Investigations into the Scope of Radical Intramolecular Carboxyarylation

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A thesis submitted for the degree of Master of Philosophy at
The Australian National University

November, 2008

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This thesis is an account of research under
2008 at the Research School of Chemistry,
University, Canberra, Australia.

This research was supervised by Associate Professor Michael Sherburn, Professor Chris Easton and Dr Alan Payne, but unless otherwise indicated, the work I present herein is my own.

None of the work presented here has ever been submitted for any degree at this or any other institution of learning.

Lucinda L. Carpinelli
6 November 2008

Minor corrections made.
10 December 2008

Acknowledgements

First off, I must thank Associate Professor
candidature and directing the preparation o
beauty and terror of organic chemistry from such an excellent teacher. From the elegance of total synthesis to the precise brutality of curly arrows he has consistently shared his knowledge with great clarity and generosity. I know I will continue to appreciate this gift of understanding more and more in the future and I am very grateful for it. I must also acknowledge his exemplary patience in the face of explosions, floods, tears, fires, personal crises, rivalries and failures.

Many thanks go to all who assisted in the preparation of this manuscript, particularly Dr Nick Kanizaj, Dr Michael Carland, Dr Alan Payne and fellow MPhil scholar Emma Wiadrowski. They took time from their own difficult studies to help me with mine and I hope I can repay them somehow in the future. For many enjoyable and enlightening conversations about chemistry I am indebted to Dr Emma Pearson and Dr Ignace Louis. As post-doctoral fellows they actively contributed to the practical and theoretical

[illegible] alongside such generous and talented people. In addition to these two, I greatly valued interacting with everyone in the research group whether on matters technical or pub-related. They have been wonderful comrades during the deepest of floods and most depressing clean-ups. The scientific and support staff at the Research School of Chemistry facilitated the collection of most of the data presented in this thesis and are the unsung heroes of research. Specifically, I thank Dr Tony Willis for his exceptional persistence in dredging through tiny crystals to provide some very useful crystal structures.

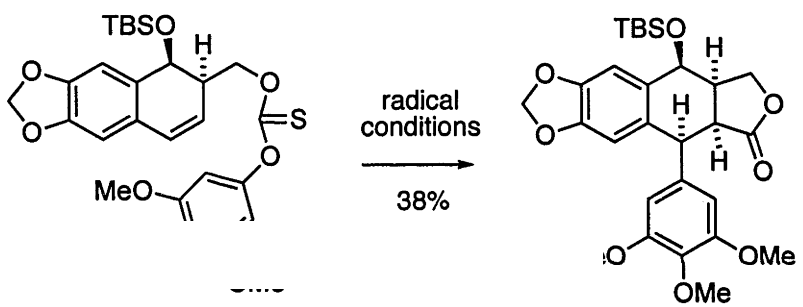
Finally, I would like to thank my friends and family. Wendy, Chrissy, Jason, James, Cath, Sonita, Fiona, Rob, Marit, Kerrie and Maria have all been very kind in listening to me for some years now. Liam and Sophie were instrumental in maintaining my sanity by being the best dance teachers one could hope for. My family has been hugely supportive and I cannot repay them for all their compassionate understanding and encouragement. And thank you to Simon. For always putting me back in chemistry when I was out crying on the lawn on University Avenue. I would never have made it without you!

Abstract

The carboxyarylation reaction emerged fro

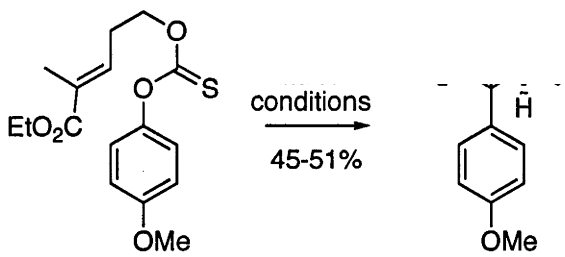
could be encountered when performing Ba[illegible] aryl thionocarbonate derivatives. More recently it is has been showcased in natural product syntheses as a useful methodology that can accommodate different functional groups and afford excellent modularity to synthetic efforts (see Scheme i). Despite these successes, the reaction has suffered from two main problems. Firstly, the yield was often quite low. Secondly, it has been applied only to a very narrow range of substrates.

Scheme i



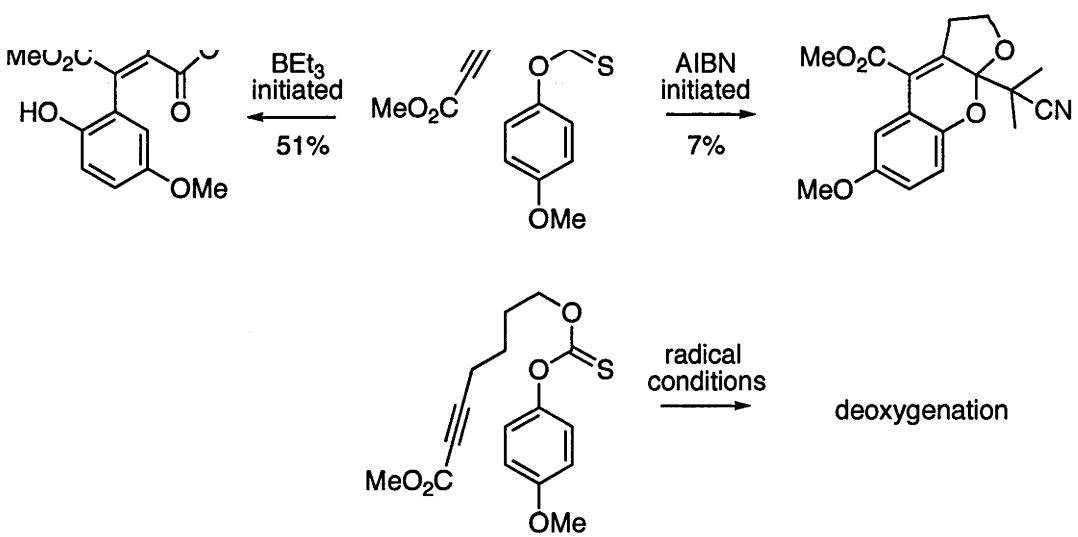
This thesis describes some attempts to address these problems. By investigating the radical chemistry of some 'optimal precursors' (incorporating Michael acceptors) higher yielding examples of carboxyarylation have been recorded (see Scheme ii). The viability of sub-stoichiometric *tris*(trimethylsilyl)silane as radical chain carrier has been demonstrated as has the usefulness of the triethylborane/air initiating couple in conducting these reactions. Despite these efforts, the yields obtained are quite similar to those already recorded in other publications.

Scheme ii



Incorporating new functional groups into radical precursors has tested the scope of carboxyarylation. Experimenting with different radical acceptors has demonstrated interesting diversions from the expected mechanism with additional variation dependent on reaction conditions (see Scheme iii). The limits of the reaction have also been found, where carboxyarylation is no longer competitive with deoxygenation.

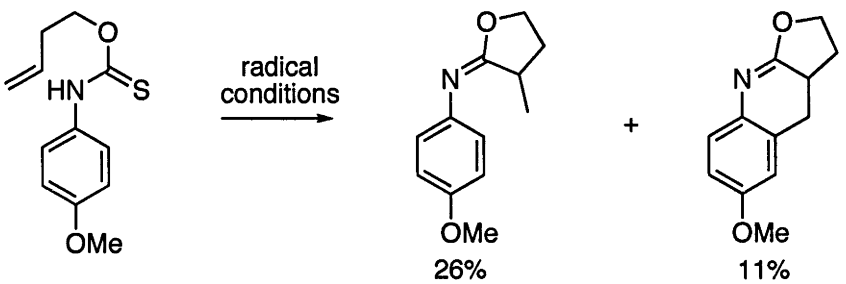
Scheme iii



Attempts to broaden the scope further by using other thiocarbonyl moieties in radical precursors largely failed. As foreshadowed by the literature, thiocarbonyl compounds like thioureas, thionocarbamates and thioamides are less reactive under radical conditions than thionocarbonates. Radical reactions of these new compounds usually yielded

complex mixtures and decomposed starting materials. One of the exceptions to this was the radical reaction of an *N*-aryl thionocarbamate which showed good stability in low yield (see Scheme iv).

Scheme iv



AIBN – Azobisisobutyronitrile

HMDO – Hexamethyldisiloxane

LUMO – Lowest unoccupied molecular orbital

TTMSS – *Tris*(trimethylsilyl)silane

SOMO – Singly occupied molecular orbital

TBAF – *tert*-butyl ammonium fluoride

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Chapter 1: Radical Chemistry of Thionocar

Chapter 2: Radical Chemistry of other Thiocarbonyl Containing Functionalities

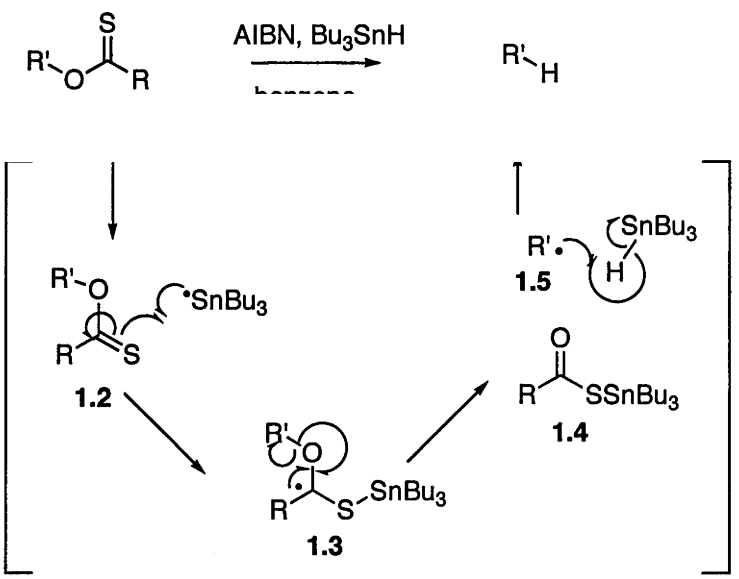
Chapter 1

1.1 Intr

1.1.1 Barton-McCombie Deoxygenation

In 1975 Derek Barton and Stuart McCombie published a novel method for deoxygenating secondary alcohols.[1] The alcohol was first converted to the corresponding thiocarbonyl derivative (xanthate, thiobenzoate, thiocarbonyl imidazolide) then subjected to the radical reducing agent tributyltin hydride to give the desired deoxygenated product. This reaction was enthusiastically adopted by synthetic chemists and has become known as the Barton-McCombie deoxygenation.[2]

Scheme 1.1



The accepted mechanism for this transformation is shown in Scheme 1.1. The initiation phase of this reaction begins when AIBN homolyses under benzene reflux to generate isobutyronitrile radicals. These radicals abstract hydrogen from tributyltin hydride to give tributylstannyl radicals. The mechanism of deoxygenation begins with the reversible addition of a tributylstannyl radical to the radicophillic sulfur of the thiocarbonyl in substrate **1.1**. This generates a tertiary carbon-centred radical **1.3** that is stabilised by

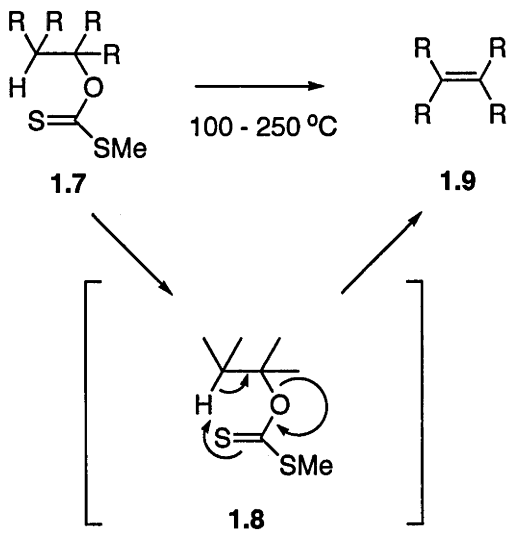
adjacent heteroatoms. Radical **1.3** can undergo irreversible beta scission to generate an alkyl radical **1.5**, which abstracts a hydrogen from tributyltin hydride to give deoxygenated product **1.6**. In doing so it p
can go on to react with the starting materi
force for the reaction is the formation of t
cleavage of the weaker C=S π and σ bonds.

Initially, this reaction was demonstrated on secondary alcohols, especially those in steroids and carbohydrates.[1] However, refinements to the initial procedure have been added over time to expand its scope and improve the yield. Robins et al[3,4] found the xanthate synthesis incompatible with base sensitive protecting groups and used *O*-phenyl thionocarbonate derivatives instead. These were easily obtained and led to fewer by-products during deoxygenation compared with the alternatives. Barton et al[5] followed up on this development and experimented with substitution patterns on the aromatic ring of the thionocarbonate. Improved yields were reported using halogenated aromatics such as pentafluoro and 2,4,6-trichlorophenyl thionocarbonates[5] although there is some doubt as to whether the electron-poor moiety is itself responsible for this observed improvement.[6]

substrates. The deoxygenation of primary alcohols is known to be a slower reaction requiring higher temperatures.[7] This is attributed to the formation of primary radicals. As primary radicals are less stable than secondary radicals, the beta scission leading to a primary radical will be slower. Consequently it is not surprising that conducting deoxygenation at room temperature, reported by Nozaki et al,[8] resulted in yields that were poorer for primary alcohols than secondary alcohols. Presumably the slowness of beta scission allowed side reactions to effectively compete with deoxygenation.

Tertiary alcohols pose a different challenge – thiocarbonyl derivatives with a beta hydrogen are likely to undergo Chugaev elimination at elevated temperatures. This proceeds by an non-radical mechanism (Scheme 1.2).[9] Despite these problems, Barton reported some success in deoxygenating tertiary alcohols via thioformates.[10]

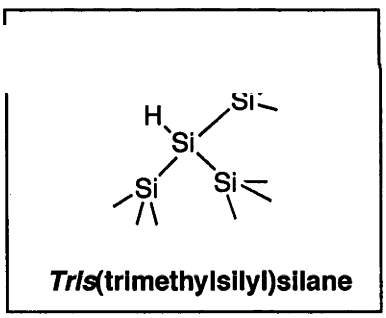
Scheme 1.2 – Ch



1.1.2 Reagents typically used for Barton-McCombie Deoxygenati

Tributyltin hydride and AIBN have been e
Deoxgenation,[1] and radical reactions in ge
of trialkyltin compounds has proved a long-term concern[12] and methods have been sought that minimised[13] or eliminated[14-16] the use of them in radical chemistry. Consequently, the radical conditions for Barton-McCombie deoxygenation have been the subject of experimentation. Deoxygenation has been achieved using catalytic tributyltin hydride[17], phospine boranes[18], diphenyl silane[19] and phosphite reagents.[20]

However, it was the development of *tris*(trimethylsilyl)silane[21] as a radical chain carrier that allowed the widespread application of tin-free radical chemistry, including radical deoxygenation.[22] It is a poorer hydrogen donor than tributyltin hydride and the decreased availability of hydrogen is advantageous for multistep cascades. It has been used extensively in synthesis.[23]



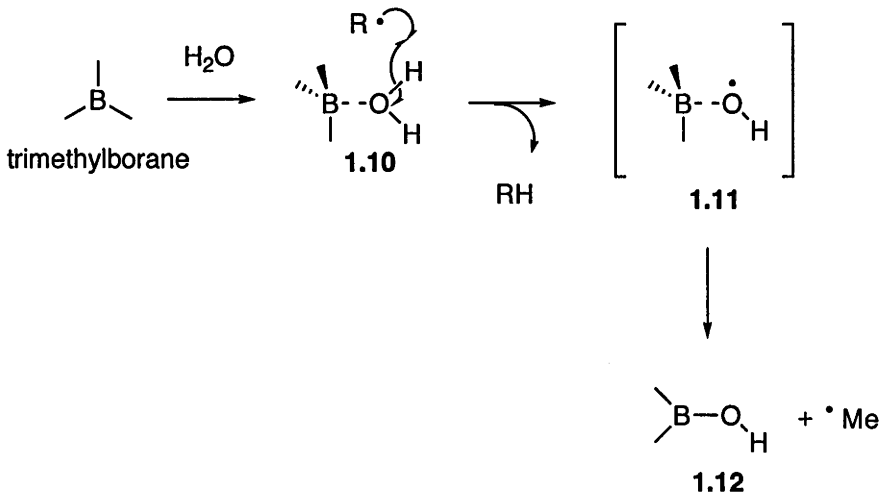
***Tris*(trimethylsilyl)silane**

The use of triethylborane/air as an initiator in free-radical reactions[24] has enabled deoxygenations to be conducted at ambient temperature[25] where previously initiation required refluxing benzene or toluene.[1] More recently Wood and co-workers[26] found that water could be used as the reducing agent in deoxygenation reactions that utilised trialkylboranes as initiators. They concluded that the use of a borane initiator is crucial as it is understood that a water-boron complex **1.10** donates the hydrogen atom (see Scheme

1.3). Hydrogen donation is facilitated by low

water-boron complex compared with that of

Scheme 1.3



eputation for capricious

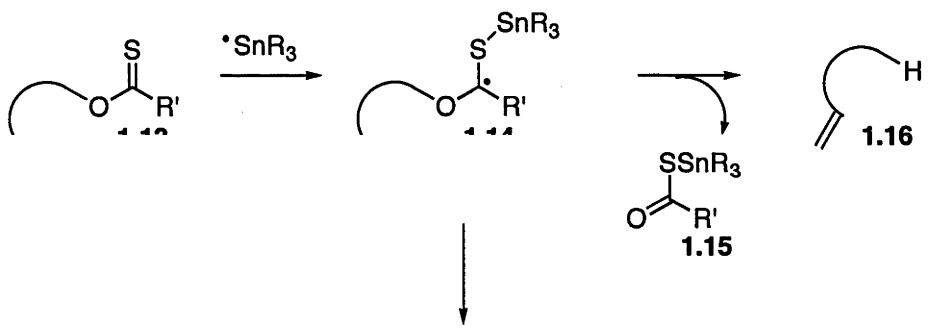
behaviour.[27] Neat triethylborane is not available in Australia.[i]

[i] Aldrich does not ship neat triethylborane to Australia.

1.1.3 Diversions from the Barton-McCombie Deoxygenation

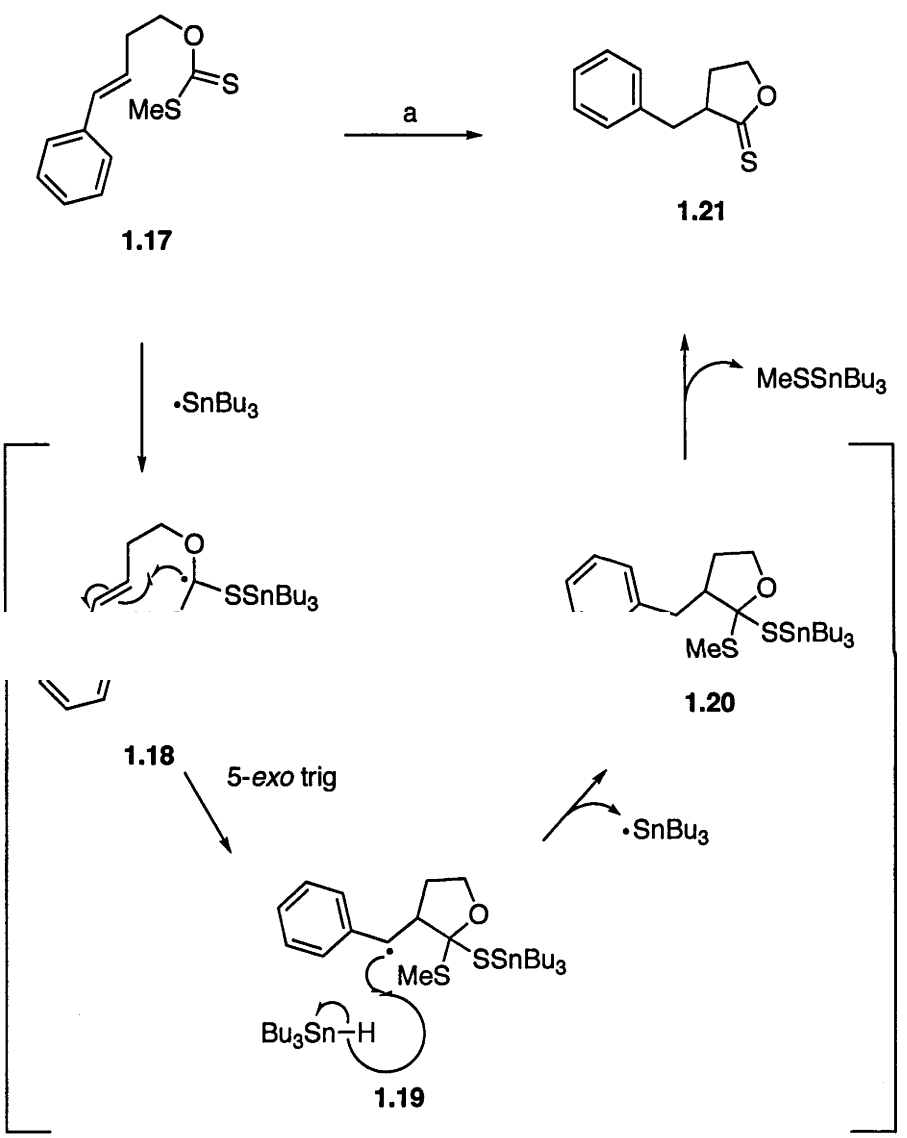
The mechanism of deoxygenation in the E
formation of carbon centred radical **1.14** t
to the desired product **1.16** (Scheme 1.4). In this mechanism, the intermediate **1.14**, requiring a slow beta scission reaction[2] to proceed to a carbon centred radical, is relatively long lived. Consequently, if there is a conveniently located radical acceptor, such as the tethered alkene in **1.14**, other radical pathways might be brought into play. If these processes can compete effectively with the breakdown of **1.14** then deoxygenation will not occur. Thus thiocarbonyl compounds are a valid source of $R_3SnS\text{-}C^{\bullet}$ radicals, which can be utilised in various reactions, especially cyclisations.

Scheme 1.4



Bachi et al[28] investigated the radical chemistry of a range of thiocarbonyl-containing derivatives of homoallylic alcohols. Xanthates, thiocarbonyl imidazolides, thionocarbonates and thiobenzoates were among those that reacted to give cyclisation products in yields of up to 77%. Scheme 1.5 shows a typical example. After the initial addition of a tin radical to the sulfur of the xanthate **1.17**, a 5-*exo*-trig cyclisation occurs to give **1.19**. The resulting secondary radical abstracts hydrogen from Bu_3SnH to give intermediate **1.20**. Finally an elimination at carbon leads to thionolactone **1.21**.

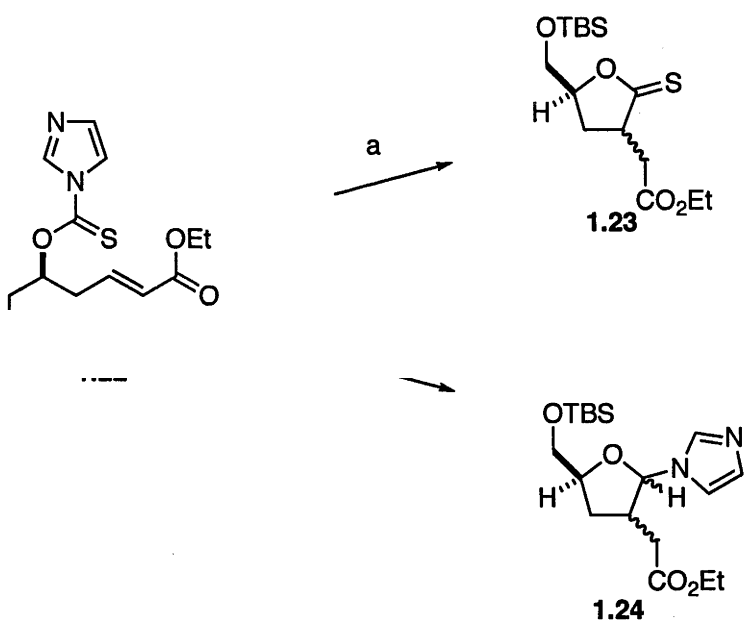
Scheme



Reagents and Conditions: a. AIBN, Bu_3SnH, benzene, reflux, 0.02M

RajanBabu et al[29] demonstrated another possible diversion from deoxygenat
from thiocarbonyl imidazolides (see Sche
expected 5-*exo*-trig cyclisation competes
thionolactone **1.23** is isolated. Interestingl
different result. Using Ph_3SnH as the chain carrier, a new product **1.24** is produced where the imidazole has been retained and the sulfur has been lost. The preferential homolysis of the carbon-sulfur bond to form **1.24** is presumably attributable to the different sterics and electronics of the triphenylstannane.

Scheme 1.6



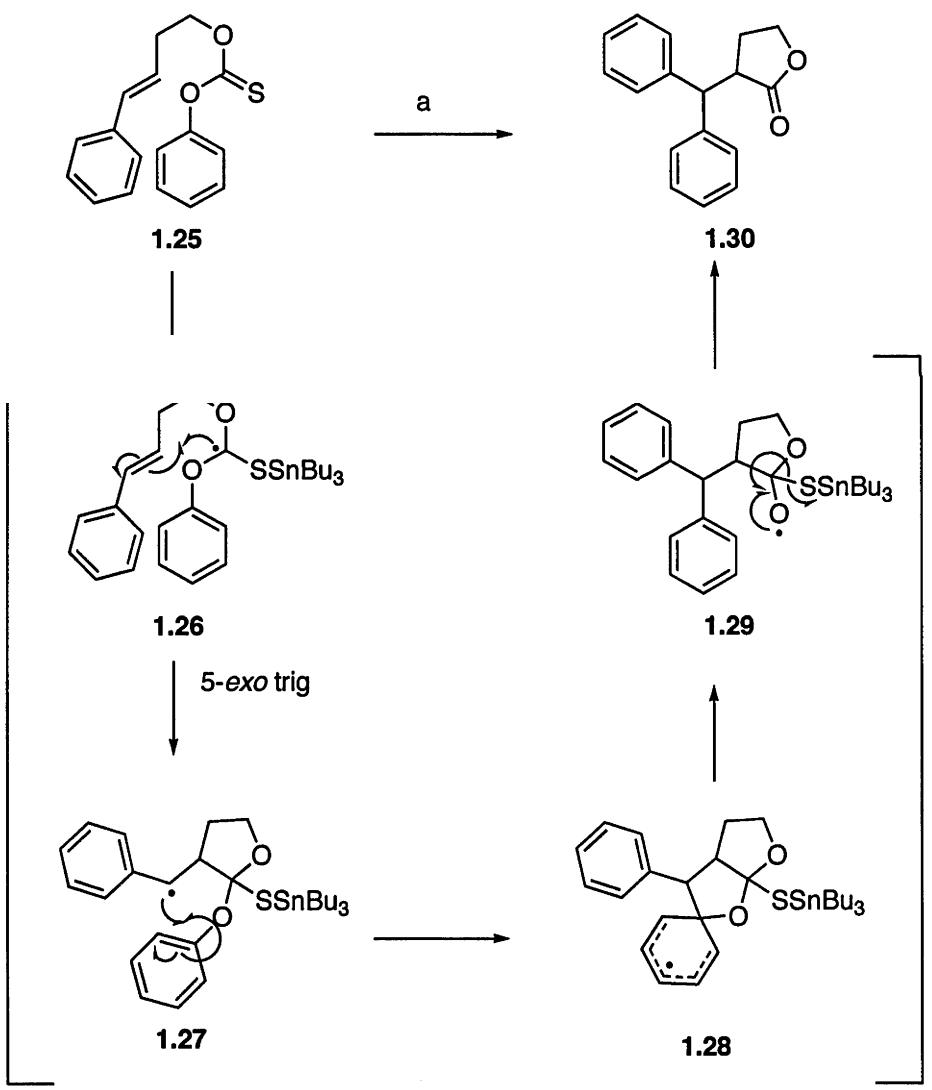
Reagents and Conditions: a. Bu_3SnH (2.0 eq), toluene, reflux, 58%
b. Ph_3SnH (5.0 eq), benzene, reflux, 88%

A mixture of diastereomers was isolated from these reactions. The lack of stereoselectivity, with respect to the ring substituents, could be attributed to negligible differences in stability between diastereomeric transition states. Improvement in stereoselectivity was achieved by using bicyclic substrates.[30]

1.1.4 A no

In addition to researching the simple radical [illegible] also came across more complex cascade reactions. One such is described in Scheme 1.7. The substrate **1.25** has undergone not only a cyclisation but also an aryl migration to form **1.30**.

Scheme 1.7

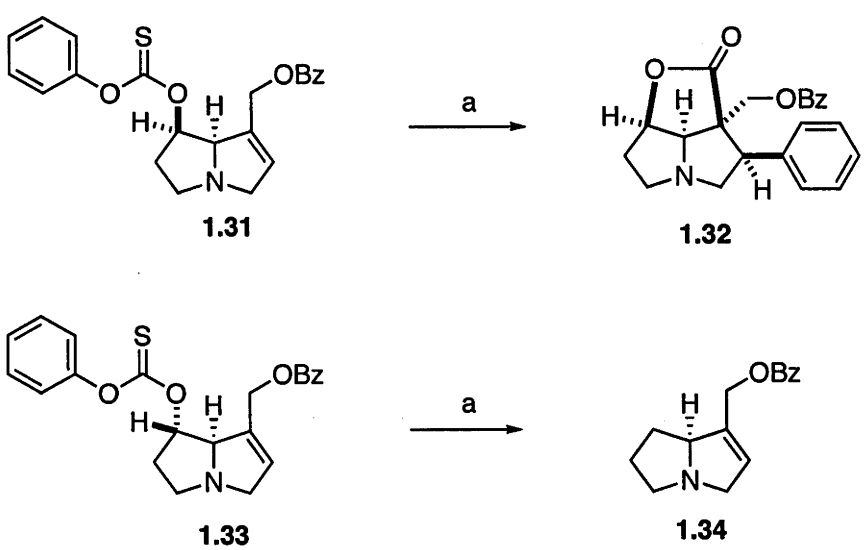


Reagents and conditions: a. Bu_3SnH, AIBN, benzene, reflux, 47%

The reaction mechanism presumably commences with a stannyl radical adding to the sulfur of the thiocarbonyl thus generating the carbon centred radical **1.26**. A cyclisation then ensues. The resulting ben
aromatic ring at the *ipso* position, affordin
rearomatise and eliminate an alkoxyl radic
product, a benzyl butyrolactone **1.30**.

Bachi et al[28] were not the only ones to encounter this particular phenomenon. Zalkow et al[31] came across it as an unwanted side reaction during their studies on the free radical chemistry of the retronecines (see Scheme 1.8). An attempted deoxygenation of compound **1.31** proved disappointing as a high yield of lactone **1.32** was obtained. The configuration of substrate **1.31** may be expected to place the phenyl thionocarbonate reasonably close to the alkene, allowing the subsequently formed $Bu_3SnSC^{\bullet}$ radical to participate in a cyclisation, ultimately leading to the product observed. Interestingly, epimer **1.33** does not undergo this cascade, presumably because the thionocarbonate does not have access to the alkene. Instead deoxygenation is achieved.

Scheme 1.8



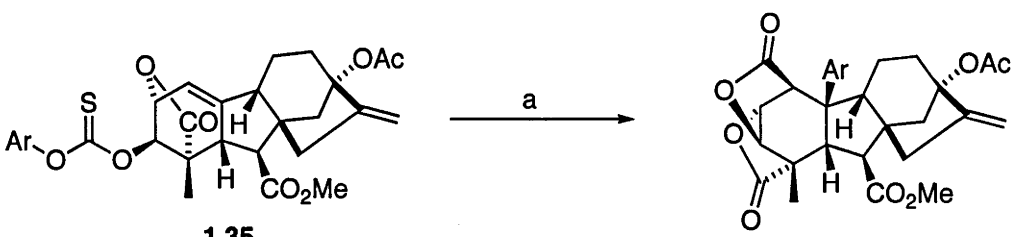
1.31 **1.32**

1.33 **1.34**

Reagents and Conditions: a. Bu_3SnH, AIBN, toluene, 75° C, **1.32**: 60%, **1.34**: 54%

Mander and Sherburn[32] reported the highest
during their attempts to deoxygenate a gibbe
of solvent being the source of the phenyl sub
substituted aryl thionocarbonates and obtained similar yields to the phenyl example.

Scheme 1.9



1.35 **1.36**

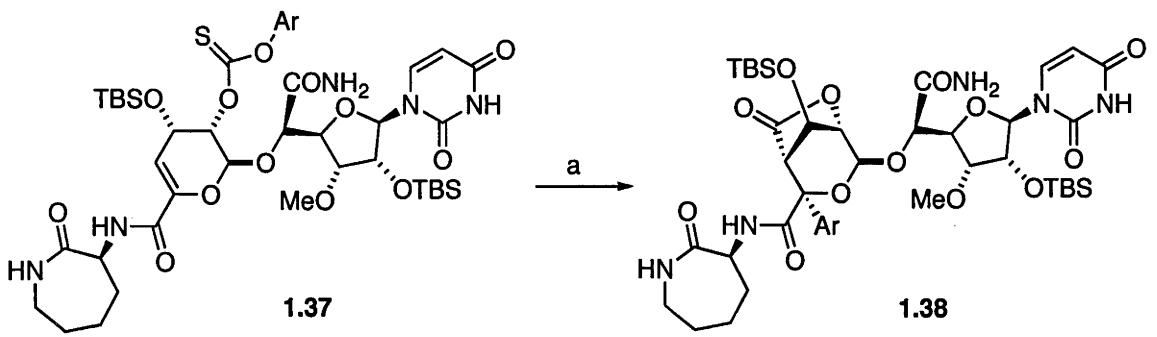
Reagents and conditions: a. AIBN, Bu_3SnH, benzene, reflux

Ar = C_6H_5, 80%

Ar = 4-F-C_6H_4, 89%

Hotoda et al[33] reported the same unexpected interruption to their deoxygenation reaction while working on capuramycin (see Scheme 1.10).

Sch



Reagents and Conditions: a. AIBN, Bu_3SnH, toluene, reflux

Ar = C_6H_5, 49%

Ar = $C_6H_4CH_3$, 63% + 36% deoxygenated product

The phenyl thionocarbonate **1.37** (Ar = C_6H_5) gave a moderate yield of the lactone **1.38**

te (Ar = $C_6H_4CH_3$) gave an

increased yield of the lactone and provided some of the deoxygenated product too. As with the previous two examples, the product is *cis* – the lactone and aromatic ring are on the same face of the ring system. This is the result of a *syn* addition. Thus the initial cyclisation must occur on whichever face of the ring is available to it and the aryl migration is suprafacial.

1.1.5 Alkene 1,2-

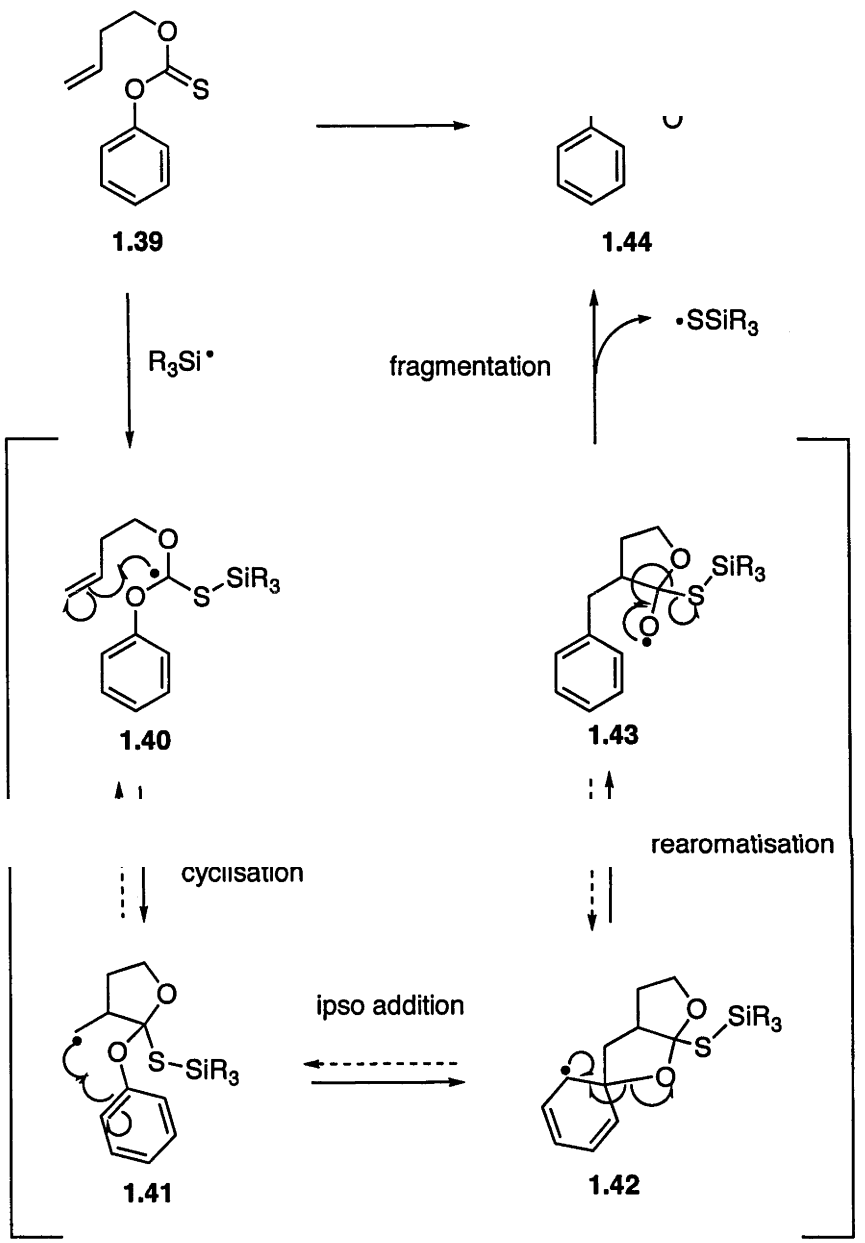
Thus far, reports of this novel cascade reaction have described it either as a curio or a nuisance. However, in our research group it was pursued as a potentially useful synthetic method and dubbed alkene 1,2-carboxyarylation. This name stems from the outcome of the reaction: the addition of both a carboxyl and aromatic group across an alkene.

Scheme 1.11 depicts the likely mechanism of the reaction using the simplest possible example. The reaction presumably begins with the addition of a radical chain carrier ($\bullet SiR_3$ represents the *tris*(trimethyl)silyl radical) to the sulfur of the thionocarbonate. This would generate radical **1.40** that may undergo a 5-*exo*-trig cyclisation. This cyclisation generates radical **1.41** that may then participate in a second 5-*exo*-trig cyclisation which is also an *ipso* addition onto the aromatic ring. Now we have cyclohexadienyl radical **1.42**. This can rearomatise, eliminating an alkoxyl radical. This alkoxyl radical can form

nolysed. Consequently a

thiyl radical is eliminated irreversibly. Overall the thiocarbonyl has been lost, a cyclisation and aryl migration achieved and an ester (lactone) formed.

Scheme 1.11



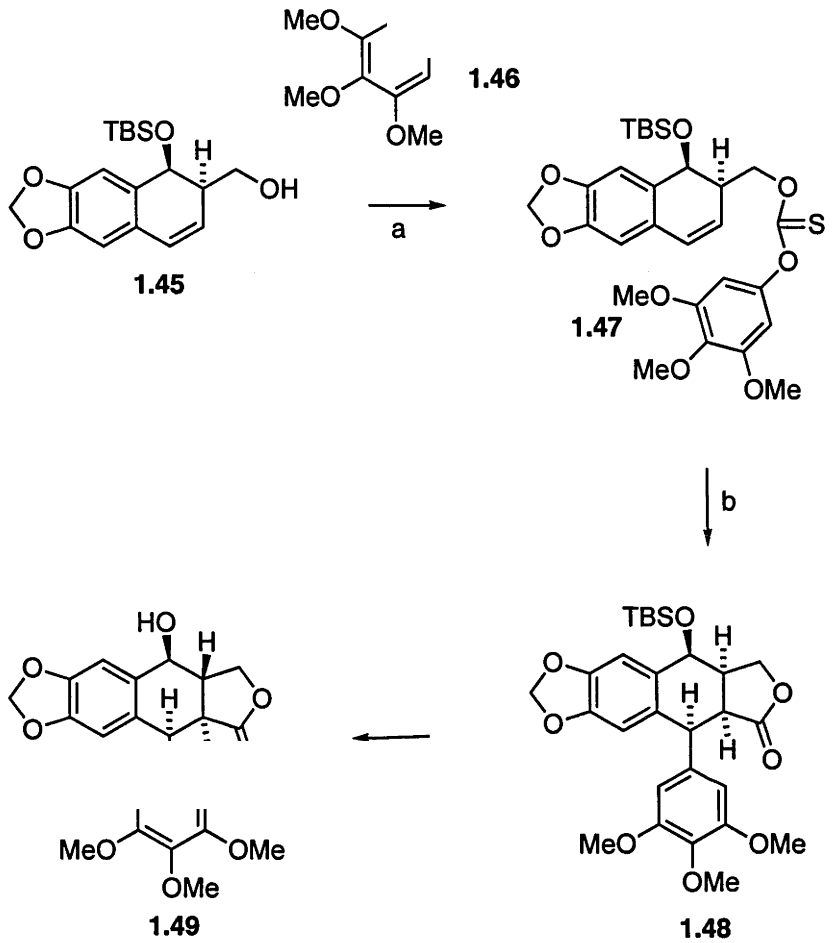
The total synthesis of a number of natural products has been achieved using carboxyarylation as shall now be described.

