 77 (38), 64 (29), 63 (37) and 51 (45).

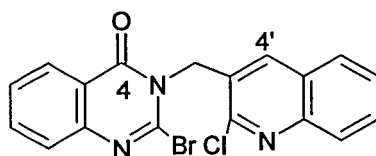
Methanesulfonic acid 2-(chloroquinolin-3-yl)methyl ester



430

Methanesulfonyl chloride (0.15 g, 1.56 mmol) and triethyl amine (0.43 cm³, 4.2 mmol) were added to a solution of 2-chloro-3-(hydroxymethyl)quinoline (0.15 g, 0.78 mmol) in toluene (20 cm³) and stirred for 24 h. The crude reaction mixture was extracted into DCM and washed with H₂O (3 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (9:1) as eluent yielding methanesulfonic acid 2-(chloroquinolin-3-yl)methyl ester as a yellow oil (0.11 g, 0.48 mmol, 62%); mp 130-131 °C; (Found: MH⁺, 272.0144. C₁₁H₁₁³⁵ClNO₃S requires 272.0143.); ν_{\max} (thin film)/cm⁻¹ 3399, 3049, 2915, 2852, 1646, 1616, 1550, 1455, 1351, 1243, 1092, 1008, 825, 777, 751, 586 and 514; δ_{H} 3.14 (3 H, s, CH₃), 5.46 (2 H, s, CH₂), 7.60 (1 H, ddd, *J* 8.0, 6.8, 1.0, 6-H), 7.76 (1 H, ddd, *J* 8.4, 6.8, 1.6, 7-H), 7.85 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.04 (1 H, dd, *J* 8.4, 1.0, 8-H) and 8.30 (1 H, s, 4-H); δ_{C} 38.10 (CH₂), 67.78 (CH₃), 125.62 (4a-H), 126.83 (3-C), 127.76 (6-H), 127.88 (5-H), 128.38 (8-H), 131.47 (7-H), 138.97 (4-H), 147.63 (8a-C) and 148.96 (2-C); *m/z*(Electrospray) 272 (M⁺, 20%), 271 (63), 172 (24), 175 (43), 140 (100), 128 (71), 101 (32), 79 (89) and 63 (27).

2-Bromo-3-[(2-chloroquinolin-3-yl)methyl]-3*H*-quinazolin-4-one

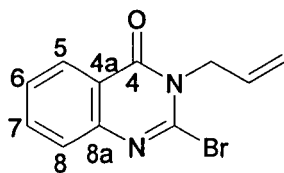


431

Potassium *t*-butoxide (0.13g, 1.2 mmol) was added to a solution of 2-bromo-3*H*-quinazolin-4-one (0.22 g, 1.0 mmol) in DMF (20 cm³) and stirred 1 h. Methanesulfonic acid 2-(chloroquinolin-3-yl)methyl ester (0.27 g, 1.2 mmol) was added and stirred for a further 12 h. The crude reaction mixture was extracted into Et₂O and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under

reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (5:1) as eluent to yield 2-bromo-3-[(2-chloroquinolin-3-yl)methyl]-3*H*-quinazolin-4-one as colourless crystals (0.058 g, 0.15 mmol, 16%); mp 180-181 °C; (Found: MH^+ , 399.9847. $C_{18}H_{12}^{79}Br^{35}ClN_3O$ requires 399.9847.); ν_{max} (thin film)/ cm^{-1} 3423, 2093, 1735, 1641, 1561, 1555, 1467, 1407 and 671; δ_H 5.68 (2 H, s, CH_2), 7.45 (1 H, ddd, J 8.1, 7.0, 1.2, ArH), 7.54-7.50 (2 H, m, ArH), 7.68-7.61 (3 H, m, ArH), 7.78 (1 H, ddd, J 8.3, 6.8, 1.1, ArH), 7.97 (1 H, d, J 8.5, ArH) and 8.24 (1 H, dd, J 8.0, 1.5, 4'-H); δ_C 49.37 (CH_2), 120.23 (ArC), 127.02 (ArC), 127.05 (ArC), 127.15 (ArH), 127.44 (ArH), 127.48 (ArH), 127.70 (4'-C), 128.15 (ArH), 128.31 (ArH), 130.64 (ArH), 134.59 (ArH), 135.56 (ArH), 135.57 (ArC), 146.97 (ArC), 147.26 (ArC), 148.62 (ArC) and 161.39 (4-C); m/z (Electrospray) 405 (M^+ , 7%), 404 (22), 402 (98), 400 (81), 364 (50), 316 (24), 286 (25), 178 (29), 176 (84), 140 (100), 89 (34), 83 (48), 51 (52) and 49 (76).

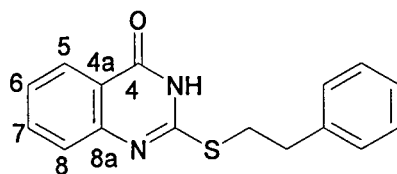
3-Allyl-2-bromo-3*H*-quinazolin-4-one



432

Potassium *t*-butoxide (0.12 g, 3.0 mmol) was added to a stirred solution of 2-bromo-3*H*-quinazolin-4-one (0.35 g, 2.0 mmol) in DMF (20 cm^3) and stirred for 1 h. Allyl bromide (0.34 cm^3 , 4.0 mmol) was added and stirred for 12 h. The crude reaction mixture was extracted into EtOAc and washed with H_2O (5 \times 50 cm^3) and brine (50 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc as eluent (5:1) yielding 3-allyl-2-bromo-3*H*-quinazolin-4-one as colourless crystals (0.17 g, 0.65 mmol, 33%); mp 106-107 °C; (Found: MH^+ , 264.9974 $C_{11}H_{10}^{79}BrN_2O$ requires 264.9971.); ν_{max} (thin film)/ cm^{-1} 3447, 1687, 1583, 1470, 1332, 1154, 1121, 592, 810, 768, 691, 577 and 523; δ_H 4.94-4.92 (2 H, m, NCH_2), 5.33-5.27 (2 H, m, CH_2), 6.02-5.92 (1 H, m, CH), 7.49 (1 H, ddd, J 8.6, 8.4, 2.0, 6-H), 7.62 (1 H, dd, J 8.6, 1.6, 8-H), 7.74 (1 H, ddd, J 8.6, 8.4, 1.6, 7-H) and 8.22 (1 H, dd, J 8.6, 1.6, 5-H); δ_C 50.74 (NCH_2), 118.82 (CH_2), 120.45 (4a-C), 126.76 (8-C), 127.32 (5-C), 127.58 (6-C), 130.69 (CH), 134.94 (7-C), 135.88 (8a-C), 147.11 (2-C) and 161.01 (4-C); m/z (Electrospray) 266 (M^+ , 16%), 264 (15), 249 (20), 185 (100), 129 (52), 102 (23), 90 (35) and 40 (53).

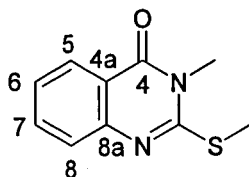
2-(Phenylethylsulfanyl)-3*H*-quinazolin-4-one



448

Sodium hydride (0.35 g, 8.8 mmol) was added to a stirred solution of 2-mercapto-3*H*-quinazolin-4-one (0.71 g 4.0 mmol) in DMF (20 cm³) and stirred for 1 h at rt. 2-Bromoethyl benzene (0.58 cm³, 4.2 mmol) in DMF (10 cm³) was added to the reaction over 1 h. The reaction was stirred for a further 12 h. The crude reaction mixture was extracted into EtOAc and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc (2:1) as eluent yielding 2-(phenylethylsulfanyl)-3*H*-quinazolin-4-one as colourless crystals (0.84 g, 2.99 mmol, 75%); mp 121-122 °C; (Found: MH⁺, 283.0898. C₁₆H₁₅N₂OS requires 283.0900.); ν_{max} (thin film)/cm⁻¹ 3417, 1732, 1698, 1666, 1581, 1556, 1446, 1398, 1247, 958, 872, 765, 722, 687, 620 and 558; δ_{H} 3.11 (2 H, t, *J* 7.8, CH₂), 3.54 (2 H, t, *J* 7.8, SCH₂), 7.27-7.21 (1 H, m, ArH), 7.35- 7.31 (4 H, m, ArH), 7.43 (1 H, ddd, *J* 8.1, 6.7, 0.3, 6-H), 7.58 (1 H, dd, *J* 8.5, 0.3, 8-H), 7.78 (1 H, ddd, *J* 8.5, 6.7, 1.5, 7-H), 8.05 (1 H, dd, *J* 8.1, 1.5, 5-H) and 12.55 (1H, brs, NH); δ_{C} 31.01 (SCH₂), 34.81 (PhCH₂), 119.98 (4a-C), 125.56 (6-C), 126.00 (8-C and ArC), 126.36 (5-C and ArH), 128.40 (2 × ArH), 128.59 (2 × ArH), 134.57 (7-C), 140.02 (8a-C), 157.31 (2-C) and 161.24 (4-C); *m/z*(Electrospray) 283 (M⁺, 36%), 179 (20), 164 (23), 147 (100) and 52 (26).

3-Methyl-2-methylsulfanyl-3*H*-quinazolin-4-one



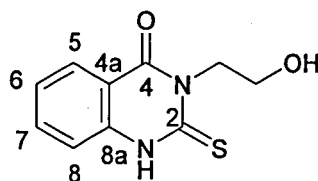
449

Sodium hydride (0.60 g, 15.0 mmol) was added to a solution of 2-mercapto-3*H*-quinazolin-4-one (1.06 g 6.0 mmol) in DMF (20 cm³) and stirred for 1 h at 80 °C. Methyl iodide (0.93 cm³,

15.0 mmol) was added to the reaction mixture and stirred for a further 12 h. The crude reaction was extracted into EtOAc and washed with H₂O (5 × 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent with light petroleum/EtOAc as eluent (5:1) yielding 3-methyl-2-methylsulfanyl-3*H*-quinazolin-4-one as colourless crystals (0.63 g, 3.0 mmol, 50%); mp 208 °C (lit.¹⁶⁹ 210 °C); δ_{H} 2.57 (3 H, s, SMe), 3.50 (3H, s, NMe), 7.28 (1 H, ddd, *J* 8.8 7.0 0.8, 6-H), 7.44 (1 H, dd, *J* 8.8 0.8 8-H), 7.59 (1 H, ddd, *J* 8.8 7.0 1.2, 7-H) and 8.14 (1 H, dd, *J* 8.8 1.2, 5-H); δ_{C} 14.93 (SMe), 30.03 (NMe), 118.86 (4a-C), 125.03 (8-C), 127.57 (6-C), 126.73 (5-C), 133.96 (7-C), 147.30 (8a-C) and 161.56 (4-C).

The data were consistent to the literature.¹⁶⁹

3-(2-Hydroxyethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one¹⁷⁰

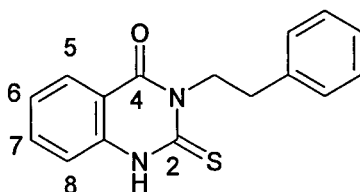


457

The reaction between 2-(methoxycarbonyl)-phenyl isothiocyanate (0.62 cm³, 4.0 mmol) and 2-hydroxyethylamine (0.24 cm³, 4.0 mmol) was heated under reflux in 2-propanol (20 cm³) for 2 h. The reaction mixture was cooled and the precipitate triturated with cold water and dried yielding 3-(2-hydroxyethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one as colourless crystals (820 mg, 3.97 mmol, 99%); mp 237-239 °C (lit.¹⁷⁰ 240 °C); ν_{max} (thin film)/cm⁻¹ 3403, 3002, 1690, 1653, 1546, 1529, 1439, 1132, 998, 775 and 694; δ_{H} (CD₃)₂SO 3.65 (2 H, t, *J* 6.6, OCH₂), 4.48 (2 H, t, *J* 6.6, NCH₂), 7.33-7.27 (2 H, m, ArH), 7.69 (1 H, ddd, *J* 8.8, 6.8, 1.2, 7-H) and 7.90 (1 H, dd, *J* 8.8, 1.2, 5-H); δ_{C} (CD₃)₂SO 47.06 (NCH₂), 56.81 (OCH₂), 115.39 (4a-C), 115.41 (6-C), 124.41 (8-C), 127.21 (5-C), 135.31 (7-C), 138.88 (8a-C), 159.42 (4-C) and 175.18 (2-C).

The data were consistent with the literature.¹⁷⁰

3-(2-Phenylethyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one¹⁷¹



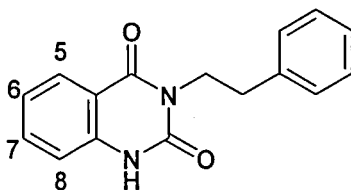
456

The reaction between 2-(methoxycarbonyl)-phenyl isothiocyanate (0.31 cm³, 2.0 mmol) and 2-phenylethylamine (0.25 cm³, 2.0 mmol) was heated under reflux in 2-propanol (10 cm³) for 2 h. The reaction mixture was cooled and the precipitate collected by filtration and recrystallised with hot propanol yielding 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one as colourless crystals (520 mg, 1.83 mmol, 92%); mp 237-238 °C (lit.¹⁷¹ 239-240 °C); (Found: MH⁺, 283.0897. C₁₆H₁₅N₂OS requires 283.0900.); ν_{\max} (thin film)/cm⁻¹ 3422, 2999, 1698, 1643, 1540, 1502, 1440, 1099, 996, 745 and 684; δ_{H} 3.10 (2 H, t, *J* 7.6, CH₂), 4.74 (2 H, t, *J* 7.6, NCH₂), 7.17 (1 H, d, *J* 8.2, 8-H), 7.28-7.23 (2 H, m, ArH), 7.37-7.32 (2 H, m, ArH), 7.43-7.40 (2 H, m, ArH), 7.68 (1 H, ddd, *J* 8.2, 6.4, 1.2, 7-H), 8.17 (1 H, dd, *J* 8.0, 1.2, 5-H) and 10.33 (1 H, brs, NH); δ_{C} 32.82 (CH₂), 48.37 (NCH₂), 114.51 (8-C), 116.15 (ArC), 125.10 (ArH), 126.61 (ArH), 128.57 (2 × ArH and 5-C), 129.05 (2 × ArH), 135.53 (7-C), 138.33 (ArC), 138.35 (ArC), 159.46 (2-C) and 175.67 (4-C); *m/z*(Electrospray) 282 (M⁺, 21%), 178 (38), 162 (18), 104 (100), 91 (38), 77 (35), 65 (34), 63 (21) and 51 (26).

The structure was confirmed by X-ray crystallography (see appendix).

The data were consistent to the literature.¹⁷¹

3-(2-Phenylethyl)-1H-quinazoline-2,4-dione¹⁷²



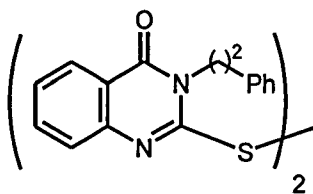
458

A solution of 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (200 mg, 0.71 mmol) and bromine (0.04 cm³, 0.85 mmol) in MeOH (20 cm³) were stirred for 1 h. The precipitate was collected by trituration with cold EtOAc yielding and dried yielding 3-(2-phenylethyl)-1H-quinazoline-2,4-dione as colourless crystals (160 mg, 0.61 mmol, 87%); mp 177-178 °C (lit.¹⁷² 179-180 °C); (Found: MH⁺, 267.1131. C₁₆H₁₅N₂O₂ requires 267.1128.);

ν_{\max} (thin film)/ cm^{-1} 3417, 1697, 1632, 1556, 1503, 1366, 1172, 1061, 889 and 789; δ_{H} (CD_3)₂SO 3.03 (2 H, t, J 8.0, CH_2), 4.33 (2 H, t, J 8.0, NCH_2), 7.13 (1 H, dd, J 8.0, 0.4, 8-H), 7.37-7.24 (6 H, m, ArH), 7.64 (1 H, ddd, J 8.0, 7.2, 1.2, 7-H), 8.15 (1 H, dd, J 8.0, 1.2, 5-H) and 10.42 (1 H, brs, NH); δ_{C} (CD_3)₂SO 34.06 (CH_2), 42.34 (NCH_2), 114.64 (ArC), 115.10 (ArH), 123.48 (ArH), 126.55 (ArH), 128.88 (ArH), 128.95 ($2 \times \text{ArH}$), 128.98 ($2 \times \text{ArH}$), 135.08 (ArH), 138.55 (ArC), 138.58 (ArC), 152.03 (4-C) and 162.27 (2-C); m/z (Electrospray) 266 (M^+ , 26%), 162 (20), 145 (23), 103 (100) and 91 (24).

The data were consistent to the literature.¹⁷²

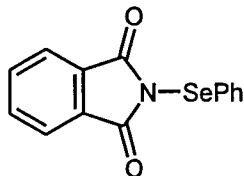
Di-[3-(2-phenylethyl)quinazolin-4-on-2-yl] disulfide



459

3-(2-Phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (0.56 mg, 2.0 mmol) and bromine (0.20 cm^3 , 4.0 mmol) were stirred in anhydrous MeOH (20 cm^3) for 4 h. The white precipitate was collected and triturated with MeOH and dried yielding di-[3-(2-phenylethyl)quinazolin-4-on-2-yl] disulfide as colourless crystals (330 mg, 0.59 mmol, 59%); mp 223-225 °C; (Found: MH^+ , 563.1566. $\text{C}_{32}\text{H}_{27}\text{N}_4\text{O}_2\text{S}_2$ requires 563.1570.); ν_{\max} (thin film)/ cm^{-1} 3607, 2354, 1672, 1555, 1469, 1336, 1130, 768 and 690; δ_{H} 3.13 (4 H, t, J 8.2, CH_2), 4.59 (4 H, t, J 8.2, NCH_2), 7.28-7.48 (14 H, m, ArH), 7.66-7.61 (2 H, m, ArH) and 8.23-8.20 (2 H, m, ArH); δ_{C} 34.90 ($2 \times \text{CH}_2$), 46.85 ($2 \times \text{NCH}_2$), 119.80 ($2 \times \text{ArC}$), 126.69 ($2 \times \text{ArH}$), 126.81 ($2 \times \text{ArH}$), 127.05 ($2 \times \text{ArH}$), 127.11 ($2 \times \text{ArH}$), 128.91 ($4 \times \text{ArH}$), 129.10 ($4 \times \text{ArH}$), 134.63 ($2 \times \text{ArH}$), 137.47 ($2 \times \text{ArC}$), 147.10 ($2 \times \text{ArC}$), 152.69 ($2 \times \text{ArC}$) and 161.50 ($2 \times \text{ArC}$); m/z (Electrospray) 563 (M^+ , 5%), 529 (100), 497 (27), 401 (17) and 321 (20).

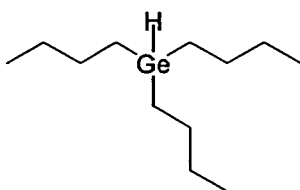
N-Phenylselanylphthalimide¹⁷³



Potassium phthalimide (3.87 g, 21.0 mmol) and phenylselanyl chloride (4.80 g, 25.1 mmol) were placed in a three necked flask (250 cm^3). The flask was connected to a vacuum line and

after several evacuations and purges with nitrogen, dry hexane (50 cm³) was added. The reaction mixture was stirred at rt for 2 h. DCM was added and the solid removed by filtration. The solution was concentrated on a rotary evaporator to 20 cm³ and was diluted with hexane (80 cm³). The resulting precipitate was collected by filtration yielding *N*-phenylselanylphthalimide as yellow crystals (6.34 g, 21.0 mmol, 83%); mp 172-174 °C (lit.¹⁷³ 171-175 °C); ν_{max} (thin film)/cm⁻¹ 3419, 1720, 1643, 1282 and 711; δ_{H} 7.57-7.85 (9 H, m, ArH); δ_{C} 122.91 (ArH), 125.78 (2 × ArH), 128.96 (2 × ArH), 131.58 (2 × ArH), 132.57 (ArC), 132.79 (ArC), 134.30 (2 × ArH), 148.85 (ArC), 168.66 (ArC) and 169.22 (ArC). The data were consistent to the literature.¹⁷³

Tributylgermanium hydride¹⁷⁴



Tetrachlorogermanium (4.38 g, 20.8 mmol) and butylmagnesium chloride (2 M solution in diethyl ether, 50 cm³) were successively added dropwise to a solution of Cp₂TiCl₂ (0.38 g, 1.5 mmol) in freshly distilled diethyl ether (100 cm³) at -78 °C over 45 min. The reaction mixture was warmed to room temperature over 45 min and refluxed for 15 h. After cooling to 0 °C the aqueous phase was extracted with Et₂O. The combined organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The crude product was distilled under reduced pressure and temperature yielding tributylgermanium hydride as a colourless oil (1.89 g, 7.75 mmol, 37%); ν_{max} (thin film)/cm⁻¹ 2955, 2925, 2857, 2005, 1463, 1457, 1375, 1339, 1172, 1082, 962, 882, 773, 724, 696 and 557; δ_{H} 0.56-0.69 (15 H, m, BuH), 1.10-1.20 (12 H, m, BuH) and 3.46 (1 H, sep, *J* 3.0, GeH); δ_{C} 11.66 (3-C), 13.76 (4-C), 26.15 (2-C) and 28.53 (1-C).

The data were consistent to the literature.¹⁷⁴

Appendix A. X-ray crystallography

Structure determination by single X-ray crystallography of 11-hydroxy-11*H*-isoquinolino[3,2-*b*]quinazolin-6,13-dione **345**. The compound was placed in a small sample vial and dissolved in a minimal amount of CDCl₃. The small sample vial was sealed. Crystals developed upon storage at room temperature for 24 h, and were submitted in the mother liquor.

Table 1. Crystal data and structure refinement for 345.

Identification code	345	
Chemical formula	C ₁₇ H ₁₁ Cl ₃ N ₂ O ₃	
Formula weight	397.63	
Temperature	120(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	triclinic, P $\bar{1}$	
Unit cell parameters	a = 6.6511(3) Å	α = 90.123(2)°
	b = 8.6274(3) Å	β = 94.525(3)°
	c = 14.5395(7) Å	γ = 99.594(3)°
Cell volume	819.97(6) Å ³	
Z	2	
Calculated density	1.610 g/cm ³	
Absorption coefficient μ	0.579 mm ⁻¹	
F(000)	404	
Crystal colour and size	pale yellow, 0.55 × 0.17 × 0.09 mm ³	
Reflections for cell refinement	3181 (θ range 1.0 to 27.48°)	
Data collection method	Bruker-Nonius 95mm CCD camera on κ -goniostat	
	ϕ & ω scans	
θ range for data collection	3.12 to 27.54°	
Index ranges	h -8 to 8, k -11 to 11, l -18 to 18	
Completeness to θ = 27.54°	98.4 %	
Intensity decay	0%	
Reflections collected	11250	

Independent reflections	3715 ($R_{\text{int}} = 0.0370$)
Reflections with $F^2 > 2\sigma$	2898
Absorption correction	none
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0492, 0.1456
Data / restraints / parameters	3715 / 0 / 230
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0353$, $wR2 = 0.0851$
R indices (all data)	$R1 = 0.0550$, $wR2 = 0.0939$
Goodness-of-fit on F^2	1.028
Extinction coefficient	0.0071(18)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.353 and $-0.328 \text{ e \AA}^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for 345. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.14244(19)	0.63569(15)	0.92173(9)	0.0146(3)
C(1)	-0.0378(2)	0.66563(18)	0.87709(11)	0.0158(3)
N(2)	-0.1702(2)	0.73348(15)	0.91529(9)	0.0166(3)
C(2)	-0.1214(2)	0.79209(18)	1.00469(11)	0.0167(3)
C(3)	-0.2519(2)	0.88209(19)	1.04353(12)	0.0196(4)
C(4)	-0.2003(3)	0.94848(19)	1.13003(12)	0.0222(4)
C(5)	-0.0183(3)	0.92780(19)	1.18015(12)	0.0213(4)
C(6)	0.1089(2)	0.83740(19)	1.14387(11)	0.0192(4)
C(7)	0.0580(2)	0.76842(18)	1.05619(11)	0.0158(3)
C(8)	0.1965(2)	0.67843(18)	1.01500(11)	0.0157(3)
O(1)	0.35078(17)	0.64334(14)	1.05530(8)	0.0212(3)
C(9)	0.3060(2)	0.58892(19)	0.86974(11)	0.0159(3)
O(2)	0.42678(17)	0.72966(13)	0.84351(8)	0.0176(3)

C(10)	0.2222(2)	0.49033(18)	0.78584(11)	0.0165(3)
C(11)	0.3409(3)	0.39065(19)	0.74902(11)	0.0197(4)
C(12)	0.2740(3)	0.3093(2)	0.66742(12)	0.0243(4)
C(13)	0.0874(3)	0.3263(2)	0.62048(12)	0.0266(4)
C(14)	-0.0312(3)	0.4249(2)	0.65622(12)	0.0238(4)
C(15)	0.0355(2)	0.50622(19)	0.73902(11)	0.0174(3)
C(16)	-0.0910(2)	0.61045(19)	0.77812(11)	0.0186(3)
O(3)	-0.23696(18)	0.65190(16)	0.73531(8)	0.0282(3)
C(17)	0.4419(3)	0.8143(2)	0.62829(12)	0.0232(4)
Cl(1)	0.46117(8)	0.68003(6)	0.53965(3)	0.03290(14)
Cl(2)	0.62940(7)	0.98375(6)	0.62257(4)	0.03665(15)
Cl(3)	0.19517(7)	0.86669(6)	0.62000(3)	0.03135(14)

Table 3. Bond lengths [Å] and angles [°] for 345.

N(1)–C(1)	1.3805(19)	N(1)–C(8)	1.408(2)
N(1)–C(9)	1.481(2)	C(1)–N(2)	1.294(2)
C(1)–C(16)	1.511(2)	N(2)–C(2)	1.388(2)
C(2)–C(7)	1.402(2)	C(2)–C(3)	1.405(2)
C(3)–C(4)	1.375(2)	C(4)–C(5)	1.401(2)
C(5)–C(6)	1.375(2)	C(6)–C(7)	1.398(2)
C(7)–C(8)	1.461(2)	C(8)–O(1)	1.2237(18)
C(9)–O(2)	1.4109(19)	C(9)–C(10)	1.501(2)
C(10)–C(11)	1.393(2)	C(10)–C(15)	1.396(2)
C(11)–C(12)	1.381(2)	C(12)–C(13)	1.398(2)
C(13)–C(14)	1.379(3)	C(14)–C(15)	1.395(2)
C(15)–C(16)	1.471(2)	C(16)–O(3)	1.2161(19)
C(17)–Cl(1)	1.7573(17)	C(17)–Cl(2)	1.7629(18)
C(17)–Cl(3)	1.7690(17)		
C(1)–N(1)–C(8)	121.36(13)	C(1)–N(1)–C(9)	121.27(13)
C(8)–N(1)–C(9)	116.16(12)	N(2)–C(1)–N(1)	124.41(15)
N(2)–C(1)–C(16)	116.85(13)	N(1)–C(1)–C(16)	118.69(14)

C(1)–N(2)–C(2)	118.17(13)	N(2)–C(2)–C(7)	121.82(14)
N(2)–C(2)–C(3)	119.06(14)	C(7)–C(2)–C(3)	119.08(15)
C(4)–C(3)–C(2)	119.91(15)	C(3)–C(4)–C(5)	120.73(15)
C(6)–C(5)–C(4)	120.03(16)	C(5)–C(6)–C(7)	119.91(15)
C(6)–C(7)–C(2)	120.31(14)	C(6)–C(7)–C(8)	120.45(14)
C(2)–C(7)–C(8)	119.15(14)	O(1)–C(8)–N(1)	120.76(14)
O(1)–C(8)–C(7)	124.61(15)	N(1)–C(8)–C(7)	114.61(13)
O(2)–C(9)–N(1)	106.36(12)	O(2)–C(9)–C(10)	110.04(13)
N(1)–C(9)–C(10)	112.35(12)	C(11)–C(10)–C(15)	118.94(15)
C(11)–C(10)–C(9)	119.39(14)	C(15)–C(10)–C(9)	121.42(14)
C(12)–C(11)–C(10)	120.23(16)	C(11)–C(12)–C(13)	120.62(16)
C(14)–C(13)–C(12)	119.65(16)	C(13)–C(14)–C(15)	119.78(16)
C(14)–C(15)–C(10)	120.77(15)	C(14)–C(15)–C(16)	120.15(14)
C(10)–C(15)–C(16)	119.07(14)	O(3)–C(16)–C(15)	123.32(15)
O(3)–C(16)–C(1)	118.83(14)	C(15)–C(16)–C(1)	117.84(13)
Cl(1)–C(17)–Cl(2)	110.52(10)	Cl(1)–C(17)–Cl(3)	110.12(9)
Cl(2)–C(17)–Cl(3)	110.03(9)		

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for 345.

	x	y	z	U
H(3)	–0.3755	0.8971	1.0101	0.024
H(4)	–0.2890	1.0090	1.1561	0.027
H(5)	0.0174	0.9763	1.2392	0.026
H(6)	0.2311	0.8218	1.1783	0.023
H(9)	0.3919	0.5290	0.9111	0.019
H(2)	0.539(3)	0.723(2)	0.8595(14)	0.026
H(11)	0.4683	0.3786	0.7801	0.024
H(12)	0.3555	0.2411	0.6430	0.029
H(13)	0.0426	0.2703	0.5643	0.032

H(14)	-0.1578	0.4374	0.6246	0.029
H(17)	0.4644	0.7632	0.6891	0.028

Table 5. Torsion angles [°] for 345.

