Investigating Radical Reactions of Thionocarbonates

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

Research School of Chemistry

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Thank you to all my friends who embellish my life. And also to my family, the most important people to me.

Enjoy.

Emma.
**Abbreviations**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>Δ</td>
<td>heat</td>
</tr>
<tr>
<td>°C</td>
<td>degree/s Celsius</td>
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<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azo-bis-isobutyronitrile</td>
</tr>
<tr>
<td>ACN</td>
<td>1,1'-azobis(cyclohexane-1-carbonitrile)</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl or argon</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthalene</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium(IV) ammonium nitrate</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wave number</td>
</tr>
<tr>
<td>COSY</td>
<td>correlated spectroscopy</td>
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<tr>
<td>d</td>
<td>day/s or doublet/s</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1-benzoquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethylazodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>DIP-Cl</td>
<td>chlorodiisopinocamphenylborane</td>
</tr>
<tr>
<td>DIPA</td>
<td>diisopropylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
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<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
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<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>El</td>
<td>electron impact</td>
</tr>
<tr>
<td>equiv</td>
<td>molar equivalent(s)</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>eV</td>
<td>electron Volts</td>
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<tr>
<td>h</td>
<td>hour/s</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>HMPT</td>
<td>hexamethylphosphorous triamide</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>J</td>
<td>coupling constant</td>
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<tr>
<td>lit.</td>
<td>literature</td>
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<tr>
<td>m</td>
<td>meta</td>
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<tr>
<td>M</td>
<td>molar</td>
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<tr>
<td>M⁺</td>
<td>molecular ion</td>
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Abbreviations

Me methyl
min minute
Ms mesyl
MHz megahertz
mol mole
mp melting point
MS mass spectrometry
m/z mass to charge ratio
n-BuLi n-butyl lithium
NBSH o-nitrobenzenesulfonylhydrazine
NMR nuclear magnetic resonance
o ortho
p para
pTSA para-toluenesulfonic acid
Ph phenyl
PMP pentamethylpiperidine
ppm parts per million
q quartet
RCAR radical carboxyarylation reaction
rt room temperature
sat. saturated
t time
TBS tert-butyldimethylsilyl
TBAB tetra-n-butylammonium bromide
TBDDS tert-butyldiphenylsilyl
temp. temperature
Tf trifluoromethanesulfonil
THF tetrahydrofuran
tlc thin layer chromatography
TMS trimethylsilyl
Ts para-toluenesulfonil
TTMSS tris(trimethylsilyl)silane
Barton and McCombie first reported the radical deoxygenation of secondary alcohols in 1975. This is a two-step process that involves conversion of an alcohol into a thiocarbonyl derivative, and then radical reaction (Scheme A). Since this time, the Barton-McCombie deoxygenation has become a widely used synthetic tool; the reaction is both mild (tolerant of functionality) and efficient. The history of the developments of the Barton-McCombie deoxygenation is outlined in Chapter 1. This chapter extends to describe variations of this reaction, and of particular interest is the radical carboxyarylation reaction (RCAR). The RCAR is a domino sequence, which results in the stereoselective 1,2-disubstitution of an unactivated carbon-carbon double bond.

Scheme A. Baron-McCombie radical deoxygenation.

The Barton-McCombie deoxygenation of primary alcohol derivatives was initially reported as being problematic, however, these problems were overcome by the use of increased reaction temperature. To date, attempts to deoxygenate these alcohol derivatives at lower temperatures has had limited success. In the present study we demonstrate that the efficient Barton-McCombie deoxygenation of primary alcohols is possible at temperatures as low as 0 °C, using triethylborane/air and tris(trimethylsilyl)silane (TTMSS) (Scheme B). These findings are described in Chapter 2.

Scheme B. Improved conditions for the Baron-McCombie radical deoxygenation of primary alcohol derivatives.

In Chapter 3 the versatility of the RCAR has been explored through it's application to the development of a general synthetic approach to xestoquinone, halenaquinone and related natural products. The approach used is illustrated in Scheme C, which clearly shows how the RCAR enables a highly convergent synthesis.
Scheme C. Progress toward the development of a general approach for the synthesis of the xestoquinone family of natural products.
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1. Barton-McCombie Radical Deoxygenation to Radical Carboxyarylation

1.1. History and Development of Barton-McCombie Radical Deoxygenation

Since the Barton-McCombie deoxygenation was first discovered in 1975,\(^1\) it has become one of the most commonly used radical reactions. This process was designed to enable a more efficient method for the deoxygenation of secondary alcohols. Deoxygenation of these alcohols was often unfeasible by ionic methods, particularly for sterically hindered secondary alcohols, such as those found in sugars. Barton and McCombie designed the deoxygenation protocol utilising radical chemistry, as this would enable pH neutral conditions, and therefore reduce the effect of steric hindrance.\(^1\)

Barton-McCombie radical deoxygenation is a two-step process. In the first step the alcohol 1.1 is derivatised as a thiocarbonyl compound 1.2; and in the second step, treatment with radical mediators and initiators, effects the deoxygenation process to yield the hydrocarbon 1.3. In the original publication, Barton and McCombie demonstrated the high yielding radical deoxygenation of various secondary alcohols via a number of thiocarbonyl derivatives (thiocarbonyl esters, thiocarbonyl-imidazolides and xanthates), using tributyltin hydride in refluxing solvent (Scheme 1.1).\(^1\)

\[ \text{ROH} \xrightarrow{1.1} \text{R} \equiv \text{C} \xrightarrow{1.2} \text{R} \equiv \text{S} \xrightarrow{\text{radical mediators/initiators}} \text{RH} \xrightarrow{1.3} \text{hydrocarbon} \]

Scheme 1.1. Barton-McCombie radical deoxygenation.

The agreed mechanism for the Barton-McCombie deoxygenation is illustrated in Scheme 1.2. For an overview of the results that support this mechanism see the referenced reviews.\(^4,5\) The reaction begins with the reversible addition of a tributyltin radical (chain carrier) to the sulfur atom of the thiocarbonyl group, affording the tertiary carbon centered radical 1.4. This radical undergoes an irreversible \(\beta\)-scission to generate the alkyl radical 1.5. Quenching of intermediate 1.5 with a hydrogen atom from
tributyltin hydride affords the deoxygenated product 1.3. In this step, the chain carrier radical is also regenerated to complete one cycle in the radical chain reaction.

Scheme 1.2. Radical-chain mechanism for the Barton-McCombie deoxygenation.

The driving forces for the Barton-McCombie deoxygenation are: (1) the energy gained by the formation of the stronger carbon-oxygen double bond of 1.6, versus the carbon-sulfur double bond of 1.2; (2) the entropy gained by the breakdown of radical 1.4 into two intermediates; and (3) the affinity of the tin-centered radical for sulfur.\(^6\)

Since its discovery, Barton-McCombie deoxygenation has become a widely used synthetic tool; it is both mild (tolerant of functionality) and efficient. The reaction conditions have evolved to include the use of various radical initiators and mediators, alternative thiocarbonyl derivatives, and application to primary and tertiary alcohols. These alternatives are explored in the following three sections.

### 1.2. Thiocarbonyl Substrates for Radical Deoxygenation

In the original example of the Barton-McCombie deoxygenation thiocarbonyl esters, thiocarbonyl-imidazolides and xanthate esters were employed as derivatives for radical deoxygenation (Scheme 1.1).\(^1\) While it is still common to use these substrates, various other thionocarbonate derivatives are now also commonly utilised.

Robins and co-workers pioneered the use of phenyl thionocarbonyl derivatives as substrates for the Barton-McCombie deoxygenation.\(^7,8\) This alternative was sought as these precursors are easily prepared under mild reaction conditions; and the alcohols
that Robins and co-workers wished to deoxygenate were sensitive to the basic conditions required to introduce the original functionalities. For example, the protecting group in the adenosine derivative 1.7 was not stable to the basic conditions required to introduce the thiobenzoate or S-methyl xanthate groups. Derivatisation of the 2'-hydroxy, using phenyl chlorothionoformate, proceeded smoothly to afford thionocarbonate 1.7, which enabled the selective 2'-deoxygenation to afford 1.9 in 78% overall yield (Scheme 1.3).  

\[
\text{Scheme 1.3. The first deoxygenation of a phenyl thionocarbonate derivative. Reagents and conditions: (a) [(i-Pr)_2SiCl]_2O, pyridine; (b) PhOCSCl, DMAP; (c) HSnBu_3, AIBN, PhCH_3, 75 °C, 78% from 1.8 to 1.9.} \]

Since the introduction of the first thionocarbonate derivatives as substrates for deoxygenation, a range of alternative thiocarbonate derivatives have been employed and include: methoxy,\(^9\) pentafluorophenoxy,\(^10\) 2,4,6-trichlorophenoxy,\(^10\) 4-methylphenoxy,\(^11\) and 4-fluorophenoxy.\(^12\)

### 1.3. Alternative Reagents for Radical Deoxygenation

To alleviate the toxicity and purification problems associated with the use of tributyltin hydride, alternative radical mediators and reaction methods have been investigated, and many of these alternatives have been applied to the Barton-McCombie deoxygenation. A number of reviews highlight the efforts to find alternatives to tributyltin hydride.\(^{13,14}\)

In an attempt to minimise tin impurities, reaction conditions for deoxygenations have been developed that are catalytic in tin or use polymer-supported tin hydrides\(^{15}\). Tin-free radical reagents have also been utilised and include tributylgermanium hydride,\(^{16}\) various phosphorus,\(^{17}\) or silane mediators. Silane chain carriers are considered the most useful replacement of tin-centred chain carriers. A review of the application of silane mediators to radical deoxygenation has been published by Chatgilialoglu.\(^6\)
Tris(trimethylsilyl)silane (TTMSS) is viewed as the superior silane reagent for radical reactions, as it has the lowest Si-H bond dissociation energy of the silanes (331 kJ/mol) commonly used for radical reactions. This value is still higher, however, than that of tributyltin hydride (308 kJ/mol).

The development of triethylborane/oxygen as a radical initiating system has allowed deoxygenation of alcohol derivatives at lower temperatures. Oshima and co-workers first demonstrated the successful deoxygenation of secondary alcohol derivatives with triethylborane/oxygen and tributyltin hydride at room temperature. Shortly thereafter, Barton and colleagues demonstrated that the silane mediators, TTMSS and diphenylsilane, were also amenable to this initiation method.

1.4. Alcohol Substrates for Radical Deoxygenation

Although the Barton-McCombie reaction was designed for secondary alcohols, later studies revealed that it was also applicable to primary and tertiary alcohols. The deoxygenation of primary alcohols was initially reported as being problematic; however, the use of increased reaction temperature later resolved this issue. The deoxygenation of primary alcohols is discussed more extensively in Chapter 2.

Like primary alcohols, tertiary alcohols were also problematic substrates for radical deoxygenation (although for differing reasons). The stability of precursors is the basis of these difficulties. At high temperatures, thiocarbonyl derivatives of tertiary alcohols have a tendency to undergo Chauguev elimination (Scheme 1.4).

Scheme 1.4. Chauguev elimination.

Due to the problems associated with the deoxygenation of tertiary alcohol thiocarbonyl derivatives, alternative derivatives have been employed. These include methyl oxalyl esters, trifluoroacetates, and selenoesters/selenocarbonates. For particular xanthate derivatives of tertiary alcohols, deoxygenations have been demonstrated in high yield using various initiators and mediators at 0–40 °C.
1.5. Derivations of Barton-McCombie Deoxygenation

By careful experimental design, the intermediates formed in the radical deoxygenation reaction can be utilised for alternative processes. The first radical 1.4 formed or the radical 1.5 formed following β-scission, can add to radical acceptors, such as those illustrated in Scheme 1.5, to afford adducts 1.10 or 1.11 respectively, instead of forming the deoxygenated product 1.3 (Scheme 1.5). Initial developments in this area are discussed in a review by Crich and Quintero.⁵

![Scheme 1.5. Utilising radical intermediates formed in the Barton-McCombie Deoxygenation for alternative radical processes.](image)

Use of the deoxygenated carbon-centred radical 1.5 in other intermolecular or intramolecular steps has been studied extensively. One example of particular importance is the xanthate group transfer reaction developed by Zard and co-workers.²⁸ This research is exploited in Reversible Addition-Fragmentation chain Transfer (RAFT) and Macromolecular Design via the Interchange of Xanthates (MADIX) technologies.²⁹

The first carbon-centred adduct radical 1.4 formed in the deoxygenation process has also been utilised in alternative processes; however, there are fewer examples than those that use the deoxygenated radical 1.5. In examples that utilise the radical 1.4, the desired
pathway must out compete $\beta$-scission of the carbon-oxygen bond. $\beta$-Scission is accepted to be the rate determining step in the deoxygenation process, and radical 1.4 is also stabilised by its surrounding steric bulk and heteroatoms. Thus, it would be expected that this radical would have a relatively long life-time, which would allow for its participation in alternative radical processes.

Bachi and Bosch were the first to utilise the intermediate radical 1.4. In these experiments Barton-McCombie deoxygenation precursors were used that contained a suitably positioned radical acceptor. They used thionocarbonyl derivatives (xanthates, imidazolides and thiocarbonate) of homoallylic alcohols, such as 1.12. In this example, $\beta$-fragmentation was suppressed so that the initial adduct radical 1.13 underwent 5-exo-trig cyclisation to give the cyclic intermediate 1.14. This intermediate then abstracted a hydrogen atom from tributyltin hydride, followed by elimination to yield thiolactone product 1.15 (Scheme 1.6). For a number of years Bachi and Bosch continued their investigation of this process, as did a number of other research groups.

\[ \text{Scheme 1.6. Mechanism for the formation of thiolactone 1.15. Reagents and conditions: HSnBu}_3, \text{ AIBN, PhH, 80 °C, 51%}.] \]
1.6. Discovery of a Novel Radical Domino Sequence

When Bachi and Bosch were investigating cyclisations like those described in Scheme 1.6, they inadvertently discovered a new domino sequence. They were attempting to convert thionocarbonate 1.16 into the thiolactone 1.17, when unexpectedly the thiolactone was formed as the minor product, and instead the benzyl substituted lactone 1.18 was formed as the major product (Scheme 1.7).

![Scheme 1.7: Reagents and conditions: (a) AIIBN, IHSnBu₃, PhH, reflux.](image)

Bachi and Bosch proposed formation of this product 1.18 through the domino radical process described in Scheme 1.8. The first two steps of the domino sequence occur as per the cyclisation outlined in Scheme 1.6. Addition of a trialkylstannyl radical to the thionocarbonyl group of derivative 1.16 to form a tertiary heteroatom-stabilised radical 1.19, followed by a 5-exo-trig cyclisation onto the double bond to give intermediate 1.20. In the novel domino process, radical 1.20 undergoes a second 5-exo-trig cyclisation onto the ipso position of the aromatic ring. This creates the delocalised radical 1.21 that rearomatises via β-fragmentation to form the oxygen-centered radical 1.22. The oxygen centered radical then undergoes a second β-fragmentation to give the product 1.18.
Chapter 1 – Barton-McCombie Radical Deoxygenation to Radical Carboxyarylation

Around the same time that Bachi and Bosch discovered this novel domino reaction, the same sequence was reported by an independent group in an attempt to prepare (+)-supinidine. In this group's efforts to deoxygenate the phenyl thionocarbonate derivative 1.23, the product 1.24 was formed in 60% yield (Scheme 1.9). The stereoselective nature of the rearrangement was also noted. The sequence has also been later reported as an unwanted process in deoxygenation reactions.

More recently, the Sherburn research group has been studying this reaction and utilising it for natural products synthesis. They have termed the process the radical carboxyarylation reaction (RCAR), as it involves the creation of two new carbon-carbon single bonds on either end of an alkene, one bearing an aryl group and the other a
carboxy group. The scope of the RCAR has also been investigated through its application to natural product synthesis.

1.7. The Radical Carboxyarylation Reaction in Synthesis

The Sherburn research group have published an application of this reaction to the formal total synthesis of the natural product (-)-podophyllotoxin, via synthesis of its precursor isopicropodophyllone (1.25).\(^2\) In this example a nucleophilic acyl substitution reaction between the arylchlorothionoformate derivative of 3,4,5-trimethoxyphenol 1.26 and alcohol 1.27 gave the precursor for the domino radical reaction 1.28. The RCAR was effected by treatment with TTMSS and AIBN, giving the lactone 1.29 in 40% yield. This product was converted to (-)-isopicropodophyllone (1.25), completing the formal total synthesis. The same approach was also used to prepare and (+)-podophyllotoxin.

![Scheme 1.10](image)

Scheme 1.10. Use of the RCAR for the preparation of (-)-isopicropodophyllone (1.25). Reagents and conditions: (a) pyridine, rt, 99%; (b) TTMSS, AIBN, 80 °C, 40%\(^2\).

The RCAR methodology has also been applied to the total synthesis of seven related lignan natural products, which are illustrated in Scheme 1.11.\(^3\) Thionocarbonate 1.30 (R = TBS or H) was converted to the benzyl-substituted lactone product in 44% yield.
and > 95% de (for both $R = \text{TBS}$ or $H$), followed by deprotection to yield the intermediate $\text{1.31}$. Subsequent reactions yielded the seven natural products.

Scheme 1.11: Use of the RCAR for the preparation of seven related lignan natural products. Reagents and conditions: (a) $1$-pyridine, $\text{CH}_2\text{Cl}_2$, rt, 2 h, 88% ($R = \text{TBS}$) and 81% ($R = \text{Me}$); (b) TTMSS, AIBN, PhH, 80 °C, 6 h, 44% (for both $R = \text{TBS}$ and $\text{Me}$); (c) $n$-Bu$_3$NF, AcOH, THF, 96% ($R = H$) and 90% ($R = \text{Me}$).$^{13}$

These two applications of the RCAR to total synthesis demonstrate that the RCAR reaction facilitates a modular and highly convergent approach. The thionocarbonate precursors can be prepared by joining two main components in straightforward and efficient nucleophilic substitution reactions. Additionally, these components can be functionalised separately, and joined toward the end of the synthesis, which enables
efficient preparation of substrates for structure based activity investigations. These examples also demonstrate the synthetic power of the RCAR: In a single stereo-controlled step, a lactone ring and two carbon-carbon bonds are formed.

1.8. Investigations of the Scope of the Radical Carboxyarylation Reaction

There have been extensive unpublished studies undertaken by the Sherburn research group to determine the scope and improve the efficiency of the RCAR. Studies indicate that TTMSS is a better reagent for these reactions than tributyltin hydride. In the RCAR of thionocarbonate 1.32, effected by tributyltin hydride, 19% of the desired product 1.33 was obtained, along with 19% of thiolactone 1.34. The thiolactone results from premature hydrogen abstraction by the intermediate radical 1.35. In the analogous reaction using TTMSS, 50% of the RCAR product, and only 10% of the byproduct 1.33 was obtained (Scheme 1.12). This is likely due to TTMSS being a poorer hydrogen atom donor, and therefore, side reactions involving hydrogen abstraction (such as formation of thiolactone 1.33) are minimised when using this reagent.\(^\text{44}\)

![Scheme 1.12. Reagents and conditions: (a) TTMSS, AIBN, PhH, 80 °C, 50% of 1.33 and 10% of 1.34; or HSnBu\(_3\), AIBN, PhH, 80 °C gave 19% of 1.33 and 19% of 1.34.](image)

In most cases the RCAR has been carried out on systems whereby the first cyclisation event is 5-exo, to afford a \(\gamma\)-lactone ring. There have been some examples of 6-exo and 7-endo cyclisations, however, generally these do not occur as readily as the 5-exo. Some
other areas that have been investigated include the nature of the: (a) aryl group; (b) alcohol; (c) radical acceptor; and (d) stereoselectivity of the reaction. Key findings resulting from these studies are outlined below:

(a) *The Nature of the Aryl Group*

To investigate the effect of the aryl group on the RCAR a simple system was used (Scheme 1.13); thionocarbonates 1.36 with various aryl groups were treated with tributyltin hydride, AIBN and heat, in benzene or cyclohexane, to yield the product 1.37.\(^{45-47}\) These studies demonstrated that both electron withdrawing and electron donating groups were tolerated, and the substrate containing the electron rich 3,4,5-trimethoxyphenyl group gave the highest yield.

![Scheme 1.13. Reactions to test the effect of the aryl group on the RCAR. Reagents and conditions: (a) HSnBu₃, AIBN, C₆H₁₂ or PhH.](image)

(b) *The Nature of the Alcohol*

The influence of substitution at all five positions (R₁ to R₅) of a homoallylic alcohol 1.38 has been investigated (Figure 1.1). All substitutions were tolerated to varying degrees.\(^{48}\) The presence of an electron-withdrawing substituent at R₃ (for example a carbomethoxy group) resulted in a significant increase in yield of the RCAR product.

![Figure 1.1. Various substitutions of a homoallylic alcohol that have been investigated.](image)
(c) The Nature of the Radical Acceptor

The RCAR has been performed on substrates containing different radical acceptors, such as arenes and alkynes have been tested. These trials, however, were not very successful.

(c) Stereoselectivity of the Reaction

The RCAR is stereoselective. For substrates that contain a cyclic alkene radical acceptor, a single diastereomeric product is obtained. This is evident in the examples described previously (Scheme 1.9, 1.10, 1.12 and 1.13), in which the product lactone was cis fused, and the aryl group was transferred syn to the lactone. This stereoselectivity is a result of the geometric constraints of the cyclisation steps in the sequence (Scheme 1.14).

In Scheme 1.14, a simple cyclic thionocarbonate substrate 1.39 is used as an example to illustrate the stereoselective nature of the RCAR. The carbon-centered radical that results from addition of the mediating radical (tris(trimethylsilyl)silyl in this case) can exist in two different orientations and add to the alkene to give two different bicyclic products 1.40 and 1.41; both result in a cis-fused system. In the geometry of intermediate 1.42, the aryl group lies close to the newly formed radical centre, enabling a second cyclisation to afford 1.43, via a 5-exo trig addition to the ipso position of the aromatic ring. Two β-fragmentations give rise to the RCAR product 1.44, where the aryl group is syn to the lactone ring.

The geometry of the other intermediate 1.45, in which the aryl ring is not proximal to the radical, does not allow the second cyclisation event to occur. Instead, this intermediate can abstract a hydrogen atom from the radical mediator to give 1.46, followed by elimination to give the thiolactone 1.47. This byproduct can also form when intermediate 1.42 abstracts a hydrogen atom to afford intermediate 1.47, and then eliminates. Another unwanted pathway in this sequence is deoxygenation, to afford 1.49 and phenol. All of the other unwanted pathways included in Scheme 1.14 form phenol as a byproduct; thus, phenol can be used experimentally as an indication that unwanted processes are occurring in place of the RCAR.
In this thesis new conditions for the Barton-McCombie deoxygenation are presented that enable the first examples of efficient deoxygenation of primary alcohol derivatives at room temperature and lower. These investigations are outlined in Chapter 2. An attempt to use the RCAR as a key step for a general sequence to prepare the xestoquinone family of Natural Products is described in Chapter 3.