Podophyllotoxin is a tetrahydronaphthalene

currently used to treat warts. A brief and con

podophyllotoxin was published in 2003.[34] Carboxyarylation constituted the key step, forming two new carbon-carbon bonds and two stereocentres (Scheme 1.12). Combining the dihydronaphthalene **1.45** and aromatic group via thionochloroformate **1.46** just prior to the key step demonstrates modularity that could be utilised in a medicinal chemistry setting. Whilst the yield of the reaction was modest (38%) it proceeded with complete diastereoselectivity.

Scheme 1.12

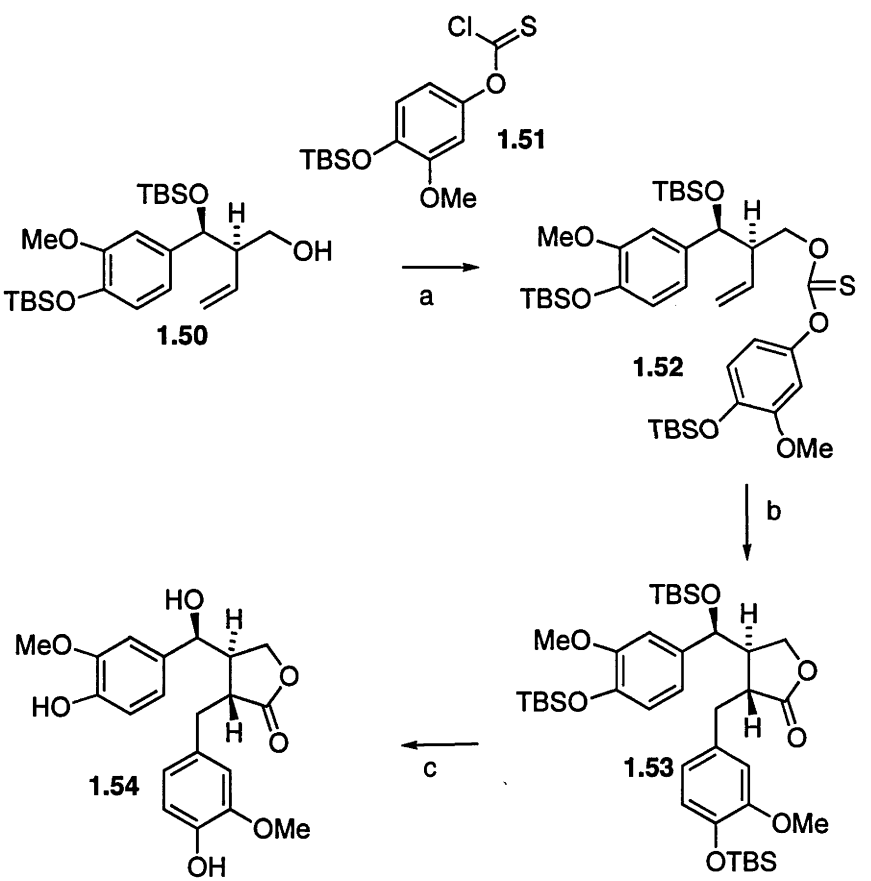


Reagents and Conditions: a. pyridine, dichloromethane 89% b. TTMSS, AIBN, benzene reflux, 38%

The rigidity of the alkene within substrate **1.47** meant that the carboxyl and aryl groups could only be added from one face of the ring system, a *syn* addition. Thus by preparing enantiomerically enriched alcohol **1.45**, the stereochemistry of the reaction, and therefore the configuration of the product, is controlled. In a further six steps, including epimerisation and deprotection, the total synthesis of *ent*-podophyllotoxin **1.49** was completed.

Arctigenin and matairesinol are dibenzyl bu
antiviral activities. The total synthesis of the
reported by Sharp et al.[35] Again carboxyarylation was a key step. Scheme 1.11 shows the total synthesis of (-)-7(*S*)-hydroxymatairesinol.

Scheme 1.13



Reagents and conditions: a. pyridine, dichloromethane, 81% b. TTMSS, AIBN, benzene reflux, 44% c. TBAF, AcOH, THF, 90%

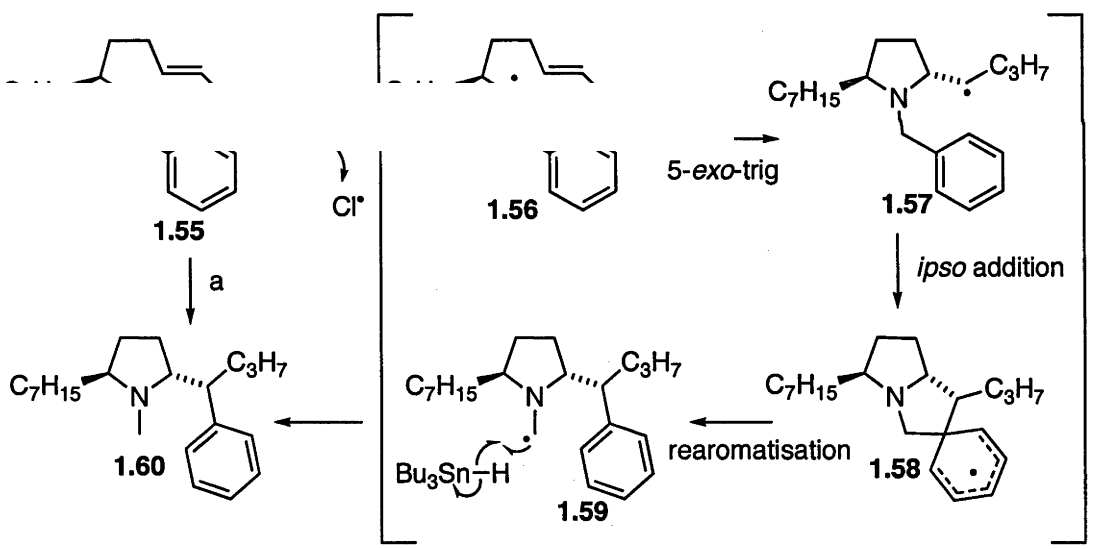
An enantiomerically enriched alcohol **1.50** was prepared and then in turn converted to an aryl thionocarbonate **1.52**. Under radical conditions this reacted to give the desired lactone **1.53**. Deprotection gave the natural product **1.54**. By varying the substitution on

the two aromatic rings, six related natural products were synthesised using this methodology.[35]

1.1.6 Related sequences of cy

The literature holds other examples of radical cascades that proceed by cyclisation then aromatic migration.[36-38] The most recent example, reported by Senboku et al,[39] starts with an *N*-chloroamine **1.55** (Scheme 1.14). Under radical conditions an aminyl radical **1.56** can be generated which can participate in a 5-*exo*-trig cyclisation to give secondary radical **1.57**. The secondary radical **1.57** can then add to the phenyl ring at the *ipso* position. Rearomatisation of the resulting cyclohexadienyl radical **1.58** would eliminate a primary radical **1.59**, which may be stabilised by the neighbouring heteroatom. The carbon centred radical in **1.59** could abstract a hydrogen atom from the Bu_3SnH to give the product **1.60**.

Scheme 1.14



Reagents and conditions: a. AIBN, Bu_3SnH, toluene reflux, 60%

Another type of cyclisation/aromatic addition sequence is demonstrated in the total synthesis of Luotonin.[40] The aromatic addition is not at the *ipso* position and thus a

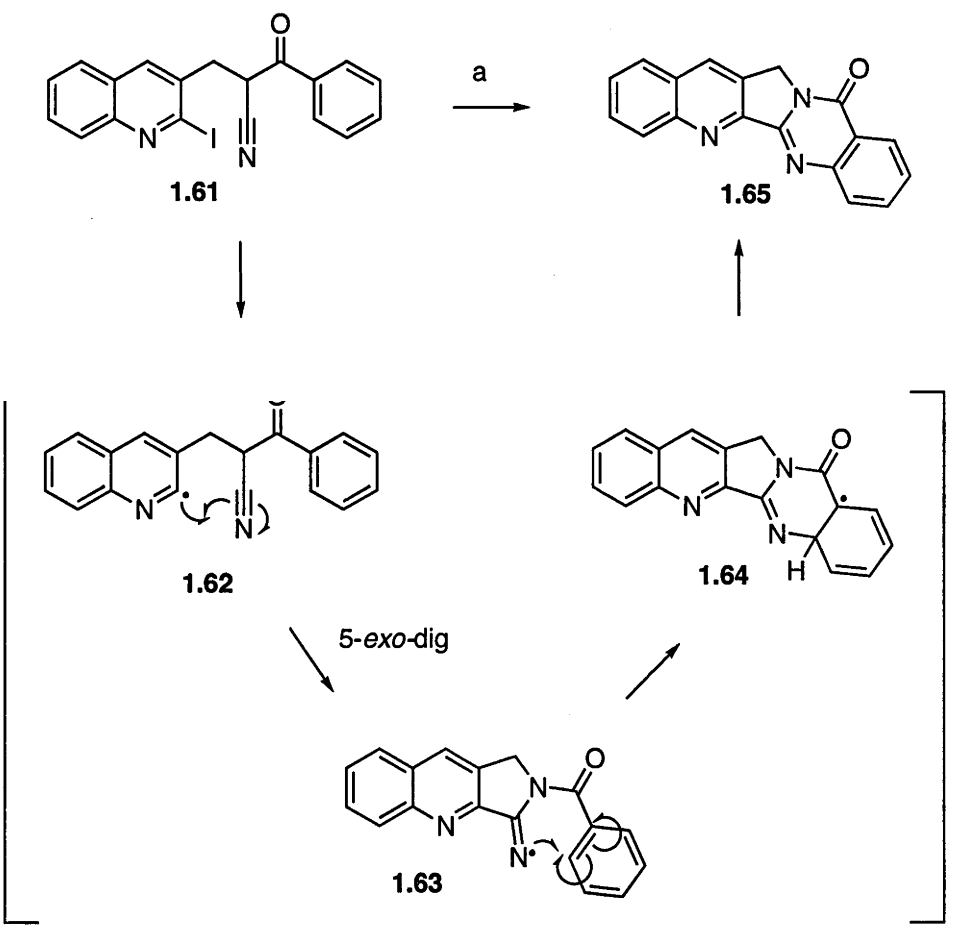
second cyclisation is achieved rather than an

synthesis is shown in Scheme 1.15.) The rad

abstracted from starting material **1.61** to give

cyclisation utilises a nitrile as radical acceptor, generating iminyl radical **1.63**. This nitrogen centred radical then adds to aromatic ring at the *ortho* position generating the pentacyclic structure in **1.64**. Aromatisation then yields the pyrroloquinazoline core **1.65** of the natural product.

Scheme 1.15



Reagents and conditions: a. Bu_6Sn_2, hν, toluene reflux, 47% (over two steps)

The final step in this sequence is the aromatisation of intermediate **1.64**. This is formally an oxidation yet, intriguingly, it occurs under reducing conditions. A study of the

eventual destiny of reagents such Bu_3SnH and AIBN in radical 'oxidative' aromatisation reactions was reported by Beckwith et al.[41] Their results implicated AIBN as suspect for this mysterious oxidation. How photolytically initiated and the mechanism

1.1.7 Previous investigations into the carboxyarylation reaction: studies on the substitution of the homoallylic alcohol

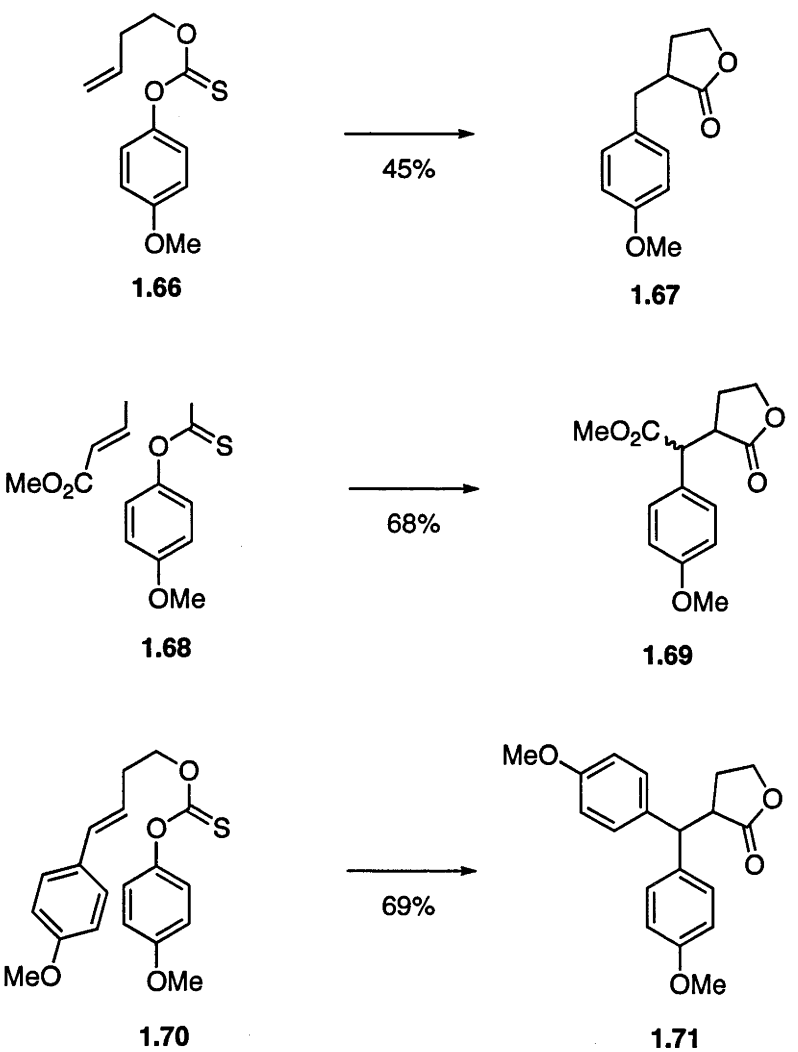
In addition to the synthetic efforts described above, there is a large amount of methodology not published in the literature but very relevant to this thesis. Lisa Sharp[42] conducted an investigation (as part of her PhD studies) into the effect that substrate structure had on the yield and stereoselectivity of the carboxyarylation reaction. She limited her study to varying substitution on the homoallylic alcohol portion of the substrate. Substitution on the aromatic ring was not varied and the *p*-methoxy aromatic group was used in all examples. Previous studies[43,44] had shown this aromatic moiety gave better yields for the carboxyarylation reaction compared with the simple phenyl ring. This is consistent with the findings of Lee et al.[45] In their studies on aryl migration they concluded that the *p*-methoxy aromatic group migrated more efficiently than the *m*-pattern conveniently gives well-defined aromatic signals in ^1H NMR spectra.

In her work varying substitution on the radical precursor Sharp maintained the same radical conditions for all carboxyarylation reactions: 1.1 eq TTMSS, 0.4 eq AIBN added as a benzene solution to the reaction via syringe pump over 6 h. The reaction was conducted in benzene at reflux with the starting material diluted to a concentration of 0.02 M. Unless specified otherwise, all of the following radical reactions used these conditions.

The yield of the radical reaction on the simplest substrate (**1.66** in Scheme 1.16) was found to be only modest (45%). However, by changing the nature of the radical acceptor the yield improved dramatically. Electron poor Michael acceptors and activated styrenes

led to yields of 68% and 69% respectively. T
acceptor compared to the simple alkene bec
radical. Michael acceptors are also known tc
withdrawing groups stabilise adjacent radicals. This is due to the interaction between the LUMO of the carbonyl and SOMO of the adjacent radical. As a consequence of this interaction, the energy of the SOMO is lowered and the radical becomes more electrophillic.[46]

Scheme 1.16

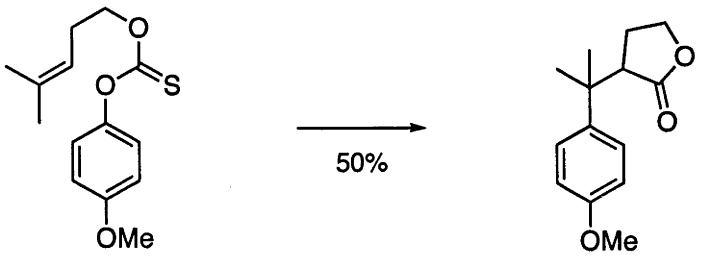


1.66 **1.67** **1.68** **1.69** **1.70** **1.71**

Product **1.69** was isolated as single diastereomer but the stereochemistry was not assigned.

A trisubstituted alkene was also tested as a radical acceptor (Scheme 1.17). U l
conditions precursor **1.72** lead to the creati
this reaction is higher than that of the simp
activated alkenes **1.68** and **1.70** shown in S

Scheme 1.17



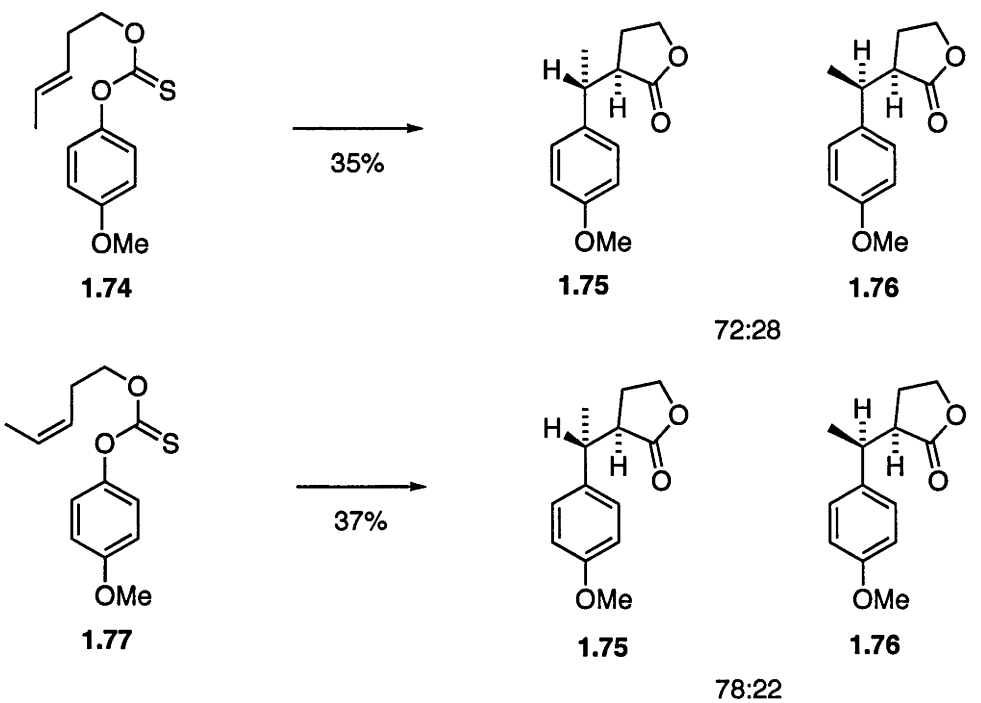
1.72 **1.73**

1.1.8 Stereochemical outcome of the carboxyarylation reaction

Examples of carboxyarylation described in this introduction thus far have yielded one
mycin and podophyllotoxin
the products obtained have resulted from a *syn* addition across the alkene due to the conformational restrictions of their polycyclic structure.

Scheme 1.18 shows a comparison between a Z and E alkene with a methyl substituent responsible for the isomerism. Their ensuing radical reactions both generate two diastereomers, at similar ratios. Sharp was able to assign relative configuration on the basis of single crystal X-ray diffraction.

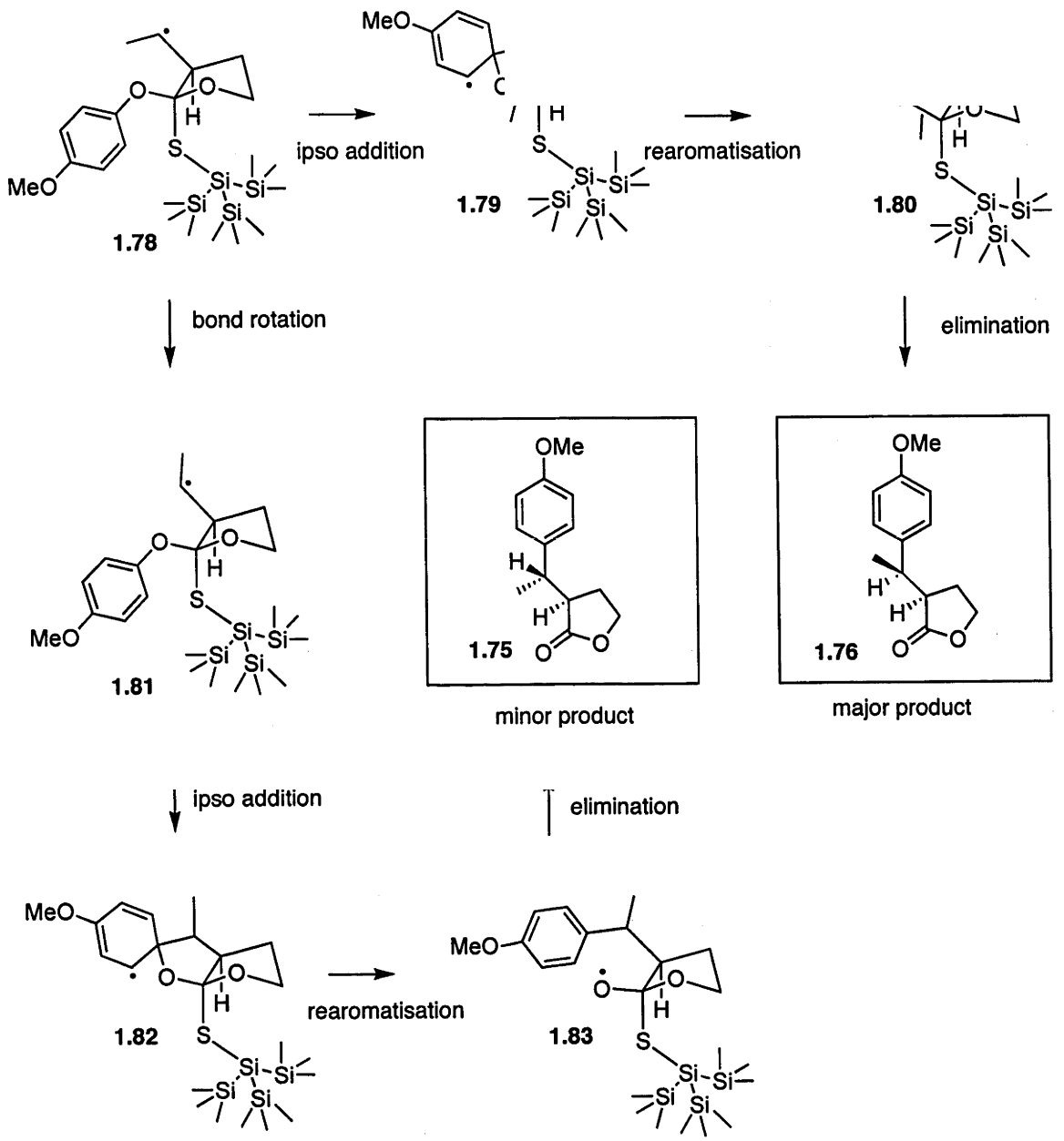
Scher



The relative configuration of the product is determined during the aryl migration that follows initial 5-*exo*-trig cyclisation. Scheme 1.19 depicts the likely mechanism of aryl migration. Migration to one face of the trigonal radical will result in product **1.75** and migration to the other face will result in product **1.76**. Either face of the radical, **1.78** and **1.81** is available by bond rotation.

The preference for forming compound **1.75** could be attributed to spirocyclic **1.79** being lower in energy than its diastereomeric competitor **1.82**. Both precursors could feed into the same transition state **1.79**, which would explain why both precursors favour one product. This suggests that the aryl migration is sufficiently slow to await bond rotations that minimise steric clashes.

Scheme 1.19

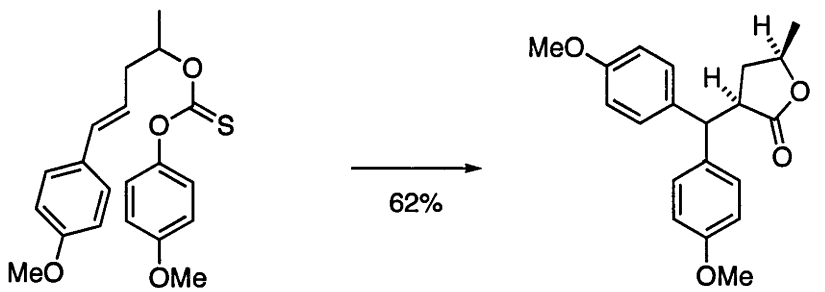


Note: The products are racemic

Scheme 1.20 demonstrates another aspect of

derivative **1.84** leads to a product with two [illegible] yet only one is observed. Sharp was able to assign the relative configuration of the ring protons by nOe: they are *cis* with respect to the ring.

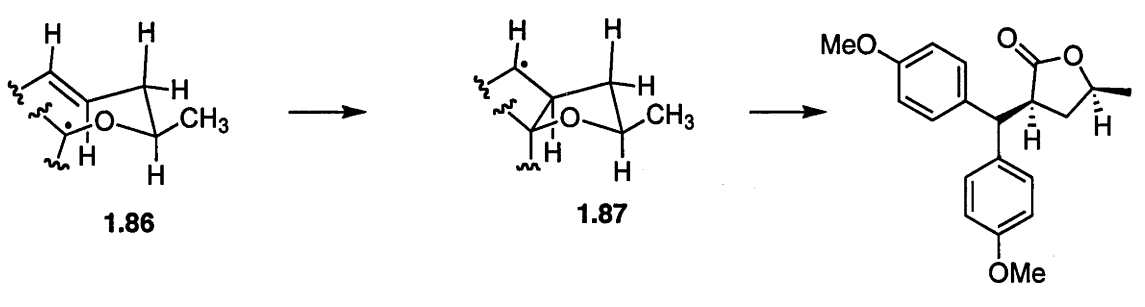
Scheme 1.20



1.84 **1.85**

This outcome is predicted by Beckwith's guidelines for radical reactions.[47] Beckwith et al [illegible]s proceed stereoselectivly due to conformational preference.[48] The stereochemistry of product **1.85** would be set during the initial 5-*exo*-trig cyclisation. In the transition state leading to **1.87** (Scheme 1.21) there is a preference to hold the methyl substituent in *pseudo*-equatorial position. This would lead to the observed stereochemistry.

Scheme 1.21

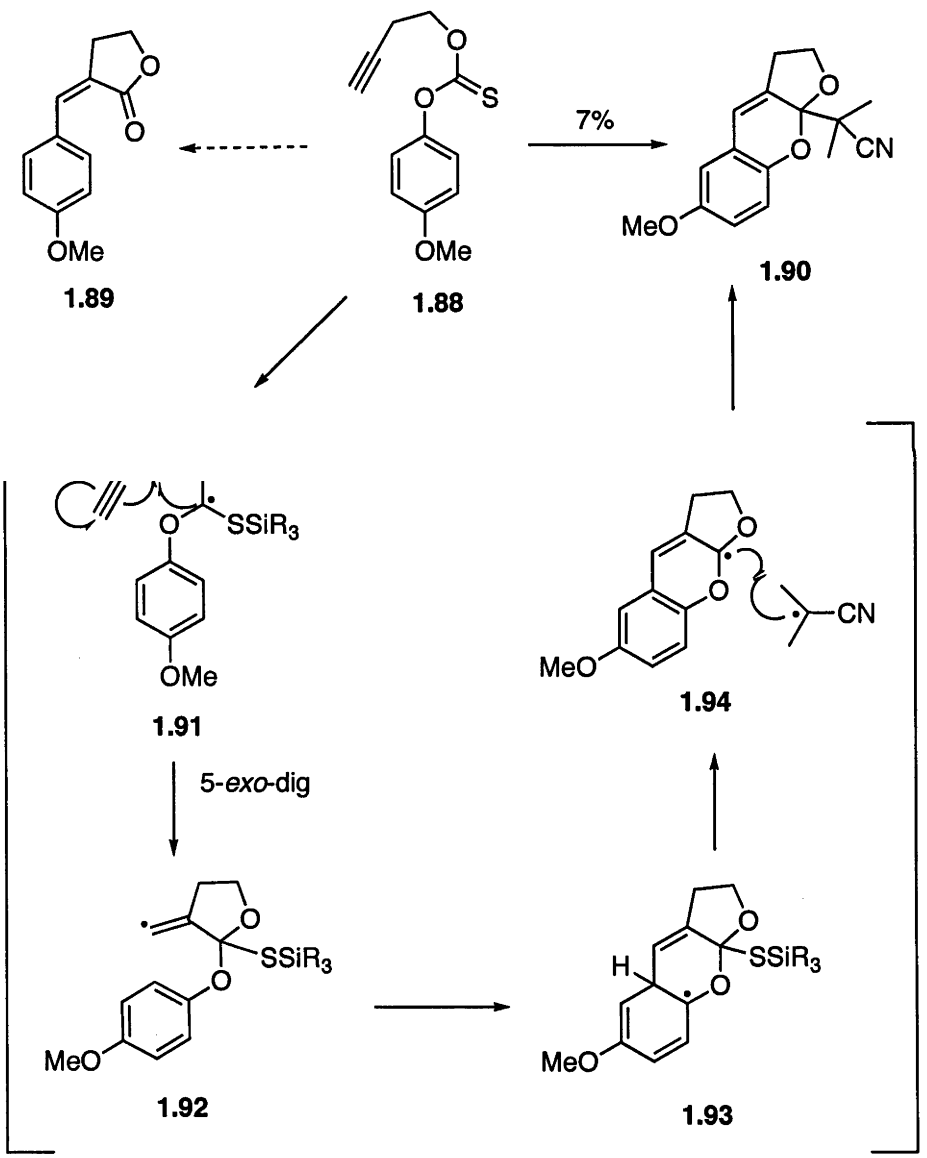


1.86 **1.87** **1.85**

1.1.9 The interesting case of a homopropargyllic alcohol-derived thionoc

By replacing the alkene in the radical preci
the scope of the carboxyarylation methodo t
did not lead to the expected product **1.89** (see Scheme 1.22). Instead a complex mixture was formed. Sharp managed to isolate a small quantity of one of the products, tricyclic **1.90**.

Scheme 1.22



Unexpected compound **1.90** was the result c

1.22. After the initial 5-*exo*-dig cyclisation t[illegible] the *ortho* position of the aromatic ring. Cyclohexadienyl radical **1.93** could undergo aromatisation and then some kind of carbon sulfur homolysis could occur to give radical intermediate **1.94**. Alternatively, a concerted homolysis/aromatisation could take place, generating intermediate **1.94**. This is stabilised by two neighbouring heteroatoms and the adjacent styrene system. Radical coupling between an isobutyronitrile radical (from AIBN) and radical **1.94** would give the product. Incorporation of initiator fragments has been previously witnessed in radical reactions.[49-51]

The mechanism depicted in Scheme 1.22 is quite different from the mechanism of alkene carboxyarylation. In carboxyarylation the substrate has only one interaction with the chain carrier: the initial addition of a radical to the thiocarbonyl. Termination occurs by elimination of the thiyl radical. Such a reaction is said to be self-terminating.[52] However,

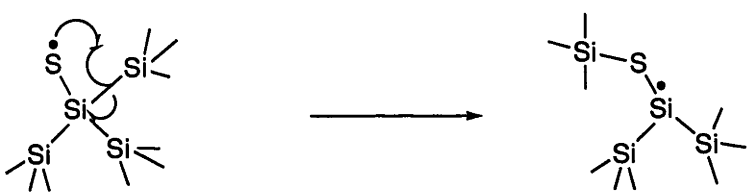
[illegible]ents: addition of silyl

radical to give **1.91**, possible AIBN oxidation of cyclohexadienyl radical **1.93** and radical coupling of **1.94** with local isobutyronitrile radical. Consequently if other pathways lead from some of the intermediates depicted in Figure 1.22 it is no surprise that a complex mixture was formed in this reaction and only a small quantity of **1.90** obtained.

1.1.10 A note on tris*(trimethylsilyl)silane*

Tris(trimethylsilyl)silane can be used in su
silyl migration[21] in sulfur substituted by-pr
in our reaction is to be attached to sulfur that is eliminated in the last step of the mechanism. However a migration of a trimethysilyl group onto sulfur (shown in Scheme 1.23) will in fact regenerate an active silyl centre, which, theoretically, can again participate in the reaction by addition to a thiocarbonyl.

Scheme 1.23

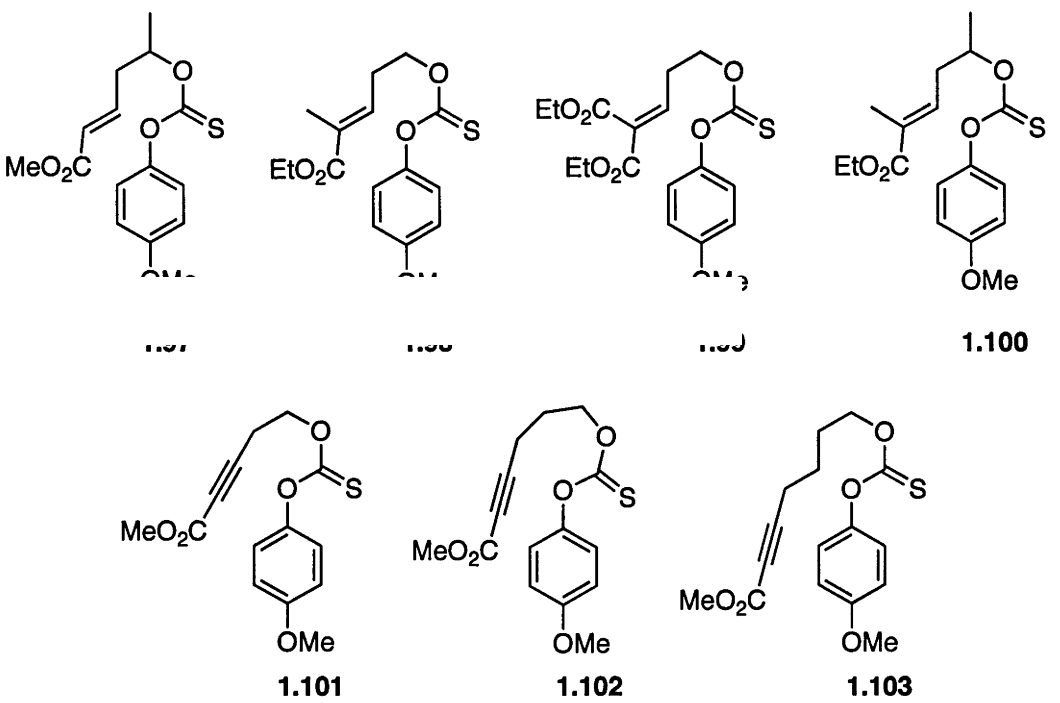


1.96

1.1.1

This chapter describes an investigation into [illegible]. Our intention is to optimise the yield of the reaction by substrate design. Building on the work of Sharp, we intend to prepare thionocarbonates featuring Michael acceptors. As this could lead to the production of multiple diastereomers the stereoselectivity of the reaction will be probed. The Michael acceptor strategy will be extended to the intriguing alkyne example. Will this change the outcome?

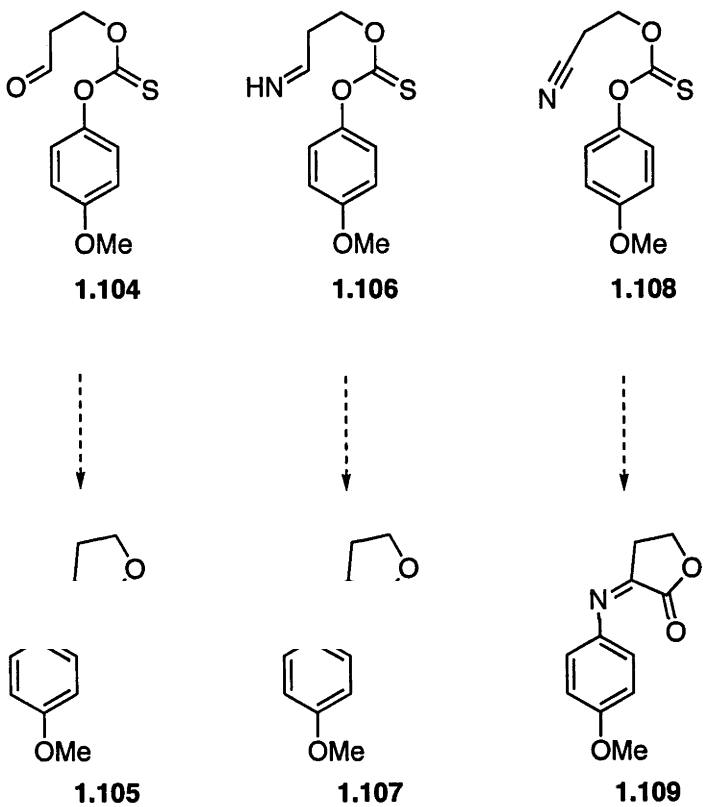
Figure 1.24



The limits of ring size will also be considered and a series of alkynic thionocarbonates prepared. These should lead to products with five-, six- and seven-membered rings. Figure 1.24 shows the library of thionocarbonates to be synthesised.

With respect to scope, we wish to try radical acceptors other than alkenes or
Aldehydes, imines and nitriles shall be inc
these react as expected under radical condi
be obtained.

Scheme 1.25

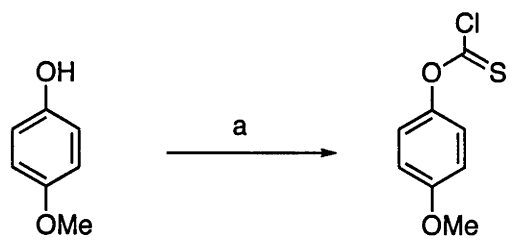


The question of what conditions are optimal for radical cyclisations will also be addressed. Attempts at using substoichiometric TTMSS will be made. Comparison will be made between the different initiators AIBN and BEt_3/O_2.

1.2 Results a

1.2.1 Synthesis of the Aryl Thionochloroformate

Scheme 1.26



1.110 **1.111**

Reagents and Conditions: a. NaOH, thiophosgene, water/dichloromethane, 0 °C - RT, 76%

Commercially available *p*-methoxyphenyl chlorothionoformate **1.111** was synthesised and thiophosgene (Scheme 1.26).[43]

1.2.2 Synthesis of Alcohols

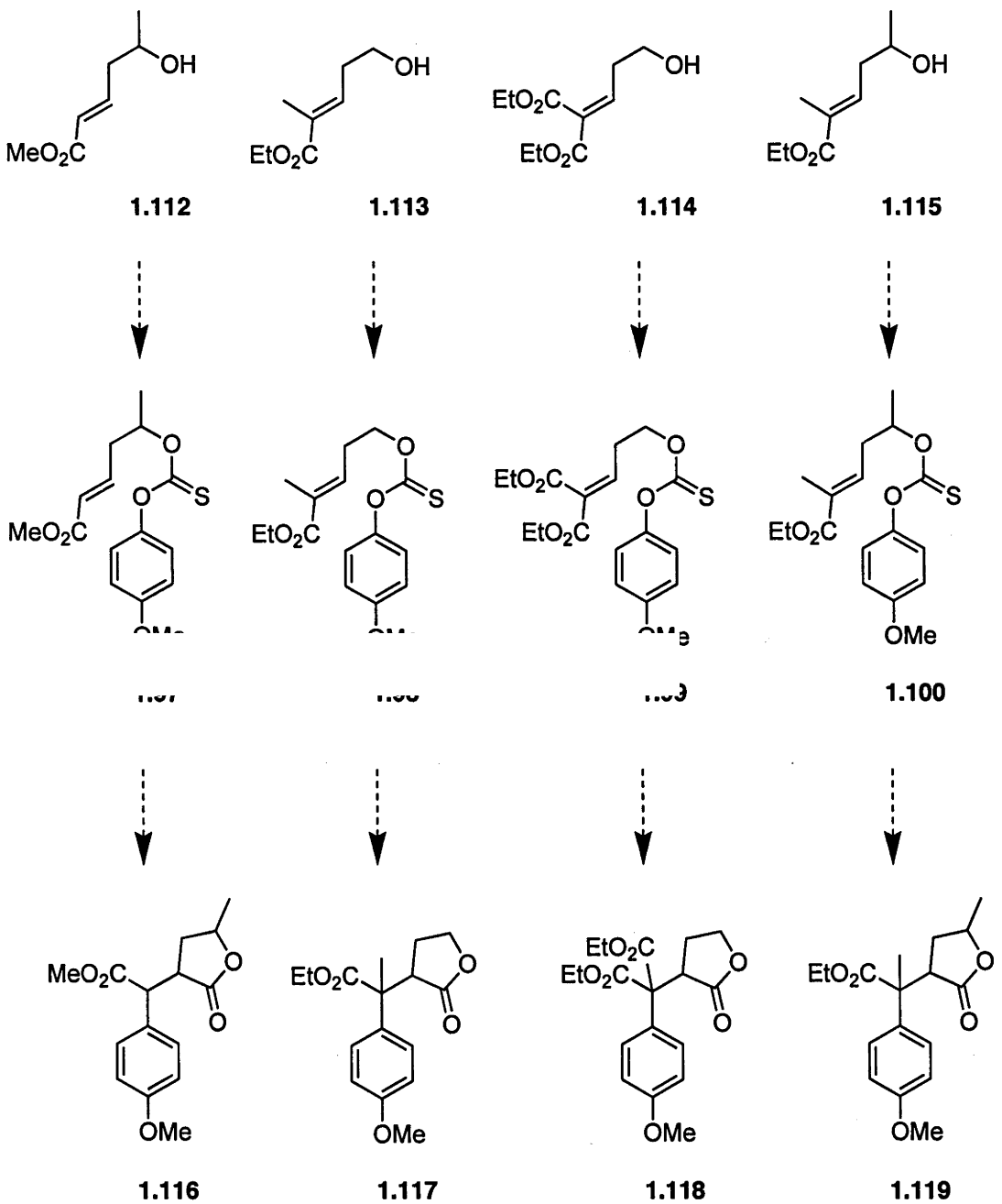
1.2.2.1 Synthesis of homoallylic alchols

A series of homoallylic alcohols were sought to convert to the corresponding thionocarbonates. This library of substrates would be used to create high yielding examples of the radical cyclisation featuring varied substitution. In particular, alcohols featuring Michael acceptors would be pursued so as to maximise the yields of the subsequent carboxyarylation reactions.