C(8)–N(1)–C(1)–N(2)	-0.1(2)	C(9)–N(1)–C(1)–N(2)	-166.96(15)
C(8)–N(1)–C(1)–C(16)	-177.39(13)	C(9)–N(1)–C(1)–C(16)	15.7(2)
N(1)–C(1)–N(2)–C(2)	5.6(2)	C(16)–C(1)–N(2)–C(2)	-177.00(13)
C(1)–N(2)–C(2)–C(7)	-5.2(2)	C(1)–N(2)–C(2)–C(3)	172.63(15)
N(2)–C(2)–C(3)–C(4)	-176.39(15)	C(7)–C(2)–C(3)–C(4)	1.5(2)
C(2)–C(3)–C(4)–C(5)	0.1(3)	C(3)–C(4)–C(5)–C(6)	-1.5(3)
C(4)–C(5)–C(6)–C(7)	1.1(3)	C(5)–C(6)–C(7)–C(2)	0.5(2)
C(5)–C(6)–C(7)–C(8)	177.03(15)	N(2)–C(2)–C(7)–C(6)	175.98(14)
C(3)–C(2)–C(7)–C(6)	-1.9(2)	N(2)–C(2)–C(7)–C(8)	-0.6(2)
C(3)–C(2)–C(7)–C(8)	-178.38(14)	C(1)–N(1)–C(8)–O(1)	175.81(15)
C(9)–N(1)–C(8)–O(1)	-16.6(2)	C(1)–N(1)–C(8)–C(7)	-5.6(2)
C(9)–N(1)–C(8)–C(7)	161.98(13)	C(6)–C(7)–C(8)–O(1)	7.7(3)
C(2)–C(7)–C(8)–O(1)	-175.76(15)	C(6)–C(7)–C(8)–N(1)	-170.85(14)
C(2)–C(7)–C(8)–N(1)	5.7(2)	C(1)–N(1)–C(9)–O(2)	86.48(16)
C(8)–N(1)–C(9)–O(2)	-81.07(15)	C(1)–N(1)–C(9)–C(10)	-34.0(2)
C(8)–N(1)–C(9)–C(10)	158.48(13)	O(2)–C(9)–C(10)–C(11)	85.06(17)
N(1)–C(9)–C(10)–C(11)	-156.63(14)	O(2)–C(9)–C(10)–C(15)	-89.25(18)
N(1)–C(9)–C(10)–C(15)	29.1(2)	C(15)–C(10)–C(11)–C(12)	0.0(2)
C(9)–C(10)–C(11)–C(12)	-174.41(15)	C(10)–C(11)–C(12)–C(13)	0.4(3)
C(11)–C(12)–C(13)–C(14)	-0.2(3)	C(12)–C(13)–C(14)–C(15)	-0.3(3)
C(13)–C(14)–C(15)–C(10)	0.7(3)	C(13)–C(14)–C(15)–C(16)	-179.40(16)
C(11)–C(10)–C(15)–C(14)	-0.6(2)	C(9)–C(10)–C(15)–C(14)	173.78(15)
C(11)–C(10)–C(15)–C(16)	179.52(15)	C(9)–C(10)–C(15)–C(16)	-6.1(2)
C(14)–C(15)–C(16)–O(3)	-12.7(3)	C(10)–C(15)–C(16)–O(3)	167.21(16)
C(14)–C(15)–C(16)–C(1)	166.13(15)	C(10)–C(15)–C(16)–C(1)	-13.9(2)
N(2)–C(1)–C(16)–O(3)	10.8(2)	N(1)–C(1)–C(16)–O(3)	-171.71(15)
N(2)–C(1)–C(16)–C(15)	-168.14(14)	N(1)–C(1)–C(16)–C(15)	9.4(2)

Table 6. Hydrogen bonds for 345 [\AA and $^\circ$].

D—H...A	d(D—H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
O(2)—H(2)...N(2')	0.78(2)	2.02(2)	2.7935(17)	171(2)
O(2)—H(2)...O(3')	0.78(2)	2.57(2)	2.9963(17)	116.7(17)

Symmetry operations for equivalent atoms

' $x+1, y, z$

Structure determination by single X-ray crystallography of 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **457**. The compound was placed in a small sample vial and dissolved in a minimal amount of hot propanol. The small sample vial was sealed. Crystals developed upon storage at room temperature for 24 h, and were submitted in the mother liquor.

Table 1. Crystal data and structure refinement for 457.

Identification code	wrb9	
Chemical formula	$\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$	
Formula weight	282.35	
Temperature	150(2) K	
Radiation, wavelength	$\text{MoK}\alpha$, 0.71073 \AA	
Crystal system, space group	monoclinic, Cc	
Unit cell parameters	$a = 4.6405(7) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 25.329(4) \text{ \AA}$	$\beta = 97.047(2)^\circ$
	$c = 12.1910(17) \text{ \AA}$	$\gamma = 90^\circ$
Cell volume	$1422.1(4) \text{ \AA}^3$	
Z	4	
Calculated density	1.319 g/cm^3	
Absorption coefficient μ	0.224 mm^{-1}	
F(000)	592	
Crystal colour and size	colourless, $0.56 \times 0.16 \times 0.02 \text{ mm}^3$	

Reflections for cell refinement	2505 (θ range 2.33 to 27.77°)
Data collection method	Bruker SMART 1000 CCD
diffractometer	ω rotation with narrow frames
θ range for data collection	1.61 to 28.73°
Index ranges	h -6 to 6, k -32 to 32, l -15 to 16
Completeness to $\theta = 26.00^\circ$	99.7 %
Intensity decay	0%
Reflections collected	5350
Independent reflections	3005 ($R_{\text{int}} = 0.0368$)
Reflections with $F^2 > 2\sigma$	2351
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.885 and 0.996
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1005, 0.0000
Data / restraints / parameters	3005 / 2 / 184
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0602$, $wR2 = 0.1444$
R indices (all data)	$R1 = 0.0837$, $wR2 = 0.1590$
Goodness-of-fit on F^2	1.026
Absolute structure parameter	0.13(13)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.432 and -0.202 e \AA^{-3}

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for 457. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.5300(6)	0.19362(12)	0.6679(2)	0.0236(7)
C(1)	0.4066(7)	0.21118(14)	0.5651(3)	0.0240(7)
S(1)	0.1436(2)	0.17829(4)	0.48714(9)	0.0331(3)

N(2)	0.5072(6)	0.25707(12)	0.5303(2)	0.0260(6)
C(2)	0.7275(8)	0.28714(14)	0.5880(3)	0.0238(7)
C(3)	0.8156(9)	0.33469(15)	0.5442(3)	0.0329(9)
C(4)	1.0351(9)	0.36289(16)	0.6036(4)	0.0364(9)
C(5)	1.1700(9)	0.34463(16)	0.7053(3)	0.0353(9)
C(6)	1.0816(8)	0.29799(15)	0.7483(3)	0.0284(8)
C(7)	0.8576(8)	0.26890(13)	0.6899(3)	0.0236(7)
C(8)	0.7576(8)	0.21945(14)	0.7327(3)	0.0242(7)
O(1)	0.8619(6)	0.19952(10)	0.8208(2)	0.0320(6)
C(9)	0.4292(8)	0.14396(14)	0.7137(3)	0.0275(8)
C(10)	0.6053(9)	0.09659(15)	0.6836(4)	0.0353(9)
C(11)	0.5129(9)	0.04717(15)	0.7388(3)	0.0343(9)
C(12)	0.2967(11)	0.01529(17)	0.6871(5)	0.0504(12)
C(13)	0.2124(16)	−0.0295(2)	0.7395(6)	0.0722(18)
C(14)	0.3406(16)	−0.0432(2)	0.8437(7)	0.075(2)
C(15)	0.5500(16)	−0.0116(3)	0.8949(6)	0.079(2)
C(16)	0.6382(13)	0.0335(2)	0.8429(5)	0.0619(14)

Table 3. Bond lengths [Å] and angles [°] for 457.

N(1)–C(1)	1.386(4)	N(1)–C(8)	1.400(4)
N(1)–C(9)	1.475(4)	C(1)–N(2)	1.341(5)
C(1)–S(1)	1.674(4)	N(2)–C(2)	1.394(4)
C(2)–C(7)	1.392(5)	C(2)–C(3)	1.398(5)
C(3)–C(4)	1.375(6)	C(4)–C(5)	1.398(6)
C(5)–C(6)	1.375(6)	C(6)–C(7)	1.396(5)
C(7)–C(8)	1.455(5)	C(8)–O(1)	1.231(4)
C(9)–C(10)	1.521(5)	C(10)–C(11)	1.508(5)
C(11)–C(16)	1.373(7)	C(11)–C(12)	1.379(6)
C(12)–C(13)	1.382(7)	C(13)–C(14)	1.379(10)
C(14)–C(15)	1.351(11)	C(15)–C(16)	1.393(8)

C(1)–N(1)–C(8)	124.0(3)	C(1)–N(1)–C(9)	120.0(3)
C(8)–N(1)–C(9)	116.0(3)	N(2)–C(1)–N(1)	116.3(3)
N(2)–C(1)–S(1)	120.6(3)	N(1)–C(1)–S(1)	123.1(3)
C(1)–N(2)–C(2)	125.2(3)	C(7)–C(2)–N(2)	118.6(3)
C(7)–C(2)–C(3)	120.8(3)	N(2)–C(2)–C(3)	120.6(3)
C(4)–C(3)–C(2)	118.6(4)	C(3)–C(4)–C(5)	121.2(4)
C(6)–C(5)–C(4)	120.0(4)	C(5)–C(6)–C(7)	119.8(3)
C(2)–C(7)–C(6)	119.6(3)	C(2)–C(7)–C(8)	118.9(3)
C(6)–C(7)–C(8)	121.4(3)	O(1)–C(8)–N(1)	119.2(3)
O(1)–C(8)–C(7)	123.9(3)	N(1)–C(8)–C(7)	116.9(3)
N(1)–C(9)–C(10)	112.1(3)	C(11)–C(10)–C(9)	110.9(3)
C(16)–C(11)–C(12)	118.5(4)	C(16)–C(11)–C(10)	120.7(4)
C(12)–C(11)–C(10)	120.8(4)	C(11)–C(12)–C(13)	120.1(5)
C(14)–C(13)–C(12)	121.2(6)	C(15)–C(14)–C(13)	118.7(5)
C(14)–C(15)–C(16)	120.7(6)	C(11)–C(16)–C(15)	120.8(6)

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for 457.

	x	y	z	U
H(2)	0.429(9)	0.2667(16)	0.467(4)	0.031
H(3)	0.7257	0.3472	0.4749	0.039
H(4)	1.0961	0.3954	0.5750	0.044
H(5)	1.3229	0.3644	0.7448	0.042
H(6)	1.1726	0.2856	0.8176	0.034
H(9A)	0.2224	0.1383	0.6852	0.033
H(9B)	0.4439	0.1469	0.7951	0.033
H(10A)	0.5779	0.0917	0.6024	0.042
H(10B)	0.8140	0.1032	0.7070	0.042
H(12)	0.2055	0.0241	0.6154	0.061
H(13)	0.0636	–0.0513	0.7031	0.087

H(14)	0.2828	-0.0743	0.8788	0.090
H(15)	0.6379	-0.0202	0.9672	0.095
H(16)	0.7869	0.0551	0.8798	0.074

Table 5. Torsion angles [°] for 457.

C(8)-N(1)-C(1)-N(2)	-3.2(5)	C(9)-N(1)-C(1)-N(2)	179.0(3)
C(8)-N(1)-C(1)-S(1)	177.5(3)	C(9)-N(1)-C(1)-S(1)	-0.4(4)
N(1)-C(1)-N(2)-C(2)	1.6(5)	S(1)-C(1)-N(2)-C(2)	-179.1(3)
C(1)-N(2)-C(2)-C(7)	0.2(5)	C(1)-N(2)-C(2)-C(3)	-179.8(3)
C(7)-C(2)-C(3)-C(4)	0.5(6)	N(2)-C(2)-C(3)-C(4)	-179.6(3)
C(2)-C(3)-C(4)-C(5)	0.4(6)	C(3)-C(4)-C(5)-C(6)	-0.8(6)
C(4)-C(5)-C(6)-C(7)	0.2(6)	N(2)-C(2)-C(7)-C(6)	179.1(3)
C(3)-C(2)-C(7)-C(6)	-1.0(5)	N(2)-C(2)-C(7)-C(8)	-0.4(5)
C(3)-C(2)-C(7)-C(8)	179.5(3)	C(5)-C(6)-C(7)-C(2)	0.6(5)
C(5)-C(6)-C(7)-C(8)	-179.9(3)	C(1)-N(1)-C(8)-O(1)	-176.7(3)
C(9)-N(1)-C(8)-O(1)	1.2(5)	C(1)-N(1)-C(8)-C(7)	2.9(5)
C(9)-N(1)-C(8)-C(7)	-179.1(3)	C(2)-C(7)-C(8)-O(1)	178.6(4)
C(6)-C(7)-C(8)-O(1)	-0.9(6)	C(2)-C(7)-C(8)-N(1)	-1.0(5)
C(6)-C(7)-C(8)-N(1)	179.5(3)	C(1)-N(1)-C(9)-C(10)	91.5(4)
C(8)-N(1)-C(9)-C(10)	-86.5(4)	N(1)-C(9)-C(10)-C(11)	175.5(3)
C(9)-C(10)-C(11)-C(16)	-88.1(5)	C(9)-C(10)-C(11)-C(12)	90.5(5)
C(16)-C(11)-C(12)-C(13)	-0.6(7)	C(10)-C(11)-C(12)-C(13)	-179.2(4)
C(11)-C(12)-C(13)-C(14)	0.2(9)	C(12)-C(13)-C(14)-C(15)	0.6(10)
C(13)-C(14)-C(15)-C(16)	-1.0(10)	C(12)-C(11)-C(16)-C(15)	0.3(8)
C(10)-C(11)-C(16)-C(15)	178.9(5)	C(14)-C(15)-C(16)-C(11)	0.6(10)

Table 6. Hydrogen bonds for 457 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(1')	0.85(5)	1.97(5)	2.787(4)	162(4)

Symmetry operations for equivalent atoms

' $x-1/2, -y+1/2, z-1/2$

Appendix B. Publications

Radical reactions with 3*H*-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine and tryptanthrin†

W. Russell Bowman,* Mark R. J. Elsegood, Tobias Stein and George W. Weaver*

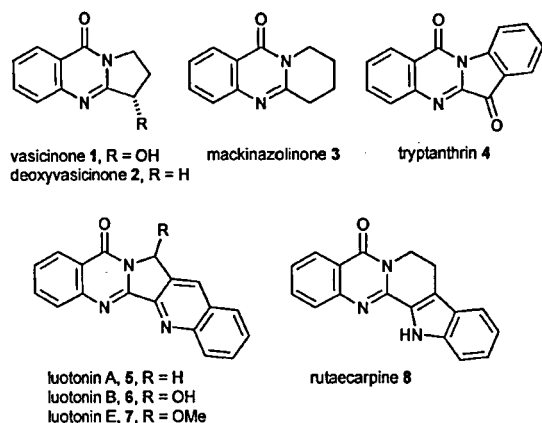
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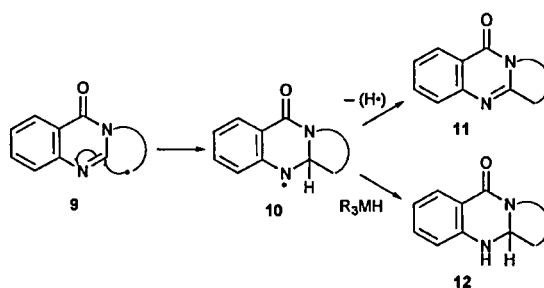
DOI: 10.1039/b614075k

Alkyl, aryl, heteroaryl and acyl radicals have been cyclised onto the 2-position of 3*H*-quinazolin-4-one. The side chains containing the radical precursors were attached to the nitrogen atom in the 3-position. The cyclisations take place by aromatic homolytic substitution hence retain the aromaticity of the 3*H*-quinazolin-4-one ring. The highest yields were obtained using hexamethylditin to facilitate cyclisation rather than reduction without cyclisation. The alkaloids deoxyvasicinone **2**, mackinazolinone **3**, tryptanthrin **4**, luotonin A **5** and rutaecarpine **8** were synthesised by radical cyclisation onto 3*H*-quinazolin-4-one.

The 3*H*-quinazolin-4-one ring system is important to the biological activity of both naturally occurring alkaloids, biosynthesised from anthranilic acid, and pharmaceuticals. The alkaloids include vasicinone **1** and deoxyvasicinone **2**,¹ mackinazolinone **3**,² tryptanthrin **4**,³ luotonins A **5**, B **6** and E **7**⁴ and rutaecarpine **8**.⁵ 3*H*-Quinazolin-4-one alkaloids have been recently reviewed.⁶ All the 3*H*-quinazolin-4-one natural products have interesting biological activity and have therefore been extensively investigated for useful pharmaceutical activity. The 3*H*-quinazolin-4-one ring is regarded as a 'privileged structure' in combinatorial synthesis.⁷ These are structures which represent molecules that are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds.⁷



Our study involved the development of protocols involving radical cyclisation for the synthesis of polycyclic 3*H*-quinazolin-3-ones (Scheme 1). The protocols have also been used for the synthesis of novel polycyclic quinazolinones including the natural



Scheme 1 General synthetic protocol.

products deoxyvasicinone **2**, mackinazolinone **3**, tryptanthrin **4**, luotonin A **5** and rutaecarpine **8**.

Radical cyclisation onto heteroarenes has been developed in recent years to considerable advantage for the synthesis of novel polycyclic heteroarenes. Examples of these cyclisations include: a. alkyl radicals onto pyrroles,^{8,9} imidazoles,⁸ pyrazoles,¹⁰ indoles,^{9,11,12} 1,2,3-triazoles,¹³ pyridinium salts,¹⁴ and quinolones;¹⁵ b. acyl radicals onto pyrroles,¹⁶ quinolines,¹⁷ pyridines¹⁸ and arenes;¹⁹ c. aryl radicals onto indoles,^{20,21} pyrroles,⁹ pyridones,²² and 5-amino- and 5-hydroxyuracils,²³ 2-quinolones,²⁴ quinolines²⁵ and pyridines.²⁶

All of the above cyclisations are 'oxidative' *i.e.* the intermediate π -radicals are not reduced by triorganometal hydrides [*e.g.* tributyltin hydride (Bu_3SnH)] as normally observed for these reagents. The cyclisations proceed by aromatic homolytic substitution with abstraction of hydrogen in a rearomatisation process. Aromatic homolytic substitution has been recently reviewed²⁷ and the mechanism of Bu_3SnH mediated 'oxidative' cyclisation elaborated.²⁸ The pyrimidin-4-one ring of the quinazolin-4-ones has some aromaticity and therefore aromatic homolytic substitution could be predicted, and was observed in our studies, as shown in Scheme 1 (**9** to **11** via the π -radical **10**). However, the lower aromaticity could favour reductive cyclisation in which the intermediate π -radical **10** is intercepted by reagents such as Bu_3SnH . Our prediction that radical cyclisation onto the quinazolin-4-one ring would be 'oxidative' was supported by the 'oxidative' radical cyclisation onto related ring systems, *e.g.* pyrimidine-2,4-diones,^{23,24}

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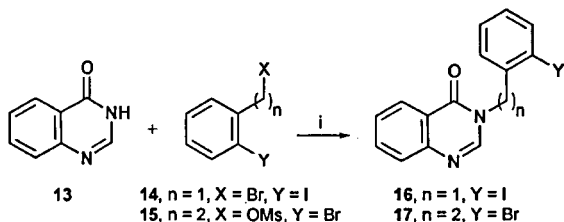
† Electronic supplementary information (ESI) available: Preparation and analytical details of 3*H*-quinazolin-4-one radical precursors and products. See DOI: 10.1039/b614075k

quinolinones¹⁵ and pyridinones.^{22,29,30} However, the lower aromaticity in the pyrrole ring of indole, facilitates both reductive and oxidative cyclisation depending on the conditions.^{11,12,31} The radical intermediate **10**, whether a π -radical or not, is still a strongly stabilised anilyl radical and therefore the rate of reduction by Bu_3SnH to yield **12** is probably too low to be competitive with loss of hydrogen to yield the 'oxidised' product. The reactions could also be regarded as *exo*-cyclisations onto imines which are well known.

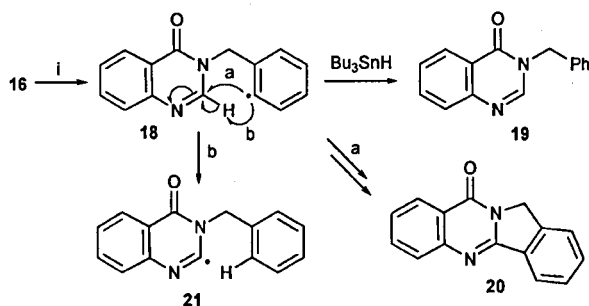
We used two general methodologies to synthesise the radical precursors. Firstly, heteroarenes containing an NH group facilitate *N*-alkylation and provide a suitable synthetic route to radical precursors for cyclisation. The radical leaving group is introduced as part of the *N*-alkyl substituent. Secondly, there is a wide variety of protocols for the synthesis of 3-substituted quinazolinones using ring synthesis from anthranilic acid derivatives, which were employed as required.

Aryl radical cyclisation

Aryl radicals have been successfully cyclised onto pyrroles, indoles and pyrazoles.³² Aryl radicals are very reactive and the most likely to cyclise onto quinazolinones. Therefore, suitable radical precursors for 5- and 6-*exo* cyclisation were prepared (Scheme 2). The 5-membered ring cyclisation with the precursor **16** using Bu_3SnH gave only the reduced uncyclised product **19** (Scheme 3). Even syringe pump addition of Bu_3SnH , with either Et_3B (r.t.) or AIBN (110 °C) as initiators, gave only **19**. We considered that the lack of cyclisation could be due to 1,5-hydrogen abstraction from the 2-position of the quinazolinone as shown in Scheme 3 (route b: **18** to **21**). This possibility was eliminated by repeating the reaction with Bu_3SnD which gave only deuteration on the aryl



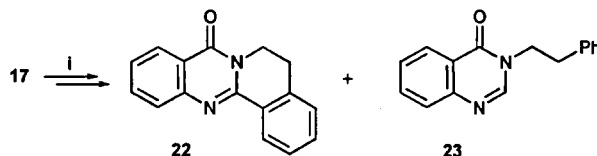
Scheme 2 Reagents and conditions: i, *tert*-BuOK, DMF, 63% (**16** from **14**), 38% (**17** from **15**).



Scheme 3 Reagents and conditions: i, Et_3B , PhMe, r.t., Bu_3SnH (fast addition) 96% (**19**), slow addition, 30% (**19**); AIBN, Bu_3SnH (slow addition), PhMe, reflux, 45% (**19**); Et_3B , TTMSS, 35% (**19**); $(\text{Me}_3\text{Sn})_2$, *tert*-BuPh, reflux, 18% (**20**), 65% (**19**).

radical position, and none on the 2-position of the quinazolinone, and these results indicated that the rate of cyclisation was not favourable compared to reduction with Bu_3SnH . Therefore, hexamethylditin $[(\text{Me}_3\text{Sn})_2]$ was used so that the intermediate radical (cf. **9** in Scheme 1) was not reduced. The reaction was repeated with $(\text{Me}_3\text{Sn})_2$ which resulted in a small amount of the cyclised product **20** (18%) as well as uncyclised **19** (65%) as the major compound.

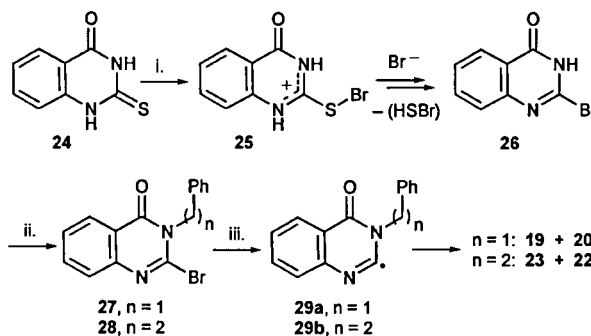
The analogous six-membered ring aryl radical cyclisation using precursor **17** gave an excellent yield of the cyclised product **22** (92%) with no reduction using $(\text{Me}_3\text{Sn})_2$ (Scheme 4). The reaction with Bu_3SnH again gave largely the uncyclised reduced product **23** (55%) but did also yield a small amount of the cyclised product **22** (8%). We have observed before that 5-ring cyclisation of radicals onto heteroarenes is difficult due to strain whereas 6-ring cyclisation is more favourable.^{8,10,16,32} Therefore, the higher yields of cyclisation from **17** relative to **16** are expected. The results indicate that the oxidative route is dominant (*i.e.* loss of hydrogen from the π -radical intermediate **10**) for cyclisation onto quinazolinones as observed for other heteroarenes.



Scheme 4 Reagents and conditions: i, $(\text{Me}_3\text{Sn})_2$, *tert*-BuPh, reflux, 92% (**22**), 0% (**23**); Et_3B , PhMe, r.t., Bu_3SnH (fast addition), 8% (**22**), 55% (**23**).