Scheme 1.14. The stereoselective nature of the RCAR.
2. Barton-McCombie Room Temperature Deoxygenation of Primary Alcohols

2.1. Introduction

2.1.1. Radical Deoxygenation of Primary Alcohols

While the first examples of the Barton-McCombie deoxygenation proceeded smoothly for secondary alcohols, primary alcohols were poor substrates. For example, when thiobenzoate 2.1, imidazolide 2.2 and xanthate 2.3 derivatives of the primary alcohol, octadecan-1-ol, were treated using the conditions that were successful for secondary alcohols (tributyltin hydride in refluxing toluene), no product of deoxygenation was observed. Instead, octadecan-1-ol and other products were isolated (Scheme 2.1).

The observed reactivity difference between primary and secondary alcohol derivatives in the Barton-McCombie reaction was attributed to slower carbon-oxygen fragmentation with the former substrates. The energy barrier for fragmentation is primarily due to the stability of the radicals formed, with the more stable having a lower activation barrier. A primary alkyl radical is less stable than the secondary alkyl radical, and therefore the energy required for fragmentation of the primary species is higher. Thus, the rate of β-fragmentation for primary alcohol derivatives is relatively slow compared to that of secondary alcohols derivatives.

The slow β-fragmentation of primary alcohol derivatives was a problem in the deoxygenation conditions employed by Barton and McCombie as there was an...
alternative competing pathway. In this pathway, instead of undergoing \( \beta \)-fragmentation (Scheme 2.2), the initially formed radical 2.4 abstracts a hydrogen atom from tributyltin hydride to give the intermediate 2.5. The resulting adduct 2.5 could undergo subsequent reactions (hydrolysis, elimination and/or reduction) to generate the unwanted products isolated from these reactions (Scheme 2.1).

The difference in reactivity between primary and secondary alcohol derivatives in the Barton-McCombie deoxygenation has been exploited. In a substrate 2.6 that contained both functionalities, the secondary alcohol was deoxygenated selectively with tributyltin hydride and AIBN in refluxing toluene. The 5-deoxy-sugar 2.7 was obtained in 67% yield, and none of the 6-deoxy-sugar 2.8 was detected.\(^\text{50,51}\) This indicated that the secondary radical was formed in preference to the primary radical.

The original problems encountered in the Barton-McCombie deoxygenation of primary alcohols were overcome through manipulation of the reaction conditions. The \( \beta \)-fragmentation step in the deoxygenation pathway is unimolecular, while the competing substitution step is bimolecular. By exploiting the differing effects of temperature and concentration on these two processes, the deoxygenation pathway can
be favoured. High reaction temperature increases the rate of \( \beta \)-fragmentation in the deoxygenation pathway. Also, the concentration of the radical mediator (usually HSnBu\(_3\)) can be minimised by adding it slowly to the reaction mixture, which disfavours the unwanted pathway (see Scheme 2.2). These manipulations were first demonstrated by Barton and co-workers. Pertinent results from this study are displayed in Table 2.1.

Table 2.1 describes the conditions used to deoxygenate various thiocarbonyl derivatives of octadecan-1-ol to yield octadecane. Entries 1 to 3 describe the deoxygenation of a xanthate derivative. These reactions illustrate the beneficial effect of adding tributyltin hydride slowly (compare entries 1 and 2), and increasing reaction temperature from 136 to 150 °C (compare entries 2 and 3). Application of the slow addition method to the deoxygenation of the imidazolidine (entry 4) and thiobenzoate (entry 5) derivatives was also successful, and a slightly lower reaction temperature (136 °C) was found to be viable.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>slow addition</th>
<th>HSnBu(_3)</th>
<th>temperature (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SMe</td>
<td>no</td>
<td>HSnBu(_3)</td>
<td>136</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>SMe</td>
<td>yes</td>
<td>HSnBu(_3)</td>
<td>136</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>SMe</td>
<td>yes</td>
<td>HSnBu(_3)</td>
<td>150</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>N____</td>
<td>yes</td>
<td>HSnBu(_3)</td>
<td>136</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>yes</td>
<td>HSnBu(_3)</td>
<td>136</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 2.1. Selected examples of the first successful deoxygenations of primary alcohol derivatives.

Nine years later, the conditions and thiocarbonyl derivatives suitable for the deoxygenation of primary alcohols were extended. In these studies arylthionocarbonate derivatives containing electron-poor aromatic systems were used. It was initially suggested that the electron withdrawing nature of the aryl ring would increase the radicophilicity of the thiocarbonyl group, and hence increase the rate of the
Chapter 2 - Introduction

desired carbon-oxygen fragmentation. However, later kinetic studies demonstrated that this was not the case. The deoxygenations were performed in refluxing benzene or toluene. Various radical reagents were employed, including: AIBN with tributyltin hydride or diphenylsilane; and triethylborane with diphenylsilane. An example of the use of electron-poor aromatic systems in the deoxygenation of a primary alcohol derivative is described in Scheme 2.4 Treatment of tetradecan-1-ol derivative 2.11 with tributyltin hydride and AIBN in toluene or benzene at reflux, yielded tetradecane (2.12) in 95 or 90% yield respectively.

![](image1.png)

Scheme 2.4. Deoxygenation of an arylthionocarbonate derivative of octadecan-1-ol 2.11 in refluxing toluene or benzene.

2.1.2. Deoxygenation of Primary Alcohols at Room Temperature

The examples presented so far demonstrate that Barton-McCombie deoxygenation of thionocarbonate derivatives of primary alcohols can occur efficiently at 80 °C or above. To date, however, deoxygenation of these alcohol derivatives at lower temperatures has not been as effective.

Oshima and co-workers found that a xanthate 2.13, derived from primary alcohol tetradecan-1-ol, gave only 18% of the desired product 2.14 when treated with tributyltin hydride and triethylborane/air at room temperature (Scheme 2.5).

![](image2.png)

Scheme 2.5. Low yielding deoxygenation of tetradecan-1-ol xanthate derivative at 20 °C.

4-Fluorophenylthionocarbonate derivatives of primary alcohols phenethan-1-ol 2.15 and hexadecan-1-ol 2.16 also gave poor yields of the respective hydrocarbons 2.17 and 2.18,
when treated with diphenylsilane and triethylborane at room temperature (Scheme 2.6). Heating these reactions to 80 °C enabled the yields to be significantly improved.

![Scheme 2.6. Room temperature deoxygenation of primary alcohols.](image)

To the best of our knowledge, Wood and co-workers published the most efficient Barton-McCombie deoxygenation of a primary alcohol derivative, at room temperature, recently. They developed metal hydride-free radical conditions that utilised trialkylborane and water as the hydrogen atom source. For details on the mechanism of this reaction see Section 2.2.2.2. page 29. The procedure was applied with great success to secondary alcohol derivatives. Only one example using a primary alcohol derivative was described: The xanthate of dodecan-1-ol 2.19 was deoxygenated using trimethylborane (not commercially available in Australia), to give dodecane 2.20 in 51% yield. Interestingly, the use of triethylborane (this reagent is commercially available in Australia), instead of trimethylborane, reduced the yield to 3% (Scheme 2.7). No explanation was given.

![Scheme 2.7. The highest yielding deoxygenation of a primary alcohol derivative using the Barton-McCombie reaction. Reagents and conditions: (a) Me₃B or Et₃B, air, H₂O, PhH, rt, 51% (Me₃B), 3% (Et₃B).](image)
A significant development in radical deoxygenation of primary alcohols was published in 1997 by Myers and co-workers. Using an alternative method to the Barton-McCombie procedure, primary alcohols were deoxygenated in moderate to excellent yields at temperatures between -30 and 23 °C.

The one-pot procedure of Myers involves a Mitsunobu displacement of an alcohol 2.21 using o-nitrobenzenesulfonylhydrazine (NBSH) at -30 °C to afford the di-substituted sulfonyl hydrazine 2.22. Heating to above 0 °C promotes formation of the monoalkyl diazene intermediate 2.23, by elimination of o-nitrobenzenesulfonic acid 2.24. The diazene 2.23 then decomposes, via a free radical mechanism and the loss of nitrogen, to yield the deoxygenated product 2.25 (Scheme 2.8).

```
ROH 2.21
PPh3, DEAD, NBSH, THF -30 °C → RN-NH2
           SO2Ar 2.22
> 0 °C [RN=NH] + ArSO2H 2.23 2.24
               free-radical mechanism
                       RH + N2 2.25
```

Scheme 2.8. An alternative method to deoxygenate primary alcohols at low temperatures. NBSH 2-nitrobenzenesulfonyl hydrazine, DEAD diethylazodicarboxylate.

The methodology of Myers and co-workers offers a useful alternative to the standard Barton-McCombie deoxygenation conditions since it enables the efficient deoxygenation of primary alcohols at low temperatures. However, this procedure is not suitable for sterically hindered primary alcohols due to the difficulty of S° substitution in the Mitsunobu reaction.

### 2.1.3. New Methods for Deoxygenation at Room Temperature

A focus of the Sherburn group is the RCAR (see Chapter 1, page 9 onwards), which can be considered a variation on the Barton-McCombie deoxygenation theme. In these studies RCARs are commonly performed on thionocarbonates derived from primary alcohols. In attempt to perform the RCAR on the substrate 2.26, to give the RCAR product 2.27 (see Chapter 1, Scheme 1.8, page 8 for the mechanism), it was discovered...
that primary alcohols can be deoxygenated at lower temperatures than previously thought possible.

Scheme 2.9. The RCAR substrate that revealed that primary alcohol derivatives can be deoxygenated efficiently at temperatures lower than previously possible.

Herein, we demonstrate that efficient Barton-McCombie deoxygenation of primary alcohol derivatives at relatively low temperatures is viable. The conditions are amenable to sterically hindered alcohols, and thus offers an improvement on the methodology of Myers and co-workers.\textsuperscript{56}

The purpose of this study is to develop a general Barton-McCombie deoxygenation protocol for primary alcohol derivatives at room temperature and lower. The following features will be determined: (1) optimal reaction conditions; (2) the lower limit of temperature for deoxygenation; (3) the effect of the thiocarbonyl substituent; and (4) the scope of the protocol with respect to primary alcohol structure.
2.2. Results & Discussion

In the following sections, reaction conditions for the efficient deoxygenation of primary alcohol derivatives at lower temperatures than previously possible are presented. In Section 2.2.1 the preliminary results and efforts to optimise the reaction conditions are reported. In order to determine the most suitable thiocarbonyl substrates for this process, a comparison of various thiocarbonyl derivatives is undertaken in Section 2.2.2. The generality of the conditions is established in Section 2.2.3 by the deoxygenation of a range of primary alcohol derivatives.

2.2.1. Efficient Room Temperature Deoxygenation of a Primary Alcohol at Room Temperature

Thionocarbonate 2.26 was prepared as a possible substrate for the RCAR. It was anticipated that the aromatic ring may act as a radical acceptor during the first cyclisation step. The proposed mechanism for reaction of 2.26 to yield the RCAR product 2.27 is outlined in Scheme 2.10.

Scheme 2.10. Mechanism for the RCAR where an aromatic system acts as a radical acceptor.
The thionocarbonate 2.26 was prepared in four steps from the commercially available starting materials, methyl 4-formyl-benzoate (2.29), 4-methoxyphenol (2.30), and thiophosgene (Scheme 2.11). Firstly, a Wittig reaction of aldehyde 2.29 with methyltriphenylphosphonium bromide afforded the alkene 2.31 in 76% yield. Secondly, hydroboration of 2.31, followed by oxidative hydrolysis resulted in formation of the primary alcohol 2.32 in 76% yield. Deprotonation of the phenol 2.30 with aqueous sodium hydroxide gave the sodium phenoxide, which underwent nucleophilic substitution with thiophosgene, to afford the arylchlorothionoformate 2.33. Substitution of the arylchlorothionoformate by the primary alcohol 2.32 yielded the thionocarbonate 2.26 in 85% yield.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad 2.29 \\
\text{H} & \quad \uparrow \text{a} \\
\text{C}_6\text{H}_4\text{CO}_2\text{Me} & \quad 2.31 \\
\text{OH} & \quad \uparrow \text{b} \\
\text{C}_6\text{H}_4\text{CO}_2\text{Me} & + \\
\text{OMe} & \quad \uparrow \text{c} \\
\text{S} & \quad \uparrow \text{d} \\
\text{C}_6\text{H}_4\text{CO}_2\text{Me} & \quad 2.26
\end{align*}
\]

Scheme 2.11. Synthesis of thionocarbonate 2.26. Reagents and conditions: (a) methyltriphenylphosphonium bromide (1.0 equiv), NaH (2.0 equiv), THF, 76%; (b) 9-BBN (1.5 equiv), THF, then H_2O_2 and NaOH, 76%; (c) NaOH (1.1 equiv), CSCI (1.0 equiv), CH_3Cl/CH_2Cl_2, 0 °C to rt, 93%; (d) alcohol 2.32 (1.0 equiv), arylchlorothionoformate 2.33 (1.1 equiv), pyridine (2.0 equiv), CH_3Cl, rt, 85%.

Attempts to effect the RCAR of thionocarbonate 2.26 began with application of the conditions previously used successfully on other substrates (i.e. AIBN and TTMSS in benzene or ethyl acetate at reflux). The product resulting from the desired domino sequence was not detected upon analysis of reaction mixture using ¹H NMR
spectroscopy. Instead, the product of deoxygenation \textbf{2.28} was isolated in 85\% yield (Scheme 2.12).

![Scheme 2.12. Deoxygenation of thionocarbonate 2.26. Reagents and conditions: (a) TTMSS (1.3 equiv), AIBN (0.5 equiv), EtOAc (0.02 M), reflux, 1 h, 85\% (isolated) or 87\% \((^\text{1}\text{H NMR spectroscopy/internal standard}); (b) TTMSS (1.3 equiv), EtB (1.5 equiv)/air, EtOAc (0.02 M), 25 °C, 20 min, 75\%.]

As outlined in the introduction to this chapter, previous studies suggest that primary alcohols do not deoxygenate readily at lower temperatures. Consequently, the reaction temperature was lowered in an effort to stall deoxygenation and allow the RCAR to proceed. For initiation at lower temperatures Oshima’s method\textsuperscript{19} using triethylborane/oxygen was employed. In order to quickly and accurately compare results for these deoxygenation reactions, an internal standard suitable for analysis using \(^1\text{H NMR spectroscopy} was employed. 4,4’-Di-\textit{tert}-butylbiphenyl was selected as the internal standard, as it is neither volatile nor susceptible to radical mediated reactions (it contains no hydrogen atoms that can be readily abstracted). Surprisingly, at 25 °C deoxygenation still prevailed (Scheme, Entry 2) and \textbf{2.28} was produced in 75\% yield (estimated by \(^1\text{H NMR spectroscopy/internal standard}). This yield was significantly higher than the previous best Barton-McCombie deoxygenation at room temperature (51\%, see Scheme 2.7).\textsuperscript{35} In order to more thoroughly understand this significant result, an investigation was commenced.

This investigation had the following objectives: (a) optimise the room temperature deoxygenation; (b) identify the temperature at which deoxygenation becomes slow, thereby possibly promoting the RCAR; and (c) examine the importance of the reagent TTMSS and the initiator system triethylborane/oxygen.

The reactions documented to this point were performed using benzene as the solvent. This solvent is commonly used for radical reactions since benzenes carbon-hydrogen
bond strength, renders abstraction of hydrogen atoms by other radicals unfavourable. However, benzene also has a relatively high melting point (4 °C), and as we intended to perform reactions at lower temperatures (to determine the lower thermal limit of deoxygenation), an alternative solvent was sought. Ethyl acetate was selected due to its relatively low melting point (-83 °C). While this solvent is not commonly used for free radical reactions, it appeared to be inert to unwanted side-reactions with free-radical intermediates, as deoxygenation yields were not compromised. Furthermore, it is a cheaper and less toxic alternative to benzene.

2.2.2. Investigating the New Conditions for Room Temperature Deoxygenation

2.2.2.1. Optimising and Pushing the Lower Thermal Limit of Deoxygenation

It was anticipated that the room temperature deoxygenation of thionocarbonate 2.26 could be optimised by slow addition of the radical mediator. This technique has been used previously to improve deoxygenation yields, by reducing unwanted hydrogen atom abstraction by the initial adduct radical (see Scheme 2.2).\(^1\) Given that lower temperatures would slow the rate of carbon-oxygen fragmentation, it was likely that this unwanted process was occurring to some extent during the deoxygenation of thionocarbonate 2.26. Gratifyingly, the slow addition of TTMSS over 2 h resulted in a 10% increase in yield of the deoxygenated product 2.28 (85% isolated yield) (Table 2.2, entry 1), compared to the corresponding reaction where TTMSS was added in one portion (Scheme 2.12, 75% isolated yield).

The reaction temperature was lowered to determine the lowest temperature at which deoxygenation of thionocarbonate 2.26 would proceed. Thus, precursor 2.26 was treated with TTMSS (slow addition over 2 hours), and triethylborane/air at 0 °C and at -30 °C. At 0 °C, the deoxygenated product 2.28 was obtained in 82% yield (\(^1\)H NMR/internal standard) (Table 2.2, entry 2). At -30 °C, however, deoxygenation was slowed, and only 10% (\(^1\)H NMR/internal standard) of the product 2.28 was obtained (Table 2.2, entry 3). It had been proposed that if deoxygenation could be stalled, the radical carboxyarylation reaction might proceed. Unfortunately, no carboxyarylation products could be identified in the reaction performed at -30 °C by analysis of the reaction mixture using \(^1\)H NMR spectroscopy.
Table 2.2. Deoxygenation of Thionocarbonate 2.26 at Lower Temperatures

<table>
<thead>
<tr>
<th>entry</th>
<th>temperature (°C)</th>
<th>% yield 2.28b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>88 (85°)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>-30</td>
<td>12</td>
</tr>
</tbody>
</table>

Reagents and conditions: TTMSS (slow addition over 120 min) (1 equiv), Et$_3$B/air, EtOAc (0.02 M), 140 min; b yield estimated by $^1$H NMR spectroscopy; c isolated yield.

2.2.2.2. Investigating the Reagents

Tris(trimethylsilyl)silane

To determine the importance of TTMSS for the room temperature deoxygenation of thionocarbonate 2.26, an alternative radical mediator was used. When the precursor was treated with tributyltin hydride and AIBN in ethyl acetate at reflux, 2.28 was obtained in a 69% yield ($^1$H NMR/internal standard) (Table 2.3, entry 1). This yield was slightly lower than the equivalent reaction using TTMSS (87%) (Scheme 2.12).

Table 2.3. Deoxygenation of Thionocarbonate 2.26 using Tributyltin Hydride

<table>
<thead>
<tr>
<th>entry</th>
<th>method</th>
<th>mediator/initiator</th>
<th>temperature (°C)</th>
<th>time (min)</th>
<th>% yield 2.28b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(i)</td>
<td>HSnBu$_3$/AIBN/Δ</td>
<td>77</td>
<td>90</td>
<td>69 (65°)</td>
</tr>
<tr>
<td>2</td>
<td>(ii)</td>
<td>HSnBu$_3$/Et$_3$B/air</td>
<td>25</td>
<td>140</td>
<td>10 (70°)</td>
</tr>
</tbody>
</table>

Reagents and conditions: (i) HSnBu$_3$ (1.3 equiv), AIBN (0.5 equiv), EtOAc (0.02 M); (ii) HSnBu$_3$ (1.3 equiv), Et$_3$B (1.5 equiv)/air, EtOAc (0.02 M); b yield estimated by $^1$H NMR spectroscopy; c starting material remaining estimated by $^1$H NMR spectroscopy; d slow addition over 2 h.

The superior efficiency of TTMSS compared to tributyltin hydride was more evident at room temperature. As previously mentioned (Scheme 2.12), using TTMSS 2.26 was
deoxygenated at room temperature in excellent yield (75%). Alternatively using tributyltin hydride and otherwise analogous conditions, this compound was deoxygenated in only 10% yield, with a 70% recovery of starting material ($^1$H NMR/internal standard) (Table 2.3, entry 2). A similar result was obtained when tributyltin hydride was added in one portion.

The recovery of starting material in the room temperature experiment using tributyltin hydride was unexpected. The tin-hydrogen bond in tributyltin hydride is weaker than the silicon-hydrogen bond in TTMSS. Thus, it would be expected that unwanted abstraction of hydrogen atoms from intermediate radicals should be more facile when using tributyltin hydride, resulting in a lower yield of deoxygenation products and an increase in byproduct formation. While the yield of the deoxygenated product was low, a significant portion of the starting material 2.26 was observed. This suggests in the example using the tributylstannyl radical as a chain carrier, instead of the tris(trimethylsilyl)silyl radical, the chain process was being stalled at room temperature.

*Triethylborane*

It is plausible that the initiator triethylborane may be aiding the room temperature deoxygenation of alcohol derivative 2.26; triethylborane is a Lewis acid, and may facilitate the process through coordination to the substrate. In addition, ethyl radicals derived from triethylborane (Scheme 2.13, Initiation step) may act as the chain carrying species, whereby the ethyl radical can add directly to the thiocarbonyl sulfur of 2.26 (Scheme 2.13, eq 1 and 3), instead of abstracting a hydrogen atom from TTMSS to produce the silyl radical (Scheme 2.13, eq 1, 2 and 4).
Chapter 2 – Results & Discussion

Initiation:

\[
\text{BEt}_3 + O_2 \rightarrow \text{Et}^* + \text{Et}_2\text{BOO}^* \quad (1)
\]

\[
\text{(TMS)}_3\text{Si}^* + \text{Et}^* \rightarrow \text{(TMS)}_3\text{Si}^* + \text{Et}-\text{H} \quad (2)
\]

First step of the propagation cycle:

The phenomenon of alkyl radicals acting as chain carrying species in deoxygenation reactions has been noted previously. In the first example of deoxygenation using triethylborane/oxygen, Barton and Jaszbereznyi noted that if tributyltin hydride was omitted from the experiment, deoxygenation still occurred.\(^{51}\) Wood and colleagues undertook the first thorough investigation of this phenomenon.\(^{55}\) In this work xanthate derivatives were deoxygenated at room temperature using trialkylboranes, oxygen and water, without conventional mediators such as tributyltin hydride or TTMSS.

The proposed mechanism for this radical chain process studied by Wood and colleagues is outlined in Scheme 2.14. In the initiation step, alkyl radicals are generated from the trialkylborane (trimethyl or triethylborane; triethylborane is used in this illustration) by oxidation with oxygen. The propagation cycle begins with addition of an ethyl radical to the thiocarbonyl group of the xanthate \(2.34\) to afford intermediate \(2.35\). Subsequent \(\beta\)-fragmentation yields the deoxygenated alkyl radical \(R^*\). This radical abstracts a hydrogen atom from a water-triethylborane complex \(2.36\), to give the deoxygenated product and generate another ethyl radical to react in the next chain cycle. Other research groups have also investigated the mechanism of this process.\(^{57,58}\)
Chapter 2 – Results & Discussion

Initiation:

\[ \text{BEt}_3 + O_2 \rightarrow \text{Et}^* + \text{Et}_2\text{BOO}^- \]

Propagation:

\[ \text{R-O-S}^+ \quad \text{SMe} \]

\[ \text{Et}^* \quad \text{radical chain reaction} \]

\[ \text{R-H} + \text{BEt}_2\text{-OH} \quad 2.36 \]

\[ \text{BEt}_3\text{-OH} \quad 2.36 \]

\[ \text{R}^* \quad \text{S}^+ \quad \text{Et} \quad \text{SMe} \]

Scheme 2.14. Wood’s deoxygenation using a trialkyl borane-water complex as a hydrogen atom source.