Secondary alcohol **1.112** (once converted into a thionocarbonate) should lead to a high yielding radical reaction and the formation of two new stereocentres. Alcohol **1.113** featuring a trisubstituted alkene would lead to the formation of a quaternary centre. Alcohol **1.114** with a diester substitution on the alkene could be expected to give an even

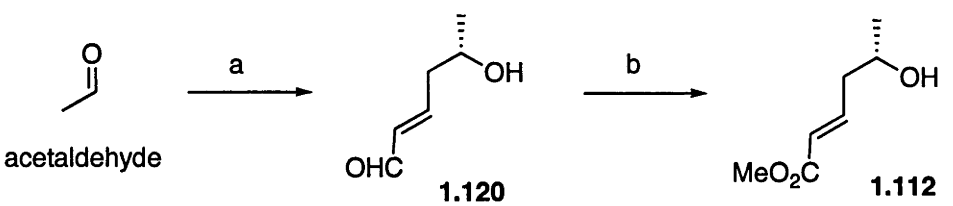
higher yield of product while secondary alcohol **1.115** is a combination of **1.112** and **1.113** and will allow further insights into the stereoselectivity of the reaction.

Scheme 1.27: Alcohols to t



The secondary alcohol **1.112** was synthesise
Adherence to the literature procedure failed
initial trimerisation-dehydration was found t
was added. This phenomenon in proline catalysed reactions has been investigated by Zotova et al.[54] They found that water suppressed catalyst poisoning among other complex effects. Pinnick oxidation of the resulting aldehyde **1.120** and esterification with diazomethane was carried out in accordance with the reported procedure, giving the known alcohol in good yield over two steps.

Scheme 1.28

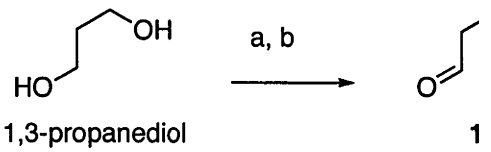


Reagents and Conditions: a. 5mol% L-Proline, THF, water, 4°C; b. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-butanol/water then CH_2N_2, diethyl ether, 68% over two steps

Alcohol **1.112** was found to have an optical rotation of +7.25, indicating enantio-enrichment had occurred. Barbas et al[53] did not include an optical rotation in their characterisation data.

Known alcohol **1.113**[55] was synthesised in four steps from 1,3-propanediol (see Scheme 1.29). Mono-protection of 1,3-propanediol with TBSCl[56] was followed by oxidation with pyridinium chlorochromate. The resulting aldehyde was then converted to the olefin by reaction with a stabilised ylide. TBAF deprotection gave known[55] alcohol **1.113** in good yield.

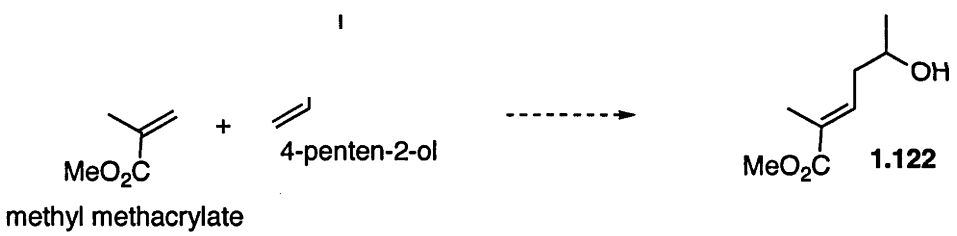
Scheme 1.29



Reagents and Conditions: a. NaH, TBSCl, THF, 68%;
b. PCC, $NaHCO_3$, NaOAc, dichloromethane, 81%;
c. $Ph_3PCH_2C(CH_3)CO_2Et$, dichloromethane, 63% d. TBAF, THF, 63%

It was envisaged that alcohol **1.122** could be made in one step by olefin metathesis. The coupling of methyl methacrylate with terminal olefins was described by Grubbs and co-workers in 2000.[57] They used the then new Grubbs 2nd generation catalyst and reported moderate to high yields.

Scheme 1.30



Reagents and Conditions: a. 10 mol% Grubbs II catalyst, dichloromethane

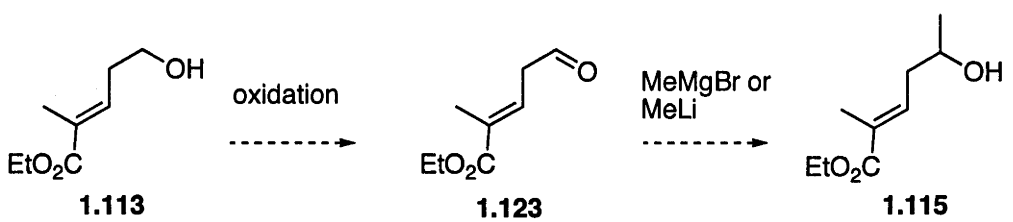
A range of solvents and reactions times were trialled but all attempts at this reaction failed. The first step of the reaction, homodimerisation of the more reactive 4-penten-2-ol, appeared to proceed when monitoring the reaction by ^1H NMR. However, this did not seem to react any further and broad peaks suggestive of a methyl methacrylate oligomer were also observed in the ^1H NMR of the reaction mixture. The desired product was not observed.

Closely examining the work by Grubbs clari
approaches. These could explain the diverge
Grubbs' terminal olefin coupling partners b[illegible]
distant from the olefin. Furthermore these substituents were not free alcohols but ethers and esters. A 2:1 stoichiometry of terminal olefin to methyl methacrylate was employed. As methyl methacrylate is obviously the less valuable of the two starting materials, this stoichiometry must be chosen to favour metathesis, perhaps by reducing the opportunities for oligomerisation.

It seems that cross metathesis utilising methyl methacrylate will work only under specific conditions. While some of these could be accommodated (by protecting the hydroxyl group and adjusting the stoichiometry) others could not (substitution at the homoallylic carbon) and a new route was investigated.

The demonstrated easy availability of primary alcohol **1.113** tempted us to try an alpha

Scheme 1.31



1.113 **1.123** **1.115**

This approach faltered on the formation of the aldehyde. A variety of oxidation conditions were employed (TEMPO/BAIB, PCC, DMP, TPAP/NMO) but the reaction always gave a number of products. We considered aldehyde **1.123** would be an unsuitable candidate for chromatography due to the possibilities for tautomerisation to a conjugated enol. Furthermore, a mixture of compounds possibly containing aldehyde **1.123** is an unsuitable starting material for subsequent alkylation reaction. Such an alkylation reaction would be difficult in any case due to the possibility for multiple

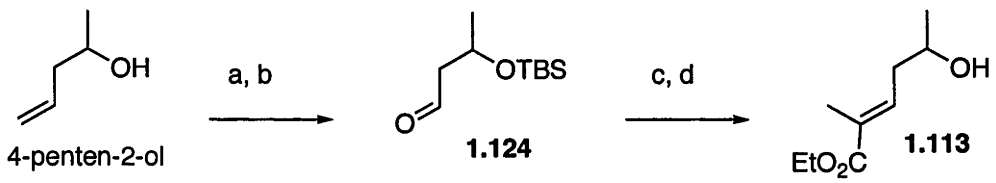
alkylations on the substrate. For these reasons we returned to our previously successful strategy of building these homoallylic alcohols directly via Wittig reactions.

The following synthesis, shown in Scheme

Starting with commercially available 4-pen

TBS ether and the alkene ozonolysed to the aldehyde **1.124**. The crude aldehyde was then olefinated using a stabilised ylide and the alcohol deprotected under acidic conditions.

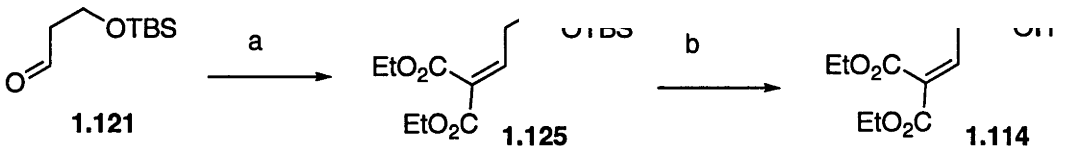
Scheme 1.32



Reagents and Conditions: a. TBSCl, imidazole, 92%; b.ozone, PPh_3; c. $Ph_3PCH_2C(CH_3)CO_2Et$, $PhCH_3$, 86% (over two steps) d. HCl, MeOH 82%

viously reported (but not characterised) TBS ether **1.125**.[58] The doubly activated olefin in **1.125** is a classic Knoevenagel condensation product from the reaction between diethyl malonate and aldehyde **1.121**. Initial attempts utilising a proline catalysed Knoevenagel condensation[59] failed. The $TiCl_4$ mediated method[60] went well, presumably by forming a robust complex between the titanium and oxygen of the aldehyde **1.121**, that was now sufficiently electrophilic to attract the interest of the nucleophile.

Scher



Reagents and Conditions: a. $TiCl_4$, diethyl malonate, pyridine, THF, 44%; b.TBAF, AcOH, THF, 82%

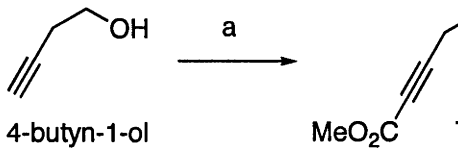
Attempted deprotection using TBAF in THF converted the starting TBS ether **1.125** to a complex mixture. This can be attributed to either to the nucleophilic fluoride adding to the electrophilic Michael acceptor and/or fluoride acting as a base at the allylic position and a variety of ensuing side reactions. A milder deprotection protocol that ameliorated the nucleophilicity/basicity of the fluoride ion with acetic acid[61] was adopted and the desired alcohol **1.114** obtained.

1.2.2.2 Synthesis of alcohols containing alkynes

A series of alcohols containing alkynes were prepared with varying chain lengths. Assuming successful radical cyclisation of the corresponding thionocarbonates, this series should furnish us with products of varying ring sizes, thus further extending the scope of the reaction. Following the unexpected result recorded by Sharp when using alkynes as radical acceptors (see Scheme 1.22 in the introduction), this series could also lead to further mechanistic insights regarding the aromatic substitution step in the cascade.

The synthesis of alcohol **1.127** began with 4-butyn-1-ol, which was first converted to the known TBS ether.[62] This was then treated with butyllithium generating the lithium acetylide which was quenched with methyl chloroformate to give **1.126**. Buffered TBAF conditions gave the desired homopropargyllic alcohol **1.127**.

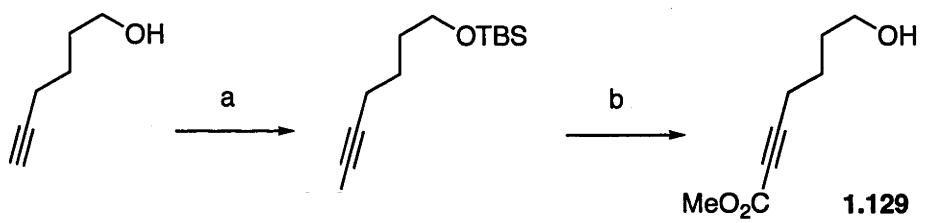
Scheme 1.34



Reagents and conditions: a. i. TBSCl, imidazole, THF, 94% ii. nBuLi, methyl chloroformate, THF, 78% b. TBAF, AcOH, THF, 62%

By replacing butynol with 5-hexyn-1-ol, alcohol **1.129** was obtained using the same synthetic route.

Scheme 1.35



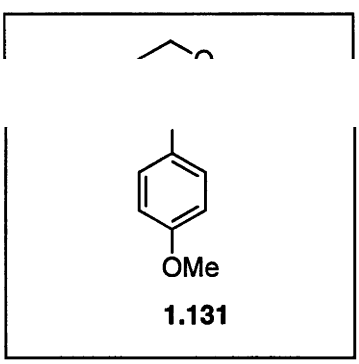
Reagents and conditions: a. i. TBSCl, imidazole, THF, 99% ii. nBuLi, methyl chloroformate, THF, 93% b. TBAF, AcOH, THF, 55%

The pentynol derived alcohol **1.130** (a known compound[63]) was synthesised by postdoctoral fellow Dr Ignace Louis.

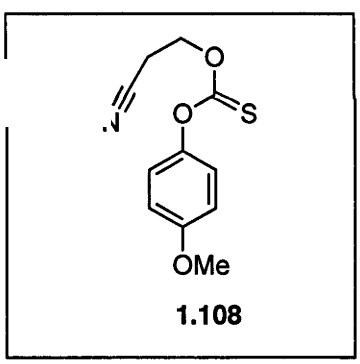
1.2.3 Synthesis o

Thionocarbonates were synthesised by comb[illegible] phenyl chlorothionoformate and pyridine in dichloromethane. Some thionocarbonates were sufficiently pure from the work up of this reaction to use without further purification. Compounds **1.100** and **1.102** were made from alcohols **1.115** and **1.130**, which were prepared by Dr Ignace Louis.

Compounds **1.131** and **1.108** were made from commercially available 1,3 propanediol and hydroxy propionitrile, respectively. The resulting thionocarbonates form another avenue of investigation, namely cyclisation onto double bonds incorporating heteroatoms. It was envisaged that primary alcohol **1.131** could be converted to the corresponding aldehyde and imine.



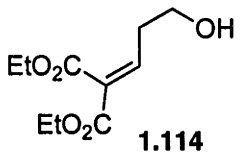
1.131



1.108

The reaction of doubly activated homoallylic alcohol **1.114** with thionochloroformate went to completion (the starting material was consumed), however, the desired product **1.99** was not isolated.

Scheme 1.36



1.114

1.99

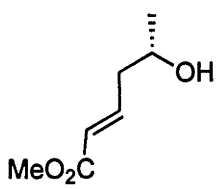
Reagents and conditions: a. 1.1 eq *p*-methoxy phenyl thionochloroformate, 2.0 eq pyridine, dichloromethane, RT

^{1}H NMR of the crude product suggested more than one thionocarbonate product was present in addition to the *p*-methoxyphenol commonly encountered in these reactions. Attempts to isolate the desired compound by flash chromatography failed due to *p*-methoxy phenol, which commonly co-eluted with the product. The relative quantity of phenol observed in the columned material compared with the quantity of phenol in the crude material suggested the product was decomposing on silica. Extraction of phenol produced a substantial new impurity. Elimination of the thiocarbonate was flagged as a potential pathway to decomposition. The material was sensitive to both acidic and basic environments. Due to these difficulties the synthesis of **1.99** was abandoned.

Table 1.37 shows the successful conversion of alcohols to thionocarbonates using 1.1 eq *p*-methoxy phenyl thionochloroformate, 2.0 eq pyridine in dichloromethane at room temperature. Yields range from 53-98%.

Table

alcohol ⟶



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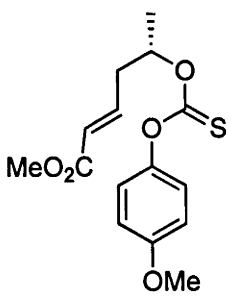

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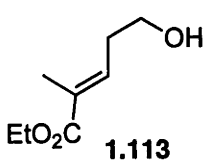

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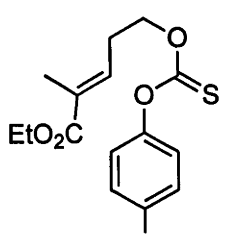

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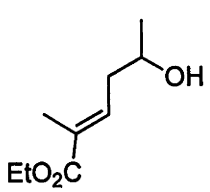
1.98



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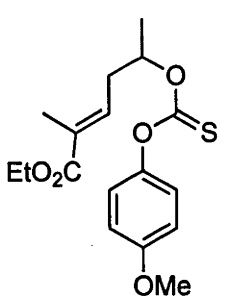

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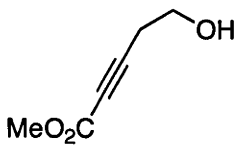

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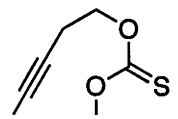

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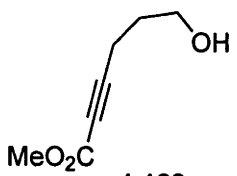

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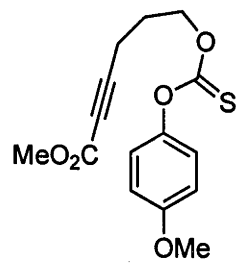

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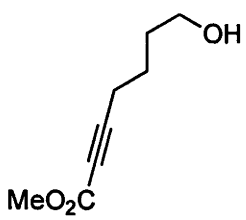
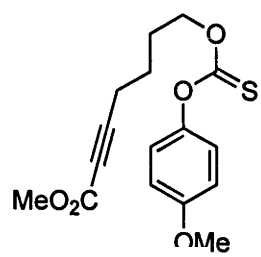


1.129



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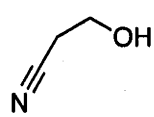
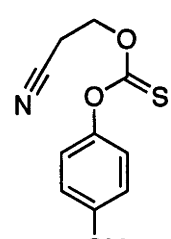
03



hydroxypropionitrile



86%

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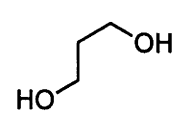
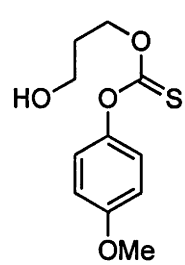


1,3-propanediol



94%

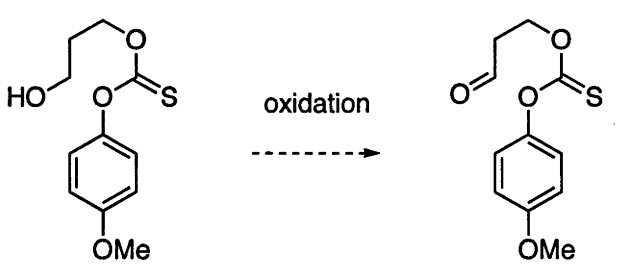
1.131

Thionocarbonate **1.131** had been synthesise
oxidised to an aldehyde to give radical prec
the desired thionocarbonates directly from t
case as the required 3-hydroxypropanal is not readily available. It seemed sound to first create the more robust thionocarbonate functionality and then introduce the aldehyde via oxidation of an alcohol (see Scheme 1.38).

We anticipated that aldehyde **1.104** would be unstable to column chromatography (as aldehydes commonly trimerise on exposure to acid even in the presence of triethylamine.) Also, the small quantities we were working with (due to a temporal scarcity of thiophosgene) did not lend themselves to distillation. Consequently we sought a set of oxidation conditions that would give material of sufficient purity to use directly in the radical reaction. Unfortunately this eluded us.

Oxidation with pyridinium chlorochromate did not go to completion (even with excess
of the crude isolate showed a promising aldehyde peak but also starting material, present in a similar quantity, along with *p*-methoxy phenol and other minor impurities. Given sulfur's reputation for poisoning metal oxide reagents we turned to a metal free oxidation: catalytic TEMPO with BAIB. In this case an aldehyde peak was observed along with starting material and numerous impurities.

Scheme 1.38



1.131 **1.104**

These difficulties are precedented by the attempts of Lisa Sharp to oxidise a benzylic alcohol in the presence of a thionocarbonate during her studies towards the tc s of totarol.[42] Consequently, we moved forw

1.2.4 Radi

In pursuing the radical chemistry of these thionocarbonates we hoped firstly to improve the yield of the carboxyarylation product. With this in mind, two standard sets of radical conditions were developed. 'Thermal' conditions refers to the use of *azo-bis*-isobutyronitrile (AIBN) as an initiator, *tris*(trimethylsilyl)silane (TTMSS) as a radical chain carrier in benzene. The thermal reaction employs a minimal quantity of reagents, 0.2 eq AIBN and 0.5 eq TTMSS (in benzene at reflux, 0.020 M concentration.)

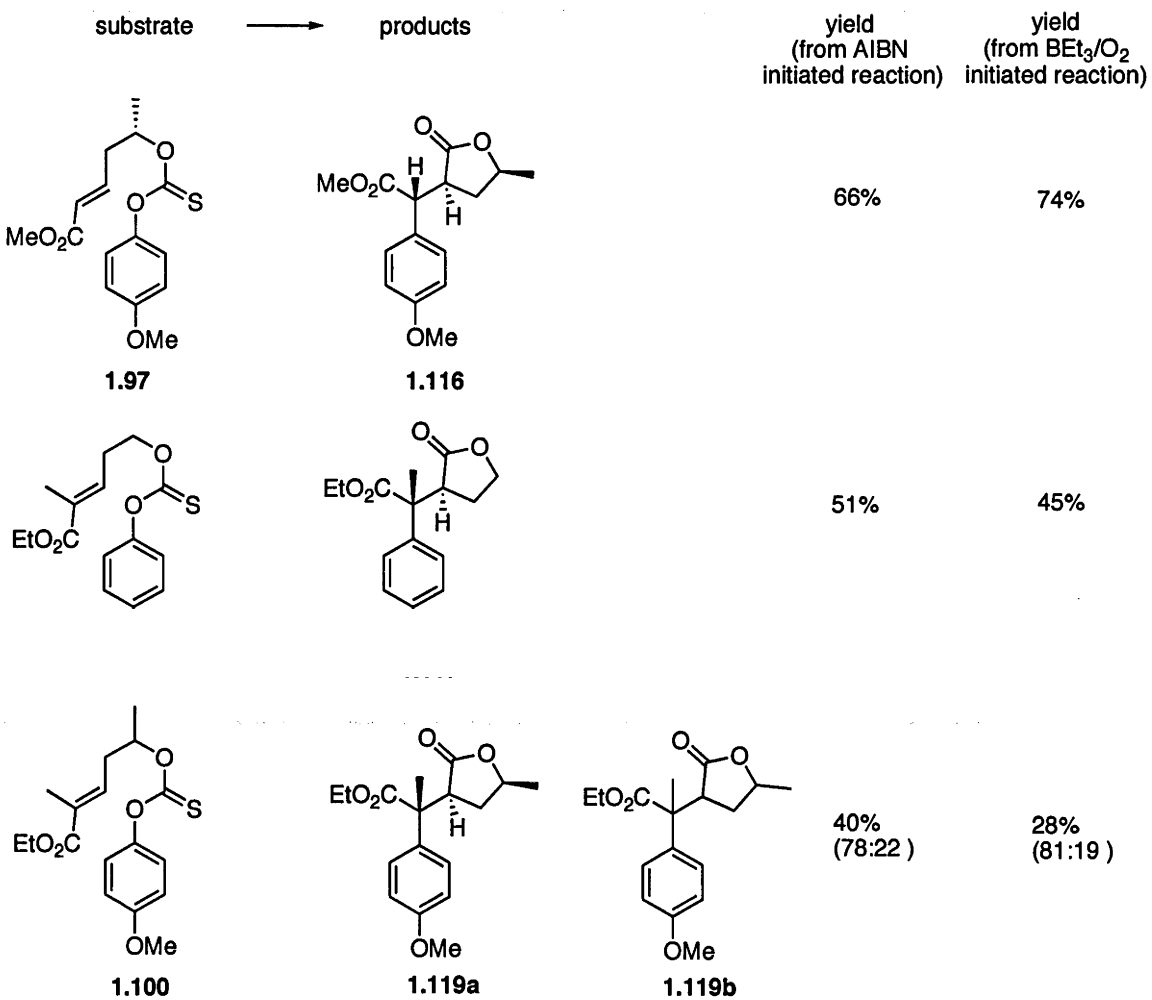
Triethylborane conditions refers to the use of triethylborane and oxygen as an initiating couple and TTMSS as the radical chain carrier. As the quality of triethylborane is variable and difficult to quantify an excess was employed. An excess of air, typically 1 mL, was bubbled into the reaction to allow oxygen to react with the triethylborane, in turn generating the ethyl radicals that will react with TTMSS. An excess of TTMSS is which is essential for initiation) also reacts (unfavourably) with the TTMSS. Thus a triethylborane reaction employs 1.5 eq BEt_3 (1.0 M solution in hexanes), 2.0 eq TTMSS, 1.0 mL air, (in acetone[#] at room temperature, 0.020 M concentration.)

1.2.5 Radical Chemistry of Thionocarbonates containing Michael acceptors

The following Table 1.39 shows the results of the radical reactions of the alkenic precursors under the two sets of conditions.

[#] Acetone was chosen as a less reactive alternative to ethereal solvents such as diethyl ether and tetrahydrofuran which possess readily abstractable hydrogen atoms.

Tabl_ ___



1.2.6 Issues of stereoselectivity arising from these three examples

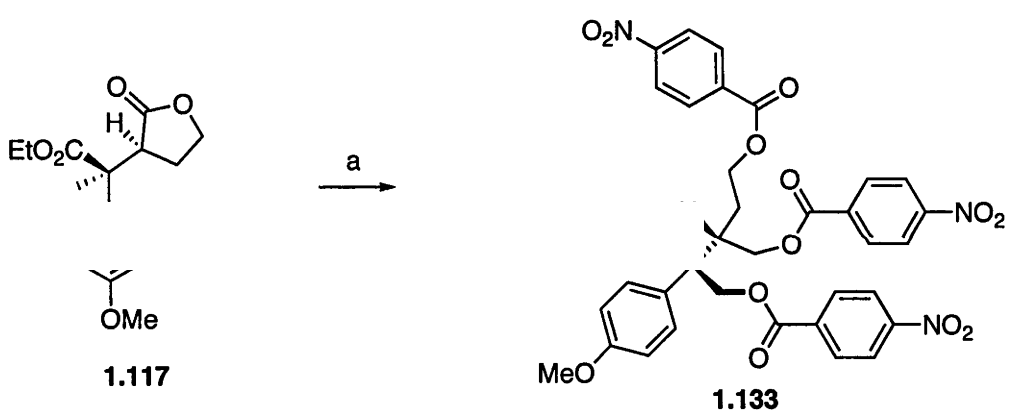
*1.2.6.1 Lactone **1.117***

Thionocarbonate **1.98** was converted to the aryl lactone **1.117** as a single diastereomer. While the diastereoselectivity is pleasing, the reaction proceeded in only moderate yield (51% and 45%). We had hoped that by using an electron withdrawing group on the alkene the yield would be improved compared with a simple tri-substituted alkene. This was not the case as the yield for this reaction is very similar to one recorded by Sharp for

her unactivated system with a tri-substituted alkene (Scheme 1.17 in the introduction). Possibly an increase in steric interactions caused by carrying an ester group h
cyclisation and these effects are not effecti
electronics.

In order to assign the relative stereochemistry of this compound, crystalline derivatives were sought. As the product has an acidic proton at one of the stereocentres it was important to derivatise without epimerising. Consequently aryl lactone **1.117** was reduced to the triol with DibAlH and the crude triol esterified with *p*-nitrobenzoyl chloride. Fortunately, the triester **1.133** was crystalline and single crystal X-ray diffraction provided the structure.

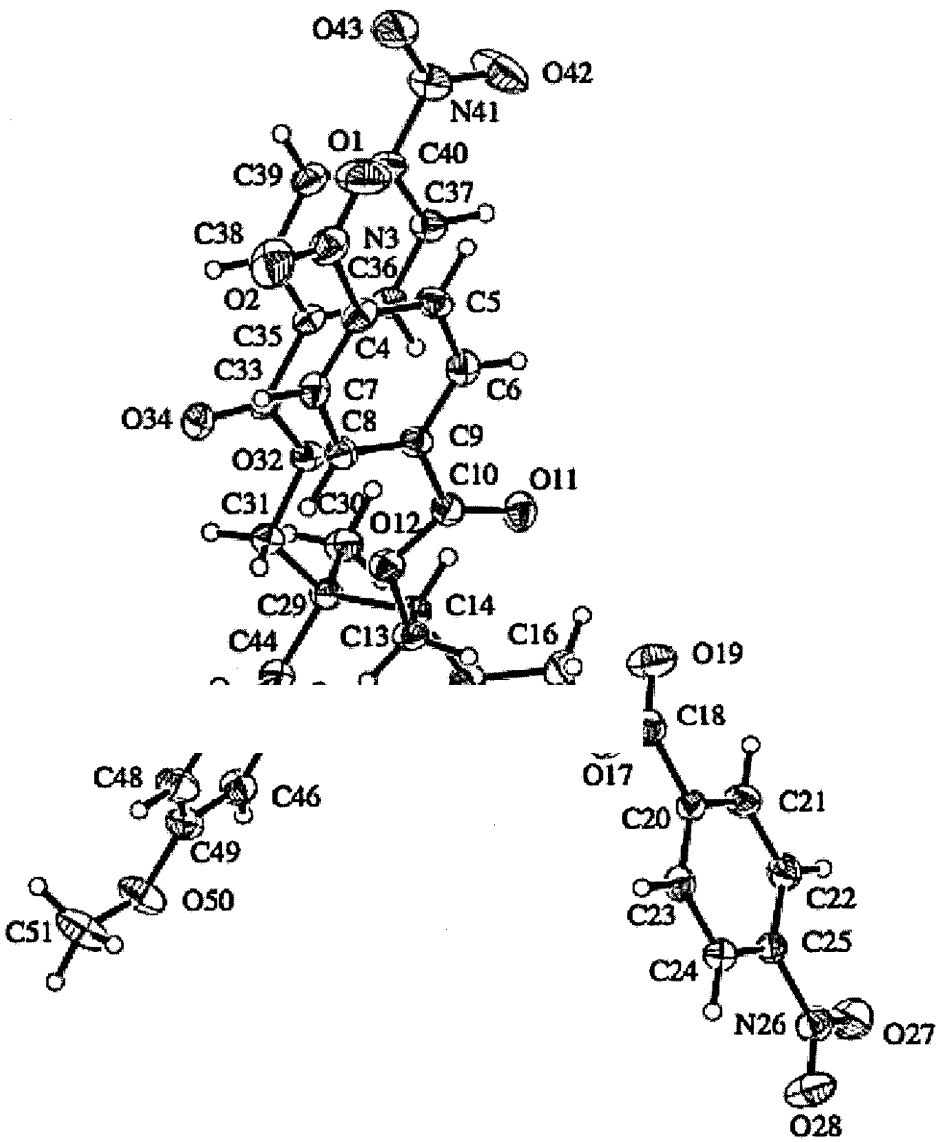
Scheme 1.40



1.117 **1.133**

Reagents and conditions: a. DibAlH, dichloromethane, 0 °C - RT b. 4-nitrobenzoyl chloride, pyridine, dichloromethane

Schem



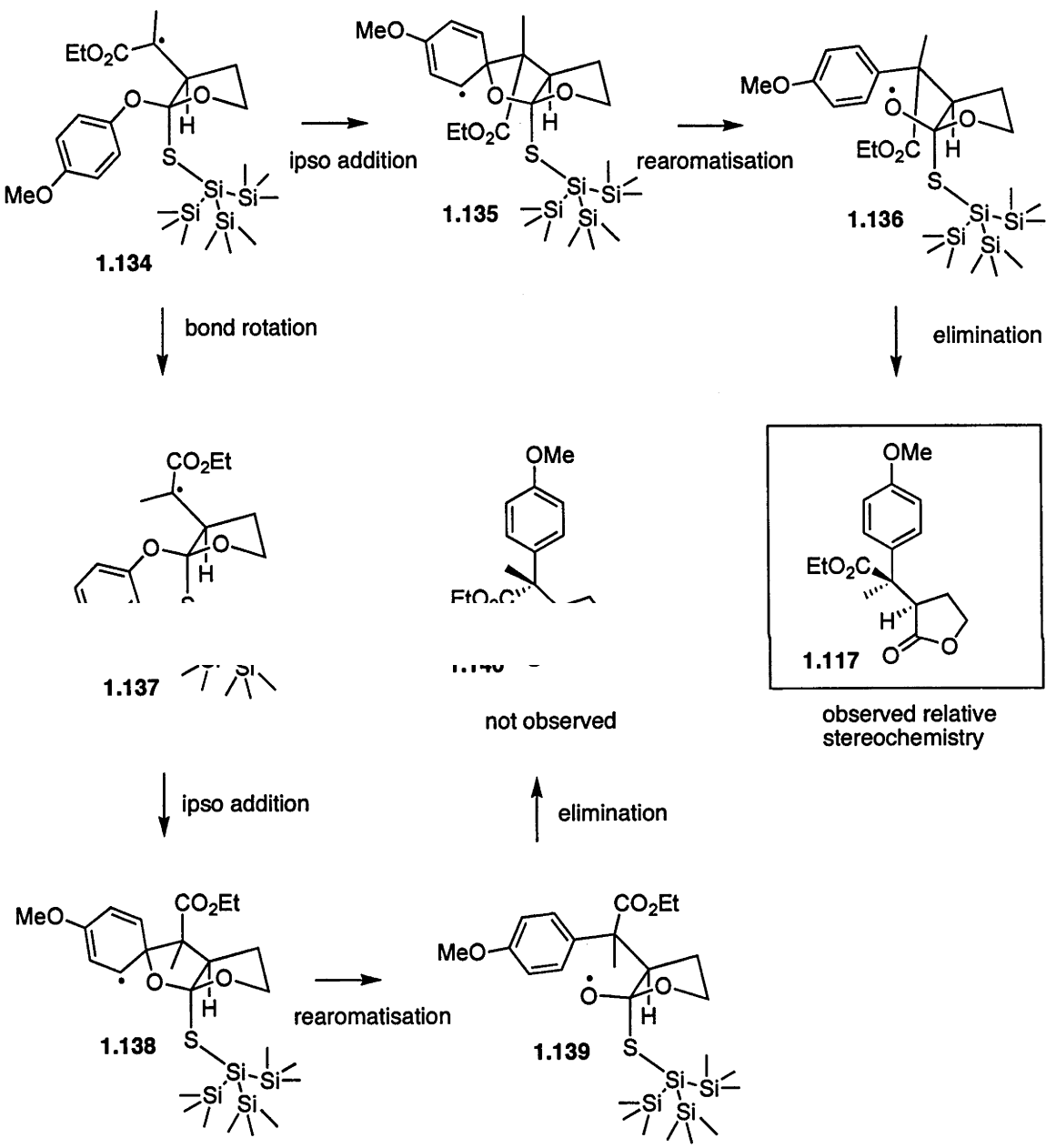
Structure of **1.133**

Compound **1.117** has two stereocentres, consequently two diastereomers could be formed during its formation. The diastereomer that is formed from thionocarbonate **1.98** is derived from the *syn* addition of the carboxyl group and the aromatic ring to the trans-alkene of the starting material. The key to the relative stereochemistry of the product is the orientation of the trigonal radical during the 1,4 – aryl migration.

In the mechanistic pathway that leads to **1.140**, the diastereomer that is not ol
this reaction, there is a bond rotation prior
this, the ester group is placed in the *pseudc*
transition state leading to spirocyclic **1.138**
mechanistic pathway leading to the observed diastereomer does not have a bond rotation to accomplish nor a substituent held in a *pseudo*-axial position in a transition state. Conceivably this is why one mechanistic pathway is favoured and only one product is observed in this reaction.

An alternative theory would consider the bond rotation that leads to spirocyclic **1.138** simply too slow to compete with *ipso* addition. Under this mechanism, the ratio of products should correlate with the ratio of *E* and *Z* alkene isomerism.

Schen


ipso addition
rearomatisation
bond rotation
elimination
1.134
1.135
1.136
1.137
1.117
observed relative stereochemistry
not observed
ipso addition
elimination
rearomatisation
1.138
1.139

*1.2.6.2 Lactone **1.116***

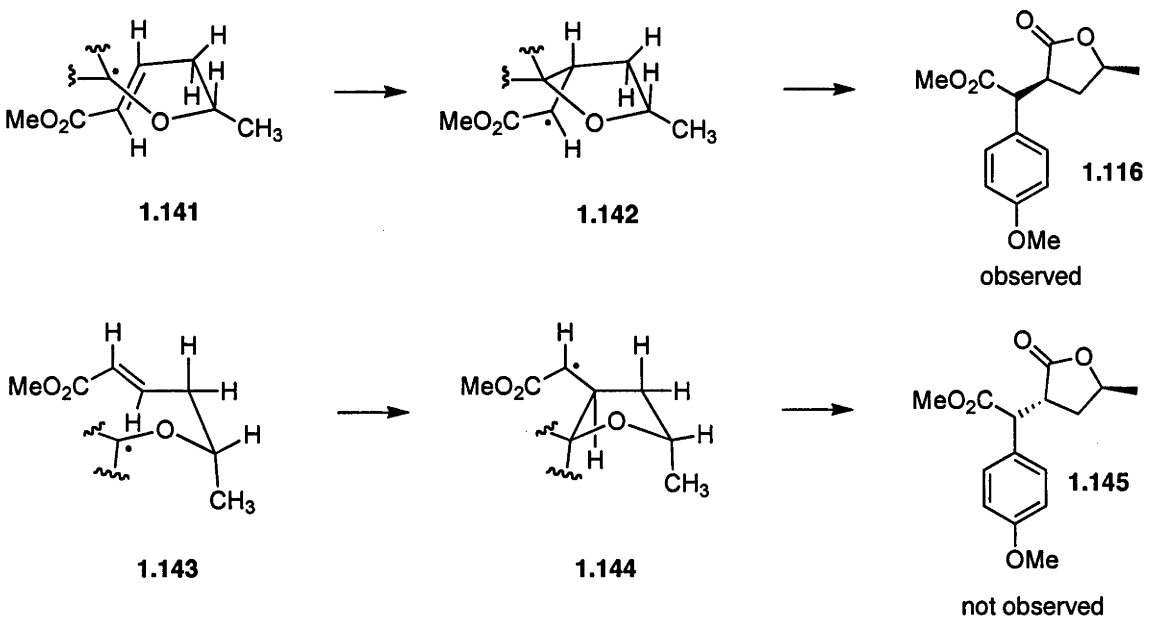
As was expected, thionocarbonate **1.97** rea
lactone **1.116** as a single diastereomer in g
be expected to compete effectively with ca
reported to be good candidates for Barton McCombie deoxygenation. However, the high yield of the reaction shows this is not the case.

It is conceivable that the Thorpe-Ingold effect[64] favours the cyclisation. Thorpe and Ingold state that by placing substituents between reacting centres the population density of reactive conformations is maximised. In a reaction such as ours, which is competing with de-oxygenation, increasing the rate of reaction is key to increasing the yield.

The product contains three stereocentres and consequently there are four diastereomeric products possible. However, only one product is obtained. While one of the stereocentres is present in the starting material, two are formed in the reaction: one is formed during the initial 5-*exo*-trig cyclisation and the other is formed during the aryl migration. As seen with Sharp's example in the introduction (see Scheme 1.21), Beckwith's rules[47] on
cording to Beckwith, by placing the larger substituents in the equatorial positions on a cyclic transition state, the energy of the transition state is minimised and is favoured over other transition states. As shown in Scheme 1.42, intermediate **1.142** features *pseudo*-equatorial substituents. Compare this with intermediate **1.144** where one of the substituents is in *pseudo*-axial position. If we were to follow Beckwith's rules, **1.142** should be the favoured transition state, leading to lactone **1.116**.