3H-4-Oxoquinazolin-2-yl radical cyclisation

As shown in Scheme 5 we envisaged an alternative route to polycyclic quinazolinones by cyclisation of 3H-4-oxoquinazolin-2-yl radicals onto pendant side chains attached to the 3-position instead of cyclisation of side chain radicals onto the quinazolinone moiety. 3H-4-Oxoquinazolin-2-yl radicals,³³ generated photochemically from 3-(but-1-en-4-yl)-3H-quinazolin-4-one, have been reported to undergo 5-*exo* cyclisation onto the pendant alkene.^{33a} The procedure however was not suitable for synthetic application. During our studies, a synthesis of luotonin A analogues using 3H-4-oxoquinazolin-2-yl radicals was reported.^{33b}



Scheme 5 Reagents and conditions: i, Br_2 , EtOH, 50% (**26**); ii, NaH, DMF, BnBr, 46% (**27**); NaI, $\text{PhCH}_2\text{CH}_2\text{Br}$, 6% (**28**); iii, Bu_3SnH , Et_3B , slow addition, 62% (**19**); Bu_3GeH , Et_3B , slow addition, 41% (**19**); $(\text{Me}_3\text{Sn})_2$, *tert*-BuPh, reflux, 41% (**19**), 27% (**20**); **28**: $(\text{Me}_3\text{Sn})_2$, *tert*-BuPh, reflux, 0% (**23**), 97% (**22**).

The plan of our protocol was to alkylate 2-bromo-3*H*-quinazolin-4-one to provide suitable radical precursors (Scheme 5). 2-Bromo-3*H*-quinazolin-4-one **26** was prepared by an adapted literature procedure from 2-mercapto-3*H*-quinazolin-4-one **24**.³⁴ Alkylations with activated halides, *e.g.* benzyl bromide, allyl bromide and methyl iodide were successful but alkylations with unactivated halides were very poor or failed. Alkylation with activated propargyl halides has also recently been reported.^{33b} A maximum yield (6%) of alkylation was obtained with 2-phenylethyl bromide and alkylation with 3-phenylpropyl bromide failed. Alkylation with the corresponding triflates failed to give improved results. We suggest that the anion of 2-bromo-3*H*-4-oxoquinazoline is too stabilised and hence not nucleophilic enough to react with unactivated halides.

Various protocols were attempted to circumvent the alkylation problem. For instance, the successful bromination suggested that other 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones with the 3-alkyl side chain in place could also be converted to the corresponding 2-bromo compounds. In order to test this hypothesis, 2-(phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **30** was prepared by ring synthesis using the reaction between 2-(methoxycarbonyl)phenyl isothiocyanate and amines.³⁵ The structure of **30** was confirmed by X-ray crystallography (Fig. 1). However, the bromination procedure yielded only the corresponding disulfide instead of the 2-bromoquinazolinone **28**.

The mechanism of these brominations is unknown. The most likely intermediate is the sulfenyl bromide **25** which can either lose a proton and undergo substitution with bromide, or undergo direct substitution with bromide. The intermediate sulfenyl bromide from 2-(phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one cannot lose a proton which is possibly significant in directing the reaction towards disulfide formation. Examples from the literature show bromoimine formation for thioureas with *N,N'*-substitution (*i.e.* can lose a proton)³⁶ and disulfides and sulfides from thioamides.³⁷

We carried out radical cyclisations with the precursors **27** and **28** (Scheme 5). As observed for the cyclisation of precursor **16**, the 5-membered ring cyclisation from **27** was unfavourable with both Bu₃SnH and Bu₃GeH and yielded only the reduced uncyclised product **19**. Radical abstraction of hydrogen from Bu₃GeH is

20 times slower than from Bu₃SnH which would favour cyclisation over reduction,³⁸ but still only reduction was observed from the intermediate **29a**. When (Me₃Sn)₂ was used, a moderate yield of cyclisation product (27%) was obtained but reduction was still the major route (41%). The 6-membered ring cyclisation from precursor **28** via **29b** gave a quantitative yield of cyclisation to **22** with none of the reduced compound **23** formed. This cyclisation could either proceed by 5-*exo* cyclisation followed by a neophyl rearrangement or directly by 6-*endo* cyclisation. The results show that radical cyclisation can be used onto, or from, the quinazolinone moiety, but that a useful method of synthesis of the 2-bromoquinazolinones is still required. Addition of 3*H*-4-oxoquinazolin-2-yl radicals onto isonitriles has also recently been reported.^{33b}

Alkyl radical cyclisation

Several methods have been used for the synthesis of both deoxyvasicinone **2** and mackinazolinone **3** but none involving radicals.³⁹ Our protocol using cyclisation of an alkyl radical onto 3*H*-quinazolin-4-one rings was aimed at the synthesis of both natural products (Scheme 6). Routine alkylation yielded the required radical precursors **31a,b**. An initial study with Bu₃SnH using precursor **31a** yielded only reduced uncyclised product **33a** (78%). The rate of cyclisation of the alkyl radical is obviously slow, and it is intercepted by Bu₃SnH to yield the respective reduced uncyclised product **33a**. Therefore, (Me₃Sn)₂ was used to facilitate cyclisation which gave moderate yields of deoxyvasicinone **2** and mackinazolinone **3**.

The use of Et₃B mediated reactions gave better yields of both **2** and **3** (Scheme 6). We suggest that the ethyl radical generated from the reaction between Et₃B and oxygen is able to abstract iodine from the radical precursors **31a,b** to yield alkyl radicals and ethyl iodide, which is lost from the reaction. The hydrogen in the π -radical intermediates (*cf.* **10**) is also most likely abstracted by ethyl radicals to facilitate rearomatisation.⁴⁰ Unusually, some cyclised reduced material **32a,b** was obtained suggesting disproportionation was also taking place. GCMS analysis of the crude product from the Et₃B facilitated reaction with **31a** indicated traces (*ca.* 5%) of 2-ethyl-3-propyl-3*H*-quinazolin-4-one and

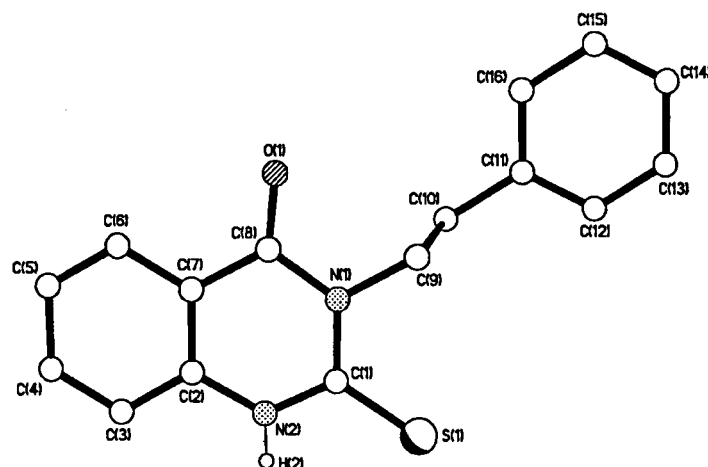
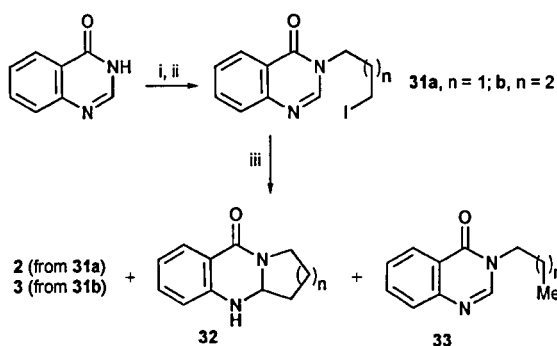


Fig. 1 X-Ray structure of 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **30** with atom labelling.



Scheme 6 Reagents and conditions: i, NaH, DMF, a. 1-chloro-3-iodopropane, 51%; b. 1-chloro-4-iodobutane, 65%; ii, NaI, acetone, reflux, 53% (31a), 67% (31b); iii, (Me₃Sn)₂, *tert*-BuPh, reflux, hv: a. 31a gave 20% (2), 13% (32a) and 6% (33a); b. 31b gave 30% (3), 23% (32b) and 0% (33b); Et₃B (20 equiv.), *tert*-BuPh, air (yields by ¹H NMR analysis): a. 31a gave 40% (2), 10% (32a) and 30% (33a); b. 32b gave 61% (3), 23% (32b) and 0% (33b).

3-pentyl-3*H*-quinazolin-4-one indicating addition of ethyl radicals to intermediates. No uncyclised reduced material 33b was observed for the 6-ring cyclisation of 31b. Again, this provides evidence that 5-ring cyclisation onto heteroarenes is strained and that 6-ring cyclisation (84% of cyclised products) is more favourable.

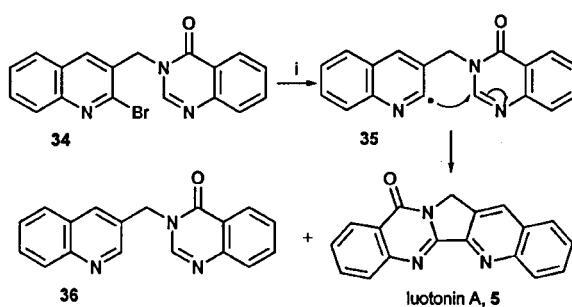
Heteroaryl radical cyclisation

During our studies, Pd(0) catalysed cyclisations were reported for 2-bromoindole⁴¹ and 2-bromoquinoline^{41,42} moieties onto the 2-position of quinazolin-4-one to yield rutaecarpine in poor yield (24% maximum) and luotonin A in good yield (86%) respectively.

Luotonin A 5. The luotonins make up a group of pyrrolo-quinazolino-quinoline alkaloids of which the pentacyclic luotonins A 5, B 6 and E 7 are of most interest. The luotonins are used in traditional Chinese medicine and are reported to exhibit activity against a range of ailments including rheumatism, inflammation, influenza, hepatitis and leukemia.⁴³ Luotonin A has been reported to show activity as an antitumour compound and is an inhibitor for human DNA topoisomerase I.⁴³ The compounds were isolated some ten years ago⁴ and luotonin A has been a popular synthetic target.^{43,44} Two radical syntheses of luotonin A have been reported; a radical domino cyclisation reaction using vinyl radical cyclisation onto nitriles⁴⁵ and a bimolecular reaction involving radical addition onto isonitriles.^{33b}

The synthesis of luotonin A 5 using 2-quinolinyl radicals was carried out as a further example of cyclisation onto the quinazolinone moiety (Scheme 7). The use of 2-quinolinyl radicals in cyclisation has two literature precedents; synthesis of camptothecin using cyclisation of 2-quinolinyl radicals onto a pyridone moiety²⁹ and synthesis of 10,11-methylene-14-azaxamptothecin and 14-azaxamptothecin using cyclisation of 2-quinolinyl radicals onto 3*H*-pyrimidin-4-one moieties.³⁰ These cyclisations also proceeded by 'oxidative cyclisation' as observed for the 3*H*-quinazolin-4-ones.

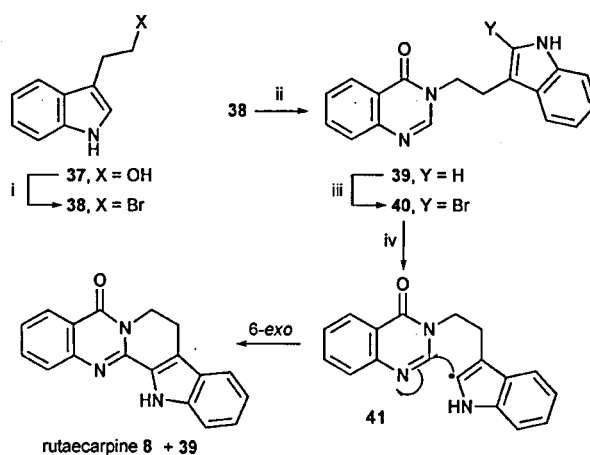
The required starting material 34 was prepared by a literature procedure from 2-chloroquinoline-2-carbaldehyde⁴⁶ and reacted



Scheme 7 Reagents and conditions: i, (Me₃Sn)₂, *tert*-BuPh, reflux, hv: 51% (5), 15% (36); Et₃B (20 equiv.), PhMe, r.t., air: Bu₃SnH (fast addition), 0% (5), 53% (36) Bu₃SnH (slow addition), 14% (5), 32% (36); Bu₃GeH (fast addition), 18% (5), 11% (36).

under several radical conditions. Unusually, the yield from 5-*exo* cyclisation was significant. The use of (Me₃Sn)₂ gave a reasonable yield (53%) of luotonin A 5 but also some of the reduced product 36. The yield was high in comparison to the 5-*exo* cyclisation of the phenyl analogue 16. Luotonin A was even obtained with Bu₃SnH and Bu₃GeH, clearly indicating that the cyclisation is more favourable for 2-quinolinyl radicals as compared to phenyl radicals. The yield was not as high as the Pd(0)-catalysed cyclisation⁴² but further optimisation could improve the yield.

Rutaecarpine 8. Rutaecarpine 8 has been synthesised by a wide variety of protocols but none involving radicals.⁴⁷ Our synthesis of rutaecarpine uses indol-2-yl radical cyclisation onto the quinazolinone motif as a further example of natural product synthesis using the general protocol (Scheme 8). Indol-2-yl radicals have been previously used in radical cyclisation onto pendant 1- ω -alkenes⁴⁸ and -arenes⁴⁹ and in H-translocation reactions towards the synthesis of mitomycin.⁵⁰



Scheme 8 Reagents and conditions: i, PBr₃, DCM, 56% (38); ii, *tert*-BuOK, DMF, 3*H*-quinazolin-4-one, 39% (39); iii, NBS, DCM, 0 °C, 30 min, 38% (40); iv, (Me₃Sn)₂, *tert*-BuPh, reflux, hv: 55% (8), 0% (39); Et₃B (20 equiv.), PhMe, r.t., air: Bu₃SnH (slow addition), 15% (8), 57% (39).

The preparation of the 2-bromoindole part of the precursor proved troublesome even with protection of the side chain and

the NH. The use of NBS has been reported in the literature but the reaction is very sensitive, and can be adversely affected by the NH and side chain groups.^{48,49,51} We finally used an adapted literature procedure⁴¹ whereby the 3*H*-quinazolin-4-one moiety was used as the 'protective group' for the indole side chain (*i.e.* 39). The bromination was rapid and short reaction times and low temperature gave the best yields of the 2-bromoindoles precursor 40. As reported in the literature for 2-bromoindoles,^{48,49,51,52} decomposition of the product was a problem until it was purified. The free indole-NH did not interfere and was therefore not protected. A blank reaction between NBS and 3-methylquinazolin-4-one gave no reaction after two days indicating that in the NBS reaction with 39, bromination of the quinazolinone ring is unlikely to be the cause of the decomposition.

3-[2-(1*H*-Indol-3-yl)ethyl]-4(3*H*)-quinazolinone 39 was prepared by alkylation of 4(3*H*)-quinazolinone with 3-(2-bromoethyl)-1*H*-indole 38 which was prepared by bromination of tryptophol 37.

Radical cyclisation of the precursor 40 gave the predicted 6-*exo* cyclisation of the intermediate radical 41 to yield rutaecarpine 8. Only cyclisation was obtained when (Me₃Sn)₂ was used and even reductive conditions with Bu₃SnH yielded a small amount of cyclisation product. The 6-*exo* cyclisation yields were similar to the equivalent cyclisation with aryl radicals (see Scheme 4). Longer reactions times led to decomposition.

Acyl radicals—synthesis of tryptanthrin

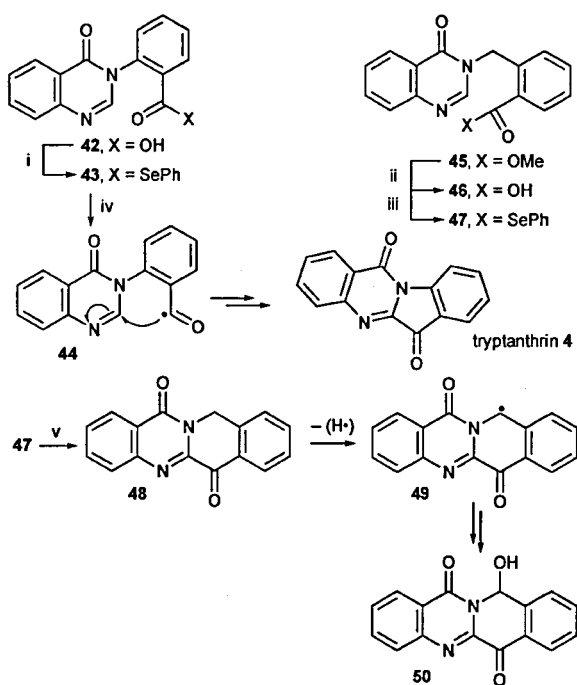
Tryptanthrin has been synthesised by a range of protocols.^{3,6,53}

We prepared an authentic sample of tryptanthrin 4 by a literature procedure in order to obtain full spectroscopic data for comparison.⁵³

Aromatic acyl radical cyclisation has recently been shown to be a useful synthetic technique.^{17–19,54} Although 5-membered ring cyclisation was reported to be unsuccessful,¹⁹ we have shown that 5-ring cyclisation onto the 3*H*-quinazolin-4-one moiety was possible (*e.g.* the luotonin synthesis). Therefore, we carried out the syntheses as shown in Scheme 9. The aryl-CO bond in the intermediate acyl radical 44 is strong enough to avoid decarbonylation which is a rapid reaction for alkyl-CO radicals.⁵⁵ However, it is possible that we failed to isolate products resulting from CO loss.

The starting material 42 was prepared in one step by a literature procedure⁵⁶ and converted to the acyl selenide 43 by standard procedures.¹⁶ Several conditions were used based on literature reports.^{17–19,54} The highest yield (15%) was obtained by photolysis at r.t. Although the yield is poor, we believe this is the first example of a 5-*exo* acyl radical cyclisation onto a heterocycle. When AIBN was added to the reaction, an intractable mixture was obtained. Heating under reflux was not required and UV photolysis alone was enough to facilitate the reaction, presumably by homolysis of the carbonyl-SePh bond. In a blank reaction, heating under reflux in benzene yielded only unaltered starting material after 24 h. The mechanism is unclear, other than 5-*exo* acyl radical cyclisation followed by hydrogen abstraction from the resulting π -radical intermediate. Large amounts of diphenyl diselenide were isolated indicating CO–Se bond homolysis.

We also investigated the 6-membered ring cyclisation because these had proved to be more successful than the 5-ring cyclisations



Scheme 9 Reagents and conditions: i, Bu₃P, PhSeSePh, DCM, 73% (42); ii, LiOH, EtOH, H₂O; iii, Bu₃P, PhSeSePh, DCM, 68% (47); iv, (Me₃Sn)₂, *tert*-BuPh, reflux, hv, 3% (4); PhH, r.t., hv, 12 h, 15% (4); PhH, reflux, hv, 10 h, 11% (4); AIBN, PhH, reflux, hv, 0% (4); v, (Me₃Sn)₂, PhH, reflux, hv, 39% (50).

(Scheme 9). The acyl radical precursor 47 was prepared by standard procedures. The ester 45 was synthesised by alkylation of 3*H*-quinazolin-4-one with methyl 2-(bromomethyl)-benzoate. Cyclisation using Et₃B only, UV photolysis only and slow addition of TTMSS with Et₃B as initiator all gave intractable mixtures. However, reaction with (Me₃Sn)₂ gave a moderate yield of the unusual product 50 along with an intractable mixture of other products. The structure of the hydroxylated product 50 was confirmed by X-ray crystallography (Fig. 2). The product indicated 6-ring cyclisation as expected but that the product 48 was unstable to the reaction conditions and was readily oxidised introducing an OH group onto the newly formed ring.

Analogous reactions with 2-indolyl acyl radicals have yielded a range of unexpected products which included a 'quinone' product caused by oxidation of the benzylic methylene during the reaction.^{17,18} 2-Cyanoprop-2-yl radicals from the breakdown of AIBN were proposed as the abstracting radicals. In our reaction, no AIBN is present so we suggest that any of the intermediate radicals (*e.g.* intermediate acyl or π -radical, PhSe \cdot) can abstract the benzylic hydrogen, which is a favourable process, to form a stable radical intermediate 49. Although air was excluded, traces of oxygen are likely to be present and to react rapidly with trimethylstannyl radicals to form a peroxy radical (Me₃SnOO \cdot).^{45,57} Combination of the peroxy radical with the benzylic radical 49 would yield a peroxide which could easily break down to yield 50. Alternatively, a standard auto-oxidation mechanism with the traces of oxygen present could explain this unusual product.

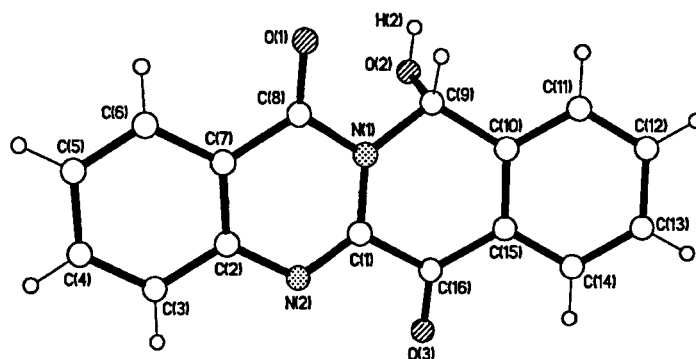


Fig. 2 X-Ray structure of 11-hydroxy-11H-isoquinolino[3,2-*b*]quinazolin-6,13-dione **50** with atom labelling.

Conclusions

Our results show that radical cyclisation on the quinazolinone moiety can be used for synthesis. The results show that radical cyclisation is also favourable for radicals centred on the 2-position of the quinazolinone moiety but that a better method for the synthesis of 2-bromoquinazolinones is still required.

Experimental

General

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from CaCl_2 and dichloromethane which was distilled from CaH_2 . Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil. A 2.5 M solution of *n*-butyl lithium in hexane was used. A solution of Et_3B in hexane (1.0 M) was used in all cases. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 instrument, or ^1H (250 MHz) spectra were obtained using a Bruker AC-250 spectrometer. Spectra were obtained from solutions in CDCl_3 with TMS as the internal standard for ^1H NMR spectra and deuteriochloroform as the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Assignments were made using a combination of COSY and HMQC analysis. Mass spectra were recorded on a Jeol SX102 high resolution mass spectrometer or were run by the EPSRC MS Service at the University of Wales, Swansea. GCMS was carried out on a Fisons 8000 series mass spectrometer using a 15 m \times 0.25 mm DB-5 GC column. TLC using silica as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}), and TLC using alumina as absorbent was carried out with aluminium backed plates coated with neutral aluminium oxide (Merck 150 F_{254} , TypeT). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified. Column chromatography using alumina was carried out with Aldrich aluminium oxide, activated neutral,

Brockmann 1, STD Grade, 150 mesh size. Prep-TLC was carried out using aluminium oxide (Merck 60 PF_{254} , Type E). Bu_3GeH was prepared from GeCl_4 by a known procedure.³⁸

General procedure for alkylation of 3H-quinazolin-4-ones. **3-(2-Iodobenzyl)-3H-quinazolin-4-one 16.** Potassium *tert*-butoxide (1.35 g, 12 mmol) was added to 3H-quinazolin-4-one **13** (1.17 g, 8 mmol) in dry DMF (50 cm^3) and the mixture stirred for 1 h under an atmosphere of nitrogen. 2-Iodobenzyl bromide **14** (2.84 g, 9.6 mmol) was added and the reaction mixture stirred for a further 16 h. The mixture was diluted with DCM and washed with H_2O and brine. The organic layer was dried and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (2 : 1) as eluent yielding 3-(2-iodobenzyl)-3H-quinazolin-4-one **16** as pale yellow crystals (1.82 g, 5.0 mmol, 63%), mp 94–95 °C; Found: M^+ , 362.9987. $\text{C}_{15}\text{H}_{11}\text{IN}_2\text{O}$ requires 362.9989; ν_{max} (thin film)/ cm^{-1} 3055, 1689, 1469, 1230, 962 and 734; δ_{H} 5.71 (2 H, s, CH_2), 6.93 (1 H, ddd, *J* 7.9, 7.4, 1.7, BnH-4), 7.09 (1 H, dd, *J* 7.9, 1.8, BnH-3), 7.22 (1 H, ddd, *J* 8.0, 7.4, 1.2, BnH-5), 7.45 (1 H, ddd, *J* 8.0, 5.5, 1.7, 6-H), 7.75–7.64 (2 H, m, 7,8-H), 7.81 (1 H, dd, *J* 8.0, 1.2, BnH-6), 8.11 (1 H, s, 2-H) and 8.26 (1 H, dd, *J* 8.0, 1.6, 5-H); δ_{C} 54.90 (CH_2), 98.6 (C), 122.1 (4a-C), 126.9 (5-C), 127.5 (6-C), 127.6 (8-C), 128.9 (CH), 129.1 (CH), 129.9 (CH), 134.5 (7-C), 137.7 (8a-C), 139.9 (CH), 146.4 (2-C), 148.0 (C) and 161.1 (4-C); *m/z* (EI) 252 (M^+ , 98%), 129 (43), 107 (41), 90 (100), 89 (77), 76 (51), 63 (58), 50 (42) and 40 (85).

3-[2-(Bromophenyl)ethyl]-3H-quinazolin-4-one 17. The general procedure for alkylation with 2-(2-bromophenyl)ethyl methanesulfonate **15** (4.90 g, 18.6 mmol) for 48 h was used to yield 3-[2-(bromophenyl)ethyl]-3H-quinazolin-4-one **17** as colourless crystals (1.93 g, 5.9 mmol, 38%), mp 119–120 °C; Found: M^+ , 328.0206. $\text{C}_{16}\text{H}_{13}^{79}\text{BrN}_2\text{O}$ requires 328.0206; ν_{max} (thin film)/ cm^{-1} 3423, 1972, 1609, 1470, 1069, 1027 and 773; δ_{H} 3.25 (2 H, t, *J* 7.2, CH_2), 4.25 (2 H, t, *J* 6.9, NCH_2), 7.22–7.07 (3 H, m, ArH), 7.58–7.48, 4.25 (2 H, m, ArH), 7.78–7.64 (3 H, m, ArH) and 8.34 (1 H, ddd, *J* 8.1 1.5 0.5, 5-H); δ_{C} 35.3 (CH_2), 46.7 (NCH_2), 122.0 (C), 124.4 (C), 126.6 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.9 (CH), 131.4 (CH), 133.1 (CH), 134.2 (CH), 136.7 (C), 146.4 (CH), 148.1 (C) and 161.1 (C); *m/z* (EI) 330/328 (M^+ , 52/51%), 251 (49), 249 (56) and 52 (14).

Cyclisation reactions of 3-(2-iodobenzyl)-3H-quinazolin-4-one 16.

General procedure for Bu₃SnH reactions using Et₃B as initiator. A solution of Bu₃SnH (0.76 g, 2.6 mmol) and 3-(2-iodobenzyl)-3H-quinazolin-4-one (0.44 g, 1.2 mmol) in dry toluene (40 cm³) was deoxygenated under an atmosphere of nitrogen and stirred for 1 h. Triethylborane (3.6 cm³, 3.6 mmol) was added *via* a needle through a septum; the needle was then left open to allow air (oxygen) to enter the reaction and the mixture stirred for 1 h. More triethylborane (3.6 cm³, 3.6 mmol) was added and the reaction mixture stirred for a further 10 h. Dilute hydrochloric acid was added to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum to remove tributyltin residues. The aqueous layer was basified with sodium hydroxide to pH 14 and extracted with DCM. The combined organic layers were dried and evaporated under reduced pressure yielding the reduced product 3-benzyl-3H-quinazolin-4-one 19 as colourless crystals (0.27 g, 1.2 mmol, 96%), mp 116–117 °C (lit.³⁸ 117–118 °C); ν_{max} (thin film)/cm⁻¹ 3419, 1675, 1609, 1559, 1473, 1369, 1332, 1161, 1026, 773, 709, 694 and 645; δ_{H} 5.08 (2 H, s, CH₂), 7.24–7.23 (5 H, m), 7.48 (1 H, ddd, *J* 8.2, 6.3, 1.8, 6-H), 7.74–7.68 (2 H, m, 7,8-H), 8.11 (1 H, s, 2-H) and 8.32 (1 H, dd, *J* 8.2, 2.0, 5-H); δ_{C} 49.6 (CH₂), 122.2 (4a-C), 126.9 (5-H), 127.4 (6-H), 127.5 (8-H), 128.0 (CH), 128.3 (CH), 129.0 (CH), 134.3 (7-H), 135.8 (C), 146.4 (2-H), 148.0 (8a-C) and 161.1 (4-C). The data were identical to that in the literature.³⁸ The procedure was repeated using TTMSS in place of Bu₃SnH to yield 3-benzyl-3H-quinazolin-4-one 19 (35%).