In order to study the influence of triethylborane on the room temperature deoxygenation of compound 2.26, the reaction was repeated using an alternative method of initiation. Photochemical irradiation (supplied by a medium pressure mercury lamp, which has emissions in the UV-visible region between 200 nm to 600 nm) was used to initiate the process in the presence of TTMSS at room temperature, with or without AIBN. The deoxygenated product was obtained in 73% and 70% yields (\(^1\)H NMR/internal standard) for the reactions with or without AIBN respectively (Table 2.4, entry 8). Deoxygenation does occur in the absence of triethylborane, demonstrating that this reagent is not required for the deoxygenation of 2.26 at room temperature. Thus, it is unlikely that triethylborane is acting as a Lewis acid to facilitate deoxygenation.
Table 2.4. Deoxygenation of Thionocarbonate 2.26 without Triethylborane$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>mediator/initiator</th>
<th>temperature ($^\circ$C)</th>
<th>time (min)</th>
<th>% yield 2.28$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TTMSS/AIBN/hv</td>
<td>25</td>
<td>200</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>TTMSS/hv</td>
<td>25</td>
<td>140</td>
<td>70</td>
</tr>
</tbody>
</table>

$^a$ Reagents and conditions: reactant 2.26 (1.0 equiv), TTMSS (1.3 equiv), with or without AIBN (1.5 equiv), EtOAc (0.02 M), medium pressure mercury lamp irradiation; $^b$ yield estimated by $^1$H NMR spectroscopy; $^c$ slow addition over 2 h.

2.2.3. Assessing the Scope – Choice of Thiocarbonyl Moiety

Many different thiocarbonyl precursors have been used for Barton-McCombie deoxygenation (see Chapter 1, Section 1.4, page 4). In the first example of deoxygenation, Barton and McCombie used imidazolide, xanthate, and thiobenzoate thio carbonyl derivatives. In later studies, Robins and co-workers developed the use of phenylchlorothionoformate to derivatise alcohols for Barton-McCombie deoxygenations.$^7$,$^8$ These derivatives were pursued as they could be prepared from base sensitive substrates. Later, Barton and McCombie introduced substituted aryl thionocarbonate derivatives, which contained electron-poor aryl substituents (see Section 2.1, page 17).$^{20,52}$

The deoxygenation of primary alcohol derivatives is known to be susceptible to unwanted hydrogen atom trapping of the radical intermediate (especially at room temperature). Thus, these alcohols are challenging substrates. Consequently, it was anticipated that by reacting various thiocarbonyl derivatives of the primary alcohol 2.32 under identical room temperature conditions would test their relative efficiencies. A number of derivatives (see Figure 2.1) were selected for the study and included: six arylthionocarbonates 2.37a–e and 2.26 (the preparation and deoxygenation of this derivative has been described in Section 2.2.1), thiocarbonyl imidazolide 2.37f, and methyl xanthate 2.37g. These substrates were treated with TTMSS and triethylborane and air at room temperature.
2.2.3.1. Preparation of Precursors

The arylthionocarbonates $2.37a$–$e$ were prepared in (unoptimised) good yields from the corresponding arylchlorothionoformates $2.38a$–$e$ (either sourced commercially or prepared from the corresponding phenol and thiophosgene) and alcohol $2.32$ using the method previously described for the preparation of $2.36$ (Section 2.2.1, Scheme 2.11, page 23). Yields obtained for the synthesis of these compounds are displayed in Table 2.5.
Table 2.5. Preparation of Various Aryl Thionocarbonate Derivatives of Alcohol 2.32.$^a$

\[
\begin{array}{ccc}
\text{entry} & \text{R} & \text{yield 2.38 (%)} & \text{yield 2.37 (%)} \\
1^b & \begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array} & 93 & 85 \\
2 & \begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array} & 79 & 71 \\
3 & \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} & 87 & 70 \\
4 & \begin{array}{c}
\text{F}
\end{array} & 81 & 88 \\
5 & \begin{array}{c}
\text{commercially}
\end{array} & \text{sourced} & 77 \\
6 & \begin{array}{c}
\text{commercially}
\end{array} & \text{sourced} & 78 \\
\end{array}
\]

$^a$ Reagents and conditions: (a) NaOH (1.05 equiv), CS\(_2\)Cl\(_2\) (1.0 equiv), CH\(_2\)Cl\(_2\)/H\(_2\)O, 0 °C to rt; (b) arylchlorothionoformate (1.1 equiv), alcohol (1.0 equiv), pyridine (2.0 equiv), CH\(_2\)Cl\(_2\), rt; $^b$ results from Section 2.2.2.

Synthesis of the imidazolide precursor 2.37f is outlined in Scheme 2.15. This precursor was prepared using 1,1'-thiocarbonyldiimidazole (2.39). While commercially available, this reagent is prone to decomposition, so it was freshly prepared from 1-(trimethylsilyl)imidazole (2.40) and thiophosgene.$^{59}$ The product was obtained in 93% yield. By heating 2.39 and alcohol 2.32 in THF at reflux, the desired precursor 2.37f was obtained in 71% yield.
Scheme 2.15. Synthesis of imidazolidine 2.37f. Reagents and conditions: (a) l-(trimethylsilyl)imidazole (2.0 equiv), thiophosgene (1.0 equiv), PhH, 0 °C, 93%; (b) alcohol 2.32 (1.0 equiv), 1,1'-thiocarbonyldiimidazole (1.3 equiv), THF, reflux, 71%.

The S-methyl xanthate 2.37g was prepared by a modified literature method.\(^{60}\) Deprotonation using sodium hydride at -78 °C, followed by nucleophilic addition to carbon disulfide and finally nucleophilic substitution of iodomethane, led to the formation of the product 2.37g in 85% yield (Scheme 2.16).

Scheme 2.16. Synthesis of xanthate 2.37g. Reagents and conditions: (a) i. alcohol 2.32 (1.0 equiv), NaH (1.5 equiv), THF, -78 °C, 1h; ii. carbon disulfide (1.5 equiv), -78 °C to rt, 15 h; iii. iodomethane (1.5 equiv), 1.5 h, 85%.

2.2.3.2 Deoxygenation Reactions

The deoxygenation precursors 2.37a-g, containing various thionocarbonyl groups, were treated with TTMSS (added slowly over 2 h) and triethylborane/air in ethyl acetate at room temperature. The results for these deoxygenation reactions are displayed in Table 2.6. Once again, to enable easy and accurate comparison of derivatives, yields of the product 2.28 were determined through \(^{1}H\) NMR spectroscopic analysis of crude reaction mixtures containing 4,4'-di-tert-butylbiphenyl as an internal standard.
Table 2.6. Deoxygenation of Various Aryl Thionocarbonate Derivatives of Alcohol

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>(i) yield 2.28 (%)</th>
<th>(ii) % yield 2.28 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="R1" /></td>
<td>88</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="R2" /></td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="R3" /></td>
<td>86</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="R4" /></td>
<td>25 (35%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="R5" /></td>
<td>83</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="R6" /></td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="R7" /></td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="R8" /></td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Reagents and conditions: (i) reactant (1.0 equiv), TTMSS (1.3 equiv) slow addition over 2 h, Et3B (1.5 equiv)/air, EtOAc (0.02 M), 25 °C, 140 min; (ii) reactant (1.0 equiv), TTMSS (1.3 equiv) single addition, Et3B (1.5 equiv)/air, EtOAc (0.02 M), 25 °C, 20 min. * yield estimated by 1H NMR spectroscopy; † results from Section 2.2.2. ‡ starting material remaining.
The results presented in Table 2.6 indicate that the 2,4,6-trimethoxy derivative 2.37b was the highest yielding substrate for deoxygenation (entry 3). However, other arylthionocarbonates were also effective (entries 1-3, 5-6). An exception was trichloro-substituted aryl substrate 2.37d (entry 4). Treatment of this derivative resulted in low conversion to the deoxygenated product (25%), and 35% (\(^1\)H NMR/internal standard) of the starting material remained after 140 minutes. The imidazolide 2.37g and xanthate 2.37h precursors were also poor substrates. \(^1\)H NMR analysis of the crude reaction mixtures of these two precursors indicated that the starting material was consumed.

Under the standard reaction conditions involving the slow addition of TTMSS, with the exception of the trichlorophenyl precursor conditions, all arylthionocarbonates reacted to give high yields of the deoxygenation product. In an effort to differentiate between the reactivity of the successful arylthionocarbonates, the reactions were performed by adding the mediator, TTMSS, in one portion. A high concentration of hydrogen atom source (TTMSS) would favour hydrogen atom substitution of the initial C=S radical adduct relative to \(\beta\)-elimination. Consequently, substrates that were more susceptible to this unwanted process would be identified through lower yielding reactions. In the event, only a marginally lower yield for two derivatives (entries 1 and 3) were observed. It is concluded that the trimethoxy (entry 2), para-fluoro (entry 5) and penta-flurophenyl (entry 6) analogues are the most efficient for radical deoxygenation.

The poor result obtained for the 2,4,6-trichlorophenyl thionocarbonate precursor 2.27c was unexpected. While recovery of some starting material (35%) suggested that the radical chain process was being stalled, the mass balance of the reaction was relatively low (60%) suggesting other unwanted processes were occurring, consuming starting material.

2,4,6-Trichlorophenyl thionocarbonates have been used as successful substrates for deoxygenation of secondary,\(^{53,10,20}\) and even primary alcohols (at 110 °C).\(^{20}\) In the majority of these deoxygenations tributyltin hydride and AIBN are used, with diphenylsilane employed in an isolated example.\(^{61}\) Interestingly, in this last example no yields are supplied and a footnote explains that high yielding deoxygenation required the use of tributyltin hydride and AIBN in refluxing solvent.
Possible steric and electronic rationalisations of the low yield obtained for 2,4,6-trichlorophenyl thionocarbonate derivative 2.27c are outlined in Scheme 2.17. It is well known that alkenyl and aryl chlorides are inert to tributyl tin radicals, since the carbon-chlorine bonds are relatively strong. There is an example of radical processes (not deoxygenation), using silane chain carriers, on substrates that contain a chloro-substituted aryl group, suggesting that aryl chlorides are likely to be inert to silyl radical as well. Another possible explanation of the result obtained for the 2,4,6-trichlorophenyl thionocarbonate 2.27c relates to the steric bulk brought to bear by the two ortho-chlorine atoms. This congestion may: (a) slow the rate of addition of the silyl radical to the sulfur atom; or (b) stabilise/restrict the geometry the initial adduct radical; this may slow the rate of the β-elimination process and increase the life-time of this radical to enable other unwanted, chain terminating processes to occur. However, the derivative 2.27a also contains two ortho substituents, and this is the most effective deoxygenation substrate (Table 2.6, entry 2). It is evident that further experimentation is required to determine the basis of the results obtained for the 2,4,6-trichlorophenyl thionocarbonate.

Scheme 2.17. Possible reasons for the low deoxygenation yield from the 2,4,6-trichlorophenyl thionocarbonate substrate.

The imidazolide 2.27g was also an unsuitable derivative for the deoxygenation of primary alcohol 2.32 at room temperature. Analysis of the crude reaction mixture using $^1$H NMR spectroscopy showed a complex mixture of products. Byproducts were not isolated and characterised. While imidazolide derivatives have been used successfully for a wide variety of deoxygenations, some unsuccessful attempts have been noted.
Previous unsuccessful deoxygenation reactions using imidazolide derivatives have noted conversion to complex mixtures. Some of the byproducts that have been isolated from these unsuccessful reactions are illustrated in Scheme 2.18, and include the alcohol 2.32, methoxy compounds 2.41, hemithioacetal 2.42, or the Sn-containing monothioacetal 2.43.

Scheme 2.18. Unwanted products formed during attempted deoxygenations of imidazolide derivatives.

The xanthate 2.27h was not a suitable substrate for deoxygenation of alcohol 2.32 at room temperature; only 27% (1H NMR/internal standard) of the desired product was detected (Table 2.6, entry 8). While no effort was made to identify and isolate other products from this reaction, it is likely that preferential cleavage of the carbon-sulfur bond (rather than the desired carbon-oxygen bond) is causing the poor yield. It has been noted that in deoxygenation reactions of certain xanthates, such as the 2.44, in which collapse of the initial adduct radical 2.45 by carbon-oxygen or carbon-sulfur bond scission gives alkyl radicals of similar stability (2.46 or 2.47), the latter proceeds preferentially. The example in Scheme 2.19 was the first time this phenomenon was noted. The deoxygenation yielded none of the desired product cholestane (2.48), instead, propane 2.49, resulting from carbon-sulfur bond cleavage, was produced in approximately 75% yield (Scheme 2.19). Thus, in the deoxygenation of 2.27h, there is the possibility of β-fragmentation by carbon-oxygen or carbon-sulfur bond scission, which would give the desired primary alkyl radical or the methyl radical respectively. This is a potential cause of low yield obtained for the deoxygenated product in this example.
2.2.4. Assessing the Scope – Nature of the Primary Alcohol

Five different primary alcohols were selected to assess to scope of the room temperature deoxygenation conditions. These alcohols were methyl 4-(2-hydroxyethyl)benzoate (2.32), 2-phenylethanol (2.50), a protected galactose derivative 1,2:3,4-bis-O-(1-methylethylidene)-α-D-galactopyranose (2.51), octadecan-1-ol (2.52), and the steroidal compound, betulin (2.53). The alcohols were converted to 4-methoxyphenylthionocarbonate derivatives and were treated with TTMSS and triethylborane/air at room temperature.
2.2.4.1. Preparation of Precursors and Deoxygenation Reactions

In the previous section the 2,4,6-trimethoxyphenyl thionocarbonate derivative 2.37b gave the highest deoxygenation yield. As the 4-methoxy derivative 2.37a also worked well, and 4-methoxyphenol required to make the substrate was readily available, 4-methoxyphenyl thionocarbonates were used in this investigation. Using the same method described previously (Section 2.2.1, Scheme 2.11, page 23) the 4-methoxyphenyl thionocarbonates derivatives were prepared from the corresponding alcohol 2.50a-2.53a and the arylchlorothionoformate 2.33 to afford the thionocarbonates 2.50b-2.53b. The yields obtained are displayed in Table 2.7.
Table 2.7. Deoxygenation of Various Primary Alcohols

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>thionocarbonate</th>
<th>deoxygenation yield (%)</th>
<th>method</th>
<th>deoxygenation yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.32c</td>
<td>MeO&lt;sup&gt;-&lt;/sup&gt;</td>
<td>85</td>
<td>(ii)</td>
<td>88&lt;sup&gt;d&lt;/sup&gt;, 85</td>
</tr>
<tr>
<td>2</td>
<td>2.50a</td>
<td></td>
<td>80</td>
<td>(iii)</td>
<td>78&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>2.51a</td>
<td></td>
<td>86</td>
<td>(ii)</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>2.52a</td>
<td></td>
<td>75</td>
<td>(ii)</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>2.53a</td>
<td></td>
<td>64</td>
<td>(iv)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reagents and conditions: (i) arylchlorothionoformate (1.1 equiv), alcohol (1.0 equiv), pyridine (2.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt; (b) reactant (1.0 equiv), TTMSS (1.3 equiv) slow addition over 2 h, Et<sub>3</sub>B (1.5 equiv)/air, EtOAc (0.02 M), 25 °C, 240 min; (c) reactant (1.0 equiv), TTMSS (1.3 equiv) slow addition over 2 h, Et<sub>3</sub>B (1.5 equiv)/air, C<sub>6</sub>D<sub>6</sub> (0.02 M), 25 °C, 240 min; (i) reactant (1.0 equiv), TTMSS (1.3 equiv), Et<sub>3</sub>B (1.5 equiv)/air, EtOAc (0.01 M), 25 °C, 90 min; <sup>b</sup> isolated yield; <sup>c</sup> results from Section 2.2.2; <sup>d</sup>yield estimated by <sup>1</sup>H NMR spectroscopy; <sup>e</sup> using the slow addition method (b) led to incomplete conversion.

Primary alcohol thionocarbonates 2.50a-2.53a were treated with TTMSS and triethylborane/air in ethyl acetate at room temperature. The deoxygenated products 2.50c-2.53c were measured (<sup>1</sup>H NMR/internal standard) or isolated in yields ranging from 78 to 94% (Table 2.7). Both sterically unhindered (entries 1 to 3) and hindered (entries 4 and 5) alcohols were found to be suitable substrates under these deoxygenation reaction conditions. Thus, this method offers an improvement not only...
on the existing Barton-McCombie reaction conditions, but also on the deoxygenation method of Myers and co-workers (see Section 2.1.2, page 20),\textsuperscript{56} which is unsuitable for hindered primary alcohols. For example, the protected galactose derivative \textbf{2.51a} was recovered quantitatively when exposed to Myers deoxygenation conditions (Scheme 2.20).\textsuperscript{56} In the present study, the same alcohol was deoxygenated successfully in 66\% isolated yield over two steps from the alcohol (Table 2.7, entry 4).

![Scheme 2.20. Unsuccessful deoxygenation of 1,2:3,4-bis-O-(1-methylethylidene)-\(\alpha\)-D-galactopyranose (\textbf{2.51a}) reported by Myers et al.\textsuperscript{56} Reagents and conditions: (a) PPh\textsubscript{3}, diethylazodicarboxylate, o-nitrobenzenesulfonylhydrazine, THF, -30 °C to rt, 0\%.\textsuperscript{56}](image)

The deoxygenation of the primary alcohol of betulin \textbf{2.53a} was achieved in the presence of the unprotected secondary alcohol. This selectivity was possible as the less sterically hindered primary alcohol was thioacylated preferentially. Interestingly, the mode of addition of TTMSS affected the success of the deoxygenation of this derivative. Slow addition of TTMSS resulted in isolation of only 25\% of the deoxygenated product and recovery of 74\% of the starting material. Conversely, addition of the silane in one portion enabled the deoxygenation product to be isolated in 78\% yield. It is proposed that steric bulk of the substrate disfavours addition of the large tris(trimethylsilyl)silyl radical to the sulfur atom in the first step of the radical chain cycle (see Scheme 7.21). Thus, when the concentration of the silane is low, the adduct \textbf{2.54} is formed in insufficient concentration to permit an efficient radical chain process, resulting in recovery of the starting material. Increasing the concentration of the silane increases the flux of radicals to support the chain process.
2.2.4.2. Deoxygenation of a Challenging Secondary Alcohol

Deoxygenation of cholesterol can be problematic and can result in the formation of a number of products. This problem was originally reported by Barton and McCombie,\(^1\) who suggested that side products were formed by hydrogen atom transfer to the initial \(\text{C}=\text{S}\) adduct radical (Section 2.11, Scheme 2.2). Improved deoxygenation of cholesterol derivatives has been achieved by use of increased reaction temperature\(^{70}\) and/or by slow addition of the hydride source.\(^1\) In contrast, Wood et al. have demonstrated efficient deoxygenation of a cholesterol derivative at room temperature.\(^{55}\) Wood makes no comment on this high yield.

To further challenge the optimised room temperature conditions presented in this study, attempts were made to deoxygenate cholesterol (2.55). Cholesterol was derivatised using the arylchlorothionoformate 2.38c to yield thionocarbonate 2.56. The thionocarbonate was treated with TTMSS and triethylborane/air at room temperature. Once again, addition of TTMSS in a single portion was required to push the reaction to completion, but nevertheless, this reaction afforded cholest-5-ene (2.57) in a gratifying 88% yield (Scheme 2.22).
Scheme 2.22. Reagents and conditions: (a) Phenylchlorothionoformate (1.1 equiv), alcohol (1.0 equiv), pyridine (2.0 equiv), CH$_2$Cl$_2$, rt, 67%; (b) thionocarbonate 2.56 (1.0 equiv), TTMSS (1.3 equiv), Et$_3$B (1.5 equiv)/air, EtOAc (0.02 M), 25 °C, 90 min, 88%.
2.3. **Conclusions and Future Work**

It was originally thought that primary alcohols were difficult substrates to deoxygenate, on account of the relative instability of the primary alkyl radicals formed in the deoxygenation process. This instability rendered cleavage of the carbon-oxygen bond slow enough to permit unwanted radical processes. Initially, these problems were primarily overcome by increasing the reaction temperature. This study demonstrates that through the use of TTMSS, primary alcohols can be deoxygenated in excellent yield at low (0–25°C) temperatures. This successful outcome is highly dependent upon the identity of the radical mediator, type of thiocarbonyl substrate, and the reagent concentration.

A variety of primary alcohol derivatives were successfully deoxygenated at room temperature, including sterically hindered derivatives. The choice of radical mediator was paramount to the success of the reaction. TTMSS was an effective mediator for the room temperature deoxygenation of a primary alcohol while tributyltin hydride was not. The concentration of the radical mediator TTMSS also affected reactivity: In the case of sterically hindered substrates and those known to be challenging (betulin and cholesterol), a high concentration of silane was required.

The efficiency of different thiocarbonyl substrates has been compared. The arylthionocarbonates (with the exception of the 2,4,6-trichloro substrate) gave a significantly higher yield of deoxygenation product compared to the original xanthate and imidazolide precursors.

The conditions presented in this study to deoxygenate primary alcohols in high yield will find application in other difficult deoxygenations where unwanted hydrogen abstraction occurs. This has been demonstrated by the successful room temperature deoxygenation of cholesterol, a secondary alcohol that was frequently a poor substrate for radical deoxygenation.
3. Application of the Radical Carboxyarylation Reaction in Synthesis

3.1. The Xestoquinone-like Natural Products

Xestoquinone \(^{71}\) (3.1) and related natural products are part of a growing group of structurally similar compounds that have been isolated from sponges of the *Xestospongia* and *Adocia* genera.\(^{72,73,74}\) Xestoquinone is structurally the simplest of this family, and consists of a fused pentacyclic quinone-containing structure with a quaternary stereocentre at C6 (Figure 3.1). Other xestoquinone-like natural products include halenaquinone (3.2),\(^{75}\) and adociaquinone A (3.3) (Figure 3.1). Related quinol, or quinone derivatives have also been isolated; some examples include tetrahydroxestoquinol (3.4),\(^{73}\) halenaquinol (3.5),\(^{76}\) and tetrahydrohalenaquinone A (3.6)\(^{74}\) (Figure 3.1). It is believed that the biosynthetic origins of these compounds are from a triketide (D and C ring) and a sesquiterpene (A, B, C and E rings).\(^{74}\)

![Figure 3.1: Examples of xestoquinone and related compounds.](image)

Xestoquinone-like metabolites are recognized as a structurally discrete group based on the parent 1 *H*-benzo[6,7]phenanthro[10,1-\(b,c\)]-furan ring system.\(^{77}\) Xestoquinone and related compounds share a structural motif with the viridin family of natural products.\(^{78}\) Members of the viridin family are not marine metabolites; instead they are produced by
fungi and are steroidal in origin. The structure of viridin (3.7) is displayed (Figure 3.2) to illustrate the common ABCE tetracyclic ring moiety.