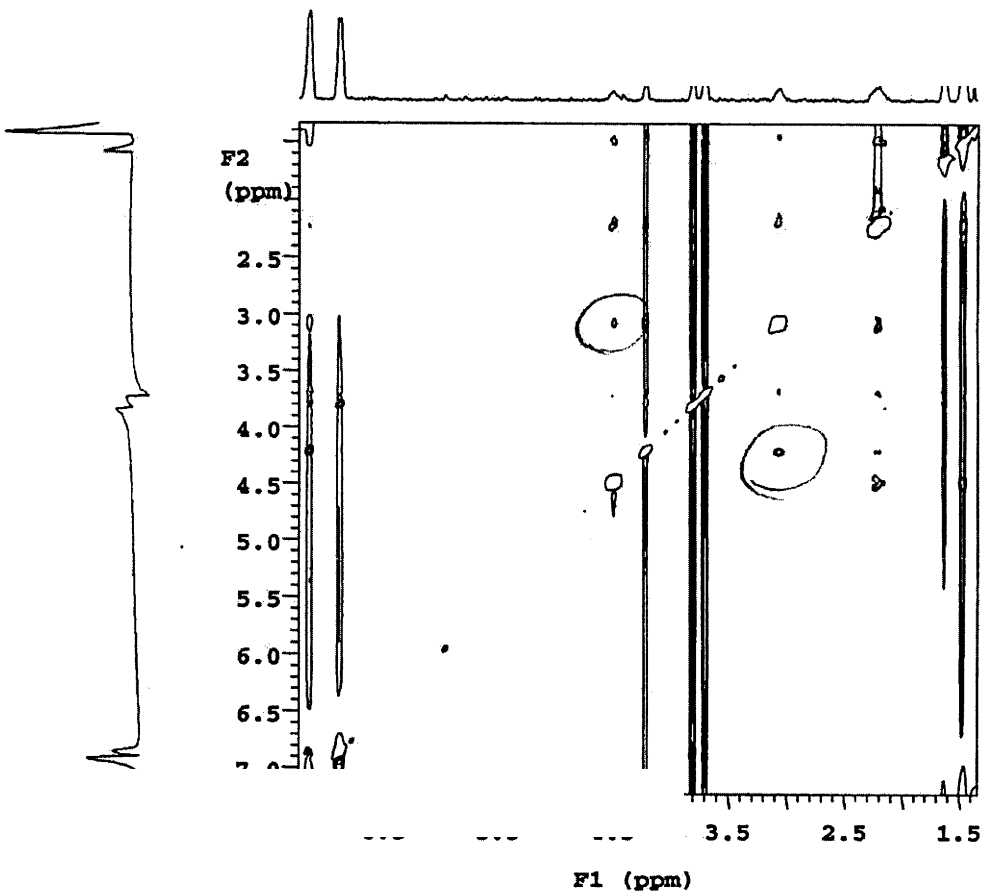
A 2D NOESY spectrum of this compound was obtained (see Scheme 1.42a). The observation of a nOe between the two methine ring protons supports the assignment of the structure **1.116**. Consequently the product has the methyl and benzyl substituents on the same side of the ring.

Schei



:e of the trigonal radical will receive the migrating aryl group. This will set the stereochemistry of the benzylic carbon relative to its neighbouring carbon in the ring. According to the previous case of lactone **1.117** and its crystal structure, *syn* addition of both the carboxyl group and the aromatic ring to the same face of the *trans* alkene could be expected and **1.116** has been assigned accordingly.

Scheme 1.42a



2D NOESY spectrum of **1.116**

*1.2.6.3 Lactones **1.119a** and **1.119b***

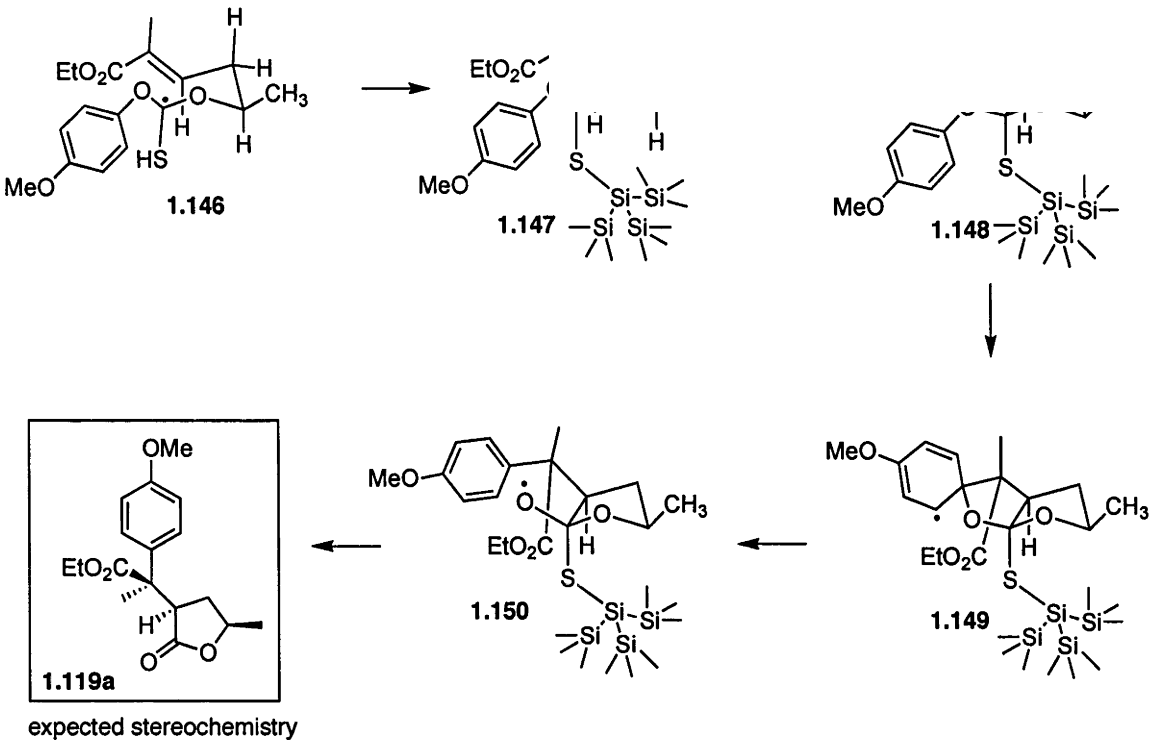
Racemic thionocarbonate **1.100** reacted under radical conditions to give two aryl lactones **1.119a** and **1.119b** (see Table 1.39), stereoisomers separable by HPLC. The recovery from HPLC was only moderate as the peaks on the chromatogram overlapped.

It is interesting to note that in the previous examples, a thionocarbonate featuring an alpha substituent, **1.97**, or a thionocarbonate featuring a tri-substituted alkene, **1.98**, have both demonstrated diastereoselective radical cyclisations. However, when a substrate has both an alpha substituent and a tri-substituted alkene, as in **1.100**, the diastereoselectivity is lost.

Based on the observations described above, a proposed mechanism is shown below in Scheme 1.43. The configuration of the product is expected be *cis* around the lactone ring.

ıe formation of **1.116**. A 2-D NOESY spectrum of **1.119a** showed very faint signals that could be due to a nOe between the two methine ring protons. However, the spectrum suffers from substantial noise and, thus, is inconclusive. There may be a *syn* relationship between the aryl group and carboxyl group relative to the starting *trans* alkene in the transition state. This was observed in the example with the quaternary centre. Conceivably, the major isomer has the stereochemistry as shown.

Scheme 1.43



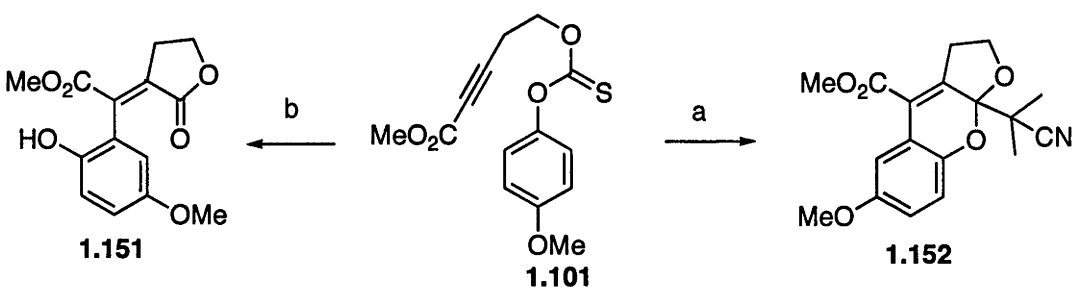
ıserved nOe between the methine ring protons of the minor isomer. However, this is not conclusive proof that the orientation of those protons is *anti*. Consequently, the precise identity of **1.119b** is unknown.

1.2.7 Radical chemistry of thionocarbonates containing triple bonds

Previous work by Lisa Sharp touched on the use of alkynic precursors for carboxyarylation (see Scheme 1.22). The previous example of an alkynic precursor demonstrated a different mode of reaction had been adopted including an *ortho* substitution on the aromatic ring. We were curious to see if this different reactivity would be conserved as we moved up in ring size using activated alkynes.

Under thermal conditions precursor **1.101** g
predictably low yield. The assigned structu
crystal X-ray diffraction (see Scheme 1.44a
eq TTMSS) were insufficient to drive the reaction of **1.101** to completion and higher than usual quantities of AIBN and TTMSS were required to ensure consumption of starting material. This reaction produces a complex mixture of other (uncharacterised) products.

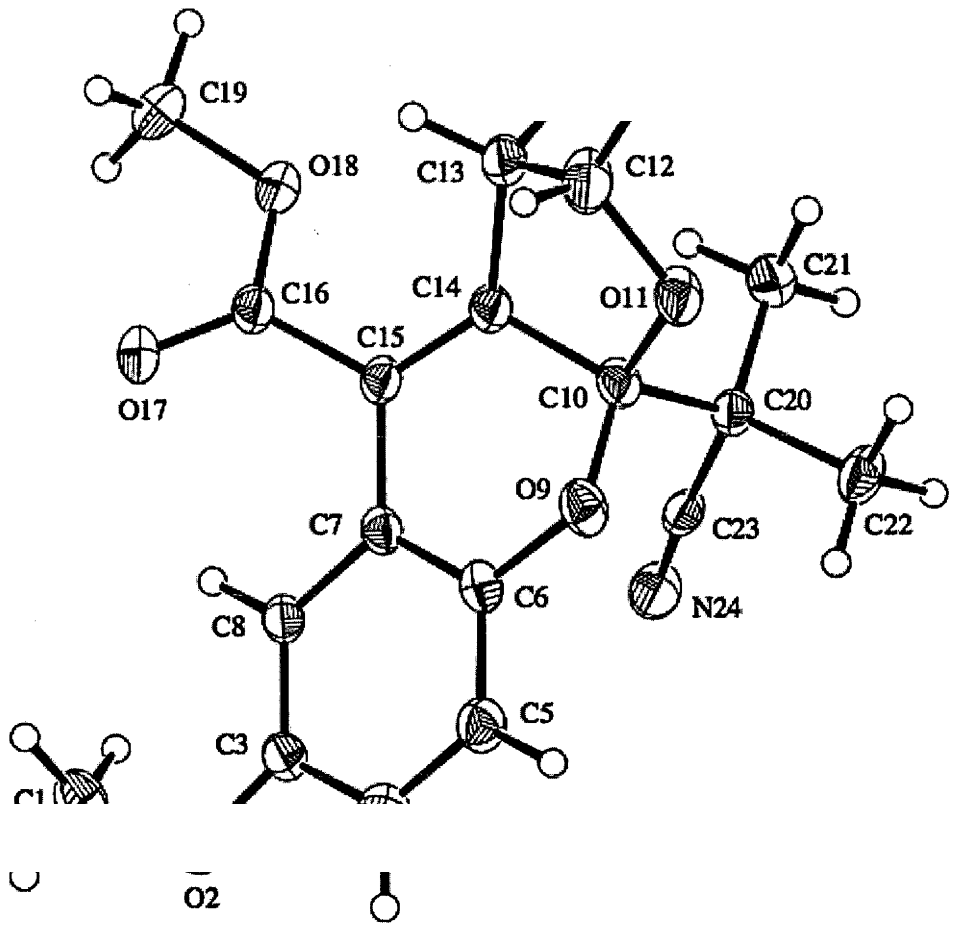
Scheme 1.44



S, benzene, reflux, 7%

b. 1.5 eq BEt_3/air, 2.0 eq TTMSS, acetone, -78 °C-RT, 51%

Scheme 1.44a



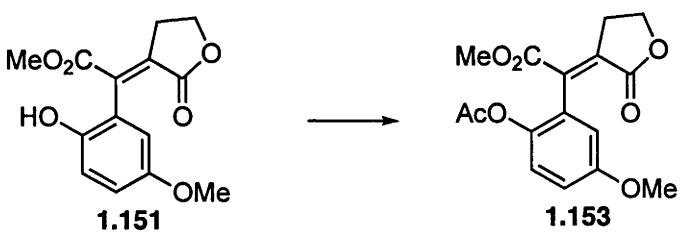
Structure of **1.152**

Interestingly, reaction of the same precursor **1.101** under triethylborane conditions gave a different product, **1.151**. While initially a moderate yield of 51% was observed for the formation of **1.151**, this was not repeatable and yields around 30% were more common. This can be attributed to the limited stability of the product. Leaving an NMR sample of the compound **1.151** in deuterated chloroform at ambient temperature over 24 hours led to the appearance of new peaks in the ^{1}H NMR spectrum. We never isolated any by-products and following this upsetting loss of material resolved to keep the product frozen

in benzene. The variable yield of the reactio
associated with commercial triethylborane.

Compound **1.151** is an oil and we sought a crystalline derivative so as to confirm our structural assignment that was based on NMR spectra. The acetate was obtained by the reaction with acetic anhydride in the presence of pyridine (see Scheme 1.45) and **1.153** proved crystalline. Thus the structure of compound **1.151** was confirmed by single crystal X-ray diffraction of its acetate derivative (see Scheme 1.45a).

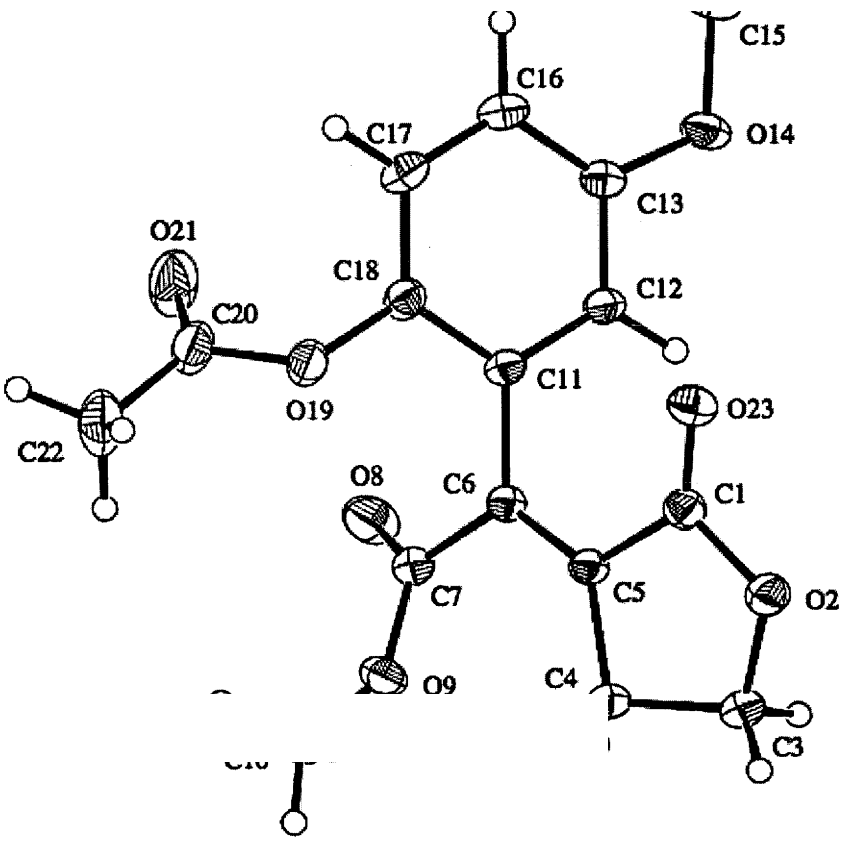
Scheme 1.45



1.151 **1.153**

dichloromethane, 35%

Scheme 1.45a



Structure of **1.153**

This divergence of outcomes is rationalised

thermal and triethylborane-mediated reactions begin in the same way, with a 5-*exo*-*dig* cyclisation onto the alkyne to give vinyl radical **1.155** followed by *ortho* addition to the aromatic ring. In both cases the cyclohexadienyl radical **1.156** undergoes oxidative aromatization, presumably by either AIBN or triethylborane/air.[41] At this point the mechanism diverges. Under the triethylborane conditions, hydrolysis occurs, breaking open the tricycle, forming the lactone and eliminating the sulfur substituent to give the *ortho* phenol **1.151**. Possibly there are boranes complexing the oxygen atoms in the system and facilitating this process. Water isn't added to the reaction mixture but could be present in the undistilled acetone.[#]

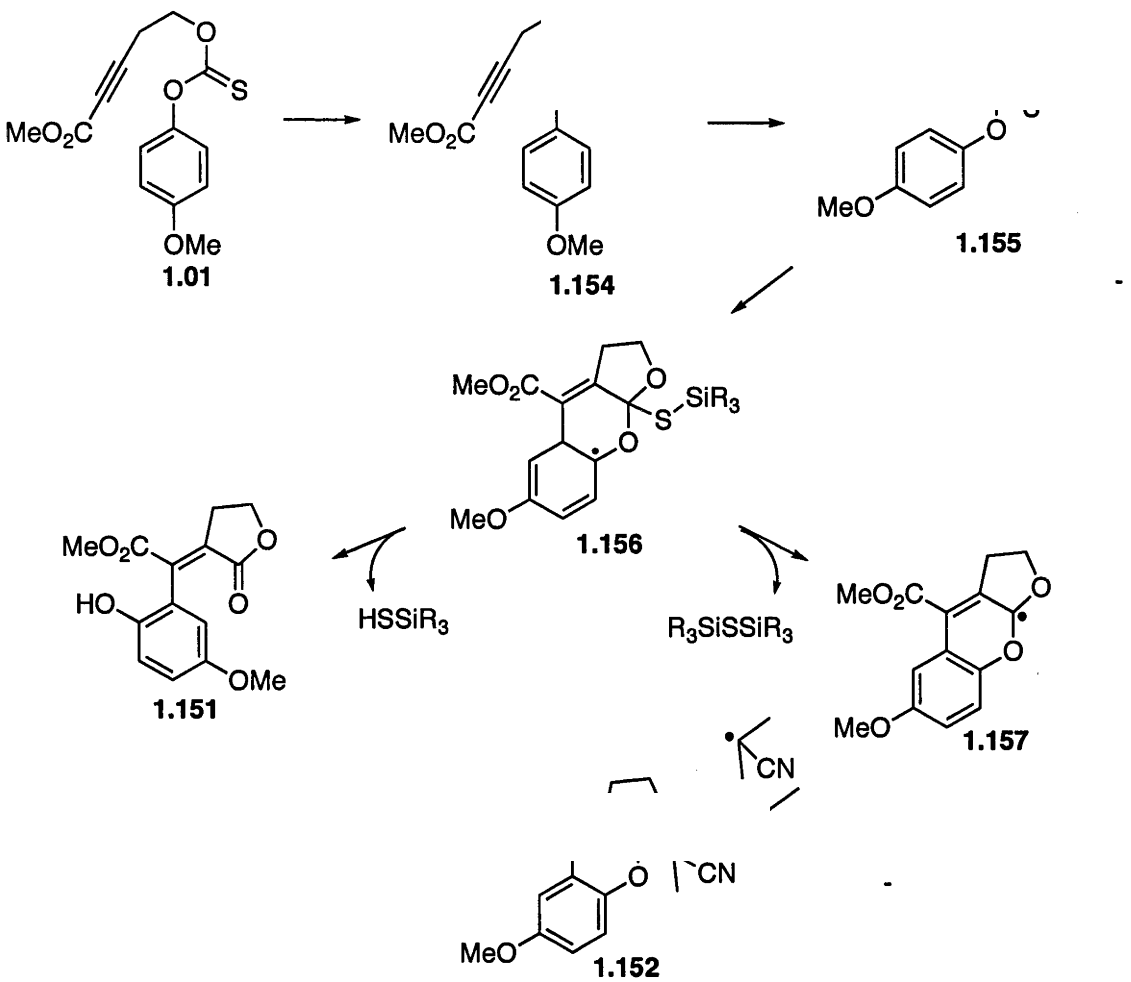
Under thermal conditions, the sulfur substituent in **1.156** is presumably lost by homolytic substitution at sulfur by a silyl radical, thus generating stabilised radical **1.157**. This can then couple with a fragment of the initiator. Presumably, the product **1.152** is obtained in

nirrors the result reported

by Sharp (Scheme 1.22) and little difference is made by the inclusion of an electron withdrawing group in the radical precursor **1.101**.

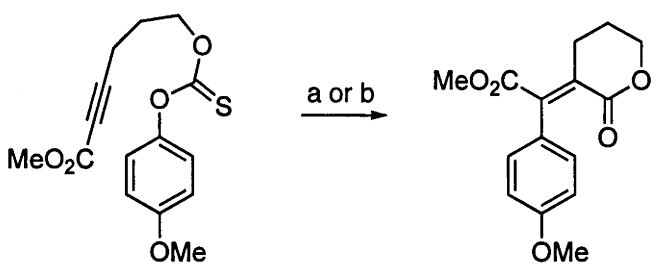
[#] The acetone was not distilled as it was drawn from a newly opened bottle of high grade solvent.

Scheme 1.46



The improvement in this reaction using the triethylborane conditions boded well for the next example in the series of alkynic precursors. Surprisingly, compound **1.102** reverted to the orthodox reactivity giving a single product from the mechanism arising from *ipso* addition using either thermal or triethylborane conditions (see Scheme 1.47.)

Schei

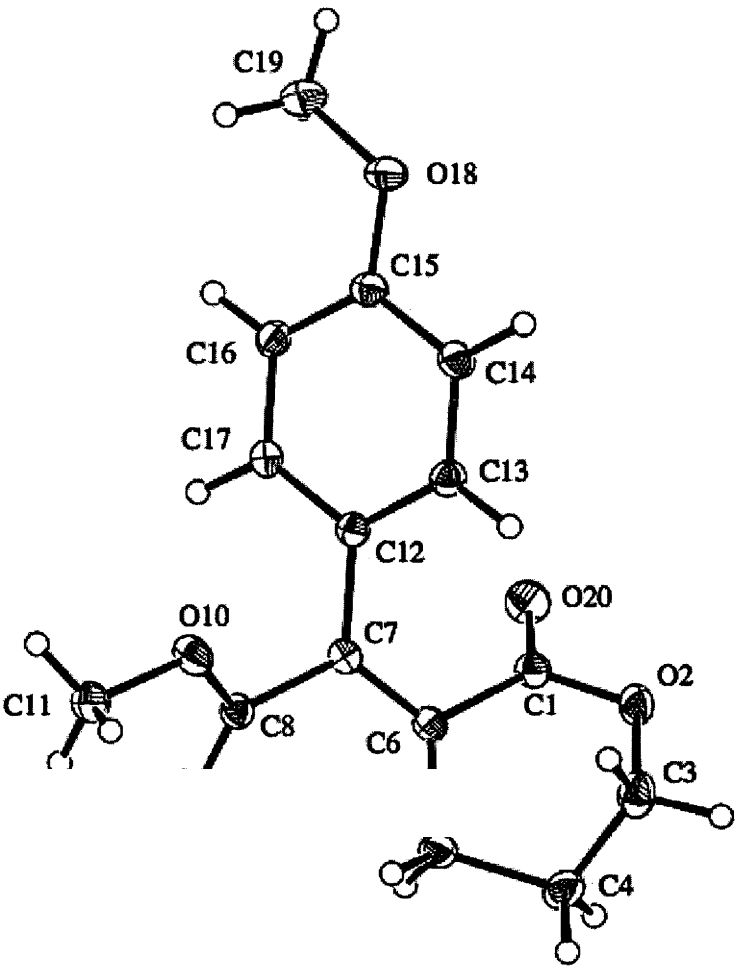


1.102 **1.158**

Reagents and Conditions: Either a. 0.7eqs AIBN, TTMSS, benzene reflux, 36% or b. 1.5 eq BEt_3/air, 2.0 eq TTMSS, acetone, RT, 62%

Single crystal X-ray diffraction of **1.158** (see Scheme 1.47a) unambiguously proved the structure of the 6-membered lactone and assigned the configuration of the alkene.

Scheme 1.47a

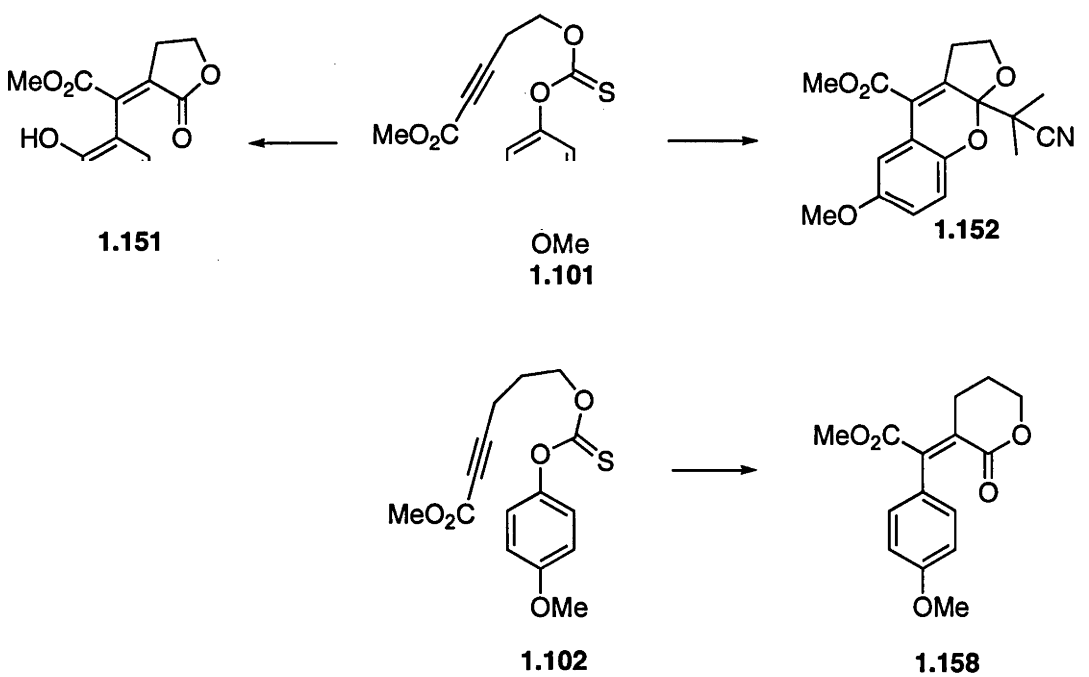


Structure of **1.158**

1.2.8 Comparing the outcome

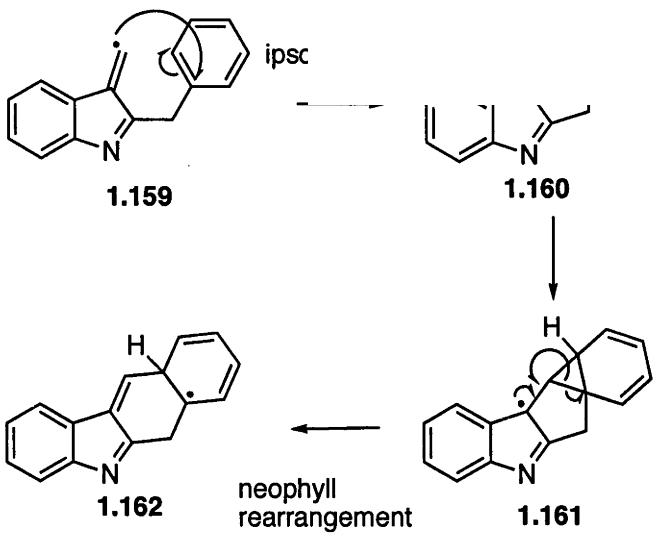
It seems reasonable to ask, why is it that these two, very similar, alkynic precursors lead to such different products? Radical products **1.151** and **1.152** are both formed via *ortho* addition to the aromatic ring. Six-membered lactone **1.158** is formed via *ipso* addition, as is every other example previously encountered in our investigations into carboxyarylation. Scheme 1.48 summarises these results. So why does thionocarbonate **1.101** proceed via *ortho* addition under radical conditions?

Scheme 1.48



Bowman[65] discussed the mechanism of *ortho* addition of a vinyl radical during his total synthesis of ellipticine (described in more detail Chapter 2). He postulated that aromatic addition occurred by an *ipso* addition followed by the formation of a strained cyclopropyl intermediate **1.161** that would undergo a neophyll rearrangement to give *ortho* substituted intermediate **1.162**, ready for aromatisation to the product.

Scheme 1.49



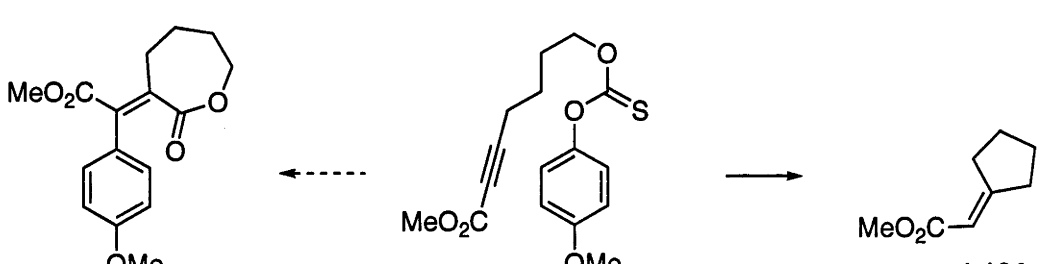
Another possibility is that *ortho* addition occurs, simply, via *ortho* addition. This theory is invoked by Curran[66] in his own radical cascade work (see Chapter 2 for relevant work.)

[illegible] one **1.158** and acetate [illegible]ve **1.153** features a fairly planar five-membered ring. One could imagine its preceeding vinyl radical having minimal conformational freedom, minimising its opportunites for an intramolecular bond forming event. In contrast, lactone **1.158** has an almost chair-like six-membered ring and its preceeding intermediate is presumably similarly flexible. So the different radical chemistry arising from thionocarbonate **1.101** could be attributed to unavailability of the *ipso* position to the vinyl radical due to its conformational restriction.

1.2.9 Unexpecte

Compound **1.103** was synthesised in the hope that it would give a seven-membered lactone **1.163** under radical conditions, thus further extending the scope of this reaction. However, it failed to do this under a wide range of conditions including thermal AIBN, photolytic initiation of AIBN at room temperature and triethylborane/air. The only compound isolable from the reaction was *p*-methoxyphenol. Examination of ^{1}H NMR spectra of the reaction mixture suggested the presence of carbomethoxy methylene cyclopentane **1.164** however numerous attempts to isolate this material failed (see Scheme **1.50**). This is a known compound[67] with a reported boiling point of 90-100 °C at 15 mmHg. ^{1}H NMR was used to calculate an approximate yield of the reaction in the following way. The crude product was subjected to flash chromatography. Brief concentration *in vacuo* of the relevant fractions gave a dilute solution of the product. The approximate concentration of **1.164** was calculated by integration with respect to solvents diethyl ether and pentane. Concentrating the NMR sample (made up with $CDCl_3$) *in*

Scheme 1.50

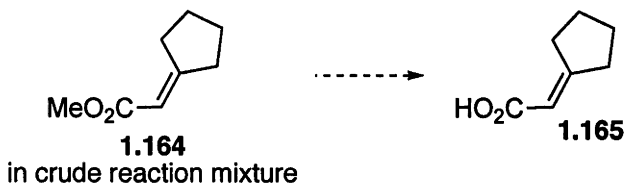


Reagents and Conditions: 0.5 eq AIBN, 1.0 eq TTMSS, benzene, 23° C, hv, 58%

In an attempt to mitigate the troublesome volatility of this compound and obtain a more accurate yield, the crude reaction mixture was subjected to hydrolytic conditions (see

Scheme 1.51) to form the known[68] acid **1.165** but again only *p*-methoxyphenol was recovered, presumably the acid **1.165** was lost on silica during purification.

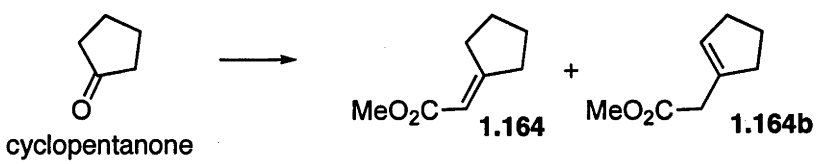
Sch



Reagents and Conditions: KOH, water/MeOH

An authentic sample of carbomethoxy methylene cyclopentane was prepared from cyclopentanone and the appropriate ylide.[69] However, it appeared to be contaminated by its (reported yet not characterised) tautomer **1.164b**.[70,71] Unsurprisingly, these were found to be inseparable by flash chromatography.

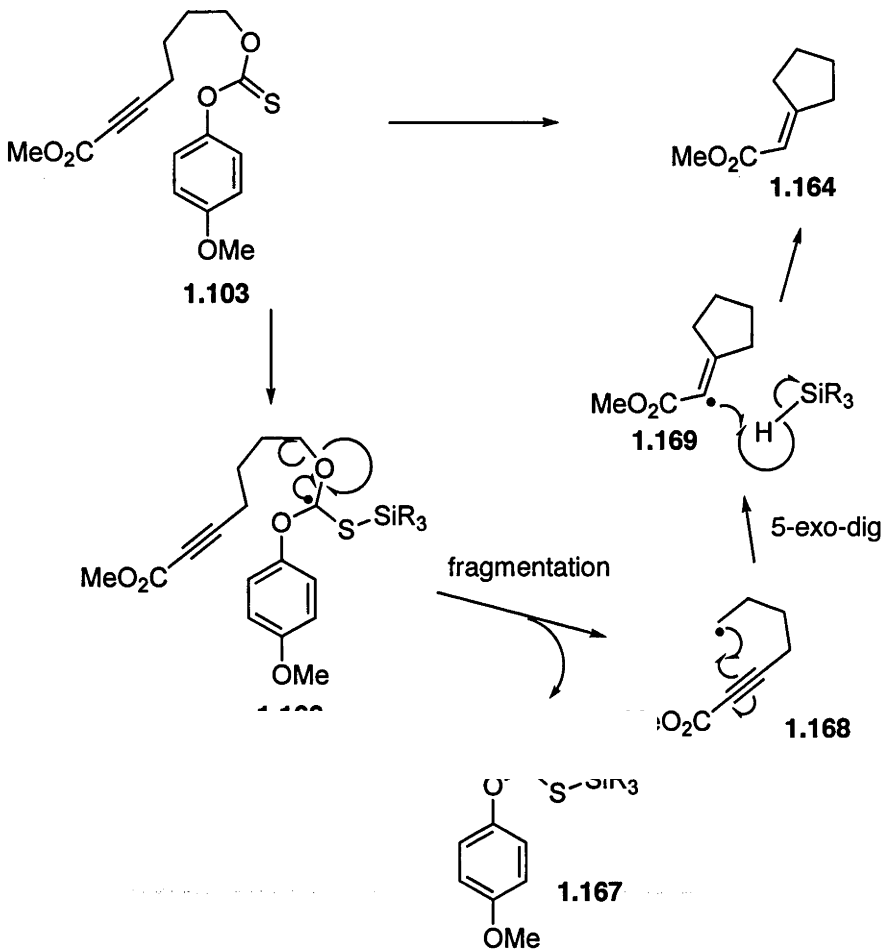
Scheme 1.52



Reagents and Conditions: $CH_3CO_2CHPPh_3$, 100 °C, 48%

Despite the difficulties encountered obtaining an accurate yield, the fact remains that the product observed is not one from carboxyarylation but from de-oxygenation (see Scheme 1.53). In this example, a 7-*exo*-dig cyclisation does not compete with the propensity to fragment via beta scission. Fragmentation results in a primary radical **1.168** that participates in a 5-*exo*-dig cyclisation to give a vinyl radical **1.169** that picks up a hydrogen from TTMSS.

Schei



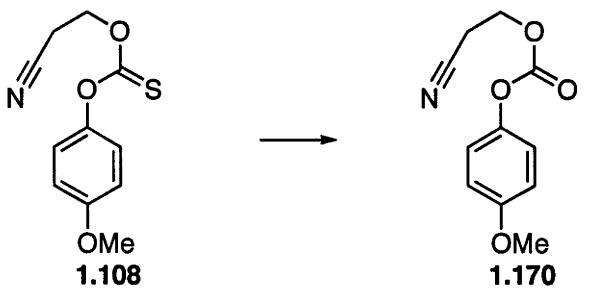
The curious aspect of this reaction is not that it occurs, but that it occurs so readily at room temperature. De-oxygenation of primary alcohol derivatives is reported as requiring forcing conditions due to the energy consuming process of forming a primary radical.[7] Thus this is a surprise result and investigations into ambient deoxygenation of primary alcohols continue within the group.

1.2.10 Thionocarbonate with nitrile as radical acceptor

The thionocarbonate containing a nitrile radical acceptor **1.108** proved itself to be quite unreactive under thermal radical conditions. It failed to give the desired cyclized product and returned only starting material. Triethylborane and air similarly failed to mediate the

desired reaction. Their only effect upon the starting material was to oxidise/hydrolyse the thionocarbonate to the corresponding carbonate (see Scheme 1.54.)

Sch



Reagents and Conditions: 1.5 eq BEt_3/air, 2.0 eq TTMSS, acetone, RT, 21%

Our first suspicion was whether precursor **1.108** was in fact a thionocarbonate. The assigned structure of **1.108** is supported by characterisation data. The presence of a thionocarbonyl is confirmed by the observation of an indicative ^{13}C NMR peak at 194.8 ppm. Low resolution mass spectrometry shows a substantial fragment of mass 123 which

eak of 2260 cm^{-1} is

consistent with the presence of a nitrile. Thus it seems likely that the assigned structure of **1.108** is correct.

The reluctance of thionocarbonate **1.108** to deoxygenate is consistent with literature descriptions of derivatives of primary alcohols requiring forcing conditions and extended reactions times.[7] However, the unreactive nature of **1.108** is odd when compared to the previous example of **1.103**, where a thionocarbonate deoxygenated under ambient conditions. Clearly there are other factors at play, whether relating to the sterics or electronics of deoxygenation precursors, it is not yet known.

1.2.11 C

Seven thionocarbonate radical precursors were prepared out of the ten identified. Of these, four gave the expected products of carboxyarylation. X-ray crystallography and nOe data were used to assign some aspects of the stereochemistry where relevant. One thionocarbonate showed a divergence from the carboxyarylation mechanism, proceeding via an *ortho* addition to give a benzylic lactone with different aryl substitution. One deoxygenated, unexpectedly at room temperate and another was found to be comparatively unreactive for reasons unknown.

An obvious extension of this work is to consider other thiocarbonyl moieties, like thioamides and thionocarbamates, as potential precursors for carboxyarylation. This is the subject of the following chapter.

Chapter 2

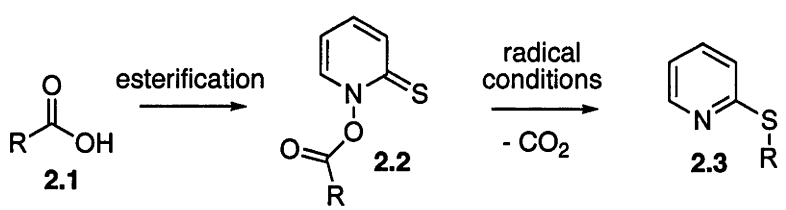
2.1 Int

2.1.1 Radical reactions using other thiocarbonyl functionalities

Thiocarbonyls are useful centres of radicophilicity as shown in the investigation of thionocarbonates detailed in Chapter 1. The radical chemistry of thiocarbonyls is not restricted to thionocarbonates - xanthates, thionobenzoates and thionoimidazolides were also used as Barton McCombie deoxygenation substrates.[1] But why leave it there? If the essential ingredients for a radical generating centre are a thiocarbonyl and an adjacent heteroatom, there are obviously yet more options to be investigated. The research in this area will be briefly reviewed in the following pages.

Thiohydroxamate esters are used in Barton decarboxylation (see Scheme 2.1).[72] This reaction removes the carboxyl group of a given compound **2.1** via esterification into hydroxamate ester **2.2** and then reaction under radical conditions.

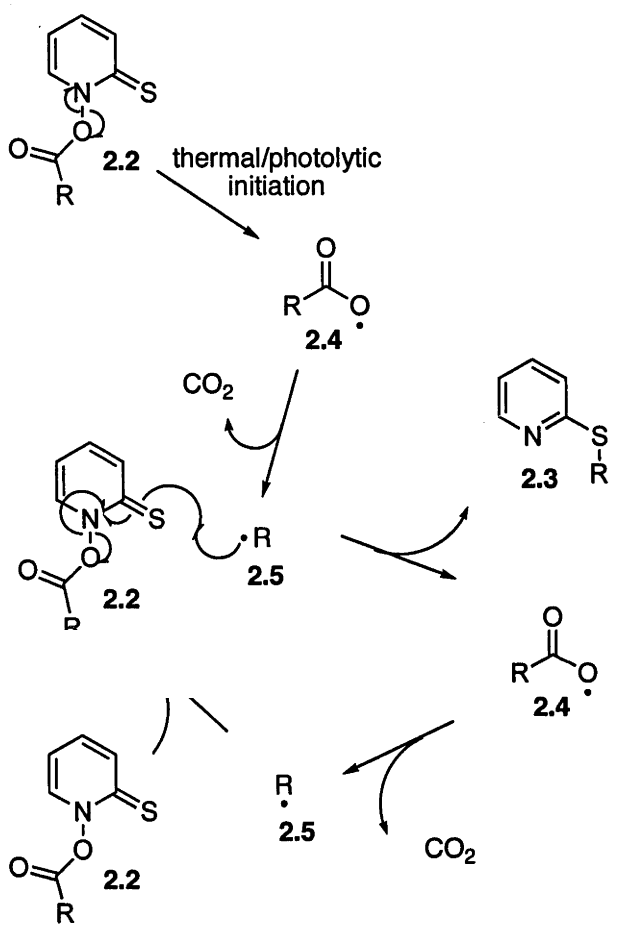
Scheme 2.1



Barton decarboxylation can be initiated by both thermal and photolytic methods.[72] The mechanism (Scheme 2.2) is thought to proceed, first, by homolysis of the nitrogen oxygen bond. As a consequence, carboxyl radical **2.4** is generated. Decarboxylation of radical **2.4** then occurs, generating an alkyl radical **2.5** and releasing carbon dioxide. This comprises the initiation phase of the reaction. The propagation steps are shown in the cycle whereby alkyl radical **2.5** adds to the thiocarbonyl of starting material **2.2**, generating carboxyl radical **2.4**. Radical **2.4** decarboxylates and generates an alkyl radical **2.5**. Thus the chain reaction is propagated until the starting material is consumed.