General procedure for slow addition of Bu₃SnH reactions using Et₃B as initiator. The general procedure for Bu₃SnH reactions using Et₃B as initiator was repeated except that Bu₃SnH was added by a syringe pump over 6 h to give 3-benzyl-3H-quinazolin-4-one 19 (30%).

General procedure for slow addition of Bu₃SnH reactions using AIBN as initiator. The general procedure for Bu₃SnH reactions using Et₃B as initiator was repeated except that AIBN (0.25 molar equiv.) was used as initiator and the reaction was heated under reflux for 6 h to yield 3-benzyl-3H-quinazolin-4-one 19 (45%).

General procedure for reactions using photolysis and hexamethylditin. A solution of 3-(2-iodobenzyl)-3H-quinazolin-4-one 16 (0.36 g, 1.0 mmol) and hexamethylditin (0.99 g, 3.0 mmol) in *tert*-butylbenzene (20 cm³) in a two-necked pyrex flask (5 × 1 cm and 25 cm high, wall thickness = 1 mm), was purged with nitrogen for 30 min. The mixture was irradiated with a combined 300 W sunlamp at 150 °C for 10 h. The reaction mixture was cooled to room temperature, diluted with MeOH and evaporated under reduced pressure to a small volume. The residue was purified using column chromatography with light petroleum as eluent to remove the *tert*-butylbenzene. A precipitate of polymeric dimethyltin was produced. The product was eluted with ethyl acetate and further worked-up as for the general procedure for Bu₃SnH reactions using Et₃B as initiator. 3-Benzyl-3H-quinazolin-4-one 19 and cyclised 12H-isoindolo[1,2-*b*]quinazolin-10-one 20 were obtained as an inseparable white solid. Analysis using ¹H NMR spectroscopy showed 19 (65%) and 20 (18%). 12H-Isoidolo[1,2-*b*]quinazolin-10-one 20 was identified in the mixture and therefore not fully

characterised. δ_{H} 5.19 (2 H, s, CH₂), 7.28–7.35 (3 H, m), 7.51 (1 H, ddd, *J* 8.0, 8.0, 1.6, 7-H), 7.81 (1 H, ddd, *J* 8.0, 8.0, 1.6, 8-H), 7.85 (1 H, dd, 8.0, 1.6, 6-H), 8.21 (1 H, d, *J* 7.2, 4-H) and 8.41 (1 H, dd, *J*, 8.0, 1.6, 9-H); δ_{C} 49.6 (CH₂), 120.6 (C), 123.4 (CH), 123.5 (CH), 126.4 (CH), 126.4 (CH), 127.3 (CH), 128.8 (CH), 132.3 (CH), 132.6 (C), 134.2 (CH), 139.6 (C), 149.4 (C), 154.9 (C) and 160.5 (C). The data were the same as that in the literature.³⁹ GC-MS analysis showed the ratio of the two products to be in the ratio 4 : 1 of the reduced product and cyclised product: 12H-isoidolo[1,2-*b*]quinazolin-10-one; *R*_T 22.8 min, *m/z* 234 (M⁺, 95%), 205 (24), 179 (15), 151 (16), 130 (25), 102 (28), 91 (100) and 77 (20) and 3-benzyl-3H-quinazolin-4-one; *R*_T 24.5 min, *m/z* 236 (M⁺, 51%), 130, (37), 91 (100) and 65 (27).

3-(2-Deuterio)benzyl-3H-quinazolin-4-one. The general procedure for reductive reactions with Et₃B with Bu₃SnD as reductant were used with 3-(2-iodobenzyl)-3H-quinazolin-4-one 16 to yield 3-(2-deuterio)benzyl-3H-quinazolin-4-one as colourless crystals (41%); mp 100–101 °C (Found: M⁺, 238.1084. C₁₅DH₁₁N₂O requires 238.1085); ν_{max} (thin film)/cm⁻¹ 3421, 2359, 1670, 1610, 1471, 1396, 1153 and 773; δ_{H} 5.21 (2 H, s, CH₂), 7.38–7.29 (4 H, m, PhH), 7.52 (1 H, dd, *J* 8.1, 1.4, 6-H), 7.79–7.69 (2 H, m, 7,8-H), 8.12 (1 H, s, 2-H) and 8.34 (1 H, ddd, *J* 8.1, 2.1, 0.6, 5-H); δ_{C} 49.7 (CH₂), 104.1 (CD), 122.2 (4a-C), 126.9 (5-C), 127.4 (6-C), 127.6 (CH), 128.0 (CH), 128.3 (CH), 128.9 (CH), 129.1 (CH), 134.3 (CH), 135.7 (C), 146.3 (5-C), 148.1 (8a-C) and 161.1 (4a-C); *m/z* (EI) 237 (M⁺, 48%), 235 (21), 130 (33), 92 (100), 91 (75), 65 (21) and 51 (23).

Cyclisation reactions of 3-[2-(bromophenyl)ethyl]-3H-quinazolin-4-one 17.

Hexamethylditin. The general procedure for reactions using photolysis and hexamethylditin yielded 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one 22 as colourless crystals (92%), mp 195–197 °C (lit.⁶⁰ 196 °C); Found: M⁺, 249.1025. C₁₆H₁₂N₂O requires 249.1022; ν_{max} (thin film)/cm⁻¹ 3421, 1682, 1590, 1556, 1471, 1150, 762 and 692; δ_{H} 3.06 (2 H, t, *J* 6.4, CH₂), 4.35 (2 H, t, *J* 6.4, NCH₂), 7.22–7.13 (1 H, m, ArH), 7.43–7.37 (3 H, m, ArH), 7.71–7.69 (2 H, m, ArH), 8.25 (1 H, d, *J* 7.6, ArH) and 8.43–8.40 (1 H, m, ArH); δ_{C} 27.4 (CH₂), 39.5 (NCH₂), 120.7 (C), 126.5 (CH), 126.8 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 129.5 (C), 131.7 (CH), 134.2 (CH), 137.0 (C), 147.7 (C), 149.3 (C) and 161.6 (CO); *m/z* (EI) 249 (M⁺, 17%), 247 (100), 128 (20), 116 (46), 104 (30), 90 (34), 89 (62), 77 (85), 76 (97), 63 (53) and 39 (54). One CH signal was coincident or could not be detected.

Bu₃SnH and Et₃B. The general procedure for Bu₃SnH reactions using Et₃B as initiator yielded an inseparable mixture of 3-[2-(phenylethyl)]-3H-quinazolin-4-one 23 (55%) and 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one 22 (8%). The yields were estimated using ¹H NMR spectroscopic analysis.

3-Benzyl-2-bromo-3H-quinazolin-4-one 27. The general procedure for alkylation of 3H-quinazolin-4-ones (3 h) yielded 3-benzyl-2-bromo-3H-quinazolin-4-one 27 as colourless crystals (46%), mp 109–111 °C; Found: M⁺, 315.0128. C₁₅H₁₁BrN₂O requires 315.0128; ν_{max} (thin film)/cm⁻¹ 3457, 3064, 1653, 1558, 1494, 1430, 1339, 1234, 1134, 1074, 1023, 901 and 819; δ_{H} 5.56 (2 H, s, CH₂), 7.29–7.37 (5 H, m, PhH), 7.52 (1 H, ddd, *J* 8.2, 8.1, 2.0, 7-H), 7.66 (1 H, dd, *J* 8.2, 1.2, 8-H), 7.79 (1 H, ddd, *J* 8.1, 8.0, 1.2, 6-H) and 8.27 (1 H, dd, *J* 8.0, 2.0, 5-ArH); δ_{C} 51.8 (CH₂), 120.5 (4a-C),

126.9 (6/8-CH), 127.5 (CH), 127.6 (6/8-CH), 127.7 (5-CH), 127.8 (CH), 127.9 (7-CH), 135.1 (CH), 135.4 (C), 136.2 (8a-C), 147.2 (2-C) and 161.6 (4-C); m/z (EI) 318 (M^+ , 15%), 317 (100), 315 (100), 237 (75), 235 (39) and 52 (79).

2-Bromo-3-(phenylethyl)-3H-quinazolin-4-one 28. The general procedure for alkylation of 3H-quinazolin-4-ones (12 h) yielded 2-bromo-3-(phenylethyl)-3H-quinazolin-4-one as colourless crystals (6%), mp 109–110 °C; Found: M^+ , 328.0206. $C_{16}H_{13}^{79}BrN_2O$ requires 328.0206; mp 195–197 °C; ν_{\max} (thin film)/ cm^{-1} 3060, 2930, 2359, 1866, 1714, 1655, 1621, 1604, 1493, 1452, 1405, 1072, 1028, 938 and 908; δ_H 2.99 (2 H, t, J 7.6, CH_2), 4.37 (2 H, t, J 7.6, NCH_2), 7.26–7.15 (5 H, m, PhH), 7.34–7.30 (1 H, m, 6-H), 7.49 (1 H, d, J 7.6, 8-H), 7.67–7.63 (1 H, m, 7-H) and 8.20 (1 H, d, J 7.6, 5-H); δ_C 34.0 (CH_2), 42.2 (NCH_2), 114.5 (4a-C), 114.9 (CH), 123.1 (8-C), 126.4 (6-C), 128.3 (5-C), 128.4 (CH), 128.9 (CH), 134.8 (7-C), 138.5 (C), 138.7 (C), 151.2 (2-C) and 162.3 (4-C); m/z (EI) 266 (M^+ , 16%), 264 (15), 249 (20), 185 (100), 129 (52), 102 (23), 90 (35) and 40 (53).

Cyclisation reactions of 3-benzyl-2-bromo-3H-quinazolin-4-one 27.

Bu_3SnH and Et_3B . The general procedure for Bu_3SnH reactions using Et_3B as initiator were used with Bu_3SnH added by syringe pump over 6 h and the reaction stirred for a further 5 h. Work-up yielded 3-benzyl-3H-quinazolin-4-one **19** as colourless crystals (0.15 g, 0.62 mmol, 62%). The data were identical to authentic material. A repeat experiment using Bu_3GeH in place of Bu_3SnH gave 3-benzyl-3H-quinazolin-4-one **19** in reduced yield (47%).

Hexamethylditin. The general procedure for reactions using photolysis and hexamethylditin yielded an inseparable mixture of 1H-isoidolo-[1,2-*b*]quinazolin-10-one **20** (27%) and 3-benzyl-3H-quinazolin-4-one **19** (41%). The yields were estimated using 1H NMR spectroscopic analysis.

Cyclisation reactions of 2-bromo-3-(phenylethyl)-3H-quinazolin-4-one 28.

Hexamethylditin. The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded 5,6-dihydroisouino[1,2-*b*]quinazolin-8-one **22** as colourless crystals (97%). The data were identical to authentic material.

Cyclisation reactions of 3-(3-iodopropyl)-3H-quinazolin-4-one 31a.

Hexamethylditin. The general procedure for reactions using photolysis and hexamethylditin with 3-(3-iodopropyl)-3H-quinazolin-4-one **31a** (24 h) yielded: 2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one **2** as colourless crystals (20%), mp 190–192 °C (lit.,⁶¹ 196–198 °C); ν_{\max} (thin film)/ cm^{-1} 3418, 2355, 1651, 1621, 1470, 1385, 1285, 775, 695 and 667; δ_H 2.35–2.23 (2 H, m, CH_2), 3.18 (2 H, t, J 12.6, CH_2), 4.21 (2 H, t, J 11.5, NCH_2), 7.47–7.62 (1 H, m, ArH), 7.76–7.62 (2 H, m, ArH) and 8.28 (1 H, dd, J 12.6, 2.4, ArH); δ_C 19.5 (CH_2), 32.5 (CH_2), 46.5 (NCH_2), 120.4 (C), 126.2 (CH), 126.4 (CH), 126.8 (CH), 134.2 (CH), 149.1 (C), 159.5 (C) and 161.0 (C). 2,3,3a,4-Tetrahydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one **32a** as colourless crystals (12%), mp 187–188 °C (lit.,⁶² 184–185 °C); ν_{\max} (thin film)/ cm^{-1} 3421, 1633, 1503, 1470, 1434, 1337, 1151, 752 and 695; δ_H 2.32–2.29 (2 H, m, 2- CH_2), 3.19 (1 H, t, J 8.0, 1-H), 3.75–3.67 (2 H, m, $CHCH_2$), 4.21 (1 H, dd, J 8.0, 7.2, 1-H), 4.5 (1 H, bs, NH), 5.03 (1 H, dd, J 7.2, 5.6, 3a-H), 6.69

(1 H, d, J 12.9, ArH), 6.92–6.88 (1 H, m, ArH), 7.27–7.24 (1 H, m, ArH) and 7.91–7.87 (1 H, dd, J 12.3, 9.9, ArH); δ_C 21.7 (CH_2), 33.2 ($CHCH_2$), 44.3 (NCH_2), 69.9 (CH), 114.9 (CH), 118.4 (CH), 119.9 (C), 126.8 (CH), 132.9 (CH), 149.1 (C) and 162.2 (C). 3-Propyl-3H-quinazolin-4-one **33a** as colourless crystals (6%). The data were identical with those from an independently prepared authentic sample.

Bu_3SnH and Et_3B . 3-Propyl-3H-quinazolin-4-one **33a** (78%) was the only product.

Et_3B only. The general procedure for Bu_3SnH and Et_3B reactions were used except that the Bu_3SnH was not added. 1H NMR spectral analysis showed 2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one **2** (40%), 2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one **32a** (10%) and 3-propyl-3H-quinazolin-4-one **33a** (30%).

Cyclisation reactions of 3-(3-iodobutyl)-3H-quinazolin-4-one 31b.

(Me_3Sn)₂ and photolysis. The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: 6,7,8,9-tetrahydropyrrolo[2,1-*b*]quinazolin-11-one **3** as colourless crystals (30%), mp 94–95 °C (lit.,⁶³ 96–97 °C); Found: MH^+ , 201.1020. $C_{12}H_{13}N_2O$ requires 201.1022; ν_{\max} (thin film)/ cm^{-1} 3423, 2948, 2110, 1655, 1614, 1565, 1477, 1173, 1102, 990, 870, 771 and 583; δ_H 2.18–1.91 (4 H, m, CH_2CH_2), 3.00 (2 H, t, J 6.6, $NCCH_2$), 4.09 (2 H, t, J 6.3, NCH_2), 7.44–7.40 (1 H, m, ArH), 7.59 (1 H, dd, J 8.3, 0.5, ArH), 7.73–7.69 (1 H, m, ArH) and 8.26 (1 H, dd, J 8.0 1.5, ArH); δ_C 19.3 (CH_2), 22.1 (CH_2), 31.9 (CH_2), 42.3 (CH_2), 120.4 (C), 126.1 (CH), 126.4 (CH), 126.6 (CH), 134.1 (CH), 147.4 (C), 154.9 (C) and 162.2 (C); m/z (EI) 200 (M^+ , 50%), 199 (40), 90 (33), 76 (34), 63 (33), 50 (34) and 41 (90). 5,5a,6,7,8,9-Hexahydropyrrolo[2,1-*b*]quinazolin-11-one **32b** as colourless crystals (23%), mp 128–130 °C (lit.,² 132–133 °C); Found: MH^+ , 203.1180. $C_{12}H_{15}N_2O$ requires 203.1179; ν_{\max} (thin film)/ cm^{-1} 3398, 3058, 2938, 2224, 1632, 1518, 1416, 1218, 1153, 1026, 754 and 692; δ_H 1.52–1.49 (2 H, m), 1.91–1.75 (4 H, m), 2.66–2.59 (1 H, m, 9-H), 4.25 (1 H, m, NH), 4.64–4.59 (1 H, m, 9-H), 4.78 (1 H, dd, J 13.5, 3.1, 5a-H), 6.57 (1 H, d, J 7.1, ArH), 6.79 (1 H, ddd, J 7.8, 2.9, 1.0, ArH), 7.27–7.22 (1 H, m, ArH) and 7.90 (1 H, dd, J 7.8 1.6, ArH); δ_C 22.3 (CH_2), 24.2 (CH_2), 33.4 (CH_2), 42.0 (CH_2), 68.5 (CH), 113.7 (CH), 115.2 (C), 118.8 (CH), 128.7 (CH), 133.4 (CH), 145.9 (C) and 164.3 (C); m/z (EI) 202 (M^+ , 30%), 146 (42), 119 (48), 92 (42), 55 (79) and 41 (100).

Et_3B only. The general procedure for Bu_3SnH and Et_3B reactions were used except that the Bu_3SnH was not added. 1H NMR spectral analysis showed 6,7,8,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-11-one **3** (61%) and 5,5a,6,7,8,9-hexahydropyrrolo[2,1-*b*]quinazolin-11-one **32b** (23%).

Cyclisation of 3-[(2-bromoquinolin-3-yl)methyl]-4(3H)-quinazolinone 34.

(Me_3Sn)₂ and photolysis. The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: luotonin A **5** (51%). All data were the same as reported.⁴⁵ 3-[[Quinolin-3-yl)methyl]-3H-quinazolin-4-one **36**, colourless crystals, mp 252–253 °C; Found: MH^+ , 288.1130. $C_{18}H_{13}N_3O$ requires 288.1131; ν_{\max} (thin film)/ cm^{-1} 3420, 2357, 2107, 1646, 1558, 1450, 1361, 1332, 510 and 454; δ_H 5.39 (2 H, s, CH_2), 7.58–7.53 (2 H, m, ArH), 7.81–7.70 (4 H, m, ArH), 8.10 (1 H, dd, J 8.9, 0.4, ArH), 8.17 (1 H,

d, J 1.8, ArH), 8.35–8.32 (1 H, m, ArH) and 8.99 (1 H, d, J 1.8, ArH); δ_c 47.7 (CH₂), 122.1 (CH), 126.9 (CH), 127.3 (CH), 127.7 (2 \times CH), 127.9 (CH), 128.6 (2 \times C), 129.3 (CH), 130.0 (CH), 134.6 (CH), 135.4 (CH), 145.9 (CH), 147.9 (C), 148.0 (C), 150.1 (CH) and 161.1 (C); m/z (EI) 287 (M⁺, 45%), 270 (42), 132 (100), 115 (70), 89 (20), and 63 (21).

Bu₃SnH and Et₃B. The general procedure for Bu₃SnH reactions using Et₃B as initiator were used with Bu₃SnH added by syringe pump over 5 h and the reaction stirred for a further 5 h to yield luotonin A 5 (14%) and 3-[(quinolin-3-yl)methyl]-3H-quinazolin-4-one 36 (32%). When the Bu₃SnH was added at the beginning of the reaction only 3-[(quinolin-3-yl)methyl]-3H-quinazolin-4-one 36 was obtained (53%).

Bu₃GeH and Et₃B. Luotonin A⁺ (18%) and [(3-quinolin-3-yl)methyl]-3H-quinazolin-4-one 36 (11%) were obtained.

Cyclisation of 3-[2-(2-bromoindol-3-yl)ethyl]-4(3H)-quinazolinone 40.

Bu₃SnH addition. The general procedure for Bu₃SnH reactions using Et₃B as initiator were used with Bu₃SnH added by syringe pump over 12 h to yield rutaecarpine 8 (15%), mp 254–255 °C (lit.⁴¹ 256–257 °C) and 3-[2-(1H-indol-3-yl)ethyl]-4(3H)-quinazolinone 39 (57%), both as colourless crystals. The data for rutaecarpine were the same as those in the literature.⁴¹ The data for 39 were the same as obtained in the previous synthesis.

(Me₃Sn)₂ and photolysis. The general procedure for reactions using photolysis and hexamethylditin (6 h) yielded rutaecarpine (55%) as the only product.

2-(4-Oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester 43. Tributylphosphine (2.5 cm³, 10 mmol) was slowly added to diphenyl diselenide (2.47 g, 7.9 mmol) in anhydrous DCM and the mixture left to stir for 15 min. 2-(4-Oxo-4H-quinazolin-3-yl)benzoic acid 42 (1.40 g, 5.2 mmol) was then added and the reaction stirred for 12 h till no precipitate was visible. The reaction mixture was diluted with DCM and washed with H₂O (3 \times 50 cm³) and brine (50 cm³). The organic layer was dried over MgSO₄ and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum/EtOAc (4:1). The resulting yellow solid was recrystallised from hot EtOH yielding 2-(4-oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester 43 as long yellow needles (1.55 g, 3.8 mmol, 73%); (Found: M⁺, 407.0289. C₂₁H₁₄N₂O₂Se requires 407.0293); mp 234–236 °C; ν_{\max} (thin film)/cm⁻¹ 3165, 2831, 2063, 1798, 1519, 1367, 1118, 960 and 915; δ_H 7.36–7.30 (3 H, m, ArH), 7.42 (1 H, dd, J 9.2 1.6, ArH), 7.55–7.45 (3 H, m, ArH), 7.70–7.66 (1 H, m, ArH), 7.81–7.72 (3 H, m, ArH), 8.02 (1 H, s, 2-H), 8.14 (1 H, dd, J 9.2 1.6, ArH) and 8.34–8.32 (1 H, m, ArH); δ_c 122.3 (C), 125.9 (C), 127.1 (5-C), 127.6 (6-C), 127.7 (CH), 129.2 (CH), 129.4 (2 \times CH), 129.4 (CH), 129.8 (CH), 130.1 (CH), 133.6 (C), 133.7 (CH), 134.6 (CH), 136.0 (2 \times CH), 136.9 (C), 145.6 (2-C), 148.0 (C), 160.7 (4-C) and 192.7 (CO); m/z (EI) 407 (M⁺, 100%), 251 (39), 235 (55) and 223 (46).

Radical reactions of 2-(4-oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-methyl ester 43.

UV and reflux. -(4-Oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester 43 (0.24 g, 0.59 mmol) was heated under reflux in benzene (20 cm³) for 12 h under UV irradiation. The solvent

was removed under vacuum and the crude product was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (2 : 1) yielding tryptanthrin 4 as yellow crystals (0.02 g, 0.07 mmol, 13%), mp 213–214 °C (lit.⁵³ 215–217 °C); Found: M⁺, 249.0659. C₁₅H₉N₂O₂ requires 249.0660; δ_H 7.43 (1 H, t, J 8.0, ArH), 7.68 (1 H, t, J 8.0, ArH), 7.79 (1 H, t, J 8.0, ArH), 7.86 (1 H, t, J 8.0, ArH), 7.92 (1 H, d, J 8.0, ArH), 8.04 (1 H, d, J 8.0, ArH), 8.44 (1 H, d, J 8.0, ArH) and 8.64 (1 H, d, J 8.0, ArH); δ_c 118.0 (CH), 122.0 (C), 123.8 (C), 125.4 (CH), 127.2 (CH), 127.6 (CH), 130.2 (CH), 130.7 (CH), 135.1 (CH), 138.3 (CH), 146.4 (C), 146.7 (C), 158.1 (C) and 171.1 (2 \times CH); m/z (EI) 248 (M⁺, 51%), 220 (22), 130 (28), 102 (54), 90 (100), 76 (81), 63 (55) and 50 (74). The data were identical to the literature data⁵³ and those of authentic material. Repeating the reaction for 10 h gave a yield of 11% of 4. The procedure was repeated using the same conditions but with the addition of AIBN (2.0 equiv.) for 8 h. An intractable mixture was obtained. A blank reaction with no sunlamp photolysis or added AIBN, in benzene heated under reflux for 24 h gave a quantitative recovery of unaltered starting material 43.

(Me₃Sn)₂, sunlamp. The reaction between 2-(4-oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester 47 (0.29 g, 0.72 mmol) and hexamethylditin (0.70 g, 2.15 mmol) was carried out in *tert*-butylbenzene (20 cm³). The mixture was heated under reflux and irradiated with a sunlamp for 4 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolinone products into the aqueous layer. The aqueous layer was washed with light petroleum to remove tin residues. The aqueous layer was basified with sodium hydroxide to pH 14 and extracted with DCM. The combined organic layers were dried and evaporated under reduced pressure. The residue was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (2 : 1) yielding tryptanthrin 4 (5 mg, 0.02 mmol, 3%).

Sunlamp. When the sunlamp irradiation alone was used for 30 min, the highest yield of tryptanthrin (15%) was obtained.

2-[(4-Oxo-4H-quinazolin-3-yl)methyl]benzoic methyl ester 45. *N*-Bromosuccinimide (19.0 g, 107.1 mmol, 1.5 equiv.), methyl 2-methylbenzoate (10.0 cm³, 71.4 mmol) and AIBN (1.16 g, 7.1 mmol) were refluxed in cyclohexane in the dark for 5 h. The reaction mixture was cooled to 0 °C and filtered. The filtrate was diluted with DCM, washed with H₂O (3 \times 50 cm³) and brine (50 cm³) and then dried and evaporated to dryness under reduced pressure. The unpurified methyl 2-bromomethylbenzoate was added to a solution of 3H-quinazolin-4-one (7.3 g, 50 mmol) and potassium *tert*-butoxide (07.3 g, 65 mmol) in DMF (50 cm³) that had been stirred for 40 min. The resulting mixture was stirred for 12 h then diluted with DCM, and the solution washed with H₂O and brine. The organic layer was dried and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (4 : 1) as eluent yielding 2-[(4-oxo-4H-quinazolin-3-yl)methyl]benzoic methyl ester as a pale oil 45 (4.98 g, 16.6 mmol, 34%); (Found: M⁺, 295.1077. C₁₇H₁₄N₂O₃ requires 295.1077); ν_{\max} (thin film)/cm⁻¹ 3541, 3417, 1715, 1681, 1563, 1367, 1322, 1079, 968 and 774; δ_H 3.88 (3 H, s, OMe), 5.62 (2 H, s, CH₂), 7.31–7.22 (2 H, m, ArH), 7.70–7.69 (2 H, m, ArH), 7.97 (1 H, dd, J 7.8 1.4, ArH) and 8.28–8.23 (2 H, m, ArH); δ_c 47.9 (CH₂), 52.4 (Me), 122.2 (4a-C), 126.9 (CH), 127.3 (CH), 127.5 (CH), 128.0 (CH),

128.6 (C), 129.1 (CH), 131.3 (CH), 133.0 (CH), 134.7 (CH), 147.1 (CH), 148.1 (8a-C), 161.4 (4-C) and 167.4 (CO₂Me); *m/z* (EI) 262 (*M*⁺, 53%), 132 (80), 118 (30), 102 (60), 91 (100), 77 (58), 63 (33) and 50 (23).

2-[(4-Oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl acid 46. A solution of 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl ester 45 (1.93 g, 6.14 mmol) in ethanolic LiOH (1 M, 200 cm³) and water (20 cm³) was stirred for 18 h. The mixture was acidified with HCl and extracted with EtOAc. The organic layers were combined and washed with H₂O and brine. The organic extract was dried over MgSO₄ and evaporated to dryness under reduced pressure yielding 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl acid 46 as a colourless oil (0.63 g, 2.1 mmol, 34%); Found: *M*⁺, 281.0918. C₁₆H₁₂N₂O₃ requires 281.0921; *m/z* (EI) 262 (*M*⁺, 31%), 146 (35), 132 (86), 118 (38), 104 (47), 90 (58), 77 (100), 63 (28), 51 (32) and 43 (53). The carboxylic acid 46 was converted to the acyl selenide without further characterisation.