![Image of viridin](image)

Figure 3.2. The structure of viridin, which shares a common ABCE tetracyclic moiety with the xestoquinone-like natural products (Figure 3.1).

Xestoquinone and related natural products exhibit a range of biological activities.\(^74,79\) For example, xestoquinone (3.1) has displayed potential as an anticancer\(^73,74,79-81\) and antimalarial therapeutic.\(^82\) Consequently, these compounds are appealing lead structures in drug development.

There have been numerous attempts to prepare halenaquinone (3.2) and xestoquinone (3.1), as these are the simplest targets in the family. Despite this, an approach that can be applied to the synthesis of more complicated members in this family, has not yet been developed. Design of a general synthetic route is desired as it would allow further investigation of the biological effects of the natural products and also the design of new related therapeutics. In this following section the successful endeavours to prepare xestoquinone (3.1), and halenaquinone (3.2) are discussed.

### 3.1.1. Total Syntheses of Halenaquinone and Xestoquinone

Xestoquinone (3.1) and halenaquinone (3.2) differ only in the oxidation level at C3 (Figure 3.1). Halenaquinone (3.2) was the first member of this family of natural products to be synthesised, via a catalytic enantioselective approach reported by Harada and co-workers in 1988.\(^83\) Since then, there have been three more successful syntheses of this natural product.

In 1996, Shibasaki reported a catalytic enantioselective synthesis of (+)-halenaquinone (3.2).\(^84\) In 2001, Rodrigo and colleagues published a shorter synthesis to access the racemic natural product.\(^85\) More recently, Trauner and colleagues published a short catalytic asymmetric route to (+)-halenaquinone.\(^86\)
To date there have been four distinct total syntheses of xestoquinone (3.1) reported. The groups of Rodrigo and Harada applied the same approaches that they used for halenaquinone.\textsuperscript{87,88} In 1991 Kanemastu reported an alternative preparation of the racemic natural product,\textsuperscript{89} and in 1996 Keay and co-workers completed a catalytic enantioselective synthesis.\textsuperscript{90} The preparations of xestoquinone and halenaquinone are outlined in more detail below, and are described by the order in which the ABCDE pentacyclic ring structure is constructed.

In their preparation of (+)-halenaquinone (3.2) and (+)-xestoquinone (3.2), Harada and co-workers constructed the rings in an A $\rightarrow$ AB $\rightarrow$ ABCD $\rightarrow$ ABCDE sequence (Scheme 3.1). They utilised the Wieland-Miescher ketone to install the required stereochemistry at C6.\textsuperscript{83,87} Using commercially available 2-methylcyclohexane-1,3-dione (3.8) and but-3-en-2-one (3.9), ketone 3.10 was prepared. Using $(+)$-proline as a organocatalyst, ketone 3.10 underwent an enantioselective cyclisation to afford the Wieland-Miescher ketone 3.11, in 82\% yield and 69\% ee over two steps from 3.8 (recrystallisation was used to obtain enantiomerically enriched ketone).\textsuperscript{87} Elaboration of ketone 3.11 to enone 3.12 (nine steps for halenaquinone or eleven steps for xestoquinone), and subsequent Diels-Alder reaction with intermediate 3.13 afforded the tetracyclic ABCD adduct 3.14. Intermediate 3.13 was derived \textit{in situ} by electrocyclic ring-opening of 3,6-dimethoxybenzocyclobutene (3.15), which was prepared from commercially available 2,3-dimethylphenol (3.16) in six steps. Adduct 3.14 was converted to 3.17 in three steps (aromatisation, oxidation and deprotection), and a further two steps installed the furan E ring to give advanced intermediate 3.18. Oxidative demethylation yielded the natural product 3.2. For the preparation of halenaquinone, the longest linear sequence was 17 steps (1.6\% yield), with 23 steps in total. For the synthesis of xestoquinone, the longest linear sequence was 19 steps (0.85\% yield), with 25 steps in total. While this approach to prepare xestoquinone and halenaquinone is convergent, the sequences are long and the overall yields are low.
Scheme 3.1. The first total synthesis of (+)-halenaquinone (3.2) and (+)-xestoquinone (3.1) by Harada and co-workers. CAN = cerium(IV) ammonium nitrate.

In 1991 Kanematsu and co-workers completed a formal synthesis of (±)-xestoquinone using an AE → ABE → ABCDE sequence (Scheme 3.2). In their synthesis, novel furan ring transfer (FRT) methodology was used to prepare the AE portion of the natural product. 3-Bromo-1-propyne (3.19) and furfuryl alcohol (3.20) were used to prepare the 2-substituted furan 3.21 required for the FRT reaction. In this reaction, treatment of the furan 3.21 with base gave allenyl furfuryl ether 3.22, which underwent...
a spontaneous intramolecular Diels-Alder reaction followed by a base-catalysed ring opening to afford the AE bicyclic compound 3.23. Bicycle 3.23 was converted into \(\alpha,\beta\)-unsaturated ketone 3.24 in nine steps. This ABE tricycle was used in a Diels-Alder cycloaddition with the \(o\)-quinodimethane intermediate 3.13 to afford the pentacyclic ABCDE product 3.25. The intermediate 3.13 was generated \textit{in situ} from 3.26, the synthesis of which was not described or referenced in the publication. This intermediate, however, can be prepared in two steps from commercially available 2,3-dimethylhydroquinone (3.27). Aromatisation of the C ring of the Diels-Alder adduct 3.25 yielded the precursor to xestoquinone, 3.28 previously made by Harada. Synthesis of this precursor was achieved in a total of 15 steps and the longest linear sequence was 13 steps (1.5% yield). While this approach is shorter and more convergent than the previous attempt, the overall yield is not greatly improved.

Scheme 3.2. Formal synthesis of \((\pm)\)-xestoquinone using furan ring transfer methodology (HMPT = hexamethylphosphoramide).\(^9\)
Shibasaki and co-workers published a catalytic enantioselective total synthesis of halenaquinone in 1996, using a CD → BCD → ABCDE sequence (Scheme 3.3).\textsuperscript{84} Commercially available 6,7-dimethoxy-1-tetralone (3.29) was used to prepare the required CD naphthalene derivative 3.30. This derivative was converted into the BCD containing intermediate 3.31 through different sequences of reactions. Two shorter sequences were lower yielding. In the highest yielding sequence, naphthalene 3.30 was converted into 3.32 via a palladium catalysed cross-coupling reaction. Subsequently, a one-pot hydroboration/Suzuki cross-coupling with iodide 3.34 (prepared from commercially available 2-butyne-2-ol (3.35)) yielded intermediate 3.36. An enantioselective intramolecular Heck reaction of triflate 3.37 was used to close the B ring. Enantioselectivity was achieved using the chiral ligand (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP), and silyl enol ether 3.31 was obtained in 78% yield and 87% ee. In three additional steps the silyl enol ether was converted into the saturated triflate 3.38. Reaction with the acyl anion equivalent 3.39 derived from commercially available 3-(trimethylsilyl)-2-propynal (3.40), gave the ketone 3.41, and protection, followed by benzylic oxidation afforded intermediate 3.42. The iodide 3.43 was prepared in three steps, via conversion to the 1,2-diketone, introduction of iodine and hydrolysis of the acetal. A one-pot palladium-catalysed annulation enabled construction of the two remaining rings to afford the ABCDE pentacyclic precursor 3.44. Desilylation and oxidative demethylation afforded halenaquinone 3.2. The longest linear sequence was 25 steps (6% yield). While this approach uses different disconnections to those previously described, the sequence is long and not convergent. Most processes are high yielding, however, enabling a relatively good overall yield.
Scheme 3.3. A catalytic enantioselective synthesis of (+)-halenaquione (3.2).
In 1996, Keay and co-workers published a catalytic enantioselective synthesis of (+)-xestoquinone (3.1) using a D → CD → CDE → ABCDE sequence.\textsuperscript{90} In this study, similar to the asymmetric synthesis of halenaquinone by Shibasaki and co-workers,\textsuperscript{84} enantioselectivity was effected by a palladium-catalysed cyclisation step using the chiral ligand (S)-BINAP. The synthetic sequence is illustrated in Scheme 3.4, and began with benzocyclobutene 3.45, which can be prepared from commercially available 2,5-dimethoxybenzoic acid (3.46) in at least 5 steps\textsuperscript{93,94} (details for the preparation of this intermediate were not outlined or referenced in this publication). The benzocyclobutene 3.46 underwent an electrocyclic ring opening to yield the intermediate 3.47. Reaction of this intermediate with alkyne 3.48 (prepared from commercially available ethyl propiolate (3.49)), in an intermolecular Diels-Alder reaction, yielded compound 3.50. This intermediate was converted to the acyl chloride 3.51 in three steps. Preparation of the second intermediate, furan 3.52, was achieved in five steps from commercially available 3-hydroxymethylfuran (3.53).\textsuperscript{90,95} Intermediates 3.51 and 3.52 were combined to give the CDE tricyclic intermediate 3.54. Deprotections to 3.55, followed by incorporation of a triflate gave 3.56. Asymmetric palladium-catalysed bi-cyclisation enabled closure of the A and B rings and yielded 3.57 in 82% yield and 68% ee. The natural product 3.1 was formed in two additional steps. The longest linear sequence was 15 steps (all yields for this sequence were not reported), with 21 steps in total. The overall yield from 3-hydroxymethylfuran (3.53) to advanced intermediate 3.57 (10 steps) was 34%.
Shibasaki and co-workers also investigated the same asymmetric approach described in Scheme 3.4. They attempted the polyene cyclisation using the corresponding bromide instead of the triflate 3.56, as this would furnish a more direct route. Keay also investigated this alternative, however, poor enantioselectivity was encountered.
Although Shibasaki and colleagues were able to improve on the results reported by Keay when using the bromide, unfortunately, these are not as good as those obtained when the triflate is employed (Scheme 3.4).

More recently, Rodrigo and co-workers published a short and efficient approach to (±)-xestoquinone using an ABE → ABCDE ring construction sequence (Scheme 3.5).\(^8\) In a similar approach to those of Harada\(^8\) and Kanemastu,\(^9\) the ABE tricyclic ring moiety was prepared and then joined to the D ring through generation of the C ring via a cycloaddition reaction. Commercially available 3-buten-2-one (3.58) and malonic acid (3.59) can be used to prepare (E)-2,4-pentadienol (3.60). In the synthesis reported by Rodrigo and co-workers, the dienol 3.60 was reacted with commercially available 2-methoxy-4-methylphenol (3.61) to yield intermediate 3.62 in situ, which then underwent an intramolecular Diels-Alder reaction to yield the ABE tricycle 3.63, and by-product 3.64. Fortunately, they found that heating this by-product induces a Cope rearrangement to yield the desired tricycle.\(^9\) The isobenzofuran 3.65 can be accessed in two steps from commercially available 2-bromo-1,4-dimethoxybenzene (3.66).\(^9\) In another Diels-Alder process, intermediates 3.63 and 3.65 were reacted to provide the ABCDE pentacyclic adduct 3.67. The natural product (±)-3.1 was obtained from five further reactions. From 2-methoxy-4-methylphenol (3.61) the total synthesis was achieved in eight linear steps (18% overall yield). From commercially available materials the longest linear sequence was ten steps, with 12 steps in total.\(^8\)
Rodrigo and co-workers also applied this same methodology in a formal total synthesis of (±)-halenaquinone (3.2) (Scheme 3.6). They discovered that carrying the C3 carbonyl group of halenaquinone through the synthesis was not possible, and therefore, they used an alkenyl sulfide as 'potential oxygen'. The required dienol 3.69 was prepared in four steps from commercially available propargylic alcohol (3.68). This was transformed using the intramolecular Diels-Alder/Cope sequence described for the synthesis of xestoquinone (Scheme 3.5) to yield the adduct 3.70 in 36% yield over two steps. In three straightforward transformations (aromatization, elimination, and another aromatization step), formation of advanced intermediate 3.72 was achieved. Hydrolysis of the thioenolether afforded the pentacyclic precursor to halenaquinone 3.73. To this point the longest linear sequence was 11 steps (2% overall yield). The efficiency of this approach suffered when applied to the more complex of the two natural products.
Most recently, a relatively short enantioselective synthesis of (−)-halenaquinone (3.2) has been published using a E → AE → ADE → ABDCE ring construction sequence (Scheme 3.7). This approach showcased a novel application of the Diels-Alder reaction that utilised a vinyl quinone as a diene. The synthesis started with a two step sequence from commercially available 2-butyne-1,4-diol (3.74) to afford the diiodofuran 3.75. Diiodofuran 3.75 was mono-lithiated and then added to aldehyde 3.76 (prepared in four steps from commercially available 2-methylacrylaldehyde (3.77)), and the resulting product was oxidised to afford ketone 3.78. Using the chiral reducing agent (−)-B-chlorodiisopinocamphenylborane ((−)-DIP-Cl), the ketone was reduced to the enantioenriched alcohol 3.79. Functional group modifications afforded the intermediate 3.80, and an intramolecular Heck cyclisation yielded the bicyclic compound 3.81, which incorporated the AE rings of the natural product. This installed the C6 stereocentre of halenaquinone, as the Heck reaction proceeded diasteroselectively (dr = 7:1). Addition of the organolithium species derived from organostannane 3.82 to the aldehyde functional group of 3.81 afforded the AED tricyclic compound 3.83. A further three steps (desilylation, oxidation and oxidative demethylation) afforded the quionone 3.84. An intramolecular Diels-Alder reaction of this quinone under high pressure (10 kbar) resulted in formation of the B and C rings to afford the pentacycle 3.85 in 78% yield. The initial cycloaddition product 3.86 could not be detected as it underwent rapid tautomerisation to the vinyl hydroquinone
pentacycle 3.85. Oxidation and aromatization afforded the natural product (−)-3.2. The target was produced in 12 steps (5% yield for these steps) from diiodofuran 3.75, whereby the longest linear sequence was 16 steps.

Scheme 3.7. Synthesis of (−)-halenaquinone (3.2)
3.1.2. A Novel Radical Approach to the Xestoquinone-like Natural Products

In this thesis a novel approach to xestoquinone-like natural products is explored. The envisioned sequence uses different disconnections to all previous syntheses of halenaquinone and xestoquinone. Furthermore, the domino RCAR will be utilised as a key step and facilitates a highly convergent sequence.

The model compound 3.87 was targeted in this study to test the viability of the proposed approach to the xestoquinone/halenaquinone-related natural products. Scheme 3.8 illustrates the differences between the model compound 3.87 and xestoquinone 3.1 and halenaquinone 3.2. The target compound 3.87 does not contain a ketone (green) functional group at C3 and the D-ring quinone (blue) is simplified to a benzene ring.

The xestoquinone-related natural products make ideal targets for synthesis using the RCAR due to the presence of a benzyl-substituted furan structural element. This is highlighted in red on the target model compound (Scheme 3.8). The RCAR will enable product 3.88 to be formed from the thionocarbonate 3.89; this reaction involves simultaneous formation of two carbon-carbon bonds, a benzyl-substituted lactone (that can be simply converted to the furan) and the stereocentre at C6 is achieved. Thus, from a relatively simple thionocarbonate starting material, an advanced intermediate towards the natural product can be prepared.

Scheme 3.8. The RCAR as a key step in the synthesis of xestoquinone-like natural products.
The retrosynthetic plan for the model compound 3.87 is outlined in Scheme 3.9. This target can be accessed via a series of functional group interconversions from 3.88, the product resulting from the RCAR. The precursor for the radical reaction, thionocarbonate 3.89, can be prepared simply by two stepwise nucleophilic substitutions of thiophosgene (3.90) with alcohol 3.91 and naphthol (3.92). Thiophosgene (3.90) is commercially available, while the alcohol 3.91 and naphthol 3.92 can be prepared from commercially available starting materials.

The power in this plan lies in the application of the RCAR as the key step. The precursor for the RCAR, 3.89, can be prepared simply and in a modular fashion. Furthermore, this key step is positioned at a relatively late stage in the synthesis. These two features make the sequence highly convergent. This is advantageous as substrates for the key step can be screened more readily, which facilitates application of the same approach to similar natural products, with the least amount of modification of the synthetic sequence.

3.1.3. Project Objective

The intention of this study is to prepare the model compound 3.87, using the RCAR as a key step. Through the preparation of this compound we hope to confirm the suitability of this novel approach for the synthesis of xestoquinone-like natural products.
3.2. Results and Discussion

The proposed approach to the model compound 3.87 involves three main phases: (1) formation of thionocarbonate 3.88; (2) the radical carboxyarylation reaction to afford naphthyl-substituted lactone 3.89; and (3) functional group interconversions to the final target 3.87. The first two phases are straightforward and have been described in the introduction to this chapter. The approach for the final set of transformations requires further discussion.

3.2.1. Further Retrosynthetic Analysis

In the final series of functional group interconversions, the two requirements were to: (a) convert the five-membered lactone ring of 3.88 to a furan; and (b) to close ring B via incorporation of a carbonyl bridge between the furan and the naphthalene system (Figure Scheme 3.10).

![Scheme 3.10. Planned approach to model compound 3.87.](image)

3.2.1.1. Conversion of the Lactone to the Furan

Experimental procedures for the conversion of a lactone to a furan are not common in the literature. Previous studies carried out in the Sherburn group have revealed a three step sequence to convert a lactone to a furan, and it was anticipated that this process could be applied in this investigation. These steps are outlined in Scheme 3.11 and...
involve: (1) controlled reduction to the lactol 3.93; (2) elimination to access the dihydrofuran 3.94; and (3) dehydrogenation to form the furan 3.95.

![Scheme 3.11: Proposed strategy to convert the lactone 3.88 to furan 3.95.](image)

### 3.2.1.2. Closure of the B Ring

Closure of the six-membered B ring as depicted in Scheme 3.10 (i.e. 3.88 to 3.87) is a transformation that has thus far not been reported in the literature.

In this study, the intention was to use the functionality X of intermediate 3.96 to close the B ring, and two options were considered (Scheme 3.12). The first involved preparation of triflate 3.97, followed by a palladium catalysed carboxymethylation reaction to yield carbomethoxy-substituted naphthalene 3.98. The ring closing step involves deprotonation at the 2-position of the furan and intramolecular nucleophilic acyl substitution of the carboxylic acid derivative to yield the product 3.87.

The second option considered was a diversion of the first, in which the carbonylation and ring closing event occur in a single step. The carbonylation of 3.87 involves an acyl palladium intermediate, and it was anticipated that this may be able to undergo an intramolecular Heck reaction to the 2-position of the furan (or dihydrofuran ring) to close the B ring. Thus, triflates 3.97 or 3.99 may be converted to 3.87, via the acyl palladium intermediate 3.100. A carbonylative Heck coupling like this, between a dihydrofuran or furan and an aryl triflate, is unknown. Non-carbonylative coupling
reactions with iodides and furans\textsuperscript{105} or dihydrofurans\textsuperscript{106} have been reported, but are uncommon. In the Sherburn research group, preliminary attempts to perform this carbonylative-Heck reaction on similar systems were unsuccessful, however, these studies were not extensive.\textsuperscript{48} Due to the lack of a successful precedent for the second option, the nucleophilic acyl substitution approach was investigated.

The next decision focussed on what functional group (X on 3.96 in Scheme 3.12) would be carried through the RCAR. This was determined by the impact that it would have on the length and convergence of the synthetic sequence and also the effect it may have on the RCAR.

Since the intention was to close the B ring through a nucleophilic acyl substitution of the precursor 3.98 (Scheme 3.12), carrying the substituent (X = CO$_2$Me) on the naphthyl system through the RCAR would provide the most convergent route. The carbomethoxy compound 3.98 could be accessed from the triflate 3.97 via a palladium catalysed carbonylation. Consequently, carrying the triflate functional group through the
RCAR would be the next most convergent route. A less convergent route still, would involve carrying a protected naphthol (X = OP, P = protecting group) through the RCAR reaction. Following the radical reaction, this intermediate could be deprotected, converted to the triflate, and then carbonylated.

In this study, two different RCAR substrates 3.101 and 3.102 were targeted (Scheme 3.13). The carbomethoxy substrate 3.102 was selected as it would enable a significantly shorter sequence than the other option: This RCAR substrate could be prepared in the least number of steps, since the carbomethoxy-substituted naphthol, required for the preparation of 3.102, is commercially available. Furthermore, the radical product 3.98 would require the least manipulation following the RCAR to obtain the target model compound, making the sequence even more convergent.

![Scheme 3.13. Options for the final set of transformations following the RCAR.](image)

The methoxy containing precursor 3.101 was also selected, as this was considered to be a more reliable, albeit a longer option. Previously, RCARs have been performed on substrates containing ortho-methoxy or carbomethoxy substituted, monocyclic aryl systems, and consideration of all these results suggested that the methyl ether containing precursors give generally higher yields of the RCAR products. However, it is worth noting that the results are sometimes unpredictable, indicating that the RCAR is controlled by a number of factors, not only the nature of the ortho substituent. Furthermore, in this investigation a bicyclic aromatic system was to be used in place of a monocyclic aromatic, and this may affect the RCAR.
Previous studies in the Sherburn group have demonstrated that the RCAR can be performed successfully on a thionocarbonate derived from 2-naphthol through conversion of the thionocarbonate $\text{3.103}$ to lactone $\text{3.104}$ in an unoptimised 36% yield (Scheme 3.14).\textsuperscript{45} Two obvious differences exist, however, between this previously successful RCAR and the proposed $\text{3.102} \rightarrow \text{3.98}$ conversion: (a) substrate $\text{3.103}$ has a more activated styrene olefin acceptor, and (b) substrate $\text{3.102}$ has an additional carbomethoxy group at the 3-position of the naphthalene ring.

![Scheme 3.14. Reagents and conditions: (a) TTMSS, AIBN, C$_6$H$_{12}$, reflux, 36%.
](image)

The carbomethoxy route was investigated initially, since if successful, it would be much shorter than the methyl ether approach. As this investigation was the first trial, precursors were prepared as racemic mixtures.

### 3.2.2. The Carbomethoxy Approach

Before RCAR studies began on the carbomethoxy approach, a test reaction was carried out, whereby a substrate containing the O-naphthyl thionocarbonate to be used in the preparation of the model compound $\text{3.87}$ was exposed to TTMSS/AIBN. This substrate is derived from the primary alcohol $\text{2.32}$, a system that is known to undergo Barton-McCombie radical deoxygenation (Chapter 2).

Preparation of the test thionocarbonate is described in Scheme 3.15. Primary alcohol $\text{2.32}$ was treated with the chlorothionoformate $\text{3.105}$ (supplied by a colleague), in the presence of pyridine, to give the thionocarbonate $\text{3.106}$ in 75% yield. The thionocarbonate $\text{3.106}$ was treated with TTMSS and AIBN in refluxing benzene, resulting in radical deoxygenation to afford $\text{2.28}$ in 67% yield (determined by $^1$H NMR/internal standard). This result indicates that the naphthyl system does not interfere with the radical process.
With this result in hand, we confidently approached the targeted RCAR. The carbomethoxy-containing RCAR precursor 3.102 was prepared by a colleague from the primary alcohol (±)-3.191, and chlorothionoformate 3.105 (Scheme 3.16).