Elimination of the carboxyl radical **2.4** allows aromatisation of the starting pyridyl thione **2.2**. This aromatisation is considered to be the driving force of the reaction. F[illegible], the isolated sulfide **2.3** can be used for furt[illegible]

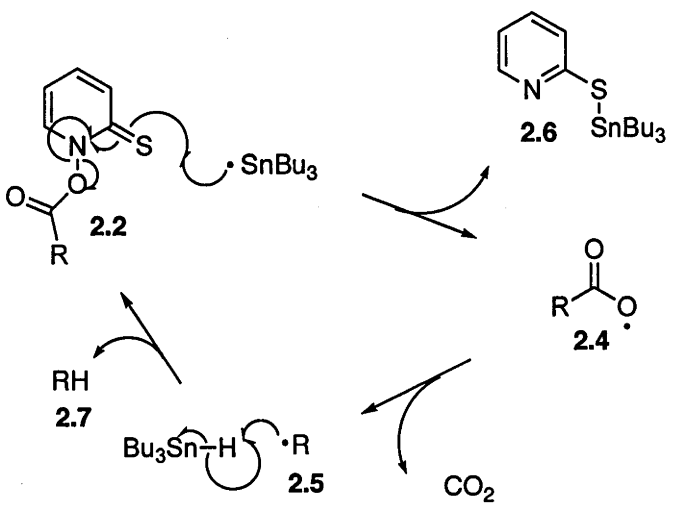
Sch[illegible]



The radical conditions for Barton decarboxylation can be varied. For example, Bu_3SnH and AIBN can be used to mediate the reaction[72] (see Scheme 2.3). In this case, the radical reaction begins when $\bullet SnBu_3$ adds to the sulfur of the thiocarbonyl of the starting thiohydroxamate **2.2**. Subsequent aromatisation and homolysis of the weak nitrogen-oxygen bond leads to the elimination of the carboxyl radical **2.4**. Decarboxylation of **2.4** gives alkyl radical **2.5** that abstracts a hydrogen atom from Bu_3SnH completing the chain

reaction. The formation of the strong sulfur-
to that derived from aromatisation of the sta

Scheme 2.3



n the substitution with halogen, sulfide, selenide and hydroxyl groups.[73]

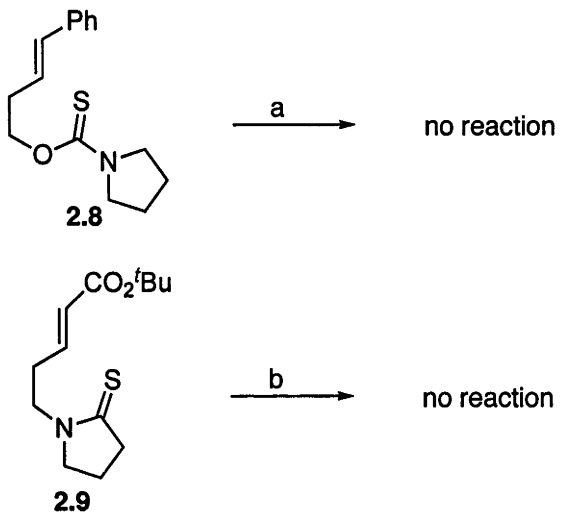
2.1.2 Radical cyclisations of other thiocarbonyl funtionalities

While investigating the radical cyclisation possibilities of thionocarboxylic acid derivatives, Bachi et al[28] looked beyond xanthates and thionocarbonates. The radical chemistry of other thiocarbonyl moieties (a thionocarbamate, monothiosuccinimide, thiosaccharide and two thioamides) were tested. The outcome of these studies is shown in Scheme 2.4 and 2.5.

The first two examples failed to provide products. They witnessed no reaction of thionocarbamate **2.8** under their standard radical conditions (slow addition of 1.15 eq Bu_3SnH, 0.15 eq AIBN, over 2 h to a benzene reflux). These conditions were sufficient for xanthate and thionocarbonate precursors to give radical cyclisation products in yields up to 70%. Thioamide **2.9** was also unreactive, even when using higher boiling toluene.

Increasing the temperature further using xylenes at reflux resulted in decomposition of the starting material.

Sch

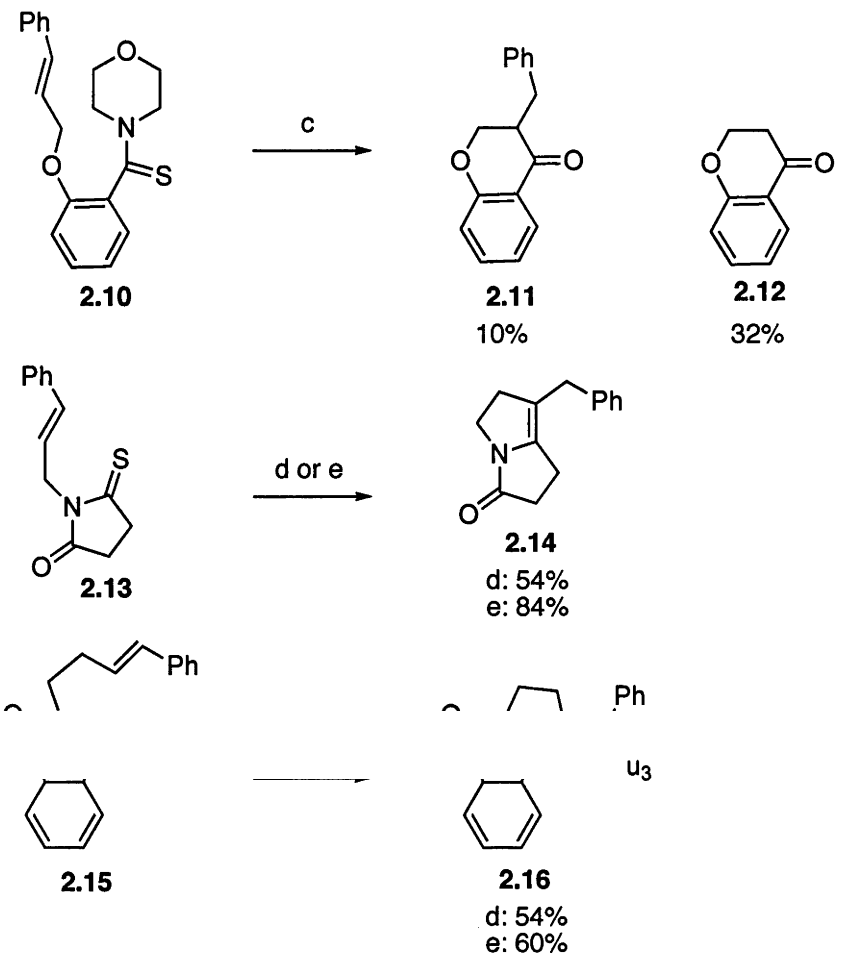


Reagents and conditions: a. slow addition of 1.15 eq Bu_3SnH, 0.15 eq AIBN, benzene reflux b. 1.15 eq Bu_3SnH, 0.15 eq AIBN, toluene reflux

It was reasoned that the $\bullet CSSnBu_3$ radical was stabilised by the lone pairs on adjacent oxygen and nitrogen atoms. Presumably electron-withdrawing groups adjacent to these heteroatoms would decrease their ability to stabilise the $\bullet CSSnBu_3$ radical and thus make the precursor more susceptible to cyclisation.

Salicyl thioamide **2.10** (see Scheme 2.5) was found to be unreactive (starting material recovered) under standard conditions but replacing benzene with xylenes led to the formation of two products **2.11** and **2.12** in low yields. Monothiosuccinimide **2.13** reacted under similar conditions to give the expected bicyclic **2.14** in moderate to good yield. **2.14** is the result of a 5-*exo*-trig cyclisation followed by hydrogen abstraction and elimination of $HSSnBu_3$.

Sche

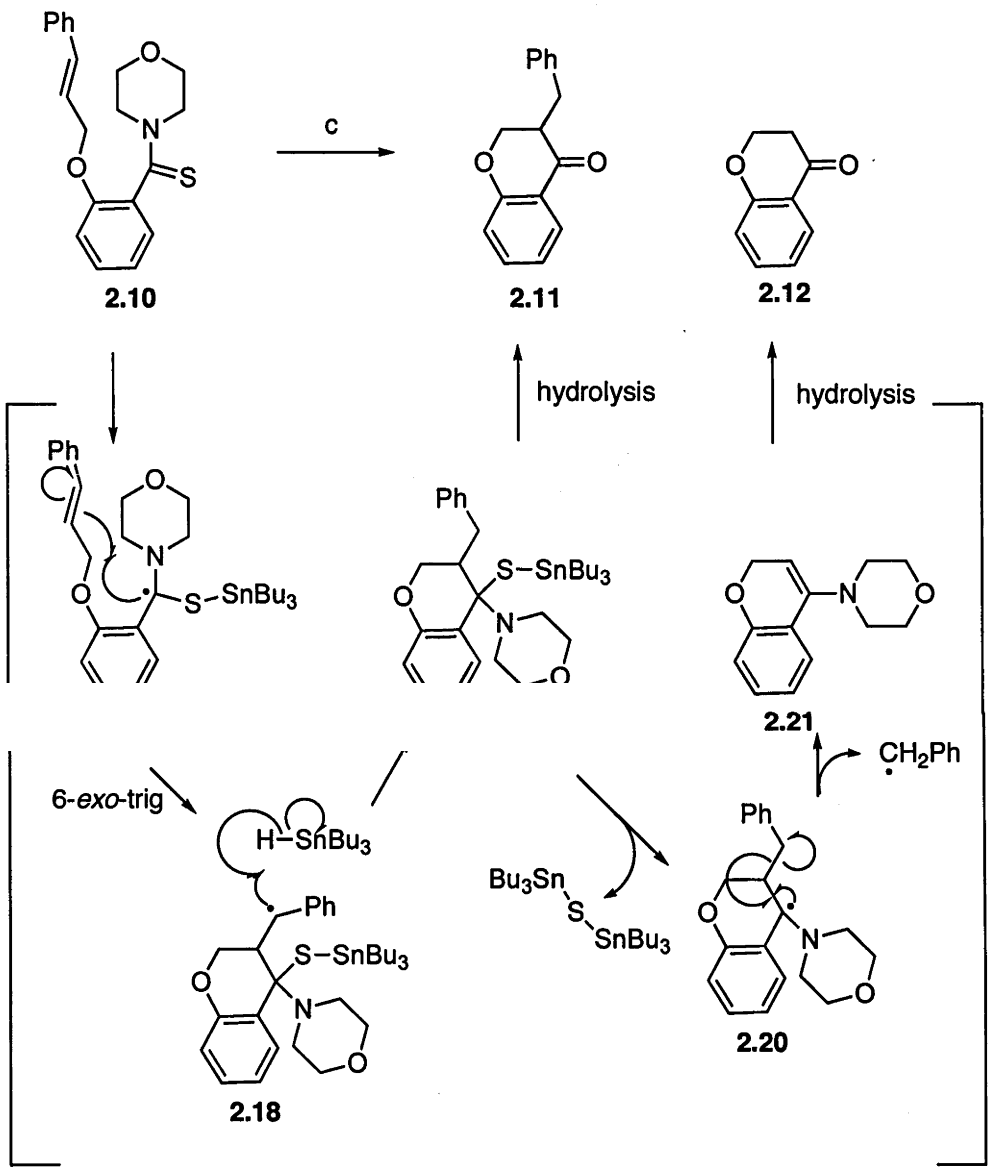


Reagents and conditions: c. slow addition of 1.15 eq Bu_3SnH, 0.15 eq AIBN, xylenes reflux d. slow addition of 1.15 eq Bu_3SnH, 0.15 eq AIBN, toluene reflux e. 1.15 eq Bu_3SnH, 0.15 eq AIBN, xylene reflux

The origin of the two products obtained from the radical reaction of salicyl thioamide **2.10** can be explained as follows (see Scheme 2.6.). After the initial 6-*exo*-trig cyclisation and hydrogen abstraction, the mechanism diverges, leading to two different products. Hydrolysis on silica leads to product **2.11**. Alternatively, homolytic substitution at sulfur will lead to intermediate **2.20** with the radical beta to the benzyl group, a good radical

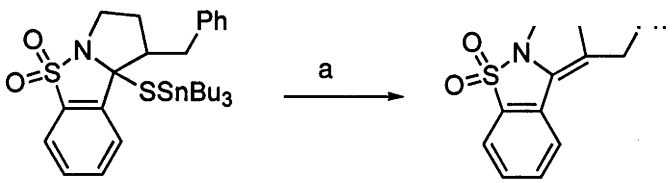
leaving group. Beta scission occurs, eliminating a benzyl radical. The resulting enamine **2.21** is hydrolysed, via the corresponding iminium ion, and **2.12** obtained.

Sch



Thiosaccharide **2.15** also gave a cyclisation product in moderate to good yield. Interestingly, tricyclic **2.16** retains the $SSnBu_3$ substituent. Treatment of the crude product with trifluoroacetic acid gave the product of elimination, **2.22** (see Scheme 2.7).

Sche



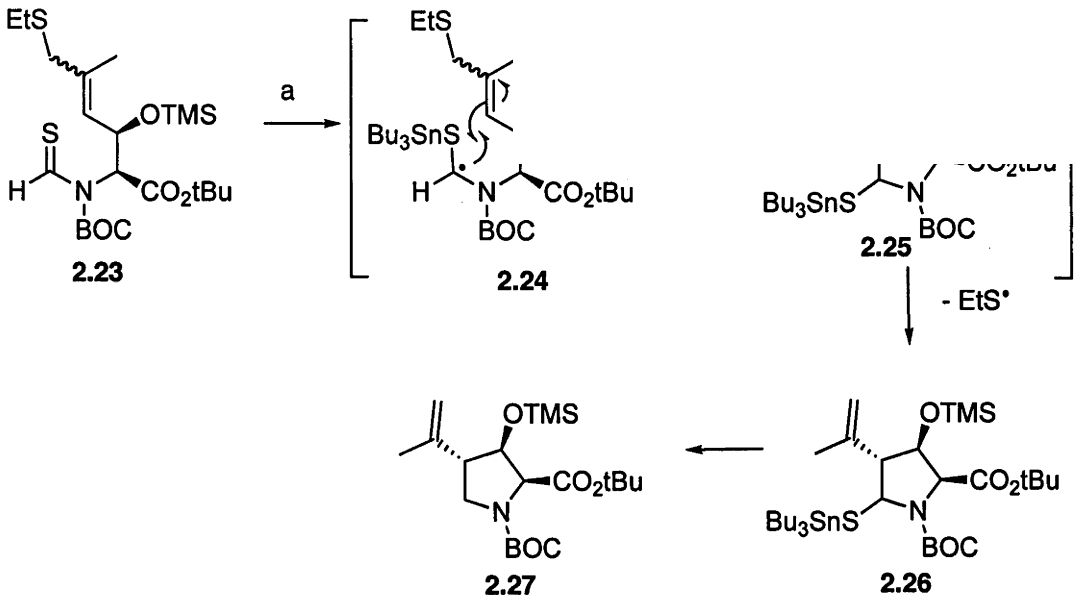
2.16 **2.22**

Reagents and conditions: a. excess trifluoroacetic acid

Bachi et al[74] later published an enantioselective total synthesis of Kainic Acid with a radical cascade as the key step. The deceptively simple pyrrolidine **2.26** is formed from the radical cyclisation arising from the terminal thioformimide **2.23**. Bachi notes that radicals derived from thioamides 'are highly stabilised by the two adjacent heteroatoms and may fail to maintain a viable chain reaction required to support an efficient ring closure.'[74] Thus they rationalise that the BOC group on the nitrogen in **2.23** will attract y activating it and in this way favouring the desired cyclisation.

Tributyltin hydride and AIBN are used to effect the 5-*exo*-trig cyclisation which proceeds with complete diastereoselectivity. This cyclisation generates a carbon-centred radical beta to a sulfide substituent. Subsequent elimination of an ethanethiyl radical gives the desired alkene in **2.26**. The next step to be achieved is replacement of sulfur with hydrogen on the pyrrolidine ring. It is not explained in the paper how this occurs. Possibly homolytic substitution at sulfur with $\bullet SnBu_3$ would break the carbon sulfur bond and generate a secondary radical. This could abstract hydrogen from another Bu_3SnH molecule. In any case, pyrrolidine **2.27** is duly isolated from the reaction.

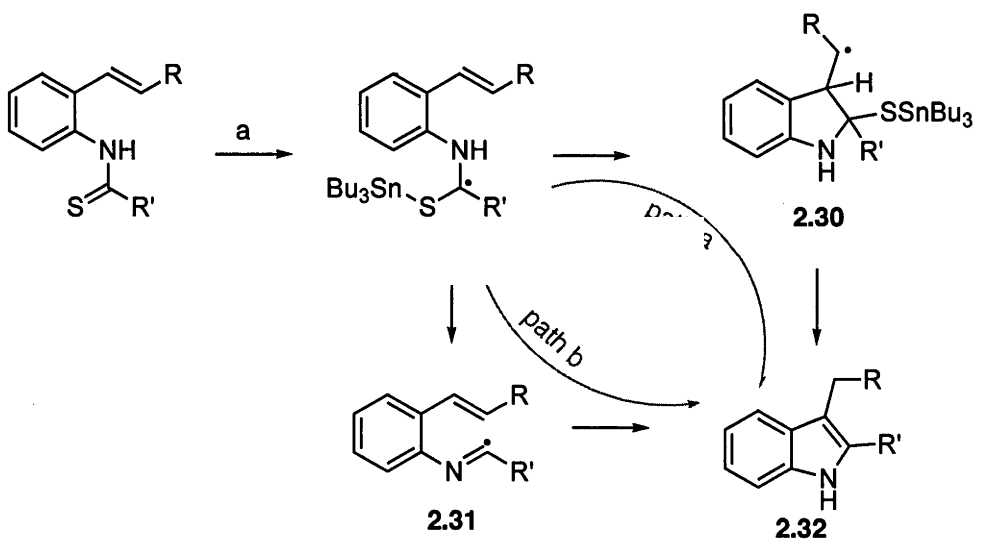
Scheme 2.8



Reagents and conditions: a. AIBN, 2.0 eq Bu_3SnH

Fukuyama et al[75] developed a new indole sy
thioamide. Tributyltin hydride was used wit
cyclisation. A wide range of substituents were shown to be tolerated including THP ethers and beta lactams. Fukuyama presents a branched mechanism (see Scheme 2.9), beginning with the stannyl radical adding to the thiocarbonyl, generating intermediate **2.29**, which could then undergo a 5-*exo*-trig cyclisation followed by an elimination and hydrogen abstraction to give the observed indole (path a). Alternatively the initial radical could undergo an elimination followed by cyclisation, tautomerisation and hydrogen abstraction (path b).

Scheme 2.9



Reagents and conditions: a. Bu_3SnH, AIBN, toluene reflux or 0.10 eq BEt_3 (1.0 M in hexanes), 2.0 eq Bu_3SnH, toluene, room temperature

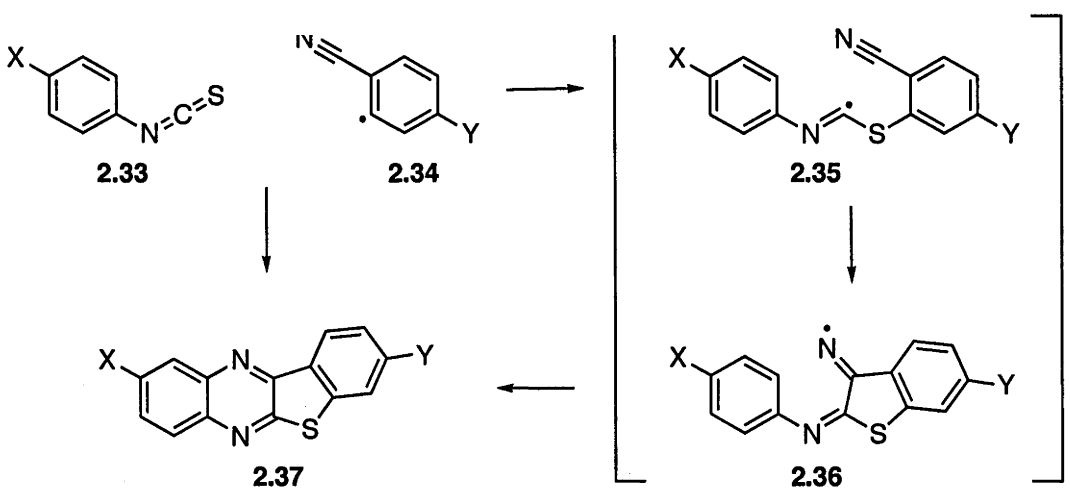
Interestingly while *cis* and *trans* alkenes worked equally well under the AIBN/Bu_3SnH conditions, the BEt_3/Bu_3SnH conditions favoured the *cis*, giving lower yields and returning starting material for the *trans* case. Theoretically, the initiator should interact only with the radical chain carrier and this preference for one geometric isomer suggests that triethylborane or triethyborane-related compounds are associated with the reacting

centres. This elegant methodology was utilised in the highly regarded total syntheses of Caranthine[76] and Vinblastine.[77]

An interesting series of radical reactions ut
Spagnolo et al.[78-80] Their strategy was to cr
appropriately substituted aryl radical (generated from the corresponding diazonium salt) to an isothiocyanate, forming an imidoyl radical. The ensuing radical cyclisations lead to the formation of complex heterocycles.

Their initial series of reactions used a nitrile as radical acceptor.[78] A general example is shown in Scheme 2.10. After initial intermolecular addition between **2.33** and **2.44**, the resulting sulfanyl imidoyl radical **2.35** would then participate in a 5-*exo*-dig cyclisation onto a nitrile. This would lead to an iminyl radical **2.36**. This would then add to the aromatic ring. The iminyl radical added exclusively at the *ortho* position of the aromatic ring and a single product was consistently isolated from these reactions.

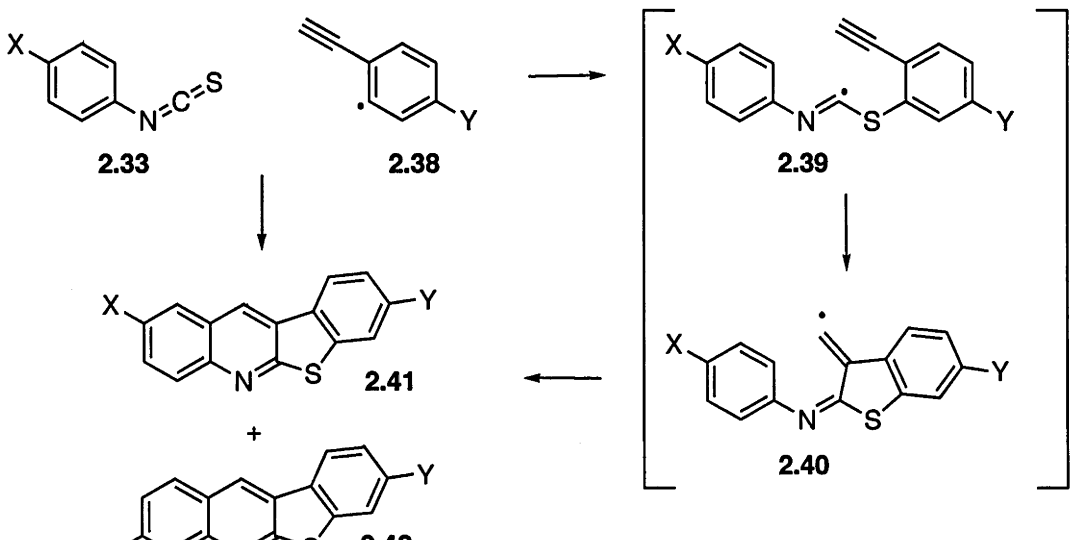
Scheme 2.10



An extension of this reaction was demonstrated in a subsequent paper,[80] exchanging the nitrile for an alkyne (see Scheme 2.11). These reactions were observed to give two products. Product **2.41** arose from the previously observed mechanism shown in Scheme

2.10 but the product **2.42** had scrambled sut
kind of rearrangement had occurred.

Scheme 2.11

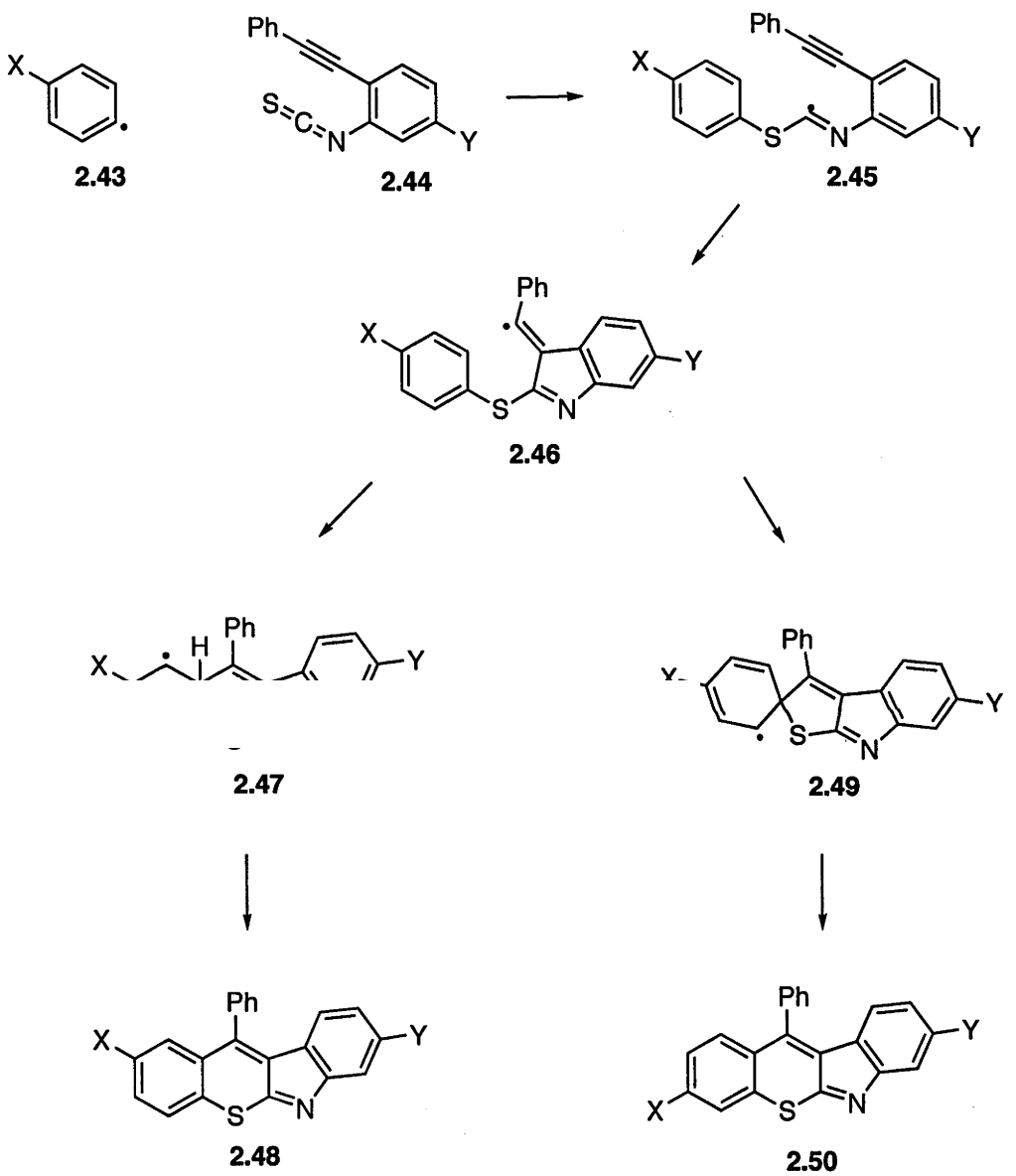


A more thorough investigation of this phenomenon was reported with another series of reactions.[79] This time the starting material **2.44** possessed an alkyne attached to the same ring as the isothiocyanate. Two products were obtained in yields of 40-50% overall. Scheme 2.12 shows the suggested mechanisms for the competing pathways to the two products. The intermolecular radical addition forming **2.45** and 5-*exo*-dig cyclisation onto the alkyne proceed as expected. Presumably, the resulting vinyl radical in **2.46** can add to either the *ortho* or *ipso* position of the aromatic ring. This leads to two different cyclohexadienyl radicals **2.47** and **2.49** that generate two different products.

The identity of the X substituent was found to alter the relative quantities of the products arising from *ipso* and *ortho* addition. Substituents that stabilised the cyclohexadienyl radical best (as previously investigated by Wu et al[81]) accordingly led to ratios in favour of *ipso* addition. Acetyl and azido substituents favoured *ipso*:*ortho* addition by ratios of

20:1 and 10:1, respectively. Interestingly, the methoxy substituted precursor led to a 1:1 mixture of products.

Sch

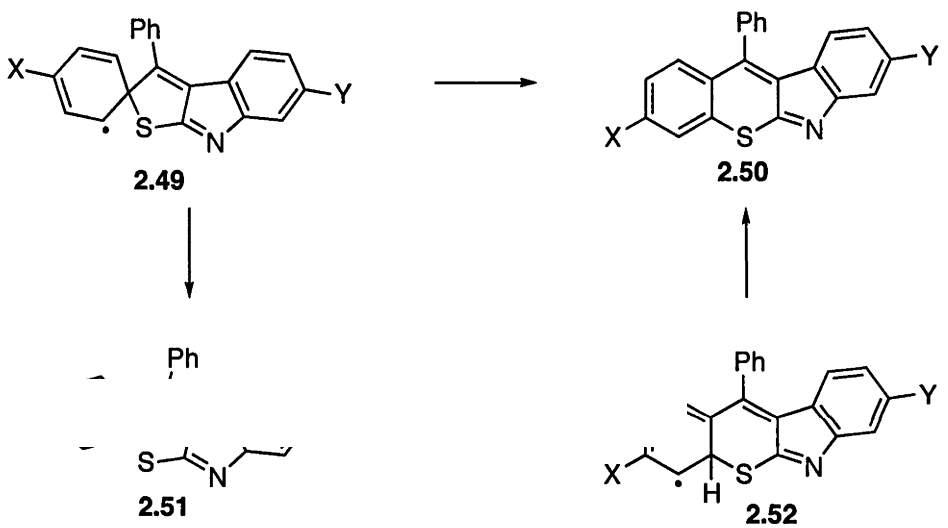


Spagnolo et al[79] used semi-empirical and DI

likely mechanism leading to product **2.50** (s

the spirocyclic intermediate **2.49** would reopen and the radical centre would be transferred to the sulfur as in **2.51**. This would then add back to the aromatic ring at the *ortho* position to give **2.52**, which would aromatise to the observed product **2.50**.

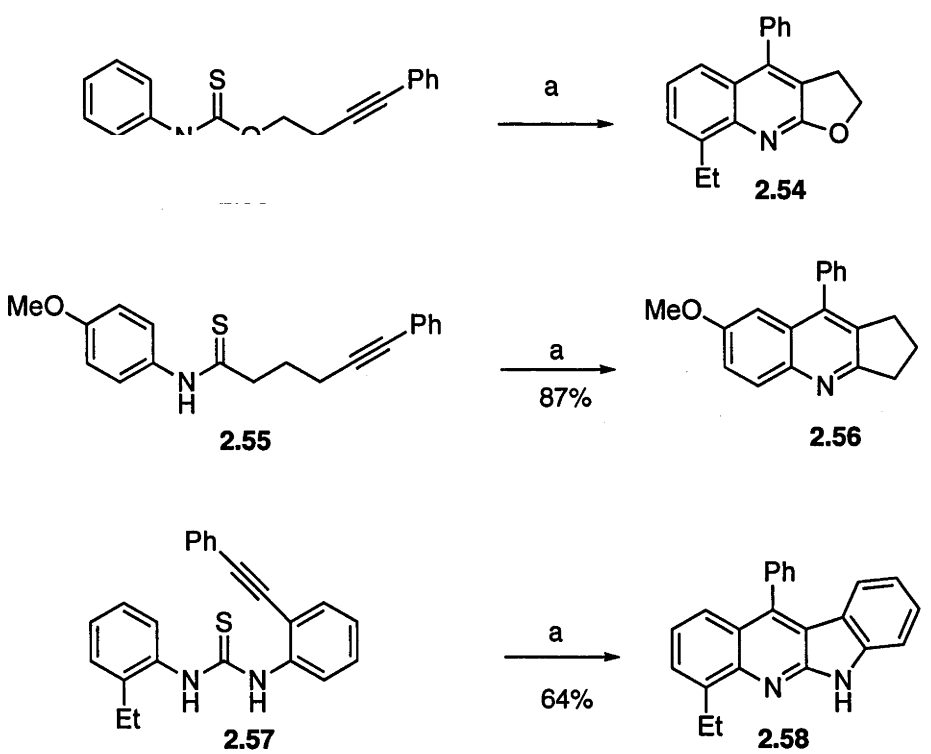
Scheme 2.13



Most closely related to our own carboxyarylation chemistry is the work of Curran et al.[66] Thiocarbamates, thioamides and thioureas were used as precursors for a radic... cascade, comprising two cyclisations, to give a varie
the 'synthetic equivalent of imidoyl radical
conditions developed for this methodology
in the presence of large excess of TTMSS (4.0 eq) over 20 hours. It was noted that tributyltin hydride and hexamethylditin did not effect the reaction, under either photolytic or thermal conditions.

Three examples are shown in Scheme 2.14. Thionocarbamate **2.53** and thioamide **2.55** give furoquinoline **2.54** and quinoline **2.56**, respectively, in high yields. Thioureas proved less reactive in general but precursor **2.57** gave indoloquinoline **2.58** in a good yield of 64%.

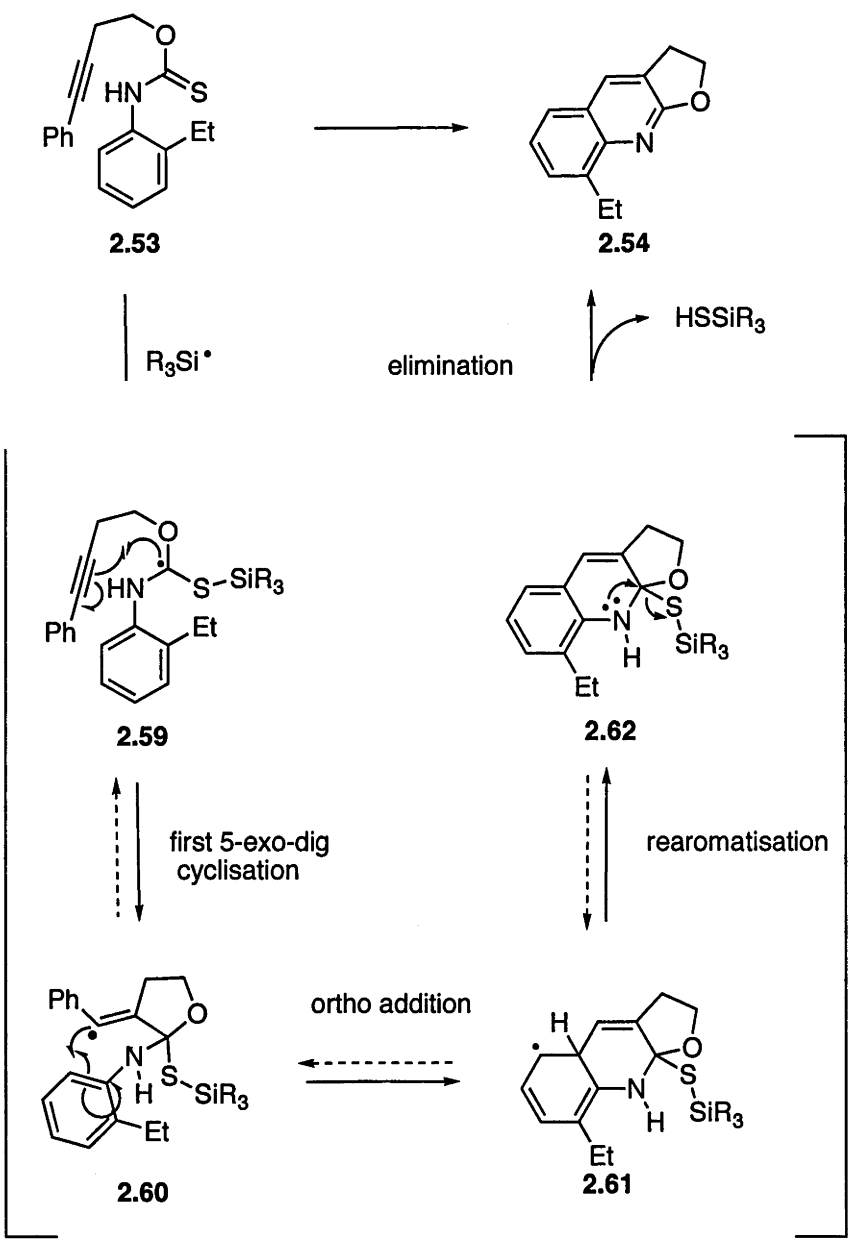
Scheme 2.14



Reagents and conditions: a. 1.0 eq AIBN, 4.0 eq TTMSS, benzene (0.05 M), hv

The transformation proceeds as shown in Sc
addition of a silyl radical to the sulfur of the
The resulting carbon centred radical in **2.59** adds to the alkyne in a 5-exo-dig cyclisation. This gives a vinyl radical in **2.60** that adds to the aromatic ring at the *ortho* position. An oxidation follows and the sulfur substituent is eliminated with some encouragement from the adjacent nitrogen to give the tricyclic furoquinoline **2.54**.

Scheme 2.15

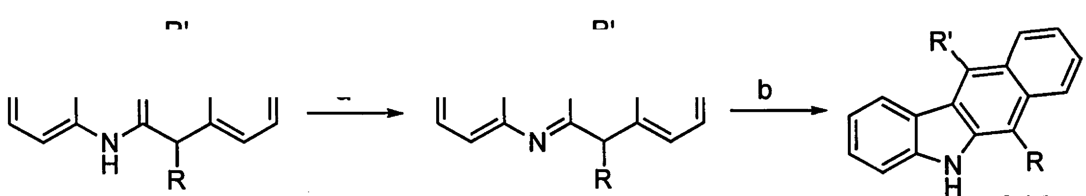


Curran acknowledges that the *ipso*/*ortho* competition observed by Spagnolo i... apparent and no 'rearranged' products wer... radicals only gave the products of *ortho* ad...

2.1.3 Related reactions using imidoyl radicals

Bowman et al[65] reported the use of an imidoyl radical cascade in their total synthesis of ellipticine. Unlike the previous examples, they eschewed the use of thiocarbonyls in favour of an imidoyl selanide precursor **2.64** (see Scheme 2.16). This was derived from the amide **2.63** via the imidoyl chloride. The ensuing radical reaction created two new rings in poor to moderate yields. Their radical reaction worked best with tributyltin hydride and triethylborane: they prescribed 10 eq of BEt_3, 24 h reaction time followed by another 10 eq BEt_3 and yet more reaction time.