2-[(4-Oxo-4*H*-quinazolin-3-yl)methyl]seleno benzoic acid Se-phenyl ester 47. The same procedure as for the seleno-ester 43 was used to convert 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl acid 46 to 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]seleno benzoic acid Se-phenyl ester 47 as colourless crystals (0.31 g, 0.71 mmol, 68%), mp 314–316 °C; Found: *M*⁺*H*⁺, 421.0450. C₂₂H₁₇N₂O₂Se requires 421.0451; *v*_{max}(thin film)/cm⁻¹ 3361, 1911, 1659, 1589, 1542, 1392, 1336, 1188, 801, 760 and 722; *δ*_H 5.43 (2 H, s, CH₂), 7.37–7.35 (1 H, m, ArH), 7.53–7.45 (6 H, m, ArH), 7.61–7.59 (2 H, ArH), 7.79–7.73 (2 H, m, ArH), 8.04 (1 H, dd, *J* 7.6 1.3, ArH), 8.13 (1 H, s, 2-H) and 8.33–8.30 (1 H, m, ArH); *δ*_C 47.2 (CH₂), 122.1 (4a-C), 126.3 (C), 126.9 (CH), 127.4 (CH), 127.5 (CH), 128.5 (CH), 129.4 (CH), 129.6 (CH), 129.6 (CH), 129.7 (CH), 133.2 (CH), 133.6 (C), 134.4 (CH), 136.2 (CH), 137.6 (C), 147.0 (CH), 148.0 (8a-C), 161.3 (4-C) and 196.7 (CO); *m/z* (Electrospray) 421 (*M*⁺, 7%), 263 (60), 156 (45), 129 (100), 102 (43), 89 (46), 77 (60), 63 (23) and 51 (33).

11-Hydroxy-11*H*-isoquinolino[3,2-*b*]quinazolin-6,13-dione 50. The reaction between 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]seleno benzoic acid Se-phenyl ester 47 (0.044 g, 0.1 mmol) and hexamethylditin (0.099 g, 0.3 mmol) was carried out in benzene (20 cm³) and was refluxed and irradiated with a UV lamp for 3 h. The benzene was removed under vacuum and the crude product was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (4 : 1) as eluent yielding 11-hydroxy-11*H*-isoquinolino[3,2-*b*]quinazolin-6,13-dione 50 as colourless needles (0.011 g, 0.04 mmol, 39%), mp 176–177 °C (CHCl₃); Found: (*M* + *H*)⁺, 279.0768. C₁₆H₁₁N₂O₃ requires 279.0764; *v*_{max}(thin film)/cm⁻¹ 3421, 2919, 2360, 1699, 1683, 1653, 1559, 1465, 1260, 1100, 963, 910, 728 and 667; *δ*_H 5.29 (1 H, d, *J* 4.6, OH), 7.21 (1 H, d, *J* 4.6, CH), 7.69–7.65 (2 H, m, ArH), 7.80 (1 H, d, *J* 8.0, ArH), 7.93–7.84 (2 H, m, ArH), 8.10 (1 H, d, *J* 8.0, ArH), 8.32 (1 H, dd, *J* 7.6 1.2, ArH) and 8.39 (1 H, dd, *J* 8.0 1.2, ArH); *δ*_C 75.5 (CH), 121.9 (C), 126.7 (CH), 128.0 (CH), 128.7 (CH), 129.2 (C), 129.6 (CH), 130.0 (CH), 130.3 (CH), 135.6 (CH), 135.7 (CH), 137.0 (C), 142.6 (ArC), 146.7 (C), 162.7 (C) and 176.6 (C); *m/z* (Electrospray) 278 (*M*⁺, 50%), 262 (43), 249 (40), 221 (26), 135 (38), 119 (36), 105 (100), 91 (45), 84 (60), 77 (68) and 51 (69). The structure was confirmed by X-ray crystallography.

X-Ray crystallography

Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer with sealed tube source⁶⁴ for 30 and Bruker-Nonius CCD diffractometer with rotating anode source⁶⁵ for 50. The structures were solved by direct methods and refined by full-matrix least-squares on *F*² using the SHELXTL suite of programs.⁶⁶ All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model except for H(2) for which coordinates were freely refined in both structures. In 30, molecules form into chains *via* intermolecular H-bonds N(2)–H(2)···O(1'). The structure of 50 additionally contains one molecule of CHCl₃ in the asymmetric unit and molecules are linked into chains *via* strong intermolecular H-bonds O(2)–H(2)···N(2'). Off-set π – π stacking is also dominant with separations in the range 3.33–3.5 Å.

Crystal data for 30: C₁₆H₁₄N₂OS, *M* = 282.35, monoclinic, *Cc*, *a* = 4.6405(7), *b* = 25.329(4), *c* = 12.1910(17) Å, β = 97.047(2)°, *U* = 1422.1(4) Å³, *T* = 150(2) K, *Z* = 4, μ (Mo–K α) = 0.224 mm⁻¹, 5350 reflections measured, 3005 unique (*R*_{int} = 0.0368) which were used in all calculations, *wR* = 0.1590 for all data, *R*1 = 0.0602 for 2351 data with *F*² ≥ 2 σ (*F*²). Absolute structure parameter = 0.13(13)—thus reliably determined.

Crystal data for 50: C₁₇H₁₁Cl₃N₂O₃, *M* = 397.63, triclinic, *P* $\bar{1}$, *a* = 6.6511(3), *b* = 8.6274(3), *c* = 14.5395(7) Å, α = 90.123, β = 94.525(3), γ = 99.594(3)°, *U* = 819.97(6) Å³, *T* = 120(2) K, *Z* = 2, μ (Mo–K α) = 0.579 mm⁻¹, 11250 reflections measured, 3715 unique (*R*_{int} = 0.0370) which were used in all calculations, *wR* = 0.0939 for all data, *R*1 = 0.0353 for 2898 data with *F*² ≥ 2 σ (*F*²).†

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References

- 1 A. Al-Shamma, S. Drake, D. L. Flynn, L. A. Mitscher, Y. H. Park, G. S. R. Rao, A. Simpson, J. K. Swayze, T. Vaysogly and S. T.-S. Wu, *J. Nat. Prod.*, 1981, 745–747.
- 2 S. R. Johns and J. A. Lambertson, *J. Chem. Soc., Chem. Commun.*, 1965, 267; J. S. Fitzgerald, S. R. Johns, J. A. Lambertson and A. H. Redcliffe, *Aust. J. Chem.*, 1966, 19, 151–158.
- 3 M. Hamburger, *Phytochem. Rev.*, 2002, 1, 333.
- 4 Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles*, 1997, 46, 541–546.
- 5 Y. Asahina, *Acta Phytochim.*, 1922, 1, 67; Y. Asahina and K. Kashiwaki, *J. Pharm. Soc. Jpn.*, 1915, 35, 1293.
- 6 J. P. Michael, *Nat. Prod. Rev.*, 2004, 21, 650–668.
- 7 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, 103, 893–930.
- 8 F. Aldabbagh, W. R. Bowman and E. Mann, *Tetrahedron Lett.*, 1997, 38, 7937–7940; F. Aldabbagh, W. R. Bowman, E. Mann and A. M. Z. Slawin, *Tetrahedron*, 1999, 55, 8111–8128.
- 9 Y. Antonio, E. De La Cruz, E. Galeazzi, A. Guzman, B. L. Bray, R. Greenhouse, L. J. Kurz, D. A. Lustig, M. L. Maddox and J. M. Muchowski, *Can. J. Chem.*, 1994, 72, 15–22.

† CCDC reference numbers 622451 and 622452. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614075k

- 10 S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McNally, *Tetrahedron Lett.*, 2002, **43**, 4191–4193.
- 11 F. E. Ziegler and M. Belema, *J. Org. Chem.*, 1997, **62**, 1083–1094 and references therein.
- 12 C. J. Moody and C. L. Norton, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2639–2643.
- 13 J. Marco-Contelles and M. Rodríguez-Fernández, *Tetrahedron Lett.*, 2000, **41**, 381–384; J. Marco-Contelles and M. Rodríguez-Fernández, *J. Org. Chem.*, 2001, **66**, 3717–3725.
- 14 J. A. Murphy and M. S. Sherburn, *Tetrahedron*, 1991, **47**, 4077–4088.
- 15 Y. Z. Osornio, L. D. Miranda, R. Cruz-Almaza and J. D. Muchowski, *Tetrahedron Lett.*, 2004, **45**, 2855–2858.
- 16 S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McNally, *Tetrahedron Lett.*, 2001, **42**, 7887–7890.
- 17 M.-L. Bannasar, T. Roca and F. Ferrando, *Org. Lett.*, 2006, **8**, 561–564.
- 18 M.-L. Bannasar, T. Roca and F. Ferrando, *J. Org. Chem.*, 2005, **70**, 9077–9080.
- 19 M.-L. Bannasar, T. Roca and F. Ferrando, *Tetrahedron Lett.*, 2004, **45**, 5605–5609.
- 20 S. R. Flannagan, D. C. Harrowven and M. Bradley, *Tetrahedron Lett.*, 2003, **44**, 1795–1798.
- 21 T. C. T. Ho and K. Jones, *Tetrahedron*, 1997, **53**, 8287–8294.
- 22 A. Nadin and T. Harrison, *Tetrahedron Lett.*, 1999, **40**, 4073–4076.
- 23 K. C. Mujumbar and P. P. Mukhopadhyay, *Synthesis*, 2003, 920–924; K. C. Mujumbar, P. K. Basu, P. P. Mukhopadhyay, S. Sarkar, S. K. Ghosh and P. Biswas, *Tetrahedron*, 2003, **59**, 2151–2157.
- 24 K. Orito, Y. Satoh, H. Nishizawa, R. Harada and M. Tokuda, *Org. Lett.*, 2000, **2**, 2535–2537.
- 25 D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron*, 2002, **58**, 3387–3400; D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron Lett.*, 2001, **42**, 2907–2910.
- 26 D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron Lett.*, 2001, **42**, 9061–9064; D. C. Harrowven, B. J. Sutton and S. Coulton, *Org. Biomol. Chem.*, 2003, 4047–4057.
- 27 Review: A. Studer and M. Bossart, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, vol. 2, pp. 62–80.
- 28 A. L. J. Beckwith, W. R. Bowman, V. W. Bowry, E. Mann, J. Parr and J. M. D. Storey, *Angew. Chem., Int. Ed.*, 2004, **43**, 95–98.
- 29 D. L. Comins, H. Hong and G. Jinhua, *Tetrahedron Lett.*, 1994, **35**, 5331–5334.
- 30 M. A. Elban, W. Sun, B. M. Eisenhauer, R. Gao and S. M. Hecht, *Org. Lett.*, 2006, **8**, 3513–3516; N. J. Rahier, K. Chen, R. Gao, B. M. Eisenhauer and S. M. Hecht, *Org. Lett.*, 2003, **5**, 835–837.
- 31 J. B. Bremner and W. Sengpracha, *Tetrahedron*, 2005, **61**, 941–953.
- 32 S. M. Allin, W. R. Bowman, M. R. J. Elsegood, V. McKee, R. Karim and S. S. Rahman, *Tetrahedron*, 2005, **61**, 2689–2696.
- 33 (a) C. Kaneko, K. Kasai, N. Katagiri and T. Chiba, *Chem. Pharm. Bull.*, 1986, **34**, 3672–3681; (b) R. Tangirala, S. Anthony, K. Agami, Y. Pommier and D. P. Curran, *Synlett*, 2005, 2843–2846.
- 34 R. Hull and M. L. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1976, 653–659.
- 35 J. Azizian, A. A. Mohammadi and A. R. Karimi, *Synth. Commun.*, 2003, **33**, 415–420.
- 36 A. Andrzejewska, M. A. Pagano, F. Meggio, A. M. Brunati and Z. Kazimierzczuk, *Bioorg. Med. Chem.*, 2003, **11**, 3997–4002; W. M. David, D. Kumar and S. M. Kerwin, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2509–2512; J. W. Ellingboe, W. Spinelli, M. W. Winkley, T. T. Nguyen, R. A. Parsons, J. F. Moubarak, J. M. Kitzen, D. Von Engen and J. F. Bagli, *J. Med. Chem.*, 1992, **35**, 705–716; C. R. Petrie, H. B. Cottam, P. A. McKernan, R. K. Robins and G. R. Revanker, *J. Med. Chem.*, 1985, **28**, 1010–1016; M. C. Huang, T. L. Avery, R. L. Blakley, J. A. Secrist and J. A. Montgomery, *J. Med. Chem.*, 1984, **27**, 800–802; R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, 1964, **86**, 1242–1245; A. G. Beaman, J. F. Gerster and R. K. Robins, *J. Org. Chem.*, 1962, **27**, 986–990.
- 37 M. K. Ali and M. McDermott, *Tetrahedron Lett.*, 2002, **43**, 6271–6273; M. Joshaghani, A. R. Khosropour, H. Jafari and I. Mohammadpour-Baltork, *Phosphorus Sulfur Silicon Relat. Elem.*, 2005, **180**, 117–123.
- 38 W. R. Bowman, S. L. Krintel and M. B. Schilling, *Org. Biomol. Chem.*, 2004, 585–592; W. R. Bowman, S. L. Krintel and M. B. Schilling, *Synlett*, 2004, 1215–1218.
- 39 J.-F. Liu, P. Ye, K. Sprague, K. Sargent, D. Yohannes, C. M. Baldino, C. J. Wilson and S.-C. Ng, *Org. Lett.*, 2005, **7**, 3363–3365; E. S. Lee, J.-G. Park and Y. Jahng, *Tetrahedron Lett.*, 2003, **44**, 1883–1886; A. Kamal, K. V. Ramana, H. B. Antaki and A. V. Ramana, *Tetrahedron Lett.*, 2002, **43**, 6861–6863; K. G. Nazarenko, T. I. Shyrokyaya and A. A. Tolemyev, *Synth. Commun.*, 2003, **33**, 303.
- 40 W. R. Bowman, M. R. J. Elsegood, A. J. Fletcher, P. J. Lovell and J. M. Pedersen, *J. Org. Chem.*, 2005, **70**, 10615–10618; W. R. Bowman, A. J. Fletcher, P. J. Lovell and J. M. Pedersen, *Synlett*, 2004, 1905–1908.
- 41 T. Harayama, A. Hori, G. Serban, Y. Morikami, T. Matsumoto, H. Abe and Y. Takeuchi, *Tetrahedron*, 2004, **60**, 10645–10649.
- 42 T. Harayama, Y. Morikami, Y. Shigeta, H. Abe and Y. Takeuchi, *Synlett*, 2003, 847–848.
- 43 A. Cagir, S. H. Jones, R. Gao, B. M. Eisenhauer and S. M. Hecht, *J. Am. Chem. Soc.*, 2003, **125**, 13628–13629.
- 44 H. Twin and R. A. Batey, *Org. Lett.*, 2004, **6**, 4913–4916; S. B. Mhaske and N. P. Argade, *J. Org. Chem.*, 2004, **69**, 4563–4566; S. P. Chavan and R. Sivappa, *Tetrahedron*, 2004, **60**, 9931–9935; D. Osborne and P. Stevenson, *Tetrahedron Lett.*, 2002, **43**, 5469–5470; M. Toyota, C. Komori and M. Ihara, *Heterocycles*, 2002, **56**, 101–103; S. Dallavalle and L. Merlini, *Tetrahedron Lett.*, 2002, **43**, 1835–1837; P. Molina, A. Tárraga and A. González-Tejero, *Synthesis*, 2000, 1523–1525; Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles*, 1999, **51**, 1593–1596; H. Wang and A. Ganesan, *Tetrahedron Lett.*, 1998, **39**, 9097–9098.
- 45 W. R. Bowman, M. O. Cloonan, A. J. Fletcher and T. Stein, *Org. Biomol. Chem.*, 2005, **3**, 1460–1467.
- 46 (a) M. A. Ciufolini and F. Roschangar, *Tetrahedron*, 1997, **53**, 11049–11060; (b) H. Abe, T. Harayama, A. Hori, T. Matsumoto, Y. Morikami, G. Serban and Y. Takeuchi, *Tetrahedron*, 2004, **60**, 10645–10649.
- 47 Selected syntheses: (a) T. Harayama, A. Hori, G. Serban, Y. Morikami, T. Matsumoto, H. Abe and Y. Takeuchi, *Tetrahedron*, 2004, **60**, 10645–10649; (b) S. P. Chavan and R. Sivappa, *Tetrahedron Lett.*, 2004, **45**, 997–999; P. K. Mohanta and K. Kim, *Tetrahedron Lett.*, 2002, **43**, 3993–3996; S. H. Lee, S. I. Kim, J. G. Park, E. S. Lee and Y. Jahng, *Heterocycles*, 2001, **55**, 1555–1559; A. Ikuta, H. Urabe and H. Nashimura, *J. Nat. Prod.*, 1998, **61**, 1012–1014; J. Bergman and S. Bergman, *J. Org. Chem.*, 1985, **50**, 1246–1255; J. Kokosi, I. Hermez, G. Szaz and Z. Meszaros, *Tetrahedron Lett.*, 1981, **22**, 4861–4862; Y. Asahina, R. H. F. Manske and R. Robinson, *J. Chem. Soc.*, 1927, 1708–1710.
- 48 A. P. Dobbs, K. Jones and K. T. Veal, *Tetrahedron Lett.*, 1995, **36**, 4857–4860.
- 49 A. Fiumana and K. Jones, *Tetrahedron Lett.*, 2000, **41**, 4209–4211.
- 50 G. W. Gribble, H. L. Fraser and J. C. Badenock, *Chem. Commun.*, 2001, 805–806.
- 51 R. Liu, P. Zhang, T. Gan and J. M. Cook, *J. Org. Chem.*, 1997, **62**, 7447–7456; U. Schmidt and S. Weinberger, *Synthesis*, 1996, 28–30.
- 52 A. R. Katritzky and K. Akutagawa, *Tetrahedron Lett.*, 1985, 5935–5938.
- 53 R. Ajaykumar, P. A. Bapu, D. S. Deevi, G. S. Kumar, K. B. S. Kumar, N. V. S. R. Mamidi, C. P. Narasimulu, P. Prasanna, R. C. Puranik, C. S. Rao, C. V. L. Rao, S. Rajaopal, R. Rajagopalan, B. Renuka, K. V. A. Seshu, V. M. Sharma, D. Subramanyam and A. Venkateswarlu, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2303–2307.
- 54 M.-L. Bannasar, T. Roca and F. Ferrando, *J. Org. Chem.*, 2006, **71**, 1746–1749.
- 55 C. Chatgililoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991–2069.
- 56 S. John and M. Süss, *J. Prakt. Chem.*, 1984, **326**, 1027–1033.
- 57 J. A. Howard and J. C. Tait, *Can. J. Chem.*, 1979, **57**, 2761; S. B. Tong, I. P. Beletskaya, A. S. Sigeev, V. A. Kuzmin and A. S. Tatikolov, *J. Chem. Soc., Perkin Trans. 2*, 2000, 107.
- 58 M. Baghbanzadeh, M. Dabiri, A. Mohammadi and P. Salehi, *Synth. Commun.*, 2005, 279–287.
- 59 S. Petersen and E. Tietze, *Justus Liebigs Ann. Chem.*, 1959, **623**, 166–176; K. Nesmerak, H. Pelouchova, V. Vsetecka, I. Nemecek and J. Gabriel, *Folia Microbiol. (Prague)*, 1998, **43**, 39–41.
- 60 L. Jung, I. Kranmacker and J.-F. Stambach, *Heterocycles*, 1990, **31**, 2131–2138.
- 61 T. Kametani, C. Van Loc, T. Higa, M. Koizumi, M. Ihara and K. Fukumoto, *J. Am. Chem. Soc.*, 1977, 2306–2308.
- 62 V. Gatta and R. L. Vittory, *Gazz. Chim. Ital.*, 1969, 59.
- 63 J. S. Yadav and B. V. Reddy, *Tetrahedron Lett.*, 2002, **43**, 1905–1908.
- 64 *SMART and SAINT software for CCD diffractometers*, Bruker AXS Inc., Madison, WI, 2001.
- 65 R. W. W. Hoofd, *COLLECT data collection software*, Nonius B.V., 1998.
- 66 G. M. Sheldrick, *SHELXTL user manual, version 6.10*, Bruker AXS Inc., Madison, WI, 2001.

Synthesis of heteroarenes using cascade radical cyclisation via iminyl radicals†

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Cascade radical cyclisation involving homolytic aromatic substitution has been used to synthesise new tetracycles. Treatment of vinyl iodide radical precursors with $\text{Me}_3\text{Sn}^\bullet$ radicals (from hexamethylditin) yielded intermediate vinyl radicals which undergo 5-*exo* cyclisation onto suitably placed nitrile groups to yield intermediate iminyl radicals. The iminyl radicals undergo radical homolytic substitution via 6-*endo* cyclisation (or 5-*exo* cyclisation followed by neophyl rearrangement) with loss of hydrogen (H^\bullet) in a H-abstraction step. We propose that this abstraction was facilitated by *tert*-butoxyl (*t*-BuO $^\bullet$) radicals from di-*tert*-butyl peroxide or methyl radicals, generated from breakdown of trimethylstannyl radicals ($\text{Me}_3\text{Sn}^\bullet$). The biologically active alkaloids mappicine and luotonin A were synthesised using the new methodology. A novel radical conversion of nitriles to primary amides is proposed.

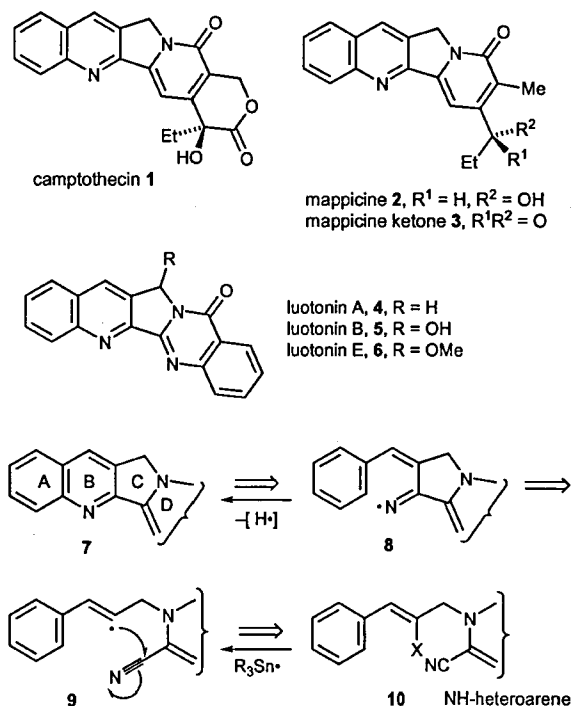
Introduction

Tetracyclic and pentacyclic alkaloids with the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system making up rings A–C have been of intense interest in recent years. In particular, interest has centred around the anticancer and antiviral camptothecin 1 and analogues mappicine 2 and mappicine ketone (nothapodytine B) 3.¹ The chemistry and pharmacology of camptothecins and analogues have been fully reviewed.¹ Camptothecin^{1,2} and mappicine^{1,2,3} have been popular targets of synthesis and a wide variety of protocols have been reported including hetero Diels–Alder reactions, condensation to form the pyridone ring in the synthesis and biomimetic synthesis. Few of these studies have used radical methodology. The major studies using radical synthesis have been reported by Curran and co-workers who have synthesised camptothecin and analogues^{4–6} and mappicine⁷ via bimolecular radical additions of radicals derived from 6-iodo-1*H*-pyridin-2-ones onto aryl-isonitriles. A synthesis of camptothecin using cyclisation of 2-quinolinyl radicals onto pyridones has also been reported.⁸ Synthetic studies towards mappicine using radical cyclisation onto enamides have also been reported.⁹

Another group of alkaloids containing the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system are the recently discovered pyrroloquinazolinoquinoline alkaloids, luotonins A 4, B 5 and E 6 and other congeners.¹⁰ Although the compounds were only isolated four years ago¹⁰ there are already several syntheses of luotonin A, which has proved a popular synthetic target.¹¹ None of the syntheses have used radical protocols. The luotonins are used in traditional Chinese medicine and are reported to exhibit activity against a range of ailments including rheumatism, inflammation, influenza, hepatitis and leukemia.^{10,11} More recently, luotonin A has shown great promise as an antitumour compound and is a poison for human DNA topoisomerase I.^{10b}

In our studies of radical reactions of nitriles we showed that the cyclisation onto the nitrile group could be used in synthesis with understanding of the reactivity and rates of reactions.¹² The rates of cyclisation onto nitriles are slow, and faster, competing reactions need to be avoided in the design

of syntheses. For example, the rate cyclisation of 4-cyanobutyl radicals [$\text{CH}_2(\text{CH}_2)_3\text{CN}$] is slow ($4 \times 10^3 \text{ s}^{-1}$ at 25 °C).¹³ We showed that 5-*exo* cyclisation of reactive aryl and vinyl radicals was faster than alkyl radicals thus providing more suitable reactions for synthesis and that cyclisation onto nitriles to generate intermediate iminyl radicals could be used for further tandem cyclisations onto alkenes.¹² We have developed these studies to a new protocol for the synthesis of the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system 7 which depends on several radical reactions in a cascade sequence (Scheme 1).¹⁴



Scheme 1

In this synthetic protocol, the first of the radical cyclisations in the cascade sequence is 5-*exo* cyclisation of vinyl radicals onto nitriles, i.e. 9 to 8. Vinyl^{16,14,15} and imidoyl¹⁶ radical cyclisations onto nitriles have been reported in a few examples. In the second

† Electronic supplementary information (ESI) available: preparation and analytical details for heteroarene compounds. See <http://www.rsc.org/suppdata/ob/b5/b501509j/>

step of the cascade process (8 to 7), the newly formed iminyl radical intermediate 8 undergoes 6-*endo* (or 5-*exo* cyclisation followed by neophyl rearrangement) cyclisation onto the arene. The cyclisation reactions of the iminyl radical have been extensively studied by Zard and co-workers.¹⁷ The final step is formally an aromatic homolytic substitution in which the iminyl radical substitutes for a hydrogen radical (H[•]). Aromatic homolytic substitution is a much under-used and maligned synthetic reaction but importantly is usefully regioselective when intramolecular.¹⁸ In recent years many of the aromatic homolytic substitutions have been facilitated using tributyltin hydride to excellent synthetic application.¹⁹ While these reactions can be formally described as aromatic homolytic substitution, the exact mechanism is unclear.¹⁹

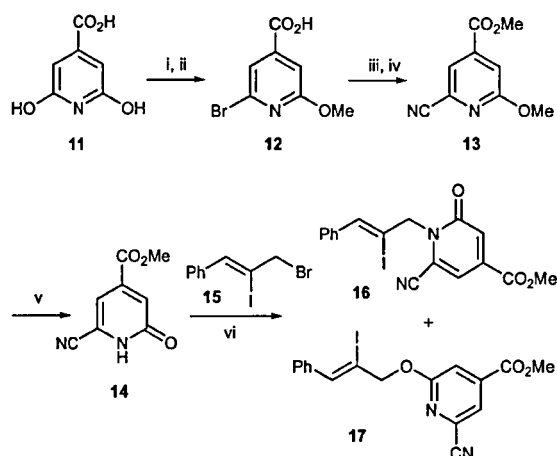
With the dual aim of further studying cyclisation onto nitriles and investigating its use in synthesis, we report the application of the methodology to the synthesis of mappicine (2) and mappicine ketone (nothapodytine B; 3) and luotonin A (4).