A number of attempts were made to convert thionocarbonate 3.102 to the RCAR product 3.98. Reaction conditions and reactants were varied, and each of these attempts is outlined in Table 3.1. Unfortunately, in all examples, none of the desired product was detected by analysis of crude reaction mixtures using ¹H NMR spectroscopy.
Table 3.1. Attempted RCARs of the carbomethoxy-containing precursor 3.102.

<table>
<thead>
<tr>
<th>entry</th>
<th>initiator</th>
<th>mediator</th>
<th>solvent</th>
<th>temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIBN (0.6 equiv)</td>
<td>Ph$_3$SiH$_2$ (1.3 equiv)</td>
<td>PhH</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>AIBN (0.6 equiv)</td>
<td>TTMSS (1.3 equiv)</td>
<td>PhH</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$B (1.5 equiv)</td>
<td>TTMSS (1.3 equiv)</td>
<td>EtOAc</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>AIBN (2 × 0.6 equiv)</td>
<td>HSnBu$_3$ (2 × 1.3 equiv)</td>
<td>PhH</td>
<td>80</td>
</tr>
</tbody>
</table>

In the first three entries, different silane radical mediators were used (diphenylsilane and TTMSS). The $^1$H NMR spectra of the crude reaction mixtures for these reactions consisted mainly of the starting material. Tributyltin hydride was also used as the chain carrier (entry 4). By adding another portion of the reagents, tributyltin hydride and AIBN, most of the starting material was consumed. $^1$H NMR spectroscopy of the crude reaction mixture indicated that a complex mixture of products had formed; however, chromatographic separation of this mixture did not yield any of the desired product. These results demonstrated that the carbomethoxy precursor 3.102 was not a suitable substrate for the radical carboxyarylation reaction.

The recovery of starting material in the reactions using silane mediators was unexpected. The only difference between the RCAR substrate 3.102 and the deoxygenation substrate 3.106 is the alcohol-derived portion. Since 3.106 undergoes smooth deoxygenation, addition of R$_3$Si$^-$ to the thiocarbonyl group must have occurred. The isolation of mainly unreacted precursor from entries 1-3 of Table 3.1 indicates that either: (a) the alcohol portion of 3.102 disfavours addition of R$_3$Si$^-$ to the thiocarbonyl group relative to that of 3.106, or (b) some unidentified inhibitor was present in the reactions of entries 1-3 in Table 3.1, which compromised a successful outcome. Further studies are necessary for a complete explanation of these results. In light of time constraints, an alternative synthetic approach was investigated.
3.2.3. The Methyl Ether Approach

Due to the lack of success encountered for the RCAR of the carbomethoxy-containing precursor 3.102, attention was shifted to the methyl ether route. The methyl ether containing precursor 3.101 could be obtained from two building blocks, the homoallylic alcohol 3.91 and the chlorothionoformate 3.107 (Scheme 3.17).

Scheme 3.17. Retrosynthetic analysis for the preparation of the methoxy containing precursor 3.101.

3.2.3.1. Preparation of the Homoallylic Alcohol

The homoallylic alcohol 3.113 has been prepared in a number of ways previously.\textsuperscript{108,109} The method reported by Inouye and co-workers involved conversion of m-toluic acid to the alcohol in six steps and low overall yield.\textsuperscript{108,110} In this study, a shorter approach from the same starting material was employed.

Synthesis of the homoallylic alcohol 3.91 is illustrated in Scheme 3.18, and commenced with a Birch reduction of m-toluic acid (3.108) to form diene 3.109. Esterification with ethanol yielded ester 3.110 in 93% yield over two steps. These first two steps were carried out by a colleague. In this study, selective reduction of the less-substituted double bond of 3.110 was achieved using Wilkinson’s catalyst and hydrogen to afford the alkene 3.111 in 97% yield. Reduction of this ethyl ester to the primary alcohol 3.91 was achieved using lithium aluminium hydride. The alcohol was obtained in four steps from commercially available materials in an overall yield of 84%.
Scheme 3.18. Preparation of the homoallylic alcohol 3.91. Reagents and conditions: (a) Li metal, NH₃, H₂O, 100%, (b) pTSA (10 mol%), EtOH, CHCl₃, Dean-Stark, 93%, (c) (PPh₃)₃RhCl (0.05 equiv), H₂, THF, rt, 97%, (d) LiAlH₄ (2.5 equiv), Et₂O, 0 °C, 93%.

3.2.3.2. Preparation of the Radical Carboxyarylation Reaction Precursor

The RCAR precursor 3.101 was prepared as illustrated in Scheme 3.19. 2,3-Dihydroxynaphthalene (3.112) was used to prepare the mono-protected naphthol 3.113 in 65% yield, via a SN₂ substitution of iodomethane. Naphthol 3.113 was converted into the corresponding chlorothionoformate 3.107 in 96% yield, by nucleophilic substitution of thiophosgene. The thionocarbonate was prepared in 86% yield by thioacylation of alcohol 3.91 by chlorothionoformate 3.107 in the presence of pyridine.
Chapter 3 – Results and Discussion

Scheme 3.19. Preparation of RCAR substrate 3.101. Reagents and conditions: (a) Mel (1.0 equiv), K$_2$CO$_3$ (1.0 equiv), acetone, reflux, 65%; (b) NaOH (1.05 equiv), C$_5$H$_5$N(1.0 equiv), $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, 0 °C – rt, 96%; (c) alcohol (1.0 equiv), chlorothionoformate (1.1 equiv), pyridine (2.0 equiv), CHCl$_3$, rt, 86%.

3.2.3.3. The Radical Carboxylation Reaction

Initially, reaction conditions based upon those previously optimised in the Sherburn group were employed to carry out a RCAR of thionocarbonate 3.101 (Scheme 3.20). TTMSS (1.1 equiv) and AIBN (0.5 equiv) were added to a 0.02 M solution of thionocarbonate in refluxing benzene over 5 hours. The desired product 3.114 was isolated in 32% yield.

Scheme 3.20. Reagents and conditions: (a) TTMSS (1.1 equiv), AIBN (0.5 equiv), PhH, reflux, 6 h, slow addition of reagents, 32%.

In an attempt to improve the yield of the RCAR product 3.114, a series of experiments were undertaken, changing the following variables: reagent and substrate concentration,
azo-initiator; and reaction temperature/solvent. The results of this optimisation study are displayed in Table 3.2.

Table 3.2. Optimising the yield for the RCAR of 3.101

<table>
<thead>
<tr>
<th>entry</th>
<th>initiator</th>
<th>solvent &amp; [reactant] (M)</th>
<th>time (m)</th>
<th>3.101 (3.114 (% yield)$^a$</th>
<th>3.114 (% yield)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIBN</td>
<td>PhH 0.02</td>
<td>150</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>AIBN</td>
<td>PhH 0.07</td>
<td>150</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>AIBN</td>
<td>PhCl 0.07</td>
<td>60</td>
<td>not detected</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>ACN</td>
<td>PhCl 0.07</td>
<td>60</td>
<td>not detected</td>
<td>39</td>
</tr>
</tbody>
</table>

$^a$ % yield determined using $^1$H NMR spectroscopy.

The product yields were determined using an internal standard (butadiene sulfone) and $^1$H NMR spectroscopy of crude reaction mixtures (unless otherwise stated). This method enabled quick and accurate comparison of reaction conditions. Comparing isolated yields for these reactions would have been imprecise, as purification of the reaction mixtures was complicated by the presence of by-products and silane impurities.

In previous investigations, the optimum reaction concentration of 0.02 M and slow addition of reagents was employed for RCARs. It was supposed that these dilute reaction conditions would disfavour hydrogen abstraction, by reaction intermediates, from the radical mediator TTMSS. In this study, two reaction concentrations were tested, = 0.02 M, and 0.07 M (Table 3.2, entries 1 and 2 respectively). As this concentration difference had little effect on the yield of the deoxygenation product, subsequent studies were performed with the higher concentration (in relation to solvent use) of 0.07 M.

In an attempt to increase the rate of the cyclisation steps in the RCAR, higher reaction temperatures were employed. Changing the reaction solvent from benzene to
chlorobenzene allowed the temperature to be increased to 132 °C. The effect of this modification is evident through comparison of the results in entries 2 and 3 (Table 3.2). The reaction in benzene (entry 2) did not go to completion, and after 2.5 h, 15% of starting material 3.101 was detected along with 21% of product 3.120 (1H NMR). In comparison, the reaction using chlorobenzene went to completion, and in less than 1 h, 30% (1H NMR) of the RCAR product was detected.

Two different azo-radical initiators, AIBN and 1,1'-azobis(cyclohexanecarbonitrile) (ACN) were examined. ACN has a longer half-life than AIBN and therefore at higher reaction temperatures this reagent will not decompose as quickly. When using ACN, instead of AIBN, in refluxing chlorobenzene (Table 3.2, entries 3 and 4), the yield of RCAR product 3.114 was determined to be 39% (1H NMR). This was the best result so far, and these conditions were applied to the synthesis. When the reaction was scaled up (using approx. 3 g of starting material) the product was isolated in 37% yield.

3.2.3.4 Final Transformations

With the RCAR product in hand, the final set of functional group transformations was performed. Firstly, the lactone required to be converted into the furan, and then the B ring required to be closed through incorporation of a carbonyl bridge.

The first step to convert the RCAR product, lactone 3.114, to the furan 3.115 was reduction to afford the lactol 3.116 (Scheme 3.22). In order to achieve this transformation, the reducing agent DIBAL-H was employed at low reaction temperatures. As the tetrahedral dialkylaluminium alkoxide intermediate that is formed using this reagent is stable at low temperature, over reduction of the lactone can be minimised. Reproducible results were obtained by maintaining the reaction temperature below -90 °C. The lactol 3.116 was isolated in 85% yield as a mixture of two diastereomers.

Elimination of water from lactol 3.116 was facilitated by formation of the mesylate in situ. Experiments were initially performed by addition of the reagents at -78 °C, followed by warming to room temperature. However, incomplete conversion of the lactol was observed. It was possible that formation of the mesylate was occurring, but the elimination step was not going to completion. The starting material – detected by 1H
NMR analysis of crude reaction mixtures – might then be the result of hydrolysis of the mesylate upon aqueous work-up. In an attempt to push the elimination to completion, the reaction temperature was increased. Addition of the reagents at 0 °C followed by heating to 40 °C permitted full conversion of the lactol and isolation of the elimination product \(3.117\) in 72% yield. Finally, oxidation of the dihydrafuran \(3.117\) to the furan \(3.115\) was achieved in 81% yield, using 2,3-dichloro-5,6-dicyano-1-benzoquinone (DDQ) in toluene at reflux (Scheme 3.21).

The final set of transformations would involve conversion of \(3.115\) into \(3.87\). The first step of this sequence involves removal of the methyl ether protecting group. Initially, boron tribromide was trailed, however, \(^1\)H NMR spectroscopy of the crude reaction mixture indicated that the starting material was consumed and that no naphthol was produced. Next, deprotection using sodium ethanethiolate was investigated. This had been used previously in the Sherburn group for deprotection of a similar system. A test-scale reaction using this reagent looked promising; the reaction mixture contained only starting material and phenol. The reaction was repeated and left for a longer period of time, and while this led to the full consumption of starting material, only 46% of the deprotected product, naphthol \(3.118\), was isolated. Due to time constraints this deprotection was not optimised. In the following step, naphthol \(3.118\) was converted...
into triflate 3.119 in 81% yield using the triflating agent N-phenyltrifluoromethanesulfonamide. This sequence of reactions is outlined in Scheme 3.22.

![Scheme 3.22](image)

Reagents and conditions: (a) EtSH (3 equiv), NaH (3.1 equiv), DMF, 46%; (b) PhNTf₂ (1.7 equiv), Et₃N (20 equiv), acetonitrile, reflux, 81%.

Next, the triflate of 3.119 required conversion to the carbomethoxy group using a palladium-catalysed carboxymethylation reaction. Most commonly, the transformation of naphthyltriflates is effected by palladium acetate, dppp, a trialkylamine base, under a carbon monoxide atmosphere (in most cases 1 atm is sufficient), and in a mixture of methanol and DMF or DMSO. The reactions are also generally heated to at least 60 °C.

Using conditions based on those commonly documented in the literature, attempts were made to carboxymethylate the triflate 3.119 (Scheme 3.23). The reaction conditions trialled involved Pd(OAc)₂ (0.1 equiv), dppp (0.1 equiv), carbon monoxide, Hüning's base in methanol and DMF. The reaction temperature and method of introducing carbon monoxide were altered in an attempt to obtain the desired product 3.120. Carbon monoxide was introduced using either a balloon or the reactions were performed in a sealed tube purged with carbon monoxide. In each case the reactions were performed between 25 - 35 °C or 90 - 100°C. Disappointingly, the crude ¹H NMR spectrum of the reactions revealed a complex mixture of products, which contained no peak corresponding to the methoxy protons of the product 3.120. An effort to isolate any by-products, using flash chromatography on silica gel, was unsuccessful.
Unfortunately, due to insufficient time, the carbonylation of the triflate 3.119 was not achieved. This reaction has not been extensively investigated and it is possible that a more widespread screening of conditions and reagents may overcome this problem.

The difficulties encountered in trying to carbonylate triflate 3.119 may be due to steric congestion. Carbonylation reactions are known to be very sensitive to steric hindrance due to the geometric requirements for coordination of carbon monoxide to palladium. Increasing the carbon monoxide pressure may alleviate this problem. If the carbonylation of 3.119 still proves to be problematic, it may be necessary to reorder the synthetic sequence to perform the carbonylation step on an earlier intermediate. The precedent for this is the carbonylation of precursor 3.121 to give 3.122 in 71% yield (Scheme 3.24). This precursor is similar to that used in this study (triflate 3.119), except that it contains a lactone ring instead of a furan ring, and an indanone instead of the naphthyl ring system.

Scheme 3.23. Attempted carbonylation of 3.120. Reagents and conditions: (a) Pd(OAc)$_2$ (0.1 equiv), dppp (0.1 equiv), i-$\text{Pr}_2$NEt, CO, MeOH and DMF. See text for further details.

Scheme 3.24. Reagents and conditions: (a) Pd(OAc)$_2$, dppp, i-$\text{Pr}_2$EtN, CO, MeOH, DMF, sealed tube, 60 °C, 71%.
3.3. **Conclusions and Future Work**

Considerable progress has been made toward the synthesis of the model compound 3.87 (Scheme 3.25). Thionocarbonate 3.101 was prepared in 6 steps and 69% overall yield from commercially available starting materials. The key radical step afforded the advanced intermediate 3.114 in 37% yield. In three steps, and 50% yield, the radical product was transformed into the furan-containing intermediate 3.115. Deprotection followed by incorporation of the triflate functional group yielded the intermediate 3.119. Unfortunately, preliminary efforts to carbonylate the triflate to give the precursor 3.120, necessary to close the final ring by a nucleophilic acyl substitution, were unsuccessful.

![Scheme 3.25: Progress toward the synthesis of the model compound 3.87.](image)

3.3.1. **Problems Encountered with the Current Approach**

While most of these steps performed toward the synthesis of 3.87 were high yielding, there is room for improvement. The deprotection of the methyl ether 3.124 was
particularly low yielding. If optimisation of this reaction is not possible, alternative protecting groups will need to be considered.

The other low yielding step of this sequence is the RCAR. Studies in the Sherburn group investigating this reaction are ongoing. As this process is more thoroughly understood, the yields for this reaction may be improved. Furthermore, by comparing the RCAR results presented in this study with those obtained previously,\textsuperscript{43,48,107} it is apparent that the success of the RCAR is highly substrate-dependent. Consequently, is it feasible that when working with the actual system for the xestoquinone related natural products, or even using different substituents on the naphthalene system, the yield for the RCAR may be altered significantly. Similarly, the carbomethoxy functionality may be tolerated in the syntheses of the natural products, which would allow a more direct approach.

### 3.3.2. Application of the Approach to Xestoquinone-like Natural Products

A few minor modifications of the approach presented in this study would enable its application to the synthesis of xestoquinone. The RCAR is completely diastereoselective therefore, by incorporation of the correct absolute stereochemistry in the substrate for this step it would enable an asymmetric synthesis. In order to do this, an enantioselective preparation or resolution of the alcohol 3.91 is required.

A possible way to prepare the alcohol in an enantiomerically enriched form is based on a synthesis described in a patent.\textsuperscript{109} Thus, racemic alcohol 3.81 was prepared in two steps from the commercially available enone 3.123. A Wittig reaction of the ketone 3.123 afforded the conjugated diene 3.124, and regioselective hydroboration of the exocyclic alkene afforded the desired alcohol 3.81. It is possible that enantioselective hydroboration may be employed in the latter step to form the desired enantioenriched alcohol (S)-3.81 (Scheme 3.26). This sequence to prepare the alcohol 3.81 is also shorter than the one described in the present study.
The sequence also needs to be altered to incorporate the quinone (or other) D ring structure in the natural products. In the case of xestoquinone or halenaquinone, for example, it was briefly considered that the D ring of the naphthalene system in the model compound $\text{3.87}$ could be oxidized to access the ring system found in the natural products directly (Scheme 3.27). Thus, from the model compound $\text{3.87}$, xestoquinone $\text{3.1}$ could be obtained in one step. However, previous efforts suggest that this may not be a feasible pathway. Alternatively, the naphthoquinone group would require protection (as the dimethoxy naphthalene for example) throughout the synthesis, and a final oxidation, of an advanced intermediate such as $\text{3.125}$, would yield the desired product. This method was utilised in all the syntheses of xestoquinone and halenaquinone reported in the literature.

Scheme 3.27. Options that were considered for incorporation of the quinone ring of xestoquinone.

A modified retrosynthetic plan required for the synthesis of ($\pm$)-xestoquinone (3.1) is illustrated in Scheme 3.28. The natural product could be accessed by oxidation of the hydroquinone dimethyl ether $\text{3.125}$. This intermediate would be accessed from the radical carboxyarylation product $\text{3.126}$, which is obtained diastereoselectively from the
thionocarbonate 3.127. The thionocarbonate is derived from the three components 3.128, (S)-3.91 and thiophosgene. Alcohol (S)-3.91 could be obtained from 3.123 in two steps. The required protected hydroquinone 3.128 could be prepared from the quinone 3.129, which in turn could be accessed from the cycloaddition reaction of diene 3.130 and quinone 3.131. Alternatively the required dihydroxynaphthalene 3.128 (X = OH) may be accessed from commercially available 6,7-dimethoxy-1-tetralone 3.132.

Scheme 3.28. Second generation retrosynthetic analysis for (+)-xestoquinone (3.1).
Chapter 4 – General Synthetic Methods

4. Experimental

4.1. General Synthetic Methods

Reactions were performed under a positive pressure of dry argon or nitrogen in flame-dried glassware with stirring, unless otherwise stated. Toluene was dried over sodium wire and distilled before use. Dichloromethane was distilled from calcium hydride. Commercially available chemicals were purified by standard procedures or used as purchased. Magnesium sulfate was dried at 110 °C for 24 h prior to use. Analytical thin layer chromatography (TLC) was performed with Merck (A.T. 5554) silica gel 60 F254 (0.2 mm) pre-coated on aluminium sheets. Compounds were first visualized under UV light (254 nm) followed by treatment with alkaline potassium permanganate or vanillin dips and developed by strong heating. Flash chromatography employed Merck Kieselgel 60 (230–400 mesh) silica gel or SDS silica 60 ACC (40–63 μm) Chromagel silica gel.

NMR spectra were recorded at 298 K using Varian INOVA 500 or Varian INOVA 300 spectrometer. Residual chloroform (δ = 7.26) and benzene (δ = 7.15) were used as internal references for 1H NMR spectra measured in these solvents. The central peak of the deuterochloroform triplet (δ = 77.0) was used as the internal reference for 13C NMR spectra. 1H NMR signals are described in terms of chemical shifts, intensity and multiplicity (the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiple and br, broad) and coupling constants. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer as neat films on NaCl plates or as KBr disks. Mass spectra were recorded by the Mass Spectrometry Facility of the Research School of Chemistry, Australian National University, Canberra on a VG Autospec M series sector (EVE) MS for EI, VG Quattro II triple quadrupole MS for LR ESI and Bruker Apex3 4.7TFTICR-MS for HR ESI. Melting points were measured on a Reichert hot stage melting apparatus or using an automated melting point apparatus, Optimelt – Automated Melting Point System (Stanford Research Systems), and are uncorrected.
4.2. General Procedures

4.2.1. Preparation of Thionocarbonate Derivatives

Scheme 4.1. General synthesis of thionocarbonates. Reagents and conditions: (a) NaOH (1.05 equiv), CSCl₂ (1.0 equiv), CH₂Cl₂/H₂O; (b) arylchlorothionoformate (1.1 equiv), alcohol (1.0 equiv), pyridine (2.0 equiv), CH₂Cl₂.

4.2.1.1. General procedure #1

Arylchlorothionoformates were prepared in a similar manner to that described in the literature. The phenol (1.0 equiv) was dissolved in a 5 M NaOH (1.1 equiv) solution, diluted 4 × with water and transferred (drop-wise via cannula over 5 min) to a stirred 1.5 M solution of thiophosgene (1.0 equiv) in CH₂Cl₂, cooled at 0 °C. The mixture was left to warm to rt, and after 1-2 h was diluted with CH₂Cl₂ and water. The layers were separated and the aq layer was extracted with CH₂Cl₂ (3 ×). Combined organic extracts were washed sequentially with sat. aq NaHCO₃, water and brine, and then dried (MgSO₄). The solvent was removed in vacuo to yield the crude product, which was used without further purification (unless otherwise stated).

4.2.1.2. General Procedure #2

To a solution of the alcohol and pyridine (2.0 equiv) in CH₂Cl₂ (0.1 M) was added the arylchlorothionoformate (1.1 equiv) as a solution in CH₂Cl₂ (approx. 2.5 M). After stirring for 4 to 15 h the reaction was diluted with CH₂Cl₂; washed sequentially with aq 1M HCl, sat. aq NaHCO₃, and brine; and dried (MgSO₄). The solvent was removed in vacuo to afford the crude material, which was purified using flash chromatography.
4.3. Chapter 2 - Experimental

4.3.1. Preparation of Deoxygenation Substrates

4.3.1.1. Preparation of Methyl 4-vinyl-benzoate

Methyl 4-vinyl-benzoate (2.31): The commercially available olefin was prepared, according to the literature procedure, by a Wittig reaction between methyltriphenylphosphonium bromide (15.830 g, 44.3 mmol, 1.0 equiv) and methyl 4-formyl-benzoate (2.29) (7.270 g, 44.3 mmol, 1.0 equiv). The alkene 2.31 was obtained as a colourless solid (5.450 g, 76%). Spectroscopic data for this compound corresponded to that quoted in the literature;¹¹⁶ mp 32.1–34.0 °C (lit. 33–34.5 °C)¹¹⁸; ¹H NMR (300 MHz, CDC₃): δ 7.99 (2H, dm, J = 8.4 Hz), 7.46 (2H, dm, J = 8.4 Hz), 6.75 (1H, dd, J = 17.4, 10.8 Hz), 5.86 (1H, d, J = 17.4 Hz), 5.38 (1H, d, J = 10.8 Hz), 3.91 (3H, s) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 166.9, 141.8, 135.9, 129.8, 129.2, 126.1, 116.5, 52.1 ppm; MS (70 eV, El): m/z (%): 162 (57) [M]+, 131 (100); HRMS (70 eV, El): calcd for C₁₀H₁₀O₂ [M]: 162.0681; found 162.0679.