Scheme 2.16

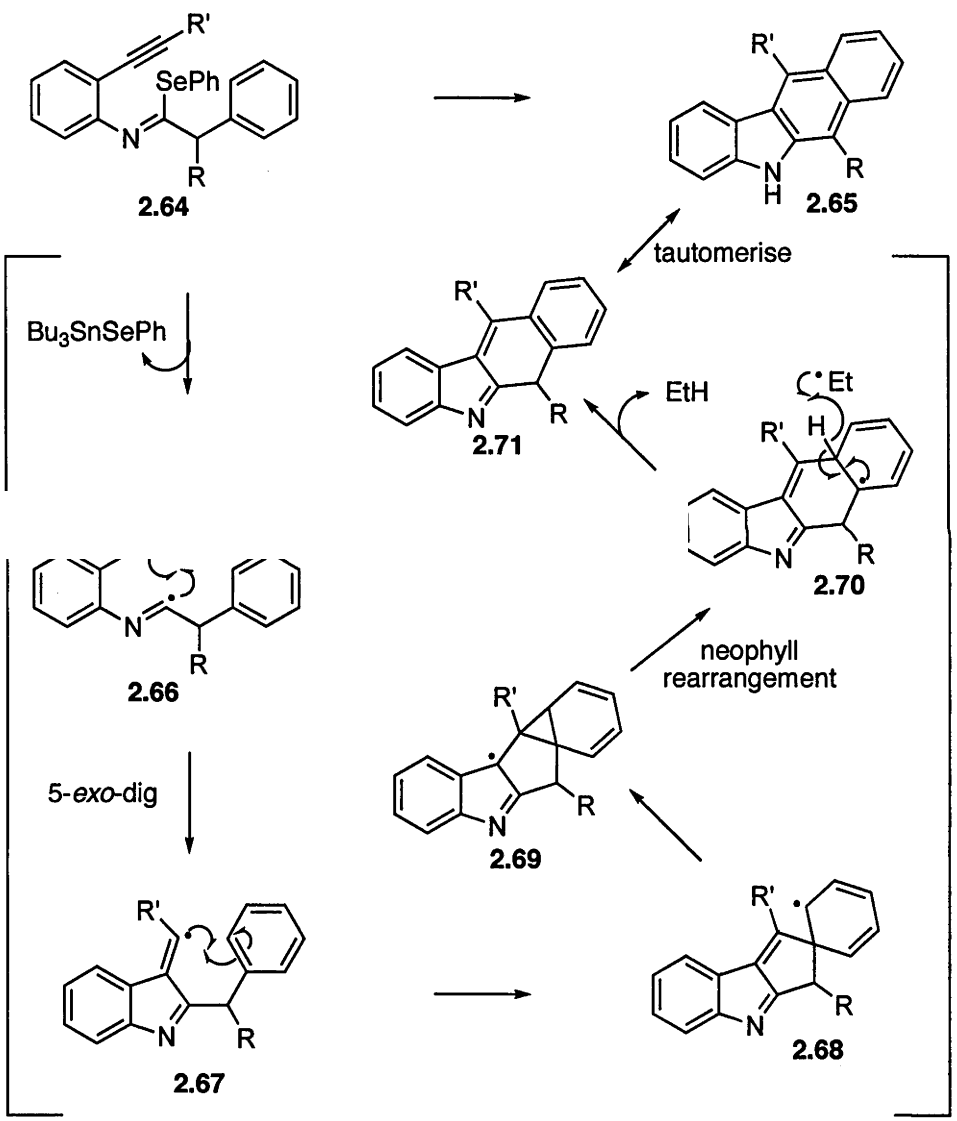


Reagents and Conditions: a. i. $COCl_2$, DCM, cat DMF ii. $PhSe^-$, THF, 22-71% over two steps b. Bu_3SnH, BEt_3/O_2, PhMe, 15-55%

The mechanisms by which these reactions proceed is described in Scheme 2.17. Radical substitution at selenium cleaves the C-Se bond and gives imidoyl radical **2.66**. This participates in a 5-*exo*-dig cyclisation, forming a vinyl radical. Having obtained some minor products that were the result of aryl migration, Bowman et al theorise that aromatic addition occurs at the *ipso* position to give spirocycle **2.68**. If this were to undergo rearrangement as shown it would lead to highly strained intermediate **2.69**. A neophyll

rearrangement would take place, giving inte
cyclohexadienyl radical **2.70** is the next ste
hydrogen by an ethyl radical. Tautomerisation of **2.71** gives the observed product **2.65**.

Scheme 2.17



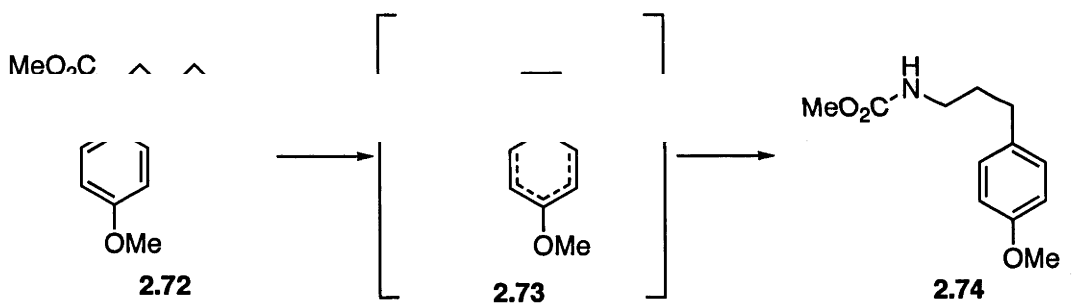
As the aromatic portions of the precursors and products do not feature substitution there is no direct evidence that *ortho* addition is achieved via a rearrangement in this case. Spagnolo et al[79] considered a similar mechanism in dealing with their own rearranged

radical products. Their DFT calculations suggested the formation of a strained intermediate analogous to **2.69** was unlikely.

2.1.4 Aryl transfer

Many of the preceeding examples demonstrate radical cyclisations involving anilide moieties (sometimes generated from the corresponding thioanilides.) The cyclisations have lead to fused aromatic products either via *ortho* or *ipso* addition followed by rearrangement. However, aryl migration from nitrogen to carbon can occur. Lee et al[45] undertook a simple experiment to test substituent effects and demonstrated radical 1,4-aryl migration, presumably occurring by *ipso* addition to form cyclohexadienyl **2.73**. The low yield reflects the large amount of proto-dehalogenation occurring (45% in the example shown.)

Scheme 2.18



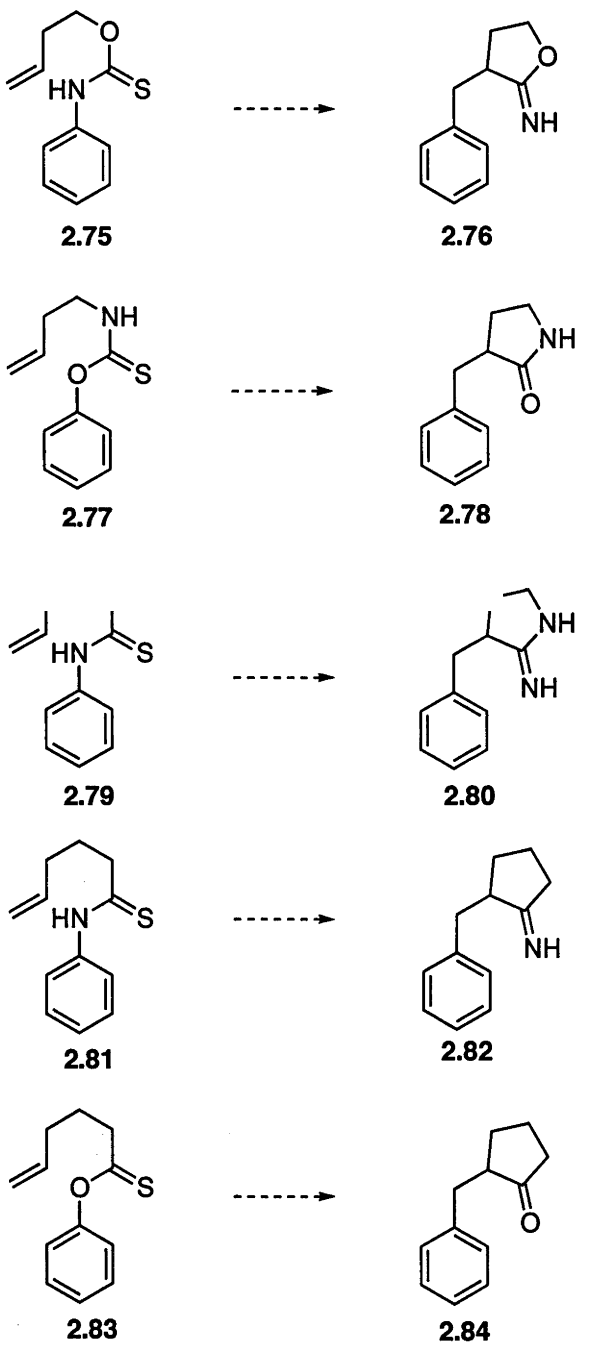
Reagents and conditions: 1.2 eq Bu_3SnH, 0.2 eq AIBN, benzene reflux, 0.03 M, 25%

2.1.5 Aims

As shown, there is literature precedent for successful radical chemistry utilising thioamides, thionocarbamates, thionoesters and thioureas. The aim of this work is to further expand the scope of the carboxyarylation reaction by incorporating different atoms around the central thiocarbonyl in the starting material. Naturally the incorporation

of nitrogen is a priority to establish this met
medicinal chemistry. Scheme 2.19 shows th
the expected products from their ensuing radical reactions.

Scheme 2.19



N-aryl thionocarbamates should lead to cyclic imidates **2.76**, O-aryl thionocarbamates should lead to lactams **2.78**. Thioureas should form imino pyrrolidinones **2.80** ___ thioamides should give imine substituted ca
generate carbocyclic ketones **2.84**.

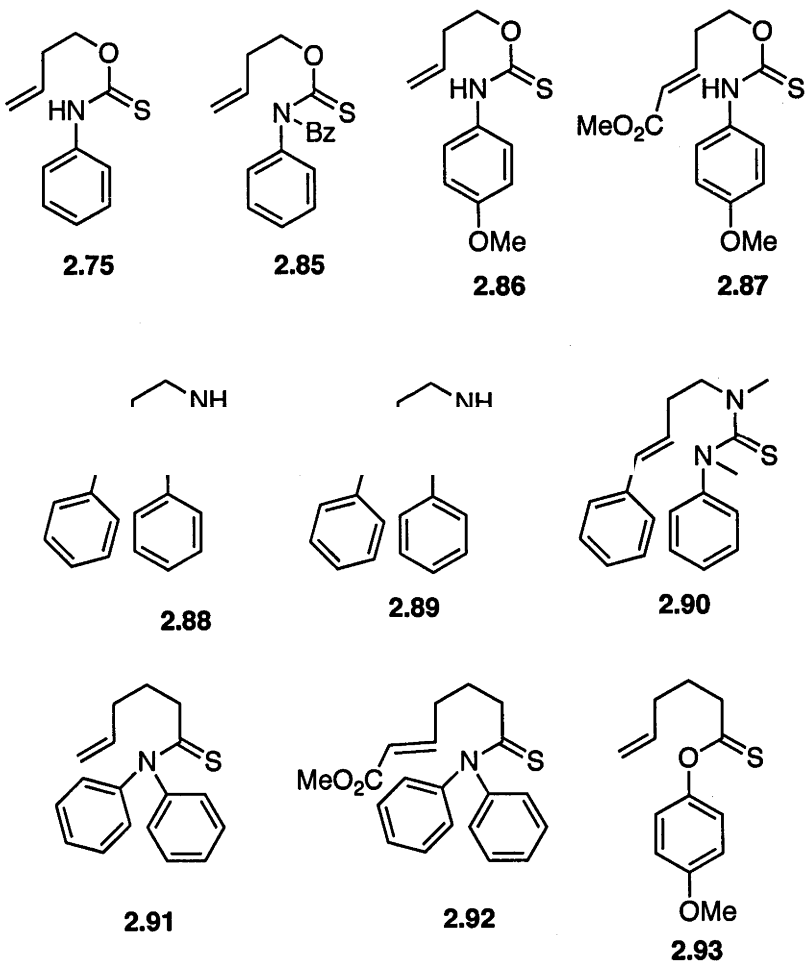
Another consideration is one of substitution. Where there is nitrogen, there is opportunity for further substitution. Consequently N-acyl, N-alkyl and N-aryl derivatives will be pursued. Furthermore, the use of favourable radical acceptors (Michael acceptors, styrenes) will be implemented where possible.

2.2 Results and Discussion

2.2.1 A series of

The series of ten compounds to be synthesised includes thionocarbamates (*O*-aryl and *N*-aryl), thioamides, thioureas and a thionoester.

Figure 2.20



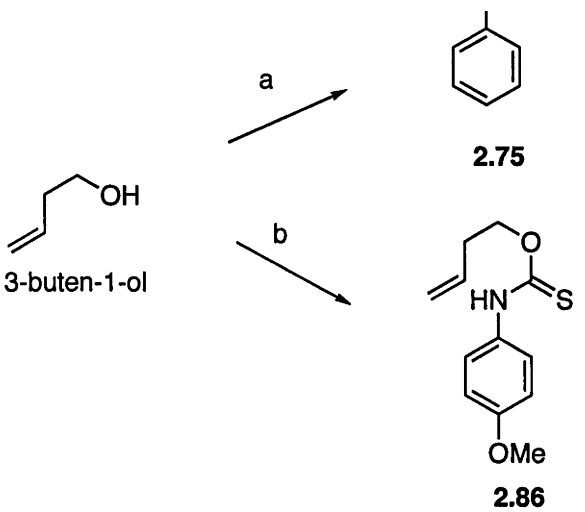
N-aryl thionocarbamate **2.75** is the simplest available example. The effect of N-benzoylation on subsequent radical chemistry will be tested with **2.85**. Compound **2.87**

(derived from simple **2.86**) is expected to give the highest yielding radical reaction for the N-aryl thionocarbamates class of compounds by incorporating favourable aromatic and alkene substituents. O-aryl thionocarbama
styryl radical acceptor, which again shoul
substitution will be tested with **2.90**. Thio
substitution. Its analogue **2.92** with Michael acceptor would be expected to lead to a higher yielding radical reaction. Thionoester **2.93** is a simple precursor, with no opportunities for nitrogen substitution. It will nevertheless allow for the radical chemistry of this unusual moiety to be studied.

2.2.2 Synthesis of N-Aryl Thionocarbamates

N-aryl thionocarbamates can be prepared by treating an alcohol or an alkoxide with an isothiocyanate.[82] The conditions described by Oba et al[83] were employed to synthesise the known phenyl thiocarbamate **2.75**[84] and the unknown *p*-methoxy phenyl thiocarbamate **2.86**. As previously discussed in Chapter 1, superior yields were expected to result from using *p*-methoxy substituted aromatic group. The simplest homoalyllic
hese compounds were
synthesised in one step by treating the sodium alkoxide of 3-butene-1-ol with the corresponding aryl isothiocyanate (see Scheme 2.21).

Scheme 2.21



Reagents and conditions: a. NaH then phenylisothiocyanate, THF, 81%
b. NaH then *p*-methoxyphenylisothiocyanate, THF, 75%

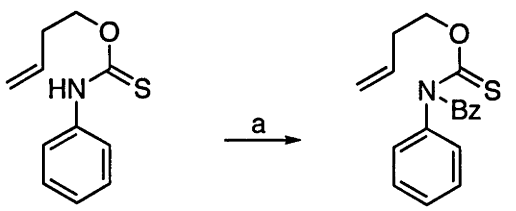
'H NMR data obtained for the known phenyl thionocarbamate **2.75** corresponded to the literature[84] but appeared to be poorly resolved with broad resonances. Better resolution was achieved by recording the ^{1}H NMR spectrum at 125° C in deuterated dimethylsulfoxide.

This suggests that thionocarbamate **2.75** is composed of more than one rotamer at room temperature. Heating the NMR sample allows the rotamers to exchange more rapidly and the resolved spectrum reflects the average structure. Similar behaviour in NMR was observed from *p*-methoxy phenyl thiocarbamate **2.86**.

The known N-benzoylated thiocarbamate **2.85**[84] was obtained from **2.75** using a literature procedure.[84] Radical bearing carbons are stabilised by adjacent lone pairs. It seems likely that a benzoyl substitution on the nitrogen next to a thiocarbonyl will reduce the electron

density of the subsequent carbon centred radical. Bachi and Melman argue that the resulting radical will favour cyclisation more effectively than the more stabilised (non-benzoylated) variant, which they argue is ; chain reaction'.[74]

Scheme 2.22



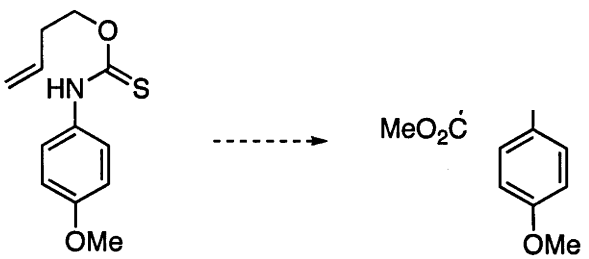
2.75 **2.85**

Reagent and conditions: a. benzoyl chloride, triethylamine, dichloromethane, 0°C - RT

94%

A thionocarbamate with an activated alkene **2.87** was sought after, as such a substrate is seemed the simplest way to incorporate a Michael acceptor into these allocarbamates. Unfortunately this uniformly failed with either Grubbs 1st or 2nd generation catalyst and the reaction returned starting material **2.86**.

Scheme 2.23



2.86 **2.87**

Reagent and conditions: methyl acrylate, Grubbs catalyst, benzene reflux

Initial homodimerisation of methyl acrylate should give the non-volatile dimethyl fumarate but this was not observed in the ^{1}H NMR of the crude product suggesting that no metathesis took place. This was surprising because the cross-metathesis of terminal olefins is a well characterised reaction with good yields.[57,86] Observation of the reaction suggested that the catalyst was decomposing as the reaction readily blackened within minutes of commencing. While the cross metathesis of compounds containing thiols has thiocarbonyl functionality being successfully carried through. Consequently we suspected it was the thiocarbonyl that could be poisoning the catalyst.

Due to this incompatibility of reagents another route was devised: preparing a thionocarbamate from an alcohol carrying the activated alkene. Walter et al[82] reported that thionocarbamates can be prepared by refluxing an isothiocyanate in 10 eq of the desired alcohol with no base required. This is an appealing route because we foresaw that activated homoallylic alcohol **1.113** would be unlikely to tolerate a base. Unfortunately **1.113** did not seem to react with the isothiocyanate which was used in excess. Heating alcohol **1.113** and the *p*-methoxy isothiocyanate returned only starting materials.

Scheme 2.24

1.113 **2.94**

Reagent and conditions: phenyl isothiocyanate. DMF, 70°C

In view of these difficulties we decided to abandon the use of Michael acceptors in the preparation of these new nitrogenous compounds for the time being.

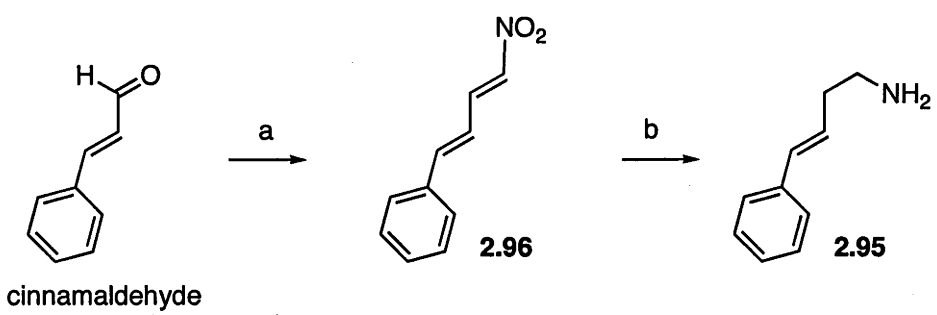
2.2.3 Synthesis of O-Aryl thionocarbamates

O-Aryl thionocarbamates precursors should lead to lactams under radical conditions. Considering the stability and ease of the synthesis of *O*-aryl thionocarbamates were hoped to be suitable partners for the tandem cyclization reaction.

We targeted amine **2.95** as a synthon. It contains a styryl moiety that could be expected to favour our radical reaction as it should be more receptive to radical addition than a terminal olefin.[42] Furthermore we hoped to avoid the potential problems associated with having a Michael acceptor and amine in the same compound.

Scheme 2.25

Amine **2.95** is a known (though incompletely characterised[88,89]) compound obtainable in two steps from cinnamaldehyde.[89] The initial Knoevenagel-Walter condensation was conducted according to the conditions of Lautens et al[90] who provided a procedure modified from the original (published in 1958 by Kochetkov and Dubykina[89]). The following $LiAlH_4$ reduction was also performed with modifications from the original procedure:[88] the reaction was conducted in heated THF rather than boiling diethyl ether as we considered it safer.[#] The cheapness of the reagents and amenability to scale up made the poor yields of this sequence survivable.



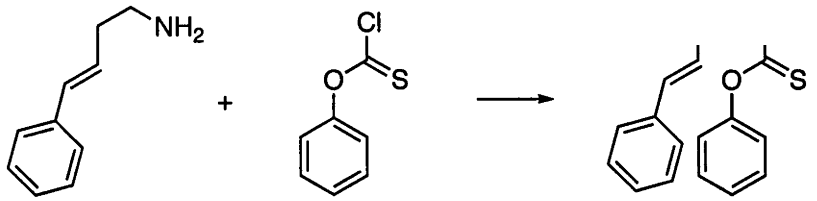
Reagents and conditions: a. NaOH, nitromethane, MeOH, 21% b. $LiAlH_4$, THF, 35°C, crude yield 72%

[#] It is important to keep $LiAlH_4$ in a solvent matrix (heating dry $LiAlH_4$ can lead to an explosion) and diethyl ether at reflux can be lost via a nitrogen line.

Purification of amine **2.95** proved difficult. Attempts to perform the distillation described in the original paper[89] resulted in a very poor recovery with concomitant production of black tar. Chromatography also gave a po
partial degradation of the material, thus pr
corresponding hydrochloride was formed
this was difficult to isolate from impurities and formed in poor yield. Liberating the free amine from the hydrochloride gave a bad return of a contaminated product. Optimising the $LiAlH_4$ reaction by reducing the reaction time and using commercial $LiAlH_4$ powder gave a product sufficiently pure to use in its crude form. A smaller portion was distilled at reduced pressure then subjected to flash chromatography to provide a sample for characterisation.

Conversion to the thionocarbamate was also more difficult than anticipated. A range of reaction conditions was trialled, but clearly several products were being formed. These included the bis-thioformylated thiocarbamate **2.97**. ^1H NMR of the crude also suggested that isothiocyanate **2.98**, derived from the amine, was present. The desired product **2.88** was not isolated. HRMS of a mixed fraction gave the correct molecular ion for the
chromatography and
analytical HPLC, failed. ^1H NMR was employed to rule out the possibility of some kind of rotamer effect but no coalescence of peaks was witnessed at 100 °C.

Scheme 2.27



2.95 phenyl thiochloroformate **2.97**

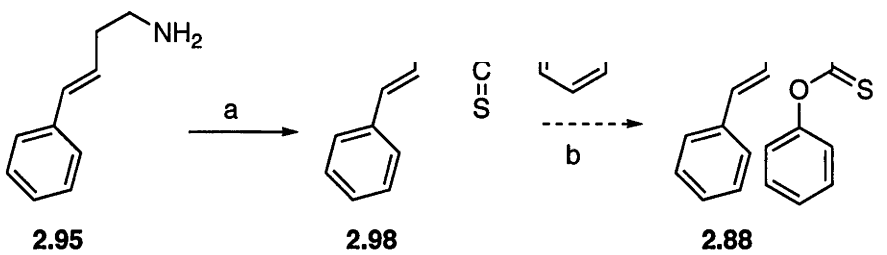
Reagents and conditions: DIPEA, 1.3 eq thionochloroformate, dichloromethane, 21%

Changing to a weaker base (pyridine) minimised the production of the bis-thioformylated product regardless of whether stoichiometric or excess (2.0 eq) thionochloroformate was present.

An alternate route was devised, disconnecting between the phenol and thiocarbamoyl

e easy introduction of different aromatic groups. Reactions between phenols or alcohols and thiocarbamoyl chlorides are known, however primary thiocarbamoyl chlorides are reported as being unstable.[82] For this reason we targeted isothiocyanate **2.98**, an equivalent synthon of the thiocarbamoyl chloride. The unknown aliphatic isothiocyanate was synthesised from amine **2.95** using a standard procedure in the literature.[91] However, the attempted reaction with phenol returned only starting material. Extended heating in the presence of a base failed to effect the reaction and starting materials were returned.

Scheme 2.28



2.95 **2.98** **2.88**

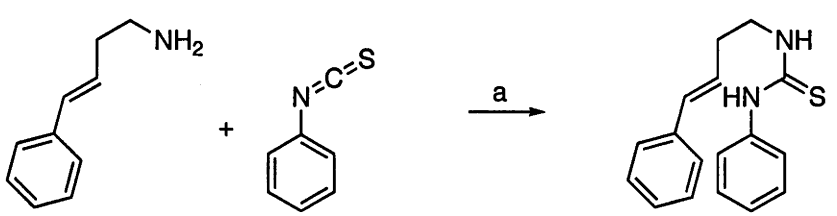
Reagents and conditions: a. thiophosgene, K_2CO_3, DCM, water, 0°C b. NEt_3, DCM reflux

The difficulty associated with this reaction could be due to its reversibility.[92] Another possibility is that minor impurities present in the isothiocyanate or amine are hampering the reaction.

2.2.4 Synthesis of thioureas

Thiourea **2.89** was synthesised from amine **2.95** and commercially available phenyl isothiocyanate.

Scheme 2.29

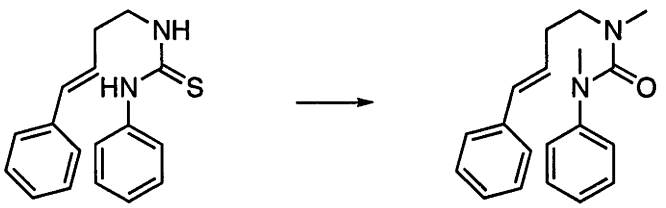


2.95 phenyl isothiocyanate **2.89**

Reagents and conditions: a. dichloromethane, 0°C, 57%

N-alkylation of the thiourea **2.89** was attempted using standard conditions for *l*.
alkylation of ureas as there were no analogou
this reaction gave the *N*-methylated urea **2.9**

Scheme 2.30



2.89 **2.99**

Reagents and conditions: NaH, MeI, THF, 29%

Presumably hydrolysis of the thiocarbonyl proceeded either with trace levels of water in the reaction or during the work up.

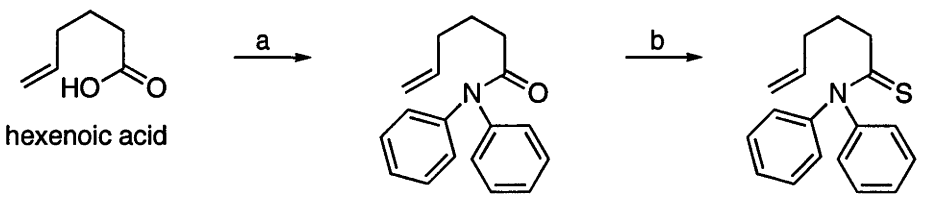
oesters

We devised thioamide **2.91** as a good candidate for our radical reaction. By having two phenyl rings on the nitrogen the radical reaction is favoured as the primary radical, which would result from a 5-*exo*-trig cyclisation, has a better chance of finding an aromatic ring to react with.

The synthesis of thioamide **2.91** was completed in two steps (see Scheme 2.31). Firstly hexenoic acid was converted to the corresponding acid chloride by treatment with thionyl chloride. The addition of diphenylamine gave desired amide **2.100**; refluxing chloroform was found to be the best medium for this. Amide **2.100** was then converted to thioamide **2.91** by reaction with Lawesson's Reagent. Dichloromethane at reflux was found to work well for this reaction. Higher temperatures (toluene reflux) returned diphenylamine from

the decomposition of the starting amide while, not unexpectedly,[93] room temperature did not effect the conversion.

Sch



hexenoic acid

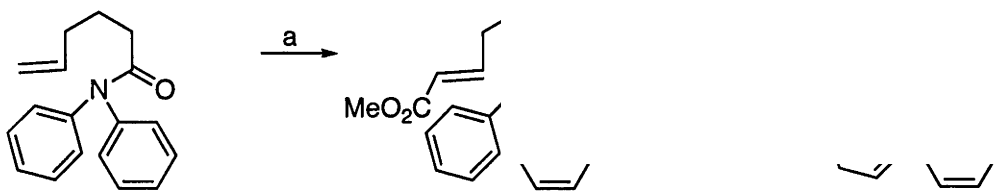
2.100 **2.91**

Reagents and Conditions: a. thionyl chloride, catalytic DMF then diphenylamine, dichloromethane, 70% b. Lawesson's Reagent, dichloromethane, 81%

As always we were hoping to prepare compounds with activated alkenes. Consequently, thioamide **2.92** was identified as it improved upon the simple thioamide **2.91** by possessing a carbomethoxy group on the alkene. Metathesis is an obvious route to this ; Grubbs catalyst in the presence of a thiocarbonyl. We strategised that it would be best to perform the cross metathesis on amide **2.100** and then convert the resulting product to thioamide **2.92** with Lawesson's Reagent. Amides react more readily with Lawesson's Reagent than esters,[94] thus selectivity seemed plausible.

Methyl acrylate and **2.100** were successfully coupled using Grubbs 2nd generation catalyst (see Scheme 2.32). Grubbs 1st generation catalyst was unsatisfactory giving only 21% of the desired product. Unfortunately the subsequent thionation step proved difficult producing a variety of products. Presumably the superior reactivity of the amide is negated by the steric crowding of its substituents and thionation can occur at either or both carbonyls in the compound. The problematic thionation coupled with the expense of producing amide **2.92** via metathesis made this route unattractive and it was abandoned.

Scheme 2.32



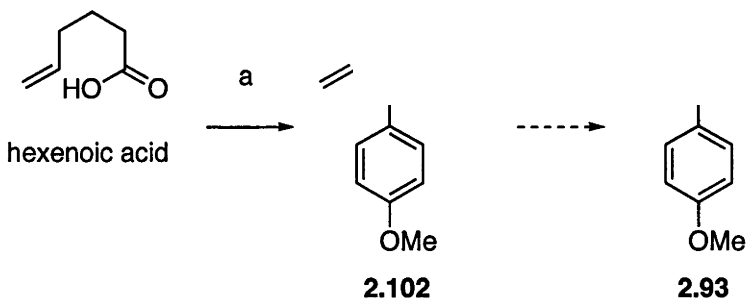
2.100 **2.101** **2.92**

Reagents and Conditions: a. Grubbs II, methyl acrylate, 87% b. Lawesson's Reagent

However, while this thionation failed it was envisaged that an analogous strategy could be used to provide thioesters from esters. Indeed there are few other ways of making such compounds.[95]

With this in mind ester **2.102** was synthesised from hexenoic acid and *p*-methoxy phenol using a DCC coupling. The next step showed Lawesson's reagent to be wholly ineffective at providing the desired thionoester. Refluxing toluene, xylene and [illegible] in all cases along with [illegible] Lawesson's Reagent and some small quantities of decomposition products. A modified thionation reaction using P_4S_{10} and HMDO[96] resulted in complete decomposition of the starting material.

Scheme 2.33



2.102 **2.93**

Reagents and Conditions: a. DCC, *p*-methoxy phenol, 80% b. Lawesson's reagent, toluene or P_4S_{10}, HMDO, toluene

A more careful examination of the literature revealed that *O*-aryl thioesters were rarely reported and their synthesis usually featured very poor yields.[97] Furthermore the reaction conditions were postulated to lead to a Fries re-arrangement of the starting material which in turn would lead to the formation of more complex products.[96] More recent developments in this field have improved the availability of these compounds.[98]

2.2.5 Radical Chemistry

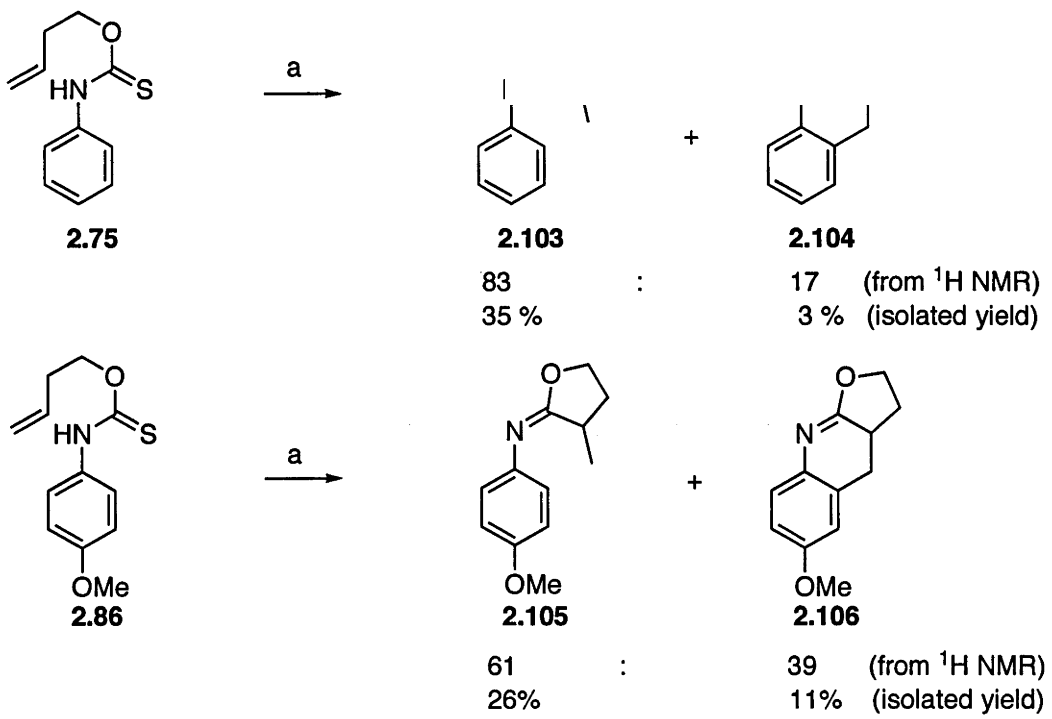
Radical conditions for the reactions of the thionocarbamates, thionoamide and thionourea prepared were initially based on those used for the thionocarbonates, using AIBN or triethylborane/air as initiators, TTMSS as a radical chain carrier and acetone or benzene as solvent. However it rapidly became clear that these new radical substrates were less reactive than the thionocarbonate series and required higher doses of reagents for the reaction to go to completion. Typical reaction conditions utilised 1.0 eq AIBN, 2.0 eq TTMSS in benzene reflux for 1-3 h. Interestingly, triethylborane/air did not successfully initiate any radical reactions in this series.

2.2.5.1 Radical chemistry of N-aryl thionocarbamates

Compounds **2.75** and **2.86** were subjected to
products (see Scheme 2.34). Although two p
carboxyarylation product was not observed in either case. The major products from these reactions are imidate esters **2.103** and **2.105** and the minor products are dihydroquinolines **2.104** and **2.106**. **2.104** is a previously reported (though not fully characterised) compound.[99]

The imidate esters were isolable from flash chromatography however, the dihydroquinolines co-eluted with silane impurities. Further purification by HPLC or additional flash chromatography provided a sample for characterisation. None of these products are bench stable, decomposing into complex mixtures after 24 hours. The ratios of the products were calculated from ^{1}H NMR of the crude product. The discrepancy between the ratio of products from ^{1}H NMR and the ratio of products isolated can be attributed to decomposition during chromatography that was experienced by all products [illegible] lated from separate [illegible] tailored to the product being sought after. In order to obtain sufficient quantities of quinoline **2.104** and **2.106** it was necessary to scale up the radical reaction.

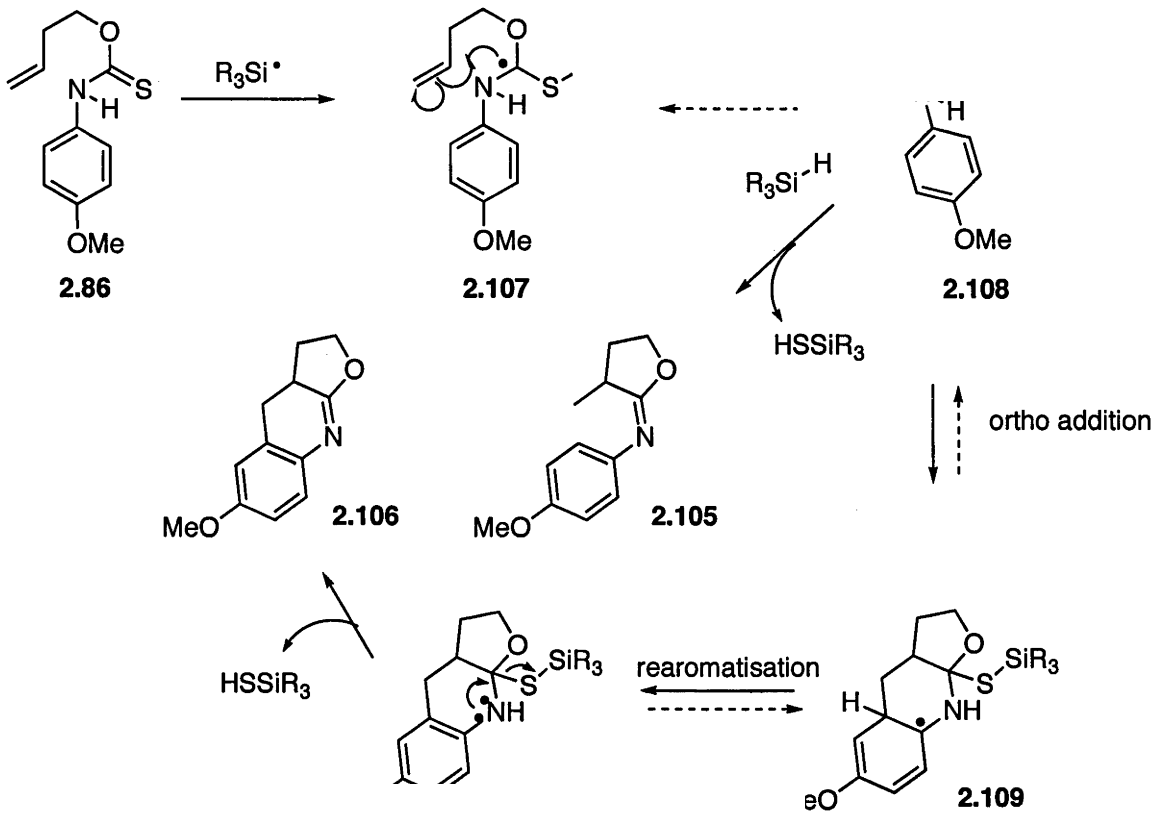
Scheme 2.34



SS, benzene reflux, 1.5 h,

While this outcome was unexpected it is perfectly believable when considering the likely mechanism shown in Scheme 2.34. The major product, **2.105**, is a result of premature quenching of the primary radical **2.108** formed in the first *5-exo-trig* cyclisation. Subsequent elimination of a thiol gives the observed compound **2.105**. Presumably this pathway could be minimised by limiting exposure to free hydrogen from TTMSS.

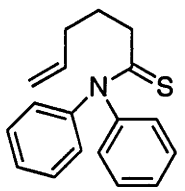
Scheme 2.34



The minor product, **2.106**, could be formed when primary radical **2.108** is not quenched but adds to the aromatic ring at the *ortho* position instead to give cyclohexadienyl radical **2.109**. Aromatisation would then give **2.110**. The lone pair on nitrogen could then eliminate the sulfur to give the isolated product **2.106**.

There are conflicting explanations in the literature[65,66,79] as to why some reactions lead to *ipso* or *ortho* addition. *Ipso* addition (or aryl migration) results in the formation of a radical on the *ipso* substituent: in this case, an aminyl radical would be formed. According to Zard[100] 'aminyl radicals are less reactive than alkyl radicals and their addition to olefins is reversible.' Thus *ipso* addition may be an easily reversed process that doesn't lead to any isolable products. When *ortho* addition occurs, it consumes the

Sch



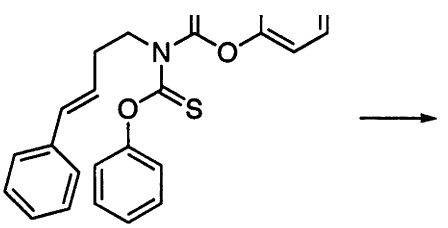
2.91

Reagents and conditions: 1.0 eq AIBN, 2.0 eq TTMSS, benzene reflux

2.2.5.4 Radical chemistry of an O-Aryl thionocarbamates

Radical chemistry of bis-thioformylated thionocarbamate **2.97** was not promising and silanes were the only identifiable products to be isolated from these reactions.

Scheme 2.38



2.97

Reagents and conditions: 1.0 eq AIBN, 2.0 eq TTMSS, benzene reflux

2.2.6 Conclusion

The preparation of six radical precursors was
limited literature precedent for some of these
problems. Of the six precursors prepared four of these are new compounds. The radical chemistry of these precursors was extremely disappointing, with four out of six not leading to isolable or identifiable products. It was not clear if this was due to degradation of the starting material or the products under the reaction conditions or if various complex radical pathways operate in these reactions leading to complex mixtures of products. Conceivably all of these factors may be at play.

N-aryl thionocarbamates **2.75** and **2.86** did successfully react under radical conditions to give obtainable products. Again the *ortho* carboxyarylation reaction was observed. This was foreshadowed by the work of Curran, who observed *ortho* addition in radical reactions of *N*-aryl thiocarbonyl compounds using alkynes as radical acceptors.[66]

Future work could look into the usefulness of N-aryl thionocarbamates in the synthesis of
than previously published.
If the premature quenching that leads to the major product could be minimised (through the use of hexamethylditin, catalytic tin hydride methods or further dilution) this could be a useful reaction.

Future work could also consider new ring sizes. Chapter 1 showed an interesting divergence of reactivity for 5- and 6-membered rings in the alkyne series. Would the same results be obtained if the ubiquitous 5-*exo*-dig cyclisation was replaced by a 6-*exo*-dig or another cyclisation?