Results and discussion

Mappicine 2 and nothapodytine B 3

Our first investigation was the synthesis of mappicine 2 and mappicine ketone 3. We sought to synthesise the simplest relay 21 which has been used in the synthesis of mappicine, thereby constituting a formal synthesis.^{2,20} The use of the electron-withdrawing substituent also provides an interesting test for the chemistry. The interconversion between the ketone of nothapodytine B and the alcohol of mappicine are facile so both present a formal synthesis of each other.

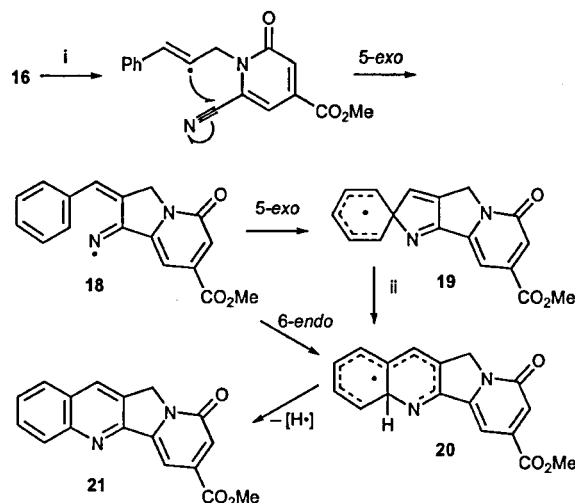
The radical precursor 16 was synthesised as shown in Scheme 2 using a similar procedure to our earlier study.¹⁴ 2,6-Dibromopyridine-4-carboxylic acid was synthesised from the commercially available citrazinic acid 11 in an 80% yield.²¹ S_NAr substitution with methoxide yielded 2-bromo-6-methoxypyridine-4-carboxylic acid 12 in a 96% yield.^{14,22} The usual procedure¹⁴ for the introduction of the nitrile group using CuCN and decomposition of the resultant copper complex to liberate the aryl nitrile proved problematic and black tars were observed. Therefore, the copper(i)-catalysed cyanation was carried out on the methyl ester, methyl 2-bromo-6-methoxypyridine-4-carboxylate, instead of the free carboxylic acid. Various alternative procedures were attempted but the yield of 40% could not be further maximised, indicating that the ester group hinders the reaction. The product 13 was only obtained when methanol was used in place of water in the decomposition of the copper complex. The low yield is likely



Scheme 2 Reagents and conditions: i, POBr₃, 180 °C, 80%; ii, NaOMe, MeOH, 60 °C, 96% (12); iii, MeOH, conc. H₂SO₄, 87%; iv, CuCN, DMF, reflux, 48 h, 40% (13); v, TMSCl, NaI, MeCN, 63% (14); vi, 15, NaH, LiCl, DME, DMF, 32% (16), 30% (17).

to be due to some hydrolysis to 2-cyano-6-methoxypyridine-4-carboxylic acid which binds to the copper in the reaction. Conversion of 13 to the cyanopyridone 14 was carried out using a literature procedure.^{5,14} The cyanopyridone 14 was alkylated with the α-iodocinnamyl bromide¹⁴ 15 using conditions that normally favour *N*-alkylation of pyridones.^{14,23} The radical precursor 16 was obtained in only a 32% yield. The low yield was due to *O*-alkylation (17, 30%) and the formation of small amounts of methyl 6-cyano-1,2-dihydro-1-methyl-2-oxo-4-pyridine-carboxylate. The reasons for the low *N*-selectivity are not obvious.

The radical precursor 16 was reacted under similar conditions to those reported in our earlier paper,¹⁴ *i.e.* hexamethylditin (7.5 equiv.) in *tert*-butylbenzene with sun lamp irradiation (Scheme 3). Hexamethylditin was used in order to prevent trapping of intermediate radicals with a reagent such as tributyltin hydride. Irradiation and heating at 150 °C gave considerable decomposition with an isolated yield of methyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-7-carboxylate 21 of only 15%. Reaction at a lower temperature of 85 °C with a smaller amount of hexamethylditin (2 equiv.) gave a better yield of 21 (50% crude, 21% purified). These lower yields were disappointing compared with yields of up to 80% in earlier studies but indicate that the ester group makes the substrate 16 more reactive.¹⁴ The use of di-*tert*-butyl peroxide as an initiator¹⁴ largely resulted in decomposition with only a trace of 21. This may be related to the presence of the methoxy functional group, as decomposition under these conditions was also observed in the synthesis of the tetracyclic rings A–D of nothapodytine A which contains a 1-methoxy substituent.¹⁴ Hydrogen-abstraction from methoxy groups is unfortunately common due to the formation of a stable radical.



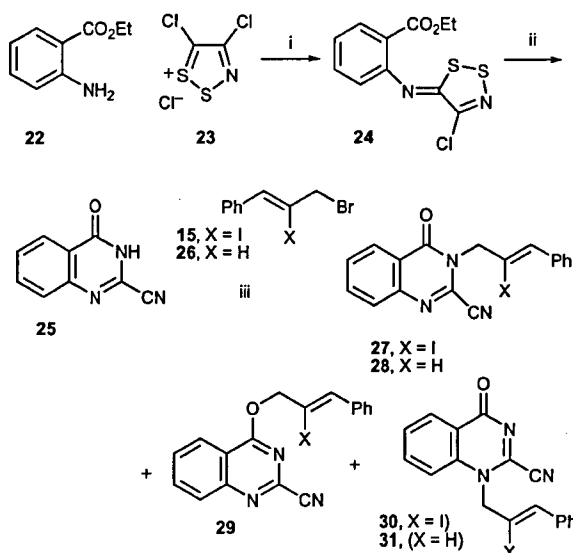
Scheme 3 Reagents and conditions: i, (Me₃Sn)₂, *tert*-BuPh, hv, 85 °C, 24 h, 21% (21).

Scheme 3 shows the putative mechanism of the cascade reaction.¹⁴ Abstraction of iodine by the trimethyltin radical (Me₃Sn[•]) yields the vinyl radical which undergoes 5-*exo* cyclisation onto the nitrile group to yield an intermediate iminyl radical 18. The rate of bromine abstraction by Bu₃Sn[•] radicals of bromine from vinyl bromides is fast (10⁶–10⁷ M^{−1} s^{−1}),²⁴ and therefore, abstraction of iodine by Me₃Sn[•] will be faster and is unlikely to be rate determining in the reaction sequence. Both the 5-*exo* cyclisation onto the nitrile to yield 18 and cyclisation of the iminyl radical intermediate onto the phenyl ring (5-*exo* to 19 or 6-*endo* to 20) are slow. The abstraction of the hydrogen from 20 is the second step of the aromatic homolytic substitution. The mechanism of this step is not clear but we have proposed that the abstracting species are methyl radicals from the breakdown of

trimethyltin radicals.¹⁴ Blank reactions without hexamethylditin gave traces of **21** indicating iodine-homolysis or Diels-Alder cyclisation as possible minor mechanisms.

Luotonin A (**4**)

Our initial aim for the synthesis of luotonin A **4** was to use the same methodology, *i.e.* to alkylate a suitable α -cyano NH-heteroarene (Scheme 4) and carry out the [4 + 2] cascade radical cyclisation as exemplified in Scheme 3 for the synthesis of mappicine and our earlier studies.¹⁴ To this end we decided to use 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25** (Scheme 4). This model would allow study of the quinazoline ring system in the radical cascade protocol.



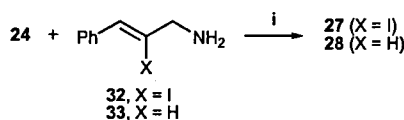
Scheme 4 Reagents and conditions: i, pyridine, DCM, rt, 24 h, 92% (**24**); ii, NH₃, dioxane, rt, 5 d, 98% (**25**); iii, NaH, LiCl, DME, DMF, rt, 5 h: **15** gave 16% (**27**), 0% (**29**, X = I), 6% (**30**) and **26** gave 45% (**28**), 9% (**29**, X = H), <1% (**31**); NaH, DMF, 60 °C, 20 h, **26** gave 44% (**28**), trace (**29**, X = H), 0% (**31**).

4-Oxo-3,4-dihydroquinazoline-2-carbonitrile **25** was synthesised in high yield (98%) from ethyl 2-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzoate **24** and ammonia. This represents a new route to quinazoline-2-carbonitriles. This unusual reaction between amines and the (4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino ring system, developed by Rees and co-workers,²⁵ proved useful in our studies. A similar application has been reported by Kim and Mohanta for the 2-cyanoquinazoline system.²⁶ The protocol relies on the reaction between Appel's salt²⁷ **23** and anthranilate esters (*e.g.* **22**) to yield **24**.²⁵

The procedure for regioselective *N*-alkylation over *O*-alkylation which has been successfully applied to 6-cyano-pyridones¹⁴ and to 6-iodopyridones²³ again gave only small amounts of *O*-alkylation (Scheme 4). In contrast, *O*-alkylation can be selectively facilitated over *N*-alkylation by using the Mitsunobu reaction with alcohols instead of halides for quinazolines and isoquinolines based on low (hard) polarisability factors.²⁸ We have observed the same *O*-selectivity with the Mitsunobu reaction when attempting alkylation of 6-oxo-1,6-dihydro-pyridine-2-carbonitrile with 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene **15** and DEAD.²⁹ However, in this study the protocol was largely *N*-selective but it was not completely selective between alkylation at the 1-*N* and 3-*N* and the isomers were difficult to separate. At ambient temperatures, alkylation of **25** with cinnamyl bromide **26** gave a moderate yield of the required 3-*N* alkylated product **28**. When the temperature was raised, *O*-alkylation (to **29**, X = H) and 1-*N* alkylation

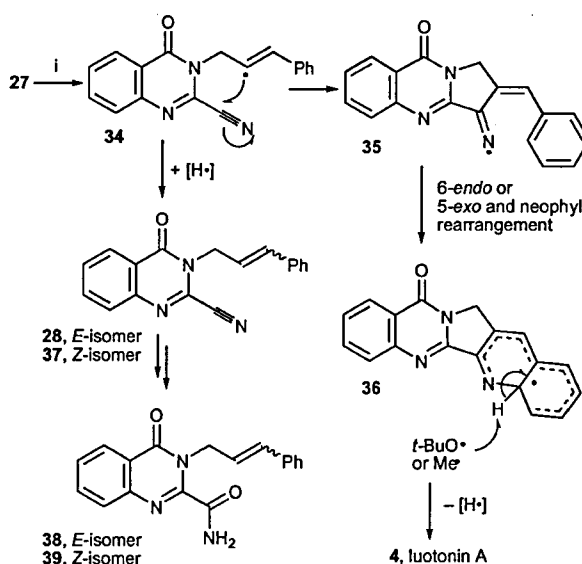
(to **31**) were largely eliminated. Unfortunately, the yields for alkylation with 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene¹⁴ **15** were poor and the two regio-isomers could not be separated even after extensive chromatography.

We therefore developed a protocol which would be regioselective to the required 3-*N* product. Ethyl 2-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzoate **24** was reacted with the required cinnamylamines **32** and **33** (Scheme 5). The cinnamylamines were prepared by standard methodology. Both cinnamylamines gave moderate yields of the required products **27** and **28**. The quinazoline **28** was synthesised as a possible product of unsuccessful cascade cyclisation for comparison and identification purposes. The yields could not be optimised but are similar to reported reactions of similar compounds in the literature.^{25,26} An excess (1.5 equiv.) of Appel's salt was used to ensure complete conversion of ethyl 2-aminobenzoate **22** because it co-elutes with the product **24** creating yet further separation problems. The advantage of the Rees method in the synthesis of the radical precursor is that it avoids the possibility of alkylation at oxygen and 1-*N*. The *Z*-stereochemistry of the alkene **27** and the *E*-stereochemistry of **28** were determined by NOE difference NMR spectroscopy.



Scheme 5 Reagents and conditions: i, THF, rt, 48 h, **32** gave 42% (**27**); **33** gave 40% (**28**).

The radical precursor **27** was reacted under the general reaction conditions¹⁴ using hexamethylditin (14 equiv.) in *tert*-butylbenzene with sun lamp irradiation at 150 °C for 46 h (Scheme 6). Luotonin A **4** was formed as predicted in 21% yield along with other products (30%, an *E/Z* isomeric mixture). We initially assumed that the other product was the reduced uncyclised compound **28**. However, after independent syntheses of potential products, we realised that the unknown products were an *E/Z* isomeric mixture of the primary amides **38** and **39**. No unaltered starting material or other products were observed in the radical reactions except for large amounts of a polymeric organotin compound.¹⁴



Scheme 6 Reagents and conditions: i, (Me₃Sn)₂, *tert*-BuPh, *hν*.

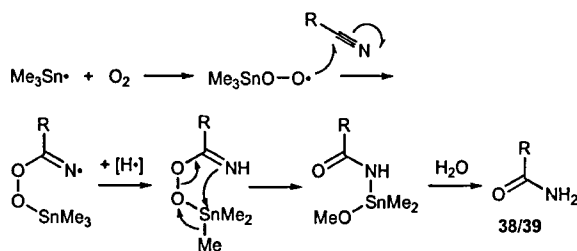
In order to improve the yield of luotonin A, milder conditions using di-*tert*-butyl peroxide were studied.¹⁴ *tert*-Butoxyl radicals

are formed by thermal or photochemical homolysis at lower temperatures and react rapidly with hexamethylditin to yield trimethyltin radicals. The use of *tert*-butylperoxyl radicals also has the advantage of providing a reactive and efficient H-abstractor for the final rearomatisation step (Scheme 6, 36 to 4). The reaction was carried out with **27** (6.33×10^{-2} M) and fewer equivalents of hexamethylditin (3.8 equiv.) and di-*tert*-butyl peroxide (2.0 equiv.) in a sealed tube at 120 °C and for a shorter reaction time (24 h) and yielded luotonin A (30%) and **38/39** (16%). The reaction was repeated at lower dilution (1.47×10^{-2} M) to encourage cyclisation over potential bimolecular reactions. None of the unwanted products **38/39** were observed but the yield of luotonin A dropped to 22%. This result indicates a bimolecular reaction in the formation of **38** and **39**. However, it was not clear whether formation of **38** and **39** had been prevented or whether there were subtle differences in the conditions of the reaction, *e.g.* traces of oxygen. All the starting material was consumed in these reactions, therefore, it may be possible to improve the yield under milder conditions and shorter reaction times.

The proposed mechanism of the cascade cyclisation is shown in Scheme 6. 5-*exo*-Cyclisation of the vinyl radical **34** onto the nitrile yields the iminyl intermediate **35** which undergoes cyclisation onto the phenyl ring (5-*exo* followed by a neophyl rearrangement, or 6-*endo*, to **36**). In this case both 5-*exo* and 6-*endo* routes yield the same product. We have provided evidence in previous examples of cyclisation proceeding *via* initial 5-*exo* cyclisation to a spirodienyl intermediate.¹⁴ The abstraction of the hydrogen from the π -radical intermediate **36** to yield luotonin A **4** is formally the second step of the aromatic homolytic substitution. The mechanism of this step is not clear but we have proposed that the abstracting species are methyl radicals from the breakdown of trimethyltin radicals or *tert*-butoxyl radicals when di-*tert*-butyl peroxide was used.¹⁴ The synthesis provides a further example, albeit in moderate yield, of our cascade methodology indicating that cyanoquinazolines can also be used and furthermore represents the first synthesis of luotonin A using radical methodology.

In order to gain further mechanistic understanding of the radical reactions of **27**, blank reactions were carried out with the radical precursor **27** and also the equivalent non-iodo 3-alkylated compound **28** in which the hexamethylditin (and di-*tert*-butyl peroxide) were omitted. Both reactions gave near quantitative recovery of unaltered starting materials with only traces of luotonin A (<1%). These blank reactions served several purposes. Firstly, the reaction with **27** proved that the radical reagents were required and hence that the reaction was radical mediated. A putative mechanism initiated by iodine-homolysis is also eliminated by the lack of reaction under these conditions. Secondly, a mechanism involving a purely thermal Diels–Alder reaction followed by loss of hydroiodic acid for the synthesis of luotonin A **4** could be envisaged for **27** but is ruled out by the blank reaction. There is literature precedence for an intramolecular Diels–Alder reaction in which a nitrile functional group behaves as the 2π component, the product in this case was also luotonin A.^{11a}

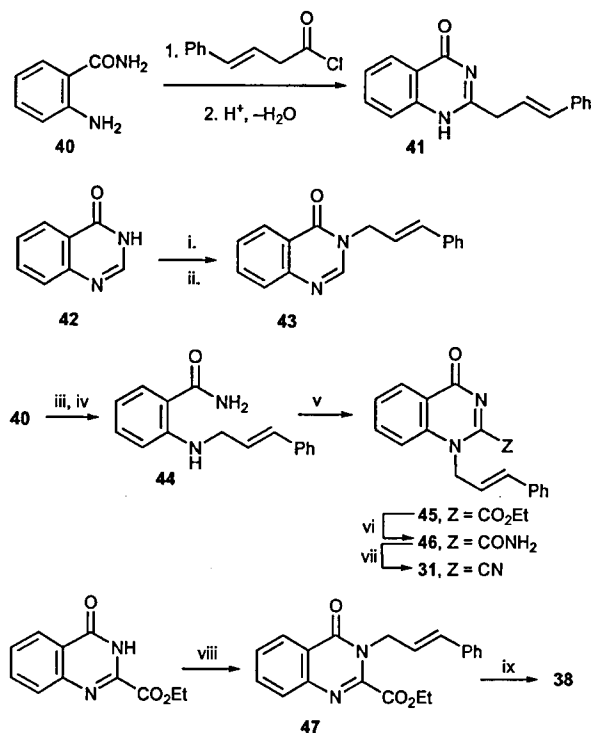
The mechanism of formation of the primary amide by-products **38** and **39** is difficult to explain. The products are clearly formed by a radical mechanism because they are not formed in the blank reaction. The most likely scenario is a competing reaction whereby the initial intermediate radical **34** can either undergo cyclisation onto the nitrile or H-abstraction to yield **28** and **37** (Scheme 6). The isomerism to an *E/Z* mixture can be explained by the radical intermediate **34**. We have previously observed the formation of primary amides from reactions between nitriles and hexamethylditin under radical conditions. The mechanism is not obvious but we propose that the most likely explanation is that traces of oxygen react with the trimethylstannyl radicals as shown in Scheme 7.³⁰ Even with careful freeze–thaw techniques traces of oxygen are difficult to eliminate completely. The nucleophilic peroxyl



Scheme 7 RCN = **38/39**.

radicals add to the electrophilic nitrile. The resulting iminyl radicals undergo 1,5-hydrogen abstraction or H-abstraction from π -radical intermediates to yield unstable intermediates which rearrange under the high temperature conditions. The rearranged products rapidly hydrolyse on work-up to yield the primary amides. A precedent has been reported for an analogous compound which has an acyl group in place in the iminyl group.³¹

The characterisation of the unknown products **38/39** isolated from the radical reactions was ambiguous and the purification was hindered by two geometrical isomers which co-eluted on chromatography. In order to be certain of the assignment of the structures, possible products were synthesised by unoptimised but unambiguous routes (Scheme 8).



Scheme 8 Reagents and conditions: i, NaH, DMF, DME, LiBr; ii, cinnamyl bromide, 2 h; iii, cinnamaldehyde, EtOH, reflux, 15 min (46%); iv, NaBH₄, MeOH, 30 min, 94% (44); v, methyl oxalyl chloride, Et₃N followed by H⁺, 83% (45); vi, NH₄OH, EtOH, 64% (46); vii, EDCI, HOAT (1-hydroxy-7-azabenzotriazole) (catalytic), DCM, reflux, 3 d, 36% (31); viii, NaH, DMF; cinnamyl bromide, 50% (47); ix, NH₃, EtOH, 69% (38).

The absence of a nitrile absorption in the IR spectrum and the absence of a molecular ion including the nitrile in the mass spectrum suggested a product without a nitrile group. 2-[(*E*)-3-Phenylprop-2-enyl]-3*H*-quinazolin-4-one **41** was synthesised from anthranilamide **40** and the acid chloride of cinnamic acid using a protocol adapted from the literature.^{32,33} Radical abstraction of iodine and the nitrile group presents another possibility to yield 3-[(*E*)-3-phenylprop-2-enyl]-3*H*-quinazolin-4-one **43**. The 3-cinnamyl derivative **43** was prepared by

alkylation of 3*H*-quinazolin-4-one **42**. The data for **41** and **43** were similar to the unknown **38** but clearly different, thereby ruling out these structures.

Although unlikely, we considered that a radical rearrangement to the 1-*N*-substituted 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carbonitrile **31** may be possible. The nitrile **31** was prepared by an adapted literature procedure for the synthesis of 1-*N*-substituted 2-cyano-3*H*-quinazolin-4-ones (Scheme 8).^{33,34} The conversion of the primary amide to the nitrile proved troublesome. The use of phosphorus oxychloride for dehydrating the primary amide to the nitrile led to removal of the cinnamyl group by S_N2 substitution by chloride on the cinnamyl methylene group. An alternative method of dehydration using EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] proved satisfactory for converting **46** to **31**.³⁵ Again, the data for **46** and **31** were similar to **38** but not identical. Finally, we synthesised the unexpected primary amide **38** as shown in Scheme 8. The synthesised primary amide **38** was identical to the *E*-isomer of the isomeric mixture of unknown compounds isolated from the radical reactions.

Our studies report novel cascade radical reactions and have indicated that the methodology shown in Scheme 1 can be applied to a range of radical precursors. Further studies are underway to apply the general protocol to a wider range of syntheses.

Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from CaCl₂ and dichloromethane (DCM) which was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as a 60% dispersion in oil and was washed with light petroleum. Mps were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ¹H (250 MHz) and ¹³C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of CDCl₃ with tetramethylsilane (TMS) as the internal standard for ¹H NMR spectra and deuteriochloroform the standard for ¹³C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. GC–MS was carried out on a Fisons 8000 series GC–MS using a 15 m × 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer. TLC using silica gel as adsorbent was carried out with aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F254). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified.

Methyl 6-cyano-2-oxo-1,2-dihydropyridine-4-carboxylate **14**

Chlorotrimethylsilane (0.560 g, 5.16 mmol) was added slowly to a mixture of methyl 2-cyano-6-methoxypyridine-4-carboxylate **13** (0.323 g, 1.681 mmol) and sodium iodide (0.773 g, 5.16 mmol) in acetonitrile (2.5 cm³) and the mixture stirred at 80 °C for 6 h. The solution was cooled to room temperature, evaporated under reduced pressure and water was added (2 cm³). This suspension was purified by column chromatography using DCM/light petroleum as eluent to yield methyl 2-cyano-6-methoxypyridine-4-carboxylate **13** (0.12 g, 37%). Elution with a gradient mixture of DCM/EtOAc gave the product methyl 6-cyano-2-oxo-1,2-dihydropyridine-4-carboxylate **14** (0.189 g, 63%), mp 201–203 °C (Found: C, 53.8; H, 3.35; N, 15.51. C₈H₆N₂O₃ requires C, 53.94; H, 3.39; N, 15.73%; ν_{\max} (Nujol)/cm⁻¹ 3100–2400 (broad NH); 2245 (CN), 1721, 1658 (C=O, pyridone), 1615, 1573, 1343,

1283, 1243, 1198, 1024, 993, 947, 909, 884, 775 and 759; δ_{H} (d₇-DMF) 3.91 (3 H, s, OMe), 7.31 (1 H, s, 5-H), 7.74 (1 H, s, 3-H) and 12.38 (1 H, br s, NH); δ_{C} (d₆-DMSO) 51.45 (OMe), 163.14 and 161.83 (C=O ester and 2-C), 139.70 (4-C), 128.05 (6-C), 117.49 (3-C), 114.77 (5-C) and 114.27 (CN); *m/z* (EI) 178 (M⁺, 93%, Found: 178.0381. C₈H₆N₂O₃ requires 178.0378), 147 (75), 119 (100), 110 (15), 91 (45), 76 (10) and 64 (18).

Methyl 6-cyano-1-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2-oxo-1,2-dihydropyridine-4-carboxylate **16**

60% NaH (0.445 g, 11.13 mmol) was added portion-wise to a solution of methyl 6-cyano-2-oxo-1,2-dihydropyridine-4-carboxylate **14** (1.894 g, 10.64 mmol) in 1,2-dimethoxyethane (monoglyme) (21 cm³) and dimethylformamide after 10 min. The mixture was stirred for 15 min at room temperature, 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene¹⁴ **15** (1.6 g, 4.97 mmol) added, and the reaction heated at 65 °C for 20 h. The mixture was cooled to room temperature and poured into brine (50 cm³), extracted with EtOAc and dried. The solution was evaporated under reduced pressure to give an orange solid which was purified by column chromatography using EtOAc/DCM as eluent to give methyl 6-cyano-1-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2-oxo-1,2-dihydro-pyridine-4-carboxylate **16** (1.398 g, 31%), mp 122–123 °C (DCM/light petroleum) (Found: M⁺, 419.9971. C₁₇H₁₃IN₂O₃ requires 419.9971); ν_{\max} (DCM)/cm⁻¹ 2230 (CN), 1736, 1674 (C=O, pyridone), 1605, 1543, 1219, 1080, 988, 864, 772 and 694; δ_{H} 3.95 (3 H, s, CO₂Me), 5.22 (2 H, d, *J* = 1.2 Hz, CH₂N), 7.07 (1 H, s, vinylic 3-H), 7.27 (3 H, d, *J* 2.0, pyridone 5-H), 7.32–7.38 (3 H, m, phenyl 3,4-H) and 7.48–7.50 (3 H, m, phenyl 2,6-H and pyridone 3-H); δ_{C} 53.41 (OMe), 58.20 (CH₂N), 95.70 (vinylic 2-C), 163.13, 160.34 (ester C=O, pyridone C=O), 139.33, 136.63 (pyridone 4-C, phenyl 1-C), 139.18 (vinylic 3-C), 128.96 (phenyl 4-C), 128.61 (phenyl 3-C), 128.59 (pyridone 3-C), 128.19 (phenyl 2-C), 121.67 (pyridone 6-C), 114.40 (pyridone 5-C) and 112.32 (CN); *m/z* 420 (M⁺, 77%), 388 (3), 328 (7), 293 (13), 281 (4) 268 (30), 192 (7), 181 (6), 133 (9), 115 (14), 91 (100), and 65 (5). Methyl 2-cyano-6-[(*Z*)-2-iodo-3-phenylprop-2-enyl]oxy}pyridine-4-carboxylate **17** was also eluted (1.37 g, 30%), Found: M⁺, 419.9973. C₁₇H₁₃IN₂O₃ requires 419.9971; δ_{H} 3.97 (3 H, s, CO₂Me), 5.25 (2 H, d, *J* = 1.1 Hz, CH₂O), 7.21 (1 H, s, vinylic 3-H), 7.33–7.37 (3 H, m, phenyl 4- and 3-H), 7.54–7.56 (2 H, m, phenyl 2-H), 7.64 (1 H, d, *J* 1.1, 5-H) and 7.85 (1 H, d, *J* 1.1, 3-H); δ_{C} 53.23 (ester OMe), 75.71 (CH₂O), 97.48 (vinylic 2-C), 116.51 (CN), 116.67 (5-C), 121.78 (pyridine 3-C), 128.17 (phenyl CH), 128.52 (phenyl CH), 128.62 (phenyl CH), 131.01 and 136.55 (2-C, phenyl 1-C), 137.74 (vinylic 3-C), 141.55 (4-C) and 163.43 and 163.69 (ester C=O, 6-C). Methyl 6-cyano-1,2-dihydro-1-methyl-2-oxo-4-pyridine-carboxylate was eluted (0.2133 g), mp 144–145 °C (DCM/light petroleum) (lit.,³⁶ 143–144 °C) (Found: M⁺, 192.0536. C₉H₈N₂O₃ requires 192.0535); ν_{\max} (DCM)/cm⁻¹ 2233, 1737 (C=O, ester), 1675 (C=O, pyridone), 1603, 1543, 1220, 1128, 1081, 1000, 992, 964, 909 and 856; δ_{H} 3.73 and 3.95 (3 H each, s, CO₂Me, N–Me), 7.22 (1 H, d, *J* = 2.0 Hz, 5-H), 7.43 (1 H, d, *J* 2.0, 3-H); δ_{C} 34.83 (NMe), 53.36 (ester OMe), 112.27 (6-C), 113.63 (5-C), 122.08 (CN), 128.31 (3-C), 139.12 (4-C), 163.29, 161.00 (ester C=O, pyridine C=O); *m/z* 192 (M⁺, 63%), 153 (8), 136 (8), 133 (100), 115 (16), 105 (18), 91 (10), 89 (14), 77 (36), 67 (25), 63 (9), 59 (19), 51 (18) and 43 (17).

Methyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-7-carboxylate **21** using a 300 W sun lamp

A solution of methyl 6-cyano-1-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2-oxo-1,2-dihydropyridine-4-carboxylate **16** (0.10 g, 0.24 mmol) in *tert*-butylbenzene (6.5 cm³) in a flat-bottomed, two-necked flask (Pyrex, 5 × 1 × 20 cm³, wall thickness 1 mm) was purged with nitrogen for 20 min. Hexamethylditin (0.156 g, 0.48 mmol) was added by syringe and the resultant solution purged with nitrogen for a further 30 min. The mixture was

irradiated with two 150 W sun lamps at 85 °C for 24 h. The reaction was cooled to room temperature, diluted with methanol and evaporated under reduced pressure. Analysis by LCMS and ¹H NMR spectroscopy showed **21** (50%) along with a number of unidentified products. The residue was purified using column chromatography with an eluent gradient of DCM/EtOAc/MeOH and gave methyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-7-carboxylate **21** (14.6 mg, 21%), mp 184–186 °C (lit.,³⁷ 185–187 °C) (Found: M⁺, 292.0848. C₁₇H₁₂N₂O₂ requires 292.0848); δ_H 3.99 (3 H, s, CO₂Me), 5.30 (2 H, s, 11-H), 7.37 (1 H, s, 6-H), 7.66 (1 H, ddd, *J* = 7.5, 7.8, 1.0 Hz, 2-H), 7.81 (1 H, s, 8-H), 7.83 (1 H, ddd, *J* 7.5, 7.8, 1.2, 3-H), 7.93 (1 H, dd, *J* 7.8, 1.0, 1-H), 8.24 (1 H, dd, *J* 7.8, 1.2, 4-H), 8.39 (1 H, s, 12-H); δ_C 50.59 (11-C), 53.39 (OMe), 100.09 (6-C), 122.45 (8-C), 128.37, 128.53 (1-C, 2-C), 128.59, 129.01 (12a-C, 11a-C), 130.24, 130.97, 131.46 (12-C, 4-C, 3-C), 142.36 (7-C), 147.13, 149.37 (4a-C, 5b-C), 152.93 (5a-C), 161.58 (9-C) and 165.50 (ester C=O); *m/z* 292 (M⁺, 100%), 277 (8), 263 (6), 249 (2), 233 (12), 205 (27), 177 (6), 140 (8), 121 (6), 115 (14), 105 (7), 95 (11), 84 (30), 77 (14), 69 (29), 57 (23) and 49 (31).

The reaction was carried out under similar conditions at 150 °C with a larger excess of hexamethylditin (3.66 mmol) and **16** (0.048 mmol) in *tert*-butylbenzene (6.5 cm³) which yielded **21** (15%). The reaction was also repeated with the addition of di-*tert*-butyl peroxide in a sealed tube and heated which yielded **21** in less than 5%.

4-Oxo-3,4-dihydroquinazoline-2-carbonitrile **25**

Ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]benzene-1-carboxylate **24** (4.453 g, 14.84 mmol) was added to an ammonia solution (0.5 M) in 1,4-dioxane (100 cm³, 0.05 mol). The solution was sealed under nitrogen and stirred at room temperature for 5 d. The brown precipitate was filtered and washed with light petroleum to give 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25** (2.48 g, 98%). (Found: [M + NH₄]⁺ 189.0772, C₉H₇N₃O + NH₄ requires 189.0776; Found: M⁺, 171.0432. C₉H₇N₃O requires 171.0433); *v*_{max} (Nujol)/cm⁻¹ 3134 (NH), 2236 (CN), 1698 (C=O), 1608, 1574, 1521, 1408, 1367, 1346, 1112, 998 and 776; δ_H (DMSO-*d*₆) 7.34–7.37 (1 H, m, 6-H), 7.50–7.52 (1 H, m, 8-H), 7.59–7.61 (1 H, m, 7-H) and 7.99–8.00 (1 H, m, 5-H); δ_C 118.08 (CN), 123.75 (4a-C), 126.49 (5-C), 126.03 (6-C, 8-C, overlap), 132.35 (7-C), 143.62 (8a-C), 150.73 (2-C) and 171.21 (C=O); *m/z* [CI+(NH₃)] 189 [(M + NH₄)⁺, 50%], 172 (92), 161 (30) and 147 (100); GC–MS shows one peak, (EI) 171 (M⁺, 100%), 143 (50), 116 (25), 90 (25), 76 (10), 63 (30), and 53 (25).

4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carbonitrile **28**: procedure for the alkylation of 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25**

NaH (93.9 mg, 2.35 mmol) was added slowly with stirring to a solution of 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25** (0.402 g, 2.35 mmol) in anhydrous dimethyl sulfoxide (4.7 cm³) under an atmosphere of nitrogen. Cinnamyl bromide (0.4631 g, 2.35 mmol) was added after 1 h and the solution stirred at room temperature under nitrogen for 5 h. Water was added and the mixture extracted with DCM. The organic fractions were evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to give an inseparable mixture of 4-oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carbonitrile **28** (0.302 g, 45%) and 4-[[(*E*)-3-phenylprop-2-enyl]oxy]quinazoline-2-carbonitrile **29** (X = H) (59 mg, 9%). Further elution gave 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-1,4-dihydroquinazoline-2-carbonitrile **31** (<1%).

28: mp 147–148 °C (from DCM/light petroleum) (Found: C, 75.4; H, 4.4; N, 14.4. C₁₈H₁₃N₃O requires C, 75.25; H, 4.56; N, 14.63%); *v*_{max} (Nujol)/cm⁻¹ 2207 (CN), 1693 (C=O), 1590, 1558, 776 and 692; δ_H 5.02 (2 H, d, *J* = 6.7 Hz, CH₂), 6.33 (1 H, dt,

J 6.7, 15.8, propenyl 2-H), 6.81 (1 H, d, *J* 15.8, propenyl 3-H), 7.24–7.31 (3 H, m, phenyl 3,4,5-H), 7.36–7.38 (2 H, m, phenyl 2,6-H), 7.63 (1 H, dd, *J* 7.9, 7.9, 6-H), 7.78–7.83 (2 H, m, 7- and 8-H) and 8.32 (1 H, d, *J* 7.9, 5-H); values were assigned using NOE difference spectroscopy; important NOEs were observed between the methylene protons and the propenyl 2-H (2.6%) and propenyl 3-H (3.6%) indicating the *E*-stereochemistry but not with 8-H indicating the 3-*N* isomer; δ_C 48.11 (CH₂), 111.64 (CN), 120.91 (propenyl 2-C), 122.79 (4a-C), 126.75 (phenyl 2,6-C), 127.11 (8-C), 128.45 and 128.49 (propenyl 3-C, phenyl 4-C), 128.63 (phenyl 3,5-C), 130.02 (6-C), 131.32 (phenyl 1-C), 135.09 (5-C), 135.58 (8a-C), 136.13 (7-C), 146.37 (2-C), and 159.72 (C=O); *m/z* 287 (M⁺, 37%), Found: M⁺, 287.1058. C₁₈H₁₃N₃O requires 287.1058), 258 (2), 196 (43), 117 (100), 102 (4), 91 (14), 77 (5) and 76 (4).

29 (X = H) (Found: M⁺, 287.1058. C₁₈H₁₃N₃O requires 287.1059); δ_H 5.25 (2 H, d, *J* = 6.2 Hz, OCH₂), 6.64–6.61 (1 H, dt, *J* 6.2, 15.9, propenyl 2-H), 6.83 (1 H, d, *J* 15.9, propenyl 3-H), 7.24–7.31 (3 H, m, phenyl 3, 4, 5-H), 7.41–7.43 (2 H, m, phenyl 2, 6-H), 7.68 (1 H, dd, *J* 7.9, 7.9, 6-H), 7.85 (1 H, dd, *J* 7.9, 7.9, 7-H), 7.98 (1 H, d, *J* 7.9, 8-H) and 8.21 (1 H, d, *J* 7.9, 5-H); δ_C 68.83 (OCH₂), 116.27 and 116.94 (CN, 4a-C), 122.08 (propenyl 2-C), 139.60 (2-C), 123.71, 129.68, 135.03 and 135.55 (5,6,7,8-C), 150.50 (8a-C), 166.90 (4-C), the remaining resonances overlap with those of **28**; *m/z* 244 (31%), 230 (9), 171 (4), 153 (4), 131 (49) and 84 (18). **31** was not fully characterised but exhibited a similar mass spectrum using GC–MS.

The alkylation was repeated with **25** (0.275 g) using only NaH and DMF with heating at 65 °C for 20 h after the addition of cinnamyl bromide. **28** (0.203 g, 44%) was obtained with only a trace of the *O*-alkyl **29** and none of the *N*-1 alkylated product was observed.

3-[(*Z*)-2-Iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile **27** using amine **32**

(*Z*)-2-Iodo-3-phenylprop-2-en-1-amine **32** (0.7856 g, 3.03 mmol) was added to a solution of ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]benzene-1-carboxylate **24** (0.2275 g, 0.76 mmol) in anhydrous tetrahydrofuran (20 cm³). The mixture was stirred for 2 d at room temperature under an atmosphere of nitrogen. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to yield **27** (0.128 g, 42%), mp 152–152.5 °C (DCM/light petroleum). (Found: C, 52.4; H, 2.7; N, 9.8. C₁₈H₁₂IN₃O requires C, 52.32; H, 2.93; N, 10.17%); *v*_{max} (DCM)/cm⁻¹ 2234 (CN), 1698 (C=O), 1605 (C=N), 1586, 1561, 1471 and 1383; δ_H 5.32 (2 H, s, CH₂, NOE enhancement from propenyl 3-H, 6%), 7.17 (1 H, s, propenyl 3-H, NOE enhancement from CH₂, 6%), 7.32–7.34 (3 H, m, phenyl 3,4,5-H), 7.52–7.49 (2 H, m, phenyl 2,6-H); 7.67–7.62 (1 H, m, 6-H), 7.81–7.85 (2 H, m, 7,8-H), 8.32–8.34 (1 H, m, 5-H); δ_C 56.94 (CH₂), 96.14 (propenyl 2-C), 111.59 and 122.61 (CN, 4a-C), 127.36 (CH), 128.16 (CH) and 128.59 (CH) with two overlapping CH peaks, 130.20 (CH), 131.25 (phenyl 1-C), 135.31 (7-C), 136.48 (8a-C), 139.26 (propenyl 3-C), 146.13 (2-C), and 159.51 (4-C); *m/z* (FAB), 414 [(M + H)⁺, 12%, Found: 414.0101. C₁₈H₁₂IN₃O + H requires 414.0105], 286 (100), 259 (41), 254 (35), 243 (45), 219 (15), 208 (25), 165 (29), 116 (70) and 105 (40); *m/z* (EI) 354 (6%), 286 (92), 262 (4), 146 (7), 125 (7), 115 (100), 97 (18), 83 (20), 69 (22), 63 (10), 57 (37) and 43 (33).

11,13-Dihydroquino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11-one (luotonin A) **4** and 4-oxo-3-(3-phenylprop-2-enyl)-3,4-dihydroquinazoline-2-carboxylic acid amide **38/39** (*E/Z* mixture **2**: **1**)

Sun lamp irradiation at 150 °C. A solution of 3-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile **27** (107.0 mg, 0.26 mmol), hexamethylditin (1.20 g,

3.66 mmol, 14 equiv.) and *tert*-butylbenzene (6.5 cm³), in a flat-bottomed, two-necked Pyrex flask (5 × 1 cm and 25 cm high, wall thickness = 1 mm), was purged with nitrogen for 30 min. The mixture was irradiated with a combined 300 W sun lamp at 150 °C for 46 h. The reaction was cooled to room temperature, diluted with MeOH and evaporated under reduced pressure to a small volume. The residue was purified using column chromatography with light petroleum as eluent to remove the *tert*-butylbenzene. Further elution with DCM/diethyl ether gave luotonin A 4 as a white solid (15.4 mg, 21%) and 4-oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid amide 38/39 (*E/Z* mixture = 2.8 : 1) (22.3 mg, 30%) as a mixture. Separation was achieved using preparative silica gel plates and DCM as eluent. Data for 4: mp 277–279 °C (DCM/light petroleum ether) (lit.,¹⁰ 281–283 °C) (Found M⁺, 285.0904. C₁₈H₁₁N₃O requires 285.0902); ν_{\max} (DCM)/cm⁻¹ 1674, 1628, 1605, 1465, 1352, 1320, 1234, 1189, 1134, 1026, 768 and 686; δ_{H} 5.36 (2 H, s, 13-H), 7.57–7.61 (1 H, dd, *J* = 8.0, 8.0 Hz, 9-H), 7.69–7.73 (1 H, ddd, *J* 0.8, 8.0, 8.0, 2-H), 7.86 and 7.87 (2 H, dd and dd, *J* 8.0, 8.0, 3-H and 8-H, overlap), 7.97 (1 H, d, *J* 7.6, 1-H), 8.13 (1 H, d, *J* 8.0, 7-H), 8.44 (1 H, dd, *J* 0.8, 8.0, 4-H H-4), 8.47 (1 H, s, 14-H) and 8.49 (1 H, d, *J* 8.0, 4-H), values were assigned using NOESY and COSY correlation spectra; δ_{C} 47.33 (13-C), 121.38 (10a-C), 126.49 (10-C), 127.49 (9-C), 128.00 (1-C), 128.59 (2-C), 128.79 (7-C), 128.85 (14a-C), 129.45 (13a-C), 130.71 and 130.75 (3-C and 4-C), 131.56 (14-C), 134.60 (8-C), 149.40 and 149.47 (6a-C, 4a-C), 151.22 (5a-C), 152.58 (5b-C) and 160.68 (11-C); *m/z* (FAB) 286 [(M + H)⁺, 100%, Found 286.0984. C₁₈H₁₁N₃O + H requires 286.0980], 249 (45), 190 (30), 167 (12), 127 (14), 115 (45) and 105 (25); *m/z* (EI) 285 (M⁺, 100%), 257 (10), 229 (8), 189 (3), 149 (8), 128 (5), 115 (11), 84 (28), 77 (9), 71 (18), 57 (29) and 43 (14).

Data for 38/39 [(mixture of *E/Z*-isomers (2.8 : 1))]: [Found (M – CONH₂)⁺ 261.1027. C₁₈H₁₁N₃O – CONH₂ requires 261.1027]; ν_{\max} (DCM)/cm⁻¹ 1682, 1587, 1265 and 727; δ_{H} (400 MHz) 5.40 (2 H, dd, *J* = 1.2, 6.6 Hz, CH₂, *E*-isomer), 5.50 (2 H, dd, *J* 2.0, 6.0, CH₂, *Z*-isomer), 5.67 (1 H, dt, *J* 6.0, 11.8, propenyl 2-H, *Z*), 5.77 (1 H, brs, NH, *E*), 6.39 (1 H, dt, *J* 6.6, 15.8, propenyl 2-H, *E*), 6.61 (1 H, dd, *J* 2.0, 11.8, propenyl 3-H, *Z*; NOE with *Z*-propenyl 2-H of 8.4% but none with the methylene indicating *Z*-stereochemistry), 6.73 [1 H, br d, *J* 1.2, 15.8, propenyl 3-H, *E*; NOE with *Z*-propenyl 2-H (1.7%) and the methylene (3.8%) indicating *E*-stereochemistry], 7.21 (1 H, ddd, *J* 8.0, 1.6, 1.6, phenyl *o*-H, *Z*), 7.22 (1 H, ddd, *J* 8.0, 8.0, 1.6, phenyl *p*-H, *E*), 7.25–7.31 (2 H each, m, phenyl-H, *E,Z* overlap), 7.35–7.37 (2 H each, m, phenyl-H, *E,Z* overlap), 7.47 (1 H, brs, NH), 7.56 (1 H, ddd, *J* 1.3, 7.9, 7.9, 6-H, *Z*), 7.58 (1 H, ddd, *J* 1.3, 7.9, 7.9, 6-H, *E*), 7.69 (1 H, ddd, *J* 0.6, 1.3, 7.9, 8-H, *Z*), 7.70 (1 H, ddd, *J* 0.6, 1.3, 7.9, 8-H, *E*), 7.75 and 7.77 (1 H each, ddd, *J* 1.3, 7.9, 7.9, 7-H, *E,Z* overlap), 8.30 (1 H, ddd, *J* 0.6, 1.3, 7.9, aryl 5-H, *Z*) and 8.34 (1 H, ddd, *J* 0.6, 1.3, 7.9, 5-H, *E*); values were assigned using COSY correlation; *m/z* (GC–MS, EI) GC–MS showed two peaks with similar retention times and mass spectra; major isomer: 287 (25%), 279 (5), 258 (2), 196 (50), 167 (10), 117 (100), 91 (34), 76 (13), 63 (12) and 51 (8). The structure of 38 was confirmed by unambiguous synthesis (TLC, IR and ¹H NMR spectra).

With di-*tert*-butyl peroxide. A solution of 3-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile 27 (90.6 mg, 0.219 mmol), hexamethylditin (274.2 mg, 0.837 mmol, 3.8 equiv.) and di-*tert*-butyl peroxide (98%, 64.9 mg, 0.423 mmol, 2.0 equiv.) in *tert*-butylbenzene (3.5 cm³) in a Schlenk tube was subjected to the freeze–thaw method (six times). The sealed tube was immersed in an oil bath at 120 °C for 24 h surrounded by a safety shield in a fumehood. The reaction mixture was cooled to room temperature and placed directly on a silica gel column. Elution with light petroleum removed the *tert*-butylbenzene. Further elution with

DCM/diethyl ether gave luotonin A 4 as a white solid (18.8 mg, 30%) and 38/39 (*E/Z* mixture 3.5 : 1) (10 mg, 16%) as a mixture. All data agreed with authentic materials.

The reaction was repeated except that a higher dilution was used [*tert*-butylbenzene (15 cm³)]. The reaction gave only luotonin A 4 as a white solid (13.8 mg, 22%).

4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid ethyl ester 47

To a pre-dried flask was added 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid ester (1.00 g, 4.61 mmol), anhydrous DMF (30 cm³) and sodium hydride (60% mineral oil suspension, 0.28 g, 6.92 mmol) and the reaction stirred for 10 min. Cinnamyl bromide (0.61 g, 3.09 mmol) was added and the mixture stirred for 1.5 h. The DMF was removed under reduced pressure and the residue washed with saturated brine and extracted into ethyl acetate. The product was purified by flash silica column chromatography to yield 47 as a pale yellow semi-solid (0.52 g, 50%) (Found M⁺ 334.1319. C₂₀H₁₈N₂O₂ requires: 334.1317); ν_{\max} (thin film)/cm⁻¹ 2359, 1734, 1683, 1596, 1464, 1301, 1262, 1153 and 1033; δ_{H} (400 MHz) 1.03 (3 H, t, *J* = 7.1 Hz, CH₃), 4.14 (2 H, q, *J* 7.1, CH₂O), 4.75 (2 H, dd, *J* 6.4, 1.4, CH₂N), 5.97 (1 H, dt, *J* 15.9, 6.4, propenyl-2-H), 6.35 (1 H, dd, *J* 15.9, 1.4, propenyl-3-H), 6.91–7.08 (5 H, m, phenyl-H), 7.23–7.30 (1 H, m, 8-H), 7.48–7.50 (2 H, m, 6-H and 7-H) and 8.04 (1 H, ddd, *J* 1.2, 1.2, 8.1, 5-H); δ_{C} (100 MHz) 161.6 (qC), 160.8 (qC), 146.7 (qC), 146.2 (qC), 135.8 (qC), 134.7 (CH), 134.6 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.5 (CH), 122.9 (CH), 121.9 (qC), 63.3 (CH₂), 45.9 (CH₂) and 13.8 (CH₃); *m/z* (EI) 334 (M⁺, 8%), 261 (100), 145 (5), 115 (30) and 91 (16).

4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid amide 38

4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid ethyl ester 47 (0.50 g, 1.5 mmol) was dissolved in an absolute ethanol (10 cm³) to which was added concentrated aqueous ammonia (100 cm³). The reaction was stirred for 30 min and the resultant precipitate filtered off. The precipitate was washed with water and dried to yield the title compound 38 as a white solid (0.315 g, 69%) (Found 306.1237. C₁₈H₁₅N₃O₂ + H requires 306.1237); ν_{\max} (thin film)/cm⁻¹ 1675, 1653, 1585, 1559, 1457 and 1436; δ_{H} (400 MHz, d₆-DMSO) 4.93 (1 H, *J* = 6.8 Hz, CH₂N), 6.36 (1 H, *J* 6.8, 16.1, propenyl-2-H), 6.55 (1 H, *J* 16.1, propenyl-3-H), 7.23 (1 H, t, *J* 7.6, Ph *p*-H), 7.31 (2 H, t, *J* 7.6, 7.6, Ph *m*-H), 7.40 (2 H, t, *J* 7.6, 7.6, Ph *o*-H), 7.62 (1 H, ddd, *J* 1.2, 7.9, 7.9, 6-H), 7.74 (1 H, ddd, *J* 0.5, 1.2, 7.9, 8-H), 7.90 (1 H, ddd, *J* 1.2, 7.9, 7.9, 7-H), 8.19 (1 H, ddd, *J* 0.5, 1.2, 7.9, 5-H), 8.15 (1 H, brs, NH) and 8.45 (1 H, brs, NH); δ_{C} (100 MHz, d₆-DMSO) 50.8 (CH₂), 126.3 (qC), 129.3 (propenyl-2-C), 131.5 (Ph *o*-C), 131.6 (5-C), 132.6 (8-C), 133.0 (6-C), 133.1 (Ph *p*-C), 133.8 (Ph *m*-C), 137.8 (propenyl-3-C), 140.0 (7-C), 141.2 (qC), 151.5 (qC), 155.5 (qC), 165.5 (qC), and 168.8 (qC). The assignments were confirmed with COSY, HMQC and NOESY techniques; *m/z* (EI) no M⁺; (CI) 306 [(M + H)⁺, 90%), 263, (100) and 190 (28). The ¹H NMR spectra in CDCl₃ and TLC were identical to those in the mixture from the radical reaction to synthesise luotonin A. All peaks in the IR spectrum taken in DCM were identified in the IR spectrum of the mixture.