Methyl 4-(2-hydroxyethyl)benzoate (2.32): The primary alcohol was prepared from the olefin 2.31 (2.090 g, 12.8 mmol) using a hydroboration procedure that was modified from the literature.¹¹⁹ The alcohol 2.32 was obtained as a colourless oil (1.742 g, 76%). Spectroscopic data for this compound corresponded to that quoted in the literature;¹¹⁹ ¹H NMR (300 MHz, CDCl₃): δ 7.91 (2H, dm, J = 8.1 Hz), 7.24 (2H, dm, J = 8.1 Hz), 3.84 (3H, s), 3.80 (2H, t, J = 6.6 Hz), 2.85 (2H, t, J = 6.6 Hz), 2.50 (1H, brs) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 167.0, 144.2, 129.6, 128.9, 128.0, 62.9, 51.9, 38.9 ppm; MS (70 eV, El): m/z (%): 180 (75) [M]+, 150 (100), 149 (97); HRMS (70 eV, El): calcd for C₁₀H₁₃O₃ [M]+: 180.0786; found 180.0785.

4.3.1.2. Synthesis of Arylchlorothionoformates:

O-4-Methoxyphenyl chlorothionoformate (2.33): The title compound was prepared, according to the General Procedure #1, from 4-methoxyphenol (2.30) (2.269 g,
18.3 mmol). The arylchlorothionoformate 2.33 was obtained as a yellow oil (3.432 g, 93%). Spectroscopic data for this compound corresponded to that quoted in the literature;\(^\text{1}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.06 (2H, dm, \(J = 6.9 \text{ Hz}\)), 6.95 (2H, dm, \(J = 6.9 \text{ Hz}\)), 3.82 (3H, s) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 186.4, 158.2, 148.4, 121.0, 114.7, 55.6 ppm; MS (70 eV, EI): \(m/z\) (%): 202 (35) [M\(^+\)], 139 (100), 123 (90); HRMS (70 eV, EI): calcd for C\(_3\)H\(_7\)ClO\(_2\)S [M\(^+\)]: 201.9855; found 201.9855.

\[\text{O-2,4,6-Trimethoxyphenyl chlorothionoformate (2.38a):}\]
The title compound was prepared, using General Procedure #1, from 2,4,6-trimethoxyphenol (1.516 g, 8.2 mmol). Purification of the crude material by flash chromatography, eluting with EtOAc:hexanes (15:85), afforded 2.38a as a yellow solid (1.715 g, 79%); mp 73.3–73.8 °C; R\(_t\) 0.4 EtOAc/hexanes (15:75); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.38 (2H, s), 3.85 (3H, s), 3.84 (6H, s) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 185.6, 153.8, 136.7, 98.5, 61.0, 56.3 ppm; IR (KBr disc) \(v = 2942, 2837, 1609, 1503 \text{ cm}^{-1}\); MS (70 eV, EI): \(m/z\) (%): 262 (85) [M\(^+\)], 247 (18), 183 (90), 168 (72); HRMS (70 eV, EI): calcd for C\(_{10}\)H\(_{11}\)ClO\(_4\)S [M\(^+\)]: 262.0067; found 262.0063; elemental analysis calcd for C\(_{10}\)H\(_{11}\)ClO\(_4\)S: C 45.72, H 4.22, Cl 13.50, S 12.20; found: C 45.76, H 4.35, Cl 13.53, S 11.98.

\[\text{O-Phenyl chlorothionoformate (2.38b):}\]
This commercially available compound was prepared, using General Procedure #1, from phenol (2.010 g, 21.4 mmol). The arylchlorothionoformate 2.38b was obtained as a yellow oil (3.201 g, 87%); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.50-7.44 (2H, m), 7.39–7.33 (1H, m), 7.20-7.15 (2H, m) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 185.7, 155.0, 129.9, 127.3, 121.0 ppm; IR (thin film) \(v = 3060, 1487, 1243, 1180, 1153 \text{ cm}^{-1}\); MS (70 eV, EI): \(m/z\) (%): 172 (8) [M\(^+\)], 137 (58), 77 (100); HRMS (70 eV, EI): calcd for C\(_7\)H\(_5\)ClO\(_2\)S [M\(^+\)]: 171.9755; found 171.9757.
O-2,4,6-Trichlorophenyl chlorothionoformate (2.38d): The title compound was prepared, using General Procedure #1, from 2,4,6-trichlorophenol (2.010 g, 10.2 mmol). The arylchlorothionoformate 2.38c was obtained as a yellow oil (2.270 g, 81%). Spectroscopic data for this compound corresponded to that quoted in the literature: \[ R_f \text{ 0.66 EtOAc/hexanes (5:95); } \] \[ ^1H \text{ NMR (300 MHz, CDCl}_3): \delta 7.42 (2H, s) \text{ ppm; } \] \[ ^13C \text{ NMR (75 MHz, CDCl}_3): \delta 181.9, 145.7, 133.5, 129.2, 129.0 \text{ ppm; IR (thin film) } \nu = 3080, 1569, 1443, 1217, 1138 \text{ cm}^{-1}; \] MS (70 eV, EI): \[ m/z (%) : 276 (6) [M]^+, 241 (30), 79 (100); \] HRMS (70 eV, EI): calcd for C\textsubscript{13}H\textsubscript{9}Cl\textsubscript{3}O\textsubscript{3}S [M]^+: 275.8551; found 275.8555.

4.3.1.3. Synthesis of Thionocarbonates

Methyl 4-{2-[(4-methoxyphenoxy)carbonothioyloxy]ethyl}benzoate (2.26): The title compound was prepared, using General Procedure #2, from alcohol 2.32 (292 mg, 1.6 mmol) and arylchlorothionoformate 2.33 (362 mg, 1.8 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with Et\textsubscript{2}O/CH\textsubscript{2}Cl\textsubscript{2}/hexanes (5:20:75), afforded 2.26 as a colourless solid (562 mg, 85%); recrystallisation with CH\textsubscript{2}Cl\textsubscript{2}/hexanes gave colourless needles mp 90.8–91.3 °C; \[ R_f \text{ 0.60 EtO/hexanes (50:50); } \] \[ ^1H \text{ NMR (300 MHz, CDCl}_3): \delta 8.00 (2H, dm, } J = 8.1 \text{ Hz), 7.28 (2H, dm, } J = 8.1 \text{ Hz), 6.99 (2H, dm, } J = 9.3 \text{ Hz), 6.90 (2H, dm, } J = 9.3 \text{ Hz), 4.73 (2H, t, } J = 6.9 \text{ Hz), 3.91 (3H, s), 3.80 (3H, s), 3.18 (2H, t, } J = 6.9 \text{ Hz) ppm; } \] \[ ^13C \text{ NMR (75 MHz, CDCl}_3): \delta 195.3, 166.8, 157.6, 146.8, 142.3, 129.8, 128.9 128.7, 122.5, 114.3, 73.5, 55.4, 52.0, 34.4 \text{ ppm; IR (KBr disc) } \nu = 2952, 1714, 1607, 1506 \text{ cm}^{-1}; \] MS (70 eV, EI): \[ m/z (%) : 346 (8) [M]^+, 163 (80), 49 (100); \] HRMS (70 eV, EI): calcd for C\textsubscript{18}H\textsubscript{18}O\textsubscript{5}S [M]^+: 346.0875; found 346.0880; elemental analysis calcd for C\textsubscript{18}H\textsubscript{18}O\textsubscript{5}S: C 62.41, H 5.24, S 9.26; found: C 62.47, H 5.30, S 9.23.
Methyl 4-{2-[(2,4,6-trimethoxyphenoxy)carbonothioyloxy]ethyl}benzoate (2.37a):
The title compound was prepared, using General Procedure #2, from alcohol 2.32
(257 mg, 1.4 mmol) and arylchlorothionoformate 2.38a (401 mg, 1.5 mmol, 1.1 equiv).
Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes
(30:70), afforded 2.37a as a pale yellow oil (413 mg, 71%); Rf 0.3 EtOAc/hexanes
(30:70); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.90 (2H, dm, J = 8.4 Hz), 7.23 (2H, dm,
J = 8.4 Hz), 6.21 (2H, s), 4.63 (2H, t, J = 6.9 Hz), 3.81 (3H, s), 3.74 (3H, s), 3.71 (6H,
s), 3.08 (2H, t, J = 6.9 Hz) ppm; \(^1^3\)C NMR (75 MHz, CDCl\(_3\)): δ 194.6, 166.8, 153.4,
149.1, 142.3, 136.1, 129.8, 129.0, 128.8, 99.3, 73.6, 60.9, 56.1, 52.0, 34.5 ppm;
IR (thin film) v = 2924, 1718, 1607, 1498 cm\(^{-1}\); MS (70 eV, EI): m/z (%): 406 (90)
[M]+, 375 (8), 163 (100); HRMS (70 eV, EI): calcd for C\(_{20}\)H\(_{22}\)O\(_7\)S [M]+: 406.1086;
found 406.1085.

Methyl 4-{2-(phenoxycarbonothioyloxy)ethyl}benzoate (2.37b):
The phenoxythionocarbonate compound was prepared, using General Procedure #2, from
2.32 (245 mg, 1.36 mmol) and arylchlorothionoformate 2.38b (285 mg, 1.7 mmol, 1.2 equiv).
Purification of the crude material by flash chromatography, eluting with
Et\(_2\)O/CH\(_2\)Cl\(_2\)/hexanes (10:15:75), afforded 2.37b as a colourless solid (302 mg, 70%);
re-crystallisation with CH\(_2\)Cl\(_2\)/hexanes gave colourless rectangular prisms mp
84.0–84.5 °C; Rf 0.3 EtOAc/hexanes (10:80); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.00
(2H, dm, J = 8.4 Hz), 7.45-7.38 (2H, m), 7.33 (2H, dm, J = 8.4 Hz), 7.30-7.27 (1H, m),
7.12-7.04 (2H, m), 4.74 (2H, t, J = 6.9 Hz), 3.92 (3H, s), 3.19 (2H, t, J = 6.9 Hz) ppm;
\(^1^3\)C NMR (75 MHz, CDCl\(_3\)): δ 194.8, 166.9, 153.2, 142.3, 129.9, 129.5, 129.0, 128.8,
126.5, 121.8, 73.7, 52.1, 34.5 ppm; IR (KBr disc) v = 2947, 1718, 1491 cm\(^{-1}\);
MS (70 eV, EI): m/z (%): 316 (1) [M]+, 163 (95), 162 (100), 131 (78); HRMS (70 eV, EI):
calcd for C\(_{17}\)H\(_{16}\)O\(_4\)S [M]+: 316.0769; found 316.0775; elemental
analysis calcd for C\(_{17}\)H\(_{16}\)O\(_4\)S: C 64.54, H 5.10, S 10.13; found: C 64.65, H 5.21,
S 10.31.
Methyl 4-(2,4,6-trichlorophenoxy)carbonothioyoxyethyl)benzoate (2.37c): The title compound was prepared, using General Procedure #2, from 2.32 (220 mg, 1.2 mmol) and arylchlorothionoformate 2.38c (380 mg, 1.4 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (5:95 to 10:90), afforded 2.37c as a colourless solid (447 mg, 88%); recrystallisation with CH₂Cl₂/hexanes gave colourless cubes mp 100.8-101.3 °C; Rf 0.3 EtOAc/hexanes (10:90); \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 8.00 (2H, dm, \(J = 8.4\) Hz), 7.38 (2H, s), 7.34 (2H, dm, \(J = 8.4\) Hz), 4.80 (2H, t, \(J = 6.9\) Hz), 3.92 (3H, s) 3.22 (2H, t, \(J = 6.9\) Hz) ppm; \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta\) 191.0, 166.9, 144.5, 141.9, 132.5, 129.9, 129.8, 129.0, 128.9, 128.8, 74.6, 52.1, 34.4 ppm; IR (KBr disc) \(\nu = 2948, 1712, 1570\) cm\(^{-1}\); MS (70 eV, EI): \(m/z\) (%): 387 (4) [M-OCH₃], 163 (100), 162 (75); HRMS (ESI): calcd for C₁₇H₁₃Cl₂O₄SNa [M+Na]^+: 440.9498; found 440.9511; elemental analysis calcd for C₁₇H₁₃Cl₂O₄S: C 48.65, H 3.12, S 7.64, Cl 25.34; found: C 48.42, H 3.32, S 7.56, Cl 25.57.

Methyl 4-(2-(4-fluorophenoxy)carbonothioyoxyethyl)benzoate (2.37d): The title compound was prepared, using General Procedure #2, from 2.32 (200 mg, 1.1 mmol) and the commercially available 4-fluorophenyl chlorothionoformate 3.38d (240 mg, 1.3 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with Et₂O/CH₂Cl₂/hexanes (10:20:70), afforded 2.37d as a colourless solid (296 mg, 77%); recrystallisation with CH₂Cl₂/heptane gave colourless rectangular prisms mp 116.0-116.7 °C; Rf 0.4 Et₂O/CH₂Cl₂/hexanes (10:20:70); \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 8.01 (2H, dm, \(J = 8.7\) Hz), 7.34 (2H, dm, \(J = 8.7\) Hz), 7.12-7.00 (4H, m), 4.74 (2H, t, \(J = 6.9\) Hz), 3.92 (3H, s), 3.19 (2H, t, \(J = 6.9\) Hz) ppm; \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta\) 194.9 (\(J_{C-F} = 1.1\) Hz), 166.9, 160.6 (d, \(J_{C-F} = 244.2\) Hz), 149.1 (d, \(J_{C-F} = 2.8\) Hz) 142.2, 129.9, 129.0, 128.8, 123.4 (d, \(J_{C-F} = 8.4\) Hz), 116.2 (d, \(J_{C-F} = 23.9\) Hz), 73.8, 52.1, 34.5 ppm; IR (KBr disc) \(\nu = 2957, 1722, 1503\) cm\(^{-1}\); MS (ESI): \(m/z\) (%): 357 (50) [M+Na]^+, 163 (75), 131 (100); HRMS (ESI): calcd for
Methyl 4-{2-[(perfluorophenoxy)carbonothioyloxy]ethyl}benzoate (2.37e): The title compound was prepared, using General Procedure #2, from 2.32 (189 mg, 1.0 mmol) and the commercially available pentafluorophenyl chlorothionoformate (314 mg, 1.2 mmol, 1.2 equiv). Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (7:93), afforded 2.38e as a colourless solid (340 mg, 78%); re-crystallisation with CH₂Cl₂/heptane gave colourless rectangular prisms mp 83.0–83.4 °C; Rf 0.3 EtOAc/hexanes (10:80); ¹H NMR (300 MHz, CDCl₃): δ 8.02 (2H, dm, J = 8.7 Hz), 7.34 (2H, dm, J = 8.7 Hz), 4.78 (2H, t, J = 6.9 Hz), 3.91 (3H, s), 3.22 (2H, t, J = 6.9 Hz) ppm; ¹³C (150 MHz, CDCl₃): δ 191.6, 166.8, 141.7, 141.1 (dm, J'ₐ-C-F = 251.6 Hz), 140.0 (dm, J'ₐ-C-F = 252.8 Hz), 138.0 (dm, J'ₐ-C-F = 251.1 Hz), 130.0, 129.1, 129.0, 127.4 (m), 75.5, 52.1, 34.4 ppm; IR (KBr disc) ν = 2958, 1713, 1611, 1520 cm⁻¹; MS (70 eV, EI): m/z (%) 375 (8) [M-CH₃]⁺, 163 (83), 162 (100), 131 (90); HRMS (ESI): calcd for C₁₇H₁₅F₆O₄SNa [M+Na]⁺: 429.0196; found 429.0174; elemental analysis calcd for C₁₇H₁₁F₅O₄S: C 50.25, H 2.73, F 23.38, S 7.89; found: C 50.42, H 2.76, F 23.52, S 7.89.

O-4-Methoxyphenyl O-phenethyl carbonothioate (2.50b): The title compound was prepared, using General Procedure #2, from alcohol 2.50a (310 mg, 2.5 mmol) and arylchlorothionoformate 2.33 (560 mg, 2.7 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (10:90), afforded 2.50b as a colourless solid (578 mg, 80%); recrystallisation with CH₂Cl₂/hexanes gave colourless cubes mp 59.6–60.3 °C; Rf 0.6 EtOAc/hexanes (15:85); ¹H NMR (300 MHz, CDCl₃): δ 7.42-7.28 (5H, m), 7.05 (2H, dm, J = 9.0 Hz), 6.95 (2H, dm, J = 9.0 Hz), 4.77 (2H, t, J = 7.0 Hz), 3.03 (3H, s), 3.18 (2H, t, J = 7.0 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 195.4, 157.6, 146.8, 136.8, 128.9, 128.5, 126.7, 122.5, 114.3, 74.3, 55.4, 34.5
ppm; IR (KBr disc) ν = 2959, 1503 cm⁻¹; MS (70 eV, EI): m/z (%): 288 (7) [M⁺], 124 (54), 105 (100); HRMS (70 eV, EI): calcd for C₁₆H₁₀O₅S [M⁺]: 288.0820; found 288.0820; elemental analysis calcd for C₁₆H₁₀O₅S: C 66.64, H 5.59, S 11.12; found: C 66.41, H 5.51, S 11.00.

**O-4-Methoxyphenyl O-octadecyl carbonothioate (2.51b):** The octadecyl thionocarbonate was prepared, using General Procedure #2, from octadecan-1-ol (2.51a) (320 mg, 1.2 mmol) and arylchlorothionoformate 2.33 (260 mg, 1.3 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (5:95), afforded 2.51b as a colourless solid (445 mg, 86%); recrystallisation with CH₂Cl₂/hexanes gave colourless flakes mp 61.4–62.2 °C; Rf 0.4 EtOAc/hexanes (5:95); ¹H NMR (500 MHz, CDCl₃): δ 7.02 (2H, dm, J = 7.0 Hz), 6.91 (2H, dm, J = 7.0 Hz), 4.51 (2H, t, J = 6.9 Hz), 3.81 (3H, s), 1.82 (2H, tt, J = 6.9, 6.9 Hz), 1.44–1.26 (30H, m), 0.88 (3H, t, J = 6.9 Hz) ppm; ¹³C NMR (150 MHz, CDCl₃): δ 195.8, 157.7, 147.0, 122.7, 114.4, 74.6, 55.5, 31.9, 29.7 (6 coincident signals), 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 28.2, 25.8, 22.7, 14.1 ppm; IR (KBr disc) ν = 2921, 2851, 1507 cm⁻¹; MS (70 eV, El): m/z (%): 436 (8) [M⁺], 140 (47), 124 (100); HRMS (70 eV, EI): calcd for C₂₆H₄₄O₅S [M⁺]: 436.3011; found 436.3011; elemental analysis calcd for C₂₆H₄₄O₅S: C 71.51, H 10.16, S 7.34; found: C 71.38, H 10.10, S 7.16.

**1,2:3,4-Di-O-isopropylidene-alpha-D-galactopyranose (2.52a):** The commercially available protected galactose derivative 2.52a was prepared, according to the literature procedure, from D-galactose (700 mg, 3.9 mmol). All spectroscopic data corresponded to that quoted in the literature. 2.52a was obtained as a colourless oil (760 mg, 75%); ¹H NMR (300 MHz, CDCl₃): δ 5.56 (1H, d, J = 5.1 Hz), 4.61 (1H, dd, J = 8.0, 2.4 Hz), 4.33 (1H, dd, J = 5.1, 2.4 Hz), 4.27 (1H, dd, J = 8.0, 1.5 Hz), 3.89–3.82 (2H, m), 3.77–3.69 (1H, m) 2.21 (1H, brs), 1.52 (3H, s), 1.45 (3H, s), 1.33 (6H, s) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 109.4, 108.6, 96.2, 71.5, 70.7, 70.5, 68.0, 62.3, 26.0, 25.9, 24.9, 24.3 ppm; MS (70 eV, EI): m/z (%): 245 (91) [M–CH₃]⁺,
1.2:3,4-Di-O-isopropylidene-alpha-D-galactopyranose O-(4-methoxyphenyl) carbonothioate (2.52b): Diisopropylidene galactose 2.52a (276 mg, 1.1 mmol) was acylated using General Procedure #2 and arylchlorothionoformate 2.33 (241 mg, 1.2 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with Et\(_2\)O/CH\(_2\)Cl\(_2\)/hexanes (10:25:65), gave 2.52b as a colourless oil (338 mg, 75%); R\(_f\) 0.4 Et\(_2\)O/CH\(_2\)Cl\(_2\)/hexanes (10:25:65); \(^1\)H NMR (500 MHz, (CD\(_3\))\(_2\)CO): \(\delta\) 7.06 (2H, dm, \(J = 9.5\) Hz), 6.97 (2H, dm, \(J = 9.5\) Hz), 5.52 (1H, d, \(J = 5.0\) Hz), 4.69 (1H, dd, \(J = 8.0, 2.5\) Hz), 4.67 (1H, dd, \(J = 11.0, 3.5\) Hz), 4.54 (1H, dd, \(J = 11.5, 8.0\) Hz), 4.41 (1H, dd, \(J = 5.0, 2.5\) Hz), 4.37 (1H, dd, \(J = 8.0, 2.0\) Hz), 4.28 (1H, ddd, \(J = 8.0, 3.5, 2.0\) Hz), 3.81 (3H, s), 1.48 (3H, s), 1.34 (3H, s), 1.33 (3H, s) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 195.6, 157.7, 147.1, 122.6, 114.4, 109.8, 108.9, 96.3, 72.4, 71.0, 70.7, 70.4, 65.5, 55.5, 26.1, 25.9, 24.9, 24.5 ppm; IR (thin film) \(v\) = 2988, 1505, 1456 cm\(^{-1}\); MS (70 eV, EI): \(m/z\) (%): 426 (4) [M]\(^+\), 411 (22), 43 (100); HRMS (70 eV, EI): calcd for C\(_{20}\)H\(_{27}\)O\(_8\)S [M+H]\(^+\): 427.1427; found 427.1443.