Chapter 3

General Methods

Reactions were conducted under a positive p
glassware. Diethyl ether, toluene and tetrahy
distilled from sodium benzophenone ketyl. D
hydride. Methanol, ethanol, dimethylformamide and dimethyl sulfoxide were purified by the methods of Perrin and Amarego.[103] Commercially available chemicals were purified by standard procedures or used as purchased. Commercially available anhydrous sodium sulfate and magnesium sulfate were used without further drying. Analytical thin layer chromatography (TLC) was performed with Merck (A.T. 5554) silica gel 60 F_{254} (0.2 mm) precoated on aluminium sheets. Compounds were first visualised under UV light (254 nm), then dipped in vanillin TLC dip or potassium permanganate TLC dip and then developed by heating at approximately 200 °C. Flash chromatography employed Merck Kieselgel 60 (230-400 mesh) silica gel or SDS silice 60 ACC 40-63 μm Chromagel silica gel. Analytical HPLC was performed using a Shimadzu Prominence LC-20AD chromatograph pump and SIL-20A auto sampler monitored by a Shimadzu SPD-M20A diode array detector. Preparative HPLC was performed using a Shimadzu LC-8A
iode array detector.
Separation on preparative HPLC employed a Altima silica 5μ silica column.
Nuclear Magnetic Resonance (NMR) spectra were recorded at 298 K using a Varian INOVA 500 or 300 spectrometer. Residual benzene, chloroform, dimethylsulfoxide were used as internal references for ^{1}H NMR spectra measured in these solvents. Residual benzene, chloroform and dimethyl sulfoxide were used as internal references for ^{13}C NMR spectra. Signals were described in terms of chemical shifts, intensity, multiplicity (the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad) and coupling constants. Assignment of carbon signals was assisted by DEPT experiments. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer as neat films on NaCl or as KBr discs for solid products. Mass spectra were recorded by the Mass Spectrometry Facility of the Research School of Chemistry, Australian National University, Canberra on a VG Austospec M series sector (EBE) MS for EI (70eV), VG Quattro II triple quadrupole MS for LR ESI and Bruker Apex3 4.7T

FTICR-MS for HR ESI. Melting points were measured on a Reichert hot stage melting point apparatus and are uncorrected.

General Procedure for

Tert-butyldimethylsilyl chloride (2.0 eq) was added in portions to a stirred solution of imidazole (4.0 eq) and alcohol (1.0 eq) in THF (0.2 M) at 0 °C. The cold bath was then removed and after stirring 2 h, the reaction was quenched with water. The aqueous layer was extracted with ether and the combined organics then washed with brine, dried over magnesium sulfate and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography typically eluting with 0-10% EtOAc/Pet.Spirits to give the desired TBS ether.

General Procedure for buffered TBAF deprotection of TBS ethers

Acetic acid (4.0 eq) was added to a solution of silyl ether (1.0 eq) in THF (0.05 M). TBAF (2.0 eq) was then added. After 24 h the reaction was partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether. The combined organics were washed with saturated sodium hydrogen carbonate aqueous solution then dried over sodium sulfate and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography.

General Procedure for the Formation of Thionocarbonates

The thionochloroformate **1.111** (1.1 eq) was added to a solution of the alcohol in dichloromethane (0.10 M) and pyridine (2.0 eq) at room temperature. The reaction mixture was stirred for 2 h then diluted with water. The aqueous layer was extracted with dichloromethane and the combined organics washed in turn with saturated aqueous sodium hydrogen carbonate, 1.0 M aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The organic phase was dried

over magnesium sulfate and the solvent was removed *in vacuo*. Thionocarbonates were purified by flash chromatography.

General procedure for therr

The thionocarbonate (1.0 eq) was dissolved in benzene (0.020 M) and heated at reflux for 30 min. *Tris*(trimethylsilyl)silane (0.55 eq) and AIBN (0.20 eq) were combined and dissolved in minimal benzene then added to the reaction via syringe. The reaction was monitored by TLC and after 0.5-2.5 h the reaction mixture was concentrated under a stream of nitrogen gas. Aryl lactones were isolated by flash chromatography.

General procedure for ambient photolytic radical reaction (AIBN)

The thionocarbonate, *tris*(trimethylsilyl)silane (1.1 eq) and AIBN (0.6 eq) were dissolved in benzene (0.020 M) and degassed by bubbling N_2 through the solution for 10 min. The reaction vessel (typically a quickfit pyrex test tube) was placed at close proximity (3 cm) [illegible] g jacket. Both lamp and [illegible]. The reaction was monitored by TLC and after 12-72 h the reaction mixture was concentrated under a stream of nitrogen gas.

General procedure for radical reaction (BEt_3)

The starting thionocarbonate was dissolved in acetone (0.020 M) and *tris*(trimethylsilyl)silane (2.0 eq) added. Triethylborane solution in hexanes (1.0 M, 1.5 eq) was then added followed by 1.00 mL of air (bubbled through reaction mixture via syringe.) The reaction was monitored by TLC and after 10 min-14 h the reaction mixture concentrated under a stream of nitrogen gas. Aryl lactones were isolated by flash chromatography, typically eluting with 30% EtOAc/Pet.Spirits.

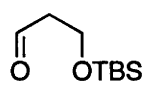
Experimental for Chapter 1

3-(*tert*-Butyldim

1.121a

The commercially available alcohol **1.121a** (16.9 g, 88.8 mmol, 68%, R_f = 0.40 in 20% EtOAc/Pet.Spirits) was prepared from 1,3-propanediol (10.0 g, 131 mmol) according to the literature procedure.[56] ^{1}H NMR data corresponded to those quoted in the literature.[56]

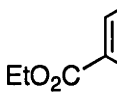
3-(*tert*-Butyldimethylsilyloxy) propanal



1.121

Alcohol **1.121a** (5.00 g, 26.3 mmol, 1.0 eq) was added to a vigorously stirred suspension of pyridinium chlorochromate (11.3 g, 52.4 mmol, 2.0 eq), sodium acetate (2.13 g, 26.0 mol, 1.0 eq) and celite (10 g) in dichloromethane (80.0 mL) at room temperature. After 1 h, the black suspension was filtered off, the filtrate was concentrated and then passed through a plug of silica gel eluting with dichloromethane. The eluent was then concentrated *in vacuo* to give the aldehyde **1.121** (4.00 g, 21.3 mmol, 81%) as a yellow oil (R_f = 0.55 in 10% EtOAc/Pet.Spirits). ^{1}H NMR data corresponded to those quoted in the literature.[104]

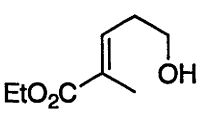
(*E*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-2-methylpent-2-enoate



1.1

To a solution of the aldehyde **1.121** (4.00 g, 21.3 mmol) in dichloromethane (50.0 mL) was added (carboethoxyethylidene)triphenylphosphorane (11.6 g, 32.0 mmol, 1.5 eq). After stirring at room temperature for 20 h the reaction mixture was concentrated *in vacuo* and purified *via* flash chromatography eluting with 2-20% EtOAc/Pet.Spirits to give the title compound **1.113a** (3.68 g, 13.5 mmol, 63%) as a colourless oil (R_f = 0.59 in 10% EtOAc/Pet.Spirits). ^{1}H NMR data corresponded to those quoted in the literature.[105]

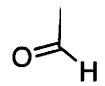
(*E*)-ethyl 5-hydroxy-2-methylpent-2-enoate



1.113

TBAF (27.0 mL, 1.0 M, 27.0 mmol, 2.1 eq) was added to a solution of silyl ether **1.113a** (3.57 g, 13.1 mmol) in THF (50.0 mL). After 1 h the reaction mixture was partitioned between ether (50 mL) and water (50 mL). The aqueous layer was extracted with ether (50 mL), the combined organics were dried over magnesium sulfate and were concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography eluting with 50% EtOAc/Pet.Spirits to give homoallylic alcohol**1.113** as a colourless oil (1.31 g, 8.29 mmol, 63%, R_f= 0.73 in EtOAc). ^{1}H NMR data corresponded to those quoted in the literature.[55]

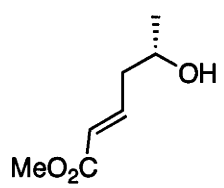
(*S*,*E*)-5-hydroxyhex-2-enal



1.120

S-Aldehyde **1.120** was prepared by a modified literature procedure.[53] Acetaldehyde (50 mL, 0.89 mol) was combined with THF (200 mL) and water (5 drops) and brought to 4 °C. Proline (900 mg, 7.8 mmol, 0.11eq) was added and the mixture stirred at 4 °C for 22 h. The resulting yellow mixture was filtered through a small quantity of silica gel with 1% NEt_3/THF and the filtrate concentrated *in vacuo*. The resulting oil was purified via a short column eluting with 0-100% EtOAc/Pet.Spirits. The crude isolate (approx. 2 g) was further purified by another, longer flash column to give the crude aldehyde **1.120** as a colourless oil (1.18 g, 10 mmol, 3%, R_f = 0.36 in 50% EtOAc/Pet.Spirits.) The purity of this material was estimated to be 75% by internally standardised (*tert*-butyl methyl ether) ^{1}H NMR.

(*S*,*E*)-methyl 5-hydroxyhex-2-enoate

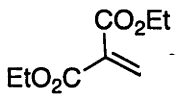


1.112

The title compound **1.112** (350 mg, 2.43 mmol, 46%, R_f = 0.28 in 20% EtOAc/Pet.Spirits) was prepared in two steps from the aldehyde **1.120** (600 mg, 5.26 mmol) according to the literature procedure.[53] ^{1}H NMR data corresponded to those quoted in the literature.[106]

$[\alpha]^{22}_D$ = +7.25 ° (*c* 0.40, $CHCl_3$)

Diethyl 2-(3-(*tert*-butyldimethylsilyloxy)propylidene)malonate



1.1

The title compound **1.125** was prepared using a literature procedure for Knoevenagel condensation promoted by titanium tetrachloride.[60] Titanium tetrachloride (1.00 mL, 1.73 g, 9.12 mmol, 3.7 eq) was added to THF (20 mL) at 0°C creating a yellow suspension. Aldehyde **1.121** (1.00 g, 5.32 mmol, 1.0 eq), diethyl malonate (900 μL, 945 mg, 5.90 mmol, 1.1 eq) and pyridine (1.60 mL, 1.56 g, 19.7 mmol, 3.7 eq) were added sequentially to the reaction mixture. After stirring 2 d at room temperature the reaction mixture was quenched by the addition of water and then extracted with ether (30 mL × 3) and the combined organics were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography of the crude material eluting with 10% EtOAc/Pet.Spirits gave the title compound **1.125** (765 mg, 2.32 mmol, 44%, R_f = 0.41 in 10% EtOAc/Pet.Spirits) as a colourless oil.

[z, $CDCl_3$) : δ 7.08 (1H, t, J = 7.7Hz), 4.29 (2H, q, J = 7.1 Hz), 4.23 (2H, q, J = 7.1 Hz), 3.73 (2H, t, J = 6.3 Hz), 2.54 (2H, dd, J = 7.8, 6.3 Hz), 1.32 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 0.88 (9H, s), 0.048 (6H, s); ^{13}C NMR (300MHz, $CDCl_3$): δ 165.3 (s), 163.9 (s), 146.6 (d), 129.6 (s), 61.2 (t, two coincident peaks), 33.2 (t), 25.8 (q), 18.2 (), 14.1 (q), 14.0 (q), -5.5 (q); MS (70 eV, EI): *m/z* (%): 315 (5) $[M\text{-}CH_3]^+$, 73 (100), 273 (84), 199 (76); HRMS (EI) *m/z* calculated 315.1628 for $C_{15}H_{27}O_5Si$ ($M\text{-}CH_3^+$) found 315.1643

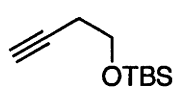
Diethyl 2-(3-hydroxypropylidene)malonate

1.114

The homoallylic alcohol **1.114** (170 mg, 0.791 mmol, 82%, $R_f = 0.35$ in 50% EtOAc/Pet.Spirits) was prepared from TBS ether **1.125** (317 mg, 0.961 mmol) according to the general procedure for buffered TBAF deprotection.

IR (film): ν_{max} 3442, 2983, 1728, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 7.07 (1H, t, $J = 8.0$ Hz), 4.28 (2H, q, $J = 7.1$ Hz), 4.22 (2H, q, $J = 7.1$ Hz), 3.76 (2H, t, $J = 6.0$ Hz), 2.55 (2H, dt, $J = 8.1, 6.2$ Hz), 2.35 (1H, br s), 1.31 (3H, t, $J = 7.2$ Hz), 1.27 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) : δ 165.6 (s), 163.7 (s), 146.2 (d), 130.5 (s), 61.7 (t), 61.5 (t), 61.3 (t), 60.6 (t), 32.9 (t), 14.0 (q), 13.9 (q); MS (70 eV, EI): *m/z* (%): 215 (9) $[M]^{+\bullet}$, 140 (100), 186 (57), 171 (44); HRMS (EI) *m/z* calculated 215.0919 for $C_{10}H_{15}O_5$ ($M^{+\bullet}$) found 215.0916

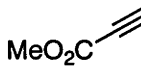
tert-Butyldimethylsilyloxybut-3-yne



1.126a

The commercially available silyl ether **1.126a** (2.49 g, 13.5 mmol, 94%, $R_f = 0.30$ in Pet.Spirits) was prepared according to the general procedure for the TBS protection of alcohols from 3-butyn-1-ol (1.00 g, 14.3 mmol, 1.0 eq). ^1H NMR data corresponded to those quoted in the literature.[62]

Methyl 5-(*tert*-butyldimethylsilyloxy)pent-2-ynoate

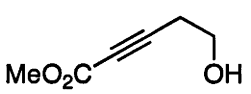


1.1

n-Butyllithium (10.0 mL, 1.6 M, 16.0 mmol, 1.1 eq) was added to a solution of alkyne **1.126a** (2.50 g, 13.6 mmol, 1.0 eq) in ether (50.0 mL) at -78 °C under N_2. After 30 min methyl chloroformate (1.25 mL, 16.2 mmol, 1.1 eq) was added dropwise and the cooling bath removed. After 1.5 h, water (30 mL) was added and the mixture extracted with ether (30 mL × 2). The ethereal solution was dried over magnesium sulfate and then concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography eluting with 5-10% EtOAc/Pet.Spirits. The title compound **1.126** (2.64 g, 10.9 mmol, 78%) was isolated as a colourless oil (R_f = 0.74 in 10% EtOAc/Pet.Spirits).

IR (film): ν_{max} 2955, 2858, 2244, 1720 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 3.77 (2H, t, *J* = 7.2 Hz), 3.75 (3H, s), 2.54 (2H, t, *J* = 6.9 Hz), 0.88 (9H, s), 0.07 (6H, s); ^{13}C NMR (300MHz, $CDCl_3$): δ 154.0 (s), 86.8 (s), 72.7 (s), 60.6 (t), 52.5 (q), 25.8 (q), 23.0 (t), [illegible], 185 (100), 155 (56); HRMS (EI) *m/z* calculated 227.1103 for $C_{11}H_{19}O_3Si$ $[M-CH_3]^+$ found 227.1103

Methyl 5-hydroxypent-2-ynoate

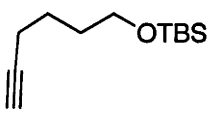


1.127

The homopropargyl alcohol **1.127** (873 mg, 6.82 mmol, 62%, R_f = 0.48 in 50% EtOAc/Pet.Spirits) was synthesised according to the general procedure for the buffered TBAF deprotection of TBS ethers from silyl ether **1.126** (2.64 g, 10.9 mmol, 1.0 eq).

IR (film): ν_{max} 3410, 2956, 2891, 2241, 1718 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) : δ 3.78 (2H, t, J = 6.3 Hz), 3.75 (3H, s), 2.58 (2H, t, J = 6.3 Hz);^{13}C NMR (300MHz, $CDCl_3$) : δ 154.1 (s), 86.7 (s), 73.9 (s), 59.9 (t), 52.7 (
[M] $^{+\bullet}$, 98 (93), 53 (100), 39 (94); HRMS)
found 129.0553

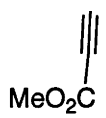
tert-Butyldimethylsilyloxyhex-5-yne



1.128a

The silyl ether **1.128a** (1.58 g, 7.45 mmol, 99%, R_f = 0.45 in 5%EtOAc/Pet.Spirits) was prepared from 5-hexyne-1-ol (738 mg, 7.53 mmol) according to the general procedure for TBS protection of alcohols. ^1H NMR data corresponded to those quoted in the literature.[107]

Methyl 7-(*tert*butyldimethylsilyloxy)hept-2-ynoate

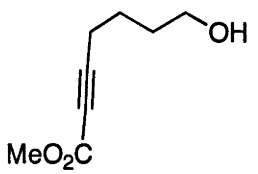


1.128

n-Butyllithium (3.8 mL, 1.6 M, 6.02 mmol, 1.4 eq) was added to a solution of alkyne **1.128a** (920 mg, 4.34 mmol, 1.0 eq) in THF (43 mL) at -78 °C under N_2. After 30 min methyl chloroformate (470 μL, 6.08 mmol, 1.40 eq) was added dropwise and the cooling bath removed. After 14 h, water (50 mL) was added and the mixture extracted with ether (2 × 30 mL). The ethereal solution was dried over magnesium sulfate and then concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography eluting with 5-10% EtOAc/Pet.Spirits. The title compound **1.128** (1.085 g, 4.02 mmol, 93%) was isolated as a colourless oil (R_f = 0.20 in Pet.Spirits).

IR (film): 2954, 2238, 1718 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) : δ 3.74 (3H, s), [illegible]
t, J = 5.7 Hz), 2.36 (2H, t, J = 6.9Hz), 1.65-1
NMR (300MHz, $CDCl_3$) : δ 154.2 (s), 89.7 (
(q), 24.0 (t), 18.4 (t), -5.4 (q); MS (70 eV, EI
(41), 213 (99); HRMS (EI) *m/z* calculated 255.1416 for $C_{13}H_{23}O_3Si$ (M^+- CH_3) found 255.1415

Methyl 7-hydroxyhept-2-ynoate



1.129

The alcohol **1.129** (95 mg, 0.605 mmol, 55%, R_f = 0.54 in 50% EtOAc/Pet.Spirits) was prepared from the TBS ether **1.128** (300 mg, 1.11 mmol) according to the general procedure for the deprotection of TBS ethers. It was isolated as a colourless oil.

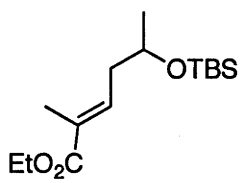
IR (film): 3394, 2952, 2237, 1713 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) : δ 3.74 (3H, s), 3.69-3.64 (2H, m), 2.40-2.36 (2H, m), 1.78 (1H, br s) 1.69-1.65 (4H, m); ^{13}C NMR (300MHz, $CDCl_3$) : δ 154.2 (s), 89.4 (s) 73.0 (s), 62.0 (t), 52.6 (q), 31.5 (t), 23.8 (t), 18.4 (t); MS (70 eV, EI): *m/z* (%): 157 (5) $[M+1]^{+\bullet}$, 79 (100), 124 (82), 98 (58), 66 (86); HRMS (EI) *m/z* calculated 157.0865 for $C_8H_{13}O_3$ ($M+1^{+\bullet}$) found 157.0860

Pent-4-en-2-ol

1.124a

The racemic silyl ether **1.124a** (480 mg, 2.40 mmol, 92%, R_f = 0.84 in Pet.Spirits) was prepared from 4-penten-2-ol (225 mg, 2.61 mmol) according to the general procedure for the TBS protection of alcohols. ^{1}H NMR spectroscopic data corresponded to those quoted in the literature.[108]

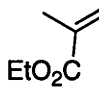
(*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2-methylhex-2-enoate



Ozone was bubbled through a solution of alkene **1.124a** (4.00 g, 20.0 mmol, 1.0 eq) in dichloromethane (130 mL) at -78°C until a blue colour persisted in the solution. Nitrogen was then bubbled through until a colourless solution was achieved. Triethylamine (5.60 mL, 40.2 mmol, 2.0 eq) was then added. After stirring at room temperature for 1 h the solvent was removed *in vacuo* to give the crude aldehyde as a pale yellow oil (3.30 g). This was carried on to the next step without further purification.

The aldehyde (6.20 g, 30.7 mmol) was combined with (carboethoxyethylidene)triphenylphosphorane (13.0 g, 35.9 mmol, 1.2 eq) in toluene (180 mL) and the resulting mixture heated to reflux for 16 h. After removal of solvent, the residue was purified by flash chromatography eluting with 5% EtOAc/Hexanes to give the desired alkene **1.113a** (7.60 g, 26.6 mmol, 86%, R_f = 0.65 in 10% EtOAc/Pet.Spirits) as a colourless oil. ^{1}H NMR data corresponded to those quoted in the literature.[109]

(*E*)-Ethyl 5-hydroxy-2-methylhex-2-enoate

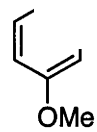


1.113

Silyl ether **1.113a** (500 mg, 1.74 mmol) was dissolved in methanol/dichloromethane (4:1, 22.0 mL) and 1.0 M aqueous hydrochloric acid (2.97 mL, 2.97 mmol, 1.7 eq) added. After stirring at room temperature for 14 h the reaction mixture was partitioned between dichloromethane and water, the aqueous extracted with dichloromethane (20mL), the combined organics dried over sodium sulfate and the solvent removed *in vacuo*. The residue was purified by flash chromatography eluting with 50% EtOAc/Hex to give the homoallylic alcohol **1.113** (246 mg, 1.43 mmol, 82%, $R_f = 0.63$ in 50% EtOAc/Pet.Spirits) as a colourless oil.

IR (film): ν_{max} 3435, 2974, 1709, 1649 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 6.79 (1H, dt, 5, 6.3 Hz), 2.43-2.26 (2H, m), 1.84 (3H, d, $J = 1.2$ Hz), 1.26 (3H, ddt, $J = 12.0, 6.3, 0.5$ Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 168.0 (s), 137.7 (d), 129.9 (s), 67.2 (d), 60.5 (t), 38.3 (t), 23.2 (q), 14.2 (q), 12.6 (q) MS (70 eV, EI): *m/z* (%): 173 (30) $[M]^{+\bullet}$, 155 (40), 127 (78), 43(100); HRMS (EI) *m/z* calculated 173.1178 for $C_9H_{16}O_3$ ($M^{+\bullet}$) found 173.1180.

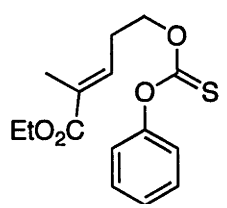
p-Methoxyphenyl thiochloroformate



1.111

The commercially available title compound **1.111** (3.80 g, 18.7 mmol, 94%) was prepared from 4-methoxyphenol (2.47 g, 19.9 mmol) using the method described by Barton et al.[5] ^{1}H NMR spectroscopic data corresponded to those quoted in the literature.[43]

O-(*E*)-4-(Ethoxycarbonyl)pent-3-enyl *O*-4-methoxyphenyl carbonothioate



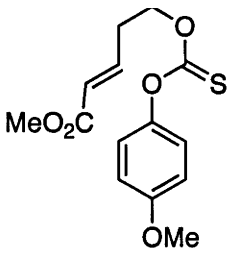
1.98

The title compound **1.98** was prepared according to the general procedure. Alcohol **1.113** (400 mg, 2.53 mmol) was converted into thionocarbonate **1.98**. **1.98** (R_f = 0.36 in 20% EtOAc/Pet.Spirits) was obtained as a colourless oil (600 mg, 1.85 mmol, 73%).

IR (film): ν_{max} 2980, 2958, 2837, 1710, 1653 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.02 (2H, d, *J* = 6.3 Hz), 6.91 (2H, d, *J* = 6.3 Hz), 6.78 (1H, qt, *J* = 7.5, 1.5 Hz), 4.60 (2H, t, *J* = 6.6 Hz), 4.22 (2H, q, *J* = 7.1 Hz), 3.81 (3H, s), 2.72 (2H, dq, *J* = 6.9, 0.9 Hz), 1.90 (3H, dd, *J* = 2.4, 0.9 Hz), 1.31, (3H, t, *J* =7.2 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 195.6 (s), 167.6 (s), 157.7 (s), 146.9 (s), 135.7 (d), 130.9 (s), 122.6 (d), 114.4 (d), 72.1 (t), 60.7 (t),

55.5 (q), 27.7 (t), 14.3 (q), 12.6 (q); MS (70 eV, EI): *m/z* (%): 324 (11) $[M]^{+\bullet}$, 141 (100), 124 (96); HRMS (EI) *m/z* calculated for $C_{16}H_{20}O_5S$ 324.1031 ($M^{+\bullet}$) found 324.1032.

O-(*S*,*E*)-5-(Methoxycarbonyl)pent-4-en-

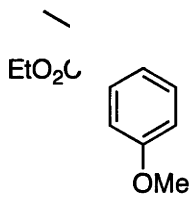


1.97

The title compound **1.97** was prepared according to the general procedure. Alcohol **1.112** (200 mg, 1.39 mmol) was converted into thionocarbonate **1.97**. **1.97** (R_f = 0.73 in 25% EtOAc/Pet.Spirits) was obtained as a colourless oil (229 mg, 0.73 mmol, 53%).

$[\alpha]^{22}_D$= -36.7 ° (*c* 0.75, $CHCl_3$); IR (film): ν_{max} 2951, 2838, 1723, 1660 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.01 (2H, d, *J* = 9.3 Hz), 6.98-6.93 (1H, m), 6.91 (2H, d, *J* = 9.0 Hz), 3.81 (3H,s), 3.75 (3H, s), 2.68 (2H, m), 1.45 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 194.8 (s), 166.4 (s), 157.7 (s), 146.8 (s), 142.8 (d), 124.3 (d), 122.6 (d), 114.4 (d), 79.6 (d), 55.5 (q), 51.6 (q), 37.8 (t), 18.9 (q); MS (70 eV, EI): *m/z* (%): 310 (4) $[M]^{+\bullet}$, 140 (49), 124 (91), 59 (100); HRMS (EI) *m/z* calculated 310.0875 for $C_{15}H_{19}O_5S$ ($M^{+\bullet}$) found 310.0874

O-(*E*)-5-(Ethoxycarbonyl)hex-4-en-2-yl *O*-4-methoxyphenyl carbonothioate

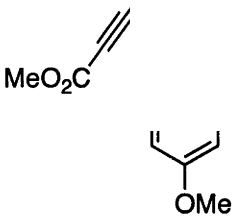


1.100

The title compound **1.100** was prepared according to the general procedure. Alcohol **1.113** (350 mg, 2.03 mmol) was converted into thionocarbonate **1.100**. **1.100** (R_f = 0.41 in 20% EtOAc/Pet.Spirits) was obtained as a colourless oil (405 mg, 1.20 mmol, 59%).

IR (film): ν_{max} 2981, 2837, 1710, 1652 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.01 (2H, d, *J* = 9.3 Hz), 6.91 (2H, d, *J* = 6.0 Hz), 6.77 (1H, dt, *J* = 7.5, 1.2 Hz), 5.48 (1H, dt, *J* = 6.3, 12.6 Hz), 4.21 (2H, q, *J* = 7.1 Hz), 3.81 (3H, s), 2.77-2.55 (2H, m), 1.89 (3H, s), 1.45 (3H, d, *J* = 6.3 Hz), 1.31 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 194.8 (s),), 114.4 (d), 80.3 (d), 60.6 (t), 55.5 (q), 34.3 (t), 18.9 (q), 14.2 (q), 12.7 (q); MS (70 eV, EI): *m/z* (%): 338 (7) $[M]^{+\bullet}$, 155 (76), 124 (100); HRMS (EI) *m/z* calculated 338.1188 for $C_{17}H_{22}O_5S$ ($M^{+\bullet}$) found 338.1188

O-4-(Methoxycarbonyl)but-3-ynyl *O*-4-methoxyphenyl carbonothioate

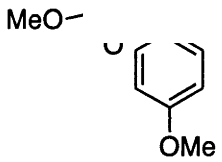


1.101

The title compound **1.101** was prepared according to the general procedure. Due to its instability on silica this product was used as a crude material. Alcohol **1.127** (400 mg, 3.12 mmol) was converted into thionocarbonate **1.101**. The crude **1.101** (R_f = 0.62 in 20% EtOAc/Pet.Spirits) was obtained as a brown heterogeneous mixture (900 mg, 3.06 mmol, 98%).

IR (film): ν_{max} 2955, 2838, 2243, 1716cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.03 (2H, d, *J* = 9.3 Hz), 6.91 (2H, d, *J* = 9.3 Hz), 4.65 (2H, t, *J* = 6.8 Hz), 3.81 (3H, s), 3.78 (3H, s), 2.89 (2H, t, *J* = 6.8 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 195.1 (s), 157.7 (s), 153.7 (s), (q), 52.8 (q), 18.8 (t); MS (70 eV, EI): *m/z* (%): 294 (85) $[M]^{+\bullet}$, 123 (96). 124 (95), 53 (100); HRMS (EI) *m/z* calculated 294.0562 for $C_{15}H_{19}O_5S$ 294.0562 ($M^{+\bullet}$) found 294.0564

O-5-(Methoxycarbonyl)pent-4-ynyl *O*-4-methoxyphenyl carbonothioate

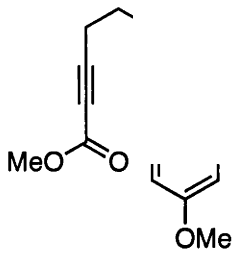


1.102

The title compound **1.102** was prepared according to the general procedure. Alcohol **1.130** (200 mg, 1.41 mmol) was converted into thionocarbonate **1.102**. **1.102** (R_f = 0.10 in 10% EtOAc/Pet.Spirits) was obtained as a colourless oil (350 mg, 1.14 mmol, 81%) which later solidified to a colourless solid, mp: 43-45 °C.

IR (film): ν_{max} 2954, 2838, 2238, 1714 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.00 (2H, d, J = 9.0 Hz), 6.89 (2H, d, J = 9.0 Hz), 4.57 (2H, t, J = 6.0 Hz), 3.78 (3H, s), 3.74 (3H, s), 2.52 (2H, t, J = 6.9 Hz), 2.08 (2H, quin, J = 6.6 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ), 87.4 (s), 73.4 (s), 71.9 (t), 55.4 (q), 52.5 (q), 26.2 (t), 15.3 (t); MS (70 eV, EI): *m/z* (%): 308 (50) $[M]^{+\bullet}$, 124 (100); HRMS (EI) *m/z* calculated 308.0718 for $C_{15}H_{19}O_5S$ ($M^{+\bullet}$) found 308.0718

O-6-(Methoxycarbonyl)hex-5-ynyl *O*-4-methoxyphenyl carbonothioa..

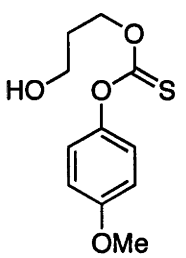


1.103

The title compound **1.103** was prepared according to the general procedure. Alcohol **1.129** (471 mg, 3.04 mmol) was converted into thionocarbonate **1.103**. **1.103** (R_f = 0.39 in 20% EtOAc/Pet.Spirits) was obtained as a colourless oil (892 mg, 2.77 mmol, 92%).

IR (film): ν_{max} 2954, 2237, 1759, 1713 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.02 (2H, d, J = 9.0 Hz), 6.91 (2H, d, J = 9.0 Hz), 4.53 (2H, t, J = 6.3Hz), 3.81 (3H, s), 3.76 (3H, s), 2.43 (2H, t, J = 7.1Hz), 2.00-1.91 (2H, m), 1.81-1.70 (2H, m); ^{13}C NMR (300MHz, $CDCl_3$): δ 195.7 (s), 157.7 (s), 154.1 (s), 146.9 (s), 122.6 (d), 114.4 (d), 88.5 (s), 73.4 (t), 55.5 (q), 52.6 (q), 27.3 (t), 23.9 (t), 18.3 (t); MS (70 eV, EI): *m/z* (%): 322 (42) $[M]^{+\bullet}$, 79 [illegible] for $C_{16}H_{18}O_5S$ ($M^{+\bullet}$) found 322.0876

O-3-Hydroxypropyl *O*-4-methoxyphenyl carbonothioate



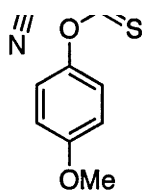
1.131

The thionochloroformate **1.111** (125 mg, 0.617 mmol, 1.0 eq) was added to a solution of 1,3-propanediol (300 mg, 3.94 mmol, 6.4 eq) in dichloromethane (12.0 mL) and pyridine

(70 μL, 0.867 mmol, 1.4 eq) at room temperature. The reaction mixture was stirred for 2 h then diluted with water. The aqueous layer was separated then extracted with dichloromethane and the combined organi
sodium hydrogen carbonate, 1.0 M aqueo
hydrogen carbonate and saturated aqueous
over magnesium sulfate and the solvent was removed *in vacuo* to give thionocarbonate **1.131**, as a colourless oil (141 mg, 0.583 mmol, 94%). **1.131** was found to be unstable to flash chromatography and was used without further purification.

IR (film): ν_{max} 3255, 2954, 1760 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.02 (2H, d, J = 9.0 Hz), 6.91 (2H, d, J = 9.0 Hz), 4.67 (2H, t, J = 3.2 Hz), 3.83 -3.79 (2H, m), 3.81 (3H, s), 2.07 (2H, dt, J = 12.3, 6.0 Hz), 1.91 (1H, br s); ^{13}C NMR (300MHz, $CDCl_3$): δ 195.8 (s), 157.6 (s), 146.9 (s), 122.6 (d), 114.4 (d), 71.2 (t), 59.0 (t), 55.5 (t), 31.1 (t); MS (70 eV, EI): *m/z* (%): 242 (12) $[M]^{+\bullet}$, 124 (100), 109 (93); HRMS (EI) *m/z* calculated 242.0613 for $C_{11}H_{14}O_4S$ ($M^{+\bullet}$) found 242.0626

O-2-Cyanoethyl *O*-4-methoxyphenyl carbonothioate



1.108

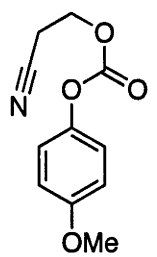
The title compound **1.108** was prepared according to the general procedure. Hydroxypropionitrile (70 mg, 0.986 mmol, 1.0 eq) was converted into thionocarbonate **1.108**. **1.108** (R_f = 0.15 in 20% EtOAc/Pet.Spirits) was obtained as a brown oil (200 mg, 0.844 mmol, 86%).

IR (KBr): ν_{max} 3432, 3008, 2962, 2838, 2260, 1758 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.04 (2H, d, J = 9.3 Hz), 6.93 (2H, d, J = 9.0 Hz), 4.70 (2H, t, J = 6.3Hz), 3.81 (3H, s),

2.91 (2H, t, J = 6.3Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 194.8 (s), 157.8 (s), 146.8 (s), 122.5 (d), 122.4 (d), 116.3 (s), 114.5 (d), 67.0 (t), 55.5 (q), 17.5 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 237 (91), 123 (100), 139 (79), 10

237.0460 for $C_{11}H_{11}NO_3S$ ($M^{+\bullet}$) found 237.0

2-Cyanoethyl 4-methoxyphenyl carbonate



1.170

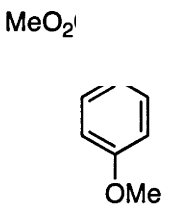
The thionocarbonate **1.108** (50 mg, 0.211 mmol, 1.0 eq) was dissolved in acetone (10 mL) and *tris*(trimethylsilyl)silane (130 μL, 0.421 mmol, 2.0 eq) added. Triethylborane solution in hexanes (500 μL, 1.0 M, 0.500 mmol, 2.4 eq) was added followed by 0.50 mL of air (bubbled through reaction mixture via syringe over 20 seconds.) The reaction was

ıcentrated under a stream of

nitrogen gas. Carbonate **1.170** (10 mg, 0.045 mmol, 21%) was obtained by flash chromatography eluting with 10-40% EtOAc/Pet.Spirits as a colourless oil (R_f = 0.19 in 20% EtOAc/Pet.Spirits).

IR (film): ν_{max} 3516, 2969, 2839, 2254, 2055, 1762, 1609 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.00 (2H, d, J = 9.3 Hz), 6.90 (2H, d, J = 9.0 Hz), 4.44 (2H, t, J = 6.5Hz), 3.00 (3H,s), 2.83 (2H, t, J = 6.3Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 157.6 (s), 153.5 (s), 144.3 (s), 121.7 (d), 116.2 (s), 114.5 (d), 62.4 (t), 55.6 (q), 18.0 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 221 (50), 123 (100), 151 (8), 54 (19); HRMS (EI) *m/z* calculated 221.0688 for $C_{11}H_{11}NO_4$ ($M^{+\bullet}$) found 221.0684

(*S*)-Methyl 2-((3*S*,5*S*)-tetrahydro-5-methyl-2-oxofuran-3-yl)-2-(4-methoxyphenyl)acetate



1.116

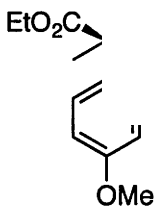
The enantio-enriched title compound **1.116** (R_f = 0.31 in 20% EtOAc/Pet.Spirits) was prepared by both general procedures.

Thermal: Thionocarbonate **1.97** (56 mg, 0.19 mmol) was converted to aryl lactone **1.116**. **1.116** was obtained as a colourless oil (33 mg, 0.12 mmol, 66%).

Triethylborane: Thionocarbonate **1.97** (50 mg, 0.16 mmol) was converted to aryl lactone **1.116**. **1.116** was obtained as a colourless oil (33 mg, 0.12 mmol, 74%).

$[\alpha]^{22}_D$= +18.5 ° (*c* 0.60, $CHCl_3$); IR (film): ν_{max} 2954, 2839, 1767, 1783, 1612cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.14 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 4.48 (1H, 3H, s), 3.687 (3H, s), 3.07 (1H, ddd, 11.7, 9.2, 5.4 Hz), 2.28-2.11 (2H, m), 1.46 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 176.8 (s), 172.4 (s), 159.0 (s), 129.3 (d), 128.6 (s), 114.3 (d), 75.3 (d), 55.2 (q), 52.3 (q), 49.1 (d), 45.6 (d), 33.4 (t), 20.9 (q); MS (70 eV, EI): *m/z* (%): 278 (84) $[M]^{+\bullet}$, 175 (100), 179 (94); HRMS (EI) *m/z* calculated 278.1154 for $C_{15}H_{18}O_5$ ($M^{+\bullet}$) found 278.1156

Ethyl 2-(-tetrahydro-2-oxofuran-3-yl)-2-(4-methoxyphenyl)propanoa..



1.117

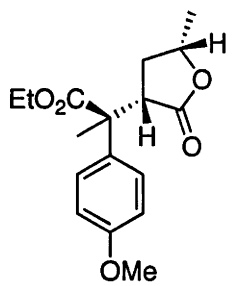
The racemic title compound **1.117** (R_f = 0.15 in 20% EtOAc/Pet.Spirits) was prepared by both general procedures.

Thermal: Thionocarbonate **1.98** (50 mg, 0.15 mmol) was converted to aryl lactone **1.117**. **1.117** was obtained as a colourless oil (23 mg, 0.078 mmol, 51%).

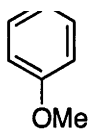
Triethylborane: Thionocarbonate **1.98** (50 mg, 0.15 mmol) was converted to aryl lactone **1.117**. **1.117** was obtained as a colourless oil (19 mg, 0.065 mmol, 45%).

IR (film): ν_{max} 2986, 1766, 1724, 1611 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.17 (2H, d, *J* = 9.0 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 4.30-4.19 (2H, m), 4.13-4.04 (2H, m), 3.80, (3H, s), 1H, m), 1.86 (3H, s) 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 176.7 (s), 174.3 (s), 158.3 (s), 133.5 (s), 127.4 (d), 127.3(d), 113.8 (d), 113.6 (d), 65.7 (t), 61.2 (t), 55.1 (q), 51.2 (s), 48.1 (d), 26.6 (t), 23.4 (q), 13.8 (q); MS (70 eV, EI): *m/z* (%): 292 (98) $[M]^{+\bullet}$, 207 (97), 175 (100), 133 (92); HRMS (EI) *m/z* calculated for $C_{16}H_{20}O_5$ 292.1311 ($M^{+\bullet}$) found 292.1309

Ethyl 2-(tetrahydro-5-methyl-2-oxofuran-3-yl)-2-(4-methoxyphenyl)propanoate)



1.119a



1.119b

The racemic title compounds **1.119a** and **1.119b** (R_f = 0.13 in 20% EtOAc/Pet.Spirits) were prepared by both general procedures.

Thermal: Thionocarbonate **1.100** (52 mg, 0.15 mmol) was converted to aryl lactones **1.119a** and **1.119b**. The mixture of two diastereomers was obtained as a colourless oil (19 mg, 0.062 mmol, 40%). The ratio of major to minor product was estimated (by ^{1}H NMR) to be 3.5:1.

Triethylborane: Thionocarbonate **1.100** (55 mg, 0.16 mmol) was converted to aryl lactones **1.119a** and **1.119b**. This mixture of two diastereomers was obtained as a

r to minor product was estimated (by ^{1}H NMR) to be 4.2:1.