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References

- 1 M. Potmesil and H. Pinedo, *Camptothecins: New Anticancer Agents*, CRC Press, Boca Raton, Florida, 1995.
- 2 Some representative leading references: (a) J. Yu, J. DePue and D. Kronenthal, *Tetrahedron Lett.*, 2004, 45, 7247; (b) C. H. Lin, M. R. Tsai, Y. S. Wang and N. C. Chang, *J. Org. Chem.*, 2003, 68, 5688; (c) B. S. J. Blag and D. L. Boger, *Tetrahedron Lett.*, 2002, 58, 6343; (d) R. T. Brown, L. Jianli and C. A. M. Santos, *Tetrahedron Lett.*, 2000, 41, 859; (e) M. Toyota, C. Komori and M. Ihara, *J. Org. Chem.*, 2000, 65, 7110; (f) R. Mekouar, Y. Génisson, S. Leue and A. E. Greene, *J. Org. Chem.*, 2000, 65, 5212; (g) D. L. Boger and J. Hong, *J. Am. Chem. Soc.*, 1998, 120, 1218; (h) I. Pendrak, S. Barney, R. Wittrock, D. M. Lambert and W. D. Kingsbury, *J. Org. Chem.*, 1994, 59, 2623.
- 3 Leading references: S. P. Chavan and R. Sivappa, *Tetrahedron Lett.*, 2004, 45, 3941–3943; D. P. Curran and W. Du, *Synlett.*, 2003, 45, 1299–1343; D. P. Curran and W. Du, *Org. Lett.*, 2002, 4, 3215–3943.
- 4 A. E. Gabarda, W. Du, T. Isarno, R. S. Tangirala and D. P. Curran, *Tetrahedron*, 2002, 58, 6329; B. Dom, D. P. Curran, S. Kruszewski, S. G. Zimmer, J. T. Strode, G. Kohlhaas, W. Du, A. J. Chavan, K. A. Fraley, A. L. Bingcan, L. J. Latus, Y. Pommier and T. G. Burke, *J. Med. Chem.*, 2000, 43, 3970; H. Josien, D. Bom, D. P. Curran, Y.-H. Zheng and T.-C. Chou, *Biorg. Med. Chem. Lett.*, 1997, 7, 3189; D. P. Curran, H. Liu, H. Josien and S.-B. Ko, *Tetrahedron*, 1996, 52, 11385; D. P. Curran, S.-B. Ko and H. Josien, *Angew. Chem., Int. Ed. Engl.*, 1995, 34, 2683; H. Liu and D. P. Curran, *J. Am. Chem. Soc.*, 1992, 114, 5863.
- 5 H. Josien, S.-B. Ko, D. Bom and D. P. Curran, *Chem. Eur. J.*, 1998, 4, 67.
- 6 D. P. Curran and H. Liu, *J. Am. Chem. Soc.*, 1991, 113, 2127.
- 7 H. Josien and D. P. Curran, *Tetrahedron*, 1997, 53, 8881; W. Zhang, Z. Luo, C. H.-T. Chen and D. P. Curran, *J. Am. Chem. Soc.*, 2002, 124, 10443.
- 8 M.-L. Bennasar, C. Juan and J. Bosch, *Chem. Commun.*, 2000, 2459.
- 9 H. Ishibashi, I. Kato, Y. Takeda and O. Tamura, *Tetrahedron Lett.*, 2001, 42, 931.
- 10 (a) Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles*, 1997, 46, 541; Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles*, 1997, 46, 1883; (b) A. Cagir, S. H. Jones, R. Gao, B. M. Eisenhauer and S. M. Hecht, *J. Am. Chem. Soc.*, 2003, 125, 13628.
- 11 (a) M. Toyota, C. Komori and M. Ihara, *Heterocycles*, 2002, 56, 101; (b) S. B. Mhaske and N. P. Argade, *J. Org. Chem.*, 2004, 69, 4563; T. Harayama, Y. Morikami, Y. Shigeta, H. Abe and Y. Takeuchi, *Synlett.*, 2003, 69, 847; D. Osborne and P. Stevenson, *Tetrahedron Lett.*, 2002, 43, 5469; J. S. Yadav and B. V. S. Reddy, *Tetrahedron Lett.*, 2002, 43, 1905; S. Dallavalle and L. Merlini, *Tetrahedron Lett.*, 2002, 43, 1835; P. Molina, A. Tárraga and A. González-Tejero, *Synthesis*, 2000, 43, 1523; Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles*, 1999, 51, 1593; H. Wang and A. Ganesan, *Tetrahedron Lett.*, 1998, 39, 9097.
- 12 W. R. Bowman, C. F. Bridge and P. Brookes, *Tetrahedron Lett.*, 2000, 41, 8989.
- 13 D. Griller, P. Schmid and K. U. Ingold, *Can. J. Chem.*, 1979, 57, 831.
- 14 W. R. Bowman, C. F. Bridge, M. O. Cloonan and D. C. Leach, *Synlett.*, 2001, 765; W. R. Bowman, C. F. Bridge, P. Brookes, M. O. Cloonan and D. C. Leach, *J. Chem. Soc., Perkin Trans. 1*, 2002, 58.
- 15 P. C. Montevecchi, M. L. Navacchia and P. Spagnolo, *Tetrahedron*, 1998, 54, 8207.
- 16 I. Lenoir and M. L. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 641.
- 17 Reviews: A. G. Fallis and I. M. Brinza, *Tetrahedron*, 1997, 53, 17543; S. Z. Zard, *Synlett.*, 1996, 53, 1148.
- 18 Review: A. Studer and M. Bossart in *Radicals in Organic Synthesis*, P. Renaud and M. P. Sibi, eds., Wiley-VCH, Weinheim, 2001, vol. 2, p. 62.
- 19 Recent leading references include: A. L. J. Beckwith, V. W. Bowry, W. R. Bowman, E. Mann, J. Parr and J. M. D. Storey, *Angew. Chem., Intl. Ed.*, 2004, 43, 95; S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2002, 41, 4191; S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2001, 42, 7887; W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans. 1*, 2000, 42, 2991; F. Aldabbagh, W. R. Bowman, E. Mann and A. M. Z. Slawin, *Tetrahedron*, 1999, 55, 8111; W. R. Bowman, H. Heaney and B. M. Jordan, *Tetrahedron*, 1991, 47, 10119; E. Bonfand, L. Forslund, W. B. Motherwell and S. Vázquez, *Synlett.*, 2000, 47, 475; A. Fiumana and K. Jones, *Tetrahedron Lett.*, 2000, 41, 4209; J. Marco-Contelles and M. Rodríguez-Fernández, *Tetrahedron Lett.*, 2000, 41, 381; V. Martínez-Barrasa, A. García de Viedma, C. Burgos and J. Álvarez-Builla, *Org. Lett.*, 2000, 2, 3933; S. R. Flannagan, D. C. Harrowven and M. Bradley, *Tetrahedron Lett.*, 2003, 44, 1795; D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron*, 2002, 58, 3387; M.-L. Bennasar, T. Roca, R. Griera and J. Bosch, *J. Org. Chem.*, 2001, 66, 7547; A. L. J. Beckwith and J. M. D. Storey, *J. Chem. Soc., Chem. Commun.*, 1995, 66, 977.
- 20 T. Kametani, H. Takeda, H. Nemoto and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1825.
- 21 K. Abe, Y. Kitagawa and A. Ishimura, *J. Pharm. Soc. Jpn.*, 1953, 73, 969; R.-A. Fallahpour, *Synthesis*, 2000, 73, 1138; R.-A. Fallahpour, *Synthesis*, 2000, 73, 1665.
- 22 M. Adamczyk, S. R. Akireddy and R. E. Reddy, *Org. Lett.*, 2000, 2, 3421.
- 23 H. Liu, S.-B. Ko, H. Josien and D. P. Curran, *Tetrahedron Lett.*, 1995, 36, 8917.
- 24 D. P. Curran, C. P. Jasperse and M. J. Tottleben, *J. Org. Chem.*, 1991, 56, 7169.
- 25 T. Besson, K. Emayan and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2097.
- 26 P. K. Mohanta and K. Kim, *Tetrahedron Lett.*, 2002, 43, 3993.
- 27 R. Appel, H. Janssen, M. Siray and F. Knoch, *Chem. Ber.*, 1985, 118, 1632.
- 28 S. Ferrer, D. P. Naughton, H. Parveen and M. D. Threadgill, *J. Chem. Soc., Perkin Trans. 1*, 2002, 335 and refs. cited therein.
- 29 W. R. Bowman and M. O. Cloonan, unpublished results.
- 30 J. A. Howard, J. C. Tait and S. B. Tong, *Can. J. Chem.*, 1979, 57, 2761; I. P. Beletskaya, A. S. Sigeev, V. A. Kuzmin and A. S. Tatikolov, *J. Chem. Soc., Perkin Trans. 2*, 2000, 57, 107.
- 31 E. Buncl and A. G. Davies, *J. Chem. Soc.*, 1958, 1550; A. G. Davies, *Organotin Chemistry*, VCH Publishers, Weinheim, 1997, p. 182.
- 32 K.-I. Ozaki, Y. Yamada and T. Oine, *Chem. Pharm. Bull.*, 1983, 31, 2234.
- 33 K. Undheim and T. Benneche, in *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees and E. F. V. Scriven, eds., Elsevier, Oxford, 1996, vol. 6, p. 208.
- 34 K.-I. Ozaki, Y. Yamada, T. Oine, T. Ishizuka and Y. Iwasawa, *J. Med. Chem.*, 1995, 28, 568.
- 35 C. Ressler, G. R. Nagarajan, M. Kirisawa and D. V. Kashelkar, *J. Org. Chem.*, 1971, 36, 3960.
- 36 S. M. Vandenburghe, K. J. Buysens, L. Meerpoel, P. K. Lossen, S. M. Topper and G. J. Hoornaert, *J. Org. Chem.*, 1996, 61, 304.
- 37 I. Hagedorn and W. Hohler, *Angew. Chem., Int. Ed. Engl.*, 1975, 14, 486.

References:

1. Andrew F. Parsons, *An Introduction to Free Radical Chemistry*, 1st edition, Blackwell Science Ltd., 2000, Oxford UK.
2. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron*, **1985**, *41*, 3925-3941.
3. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.*, **1976**, 734-736.
4. Corey, E. J.; Suggs, J. W. *J. Org. Chem.*, **1975**, *40*, 2554-2555.
5. Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Eng.*, **1972**, *11*, 692-697.
6. Olivier, C.; Renaud, P. *Chem. Rev.*, **2001**, *101*, 3415-3434.
7. Roberts, B. P. *Chem. Soc. Rev.*, **1999**, *28*, 25-35.
8. Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.*, **2004**, 585-592.
9. Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed.*, **2004**, *43*, 95-98.
10. Crich, D.; Hwang, J.-T. *J. Org. Chem.*, **1998**, *63*, 2765-2770.
11. a) Curran, D. P.; Liu, H. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 1377-1393; b) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron*, **1994**, *50*, 7343-7366.
12. Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles*, **1989**, *28*, 489-519.
13. Murphy, J. A.; Sherburn, M. S. *Tetrahedron*, **1991**, *47*, 4077-4088.
14. Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.*, **1997**, *38*, 5383-5386.
15. Zhang, W.; Pugh, G. *Tetrahedron Lett.*, **2001**, *42*, 5613-5615.
16. Antonia, Y.; De La Cruz, M. E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.*, **1994**, *72*, 15-22.
17. Escolano, C.; Jones, K. *Tetrahedron. Lett.*, **2000**, *41*, 8951-8955.
18. Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron*, **2002**, *58*, 3387-3400.
19. Bennasar, M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. *J. Org. Chem.*, **2002**, *67*, 7465-7474.
20. Bremner, J. B.; Sengpracha, W. *Tetrahedron*, **2005**, *61*, 5489-5498.
21. Miranda, L. D.; Cruz-Almanza, R.; Alva, E.; Pavón, M.; Muchowski, J. M. *Tetrahedron Lett.*, **1999**, *40*, 7153-7157.
22. Patro, B.; Murphy, J. A. *Org. Lett.*, **2000**, *2*, 3599-3601.

23. Fiumana, A.; Jones, K. *Tetrahedron Lett.*, **2000**, *41*, 4209-4211.
24. Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.*, **2001**, *9*, 805-806.
25. Bergman, J.; Venemalm, L. *J. Org. Chem.*, **1992**, *57*, 2495-2497.
26. Bennasar, M.-L.; Roca, T.; Ferrando, F. *Tetrahedron Lett.*, **2004**, *45*, 5605-5609.
27. Batty, D.; Crich, D. *Synthesis*, **1990**, 273-275.
28. Kyei, A. S.; Tchabanenko, K.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.*, **2004**, *45*, 8931-8934.
29. Ganguly, A. K.; Wang, C. H.; Chan, T. M.; Ing, Y. H.; Buevich, A. V. *Tetrahedron Lett.*, **2004**, *45*, 883-886.
30. Marco-Contelles, J.; Rodríguez-Fernández, M. *J. Org. Chem.*, **2001**, *66*, 3717-3725.
31. Cossy, J.; Pardo, D. G.; Tresnard, L. *Eur. J. Org. Chem.*, **1999**, *5*, 1925-1933.
32. Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M.; *Org. Lett.*, **2000**, *2*, 307-310.
33. a) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.*, **1976**, 736-738; b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.*, **1980**, 482-483; c) Kunka, C. P.; Warkentin, J. *Can. J. Chem.*, **1990**, *68*, 575-580.
34. Nadin, A.; Harrison, T. *Tetrahedron Lett.*, **1999**, *40*, 4073-4076.
35. Josein, H.; Curran, D. P. *Tetrahedron*, **1997**, *53*, 8881-8886.
36. Camaggi, C. M.; Leardini, R.; Nanni, D.; Zanardi, G. *Tetrahedron*, **1998**, *54*, 5587-5598.
37. Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.*, **2005**, *70*, 10615-10618.
38. Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron*, **2005**, *61*, 10153-10202.
39. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.*, **2003**, *103*, 893-930.
40. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.*, **1988**, *31*, 2235-2246.
41. Mhaske, S. B.; Argade, N. *Tetrahedron*, **2006**, *62*, 9787-9826.

42. Hooper, D. *Pharma. J.*, **1888**, *18*, 841-843.
43. Koepfli, J. B.; Mead, J. F.; Brockmann, Jr. J. A. *J. Am. Chem. Soc.*, **1947**, *69*, 1837. US Patent, 2504847 (**1950**).
44. Lee I.-K.; Yun, B.-S.; Han, G.; Cho, D.-H.; Kim, Y.-H.; Yoo, I.-D. *J. Nat. Prod.*, **2002**, *65*, 1769-1772.
45. Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Sørensen, D.; Frisvad, J. C.; Hansen, M. E. *J. Nat. Prod.*, **2005**, *68*, 871-874.
46. McWhorter, W. W. Jr.; Liu, Y. *Curr. Opin. Drug Discov. Devel.*, **2003**, *6*, 930-944.
47. Tahara, Y. *Biochem. Z.*, **1911**, *30*, 255-275.
48. Astra Zeneca, Raltitrexed disodium, ZD-1694.
49. Phase II trials carried out by Cytokinetics, sponsored by GSK, Ispinesib SB-715992.
50. Kentanserine tartrate, Tocris Bioscience, R41468.
51. Quinethazone (Hydromox®, Lederle US).
52. Phase II trials carried out by Collgard Biopharmaceuticals.
53. Other names include Citexal®, Omnyl® and Soverin®.
54. Prazosin hydrochloride salt Minipress® sold by Pfizer.
55. Iressa™ sold by AstraZeneca since 2002.
56. Paul M. Dewick, Medicinal and natural products, 2nd edition, Wiley, 2004, West Sussex England.
57. Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers, Organic Chemistry, 1st edition, Oxford University Press, 2001, Oxford UK.
58. Yamazaki, M.; Ikuta, A.; Mori, T.; Kawana, T. *Tetrahedron Lett.*, **1967**, *8*, 3317-3320.
59. Akiyama, T.; Kinoshita, T.; Sankawa, U.; Shibata, S.; Takagi, S. *Shoyakugaka Zasshi*, **1979**, *33*, 30-35.
60. Wiedemann, S. H.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.*, **2006**, *71*, 1969-1976.
61. Cornet, H.; Couture, A.; Grandclaudeudron, P. *Synthesis*, **1991**, 1609-1610.
62. Kundu, N. G.; Chaudhuri, G. *Tetrahedron Lett.*, **2001**, *42*, 2883-2886.
63. Larksarp, C.; Alper, H. *J. Org. Chem.*, **2000**, *65*, 2773-2777.
64. Eguchi, S. *ARKIVOC*, **2005**, 98-119.

65. Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.*, **1996**, *61*, 7316-7319.
66. Croce, P. D.; Ferracioli, R.; La Rosa, C. *Heterocycles*, **1997**, *45*, 1309-1317.
67. Paterson, T. M.; Smalley, R. K.; Suschitzky, H. *Synthesis*, **1975**, 187-189.
68. a) Reid, W.; Stephen, W. *Chem. Ber.*, **1962**, *95*, 3042-3047. b) Reid, W.; Stephen, W. *Chem. Ber.*, **1963**, *96*, 1218-1220. c) Reid, W.; Sinharay, A. *Chem. Ber.*, **1963**, *96*, 3306-3311.
69. Connolly, D. J.; Guiry, P. J. *Synlett*, **2001**, 1701-1710.
70. Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron*, **2005**, *61*, 2689-2696.
71. Bowman, W. R.; Bridge, C. F.; Brookes, P. Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 58-68.
72. Liu, H.; Ko, S.-B.; Josien, H.; Curran, D. P. *Tetrahedron Lett.*, **1995**, *36*, 8917-8920.
73. Bowman, W. R.; Cloonan, O. M.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.*, **2005**, *3*, 1460-1467.
74. Harayama, T.; Morikami, Y.; Shigeta, Y.; Abe, H.; Takeuchi, Y. *Synlett*, **2003**, 847-848.
75. Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127-2132.
76. Dounag, A. B.; Overman, L. E. *Chem. Rev.*, **2003**, *103*, 2945-2946.
77. Al-Shamma, A.; Drake, S.; Flynn, D. L.; Mitscher, L. A.; Park, Y. H.; Rao, G. S. R.; Simpson, A.; Swatze, J. K.; Veysoglu, T.; Wu, T.-S. *J. Nat. Prod.* **1981**, *44*, 745-747.
78. Deai, R. M.; Mehta, D. R.; Naravane, J. S. *J. Org. Chem.*, **1963**, *28*, 445-448.
79. Hamid, A.; Elomri, A.; Daich, A. *Tetrahedron Lett.*, **2006**, *47*, 1777-1781.
80. Johns, S. R.; Lamberton, J. A. *Chem. Commun.*, **1965**, 267.
81. Fitzgerald, J. S.; Johns, S. R.; Lamberton, J. A.; Redcliffe, A. H. *Aust. J. Chem.* **1966**, *19*, 151-159.
82. Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.*, **2005**, *7*, 3363-3366.
83. Chan, T.-H.; Li, C.-J. *Tetrahedron*, **1999**, *55*, 11149-1117.
84. Chen, Y.-J.; Hano, Y.; Ma, Z.-Z.; Nomura, T. *Heterocycles*, **1997**, *46*, 541-546.
85. Lee, E. S.; Park, J. G. Kim, S.; Jahng, Y. *Heterocycles*, **2006**, *68*, 151-158.

86. Cheng, K.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M.; Rahier, N. J. *Org. Lett.* **2005**, *7*, 835-837.
87. Chrencik, J. E.; Staker, B. L.; Burgin, A. B.; Pourquier, P.; Pommier, Y.; Stewart, L.; Redinbo, M. R. *J. Mol. Bio.*, **1997**, *339*, 773-784.
88. Elban, M. A.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M.; Sun, W. *Org. Lett.*, **2006**, *8*, 3513-3516.
89. Dumouchel, S.; Mongin, F.; Quéguiner, G.; Trécort, F. *Tetrahedron*, **2003**, *59*, 8629-8640.
90. Asahina, Y.; Kashiwaki, K. *Yakugaku Zasshi*, **1915**, *405*, 1293.
91. Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 1708-1710.
92. Chavan, S.; Sivappa, R.; *Tetrahedron Lett.*, **2004**, *45*, 997-999.
93. a) Chu, J.; *Sci. Rec. (China)*, **1951**, *4*, 279-284; b) Li, M.-T.; Hung, H.-I.; Yao Hseuh Pao, **1966**, *13*, 265-272.
94. Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66-87.
95. a) Wu, S.-N.; Lo, T.-K.; Chen, H.; Li, H.-F.; Chiang, H.-T. *Neuropharmacology*, **2001**, *41*, 834-843; b) Sheu, J. R.; Hung, W. C.; Wu, C. H.; Lee, Y. M.; Yen, M. H. *Br. J. Haematol.* **2000**, *110*, 110-115; c) Wang, G. J.; Shan, J.; Pang, P. K. T.; Yang, M. C. M.; Chou, C. J. *J. Pharmacol. Exp. Therap.*, **1996**, *270*, 1016-1021.
96. Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.*, **1985**, *26*, 5935-5938.
97. Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.*, **1995**, *36*, 3103-3106.
98. Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron*, **1998**, *54*, 2149-2160.
99. Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.*, **2004**, *6*, 2785-2788.
100. Kuethe, J. T.; Wong, A.; Davies, I. W.; Reider, P. J. *Tetrahedron Lett.*, **2002**, *43*, 3871-3874.
101. Castro, J. L.; Lewis, S.; Patel, S.; Smith, A. L.; Stevenson, G. I. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 2693-2696.
102. Abe, H.; Harayama, T.; Hori, A.; Matsumoto, T.; Morikami, Y.; Serban, G.; Takeuchi, Y. *Tetrahedron*, **2004**, *60*, 10645-10649.
103. Hamburger, M. *Phytochem. Rev.*, **2002**, *1*, 333-349.
104. Dannhardt, G.; Dnaz, H.; Hamburger, M.; Simon, H.-U.; Stoyanova, S.; Thomet, O. A. R.; Ulbrich, H. *Planta Med.*, **2002**, *68*, 875-880.

105. Aga, M.; Ikeda, M.; Inoue, S.; Iwaki, K.; Kunikata, T.; Kurimoto, T.; Takei, Y.; Ushio, S. *Biol. Pharma. Bull.*, **2003**, *26*, 365-367.
106. Benfeldt, E.; Elsner, P.; Hamburger, M.; Heinemann, C.; Oberthür, C. *Planta Med.*, **2003**, *69*, 385-389.
107. Ajaykumar, R.; Bapu, P. A.; Deevi, D. S.; Kumar, G. S.; Kumar, K. B. S.; Mamidi, N. V. S. R.; Narasimhulu, C. P.; Prasanna, P.; Puranik, R. C.; Rao, C. S.; Rao, C. V. L.; Rajaopal, S.; Rajagopalan, R.; Renuka, B.; Seshu, K. V. A.; Sharma, V. M.; Subramanyam, D.; Venkateswarlu, A. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 2303-2307.
108. Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.*, **1999**, *99*, 1991-2069.
109. Khajavi, M. S.; Montazari, N.; Hosseini, S. S. S. *J. Chem. Research*, **1997**, 286-287
110. Johne, S.; Süsse, M. *J. Prakt. Chem.*, **1984**, *326*, 1027-1033.
111. Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett.*, **2006**, *8*, 561-564.
112. Drake, S.; DeMeulenaer, T.; Mitscher, L. A.; Sulko, J.; Wong, W.-C. *Heterocycles*, **1981**, *15*, 1017-1021.
113. Dvornikis, V.; Smithrud, D. B. *J. Org. Chem.*, **2002**, *67*, 2160-2167.
114. Liu, J.-F.; Kaselj, M.; Isome, Y.; Ye, P.; Sargent, K.; Sprague, K.; Cherrak, D.; Wilson, C. J.; Si, Y.; Yohannes, D.; Ng, S.-C. *J. Comb. Chem.*, **2006**, *8*, 7-10.
115. Kurodo, K.; Matsumoto, M. *Tetrahedron Lett.*, **1980**, *21*, 4021-4024.
116. Köllner, C.; Molander, G. A. *J. Org. Chem.*, **2000**, *65*, 8333-8339
117. Brinker, U. H.; Nordvik, T. *J. Org. Chem.*, **2003**, *68*, 7092-7093.
118. Crandall, J. K.; Michaely, W. J. *J. Org. Chem.*, **1984**, *49*, 4244-4248.
119. Cronin, T. H.; Hess, H.-J.; Scriabine, A. *J. Med. Chem.*, **1968**, *11*, 130-136
120. Janeba, Z.; Liu, J.; Robins, J. M. *Org. Lett.*, **2004**, *6*, 2917-2919.
121. Hull, R.; Swain, M. L. *J. Chem. Soc., Perkin Trans. I*, **1976**, 653-659.
122. Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem.*, **2003**, *68*, 8693-8696.
123. Moghaddam, M. F.; Boeini, H. Z. *Synlett*, **2005**, 1612-1614.
124. Shanmugan, P.; Kanakarajan, K.; Soundaraarajan, N.; Gnanasekaran, A. *Synthesis*, **1976**, 253-255.
125. Ali, M. H.; McDermott, M. *Tetrahedron Lett.*, **2002**, *43*, 6271-6273.

126. Joshaghani, M.; Khosropour, A. R.; Jafray, H.; Mohammadpoor-Baltork, I. *Phosphorus, Sulfur, Silicon Relat. Elem.*, **2005**, *180*, 117-123.
127. Rai, R.; Verma, V. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **1979**, *18*, 284-286.
128. Gewald, K.; Schaefer, H.; Schlegel, U. *J. Praktische Chemie (Leipzig)*, **1976**, *318*, 779-784.
129. Bossio, R.; Marcaccini, S.; Parrini, V.; Pepino, R. *Heterocycles*, **1985**, *23*, 2705-2708.
130. Junge, B. *Justus Liebigs Ann. Chem.*, **1975**, 1961-1966.
131. Goerdeler, J.; Ulrich, K. *Chem. Ber.*, **1964**, *97*, 3106-3117.
132. Gabriel, S.; Stelzner, R. *Chem. Ber.*, **1896**, *28*, 1300-1316.
133. Beaman, A. G.; Gerstner, J. F.; Robins, R. K. *J. Org. Chem.*, **1962**, *27*, 986-990.
134. Petrie III, C. R.; Cottam, H. B.; McKernan, P. A.; Robins, R. K.; Revankar, G. *J. Med. Chem.*, **1985**, *28*, 1010-1016.
135. Holmes, R. E.; Robins, R. K. *J. Am. Chem.*, **1964**, *86*, 1242-1245.
136. Bowman, W. R.; Coghlan, D. R. *Tetrahedron*, **1997**, *53*, 1587-15798.
137. Comins, D. L.; Jianhua, G. *Tetrahedron Lett.*, **1994**, *35*, 2819-2822.
138. Tangirala, R.; Antony, S.; Agama, K.; Pommier, Y.; Curran, D. P. *Synlett*, **2005**, 2843-2846.
139. Robins, R. K.; Stout, M. G. *J. Org. Chem.*, **1969**, *33*, 89-91.
140. Chang, C.-S.; Chen, G. S.; Chern, J.-W.; Kalchar, S.; Kuo, C.-W.; Usifoh, C. *J. Org. Chem.*, **2003**, *68*, 2502-2505.
141. Drushlyak, O. G.; Ivanchtchenko, A. V.; Kovalenko, S. M. *J. Comb. Chem.*, **2003**, *5*, 775-788.
142. Burawoy, A. Chaudhuri, A.; Vellins, C. E. *J. Chem. Soc.*, **1955**, 3798-3804.
143. Bianchi, M.; Hausermann, E.; Rossi, S. *J. Heterocycl. Chem.*, **1971**, *16*, 1411-1416.
144. Baghbanzadeh, M.; Dabiri, M.; Mohammadi, A.; Salehi, P. *Synthetic Commun.*, **2005**, 279-287.
145. a) Petersen, S.; Tietze, E. *Justus Liebigs Ann. Chem.*, **1959**, *623*, 166-76; b) Nesmerak, N.; Pelouchova, H.; Vsetecka, V.; Nemec, I.; Gabriel, J. *Folia Microbiologica (Prague)*, **1998**, *43*, 39-41.
146. Kranmacher, I.; Stambach, J.-F.; Jung, L. *Heterocycles*, **1990**, *31*, 2131-2138.

147. Baker, B. R.; Shaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H. J. *Org. Chem.*, **1952**, *17*, 149-153.
148. Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron*, **1996**, *52*, 11445-11462.
149. Kametani, T.; Van Loc, C.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. J. *Am. Chem. Soc.*, **1977**, *99*, 2306-2308.
150. Gatta, V.; Vittory, R. L. *Gazz. Chim. Ital.*, **1969**, 59-65.
151. Hanford, W. E.; Liang, P.; Adams, R. J. *Am. Chem. Soc.*, **1934**, *56*, 2780-2783.
152. Yadav, J. S.; Reddy, B. V. *Tetrahedron Lett.*, **2002**, *58*, 1905-1908.
153. Ciufolini, M. A.; Roschangar, F. *Tetrahedron*, **1997**, *57*, 11049-11060.
154. Bazzini, C.; Brovelli, S.; Caronna, T.; Gambarotti, C.; Giannone, M.; Macchi, P.; Meinardi, F.; Mele, A.; Panzeri, W.; Recupero, F.; Sironi, A.; Tubino, R. *Eur. J. Org. Chem.*, **2005**, 1247-1257.
155. Liu, R.; Zhang, P.; Gan, T.; Cook, J. M. *J. Org. Chem.*, **1997**, *62*, 7447-7456.
156. Barton, D. H. R.; Lusinch, X.; Milliet, P. *Tetrahedron*, **1985**, *41*, 4727-4738.
157. Sole, D.; Vallverdu, L.; Solan, X.; Font-Bardia, M.; Bonjoch, J. J. *Am. Chem. Soc.*, **2003**, *125*, 1587-1594.
158. DeKoning, C. B.; Michael, J. P.; Pathak, R.; Van Otterlo, W. A. L. *Tetrahedron Lett.*, **2004**, *45*, 1117-1119.
159. Horton, J. R.; Stamp, L. M.; Routledge, A. *Tetrahedron Lett.*, **2000**, *41*, 9181-9184.
160. Kubo, A.; Nakai, T. *Synthesis*, **1980**, 365-356.
161. Gordon, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron*, **2002**, *58*, 8399-8412.
162. Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.*, **2006**, *8*, 1073-1076.
163. Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith III, A. B.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550-12650.
164. Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry*, **2006**, *17*, 521-535.
165. Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.*, **1999**, *64*, 3237-3243.

166. Contour-Galcera, M.-O.; Plas, P.; Roubert, P.; Sidhu, A. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 3555-3559.
167. Baker, B. R.; Query, M. V.; Kadish, A. F.; Williams, J. H. *J. Org. Chem.*, **1952**, *17*, 35-51.
168. Rychnovsky, S. D.; Swenson, S. S. *Tetrahedron*, **1997**, *53*, 16489-16502.
169. Yun, L. M.; Yangibaev, S.; Shakhidoyatov, Kh. M.; Alekseava, V. Ya.; Vyunov, K. A. *Chem. Heterocycl. Compd.*, **1986**, 1001-1003.
170. Cherbuliez, E.; Willhalm, B.; Espejo, O.; Jaccard, S.; Rabinowitz, J. *Helv. Chem. Acta.*, **1967**, *50*, 1440-1452.
171. Azizian, J.; Mohammadi, A. A.; Karimi, A. R. *Synth. Commun.*, **2003**, *33*, 415-420.
172. Cortez, R.; Rivero, I. A.; Somanathan, R.; Aguirre, G; Ramirez, F.; Hong, E. *Synth. Commun.*, **1991**, *21*, 285-292.
173. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron*, **1985**, *41*, 4835-4841.
174. Colacot, T. J. *J. Organomet. Chem.*, **1999**, *580*, 378-380.