Betulin-O-(4-methoxyphenyl) carbonothioate (2.53b): To a solution of betulin (310 mg, 0.70 mmol) and pyridine (113 \(\mu\)L, 1.40 mmol, 2 equiv) in THF (30 mL, 23 mM), cooled to 0 °C, was added the arylchlorothionoformate 2.33 (156 mg, 0.77 mmol, 1.1 equiv) as a solution in THF (approx. 2.5 M). The reaction was left to warm to rt and after 13 h the solvent was removed in vacuo. The resulting residue was: diluted with CH\(_2\)Cl\(_2\) (30 mL); washed sequentially with aq 1M HCl (20 mL), sat. aq NaHCO\(_3\) (20 mL), and brine (20 mL); and dried (MgSO\(_4\)). Removal of the solvent
in vacuo afforded the crude material. Purification by flash chromatography, eluting with EtO\textsubscript{2}/hexanes (50:50), gave \textbf{2.53b} as a colourless solid (273 mg, 64%); Recrystallisation with CH\textsubscript{2}Cl\textsubscript{2}/hexanes gave colourless prisms mp 122-124 °C; R\textsubscript{f} 0.50 EtOAc/hexanes (30:70); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.06 (2H, dm, \textit{J} = 9.0 Hz), 6.93 (2H, dm, \textit{J} = 9.0 Hz), 4.76 (1H, d, \textit{J} = 11.0 Hz), 4.73 (1H, s), 4.63 (1H, s), 4.29 (1H, d, \textit{J} = 11.0 Hz), 3.82 (3H, s), 3.18 (1H, dd, \textit{J} = 11.5, 5.0 Hz), 2.49 (1H, ddd, \textit{J} = 11.0, 11.0, 6.0 Hz), 2.09-1.05 (45H, m), 1.07 (3H, s), 1.02 (3H, s), 0.99 (3H, s), 0.95-0.90 (1H, m), 0.86 (3H, s), 0.78 (3H, s), 0.70 (1H, d, \textit{J} = 9.0 Hz) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 196.3, 157.6, 149.9, 147.0, 122.7, 114.4, 110.0, 78.9, 73.8, 55.5, 55.2, 50.3, 48.9, 47.7, 46.7, 42.7, 40.8, 38.8, 38.7, 37.7, 37.1, 34.5, 34.1, 29.7, 29.5, 27.9, 27.3, 27.1, 25.1, 20.7, 19.1, 18.2, 16.1, 16.0, 15.3, 14.8 ppm; IR (KBr disc) \textit{v} = 3409, 2944, 1505, 1458 cm\textsuperscript{-1}; MS (70 eV, EI): m/z (%): 608 (4) [M\textsuperscript{+}], 424 (100); HRMS (70 eV, EI): calcd for C\textsubscript{38}H\textsubscript{56}O\textsubscript{4}S [M\textsuperscript{+}]: 608.3899; found 608.3896.

\textbf{O-Cholesteryl O-phenyl carbonothioate (2.56)}: The title compound was prepared, using General Procedure #2, from cholesterol (re-crystallised from EtOH) (691 mg, 1.77 mmol) and phenyl chlorothionoformate \textbf{2.38c} (337 mg, 1.96 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (3:97), afforded \textbf{2.56} as a colourless solid (627 mg, 67%). All spectroscopic data corresponded to that quoted in the literature;\textsuperscript{53} mp 149.5-153.1 °C (lit. 157.2-158.8 °C\textsuperscript{53}); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.45-7.40 (2H, m), 7.31-7.29 (IH, m), 7.13-7.10 (2H, m), 5.45 (1H, brs), 5.16-2.06 (1H, m), 2.64-0.69 (43H, m) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 194.2, 153.3, 139.0, 129.4, 126.5, 123.4, 122.0, 84.3, 56.6, 56.1, 50.0, 42.3, 39.7, 39.5, 37.2, 36.8, 36.6, 36.1, 35.8, 31.9, 31.8, 28.2, 28.0, 27.0, 24.3, 23.8, 22.8, 22.6, 21.0, 19.3, 18.7, 11.9 ppm; MS (ESI): \textit{m/z} (%): 545 (45) [M + Na\textsuperscript{+}], 383 (75), 371 (100), 242 (65); HRMS (ESI): calcd for C\textsubscript{38}H\textsubscript{50}O\textsubscript{2}SNa: [M\textsuperscript{+}]: 545.3429; found 545.3428.
4.3.1.4. Synthesis of the Imidazolide

1,1'-Thiocarbonyldiimidazole (2.39): Initially commercially available 1-(trimethylsilyl)imidazole (2.40) was prepared, according to the literature procedure,\textsuperscript{122} from imidazole (4.90 g, 72.0 mmol, 1.3 equiv) and hexamethyldisilazane (11.6 mL, 55.6 mmol, 1 equiv). The product was purified by distillation and obtained as a colourless oil (10.09 g, 54%). Using 1-(trimethylsilyl)imidazole (2.40) (5.450 g, 38.8 mmol), commercially available 2.39 was prepared according to the literature procedure,\textsuperscript{59} and was obtained as a bright yellow solid (3.210 g, 93%); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 8.13 (2H, s), 7.54 (2H, s), 7.20 (2H, s) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 172.7, 138.2, 132.0, 120.6 ppm; IR (KBr disc) ν = 3144, 3109 cm\textsuperscript{-1}; MS (70 eV, EI): m/z (%): 178 (100) [M\textsuperscript{+}], 120 (35), 111 (98); HRMS (70 eV, EI): calcd for C\textsubscript{7}H\textsubscript{6}N\textsubscript{4}S [M\textsuperscript{+}]: 178.0313; found 178.0316.

Methyl 4-(2-(1H-imidazole-1-carbonothioyloxy)ethyl)benzoate (2.37f): To a solution of alcohol 2.32 (300 mg, 1.7 mmol) in THF (3.5 mL) was added 1,1'-thiocarbonyldiimidazole (2.39) (385 mg, 2.2 mmol, 1.3 equiv). The resulting mixture was heated at reflux for 2 h and then allowed to cool to rt. The mixture was diluted with water and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 20 mL). The combined organic extracts were washed with aq 1M HCl (30 mL), sat. aq NaHCO\textsubscript{3} (30 mL), brine (20 mL) and dried (MgSO\textsubscript{4}). The solvent was removed \textit{in vacuo} to yield the crude material. Purification by flash chromatography, eluting with EtOAc/hexanes (40:60), afforded 2.37f as a pale yellow solid (343 mg, 71%); recrystallisation with CH\textsubscript{2}Cl\textsubscript{2}/hexanes gave colourless cubes mp 63.3–64.5 °C; R\textsubscript{f} 0.2 EtOAc/hexanes (40:60); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 8.25 (1H, s), 8.01 (2H, dm, J = 6.6 Hz), 7.54 (1H, s), 7.34 (2H, dm, J = 6.6 Hz), 7.01 (1H, s), 4.88 (2H, t, J = 6.6 Hz), 3.91 (3H, s), 3.23 (2H, t, J = 6.6 Hz) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 183.8, 166.6, 141.9, 136.6, 130.8, 130.0, 129.0, 128.8, 117.7, 72.9, 52.1, 34.4 ppm; IR (KBr disc) ν = 3113, 2951, 1713, 1609, 1468 cm\textsuperscript{-1}; MS (70 eV, EI): m/z (%): 290 (6) [M\textsuperscript{+}], 259
4.3.1.5. Synthesis of Xanthate 2.37g

Methyl 4-(2-(methylthiocarbonothioyloxy)ethyl)benzoate (2.37g): Sodium hydride (60 % in mineral oil, 106 mg, 2.65 mmol, 1.5 equiv) was added to a solution of alcohol 2.32 (320 mg, 1.77 mmol) in THF (12 mL) at -78 °C. The reaction was stirred at this temperature for 1 h. Carbon disulfide (0.16 mL, 2.65 mmol, 1.5 equiv) was added and then the reaction was warmed to rt. After 15 h iodomethane (165 μL, 2.65 mmol, 1.5 equiv) was added. After 1.5 h the reaction was quenched with sat. aq ammonium chloride. The layers were separated and the aq layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine, dried (MgSO₄) and the solvent was removed *in vacuo* to give the crude product 2.37g as a colourless solid (410 mg, 85%), which was used without further purification; recrystallisation with CH₂Cl₂/hexanes gave colourless cubes mp 67.7–69.7 °C; Rₙ 0.40 EtOAc/hexanes (10:90); ¹H NMR (300 MHz, CDCl₃): δ 7.98 (2H, dm, J = 13.0 Hz), 7.31 (2H, dm, J = 13.0 Hz), 4.81 (2H, t, J = 6.9 Hz), 3.90 (3H, s), 3.18 (2H, t, J = 6.9 Hz), 2.51 (3H, s) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 215.6, 166.9, 142.6, 129.8, 128.9, 128.7, 73.2, 52.0, 34.6, 18.9 ppm; IR (KBr disc) ν = 2960, 1721, 1431 cm⁻¹; MS (70 eV, EI): m/z (%): 239 (3) [M-OMe]⁺, 163 (31), 162 (100), 131 (62); HRMS (70 eV, EI): calcd for C₁₂H₁₄O₃S₂ [M-OCH₃]⁺: 239.0200; found 239.0203; elemental analysis calcd for C₁₃H₁₄O₃S₂: C 53.31, H 5.22, S 23.72; found: C 53.34, H 5.05, S 23.82.

4.3.2. Radical Deoxygenation Reactions

All rt radical reactions were carried out in an oil bath at 25 °C. Triethylborane was purchased from Aldrich as 1 M solution in hexanes. The quality of this reagent was maintained by storage under N₂ in a Schenck flask.
\( \text{H} \) NMR yields were determined using 4,4'-di-\textit{tert}-butylbiphenyl as an internal standard. Comparison of the peak areas for the singlet corresponding to the \textit{t}-butyl (1.25 ppm in \( \text{C}_6\text{D}_6 \)) and the aromatic protons (7.58 & 7.36 ppm in \( \text{C}_6\text{D}_6 \)) of the internal standard were compared to the \( \text{CH}_2 \) signals of the starting material 2.26, and product 2.28 (4.44 and 3.92 ppm in \( \text{C}_6\text{D}_6 \) respectively). Yields were calcd by comparing the \( \text{H} \) NMR spectra of the reaction mixture before and after the reaction was complete (determined using TLC). If replicate samples were taken an average yield was quoted.

4.3.2.1. Radical Reactions from Section 2.2.1 and 2.2.3.

Deoxygenation of Thionocarbonate 2.26 to Yield 2.28:

\[
\begin{align*}
\text{Thionocarbonate} & \quad 2.26 \\
\text{Methyl 4-ethylbenzoate (2.28)} & \quad \text{RF} 0.57 \text{ EtOAc/hexanes (15:85)}; \quad \text{\( \text{H} \) NMR (300 MHz, CDCl}_3\):} \quad \delta 7.95 (2H, dm, \( J = 6.0 \text{ Hz} \)), 7.25 (2H, dm, \( J = 6.0 \text{ Hz} \)), 3.90 (3H, s), 2.70 (2H, \( J = 7.8 \text{ Hz} \)), 1.25 (3H, t, \( J = 7.8 \text{ Hz} \)) ppm; \quad \text{\( \text{C} \) NMR (75 MHz, CDCl}_3\):} \quad \delta 167.2, 149.7, 129.6, 127.8, 127.5, 51.9, 28.9, 15.2 ppm; \quad \text{IR (thin film) \( \nu = 2966, 1720, 1611, 1435 \text{ cm}^{-1} \); MS (70 eV, EI):} \quad m/z (%) 164 (35) [M]+, 149 (14), 133 (100), 105 (36); \quad \text{HRMS (70 eV, EI):} \quad \text{calcld for \( \text{C}_{10}\text{H}_{12}\text{O}_2 \) [M]+:} \quad 164.0837; \quad \text{found 164.0837.}
\end{align*}
\]

Experimental Procedures

Scheme 2.12. Thermal radical reaction of thionocarbonate 2.26 using TTMSS: Thionocarbonate 2.26 (70.0 mg, 0.20 mmol) and internal standard (4,4'-di-\textit{tert}-butylbiphenyl) (9.4 mg) were mixed in EtOAc (10.0 mL, 0.02 M). A 2 mL sample was removed from the mixture and retained for later analysis. TTMSS (65 \( \mu \text{L}, 0.21 \text{ mmol}, 1.3 \text{ equiv} \)) was added and the reaction was heated to reflux. After heating for 15 min at reflux to degas, AIBN (13 mg, 0.08 mmol, 0.5 equiv \)) was added. When TLC analysis indicated that the starting material was consumed, 2 \( \times \) 2 mL samples of the reaction mixture were removed. The solvent was removed from all samples. The yield (\( \text{H} \) NMR) of the deoxygenated product 2.28 was determined to be 87%.

\( \ast \) molar equivalents were calcld relative to the amount of thionocarbonate remaining after the 2 mL sample was removed.
Scheme 2.12. *Room temperature radical reaction of thionocarbonate 2.26 using TTMSS:* Thionocarbonate 2.26 (100 mg, 0.299 mmol) and internal standard (4,4'-di-tert-butylbiphenyl) (8.2 mg) were combined in EtOAc (14.5 mL, 0.02 M). A 2 mL sample was removed from the mixture and retained for later analysis. TTMSS (100 μL, 1.3 equiv) and then triethylborane (370 μL of 1 M solution in hexanes, 1.5 equiv) were added to the reaction. Air (0.045 equiv of O₂) was immediately injected over 30 s into the solution. After 20 min 2 × 2 mL samples of the reaction mixture were removed. The solvent was removed from all samples. The yield (¹H NMR) of the deoxygenated product 2.28 was determined to be 75%.

Table 2.2, entry 1. **Radical reaction of thionocarbonate 2.26 at room temperature using TTMSS (slow addition).** Thionocarbonate (520 mg, 1.51 mmol) and internal standard (4,4'-di-tert-butylbiphenyl) (35 mg) were combined in EtOAc (78 mL, 0.02 M). A 2 mL sample was removed from the mixture and retained for later analysis. Using a syringe pump TTMSS (609 μL, 1.97 mmol, 1.3 equiv) was set to add over 120 min to the remaining mixture. After 5 min triethylborane (1 M solution in hexanes, 1.5 equiv) was added in one portion. Air (0.045 equiv of O₂) was immediately injected over 30 s into the solution. After 140 min 2 × 2 mL samples of the reaction mixture were taken. The solvent was removed from all samples. The yield (¹H NMR) of the deoxygenated product 2.28 was 88%. The solvent was removed *in vacuo* from the remaining reaction mixture to give the crude residue. Purification of the residue by flash chromatography, eluting with EtOAc/hexanes (3:97), afforded 2.28 as a colourless oil (210 mg, 85%).

Table 2.2, entry 2. **Radical reaction of thionocarbonate 2.26 at 0 °C using TTMSS (slow addition):** The procedure was repeated according to the procedure for entry 1, except the reaction was performed at 0 °C. After 140 min thionocarbonate 2.26 (61.1 mg, 0.18 mmol) was consumed, and the yield (¹H NMR) of the deoxygenated product 2.28 was 82 %.

Table 2.2, entry 3. **Radical reaction of thionocarbonate 2.26 at −30 °C using TTMSS (slow addition):** The procedure was repeated according to the procedure for entry 1,
except the reaction was performed at -30 °C and the reagents (TTMSS and triethylborane) were added in two equal portions, the second after 60 min. After 140 min the starting material 2.26 (53.4 mg, 0.15 mmol) was consumed, and the yield (1H NMR) of the deoxygenated product 2.28 was 10%.

**Table 2.3 entry 1. Thermal radical reaction of thionocarbonate 2.26 using HSnBu₃:**

Thionocarbonate 2.26 (79.8 mg, 0.23 mmol) and internal standard (4,4'-di-tert-butylbiphenyl) (9.0 mg) were mixed in EtOAc (11.5 mL, 0.02 M). A 2 mL sample was removed from the mixture and retained for later analysis. HSnBu₃ (73 μL, 0.28 mmol, 1.3 equiv) was added and the reaction was heated to reflux. After heating for 15 min at reflux to degas, AIBN (15.6 mg, 0.09 mmol, 0.5 equiv) was added. When TLC analysis indicated that the starting material was consumed, 2 x 2 mL samples of the reaction mixture were removed. The solvent was removed from all samples. The yield (1H NMR) of the deoxygenated product 2.28 was determined to be 69% (6% starting material remaining).

**Table 2.3, entry 2. Room temperature radical reaction of thionocarbonate 2.26 using HSnBu₃:**

Thionocarbonate 2.26 (75.3 mg, 0.2 mmol) and internal standard (4,4'-di-tert-butylbiphenyl) were combined in EtOAc (11 mL, 0.02 M). A 2 mL sample was removed from the mixture and retained for later analysis. HSnBu₃ (69 μL of 0.47 M in EtOAc, 1.3 equiv), was set to add over 2 h to the remaining mixture using a syringe pump. After 5 min triethylborane (0.27 mL, 1 M solution in hexanes, 1.5 equiv) was added in one portion. Immediately air (0.045 equiv of O₂) was injected over 30 s into the solution. After 140 min a second 2 mL sample of the reaction mixture was taken. The solvent was removed from both samples. The yield (1H NMR) of the deoxygenated product 2.28 was 10% (70% starting material). The reaction was repeated without using the slow addition technique, and similarly, after 140 min the reaction contained mostly starting material.

**Table 2.4, entry 1. Room temperature radical reaction of thionocarbonate 2.26 using TTMSS and AIBN/hv.**

Thionocarbonate 2.26 (64.3 mg, 0.19 mmol) and internal standard (4,4'-di-tert-butylbiphenyl) (7.2 mg) were combined in EtOAc (9.3 mL, 0.02 M) under

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*In this example using the slow addition of TTMSS gave incomplete conversion of the starting material

† molar equivalents were calcd relative to the amount of thionocarbonate remaining after the 2 mL sample was removed
Ar atmosphere. A 2 mL sample was removed from the mixture and retained for later analysis. Ar was bubbled through the remaining mixture for 15 min to degas. A syringe pump containing a degassed solution of TTMSS (0.38 mL of 0.5 M in EtOAc, 1.3 equiv*) was set to add over 120 min. After 5 min AIBN (37 mg, 0.2 mmol, 1.5 equiv*) was added and the reaction was irradiated with a medium pressure mercury lamp. After 200 min a second 2 mL sample was taken. The solvent was removed from both samples. The yield (¹H NMR) of the deoxygenated product 2.28 was 73%.

**Table 2.4, entry 2.** Room temperature radical reaction of thionocarbonate 2.26 using TTMSS and hv: Thionocarbonate 2.26 (41.2 mg, 0.12 mmol) and internal standard (4,4'-di-‘m-butylbiphenyl) (9.9 mg) were combined in EtOAc (6.0 mL, 0.02 M) under Ar atmosphere. A 1 mL sample was removed from the mixture and retained for later analysis. Ar was bubbled through the remaining mixture for 15 min to degas. A syringe pump containing a degassed solution of TTMSS (39 μL, 0.13 mmol, 1.3 equiv*) was set to add over 120 min and the reaction was irradiated with a medium pressure mercury lamp. After 140 min a second 1 mL sample was taken. The solvent was removed from both samples. The yield (¹H NMR) of the deoxygenated product 2.28 was 70%.

4.3.2.2. Radical Reactions from Section 2.2.3.

**Table 2.6, entry 1.** See Experimental Section 4.3.2.1, page 92

**Table 2.6.** Experimental Procedures: Thiocarbonyl compounds 2.37a-2.37g were treated at room temperature with triethylborane/air and TTMSS. Slow addition of TTMSS, method (i), was employed in all examples. Thionocarbonates 2.37a-b, d-e were also treated with TTMSS in one portion, method (ii). Yields were determined using the internal standard (4,4'-di-‘m-butylbiphenyl) and ¹H NMR spectroscopy.

**Table 2.6, method (i):** Slow addition of TTMSS: Thiocarbonyl compounds 2.37a-2.37g (70 – 100 mg) were deoxygenated using the procedure supplied for Table 2.2 entry 1. After 240 min the yield (¹H NMR) of the deoxygenated product 2.28 was determined. Yields for each substrate are displayed in Table 2.6.

* molar equivalents were calculated relative to the amount of thionocarbonate remaining after the 2 mL sample was removed
Table 2.6, method (ii): Single addition of TTMSS: Thionocarbonates 2.37a-b, and d-e (70 – 100 mg) were deoxygenated according to the procedure described for Scheme 2.12 (room temperature example). All reactions were complete within 20 min and the yield (^1H NMR) of the deoxygenated product 2.28 was determined. Yields for each substrate are displayed in Table 2.6.

4.3.2.3. Radical Reaction from Section 2.2.4.

Table 2.7, entry 1. See Experimental Section 4.3.2.1, page 92.

Table 2.7, entry 2: Deoxygenation of thionocarbonate 2.50b to yield ethyl benzene (2.50c). This reaction was performed as described for Table 2.2 entry 1, however, C₆D₆ was used as a solvent in place of EtOAc, to prevent loss of the volatile product of deoxygenation. An internal standard (4,4'-di-tert-butylbiphenyl) and ^1H NMR spectroscopy were used to determine the product yield. Samples for ^1H NMR analysis were taken directly from the reaction mixture. The product was identified by comparison of ^1H NMR data of the crude reaction mixture to an authentic sample of the product.

Table 2.7, entry 3: Deoxygenation of thionocarbonate 2.51b to yield octadecane (2.51b). To a solution of thionocarbonate 2.51b (197 mg, 0.45 mmol) in EtOAc (0.02 M), TTMSS (0.5 M in EtOAc, 1.3 equiv) was set to add over 120 min, using a syringe pump. After 5 min triethylborane (1 M solution in hexanes, 1.5 equiv) was added in one portion. Air (0.045 equiv of O₂) was immediately injected over 30 s into the solution. After 140 min the solvent was removed in vacuo to give the crude material. Products were purified using flash chromatography on silica, and/or by recrystallisation. Purification of the crude material by flash chromatography (0:100 to 5:95 EtOAc:hexanes) gave 2.51c as a colourless oil (108 mg, 94%). Spectroscopic data for this compound matched that of an authentic sample; ^1H NMR (300 MHz, CDCl₃): δ 1.30-1.20 (32H, m), 0.88 (6H, t, J = 6.8 Hz) ppm; ^13C NMR (75 MHz, CDCl₃): δ 31.9, 29.7-29.7 (coincident signals), 19.4, 22.7, 14.11
Table 2.7, entry 4. Deoxygenation of thionocarbonate 2.52b to yield 6-deoxy-1,2:3,4-Di-O-(1-methylethylidene)-alpha-D-galactopyranose (2.52c). The title compound 2.52c was prepared using method (b) from thionocarbonate 2.52b (341 mg, 0.80 mmol). Purification of the crude material by flash chromatography (40:60 EtOAc/hexanes) gave 2.52b as a colourless oil (172 mg, 88%). Spectroscopic data for this compound corresponded to that quoted in the literature;\textsuperscript{123,124} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 5.52 (1H, d, \( J = 5.1 \) Hz), 4.58 (1H, dd, \( J = 8.0, 2.4 \) Hz), 4.28 (1H, dd, \( J = 5.1, 2.4 \) Hz), 4.08 (1H, dd, \( J = 8.0, 1.8 \) Hz), 3.91 (1H, qd, \( J = 6.6, 1.8 \) Hz), 1.52 (3H, s), 1.46 (3H, s), 1.35 (3H, s), 1.32 (3H, s), 1.25 (3H, d, \( J = 6.6 \) Hz) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 108.9, 108.2, 96.5, 73.5, 70.9, 70.3, 63.4, 26.0 (2 coincident signals), 24.9, 24.4, 15.9 ppm; MS (70 eV, EI): \textit{m/z} (%) 229 (98) [M-CH\textsubscript{3}]; 43 (100); HRMS (ESI): calcd for C\textsubscript{12}H\textsubscript{20}O\textsubscript{5}Na [M+Na]\textsuperscript{+}: 267.1208; found 267.1209.