The diastereomeric mixtures from both thermal and triethylborane reactions were combined. The two diastereomers were separated by HPLC (10% EtOAc/Pet.Spirits). From the mixture of diastereomers (40 mg) the major diastereomer **1.119a** was isolated as a colourless oil (20 mg, 0.065mmol):

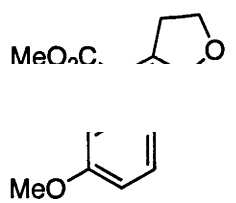
IR (film): ν_{max} 2982, 1766, 1725 cm^{-1}; ^{1}H NMR (300MHz, C_6D_6): δ 7.05 (2H, d, J = 8.7 Hz), 6.72 (2H, d, J = 9.0 Hz), 4.02 (2H, dq, J = 6.9, 3.2 Hz), 3.77 (1H, dt, J = 10.5, 6.0 Hz), 3.29 (3H, s), 2.55 (1H, dd, J = 12.6, 8.6 Hz), 1.96 (3H, s), 1.79 (1H, dd, J =22.8, 12.3 Hz), 1.38 (1H, ddd, J = 12.2, 8.8, 5.8 Hz), 1.01 (3H, d, J = 6.0 Hz), 0.930 (3H, t, J = 7.2 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 176.3 (s), 174.4 (s), 158.4 (s), 133.9 (s), 127.46 (d), 113.7 (d), 74.4 (d), 61.3 (t), 55.2 (q), 50.9 (d), 50.8 (s), 35.1 (t), 23.8 (q), 14.0 (q);

MS (70 eV, EI): *m/z* (%): 306 (72) $[M]^{+\bullet}$, 189 (100), 233 (90), 207 (76), 133 (56); HRMS (EI) *m/z* calculated 306.1467 for $C_{17}H_{22}O_5$ ($M^{+\bullet}$) found 306.1464

The minor diastereomer **1.119b** was isolated

IR (film): ν_{max} 2980, 1765, 1725 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.18 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 9.0 Hz), 4.55 (1H, ddd, J = 8.4, 6.3, 3.2 Hz), 4.24 (2H, q, J = 7.1 Hz), 3.80 (3H, s), 3.19 (1H, t, J = 9.8 Hz), 2.32 (1H, ddd, J = 13.1, 9.0, 8.9 Hz), 1.85 (3H, s), 1.60 (1H, ddd, J =13.4, 9.6, 3.6 Hz), 1.29 (3H, d, J = 6.6 Hz), 1.26 (3H, t, J = 7.2 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 176.6 (s), 158.5 (s), 133.5 (s), 127.6 (d), 113.7 (d), 74.0 (d), 61.4 (t), 55.2 (q), 51.8 (s), 47.8 (d), 33.1 (t), 23.4 (q), 21.7 (q), 14.0 (q); MS (70 eV, EI): *m/z* (%):306 (66) $[M]^{+\bullet}$, 189 (100), 233 (91), 207 (97), 133 (69); HRMS (EI) *m/z* calculated 306.1467 for $C_{17}H_{22}O_5$ ($M^{+\bullet}$) found 306.1467

Methyl 9a-(2-cyanopropan-2-yl)-2,3-dihydro-6-methoxyfuro[2,3-*b*]chromene-4-carboxylate

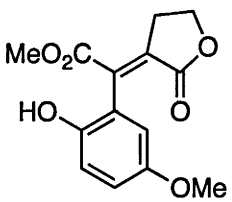


1.152

Thionocarbonate **1.101** (50 mg, 0.17 mmol) was dissolved in benzene (7.0 mL) and heated at reflux for 30 min under Ar. A solution of *tris*(trimethylsilyl)silane (80 μL, 0.26 mmol, 1.5 eq) and AIBN (44 mg, 0.27 mmol, 1.6 eq) in benzene (0.8 mL) was added to the reaction via syringe. After 2 h, the reaction mixture was concentrated under a stream of nitrogen gas and purified by flash chromatography (10-50% EtOAc/Pet. Spirits) to give the product **1.152** (R_f = 0.59 in 50% EtOAc/Pet.Spirits) as a colourless oil (4 mg, 7%) that was crystallised with diethyl ether to give colourless crystals, mp 94-95°C.

IR (film): ν_{max} 2962, 2917, 2849, 1721, 1647, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.09 (1H, d, J = 2.1 Hz), 6.93 (1H, dd, J = 8.7, 0.9 Hz), 6.84-6.80 (1H, m), 4.39-4.34 (1H, m), 4.13-4.05 (1H, m), 3.94 (3H, s), 1.23 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) 125.6 (s), 122.6 (s), 120.0 (s), 116.5 (d), 1 52.4 (q), 42.6 (s), 33.1 (t), 21.8 (q), 21.4 (q); MS (70 eV, EI): *m/z* (%): 329 (12) $[M]^{+\bullet}$, 261 (100); HRMS (EI) *m/z* calculated 329.1263 for $C_{18}H_{19}NO_5$ ($M^{+\bullet}$) found 329.1262

(*E*)-Methyl 2-(dihydro-2-oxofuran-3(2*H*)-ylidene)-2-(2-hydroxy-5-methoxyphenyl)acetate



1.151

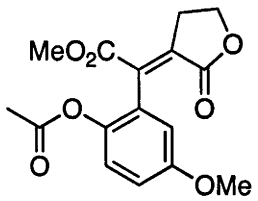
Thionocarbonate **1.101** (50 mg, 0.17 mmol) was dissolved in acetone (8.5 mL). ıdded and the resulting mixture was chilled to -78 °C under nitrogen. Trimethylborane in hexanes (260 µL, 1.0 M, 0.26 mmol, 1.5 eq) was added and air introduced to reaction with a pasteur pipette (approximately 3 mL). After 3 h, the reaction was allowed to warm to room temperature. After 14 h at room temperature, the reaction mixture was concentrated under a stream of nitrogen gas and purified by column chromatography (10-75% EtOAc/Pet. Spirits) to give the product **1.151** (R_f = 0.29 in 50% EtOAc/Pet.Spirits) as a colourless oil (24 mg, 0.086 mmol, 51%).

IR (film): ν_{max} 3400, 2954, 2924, 1755, 1717 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 6.80-6.76 (2H, m), 6.62 (1H, d, J = 3.0 Hz), 4.39 (2H, t, J = 7.1 Hz), 3.76 (3H, s), 3.73 (3H, s), 3.43 (2H, t, J = 7.1 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 168.6 (s), 167.4 (s), 153.0 (s), 146.9 (s), 136.5 (s), 134.1 (s), 122.0 (s), 117.0 (d), 115.6 (d), 115.4 (d), 65.2 (t), 55.7 (q),

52.8 (q), 29.9 (t); MS (70 eV, EI): *m/z* (%): 278 (27) $[M]^{+\bullet}$, 246 (100), 201 (39); HRMS (EI) *m/z* calculated for $C_{14}H_{14}O_6$ 278.079 ($M^{+\bullet}$) found 278.0781

(*E*)-Methyl 2-(dihydro-2-oxofura

methoxyph

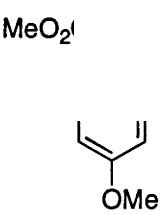


1.153

Phenol **1.151** (25 mg, 0.090 mmol) in dichloromethane (1.00 mL) was treated with acetic anhydride (20 μL, 0.21 mmol, 2.3 eq) then pyridine (15 μL, 0.19 mmol, 2.1 eq). After 2 h, water (1 mL) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (2 mL) and the combined organics were washed with saturated aqueous sodium hydrogen carbonate (2 mL), 1M hydrochloric acid (2 mL), saturated aqueous sodium hydrogen carbonate (2 mL) and saturated aqueous sodium chloride (2 mL). The [illegible] nt was removed *in vacuo*. [illegible] eluting with 20% EtOAc/Pet.Spirits to give the product **1.153** (R_f = 0.28 in 20% EtOAc/Pet.Spirits) as a yellow oil (10 mg, 0.031 mmol, 35%) which was subsequently crystallised from diethyl ether to give yellow prisms, mp 143-145 °C.

IR (KBr disc): ν_{max} 2919, 1762, 1719 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ ^1H NMR: δ 7.08 (1H, d, *J* = 9.0 Hz), 6.93 (1H, dd, *J* =9.0, 3.0 Hz), 6.75 (1H, d, *J* = 3.0 Hz), 4.42 (2H, t, *J* = 7.1 Hz), 3.79 (3H, s), 3.73 (3H, s), 3.48 (2H, t, *J* = 7.1 Hz), 2.16 (3H, s); ^{13}C NMR (300MHz, $CDCl_3$): δ 169.0 (s), 167.6 (s), 166.4 (s), 156.6 (s), 141.3 (s), 135.4 (s), 135.2 (s), 127.3 (s), 122.7 (d), 116.0 (d), 114.9 (d), 65.0 (t), 55.6 (q), 52.8 (q), 30.0 (t), 20.7 (q); MS (70 eV, EI): *m/z* (%): 320 (19) $[M]^{+\bullet}$, 278 (94), 246 (100), 201 (65); HRMS (EI) *m/z* calculated 320.0896 for $C_{16}H_{16}O_7$ ($M^{+\bullet}$) found 320.0896

(*E*)-Methyl 2-(dihydro-2-oxo-2*H*-pyran-3(4*H*)-ylidene)-2-(4-methoxyphenyl)acetate



1.158

The title compound **1.158** (R_f = 0.07 in 20%EtOAc/Pet.Spirits) was prepared by the general procedure utilising triethylborane. The general procedure for the thermal reaction was slightly modified using larger amounts of AIBN (0.7 eq) and *tris*(trimethylsilyl)silane (1.0 eq).

Thermal: Thionocarbonate **1.102** (50 mg, 0.16 mmol) was converted to aryl lactone **1.158**. **1.158** was obtained as colourless solid (16 mg, 0.058 mmol, 36%).

Triethylborane: Thionocarbonate **1.102** (50 mg, 0.16 mmol) was converted to aryl lactone **1.158**. **1.158** was obtained as colourless solid (28 mg, 0.10 mmol, 62%.) Recrystallisation from diethyl ether gave colourless plates, mp 103-104 °C.

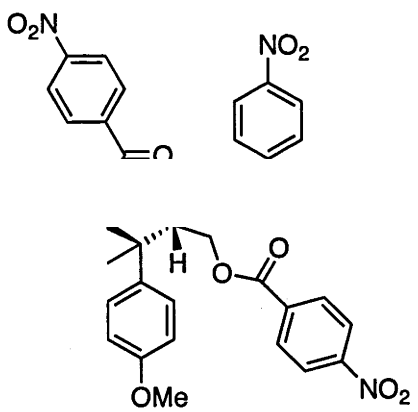
IR (KBr disc): ν_{max} 2958, 2839, 1709, 1608 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.20-7.15 (2H, m), 6.89-6.84 (2H, m), 4.34 (2H, t, J = 5.4 Hz), 3.80 (3H, s), 3.79 (3H, s) 2.96 (2H, t, J = 7.4 Hz), 2.08-2.00 (2H, m); ^{13}C NMR (300MHz, $CDCl_3$): δ 168.0 (s), 166.5 (s), 159.8 (s), 142.1 (s), 130.6 (s), 129.8 (d), 129.4 (d), 127.3 (s), 114.1 (d), 113.7 (d), 67.6 (t), 55.2 (q), 52.5 (q), 25.9 (t), 22.9 (t); MS (70 eV, EI): *m/z* (%): 276 (82) $[M]^{+\bullet}$, 244 (100); HRMS (EI) *m/z* calculated 276.0998 for $C_{15}H_{16}O_5$ ($M^{+\bullet}$) found 276.0996

Methyl 2-cyclopentylideneacetate

MeO_2C

1.164

The title compound **1.164** (5 mg, 0.036 mmol, 58%) was prepared from thionocarbonate **1.103** (20 mg, 0.062 mmol) according to the general procedure for an ambient photolytic radical reaction. Flash chromatography of the crude product eluting with 20% diethyl ether in pentane allowed the collection of product **1.164** contaminated with solvents (15 mg). The yield of 58% was calculated by integration of the ^1H NMR peaks with respect to the product, diethyl ether and pentane. ^1H NMR data corresponded with those quoted in the literature.[67]



Triester **1.133**

Lactone **1.117** (19 mg, 65 μmol, 1.0 eq) was dissolved in dichloromethane (6.0 mL) and chilled with stirring in an ice bath. After ten min, diisobutylaluminium hydride (650 μL, 1.0 M solution in hexanes, 0.65 mmol, 10.0 eq) was added dropwise. After the addition, the reaction was allowed to warm to room temperature and then stirred for 14 h. The reaction was quenched by the addition of ice and saturated aqueous potassium sodium tartrate (20 mL). After stirring for 1 h, the organic and aqueous layers were separated and the aqueous layer extracted with dichloromethane (10 mL × 2) then EtOAc (10 mL × 3).

The combined organics were then dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the crude product (20 mg). The crude triol (20 mg, 65 μmol, 1.0 eq) was then dissolved in dichloromethane (10 mL
p-nitrobenzoyl chloride (140 mg, 0.75 mm
stirring 24 h at room temperature the dichl
dried over sodium sulfate and concentrated *in vacuo*. The resulting crystalline material was purified by flash chromatography eluting with 20% EtOAc/Hexanes to give the desired triester **1.133** (R_f = 0.18 in 20% EtOAc/Pet.Spirits) as a colourless solid (10 mg, 14 μmol, 22%). Recrystallisation from dichloromethane/heptane gave colourless plates, mp 192-195 °C.

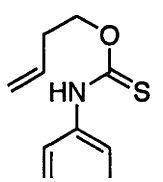
IR (KBr disc): ν_{max} 3112, 2962, 1724, 1608 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 8.28 (2H, d, J = 1.8 Hz), 8.24 (2H, d, J = 2.1 Hz), 8.22 (2H, d, J = 9.0 Hz), 8.13 (2H, d, J = 9.0 Hz), 8.08 (2H, d, J = 9.0 Hz), 8.01 (2H, d, J = 9.0 Hz), 7.33 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 9.0 Hz), 4.73 (1H, d, J = 11.1 Hz), 4.63 (1H, d, J = 10.8 Hz), 4.56 – 4.41 (3H, m), 4.33 (1H, dd, J = 11.6, 5.6 Hz), 3.76 (3H, s), 2.54 – 2.52 (1H, m), 2.25 – 2.17 (1H, m), 1.96 – 1.86 (1H, m), 1.58 (3H, s); ^{13}C NMR (300MHz, $CDCl_3$): δ 164.5, 164.4, 158.3, 5, 127.3, 123.6 (two coincident peaks), 114.0, 71.2, 66.2, 64.7, 55.2, 43.5, 42.3, 27.4, 20.1; MS (70 eV, EI): *m/z* (%): 701 (4) $[M]^{+\bullet}$, 120 (100), 150 (63); HRMS (EI) *m/z* calculated 701.1857 for $C_{35}H_{31}N_3O_{13}$ ($M^{+\bullet}$) found 701.1857

Experimental

General procedure for thermal (AIBN in
thionourea and thionocarbamates precursors

The starting material was dissolved in benzene (0.020 M) and heated at reflux for 30mins. *Tris*(trimethylsilyl)silane (2.0 eq) and AIBN (1.0 eq) were combined and dissolved in minimal benzene and added to the reaction via syringe. The reaction was monitored by TLC and after 1.5-3 h the reaction mixture was concentrated under a stream of nitrogen gas. Products were isolated by flash chromatography.

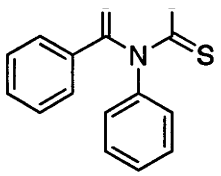
O-but-3-enyl *N*-phenylcarbamothioate



2.75

The title compound **2.75** (808 mg, 3.92 mmol, 81%, R_f = 0.40 in 10% EtOAc/Pet.Spirits) was prepared from 3-butene-1-ol (350 mg, 4.86 mmol) according to the literature procedure.[83] ^{1}H NMR and ^{13}C NMR corresponded to those quoted in the literature.[84]

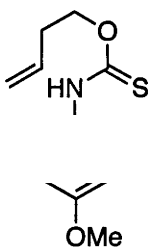
O-But-3-enyl *N*-benzo



2.85

The title compound **2.85** (712 mg, 2.29 mmol, 94%, R_f = 0.38 in 10% EtOAc/Pet.Spirits) was prepared from thionocarbamate **2.75** (500 mg, 2.43 mmol) according to the literature procedure.[84] ^{1}H NMR and ^{13}C NMR data corresponded to those quoted in the literature.[84]

O-But-3-enyl *N*-4-methoxyphenylcarbamothioate



2.86

Sodium hydride (310 mg, 60% dispersion in mineral oil, 7.75 mmol, 1.1 eq) was rinsed with pentane. THF (7.5 mL) was added and the suspension cooled in an ice bath. 3-Butene-1-ol (500 mg, 6.94 mmol) was added followed by *p*-methoxy isothiocyanate (1.27 g, 7.69 mmol, 1.1 eq) and after 5 min the reaction was allowed to warm to room temperature. After 2 h, water (2 mL), dichloromethane (10 mL) and ether (5 mL) were added to the reaction mixture. The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a brown solid. Purification by flash chromatography eluting with dichloromethane gave the title compound **2.86** (1.23 g, 5.21 mmol, 75 %, R_f = 0.43 in 20% EtOAc/Pet.Spirits) as an off white solid, mp 42-45 °C.

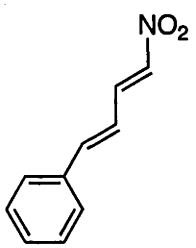
IR (KBr): ν_{max} 3227, 3056, 2932, 2832, 1642

δ 10.04 (1H, br s), 6.94 (2H, d, J = 2.5 Hz), (

4.74-4.66 (2H, m), 4.13-4.10 (2H, m), 3.35-

^{13}C NMR (300MHz, $CDCl_3$): δ 188.3 (s), 133.9 (d), 129.9 (s), 126.0 (s), 123.6 (d), 117.6 (t), 114.0 (d), 71.6 (t), 55.4 (q), 32.9 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 237 (24), 183 (78), 165 (75), 122 (100); HRMS (EI) *m/z* calculated 237.0824 for $C_{12}H_{15}NO_2S$ ($M^{+\bullet}$) found 237.0824

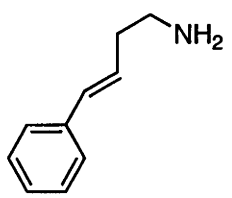
1-((1*E*,3*E*)-4-Nitrobuta-1,3-dienyl)benzene



2.96

The title compound **2.96** (5.50 g, 31.4 mmol, 21%, R_f 0.61 in 20% EtOAc/Pet.Spirits) was prepared from cinnamaldehyde (20.0 g, 151 mmol) according to the literature procedure.[90] All spectroscopic data corresponded to those quoted in the literature.[90]

(*E*)-4-Phenylbut-3-en-1-amine



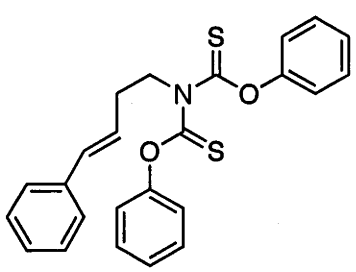
2.95

The commercially available amine **2.95** was prepared by a modified literature procedure.[88,89] Diene **2.96** (12.0 g, 68.5 mmol, 1.0 eq) was dissolved in THF (200 mL) and the resulting solution was cooled to 0 °C. Lithium aluminium hydride powder (3.80

g, 100 mmol, 1.5 eq) was then added in portions. After the addition was complete, the reaction mixture was heated at 35°C for 2 e gel-like reaction mixture was cooled to 0 ° water (4.0 mL), 15% aqueous sodium hyd stirring 20 min the resulting suspension was filtered through celite and the residue rinsed with ether (4 × 50 mL). The ethereal solution was concentrated *in vacuo* to give the crude amine as a brown oil (7.27 g, 49.4 mmol, 72% crude yield.) A small quantity (1.243 g) of the amine was distilled under reduced pressure (80 °C at 2.1 mbar) to give a colourless oil (270 mg) that was then purified by flash chromatography eluting with 5% NEt_3/10% EtOAc in dichloromethane (R_f = 0.13 in 5% NEt_3/10% EtOAc in dichloromethane) to give the pure amine (220 mg, 1.50 mmol).

IR (film): ν_{max} 3365, 3025, 2929, 1947, 1877, 1803 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.38 – 7.27 (4H, m), 7.23 – 7.18 (1H, m), 6.46 (1H, d, J = 15.9 Hz), 6.18 (1H, dt, J = 15.9, 7.1 Hz), 2.84 (2H, t, J = 6.5 Hz), 2.36 (2H, dq, J = 6.8, 4.8 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 137.3 (s), 131.8 (d), 128.4 (d), 127.8 (d), 127.0 (d), 125.9 (d), 41.6), 115 (72), 91 (72); HRMS (EI) *m/z* calculated 147.1048 for $C_{10}H_{13}N$ ($M^{+\bullet}$) found 147.1049

O-Phenyl *N*-*O*-phenyl methanethioyl-*N*-(*E*)-4-phenylbut-3-enylcarbamothioate



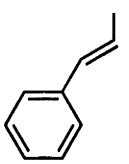
2.97

Amine **2.95** (50 mg, 0.34 mmol, 1.0 eq) was dissolved in dichloromethane (5.0 mL) and cooled to 0 °C. Di-isopropylethylamine was added (120 μL, 0.69 mmol, 2.0 eq) followed by phenyl thionochloroformate (75 mg, 0.43 mmol, 1.3 eq). The reaction was stirred at room temperature for 14 h. Then water (2 mL) was added and the layers separated. The

organic layer was washed with 1.0 M aqueous hydrochloric acid (2 mL), 10% aqueous sodium bicarbonate (2 mL), 1.0 M aqueous l
aqueous sodium chloride (2 mL) then dried
vacuo. The crude product was subjected to f
dichloromethane/Pet.Spirits to give the product **2.97** (30 mg, 0.072 mmol, 21%, $R_f = 0.61$ in 50% dichloromethane/Pet.Spirits) as a bright yellow oil.

IR (film): ν_{max} 3061, 2953, 1944, 1780 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.45 – 7.24 (11H, m), 7.02 (4H, d, $J = 8.4$ Hz), 6.57 (1H, d, $J = 15.9$ Hz), 6.29 (1H, dt, $J = 15.6$, 7.3 Hz), 4.66 (2H, t, $J = 7.2$Hz), 3.00 (2H, dd, $J = 14.1$ 7.5 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 191.5 (s), 153.8 (s), 137.2 (s), 132.7 (d), 129.6 (d), 128.6 (d), 127.3 (d), 126.6 (d), 126.2 (d), 126.0 (d), 121.8 (d), 56.7 (t), 31.8 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 419 (10), 77 (100), 326 (12), 196 (16), 130 (44), 117 (55), 94 (38); HRMS (EI) *m/z* calculated 419.1014 for $C_{24}H_{21}NO_2S_2$ ($M^{+\bullet}$) found 419.1010

1-((*E*)-4-Isothiocyanatobut-1-enyl)benzene



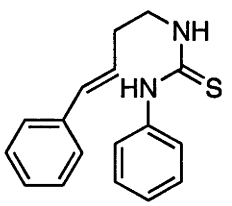
2.98

The isothiocyanate **2.98** was prepared from crude amine **2.95** by a modified literature procedure.[91] Amine **2.95** (150 mg, 1.02 mmol, 1.0 eq) was dissolved in dichloromethane (10.0 mL) and cooled to 0 °C. Saturated aqueous potassium carbonate (5.0 mL) was added. Thiophosgene (236 mg, 2.05 mmol, 2.1 eq) was added directly into the organic phase. The reaction mixture was allowed to warm to room temperature and stirred vigorously for 2.5 h. The organic and aqueous phases were then separated and the organic phase washed with water, 1.0 M aqueous hydrochloric acid and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*

to give the title compound **2.98** (123 mg, 0.651 mmol, 64%, R_f = 0.88 in dichloromethane) as a brown oil.

IR (film): ν_{max} 3026, 2939, 2184, 2103, 16
7.21 (5H, m), 6.54 (1H, d, J = 15.9Hz), 6.16 (1H, dt, J = 15.9, 7.1 Hz), 3.63 (2H, t, J = 6.6Hz), 2.61 (2H, dt, J = 6.8, 1.2Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 136.7 (d), 133.9 (s), 128.6 (d), 127.6 (d), 126.2 (d), 124.4 (d), 45.0 (t), 33.7 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 189 (89), 117 (100); HRMS (EI) *m/z* calculated 189.0612 for $C_{11}H_{11}NS$ 189.0612 ($M^{+\bullet}$) found 189.0616

1-Phenyl-3-((*E*)-4-phenylbut-3-enyl)thiourea

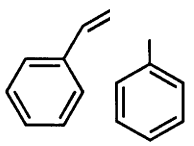


2.89

Amine **2.95** (1.00 g, 6.79 mmol, 1.0 eq) was dissolved in dichloromethane (12.0 mL) then cooled to 0°C. Phenyl isothiocyanate (850 μL, 7.11 mmol, 1.0 eq) was added and the reaction mixture was allowed to reach room temperature. After stirring 14 h the reaction mixture was concentrated *in vacuo* and the crude product purified by flash chromatography, eluting with 0-10% EtOAc/DCM to give the product **2.89** (1.10 g, 3.90 mmol, 57%, R_f = 0.24 in dichloromethane) as a light yellow solid, mp. 122-124 °C.

IR (KBr): ν_{max} 3355, 3168, 3019 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.61 (1H, br s), 7.34-7.17 (8H, m), 7.13-7.10 (2H, m), 6.36 (1H, d, J = 15.6 Hz), 6.10 (1H, dt, J = 15.9, 7.2 Hz), 3.78 (2H, dd, J = 11.7, 6.6 Hz), 2.51 (2H, q, J = 6.7 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 179.9 (s), 136.6 (s), 135.8 (s), 132.9 (d), 129.9 (d), 128.4 (d), 128.2 (d), 127.3 (d), 126.9 (d), 126.4 (d), 125.9 (d),124.9 (d), 44.3 (t), 32.3 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 282 (46), 189 (6), 130 (100) 117 (48); HRMS (EI) *m/z* calculated 282.1191 for $C_{17}H_{18}N_2S$ ($M^{+\bullet}$) found 282.1192

1,3-Dimethyl-1-phenyl-3-(



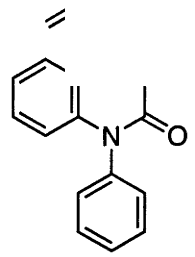
2.99

Thiourea **2.89** (100 mg, 0.355 mmol, 1.0 eq) was dissolved in THF (5.0 mL) and cooled to 0°C. NaH (60 mg, 60% dispersion in mineral oil, 1.50 mmol, 4.3 eq) was added. The reaction was then brought to room temperature and methyl iodide (50 μL, 0.803 mmol, 2.3 eq) added. After stirring at room temperature for 24 h, the reaction was quenched with water (1 mL). The reaction mixture was extracted with EtOAc (10 mL × 2) and the combined organic extracts were washed with 1 M aqueous hydrochloric acid, dried over sodium sulfate and concentrated *in vacuo*. The crude product was subjected to flash chromatography eluting with 0-10% EtOAc/Pet.Spirits to give the title compound **2.99**

EtOAc/Pet.Spirits).

IR (film): ν_{max} 3025, 2927, 1650 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.29-7.12 (7H, m), 7.03-6.98 (3H, m), 6.31 (1H, t, J = 15.6 Hz), 6.04 (1H, dt, J = 15.9, 7.1 Hz), 3.28 (2H, t, J = 7.2 Hz), 3.12 (3H, s), 2.53 (3H, s), 2.32-2.52 (2H, m); ^{13}C NMR (300MHz, $CDCl_3$): δ 161.8 (s), 146.9 (s), 137.3 (s), 131.8 (d), 129.4 (d), 128.5 (d), 127.2 (d), 127.1 (d), 126.0 (d), 124.3 (d), 124.0 (d), 49.7 (t), 39.8 (q), 36.4 (q), 31.2 (t) MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 294 (46), 106 (100), 188 (5), 177 (64), 163 (51), 135 (73); HRMS (EI) *m/z* calculated 294.1732 for $C_{19}H_{22}N_2O$ ($M^{+\bullet}$) found 294.1734

N,N-Diphen



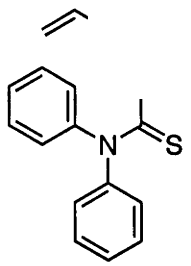
2.100

5-Hexenoic acid (1.99 g, 17.4 mmol, 2.9 eq) was treated with oxalyl chloride (1.57 ml, 18.0 mmol, 3.1 eq) in the presence of catalytic DMF (1 drop). After 15 min the resulting known acid chloride [110] was diluted with chloroform (2 mL) and added to a solution of diphenylamine (1.00 g, 5.91 mmol, 1.0 eq) and pyridine (1.50 mL, 18.6 mmol, 3.2 eq) in chloroform (8.00 mL) at 0 °C. The resulting solution was heated to reflux for 2 h and then the reaction was cooled to room temperature. Dichloromethane (10 mL) was added to the reaction mixture and the combined organics were washed with water, aqueous 1.0 M

combined organics were then dried over magnesium sulfate and solvent removed *in vacuo* to give the crude product as a light yellow oil. Flash chromatography eluting with 0-50% EtOAc/Pet.Spirits gave the product **2.100** (1.19 g, 4.48 mmol, 70%, R_f = 0.38 in 20% EtOAc/Pet.Spirits) as a colourless solid, mp 52-54 °C.

IR (KBr): ν_{max} 3061, 2956, 2910, 1666, 1642 cm^{-1}; ^1H NMR (500MHz, DMSO, 100 °C): δ 7.39 (4H, t, J = 4.7 Hz), 7.33 (4H, d, J = 4.8 Hz), 7.27 (2H, t, J = 4.2 Hz), 5.72 (1H, ddq, J = 10.2, 6.2, 4.0 Hz), 4.98-4.91 (2H, m), 2.22 (2H, t, J = 4.2 Hz), 2.01 (2H, q, J = 4.1 Hz), 1.67 (2H, quint, J = 4.3 Hz); ^{13}C NMR (500MHz, DMSO, 100°C): δ 171.3, 142.7, 137.6, 128.7, 127.2, 126.2, 114.4, 33.4, 32.0, 23.7; MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 265 (16), 169 (100), 211 (14); HRMS (EI) *m/z* calculated 265.1467 for $C_{18}H_{19}NO$ ($M^{+\bullet}$) found 265.1466

N,N-Diphenylhe



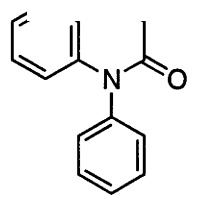
2.91

Lawesson's reagent (850 mg, 2.11 mmol, 1.2 eq) was added to a solution of amide **2.100** (455 mg, 1.72 mmol, 1.0 eq) in dichloromethane (14.0 mL) and heated to reflux. After 13 h, the resulting suspension was filtered and the filtrate concentrated under a stream of nitrogen. The crude product was purified by flash chromatography eluting with 1-5% EtOAc/Hexanes to give the product **2.91** (393 mg, 1.40 mmol, 81%, R_f = 0.36 in 10% EtOAc/Pet.Spirits) as a light yellow solid, mp 68-69 °C.

Hz, $CDCl_3$): δ 7.46-7.29 (10H, m), 5.66 (1H, ddt, *J* = 6.5, 10.4, 17.0Hz), 4.96-4.87 (2H, m), 2.72 (2H, t *J* = 7.5Hz), 2.03-1.91 (4H, m); ^{13}C NMR (300MHz, $CDCl_3$): δ 209.2 (s), 146.7 (s), 144.5 (s), 137.7 (d), 129.8 (d), 129.5 (d), 128.3 (d), 127.6 (d), 127.3 (d), 126.9 (d), 115.0 (t), 43.7 (t), 33.0 (t), 29.3 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 281 (53), 172 (100), 226 (42); HRMS (EI) *m/z* calculated 281.1238 for $C_{18}H_{19}NS$ 281.1238 ($M^{+\bullet}$) found 281.1236

(*E*)-Methyl 6-(dipher

MeO_2C

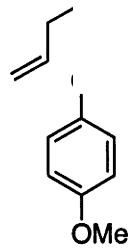


2.101

Dichloromethane (2.00 mL) was degassed by the freeze-thaw method then Grubbs 2nd generation catalyst (30 mg, 0.035 mmol) was added and the maroon solution was degassed again. Amide **2.100** (100 mg, 0.377 mmol) and methyl acrylate (70 μL, 0.78 mmol, 2.1 eq) were added and the reaction mixture was heated at reflux for 4 h. After an additional 14 h at room temperature the reaction mixture was concentrated *in vacuo* and the crude product purified by flash chromatography eluting with 0-40% EtOAc/Pet.Spirits to give the product **2.101** as a grey oil (106 mg, 0.33 mmol, 87%, R_f =

IR (film): ν_{max} 3062, 3036, 2949, 1721, 1672 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.36 (4H, br s), 7.25 (8H, d, J = 7.8 Hz), 6.88 (1H, dt, J = 15.6, 7.0 Hz), 5.79 (1H, dt, J = 15.6, 1.5 Hz) 3.72 (3H, s), 2.27 (2H, t, J = 7.2 Hz), 2.21 (2H, dq, J = 6.6, 1.5 Hz), 1.83 (2H, dt, J = 14.4, 7.2 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 172.3 (s), 166.8 (s), 148.5 (d), 142.6 (s), 128.2 (d), 121.3 (d), 51.3 (q). 34.2 (t), 31.4 (t), 23.6 (t); MS (70 eV, EI): *m/z* (%): $M^{+\bullet}$ 323 (8), 169 (100); HRMS (EI) *m/z* calculated 323.1521 for $C_{20}H_{21}NO_3$ ($M^{+\bullet}$) found 323.1511

4-Methoxyphe

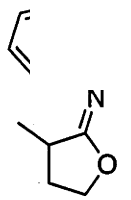


2.102

Hexenoic acid (1.00 g, 8.77 mmol, 1.0 eq) was added to a solution of 1,3-dicyclohexylcarbodiimide (1.80 g, 8.74 mmol, 1.0 eq) in dicholoromethane (40.0 mL). After cooling the solution to 0°C, 4-methoxyphenol (1.20 g, 9.68 mmol, 1.1 eq) was added in portions. The reaction was then allowed to reach room temperature and stirred for 24 h. The resulting white suspension was filtered and the filtrate concentrated *in vacuo* to give a colourless oily solid. The solid was purified by flash chromatography eluting with 20-50% dichloromethane in Pet.Spirits to give the title compound **2.102**) as a colourless oil.

IR (film): ν_{max} 3077, 2935, 1756, 1641, 1609, 1596 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.01-6.97 (2H, m), 6.90-6.86 (2H, m), 5.82 (1H, dtdd, J = 17.1, 10.2, 6.2, 1.7 Hz), 5.11-5.01 (2H, m), 3.79 (3H, s), 2.55 (2H, dt, J = 7.5, 1.5 Hz), 2.18 (2H, q, J = 7.1 Hz), 1.85 (2H, quint, J = 7.4 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 172.5 (s), 157.1 (s), 144.1 (s), 137.5 (d), 122.3 (d), 115.6 (t), 114.4 (d), 55.5 (q), 33.5 (t), 33.0 (t), 24.0 (t); MS (70 eV, EI): *m/z* (%): $M^{+\bullet}$ 220 (38), 124 (100), 84 (86); HRMS (EI) *m/z* calculated 220.1099 for $C_{13}H_{16}O_3$ ($M^{+\bullet}$) found 220.1089

N-(Dihydro-3-methylfura

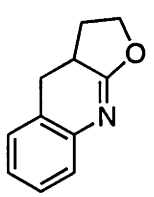


2.103

The title compound **2.103** (R_f = 0.25 in 50%EtOAc/Pet.Spirits) was prepared by the general procedure. Thionocarbamate **2.75** (120 mg, 0.583 mmol) was converted to imidate ester **2.103**. **2.103** was obtained as colourless oil (35 mg, 0.200 mmol, 35%).

IR (film): ν_{max} 3058, 2971, 1699 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.31-7.27 (2H, m), 7.07-7.02 (3H, m), 4.30 (1H, dt, *J* = 8.4, 3.6 Hz), 4.16 (1H, dt, *J* = 9.0, 6.5 Hz), 2.88 (1H, dt, *J* =15.0, 8.1 Hz), 2.37 (1H, dddd, *J* = 12.3, 8.4, 6.5, 3.8 Hz), 1.84 (1H, ddt, *J* = 12.4, 9.2, 8.0 Hz), 1.38 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 166.4 (s), 147.4 (s), .9 (q); MS (70 eV, EI): *m/z* (%): [M] 175 (94), 119 (100), 93 (70), 77 (65), 56 (50); HRMS (EI) *m/z* calculated 175.0997 for $C_{11}H_{13}NO$ ($M^{+\bullet}$) found 175.0998

2,3,3a,4-Tetrahydrofuro[2,3-*b*]quinoline



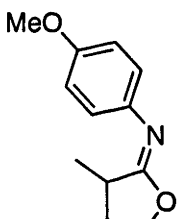
2.104

The quinoline **2.104** (R_f = 0.34 in 50% EtOAc/Pet.Spirits) was prepared by the general procedure from thionocarbamates **2.75** (212 mg, 1.03 mmol). Flash chromatography of the crude product eluting with 1% NEt_3 in dichloromethane gave title compound **2.104** contaminated with silanes (50 mg). Further purification of this mixed fraction by HPLC

eluting with 50% EtOAc/Pet.Spirits gave the pure quinoline **2.104** (5 mg, 0.02ϭϵ mmoi, 3%) as an amber solid, mp, 82-84 mp °C.

IR (film): ν_{max} 3066, 2907, 1666 cm^{-1}; ^1H N
7.11 (1H, d, J = 7.5 Hz), 7.06–7.00 (1H, m), 4.54 (1H, t, J = 8.7 Hz), 4.22 (1H, ddd, J = 11.7, 9.0, 5.7 Hz), 3.11 (1H, dd, J = 13.4, 6.2 Hz), 2.88-2.67 (1H, m), 2.61-2.52 (1H, m), 2.12-1.97 (1H, m); ^{13}C NMR (300MHz, $CDCl_3$): δ 174.5 (s), 145.2 (s), 127.8 (d), 127.5 (d), 124.9 (d), 124.8 (s), 124.4 (d), 68.9 (t), 33.7 (d), 32.4 (t), 31.2 (t); MS (70 eV, EI): *m/z* (%): $[M]^{\bullet+}$ 173 (100), 144 (17), 130 (40), 117 (37), 77 (23); HRMS (ESI) *m/z* calculated 174.0919 for $C_{11}H_{12}NO$ ($M+1^{+\bullet}$) found 174.0917

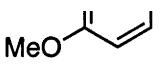
N-(Dihydro-3-methylfuran-2(3*H*)-ylidene)-4-methoxybenzenamine



The title compound **2.105** (R_f = 0.19 in 50% EtOAc/Pet.Spirits) was prepared by the general procedure. Thionocarbamate **2.86** (110 mg, 0.465 mmol) was converted to imidate ester **2.105**. **2.105** was obtained as a colourless oil (25 mg, 0.121 mmol, 26%).

IR (film): ν_{max} 3218, 2954, 1694 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.11 (2H, dd, J = 6.9, 2.1 Hz), 6.84 (2H, dd, J = 6.8, 2.3 Hz), 4.35 (1H, dt, J = 8.3, 4.3 Hz), 4.23 (1H, dq, J = 8.6, 1.8 Hz), 3.70 (3H, s), 3.00-2.88 (1H, m), 2.42-2.32 (1H, m), 1.86 (1H, ddd, J = 16.8, 12.5, 8.5 Hz), 1.39 (3H, d, J = 6.9 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 166.0 (s), 155.8 (s), 140.2 (s), 123.8 (d), 113.8 (d), 68.8 (t), 55.4 (q), 35.8 (d), 31.5 (t), 17.0 (q); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 205 (65), 123 (59), 86 (77), 49 (100); HRMS (EI) *m/z* calculated 205.1103 for $C_{12}H_{15}NO_2$ ($M^{+\bullet}$) found 205.1107

2,3,3a,4-Tetrahydro-6-methoxyfuro[2,3-*b*]quinoline



2.106

The quinoline **2.106** (R_f = 0.29 in 1% NEt_3 in dichloromethane) was prepared by the general procedure from thionocarbamate (190 mg, 0.805 mmol). Flash chromatography of the crude product eluting with 50% EtOAc/Pet.Spirits gave a mixture the title compound **2.106** contaminated with silanes (50 mg). Further purification of this mixed fraction by flash chromatography eluting with 1% NEt_3 in dichloromethane gave the pure quinoline **2.106** (18 mg, 0.0887 mmol, 11%) as an amber solid, mp 124-128°C.

IR (film): ν_{max} 2930, 1671 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.11 (1H, d, J=8.7 Hz), 6.74 (1H, dd, J= 8.6, 2.9 Hz), 6.67 (1H, d, J= 2.7 Hz), 4.51 (1H, t, J= 8.7 Hz), 4.19 (J= 12.8, 5.3 Hz), 2.85-2.63 (2H, m), 2.59-2.50 (1H, m), 2.02 (1H, ddd, J = 24.0, 11.7, 8.8 Hz); ^{13}C NMR (300MHz, $CDCl_3$): δ 173.0 (s), 156.5 (s), 138.6 (s), 126.0 (s), 125.5 (d), 113.8 (d), 112.0 (d), 68.7 (t), 55.4 (q), 33.5 (d), 32.7 (t), 31.2 (t); MS (70 eV, EI): *m/z* (%): $[M]^{+\bullet}$ 203 (100), 188 (92), 160 (41) HRMS (ESI) *m/z* calculated 203.0946 for $C_{12}H_{13}NO_2$ ($M^{+\bullet}$) found 203.0945

Refe

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Errata

Page 24, line 3
'trigonal' should be 'tetrahedral'

Page 112, line 14
2.04 should be **2.104**