Table 2.7, entry 5. Deoxygenation of thionocarbonate 2.53b to yield deoxy-betulin 2.53c: To a solution of thionocarbonate 2.53b (136 mg, 0.22 mmol) in EtOAc (0.02 M) was added TTMSS (1.3 equiv), followed by triethylborane (334 \( \mu \)L (1 M solution in hexanes), 1.5 equiv). Air (1.4 mL (0.045 equiv of O\textsubscript{2})) was immediately injected over 30 s into the solution. After 90 min the solvent was removed \textit{in vacuo} to give the crude material. Purification of the crude material by flash chromatography (15:85 EtOAc/hexanes) gave the deoxygenated product 2.53c as a colourless oil (74 mg, 78%); re-crystallisation with CH\textsubscript{2}Cl\textsubscript{2}/heptane gave colourless flakes mp 220-223 °C; \( R_f \) 0.48 EtOAc/hexanes (20:80); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 4.68 (1H, d, \( J = 2.4 \) Hz), 4.57-4.55 (1H, m), 3.18 (1H, dd, \( J = 10.8, 5.4 \) Hz), 2.37 (1H, ddd,
$J = 11.1, 11.1, 5.7$ Hz), 1.98-1.84 (1H, m), 1.67-0.66 (44H, m) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 151.0, 109.3, 79.0, 55.2, 50.3, 48.2, 48.0, 43.0, 42.8, 40.8, 40.0, 38.8, 38.6, 38.0, 37.1, 35.5, 34.2, 29.8, 28.0, 27.4, 27.4, 25.1, 20.9, 19.3, 18.3, 18.0, 16.1, 15.9, 15.4, 14.5 ppm; IR (KBr disc) $\nu = 3383, 2942, 1727 \text{ cm}^{-1}$; MS (70 eV, EI): $m/z$ (%): 426 (100) [M]$^+$, 218 (55), 207 (92), 189 (92), 135 (90); HRMS (70 eV, EI): calcd for C$_{30}$H$_{50}$O [M]$^+$: 426.3862; found 426.3865.

4.3.2.4. Radical Reaction from Section 2.2.5.

Deoxygenation of thionocarbonate 2.56 to yield cholest-5-ene (2.57): Deoxygenation of the cholesterol derivative 2.56 (96 mg, 0.18 mmol) was performed using method (d) Section 4.3.2.3. Purification of the crude material by flash chromatography (hexanes), followed by re-crystallisation (EtOH/CH$_2$Cl$_2$) gave the deoxygenated product 2.57 as a colourless solid (60 mg, 88%). All spectroscopic data corresponded to that quoted in the literature.$^{125}$ mp 87.0-90.9 °C (lit. 87-89 °C)$^{16}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.30-5.26 (1H, m), 2.30-2.18 (1H, m), 2.05-0.84 (41H, m), 0.67 (3H, s) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.7, 119.0, 56.9, 56.2, 50.6, 42.3, 39.9, 39.9, 39.5, 37.5, 36.2, 35.8, 32.9, 31.9, 31.8, 28.3, 28.1, 28.0, 24.3, 23.8, 22.8, 22.6, 20.8, 19.5, 18.7, 11.9 ppm; MS (70 eV, EI): $m/z$ (%): 370 (100) [M]$^+$, 355 (50), 257 (35); HRMS (70 eV, EI): calcd for C$_{27}$H$_{46}$ [M]$^+$: 370.3600; found 370.3591.
4.4. Chapter 3 - Experimental

4.4.1. Carbomethoxy Approach

Methyl 3-((4-(methoxycarbonyl)phenethoxy)carbonothioyloxy)-2-naphthoate (3.106): The title compound was prepared, using General Procedure #2, from alcohol 2.32 (107 mg, 0.59 mmol) and methyl 3-(chlorocarbonothioyioxy)-2-naphthoate 3.105 (supplied by a colleague) (250 mg, 0.89 mmol, 1.5 equiv). Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (3:97), afforded 2.28 as a colourless solid (212 mg, 84%); recrystallisation with CH₂Cl₂/heptane gave colourless needles mp 115.9–116.8 °C; R₁ 0.52 EtOAc/Hexanes (17:83); ¹H NMR (300 MHz, CDCl₃) δ 8.62 (1H, s), 7.99-7.95 (3H, m), 7.85-7.82 (1H, m), 7.65-7.54 (3H, m), 7.35-7.31 (2H, m), 4.79 (2H, t, J = 6.9 Hz), 3.92 (3H, s), 3.84 (3H, s), 3.22 (2H, t, J = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 195.0, 166.9, 164.6, 148.6, 142.4, 135.4, 134.0, 130.8, 129.9, 129.1, 129.0, 128.7, 127.5, 127.0, 121.7, 121.1, 73.9, 52.4, 52.1, 34.5 cm⁻¹; IR (thin film) ν = 2953, 1713, 1631, 1599 cm⁻¹; MS (70 eV, EI): m/z (%): 424.1 (5) [M⁺], 163.1 (100), 142 (55), 131.0 (70); HRMS (70 eV, EI): calcd for C₂₃H₂₀O₆S [M⁺]: 424.0981, found 424.0981; elemental analysis calcd for C₂₃H₂₀O₆S: C 65.08, H 4.75, S 7.55; found: C 65.16, H 4.88, S 7.46.

4.4.2. Methyl Ether Approach

4.4.2.1. Preparation of the Thionocarbonate

Ethyl 3-methylcyclohex-2-ene-carboxylate (3.111): Wilkinson’s catalyst (0.316 g, 0.34 mmol, 0.05 equiv) was added to a solution of ethyl 3-methylcyclohexa-2,5-dienecarboxylate (3.110) (1.14 g, 6.83 mmol) (supplied by a colleague) in THF (34 mL, 0.2 M). The reaction was flushed with hydrogen and placed under a hydrogen atmosphere using a balloon. The mixture was stirred at rt for 20 h, and after this time the solvent was removed in vacuo. The crude residue was purified using flash chromatography, eluting with (7:93 Et₂O/Hexanes), to afford the alkene 3.111 as a colourless oil (1.11 g, 97%); R₁ 0.52 EtOAc/Hexanes (15:85);
(3-Methylcyclohex-2-enyl)methanol (3.91): Alkene 3.111 (6.87 g, 40.9 mmol) was dissolved in diethyl ether (130 mL) and added carefully via cannula to a suspension of lithium aluminium hydride (3.90 g, 103 mmol, 2.5 equiv) in diethyl ether (400 mL) cooled at 0 °C. After stirring at this temperature for 3 hours the reaction was quenched by the sequential addition of water (3.9 mL), aq sodium hydroxide (15% w/v solution, 3.9 mL) and water (7.8 mL). The mixture was filtered through a pad of celite with diethyl ether (500 mL), and the solvent was removed in vacuo. Purification of the crude residue using flash chromatography, eluting with (40:60 Et₂O/Hexanes), afforded the alcohol 3.91 as a colourless oil (4.80 g, 93%). Spectroscopic data for this compound was in accordance with the literature: R f 0.25 EtOAc/hexanes (15:85); ¹H NMR (300 MHz, CDCl₃) δ 5.29 (1H, brs), 3.48 (2H, d, J = 6.0 Hz), 2.28–2.0 (1H, m), 1.91–1.85 (2H, m), 1.78–1.69 (2H, m), 1.65 (3H, s), 1.56–1.46 (1H, m), 1.33–1.26 (1H, m) ppm ¹³C NMR (75 MHz, CDCl₃): δ 136.8, 121.7, 67.1, 38.4, 30.1, 25.2, 23.9, 21.3 ppm; IR (thin film) ν = 3337, 2925, 2861, 1670 cm⁻¹; MS (70 eV, EI): m/z (%): 126 (6) [M⁺], 95 (60), 83 (100); HRMS (70 eV, EI): calcd for C₈H₁₄O [M⁺]: 126.1045; found 126.1047.

3-Methoxynaphthalen-2-ol (3.113): The mono-protected napthol derivative was prepared using a procedure modified from the literature. 2,3-Dihydroxynaphthalene (3.112) (9.26 g, 57.8 mmol) was dissolved in acetone (290 mL). Potassium carbonate (7.99 g, 57.8 mmol, 1.0 equiv) followed by iodomethane (3.6 mL, 57.8 mmol, 1.0 equiv) was added to the reaction mixture. The reaction was heated at reflux for 12 hours. After cooling to rt the mixture was diluted with water (200 mL) and the
acetone was removed in vacuo. The remaining aq phase was extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with water and then brine; dried (MgSO₄); and concentrated in vacuo. Recrystallisation from dichloromethane/hexanes afforded the phenol 3.113 as a white solid (6.53 g, 65%). Spectroscopic data for this compound corresponded to that quoted in the literature;¹¹¹,¹²⁶

\[ \text{¹H NMR (300 MHz, CDCl₃): } \delta 7.72-7.68 (2H, m), 7.37-7.34 (2H, m), 7.30 (1H, s), 7.13 (1H, s), 5.99 (1H, s), 4.00 (3H, s) \text{ ppm; } \text{¹³C NMR (75 MHz, CDCl₃): } \delta 147.2, 145.6, 129.6, 128.9, 126.4, 126.3, 124.3, 123.8, 109.3, 105.6, 55.8 \text{ ppm; MS (70 eV, EI): } m/z (%) : 174 (98) [M]+, 159 (70), 131 (100); HRMS (70 eV, EI): calcd for C₁₁H₁₀O₂ [M]+ : 174.0681; found 174.0680.

**O-3-Methoxynaphthalen-2-yl chlorothionoformate (3.107):** The title compound was prepared, using General Procedure #1, from 3-methoxynaphthalen-2-ol (3.113) (5.17 g, 29.7 mmol). Purification of the crude material by flash chromatography, eluting with EtOAc:hexanes (15:85), afforded 3.107 as a red solid (7.23 g, 96%). Recrystallisation from dichloromethane/hexanes afforded a pale yellow solid; mp 110.8–11.3 °C; Rf 0.63 EtOAc/Hexanes (15:85); ¹H NMR (300 MHz, CDCl₃): \( \delta 7.80-7.77 \) (2H, m), 7.57 (1H, s), 7.51 (1H, ddd, \( J = 8.1, 6.9, 1.2 \text{ Hz} \)), 7.42 (1H, ddd, \( J = 8.1, 6.9, 1.2 \text{ Hz} \)), 7.27 (1H, s), 3.97 (3H, s) \text{ ppm; } [M]+, 189 (70); HRMS (70 eV, EI): calcd for: C₁₂H₁₂O₂S⁻Cl [M]+ : 253.9982; found 253.9975; elemental analysis calcd for C₁₂H₁₀O₂SCl: C 77.39, H 7.14; found: C 77.41, H 7.15.

**O-3-Methoxynaphthalen-2-yl O-(3-methylcyclohex-2-enyl)methyl carbonothioate (3.101):** The title compound was prepared, using General Procedure #2, from alcohol
3.91 (4.53 g, 35.9 mmol) and arylchlorothionoformate 3.107 (9.97 g, 39.5 mmol, 1.1 equiv). Purification of the crude material by flash chromatography, eluting with CH$_2$Cl$_2$/hexanes (30:70), afforded the thionocarbonate 3.101 as a colourless oil (10.52 g, 86%); R$_f$ 0.70 EtOAc/hexanes (15:85); $^1$H NMR (300 MHz, CDCl$_3$): δ 7.78-7.75 (2H, m), 7.54 (1H, s), 7.46 (1H, ddd, J = 8.4, 6.9, 1.5 Hz), 7.38 (1H, ddd, J = 8.1, 6.9, 1.5 Hz), 7.24 (1H, s), 5.36 (1H, brs), 4.43-4.40 (2H, m), 3.95 (3H, s), 2.73-2.61 (1H, m), 1.97-1.89 (2H, m), 1.86-1.73 (2H, m), 1.69 (3H, s), 1.62-1.54 (1H, m), 1.40 (1H, ddd, J = 12.3, 8.4, 2.4 Hz) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 194.8, 150.0, 142.4, 137.3, 132.6, 128.2, 127.5, 126.6, 126.4, 124.3, 120.5, 120.2, 107.6, 78.2, 55.8, 34.7, 30.0, 25.2, 23.9, 20.8 ppm; IR (thin film) ν = 2925, 2858 cm$^{-1}$; MS (70 eV, El): m/z (%) 342 (1), 234 (50), 174 (100); HRMS (70 eV, El): calcd for C$_{20}$H$_{22}$O$_4$S [M$^+$]: 342.1290; found 342.1292.

4.4.2.2. Radical Carboxyarylation Reaction

7-(3-Methoxynaphthalen-2-yl)-7-methylhexahydroisobenzofuran-1(3H)-one (3.114): The thionocarbonate 3.101 (3.01 g, 8.79 mmol), and TTMSS (2.98 mL, 9.67 mmol, 1.1 equiv) were dissolved in chlorobenzene (125 mL, 0.07 M) and heated to reflux for 20 minutes. 1,1’-azobis(cyclohexane-1-carbonitrite) (ACN) (1.07 g, 4.38 mmol, 0.5 equiv.) was added and reflux continued for 2 h. The reaction was cooled to rt and concentrated in vacuo. Purification of the crude residue was by flash chromatography, eluting with Et$_2$O/CH$_2$Cl$_2$/hexanes (10:30:70), afforded the title compound 3.114 as a colourless solid (1.01 g, 39%); recrystallisation from CH$_2$Cl$_2$/heptane afforded colourless prisms, mp 181-183 °C; R$_f$ 0.29 EtOAc/hexanes (15:85); $^1$H NMR (500 MHz, CDCl$_3$): δ 7.74 (1H, d, J = 8.0 Hz), 7.70 (1H, s), 7.69 (1H, d, J = 8.0 Hz), 7.38 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.30 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.13 (1H, s), 4.17 (1H, ddd, J = 8.5, 4.5 Hz), 4.01 (1H, d, J = 6.0 Hz), 3.93 (3H, s), 3.89 (1H, d, J = 8.5 Hz), 2.72-2.66 (1H, m), 2.08 (1H, dm, J = 13.0 Hz), 1.98 (1H, ddd, J = 13.0, 13.0, 3.5 Hz), 1.88-1.85 (2H, m), 1.80-1.71 (1H, m), 1.47 (3H, s), 1.32 (1H, dddd, J = 13.0, 13.0, 13.0, 4.5 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 75 MHz,): δ 175.4, 156.9, 137.2, 133.0, 128.7, 127.8, 125.9, 125.9,
125.6, 123.4, 105.7, 70.8, 55.0, 46.7, 37.3, 35.0, 33.8, 26.8, 24.9, 19.9 ppm; IR (thin film) $\nu = 2937, 1770$ cm$^{-1}$; MS (70 eV, EI): $m/z$ (%): 310 (100) [M$^+$], 295 (8), 280 (5); HRMS (70 eV, EI): calcd for C$_{20}$H$_{22}$O$_3$: [M$^+$]: 310.1569; found 310.1567; elemental analysis calcd for C$_{20}$H$_{22}$O$_3$: C 77.39, H 7.14; found: C 77.41, H 7.15.

4.4.2.3. Final Transformations

7-(3-Methoxynaphthalen-2-yl)-7-methyloctahydroisobenzofuran-1-ol (3.116): The lactone 3.114 (1.75 g, 5.64 mmol) was dissolved in PhMe (260 mL) and cooled to –90 °C in a EtOH/liquid N$_2$ cooling bath. DIBAL-H (12.72 mL, 1 M in PhMe, 1.2 equiv) was added drop-wise, ensuring the reaction temperature remained constant. After stirring at this temperature for 1 h EtOAc (20 mL) was added carefully to the mixture, again ensuring the temperature remained constant. After 30 min the mixture was removed from the cooling bath and sat. aq rochelles (60 mL) was added and the reaction mixture. After stirring for 30 min the layers were separated, and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (100 mL) and dried (MgSO$_4$). The solvent was removed in vacuo to leave a colourless oil. Purification by flash chromatography afforded lactol 3.116 (mixture of diastereoisomers) as a while solid (1.50 g, 85%).

4-(3-Methoxynaphthalen-2-yl)-4-methyl-1,4,5,6,7,7a-hexahydroisobenzofuran (3.117): To a solution of lactol 3.116 (2.50 g, 8.01 mmol) in dichloromethane (80 mL, 0.1 M) at 0 °C was added triethylamine (11.16 mL, 80.1 mmol, 10 equiv), followed by methanesulfonylchloride (2.48 mL, 32.0 mmol, 4.0 equiv). After stirring for 5 min the reaction was heated to reflux. After 1 h the reaction was cooled and quenched by the addition of sat. aq NaHCO$_3$ (20 mL). The organic layer was separated and the aq layer was extracted with dichloromethane (2×30 mL). The combined organic
extracted were dried (MgSO₄) and the solvent was removed in vacuo. Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (6:94), afforded dihydrofuran 3.117 as a colourless oil (1.69 g, 72%); Rf 0.65 EtOAc/hexanes (15:85);

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl₃): } \delta \text{ values as in Table 3.117} \]

Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (6:94), afforded dihydrofuran 3.117 as a colourless oil (1.69 g, 72%); Rf 0.65 EtOAc/hexanes (15:85);

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl₃): } \delta \text{ values as in Table 3.117} \]

4-(3-Methoxynaphthalen-2-yl)-4-methyl-4,5,6,7-tetrahydroisobenzofuran (3.115):
A mixture of dihydrofuran 3.117 (915 mg, 3.12 mmol) and DDQ (776 mg, 3.41 mmol, 1.1 equiv) in toluene (155 mL) was heated at reflux for 30 min. After this time the reaction was cooled to rt and the solvent was removed in vacuo. Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (4:94) yielded the furan 3.115 as a colourless oil (737 mg, 81%); Rf 0.60 EtOAc/hexanes (10:90);

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl₃): } \delta \text{ values as in Table 3.115} \]

\[ \text{\textsuperscript{13}C NMR (75 MHz, CDCl₃): } \delta \text{ values as in Table 3.115} \]

IR (thin film) \( \nu = 2926, 2863 \text{ cm}^{-1} \); MS (70 eV, EI): \( m/z \) (%) as in Table 3.115; HRMS (70 eV, EI): calcd for C₂₀H₂₂O₂ [M]⁺: 294.1620; found 294.1621.

\[ \text{4-(3-Methoxynaphthalen-2-yl)-4-methyl-4,5,6,7-tetrahydroisobenzofuran (3.115):} \]

A mixture of dihydrofuran 3.117 (915 mg, 3.12 mmol) and DDQ (776 mg, 3.41 mmol, 1.1 equiv) in toluene (155 mL) was heated at reflux for 30 min. After this time the reaction was cooled to rt and the solvent was removed in vacuo. Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (4:94) yielded the furan 3.115 as a colourless oil (737 mg, 81%); Rf 0.60 EtOAc/hexanes (10:90);

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl₃): } \delta \text{ values as in Table 3.115} \]

\[ \text{\textsuperscript{13}C NMR (75 MHz, CDCl₃): } \delta \text{ values as in Table 3.115} \]

IR (thin film) \( \nu = 2926, 2863 \text{ cm}^{-1} \); MS (70 eV, EI): \( m/z \) (%) as in Table 3.115; HRMS (70 eV, EI): calcd for C₂₀H₂₂O₂ [M]⁺: 294.1620; found 294.1621.
3-(4-Methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)naphthalen-2-yl (3.118): Ethanethiol (555 µL, 7.51 mmol, 3.0 equiv) and sodium hydride (310 mg, 60% dispersion in mineral oil, 7.76 mmol, 3.1 equiv) were combined in DMF (10 mL) and stirred until the reaction subsided. The resulting mixture was added to a solution of methyl ether 3.115 (732 mg, 2.50 mmol) in DMF (10 mL) via cannula and then the reaction was heated in an oil bath at 110 °C for 15 h. After this time the reaction was diluted with CH₂Cl₂, and then washed with 1N HCl (50 mL) and then water (50 mL). The organic layer was dried (MgSO₄) and the solvent removed in vacuo. Purification of the residue by flash chromatography, eluting with EtOAc/hexanes (4:96 to 6:92), yielded the naphthol 3.118 as a colourless oil (320 mg, 46%); Rf 0.57 EtOAc/hexanes (10:90); ¹H NMR (500 MHz, CDCl₃): δ 7.77 (1H, s), 7.76 (1H, d, J = 8.0 Hz), 7.66 (1H, d, J = 8.0 Hz), 7.40 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.33 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.26 (1H, d, J = 1.0 Hz), 7.18 (1H, s), 7.14 (1H, d, J = 1.5 Hz), 5.05 (1H, brs), 2.77 (1H, ddd, J = 16, 4.5, 4.5 Hz), 2.62-2.55 (1H, m), 2.37 (1H, ddd, J = 14, 9.5, 4.5 Hz), 1.86–1.80 (5H, m), 1.66-1.62 (1H, m) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 152.5, 139.2, 138.3, 137.2, 133.5, 128.7, 128.7, 127.7, 126.5, 126.0, 125.7, 123.7, 120.3, 112.6, 36.9, 36.7, 29.2, 20.2, 19.6 ppm; IR (thin film) ν = 3477, 2933, 2862, 1634, 1600 cm⁻¹; MS (70 eV, EI): m/z (%): 278 (90) [M⁺], 263 (100); HRMS (70 eV, EI): calcd for C₁₉H₁₈O₂ [M⁺]: 278.1307; found 278.1306.

3-(4-Methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)naphthalen-2-yl trifluoromethanesulfonate (3.119): N-Phenyltrifluoromethanesulfonamide (532 mg, 1.49 mmol, 1.7 equiv) was added to a mixture of phenol 3.118 (244 mg, 0.877 mmol), triethylamine (2.44 mL, 20 equiv) and acetonitrile (5.8 mL, 0.15 M). The reaction was heated at reflux for 15 h. After cooling the mixture was diluted with water (30 mL) and


CH₂Cl₂ (40 mL). The two phases were separated, and the aq layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried (MgSO₄) and the solvent was removed in vacuo. Purification of the crude material by flash chromatography, eluting with EtOAc/hexanes (2:98), afforded the triflate 3.119 as a colourless solid (291 mg, 81%); recrystallisation from CH₂Cl₂/heptane afforded colourless prisms, mp 121.1–122.2 °C; R_f 0.76 EtOAc/Hexanes (15:85); ¹H NMR (500 MHz, CDCl₃): δ 7.84 (1H, s), 7.83-7.78 (2H, m), 7.74 (1H, s), 7.54-7.52 (2H, m), 7.27-7.26 (1H, m), 7.29 (1H, brs), 2.64 (2H, m), 2.41 (1H, ddd, J = 13.5, 9.5, 2.5 Hz), 1.84 (3H, s), 1.83-1.78 (1H, m), 1.72 (1H, ddd, J = 13.5, 8.5, 2.5 Hz), 1.64-1.58 (1H, m) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 147.4, 138.3, 138.2, 137.7, 132.1, 131.4, 130.3, 130.1, 127.9, 127.2, 127.1, 127.0, 120.7, 118.5, 118.4 (q, J C-F = 318 Hz), 38.0, 36.7, 29.4, 20.0, 19.3 ppm; IR (thin film) ν = 2937, 1769 cm⁻¹; MS (70 eV, EI): m/z (%): 410 (85) [M]+, 395 (80), 261 (100); HRMS (70 eV, EI): calcd for C₂₀H₁₇F₃O₄S [M]+: 410.0800; found: 410.0803; elemental analysis calcd for C₂₀H₁₇F₃O₄S: C 58.53, H 4.17, S 7.81, F 13.89; found: C 58.28, H 4.25, S 7.54, F 13.89.